Abstract

1. Flexible Marginal Structural Cox Models for Estimating Cumulative Effect of Time-Dependent Treatment on the Hazard

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Background: Attempts to assess causal effects of time-varying treatments in observational longitudinal studies face two analytical challenges: (1) the need to account for cumulative effects of past treatment and (2) the need to control for time-dependent (TD) confounders which can mediate the effect of past treatments. The marginal structural Cox model (Cox MSM) and the weighted cumulative exposure (WCE) model, have been proposed to overcome, respectively, one of the two challenges, while ignoring the other. However, no published methodology addresses both challenges simultaneously.

Objectives: To propose a flexible marginal structural Cox model for estimating the causal cumulative effect of TD treatments, to validate the model in simulations, and to illustrate its application in a real-life pharmaco-epidemiological study.

Methods: We develop a novel marginal structural Cox model with weighted cumulative exposure (Cox WCE MSM model). The model uses inverse-probability-of-treatment (IPT) weights to control for all the confounders. Then, the weight function that reflects the impact of past treatments on the current hazard is estimated using regression splines. The resulting WCE is then used to estimate the total causal treatment effect that accounts for both direct cumulative effects of past treatments and their 'indirect effects', mediated by the TD variables. We validated the performance of the new model using simulations. We then applied the model to reassess the association between the antiretroviral treatment didanosine (DDI) and cardiovascular (CVD) risk in HIV-positive persons in the Swiss HIV Cohort Study (SHCS).

Results: Simulations confirm that the Cox WCE MSM yields accurate estimates of the causal treatment effect under complex exposures and TD confounding. In the SHCS data, the new model fit much better than alternative Cox MSM models and suggested a dual effect of DDI use on CVD risks, with short-term risk increase followed by a longer-term protective effect.

Conclusions: The proposed model may provide novel insights regarding complex effects of time-dependent treatments.

2. De-Constructing a Marginal Structural Model: Effects of Follow-Up Duration on Stabilized Weights and Findings in a Study of Myocardial Infarction Risk in Hemodialysis Patients

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Background: Pharmacoepidemiologists often use marginal structural models (MSMs) to balance groups on baseline and time-varying confounders. In MSMs, when a person receives unexpected treatment (given confounders and treatment history), the observation receives a large weight. Weights accumulate during follow-up; repeated departures from usual treatment could cause very large weights, increasing variance and making estimates sensitive to extreme observations.

Objectives: In studying the effect of cumulative intravenous iron exposure on risk for myocardial infarction (MI) in dialysis patients, we assessed the effect of varying follow-up duration on MSM weights, treatment effect estimates, and variance. With longer follow-up, we expected a trade-off between increased information and increased variance.

Methods: We linked 2004–2008 data from 99,702 hemodialysis patients of a large dialysis organization with the US Renal Data System. With a 6-month baseline, we varied follow-up length from 4 to 24 months. Adjusting for baseline variables, recent lab values, and treatment history, we used monthly observations to estimate MSMs of the effect of number of months receiving (1) > 200 mg iron and (2) 1–200 mg iron on MI risk in the next month.

Results: Increased follow-up length yielded exponential increases in the mean (from 1 to 7), standard deviation (0.3–1,563), and maximum (10–1,221,970) stabilized weight. With 4 months of follow-up, a high-dose month was positively associated with MI risk (RD: 0.31 per 1,000 person-months; 95% CI: −0.02, 0.64), but the effect decreased over time and was negative for

follow-up lengths > 12 months (RD for 24 months: −0.13; 95% CI: −0.17, −0.9). Findings suggested no effect of low-dose iron on MI risk. As follow-up length increased, standard errors generally decreased, but with large fluctuations.

Conclusions: Increasing follow-up duration can lead to extreme MSM weights, fluctuation in standard errors, and sensitivity of results to outliers. Preliminary results show no increase in MI risk for hemodialysis patients with long-term exposure to intravenous iron.

3. Evaluating Newly-Marketed Medications with a High-Dimensional Disease Risk Score Estimated in a Historical Cohort

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Background: Assessing the effectiveness and safety of newly-marketed medications is crucial, but new drugs may have too few outcome events for multivariate adjustment and too few exposed patients to estimate a propensity score. A disease risk score (DRS) may be a viable alternative, if, as literature suggests, the DRS is estimated in a historical population.

Objectives: To use a historical population in a period preceding the marketing of a newly-marketed medication to estimate a high-dimensional DRS that includes hundreds of empirically-selected outcome risk factors. To assess the DRS's calibration and ability to discriminate in a cohort of patients using the new drug.

Methods: For our historical population, we assembled a cohort of commercially-insured clopidogrel initiators from January 2005 to August 2009, the time preceding prasugrel's entry on the market. In the historical data, we identified the 200 pre-exposure procedures, diagnoses and drugs that most strongly predicted the outcome of acute myocardial infarction (AMI) in the year after initiation. Along with age, sex and 25 other pre-defined covariates, we entered these 200 variables into a logistic regression model for risk of outcome. We then created a 'current patients' cohort of prasugrel and clopidogrel initiators from September 2009 to December 2011 and used our model to obtain predictions of disease risk. We assessed the DRS's discrimination (c-statistic) and calibration (Hosmer-Lemeshow goodness-of-fit statistic) in both the historical and current cohorts.

Results: In the historical cohort, there were 30,623 clopidogrel initiators and 3,241 events. The DRS model showed reasonable discrimination (c-stat = 0.68)

and was well-calibrated (p = 0.10). The current cohort had 8,320 initiators and 578 events. In that cohort, the DRS discrimination fell (c = 0.61) and calibration no longer held (p < 0.0001). Within deciles, the DRS consistently overestimated patients' observed risk by an average of 3%.

Conclusions: Though this approach appears to be promising, strategies to prevent model overfitting, handling of variables that exist in the historical but not the current cohort, and the underlying effect of time should be considered.

4. Using Predicted Probabilities of Exposure and Outcome To Assess Confounding

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Background: Investigators rarely know about the direction and strength of confounding in a population before starting a study. Such information could aid design decisions.

Objectives: We propose an approach for assessing confounding using propensity scores (PSs) and historical disease risk scores (DRSs) and apply it to four examples comparing a new drug to an active comparator.

Methods: Using US Medicare data, we identified initiators of three drugs (raloxifene, risedronate, rofecoxib) and comparators (alendronate for raloxifene and risedronate; non-selective non-steroidal anti-inflammatory drugs [NSAIDs] for rofecoxib) and outcomes (fracture for bisphosphonates; myocardial infarction [MI] and gastrointestinal [GI] bleed for rofecoxib) for each. The study period began at market entry of each drug of interest. We developed an historical DRS model for each example among comparator drug initiators before the study period. We applied the model coefficients to estimate the outcome probability for each initiator in the study period. We also estimated these patients' PSs for receiving the drug of interest. We calculated the Pearson correlation coefficient between PSs and the DRSs as an indicator of the direction and strength of likely confounding. We compared mean DRSs and outcome rates among initiators of each drug of interest and comparator before and after PS matching.

Results: The Pearson coefficient between the PS and DRS was −0.05 for raloxifene, −0.16 for risedronate, 0.08 for rofecoxib and MI, and 0.25 for rofecoxib and GI bleed, indicating strongest correlation between probability of treatment with rofecoxib and GI bleed

and hence upward confounding. Mean DRSs were similar among risedronate and alendronate initiators and differed proportionally to the Pearson coefficient for the other examples. PS matching resulted in similar mean DRSs between groups in each example. Crude outcome rate comparisons exhibited confounding consistent with the Pearson coefficients, which was mitigated by PS matching.

Conclusions: Correlations between PSs and DRSs developed in historical data indicate the direction and strength of confounding. DRS balance after PS matching is a useful metric for confounding adjustment.

5. Relative Performance of Approaches Handling Immortal Person-Time in Comparative Effectiveness Research: A Simulation Study

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Background: Observational comparative effectiveness studies are often subject to immortal person-time. A few approaches, such as the Mantel-Byar and landmark methods, have been proposed to appropriately handle the immortal time. A common approach, excluding immortal time, is known to cause bias. However, little is known about the relative performance of these approaches in different settings.

Objectives: To compare the performance of methods handling immortal person-time: (1) Mantel-Byar; (2) landmark (at 30, 90, 180 and 365 days following index date); and (3) exclusion.

Methods: We conducted Monte-Carlo simulation to assess the performance of these methods. We assumed that treatment times followed exponential distributions and event times followed Weibull ($\alpha\beta$, β) distributions with the treatment as a time varying predictor. We created different scenarios by varying $\alpha\beta$, β (β = 0.5 1 1.5), strength of the treatment effect (HR = 0.5 0.7 1 1.2 1.5) and prevalence of treatment (5–10%) at index date. Data were fitted using Cox proportional hazard models. The performance of the different methods was evaluated by computing bias, mean squared error, and coverage of the true hazard ratio.

Results: The Mantel-Byar method produced unbiased estimates as expected. Small biases ranging from −5% to 7% were observed when landmark methods were used. The amount of bias was associated with the size of the treatment effect. Larger effect sizes (HR: 0.5; 1.5) led to more bias. Large biases ranging from −55% to 10% were observed when the exclusion method was used. The magnitude and direction of bias depended on the shape parameter β and strength of the treatment effect.

Conclusions: Immortal person-time can bias results substantially when mishandled using the exclusion method. Landmark methods produced minimally biased results in all scenarios, while the magnitude of bias depended on the effect size. Considerations on hazard function, expected size of the effect, and presence of latency period are needed to select appropriate landmark time. The exclusion method should be avoided.

6. Misclassification in Assessment of Diabetogenic Risk Using Laboratory-Enhanced Claims Data

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Background: Suspected diabetogenic risk or drug indication may result in increased screening for diabetes mellitus (DM), resulting in potential measurement bias when evaluating diabetogenic risk.

Objectives: We sought to evaluate the validity of glucose test data in determining DM onset from a group model HMO Electronic Health Record Database.

Methods: We used a retrospective cohort design to assess the association between various drug classes and (1) first DM test and (2) DM onset. Subjects aged 35–65 enrolled in Kaiser Permanent Northwest between 1997–2010 entered the cohort at the first negative blood glucose (BG) test after ≥ 6 month continuous eligibility without DM diagnoses or antidiabetic drug use. They were followed for ≥ 12 months until end of eligibility or study end. Exposure to seven drug classes was ascertained from claims records for: β-blockers (BB), statins (ST), thiazide diuretics (TD), antidepressants (AD), atypical antipsychotics (AAP), renin-angiotension-system blockers (RASB), and calcium channel blockers (CCB). Diabetes onset was defined as fasting (random) BG ≥ 126 (≥ 200) mg/dL, HbA1C ≥ 7%, and/or antidiabetic drug initiation. We used time-dependent Cox Proportional Hazards Models to assess risk for both endpoints, adjusting for diabetic and cardiac risk factors.

Results: Our cohort included 134,967 patients, 105,893 (78.5%) with ≥ 1 BG test during follow-up, and 9,105 with incident DM. Compared to non-users, time to first BG test was significantly shorter in each drug class. AAP had the greatest propensity for testing (HR = 1.88, 95% CI: 1.74–2.03) and the greatest DM risk (1.77 [1.49–2.11]). Although RASB and CCB have shown no diabetogenic effect in clinical trials, both had a positive association with DM (1.17 [1.11–1.24] and 1.34 [1.24–1.44]), but also greater testing (1.30 [1.26–1.33] and 1.23 [1.19–1.28]). DM risk with BB (1.42 [1.35–1.49]) and TZ (1.40 [1.32–1.47]) was greater than testing propensity (1.23 [1.21–1.26] and 1.22 [1.19–1.25], respectively).

Conclusions: Patients receiving any considered antihypertensive drug class or APPs had higher propensity for diabetes testing resulting in potential measurement bias when diabetogenic effects are evaluated.

7. Risk of Hemorrhagic Stroke and Seizure Are Increased in Patients with Alzheimer's Disease

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Background: Patients with Alzheimer's Disease (AD) may be at increased risk of stroke, seizure, and venous thromboembolism (VTE) compared to the general population.

Objectives: Estimate rates of ischemic and hemorrhagic stroke, seizure, and VTE among a community-based sample of persons with and without AD.

Methods: A retrospective cohort study was conducted using The Health Improvement Network General Practitioner (GP) electronic medical record database from the UK. Patients diagnosed with AD on or after age 50-years from January 1, 1990 through July 31, 2009 with at least 6-months of baseline data were included. We selected a 1:1 comparator cohort of non-AD patients matched to AD patients on GP practice, birth year, sex and start date of follow-up. Age-sex-specific rates of first-time stroke, seizure and VTE in the AD and non-AD cohorts were estimated. Patients were followed until the date they left the practice, the endpoint of interest occurred, or July 31, 2009, whichever came first. Endpoints were validated using GP questionnaires and free-text notes to evaluate the positive predictive value (PPV) of the diagnoses codes.

Cox models were used to compute hazard ratios comparing AD patients to non-AD patients after adjusting for measured covariates.

Results: The AD and non-AD matched subcohorts included 11,042 patients without a history of seizures, 10,864 patients without a history of VTE, and 9,951 patients without a history of stroke. Cohorts were 33% male with a mean age of 80-years. Validation showed a PPV of 89% for seizure, 82% for VTE, and 91% for stroke. AD and non-AD patients had similar rates of VTE (HR = 1.04, 95% CI: 0.82, 1.30). AD patients had an increased rate of seizure (HR = 5.31, 95% CI: 3.97, 7.10) and any stroke (HR = 1.29, 95% CI: 1.11, 1.50). The higher incidence of any stroke was confined to hemorrhagic stroke (HR = 1.49, 95% CI: 1.06, 2.08), and not ischemic stroke (HR = 1.02, 95% CI: 0.84, 1.25). The relative risks of stroke and seizure were higher in the younger age groups.

Conclusions: In this retrospective cohort study, persons diagnosed with AD, especially younger patients, were at increased risk of hemorrhagic stroke and seizure compared to the general population.

8. Incidences of Herpes Zoster, Its Manifestations and Complications for 2005–2009 in Germany – A Retrospective Cohort Study

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Background: The disease burden of herpes zoster (HZ) infection and its painful complication postherpetic neuralgia (PHN) increases with age. Data on the epidemiology of HZ, its manifestations and PHN are scarce. These baseline data provide important information for vaccine effectiveness studies.

Objectives: To estimate incidence rates (IR) of HZ, its manifestations and complications stratified by sex, age and immune status.

Methods: Source data for this retrospective cohort study were three statutory health insurance providers from the German Pharmacoepidemiological Research Database (GePaRD), with about 7 million insurants throughout Germany. IRs with 95% confidence intervals (CI) of HZ, its manifestations and complications were estimated in insurants aged 0–100 years for the years 2005–2009.

Results: Overall IRs ranged from 6.7/1,000 person-years (PY) (CI: 6.6–6.8) to 8.0 (CI: 7.9–8.1) between 2005 and 2009, with 50% higher rates in females than

in males for all years. IRs increased with age with threefold higher IRs in > 80 year old persons compared to < 44 year old persons. The highest IRs were found for HZ without complications (5.2/1,000 PY [CI: 5.1–5.2]) followed by HZ with other nervous system involvement (1.1/1,000 PY [CI: 1.0–1.1]) and zoster opthalmicus (0.36/1,000 PY [CI: 0.35–0.37]). IRs in immunocompromised individuals were twice as high as in immunocompetent individuals (12.4/1,000 PY [CI: 12.2–12.5] vs. 6.7 [CI: 6.6–6.7]). In about 6.2% PHN was diagnosed after a HZ infection with women being more likely to develop this complication (6.5% [CI: 6.4–6.6] vs. 5.7% [CI: 5.5–5.9]).

Conclusions: Our study found substantially higher IRs in females than in males and in immunocompromised persons. Our study supports the previously reported increase with age and adds data on younger age groups and HZ manifestations, thus providing useful information for the planning of vaccine effectiveness studies. Against the background of an aging population, the disease burden of HZ is of considerable public health relevance.

9. Dyslipidemia, Inflammation and Cardiovascular Risk in Patients with Rheumatoid Arthritis

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Background: The contribution of concurrent inflammation and dyslipidemia to increased cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) is not clearly understood.

Objectives: To describe the prevalence of dyslipidemia and inflammation and to evaluate CVD risk in a cohort of RA patients (pts) using Reynolds risk score (RRS), which evaluates the 10 year CVD risk by combining traditional risk factors with the degree of inflammation, even though it is not yet validated in RA pts.

Methods: RA pts with at least moderate disease activity (CDAI > 10) enrolled in the CORRONA CERTAIN study were included in a cross-sectional analysis excluding diabetics. Characteristics, including lipid values and high sensitivity C-reactive protein (hsCRP), were measured in a central laboratory. RRS was used to assess CVD risk.

Results: Characteristics (N = 718): 75.8% women, 87.3% Caucasian, 65.2% seropositive. Age (mean ± SD): 55.8 ± 13.5 years; RA disease duration: 8.8 ± 9.4 years; CDAI: 28.6 ± 12.8, BMI: 29.6 ± 6.9 (37.7% obese). At the time of the analysis 36.5% of pts were biologic naïve, 39.6% were receiving prednisone (4.2% of them received > 10 mg) and 22.2% were receiving antilipidemic therapy. History of prior CVD was present in 6.7% of pts. LDL levels were 113.7 ± 34.3 mg/dL (29.5% with LDL > 130), HDL 60.3 ± 17.7 mg/dL (10.5% with HDL < 40), triglycerides (TG) 151.9 ± 94.5 mg/dL (19.5% with TG > 200), total cholesterol (TC) 193.8 ± 39.0 mg/dL (41.1% with TC > 200). CRP levels were 10.0 ± 17.1 mg/L (44.4% with CRP ≥ 5). RRS was 5.5 ± 7.6 (27.6% of pts had RRS < 1%; 39.4 had RRS between 1 and 5%; 33% had RRS ≥ 5%).

Conclusions: Dyslipidemia is common in pts with RA. The impact of lipid levels on CVD risk should be considered in light of the burden of inflammation in this population. RRS, even though not yet validated for RA, showed that a third of patients had ≥ 5% risk for CVD in the next 10 years.

10. Incidence of Venous Thromboembolic Events among ALS Patients in a U.S. Health Insurance Claims Database

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Background: Immobility may put amyotrophic lateral sclerosis (ALS) patients at increased risk for venous thromboembolic (VTE) events. Data from clinical trials and tertiary clinics, which may not be representative of all ALS patients, suggest the incidence of VTE is higher than the general population.

Objectives: Estimate the risk of VTE events in ALS patients compared to controls within the i3 InVision Data Mart Multiplan database.

Methods: Two cohorts of patients ≥ 18 years of age were included in this analysis: ALS patients (n = 4,102, any patient with 1 inpatient or 2 outpatient medical claims containing ICD-9 code 335.20) and controls (n = 65,000 randomly selected patients with no medical claims for ALS [ICD-9 code 335.20] or other motor neuron diseases [ICD-9 codes 335.2, 335.21, 335.22, 335.23, 335.24, 335.29]). VTE events were defined as any inpatient or emergency room medical claim with the following ICD-9 codes: 415.1x (pulmonary embolism and infarction), 451.xx (phlebitis and thrombophlebitis), and 453.xx (other venous embolism and thrombosis). Pulmonary embolism (PE) and deep vein thrombosis (DVT) were analyzed

separately as secondary outcomes. Poisson regression was used to calculate incidence rates while Cox proportional hazards models were used to calculate hazard ratios (HR).

Results: The crude incidence rates of VTE, DVT, and PE in ALS patients and controls were 15.5/1,000 person-years (PYs) and 1.3/1,000 PYs, 14.7/1,000 PYs and 1.0/1,000 PYs, and 1.9/1,000 PYs and 0.3/1,000 PYs, respectively. The age- and gender-adjusted HRs of VTE, DVT, and PE in ALS and controls were 7.4 (95% CI: 5.1, 10.7), 9.5 (95% CI: 6.4, 14.1), and 3.3 (95% CI: 1.4, 7.8). Further results from multivariate models will be presented at the conference.

Conclusions: The present analysis found an increased risk of VTE, DVT, and PE in ALS patients relative to the general population. Clinicians should be vigilant for signs of VTE in ALS patients.

11. Predictors of Clinical Metastases and Survival among Non-Metastatic Prostate Cancer (PC) Patients (pts) Treated with Androgen-Deprivation Therapy (ADT) in Sweden

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Background: ADT is the standard of care in Sweden for PC pts with signs of recurrence after primary therapy (tx). Studies of predictors of metastasis (mets) and survival have largely focused on pt characteristics at cancer diagnosis. Time-varying factors, such as prostate-specific antigen (PSA) levels, may have greater impact on a pt's risk of disease progression.

Objectives: To examine predictors of mets and survival among men with PC treated with ADT.

Methods: Using electronic medical records from Swedish urology clinics linked to national registries (Cancer Registry, National Pt Registry, Cause of Death Registry), we identified men with PC and no evidence of mets treated with ≥ 6 months (mos) ADT (gonadotropin-releasing hormone agonists/antagonists or bilateral orchiectomy) between 2000–2010 with ≥ 2 PSA values. Men were followed from ADT to mets, death, or end of follow-up (12/31/2010). Multivariate competing risks regression analysis was used to estimate hazard ratios (HR) and 95% CIs; predictors and covariates of

interest included PC diagnosis year (yr), age, comorbidities, anti-androgen tx, region, and time-varying characteristics (PSA absolute value, PSA doubling time [DT]).

Results: Cohort was 446 men with mean follow-up of 3.3 years. Most mets were to the bone (7-year cumulative incidence 25% for bone, 30% for any mets). Median survival was 6 years (5.9 mos after bone mets, 6.1 mos after any mets). Higher PSA and shorter PSA DT were strong predictors of all outcomes. In particular, PSA DT ≤ 6 mos was associated with increased risk of bone mets (13.9 [8.0–24.1]), any mets (7.9 [4.9–12.8]), mortality (5.7 [3.9–8.5]), and bone mets-free survival (6.9 [4.7–10.1]) when compared to PSA DT > 6 mos. HRs were adjusted for age, Charlson comorbidity index, anti-androgen tx, and region.

Conclusions: PC pts treated with ADT remain at risk of bone mets, any mets, and death. This study based on real-world data demonstrates the importance of PSA levels and kinetics, particularly PSA DT ≤ 6 mos, in defining high risk of PC-related outcomes.

12. Rising Trends in the Incidence of Nonmelanoma Skin Cancer in the United States: Findings from an Administrative Database

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Background: Nonmelanoma skin cancer (NMSC) is the most common malignancy in the U.S. and is associated with rising morbidity and health care costs for more than a decade. Recent literature suggests an under-recognized 'epidemic' of NMSC that is further expected to increase as the population ages. Despite this, precise NMSC incidence is unknown as this condition is not typically reported to cancer registries.

Objectives: To estimate the age-, gender- and region-specific NMSC incidence rates among U.S. health plan enrollees.

Methods: We conducted a retrospective cohort study among adults (aged 18 +) using the MarketScan® commercial and Medicare supplemental insurance claims data. Eligible individuals needed to have at least 12 months of continuous enrollment including a 6 month baseline period. Patients with a prior history of NMSC were excluded from this analysis. Incident cases of NMSC were identified between Jan 1, 2007 and Dec 31, 2009. Both ICD-9-CM and CPT codes were used to identify the cases to get a higher positive predictive value. Incidence rates were computed as the number of new cases of NMSC per 1,000 person-years (PY).

Results: We identified 337,360 new cases of NMSC (3.94 per 1,000 PY) (95% CI: 3.93–3.95 per 1,000 PY) during the study period. NMSC rate per 1,000 person-years was higher among males (4.60) than females (3.34) (p < 0.0001). Five-year NMSC rates rose sharply with age, and were highest among individuals over 75 (19.86 per 1,000 person-years) (95% CI: 19.74 to 19.98 per 1,000 PY). The rates per 1,000 PY were also higher for health plan enrollees in the South (4.25) and West (4.20) regions as compared to the Northeast (3.30) and North Central (3.77) (p < 0.0001).

Conclusions: The overall NMSC incidence reported in this study was higher than those reported 10–20 years earlier. Our findings also show significant differences in NMSC incidence rates by age, gender and geographic region. This information is critical to understand the public health burden of NMSC and will provide opportunities for future research to examine factors (such as increasing age and comorbid conditions) that may contribute to NMSC disease etiology.

13. Ambulatory Diagnosis and Treatment of Non-Malignant Pain in the United States, 2000–2010

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Background: Escalating rates of prescription opioid use and abuse have occurred in the context of efforts to improve the identification and management of non-malignant pain.

Objectives: We sought to characterize the diagnosis and pharmacologic management of non-malignant pain in ambulatory, office-based settings between 2000 and 2010.

Methods: We conducted a serial cross-sectional analysis of the National Ambulatory Medical Care Survey, a nationally representative audit of office-based physician visits. Analyses were limited to adults without malignancy. Our outcomes included the annual volume of visits with a primary symptom or diagnosis of pain and reported prescription opioid or non-opioid pharmacologic therapy in visits for new musculoskeletal pain. We conducted multivariate logistic regression to examine patient, practice and physician characteristics associated with the likelihood of receiving an opioid vs. a non-opioid analgesic for a new primary symptom or diagnosis of musculoskeletal pain.

Results: Primary symptoms or diagnoses of pain consistently represented one-fifth of visits, varying little from 2000 through 2010. Patient-reported pain comprised 17–19% of visits, whereas provider primary diagnoses of pain increased nearly 50% from 2000 (5.7% of all visits) to 2010 (8.5%). Among all pain visits, opioid use nearly doubled from 11.3% to 19.6%, whereas use of non-opioid analgesics remained unchanged (26–29% of visits). One-half of new musculoskeletal pain visits resulted in pharmacologic treatment, though the use of non-opioid pharmacotherapies decreased from 38% of visits (2000) to 29% of visits (2010). After adjusting for covariates, few patient, physician or practice characteristics were associated with the use of an opioid rather than a non-opioid analgesic for new musculoskeletal pain, and increases in opioid use occurred non-selectively over time.

Conclusions: Increased opioid use during the past decade has not been accompanied by similar increases in non-opioid analgesics or the frequency of patient-reported pain symptoms. Clinical alternatives to prescription opioids may be underutilized as a means of treating ambulatory non-malignant pain.

14. Patient Requests for Specific Narcotics Influence Physician Prescribing

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Background: Physicians struggle to manage pain adequately while avoiding overuse of narcotics.

Objectives: Assess how patient requests for pain medication affect primary care physician (PCP) decisions.

Methods: We performed a factorial experiment in which PCPs viewed clinically authentic videos of 'patients' with sciatica symptoms. The patients were played by professional actors who differed by sex, race (white, Black, Hispanic) and SES (higher, lower). One-hundred and ninety twoUS PCPs were recruited. The patient described driving as a work requirement that was adversely affected by the pain. In half of vignettes the patient made a specific request for oxycodone: 'my wife/husband had some oxycodone left over from some dental surgery and I took one … it really worked

… I'd like to try some of that.' The other half of patients presented an open-ended request for pain relief. Vignettes were balanced on sex, race and SES. PCPs were balanced by sex and experience. After viewing the video, PCPs completed a questionnaire indicating the treatment(s) they would likely order. We used multivariate ANOVA models to examine the association between patient attributes and PCP narcotic prescribing.

Results: Twenty percent of PCPs seeing an active request for oxycodone reported that they would prescribe a form of oxycodone, compared to 1% of PCPs seeing an open-ended request (p < 0.001). PCPs seeing active requests were more likely to report that they would prescribe a strong narcotic (56% vs. 30%; p < 0.001) and less likely a weak narcotic (13% vs. 26%; p = 0.01). Patients with higher SES were more likely to receive a narcotic (69% vs. 52%; p = 0.01). Patient sex and race were not associated with narcotic choice.

Conclusions: PCPs seeing a request for oxycodone were almost twice as likely to prescribe a strong narcotic, while PCP's seeing an open-ended request rarely selected oxycodone. PCPs were more likely to prescribe narcotics for patients with higher apparent SES, suggesting potential disparities in pain management. Given current concerns about overuse or diversion of narcotic pain medications and the safety concerns related to the patient in the vignette driving for work, these findings suggest that active patient requests may lead to overuse of strong narcotics.

15. Changes in Rates of Doctor Shopping after Introduction of a Reformulated ER Oxycodone Product

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Background: In August 2010, Purdue Pharma introduced reformulated extended release oxycodone (ERO, OxyContin) in the US. The new formulation (ORF) possesses physicochemical properties intended to deter abuse by routes of administration that require tampering.

Objectives: Determine if rates of 'doctor shopping' (ie, use of multiple prescribers and pharmacies to obtain controlled substances for abuse or diversion) for ERO decreased following ORF introduction.

Methods: IMS LRx longitudinal patient data for > 150 million patients covering approximately 65% of retail prescriptions filled in the US were used. Doctor shopping was defined as having overlapping prescriptions for ERO and ≥ 2 prescribers and ≥ 3 pharmacies in a 6-month period. Rates were estimated in six-month periods by the number of individuals doctor shopping for ERO divided by the total number of individuals prescribed ERO. Changes in rates from the period preceding (January–June 2010) to following (July–December 2011) ORF introduction were calculated.

Results: In January–June 2010 preceding introduction of ORF, rates of doctor shopping were higher for men than women (0.26% vs. 0.16%) and for those 18–29 years than 55–64 years old (0.50% vs. 0.12%). Most (62%) of doctor-shopping events involved cash payment and half (49%) included the highest (80 mg) ERO dosage strength. After ORF introduction, rates of doctor-shopping decreased overall by 38%, from 0.20% preceding ORF to 0.13% following ORF introduction. Among 18–29 year-olds, doctor-shopping decreased 64% and among males decreased 48%. Doctor shopping that included ≥ 1 prescription for 80 mg OxyContin decreased 54%, that included a cash payment decreased 54%, and that included both decreased 62%.

Conclusions: These findings indicate doctor shopping for ERO decreased following introduction of ORF. The decreases were larger for indicators associated with higher risk for abuse and diversion, including younger age, men, high dosage strength and cash payment. The results suggest that reformulated OxyContin resulted in reduced demand for the purpose of abuse and diversion.

16. Use of Opioids and Risk of Dementia in Older Adults

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Background: Prescription opioids can cause delirium and sedation, and some autopsy studies have found Alzheimer's Disease (AD)-like changes in opioid abusers' brains. But little is known about prescription opioids' long-term cognitive effects.

Objectives: To examine whether use of prescription opioids is associated with higher dementia risk.

Methods: A prospective cohort study enrolled community-dwelling people age 65 and older from an integrated healthcare delivery system. Participants underwent biennial cognitive screening, with abnormal screens triggering detailed evaluation. A multidisciplin-

ary committee assigned dementia/AD diagnoses. This analysis included 3,436 people with 10 + years of prior health plan enrollment. Opioid exposure was measured from automated pharmacy data. Cumulative exposure was the total morphine equivalent doses dispensed in the past 10 years, excluding the most recent 1 year (prescriptions potentially for prodromal symptoms). We categorized cumulative exposure as ≤ 10, 11–30, 31–90, or 91 + total standardized doses (TSD) where 1 TSD = 30 mg morphine. Recent use was defined as filling 2 + prescriptions in the past 6 months. We used similar methods to characterize use of nonsteroidal anti-inflammatory drugs (NSAIDs). We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia and AD using Cox regression models adjusted for education, comorbidity, physical activity, obesity, and depression.

Results: Among 3,436 participants, 797 developed dementia (637 AD) over a mean follow-up of 7.3 years. For cumulative opioid use, the HRs for dementia were as follows: 11–30 TSD, HR 1.1 (0.9–1.3); 31–90 TSD, HR 0.9 (0.7–1.1); and 91 + TSD, HR 1.3 (1.0–1.6), compared to 0–10 TSD. For comparison, the HR for the heaviest NSAID use was 1.3 (1.1–1.6). The HR for dementia in relation to recent opioid use was 1.2 (1.0–1.6) vs. no current use. Results were similar for AD.

Conclusions: People with the heaviest use of either opioids or NSAIDs had slightly higher dementia risk than those with little/no use. Given the similar magnitude of risk for both medication classes, these results may represent the effect of chronic pain on dementia risk or residual confounding rather than a true causal association.

17. Comparative Safety of Nonsteroidal Anti-Inflammatory Drugs Commonly Used in Asia–Preliminary Findings from Asian Pharmacoepidemiology Network (AsPEN) Association Study

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Background: Some nonsteroidal anti-inflammatory drugs (NSAIDs) are only or more commonly used in Asian countries (i.e., loxoprofen, mefenamic acid) and their safety has not been well-studied.

Objectives: To compare the risk of major safety events among initiators of 4 NSAIDs which are commonly used in Asian countries: celecoxib, diclofenac, loxoprofen, and mefenamic acid.

Methods: Operating under a modified distributed network, we conducted a retrospective cohort study using multiple administrative databases in Japan, Korea, and Taiwan (2002–2010). We identified new users of the 4 NSAIDs among those with chronic conditions (diabetes, hypertension, myocardial infarction, stroke, acute coronary syndrome, rheumatoid arthritis) to minimize the exposure miss-classification due to over-the-counter NSAID use. We used stratified Cox model (stratified by country) adjusting for high-dimensional propensity score to compare two safety outcomes among NSAID users: hospitalization for cardiovascular (CV) events (i.e., coronary events, heart failure, stroke) and hospitalization for gastrointestinal tract (GI) events (i.e., peptic ulcer, upper/lower GI bleeding) using diclofenac users as the reference.

Results: We identified 212,197 diclofenac users, 32,987 celecoxib users, 82,829 loxoprofen users, and 35,084 mefenamic acid users. Mean age was similar among users (71 for diclofenac and loxoprofen, 72 for celecoxib and mefenamic acid). Many users were female (range: 71% in celecoxib to 59% in loxoprofen) and had co-existing hypertension (> 80%). Among diclofenac users, the crude risk of CV hospitalization varied across countries (range: 13 per 1,000 pt-yr in Japan to 37 per 1,000 pt-yr in Taiwan), while the risks of GI hospitalizations did not differ. Compared to diclofenac users, the risk of CV hospitalization did not differ from celecoxib users but was lower among loxoprofen users and mefenamic acid users. Similar trend was observed for the risk of GI hospitalization.

Conclusions: The NSAIDs that were only commonly used in Asian countries–loxoprofen and mefenamic acid appear to have a better safety profile than diclofenac.

18. Use of Over-the-Counter Non-Steroidal Anti-Inflammatory Drugs in the General Population and in Patients with a High Risk of Adverse Drug Events

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Background: The use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with serious adverse drug events (ADEs). In many countries, including the Netherlands, NSAIDs are available over-the-counter (OTC).

Objectives: To determine the prevalence of OTC NSAID use in the general population and in patients with a high risk of developing a serious NSAID-related ADE.

Methods: We conducted a cross-sectional study among adults registered with four general practitioners in the Netherlands. Two samples of patients were selected: (1) a random sample of adults (general population), and (2) a sample of adult patients with a high risk of developing a serious ADE in case of NSAID use (high-risk population). Patients were considered at high risk if they had a history of a peptic ulcer or ulcer complication, myocardial infarction, stroke or heart failure, were aged over 70, had a glomerular filtration rate < 30 ml/L, or had a combination of two or more of the following: use of an anticoagulant, aspirin, corticosteroid or selective serotonin reuptake inhibitor; age 60–70; history of severe rheumatoid arthritis or diabetes mellitus. All included patients in both samples were sent a questionnaire regarding their use of OTC NSAIDs in the four weeks prior to participation.

Results: In the general population, 120 of 456 included patients chose to participate. Of these, 35 (29%) had used an OTC NSAID in the four weeks prior to participation. In the high-risk population, 265 of 713 included patients chose to participate and 33 (13%) had used an OTC NSAID. Over 20% of OTC NSAID users had used the OTC NSAID for more than seven days in both populations. OTC NSAIDs were used in a dosage exceeding the recommended daily maximum by 9% and 3% of OTC NSAID users in respectively the general and the high-risk population.

Conclusions: OTC NSAIDs are used by around one third of the general population and by one in eight patients with a high risk of developing a serious ADE. Continued efforts by healthcare professionals to inform patients of the risks of these drugs is warranted.

19. Outcomes after Carotid Artery Stenting (CAS) in Real-World vs. Trial Settings

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Background: The landmark clinical trials CREST and SAPPHIRE demonstrated equivalence of CAS and carotid endarterectomy (CEA) for carotid stenosis treatment. Differences in patient characteristics and provider proficiency could alter the real-world risk-benefit assessment of CAS.

Objectives: To compare CAS Medicare and landmark trial patient outcomes and to assess the impact of applying trial enrolment criteria on outcomes of Medicare patients.

Methods: Using the Centers for Medicare and Medicaid Services' (CMS) CAS Database (CAS-D) and Medicare data, we estimated short- and long-term mortality, stroke/transient ischemic attack (TIA), and myocardial infarction (MI) among beneficiaries at least 66 years of age undergoing CAS (2005–2009). We applied trial-specific enrolment criteria to identify Medicare patients who met criteria similar to those used for enrollment in CREST or SAPPHIRE trials (SAPPHIRE-like and CREST-like subgroups).

Results: Of 23,174 Medicare CAS patients (mean age: 76.3; male: 60.2%, white: 93.8%), crude 30-day mortality, stroke/TIA, and MI risks were 1.8% (95% CI: 1.6–2.0), 3.4% (95% CI: 3.1–3.6%), and 2.5% (95% CI: 2.3–2.7%), respectively. Medicare patients were older and sicker than trial patients and most were treated by providers not meeting trial proficiency requirements. Among SAPPHIRE-like Medicare patients (N = 1,322), peri-procedural mortality (1.6%; 95% CI: 0.9–2.3) and stroke/TIA (2%; 95% CI: 1.2–2.7) risks tended to be lower than those observed in the full Medicare cohort. Long-term mortality and stroke/TIA risks were lower in SAPPHIRE- and CREST-like

Medicare patients than in the full Medicare cohort. Peri-procedural mortality among overall Medicare patients as well as in the subgroups meeting trial enrolment criteria was much higher than in the SAPPHIRE (0.6%) or CREST (0.7%) trials.

Conclusions: Better outcomes in trial patients stemming from differences in age, comorbidity burden, and provider proficiency and the small number of Medicare patients satisfying SAPPHIRE and CREST enrollment criteria substantiate concerns regarding the highly selected nature of trial patients and underscore the importance of evaluating CAS in real-world settings.

20. Transatlantic Active Surveillance of Cardiovascular Safety (TASC) of an Etonogestrel/Ethinylestradiol-Containing Vaginal Ring

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Background: The TASC study investigated the cardiovascular safety of a contraceptive vaginal ring (VR) compared to combined oral contraceptives (COCs) in 5 European countries and in the United States

Objectives: To assess the risks of short- and long-term use of an etonogestrel/ethinylestradiol-containing VR and to compare it to the risks of established COCs in a study population that is representative of the actual users of the individual preparations.

Methods: Transatlantic, prospective, controlled, non-interventional cohort study with two cohorts: new users of VR and COCs (starters, switchers or restarters). Patient enrollment started in 2007. Study population, 33,295 users of VR or COCs recruited by 1,661 study centers. Information was collected via self-administered questionnaires at study entry and at months 6, 12, 24, 36 and 48 after study entry. Questions included information on cardiovascular risk factors, medical and gynecological history, other demographic and life-style data, reasons for hormonal contraceptive use and concomitant medication. All self-reported clinical outcomes of interest (OoI) were validated via attending physicians. Main OoI were serious clinical outcomes, in particular venous (VTE) and arterial thromboembolism (ATE). Comprehensive follow-up ensured low loss to follow-up. Statistical analyses were based on Cox regression models. Primary statistical variable was the VTE hazard ratio (HR) for VR vs. COCs.

Results: Study participants were followed for 66,489 woman-years (WY). Loss to follow-up was 2.9%. Serious adverse events were rare, and the rate ratio for VR vs. COCs was close to unity (0.9). The VTE incidence rates for VR and COCs were 8.3 and 9.2/10,000 WY, respectively. Cox regression analysis yielded crude and adjusted HRs for VR vs. COCs of 0.9 and 0.8 (95% confidence intervals, 0.5–1.6 and 0.5–1.5) for venous, and 0.8 and 0.7 (95% confidence intervals, 0.2–2.5 and 0.2–2.3) for arterial thromboembolism, respectively.

Conclusions: VR and COC use were associated with a similar VTE and ATE risk during routine clinical use.

21. Comparison of Early Mortality after Aortic Valve Replacement with Biological vs. Mechanical Prosthetic Valve among Medicare Beneficiaries

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Background: Nearly 70% of all Aortic Valve Replacements (AVR) are performed in patients 65 years or older. Patient outcomes may differ for elderly patients who received mechanical or biological prosthetic valve.

Objectives: To compare early mortality after AVR with mechanical or biological prosthetic valve.

Methods: Retrospective analysis of patients 65 years or older in the Medicare databases, 2006–2011, who underwent AVR. In propensity score matched analyses, we estimated odds ratios of early mortality, comparing mechanical and biological prosthetic valve. Early mortality was measured as death within 30 days after AVR procedure, death within 30 days after hospital discharge, and operative mortality–death during procedure stay or 30 days following surgery, whichever is longer.

Results: There were 277,835 US Medicare beneficiaries 65 years and older who underwent AVR between 2006 and 2011; of these patients, 66,453 met inclusion and exclusion criteria, 19,190 (28.9%) received a mechanical valve and 47,263 (71.1.1%) received a bioprosthetic valve during the study period. There were 1,367 (7.08%) mechanical valve recipients and 2593 (5.45%) bioprosthetic valve recipients who died within 30 days after AVR. There were 466 (2.41%) mechanical valve recipients and 1,077 (2.27%) biological valve recipients who died within 30 days after hospital discharge. In the propensity score matched analyses, the adjusted odds ratio (OR) of death within 30 days after AVR in patients received mechanical valve was 1.17 (95% CI:

1.07–1.27) compared with mortality in patients received bioprosthetic valve. Similar results were found for operative death outcome. The OR of death within 30 days after hospital discharge in patients who received a mechanical vs. a bioprosthetic valve was 0.96 (95% CI: 0.84–1.10).

Conclusions: In a cohort Medicare Beneficiaries aged 65 years and older undergoing AVR, patients who received mechanical valve had higher odds of operative death and of death within 30 days after AVR procedure compared with patients who received bioprosthetic valve. Mortality within 30 days after discharge was similar between the two types of heart valve.

22. Breastfeeding as a Risk Factor for Uterine Perforation during IUD Insertion: Interim Results from the EURAS-IUD Study

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Background: Uterine perforation is a potentially serious complication of intrauterine device (IUD) insertion. Concurrent breastfeeding has been described as a potential risk factor, but little is known about the magnitude of the association.

Objectives: The primary objective of the analysis is to evaluate the association between breastfeeding and uterine perforation after IUD insertion.

Methods: Large, controlled, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: levonorgestrel (LNG) IUDs and copper IUDs. In total, more than 60,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden) were recruited. The study started in 2006, follow-up will end in 2013. Both women and their treating physicians receive a single follow-up 12 months after enrolment. All patient-reported outcomes of interest are validated by the women's treating physicians. A multifaceted 4-level follow-up procedure ensures low loss to follow-up rates.

Results: In October 2012, 61,380 women were enrolled (70.1% using LNG IUDs, 29.9% using copper IUDs). One-year follow-up data were already available for 37,184 LNG and 15,561 copper IUD users. Interim results showed 58 uterine perforations, giving an incidence of 0.94 per 1,000 insertions (95% CI: 0.72–1.22). Twenty-six perforations occurred in women who were breastfeeding at the time of insertion, resulting in a perforation rate of 3.91 per 1,000 insertions (95% CI: 2.56–5.73). The corresponding rate for women not breastfeeding at baseline was 0.59 (95% CI: 0.40–0.83). The relative risk of perforation for women breastfeeding vs. not breastfeeding was 6.7 (95% CI:

4.0–11.2). When additionally stratified by time since last delivery, the association between breastfeeding and perforation was notably stronger than the association between time since last delivery and perforation.

Conclusions: Breastfeeding at time of IUD insertion appears to substantially increase the risk of uterine perforation, independently of time since last delivery.

23. Long-Term Outcomes of Vaginal Mesh vs. Native Tissue Repair for Anterior Vaginal Wall Prolapse

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Background: The potential advantage of mesh augmentation for prolapse surgery is a lower risk of recurrent prolapse; however, data regarding long-term outcomes are limited and there are .

Objectives: To estimate the risk of repeat surgery for recurrent prolapse or mesh removal after vaginal mesh vs. native tissue repair for anterior vaginal wall prolapse.

Methods: We utilized longitudinal healthcare claims from 2005 to 2010 to identify women ≥ 18 years who underwent an anterior colporrhaphy (CPT 57420) with or without concurrent vaginal mesh (CPT 57267). The primary outcome was repeat surgery for anterior or apical prolapse or for mesh removal/revision; these outcomes were also analyzed separately. We utilized Kaplan–Meier curves to estimate the cumulative risk of each outcome after vaginal mesh vs. native tissue repair. Cox proportional hazards models were used to estimate the hazard ratio (HR) with 95% confidence intervals (CI) for vaginal mesh vs. native tissue repair, adjusted for age, concurrent hysterectomy, and concurrent or recent sling.

Results: We identified 27,809 anterior prolapse surgeries with 49,658 person-years of follow-up. Of those, 6,871 (24.7%) included vaginal mesh. The 5-year cumulative risk of any repeat surgery was significantly higher for vaginal mesh vs. native tissue (15.2% vs. 9.8%, p < 0.0001) with a 5-year risk of mesh revision/removal of 5.9% (95% CI: 5.0–6.9%). The 5-year risk of surgery for recurrent prolapse was similar between vaginal mesh and native tissue groups (10.4% [95% CI: 8.8–12.1] vs. 9.3% [95% CI: 8.6–10.0], p = 0.70). The results of the adjusted Cox model were similar (HR 0.93, 95% CI: 0.83, 1.05).

Conclusions: The use of mesh for anterior prolapse was associated with an increased risk of any repeat surgery, which was driven by surgery for mesh removal. Native tissue and vaginal mesh surgery had similar 5-year risks for surgery for recurrent prolapse.

24. Acute Kidney Injury after Routine Colonoscopy: A Comparative Safety Study of Sodium Phosphate and Polyethylene Glycol

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Background: Oral sodium phosphate (OSP) has been used as a bowel purgative for colonoscopy. Concern about renal injury from the absorbed phosphorus and dystrophic calcification led to FDA recommendations against OSP use as a bowel preparation agent. However, it remains unclear if acute kidney injury (AKI) is associated with OSP in the general population, or in subgroups know to have an increased risk of AKI.

Objectives: We estimated the risk of post-procedure AKI in screening colonoscopy patients using OSP vs. polyethylene glycol (PEG)–another common bowel prep agent–in a large, US-based claims database.

Methods: We identified patients aged 50–75 years undergoing outpatient, screening colonoscopies in a large, US-based administrative claims database, January 2000–November 2008 (when the FDA warning was issued). Patients initiating either OSP or PEG in the 30 days prior to colonoscopy without use of either drug in the prior year were included. Patients were followed for 6 months from colonoscopy for diagnosis codes of AKI. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated with multivariable Cox proportional hazards models. We propensity score matched OSP to PEG users, and estimated HRs in the matched populations. We also investigated the effect in subgroups suspected to be at higher AKI risk (users of antihypertensives or non-steroidal anti-inflammatory drugs, patients with a history of kidney stones, hypertension, diabetes mellitus, reduced renal function, or a history of kidney stones or hypercalciuria).

Results: We included 56,771 OSP initiators and 590,068 PEG initiators. AKI occurred in 0.2% of OSP users and 0.3% of PEG users. After adjustment, Cox models yielded HR = 0.94 (95% CI: 0.78, 1.13). OSP users matched very well to PEG users, resulting in 56,769 matched pairs. Cox models in the matched cohort gave similar estimates to multivariable adjustment: HR = 0.95 (0.75, 1.21). Results were similarly null in all subgroups regardless of estimation technique.

Conclusions: OSP initiation prior to colonoscopy was not associated with an increased risk of post-procedure AKI, even in high-risk clinical subgroups.

25. Ondansetron Use in Early Pregnancy and the Risk of Congenital Malformations – A Register Based Nationwide Cohort Study

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Background: Ondansetron is an effective antiemetic for the treatment of hyperemesis gravidarum. It acts as a 5-hydroxytryptamine receptor antagonist, a receptor which plays a role in the development of emesis and nausea. Only limited data concerning the safety of ondansetron in pregnancy is available.

Objectives: Therefore we conducted a nationwide cohort study testing if use of ondansetron during the first trimester is associated with a higher prevalence of congenital malformations.

Methods: The study included all women giving birth in Denmark between 1997 and 2010. The Medical Birth Registry was used to identify all women giving birth and the National Hospital Register was used to identify all offspring with a record of congenital malformation. Prescription data was obtained from the National Prescription Register. The primary outcome was the prevalence of major congenital malformations according to the EUROCAT classification system and subgrouping among first trimester users of ondansetron compared to non-users.

Results: We identified 897 018 births in the study period. About 1,248 women redeemed a prescription of ondansetron in the first trimester of which 58 (4.7%) had offspring with a congenital malformation compared to 31,357 (3.5%) in the unexposed group. The adjusted odds ratio (OR) of having an offspring with a major malformation after exposure to ondansetron was 1.3 (95% CI: 1.0–1.7). This was mainly caused by an increased prevalence of heart defects (adjusted OR = 2.0 (95% 1 CI: 0.3–3.1). To rule out confounding by indication we also analysed the risk of another drug frequently used in hyperemesis gravidarum, metoclopramide. We found no association with first trimester exposure and having an offspring with a congenital

malformation (adjusted OR = 1.0 (95% CI: 0.95–1.1). Furthermore we found no increased OR in any of the EUROCAT subgrouping among women exposed metoclopramide.

Conclusions: We found a doubling in the prevalence of major congenital heart defects in children whose mothers redeemed a prescription of ondansetron in the first trimester of pregnancy.

26. Ondansetron Use in Pregnancy and Risk of Adverse Fetal Outcomes

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Background: Ondansetron is frequently used for nausea and vomiting in pregnancy, but its fetal safety is not well studied.

Objectives: To investigate the risk of adverse outcomes associated with use of ondansetron in pregnancy.

Methods: We conducted a register-based cohort study in Denmark, January 1, 2004, to March 31, 2011. From a historical cohort of 608,385 pregnancies, ondansetron-exposed and unexposed women were included in propensity score-matched (1:4) analyses of spontaneous abortion (1,849 exposed vs. 7,396 unexposed), stillbirth (1,915 vs. 7,660), any major birth defect (1,233 vs. 4,932), preterm birth (1,792 vs. 7,168), and low birth weight and small for gestational age (1,784 vs. 7,136). Additionally, estimates were adjusted for hospitalization for nausea and vomiting during pregnancy (as proxy for severity) and the use of other antiemetics. Cox regression was used to estimate hazard ratios (HR) for spontaneous abortion and stillbirth and logistic regression to estimate prevalence odds ratios (POR) for birth defects, preterm birth, low birth weight, and small for gestational age.

Results: Ondansetron use was not associated with significantly increased risks of spontaneous abortion (1.1% cases among exposed and 3.7% cases among unexposed, HR 0.49, 95% CI: 0.27–0.91, in gestational weeks 7–12; 1% and 2.1%, HR 0.60, 95% CI: 0.29–1.21, in weeks 13–22), stillbirth (0.3% and 0.4%; HR 0.42, 95% CI: 0.10–1.73), any major birth defect (2.9% and 2.9%; POR 1.12, 95% CI: 0.69–1.82), preterm birth (6.2% and 5.2%; POR 0.90, 95% CI: 0.66–1.25), low birth weight (4.1% and 3.7%; POR 0.76, 95% CI: 0.51–1.13), and small for gestational age (10.4% and 9.2%; POR 1.13, 95% CI: 0.89–1.44).

Conclusions: Ondansetron use in pregnancy was not associated with significantly increased risks of adverse fetal outcomes.

27. Risks and Safety of Pandemic H1N1 Vaccine in Pregnancy: Birth Defects, Spontaneous Abortion, Preterm Birth, and Small for Gestational Age Infants

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Background: There is insufficient information available on the fetal risks and relative safety of the pandemic H1N1 influenza (pH1N1) vaccine in women exposed during pregnancy.

Objectives: To assess risks and relative safety of pH1N1-containing vaccines relative to major birth defects, spontaneous abortion, preterm delivery and fetal growth.

Methods: We conducted a prospective cohort study of pH1N1 vaccine-exposed and unexposed comparison women residing in the U.S. or Canada recruited during pregnancy and followed to outcome between October 2009 and August 2012. For exposure to the pH1N1 vaccine, adjusted relative risks (RRs) were estimated with 95% confidence intervals (CIs) for major birth defects and infants < 10th centile on birth weight, length and head circumference. Adjusted hazard ratios (HRs) were estimated with 95% CI for spontaneous abortion and preterm delivery for time-varying exposure.

Results: There were 1,032 subjects available for analysis: 841 exposed to a pH1N1 vaccine in pregnancy, and 191 unexposed to any influenza vaccine in pregnancy. Nine of 328 (2.7%) first-trimester-exposed pregnancies resulted in an infant with a major birth defect compared to 6/188 (3.2%) in the unexposed (adj RR 0.79, 95% CI: 0.26–2.42). The risk of spontaneous abortion was not elevated (adj HR 0.92, 95% CI: 0.31–2.72). Adjusted HRs for preterm delivery were elevated for exposure anytime in pregnancy (3.28, 95% CI: 1.25, 8.63), specifically with exposure in the 1st or 2nd trimester. Risks for preterm delivery differed across the vaccination seasons and were most elevated in the 2009–10 season when 1st trimester exposure to the pH1N1 vaccine was preceded by receipt of the seasonal vaccine. Adjusted risks for small for gestational age infants on weight and length approximated 1.0.

Conclusions: For the 2009–12 influenza seasons combined, we found no meaningful evidence of increased risk of major birth defects, spontaneous abortion, or small for gestational age infants on weight or length.

There was some evidence of increased risk for preterm delivery following pH1N1-influenza vaccine exposure, particularly in the 2009–10 season.

28. The Influence of Vaccination Against Influenza A (H1N1) during Pregnancy on Pregnancy Outcomes in the Netherlands: A Cross Sectional Linkage Study

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Background: In 2009 an Influenza A(H1N1) pandemic occurred. Dutch pregnant women in their second and third trimester were eligible for vaccination. However, information on the safety of influenza vaccination during pregnancy was scarce and merely based on non-adjuvanted seasonal influenza vaccines.

Objectives: To assess the possible influence of vaccination with Focetria® against Influenza A(H1N1) during the second and third trimester of pregnancy on pregnancy outcomes.

Methods: Pregnant women, willing to participate in a follow-up study on safety of H1N1-vaccination (n = 2672), filled in questionnaires about coverage and safety, and gave permission to link questionnaire data with data of the Netherlands Perinatal Registry (PRN). Multivariate logistic regression analysis was used to assess the association between H1N1-vaccination and (1) Small-for-date, (2) Preterm delivery, (3) Need for assisted delivery and (4) A composite outcome, i.e. having at least one of the following characteristics: low apgar-score, admission to NICU, neonatal reanimation or perinatal death. Potential confounding variables (maternal age; country of birth; education; self-reported use of alcohol, drugs or cigarettes during pregnancy; parity; underlying medical reasons for annual influenza vaccination; Influenza A (H1N1)-infection; life philosophy) were included in the model.

Results: About 2034 Women gave permission to use questionnaire data, of which 66.7% (n = 1,357) were vaccinated and 33% (n = 669) not. Linkage with PRN-data was possible for 1,736 women. We found no association between H1N1-vaccination and small-for-date (OR 1.19; 95% CI: 0.70–2.02) adjusted for all possible confounders. The same holds for preterm delivery (OR 1.02; 95% CI: 0.61–1.68), need for assisted delivery (OR 1.10; 95% CI: 0.85–1.42) and the composite outcome (OR 1.16; 95% CI: 0.61–2.20).

Conclusions: Influenza A(H1N1) vaccination during second or third trimester of pregnancy, using Focetria®, does not seem to be associated with an increased risk of adverse pregnancy outcomes in the Netherlands.

29. Use of Fluconazole during Pregnancy and the Risk of Major Birth Defects

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Background: Case reports suggest that high-dose fluconazole use during pregnancy may cause a characteristic pattern of birth defects but there are no controlled studies of lower doses or individual defects.

Objectives: To evaluate the association between first-trimester fluconazole exposure and the risk of major birth defects including analyses of defects previously linked to azole antifungals and analyses according to fluconazole dose.

Methods: In a register-based nationwide cohort of 976,300 liveborn infants in Denmark from January 1, 1,996, through March 31, 2011, we evaluated the association between first-trimester fluconazole exposure and the risk of major birth defects diagnosed within the first year of life. Prevalence odds ratios of major birth defects were estimated by logistic regression.

Results: Fluconazole use (n = 7,352) was not associated with significantly increased risk of birth defects overall (210 exposed [2.86%] and 25,159 [2.60%] unexposed cases; adjusted prevalence odds ratio [APOR] 1.06, 95% confidence intervals [CI] 0.92–1.21) or most of the birth defects previously linked to azole antifungals: craniosynostosis, cleft palate, cleft lip with or without cleft palate, limb defects, limb reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, ventricular septal defects, and hypoplastic left heart. A significantly increased risk was observed for tetralogy of Fallot (7 fluconazole-exposed [0.10%] and 287 unexposed [0.03%] cases; APOR 3.16; CI: 1.49–6.71). In analyses according to total fluconazole dose, no significantly increased risk of birth defects overall was observed for either 150 mg (107 exposed cases [2.62%]; APOR, 0.99; CI: 0.82–1.20), 300 mg (71 exposed cases [3.15%]; APOR, 1.15; CI: 0.91–1.46), or ≥ 350 mg (32 exposed cases [3.14%]; APOR, 1.12; CI: 0.79–1.59).

Conclusions: Fluconazole was not associated with significantly increased risk of birth defects overall or most specific birth defect categories of previous concern. Fluconazole may confer increased risk of tetralogy of Fallot although the absolute risk is small.

30. A Methodological Comparison of Antiepileptic Drug Pregnancy Registries and Implications on Estimated Birth Defect Rates

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Background: While methodological differences among antiepileptic drug (AED) pregnancy registries have been described elsewhere, the implications on estimated birth defect (BD) rates have not been explored.

Objectives: To describe methodological differences between 4 AED pregnancy registries and explore the impact of differences on BD rates in infants of women treated with the AED levetiracetam (LEV).

Methods: BD rates for LEV were calculated using data from the UCB AED Pregnancy Registry and compared to published rates from the International AED and Pregnancy Registry (EURAP), North American AED Pregnancy Registry (NAAPR), and United Kingdom (UK) and Ireland (IE) Pregnancy Registers. The methodology for each pregnancy registry was examined for differences in BD criteria and length of infant follow-up (FU).

Results: The BD rate for LEV monotherapy in the UCB Registry was 9.5% (n = 28/296) compared with 1.6% (n = 2/126) in EURAP, 2.4% (n = 11/450) in NAAPR, and 0.7% (n = 2/286) in UK and IE Registers. Similar differences were noted for LEV polytherapy. The UCB Registry BD criteria include major structural or chromosomal abnormalities and clusters of two or more non-major abnormalities. BD criteria among the other three registries include major structural abnormalities, but exclude minor BDs and chromosomal abnormalities. A case review of BDs reported to the UCB Registry performed by NAAPR investigators found that approximately 50% would not constitute a BD based on NAAPR criteria. Differences in the length of infant FU between the registries were also noted. The UCB Registry has the longest FU (3 years) followed by EURAP (1 year), and NAAPR and UK and IE Registers each with 3 months of FU. An estimated 16% of BD cases in the UCB Registry were reported after 1 year of FU.

Conclusions: The large variability in the estimated BD rates across AED pregnancy registries illustrates the impact of methodological differences on study results. These findings highlight the need for cautious interpretation when comparing results across registries.

31. Warfarin Safety in a Residential Aged Care Setting

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Background: Warfarin is a well-known high-risk drug used in many older people. A large number of medications are reported to interact with warfarin resulting increasing the risk of adverse events. However the majority of studies looking at interactions and adverse events focused on outcomes resulting in hospitalization or medical care, and may underestimate the risk profile of anti-coagulation.

Objectives: The aim of this study was to explore the impact of medications with a potential destabilizing effect on warfarin in an elderly residential aged care population.

Methods: A cross sectional survey of aged care residents (n = 3,442) from 26 residential aged care facilities in the Sydney metropolitan was conducted during 2010. Patients on a stable warfarin regime who were prescribed a medication known to interact with warfarin were included in the study. Exposure was defined to be a drug interaction episode; the outcome measure was a change in warfarin dose regimen within one month of the exposure. Relative risks and 95% confidence intervals were calculated to determine the association between exposures and outcomes.

Results: Warfarin was used by 8.9% (n = 307) of the study cohort. Over two thirds (67%) of stable warfarin patients received one or more potentially destabilizing medications that are known to destabilize warfarin regimens during the 12 month study period. No association was found between drug interaction episodes and changes in warfarin dose regimen (RR = 0.77, 95% CI: 0.58–1.02). Aspirin was the only individual medication to have an impact on warfarin regimen stability (RR = 1.41, 95% CI: 1.29–1.56).

Conclusions: The relatively high use of medications with the potential to destabilize warfarin, in an elderly high risk population is of concern given the high risk nature of anticoagulants in the elderly. In contrast to reports that have demonstrated changes in anticoagulant effect with potentially interacting medicines, in this study exposure to potentially interacting medicines did not destabilize warfarin regimens. This may reflect a lack of identification and management of minor bleeding and bruising in the aged care setting and further large-scale exploration from a risk-benefit perspective is warranted.

32. Drug Use Pattern of Rivaroxaban in the UK

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Background: Rivaroxaban (Rvx) is a new oral anticoagulant indicated for the prophylaxis of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery. In the UK Rvx is primarily dispensed in hospitals. The lack of in-hospital pharmacy data limits the conduct of drug utilization studies for medications dispensed in hospitals.

Objectives: To explore the feasibility of studying the drug use pattern of Rvx in primary and secondary care, i.e. mainly the indication and duration of use.

Methods: Data sources were the UK Clinical Practice Research Datalink (CPRD) and the link to the Hospital Episodes Statistics (HES). CPRD is based on primary care and HES include dates of hospital stay, discharge diagnoses, and surgical and other procedures performed during hospital stay. A non-comparative cohort was formed from the CPRD/HES consisting of patients with at least one recording for Rvx between Oct 2008 and Jan 2012. Use of Rvx was identified from prescription files, and electronic search of clinical notes in the entire CPRD. Surgical procedures, medical illness and duration of use were extracted from medical records, discharge diagnoses and manual review of clinical notes entered in the 90 days prior to the index Rvx use. Descriptive statistics consisted of cross tabulations.

Results: The study cohort comprised 754 Rvx users, 495 identified from free text notes only. The mean age was 68.7 years with 60.2% women. An elective hip or knee procedure within 90 days of the index Rvx use was identified in 706 of the 754 patients (93.6%). Thirty (4.2%) had an elective orthopaedic procedure other than hip or knee, 14 (2%) an orthopaedic procedure following a fracture, and one patient (0.1%) a non-orthopaedic indication. Rvx was not given for the treatment of VTE, atrial fibrillation or following a cardiac intervention. The median duration was 14 and 35 days following knee and hip replacement respectively. Rvx was not used in the paediatric population or during pregnancy.

Conclusions: The lack of in-hospital pharmacy data limits the use of primary care databases. The electronic search for Rvx in clinical notes in CPRD and their subsequent manual review was found a feasible approach to overcome this limitation.

33. Adherence to the JNC 7 Treatment Guideline and Impact on Patient Outcomes

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Background: The Joint National Committee guidelines 7 (JNC 7) advocate that achieving target blood pressure (BP) is key to reducing the burden of hypertension-associated morbidity and mortality. However, discrepancies exist between guideline recommendations and clinical implementation.

Objectives: The study objectives were to: characterize adherence to JNC 7, evaluate the association between JNC 7 adherence and achieving target BP control, and determine predictors of non-adherence.

Methods: De-identified EMR data from 11 medical groups in the US were retrospectively collected from 2008–2011. Inclusion criteria: adults, elevated BP or a hypertension diagnosis code, antihypertensive treatment, 12 month baseline with no anti-hypertensive prescriptions or history of hypertension. We excluded patients with: secondary hypertension (including pregnancy-related hypertension), continuous prednisone use, and stage 5 CKD and ESRD. We categorized antihypertensive treatment as adherent or non-adherent to JNC 7 during the 6 month period following the hypertension diagnosis date. Using multivariable logistic regression, we determined the relative odds of achieving target BP control for JNC 7 adherent vs. non-adherent treatment. We also determined predictors of non-adherence. We present findings for hypertensive patients overall and by stage.

Results: There were 14,910 stage 1 and 2 hypertensive patients included. Overall, 11,833 (79.4%) received treatment according to JNC 7 guidelines. JNC 7 adherence for stage 1 and 2 hypertensive patients was 89% and 49.7%, respectively. The overall odds ratio (95% CI) of achieving target blood pressure control was 1.53 (1.40, 1.68). Stratified by stage the odds ratios were 1.213 (1.02, 1.432) and 1.105 (0.96, 1.270) for stage 1 and 2, respectively. The predictors of JNC 7 non-adherence were ckd, diabetes, and heart failure.

Conclusions: Adherence to JNC 7 guidelines is especially low for patients with stage 2 hypertension. Treating patients according to JNC 7 guidelines is associated with a 53% increased odds of achieving blood pressure control. Patients with ckd, diabetes, or heart failure were less likely to receive antihypertensive treatment that is JNC 7 adherent.

34. National Trends in the Treatment of Hypertension in the United States, 1997–2012

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Background: Hypertension is common and costly. During the past decade, new therapies have been brought to market, several have lost patent protection, and additional evidence regarding the safety and effectiveness of different agents has accrued.

Objectives: We examined trends in the use of antihypertensive therapies in the United States between 1997 and 2012 using a nationally representative audit of ambulatory providers.

Methods: We used the IMS Health National Disease and Therapeutic Index (NDTI) and restricted analyses to individuals 18-years and older and use of six therapeutic classes: angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, beta-blockers (BBs), diuretics and direct renin inhibitors (DRIs). Our primary unit of analysis was a visit where hypertension was diagnosed and treated with a pharmacotherapy (treatment visit).

Results: Annual hypertension treatment visits increased from 60.2 million [M] visits (1997) to 86.4M (2008), and declined steadily to 73.3M by 2012. There was large increase in use of ARBs from 3% (1997) to 18% (2012) of treatment visits. There was moderate reduction in use of CCBs, from 26% of visits in 1997–18% in 2012. Use of diuretics (24% to 30% of visits) and beta blockers (14% to 16% of visits) was stable over the years examined. Following their market introduction in 2007, DRIs were used rarely, accounting for less than 1% of visits in any given year. Fixed dose combination products were used in approximately one-fourth of visits in 1997 (27%), and their use increased to approximately one-third of visits (37%) by 2012. Although there was evidence of intensification of therapies between 1997 (1.46 mean therapies per visit) and 2003 (1.54), by 2012 there was a mean of 1.43 therapies per visit. Additional analyses will quantify changes in use of generic therapies and utilization in disease-specific subpopulations such as individuals with diabetes.

Conclusions: Several important changes have occurred in the landscape of antihypertensive treatment in the U. S. during the past decade. Despite their novel mechanism of action, rates of adoption of direct renin inhibitors have remained low.

35. Increasing Age Is Associated with Underuse of Evidence-Based Treatment for Heart Failure

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Background: The 2006 Canadian guidelines for the treatment of heart failure (HF) recommend for those with reduced left ventricular ejection fraction irrespective of age, an evidence-based treatment including a beta-blocker in combination with an ACE inhibitor (or an angiotensin receptor blocker if indicated) or a combination of hydralazine plus isosorbide dinitrate. Little is known about the effect of increasing age on the use of evidence-based treatment of HF.

Objectives: In a population of elderly aged ≥ 65 years, we estimated the association between age and exposure to an evidence-based treatment at five time points (at HF diagnosis, 6, 12, 36 and 60 months after).

Methods: We conducted a population-based inception cohort study including all individuals aged ≥ 65 years with a first HF diagnosis between 2000 and 2009. Only patients with a previous diagnosis of ischemic heart disease were included. Data were withdrawn from the Quebec health insurance board database, the Quebec registry of hospitalizations and the death registry. Age was assessed at HF diagnosis. Individuals were assumed to use an evidence-based treatment if they had an active claim for each of the recommended combination drugs at specific time point. Adjusted prevalence ratios (with 95% confidence intervals) between age and use of an evidence-based treatment at each time point were assessed using Working-Poisson regressions. Ratios were adjusted for socio-demographic variables, comorbidities and use of medical services.

Results: In our population of 86,428 individuals, adjusted prevalence ratios (65–74 years: reference) for the use of an evidence-based treatment were 0.89 (0.87–0.92) and 0.68 (0.65–0.70) at baseline, 0.87 (0.85–0.90) and 0.69 (0.67–0.72) at 6 months, 0.87 (0.85–0.89) and 0.67 (0.65–0.70) at 12 months, 0.85 (0.82–0.87) and 0.62 (0.59–0.66) at 36 months and 0.82 (0.79–0.86) and 0.60 (0.55–0.66) at 60 months for the 75–84 and 85 + age groups, respectively.

Conclusions: Increasing age is associated with a decrease in the use of evidence-based treatment for

HF. Determinants should be identified and targeted through interventions aiming to optimise the treatment of HF in very old patients.

36. Persistence with Statin Therapy: Does Family History of Cardiovascular Events Influence Medication-Taking Behaviour?

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Background: Although many predictors of statin adherence have been studied, the ability to explain the medication-taking behavior remains poor. There are reasons to believe that therapy adherence may be related to whether patients feel susceptible to the disease. No study has examined the importance of the family history of Cardiovascular Disease (CVD) in explaining adherence to statin therapy.

Objectives: To assess whether family history of CVD influences the discontinuation of statin treatment, adjusting for several potential confounders.

Methods: A population-based cohort study was performed using Swedish registers. Incident statin users 20–72 years of age were identified between July 1, 2006 and June 30, 2007. Family history of CVD was defined as the presence of first degree relatives with a previous cardiovascular event (death/hospitalization). The cohort was followed until the switch from regular to irregular dispensing, inpatient hospital admission, emigration, death or end of the observation period (June 30, 2009), whichever occurred first. Discontinuation was studied using Kaplan–Meier survival analysis and Cox proportional hazards regression was used to estimate the effect of the family history of CVD on statin discontinuation adjusting for confounders (gender, age, education, income, prescriber's work place, health care center, type of prevention, country of birth, county of residence).

Results: A total of 86,002 patients were enrolled in the cohort of which 61.5% had a family history of CVD. Discontinuation of statin therapy was not associated with family history of CVD (HR: 0.98; 95% CI: 0.96–1.01). Young age, foreign origin, low income, primary prevention and statin prescribed in primary care was associated with higher risk of statin therapy discontinuation.

Conclusions: We found no association between family history of CVD and discontinuation of statin therapy.

37. Risk of Venous Thromboembolism and Use of Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis

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Background: Recent research suggests that rheumatoid arthritis (RA), an autoimmune systemic inflammatory disease, increases the risk of venous thromboembolism (VTE) such as pulmonary embolism and deep vein thrombosis.

Objectives: To examine the incidence rate (IR) of VTE in RA patients relative to treatment with biologic and/or non-biologic disease-modifying antirheumatic drugs (DMARD) and to compare the risk of VTE for patients starting or switching to biologic DMARDs or methotrexate (MTX) with those starting or switching to a nonbiologic DMARD (nbDMARD).

Methods: We conducted a population-based, propensity score (PS)-matched cohort study combining two U.S. commercial insurance claims data (2001–2011). Among patients with a new diagnosis of RA, starters or switchers of various DMARDs were identified. Drug regimens were categorized into three mutually exclusive hierarchical groups: (1) a biologic DMARD with or without nbDMARDs, (2) MTX without a biologic DMARD, or (3) a nbDMARD without a biologic DMARD or MTX. Our main outcome was hospitalized VTE risk measured as the incidence rate (IR) and hazard ratio (HR) with 95% confidence intervals (CI). Two-way PS matching was done with a variable ratio up to 1:7 for each comparison.

Results: A total of 27,350 RA patients with 31,390 treatment episodes were initially identified. After PS matching, baseline characteristics were well-balanced across the groups. The IR of VTE per 1,000 person-years was twice higher in the bDMARDs group (7.45, 95% CI: 4.95–11.21) compared to nbDMARDs and MTX. Ninety-six percent of VTE cases in the bDMARDs group were on tumor necrosis factor-α inhibitors. Initiation of bDMARDs is associated with an increased risk of VTE (HR 2.75, 95% CI: 1.15–6.58) compared to nbDMARDs and MTX (HR 1.75, 95% CI: 0.77–3.96). There was no difference in the risk of VTE between MTX and nbDMARD groups. In a sensitivity analysis limiting the follow-up time up to 180 days, the elevated risk in bDMARDs was more pronounced.

Conclusions: The risk of incident VTE was low, but increased in RA patients starting or switching to a bDMARD compared to those starting or switching to MTX or nbDMARDs. Our results were robust in various sensitivity analyses.

38. Hyperimmune Globulins (HIGs) and Same-Day Thrombotic Adverse Events (TEs) in a Large Health-Care Database

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Background: Thrombotic events (TEs) are rare and serious, adverse events that can occur following administration of immune globulin products.

Objectives: To assess occurrence of TE diagnosis code (s) (DCs) on the same day as administration of hyper-immune globulin (HIG) products and examine potential risk factors for same-day TE DCs.

Methods: This retrospective claims-based study identified individuals exposed to HIG products from January 2008 to August 2011 using HealthCore's Integrated Research Database (HIRD^{SM}). HIG product exposures were ascertained using recorded HCPCS and CPT procedure codes. TEs were identified based on recorded ICD-9-CM diagnosis codes. Unadjusted TE DC rates were calculated overall and by age, gender and product group. Multivariable logistic regression was used to estimate same-day TE risk for different HIG products. Propensity Score (PS) analyses were conducted to account for confounding by indication.

Results: Of 101,956 persons exposed, 86 (0.8 per 1,000 persons) had claims evidence of TE DC recorded on the same-day as the HIG administration. Unadjusted same-day TE DC rates (per 1,000) ranged from 0.4 to 148.9 for the 10 HIG product groups with TE DCs recorded. GamaSTAN S/D IG > 10 cc had a statistically significant higher same-day TE DC risk compared to the reference Tetanus IG user group (OR = 57.6; 95% CI: 19.7–168.1), while controlling for potential confounders. The same-day TE DC risk for GamaSTAN S/D IG > 10 cc remained statistically significant in the PS analyses. Other products, Hepatitis B IGIV and RhoD IGIV SD, had elevated, but not statistically significant, same-day TE DC risk. Increased TE DC risk was identified for persons with older age (≥ 45 years), prior TE occurrence, and hypercoagulable state(s).

Conclusions: Our retrospective claims-based cohort study consistently identified a significantly increased same-day TE DC risk among individuals exposed to GamaSTAN S/D high-dose (> 10 cc). The study also identified potential recipient TE risk factors and suggests that patients' age and history of specific medical conditions should be taken into account prior to HIG administration.

39. Comparative Safety of Biological Agents among Medicare Rheumatoid Arthritis Patients

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Background: Several new biologic disease-modifying antirheumatic drugs (DMARDs) have been approved for treatment of rheumatoid arthritis (RA) in US. However, their comparative risks of serious infections are unclear.

Objectives: To determine if the risks of hospitalized infections associated with biologics used for RA differs.

Methods: Using Medicare data from 2006 to 2010 for 100% of patients with RA, we identified new users of etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, rituximab and tocilizumab. New users were defined specific to each drug as no use of that therapy in the prior 12 month 'baseline'. To increase homogeneity of patients for biologics, patients were required to have used another biologic DMARD during baseline (i.e.'switchers'). Eligible subjects were enrolled in Medicare Parts A, B and D in baseline and were censored at the earliest date of: 6 months after biologic initiation, a 90 day gap in current exposure, death, or loss of coverage. Confounding was controlled through a person-specific infection risk score derived among biologic-naïve users of anti-TNF and non-biologic DMARDs. We calculated the incidence rate of hospitalized infection for each biologic and compared their risks using Cox regression adjusting for infection risk score decile and other potential confounders (e.g. disability).

Results: Of 21,423 new biologic switchers, 11.5% was etanercept, 15.6% adalimumab, 4.9% certolizumab, 3.9% golimumab, 13.5% infliximab, 30.2% abatacept, 16.6% rituximab and 3.7% tocilizumab. During follow-up, we identified 788 hospitalized infections yield-

ing infection incidence rates from a low of 7.2 (certolizumab) to a high of 11.5 (infliximab) per 100 person years across biologics. After adjustment and compared to infliximab, hazard ratio (HR) was 0.61 for certolizumab (95% CI: 0.40–0.93), 0.63 tocilizumab (0.38–1.03), 0.64 abatacept (0.50–0.81), 0.69 golimumab (0.44–1.07), 0.75 adalimumab (0.58–0.98), 0.78 etanercept (0.58–1.03), and 0.93 rituximab (0.73–1.19).

Conclusions: Among RA patients with previous exposure to biologics, abatacept, adalimumab, and certolizumab were associated with a lower short-term risk of serious infection compared to infliximab.

40. Women with Autoimmune Disease Who Receive the Influenza Vaccine during Pregnancy Have Rates of Influenza-Like Illness Similar to Healthy Women Who Are Vaccinated during Pregnancy

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Background: Influenza vaccine is specifically recommended for groups of individuals that may be at increased risk of infection such as those with autoimmune disease; it is further recommended that all pregnant women be vaccinated. However, it is unknown whether influenza vaccination is as effective in preventing influenza infection in pregnant women with autoimmune disease as in healthy pregnant women.

Objectives: To assess the incidence of influenza-like illness (ILI) in pregnant women with autoimmune disease who have been vaccinated compared to the incidence of ILI in vaccinated pregnant women without autoimmune disease.

Methods: Data were obtained from an ongoing prospective cohort study of pregnancy outcome among women in the U.S. and Canada with or without autoimmune diseases. The autoimmune diseases included rheumatoid arthritis, Crohn's Disease, psoriasis or psoriatic arthritis, and ankylosing spondylitis. We selected women enrolled between 2009 and 2012 who reported receipt of an influenza vaccine sometime in pregnancy and had completed a subsequent maternal outcome interview which contained structured questions on the occurrence of ILI from the time of vaccination to pregnancy completion. We estimated the hazard ratio (HR) and 95% confidence interval (CI) for ILI comparing women with autoimmune disease to women without using time varying vaccine exposure and adjusting for season of enrollment.

Results: There were 1,028 subjects available for analysis: 347 women with autoimmune disease and 681 healthy comparison women, all of whom were vaccinated for influenza during pregnancy. Fifteen (4.3%) of women in the autoimmune disease group and 28 (4.1%) of women in the comparison group reported an ILI at some time in pregnancy after vaccination. The adjusted HR ratio for ILI in women with autoimmune disease vs. those without was 1.15 (95% CI: 0.61–2.16).

Conclusions: We found no evidence that pregnant women with autoimmune diseases were more likely than healthy pregnant women to develop ILI in pregnancy following influenza vaccination.

41. Cancer Risk Following beta-Interferon Treatment for Multiple Sclerosis: Findings from the Malignancy in MS [MaMS] Study

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Background: It is not known whether long term treatment with the beta interferons (IFN*B*s) for multiple sclerosis (MS) is associated with a change in cancer risk. IFN*B* treatment for MS often starts at a young age with the potential for a long period of exposure. As the immune system is the primary defense against cancers and IFN*B*s are known to modulate the immune system, exposure might alter the risk of cancer in MS patients.

Objectives: To determine whether overall cancer risk, or risk of specific cancers, was associated with exposure to IFN*B* for MS.

Methods: Data for patients in the British Columbia (BC) MS database with relapsing-onset MS who first visited a BC MS Clinic before 2005 were linked to the BC Cancer Agency Registry (to capture invasive cancers); BC Vital Statistics files (to capture deaths); and BC Ministry of Health Registry and Premium Billing Files (to confirm residency in BC). Study entry was the later of MS onset, immigration or Jan/96; and exit was the earlier of cancer diagnosis, initiation of a non-IFN*B* disease-modifying therapy, emigration, death or Jan/08. Using a nested case control study design, all MS cancer cases were matched to up to 20 randomly selected MS controls at the time of cancer diagnosis by sex, age (± 5 years), and year of study entry, using incident density sampling. The association between overall and specific cancers (breast, colon, lung and prostate) and IFN*B* exposure (≥ 90 days) was estimated by conditional logistic regression, adjusted for MS disease duration and age at study entry.

Results: During 48,807 patient-years, 5,154 MS patients developed 227 cancers. Exposure to IFN*B*

was not different for cases and controls (OR:1.26;95% CI: 0.86–1.86). There was a non-significant trend towards an increased risk of exposure in the breast cancer cases (OR:1.88;95% CI: 0.97–3.65). No increased odds of IFN*B* exposure was found for colorectal, lung, or prostate cancer.

Conclusions: We found no evidence of an altered cancer risk with exposure to IFN*B* ($\geq$ 3 months) over an observation period of up to 12 years. A potential association between IFN*B* use and breast cancer risk was suggested and should be investigated further.

42. Persistence with Biologics for Rheumatoid Arthritis Associated with Concomitant Methotrexate Use

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Background: Concomitant methotrexate (MTX) is associated with improved treatment efficacy in randomized controlled trials of biologic agents to treat rheumatoid arthritis (RA). Despite this, many patients receive biologics without MTX.

Objectives: To compare persistence among RA patients who initiated a biologic agent with and without MTX.

Methods: We conducted a retrospective cohort study among RA patients using Medicare administrative claims data from 2006 to 2010. Eligible patients were new users of etanercept, infliximab, adalimumab, or abatacept and were required to have $\geq$ 12 months continuous Medicare coverage after treatment initiation. Exposure groups were biologics as monotherapy or in combination with MTX. The outcome was persistence on biologics (without a gap > 90 days) at one year after treatment initiation. Patients were censored if they changed from monotherapy to combination therapy or vice versa. The crude hazard ratio for non-persistence of biologic therapy for users of monotherapy vs. combination therapy was calculated overall and for users of each biologic agent separately.

Results: Of 22,088 eligible RA patients, 8,767 initiated a biologic monotherapy and 13,321 initiated a biologic in combination with MTX. At treatment initiation, mean ages (standard deviation) of the 2 exposure groups were 65.0 (13.4) and 66.0 (12.1) years, 82% and 82% were women, and 78.8% and 80.9% were Caucasian. At 12 months, 53.4% of patients on biologic monotherapy were persistent compared with 70.1% of those on combination therapy (HR for non-

persistence: 1.69, 95% CI: 1.61–1.76). The association between use of concomitant MTX and biologic persistence differed significantly by biologic agent (p < 0.0001); the largest absolute difference between proportions of persistent patients at 12 months comparing biologic monotherapy vs. combination therapy was observed for infliximab users (57.8% vs 77.5%) and the least for abatacept users (59.6% vs 69.6%).

Conclusions: Concomitant MTX was associated with improved persistence on biologic therapy, an important indicator of treatment effectiveness in RA.

43. Germline Polymorphisms and Response to Cetuximab in Colorectal Cancer: A Meta-Analysis of Published Studies

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Background: Pharmacogenomics has great relevance for cetuximab, a monoclonal antibody targeting EGFR used in colorectal cancer. Because some patients fail to respond to the drug, testing of tumor genetics to predict non-response is already standard practice, but remains unhelpful in 40–60% of patients. The need for further biomarkers has prompted numerous studies proposing efficacy associations with particular polymorphisms, but disparate results have made interpretation difficult and motivate a more integrated analysis.

Objectives: To perform a systematic review and meta-analysis on studies of germline polymorphisms and tumor response in cetuximab-treated colorectal carcinoma.

Methods: Ovid MEDLINE was searched on 2012–09 using both MeSH subject headings and keywords (date range 1946–2012). Non-primary articles or case reports (n = 14), studies with fewer than 25 patients (n = 2), and duplicate studies/citations (n = 5) were excluded. Papers passing inclusion criteria were reviewed in full, with abstraction of methodologic information and results. Polymorphisms with at least three studies reporting sufficient raw data or summary statistics were examined by random-effects meta-analysis (using R, v2.15.1, metafor package).

Results: Of 50 initial articles, 16 passed inclusion criteria and were analyzed. Six polymorphisms were suitable for meta-analysis: FCGR2A 131 R>H, FCGR3A 158 F>V, EGFR 497 R>K, EGFR 5′UTR (CA)n, EGF 61 A>G, and CCND1 870 A>G. Analysis revealed only one significant result: the G allele of the EGF 61 A>G polymorphism, with the G/G genotype, relative to A/- genotypes, yielding a risk ratio of 2.50 (95% CI: 1.48–4.24) for tumor response. The I^2 for study heterogeneity was 40.29%. Statistical significance was robust to the choice of genetic model.

Conclusions: Systematic review and meta-analysis indicates that the EGF 61 A>G polymorphism, which produces a putatively functional variant of the EGF ligand, is associated with response to Cetuximab therapy. Limitations include an inability to consider tumor KRAS status or distinguish prognostic from predictive effects.

44. Polymorphisms in microRNA (miRNA) Pathways as Predictors of Survival and Response to Cisplatin in Esophageal Cancer (EC) Patients

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Background: miRNAs and their regulation/biogenesis can impact response to chemotherapy (including treatment with cisplatin) and carcinogenesis pathways in EC patients. To understand pharmacogenetics properly, the baseline prognostic effects of single nucleotide polymorphisms (SNPs) should be assessed.

Objectives: We assessed baseline prognostic associations of SNPs in the miRNA related pathways on outcome of EC cisplatin-treated patients.

Methods: Three-hundred and twenty four EC patients of all stages, histological subtypes and treatment plans were screened for 62 candidate SNPs in 21 miRNA or miRNA biogenesis pathway genes. Multivariate Cox-proportional hazard models adjusted for key prognostic factors evaluated the association of each SNP on overall (OS) and progression free survival (PFS). Significant SNPs were further analysed for joint effects analysis within the same chromosome (chr). In addition, exploratory cisplatin subgroup analyses was conducted. All results were internally validated through bootstrapping.

Results: Five polymorphisms in the miRNA biogenesis pathway genes and one in a miRNA gene were associated with OS/PFS, with adjusted hazard ratios (aHR) between (1.23–1.41): AGO1 (rs595961; chr 1; $aHR_{OS} = 1.31$, p = 0.03), GEMIN3 (rs197412; chr1; $aHR_{OS} = 1.31$, p = 0.02), CD86 (rs17281995; chr 3; $aHR_{OS} = 1.38$, p = 0.03), hs-miRNA-26a1 (rs7372209; chr 3; $aHR_{OS} = 1.41$, p = 0.003 and $aHR_{PFS} = 1.23$, p = 0.04), GEMIN4 [(rs7813; $aHR_{PFS} = 1.36$, p = 0.007) and rs910924 ($aHR_{PFS} = 1.38$, p = 0.01); chr 17]. Joint effects analysis of SNPs in the same chr found additive effects of these risk alleles (RA) on outcome: chr 1 (2–4 vs. 0–1: $aHR_{OS} = 1.82$, 95% CI[1.21–2.75]), chr 3 (3–4 vs. 0: $aHR_{OS} = 4.07$[1.91–8.67]), chr 17 (4 vs. 0: $aHR_{PFS} = 2.21$[1.13–4.31]). Exploratory gene-drug interaction analysis found a strong interaction between hs-miRNA-631 (rs5745925) and cisplatin therapy with both OS (p = 7.9E-3) and PFS (p = 1.1E-2).

Conclusions: We identified the miRNA biogenesis pathway as having an important role in the prognosis of EC patients, with a 50% increase in death or disease progression when carrying two additional miRNA risk alleles. Assessments of predictive capabilities of these SNPs are warranted.

45. Genetic Variation in the *PPARA* Gene Is Associated with Simvastatin-Mediated Cholesterol Reduction in the Rotterdam Study

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Background: Simvastatin is metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. Recently, the minor alleles of two strongly linked polymorphisms in

the *PPARA* gene, rs4253728 G>A and rs4823613 A>G, have been related to a decrease in CYP3A4 expression and activity, and thus may influence simvastatin pharmacokinetics.

Objectives: The objective was to study whether these polymorphisms are associated with the cholesterol-lowering effect of simvastatin therapy. We also investigated the association in users of other statins to exclude the possibility of a pharmacodynamic group-effect.

Methods: We identified 123 incident statin users (simvastatin: 77, atorvastatin: 29, other: 17) with total and LDL cholesterol measurements both before and after start of therapy in the Rotterdam Study, a prospective population-based cohort study. Associations between the *PPARA* polymorphisms and change in total and LDL cholesterol levels were analyzed using linear regression models.

Results: The minor G allele of the rs4823613 A>G polymorphism was associated with a 0.258 mmol/L (95% CI: −0.470; −0.046, P: 0.018) and a 0.294 mmol/L (95% CI: −0.495; −0.093, P: 0.005) larger reduction in total and LDL cholesterol respectively after start of simvastatin therapy. Categorical analyses demonstrated a −0.614 mmol/L (95% CI: −01.140; −0.088, P .023) and a −0.672 mmol/L (95% CI: −1.164; −0.180, P 0.008) larger reduction in total and LDL cholesterol respectivly, for the homozygous minor allele GG genotype compared to the reference homozygous major allele AA genotype. The results were similar for the strongly linked rs4253728 G>A polymorphism. No association was found when we analyzed only incident atorvastatin users or all incident statin users combined.

Conclusions: In the Rotterdam Study, the minor alleles of the *PPARA* rs4253728 G>A and rs4823613 A>G polymorphisms are associated with a better total and LDL cholesterol-lowering response after start of simvastatin therapy. This has not been demonstrated before. With this study, we contribute further evidence that the influence of these polymorphisms on the cholesterol-lowering effect of simvastatin acts through their influence on the CYP3A4 enzyme.

46. Risks of Venous Thromboembolism in Women Using Combined Hormonal Contraception and Carrying Genetic Hemostatic Variations

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Background: Knowledge concerning associations between genetic hemostatic variations and venous thromboembolism (VTE) in women using combined hormonal contraceptives (CHCs) is limited.

Objectives: For women using CHC, assessing associations between VTE and mutations affecting hemostasis, such as Factor V Leiden (FVL), the prothrombin gene mutation (PGM), Factor XIII, methylenetetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor-1 (PAI-1), glycoprotein IIb/IIIa (GPIIb/IIIa) and nitric oxide synthase 3 (NOS3).

Methods: Case-control study conducted in Sweden 2003–9. All cases had a first episode of VTE objectively verified. Controls were matched by age to the cases and randomly selected from the population. The participants were interviewed concerning risk factors for VTE and they donated a blood sample for genetic analyses. Comparisons were made using controls without CHC and not carrying the specific mutation as references. Associations were assessed by logistic regression analyses after excluding obese and immobilized women and are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: We included 948 cases and 902 controls. Risks of VTE was much higher in users of CHC carrying FVL than in non-carriers [OR = 38 (15–121) vs. OR = 4.1 (2.9–5.8)]. For PGM, the corresponding risks were OR = 22 (5.1–192) and OR = 4.3 (3.2–5.9), respectively. Factor XIII was associated with a decreased risk of VTE in carriers [OR = 3.5 (2.3–5.3) vs. OR = 6.0 (3.9–9.4)] in non-carriers. There were only slight differences in ORs for carriers and non-carriers of MTHFR, PAI-1, GPIIb/IIIa and NOS3.

Conclusions: Women using CHCs and carrying FVL or PGM had very high risks of VTE. Factor XIII seemed to have a slightly protective effect, whereas none of the other genetic hemostatic variations affected VTE risk.

47. *ST13* Polymorphisms Increase the Risk of Exacerbations in Steroid-Treated Asthmatic Children and Young Adults

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Background: The clinical response to inhaled steroids in asthma varies between children and might be associated with genetic variation.

Objectives: To study whether SNPs in 17 candidate genes are associated with exacerbations in asthmatic children and young adults treated with inhaled corticosteroids.

Methods: A meta-analysis assuming random effects with the inverse variance weighing method was performed of three asthma cohort-studies: PACMAN (n = 357, age: 4–12 years, the Netherlands), BREATHE (n = 818, age: 3–22 years, UK), PAGES (n = 391, age: 2–16 years, UK). All participants were treated with inhaled corticosteroids. Genes were selected based on their role in the glucocorticoid signaling pathway or a previously reported association with asthma. Two outcome parameters were used to reflect exacerbations: (1) asthma-related hospital visits, (2) course(s) of oral corticosteroid (OCS) use in the previous year. The model was adjusted for age, sex and treatment step. Q-values were calculated to account for multiple testing. Identified associations were replicated in a fourth study: CAMP (n = 172, age: 5–12 years, USA). CAMP was included in a second-meta-analysis to test the robustness of the findings.

Results: In a meta-analysis of PACMAN, BREATHE and PAGES two SNPs in *ST13* were associated with severe exacerbations despite corticosteroid treatment. The *ST13* SNP rs138335 increased risk of asthma-related hospital visits (OR = 1.35 per G allele; 95% CI: 1.07–1.70, OR: 1.35, p = 0.01, q = 0.25), rs138337 had a similar effect (OR = 1.36 per G allele; 95% CI: 1.11–1.67, p = 0.003, q = 0.11). The two SNPs were not associated with risk of severe exacerbations in CAMP, however, when CAMP was included in the meta-analysis rs138337 and rs138335 were significantly associated with both outcomes. Hospital visits OR for rs138335 was 1.28 (95% CI: 1.03–1.59, p = 0.02, q = 0.36) and 1.31 for rs138337 (95% CI: 1.07–1.59, p = 0.007, q = 0.19). OCS use OR for rs138335 was 1.18 (95% CI: 1.01–1.38, p = 0.03, q = 0.41) and 1.28 for rs138337 (95% CI: 1.09–1.54, p = 0.003, q = 0.10).

Conclusions: A novel susceptibility gene, *ST13,* is associated with the occurrence of exacerbations in asthmatic patients despite corticosteroid treatment.

48. Plasma Fibrinogen Predicts Mortality in Patients with COPD

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Background: Enriching study populations with patients more likely to experience outcomes can enhance the ability of randomized clinical trials to demonstrate a clinical benefit. The COPD Foundation Biomarkers Qualification Consortium (CBQC) is submitting plasma fibrinogen to regulatory agencies for qualification as a biomarker for the enrichment of COPD clinical trial populations.

Objectives: To determine whether COPD patients with high fibrinogen are at increased risk of mortality.

Methods: Six studies were identified that measured plasma fibrinogen, spirometry, and clinical outcomes, had at least 6 months of follow-up, and for which patient level data were available: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), Atherosclerosis Risk in Communities (ARIC) cohort, Cardiovascular Health Study

(CHS), Multi-Ethnic Study of Atherosclerosis (MESA), the Third National Health and Nutrition Examination Survey (NHANES III), and the Framingham Heart Study (FHS). We conducted pooled analyses to identify patients aged > 40 years with spirometric evidence of COPD. We categorized patients according to baseline characteristics, and we used Cox proportional hazards models to compute hazard ratios (HR) and 95% confidence intervals (CI) for mortality at 36 months adjusting for age and baseline fibrinogen.

Results: The study population included 6,703 participants with a mean age of 64 years, and who were 62% male with a mean fibrinogen level of 352 mg/dL. After 3 years, 83% of patients with high fibrinogen at baseline ($\geq$ 350 mg/dL) remained elevated. High baseline fibrinogen was associated with increased risk of mortality (HR: 1.93; 95% CI: 1.62–2.31). In ECLIPSE, high fibrinogen was more strongly associated with mortality than a recent COPD exacerbation and predicted mortality after adjustment for recent COPD exacerbations (HR: 1.53; 95% CI: 1.10–2.13).

Conclusions: Preliminary analyses of this integrated database including 6 studies indicate that plasma fibrinogen is a useful biomarker for identifying COPD patients at increased risk of mortality. (ECLIPSE was funded by GlaxoSmithKline, NCT00292552, GSK Study No. SCO104960).

49. Adherence to Oral Diabetes Medications and Glycemic Control during and Following Breast Cancer Treatment

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Background: Breast cancer is most prevalent among older women also commonly burdened with comorbidities such as diabetes mellitus (DM). Poor adherence to DM medications is associated with increased glycometabolic disturbance, healthcare utilization, and all-cause mortality. General population estimates of adherence to DM medications are considerably low, < 60% on average. Understanding influences of cancer on DM management is important to the growing population of breast cancer survivors.

Objectives: We evaluated changes in oral DM medication adherence and persistence, as well as glycemic control during breast cancer treatment and in subsequent years of clinical management.

Methods: We sampled from an existing cohort of 4,221 women diagnosed with incident early stage (I,II) invasive breast cancer from 1990 to 2008, enrolled in Group Health, a large integrated health delivery system. Adherence and persistence were measured in prevalent users (N = 509) at cancer diagnosis using medication possession ratio (MPR),% adherent (MPR $\geq$ 0.80) and discontinuation rates (DR). Laboratory data on FPG and HbA1c were obtained for the corresponding periods.

Results: Mean MPR for metformin and sulfonylureas (0.86 vs. 0.49 p < 0.001) and% adherent (75.3% vs. 24.6% p < 0.001) declined during treatment. Subsequently, MPR and% adherent rose slightly but never returned to baseline. DR increased in Year +1 (59.3% vs. 75.6% p < 0.001) and remained elevated during subsequent observation periods. Increased mean HbA1c (7% vs. 7.3% p = 0.001) and% not at goal with HbA1c of $\leq$ 6.5% (47.9% vs. 68.7% p < 0.001) from baseline to treatment coincided with decreases in adherence.

Conclusions: DM medication adherence declined following breast cancer diagnosis while discontinuation rates were relatively stable but poor overall.% adherent users increased only marginally following treatment, while HbA1c and women not meeting treatment goals continued to increase considerably. These data support correlation between adherence and glycemic control that may be sensitive to breast cancer diagnosis/treatment. Further study is warranted on reasons for non-adherence post cancer diagnosis and subsequent indicators of glycemic control.

50. Glucagon-Like Peptide-1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes: Population Based Matched Case-Control Study

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Background: Acute pancreatitis has significant morbidity and mortality. Previous studies have raised the possibility that glucagon-like peptide-1-based therapies (GLP-1) including the GLP-1 mimetic (exenatide) and the dipeptidyl peptidase 4 inhibitor (sitagliptin) may increase the risk of acute pancreatitis.

Objectives: We aimed to test whether GLP-1 based therapies, such as exenatide and sitagliptin, are associated with an increased risk of acute pancreatitis.

Methods: We conducted a population based case-control study in a large administrative database in the United States from 2005 to 2008. We included adults with type 2 diabetes aged 18–64; 1,269 hospitalized cases with acute pancreatitis were identified using a validated algorithm and 1,269 controls matched on age category, sex, enrollment pattern, and diabetes complications. Conditional logistic regression was used to analyze the data.

Results: The mean age of included individuals was 52 years and 57% were male. Cases with pancreatitis were significantly more likely than controls to have hypertriglyceridemia (12.9% vs. 8.3%), alcohol use (3.2% vs. 0. 2%), gallstones (9.1% vs. 1.3) tobacco abuse (16.2% vs. 5.5%), obesity (19.6% vs. 9.8%) biliary and pancreatic cancer (2.8% vs. 0%), cystic fibrosis (0.8% vs. 0%) and any neoplasm (29.9 vs. 18%). After adjusting for available confounders and metformin use, both current use of GLP-1-based therapies within 30 days (adjusted Odds Ratio [aOR], 2.24, 95% Confidence intervals 1.36–3.68) and recent use greater than 30 days and less than 2 years (aOR, 2.01, 95% CI: 1.27–3.18) were associated with significantly increased odds of acute pancreatitis relative to the odds in non-users.

Conclusions: Acute pancreatitis has significant morbidity and mortality. In this administrative database study of US adults with type 2 diabetes, treatment with GLP-1-based therapies, sitagliptin and exenatide, was associated with an increased odds of hospitalization for acute pancreatitis. The benefits of these agents on glycemic control needs to be balanced against the the risk of acute pancreatitis.

51. Incretin-Based Drugs and Comparative Pancreatic Cancer Risk among Older Adults

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Background: A study using FDA Adverse Events Reporting System (FAERS) data reported increased pancreatic cancer rates with Incretin-based antidiabetic drugs (IBRx) exenatide and sitagliptin compared with other antidiabetics (CompRx). FAERS data are limited by lack of denominators and reporting bias.

Objectives: We compared the incidence of pancreatic cancer after initiation of IBRx or CompRx. To address concerns about potential outcome detection bias, we compared the cumulative incidence of diagnostic work-up in the two cohorts before and after initiation (index date).

Methods: We identified new-user cohorts of patients > 65 years from the 2006–10 Medicare claims data to compare sitagliptin with sulfonylureas (SU) and thiazolidinediones (TZD) and exenatide with long acting insulins (LAI). Follow-up started at the second prescription of the same drug within 180 days after initiation. We used Cox models to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) and compared diagnostic workup after and before initiation using risk ratios (RR).

Results: Based on preliminary 07–09 data, we identified 11,821 sitagliptin and 1,140 exenatide initiators. Over a 9-month median follow-up, 12 sitagliptin initiators had a pancreatic cancer diagnosis (preliminary exenatide numbers too small to report). The hazard of pancreatic cancer with sitagliptin was lower relative to SU (HR = 0.5, CI: 0.2–1.4) and slightly higher than TZD (HR = 1.5; CI: = 0.6–3.4) but the CI was wide. In the 6 months post index, the cumulative incidence of diagnostic procedures in sitaglitpin initiators (78.6%) was almost similar to TZD (73.5%) (RR = 1.07; CI: 1.06–1.08) and SU (74.3%) (RR = 1.05; CI: 1.04–1.07) and that of GLP initiators (80.4%) was similar to LAI (79%) (RR = 1.00; CI: 0.95,1.01). The probability of diagnostic workup pre-index was 79–83% for all groups.

Conclusions: Though limited by sample size, preliminary data suggest no increased pancreatic cancer risk with sitagliptin relative to CompRx and that the probability of diagnostic work-up is not affected by IBRx. Analyses including an additional year (2010) of Medicare data and implementing propensity scores will be presented.

52. Duration of Metformin Use and Risk of Colon Cancer in Patients with Diabetes

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Background: Several observational studies have reported a lower incidence of cancer, including colorectal cancer, among patients with diabetes treated with metformin. However, many of these studies have suffered from time-related biases that may explain these chemopreventive findings.

Objectives: To examine the association between risk of colorectal cancer and duration of metformin use among patients with diabetes mellitus using methods that minimize time-related biases.

Methods: We conducted a retrospective cohort study of 50,722 health plan members of Kaiser Permanente Northern California (KPNC) aged 40 years or older who were in the KPNC Diabetes Registry and completed a mailed survey on health-related traits and behaviors in 1994 to 1996. Electronic pharmacy dispensing records were used to identify prescriptions for diabetes medications. Using the KPNC Cancer Registry, patients were followed for colorectal cancer from 1997 to 2009 (median 8.1 years). Patients who had any invasive cancer diagnosed prior to 1997 (i.e., prevalent cancer) or who had used metformin prior to 1997 (i.e., prevalent users) were excluded. Cox regression modeling, with age as the time scale, was used to estimate relative risks (RR) of colorectal cancer associated with duration of metformin use, adjusted for sex, race/ethnicity, BMI, income, education level, alcohol use, diabetes duration, baseline measures of hemoglobin A1c and creatinine, and ever use of other types of diabetes medications. Duration of metformin use, and ever use of other diabetes medications, were modeled as time-dependent variables.

Results: During 389,887 person-years of follow-up, 744 patients were diagnosed with colorectal cancer. The crude and adjusted RRs for colorectal cancer associated with different durations of metformin use were almost identical. The adjusted RRs for < 2.0, 2.0–4.9, and 5.0 + years of metformin use were 0.87 (95% confidence interval (CI), 0.69–1.09), 1.03 (95% CI: 0.82–1.29), and 0.87 (95% CI: 0.66–1.16), respectively.

Conclusions: Our results do not confirm earlier findings of a lower risk of colorectal cancer associated with metformin use.

53. Mortality after Cancer in People with and without Pre-Existing Diabetes: Diabetes Duration and Treatment Effect

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Background: It is known that cancer patients with pre-existent diabetes experience higher mortality compared to cancer patients without diabetes. However, the role of different diabetes treatment types has not been studied in detail.

Objectives: We compared mortality rates among cancer patients with and without diabetes, accounting for diabetes treatment and diabetes duration.

Methods: The study is based on all cancer patients diagnosed in Denmark in the period 1995–2009. We linked the Danish Cancer Register and the Danish National Diabetes Register. Cancer patients were classified into 4 groups by diabetes status at the time of diagnosis of cancer: no diabetes, diabetes without medication, diabetes with OAD treatment or diabetes with Insulin treatment. The Cox proportional hazard and the multiplicative Poisson model were used to examine the association between mortality and pre-existing diabetes in cancer patients relative to non-diabetic cancer population.

Results: Among 426,129 new cancer cases, we found 40,596 with diabetes prior to the cancer diagnosis (14,315 without medications, 17,699 on OADs and 8,582 on Insulin). Overall, diabetes patients had higher mortality rates compared to non-diabetic cancer patients with the highest among the OAD and insulin treated. The mortality rate ratios relative to non-diabetics, as function of time since cancer diagnosis, showed a general increase. With diabetes duration of 2 years, insulin treated patients had the highest mortality rate ratios starting from 2 for men and 1.75 for women one year after cancers, increasing to around 2.7 for both men and women after 9 years. The OAD treated patients had a bit lower rate-ratios of 1.15 to 1.6 for men, and 0.9 to 1.7 for women.

Conclusions: Based on a nation-wide register linkage study, we confirmed that cancer patients with pre-existing diabetes experience higher mortality than cancer patients without diabetes. The higher mortality seen among cancer patients with OAD and insulin treated diabetes respectively is in accordance with the notion that more intensive diabetes treatment reflects a larger degree of co-morbidity at the time of cancer diagnosis, and hence poorer survival.

54. Trends in First Anti-Diabetes Drug Initiated among Adults with Incident Diabetes in SUPREME-DM

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Background: Initial drug therapy in newly-diagnosed adult patients with diabetes is not well characterized.

Objectives: To describe initial anti-diabetes drug therapy among adults in the SUveillance PREvention and ManagEment of Diabetes Mellitus (SUPREME-DM) 2005–2010 incident cohort.

Methods: This retrospective study uses the SUPREME-DM DataLink, which brings together clinical, EHR, and administrative data from 11 health systems into the largest distributed database of privately-insured diabetes patients in the US. The study cohort included patients meeting an incident diabetes case definition based on diagnosis codes or laboratory results. Patients dispensed a diabetes drug in the 2 years prior to their diabetes incidence date were excluded. Initiators were patients with a diabetes drug dispensed during the first 6 months after their diabetes incidence date. Initiators were categorized as starting metformin (MET), sulfonylurea (SULF), insulin, or other agents; patients were in multiple categories if they started > 1 drug the same day. Analyses included chi-square or Wilcoxon rank sum tests.

Results: Among 241,327 patients (mean age 59, 47% female, mean glycosylated hemoglobin 7.5%), 40% (n = 97,350) initiated drug within 6 months of diabetes incidence date, increasing from 37% in 2005 to 44% in 2010 (p < 0.001). 60% of initiators started drug within 1 week; 93% started within 3 months. Across all years, 75% started MET, 28% started SULF, and 6% started insulin. From 2005 to 2010, MET initiation increased (63 to 85%) (p < 0.001), while SULF initiation decreased (38–20%) (p < 0.001). Among patients starting MET, 9% were aged ≥ 70 compared to 20% starting SULF (p < 0.001); MET starts were consistently lower among those aged ≥ 70, but rate of increase was greatest among older patients (e.g., from 30 to 58% of those 80 +) (p < 0.001).

Conclusions: The proportion of incident diabetes patients starting anti-diabetes drug therapy is growing over time, but more than half remain untreated at least 6 months. MET is increasingly the first drug initiated; relative increase is greatest among older patients. This is consistent with the ADA recommendation of MET as first line for type 2 DM.

55. Comparing Effectiveness Estimates from Randomized and Nonrandomized Studies, Using Subgroup Analyses and Individual Patient Data

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Background: A possible explanation for differences in results from randomized clinical trials (RCTs) and those from nonrandomized studies is confounding. Besides this, it is well know that different patients are included by RCTs and nonrandomized studies. When there is effect modification the inclusion of different patient types may also cause differences between results from RCTs and nonrandomized studies.

Objectives: To show how comparability of results across different designs is affected by the inclusion of different patient types and how to adjust for this.

Methods: The effect of beta-blocker vs. diuretics use on the risk of non-fatal myocardial infarction (MI) was compared using data from 2 RCTs (the antihypertensive MRC trials), a case-control study, and a cohort study. Age by treatment interaction was assessed and confounding was adjusted for using restriction and (time-varying) regression. Effects were estimated as hazard ratios (HRs) or odd ratios (ORs), with 95% confidence intervals (95% CI), for beta-blocker vs. diuretic use.

Results: After adjusting for confounding, both the RCT and case control estimates were similar, HR 1.09

(95% CI: 0.78;1.52) and OR 1.25 (95% CI: 0.91;1.72), but different from the cohort study HR 2.55 (95% CI: 1.90;3.42). The age by treatment interaction was non-significant. However, restriction to subjects aged > 65 years, showed comparable effect estimates: RCT HR 2.28 (95% CI: 1.16;4.52), case-control OR 1.61 (95% CI: 0.91;2.85) cohort study, HR 2.30 (95% CI: 1.53;3.45).

Conclusions: In the presence of interaction, differences between results from RCT and nonrandomized studies can be due to the inclusion of different patients groups.

56. Information Gained by Linking Administrative Claims to Structured Electronic Health Record Data in a Statin Comparative Effectiveness Study

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Background: It is hoped that unmeasured confounding in observational comparative effectiveness research (CER) may be addressed by linking patient claims to electronic health record (EHR) data. However, EHR data are themselves subject to missingness.

Objectives: Assess the gain in information achieved by linking administrative claims to a regional health information exchange (HIE), for important clinical covariates in a population of statin initiators.

Methods: We identified adults ($\geq$ 18 years of age) with $\geq$ 6 months health plan enrollment and no statin use during the 6-month period prior to new statin use between July 2004 and May 2010 in the HealthCore Integrated Research Database. We then linked a subset residing in Indiana to a regional HIE and extracted demographic, clinical and laboratory parameters for key potential confounders available in the 6-month pre-index period. Proportions of patients with missing claims and EHR-based data were calculated.

Results: About 22,300 linked patients had non-null structured or free text data available at any time pre- or post-index in the EHR. Of these, 51% were male, and 73% were 41–64 years of age. Fourty-four percent initiated therapy with simvastatin. 99%, 89%, and 90% of the linked cohort were missing outpatient claims laboratory values for glucose, triglycerides and LDL/HDL,

respectively. Race was systematically unavailable in claims data. Virtually all patients (98%) were missing at least one of the EHR covariates of interest. Supplementing outpatient claims with EHR data from the 6 month pre-index period reduced the missingness to 13%, 63%, 81% and 82% for race, glucose, triglycerides and LDL/HDL, respectively. Blood pressure was missing in 99% and body mass index in 98% of the linked cohort during the 6 month pre-index period.

Conclusions: Linking claims to a regional HIE provided modest improvement in the availability of lab test results and yielded mostly complete race data. Most patients in a given study are likely to have at least one confounder missing, making it a challenge to simultaneously adjust for multiple confounders.

57. Imaging and Electronic Health Record (EHR) Data for Comparative Effectiveness Research (CER): Experience from a Tertiary Care Hospital

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Background: With increased adoption of EHRs, there has been a rising expectation that EHRs will enhance the validity and efficiency of CER.

Objectives: The objective of this study was to compare the effectiveness of carotid artery stenting (CAS) or carotid endarterectomy (CEA) to medical management (MM) for the treatment of carotid stenosis using imaging, EHR, and claims data.

Methods: We collected carotid ultrasound studies (2006–2009) from a vascular laboratory at a tertiary care hospital, which we linked to institutional EHR and Medicare data, including medication (Part D) files (2006–2009). Patients were at least 65 years of age, eligible for Medicare for at least 3 months, and did not have a prior carotid revascularization. We identified new users of antiplatelets, statins, ACE-inhibitors, and beta-blockers from EHRs for patients whose primary care physician (PCP) was at the hospital and from Part D. We assessed concordance of medication information in claims and EHR data in a subset of patients with data in both sources.

Results: Of 5,751 Medicare patients (mean age: 76.2; male: 55.1%; white: 95.7%; symptomatic carotid stenosis: 11.7%; carotid stenosis ≥ 50%: 46%) undergoing 8,846 carotid duplex ultrasound exams at the vascular laboratory, 1,363 had their PCP at the hospital and 2496 had Part D drug data. Among a subset (n = 937) with both Part D and EHR drug data, substantial discrepancies in the exposure to medications was observed; EHRs generally failed to capture drug exposure 50% of the time. Among users of the target medications in claims, 15% (clopidogrel) to 60% (statins) were prevalent users at the time of vascular laboratory referral. Due to the small number of new users of medications and poor quality of the medication data from EHRs, it was not feasible to assess the effectiveness of CAS, CEA, and MM.

Conclusions: Despite the promise of EHRs for CER, we were not able to compare CAS and CEA to MM due to the limited utility of EHR drug data at our institution and the small number of new users. Increasing number of EHR systems meeting meaningful use criteria may overcome the limitations observed in our study.

58. Preference-Based Instrumental Variable Methods in the Comparative Effectiveness of Osteoporosis (OP) Medications in Women with Postmenopausal Osteoporosis (PMO)

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Background: Observational studies of intended drug effects are particularly susceptible to confounding by indication. Instrumental variable (IV) methods may control for unmeasured confounding in these studies.

Objectives: To construct an IV based on physician preference and to test the assumptions of the IV method in assessing the potential effect of bisphosphonate (BP) vs. other OP medications on the risk of osteoporotic fracture (Fx) in women with PMO.

Methods: Women ≥ 55 years old initiating a BP or other OP medications (index treatment) were identified from the United Healthcare database (2008–2011) and followed for incident osteoporotic Fx. Baseline covariates were assessed over the 1-year period pre-index treatment. IV was defined by the prescribing physician's preference (IV = BP vs. other), characterized by filled prescriptions in the baseline period. Assumptions of the IV method including the strength of the IV as reflected by its association with the index treatment and osteoporotic Fx, the balance of covariates across

levels of the IV, and the heterogeneity of treatment effect were evaluated.

Results: The odds ratio of receiving BP vs. other OP medications was 1.75 (95% CI: 1.64, 1.87) for IV = BP vs. other. The incidence rate ratios (IRR) (95% CI) of osteoporotic Fx comparing index treatment (BP vs. other) and IV (BP vs. other) were 0.53 (0.44, 0.65) and 1.07 (0.90, 1.26), respectively. The imbalances in measured confounders between initiators of BP and initiators of other OP medications were slightly improved by the IV. The strength of the IV varied moderately by baseline covariates.

Conclusions: Physician preference may be a potential IV when evaluating the comparative effectiveness of BP vs. other OP medications in women with PMO. Unmeasured confounding may account for the disparate results suggested by the IRRs for the index treatment and IV. The IV may be improved by excluding refills in the determination of physician preference and by stratifying by physician specialty in future studies.

59. Comparing Propensity Score Estimation Using Logistic Regression and Generalized Boosted Regression in a Real-World Comparative Effectiveness Study of Glaucoma Therapies (RiGOR)

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Background: Propensity scores (PS) are traditionally estimated using logistic regression in comparative effectiveness research, but growing evidence suggests generalized boosted modeling (GBM) may further reduce bias by fitting nonlinear effects and interaction terms.

Objectives: To compare the performance of PS estimation weighting methods using data from a real-world comparative effectiveness study of glaucoma therapies.

Methods: RiGOR, a prospective observational study conducted at U.S. ophthalmology practices, aims to compare the effectiveness of glaucoma therapies. The *twang* R package was used to estimate the PS with logistic and GBM methods. The data were weighted by the PS to estimate the average treatment effect among the treated (ATT, procedures). Performance was assessed using the effective sample size (ESS) of

the untreated (medications) and the average standardized absolute mean difference (ASAM). We calculated the association between procedures (N = 636) and medications (N = 1,061) with 3-month treatment success (≥ 15% reduction in intraocular pressure) among clinically diagnosed glaucoma patients.

Results: Glaucoma severity, past glaucoma therapy, and reasons to initiate new therapy differed by therapy type at baseline and all had the largest relative influence on estimating the PS. ASAM was 11%, 2.9%, and 3.6% for the unweighted, weighted logistic and GBM methods, respectively. The ESS for medication users was smaller for logistic (ESS = 384) than GBM (ESS = 581). We observed similar associations between therapy and 3-month success for the unweighted (OR = 0.85; 95% CI: 0.69–1.09), weighted logistic (OR = 0.95; 95% CI: 0.73–1.22) and GBM (OR = 0.91; 95% CI: 0.72–1.14) methods.

Conclusions: Weighting the PS improved covariate balance, but the loss of information reflected by the ESS suggests a substantial number of patients on medications were not comparable to those with procedures. Empirical comparisons which lack a 'gold standard' suggest similar results between the weighted logistic and GBM adjustment methods in estimating an ATT, with the latter yielding a larger ESS for analysis.

60. Identifying Appropriate Comparisons for Comparative Effectiveness Research (CER)

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Background: CER can inform the decision-making of both practitioners and health services administrators. A prerequisite to valid observational CER is that the alternative interventions are used in roughly similar ways. Baseline comparability among the patients exposed to the alternatives reduces the extent of channeling bias and the demands on multivariate adjustment in both safety and effectiveness studies.

Objectives: To design and implement a standardized approach to determine whether treatments in a healthcare database are sufficiently comparable to be candidates for CER.

Methods: We implemented an automated heuristic that compares two treatments to determine whether they appear to be used similarly. We fit a propensity score model by applying Lasso logistic regression with 35,249 baseline covariates representing patient demographics, comorbidities, concomitant medications, and health service utilization behaviors. We evaluated the comparability of two treatments by assessing the proportion of patients in each cohort near clinical equipoise based on the propensity score distribution. We applied the heuristic within a claims database to 138 drugs across eight indications.

Results: About 1,233 pairwise assessments of alternative treatments yielded 427 (35%) candidates for CER. Many of the empirically identified appropriate comparators were consistent with expectations based on clinical judgment, such as comparisons among TNF inhibitors for rheumatoid arthritis and SSRIs for depression. However, several comparisons that may have been considered reasonable based on clinical judgment, such as dabigatran and warfarin for atrial fibrillation, were observed to be sufficiently different to raise questions about potential bias in the conduct of head-to-head studies.

Conclusions: Large-scale regularized regression can be used to evaluate the appropriateness of studying alternative treatments. By applying an objective heuristic consistently across all treatments, this approach can provide empirical evidence to support the selection and prioritization of comparative effectiveness research questions, and identify potential threats to validity which could be considered when designing the study.

61. Application of Instrumental Variables Method in Pharmacoepidemiology: An Example of Beta2-Agonist Use and Myocardial Infarction

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Background: Unobserved confounding may impair the validity of observational research. Instrumental variable (IV) analysis theoretically controls for unobserved confounding, yet it has not widely been used in pharmacoepidemiologic studies.

Objectives: To assess the applicability and apparent validity of different IVs in a study of long-acting beta2-agonist (LABA) use and the risk of myocardial infarction (MI).

Methods: Information on adult patients with a diagnosis of asthma and/or chronic obstructive pulmonary disease and at least one prescription of inhaled beta2-agonist/Muscarinic antagonist was extracted from

Dutch Mondriaan NPCRD General Practice (GP) database (N = 360,000). Effects of LABA vs. no-LABA on the risk of MI were estimated by using a Cox proportional hazards model. Physician's prescribing preference (PPP), measured by the last prescription written by a physician, GP centers (GPC), and proportions of LABA prescriptions per GP center (PLP) were used as IVs in two-stage IV analysis. Ninety-five percent confidence intervals (CI) for IV estimates were estimated by using bootstrapping. Quantitative methods (e.g., F-statistic, standardized difference for binary IV, and empirical cumulative density function for continuous IV) were applied to assess the validity of the IVs.

Results: IV analysis showed that GPC was weakly (F = 11) associated with LABA in contrast to the other IVs: PPP (F = 200) and PLP (F = 975). Observed confounders were approximately balanced across IV levels for PPP and PLP, but not for GPC. As this study has been performed under the PROTECT project examining the variability of results from studies using a same protocol, or a protocol with defined differences, applied to a same drug-adverse event pair in different databases, in order to maintain the blinding of investigators from one another's results, results on the association between LABA and MI will be disclosed during the ICPE conference.

Conclusions: Our IV analysis suggests that PLP appears to perform better as an IV than PPP and GPC. We recommend researchers to start IV analysis with more than one possible IV in order to evade uncertainty of the effect estimate based on a single IV.

62. Factors Associated with Time to Triple Therapy in Newly Diagnosed COPD Patients in the UK General Practice Research Database

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Background: Triple therapy for COPD, consisting of a long-acting muscarnic (LAMA), a long-acting beta-agonist (LABA), and an inhaled corticosteroid (ICS), is often prescribed as patients worsen.

Objectives: To determine the proportion of newly diagnosed COPD patients progressing to triple therapy, mean time to and factors associated with progression.

Methods: A retrospective cohort of newly diagnosed COPD patients was identified in the General Practice Research Database from 1/1/2008 to 12/31/2009 and followed for 24 months. Initial maintenance therapy (IMT) was defined as short-acting bronchodilator (SABD), LAMA, ICS, LABA, and combinations prescribed within 30 days. Time to triple was calculated as number of days between date of first triple therapy prescription and date of new COPD diagnosis. A Cox proportional hazards model was used to identify factors associated with time to first prescription of triple therapy producing hazard ratios (HR) with 95% confidence intervals (CI). Characteristics including age, gender, body mass index, smoking, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage of airflow limitation, co-morbidities, exacerbations, healthcare utilization and IMT were examined. For analytical purposes long acting bronchodilators (LABD) and ICS combinations (ICS+LABA or LAMA) were combined.

Results: Among 7,881 COPD patients, 11% had an IMT of triple therapy. In the remaining 6,998 patients, progression to triple therapy varied by IMT group, ranging from those prescribed ICS (12%), SABD (13%), ICS+LABA (32%), to LAMA (41%). The mean time to triple therapy ranged from 182 days (LAMA+LABA) to 381 days (SABD). Factors associated with triple therapy progression, included GOLD stage 4 (HR 2.38 CI: 1.86–3.04), 1 + COPD exacerbation (HR 1.95 CI: 1.75–2.16), and IMT [LABD (HR 3.44 CI: 2.93–4.04); ICS combination (HR 2.5 CI: 2.1–2.9)].

Conclusions: Approximately 30% of the newly diagnosed cohort progressed to triple therapy during follow-up. Time to triple was associated with type of IMT therapy, degree of airflow limitation, and exacerbation frequency 12 months post diagnosis.

63. Role of Tiotropium in Reducing Exacerbations in Chronic Obstructive Pulmonary Disease (COPD) Patients When Added to Long-Acting β2-Agonists (LABA) and Inhaled Corticosteroids (ICS)

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Background: For COPD patients, guidelines advocate the use of more than one long-acting bronchodilator in addition to ICS. Tiotropium has been shown to

reduce COPD exacerbations (COPD-E), however benefits when it is used in conjunction with LABA/ICS still have to be demonstrated.

Objectives: To evaluate the effect of tiotropium in reducing COPD-E when combined with LABA/ICS.

Methods: A cohort study based on linked health information systems (hospital, mortality, drug) in three Italian regions was performed. We identified subjects (45 + years old) with COPD hospitalization in 2006–2009 and at least one prescription of LABA/ICS in fixed combination within 6 months post-discharge. On the basis of the index prescription date, we classified patients as with or without tiotropium. We restricted the analysis to new users and followed them for 12 months in an intention-to-treat approach to measure COPD-E rates, either severe (hospitalization) and/or moderate (concomitant oral corticosteroids and antibiotics). We compared the risk of first COPD-E between patients with or without tiotropium, using Cox proportional hazard models (HR, 95% CI) adjusting for sex, age, residency, comorbidities, prior drug use. In sensitivity analyses, we used an as-treated approach and applied propensity score adjustment.

Results: We identified 5,657 patients taking LABA/ICS. Among those, 31.8% received triple therapy. The overall COPD-E rate was 26.3%. Previous COPD hospitalization, respiratory failure, use of systemic corticosteroids or xanthines were associated with high probability of COPD-E. The adjusted HR in patients with tiotropium vs. patients without was 1.02 (0.89–1.17). Similar HRs were observed when severe and moderate COPD-E were considered separately, 1.07 (0.90–1.27) and 0.94 (0.77–1.15) respectively. The as-treated analysis and propensity score adjustment produced consistent results, e.g. overall COPD-E HRs: 0.97 (0.73–1.29) and 1.05 (0.92–1.20), respectively.

Conclusions: Use of tiotropium in combination with LABA/ICS was not significantly associated with a reduction in the risk of COPD-E vs. LABA/ICS alone.

64. Feasibility of Ruling out Small Treatment-Associated Increase in Asthma Mortality Risk

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Background: Asthma mortality is rare. Published studies evaluating possible increased mortality risk with use of long-acting beta-agonists (LABA) in fixed-dose combination with inhaled corticosteroids (ICS) had limited sizes. Ongoing safety trials are evaluating a composite endpoint including asthma hospitalizations.

Objectives: Using a new user design, assess feasibility of establishing with sufficient precision an asthma mortality ratio (MR) of ≤ 1.40 for LABA+ICS relative to selected non-LABA maintenance therapy.

Methods: We established a distributed network to assemble a cohort of asthma patients aged 4–100 years from 10 US health plans–total > 70 million enrollees between 2001–2010. We identified a persistent asthma cohort (PAC): ≥ 4 asthma medication dispensings and ≥ 1 asthma diagnosis in 12 months. New use was the first exposure of interest after the cohort entry and without any prior exposure of interest. Exposures of interest included Advair (salmeterol+fluticasone propionate), ICS monotherapy, and leukotriene receptor antagonist+ICS. To identify asthma deaths, data partners linked PAC data to the National Death Index. From person-years (PY) of exposure and asthma mortality rate in the PAC over all follow-up regardless of exposure, we derived the MR threshold that could be ruled out with probability of 0.80 based on the upper 95% confidence limit if the true MR = 1.00.

Results: Of 5,881,438 patients with an asthma diagnosis from 10 data partners 17% fulfilled the PAC definition (2,399,564 PY). The most common exclusion (65%) was having < 4 asthma medication dispensings in 12 months. There were 11,531 PY of Advair new use and 17,231 PY of comparator exposures new use. Across the PAC, there were 278 asthma deaths; overall asthma mortality rate was 1.16 per 10,000 PY. If the true asthma MR = 1.00, the study could rule out an MR > 29.

Conclusions: Even with 10 data sources, use of guideline definitions for persistent asthma and strict

exposure definitions yielded a study size too small to address the objective. We are reconsidering PAC inclusion criteria, exposure definitions, and MR threshold as part of an ongoing feasibility assessment.

65. Profile of Asthma Exacerbation Patients in a US Administrative Claims Database

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Background: Having a good understanding of the characteristics of patients with exacerbation events can facilitate to minimize the risk of asthma exacerbation.

Objectives: To evaluate patient characteristics associated with asthma exacerbations in different age groups by using the HealthCore Integrated Research Environment (HIRE).

Methods: This is a retrospective observational cohort study utilizing administrative claims data for commercially-insured individuals from HIRE. The eligibility criteria were: ≥ 1 asthma exacerbation (index-event), ≥ 1 asthma diagnosis and pharmacy claim for an asthma medication, ≥ 12 months pre and ≥ 12 months of post continuous health plan enrolment. Exacerbation is defined as an oral corticosteroid (OCS) prescription fill, asthma related emergency department visit or inpatient visit with a primary diagnosis of asthma.

Results: Slightly fewer than one million asthma patients were identified for each calendar month for the years 2007 through 2010 combined. On average, 6.7% of patients had an asthma exacerbation during a given month, and exacerbations were more common within patients aged 65 years and older (9.9%). Amongst patients aged 6 years and older with an asthma exacerbation, there were 94,883 patients who met all eligibility criteria. The mean age for this cohort was 41.6 years and 62.4% were female. Other comorbid respiratory conditions were common, including allergic rhinitis (37.1%), sinusitis (29.9%), and COPD (15.9%). The index exacerbation was mostly a fill for OCS (84%) while asthma related emergency room visits made up most of the remaining exacerbations (15%), with very few patients having an asthma related inpatient hospitalization as the index event (0.9%). Nearly half of all patients (47.8%) had a subsequent exacerbation. The subgroups of patients with and without a prior COPD diagnosis were analyzed separately, and it was found that healthcare utilization was higher within the patients having a prior COPD diagnosis in both the pre- and post-index periods.

Conclusions: The results of this study provide real world data regarding asthma patients with exacerbations, serving as the foundation for future clinical trials and observational studies.

66. Type of Stress Ulcer Prophylaxis and the Risk of Nosocomial Pneumonia in Cardiac Surgical Patients

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Background: Each year, approximately 800,000 patients undergo coronary artery bypass graft surgery (CABG) worldwide, making it one of the most commonly performed operative procedures. The most important postoperative infectious complication is pneumonia, which is associated with substantial morbidity and mortality. Proton pump inhibitors (PPIs) and histamine$_2$ receptor antagonists (H2RAs) are acid suppressing agents that are frequently administered following CABG for stress ulcer prophylaxis. Recent data suggest that there may be an increased risk of postoperative pneumonia associated with treatment with PPIs relative to H2RAs.

Objectives: To examine the relationship between the type of stress ulcer prophylaxis administered and the risk of postoperative pneumonia in CABG patients.

Methods: We conducted a retrospective cohort study of 21,214 patients undergoing CABG surgery between 2004 and 2010 from the Premier Perspective Comparative Database; 9,830 (46.3%) initiated PPIs and 11,384 (53.7%) initiated H2RAs in the immediate postoperative period. Confounding was addressed using stratification by propensity score decile and propensity score matching. An instrumental variable analysis among those patients treated at hospitals with a strong preference for either of the two drug classes was also performed. The occurrence of postoperative pneumonia was defined using appropriate diagnosis codes.

Results: Overall, 492 (5%) of the 9,830 patients receiving a PPI and 487 (4.2%) of the 11,384 patients

receiving H2RA developed postoperative pneumonia during the index hospitalization. After propensity-score adjustment, there remained an elevated risk of pneumonia associated with treatment with PPIs compared to H2RAs (relative risk 1.19, 95% confidence interval (CI), 1.03–1.38). In the instrumental variable analysis, use of PPI (compared to H2RA) was associated with an increased risk of pneumonia of 8.2 cases per 1,000 patients (95% CI: 0.5–15.9).

Conclusions: Patients treated with PPIs for stress ulcer had a small increase in the risk of postoperative pneumonia compared to patients treated with H2RA; this risk remained after accounting for confounding using multiple analytic approaches.

67. TNF Inhibitors Exposure and Cancer? Data of Case/Non Case Study in French PharmacoVigilance Database

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Background: Tumor Necrosis Factor (TNF) inhibitors can increase lymphoma risk in patients who have been exposed to these drugs. However, studies considering the increase of solid cancer risk remain not relevant.

Objectives: The aim of the study was to investigate the association between anti-TNF exposure and reporting of 'cancer' using the French PharmacoVigilance Data-Base (FPVDB).

Methods: All cases with a criteria of 'seriousness' registered in FPVDB were analysed retrospectively from January 2000 to October 2010. The case/non-case method was used to measure the association between cancer and exposure to anti-TNF vs. classic immunosuppressant drugs. Cases were defined as reports corresponding to the ADR of interest (i.e. cancer) and non-cases were all reports of ADRs other than that being studied. Exposure was considered as the presence in a report of the drug interest (e.g. anti-TNF). We applied the case/non-case method, comparing cases of cancer to other 'serious' cases of ADRs reported in the database regarding the exposure to anti-TNF in comparison to other immunosuppressants drugs. The method allowed us to calculate ADR Reporting Odds Ratio (ROR) or adjusted ROR (aROR) on risk factors of cancer and its confidence interval.

Results: During this period, 3,315 cases were registered in the FPVD corresponding to 2035 cases for exposure to at least one anti-TNF and 1,280 cases for other immunosuppressant drugs. Sex ratio was 0.55 and mean age was 52 years old. Indications were rheumatoid arthritis (53%), Crohn's disease (17%), ankylosing spondylitis (11%) or psoriasis (7%). A total of 368 reports of cancer was identified for both with 305 cases for the anti-TNF group (83%). Eighty-eight lymphomas (70 in the anti-TNF group), and 57 skin cancers (49 in the anti-TNF group) were reported. The rate of cancer reports was significantly higher in the anti-TNF group (OR = 3.41 [2.57–4.51], p < 0.0001).

Conclusions: The rate of cancer reports was significantly higher in patients exposed to TNF inhibitors in comparison to patients treated with other immunosuppressant drugs. Haematological and skin cancers were the most frequent types of cancer reported.

68. Designing a Fit-for-Purpose Data Extraction Tool for Australian General Practice Electronic Health Records

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Background: NPS MedicineWise is implementing a national Australian quality improvement program based on the collection of clinical data from primary care doctors and their electronic health records (EHRs). A number of data extraction tools (DETs) are available and currently used in other programs, but have not been assessed for fitness of purpose.

Objectives: To assess the completeness and accuracy of data extracted, and whether available DETs are fit for purpose for this program.

Methods: In an *in vitro* experiment, we entered eight comprehensive clinical patient scenarios into three commonly used EHR clinical systems in the NPS test environment. The scenarios covered a range of prescribing behaviour. Three vendors were invited to install their DET in the test systems and extract all clinical information. Data extracts from each DET and each clinical system were analysed to assess completeness, accuracy and the fidelity of the extraction process.

Results: The same data were extracted in different formats by different DETs, with further differences for each clinical system. The specificity of the extracted

data varied; demographic data were extracted with greater fidelity than clinical data. One vendor did not extract the actual information entered into the clinical system but reported items as 'present/non present'. Two of the 3 DETs also 'transformed' the extracted data into reports using an undisclosed proprietary process.

Conclusions: Data extraction from primary care clinical systems is complicated by data models that differ between the DET and clinical systems. To increase fidelity in the extraction process, it is essential to specify the intended uses for the data, and to ensure any transformation or processing is transparent and can be validated for completeness and accuracy.

69. Evaluating an ICD-10 Algorithm To Detect ONJ among Cancer Patients in Denmark

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Background: Osteonecrosis of the jaw (ONJ) has been reported in patients treated with potent antiresorptive therapies. For a pharmacovigilance (PV) study of ONJ incidence among cancer patients treated with denosumab or zoledronic acid, we evaluated an ICD-10-based algorithm to detect ONJ. There is no specific ICD-10 code for ONJ.

Objectives: We had 3 objectives: (1) to evaluate the positive predictive value (PPV) of the algorithm based on expert adjudication; (2) to evaluate, for a sample of known ONJ cases, the sensitivity of the algorithm; (3) to determine the completeness of information on ONJ stage for confirmed cases.

Methods: For objective 1, we identified patients from 3 Danish hospital-based Departments of Oral and Maxillofacial Surgery (DOMS) (2005–2010), who had a cancer diagnosis followed by an algorithmic ICD-10 code supplied by surgeons specializing in ONJ at DOMS (K04.6, K10.2, K10.3, M87.0-M87.3, M87.8-M87.9). Records for these patients were adjudicated. PPV was calculated as the proportion of patients adjudicated positive. For objective 2, we identified confirmed ONJ cases from 2 DOMS (2005–2010) and evaluated the proportion (viz. sensitivity) who had at least one ICD-10 code from our algorithm. For objec-

tive 3, we abstracted information on stage, when available, for the positively adjudicated cases from objective 1.

Results: One-hundred and ninety three potential ONJ cases were identified by the algorithm. The PPV was 43% (95% confidence Interval (CI) 36%, 50%). PPVs were similar by sex, department, and year. Among the 101 confirmed ONJ cases from 2 DOMS, sensitivity was 73% (95% CI: 64%, 81%) and was consistent by department and year. All adjudicated positive cases had documentation of stage: stage at diagnosis was 66% stage 1, 29% stage 2, and 5% stage 3.

Conclusions: The PPV of 45%, though better than earlier reports, is too low for case identification in PV studies, making adjudication necessary. Our ICD-10 algorithm failed to identify approximately 25% of known ONJ cases and would underestimate ONJ incidence. Additional case finding measures, coupled with adjudication, are necessary to estimate ONJ incidence accurately.

70. Pharmacosurveillance Using Real-Time Electronic Medical Records

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Background: Current pharmacosurveillance methods are plagued by high rates of underreporting and are too slow to adequately monitor drug safety and effectiveness. Recent advances in electronic health records (EHR) enable real-time collection of the reasons for both drug prescriptions (treatment indications) and drug discontinuation, creating an opportunity to evaluate the safety and effectiveness of drugs.

Objectives: To evaluate rates of drug discontinuations and dose changes and the reasons for these changes from validated EHR data in a primary care.

Methods: We extracted data from 2005 to 2009 from a Canadian EHR system (MOXXI). In this system, physicians record prescription and treatment indications for each patient, as well as any subsequent drug discontinuation or dose change and the reason for the change. For all prescribed drugs, we calculated the proportion of drug discontinuations and dose changes from all electronic prescriptions. We further identified the reasons for these changes.

Results: There were 133,162 electronic prescriptions written by 119 physicians, among which 10,230 (7.8%) were discontinued (3.9%) or underwent a dose change (3.7%). The rate of dose change was highest for central nervous system drugs (11.2%), hormones and synthetics (10.3%), and cardiovascular drugs (9.2%), while anti-infectives had the lowest rate (2.2%). Reasons for drug discontinuations include ineffectiveness (20.4%) and adverse drug reactions (ADR) (20.7%). Increases in dosage accounted for 65.8% of dose changes, with the major reasons being ineffectiveness at the current dose (12.6%) and dose optimization to achieve a desired outcome (53.2%). Pregabalin (22.9%), citalopram (19%), and venlafaxine (17.4%) had the highest rates of drug discontinuation and dose changes. In treatment of depression, trazodone and citalopram had higher discontinuation rate due to ADRs and ineffectiveness, respectively.

Conclusions: Our results suggest primary care practice data collected routinely by EHRs could be used for prospective pharmacosurveillance. Ineffectiveness and ADRs were the two most frequent reasons for discontinuing a drug. Drug doses were increased more often due to lack of or suboptimal effect.

71. Active Surveillance of Adverse Events Following Immunization with Meningococcal A Conjugate Vaccine MenAfriVac™ in Mali

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Background: New vaccines are being developed exclusively for use in low-income countries, making post-licensure safety surveillance infrastructure in these settings a priority. We conducted a post-marketing active vaccine safety surveillance study in Mali using novel methods that have been only used in industrialized countries previously.

Objectives: To assess the safety of the meningococcal A conjugate vaccine (MenAfriVac™) in Mali.

Methods: We abstracted routine data from 40 government clinics in southern Mali with a catchment population of approximately 400,000 individuals in the indicated age range (1–29 years). Exposure to MenAfriVac™ was based on self-reporting. Nineteen pre-speci-fied adverse events of interest and 18 syndromic categories were chosen with risk and control windows set *a priori*. We conducted both population and individual analyses and calculated rates of adverse events using the conditional exact test, the vaccine cohort risk interval method, and self-controlled case series method.

Results: Many pre-specified adverse events were infrequently reported. The data suggest an increased rate of fever within pre-defined risk windows after vaccination for eight of nine analyses. The incidence rate ratios ranged between 0.9 (95% CI: 0.8–1.0) to 1.8 (95% CI: 1.6–2.1). If a true association, MenAfriVac™ could contribute around 800 episodes of clinically relevant fever per 100,000 doses, depending on the season and background incidence of fever. The vaccination campaign and follow up occurred during the decline of the malaria season, and some associations may reflect declining rates of fever due to malaria in control windows used in self-controlled analyses. Rates of other outcomes did not suggest an association with MenAfriVac™ across campaigns and methods.

Conclusions: Our results are consistent with other studies indicating a strong safety profile for MenAfriVac™. Active pharmacovigilance is needed in developing countries as new products are used exclusively in these markets. Our study provides useful data for MenAfriVac™ safety and serves as a model for future active vaccine safety monitoring in low-income countries.

72. Comparison of Disproportionality Measures in EudraVigilance

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Background: Different statistical methods based on disproportionality are used to identify tentative safety signals in spontaneous reporting databases. Whether some methods have superior performance and whether performance varies with size of database or heterogeneity of products is unknown. These are questions addressed by the IMI PROTECT consortium, a public/private partnership. Here we present a comparison of signal detection methods within the EudraVigilance database.

Objectives: The aim was to consider the effectiveness of the methods in relation to detection of known ADRs and compare this with the total work load. Time to detection was also investigated as earlier detection is vital to effective pharmacovigilance.

Methods: The reference standard chosen was ADRs listed in the SPCs or core data sheets. A set of 232 drug substances were chosen and known ADRs were mapped to MedDRA PTs. The statistical methods used were PRR, ROR, EBGM, IC and the 'urn' method. The rules used to define signals, based on the statistics, were mainly those in current use by regulatory or industry partners. In total 14 algorithms were tested. The main outcome measures were sensitivity, precision (positive predictive value) and time to detection. These were calculated on the entire dataset and also as they evolved over time. The impact on performance of qualitative assessment used in combination with quantitative methods was not assessed.

Results: Very clear differences were seen among the 14 algorithms. However, these owed more to the rule-sets than to the statistical methods used. The expected trade-off between sensitivity and precision was observed. When results were plotted against time on the market a steep fall in precision was seen. The best precision at 1 year was 0.6 but this fell to 0.28 by 5 years and 0.16 at 10 years.

Conclusions: Choice of disproportionality measure seems to have quite little effect on signal detection but the rules used to define a signal do make a difference. The decline in precision over the life-time of a drug may suggest that different rules for old and new products are appropriate. This research received support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

73. Benefit-Risk Assessment, Communication and Evaluation (BRACE): Embrace the Challenges and Opportunities (Submitted on Behalf of the BRACE SIG)

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Background: Understanding methods used to assess and how to communicate about benefit-risk is impor-tant for health care professionals and patients when making treatment decisions. In recent years significant progress, via multiple initiatives, has been made toward more transparent, rational, and defensible decision making and communication that benefits all stakeholders. The Institute of Medicine recommended implementation of benefit-risk assessment and management plan throughout the life cycle of a drug. Following International Conference on Harmonisation, European Medicines Agency (EMA) made similar recommendations for periodic benefit risk evaluation reporting. The goal of the ongoing European Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) initiative is to strengthen benefit-risk monitoring by developing innovative methods.

Objectives: To explore recent developments, methodological challenges and opportunities in integrating benefit-risk assessment and communication across the lifecycle of a drug. To share best practices in implementing BRACE for informed decision making by health care professionals, patients and other stakeholders.

Description: The symposium will consist of five talks providing perspectives from academia industry and regulatory agencies. *Speakers:* Benefit-Risk Frameworks: Global Approaches and Preferences. Rebecca Noel, Eli Lilly (15 min). Experience in Using the BRAT (Benefit Risk Action Team) Framework: Example from PROTECT. Paola Primatesta, Novartis (15 min). FDA Perspective on Postmarketing Benefit-Risk Assessment. Gerald Dal Pan, FDA (15 min). Best Practices in Presenting Risk Information to Healthcare Professionals and Patients. Meredith Smith, AbbVie; Michael Wolf, Northwestern University (15 min). Talking Benefit-Risk: Lessons Learnt Globally – Plan Strategies Locally! Priya Bahri, EMA (15 min). *Discussion*: (15 mins): Moderated open discussion. *Moderators:* Debashish Dey, Eli Lilly; Elaine Morrato, University of Colorado.

74. Design and Methodological Considerations in Conducting Relative Effectiveness Studies of Newly Launched Products

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Background: Regulatory agencies, policymakers, and providers are increasingly seeking information about the relative effectiveness (RE) of new treatment

options to decide upon the value of these treatments. Appropriate design and methodology must be applied to derive valid inferences from RE studies evaluating the risks and benefits of newly marketed products.

Objectives: To review the concept of RE and the current European RE legislation as well as to describe design and methodological considerations when conducting RE studies of newly launched medications, using recent or ongoing post-marketing RE studies as case examples.

Description: We will have a series of presentations followed by a 30-min panel discussion (moderated by JJJ and MR). The symposium will provide an overview of the concept of RE and RE legislation and will cover design and methodological considerations when conducting RE studies. We will illustrate design and methodological issues drawing from our experience with large prospective and retrospective RE studies of newly launched medications for chronic disease. The session will feature the following topics and presenters (shown by initials):

(1) Overview of RE and RE legislation: An overview of what RE is, how it differ from comparative effectiveness, the new European legislative requirements to carry out RE studies of newly marketed therapies, and the concept of risk sharing. (XK)

(2) Design issues in conducting RE studies of newly launched therapies: Discussion of considerations in selecting the appropriate study design, data sources, and timelines as shaped by technical aspects including but not limited to timing of launch, projected market penetration, and drug reimbursement status (TVS).

(3) Methodological issues in conducting RE of newly launched therapies: Discussion of channeling bias, confounding by severity, depletion of susceptibles, heterogeneity of treatment effects, and necessity of determining time to maximum therapeutic effect in real-world patients. (RBL).

intrinsic factors such as geographic ancestry, age, gender, organ dysfunction (e.g. liver or renal failure), and extrinsic factors like environment, diet, drug-drug interactions and cultural differences, e.g. local medical practice, can contribute to the inter-ethnic differences in drug responses observed. In addition, the profile of some diseases can vary across ethnic groups, reflecting differences in the frequency of genetic, physiological and pathological factors across populations. Collectively these ethnic factors may influence disease epidemiology. Ethnic factors can influence drug pharmacokinetics and pharmacodynamics, with consequences for drug efficacy and safety. Examples include rosuvastatin, recommended at a lower starting dose for patients of Asian ancestry relative to other populations, and carbamazepine where there is an association between HLA-B*1502, a genetic marker found almost exclusively in people of Asian ancestry, and SJS/TEN. This symposium is sponsored by the Molecular Epidemiology, Biomarker and Pharmacogenomics SIG.

Objectives: To provide an overview of the relative contribution of intrinsic and extrinsic factors and their influence on inter-ethnic differences in (1) disease characteristics and (2) drug response and (3) how these differences influence drug development and clinical practice in different geographic regions.

Description: Dr. Pulford will provide a 15 min introduction to ethnicity definitions in clinical research and intrinsic and extrinsic ethnic factors. Dr. Gross will review key examples in our understanding of medicine response in populations from different geographic regions and drug development perspectives. Dr. Liu will consider biological diversity in an oncology setting, considering manifestation of disease and subsequent impact on response to therapy. Dr. Carleton will conclude the session by considering the impact of genetic variability on drug safety across populations of differing geographic ancestry. Each speaker will present for 20 min with 5 min reserved for discussion.

75. Drug Response in Diverse Populations: Role of Ethnicity

David J Pulford,[1] Geoffrey Liu,[2] Annette S Gross,[1] Bruce Carleton.[4] [1]*Quantitative Sciences, Genetics, GlaxoSmithKline, Stevenage, Herts, United Kingdom;* [2]*Medicine, University of Toronto, Toronto, ON, Canada;* [3]*Quantitative Sciences, Ethnopharmacology, GlaxoSmithKline, Ermington, NSW, Australia;* [4]*Pharmacy, University of British Columbia, Vancouver, BC, Canada.*

Background: Differences in response to medicines have been reported across ethnic groups. A wide variety of

76. Harmonizing Methods and Data across Multiple Databases: Beautiful Music or Cacophony?

Xiaofeng Zhou,[1] Miriam Sturkenboom,[2] Kevin Haynes,[3] Patrick B Ryan,[4] Alison D Bourke,[5] Andrew Bate.[1] [1]*Epidemiology, Pfizer Inc, New York, NY, United States;* [2]*Erasmus University Medical Center, Rotterdam, The Netherlands;* [3]*Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, United States;* [4]*Epidemiology, Janssen Research and Development, Titusville, NJ, United States;* [5]*CSD MR UK, CSD Medical Research, London, United Kingdom.*

Background: There is increasing interest in using multiple observational databases to explore the safety pro-

file of medical products. However, it is challenging to perform analyses across these heterogeneous data sources. Exploring data harmonization methods is important to enable a consistent and efficient analysis across multiple databases.

Objectives: To share practical learning experience of applying data harmonization methods, including common data models (CDMs), in industry and academic research settings for phamacoepidemiological studies and active safety surveillance. Researchers and analysts considering applying methods for data harmonization would benefit by attending this workshop.

Description: This workshop will initially set out why data harmonization is needed. Then experienced academic and industry research groups will describe specific projects and their lessons learnt from implementing data harmonization methods. The co-chairs will facilitate an interactive discussion with the audience exploring the feasibility and challenges in such work. Speakers: Erasmus, NL – Miriam Sturkenboom will discuss the EU_ADR approach to analysis of multiple disparate databases from across the EU, and contrast this with recent experience from testing the OMOP CDM. Pfizer, US – Xiaofeng Zhou will describe the practical experience implementing OMOP CDM into UK THIN database in an industry setting: Benefits of using the standardizing database structure through a CDM vs. limitations of this model. Mini-Sentinel Data Core, US – Kevin Haynes will discuss the implementation of modular program requests across a distributed data network utilizing a CDM. The discussion will highlight the steps involved from query initiation to report review. OMOP, US – Patrick Ryan will discuss progress and observations from across the OMOP community to apply a CDM to disparate international observational healthcare data; and opportunities for standard analytics to support multiple use cases. Alison Bourke/Andrew Bate will lead a Panel/Audience discussion to share experiences on data harmonization and current thinking on the use of Common Data Models.

77. Non-Database Pharmacoepidemiology in Low Resource Settings: Current Status and Unique Opportunities To Advance Methods

Veronika Wirtz,[1] Soko Setoguchi,[2] Frank May,[3] Marcela Jirón,[4] Parthasarathi Gurumurthy,[5] Hisham Aljadhey,[6] Penkarn Kanjanarat,[7] Alec Walker.[8] *[1]Center for Global Health and Development, Boston University, Boston, MA, United States; [2]Duke Clinical Research Institute, Durham, NC, United States; [3]The Drug and Therapeutics Information Service DATIS-Australia, Adelaide, SA, Australia; [4]Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile; [5]Department of Clinical Pharmacy, JSS College of Pharmacy and JSS Medical College Hospital, Mysore, India; [6]Medication Safety Research, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [7]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Suthep, Chiang Mai, Thailand; [8]WHISCON, Newton, MA, United States.*

Background: Large electronic databases have been used to study drug use, outcomes, and safety in high-income countries. However, in low and middle-income countries (LMIC), suitable databases are not available currently or in the near future and most studies in LMIC depend on manual data collection from existing records or by conducting surveys. While this is challenging, it also provides unique opportunities to advance pharmacoepidemiology methods that achieve efficient resource use. Such methods are needed even in high-income countries as database studies do not always provide sufficient information for valid pharmacoepidemiologic studies.

Objectives: The objective of the symposium is to learn about non-database pharmacoepidemiology carried out in different regions of the world and to illustrate the unique opportunities to advance the methods, including design and analysis, for efficient resource use. Practical and methodological challenges and opportunities in resource-limited settings will be the focus.

Description: The symposium will be moderated by FM and SS. The presentations/panel discussion are:

(1) Introduction: relevance of non-database pharmacoepidemiology in LMIC and high-income countries (VW, 5 min)
(2) Recent pharmacoepi studies in Chile: outcomes and non-technological interventions for health decision makers (MJ, 10 min)
(3) Overview of ongoing efforts in India: pharmacoepidemiology in a country with a billion people and increasing access to medicines (PG, 10 min)
(4) Conducting pharmacoepidemiological studies in Saudi-Arabia: new insights into medicines utilization (HA, 10 min)

(5) Non-databases and databases pharmacoepidemiology in Thailand: seamless linkage of clinical and economic data (PK, 10 min)

(6) Methods in low resource settings: designs to keep the variance low when data cost a lot (AW, 15 min)

(7) Panel discussion: the key points of the presentations will be summarized and the audience invited to participate in a discussion of the lessons learned from the experience in low resource settings and the opportunities in both settings, high and low resources, to advance the methods for nondatabase pharmacoepidemiology and optimize the use of nondatabase studies. (moderated by FM & SS, 30 min).

78. Post-Marketing Pharmacoepidemiologic (PE) Database Studies To Assess Drug Safety

Cathy Critchlow,[1] Jeffrey Curtis,[2] David Dore,[3] Kenneth Rothman,[5] Lars Pedersen,[6] Michael Sprafka,[1] Judy Staffa,[7] Miriam Sturkenboom,[4] Fei Xue.[1] [1]Center for Observational Research (CfOR), Amgen Inc., Thousand Oaks, CA, United States; [2]University of Alabama at Birmingham, Birmingham, AL, United States; [3]Brown University, Providence, RI, United States; [4]Erasmus University, Rotterdam, The Netherlands; [5]RTI International, Boston, MA, United States; [6]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [7]Division of Epidemiology II, US Food and Drug Administration (FDA), Washington, DC, United States.

Background: With enhanced authority and emphasis of regulatory agencies on ensuring drug safety, PE studies are assuming increasingly important roles in post-marketing pharmacovigilance activities. Both FDA and EMA have recently published specific guidance for PE database studies if they are to be used for regulatory decision-making.

Objectives: To discuss strategies in developing and implementing database studies to support the safety assessment of a new or mature product. This symposium will improve the understanding among scientists from industry, academia, CRO and regulatory agencies on approaches to optimize the design and conduct of PE database studies.

Description: PE studies are important sources of information on drug safety which complement clinical trials and spontaneous reports. In today's regulatory environment, PE studies are frequently mandated to support filing of a new product or assess new safety signals of a mature product. Existing databases provide cost- and time-efficient data for large populations. However, such efficiency comes at a price, such as mis-

classification, missing values, variable follow-up time, and data lag. Therefore, comprehensive evaluation of study questions and feasibility assessment are needed to decide whether, which and how existing database(s) should be used for a PE study. In this symposium, presentations from top epidemiologists and database experts from a regulatory agency, CRO, academia, and industry will facilitate a discussion on how to optimize the design and conduct of database studies in an era of ever-increasing expectations of PE studies. Proposed agenda:

(1) Updated perspective from regulatory agency (JS – 15 min)

(2) Introduction of existing databases: insurance claims, health records, registries, etc. (DD – 10 min)

(3) European databases and PASS studies (LP – 10 min)

(4) Linkage of multiple databases and supplemental data collection (JC– 10 min)

(5) Overview of methods for existing databases and the usage in PE studies (KR – 15 min)

(6) PE study development and feasibility assessment– a case example (CC – 15 min)

(7) Panel Discussion: PE database studies under updated regulatory expectations: challenges and opportunities (15 min).

79. Strategies To Enhance Validity in the Design of Comparative Effectiveness Studies

Robert J Glynn,[1] Til Sturmer,[2] Jeremy A Rassen,[1] Alan Brookhart,[2] Sebastian Schneeweiss.[1] [1]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham & Women's Hospital, Boston, MA, United States; [2]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, United States.

Background: Causal inference must be restricted to study populations where individuals at all levels of confounders and their interactions have a reasonable chance to receive any of the compared treatments (positivity assumption). Often study design has not considered this concern, and relative treatment effects may be quite sensitive to inclusion of subjects with no or few comparable subjects treated alternatively in some parts of the confounder space.

Objectives: To discuss approaches to trimming based on propensity and disease risk scores, and instrumental variable analysis (marginal patients), and implications for causal inference and generalizability of findings.

Description: While the propensity score is often viewed as a tool for analysis after population identification,

Rubin (Stat Med 2007) has emphasized its critical role in study design for causal inference. Matching on the propensity score can appropriately eliminate from a study those individuals for whom one of the compared treatments is virtually never used. Emerging evidence suggests that further trimming from the study population those individuals in the tails of the propensity score distribution can enhance validity. Til Sturmer will discuss the rationale for and practical implementation of a trimming strategy in study design. When interest focuses on simultaneous comparisons of more than two alternative treatments, Jeremy Rassen will discuss the implications of an *a priori* focus on the population with a reasonable likelihood of use of any of the several alternatives, based on a multinomial propensity score, as contrasted with separate pairwise comparisons of treatments. A disease risk score often plays a role in treatment decisions, and Robert Glynn will consider the implications of focusing a study on those individuals with disease risk scores in the range broadly shared by all treatment groups. In a planned instrumental variable analysis with a potential instrument such as calendar time, Alan Brookhart will consider the tradeoffs between a wide time interval which can enhance instrument strength vs. a narrower window which is less subject to potential bias from time-varying confounder distributions.

80. Association between Antidepressant Use and Sleep Quality: A Population-Based Study

Nikkie Aarts,[1,2] Raymond Noordam,[1,2] Lisette Zuurbier,[1] Albert Hofman,[1] Henning Tiemeier,[1] Bruno H Stricker,[1,2] Loes E Visser.[1,2,3] [1]*Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands;* [2]*Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands;* [3]*Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands.*

Background: Sleeping disorders are present in 60–80% of depressed patients. These sleeping disorders are a frequent complication of depression and its treatment. From clinical trials, it is known that antidepressant drugs can worsen sleep quality, while sleep quality should improve to endorse recovery from depressive symptoms.

Objectives: We assessed the association between the use of Tricyclic Antidepressants (TCAs) or Selective Serotonin Reuptake Inhibitors (SSRI) and sleep parameters in a population-based study of ambulatory elderly.

Methods: A total of 5,465 ambulatory elderly from the prospective Rotterdam Study were included with interview data on depression and sleep. Users of benzodiazepines and cognitively impaired participants were excluded from the analysis. Sleep parameters (total questionnaire score, total sleep time, sleep onset latency and sleep quality) were assessed with the Pittsburg Sleep Quality Index. Medication use was available on a daily basis from pharmacy records. Associations between antidepressant use and sleep parameters were analysed with linear and logistic regression analyses, with non-users as a reference group.

Results: The study population included 3,799 individuals. SSRIs use (N = 72) was significantly associated with a better overall sleep score (OR = 0.42; 95% CI: 0.22; 0.80), shorter sleep onset latency (OR = 0.35; 95% CI: 0.17; 0.74) and better self-reported sleep quality (OR = 0.21; 95% CI: 0.07; 0.60). In contrast, TCA use (N = 37) was significantly associated with a higher risk of being a poor sleeper (3.02; 95% CI: 1.50; 6.09). Results were consistent when considering the sleep parameters as continuous outcomes (where possible).

Conclusions: The results of this study indicate an association between SSRI use and a good sleep in a population-based cohort study of ambulatory elderly, while TCA users perceived themselves more as being poor sleepers.

81. Glyburide, in Contrast to Gliclazide, Has a Dose-Response Relationship with Adverse Cardiovascular Outcomes in Type 2 Diabetes Patients

Ahmed Abdelmoneim,[1] Dean Eurich,[2] Ambikaipakan Senthilselvan,[2] Weiyu Qiu,[2] Scot Simpson.[1] [1]*Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada;* [2]*School of Public Health, University of Alberta, Edmonton, AB, Canada.*

Background: Although sulfonylureas might increase the risk of adverse cardiac events in type 2 diabetes, we previously showed the risk differs between glyburide and gliclazide.

Objectives: We hypothesized there would be a dose-response relationship between glyburide and risk of acute coronary syndrome (ACS) events, but not with gliclazide.

Methods: Using administrative health records (Alberta, Canada; 1998–2008), we conducted a population-based retrospective cohort study among new users of glyburide or gliclazide as their sole sulfonylurea. Subjects were followed from their first glyburide or gliclazide exposure until reaching an ACS event, or censoring. The subject's average daily dose was calculated as: total amount of glyburide or gliclazide dispensed divided by the duration of follow up. Subjects were assigned higher- or lower-dose subgroups if their average daily dose was above or below the median daily dose, respectively. Multivariate Poisson regression

models were used to estimate the incidence rate ratio (IRR) of an ACS event associated with higher vs. lower dose subgroups; while adjusting for baseline drug use and comorbidities.

Results: Our cohort included 3,450 new glyburide users and 5,207 new gliclazide users. The overall cohort had a mean age of 75.2 (SD 6.5) years, 4,630 (53.5%) were males and their mean duration of follow up was 3.8 (SD 2.7) years. The median daily dose was 3.9 mg for glyburide and 32.0 mg for gliclazide. Within the glyburide users, patients in the higher-dose subgroup had a higher ACS event rate compared to the lower-dose subgroup (56.5 vs. 43.1 per 1,000 person-years, respectively; adjusted IRR 1.31, 95% CI: 1.13–1.52). In contrast, the ACS event rate was similar between higher- and lower-dose subgroups of gliclazide users (46.5 vs. 45.2 per 1,000 person-years, respectively; adjusted IRR 1.03; 95% CI: 0.90–1.18).

Conclusions: This study confirms a dose-response relationship between glyburide exposure and adverse cardiovascular events; however, gliclazide didn't show a similar relationship. This might be explained by higher affinity of glyburide to cardiac tissue to prevent ischemic preconditioning.

82. Calcium Channel Blockers and Esophageal Cancer: A Case-Control Analysis

Claudia Becker,[1] Susan S Jick,[2] Christoph R Meier.[1,2,3] [1]*Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland;* [2]*Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, United States;* [3]*Hospital Pharmacy, University Hospital Basel, Basel, Switzerland.*

Background: In addition to possible anti-apoptotic effects, calcium channel blockers (CCBs) potentially decrease the pressure of the lower esophageal sphincter, thus facilitating esophageal cancer development by promoting gastrointestinal reflux disease.

Objectives: To explore the association between use of CCBs and the risk of esophageal cancer.

Methods: Design: Case-control analysis. Cases had an incident diagnosis of esophageal cancer. Up to 10 controls per case were matched on age, sex, calendar time, general practice, and number of years of history in the GPRD prior to the index date. The index date was shifted back by 2 years in time both for cases and controls, to take into account the latency of the disease diagnosis. The contribution sof various potential confounders including hypertension, diabetes mellitus, and esophageal cancer comorbidities were evaluated in uni-

variate models. Final results were adjusted for BMI, smoking, alcohol use and antihypertensive drugs. Setting: The UK-based General Practice Research Database (GPRD, now Clinical Practice Research Datalink, CPRD). Exposure: Number of prescriptions for CCBs and other antihypertensive drugs before the index date. Main outcome measures: Odds ratios (ORs) with 95% confidence intervals (CI). Statistical analysis: Conditional logistic regression.

Results: Overall, long-term use (≥ 30 prescriptions) of CCBs was not associated with a increased risk of esophageal cancer (adj. OR 1.07, 95% CI: 0.95–1.22). However, stratified analyses revealed a slightly increased risk for long-term users of diltiazem (adj. OR 1.29, 95% CI: 1.00–1.67), especially in those younger than 65 years (adj. OR 1.98, 95% CI: 1.05–3.72). Additionally, reflux was diagnosed more often in diltiazem users than in other CCB users. Long-term use of other antihypertensive drugs was not associated with an increased risk of esophageal cancer.

Conclusions: In our study, we did not observe an increased risk of esophageal cancer in long-term users of CCBs (if analyzed as a group). Our findings suggest an association between diltiazem and esophageal cancer, especially in individuals below 65 years, although the risk difference between the age groups was not statistically significant.

83. Case-Control Analysis on Metformin and Cancer of the Esophagus

Claudia Becker,[1] Christoph R Meier,[1,2,3] Susan S Jick,[3] Michael Bodmer.[1,4] [1]*Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland;* [2]*Hospital Pharmacy, University Hospital Basel, Basel, Switzerland;* [3]*Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, United States;* [4]*Emergency Department, Kantonsspital Bruderholz, Basel, Switzerland.*

Background: Metformin use has been associated with decreased cancer risks, though data on esophageal cancer are scarce.

Objectives: To explore the relation between use of metformin or other anti-diabetic drugs and the risk of esophageal cancer.

Methods: Design: Case-control analysis. Cases were individuals aged 40–89 years with an incident diagnosis of esophageal cancer between 1994 and 2010. Ten controls per case were matched on age, sex, calendar time, general practice, and number of years of active history in the GPRD prior to the index date. In the

main analysis, the index date was shifted back by 2 years in time both for cases and controls (i.e., we assessed all exposure and covariate information 2 years prior to the recorded diagnosis date), to take into account the latency of the disease diagnosis. Various potential confounders including diabetes mellitus, gastro-esophageal reflux, and use of proton pump inhibitors (PPIs) were evaluated in univariate models, and the final results were adjusted for BMI and smoking. Setting: The UK-based General Practice Research Database (GPRD, now Clinical Practice Research Datalink, CPRD). Exposure: Number of prescriptions for anti-diabetics drugs before the index date. Main outcome measures: Results are presented as odds ratios (ORs) with 95% confidence intervals (CI). Statistical analysis: Conditional logistic regression.

Results: Long-term use ($\geq$ 30 prescriptions) of metformin was not associated with a materially altered risk of esophageal cancer (adj. OR 1.23, 95% CI: 0.92–1.65), nor was long-term use of sulfonylureas (adj. OR 0.93, 95% CI: 0.70–1.23), of insulin (adj. OR 0.87, 95% CI: 0.60–1.25) or of thiazolidinediones (adj. OR 0.71, 95% CI: 0.37–1.36).

Conclusions: In our population-based study, use of metformin was not associated with an altered risk of esophageal cancer.

84. Prescription Patterns of Antihypertensive Drugs in Morocco and Their Changes in Ambulatory Care

Ghizlane Berrada El Azizi,[1] Samir Ahid,[1] Saadia Abir-Khalil,[2] Fedoua Ellouali,[3] Amine El Majhad,[3] Mouna Charif D'Ouazzane,[3] Sahar Mouram,[3] Abdelali Boukili,[4] Mohammed Cherti,[3] Mohammed Hassar,[1] Yahia Cherrah.[1] [1]*Faculty of Medicine & Pharmacy, Research Team of Pharmacoepidemiology & Pharmacoeconomics, Laboratory of Pharmacology & Toxicology, University Mohammed V-Souissi, Rabat, Morocco;* [2]*Department of Cardiology, Clinic Agdal, Rabat, Morocco;* [3]*Department of Cardiology B, Hospital Ibn Sina, Rabat, Morocco;* [4]*Department of Cardiology, Military Hospital Military instruction Mohammed V, Rabat, Morocco.*

Background: Hypertension is a major risk factor for the development of cardiovascular disease. Effective and well tolerated once a day antihypertensive drugs are now available.

Objectives: The aim of the present study was to record the prescription patterns of antihypertensive drugs and their changes in ambulatory care.

Methods: This retrospective population study conducted between November 2010 and May 2012, including 431 outpatients with essential HBP followed at

cardiology centers. We have retained the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) definition and classification of hypertension.

Results: In the second visit the majority of patients received antihypertensive (79.3%). About half of them were prescribed monotherapy (52.8%) and the rest received a combination of two (33.4%), three (10.9%), four (2.3%) or five (0.6%) different antihypertensive agents. The top two prescription patterns were calcium channel blockers (CCBs) (15.3%) and angiotensin converting enzyme inhibitors (ACEIs) (12.1%) for monotherapy, and ACEIs plus diuretic (8.5%) and CCBs plus b-blockers (7.04%) for combination therapy. The number of treated patients increased significantly in the third visit (93.7%) (p < 0.0001). No statistical difference was observed between the two visits regarding prescribed drugs in monotherapy, while the rate of three drugs combination therapy increased significantly (18.5%, p = 0.0008).

Conclusions: Changes in prescription patterns of antihypertensive drugs were observed between second and third visit in an outpatient hypertension clinic, as treatment was individualized for each patient in regard to blood pressure control and tolerance. Combination treatment with two or more antihypertensive drugs was common.

85. Prevalence of Masked Hypertension in Morocco in the Antecedents of Hypertension

Ghizlane Berrada El Azizi,[1] Samir Ahid,[1] Saadia Abir-Khalil,[2] Fedoua Ellouali,[3] Amine El Majhad,[3] Mouna Charif D'Ouazzane,[3] Sahar Mouram,[3] Abdelali Boukili,[4] Mohammed Cherti,[3] Mohammed Hassar,[1] Yahia Cherrah,[1] Yahia Cherrah.[1] [1]*Research Team of Pharmacoepidemiology & Pharmacoeconomics. Laboratory of Pharmacology & Toxicology, Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco;* [2]*Department of Cardiology, Clinic Agdal, Rabat, Morocco;* [3]*Department of Cardiology B, Hospital Ibn Sina, Rabat, Morocco;* [4]*Department of Cardiology, Military Hospital Military instruction Mohammed V, Rabat, Morocco..*

Background: A positive family history of hypertension has been pointed out as risk factor for developing masked hypertension in some studies.

Objectives: To determine the prevalence of masked hypertension in normotensive relatives of hypertensive patients and analyze which factors could be predictors of this situation.

Methods: This is a prospective study in November 2010 and February 2012, We have selected normoten-

sive subjects, with at least two office blood pressure measurement < 140/90 mm Hg, that were relatives of first degree from hypertensive outpatients. All the subjects underwent an ambulatory blood pressure monitoring and anthropometric data, as blood and urine analysis, and an electrocardiogram were collected. Masked hypertension was defined with mean activity blood pressure on ABPM > 135/85 mmHg.

Results: Data from 438 subjects were collected (50.9% men) with a mean age of 47.3 ± 10.9 years. Subjects with masked hypertension had a greater body mass index (27.32 vs. 25.68 Kg/m^2),were older (44.01 vs 47.1) with a greater proportion of men (66.7% vs 44.3%), with higher office blood pressure measurements (132.5/ 80.8 vs. 120.9/76.1 mmHg), with a worse lipid profile (LDL Cholesterol 132.5 vs. 123.3 mg/dL, HDL Cholesterol 50.5 vs. 54.9 mg/dL, Triglycerides 140.6 vs. 111.2 mg/dL) and a higher proportion of office BP > 130/80 mmHg (77.8 vs. 50.4%), and all these differences were statistically significant (p < 0.05), higher Albumin to Creatinine ratio (9.06 vs. 5.98 μg/g creat), LDL Cholesterol 130.4 vs. 122.3 mg/dL, HDL Cholesterol 51.5 vs. 55.04 mg/dl, Triglycerides 138.02 vs. 107.2 mg/dL) (77.8 vs. 50.4%). After logistic regression analysis only Office BP > 130/80 mmHg remained statistically significant (HR 4.21; CI: 95% 2.32–7.63; p < 0.001) and being man (HR 3.72; IC 95% 1.17–11.85; p = 0.02) remained statistically significant.

Conclusions: In our study masked hypertension is present in almost one of three normotensive relatives of hypertensive patients, and is more frequent in men with overweight and a worse cardiovascular risk profile. The better predictor of masked hypertension is having an office BP in the high normal range.

86. The Effect of Statins on Influenza Morbidity and Mortality

Paul Brassard,[1,2] Jennifer Wu,[1] Brielan Smiechowski,[1] Sophie Dellaniello,[1] Pierre Ernst,[1,2] Samy Suissa.[1,2] [1]*Center for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada;* [2]*Medicine, McGill University, Montreal, QC, Canada.*

Background: The observed effects of statins on the cytokine-mediated inflammatory responses in cardiovascular disease may also influence, through similar mechanisms, the progression of bacterial infections, pneumonia and influenza.

Objectives: Can statins use decrease influenza related hospitalizations and all-cause mortality within 30 days of diagnoses.

Methods: *Design/Setting:* We used the United Kingdom Clinical Practice Research Database and Hospital Episodes Statistics databases. The study population included all patients aged 30 or older with a diagnosis of influenza between January 1st, 1997 and September 30th, 2010. Cohort entry was defined as a patient's first recorded diagnosis of influenza in their general practice file within the study period. *Exposure:* Statin users were defined as receiving a statin prescription in the one year period prior to their influenza and compared to patient not receiving statin in the same period. *Main Outcome Measures:* Event was defined with any hospitalization for influenza (ICD-10 code: J09-J12, J14, and J18) or death from any cause within a 30-day time window after cohort entry. *Statistical Analysis:* Each Statin users were matched to one nonuser based on their propensity scores to receive a statin. In the matched cohort, a logistic regression was used to calculate the odds ratio (OR) with 95% confidence intervals (CIs) for the effect of statin use on outcomes, adjusting for potential confounders. Stratified analyses among individuals exposed to respiratory medications and with cardiac disease were also conducted.

Results: In the adjusted model, statin users had a 36% reduced odds of influenza related hospitalization and death from any cause (OR: 0.64, 95% CI: 0.53–0.78) compared to nonusers. Statin users who were non exposed to respiratory medications or did not have cardiac disease showed a significant decreased risk of influenza related hospitalization (OR: 0.69, 95% CI: 0.53–0.89 and OR: 0.56, 95% CI: 0.37–0.85, respectively) but not those who were on respiratory medications or had cardiac disease.

Conclusions: Statins use appears to reduce the odds of influenza related hospitalizations and all-cause mortality especially among healthy users.

87. Diabetes and the Risk of Incident Gout

Saskia G Bruderer,[1,2] Michael Bodmer,[1,3] Susan S Jick,[4] Christoph R Meier.[1,2,4] [1]*Department of Pharmaceutical Sciences, Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Basel, Switzerland;* [2]*University Hospital Basel, Hospital Pharmacy, Basel, Switzerland;* [3]*Emergency Department, Kantonsspital Bruderholz, Bruderholz, Switzerland;* [4]*Boston University School of Public Health, Boston Collaborative Drug Surveillance Program, Lexington, MA, United States.*

Background: Information on the risk of gout in patients with diabetes mellitus compared to non-diabetic subjects is sparse in the medical literature. Most available data did not account for potential confounding by co-morbid conditions to diabetes mellitus.

Objectives: Compared to non-diabetic subjects, we explored the risk of incident gout in diabetic patients

with insulin use only (presumably patients with type 1 diabetes mellitus [T1DM]) and diabetic patients treated with diet only and using oral anti-diabetic drugs with or without concomitant use of insulin (presumably type 2 diabetes mellitus [T2DM]).

Methods: We conducted a case-control study using the UK-based General Practice Research Database (GPRD). We identified case patients aged between 18 and 80 years with an incident diagnosis of gout between 1995 and 2009 and matched them to one control patient on age, sex, general practice, calendar time, and years of history in the database. Conditional logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CIs). The results were adjusted for the potential confounders body mass index (BMI), smoking, alcohol consumption, ischemic heart disease, congestive heart failure, hypertension, and chronic kidney disease in the final multivariable model.

Results: The study encompassed 91,530 cases with a first-time diagnosis of gout and the same number of gout free controls. Patients with T1DM and T2DM had a significantly decreased risk of developing incident gout [adj. OR 0.50 (0.44–0.57) and adj. OR 0.72 (0.69–0.75)], respectively. Compared to an A1C level of < 7%, increasing A1C values (7.0–7.9%, 8.0–8.9%, > 9% were associated with a decreased relative risk estimates of incident gout [adj. OR 0.71 (95% CI: 0.65–0.78), 0.57 (95% CI: 0.50–0.65), and 0.47 (95% CI: 0.41–0.54)], respectively. Results of analyses restricted to diabetic patients only to assess the influence of diabetes duration and anti-diabetic treatments on the risk of incident gout will be presented at the conference.

Conclusions: The data from this large observational study suggests that a diagnosis of diabetes mellitus is associated with a decreased risk of incident gout.

88. Association of Antibiotic Use with Colorectal Cancer Risk in Type 2 Diabetes Mellitus

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Background: Previous studies suggested a possible link between the composition of human gut microbiota and colorectal cancer.

Objectives: We hypothesized that systemic antibiotic use might disrupt homeostasis within intestinal microbiota and increase colorectal cancer risk.

Methods: Design and setting: Nested case control study. A total of 592,515 patients with type 2 diabetes mellitus, aged 30 years and above, and without a history of cancer, were identified from the Taiwan National Health Insurance claims database in 2000. As of 31 December 2007, patients with incident colon cancer and rectal cancer were included as cases and up to four age- and sex-matched controls were selected by risk-set sampling. Exposures: Anti-aerobics and anti-anaerobic antibiotics use. Main outcome measures: Occurrence of colon cancer and rectal cancer, ascertained by linkage through National Cancer Registry. Statistical analysis: Logistic regression models were applied to estimate the odds ratio (OR) and the 95% confidence interval (95% CI) between antibiotic use and colorectal cancer incidence.

Results: A total of 3,593 incident colon cancer cases, 1979 rectal cancer cases, and 22,288 diabetic controls were included. A significantly increased colon and rectal cancer risk was found among participants using anti-anaerobic agents, with OR values of 2.31 (95% CI: 2.12–2.52) and 1.69 (1.50–1.90), respectively, but not for those using anti-aerobic agents. A significantly increased risk was found for imidazoles, with OR of 10.2 (8.79–11.9) for colon cancer and 7.99 (6.41–9.96) for rectal cancer, while cephamycin, carbapenems, piperacillin/tazobactam, and lincosamides were associated with a modest risk.

Conclusions: The results suggested a positive association between anti-anaerobic antibiotic use and colorectal cancer incidence in a large diabetic cohort. Anti-anaerobic antibiotics might lead to the disruption of microbiota homeostasis and should not be prescribed unrestrictedly and without clinical indications.

89. Risk of Tuberculosis and Influenza Associated with Use of Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: The safety information on respiratory infections other than pneumonia for inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) is limited.

Objectives: We aimed to examine the risk of tuberculosis and influenza for ICS in COPD patients.

Methods: Through systematic database searching, we identified randomized controlled trials of ICS that had a duration of at least six months. Two investigators independently performed the study selection, data extraction, and assessment of the risk of bias. Pooled Peto odds ratios (ORs) were computed to estimate the risk of tuberculosis and influenza for ICS treatment vs. non-ICS treatment.

Results: We identified 25 eligible trials for the qualitative synthesis. Among trials that reported at least one tuberculosis event, a larger number involved the high-dose ICS treatment arm for a longer period compared to trials that reported zero events. In addition, trials with at least one event enrolled more patients of male gender, more patients with severe airflow limitation, and more patients from Asia/Africa. Based on trials with at least one event for tuberculosis (five trials with 10,203 subjects) or influenza (eight trials with 13 196 subjects), ICS treatment was associated with a significantly increased risk of tuberculosis (Peto OR 2.29; 95% CI: 1.04 to 5.03) and a marginally increased risk of influenza (Peto OR 1.31; 95% CI: 0.99–1.73) compared to non-ICS treatment.

Conclusions: The results of our study raise safety concerns about respiratory infections associated with the use of ICS which deserve special attention and further investigation.

90. The 3.5-Year Mortality Impact of Drugs in Secondary Prevention of Myocardial Infarction in Real-Life (Interim Analysis of the EOLE Cohort)

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Background: Few studies have assessed the real-life impact of secondary prevention drugs on all-cause mortality post-myocardial infarction (MI), especially in countries with low incidence of MI.

Objectives: To assess the real-life all-cause mortality impact of drugs reimbursed for MI secondary prevention in France: Acetylsalicylic acid (ASA), anti-platelet agents (APA), beta-blockers (ß-), Angiotensin Converting Enzyme Inhibitors (ACEI), statins, and omega-3 supplementation (Om3).

Methods: Cohort study of patients with recent (≤ 3 months) acute MI included by hospital and non-hospital cardiologists, with 6-year follow-up. Vital status was obtained from the National death registry, and failing that by patient/relatives/physicians investigation. Drug exposure was defined using both physician and patient reports at inclusion. Cox proportional hazard model was used to estimate for each drug, mortality hazard ratio (HR) of exposed vs. non exposed patients, adjusted for gender, age, cardiovascular risk factors, other MI prevention drugs and propensity score to be exposed at inclusion. Results presented concern an interim analysis after 3.5-year of follow-up.

Results: Between May 2006 and June 2009, 596 physicians included 5,538 patients: mean age 62.1 years, 77.6% male, 9.6% current smokers, 14.5% diabetic, 44.6% hypercholesterolemic, 43.6% hypertensive, 8.2% with LVEF < 40%. At inclusion, 97.5% were exposed to ASA, 91% to APA, 89.7% to ß-, 71.1% to

ACEI, 92% to statins, and 15.7% to Om3. The 3.5-year mortality was 7.8% (95% CI: [7.1–8.5%]) with an incidence rate of 23.2 per 1,000 patient-years. Adjusted HR were: 0.98 [0.60–1.61] for ASA, 0.86 [0.60–1.24] for APA, 0.84 [0.63–1.11] for ß-, 0.80 [0.61–1.03] for ACEI, 0.67 [0.45–1.00] for statins, and 0.82 [0.58–1.16] for Om3.

Conclusions: The 3.5 year interim all-cause real-life death reduction point estimates were close to those of large randomized controlled trials, except for ASA, for which almost all patients were exposed. The study's statistical power will be sufficient to confirm or not these trends at the final 6-year analysis.

91. Drug-Associated Acute Liver Failure Leading to Registration for Transplantation in France from the SALT Study, 2005–2007

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Background: Drug-associated acute liver injury is a common concern in drug safety, especially acute liver failure leading to registration for transplantation (ALFT).

Objectives: SALT was designed to explore drug-associated ALFT.

Methods: French ALFT cases exposed to drugs within 30 days of first symptoms were compared to drug utilisation data from the 1/97 sample of the French National Healthcare database (EGB). Event rates were computed per billion DDD dispensed over the period and per million users, compared with the average number of DDD dispensed per user over 3 years. Chronic liver disease, documented clinical causes and drug overdoses were excluded.

Results: The 65 cases of ALFT identified in France (2005–2007) had been exposed to 235 different drugs. The drug classes most found were paracetamol (47 cases), anxiolytics 13, antiepileptic drugs 11, NSAIDs 10, H1 antihistamines 8, proton pump inhibitors 7, antidepressants 6. Other classes were associated with 5 or fewer cases. Rates ranged from 1.9 (bromazepam) to 372 cases per billion DDD (prazepam). Per user rates ranged from 0.19 (pantoprazole) to 56 per million (phenytoin). For NSAIDs, PPI, and some H1 antagonists, event rates decreased with increasing average number of DDD dispensed. In these classes the event rate per user was below 1 per million users. For other

drug classes such as antiepileptic drugs, the event rates per billion DDD were similar, and rates per million users increased with increasing average number of DDD dispensed per subject. Drugs fell into three main categories: event rates below one per million users (NSAIDs, PPI, most antihistamines, some benzodiazepines), from 1 to 10 per million users (paracetamol, benzodiazepines, antiepileptic drugs), and above 10 per million users. Antidepressants were around one case per million users. Two antiepileptic drugs had event rates at or above 10 per million users. Overall, drugs with longer duration of use tended to have higher per user event rates.

Conclusions: These results are still tentative because of the small number of cases for individual drugs. SALT should be extended.

93. Withdrawn by Author

94. Withdrawn by Author

95. Breast Cancer and Postmenopausal Hormone Therapy in a Japanese Cohort of Women: An Interim Analysis of Japan Nurses' Health Study

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Background: The incidence rate of breast cancer shows a bell-shaped pattern with a peak at 45–49 years in Japan, unlike in Western countries whose incidence increases with age at midlife. Therefore, the association between the incidence of breast cancer and menopause including postmenopausal hormone therapy (HT) in Japan may differ from it in Western countries.

Objectives: To assess breast cancer risk of menopause and HT use in a prospective cohort study.

Methods: [Design] A prospective cohort study, Japan Nurses' Health Study. [Setting] A baseline questionnaire survey was conducted in 2001–2007 among Japanese female nurses. The questionnaire includes hormonal drug use identified by a list of drug-pictures as well as other questions of life style and history of diseases. We analyzed the data of a 4-year followup

period for 9,549 women from 35 to 59 years old, without history of breast cancer at the baseline survey. [Exposures] Menopause and HT use were determined by biennial surveys. Current user indicates women who used HT during the followup period, and ex-user indicates women who had stopped using HT before the baseline survey. [Main outcome] Main outcome was incidence of clinically diagnosed breast cancer during the 4-year followup. [Statistical analysis] Logistic regression models were used to estimate odds ratios (ORs).

Results: A total of 4,073 women were postmenopausal at the end of followup period. Out of these postmenopausal women, 439 women (11%) were current users and 120 women (3%) were ex-users. Median duration of HT use was 2 years. We identified 77 breast cancer cases during the followup period. The 44 cases (57%) were premenopausal women. Age-adjusted ORs (95% CI) of breast cancer among postmenopausal HT non-users, current users, and ex-users were 0.60 (0.31–1.2), 0.70 (0.22–2.2), and 0.61 (0.08–4.9), respectively, compared with premenopausal women. Multivariable-adjusted analyses for life style factors gave the same results.

Conclusions: The breast cancer risk was likely to reduce after menopause, irrespective of HT use, suggesting that short duration of HT use does not increase postmenopausal breast cancer risk in Japanese women.

96. Trends in the Prevalence and Incidence of ADHD-Drugs among Children, Adolescents, and Adults in Sweden 2006–2012

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Background: Metylphenidate is the only stimulant licensed for the treatment of adhd among children and adolescent in Sweden. It is not licensed for initiation of treatment of adhd among adults.

Objectives: To describe the trends in prevalence and incidence of adhd-drugs among gender, different age groups, and counties in Sweden. To study persistence of adhd-treatment.

Methods: Data on individual dispensations of adhd-drugs (N06BA excluding N06BA07 modafinil) was collected from the Swedish Prescribed Drug Register for 2006–2012. Period prevalence for the seven years, as well as incidence for the last six years were calculated using a run-in period of 12 months. Individuals in the age of 5–64 in 2006 who had at least one dispensation of metylphenidate in 2006 were followed up through 2011. Persistence of treatment was defined as at least three dispensations yearly.

Results: The period prevalence for all adhd-drugs increased from 1.7 to 7.0 per 1,000 inhabitants (n = 14,862–66,171). The corresponding figure for men 0–19 years was 7.3–21.8 and for women 0–19 years 2.0–9.3. The incidence increased from 0.9 to 2.2 per 1,000 inhabitants from 2007 through 2012 (n = 8,476–20,554). The corresponding figure for men 0–19 years was 3.4–6.2 and for women 0–19 years 1.3–3.3. The incidence increased in all ages and both sexes over time. In 2011, after five years follow-up, 80% of children 5–9 years in 2006, and 30% of adults 55–64, were still treated with metylphenidate.

Conclusions: During 2006–2012 there was a marked increase both in prevalence and incidence for adhd-drugs in all age-groups and both sexes in Sweden even though none of the drugs are licensed for initiation of treatment of adults. In 2012 48% of the treated individuals were 20 years or older and represented 54% of the costs for adhd-drugs. Persistence of treatment was high among children.

97. Comparison of Validation Studies for the External Control for Confounding by Body Mass Index and Smoking When Assessing the Effects of Metformin vs. Sulfonylureas on Cancer Incidence

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Background: Unmeasured confounding by body mass index (BMI) and smoking may bias observational studies of the effects of antidiabetic drugs on cancer risk. While the effects of BMI and smoking on most cancer outcomes are well established, little is known about whether they affect the physicians' decision on the initial choice of antidiabetic drugs.

Objectives: To examine different ways to quantify the association of obesity and smoking on the initiation of metformin vs. sulfonylureas using validation data.

Methods: Two cross-sectional studies were conducted using data from the Medicare Current Beneficiary Survey (MCBS) 2006–2009 panels and from electronic medical records in Carolina Data Warehouse (CDW). MCBS participants who initiated monotherapy of metformin or sulfonylureas were eligible for the MCBS study; for the CDW study, 100 initiators of metformin

and 100 initiators of sulfonylureas were randomly selected from patients aged 65 + who visited UNC hospitals in 2006–2011. Obesity was defined as BMI ≥ 30 kg/m^2; smoking status was categorized into three groups: never smoking, ever smoking (current and past smoking), and unknown. We used logistic regression to estimate odds ratios (OR) for use of metformin vs. sulfonylureas.

Results: In preliminary analyses of MCBS 06–07 panels, 63 participants received monotherapy with metformin and 48 with sulfonylureas. Characteristics were similar between the two groups. The median age was 77 years, 71% were female, 88% were white, and the median BMI was 29.9. After adjusted for age, gender, and race, obesity was associated with slightly lower odds of receiving metformin vs. sulfonylureas (OR = 0.82; 95% CI: 0.33–2.04); as were those who ever smoked compared to never-smoked (OR = 0.58; 95% CI: 0.23–1.43).

Conclusions: Preliminary results indicate weak inverse associations of obesity and smoking with receipt of metformin vs. sulfonylureas. Based on the internal validation study, estimates were imprecise. External validation studies based on additional MCBS and CDW data will address this issue but make additional assumptions about the populations studied.

98. Comparing the Risk for Breast Cancer in Older Adults Initiating Metformin or Sulfonylureas

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Background: Preclinical studies and observational studies have shown that metformin may have anti-tumor effect on breast cancer. However, the findings from observational studies were not consistent and many of them were potentially affected by time-related bias.

Objectives: To examine the relative risk of breast cancer for metformin initiators in comparison with sulfonylureas initiators in older women.

Methods: We identified cohorts of women aged 65 + who initiated metformin or sulfonylureas, had a diabetes diagnosis, and were free of any cancer related diagnoses and any anti-diabetic drugs within 6 months before treatment initiation from 2007 through 2010 using Medicare data. The outcome was incident breast cancer, defined as ≥ 2 diagnosis codes in 60 days. All initiators were followed from the date of the first refill of the index prescription until 90 days after treatment discontinuation, any cancer diagnosis, death, or end of

study. We estimated adjusted hazard ratios using standardized mortality ratio weighted Cox proportional hazard models.

Results: The preliminary cohort (07–09 data) consisted of 25,698 and 12,826 women who initiated metformin and sulfonylureas, respectively. Metformin initiators were less likely to have a prior history of chronic obstructive pulmonary disease, chronic heart failure, or renal failure, but were more likely to receive prescription of estrogen, statins, or bisphosphonates, and to undergo mammography, than sulfonylureas initiators. The median follow-up time was 0.64 years. We observed a total of 272 breast cancer events. The crude breast cancer rates per 100,000 person-years were 802 for metformin initiators and 644 for sulfonylureas initiators. The adjusted hazard ratio for breast cancer comparing metformin to sulfonylureas was 1.24 (95% CI: 0.93–1.66), indicating no difference in the risk of breast cancer between the two cohorts.

Conclusions: The findings of this study provide no support for a beneficial effect of metformin compared with sulfonylureas on the risk for breast cancer in older women. This study is limited by the relatively short follow-up time. Thus, the possibility of beneficial effect of long-term metformin use cannot be excluded.

99. Ocular Safety of Intravitreal Injection of Age-Related Macular Degeneration (AMD) Treatments in a Prospective Observational Cohort Study in Europe

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Background: AMD is the leading cause of blindness in persons 65 years of age or older in western populations. Macugen® was the first approved intravitreal vascular endothelial growth factor (VEGF) antagonist treating AMD in Europe.

Objectives: To estimate the incidence of pertinent ocular adverse events (POAEs) related to intravitreal injection (IVT) of Macugen in Europe.

Methods: This prospective, multinational, observational study was conducted at ophthalmic clinical centers in Europe. The study population consisted of patients who received at least one IVT of Macugen. Ophthalmologists prospectively followed patients and

determined outcomes of interest as clinically appropriate. POAEs included endophthalmitis, retinal detachment, vitreous hemorrhage, retinal tear, traumatic cataract, increased intraocular pressure (IOP).

Results: Five hundred and one patients from 69 sites in 13 countries were enrolled. The mean age was 73.6 years. Most patients received Macugen monotherapy (80.4%), were white (97.4%), and never smoked (65.3%). 11.8% of patients received IVT AMD treatment in both eyes. The mean number of Macugen injections was 6.9 ± 4.2 injections. The incidence of POAEs was low overall (0 to 1.3% per injection, 0 to 6.6% per patient, and 0 to 75.9 patients per 1,000 patient-years at risk). Increased IOP was the most frequently reported POAE (1.3% per injection, 6.6% per patient, and 75.9 patients per 1,000 patient-years at risk), with a total of 48 occurrences in 33 patients. There was a positive association between the incidence of increased IOP and the number of injections received. Endophthalmitis was not reported.

Conclusions: The incidence of POAEs related to IVT in this study was low and similar to that in the literature. Macugen was safe and well tolerated among patients in the study.

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100. What Is the Delay in Insulin Therapy Initiation in Patients with T2DM Not Responding to Oral Glucose Lowering Agents?

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Background: Available data suggest that insulin therapy is initiated late in patients failing to respond adequately to oral glucose lowering agents (OGA). Determinants of this delay are unknown.

Objectives: The study aimed to assess the time to insulin initiation in T2DM patients inadequately controlled with OGA. The influence of BMI, diabetes duration and type of general practitioner practice (GPP) was also investigated.

Methods: This dynamic cohort exists of 2921 T2DM patients who entered a regional diabetes care system (DCS) in the Netherlands between 1998 and 2011, aged 40 years and over, with a follow-up of a minimum of 2 years, with at least once a HbA1c ≥ 58 mmol/mol (7.5%) whilst on OGA. The time to

insulin initiation was calculated. GPP were categorized into three types; involvement of a practice nurse (PN); involvement of a PN and insulin initiation transferred to the DCS; no PN and insulin initiation transferred to the DCS. A Cox proportional hazard model was used to determine the influence of BMI, diabetes duration, and GPP type on insulin initiation in two groups of patients. The first group were patients < 70 years, the second group were patients ≥ 70 years. Analyses were adjusted for age and gender.

Results: The median time to insulin initiation was 5.6 year (25, 75 percentiles 2.7, 9.4). The mean HbA1c level preceding initiation of insulin was 65 mmol/mol (8.1%). Diabetes duration and BMI showed a significant association with insulin initiation in patients younger than 70 years. With a diabetes duration of 0–2 year as reference category, the hazard ratios were respectively for 2–5 years 1.23 (95% CI: 1.02–1.47) and for 5–10 years 1.26 (95% CI: 1.02–1.6) at insulin initiation. The hazard ratio for BMI was 2.11 (95% CI: 1.0–1.2). GPP was not associated with insulin initiation.

Conclusions: Despite current guidelines advising insulin therapy for patients not responding adequately to OGA the mean time to insulin initiation in these patients was 5.6 years. Diabetes duration and BMI showed a weak association with the timing of insulin initiation in patients < 70 years. There was no association between GPP type and the timing of insulin therapy.

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101. Antiepileptic Drugs and Suicide: A Systematic Review

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Background: Since the release in 2008 of the Food and Drug Administration report on increased risk of suicide with antiepileptic drugs (AEDs), several reviews and studies have been published with contradictory results.

Objectives: To conduct a systematic review of randomised and non-randomised studies to assess the association between AED use and risk of suicide.

Methods: We searched five bibliographic databases combining MeSH terms and free-text words, and the registry clinicaltrials.gov, up to February-April 2012. Two authors extracted data in a standardized form and assessed the quality of the included studies. Dis-

crepancies were resolved by discussion. Ten publications and five clinical trials retrieved from clinicaltrias.gov met the inclusion criteria. We conducted a narrative synthesis.

Results: The five clinical trials reported no suicide events. We included four cohort studies, one case-crossover, two community-based case-control studies, and three systematic reviews. One cohort study was excluded post-hoc due to inconsistencies in reporting statistics. Five studies reported an effect measure for AEDs as a group: three of them reported an overall 2–3-fold increase risk of suicide; one study reported an increased risk of suicide in epilepsy patients taking AEDs with high risk of depression but no effect for AEDs with low risk of depression; and one study, conducted in bipolar disorder patients, reported a protective effect. Another study, also conducted among bipolar disorder patients, showed a 3-fold increase risk of suicide with any AED prescription. The other three studies reported results for single AEDs. An increased risk was reported for phenobarbital (1 study), valproic acid (1 study), lamotrigine (2 studies), topiramate (2 studies), and levetiracetam (1 study). Systematic reviews of randomised trials of efficacy did not report how adverse events were collected. Confounding by indication, and non-differential suicide misclassification, among other biases may have affected the results of non-randomised studies.

Conclusions: There is no clear evidence to confirm or rule out an association between the use of AEDs and suicide, due to heterogeneity at clinical and methodological level.

102. A Systematic Review of Pharmacological Pain Management in Multiple Sclerosis

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Background: Spasticity and trigeminal neuralgia are common pain syndromes in multiple sclerosis (MS). While the evidence for pharmacological treatments for these two conditions in MS has been systematically reviewed, no equivalent reviews have been published concerning other types of MS pain.

Objectives: To systematically review pain management strategies for the reduction of pain unrelated to spasticity or trigeminal neuralgia in patients with MS.

Methods: Experimental studies published after 1965 were chosen for review by searching electronic databases (e.g. PubMed, Cumulative Index to Nursing and Allied Health Literature, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, and clinicaltrials.gov) and bibliographies/citations of previously published reviews. Studies were included if all participants were adults clinically diagnosed with MS, study sample was not restricted to participants with spasticity or trigeminal neuralgia, and participant-reported pain was a primary or secondary outcome measured with a previously validated tool. Records were screened and methodological qualities of included studies were assessed independently by two reviewers under the supervision of another reviewer.

Results: A total of 15 studies were identified for review; interventions included antidepressants, anticonvulsants, NMDA receptor antagonists, cannabinoids, and opioids/opioid antagonists. Meta-analyses were not performed as no more than three trials were identified per treatment within these classes. The two trials with highest methodological quality evaluated nabiximols and dextromethorphan/quinidine (DM/Q), respectively, in participants with central neuropathic pain. Pain relief was reported compared to placebo for both interventions (nabiximols: Cohen's d: −0.61; DM/Q: Cohen's d: −0.22), and dizziness was the most commonly reported adverse event (nabiximols: 53% of treated participants; DM/Q: 26%).

Conclusions: Nabiximols and off-label use of DM/Q may be effective in reducing central neuropathic pain in MS. More clinical trials with rigorous design and reporting are needed to determine effective treatments for specific pain types presenting in people living with MS.

103. Withdrawn by Author

104. Prevalence of Potentially Inappropriate Medication Prescribing among Older US Adults Using the New 2012, Beers Criteria

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Background: Potentially inappropriate medications (PIM) increase the risk for adverse effects of drugs in

older adults. In 2012, a revised version of Beers Criteria to identify PIM has been published.

Objectives: To determine prevalence of PIM among US elderly population.

Methods: We used fee-for-service Medicare Parts A, B, and D claims data from 2007–2010 to estimate the prevalence of PIM in the US population aged ≥ 65 years. PIM was defined by Beers Criteria 2012. We estimated the point prevalence of PIM within each calendar month by dividing the number of older adults with ≥ 1 PIM by the number of older adults beneficiaries during the month. We also estimated the period prevalence of older adults with ≥ 1 PIM anytime during the calendar year. We used generalized estimating equations (GEE) to identify independent determinants of the prevalence of PIM and its 95% confidence interval (CI).

Results: We report preliminary results for a 0.2% random sample of the study population. A total of 25,469, 25,469 and 25,086 patients were included during 2007, 2008 and 2009, respectively. The mean age was 76.8 ± 7.9 years, 64.7% were women, and 84.9% were white. The point prevalence of PIM was 26.5% (CI: 26.1–27.0) in 2007, 27.3% (CI: 26.9–27.8) in 2008, and 27.2% (CI: 26.7–27.6) in 2009. In contrast, the period prevalence was 49.3%, 49.8%, 49.9% in 2007, 2008 and 2009, respectively. African Americans (30.5%) and those ≥ 85 years (31.5%) had higher point prevalence. The most common PIMs were NSAIDs (> 30 days) (13.8%) and nonbenzodiazepine hypnotics (> 90 days) (12.5%), and anticholinergic, benzodiazepines, H2-receptors antagonists and antipsychotics in patients with a diagnostic code for dementia or cognitive impairment (13.5%).

Conclusions: Approximately one in 4 older US adults received at least one PIM. The PIM prevalence using 2012 Beers Criteria was higher than it has been reported using Beers Criteria 2003. NSAIDS and psychotropic products were found to have the highest potential for inappropriate prescribing. We will compare Beers 2012 with the STOPP&START criteria to estimate PIM point prevalence.

105. Replication Study on the Risk of Liver Injury Associated with the Use of Antibiotics Using a US Database with Linkage with Hospital Data

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Background: Various studies have addressed the potential association between antibiotics use and the risk of acute liver injury (ALI). IMI-PROTECT aims to identify sources of methodological variations in pharmacoepidemiology studies using a common protocol and analysis plan across different databases in Europe. This work was carried out as part of PROTECT work package six (WP6) which aims to replicate in different conditions work package two (WP2) studies.

Objectives: To investigate the effect of use of an external database in the study of the association of antibiotics and ALI and to validate the outcome definition through in hospital data review.

Methods: This study used a case-control methodology in a large US health insurance database, InVision Datamart, offering a linkage to a repository of hospital administrative data (Premier perspective) in around 10% of patients. Patients were followed from January 2004 to December 2009. Cases and controls were compared for antibiotics use and odds ratios (ORs) were estimated using conditional logistic regression with different definitions of outcomes, exposures of interest, as well as windows of exposure.

Results: A total of 19,485,012 patients in the InVision Datamart were included as the study population, from which 5,519 cases and 27,595 matched controls were identified. Linkage with Premier was available for 194,988 participants. This study was performed in the context of the PROTECT project examining the variability of results from studies using the same protocol, applied to the same drug-adverse event pair in different databases. In order to maintain the blinding of investigators from one another's results, these results will only be disclosed during the ICPE conference.

Conclusions: Results will be discussed in light of the results achieved by WP2 on the same adverse event-drug pair. This research received support from the Innovative

Medicine Initiative Joint Undertaking through the PROTECT project.

106. Risks of Venous Thromboembolism in Women Using Progestogen-Only Contraception

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Background: Progestogen-only contraception (POC) is considered a safe alternative to combined hormonal contraception concerning risks of venous thromboembolism (VTE). Knowledge of risks associated with use of POC is, however, limited.

Objectives: To assess risks of VTE in association with POC by dose and duration of use.

Methods: Case-control study conducted in Sweden 2003–9. Cases had a first episode of VTE objectively verified. Controls were randomly selected from the population. The participants were interviewed concerning risk factors for VTE. POCs were stratified by dose of progestogen: 'very low dose' (intrauterine device with levonorgestrel), 'low and medium dose' (minipills) and 'high dose' (medroxyprogesterone acetate depot injections). Current users had reported use of POC within a 3 month period. Duration of use was stratified as: ≤ 3 months, 3–12 months and > 12 months. We computed odds ratios (ORs) with 95% confidence intervals (CIs) by means of logistic regression analyses. Adjustments were made for age, smoking, body mass index and immobilization.

Results: Current use of POC, which was reported by 145 of 948 cases and 177 of 902 controls was not associated with increased risks of VTE (OR 0.9, CI: 0.69–1.23). A decreased risk (OR 0.6, CI: 0.42–0.95) was found in 'very low dose' users and users of 'high dose' had an increased risk (OR 2.2, CI: 1.27–3.95). Duration of use had no impact on VTE risk.

Conclusions: Though POC generally was not associated with increased risks of VTE, medroxyprogesterone acetate depot injections were.

107. Clinical and Health Care Use Characteristics of Patients Newly Prescribed Allopurinol, Febuxostat and Colchicine for Gout

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Background: Gout is a common inflammatory arthritis with the increasing prevalence in the developed countries. It is well-known that many patients with gout have significant comorbidities and high health care utilization.

Objectives: To describe clinical characteristics and health care utilizations of patients with gout before and after initiating allopurinol, febuxostat, or colchicine and to evaluate the patterns of these gout treatments and other gout-related drug use over time in a large U.S. population-based cohort.

Methods: Using US insurance claims data, a population-based cohort study was conducted. Adults with a diagnosis of gout who newly started allopurinol, febuxostat or colchicine were identified. Colchicine starters could not be exposed to allopurinol or febuxostat prior to the first colchicine prescription and were required to continue colchicne for at least a month.

Results: There were 25,832 allopurinol, 4,361 febuxostat and 6,238 colchicine initiators. Mean age was 53 years and 84–87% were male. More than half of patients had hypertension and hyperlipidemia, 20% had diabetes and 10% CVD. The mean uric acid level (mg/dL) was similar at baseline ranging from 8.1 to 8.5 across the groups. Compared to allopurinol or colchicine initiators, febuxostat initiators had more comorbidities and greater health care uses both at baseline and during the follow-up. Use of gout-related drugs was most common in febuxostat and least common in colchicine initiators. The median daily dose at both start and end of treatment was 300 mg for allopurinol, 40 mg for febuxostat, and 1.2 mg for colchicine. The dosage of allopurinol was increased in 1% during the follow-up. Acute gout attacks occurred most frequently in 30 days after starting febuxostat compared to other drugs.

Conclusions: Patients who started allopurinol, febuxostat or colchicine for gout generally had hyperuricemia and multiple comorbidities. Febuxostat initiators had more comorbidities and greater use of health care resources and gout-related drugs than other groups. Overall, the dosages of allopurinol or febuxostat remained unchanged over time.

108. Aminoglycoside Ophthalmic Agents Use and Risk of Acute Renal Failure in Elderly Patients: A Case-Crossover Design

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Background: Despite aminoglycoside were well-known nephrotoxic agents, aminoglycoside ophthalmic agents were known as systemically safe agents.

Objectives: To evaluate the possibility of acute renal failure (ARF) due to aminoglycoside ophthalmic agents use in the elderly patients using a Korean Health Insurance Review and Assessment Service (HIRA) database.

Methods: We conducted a population-based case-crossover study using the HIRA database from January 1, 2005 to June 30, 2006. HIRA database contains information on prescription and diagnosis of all Korean patients. The study population consisted of elderly patients who received aminoglycoside ophthalmic agents prior to experiencing their first ARF-related hospitalization from July 1, 2005 to June 30, 2006. We excluded patients who were previously diagnosed as the any kind of renal failure before the ARF-related hospitalization. For each eligible study subject, one hazard period and four control periods were matched. Time window of hazard and control periods was defined as 1, 2, 3, or 4 weeks with 4 weeks interval between hazard and last control period. The exposure was defined as aminoglycoside marketed in Korea that is gentamicin, tobramycin, and neomycin. Conditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% CI, adjusting use of 10 concomitant nephrotoxic drug.

Results: Within the HIRA database which contained 4,159,305 elderly patients, 8,566 were experienced the first ARF-related hospitalization in study period. The eligible study subjects were 22 patients who were prescribed gentamicin ophthalmic agents prior to ARF-related hospitalization. When hazard period was defined as 3 weeks, gentamicin ophthalmic agents were prescribed to 4 (15.8%) patients in hazard period. The crude ORs and adjusted ORs were 4.22 (95% CI: 1.03–17.93) and 2.57 (95% CI: 0.22–33.74), respectively.

Conclusions: It is not statistically significance that use of gentamicin ophthalmic agents induces acute renal failure in elderly patients. However, based on the limited number of study subjects, further studies should be performed to confirm these results.

109. Relative Risk of Hip/Femur Fractures during the Initiation Period of alpha-Blockers Therapy in Male Elders

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Background: Some observational studies found an increased risk of hypotension-related adverse events during the initiation period of alpha-blockers therapy.

Objectives: The aim of this study was to evaluate the relative risk of hip/femur fractures during the initiation period of alpha-blockers therapy using a self-controlled case series design.

Methods: All male beneficiaries aged over 50 years at 1 January 2006 were identified from the National Health Insurance Research Database, Taiwan and their longitudinal health care data were collected. Incident users of alpha-blockers who also had hip or femur fracture between 1 January 2006 and 31 December 2010 were extracted. The first prescription of alpha-blocker therapy was set as the index date. We defined the initial 21-day period after the index date as the post-exposure risk period 1 and the day 22–60 after the index date as the post-exposure risk period 2. Besides, the 21-day period prior to the index date was defined as the pre-exposure risk period 1 and the day 22–60 prior to the index date as the pre-exposure risk period 2. All the remaining person-time of the 5-year study period was considered as unexposed period. The relative risks of hip/femur fractures within the different risk periods were compared with the baseline unexposed period using conditional Poisson regression model.

Results: Totally, 14,005 men with age of 74.7 ± 9.4 years were included. Compared with the

baseline unexposed period, the relative risk of hip/femur fractures was 1.23 (p = 0.002, 95% CI: 1.08–1.40) within the post-exposure risk period 1 and 0.99 (p = 0.86, 95% CT: 0.89–1.10) within the post-exposure risk period 2. However, the relative risk of hip/femur fractures was 3.56 (p < 0.001, 95% CT: 3.28–3.87) within the pre-exposure risk period 1 and 2.04 (p < 0.001, 95% CT: 1.88–2.22) within the pre-exposure risk period 2.

Conclusions: The use of alpha-blockers therapy was associated with a small increased risk of hip/femur fractures during the early initiation period even though the association between alpha-blockers therapy and hip/femur fractures was mostly driven by prescriptions of alpha-blockers following hip/femur fractures.

110. Withdrawn by Author

111. Discontinuation of Statin Therapy Associates with Parkinson's Disease: A Population-Based Study

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Background: Statins are recently found to reduce the risk of Parkinson's disease (PD)

Objectives: We aim to evaluate the association of discontinuing statin therapy on the incidence of PD in statin users.

Methods: Participants who were free of PD and initiated statin therapy were recruited between 2001 and 2008. We examined the association between discontinuing use of statins with different lipophilicity and the incidence of PD using the Cox regression model with time-varying statin use.

Results: Among the 43,810 statin initiators, the incidence rate for PD was 1.68 and 3.52 per 1,000,000 person-days for lipophilic and hydrophilic statins users, respectively. Continuation of lipophilic statins was associated with a decreased risk of PD (hazard ratio: 0.42, 95% CI: 0.27–0.64) as compared with statin discontinuation, which was not modified by co-morbidities or medications. There was no association between hydrophilic statins and occurrence of PD. Among lipophilic statins, a significant association was observed for simvastatin (HR 0.23 [0.07–0.73]) and atorvastatin (HR 0.33 [0.17–0.65]), especially in female users (HR 0.11 [0.02–0.80] for simvastatin; HR 0.24 [0.09–0.64] for atorvastatin). As for atorvastatin users, the beneficial effect was obviously seen in the elderly subgroup (HR 0.42 [0.21–0.87]). However, long-term use of statins, either lipophilic or hydrophilic, was not significantly associated with PD in a dose/duration-response relation.

Conclusions: Continuation of lipophilic statin therapy associated with a decreased risk of PD as compared to discontinuation statin users, especially in subgroups of women and elderly. Long-term follow up study is needed to clarify the potential beneficial role of lipophilic statins in PD.

112. Baseline Characteristics and Cardiovascular (CV) Comorbidities among United States Males Prior to Testosterone Treatment as Compared to Non-Users

Hu Li, Karin Benoit, Jonathan Swain, Nancy Ostrowski, Stephen Motsko. *Eli Lilly and Company, Indianapolis, United States.*

Background: There is limited data characterizing the pre-treatment baseline characteristics and CV comorbidities in males who use testosterone therapy.

Objectives: This study explored pre-treatment baseline characteristics and CV comorbidities among adult males treated with testosterone vs. non-users.

Methods: The study used the US-based Truven Health MarketScan® Databases. Adult males who were prescribed with any testosterone between 2004 and 2011 were obtained, and compared to males with a hypogonadism diagnosis or a low total serum testosterone measurement (TT ≤ 300 ng/dL). The index date was the first testosterone prescription or hypogonadal diagnosis/qualifying low TT. The baseline period was 12 months prior to the index date. Information on CV disorders, CV risk factors, prescriptions, comorbidities and hospital utilization was obtained. Descriptive analyses were performed to describe and compare pre-treated baseline demographics, prevalence of CV disorder and associated risk factors.

Results: About 200,788 testosterone-users and 152,694 non-users were identified. Compared to untreated males, the treated men were slightly older (aged 52.4 ± 11.3 vs. 50.9 ± 12.8) and had more healthcare utilization, which was illustrated by more office visits, longer hospital stays, and more prescriptions at pre-treatment baseline. Notably, treated males had higher cardiovascular events (64.8% vs. 56% [crude odds ratio (OR): 1.45: 1.43–1.47]). In addition, testosterone users had been prescribed more medication for treating CV disorder related conditions compared to non-users

at pre-treatment baseline, including erectile function, hypertension, hyperlipidemia and diabetes.

Conclusions: This study found a higher prevalence of baseline cardiovascular events and CV risk factors among males prior to initiating treatment with testosterone compared to those who did not receive treatment Thus, future studies comparing testosterone users to non-users might benefit from considering the important baseline differences prior to treatment.

113. Baseline Characteristics and Comorbidities among United Kingdom Males Prior to Testosterone Treatment Compared to Non-Users Stratified by Body Mass Index (BMI)

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Background: There is limited data characterizing the pre-treatment baseline characteristics and comorbidities by BMI in males who use testosterone therapy.

Objectives: This study explored pre-treatment baseline characteristics and comorbidities among adult males treated with testosterone medication vs. non-users stratified by BMI category.

Methods: The study utilized a UK-based electronic medical records – Clinical Practice Research Datalink (CPRD) with valid recorded BMI. Adult males treated with testosterone were obtained from 1989 to 2012, and compared to males with a hypogonadal diagnosis or a low total serum testosterone measurement (TT $\leq$ 300 ng/dL). The index date was the first testosterone prescription or hypogonadal diagnosis/qualifying low TT. The baseline period was 12 months prior to the index date. BMI was categorized as normal (BMI < 25 kg/m^2), overweight (25 $\leq$ BMI < 30 kg/m^2), obese (BMI $\geq$ 30 kg/m^2). Descriptive analyses were performed.

Results: About 6,914 testosterone-users and 10,205 non-users were identified. Overall, no difference was found in age (54.6 $\pm$ 13 vs. 54.8 $\pm$ 13 years) and BMI (29.9 $\pm$ 6 vs. 30.4 $\pm$ 6 kg/m^2) between testosterone users and non-users at pretreatment baseline. Among males with recorded levels, the serum TT was numerically decreasing with increased BMI among testosterone users, in contrast, such trend was not observed among non- users at pre-treatment baseline. Additionally, testosterone users had a lower comorbidity index (CCI) among normal and overweight patients, but a higher CCI among the obese patients (0.45 $\pm$ 0.8 vs. 0.40 $\pm$ 0.7). Compared to non-users in the same BMI category, obese testosterone users were prescribed more medication to treat hypertension, diabetes,

hyperlipidemia, erectile dysfunction and sleep disturbance at pre-treatment baseline.

Conclusions: This study found a higher prevalence of pre-treatment baseline comorbidities among obese testosterone users compared to non-users in the same BMI category. Thus, future studies comparing testosterone users to non-users might benefit from considering baseline differences prior to treatment, especially among obese males.

114. Statins for Prevention of Alzheimer's Disease: Systematic Review and Meta-Analysis

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Background: Based on recent studies it has been suggested that statins may reduce the risk of Alzheimer's disease (AD). However, observational studies and randomized clinical trials assessing the relationship between statins and the risk of AD have presented conflicting results.

Objectives: To conduct a systematic review of observational studies and to examine the association of statin use and the risk of AD through a meta-analysis of studies published in peer-reviewed journals.

Methods: A search to identify cohort and case-control studies that provided adjusted risk estimates for AD among statin users was performed in PubMed through the end of 2012. The following search terms were used: ('hydroxymethylglutaryl-coA reductase inhibitors'[mesh] or *statin*) AND ('delirium, dementia, amnestic, cognitive disorders'[mesh] or alzheimer*). The lists of references of relevant articles were examined for additional publications. We estimated the pooled RR and its 95% confidence interval (CI) using random effects methods for all the studies that met inclusion criteria and for the subset of studies that defined study outcome as incident AD. The Tau^2 and I^2 tests were used to assess the heterogeneity of studies.

Results: Of 186 articles identified, 148 were excluded after reviewing the title and abstract. Of the remaining 38, 28 were excluded (1 specific population, 1 review paper, 2 same population with overlapping period, and 24 which studied an outcome other than AD) based on the review of the full-text article. A total of 10 studies were included in the meta-analysis. In statin users compared with non-users, the pooled RR was 0.79 (95% CI: 0.65–0.97) with moderate heterogeneity of studies (I^2 = 50%, p = 0.03). When performing the analyses restricted to studies on incident AD, the pooled RR was 0.87 (95% CI: 0.69–1.08) with moderate heterogeneity (I^2 = 46%, p = 0.07). Further sensi-

tivity analyses were not performed due to the small number of studies.

Conclusions: Our results do not provide solid evidence to support a protective effect of statins for AD. However, risk estimates below unit and reasons for the heterogeneity of the studies deserve careful assessment and are to be addressed in further research.

115. Serious Infections Associated with Anti-Tumor Necrosis Factor (anti-TNF) Agents among Rheumatoid Arthritis Patients in Brazil

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Background: Anti-TNF drugs have been increasingly used in patients with rheumatoid arthritis (RA) in Brazil. Therefore, these agents have been shown to increase the risk of serious infection.

Objectives: To estimate the incidence rate of serious infections in patients with RA treated with anti-TNF or DMARD therapy in Minas Gerais state, Brazil.

Methods: National administrative databases of pharmacy claim and hospital discharge were used to identify a cohort of new users of DMARD or Anti-TNF agents. Those were defined as individuals aged over 18 years who had a first prescription of either an anti-TNF drug (adalimumab, infliximab or etanercept) or DMARD (methotrexate, leflunomide, hidroxicloroquine and sulphasalazine) with an index date within the period from July 2008 through December 2010. Patients who had been prescribed with the same entry drug during the 6 months prior to the index date were excluded. A serious infection was defined as one ICD-10 code for infection associated with an outpatient procedure (antibiotic dispensing) or inpatient visit (hospital admission). Any event occurring during the following-up was attributed to current therapy, allowing a period of discontinuation of 30 days. Crude incidence rate (IR) and 95% confidence interval (95% CI) were estimated for each drug.

Results: A total of 5,276 RA patients, new users of anti-TNF or DMARDs, were identified; over 80% of these (4,351) were female and the mean age at first prescription was 52.1 ± 12.9 years. Total person-time was 11,304 years; patients on leflunomide contributed with 6,937 person-years and patients on adalimumab with 1,211. There were 28 events of serious infectious, most of them (68%) occurring within 6 months after follow-up. Crude IR for all drugs was 2.48/1,000 person-years (95% CI: 1.68–3.53); IRs were 4.04 for leflunomide (95% CI: 2.74–5.76); 1.65 for adalimumab (0.28–5.46) and 1.03 for etanercept (0.05–5.08).

Conclusions: RA patients on DMARD or anti-TNF are in risk of serious infections. Crude rates found were below those reported in similar studies, due probably to incomplete medical history on the database.

116. Preadmission Use of Antibiotics and 30-Day Mortality after Hospitalization with Pneumonia: A Population-Based Cohort Study

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Background: There are little data about how use and type of preadmission antibiotic therapy may have impact on the prognosis in patients hospitalized with pneumonia.

Objectives: To examine the association between preadmission antibiotic use and 30-day mortality following pneumonia hospitalization.

Methods: Through the Danish National Registry of Patients we found all adult patients in Northern Denmark with a first time primary hospital diagnosis of pneumonia from 1997 to 2009. The outcome was death from any cause within 30 after the admission date. The prescription database at Aarhus University was used to find antibiotic prescriptions filled within 3 months and 7 days (main exposure) before admission. 30-day mortality rate ratios (MRRs) for preadmission use and type of antibiotics compared with no use were computed using Cox regression analysis for confounder adjustment.

Results: We identified 43,084 patients hospitalized with pneumonia during the study period. Of these, 46% had received antibiotics within 3 months, and 25% within 7 days of the hospital admission. Penicillin V was the most often prescribed antibiotic (within 3 months: 51%, 7 days: 49%) followed by macrolides (27%, 26%), and amoxicillin (11%, 9%). The adjusted 30-day MRR in pneumonia patients who received antibiotics within 3 months was 1.03 (95% CI: 0.97–1.09), compared to no preadmission antibiotics. For those who received antibiotics within 7 days it was 0.95 (0.89–1.01). The MRR was reduced in patients who received macrolides 0.66 (0.56–0.77) or penicillin V 0.80 (0.72–0.88) within 7 days. For amoxicillin use within 7 days, MRR was 1.52 (1.32–1.72).

Conclusions: In general, antibiotic therapy before hospitalization with pneumonia did not have an impact on 30-day mortality. However, patients with preadmission use of penicillin V and in particular macrolides had improved pneumonia outcomes.

117. Real-Life Usage Patterns and Effectiveness of Sunitinib in Patients with Clear Cell Metastatic Renal Cell Carcinoma: The SANTORIN Study

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Background: Until 2006, treatment options for metastatic renal cell carcinoma (mRCC) were limited to cytokine therapy and surgery. Sunitinib, an oral anti-angiogenic agent, received European marketing authorisation in January 2007 for first-line treatment in advanced and/or mRCC after having demonstrated to improve survival outcomes in a randomized controlled trial. However, little is known on the usage and effectiveness of this drug in daily clinical practice.

Objectives: To describe usage patterns and estimate survival outcomes in clear cell mRCC patients treated by sunitinib in a real-life setting.

Methods: SANTORIN was an observational cohort conducted in 36 French centres including patients initiating first-line treatment with sunitinib from January 2008 to April 2010. Patients were followed 2 years after treatment onset. Clinical and treatment characteristics, response (evaluated by investigator based on Response Evaluation Criteria In Solid Tumors) and survival outcomes were collected from medical files. Overall and progression-free survival (OS and PFS) rates were estimated using Kaplan-Meier method.

Results: A total of 258 patients were included: mean age 64.8 years; male 72.9%; ECOG performance status ≥ 2 10.1%, prior nephrectomy 89.5%. Baseline sunitinib dose was 50 mg/day for 82.2% of patients. The median duration of first-line treatment was 11.9 months (median number of cycles: 6). Dose reduction occurred in 68.2% of patients. Reasons for discontinuation of first-line treatment were progressive disease (61%), death (31.9%), adverse events (6.6%), and other reasons (0.5%). Overall best response was 34.1% (2.7% complete, 31.4% partial), 38.8% had stable and 16.7% progressive disease. OS was 73.9% at 1 year (95% CI [68.1;78.8]) and 52.5% at 2 years [46.2;58.5]. Median OS was not reached. PFS was 40.9% at 1 year [34.8;46.8] and 17.3% at 2 years [13.0;22.2]. Median PFS was 9.5 months [8.1;11.0].

Conclusions: These results suggest that effectiveness of sunitinib in clear cell mRCC is close to efficacy reported in the pivotal clinical trial (median OS: 26.4 months [95% CI: 23.0;32.9], median PFS: 11.0 months [11.0;13.0]).

118. Cetuximab with Irinotecan or Oxaliplatin for 1st-Line Metastatic Colorectal Cancer: Effectiveness in the EREBUS Cohort Compared to Pivotal Trials

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Background: Cetuximab (CTX) has demonstrated improved survival outcomes in metastatic colorectal cancer (mCRC) but data from real-life use are sparse.

Objectives: To compare CTX effectiveness to efficacy from OPUS and CRYSTAL trials.

Methods: EREBUS, a French multicentre (n = 65) cohort, included in 2009–2010 patients with unresectable mCRC and wild-type KRAS initiating CTX as 1st-line therapy who were followed 1 year. Clinical data, treatment, response and survival were collected from medical files. Overall and progression-free survival (OS and PFS) were analyzed using Kaplan-Meier method.

Results: Among 389 included patients, 218 received CTX with irinotecan-based chemotherapy (CTX+IRI), and these were compared to the 316 patients similarly treated in the CRYSTAL trial. The main characteristics were: median age 64 vs. 61 years (EREBUS vs. CRYSTAL); male 68.8 vs. 62%, ECOG≥ 2 16.5 vs. 4.1%, liver only metastases 35.3 vs. 21.5%. Median

PFS (95% CI) was 9.7 months (8.8–11.3) for CTX+IRI patients of EREBUS vs. 9.9 months (9.0–11.3) in CRYSTAL. Best overall response rates were respectively 51.9% (45.3–58.5) and 57.3% (51.6–62.8). Half of CTX+IRI patients of EREBUS (50%) had grade 3–4 adverse events vs. 81.1% in CRYSTAL. For the 147 patients treated by CTX with oxaliplatin-based chemotherapy (CTX+OX) compared to the 82 patients similarly treated in the OPUS trial, the main characteristics were: median age 63 vs. 62 years (EREBUS vs. OPUS); male 65.3 vs. 51%, ECOG≥ 2 18.4 vs. 7%, liver only metastases 40.8 vs. 30%. Median PFS was 9.8 months (7.7–10.8) for CTX+OX patients of EREBUS vs. 8.3 months (7.2–12.0) in OPUS. Best overall response rates were respectively 55.9% (47.9–64.0) and 57% (46–68). Two-thirds of CTX+OX patients of EREBUS (65.3%) had grade 3–4 adverse events vs. 82% in OPUS. Independently of the combined chemotherapy, median OS was not reached in the EREBUS cohort.

Conclusions: Despite differences in patient characteristics, in particular ECOG performance status, effectiveness of CTX in 1st-line mCRC was close to efficacy reported in pivotal trials. The lower frequency of adverse events could be due to under-notification in real-life.

119. Association of Acetylsalicylic Acid and the Risk of Hospitalization for Vascular Access-Related Infections and Septicemia among Hemodialysis Patients

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Background: Vascular access-related infections and septicemia are the main cause of infections among hemodialysis patients, and Staphylococcus species are implicated in the majority of them. Acetylsalicylic acid (ASA) has recently been reported as having a certain antistaphylococcal activity.

Objectives: The purpose of this study was to evaluate the effect of ASA on the risk of vascular access-related infection and septicemia among incident chronic hemodialysis patients.

Methods: For this nested case-control study, we built a cohort of adult patients initiating chronic hemodialysis (n = 4,933) in Quebec, Canada, using dialysis registry and administrative databases (2001–2007). Cases were defined as patients hospitalized with a main diagnosis of vascular access-related infection or septicemia according to ICD-9 codes on the discharge sheet. Up to 10 controls per case were selected by incidence density sampling and matched to cases according to their age and follow-up time. ASA exposure was measured at the time of the admission and categorized as follow: no use, low dose (80–324 mg/day), and high dose (≥ 325 mg/day). Odds ratios (OR) for infections were estimated using conditional logistic regression multivariate analysis, adjusting for demographics, smoking, body mass index, comorbidities, antiplatelet use, anticoagulant use, and laboratory values.

Results: We identified 572 cases of vascular access-related infections and septicemia, and 5,407 controls during the study period. Compared to no use, neither dose of ASA was associated with a statistically significant change in the risk of infection: low dose (OR 0.96, 95% CI: 0.78–1.17) and high dose (OR 1.21, 95% CI: 0.92–1.61). However, younger age (OR = 1.23 per 10y, 95% CI: 1.06–1.45), Black race (OR = 1.46, 95% CI: 1.04–2.04), diabetes (OR = 1.40, 95% CI: 1.16–1.69), and anticoagulant use (OR = 1.65, 95% CI: 1.35–2.02) were associated with a higher risk.

Conclusions: Among hemodialysis patients, ASA use did not influence the risk of hospitalizations for dialysis-related infections or septicemia. However, ASA may remain beneficial for its cardiovascular indications.

120. Using Epidemiological Registry Data To Provide Background Rate Context for Adverse Events in a Rheumatoid Arthritis (RA) Drug Development Program – A Coordinated Approach

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Background: Observational studies may provide context for adverse events observed in clinical trials, especially infrequent events or long-term risks.

Objectives: To develop methods for improving safety contextualization for an RA drug development program using a coordinated approach across multiple registries.

Methods: We included 4 existing RA registries: Swedish Rheumatology Registry, Sweden; CORRONA, USA; NOAR, UK; IORRA, Japan and a new registry (CORRONA International) for East Europe, Latin

America and India. We identified differences and similarities across registries and investigated how selecting restricted subcohorts might improve comparability with trial populations. We also identified risk predictors for outcomes of interest (mortality, CVD, infection, malignancy). We used a coordinated approach with patient (pt)-level analyses at each registry, then a central analysis of standardized data.

Results: Despite differences in data collection, the collaborative approach enabled more consistent definition of variables for key baseline characteristics and outcomes. Selection of subcohorts (e.g. based on active joint count criteria) improved baseline comparability with trial pts for some RA disease activity measures (e.g. DAS28, HAQ), but less for other characteristics (e.g. age); this did decrease sample size considerably. For most outcomes, age was the most important risk predictor, emphasizing the importance of age/sex standardization (e.g. HR of death for men > 70 years vs. women < 50 ranged from 19.5 to 71.1 across registries). The new registry broadened the geographical base. The prospective approach ensured current data were used, while the distributed analysis safeguarded confidentiality of registry data.

Conclusions: In using observational data to provide context for safety observations from clinical trials, a forward-looking coordinated approach across many data sources can provide improved comparability and consistency, and give better support for sensitivity and exploratory analyses and data interpretation, than using published data alone.

121. Validation of the Health Improvement Network for the Study of Psoriatic Arthritis

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Background: The Health Improvement Network (THIN) can be used to study long term outcomes in psoriatic arthritis (PsA) but the validity of diagnostic codes and treatments for PsA has not been examined.

Objectives: (1) Validate the diagnostic codes for PsA in THIN, and (2) Examine agreement between general practitioner (GP) and THIN recording of prescriptions for disease modifying antirheumatic drugs (DMARD).

Methods: Among patients with at least one READ code for PsA in THIN, we randomly selected 100 aged 18–89 in participating practices. GPs were asked to complete a survey to ascertain accuracy of PsA diagnosis, disease characteristics, and history of DMARD use. The positive predictive value (PPV) and 95% confidence interval was calculated for each algorithm with GP confirmed diagnosis as the gold standard. Strategies for defining PsA included (1) 1 code for PsA, (2) 2 codes for PsA, (3) 1 code for PsA and 1 code for psoriasis, (4) 1 code for PsA and 1 code for a DMARD, and (5) a code for PsA in the absence of rheumatoid arthritis or osteoarthritis. Finally, we examined percent agreement between GP and medical record notation of DMARD use.

Results: Of the 100 surveys, 87 were returned within 6 months. The GP confirmed the diagnosis in 74 with at least one code for PsA (PPV 85.1%, 95% CI: 75.8–91.7%), 62 (83.7%) had been seen by a rheumatologist who corroborated the diagnosis and 43 met Classification for Psoriatic Arthritis (CASPAR) criteria. The remaining 31 did not have enough information to examine CASPAR criteria. Of the algorithms tested, none had a substantially higher PPV than a single code for PsA except when a DMARD was required (PPV 91%, 76.3–98.1). However, this lowered the sensitivity (42%). Among patients with confirmed PsA, 31 had a drug code consistent with an oral DMARD in THIN. The GP reported 51 of the 74 had been prescribed an oral DMARD. Percent agreement was 68.9%.

Conclusions: The PPV for a single READ code for PsA was 85% suggesting that THIN is valid for the study of PsA. While adding a prescription for a DMARD increased the PPV, fewer patients met the definition. Finally, there is moderate agreement between DMARD prescriptions in the database and GP report of DMARD use.

122. Withdrawn by Author

123. The Association between Obesity and Major Bleeding Risk in Warfarin Users in a Community Setting

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Background: Warfarin is an anticoagulant that is effective at reducing thromboembolic event risk, and is used by 2 million Americans annually. Body mass index (BMI) is positively correlated with coagulation factor levels, and may therefore play a role in warfarin outcomes, including safety. Several studies evaluated the association between BMI and warfarin dose, but few examined the association between BMI and major bleeding. This is a clinically important outcome because bleeding risk is a noted barrier to appropriate warfarin use.

Objectives: To evaluate the association between obesity and major bleeding in warfarin users in a community setting.

Methods: We used a case-control design and recruited patients from Group Health (GH), an integrated healthcare system. Cases had major bleeding while receiving warfarin. Controls received warfarin on a randomly assigned index date, and had no major bleeding in the prior year. We identified major bleeding with an ICD-9 algorithm, and validated events with chart review. We used logistic regression to estimate the odds of major bleeding for obese patients (BMI > 30) vs. non-obese patients (BMI < 30), adjusting for potential confounders (age, sex, indication, care setting, duration of use, and Charlson comorbidity index) derived from health plan databases and a self-reported survey.

Results: Our analysis included 225 cases and 255 controls with an average of 3.4 and 3.7 years of warfarin use at the index date, respectively. Obese patients had significantly lower major bleeding risk vs. non-obese patients (Odds Ratio (OR): 0.60, 95% CI: 0.42–0.88). Stratified by duration of warfarin use, the major bleeding OR was 0.56 (0.35–0.90) in patients with > 1-year, and 0.78 (0.40–1.54) in patients with < 1-year.

Conclusions: We found that obese patients receiving warfarin in a community setting had 40% lower risk of major bleeding vs. non-obese patients. Our results are consistent with studies that demonstrate increased thromboembolic event risk in obese anticoagulation patients. This evidence suggests that many obese patients may receive sub-therapeutic warfarin doses, and that BMI is generally an important clinical factor in anticoagulation therapy.

124. Psychiatric Comorbidity among Children, Adolescents, and Adults Treated with Metylphenidate

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Background: Metylphenidate is the only stimulant licensed for the treatment of adhd among children and adolescent in Sweden. The drug is not licensed for initiation of treatment of adhd among adults.

Objectives: To describe the prevalence of psychiatric comorbidity in different age groups in Sweden among users of metylphenidate.

Methods: Record-linkage study using data from the Swedish Prescribed Drug Register and the Swedish Patient Register at the Board of Health and Welfare. Individuals aged 5–64 with at least one dispensation of methylphenidate during 2011 were studied for the occurrence of either an in- or out-patient treatment episode with a diagnosed psychiatric disorder during 2001–2010.

Results: Among men 25 + more than a third had a diagnosis of substance-related disorders or of anxiety, one out of four had a diagnosis of depression, and one out of ten a diagnosis of personality disorder. The corresponding figures for women 25 + were one out of four, one out of three, and one out of six. Among children and adolescents below 18 year approximately one out of five had a diagnosis of neuropsychiatric disorder, other than adhd.

Conclusions: Comorbidity of adhd with substance-related disorders, depression or anxiety was common among adults. Among children and adolescents comorbidity between adhd and neuropsychiatric disorders was common.

125. Co-Prescription of Metylphenidate with Psychotropic Drugs among Children and Adults

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Background: Metylphenidate is the only stimulant licensed for treatment of adhd among children and

adolescent in Sweden. It is not approved for initiation of treatment of adhd among adults. Evidence supporting the effectiveness and safety of combined treatment with metylphenidate and psychotropic drug is lacking.

Objectives: To describe the prevalence of co-medication of different groups of psychotropic groups in Sweden among users of metylphenidate.

Methods: Data on drugs dispensed from the Swedish Prescribed Drug Register for 2011. Individuals with a least one dispensation of metylphenidate with at least three dispensations in respective group were defined as users of either lithium, antidepressants, anxiolytics, hypnotics, melatonin or prescription drugs classified as narcotics, including e.g. opioids and benzodiazepines.

Results: A total of 50,731 individuals (32,415 men and 18,316 women) were treated with metylphenidate. Co-medication was common among adults 25 years and above with approximately one third of men and four out of ten women being treated with anti-depressants. One out of three was treated with hypnotics, one out of five with anxiolytics, and one out of eight with anti-psychotics. For children below 18 more than one out of ten was treated with melatonin. In total, 29% or 7,862 out of 27,101 individuals aged 18–64 who were dispensed metylphenidate were users of other prescription drugs classified as narcotics. Both the average dispensed daily dose of metylphenidate and the numbers of unique work-place codes per individual were higher for users of prescription drugs classified as narcotics.

Conclusions: Co-medication of methylphenidate with melatonin among children is common. Among adults, co-medication with hypnotics, anxiolytics, or antidepressants is common. The co-medication could be a result of co-morbidity and/or a result of inappropriate prescribing. The higher numbers of unique work-place codes, and on average higher dose of metylphenidate among users of prescription drugs classified as narcotics, might reflect a combination of co-morbidity and treatment for different disorders at different clinics, but might also be explained by inappropriate prescribing.

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126. Evaluating the Impact of the Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain on Opioid Prescribing in Utah, 2002–2009

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Background: In response to increasing numbers of adverse events related to prescription opioid medications, the Utah Department of Health implemented a multi-pronged program to reduce opioid-related harms. An expert panel was convened in 2007 to develop Utah guidelines using a consensus process. The Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain, hereafter Guidelines, were released for public comment in early 2008, and advertised and published in July 2008.

Objectives: The objective of this analysis was to quantify changes in opioid prescribing and adverse events before guideline development (pre-period) during development and reporting of opioid concerns (intermittent period) and after promulgation of the Guidelines (post-period).

Methods: This study was IRB approved by the University of Utah. Multiple data sources were used for this analysis including the Utah Controlled Substances Database (CSD), Utah ED encounter database, and the state medical examiner database. Process flags included the dual use of long-acting opioids or short-acting opioids, combined use of benzodiazepines and long-acting opioids, methadone titration. Outcome flags included the opioid related ED visits and deaths. Opioid users were categorized as acute, intermittent, chronic or palliative. Flags were compared by opioid user type across the pre-intervention period (07/2006–06/2007), intermittent period (08/2007–07/2008), and post-period (04/2009–03/2010).

Results: During each period there were approximately 380,000 acute uses, 32,000 chronic, 220,000 intermittent and 5,000 palliative users. Most process and outcome measures improved during the post-guideline periods (Tables 1 and 2). Chronic users had the highest proportion of poly-pharmacy and outcome flags. Opioid users classified as palliative had the highest proportion of initial methadone dosing violations.

Conclusions: While the number of opioid users remained constant across time periods there has been a decrease in unsafe use of opioids and opioid-related adverse events in Utah since the opioid prescribing guidelines were promulgated and received media attention.

127. Anti-Malarial Chemoprophylaxis and the Risk of Developing Neuropsychiatric Disorders

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Background: There have been numerous reports of neuropsychiatric adverse events in users of mefloquine.

Objectives: To assess the risk of developing neuropsychiatric disorders associated with use of malaria chemoprophylaxis.

Methods: The UK-based General Practice Research Database was used to conduct a follow-up study with a nested case-control analysis. The risk of developing a first-time diagnosis of anxiety, stress-related disorders/psychosis, depression, epilepsy or peripheral neuropathies in patients using mefloquine (MQ), chloroquine and/or proguanil (CP), or atovaquone/proguanil (AP) for malaria chemoprophylaxis was assessed, and compared to travellers not using anti-malarials (NU).

Results: The incidence rate of anxiety, stress-related disorders or psychosis combined in users of mefloquine was 6.2 (95% CI: 5.1–7.5)/1,000 person years. The incidence rates of depression, epilepsy or peripheral neuropathies in MQ were 4.2 (95% CI: 3.3–5.4), 0.8 (95% CI: 0.5–1.4) and 0.5 (95% CI: 0.2–0.9)/1,000 person years, respectively. As compared to NU, the adjusted odds ratio (OR) in the nested case-control analysis for MQ, CP, or AP compared to NU were 0.71 (95% CI: 0.56–0.90), 1.04 (95% CI: 0.74–1.46), and 0.73 (95% CI: 0.61–0.86) for anxiety or stress-related disorders or psychosis combined, 0.54 (95% CI: 0.41–0.71), 1.06 (95% CI: 0.71–1.59), and 0.75 (95% CI: 0.62–0.91) for depression, 0.69 (95% CI: 0.35–1.36), 1.41 (95% CI: 0.54–3.67), and 0.75 (95% CI: 0.42–1.36) for epilepsy, and 1.22 (95% CI: 0.50–2.99), 1.59 (95% CI: 0.41–6.15), and 1.05 (95% CI: 0.54–2.03) for neuropathies, respectively. The risk of psychosis was statistically non-significantly elevated for MQ compared to NU (OR 2.17, 95% CI: 0.85–5.59) though the numbers were small. The risk of depression, but not of other CNS outcomes, tended to be higher in underweight users of anti-malarials and the risk of all outcomes was higher in females across all exposure categories.

Conclusions: The risk of developing neuropsychiatric disorders was overall similar for MQ, CP, AP or NU, though there was a non-significant increased risk of psychosis in MQ compared to non-users. These findings may influence treatment practices for the prevention of malaria.

128. Risks of Adverse Events in Treated Chronic Hepatitis C Patients with Cirrhosis Compared to without Cirrhosis in Real-World Settings

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Background: Treatment with peginterferon alfa (alfa) alone or in combination with ribavirin (RBV) has been used cautiously in chronic hepatitis C (CHC) patients with advanced liver disease. There is lack of comprehensive safety assessment of adverse events (AE) in treated CHC patients with cirrhosis compared to those without cirrhosis in real-world clinical practice.

Objectives: To estimate the relative risks of AEs in cirrhotic compared to non-cirrhotic CHC patients treated with alfa, or in combination with RBV in a real-world setting.

Methods: An observational cohort study was conducted using a US health insurance claims database between January 2005 and March 2009. Patients age 18 or older with at least 2 claims of CHC ICD-9 diagnoses were selected; HIV or hepatitis B virus co-infected patients were excluded. Cirrhotic and non-cirrhotic CHC patients were identified using ICD-9 diagnostic codes for cirrhosis. Treated patients were identified using procedure and drug codes. Potential AEs of interest were identified using ICD-9 diagnostic codes. Cox proportional hazard models were used to estimate the relative hazard of AEs among cirrhotic vs. non-cirrhotic CHC patients.

Results: A total of 733 (37%) cirrhotic and 3,757 (12.8%) non-cirrhotic CHC patients were treated with alfa with or without RBV. No difference in age was observed. Cirrhotic patients were more likely male (70% vs. 63%, p = 0.0003), and have more patients with co-morbidities such as diabetes, hypertension and cardiovascular diseases at baseline compared to non-cirrhotic patients. In the adjusted cox proportional hazards models, increased risks of coagulopathy (HR = 4.12, 95% CI: 2.04–8.33), cardiovascular disorders (HR = 2.11, 95% CI: 1.39–3.21), hematologic abnormalities (HR = 1.91, 95% CI: 1.62–2.25), pneumonities (HR = 1.85, 95% CI: 1.30–2.63), and fever

(HR = 1.60, 95% CI: 1.17–2.20) AEs were detected among cirrhotic patients compared to non-cirrhotic patients.

Conclusions: The results of this study indicate that treated CHC patients with cirrhosis are at an increased risk of AEs. Alternative therapy options with better AE profile are needed for CHC patients with advanced liver disease.

130. Use of Azithromycin and Cardiovascular Death

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Background: Azithromycin use is associated with increased risk of cardiovascular death among patients at high baseline cardiovascular risk. It is unknown whether azithromycin confers a similar risk in the general population.

Objectives: To investigate whether azithromycin is associated with increased risk of cardiovascular death in the unselected general population.

Methods: We conducted a nationwide historical cohort study in Danish adults aged 18 to 64 years, linking individual-level register data of filled prescriptions, causes of death, and patient characteristics in 1997–2010. We estimated rate ratios (RRs) for cardiovascular death, comparing 1,102,419 5-day treatment episodes of use of azithromycin with no use of antibiotics in propensity score matched (1:1) analysis, including a total of 2,204,100 episodes, and 7,364,292 episodes of use of penicillin V (comparator antibiotic with similar indications) in propensity score adjusted analysis.

Results: Compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of cardiovascular death (RR 2.85, 95% CI: 1.13 to 7.24). The analysis relative to an antibiotic comparator included a total of 720,564 person-years of follow-up and 459 cardiovascular deaths. Among these, 17 occurred during current azithromycin use (crude rate 1.1 per 1,000 person-years) and 146 during current penicillin V use (rate 1.5 per 1,000 person-years). After adjusting for propensity scores, current use of azithromycin was not associated with increased risk of cardiovascular death (RR 0.93, 95% CI: 0.56–1.55). The adjusted absolute risk difference, relative to penicillin V, was −1 (95% CT: −9 to 11) cardiovascular deaths per 1,000,000 treatment episodes with azithromycin.

Conclusions: Use of azithromycin was not associated with increased risk of cardiovascular death in a general population of young and middle aged adults.

131. QT Interval Prolongation in Elderly Users of Selective Serotonin Reuptake Inhibitors

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Background: Despite the limited evidence, some selective serotonin reuptake inhibitors (SSRIs) are nowadays listed as QT prolonging agents carrying a potential risk of Torsade de Pointes. It is unknown whether the risk of QT interval prolongation is a property of specific SSRIs or a class effect.

Objectives: The aim of our study was to investigate the association between the use of a selective serotonin reuptake inhibitor (SSRI) and the occurrence of QT interval prolongation in an elderly population.

Methods: A cross-sectional study was conducted among patients scheduled for outpatient preanesthesia evaluation in University Medical Center Utrecht in the period 2007–2012. The index group included elderly (> 60 years) users of an SSRI. The reference group of nonusers of antidepressants was matched to the index group on sex and year of scheduled surgery (ratio 1:1). The primary outcome was the occurence of QT interval prolongation. The QT interval was corrected for heart rate according to Bazett's formula: $QTc = QT/\sqrt{RR}$. A prolonged QTc interval was defined as > 450 ms for males and > 470 ms for females. The secondary outcome was the duration of the QTc interval. Multivariate conditional logistic regression analysis and linear regression analysis were used to estimate the strength of the assocation between the use of an SSRI and the occurence of QTc prolongation and the duration of the QTc interval, respectively.

Results: The index and reference group included 397 users of an SSRI and 397 nonusers, respectively. QTc interval prolongation occurred in 25 (6%) and 19 (5%) index and reference patients, respectively. After adjustment for confounding factors, users of an SSRI did not have a higher risk for QTc interval prolongation compared to nonusers: OR 0.9 (95% CI: 0.4 to 2.1). The adjusted mean QTc interval length in users of an SSRI and nonusers was comparable (difference of 1.5 ms, 95% CI: −1.6 to 4.6). Use of the most frequently used SSRIs citalopram and paroxetine was neither significantly associated with a higher risk of

QTc interval prolongation nor with lengthening of QTc interval duration.

Conclusions: The use of an SSRI by elderly patients was not associated with QT interval prolongation.

132. The Association of Oral Fluoroquinolone Use with the Need for Retinal Detachment or Retinal Tear Repair

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Background: Recent evidence (Etminan, Forooghian et al. 2012) suggests that oral fluoroquinolone use may be associated with an increased risk for retinal detachment.

Objectives: To determine the odds of retinal breaks (RB) in people with fluoroquinolone exposure compared to matched controls.

Methods: This is a case-control study nested within The Health Improvement Network (THIN) database which contains the medical records of 11.1 million patients collected from 562 general medical practices in the UK. Subjects who had < 365 days of data in THIN were excluded from this study. Cases included all subjects with a procedure for a retinal detachment or a retinal tear. Index date was defined as the earlier of the procedure date or the date of procedure associated diagnosis. Four controls were selected for each case using density sampling from those who had a previous eye diagnosis, but not a diagnosis of RB stratified on age, sex, and medical practice. Oral fluoroquinolone use was determined through recorded prescriptions. The primary outcomes were the odds of a case having a fluoroquinolone exposure at 8, 45 and 180 days prior to the index date compared to controls. Univariate and multivariate conditional logistic regression (controlling for myopia and lattice) were performed.

Results: There were 3,099 cases with a procedure for a RB matched to 10,926 controls. A total of 7,996 prescriptions for oral fluoroquinolones were written during the observation period for both cases and controls. Univariate conditional logistic regression analysis showed no association between fluoroquinolone exposure and RB procedures at any of the examined time points (8dys: OR = 0.51[95% CI: 0.12, 2.24]; 45dys OR = 0.61 [95% CI: 0.32, 1.16]; 180dys: OR = 0.74 [95% CI: 0.53, 1.05]). Multivariable logistic regression analysis again showed no association with little change in the odds ratios (8dys: OR = 0.53 [95% CI: 0.12, 2.32]; 45dys OR = 0.61 [95% CI: 0.32, 1.16]; 180dys: OR = 0.75 [95% CI: 0.53, 1.06]).

Conclusions: Our results do not support the idea that there is an association between oral fluoroquinolone use and the need for a procedure to repair a retinal detachment or tear.

133. The SOS Project: Risk of Heart Failure and Use of Nonsteroidal Anti-Inflammatory Drugs–A Meta-Analysis of Observational Studies

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Background: The European Commission funded the Safety Of non-Steroidal anti-inflammatory drugs (SOS) project to assess the cardiovascular and gastrointestinal safety of individual nonsteroidal anti-inflammatory drugs (NSAIDs).

Objectives: To perform a systematic review of observational studies evaluating the use of individual NSAIDs and the risk of heart failure (HF).

Methods: A systematic search of studies published from 1990 to 2012 identified 8 observational studies of the risk of HF associated with individual NSAID use. Relative risks (RRs) of current use compared with nonuse were estimated using fixed- and random-effects models.

Results: Six studies evaluated the risk of incident HF, mainly identified by hospitalizations, and 1 study included all types of HF hospitalizations; of these, six studies provided RRs associated with current use for our main analysis. For NSAIDs with at least three independent estimates, the summary RRs (95% confidence intervals [CIs]) were 0.91 (0.71–1.16) for celecoxib, 1.53 (1.09–2.15) for naproxen, and 1.73 (1.45–2.06) for rofecoxib. For NSAIDs with two independent estimates, the RRs (95% CIs) were 1.09 (0.83–1.44) for diclofenac, 1.46 (1.12–1.90) for ibuprofen, 1.57 (0.79–3.11) for piroxicam, 1.73 (0.81–3.71) for ketoprofen, and 3.39 (1.89–6.09) for indometacin. Fixed and random estimates were almost identical. No data were available on dose or duration. In a single study estimating the risk of recurrent HF hospitalization and all-cause mortality associated with current use compared with nonuse of individual NSAIDs, naproxen,

ibuprofen, diclofenac, celecoxib, and rofecoxib were associated with a high risk of recurrent HF and death. Only rofecoxib was associated with a dose-dependent increase in HF risk, with RRs (95% CIs) of 1.33 (1.20–1.49) for doses of ≤ 25 mg/day and 1.86 (1.46–2.35) for doses > 25 mg/day.

Conclusions: Summary estimates from few published observational studies suggest variability in the risk of HF for the most frequently used NSAIDs, with the lowest estimate for current use of celecoxib and the highest for indometacin as compared with nonuse of NSAIDs.

134. Cardiovascular Risk with Glitazones and Metformin: Results from a Systematic Review of Observational Studies

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Background: The goal of the Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project, sponsored by the European Commission, is to evaluate the cardiovascular (CV) and pancreatic safety of oral glucose-lowering drugs in type 2 diabetes mellitus (T2DM). We systematically reviewed published observational studies on the risk of acute myocardial infarction (AMI), stroke, heart failure (HF) or CV mortality in T2DM users of rosiglitazone or pioglitazone vs. metformin users.

Methods: We searched Medline, Embase and the Cochrane Library to identify cohort or case-control studies published through November 2011 reporting the risk of CV endpoints in T2DM patients using any oral glucose-lowering medication. Of 1929 publications, 44 studies were selected; 7 reported the risk of AMI or HF in users of rosiglitazone or pioglitazone compared with risk in metformin users. No studies reported on stroke or CV mortality. Summary relative risks (sRR) were estimated using random-effects models. Heterogeneity was assessed using the chi-squared test.

Results: All studies used a cohort design with one performing a nested case-control analysis. For AMI, for monotherapy regimens, the sRR (95% CI) for rosiglitazone was 1.43 (0.98–2.08; p < 0.0001 for heterogeneity; n = 6); for pioglitazone 1.21 (0.87–1.70; n = 2),

compared with metformin. If rosiglitazone or pioglitazone was added to a based metformin regimen or combined with other T2DM drugs, sRR was closer to the null as compared to metformin. For HF, the sRR (95% CI) for rosiglitazone, monotherapy or in combination with other blood glucose-lowering agents, vs. metformin was 1.34 (1.10–1.62; n = 3). Based on only 2 studies, the sRR (95% CI) for pioglitazone vs. metformin was 1.14 (0.86–1.50). No studies reported on dose or duration effects.

Conclusions: Observational studies reporting on the risk of CV events associated with individual glitazones compared with metformin are scarce and heterogeneous. Results of the large ongoing SAFEGUARD project will help elucidate the CV safety of these medications.

135. Beta Blockers and Breast Cancer: Results from a Collaborative Study

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Background: Clinical trials and observational studies have shown the effect of non-selective beta blockers on incidence of some tumors as well as their role in reducing disease progression and metastasis. Cancer registries, through their information system, can investigate complex hypotheses that would otherwise require substantial investment of resources.

Objectives: To assess the association between beta blockers and incidence of breast cancer.

Methods: A matched case-control study nested in a cohort of new beta blockers users was performed. Data were retrieved from the 6 Local Health Authorities, accounting for nearly 5 million subjects, joined in the OSSERVA consortium. Breast cancers diagnosed before the beginning of the therapy (cohort entry) or occurred within one year from the cohort entry (to account for biologically meaningful latency time window) were excluded. Up to 50 controls per case, matched on age, index date and cohort entry, were selected by risk set sampling. Cases and controls were grouped into one of the following mutually exclusive categories, defined by ever use of: (1) propranolol, (2) atenolol, (3) any other beta blocker; a fourth group, including subjects belonging to more than one of the above categories, was then defined. Odds Ratios and 95% confidence intervals, adjusted for use of statins

and antidiabetic drugs, were estimated using conditional logistic regression.

Results: About 171,000 women (mean age 64.7) were enrolled and followed for 66 months on average. Among them, 6,266 (3.7%) were treated with propranolol and 69,732 (40.8%) with atenolol. We identified 2539 cases. Four hundred and fifty two were excluded because occurred within one year from the cohort entry whereas the remaining 2087 (28 in the propranolol and 631 in the atenolol group) were matched to 104,526 controls. Compared to other beta blockers, propranolol and atenolol reduced the risk of breast cancer (OR = 0.83, CI: 0.57, 1.22 and OR = 0.91, CI: 0.82, 1.00, respectively).

Conclusions: This study shows reduced risk of breast cancer associated with use of propranolol and atenolol among women taking these drugs instead of other beta blockers used in the treatment of hypertension. This finding may open interesting scenarios in public health.

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136. Validity Threats in Multi-Center Retrospective Chart Abstraction Studies

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Background: Multi-center retrospective medical chart abstraction is one possible design option to study real-world effects of pharmaceutical products. Ideally, in order to ensure validity of results in such studies, the following should hold:

(1) Study centers are representative of all centers giving rise to patient population
(2) Within centers, there is no differential selection of qualified patient charts for abstraction

In practice these conditions can be violated, potentially threatening external or internal (e.g. selection bias) validity.

Objectives: Summarize threats to study validity using real world study examples and provide recommendations on how to optimally address them.

Methods: Review of categories of threats to validity that may arise in chart abstraction studies based on published literature and experience with ongoing studies, including examples of each category, and the impact on generalizability or possible direction of bias from each example.

Results: Threats to study results validity (external or internal) can be introduced by differential center or patient participation. Center participation may be affected by factors such as center's ability to retrieve the charts, types of charts, number of eligible charts and others. Patient participation may be influenced by possible requirement to seek informed consent prior to abstraction. Depending on patient population and other factors, proportion of consenting patients may vary and they may differ systematically from those not consenting (e.g. more/less likely to experience outcome).

Conclusions: It is important to address these threats to validity at study design and analysis stages. Measures to ensure balanced representation of centers with various characteristics may be taken. Waivers of consent should be sought where legally possible to avoid differential patient participation. Limiting study to countries where waivers are granted may be considered; if centers with and without waivers are included, patient factors can be compared between these two center types. Consenting vs. non-consenting patients may also be compared within centers to identify any differences linked to reasons for consent refusal.

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137. Effervescent, Dispersible and Soluble Medications Increase Cardiovascular Events

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Background: Excess dietary sodium is a major public health issue worldwide. Commonly prescribed effervescent, dispersible and soluble formulations of medications contain significant amounts of sodium and the effect of this on cardiovascular outcomes is not known.

Objectives: To compare prescribed sodium-containing formulations (sodium) with standard tablet or capsular forms of the same drug (standard) on cardiovascular events using the composite Antithrombotic Trialists' Collaboration serious vascular event endpoint of non-fatal myocardial infarction, non-fatal stroke or vascular death. All-cause mortality was a secondary outcome.

Methods: A nested case-control study was conducted using the UK Clinical Practice Research Datalink (CPRD) database. We studied a cohort of patients prescribed medicines available both as sodium and standard between January 1987 and December 2010. All cases of cardiovascular events occurring during the follow up were identified from the cohort and matched (1:1) using incidence density sampling to one control

on year of birth, gender and general practice attended. Odds ratios (ORs) of cardiovascular events associated with sodium exposure were calculated.

Results: About 1,292,337 patients were included in the study cohort. The mean follow-up time was 5.4 years. About 79,888 cardiovascular event cases were matched with the same number of controls from the study cohort. Compared with the standard group, the adjusted ORs for the cardiovascular events were 1.18 (95% CI: 1.14–1.23) for the sodium group, 3.00 (95% CI: 0.31–28.84) for patients with sodium exposure duration ≤ 30 days and 1.15 (95% CI: 1.11–1.20) for patients with sodium exposure duration > 30 days. There was no difference in cardiovascular risk between patients in the standard group and patients in the switch group. The OR for all-cause mortality was 1.29 (95% CI: 1.25–1.34) for the sodium group compared with the standard group.

Conclusions: Sodium-containing formulations are associated with significantly increased risk of adverse cardiovascular events and all-cause mortality compared to standard formulations. It should therefore be prescribed with caution and only if the perceived benefits outweigh these risks.

138. An Epidemiological Study Examining the Risk of Malignancy in Patients with Inflammatory Bowel Disease

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Background: Recent studies suggest an increased risk of malignancy in patients with inflammatory bowel disease (IBD), though findings are inconsistent.

Objectives: Using data from the Clinical Practice Research Datalink (CPRD), this study set out to further examine this relationship, investigating the effect of disease related factors (i.e. severity, disease duration) and IBD therapy on cancer risk.

Methods: Patients with a first time IBD diagnosis were randomly matched, at the date of IBD diagnosis, to an equally sized IBD-free comparison group. Follow up of 39,998 patients between 1995–2012 identified 1,093 cancer outcomes (IBD 577: IBD-free 516). Using COX proportional hazard regression, multivariable adjusted hazard ratios (HRs) for cancer risk were estimated. A nested case-control analysis using the IBD patients included in the cohort was conducted. Conditional logistic regression was utilised to estimate the risk of cancer development by IBD severity, disease duration and IBD therapy.

Results: Overall, a near significant increase in all cancer risk was observed in patients with IBD compared with IBD-free patients (AHR 1.11, 95% CI: 0.99–1.26). An increased risk of lymphoproliferative malignancies was observed in patients with IBD (AHR 1.51, 95% 1.01–2.26). Findings from the case-control analyses revealed an increase in all cancer risk with increasing disease severity, and duration. A reduction in all cancer (AOR 0.76, 95% CI: 0.58–0.99), intestinal cancer risk (AOR 0.31, 95% 0.14–0.65), and also prostate cancer (AOR 0.42, 95% CI: 0.18–0.98) was observed in association with use of aminosalicylates.

Conclusions: This study suggests a greater risk of cancer development, in particular lymphoproliferative malignancies, in individuals with IBD compared to IBD free individuals. There was evidence to suggest that increased IBD severity and duration may be associated with an increase in cancer risk. Consistent with previous findings a reduction in cancer risk was observed in IBD patients using aminosalicylates, with a significant reduction in prostate cancer risk.

139. Factors and Characteristics for Medication Initiation in Type 2 Diabetes Patients in the UK

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Background: Metformin is recommended as the first-line therapy in type 2 diabetes patients (T2D) but there is limited population-level data describing the prescribing patterns of first-line agents for this condition.

Objectives: To describe the patterns of use, characteristics and determinants of the first antidiabetic medication (ADM) prescription in patients with T2D.

Methods: All newly-diagnosed adult T2D patients (≥ 18 years) were identified from the Clinical Practice Research Datalink (CPRD) between 01/01/05 and 31/12/09 with follow-up until 31/12/12. Cox regression was used to test for associations between patient characteristics and time to initiation of ADM. Logistic

regression models were constructed to identify predictors of receiving initial therapy with metformin.

Results: Of the 72,430 T2D patients; 51,912 (71.2%) initiated therapy with an ADM with a mean time from diagnosis to treatment initiation of 10 months. Increasing age was associated with a longer time to treatment initiation (HR = 0.995 [95% CI: 0.994, 0.996]; p < 0.0001). Younger patients (18–29 years) proceeded onto a treatment faster than older age groups (> 45 years); the mean time was 3 months and 9 months respectively. The majority of patients initiated therapy with metformin (84%), and a smaller proportion with a sulphonylurea (12%). Dual therapy combination was initiated in 1,712 patients (3.4%), of which, 46% was for metformin/sulphonylurea. Triple therapy accounted for <1% of all initial prescriptions. Compared to those aged > 50 years, younger patients (18–50 years) had twice the odds of initiating with metformin (OR = 2.05 [95% CI: 1.94, 2.17]). Women were 15% more likely to receive metformin than men (OR = 1.15 [95% CI: 1.08,1.21]).

Conclusions: The majority of patients initiated therapy with metformin which follows the recommended guidelines. Age and gender were independent factors for the time to therapy initiation and to the choice of therapy.

140. Withdrawn by Author

141. Relative Risk of Myocardial Infarction for Canadian Patients with Psoriasis Treated Systemically as Compared to Patients Treated with Phototherapy

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Background: Several studies have shown that psoriasis is associated with a higher risk of myocardial infarction (MI) and stroke. A few cohort studies have suggested that TNF-alpha inhibitors and/or methotrexate could reduce the incidence of occlusive vascular disease.

Objectives: The objective of this project was to study the relative risk of MI in Canadian patients treated with systemic treatments as compared to patients treated with phototherapy.

Methods: A total of 5,157 patients registered in the Régie de l'Assurance Maladie du Québec (RAMQ) who received at least one diagnosis of psoriasis between 2005 and 2010 and who used phototherapy or an oral or injectable treatment for psoriasis were identified and included in this retrospective cohort study.

Results: A total of 1,221 (23.7%) received methotrexate, 109 (2.1%) cyclosporine, 547 (10.6%) acitretin, 8 (0.16%) ustekinumab, 246 (4.8%) TNF-alpha antagonist and 2940 (57%) UVB-phototherapy. After adjusting for MI risk factors and the use of systemic corticosteroids, there was no significant difference between the relative risk (RR) of MI in patients treated with methotrexate (0.85, (95% Confidence interval [CI]): 0.40–1.84), cyclosporine (1.49, CI: 0.20–11.39), acitretin (0.65, CI: 0.24–1.75) or TNF-alpha antagonist (0.87, CI: 0.19–4.02) vs. patients treated with UVB-phototherapy.

Conclusions: There was no significant difference in RR of MI between psoriasis patients treated with various systemic agents as compared to UVB-phototherapy. However these results are limited by the fact that only 4.8% of patients with psoriasis treated with systemic agents received a TNF-alpha antagonist. This is very low when compared to a recent study performed with a California database which showed that 44.4% of psoriasis patients treated systemically were on a TNF-alpha antagonist. The PASI 15 and DLQI 15 requirement to be eligible to receive a biologic for Quebec patients under the public reimbursement plan may explain this phenomenon.

142. Withdrawn by Author

143. Comparative Effectiveness and Safety of Concomitant Use of SSRIs in Combination with NSAIDs or Paracetamol

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Background: Increased risk of adverse events, e.g. gastrointestinal bleeding (GIB) due to concomitant use of selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs) is well known, however, results regarding their proposed synergistic antidepressant effect are inconclusive.

Objectives: To perform a register-based follow-up study among SSRI users with and without concomitant NSAID or paracetamol use to investigate safety and antidepressant treatment outcomes.

Methods: Within a 25% random sample of the Danish population, we identified all incident SSRI users between 1997 and 2006. We compared rates of all-cause and cause-specific mortality, any psychiatric hospitalization, hospitalization with depression or somatic

events during periods of SSRI use only with rates during periods of combined SSRI and NSAID or paracetamol use. We applied COX regression and competing risk analyses with adjustment for confounders and report adjusted hazard rate ratios (HRR) with 95% confidence intervals (CI).

Results: We identified 124,465 SSRI users, 24,284 (19.5%) using NSAIDs and 13,286 (10.7%) paracetamol concomitantly. SSRI in combination with NSAIDs was associated with a decreased risk for any psychiatric hospitalization [HRR (95% CI): 0.75 (0.67; 0.85)] and hospitalization with depression [0.80 (0.67; 0.94)] and no increased mortality [1.08 (0.96; 1.21)]. Paracetamol together with SSRI revealed an increased mortality [2.72 (2.46; 3.00], especially cardiovascular [3.02 (2.42; 3.75)]. No associations with GIBs were observed. Low-dose acetylsalicylic acid together with SSRIs reduced the risk for any psychiatric hospitalization [0.49 (0.38; 0.63)], depression [0.46 (0.34; 0.63)] and death [0.86 (0.73; 0.99)]. Diclofenac [1.88 (1.39; 2.54)] and selective COX-2 inhibitors [1.79 (1.35; 2.36)] showed increased mortality.

Conclusions: Analyses of the different NSAIDs in combination with SSRIs highlighted the heterogeneity of safety and treatment outcomes of this therapeutic class. Specific NSAIDs may represent a beneficial adjunctive antidepressant treatment option. The increased mortality finding concerning paracetamol requires further investigation.

144. Comparative Effectiveness of Oxcarbazepine and Carbamazepine in Adult Patients with Epilepsy

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Background: There is no information on direct comparison of effectiveness between oxcarbazepine (OXC) and carbamazepine (CBZ) in the real-world setting.

Objectives: To compare the effectiveness between OXC and CBZ in adult patients with epilepsy.

Methods: A retrospective cohort study was conducted by analyzing the Taiwan National Health Insurance Research Database. Patients with epilepsy aged 18 and older and newly prescribed with a single CBZ and OXC between years 2005 and 2009 were included. The primary outcome was the drug persistence, which is regarded as a primary measure recommended by the International League Against Epilepsy for AED effec-

tiveness. We calculated the treatment duration from the index date to the end of a 1-year follow-up period or to the end of the last prescription supply for those who had encountered a treatment change defined as: (1) Discontinuation, (2) Switching/add-on, (3) Hospitalization due to episodes of seizure, and (4) Disenrollment. Inverse probability weighting (IPW) were used to adjust for differences between the two treatment groups, which based on the propensity score (PS) generating by logistic regression to estimates the probability that patients would be selected for CBZ. Several sensitivity analyses were performed by selecting more homogenous subgroups, including 1:1 PS matched cohort, to test the robustness of the results. Cox regression models were used to estimate the persistence of drugs. Unmeasured confounders were evaluated by using rule-out approach.

Results: A total of 2186 and 5,588 patients were included in OXA and CBZ groups respectively. After IPW, the average age of all patients was 52.8 years and 50% of them were male. The risk of treatment change was significantly higher in patients receiving CBZ (hazard ratio [HR], 1.27; 95% CT: 1.20–1.34), as compared with OXA by regression models. The results of sensitivity analyses showed a consistent trend of higher non-persistence risk with CBZ use.

Conclusions: This study provided strong evidence that the effectiveness of OXC is better than CBZ in the real-world scenario.

145. Gastrointestinal Adverse Events of Glucagon-Like Peptide-1 Receptor Agonists for Type 2 Diabetes Mellitus: A Pairwise and Network Meta-Analysis

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1s) are a new class of drugs for type 2 diabetes mellitus (T2DM). Gastrointestinal (GI) adverse events (AEs) are the most frequent AEs reported for GLP-1s. However whether there is difference of occurrence on GI-AEs between GLP-1s is unclear.

Objectives: Our meta-analysis is to integrate evidence from all RCTs comparing a GLP-1 with placebo or active comparator to assess the GI-AEs in T2DM patients.

Methods: We searched independently, in duplicate, MEDLINE, EMBASE and Cochrane library databases (from inception to May 1st 2012), and retrieved references of previous review. Unpublished studies were identified from www.clinicaltrials.gov. We identified RCTs comparing GLP-1 with another treatment with minimum treatment duration of four weeks. Nausea, vomiting and diarrhea were considered as our primary GI-AEs. A pairwise and a network meta-analysis using Bayesian models were performed for summary estimates.

Results: Fourty-two RCTs were included involving 114,728 participants and six kinds of GLP-1s (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide and LY2189265). We found all GLP-1dose groups significantly increased the probability of GI-AEs relative to placebo or conventional treatment. The occurrence of GI-AEs was observed unequivalent with different dosage forms of GLP-1s not only between high and low dosage within the same GLP-1 but also between different GLP-1s. Bayesian model showed that TAS30QW (taspoglutide-30-mg-once-weekly) had maximum probability (84.34% and 91.79% respectively) making a higher proportion of patients to occur nausea and vomiting, while LIX30BID (lixisenatide-30-μg-twice-daily) had maximum probability (85.15%) on developing diarrhea than any other treatment.

Conclusions: Our network meta-analysis from Bayesian analysis, for the first time, provides a useful and complete picture of the associations between GLP-1s with another treatment on GI-AEs. GI-AEs were observed more common than conventional drugs and placebo, and existed difference between GLP-1s. However, yet further evidence is necessary for more conclusive inferences.

146. Frequent Antibiotic Use and Breast Cancer Outcomes

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Background: Frequent antibiotic use is common and may be associated with higher breast cancer risk and breast cancer mortality, but no study to date has evaluated the relation between antibiotic use and breast cancer outcomes among women with a history of breast cancer.

Objectives: To examine the association between frequent antibiotic use, second breast cancer events (SBCE), and disease free survival (DFS).

Methods: We conducted a retrospective cohort study among female health plan enrollees aged $\geq$ 18 years who were diagnosed with incident stage I or II breast cancer between 1990 and 2008 via a tumor registry. Antibiotic use and covariates were obtained from health plan administrative databases and medical record review. We evaluated frequent antibiotic use defined as $\geq$ 4 antibiotic dispensings in any moving 12-month period after diagnosis. Our primary outcome measure was SBCE defined as the first occurrence of recurrence or second primary breast cancer. We evaluated DFS events as first occurrence of death, SBCE, or other cancers. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) while accounting for competing risks.

Results: About 4,216 women were followed for a median of 6.7 years (range 0.3–20.0 years). Fourty percent of women were frequent antibiotic users after diagnosis and 13% had a SBCE. There was a non-significant higher risk of SBCE (HR 1.15, 95% CI: 0.88–1.50) compared to nonusers. Risk of DFS events was higher among frequent antibiotic users (HR 1.25, 95% CI: 1.03–1.51). We observed a significant trend for higher risk of DFS events (p = 0.0056) and death (p = 0.0014) with increasing duration of antibiotic use. Findings were robust to sensitivity analyses that varied exposure definition and lag periods.

Conclusions: Our findings suggest frequent antibiotic use is associated with higher risk of DFS events among women with early stage breast cancer, but any association with SBCE is less clear. The association with DFS events appeared driven by death, which may be influenced by residual confounding. Additional evaluations in different study populations and investigation of frequent use by antibiotic class are important given the high prevalence of frequent antibiotic use.

147. ITP and Pregnancy

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Background: ITP exacerbates low platelets seen in some uncomplicated pregnancies. Pregnancy in women with ITP has been reported to be safe, yet information about treatment during pregnancy and outcomes is scarce.

Objectives: To describe pregnancy outcomes for women with ITP and chronic ITP (cITP), focusing on major congenital malformations (MCMs).

Methods: This retrospective study uses data from the Optum Research Database and STORK (Systematic Tracking of Real Kids), 1995–2009, and links mothers with their infants when both are covered by the same health insurer. The study population consists of patients with at least one diagnostic claim for ITP (ICD-9, 287.31 or 287.3 if before 01DEC2005). Eligible women had complete medical and pharmacy benefits, indication of pregnancy, $\geq$ 280 days of continuous enrollment before the end of pregnancy and a 9-month baseline period. Patients with at least one claim for ITP were classified as having ITP. Those with 2 claims separated by $\geq$ 6 months, one claim and treatment with recognized medications for ITP $\geq$ 6 months later, and those with a splenectomy after the first diagnostic ITP claim were classified as having cITP. Outcome measures included maternal outcomes of live births, preterm births, non-live births including abortions, miscarriages, and MCMs in infants.

Results: We identified 446 women with claims for pregnancy and ITP, 346 of whom were linked to infants. Among these, 27 infants (7.8%) had at least one claim for MCMs. We sought medical records corresponding to these, and obtained 17 (63%). A diagnosis of MCM was confirmed for 10 (PPV = 59%). The prevalence of infant claims for MCMs was higher among mothers with a claims-based diagnosis of cITP, the 7/68 (10.3%). The chart-confirmed MCMs occurred among 3% (10/336) of infants of mothers with ITP and 6.1% (4/66) of infants of mothers with cITP. The prevalence of MCMs was higher among mothers with ITP diagnoses prior to pregnancy 5.7% (3/53) than among those diagnosed during pregnancy 2.5% (7/283). Preterm births were also higher (11.2% vs. 7.8%).

Conclusions: Women with ITP diagnosed prior to pregnancy or with cITP may be at elevated risk of infants with MCMs.

148. Chats about Drugs and Pregnancy on Forum Websites: A French Descriptive Study

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Background: In 2010, 64% of French households owned a personal device having access to the Internet. Internet provides a large amount of information such as medical advice. However, the quality of information on the web is inconstant and not verified.

Objectives: To describe online forum chats about drugs and pregnancy.

Methods: This retrospective descriptive study was conducted in November 2012. Google was used to identify forum websites dealing with drugs and pregnancy. Three French key-words were used for forum, pregnancy and drug. We explored the first 10 forum websites from the google search result. For each website, we selected the first 20 questions about drugs and pregnancy and, for each question, the first 5 answers. Diseases were coded and described using the 10th International Classification of Diseases. Drugs were described using the Anatomical Therapeutic Chemical classification and the FDA pregnancy categories.

Results: One-hundred and fifteen questions were selected. All of them were posted between 2005 and 2012, mostly by women. 36.5% concerned the first trimester of pregnancy. 18.3% of the women were not pregnant or had a desire to become pregnant. Questions about Nervous System drugs, anti-infective for systemic use drugs or alimentary tract and metabolism drugs were the most frequent. Fourty-seven percent were drugs for which the risk has not been correctly evaluated during pregnancy. Only 5% of the 213 answers were made by health professionals. 21.2% of the answers advised to take a drug. Thirty-four percent of the advised drugs are not well-known (category C of FDA classification) or potentially at risk (category D). Finally, 14% of the answers could be at risk for pregnant woman.

Conclusions: This study shows that information about drugs and pregnancy on online chats could be at risk for pregnant women. Pregnant women must be aware that online forums are not reliable sources of information.

149. Medication Use during Pregnancy: A Multinational Perspective

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Background: Inter-country comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology.

Objectives: To examine patterns and predictors of medication use in pregnancy from a multinational perspective, with emphasis on type of medication utilized.

Methods: The study is a multinational, cross-sectional, internet-based study simultaneously performed in several regions worldwide: North and South America, Australia, Northern, Eastern and Western Europe. Pregnant women and new mothers were eligible to participate. The study period was from 1 October 2011 to 29 February 2012. By using an anonymous on-line questionnaire we collected information about maternal demographics, acute and chronic illnesses, and medication use during pregnancy. We measured prevalence and predictors of medication use for acute illnesses during pregnancy, OTC and chronic disorders. Descriptive statistics and logistic regression were used.

Results: A total of 9,483 women completed the on-line questionnaire. Socio-demographic characteristics of our study population were satisfactorily similar to those of the general birthing population in each country. Prevalence estimates for overall medication use ranged from 86.2% in Australia to 84.8% in North America and Northern Europe; lower rates were identified in South America (81.2%), Western Europe (81%) and Eastern Europe (75.7%). Women in Northern Europe and Australia had significant 54–57% increased likelihood to take OTC medications during pregnancy when compared to Western Europe. Similarly, women in Northern Europe, North America and Australia were significantly more likely to use a chronic medication during pregnancy. Working status, educational attainment and alcohol use during pregnancy were significant determinants of acute and OTC medication use. Age and unplanned pregnancy were significant determinants for chronic medication use only.

Conclusions: Although the prevalence of medication use during pregnancy was high in all participating countries, inter-regional differences were apparent. Multinational studies on medication use in pregnancy offer the possibility of inter-country comparability.

150. Medication Discrepancy at Discharge in a Tertiary Hospital in Saudi Arabia

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Background: Medication reconciliation plays a major role in improving medication use safety. The ultimate goal is to facilitate continuity of pharmaceutical care for patients at admission, transition and or at discharge. Discharge is particularly a vulnerable stage since patients are abruptly expected to assume full responsibilities of their medications.

Objectives: To demonstrate that the incorporation of medication reconcili-ation into hospital practice at discharge is a vital step towards improving medication-use safety. And to identify the discrepancies number and type upon conducting discharge reconciliation.

Methods: The study was conducted over 8 weeks period in 2012 at a tertiary hospital in Riyadh, Saudi Arabia. Internal medicine wards were selected and discrepancies (number and type) were recorded in a data collection sheet. Then the discharge counseling phar-

macist conducted medication reconciliation by comparing the discharge medication list with the best possible medication history, the last medication administration record and the take home medications provided by pharmacy.

Results: One-hundred and seventy three patients were screened and 568 discrepancies were identified in 121 patients, with a mean of 4.7 ± 2.8 per patient. Eighteen percent of patients presented with at least one unintentional discrepancy. Sixty-eight percent of unintentional discrepancies involved omission, 11% commission, 9% changed frequency, 9% duplication and 3% wrong duration.

Conclusions: Discrepancies at hospital discharge are common. A qualified pharmacist can effectively identify discrepancies upon discharge and reduce medication errors.

151. The Number of Included Older People in Recent Pre-Authorization Trials

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Background: Older people have often been excluded from pre-authorization trials. Therefore, the regulatory ICH E7 guideline requires a minimal number of older subjects for trials regarding diseases primarily related to aging ($> 50\%$ of database $65 +$) and for diseases not typical for, but present in old age (> 100 subjects $65 +$).

Objectives: To analyze the number of older people in trials of recently authorized drugs indicated for diseases regularly present in old age.

Methods: Eligible drugs for this descriptive study were registered by the European Medicines Agency between January 2008 and December 2010, inclusive. Chosen indications: prevention of venous thromboembolism after replacement arthroplasty (dabigatran, rivaroxaban), osteoporosis (lasofoxifene, bazedoxifene, denosumab), atrial fibrillation (dronedarone, vernakalant), diabetes mellitus type II (liraglutide, saxagliptin), depression (agomelatine), bipolar disorder (asenapine) and epilepsy (eslicarbazepine). Data of all phase II and III trials were identified in the European public assess-

ment reports, the WHO Trials Registry and PubMed. Outcome measures: the number of randomized subjects and the number of those aged $65 +$ and $75 +$. Trials with missing data were not included in the calculation of that outcome. Rates of trials giving information about the number of older subjects and the proportions of older people were calculated.

Results: The number of people aged $65 +$ and $75 +$ was available in 39% and 48% of the 116 included trials, respectively. The proportion of older people varied from 0 to 93%. In trials for indications primarily related to aging ($n = 7$), 47.1% of the subjects were $65 +$ (median 2681, range 524–5,848); 20.6% were $75 +$ (median 1,575; range 216–5,848). In trials for indications present in old age ($n = 5$), 7.5% of the subjects were $65 +$ (median 108; range 14–887); 0.9% were $75 +$ (median 26; range 0–83).

Conclusions: This study on the number of older subjects in clinical trials shows that in trials for indications primarily related to aging, half of the randomized subjects is $65 +$. In trials for indications not specific for, but present in old age, the number and especially the proportion of older subjects is limited, with less than 1% $75 +$ subjects.

152. Expected Timelines To Set-Up an Observational Study in Europe: Example of 4 Pharmaco-Epidemiological Registries

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Background: Post-approval, observational studies encompass various designs and purposes. The approaches to manage them are crucial to their success. One of the key factors for a successful study launch is anticipation of the timelines needed during the start-up to meet sites activation and patient enrolment milestones.

Objectives: To assess the regulatory approval timelines across Europe to highlight the importance of time for study preparation.

Methods: We used four observational studies based on similarity in design and geographic coverage to assess the duration of regulatory process. Those studies were conducted in France, UK, Spain, Italy, Germany, Sweden and Netherlands. Timelines for regulatory procedures encompassed time for approval and contract execution duration in each country. The participating investigators were all specialists treating adult patients.

Results: A total of 507 sites were recruited, ranging from 19 to 204 depending on the study. In Sweden and France the submissions were to Central Authori-

ties, the rest of the countries were submitted to Central and/or Local Ethics Committees. Overall, the average duration for regulatory approval was 5.1 months with a minimum of 2.6 months in Sweden and a maximum of 9.2 months in UK. Contract negotiation was performed either in conjunction with the submissions or following regulatory approvals according to local regulation. On average the time for contract execution was 3 months but again varied by country (1.5 in UK to 4.6 in Italy). An extreme case was the designation of a French study as interventional, despite the observational design, because of numerous PRO questionnaires. In this case, the timelines for regulatory can be significantly extended.

Conclusions: Even if the European countries have common guidelines, the difference in regulatory and ethics evaluation timelines can be different across Europe. An appropriate estimation of the start-up duration is a key factor to launch properly an observational study.

153. Evaluation of Knowledge and Use of Prescription Tools by Hospital Physicians in a Teaching Hospital

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Background: The multiplication of therapeutic classes, the complexity and the multiplicity of scientific data and the regulatory framework make the act of prescribing medicines difficult. In order to help physicians in this activity, prescription tools have been developed in hospitals. However, the question arises of the knowledge and the ownership of these prescription tools by physicians.

Objectives: To evaluate knowledge and use of prescription tools by hospital physicians at the teaching Hospital of Bordeaux, France

Methods: A cross-sectional study was conducted between March and August 2012 among 240 randomly selected physicians of the teaching Hospital of Bordeaux: 60 interns, 60 residents, 90 consultants, 10 associate professors and 20 full professors. Each selected physicians has been asked to fill in a standardized questionnaire exploring their knowledge and usage of prescriptions tools available in this hospital (i.e. the French drug formulary, recommendations from French health authorities, local recommendations elaborated by the hospital drug committee). Data were collected through face-to-face interviews.

Results: A total of 90 out of 240 physicians participated in the survey: 29 interns, 23 residents, 26 consultants, two associate professors and 10 full professors. All respondents reported to use the French drug for-

mulary. Good practice recommendations for drug use (from health authorities or learned societies) were reported to be used by all physicians in their practice with the exception of interns (55%). The hospital drug committee was known by 41% of physicians (N = 37). Eighty percent of physicians (N = 72) reported prescribing off-label. Seventy-four percent of physicians (N = 67) felt that their initial training did not prepare them appropriately for the act of prescribing.

Conclusions: The results show that the knowledge and use of prescription tools of the teaching hospital of Bordeaux can be improved. Several factors may explain these results: lack of practicality (accessibility, intuitivity), lack of adaptation to clinical practice and lack of communication. Simplification, improved accessibility and updating of prescription tools should allow better appropriation by physicians.

154. A Cohort Study Examining Aspirin Use and Mortality in Men with Localised Prostate Cancer

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Background: Expression of cyclooxygenase-2 (COX-2) in prostate cancer (PC) has been associated with high grade tumours and poorer prognosis. Use of aspirin, a COX-2 inhibitor, has been associated with reduced PC-specific mortality. These studies have not, however, provided information on the dose and timing of aspirin use.

Objectives: To examine aspirin use and mortality in men with localised prostate cancer.

Methods: National Cancer Registry of Ireland data was used to identify men with stage I-III PC (ICD10 C61) diagnosed 2001–2006. Linked prescription refill data (General Medical Services) was used to identify aspirin use in the year prior to PC diagnosis; stratified by dose (low <75 mg, high > 75 mg) and dosing intensity (proportion of days / year with aspirin supply available). Cox proportional hazards models, adjusting for age, smoking status, year of incidence, comorbidity score, Gleason score, tumour size, pre-diagnostic statin use, and receipt of radiation (time-varying) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between aspirin use and all-cause and PC-specific mortality. Interactions with tumour characteristics were examined.

Results: About 2,936 men with stage I-III PC were identified (aspirin users, N = 1,131; 38.5%). Median patient follow-up was 5.5 years. In multivariate analyses, aspirin use was not associated with a significant

reduction in PC-specific (HR 0.90, 95% CI: 0.68–1.20) or all-cause mortality (HR 0.98, 95% CI: 0.84–1.15). In dose response analyses, aspirin use was associated with a significantly lower risk of PC-specific mortality in men receiving > 75 mg of aspirin (HR 0.59, 95% CI: 0.35–1.00, p = 0.048) but not <75 mg aspirin (HR 1.01, 95% CI: 0.75–1.37, p = 0.938). Stronger associations were also observed in men with higher aspirin dosing intensity or a Gleason score > 7.

Conclusions: Pre-diagnostic aspirin use, measured using objective prescription refill data, was associated with a significant reduction in PC-specific mortality in men with stage I-III PC receiving > 75 mg of aspirin. These results confirm previous findings, and provide important new information regarding the dose of aspirin associated with survival benefit.

155. Clinical Pharmacy Interventions in a Tertiary Care Teaching Hospital in Southern India

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Background: Medication related problems (MRPs) are one of the contributing factors for patient's morbidity and mortality. Identifying and resolving the MRPs can improve therapeutic outcome.

Objectives: To explore the role of a clinical pharmacist in identifying and resolving actual MRPs and preventing potential MRPs.

Methods: Trainee clinical pharmacists followed the patients admitted to different wards over a period of 12 months. Medication orders and medical records of patients were reviewed for identifying any MRPs with the assistance of senior academic clinical pharmacists. Interventions made were systematically documented and analyzed; categorized as minor, moderate and major based on significance. Rate of acceptance and potential impact of interventions in terms of cost savings, preventing toxicities and improving therapeutic outcomes were measured.

Results: A total of 989 interventions were made from 8,540 patients followed. Majority (70%) of the interventions made were of moderate significance. The common reasons for interventions were drug-drug interaction (14%), untreated indication (12.4%,), drug duplication (11.7%,), drug use without indication (11%), improper drug selection (8.9%), dosage adjustment (8.5%), failure to receive drug (7.5%) and overdose (5%). Maximum number (35.3%) of interventions was in medicine wards followed by surgery (16%) and pulmonology (8%). Interventions made led to cessation of drug in 37.2% of cases, change in drug dose (17%), addition of drug (12.6%) and change in administration time (6.9%). Clinicians accepted majority (98%) of the interventions. However, 2% (n = 17) of total interventions were not accepted and 8% (n = 77) of interventions accepted were not implemented by clinicians. Majority (84%) of the MRPs were identified and intervened within a day of occurrence of MRP. Interventions by pharmacists influenced patient care by improved therapeutic outcome (48.5%), followed by cost savings (26.2%) and prevention of toxicities (26%).

Conclusions: High level of acceptance of clinical pharmacist's recommendations by the clinicians signifies that clinical pharmacists can help deliver and improve overall patient care.

156. Use of Antidepressants and Risk of Developing First-Time Acute Myocardial Infarction: A Systematic Review and Meta-Analysis of Observational Studies

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Background: Increased risk of myocardial infarction (MI) in depressed patients has been well described.

Objectives: This study was to clarify and quantify the effect of antidepressants on the risk of MI.

Methods: We performed a systematic review and meta-analysis of observational studies. A PubMed/MEDLINE search was conducted for studies published up to December 31, 2012 with the limits; humans and English. The studies were first evaluated for publication bias and heterogeneity. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated using random-effects model. Cumulative meta-analysis, subgroup and sensitivity analyses were also performed.

Results: Fourteen (5 cohort and 9 case-control) studies satisfying the inclusion criteria were considered. There was heterogeneity among the studies (pheterogeneity < 0.001, $I^2 = 96\%$) but no publication bias (Begg's p = 0.11 and Egger's p = 0.32). We observed no association between any antidepressant use and risk of MI (RR 1.06, 95% CI: 0.84–1.35, p = 0.619). Further,on secondary analysis a non-significant reduced risk of MI was observed among selective serotonin reuptake inhibitor (SSRI) users (RR 0.84, 95% CI: 0.57–1.22, p = 0.351) and non-SSRI users (RR 0.92, 95% CI:

0.82–1.04, p = 0.204). However,there was a non-signifi-cant increased risk of MI observed among tricyclic antidepressants users (RR 1.14, 95% CI: 0.67–1.96, p = 0.622). Stratification by study design did not substantially influence the RR. Sensitivity analysis confirmed the stability of results. Further, cumulative meta-analysis showed a change in trend of reporting MI risk from positive to no association in antidepressants users between 1996 and 2011.

Conclusions: Findings of our meta-analysis did not support a protective or harmful association between 'any antidepressant' use and risk of MI. Further research is needed to confirm these findings and to identify the underlying biological mechanisms.

157. Eight-Year Results from the US Osteosarcoma Surveillance Study

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Background: The Osteosarcoma Surveillance Study, an ongoing 15-year drug safety surveillance study, was initiated in 2003 to monitor for a possible association between teriparatide treatment and osteosarcoma in adults aged 40 years or older in the US.

Objectives: To provide an update on results, including descriptive characteristics of patients aged 40 years and older with osteosarcoma in the US.

Methods: Incident cases of adult osteosarcoma diagnosed on or after January 1, 2003, are identified through cancer registries in the US. After consent, case information including demographics, prior treatment with medications, and exposure to possible risk factors is ascertained via telephone interview. Medical record review is performed for a random sample each year to validate self-reported information.

Results: As of September 30, 2012, 1,729 patients diagnosed between 2003 and 2010 had been identified from the 16 participating cancer registries and 643 had been interviewed. Characteristics were similar for interviewed and noninterviewed patients. Among patients interviewed, mean age was 60 years, 47% were female, and 86% were white. Osteosarcoma, NOS (72%) and chondroblastic osteosarcoma (11%) were the most common morphologic types; leg bones (31%) and pelvis/sacrum (16%) were the most common anatomical tumor sites. Reported prevalence of known risk factors was 20% for history of radiation and 6% for history of Paget's disease of bone. The prevalence of other possible risk factors included 27% for prior history of

cancer and 18% for prior trauma or infection at site of cancer. No patients reported use of teriparatide prior to the diagnosis of osteosarcoma.

Conclusions: Data from this 15-year surveillance study contribute to knowledge about the long-term safety of teriparatide. After 8 years of data collection, the study has not detected a pattern indicative of a causal association between treatment with teriparatide and osteosarcoma.

158. Withdrawn by Author

159. Medication Safety Resources Available through a New Public Access Repository: A Descriptive Analysis

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Background: There is increasing need for and interest in publicly available scientific information related to diverse aspects of medical product safety. Public health agencies such as the U.S. Centers for Disease Control and Prevention (CDC) are one potential source of relevant documents.

Objectives: We sought to characterize the number and type of documents related to medication safety available through a recently released U.S. government website.

Methods: We conducted searches for CDC-authored documents available for review and download in CDC Stacks (stacks.cdc.gov/), a searchable online repository available to the public. Searches were conducted using keywords relevant to contemporary and historical medical product use and safety issues, and representative publications were downloaded.

Results: A search for 'medication safety' retrieved 2,021 documents (out of over 9,700 total) including 356 articles published in peer-reviewed journals. Other types of media retrieved included videos (n = 5) and software (n = 7). Nine hundred thirty-two documents mentioned 'drug utilization' and 619 'antimicrobial use'. Searches for 'thalidomide', 'Reyes Syndrome', and 'influenza antivirals' located 10, 192, and 213 documents, respectively.

Conclusions: CDC Stacks is a readily accessible source of reference materials for researching current and past medication use and safety issues of interest to the public health community. Stacks may serve as a model institutional information repository for government, academia and non-profit organizations. The public access model exemplified by CDC Stacks complements

open access publishing by making available resources beyond traditional peer-reviewed scientific literature. Advantages for researchers include the ability to access documents without having to pursue Freedom of Information requests. Public access repositories are also a potential tool to combat the 'digital divide' by providing broader access to information at subnational levels and in areas with limited formal information infrastructure. Advanced (i.e. Boolean) searching features currently under development will facilitate wider use of CDC Stacks by scholars and policy professionals.

160. Medication Adherence in Pediatric Patients with Epilepsy Using Prescription Refilled Rate and Self-Reported Questionnaire

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Background: Both self-report questionnaire (e.g., Morisky medication adherence scale; MMAS) and prescription refilled rate (e.g., medication possession ratio; MPR) are widely used methods for assessing adherence to antiepileptic drugs (AEDs) therapy in pediatric patients with epilepsy. However, no study has provided the information on the agreement between these two methods.

Objectives: To measure AEDs adherence and assess the agreements between self-report questionnaire and pharmacy refilled rate on measuring drug adherence.

Methods: A cross-sectional study was conducted in one medical center in Taiwan from February to April 2012. Pediatric patients aged 18 and younger who received continuous prescriptions of AEDs more than one year were included. Eligible patients or his/her family caregivers were interviewed and assessed on their AEDs adherence by the eight-item MMAS. Electronic prescription records were used to calculate the MPR of patients within one year. Patients were classified into dichotomous adherence level based on MMAS score at 8 and MPR at 0.8, respectively. Kappa statistics was used to evaluate the agreement between MMAS and MPR on the adherence classification.

Results: Fourty eight patients with 64.8% male gender and mean age of 11.1 ± 4.1 years were included in the analysis. Most of them had the history of epilepsy more than 4 years (64.6%), and no seizure attack in previous 6 months (75%). The mean score of MMAS and MPR was 7.06 ± 1.08 and 0.96 ± 0.07, respectively. Substantially higher proportion of patients was defined as adherent accessed by MPR (97.9%) than by MMAS (41.7%) (Kappa = 0.02).

Conclusions: The agreement between MMAS and MPR was poor, which implied that the regular refill of prescription was not consistent with the actual administration of dispensed medicines.

161. Methods Issues in Observational Studies of the Cardiovascular Risk Associated with Glucose-Lowering Medications: Results of a Systematic Review and Evaluation

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Background: The evaluation of methods and risk of bias in observational studies included in systematic reviews is essential to interpretation of results. In the context of the SAFEGUARD project, we conducted a systematic review of observational studies on the use of glucose-lowering drugs and the risk of cardiovascular events.

Objectives: To describe the methodological issues of included studies, using the RTI item bank (RTI IB).

Methods: The RTI IB consists of 29 items organized in 11 domains. We added another 4 items (a 12th domain) to evaluate aspects specific to this research question. Methodological issues covered by the 12 domains were summarized in study population, exposure, outcome, analysis, immortal-time bias, confounding by indication and residual confounding, and formulary restrictions. Two investigators independently evaluated methods and risk of bias in 44 included studies.

Results: Although some studies did not describe the study population in detail, only four studies were at high risk of bias in this domain. Exposure definition was very heterogeneous across studies and the information on how exposures were assessed was incomplete. The most frequent outcomes were acute myocardial infarction and heart failure. Very few studies conducted validation by comparing source medical records. Statistical methods were evaluated as appropriate in 57% of studies. Overall, 43% and 30% of the studies were at high risk of confounding by indication or of residual confounding, respectively; 25% of the studies were at risk of immortal-time bias. Few studies provided information on formulary restrictions. Dose

information was very limited, and there was no information on duration.

Conclusions: There was great heterogeneity across the included studies regarding outcomes, exposures of interest, and the comparison groups used. Confounding could affect a large proportion of the studies. The large number of reference groups in the included studies could make quantitative synthesis of risk estimates challenging.

162. The Extent and Origin of Resistance to Antituberculosis Drugs in the Netherlands in the Period 1993–2011

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Background: The elimination of tuberculosis (TB) is threatened by an apparent increase in the level of resistance in *Mycobacterium tuberculosis*. In the Netherlands, where the majority of TB patients are immigrants, resistance may also be increasing.

Objectives: To determine the trends in resistance to antituberculosis drugs in the Netherlands in the period 1993–2011, focusing on the origin of the patients. To determine the extent to which resistance was acquired or transmitted.

Methods: We conducted a retrospective study on 18,294 *M. tuberculosis* isolates from TB cases notified in the Netherlands between 1993 and 2011. Standard drug susceptibility testing for isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide was performed on each isolate. In case of resistance to isoniazid and/or rifampicin, susceptibility to the second-line drugs amikacin, capreomycin, ciprofloxacin, clarithromycin, clofazimin, cycloserin, kanamycin, linezolid, moxifloxacin, ofloxacin, protionamide, and rifabutin was assessed. We investigated whether resistance was acquired or transmitted, and for both scenarios we determined whether this happened in, or outside the Netherlands. We used logistic regression analyses to assess the statistical significance of trends in resistance.

Results: Anti-TB drug resistance was found in 13% of all cases, and was more frequent among non-native (16%) than among native Dutch TB patients (6%, p < 0.001). The trend in resistance increased among native patients (p < 0.001), and decreased among non-natives (p = 0.02) in the period 1993–2011. Since 2005, resistance has increased in both groups (p = 0.03 and p = 0.01, respectively). Overall, we found a significantly increasing trend when excluding streptomycin resistance (p < 0.001). The trend was most markedly increased for isoniazid resistance and multidrug-resistant TB (p = 0.01 and p < 0.001, respectively). Although 92% of resistance was due to transmission, mostly outside the Netherlands or before 1993, in some cases (n = 45) resistance was acquired in the Netherlands.

Conclusions: We conclude that antituberculosis drug resistance is increasing in the Netherlands, mostly related to immigration, but also to domestic acquisition.

163. Potential Predictors of Naltrexone Response in Alcohol Dependence: A Systematic Review

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Background: Currently, naltrexone shows only modest effectiveness for alcohol dependence though some individuals demonstrate a robust response. Identifying predictors of response to naltrexone in alcohol dependence is an important goal to advancing clinical care.

Objectives: To conduct a systematic literature review of publications through mid-2012 to determine whether factors such as age, sex, baseline craving for alcohol, family history, and genetic polymorphisms predict naltrexone response in alcohol dependent patients.

Methods: A systematic search of Pubmed, CINHAL, Embase, Psycinfo and the Cochrane Library from 1/1/1990 through 2/28/2011 yielded 753 citations, with an updated PubMed search conducted on 4/26/2012. Each title and abstract was dually reviewed for inclusion with disagreements adjudicated by discussion. We reviewed the full text of papers meeting the inclusion criteria to determine if they contained analyses of factors influencing naltrexone response. Publications with predictor information were abstracted into standardized evidence tables that also captured risk of bias. The strength of evidence was assessed based on risk of bias.

Results: We abstracted 75 articles containing information on one or more predictors. The evidence sug-

gested that male gender, higher craving for alcohol at baseline, the Asp40 polymorphism of the u-opioid receptor, and positive family history of alcoholism were potential predictors of naltrexone response. The risk of bias for this literature was relatively high as there were very few *a priori* studies examining predictors. Many studies were secondary analyses on subsets of subjects, sample sizes were generally small, and there were significant methodological weaknesses including differences in how predictors and treatment outcomes were defined.

Conclusions: While weak associations have been noted for a number of clinical and biological factors associated with naltrexone response, the overall strength of evidence at this time is not sufficient to support their use for clinical care. Future studies must be designed to identify best treatments for important patient subgroups before clinical practice can advance.

164. Reliability of Outcome Definitions Using Japanese Standardized Electronic Medical Records Data

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Background: Several pilot studies for drug safety assessment are ongoing in PMDA's MIHARI project. This is one of those studies using standardized electronic medical records (EMR) data. Reliable outcome definitions in database studies largely depend on how the data were generated from clinical settings which would vary by country. It is said that outcome definitions by diagnosis codes only often have low validity in Japanese EMR data. Therefore, more appropriate outcome definitions are needed to utilize the data in drug safety assessment. However, the number of validation studies for outcome definitions has been very few in Japan. This validation study was designed using simplified procedure to evaluate 'reliability' of three outcome definitions.

Objectives: To determine the most reliable outcome definitions using the standardized EMR data.
  Methods.

Data source: The EMR data from April 1, 2007 to December 31, 2011 were collected from six hospitals in Japan. *Outcomes of interest:* (1) diabetes mellitus, (2) hyperlipidemia and (3) hyperthyroidism. Each outcome was defined by 3 ways – diagnosis codes only, treatment drug codes only, or both codes. Potential cases were automatically identified from the EMR data. *Adjudication of true cases:* All potential cases from the above (1–3) were adjudicated by laboratory test results. The adjudication criteria were set according to the published clinical guidelines in Japan. *Statistical analysis:* Positive predictive values (PPV) of the outcome definitions were calculated, and distributions of patient characteristics were compared between true cases and false cases.

Results: The PPVs of diabetes mellitus defined by diagnosis codes only, treatment drug codes only and both codes were 21%, 38%, and 45.4%, respectively. The PPVs for hyperlipidemia were 54.1%, 61.8%, and 63.8%, and those for hyperthyroidism were 18.5%, 61.2%, and 66.7%.

Conclusions: The results from this study suggested that the combination of diagnosis codes and drug codes provided the most reliable outcomes.

165. Withdrawn by Author

166. Public Perception towards Adverse Drug Reaction Reporting in Saudi Arabia

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Background: Consumers' adverse drug reaction (ADR) reporting can increase the chance to detect a new ADR signals. In the United States, consumers and HCPs had almost the same number of ADR reports in 2010. In Saudi Arabia, the Saudi Food and Drug Authority developed a pharmacovigilance system to receive ADR reports from HCPs and public.

Objectives: To assess the perception of Saudi community about adverse drug reaction reporting and pharmacovigilance.

Methods: A cross-sectional study using a self-administered validated questionnaire distributed during awareness campaign held in two malls in Riyadh city for two days. The questionnaire consisted of three parts to assess the perception of Saudi public about pharmacovigilance and ADR reporting.

Results: Two hundred and four questionnaires were collected. Only 23% of participants can define the meaning of ADR, 13% of the participants had heard about pharmacovigilance term, and only 7% heard about Saudi Pharmacovigilance Center. More than 80% of the respondents believe that it is important to gather information about ADRs and educate public on how to report ADRs. Fifty six percent they will report if they have a non-serious ADR. Fifty seven percent ask about ADRs associated with medications they are using. About 28% of the participants are usually informed by their physicians and pharmacists about the importance of reporting ADR.

Conclusions: This study highlights that public in Saudi are not aware about ADRs and it is reporting system. Also they do not know how and to whom they should report ADRs. Future intervention studies should focus on educating public about medications and how to report ADRs.

167. Evaluation of Knowledge and Barriers among Physicians towards Adverse Drug Reactions (ADRs) Reporting in Saudi Arabia

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Background: Recently, the Saudi Food and Drug Authority developed a spontaneous reporting system of Adverse drug reactions (ADRs). Under-reporting is a major issue with any spontaneous reporting system.

Objectives: To assess the knowledge and attitude of physicians towards spontaneous reporting of ADRs, to identify the barriers for ADR reporting by physician, and identify the factors which encourage ADR reporting among physicians.

Methods: This was a cross-sectional questionnaire-based study including physicians working at King Abdulaziz Medical City in Riyadh, Saudi Arabia. A total of 600 physicians were approached for their knowledge and attitude towards ADR reporting. The questionnaire sought the demographics of the physician, their knowledge of ADRs and their reporting behavior, barriers to ADRs reporting, and the factors that they perceived may influence ADR reporting. Provision was also made for suggestions on possible ways to improve ADR reporting.

Results: A total of 240 filled questionnaires were returned giving response rate of 40%. Majority of the respondents (85%) appeared to be knew the definition of Adverse Drug Reaction. Seventy-five percent of the respondent physicians were not familiar with the spontaneous reporting system to the Saudi Food and Drug Authority. One hundred seventy five (73%) respondent did not report any ADR in the last year. And 40% of the respondent physicians do not report because they are not aware of online reporting methods. Providing instructions on reporting and regular bulletins on ADRs is the main factor that encourages physicians to report (51%).

Conclusions: The knowledge of ADRs and how to report them are inadequate among physicians working in a tertiary hospital in Riyadh. Continuous medical education, training and integration of ADR reporting into the clinical activities of the physicians might improve reporting.

168. Adverse Events Associated with Colchicine Drug Interactions: Analysis of the Public Version of the FDA Adverse Event Reporting System

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Background: Colchicine was originally used, and continues to be used, to treat rheumatic diseases. It is used most frequently for the treatment of gout but is also used to treat familial Mediterranean fever, pericarditis, and Behcet's disease. However, because of its pharmacokinetics, colchicine can interact dangerously with other drugs.

Objectives: The objective of the study was to analyze the association between drug-drug interactions involving colchicine and major adverse events as reported in the U.S. FDA Adverse Event Reporting System (FAERS).

Methods: All major adverse events (including death, initial or prolonged hospitalization, and persistent or significant disability) related to colchicine between 2004 and 2011 were retrieved from FAERS. Then, events evidently caused by interactions with drugs (such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, cyclosporine, and ranolazine) were distinguished from events evidently caused by colchicine as the primary suspect drug. Major adverse event rates were calculated.

Results: Between 2004 and 2011, a total of 2,655 adverse event reports involving colchicine interactions with other drugs were found in the FAERS database, of which 718 reported a death (implying a fatality ratio of 27%), 762 reported a hospitalization (giving a 28.7% hospitalization rate), 78 referred to life-threatening events, and 56 reported disability. Pancytopenia, renal failure, vomiting, drug toxicity, and diarrhea were the most common reported events. There were 4,717 reports involving colchicine as the primary suspect drug, of which 527 reported a death (fatality ratio of 11.2%). A statistically significant ($p < 0.001$) difference between the two fatality ratios was found.

Conclusions: When combined with certain other drugs, evidence suggests that colchicine may be associated with a relatively high death rate, especially if not dosed appropriately. In light of the current data, physicians should be keenly aware of all potentially fatal

drug-drug interactions and follow therapeutic guidelines on using colchicine.

169. Risk of Major Bleeding with Dabigatran vs. Active Controls: A Systematic Review and Meta-Analysis of Randomised Clinical Trials

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Background: The direct thrombin inhibitor dabigatran is approved for atrial fibrillation (AF) and for prophylaxis of venous thromboembolism (VTE). The standard dose is 300 mg/day for AF and 220 mg/day for VTE. As for other anticoagulants, major bleeding represents a safety issue of this drug.

Objectives: To evaluate major bleeding risk of dabigatran in AF and VTE.

Methods: A systematic review and meta-analysis was conducted applying keywords related to Dabigatran and Randomised Controlled Trials (RCTs) in Medline, SCOPUS, and Cochrane database. RCTs with at least 100 patients treated with dabigatran, at doses approved in clinical practice for AF and VTE, were included in this meta-analysis. Data were extracted independently by two investigators and verified by a third one. The relative risk (RR) of major bleeding associated with dabigatran was estimated for each indication and then stratified by dose. The pooled RR was computed using fixed-model effect.

Results: Eight trials (34,078 patients) were included in the quantitative analysis. In AF there was a reduced risk of major bleeding for dabigatran compared to warfarin (risk ratio, RR, 0.88, 95% confidence interval, 95% CI: [0.78–0.98]); a reduced risk was found for dabigatran 220 mg/day (RR 0.81, 95% CI: [0.71 to 0.94]) and no difference in risk for dabigatran 300 mg/day (RR 0.94, 95% CI: [0.82–1.07]). In VTE prophylaxis there was no difference in risk for dabigatran compared to enoxaparin 40 mg/day (RR, 1.07, 95% CI: [0.72 to 1.58]), or specifically for 220 mg/day dabigatran (RR, 1.31, 95% CI: [0.85 to 2.02]. No evidence of heterogeneity was found.

Conclusions: In AF and prophylaxis of VTE the risk of major bleeding at standard doses of dabigatran was not different to that of active comparators.

170. Evaluation of Signal Scores over Time

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Background: There is increasing interest in augmenting current post-marketing safety surveillance signal detection activities utilizing spontaneous data with observational data. Because post-marketing safety surveillance occurs prospectively it is of interest to evaluate how signal scores perform over time.

Objectives: To evaluate and compare how signal scores generated from spontaneous and observational data perform over time.

Methods: We identified a range of well known drug-condition pairs that were published from 2005 to 2010. Data-mining scores (point estimate, lower and upper bounds) were generated for spontaneous (EBGM, EB05, EB95) and observational data (SRR, SRRLB95, SRRUB95) using commercially available data-mining software. Drug-condition pairs that crossed a predefined threshold as of 2010 were included in the analysis. Data-mining scores were generated cumulatively by year for each drug-condition pair using both data sources. Results were evaluated for each data source for over all trends, trends before and after the drug-condition pair was published, and trends between spontaneous and observational data.

Results: In observational data, drug-condition pairs generally exceeded the predefined threshold prior to publication and black-box warnings. Signal scores generally increased at a gradual rate both prior to and after publication. In some instances there was a spike in the signal score immediately following a publication or a black-box warning being issued, followed by signal scores eventually reverting to gradual change over time. In spontaneous data, when predefined thresholds were exceeded the signal scores behaved in a similar fashion to observational data but were more prone to higher peaks initially as well as increases in signal scores after a publication or black-box warning.

Conclusions: Signal scores from both data sources tended to stabilize relatively quickly, with more variance seen with spontaneous data which is probably

related to the smaller sample size relative to observational data.

171. Reducing Words without Losing Clinical Meaning – Can Text Mining Accelerate Review of Spontaneous Reports?

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Background: Individual case review of spontaneous adverse event (AE) reports remains a cornerstone of medical product safety surveillance for industry and regulators. Text mining offers automated information extraction to potentially accelerate the evaluation of large volumes of unstructured data and facilitate signal detection. We developed the Vaccine adverse event Text Mining (VaeTM) system for this purpose.

Objectives: To evaluate the accuracy of information extraction by VaeTM and assess the gains in efficiency of review.

Methods: The diagnosis, onset time and alternative explanation were extracted from 1,000 reports from the Vaccine Adverse Event Reporting System (VAERS) using the VaeTM system. We compared the clinical interpretation of the VaeTM extracted data with traditional manual review of full text reports for these three variables. Two experienced clinicians alternately reviewed text miner output and full text. A third clinician scored the match rate using a predefined algorithm; the proportion of matches and 95% confidence intervals (CI) were calculated. Review time per report was analyzed.

Results: Proportion of matches between the interpretation of the VaeTM extracted data, compared to the interpretation of the full text: 93% for diagnosis (95% CI: 91–94%) and 78% for alternative explanation (95% CI: 75–81%). Extracted data on the time to onset was used in 14% of cases and was a match in 54% (95% CI: 46–63%) of those cases. When supported by structured time data from reports, the match for time to onset was 79% (95% CI: 76–81%). The extracted text averaged 136 (73%) fewer words, resulting in a mean reduction in review time of 64 (60%) seconds per report.

Conclusions: Despite a 73% reduction in words, the clinical conclusion from VaeTM extracted data agreed with the full text in 93% and 78% of reports for the diagnosis and alternative explanation, respectively. The limited use of the extracted time interval data indicates the need for inclusion of time-related structured fields. VaeTM may improve review efficiency, but further study is needed to determine if this level of agreement is sufficient for routine use.

172. Pharmacovigilance from a Public Health Point of View – A Survey of Simplified Recording of Adverse Drug Reactions (ADR) in Medical Records

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Background: To increase the awareness of possibly avoidable ADRs, dose-dependent and well-known reactions (50–70% of all ADRs), the Drug & Therapeutics Committee in Stockholm stated as a wise advice: 'Beware of adverse drug effects! Document these by adding an ICD-10 diagnosis, i.e. Y57.9 'Adverse drug effect in therapeutic use' to the other diagnoses.

Objectives: To determine if the use of the ICD diagnosis Y57.9 ('Adverse drug effect in therapeutic use') can provide meaningful clinical data for a quality drug prescribing report.

Methods: *Design:* Review of medical records with Y57.9 diagnosis by eight physicians with a protocol focusing on ADR determination. *Setting:* Intermediary Care Unit of Internal Medicine within the Emergency Dept. Karolinska University Hospital (50 patients, 1.1% of all patients) median age 77 (26–94) and Dept. Internal Medicine, St Göran Hospital (122 patients, 0.8%) median age 78 (21–97) in Stockholm. *Main outcome measures:* We focused on augmented pharmacological (Type A) vs. idiosyncratic (Type B) reactions related to estimated renal function by Cockcroft Gault (CG) equation (eCrCl mL/min). *Statistical analysis:* Descriptive statistics.

Results: Pharmacological (Type-A) reactions were judged in 74 of 109 women (68%) and in 46 of 63 (73%) men. Idiosyncratic (Type-B) reactions were seen in 35 (32%) women and 17 (27%) men. Among patients with a Type-A reaction 68% had eCrCl below 60 mL/min (level of concern for drug treatment). In Type-B reactions only 23% had a clearance below 60 mL/min. Warfarin, digoxin, oxycontin and trimethoprim were the drugs most frequently causing ADRs.

Less than 5% of these 172 ADRs were reported to the regulatory agency. The physicians filling in the protocols rated this feed-back survey as increasing awareness of ADRs in a meaningful way.

Conclusions: By use of a protocol it was possible to classify medical records with the Y57.9 diagnosis into Type-A and Type-B reactions. The estimated creatinine clearance confirmed this classification. From a quality of drug prescribing point of view this will increase the awareness of ADRs that are not reported to the regulatory agency.

173. Comparison of 7 Patient Information Leaflets (PILs) of Narcotic Pain Medications Marketed by Indian Generic Companies with Original SmPC from Innovator Companies

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Background: Long-term implications of prescribing narcotic pain medication to patients suffering from chronic pain remains a serious concern. In recent times there have been several safety issues with increased use of these drugs. In an era where consumer awareness is at an all-time high and rapidly increasing, information available to patients and prescribers for safe and efficient use of medicines is still an area of concern.

Objectives: Compare PILs of Indian generic drugs with the SmPCs of Innovator company drugs and review if the package inserts adhere to standard guidelines for narcotic pain medications.

Methods: To collect unbiased information pharmacists were requested to provide PILs for narcotic pain drugs randomly from local pharmacies. For SmPCs, Innovator companies were contacted, if not obtained we used the internet. Two documents were then compared for each section and missing information highlighted. Drugs for which SmPC and PI were compared were acetaminophen/hydrocodone, oxymorphone, oxycodone, tramadol, methadone, morphine and fentanyl.

Results: Most of the drugs were not accompanied by PIs in India. Documents compared showed standard labeling guidelines were not adhered and details not updated on the PILs. Discrepancies were found in undesirable effects section, contraindication, special warnings and precautions for use and interaction with other drugs. Serious adverse events i.e. tolerance, dependence, serious visual disturbances, abuse potential, suicidal ideation, withdrawal reactions, increased hepatic enzymes and anaphylactic reaction were missing in the PIL for drugs manufactured by the Indian companies when compared with the innovator companies.

Conclusions: Our research highlighted that Indian generic companies do not have a mechanism/process for development of PIL with several important events on safety of these drugs missing. With increase of Indian generic drug use world-wide, it is essential that generic PILs should be consistent and include adverse events in line with innovator company SmPCs to help both patients and prescribers mitigate risk and use drugs judiciously.

174. ENCePP Supporting Regulatory Decision Making

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Background: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EN-CePP) is coordinated by the European Medicines Agency (EMA) to strengthen post-authorisation medicines research. On 12 February 2013, ENCePP included 116 centres, 17 networks and 46 data sources thereby increasing capacity to perform studies by streamlining access to resources. ENCePP's guiding principles are transparency, scientific independence and improved methodological standards irrespective of a study being sponsored by academia, industry or a regulatory authority. ENCePP's E-Register serves as the register for post-authorisation studies referred to in the good pharmacovigilance practices (GVP).

Objectives: ENCePP may be viewed in the context of initiatives aimed at generating evidence to support regulatory decision making. Since 2010 these have included EMA commissioning of independent academic researchers to conduct studies to assess new and emerging safety concerns. It is a requirement that these are conducted as 'ENCePP Studies' to ensure a maximum level of transparency and scientific independence from the study sponsor.

Methods: The present report concerns an overview of this experience with implications for ENCePP.

Results: To date 7 such EMA funded studies have either been conducted or are on-going relating to A/H1N1 pandemic vaccines, rosi- and pioglitazone, bisphosphonates, anxiolytic/hypnotics, isotretinoin and oral contraceptives. For all, the principal investigators are from ENCePP partner centres. Six have been awarded an ENCePP Study Seal – the start of the first study preceding its development. Three relate to monitoring of the effectiveness of risk minimisation measures. Findings have already been used to support regulatory discussions.

Conclusions: The experience with EMA commissioning of ENCePP Studies has demonstrated that ENCePP

can deliver results in a timely manner. Transparency has resulted from the registration of study protocols and results. Relationships in terms of roles and responsibilities of the study sponsor, namely the EMA, are clear in line with adherence to the Code of Conduct. The role of ENCePP in changing the way post-authorisation medicines research works continues to be consolidated.

175. Post-Marketing Requirements in Diabetes Mellitus in Europe (EMA) and the USA (FDA)

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Background: Post-marketing requirements (PMRs) include studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations.

Objectives: The objective of this research is to quantify the PMRs requested in diabetes mellitus by the Food and Drug Administration (FDA, USA) and the European Medicines Agency (EMA, EU).

Methods: The Post-Marketing Requirements Database was used to explore requirements for post-approval studies in diabetes mellitus published on the websites of the FDA and the EMA since 2005. The search was performed on January 14, 2013.

Results: Thirty-three PMRs, corresponding to 21 different products, were retrieved. All were requested by the FDA. Not a single EMA PMR was identified. Several reasons for this discrepancy were identified: (1) Lack of correspondence in marketing authorizations: Out of the 21 products authorized in the USA, eight are either not authorized (five products, five PMRs), or are suspended/withdrawn (three products, three PMRs) for safety reasons in Europe; (2) Lack of correspondence in the definition of PMRs: Out of the 33 FDA PMRs, 13 represent pediatric studies (corresponding to 12 products, of which only nine are authorized in Europe). However PIPs are not labeled PMRs in Europe, but are considered 'pre-marketing' requirements: unlike in the USA, a marketing authorization application in Europe (equivalent to NDA) must contain a pediatric plan, waiver or deferral, or the filing will be denied. A search on the EMA pediatrics database shows that the EMA has requested five pediatric investigation plans (PIPs) with a US correspondence to five products. Therefore, with the exclusion of FDA PMRs corresponding to products not authorized or withdrawn/suspended in Europe (eight PMRs) and to EMA PIPs (five PMRs), there are 20 FDA PMRs corresponding to ten different products, for which there are no equivalent PMRs in Europe.

Conclusions: This review of PMRs in diabetes mellitus shows that discrepancies exist between the EMA and the FDA due to legislative differences or in marketing authorizations.

176. Post-Marketing Requirements: An Overview of the Therapeutic Areas Targeted by the EMA and the FDA

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Background: Post-marketing requirements (PMRs) include studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations.

Objectives: The objective of this research is to identify which therapeutic areas, and within these areas, which therapeutic indications have been subjected to the highest number of PMRs from the Food and Drug Administration (FDA, USA) and the European Medicines Agency (EMA, EU).

Methods: The Post-Marketing Requirements Database was used to explore requirements for post-approval studies published on the websites of the FDA and the EMA since 2005. The search was performed on January 2, 2013.

Results: The therapeutic area for which the EMA required the highest number of studies was *factors influencing health status and contact with health services* (n = 36) for the indication *prophylaxis of influenza in a pandemic situation* (n = 36). Within this indication, ten different products were concerned with Pandemrix and Cepalvan being the products with the highest number of studies requested (n = 6 for each product). In comparison, the FDA had requested only 27 studies for the same therapeutic area, and neither Pandemrix nor Cepalvan were approved in the USA. The area for which the FDA requested the highest number of studies was *endocrine, nutritional, and metabolic diseases* (n = 80), and within this area, the more populated indication was *diabetes mellitus* (n = 41). Within this indication, Onglyza, Byetta and Victoza were the products with the highest number of studies requested (n = 4, 5, and 6 respectively). In comparison, the EMA had requested only 14 studies for the same area, and none for diabetes. Onglyza, Byetta and Victoza were approved in Europe but not subjected to PMRs.

Conclusions: This brief review showed discrepancies in PMRs between the FDA and the EMA. More research is needed to explain these differences.

177. Withdrawn by Author

178. Development of Systematic Target Drug Prioritization Process in Korea

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Background: Spontaneous adverse drug reaction (ADR) reports are the basis of pharmacovigilance activities. In Korea, spontaneous ADR reports were received by the regulatory authority since 1988, and approximately 300,000 reports have cumulated since. The Korea Institute of Drug Safety and Risk Management (KIDS) was established in 2012, and one of the major objectives of KIDS is handling these reports. Due to vast amount of information, prioritizing target drugs to analyze signals from the Korea Adverse Event Reports database (KAERS) was a major task.

Objectives: We aimed to identify appropriate target drugs for detecting signals by developing and applying systematic procedures for drug prioritization.

Methods: Criteria for selecting target drugs were investigated, which included; drugs that safety issues were raised, frequently reported drugs in KAERS, substances which signals were detected worldwide, widely prescribed drug detected in the Health Insurance Review and Assessment Service claims database, and newly approved drugs in Korea. Each criterion was reviewed and drugs according to the measures were listed. Consultations from healthcare professionals were received to confirm the criteria and also the selected drugs.

Results: A total of 58 drugs were prioritized for signal detection, which included sildenafil and oral contraceptives, drugs of major interest in the Korean society due to safety and social issues. Other criteria were thoroughly applied to select the target drugs, which were aligned in order of importance to be analyzed for potential signals.

Conclusions: To detect potential safety issues from ADR reports database, prioritization of the target drugs is essential. A systematic process including feasible criterion can be applied to utilize the ADR reports database for generating safety information in an efficient manner.

179. Effects of Opioid Analgesic Tablets Resistant to Breaking, Crushing and Dissolving on Patient Safety Outcomes

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Background: Prescription opioids provide analgesia to millions of patients but can be fatal when misused. Reformulating opioids with physicochemical barriers to tampering may prevent fatal misuse in the intended patient population.

Objectives: To assesses changes in patient-safety outcomes (ie, non-abuse) after introduction of reformulated brand extended-release oxycodone (ERO, OxyContin) with barriers to breaking, crushing, chewing and dissolving on August 9, 2010.

Methods: Patient safety outcomes were assessed in four studies: (1) Kaiser Permanente Northwest and Northern California study of opioid overdoses among patients prescribed opioids, (2) RADARS System study of therapeutic errors affecting patients and accidental exposures (unintentional general exposures) reported to US poison centers, (3) National Poison Data System (NPDS) of the same outcomes as #2 and 4) adverse events reported to the manufacturer. Adverse consequences preceeding vs. following reformulated ERO introduction were compared.

Results: Prescriptions for brand ERO declined 11% nationally 2 years after reformulation. Over the 4-year Kaiser study, the number of opioid overdose events among people prescribed ERO decreased 68% and the number of people prescribed ERO decreased 72%, so prescription-adjusted rates were unchanged. In NPDS, therapeutic errors affecting patients decreased 20% (15% when prescription-adjusted) and accidental exposures decreased 39% (34% when prescription-adjusted) from 1 year proceeding to 2 years following ERO reformulation. In the RADARS System, therapeutic errors affecting patients decreased 21% (11% when prescription adjusted) and accidental exposures 41% (34% when prescription adjusted) from 1 year proceeding to 2 years following ERO reformulation. Medication error reports to manufacturer decreased 16% (fatal error reports decreased 50%) from 2010 to 2011. Fatal reports decreased by 52% while overdose fatali-

ties declined 66% from 1 year proceeding to 2nd year following ERO reformulation.

Conclusions: Patient-related adverse outcomes assessed in four studies decreased following reformulated ERO (OxyContin) introduction. Prescription-adjusted rates decreased in three of four studies.

180. MIHARI – Medical Information for Risk Assessment Initiative Year 4

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Background: PMDA, the Japanese regulatory agency, is being in a process of reinforcing and enhancing its post-marketing safety measures as stated in its second mid-term (FY 2009–2013) plan. MIHARI project has started in PMDA since FY 2009 to develop a new safety assessment system for post-marketing drugs, which will address: (1) secure access to claims databases and electronic medical records (EMR) databases, and (2) appropriate skillss for pharmacoepidemiology studies using data from such databases. The update from MIHARI in the fourth year is reported.

Objectives: To develop a new safety assessment system for post-marketing drugs using Japanese medical databases.

Methods: The following five steps are applied to multiple Japanese medical databases. (1) Establishment of accessibility to multiple databases. (2) Evaluation of each database by characterization studies, validation studies, and other pilot studies. (3) Development of skills to select appropriate study designs and statistical analysis for each characterized database. (4) Practice about real drug safety issues using the developed safety assessment system. (5) Implementation of this system.

Results: In the fourth year, MIHARI was at the third and the fourth steps described in the methods. Some pilot studies about risk assessment using claims data and EMR data in the standardized format were performed. Simplified validation study about four outcomes using claims and EMR data was completed. Normal validation studies about one outcome were also performed with collaborative two hospitals. Data-mining as a new signal detection method applied to the claims data is ongoing. In addition to those pilot studies, a guideline for pharmacoepidemiology study using electronic medical database was developed to enhance conducting pharmacoepidemiology studies appropriately for the purpose of drug safety assessment.

Conclusions: MIHARI has been making good progress. Accumulated findings, knowledge, and experiences from the pilot studies may contribute to establish the new safety assessment system in PMDA.

181. Classification and Evaluation Algorithm of Drug Safety Information of KFDA

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Background: Diverse drug safety information with different reliability are generated after marketing authorization, regulatory agencies are need to identify and confirm new risk factors from available information and perform scientific evaluation to ensure safety quickly and soundly.

Objectives: To develop the classification and evaluation algorithm of drug safety information for KFDA, the Korean regulatory agency.

Methods:

(1) Design: Literature investigation and evaluation algorithm development
(2) Setting: Flow chart or algorithm diagram
(3) Exposure or interventions: Signal or not, scientific validity, and possibility of risk management etc.
(4) Main Outcome Measures: Safety measures (restriction of indication, labeling change, withdrawal etc.)
(5) Statistical analysis: None.

Results: Based upon the analysis results from WHO-UMC publications and PV guidelines of ICH, EMA, FDA and PMDA, safety information collected domestically (i.e. spontaneous reporting database etc) were used for drug safety evaluation and decision-making. First, search signals using basic safety information and scientific validity of confirmed signals is supposed to be evaluated. Valid safety issues are delivered to benefit/risk balance assessment and possibility of risk management affects the final safety measures.

Conclusions: We invented the classification and evaluation algorithm of domestic drug safety information and it is expected to appropriate and expeditious safety measures.

182. Reporting Patterns of Adverse Drug Reactions over Recent Years in China: Analysis from Publications

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Background: Supervision of adverse drug reactions (ADRs) now is a working priority for the drug authori-

ties of China. In recent years, the authorities have endeavored to improve ADR monitoring. A great amount of investment has been assigned to this field, including reporting system development and bureau establishment. However, figures from the reporting patterns of ADR over recent years in China remains unclear for the world due to the limitation of language.

Objectives: To clarify the reporting patterns of ADRs in China and discuss the development and limitations of ADR monitoring in recent years.

Methods: A variety of sources were searched, including the official website of the State Food and Drug Administration, the national center for ADR monitoring center, and publications from Pubmed. We collected the relevant information and made descriptive and comparative analysis from the year 2006 to 2011.

Results: The past 6 years witness a huge increase in the reporting number of ADRs. The corresponding number is 369392, 547000, 602000, 638996, 692904, 852799 from the year 2006 to 2011, respectively. Manufactories make little contribution to the database and the proportion hit 13.7% in the year of 2011, which is the highest in recent years. The average report per million inhabitants is 637 in the year 2011, which satisfy the recommendation by WHO. However, the proportion of new and severe report is still quite low, with 17.1% in the year 2011. From the perspective of reporting drug classification, the reports mainly concern anti-infection drugs and traditional Chinese medicines. In addition, we found that only 2433 reports from China were submitted to the global database, VigiBase, from 2000 to 2009.

Conclusions: Numbers of reports of adverse drug reactions in China are on the rise, while there is still a long way for China to contribute for the global ADR monitoring. The authorities still face a lot of challenges in the near future.

183. Post Authorization Safety Study Comparing Quetiapine to Risperidone and Olanzapine

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Background: This PASS study (registration ID: NCT01342120) was a post-approval commitment for the bipolar depression application of quetiapine.

Objectives: To compare incidence rates of specific outcomes of interest between new users of quetiapine, olanzapine or risperidone in The The Netherlands

Methods: From the PHARMO Database Network containing linked community pharmacy and hospitalization records, patients starting immediate or extended release quetiapine, olanzapine or risperidone in the period 2000–2009 for any indication were selected. Incidence rates (IRs) of all-cause mortality, failed suicide attempts, extrapyrimidal symptoms (EPS), diabetes mellitus (DM), hypothyroidism, acute myocardial infarction (AMI) and stroke were compared using Cox proportional hazards regression modeling.

Results: The observational study included 4,658 patients starting quetiapine, 7,229 starting risperidone and 5,856 starting olanzapine. Median duration of use was 0.6 years. Prescribed doses were generally lower than the approved defined daily doses, especially for quetiapine. IRs for EPS were statistically significantly lower with quetiapine compared to risperidone (HR 0.18; 95% CI: 0.13–0.24) and olanzapine (HR 0.59; 95% CI: 0.42–0.84). IRs for failed suicide attempts were significantly higher among quetiapine users compared to risperidone users (HR 2.07; 95% CI: 1.35–3.16), and slightly higher, but not statistically significant, compared to olanzapine users (HR 1.32; 95% CI: 0.90–1.94). IRs for DM were significantly lower among quetiapine users compared to olanzapine users (HR 0.66; 95% CI: 0.44–0.97), but not significantly compared to risperidone users (HR 0.85; 95% CI: 0.57–1.25). IRs for all-cause mortality, hypothyroidism and stroke were similar for quetiapine users and risperidone or olanzapine users. The number of AMI events was too small to draw any conclusions (quetiapine 4, risperidone 3, olanzapine 13).

Conclusions: Quetiapine was associated with lower EPS, but higher failed suicide attempt rates compared to risperidone. Quetiapine was associated with lower EPS and DM rates compared to olanzapine. The results should be interpreted with caution because of possible channeling and residual confounding.

184. Application of Propensity Score Methods to Japanese Claims Data

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Background: Several pilot studies for drug safety assessment are ongoing in PMDA's MIHARI project. This is one of the pilot studies focusing on application of propensity score (PS) methods to Japanese claims data. Data elements in the Japanese claims data are specifically designed to the national health insurance reimbursement system, and generated claims data are closely linked to Japanese clinical settings. Feasibility

of applying the PS methods to the claims data is unclear since there have been very limited number of pharmacoepidemiologic studies using the claims data.

Objectives: To evaluate the feasibility of applying the PS methods in a cohort study using the Japanese claims data.

Methods: *The cohort study:* To estimate the association of atypical antipsychotics (AAP) with glucose metabolism disorder (GMD) relative to typical antipsychotics (TAP). *Data source:* Medical and prescription claims data of about 1.2 million patients from Japan Medical Data Center Co., Ltd. (2005–2010). *Study population:* New users of any AAP and those of any TAP as a comparator. *Outcome:* Incidence of GMD was defined by a prescription of any anti-diabetes drugs. *Statistical analysis:* We conducted 2 analyses using the PS methods. One used PS matching and another used PS standardization by standardized mortality ratio (SMR) weights. The balances between the AAP group and TAP group in terms of baseline covariates were assessed by standardized difference. Risk of GMD for AAP users was compared with TAP users using Cox proportional hazard regression model.

Results: In both analyses, the standardized differences of each covariate were small, and all covariates were well-balanced between treatment groups. The PS model had a c-statistic of 0.879. AAP users have no increased risk of GMD relative to TAP users (PS matching analysis, hazard ratio (HR) 0.96 [95% CI: 0.30, 3.14]; PS standardization analysis, HR 0.88 [95% CI: 0.28, 2.80]).

Conclusions: Measurable many potential confounders necessary for PS modeling could be obtained from the Japanese claims data, and the PS methods produced comparable groups. Application of the PS methods to the Japanese claims data was feasible in this study.

185. Quinine Sulfate Use and Hematologic Adverse Events: Active Surveillance in Medicare

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Background: In August 2005, FDA approved quinine sulfate (QS) for treatment of malaria. In December 2006 FDA ordered unapproved QS formulations off the market and cautioned consumers of risks associated with 'off-label' use of QS for leg cramps (LC). FDA continued to receive spontaneous reports of serious adverse hematologic events with QS and drug utilization trends have suggested ongoing use for LC.

Objectives: Examine QS use trends among US Medicare beneficiaries, as part of FDA/CMS SafeRx Project, focusing on use of QS for malaria treatment, babesiosis (compendial indication), or LC. Assess associations with adverse hematologic outcomes compared to Diltiazem (DZ).

Methods: Medicare beneficiaries, aged 65 +, in 2006 – 2011, were enrolled in new-user QS or DZ cohorts if during 183 days prior to index dispensing they were enrolled in Medicare Parts A, B and D, had no dispensings of QS or DZ, ticlodipine, clopidogrel, and sulfa drugs, and no diagnoses of immune thrombocytopenic purpura (ITP), thrombotic microangiopathy (TTP), or hemolytic-uremic syndrome (HUS). Diagnoses of malaria, babesiosis, or LC were determined during 183 days prior to index dispensing from medical claims. Outcomes of ITP, TTP, or HUS in in-patient or emergency room settings were determined during drug exposure.

Results: From 2006 to 2011, prevalent use of QS decreased by 98%, from 421,553 to 8819 users. There were 87,606 new users in the QS cohort and 606,813 in the DZ cohort. Nine QS new users had diagnoses of malaria, 23 of babesiosis, 35,975 of LC, and 51,599 had none of these diagnoses. During follow-up, incidence rates (per 1,000 person-years) for ITP, TTP and HUS for QS were: 1.78, 0.23, and 0 and for DZ: 0.4, 0.04, and 0.01. Incidence rate ratios for ITP and TTP comparing QS to DZ were 4.5 and 5.8 respectively. Limiting exposure time to 30 days, gave incidence rate ratios for ITP and TTP comparing QS to DZ of 3.4 and 5.5.

Conclusions: Use of QS decreased substantially, although diagnoses of LC persist. To our knowledge this is the first demonstration of an association for QS and ITP and TTP in claims data.

186. Outlier Removal Expedites Adverse Drug Reaction Surveillance – Evaluation of a Simple Unmasking Strategy

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Background: Reports of suspected adverse drug reactions (ADR) are the cornerstone of post-marketing surveillance for harmful effects of medicines. In the absence of reliable usage data, disproportionality analysis is used to highlight drug-ADR pairs for manual review. This is vulnerable to distortion from outlying reporting rates of specific drug-ADR pairs that may mask other associations involving that drug or ADR.

Objectives: To characterize masking by influential outliers in two spontaneous reports databases and evaluate the impact of outlier removal on disproportionality analysis.

Methods: A simple unmasking algorithm that identifies and excludes reports on influential outlier drug-ADR pairs was developed. A disproportionality analysis is carried out for the modified data set with more conservative confidence intervals in parallel to an unadjusted analysis. The algorithm uses a direct measure of the masking effect, and makes no assumptions on the number of outliers per drug or ADR. Statistical shrinkage ensures robustness of the outlier identification, and a permutation analysis ensures that the rate of spurious associations from the parallel analysis is kept in the order of 1%. The occurrence of masking was characterized in the WHO global ICSR database, VigiBase™, and a regional collection of reports from China, Shanghai SRS.

Results: For WHO-ART critical ADR terms such as myocardial infarction, rhabdomyolysis, and hypoglycaemia outlier removal led to an increase in the number of Statistics of Disproportionate Reporting (SDR) of 25–50% and gains in time to detection of 1–2 years. Twenty-three percent of the reports in VigiBase and 18% of reports in Shanghai SRS listed an influential outlier. Twenty-seven percent of the ADRs and 5% of the drugs in VigiBase, and 2% of the ADRs and 3% of the drugs in Shanghai SRS were involved in an outlier. The overall increase in the number of SDRs for both datasets was 3%.

Conclusions: Unmasking through removal of influential outliers led to substantial increases in the number of drugs highlighted for specific ADRs including rhabd-omyolysis, myocardial infarction, and hypoglycaemia. Masking involves a fair number of reports but a small proportion of drugs and ADRs.

187. Comparison of seven Patient Information Leaflets (PILs) of Anesthetic Drugs Marketed by Indian Generic Companies with Original SmPC from Innovator Companies

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Background: Anesthetic drugs are used during surgical procedures to cause sedation or reduce the ability to feel pain. There have been several safety issues with use of general anesthetic drugs during and after surgery.

Objectives: Compare PILs of the Indian generic drugs with that of the SmPCs of Innovator company drugs and review if the package inserts adhere to standard guidelines for anesthetic drugs routinely used for surgical procedures.

Methods: Seven common drugs used routinely for general anesthesia – propofol, rocuronium, sevoflurane, thiopental, ketamine, desflurane and halothane were chosen randomly, for which the SmPC and PI were compared. For SmPCs and PILs both the Innovator companies and Indian generic companies were contacted, if not obtained we used the internet. Two documents were then compared for each section and missing information highlighted.

Results: Documents compared showed standard labeling guidelines were not adhered and details not updated on the PILs. Discrepancies were found in undesirable effects section, contraindication, special warnings and precautions for use and interaction with other drugs. Serious adverse events i.e. metabolic acidosis, hyperlipidemia, hyperkalemia, pancreatitis, rhabdomyolysis, steroid myopathy, increased hepatic enzymes and anaphylactic reaction were missing in the PIL for drugs manufactured by the Indian companies when compared with the innovator companies. However for halothane, liver damage and malignant hyperthermia were included in the generic PIL but not in innovator SmPC.

Conclusions: Our research highlighted that Indian generic companies do not have any proper mechanism/process for development of PIL with important events on safety of these drugs missing. Provision of good quality patient information is intended to both the patient and the prescriber to mitigate serious risks and use of drugs judiciously. With increase of generic drug use world-wide, it is essential that generic PILs be consistent and include adverse events in line with innovator company SmPCs.

188. Survey of Demand to Postmarketing Adverse Drug Event Reporting Data

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Background: While the Korea Institute of Drug Safety and Risk Management (KIDS) receives and manages postmarketing adverse drug event reporting data, there have been growing demands to open up data analyses or case reports to the public. However, there is no consensus on the opening data to the public including the methods and defined range of disclosing.

Objectives: The objective of this study is to find out the size of demands requested to the KIDS to disclose postmarketing adverse drug event reporting data analyses or specific case reports.

Methods: We identified the number of requests received in the KIDS (January 13, 2012 to February 14, 2013) related to disclose the data analyses or case reports. Then, the requests were classified by their details and the occupation of the requester and investigated.

Results: From January 13, 2012 to February 14, 2013, a total of 56 requests related to disclose the data analyses or case reports were identified. Amongst those, the Korea Food and Drug Administration (KFDA) made 22 requests for the analyses of specific drugs and adverse events and 17 requests by phone for adverse event report statistics and case report details. Classifying by the occupation of the requester, there were eight requests from health care professionals, 26 requests from health related institutions or groups, three requests from customers and two requests from media. Classifying by the detail of the request, there were 30 requests for adverse event report statistics, seven requests for case reports and two requests for causality assessment results.

Conclusions: Identifying the size of demands requested to the KIDS to disclose the data analyses or specific case reports can be a valuable resource to help suggesting proper ways of opening data to the public including the methods and defined range of disclosing.

189. Low Renal Function in Hospitalized Geriatric Patients: Potentially Serious for Use of Renal Risk Drugs

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Background: Pharmacokinetic and pharmacodynamics changes are common in old age, particularly decreasing renal function, requiring drug adjustment.

Objectives: To study the use of renal risk drugs (RRD) in relation to renal function estimated with two routine methods in hospitalized geriatric patients in Stockholm, Sweden.

Methods: *Design:* Observational study of patients aged 75 and older, with an expected 3-month survival and minimum a week in hospital. Renal function was estimated by creatinine clearance (eCrCl) using Cockcroft Gault (CG) equation (mL/min, absolute Cl) and the abbreviated Modification of Diet in Renal Disease (MDRD4) equation (mL/min/1.73 m^2, relative Cl), estimated Glomerular Filtration Rate (eGFR).

Setting: One-hundred and eight patients, aged 75–104 years, most with multi-morbidity, in the Department of Geriatrics, Karolinska University Hospital.

Main outcome measures: Proportion of men and women, treated with RRD, defined as those drugs that may need any sort of intervention to prevent adverse drug reactions (ADR) in relation to renal function < 60 (level of concern!) or < 30 (contraindication for many drugs).

Statistics: Descriptive.

Results: Included were 70 women and 38 men, mean age 87.7 and 86.5 years, respectively. eCrCl was (mean, SD) 37 ± 15 mL/min, (range 12–85) in women; 44 ± 17; (14–94) in men. eGFR was 53 ± 20 mL/min/1.73 m^2 (range 13–97) in women; 61 ± 23 mL/min/1.73 m^2 (22–116) in men. With CG and MDRD4 89% and 64%, resp. of the patients were < 60. A value < 30 were present in 26% of the patients measured with CG, in 12% with MDRD4. Patients had a mean of 3 RRD, 1.8 of them requiring dose adjustment. Cardiovascular drugs and analgesics were the most common RRD. Oral anti-diabetics, digoxin, and ACE-inhibitors were drugs most often dose adjusted or discontinued.

Conclusions: We found surprisingly low renal function, particularly in women, in these geriatric patients. This may require dose adjustment for many drugs based on CG used in clinical trials. If therapy is based on other

renal function methods (MDRD4) the risk of dose dependent ADR may increase, particularly important for RRDs with a narrow safety window.

190. Use of Antiepileptic Drugs and Risk of Infection in Taiwan and Denmark: A Collaborative Cross-National Sequence Symmetry Analysis

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Background: Antiepileptic drugs (AED) have been reported to be associated with infectious disorders; however, the association is potentially confounded by other chronic conditions related to epilepsy, such as stroke. The phenotypes of the metabolic liver enzymes are different between Caucasian and Asian, which may result in discrepancy in metabolism of AED and risk of infections.

Objectives: Using the data from two different nations to investigate AED and the risk of infections. The potential confounders were considered.

Methods: Data was extracted from the Taiwan National Health Insurance Research Database and the Danish Patient Registry and the Danish Prescription Register. We performed sequence symmetry analysis (SSA) to test the propensity to initiate an outcome drug (antibiotics; ATC code J01) following the use of an index drug (AED; ATC code N03A), where the index drug is suspected to induce a side effect (in this case infection) that warrants the treatment with the outcome drug. A causal relationship is suspected if there was a significantly higher proportion, describing as the sequence ratio (SR), of patients initiated marker drugs after index drug than those before index drug. New AED users from 2006–2010 without history of cerebral palsy, stroke, dementia, and disability after head trauma were included. The adjusted SR and 95% confidence intervals (CI) were derived from dividing the crude SR by the null-effect SR. Outcomes defined as admissions due to infectious disease were also tested for their association with AED by SSA.

Results: A total of 1,376,220 AED users were found in the Taiwan NHIRD, 192,291 of which also filled an antibiotic. Overall, the use of AED was not associated with the use of antibiotics, showing an adjusted SR of 0.79, (95% CT: 0.78–0.79). Individual drug classes also showed no association except miscellaneous antibiotics defined by ATC code J01X (1.07; 1.05–1.08). The sig-

nals from events analyses were consistent with main analysis. The analyses of the Danish data are currently in progress.

Conclusions: Our study does not support the hypothesis that the use of AED is associated with infections in Taiwan

191. Strategies To Optimize Physician Survey Research: Results from a Survey of Urology and Oncology Practitioners in 19 Countries

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Background: Physician surveys are increasingly requested to assess the effectiveness of risk minimization measures as part of new EU legislation for pharmacovigilance (PV). Strategies to ensure representative sample and maximized response rates have been developed by market research (MR) partners on behalf of drug manufacturers.

Objectives: We conducted a detailed physician survey with urology and oncology practitioners (MDs) to measure treatment of non-metastatic (M0) prostate cancer (PC) using MR strategies.

Methods: A 45-min online survey was completed by MDs from 19 countries with high/increasing incidence of M0 PC (Ferlay 2010): US, Canada, Australia, and 16 European countries. The survey instrument was developed from in-depth interviews with MDs in France, Germany, and Spain (n = 18). Eligibility ensured MDs were responsible for treatment (tx) decisions in the care of M0 PC and had ≥ 10 patients (pts) treated with androgen-deprivation therapy (ADT). Sampling of oncology (vs. urology) specialists reflected M0 PC tx pattern in the country. Sampling ensured regional distribution and practice type. Country-level weights were applied during analysis to account for differences in prevalence of M0 PC.

Results: In total, 441 MDs completed the survey over a 1-month period. The response rate was 12% overall (from email invitations, and via telephone), and 20% of responders qualified for the study. MDs had 98689 PC pts under their care, 76,386 (77%) were M0 PC. Of M0 PC, 38% received ADT: 37% (28104) received gonadotropin-releasing hormone agonists/antagonists and < 2% (1,251) had bilateral orchiectomy. The 34% tx rate reported by US MDs was consistent with decreasing ADT use (Shahinian 2010), whereas rates were higher in Europe, and highest among Eastern European pts.

Conclusions: This physician survey was completed over a 1-month timeframe by 441 MDs in 19 countries. Efficiencies were gained by utilizing MR strategies to achieve good response rates, timely execution, and user-friendly online questionnaire with real-time progress updates while ensuring representativeness of the sample.

192. Evaluation of Drug Induced Liver or Renal Toxicity with National Health Insurance Claim Database

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Background: The incidences of viral hepatitis and uremia in Taiwan are higher than western countries. Therefore, we need an active surveillance for monitoring hepatotoxicity and nephrotoxicity of new chemical entities (NCEs).

Objectives: The purpose of this study is to find NCEs that got the reimbursement price after 2005 and have higher ratio of hepatotoxicity or nephrotoxicity.

Methods: The data source was the database of national health insurance from 2005 to 2010. The study was separated into two steps. First, the patients who had hepatotoxicity or nephrotoxicity after administration of NCEs were selected from inpatient database. The patients who already had hepatotoxicity or nephrotoxicity before drug taking were excluded. Second, we used nested case control study to evaluated erlotinib and gefitinib. The patients who were younger 15 years old and no diagnoses of lung cancer would be excluded. We matched age (± 3 y/o), sex, start year with 1:4 ratio. If the patients got hepatotoxicity or nephrotoxicity before starting drugs, they would be excluded. The factors of hepatic or renal function, concurrent drugs with high hepatotoxicity or nephrotoxicity, hepatitis, clinics of Chinese medicine, chemotherapy were adjusted in the statistic model. The medical cost will also be evaluated in the study.

Results: Among NCEs from 2005 to 2010, 7 of 48 NCEs had higher incidence of hepatotoxicity and 14 of 48 NCEs had nephrotoxicity than mean incidence in Taiwan. The odds ratios of using erlotinib or gefitinib, previous hepatitis or hepatic impairment were adjusted in the statistic model of hepatotoxicity. The odds ratios of using erlotinib or gefitinib, previous renal impairment, previous chemotherapy, concurrent use of drugs with nephrotoxicity were adjusted in the statistic model of nephrotoxicity. The medical cost of patients with hepatotoxicity or nephrotoxicity was higher than patients without hepatotoxicity or nephrotoxicity.

Conclusions: We need an active surveillance of hepatotoxicity and nephrotoxicity in Taiwan. The result of this pilot study provide a model of active safety surveillance for policymaking.

193. Risk of HBV Reactivation in Patient Receiving Rituximab: Results from Taiwan National Adverse Drug Reaction Reporting System

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Background: The use of rituximab in non-Hodgkin's lymphoma (NHL) is known to be associated with increased risk of hepatitis B virus (HBV) reactivation, which could be explained by depletion of B cells. Since HBV infection is a high-prevalent disease in Taiwan, serologic testing for prior viral HBV exposure and anti-viral agents have been covered by National Health Insurance for rituximab-containing chemotherapy in NHL patients for the prophylaxis of HBV reactivation since 2009. However, it's still unclear whether the same risk exists when used for other indications, such as autoimmune disorders which have been widely used in Taiwan.

Objectives: The aim of this study is to review the patterns of HBV reactivation cases in patients receiving rituximab in Taiwan National ADR reporting database.

Methods: We collected rituximab cases containing MedDra LLT coded with hepatitis B reactivation from 2005 to 2012 in our database.Characteristics of the cases was further reviewed and analyzed.

Results: From a total of 358 rituximab reported cases, 27 (7.54%) were suspected of having HBV reactivation. Median age was 58 ± 10.9 years (13 males vs. 14 females).The average days between the last dose of rituximab and HBV reactivation was 78 days. Nineteen cases (70%) were reported as HBV carriers, with histories of hepatitis B or tested as HBsAg positive. Of the 27 HBV reactivation cases, 21 cases (77.8%) were indicated for NHL;four cases (14.8%) for rheumatoid arthritis and one case (3.7%) for Idiopathic thrombocytopenic purpura. 9 (33%) and 2 (33%) fatal cases were indicated for NHL and non-NHL respectively.

All patients indicated for NHL had HBV serologic testing (HBsAg at least) before treatment of rituximab; however, only one patient treated for non-NHL indication was tested.

Conclusions: The risk of rituximab associated HBV reactivation in patients treated for autoimmune disorders cannot be overlooked. HBV tests are suggested to be performed before the treatment of rituximab. HBV carriers on rituximab should be monitored closely during and for at least 6 months after completion of therapy, also prophylactic antiviral agents are recommended.

194. Post-Marketing Study of Denosumab in Male Osteoporosis: A Model Feasibility Assessment

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Background: Post-marketing observational safety studies are becoming increasingly important in assessing the long-term safety of drugs. Assessing the feasibility of such studies is challenging but necessary, as parameters such as disease prevalence and case algorithms need to be evaluated before study initiation.

Objectives: To describe and present, as a model, a feasibility assessment of a post-marketing study of the long-term safety of denosumab for the treatment of osteoporosis (OP) in men using two large US health claims databases.

Methods: We undertook several steps for feasibility assessment. First, we examined key characteristics of the Medicare and United Healthcare databases. Second, we considered algorithms to identify OP in men based on an OP diagnosis, fracture at a site normally associated with OP, or use of an OP medication. Third, we determined the prevalence of eligible men with OP in both databases, and estimated the number of men with OP who would be exposed to denosumab based on market projection through 7 years post approval. Statistical power to evaluate the relative risk of nine predefined adverse events of special interest (AESI) was then determined.

Results: OP prevalence estimates ranged from 0.4% to 7.3%, depending on age, specific algorithm, and database. Although it may be difficult to identify osteoporotic fractures in men, given the under-diagnosis of OP

in men we recommend an OP case algorithm that uses diagnosis, fracture, and treatment. Assuming that 0.25% of men with OP will be treated with denosumab during the first 2 years and 0.5% thereafter, we anticipate this study would include 7,487 denosumab-treated men with 18,915 person-years of exposure in US Medicare, and 404 denosumab-treated men with 687 person-years of exposure in the United Healthcare database. Despite the relatively large size of the Medicare database, we noted limited power to detect rarer AESIs such as osteonecrosis of the jaw.

Conclusions: The above-described steps for determining the feasibility of a post-marketing safety study can inform the design of similar studies in the future.

195. Drug Safety and Corporate Governance

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Background: Pharmacovigilance in low and middle income countries is implemented in the context of poverty where the health care system is overburdened and under-resourced.. The integration of pharmacovigilance into the corporate governance of global pharmaceutical corporations may support postmarket drug safety in limited capacity settings.

Objectives: It was hypothesized that pharmacovigilance will be similar for all Global Pharmaceutical Corporations operating within the host country. The objective of this study was to investigate the relationship between corporate governance and pharmacovigilance by global pharmaceutical companies (GPCs) in India.

Methods: Qualitative research methods were used in this study of corporate governance and pharmacovigilance. Data were collected from corporate annual reports, reports of corporate social responsibility, corporate websites and Food and Drug Administration filings. Documents were analyzed for discourse on pharmacovigilance, framing, policies adopted, and actions taken by or against the corporations. Documents were read iteratively to identify key themes that explain how post market drug safety is integrated into the corporate governance of global pharmaceutical companies. The data were read and coded using an open coding process. A conceptual framework was developed to guide the comparative analysis of pharmacovigilance governance of GPCs doing business in India.

Results: All of the corporations studied showed compliance with minimum regulatory requirements however some firms exceeded minimum requirements. The results reject the study hypothesis and findings suggest

that additional factors may make global pharmaceutical corporations establish different pharmacovigilance practices.

Conclusions: Findings reveal that pharmacovigilance is not fully integrated into the corporate governance of any of the global pharmaceutical corporations operating in India. Corporations with the least integration have the most outstanding drug safety actions. More research is needed to explain why Daiichi Sankyo has a higher degree of integration than other companies studied and to identify policy incentives to support increased integration of pharmacovigilance into corporate governance.

196. Pharmacovigillance of Oral Antituberculosis in Indonesian TB Patients

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Background: Tuberculosis (TB) is common communicable disease that still being a burden in Indonesia. The information of safety profile of TB treatment in Indonesia is lacking. Thus, activities to strenghtened and to deploy the systems to support TB medicine safety needs to be enhanced.

Objectives: This study's objective is to study the safety profile of tuberculosis drugs.

Methods: The study were conducted in public health centers with the highest incidence of TB in Lampung and DI Yogyakarta, Indonesia. The study design was cohort event monitoring. We analyzed the hepatotoxicity signs and symptoms in naive TB patients treated with Fixed Dose Combination (FDC) od TB drugs.

Results: We recruited 137 naive TB patients from 21 public health cares. Most of the patients had characteristics as; male (56.3%), age between 35–64 y.o (63.5%), did not have smoking habist history (49.2%), positive AFB test (75%) and infiltration was seen in rontgen (41%). On the baseline assessment, the patients experienced chronic cough (62.7%) and less than 80% patients experienced other TB symptoms. The complains of respiratory and gastrointestinal systems, fever and headache were decrease on the first and second month of FDC treatment ($p < 0.05$). The monthly assesment in the high-intensity phase showed that skin, musculoskeletal and respiration systems were getting worse, the body weight were seen significantly increased and the alanine and aspartate transaminase did not differ from the baseline.

Conclusions: We did not find significant adverse event in this study. We still collect the patients data from the monitoring of continuation phase to understand the adverse event.

197. Withdrawn by Author

198. Changes in Prescription Drug Opioid Abuse Following Reformulation of an Abuse Deterrent Product: A National Study of Substance Abuse Treatment Clients

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Background: In August, 2010, the manufacturers of OxyContin introduced a reformulated product OxyContin (OP), which had been determined by *in vitro* abuse liability studies to be much harder to abuse via tampering compared to the old abuse deterrent formulation, OxyContin (OC).

Objectives: The current study used an enriched population of active abusers of opioid pain reliever products to examine whether the introduction of the reformulated OxyContin resulted in (a) changes in consumption of OxyContin, and/or (b) tampering of OxyContin.

Methods: *Setting*: The data are drawn from a national sample (n = 930,206) of clients (ages 12 or older) entering publicly-funded substance abuse treatment between July 1, 2009 and March 30, 2012 in the United States and District of Columbia. *Exposures*: Outcomes included abuse of OxyContin in the 30 days prior to admission and tampering (e.g., non-oral routes of consumption) among those reporting abuse. *Statistical Analyses*: Comparisons between the pre (Q2 of 2010 or earlier) and post (Q3 of 2010 or later) periods marked by release of the reformulated OxyContin were examined using the generalized linear mixed model (GLMM), with adjustments for time and treatment population characteristics.

Results: In the 12 months days the reformulation, 2.6% of clients reported abusing OxyContin. In the 12 months after reformulation, there was a significant increase to 2.9% in reported abuse ($p = 0.008$). Among abusers, tampering also increased from 44% to 46% ($p = 0.010$). No effect on tampering behaviors was observed.

Conclusions: These data indicate that abuse deterrent formulations hold the potential to alter consumption behavior involving abuse, both in terms of positive

and negative consequences involving increasing or decreasing risk for abuse. Additional community-based ethnographic surveillance data are needed to help elucidate the risk perceptions toward ADFs that may alter patterns of abuse in relation to abuse deterrent properties of opioid medications.

199. Results of the Experience with the Use of Varenicline in Daily Practice Using Intensive Monitoring

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Background: Although a concise overview of Adverse Drug Reactions (ADRs) of varenicline is known, little is known about the time related information about ADRs of varenicline such as for example latencies.

Objectives: To gain insight in the experience and safety of varenicline in daily practice as reported by patients through web-based questionnaires using an intensive monitoring system.

Methods: Design A prospective, observational, non-interventional cohort study. *Setting*: First-time users of varenicline were defined as patients who have not filled in a prescription of varenicline in the previous 12 months using the first prescription signal in that particular pharmacy. *Participants*: All first-time users of varenicline in participating pharmacies between 1 December 2008 and 31 March 2012 were invited for the study. Patients could sign up for the study on a dedicated website. Electronic questionnaires were sent after 1, 2 and 6 weeks, 3 months and 4 months after they started to use varenicline. In these questionnaires questions about drug use and ADRs were asked for. *Main outcome measurements*: Information about the ADR, seriousness, and action taken when experiencing an ADR. *Statistical analysis*: Descriptive analysis was done using Microsoft Access.

Results: About 1,418 patients signed up for the study. Response rates for the various questionnaires vary from 31.3% to 62.5%. 58.8% of the patients reported at least one ADR. The most frequently reported ADRs were nausea (30.8%), abdominal pain (11.2%) and abnormal dreaming (10.3%) which are listed in the Summary of Product Characteristics (SmPC) of varenicline. Median latency times were 3–7 days, with exception for depressed mood (10 days). The number of ADRs did not abate over time. No signals were detected. During treatment 43.9% of the patients stopped using varenicline. The main reasons for stopping were the occurrence of ADRs (42.2%) and other (40%) unspecified reasons.

Conclusions: This study indicates that varenicline is a relatively safe drug. The reported ADRs correspond with the ADRs mentioned in the SmPC of varenicline with a median latency of 3–7 days. The number of ADRs do not abate over time.

200. Improving Pharmacovigilance Knowledge and Practice amongst Health Care Providers: A Case Study of Community Pharmacists in Lagos, Nigeria

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Background: Pharmacovigilance (PV) is important in promoting patients' quality of life and healthcare providers require PV training to achieve this goal.

Objectives: The study was aimed at comparing the knowledge, attitude and practice (KAP) on PV of trained Health Care Providers (HCPs) with those yet to be trained and to assess the outcome of a PV educational intervention on the knowledge and practice of a selected group of community pharmacists (CPs) in Lagos.

Methods: Design: The phase I was a preliminary cross sectional KAP study; Phase II was a quasi experimental study design. Setting: Phase I involved 120 selected health care providers (HCPs) trained by the National PV Centre, in 2011. Phase II involved 240 CPs; study group (n = 120) received PV training. The control group (n = 120) did not receive PV training. Exposures or interventions:The study group were further divided into actively followed-up group (n = 60) through Short Message Service (SMS) reminders and passively followed-up group (n = 60). The control group was passively followed up. Follow up time was one month. Main outcome measures: knowledge and practice score of PV. Statistical analysis:ANOVA and paired t-tests were used to compare the means of the knowledge scores in the groups. Linear regression model was used to determine the predictors of PV knowledge and the frequency of ADR reporting.

Results: The cross sectional study showed better KAP scores ($p < 0.05$) amongst the trained HCPs. In the phase II study, the mean baseline, post test and one month post test knowledge scores was 65.4 ± 8.3, 74.9 ± 7.8 and 78.1 ± 7.8 respectively for active follow up group, 64.1 ± 11.5, 71.9 ± 10.6 and 76.3 ± 9.1 for passive follow up group and 65.6 ± 9.0, 63.9 ± 16.1 and 70.7 ± 7.1 for control group. Age, sex and place of work were identified predictors of

knowledge of pharmacovigilance. However, no soci-odemographic variable predicted the frequency of ADR reporting.

Conclusions: Training of HCPs led to improvement in their KAP of PV. Educational intervention of community pharmacists accompanied by SMS reminders improved their knowledge and practice of pharmacovigilance.

201. Pattern of Adverse Drug Reactions Reported in a South Indian Tertiary Care Teaching Hospital, 2001–2011

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Background: Spontaneous reporting of adverse drug reactions (ADRs) that generate safety alerts is not well practiced in India. In our hospital, ADRs monitoring programme was initiated in 2001 and has been continuing for over a decade.

Objectives: The current study aims to analyse the pattern of ADRs reported to the study centre between 2001 and 2011.

Methods: The ADRs reported in the hospital database were extracted and analysed. ADRs were classified based on WHO-Adverse Reaction Terminology and the drugs implicated were classified according to WHO-Anatomical Therapeutic Chemical classification. The pattern of ADRs reported was descriptively analysed and reported.

Results: A total of 2560 ADRs were reported. Patients had a median age 46 (range 1–94) years, and more men (n = 1,424; 55.6%) were affected. Majority of ADRs (n = 502; 19.6%) were related to skin and appendages, rash being the most common (n = 158). The least reported ADRs were related to systemic lupus erythematous under collagen disorder (n = 1) and testicular pain of male reproductive system (n = 1). Antibiotics for systemic use were the most commonly implicated drug class (n = 808; 31.6%), followed by the drugs acting on cardiovascular system (17.3%). The drugs acting on sensory organs were least involved (0.2%). According to WHO-causality assessment, majority of ADRs were classified as possible 50.1% (1,282) while 1.6% was unassessable. Most ADRs were predictable (n = 1,987; 77.6%) and 60.3% were preventable. Type A (n = 1,957; 76.4%) reactions

were more common. Majority of ADRs (68.6%) were managed by de-challenge while only a minority of cases underwent (n = 131; 5.1%) re-challenge. While most ADRs were mild (n = 1,429; 56%), only 166 (6.5%) were severe and 10 (0.4%) were fatal.

Conclusions: This is the first report from India on the pattern of ADRs over a decade in a tertiary care hospital. Most ADRs affect skin and appendages. Antibiotics are the most frequent cause. The high prevalence of predictable and preventable ADRs suggest the need and value of implementing preventive measures.

202. Development and Validation of an Instrument Classifying Preventable Adverse Drug Events – A Pilot Study

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Background: Adverse drug events (ADEs), of which many are preventable, are a major patient safety issue. Classifying preventable ADEs is crucial for investigating their underlying causes and from there designing interventions. Many attempts have been made to classify preventable ADEs but there is no validated instrument.

Objectives: To develop and validate an instrument classifying preventable ADEs.

Methods: Based on classifications of medication errors or ADEs identified in a literature search, a preliminary classification instrument for preventable ADEs was developed. The classification was grouped according to the steps in treatment process; prescribing, preadministration, administration, monitoring and ending treatment. Using the instrument as described in a manual, an expert group of two physicians and two pharmacists classified 20 previously detected preventable ADEs from two datasets; spontaneously reported adverse drug reaction (ADR) reports and cases from a medical record study in emergency care in which ADEs were identified using trigger tools. For the reliability of the instrument, agreement between the reviewers' classifications was determined. To assess the validity of the instrument, the expert group also rated the relevance of each item in the instrument using a four-point scale. The content validity index (CVI) for each item and the entire instrument were determined. The classification will be revised according to the experts' suggestions.

Results: Of 25 items in the preliminary classification instrument, 17 were rated as relevant or very relevant by all experts. Eight categories were rated as not relevant by at least one reviewer. The total CVI for the whole instrument was 0.68. The agreement between all reviewers was 15%, between pharmacists 55% and between physicians 20%. The agreement between all reviewers was 20% for the ADR reports and 10% for the cases from medical records in emergency care.

Conclusions: The relatively high CVI in combination with the modest interrater agreements indicate that further development of the manual and the description of the categories in the instrument are needed.

203. QT Prolongation and Ventricular Arrhythmias Related to Antidepressants: An Analysis of the French Spontaneous Reporting Database

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Background: Antidepressants (ADs) have been flagged as drugs potentially inducing QT prolongation (QTP) and ventricular arrhythmia (VA), either in the Arizona CERT lists, FDA warnings (for citalopram), or publications. This potential risk still needs to be further investigated, especially to identify drug specificities.

Objectives: To estimate, using disproportionality analyses of spontaneous reporting data, the associations between AD use and reporting of QTP/VAs.

Methods: Reports registered in the French Pharmacovigilance database (January 2000 – August 2010) were analysed. Adverse reactions were coded according to MedDRA, drugs according to ATC. Based on the A-RITMO project (ww.aritmo-project.org) pharmacovigilance approach, cases of QTP/ VAs (including also torsades de pointe, ventricular tachycardia, sudden cardiac death, and serious syncope) were identified through: i) MedDRA preferred term codes, ii) a review of reports free text. Associations between single AD drugs use and reports of QTP/VAs were estimated using case/non-case approach and reporting odds ratio (ROR) for all drugs with ≥ 3 cases. Associations involving individual ADs for which no risk of QTP/Vas has been identified to date were considered as potential signals.

Results: In the used subset of the French Pharmacovigilance database, 4,350 cases of QTP/VAs were identified, 258 (5.9%) being related to ADs. AD users age and gender did not differ between reports of QTP/Vas and reports of other reactions. The most frequent AD subclasses incriminated in QTP/VAs reports were: Selective serotonin reuptake inhibitors (SSRI, 136 cases), other antidepressants (85 cases), and non-selective monoamine reuptake inhibitors (NSRI, 44 cases). Thirteen ADs were reported in at least three cases of QTP/VAs; disproportionality analyses were significant for milnacipran (ROR 2.24; IC–95%1.19–4.24), escitalopram (1.93; 1.25–2.99), and clomipramine (1.64; 1.04–2.60). The association with milnacipran represented a potential signal.

Conclusions: This disproportionality analysis of the French pharmacovigilance database identified a potential signal for milnacipran and QTP/VAs. This should be further investigated.

204. Geospatial Analysis of Adverse Event Reports

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Background: Over the past few years there has been increased interest in developing new tools/methodologies to augment current pharmacovigilance practices. Traditionally data elements such as drugs and events have been primarily used and the employment of additional factors, such as geographic information, has been limited.

Objectives: To evaluate the potential benefits of geographic information to augment current pharmacovigilance practices.

Methods: For the purposes of this study, Stephens Johnson Syndrome (SJS) was chosen as a test case. Observational data was extracted from the entire IH-CIS database where a diagnosis of SJS (ICD9 codes 695.13 and 695.14) was made. Data was obtained on the patient's sex and age, their Census Region and 3-digit zip code. The data was pivoted to obtain the number of SJS cases per zip code region and utilized in geospatial analysis. Spontaneous adverse event report data was obtained from OCEANS, GSK's internal safety database. Cases from the USA were extracted and the 3-digit zip code calculated from the postal code column, the data was then pivoted in a similar manner to the observational set.

Results: Dramatic differences were seen in the geographic distribution of SJS incidence and reporting. Hot spot analysis of the spontaneous data showed the highest incidence of adverse event reports are in Washington State, Southern California, Michigan, Illinois, Mid-Atlantic and Florida. In contrast, for the observational data the majority of cases reported are in Arizona, Texas, Florida and noticeably the North East. Detailed examination of certain locations identifies individual zip code regions where there may be a significant number of observational reports of SJS with few or no spontaneous incidents and vice versa, for example Southern California and Arizona.

Conclusions: Geospatial information offers the potential to supplement current pharmacovigilance practices. The results of our preliminary investigation into differences in the geospatial pattern of SJS incidence reporting from observational and spontaneous sources indicate dramatic regional variance; however more research is needed to better understand its appropriate use.

205. A Cohort Study of Sitagliptin and Risk of Acute Renal Failure Using Standardized Electronic Medical Record Data

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Background: There have been several pilot studies for drug safety assessment in PMDA's MIHARI project, and this is one of those studies using standardized electronic medical record (EMR) data. Standardized EMR databases have been built based on a standard specification for EMR data published by the Ministry of Health, Labour and Welfare. They include data of diagnoses, prescriptions, and laboratory test results in the standardized format. This study would be the first attempt to use EMR data to carry out a cohort study.

Objectives: We investigated an association between use of sitagliptin, a new class of antidiabetics, and the risk of acute renal failure (ARF). We also aimed to evaluate the feasibility of EMR data use.

Methods: We collected standardized data between June 1, 2009 and December 31, 2011 from six collaborative hospitals. *Study population:* We defined study population as new users of sitagliptin and sulfonylurea (SU) (a reference). Follow-up was started on the first prescription day of the study drugs. Patients who did not visit hospitals before follow-up, aged less than 20, or had any evidence of former renal failure were excluded. Exposure period was determined from durations of prescriptions. Before starting the study, we

evaluated whether the cohorts have continuous enrollment in the database by looking frequencies of visits. *Outcome:* Incidence of ARF was defined as a serum creatinine value which was 1.5 times or 0.3 mg/dL higher than a previous value. *Statistical analysis:* We estimated unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) by Cox proportional hazard model.

Results: Outpatients were more difficult to follow up than inpatients due to the nature of EMR data. The cohorts consisted of 1,605 sitagliptin users and 2,036 SU users. The risk for ARF in sitagliptin users comparing SU users were low contrary to our expectation (unadjusted HR 0.62, 95% CI: 0.50–0.78; adjusted HR 0.81, 95% CI: 0.64–1.02).

Conclusions: We evaluated the risk of drug using standardized EMR database which include laboratory test results permitting to carry out relatively valid studies, although they have some limitations.

206. Hit-Miss Model Detects Duplicates Missed by Rule-Based Screening of Individual Case Safety Reports

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Background: Spontaneous reports are fundamental for signal detection in post-marketing surveillance. Their effective analysis requires reliable data and one challenge is report duplication. These are multiple unlinked records describing the same suspected adverse reaction (ADR) in a particular patient. They distort computerized screening and can mislead clinical assessment. Many organizations rely on rule-based detection but probabilistic record matching is an alternative.

Objectives: Evaluate hit-miss model record matching for duplicate detection in spontaneous reporting systems.

Methods: A published hit-miss model algorithm for record matching was applied to the WHO Global Individual Case Safety Reports Database, VigiBase, between 2000 and 2010. Reported drugs, ADRs, patient age, sex, country of origin, outcome, and date of onset, were considered in the matching. Suspected duplicates for the two countries were reviewed and classified by the MHRA & DHMA. This included

evaluation to determine whether confirmed duplicates had already been identified by rule-based screening.

Results: Over the 11 years, the algorithm identified 1,371 clusters of suspected duplicates from MHRA and 84 for DHMA. The MHRA data set is around 10 times the DHMA set. Houndred and 80 of these were evaluated in this study. Of these, 85% & 65% were confirmed as duplicates and of those 60% & 38% were previously unknown. A total of 4% &1% of the highlighted clusters were considered likely but yet unconfirmed duplicates, whereas 11% & 30% were classified as non-duplicates but otherwise related. This includes reports of different reactions for the same patient, and reports for different patients in the same study or from the same reporter. Three clusters (4%) from DHMA were classified as unrelated, while 3 MHRA suspected duplicates (3%) were not in the national dataset.

Conclusions: The hit-miss model achieved high positive predictive value for duplicates in both data sets over and above implemented rule based methods. A very small proportion of highlighted clusters were classified as unrelated. This research recieved support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

207. Advantages of Using Well Fitting Models To Assess the Effects of Time-Varying Drug Exposures in Prospective Surveillance

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Background: Prospective surveillance of possible adverse drug reactions (ADR's) relies on simple exposure measures, such as current use or any use within an arbitrary time interval. The true relationship between past drug use and the risk of ADR's, however, is usually unknown and may involve cumulative or lagged effects. Accounting for such complex effects in prospective surveillance may improve the accuracy and timeliness of ADR detection.

Objectives: To assess, through simulation, the impact of the exposure model used for prospective surveillance on the time to signal detection.

Methods: We have simulated cohorts of time-varying drug use and generated their outcomes under different assumptions about the 'true' exposure-risk association using previously validated methods [Abrahamowicz et al, Stat-in-Med 2011]. We then simulated both (1) a classic cohort study, with a fixed follow-up duration, and (2) a dynamic, prospective surveillance study. The latter involved repeated re-analyses of gradually accumulating data until the 'signal' of the association was detected, based on pre-specified criterion for rejecting the null hypothesis of no association. In both settings, we fit several Cox models with alternative exposure metrics and use AIC to select the best-fitting model(s). Power and time to detect the association (in a dynamic setting) were compared across different models and analytical strategies.

Results: In the classic cohort study, the power to detect an ADR varied from 100%, when the correct exposure model or the best-AIC model was used, to as low as below 10%, with *a priori* selected models that mis-specified the true effect of past drug exposure. AIC identified the correct model as the best-fitting model with higher than 90% probability. Accordingly, in prospective surveillance, the time to signal detection was significantly reduced if either the 'correct' model or, more realistically, the best-fitting model was used.

Conclusions: The efficiency of prospective surveillance of ADR's can be enhanced by using statistical criteria to identify the best-fitting among alternative exposure models.

208. Asymptotic Limit to the Relative Reporting Ratio – A Measure of the Violation of Hidden Assumptions behind Some Disproportionality Measures Used in Signal Detection

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Background: For disproportionality measures based on the Relative Reporting Ratio (RRR) like the Information Component (IC) and the Empirical Bayes Geometric Mean (EBGM), each product and event is assumed to represent a negligible fraction of the spontaneous report database.

Objectives: To quantitatively evaluate whether the violation of that assumption makes the RRR unable to detect potential disproportionate reporting for some product-event pairs (P-Es) within the GlaxoSmithKline vaccine safety database.

Methods: The asymptotic effect was defined for each P-E as the asymptotic value that cannot be exceeded by the RRR regardless of the distribution of events reported for the different products. Quantification of the asymptotic effect was performed at three levels: for

the entire GlaxoSmithKline safety database, for one product, and for a specific P-E. Different combinations of stratification factors (age, sex, region and reporting year) were also investigated.

Results: Depending on the choice of stratification factors, the RRR could not exceed an asymptotic value of 2 for up to 2.4% of the P-Es and could not exceed an asymptotic value of five for up to 12.5% of the P-Es in the database. There was a greater impact of the asymptotic effect for the hepatitis B vaccine (representing 23.4% of spontaneous reports in the safety database); the RRR could not exceed an asymptotic value of two for up to 13.8% and could not exceed an asymptotic maximal value of 5 for a minimum of 60% of these P-Es. For the P-E rotavirus vaccine-intussusception, the choice of stratification factors considerably impacted the asymptotic value of RRR: from 52.5 for an unstratified RRR to 2.0 for a fully stratified RRR.

Conclusions: The quantification of the asymptotic effect can indicate whether measures such as the EBGM, IC or RRR can be used for safety databases for which products or events cannot be assumed to represent a negligible fraction of the total. At the level of the product or P-E, it can also highlight overstratification behaviour, equivalent here to an increase in the fraction the product (or event) of interest represents.

209. Signal Detection Based on the Time-to-Onset: Extending a New Method from Spontaneous Reports to Observational Studies

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Background: A proof-of-concept study has previously highlighted the added value of a method using time-to-onset (TTO) data for quantitative and non-parametric signal detection on spontaneous report data.

Objectives: To assess the added value of this new TTO signal detection method adapted to the context of observational studies.

Methods: For each adverse event reported during the conduct of a post-authorization safety surveillance study for AS03-adjuvanted split virion H1N1 pandemic influenza vaccine, the distribution of TTO data for reported safety events was tested against the distribution of follow-up time by a Kolmogorov-Smirnov test. Events showing significantly different distributions of TTO data for first occurrence of the event from the theoretical distribution were flagged as signals and a safety physician evaluated their relevance for further medical assessment. We also retrospectively performed weekly signal detection using this method to simulate ongoing surveillance.

Results: The TTO method detected 21, 15 and 4 signals within a 30-day period post-dose 1 with confidence levels set at 90%, 95% and 99%, respectively. Of these signals, 14 (67%), 10 (67%) and 2 (50%) were considered as relevant. Among the 14, 6 had not been identified by previous signal detection activities. When performed weekly, the Kolmogorov-Smirnov test detected 26 events as signals at least once with an alpha level of 0.05. Three weeks after first patient first dose, 1 of the 6 new signals could theoretically have been detected.

Conclusions: This study provided evidence that the Kolmogorov-Smirnov signal detection method based on TTO may add value to other methods, leading to earlier detection of signals, and thus potential safety issues. This method is relatively simple to implement and can be used to detect time-dependent signals. As this method does not require comparative data, it potentially could also be implemented for ongoing surveillance of blinded clinical trials to complement other qualitative/quantitative tools and increase the chance to detect events with potential safety concerns.

210. Drug Exposure Registry To Monitor Safety of Investigational Product

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Background: Fosdevirine (FDV, GSK2248761) is a non-nucleoside reverse transcriptase inhibitor with HIV-1 activity against common efavirenz-resistant strains. Two partially blinded, randomized, phase 2b studies were initiated in HIV-1 positive subjects to select a phase 3 dose. A total of 35 subjects were exposed to FDV 100 or 200 mg. Dosing was halted when 5 treatment-experienced subjects developed new-onset seizures after $\geq$ 4 weeks exposure to FDV. A drug exposure registry was established to continue monitoring for adverse events after conclusion of the randomized trials.

Objectives: To monitor subjects exposed to FDV for late-onset seizures and other relevant adverse events.

Methods: Quarterly chart reviews were requested to collect clinical and safety data from each subject. Subjects with seizures were followed for at least 2 years

and non-seizure subjects for 1 year from last FDV dose. Treatment decisions on HIV and seizure management were made by the health care providers. Subject narratives with clinical course and assessment of evidence of residual or new adverse events potentially related to their exposure to FDVs were generated.

Results: Out of the 35 FDV exposed patients 19 consented to enroll in the registry, including 4 of the 5 seizure subjects. After one year of follow up, no related adverse events were reported in non-seizure subjects. No additional seizures or neuropsychatric events were detected in three seizure subjects. Multiple seizure events were detected via the registry for one seizure subject who has been diagnosed with chronic epilepsy and was reported to have low adherence to both antiretroviral and antiepileptics.

Conclusions: A drug exposure patient registry with chart abstraction is a time-efficient and cost-effective non-interventional way of monitoring long-term safety after a development program is terminated. Among the affected five patients, one refused to enroll, and four were effectively followed within the designed registry.

211. Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis

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Background: Multidrug-resistant tuberculosis (MDR-TB) is a growing global concern. Due to long duration and concurrent use of multiple second-line drugs, adverse drug reactions (ADRs) are regarded as the most important clinical consideration in MDR-TB patients.

Objectives: To evaluate the frequency and type of treatment-related ADRs owing to MDR-TB therapy and examine factors associated with occurrence of ADRs.

Methods: The Cochrane library,MEDLINE and EMBASE were searched from inception through October 1st, 2012 with additional manual search of International Journal of Tuberculosis and Lung Disease. Cohort studies with available outcome of adverse events were selected if MDR-TB cases were treated with regimen including second-line drugs. Pooled estimations for each specific type of ADRs were calculated with 95% confidence intervals (CIs) using a random-effect model owing to substantial heterogeneity across studies.

Results: Among 39 studies included, 31 studies reported the number of patients who experienced at least one ADR. About 2602 of totally 5346 MDR-TB patients experienced at least one ADR, and the overall incidence was 57.3% (95% CI: 46%, 67.8%). The most six common ADRs were gastrointestinal disorders (32.1%, 95% CI: 23.5%, 42.1%), ototoxicity (14.6%, 95% CI: 10.9%, 19.4%), psychiatric disorders (13.2%, 95% CI: 9.9%, 17.3%), arthralgia (8.1%, 95% CI: 5.1%, 12.8%), peripheral neuropathy (8.1%, 95% CI: 4.5%, 14.1%) and hepatotoxicity (7.3%, 95% CI: 5.1%, 10.5%). Subgroup analyses by each characteristic (study population, regimen, previous TB treated, HIV prevalence, treatment length) did not show any significantly difference between groups. Besides, in 17 studies with available data of impact on MDR-TB therapy, 1,147 (70.4%, 95% CI: 54.7%, 82.4%) of totally 1,519 patients who developed ADRs were required change of MDR-TB therapy, including temporary suspension, dose change, or permanent discontinuation.

Conclusions: ADRs were common among MDR-TB cases, occurring in more than half of the cases, with over two thirds requiring change of MDR-TB regimen. MDR-TB patients should be monitored closely and managed aggressively for side effects during therapy, especially for ototoxicity and psychiatric disorders.

212. The Opportunities and Challenges of Delivering the Quetiapine Post-Authorization Safety Studies (PASS): A Diverse Program of Work

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Background: Quetiapine fumarate (QTP) an atypical antipsychotic is available as both immediate and extended-release (XR) formulations. In most countries both formulations are indicated for treatment of schizophrenia and bipolar disorder. QTP XR is approved as adjunctive therapy for major depressive episodes in patients with a sub-optimal response to antidepressant (AD) monotherapy. As a condition of marketing authorization for new disease indications for the QTP formulations, over time (2007–12) 8 PASS and a multi-national drug utilization (DU) study have been agreed with the European Regulatory Health Authorities and form part of AstraZeneca's (AZ) long term commitment to pharmacovigilance.

Objectives: To provide the background and scope of the PASS program for the 2 formulations of QTP.

Methods: Nine studies focus on DU, safety, and treatment patterns across indications, doses and formula-

tions. Pre-specified statistical analysis plans are designed to address comparisons across these studies and with AZ's clinical program.

Results: The PASS program includes two prescription event monitoring studies based upon input from GP's and investigators within UK mental health trusts, three retrospective database studies including DU and comparative safety vs. other AP and AD drugs (involving the PHARMO, GPRD and Swedish population-based prescription and health registries), and a naturalistic study of real-world use and safety in France. Two new PASS will assess the effectiveness of risk minimization using a multi-national physician survey and analysis of electronic health records from physician practices in two countries.

Conclusions: The QTP PASS program will inform on DU in clinical practice and safety for specific points of interest, and thereby contribute to the overall pharmacovigilance for QTP. These individual studies have diverse designs with objectives and populations having undergone modification with newly approved indications for the two formulations of QTP. The planning and execution of these studies requires engagement of a multidisciplinary team involving interactions among industry, investigators and regulators in order to be successful.

213. Assessing Current Awareness, Perception and Knowledge of Pharmacists on Anti-Counterfeiting Efforts in Singapore

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Background: Counterfeit health products pose serious threats to public health. Healthcare professionals ncluding pharmacists can play crucial roles in safeguarding public from such products. However, little is known about pharmacists' abilities and contributions to anti-counterfeiting efforts in Singapore.

Objectives: To assess current awareness, perception and knowledge of pharmacists on anti-counterfeiting efforts in Singapore.

Methods: A multi-center cross-sectional survey was conducted using self-administered questionnaire, consisting of Likert scale, true/false and open-ended questions, that was developed based on available literature and pilot-tested. Data were analyzed using descriptive statistics and t-test for comparison between groups, with statistical significance set at p < 0.05.

Results: Three-hundred amd nine pharmacists from hospitals (61.8%), community (retail) (19.7%), poly-

clinics (7.4%) and health product distribution chain (11%) were surveyed between October 12 and January 13. Their mean knowledge score for four true/false questions on the definitions of counterfeit products, was 2.66 ± 1.02, with significantly higher scores for those receiving prior training on counterfeit products (3.00 ± 0.85) than those without (2.51 ± 1.03) (p = 0.009). Interestingly, 86.4% of pharmacists did not check the authenticity of health products they dispensed, sold or distributed, with 72.8% unaware of the specific features to check in a counterfeit product. 72.8% perceived pharmacists as responsible in anti-counterfeiting efforts through public education, but expressed less confidence (mean score of 2.55 ± 0.91 on a 5-point Likert scale) in counseling consumers on product authentication. Most pharmacists perceived the lack of formalized training (85.7%), level of knowledge in combating counterfeit products (78%), and purchasing health products when overseas (81.6%) or online (79.6%) as key barriers to anti-counterfeiting efforts.

Conclusions: There are barriers that limit pharmacists' anti-counterfeiting efforts in Singapore. Our findings suggest a need for continuing professional education and training to increase confidence and greater involvement of pharmacists in combating counterfeits.

214. Thalidomide Imported by the Individual Doctors and its Use in Japan

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Background: In October 2008, thalidomide was approved by the Ministry of Health, Labour and Welfare (MHLW) for multiple myeloma (MM) under the Thalidomide Education and Risk Management System for the real time monitoring of prescription/dispensing of thalidomide and pregnancy test results. For patients with disorders other than MM, thalidomide is still imported by the individual doctors and those patients are registered to the Safety Management system for Unapproved Drugs (SMUD) introduced by the MHLW in 2009. The SMUD is a web-based registration system without the capability of real time intervention.

Objectives: To examine the range of indication and time trend of import of thalidomide after 2009 of the patients registered to the SMUD.

Methods: The number and indication of patients registered to the SMUD and the amount of imports of tha-

lidomide were obtained from the website (http://www. smud.jp). We estimated and compared the amount of imports for the patients with MM, oncological diseases (ODs) other than MM, and non-ODs.

Results: A total of 585 patients (females: 46%) were registered to the SMUD by December 2012. The number of patients was 143 (median age: 71; females:54.5%), 308 (63; 47.1%) and 134 (65; 34.3%) for MM, ODs and non-ODs, respectively. ODs included solid carcinoma, lymphoma and leukemia, and non-ODs included Behcet's disease, myelofibrosis, amyloidosis, etc. The number of females of child bearing potential (FCBPs) was 1 (0.70%), 16 (5.2%) and 16 (11.9%) for MM, ODs and non-ODs, respectively (p < 0.0001, chi-square test). The average (SD) of monthly imports of thalidomide in 2010 and 2012 were 411 (507) and 44.4 (42.1) g (p = 0.027, t-test) for MM, 194.3 (200.4) and 60.7 (62.2) g (p = 0.050) for ODs, and 181.6 (113.7) and 104.3 (54.5) g (p = 0.061) for non-ODs.

Conclusions: The fraction of FCBPs with ODs and non-ODs were larger than that with MM. The monthly imports of thalidomide for MM tend to decrease but those for non-ODs are relatively stable even if the absolute amount is not large. This indicates that the risk of fetal exposure to thalidomide remains to be a concern for ODs and non-ODs. The function of the SMUD may be enhanced so that FCBPs should be more properly monitored.

215. The Observational Safety Evaluation of Asenapine (OBSERVA) Study: Rationale and Design

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Background: Specialist Cohort Event Monitoring (SCEM) post marketing studies (registries) are designed to monitor the use and safety of new drugs prescribed by specialists. Thus SCEM studies complement primary care based studies by monitoring use and safety in the more complex patient population seen by specialists. OBSERVA is being conducted as part of the Risk Management Plan to monitor the short-term (≤ 12 weeks) safety and utilisation of asenapine (Sycrest®) as prescribed by psychiatrists in a mental health care setting in England and Wales.

Objectives: To describe the rationale, challenges and study design choice of OBSERVA.

Methods: A single exposure observational cohort study of > 1000 patients identified over 2 years with no specific exclusion criteria. Important considerations in the design include facilitating recruitment of patients with mental health conditions who may have difficulty in providing consent/participation in research, risk estimation in the absence of a counterfactual comparator cohort, external factors (prescribing guidelines) influencing drug availability and case definition of outcomes often subject to mis-ascertainment (adherence, reported misuse/diversion).

Results: OBSERVA has been adopted by the Mental Health Research Network who will collaborate in: enrolment of investigative sites where asenapine is on the drug formulary; patient recruitment and help maintain psychiatrist engagement. Thus potential obstacles affecting recruitment are likely to be minimised. For estimating strength of association between exposure to asenapine and acute events associated with administration in such a diverse study population and lack of comparator cohort, the self controlled case series method will be employed. Since December 2012, 9 investigative sites have engaged.

Conclusions: Well designed observational studies/registries are an important and valuable approach to monitoring the post-marketing safety of new treatments. Identifying appropriate strategies during study design may help overcome recruitment challenges. This is anticipated to be of particular value given increasing legal demands for post-authorisation Pharmacovigilance.

216. Methodological Considerations in Evaluating the Safety of Novel Anticoagulants in Secondary Care Setting in the UK: Defining the Contextual Comparator Cohort

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Background: Increasingly the choice of medicines for patients in healthcare is guided by published national/regional guidelines. A post-marketing Specialist Cohort Event Monitoring (SCEM) safety study has been initiated by the DSRU as part of a broader Post-Authorisation Commitment requested by CHMP to further investigate the safety of rivaroxaban (XARELTO®) in clinical practice. It aims to monitor short-term (first 3 months) safety and drug utilisation of rivaroxaban prescribed for medical conditions requiring anticoagulation by specialists in the secondary care setting in England and Wales.

Objectives: To discuss methodological considerations in identifying a comparator cohort within a large pharmacoepidemiological study.

Methods: The SCEM study aims to collect data on 1700 evaluable patients treated for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF) (with ≥ 1 stroke risk factors) [n = 561], and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults [n = 1005]. They will be identified via a network of specialists, and data obtained post consent on prognostic/risk factors, exposure and specific outcomes. Since the counterfactual ideal comparator cohort cannot be identified, a contextual comparator cohort of evaluable new user patients treated via best practice standard care is proposed to characterise the adoption of rivaroxaban into clinical practice. Analysis will explore the importance of measured explanatory factors on variability of treatment decisions and selected safety risks across institutions.

Results: The study has been adopted by the Stroke Research Network and identification of site specific investigators, recruitment and data collection is in progress.

Conclusions: By capturing data on a contextual cohort we hope to gain better understanding of the variability of, and influence on, treatment decisions and prescribing of novel treatments which appear to have some advantages but for which there are significant differences within the health care community about recommended use.

217. First-Year Review of Implemenatation of the Legal Requirements for Labels and Package Inserts of Proprietary Chinese Medicines

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Background: Drug labels and package inserts contain essential information including ingredients, dosage, side effects and contraindications of individual drug. They are important means to enable the public to make informed choices.

Objectives: To review the trade compliance for the first year since the implementation of the legal requirements for labels and package inserts for proprietary Chinese medicines (pCms) and the impact of the Department of Health (DH)'s publicity efforts.

Methods: Enforcement statistics were collected continuously since the legal provisions took effect on 1 December 2011 and analysed at the end of the first year. Sub-group analysis was performed to identify traders with lower compliance rates. A questionnaire survey was conducted to assess public knowledge on the subject.

Results: DH's inspections covered all types of pCm traders in the 18 administrative districts of Hong Kong. A total of 16,495 pCms had been examined for their labels and package inserts. The monthly non-compliance rates were consistently low with an average of 1.34%, which also demonstrated a downward trend with time. Irregularities were minor. Risk factors for non-compliance identified were: (1) traders who were registration holders of at least 50 pCms; and, (2) traders who had committed offence(s) related to Chinese medicines or who had been disciplined by the regulatory authority. The questionnaire survey revealed that only 67.7% and 72.5% of respondents could recall at least half of the legal requirements of labels and package inserts, respectively.

Conclusions: The trade generally demonstrated a high degree of compliance with law. The current enforcement strategies can be enhanced by establishing a database to keep track of the performance of high-risk groups. Publicity efforts should be stepped up to further raise public awareness.

218. Effectiveness of Risk Minimization Interventions in Drug Safety: An Assessment of Methodological Gaps

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Background: An increase in the number of risk minimization interventions (RMIs) published in the literature has been observed over the past decade. However, methods to assess their effectiveness remain inadequately examined.

Objectives: To conduct a systematic review of the literature on RMIs in order to determine which intervention(s) appear most effective, and to identify methodological gaps in the assessment of effectiveness.

Methods: The bibliographical search was conducted through MEDLINE and Embase between 1st January 2000 and 31st December 2010 with an update for 2011–2012. The following characteristics were extracted from each study: target population for the RMI, target population for the assessment of effectiveness, study design, data sources, and effectiveness outcome(s).

Results: A total of 135 unique RMIs were identified, of which effectiveness was evaluated in only 52

(38.5%). The most frequent designs used to evaluate effectiveness were: retrospective cohort study with time series analysis (n = 22, 38.6%), knowledge and attitude survey (n = 14, 24.7%), retrospective cohort study with pre- and post-RMI analyses (n = 10, 17.5%). Effectiveness outcomes were heterogeneous consisting mainly of dispensing rate (n = 20, 35.1%), frequency of adverse events (n = 11, 19.3%), contraindicated co-dispensing rate (n = 10, 17.5%), laboratory testing rate (n = 7, 12.3%), knowledge retention and attitude (n = 7, 12.3%), changes in medical practice (n = 6, 10.5%). In 19 (36.5%) studies, effectiveness outcome or target population were not consistent with the aim of the intervention. Some of the data sources may also have introduced bias in the assessment. In other cases, inaccuracy of diagnostic codes in physician billing claims is likely to be associated with an under-ascertainment of cases of adverse events, resulting in an over-estimation of the effectiveness of the RMI. Trend over the time in the quality of studies will be presented.

Conclusions: Despite regulatory guidances, only a minority of studies published in the literature report an assessment of effectiveness of RMIs. In addition, several methodological gaps were uncovered.

219. Observational Methods and Post Authorization Studies: Lessons Learned from Bosentan European Risk Management

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Background: Bosentan is a dual endothelin receptor antagonist approved in Europe Union (EU) in 2002 as the first oral treatment for pulmonary arterial hypertension (PAH); a rare, life-threatening disease. This indication was extended to include digital ulcers in systemic sclerosis (SSc) in 2008. A novel formulation for treatment of pediatric PAH was approved in 2010.

Objectives: To report on the use of and challenges to implement observational studies in the EU bosentan risk management program over 10 years.

Methods: Observational studies were included in the annually updated EU-Risk Management Plan to address liver toxicity and teratogenicity as safety concerns.

Results: Bosentan was initially approved for PAH under exceptional circumstances in 2002; a Post Marketing Surveillance (PMS) program, special warnings within the label and routine pharmacovigilance were required. The PMS was designed to collect real-world PAH patient data, obtain real-time adverse event reporting and validate optimal guidance for liver function and pregnancy monitoring from 17 countries. In 2008, the Digital ulcer outcome (DUO) registry, a prospective, non-interventional study was initiated to describe the occurrence of safety events, outcomes and to evaluate the adherence to risk minimization measures in a new set of prescribers and patients. In 2010, a Systematic Review of data from four prospective, observational PAH registries, was initiated to collect long-term data on safety and outcomes from pediatric PAH patients. Major challenges to implement these observational studies include: varied national regulations, time and resource consuming, advancing technology, and motivating prescribers to participate given the balance of regulatory concerns and scientific interest of data collected.

Conclusions: Observational studies generate data on drug safety and real-world utilization; and are critical to the EU risk management of marketed products. Implementation of the PMS was pivotal for bosentan marketing approval; over time, expanding patient populations and novel formulations require the challenge to initiate additional observational studies.

220. Characteristics of Patients with Aberrant Behaviours Using Fentanyl Citrate Buccal Tablets: Results from a Post-Marketing Cohort Study

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Background: Fentanyl citrate buccal tablets (Effentora™; Cephalon) are indicated for Breakthrough Pain (BTP) in cancer, in adults receiving maintenance opioid therapy for chronic cancer pain. This study was conducted as part of the risk management plan and requested information on aberrant behaviours (ABs) such as escalating drug use and unclear aetiology of pain.

Objectives: To describe characteristics of patients with reported ABs and patients without ABs, quantifying off-label use.

Methods: An observational cohort post-marketing study. Exposure data from dispensed prescriptions issued by general practitioners (GPs) March 2009–April 2011. Outcome data (utilisation and events) from questionnaires sent to GPs ≥ 6 months after 1st prescription. Descriptive statistics calculated and univariate analysis performed.

Results: Final cohort = 551 patients. Of 46 patients (8.4%) had ≥ 1 ABs reported. Median age of patients with ABs reported was lower than patients without ABs reported (48 years [IQR: 35, 63] vs. 63 years [IQR: 52, 73]). Age was found to be significantly associated with ABs (χ^2 d.f.(9) = 35.1; p < 0.001). Patients with ABs had 3.5 times the odds of having an indication other than BTP in cancer, compared to patients with no ABs reported (95% CI: 1.1, 10.8). For dose, there was significantly different distributions between patients with and without ABs. Median duration of treatment was 87 days (IQR: 14, 276) for patients with ABs reported and 21 days (IQR: 1, 64) for patients with no ABs reported. Duration of treatment was found to be significantly differently distributed between patients with and without ABs (rank-sum p < 0.001). The odds of alcohol misuse, substance misuse and psychiatric disorders were significantly increased in AB patients. Where specified (n = 20), 11 patients with ABs had these prior to starting. Median time to onset of ABs for the remaining nine patients was 265 days (IQR: 140, 329).

Conclusions: In conclusion, patients with ABs reported whilst using Effentora™ had several different characteristics to patients without ABs. Use outside the terms of the license occurred more frequently in these patients, however the prevalence was low.

221. Number of Biochemical Tests as a Trigger for Adverse Drug Events

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Background: Adverse drug events (ADEs) in hospitalized patients are not always recognized in daily clinical practice. However, the occurrence of ADEs might be preceded by a physician's 'gut feeling', leading to increased diagnostic procedures, such as biochemical tests.

Objectives: The objective of this study was to investigate whether the number of biochemical tests increases before the manifestation of ADEs.

Methods: During 5 months all patients admitted to five medical wards of two Dutch hospitals for more than 24 h using one or more drugs were included in this cohort study. During admission the total number of laboratory tests per day was counted and all tests were assigned to one of eight test groups (among others metabolic tests, therapeutic drug monitoring and haemostasis tests). The occurence of ADEs was the primary outcome and patients were included in the analysis until the occurrence of an ADE, discharge or death, whichever occured first. For every day of the admission patients experiencing an ADE were compared with patients without ADEs on the same day (index date). Univariate and multivariate cox-regression analyses were performed using the number of biochemical tests performed in the 2 days before the ADE or index date as time-dependant variable.

Results: In this study 586 admissions were included; ADEs were identified during 344 admissions (59%). After univariate analysis the number of metabolic tests showed an association with the occurrence of ADEs (Hazard Ratio [HR] 1.22, 90% Confidence Interval [CI] 1.05–1.41), but after correction for possible confounders the association was not statistically significant ($HR_{adjusted}$ 1.14, 95% CI: 0.95–1.36). Neither the total number of tests nor other types of tests were statistically significantly associated with ADEs. However, after univariate analysis a trend towards an increased risk of ADEs was observed for therapeutic drug monitoring (HR 1.16, 95% CI: 0.73–1.82) and haemostasis tests showed a trend towards a decreased risk of ADEs (HR 0.88, CI 0.76–1.03).

Conclusions: The number of laboratory tests does not increase prior to an ADE. Therefore, the number of tests cannot be used to identify patients at risk of an ADE.

223. Withdrawn by Author

224. Withdrawn by Author

225. Metformin Use in Prostate Cancer and the Risk of Death and Metastasis in Patients with Type 2 Diabetes

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Background: Several observational studies have reported that the use metformin, an oral hypoglycemic agent, is associated with improved prostate cancer outcomes. However, several of these studies had important methodological limitations.

Objectives: To determine whether the use of metformin after prostate cancer diagnosis is associated with decreased risk of prostate cancer mortality, distant metastasis, and all-cause mortality.

Methods: This study was conducted using the UK Cancer Registry, Clinical Practice Research Datalink, Hospital Episodes Database, and the Office of National Statistics. The cohort consisted of men newly-diagnosed with non-metastatic prostate cancer with a history of treated type 2 diabetes between April 1, 1998 and December 31, 2009. All patients were followed until death, distant metastasis, or October 1, 2012. Nested case-control analyses were performed for each outcome, where each case was randomly matched with up to 10 controls on year of birth, year of cohort entry, and duration of follow-up. Exposure was defined as use of metformin during the matched follow-up period, along with measures of cumulative duration and dose. Conditional logistic regression was used to estimate adjusted rate ratios (RRs) with 95% confidence intervals (CIs) for each outcome.

Results: The cohort consisted of 935 men with both prostate cancer and diabetes, followed for a mean 3.7 (SD: 2.8) years during which 258 deaths occurred, including 112 cases from prostate cancer, and 107 cases of distant metastasis. Overall, the use of metformin was not associated with a decreased risk of prostate cancer mortality (RR: 1.29, 95% CI: 0.55–3.01), distant metastasis (RR: 0.71, 95% CI: 0.20–2.03), or all-cause mortality (RR: 0.83, 95% CI: 0.52–1.34). In terms of cumulative duration of use and dose, increased risks of prostate cancer mortality were observed in the highest tertile categories ($\geq$ 882 days, RR: 5.76, 95% CI: 1.49–22.22 and $\geq$ 944,000 mg, RR: 3.63, 95% CI: 1.17–11.26, respectively).

Conclusions: Overall, the use of metformin after prostate cancer diagnosis was not associated with a decreased risk of prostate cancer mortality, distant metastasis, and all-cause mortality.

226. Medication Adherence and Severe Asthma Exacerbations: Systematic Review

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Background: Asthma is a chronic inflammatory disease with a high prevalence worldwide. Asthma therapy includes drugs for asthma control and for urgent relief. Especially for asthma controller therapy, adherence is crucial to avoid asthma exacerbations.

Objectives: To provide a comprehensive summary and a critical appraisal of studies examining the association between asthma controller treatment adherence and risk of severe asthma exacerbations in children and adults.

Methods: A systematic literature search of the PUBMED, EMBASE and Web of Knowledge databases for literature published from inception until January 2013 was performed. Studies were included if there was empirical data about adherence and exacerbations, and the association between adherence and exacerbations was evaluated. Reference lists of retrieved articles were hand searched. Quality was assessed using a modified version of the Newcastle Ottawa Scale.

Results: The search yielded 2,956 publications. A total of 33 articles met the inclusion criteria and underwent data extraction and quality scoring. Of these studies, 24 studies used objective measures to assess adherence, with pharmacy claims (n = 15), weighing/counting measures (n = 4), electronic monitoring (n = 3), or blood samples (n = 2). The remaining nine studies used subjective adherence measures. All included studies were published between 1993 and 2013 and were mostly cohort design. Sample sizes ranged from 24 to 97,743 individuals. High levels of heterogeneity across studies in adherence and exacerbations measurements, and in strategies for evaluating the association, precluded a formal meta-analysis. Although the reported effect measures varied widely and sometimes were inconsistent, in high quality studies higher levels of adherence tended to be associated with fewer exacerbations.

Conclusions: Based on current literature, it is difficult to make strong statements on treatment adherence and risk of asthma exacerbations. There is a need for new, well designed prospective studies, using standardized definitions for treatment adherence and treatment outcome. This is essential to disentangle the association between adherence and treatment outcomes, and to ultimately increase patient adherence.

Conclusions: Several patient characteristics were associated with shorter persistence and a lower MPR. Although we missed information on the indication of treatment, long term persistence and good adherence is advised for almost all antidepressants indications. Some of these characteristics have been studied before, but no consistent results were presented to identify the patient at high risk.

227. Association of Patient and Drug Characteristics with Adherence and Persistence

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Background: Persistence and adherence are important determinants for successful antidepressant drug therapy. Long-term treatment is required for full recovery and to prevent recurrence of disease. A low medication adherence might influence the effectiveness of the drugs.

Objectives: To study which patient- and drug characteristics are associated with persistence or adherence of antidepressant drug treatment.

Methods: The study population consisted of 2,114 incident elderly antidepressant drug users from the Rotterdam Study between January 1st 1992 and December 31st 2011. Antidepressant users still taking antidepressants at the end of follow-up were excluded (n = 321). Medication use was available on a daily basis from pharmacy records. Persistence was calculated as days between start and end of episode. End of episode was defined as a prescription gap of $\geq$ 90 days. Adherence was defined as the medication possession ratio (MPR = the total duration of all prescriptions in the episode divided by days between start and end episode). Cox and multivariate linear regressions were performed.

Results: Of all incident users, 37% received only one antidepressant prescription, of which the majority were Tricyclic Antidepressants (TCAs, > 50%). The participants who received multiple prescriptions (n = 1775) were on average 72.6 years (SD = 9.6) and 68.3% was female. Moreover, only 45.7% used the antidepressant drugs for more than 6 months. Male sex (HR = 0.77, 95% CI: 0.68–0.87), older age (HR = 1.01, 95% CI: 1–1.02), and a lower start dose (p-trend > 0.01) were associated with a shorter persistence. Factors that were associated with a lower MPR were lower age (p = 0.02), lower start dose (p < 0.01) and two antidepressant units per day or more (p < 0.01).

228. Predicting Persistence with Antidepressant Treatment at 6 Months

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Background: Recommendations on length of antidepressant treatment center around 6 months to prevent relapse and recurrence. Prior study results show antidepressants are often discontinued before this time.

Objectives: To determine baseline factors that predict antidepressant treatment persistence at 6 months post treatment initiation.

Methods: Using the PharMetrics Claims Database new users of antidepressants with index prescriptions for Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram, Duloxetine, or Venlafaxine between January 1, 2003 and June 30, 2010 were identified. Persistence at 180 days was defined as treatment without gaps based on days supply of dispensed prescriptions, allowing for a 30 day grace period without drug coverage. We used multivariable log binomial regression to identify independent predictors of persistence and estimate risk ratios (RR) and their 95% confidence intervals (CI). Potential predictors, collected in the year prior to index date, included demographics, antidepressant type, psychiatric/non-psychiatric conditions, depression measures, suicide attempts, and healthcare utilization. We retained predictors that changed the RR by 5% and had a p-value $\leq$ 0.05. Final sample was split for model validation.

Results: Of the test cohort (n = 508,613), 85% were still enrolled 6 months post index date and 39% of those were persistent at 6 months ranging from 44% (Venlafaxine) to 37% (Paroxetine). Given sample size, CIs were narrow. Patients aged 12–17 (RR 0.95) and

18–24 (RR 0.74) years were less likely and patients 0–11 (RR 1.07), and 50+ years were more likely to persist than those aged 35–49. Diagnoses of dementia (RR 1.19), anxiety (RR 1.08), and depression were associated with increased persistence. Substance abuse (RR 0.85), colorectal cancer (RR 0.88), lung cancer (RR 0.91), opiate usage, and having 1+ other prescriptions were associated with lessened persistence. Concordance (c) statistic was extremely similar between test and validation (0.57) samples.

Conclusions: It is difficult to predict antidepressant persistence; however, certain patient characteristics at baseline may help identify patients less likely to persist.

229. Withdrawn by Author

232. Persistence to Tamoxifen and Aromatase Inhibitors for the Treatment of Breast Cancer – Accounting for Temporary Treatment Discontinuations

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Background: Many studies have been conducted to estimate persistence to hormonal therapy in breast cancer (BC). Most studies focus on first treatment discontinuation. However patients can have numerous periods of treatment discontinuations as well as numerous periods of treatment exposure.

Objectives: Our objective is to estimate persistence to tamoxifen and aromatase inhibitors (AI) in patients with BC accounting for temporary treatment discontinuations.

Methods: We constituted a cohort of 13,479 women with BC who received at least one prescription of tamoxifen or AI between 1998 and 2008, in the United Kingdom General Practice Research Database. We fitted a semi-markov model with three states to estimate the probability of being exposed to treatment over 5 years accounting for treatment discontinuations (transient state) and competing risks (recurrence of BC or death).

Results: The non-persistence estimated from the multistate model ranged from 7.3% at 1 year to 15.2% at 5 years for tamoxifen and from 4% to 6.4% for AI. Estimations of non-persistence based on Kaplan–Meier method were higher (31% and 20.7% at 5 years for tamoxifen and AI respectively). Most temporary discontinuations (80.2%) lasted < 6 months.

Conclusions: Temporary treatment discontinuations are frequent and should be accounted for when measuring adherence to treatment. Multi-state model may provide the frame-work for such analysis. This may be helpful to tailor interventions to improve persistence by providing data on patients' complex behaviors.

233. Adherence and Persistence to Hormonal Therapy in Breast Cancer: A Meta-Regression to Summarize the Available Data

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Background: In the literature, reported measures of adherence and persistence to anti-hormonal therapy for breast cancer are highly variable. The variability of the measures found in the literature limits the usefulness of raw data for clinicians.

Objectives: Our objective was to conduct a meta-regression analysis to summarize results on persistence to hormonal therapy in order to provide measures clinicians might use effectively, and to assess the different sources of variability in the previously published measures of persistence.

Methods: We conducted a meta-regression analysis based on 29 studies previously selected in a systematic, qualitative, review recently published. We investigated different sources of variation including: study type, data source, age of patients, measure of outcome, and type of analysis. Persistence to hormonal therapy over a 5-years period was studied using a mixed model for longitudinal meta-analytic data.

Results: Taking into account type of treatment as well as study methodology, adherence to hormonal therapy ranged from 79.6% (95% Confidence Interval [CI]: 68.2–87.3) at one year to 68.3% (95% CI: 52.4–79.9) at 5 years. Similarly, persistence ranged from to 86.4% (95% CI: 83.4–88.9) at one year to 59.1% (95% CI: 52.1–65.5). Persistence was higher for aromatase inhibitors than for tamoxifen. Data source was the only significant source of heterogeneity between studies, explaining 27.2% and 68.1% of the variations observed in the measures of persistence to tamoxifen and to aromatase inhibitors respectively.

Conclusions: Our meta-regression provides summary estimates information that may help clinicians monitor patients' treatment. Adherence and persistence to hormonal therapy is largely sub-optimal. This efficacy of hormonal therapy, proven in clinical trials, is likely to be highly reduced in real life if interventions to improve adherence are not systematically promoted.

234. Adherence Explored as Patient-Centered Medication Management: Results of a Literature Review and Stakeholder Workshop

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Background: Medication adherence research has traditionally focused on predictors of medication-taking behavior and ways to change patients' behavior based on those predictors. However, patient-centered medication management (PCMM) encompasses a wider range of medication-related interactions including shared decision making between prescriber and patient, effective prescribing, and revising prescriptions and treatment goals based on patient feedback. Approaches to care that incorporate patient beliefs and barriers into decisions about prescribing and medication use have been relatively absent in the adherence literature.

Objectives: To describe the current state of research and propose a research agenda in PCMM.

Methods: In 2012, the Centers for Education and Research on Therapeutics (CERTs) conducted a literature review to identify interventions aimed at improving PCMM and convened a workshop to solicit patient and other stakeholder priorities for PCMM research.

Results: PCMM interventions were generally characterized by patient education and engagement during and after treatment choice, alignment of treatment choice and patient goals, and individualized approaches to assist patients in medication-taking. Limitations included inadequate impact on measured clinical outcomes, a lack of information about long-term efficacy, and concerns about the resource-intensive nature of patient-focused interventions. Workshop participants identified priorities for advancing PCMM, the top four being: (1) define prescribing competencies and develop curriculum to improve patient-centered prescribing; (2) create customizable tools to overcome patient barriers to medication taking; (3) change the culture of therapeutics from 'providing care to patients' to 'creating health with patients'; and (4) advance the epidemiological knowledge on long-term medication-taking.

Conclusions: Little research has been conducted to develop and implement PCMM. Stakeholders expressed a need for future work in this area and suggested research priorities, patient educational efforts, and approaches to clinical education and care that may advance PCMM.

235. Effectiveness of the *Persistence* Telephone Assessment and Communication Program for Patients with Treated Depression: Pragmatic Randomized Controlled Trial

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Background: In real-life, more than half of patients discontinue antidepressant treatment before the minimum recommended duration. The *Persistence* program is a patient-centered communication intervention: (1) telephone follow-up; (2) modules on depression and psychotherapy, mailed; (3) feedback letter to prescriber summarizing patient's experience and symptomatic response to treatment. Key messages highlight the importance of adherence and of seeking follow-up care if poor tolerance or perceived lack of efficacy.

Objectives: To assess the effectiveness of the *Persistance* program on antidepressant adherence and patient reported outcomes, compared with usual care.

Methods: A randomized trial was conducted. Adults (age 18–64) who initiated an antidepressant for depression or anxiety identified in community pharmacies were individually randomized into the *Persistance* intervention group or usual care. Primary outcomes, measured at baseline and 6 months, included compliance and adherence (Medication Adherence Questionnaire) and severity of depression (QIDS). Secondary outcomes included knowledge about depression, attitude with treatments, quality of life (SF-12).

Results: Of 48 patients allocated to *Persistance* and 53 to usual care, 77% provided primary outcome data at 6 months (41 and 35, respectively). At 6 months, a greater proportion of *Persistance* patients were compliant (68% vs. 45%, p = 0.08), and severity of symptoms was lower among *Persistance* patients than usual

care patients (difference in means = −2.8 (−0.6; −5.1 p = 0.01). Attitude with antidepressants was also more improved (difference in change from baseline = +3.8 (+0.8; +6.7 p = 0.01), quality of life was better in *Persistance* patients than in usual care patients (difference in means SF-12 scores = +4.5 (+0.4;+ 8.6) p = 0.03 for mental component; +7.1 (+3; +13) p = 0.02 for physical component).

Conclusions: Despite small sample size, study showed that the *Persistance* program appears to be effective in improving treatment adherence, symptoms of depression, and quality of life. Further studies would be required to assess the long-term effects.

236. Beliefs about Medicines in Dutch Acenocoumarol and Phenprocoumon Users

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Background: The Beliefs about Medicines Questionnaire (BMQ) can be used to assess the beliefs that patients may have about their medication.

Objectives: In this study we validated the psychometric properties of a Dutch version of the BMQ in coumarin users. We also aimed to assess the beliefs about acenocoumarol and phenprocoumon in patients with atrial fibrillation or venous thromboembolism. Lastly, we compared the beliefs about coumarin derivatives with the beliefs about other cardiovascular drugs.

Methods: The BMQ was completed by acenocoumarol and phenprocoumon users from the Dutch population of the EU-PACT trial, approximately 1 week after treatment initiation. Principal component factor analysis (PCA) was performed to validate the framework-structure of the needs and concerns scales. A needs score was calculated for all patients, as well as a concerns score and a needs-concerns differential. The analyses were repeated using data from a study with users of antihypertensive drugs or statins. Differences between groups of patients were tested using Mann–Whitney U and Kruskal–Wallis tests.

Results: In total, 320 patients were included in the analysis on the beliefs about acenocoumarol and phenprocoumon. PCA confirmed the original structure of the questionnaire in this patient population. The mean needs score was 15.3 and the mean concerns score was 12.3. This led to a positive needs-concerns differential of 3. Patients with VTE had significantly higher needs

scores than patients with AF (16.8 vs. 14.9, p < 0.001). Also, 493 users of other cardiovascular drugs were included. The mean needs score in this group was 16.1, the mean concerns score was 13.5 and the needs-concerns differential 2.6. The needs score was higher in chronic users than in starters (17.9 vs. 14.9, p < 0.001).

Conclusions: The BMQ is a suitable instrument for measuring the beliefs of Dutch acenocoumarol and phenprocoumon users. Users of acenocoumarol or phenprocoumon score higher on the needs scale than on the concerns scale, which is also the case in users of other cardiovascular drugs. This would indicate a positive attitude towards these drugs, especially in patients with VTE or chronic users of cardiovascular drugs.

237. Antidepressant Utilization after Hospitalization with Depression: A Comparison Between Non-Western Immigrants and Danish-Born Residents

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Background: Antidepressant (AD) therapy is recommended in patients hospitalized with depression several months after remission. While prevalence of depression is high among non-Western immigrants in Europe, this immigrant group may not be adequately covered by AD therapy after hospitalization.

Objectives: To examine whether non-Western immigrants (as refugees or family reunification) are at greater risk than Danish-born residents of (1) no AD purchase after discharge and (2) early AD discontinuation.

Methods: A cohort of non-Western immigrants (n = 132) and matched Danish-born residents (n = 396) discharged after first admission with moderate-severe depression during January 1, 1996–May 31, 2008 was followed in the Danish registries as to filling of AD prescriptions, hospitalization and emigration or death. Logistic regression models were applied to explore AD dispensing within 30 days after discharge, estimating odds ratio (OR) for immigrants vs. Danish-born residents. Early discontinuation was explored by logistic regression, estimating OR for no AD redemption within 180 days after the first dispensing, and by cox regression, estimating hazard ratio (HR) for discontinuation (maximum gap in drug supply) within 180 days. Age and sex were used as confounders. Afterwards potential intermediate variables, e.g. income, were included in the model.

Results: Over one fourth of the patients did not initiate AD therapy within 30 days after discharge, and immigrants had higher odds for no AD dispensing than Danish-born residents (OR = 1.55, 95% CI: 1.01–2.38). Including income, the strength of the association was attenuated. Odds for early discontinuation were non-significantly higher among immigrants than Danish-born residents (OR = 1.80, 95% CI: 0.87–3.73). Immigrants had also a non-significant higher hazard of early discontinuation (HR = 1.46, 95% CI: 0.87–2.45). Including income as potential mediator hardly changed these associations.

Conclusions: Immigrants seem to be less likely to receive the recommended AD therapy after hospitalization with depression, indicating a need for better understanding of this patient group including migrant background and history.

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238. Guidelines Adherence in the Treatment of Patients with Newly Diagnosed Type 2 Diabetes: Comparing the Use of Metformin in Quebec Pre and Post-Canadian Diabetes Association Guidelines

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Background: Given the high prevalence of diabetes, guidelines are updated frequently to reflect optimal treatment recommendations, but few researches published have revealed low adherence to guidelines (patients' or physicians' adherence).

Objectives: Our study aims to measure the response of primary care physicians to changes in choice of initial therapy for patients with type 2 diabetes in relationship to a change in Canadian Diabetes Association (CDA) Guidelines in 2008. We also assessed patients' and physicians' factors which may affect this change.

Methods: Historical cohort study of primary care physicians' participating in an electronic medical record research network in Quebec, Canada. Of 111 primary care physicians and 1279 newly treated patients with diabetes with a prescription of an oral hypoglycemic agent (OHA) between January 20 2003 and December 29 2011 were included. Multivariate GEE logistic regression was used to estimate the impact of guideline change on treatment choice controlling for patients' and physicians' characteristics.

Results: After the new CDA guidelines, there was an 86% increase in incident use of metformin (OR 1.86, 95% CI: 1.20–2.90) with an accompanying reduction of 79% in the use of thiazolidinediones (OR 0.21, 95% CI: 0.08–0.55), and 32% reduction in the initiation of sulfonylureas (OR 0.78, 95% CI: 0.43–1.09). Physicians' attitudes to evidence-based practice did not significantly modify response to a change in guidelines recommendations. However, older patients and those with renal failure were less likely to receive metformin.

Conclusions: Primary care physicians modified their prescriptions patterns in early type 2 diabetes management after a change in diabetes guideline recommendation.

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239. Access to Medicines among the Brazilian Adult Population with Chronic Diseases

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Background: Non-adherence to medication is a major problem for society in general. In developed countries, approximately 50% of patients with chronic adhere to the prescribed treatment. Studies have shown that the costs of drug acquisition are strongly associated with non-adherence to treatment.

Objectives: Aanalyze the access to medications among people with self-reported non communicable chronic diseases (NCCD) on the Brazilian population.

Methods: This analysis is based on a research from the Brazilian Institute for Statistics and Geography- The National Survey by Domicile Sample (PNAD)- realized between 2008 and 2009 among the Brazilian population, with a total of 391,868 people interviewed. The information contained on the results was all self-reported by the participants. The questions about the presence of non-communicable chronic diseases, use of a continuous medication and its acquisition were the main questions on analysis. In this study, we try to describe whether these people with NCCD are able to get their complete treatment or not. The results are for the adult population, above 30 years old.

Results: Seven percent of the population studied reported to have been already diagnosed with diabetes; 27.1% with hypertension, 4% asthma and 1.1% with cancer. Among those with diabetes 87.9% used continuous medication, in the last time they needed acquire it, only 36.8% could get it free. With the hypertensive population, 83.7% used continuous medication, and 37.5% could get them for free. In the asthmatic population, 60.8% used continuous medications and 25.8% could have their medications for free. 73.8% of the cancer patients used continuous medication, but only 22.7% could have them for free. Among all the patients that didn't get their medications from the SUS, most of them (> 70%) bought it themselves.

Conclusions: Although Brazil has one of the largest public health systems in the world, is not yet able to provide the complete treatment to all its users free of

charge. A great part of the population with chronic diseases still need to pay out of pocket its own treatment. This may lead to non-adherence, witch can result in severe complications and overwhelm the health system.

240. Potential Impact of Errors in the Days Supply of Osteoporosis Medications on Estimates of Drug Adherence

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Background: Days supply (DS) values are commonly used to identify drug utilization, estimate drug exposure and quantify adherence to therapy. We recently identified potential reporting errors in DS values for weekly, monthly and cyclical osteoporosis medications, particularly in long-term care (LTC).

Objectives: To examine the potential impact of DS reporting errors on measurement of adherence with osteoporosis medications.

Methods: We identified all oral bisphosphonate prescriptions dispensed through the Ontario public drug plan for seniors (66+ years) from 2000/04 to 2011/03. DS values were examined by dosing regimen, and illogical values for weekly, monthly and cyclical regimens (e.g., 1 DS for weekly regimens) were flagged for data cleaning. DS values were cleaned using dose specific algorithms (e.g., 7 DS value was imputed if 1 DS value was observed for a weekly regimen). Compliance with therapy was estimated using the proportion of days covered (PDC), calculated as the total DS in 1-year divided by 365 days, and categorized as high compliance (PDC $\geq$ 80%). Persistence with therapy was defined using a 60-day grace-period. High compliance and median persistence were compared using the observed and cleaned DS values. Results were examined separately for patients residing in LTC and community.

Results: A total of 356,134 eligible new users were identified, 25% in LTC. Among LTC users, high compliance (PDC $\geq$ 80%) increased from 48% to 79% following data cleaning, and the median persistence increased from 1.7 to 3 years. Fewer DS errors were noted in the community setting: high compliance increased from 60% to 65% and median persistence increased from 1.6 to 1.8 years.

Conclusions: Results suggest that adherence to oral bisphosphonate therapy is underestimated in LTC. With

25% of oral bisphosphonates dispensed in LTC, careful attention to potential exposure misclassification is important. For example, differential misclassification may exaggerate healthy adherer bias since adherence is underestimated among LTC patients, who are also more likely to experience a clinical outcome, such as fracture or death compared to community-dwelling patients.

241. Antihypertensive Persistence in Older Americans: Intent-To-Treat vs. As-Treated Analysis

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Background: Treatment changes during follow-up are common. The 'as treated' (AT) analysis avoids the increasing misclassification of treatments inherent in the intent-to-treat (IT) analysis but may introduce selection bias through informative censoring.

Objectives: To compare IT vs. AT estimates of the effect of antihypertensive treatment on cardiovascular outcomes in older Americans.

Methods: We identified new users of ACE inhibitors (ACEI) or thiazides (TZ) among Medicare beneficiaries, $\geq$ 66 years of age, continuously enrolled for 12 months before initiation in 2007–2010. Outcomes included all-cause mortality, myocardial infarction (MI) and stroke. We used inverse probability of treatment weights to control for baseline differences. In the IT analysis, users were censored on December 31, 2010. In the AT analysis, individuals were also censored at any treatment change (switching, augmenting, stopping the index drug) or disenrollment. We estimated hazard ratios (HR) and their 95% confidence intervals (CI) comparing ACEI vs. TZ using Cox models. To further explore the effect of censoring, we estimated Kaplan-Meier based risks and risk differences per 100 at 6 months after initiation.

Results: In preliminary results through 2009, we identified 61,832 new users (ACEI n = 44,086, TZ n = 17,746). Treatment changes were more common among ACEI users (ACEI = 65.2%, TZ = 58.7%). The IT HR for all-cause mortality was 0.85 (CI 0.80–0.91) but no difference was observed for MI (1.03, CI 0.84–1.25) or stroke (1.14, CI 0.96–1.35). The corresponding AT HRs were 0.86 (CI 0.78–0.96), 1.10 (CI 0.81–1.49) and 1.15 (CI 0.91–1.45). Among TZ users, the AT and IT estimates of risk at 6mo for MI and stroke were similar (RD: MI = 0.02, stroke = 0.05) but

those for death were not (RD = 1). Among ACEI users, the IT estimates of 6 months risk were higher than AT estimates (RD: death = 0.8, MI = 0.1, stroke = 0.1).

Conclusions: Our findings suggest that the magnitude of disagreement between IT and AT estimates of cumulative risk may differ across treatments and outcomes. Isolating the types and timing of censoring events will allow us to better understand the potential for bias in both IT and AT analyses and the effect of these biases on HRs.

242. Self-Reported Visual Analogue Scale has Poor Sensitivity for Antiretroviral Non-Adherence in Botswana

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Background: Identifying simple and effective ways of measuring adherence to antiretroviral therapy (ART) and predicting virologic outcomes may allow for interventions to increase ART success rates.

Objectives: Evaluate the self-reported visual analogue scale (VAS) as a method for measuring adherence and predicting virologic outcomes among patients on ART in Botswana.

Methods: We enrolled a prospective cohort of HIV+ patients initiating efavirenz-based ART in Botswana. At months 1 and 6 of treatment patients were asked to report their percent adherence to ART over the prior month by marking a line on a VAS. Viral load was measured at month 6 of therapy and dichotomized as undetectable (< 24 copies/mL) or not. Adherence was dichotomized with < 100% considered sub-optimal.

Results: Data were available for 315 patients with self-reported adherence at month 1, of whom 268 (85.1%) achieved virologic suppression and 47 (15%) reported < 100% adherence, with a risk ratio for virologic failure of 1.39 (95% confidence interval [CI] 0.75–2.58) if < 100% adherent. The sensitivity and specificity of self-reported < 100% adherence at month 1 for predicting virologic failure were 19.6% (95% CI: 10.3–33.5%) and 85.9% (95% CI: 81.1–89.8), respectively. Data were available for 271 patients with self-reported adherence at month 6, of whom 233 (86%) achieved virologic suppression and 39 (14.4%) reported < 100% adherence, with a risk ratio for virologic failure of 1.34 (95% CI: 0.65–2.83) if < 100% adherent. The sensitivity and specificity of self-reported < 100% adherence at month 6 for predicting virologic failure were 18.4% (95% CI: 8.3–34.9) and 86.2% (95% CI: 81–90.3%), respectively.

Conclusions: Self-reported adherence at both months 1 and 6 of therapy was very insensitive for virologic failure, although relatively specific. Our data suggest that the VAS is not an effective tool to screen patients for risk of virologic failure in this setting.

243. Withdrawn by Author

244. Cost-Effectiveness of Statins for Primary Prevention in Newly Diagnosed Type 2 Diabetes Patients: An Illustration for the Netherlands

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Background: Patients with type 2 diabetes have an increased risk of cardiovascular events, which can be reduced by statin treatment.

Objectives: The aim of this study is to determine if statin treatment for primary prevention started at the time of type 2 diabetes diagnosis is cost-effective, taking non-adherence and different age groups into account.

Methods: A cost-effectiveness analysis has been performed using a Markov model with a time horizon of 10 years. The 10-years cardiovascular risk was estimated in a Dutch population of primary prevention patients with newly diagnosed diabetes from the GIANTT database (Groningen Initiative to Analyse Type 2 Diabetes Treatment) using the UKPDS risk engine. Statin adherence of a Dutch type 2 diabetes population was measured as pill days covered (PDC) in the IADB pharmacy research database. PDC of ≥ 80% and ≤ 20% were associated with full and no efficacy of the treatment. Cost-effectiveness was measured in costs per

quality-adjusted life-year (QALY) from the healthcare payers perspective, also stratified for cardiovascular risk and age. A probabilistic sensitivity analysis was performed.

Results: Characteristics of 4,683 primary prevention type 2 diabetes patients were inserted into the UKPDS risk engine. The mean 10-years risk of the population was 23% for coronary heart disease (CHD), 14% for fatal CHD, 10% for stroke and 2% for fatal stroke. PDC in the type 2 diabetes population was 81%, 77% and 75% in years one, two and three, respectively. In general, statin treatment was highly cost-effective at around €2,500 per QALY. Favorable cost-effectiveness was robust in sensitivity analysis. Differences in age and 10-years cardiovascular risk showed large differences in cost-effectiveness ranging from more than €800,000 per QALY to being cost saving.

Conclusions: Statin treatment for primary prevention in patients newly diagnosed with type 2 diabetes is cost-effective. Due to large differences in cost-effectiveness according to different risk groups, the efficiency of the treatment could be increased by focusing on patients with higher cardiovascular risk and higher ages.

245. Tumor Necrosis Factor Treatment Patterns in Medicare Patients with Inflammatory Conditions

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Background: Inflammatory diseases have no surgical or pharmaceutical cure. Anti-tumor necrosis factor (TNF) and non-TNFs are effective treatments. Patients often switch TNFs; real-world treatment pattern research is scarce.

Objectives: Explore Medicare patient treatment patterns for Crohn's disease (CD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), ulcerative colitis (UC) and psoriasis (PS).

Methods: Eligible patients had ≥ 1 CD, RA, AS, UC, or PS diagnosis, initiated anti- or non-TNFs, were age ≥ 65 and followed for 2 years, examining persistence, discontinuation and anti- or non-TNF switches.

Results: Of CD (N = 3,287), UC (N = 1,643), RA (N = 50,455), AS (N = 1,159) and PS (N = 2,208) patients initiating anti-TNFs, RA persistence was 28.31–36.96% in PS. Over half discontinued anti-TNFs (53.35%: PS-61.52%: RA). First-line switches occurred in about 5% of CD and UC patients (RA: 10.17%, AS: 8.37%, PS: 9.69%). More PS patients switched to another anti-TNF (7.47%). More RA

patients switched to non-TNFs (5.81%). Of first-line CD (N = 2,140), UC (N = 2,628), RA (N = 41,985), AS (N = 532) and PS (N = 991) non-TNF initiators, persistence never exceeded 5% (1.33%: UC-4.71%: RA). More PS patients switched to anti-TNFs (2.22%). Highly persistent patients switched to another non-TNF (RA: 1.32%). Initial anti-to-anti-TNF switchers (CD: N = 139, UC: N = 80, RA: N = 5132, AS: N = 97, PS: N = 214) had higher persistence (37.36%: RA-49.70%: PS). CD second-line patients (10.07%) switched to a third anti-TNF (UC: 10.53%, RA: 8.40%, AS: 15.15%, PS: 20%). For all diseases, fewer switched to non-TNFs (CD: 0.72%, UC: 0%, AS: 3.03%, RA: 7.54%, PS: 0.61%). More initial RA and PS non-to-anti-TNF patients switched to a non-TNF. Second-line persistence was 22.73–62.50% in PS and AS patients. RA patients switched from non-to-non-TNFs; most discontinued (91.88%). More subsequent RA switchers were prescribed non- (3.07%) than anti-TNFs (1.08%).

Conclusions: More RA and AS patients switched from anti-to non-TNFs. More CD and UC patients switched to anti-TNFs. PS patients had highest anti-TNF persistence. First-line persistence was higher for anti- than non-TNF patients. More high persistence patients switched to the same drug type.

246. Factors Associated with Reported Difficulty Taking Antiretroviral Therapy in Brazilian Patients

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Background: Antiretroviral therapy (ART) requires strict adherence for optimal suppression of HIV. Difficulty in taking ART may lead to non-adherence.

Objectives: To identify personal, socioeconomic and treatment-related factors associated with self-reported difficulty taking ART.

Methods: Cross-sectional national study of HIV-positive adults (n = 598; 61% males) under care in 17 AIDS referral services in Brazil. Pregnant HIV-positive women were excluded of the study. Patients were proportionally sampled according to seven Brazilian Regions, strata of service quality and total number of patients under care in each service. Patients answered to a face-to-face interview with 38 structured questions

and three open-ended questions on ART. Responses to the question 'Could you tell me three things that make it difficult taking drugs for HIV?' were dichotomized in yes/no (yes: those who reported at least one thing; no: those who reported having no difficulty). To assess the association of personal, socioeconomic and treatment-related factors with self-reported difficulty taking ART we conducted bivariate analysis using the χ^2-test at the level of $\alpha = 0.05$.

Results: Among 598 patients, 382 (63.9%) reported at least one barrier to take ART. Factors found to be statistically associated with reported difficulty taking ART ($p \leq 0.05$) included younger age, alcohol and party drug use in the last 3 months, low CD4 count and high viral load in the last medical exam, missing doses and any medical appointment in the last 6 months, experiencing physical adverse events, poor self-reported quality of life and health, and diagnosis of anxiety and depression.

Conclusions: In our study, mental health conditions, lifestyle and treatment-related factors were associated with reported difficulty taking ART, while socioeconomic factors were not. The findings are important to assist health-care providers to target individuals with greater likelihood of experiencing difficulty taking ART. Interventions such as multidisciplinary attention at the health-care service are needed to improve patient's adherence to antiretroviral treatment.

247. The Evaluation of Various Published Scales to Assess the Patient's Adherence to Medication

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Background: Patient's adherence to prescribed medication is an important indicator of drug effectiveness. Drug utilization data should be corrected considering the adherence rate. Measuring of the adherence rate is not standardized. Self-reporting questionnaires are very often used.

Objectives: Self reporting questionnaires have benefits of being cheap, easy to administer, and provide the additional information on patient's attitudes and beliefs about medication treatment. The limitations are the ability to understand the items and willingness to disclose the information about the behavior. Seven different questionnaires were identified by literature reviewing. The aim was to evaluate adherence measuring in clinical settings.

Methods: A computerized systemic search of the Pub-Med databases in the period 2005–2012 identified

articles on measuring the adherence medication rate using the MeSH terms: medication adherence, compliance and persistence combined with the terms self-report questionnaire. The articles were included in a survey if they evaluated adherence medication rate in chronic diseases patients and if they were reliable with good coefficient of internal consistency (Cronbach's alpha).

Results: A total number of hundred articles were identified. Of them 20% were included in the reviewing as relevant to the objectives of the study. The adherence was determined in the eight different chronic diseases. Cronbach's alpha coefficient were highest at SEAMS (0.89–0.82) and Zagreb scales (0.89). The Morisky-Green scale were used very frequently, but the coefficient was low (0, 61). The Morisky scale is structured of four-item self-reported adherence measures and the Zagreb scale was designed as 33-item questionnaires with 16 listed common reasons for nonadherence.

Conclusions: There are seven different self-reporting scales used in published studies until now. They were applied in different groups of patients with chronic diseases. Due to several reasons the scales were different in coefficient of internal consistency reliability (Cronbach's alpha). This should be kept in mind when planning a new adherence research using self-reporting scale.

248. Attitudes towards Medication Use in a General Population of Adolescents

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Background: Adolescents are less studied than younger and older age groups, but it is known that medication adherence for chronic disorders such as asthma and diabetes worsens as children become teenagers. Perceptions towards medication use have shown to be important drivers of adherence and disease outcomes in adults. Adolescents are becoming more independently responsible for medication use, therefore this is a crucial period to address medication beliefs, as many of the beliefs formed at this age may persist into adulthood and can impair adherence.

Objectives: To explore medication beliefs in a general population of adolescents.

Methods: We conducted a cross-sectional study among adolescents attending five different secondary schools in the Netherlands (total of 2,500 students). During a

2-week period, students were invited -through social media- to fill in a short (anonymous) online questionnaire. Perceptions towards medication were assessed by using the 'Beliefs About Medicines Questionnaire' (BMQ-general) comprising a general-harm ('perceptions about medicines as harmful') and general-overuse ('perceptions about over-prescribing of medicines') scale. Regression analysis was used to study factors associated with medication beliefs.

Results: During the study period, valid questionnaire data was received from 443 adolescents (age 11–19 years), giving a response rate of approximately 15%. Almost half of the study sample (47%) thought that doctors overprescribed medication and 21% perceived medication in general as harmful. Being religious was associated with both stronger harm (OR 2, 95% CI: 1.3–3.3) and overuse beliefs (OR 1.5, 95% CI: 1–2.2). Adolescents of native background had lower concerns about overuse (OR 0.4, 95% CI: 0.2–0.8). Adolescents who used prescription drugs or had visited a physician during the previous 6 months were less worried about overuse (OR 0.7, 95% CI: 0.4–1 and OR 0.6, 95% CI: 0.4–1, respectively).

Conclusions: Adolescents have stronger beliefs in the general overuse of medicines than in general harm of medicines. An individual's religious and cultural/ethnic background seem to influence medication beliefs, as do previous experience with medicines and healthcare use.

249. Comparative Effectiveness of Biologic DMARDs in Older and Disabled Patients with Rheumatoid Arthritis (RA) in Medicare

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Background: Evaluating clinical effectiveness of biologic disease-modifying anti-rheumatic drugs (DMARDs) in RA using claims data was no possible due to a lack of clinical information in claims. There are limited effectiveness data in older populations that are rarely present in large numbers in clinical trials or registries. A novel, validated, claims-based clinical effectiveness algorithm provides the potential to compare effectiveness of biologics using large administrative databases.

Objectives: To compare effectiveness of biologic DMARDs, in Medicare patients.

Methods: We evaluated effectiveness of abatacept (ABA), adalimumab (ADA), etanercept (ETN), and infliximab (INF) in 100% of Medicare beneficiaries (eligible based on age ≥ 65 or disability) with RA and ≥ 24 months of fee-for-service plus drug coverage during 2006–2010. Subjects were biologic naïve, without evidence of biologic use for 12 months before their first claim for a biologic DMARD. The outcome was effectiveness at 365 days according to the algorithm, which required six dichotomous conditions to be met. We calculated the proportion meeting effectiveness criteria by biologic and compared effectiveness between them using robust Poisson regression to compute risk ratios (RR), adjusted for demographics, comorbidities and other medications.

Results: We identified 2,129 ABA, 2,944 ADA, 3,517 ETN, and 5,654 INF patients. Overall, 27% were disabled and under age 65. The algorithm classified the biologic as effective in 27% of ABA, 24% of ADA, 29% of ETN and 24% of INF patients. After adjustment and compared to INF, the RR for effectiveness were 1.17 (95% confidence interval [CI]: 1.06–1.29) for ABA, 1.10 (95% CI: 1–1.21) for ADA and 1.29 (95% CI: 1.18–1.40) for ETN. All biologics were effective in a greater percentage of patients who were not disabled than patients who were (RR = 1.18, CI: 1.08–1.28).

Conclusions: A significantly higher proportion of ABA and ETN patients were classified as effective using the claims-based algorithm than INF patients. Similarly, a significantly higher proportion of older RA patients were classified as effective than younger but disabled RA patients.

250. Opioid Analgesic Dosage Strength as a Predictor of Overdose Risk in the UK

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Background: Based on four studies reporting that US patients prescribed higher daily doses (≥ 120 mg morphine equivalent doses [MED]) of opioid analgesics have 3- to 11-fold higher risk of opioid overdose, several US states are imposing limitations on prescribing ≥ 120 mg MED of opioids. The four dose-risk studies are potentially confounded by differences in high- vs. low-dose users arising from: (1) pooling all opioids despite differences in indications (e.g., acute vs. chronic pain), formulations (e.g., IR vs. ER) and opioid types (e.g., tramadol vs. morphine), and (2) opioid abuse, since abusers have a high risk of overdose and seek high doses.

Objectives: To assess the risk of opioid overdose by prescribed dosage strength by individual extended-release (ER) opioids in the UK.

Methods: Dose-risk relationship was assessed separately within three ER opioid analgesics: morphine tablets, fentanyl patch and buprenorphine patch. To minimize the impact of abuse, we used a UK medical record database maintained by general practitioners, who control access to healthcare and have long-term relationships with patients. Person-time on opioids by dose was calculated. Overdoses were ascertained from diagnostic codes. Poisson regression was used to calculate relative risks of overdose by dose controlling for age, gender, cancer, mental illness, and concomitant opioids. All data analyses were conducted independently by Analytical Consulting Solutions, Inc.

Results: Between 2005 and 2010, 38,861 patients (287 overdoses) were prescribed ER morphine, 23,909 fentanyl patches (108 overdoses), and 20,560 buprenorphine patches (56 overdoses). The relative risk of overdose among patients prescribed ≥ 120 mg vs. ≤ 30 mg MED was 0.78 (95% CI: 0.36–1.72) for buprenorphine, 1.44 (95% CI: 1.04–1.99) for morphine, 1.58 (95% CI: 0.55–4.49) for fentanyl patch and 1.18 (95% CI: 0.90–1.55) for all three opioids combined.

Conclusions: Higher doses (≥ 120 mg MED) of morphine tablets, fentanyl patch and buprenorphine patch was not a risk factor for opioid overdose among UK patients, especially not buprenorphine patches. The dosage risk seen in US studies may be due to pooling all opioids and higher abuse rates in the US than the UK.

251. Application of a Cox Model across a Refunds Database: A New Approach to Compare Selective Serotonin Reuptake Inhibitors (SSRI)

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Background: SSRI are considered as an homogeneous antidepressant drugs class. Current guidelines for major depressive disorder uniformly recommend SSRIs as first line treatment. Effectiveness and tolerance evaluation must be made during the first weeks after the start of treatment. If the treatment fails despite a good persistence, practitioners should increase the dose, add a new antidepressant or switch. But are all the SSRIs similar in terms of effectiveness and tolerance in the real life?

Objectives: The aim of the study was to compare escitalopram, paroxetine, fluoxetine, citalopram and sertraline in persistent outpatients (treated during at least 6 months with antidepressants) during the 90 first days of treatment across a refunds database. Using increase of dose and/or switch and/or antidepressant added as a proxy of lack of effectiveness or tolerance.

Methods: Data comes from a health insurance system covering the majority of the French population. Persistent patients older than 18 were selected. Outcomes of drugs refunds were analyzed. An algorithm that spotted for each patient's trajectory an increasing dose or the occurrence of a new antidepressant has been developed. A Cox model allowed comparing the SSRIs on time occurrence before the first event (increase of the dose or new antidepressant) during the 90 first days. This Cox model assessed the relative effect of the first prescribed SSRI on the risk of lack of effectiveness or tolerance.

Results: Among the 3,542 included outpatients, 489 (14%) presented an event during the 90 first days. The adjusted Cox model identified significant higher rates of events for patients treated by paroxetine (HR = 1.25; p = 0.04), citalopram (HR = 1.46; p = 0.02) or sertraline (HR = 1.40; p = 0.04) than escitalopram. Fluoxetine's hazard ratio was not significant (HR = 1.08; p = 0.61).

Conclusions: Patients having as first antidepressant paroxetine, sertraline or citalopram seem to present more precocious events than those treated by escitalopram or fluoxetine. Ours results are in accordance with previous studies and it could initiate a reflexion about a possible graduation between SSRIs.

252. Treatment in the Morning vs. Evening (TIME) with Antihypertensives: A Pilot Study

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Background: Nocturnal blood pressure (BP) is a better predictor of cardiovascular outcome than daytime BP. The BP lowering of treatments are larger in the first 12 h compared to the next 12 h. Is treatment taken in the evening more cardio-protective than treatment taken in the morning?

Objectives: To test feasibility of a trial to determine if nocturnal dosing has improved cardiovascular outcomes compared to morning dosing, using web-based technology.

Methods: Responding to advertising, subjects with hypertension registered at www.timestudy.co.uk. 1794 hypertensive subjects were written to in three primary care practices. Subjects consent, enter demographics and drug treatments on-line. Email follow-ups track outcomes from patients. Record-linkage detects the primary end-point: non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Inclusions: treated for hypertension, over 18 years old, a valid email address. Exclusions: those taking twice daily therapy, working shifts, unwilling to consent, participating in another trial. Patient sign up, consent rates, age and sex have been determined. ASSIGN risk scores (assign-score.com) are calculated for participants. We calculated the number of participating practices, number of subjects and duration of a trial to detect a 20% benefit of nocturnal dosing.

Results: TIME randomised 355 participants; 16 withdrew over 1 year. 59 were recruited from three practices who wrote to patients giving a rate of 3.6 per 1000 patients or 33 per 1000 written to. Participant risk varies by age: 21% for all ages (n = 355), 25% for > 55 (n = 269), 27% for > 60 (n = 227) and 30% for > 65 (n = 150). A trial with 80% power to detect a 20% improved outcome of nocturnal dosing requires 631 events. This requires 9780 subjects of all ages, 8260 ≥ 55, 7680 ≥ 60 or 6454 ≥ 65 all followed for 4 years. Figures require to be inflated by 5% for drop-outs. We would expect 20 subjects per average sized (n = 5581) practice, so would need to recruit between 489 and 384 practices.

Conclusions: TIME achieves recruitment at low cost. If funded, recruitment of patients in primary care would be provided by NHS research networks at no cost. The TIME study is a viable trial.

253. Thiazolidinedione Use and Risk of Hospitalization for Pneumonia in Type 2 Diabetes: Population Based Matched Case-Control Study

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Background: Previous randomized clinical trials and their meta-analyses have raised the possibility that thiazolidinediones (rosiglitazone and pioglitazone) may increase the risk of pneumonia.

Objectives: We aimed to test the hypothesis that thiazolidinediones may increase the risk of pneumonia.

Methods: We conducted a population based case-control study in a a large administrative database in the United States from 2002 to 2008. We included Adults with type 2 diabetes aged 18–64; we restricted our analysis to 8,010 hospitalized pneumonia cases and 8,010 controls without congestive heart failure matched on age, sex, enrollment pattern and diabetes complication severity index matched controls. Conditional logistic regression was used to analyse the data.

Results: Compared with controls, cases were more likely to have chronic obstructive pulmonary disease, tobacco use, cancer and receive influenza and pneumococcal vaccination. During the pre-defined recent exposure window (> 60 days prior and < 2 years) 4.8% of case patients were exposed to thiazolidinediones (3.9% on pioglitazone and 1% on rosiglitazone) compared to 4% of controls (3.1% on pioglitazone and 0.9% on rosiglitazone).After adjusting for COPD, cancer, tobacco use, and receipt of influenza and pneumococcal vaccination, and exposure in other period, recent exposure to pioglitazone was associated with a small statistically significant increased odd of pneumonia (adjusted Odds Ratio [aOR], 1.27, 95% Confidence intervals 1.04–1.55). However neither recent exposure to rosiglitazone (aOR 1.20, 95% CI, 0.82–1.75) nor current exposure to either thiazolidinedione within 60 days (aOR, 1.11, 95% CI: 0.98–1.25 for pioglitazone; aOR, 0.98, 95% CI: 0.72–1.32 for rosiglitazone) was associated with statistically significant odds of pneumonia.

Conclusions: This study of US adults with type 2 diabetes although pioglitazone use for more than 60 days was associated with a small increased risk of hospitalization for pneumonia, but shorter duration of pioglitazone use and use of rosiglitazone was not associated with such a risk.

254. Comparative Effects of Different Combination Antiretroviral Therapies on the Risk for Myocardial Infarction among HIV Patients Enrolled in Medicaid: A New User, Active Comparator Cohort Study

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Background: Cohort studies have demonstrated a greater risk of myocardial infarction (MI) associated with specific antiretroviral (ARV) use while meta-analyses of randomized controlled trials (RCT) have not. Inherent biases may be related to using observational data and associated study design or limited duration of RCTs.

Objectives: To examine the effects of initiating specific ARVs on the risk for MI among previously untreated

HIV-infected patients receiving combination ARV therapy (cART).

Methods: We conducted an intention to treat, new user, active comparator cohort study emulating a population that would be enrolled in a RCT evaluating the relationship between initiation of specific ARVs as part of a standard cART regimen and MI. We included HIV-infected North Carolina Medicaid beneficiaries enrolled between 2002 and 2008 and previously untreated with cART. We compared hazard rates (HR) and 95% confidence intervals (CI) of MI between recipients of abacavir to tenofovir, and lopinavir-ritonavir or atazanavir to non-nucleoside reverse transcriptase inhibitor (NNRTI). Confounding was adjusted for using standardized morbidity/mortality ratio weights.

Results: There were 3,481 new cART recipients that contributed 6399.25 person-years and experienced 38 MI events. The unadjusted incidence rate of MI for the new cART population was 5.9 (95% CI: 4.3, 8.2) per 1000 person-years of follow-up. Receiving abacavir as part of cART was associated with an increased rate of MI compared to tenofovir in unadjusted and adjusted models (HR: 2.70 [95% CI: 1.24, 5.91], HR: 2.05 [95% CI: 0.72, 5.86] respectively). Point estimates suggest a relationship between receipt of atazanavir or lopinavir-ritonavir compared to an NNRTI and MI, however, estimates were imprecise.

Conclusions: We found an increased rate of MI among patients initiating abacavir compared to tenofovir that decreased after confounding adjustment. Without a very large prospective comparative clinical trial, a much larger observational study of patients initiating cART is needed to better define this apparent association.

255. Long-Term Effectiveness of Ribavirin Plus Pegylated Interferon Combination Therapy for Patients with Dual Hepatitis C and B in Taiwan: A Population-Based Study

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Background: Patients dually infected with hepatitis C virus (HCV) and hepatitis B virus (HBV) have a signifi-

cantly higher risk (2–3 folds) of developing advanced liver disease or hepatocellular carcinoma (HCC) than patients mono-infected with either virus. Whether peginterferon alfa and ribavirin combination therapy reduce risk of HCC or improve survival in these patients is unknown.

Objectives: Evaluate the long-term effectiveness of ribavirin plus pegylated interferon combination therapy among dual-infected patients.

Methods: Data for this population-based retrospective cohort study was obtained from the treatment program, Cancer Registry, National Health Insurance, and death certification. Patients in the treatment group received combination therapy; patients in the control group received no treatment. We examined the risk of HCC and mortality in 1,096 treated and 18,988 untreated HCV/HBV dually-infected patients. Outcomes were analyzed using the bias corrected inverse probability weighting by propensity scores (IPW).

Results: Since 2003, when a program to reimburse hospitals for Hepatitis treatment was launched, the number of patients receiving treatment has been increasing. After adjustment, combination therapy significantly reduced the risk of HCC (hazard ratio [HR] 0.76, 95% confidence interval [95% CI] 0.59–0.97), liver-related mortality (HR 0.47, 95% CI: 0.37–0.6), and all-cause mortality (HR 0.42, 95% CI: 0.34–0.52).

Conclusions: Antiviral treatment using a combination of ribavirin plus pegylated interferon is effective to prevent hepatocellular carcinoma and improve the survival in HCV/HBV dually-infected patients.

256. The Effect of Adding Inhaled Corticosteroids to Long-Acting Bronchodilators for COPD: A Real Practice Analysis in Italy

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Background: Long-acting bronchodilators (LB) comprising beta(2)-agonists (LABAs) and tiotropium are commonly used for COPD management. Patients with severe COPD who experience repeated exacerbations are recommended to add inhaled corticosteroids (ICS) to their bronchodilator treatment. However, the benefits of adding ICS to LB are unclear.

Objectives: To estimate whether adding ICS to LB therapy reduces mortality in severe COPD patients.

Methods: A cohort study based on linked health information systems in three Italian regions was performed. Patients aged 45+ years, discharged from hospital with diagnosis of COPD between 2006 and 2009 were enrolled. The exposure definition began on the date of the first prescription for LB or ICS following discharge, considering new users only. A 4-day window was used to classify patients into LB alone or LB plus ICS initiators. Follow-up started the day following this time window. LB plus ICS therapy was compared with LB alone. The same comparison was made restricting LB to LABA only, while excluding patients using tiotropium. Patients were censored at the time of discontinuation of the initial drug, outcomes, end of one-year follow-up, or study end (December 2010), whichever came first. Hazard ratios (HR) were calculated by Cox regression using propensity score matching, including more than 50 comorbidities and proxies of severity measures. Sensitivity analysis using an intention to treat (ITT) approach was performed.

Results: Among the 5469 adults enrolled, 742 were exposed to LB + ICS therapy. The overall mean age was 74 years, the mortality rate was 110/1000. Adding ICS to LB reduced mortality, both defining LB as 'LABA or tiotropium' (HR = 0.82, 95% CI: 0.41–1.63) and defining LB as LABA alone (HR = 0.43, 95% CI: 0.11–1.74). Using the ITT, HRs moved towards 1 (HR = 0.91, 95% CI: 0.67–1.22 and HR = 0.86, 95% CI: 0.49–1.51).

Conclusions: The 'as treated' analysis is compatible with a reduction in mortality when adding ICS to LB, even if the results were not statistically significant. Further analyses will be carried out in a two years follow-up, including other relevant outcomes, such as respiratory mortality and exacerbations.

257. Registry of Patient Registries (RoPR): Advancing Registries for Comparative Effectiveness Research

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Background: Patient registries generate important evidence on the comparative effectiveness of different diagnosis and treatment options. Until recently, information on ongoing and completed registries was not publicly available in a central location. This made it difficult to determine the current state of CER evidence for a particular disease area, diagnostic test, or treatment, and the potential future body of CER evidence.

Objectives: Sponsored by the Agency for Healthcare Research and Quality (AHRQ), the objective of this project was to design and build the Registry of Patient Registries (RoPR), the first searchable, public database designed specifically to provide information about ongoing and completed patient registries.

Methods: An iterative, stakeholder-driven process was used to determine the requirements for RoPR design and functionality. Based on stakeholder requirements, the RoPR was built, tested, and fully implemented with ClinicalTrials.gov, a well-known existing database for clinical trials.

Results: The RoPR was launched on December 1, 2012, and is currently used by registry sponsors to publish information about ongoing and completed registries. Members of the public can search the RoPR to identify registries in which they may wish to participate, discover registries that may be suitable for collaborative research projects such as data linkage or embedded studies, or to research the state of comparative effectiveness evidence for a specific disease area, diagnostic test, or treatment.

Conclusions: By making this information readily available, the RoPR facilitates research collaboration, reduces redundancy, encourages the efficient use of resources, and improves transparency in registry research. Registries are already important tools in generating comparative effectiveness evidence; the RoPR complements and advances this role by providing important summary information about ongoing and completed registries.

258. Prioritizing Comparative Effectiveness Research: Utility of Disease-Specific Spending Estimates

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Background: One of the pillars of healthcare reform in the US is investment in comparative effectiveness research (CER).

Objectives: To explore the utility of population-level, disease-specific healthcare utilization and spending estimates for prioritizing allocation of CER resources.

Methods: The study population consisted of persons enrolled for the full year of 2006 (N~8 million) and/or 2011 (N~12 million) in employer-sponsored, fee-for-service health insurance plans. Total spending on covered services (including patient and health plan amounts) was allocated across 560 disease categories using Medical Episode Groups (MEG). MEG categories were

ranked by prevalence and total spending per member per year (PMPY) in 2011, and by growth in prevalence and spending PMPY from 2006 to 2011.

Results: Among persons with private health insurance, 2011 spending was $4,509 PMPY and had grown by $1,017 since 2006. The top 20 MEGs on each respective measure contributed 32% and 36% of the totals. The MEG for preventive health services was the most prevalent (50% of plan members), most costly ($214 PMPY), and fastest growing (5-year increase of 9% points over 5 years and $78 PMPY). Four other MEGs also ranked in the top 20 of each of those measures: type 2 diabetes; 'other' spinal and back disorders; 'other' arthropathies; and 'other' skin inflammations. Five of the 20 most costly and 6 of the 20 fastest growing MEG were musculoskeletal disorders. Other high cost/high growth MEGs include: breast cancer; vaginal and caesarean delivery; complications of surgical and medical care; and renal failure.

Conclusions: In private health plans, which cover the majority of the US population, preventive care and treatment of osteoarthritis, low back pain, and other common orthopedic problems are some of the high-impact medical services that should be put under the CER microscope. This illustrates how attribution of total medical care utilization and spending to particular disease categories can help target CER resources where the benefits can be greatest, both in terms of persons affected and healthcare cost burden.

259. Does the Risk Reduction Provided by Longer Durations of Clopidogrel Use after Stent Placement in Taiwan's National Health Insurance

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Background: Evidence regarding the effect of the prolonged use of combining clopidogrel with aspirin on risk of death or myocardial infarction remains inconclusive.

Objectives: he purpose of the study was to examine the value of prolonged dual antiplatelet therapy with a clopidogrel and aspirin after drug-eluting stent placement.

Methods: All patients in the Taiwan's National Health Insurance (NHI) program receiving either drug-eluting stents from 2007 to 2008 were included in our study. The patients who received more than one stent at the index procedure or received percutaneous coronary intervention within 5 years prior to the index procedure were excluded. The National Health Insurance claim databases were used to extract patient characteristics, duration of clopidogrel and aspirin use, and outcomes after the index procedure. Cox proportional hazards regression model were used to estimate hazard ratios for death, revascularization, Ischemic stroke, and bleeding from a 240 days landmark after stenting.

Results: A total of 844 patients met the study inclusion criteria treated with non-prolonged (240–390 days) clopidogrel use (n = 405) or prolonged (> 390 days) clpidogrel use (n = 439). Compared with non-prolonged of clopidogrel, prolonged clopidogrel was not associated with risk of death (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.45, 1.99; p = 0.204) as well as risk of revascularization (HR, 0.85; CI, 0.56–1.27; p = 0.427) and Ischemic stroke (HR, 2.70; CI, 0.99–7.39; p = 0.053). However, the effect of prolonged clopidogrel on GI bleeding was associated with a lower adjusted risk (HR,5.16; CI, 1.36–19.58; p = 0.016) compare with non-prolonged clopidogrel.

Conclusions: Patients receiving clopidogrel beyond 390 days had a lower risk of GI bleeding compared patients receiving clopidogrel ≤ 390 days. These data support longer durations of dual antiplatelet therapy for patients receiving a drug-eluting stent.

260. Effectiveness of Cholinesterase Inhibitors for Mild to Moderate Alzheimer's Disease: A Systematic Review of Observational Studies

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Background: Cholinesterase inhibitors (ChEI) are used in mild and moderate Alzheimer's disease (AD). Evidence based on randomized clinical trials (RCT) and meta-analysis of RCT indicates a clinical benefit with a delayed cognitive impairment of at least 6 months. However, in clinical practice, the benefit of ChEI is debated.

Objectives: To assess the effectiveness of ChEI for mild and moderate AD in the real world setting.

Methods: We searched MEDLINE and Embase for all original articles about observational studies, extending over at least 6 months, studying the effectiveness and safety of donepezil, galantamine and rivastigmine in mild and moderate AD, published up to March 2012. Effectiveness was assessed on cognitive function (MMSE), on general clinical function (CIBIC+, CGI-C),

on autonomy (IADL/ADL) and on behavioral disorders (NPI). Two independent authors reviewed all titles/abstracts and retrieved detailed full-text of potentially relevant articles to identify studies according to predefined selection criteria.

Results: Six prospective cohort studies were selected from 1,675 articles. The number of subjects ranged from 24 to 5462, mean age from 72 to 79 years and study duration from 6 to 36 months. Donepezil was evaluated in four studies, rivastigmine in 3 and galantamine in 2. At 6 months, the cognitive function progressed by +1.20 points with donepezil, +1.84 with rivastigmine and +2 with galantamine. With rivastigmine, the memory domain of the CGI score improved or remained unchanged in 84% of the patients. With galantamine, the CIBIC+ score improved or was unchanged in 54% of the patients. Autonomy only evaluated with galantamine did not deteriorate in 26% of the patients. No statistical improvement was noted for behavioral disorders.

Conclusions: These results tend to demonstrate a little benefit gained from ChEI use in AD at 6 months in real life. The impact of this analysis is limited because observational studies are too scarce, criteria and periods of evaluation are too different between studies to conduct a meta-analysis. Further observational studies should use common criteria and should extend over longer periods.

261. Comparative Effectiveness Research (CER): Where to Begin? A Literature Review of CER Methods Guides

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Background: Given the obstacles facing healthcare systems worldwide, an increased interest in CER has emerged as we seek to determine which treatments work best under real-world conditions. Currently, there is a lack of consensus regarding standardized approaches to the planning and conduct of CER. Formal methodological guidance can assist researchers in applying accepted and appropriate CER methods. However, it is unknown how many CER methods guides exist and the extent of agreement or differences between recommendations in these documents.

Objectives: To identify formal CER methods guides through a review of the literature.

Methods: Literature searches were conducted on Pubmed and Google Scholar using 'comparative effectiveness research methods' as the search term. Guidance documents were identified from peer-reviewed journals, professional organizations and societies, and government funding agencies including the Agency for Healthcare Research and Quality (AHRQ) and Patient-Centered Outcomes Research Institute (PCORI). We cataloged, examined, summarized, and compared formal documents providing methodological guidance for the design and conduct of CER. Search results were categorized by author and content.

Results: From an initial selection of 102 documents, 88 abstracts were selected for topical relevance and reviewed. Specific methodological procedures were described in 40% (n = 35) of the articles, while 8% (n = 7) detailed specific therapeutic applications of CER methods. The majority (52%) of documents represented general overviews of CER techniques. Of these overview documents, 15% (n = 7) were authored by professional organizations, whereas 85% (n = 39) were written by individuals. We identified seven documents, from AHRQ, PCORI, National Pharmaceutical Council, GRACE Initiative, and the American Heart Association, which serve as formal methods guides.

Conclusions: Based on our search, the majority of articles identified were overviews of CER methods rather than actual recommendations or guidelines for standardized methodological approaches. The formal methods guides identified in our literature review can assist researchers in developing CER protocols.

262. Improving the Validity of CER through Principled Exploration of Data

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Background: Comparative effectiveness research (CER) using secondary data critically depends on a detailed understanding of the origins and structure of the underlying data.

Objectives: We outline discrete steps for evaluating and effectively using secondary data, with the goal of improving exposure and outcome definitions and informing study designs.

Methods: We used population-based cancer registry data linked with Medicare claims from recently-published

comparative effectiveness research studies of FOLFOX in stage III colon cancer cases. In a retrospective cohort, we examined how exposure and outcome definitions are influenced by the inherent data structures and underlying contextual information within the Healthcare Common Procedure Coding System (HCPCS) and other clinical coding terminology used in claims data.

Results: Study design and variable specification can be improved by using discrete steps to evaluate the structure and intent of the dataset. We significantly changed the exposure definitions of the existing CER study though integrating information about the data structure and coding changes over the course of therapeutic adoption of FOLFOX. Applying this information in the claims-based cohort, we saw up to 10–20% differences between our exposure definitions, which had important implications for both study design and bias reduction.

Conclusions: By carefully evaluating secondary data, pharmacoepidemiologists can improve algorithms that define treatment and outcomes, and thus reduce bias related to misclassification. It is increasingly important to define and publish discrete processes to better understand sources of secondary data and obtain more nuanced information from clinical coding schema and standard clinical terminology.

263. Withdrawn by Author

264. Do SSRIs Increase the Risk of Gastrointestinal Adverse Effects?

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Background: Selective serotonin reuptake inhibitors (SSRIs) have been associated with gastrointestinal (GI) adverse effects. However, conflicting results were obtained by studies that evaluated the association between SSRIs, whether or not in combination with NSAIDs, and GI adverse effects.

Objectives: To assess whether SSRIs increase the risk of GI adverse effects.

Methods: Drug dispensing data between 1994 and 2011 were retrieved from the IADB.nl database. A prescription sequence symmetry analysis was used to assess whether peptic ulcer drugs, a proxy for GI adverse events, were prescribed more often following SSRI therapy initiation, whether or not in combination with NSAIDs, than the other way around. A relative short maximum time-span of four weeks between both pre-

scriptions was used to limit time-variant confounding. We adjusted for trends in prescribing and estimated 95% confidence intervals using exact confidence intervals for binomial distributions. The association between NSAIDs alone and peptic ulcer drugs was also evaluated, as a positive control.

Results: In total, 253,588 incident SSRI users were identified. Of these patients, 277 were incident users of both SSRIs and peptic ulcer drugs within a 4 week time-span. Less patients received peptic ulcer drugs after SSRI therapy initiation than the other way around (126 vs. 151), corresponding to an adjusted sequence ratio (ASR) of 0.83 (95% confidence interval [CI] 0.65–1.06). The ASR of concurrent use of SSRIs and NSAIDs (1.48, 95% CI: 0.90–2.49) did not exceed the ASR of NSAIDs alone (2.50, 95% CI: 2.27–2.76).

Conclusions: This study provides evidence that SSRIs do not increase the risk of GI adverse effects. Our findings indicate that at least part of the association between SSRIs with or without NSAIDs and GI adverse events might be attributed to unmeasured or residual confounding.

265. Angiotensin-Converting Enzyme Inhibitor Treatment and the Development of Urinary Tract Infection

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Background: Angiotensin-converting enzyme inhibitors (ACEi) can reduce the urine output, especially when treatment is started. Since bacterial clearance from the urinary tract is dependent on the urine output, it was hypothesized that ACEi may also increase the risk of urinary tract infections (UTIs).

Objectives: To assess the risk of UTIs associated with ACEi therapy initiation in the general population.

Methods: A prescription sequence symmetry analysis was performed with the IADB.nl pharmacy prescription database. We selected all patients from the IADB that were incident users of both ACEi and nitrofurantoin (a proxy for UTIs). A relative short maximum time-span of four weeks between both prescriptions was used to limit time-variant confounding. The sequence ratio was calculated by dividing the number of individuals starting ACEi first and nitrofurantoin second by the number of individuals starting nitrofurantoin treatment first and ACEi second. We adjusted for trends in prescribing and estimated 95% confidence intervals using exact confidence intervals for binomial distributions. To evaluate whether the effect is specific to ACEi and to assess whether the possible mechanism

behind an increased risk of UTI is related to the renin-angiotensin-aldosterone system, we also estimated the risk for β-blockers.

Results: In total, 22,959 incident users of ACEi therapy were eligible for analysis. Of these, 161 patients started ACEi therapy within 4 weeks prior to or after nitrofurantoin therapy initiation. 101 (63%) started ACEi therapy first followed by nitrofurantoin treatment while 60 (37%) patients started nitrofurantoin treatment first with a corresponding statistically significant adjusted sequence ratio (ASR) of 1.68 (95% CI: 1.21–2.36). No association was found between β-blocker therapy initiation and urinary tract infection treatment (ASR 1.01, 95% CI: 0.74–1.38).

Conclusions: A significant excess of patients received UTI medication prescriptions following the first month after ACEi initiation. This prescription sequence asymmetry suggests that ACEi initiation increases the risk of developing UTIs.

266. Feasibility of Linking Administrative Claims Data to Institution-Specific Laboratory and Electronic Health Record Data for Comparative Effectiveness Research

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Background: The conduct of comparative effectiveness research is increasingly dependent on the ability to combine detailed clinical data from specialized patient care with routinely-collected administrative information such as health insurance claims.

Objectives: The objective of this study was two-fold: (1) to explore the feasibility of linking carotid artery ultrasound results from vascular laboratories to Medicare data and institutional electronic health records (EHRs) in two large tertiary care centers; and (2) to investigate the feasibility of linking similar data in other institutions more generally across the US.

Methods: We collected carotid ultrasound studies from vascular laboratories based in two tertiary care hospitals and linked them to institutional EHR data and Medicare claims data for the same patients using unique patient identifiers. We then outreached and surveyed additional institutions to assess readiness of vascular laboratory imaging data for linkage and analysis

in CER. We employed a stratified sampling strategy to represent each type of vascular laboratory from each US Census region in the survey.

Results: From the two hospitals, of the 29,607 imaging results that were either manually input to a database or imported from existing electronic vascular laboratory database, 6,810 were linked to complete Medicare claims using patient unique identifiers. The survey responses came from nine vascular and radiology labs across the US with representation across regions of the country and affiliation with a hospital. Imaging data is frequently available in electronic form, 7 of 9 (77.8%) institutions have electronic data with a mean of 9 years stored, but the data are less frequently suitable for research: 4 of 9 (44%) considered the data suitable for research.

Conclusions: Linkage of carotid imaging results with claims is feasible, and many vascular labs have data that would be suitable for such linkage. However, current utility of these data for research purposes seems generally limited.

267. FDA's Partnership in Applied Comparative Effectiveness Sciences

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Background: The U.S. Food and Drug Administration does not require comparative evaluation of products and only recently has encouraged patient-centered outcomes for drug or device approval. In 2010, the FDA launched the Partnership in Comparative Effectiveness Sciences (PACES) with an academic partner.

Objectives: To describe how PACES is advancing comparative effectiveness research methods at the FDA.

Methods: Projects were conducted by Hopkins investigators in collaboration with statisticians and clinical experts from the FDA and subcontractors. FDA permitted the use of submitted trial data, accessed via secure laptops, for the purpose of simulation. Hopkins investigators met monthly with FDA scientists, and conducted interim workshops at FDA to receive feedback. Final results will be delivered in June 2013.

Results: Three of four projects converged around methods for subgroup analyses, relevant when translating efficacy results into effective use of therapies. Data from trials of medications were used to make an

R-package that simulates adaptations that trialists may use to minimize exposure of groups, defined at baseline, as least likely to benefit. Data from trials of a device allowed testing of new Bayesian methods to combine trial results to know safety outcomes in key subgroups. Data from trials of other drugs allowed testing of methods for predicting outcomes for subgroups defined by combinations of moderators rather than by a single characteristic. The 4th project tested the analytic hierarchy process to elicit treatment preferences of experts –to learn how experts balance benefit and risk. Their goal was to inform risk-benefit management by decision makers at the FDA and their Advisory Committees.

Conclusions: There were no breeches of data safety. A challenge was conversion of trial data into a format appropriate for methods research. The FDA acquired valuable software tools, to be made publicly available, to forecast effects in subgroups and to inform quantitative risk-benefit analysis. As FDA gains influence in post-approval evaluation of products, it is expected that comparative effectiveness methods will be increasingly important.

268. Confounding by Indication in Comparative Effectiveness Research: Does Adding Registry to Claims Data make a Difference?

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Background: Claims data are often lacking clinical details needed for categorizing indication or adjusting for confounding by indication. Clinical registries often lack long-term follow-up data. Linking the two sources can overcome shortcomings in either data source and may be necessary for answering certain comparative effectiveness questions.

Objectives: To assess the effect of adding registry data on comparativeness effectiveness estimates (CEEs) of carotid artery stenting (CAS) relative to carotid endarterectomy (CEA) derived using claims data only.

Methods: The study population consisted of Medicare fee-for-service beneficiaries at least 66 years of age who had undergone CAS or CEA between 2005 and 2008 and had a record in the Society for Vascular Surgery's Vascular Registry (SVS-VR). CAS is only indicated and reimbursed for high-surgical risk patients whereas CEA does not have such restrictions.

A priori, we expected estimates biased in favor of CEA. We derived various high-dimensional propensity scores (hd-PS): (1) hd-PS using claims data only, (2) hd-PS with the following registry dimensions added one-at-a-time: medical history, carotid stenosis symptoms, carotid stenosis imaging results, pre-procedural medications, and high-surgical risk. We compared mortality in CAS relative to CEA using Cox regression, adjusting for hd-ps.

Results: The study included 1,999 CAS and 3,255 CEA patients in the SVS-Medicare linked dataset. CAS patients were comparable to CEA patients in terms of age, gender, and race but were more often symptomatic (38.5% vs. 30.7%) and at high-surgical risk (96.7% vs. 44.5%). Adjusting for hd-PS corrected the upward bias and drove the CEEs downward. Relative to crude estimates (most biased), hd-ps using claims dimensions only brought the estimate down by 16.5% and addition of registry data dimensions progressively decreased the CEEs from 22% to 32.4%, when all registry dimensions were included. The variables that affected CEEs most were those in the high-surgical risk dimension.

Conclusions: In comparing CAS to CEA, high-surgical risk information was necessary to control for confounding by indication, even in hd-PS adjusted models.

269. Dose and Duration Relationship between Pioglitazone and Associated Risk of Bladder Cancer: A Systematic Review and Meta-Analysis

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Background: There have been some concerns that pioglitazone may be associated with a risk of bladder cancer.

Objectives: Our objective was to determine whether pioglitazone is associated with an increased risk of bladder cancer.

Methods: We conducted a systematic review and meta-analysis with a focus on investigating dose and duration effects, and whether risk with pioglitazone differs from rosiglitazone.We searched MEDLINE, EMBASE and regulatory documents in June 2012 and conducted meta-analysis on the overall risks of bladder cancer with pioglitazone or rosiglitazone and the risk with different categories of cumulative dose or duration of pioglitazone use.

Results: 14 studies were included: 5 RCTs (total > 16,000 participants) and nine observational studies (pooled cohort > 1.5 million). There was a significantly higher overall risk of bladder cancer with pioglitazone (RCTs: OR 2.51, 95% CI: 1.09–5.80, p = 0.03, I^2 = 27%; cohort studies: OR 1.20, 95% CI: 1.07–1.34, p = 0.001, I^2 = 0%) but not rosiglitazone (RCTs: OR 0.84, 95% CI: 0.35–2.04, p = 0.71, I^2 = 0%; cohort studies: OR 1.08, 95% CI: 0.95–1.23, p = 0.24, I^2 = 0%). Subgroup analysis by cumulative dose showed the greatest risk with > 28 g of pioglitazone (OR 1.64, 95% CI: 1.28–2.12, p = 0.0001, I^2 = 0%) which differed significantly from < 10.5 Grams (p = 0.02). Similarly, there was a significant difference with the risk of longer (> 24 months) compared to shorter (< 12 months) cumulative durations (p = 0.004) of pioglitazone use. Direct comparison of pioglitazone and rosiglitazone yielded an OR of 1.25 (95% CI: 0.91–1.72, p = 0.16).

Conclusions: A modest but clinically significant increased risk of bladder cancer with pioglitazone was found that appears related to cumulative dose and duration of exposure. We recommend prescribers consider alternative oral hypoglycaemics and limit pioglitazone use to shorter durations.

270. Comparative Effectiveness of Pharmacologic and Mechanical Strategies for Prevention of VTE among Special Populations

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Background: Venous thromboembolism is a prevalent and avoidable complication of hospitalization among patients hospitalized with trauma, traumatic brain injury, burns, or liver disease; patients on antiplatelet therapy, obese or underweight patients, those having obesity surgery, or with acute or chronic renal failure.

Objectives: To systematically review the comparative effectiveness and safety of pharmacological and mechanical methods of prophylaxis of VTE in these special populations.

Methods: We conducted a systematic review and meta-analysis. We searched MEDLINE®, EMBASE®, SCOPUS, CINAHL®, www.clinicaltrials.gov, International Pharmaceutical Abstracts (IPA), and the Cochrane Library in July 2012. Two reviewers evaluated studies for eligibility, serially abstracted data using standardized forms, and independently evaluated the risk of bias in the studies and strength of evidence for major outcomes and comparisons. We qualitatively synthesized the evidence and also pooled the relative risks from the controlled studies. We included RCTS and controlled observational studies of pharmacologic agents, and uncontrolled observational studies and case series of inferior vena cava filter use.

Results: After a review of 30,902 unique citations, we included 102 studies of which just eight were trials. The majority of observational studies had a high risk of bias. The strength of evidence is low that IVC filter placement is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma compared to no IVC filter placement. The strength of evidence is low that enoxaparin reduces DVT and that UFH reduces mortality in patients with TBI when compared to patients without anticoagulation. Low grade evidence supports that IVC filters with usual care are associated with increased mortality and do not decrease the risk of PE in patients undergoing bariatric surgery compared to usual care alone. All other comparisons had insufficient evidence to permit conclusions.

Conclusions: Our comparative effectiveness review demonstrates that there is a paucity of high quality evidence to inform treatment of these special populations.

271. Comparative Gastrointestinal Safety of Bisphosphonates: A Network Meta-Analysis

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Background: Bisphosphonates are first line treatment for primary osteoporosis. Gastrointestinal (GI) adverse events (AEs) are cited as a primary reason for non-adherence with therapy. Little information is known about the comparative GI safety of bisphosphonates.

Objectives: To use published clinical trial data to assess the comparative GI safety of bisphosphonates.

Methods: We completed a systematic review of all English language clinical trials that assessed bisphosphonate

safety and/or efficacy in primary osteoporosis. Randomized, blinded, and controlled studies were eligible. Extension, open-label, and studies not reporting AEs were excluded. The primary outcome was any GI-related AE. Subanalyses were completed for upper GI, serious GI, nausea, esophageal-related events, and discontinuation due to AEs. A Bayesian based network meta-analysis was completed using WINBUGS and GeMTC to allow for indirect comparisons.

Results: We identified 52 studies eligible for analysis: 33 alendronate, 13 risedronate, 5 etidronate, 7 zoledronic acid, and 45 placebo. Zoledronic acid had the highest probability (91%) of causing the greatest number of any GI AEs and highest probability (70%) of the greatest incidence of nausea. Etidronate (70%) and zoledronic acid (28%) had the highest probability of the greatest attrition due to AEs. Etidronate also had the highest probability (56%) of having the greatest number of upper GI symptoms among oral bisphosphonates. Only risedronate and alendronate had data on both serious GI and esophageal related AEs with no significant difference between drugs or compared to placebo.

Conclusions: Zoledronic acid had the highest probability of having the greatest number of GI AEs. Discontinuation due to AEs may be a more clinically relevant outcome, with the highest probability of greatest occurrence found with etidronate and zoledronic acid. These results question the assumption that annual zoledronic acid will translate into better adherence long-term. More research into real-world implications of the comparative safety of bisphosphonates is needed.

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272. The Comparative Safety and Effectiveness of Sitagliptin in Patients with Type 2 Diabetes and Heart Failure

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Background: Sitagliptin belongs to a new class of antidiabetic agents called incretins, which are hypothesized to have pleiotropic effects on the cardiovascular system including chronotropic and positive inotropic effects, as well as improved ventricular function, stroke volume and cardiac output. Incretins are also hypothesized to have heart failure specific effects.

Objectives: The objective of this study was to determine if the use of sitagliptin was associated with any

benefit or risk on clinical outcomes in a population-based cohort of patients with type 2 diabetes and incident heart failure.

Methods: Using a large commercially insured US claims and integrated laboratory database, 11,967 subjects with type 2 diabetes and incident heart failure were identified through physician claims, hospital discharge abstracts, and/or ambulatory care visits based on ICD-9 CM codes. Our population-based cohort was followed from January 1, 2004 until death, termination of medical insurance, or December 31, 2010. Time-varying multivariable Cox proportional hazards models were used to asses differences in all-cause mortality.

Results: Average age of subjects was 56 years, 39.6% were female, and median duration of follow-up was 1.94 years. In total, 653 subjects died (5.5%). No association between all-cause death and sitaglitpin use was observed compared to other glucose lowering agents. After adjustment for demographics, clinical and laboratory data, pharmacy claims, health care utilization and time-varying propensity scores, any sitagliptin use was not associated with a statistically significant increase in mortality (adjusted HR 0.64, 95% CI: 0.37–1.12) compared to no sitagliptin use. Similarly, compared to metformin/sulfonylurea combination therapy, sitagliptin combination therapy was not associated with an increase in mortality (adjusted HR 1.01, 95% CI: 0.40–2.56).

Conclusions: Sitagliptin therapy was not associated with excess risk of all-cause death among patients with type 2 diabetes and heart failure nor was it found to be associated with any benefit.

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273. Adjuvant Trastuzumab Therapy in HER2-Positive Breast Cancer Patients: A Meta-Analysis of Published Randomized Trials

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Background: Breast cancer is the most common cancer in women as well as the principle cause of death from cancer among women worldwide. Approximately 20–30% of women with breast cancer over-express the human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells. Trastuzumab is a recombinant humanized monoclonal antibody that targets HER2. It has been shown to be effective as monotherapy and, as adjuvant therapy, has been shown to improve results of chemotherapy in patients with HER2-positive metastatic breast cancer.

Objectives: The objective of this study was to conduct a meta-analysis of the available evidence on the benefit of receiving adjuvant trastuzumab in HER2-positive breast cancer patients who are concomitantly receiving chemotherapy.

Methods: We performed a literature search in MEDLINE® (1996–2012) to find peer-reviewed publications and academic conference proceedings relevant to the objective. A meta-analysis of randomized controlled trials comparing chemotherapy patients with or without adjuvant trastuzumab treatment was conducted. The primary outcome was disease-free survival (DFS), while a secondary outcome was mortality. Both the random-effect model and the fixed-effect model were used to combine and analyze data.

Results: Six eligible clinical trials were identified, and 14,299 patients with HER2-positive breast cancer were included. Results indicated superior outcomes in the adjuvant trastuzumab group relative to the group without trastuzumab. For DFS, the trastuzumab group had an odds ratio (OR) of 0.62 (95% CI: 0.48–0.80).For mortality, it had an OR of 0.77 (95% CI: 0.64–0.93).

Conclusions: According to the meta-analysis, adjuvant trastuzumab therapy both improves DFS and reduces mortality relative to patients treated with chemotherapy only. Other issues surrounding trastuzumab include optimum length of therapy, the high cost of therapy, and the high risk of cardiovascular side effects, which may themselves lead to death.

274. Comparative Effectiveness of Interferon and Pegylated Interferon against Chronic Hepatitis B in Taiwan

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Background: Previous studies have reported that pegylated interferon antiviral therapy provides better outcomes than interferon alone, in terms of virological and biochemical responses. However, the effectiveness of this treatment in reducing the incidence of hepatocellular carcinoma (HCC) or all-causes mortality in the long-term remains a matter of contention.

Objectives: This study compared the effectiveness of interferon and pegylated interferon on patients with the hepatitis B virus (HBV).

Methods: A population-based cohort was assembled using National Health Insurance claims data covering the period from 2004 to 2007. All patients included in the study were diagnosed with HBV and received interferon or pegylated interferon. The outcomes were defined as all-causes mortality (ACM), liver-related mortality (LRM) and hepatocellular carcinoma incidence (HI). Multivariate hazard ratios were estimated using the Cox proportional hazard model.

Results: A total of 580 patients were included in the final analysis. Interferon therapy was administered to 142 patients (24.5%) and pegylated interferon therapy was administered to 438 patients (75.5%). The median duration of treatment was 5.9 months (range: 0.9–7.6 months) for interferon and 6.4 months (range: 0.9–13.7 months) for pegylated interferon. The adjusted hazard ratios (95% confidence interval) for pegylated interferon compared with interferon were as follows: 0.87 (0.14–5.45) for ACM and 0.66 (0.08–5.58) for LRM, and 0.44 (0.07–2.89) for HI respectively.

Conclusions: This study observed no difference between the effectiveness of interferon and pegylated interferon in the long-term outcomes of HBV patients in Taiwan.

275. Comparative Effectiveness of Lamivudine and Interferon or Pegylated Interferon Against Chronic Hepatitis B in Taiwan

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Background: Since October 1, 2003, Lamivudine and interferon or pegylated interferon have been included in the reimbursement program of the National Health Insurance (Taiwan) as a first-line antiviral therapy for the hepatitis B virus (HBV). The efficacy of both of

these treatments has previously been demonstrated in terms of virological and biochemical responses.

Objectives: The purpose of this study was to compare the effectiveness of Lamivudine and interferon or pegylated interferon on patients with HBV.

Methods: This study selected patients diagnosed with HBV who received lamivudine and interferon or pegylated interferon as their first-line antiviral therapy. Data was obtained from National Health Insurance claims data covering the period from 2004 to 2007. Outcomes were defined as all-causes mortality (ACM), liver-related mortality (LRM) and hepatocellular carcinoma incidence (HI). Multivariate hazard ratios were estimated using the Cox proportional hazard model in conjunction with propensity score matching.

Results: A total of 7,674 patients with viral hepatitis B were selected. After propensity score matching, 579 matched-pairs were selected for final analysis. Patients who received interferon or pegylated interferon therapy presented lower ACM and LRM, with adjusted hazard ratios of 0.21 (95% CI: 0.08–0.52) for ACM and 0.29 (95% CI: 0.10–0.82) for LRM. However, the effectiveness of interferon treatment on HI was not significant (HR: 1.30) (95% CI: 0.36–4.66).

Conclusions: These results demonstrate that therapy with interferon or pegylated interferon provides better survival benefits than Lamivudine for patients with HBV; however, these effects were not observed in the incidence of hepatocellular carcinoma.

276. Assessment of Balance in Propensity Score Analysis in the Medical Literature: A Systematic Review

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Background: Assessing balance on co-variate distributions between treatment groups with a given propensity score (PS) is a crucial step in PS analysis. Several methodological papers comparing different balance measures have been published in the last decade. However, the current practice on measuring and reporting of balance in PS analysis is not well documented.

Objectives: To investigate the current practice of PS analysis with emphasis on assessment of balance of confounders.

Methods: A PubMed search was performed to identify studies using propensity score methods published December 2011–May 2012. We extracted information on the applied PS method, whether and how balance on confounders was checked, if PS matching was applied (including the algorithm), and information on the initial sample size of the number of matched pairs.

Results: In total, 261 studies that employed PS methods were found. Balance of confounders between treatment groups was checked and reported in 149 (57.1%) of the articles. p-Values from hypothesis testing was the most commonly used statistical tool to report balance (110 studies, 73.8%). The standardized difference and graphical displays of balance were used in 42 (28.2%) and nine (6%) articles, respectively. The most commonly used approach to control for confounding using PS was matching on the PS (67%), followed by co-variate adjustment for the PS (22.2%), PS stratification (14.6%) and inverse probability weighting (7.3%). Balance was most often checked in articles using PS matching and inverse probability weighting: 68.6% and 73.6% respectively.

Conclusions: When using PS methods, assessment of balance on confounders between treatment groups is not often conducted or reported. Appropriate methods such as standardized difference should be used to quantify and report balance.

277. Balance Measures for Determining Optimal Caliper Width in Propensity Score Matching: A Simulation Study

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Background: When estimating the effects of exposure in observational data, propensity score (PS) methods can be used to control for confounding. When PS matching is used, often a pre-specified caliper width is applied. A crucial part of this matching approach is assessment of how close the co-variate distributions are in the two treatment groups, i.e. balance. The choice of the caliper may influence the balance of co-variates between treatment groups and, therefore, the bias and precision of the PS adjusted effect estimate.

Although several balance measures have been described as tools for PS model selection, their role in choosing optimal caliper widths is not well studied.

Objectives: To explore the usefulness of balance measures in selecting the optimal caliper width for propensity score matching.

Methods: We conducted Monte Carlo simulations to assess the usefulness of balance measures (standardized difference) to select optimal caliper width and PS models that yielded the least biased estimates. In different simulations with binary covariates, exposure and outcome status, different sample sizes (n = 500, 1,000, 3,000) and strength of exposure-outcome association (OR = 1, 2) were considered. Caliper widths were varied between 0.05 and 0.6 (steps of 0.05) of the standard deviation of the PS. The balance of covariates between PS matched groups was assessed using the standardized difference (SDif) for each PS model-caliper width combination. PS model with the lowest value of SDif (i.e. most optimal balance) was selected and treatment effects were estimated using conditional logistic regression.

Results: The PS models selected using various caliper widths were closely related and these models often included interaction and squared terms. When using balance measures to select a certain PS model, the choice for a certain PS model seems to have much more impact on bias and precision of exposure effects than the caliper width used.

Conclusions: Balance measures are useful tools for selecting the optimal PS model and the PS model selected has more impact on bias and precision than the caliper width that is used in PS matching.

278. Automated Office Blood Pressure Measurements vs. Morning Home Blood Pressure Monitoring in the Assessment of Hypertension in Morocco

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Background: Morning ambulatory blood pressure (mABP) and morning home blood pressure (mHBP) monitoring have considerable similarities in the assessment of morning BP. Although automated office blood pressure (AOBP) readings have been recognized as a valuable tool in the diagnosis of hypertension, the agreement between mHBP and AOBP in the assessment of morning BP rise has not been explored.

Objectives: To investigate whether morning BP assessed by AOBP readings and mHBP are equally reliable in the diagnosis of arterial hypertension.

Methods: A total of 106 individuals were included, 54 men and 52 women, mean age 53 ± 13 years. The average mHBP was compared against AOBP as measured with a Microlife Watch BP office device taking triplicate automated simultaneous readings of both arms. HBP was monitored on six routine days within 2 weeks using a validated automated electronic device. The average of the total of BP measurements taken in the morning by the HBP device was defined as mHBP. Morning hypertensives, according to each method, were defined as individuals with mHBP, mABP or AOBP of 135/85 mmHg or more.

Results: Systolic and diastolic AOBP was strongly correlated with mHBP (r = 0.65, p < 0.001 and r = 0.66, p < 0.001, respectively). AOBP values were close to mHBP: mean difference 0.69 mmHg, 95% limits of agreement, −25.96 to 27.35 mmHg for systolic BP; mean difference 0.63 mmHg, 95% limits of agreement, −18.56 to 19.82 mmHg for diastolic BP. There was poor agreement between AOBP and mHBP in the detection of morning hypertensives (agreement 69%). Agreement was moderate between AOBP and morning ABP (agreement 73%) and between mHBP and morning ABP (agreement 71%).

Conclusions: AOBP appears to be a reliable method in the diagnosis of morning hypertension. The discrepancy between AOBP and mHBP calls for better education in performing home BP measurements.

279. Propensity Score Estimation to Address Calendar Time-Specific Channeling in Comparative Effectiveness Research of Second Generation Antipsychotics

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Background: Channeling occurs when a medication and its potential comparators are selectively prescribed based on differences in underlying patient characteristics. Drug safety advisories can provide new information regarding the relative safety or effectiveness of a drug product which might increase selective prescribing.

In particular, clinicians may channel patients toward or away from a drug based on the patient's underlying risk for an adverse outcome.

Objectives: To demonstrate channeling among second generation antipsychotic (SGA) initiators following a FDA safety advisory and to evaluate the impact of channeling on cardiovascular risk estimates over time.

Methods: We constructed a retrospective cohort study within Florida Medicaid claims (2001–2006). Adults (ages 18–64) who initiated a SGA between January 2001 and December 2006 and who were continuously enrolled in Medicaid for 6 months prior to initiation were included. We used calendar time-specific propensity scores (PSs) to evaluate channeling away from olanzapine following an FDA safety advisory and to match olanzapine initiators with other second generation antipsychotic initiators. We compare the performance of these calendar time-specific PSs with conventional PSs on estimates of cardiovascular risk.

Results: Increased channeling away from olanzapine was evident for several cardiovascular risk factors corresponding with the timing of the FDA advisory. Covariate balance was optimized within periods when using the calendar time-specific PS. Hazard ratio estimates for cardiovascular outcomes did not differ across models (calendar time-specific PS: 0.93, 95% CI: 0.77–3.04 vs. conventional PS: 0.97, 95% CI: 0.81–3.18).

Conclusions: Among our sample of new SGA users, channeling away from olanzapine was evident for several covariates but had limited impact on relative cardiovascular risk estimates, possibly due to lack of data on cardio-metabolic risk factors. Researchers concerned with investigating within-year differences should use calendar time-specific propensity scores.

280. The Complex Role of the Prescriber in Comparative Effectiveness Research

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Background: In nonrandomized comparative medication studies, the variation in treatment patterns across prescribers can be utilized to isolate the unconfounded variation in exposure and improve treatment effect estimation, yet the majority of analyses ignore prescriber-level information.

Objectives: The objective of this study was to compare the relative performance of different approaches to accounting for the prescriber vs. the usual practice of ignoring the prescriber and to evaluate the use of empirical diagnostics in choosing among approaches.

Methods: We evaluated approaches in two example studies: (1) nonsteroidal antiinflammatory drugs (NSAIDs) and gastrointestinal complications and (2) statin medications and cardiovascular events. In each example, we identified a range of expected treatment effect estimates based on results from randomized trials, we calculated diagnostic data summaries aimed at guiding the choice among estimation approaches, and we estimated treatment effects using five approaches: ignore the prescriber, stratify on prescriber, include the prescriber as a random intercept in the propensity score model, and two instrumental variable (IV) approaches that utilize prescriber preference. Estimates were compared with results from randomized studies.

Results: In the NSAID study, we found expected risk ratios (RRs) of 0.21–0.41 based on randomized trials. The diagnostic analyses indicated that the IV assumptions were not obviously violated, and the best estimate (0.30 [0.12–0.75]) came from the IV analysis using treatment choice for the prior patient within each prescriber as the IV. In the statin study, we found expected RRs of 0.81–0.93. Diagnostic analyses indicated that the clustering of treatment choice within prescriber was low and IV assumptions were likely violated, and the best estimate (0.90 [0.88–0.92]) came from the analysis that included the prescriber in the propensity score.

Conclusions: In each study, at least one approach for including the prescriber in the analysis improved treatment effect estimates over ignoring the prescriber. Better diagnostics are needed to guide the analytic strategy in comparative effectiveness data that contains prescriber information.

281. Using Covariate Data to Inform Large-Scale Studies and Application in the Global Registry Program on Long-Term Oral Anti-Thrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF)

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Background: GLORIA-AF is projected to be one of the largest international, prospective registry programs of newly diagnosed AF patients at risk for stroke. In Phase I feasibility is assessed, and treatment patterns before approval of new oral anti-coagulants are evalu-

ated. Phase II, beginning after approval of dabigatran, monitors safety and assesses channeling. Once treatment groups are sufficiently comparable, Phase III starts and longitudinal data on all patients are collected, allowing for comparative effectiveness analyses.

Objectives: To develop metrics for evaluating the comparability of patients receiving different treatments and design rules for transitioning to GLORIA-AF Phase III.

Methods: Methods include assessments of covariate balance across treatment groups, such as the C-statistic from the propensity score (PS) model, covariate mean differences, and estimated bias due to imbalance, as well as assessments of overlap, such as graphical evaluation of covariate or PS distributions, the proportion of patients in the region of overlap on the PS, and estimated bias due to model extrapolation. We demonstrated methods in an example study of the Cox-2 inhibitor celecoxib during its postmarketing period (1999–2005) vs. nonselective nonsteroidal anti-inflammatory (ns-NSAID) drugs with a study design that mirrored that of GLORIA-AF.

Results: In the example study, the C-statistic was reduced from 0.68 at the first interim analysis to 0.62 at the 6th analysis, but subsequently varied little. Estimated bias due to imbalance was not reduced over time. Overlap was generally strong on all covariates across the study period, resulting in low estimated model extrapolation bias (< 3% in all analyses).

Conclusions: A sequential study design that uses pilot covariate data to evaluate treatment selection can improve the efficiency of large-scale outcome studies with primary data collection, but the benefit of such an approach is highly dependent on the specific treatment situation. The methods for evaluating covariate data will guide the decision when to start Phase III in GLORIA-AF.

282. Combined Disease Risk Score Stratification and Propensity Score Matching When Comparing Multiple Drugs

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Background: Stratification by historically derived disease risk scores (DRSs), which possess better theoretical properties than DRSs derived in the study population, offer simultaneous confounding control and the ability to assess effect measure modification (EMM) across a natural scale, and can be easily applied to the setting of three or more drugs.

Objectives: To empirically evaluate the benefits of stratification by a historically developed DRS when comparing three drugs.

Methods: In a large US commercial claims database, we developed a DRS for a composite outcome of myocardial infarction, stroke, and all-cause death in a historical cohort of 20,011 atorvastatin initiators in 2006. We used the DRS to stratify a cohort of patients who initiated atorvastatin, rosuvastatin, or simvastatin in 2007–2008. We also estimated a multinomial propensity score among initiators in 2007–2008 and three-way-matched these patients within each DRS stratum. We compared hazard ratios (HRs) and incidence rate differences (IRDs) from this approach to HRs from a crude analysis and a PS-matched only analysis.

Results: The historical DRS model, which included 59 covariates, demonstrated good ability to discriminate risk of the composite endpoint (c-statistic, 0.77). In crude analyses, simvastatin (HR, 0.89; 95% CI: 0.83–0.94) and rosuvastatin (HR, 0.54; 95% CI: 0.47–0.61) were both associated with lower rates of the composite outcome relative to atorvastatin. PS-matching alone resulted in HRs closer to the null: simvastatin, 1.01 (0.82–1.23); rosuvastatin, 0.79 (0.64–0.98). DRS stratification with PS-matching within quintiles moved the rosuvastatin estimate closer to the null (HR, 0.86; 95% CI: 0.69–1.06) and did not change the simvastatin HR (1.01; 0.83–1.24). Outcome rates increased monotonically across DRS quintiles for each drug, but HRs and IRDs were consistently null across strata for each comparison.

Conclusions: Simultaneous PS-matching within strata of a historically developed DRS resulted in effect estimates that were more consistent with expectation than PS-matched only results. The historically developed DRS also demonstrated the ability to provide an intuitive scale for assessing EMM.

283. Differential Diagnostic Work-Up among Initiators of Antihypertensive Drugs

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Background: Differential diagnostic work-up associated with a drug relative to a comparator drug, for example based on known side effects, may result in biased effect measures due to an increased detection of the outcome in one cohort relative to the comparator. Persistent cough is a common side effect with angiotensin converting enzyme inhibitors (ACE) and we hypothesized

that ACE initiators would get chest Xrays potentially leading to a diagnosis of lung cancer.

Objectives: We compared the cumulative incidence of chest Xrays among initiators of ACE and Angiotensin receptor blockers (ARB) before and after drug initiation.

Methods: We included patients > 65 years, initiating ACE or ARB after a 6 month washout into a retrospective cohort study using 2006–2010 Medicare claims data. Patients had continuous enrollment for 6 months before and after drug initiation. We calculated monthly cumulative incidence of Xrays for ACE and ARB initiators and estimated age, sex and race adjusted% risk differences (RD) and their 95% confidence intervals (CI).

Results: Based on 06-09 data, there were 72,177 and 17,643 initiators of ACE and ARB, respectively. ACE initiators were more likely than ARB initiators to undergo chest Xrays in the 6 months pre (RD = 3.5; CI 2.8–4.3) and post initiation (RD = 1.8; CI 1–2.5). The difference was most pronounced in the 30 days before the first recorded claim (RD = 5.1; CI 4.6–5.6) and was negligible (RD < 1.3) in all other months.

Conclusions: We found strong evidence for differential diagnostic work-up consistent with our hypothesis. Contrary to our expectation, however, the difference in diagnostic workup of ACE vs. ARB initiators was observed in the 30 days before the first recorded prescription instead of post-initiation. This suggests that ACE initiators defined by our algorithm may have been on ACE therapy before their first prescription was captured in claims. While speculative, a plausible explanation is free drug samples provided by physicians. Our study points to a potential limitation of the new-user design based on data on dispensed drugs which has implications for studying short term outcomes and drug safety (e.g., symmetry analyses).

284. Instrumental Variable Analyses Using Nursing Home Prescribing Preferences for Comparative Effectiveness Research

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Background: Nursing home residents are of particular interest for comparative effectiveness research given their susceptibility to adverse treatment effects and systematic exclusion from trials. However, the risk of residual confounding in non-randomized studies using conventional methods is high because of the disease burden in these patients. Instrumental variable (IV) analyses have the potential to improve control of confounding.

Objectives: Our aim was to evaluate the validity of IV analyses based on nursing home prescribing preference, to study a range of psychotropic medications for treating behavioral disturbances in dementia.

Methods: A cohort using linked data from Medicaid, Medicare, Minimum Data Set (MDS) and Online Survey, Certification and Reporting (OSCAR) for 2001–2004 was established. Dual-eligible patients ≥ 65 years who initiated psychotropic medication use after admission were selected. Nursing home psychotropic prescribing preference was characterized using mixed-effects logistic regression models. The plausibility of IV assumptions was explored, and estimates of the association between psychotropic medication class and 180-day mortality from conventional and IV analyses were compared.

Results: Substantial between-nursing home variability in treatment choice remained after accounting for case-mix and facility characteristics, with high- and low-prescribing nursing homes differing by a factor 2. Each preference-based IV measure described a substantial proportion of variation in psychotropic medication use (β(IV→treatment): 0.22–0.36; semi-partial R^2: 6–10%). Measured patient characteristics were well balanced across patient groups based on each IV (52% average reduction in Mahalanobis distance). There was no evidence that IV status was associated with markers of nursing home quality of care.

Conclusions: Findings suggest IV analyses using nursing home prescribing preference may be a useful approach in comparative effectiveness studies in nursing home populations, and should extend naturally to analyses including untreated comparison groups, which are of great scientific interest but marred with problems.

285. Confounding by Indication in Comparative Effectiveness Research: Does Adding Registry to Claims Data Make a Difference?

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Background: Claims data are often lacking clinical details needed for categorizing indication or adjusting for confounding by indication. Clinical registries often

lack long-term follow-up data. Linking the two sources can overcome shortcomings in either data source and may be necessary for answering certain comparative effectiveness questions.

Objectives: To assess the effect of adding registry data on comparativeness effectiveness estimates (CEEs) of carotid artery stenting (CAS) relative to carotid endarterectomy (CEA) derived using claims data only.

Methods: The study population consisted of Medicare fee-for-service beneficiaries at least 66 years of age who had undergone CAS or CEA between 2005 and 2008 and had a record in the Society for Vascular Surgery's Vascular Registry (SVS-VR). CAS is only indicated and reimbursed for high-surgical risk patients whereas CEA does not have such restrictions. A priori, we expected estimates biased in favor of CEA. We derived various high-dimensional propensity scores (hd-PS): (1) hd-PS using claims data only, (2) hd-PS with the following registry dimensions added one-at-a-time: medical history, carotid stenosis symptoms, carotid stenosis imaging results, pre-procedural medications, and high-surgical risk. We compared mortality in CAS relative to CEA using Cox regression, adjusting for hd-ps.

Results: The study included 1,999 CAS and 3,255 CEA patients in the SVS-Medicare linked dataset. CAS patients were comparable to CEA patients in terms of age, gender, and race but were more often symptomatic (38.5% vs. 30.7%) and at high-surgical risk (96.7% vs. 44.5%). Adjusting for hd-PS corrected the upward bias and drove the CEEs downward. Relative to crude estimates (most biased), hd-ps using claims dimensions only brought the estimate down by 16.5% and addition of registry data dimensions progressively decreased the CEEs from 22% to 32.4%, when all registry dimensions were included. The variables that affected CEEs most were those in the high-surgical risk dimension.

Conclusions: In comparing CAS to CEA, high-surgical risk information was necessary to control for confounding by indication, even in hd-PS adjusted models.

286. Withdrawn by Author

287. Quantitative Verification of Instrumental Variables Assumption Using Balance Measures

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Background: Instrumental variable (IV) analysis appears to be an attractive method to adjust for confounding in pharmacoepidemiological research. One of the underlying assumptions is that the IV should be independent of confounders. If this assumption is violated, the IV estimate can be severely biased.

Objectives: To explore the usefulness of balance measures commonly used in propensity score methods, using a simulated data, to quantitatively verify the assumption that the IV should be independent of confounders.

Methods: We simulated cohorts of varying sample sizes, binary IV and exposure, continuous outcome, and several confounders. Different associations among IV, exposure, and confounders were considered and 10,000 replications were used in each scenario. Data were analyzed using the two-stage least squares method. The balance of confounders across IV levels was assessed using the standardized difference. Values of the standardized difference that are close to zero indicate a balance of confounders across IV groups. We also estimated the correlation between the standardized difference and bias of the IV estimates.

Results: Bias of IV estimates increased with weaker IVs (i.e., weak association between IV and exposure) and increasing values of the standardized difference (i.e. decreasing balance of confounders across IV categories). IV estimates were more biased than those of classical regression estimates with increasing values of the standardized difference, and a weak IV amplified this bias.

Conclusions: Balance measures that are commonly used in propensity score methods can be useful tools to quantitatively verify one of the assumptions underlying IV analysis, i.e., that the IV should be independent of confounders. However, these balance measures only quantify the balance of observed confounders and not of unobserved confounders.

288. Severity Index for Rheumatoid Arthritis: Impact on Healthcare Costs and Utilization

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Background: Statistically omitting variables related to population models offers biased and conflicting estimates. Failure to control disease severity can create a spurious association between treatment and outcome.

Objectives: Develop a claim-based severity index for rheumatoid arthritis (SIFRA). Examine its impact on healthcare costs and utilization in RA patients.

Methods: Using US Veterans Affairs data (10/1/08–9/30/09), adult patients had ≥ 2 RA diagnoses 12 months pre- and post-index date. SIFRA was derived from 34 RA-related markers (laboratory, clinical and functional status, extra-articular manifestations, surgical history, medications, etc) reviewed by an RA expert Delphi panel. SIFRA was developed with and without laboratory values. Correlations between SIFRA and previously confirmed claim-based index for RA severity (CIRAS) and other comorbidity indices were determined. Histograms assessed SIFRA tercile and all-cause/RA-related healthcare utilization and cost relationships. A regression model assessed model fitting enhancement by including SIFRA.

Results: Total 25,042 RA patients were identified, of which 1,091 missed laboratory claims. Spearman's rank correlations between SIFRA and CIRAS were moderate (0.539 SIFRA with; 0.525 SIFRA without laboratory values). Correlations between SIFRA and other indices were low (Charlson Comorbidity Index: 0.1135 with, 0.1503 without laboratory data/Elixhauser index: 0.079 with, 0.105 without laboratory data/Chronic Disease Score: 0.239 with, 0.255 without laboratory data). Low SIFRA tercile patients had fewer total office (77.16 vs. 110.14, p-value<0.001) and RA-related visits (3.93 vs. 6.72, p-value < 0.001) than high tercile patients. High SIFRA tercile patients had $9,123 higher all-cause and $1,326 higher RA-related costs than low tercile patients. Regression results show that outcomes variation was 6+ times (611%) better explained after adding SIFRA to the regression model.

Conclusions: SIFRA demonstrated moderate correlation with CIRAS and offered evidence of being a determinant of total and RA-related healthcare costs. Disease severity is an essential methodological tool to control for severity in RA-related outcomes research.

289. A Validated Outcomes Measure to Assist the Pharmacoepidemiological Study of Opiate Maintenance Treatment

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Background: Opioid dependence is a chronic, relapsing condition that requires lifelong management for which medical assisted therapy (MAT) is an important strategy. Current estimates of the effectiveness of OMT vary according to the outcome used for its evaluation.

Objectives: A multi outcome responder scoring system is being validated to achieve robust outcomes data in OMT.

Methods: An expert panel has convened to define a outcomes system. Metrics are being employed to capture outcomes across three domains: mortality in treatment, individual, and societal to achieve success using a scoring approach across a number of metrics.

Results: Mortality is measured by assessing Mortality rate on treatment, with the goal of achieving a 95% reduction compared to no treatment. Outcome of treatment for the individual is assessed with metrics of Concordance, Abstinence, Quality of Life, Family, criminal activity, Health. Concordance: retention in treatment at correct dose, Abstinence: avoiding compulsive, regular use of on-top opioid or other agents (e.g., alcohol, cocaine, benzodiazepines). The goals for the 'individual' metrics are: not using on-top opioids (heroin or other prescription) more than 1–2 times per month, not using cocaine more than 1–2 times per month, benzodiazepine use as per local practice guidance, capacity to control use. Quality of life: improvement in QoL compared to others living with opioid dependence. Goal: step change in Quality of life. Family: having a significant sustained relationship with another person. Health: reduction in viral infection; goals: no risk behaviours for infection. Assessment of outcomes at level of society. The following metrics are chosen: work, having potential to work in a role appropriate to individual's previous level. Goal: being involved in work or seeking work.

Conclusions: A set of outcomes as defined here can be a useful system for assessing outcomes at population and individual level, in the complex multifaceted therapeutic area of opioid dependence management; assessment should be made of the success of different treatment systems using outcome systems such as this.

290. Design and Feasibility of a Study Using the Clinical Practice Research Datalink General Practice OnLine Database (CPRD GOLD) to Assess the Risk of Spontaneous Abortion (SA) Following Administration of the Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine

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Background: The HPV-16/18 AS04-adjuvanted vaccine (HPV-16/18 vaccine) is indicated for protection against cervical cancer in > 100 countries. Safety of inadvertent exposure during pregnancy needs to be further investigated, given the reproductive age of the target population. Such studies are challenging due to low vaccine exposure in pregnant women, rare events, case definition, and sources of bias.

Objectives: As part of a safety study (Study ID: EPI-HPV-018 [114101]) assessing whether administration of the HPV-16/18 vaccine around the time of conception increases the risk of SA; an observational cohort study design using a large population clinical database in a country with high vaccine coverage has been assessed for feasibility.

Methods: Two cohorts have been defined: exposed pregnant women with onset of pregnancy from 30 days before to 90 days after any dose of HPV-16/18 vaccine; and unexposed pregnant women with onset of pregnancy between 120 days and 18 months after the last vaccine dose. Both cohorts are HPV-16/18 vaccinated to ensure similar healthcare criteria. A large database in the UK, CPRD GOLD (12 million subjects), was the data source.

Results: A feasibility assessment allowed quantification of the eligible populations (379 exposed and 667 unexposed subjects). Pregnancy outcomes are yet to be identified in the database using specific algorithms to search medical codes. Confirmation of the outcomes will be assessed by conducting a review of the information captured in the free text field of the CPRD GOLD data source. Final case ascertainment will be performed by two blinded and independent teratology experts. The risk of SA will be compared between cohorts using a Cox regression model. The designed study has 80% power to detect a hazard ratio of 1.7.

Conclusions: The use of large observational databases may be a valuable alternative to prospective field studies when assessing the risk of rare events in a large vaccinated population.

291. Lessons Learned from Implementation of a Prospective, Observational Cohort Study to Assess Risk of Spontaneous Abortion (SA) Following Administration of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine around Conception

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Background: One of the most challenging pregnancy outcomes to study is incidence of SA.

Objectives: To review lessons learned from implementation of a prospective study in young women assessing SA risk following exposure to HPV-16/18 AS04-adjuvanted vaccine around conception (Study 114176/NCT01290393).

Methods: A prospective cohort study was selected after considering factors such as: data sources; report of SA; gestational age at time of event; comparison group; exposure level. Exposure was defined as pregnancy onset 30 days before to 90 days after any dose of HPV-16/18 vaccine, and non-exposure as pregnancy onset 120 days to 18 months after last dose (HPV-16/18 or HPV-16/18/6/11 vaccine). Recruitment of 450 pregnant women aged 15–25 years was planned over 2 years via the Organization of Teratology Information Specialists (OTIS), a telephone-based network of pregnancy exposure counseling services in the USA and Canada.

Results: At study start (June 2011) an awareness campaign was initiated, including online advertising and outreach to health professionals/networks involved with vaccination, pregnancy or adolescents, focusing on states with highest HPV-16/18 vaccine distribution. After 18 months and ~63,000 caller contacts, 39 were referred for recruitment and two enrolled. Primary reasons for non-enrollment were: refusal (n = 16); ≥ 20 weeks gestation (n = 7); no contact (n = 6); vaccine exposure outside window (n = 5). Major reasons for study non-feasibility were: lower than expected vaccine coverage; vaccine exposure before pregnancy. An alternative, retrospective cohort study using a similar design was consequently developed using the Clinical Practice Research Datalink (CPRD) database in the UK, where HPV-16/18 vaccine coverage was up to 80% in 2008–2011.

Conclusions: Lessons learned include: value of conducting a pilot even if study feasibility is assessed pre-implementation; need to focus recruitment efforts on clinics/programs with known exposure to vaccine; importance of flexibility if unexpectedly low exposure levels (i.e., change of study setting).

292. Is there any Evidence for Fetal Harm with Prolonged Use of Magnesium Sulfate in Pregnant Women?

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Background: Injectable magnesium sulfate ($MgSO_4$) is approved for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy and is used off-label as a tocolytic agent. There is some evidence from published case reports and epidemiological studies that continuous, prolonged use of $MgSO_4$ in pregnant women is associated with fetal harm including bone abnormalities.

Objectives: To determine if postmarket and epidemiological data support the hypothesis that fetal harm, including bone abnormalities, can occur in association with prolonged $MgSO_4$ use in pregnant women.

Methods: A search was done in (1) the FDA Adverse Event Reporting System (AERS) database from September 1986 (United States approval date for Magnesium sulfate) to November 2011 to identify case reports, and (2) the PubMed to identify epidemiological studies suggesting fetal harm with in-utero exposure greater than 48 h to intravenous $MgSO_4$.

Results: Our AERS search identified 18 case reports supporting an empirical association between prolonged administration of intravenous $MgSO_4$ in pregnant women and the development of laboratory abnormalities (especially hypermagnesemia and hypocalcemia) and skeletal abnormalities including osteopenia and fractures in neonates. The epidemiological data also support an association between prolonged administration of intravenous $MgSO_4$ in pregnant women and skeletal abnormalities and hypermagnesemia but do not confirm or refute the fracture signal observed in case reports. The epidemiological studies identify radiographic findings of transverse radiolucent, and/or sclerotic bands in the long bones and that the effects

on laboratory values resolve within days of birth. Due to the short follow-up periods in the epidemiological studies it is unclear whether these skeletal and laboratory abnormalities had clinically significant long-term bone effects, such as fractures.

Conclusions: The postmarket and epidemiological data support an association between prolonged maternal administration of $MgSO_4$ and neonatal hypermagnesemia, hypocalcemia, and skeletal abnormalities.

293. Impact of the FDAAA on Post-Marketing Commitments Related to Pregnancy and Lactation

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Background: Five years ago, the United States government expanded the FDA's authority to require post-marketing studies with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Prior to this, pregnancy registries, a valuable tool for studying the teratogenicity of newly marketed drugs, were primarily voluntary efforts. Both the FDA (2002) and EMA (2005) issued guidance on conducting post-marketing studies during pregnancy.

Objectives: To evaluate the impact of FDAAA on childbearing populations and trends in post-marketing commitments/requirements (PMC/Rs) including risk evaluation and mitigation studies (REMS).

Methods: Publicly available FDA databases were searched to identify all new molecular entities approved between January 2008 and May 2012 and corresponding drug-specific PMC/Rs and REMS data. These compounds were linked to the FDA's list of pregnancy registries. The assigned FDA pregnancy category was obtained from the prescribing information. Studies related to pregnancy and/or lactation in humans were identified and descriptive statistics were calculated.

Results: Over the 4.5 year period, the FDA approved 125 new compounds (100 drugs, 25 biologics). Overall 78% had at least one PMC/R (79% of drugs and 84% of biologics). The proportion of new drugs with a pregnancy related PMC/R was 9% overall and increased over time from 5% in 2008 to a peak of 19% in 2010 before declining to 4% in 2011. Pregnancy categories were B (26), C (70), D (17), X (12). Of the 57 pregnancy registries listed on the FDA's website, 13 are associated with drugs approved during the time period under study although only 6 of these were PMC/R and all were for category C compounds.

A single category X drug had a pregnancy/lactation related PMC/R.

Conclusions: The majority of pregnancy registries are for medicines with FDA assigned pregnancy category C. Category X drugs are not more likely to have REMS or PMC/Rs despite their known potential for reproductive harm. Population characteristics such as gender, age, and indication for the prescription are powerful indicators of when PMC/Rs are necessary.

294. Predictors of Stopping Medication Use in Pregnancy among Women with Chronic Conditions

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Background: Exploring the predictors of non-compliance in pregnancy is imperative because poorly managed chronic conditions can adversely impact both maternal and fetal health.

Objectives: This study attempts to identify the determinants of stopping medication use in women taking three types of medication prior to pregnancy: antidepressants, antihypertensives and hypothyroid medication.

Methods: Pregnant women 15–45 years delivering between 1998 and 2002 were identified using Quebec's health administration databases. Women with at least one prescription for one of the three drug classes in the 24 months before delivery were included, and these three cohorts were analyzed separately. Women were considered 'stoppers' if they had filled at least one prescription in the pre-pregnancy period, and then had no prescriptions filled during pregnancy. Generalized linear mixed models were used to assess the association between demographic, health and medication characteristics, and discontinuation of medication use in pregnancy.

Results: The proportion of women who discontinued their medication was highest among women taking antidepressants and antihypertensives at 62.7% and 62.5%, respectively, and lowest for those on thyroid medication (11.3%), Women on antidepressants (n = 2107) were less likely to discontinue medication if they were older or on welfare, had received a depression diagnosis (OR: 0.72; 95% CI: 0.54, 0.97), and were concurrently on more than 1 antidepressant before pregnancy (OR: 0.66; 95% CI: 0.44, 0.99). Results were similar for women prescribed antihypertensives before pregnancy (n = 652). Women on hypothyroid therapy (n = 723) were less likely to discontinue if they were on a higher dose of levothyroxine (> 88 mcg), had changed doses several time

before pregnancy, and were prescribed a greater number of non-thyroid medications.

Conclusions: For all classes of medication, the main predictors of discontinuing use in pregnancy were factors related to disease severity and overall health. Women have a tendency to give up medication in pregnancy, presumably due to teratogenic fears, unless they have more severe disease, in which case the benefits of treatment may outweigh the risks.

295. The Use of Medications Pregnancy Categories among Healthcare Professionals in Saudi Arabia Hospitals

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Background: Worldwide, there are several classifications for the risks of medications during pregnancy. In Saudi Arabia, the United States Food and Drug Administration (FDA) pregnancy categories are used widely. However, the use and opinion of healthcare professionals (HCPs) towards these categories was not investigated.

Objectives: To assess HCPs knowledge and attitude towards FDA pregnancy categories.

Methods: A cross sectional self administered survey has been conduct in four tertiary hospitals in Riyadh, Saudi Arabia in the period between March and May, 2012. The validated survey contained three main sections; the first section assesses HCPs practice toward prescribing or dispensing medications during pregnancy while the second and third section assess the knowledge and attitude of HCPs toward FDA pregnancy category and narrative pregnancy system that used in the United Kingdom (UK), respectively. All analyses were performed using SAS version 9.2.

Results: A total of three hundred ninety nine HCPs responded to the survey with response rate of 97%. Half of the respondents were physicians and the other half were pharmacists with 60% of the HCPs were males. Approximately 41% of the respondents in this study have prescribed or dispensed a drug to pregnant women on daily bases. Further, majority preferred to use Micromedx® as source of teratogenicity information. Further, a quite high number (66%) of the respondents have used to their patients a drug that

may cause teratogenicity. Moreover, 87% of the respondents – pharmacists 48%, physicians 39%- are aware of the FDA pregnancy category and majority of them (72%) found it to be helpful. In addition, 86% of the respondents are using only FDA classification system. Whereas, 54% are using both FDA classification with narrative system.

Conclusions: HCPs in Saudi Arabia hospitals have a good knowledge and attitude toward FDA pregnancy classification system which might reduces using of teratogenic medications and they preferred it over narrative system. In this study, we found that most HCPs have prescribed or dispensed a teratogenic medication thus further studies on the safety of medication during pregnancy are recommended.

296. Safety of Neuraminidase Inhibitors during Pregnancy: A Comparative Study in the EFEMERIS Database

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Background: Pregnant women are at increased risk of severe disease and death due to influenza infection. During AH1N1 influenza pandemic in 2009–2010, recommendations in USA and Europe were to treat pregnant women who are infected with the H1N1 virus, with oseltamivir or zanamivir. Few data are available concerning these drugs in pregnant women.

Objectives: To compare birth outcomes between exposed and unexposed women to oseltamivir or zanamivir during pregnancy.

Methods: This observational study compared exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and Antenatal diagnosis Centre). Women who delivered from July 1st 2004 to December 31th 2010 in Haute-Garonne and were registered in the French Health Insurance Service have been included. We compared pregnancy outcomes between women exposed to oseltamivir or zanamivir during pregnancy and unexposed women. Unexposed were individually matched to exposed by maternal age, month and year of delivery. Malformations were classified according to Eurocat classification.

Results: Of 338 (0.58% of EFEMERIS) women exposed to neuraminidase inhibitors were compared

with 676 unexposed women. Only one pregnant woman received zanamivir and 337 received at least one prescription of oseltamivir. The mean number of drugs taken during pregnancy was higher in the exposed group (12.5 ± 7 vs. 9.7 ± 6.9; $p < 10^{-4}$). Pregnancies led to 96.4% vs. 93.3% of live-births ($p < 10^{-4}$) in exposed and unexposed groups respectively. No increased risk of preterm birth associated with oseltamivir during pregnancy was found (adjusted OR = 0.7; 95% CI = 0.2–1.8). When exposure during organogenesis was considered, 1 congenital malformation (2%) among those exposed and 14 (2.2%) among the unexposed were observed (crude OR = 2, 95% CI = 0.1–32).

Conclusions: We found no increased risk of adverse pregnancy outcomes (preterm birth, low birth weight, neonatal pathology and congenital abnomalies) among women exposed to oseltamivir compared with unexposed women.

297. First Trimester Exposure to Sertraline and the Risk of Major Congenital Malformations in a Cohort of Depressed Women

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Background: Conflicting findings on the teratogenicity of sertraline have been reported, which could partially be explained by confounding by indication.

Objectives: To quantify the association between 1st trimester exposure to sertraline and the risk of major congenital malformations in a cohort of depressed women.

Methods: This study was performed within the Quebec Pregnancy Registry, which includes data on all pregnancies in Quebec between January 1 1998 and December 31 2009. Date of entry in the registry is the date of the first day of the last menstrual period. For this study, women had to (1) have a diagnosis or a hospitalisation for depression, or have used antidepressants in the 12 months pre-pregnancy, (2) be covered by the RAMQ drug plan for at least 12 months before and during pregnancy, (3) be using only one type of antidepressant during the first trimester, and (4) have a livebirth. Sertraline use during the first trimester, other SSRI use, and non-SSRI antidepressants use were compared to non-use. Major congenital malformations were identified using validated diagnosis codes in the child first year of life. GEE models were used.

Results: Among the 18,493 pregnancies meeting inclusion criteria, 366 were exposed to sertraline, 1963 to other SSRIs, 1296 to non-SSRI antidepressants. 2094 infants with major congenital malformations were identified; 433 had cardiac malformations (344 ventricular/atrial septal defects), and 92 had cranyosynostosis. Adjusting for potential confounders including maternal depression, the use of sertraline in the 1st trimester (OR: 1.13, 95% CI: 1, 1.54) was significantly increasing the risk of major congenital malformations (other SSRIs; OR: 1.09, 95% CI: 0.94–1.26). Women using sertraline were 17% more at risk of having a child with cardiac malformations (OR: 1.17, 95% CI: 0.62, 2.20), 34% more at risk of ventricular/atrial septal defect (OR: 1.34, 95% CI: 0.69–2.61), and twice at risk of cranyosynostosis (OR: 1.99, 95% CI: 0.62–6.41), although none of these reached statistical significance.

Conclusions: Adjusting for maternal depression, sertraline use during pregnancy was increasing the risk of major congenital malformation.

298. Risk of Preterm Delivery in Women with Inflammatory Bowel Disease – Effects of Disease Activity and Drug Exposure

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Background: Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, occurs in 0.5% of women who give birth. Women with IBD have increased risks of preterm delivery and risks have been associated with both high disease activity and drug exposure during pregnancy.

Objectives: To assess risks of preterm delivery, i.e., before 37 weeks' of gestation, in women with Crohn's disease and ulcerative colitis by start of labour, disease activity and drug exposure.

Methods: We included all 470,110 singleton births in Sweden from July 2006 to December 2010, of which 1,220 were to women with Crohn's disease and 1,833 were to women with ulcerative colitis. Data were obtained from National Health Registers. IBD women were categorized as: (1) no drug exposure or clinical events, (2) maintenance therapy and (3) corticosteroids, surgery or admission to hospital because of flaring disease. Timing of flare was defined by trimester. Exposure to azathioprine was assessed as a dichotomous variable. Logistic regression was used to calculate odds ratios (OR) adjusted for maternal age, parity, smoking status and comorbidity with 95% confidence intervals (CI).

Results: There were increased risks of preterm delivery for both ulcerative colitis (OR 1.78, CI: 1.49–2.13) and Crohn's disease (OR 1.65, CI: 1.33–2.06). The risks persisted when excluding induced delivery and cesarean section. In both groups of women with treatment during pregnancy, risks were higher among women who had been exposed to azathioprine. For women with flaring disease, the risk of preterm delivery was increased almost threefold, and for those with flaring disease in more than one trimester, almost fourfold.

Conclusions: Women with IBD are at increased risks of preterm delivery in general and spontaneous preterm delivery. Flaring disease, flares throughout pregnancy and azathioprine treatment was associated with increased risks.

299. Public Perception of Risk Factors for Birth Defects: *HealthStyles*, 2010–2011

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Background: Birth defects affect approximately 1 in every 33 babies, yet public perception of what causes birth defects is not well understood.

Objectives: We sought to describe public perceptions of risk factors for birth defects and to explore possible differences in perceptions based on select demographic characteristics.

Methods: We analyzed data from the 2010 and 2011 fieldings of the *HealthStyles* consumer panel survey, which was sent to 12,124 individuals. Survey respondents were asked to rate the extent to which eleven factors (diabetes before pregnancy, obesity before pregnancy, vaccines during pregnancy, infections during pregnancy, prescription medication use during pregnancy, over-the-counter medication use during pregnancy, herbal use during pregnancy, environmental exposures during pregnancy, genetics, mother's use of tobacco or alcohol during pregnancy, and mother's age) 'increased the risk of birth defects.' Weighted frequencies and proportions were calculated. Responses were also stratified by age, sex, race/ethnicity, annual household income, and educational attainment. Additional analyses focused on the subgroup of women of childbearing age (18–44 years of age).

Results: A total of 8,234 participants completed the *HealthStyles* 2010 or 2011 survey. Of this sample, 7,984 responded to at least one of the birth defects focused items. Herbal use during pregnancy was perceived as the least likely factor to increase risk (51.6%

believed it 'never or rarely' increased risk). Thirty-eight percent and 27% believed that over-the-counter and prescription medication use 'never or rarely' increased risk, respectively. Tobacco or alcohol use during pregnancy was perceived as most likely to increase risk (70.6% believed it 'often or always' increased risk). Women of childbearing age (n = 2,272) generally had perceptions similar to other respondents.

Conclusions: Awareness of established risk factors for birth defects, such as diabetes and obesity, is low in the general population and among women of childbearing age. Efforts to increase public awareness of risk factors for birth defects can be strengthened.

300. Use of Glyburide vs. Insulin for Treatment of Gestational Diabetes in the U.S., 2000–2010

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Background: Insulin is the only approved treatment for gestational diabetes (GD) in the United States. Glyburide is a sulfonylurea used off-label as an alternative treatment but its dissemination and factors associated with choice of treatment are unknown.

Objectives: To describe trends and identify factors associated with treatment with glyburide and insulin in women with GD, 2000–2010.

Methods: We conducted a retrospective cohort study of women with GD with a pharmacy claim for glyburide or insulin in the year prior to delivery, identified in MarketScan Databases® from 2000–2010. Women < 15 years or > 45 years, with prior type 2 diabetes, or multiple gestations were excluded. Trends in the use of glyburide vs. insulin were estimated. Binomial regression was used to estimate prevalence ratios (PR) and 95% CI for the association between calendar year, infertility treatment, obesity, hypothyroidism, hyperandrogenism, metabolic syndrome, polycystic ovarian syndrome, history of metformin use and treatment with glyburide vs. insulin. In a subgroup, the association between baseline glucose levels and initial treatment was estimated.

Results: We identified 7,509 women with a prescription for glyburide (N = 3,913) or insulin (N = 3,596). From 2000 to 2010, glyburide use increased steeply from 8.5% to 62.5% with an adjusted annual percent change of 20.3 (CI: 12.1–29.1). Women with hyperandrogenism and obesity were more likely to be pre-

scribed glyburide than insulin (1.21;CI: 1.05–1.41; and 1.13; CI: 1.05–1.21, respectively). Those with metabolic syndrome were 44% less likely to be prescribed glyburide. For every 10 years increase in age, the probability of getting glyburide rather than insulin decreased by 5% (0.95% CI: 0.91–1.02). Higher fasting and 1-h tolerance test glucose values were also associated with a higher probability of being prescribed with glyburide.

Conclusions: Glyburide has replaced insulin as the standard treatment of GD over the last decade. Identification of subgroups of women who are more likely to be treated with glyburide rather than insulin is fundamental for the assessment of its comparative effectiveness in the prevention of adverse maternal and neonatal outcomes.

301. Hypertension and Patterns of Prescription of Antihypertensive Medications during Pregnancy Using THIN Database

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Background: Little is known about the pharmacologic management of chronic hypertension during pregnancy in clinical practice.

Objectives: To describe the utilization patterns of antihypertensive medications in pregnancy.

Methods: We used electronic medical records fromThe Health Improvement Network (THIN) database from 1996 to 2010 to identify completed pregnancies. The study cohort included the first pregnancy identified during the study period in women aged 13–49 years who had pre-existing hypertension before their last menstrual period (LMP). Prescription of specific antihypertensive medications within the pre-pregnancy period (90 days before LMP) and during pregnancy was ascertained from primary care provider records.

Results: Among 148,544 pregnancies included, we identified a total of 1995 (1.3%) with pre-existing hypertension; 36.1% received an antihypertensive medication in the pre-pregnancy period, with beta-blockers being the most commonly prescribed class. Among those on medications in the pre pregnancy period, 9.6% did not receive an antihypertensive medication, 88.2% continued the same medication and 2.2%

switched classes during the first trimester. The corresponding numbers by second trimester were 22.1%, 54.4% and 23%, respectively. Women who switched therapy by the first or second trimester received preferably a central agonist, followed by an alpha-beta blocker. Among women on contraindicated drugs such as angiotensin-converting-enzyme inhibitors (N = 192) and angiotensin receptor blockers (N = 45), around 30% received at least one prescription during the second trimester.

Conclusions: Prescription patterns by primary care providers in the UK were in agreement with current guidelines on the management of hypertension during pregnancy. However, some women continued on contraindicated drugs throughout pregnancy.

302. Meta-Analysis of the Use of Assisted Reproductive Technologies and the Risk of Multiple Birth and Major Congenital Malformations

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Background: The relationship between assisted reproductive technologies (ART) use and the risk of major congenital malformations (MCM) is controversial. Multiple births are a recognized adverse effect of ART; nevertheless, there is no consensus on the incremental risk.

Objectives: Our meta-analysis summarizes the literature on ART risks for the newborn, explains discrepancies between studies, and identifies the gaps in knowledge for future research.

Methods: We carried out a systematic review to identify all papers published between 1966 and 2012 in Medline, Embase and the Cochrane Central Register of Controlled Trials. A hand search was also performed. We included observational studies, randomized and non-randomized clinical trials related to the risk or the prevalence of MCM or multiple birth

conceived following ovarian stimulation (OS) used alone, intrauterine insemination (IUI) and *in-vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) compared to spontaneously conceived infants or infants conceived using other ART.

Results: We identified 2035 citations, 1799 citations were excluded after screening titles and abstracts leading to 236 eligible studies. Among them, 75% reported data on IVF/ICSI use, 16% on OS use alone and 9% on IUI use. All studies comparing infants conceived following OS use alone and spontaneously conceived babies showed at least a 40% increased risk of multiple birth. Several studies suggested an increased risk of multiple birth when other fertility agents were used in addition to clomiphene citrate (CC) compared to CC used alone. Half of the studies comparing infants conceived following the use of OS alone to spontaneously conceived infants showed at least a 7% increased risk of MCM. Studies comparing OS use with or without other fertility agents with spontaneously conceived infants suggested an increased risk of certain neural tube defects and DandyWalker malformation.

Conclusions: A limited number of observational studies focused on the risk of multiple birth and MCM following OS use alone. Results suggest that overall OS use without other ART increases the risk of multiple birth and MCM.

303. Congenital Malformations in the Offspring of Women with Asthma

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Background: Asthma is common in pregnancy; however population-based research is limited regarding the risk of major congenital malformations (MCM) in the offspring of women with asthma.

Objectives: To describe the frequency of MCMs in the offspring of women with asthma and compare this with external sources.

Methods: All pregnancies in women with asthma were identified from the UK General Practice Research Database (GPRD) from 2000 to 2010. Where possible the mother's medical record was linked to that of the child. For mother-baby pairs, MCMs were identified based on Read codes in the child's record. A case verification exercise is ongoing using additional Read codes providing supporting evidence, free text comments and questionnaires sent to GPs. For stillbirths and induced pregnancy terminations, MCMs were

identified by requesting free text comments associated with pregnancy codes in the vicinity. The frequency of a range of specific MCMs and MCM classes were calculated with CI95 and compared to those of the UK registries reporting to EUROCAT during the same time period.

Results: Of 14,793 mother-baby pairs were identified in addition to 106 stillbirths and 44 induced terminations following a prenatal MCM diagnosis. The MCM frequency (per 10,000 pregnancies) in the GPRD asthma cohort was in line with EUROCAT for a range of MCM classes including neural tube defects (11.4 vs. 11.9), orofacial clefts (14.7 vs. 14.8) and limb reductions (6.7 vs. 5.8). The MCM frequency was lower in the asthma cohort for chromosomal, respiratory and abdominal wall defects (24.8 vs. 44.5; 1.3 vs. 7.1 and 2 vs. 7.8 respectively). Higher rates were observed in the asthma cohort for hypospadias (36.8 vs. 16.9), less serious congenital heart defects (83.1 vs. 42.9), craniosynostosis (7.4 vs. 1.7), hip dislocation/dysplasia (25.5 vs. 5.7), and talipes equinovarus (32.2 vs. 9.4). Of note, of the six upper limb reduction defects identified, five were of the hand.

Conclusions: The frequency of MCMs recorded in the offspring of women with asthma appears to be largely in line with those of EUROCAT. Many of the higher frequencies observed in the GPRD are likely to result from different data collection methods with less serious/more common MCMs being under-reported to EUROCAT.

304. Healthcare Databases in Europe for Studying the Safety of Medicine Use during Pregnancy

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Background: In recent years the use of electronic healthcare databases for monitoring the safety of medicine use during pregnancy has been increasing.

Objectives: To describe electronic healthcare databases within Europe in terms of the population covered, the source of the data captured and the availability of data on key medicine exposure, pregnancy outcome, and confounding variables required for evaluating the safety of medicine use during pregnancy.

Methods: Countries with electronic healthcare databases covering populations captured by a EUROCAT congenital anomaly registry were identified from the literature. An invitation to participate in the study was circulated to researchers via the EUROCAT network. Those who accepted were asked to complete a database inventory.

Results: Eight centres agreed to participate, two in the UK and Italy and one in each of Denmark, the Netherlands, Norway and France. The total population covered by the 8 databases was 25 million. The annual number of pregnancies captured ranged from 2,000 to 90,000. Seven databases captured stillbirths in addition to live birth outcomes and six also captured spontaneous pregnancy losses and induced terminations. In five databases data were commonly available to calculate the date of the woman's last menstrual period whereas in the remainder algorithms often needed to be created to determine a best estimate. With the exception of one database it was possible to identify pregnancies where the offspring had a congenital anomaly. The availability of information on confounding variables, such as alcohol and smoking status, varied between databases and was more commonly available in those that captured data recorded by general practitioners. All databases captured data on maternal co-prescribing and socioeconomic status.

Conclusions: Within Europe, electronic healthcare databases may be valuable data sources for evaluating the safety of medicine use during pregnancy. The suitability of a database, however, will depend on the research question and more specifically on the type of medicine to be evaluated, the prevalence of its use, the adverse outcome(s) of interest and the magnitude of the risk to be identified or ruled out.

305. Outcomes of Pregnancies for Women Prescribed Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists in Semester 2 or 3

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Background: When used in pregnancy during the second and third trimesters, drugs that act directly on the

renin-angiotensin system can cause harm and even death in the developing fetus.

Objectives: This study describes the dispensing patterns of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARB) in pregnant women.

Methods: The study population included all women giving birth in Western Australia during 2002–2005 with a birth record in the Midwives' Notification System and a hospital admission record in the Hospital Morbidity Data System: N = 96,698. Records were linked to the Pharmaceutical Benefits Scheme and the Birth Defects Registry of Western Australia. Outcomes for pregnancies of women dispensed either an ACE inhibitor or an ARB were compared with all other women not dispensed an antihypertensive.

Results: There were 95 women dispensed an ACE inhibitor and 40 women dispensed an ARB, which represented 132 individual pregnancies and 134 infants. 44 (33.3%) of these women were dispensed either medicine in trimester 2 or 3, contrary to recommendations for use in pregnancy. There were 2 (2.1%) children still born, compared with 634 (0.7%) in the children of women not dispensed an antihypertensive during their pregnancy: OR (95% CI): 2.3(0.6–9.4).

Conclusions: A number of pregnant women are being prescribed medicines that may cause serious harm or death to their infant, contrary to recommendations.

306. Treatment of Acute Asthma Exacerbations during and Outside Pregnancy at a Canadian Teaching Hospital

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Background: The prevalence of asthma exacerbations during pregnancy was found to be 12.6% and 51.9% among women with mild and severe asthma, respectively. American studies have shown discrepancies in the use of systemic corticosteroids (SCSs) for the treatment of asthma exacerbations between pregnant and non-pregnant women.

Objectives: To compare the treatment of asthma exacerbations during and outside pregnancy at a Canadian teaching hospital.

Methods: We formed a cohort of women who sought medical care for an asthma exacerbation at a teaching hospital, during or in the year preceding pregnancy, between 1998 and 2008. An exacerbation was composed of one or more medical encounters including outpatient clinic, emergency department or hospitalization. Data were retrieved from computerized medical chart and Quebec (Canada) health administrative databases. The use of SCSs was compared between pregnant and non-pregnant women with a Cox proportional hazards model.

Results: The cohort was formed of 41 women who had 43 exacerbations during and 39 exacerbations outside pregnancy. Use of SCSs to treat exacerbations was less frequent (adjusted hazard ratio: 0.52; 95% CI: 0.32–0.85) during pregnancy. Moreover, when administered, SCSs were given later during the exacerbation to pregnant than non-pregnant women (84% vs. 100% during the first medical encounter). In 64% and 67% of exacerbations of pregnant and non-pregnant women, when a discharge prescription of SCSs was documented, it was filled at a community pharmacy. In 23.3% and 30.8% of exacerbations occurring during and outside pregnancy, no inhaled corticosteroid was taken in the preceding year, while corresponding figures were 58.2% and 82% for the use of > 3 doses/week of short-acting beta-agonists.

Conclusions: We observed a reduced and delayed use of SCSs for the treatment of asthma exacerbations in pregnant compared to non-pregnant women. With a similar proportion of pregnant and non-pregnant women filling their SCSs prescription in community pharmacy, the difference in SCSs use can be attributed to different prescribing practices.

307. EXPECT Enrollment: Impact of Recruitment Strategy on Enrollment in the Xolair® Pregnancy Registry

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Background: Recruitment is one of the greatest challenges faced by pregnancy registries. EXPECT, the Xolair® Pregnancy Registry, was established to evaluate outcomes in pregnant women exposed to Xolair (omalizumab) for treatment of asthma. Eligible U.S. women self-enroll and the enrollment goal is 250. Various recruitment activities have been employed since registry implementation in 2006.

Objectives: To examine impact of recruitment activities on enrollment.

Methods: Recruitment activities targeted three groups: (1) HCPs, via informational faxes, emails, mailings, journal ads and scientific meeting presentations; (2) patients, via internet 'banner' ads on social media, health and pregnancy websites; and (3) other omalizumab studies, via presentations at investigator meetings and registry information in site and patient newsletters. The online recruitment tool, xolairpregnancyregistry.com, was universally accessible. Enrollment and recruitment activities were plotted on a monthly timeline. Average monthly enrollment was calculated and stratified by number of activities/month and by target group.

Results: From 10/2006 to 12/2012, overall average monthly enrollment was 2.9 participants, range 0–8. Average number of monthly recruitment activities was 1.3, range 0–9. In months in which no recruitment activity occurred, average monthly enrollment was 2.3. It increased to 3.2 in months in which any activity occurred and to 4.1 when 3 or more recruitment activities occurred. Average monthly enrollment was 3 when only patients were targeted, 2.9 when only HCPs were targeted, and 2.7 when omalizumab study participants were targeted. Limitations: Analyses do not account for timing of recruitment activity within a given month or the potential for impact during subsequent months.

Conclusions: Number of monthly recruitment activities positively affected enrollment. Activities targeting patients were associated with the highest monthly enrollment, but differences were small between the three groups. These results suggest the greatest impact on enrollment can be achieved by using multiple recruitment activities each month, especially those targeting patients.

308. Prospective Enrollment in Pregnancy Registries: Definitions and Potential Impact on Birth Defect Prevalence

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Background: The prospective orientation of pregnancy registries is a powerful strategy for defining birth defect prevalence and investigating the potential impact of drug exposure because exposure is measured before outcome occurs. The widespread use of early prenatal testing, which could provide information on pregnancy outcome, complicates the classification of prospective enrollments.

Objectives: To examine the definitions of prospective enrollment in ongoing pregnancy registries and discuss potential impact on birth defect (BD) prevalence.

Methods: Pregnancy registries were identified through the FDA pregnancy registry website and ClinicalTrials.gov. Definitions of prospective enrollments were obtained from ClinicalTrials.gov and publications identified in PubMed through 12/2012.

Results: A total of 45 pregnancy registries were identified; 18% on ClinicalTrials.gov, 33% on FDA website, and 49% on both. Definitions of prospective enrollments were available for 29 of the 45 (64%). Among the 29 registries, 77% defined prospective as enrollments prior to pregnancy outcome and prior to an abnormal finding on a prenatal test. The remaining 23% defined prospective as enrollments prior to pregnancy outcome and prior to diagnostic prenatal testing. Routine prenatal ultrasounds to confirm pregnancy viability and dating are permitted up to 13 weeks gestation by some and up to 16 weeks by the others.

Conclusions: Most pregnancy registries studied employ a quasi-prospective enrollment definition that could lead to underestimation of BD risk by preferentially selecting uneventful pregnancies. Registries that preclude diagnostic prenatal testing yield a pure prospective cohort with lower likelihood of biased BD estimates. The cutpoints of 13 and 16 gestation weeks used in these registries may need to be re-examined, however. Current literature suggests a surprising number of structural defects can now be detected at 10–14 weeks gestation with today's ultrasound technology. A cutpoint of 10–12 weeks may minimize the potential for bias.

309. Which Therapeutic Option is the Safest for the Fetus in the Treatment of Maternal Asthma: Higher Dose Inhaled Corticosteroids or Long-Acting beta$_2$-Agonists Plus Lower Dose Inhaled Corticosteroids?

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Background: Asthma is the most common chronic disease in pregnancy, affecting 4–8% of pregnancies. Current recommendations for managing persistent asthma during pregnancy when low dose inhaled corticosteroids (ICS) is not sufficient include combining an ICS with a long-acting beta$_2$-agonists (LABA) or increasing the dose of ICS. However, the literature does not provide any data that could help clinicians to evaluate which regimen is safer for the fetus.

Objectives: To compare the risk of major congenital malformation between users of LABA + ICS and users of ICS monotherapy during the first trimester.

Methods: A cohort of pregnancies from asthmatic women exposed to ICS during the first trimester who delivered between 1990 and 2010 was formed through the linkage of administrative health databases from Québec (Canada). The primary outcome was any major malformation identified using ICD-9/ICD-10 diagnostic codes recorded at birth or during the first year of life in the databases. Two sub-cohorts were formed to fulfill the objectives: (1) first trimester users of LABA + low dose ICS vs. medium dose ICS (LL vs. M), (2) first trimester users of LABA + medium dose ICS vs. high dose ICS (LM vs. H). Potential confounders were sociodemographic variables, maternal chronic diseases and markers of asthma exacerbations. Generalized estimating equation models were used to compare the risk of malformation between the groups.

Results: From 6,723 pregnancies of ICS users, 370 used LABA + low dose ICS, 699 used medium dose ICS, 226 used LABA + medium dose ICS and 170 used high dose ICS. The prevalence of major malformations in both sub-cohorts was 4.8%. The adjusted odds ratio (95% confidence interval) for major malformations was 0.9 (0.4–1.7) for the LL vs. M comparison and 1 (0.4–2.8) for the LM vs. H comparison.

Conclusions: LABA plus low/medium dose ICS regimens were not associated with a higher risk of major malformations compared to higher doses of ICS in monotherapy, providing evidence on the safety of the combination regimen.

310. Best Practices for Pregnancy Registries

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Background: Pregnancy registries can provide valuable data for health care providers to use when treating and counseling patients who are pregnant or wish to become pregnant. However, there are unique methodological considerations that differentiate pregnancy registries from other types of registries or surveillance.

Objectives: The Agency for Healthcare Research and Quality (AHRQ) commissioned a white paper to explore the unique requirements and considerations for designing, operating, and interpreting data from pregnancy registries, and to propose guidance for registry sponsors.

Methods: Pregnancy registry experts from government, industry and academia collaborated to produce a white paper addressing this topic. The paper underwent peer and public review, and will be included as a new chapter in the forthcoming 3rd edition of the AHRQ publication, 'Registries for Evaluating Patient Outcomes: A User's Guide.'

Results: Critical methodological issues to consider in the design and operation of pregnancy registries include the prospective enrollment of women before the pregnancy outcome is known, inclusion of a comparable reference group, thoughtful assessment of drug exposure, ascertainment of prenatal and postnatal diagnosis, and validation of outcomes. Chance and potential biases should be considered when interpreting results from pregnancy registries and any observational study.

Conclusions: Well-designed and executed pregnancy registries can efficiently assess the safety of biopharmaceuticals during pregnancy and provide valuable data to health care providers, patients, and policy makers. When used appropriately, pregnancy registries can identify or rule out large increases in the risk for malformations, and can be an important tool to establish safety boundaries around risk estimates as data accumulate.

311. Use of Serotonin Reuptake Inhibitors in Late Gestation and Lactation Difficulties

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Background: Serotonin [5-hydroxytryptamine (5-HT)] is an important local feedback inhibitor involved in lactation. Few studies have investigated whether medications which increase 5-HT, such as Serotonin Reuptake Inhibitors (SRIs), are associated with lactation difficulties.

Objectives: To evaluate the association between SRI use in late gestation and lactation difficulties after delivery.

Methods: Retrospective cohort study using linked records from the Women's and Children's Health Network in South Australia. This included electronic data from the Women's and Children's Hospital (WCH) Perinatal Statistics Collection and the WCH Hospital Pharmacy Dispensing Records. Women delivering a live-born singleton between Jan 2004 and Dec 2008 were included (n = 21,646). Women exposed to psychotropic medications other than SRIs were excluded (n = 268). The primary outcome, of lactation difficulties, was defined according to whether women received a dispensing for domperidone in the postnatal period. Domperidone is a galactagogue which stimulates and promotes milk production and therefore can be used as a pharmacological treatment for mothers who are experiencing lactation difficulties. Logistic regression models were used to calculate ORs and 95% confidence intervals (CIs), adjusting for confounders identified *a priori*.

Results: Of eligible pregnant women, 304 received a dispensing for a SRI in late gestation (exposed), 961 did not receive a dispensing for a SRI but had a reported psychiatric illness during pregnancy (untreated psychiatric illness) and 20,381 did not receive a dispensing for a SRI and had no reported psychiatric illness during pregnancy (unexposed). Women exposed to a SRI were not at increased risk of experiencing lactation difficulties compared to women who were unexposed (aOR 1; 95% CI: 0.63–1.59), or women with an untreated psychiatric illness (aOR 0.69; 95% CI: 0.40–1.21). Notably, women with an untreated psychiatric illness appeared to be at increased risk of experiencing lactation difficulties compared to women who were unexposed (aOR 1.33; 1–1.77).

Conclusions: No association was observed between SRI use in late gestation and an increased risk of lactation difficulties.

312. Prenatal Antidepressant Exposure and Child Behavioural Outcomes at 7-Years of Age

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Background: Potential long-term effects of prenatal antidepressant exposure on child development have not been adequately studied.

Objectives: To evaluate the association between prenatal antidepressant exposure and behavioural problems at 7-years of age.

Methods: Information on exposures was obtained from the Danish National Birth Cohort. We studied the children of 210 mothers who had used antidepressants during pregnancy (exposed) and compared these to 231 children of mothers with prenatal depression but no use of antidepressants during pregnancy (untreated depression) and 48,737 children of mothers with no prenatal depression and no use of antidepressants during pregnancy (unexposed). Behavioural problems were assessed at 7-years of age and were indicated by scores falling above defined clinically relevant cut-offs on the parent-report version of the Strengths and Difficulties Questionnaire (SDQ). Overall problem behavior, emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviours were evaluated. Logistic regression models were used to calculate ORs and 95% confidence intervals (CIs), adjusting for confounders identified *a priori*.

Results: Prenatal antidepressant exposure was not associated with abnormal overall problem behaviors compared to prenatal exposure to untreated prenatal depression (aOR 0.44; 0.16–1.21) or to no exposure (aOR 0.93; 0.41–2.12). Prenatal antidepressant exposure was associated with a higher rate of abnormal SDQ scores on the subscales of conduct problems (aOR 1.55; 0.94–2.58) and emotional symptoms (aOR 1.80; 1.17–2.75) compared to unexposed children, but not when compared to children exposed to prenatal depression (aOR 0.79; 0.39–1.54 and aOR 0.69; 0.39–1.22 respectively).

Conclusions: After adjustment for important maternal factors, including prenatal depression, prenatal antidepressant exposure was not associated with an increased risk of any behavioural difficulties in children at 7-years of age.

313. Use of Acid-Suppressive Drugs in Pregnancy and the Risk of Childhood Asthma: Bidirectional Case-Crossover Study Using the General Practice Research Database

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Background: Recent studies have reported an association between maternal use of gastric acid-suppressive drugs during pregnancy and asthma in the offspring, but the association could have been confounded by unmeasured risk factors.

Objectives: To assess the association between the use of acid-suppressive drugs during pregnancy and the risk of developing childhood asthma using a bidirectional case-crossover design.

Methods: Mother-infant matched sets in the United Kingdom General Practitioners Research Database were used to identify children with a drug-treated asthma diagnosis during the years 2006–2010 who were matched to a sibling without asthma as controls. Primary exposure was use of any anti-suppressive drug during pregnancy, and subgroup analyses were conducted according to drug class (e.g., proton-pump inhibitors or H2-receptor antagonists), trimester and mother's age. Conditional logistic regression was used to estimate odds ratios with their corresponding 95% confidence intervals (CI).

Results: Of 1,874 children with asthma and 1,874 control siblings were included in the analysis. The exposure rate among case and control pregnancies was 22% and 20% respectively. After adjustments for gender, birth order, mother's age and GP visits, the exposure to any gastric-acid suppressive drug during pregnancy slightly increased the risk for developing asthma (OR 1.23; 95% CI: 1.01 to 1.51, p-value 0.042). Risks were increased for proton pump inhibitors (PPI) or H2-antagonists (adjusted OR 1.72; 95% CI: 1–2.98; p-value: 0.048).

Conclusions: These findings lend support to the emerging evidence that exposure to acidsuppressive drugs during pregnancy is associated with childhood asthma. More basic research is now warranted to investigate the mechanisms.

314. Prenatal Exposure to Antidepressants and Motor Development in the 3 Years Old Child. Results from MoBa, a Large Population Based Pregnancy Cohort in Norway

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Background: Human data on the association between SSRI exposure and psychomotor development in the child is limited and inconclusive.

Objectives: To examine if exposure to SSRIs in pregnancy was associated with delay in motor development in the children at 3 years of age.

Methods: Design: The Norwegian Mother and Child Cohort Study (MoBa) is a prospective observational pregnancy cohort. Setting: Women were recruited between 1999 and 2008. Data on children whose mothers had returned the 3-year follow up were included (N = 58 410). Multiple pregnancies, children with malformation and/or chromosomal abnormalities and children with missing data on the motor development measures were excluded ($N_{excluded}$ = 6 975). Exposure: Self-reported use of SSRI during one or more trimesters. Outcome: Fine and gross motor development measured by items from the Ages and Stages Questionnaire (ASQ) reported by the mother. The response fell into five categories where category 1 was the best. Statistical analysis: Ordinal logistic regression with estimated standard errors allowing for clustering of multiple pregnancies per woman. To study the effect of the underlying disease depression was measured as a score of ≥ 2 on SCL-5 during pregnancy.

Results: Of 45,026 women with 51 435 children were included in the study. 412 women (0.8%) reported use of SSRI during pregnancy, of these 167 used SSRIs in at least two trimesters. Of all the children 49%, 24%, 16%, 7% and 3% respectively were rated in category 1–5 of fine motor development. Children of mothers who used SSRIs in more than one trimester had increased risk of delay in fine motor development, aOR 1.63 (1.22–2.15) compared to women who did not use SSRIs and who did not report depression. Depression alone did not result in delay in motor development, aOR 1.05 (0.99–1.11). Effects of SSRIs and depression on gross motor development were similar to the fine motor development results.

Conclusions: Prenatal use of SSRIs for extended pregnancy periods was associated with a higher risk of delay in fine and gross motor development by age 3, while untreated depression did not affect the development.

315. Reproductive Calls to the Norwegian Poison Information Center – Women are Frightened of Exposures to Gases and Household Chemicals, not only Medicines

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Background: Studies have shown that pregnant and lactating women often have an unrealistic fear of medications, however few studies have focused on how they perceive exposure to other substances such as gases and household chemicals.

Objectives: We aimed to characterize reproductive calls received by the Norwegian Poison Information Center during the period 2007–2012 with special emphasise on the category 'gases and household chemicals'. In addition, we wanted to evaluate the women's risk perception of chemical exposures.

Methods: The study consisted of a retrospective and a prospective part. All reproductive calls in a 6-year time period (2007–2012) were assessed retrospectively. Prospective data included calls from pregnant and lactating women from May 2011. Study participants were asked to score the exposure they called about, using numeric rating scale ranging from 0 (no risk to the foetus or infant) to 10 (very high risk for endanger the foetus or infant) prior to receiving counselling to evaluate their own perceptions of the teratogenic risk. After literature search and counselling, the poisons information specialists (SPIs) scored their own risk perception (scale 0–100%).

Results: In total 3046 reproductive calls were received. The majority of the calls were from the public concerning exposures during pregnancy. In about 50%, the call was made prior to exposure. In fewer than 3% of the enquiries, there was a need for medical referral. In total, 49% of the substances of concern were chemicals, and 36% were medicines. The product group 'paints, vanishes and glues' constituted of 32% of the calls concerning chemical exposures. Between May 2011 and February 2013, 115 women were enrolled in the prospective risk perception study. In total, 22 percent perceived that their risk was ≥ 6. In over 80% of the calls, the SPIs considered the exposure to involve no risk at all.

Conclusions: Women have concerns about gases and household chemical, not only medicines. They tend to overestimate the risk of chemical exposures during pregnancy and lactation.

316. Pregnancy Outcome in Women Exposed to Dopamine Agonists during Pregnancy: A Study in EFEMERIS Database

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Background: Dopamine agonist drugs can be prescribed for several indications like hyperprolactinemia or Parkinson's disease. Little is known on the possible effect of dopaminergic agonists on embryo-fetal development.

Objectives: To describe pregnancy outcomes in women having a prescription of dopamine agonists and compare to an unexposed group.

Methods: An 'exposed-non exposed' study was conducted using data from EFEMERIS, a cohort of 57,408 pregnant women living in South West France (database of all prescribed and dispensed reimbursed drugs during pregnancy and their outcomes). Of 183 women (0.3%) who get at least one dispensation of dopamine agonist drug (bromocriptine, cabergoline, quinagolide, lisuride, piribedil, ropinirole) during pregnancy constituted the 'exposed group' (no prescription of levodopa was dispensed to pregnant women). They were individually matched with two 'unexposed' women according to their age and the month-year of the beginning of their pregnancy. Pregnancy terminations, birth defects, preterm births, low birthweight and psychomotor development were studied. We used a conditional logistic regression to analyse risks for each outcome associated with dispensation of dopamine agonist drugs.

Results: Bromocriptine was the most prescribed dopamine agonist followed by cabergoline and quinagolide. 75% of dopamine agonist prescriptions concerned the beginning of pregnancy (first trimester of pregnancy). There was no difference between the two groups concerning pregnancy history and demographic data. After adjustment for potential confounders, prescription and dispensation of dopamine agonists was associated with an increased risk of pregnancy termination (PORa = 3.7; 95% CI: 1.8–7.4) and preterm birth (PORa = 3.6; 95% CI: 1.5–8.3). The prevalence of birth defect and low birthweight was not statistically different between both groups. No difference in psychomotor development at 9 and 24 months was observed between the two groups.

Conclusions: The results of this study suggest that situations involving fetal exposure to dopamine agonist drugs are at increased risk of pregnancy termination and preterm birth.

317. Antidepressant Medication Use during Pregnancy and the Risk of Preterm Birth

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Background: Preterm birth is a major contributor to neonatal morbidity and mortality, and its rate has been increasing over the past two decades. Antidepressant use during pregnancy has also been rising, with reported rates up to 7.5% in the US. Numerous studies have examined the effects of antidepressants on pregnancy outcomes, including preterm birth.

Objectives: We systematically reviewed the literature to assess the association between antidepressant use during pregnancy and preterm birth.

Methods: Computerized search in PUBMED, MEDLINE and PsycINFO through September 2012, supplemented with a manual search of reference lists, to identify all original published research on preterm birth rates in women taking antidepressants during pregnancy. Data were independently extracted by two reviewers, and absolute and relative risks abstracted or calculated. We grouped studies by their level of confounding adjustment and the timing of antidepressant use during pregnancy, and used random-effects models to calculate summary measures of effect.

Results: Of 41 studies met inclusion criteria. Pooled adjusted odds ratios for pre-term birth and antidepressant use (and 95% CI) ranged from 1.16 (0.92–1.45) for early (typically 1st trimester) exposure only to 1.53 (1.40–1.66) for exposure at any time during pregnancy, and 1.96 (1.62–2.38) for antidepressant use late in pregnancy (typically 3rd trimester). Controlling for a diagnosis of depression did not eliminate the effect, although the strength of the observed associations was attenuated (OR = 1.61 vs. 1.88, in subset of studies controlling for psychiatric illness). Sensitivity analyses demonstrated that strong unmeasured confounding would be needed to fully explain the observed depression-adjusted association.

Conclusions: The published evidence is consistent with an increased risk of preterm birth in women taking antidepressants during pregnancy, although the possibility of residual confounding cannot be completely ruled out. Given the widespread use of these drugs, these findings reinforce the concept that antidepressants should be used in pregnancy only if there is a clear benefit against which to consider this likely risk.

318. In Utero Exposure to Antipsychotics and Congenital Malformations – A Nation Wide Cohort Study

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Background: Use of antipsychotics during pregnancy is associated with great concern. Few studies have estimated the fetal risk after exposure to these drugs, and dealt with confounding by indication.

Objectives: To analyze the relation between exposure to antipsychotics during the first trimester and congenital malformations, with focus on comparison with paused use during pregnancy to account for special characteristics of patients using antipsychotics.

Methods: We identified all births in Denmark between 1997 and 2009 and their diagnoses of congenital malformations using the Danish Medical Birth Register and The National Hospital Register. Exposure to antipsychotics (ATC N05A) was assessed using the National Prescription Register. Multivariate logistic regression was used to adjust for available confounders.

Results: We identified 912,342 births, of which 1,250 (0.1%) redeemed a prescription for an antipsychotic during the first trimester. Adjusted odds ratio for major malformations was 1.35 (95% CI: 1.03–1.76) for first trimester exposure. Women exposed to an antipsychotic before and after pregnancy, but not during pregnancy, had an adjusted odds ratio of 1.74 (95% 1.03–2.93) for major congenital malformations. The risk did not differ between these two groups (p = 0.41).

Conclusions: The apparent association between use of antipsychotics and congenital malformations may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk vs. benefit to be evaluated in each individual case.

319. Topical Pharmacological Treatment of Hemorrhoids during Pregnancy and Congenital Malformations – A Nation-Wide Cohort Study

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Background: Hemorrhoids are common during pregnancy. In spite of this, safety of their pharmacological treatment has not been assessed.

Objectives: The aim of this study is to determine the association between exposure to antihemorrhoidal agents during the first trimester and congenital malformations.

Methods: We identified all pregnancies resulting in a live birth between 1997 and 2009 through the Danish Medical Birth Registry. Redeemed prescriptions were identified through the Danish Register of Medicinal Product Statistics, and diagnoses of major congenital malformations through the Danish National Hospital Register. The risk of congenital malformations was calculated using multivariable logistic regression models adjusted for potential confounding variables.

Results: We identified 844,194 pregnancies; of which 7210 (0.85%) redeemed a prescription for an antihemorrhoidal agent during the first trimester. All redeemed drugs contained corticosteroids; either hydrocortisone (n = 4553) or fluocortolone (n = 2433). The risk of major congenital malformations for any antihemorrhoidal agent was; adjusted OR 1.03 (95% CI: 0.91–1.17). We found no elevated risk of specific major malformations. Stratifying analyses for different corticosteroids gave no elevated risk of major congenital malformations.

Conclusions: We found no association between redeeming a prescription for an antihemorrhoidal agent during the first trimester and congenital malformations. To our knowledge, this is the first study to analyze this relation.

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320. Can we Rely on Pharmacy Claims Databases to Ascertain Maternal Use of Medications during Pregnancy?

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Background: Administrative databases are increasingly used in perinatal pharmacoepidemiology. They have many benefits but do not provide accurate data on real drug used since they are claims databases. Hence the debate on whether these databases provide valid measures of drug use during gestation. Few data exists on the concordance between maternal report on drug use and data from claims databases.

Objectives: To determine the concordance between pharmacy records on prescriptions filled in the Quebec Pregnancy Registry using the RAMQ medication data, and maternal report of drug use during pregnancy.

Methods: The OTIS Antidepressants (AD) in Pregnancy Study cohort was used. Women were recruited via 9 North American teratology information services between 2006 and 2011. Information on drug use during pregnancy was prospectively collected each trimester. Women were eligible if they were Quebec resident and provided their pharmacist's contact information. Pharmacy records on prescriptions filled were retrieved and compared to maternal recall. Positive and negative predictive values (PPV and NPV) for drugs taken chronically (AD and thyroid hormones), acutely (antibiotics) and as needed (antiemetics and asthma drugs) were calculated.

Results: We included 80 women (mean age = 30.1 ± 3.8); 42.5% reported AD use, 8.8% thyroid hormones, 18.8% antibiotics, 22.5% antiemetics and 13.8% asthma medications. In average, women were taking 2.4 different drugs (range:1–7). PPV and NPV for AD were 100% (95% CI: 100–100) and 97.9% (95% CI: 90–100). For thyroid hormones PPV and NPV were 100% (95% CI: 100–100) and 100% (95% CI: 100–100). For antibiotics, PPV and NPV were 84.5% (95% CI: 70–100) and 94% (95% CI: 90–100). For antiemetics, the PPV and NPV were 78.9% (95% CI: 60–100) and 95% (95% CI: 90–100), for asthma drugs 63.6% (95% CI: 30–100) and 94.2% (95% CI: 90–100).

Conclusions: The PPVs and NPVs were high for all drug classes during pregnancy although these estimates were even higher for drugs taken for chronic conditions. This validates the use of prescription fillings data to determine medication exposure in large administrative databases.

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321. How much Ortho-Phthalate may be Present in Medications and Dietary Supplements?

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Background: In animal studies, some ortho-phthalates, including di-n-butyl phthalate (DBP), have been shown to be reproductive and developmental toxicants. Urinary concentrations of the diethyl phthalate (DEP) metabolite, monoethyl phthalate, have been associated with reduced anogential distance in male infants. It has previously been shown that high human exposure may result from orally ingested medications and supplements containing phthalates as inactive ingredients. However, the amount of inactive ingredient in a given product is not publicly available, and the absence of such data limits risk assessment.

Objectives: To determine the amount of DBP and DEP in samples of selected OTC and RX medicinal products and dietary supplements.

Methods: Samples of RX and OTC products labeled as containing DEP and DBP, as well as products without phthalate listed as an inactive ingredient, were analyzed for the presence and content of labeled phthalates. Extraction and analysis of 10–15 samples of each product was conducted using dissolution in methanol followed by sonication and high performance liquid chromatography (HPLC).

Results: Among samples of OTC products labeled as containing DEP, amounts of DEP in three 75 mg ranitidine products ranged from 305 ± 49.9 to 382 ± 56.4 μg/tablet (Mean $\pm$ SD) and for two 150 mg products the range was 495 ± 73.2 to 514 ± 72.2 μg/tablet. One non-DEP labeled 150 mg ranitidine product produced no detectable levels. For DEP in OTC supplements, 1 DEP labeled garlic supplement tablet product yielded 5.41 ± 0.61 mg/tablet and one brand of probiotic capsules labeled as using an unspecified 'aqueous enteric coating' yielded 3.95 ± 0.49 mg/capsule. DBP in 1 OTC bisacodyl product averaged 1.37 ± 0.22 mg/tablet. In RX mesalamine products, DBP in DBP-labeled products ranged from 3.45 ± 0.40 mg/tablet (400 mg tablet) to 7.20 ± 0.89 mg/tablet (800 mg tablet), and was undetected in 1 non-DBP labeled capsule product.

Conclusions: The amount of DEP and DBP in several samples of RX and OTC medicinal products and dietary supplements may represent a significant source of phthalate exposure. The potential health impacts of high exposure from medications and supplements are unclear.

322. Veinotonics in Pregnancy: A Comparative Study in the EFEMERIS Database

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Background: There are few published data about possible effects of veinotonics in pregnant women. However, many French women use these medications during their pregnancy.

Objectives: To investigate potential adverse drug reactions of veinotonics in pregnancy.

Methods: This observational study compared exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnosis Centre). Women who delivered from July 1st 2004 to December 31th 2007 in Haute-Garonne (time period when veinotonics were still reimbursed) and were registered in the French Health Insurance Service have been included. We compared pregnancy outcomes and newborn health between women exposed to veinotonics during pregnancy and unexposed women. Malformations were classified according to Eurocat classification.

Results: Of 9,116 (24.6%) women exposed to veinotonics during pregnancy were compared with 27,963 unexposed. The most widely used veinotonics were diosmin, hesperidin, and troxerutin. The mean age of the mothers was 31.2 ± 4.8 years in the exposed group and 30 ± 5.1 in the unexposed group ($p < 10^{-4}$). The mean number of drugs taken during pregnancy was higher in the exposed group (13.4 ± 8 vs. 9.4 ± 7; $p < 10^{-4}$). Pregnancies led to 98.4% vs. 93.6% of live-births and 0.2% vs. 0.2% of postnatal deaths in exposed and unexposed groups respectively. When only exposure to veinotonics during organogenesis was considered, 39 (3.4%) congenital malformations were observed in the exposed group vs. 789 (3%) in the unexposed ($p = 0.44$). There is no difference in the rate of neonatal pathologies in the exposed group and unexposed (5.7% vs. 6.4%, adjusted OR = 1.07 (0.95–1.12).

Conclusions: We found no increased risk of adverse pregnancy outcomes (neonatal pathology and congenital malformation) among women exposed to veinotonics compared with unexposed pregnant women.

323. Safety of Influenza AH1N1 Pandemic Vaccination during Pregnancy: A Comparative Study in the EFEMERIS Database

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Background: Pregnant women are at increased risk of severe disease and death due to influenza infection. During the influenza AH1N1 pandemic in 2009–2010, recommendations in France were to vaccinate pregnant women during the second and third trimester preferably with a non-adjuvant vaccine. However, few data are available concerning this drug in pregnant women.

Objectives: To compare birth outcomes between exposed and unexposed women to influenza AH1N1 vaccine during pregnancy.

Methods: This observational cohort study compared two groups of exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnosis Centre). Women who delivered from October 21th 2009 to November 30th 2010 in Haute-Garonne and were registered in the French Health Insurance Service have been included. We compared pregnancy outcomes and newborn health between women exposed to a pandemic vaccine during pregnancy and unexposed women. Unexposed women were individually matched to exposed women by month and year of delivery or pregnancy termination. Malformations were classified according to Eurocat classification.

Results: Of 1,645 (13.6%) women exposed to a pandemic vaccine were compared with 3290 unexposed women. Most were exposed to a vaccine in December 2009 (61%) and Panenza° was used in 92.7% of the cases. The average maternal age in the exposed group was 31.4 ± 4.3 and 29.9 ± 5.4 in the unexposed ($p < 10^{-4}$). The pregnancies led to 99.2% vs. 95.2% of live-births in exposed and unexposed groups respectively, the difference was not significant (adjusted HR = 0.56, 95% CI = 0.31–1.01). When exposure during organogenesis was considered, no increased risk of congenital malformations was found (adjusted OR = 0.73 [0.10–2.34]).

Conclusions: We found no increased risk of adverse pregnancy outcomes (pregnancy termination, preterm birth, low birth weight and congenital malformation) among women exposed to Panenza° compared with unexposed pregnant women.

324. Risks and Safety of Pandemic H1N1 Vaccine in Pregnancy: Preterm Birth and Specific Defects

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Background: There are insufficient data about potential fetal risks among women exposed to non-adjuvanted pandemic H1N1 (pH1N1) vaccine during pregnancy.

Objectives: To determine exposure prevalence for pH1N1 vaccine and to assess risks and relative safety of the pH1N1-containing vaccines in the 2009–2010 and 2010–2011 influenza seasons with respect to preterm delivery (PTD) and specific birth defects.

Methods: We used data gathered in four regional centers in the U.S. between September 2009 and August 2011 as part of the Slone Epidemiology Center's Birth Defects Study. For PTD, the analysis was limited to nonmalformed subjects. Propensity score-adjusted time-varying hazard ratios (HRs) and 95% confidence intervals (CIs) for PTD were estimated for exposure anytime in pregnancy and for each trimester. Propensity score-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for 41 specific birth defects.

Results: There were 4,191 subjects available for analysis: 3,104 malformed (cases) and 1,087 nonmalformed (controls). For PTD, numbers were too sparse for the 2010–2011 season to permit risk calculations; the adjusted HR for first trimester exposure in the 2009–2010 season was 4.84 (95% CI: 1.45–16.10), though risks differed appreciably when preceding receipt of seasonal vaccine was considered. For 41 specific birth defects, most adjusted ORs were close to 1. Three defects had adjusted ORs > 2 and four had risks < 0.5; however, 95% CIs for these 7 ORs were quite wide.

Conclusions: For the 2009–2010 season, we found an increased risk of PTD following first trimester pH1N1, particularly when preceded by the seasonal vaccine. For the 2009–2010 and 2010–2011 seasons, we found no meaningful evidence of increased risks for specific congenital malformations following pH1N1 influenza vaccinations. For the 41 specific birth defects studied, our estimates excluded risks of 4-fold or greater for most defects, and risks of two-fold or greater for 14.

325. First Trimester Exposure to Bupropion and Cardiac Defects

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Background: Bupropion is a unique drug that is used both to treat depression and as an aid in smoking cessation. Recent reports have suggested that it may be associated with increased risks of specific cardiac defects including VSDs, coarctation of the aorta, and left-sided defects as a group.

Objectives: To investigate if bupropion is associated with an increased risk of selected cardiac defects.

Methods: We used data gathered since 2003 by the Slone Epidemiology Center's ongoing case control Birth Defects Study. Subjects with cardiac defects were classified into subgroups by a pediatric clinical cardiologist. We created exposure categories identifying 1st trimester exposure to bupropion alone or in combination with other antidepressants, 1st trimester exposure to antidepressants other than bupropion, and no exposure to any antidepressant at any time from 2 months prior to pregnancy through delivery.

Results: There were 8611 nonmalformed infants and 7913 infants with cardiac defects available for study. Seven cardiac subgroups had sufficient subjects for analysis: left-sided defects, right-sided defects, conotruncal and major arch anomalies, AV canal defects, hypoplastic left heart syndrome, VSDs, and ASDs. The adjusted odds ratio (OR) for first trimester bupropion use in relation to VSD was slightly elevated (1.6) with a 95% lower confidence bound of 1. For exposure to bupropion alone, the OR was 2.5, with a lower bound of 1.3. Risks were not materially elevated for bupropion and other cardiac subgroups. There were too few users for smoking cessation to allow for analyses stratified on indication.

Conclusions: We did not confirm previously-reported associations for left-sided defects overall and had too few exposed cases to evaluate specific defects in this category. We did, however, observe an elevated risk of VSD following first trimester bupropion use, particularly when used without other antidepressants. Of note, this pattern for bupropion alone was observed in all our risk comparisons and was not explained by higher doses or gestational timing.

326. Withdrawn by Author

327. The Fetal Safety of Macrolides – A Systematic Review and Meta-Analysis

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Background: Pregnant women with bacterial infections require safe and effective antimicrobial treatment. Macrolides are commonly used in pregnancy, although the results related to fetal safety have been conflicting.

Objectives: This meta-analysis was conducted to determine whether exposure to macrolides during the first trimester is associated with risk for congenital malformations.

Methods: *Data sources:* MEDLINE, EMBASE and Biological Abstracts were searched to February 2013. Various combinations of key words were used including 'pregnancy', 'birth defect'; 'teratogenicity', 'cardiovascular defects', 'malformation' in intersection with 'macrolide', 'erythromycin', 'azithromycin', 'clarithromycin', 'roxithromycin' and 'spiramycin'. *Study selection:* All studies reporting pregnancy outcome with data on exposure to a macrolide during the first trimester (all languages) were included. Of 3,806 records were reviewed. *Data extraction:* Two independent researchers extracted data. Outcomes included any malformation, major malformation and cardiovascular. Data was combined into pooled odds ratio using Mantel and Henzel random-effects method.

Results: Twenty four studies met the inclusion criteria, which included 12,304 exposed and 1,671,848 unexposed women. Macrolides were not associated with congenital malformations (OR = 1.04, 95% Confidence interval: 0.93–1.16) or cardiovascular malformations (OR = 1.08, 95% Confidence interval: 0.86–1.36).

Conclusions: Overall, macrolides do not appear to be associated with an increased risk of congenital malformations. These results are reassuring for women who need to use macrolides during the first trimester of pregnancy, and their health professionals.

328. Validity of Maternal and Infant Outcomes within Medicaid Data

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Background: The US Medicaid Analytic eXtract (MAX), a nationwide healthcare utilization database, is a useful resource for studies of medications in pregnancy. However, the accuracy of maternal and infant outcomes, and obstetric factors such as parity, identified within MAX has not been established.

Objectives: To assess the validity of claims to detect preeclampsia, congenital cardiac malformations and persistent pulmonary hypertension of the newborn (PPHN).

Methods: Using 2000–2007 MAX data, we selected a cohort of > 1 million pregnancies. We identified

women with diagnostic codes indicative of preeclampsia and infants with codes indicative of cardiac malformations or PPHN. Codes for preterm delivery and multiparity according to the Medicaid eligibility variable were also abstracted. We reviewed hospital medical records for a sample of pregnancies with possible outcomes based on claims, and calculated the positive predictive value (PPV) and 95% confidence intervals (CI) for each outcome.

Results: Among women with inpatient preeclampsia diagnoses (N = 120), the PPV was 92% (CI: 86–96%); there was no evidence of differential misclassification by antidepressant use. The PPV for cardiac malformations overall was 80% (CI: 69–89%) when > 1 inpatient code was required (N = 60). Requiring ≥ 1 inpatient code for selected cardiac malformations more than doubled the number of possible cases, but reduced the PPV to 70%. The PPV was 68% (CI: 58–78%) for PPHN when ≥ 1 inpatient code was required (N = 79), but it increased to 92% (CI: 81–97%) when restricting to infants who were not transferred to another facility (N = 47). The PPV for multiparity was 88% (81–92%) and was 75% (61–85%) for preterm delivery.

Conclusions: Inpatient preeclampsia identified in MAX had high validity, and the Medicaid eligibility variable can be used to identify parity. However, as had been reported for other databases, the validity of claims to identify cardiac malformations, preterm delivery, and PPHN was fair. PPVs estimated from hospital record validation may be conservative when patients are transferred or receive outpatient diagnoses. Sensitivity analyses or medical record confirmation may be necessary when studying PPHN or birth defects in MAX data.

329. Antidepressant Use Late in Pregnancy and Risk for Persistent Pulmonary Hypertension of the Newborn (PPHN) among Low-Income Women

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Background: The association between selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and risk of PPHN has been controversial since the US Food and Drug Administration issued a Public Health Advisory in 2006. Previous studies reached discrepant conclusions and were limited by insufficient size, potential confounding by indications, and improper adjustment for potential mediators.

Objectives: To evaluate the association in a large cohort of pregnant women enrolled in Medicaid, the health insurance program for low-income individuals in the US.

Methods: We identified a cohort of 103,491 pregnancies in which women had a depression or anxiety disorder diagnosis from 2000 to 2007 Medicaid healthcare data. Women were classified according to pharmacy dispensing records as exposed to SSRI or non-SSRI monotherapy in the 90 days before delivery or as unexposed. We then estimated propensity scores for exposure based on depression severity proxies, other antidepressant indications, other medications, and PPHN risk factors but not on potential mediators such as preterm and cesarean delivery. We estimated relative risks (RR) and 95% confidence intervals (CI) for PPHN stratified by propensity score. PPHN claims had a positive predictive value between 68-92% according to medical record validation.

Results: The risk for PPHN among women with depression unexposed to antidepressants was 0.14%. Compared to unexposed women, the unadjusted RR for PPHN among women exposed to SSRIs was 1.4 (CI: 0.9–2) and it was 1.5 (CI: 0.8–2.8) for non-SSRIs. After adjustment for a large number of potential confounders, the RR was 1.2 (CI: 0.8–1.8) for SSRIs and 1.2 (CI: 0.6–2.3) for non-SSRIs.

Conclusions: In this Medicaid population, the association between antidepressants and PPHN was weak. The risk of PPHN increases from approximately 1 case per 1000 births among women with depression/anxiety not using antidepressants to 1.5 cases per 1000 births among those using antidepressants.

330. Drug Use in Pregnancy, Gestational Age and Date of Delivery: Comparison of Health Database and Self-Reported Information in a Cohort

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Background: To study drug use in pregnancy maternal self-reports and health databases are used, neither is gold standard. Recall inaccuracy, nonuse of prescribed drugs or use of OTC are of concern.

Objectives: The aim of this study is to compare self-reported drug use in pregnancy with data from outpatient prescriptions (OP) and birth certificate (BC) regional databases in a cohort of women in Friuli Venezia Giulia, Italy.

Methods: Pregnant women recruited at first visit in a prenatal clinic in 2007–2009 compiled a structured questionnaire (Q) between the 28th week of estimated gestational age and 1 month after delivery. Information on drug use in pregnancy (brand name, active substance, indication), date of delivery, gestational age at birth was collected. For each woman we extracted prescriptions from 2006 to 2010 and records from BC through a unique personal identifier. Prescriptions from the estimated conception date (date of delivery less gestational age, both from BC) to the earliest of delivery or Q compilation (pre-delivery in 38.7%) were considered in pregnancy. We calculated percent agreement and K coefficient with 95% confidence interval (95% CI).

Results: In this cohort of 767 women 39.2% reported drug use and 70% had prescriptions in pregnancy, gestational age matched exactly in 85.2% (± 2 days in 14.6%) and date of delivery in 99.5% (± 2 days in 0.5%). K value was high for thyroid hormones 0.88 (95% CI: 0.80–0.96), antihypertensives 0.86 (0.65–1) and antithrombotics 0.70 (0.55–0.83). K was low for iron 0.49 (0.42–0.56), folic acid 0.11 (0.04–0.18) and systemic antibacterials 0.11 (0.05–0.18). Folic acid (35.6%) and iron (26.1%) were the most frequently reported drugs. Six women had prescriptions for antidepressants and 1 for methadone. Their use was not reported.

Conclusions: Agreement was very good/good for gestational age, date of delivery and for drugs for chronic conditions (thyroid hormones, antihypertensives, antithrombotics). Agreement was low for drugs obtainable as OTC (folic, iron) or episodically taken (antibacterials). Antidepressants and methadone were prescribed but not reported.

331. Perception of Teratogenic Risk Related to Medications: Agreement between Two Techniques of Measuring

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Background: Studies have demonstrated that the perception of teratogenic risk related to medications is overestimated. Most studies about the perception of teratogenic risk used Visual Analogue Scales (VAS).

Objectives: To evaluate the agreement between two techniques of measuring the perception of teratogenic risk related to medications and exposure to radiation therapy.

Methods: The sample comprised 287 women aged between 15 and 49 years consecutively recruited at public health centers in Porto Alegre, Brazil. The perception of risk for congenital malformations in the general population and the perceptions of teratogenic risk for exposures to paracetamol, metoclopramide, misoprostol and radiation therapy during pregnancy were measured by two techniques: Visual Analogue Scales (VAS) and numerical questions. The agreement between the measurement techniques was assessed using the Bland-Altman plot. The degree of association was measured by Spearman's correlation coefficient.

Results: The medians for the perceptions of teratogenic risk measured by the VAS were higher than those obtained through the numerical question for all variables. The perception of risk for paracetamol showed the lower bias between the two measurement techniques (bias = 13.17; $p < 0.001$) and for exposure to radiation therapy, the higher one (bias = 25.02; $p < 0.001$).

Conclusions: There was no agreement between the measurements obtained by the VAS and by the numerical question for none of the risk perceptions under study. The VAS overestimated the results of risk perceptions. Considering that the VAS is broadly used for measuring health outcomes, we suggest that studies be conducted to assess if there is also overestimation in other situations and social contexts due to the use of the VAS.

332. Hypertensive Disorders and Antihypertensive Medication during Pregnancy and the Risk of Birth Defects: A Case-Control Study

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Background: Several studies have reported associations between early prenatal antihypertensive medication exposure and a number of specific birth defects, but they were unable to distinguish among the different types of hypertensive disorders.

Objectives: To investigate previously-identified associations between maternal hypertensive disorders and prenatal exposure to antihypertensive medication and the

occurrence of selected birth defects taking into account specific types of hypertensive disorders in different time windows during pregnancy.

Methods: In the Slone Birth Defects Study, we selected mothers of 5,568 infants with birth defects as cases and 7,253 non-malformed live born infants as controls. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for birth defects previously associated with prenatal exposure to maternal hypertensive disorders and/or antihypertensive medications.

Results: Our findings provide support for some, but not all, associations linked to maternal hypertension or antihypertensive medication use in prior epidemiologic studies. Among those we supported, untreated chronic hypertension was associated with a three-fold risk of esophageal atresia (95% CI: 1.2–8.3) and pre-eclampsia superimposed on chronic hypertension was associated with ventricular septal defects (OR: 3.9; 95% CI: 1.3–11.7) and atrial septal defects (OR: 7.1; 95% CI: 1.5–28). For chronic hypertension that was pharmacologically treated early in pregnancy, increased risks were observed for 1st degree hypospadias (OR: 2.9; 95% CI: 1.1–7.4). Untreated preeclampsia was related to 2nd/3rd degree hypospadias and ventricular septal defects. Treatment for gestational hypertension was associated with a number of cardiovascular defects.

Conclusions: Our findings support the hypothesis that the underlying hypertensive disorder or its subclinical state itself may increase the risk of selected malformations, since for several birth defects, manifestation of the hypertensive disorder or its pharmacological treatment took place after the etiologically relevant time period.

333. Validation of Pregnancy Information in the German Pharmacoepidemiological Research Database (GePaRD)

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Background: The use of large electronic healthcare databases for the investigation of teratogenic effects of drugs during pregnancy requires valid coding of pregnancy information.

Objectives: To validate the coding of pregnancy outcomes (POs) and to assess the potential application of pregnancy markers (PMs) to identify pregnancies in the German Pharmacoepidemiological Research Database (GePaRD).

Methods: We selected females aged 10–49 years in 2005 and identified the following POs using pre-specified algorithms: ectopic pregnancies, spontaneous and induced abortions and births. Births were further categorized into term or preterm births, live or stillbirths and hospital or home births. In addition, we assessed whether eight categories of PMs (i.e. diagnoses, procedures or medical services indicating an existing pregnancy) can be used to identify women with POs in 2005. We used data from the German Federal Statistical Office (GFSO) and the literature to compare the percentages of home births and preterm births among all births and spontaneous abortions among all pregnancies and the ratios of stillbirths, ectopic pregnancies and induced abortions per 100 live births. Further, we calculated positive predictive values (PPVs) and the sensitivity of PMs for identification of POs.

Results: We identified 94,261 POs among 3,075,744 women in 2005. The percentage of home births (1.2%) and preterm births (11.6%) agreed well with the data from GFSO (1.8% and 8.9% respectively). The percentage of spontaneous abortions in GePaRD (5.4%) was lower than expected from the literature (10–15%). The ratio of stillbirths (0.3/100 live births) and ectopic pregnancies (2/100 live births) were also similar to data from GFSO (0.36/100 and 1.85/100 respectively). The ratio of induced abortions was underestimated in GePaRD compared to the national data (4.1 vs. 18.1/100 live births). All considered PMs taken together had a PPV of 85.1%. The PPV and sensitivity of PMs varied across marker categories and for different POs.

Conclusions: Completeness of POs recorded in GePaRD varied by pregnancy outcome and should be considered in studies of drug safety in pregnancy.

334. Prenatal Exposure to Antidepressants and Language Competence at 3 Years of Age. Results from a Large Population Based Pregnancy Cohort in Norway

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Background: There is evidence that maternal SSRI treatment during pregnancy may cause adverse reproductive outcomes.

Objectives: To examine associations between mothers' use of SSRI in pregnancy and language competence in their children at age 3 years.

Methods: The Norwegian Mother and Child Cohort Study recruited pregnant women between 1999 and 2008. Maternal depression, use of SSRI (during one or

more than one trimester) and confounders were measured by self-reported questionnaires. Children's language competence was measured by maternal report on a validated language grammar scale and ranged from 'long complicated sentences' to 'not yet talking'. We used ordinal logistic regression with estimated standard errors allowing for clustering of multiple pregnancies. We have defined six different groups. Group (1) no depression and no use of SSRIs, (2) depression but not use of SSRIs, (3–4) SSRIs use (only one trimester) without and with depression and (5–6) SSRIs use (at least two trimesters) without and with depression. A woman was defined as depressive if she had a score of 2 or higher on SCL 5 measured either in weeks 7 or in week 30.

Results: Of 45,289 women with 51,779 pregnancies were included in this study. Women reported use of SSRI in 417 pregnancies (0.8%), of these 169 during more than one trimester. Of all children 0.2% were rated as not yet talking, 0.4% talked in one-word utterances, 3.3% in 2–3 –word phrases, 19% in fairly complete sentences and 77% talked in complicated sentences. Children whose mothers took no SSRI and did not report depression was reference group. Odds ratios were 1.4 (0.9–2.2) and 1.3 (0.9–2) for SSRI use in one trimester without and with reported depression, respectively. For SSRI use in at least two trimesters OR 2.3 (1.5–3.5) and 2.7 (1.6–4.5) were registered for the group without and with depression respectively. Measured depression without use of SSRI had an OR of 1.2 (1.1–1.3).

Conclusions: Maternal use of SSRI for extended pregnancy periods was associated with lower language competence in children at age 3 years independently of depression. Reported depression had minor effect.

335. Withdrawn by Author

336. Antimalarial Drug Use during Pregnancy and the Risk of Low Birth Weight (LBW): A Systematic Review

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Background: Untreated malaria increases the risk of low birth weight (LBW) during pregnancy but little is known on whether antimalarial use is also associated with an increased risk of LBW.

Objectives: This review aims to investigate the risk of LBW associated with antimalarial use during gestation.

Methods: We systematically searched PubMed, Embase, the Cochrane Infectious Group, and the reference lists of all relevant articles published in English or French from 1966 through 2012 for studies that reported associations between LBW and gestational exposure to antimalarials. Only comparative studies such as clinical trials and cohort studies were considered. LBW was defined as birth weight below 2500 g. Antimalarials considered were moslty sulfadoxine combined with pyrimethamine and chloroquine.

Results: Among the 39 studies that met inclusion criteria, 30 (77%) were randomized and non-randomized clinical trials and 9 (23%) were prospective and retrospective cohort studies. When compared to placebo, sulfadoxine combined with pyrimethamine use during pregnancy was shown to significantly decrease the risk of LBW (RR = 0.26; 95% CI = 0.14–0.47; RR = 0.35; 95% CI = 0.22–0.56; RR = 0.35; 95% CI = 0.2–0.59 RR = 0.5; 95% CI = 0.27–0.94; four studies). However, when compared to other antimalarials, sulfadoxine combined with pyrimethamine use during pregnancy significantly increased the risk of LBW (RR = 2.62; 95% CI = 1.29–5.39; one study). When compared to no exposure, quinine (RR = 1.4; 95% CI = 1.1–1.9; one study), and mefloquine (RR = 1.7; 95% CI = 1.1–1.8; one study) significantly increase the risk of LBW. Artemisinin and its derivatives significantly increases the risk of LBW when compared to the population-based risk of LBW (RR = 1.4; 95% CI = 1.76–1.11; one study). When compared to other antimalarials, chloroquine significantly increases the risk of LBW (RR = 5.39; 95% CI = 1.22–23.85; RR = 2.79; 95% CI = 1.32–5.96; RR = 1.4; 95% CI = 1.03–1.9; three studies).

Conclusions: Although many antimalarial use during pregnancy increase the risk of LBW, indication bias could not be rule out especially in regions where drug resistance is high.

337. Zidovudine Exposure during Pregnancy and Birth Outcomes: Data from the Antiretroviral Pregnancy Registry

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Background: Zidovudine (ZDV) is commonly used during pregnancy, but data on association between

prenatal ZDV exposure and birth outcomes are limited. The Antiretroviral Pregnancy Registry (APR) an international, voluntary, prospective cohort study monitors for early signals of teratogenicity associated with prenatal ARV use. Results of primary analyses reported by the APR for data through 31st January 2012 noted an overall birth defects rate of 2.9/100 live births (95% CI: 2.6, 3.2), not substantially different from that reported by the CDC's birth defects program (2.72/100 live births).

Objectives: To assess the effect of ZDV exposure during pregnancy on birth outcomes other than birth defects.

Methods: Using data on 13,537 prospectively reported HIV infected, singleton pregnancies from the APR, we estimated frequency of adverse birth outcomes, and odds ratios comparing those exposed to ZDV-containing regimen to those exposed to non-ZDV ARV regimen.

Results: Of 12,037 pregnancy outcomes with ZDV exposure, 11,562 (96.1%) were live births and 475 (3.9%) resulted in spontaneous/induced abortions or still births. Among live births 1,672 (16.1%) had low birth weight (LBW; < 2,500 g), 215 (2.1%) had very LBW (< 1,500 g), 1,372 (12.2%) were preterm (< 37 weeks), and 240 (2.1%) were very preterm (< 32 weeks). Of 1,500 outcomes with non-ZDV exposure, 1,269 (84.6%) were live births and 231 (15.4%) resulted in spontaneous/induced abortions or still births. Among live births 170 (14.7%) had LBW, 25 (2.2%) had very LBW, 170 (13.8%) were preterm, and 31 (2.5%) were very preterm. The odds ratios comparing exposure to ZDV-containing to non-ZDV ARV regimens, were, for spontaneous abortion 0.15 (95% CI: 0.12, 0.19); induced abortion 0.26 (95% CI: 0.20, 0.34); still birth 0.66 (95% CI: 0.43, 0.99); preterm births 0.87 (95% CI: 0.73, 1.03); and LBW 1.11 (95% CI: 0.94, 1.32).

Conclusions: No difference in the risk for non-defect-adverse birth outcomes was observed between ZDV and non-ZDV ARV exposure during pregnancy. We are investigating contributing factors for the adverse outcomes.

338. Health Beliefs, Attitudes and Knowledge of Expectant Mothers Regarding Medicine and Substance Use in Pregnancy: A Literature Review

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Background: Pregnant women are of special interest in terms of medicine and recreational substance use. The beliefs and attitudes of expectant mothers influence whether or not they will use medicines or substances and their conformation to healthy behaviours. It is therefore important to recognise and understand the common health beliefs, attitudes and knowledge in this population and to identify the gaps in the international literatures.

Objectives: To provide a narrative summary of the health beliefs, attitudes and knowledge of pregnant women about medicine and substance use.

Methods: A comprehensive search was performed using a combination of keywords related to the subject matter in PubMed, CINAHL Plus, EMBASE and International Pharmaceutical Abstracts from the inception of the databases to October 2012. An article was included if: (1) it was an original research which studied health beliefs, attitudes and knowledge and (2) it was written in English Language. Reference lists of included articles were also searched for relevant studies.

Results: Thirty-five articles met the inclusion criteria; 27 of these were quantitative while eight were qualitative studies. Although some of the articles studied more than one medicine or substance, 31 of the reports were on alcohol and tobacco; few articles studied prescription, over-the-counter and complementary and alternative medicines while only one article studied the attitudes of pregnant women to illicit drugs. In terms of alcohol and tobacco, participants demonstrated some common health beliefs, attitudes and knowledge such as risk to the mother and baby and that abstinence or reduction in intake were the safe options. In the case of medicines, the studies revealed that women's health beliefs and attitudes were more of being restrictive and not to use medicines without consulting the doctor. In addition, the participants had positive attitudes and health beliefs about the safety and efficacy of complementary and alternative medicines.

Conclusions: Findings from this review provide background information which is useful for further research and possibly development of intervention strategies.

339. Complementary and Alternative Medicine Use in the First Trimester: Safety Perceptions and Preference of Pregnant Women

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Background: The use of complementary and alternative medicines (CAM) to support health in pregnancy is on the increase worldwide. However, most of the therapies used during pregnancy have not been subjected to rigorous clinical trials to demonstrate their safety. The remarkably limited knowledge regarding the effects of these modalities on the foetus drives the need to carry out studies such as ours.

Objectives: To assess the use of CAM during the first trimester, the perceptions of the women on the safety of CAM and their preferences for CAM.

Methods: As part of an on-going longitudinal study in two London teaching hospitals, expectant mothers who attended hospital for their 11–13 week scan were interviewed using a structured questionnaire to ascertain their CAM use during the first trimester; perception of CAM safety in comparison to conventional medicines; and preference for CAM in treating medical conditions. The inclusion criteria were women above 16 years who could communicate in English. The study was approved by the local ethics committee.

Results: Six hundred and seven women were approached of which 560 participated in the study; their age was 31.9 ± 5.1 years. 40.5% of them had used at least one form of CAM in the first trimester. When asked to compare the safety of CAM to conventional medicines, 12.3% felt CAM is safer, 27% thought both CAM and conventional medicines are equally safe, 15.9% felt CAM is less safe while 44.8% felt they did not know about the safety of CAM compared to conventional medicines. Furthermore, in treating a new medical condition, 17.1% of the participants would choose CAM rather than conventional medicines as their most preferred therapy.

Conclusions: These findings demonstrate that a considerable proportion of the women (about 40%) had used CAM in early pregnancy. Although almost half of the participants did not know about the safety of CAM compared to conventional medicines, nearly a fifth would want CAM as a first choice therapy. Therefore, clinicians need to integrate questions about this seemingly common practice into their assessments. Further research is also necessary to better understand CAM use in pregnancy.

340. Exposure to Inhalation Zanamivir during Pregnancy and Pregnancy Outcomes

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Background: Use of neuraminidase inhibitors (NIs) to treat influenza in pregnant women benefits the mother and helps maintain the pregnancy. However, there is little data on the effect of NIs on birth outcomes.

Objectives: To assess the effect of one NI, zanamivir, on pregnancy outcomes.

Methods: The Health Improvement Network (THIN) provided data from UK GPs for 144 women who were prescribed zanamivir during pregnancy and 144 age- and date-matched comparators. The two groups were assessed for pretreatment baseline characteristics, treatment-emergent diagnoses in the mother, pregnancy outcomes and congenital malformations diagnosed in the offspring within 28 days of birth.

Results: Treatment and comparator groups were similar in baseline medical status. The majority (100/144) of zanamivir prescriptions occurred during 2nd and 3rd trimesters. Groups were similar in reported smoking during pregnancy but more women in the comparator group reported alcohol use. The zanamivir group had more diagnoses compatible with influenza-like illness (ILI) and were more often prescribed antibiotics, analgesics and medicines for respiratory and gastrointestinal symptoms. Pregnancy outcomes other than live birth were not found in the GP record, possibly due in part to the cohort entry having occurred late in most pregnancies. There was no evidence for a difference between zanamivir and comparator in the risk of any treatment-emergent diagnosis. Congenital anomalies occurred in similar proportions, except that the infants born to zanamivir-exposed women had substantially fewer diagnoses from the cluster of cardiac defects

consisting of atrial and ventricular septal defects and patent ductus arteriosus (one zanamivir, six comparators).

Conclusions: Because of the indication, zanamivir-exposed pregnant women have a wide range of symptoms of and treatments for ILI that complicate comparisons with untreated women. There was here no indication of increased risk to the mother or the infant following exposure.

341. Dispensing of Potential Teratogenic Drugs before and during Pregnancy: A Population Based Study

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Background: Prescribing potential teratogenic drugs shortly before conception or during pregnancy is strongly discouraged or contra-indicated. A careful weighing of expected benefits vs. possible harm is always important especially when unborn children are involved.

Objectives: To study the dispensing of potential teratogenic drugs during a three month period before as well as during pregnancy among Dutch women between 2000 and 2007.

Methods: The PHARMO database network, which covers 20% of the Dutch population and includes information on drug dispensing was linked to the Netherlands Perinatal Registry (PRN), which includes perinatal medical case records of neonates with gestational age > 16 weeks. The birth cohort comprised of 203,972 pregnancies between 2000 and 2007. We considered drugs with either a Swedish FASS 'D' classification, an Australian ADEC or American FDA 'D' or 'X' classification as potential teratogenic. The dispensing of 202 potential teratogenic drugs was studied within 3 month period before and during pregnancy (first, second and third trimester).

Results: In 10% of the pregnancies a potential teratogenic drug was dispensed within 3 months before or during pregnancy. In 7% of the pregnancies these drugs were dispensed within 3 months before pregnancy; in respectively the first, second and last trimester, percentages lowered to 4, 2 and 2%. Paroxetine was the most frequently dispensed potential teratogenic drug (14%); moreover, dispensing in 3 months

before or during pregnancy was still present with 1.2% of the pregnancies. Twenty-four percentage of the studied dispensings concerned antiinfectives, mainly doxycycline or fluconazole (3.7% of pregnancies). The anticonvulsants carbamazepine and valproic acid covered 6% of all dispensings (0.3% of pregnancies) and statins 1.3% (0.1% of pregnancies).

Conclusions: The prescribing of potentially teratogenic drugs deserves attention since in at least 10% of the pregnancies these drugs were dispensed to women in the 3 month period before or during pregnancy. Although the benefits of disease control during pregnancy should be weighed against the risks, this number is still high, particularly for depression and epilepsy therapy.

342. Drug Dispensing before and during Pregnancy and Congenital Malformations: A Population Based Study

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Background: Drugs with a teratogenic potential can cause congenital malformations. The actual teratogenic effects are however only established for a small proportion of drugs.

Objectives: To study the association of dispensing potential teratogenic drugs during a 3 month period before as well as during pregnancy on the occurrence of congenital malformations.

Methods: We performed a population based case-control study in the Netherlands using a linkage of the PHARMO database network and the Netherlands Perinatal Registry. The birth cohort comprised of 203,972 pregnancies between 2000 and 2007. 182,505 pregnancies were selected based on at least one dispensing of any drug within the year before or during pregnancy. Drugs with either a Swedish FASS 'D', an Australian ADEC or American FDA 'D' or 'X' classification were considered potential teratogenic (n = 202). We calculated odds ratios (ORs) and 95% confidence intervals (CI) for associations between dispensing of potential teratogens 3 months before and during pregnancy (first, second, third trimester) on the occurrence of congenital malformations. The OR is adjusted for maternal age, birth year, gender of neonate, gestational age on delivery and dispensing of other potential teratogens.

Results: We identified 5,881 neonates with congenital malformations (cases) and 180,545 healthy neonates (controls). Cases were more likely to have a dispensing within 3 months before or during pregnancy than controls (OR 1.08; 95% CI: 1–1.17), especially for malformations on the nervous- (OR 1.29, 95% CI: 1.03–1.61) and musculoskeletal system (OR 1.31; 95% CI: 1.09–1.57). We found associations between dispensing in the 1st trimester and urogenital malformations (OR 1.68, 95% CI: 1.31–2.15) and between dispensing 3 months before pregnancy and malformation on the nervous system (OR 1.36, 95% CI: 1.03–1.80). Paroxetine was most frequently dispensed, i.e. in 1.8% of cases and 1.6% of the controls.

Conclusions: Dispensing of potential teratogenic drugs within a 3 month period before or during pregnancy is associated with an increased risk on congenital malformations, especially malformations on the nervous- and musculoskeletal system.

343. Are Women with Major Depression in Pregnancy Identifiable in Population Health Data?

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Background: Data linkage of administrative data has been a rich resource for Australian researchers for a number of years. As the data were not originally collected for research purposes, the prevalence of specific morbid conditions may differ across the datasets.

Objectives: This study aimed to investigate the differences in ascertainment of major depression in pregnant women, a common condition in pregnancy, using three population-based datasets: pharmaceutical claims, hospital admissions, and midwives' records of birth.

Methods: The study population included all women giving birth in Western Australia during 2002–2005 with a birth record in the Midwives' Notification System (MNS) and a hospital admission record in the Hospital Morbidity Data System (HMDS): N = 96,698. Records were linked to the Pharmaceutical Benefits Scheme (PBS). The women with depression during their pregnancy were ascertained in two ways: women with dispensing records relating to dispensed antidepressant medicines with an WHO ATC code to the 3rd level, pharmacological subgroup, 'N06A Antidepressants'; and, women with any hospital admission during pregnancy, including the birth admission, if a comorbidity was recorded relating to depression.

Results: There were a total of 7,495 pregnancies identified by either set of records. Using data linkage, we determined that these records represented 6,596 individual pregnancies. Only 899 pregnancies were found in both groups (13.6% of all cases). 80% of women dispensed an antidepressant did not have depression recorded as a comorbidity on their hospital records. A simple capture-recapture calculation suggests the prevalence of depression in this population of pregnant women to be around 16%.

Conclusions: No single data source is likely to provide a complete health profile for an individual. For women with depression in pregnancy and dispensed antidepressants, the hospital admission data do not adequately capture all cases. The very large proportion of women dispensed an antidepressant but without depression recorded on their hospital records is of concern. This may be impacting upon neonatal care for both mother and infant.

344. Identification of Pregnancy by a Coding Algorithm in a U.S. Administrative Healthcare Database

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Background: The development of a coding algorithm to accurately identify pregnancies in healthcare claims databases is useful for pharmacoepidemiology pregnancy research.

Objectives: To develop and evaluate a coding algorithm to identify pregnancies in a large U.S. claims database.

Methods: Women aged 18–44 years with at least 12 months of continuous enrollment during 2008–2009 were selected from a large U.S. commercially-insured claims database, and a coding algorithm (consisting of 1,379 ICD-9 diagnosis codes) applied to identify pregnancies. Annual crude, age-specific and age-adjusted pregnancy rates, standardized to the 2010 U.S. census population, were estimated and compared with published rates for 2008 (CDC/NCHS, 2012). Clinical assessments of two physicians who independently reviewed the electronic patient claims history of 100 randomly selected potentially pregnant women, were used as a 'gold standard' to calculate the positive predictive value (PPV) of the algorithm. The results of the medical reviews were subsequently used to refine the algorithm.

Results: In 2009, we identified 687,832 pregnancies among 6,755,582 eligible women. Crude and age-standardized pregnancy rates were estimated at 101.8 and 105.5 per 1,000 women, respectively. Pregnancy rates per 1,000 women were estimated by age groups 18–19 years (40), 20–24 years (73.5), 25–29 years (176.7), 30–34 years (183.6), 35–39 years (96.2) and 40–44 years (28.3), respectively. Similar crude, age-standardized and age-specific pregnancy rates were observed for 2008. The PPV of the algorithm was 0.93. Annual pregnancy rates for the 25–29 and 30–34 year age groups were similar to CDC-published rates, but were lower for females < 25 years of age and higher for those aged ≥ 35 years.

Conclusions: Overall crude pregnancy rates were consistent with published data. Differences seen with age-specific pregnancy rates likely reflected characteristics of the underlying population of the claims database. The high PPV of the coding algorithm in identifying pregnancies makes it useful for pregnancy-related pharmacoepidemiology studies using this claims database.

345. Relation between the Prevalence of Attention Deficit and Hyperactivity Disorders (ADHD) and Autism Spectrum Disorders (ASD), and Maternal Depression and Antidepressant Use during Pregnancy

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Background: Although the impact of gestational use of antidepressant on children's overall cognitive development remains controversial, a recent study has shown an association between antidepressant use during pregnancy and the risk of ASD. Given that ADHD and ASD are two entities sharing similar features, this finding could potentially have great implications.

Objectives: To compare annual trends in the prevalence of maternal depression and antidepressant use during pregnancy, ADHD and ASD over time.

Methods: This study was performed within the Quebec Pregnancy Registry which includes data on all pregnancies/children in Quebec from 1998 to 2009. Women are followed from the date of entry in the Registry (beginning of pregnancy) until the end of pregnancy; children are followed from birth until 12/31/2009. A child was defined as having ADHD or ASD if he had 1 diagnosis made by a psychiatrist or developmental pediatrician, or at least two diagnoses made by other physicians. Maternal depression was identified using validated ICD9/ICD10 codes, and exposure to antide-

pressants during pregnancy was defined as having filled at least one prescription between the first day and the end of pregnancy.

Results: Of 157,802 pregnancies and 159,067 children comprised the study population. Between 1998 and 2009, diagnosed maternal depression during pregnancy significantly increased (p = 0.04) from 48.4/1000 pregnancies in 1998 to 54/1000 pregnancies in 2009. Gestational use of antidepressants more than doubled during the same period: 21.8/1000 pregnancies in 1998 to 43/1000 pregnancies in 2009 (p = 0.01). In parallel, the prevalence of diagnosed ADHD increased from 0.53/1000 livebirths in 1998 to 15.8/1000 livebirths in 2009 (p = 0.01), and a similar trend was observed for ASD (0.12/1000 births in 1999 and 1.52/1000 births in 2009, p = 0.02).

Conclusions: Although the increase in the annual prevalence of maternal depression during pregnancy, ADHD and ASD could be partly explained by increased detection, the increase in children with ADHD and ASD is higher than expected and could be explained by an epigenetic phenomenon.

346. Adverse Developmental Events Reported to FDA in Association with Maternal Use of Topiramate in Pregnancy

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Background: The use of antiepileptic drug topiramate in pregnancy has been associated with increase in the prevalence of major malformations in recent studies based on pregnancy registries.

Objectives: We reviewed the adverse developmental events reported to the US FDA in cases of topiramate exposure during pregnancy to further explore topiramate association to developmental abnormalities.

Methods: In this retrospective observational study, all MedWatch reports of adverse developmental events (AE) following prenatal exposures to topiramate submitted to FDA's Adverse Events Reporting System (AERS) from 1997 through 2012 were reviewed to determine the adverse event profile and reporting frequency. Other factors, i.e., concomitant medication, concurrent maternal disease, and genetic background were taken into account where available.

Results: After excluding duplicate reports, a total of 108 cases of adverse developmental events associated with topiramate use in pregnancy) were retrieved from FDA's AERS. In over 90% of these cases topiramate was administered as a monotherapy for treatment of maternal epilepsy; the prevailing dose range was up to

200 mg/day and in about 90% of cases, the exposure involved the 1st trimester of pregnancy. Congenital malformations (CM) were almost exclusively the reason for AE reporting; other AEs were reported in < 10% of the cases. The reported malformations displayed a distinct pattern, craniofacial defects being the most frequent. The reporting frequency of oral clefts dominated over all other CM types, accounting for over 60% of all malformations reported. This malformation profile is consistent with that seen in experimental animals prenatally treated with topiramate.

Conclusions: The pattern of the reported CM and the concordance with the animal data indicate that an association with maternal exposure to topiramate is plausible. This conclusion is further supported by the lack of concomitant drug exposure (since topiramate was almost exclusively used as a monotherapy), as well as by the timing of topiramate exposure, involving the period of major organogenesis, most susceptible to induction of malformations.

347. Prenatal Antidepressant Exposure and Neurodevelopmental Outcomes in a Cohort of Typically-Developing Children

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Background: Depression is common in pregnant women, and 7–13% of women take an antidepressant (AD) during pregnancy. Few studies have examined neurodevelopment in older children, and no previous studies have compared neuroanatomy of AD exposed and unexposed children.

Objectives: To compare the neuroanatomy and cognition of AD exposed and unexposed children. Secondarily, to compare rates of maternal substance use and child behavioral outcomes.

Methods: The PING study is a cross-sectional multisite study of neurotypical children. This analysis studied a subset of the PING cohort that included 770 children aged 4–15, for whom a maternal report of pregnancy exposures was obtained. Neuroanatomy was measured using FreeSurfer on MP-RAGE scans acquired for each participant. Regions of interest were determined prior to data analysis based on literature review. Neurocognition was assessed using a battery designed to measure attention executive function vocabulary and working memory. Family demographics, substance use, child characteristics and behavioral outcomes were assessed by questionnaire. Separate multivariable linear regression models were fit for each outcome variable. Predictors in each model included sex, age, PAE, and the interaction of age and AD exposure. We also visually compared the slopes for exposure groups, and performed bivariate analyses to compare demographics, other exposures, and behavioral outcomes.

Results: Of 18 children with PAE were identified. Mothers who reported AD use had higher rates of smoking and alcohol use. AD significantly modified the associations between age and attention and executive function, but not other tasks. A borderline significant interaction was noted for the caudate nucleus; comparisons of brain structures suggest differences in several cortical areas and thalamus. AD-exposed children received more special services in school but did not differ on rates of ADHD or LD diagnosis.

Conclusions: These results suggest differences in neurodevelopment in AD-exposed children. The small sample size of exposed children and potential for residual confounding mean that results must be interpreted with caution.

348. First Trimester Fluoxetine Use and Major Malformations: A Meta-Analysis of Epidemiological Studies

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Background: Major malformations in newborns of mothers exposed to fluoxetine during the first trimester of pregnancy have been reported, but with inconsistent findings.

Objectives: To assess the potential association between the first trimester fluoxetine exposure and the risk of major malformations, with a particular focus on major cardiovascular defects.

Methods: A systematic literature search in PubMed and EMBASE was conducted for epidemiological studies published through March 1, 2011. Relevant data were extracted using predefined criteria, and original study authors were contacted for additional data when necessary. Random effect and fixed effect summary estimates were calculated and sensitivity analyses were performed as appropriate.

Results: A total of 17 epidemiological studies (15 cohort studies and two case-control studies) were included in the analysis. The primary analysis, consisting of the 15 cohort studies, found that, compared to women unexposed to fluoxetine, women exposed to fluoxetine during the first trimester of pregnancy had an odds ratio (OR) of 1.24 (95% confidence interval: 1.08–1.44) for the risk of major malformations in general, and an OR of 1.60 (1.27–2.01) for the risk of cardiovascular defects in particular. In a sensitivity analysis where the 15 cohort and two case-control studies were included, ORs of 1.17 (1.03–1.33) and 1.42 (1.12–1.79) were noted for major malformations and cardiovascular defects, respectively. Further analysis on the outcome of noncardiovascular malformations indicated an OR of 1.10 (0.91–1.32).

Conclusions: A correlation between the first trimester fluoxetine exposure and the potential risk of cardiovascular defects is suggested; however, causality has not been established. Important confounding factors such as depression during pregnancy, alcohol use and smoking were not controlled in the analysis and their impact could not be excluded in the interpretation of results.

349. Use of Antiepileptic Drugs and the Risk of Severe Cutaneous Adverse Drug Reactions in Elderly Patients: A Nationwide Case-Control Study

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Background: Severe Cutaneous Adverse Drug Reactions (SCADRs), such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening, drug-induced cutaneous reactions.

Objectives: The purpose of this study was to evaluate the risk of SCADRs associated with antiepileptic drugs use in the elderly patients.

Methods: We used the Korean Health Insurance Review and Assessment Service (HIRA) claims database from January 1, 2005 to June 30, 2006. We identified case patients aged 65 years or more who had an inpatient newly diagnosis of erythema multiforme (EM, the ICD-10 code, L51) from the primary and secondary discharge diagnoses between April 1, 2005, and June 30, 2006. The index date was defined as the first hospital admission date for EM. Each case was

matched to four controls for gender, age (± 5 years), and index day (± 5 days). The use of carbamazepine, gabapentin, lamotrigine, topiramate, phenobarbital, phenytoin and valproate during the 60 days before the index date of diagnosis of EM was compared. The conditional logistic regression model was used to calculate odds ratios (ORs). Comorbidities and concomitant medications could induce SCADRs were adjusted.

Results: Our study included 286 cases with incident EM and 1,144 matched controls. The proportion of patients who diagnosis SJS or TEN was 134 cases (46.9%). Antiepileptic drugs were prescribed to 25 case patients and 30 control patients during the 60 days before the index date of diagnosis of EM. All antiepileptic drugs (adjusted ORs [aOR], 3.42; 95% CI: 1.75–6.63) and carbamazepine (aOR, 10.39; 95% CI: 2.64–40.86) increased the risk for the incident SCADRs. In the more severe patients who diagnosis SJS (L51.1) or TEN (L51.2), antiepileptic drugs increased higher risk of the incident SCADRs (aOR, 7.48; 95% CI: 2.19–25.52).

Conclusions: Our study suggests that antiepileptic drugs increase the risk for SCADRs in the Korean elderly patients. Physicians should be cautious about prescribing antiepileptic drugs. Further research will be needed for unexpected risk factors in the elderly.

350. Comparative Risks of Severe Cutaneous Reactions Associated with Individual Antiepileptic Drugs Following FDA Black Box Warning

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Background: Despite a lack of evidence to support efficacy and FDA's 'black box' warning of severe cutaneous reactions (Steven Johnson Syndrome and toxic epidermal necrolysis) with lamotrigine use, prescribing rates of lamotrigine to treat epilepsy remain high. Some studies with small sample sizes suggest that other antiepileptic drugs (AEDS) may be safer, but the comparative effectiveness associated with individual AEDS remains unclear.

Objectives: To evaluate the relative likelihood of severe cutaneous reactions associated with individual AEDS in children (aged 2–18 years) and adults (aged 19+) with epilepsy.

Methods: This retrospective cohort study analyzed patients in a large nationally representative administrative claims database between 2006 and 2011. The sample consisted of Medicaid, Medicare, and Commercial patients continuously enrolled with both medical and

pharmacy benefits for 6-months prior to the index fill for AED. Patients were included if they had a diagnosis of epilepsy (ICD-9-CM 345.X) and had no prior AEDS fills (new users). Logistic regression was used to follow eligible patients up to six months after AED initiation to assess the relative odds of adverse events.

Results: The study population included 1,803,871 new users of AEDS. Children comprised 7.9% (N = 142,874, female = 50.7%, age = 12.4 [± 4.7]) and adults 92.1% (N = 1,660,997, female = 64.6%, age = 52.8 [± 17.7]). Compared to adults, children were significantly more likely to have severe cutaneous reactions (OR = 1.20, 95% CI: 1.15–1.26, p < 0.0001) after controlling for potential confounders. Findings reveal that patients of all ages taking lamotrigine were significantly more likely to have severe cutaneous reactions compared to most other individual AEDS; e.g., lamotrigine vs. valproate (OR = 1.50, 95% CI: 1.40–1.60, p < 0.0001). Patients prescribed phenytoin were more likely to have severe cutaneous reactions, but results were not significant (OR = 1.09, 95% CI: 1–1.18, p = 0.0545).

Conclusions: This study provides new information about the comparative risks of individual AEDS that can be used to guide optimal prescribing practices for patients with epilepsy.

351. Comparative Effectiveness of Antidepressants in Reducing Risk of Dementia in Older Adults with Depression

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Background: Several studies have shown strong association between late-life depression and subsequent development of dementia. However, whether antidepressants reduces the risk of dementia has not been widely studied.

Objectives: To examine comparative effectiveness of antidepressants classes on risk of dementia in elderly with depression.

Methods: Retrospective cohort study using GE Centricity EMR data was conducted. The study population consisted of older adults with depression (60 years and old) who initiated antidepressant treatment from January 1, 1996 and October 31, 2008. Patients having diagnosis of dementia or taking anti-dementia drug before starting antidepressant medication were excluded from the study. The inclusion in the cohort required patients to have at least three refills of the antidepressant medication and one additional office

visit within 6-months from the start of the medication. The patients were followed for three years to examine incidence of dementia. Older adults were grouped into the following most frequently prescribed antidepressants class: Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs), phenylpiperazine-derivative antidepressant and tetracylics. Multivariate Survival Model was used to examine relationships between different antidepressant classes and risk of dementia.

Results: Of 16,320 new users of antidepressant medication was obtained after applying inclusion and exclusion criteria; 12,870 (78.86%) patients were SSRI users, 2,171 (13.22%) SNRI users, 829 (5.02%) modified cyclic users and 450 (2.85%) tetracyclics users. There were (6.15%) new cases of dementia in the study cohort. The multivariate survival analysis found no significant difference in risk of dementia SNRI (HR 1.12 [95% CI: 0.92–1.35]), Modified Cyclics (HR 0.79 [0.57–1.10]) and Tetracyclics (HR 1.15 [0.85–1.55]) across different antidepressant classes after controlling for potential confounders.

Conclusions: No significant difference was found in risk of dementia across different antidepressant classes. Large-scale prospective studies are needed to examine cognitive effects of antidepressant treatment in elderly with depression.

352. Angiotensin II Receptor Blockers and the Risk of Dementia

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Background: Drugs targeting the renin–angiotensin system may protect against dementia. There is some evidence that angiotension-II receptor blockers (ARBs) may have a greater protective effect than angiotensin-converting enzyme inhibitors (ACEis).

Objectives: To evaluate if individuals exposed to ARBs have a reduced risk of dementia compared with those exposed to ACEis.

Methods: A study was conducted in a cohort of patients started on ARBs or ACEis between 1995 and 2010 in the UK Clinical Practice Research Datalink. The study outcome was incident diagnosis of dementia. Cox proportional hazards was used to compare the risk of dementia in patients on ARBs with those

on ACEIs, with age as the timescale and adjusted for potential confounding factors (e.g. history of heart failure and diabetes). In the primary analysis, the follow-up time started at 1 year after index date (first prescription date for ACEi/ARB), when the drug is expected to exert its pharmacological effect, and ended at the earliest of these dates: diagnosis of dementia, switch in ACEi/ARB treatment, death or exit from the cohort. Analysis of the effect of ARB exposure on dementia risk in the initial 12-month period after the index date was also conducted.

Results: A total of 617,569 patients with 2.4 million person-years of follow-up were included in the study. 58,345 patients were exposed to ARBs with a total follow-up of 260,000 person-years. There was a higher percentage of patients with diabetes and heart failure in the ARB group vs. the ACEi group. In the primary analysis (follow-up started at 1 year after index date), the hazard ratio(HR) of dementia in patients exposed to ARB was 0.92 [0.85–1] (p = 0.040). An analysis restricted to the first 12 months after the index date showed a larger effect on dementia risk (HR 0.61 [0.51–0.73]). The 'survival' curves were furthest apart at the start of treatment and tend to come together.

Conclusions: The observed association between ARB and dementia risk is likely to be due to selection bias or unmeasured confounding and there is no true treatment effect. A possible explanation for the curves coming together is a large effect at treatment start followed by depletion of susceptibles, but this seems unlikely.

353. Antidepressants and the Risk of Fractures

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Background: Use of antidepressants (AD) has been associated with a higher risk of fractures due to dizziness caused by cardiovascular or central nervous side effects. In most studies, AD use has been compared to non-use. Data directly comparing the different AD classes is scarce.

Objectives: To compare the risk of fractures associated with serotonin reuptake inhibitors (SSRI) or other AD (oAD) in comparison to tricyclic AD (TCA) and to assess the effect of dementia on that risk.

Methods: We performed a nested case control study based on data from 3 of the 4 statutory health insurance providers (SHI) included in the German Pharmacoepidemiological Research Database (GePaRD), with about 7 million insurants throughout Germany. All insurants older than 65 years who had at least one AD dispensation during the study period from January 2005 to December 2009 were included. Fracture cases were defined as hospitalizations with a main discharge diagnosis of a pelvis, femur, humerus, tibia or fibula fracture or a syncope with a secondary diagnosis of one of these fractures. To each case up to 10 controls were matched on age, sex, calendar time, and SHI. Confounder adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to compare the risk of fractures between current users of TCA (reference), SSRI and oAD using a binary logistic regression model.

Results: During the study period 5,016 fracture cases could be observed in a cohort of 136,829 AD users. Current users of SSRI had a 1.49 (95% CI: 1.37–1.63) higher risk of fractures than current users of TCA. No increased risk was observed in current users of oAD (OR: 1.02, 95% CI: 0.90–1.16). Higher ORs were observed in the subgroup of patients without dementia with 1.67 (1.49–1.87) for SSRI and 1.18 (1.03–1.35) for oAD, respectively.

Conclusions: This study suggests that current use of TCA is associated with a 50% higher risk of fractures than current use of SSRI, whereas no increased risk was observed for current use of oAD.

354. A Case-Crossover Study of Age-, Gender-, and Dose-Specific Effects of Non-Benzodiazepine Hypnotics on the Occurrence of Hip Fracture in Nursing Home Residents

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Background: Psychomotor harms associated with non-benzodiazepine hypnotics (e.g., zolpidem) may be worse with advanced age, among women, older persons, and at higher doses.

Objectives: To estimate age-, gender-, and dose-specific effects of non-benzodiazepine hypnotics on the rate of hip fracture among nursing home residents.

Methods: This case-crossover study using Medicare Parts A and D data and the Minimum Data Set (2007–2008) included 691 women and 179 men with hip fracture sampled from all US long-stay residents. We estimated relative rates (RR) and 95% confidence intervals (CI) from conditional logistic regression models for non-benzodiazepine hypnotics (vs. non-use) comparing 0–29 days before hip fracture (hazard

period) with 60–89 and 120–149 days before hip fracture (control periods). We stratified analyses by age, gender, and dose.

Results: During 2007–2008, 1,845,065 individuals met our definition of being a long-stay nursing home resident (100 consecutive days in a facility) with Medicare Part D coverage. Of these, 208,849 (11.3%) had at least one dispensing of eszopiclone, zaleplon, or zolpidem for a total of 1,320,223 dispensings of these drugs. Twenty-eight percent of residents used high doses. The average RR of hip fracture was 1.7 (CI 1.5–1.9) for any use and 1.9 (CI 1.6–2.4) for new users. The RR was 1.7 times higher for age 90 years or older vs. < 70 years (2.2 vs. 1.3); however, the CIs overlapped. No differences in the effect of the hypnotics on risk of hip fracture were evident by gender. The risk of hip fracture was elevated among residents dispensed high-dose vs. low-dose hypnotics (RR 1.9 vs. 1.6 overall, with larger subclass differences), but some of the differences were ascribable to chance.

Conclusions: Use of non-benzodiazepine hypnotics is common in the nursing home. Older residents and those prescribed higher doses of hypnotic drugs may be more vulnerable to the risk of hip fracture. Non-benzodiazepine hypnotic drugs should be used cautiously in these residents. No differences by gender were evident.

355. Impact of the Type of Drug Insurance Plan on Adherence and Cost of Antihypertensive Agents

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Background: The impact of the type of drug plan on adherence to and cost of antihypertensive agents within the context of the Quebec universal drug insurance program is not known.

Objectives: To compare patient's adherence to and cost of antihypertensive agents between adult patients with public and private drug insurance.

Methods: A matched retrospective cohort was reconstructed from the linkage of administrative databases from Quebec, Canada. The cohort included 186 privately and 1,747 publicly-insured patients aged 18–64 years who filled at least one prescription for an antihypertensive agent between March 2008 and May 2010. Adherence was measured with the proportion of days covered (PDC) over one year. Cost of antihypertensives included the cost of the medication, the mark-up and the dispensing fees. Linear regression models were used to estimate the adjusted mean difference of the PDC and the monthly cost per patient for antihypertensive therapy between the two groups.

Results: In the cohort, more than 70% of patients were aged 50–64 years, 43% were male, more than 90% were prevalent users of antihypertensive agents, and 90% of the publicly-insured patients used only one hypertensive agent (monotherapy), while it was 72% among privately-insured patients. In privately-insured patients, the mean PDC for an antihypertensive agent prescribed in monotherapy was 90.3%, while it was 94% for publicly-insured patients, and the adjusted mean difference was −1% (95% CI: −4; 3). Corresponding figures were 92.9%, 80.7%, and 15% (95% CI: 7; 24) when two antihypertensive agents were used by the patient (polytherapy). The average monthly cost per patient for antihypertensive agents was $41.52 in the private and $32.21 in the public group, and the adjusted mean difference was $10.16 (95% CI: 7.40; 12.92).

Conclusions: The cost of antihypertensive agents was higher for patients with private drug insurance, although adherence was high and similar between the two groups. Regulation of dispensing fees on the public side and the high percentage of prevalent users in both groups may explain the results.

356. Cost-Utility Analysis of Various Chemotherapy Regimens among Elderly Ovarian Cancer Patients: A Longitudinal Cohort Study

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Background: Most economic evaluations for chemotherapies in ovarian cancer patients have been carried out using hypothetical cohorts but evidence integrating real world survival, cost, and utility data is limited.

Objectives: To compare the costs and quality adjusted life years (QALYs) gained from various chemotherapy regimens among ovarian cancer patients using a cost-utility analysis.

Methods: A propensity score matched cohort of 6,856 (65 years and older) ovarian cancer patients, from the Surveillance, Epidemiology, and End Results (SEER)-

Medicare claims data, diagnosed from 1991 to 2005 were included. Chemotherapy treatments (i.e. no chemotherapy; platinum-based only; platinum plus taxane and other non-platinum based regimens) were identified in the first 6 months after diagnosis. Patients were followed until death or the end of study period (December 2006). Effectiveness was measured in QALYs by adjusting the overall survival benefit with phase and disease specific utilities obtained from the literature. Total direct health care costs were measured using a payer's perspective and were adjusted for inflation as well as geographic differences in costs. Costs are presented as 2009 US $ with 3% annual discounting applied to both costs and QALYs. Methodological and statistical uncertainties were accounted for by including alternate scenarios (for utility values) and a net monetary benefit approach, respectively. Incremental cost effectiveness ratios (ICERs) were calculated and stratified by various tumor stages and age groups.

Results: Compared to the no chemotherapy group, ICER in the platinum-based only group was $60,084/QALY in the base case, while other non-platinum and platinum plus taxane groups were dominated. Similar results were found across various tumor stages and age groups. However, for patients 85 years and older platinum plus taxane group was not dominated by the platinum-based only group, with an ICER of $133,892/QALY.

Conclusions: Following ovarian cancer patients using real world longitudinal claims data and adjusting for quality of life, we found that treatment with platinum based only regimen was the most cost-effective treatment.

357. Mental Disorder Treatment, Healthcare Costs and Utilizations for US Veterans

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Background: Mental disorder prevalence is estimated at 19–44% among US veterans returning from Iraq or Afghanistan. Most do not seek treatment, impacting healthcare costs and utilization.

Objectives: Examine treatment, clinical and economic burden of mental disorder on U.S. veterans.

Methods: Mental disorder patients were selected from US Veterans Health Administration Data (0/01/06–05/31/12), including mood, attention deficit hyperactivity, panic, post-traumatic stress (PTSD), obsessive-compulsive, generalized anxiety and personality disorders, depression, anxiety, suicide, and intentional injuries. The first diagnosis date was the index date. Patients had ≥ 12 months continuous health plan benefits pre- and post-index date. Comorbidities were calculated for 12 months baseline. Healthcare utilization and costs were assessed for 12 months follow-up. Top ten treatments were examined for 60 days post-index date. Patients with PTSD as the index diagnosis were also examined. Descriptive statistics were calculated as means±standard deviation (SD) and percentages to measure treatment, costs and utilization.

Results: Among mental disorder patients (n = 1,644,214), depression (48.60%), mood disorder (46.56%), intentional injuries (21.57%), anxiety (21.4%0) and PTSD (17.65%) were most prevalent. Common baseline comorbidities were unspecified essential hypertension (21.07%), diabetes (12.54%) and hyperlipidemia (6.92%). 60 days post-index diagnosis, 38.88% were prescribed antidepressants and 15.99% anticholinergics. Simvastatin (20.09%), lisinopril (15.36%), omeprazole (14.49%), citalopram hydrobromide (14.26%) and hydrochlorothiazide (8.47%) were most often prescribed. In follow-up, 18.9% had at least one inpatient and 27.5% at least one emergency room (ER) visit. Costs were $16,007 (SD = $42,163) for total, $6,893 (SD = $36,727) for inpatient, $312 (SD = $1,085) for ER, $7,249 (SD = $11,523) for physician office and $7,820 (SD = $12,262) for outpatient visit costs.

Conclusions: Almost half the patients suffered from depression and mood disorders. Antidepressants were most often prescribed 60 days post-diagnosis. Mental disorder was linked to high healthcare utilization, leading to high costs for the healthcare system.

358. Final Results from the Multicenter COMPACT Study of Complications in Patients with Sickle Cell Disease (SCD) and Utilization of Iron Chelation Therapy: A Retrospective Medical Records Review

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Background: Lifespans of SCD patients (pts) are increasing; hence, they encounter multiple clinical complications (CCs). Early detection and appropriate comprehensive care may prevent or delay onset of CCs.

Objectives: To describe the SCD CC rates, blood transfusion patterns, iron chelation therapy (ICT) use, and associated resource utilization in SCD pts ≥ 16 years old.

Methods: Medical records of 254 SCD pts ≥ 16 were retrospectively reviewed between 08/2011 and 07/2012 at three US tertiary care centers. The observation period spanned pt's first visit after age 16 until the earliest of death, loss to follow-up, or last pt record. Three cohorts of pts were defined based on cumulative units of blood transfused and history of ICT: < 15 units of blood and no ICT (Cohort 1 [C1]), ≥ 15 units of blood and no ICT (Cohort 2 [C2]), and ≥ 15 units of blood and receiving ICT (Cohort 3 [C3]). SCD CCs recorded from pt charts per pt per yr (PPPY) were reported and compared among cohorts using rate ratios (RRs).

Results: Cohorts 1, 2, and 3 consisted of 69, 91, and 94 pts, respectively. Age was similar across cohorts (27 yrs [16–65]) and all pts were African American. Length of observation was shorter among pts in C1 (years, C1: 6.6; C2: 8.2; C3: 8.1). Pts in C1 received an average of 1 unit of blood PPPY (p < 0.001 vs. C2 and C3), whereas pts in C2 and C3 received an average of 10 and 15 units PPPY (p = 0.112), respectively. The most common SCD CC was acute pain crisis (69.8%), followed by infection/sepsis (5.1%), leg ulcers (2.9%), and avascular necrosis (2.3%). The rate (95% CI) of any SCD CCs was the highest in C2 at 3.02 PPPY (2.89–3.14), followed by 2.26 PPPY (2.16–2.37) in C3, and 1.66 PPPY (1.54–1.77) in C1. Among trans-fused pts, those not receiving ICT had more SCD CCs than those who did (RR [95% CI] C2 vs. C3: 1.33 [1.25–1.42]).

Conclusions: The results suggest that among regularly transfused pts, those who received ICT had less CCs than those without ICT. However, pts receiving ICT may also receive closer monitoring, which may help with early identification and intervention to delay or prevent CCs.

359. Impact of the Maximum Quantity Policy on Dispensing Fee and Prescribed Drug Expenditures in the Ontario Public Drug Benefit Program

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Background: Growth in drug expenditures remains a major public health and economic challenge internationally. In Canada, drug expenditure has risen at a faster rate than total health expenditure and makes up the second-largest component of health spending. In August 2008, the government of Ontario introduced the 'Maximum Quantity' policy as a means to contain dispensing fee expenditures. Under this regulation, pharmacies are required to supply the entire quantity specified on the prescription or for a maximum duration of 100-day supply.

Objectives: To assess the impact of the Maximum Quantity policy on dispensing fee and prescribed drug expenditures.

Methods: A time-series analysis using interventional autoregressive integrated moving average (ARIMA) models was performed using data from the Ontario Drug Benefit (ODB) database. All prescriptions eligible under this policy and filled by Ontario's community-dwelling seniors between January 1, 2004 and June 30, 2012 were included, and the outcomes of interest were the total costs of dispensing fees and overall prescription costs for the Ontario Public Drug Program. The appropriateness of the models was assessed using the augmented Dickey-Fuller's test, autocorrelation, partial autocorrelation, inverse autocorrelation functions, and the Ljung-Box Chi-squared statistics.

Results: Dispensing fee expenditures were reduced by approximately 13% after implementing the Maximum Quantity policy (p < 0.01), from $51 to $44 per capita immediately after the policy enactment. However, dispensing fee expenditures rose again within 9 months

following policy implementation, and by June 2012, had reached $55 per capita. In contrast, total prescription drug costs were stable over the study period and were not significantly affected by the policy change ($327 vs. $328 per capita, p = 0.85).

Conclusions: The ODB Maximum Quantity policy significantly reduced dispensing fee expenditures but insignificantly changed total prescribed drug costs. Our findings highlight the effectiveness but also the short-term impact of a policy designed to contain drug costs.

360. High Resource Beneficiaries of the Ontario Drug Benefit (ODB) Formulary

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Background: The Ontario Drug Benefit (ODB) program covers prescription medications for Ontario seniors aged 65 years and older and those requiring social assistance. While the total expenditure on public plan prescription drug coverage has remained relatively steady at approximately $3 billion per year in Ontario ($1,300 per beneficiary), previous studies in other jurisdictions have suggested a disproportionate percentage of those costs may be incurred by a small number of beneficiaries ('high resource beneficiaries').

Objectives: The objective of this study was to describe the characteristics of high resource beneficiaries.

Methods: We used the Ontario Drug Benefit (ODB) database to identify a cohort of ODB beneficiaries between April 1, 2010 and March 31, 2011. Various administrative databases were used to obtain demographic information, comorbidities (measured using the Charlson comorbidity index), palliative care services, and health utilization data in the year prior to cohort entry. We calculated the total cost incurred by each beneficiary over a 1-year follow-up period, and defined the 10% with the highest costs as 'high resource beneficiaries'.

Results: We identified 2,730,199 ODB beneficiaries in our study period, incurring a total cost of $3.2 billion. More than half (52.2%) of that cost was attributed to High Resource Beneficiaries, who incurred a total drug cost of $1.7 billion ($6,100 per beneficiary). One-third of the High Resource Beneficiary group was under

65 years of age, and the majority (92.6%) were living in non-institutional (i.e. non-long-term care) settings. Almost 30% of High Resource Beneficiaries had a high comorbidity burden, and almost 1 in 10 had a prior diagnosis of cancer. Approximately one-fifth of all physician, emergency department, and hospital costs incurred by ODB beneficiaries were attributable to the High Resource group.

Conclusions: Ten percent of public plan beneficiaries in Ontario accounted for more than half of drug expenditures in 2010/2011. Further research is needed to understand the health care needs of this important and growing patient population.

361. Risk of Suicide and Suicide Attempt Associated with Atomoxetine Compared to Central Nervous System Stimulant Treatment

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Background: In 2005, the FDA mandated a boxed warning for atomoxetine regarding increased risk of suicidal ideation in youths treated for attention deficit/hyperactivity disorder (ADHD). The decision was mainly based on a meta-analysis of clinical trials. It remains unknown if this risk translates to general practice and more severe clinical outcomes.

Objectives: To evaluate the risk of suicide attempt and suicide in youth treated with atomoxetine compared to central nervous system stimulants.

Methods: For this population-based retrospective cohort study, we analyzed youths eligible for 26 state Medicaid programs from 1999 to 2006 linked to the National Death Index. Youths age 5–18 entered the cohort at the first prescription (index date) for atomoxetine or stimulants, following ≥ 6 months continuous eligibility with ≥ 1 diagnosis of a mental disorder commonly treated with atomoxetine/stimulants (new user cohort). Subjects starting atomoxetine therapy

after initial stimulant treatment were matched on time since index date to subjects on stimulants (subsequent user cohort). We used propensity score adjusted Cox proportional hazard models to estimate the composite hazard of suicide attempts requiring hospitalization or emergency department visits and suicides for periods of atomoxetine use and former-use compared to stimulant use.

Results: A total of 230 suicide events occurred during 778,940 years of follow-up. Compared to stimulant use in the new user cohort, the adjusted hazard ratio (HR) for atomoxetine was 0.94 (95% confidence interval [CI] 0.5–1.7), and 0.95 (95% CI: 0.5–2.7) and 0.83 (95% CI: 0.5–1.4) for former atomoxetine and former stimulant use. For subsequent atomoxetine use, the adjusted HR was 0.6 (95% CI: 0.3–1.3), and 0.7 (95% CI: 0.4–1.4) and 0.5 (95% CI: 0.3–0.9) for former atomoxetine and former stimulant use, respectively.

Conclusions: Initial and subsequent treatment of youths with atomoxetine compared to stimulants was not significantly associated with an increased risk of suicide attempts and suicides in general practice. The small incidence resulted in wide confidence intervals and did not allow stratified analysis of high-risk groups.

362. Pediatric Sleep Disorders: Trends, Treatment and Association with Adolescent Depression

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Background: Little is known on the epidemiology of pediatric sleep disorders, their pharmacological treatment and association with adolescent depression.

Objectives: The aim of the study was to study trends in pediatric sleep disorders, hypnotic prescriptions, and their association with adolescent depression.

Methods: We used The Health Improvement Network (THIN) UK primary care database to identify 1,224,100 children aged 5–18 years who were registered with a general practice for at least one year between 1995 and 2011. We identified children diagnosed with sleep disorders and assessed time, age and prescription trends, adjusting for deprivation and sex. We used Cox regression to assess the association between sleep disorders and adolescent depression.

Results: Overall, 19,518 (2%) children were diagnosed with a sleep disorder and hypnotics were prescribed to 9,816 (1%) children. Diagnoses increased from 25.8 (95% CI: 22.4–29.6) per 10,000 PYAR in 1995 to 36.2 (95% CI: 34.6–37.8) in 2011. Of the different types of sleep disorders, insomnia (12,273 children, rate 18.4 [95% CI: 18.1–18.7] per 10,000 person-years at risk [PYAR]) was the most common. Prescription rates for hypnotics increased from 13.7 (95% CI: 11.2–16.5) per 10,000 PYAR in 1995 to 32.6 (95% CI: 31.1–34.1) in 2011. This increase was mainly caused by increase in prescribing of melatonin, which increased from no prescriptions in 2000 to 11.9 (95% CI: 11.0–12.9) per 10,000 PYAR in 2011. Children aged < 12 years who were prescribed hypnotics were more likely to be diagnosed with a developmental or behavioral disorder. Pediatric sleep disorders were associated with later adolescent depression both for children aged 5–12 years (HR: 4.42; 95% CI: 3.78–5.18) and children aged 13–18 years (HR: 2.11; 95% CI: 2.03–2.20).

Conclusions: Our results suggest that there has been a slight rise in pediatric sleep disorders diagnosed in primary care over time, particularly insomnia. In addition, hypnotics are prescribed more commonly, with a distinct rise in the prescription of melatonin. Importantly, pediatric sleep disorders seem to be related to later adolescent depression.

363. Risk of Febrile Seizure Following Inactivated Influenza Vaccine and Concomitant Vaccines

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Background: Febrile seizures occur in children, with the highest rates before age 2. In 2010, an acute risk of febrile seizure was found following receipt of trivalent inactivated influenza vaccine (TIV) or pneumococcal conjugate vaccine 13-valent (PCV13), which was licensed in the US in 2010, and a higher risk with both given together.

Objectives: To assess whether vaccines given concomitantly affect the risk of post-vaccination febrile seizure.

Methods: The Vaccine Safety Datalink combined data from 10 US medical care organizations. Of 6–23 month olds who received any vaccine from 2003 through 2011 were included. Febrile seizure was defined as an inpatient or emergency room visit with an ICD-9 diagnosis code 780.3x ('convulsions') with no prior occurrence in 42 days. A self-controlled risk interval analysis was done to estimate the adjusted relative risk (aRR) of febrile seizure in the 0–1 days post-vaccination compared to days 14–20. Multivariate Poisson regression was used to assess confounding and interaction between multiple vaccines.

Results: There were 283 and 655 febrile seizures in the 0–1 and 14–20 day intervals respectively following

8,873,839 doses of 16 different vaccines given at 3,334,781 visits. There were 955,720 TIV doses; among the 51% given alone, the RR was 2.19 in 2010–2011, which was different from the pooled RR of 0.55 for 2003–2004 through 2009–2010 (p = 0.03). Separate regression models were done for the periods 2010–2011 and 2003–2009. For the 2010–2011 period, the aRR (95% CI) for vaccines in the final model were: TIV 2.01 (1.07–3.76); PCV13 1.70 (0.81–3.56); Diphtheria-Tetanus-acellular Pertussis-containing vaccine (DTaP) 1.52 (0.70–3.28); PCV13 with DTaP 2.58 (1.40–4.77); TIV with DTaP 3.05 (1.25–7.42); TIV with PCV13 3.42 (1.46–8.01); all three together 5.19 (2.85–9.44). For 2003–2009, the aRR for PCV7 + DTaP, TIV + DTaP, TIV + PCV7, and TIV + PCV7 + DTaP were elevated in a similar pattern, but the aRR for TIV was 0.63 (0.42–0.96).

Conclusions: There was an increased risk of febrile seizure following TIV given alone in 2010–2011, but not in prior years. The risk was increased in all years when two or more of the vaccines (TIV, PCV7/PCV13, DTaP-containing) were given concomitantly.

364. Antibiotics and Hepatotoxicity in Pediatric Primary Care: A Case-Control Study Using Electronic Healthcare Databases

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Background: Antibiotics have been associated with hepatotoxicity but the risk has not been quantified in pediatrics.

Objectives: To quantify the association between antibiotic use and hepatotoxicity in children and adolescents.

Methods: We performed a population-based case-control study combining three European electronic primary care databases over the years 2000–2008: The Integrated Primary Care Information database in the Netherlands, plus the PEDIANET and Health Search/CSD Longitudinal Patient Database in Italy. Cases of hepatotoxicity in the pediatric population (< 18 years old) were identified. Cases were validated in each database, retaining only idiopathic cases. Up to 100 controls were matched to each case based on age, gender and index date. Users of antibiotics were defined as current if a prescription for the drug of interest lasted until index date or ended within 15 days prior to the index date. Risks for hepatotoxicity following antibiotic use were estimated using conditional logistic regression.

Results: Of 1,035 pediatric cases of hepatotoxicity were matched to 103,306 controls. Current use of antibiotics was associated with a 4-fold increased risk for hepatotoxicity compared to non-use (OR adj. 4.1 [95% CI: 3.2–5.3]). Significant associations were found for current use of the following single agents: co-trimoxazole (OR adj 5.9 [2.3–15.1]); rokitamycin (4.5, 1.4–15) and clarithromycin (3.2, 2–5.2) among macrolides; amoxicillin/clavulanic (2.6, 1.8–3.9) and amoxicillin (2, 1.3–3.1), among penicillins; and ceftriaxone (5, 2–12.7), cefuroxime (4.7, 1.4–15.2), ceftibuten (4.1, 1.8–9.4), cefpodoxime (3.6, 1.3–10), cefixime (3.5, 1.9–6.4) and cefaclor (2.7, 1.3–5.6), among cephalosporins. Except for rokitamycin, the associations remained significant when studying cases confirmed by specialist only.

Conclusions: This study provides estimates of the association between use of antibiotics and hepatotoxicity in children and adolescents. Current use of co-trimoxazole, some cephalosporins and macrolides and amoxicillin with or without clavulanic acid in paediatrics is associated with an increased risk for hepatotoxicity.

365. Growth Impairment and Risk of Cancer and Cardiovascular Disease in Children

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Background: There have been reports of excess mortality, mainly due to cancers and cardiovascular causes, in children treated with recombinant human growth hormones (rhGH) for treatment of growth impairment. However, little is known about the risk of these events in children with Growth Impairment (GI) compared with children in the general population.

Objectives: To estimate incidence rates of all malignant cancers, bone cancer, acute myocardial infarction (AMI), and cerebrovascular disease (CVD) in children with GI and compare with children without GI and with those in the general population.

Methods: Using the US Marketscan claims data, we identified all subjects alive on 1st January 2005 (index date), aged below 25 years, with at least one year prior history in the database. From these subjects, we defined the GI cohort as anyone who had a diagnosis of GI prior to the index date. The remaining subjects formed a non-GI cohort. The cohorts were followed forward from the index date until their last date in the database. Incidence rates of events and relative risks (RR) comparing the two cohorts were estimated after adjusting for sex and age.

Results: Of the 3.4 million children, the GI cohort consisted of 12,398 (0.4%) and the non-GI cohort 3.4 million (99.6%). The GI group had more males than non-GI (63% vs. 51%). The mean follow up time was 2.5 years. Crude incidence rates per 1,000 person-years between GI and non-GI were: 26.9 vs. 11.1 (all cancers); 0.6 vs. 0.1 (bone cancer); 0.08 vs. 0.04 (AMI); 3.3 vs. 0.9 (CVD). The corresponding age-sex adjusted RRs were: all cancers 2.6 (95% CI: 2.4–2.8); bone cancer 6.1 (4–9.4); AMI 2 (0.7–6.4); CVD 3.6 (3–4.4). Given the relative very small percent of GI children, the rates in the general population were materially unchanged from those in the non-GI cohort. Hence RRs (GI vs. general population) remained materially similar to those above.

Conclusions: In a US claims database, children with Growth Impairment had an increased risk of cancers and cardiovascular disease compared with both the non-Growth Impaired children as well as those in the general population. This may contribute to our understanding of reports of excess mortality in children treated with rhGH.

366. Effectiveness of Rotavirus Vaccines in Preventing Rotavirus Gastroenteritis Related Hospitalizations in Privately-Insured US Children, 2007–2010

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Background: To understand the public health impact of a vaccine, estimating both direct and indirect benefits is essential. Since rotavirus vaccine became available in the US in 2006, hospitalizations for rotavirus gastroenteritis (RGE) have declined sharply.

Objectives: To explore how direct, indirect, total and overall effectiveness estimates and absolute benefits of rotavirus vaccines in preventing RGE hospitalizations vary through time and in relation to each other.

Methods: Privately-insured US children in a large claims database were followed from age eight months until they (1) experienced a RGE hospitalization; (2) lost continuous health plan enrollment; (3) turned age 20 months; or (4) reached the end of the study period. Direct, indirect, total and overall vaccine effectiveness estimates in preventing RGE hospitalizations were calculated using Cox proportional hazards regression, stratifying by calendar year and adjusting for birth month. Incidence rate differences were calculated to determine the absolute number of RGE hospitalizations prevented.

Results: Among 905,718 children, 51%, 65%, 80%, and 86% received ≥ 1 dose of rotavirus vaccine each year from 2007 to 2010. The direct effectiveness of ≥ 1 dose of any rotavirus vaccine in preventing RGE hospitalization was 87% in 2007 (95% CI: 58–96%), 87% in 2008 (95% 80–92), 92% in 2009 (95% CI: 87–95), and 90% in 2010 (95% CI: 75–96). Accounting for indirect protection increased these estimates by a minimum of 3% in 2009 (95%, 95% CI: 92–97) to a maximum of 8% in 2010 (98%, 95% CI: 96–99). Between 31 (95% CI: 28–33) and 33 (95% CI: 30–35) RGE hospitalizations per 10,000 child-years were prevented in rotavirus vaccinated children each year. Failing to account for indirect protection underestimated these values by 1.5 to 5.3-fold.

Conclusions: For vaccines with direct effectiveness < 100% (including rotavirus vaccine), failing to account for indirect benefits may severely underestimate the impact of vaccination on important public health outcomes.

367. Poor Performance of High-Dimensional Propensity Score Matching in Primary Care Medical Records Data

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Background: The high-dimensional propensity score (hd-PS) has mainly been evaluated in claims databases. It is unknown to what extent data registered during regular care in Dutch medical records can be used as confounder proxies.

Objectives: To assess the performance of the hd-PS in a medical records database, using the effect of metformin vs. SU-derivatives on Body Mass Index (BMI) or LDL-cholesterol (LDL-c) as a test case, since strong

confounding by indication is expected. Clinical trials favor metformin for these outcomes.

Methods: Design: In the GIANTT database, consisting of medical records of > 35,000 patients with type 2 diabetes in The Netherlands, 10,614 and 3,832 new users of resp. metformin and SU-derivatives were identified. Over 3,000 binary confounder proxies were generated from the domains prescriptions, morbidity codes and clinical measurements based on frequency and date of occurrence. Analysis: The hd-PS models were built using increasing numbers of confounder proxies, excluding known confounders like baseline BMI and LDL-c. Between 86 and 94% of the patients were matched in the hd-PS models. Balancing of known confounders and effect sizes of metformin vs. SU-derivatives were compared with crude and known confounder corrected unmatched regression models.

Results: Baseline BMI was strongly imbalanced (standardized difference [SDD] of 0.58). The hd-PS models reduced this to 0.48, irrespective of the number of proxies used. The crude regression model for BMI showed a biased effect size of 2.8 kg/m² for metformin. The hd-PS model showed an effect estimate of 2.3, while the unmatched model including baseline BMI resulted in an effect size of −0.2, in accordance with clinical trial results. The imbalance of baseline LDL-c improved from 0.33 to 0.22 by the hd-PS method. The crude effect size for metformin was −0.23 mmol/L. The effect sizes of the hd-PS method did not show a trend with the number of proxies, fluctuating around −0.24. The model including baseline LDL-c showed an effect size of −0.12.

Conclusions: The confounder proxies as used were not effective in reducing indication bias for the BMI outcome, and moderately effective for LDL-c.

368. High-Dimensional Confounding Adjustment with Area-Based Socioeconomic Measures

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Background: Geographic area-based socioeconomic measures (ABSMs) can influence patients' health behaviors, making them important potential confounders of drug exposure-clinical outcome relationships. Example studies are needed to see if additional adjustment for ABSMs meaningfully impacts confounding control. Our test example is the comparative effectiveness of high- vs. low-intensity statin initiation on subsequent cardiovascular event among patients post-coronary event.

Objectives: To assess whether controlling for potential confounding by ABSMs impacts parameter estimates as compared to the MIRACL randomized trial estimate: a 16% reduced hazard (95% CI: 0.70–1) of a cardiovascular event among high- vs. low-intensity statin initiators.

Methods: Among 6,486 patients aged 65+ who initiated a statin post-coronary event, we linked US Census-based ABSM data to individual-level Medicare eligibility, health care and prescription drug claims. We used three approaches for confounding control. We fit a propensity score (PS) model with 46 covariates. We next constructed a high-dimensional propensity score (hdPS) model with the predefined PS covariates and 400 empirically selected covariates from seven domains: inpatient, outpatient, and skilled nursing facility diagnoses and procedures; and prescription drug claims. In a third approach, (hdPSgeo) a 13-co-variate ABSM domain was added. Cox proportional hazards models with the PS, hdPS, or hdPSgeo entered as a continuous variable examined the hazard for cardiovascular event (death, myocardial infarction or stroke).

Results: Of 2,532 (39%) initiated high- vs. low-intensity statins. Adjusted for PS, high-intensity initiators had a reduced hazard of an event, HR = 0.96, 95% CI: 0.82–1.13. hdPS adjustment minimally improved confounding control: HR = 0.92, 95% CI: 0.78–1.09. Including an ABSM domain in the hdPS showed identical results to the hdPS estimate alone.

Conclusions: In an empirical example, a comparison of confounding adjustment approaches to randomized trial results found no improvements in confounding control with ABSM variables. The promise of ABSMs for confounding control merits further examination.

369. Propensity Score Matching with Multiple Treatment Comparisons: The Shifting Reference Group

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Background: Propensity score (PS) matching is common in comparative effectiveness research. However, effect estimates resulting from PS matching multiple treatment groups to the same reference may result in quantitatively different reference groups for each comparison and therefore effect estimates that are not directly comparable.

Objectives: We illustrate the shifting reference group in a study of the effect of statin formulation on acute kidney injury (AKI).

Methods: We identified statin initiators, ages 65+, in a large Medicare supplemental insurance database. Formulations were classified by statin and dosage and PS matched to lower-potency simvastatin–the most widely used formulation. Plots of the PS distribution overlap by treatment group and the distribution of covariates in the resulting simvastatin reference groups were examined. To make directly comparable groups, we weighted treatment groups to the PS distribution of the simvastatin referent.

Results: We identified 395,741 low-dosage simvastatin initiators and 777,575 initiators of other statins. All statin formulations matched well to low-dose simvastatin (70.7–99.9%), although the resulting simvastatin reference groups reflected small subsets of the original simvastatin group (0.5–45.6%). Some baseline characteristics varied widely between matched simvastatin reference groups: myocardial infarction (1.1% in fluvastatin-matched, 4.1% in high-dose atorvastatin-matched); diabetes (19.9% in low-dosage atorvastatin-matched, 31.3% in high-dose simvastatin-matched); and ischemic heart disease (15.7% in low-dose lovastatin-matched, 32.2% in high-dose simvastatin-matched). AKI incidence ranged from 1.2% in the low-dose fluvastatin-matched group to 2.5% in the high-dose simvastatin-matched group.

Conclusions: PS matching standardizes covariate distributions to the treatment group rather than the reference. Thus when multiple matches are made to the same reference, the resulting effect estimates are not directly comparable, due to differences in the matched referent groups. Standardizing each treatment group to a common reference would allow direct comparisons of treatment effects.

370. Validation of Propensity Score Calibration Method to Control for Unmeasured Confounding in Time-to-Event Analyses

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Background: Observational studies of the effects of treatments on clinical outcomes typically rely on large administrative databases, which usually lack information on important confounders such as clinical and lifestyle characteristics. Propensity Score Calibration (PSC) method has been proposed to control for confounding bias in studies where such confounders are available in smaller, clinical 'validation' datasets [1]. PSC relies, however, on an important 'surrogacy' assumption [1].

Objectives: To use simulations to evaluate PSC estimates in Cox Proportional Hazards regression analyses of time-to-event data.

Methods: Simulation studies were performed using PSC with a variety of different underlying assumptions. First, we simulate data assuming the effects of confounders on the probability of treatment are similar to their effects on the risk of the outcome, in which case the surrogacy assumption is met [1]. Then, we simulate studies in which the surrogacy assumption does not hold. We compare the PSC estimates with the known truth, and with the estimates based on the conventional PS that adjusts only for confounders available in the main database.

Results: When the surrogacy assumption was valid, PSC estimates were almost un-biased [mean bias 0.03, 95% confidence interval (−0.14, 0.20)], with 89% coverage, in contrast to seriously biased conventional estimates [mean bias = −0.19, 95% confidence interval (−0.27, −0.11), coverage = 2%]. However, when the surrogacy assumption was incorrect the PSC estimates were biased and sometimes even less accurate than the conventional estimates.

Conclusions: PSC can reduce bias due to unmeasured confounding in Cox regression analyses when validation data is available, but further work is needed to assess when the assumption of surrogacy will be violated. [1] Stürmer, et al., AJE 2005 162.3: 279–289.

371. Bias When Using Propensity Score Methods

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Background: Propensity score methods are widely accepted as appropriate means of confounding control in pharmacoepidemiology. We conducted a simulation study to investigate the merits of various propensity score methods (PSM) when compared to standard regression models (SRM) in the settings of logistic regression (LtR) and linear regression (LinR).

Objectives: To estimate Monte Carlo mean bias, relative efficiency (RE) and coverage probability (CP) of different estimators (log odds ratio and mean difference) in causal networks of varying complexity, five different modeling strategies were studied: (1) unadjusted model (UM) (2) SRM, (3) propensity score as a linear covariate (PSLC), (4) propensity score as a smoothed covariate using restricted cubic splines (PSSC), and (5) matching on the propensity score (MPS). Theory and results will be reviewed.

Methods: We conducted 1,000 Monte Carlo simulations of known causal networks (of varying complexity). Estimation of the effect of exposure on the outcome for logistic and linear models with UM, SRM, PSLC, PSSC and MPS. Estimation was repeated on trimmed versions of the data to impose common support for both propensity score distributions. Except for unadjusted models, all statistical models were correctly specified.

Results: For a causal network with 15 common causes of a binary exposure and a binary outcome, using ltR, Monte Carlo bias, standard error (SE), RE and CP for SRM were −0.03, 0.01, 1.0, and 0.96. The bias, SE, RE and CP for PSSC were 0.23, 0.01, 1.0, and 0.91. Corresponding results for MPS were 0.20, 0.01, 0.79 and 0.95 respectively. Results were not significantly different for trimmed datasets. Bias tended to be less for causal networks with fewer confounders. In the setting of linR, PSMs were unbiased, but were less efficient compared to SRM.

Conclusions: In this study, PSMs were biased with the logistic link function. Additionally, bias and relative efficiency deteriorated as model complexity increased. Epidemiologists and decision makers need to be aware that propensity score methods may be misleading in some contexts. Caution should be exercised when using these methods for models with non-linear link functions.

372. Effects of Aggregation of Medical Codes on the Performance of the High-Dimensional Propensity Score (hd-PS) Algorithm

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Background: The hd-PS algorithm can select and adjust for baseline confounders of treatment-outcome associations in pharmacoepidemiologic studies that use healthcare claims data. How hd-PS performance is affected by aggregating medications or medical diagnoses has not been assessed.

Objectives: Evaluate the effects of aggregating medications or diagnoses on hd-PS performance using an empirical example and resampled cohorts with small sample size, rare outcome incidence, or low exposure prevalence.

Methods: In an incident-user cohort of rheumatoid arthritis and osteoarthritis patients with upper gastrointestinal complications celecoxib or traditional NSA-IDs (diclofenac, ibuprofen) use, we (1) aggregated medications and International Classification of Diseases-9 diagnoses into hierarchies of the Anatomical Therapeutic Chemical classification (ATC) and the Clinical Classification Software (CCS), respectively, and (2) sampled the full cohort using techniques validated by simulations to create 9,600 samples to compare 16 aggregation scenarios across 50% and 20% samples with varying outcome incidence and exposure prevalence. We applied hd-PS to estimate relative risks (RR) using five dimensions, predefined confounders, ≤ 500 hd-PS covariates, and propensity score deciles. For each scenario, we calculated: (1) the geometric mean RR; (2) the difference between the scenario mean ln(RR) and the ln(RR) from published randomized controlled trials (RCT); and (3) the proportional difference in the degree of estimated confounding between that scenario and the base scenario (no aggregation).

Results: Aggregations of medications into ATC level 4 alone or in combination with aggregation of diagnoses into CCS level 1 improved the hd-PS confounding adjustment in most scenarios, reducing residual confounding compared with the RCT findings by up to 19%.

Conclusions: Aggregation of codes using hierarchical coding systems may improve the performance of the hd-PS to control for confounders in some research settings. The balance of advantages and disadvantages of aggregation is likely to vary across settings.

373. Rosiglitazone vs. Pioglitazone and Acute Myocardial Infarction: Systematic Review and Meta-Analysis of Observational Studies

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Background: The European Commission–sponsored Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project evaluates the pancreatic and cardiovascular safety of oral glucose-lowering drugs in persons with type 2 diabetes mellitus (T2DM). We present the results of the meta-analysis component.

Objectives: To combine results from observational studies comparing the risk of acute myocardial infarction (AMI) between rosiglitazone and pioglitazone.

Methods: We searched PubMed, Embase, and the Cochrane library to identify observational studies of persons with T2DM reporting age-and-sex-adjusted relative risks (RR) on the associations of any oral glucose-lowering drug and AMI, heart failure, stroke, or cardiovascular mortality, published in 2000-2011. Of the 44 studies abstracted, 11 compared AMI risk for the use of rosiglitazone and pioglitazone. Estimates were pooled when there were at least three independent data points for the overall analysis and two for subgroup analyses, using random effects models. Heterogeneity of studies was evaluated using the chi-squared test.

Results: Nine cohort and two nested case-control studies, published between 2007 and 2010, were included in the meta-analysis; three studies reported estimates for monotherapy drug use. The summary RR (95% CI) for AMI for rosiglitazone vs. pioglitazone monotherapy was 1.33 (0.98–1.79); the RR when cotreatment with other glucose-lowering drugs was allowed was 1.08 (1.02, 1.15). Based on two studies, the RR for incident AMI was 1.10 (1–1.21), for incident or prevalent AMI, 1.14 (1, 1.30). For new drug users, the RR was 1.10 (1.01, 1.20), whereas for new or prevalent users it was 1.24 (0.86–1.80). Significant and relevant heterogeneity was present in most analyses. No studies reported on dose or duration effects.

Conclusions: Heterogeneity among estimates is present and needs to be investigated further. Overall estimates suggested a small increase in risk for rosiglitazone over pioglitazone but some estimates were compatible with a null effect. The new database study in the SAFE-GUARD project will provide results to better elucidate the AMI risk of these drugs.

374. International Pharmacosurveillance: Modeling Exposure to Diabetic Drugs in Relationship to Cardiovascular Effects

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Background: There is controversy about the cardiovascular effects of diabetic drugs, particularly for sulfonylureas. Studies of cardiovascular effects have employed simple use/non-use classifications by therapy class, yet time-dependent cumulative measures of exposure are better predictors of adverse effects such as cancer with diabetic drugs.

Objectives: In this study we compared the goodness of model fit of three time-dependent measures of exposure to diabetic drugs on the risk of adverse cardiovascular outcomes: current use, cumulative use and cumulative dose.

Methods: A cohort of Type 2 diabetics who were incident users of oral hypoglycemics was assembled from two electronic health record systems in Canada and the UK between 2003 and 2011. All prescriptions, visits and hospitalizations for 1 year before the start of treatment and up to 9 years of follow-up were retrieved to characterize drug use by class, dose and duration using time-dependent covariates, the date of cardiovascular events, and relevant confounders. Separate multivariate Cox proportional hazards models were estimated to compare the three methods of summarizing time-dependent measure of exposure to metformin, sulfonylurea, and other oral hypoglycemics. Models were replicated in each national cohort to assess reproducibility.

Results: Metformin was prescribed in 93% of the 1,317 newly treated Canadian diabetics and 86% of 47,258 diabetics in the UK, followed by sulfonylureas (Canada: 6%; UK: 12%). During follow-up, the cardiovascular event rate was 8.3 (Canada) and 3.2 (UK)/ 100 person-years. Models that represented exposure by cumulative dose provided the best fit for the data (BIC reduction: 22.2). In the Canadian cohort, only cumulative dose showed a significant increase in risk of cardiovascular events for sulfonylureas (HR for 2 year exposure: 1.33; 95% CI: 1.11–1.59), whereas both current use and cumulative dose was significant in the UK cohort.

Conclusions: Modeling temporal aspects of drug exposure provided a better fit for examining the association between diabetic drugs and cardiovascular effects and may elucidate possible mechanisms.

375. Diabetes Performance Measures: Potential Overtreatment and Undertreatment

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Background: Concerns have been raised that performance measures, which are intended to decrease undertreatment, may encourage too aggressive treatment in patients where this is not warranted.

Objectives: Our aim was to assess the extent of potential overtreatment and undertreatment since the introduction of diabetes performance measures in the Netherlands.

Methods: A study of five annual cohorts including almost 7.000 to 9.000 diabetes patients managed in 66 general practices in the Netherlands. Data were collected from the Groningen Initiative to ANalyse Type 2 diabetes Treatment (GIANTT) database. We used measures of potential overtreatment and undertreatment derived from practice guidelines, linking levels of glycemic (HbA1c) and systolic blood pressure (SBP) control to the start or intensification of glucose lowering and antihypertensive drug treatment. Percentages of patients with overtreatment or undertreatment in 2007 were compared with those in subsequent years using z-approximation for differences between proportions.

Results: Among patients with low blood pressure levels (SBP < 130 mmHg), potential overtreatment was common and increased slightly after 2007 (24.2% in 2007 to 28.6% in 2011, $p < 0.05$). Percentages of patients with high blood pressure (SBP $\geq$ 140 mmHg) not receiving recommended actions, indicating undertreatment, decreased over time (61.3% in 2007; 54.4% in 2011; $p < 0.05$). Potential overtreatment was seen in around 10% of patients with low HbA1c levels (< 48 mmol/mol), and no trends over time were observed. The percentage of patients with an HbA1c of $\geq$ 53 mmol/mol not receiving recommended actions increased after 2007 (49.8% in 2007; 56.2% in 2011; $p < 0.05$).

Conclusions: Following the introduction of diabetes performance measures, there was a small increase in overtreatment and decrease in undertreatment for hypertension in line with the expectations. On the other hand, there was not much change in potential overtreatment and an unexpected increase in undertreatment for glycemic control. These findings do not support the view that current performance measures for diabetes care stimulate aggressive prescribing in general.

376. Incident Type II Diabetes Mellitus among Patients Exposed to the Combination of Pravastatin and Paroxetine

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Background: A previously published study indicated a potential synergistic relationship between the combined use of pravastatin and paroxetine and increased blood glucose.

Objectives: To further evaluate, we employed a new user design to evaluate the effects of concomitant pravastatin and paroxetine use on incident Type 2 Diabetes Mellitus(T2DM).

Methods: Data were abstracted from 2 US health insurance claims databases (OptumInsight & Market-Scan) between July 1, 2002 and December 31, 2009 and separately analyzed in a new user design. Patients included were age $\geq$ 18; newly prescribed pravastatin or paroxetine and enrolled in the database for $\geq$ 180 days prior to index date(1st Rx of incident drug). Patients were assigned to either incident pravastatin or incident paroxetine groups. Patients were followed until study endpoint(incident T2DM), discontinuation of incident drug, or end of study. Among new users of pravastatin, Cox proportional hazards models compared incident diabetes in those who were also taking paroxetine at index date (combination users) vs. those who not taking paroxetine at index date. A similar analysis among new users of paroxetine evaluated use or non-use of pravastatin at index date.

Results: OptumInsight yielded 307,099 patients; 487,351 from MarketScan. Incidence of T2DM in new users of pravastatin ranged from 2 to 6 events per 100 person-years. In new users of paroxetine, incidence of T2DM ranged from 1 to 4 events per 100 person-years. The risk of T2DM among combination users compared to incident pravastatin only was 1.04 (95% CI: 0.77, 1.45) and 0.94 (95% CI: 0.90, 0.97) in the OptumInsight and MarketScan databases, respectively. The risk of T2DM among combination users compared to incident paroxetine only users was 1.09 (95% CI: 0.60, 2.01) in OptumInsight and 1.02 (95% CI: 0.97, 1.07) in MarketScan.

Conclusions: Results indicate no increased risk of T2DM among the combination use of pravastatin and paroxetine compared to use of the two drugs alone. The order in which the drugs were initiated does not alter this relationship. The study highlights the role of formal pharmacoepidemiology methods and new user design in the assessment of medication interactions.

377. Association between Active Vitamin D and the Risk of Infection-Related Hospitalizations in Patients Receiving Chronic Hemodialysis: A Nested Case-Control Study

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Background: Recent studies led to conflicting results in evaluating whether active vitamin D (AVD) is beneficial or not to reduce infections.

Objectives: Our aim was to evaluate the association between oral AVD and the risk of infection-related hospitalizations (IRH) among incident chronic hemodialysis patients.

Methods: For this nested case-control study, we built a cohort of adult patients initiating chronic hemodialysis (n = 4933) in Quebec, Canada, using dialysis registry and administrative databases (2001–2007). Cases were defined as patients hospitalized with a main diagnosis of infection according to ICD-9 codes on the discharge sheet. Up to 10 controls per case were selected by incidence density sampling and matched to cases according to their age and follow-up time. Use of oral AVD was measured (1) as current use or not at the time of the hospitalization, and (2) as a cumulative dose during the prior 6 months. Odds ratios (OR) for IRH were estimated using conditional logistic regression multivariate analysis, adjusting for demographics, smoking, body mass index, comorbidities, and laboratory values.

Results: We identified 1,136 cases of IRH and 10,396 controls. Current intake of AVD had no effect on the IRH risk (OR = 1.07, 95% CI = 0.95–1.20). Using the cumulative dose of AVD, we also found that a 6-month cumulative dose of ≤ 45 μg (OR = 1.05, 95% CI = 0.92–1.19) or > 45 μg (OR = 1.15, 95% CI = 0.96–1.36) had no effect on the risk of IRH when compared to no use. Chronic pulmonary disease (OR = 1.42, 95% CI = 1.24–1.63), diabetes (OR = 1.27, 95% CI = 1.11–1.46), lower serum albumin (OR = 0.90 per 10 g/L, 95% CI = 0.80–1) and higher estimated glomerular filtration rate (OR = 1.01 per 1 mL/min/1.73 m^2, 95% CI = 1–1.03) were associated with a higher risk of IRH.

Conclusions: Oral AVD was not associated with a lower risk of IRH in hemodialysis patients. This study puts a damper on the excitement around the potential role of vitamin D in the prevention of infections in humans.

378. Achieving Glycemic Control Differs between Patients with Type 2 Diabetes Mellitus Starting on Metformin and Sulfonylureas

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Background: Antidiabetic medication is aimed at attaining tight glycemic control, but patients do not always achieve guideline recommended targets. Available observational studies focusing on both drug treatment and glycemic control have some methodological limitations.

Objectives: To describe the relation between long-term medication use and changes in HbA1c level in various subgroups of patients with type 2 diabetes mellitus.

Methods: A cohort study was performed among new users of metformin (Met) or sulfonylurea (SU), aged ≥ 35 years, enrolled in the Diabetes Care System (DCS) in the Dutch region of West-Friesland (200,000 inhabitants). Patients receiving care from the DCS were linked to drug dispensing data obtained from 15 community pharmacies and two dispensing general practices in the region. Patients visit the DCS annually for a check-up. The study period was between 1998 and 2007. To be eligible, subjects had to remain on the initially prescribed OAD for at least 3 years, have a Hba1c-measurement in 3 months around treatment start and have at least three Hba1c measurements overall. We categorised patients according to Hb1ac level at treatment initiation ($\leq 7\%$, $> 7\%$) and assessed time to reaching either a HbA1c $> 7\%$ or $\leq 7\%$, respectively. Cox regression analysis was conducted to compare Met and SU, while adjusting for confounders.

Results: There were 382 and 149 starters of Met and SU, respectively. The majority of patients (63%) entered the cohort with a Hba1c $> 7\%$. Patients initiating Met at an HbA1c $> 7\%$ showed a statistically significant faster progression to a HbA1c $\leq 7\%$ compared to those starting SU (adjusted hazard ratio 0.74, 95%CI: 0.56–0.96). Stratification revealed no statistically significant differences between age, sex, and BMI subgroups. The proportion of patients with add-ons was high (50.5%). No difference between Met en SU was found among patients on monotherapy. In patients starting with an HbA1c $\leq 7\%$ no obvious differences were observed between Met and SU.

Conclusions: Overall results confirmed Met as the first choice OAD in T2DM patients with an HbA1c $\geq 7.0\%$, but treatment intensification in order to reach glycemic control is frequent.

379. Suboptimal Prescribing of Proton Pump Inhibitors in Low-Dose Aspirin Users in General Practice: A Population-Based Cohort Study

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Background: Treatment of low-dose aspirin (LDASA) is recommend for the prevention of cardiovascular events in high risk patients, yet LDASA increases the

risk of gastrointestinal (GI) complications. Therefore, it is recommended to treat patients at increased risk of GI complications with a concomitant proton pump inhibitor (PPI). General practitioners are not always aware of the need for gastrointestinal protection when prescribing LDASA.

Objectives: We assessed adherence to recommendations of concomitant PPI treatment in regular LDASA users, taking factors associated with the probability of receiving a PPI into account.

Methods: Data were obtained from the Netherlands Information Network of General Practice (LINH) database. All patients 18 years and older who were regularly prescribed LDASA (30–325 mg) in 2008–2010 were included. Based upon HARM-WRESTLING recommendation, we categorised LDASA users into low and high GI risk. Regular medication use was defined as receiving each consecutive prescription within 6 months after the previous one. Adherence to recommendations was determined by applying multilevel multivariable logistic regression analyses in order to identifying the relative influence of patient characteristics on the probability to obtain regular PPI prescriptions in daily practice.

Results: We identified 12,343 patients who started LDASA treatment, of whom 3,213 (26%) were at increased risk of GI complications. Concomitant regular use of PPI was 46% in the high GI risk group compared to 30% in the low GI risk group. In the high GI risk group 36% did not receive PPI prescriptions and 18% obtained prescriptions for PPI irregularly. In the low GI risk group 20% received irregular PPI prescriptions. Most important factors that increased the change to obtain regularly PPI prescriptions were previous GI complications, use of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, selective serotonin receptor inhibitors (SSRIs), drugs for functional GI disorders and age.

Conclusions: More than 50% of regular LDASA users who were at increased GI risk did not receive (36%) or received irregular (18%) PPI treatment.

380. Prevalence and Trend of Proton Pump Inhibitor Use among Current Users of Non-Steroidal Anti-Inflammatory Drugs and Risk Factors for Gastrointestinal Complications – A Population-Based Longitudinal Study in Sweden

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Background: Use of non-steroidal anti-inflammatory drugs (NSAIDs) is strongly related to gastrointestinal (GI) complications. To prevent GI complications, proton pump inhibitors (PPI) are recommended to individuals using NSAIDs with high risk of complications.

Objectives: To estimate prevalence, and identify predictors and time trends of concurrent PPI use in NSAID users.

Methods: Data were retrieved from the Swedish Prescribed Drug Register and Patient Register. We studied PPI use in 1.4 mol/L NSAID users, establishing four cross-sections of current NSAID users with index date on 1 January each year, 2007–2010. A person was classified as current user if the last dispensing before the index date lasted until this date assuming use of 0.5 DDD/day. Current PPI use was defined similarly. Co-morbidities and -medications were defined as diagnosis/dispensing within 1 year prior to index date. Age 70+ years, previous ulcer/GI bleeding, use of aspirin, other antiplatelet drugs, vitamin K antagonists or SSRIs were considered risk factors. PPI use was analyzed using Generalized Estimating Equation models accounting for dependence between cross-sections. Models included annual trend, age, sex, co-morbidities and co-medications.

Results: The number of NSAID users varied from 341,000 to 349,000 between cross-sections. Prevalence of PPI use increased from 16.2% in 2007 to 20.5% in 2010, and was higher in females, the elderly (24%) and patients with ≥ 4 risk factors (48%). PPI use was positively associated with dispensed amount of NSAIDs, previous ulcer, GI bleeding, dyspepsia/reflux, aspirin and anticoagulant use, and chronic disease. The adjusted odds ratio for annual trend in prevalence was 1.10 (95% CI 1.09–1.10). The trend was present in all age groups.

Conclusions: PPI use in NSAID users increased between 2007 and 2010, and was positively related to risk factors for GI bleeding. This may indicate rational prescribing, but PPI use is still too low in high risk

patients. Also, concurrent use of PPIs seems related to other indications than gastroprotection, e.g. reflux and dyspepsia.

381. The Influence of Hospital Drug Policy on the Prescribing Patterns of Proton Pump Inhibitors in Primary Care

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Background: The influence of drug policy in hospital on drug prescribing behaviour in primary care is less described. At Odense University Hospital, Denmark, the first-choice recommendation of proton pump inhibitors (PPI) was changed from esomeprazole to lansoprazole in 2010.

Objectives: The aim of this study was to describe how prescription patterns of PPIs in primary care are influenced by hospital drug policy.

Methods: We carried out an observational register study of 460 patients discharged with a PPI from a geriatric department. The individual patients' drug use was followed across hospital stay by use of pharmacy dispensing data and a hospital-based pharmacoepidemiological database.

Results: Followed by the change of hospital drug policy, the proportion of esomeprazole users in hospital decreased from 67.1% (95% confidence interval [CI]: 59.9–74.3) to 13.3% (CI 7.8–18.8) for prevalent users (n = 327) and from 74.0% (CI 63.7–84.3) to 17.7% (CI 8.0–27.5) for incident users (n = 135), respectively. For the prevalent users of PPI, the proportion of prescribings carried over into primary care was 69.2% (CI 62.9–75.0) and 74.0% (CI 66.2–80.8) after change of hospital drug policy. There was no significant difference between esomeprazole and lansoprazole. For incident users, the proportion of prescribings carried over into primary care was 79.0% (66.8–88.3) for all users of PPI. After intervention, 18.2% (CI 2.3–51.8) of esomeprazole prescribings were carried over into primary care and for lansoprazole, 92.2% (CI 81.1–97.8) of prescribings were carried over.

Conclusions: A change of hospital drug policy reduced the use of esomeprazole both in hospital and primary care. In 2009, the prescribings of PPI in hospital care carried over into primary care were the same for all PPI. A synergistic effect of drug policy was observed for incident users, if drug policy had been coordinated between health care sectors.

382. Oral Bisphosphonates and Upper Gastrointestinal Toxicity: A Study of Cancer and Early Signals of Esophageal Injury

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Background: Bisphosphonates can irritate the esophagus; their association with gastrointestinal (GI) cancer remains unsettled. Their widespread use compels continued investigation of potential GI toxicity.

Objectives: To assess the relationship between cumulative bisphosphonate use and (1) upper GI cancer, (2) upper endoscopy, and (3) proton pump inhibitor (PPI) initiation.

Methods: A 40% Medicare sample of inpatient, outpatient (3–10) and prescription (6–10) claims permitted retrospective study of patients > 50 diagnosed with osteoporosis or treated with oral bisphosphonates. Inverse probability of treatment weighted logistic regression estimated the association between cumulative bisphosphonate pills received and upper GI cancer. Secondary analyses, restricted to a 'clean look-back' cohort (no past bisphosphonates or upper endoscopy), modeled (1) receipt of endoscopy and (2) initiation of prescription PPIs.

Results: Of 1.64 million patients; 87.0% were women, mean age was 76.8. Mean follow up was 33.3 months; 37.3% received oral bisphosphonates. Cumulative bisphosphonate receipt, among users, ranged from 4 to 216 pills. We identified 1,968 upper-GI cancers (0.43/ 1000 person years). We found no association between cancer and cumulative bisphosphonate use, OR of 10 additional pills 1.00 (95% CI 1.00, 1.00). Analyses of the clean look-back cohort revealed 12.8% underwent endoscopy (51.5/1000 person years). Compared to no use, risk of endoscopy was greatest with lowest cumulative pills, 1–9, OR 1.11 (95% CI 1.08, 1.15); 22.5% of PPIs non-users initiated PPIs. Compared to none, highest risk of PPI initiation was seen with lowest cumulative bisphosphonates, 1–9 pills, OR 1.18 (95% CI 1.14, 1.21).

Conclusions: We found no bisphosphonate cancer association. That endoscopy and PPI initiation were most likely with lowest exposure, suggests early bisphosphonate use identifies patients susceptible to irritating pill effects. Studies reporting a cancer protective effect of greater use may suffer a healthy user bias. Knowledge

of a population intolerant of minimal bisphosphonate use may prompt clinicians to offer alternatives and to forgo or delay endoscopy and PPIs.

383. Peripheral and Total Parenteral Nutrition as Primary Risk Factors for Nosocomial Candidemia among Elderly Adult Patients

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Background: Nosocomial Candidemia (NC) is an important cause of morbidity and mortality, however, information about characteristics and risk factors for NC among elderly adult patients is limited.

Objectives: To determine the incidence rate, *Candida* species distribution, 30-day crude mortality and to identify risk factors for NC in a hospitalized population of elderly adults.

Methods: We analyzed all the events recorded in the NC surveillance program and conducted a matched case-control study among subjects admitted to the University Hospital of Trieste, Italy. Cases were all 2008–2011 consecutive NC. For each case, two controls were selected among patients admitted to the same hospital, and individually matched by sex, age, time of admission, hospital ward, and duration of hospitalization. Underlying diseases and in-patient invasive procedures and treatments were assessed by medical records abstraction. The adjusted odds ratio (OR) was calculated using multiple conditional logistic regression.

Results: We identified 145 episodes of NC occurring in 140 patients (67 females, 48%) with a median age of 80 years. Incidence of NC was 1.56 episodes per 10,000 patient-days per year. Ninety-three (66.4%) NC cases were hospitalized in general medicine. Candida albicans (80 isolates) was 55% of all candidemia. After adjustment, NC was strongly associated with duration (> 7 days) of total (OR = 20.09; 95% confidence interval [CI]: 3.44–117.52), and peripheral parenteral nutrition (OR = 26.83; 95%CI: 6.54–110.17), other central vascular catheters (OR = 5.17; 95%CI: 1.24–23.54), and glicopeptyde antibiotics (OR = 6.45; 95%CI: 1.90–21.91). Duration of total and/or peripheral parenteral nutrition and antibiotics predicted over 50% of

NC. The 30-day mortality was 45% in candidemia cases and 20.7% in controls.

Conclusions: Along with known risk factors, duration of intravenous nutrient administration was strongly associated with NC regardless of administration route. For peripheral parenteral nutrition in adult patient populations this is a new and unexpected finding since similar evidence exists only in neonates.

384. Proton Pump Inhibitors and Clostridium Difficile-Associated Disease in Canadian and Australian Community Settings – A Prescription Sequence Symmetry Analysis

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Background: There have been a number of studies suggesting a possible link between proton pump inhibitors (PPIs) and an increased risk of Clostridium difficile-associated disease (CDAD), particularly in vulnerable patients. A definite association has not been confirmed. Analysis of community settings may provide a clearer estimate for the effect of PPIs on the risk of CDAD than hospital settings.

Objectives: to explore the association between PPIs and CDAD in community settings using prescription sequence symmetry analysis (PSSA).

Methods: The study was restricted to seniors aged 65 years or older. Oral vancomycin prescription was used as a proxy for CDAD diagnosis. PSSA was used to compare the number of individuals in whom oral vancomycin use followed their use of a PPI (defined as 'causal sequence group') with the number of individuals in whom oral vancomycin use preceded it ('the noncausal sequence group'). Crude and adjusted sequence ratios (SR) with 95% confidence intervals (CI) were calculated. Independent analyses were conducted using administrative databases in Canada and Australia for the period of 2001–2012.

Results: In Canada, a total of 388 individuals were included in the analysis. Two hundred and seventy individuals started PPIs prior to oral vancomycin treatment and 118 started PPIs after oral vancomycin treatment, giving a crude SR of 2.29. However, the

prescribing rate of oral vancomycin drugs increased more than that of PPIs. Accordingly, the adjusted SR was 1.45 (95% CI = 1.16–1.79). In Australia, 77 individuals were included in the analysis, of which 49 in the causal sequence group and 28 in the noncausal sequence group, giving a crude SR of 1.75. The adjusted SR was 1.76 (95% CI = 1.11–2.80) after adjusting for time trends in population prescribing.

Conclusions: CDAD treatment was more likely in the year following introduction of PPIs for both Canadian and Australian databases. Prescription databases are useful sources to explore drug safety. However, because of the limitations inherent to the prescription sequence methodology and claims data, PSSA is likely to be more useful for exploratory hypothesis driven testing than as a data mining tool.

385. Reporting of Instrumental Variable Analyses in Comparative Effectiveness Research

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Background: Instrumental variable (IV) methods are becoming mainstream in comparative effectiveness research, yet such methods rely on radically different assumptions than traditional epidemiologic methods. Specifically, IV methods require a variable that meets three conditions: (1) it is associated with treatment, (2) it does not affect the outcome except through treatment, and (3) it does not share any causes with the outcome. To obtain a point estimate, an untestable fourth condition must also be met.

Objectives: To assess whether the IV conditions were conveyed appropriately in the literature.

Methods: We performed a systematic review of observational studies using IV methods to estimate effects of relatively well-defined medical interventions. After obtaining 2,269 unique publications from PubMed, Embase, PsycInfo, Web of Science, and Econlit, we found 81 studies that met these eligibility criteria.

Results: The acknowledgment and discussion of the IV conditions varied considerably. While most studies (93%) empirically verified condition (1), few studies (15%) clearly stated and discussed theoretical justifications for both conditions (2) and (3). Only 20% reported a falsification test of the IV conditions, and no study reported two or more such tests. Moreover, all studies reported a point estimate, meaning they implicitly assumed a fourth condition, while only 10% clearly stated and discussed the condition they were evoking.

Conclusions: Causal inference relies on transparency of assumptions, but the conditions underlying IV methods are often not presented in a transparent manner. This is particularly disconcerting because even relatively small violations of the IV conditions can lead to large biases in unpredictable or counterintuitive direction. We will outline steps for the reporting of IV methods in order to help investigators present IV analyses in such a way that colleagues can better evaluate the estimates.

386. Considerations for Creating a Calendar Time Instrumental Variable in Specific Settings of Nonexperimental Comparative Effectiveness Research

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Background: Calendar time may be a strong instrumental variable (IV) for new-to-market therapies that have experienced dramatic changes in clinical practice. This is an important option in large database studies where unmeasured confounding is likely. However, the optimal approach for defining a calendar time IV is unclear.

Objectives: Evaluate approaches for creating a calendar time IV in a comparative effectiveness study of 5-flourouracil (5-FU) vs. oxaliplatin (Ox) for stage III colon cancer (CC), anchored around Ox FDA approval in November 2004.

Methods: Stage III CC patients aged 65+ initiating chemotherapy between 2003 and 2008 were examined using population-based cancer registry data linked with Medicare claims (N = 3660). Fifteen variations of a calendar time IV were constructed to delineate patients treated prior to vs. after Ox uptake. We examined the use of cutpoints vs. interim exclusion ranges during transition months surrounding FDA approval; removal of time distant from FDA action that may violate IV assumptions; and categorical vs. continuous IV. We examined IV strength based on percent compliers, prevalence difference (PD) ratios, and IV assumption legitimacy. We compared risk difference (RD) estimates using Kaplan–Meier survival curves.

Results: Calendar time was a strong IV in all scenarios, with strength ranging from 48.4% to 56.0% compliers and improved PD for age, physician affiliations, substage and cardiovascular comorbidities. Excluding patients treated more than 2.5 years after FDA approval optimized strength while improving confidence in IV assumptions. Removing an interim time

period enhanced strength compared with using a cut-point, and did not substantially change RDs. Sample size decreased 0–25% across options. The strongest IV yielded 3-year all-cause mortality risk = 30/100 vs. 25/100 patients for 5-FU vs. Ox, with Wald IV RD = −0.09 (95% CI: −0.15, −0.03).

Conclusions: All IVs were strong and indicated a survival advantage in patients treated with Ox, in agreement with adjusted analyses and clinical trials. Truncating the cohort based on IV assumptions and dissemination patterns appeared to create the strongest IV.

387. Improvement of 1:M Matching Using an Adaptive Algorithm: Proof of Concept

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Background: The goal of individual cohort matching is to create matched sets comprising exposed and unexposed subjects in which the matching covariate has nearly the same value for all subjects in the matched set. The precision of the ensuing exposure effect estimate can be increased by increasing the number of unexposed individuals matched to each exposed one (1:M matching).

Objectives: To assess whether residual confounding bias could be reduced with 1:M matching by choosing consecutive unexposed matches that take the covariate value of the previous unexposed matches into account to maximize similarity between the covariate value for the exposed person and an overall measure of central tendency, such as the mean, for the corresponding matched unexposed persons.

Methods: We simulated cohort studies with two dichotomous and two continuous covariates affecting a dichotomous exposure via a logit link, and all these affecting a Poisson distributed recurrent outcome. Two additional covariates only affected either exposure or outcome. Random 1:M matching by propensity score (PS) was implemented using two different calipers (+/− 5 on the second decimal place of PS and 0.5 of the standard deviation of logit(PS)) and exposure prevalences (0.2 and 0.04). The caliper midpoint for the Mth unexposed match was either kept at the value of the exposed (conventional non-adaptive) or adjusted so that the mean of all M unexposed matches would be the same as the value in the exposed if the Mth unexposed match had exactly the midpoint value.

Results: Adaptive 1:M matching outperformed non-adaptive (conventional) 1:M matching in all scenarios

assessed. Bias and MSE reduction ranged from 44%–93% to 8%–45%, respectively. Adaptive matching led to an almost monotonic decrease in residual confounding bias with increasing M while no such pattern was observed for non-adaptive matching.

Conclusions: We conclude that adaptive 1:M matching can reduce residual bias in specific settings. So far this is a proof of concept and parameters affecting bias reduction achieved by adaptive matching need to be identified before widespread use can be recommended.

388. Comparison among EU-ADR, OMOP, Mini-Sentinel and MATRICE Strategies for Data Extraction and Management

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Background: Data collection for epidemiologic studies is increasingly performed as data transformation from local organizations. Several research teams in Europe and US have recently tackled the additional challenge of pooling heterogeneous data sources. A conceptual framework describing the whole data transformation process is lacking.

Objectives: Compare the strategies adopted by four projects: EU-ADR (EU), Mini-Sentinel (US), OMOP (US) and MATRICE (IT).

Methods: The data sources were compared. A conceptual framework describing the data transformation process was introduced splitting the process in three steps: metadata reorganization (T1), semantic transformation to produce datasets of specific events (T2), data linkage to produce datasets for analysis (T3). The strategies of the four groups were mapped onto this model and compared. Quality procedures and software tools were compared as well.

Results: EU-ADR managed the most heterogeneous pool of data sources with respect to country of origin, settings of data collection, coding systems and natural languages of clinical notes in free text. OMOP and Mini-Sentinel data sources had similar level of heterogeneity while MATRICE pooled data from homogeneous local databases. As for data transformation, step T3 was the most comparable across groups: common procedures were implemented in software tools. Step T1 was the most heterogeneous: from informal documentation (EU-ADR) to formally coded loading procedures (Mini-Sentinel and OMOP) to text files feeding a common software (MATRICE). Multiple definitions for the same clinical event were adopted in Step T2: in OMOP they all entered the study and impact of different definitions was evaluated on performance; in EU-ADR definitions were compared in terms of incidence rates within and between local data providers; Mini-Sentinel and EU-ADR conducted medical chart review, MATRICE and Mini-Sentinel performed validation studies. Ad-hoc programming languages were developed for T2 in OMOP, Mini-Sentinel and MATRICE.

Conclusions: The framework we introduced made comparison possible. EU-ADR pooled the most heterogeneous data with the least formally coded data transformation procedures.

There remains uncertainty regarding which estimation strategy is optimal in settings involving large automated databases.

Objectives: To evaluate the performance of proposed methods for estimating DRSs in large automated databases compared with traditional outcome regression models and PS methods.

Methods: New users of glucagon-like peptide-1 agonists (GLP-1) and new-users of Thiazolidinedione (TZD) were identified within an elderly diabetic population using Medicare claims data. We evaluated the performance of GLP-1 compared to TZD in reducing CVD events and all cause mortality. We controlled for confounding using DRS stratification, PS stratification, and traditional outcome regression. We estimated the DRS within the full cohort of exposed and unexposed individuals and then within the unexposed cohort only (TZD users).

Results: The crude, or unadjusted, hazards ratio (HR) was 0.93 (0.79–1.10). Adjustment for potential confounders resulted in a HR of 0.76 (0.65–0.91) when using outcome regression and 0.80 (0.68–0.94) when using PS stratification. DRS stratification resulted in a HR of 0.75 (0.66–0.91) when the DRS was only estimated within the unexposed (TZD users) and 0.77 (0.66–0.91) when the DRS was estimated within the full cohort.

Conclusions: Although the various methods yielded similar results in this example, the use of DRSs for confounding control may be advantageous during periods of evolving patterns of drug use. Alternative strategies for estimating DRSs include out of sample estimation using historical data or an alternative data set. Additional research will be conducted to evaluate these estimation strategies in new users of recently introduced anticoagulants for atrial fibrillation.

389. Comparing Disease Risk Scores with Propensity Scores for Confounding Control When Evaluating Newly Introduced Treatment Therapies

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Background: During early periods of drug approval, modeling the propensity score (PS) can be difficult due to rapidly changing patterns of drug use. The disease risk score (DRS) summarizes the relationship of risk factors with the outcome and is more stable over time. Although the DRS is a valid alternative to PSs, valid estimation of the DRS presents additional challenges.

390. Evidence of Free Sample Use among New Users of Branded Statins

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Background: Incomplete capture of prescription medication use by healthcare claims databases can occur when patients use free sample drugs, which could result in drug exposure misclassification and adversely affect research and quality improvement activities that rely on these data.

Objectives: To assess the extent of free sample use among branded vs. generic statin initiators who received low-density lipoprotein (LDL) tests in a large healthcare database.

Methods: Statins are shown to be highly effective at lowering LDL cholesterol level. Therefore, patients on treatment will have a different distribution of LDL compared to those not on treatment. If patients filling a first statin prescription are a mix of patients already being treated and newly treated patients, the distribution of LDL prior to first fill will follow a mixture distribution. Using the MarketScan Research Databases, we created a retrospective cohort of statin users who filled a prescription claim after at least six statin-free months of observed plan enrollment during July 1, 2007–July 1, 2010. LDL results obtained within the 15 days preceding the first fill were analyzed using a two-component Gaussian mixture model to estimate the proportion of patients filling a new prescription who may already be on treatment.

Results: Among 9,213 patients filling a branded statin, LDL values were bimodal, consisting of two Gaussian distributions (mean [SD] = 71.7[20.7], 148.1[36.7] mg/dL) and the lower distribution made up 13.5% of the population, suggesting drug use prior to first prescription claim. Among 16,848 patients filling a generic statin, LDL levels were substantially higher with no evidence of bimodality that would suggest prior sample use.

Conclusions: In this healthcare claims database, about one in seven patients had evidence of drug sample use prior to first prescription claim. Our study contributes compelling evidence that exposure misclassification due to free sample use does exist when using pharmacy claims data to define exposure status, particularly in studies involving branded medications. Future research is needed to examine approaches that can be used to better identify true incident medication use.

391. Risk of Cardiovascular Events, Stroke, Congestive Heart Failure, Interstitial Lung Disease, and Acute Liver Injury: Dronedarone vs. Amiodarone and Other Antiarrhythmics

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Background: No studies have evaluated the risks of cardiovascular (CV) events, stroke, congestive heart failure (CHF), interstitial lung disease (ILD), and severe acute liver injury (ALI) related to antiarrhythmics treatment in real clinical practice setting.

Objectives: This retrospective cohort study was conducted to examine the above risks related to the antiarrhythmics treatment among adults using medical and prescription claims from the InVision Data Mart in the US.

Methods: We analyzed data of 10,455 adult patients with a diagnosis of atrial fibrillation/atrial flutter and a new treatment of dronedarone, amiodarone, sotalol, flecainide, or propafenone between 7/20/2009 and 12/31/2010, after excluding those with < 6 months of baseline enrollment period or with a diagnosis of the outcome event during the baseline period. The patients were followed up from the date of the first prescription of the exposure drug dispensed after July 20, 2009 until: (1) switch to another antiarrhythmic drug, (2) the occurrence of the outcome event, (3) the end of enrollment, and (4) the end of the study period, whichever occurred first.

Results: No significant differences were observed in the hazard ratios of the outcome events between dronedarone, amiodarone, and the other antiarrhythmics, except that amiodarone was associated with a higher risk of CV events (adjusted HR = 2.3, 95%CI: [1.8–2.9]), stroke (adjusted HR = 2.4, 95%CI: [1.5–3.8]), and CHF (adjusted HR = 2.6, 95%CI: [2.3–2.9]) compared to dronedarone. Higher risks of CV events and stroke were mainly found amongst patients without a CHF history (adjusted HR = 2.3, 95%CI: [1.4–3.8]) and 2.1, 95%CI: [1.2–3.6] respectively), not among those with a CHF history.

Conclusions: While no risk difference was observed between dronedarone and other antiarrhythmics, amiodarone was associated with higher risks of CV events and stroke than dronedarone in patients without a CHF history. There were no risk differences in the other events between dronedarone, amiodarone, and the other antiarrhythmics.

392. Do Statins Reduce Short-Term Mortality among Patients Hospitalized with Perforated Peptic Ulcers?

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Background: Statins appear to possess anti-thrombotic, anti-inflammatory, and immune-modulating properties, referred to as pleiotropic effects, which have the potential to influence a wide range of disease processes. The impact of statins in the setting of complicated ulcer disease is unknown.

Objectives: We examined whether preadmission statin use was associated with a reduction in 30-day mortality among individuals hospitalized with a perforated peptic ulcer (PPU), a particularly frail population.

Methods: We conducted a Danish nationwide register-based cohort study of 3,361 individuals age > 45 years who were hospitalized with PPU from 2005 to 2010. Statin use in the year prior to hospitalization was identified through a nationwide prescription registry. We estimated 30-day mortality risk differences (RD) and 95% confidence intervals (CI) comparing statin users with non-users by utilizing two propensity score (PS) weighting methods that standardized the RD to: (1) the covariate distribution of the statin user group (standardized mortality ratio weighting (SMRW)) and (2) the covariate distribution of the total study population (inverse probability of treatment weighting [IPTW]). Sensitivity analyses using 1% trimming assessed the impact of unmeasured confounding at the tails of the PS distribution.

Results: In total, there were 642 statin users (19%) and 1,085 deaths (32%) within 30 days from hospitalization. Statin use was strongly associated with a history of cardiovascular disease and diabetes and inversely associated with antipsychotic use. Statin use increased with age in younger patients and decreased in older patients. Statins slightly reduced 30-day mortality using both PS methods (SMRW RD = −0.05 [95% CI:−0.12, 0.02]; IPTW RD = −0.06 [95% CI:−0.12, 0.0]). After trimming patients treated contrary to indication, the reduction in mortality associated with statin use remained robust in the SMRW analysis (RD = −0.07 [95% CI:−0.12, −0.02]), but was attenuated in the IPTW analysis (RD = −0.03 [95% CI:−0.09, 0.03]).

Conclusions: Although statin users with PPU may have a slightly reduced short-term mortality, not all patients hospitalized with PPU may benefit from statin therapy.

393. Comparative Safety of Cardiovascular Medication Use and Breast Cancer Outcomes

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Background: Breast cancer tends to occur in older women who are also burdened with comorbidities. Numerous medications used to manage these comorbidities are hypothesized to alter breast cancer risk and recurrence. COMBO (COmmonly used Medications and Breast Cancer Outcomes) was developed for comparative safety of medications used in the management of co-morbid conditions and risk of poor breast cancer outcomes.

Objectives: Describe COMBO cohort and report on CVD medications and breast cancer outcomes.

Methods: We conducted a retrospective cohort study among female health plan enrollees aged ≥ 18 years who were diagnosed with incident early stage breast cancer between 1990 and 2008 via tumor registry. CVD medication use including statins, calcium channel blockers (CCB), beta blockers (BB), angiotensin converting-enzyme inhibitors (ACEI), and diuretics and covariates were obtained from health plan databases and medical record review. Our primary outcome measure of second breast cancer events (SBCE) was defined as the first occurrence of recurrence or second primary breast cancer. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) while accounting for competing risks.

Results: Of 4,216 women were followed for a median of 6.7 years (range, 0.3–20.0 years) and 13% experienced a SBCE. The median time to the first SBCE was 3.3 years. During the follow-up period, 30% of women used statins, 37% ACEIs, 37% BBs, 22% CCBs, and 44% diuretics. ACEI use was associated with an increased risk of SBCE (HR = 1.66; 95% CI, 1.06–2.58) compared to non-users, and BB use an increased risk of a recurrence (HR = 1.29; 95% CI, 1.01–1.64). Results were suggestive that statins reduced the risk of SBCE (HR = 0.82; 95% CI, 0.62–1.08) which appeared driven by effects on recurrence (HR = 0.78; 95% CI, 0.56–1.08). No associations were observed for CCBs or diuretics. We did not observe any trends by duration of CVD medication use.

Conclusions: Our findings suggest that most CVD medications are safe with respect to SBCE, but not necessarily preventive as previously hypothesized for statins and ACEIs. ACEIs and BBs warrant further evaluation.

394. Cardiac Mortality in Users of Olmesartan, Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors

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Background: Olmesartan has been a widely used ARB since 2002. There have been elevations of sudden cardiac death (SCD) in olmesartan users in two RCTs evaluating the delay in renal-related events in diabetes.

Objectives: To assess the risk of SCD in olmesartan users and in medically similar users of other ARBs and ACE inhibitors (ACEI).

Methods: With data from a large US commercial insurer in 2002–2009, we used propensity-score

matching to create new-user cohorts comparing olmesartan to (1) other ARBs and (2) ACEI. In secondary analyses, we formed cohorts with prior use of ACEI, and subcohorts of users of hypoglycemic agents. SCD was assessed using the US National Death Index, supplemented by insurance claims. Sensitivity analyses allowed for variations in the definition of continued use and for intent-to-treat analyses.

Results: There were 42,410 olmesartan initiators eligible for the primary cohort analysis, of whom 38,750 and 41,801 were matched to twice as many initiators of other ARBs and ACEI, respectively. Average follow-up on continuous treatment was 0.7 years. 84% were aged 35–64 years and 54% were men. Diagnoses, drugs and health care utilization in the 6 months before cohort entry were closely similar. SCD occurred at a rate of 0.4–0.5 per 1000 person years in the olmesartan cohorts and 0.6–0.7 in the comparators. In the secondary cohort with prior use of ACEI, SCD rates were 0.7 in olmesartan users and 1.0 in users of other ARBs. (Summary RR of olmesartan vs. other ARBs = 0.8, 95% CI: 0.5–1.3) Among users of hypoglycemic agents, there were three deaths in each cohort, giving approximately a doubling of SCD mortality in the olmesartan users over comparators. Sensitivity results resembled those of the primary analysis.

Conclusions: The study results do not raise any concerns for the relative safety of olmesartan in comparison to other ARBs or ACEI in the general population of users. The cohort sizes were adequate to assess whether there could have been two-fold or greater elevated risks of SCD associated with olmesartan. There was insufficient information to assess risks separately in diabetics.

395. Adherence to Antihypertensive Agents and Risk Reduction of End-Stage Renal Disease

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Background: Uncontrolled hypertension is associated with an increased risk of end-stage renal disease (ESRD). Intensified blood pressure control may slow progression of chronic kidney disease. However the impact of antihypertensive (AH) agents adherence on the prevention of ESRD has never been assessed.

Objectives: The objective was to assess the impact of AH agents adherence on the risk of ESRD in patients newly treated for hypertension.

Methods: A cohort of 185,476 patients was reconstructed using RAMQ databases. Patients were eligible if aged between 45 and 85 years, had a new diagnosis of hypertension and newly treated with AH agent between 1999 and 2007. A case cohort study design was used to assess the risk of ESRD. Multivariate Cox proportional models were used to estimate the adjusted hazard ratio (HR) of ESRD. Adherence level was reported as a medication possession ratio.

Results: Mean patient age was 63 years, 42.2% were male, 14.0% had diabetes, 30.3% had dyslipidemia, and mean time of follow-up was 5.1 years. High adherence level ($\geq 80\%$) to AH agent compared to the lower one was related to a risk reduction of ESRD (HR: 0.67; 0.54–0.83). Our sensitivity analysis reveals that the effect is mainly in patient without chronic kidney disease. Risk factors for ESRD were male sex, diabetes, peripheral artery disease, chronic heart failure, gout, previous chronic kidney disease, and use of more than one AH agents.

Conclusions: Our study suggests that a better adherence is related to a risk reduction of ESRD. Adherence to AH therapy needs to be improved to optimize benefits.

396. Re-Assessing the Cardiovascular Risk of Abacavir in the Swiss HIV Cohort Study (SHCS) Using a Flexible Marginal Structural Model

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Background: Recent but not cumulative exposure to the antiretroviral abacavir has been shown to increase the risk of cardiovascular disease (CVD) among HIV-infected patients in some studies. Attempts to find a mechanism that explains this increased risk have proved inconclusive.

Objectives: To determine how the risk of CVD cumulates over time in HIV+ patients exposed to abacavir.

Methods: A retrospective cohort analysis from patients enrolled in the SHCS from April 2000 to October 2012. The SHCS is an ongoing multicentre cohort of HIV+ adults followed approximately every 6 months. The primary outcome was a composite CVD endpoint – a myocardial infarction, cardiovascular related death

or invasive cardiovascular procedure. We fitted a series of Marginal Structural Cox models that accounted for time dependent confounding from CVD risk factors including conventional parametric models and a new model that estimates a flexible curve representing the cumulative exposure effect.

Results: Among 11,625 patients assessed, 4,474 were exposed to abacavir and 350 experienced the composite endpoint. In a conventional parametric Cox model, hazard ratios (95% CI) for the effect of abacavir on CVD were: 1.04 (0.99–1.09) for cumulative exposure (per year) and 1.52 (1.13–2.04) for any use within the last 6 months, similar to previously reported estimates (D:A:D study, Lancet 2008). A new flexible Cox model suggested, however, that exposure starts to affect the risk only after a short lag period and that abacavir use up to 20 months earlier was associated with a significant risk increase that gradually decreased with longer time since exposure. Indeed, when we fitted a parametric model with a different partition of time since exposure, current exposure was not associated with increased risk (HR 0.42, 95% CI: 0.25–0.69) but use in the past 1–6 months greatly increased risk (HR 3.36, 95% CI:2.04–5.53).

Conclusions: Current exposure to abacavir does not appear to present a risk; rather previous exposure, up to 20 months ago, has the most impact on cardiovascular risk, suggesting a mechanism other than acute inflammation is responsible.

397. Positive Predictive Values of Algorithms for Ascertainment of Major Congenital Malformations in Administrative Databases

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Background: Using claims data to monitor for potential teratogenic drug effects is an appealing concept, but the validity of automated case definitions for many major congenital malformations (MCMs) has not been established in commercial claims.

Objectives: To estimate the positive predictive value (PPV) of algorithms to identify 10 of the most common MCMs from claims data, using medical record review as a gold standard.

Methods: This validation exercise was part of a retrospective cohort study evaluating birth defects. Using administrative data from two of the largest commercial health insurers in the US, we identified mothers aged 15–49 who delivered a live infant from January 2004

to November 2010. We developed algorithms to identify 10 of the most common MCMs in the US based on diagnosis and procedure codes indicative of malformations and their expected process of care. Case definitions included only non-syndromic MCMs that were not caused by a genetic defect. The analysis required a minimum of 20 randomly sampled cases of each MCM. In total, 349 infants had their medical records retrieved and adjudicated by clinical geneticists. Analyses used PPVs to characterize the algorithms' validity.

Results: Across all defects, the PPV for specific MCMs was 67.9% (95% CI: 62.5–73.1). The overall PPV for ascertaining any of the MCMs of interest as a composite endpoint was 76.9% (95% CI: 71.8–81.5). PPVs for many specific MCMs were reasonably high (pyloric stenosis: 93.3%, ventricular septal defect: 90.9%, oral cleft: 89.3%, hypospadias: 80.0%, congenital hip dislocation: 75.9%). However, hydrocephalus (PPV = 47.4%) and several cardiac defects (conotruncal heart defects: 68.0%, aortic coarctation: 60.0%, pulmonary valve atresia: 44.4%, atrial septal defect: 37.9%) performed less well.

Conclusions: Many claims-based diagnoses of MCMs, especially cardiac anomalies, were not confirmed in clinical records. Other defects were more accurately identified, especially where a specific pattern of care such as corrective surgery was expected. To minimize outcome misclassification in birth defects research, certain claims-identified MCMs require additional confirmation.

398. Pitfalls of Evaluating Overall Relative Risk of Major Congenital Malformations (MCM) in Healthcare Databases

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Background: Researchers evaluating malformation risk after an exposure in pregnancy often assess *all* rather than *specific* MCM, although most known teratogens affect only a single or small numberof MCMs. Such studies using databases also sometimes report *overall* positive predictive value (PPV) among all identified MCM or a subsample of all MCM.

Objectives: To explore through simulation how the relative risk of all MCM and overall PPV are impacted in the case of increased risk of a single specific MCM after exposure during pregnancy.

Methods: We based our simulation on a published validation study of electronically identified MCM. We utilized the range of reported proportions among all MCM for each of the 10 most common MCM (spe-

cific MCM proportion). We varied from 2 to 4 the relative risk (RR_s) for a specific MCM associated with a hypothetical pregnancy exposure, set RR = 1.0 for all other MCM, varied from 4% to 26% the specific MCM proportion, set PPV for a specific MCM (PPV_s) to 50% or 95%, and set PPV for all other MCMs to 75%. We then derived corresponding relative risk for all MCM and the difference in all-MCM-PPV between the exposed and unexposed.

Results: When we set $RR_s = 2$ for the specific MCM after exposure and $PPV_s = 50\%$, over the range of specific MCM proportions the all-MCM PPV difference between exposed and unexposed varied from −4% to −8%, and the RR for all MCMs in the exposed group varied from 1.04 to 1.26. When RR_s was increased to 4, RR of all MCM varied 1.12 to 1.78. When we set $RR_s = 4$ and $PPV_s = 95\%$, the all-MCM PPV difference between exposed and unexposed varied from 2% to 6% over the evaluated range of specific MCM proportions.

Conclusions: Use of the overall PPV in a database study can result in biased estimates of the number of all MCM in the exposed and the unexposed. For the situation of exposure increasing risk of only a single MCM, evaluation of RR over all MCM results in a weighted average that reflects neither the RR for the specific MCM nor the lack of excess risk for all other MCM.

399. Methylergonovine Maleate and the Risk of Myocardial Ischemia and Infarction

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Background: Methylergonovine maleate (Methergine) is commonly used to treat uterine atony. In 2012, based on spontaneous reports, the U.S. Food and Drug Administration identified a 'potential signal of serious risk/new safety information' regarding myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.

Objectives: To examine the risk of acute coronary syndrome (ACS) and acute myocardial infarction (AMI) associated with methylergonovine use in a large database of inpatient delivery admissions in the United States.

Methods: We conducted a retrospective cohort study using data from the Premier Perspective Database, and identified 2,233,630 women hospitalized for delivery between 2007 and 2011 (approximately one-seventh of all U.S. deliveries during this period). Exposure was defined by a charge code for methylergonovine. Study outcomes included acute coronary syndrome (ACS) and acute myocardial infarction (AMI). Propensity score matching was used to address potential confounding.

Results: Methylergonovine was administered to 139,617 (6.3%) patients. Overall, six patients exposed to methylergonovine (0.004%) and 52 patients unexposed to methylergonovine (0.002%) had an ACS. Four patients exposed to methylergonovine (0.003%) and 44 patients in the unexposed group (0.002%) had an AMI. After propensity score matching, the relative risk for ACS associated with methylergonovine exposure was 1.67 (95% CI 0.40–6.97) and the risk difference was 1.44 per 100,000 patients (95% CI −2.56, 5.45); the relative risk for AMI associated with methylergonovine exposure was 1.00 (95% CI 0.20–4.95) and the risk difference was 0.00 per 100,000 patients (95% CI −3.47, 3.47).

Conclusions: Despite studying a very large proportion of U.S. deliveries, we did not find a significant increase in the risk of ACS or AMI in women receiving methylergonovine compared with those who did not; estimates were increased only modestly or not at all. The upper limit of the 95% confidence interval of our analysis suggests that treatment with methylergonovine would result in no more than 5 additional cases of ACS and three additional cases of AMI per 100,000 exposed patients.

400. Acid-Reducing Drugs in Pregnancy: Patterns of Use and Risk of Selected Birth Defects

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Background: Acid-reducing drugs are among the most commonly-used drugs in pregnancy. A few studies of maternal use of proton pump inhibitors (PPIs) and histamine-2 blockers (H2Bs) have identified modest increases in risks of several birth defects, but others offer reassurance of their relative safety.

Objectives: To identify trends in PPI and H2B use in pregnancy; to test and generate hypotheses regarding these drugs and specific birth defects.

Methods: We used data from the case-control Slone Birth Defects Study to examine patterns of maternal use of PPIs and H2Bs in 17,154 cases and 8,456

nonmalformed controls for 1997–2011. We tested previously-reported associations for first trimester exposure to PPIs and cleft palate, esophageal atresia, hypospadias, anencephaly, and heart defects, and H2Bs and neural tube and heart defects; we also tested these associations for the most commonly-used PPIs (omeprazole[M], lansoprazole [L], esomeprazole [E]) and H2Bs (ranitidine [R], famotidine [F]). Risks for other defects were estimated for case groups with five or more exposures to a particular drug.

Results: Use of PPIs increased from 0.3% to 3.0% and H2Bs from 2.65 to 7.0%, while antacid use decreased from 14.3% to 3.7%. In testing hypotheses, we observed increased risks for the PPI class and six defects (four were specific heart defects), M and two defects (one heart), and L and four defects (three heart). ORs ranged from 1.9 to 12.1 with varying stability levels. Defects differed for M and L. Increased risks were observed for the H2B class and one heart defect, R and one heart defect, and F and one non-heart defect (ORs 1.8–2.6, with varying stability). For hypothesis generation, we observed an increased risk for E and cleft lip with/without cleft palate and R and hypospadias.

Conclusions: Our analyses by specific drugs supported several hypotheses reported previously and identified two risks not reported in prior studies. Because no defects with increased risks were common to more than one drug within a class, our study does not support class-based effects for PPIs and H2Bs. The same heterogeneity suggests that confounding by indication does not explain the associations observed.

401. Use of Macrolides during Pregnancy and the Risk of Birth Defects

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Background: Anti-infective drugs are amongst the most frequently used medications during pregnancy and macrolides are the second most frequently used class of antibiotics in early pregnancy. Nevertheless, limited data on the risk of birth defects associated with their use are available.

Objectives: Quantify the association between macrolide exposure during pregnancy, with focus on newer types, and the risk of birth defects (BD).

Methods: A case-control study within the Quebec Pregnancy Registry, which includes all singleton pregnancies between January 1998 and December 2008, was performed. To be included in this study pregnancy had to be insured by the Provincial Drug Plan, and have a live birth. Exposure to erythromycin, non-erythromycin macrolides or penicillin was compared to non-use of any antibiotics during the 1st trimester of pregnancy. Three independent analyses were performed with cases defined as having a validated diagnosis of major BD; congenital heart defect (CHD); or pediatric hypertrophic pyloric stenosis (PHPS) in the first year of life according to ICD-9 codes 740–759.9 and ICD-10 codes Q00–Q99. Generalized estimating equations models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for potential confounders.

Results: Of 135,905 pregnancies met eligibility criteria; 735 were exposed to erythromycin, 1,597 to non-erythromycin macrolide, and 9,106 to penicillin in the 1st trimester. Adjusting for potential confounders and compared to non-users, erythromycin use was not associated with an increased risk of major BD (OR: 0.97, 95%CI: 0.75–1.25), CHD (OR: 1.14, 95%CI: 0.69–1.88) or PHPS (OR: 0.86, 95%CI: 0.21–3.45). However, non-erythromycin macrolides were increasing the risk of BD (OR: 1.17, 95%CI: 1.00–1.36), and PHPS (OR: 2.13, 95%CI: 1.19–3.79) but not CHD (OR: 0.89, 95%CI: 0.62–1.28). No association between penicillin exposure and major BD, CHD or PHPS was found.

Conclusions: Exposure to non-erythromycin macrolides during the 1st trimester of pregnancy was associated with an increased risk of major BD and PHPS even after adjustment for potential risk factors. This association was not found among pregnancies exposed to erythromycin or penicillin.

402. SSRI and the Risk of Miscarriage – A Register Based Nation Wide Cohort Study

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Background: In Denmark 4% of pregnant women are treated with an SSRI. Since Bassiouni found that women having a miscarriage had higher levels of serotonin, treatment with SSRIs during pregnancy has been of great concern. Several smaller studies have shown an association between in utero exposure to SSRIs and miscarriage. None of these studies have dealt with confounding by indication.

Objectives: The aim of the study was to investigate whether use of SSRIs in early pregnancy are associated with an increased risk of miscarriage.

Methods: We conducted a nationwide cohort study including all women in Denmark with a registered pregnancy between 1997 and 2007. The Danish Fertility Database was used to identify all women giving birth and the National Hospital Register was used to identify all women with a record of miscarriage or induced abortion. Prescription data was obtained from the National Prescription Register. Primary outcome was the number of miscarriages among users of SSRIs compared to non-users and women discontinuing SSRI-treatment before pregnancy. Cox proportional hazard regression models were used with exposure to SSRIs and time from conception to miscarriage as outcome. Time to birth or induced abortion was considered as censoring variables.

Results: We identified 931152 pregnancies, of which 13394 were exposed to an SSRI in at least the first 35 days of pregnancy. Among the SSRI exposed 1217 (9.1%) experienced a miscarriage compared to 76336 (8.2%) in the unexposed group. The adjusted hazard ratio of having a miscarriage after exposure to an SSRI was 1.18 (1.11–1.25). Women discontinuing SSRI treatment 3–12 months before pregnancy had an adjusted hazard of 1.15 (1.10–1.20) of having a miscarriage.

Conclusions: We found an association between redeeming a prescription of an SSRI during pregnancy and miscarriage. We found the same association in women discontinuing SSRI before pregnancy. This indicates that our results are due to special characteristics of these women (confounding by indication) and not the SSRI-treatment. This is a novel finding.

403. Technology Diffusion in the Antipsychotic Market: A Comparison of France and the USA between 1998 and 2008

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Background: Second generation antipsychotics captured the majority of the US antipsychotic market shortly after their introduction. Little is known about how second generation antipsychotics diffused in other countries with different health systems.

Objectives: To describe trends in antipsychotic use in the US and France from 1998 to 2008.

Methods: Descriptive data on quarterly prescriptions dispensed between 1/1998–9/2008 for oral antipsychotics from XponentTM for the US, and sales recorded in the GERS database for France are presented. Trends in the share of antipsychotic use for first vs. second generation antipsychotics, and in ingredient-level of second generation antipsychotics use are reported.

Results: In the US, between 1998 and 2008, total antipsychotic use increased by 78%. Total use was consistently higher in France despite a 9% decrease during the period. By 2008, second generation antipsychotics represented 90% of the antipsychotic US market vs. only 40% in France. However, average annual growth rates in second generation antipsychotics use were similar in the two countries. In France, there was a steady increase in use of all but one second generation antipsychotic; whereas trends in the use of newer drugs varied substantially by drug in the US (e.g. use of olanzapine decreased after 2003 whereas use of quetiapine increased).

Conclusions: These results highlight markedly divergent trends in the diffusion of new antipsychotics in France and the US. Some of these differences may be explained by differences in health systems, while others may reflect physicians' preferences and norms of practice.

404. Geographic and Clinical Variation in Clozapine Use in the U.S.

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Background: Antipsychotic medications (APMs) are largely ineffective for ~30% of patients with schizophrenia who are considered *treatment resistant*. Clozapine is the only APM approved for treatment-resistant schizophrenia, but it is rarely used.

Objectives: This nationwide study examines predictors of clozapine use to help identify ways to optimize its use.

Methods: Retrospective cohort study using U.S. Medicaid claims for 326,119 individuals with schizophrenia (ICD 295.x) who initiated ≥ 1 new APM treatment episodes between 1/2002 and 12/2005. Multivariable logistic regression models (GEE, logit link, clustered on county) were used to calculate adjusted odds ratios (AORs) of baseline patient and county factors associated with clozapine initiation. Treatment resistance

was defined by a claims-based algorithm that indicates instable treatment and impaired global functioning despite adequate APM adherence prior to the index date. To examine to what extent local treatment culture affects geographic variation in clozapine use, we included the county-specific clozapine use rate during the year prior to the study period among predictors of clozapine use during the study period.

Results: We observed 629,809 new APM treatment episodes, 79,934 of which showed service use patterns consistent with treatment resistance. Clozapine accounted for 2.5% of overall APM starts and for 5.5% of starts among patients with treatment resistance. State specific clozapine initiation rates varied from 0.9% to 7.8%, while county specific clozapine initiation rates varied from 0% to > 15%. Clozapine initiation was significantly associated with male sex, younger age, white race, more frequent service use for schizophrenia, and greater prior-year hospital use for mental health. Treatment resistance (AOR 1.92; 1.83–2.03) and living in a county with historically high rates of clozapine use (AOR 2.02; 1.75–2.30) were among the strongest predictors of clozapine use.

Conclusions: Only a small fraction of treatment-resistant schizophrenia patients receive a clozapine trial and use rates are substantially affected by local treatment practices. Concerted efforts are needed to improve access to clozapine and thereby optimize recovery opportunities.

405. Prevalence and Trends of Antipsychotic Utilization in Long-Term Care in Saskatchewan, Canada

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Background: Use of antipsychotics in long-term care facility (LTCF) residents should be minimized because of associated risks. Thus, surveillance on the utilization of these medications can provide information for assessing the quality of resident care and establishing targets for intervention.

Objectives: To determine prevalence and time trends in antipsychotic utilization in LTCF residents in Saskatchewan.

Methods: We identified all provincial drug plan beneficiaries (~90% of the province) ≥ 65 years residing ≥ 1 day in a LTCF between April 2002 and March 2011 (fiscal year [fy] 2002–2010) and their antipsychotic dispensations from the Saskatchewan Health

databases. Poisson regression analyses, adjusted for fiscal year and 5-year age groups were used to model the relative rate (RR) of dispensations. Typical and atypical agents were separately analyzed. Time in hospital was excluded from the person-time denominator.

Results: The cohort contained 33,589 seniors with 292,695 dispensations in 65,711 person-years. On average, the annual dispensation rate was 4.5 antipsychotics of any type per person-year (95% confidence interval [CI] 4.1–4.8). The average rate increased by 3.1% annually (95% CI 0.3%–6.1%). This was mainly driven by the 9.3% (95% CI 7.0%–11.7%) increase among the oldest residents ≥ 85 years amounting to a doubling in their dispensations from fy 2002 to 2010 (RR 2.18 95% CI 2.14–2.23). Dispensations of typical antipsychotics to all seniors declined, on average, by 10.1% (95% CI 6.6–13.8) annually.

Conclusions: Antipsychotic use has increased in LTCFs between 2002 and 2011, especially among the oldest residents. Although these time trends are only age-adjusted, they are consistent with prior studies observing increased use of atypical agents across many other patient groups. As the oldest seniors are particularly vulnerable to adverse drug events of antipsychotics, further investigation of these findings is warranted.

406. The Risk of Incident Rosacea Associated with Psychiatric Diseases and Psychotropic Drug Therapy

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Background: Rosacea is a chronic skin disease of unclear origin. Despite scarce evidence, rosacea has been linked to emotional stress and anxiety. A large case-control study reported an association of depression and the skin disease. We are not aware of any studies assessing a link between rosacea and schizophrenia or use of antidepressant or antipsychotic drugs.

Objectives: To analyze the association between psychiatric diseases and psychotropic drugs and the risk of incident rosacea.

Methods: We conducted a matched (1:1) case-control analysis using the UK-based General Practice Research Database. We included incident rosacea

cases diagnosed between 1995 and 2009, and compared the prevalence of psychiatric diseases and previous exposure to antidepressants and antipsychotics between cases and controls.

Results: We included 60,042 rosacea patients, of which 10,413 (17.3%) had been diagnosed with depression, yielding an adjusted odds ratio (OR) of 1.17 (95% CI 1.13–1.21). Other affective disorders (i.e. bipolar-/manic disorders) revealed an adj. OR of 1.16 (95% CI 1.08–1.25). With regard to antidepressant drugs, selective serotonin reuptake inhibitors and monoamine reuptake inhibitors did not affect the risk estimate, but exposure to lithium revealed significantly decreased ORs, namely in current long-term users (OR 0.59, 95% CI 0.40–0.87, i.e. 40+ prescriptions/last recorded prescription < 180 days). This effect was similar in patients with or without a concomitant schizophrenia diagnosis. Patients with schizophrenia yielded an overall significantly decreased adjusted OR of 0.71 (95% CI 0.60–0.84), which persisted across all strata of drug treatments. Neurotic, stress-related, and somatoform disorders (NSSD) revealed an OR around unity.

Conclusions: Contrarily to previous findings, depression was not associated with rosacea. On the other hand, our results suggest a decreased rosacea risk in patients with schizophrenia, independently of antipsychotic drug treatment. Furthermore, we observed decreased ORs in patients on lithium, irrespective of the underlying psychiatric diagnosis. To our knowledge, this is the first description of a potential effect of lithium on rosacea.

407. Antidepressant Treatment (ADT) Following a Cancer Diagnosis: Investigation in a Cohort of Older Patients

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Background: The psychosocial impact of a cancer diagnosis and subsequent treatment is recognised as a significant health issue. There is limited data on the impact of cancer diagnosis on the uptake of ADT.

Objectives: To investigate how ADT initiation rates are affected by the cancer diagnosis in a population-based cohort of older Australians.

Methods: Our cohort comprised 61,043 Department of Veterans' Affairs clients with full prescription drug coverage naive to ADT (July–December '04). Our outcome was ADT incidence from '05–'09. We used multivariable Cox proportional hazards models with time-varying covariates to compare ADT incidence in clients with and without cancer. We used quadratic B-splines to model the impact of time before/after cancer diagnosis on ADT incidence, adjusting for sociodemographics, prior health service use and comorbidities.

Results: 17.2% (994/5782) of cancer patients initiated ADT in the 6 months prior to and 3 years after diagnosis, (9 per 100 person-years, 95%CI: 8.5–9.6). ADT incidence was similar among future cancer patients and non-cancer controls in the 6 months prior to diagnosis (adjusted HR = 0.66, 95% CI: 0.3–1.3, p = 0.23), but varied significantly in the study period (p < 0.01), increasing slowly at 4–5 months before diagnosis and peaking between 1 month prior to and 3 months after diagnosis. In this peak incidence period cancer patients were about 40% more likely to commence ADT than non-cancer controls with similar characteristics (HR = 1.4, 1.2 to 1.8). ADT incidence between cancer and non-cancer patients returned to similar levels in the period 3–6 months after diagnosis.

Conclusions: The increase in antidepressant use following a cancer diagnosis suggests treatment for adjustment rather than major depression. This is also a time when cancer drug treatments are initiated, increasing the risk of interactions and adverse outcomes. This is especially problematic in elderly patients who are also taking drugs to manage comorbid disease.

408. Reported Off-Label Use of Psychotropic Drugs in Rehabilitation Centers for Acquired Brain Injury: A Cross-Sectional Survey in Italy

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Background: In treating patients with acquired brain injury (ABI) with multiple neuropsychological conditions, clinicians face the choice of using psychotropic drugs (PsyD) outside their registered indications. Very limited or low-level evidence is available on the effectiveness and safety of PsyD off-label use. Causes of concern include economical and ethical issues.

Objectives: To assess the prevalence of PsyD off-label use in rehabilitation centers (RCs) for ABI in Italy.

Methods: Setting: tertiary care rehabilitation centers for ABI (RCs) in Italy, between September 1 and

November 30, 2012. 40 RCs were asked to participate in the study and mailed a structured questionnaire (Q) inquiring on: (part 1) facility characteristics (type, number of beds, geographical region), use of drugs, indications, off-label use with regard to the Italian Formulary; (part 2) characteristics of ABI inpatients and drugs used at the survey. Reminders were sent to non-responders after 2 weeks and 1 month. Prevalence of use and descriptive statistics including median (M) and interquartile range (IQR, 25° and 75°percentile) were calculated.

Results: Out of 35 (87.5%) participating RCs 65.7% were in northern Italy, their number of beds varied from 67 to 4 (M 15, IQR 8-30) and of ABI inpatients at the survey from 65 to 2 (M 12, IQR 6–23). In Q part 1 all RCs reported to use levetiracetam, 97% quetiapine, 94% baclofen per os and 80% intrathecal, 91% citalopram, 91% valproate. Off-label use was frequent for PsyD: 52.9% of RCs reported to use off-label quetiapine, 61.11% risperidone, 51.7% olanzapine (all the above for agitation, sleep disturbances), 54.5% amitriptyline (for sialorrhea, neuropathic pain, and sleep disturbances), 41.9% amantadine (for agitation and as inotropic agent), 35.7% levodopa-benserazide and 26.9% levodopa-carbidopa (both as nootropic agents).

Conclusions: PsyD off-label use in RCs for ABI was frequent, in particular for atypical antipsychotics. Careful monitoring of off-label drug use is recommended in ABI inpatients.

409. Comparative Effectiveness of Oral Diabetes Drugs in Observational Data: Closing Evidence Gaps

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Background: All modern diabetes drugs have been approved based on the ability to lower glycosylated hemoglobin (HbA1c), but evidence on their comparative effectiveness on this endpoint is limited, particularly in long term therapy, drug combinations, and in subgroups defined by body-mass index (BMI) and sex.

Objectives:

(1) Assess the reduction in HbA1c associated with diabetes drugs
(2) Assess how that reduction is affected by duration of therapy

(3) Assess whether there are interactions between commonly used combinations of diabetes drugs
(4) Assess whether there are interactions between drugs and age, sex, or BMI.

Methods: An observational database that captures prescriptions for drugs and serially measured HbA1c was used to define a cohort of patients starting single-, dual-, and triple-drug therapy with four commonly used classes of oral antidiabetic agents: metformin, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase – 4 (DPP-4) inhibitors. Change in HbA1c subsequent to drug start was modeled over long-term followup using a mixed model spline with adjustment for baseline covariates.

Results: Sulfonylureas were associated with a large initial decline in HbA1c, but in long-term follow-up were no more effective than other classes. Thiazolidinediones were more effective in patients with higher BMI and in women, and the additive effects of these interactions made them the most effective class in selected populations. For example, in severely obese women thiazolidinediones were associated with a long-term change of −0.95 percentage points (95% CI −1.02 to −0.88) in HbA1c compared to −0.41 points (95% CI −0.45 to −0.36) for sulfonylureas and −0.54 (95% CI −0.67 to −0.42) for DPP-4 inhibitors.

Conclusions: Large initial responses to sulfonylureas are undermined by lack of durability. Thiazolidinediones appear to be the most effective second-line drug in selected populations, particularly obese women. DPP-4 inhibitors appear to be a viable alternative to sulfonylureas as second-line therapy. Although further research is needed on long term safety and clinical effects, these findings have important implications in the treatment of diabetes.

410. Risk of Acute Myocardial Infarction in Patients with Diabetes Mellitus Type 2 Treated with Basal Insulin

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Background: Glycemic control is important to reduce the risk of cardiovascular (CV) diseases in patients with type 2 diabetes (T2D). Results of clinical trials and observational studies are inconsistent.

Objectives: To investigate the risk of acute myocardial infarction (AMI) in patients with T2D treated with long-acting analog insulin compared to neutral protamine Hagedorn (NPH) and premixed insulin.

Methods: We used claims data of 3 German statutory health insurances from 2004–2009 to conduct a study in a cohort of patients with T2D who initiated insulin treatment. Naïve insulin users were defined as patients who were continuously enrolled for at least 9 months before the first prescription of long-acting analog, NPH or premixed insulin and who were treated with oral antidiabetic drugs during this 9 month baseline period. Patients taking any insulin during the baseline period were excluded from the cohort. Adjusted Hazard Ratios (HRs) of AMI and corresponding 95% confidence intervals (CI) for analog insulin compared to NPH and premixed insulin were calculated by gender-stratified multivariable Cox regression. Propensity-score matched analyses were conducted as sensitivity analyses.

Results: Among 9 million insurants, we identified 21,501 new insulin users with a median follow-up of 771 days in the cohort. Patients treated with premixed insulin were older than patients treated with analog or NPH insulin (mean age 70.7 vs. 64.1 and 61.6 years) and had more comorbidities. Compared to analog insulin, NPH insulin users switched more often to an intensified conventional therapy. The crude incidence rate was 10.86 AMI/1,000 person-years. Adjusted HRs revealed no difference between NPH and analog insulin (HR: 0.95, 95% CI: 0.75–1.20) and a higher risk for premixed insulin compared to analog insulin (HR: 1.27, 95% CI: 1.02–1.59). The propensity-score analysis confirmed this result.

Conclusions: Regarding the risk of AMI no difference was observed between analog- and human basal insulin in this observational study, which is in line with results of the ORIGIN RCT. However, the comparison might be distorted by the short follow-up time and emerging differences in the therapy.

411. Comparative Effectiveness of Insulin vs. Combination Insulin and Sulfonylurea on Cardiovascular Outcomes

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Background: Diabetes treatments are limited for patients with abnormal glomerular filtration rate (GFR). Often sulfonylureas are used but after failure therapy js uncertain since those with low GFR can develop adverse affects such as hypoglycemia and cardiovascular disease (CVD).

Objectives: To compare hazard of CVD events or cardiovascular death among patients who added insulin to sulfonylurea or switched to insulin monotherapy.

Methods: We assembled a national retrospective cohort of veterans who initiated diabetes treatment with sulfonylurea between 2001 and 2008 (inception cohort) and then added insulin through 2010. Follow-up continued until an outcome (CVD events: myocardial infarction; stroke hospitalization; cardiovascular death) death from any cause or study end. The composite outcome risk was compared between the two treatments using marginal structural Cox proportional hazard models adjusting for baseline and time-varying demographics, medications, cholesterol, HbA1c, creatinine, blood pressure, body mass index, and co-morbidities. Subgroup analyses evaluated risk by GFR (< 60 or ≥ 60 mL/min).

Results: Among 191,281 sulfonylurea monotherapy regimens (glipizide N = 86,979; glyburide N = 104,302), most patients (47%) remained on sulfonylurea monotherapy (mean 39.5 follow-up months). There were 23.4% who intensified therapy but not with insulin. Of 2,175 and 1,960 patients added insulin to sulfonylurea or switched to insulin monotherapy, respectively. Patients were 97% male and those who added insulin were similar in age (64 vs. 64 years), HbA1c, (8.3 vs. 8.1%), and GFR (58.3 vs. 57.2 mL/min) to those who switched to insulin. The composite outcome was 28 vs. 30 events per 1,000 person-years, among sulfonylurea + insulin vs. insulin monotherapy respectively (aHR 1.03 [0.80,1.34]). CVD rates were 15.5 and 17.5 per 1,000 person-years, respectively (aHR 1.15 [0.81,1.64]), while all-cause death rates were 67.2 and 76.0 per 1,000 person-years, respectively (aHR 1.06[0.91,1.25]). Results were consistent in GFR subgroups.

Conclusions: Preliminary analyses finds risk of the composite outcome: CVD or death was similar for those who added insulin to sulfonylurea or switched to insulin.

412. The Effect of Intravenous Iron Supplementation Practices on Infection Risk in Hemodialysis Patients

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Background: Intravenous iron may promote bacterial growth and impair host defense, yet definitive studies on iron and infection risk are lacking.

Objectives: We conducted a retrospective cohort study of hemodialysis patients to compare the safety of bolus or repletion dosing (providing a large amount of iron over a short period of time) vs. maintenance dosing (smaller, less frequent administrations designed to maintain iron repletion).

Methods: Using detailed clinical data from a large US dialysis provider merged with data from Medicare's ESRD program, 2004–2008, we estimated the effects of iron dosing during repeated 1-month exposure periods on risks of mortality and infection-related hospitalizations occurring during a 3-month follow-up period.

Results: Of 117,050 patients met study entry requirements and contributed data on 776,203 exposure/follow-up periods. Twelve percent of exposures were bolus dosing, 49% were maintenance dosing, and 38% were no iron. Multivariable additive risk models adjusting for many clinical and laboratory variables found that patients receiving bolus vs. maintenance iron were at increased risk of infection-related hospitalization (risk difference [RD] of 25 additional events per 1,000 patient-years, 95% CI 16, 33) during follow-up. Risks were largest among patients with a catheter (RD 73 per 1,000 patient-years, 95% CI 48, 99) and a recent infection (RD 57 per 1,000 patient-years, 95% CI 19, 99).

Conclusions: Bolus dosing of intravenous iron appears to increase risk of serious infection in hemodialysis patients.

413. Comparative Safety of Corticosteroids on the Risk of Acute Myocardial Infarction: A Retrospective Cohort Study

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Background: Corticosteroids are potent anti-inflammatory drugs, and are widely prescribed. There are several reports that the risk of cardiovascular diseases (CVD) associated to the current use and high dose of corticosteroids. However, studies on the comparative safety of those drugs on risk of acute myocardial infarction (AMI) are scarce.

Objectives: To assess and compare the risk of AMI associated with each corticosteroid using a national health insurance database.

Methods: We used the Korea Health Insurance Review and Assessment Service-National Patients Sample (HIRA-NPS) database. Retrospective cohort analysis was conducted on 20 years or older who prescribed corticosteroids between April 2009 and September 2009. Patients prescribed at least one corticosteroid during January to March 2009 were excluded. We included prednisolone, triamcinolone, dexamethasone, methylprednisolone, hydrocortisone, betamethasone, fludrocortisone, and deflazacort as study drugs. Corticosteroids users were followed until they were diagnosed with acute myocardial infarction (ICD 10, I21), until death (I461, R960, R961, R98) or until the end of the study. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and the 95% confidence intervals (CIs), while adjusting for comedications and comorbidities.

Results: AMI was reported in 1,483 of 183,601 corticosteroid users (15 per 1,000 person-years). Compared with prednisolone users, the HR of AMI was 1.25 (95% CI = 1.00–1.55) in methylprednisolone users, and 1.06 (95% CI = 0.86–1.30) in dexamethasone users. Patients who prescribed two or more corticosteroids showed significantly increased risk of AMI (HR 1.21, 95% CI = 1.02–1.43). Patients with cumulative dose of more than 183 mg of prednisolone-equivalent dose, showed increased risk compared with < 45 mg of prednisolone-equivalent dose (HR 1.24, 95% CI = 1.07–1.43).

Conclusions: Difference in the risk of AMI according to each corticosteroid and cumulative dose was observed. Based on the results, continuous users of corticosteroids needs monitoring for AMI, and the monitoring strategy may differ according to each corticosteroids.

414. Choice of Scale for Assessment of Comparative Treatment Effect Heterogeneity

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Background: Treatment effect heterogeneity is typically evaluated on the relative scale (hazard ratios, relative risks) but the absolute scale (risk differences, numbers needed to treat) is arguably more relevant for comparing the magnitude of benefits and harms.

Objectives: To assess heterogeneity in the effect of high vs. low potency statins on mortality among patients with a recent myocardial infarction (MI), comparing effect estimates on the relative and absolute scales for key subgroups.

Methods: We identified all Medicare beneficiaries ≥ 66 who had an MI in 2008 and received a statin during within 30 days after discharge from the hospital. We characterized baseline covariates (comorbid conditions, medication use) during the 12 months prior to hospitalization using Part A, B, and D claims. All-cause mortality was assessed through 31 December 2009. We used inverse probability of treatment weights to adjust for baseline differences when estimating the hazard ratio (HR), cumulative mortality at 1-year, risk difference at 1-year, and number needed to treat (NNT). Confidence intervals (95% CIs) for each effect measure were bootstrapped from 1,000 resamples. Subgroups of interest included gender, race/ethnicity, age (in 5-years categories), type II diabetes, and hypertension.

Results: We identified 42,925 patients treated with statins post-MI (low n = 27131, high n = 15804). Patients receiving high potency statins had a lower rate of all-cause mortality (HR = 0.95, 95%CI 0.92–0.98; risk difference at 1 year = 0.010, 95% CI: 0.005–0.015; NNT at 1 year = 96, 95%CI 65–189). Relative effect estimates were similar across the sexes (men: HR = 0.93, 0.87–0.99; women: HR = 0.96, 0.91–1.01) whereas the 1 year NNT ranged from 71 in men (95%CI: 42–222) to 109 in women (95%CI: 55–∞), reflecting a 54% increase in the number of women who would need to be treated with high potency statins for one year to prevent one death compared to men. We will present findings for additional subgroups based on demographic (race/ethnicity, age) and clinical (hypertension, type II diabetes) characteristics.

Conclusions: Important differences in the magnitude of comparative treatment effects may not be evident on the relative scale.

415. Autoimmune Disorders and Quadrivalent Human Papillomavirus Vaccination of Young Females

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Background: Alleged associations between vaccines and autoimmune disorders (ADs) continue to hamper the success of mass vaccination with new vaccines.

Objectives: To investigate whether the quadrivalent human papillomavirus (HPV) vaccine is associated with a change in the risk of ADs in young females.

Methods: For this case-control study, between December 2007 and April 2011, a network of 113 specialist centers throughout France recruited incident cases of

ADs among females aged 14–26 years. Controls were recruited from general practice settings and matched to cases on date of recruitment, age and region of residence. Centers recruiting patients were widespread throughout France to ensure generalizability to the population. Vaccinations and other potential risk factors for ADs were assessed in a standardized telephone interview of patients or their parents. The interviewer was blind to case/control status. Ninty-seven percent of reported quadrivalent HPV vaccinations were confirmed using medical records from the patient or her general practitioner. The risk of the outcome (case/control status) was described using conditional logistic regression.

Results: Three hundred and eight eligible cases of ADs were recruited and 211 were included in the analysis. Of 1,635 eligible controls were recruited and 875 were matched to cases. Of 25 cases (11.8%) and 192 controls (21.9%) received the quadrivalent HPV vaccination within predefined time windows before the index date (adjusted OR 0.9, 95% CI 0.5, 1.5). The separate ORs were: 1.0 (95% CI 0.4–2.6) for immune thrombocytopenia; 0.8 (95% CI 0.3–2.4) for connective tissue disorders; 0.3 (95% CI 0.1–0.9) for central demyelination; 1.2 (95% CI 0.4–3.6) for type 1 diabetes. No cases of Guillain-Barré syndrome or autoimmune thyroid disorders were exposed to the vaccine.

Conclusions: We found no evidence that vaccination with the quadrivalent HPV vaccine was associated with an increase in the incidence of ADs in young females.

416. Cumulative Risk of Guillain-Barré Syndrome among Vaccinated and Unvaccinated Populations during the 2009 H1N1 Pandemic

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Background: Guillain-Barré syndrome (GBS) surveillance systems during the 2009 pandemic found a small increased risk of GBS during the 6 weeks following (H1N1) 2009 (pH1N1)vaccination; however it has been suggested that this association was confounded by pH1N1 infection. There is evidence that GBS risk is much higher after influenza-like illnesses than the risk after vaccination.

Objectives: To assess the cumulative GBS risk among pH1N1 vaccinated and unvaccinated populations at the end of the (H1N1) 2009 pandemic.

Methods: We used GBS surveillance data from a population catchment area of 45 million in the U.S. from

October 15, 2009 through May 31, 2010. GBS cases meeting Brighton Collaboration criteria levels 1–3 were included. We calculated the incidence density ratio (IDR) among pH1N1 vaccinated and unvaccinated populations. We also estimated cumulative probability of incident GBS among these two groups using a lifetable analysis. Daily and monthly vaccine coverage data from representative samples and census population estimates were used to calculate denominators.

Results: Sixty-four (16%) of 392 GBS cases occurred after vaccination. At the end of the study, the vaccinated population had lower average GBS risk (IDR = 0.83, 95% confidence interval = 0.63, 1.08) and lower cumulative GBS risk (6.6 vs. 9.2 cases per million persons, p = 0.012). The cumulative GBS risk among the vaccinated group was lower throughout the study period, however during January/February the risk was similar (although still lower) to that of the unvaccinated group.

Conclusions: Although studies have demonstrated an increased GBS risk during the 6 weeks following vaccination, our findings demonstrate a lesser cumulative GBS risk among the pH1N1 vaccinated population at the end of the (H1N1) 2009 pandemic, suggesting potential benefit from pH1N1vaccination as it relates to GBS.

417. Effectiveness of Influenza Vaccination in Working Age Adults with Diabetes: A Population-Based Cohort Study

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Background: Guidelines recommend influenza vaccinations in all diabetic adults, but there is limited evidence to support vaccinating working age (< 65 years) adults with diabetes.

Objectives: We intended to examine the effectiveness of influenza vaccine in working age (< 65 years) adults with diabetes, compared with elderly (≥ 65 years) adults for whom vaccination recommendations are well accepted. Furthermore, we intended to evaluate the potential for bias in the estimates of vaccine effectiveness in this population-based observational study.

Methods: We identified all adults with diabetes, along with a sample of age- and sex-matched comparison subjects without diabetes, from 2000 to 2008, using administrative data from Manitoba, Canada. With multivariable Poisson regression, we estimated vaccine

effectiveness on influenza-like illnesses (ILI), pneumonia and influenza hospitalizations (PI), and all-cause hospitalizations (ALL), during periods of known circulating influenza. Analyses were replicated outside of influenza season to rule out residual confounding.

Results: We included 543,367 person-years of follow-up, during which 223,920 ILI, 5,422 PI, and 94,988 ALL occurred. The majority (58%) of adults with diabetes were working age. In this group, influenza vaccination was associated with relative reductions in PI (43%, 95% CI: 28–54%) and ALL (28%, 95% CI: 24–32%), but not ILI (−1%, 95% CI: −3 to 1%). Vaccine effectiveness was similar in elderly adults for ALL (33–34%) and PI (45–55%), though not ILI (12–13%). However, similar estimates of effectiveness were also observed for all three groups during non-influenza control periods, before and after the documented annual influenza seasons.

Conclusions: Working age adults with diabetes experience similar benefits from vaccination as elderly adults, supporting current diabetes-specific recommendations. However, these benefits were also manifest outside of influenza season, suggesting residual bias. Vaccination recommendations in all high risk adults would benefit from randomized trial evidence.

418. Outcome-Based Vaccine Safety Surveillance

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Background: Ongoing surveillance of adverse events following immunization (AEFI) is necessary to ensure vaccine safety and provide reassurance to maintain high rates of vaccine coverage.

Objectives: To determine the feasibility of developing a flexible, rapidly accessible system for ongoing vaccine safety monitoring.

Methods: We utilized a case-centered method, which compares: (1) the odds of vaccination of individuals who have had an AE, during a risk interval prior to the AE, with (2) the odds of vaccination with the same vaccine, in the same calendar time interval, of the entire available population, matched for age and sex. We constructed summary data tables containing the pertinent information for the entire membership of the Kaiser Permanente health plan of Northern California (KPNC) – over 3.3 million people. Using these tables, we are able to rapidly calculate the Odds Ratio (OR) of prior vaccination for any AEFI identifiable in the electronic medical records. We tested this method on multiple outcomes and vaccines in KPNC, looking retrospectively from 2009 back through 1999, using

different risk intervals, with vaccines currently in use. For our first iteration of the project we grouped diagnoses using Healthcare Cost & Utilization Project (HCUP) software, and in addition utilized International Classification of Diseases (ICD)9 codes to a 3-digit level. We used $p \leq 0.01$ for statistical significance, and generated tables ranked by OR, showing p values and confidence intervals, for all vaccines in current use and for any type of outcome.

Results: The application was found to be sensitive: an increased risk of febrile seizure was noted for Pneumococcal conjugate vaccine in the 3 days prior (OR 1.43, 95% CI 1.11–1.81), while for MMR it was only noted in the 2-week window (OR 1.61, 95% CI 1.41–1.85). For Kawasaki's disease there were no elevated ORs that were statistically significant for any vaccine exposure. We will present analyses for various other vaccines and AEFIs.

Conclusions: Outcome-based surveillance is a potentially powerful tool for ongoing monitoring of vaccine safety. We hope to expand this surveillance to the nationwide Vaccine Safety Datalink project of CDC.

419. When Marginal Structural Model Assumptions Fail: An Illustration Using Influenza Vaccine Effectiveness

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Background: Marginal structural models (MSM) are used increasingly in situations involving complex data, specifically when time-varying confounding is present. To validly estimate causal parameters, these models require several assumptions, which are generally untestable. An outcome that is known not to be affected by exposure ('negative control outcomes') can be used to identify residual bias.

Objectives: To identify the effect of residual bias in a MSM analysis of the effect of the influenza vaccine effectiveness on all-cause mortality. The pre-influenza period is used as a negative control, as the effectiveness of the vaccine should be biologically negligible prior to the start of virus circulation.

Methods: Using the United States Renal Data System, we estimated influenza vaccine effectiveness (VE) during the influenza and pre-influenza periods in adult patients on hemodialysis for the 1999–2000, 2001–2002, and

2003–2004 influenza seasons. We compared a marginal structural Cox model and a conventional Cox proportional hazards model to account for time-varying measures of health status (hospitalization and skilled nursing care). We estimated the effect of the vaccine in the pre-influenza period, where estimates showing a protective effect suggest bias.

Results: The MSM resulted in a VE for mortality ranging from 34% (95% CI: 24, 43) in 2003 to 40% (31%, 48%) in 2001, while the conventional Cox model produced estimates of VE of 20% or less. In all study years, there was a large protective effect during the pre-influenza period. This effect was stronger for the MSM models with estimates ranging from 44% (28%, 56%) in 1999 to 80% (70%, 87%) in 2003. Estimates remained biased after stratifying by baseline hospitalization, a proxy for health status.

Conclusions: The MSM accounting for time-varying confounding did not adequately control for bias when estimating influenza VE on mortality and in fact resulted in increased bias relative to conventional models. Further research is needed to understand circumstances under which MSMs may increase bias relative to standard statistical models.

420. Monitoring of Intussusception after Rotavirus Vaccines–United States, Vaccine Adverse Event Reporting System (VAERS), 2006–2012

Penina Haber, Manish Patel, Yi Pan, Frank Destefano, James Baggs, Umesh Parashar. *CDC, Atlanta, GA, United States.*

Background: In 2006 and 2008 two new rotavirus vaccines (RotaTeq [RV5] and Rotarix [RV1]) were introduced in the United States. Although these vaccines were not associated with intussusception in pre-licensure trials, a previously reported clustering of intussusception events to the Vaccine Adverse Event Reporting System (VAERS) during days 3–6 after RV5 warrants additional examination.

Objectives: To evaluate intussusception reports to VAERS after Rotavirus vaccines.

Methods: We assessed intussusception events reported to VAERS during February 2006–April 2012 for RV5 and during February 2008–April 2012 for RV1. For RV5, we conducted a self-controlled risk interval analysis using Poisson regression to estimate the daily reporting ratio (DRR) of intussusception comparing average daily reports 3–6 vs. 0–2 days after vaccination. We calculated reporting rate differences based on DRRs and background rates of intussusception. Few reports were submitted after RV1, allowing only a descriptive analysis.

Results: VAERS received 584 confirmed intussusception reports after RV5 and 52 after RV1, with clustering 3–6 days after both vaccines. The daily reports of intussusception cases was higher during the 3–6 day period than during the 0–2 day period after RV5 dose 1 (RR = 3.75; 95% CI = 1.90, 7.39), but not after dose 2 or dose 3. Over all three doses, the risk difference was 0.79 events (95% CI = −0.04, 1.62) per 100,000 vaccinations.

Conclusions: We observed a persistent clustering of reported intussusception events 3–6 days after the first dose of RV5 vaccination. This clustering could translate to a small increased risk of intussusception, which is outweighed by the benefits of rotavirus vaccination.

421. Use of Corticosteroids during Pregnancy and in the Postnatal Period and Risk of Asthma in Offspring: A Nationwide Danish Cohort Study

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Background: No studies have been conducted to date on the association between maternal corticosteroid therapy at any time during pregnancy and asthma in offspring.

Objectives: We therefore undertook a study examining maternal use of local and systemic corticosteroids during pregnancy and in the postnatal period and risk of asthma in their children.

Methods: We conducted a population-based cohort study of all live-born singletons in Denmark between 1 January 1996 and 31 December 2009, with follow-up through 2010. Data on maternal corticosteroid use, asthma in offspring, and covariates were obtained from Danish population-based medical registries. Asthma was defined as a hospital diagnosis of asthma, and/or prescriptions for anti-asthma medication. We computed the absolute risk of asthma and used Cox proportional hazards regression to estimate hazard rate ratios (aHRs) adjusted for covariates with 95% confidence intervals (95% CIs), comparing children prenatally exposed to corticosteroids with unexposed children. We also conducted a 'within-mother-between-pregnancy' analysis, comparing exposed children with unexposed siblings, to address possible bias from genetic and the environmental factors, the outcome measure was Odds ratio (aOR).

Results: We identified 877,778 eligible children, of whom 31,763 (3.6%) were prenatally exposed to systemic (n = 5,327) or local (n = 24,436) corticosteroids. The risk for asthma was 13.5% for unexposed and

18.4% for exposed children after 10 years of follow up. The aHR for asthma among children prenatally exposed to systemic corticosteroids compared with unexposed children was 1.46 (95% CI: 1.37–1.56). However, the 'within-mother-between-pregnancy' analysis indicated no increased risk of asthma among exposed children compared with their unexposed siblings (aOR = 0.95 [95% CI: 0.89–1.01]).

Conclusions: Overall, prenatal exposure to both systemic and local corticosteroids was associated with an increased risk of asthma in offspring. However, as indicated by the 'within-mother-between-pregnancy' analysis, these estimates are likely biased by genetics, underlying disease or shared exposures in the environment.

422. Advanced Topics on Database Algorithm Development and Validation

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Background: In pharmacoepidemiological studies using large automated databases, algorithms consisting of one or multiple computerized codes are used to measure clinical characteristics, drug exposure, and outcome occurrence. The validity of a given algorithm may vary in different clinical contexts, and across care settings reflected in different databases. To have well-performing algorithms is critical for any database studies. Algorithm development usually starts with reviewing completed validation studies. Previously validated algorithms can be adopted wherever appropriate. When prior evidence is lacking, de novo algorithms need to be proposed and validated against a gold standard, which often relies on clinical measures and documentation in the medical records. However, there is no generally recognized practice guidance for adopting or validating algorithms. The methods and issues are infrequently communicated in literature. Few published database studies explicitly discussed potential biases due to inadequate algorithm validity.

Objectives: To share experience, knowledge and lessons learned in algorithm development and validation for database studies, including methodology advances, practical considerations, and implications for findings. The workshop is designed to appeal to clinical researchers who use large automated databases and those interested in prospective surveillance systems.

Description: This workshop will consist of five presentations (10–15 min each) followed by interactive discussions between the panel and audience (20–30 min). The five topics are:

(1) An overview of the contemporary issues and challenges in algorithm development and validation;
(2) Systematically evaluating health outcome algorithms for adoption in prospective surveillance monitoring;
(3) A novel method for developing, applying, and validating multiple algorithms with one sampling/review of medical records;
(4) Practical considerations in conducting medical chart validation of a computer-based case definition;
(5) Alternative method of choosing optimal algorithms by empirically testing them against well-established positive and negative drug-outcome pairs using the design and database of choice.

423. Best Practices and Areas of Future Research in the Development of Educational Material To Communicate Risk to Patients and Clinicians

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Background: Risk communication to patients and clinicians in the forms of a summary of product characteristics (SmPC) and patient information leaflets are required for all medicines in the EU. In the US, FDA requires certain medical products to have safety information provided through Med Guides, while educational programs may be introduced in the EU as additional risk minimisation measures. Although such standard and product-specific risk communication materials have become essential parts of US REMS and EU Risk Minimization Plans (RMPs), there is little guidance on how to best develop this information within regulatory timelines to maximize comprehension of risk information by intended audiences. Understanding how to apply best practices to develop these types of education tools is critically important to assure materials will achieve their intended goals.

Objectives: Speakers will review existing research and remaining gaps in our current understanding of best practices for the development of risk communication tools for patient and healthcare providers, including Med Guides and supplemental education materials. Representatives from industry, government, or academics involved or seeking additional expertise in the development of these materials will benefit from this symposium.

Description: Speakers will present and invite discussion on the following topics:

Factors that influence comprehension of education materials to communicate benefit/risks in terms of: quantitative vs. non-quantitative information summaries, format, structure, end-users' health literacy and numeracy (Andrews)

Best practices for development of educational materials (Gilsenan)

Timing and importance of pre-testing of risk communication materials with intended end-users (McNeill)

Status of Med Guides and other risk communication tools: a US Regulatory Perspective (Dal Pan)

Development of educational programs as additional risk minimisation measures in EU: a regulatory perspective (Rubino)

Areas for future research: integrated evaluation of risk communication material and its effect on actual patient and behaviour (moderated discussion with audience).

detection performance testing. Researchers and statisticians in the area of pharmacovigilance would benefit by attending this workshop.

Description: This workshop will describe the need and methods to test performance of methods, important choices in criteria to define reference sets for different products: small molecules and vaccines and the impact of these choices on the final performance assessment. The workshop will be provided by experts who are working on the largest projects in this area.

Speakers: Patrick Ryan, J&J (OMOP): Introduction: Why do we need to measure performance and how should we do this? Challenges and tradeoffs in creating the OMOP reference set. Jan Bonhoeffer, Brighton Collaboration Foundation (GRIP): How to define true positive and negative vaccine-event pairs? Evidence of absence or absence of evidence? Preciosa Coloma, Erasmus University Medical Center (EU-ADR), Approaches and challenges in building EU-ADR reference set for small molecules. Martijn Schuemie, J&J (OMOP/EU-ADR): Impact of reference sets on performance of signal detection methods: Comparison of performance while crossing OMOP and EU-ADR reference sets. Niklas Noren, WHO-UMC (PROTECT): performance testing of methods in PROTECT, the choice between established risks and risks identified in the post-marketing phase as positive controls in performance evaluation. Gianluca Trifiro', Erasmus University Medical Center (EU-ADR), Impact of calendar time on comparison of performance between spontaneous reporting databases and electronic healthcare databases.

424. Impact of the Choice of Reference Set on Performance Testing of Signal Detection Methods

Patrick Ryan,[1] Martijn Schuemie,[1] Niklas Noren,[2] Jan Bonhoeffer,[3] Preci Coloma,[4] Gianluca Trifiro,[4] Miriam Sturkenboom.[4] *[1]OMOP, Washington, DC, United States; [2]WHO-UMC, Uppsala, Sweden; [3]Brighton Collaboration Foundation, Basel, Switzerland; [4]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: There is increasing interest in developing methods for safety signal detection using electronic health care records. In order to develop methods, performance testing is necessary based on test or 'reference' sets of known true positive and negative drug-event pairs. Creation of these reference sets is challenging since evidence changes over time and choices for criteria have potentially important impact on performance metrics.

Objectives: To share and discuss the methods and challenges in the creation of reference sets for signal

425. Importance of Sensitivity Analyses for Design Decisions in Comparative Effectiveness Research

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Background: Multiple study design decisions apply to pharmacoepidemiology studies of comparative effectiveness. While many researchers apply sensitivity analyses to important elements such as outcome definitions and entry criteria, other design features that are not typically subjected to sensitivity analyses could influence the results, and may help explain why studies addressing the same research question arrive at different conclusions.

Objectives: To highlight how design features can impact on interpretation of comparative effectiveness studies, such as look-back windows, exposure definitions, multiplicity and time-varying changes in health state and medication use during follow-up.

Description: Observational comparative studies from real world settings are becoming increasingly critical to address effectiveness of interventions in routine clinical practice. It is well known that such studies are subject to measured and unmeasured confounding. While the research question should drive design and analytic decisions, specific choices are not always obvious. We address how design features in observational studies, including choice of look-back window and washout period, may impact results in a new user design, and may tradeoff with accuracy in classification of outcome, exposure and confounding variables. The importance of robust and fairly extensive sensitivity analyses to allow researchers to interpret the results of observational studies will be highlighted. Methods that assess sensitivity to one particular source of bias are useful, but having an integrated summary across multiple sources of bias will better reveal true uncertainties in the observed results.

Speakers: Cindy Girman (Merck): What Design Features May Influence Results?

Xiaochun Li (Indiana U): Sensitivity of results to time intervals for defining comorbidities and exposures, and to approaches to matching in active surveillance.

Doug Faries (Lilly): Unmeasured Confounding: Bayesian and Frequentist Sensitivity Analyses

Timothy Lash (Emory): Adapting probabilistic bias analysis to conceptually misclassified variables

Til Stürmer (UNC): Summary and Wrap-up.

426. Looking for Efficient Solutions to Optimize Adherence to Drug Treatment: The Clinical, Health Services Research and Economics Perspectives

Jean-Pierre Grégoire,[1] Robert Gross,[2] Sophie Lauzier,[1] Niteesh Choudry,[3] Lisa Pont.[4] *[1]Faculty of Pharmacy, Chair on Adherence to Treatments, Laval University, Quebec City, QC, Canada; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [3]Medical School, Harvard University, Boston, MA, United States; [4]Sydney Nursing School, University of Sydney, Sydney, NSW, Australia.*

Background: Submitted on behalf of both the DUR/HSR SIG and of the Adherence SIG. The global burden of non-communicable and communicable diseases requiring long-term care is rising and adherence to treatment is a key element to improving health outcomes. Health systems are often ill-equipped to optimize patient adherence. A lot of attention has been paid to the non-adherence problem over the last 30 years yet evidence-based efficient solutions are still very few.

Objectives: This session will provide attendance with an overview of some of the issues and potential solutions. Those will be discussed from a clinical, a drug utilization/health services research and an economics perspectives.

Description: Jean-Pierre Grégoire will present non-adherence as it fits in the prescribed drug utilization process. It will serve to illustrate some of the issues. Ex.: Are we forcing some patients to adhere to a non-appropriate treatment? Are we putting pressure on some non-adherent patients whose therapeutic condition is otherwise well controlled? What about health system barriers? Are there inequalities? Is there a 'one size fits all' adherence-enhancing approach? Robert Gross will provide the perspective of a physician treating AIDS patients. Adherence to antiretroviral treatment is part of his research interests. He recently completed a trial demonstrating that an intervention, Managed Problem Solving, (MAPS) using adherence feedback and personalized solutions to barriers resulted in both improved adherence and higher rates of virologic suppression. Sophie Lauzier will provide the perspective of a researcher specializing in the identification of psychosocial determinants of adherence and the development/assessment of psychosocial adherence-enhancing interventions. Niteesh Choudhry will provide the perspective of a physician and health services researcher whose work focuses on health system barriers, such as high cost and difficulties accessing medications, that contribute to non-adherence and how, based on these factors, interventions can be designed to improve adherence. Lisa Pont, the DUR/HSR SIG Chair, will make wrap-up comments.

427. New Approaches to Account for Selection Bias and Confounding by Frail Health Status

Sascha Dublin,[1] Michael Jackson,[1] Tracey Marsh,[1] Soko Setoguchi-Iwata,[2] Wendy Camelo Castillo,[3] M Alan Brookhart.[3] *[1]Group Health Research Institute, Group Health Cooperative, Seattle, WA, United States; [2]Duke Clinical Research Institute, Duke University, Durham, NC, United States; [3]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: People who are in frail health may be considerably less likely to receive some interventions, particularly preventive therapies and aggressive

treatments ('healthy user' bias). It can be very challenging to adjust for the bias that results, because some aspects of ill health–for example, functional impairment– are poorly measured not only in administrative data but also in other data sources.

Objectives: To review the relevance of unmeasured confounding or selection by frail health status and to demonstrate cutting-edge approaches to address this bias.

Description: We will begin by describing the problem using specific examples (Dublin). The talks that follow will illustrate innovative approaches to account for this bias. (1) Using influenza vaccine effectiveness as an example, Dr. Jackson will describe and evaluate the use of restriction to exclude people in whom unmeasured confounding may operate most strongly. (2) Ms. Marsh will describe and compare approaches for incorporating more comprehensive confounder data from a validation cohort in a study of influenza vaccine effectiveness in older adults. This general approach can be useful when richer data about functional and cognitive status are available for a subset of subjects. (3) Using cardiovascular device effectiveness studies as an example, Dr. Setoguchi will describe the utility of latency analysis, bias-adjusted analysis, and high-dimensional propensity scores to reduce healthy user bias. (4) Ms. Camelo-Castillo will present an innovative model to predict frail health status from Medicare claims data. This presentation will demonstrate the value of linking existing survey data (from the Medicare Current Beneficiary Survey) with Medicare claims data to identify predictors of functional dependence, which is often an unmeasured confounder. The potential application of this model to reduce bias in future pharmacoepidemiologic studies will be discussed. (5) Dr. Brookhart will present examples of the use of natural experiments to improve control of confounding. We will conclude with panel and audience discussion.

428. Welcoming Advanced Methods into the World of Pregnancy Research

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Background: To date, advanced analytic methods to evaluate and mitigate threats to study validity are not very prevalent in perinatal epidemiologic research. All study designs, from pregnancy registries to case-control studies, may benefit from new methods. However, the increasing reliance on large healthcare databases offers not only new opportunities but also sometimes the need to implement these methods as appropriate.

Objectives: To discuss the circumstances under which advanced analytic methods may or may not offer added value over conventional approaches, to review important considerations for their implementation, and to assess the strengths and weaknesses of the various approaches as they pertain to perinatal epidemiologic research. Researchers involved in the conduct, evaluation, or interpretation of pregnancy studies will benefit from attending.

Description: Each speaker will present their experience with a particular method in pregnancy research. Examples will focus on the effects of psychoactive drug exposures on a range of maternal and neonatal outcomes. The symposium will conclude with a critical appraisal of the methods, followed by a moderated discussion.

Left censoring: Explore the influence of gestational age at enrollment and post-screening enrollment on the associations between first-trimester drug use and pregnancy outcomes.

(High-dimensional) propensity scores (PS): Evaluate the usefulness of (high-dimensional) PS to balance and account for a broad range of potential confounders and proxies for unmeasured confounders in the context of infrequent neonatal outcomes.

Instrumental variable analyses (IVA): Explore the usefulness and feasibility of IVA to address confounding by unmeasured factors, using a preference-based instrument for continuing vs. discontinuing treatment during pregnancy.

Bayesian methods: Evaluate the use of Bayesian methods to quantify the potential effects of exposure misclassification, to incorporate prior information and to support subgroup analyses.

Sensitivity analyses: Illustrate the value of simple and multiple bias modeling to quantify the total error introduced under plausible scenarios of misclassification and confounding.

429. Aspirin Use in Prostate Cancer and the Risk of Death and Metastasis

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Background: The association between aspirin in the prevention of prostate cancer outcomes remain limited.

Objectives: The objective was to determine whether the use of aspirin after prostate cancer diagnosis is associated with a decreased risk of prostate cancer mortality, distant metastasis and all-cause mortality in men newly-diagnosed with prostate cancer.

Methods: A population-based cohort of men with non-metastatic prostate cancer between 1 April 1998 and 31 December 2009 was identified using the UK Clinical Practice Research Datalink, including the Cancer Registry. All men were followed until death, distant metastasis, or 1 October 2012. A nested case-control analysis was performed where, for each case with an incident outcome event, up to 10 controls were matched on age, year of diagnosis and follow-up time. Exposure was defined as aspirin use during the matched follow-up period. Rate ratios (RR) and 95% confidence intervals (CI) were estimated using conditional logistic regression, adjusted for covariates and considering effect modification by aspirin use prior to prostate cancer diagnosis.

Results: The cohort included 13,396 prostate cancer patients, followed for 4.9 (3.1) years during which 4,425 deaths occurred, including 2,315 from prostate cancer, and 2,344 cases of distant metastasis. Aspirin use was associated with an increased risk of prostate cancer mortality (RR 1.36, 95% CI 1.18–1.55) and all-cause mortality (RR 1.33, 95% CI 1.21–1.47), but not distant metastasis (RR 1.09, 95% CI 0.94–1.27). The increased risks were limited to patients who did not use aspirin before diagnosis, for both prostate cancer mortality (RR 1.69, 95% CI 1.43–2.00) and all-cause mortality (RR 1.62, 95% CI 1.44–1.82), while those who used aspirin before diagnosis did not have increased risks (RR 0.93, 95% CI 0.76–1.15 and RR 0.98, 95% CI 0.85–1.13, respectively).

Conclusions: The use of aspirin after prostate cancer diagnosis is not associated with a decreased risk of prostate cancer outcomes. Although increased risks were observed for all-cause and prostate cancer mortality, these effects were exclusively driven by new-users of aspirin, suggesting that aspirin use in these patients was likely related to disease progression.

430. The Clinical Benefit of Warfarin in Patients with Atrial Fibrillation in Taiwan

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Background: Warfarin is suggested as the first choice of antithrombotic agents for atrial fibrillation by ACC/AHA/ESC guideline. The concern on potential intracranial hemorrhage among Asian population might have explained the lower rate than in Western countries that met with target INR in clinical practice. Also, the low compliance of anticoagulation in Taiwan was reported to be lower. Therefore, the clinical benefit of warfarin in real world setting warrants assessment but remains lacking in Taiwan.

Objectives: This study aimed to determine whether clinical benefit of warfarin in patients with atrial fibrillation weighed by risks of ischemic stroke and intracranial hemorrhage.

Methods: This retrospective cohort study was conducted using Taiwan's National Health Insurance claims database from 2000 to 2008. Patients who were 18 years or older, had at least two diagnoses of atrial fibrillation (AF) within 1 year and were prescribed with any warfarin or aspirin within 2 years after index date were included during January 1, 2001 and December 31, 2006. Patients were stratified according to CHADS2, CHA2DS2–VASc, and HAS-BLED score to evaluate their thromboembolic and bleeding risk. The clinical benefit was defined as number of ischemic strokes avoided with anticoagulation minus the number of excess intracranial bleedings. The Poisson regression model was conducted for adjusting risk factors.

Results: Of 80,771 patients aged above 18 years with 134,937 person-years was assembled, who had defined AF and prescriptions of warfarin and aspirin during follow-up. We identified 4,375 (3.2%) thromboembolic events in the study cohort, of which 1,188 (27.2%) experienced fatal events. events. Crude incidence rates for thromboembolic events and bleeding events occurred at an annual rate of 3.7% and 3.4%. With regard to clinical benefits of anticoagulation, there was a positive net clinical benefit with warfarin in patients with the all strata, but CHA2DS2-VASc score had better discrimination in identifying true low-risk patients.

Conclusions: Our finding suggests that the net benefit gained by warfarin is evident. Thus, oral anticoagulation treatment should be exerted more actively for AF patients in Taiwan.

431. The Role of the thorough QT Study in Drug Development

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Background: The use of the specific thorough QT (TQT) study to evaluate a drug's proarrhythmic potential has been criticized as a non cost-effective regulatory measure. Moreover, the added value of TQT studies compared to preclinical and phase 3 ECG evaluation in establishing a drug's proarrhythmic potential is unknown.

Objectives: To evaluate when TQT studies are performed, and whether preclinical findings predict the need for, and outcome of TQT studies and subsequently whether the outcome of the TQT study predicts need and outcome of further intensive ECG evaluation in phase 3 studies.

Methods: Assessment reports and registration files of 102 new centrally approved drugs in Europe (2009–2012) were reviewed whether the proarrhythmic potential had been evaluated in the preclinical program, TQT study, or in phase 3 studies. Associations were tested between *outcomes* (potential for QT prolongation yes/no) of preclinical data and the *decision* to subsequently perform TQT studies, respectively the *outcome* of the TQT study and the *decision* to perform further evaluation in phase 3 using Fisher's exact tests. Similarly, associations between the *outcomes* of preclinical, TQT, and phase 3 studies were tested.

Results: The pro arrhythmic potential was evaluated in 42 preclinical, 25 TQT and 34 phase 3 studies. Twenty-three of 25 TQT studies had been performed for small molecules with six showing QT prolongation. For nine of 57 small molecules, seven of 12 fixed combination products, 10 of 11 vaccines, and 14 of 23 biologicals QT effects were not specifically evaluated. There was no association between outcome of preclinical studies and the *decision* to perform TQT studies (p = 0.227. There was an association between TQT study results and the *decision* to perform further evaluation in phase 3 (p = 0.003). No association was found between *outcomes* of preclinical and TQT studies nor of TQT and phase 3 studies.

Conclusions: Companies carefully judge when to perform costly TQT studies, mostly omitting them for drugs with a low potential for QT prolongation, i.e. vaccines and biologicals. Intensive ECG evaluation in phase 3 is skipped in case of a negative TQT study, even though the outcomes of studies did not predict the outcome of the next level of testing.

432. Use of Glucocorticoids and Risk of Breast Cancer Recurrence

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Background: Synthetic glucocorticoids (GCs) are used to depress the immune response. GCs have many side effects and may be carcinogenic. The effect of GC use on breast cancer prognosis is not known.

Objectives: To assess the effect of GC use on breast cancer recurrence.

Methods: We conducted a population-based cohort study of the risk of breast cancer recurrence associated with use of GCs among incident female breast cancer patients (UICC stage I, II or III) aged > 18 years in Denmark and diagnosed 1996–2006. Data on breast cancer patients, clinical and treatment factors, follow-up (recurrence, vital status) and co-morbidities were obtained from the Danish Breast Cancer Cooperative Group, Danish Civil Registry and Danish National Registry of Patients. Data on GC prescriptions were retrieved from the Register of Medicinal Product Statistics (RMPS). Patients were categorized as ever vs. never GC use and by type of GC (systemic or inhalatory). Women were followed for 10 years or until 31 December 2009. We used Cox proportional hazards regression models to assess the risk of breast cancer recurrence among GC users compared with non-users, adjusting for potential confounders.

Results: We enrolled 18,733 breast cancer patients. Median follow-up was 6.1 years. Of the 7,268 women ever prescribed GC after diagnosis, 1,649 and 562 were exclusively prescribed systemic GC or inhalatory GC. Exclusive use of systemic GC and exclusive use of inhaled GC were each associated with a somewhat reduced rate of breast cancer recurrence compared with no GC use (adjusted HR = 0.85, 95% CI: 0.74,

0.98, and adjusted HR = 0.76, 95% CI: 0.59, 0.97, respectively). We are currently investigating any potential dose-response effects.

Conclusions: Use of GCs may be associated with a decreased rate of breast cancer recurrence, perhaps through anti-inflammatory mechanisms. The near-null associations in a large population may also be a chance finding. We discuss limitations including residual confounding, which may preclude an unambiguous interpretation.

433. Acute Non-Steroidal Anti-Inflammatory Drug Exposure in Asthma: A Meta-Analysis of Clinical Trials

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed analgesics but can trigger exacerbations in susceptible patients with asthma. This risk is thought to be greatest following acute exposure.

Objectives: To evaluate changes in respiratory function and symptoms following acute NSAID exposure in asthma.

Methods: A systematic review of MEDLINE, EMBASE and CENTRAL databases identified all blinded, placebo-controlled clinical trials evaluating acute NSAID exposure in asthma, including aspirin. Outcome measures included fall in FEV1 of $\geq 20\%$, incidence of respiratory symptoms and the mean provocative dose for aspirin. Selective NSAIDs were evaluated in patients with a prior history of NSAID-sensitive asthma. Effect estimates were reported as the risk difference (RD) and pooled using fixed-effects meta-analysis. Heterogeneity was investigated using subgroup analysis.

Results: A total of 29 trials were identified. Compared to control, aspirin exposure was associated with a fall in FEV1 of $\geq 20\%$ in 10% (RD 0.10, 95%CI 0.07–0.14) respiratory symptoms in 19% (RD 0.19, 95%CI 0.10–0.28) with a mean provocative dose of 100.8 mg. In patients with a history of NSAID-sensitive asthma, no significant difference was found following acute selective NSAID exposure in fall in FEV1 of $\geq 20\%$ (RD 0.00, 95%CI −0.02–0.02), respiratory symptoms (RD 0.01, 95%CI −0.01–0.03) or nasal symptoms (RD −0.01, 95%CI −0.03–0.03) compared to control. Only two trials which involved predominantly children

investigated exposure to non-selective NSAIDs in patients not selected on the basis of prior response. From these, no significant difference was found following acute non-selective NSAID exposure in fall in FEV1 of $\geq 20\%$ (RD 0.02, 95%CI −0.01–0.05) or respiratory symptoms (RD 0.01, 95% CI −0.02–0.04) compared to control.

Conclusions: The prevalence of aspirin-sensitive asthma was 10% as defined by fall in FEV1 of $\geq 20\%$. Aspirin-induced bronchospasm was often triggered by relatively low doses of aspirin. Based upon clinical trial evidence, selective-NSAIDs appear to be a safe alternative for patients with NSAID-sensitive asthma.

434. Acute β-Blocker Exposure in Asthma: A Meta-Analysis of Randomized Controlled Trials

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Background: β-blockers are avoided in asthma due to risk of bronchospasm. This risk is greatest following acute exposure when β2-agonists may be antagonised.

Objectives: To evaluate changes in respiratory function and β2-agonist response following acute β-blockade to inform the management of intended and unintended exposures in asthma.

Methods: A systematic review of MEDLINE, EMBASE and CENTRAL databases identified all randomized, blinded, placebo-controlled trials evaluating acute oral, topical or intravenous β-blockers in asthma. Effect estimates for changes in forced expiratory volume in 1 s (FEV1), symptoms and β2-agonist response were pooled using random-effects meta-analysis with heterogeneity investigated using subgroup analysis and meta-regression.

Results: Of 32 trials identified none evaluated topical β-blockers. Selective β-blockers were associated with a mean change in FEV1 of −6.9% (95%CI −8.5 to −5.2), symptoms in one in 33 patients; fall in FEV1 of $\geq 20\%$ in one in eight patients and reduction in β2-agonist response of −10.2% (95%CI −14.0 to −6.4). Non-selective β-blockers were associated with a mean change in FEV1 of −10.2% (95%CI −14.7 to −5.6), symptoms in one in 13 patients, fall in FEV1 of $\geq 20\%$ in one in nine patients and reduction in β2-agonist response of −20.0% (95%CI −29.4 to −10.7). Following investigation of heterogeneity; mean change in FEV1 for celiprolol was 1.8% (95%CI −2.3–5.8) vs.

−9.3% (95%CI −12.0 to −6.6) for metoprolol; mean change in FEV1 for labetalol was −2.7% (95%CI −9.6–4.1) vs. −17.0% (95%CI −21.4 to −12.6) for propranolol. A dose-response relationship was demonstrated for selective β-blockers. Neither steroid exposure nor baseline FEV1 influenced mean change in FEV1.

Conclusions: Although better tolerated, selective β-blockers are not risk free. Risk from acute exposure may be mitigated by initiating smaller doses, using β-blockers with greater β1-selectivity and possibly those with dual alpha-blocking properties. β-blocker induced bronchospasm responds reasonably well to β2-agonists but efficacy is further reduced with non-selective vs. selective β-blocker exposure.

435. Identification of Incident Cardiovascular Events Using a Computerized Hospital Database: A Feasibility Study

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Background: One limitation of the use of computerized hospital database for identification of clinical event is the validity of the recorded information.

Objectives: To evaluate the feasibility of a validation study of hospital discharge codes to identify cardiovascular events and cardiovascular morbidities in the computerized hospital database (Programme de Médicalisation du Système d'Information, PMSI) of a French teaching hospital.

Methods: Of all the hospital stays that were recorded in the hospital database for the 1 January 2011–31 December 2011 period, 200 of those registered with ICD10 (10th International Classification of Diseases) codes I20 (angina pectoris), I21 (acute myocardial infarction), I24 (others acute ischemic heart disorders), or I25 (chronic ischemic heart disorders) for the main, associated or related hospitalization diagnoses (respectively MD, AD and RD) were randomly selected. For each selected record, the validity of the hospitalization diagnosis coding was assessed using data contained in the computerized patients' medical files, according to clinical and biological criterion approved by cardiologists.

Results: One extracted record did not correspond to eligibility criteria and was excluded. Among the remaining 199 selected records, 55.5% corresponded to hospitalisation in cardiology units. 79.5% concerned

men and patients' mean age was 69 years. Events of interest were coded as MD in 22.1% of the studied records, as RD in 12.6%, and as AD in 65.3%. The corresponding medical computerized file was found for 126 hospitalizations (63.3%). According to the predefined clinical/biological validation criterion, 59.1% of codes filed as MD appeared valid, this was 5.4% for AD and 0% for RD.

Conclusions: The very low validation rate for the AD or RD indicates that in further studies, the MD may be preferably considered. Indeed, the non-validated cases for the later correspond to cardiovascular previous history or hospitalizations for post-cardiovascular event re-adaptation. AD and RD codes do not seem appropriate to identify cardiovascular events and cardiovascular morbidities.

436. Are Patients Classified as Antiretroviral Therapy Naïve Using Administrative Data Truly Naïve Based on Comprehensive Medical Record Reviews? An Exploration Using an HIV Clinical Cohort

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Background: The use of administrative data to answer HIV treatment and clinical care questions is increasing because they allow for evaluation of rare events and access to treatment patterns in generalized populations. However, these data may not capture patients' entire antiretroviral (ARV) treatment (ART) history.

Objectives: To quantify misclassification of ART naïve status based on Medicaid administrative data through linkage to the UNC CFAR HIV Clinical Cohort (UCHCC).

Methods: We identified Medicaid patients with incident exposure to common first-line ARV regimens from 2002 to 2008 that were also UCHCC patients. Incident exposure was defined as a set of claims representing a first-line ARV regimen following 180 days of Medicaid eligibility without an ARV claim. We linked patients by social security number, first and last name. Of Medicaid patients with incident exposure, we calculated the proportion of ART naïve patients based on detailed medication history recorded in the UCHCC. To examine factors associated with ART naïvety in both data sources, we used logistic regression with backwards elimination to generate prevalence odds

ratios (POR) and associated 95% confidence intervals (CI).

Results: Of 3,500 Medicaid patients with incident exposure, 1,243 were also in the UCHCC. In this sample, 28% were ART naïve at time of first exposure in Medicaid based on the UCHCC. Median time from ART start in the UCHCC to incident exposure in Medicaid was 2.4 years (Interquartile Range: 0.9, 4.6, Full Range: 0.02, 13.4). In multivariable models, higher CD4 cell counts and log HIV RNA values were associated with being ART naïve in both data sources (POR:1.35/200 μL increase) [95% CI: 1.22, 1.48] and POR: 1.64 [95% CI: 1.47, 1.83]). Younger patients were more likely to be ART naïve (POR: 0.14/10 year age increase [95% CI:0.04,0.53]).

Conclusions: Administrative data provide important information related to HIV treatment. As construction of durable and long-lasting HIV treatment plans involve knowledge of current and past ART, augmentation of this data with comprehensive clinical information is necessary.

437. Factors Affecting the Association of Cancer Risk among Patients Treated with Anti-Diabetic Medication

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Background: Many methodological limitations existed in the studies focusing on association between anti-diabetic medication and cancer risk.

Objectives: Our aim was to investigate the risk of cancer among naïve users as compared to non-users, especially to address the role of factors influencing both risk of diabetes mellitus (DM) (and thus an initiation of medication) and cancer risk, and to evaluate the variation in risk after the initiation of medication.

Methods: Study population comprised of three FINRISK cohorts and was linked to data on cancer from the Finnish Cancer Registry and on anti-diabetic medication from the Prescription Registry. The effect of anti-diabetic medication on cancer risk was analyzed by applying Poisson models without and with adjustment for age, gender, calendar time, BMI and smoking. Changes in cancer incidence by time since initiation were studied by modeling the rate ratio attributable to the medication duration that was taken either as a natural spline or categorical variable. The effect of metformin, sulfonylurea, insulin and all medication combined was evaluated separately.

Results: After a median follow-up of 9 years 53 cancer cases among users and 1,028 among non-users were diagnosed. Although a slight increase in cancer risk within 1–4 years after the initiation was observed when compared users to non-users, after adjusting for the available risk factors no significant difference was found. For all medication combined RR was 1.37 [95% CI 0.94–1.94] and results were similar for different medication groups. Rate ratio tended to be higher in insulin users with history of previous medication of 0–3 years [RR 2.3, 95% CI 0.8–4.9]. Longer duration of exposure was associated with decline of rate ratio, but this association was not significant.

Conclusions: In order to avoid biased results, special attention should be given to common risk factors when exploring the association between anti-diabetic medication and cancer risk. It is also necessary to examine the variation of risk by time since initiation whenever it is possible. That kind of analysis may provide better understanding of the link between drug exposure and cancer.

438. Comparison of Comorbidity Ascertainment Using the End-Stage Renal Disease Medical Evidence Form 2728 vs. Medicare Claims Data

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Background: Data from the United States Renal Data System (USRDS) are widely used in pharmacoepidemiology research to study medications and interventions in dialysis patients. Comorbidity data are routinely identified from Form 2728 or claims data to control for baseline comorbidities, however, the agreement between these data sources and the utility of claims data remains unclear.

Objectives: To compare ascertainment of nine comorbid conditions as recorded on Form 2728 with predialysis claims data in an end-stage renal disease (ESRD) population.

Methods: ESRD patients age $\geq$ 67 who initiated dialysis between 2005 and 2008 were identified from the USRDS. The study population was restricted to patients with $\geq$ 1 month of predialysis Medicare coverage. Comorbidity prevalence was calculated by data

source. κ was calculated to assess concordance between data sources. Sensitivity and specificity were calculated using claims data as the gold standard. Analyses were stratified by duration (i.e., 1, 6, 12, 18, or 24 months) of predialysis claims data.

Results: Of 119,630 eligible patients, 96% and 79% had ≥ 1 comorbidity according to Form 2,728 and claims data for 1 month prior to dialysis initiation, respectively. Agreement varied substantially across comorbidities (κ range, 6–53%). Compared to claims data, sensitivity was high for hypertension (86%) and diabetes (79%); intermediate for congestive heart failure (64%); and low (47–21%) for amputation, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, cerebrovascular disease, and diabetic retinopathy. Specificity ranged from 71–98%, except for hypertension (19%). Increasing duration of predialysis claims data from 1 to 6 months slightly decreased sensitivity and increased specificity. Results did not differ appreciably with > 6 months of claims data.

Conclusions: Agreement between Form 2,728 and claims data is poor. Comorbid conditions are substantially underreported on Form 2,728. Claims data provide a reasonable alternative for identification of comorbidities in the ESRD population.

439. Uptake of Methodological Innovation in Pharmacoepidemiology: Disease Risk Score Co-Authorship Network Analysis

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Background: The field of pharmacoepidemiology has experienced rapid scientific progress, growth and methodological innovation, particularly in the last decade.

Objectives: To characterize the adoption of the disease risk score (DRS) confounder summary score method in pharmacoepidemiology.

Methods: We updated a recent systematic review of the literature to identify all papers that have examined or used DRS confounder summary score methods in the area of pharmacoepidemiology. A co-authorship matrix was created in Excel and imported into UCINET. Sociograms were generated to visualize the co-authorship network, examine components (distinct authorship groups) and identify cut-points (authors whose removal would increase the number of components). First and last author affiliations were identified to ascribe institutional contributions to each component, and the overall network.

Results: We identified 37 papers by 135 distinct authors since 1981, yet only three published before 2001. The network consisted of 11 components. The largest component consisted of 66 authors (49%) and 20 papers (54%). The primary institutions in this component were Vanderbilt University (48%) and Veterans Affairs (33%), with two cut-points from Vanderbilt University to the University of Alabama at Birmingham (11%) and Kaiser Permanente (10%) or other institutions. The second largest component included five papers (14%) and 12 authors (9%) with 70% attributed to Brigham and Women's Hospital in Boston, 25% to the University of Toronto, and 5% to the University of North Carolina at Chapel Hill. Three components included two articles each, from groups in Toronto, The Netherlands and Taiwan; and six components included only one paper with representation from North America and Europe. Vanderbilt University contributed to 27% of the entire 37-paper network.

Conclusions: Vanderbilt University is leading the uptake of DRS methods in pharmacoepidemiology, yet many different institutions around the world are starting to apply the method. Understanding the spread of novel pharmacoepidemiologic methods may identify critical factors supporting their adoption and improve dissemination of innovations.

440. Identifying Patients in Electronic Healthcare Data When No Diagnostic Codes Are Available for the Disease of Interest: Critical Limb Ischemia Example

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Background: Identifying cohorts of patients with a particular disease or condition using electronic healthcare data usually relies on the use of diagnostic codes. However, in the case of conditions which present as a series of symptoms, or those which are less clearly clinically defined, specific diagnostic codes may not be available. This study investigated the feasibility of identifying a study cohort for critical limb ischemia (CLI), for which there are no specific Read codes, in UK primary care data.

Objectives: To develop a comprehensive CLI case definition based on the Classification of Peripheral Arterial Disease, Fontaine's Stages (Dormandy et al 2000), to apply to primary care data.

Methods: Clinical and primary care database experts used Fontaine stage classifications to identify the major presenting symptoms. Symptom combinations

were defined which were likely to represent patients presenting with CLI stages 3 and 4. An algorithm was developed for every combination of Read codes and freetext references which corresponded to these symptoms taking into account feasible time gaps between symptoms. These algorithms were then applied as eleven separate searches to the Clinical Practice Research Datalink (CPRD) General practice OnLine Database (GOLD). A freetext search for terms associated with CLI was also conducted to identify patients not captured by the algorithm.

Results: In total 1026 patients were identified as having a record of CLI 3 and 992 patients as having a record of CLI 4. This is equivalent to a prevalence of 0.037% for both stages. The search of the free-text for the term 'critical limb' did not identify any patients who were not already captured.

Conclusions: This cohort of CLI patients represents one of the largest ever identified. No previous study has attempted to identify CLI in such a large population. Although prevalence was low compared to previous studies (Jenson et al) this may be because the algorithm was designed to identify patients with the later stages of disease. It is possible to identify disease cohorts in electronic healthcare records when no specific diagnostic code exists.

441. Changes in Daily Dose Over Time From Longitudinal Data of Tianeptine Users: Convergence of Two Different Approaches

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Background: Several methods have been developed from French National Insurance Health System (IHS) database concerning problems in drug use, No valid indicators are available to characterize daily dose (DD) increase which could reveal drug inefficiency or compulsive use.

Objectives: To identify and quantify a DD increase during the initial use of tianeptine treatment (abuse potential known) from French reimbursement data using two different longitudinal approaches.

Methods: The French sample of national IHS was queried to assess data on tianeptine utilization from January, 1st 2006 to November, 30th 2012. Four hundred and sixty-four new tianeptine users (6-months without antidepressant drug) treated over 9 months were selected. Two methods were used: (1) changes in DD at each trimester over time were estimated using Generalized Estimating Equation (GEE) after adjustment for age and sex. Baseline DD was estimated during the first semester according to cumulative dispensed quantity to time ratio. Last quintile baseline DD were retained (< 70 years: 37 mg; ≥ 70 years: 27 mg, according to SmPC) to determine daily high dose and then changes in DD over time. (2) a second algorithm was developed in order to detect the smallest possible dose increase – e.g. in this case corresponding to one 12.5 mg pill per day. Patients DD were estimated using a two-period moving average.

Results: The first method evidenced a significant increase in changes in tianeptine DD over time ($\beta = 0.122$, 95% confidence interval: 0.022–0.078) – i.e. an increase in 13% of patients exceeding daily high dose per trimester. The second method showed that 98 (21%) consumers of tianeptine had an increase in DD. Median of maximum increase was 20 mg, IQR = [15;27]. An dose increase was higher than 53 mg (maximum 159 mg) in 5% of the selected patients.

Conclusions: Tianeptine treatment is associated with an increase in daily dose over time. Results suggest that these two approaches could be used in parallel to quantify and qualify dose increase of a therapeutic drug and could be investigated as a future useful tool in drugs monitoring. Further validation stages of those methods are needed and will be performed using simulation studies.

442. Artificial Intelligence for Drug–Drug Interaction Prediction – A Systematic Review

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Background: Drug–drug interactions (DDI) databases attached at Intelligent Health Systems improves the quality of clinical evaluation but are limited to information stored. Artificial Intelligence (AI), as well as

machine learning (ML) and data mining (DM) approaches, provides detection of DDI in clinical environment and populational studies. Also, the AI methodologies are able to predict new DDI into biological context, establishing an alternative knowledge in medication safety evaluation.

Objectives: To conduct a systematic review of IA and correlated computational techniques implemented and validated to human DDI prediction on biological, clinical or populational databases.

Methods: An standardized search was built with cognate MeSH terms of DDI and AI in the electronic databases PubMed, CENTRAL, EMBASE and LILACS until January 2013. Reference lists were handsearched. Three reviewers assessed study eligibility for implemented methods of AI, ML or DM capable to predict, simulate or detect DDI in human validated against known DDI database or manual assessment in indexed literature.

Results: Ten studies met the inclusion criteria In 574 studies searched. Three hundred and fifteen were excluded by title, 208 by title and abstract and 41 by entire paper reading. The publication year ranged between 1986 and 2012 and seven articles were published before 2010. Five studies were researched in USA and three in different asians countries. Six studies used epidemiological databases (FDA Report System and Patient Care databases). Four methods involve text mining techniques, but only one used quantitative data to predict DDI. Four studies adopted rules manual or automatic generated to make the algorithm presumptions. Clustering analysis, random forest and neural net were adopted by one research each. Five works use DrugBank database as gold standard or source of drug information. The efficacy regarding the criteria adopted by each study ranged 17.2–91.0% and it was predicted between 27 and 13.197 DDI.

Conclusions: Despite of the heterogeneity among the included studies, there is scientific evidence that artificial intelligence and data mining techniques can be used to predict DDI.

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443. Confounding Control by Traditional Covariate Adjustment, Propensity Score Matching, and High Dimensional Propensity Score in a Cohort Study

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Background: Traditional covariate adjustment in an observational cohort study is often criticized for residual confounding bias. Two new techniques including propensity score matching (PSM) and high dimensional propensity score (HD-PS) were more often used in recent years to minimize biases.

Objectives: This cohort study evaluated the traditional covariate adjustment with the two new techniques by comparing the hazard ratios (HRs) of cardiovascular risk of two anti-arrhythmic drugs using health care claims data.

Methods: We estimated HR of cardiovascular events (acute myocardial infarction and/or ischemic stroke) in adult amiodarone initiators compared to dronedarone initiators with a diagnosis of atrial fibrillation/atrial flutter (AF/AFL) in the InVision Data Mart database, from 20 July 2009 to 31 December 2010, by the three techniques: (1) traditional cohort design adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, and history of congestive heart failure (CHF), diabetes, hypertension, and dyslipidemia; (2) PSM adjusted for the same predefined covariates; and (3) HD-PS adjusted for empirically selected covariates and codes of diagnoses, procedures, and therapies.

Results: The distribution of all predefined covariates was more balanced in the PSM than in the unmatched cohorts (e.g. 39.2% and 39.3% CHF in dronedarone and amiodarone initiators in the PSM compared to 18.8% and 42.0%, respectively, in unmatched cohorts). The cardiovascular risk with amiodarone was higher than with dronedarone (adjusted HR = 1.66; 95% CI, 1.14–2.41) after traditional covariate adjustment on a basis of crude HR of 2.04 (95% CI, 1.34–3.10). The corresponding adjusted HR was 1.99 (95% CI, 1.31–3.03) in the PSM analysis, and varied in the HD-PS analysis according to the selection of codes and covariates.

Conclusions: Given more balanced distribution of the covariates and less correction of the crude HR than the traditional covariate adjustment, the PSM may offer advantages to reduce over-adjustments and/or residual confounding than the traditional method. The estimates of HR in HD-PS may depend on the choice of codes and covariates.

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444. Approaches to Long-Term Surveillance for Rare Cancer Events

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Background: Postmarketing safety studies aimed at identifying whether a medication is potentially associated with a rare cancer are challenging to implement,

especially without a national cancer registry as a single centralized data source.

Objectives: To describe innovative efforts undertaken with state cancer registries to assess for a possible association between teriparatide treatment and osteosarcoma in humans and to provide an update on study progress.

Methods: Two studies are underway: (1) a retrospective 15-year case series surveillance study, initiated in 2003 after initial drug approval; and (2) a prospective 12-year patient registry linkage study, initiated in 2009 after a new indication was approved. In the retrospective study, incident cases of adult osteosarcoma diagnosed January 1, 2003, or later are identified through cancer registries, and exposure to possible risk factors is ascertained by telephone interview in the US and chart abstraction in five Nordic countries. In the prospective linkage study, patients enrolled in a voluntary Forteo Patient Registry are linked annually to adult cases of osteosarcoma diagnosed January 1, 2009, or later from participating US state cancer registry databases.

Results: In the retrospective study, as of December 31, 2012, 1,785 cases of adult osteosarcoma have been identified from 18 registries for diagnosis years 2003–2010. Patient/proxy interviews were completed for 24% of cases. In the linkage study, as of December 31, 2012, 30,758 patients have been registered, and the third annual linkage had been completed with 38 participating cancer registries covering 86% of the US population aged 18 years and older. At this time, the studies do not support a causal association between teriparatide treatment and osteosarcoma in humans; however, both studies are still underway.

Conclusions: To monitor for a potential signal of a rare cancer event, it is necessary to apply innovative approaches to study design. It is also necessary to develop a study protocol that can be flexible with regard to specific application at individual state cancer registries where patient contact approval requirements vary.

445. Impact of Censoring on Estimates of Adverse Drug Effects: A Simulation Study

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Background: The results from studies on adverse drug effects in electronic health care databases may vary due to multiple reasons, one of them being differences in (left and right) censoring mechanisms between databases. Such censoring mechanisms can be features of the database and are therefore hard to avoid by the researcher.

Objectives: To assess the impact of left and right censoring on estimates of adverse effects of drugs.

Methods: We used simulation studies to assess the impact of left and right censoring (differential or non-differential) on bias of estimates of adverse drug effects. We studied three types of adverse drug effects: (1) a constant exposure effect; (2) a first-time exposure effect (e.g. anaphylactic reaction); and (3) a cumulative exposure effect. Effects were expressed as incidence rate ratios and estimated using Poisson regression.

Results: Non-random censoring biased all three types of adverse drug effects. Random right censoring did not result in a bias. Random left-censoring resulted in an overestimation of the drug effect in case of a cumulative exposure effect and an underestimation of the drug effect in case of a first-time exposure effect. For example, when 50% of the observation time was left censored, the observed first-time exposure effect was RR 1.4 instead of the true RR 3.0 and a cumulative exposure effect of RR 1.15 per unit time exposure was observed instead of the true RR 1.1 per unit time exposure. The impact of censoring depended on exposure prevalence, outcome incidence, and duration of the time-interval that was censored.

Conclusions: Censoring may differentially impact estimates of exposure effect in studies of constant, first-time, and cumulative exposure effects. Researchers should be aware of this when combining data from multiple databases or when comparing drug effects across databases.

446. Measures of 'Exposure Needed for One Additional Patient To Be Harmed' in Population-Based Case–Control Studies

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Background: The magnitude of risk for adverse drug reactions may be communicated by a measure of 'exposure needed for one additional patient to be harmed' (ENH). We present four ENH measures, based on four different counterfactual contrasts, as illustrated by the known association between NSAID use and peptic ulcer bleeding. In all instances, the measure is expressed as

the average number of person-years (py) of exposure, required to cause one additional outcome.

Objectives: To describe the four ENH measures and to explore the dependency on the choice of measure.

Methods: The four measures were: basic ENH (the entire source population treated vs. none treated), age-restricted ENH (the entire source population above e.g., 50 vs. none above 50 treated), standardised ENH (a population of similar age- and gender distribution as those actually treated vs. same subjects not treated) and naturalistic ENH (based on the average treatment effect on those actually treated). Data were derived from a case–control dataset on NSAID and severe peptic ulcer bleeding, collected in Funen County 1995–2006. We incorporated prescription and census data to account for the source population's drug use.

Results: Estimates of basic, age-restricted, standardised and naturalistic ENH were 619 py (95% confidence interval (CI): 558–684), 223 py (CI: 201–246), 131 py (CI: 118–144) and 162 py (CI: 151–173). The age-restricted ENH showed strong dependency on the chosen age limit.

Conclusions: Different counterfactual contrasts underlying the ENH result in widely different estimates. These differences are best understood by considering the clinical aspects of NSAID-related peptic ulcer bleeding, e.g. the risk profile in those actually treated. The ultimate choice of ENH measure will depend on clinical considerations and availability of data.

447. Impact of PSA Doubling Time (DT) Calculation Method on Estimate of Association With Bone Metastases in a Cohort of Prostate Cancer Patients Treated With Androgen Deprivation Therapy (ADT)

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Background: In an observational study examining serum prostate-specific antigen (PSA) DT as a predictor of bone metastases among men with prostate cancer (PC) treated with ADT in Sweden, we had over 10 years of PSA data available for analysis. Despite evidence supporting the importance of PSA kinetics in predicting PC outcomes, there are few evaluations of different approaches to PSA DT calculation from observational databases, and generally the focus is on PSA DT at baseline.

Objectives: To evaluate the impact of PSA DT calculation method on the estimate of association with bone metastases.

Methods: Using EMR data linked to national registries (Swedish Cancer Registry, National Patient Register, Cause of Death Registry), we identified a cohort of men with non-metastatic PC treated with ADT between 2000 and 2010 with ≥ 2 PSA tests recorded (n = 446). We evaluated PSA DT as a time-varying variable using the log-slope method, which fits a regression with the log of PSA values as the dependent variable and time as the predictor. While the log-slope can utilize all historical PSA, we examined various look-back periods to capture clinically relevant effects. Competing risk models (Fine and Gray) were used to estimate hazard ratios (HR) for the association with bone metastases (PSA DT ≤ 6 vs. PSA DT > 6 months).

Results: Mean follow-up time was 3.3 years. HRs varied depending on method used: last two PSA values (HR = 12 [7.1–22]), last three PSA values (HR = 14 [8.3–2.5]), all PSA data available (HR = 7.6 [4.4–13]), and all PSA data available in preceding 2 years (HR = 8.7 [5.1–15]). The association moved towards the null when including historical data.

Conclusions: Unlike clinical trials, observational studies rely on real-world patterns of PSA testing, where data may be recorded irregularly but can span several years. Time-dependent parameters should be examined in addition to baseline PSA DT, and a look-back period should be considered to capture most clinically relevant data when dealing with lengthy follow-up periods.

448. Identification of Patients With Chronic Kidney Disease From National Health Insurance Claims Data in Taiwan: A Validation Study

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Background: National Health Insurance Research Database (NHIRD), derived from claims data of National Health Insurance (NHI), may provide a source for outcome research about chronic kidney disease (CKD). In the absence of laboratory data, one would need to

identify patients with CKD from diagnostic codes in the health care claims. However, the validity of this approach has not been sufficiently studied in Taiwan.

Objectives: To validate several claims-based approaches for the identification of patients with CKD by using diagnosis codes from NHI claims data in Taiwan.

Methods: From stroke registry database of a single center, we obtained the first serum creatinine measurement of 1,317 elderly NHI beneficiaries upon the index admission for acute ischemic stroke and calculated each patient's estimated glomerular filtration rate (eGFR). We then searched other discharge diagnoses of the index admission as well as all other in- and outpatient claims data within 1 year before the index admission for the presence of diagnosis codes for diabetic nephropathy, hypertensive nephropathy, chronic renal insufficiency, and miscellaneous other renal diseases. Using the gold standard of an eGFR < 60 mL/min/1.73 m^2 for definition of CKD, we determined the sensitivity, specificity, and positive and negative predictive values for individual diagnosis and combinations of these diagnoses.

Results: The sensitivity of individual diagnostic code ranged from 1.6% for diabetic nephropathy to 5.3% for miscellaneous causes. Besides, the 'miscellaneous' group had a comparable specificity (97.4%) with all other individual diagnostic codes (all > 99%). Combinations of all these codes failed to improve the sensitivity. Positive predictive values generally were high (88.5–100.0%), but negative predictive values were low (46.6–47.8%).

Conclusions: The high positive predictive value indicates that NHI claims data can be used to accurately identify a group of CKD patients for study. However, the utility of NHIRD for comparative research regarding patients with and without CKD may be subject to misclassification bias due to the low negative predictive value.

449. Doubly Robust Estimator: Effects of Variable Selection into Component Models on Efficiency

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Background: Doubly robust (DR) estimators are robust in that correctly specifying a covariate in either the propensity score (PS) model or outcome regression (OR) models will control for confounding. The effect of variable selection into the PS, OR, or both component models on efficiency is not known.

Objectives: To evaluate the efficiency of adjusting for a confounder in the PS, OR, or both and to compare the efficiency of the DR estimator with conventional estimators.

Methods: We simulated a dichotomous covariate (Z), a dichotomous treatment (X), and a continuous outcome (Y). We varied the magnitude of the effect of Z on (1) treatment, (2) outcome and (3) introduced effect modification by Z. For each scenario, we simulated 5,000 iterations, and within each iteration we simulated a cohort of n = 5,000. In each cohort, we estimated the average treatment effect (ATE) using the DR estimator adjusting for Z only in the OR models (DR01), only in the PS model (DR10), or in both component models (DR11). We also estimated the ATE using the inverse probability of treatment weighted (IPTW) estimator and g-computation (GC). We calculated bias, variance, mean squared error (MSE), and relative efficiency (RE) as the ratio of MSEs using GC$_{MSE}$ as the referent.

Results: All methods produced unbiased estimates of the ATE. The RE of DR01 was 2.2% worse than GC, on average. The efficiency loss was greater when Z was included in the PS model (DR10: RE = 5.1%, DR11: RE = 5.1%). IPTW was least efficient (RE = 13.5%, on average). As the effect of Z on the choice of treatment became stronger, the efficiency of DR01 approached that of GC (RE = 1.0%) while the efficiency of DR10, DR11, and IPTW worsened (RE = 11.6%, 11.6%, and 23.9%, respectively). Varying the association between Z and the outcome did not alter the pattern of findings, nor did the presence of treatment effect heterogeneity by Z.

Conclusions: Our findings suggest that using the PS model to adjust for a confounder comes at the cost of precision with the loss of efficiency increasing as the effect on treatment strengthens. Efficiency of the DR estimator benefits from including strong predictors of treatment selection only in the OR models.

450. A Proxy of Cancer Progression in Dispensing Claims: Validation and Performance

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Background: Disease progression, an important cancer outcome, is rarely available for large-scale observational studies based on health administrative data.

Objectives: To derive and validate a proxy for disease progression in metastatic breast, lung and colorectal cancer patients using dispensing claims.

Methods: We used linked primary (prescribing and progression) and secondary (dispensing) data from a cohort study of cancer patients undergoing chemotherapy. A proxy was derived from prescription histories (n = 36), validated in prescribing data (n = 62) then subsequently adapted and validated in dispensing data (n = 110). The proxy was based on identifying progression from specific changes in drug use. We validated the proxy using the gold standard of disease progression as recorded in patient medical records. Individual progression episodes were the unit of analysis for sensitivity and positive predictive value (PPV), with GEE used to account for multiple progressions within patients. The patient was the analysis unit for calculating specificity and negative predictive value (NPV).

Results: The sensitivity of our proxy based on prescribing data was 74% (95%CI: 56–87%) and PPV was 61% (95%CI: 45–75%). Specificity and NPV were 88% (95%CI: 74–96%) and 100% (95%CI: 90–100%) respectively. Using date of dispensing from claims data, the sensitivity of our proxy was 60% (95%CI: 45–73%) and PPV 55% (95%CI: 42–67%). Specificity and NPV were 80% (95%CI: 68–89%) and 84% (95% CI: 72–92%).

Conclusions: Our proxy performed better in prescribing than dispensing data. Identifying cancer disease progression using the current proxy poses issues regarding the misclassification of patients undergoing treatment whose disease has not progressed.

451. The Impact of Methods Used for Case Ascertainment on the Association between Restless Legs Syndrome (RLS) and Cardiovascular Disease (CVD)

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Background: There is evidence of an association between RLS and CVD. These studies have used different case definitions for RLS and CVD and different methodologies, which could have an impact on study results.

Objectives: To assess the methods used to define RLS and CVD and the effect of case definition on study findings.

Methods: A literature review was conducted in PUBMED, EMBASE and OVID to identify all published studies between 2000 and 2012 reporting on the association between RLS and CVD. Data was extracted on study design, case definition and measures of association. When a study reported several methods of case definitions, a comparison of the magnitude of the measures of association was done.

Results: A total of 28 clinical studies were identified. CVD cases were ascertained using self-reported measures (n = 18), self-reported measures and physical examination (n = 4), medical records review (n = 3), and physical examination (n = 3). RLS was defined using the international restless legs syndrome study groups rating scale (IRLSSG) in 21 studies, the international classification of sleeping disorders criteria in two studies and other questionnaires in five studies. The measures of association, odds ratios (ORs) ranged from 1.4 (1.1–1.9) to 2.9 (1.2–7.2). When restricted to studies that used the IRLSSG criteria the range was 2.1–2.9 increased likelihood of RLS in adults with self-reported CVD after adjustment for confounders. For example, in one study, comparing RLS cases to healthy controls using self-reported measures, the history of myocardial infarction was 3.9% vs. 7.5% and heart failures 7.7% vs. 10.0% but using clinical history, medical review and radiography, the presence of stroke was 30.8% in RLS vs. 18.3% without RLS, and silence infarctions19.2% vs. 12.0%.

Conclusions: Methods used to define cases of RLS and CVD have an impact on the magnitude of measures of association. There is need for more robust and standardization of case definitions to accurately estimate associations, aid in interpretation of study findings and enable comparison of results across studies.

452. Conformity Between Protocol Eligibility Criteria for Electronic Patient Identification: A Comparison of Clinical Trials

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Background: Eligibility criteria for clinical trials define target patient populations for research studies, and are increasingly translated into a queriable format to use with Electronic Health Records (EHR). Queries may be standardized, providing consistency in EHR-based clinical trial feasibility and patient recruitment, decreasing both the time and cost of conducting such studies.

Objectives: To assess eligibility criteria from two disease areas to determine the extent to which protocol eligibility criteria were similar.

Methods: Eligibility criteria from 20 clinical trials in both Type II Diabetes Mellitus (diabetes) and depression

were selected from www.clinicaltrial.gov. These eligibility criteria were distilled into distinct components: (1) Test, (2) Value (responses to 'test' question), and (3) Time Clause (timeframe in which the test-value must be met). Criteria components were classified as similar when exactly the same. All similarities were tabulated and averaged at each level.

Results: Diabetes studies had an average of 15.9 criteria, and 26 tests, test-value pairs and test-value-time triplets per study. 66.9% of tests, 50.6% of test-value pairs, and 36.4% of test-value-time triplets were similar between studies. Depression studies had an average of 12.9 criteria, and 24.5 tests, test-value pairs and test-value-time triplets. 70.4% of tests, 62.9% of test-values, and 53.1% of test-value-time-triplets were similar between studies. In both disease areas similarities decreased with more restrictive criteria clauses indicating variability and/or disagreement regarding the most appropriate value and time clauses.

Conclusions: Although there is a high percentage of similar test across studies within a given disease area, the level of similarity decreases significantly as the test value and time clause components are considered. This demonstrated the need for standardization of eligibility criteria as well as the associated EHR query definitions. Standardizing criteria and query definitions between protocols will aid in consistent patient identification within disease therapy areas.

453. Validation of the Telephone-Administered Age and Stage Questionnaire and the Revised-Prescreening Denver Questionnaire: Results From the OTIS Antidepressants in Pregnancy Study

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Background: The Age and Stage Questionnaire (ASQ) and the Revised-Prescreening Denver Questionnaire (R-PDQ) are currently used to assess children development.

Objectives: To validate the ASQ and R-PDQ telephone administration.

Methods: The OTIS Antidepressants in Pregnancy Study cohort was used. Women were recruited through nine North American Teratogen Information Services and the outpatient obstetrical clinic of CHU Ste-Justine. To be included, women had to be > 18 years old, > 15 weeks pregnant, and not using known teratogens. Children and mothers are followed until 3 years postpartum. Mothers were asked to fill the ASQ and R-PDQ at home and through a telephone interview at 12-months postpartum. The ASQ includes five 6-item domains (communication, gross motor, fine motor, problem-solving and personal-social). R-PDQ tests four areas of development (gross motor, fine motor activity, personal-social and language). Socio-demographic and lifestyle variables were collected through telephone interviews. Concordance between the telephone and in-person administration of both questionnaires were assessed with Intraclass Correlation Coefficients (ICC) with 95% Confidence Intervals (CI).

Results: The ASQ and R-PDQ were administered to 61 and 56 women, respectively. Concordance between the two modes of administration of the ASQ was substantial for the communication scale (ICC = 0.76; 95% CI [0.63; 0.84]), almost perfect for the gross motor scale (ICC = 0.91; 95%CI [0.85; 0.95]), and moderate for the fine motor, problem-solving and personal-social scales (ICC = 0.44; 95%CI [0.21; 0.62]; ICC = 0.49 95%CI [0.26; 0.66]; ICC = 0.52; 95%CI [0.30; 0.68]; respectively). Regarding the R-PDQ, the following concordance estimates were found: gross motor scale (ICC = 0.90; 95%CI [0.83; 0.94]), language (ICC = 0.58; 95%CI [0.38; 0.72], personal-social scales (ICC = 0.27; 95%CI [0.07; 0.49]).

Conclusions: These results indicate that telephone administration of the ASQ is a valid method of assessing children cognitive development. However, only the gross motor and language scales of the R-PDQ remain a valid measure when administered over the telephone.

454. A Comparison of Event-Based vs. Case-Based Methods for Detection of Signals of Disproportionality With Variable Age Distributions

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Background: When performing surveillance for manufacturing related adverse events (AEs), oftentimes there are multiple AEs and batch(lot) numbers in one case report. This is also the decision on whether to use disproportionality methods based on case-based or event-based frequencies. The literature is limited in suggesting whether to use case-based or event-based frequencies.

Objectives: The objective of this study is to evaluate case-based (CB) vs. event-based (EB) frequencies for detecting signals of disproportionality for different age groups, using relative risk (RR), proportional reporting ratio (PRR), and shrinking RR based on the Empirical Bayes Poisson-gamma model (EBGM and EB05).

Methods: Each method (RR, PRR, EBGM, EB05) was evaluated using CB and EB counts to identify signals of disproportionality using simulated data under the null (no true signal) and under alternative hypothesis (greater than or equal to one true signal). Two scenarios were considered: (1) all AEs have equal probability of being reported; (2) some AEs have higher probability of being reported compared to all other AEs. For these scenarios the following age stratifications were considered: (1) disproportionately older than age 65; (2) equal distribution above and below age 65; (3) disproportionately younger than age 65; (4) no stratification.

Results: For the crude analysis with no stratification, in scenario 2, under the null hypothesis, both CB and EB approaches resulted in a large number of false positives using RR and PRR methods. Under the alternative hypothesis, the sensitivies for the RR and PRR were similar for the CB and EB approaches in both scenarios. When the probabilities of AE reporting rates were different, the EB approach did not work well using the EBGM and EB05 methods and stratification results are forthcoming.

Conclusions: Crude analysis shows that for both the CB and EB approaches the sensitivity and number of false positives detected was similar using the RR and PRR methods. For the empirical Bayes Poisson-gamma model (EBGM and EB05) the EB approach resulted in over shrinkage leading to missed signals of disproportionality.

455. Withdrawn by Author.

456. Is the Physician's Preference of Antipsychotic Medications a Valid Instrumental Variable in the German Pharmacoepidemiological Research Database?

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Background: Instrumental variable (IV) analysis can reduce bias in observational studies even in the absence of information on important confounders. However, IV methods require strong assumptions to yield consistent estimates.

Objectives: To evaluate the validity of the physician's preference of antipsychotic medications (APM) as an instrumental variable in the German Pharmacoepidemiological Research Database (GePaRD).

Methods: We conducted a study of short-term mortality risk among elderly new users of conventional vs. atypical APM. The IV was defined as the type of the APM prescription written by each physician before the index prescription. Odds ratios (ORs) and 95%-confidence intervals (CI) were calculated to estimate the strength of the IV. The independence assumption was evaluated by examining whether the patient characteristics were related to the IV calculating adjusted estimates of risk differences (RD) and 95%-CIs. To evaluate the exclusion restriction, the relationship between the IV and the concomitant prescribing of tricyclic antidepressants (TCAs) and long-acting benzodiazepines were examined using adjusted ORs and 95%-CIs. Sensitivity analysis was conducted restricting the study to patients treated by primary care physicians (PCPs).

Results: The IV was moderately associated with the actual treatment (OR: 2.9, 95%-CI: 2.7–3.0). Prescription of an atypical APM was unrelated to that of a TCA (OR: 1.1, 95%-CI: 0.9–1.3) or long-acting benzodiazepine (OR: 1.0, 0.8–1.2). Important comorbidities (e.g. heart failure, stroke, cancer) were significantly associated with the IV. Restricting the study to PCPs, the IV was weakly associated with the actual treatment (OR: 2.3, 95%-CI: 2.1–2.6) and it remained unrelated to the concomitant prescribing of TCAs and long-acting benzodiazepines. Moreover, the associations between the IV and the patient's characteristics were no longer significant.

Conclusions: Our study has shown that valid instruments in one health care system may not be directly applicable to others. Restricting the population to PCPs, the physician's preference appears to be a valid instrument in the GePaRD.

457. Statistical Methods for Estimating Treatment Effects From Randomized Clinical Trials in the Presence of Non-Randomized Post-Study Therapies

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Background: In RCTs of cancer therapies the comparison of overall survival (OS) distributions is often challenging when the goal is to assess the benefit of 1st-line therapies in the presence of non-randomized post-study therapy (PST) use. It is not uncommon for cancer trials to demonstrate statistically significant PFS effects but not significant OS effects. While patients are randomized to their initial 1st-line therapy, the use of subsequent PSTs is determined by individual clinical practice. The potential for selection bias due to the non-randomized nature of subsequent therapies is often cited as a plausible explanation for lack of demonstrable OS effects based on standard intention-to-treat (ITT) analyses.

Objectives: We propose straightforward models to account for the non-randomized nature of PST use.

Methods: Causal models such as marginal structural models (MSMs) offer the potential to estimate causal treatment effects in the presence of PST use. We propose a straightforward marginal structural Cox model (Cox MSM) which allows for PST use to result in standard Kaplan-Meier (K-M) curves which 'merge' or 'cross-over'. That is, K-M curves which would suggest negligible OS differences by standard ITT analysis. In contrast, accounting for PST use by employing the inverse probability of treatment weighting method to estimate the parameters of the Cox MSM we can obtain unbiased estimates. We evaluate the performance of the Cox MSM in simulation studies designed to mimic trial data with moderate to heavy PST use.

Results: In a key simulation experiment where the true hazard ratio for 'Treatment' vs. 'Control' was 0.70 and 'Control' subjects initiated PSTs more frequently (60% for 'Control' vs. 50% for 'Treatment') and earlier which generally resulted in 'merging' ITT K-M curves; The average of the standard ITT-analysis Cox HR estimate was 0.89, generally suggesting no benefit, whereas the average Cox MSM HR was 0.68 (virtually unbiased for the true hazard ratio of 0.70).

Conclusions: Accounting for non-randomized PST use in clinical trials can be done in a straightforward manner to complement the standard ITT primary analysis.

458. Signal Refinement of Drug-Induced Thrombocytopenia Using the Health Information Network (THIN) Database

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Background: Signal refinement is defined as an activity by which a potential association between medical products and safety outcomes detected from any source including Spontaneous Reporting System (SRS) data or Electronic Medical Record (EMR) data or the literature could be followed up and strengthened or weakened. Signal refinement using EMR/Claims databases is a novel concept and its role in safety surveillance remains a work in progress.

Objectives: To determine whether the richness of EMR data can be harvested to quickly refine a signal detected from another source. If successful, this approach could then be used to explore other outcomes of interest.

Methods: Drug-induced thrombocytopenia (DIT) was selected as a test case of the outcome and THIN database was used. Based on extensive published level-of-evidence information, an algorithm was developed to identify persuasive reports of DIT. The algorithm first detected patients with thrombocytopenia diagnosis in THIN database, who also had a platelet count of $< 100,000/\mu L$ within 30 days prior to the diagnosis. Then patients with high risk of thrombocytopenia due to other reasons were excluded. Prescription history of the remaining patients within 7 days prior to the platelet test was then listed. Finally, the effectiveness of this algorithm was assessed by cross referencing our findings with those validated in the published literature.

Results: Five hundred and fifty-six patients were indentified with both thrombocytopenia diagnosis and a low platelet count test within 30 days prior to the diagnosis. After excluding all the patients with other high risk factors, 121 patients were identified as DIT patients. Drug history of these patients were listed and four drugs were found in both the drug history and the published reference standards.

Conclusions: Our results suggest that EMR data can be useful for rapid signal refinement analysis. One of the limitations is the distinction between true negative and absence of positive information, as some of the detailed information may not be captured by this database. There are also sample size concerns. But even small numbers can provide reassurance about the limited public health impact of signals.

459. Quality Assessment of Observational Studies in a Drug-Safety Systematic Review–Comparison of Two Tools, the Newcastle-Ottawa Scale and the RTI Item Bank

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Background: The quality assessment of observational studies included in systematic reviews is key to the interpretation of those reviews. The large number of available tools and the lack of agreement on which domains to cover reflect the challenges involved in quality assessment. While no tool has been specifically designed for pharmacoepidemiologic studies, the Newcastle-Ottawa Scale (NOS) is most commonly used.

Objectives: To compare the NOS with the recently proposed RTI item bank (RTI IB) and to validate the RTI IB.

Methods: This quality assessment was performed in the context of a systematic review of the cardiovascular safety of glucose-lowering drugs in patients with type 2 diabetes mellitus, within the European Commission-funded Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project. We tailored both tools and added four questions to the RTI IB to assess aspects of pharmacoepidemiologic studies overlooked by both tools. Two reviewers assessed the quality of the 44 included studies along with the data extraction. The RTI IB was applied independently by the two reviewers, who agreed on which responses conveyed low, unclear or high risk of bias. For the 31 questions in the RTI IB, the observed agreement was calculated as the percentage of studies on which both reviewers gave the same bias assessment. Chance-adjusted inter-rater agreement was estimated with the first-order agreement coefficient (AC1) statistic.

Results: While the NOS required less tailoring and was easier and faster to use than the RTI IB, the RTI IB resulted in a more thorough assessment. The RTI IB includes most of the questions in the NOS. The median observed agreement with the RTI IB was 77% (25th percentile-75th percentile: 61–89%); the median AC1 statistic was 0.66 (0.51–0.88).

Conclusions: The RTI IB facilitates a more complete quality assessment than the NOS but is more burdensome. The observed agreement and AC1 statistic in our application of the RTI IB were higher than reported by the tool's developers.

460. Consequences of Violating Model Assumptions: An Example Using Healthcare Claims Data

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Background: Results from pharmacoepidemiology studies can have a major impact on health practices and policy; therefore, it is important that there is careful consideration of the data and analytic methods used in such studies.

Objectives: To demonstrate how relative measures vary when the assumptions for a statistical model are not met in the analysis of health data.

Methods: We used retrospective cohort data from MarketScan. The study population included 457,301 individuals enrolled in a commercial health plan between 2008 and 2011 and who received a new prescription of zolpidem. Patients were followed until a safety event (fracture, traffic accident, non-traffic accident, fall, trauma, or laceration) occurred or for 1 year if no event occurred. We compared two potential analytic approaches: (1) modeling a binary outcome (event or no event) using a logistic model, and (2) a time-to-event analysis using a Cox proportional hazards model. Relative risk estimates were calculated per every 100-mg increase of cumulative zolpidem dose.

Results: There were 105,623 (23%) safety events. The logistic model resulted in a higher, and less precise, relative measure (OR = 14.26, 95% CI = 13.94–14.58) than the Cox model (HR = 1.08, 95% CI 1.08–1.08).

Conclusions: Our results demonstrate the importance of appropriate model selection. Given the well-defined follow-up period and binary outcome, the logistic model was a reasonable approach. However, using cohort data, the OR approximates RR only if the prevalence is low (typically, < 5%). The high prevalence of events (23%) in our study population exceeded this cutoff; therefore the odds ratio was not an accurate estimate of the relative risk. Given the availability of time-to-event data, the Cox model was also a reasonable approach. However, because of the well-defined follow-up period, survival time was artificially truncated at 1 year for all patients who did not have a safety event during that year. In this scenario, the HR was also not an accurate estimate of the RR. This study illustrates the importance of understanding the data and careful model selection based on those data.

461. Comparison of Covariate Selection Approaches for Propensity Score (PS) Derivation for Multiple Health Outcomes of Interest (HOIs): An Empirical Example

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Background: Multiple strategies are available for covariate selection for PS derivation. Uncertainty remains as to the optimal strategy for multiple HOIs.

Objectives: Evaluate outcome-specific vs. overall PS derivation approaches using a priori and automated covariate selection methods when estimating comparative treatment effects on multiple HOIs.

Methods: We identified patients aged ≥ 18 years initiating regular, first (FGA) or second (SGA) generation anti-psychotics (two consecutive prescriptions within the same category) between 2000 and 2008 in the CPRD, a research database of medical records from primary care in the UK linked with other healthcare data. Confounders and risk factors for each HOI (diabetes, stroke, venous thromboembolism) were identified a priori from medical literature or by automated selection. Comparison of Cox proportional hazard ratios (HRs) for each HOI among SGA vs. FGA users were estimated from separate models with PS derived from either covariates related to any HOI (overall) or from those related only to a given HOI (outcome-specific). We implemented each PS using matching, IPTW, and stratification to balance treatment cohorts.

Results: When covariates were selected a priori, HRs produced from outcome-specific vs. overall PS were consistent within HOIs across balancing approaches. Using diabetes as an example, HRs after matching were 0.97 (0.71, 1.33) for outcome-specific PS and 1.02 (0.73, 1.42) for overall PS. Matching resulted in retention of 87% of the unmatched SGA cohort. Corresponding HRs from the outcome-specific PS and overall PS implemented from IPTW and stratification were also consistent. Imbalances in the distribution of multiple covariates across treatment groups were greatly attenuated after applying balancing methods, although results varied by approach.

Conclusions: Within each HOI, PS models including a priori overall or outcome-specific covariates produced very similar HRs, regardless of the PS implementation method. Results support the use of an overall PS for multiple HOIs in this empirical example and will be extended to automated variable selection procedure.

462. Comparison of Case-Cohort Data Analyses Using Data of Cases/Subcohort Members Only and Data of Entire Cohort

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Background: A case-cohort design is underused in Pharmacoepidemiology studies. The analysis of stratified case-cohort data has not been well studied.

Objectives: To compare efficiency of the methods of the stratified case-cohort data analysis adjusting for covariates using data of cases/subcohort members only and data of entire cohort.

Methods: We obtained the data to assess the association between statins and multiple adverse events where different sampling fraction was employed between six statins (Japan Statin Study, JSS between 2008 and 2010). Using the data of serum creatinine (SCre) elevation in statin users, we estimated hazard ratio (HR) by Cox regression analysis with two weighting methods and compared these two. Method I is the method for exposure stratified case-cohort data weighted by inverse of sampling fraction of exposure (Langholz&Jiao, 2007), while Method II uses all of the available information in the whole cohort (where three variables or age, sex and statin were measured for all of the cohort members) through adjustment of the sampling weights via calibration (given in results) or estimation (Breslow et al. in 2009).

Results: A total of 6,877 statin new users including switchers (pravastatin: 1,418, atorvastatin: 1,790, Fluvastatin: 365, Pitavastatin: 1,109, Rosuvastatin: 2,050 and simvastatin: 145) were identified (median age: 66 years; males: 52%; switchers from other statin: 25%). Number of patients with SCre elevation/subcohort was 11/116 (pravastatin), 20/124 (atorvastatin), 7/ 48 (fluvastatin), 7/94 (pitavastatin), 13/141 (rosuvastatin), and 0/28 (simvastatin), respectively. Taking pravastatin as a reference, HR was adjusted for age, sex, switcher and renal disease. Adjusted HR (95% CI) by methods (I/II) was 2.2 (0.9–5.4)/2.0 (0.8–4.9) for atorvastatin, 3.1 (1.01–9.7)/3.0 (0.99–9.2) for fluvastatin, 0.9 (0.3–2.5)/1.0 (0.4–2.7) for rosuvastatin, 1.0 (1.0–1.1)/1.0 (1.0–1.1) for age and 3.6 (1.7–7.5)/3.6 (1.8–7.0) for sex, respectively.

Conclusions: In our study, Method I (Langholz&Jiao) and Method II (Breslow et al.) gave the same point estimate. Method II using all available data in the entire cohort was slightly more efficient than Method I.

463. Investigator-Specified vs. Empirical Covariate Selection for Confounding Adjustment in Studies With Infrequent Outcomes: Anticonvulsants and Cardiovascular Risk

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Background: Propensity score (PS) methodology has value in settings of high-dimensional covariate data and few outcomes, but best estimation approaches are uncertain when outcomes are rare.

Objectives: To compare the performance for confounding control of different covariate selection strategies and adjustment methods with rare events.

Methods: We assessed the cardiovascular safety of anticonvulsants that highly induce cytochrome P450 activity vs. other anticonvulsants in a cohort of adult patients from a commercial claims database, who had initiated an anticonvulsant between 2001 and 2006 and had no recorded major cardiovascular condition. We computed PS adjusted effect estimates with different covariate selection strategies (expert knowledge only, expert knowledge informed by empirical specification, or empirical specification only) and adjustment methods (PS-matching or PS-stratification with trimming).

Results: We identified 166,031 new users and 564 ischemic cardiovascular events during a 90-day follow-up period. Of 12,580 initiated highly inducing anticonvulsants and experienced 68 events, which were further reduced to < 30 events by matching or trimming. The unadjusted cardiovascular relative risk (RR) was 1.72 (95% CI, 1.34–2.22). Adjustment for investigator-identified covariates led to 40–59% reductions in the RR; adjustment for both investigator- and empirically identified covariates led to even wider reductions in the RR by 54–71%. A selection strategy based on empirical specification alone produced less attenuated and more volatile RR estimates. This volatility was attenuated in a trimmed PS-stratified analysis.

Conclusions: The hd-PS algorithm complements expert knowledge for confounding control, but its performance without expert knowledge is less well understood when outcomes are rare. In our example, a thoughtful consideration of variable selection by the researcher combined with empirical specification and the use of trimmed PS-stratified analysis appear to improve estimation. Plotting the relationship of the RR estimates to the increasing number of empirical covariates is an important diagnostic.

464. Validation of the Adjusted Sequence Ratio in Prescription Sequence Symmetry Analysis: A Simulation Study

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Background: Prescription sequence symmetry analysis (PSSA) is a potential tool for rapid detection of adverse drug events (ADRs) associated with newly marketed medicines utilising computerized claims data. Case studies have shown that PSSA has high sensitivity and specificity for detected ADRs, however, it is sensitive to prescribing trends over time. A null sequence ratio is used to adjust for prescribing trends, however, there has been no systematic investigation to assess the validity of PSSA estimates when variable prescribing trends occur.

Objectives: To evaluate the validity of PSSA as a signal detection tool for newly marketed medicines.

Methods: Randomly simulated prescription supplies for a population of 1 million were generated for two medicines, DrugA (medicine of interest) and DrugB (adverse event), over a 5-year period. Medicine utilization trends for the newly marketed medicine (DrugA) were varied. Associations ranging from no association, 20% increased risk, 50% increased risk to a two-fold increased risk of receiving Drug B after Drug A were simulated. We generated 1,000 simulations of each scenario. Average Adjusted Sequence Ratio (ASR), bootstrapped 95% confidence intervals (CIs) and the percentage of CI's which covered the expected ASR were calculated.

Results: In simulated datasets with no association between DrugA and DrugB, over 95% of the adjusted analysis CIs covered the expected ASR (ASR = 1) regardless of the trend in prescribing. When DrugA and DrugB were associated (ASR = 2), 82% of PSSA simulations matched expected when DrugA use was stable and 78–87% matched expected when DrugA use was increasing at various rates. Unadjusted SR's ranged from 1.88 (95% CI 1.66, 2.13) for no trend in DrugA to 1.58 (1.43, 1.75) for a steeply increasing trend. After adjustment for trend ASR estimates were 1.88 (1.66, 2.13) and 1.88 (1.70, 2.08) respectively.

Conclusions: Adjustment for underlying medicine utilisation patterns effectively overcomes under-ascertainment of potential safety signals. The method was not found to over-estimate risk, suggesting PSSA may be effectively applied as a rapid safety signal detection tool for newly marketed medicines.

465. Defining a Denominator Population for Linked Datasets

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Background: The CPRD primary care data has been linked to several external datasets. In a study using multiple data sources, it can be a challenge to identify the underlying study population, as well as identify denominator populations and associated person-time.

Objectives: To identify patients who are eligible for inclusion in studies using linked data sources whose membership and coverage change over time.

Methods: Practices that consent to take part in the CPRD linkage scheme are linked anonymously via a trusted third party. The linkage process uses a stepwise matching algorithm, where the first pass identifies matches primarily on NHS number. If this fails, a second pass attempts to find a match based on date of birth, sex and postcode information. Only patients that have a valid NHS number in practice data, and therefore have the potential to be linked on NHS number are identified as eligible. A flag to indicate eligibility per individual linked data source is provided. Individual data source coverage periods allow users to define follow-up time for patients. Linkage enables CPRD to identify and flag individuals that have contributed data to more than one CPRD practice.

Results: In the latest linkage version, 8,913,933 patients from 374 CPRD English practices were linked by the trusted third party. Of 7,043,891 (79%) of people had a valid NHS flag in practice data. Of the 6,065,966 patients found to have one or more record in Hospital Episodes Statistics (HES) data, 5,824,111 (96%) were matched on NHS number. 5,482,102 (94%) of these were identified as unique CPRD patients.

Conclusions: Linked datasets provide a unique opportunity for research. To maximise research benefit from linked data, users should consider the impact of linkage methodology, presence of duplicate records, and data coverage for inclusion of patients in the study. The meta-data that CPRD provide enables users to make informed decisions about their study based on its context and design.

466. Withdrawn by Author.

467. Missing Data in Modified-PEM (M-PEM) Studies; an Application of Multiple Imputation

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Background: Missing data is a common problem in observational studies which can greatly modify results. M-PEM is an observational post-marketing safety surveillance method, with results based on complete case (CC) data under the Missing at Random (MAR) assumption. Multiple Imputation (MI) is one solution where plausible values are imputed for missing data and thus any bias in estimates can be explored. As a motivational example, the magnitude of bias in estimating prevalence of selected risk factors for the occurrence of extrapyramidal symptoms (EPS) reported in users of an atypical antipsychotic was explored.

Objectives: To examine the amount of missing data, patterns of missingness and to classify the missing data mechanism in a prototypical M-PEM study.

Methods: M-PEM study data was collected September 2008–August 2012. Selected prognostic risk factors for EPS included age, sex, start dose, indication, medical history and prescriber type. To explore the missing mechanism, correlations between the variables and a binary variable for missingness were calculated. Multivariate normal (MVN) and chained equations (MICE) methods of MI were compared and the standard errors for imputed variables were calculated. For MICE, models included auxiliary covariates and the response variable for maximum information recovery.

Results: Preliminary data analysis showed that the variables with the most amount of missing information were prior alcohol use (46% missing), history of somnolence/sedation (29%) and history of EPS (27%). The prevalence of EPS history, somnolence/sedation history and depression history was 3.11%, 15.36% and 42.74% respectively. Using the MVN method the prevalence decreased to 2.28%, 11.9% and 41.1% respectively. The decrease was smaller using MICE; 2.5%, 12.69% and 41.69% respectively.

Conclusions: This exploratory analysis showed that the application of MI is feasible as a method to assess the impact of missing data among key variables in real world M-PEM studies. Both methods produced similar results illustrating potential gains over CC analyses to

avoid introduction of biases when exploring associations between variables.

468. Estimation of the Incidence Rate of Very Rare Diseases – A Case Study of Multicentric Castleman's Disease

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Background: Studies that estimate incidence of very rare diseases (< 1 in 100,000 of the general population) often rely upon cases seen at specialized centers. However, multiple potential sources of both systematic error and random error complicate this estimation.

Objectives: To describe the main challenges of incidence estimation of rare diseases and to discuss how to improve the assessment accuracy, using our experience with estimating the incidence of Multicentric Castleman's Disease (MCD) as a case study.

Methods: All patients that were newly diagnosed with MCD at two centers were included. Incidence of MCD was estimated by defining catchment areas for each center to establish the relevant population denominator, and counting new MCD diagnoses for patients within each catchment area. Patients' locations were identified from the first three digits of their zip codes and mapped using a Geographical Information system. CENSUS data were used to estimate the size of the reference population and to calculate crude and stratified incidence rates.

Results: Catchment areas for each center were defined based on spatial patterns and center-specific clinician input. Subtle changes to catchment area definitions resulted in substantial changes to MCD incidence estimates. Additional uncertainty in the estimates resulted from: small sample size; center-specific population features and referral patterns; under-diagnosis and difficulty of diagnosis; and associations between disease risk factors and proximity to the centers. Optimizing accuracy involved a trade-off between the number of patients included in a catchment area and catchment area definition, with clearer geographical boundaries that maximized the proportion of MCD patients in the population represented in the center.

Conclusions: Small sample sizes in combination with multiple potential sources of error challenge an accurate estimate of incidence. Narrow definitions of center catchment areas further reduce the number of included cases but can improve the accuracy of the incidence estimate.

469. Comparison of a Targeted Maximum Likelihood Estimator to Other Estimation Techniques for the 1 year Risk of Myocardial Infarction Among New Users of High vs. Low Potency Statins

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Background: Targeted maximum likelihood estimation (TMLE) is a doubly robust, non-parametric method for estimating causal effects. While simulations have shown TMLE performs well in comparison to other methods of causal inference, its performance at varying sample sizes has not been well characterized.

Objectives: We examined the performance of three different statistical techniques at varying sample sizes for the estimation of the effect of statin potency upon the 1-year risk of myocardial infarction in a large commercial claims database.

Methods: We created a cohort of new users of statins in the MarketScan Commercial Claims database. New users had at least 180 days of continuous enrollment prior to the initial statin prescription. Initial statin use was classified as either high or low potency based on formulation, and we examined inpatient and outpatient billing claims for an ICD-9 code for myocardial infarction within 1 year from the initial statin claim. We compared the performance of TMLE and doubly robust estimation to a logistic regression model adjusted for demographics, LDL cholesterol, and indicators of several CVD-related comorbidities and medications. We created a subcohort by randomly sampling 50% of the patients in the original cohort and examining the effect of sample size in the performance of the estimators.

Results: Of 70,464 patients were included in the full cohort. The median age was 54 for both statin doses. Hyperlipidemia and hypertension were the most prevalent comorbidities. We found an odds ratio of approximately 1.3 in all models other than the unadjusted logistic regression model, with the TMLE and doubly robust models performing virtually identically. The TMLE and doubly robust methods gave very similar results in the 50% subcohort, but the TMLE model had slightly better precision, as measured by a 95% confidence limit ratio (TMLE: 1.62, Doubly robust: 1.85).

Conclusions: Targeted maximum likelihood estimation gave slightly improved precision in a random subsample. Additional investigation of the properties of TMLE in observational cohort data is warranted.

470. TrialViz: A Feasibility Tool Based Upon the CPRD GOLD Primary Care Database

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Background: A major problem of interventional studies is feasibility assessment. Difficulties recruiting patients into a study creates both logistical and financial issues. In the UK, primary care lends itself well to a role as a key source of study participants. Undertaking this assessment using routinely collected primary care electronic healthcare records is a route to quick and accurate feasibility analysis.

Objectives: To create a near real time feasibility tool to identify candidate patients for study recruitment based on interrogation of the CPRD GOLD primary care database.

Methods: A software tool (TrialViz) was developed based on the hierarchical concept of cards (record sets definitions), stacks (cards modelled together to represent identification criteria) and searches (logically grouped stacks to model sets of inclusion and exclusion criteria for subject selection). A graphical user interface was developed as an intuitive and flexible tool to build searches with methods for search refinement. Queries were run on the GOLD anonymised patient records within a relational database. Asynchronous query execution and stepwise query execution enables complex queries to be executed in near real time to produce a practice specific patient list. User roles and private and public search components facilitate secure sharing of information at multiple levels.

Results: Results of queries are represented as numbers of potential subjects by broad geographical area. The ability to drill down and identify patients from practices within a set catchment area relative to potential study sites is possible. Geographical representations are made available with appropriate security to enable protection of practice and patient confidentiality.

Conclusions: TrialViz goes a long way towards making fast accurate and efficient recruitment to interventional studies a reality. Further validation studies will generate feedback in terms of how well such a method identifies potential subjects. Future integration of linked data sets and modules to assist with actual recruitment will enhance the capability further.

471. Predicting a Missing Baseline Value in a Rare Disease Registry Using Extrapolation of Mixed Models Estimates

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Background: Small patient populations and heterogeneous disease characteristics and demographics in rare diseases make analysis of outcomes difficult. Registries can track disease progression and treatment outcomes of rare diseases. Unlike clinical studies, registries are observational and may not have key data collected at set time points, e.g., time of first treatment ('baseline').

Objectives: Assess the feasibility of predicting a baseline value of a key respiratory parameter using extrapolation of estimates from mixed models in a rare disease registry.

Methods: We identified adult treated patients who had ≥ 2 Forced Vital Capacity (FVC) percent predicted values recorded in either the baseline (90 days prior to 28 days after first treatment) and post-treatment time window, or post-treatment only. Demographics and disease characteristics of patients with a baseline observation were compared to those with only post-treatment observations. We used unadjusted mixed models to estimate the intercept (the predicted FVC value at the time of first infusion). The model intercept was compared to baseline FVC in patients with a baseline observation.

Results: Of 1,034 registry patients (December 2011), 289 treated adults met study entry criteria; 167 (57.8%) had a record of FVC at baseline. Demographics were similar in patients with and without a baseline value. Patients with a baseline observation reported fewer signs/symptoms and had more observations than those without a baseline observation (mean 5.7 vs. 3.8) over a longer time frame (mean 1.9 vs. 2.9 years). Using all data in the 5-year post-treatment window, the median percent difference of the extrapolated baseline value (the intercept) from the reported baseline value was 1.3% (min -21.7%, max 58.0%) in 167 patients. In the same model restricted to a 2-year window, the difference was 0.84% (min -20.5%, max 54.9%) in 162 patients.

Conclusions: In observational data where some patients do not have a baseline observation but have multiple observations over time, mixed models can be used to predict a baseline value. However, outliers exist and the extrapolation is sensitive to model fit. Results must be interpreted with caution.

472. Inclusion of Variables Associated with Exposure but Not Outcome Can Compromise Propensity Score-Based Adjustments – Examination of a Real-Life Example in Pediatric Psychopharmacology

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Background: Simulation studies have cautioned about the inclusion of strong predictors of exposure that are weak predictors of outcome in exposure propensity scores because they may amplify rather than reduce bias. Real-world examples of these scenarios are scarce.

Objectives: To explore inclusion of a strong predictor of exposure but not outcome on risk estimates.

Methods: In a large population-based study on the cardiac risk of central nervous-system stimulants, we required presence of a mental disorder that has been associated with the use of stimulants (e.g., attention deficit hyperactivity disorder [ADHD], oppositional defiant disorder). Among these, ADHD showed pronounced associations with stimulant treatment but was not expected to predict cardiac events. We evaluated the performance of two propensity score models, with and without ADHD, in terms of overall covariate balance and impact of outcome estimates.

Results: While the ADHD-model showed better model fit (C-statistic 0.735 vs. 0.823), covariate balance was worse when standardized differences among covariates in stimulant users and non-user achieved with the ADHD-model were compared to those of the base-model without ADHD. Point estimates for the two examined endpoints, severe cardiac events and mild cardiac events, changed as follows: For serious cardiac events, the association between stimulant use and outcomes increased from an odds ratio (OR) of 0.74 (95% CI 0.38–1.46) excluding ADHD, to 0.83 (0.41–1.67) including ADHD in the propensity score. For mild cardiac events, the association between stimulant use and outcomes increased from OR 1.15 (1.07–1.23) excluding ADHD to 1.25 (1.17–1.35) including ADHD in the propensity score model.

Conclusions: This is a real world example that replicates theoretical findings suggesting that strong predictors of exposure (that are not strongly related to the outcome) should be excluded from propensity score models. Studies should use caution when including strong predictors of exposure as covariates in a propensity score and examine the corresponding effect on covariate balance.

473. Development of a Claims-Based Algorithm to Identify Prolia Use in Medicare Data

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Background: Prolia, a new biologic agent for postmenopausal osteoporosis (PMO) launched 5/26/2010, was originally billed in Medicare Part B with non-specific Healthcare Common Procedure Coding System (ns-HCPCS) codes. These codes do not uniquely identify the drug being administered.

Objectives: To develop a claims-based algorithm to identify Prolia and distinguish it from other injection or infusion medications using ns-HSCPS codes in Medicare data.

Methods: We used 2010 Medicare Part B data from a cohort of beneficiaries with PMO age 65 years and older with at least 1 month of Medicare Parts A, B, and D coverage, without Medicare Advantage. We selected Part B claims with ns-HCPCS codes from launch date to 31 December 2010. We reviewed information such as service date, units given, allowed amount, submitted amount, and associated diagnosis codes from claims with the specific Prolia HCPCS code, in limited use since 10/2010, to derive the algorithm. We evaluated claims for two other agents with attributes similar to Prolia using ns-HSPCS in 2010 (tocilizumab (TCZ) & Ozurdex (OZD)). The final algorithm classified each ns-HCPCS claim as Likely, Probably, Possibly, or Unlikely Prolia. We evaluated differences in characteristics between the groups, focusing on the Likely and Unlikely claims.

Results: Our study included 89,581 beneficiaries with 197,043 claims with ns-HCPCS codes. We identified 11,557 duplicate/redundant claims, 1,610 TCZ, and 296 OZD claims. Algorithm development used 1,061 Prolia claims with the specific HCPCS code. Our final algorithm identified 10,438 Likely, 483 Probably, 134 Possibly, and 174,381 Unlikely Prolia claims. A larger proportion of Likely claims had an osteoporosis

diagnosis code on the same claim than the Unlikely claims (99.4% vs. 8.5%). Similarly, the proportion of Likely claims (85.3%) with the appropriate Prolia allowed amount, $874.50–$874.80, was larger than that of the Unlikely claims (0.0%).

Conclusions: Our algorithm appeared successful at identifying Prolia users in Medicare with good internal validity. An external source to examine the sensitivity and specificity of the algorithm is needed for further validation.

474. The Validity of Claims-Based Algorithms to Identify Serious Hypersensitivity Reactions and Osteonecrosis of the Jaw

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Background: Hypersensitivity reactions and osteonecrosis of the jaw (ONJ) are adverse events (AEs) associated with osteoporosis (OP) medications. However, validation studies of claims-based algorithms to identify these two AEs have not been performed in large OP populations.

Objectives: To estimate the positive predictive value (PPV) of claims-based algorithms to identify hypersensitivity and ONJ in older women enrolled in Medicare.

Methods: Using the 2006–2008 Medicare 5% sample data, we identified potential hypersensitivity and ONJ cases based on ICD-9 codes. Potential hypersensitivity cases had a diagnosis of 995.0, 995.2, or 995.3 on emergency room or inpatient claims. Potential ONJ cases had ≥ 1 claim with a 522.7, 526.4, 526.5, or 733.45 diagnosis code or ≥ 2 claims with a 526.9 diagnosis code. All retrieved records were redacted and reviewed by experts to determine case status: confirmed, not confirmed, or unable to determine. We calculated PPV as the number of confirmed cases over the total number of retrieved records with sufficient information.

Results: We requested 412 potential hypersensitivity and 304 potential ONJ records, of which we received 174 (42%) and 84 (28%) records, respectively. Of 174 retrieved potential hypersensitivity records (91% from institutional facilities), 95 were confirmed, resulting in a PPV (95% confidence interval [CI]) of 76.0% (67.5, 83.2). The PPV associated with anaphylaxis (ICD-9:995.0) was 100% (n = 12 cases), and 74% for other hypersensitivity codes. Of 84 potential ONJ cases (49% from institutional facilities), six were confirmed, resulting in a PPV (95% CI) of 7.1% (2.7, 14.9). The specific ONJ code (733.45) had the highest PPV of 25.0% (one out of four cases).

Conclusions: In a random sample of Medicare data, a claims-based algorithm to identify serious hypersensitivity reactions performed well, especially for anaphylaxis. An algorithm for ONJ did not. This could be partly explained by the large use of non-specific ONJ diagnosis codes. Future evaluation of an ONJ algorithm using more recent data with greater expected use of the specific ICD-9 ONJ code is warranted.

475. Evaluation of Analytical Method Performance Using Observational Medical Dataset Simulator (OSIM2)

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Background: Most electronic healthcare data are not compiled for research purposes. True drug-event associations may be difficult to ascertain using these data as 'known associations' may be affected by confounding and other issues. The Observational Medical Outcomes Partnership (OMOP) designed and developed an automated procedure to construct simulated datasets - OSIM2 as a gold standard for method evaluation. We aimed to adapt OSIM2 for analytical method evaluation.

Objectives: To compare three analytical method performance in a cohort study using OSIM2 for examining association between (1) tricyclic antidepressants (TCA) and acute myocardial infarction (AMI) and (2) typical antipsychotics (TA) and AMI.

Methods: Two study cohorts aged 18+ years, who were newly prescribed TCA and TA, respectively, during 1 January 2003–31 December 2006 were identified from OSIM2. The control cohorts did not receive any TCA or TA. Cox proportional hazards modeling was used to compare the rates between two groups. The following three methods for confounding adjustment were evaluated: (1) traditional adjustment for a set of predefined covariates, (2) propensity score matching (PSM), (3) high-dimensional propensity score (HDPS) by an automated process.

Results: A total of 38,586 TCA users and 44,619 controls were identified. The mean age was 46.0 years, and ~71% was female. TCA users had more comorbidities, including coronary heart disease, diabetes and hypertension. The crude incidence rates of AMI in TCA users and controls were 53.0 and 30.6 per 1,000 person-years, respectively. The risk of AMI was higher in TCA users after traditional covariate adjustment (adjusted HR = 1.60, 95%CI 1.31, 1.89). The adjusted HR using PSM and HDPS was 1.5 (95%CI 1.22, 1.86) and 1.45 (95%CI 1.20, 1.76), respectively. Similar findings were observed for TA users. The corresponding adjusted HR was 1.50 (95%CI 1.10, 1.98), 1.70 (95% CI 1.91, 2.42), and 1.49 (95%CI 1.12, 1.99).

Conclusions: Results based on OSIM2 using three different methods (a set of predefined covariates, PSM and HDPS) for confounding adjustment in a cohort study were similar. OSIM2 may be a useful tool as a 'true' gold standard to supplement method evaluation.

476. Validation of Stroke in the Clinical Practice Research Datalink (CPRD)

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Background: The Clinical Practice Research Datalink (CPRD) uses Read codes to record clinical events. The validity of Read codes for diagnosis of stroke in CPRD has not been validated externally by general practitioners (GPs) to the best of our knowledge.

Objectives: We requested additional information from the GPs for information external to the database (1) to verify stroke diagnosis of individual cases, (2) to evaluate the positive predictive value (PPV) of Read codes, and (3) to verify the correct date coded for incident stroke in CPRD.

Methods: We sent 1,120 questionnaires to GPs for patients 40–95 years of age with diagnoses corresponding to 75 Read codes for stroke in CPRD, during the period 1 January 1997–30 June 2011. Four questions confirmed (1) the diagnosis (2) types of supporting information (3) date of diagnosis, and (4) whether diagnosed by neurologist. The response rate is defined as valid questionnaires received as a proportion of the total sent to GPs. Positive predictive value (PPV) is defined as confirmed stroke cases as a proportion of valid questionnaires. A returned questionnaire was considered invalid if blank, or response given as 'unknown' to every question, or 'no information found'.

Results: There were 876 valid questionnaires returned of the total 1,120 sent out (78% response rate). The PPV of the 75 identified Read codes for stroke was 89% (95% CI: 87–91%) with 787 confirmed stroke cases. Of these, 558 (71%) had a correct diagnosis date, and 13% had a diagnosis date within 30 days of the date recorded in the electronic medical records. No differences in response rate and PPV between patients 40–64 and 65–95 years-old. Only 23% cases were diagnosed by a neurologist. About 54% of valid questionnaires confirmed stroke by 'Clinical notes', 50% by 'Consultation' beyond electronic medical records.

Conclusions: Questionnaires to GPs requesting additional information external to the database to verify stroke status of individual cases showed relatively high PPV. In addition, accuracy of the stroke diagnosis date in CPRD was high. This suggests that the 75 CPRD Read codes identified for this analysis are adequate to identify stroke cases.

477. A High-Performing, SEER-Validated Algorithm for Identifying Patients With Incident Cancer of the Esophagus or Cardia Using Medicare Claims Data

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Background: Validated algorithms for cancer incidence are critical to etiologic studies of cancer risk. The SEER network provides a validated repository of nearly all incident cancers within the regions it covers.

Objectives: To develop an algorithm to identify incident cancer of the esophagus and cardia using Medicare data linked to SEER.

Methods: Medicare beneficiaries age ≥ 65 residing in regions covered by SEER from January 2004 to March 2008 were linked to SEER registry files to identify members with and without incident cancer of the esophagus or cardia from 2005 to 2007. Stratified by SEER region, a 2/3rd random sample of cases and non-cases formed the training dataset. Using clinical logic and treatment guidelines, we generated a list of ICD-9, CPT, and HCPCS codes for diagnoses, procedures, therapies, and hospice care that might be associated with esophageal or cardia cancer. We constructed

candidate algorithms and in an iterative fashion, examined random samples of claims profiles of false-positive and -negative cases to refine algorithm rules. The remaining 1/3rd random sample comprised the testing dataset, wherein performance characteristics of the algorithms were determined (sensitivity, specificity, PPV, total misclassification error).

Results: The base population included 4,465,154 beneficiaries with 4,206 incident cases of esophageal or cardia cancer. The PPV for a single diagnosis of esophageal or cardia cancer was 42.2%. The best-performing algorithm required either: upper endoscopy with a cancer diagnosis on the same claim combined with a follow-up diagnosis of cancer; or ≥ 2 medical interventions, each linked to a cancer diagnosis on the same claim. For this algorithm, sensitivity = 87.3% (95% CI 86.0–88.5); specificity = 99.99%; PPV = 87.5% (95% CI 86.3–88.8); and total misclassification error = 12.6%. Sensitivity was high across SEER regions and strata defined by demographic and tumor characteristics.

Conclusions: An algorithm with high sensitivity and positive predictive value for cancer of the esophagus or cardia was generated, providing an excellent model for algorithm development with other cancers.

478. Algorithms to Identify Pancreatic Cancer and Thyroid Neoplasm from Health Insurance Claims Data

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Background: Identification of cancer cases in health insurance claims data can be complicated by false positive cases.

Objectives: To identify algorithms for pancreatic cancer and thyroid neoplasm from health insurance claims data.

Methods: Among initiators of antidiabetic agents with type II diabetes in 2005–2010, we initially identified potential cases of pancreatic cancer and thyroid neoplasm from a commercial health insurance claims database using inclusive algorithms based on ICD-9 diagnosis codes. We then sought medical charts and adjudicated the case status. The initial algorithms were refined using the adjudicated case status, incorporating important predictors of outcomes, including diagnostic procedures (e.g. biopsy) and treatments (e.g. surgery, chemotherapy, and radiotherapy) within 180 days after the initial potential diagnosis. Positive predictive values (PPVs) and 95% confidence intervals (CIs) were calculated to evaluate the algorithm performance.

Results: Initially, there were 61 potential cases of pancreatic cancer, 53 potential cases of thyroid cancer, and 38 potential cases of benign thyroid neoplasm, for which we received 123 of 152 (81%) of the medical charts sought (44 for pancreatic cancer, 44 for thyroid cancer and 35 for benign thyroid neoplasm). Twenty-six of 44 potential cases were confirmed to have pancreatic cancer for an initial PPV of 0.59 (CI 0.43–0.74). Twenty-nine of 44 potential cases were confirmed to have thyroid cancer for an initial PPV of 0.66 (CI 0.50–0.80), and 28 of 35 potential cases were confirmed to have benign thyroid neoplasm for an initial PPV of 0.80 (CI 0.63–0.92). After refining the algorithms, the PPVs increased to 0.88 (CI 0.62–0.98) for pancreatic cancer, 0.95 (CI 0.76–1.0) for thyroid cancer, and 0.92 (CI 0.62–1.0) for benign thyroid neoplasm.

Conclusions: It is feasible to identify cases of pancreatic cancer and thyroid neoplasm using multivariable algorithms, although the sensitivity of the final algorithms remains untested.

479. Validation of Outcome Definition of Acute Renal Failure in Japanese Electronic Medical Records Data

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Background: Several pilot studies for drug safety assessment are ongoing in PMDA's MIHARI project. This is one of those studies using standardized electronic medical records (EMR) data. Valid outcome definitions in database studies largely depend on how the data were generated from clinical settings which would vary by country. It is said that outcome definitions by diagnosis codes only often have low validity in Japanese EMR data. However, the number of validation studies for such outcome definitions has been very few in Japan. Thus, we conducted a validation study with a collaborative hospital.

Objectives: To evaluate validity of outcome definition of acute renal failure (ARF) in the standardized EMR data.

Methods: Data source: The EMR data from April 1, 2007 to December 31, 2011 were obtained from the collaborative hospital in Japan. Potential cases: Those who had at least one diagnosis of ARF (ICD-10 code;

N17 or N19) were identified. Adjudication of true cases: Potential cases were screened by acute increases of serum creatinine (SCr), and the remained cases were randomly sampled for chart review. Nephrologists adjudicated those sampled cases as true or false cases by reviewing medical charts. Statistical analysis: Positive predictive value (PPV) of ARF was calculated, and distributions of patient characteristics were compared between true cases and false cases.

Results: Of the 1,036 potential cases with the diagnosis of ARF, the 713 potential cases were selected by the SCr screening. Medical chart review was performed on randomly sampled 213 potential cases, and the PPV was 37.6%. True cases were grouped by prior SCr level as normal, moderately high, and high. The PPVs for those sub-groups were 92.2%, 65.6%, and 14.3%, respectively.

Conclusions: The results showed that the validity of the outcome definition by the ARF diagnosis codes was low, but it could be improved by addition of prior SCr level to the definition. Since this study was conducted at only one hospital, generalizability of the result would be limited.

480. Adverse Events Associated With Pediatric Use of Proton Pump Inhibitors: Analysis of the FDA Adverse Event Reporting System

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Background: Proton pump inhibitors (PPIs) are commonly used in children for treating gastroesophageal reflux disease and erosive esophagitis symptoms. PPI use has been related to respiratory infections as well as activity-related bone fractures. Children with asthma are much more likely to be treated with a PPI than non-asthmatic children. However, the safety profile for long-term use of PPIs in children is still largely unclear.

Objectives: The objective of this study was to identify the adverse events (AEs) associated with pediatric PPI use and stratify them by individual PPI, age of patient (child vs. infant), and whether the PPI was a primary suspect drug or used with other medications.

Methods: A retrospective, descriptive analysis was conducted. Reports of AEs related to PPIs from 1997 through 2011 for children (aged 1–17 years) and infants (≤ 1 year old) were retrieved from the FDA Adverse Event Reporting System.

Results: A total of 112,060 reports were retrieved for children. Of these, 53.8% were for omeprazole, 24.7% for lansoprazole, 9.9% for esomeprazole, 10.1% for pantoprazole, and 1.5% for rabeprazole and dexlansoprazole combined. There were 14,122 deaths, 9,221 associated with omeprazole. There were 46,046 initial or prolonged hospitalizations. There were 6,093 reports of disability. The majority (92,954) of the reports involved concomitant use of a PPI; the PPI was the primary or secondary suspect drug in the remainder of the reports. There were 3,794 reports retrieved for infants, of which 38.9% were associated with omeprazole and 39.8% with lansoprazole. There were 500 reports of infant deaths, with 236 associated with omeprazole. There were 1,524 events involving hospitalization. Concomitant use of PPIs accounted for 3,198 (84.3%) of the reports.

Conclusions: Pediatric PPI-related AEs involved death, hospitalization, disability, and life-threatening outcomes. Further investigation is warranted. Currently, the FDA recommends that healthcare providers deliver the shortest, lowest-dose PPI regimen as possible.

481. Do EMA and FDA Have Different Opinions/Requirements in Terms of Pediatric Studies for Sitagliptin (Alone or in Combination)?

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Background: Since the implementation of Pediatric Regulations/Legislations in the USA (Pediatric Research Equity Act – PREA) and in Europe (Pediatric Investigation Plans – PIPs), product development programs should include pediatric studies.

Objectives: The objective of this study is to review pediatric opinions (EMA) and requirements (FDA) given by both agencies in the case of sitagliptin (alone and combined).

Methods: The EMA and FDA websites were explored to (1) Identify the products marketed under the INN of sitagliptin (alone or in combination), and (2) Identify the associated PIPs or PREA requirements. The search was performed on January 18, 2013.

Results: Eight products were marketed in Europe (i.e., sitagliptin [Januvia, Ristaben, Tesavel, Xelvia] and sitagliptin + metformin [Janumet, Efficib, Ristfor, Velmetia]). Four products were authorized in the USA (i.e., sitagliptin [Januvia]; sitagliptin + metformin [Janumet, Janumet XR]; sitagliptin + simvastatin [Juvisync]). The FDA and the EMA provide the same opinion for Januvia, i.e., deferred pediatric study for patients aged 11–16. The FDA and the EMA disagree

on Janumet. The EMA refuses the PIP and grants a waiver for all subsets of the pediatric population on the ground that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments, while the FDA requires a pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients aged 11–16. As for sitagliptin + simvastatin, both agencies grant a waiver on the ground that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients (FDA) or that clinical studies cannot fulfill a therapeutic need of the pediatric population (EMA).

Conclusions: The FDA and the EMA have similar opinions except for the combination sitagliptin + metformin. One reason could be the higher prevalence of type 2 diabetes mellitus in children in the USA compared to Europe.

482. Did the Dutch Pneumococcal Vaccination Campaign Decrease the Need for Antibiotics in Children?

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Background: *Streptococcus pneumoniae* is responsible for a significant amount of respiratory infections and acute otitis media (AOM) and use of antibiotics in children. In June 2006 a four-dose 7-valent pneumococcal vaccination campaign (PVC) was introduced in the Netherlands; 94% of children born after April 2006 were vaccinated. Although within the first years after PVC there was a decrease in invasive pneumococcal disease (IPD), it was followed by an increase in IPD caused by non-vaccine serotypes, which might lead to decreased vaccine effectiveness in terms of antibiotic use.

Objectives: To estimate pneumococcal vaccine effectiveness, we will analyse the trends of the antibiotics use for AOM and pneumonia in children before and after PVC.

Methods: This is an ecological study performed in children 0–5 years of age. The data comes from IADB.nl database, which contains pharmacy-dispensing data from community pharmacies in the Netherlands. The outcome is expressed as monthly proportion of the users of amoxicillin, azithromycin or cotrimoxazol out of the total population. Children born before 1 April 2006 are seen as unvaccinated, and children born after

this date are seen as vaccinated. By estimating regression coefficients from segmented regression analysis we will assess whether the level and trend of antibiotic use before and after the PVC has changed noticeably (p-value of < .05 indicating the change). The analysis will be performed for age groups of children of 0, 1, 2, 3, 4 and 5 years old and controlled for sex, underlying medical conditions and seasonal effects.

Results: We expect to detect an immediate decrease in antibiotic use after the introduction of PVC followed by an increase due to the incidence in non-vaccine serotypes of *S. pneumoniae*.

Conclusions: The results will give an indication on the effectiveness of the pneumococcal vaccination campaign in the Netherlands with regard to the antibiotic use.

483. Withdrawn by Author

484. Period Prevalence of Therapy Combination and Switching among Children and Adolescents with Attention Deficit/Hyperactivity Disorder (ADHD) Treated with Stimulants in the Canadian Province of Quebec

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Background: Stimulants are the mainstay of first-line pharmacotherapy for ADHD. For various reasons, patients may combine their stimulant with another ADHD medication or switch to an alternative therapy.

Objectives: To assess therapy combination and switching 1-year period prevalence in ADHD children/adolescents treated with stimulants in Quebec.

Methods: Patients aged 6–17 years with ≥ 2 documented ADHD diagnoses and ≥ 30 days of supply of a stimulant during their most recent 12-month observation period were identified in Quebec's medical claims database, the Regie de l'assurance maladie du Quebec (03/2007–02/2012). Therapy combination was defined as ≥ 30 consecutive days of concomitant use of multiple stimulants with different active ingredients or a stimulant and atomoxetine (ATX), clonidine, atypical (AAP) and typical antipsychotics, bupropion, serotonin-norepinephrine and selective serotonin reuptake inhibitors, and tricyclic antidepressants. Therapy switching was defined as a prescription claim for one

of the aforementioned categories within $\leq$ 30 days before/after the end of supply of a stimulant. The 1-year period prevalence of therapy combination and switching was calculated among all patients, and according to psychiatric/neurologic comorbidities.

Results: The 1-year period prevalence of therapy combination and switching among ADHD patients treated with stimulants (N = 9,431) was 19.8% and 18.7% respectively. The most commonly observed combination categories were AAP (10.8%), ATX (5.5%) and clonidine (5.3%). The most commonly observed switched to categories were other stimulants (7.9%), AAP (5.5%) and ATX (4.7%). Patients with comorbidities had a higher period prevalence of therapy combination (35.9% vs. 14.8%; p < 0.01) and switching (31.6% vs. 14.8%; p < 0.01) compared to those without.

Conclusions: About one in five children/adolescents with ADHD on stimulant have recourse to therapy combination or switching. Combination or switching is more prevalent in comorbid patients. More research is needed to assess the associated risk/benefit.

485. Quantitative Vaccine Safety Signal Detection Techniques Using Vaccine Adverse Event Reporting System (VAERS)

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Background: Routine monitoring of US VAERS prompted the labeling of Kawasaki disease (KD) for rotavirus vaccine in 2007. KD mainly affects children under 5 years, with the highest incidence in Japan, Korea and Taiwan.

Objectives: Use quantitative techniques for vaccine signal detection using Hib vaccines and KD as an example.

Methods: Adverse event cases associated with Hib vaccines were compared with other vaccines recommended for children under 5 years old in the US, except for rotavirus, in VAERS from 1990 to 2012. Profile and disproportionality analyses were conducted by age (0, 1, 2, 3–4), gender, and time periods (yearly from 1990 to 2012) for cases aged 0–4 years old to remove the impact of confounding. The MedDRA preferred term 'Kawasaki's disease' was used to identify KD cases. A signal of disproportionate reporting (SDR) was defined as a proportional reporting ratio $\geq$ 2 with $\chi^2 \geq 4$ and $\geq$ 3 cases, a lower bound 95% confidence interval for Empirical Bayes Geometric Mean (EB05) $\geq$ 2, or an information component (IC) $\geq$ 1 with IC05 $\geq$ 0.

Results: There were 56,937 AE cases aged 0–4 years old in 59,884 Hib vaccines AE cases of all ages. Eighty KD cases aged 0–4 years old were identified, which accounted for 95% of total KD cases of Hib vaccines. After excluding 6,408 cases (43 KD, 0.67%) with rotavirus vaccine, 50,529 Hib vaccines cases remained and reduced the number of KD cases from 80 (0.14%) to 37 (0.07%). In contrast, there were 76,391 cases associated with comparison vaccines (i.e. no rotavirus or Hib vaccines) in children aged 0–4 years old, which included 79 KD cases (0.10%). No SDR for KD for Hib vaccines was found in overall or stratified analyses. The finding did not appreciably change after excluding rotavirus vaccine, or when the KD onset was within 30 days after vaccination.

Conclusions: Hib vaccines did not have an SDR for KD when compared all other vaccines, even when including concomitant rotavirus vaccine, which includes KD as a labeled event. The findings were consistent by age, gender, and time periods and using different measures of disproportionality. This example demonstrates that quantitative techniques are useful in vaccine signal detection.

486. Acne and Lifestyle: Results of a Survey on a Representative Sample of the French Population

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Background: Acne is influenced by lifestyle1. Smoking, weight and diet have all been identified as playing a role. Polls are a quick way to explore a population.

Objectives: The aim of our study was to investigate factors associated with acne (A).

Methods: Of 10,084 subjects constituting a representative sample of French people aged 15–69 years were interviewed by the CSA Health Institute according to the quota method. The Q explored the body mass index (BMI), lifestyle, addictions (smoking, alcohol, cannabis), diet, sexuality, stress and physical activity. Analyses: The 15–25 year bracket was extracted. Two groups, i.e. the Have A now (cases) group and the Have never had A(controls) group, were compared by univariate analysis (p < 0.05). The subjects reporting mild, moderate or severe A were also compared.

Results: Two thousand and seventy-three subjects were identified. Among these cases, 46 reported severe A, 417 moderate A and 871 mild A. Overall, the cases included significantly fewer smokers, more virgin subjects, a higher reported-stress rate, and a lower BMI. Consumption of alcohol, cannabis and soda, the frequency of fast-food consumption, and the level of

physical activity did not differ between the cases and controls. The severity of A was not associated with BMI, physical activity, oral contraception (for girls), sexuality, alcohol consumption or the feeling of being stressed. However, there was a significantly higher number of smoking subjects in the severe group compared to the subjects in the moderate and mild groups (33.3%, 18.71% and 18.37% respectively were smokers). The same correlation was observed for cannabis (8.89%, 3.6% and 3.56% respectively were regular cannabis consumers), fast-food consumption (6.67% ate it every day, compared with < 2%; 28% once or twice a week, compared with 18.7% and 11.7%), soda consumption (11.11% drank more than a liter per day, compared with 3.84% and 2.30%).

Conclusions: There is a link between lifestyle, acne and its severity. Factors such as smoking and a high-fat or high-sugar diet seem to be associated with more severe acne. Our results are obtained from a self-reported population.

487. Children With Atopic Dermatitis: Monitoring a French Cohort Over a 9-year Period

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Background: Atopic dermatitis (AD) is a chronic inflammatory cutaneous condition that most often starts in children before they reach 5 years of age. The objective of our study is to assess the diseases associated with AD or that take over during the years following the diagnosis of the infant and to calculate the annual cost of treating these children.

Methods: The cohort includes infants with AD who have undergone consultation with their general practitioners between the beginning of 2000 to the end of 2003. The data gathered through the IMS database was entered by general practitioners, enabling tracking of patients. The tracking period was started after diagnosis. Only infants who were monitored for a minimum of one year were included. A control group comprising infants without AD and who were monitored for at least a year was created.

Results: Seven hundred and twenty-three infants who met the criteria outlined were identified (sex ratio of boys to girls: 56% vs. 44%). In the first year following their birth, infants with AD had significantly more concomitant disorders, particularly respiratory disorders (85% vs. 76%), and asthma (8.9% vs. 4.6%) or other types of dermatosis (46.9% vs. 28.2%) among others. During the 9 years of monitoring, the children of the AD cohort consumed more dermatological products than the children of the control group did in terms of emollients or topical corticosteroids. As well, the AD group consumed more antiseptic products than the control group did in the first year (27.6% vs. 14%). Children with atopic disorders were observed to consume more anti-asthma drugs, with a peak occurring at age 4.

Conclusions: From an epidemiological perspective, this study was in line with current data. Pulmonary symptoms call for vigilance in monitoring children. Chronic ocular inflammation sometimes is the cause of long-term cataracts in patients with atopic disorders. Early ocular symptoms found in this cohort must be specified and suggest that an opthamological follow-up may be required in some cases. In addition, the abnormally high consumption of antiseptics – and also often the source of irritation – raises concerns about children's treatment.

488. Atopic Dermatitis: Evaluation of Two Different Drug Related Managements

Charles Taieb. *Public Health, PFSA, Paris, France.*

Background: Atopic Dermatitis (AD) is a chronic relapsing skin condition and one of the most common skin diseases worldwide. Nowadays, the prevalence of AD is estimated to be between 5% and 30% in children. AD onset is commonly before 5 years old in children. Therapeutic treatments include topical corticosteroids (CS) and long-term emollients as first-line therapy, followed by topical calcineurin inhibitors. Emollients represent one of the cornerstones of treatments for patients with AD.

Objectives: The aims of this study were to compare the drug related management and the drug related costs between children with AD treated by at least an emollient (composed of Glycerol [15 g], Vaseline [8 g] and liquid paraffin [2 g] per 100 g) and children not treated by emollient.

Methods: This was a retrospective analysis of data extracted from the 'Disease Analyzer™' database, including anonymized data from medical files of the patients seen by a representative sample of French general practitioners. Children with AD diagnosed before 1 year old were tracked for 12 months after the date of diagnosis. Only children monitored at least 1 year after the diagnosis were included in the analysis. Costs of AD treatments were calculated from a societal perspective.

Results: Forty-nine children with AD were treated by the emollient (group 1) and 59 were not (group 2). 59.2% of children of group 1 were treated by CS vs. 72.9% in group 2; the same trend was found for the

prescription of antiseptic (24.5% vs. 27.1%) and antibiotic (10.2% vs. 13.6%). On the contrary, healing was more prescribed in the emollient group (32.7% vs. 25.4%). Average annual cost of prescribed dermatological drugs was estimated to be 139.8 € in the emollient group and 146.4 € in the other group.

Conclusions: These preliminary results suggest that CS, which may have negative effects (skin fragility, infection, addiction and impact on growth), are less prescribed in the emollient group. Studies considering larger samples are warranted to confirm this trend.

489. Entacapone Containing Drugs Use and Risk of Death: Analysis of FDA AERS (FAERS) Database

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Background: Stalevo (levodopa, carbidopa and entacapone) is indicated as an adjunct to levodopa/carbidopa therapy in patients with Parkinson's Disease (PD) who experience the signs and symptoms of end-of-dose 'wearing-off'. Recent findings from the Stalevo Reduction in Dyskinesia Evaluation – Parkinson Disease (STRIDE-PD) study have raised concerns over the safety of entacapone. The US Food and Drug Administration (FDA) announced that they are evaluating data from STRIDE-PD clinical trial that may suggest that patients taking Stalevo® may be at an increased risk for developing prostate cancer and risk of myocardial infarction and death.

Objectives: To analyze the association between entacapone containing drugs and death in the FDA Adverse Event Reporting System (AERS) database.

Methods: Reports of death events submitted between January 2004 and December 2010 were retrieved and analyzed using the reporting odds ratio (ROR). Reporting odds ratio as a measure of disproportionality was used to assess the association between the drug of interests and death. The ROR of case/non-case reports of death associated with entacapone containing drugs was compared with levodopa/carbidopa combination using FDA AERS database.

Results: There were 87 reports linked entacapone containing drugs to death compared to 27 reports linked levodopa and carbidopa combination to cause death. The ROR was statistically significant of for the association between deaths with use of entacapone containing drugs (1.86 [95% CI 1.50–2.31]). In contrast, the ROR of death associated with the combination of levodopa and carbidopa was not statistically significant ROR (0.89 [95% CI 0.61–1.30)]. It was noticed that the peak of cases for entacapone group was in 2009 and 2010 while the peak of cases for levodopa and carbidopa was in 2006 and 2007. Five cases in entacapone group were occurred in clinical studies.

Conclusions: Based on FAERS analysis, there is a risk of death with the use of entacapone containing drugs. These results would have an impact on daily clinical practice. The data of this study may offer an important reference in defining the safety profile of entacapone.

490. Risk of Severe Ventricular Arrhythmia Among Outpatient Receiving Fluoroquinolones in Taiwan

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Background: The fluoroquinolones are frequently used antibiotics. Several studies raise the concern about the safety of severe arrhythmia associated fluoroquinolones.

Objectives: The objective of this study is to assess the risk of severe ventricular arrhythmia among patients who received different fluoroquinolones.

Methods: We constructed a population based inception cohort using National Health Insurance claims data between January 2006 and November 2010 to evaluate various antibiotics-related ventricular arrhythmias in outpatient oral fluoroquinolones (levofloxcacin, ciprofloxacin or moxifloxacin), macrolides (azithromycin, clarithromycin) and amoxicillin/clavulanic acid new users who treated for respiratory tract infection. The date of the first prescription of study antibiotics during study period of each patient was defined as index date. We excluded patients, who had used any study antibiotics 1 year before index date, received injection antibiotics on index date and received more than one kind of study antibiotics. The outcome was defined as emergency department visit or hospitalization for ventricular arrhythmia, sudden cardiac arrest or sudden death

within 30 days of antibiotics therapy. Results were analyzed using multiple logistic regression model with multinomial propensity score adjusted.

Results: A total of 1,005,954 patients received study antibiotics were included. The crude odds ratios (95% confidence interval) for levofloxacin, ciprofloxacin, moxifloxacin, azithromycin, clarithromycin compared with amoxicillin/clavulanic acid were 6.36 (3.11–13.01), 0.95 (0.13–6.88), 5.73 (2.70–12.15), 0.30 (0.07–1.24), 1.38 (0.62–3.07). However, the adjusted odds ratios (95% CI) for each antibiotics were 1.60 (0.76–3.35), 0.41 (0.06–2.97), 1.55 (0.72–3.34), 0.63 (0.15–2.60), 1.05 (0.47–2.33), respectively. No significant difference in ventricular arrhythmia risk between fluoroquinolones and amoxicillin/clavulanic acid initiators was found.

Conclusions: Compared with amoxicillin/clavulanic acid, the use of oral fluoroquinolones did not show a significant difference in ventricular arrhythmia risk.

491. Impact of Previous Suicide Attempts and Family History of Psychiatric Disease on the Size of the Association between Antiepileptic Drugs and Suicide Related Events

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Background: Antiepileptic drugs (AEDs) are associated with varying risk of completed suicide and suicidal behavior. Previously unconsidered adjustment for long-term history of suicide related events and family history of psychiatric disease though may contribute to this association. The current study has been performed in the context of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project examining the variability of results from studies using either identical protocols or protocols with pre-defined differences to investigate drug-adverse event pairs. In order to maintain the blinding of investigators from one another's results, detailed results will only be disclosed during the ICPE conference.

Objectives: To investigate the impact of long-term history of suicide attempts and family history of psychiatric disease on estimates of the association between AED use and suicide related events.

Methods: Retrospective, register-based cohort study of incident users of AEDs between 1996 and 2007 identi-

fied from a 25% randomly selected sample of the Danish population, 15 years or older. Exposure to AEDs was assessed based on redeemed prescriptions. Suicide related events were defined as suicide attempts or completed suicide. We performed time dependent Cox analysis of suicidal events during current and recent past use compared with past use of AEDs, adjusted for treatment indications and other treatment-related and socio-demographic variables. We assessed the impact of previous suicide attempts (at any time before 6 months prior to AED initiation) and family history of psychiatric disease separately by comparing hazard rate ratios (HRR) with and without adjustment for the respective factors, as well as by estimating HRRs stratified by these risk factors.

Results: We identified 43,069 users of AEDs (53.93% women) with no AED use within 18 months and no suicide attempt within 6 months prior to AED initiation accounting for 159,065 person years of follow up between 1996 and 2007. The mean age was 55.86 years (± 18.28 standard deviation).

492. Estimating the Association between QT Prolongation and SSRI Utilization from the FDA's Adverse Event Reports

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Background: Citalopram (Celexa®) is in the selective serotonin reuptake inhibitor (SSRI) class of antidepressants. It is taken orally. Citalopram has been linked to both QT prolongation and Torsade de pointes (TdP), and these risks may be dose related.

Objectives: The purpose of this study was to analyze the association between QT prolongation and TdP adverse events and the utilization of citalopram and other SSRIs.

Methods: This retrospective, descriptive study used the U.S. FDA Adverse Event Reporting System (FAERS) database. The database included 7,840,225 adverse events associated with SSRI drugs from 1997 fourth quarter to 2011 third quarter. The number of reported QT-prolongation and TdP cases associated with each study drug was calculated over time. Furthermore, for each case, dosage of the drug, when available in the report, was noted.

Results: A total of 1,192 reported cases of QT prolongation and TdP were associated with SSRI drugs over the 14-year study period. Only 18% (219) of the adverse event reports were related specifically to citalopram, while the rest were related to other SSRI

drugs. There were 911 reports for women, 252 for men, and 29 reports without gender information. The rate of QT prolongation and TdP associated with dosages of 20, 40, and 60 mg of citalopram per day were 39%, 21%, and 2%, respectively. However, the percentage of reports without dosage information was 37%, so we were unable to draw any conclusions regarding dosage-related events.

Conclusions: The results confirmed an association between the use of citalopram with QT prolongation and TdP. Furthermore, the association was not limited to citalopram alone but was widespread across the SSRIs. There were more adverse events observed for women than for men. Dose dependency was not established in this study. Future studies are warranted.

493. Development and Optimization Process of Benefit/Risk Balance Assessment (BRBA) Model of Medicine for KFDA

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Background: According to consecutive safety issues, the methods for systematic benefit/risk balance assessment (BRBA) reflecting national difference of healthcare circumstances from new drug application to post-market situation are desperately needed.

Objectives: To develop the strategy for optimized model invention of benefit/risk balance assessment considering drug utilization status in Korea and acceptable risks and so on.

Methods:

(1) Design: Literature investigation and study strategy establishment
(2) Setting: The objects of literature investigation were limited to the studies for quantification of benefit/risk balance and weights of major evaluation factors
(3) Exposure or interventions: Acceptable risk, preference, drug utilization etc. at national level
(4) Main Outcome Measures: Benefit/risk balance ratio and/or difference
(5) Statistical analysis: Comparative and decision analysis.

Results: MCDA (multi-criteria decision analysis) on the basis of value tree is appreciated as the most appropriate quantitative benefit/risk balance assessment model for regulatory decision, putting various reports [i.e. by EMA benefit-risk methods project, PhRMA BRAT (Leading U.S. pharmaceutical industry association, benefit/risk action team) and CMR

institute] together. And to quantification of benefit/risk balance, sociological factors (for example, preferences and weights of key evaluation factors) should be considered in addition to several adverse and additional beneficial effects. According to these trends, we have developed the Korean quantitative BRBA model. To achieve this, severity score were obtained from clinicians by delphi method for dividing serious adverse effects and quantification first. And benefit-risk trade-off and weights from different domestic subjects of decision making (clinicians, regulatory agency staffs, and the general public etc.) were surveyed also by representative 27 therapeutic classes.

Conclusions: BRBA model reflecting benefit-risk trade-offs and weights of three key players (clinicians, regulatory agency staffs and the general public) in Korea was suggested. From these results, we can make more scientific and transparent decision making.

494. A Systematic Review of the Adverse Effects of Atypical Antipsychotics in the Elderly Population

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Background: Epidemiologic studies have revealed safety concerns associated with use of atypical antipsychotics (AA) in elderly persons; however, no single systematic review of commonly studied outcomes exists.

Objectives: To systematically review epidemiologic studies of adverse effects of AAs.

Methods: We queried PubMed for English-language, epidemiologic studies published between 1 January 1950 and 2 July 2013. Two investigators conducted independent primary searches. The last author conducted an independent search to assess the sensitivity of the primary searches. One investigator extracted each article and a second investigator checked the extraction of approximately 25% of articles for accuracy. By outcome, we recorded the data source and timeframe, characteristics of the study population, exposure definitions, measures of outcome and association, and analytic approach.

Results: Of 5001 articles identified, 79 met inclusion criteria: fractures/falls (10), mortality (27), cerebrovascular events (24), pneumonia (4), cardiovascular events (13). Ninety percent of studies used regression adjustment or propensity score methods to address confounding. Ten studies compared AAs to both conventional antipsychotics (CA) and no use; 27 compared AAs to CAs only, and 42 compared AAs to no use only. For fractures/falls, relative risks compared to non-use ranged from 1.3 to 2.4; for mortality, 0.7–3.2; cerebrovascular events, 0.6–6.9; pneumonia, 2.2–6.0;

and cardiovascular events, 0.9–2.3. For CAs relative to AAs, the same estimates were: fractures/falls, 0.5–2.6; mortality, 1.2–3.8; cerebrovascular events, 0.5–1.9; pneumonia, 0.9–3.1; and cardiovascular events, 1.2–2.0.

Conclusions: AAs were consistently associated with a higher risk for all of the outcomes relative to no-use. Relative to CAs, AA's were associated with a lower risk for all outcomes, although there was some inconsistency in the literature. The variation in point estimates could be attributed to differences in design and analyses or the heterogeneity of the populations studied.

495. A Pragmatic Score to Predict the Risk of *Clostridium difficile* Infection Among Patients Receiving a Fluoroquinolone Antibiotic

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Background: Clinicians are aware that fluoroquinolone use can result in the development of *Clostridium difficile* infection (CDI); however, it is difficult for clinicians to quantify this risk for individual patients.

Objectives: To utilize patient characteristics available to clinicians to predict the 6-month risk for CDI among patients who received a fluoroquinolone during a routine outpatient healthcare visit.

Methods: We assembled a cohort of Kaiser Permanente Northwest (KPNW) patients who received a fluoroquinolone between 2005 and 2008. The outcome was the first occurrence of CDI during the 6 months after an index fluoroquinolone dispensing. CDI was identified through ICD-9 code 008.45 for 'Intestinal infection due to *C. difficile*' or a positive *C. difficile* toxin test. Applying Cox regression, we synthesized a priori predictors into a risk score for CDI. We assessed predictive performance of the risk score by calculating and plotting the observed 6-month CDI risk for each decile of predicted risk.

Results: We developed our CDI risk score among 41,449 KPNW patients, of whom 313 experienced CDI, a 6-month incidence of 7.7 CDIs per 1,000 patients (95% CI, 6.9–8.6). Of the 10 predictors in the risk score, cardiovascular disease, age 60 years or greater, and history of hospitalization or stay in a communal-living healthcare facility contributed to a doubling in the predicted risk for CDI. The highest-risk patients were over 20 times more likely to develop

CDI than the lowest-risk patients (observed 6-month risk of 30.6 vs. 1.4 CDIs per 1,000 patients). The risk score differentiated between patients who do and do not develop CDI (C-statistic of 0.75). Risk for CDI predicted by the score agreed closely with observed risk.

Conclusions: Our prognostic CDI risk score utilizes routinely collected data to provide a pragmatic approach to assist clinician decision-making when prescribing in the outpatient setting. Our risk score can be used by clinicians to estimate CDI risk and identify patients who would benefit from risk management efforts, such as more judicious fluoroquinolone prescribing.

496. Background Rates of Other New Primary Malignancies Among Locally Advanced and Metastatic Melanoma Patients: A SEER-Medicare Study

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Background: The ongoing clinical development of type I BRAF inhibitors has led to a high rate of objective tumor responses and improvement in overall survival in unresectable and metastatic melanoma patients, as compared with standard chemotherapy. However, BRAF inhibition induces keratoacanthomas and cutaneous squamous cell carcinoma and there is theoretical belief that it can induce noncutaneous *RAS*-mutant cancers. Given these, occurrence of other new primary malignancy (other than new primary cutaneous melanoma) has been raised as a potential concern among patients treated with BRAF inhibitors.

Objectives: To successfully contextualize safety signals from the randomized clinical trials, we determined the background rates of other new primary malignancies among patients targeted for anti-BRAF therapies, specifically, locally advanced (stage IIIA-IIIBN2b) and unresectable metastatic (stage IIIBN2c-IV) melanoma patients.

Methods: We included 558 locally advanced and 1,746 unresectable and metastatic melanoma patients diagnosed in 1992–2005, utilizing the US Surveillance Epidemiology and End Results (SEER)-Medicare linked database. SEER data accurately identify stage of cancer as well as new primary cancers.

Results: Among patients with initial diagnoses of locally advanced melanoma, the median age at diagnosis was 75 year; 67% died during the follow-up period; and the median survival was 43 months. Among patients with initial diagnoses of unresectable and

metastatic melanoma, the median age was 77 year; 90% died during the follow-up period; and the median survival was 10 months. Within the first 6 months after diagnosis, 2.9% of the locally advanced melanoma patients (59.9 per 1,000 person-years [PY]) and 1.5% of the unresectable and metastatic melanoma patients (38.7 per 1,000 PY) developed other new primary malignancies. Among both groups, incidence rates of other new primary malignancies did not differ by age groups (i.e., 65–74, 75–84, and 85+ years).

Conclusions: Although rare, locally advanced and metastatic melanoma patients may further develop other new primary malignancies.

497. New-Onset Non-Melanoma Malignant Skin Lesions and Non-Cutaneous Squamous-Cell Carcinoma Among Metastatic Melanoma Patients in Denmark

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Background: Inhibitors of mutant BRAF are emerging as standard of care in patients with metastatic melanoma (MM) who carry relevant oncogenic mutations. However, BRAF inhibitors are found to induce cutaneous squamous cell carcinoma (cuSCC). The spectrum of these lesions ranges from pre-cuSCC actinic keratoses (AK), well-differentiated keratoacanthoma (KA)-like SCC, to classic invasive cuSCC. A presumptive mechanism similar to that for cuSCC has been suggested for the development of non-cutaneous squamous cell carcinoma (non-cuSCC), a more serious cancer. Population-based background rates of cuSCC and non-cuSCC in a real-world MM population (not available in the literature) can contextualize safety signals from randomized clinical trials.

Objectives: We examined the background rates of new-onset non-melanoma malignant skin lesions and non-cuSCC in MM patients.

Methods: We conducted a historical cohort study of 2,814 MM patients diagnosed in 1997–2010, identified through the Danish Cancer Registry and the Danish Pathology Registry. We determined the incidence of non-melanoma malignant skin lesions and non-cuSCC that occurred post MM diagnosis, censoring patients at death, emigration, or December 31, 2011 (end of study), whichever came first.

Results: The median age at MM diagnosis was 64 years. Over 40% of patients died within 1 year of metastatic diagnosis and ~70% died within 5 years.

The percentages of patients with prior history or prevalent disease at MM diagnosis included: 8.6% with cuSCC or cutaneous basal cell carcinoma (cuBCC), 3.9% with AK, and 0.7% with Bowen's disease. No patients had past or current non-cuSCC per study exclusion criterion. The incidence of non-melanoma skin lesions during the 6 months post-MM diagnosis was as follows: BCC, 1.8% (42.5 per 1,000 person-years [PY]); AK, 0.8% (18.6 per 1,000 PY); cuSCC, 0.1% (1.7 per 1,000 PY); Bowen's disease, 0.04% (0.8 per 1,000 PY); and KA, 0%. Non-cuSCC was observed in three patients (0.1%; 2.5 per 1,000 PY) at three sites: bronchi, heart and lung.

Conclusions: CuSCC and non-cuSCC were rare events among MM patients.

498. Does Research Design Predict Estimated Risks of Venous Thromboembolism With Drospirenone-Containing Oral Contraceptives?

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Background: Venous thromboembolism (VTE) is the most frequent serious adverse event associated with use of oral contraceptives (OCs). Some studies have found that drospirenone (DRSP)-containing OCs have an increased VTE risks whereas other studies have found no difference.

Objectives: This study aims to examine the influence of research design and study quality on VTE risk estimates with DRSP-containing OCs, as compared with levonorgestrel (LNG)- and norethindrone (NOR)-containing OCs.

Methods: This is a systematic review of VTE rates with DRSP, as compared with OCs containing LNG and NOR, in women of reproductive age. Included study designs were randomized controlled trials (N ≥ 1,000), cohort and case–control studies. We searched CENTRAL, Medline, EMBASE, and regulatory websites. We developed a standardized 'risk of bias' tool for cohort and case-control studies, based on an AHRQ review of effects of bias on outcomes, and existing tools. Eight criteria were assessed for high, low, or unclear risk of bias. Key elements include representation, similar comparison groups, adjustment for confounders, exposure and outcome assessment, complete follow-up and reporting, and funding source. Data are combined using a generic inverse variance approach,

with sensitivity analyses to assess effects of risk of bias on summary estimates.

Results: Nine cohort and case–control studies compared VTE risks with DRSP and other OCs. One failed to specify comparators (Seeger 2007) and two had overlapping data (Lidegaard 2009; Lidegaard 2011); the most recent was included. Thus seven studies met inclusion criteria. Design elements associated with risk estimates included representativeness, outcome definition, age and duration modeling, blinding, and funding source. These factors influenced the magnitude of summary estimates, but not direction.

Conclusions: We found that a standardized 'risk of bias' tool, similar to the Cochrane tool for RCTs, can be practically applied to observational studies of rare medication outcomes, with important implications for safety assessments. In this systematic review, higher risk of bias was associated with lower relative VTE risk for DRSP.

499. Lay Media Attention for Serious Drug Safety Issues in the Netherlands

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Background: The full benefit-risk profile of any drug is not known at approval, inevitably leading to identification of serious safety issues postapproval. Lay media may report on these issues, and especially when the tone of reporting is negative, they may alarm patients. Healthcare professionals and regulators need to be prepared to deal with this situation, but currently it is unknown to what extent and in what tone lay media respond to these issues.

Objectives: To identify if and in what tone lay media report on post-approval serious safety issues in the Netherlands.

Methods: We performed a systematic review of lay media articles reporting on post-approval drug safety issues between 2001 and 2012 in the Netherlands. Articles were retrieved from Lexis Nexis Academic, a repository of newspaper and magazine articles. Search terms used were drug/brand name. Postapproval serious safety issues were identified from Direct Healthcare Professional Communications (DHPCs) issued for drugs used in ambulatory care. DHPCs were retrieved from the website of the Dutch Medicines Evaluation Board. We retrieved articles published from a year before to a year after the DHPC and that reported on the safety issue. Three reviewers screened the articles for eligibility and appraised the tone (consensus) of the articles on a 5-point Likert scale from (very) negative to (very) positive.

Results: In our study period 107 DHPCs were issued for 101 drugs, of which nine were issued within 1 year and combined. Of 2,353 articles on these drugs, 280 (12%) reported on the safety issue of 32 (30%) DHPCs. An average of 9.56 (SD 13.1) articles/DHPC. More than half (52%) of all articles covered three issues; cardiac risk for celecoxib (n = 75), seizures for bupropion (n = 35) and hepatitis for moxifloxacine (n = 36). The number of articles published annually (2001–2012) showed no trend (p = 0.76). The tone of 79 (28%) articles was (very) negative, 145 (52%) somewhat negative, 32 (11%) neutral, 23 (8%) somewhat positive, and 1 (0.3%) (very) positive.

Conclusions: Lay media pick up about a third of all safety issues reported in DHPCs with the majority covering a few high impact issues only. The tone is outspokenly negative in about a quarter.

500. Does Media Attention Affect Impact of DHPCs in the Netherlands?

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Background: A third of Direct Healthcare Professional Communications (DHPCs) has been shown to have a long-term impact on drug use in the Netherlands. It is suggested that impact of DHPCs may be affected by attention of the lay media. However, no empirical data are available supporting this assumption.

Objectives: To explore if lay media affect the impact of DHPCs on drug use in the Netherlands.

Methods: DHPCs issued in the Netherlands (2001–2007) and monthly dispensing data (2000–2008) were obtained. Lay media articles (2000–2008) reporting on the drug safety issues communicated in the DHPCs were retrieved from Lexis Nexis Academic.We performed a multiple linear regression analysis to examine the impact of media attention (number of articles) and as an interaction term the number of articles with a clearly negative tone (3-rater consensus classification of the tone as 1 (very) negative on a 5-point Likert scale that ranged from 1 (very) negative to 5 (very) positive). We corrected for determinants that we ear-

lier showed to be significant determinants for the impact of a DHPC; i.e specialist drugs, DHPC issued after availability of a DHPC template, and safety issue with risk of death or disability. The outcome variable was defined as the relative change in new drug use (change in use/median use 12 months pre DHPC) post DHPC as determined in interrupted time series ARIMA models for each drug and DHPC pair.

Results: In our study period 58 DHPCs for 46 drugs were issued, of which 20 (34.5%) DHPCs resulted in a mean long-term decrease in drug use of 26.7% (95% CI: −15% to −38%). Lay media reported on 23 (39.7%) DHPC drug safety issues. In those cases a median of 3 (IQR 2–9) articles reported on the issue, of which in 40% (SD39%) the tone was clearly negative. In the multiple linear regression model lay media coverage was not associated with impact of the DHPC (p = 0.928), nor was the number articles with an outspoken negative (1 on Likert-scale) tone (p = 0.830) nor the interaction term of the 2 (p = 0.872).

Conclusions: In this first paper evaluating the impact of media coverage over an extended time period did not show that lay media affected the impact of DHPCs.

501. The Additional Value of an e-Mail to Inform Healthcare Professionals of a Drug Safety Issue

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Background: The usefulness and impact of Direct Healthcare Professional Communications (DHPCs, or 'Dear Doctor letters') in changing behaviour of physicians have been debated. Changes in current risk communication methods should be based on the preferences of healthcare professionals (HCPs), to optimize uptake of the message.

Objectives: This study assesses whether safety issues are communicated more effectively with an additional e-mail that is sent by the Dutch Medicines Evaluation Board (MEB) than with a DHPC only.

Methods: A randomized controlled trial was done amongst the target group of the DHPC; ophthalmologists and hospital pharmacists in the Netherlands who were planned to receive a DHPC that was issued for pegaptanib, a drug that is administered intra-ocularly in patients with macular degeneration. The intervention group (N = 110) received the pegaptanib DHPC plus MEB e-mail and the control group (N = 105) the traditional paper-based DHPC only. Two weeks later they received an online questionnaire. Questions were asked about the respondents' knowledge and attitude regarding the pegaptanib issue, and any action they had taken. Additional questions were asked about their satisfaction with the DHPC and e-mail and the preferred source of information.

Results: Forty (18,6%) respondents completed the questionnaire. 81% of the respondents in the intervention group (N = 21) and 47% of the control group (N = 19) correctly indicated that a serious increase of the intra ocular pressure could be caused by pegaptanib injections (Fishers' Exact test p = 0.046). Nine vs. no respondents in the intervention respectively control group indicated to have taken action in response to the pegaptanib safety issue (Fishers' Exact test p = 0.01). The majority of the intervention and control group would like to receive an MEB e-mail with safety information in the future (90% and 95%, respectively).

Conclusions: The results of this study indicate that an additional e-mail strengthens the uptake of the safety information provided. HCPs indicated they prefer the MEB as source of information of email and DHPC. This study may serve as a starting point for new strategies to improve risk communication.

502. Pattern and Determinants of Self Medication in a Nigerian Urban Population- 'The Silent Epidemics'

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Background: The practice of self medication among the Nigerian population is gradually assuming an epidemic proportion with attendant negative implications on the health of individuals and the nation as a whole.

Objectives: This study aimed at defining the pattern and determinants of self medication in an urban population of Lagos, Nigeria with the hope of gaining insights into how best to promote rational uses of drugs in the country.

Methods: This was a cross sectional survey of a sub population of Lagos State,Nigeria. The multistage sampling method was used to select respondents to a structured questionnaire obtaining information on the socio demographic characteristics, drug use pattern and risk/benefit perception of self medication. The information collected was analysed using commercially

available statistical package SPSS version 15.0. Continuous variables were expressed as means (standard deviation), categorical variables as proportions.A multivariate logistic regression model was obtained for determinants of self medication.A p-value < 0.05 was taken as significant.

Results: A total of 206 respondents were studied with mean age of 35.8 (9.7) years. There were 143 males (69.1%). Eighty-five percent of the population studied have been self medicating for a mean period of 9.37 (8.69) years. 69.9% used orthodox medicines, 59.9% used Complementary and Alternative Medicines while Nutraceuticals were used by 31.9%. Analgesics were the most frequently used drugs (67.5%). Medial advertisements constituted the most frequent source of information about drugs used (36.25%). The majority of the population studied started self medication out concerns for wellness (43.5%) while 31.9% use drugs for which they have been treated in the past for similar complaints.65.7% of the population described the practice as being risky while 51.7% felt it is beneficial. The occupation category of an individual was found to influence the practice of self medication.

Conclusions: Self medication is apparently a silent epidemic in this population deserving urgent attention. A strong drive at promoting rational drug uses through public education and stricter drug regulatory activities are recommended.

503. Changes in Number of Spontaneous Adverse Event Reports of Drug Abuse, Intentional Drug Misuse, Medication Error, and Overdose after Reformulation of OxyContin

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Background: OxyContin® (oxycodone HCl controlled-release) Tablets were reformulated to be more difficult to crush and to form a gel when dissolved. In August 2010, Purdue Pharma stopped shipments of the original OxyContin formulation (OC) and started reformulated OxyContin (ORF) shipments.

Objectives: The objective of this study was to assess changes in the number of spontaneous adverse event (AE) reports of drug abuse, intentional drug misuse, medication error, and overdose following distribution of the reformulated product.

Methods: A search of the manufacturer's adverse event reporting database was performed to identify all case reports associated with extended-release (ER) oxycodone received from 1 January 2010 to 31 December 2011 containing a preferred term associated with drug abuse, intentional drug misuse, overdose, or medication error. Cases received January–September 2010 were designated OC; cases received after September 2010 were designated ORF.

Results: The total number of reported cases for OxyContin with a preferred term related to drug abuse, intentional drug misuse, overdose, and medication error declined 36%, from 1,272 in 2010 to 819 in 2011. The number of unique cases with a drug abuse preferred term declined 44% (894 vs. 499) with terms associated with fatal outcome declining 71% (48 vs. 14). The number of unique cases with an overdose preferred term declined 50% (240 vs. 120) with terms associated with fatal outcome declining 51% (162–79). The number of unique cases with a medication error preferred term declined 16% (155 vs. 131), with terms associated with fatal outcome declining 50% (8 vs. 4). The number of unique cases with an intentional drug misuse preferred term did not change, and terms with fatal outcome declined from 2 to 1. Retail prescription dispensing of OxyContin declined by 5% during the study time period.

Conclusions: There was a reduction in the number of AE cases for extended-release oxycodone associated with drug abuse, overdose and medication error, and reductions in associated fatalities, occurring after OxyContin tablets were reformulated.

504. Balancing Individual Benefits and Risks of Warfarin in Patients with Atrial Fibrillation

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Background: Anticoagulation with warfarin reduces the risk of ischaemic stroke in patients with atrial fibrillation (AF) but may increase the risk of bleeding. A positive benefit-risk balance in the overall AF population has been well established, but hardly studied on an individual level.

Objectives: To estimate benefits and risks of warfarin treatment for the individual and identify characteristics determining the benefit-risk balance.

Methods: The study cohort consisted of patients with AF exposed to warfarin in the Clinical Practice Research Datalink (CPRD). Outcomes of interest were ischaemic stroke, transient ischaemic attack, haemorrhagic stroke and major bleed. The probability of an outcome dur-

ing exposure was estimated with a Cox proportional hazard model. Attributable risks for each outcome were estimated using the individual probabilities and relative rates of warfarin effects (based on meta-analyses of trials). Each outcome was weighted by 1-year mortality. The individual net benefit was calculated as the weighted sum of benefits minus adverse effects and then characterized as being less favourable (net benefit < 0.5), neutral (net benefit 0.5–1.5) or favourable (net benefit > 1.5). Logistic regression was used to identify characteristics that explained a less favourable net benefit.

Results: The study population included 33,772 patients with AF exposed to warfarin. The mean net benefit was 1.17 (SD 16.0) ischaemic stroke cases or equivalent prevented. Characteristics that were associated with a less favourable benefit-risk balance were age > 85 years (OR 2.82, 95% CI 2.37–3.36), presence of congestive heart failure (OR 2.67, 2.27–3.14), cancer (OR 2.51, 2.19–2.88), minor bleed (OR 2.68, 2.25–3.18) and renal insufficiency (OR 3.30, 2.37–4.60). Hypertension (OR 0.41, 0.36–0.46) and vascular disease (OR 0.16, 0.13–0.19) were associated with a favourable benefit-risk balance.

Conclusions: We confirmed that the net benefit of warfarin for the overall AF population is positive. However, there is a large variation of benefit-risk balance across this population for individual patients.

505. A Systematic Review of Randomized Controlled Trials of New Oral Anticoagulants: The Search for a Net Clinical Benefit

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Background: New oral anticoagulants drugs (OACs: Apixaban, Dabigatran, Edoxaban and Rivaroxaban) are available to replace vitamin K antagonists or heparins. However, the balance between their efficacy and safety, known as the net clinical benefit (NCB), remains to be clearly demonstrated.

Objectives: We aimed to determine if there is a NCB associated with the use of new OACs compared to conventional treatments.

Methods: We conducted a systematic review of randomized controlled trials of new OACs according to PRISMA recommendations, using CINAHL, EMBASE, MEDLINE and WoS databases. MV and RH independently reviewed and selected studies for inclusion. Data

on primary efficacy and safety issues were used to determine the NCB.

Results: We identified 21 studies, of which four focused on atrial fibrillation, two on venous thromboembolic disease, and 15 on thromboprophylaxis. We found that primary efficacy and safety issues were not reported for the same subsets of the study populations. The mean ratio of patients with efficacy endpoint/total randomized patients was 80.5% (60.9–100%). In contrast, the mean ratio of patients with safety endpoints/total randomized patients was 98.8% (96.3–100%). Therefore, for 13/21 (62%) of studies, the NCB could not be determined because the populations with data for efficacy and safety outcomes were different.

Conclusions: The NCB is a practical decision-making tool for clinicians. Its determination must be based on efficacy and safety data from all patients included in a trial. However, in our review, efficacy data were lacking from an average 19.5% of patients, while safety data were presented on nearly all included patients. As missing data never occurs at random, it could be misleading to compare efficacy and safety populations (risk of selection biais). We recommend that NCB be reported in clinical trials, or, at least, data that would allow its calculation.

506. Information on QTc-Interval Prolongation in the Summary of Product Characteristics

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Background: The summary of product characteristics (SPC) is the most important source of information for healthcare providers to gain information about the safety of a product, including QTc- related adverse events. However, we have noticed that information regarding QTc prolongation may vary greatly among different products.

Objectives: To determine how, and in which sections, QTc-related adverse events are listed in the SPC.

Methods: The SPCs of 140 products, centrally approved in Europe between 2006 and 2010, were screened. All products that mentioned the word 'QT' in the SPC were included. We examined in which and in how many different section(s) of the SPC the QTc

related adverse event was described. Next we categorized the information on QT prolongation in the warning section (section 4.4) of the SPC to identify inconsistencies in the described information and recorded whether the source of evidence was reported.

Results: In total, 22 products were included. The two most common indications were anti-neoplastic drugs (32%) and cardiac therapy (18%). QT related adverse events were most commonly reported in section 4.4 (special warnings and precautions) and section 4.8 (undesirable effects). Six SPCs reported on QT related adverse events in one section (27%), nine in 2 or 3 sections (41%), and seven in 4 or 5 different sections of the SPC (32%). Within section 4.4 the information on QT prolongation varied from 'The ability to cause QT prolongation' (12 SPCs, 55%), to 'explanation of the association of QT prolongation with ventricular arrhythmias' (four SPCs, 18%), 'the advice to act with caution (14 SPCs 64%),or 'the advice to monitor patients using the product' (15 SPCs, 68%). The source of evidence was reported in seven SPCs (32%).

Conclusions: These results confirm that information regarding QTc prolongation varies greatly among different products. We advise the development of a guideline concerning reporting on QT prolonging in SPCs, in order to guide prescribers more clearly.

507. Using Multi-Criteria Decision Analysis for Quantitative Benefit Risk Assessment of Aflibercept as a Second Line Treatment in Adults with Metastatic Colorectal Cancer

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Background: Multi-Criteria Decision Analysis (MCDA) that extends decision theory to accommodate multiple attributes and provides common units for both benefits and risks is promising to be employed to assess the benefit risk balance of new drugs in development.

Objectives: Develop an MCDA model to balance favorable and unfavorable effects of an antineoplastic drug aflibercept when added to Irinotecan-Fluoropyrimidine-based chemotherapy (FOLFIRI) in adults with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen.

Methods: This study incorporated data from the randomized, double-blind VELOUR trial that compared the efficacy of aflibercept + FOLFIRI vs. placebo + FOLFIRI. The eight-stage PrOACT-URL framework was used to develop the model. Several decision conferences among stakeholders were conducted to identify evaluation criteria and make judgements about the relative utilities of the effects. These judgments were expressed as swing weights and incorporated into a multi-level value tree. Hiview 3 software was used for modelling analyses.

Results: The aflibercept value tree had two branches representing favorable and unfavorable effects of the treatment options. Favorable effects included survival data and overall response rate. Unfavorable effects spanned three components: (1) common class effects and FOLFIRI related adverse events, (2) deaths and (3) treatment discontinuation due to adverse events. The survival rate at 24 m was assigned a swing weight of 100. The adverse events seen with aflibercept+ FOLFIRI were generally manageable, their clinical impact did not outweigh the benefits. The overall added value combining favorable and unfavorable effects for aflibercept+ FOLFIRI was higher than for placebo+ FOLFIRI (53 vs. 40). Sensitivity analyses showed the model was robust.

Conclusions: The MCDA method appeared to be a useful quantitative tool for benefit risk assessment. The results indicated that the benefit-risk balance for aflibercept is favorable compared to placebo when added to FOLFIRI in adults with MCRC previously treated with an oxaliplatin-containing regimen.

508. Statin Therapy and Incident Cataract: A Meta-Analysis

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Background: The association between statin use and the development of cataract has been evaluated in several studies with inconsistent results. The risk for cataract development associated with the use of statins should be clarified, as well as a possible dose-response relationship.

Objectives: This study was aimed at identifying the risk of developing cataracts in patients exposed to statins,

according to the published evidence from both experimental and observational studies.

Methods: A meta-analysis was carried out pooling data from studies identified on a Medline and on a Cochrane Library search. Studies were eligible for inclusion if they were prospective, observational or controlled clinical trials (RCT), evaluating any statin and reporting data on cataracts incidence. Odds rations (OR) were estimated using random-effects models and statistical heterogeneity was estimated with I^2 statistics.

Results: One RCT, two case–control and three cohort studies were included. Statins use was not associated with an increased risk for cataract development (OR 1.10 [95% CI 0.88–1.37], I^2 = 52%). The sensitivity analysis according different study designs did not change the results.

Conclusions: However the statistically significant heterogeneity between included studies, particularly length of drug exposure, drug dose and comorbidities, precludes definitive conclusions.

509. Comorbidities and Medication Use in Lupus Nephritis Patients – A Comparison of Result across Case Identification Algorithms

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Background:

Objective: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE). While LN has no designated ICD-9 code, various approaches have been used to identify patients in administrative data. The objective was to compare comorbidities and medication use in LN patients using different algorithms in a single data source.

Methods: This study used the Impact Database, a commercial insurance claims database. SLE patients were identified using ICD-9 code 710.0 from ≥ 2 outpatient or 1 inpatient claims from 01/2004 to 06/2011. SLE patients with LN were further identified under four different algorithms: (A) ≥ 1 renal diagnosis, (B) ≥ 2 renal diagnoses, (C) ≥ 3 renal diagnoses, and (D) ≥ 3 renal diagnoses plus ≥ 3 nephrologist visits. Comorbid conditions and prescriptions were examined for 12 months post index date of first renal diagnosis.

Results: Of 93,957 patients were diagnosed with SLE. Among them, 24,357, 11,054, 8,895, and 6,307 cases

had LN using algorithms A–D. LN cases identified by algorithms A–D had similar mean age (48.3, 46.7, 46.3, and 45.7 years) and gender distribution (85.2, 83.1, 82.7, and 81.8% females). LN patients from different algorithms also had similar distribution of comorbid conditions (urinary tract system, hypertension, anemia, heart disease, respiratory outcomes and others)and medication use (corticoids and hormones, renin angiotensin antagonists, anti-infective drugs, analgesic narcotics, diuretics and antimalarial drugs).

Conclusion: Our results support that when studying patient profiles including comorbidities and medication use, the results do not differ significantly based on the number of renal diagnoses codes. There is a difference in outcomes when requiring number of patients plus specialty subtype; however, in the case where specialty information is either unavailable or unreliable, using algorithms A-C proved equally reliable in an administrative claims database.

510. Assessment of Tolerance of Pain Treatment in Cancer Management

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Background: Pain is a very frequent symptom in cancer disease. The practitioner has to adapt the cancer pain treatment for each patient, maximizing efficacy and security of the antalgic treatment.

Objectives: The aim of the study is to assess for patients with cancer, the prevalence of side effects caused by the antalgic treatment, their nature, their severity and how they are managed.

Methods: This cross sectional has been conducted in Palliative care unit of the National Institute of Oncology in Rabat from March to September 2012. It concerned patients who came to the consultation room for cancer pain at the palliative care center. A questionnaire intended for them has been designed in order to collect their demographic, clinical and therapeutic data.

Results: This study covered 256 patients. The average age was 53 years and the sex ratio (Male/Female) was 0.71. Gynecological and breast cancers were the most common primary site of cancer (35.7%). Before the visit, 32% of the patients on oral morphine (32%), paracetamol (26%) or on the association of tramadol and paracetamol (23%). At the visit, more than 25%

of the patients were on antalgic treatment since more than 8 weeks. Out of the patients enrolled, 26.3% experienced side effects. The most common were constipation (16.9%), stomach pain (5.4%), drowsiness (2%) and addiction (0.3%). The side effects reached grade 3 (22.6%) and grade 4 (1.7%). All grade four cases showed intestinal obstructions. These cases were assigned to the emergency service, prior to resume the antalgic treatment. An adjuvant treatment was prescribed for 38% of the patients in order to treat a side effect (24%) or for its prevention (14%). The most common were lactulose (17.3%), omeprazole (9.6%), phloroglucinol (1.7%) and the association of lactulose with omeprazole (2.3%) and lactulose with metoclopramide (1.7%). The lactulose was prescribed in association with the antalgic drugs of ladder 2 and 3. The omeprazole was prescribed in association with the NSAIDs.

Conclusions: Treatment for cancer pain in palliative care is administrated over a long period of time. Therefore, it often causes side effects. The management of these side effects has to be adapted to each patient.

511. Health-Care Professionals' Perspectives on Multi-Dose Dispensed Medicines

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Background: The system with multi-dose dispensed medicines (MDDM) was introduced in the beginning of 1980s in Sweden to reduce medication errors and improve handling of medications. Studies evaluating the MDDM system with regard to patient safety and adherence by profession perceptions are few and are not very extensive. More studies of the MDDM system are needed.

Objectives: Professionals' perceived experience of the MDDM system on patient adherence and patient safety.

Methods: The target group was health professionals involved in the prescribing and/or medication for patients without assistance from primary care nurses. A frame was set up with all Swedish municipalities (sorted by population size). A systematic sample (every 6th municipality) was drawn from the frame for the investigation. Four thousand one hundred and eighteen questionnaires were distributed electronically to assistant nurses/care assistants, 915 to physicians and 515 to nurses with experience of MDDM.

Results: The response rate among assistant nurses/care assistants, physicians, and nurses were 23%, 31% and 43%, respectively. Professionals were generally very positive to MDDM in terms to reduce duplication of medication, correct dosing, and helps the patient to take their medication at the right time, reduces confusion among patients and makes the patients feel more secure. The nurses were most positive 87–94% agreed with the various positive assertions about the MDD system. Assistant nurses and care assistants were also positive 74–81% agreed with the various positive statements. Also the physicians were positive, 63–72% agreed with the positive statements. Half of the physicians, a third of nurses and 5% of the assistant nurses and care assistants nurses and nursing assistants felt that generic substitution makes it more difficult for the patient to know which drugs are available in sachets. However, the professionals open survey comments showed that the recent introduction of a new electronic prescribing system for MDD lacked usability and is a potential threat to patient safety.

Conclusions: The professionals′ view was that the MDDM reduces duplication and medication mix-ups and contributes to the correct dosage at the right time.

512. Drug Use and Polypharmacy in Rehabilitation Center Inpatients Following Acquired Brain Injury: A Cross-Sectional Survey in Italy

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Background: Patients following acquired brain injury (ABI) suffer neurologic, psychiatric, neurocognitive and functional problems. Concurrent use of drugs is often required thus raising concern on safety, interactions and effectiveness in this vulnerable population.

Objectives: To assess drug use and polypharmacy in Italian rehabilitation centers (RCs) inpatients with ABI.

Methods: Setting: tertiary care RCs for ABI in Italy, between September 1 and November 30, 2012. Forty RCs were asked to participate in the study and mailed a structured questionnaire (Q) inquiring on: (part 1) facility characteristics, choice of drugs; (part 2) characteristics of ABI inpatients (age, sex, time since ABI, Level of Cognitive Functioning Scale score LCF) and their drug use (active substance, indication) at the survey. Reminders were sent to non-responders after

2 weeks and 1 month. Prevalence of drug use was calculated.

Results: Out of 35 (87.5%) participating RCs, 31 (88.6%) compiled part 2 Q for a total of 484 patients (63% men; 54.3% aged ≥ 50 years; 28.9% LCF two generalized response, 19.0% LCF three localized, 18.6% LCF five confused non-agitated). Overall 51.6% used 6–10 drugs, 21.1% 11–15 and 7.2% ≥ 16. The most frequently used drugs were antithrombotics (88.2%, heparin in 80.6% of users) and antiulcer agents (86.6%, PPIs in 91.9% of users). Overall 84.7% used psychotropic drugs, mostly (62.2%) two or more. Prevalence of use was: anti-epileptics 73.1% (82.1% in LCF 2); antidepressants 36.2% (61.5% in LCF 7 – 8 automatic – purposeful appropriate), most of which SSRIs (59.4%); anti-Parkinson 20.4% (31.5% in LCF-3 localized), most of which dopaminergic agents (91.9%); antipsychotics 17.1% (40.4% in LCF 4 confused-agitated); psychostimulants 3.9%. More patients used atypical (69.9% of users, n = 58) than typical antipsychotics and the most frequent agent was quetiapine (48.2%).

Conclusions: Polypharmacy, use of psychotropic drugs and of atypical antipsycotics were frequent in ABI inpatients. Prevalence of selected psychotropic drugs varied with LCF score. Monitoring of drug use and its consequences is recommended in ABI patients.

513. Relative Effectiveness of Paracetamol in Patient with Knee and Hip Osteoarthritis

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Background: Relative effectiveness studies are often concerned with the question of whether the use of a given drug spare the use of another drug. This question is increasingly in demand in order to make informed decisions about drug reimbursement.

Objectives: To determine the impact of the use of paracetamol on the use of NSAIDs in a cohort of patients with osteoarthritis and address methodological issues.

Methods: Between March 2010 and October 2012, patients with a diagnosis of osteoarthritis in France were recruited during a routine GP visit for pain. Data about medical and drug history, medication taken, comorbidities and pain or functional status were collected regularly through validated questionnaires and appropriate scales. Unit of times of analysis of 2 months were defined to take into account the time-varying nature of indication and dynamics of both exposure and outcome measurement, as their interdependency. Logistic regression modeling with general equation estimation (GEE) was used to investigate the use of NSAIDs between time units (2 months) of use of paracetamol and time units of non-use of paracetamol. Some additional analyses observed the impact of the use of paracetamol on knee and hip pain and functional scales.

Results: In October 2012, the cohort included 4,555 patients. Using paracetamol during the study period did not have a substantial effect on the use of NSAIDs (OR adjusted = 1.09 CI95%[1.00–1.19]).

Conclusions: The use of paracetamol did not seem reduce the use of NSAID. Methodological issues will be discussed.

514. Risk of Suicide Attempts Associated with Antiepileptic Drugs: A Case–Control Study Looking at the Effect of Differing Design Options

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Background: Some studies have raised concerns that antiepileptic drugs (AEDs) are associated with an increased risk of suicide. IMI-PROTECT aims to identify sources of methodological variations in pharmacoepidemiology studies using a common protocol and analysis plan across different databases. This work was carried out as part of PROTECT work package six (WP6) which aims to replicate in different conditions work package two (WP2) studies.

Objectives: To investigate with the PGRx database the effect of different design options in the study of the association of AEDs with suicide attempts (SA). The PGRx database allows using definitions of the outcome and confounders different from those used in the study performed by PROTECT WP2.

Methods: This study used a case–control methodology and a database collected specifically for pharmacoepidemiological studies purposes. Between January 2007 and September 2012, specialist centers recruited adult cases of SA. Controls were recruited from general practice settings and as many as possible were matched to each case. Potential risk factors for SA were assessed in a standardized telephone interview. Current and past episodes of depression were ascertained using the Mini-International Neuropsychiatric Interview. The interviewer was blind to case/control status. Cases and controls were compared for AED use in the prior two and 12 months, using odds ratios (OR) from conditional logistic regression.

Results: Nine specialist centers and 394 GPs agreed to participate. They recruited 709 eligible cases and 11,411 eligible referents. Five hundred and six cases were matched with 2,829 controls and included in the study. This study has been performed in the context of the PROTECT project examining the variability of results from studies using a same protocol, applied to a same drug-adverse event pair in different databases. In order to maintain the blinding of investigators from one another's results, these results will only be disclosed during the ICPE conference.

Conclusions: Results will be discussed in light of the results achieved by WP2 on the same adverse event-drug pair.

515. Benefits of Different Propensity Score Methods for Evaluation of Associations and Channeling Bias Over Time: Pneumonia and Inhaled Corticosteroid in a COPD New User Cohort

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Background: In the United Kingdom, the COPD indication for inhaled corticosteroids (ICS) granted in May 2003 changed over time, expanding from FEV1% predicted $< 50\%$ to $< 60\%$ in July 2007, which may result in changes in channeling bias and associations with safety outcomes.

Objectives: To assess different propensity score (PS) methods in evaluation of time and channeling trends in the association between any pneumonia recording and new use of ICS in periods before and after new indications for COPD.

Methods: We created a series of cohorts of COPD patients ≥ 45 years old who initiated and continued for ≥ 6 months ICS-containing (ICS, ICS + LABA, ICS + SABA) or long-acting bronchodilator medications (LABD:LABA, LAMA) including different time intervals between 2002 and 2010 using the UK CPRD. Over 50 potential confounders were included (demographics, comorbidities, clinical measures, and medications) to create PS for each cohort. Cox proportional hazards models for time to first pneumonia event were utilized with PS methods and robust variance (IPTW with stabilized weight, 1-1 greedy matching, deciles and quintiles).

Results: Overall 9,396 COPD patients with newly prescribed ICS (n = 5,549) or LABD (n = 3,847) in 2002–2010 were identified, and crude incidence rates of pneumonia were 48.4 and 36.2 per 1,000 PY, respectively. Using the IPTW, a significantly increased risk of pneumonia was observed for ICS vs. LABD new users only in 2005–2010 (HR = 1.31: 1.01–1.70). In contrast, the other methods (matching, deciles or quintiles) found a significantly increased risk of pneumonia for ICS users for some cohort time periods (2002–2007 or later) with (HRs: 1.28–1.42) but not other intervals (2002 up to 2006, or 2005 to 2010).

Conclusions: All PS methods identified a significantly increased risk of pneumonia in COPD patients following initiation of ICS-containing vs. LABD regimens; variation in estimates across PS methods, particularly prior to approval of an expanded ICS COPD indication, was observed. Using different methods to control for potential confounding may inform risk estimation, particularly for channeling over time.

516. Knowledge and Awareness of Healthcare Professionals (HCPs) Toward Pharmacovigilance Concept in Saudi Arabia

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Background: Pharmacovigilance sciences play major role in protecting patient safety through monitoring the post-marketing safety of medications. Since this concept is very new in Saudi Arabia and it was introduced due to establishment of Saudi food and Drug Authority. There is a little information available on the knowledge and awareness of healthcare professionals toward pharmacovigilance concept.

Objectives: To investigate the knowledge, awareness and attitude of the healthcare professionals to pharmacovigilance sciences and concept.

Methods: A cross sectional self administered survey has been conducted in six (three governmental and three private) hospitals in Riyadh, Saudi Arabia in the period between November and December 2012. The questionnaire comprise from 18 questions assessing the knowledge, awareness and attitude of HCPs toward sciences and concept of pharmacovigilance. It was adopted from published study and was validated. All statistical analyses were conducted using SAS version 9.2.

Results: A total of 239 HCPs responded to the survey with response rate of 73%. The type of HCPs who participated in this survey was comparable (physicians 30%, pharmacists 36% and nurses 32%). About half of the participants (50%) didn't know what pharmacovigilance is. However, 84% of HCPs believe that reporting adverse drug reaction (ADR) is responsibility of all type of HCPs and they consider it as one of their obligations as practitioner. In addition, 74% of the HCPs are aware of lookalike and sound alike medications. However, around 60% considered the difficulty of knowing if the event is ADR or not as one of the reporting barriers. Nevertheless, almost 62% of the HCPs didn't know what is the regulatory body that's responsible to receive ADR reports and other pharmacovigilance activities.

Conclusions: Healthcare professionals working at hospitals are not adequately aware of pharmacovigilance concept and its tasks. However, there is believe and a positive attitude toward the importance of the pharmacovigilance concept. The regulatory body should make efforts to enhance the awareness of all pharmacovigilance activities.

517. Data Sources Supporting Safety Warnings and the Correspondence Scientific Evidence Published in Literature: A Descriptive Study

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Background: The extent to which safety warnings issued by regulatory authorities are identifiable in the scientific and clinical literature is a relevant question.

Objectives: This study is aimed at identifying all safety warnings which have been released by regulatory authorities and comparing the studies evaluated with the available scientific published evidence for the respective safety warning.

Methods: A website search was carried out in order to identify all safety warnings published by four health regulatory authorities of reference, the US FDA, Health Canada, EMA and the Therapeutics Goods Administration. The inclusion criteria were considered the following: (1) 1st safety warning issued between January 2010 and June 2012; (2) evaluating at least one adverse drug reaction (ADR); (3) involving medicines included in one of the 20 most prescribed drug classes. For the safety warnings verifying the inclusion criteria, a literature search was conducted through Medline and Cochrane Library in order to identify all experimental and observational studies and meta-analysis evaluating the same safety issue.

Results: Forty-two safety warnings were included. Twenty-two warnings evaluated spontaneous reports, followed by clinical trails (20), cohort studies (13) and case-control studies (10). Ten warnings evaluated studies which were late published in scientific literature or were never published as full papers. Fourteen warnings were issued based on spontaneous ADRs, for which case reports were identified in literature. References were not provided for nine warnings. Two warnings were released based on information from other authority.

Conclusions: For the majority of the warnings, references were provided and simultaneously identified in literature. However, some warnings were found to be based on information not identifiable in the scientific literature.

518. Feasibility of Using Australian GP Prescribing Data for Pharmacovigilance

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Background: Prescription-event symmetry analysis (PSA) is a robust method for signal detection with applications in pharmacovigilance. It has been used previously with dispensing data but applying it to prescribing data may provide a more accurate view of the relationship between a clinical event and prescribing behaviour.

Objectives: To test the feasibility of PSA in a modestly sized Australian longitudinal primary care database.

Methods: We investigated the initiation order of proton-pump inhibitors (PPIs) and drugs thought to exacerbate gastro-oesophageal reflux. A cohort of patients was drawn from primary care electronic health records (EHRs) and consisted of 36,430 Australian adult

primary care patients with a first prescription of PPI in 2008–2010. To analyse prescription-event symmetry for a given pair of drugs, A and B, we considered only patients who received their first prescriptions for each drug within a time window of 90 days of each other, excluding cases where both drugs were prescribed the same day. We calculated the ratio of patients receiving the drugs in the sequence A-B vs. the sequence B-A, adjusting for trends in the independent prescribing rates of A and B.

Results: There was an adjusted rate ratio (ARR) of 1.25 (95% confidence interval 1.14–1.37) for prescribing non-steroidal anti-inflammatory drugs (NSAIDs) and PPIs. The ARR for calcium channel blocker (CCB) and PPI prescriptions was 0.69 (95% confidence interval 0.59–0.80). ARRs for other drug classes were not significantly different from 1.0. Initiating a PPI and a drug of interest on the same day was prevalent, possibly representing prophylactic prescribing of PPIs.

Conclusions: As in an earlier PSA study using Danish dispensing data, we found an association between NSAID and PPI prescribing. Pharmacovigilance studies using the surrogate measure of prescription-event asymmetry are feasible for commonly prescribed drugs using a modest database of EHRs.

519. Evaluation of General Public Perceptions Towards Adverse Drug Reactions Reporting

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Background: Adverse Drug Reactions (ADRs) are prevalent in drug therapy, and have been permeating our society, assuming the roles as both a health problem and an economic burden.

Objectives: The study aims to explore the perception and cognition of Penang's general public towards the Adverse Drug Reactions (ADRs) reporting.

Methods: This study was a cross-sectional study design. A self-developed validated questionnaire was used as data-gathering tool. A total of 500 questionnaires were distributed to the general public in the state of Penang, Malaysia. Each questionnaire consisted of 25 questions. related to the awareness, understanding and perception towards ADR-reporting. The data was analyzed descriptively and using the Chi-squared test ($\alpha = 0.05$).

Results: Most respondents were not aware about the definition of ADRs, and some (52.6%) were unable to differentiate between ADRs and side effects. Most were also able to relate ADRs with real-life situations based on their experiences (54.2%). only 48.2% claimed that physicians and pharmacists had asked them to make ADR reports. majority of the respondents also agreed that: everyone, irrespective of their age, is susceptible to ADRs (60.8%); it is vital to collect information regarding ADRs (96.4%); the main purpose of reporting ADRs is to prevent the occurrence of the same ADR in other individuals; the doctor who prescribed the medication needs to be informed regarding ADRs (53.8%) as they are the main source of information regarding ADRs; they have never heard of the term pharmacovigilance (94.6%); they will not make reports if the ADRs are mild (58.4%); reporting of an ADR will increase the knowledge of the ADR (48.4%); telephone is the best method to make ADR reports (38%).

Conclusions: From the findings established in this study, it can be concluded that the respondents are not aware of the importance of ADR-reporting. Most of the respondents agreed that ADR reporting has a positive impact on the public, as the public prefers physicians to forward any ADR cases that occur.

520. Cellulitis Reported to the Canadian Adverse Events Following Immunization Surveillance System (1987–2012)

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Background: Local reactions are one of the most frequent adverse events reported to The Canadian Adverse Event Following Immunization Surveillance System (CAEFISS). Extensive limb swelling and other vaccination site inflammatory reactions are often treated as cellulitis resulting in unnecessary use of antibiotics and occasionally hospitalization.

Objectives: To review and characterize cases of cellulitis reported to CAEFISS.

Methods: All cases of cellulitis reported to CAEFISS by December 31st, 2012 with date of vaccine administration between 1987 and 2012, were extracted and analyzed using SAS 9.3. Cases were characterized by age group, gender, vaccine(s) administered, time to onset, seriousness, health care utilization (HCU), treatment and duration.

Results: CAEFISS received 3,069 cases of cellulitis. 6.5% were serious. Mean reports by year was 118, median 114 and range 45–215. HCU was 6.5% hospitalization, 5.5% ER visit, 49.1% non-urgent clinic

visit, 0.2% phone advice, 1.4% none, 37.3% unknown or not stated. Age distribution in years was 20.5%< 1, 13.4% 1-< 4, 18.3% 4-< 7, 7.9% 7-< 18, 26.3% 18-< 65, 12.4% 65+ and 1.2% unknown. The proportion of serious reports was significantly higher for children aged 1 to < 18 years (10%) than for infants < 1 year (3.5%) or adults (4.5%) p < 0.0001. The Male to Female ratio was 1:0.94 in children under seven and 1:3.5 for seven and over. Implicated vaccines were most often pertussis containing vaccines for children < 7 years and Tetanus containing, Influenza and Pneu-P-23 for adults. The median onset of cellulitis was 1 day, with a median duration of 5 days. Approximately 20% of cases reported treatment with antibiotics.

Conclusions: Cellulitis is relatively a frequently reported AEFI across age groups with significant implications for health-care utilization and antibiotic use, especially in children. Most reported reactions were compatible with expected vaccination site inflammation. Criteria for distinguishing true bacterial cellulitis from non-infected inflammatory responses at the site of vaccination are needed in addition to education regarding expected local reactions for health care professionals, vaccinees and/or their care providers.

521. Reductions in Fatalities Following Introduction of a Reformulated Opioid with Abuse-Deterrent Properties

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Background: Prescription opioids provide analgesia to millions of patients annually but overdose deaths involving abuse and misuse of prescription opioids have increased in the US. One potential intervention to contribute towards reducing such deaths while preserving patient access is reformulating opioids with abuse-deterrent properties.

Objectives: This study assesses changes in the number of fatal spontaneous adverse events reported to the manufacturer after introduction of extended-release oxycodone (OxyContin®) with physicochemical barriers intended to deter abuse.

Methods: All adverse event reports of fatalities associated with OxyContin that originated in the United States and were reported 3Q2009 to 3Q2012 in the manufacturer's adverse event reporting database were identified. Numbers of fatalities reported in the year prior to distribution of the reformulation were compared to those in the 2-year period after reformulation.

Results: Three hundred and eighty-six fatal reports provided a subject date of death during 3Q2009 to 2Q2012. Following reformulated OxyContin (ORF) introduction, the number of fatality reports decreased, beginning the first year after ORF introduction and becoming more pronounced in subsequent quarters. There was a 52% (95% CI: −64 to −37) decrease in all fatalities, 66% (95% CI: −77 to −50) decrease in overdose fatalities, and a 71% (95% CI: −81 to −56) decrease in overdose fatal reports with mention of abuse from the year before to the second year after ORF introduction. Fatality reductions were similar using prescription-adjusted rates. Regression analysis showed statistically significant decreases in the slope of the trend from before to after ORF introduction for all fatalities and the subsets of fatal reports of overdose with and without mention of abuse.

Conclusions: There was a reduction in the number of fatal adverse event cases associated with OxyContin reported to the manufacturer that began after reformulation of OxyContin and grew over the observational period. Reductions were greatest for fatal cases involving overdose and those involving overdose with mention of abuse-related behavior.

522. Risk Minimization Plans in Developing Countries: A Cross Sectional Survey of Isotretinoin Use in Saudi Arabia

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Background: Due to the teratogenic effects of isotretinoin, certain precautions should be applied to reduce the inadvertent exposure during pregnancy. A study showed that dermatologists, in Saudi Arabia, have lower compliance with the precautions concerning the use of isotretinoin for female patients.

Objectives: To understand the practice and knowledge of community pharmacists for dispensing isotretinoin-containing products.

Methods: A cross sectional self administered survey of private community pharmacists at three cities in Saudi Arabia (Riyadh, Buraydah and Ha'il) over 2 months in 2012. The questionnaire comprised 13 questions besides demographics of participants. The questions were divided into general knowledge about isotretinoin precautions, patient's counseling and practice of pharmacists. All statistical analyses were conducted using

Statistical Package for the Social Sciences (SPSS version 20).

Results: One hundred sixty questionnaires were distributed with a response rate of 72.5% (n = 116). More than half of the participants (56%) knew the correct pregnancy risk classification category for oral isotretinoin (category X). The majority of participants (78%) suggested that teratogenicity is the most serious event associated with the use of oral isotretinoin. Only, 6.2% of pharmacists would recommend using two methods for contraception (hormonal and non-hormonal methods). Almost a fifth of the pharmacists dispensed isotretinoin without prescription. Approximately 45% of the pharmacists claimed to always providing counselling to patients about the risk of teratogenicity. Eleven percent of the pharmacists do not enquire about whether the patient did a pregnancy test result prior to dispensing oral isotretinoin or not.

Conclusions: Pharmacists at community pharmacies are not adequately aware about the precautions for using isotretinoin for female patients, and an alarming proportion of pharmacists dispense isotretinoin without prescription. Efforts to enhance the awareness of community pharmacists about the proper use of isotretinoin is recommended with imposing more effective regulations to limit the illegitimate dispensing of oral isotretinoin.

523. Medication Guide Reading Behaviors and Attitudes Among Patients with Migraine, Asthma, or COPD

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Background: To be effective, patient medication information needs to be both read and understood.

Objectives: FDA and industry are interested in improving Medication Guides (MG) based on concerns that the materials are not effective. This study sought to determine why patients did not read MG and understand possible changes that could improve MG readership.

Methods: This online cross-sectional survey used a panel of consumers to describe attitudes and reading behaviors toward MG among patients with migraine (n = 279) asthma (n = 252) or COPD (n = 254) who reported recent use of a migraine medication or asthma medication. Information collected included reasons for not reading the MG thoroughly & ways to improve MG reading behaviors. Patients who reported reading a MG each time it was received were excluded (2% of screened). Multivariable logistic regression analysis was used to find factors independently associated with improving patient readership of MG each time, using a list of possible factors, incl. age, sex, indication for, and time spent on, drug and others.

Results: Forty-six percent (n = 360) of patients read their MG only once, while 36% reported reading > 1 time, but not every time they received it. Eighteen percent of respondents reported never reading the MG. Patients who did not read MG with each refill, most frequently reported that they didn't expect the information to change (83%) and they expected the doctor would tell them what they needed to know (71%). Patients reported acquiring medication safety information from doctors or pharmacists more frequently than from the MG (85% and 63% vs. 38%). Patients were more likely to read a MG for a new Rx if the MG contained limited information (OR = 2.13, 95% CI 1.31–3.47) in a bulleted form (OR = 1.88, 95% CI, 1.14–3.10). Age was also associated with increased likelihood of reading the MG (5 year age category OR = 1.09, 95% CI 1.01–1.18).

Conclusions: The results from this study shed light into potential revisions to the MG that may improve reading behaviors, including providing information in bullets and abbreviated information. Changes to MG should be based on patient feedback and pilot-testing to enhance likelihood of reading and understanding materials.

524. The Impact of Pharmacist-Led Educational Interventions on the Use of High-Risk Abbreviations in a Saudi Arabian Hospital and Emergency Centers

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Background: Educational interventions initiated by pharmacists to reduce unsafe abbreviation use remained assessed in Saudi Arabia and the Middle East. Additionally, few studies have reported the interventions and abbreviation use.

Objectives: This study aimed to evaluate the impact of pharmacist-led education interventions on the use of high-risk abbreviations by healthcare professionals.

Methods: It was carried out in hospital emergency services, the Pharmacy Department and Haram Centers around the Holy Mosque in Makkah. Prescriptions from the three sources were assessed for high-risk

abbreviation use before and after the educational interventions during April–June 2011. A data collection form was specially designed and piloted. The interventions consisted of disseminating educational tools and educating all hospital staff during a medication safety week.

Results: A total of 660 and 498 prescriptions (for 482 and 388 patients) were gathered before and after the educational interventions. The highest incidence of high-risk abbreviation use was initially found in discharge prescriptions and dispensing records of the Pharmacy Department (72.7%), followed by prescriptions from Haram Centers (47.3%) and prescription charts from hospital emergency units (40.9%). After the interventions, the overall incidences of high-risk abbreviations were significantly reduced by 52% (i.e., 53.6% vs. 25.5%; p < 0.001) and incidences in individual sources also statistically decreased (all p < 0.001). Top 5 abbreviations mostly recorded prior to the interventions were 'IJ for injection', 'SC for subcutaneous', drug name and dose running together, 'OD for once daily', and 'D/C for discharge' (i.e., 28.6%, 17.4%, 9.7%, 5.8%, and 4.3%, respectively). This tendency also occurred after the interventions.

Conclusions: Pharmacist-led educational interventions can significantly reduce the use of high-risk abbreviations among healthcare providers. Their compliance should however be monitored and audited. Further studies are required to investigate the inappropriate abbreviation use in other settings.

525. Development of a Clinical Prediction Model for an INR ≥ 4.5 in Hospitalized Patients Treated with Vitamin K Antagonists

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Background: Bleeding caused by high INR is a serious complication in patients treated with vitamin K antagonists (VKAs). Some published prediction models for a high INR or bleeding complications include risk factors that are not readily available in daily practice, limiting the usability of these models.

Objectives: To develop a prediction model for the risk of an INR ≥ 4.5 in hospitalized patients treated with VKAs, based on risk factors collected during routine care.

Methods: This is a retrospective cohort study in a large university hospital in the Netherlands. We included admissions of adult patients in 2006–2009 during which a VKA was prescribed. Patients were followed from start of VKA treatment until their first INR ≥ 4.5, the end of treatment with a VKA, discharge, or until the end of the study, whichever came first. Candidate predictors were: age, sex, blood group, medical or surgical patient, an INR ≥ 4.5 during an earlier admission (previous event), and at start of VKA treatment: the number of concomitantly used medicines, concomitant use of low molecular weight heparins and/or amiodarone, and the biochemical parameters: ALAT, ASAT, γ-GT, LDH, albumin, haemoglobin, haematocrit, renal function, c-reactive protein, the number of thrombocytes and leucocytes. Obviously insignificant predictors (p-value > 0.2) were stepwise removed from the regression model.

Results: In 2006–2009 we included 4,762 admissions of 3,798 patients. During 1,128 admissions (23.7%) an INR ≥ 4.5 was found for 920 patients. Strongly significant predictors were: age (odds ratio [OR] 1.01/year, 95% confidence interval [CI] 1.004–1.014), being a medical patient (OR 1.56, 95% CI 1.29–1.89), concomitant use of amiodarone (OR 1.52, 95% CI 1.22–1.91), a previous event (OR 1.28, 95% CI 1.03–1.57) and the number of concomitantly used medicines (OR 1.15, 95% CI 1.06–1.25).

Conclusions: Ten predictors that contribute to the increased risk of an INR ≥ 4.5 were identified. The strongest predictors were: being a medical patient, concomitant use of amiodarone and an INR ≥ 4.5 during a previous hospital admission.

526. Diabetes Screening of Adults Receiving Antipsychotics: A U.S. State Survey of Prescribers

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Background: Second-generation antipsychotics (SGAs) are associated with weight gain, hyperglycemia, and dyslipidemia. Population-based studies have shown low rates of metabolic screening among SGA-treated adults despite risk management recommendations for increased monitoring.

Objectives: To assess prescriber perceptions of barriers to diabetes screening of SGA-treated adults.

Methods: Mail/Internet surveys were obtained November 2011–January 2012 from 179 SGA prescribers (84% response rate) from 24 community mental health

centers in the state of Missouri. Bivariate analyses were performed to examine the association between independent factors (demographic-practice characteristics, medical information sources, knowledge, attitudes, and barriers to screening) and whether prescribers treating adults (N = 159) 'definitely' would order a baseline glucose test. Factors with p < 0.25 in bivariate analyses were tested by using multivariate logistic regression; factors with p < 0.05 were retained in the final model.

Results: Eighty-two percent of providers strongly agreed all patients starting SGA drugs should receive baseline glucose testing; 58% definitely (27% probably) would order a glucose test. Top barriers to screening were patients forgetting (77% agreed); providers not receiving results if performed elsewhere (66%); and required fasting (60%). Factors associated with definitely ordering glucose testing were provider age (< 50 year vs. older), OR = 3.72 (95% CI: 2.02–6.85); strongly agreeing 'diabetes screening is a major part of my practice', OR = 4.71 (2.51–8.84); strongly disagreeing 'screening guidelines are unclear', OR = 3.07 (1.64–5.76); and learning about new medical information frequently/occasionally from colleagues via social media, OR = 6.65 (3.66–12.08). Providers who learned via colleagues in-person were less likely to screen, OR = 0.27 (0.14–0.50).

Conclusions: Interventions to improve screening could facilitate knowledge/attitudinal transfer from those who definitely screen to those who occasionally screen (and appear to rely more on in-person medical information exchange). Patient barriers could be addressed by encouraging non-fasting A1C testing and meaningful use of patient reminder/EHR systems.

527. Adoption of a Clinical Checklist as a Risk Minimization Tool in China

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Background: Adoption and implementation of individual risk minimization measures (RMMs) can vary from country to country due to such local factors as the healthcare system and degree of user acceptance. As part of a global risk minimization plan for an anti-tumor necrosis factor (TNF) agent, a TB Screening Checklist was developed as a RMM to reduce the likelihood of latent TB reactivation.

Objectives: (1) To describe the healthcare delivery process for rheumatoid arthritis (RA) patients in China who are eligible for an anti-TNF agent; (2) to identify factors that could impede or enhance the adoption of

the TB Screening Checklist by prescribers; and (3) determine how best to tailor the Checklist for use in China.

Methods: We conducted an ethnographic study with two national key opinion leaders and nine rheumatologists from nine hospitals across China. A native Chinese healthcare professional conducted half-to full day ethnographic observations of the clinical care process for anti-TNF patients followed by in-person debriefs with each clinician.

Results: Rheumatologists in China practice in hospital-based clinics, typically work alone, handle a caseload of ~30–80 patients per half-day session, and spend an average of < 10 min per patient. All study rheumatologists reported conducting some form of TB screening; however, none used the specified TB Screening Checklist. Barriers to use of the Checklist included length, non-relevant or missing screening steps, lack of national clinical guidelines regarding best practices for latent TB case diagnosis and prophylaxis and inadequate understanding regarding how to interpret latent TB screening test results. Recommendations for increasing physician adoption of the Checklist included revamping its content, re-formatting it (pocket-sized card), adding information regarding latent TB diagnosis and treatment, and removing the drug company's logo.

Conclusions: Results provided insight into how a clinical checklist could be redesigned to increase acceptability by clinicians in China. To maximize the effectiveness of risk minimization tools, input from the end user should be solicited regarding tool design, content and proposed implementation plans.

528. Characterization and Factors Associated with Post-Transplant Headaches: A Retrospective Survey Study

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Background: Post-transplant headache (post-TX HA) is a recognized complication in transplant procedures. Its treatment can be problematic given the status of the patient and other factors. But this complication is infrequently discussed as a significant clinical problem since this symptom is generally considered less important than other complications, like organ rejections.

Objectives: The objective of this study is to characterize post-TX HA and to assess the factors associated with post-TX HA.

Methods: A survey was developed to assess these poorly investigated factors and consisted of four sections, include patients' risk factors for headaches, the characteristics of post-TX HA, patients' headache management techniques and effectiveness, the demographics of the patients. The participants of the study were patients who received kidney transplants at University Hospital in Cincinnati, OH and who currently follow-up at the Kidney Transplant Clinic of University Hospital, where the survey was administered. Other data include current medications,alcohol/tobacco/illicit drug use, and lab values were collected as well. the primary outcome is post-TX HA. A logistic regression model was constructed to evaluate the factors associated with the post-TX HA with the consideration of common covariates.

Results: A total of 95 patients were included in this study. Forty-one patients reported they had experienced at least one headache episodefollowing transplant. Compared to the counterpart, the headaches patients experienced post transplant were significantly associated with age (OR = 0.947, 95% CI is 0.901–0.995) and presence of pre transplant headaches (OR = 14.123, 95% CI is 3.810–52.346). In terms of comorbidities, only chronic pain (neck, back, shoulder, etc.) is a factor showing statistically significant association with post-TX HA (OR = 7.269, 95% CI is 1.737–30.429).

Conclusions: Patients who had headaches pre-transplant and suffered chronic pain are more likely to have post-TX HA. In addition, compared to older patients, younger patients are more likely to experience headaches after transplant.

529. Attitudes and Beliefs on the Use of Non-Prescription Medicines in Singapore

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Background: Due to the growing importance in self-care, non-prescription medicines are increasingly used for self-medication but the general public may not know how to use them safely.

Objectives: To determine the prevalence of use of non-prescription medicines in Singapore and to assess the attitudes and beliefs on the use of non-prescription medicines.

Methods: A cross-sectional, iPad-assisted interviewer-administered questionnaire survey was conducted in shopping malls in various regions around Singapore. The pilot-tested questionnaire, that was developed based on available literature, consists of 18 questions (predominantly closed-ended questions) and is available in English and Chinese. Singapore citizens and permanent residents aged 21 and above who were willing to participate were invited to participate in the study. Healthcare professionals were excluded. Responses were analyzed using IBM SPSS Statistics software (version 20).

Results: Three hundred and eighty-four members of the public were surveyed between December 2012 and January 2013. Majority of the respondents reported using a non-prescription medicine (89.1%), with older age groups (51 and above) less likely to use such medicines than younger age groups (p = 0.016). 87.5% preferred to treat minor ailments on their own rather than consulting a doctor. Most perceived that non-prescription medicines are effective for self-treatment (74.0%) and totally safe to use (60.9%). Of the 342 respondents who had ever taken non-prescription medicines, 51.5% were not aware of the side effects of the non-prescription medicines that they took, with only 14.6% reported ever experiencing a side effect. While the majority (93.0%) did not take more than the recommended doses, 5.3% exceeded the required dose, citing faster relief as the primary reason.

Conclusions: This study revealed that there is a high prevalence of non-prescription use in Singapore and that the majority of the general public is willing to self-medicate using non-prescription medicines. However, many were also unaware of the side effects and there are still some who took more than the recommended doses. Pharmacists can play a greater role in educating the public on self-treatment with non-prescription medicines.

530. Pregnancy and Lactation Labeling Information in Cough and Cold Related Medications

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Background: Cough and cold related medications (CCRMs) are among the most commonly used medications during pregnancy and lactation. It is thus important that advice on their use in pregnancy and lactation is adequately communicated via patient information leaflets (PILs) and product inserts (PIs).

Objectives: To evaluate pregnancy and lactation labeling information in proprietary CCRM products in Singapore and to assess the consistency of the advice for use during pregnancy and lactation with those from drug information references.

Methods: The PILs and PIs of proprietary CCRM products containing antipyretics, antihistamines,

decongestants, antitussives, expectorants, mucolytics, sore throat preparations, and antibiotics for upper respiratory tract infections, were reviewed to assess the provision of pregnancy and lactation labeling information, clinical and/or preclinical data, and advice for use by pregnant and lactating mothers. Advice provided by product information was categorized as: 'can be used', 'unclear', 'not recommended' or 'no available information' and compared with that provided by two drug information references. Descriptive statistics were generated.

Results: Of 136 CCRM products evaluated, some information regarding use during pregnancy and lactation was provided in most products (89.0% and 77.9%, respectively). However, of these products with pregnancy (n = 121) and lactation (n = 106) labeling information, around half of the products provided no clinical or preclinical data (55.4% and 54.7%, respectively) and unclear advice for use (47.9% and 46.2%, respectively). Advice for use during pregnancy and lactation differed between the product information and drug information references for 82.4% and 70.6% of the products, respectively, with majority of the products (57.1% and 72.9%, respectively) providing more restrictive advice than that from drug information references.

Conclusions: The results have identified potential gaps in written consumer medication information pertaining to CCRM use during pregnancy and lactation. This raises a need to improve the communication of such information on PILs and PIs for better medication safety and use among pregnant and lactating mothers.

531. Methods to Evaluate Additional Risk Minimisation Measures: A Systematic Review

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Background: Additional risk minimisation measures (aRMMs) can be required to strengthen the benefit-risk balance of a drug. With the new EU pharmacovigilance legislation monitoring the outcome of these measures becomes mandatory. Knowledge on how the effect of aRMMs can be evaluated is however limited.

Objectives: To describe the methods used in studies that evaluated aRMMs.

Methods: A MEDLINE was searched in October 2011 using search queries focussed on seven aRMM categories i.e. educational material, pregnancy prevention program (PPP), controlled distribution, intensive patient monitoring, registry, patient consent, special packaging. Reference lists of included original articles and relevant review articles were also screened. Studies were excluded if they did not focus on medicinal products or were not written in English. The methodology of each study was described according the following characteristics: study design, data source, outcome measure.

Results: We included 77 publications in our review. Thirty studies restricted the evaluation to descriptive analysis, 22 applied a before-after design, nine a traditional comparison (intervention vs. non-intervention), eight interrupted times series and five compared different drugs. Data was most frequently obtained via surveys (37) or existing healthcare databases (30) including hospital, drug dispensing or administrative claims data. Although multiple outcomes were used, Knowledge Attitude and Awareness regarding risk or aRMM (KAA) (41), compiance to RMM (43) and events rates (31) were most frequently used. Educational material was mainly evaluated using surveys (20 of the 29) to study outcome measure KAA (16). The majority of PPP evaluations were descriptive analysis (13 of the 19) but compliance to aRMM and event rates were equally used outcome measures. Restricted pack size was mainly evaluated using existing healthcare databases to study the event rates (14 of the 16).

Conclusions: Previous studies that evaluated aRMMs used a variety of evaluation methods which provide knowledge on possible study designs, data sources and outcome measures to be used for studing effectiveness of aRMMs. Use of these methods in regulatory practice needs further assessment.

532. Drospirenone and Risk for Venous Thromboembolism; A Comparison by Dosage of Ethinyl-Estradiol

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Background: Previous studies concluded increased risk for non-fatal venous thromboembolism (VTE) with drospirenone. It is unknown whether risk is differential by ethinyl-estradiol dosage.

Objectives: To assess VTE risk with drospirenone in a US population and to determine whether drospirenone and ethinyl-estradiol 20ug (DRSP/EE20) has a lower VTE risk than drospirenone and ethinyl-estradiol 30 μg (DRSP/EE30).

Methods: Our cohort included women aged 18–46 years taking drospirenone or levonorgestrel (LNG)-containing combined oral contraceptives (COC) in the IMS claims-database between 2001 and 2009. VTE was defined using ICD-9-CM coding and anticoagulation. The hazard ratio (HR) from Cox Proportional Hazards Models was used to assess the VTE relative risk (RR) with drospirenone compared to levonorgestrel. Analyses were adjusted by a propensity score used to control for baseline comorbidity and stratified by EE dosage, user-type (new/prevalent), and calendar year.

Results: The study included 238,683 drospirenone and 193,495 levonorgestrel users. Among new and prevalent-users, a 1.90-fold (95%CI: 1.51–2.39) increased VTE relative risk was observed for drospirenone (18.0 VTE/10,000 women-years) vs. levonorgestrel (8.9 VTE/10,000 women-years). In analysis of new-users, DRSP/EE20 had a 2.35-fold (95%CI: 1.44–3.82) VTE RR vs. LNG/EE20. DRSP/EE30 new-users observed an increased RR vs. LNG/EE30 among women initiating COCs between 2001 and 2006 (2.51 95%CI: 1.12–5.64) but not 2007–2009 (0.76 95%CI: 0.42–1.39), attributable to an increased incidence-rate with LNG/EE30 from 2007 to 2009. In direct comparison, DRSP/EE20 had elevated VTE risk compared to DRSP/EE30 (RR 1.55 (95%CI: 0.99–2.41).

Conclusions: We observed modestly elevated VTE risk with drospirenone, compared to levonorgestrel. The larger VTE incidence-rate observed in DRSP/EE20 than DRSP/EE30, and the increasing VTE incidence-rate with levonorgestrel during later study years (2007–2009) were unexpected.

533. Fluoroquinolones and Risk for Acute Kidney Injury

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Background: Case-reports indicate fluoroquinolones may induce acute kidney injury (AKI).

Objectives: To determine the association between oral fluoroquinolones and hospitalized AKI and assess for an interaction with renin angiotensin system (RAS) blockers.

Methods: We formed a nested cohort of men aged 40–85, enrolled in the United States IMS healthcare-database between 2001 and 2011. Cases were hospitalizations for AKI [primary discharge diagnosis: 584.X], while controls were hospitalized with different presenting diagnoses. Using density sampling, 10 controls were matched per case on hospital admission, calendar time (± 6 weeks), cohort entrance (± 6 weeks), and age (± 5 years). Conditional logistic regression assessed the rate ratio (RR) for AKI with current, recent, and past users of fluoroquinolones, adjusted by potential confounders. Analysis was repeated with control antibiotics, amoxicillin and azithromycin. Secondary analysis utilized a case-time-control study design.

Results: We identified 1,292 cases and 12,651 matched-controls. Current fluoroquinolone use had a 2.18 (95% CI:1.74–2.73) fold increased RR for AKI, while no association was observed with recent (RR 0.88 [95% CI:0.66–1.17)] or past (RR 0.87 [95%CI:0.66–1.13]) use. The absolute increase in AKI was 6.5 events/10,000 person-years. We observed one additional case per 1,529 patients treated or 3,287 prescriptions dispensed. Dual use of fluoroquinolones and RAS blockers had a RR of 4.71 (95%CI:2.96–7.50) for AKI. A case-time-control analysis confirmed an increased RR for AKI with fluoroquinolones (2.16 [95%CI:1.52–3.18]). Amoxicillin and azithromycin were unassociated with AKI.

Conclusions: Although risk is small, we observed an increased RR for hospitalized AKI with oral fluoroquinolones, also noting a significant interaction for AKI with concomitant use of fluoroquinoloens and RAS Blockers.

534. Need for Collaborative International Vaccine Benefit-Risk Studies in Low-Income Countries: A Pilot Project

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Research Centre, Manhiça, Mozambique; [7]Navrongo Health Centre, Navrongo, Ghana; [8]Brighton Collaboration Foundation, Basel, Switzerland; [9]University Children's Hospital Basel, Basel, Switzerland.

Background: Continuous active surveillance of the benefit and risk of immunizations from pre- to post-licensure is critical for their eventual success and sustainability. Several new vaccines are under development targeting diseases with high incidence in Low- and Middle-Income Countries (LMIC; e.g., malaria, TB, HIV, schistosomiasis, and typhoid and paratyphoid vaccines for infants). The current capacity to collect benefit–risk evidence in LMICs is suboptimal, however. Many of the existing 31 INDEPTH (International Network for the Demographic Evaluation of Populations and Their Health in LMIC) centres are already participating in clinical trials of these new vaccines; we therefore created a partnership between IN-DEPTH, PREVENT (PRogram Enhancing Vaccine Epidemiology Networks and Training) project, the GRiP network (Global Research in Paediatrics-Network of Excellence) to begin building the desired capacity.

Objectives: To identify appropriate INDEPTH centres to pilot and demonstrate the feasibility of collecting vaccine benefit-risk data.

Methods: We prepared and distributed a pilot study protocol and survey of existing centres capacity among the INDEPTH centres researchers attending the INDEPTH Scientific Conference in Maputo, Mozambique, October 24–27, 2011. The survey collected data on each interested centre's capacity to collect data on vaccination exposures, adverse medical event outcomes, and unique personal identifiers. We facilitated the completion of the survey via both face-to-face meetings and subsequent emails. We scored and compared the centres based on availability and completeness of key pilot study variables.

Results: Three INDEPTH centres were selected: Kenya, Mozambique and Ghana. We will present the centre characteristics, the processes for linking exposure and outcome data, the infrastructure for international data sharing and the on-going proof of principle studies.

Conclusions: Collaborative international benefit-risk assessment in LMIC appears feasible and a model framework is evolving. Based on lessons learnt from these pilot studies, planning for expansion of such infrastructure to allow studies of larger populations can be undertaken.

535. Risk of Solid Organ Transplant Rejection Following Vaccination with GlaxoSmithKline's Inactivated Adjuvanted (AS03) A/H1N1 Pandemic Influenza Vaccine

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Background: Solid organ transplant recipients are a recommended priority group for pandemic influenza vaccination due to the substantially elevated risk of complications associated with influenza infection. The safety of pandemic H1N1 vaccination in this patient population has not been fully investigated.

Objectives: To assess the risk of solid organ transplant rejection after vaccination with the ASO3-adjuvanted H1N1 vaccine in the United Kingdom. Results of this ongoing study will be presented at the conference.

Methods: Retrospective self-controlled case-series in the UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD) in vaccinated patients of all ages. The outcome is rejection of transplanted lung, kidney, heart, liver or pancreas. Specific algorithms for searching clinical codes were applied to identify rejection events in the CPRD and the linked component of the Hospital Episodes Statistics (HES). Outcomes are ascertained via standardised questionnaires to General Practitioners. Subjects must have at least one rejection recorded in the CPRD and/or HES and confirmed by the GP during the study period 1 October 2009 to 31 October 2010. The risk periods are 1 and 2 months after any vaccine dose. The control period corresponds to the study period minus the risk periods. The case-series analysis for perturbed post-event exposure will be used.

Results: Feasibility in the CPRD showed that an estimated 117 subjects had at least one rejection during the study period, of which 64 were exposed to the vaccine. With 30 cases, the study has 80% power to detect a relative incidence of 3.0. Relative incidence estimates will be presented based on various models adjusting for time since transplantation; previous rejection(s); seasonal influenza vaccination; bacterial and viral infections; malignancy; chemotherapy.

Conclusions: This study will document the feasibility of using the CPRD for this specific patient population and will provide key safety data to inform the benefit-risk of an ASO3-adjuvanted pandemic influenza vaccine in transplanted patients in the event of a future pandemic.

536. Creating Treatment Episodes for Biologic Medications from Pharmacy and Medical Claims

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Background: Analysis of biologic medications in automated databases requires creating treatment episodes during which time a patient is considered to be using a medication. Determining treatment episodes is crucial to assessing adherence, effectiveness, and safety, but treatment episodes are not identifiable solely from information in claims.

Objectives: To identify and integrate items of information and assumptions required to create treatment episodes in database studies.

Methods: Dispensings and administrations of biologic medications in insurance claims data are identifiable from National Drug Code (NDC) codes found on pharmacy dispensing claims, and from Healthcare Common Procedure Coding System (HCPCS) codes found on medical claims. Pharmacy claims are generated when a prescription drug is dispensed by a pharmacy, and medical claims are generated when a drug is administered by a medical procedure, such as an injection or infusion. Each type of insurance claim indicates the date on which a medication was dispensed or administered. Pharmacy claims indicate the number of days supply of a medication.

Results: We identified 48,736 psoriasis patients in an insurance claims database covering the years 2000 through 2010 with 648,193 pharmacy and medical claims for biologic medications used to treat psoriasis. The use of each medication was indicated in both types of claims; however, individual biologic medications were identified by a majority of either pharmacy or medical claims. To integrate the different types of claims for each biologic medication, we combined information from the claims with information from package inserts, observed durations between administrations, and drug-specific bridging rules to create 336,012 treatment episodes for biologic agents.

Conclusions: This paper discusses the different data elements found in pharmacy and medical insurance claims pertaining to treatment episodes, recommended dosing intervals, observed patterns in the data, decision rules used to address gaps between dispensings and administrations, and the process used to integrtae these sources in creating treatment episodes and classifying patients according to exposure to biologic medication.

537. Use of the French Claims and Hospitalisations Database to Estimate the Prevalence and Incidence of Parkinson's Disease in France

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Background: Few studies have assessed the prevalence and incidence of Parkinson's disease (PD) in France.

Objectives: To estimate the prevalence and incidence of PD between 2005 and 2010 using a claims and hospitalisations database.

Methods: The EGB database is a 1/97 permanent random sample of the French healthcare insurance system database linked to the national hospital discharge summary database. Data for all adults with full insurance coverage for PD, or hospitalised with main, related, or associated PD diagnosis, or with at least three antiparkinson agent reimbursements over a 1-year period were extracted for the years 2004 to 2010. A specific and a sensitive PD criterion were defined: (1) patients with a medical diagnosis of PD from full insurance coverage or hospitalisation; (2) same patients plus those without a PD medical diagnosis in the database but a drug pattern compatible with this diagnosis (a second set of at least three antiparkinson agent reimbursements over another 1-year period and no co-medication with extrapyramidal side effects, as well as no antiparkinson agent pattern specific of another indication). EGB estimations were applied to the French population with age and gender standardization to estimate the prevalence and incidence in France.

Results: Prevalence of PD increased from 0.27% in 2005 to 0.33% in 2010 using the specific definition of disease, and from 0.38% to 0.46% using the sensitive definition. The incidence rate per year was 0.03–0.04% using the specific definition of disease, and 0.05–0.06% using the sensitive definition. Estimated population size was between 180,000 and 255,000 persons in 2010 with approximately 22,000 to 32,000 new patients per year.

Conclusions: The prevalence and incidence of PD in France are likely to be within the range of estimations found in the EGB database using the specific and sensitive definitions of disease; results are consistent with that reported internationally.

538. Audit of the Effect of Relative Age on Morbidity Among Children in the Health Improvement Network (THIN) UK Data

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Background: In North America, attention deficit hyperactivity disorder (ADHD) has been shown to be more prevalent among younger children in an academic year than older classmates, possibly because they appear more disruptive. To our knowledge, the effect of relative age on ADHD and other morbidities has not been reported in the UK, where cut off for school year entry is 31 August.

Objectives: To assess the effect of relative age on morbidity among children in the UK.

Methods: Percentages of children aged 5–15 years in The Health Improvement Network (THIN) with ADHD (based on diagnoses and prescriptions) and prescriptions for drugs as proxies for other morbidities (drugs as classified by British National Formulary chapters) during the academic year September 2010–August 2011 were calculated. Percentages across months of birth (MOB) were compared with chi-squared tests for trend. Relative risks (RRs) were calculated to compare children with later MOB (Mar-Aug) with earlier MOB (September–February).

Results: Of 436,299 children, 0.75% were diagnosed with ADHD. Percentages ranged from 0.60% (September MOB) to 0.83% (June). There was evidence at the 5% level ($p < 0.001$) to suggest a linear increase of ADHD prevalence across MOB. Younger children were 14% more likely (RR 1.14 95% confidence interval [95%CI] 1.07–1.23) to have an ADHD diagnosis or prescription than older classmates. Younger children had a higher proportion of central nervous system prescriptions ($p = 0.003$ [trend test] RR 1.01 [95% CI 0.99–1.03]) but lower proportions for some drug groups, including prescriptions for the cardiovascular system ($p < 0.001$ RR 0.85 [0.78–0.93]) and obstetrics, gynaecology and urinary tract disorders ($p < 0.001$ RR 0.78 [0.74–0.82]).

Conclusions: In the UK, younger children in a school year are more likely to be diagnosed with or prescribed for ADHD. This may be because they appear more disruptive. There are also differences in prescribing behaviour for younger and older classmates which could be investigated further. Future research could assess additional academic years, non-linear trends and differences among age groups, genders and specific drug classes.

539. Chronic Hepatitis B Virus Infection Among U.S. Medicaid Enrollees, 2000–2007

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Background: Before using computerized databases to study the pharmacoepidemiology of chronic hepatitis B virus (HBV) infection, the validity of the diagnosis must be confirmed.

Objectives: (1) To determine the positive predictive value (PPV) of chronic HBV diagnoses in U.S. Medicaid compared to medical record-confirmed diagnoses, and (2) To estimate the prevalence of chronic HBV infection in this population.

Methods: We randomly sampled 206 members who were enrolled in the U.S. Medicaid programs of CA, FL, NY, OH, and PA between 2005 and 2007 and who had two outpatient chronic HBV ICD-9 diagnoses recorded at least 6 months apart. Medical records of sampled patients were reviewed by a hepatologist and an infectious diseases physician to confirm the diagnosis. The PPV of the diagnostic coding algorithm for confirmed HBV infection was determined. Next, the period prevalence of chronic HBV among Medicaid patients with at least 180 days of membership between 2000 and 2007 was estimated, adjusting for the PPV. We conducted a sensitivity analysis estimating the period prevalence using only one chronic HBV diagnosis.

Results: Among 54 members with available records, chronic HBV was confirmed in 52 (PPV, 96.3%; 95% CI, 87.3–99.5). Using the algorithm, 31,046 cases of chronic HBV infection were identified among 31,358,010 eligible Medicaid members from the five states (prevalence, 9.9 [95% CI, 9.8–10.0] per 10,000). Adjusting for the PPV, the prevalence of chronic HBV was 9.5 (95% CI, 9.4–9.6) cases per 10,000. Identifying

chronic HBV by only one diagnosis resulted in a prevalence of 29.0 (95% CI, 28.8–29.2) cases per 10,000.

Conclusions: In Medicaid, an algorithm of two outpatient chronic HBV diagnoses recorded at least 6 months apart had high PPV for confirmed chronic HBV infection. The prevalence of chronic HBV among U.S. Medicaid enrollees ranged from 9.5 to 29.0 cases per 10,000.

540. Seizure and Associated Factors in Patients with Different Types of Dementia

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Background: Information on the occurrence of seizure in patients with different types of dementia and their association are scarce in current literature.

Objectives: To estimate the prevalence of seizure in different types of dementia and to investigate the association between dementia types and seizure in a large US longitudinal study.

Methods: The National Alzheimer's Disease Coordination Center (NACC) Uniform Data Set (UDS) is longitudinally collected from 29 Alzheimer Disease (AD) Centers across the US. The UDS from 2005 to 2011 was employed to conduct this retrospective cohort study. In the UDS, cognitive status and dementia was diagnosed and information of seizure and medical history was collected by clinicians. The association of seizure with cognitive status and dementia type was assessed by generalized estimating equations (GEE) models, after controlling for demographics and medical history.

Results: The study included 7,558 participants at baseline with a mean age of 75 years. Among them, 39.3% had AD dementia, 30.3% had amnestic MCI (aMCI), 7.6% had non-amnestic MCI (naMCI), 6.6% had non-AD dementia, 4.2% had AD dementia with other dementia (Mixed dementia), and 12.0% were cognitively normal (Normal). The prevalence of seizure was statistically significantly different across the groups, with the highest and lowest prevalences in non-AD dementia (4.8%) and Normal (1.2%) groups, respectively, and 2.6% in aMCI, 4.0% in naMCI, 2.4% in AD dementia, and 3.5% in Mixed dementia. Compared to the Normal group, the adjusted odds ratio of seizure was 3.1 (95% confidence interval [CI]: 1.3–7.1) for AD dementia, 3.7 (95% CI: 1.4–9.4) for non-AD dementia, and not statistically significant for other groups. Other factors statistically significantly associated with an increased occurrence of seizure included a history of seizure and cerebrovascular disease.

Conclusions: AD and non-AD dementia were found to be independently associated with increased odds for the occurrence of seizure, among other known risk factors. This analysis is consistent with reports of increased risk of seizure in those with AD and other types of dementia.

541. Withdrawn by Author.

542. Incidence of, and Risk Factors for Herpes Zoster in the HAART Era: An Analysis of the CHORUS Cohort

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Background: Data on the effect of highly active antiretroviral therapy (HAART) on the incidence of herpes zoster (HZ) are limited.

Objectives: Our objective was to estimate the HZ incidence among HIV infected subjects in the HAART era and to identify risk factors for developing HZ.

Methods: We conducted a retrospective analysis of data from the Collaborations in HIV Outcomes Research/US (CHORUS) Cohort on patients enrolled for at least 6 months between August 1997 and December 2004 (before licensure of a vaccine to prevent HZ), and ≥ 18 years at enrolment. Episodes of HZ were identified through ICD9 or free-text documentation of HZ following a period of at least 90 days without any HZ record. The individual person-time at risk was defined as the time between day 90 after enrolment and death, withdrawal from the cohort, or end of the study period, whichever came first. Overall HZ incidence and 95% confidence limits were estimated using a statistical model for recurrent events. The risk factors were analysed using a Cox regression model including time-dependent variables and controlling for centre effect.

Results: A total of 6,970 subjects were included in the analysis. The incidence of all HZ episodes among HIV infected subjects was 15 per 1,000 PY (95% CI: 13.56–16.62). A decrease trend for HZ incidence was observed from 1998 to 2004. The proportion of patients with recurrent HZ was 7.9% (95% CI: 5.3–11.1). In the univariate analysis, CD4 cells, CD4 nadir,

CDC clinical class and viral load were associated with the occurrence of an initial HZ episode. In the multivariate Cox regression model using backward selection, the risk of HZ was solely influenced by high viral load (compared with viral load < 400 copies/mL): HR 1.54 (95% CI 1.15–2.06) for 400–9,999 copies/mL, HR 1.88 (1.38–2.56) for 10,000–99,999 copies/mL and HR 2.18 (1.44–3.30) for > 99,999 copies/mL.

Conclusions: The incidence of HZ seems lower in the HAART era than what was reported in previous studies. The risk factor analysis highlighted a potential impact of high viral load on the risk for an initial HZ episode.

543. Diabetes as a Risk Factor for Herpes Zoster: Results of an Insurance Claims Database Study in the United States

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Background: Aging and immunosuppressive conditions are risk factors for developing Herpes Zoster (HZ). Few studies have evaluated the risk for HZ in persons with non-inflammatory co-morbid conditions and there is contradictory evidence about an association between diabetes and HZ.

Objectives: Assess whether diabetes is a risk factor for HZ and to quantify the risk.

Methods: We conducted a retrospective cohort study using the Integrated Health Care Information Services database including insurance claims data for 74 million individuals in the US. The study period was 1997–2006; ie before the introduction of a vaccine to prevent HZ. A type I diabetes cohort, a type II diabetes cohort and two non-diabetic cohorts matched on date of enrolment and length of follow-up were defined. HZ and diabetes were defined using a combination of ICD-9 codes and prescription drugs. Individuals with immunosuppressive conditions or treatments were excluded. Cox Proportional Hazards regression analysis using a stepwise method with backward elimination was applied to estimate the hazard ratios (HR) of HZ and related complications associated with diabetes.

Results: The study population comprised 380,401 and 20,397 Type II and Type I diabetic subjects respectively, as well as 1,521,604 and 81,588 control subjects. The HZ incidence was 4.59, 2.13, 1.97, and 1.82 per 1000 person-years, respectively. There was no evidence of an impact of type I diabetes on the risk of HZ.

Type II diabetes was associated with an increased risk for HZ with a HR of 3.12 (95% CI 2.77–3.52) in subjects ≥ 65 years of age and 1.51 (95% CI 1.42–1.61) in subjects between 40 and 64 years of age. Cardiac disease and chronic pulmonary disease were also risk factors (HR 1.92; 95% CI 1.73–2.13 and HR 1.52; 95% CI 1.38–1.67 in non-diabetic subjects).

Conclusions: This study suggests that type II diabetes is associated with an increased risk of developing HZ, which was particularly high in adults 65 years and older and moderate in adults < 65 years of age. Other chronic conditions appeared also as risk factors for HZ.

544. Profile of Patients with Gastric Cancer in the US Using Administrative Claims Data

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Background: Gastric cancer (GC) is the fourth most common cancer globally and an important cause of morbidity and mortality in the US. Prognosis is poor, treatment options are limited, and there has been little progress in improving outcomes over the last 25 years.

Objectives: To describe the demographic and clinical characteristics, mortality, healthcare utilization and cost of care for patients with gastric cancer.

Methods: GC cases aged ≥ 18 years, with at least two diagnosis codes for gastric cancer (first diagnosis is index) and 12 months pre-index history, were identified using the HealthCore Integrated Research Environment during 2007–2012. Cases were matched 1-to-10 with controls on age, gender, health plan type, and geographic region. Descriptive analyses were performed for pre- and post-index presence of pre-specified comorbidities, treatment patterns, healthcare utilization and cost, and mortality. Stratified analyses were conducted by patient age, cancer site, and coding for metastatic disease.

Results: There were 1,668 gastric cancer cases and 16,680 controls included: mean age was 66 years and 65% of patients were male. Comorbidity prevalence during the 12 month pre-index period was high; including GERD (11% in controls vs. 38% in cases), hypertension (50% vs. 60%), cardiovascular disease (24% vs. 34%), and liver disease (2% vs. 11%); incidence in the post-index period was also significantly higher in cases. Cases incurred more than 10 times the healthcare costs compared with controls ($96,571 vs. $8,338) during the follow-up period, particularly those

with advanced disease ($131,663). Three-year survival was 45% and 94% in cases and controls respectively (hazard ratio = 14.9). Chemotherapy and/or chemoradiation without curative surgery was the most common treatment pattern seen during the first 18 months of follow-up (53%); trastuzumab use was only detected in 11 patients.

Conclusions: GC represents a significant burden both to the individual and healthcare system, with considerably high costs, and high levels of comorbidity.

545. Posterior Reversible Encephalopathy Syndrome in the IMS Oncology Database: Case Definition, Epidemiology, and Patient Profile

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Background: Posterior Reversible Encephalopathy Syndrome (PRES) has been increasingly reported in cancer patients associated with cytotoxic and immunosuppressive agents; however, no population-based studies quantifying the epidemiology of PRES in the cancer population have been identified in the literature.

Objectives: To assess the case definition, epidemiology and patient profiles for PRES cases in the IMS Oncology database – a U.S. based oncology electronic medical records (EMR) and claims database.

Methods: A retrospective cohort study (2000–2011) of cancer patients was defined using the IMS Oncology Database. A combination of ICD-9 codes (for encephalopathy, seizures, visual disturbance, headache, and cerebral edema) and medical chart reviews was used to identify PRES cases. The identified cases were used to estimate PRES epidemiology and to report the PRES patient profiles.

Results: Among 604,903 cancer patients, 60 were selected using ICD-9 codes as potential PRES cases, but only six of those were considered possible cases of PRES after the medical record reviews, due to the unavailability of MRI findings and limited data to determine the temporality of events leading to diagnose PRES. The incidence rate of PRES was 0.37 (0.14–0.82) per 100,000 person-years; while the 11-year prevalence was 0.99 (0.36–2.16) per 100,000 persons. The most common patient characteristics observed were female gender (83.3%), age comprised 50–59 years (66.7%), Caucasian race (83.3%), diagnosis of bronchus or lung cancer (50%), and cancer-related medications (e.g. chemotherapy, anti-nausea/vomiting, or pain killers) (83.3%).

Conclusions: The rarity of PRES cases led to a limited description of the patient profile; however, due to the severity of this syndrome, it deserves to continue being monitored at clinical practice.

546. Prevalence of Depression in Patients with Type 2 Diabetes in Quebec: A Population-Based Cohort Study

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Background: Type 2 diabetes (T2D) is highly prevalent and is associated with a high health and economic burden. A higher incidence of T2D in depressed subjects compared to non-depressed has been observed for decades. In the last years a bidirectional association has been hypothesized and the association between T2D and the risk of subsequent depression has been shown.

Objectives: To assess the annual prevalence of depression in a population-based cohort of new oral antidiabetic drugs (OADs) users in the province of Quebec, Canada from 2000 to 2008.

Methods: Administrative claims data of the Public health insurance in Quebec were used to identify a cohort of new OADs users from 2000 to 2008 aged ≥ 18. All users with a prescription of OAD in the preceding year were excluded. Prevalent cases of depression were identified by one of the following criteria: (1) at least one service for depression claimed for inpatient care (2) at least two ambulatory care services for depression claimed in the same calendar year (3) at least one ambulatory care service for depression claimed with at least one prescription for an antidepressant drug in the same calendar year. Depressed patients were identified using ICD-9 or ICD-10 codes. The population of new OADs users in the current year was used as the denominator for the 1-year prevalence.

Results: Among the 188,659 new users of OADs in the period 2000–2008, 7,785 experienced a depression (4.13%). The prevalence of depression among newly treated diabetics was 4.29% in 2000, 4.42% in 2004 and 3.89% in 2008. In every year, the proportion of depression was higher among females than among males: in 2000 the prevalence was 5.40% among females and 3.08% among males. The prevalence of depression was greater within younger and middle-aged (6.75% for 18–44 years, 4.97% for 45–64 years, and 2.70% for > 65 years in 2008), in both sexes

(7.09% for 18–44 years vs. 3.53% for > 65 years among females, and 6.24% for 18–44 years vs. 1.82% for > 65 years among males, in 2008).

Conclusions: Depression is a common comorbidity among patient with T2D new users of OADs in Quebec. The prevalence is higher among females, younger and middle-aged.

547. Agreement Between Claims and Electronic Medical Records Data for CHF in Inpatients

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Background: Large electronic payer claims and electronic medical records (EMR) databases are frequently used for identifying cohort populations, covariates, or outcomes, but the accuracy of claims vs. EMR data is not well understood. Low accuracy may produce bias.

Objectives: To measure agreement between claims and EMR data (for ICD9 diagnosis code 428 for CHF) among hospitalizations.

Methods: *Design:* Retrospective study of hospitalizations (2002–2011) which had both payer and EMR data, and at least one ICD9 diagnosis of 428 (CHF) from either source. *Setting:* One large hospital system and one large healthcare payer in the Indiana Network for Patient Care. Children under 18 were excluded. *Exposures or interventions:* Two subgroups of hospitalizations: high-specificity (that is, more likely to have been for acute CHF exacerbation), based on at least one primary ICD9 diagnosis of 428, an echocardiogram performed, and a B-natriuretic peptide level > 500 pg/mL; and low-specificity, with no primary ICD9 diagnosis of 428, no echocardiogram, and no B-natriuretic peptide drawn. *Main outcome measures:* ICD9 codes in claims and in EMR data: We hypothesized that the agreement between claims and EMR would be higher in the high-specificity subgroup. *Statistical analysis:* Overall agreement and the Kappa statistic were calculated.

Results: Among 7,590 hospitalizations, an ICD9 code of 428 was in both data sources in 2,924 (39%), EMR only in 3,918 (52%), and claims only in 748 (10%). A primary diagnosis of 428 was in both sources in 1,018 (13%), EMR only in 284 (4%), claims only in 1,748 (23%), and neither source in 4,540 (60%) – overall agreement 73%, Kappa 35% (95% CI 32.8–36.9%). In the low-specificity group (N = 1,849), an ICD9 code of 428 was in both sources in 277 (15%), EMR only in 1,404 (76%), and claims only in 168 (9%). In the high-specificity group (N = 1,185), an ICD9 code of 428 was in both sources in 972 (82%), EMR only in 104 (9%), and claims only in 109 (9%).

Conclusions: Agreement between claims and EMR data was high (82%) among hospital stays likely to have been for acute CHF, and low (15%) among hospital stays less likely to have been for acute CHF.

548. Database Queries for Hospitalizations for Acute CHF: Flexible Methods and Validation Based on Set Theory

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Background: Large electronic payer claims and electronic medical records databases are frequently used for identifying cohort populations, covariates, or outcomes, but the accuracy of such clinical 'phenotypes' in multifaceted data is an ongoing challenge. Low accuracy may produce bias.

Objectives: (1) a flexible, overlapping (Venn diagram) set of query algorithms for identifying patients hospitalized with acute CHF, (2) a corresponding sampling strategy for chart review, (3) chart reviews to validate the presence/absence of acute CHF, (4) calculation of positive predictive value (PPV) and sensitivities, with standard errors.

Methods: *Design:* Retrospective study of hospitalizations (2002–2011) with some electronic evidence of CHF. *Setting:* The Indiana Network for Patient Care. Children under 18 were excluded. *Exposures or interventions:* Queries were based on any ICD9 diagnosis (428, 404.x1, 404.x3, 398.91), or ICD9 428 alone, for CHF, a primary diagnosis (any, or 428) for CHF, an echocardiogram performed, a B-natriuretic peptide drawn, or a B-natriuretic peptide level > 500 pg/mL. We used a hybrid between proportional sampling by Venn zone and over-sampling non-overlapping zones. *Main outcome measures:* Presence/absence of acute

CHF based on expert chart review using *a priori* criteria. *Statistical analysis:* PPV and sensitivities, and standard errors.

Results: Among 73,896 hospitalizations with some electronic evidence of CHF, we reviewed 870. The union of all queries with at least one ICD9 code for CHF had PPV 43.8% (SE 1.5%) for acute CHF and sensitivity 98.4% (12.5%). A primary diagnosis of 428 and B-natriuretic peptide level > 500 pg/mL had PPV 93.4% (SE 2.3%) and sensitivity 24.4% (1.1%). The zone in the Venn diagram with lowest PPV (< 10%) was this: ICD9 diagnosis of 428 that was not primary, no echocardiogram, and no B-natriuretic peptide drawn. The hospitalizations which, on chart review, were not for acute CHF were most often for other heart disease (e.g., coronary disease, arrhythmia), followed by lung disease (e.g., COPD, pneumonia).

Conclusions: This novel method successfully allowed flexible application and validation of queries for patients hospitalized with acute CHF.

549. Prevalence and Incidence of Idiopathic Pulmonary Fibrosis in UK Healthcare Databases, GPRD and THIN; Need for an IPF Registry

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Background: Idiopathic pulmonary fibrosis (IPF) is a fatal respiratory illness with limited treatment options. We previously estimated UK IPF prevalence in 2007 using The Health Improvement Network (THIN). We have now furthered this using the General Practice Research Database (GPRD).

Objectives: Calculate prevalence and incidence of IPF diagnoses in GPRD in 2010.

Calculate period prevalence of IPF diagnoses in GPRD in 2007; compare to THIN 2007 findings.

Methods: A descriptive cross-sectional study, using GPRD data.

Patients with a Read/OXMIS code corresponding to IPF diagnosis identified;

(1) H563.00 Idiopathic Fibrosing Alveolitis (IFA).
(2) H563z00 Idiopathic Fibrosing Alveolitis NOS (IFA NOS).
(3) H563.12 Cryptogenic Fibrosing Alveolitis (CFA).
(4) H563100 Diffuse Pulmonary Fibrosis (DPF).

To investigate coding variability, IPF diagnoses classified as;

(1) Broad (all).
(2) Narrow (IFA/IFA NOS).
(3) IFA + CFA.

Analysis;

(1) 2010 – Patients with first IPF record during 2010 classed as incident; prior to 2010 classed as prevalent.
(2) 2007 – Period prevalence calculated; patients with IPF record during 2007 classed as prevalent.

Results: In 2010 in GPRD, IPF was most commonly diagnosed in males (56.5%) and ≥65 year olds (80.8%). DPF was the most recorded code [prevalence: 39.4 (37.6–41.3) per 100,000 persons; incidence: 9.6 (8.8–10.6) per 100,000 person-years]. Broad definition prevalence was 50.7 (48.6–52.8) per 100,000 persons; incidence: 11.0 (10.1–12.0) per 100,000 person-years. Narrow prevalence: 10.1 (9.2–11.1) per 100,000 persons; incidence: 1.5 (1.1–1.9) per 100,000 person-years. IFA + CFA prevalence: 13.3 (12.3–14.4) per 100,000 persons; incidence: 1.6 (1.3–2.0) per 100,000 person-years. In 2007, compared to THIN findings, GPRD IPF period prevalence was lower in males and females, for all IPF diagnoses.

Conclusions: IPF rates differ among UK healthcare databases; this may be coding variability, which is an inherent limitation. Further analyses using ICD-10-CM codes is recommended as an IPF code (J84.112) has been issued, permitting specific IPF research. A prospective IPF registry is also essential to characterise this orphan disease, to better target future public health resources.

550. Incidence, Co-Morbidities, and Risk Factors of Age-Related Macular Degeneration

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Background: The natural history of Age-related Macular Degeneration (AMD) is largely unknown.

Objectives: To establish the incidence of AMD in a large cohort, and to identify co-morbidities and risk factors associated with this disease.

Methods: Data were extracted from The Health Improvement Network (THIN) database in the UK, of all individuals aged 20–89 years with a first recorded diagnosis of AMD between 1 January 2004 and 31 December 2009. Incidence rates were calculated

using the number of AMD cases and the corresponding person-years (py) at risk, sex and age stratified. A control group of 20,000 AMD-free individuals was randomly sampled from the source population and frequency-matched to AMD cases by age, gender, and calendar year of AMD occurrence. Logistic regression was used to examine co-morbidities and risk factors of four independent AMD categories. Results for AMD and wet (w)AMD are presented here.

Results: The incidence rate of AMD was 11.3 (95%CI: 11.1–11.5) per 10,000 py, while the rate of wAMD was 0.77 (95%CI: 0.72–0.83) per 10,000 py. After adjustment for age, gender, and number of primary care visits (PCVs), the odds ratios (OR) and 95% CIs for association of risk factors and AMD were: 2.23 (2.10–2.37) for diabetes; 1.93 (1.83–2.04) for cataracts; 1.39 (1.15–1.66) for inflammatory bowel disease (IBD); 1.17 (1.09–1.27) for smoking; 3.51 (3.20–3.85) for PCVs; 3.36 (3.13–3.61) for specialist referrals; 1.14 (1.07–1.21) for hospitalizations. The OR for wAMD were: 1.38 (1.15–1.65) for diabetes; 1.63 (1.39–1.91) for cataracts; 1.68 (1.06–2.68) for IBD; 1.23 (1.06–1.43) for smoking; 4.14 (2.95–5.83) for PCVs; 5.76 (4.40–7.54) for specialist referrals; 1.42 (1.21–1.68) for hospitalizations.

Conclusions: Overall AMD and wAMD patients had worse co-morbidity profiles than the AMD-free population. Yet, weak associations with AMD and wAMD were found for most co-morbidities. Diabetic patients had more than double the risk of developing AMD. No significant association was found with other co-morbidities, except for IBD, cataracts, and eye disorders. A positive association between AMD and smoking and obesity was found. Higher frequency of PCVs, referrals, and hospitalizations were found for wAMD patients.

551. The Epidemiology of Herpes Zoster (HZ) and Its Complications in Medicare Cancer Patients

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Background: The literature on the epidemiology of HZ in cancer patients (pts) is sparse, largely outdated, and does not include the elderly population.

Objectives: To determine the incidence of HZ and related complications (e.g., postherpetic neuralgia) and assess the risk factors associated with HZ in elderly cancer patients.

Methods: Elderly (≥ 65 years) patients with a cancer diagnosis in 1991–2009 were identified from the SEER cancer registry-Medicare linked database in this retrospective, longitudinal, open cohort study. The observation period spanned from first cancer diagnosis through the earlier of end of data availability or death. A random group of non-cancer Medicare patients were identified as controls. Cases of HZ (ICD-9 codes 053.0–053.11, 053.19–053.9) and HZ-related complications (e.g., cutaneous, visceral, neurological, ocular) were ascertained from medical claims. Unadjusted incidence rates (IR) and adjusted IR ratios, estimated through Poisson regression, were reported. Results were stratified by cancer site.

Results: The study population consisted of 82,832 hematologic (HEM) and 944,777 solid cancer pts (SOLID). During follow-up (mean 37.7 months for HEM; 52.1 months for SOLID), 9.3% of HEM and 6.3% of SOLID pts were diagnosed with HZ. The IR of HZ was significantly higher in HEM than SOLID pts (31.6 vs. 15.1 per 1,000 patient-years [PY], p-value < 0.01). The adjusted IR ratio was 2.38 times higher (95% CI = 2.32, 2.45) in HEM and 1.19 times higher (95% CI = 1.16, 1.21) in SOLID pts compared to non-cancer elderly pts. The proportion of patients with HZ-related complications was also higher in HEM than SOLID pts (18.7% vs. 16.7% of pts, p-value < 0.01). Age, gender, cancer therapy, and immunosuppression were statistically significant risk factors (all with p-values < 0.05) for developing HZ. Black patients were found to have lower risk for developing HZ relative to white patients (p-value < 0.01).

Conclusions: Elderly cancer pts run a 1.2–2.4 times higher risk of developing HZ than those without cancer. The rates of HZ and HZ-related complications are significantly higher among HEM than SOLID pts.

552. Benzodiazepine Use and Risk of Dementia: A Case–Control Study Using the Quebec Claims Database

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Background: We recently conducted a prospective cohort study in France, which highlighted an increased risk of dementia among incident users of benzodiazepines (BZDs). Because of the high incidence of dementia and the widespread chronic use of BZDs in the

elderly, such findings, if reproduced, would have a major public health impact.

Objectives: To conduct a population-based study in order to evaluate the association between BZD use and risk of dementia in the community-elderly population of Quebec (Canada).

Methods: A nested case–control study was undertaken using the Quebec medical services and prescription claims databases (RAMQ) between 2000 and 2009. The main cohort consisted of a random sample of elderly members (age 66+) with at least 6 years of follow-up. Dementia cases were identified through a diagnosis (index date) of Alzheimer's disease (ICD-9). For each case, four controls were matched on sex, age and duration of follow-up (incidence density sampling). Past exposure to BZDs was categorized into: past use: last BZD claim > 5 years before index date/recent use: first BZD claim < 5 years before index date/continued use: BZD claim > 5 years before and last claim < 5 years before index date/never use. The association between BZD use and dementia was assessed using multivariate conditional logistic regression.

Results: A total of 1,796 cases and 7,184 controls were identified. BZD use was associated with an increased risk of dementia in all time windows considered: odds ratio (OR) 1.94 (95% CI: 1.44–2.61) for past use, 2.00 (1.68–2.37) for recent use and 2.00 (1.76–2.26) for continued use. Adjustment for anxiety, depression and other psychotropic drugs did not change the results: OR 1.75 (1.30–2.38) for past, 1.55 (1.30–1.86) for recent, and 1.46 (1.28–1.67) for continued use.

Conclusions: BZD use was associated with an increased risk of dementia even after adjusting for anxiety, depression and other psychotropic use, which confirms our previous findings. Hence, we consider that BZDs are a major public health issue in the elderly.

553. Validation of the National Health Insurance Research Database in Taiwan with Acute Myocardial Infarction Cases

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Background: The population-based National Health Insurance Research Database (NHIRD) is a important for research of cardiovascular diseases; however, validation of the database in this disease area has not been reported.

Objectives: To evaluate the validity of AMI diagnosis in NHIRD by cross-comparison with that listed in medical records from a medical center.

Methods: Patients diagnosed with AMI in 2008 and were admitted to Cheng-Kung Medical Center (CKMD) in Taiwan were included in the evaluation. Detailed information relevant to the diagnosis of AMI was extracted from medical records, including chief complaints at admission (chest pain), ECG, laboratory data (CK, CK-MB, TnT), procedures (PCI, CABG, stent), and antiplatelet drugs. Extracted data were independently reviewed by two cardiologists to ascertain that the patients given the AMI diagnosis have indeed met the diagnostic criteria. Validation between NHIRD and medical records was performed on AMI diagnosis, related procedures, such as coronary interventions and stenting. Also evaluated was the consistency between the two data sources in aspirin and clopidogrel prescribing during hospitalization and at the first visit after discharge.

Results: A total of 349 AMI cases were extracted from medical records of CKMD, and 364 AMI cases were extracted from NHIRD. The matching rate of cases from the two sources was 90.66% (330/364); however, only 292 cases were confirmed to be true AMI cases by the reviewers, yielding a positive predictive value (PPV) of 88.5%. The PPV increased to > 90% (259/278 = 93.2%) when using principal diagnosis in NHIRD. In the matched sample, the PPV and negative predictive value (NPV) for PCI procedure were 94.2% and 82.9%, respectively. The PPV and NPV for CABG procedure were 78.3% and 96.1%, respectively. Between the two data sources, the agreement rate of clopidogrel prescription (92.4%) was slightly higher than aspirin (87.6%) during hospitalization, but both were lower after discharge (88.4% for clopidogrel and 85.9% for aspirin).

Conclusions: The NHIRD is a valuable source for pharmacoepidemiology research and drug safety surveillance in Taiwan.

554. Adverse Events of Ribavirin Plus Pegylated Interferon Combination Therapy for Hepatitis C Patients in Taiwan: A Population-Based Study

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Background: Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, cirrhosis, and liver cancer worldwide and no vaccine is currently available to prevent infection. Ribavirin plus pegylated interferon is a standard therapy to eradicate HCV infection and result in sustained virologic response; however, data related to the long-term adverse events of this combination therapy are still limited.

Objectives: Evaluate the long-term adverse events of ribavirin plus pegylated interferon combination therapy.

Methods: This retrospective longitudinal study obtained data from the Taiwan Cancer Registry, the National Health Insurance claims data, the treatment program for chronic hepatitis C, and death certification (2003–2009). Patients in the treatment group received combination therapy; patients in the control group received no treatment. Outcomes included the incidence of thyroid dysfunction and mood disorders. Cox proportional hazard model was used to control covariates, including age, sex, and comorbidity.

Results: Since 2003, when a program to reimburse hospitals for Hepatitis C treatment was launched, the number of patients receiving treatment has been increasing. After excluding patients with hepatitis B and alcoholic liver disease as well as those previously diagnosed with HCC, the treatment group included 38,087 patients. Treatment was associated with an increase in the incidence of thyroid dysfunction (HR 1.9, p < 0.001) and 1-year mood disorders (HR 1.81, p = 0.005).

Conclusions: Antiviral treatment using a combination of ribavirin plus pegylated interferon is associated with the increase of thyroid and mood disorders among patients with chronic hepatitis C.

555. Characteristics of Initiators of Asthma Maintenance Medications in 10 Health Care Populations

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Background: Level of asthma control can be a source of confounding in observational studies of medication-related asthma mortality. As part of a collaborative feasibility study of medication-related asthma mortality, we enumerated use of asthma medications across a distributed network of health care databases and explored variability in asthma control indicators among treatment groups.

Objectives: Describe characteristics of patients initiating different asthma maintenance medications and examine variation across 10 data sources.

Methods: In a cohort (n = 994,627) of persistent asthma patients aged 4–100 years enrolled at 10 US health plans (2001–2010), use of asthma medications was categorized. New use was first use of any study-defined asthma maintenance treatment medication on or after cohort entry without any prior recorded exposure of interest. We tabulated the frequency of three indicators of asthma control in the 6 months before new exposure in each treatment group, in the pooled cohort and across data sources.

Results: A total of 144,574 persons (14.5%) had new use: 42% aged ≥40 years, 56% female. The three most common treatments were salmeterol + fluticasone propionate (ADVAIR), n = 51,840; ICS monotherapy (ICS-m), n = 53,798; and ICS + leukotriene receptor agonist (LTRA), n = 26,994. ADVAIR users were older (52% ≥ 40 years vs. 33% ICS-m and 32% ICS + LTRA); this was consistent across the data sources. Overall, 13.2% had ≥ 1 asthma hospital stay or emergency room visit, ranging across data sources by exposure: ADVAIR, 8–17%; ICS-m, 7–16%; ICS + LTRA, 9–14%. Overall, 33% had ≥ 1 oral

corticosteroid dispensing–ADVAIR, 27–42%; ICS-m, 26–40%; ICS + LTRA, 27–52%–and 44% had ≥ 2 short-acting beta-agonist dispensings– ADVAIR, 44–55%; ICS-m, 49–66%; ICS + LTRA, 31–45%.

Conclusions: The observed variation in characteristics of exposure groups across data sources was beyond what would be expected from differences in size and demographics by health plan. Such information will be used in developing adjustment strategies for future pooled analyses of medication-related asthma mortality.

556. Using Automated Healthcare Databases to Study Insomnia in Real World

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Background: There are few studies about using large automated healthcare databases (AHD) to study insomnia, a condition which often is chronic and episodic in its' occurrence.

Objectives:

(1) To evaluate algorithms to identify subjects seeking healthcare for insomnia;
(2) To provide empirical evidence for the necessity of defining appropriate proxy measures to capture chronic progress of insomnia in AHD.

Methods: We compared two cohorts of adult subjects with either a principal diagnosis or any diagnosis of insomnia including medication use for insomnia from a US claim AHD between 1 January 2005 and 31 March 2011. Minimal 1 year continuous enrollment was required before subjects entered the cohorts. We defined Insomnia Chronic Period (ICP) as a continuous period, in which subjects kept seeking medical services related to insomnia. Incidence rates for preselected health outcomes (HO) during follow-up were calculated and then compared to either using or not using the constructed ICP measure in both cohorts.

Results: Ninety-three percent of subjects (14,955,634) with any diagnosis for insomnia had a principal diagnosis. The baseline characteristics, healthcare utilizations for insomnia and incidence rates for HO were similar in the two cohorts. However, the incidence rates (per 10,000 years) of HO were different when compared by ICP vs. non-ICP status in both cohorts (using principal diagnosis cohort as example): 33.2 vs. 7.6 (narcolepsy); 123.8 vs. 28.4 (excessive daytime sleepiness); 9.0 vs. 2.1 (complex sleep-related behaviors); 267.7 vs. 61.4 (falls); 6.0 vs. 1.4 (suicidality).

Conclusions: Using principal diagnosis to identify subjects seeking healthcare for insomnia captures the majority of subjects as compared to using combinations of any diagnosis and medication use for insomnia. However, our ICP analysis demonstrates the necessity of defining an appropriate proxy measure to capture chronic progress of insomnia to assess health outcomes associated with chronic insomnia. The challenges of finding appropriate proxy in AHD are discussed.

557. Risk of Upper Gastrointestinal Bleeding with Cyclo-Oxygenase-2 Inhibitors and Nonselective NSAIDs Plus Gastroprotective Agents: What To Prefer?

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Background: Strategies for prevention of upper gastrointestinal (UGI) events for non-selective (ns)NSAID users are replacement of the nsNSAID by a cyclo-oxygenase-2-selective inhibitor (coxib) or coprescription of a gastroprotective agent (GPA). Due to methodological issues of prior studies, which preventive strategy is superior in daily practice is unknown.

Objectives: To identify the risk of UGI events with these preventive strategies in daily practice.

Methods: Design: Nested case–control study within a cohort of all incident nsNSAID + GPA(≥ 80% adherence to coprescribed GPA; ≥ 80% adh) and coxib users(without GPA use) aged ≥ 50 years. Setting: Three primary care databases (UK, Netherlands, Italy). Outcome: UGI event(symptomatic UGI ulcer or bleeding [UGIB]). Cases were matched to UGI event-free cohort members on age, sex, number of UGI risk factors (UGI event history, age ≥ 65 years, concomitant use of anticoagulants, antiplatelets, or glucocorticoids) and calendar time. Statistical analysis:

Conditional logistic regression on patient level pooled data. Interaction terms were added to the model.

Results: Within the NSAID cohort (n = 617,220), 398 UGI event (UK: 307, NL: 17 and IT: 74) and 225 UGIB (UK: 194, NL: 14 and IT: 225) cases were identified. The risk of UGI events was equal for coxib and nsNSAID + GPA ($\geq$ 80% adh) users (OR: 1.0; 95% CI: 0.8–1.4) as was seen for UGIB (OR: 1.1; 95%CI: 0.8–1.7). In concurrent glucocorticoid users the risk of UGI events was significantly elevated for nsNSAID + GPA ($\geq$ 80% adh) compared to coxib use (OR: 9.0; 95%CI: 1.6–50.5), the interaction term was not significant. In non-antiplatelet users a non-significant increased risk for UGI events and UGIB for nsNSAID + GPA ($\geq$ 80% adh), whereas the opposite for concurrent antiplatelet use was observed (p < 0.001 and p = 0.008 for interaction terms).

Conclusions: The risk of UGI events and UGI bleeding was similar in nsNSAID + GPA ($\geq$ 80% adh) and coxib users. With concurrent antiplatelet use, coxib users are at increased risk of developing UGI events, whereas in patients concurrently using glucocorticoids a significant increased risk for UGI events for nsNSAID + GPA use was observed.

558. Harmonization of Diagnoses for Acute Pancreatitis Identification from Different Databases in the SAFEGUARD Project

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Background: The incidence rate (IR) of acute pancreatitis (AP) is increasing in Western countries due to increasing prevalence of etiological factors such as gallstones, obesity and alcohol use. Results from prior studies however differ due to heterogeneity on AP-definitions and data sources. Harmonization of diagnoses codes to identify AP across databases is therefore important before implementing multi database safety studies.

Objectives: To compare IRs of AP diagnoses across databases (DBs) from Western countries.

Methods: Data was retrieved from nine DBs from six Western countries participating in the Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project: Netherlands (IPCI, PHARMO), Italy (HSD, Regional DBs of Lombardy and Puglia), Germany (GePaRD), Spain (BIFAP), UK (CPRD) and USA (Medicare). Each DB covers different study periods between 1999 and 2012, depending on data availability, and comprises different types of data sources, electronic medical records or record linkage systems. Code mapping and harmonization of event extraction was performed to obtain homogeneous queries from different coding systems (ICD-9-CM, ICD-10-GM, READ and ICPC combined with free text) to identify potential AP events. Data was extracted locally from each DB without applying any restriction or exclusions criteria and processed using standardized software (Jerboa) providing age and gender specific IR and SIRs, using the WHO population as reference population, for AP per 100,000 person-years (PYs).

Results: From a source population of 35,279,358 subjects, 52,570 incident AP diagnoses during the study period were identified in 241,050,307 PYs. IRs increased with age in all DBs. Except for one DB showing quite high estimates, SIRs ranged from 6 to 15 for general practice DBs and from 8 to 24 for administrative DBs. Age-specific AP rates were higher for males than females.

Conclusions: Age-pattern of rates were similar across DBs. Harmonization workflows and code-mapping showed large heterogeneity across European DBs and the US DB. Further investigation is required to elucidate the observed difference.

559. Harmonization of Acute Myocardial Infarction Identification from Different Databases in the SAFEGUARD Project

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Background: Collaborative studies utilizing multiple healthcare databases (DBs) are increasing in the area of drug safety studies. However, an essential step in combining several types of DBs across different countries is to investigate, benchmark and harmonize event definitions and extraction.

Objectives: To compare incidence rates (IRs) and standardized incidence rates (SIRs) of acute myocardial infarction (MI) diagnoses among different DBs from EU countries and the USA.

Methods: Data was retrieved from nine DBs from six countries participating in the Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project: USA (Medicare), Netherlands (IPCI, PHARMO), Italy (HSD, Regional DBs of Lombardy and Puglia), Germany (GePaRD), Spain (BIFAP) and UK (CPRD). Each DB covers different study periods between 1999 and 2012, depending on data availability, and comprises different types of data sources (electronic medical records or record linkage systems). Code mapping and harmonization of event extraction was performed to obtain homogeneous queries from different coding systems (ICD-9-CM, ICD-10-GM, READ and ICPC combined with free text). Data was extracted locally from each DB without applying any restriction or exclusions criteria and processed using standardized software (Jerboa), providing age and gender specific IRs and SIRs, using the WHO population as reference population, for MI per 100,000 person-years (PYs).

Results: From a source population of 35,279,358 subjects, 364,151 incident MI diagnoses during the study period were identified in 239,591,637 PYs. Rates increased with age in all DBs, especially above age 45 years for males and above 60 years for females. Except for two DBs showing quite high estimates, SIRs ranged from 46 to 114 for general practice DBs and from 59 to 126 for administrative DBs. For all ages and across DBs the age standardized rates were higher for males than females.

Conclusions: Code mapping and harmonization of potential MI event extractions is important to understand differences between databases. Large heterogeneity across DB was observed, as expected, but harmonization is essential prior to implement drug safety multi database studies.

560. The Effect of Daily Dose of Individual NSAIDs on the Risk of HF in the Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS) Project

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Background: Limited data are available about the relationship between daily dose of NSAIDs and heart failure (HF) risk.

Objectives: Assess the dose–response relationship between individual NSAIDs and HF hospitalization.

Methods: Case-control studies, nested in a cohort of adult ($\geq$ 18 years) new NSAID users, were carried out in several European databases (DBs) as part of the EU-funded SOS Project. An initial dose-response analysis was performed in the PHARMO, a population-based DB recording demographic, hospitalization, and drug dispensing data (including the daily dose prescribed by the physician, the PDD) of over 3.2 million individuals in the Netherlands. Cases are patients with a first hospitalization for HF after cohort entry, and the date of hospital admission was defined as the index date. Cases were matched to up to 100 controls by sex, age, follow-up length and index date. The relationship between the PDD (transformed in daily dose equivalents, i.e. DDDs, and evaluated during the 14 days before index date) of each individual NSAIDs and HF risk was modeled through linear models and flexible models based on 2nd degree fractional polynomials (FP2s), implemented in a conditional logistic

model. FP2 regression models approximate the dose-response relationship by a function of two logarithmic or polynomial (with integer or fractional degree) terms. The best fitting model was selected on the basis of the AIC index. This initial analysis considered diclofenac, since this was the most used NSAID among HF cases in PHARMO.

Results: The case–control analysis showed that, in PHARMO, current users of diclofenac have an increased HF risk compared to past users (OR = 1.35, 95% CI: 1.21–1.50). Among the considered models, the linear one best fitted the data. From this, an OR = 1.03 (95% CI: 1.02–1.03) for a daily dose of 0.1 DDD in comparison to 0 DDD and an OR = 1.28 (95% CI: 1.17–1.39) for a daily dose of 1 DDD (100 mg of active principle) were estimated.

Conclusions: These preliminary results suggest that an increased HF risk was observed even at low doses of diclofenac.

561. Use of Glucocorticoids and 30-Day Mortality after Colorectal Cancer Surgery; A Nationwide Cohort Study in Denmark

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Background: Surgical treatment is crucial for cure in colorectal cancer. Preadmission glucocorticoids may affect mortality after surgery for colorectal cancer through immunologic, metabolic, cardiovascular, and tissue side effects.

Objectives: To examine 30-day mortality after surgery for colorectal cancer among glucocorticoid users compared to non-users.

Methods: This registry-based nationwide cohort study included all residents in Denmark (5.4 million) who underwent surgical treatment for colorectal cancer between 2001 and 2010. Individuals who filled their most recent prescription of systemic, inhaled or intestinal-acting glucocorticoids ≤ 90 days, 91–365, and > 365 days before the surgery date were classified as current, recent, and former users, respectively. Current users were subgrouped into new (first-ever prescription ≤ 90 days before the surgery date) and continuing users (others). For systemic glucocorticoids, we calculated prednisolone-equivalent doses. Cox proportional hazards regression was used to estimate mortality rate ratios (MRRs) and 95% confidence intervals (CIs) associating glucocorticoid use and 30-day mortality after colorectal cancer surgery, adjusting for candidate confounders.

Results: Of the 31,253 colorectal cancer patients included, 7,015 (22%) had prescriptions of glucocorticoids. Use of systemic glucocorticoids was associated with an increased mortality after colorectal cancer surgery among current users (MRR = 1.33, 95% CI: 1.07–1.65), but not among recent (MRR = 0.89, 95% CI: 0.65–1.20) or former (MRR = 1.03, 95% CI: 0.89–1.19) users. Among new users, MRR = 1.99 (95% CI: 1.35–2.94) and among continuing users, MRR = 1.18 (95% CI: 0.92–1.51). Among new users, MRRs increased from 1.66 (95% CI: 0.89–3.10) for a prednisolone-equivalent cumulative dose ≤ 500 mg to 2.27 (95% CI: 1.38–3.73) for doses > 500 mg. We found no clear association between use of inhaled or intestinal-acting glucocorticoids and mortality.

Conclusions: We observed increased 30-day mortality after colorectal cancer surgery among current users of systemic glucocorticoids and particularly those with new use. However, underlying disease activity may influence our findings.

562. Use of Disulfiram and Risk of Cancer: A Population-Based Case–Control Study

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Background: For decades disulfiram has been used to treat alcohol dependence. Experimental studies have demonstrated that disulfiram has growth inhibitory effects in melanoma, breast and prostate cancer cell lines.

Objectives: To evaluate whether use of disulfiram is associated with a reduced risk of melanoma, breast or prostate cancer in an observational study design.

Methods: By combining Danish nationwide administrative and health registers, we conducted a population-based case-control study nested within ever-users (≥ 1 prescription) of disulfiram. Cases were all Danish individuals who had a histologically verified first-time diagnosis of malignant melanoma, breast or prostate cancer between January 1st 2000 and December 31st 2009 and who had redeemed at least one disulfiram prescription 1 year prior to the cancer diagnosis. For each case, we selected four cancer-free controls among

ever-users of disulfiram matched by gender, birth year and year of first recorded disulfiram prescription. We estimated odds ratios (ORs) and 95% confidence intervals (CI) for cancer associated with long-term (≥ 500 daily defined doses) vs. one-time (one prescription) use of disulfiram, using logistic regression adjusting for general and site-specific confounders.

Results: Among 53,856 eligible disulfiram users during 2000–2009, we identified 166, 644 and 464 cases, respectively, with first-time melanoma, breast or prostate cancer. Adjusted ORs for the associations between long-term disulfiram use and risks of melanoma, breast or prostate cancer were 1.04 (95% CI: 0.60–1.78), 0.92 (95% CI: 0.70–1.22) and 0.77 (95% CI 0.56–1.06), respectively. Dose-response analyses revealed generally larger risk reductions with higher cumulative doses of disulfiram, however, the statistical precision of these analyses was limited and tests for trend did not reach statistical significance.

Conclusions: Our findings support a preventive effect of disulfiram against breast and prostate cancer. Further studies are warranted.

563. Harmonization of Outcome Extraction for Heart Failure Across Data Sources in the SAFEGUARD Project

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Background: The Safety Evaluation of Adverse Reaction in Diabetes (SAFEGUARD) project aims to estimate the relationship between use of glucose lowering agents and risk of selected events, including heart failure (HF), using data retrieved from nine databases (DBs), from six different countries. When combining DBs it is necessary: to identify a common definition of the outcomes under study, to map the outcome in each DB and to harmonize the extraction process. In particular the outcome harmonization is crucial to avoid inconsistencies between DBs.

Objectives: To compare standardized incidence rates (SIRs) of HF in the different DBs involved in the SAFEGUARD project for benchmarking purposes.

Methods: The data available in the project were retrieved from The Netherlands (IPCI, PHARMO), Italy (Lombardy, Puglia, HSD), Germany (GePaRD), UK (CPRD), Spain (BIFAP) and US (MEDICARE). The study period was between 1999 and 2012 depending on data availability. A terminology mapping was performed to provide a common definition for HF across DBs using different coding systems: ICD-9 (Lombardy, Puglia, PHARMO, HSD and Medicare) ICD-10 (GePaRD), READ (CPRD) and ICPC (IPCI and BIFAP). Some DBs used additional free text for the events' identification. Data extracted from each DB was processed using a standardized software (JERBOA), providing incidence rates and SIR for HF per 100,000 person-years (PY) using the WHO world standard population. The source population was the entire population covered by the DBs. The IRs and SIRs were calculated using the data available in the period covered by each DB without applying any restriction/exclusions criteria.

Results: Of 486,182 HF events were identified in 239,651,382 PY. Except for two DBs which provided higher estimate, the SIRs of HF ranged from 38 to 92 per 100,000 PY in administrative DBs and from 46 to 99 per 100,000 PY in medical records.

Conclusions: Although these results derive from the first extraction of the events in the SAFEGUARD project, the SIRs for HF seem to be consistent across most of the DBs. Further harmonization efforts are needed to identify any potential cause of inconsistencies.

564. Validation of Hospital Discharge Diagnoses and Laboratory Measurements To Identify Patients with Idiopathic Acute Liver Injury

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Background: The development and validation of algorithms to identify cases of idiopathic acute liver injury (ALI) is essential to facilitate future epidemiologic studies on drug-induced liver injury.

Objectives: To determine the ability of hospital discharge diagnoses codes and laboratory tests for liver damage to identify cases of idiopathic ALI within an administrative database.

Methods: In this retrospective cross-sectional study patients aged 18 years or older were selected from the Utrecht Patient Oriented Database (a hospital-based database comprising data on patient characteristics, laboratory test results, medication orders and hospital discharge diagnoses) between 2008 and 2010. Patients were initially identified using (1) algorithms based on ICD-9-CM codes indicative of idiopathic ALI and different sets of liver enzyme values (ALT > 2x upper limit of normal (ULN); AST > 1ULN + AP > 1ULN + bilirubin > 1ULN of which at least one of these > 2ULN; ALT > 3ULN; ALT > 3ULN + bilirubin > 2ULN; ALT > 10ULN) and (2) algorithms based solely on liver enzyme values (ALT > 3ULN + bilirubin > 2ULN; ALT > 10ULN). Patients with an ICD-9-CM code indicating a known other cause of liver injury were excluded in both algorithms. Hospital medical records were manually reviewed to confirm final diagnosis. The positive predictive value (PVV) of each algorithm for ALI was calculated.

Results: A total of 713 cases of ALI were identified. After review of medical records 194 patients had confirmed idiopathic ALI, of which 103 cases were associated with medication use. The PPV for (i) the algorithms with an ICD code as well as liver enzyme abnormalities ranged from 31% (11/36) to 47% (39/83) with the highest PPV found with ALT > 2ULN. The PPV for (ii) the algorithms with only liver test abnormalities was maximally 26% (153/599).

Conclusions: ICD-9-CM codes for idiopathic ALI in combination with abnormal laboratory test related to liver damage have the highest PVV scores, of which ALT > 2ULN has the best predictive value. Therefore this coding algorithm is the most efficient way for identifying idiopathic ALI cases.

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565. A Cohort Analysis to Measure the Effect of Orlistat or Bariatric Surgery on Weight and Body Mass Index in a General UK Population Sample

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Background: The efficacy of currently available treatments for obesity have been well characterised in randomised clinical trials, but their effectiveness in a general population is less well defined.

Objectives: To measure the change in weight and body mass index (BMI) after receiving either bariatric surgery or treatment with orlistat, in a general population sample.

Methods: We used electronic healthcare records from the United Kingdom Clinical Practice Research Datalink (CPRD). All patients with a record of bariatric surgery or any prescription for orlistat, and with at least 12 months prior research quality registration were included. Weight and height measures were extracted and in patients with an available height measure, BMI was calculated at all time points when weight was recorded. For patients who received orlistat and later had bariatric surgery, follow up in orlistat analyses was censored at the date of surgery. Patients receiving orlistat post-surgery were only analysed in the surgery group, with no censoring at first orlistat. Multilevel models were developed using repeated measures of weight and BMI after treatment, to characterise changes in these parameters over time following each intervention.

Results: We identified 2,474 patients undergoing bariatric surgery (median age 45 year, 82% female), and 94,464 receiving orlistat (median age 46, 77% female). Mean BMI before the intervention was 44.5 kg/m^2 (standard deviation [SD] = 8.7) for bariatric surgery and 37.2 (SD = 6.4) for orlistat. Subsequent measures of BMI were available for 80% bariatric surgery patients and 89% orlistat users. Mean follow up time post intervention was 2.3 years for bariatric surgery patients and 4.3 years for patients receiving orlistat. As a measure of short term effects, the mean first post-intervention BMI was 40.7 for surgery patients and 36.8 for orlistat users. More detailed results will be presented to further quantify changes in weight and BMI.

Conclusions: Our results will help to clarify whether the effects of orlistat treatment and bariatric surgery that have been demonstrated in clinical trials are carried over in broad clinical practice.

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566. Antidepressant Prescribing in Five European Countries: Application of Common Methods to Assess the Variation in Prevalence

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Background: Drug utilization studies have applied different methods on various data types to describe medication use which may hamper comparisons across populations.

Objectives: The aim of this study was to describe the variation in the prevalence of antidepressant prescribing, applying standard methods, in seven European electronic healthcare databases from five countries.

Methods: Patients prescribed with antidepressants were identified from databases from the United Kingdom (UK) (THIN and CPRD), Spain (BIFAP), Denmark (National prescription registry), Germany (Bavarian claims), and the Netherlands (Mondriaan-NPCRD/AHC) for 2001–2009. Annual prevalence per 10,000 person-years (PYs) was calculated. Prevalence data were standardized according to age/sex distribution of the 2008 European reference population. Stratification was done according to age, sex, antidepressant type (selective serotonin re-uptake inhibitor [SSRI] or tricyclic antidepressants [TCA]) and indications (only year 2008).

Results: The age- and sex-standardized prevalence was lowest in the two Dutch (391 and 429 users per 10,000 PYs) and highest in the two UK (913 and 936 users per 10,000 PYs) databases in 2008. Antidepressants were prescribed most often in 20–60 year-olds in the two UK databases compared to the other databases. Prescription of antidepressants was also very high in patients 70 years and older in Denmark with differences being profounder among females than males. SSRIs were prescribed more often than TCAs in all databases except in the German database. The proportion of patients with depression as the recorded indication varied between 12% and 57% in 2008.

Conclusions: Despite applying standard methods, variations in the prevalence of antidepressant prescribing were observed between the countries. These variations may be explained in terms of clinical factors as well as database characteristics such as level and frequency of the recorded information.

567. Is the CPRD GOLD Population Comparable to the U.K. Population?

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Background: GOLD, a UK primary care database held by the Clinical Practice Research Datalink (formerly GPRD), is a gold standard for primary care data and usage has resulted in > 890 clinical reviews and papers. It is important to understand how representative GOLD is of the UK population.

Objectives: To compare GOLD data to publically available UK Census, mortality, and practice data for 2011.

Methods: The number of patients actively registered on 27th March 2011 (census day) was compared to the 2011 UK census data, overall and by age, gender, and region. Using derived death dates, age-specific mortality rates (MR) were calculated in 5 year intervals. Age-standardised mortality rates (ASMR) using the European Standard Population were calculated by gender, overall and by country. Practice list size was defined as the number of non-temporary patients registered at each practice on 1 September 2011 for England and Scotland.

Results: There were 4.6 million patients on Census Day in GOLD, 7.3% of the UK population with little variation by gender but a lower representation of younger age patients. Crude death rates were nearly identical to national rates (8.70 per 1,000 vs. 8.69 in GOLD). ASMR in GOLD were lower than national rates by 11% in men (582.8 per 100,000) and 8.6% in women (426.9 per 100,000), with only slight variation by country. Age-specific MR's among the GOLD population ranged from 3% to 25% below those reported for the UK population except among children ≤ 10 years where MR's were more than 50% lower. The median list size was higher in GOLD practices (England 8,355 pts., Scotland 5,998 pts.) than for all England (5,918 pts.) and all Scotland (4,943 pts).

Conclusions: The GOLD population is generally representative of the UK population despite some underrepresentation in younger age groups. ASMR and age-specific MRs are slightly lower in GOLD with

variation by gender, larger in men, and age (pronounced in younger age groups). Practice sizes in GOLD are larger than the national averages. Possible reasons for the observed differences will be explored and discussed.

568. Effects of Glargine in Patients with Type 1 Diabetes in Belo Horizonte, Brasil

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Background: We question the relevance of providing free glargine in the public system, since recent studies do not support its superiority compared to NPH insulin and the cost of the drug is about 500% more expensive in Brazil.

Objectives: This paper intends to describe the usage profile of the drug in the public health system, including glycemic control of patients in order to support the manager in decision-making.

Methods: For a description of the usage profile of glargine was built a historical cohort of patients assigned to the Regional Health of Belo Horizonte diagnosed with type 1 diabetes mellitus, who received the drug during the period from June 2009 to January 2011. The variable glycemic control was built, considering the appropriate control value of glycated hemoglobin $\leq 7.0\%$ for patients from 20 years, $\leq 7.5\%$ for patients between 13 and 19 years and $\leq 8\%$ for patients under 12 years. For all statistical analysis was adopted significance level of 5%.

Results: Of the 393 patients studied, 57.5% were female, with a mean weight of 61.16 (SD 15.08) and prevalence in the age group of 20–39 years (39.9%). The average daily dose of glargine prescribed was 34.18 IU (SD 15.05 IU). 21.4% of patients had at least one prescription determining the use of the drug twice a day or more. The mean levels of HA1c remained high in all measurements, with a maximum reduction of up to 1 percentage point in about 67 months of follow-up. Adequate control medium was 28% throughout the observation period. On average 12% of patients benefited from treatment compared to baseline. Among the results considered controlled 40% on average were $\leq 6.5\%$ indicating increased risk of hypoglycemia. On average 61% of the measures were HbA1c > 8%. There was an increase of inadequate control during the follow-up. The change of HA1c ranged between -0.39 and 0.16 over time.

Conclusions: The results found no more effective or fully proven convenience in the use of glargine. It is suggested to the public health manager to disinvest or renegotiate the prices with the manufacturer. In search of better evidence additional studies must be realized including about self-management of diabetes programs.

569. Translating Prescribing Data into Practice – Down Under

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Background: Primary care doctors in Australia have widely adopted the use of electronic health records (EHRs) in clinical encounters. Data contained in these records are an untapped source of valuable information to improve prescribing practice by identifying trends, gaps or unintended harm.

Objectives: NPS MedicineWise will establish an Australian longitudinal database as part of a quality improvement program with nationwide indicators of prescribing behaviours and clinical practice. As a first step, an understanding of the barriers and facilitators for GPs participation is needed.

Methods: The database will collect routine clinical data from EHRs of 500 practices with a population base of approximately two million patients – a strong representative sample size of the 22.6 million Australian population. The needs assessment to underpin this program used qualitative and quantitative methods to elicit barriers and facilitating factors. We collected data from doctors, nurses, patients and other stakeholders.

Results: The program must clearly communicate the benefits to doctors and show improvements in clinical care and outcome improvements for patients. The major barriers to the uptake of this program in Australia were concerns associated regarding: privacy, confidentiality, security, data governance, technology functionality, how the data will be used and the effectiveness of the practice improvement data-driven interventions.

Conclusions: A national program to establish automated data collection from primary care EHRs will provide invaluable information for pharmacovigilance and pharmacoepidemiological research, and inform

clinical practice improvement. A fit-for-purpose technology solution is essential, but not sufficient for successful implementation. Critically, we must specify how the data will be translated into useful and usable information to influence practitioner behaviour and ensure a representative sample of participating general practices.

570. Times Trends in Antihypertensive Drug Use and Hypertension in Cohort Database 2005–2009 of Employees of Oil and Gas Mining in East Kalimantan, Indonesia

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Background: There is limited data on time trends in utilization of antihypertensive drugs in Indonesia.

Objectives: To describe long-term trends in antihypertensive drugs and hypertension in cohort database 2005–2009 of employees of oil and gas mining in East Kalimantan, Indonesia.

Methods: Design: A cohort retrospective study. Setting: Data was extracted from electronic employee records in cohort database. All employees with a recorded of medical checkup who consulted the general practitioner between 2005 and 2009 were included (n = 6,638). Clinical data of patients with hypertension (n = 593) linked to data on dispensed antihypertensive drugs (n = 16,001) to monitor drug utilization over time. Exposures or interventions: Antihypertensive drugs. Main outcome measures: Proportion of employees/patients with hypertension, the percentage of dispensed different antihypertensive drugs. Statistical analysis: t-test, analysis of variance and Chi square test.

Results: The proportion of employees with hypertension decreased by 3% from 10% in 2005 to 7% in 2009 (p < 0.05). The number of patients with hypertension decreased by 50 percent from 145 patients in 2005 to 72 patients in 2009 (p < 0.001). The dispensed of ACE inhibitors, calcium channel blockers, angiotensin II antagonists, beta blocking agents, diuretics, selective calcium channel blocker with direct cardiac effects, angiotensin II antagonist in combination with diuretic 31.8%, 22.5%, 16.5%, 9.7%, 9.6%, 7.9%, 2% in 2005 to 27.6%, 21.8%, 17.2%, 10.1%, 4.5%, 4.7%, 14.1% in 2009 respectively (p < 0.001). During the same period there were decrease in the use of ACE inhibitor and increase of angiotensin II antagonist in combination with diuretic (p < 0.001).

Conclusions: There is a positive trend in the proportion of patient with diagnosed hypertension that change to normotension. The explanation may be by changing the pattern of antihypertensive drugs.

571. Utilisation Patterns of Inhaled Corticosteroids in Patients with Asthma: A Study Using the UK Clinical Practice Research Datalink (CPRD)

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Background: Inhaled corticosteroids (ICS) are used for the treatment of asthma requiring regular preventer treatment. The British Thoracic Society (BTS) asthma treatment guidelines describe a stepped management system (steps 1–5) where patients step up and down based on their level of asthma control.

Objectives: To calculate utilisation rates of different ICS pharmacological substances in the CPRD population and the proportion of patients assigned to different treatment steps during the study period.

Methods: Asthma medicine use was mapped for each patient with asthma on the CPRD using prescription data from 1 January 98 to 31 December 10. Combinations of treatments were assigned to each of the BTS asthma management steps. Monthly utilisation rates were calculated for each pharmacological substance stratified by age. The proportion of patients assigned to each BTS step was calculated for each month of the study period.

Results: Utilisation of ICS increased with increasing age, from ~35% of children to > 60% of elderly patients. There was a seasonal pattern of use in children that disappeared with increasing age. There was a rapid increase in the use of combined ICS + long-acting β2 agonist (LABA) products from 1999 to 2010. This was particularly significant in adults and patients on Steps 4 and 5 where more than 50% of patients were being prescribed ICS + LABA combination inhalers by mid-2004. The majority of patients (85–92%) using ICS products other than fluticasone were prescribed standard dose ICS (BDP equivalent dose ≤ 800 μg/day) whereas 58% of patients using fluticasone were prescribed high doses. The proportion of patients on each BTS asthma management step was stable during the study period with the proportion of patients on steps 3–5 increasing with increasing age.

Conclusions: Utilisation patterns of ICS changed significantly in the UK between 1998 and 2010 with a rapid increase in the use of ICS + LABA combined inhaler products. Utilisation rates revealed a decrease in patterns of seasonality and an increase in the use of

higher doses of ICS with increasing age reflecting an increased chronicity and severity of asthma with increasing age.

572. Anticholinergic Load as a Modifiable Risk Factor of Sitter Use in Acute Care Hospitals

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Background: Patient sitters are unlicensed assistive health care providers whose function is to provide close surveillance to patients at risk of harming themselves or others. Prior research has provided evidence that psychotropic drugs are associated with a higher likelihood of sitter use in acute care hospitals. However, the mechanisms linking psychotropic drugs to sitter use is unknown.

Objectives: The aims of this study were to describe the prevalence and characteristics of three potentially modifiable pharmacological mechanisms that may account for this association (namely the anticholinergic load, drugs not adjusted for renal function, and drug-drug interactions), and their association with sitter use.

Methods: A retrospective case–control study was conducted. All medical patients 65 years and older who received a sitter (cases) were selected from a cohort of 43,212 patients who had been admitted to an academic health centre in Montreal (Canada) in 2010. For each case (n = 143), one control was randomly selected among all medical patients 65 years and older who did not receive a sitter. For each patient we determined the: (1) number of psychotropic drugs that were non-adjusted for renal function; (2) total anticholinergic load; (3) number of clinically significant drug-drug interactions. Multivariate logistic regression was used to assess the association between sitter use and the three pharmacological mechanisms, while controlling for patient demographic characteristics and comorbidities and other risk factors for sitter use.

Results: Compared with controls, patients with sitters had a higher overall anticholinergic load and more drug–drug interactions in the period prior to sitter use. In multivariate analysis, every additional drug with an anticholinergic load of 1 increased the likelihood of sitter use by 1.4 (95%CI: 1.1–1.7).

Conclusions: To decrease sitter use in elderly patients, physicians should prescribe, when possible, drugs with a low anticholinergic load.

573. Use of Antidepressant Drugs Among Diabetic Population: A Prescription Sequence Symmetry Analysis

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Background: Diabetes mellitus (DM) is a chronic disease that has many implications on general health and well being. There is growing evidence that DM is associated with higher incidence of depression but there are some issues with studies reporting higher incidence, like lack of control groups and questionnaire only studies. Antidepressant drugs are corner stone of treatment of depression. It remains unclear whether there is an association between onset of diabetes mellitus and subsequent use of antidepressant drugs.

Objectives: To study association between diabetes mellitus and use of antidepressant drugs by the method of prescription sequence symmetry analysis.

Methods: We used prescription data from Odense Pharmacoepidemiological Database (OPED) for the period of 1 January 2002–31 December 2007 to perform prescription sequence symmetry analysis. We retrieved all prescriptions of drugs used to treat DM with ATC code A10 and all antidepressant drugs that have an ATC code N06A from OPED. Crude and adjusted sequence ratios (ASR) with 95% confidence intervals were calculated.

Results: We identified 272 incident users who started treatment with drugs used to treat diabetes (ATC A10) and then with in specified period of time began treatment with one of antidepressant drugs with ATC N06A. Adjusted sequence ratio for this group was 1.67. ASR for ATC group A10A (Insulins) and A10B (Oral Hypoglycemic Agents) were calculated and were shown to be 1.98 and 1.65 respectively.

Conclusions: This study suggests that treatment of diabetes mellitus is associated with subsequent use of antidepressant drugs.

574. Therapeutic Consequences of Dextropropoxyphene Withdrawal in France

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Background: Dextropropoxyphene (DXP) is an opioid analgesic used to treat mild pain. Given the European decision of its withdrawal due to concerns of fatal overdoses and arrhythmias, it was removed from the French market in March 2011. Therapeutic consequences of this withdrawal have been little investigated in France.

Objectives: To describe dispensing patterns of DXP before withdrawal and to determine which analgesic drugs have replaced DXP afterwards.

Methods: An extraction of aggregated data from 2009 to 2012 was obtained from claims data from the French Rhone-Alpes Region (6 million inhabitants) for a selection of analgesic drugs including step-1 analgesics (acetaminophen, celecoxib), step-2 analgesics (DXP, codeine, dihydrocodeine, tramadol, lamaline) and step-3 analgesics (morphine, hydromorphone, buprenorphine, pethidine, Fentanyl, oxycodone, methadone). The changes in dispensing levels were studied during a period (2009–2012) including DXP withdrawal in France (March 2011). Time-series analyses approach was used.

Results: *Preliminary Results:* A two-stage downward trend was identified for DXP use, with an initial drop during summer 2009, followed by a 16-month plateau before complete dispensing cessation in spring 2012 (effective withdrawal). Among overall dispensing of selected analgesics, we observed an increase in the annual parts of acetaminophen, codeine and tramadol, in parallel to a decreasing use of DXP. DXP was mainly replaced by acetaminophen (from 71% to 79%) and, to a lesser extent by codeine (4–7%) and tramadol (8–11%). The time-series analysis test was statistically significant for acetaminophen (p < 0.0001). No substantial change was identified for other drugs.

Conclusions: DXP was mainly replaced by acetaminophen, and partially by tramadol and codeine. These preliminary results will be confirmed from the national claims data (EGB database, a 1/97th sample of the French population) on an extended study period (2003–2013), and using more elaborated analyses (including prescriber and patient-related data). The hypothesis of DXP storage by patients will also be investigated and analyses will be further extended to NSAIDs.

575. Changes in Therapeutic Management of COPD Between 2006 and 2001: French Claims Data

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Background: The management of COPD has changed in recent years, with the launch of new therapy.

Objectives: We investigated the changes in dispensed therapy in a cohort of COPD patients between 2006 and 2011.

Methods: A cohort of patients aged ≥ 45, with a follow-up documented from 2005 to 2011, and ≥ 3 dispensations in 2005 of a same drug-class were selected in French Claims data (EGB). Drug classes were long-acting beta agonists (LABAs) except those in fixed combinations with inhaled corticosteroids (ICS), short-acting beta agonists (SABAs), short-acting muscarinic antagonist (SAMAs), xanthines, SAMA/SABA fixed combinations. For each patient, the percentages of annual users (at least one dispensing) were determined for the different drug-classes, both for respiratory therapy and non-specific drugs from 2006 to 2011.

Results: In this cohort of 3,438 patients (mean age 66.4, 54.5% women), a decrease in the percentages of annual users were observed between 2006 and 2011 for LABAs (from 33.8% to 23.5% p < 0.0001) and SAMA/SABA fixed combinations (from 22.2% to 7.7% p < 0.0001), in favour of LABA/ICS fixed combinations (from 43.3% to 50.8% p < 0.0001) and LAMAs (from 13.6% to 24.7% p < 0.0001). Dispensing levels of antibiotics and systemic steroids remained high throughout follow-up period (68.1% and 46.2% in 2011, respectively), without any noticeable change over time. This was also the case for anxiolytics,

antidepressants and antitussives (36.5%, 21.4% and 21.4% in 2011, respectively).

Conclusions: In this cohort of COPD patients, medical management has noticeably changed over time, with a more common use of LAMAs over time, probably due to its prolonged clinical effect. Claims data allow observing long-term changes in drug therapy management of chronic diseases.

576. Comparison of Six Electronic Healthcare Databases in Europe Using Standardized Protocols: A Descriptive Study on the Incidence of Cancer

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Background: There are several national cancer registries available across Europe, but information on cancer incidence from routine electronic healthcare record (EHR) databases (DBs), such as General Practitioners (GPs) and comparisons across different databases are rather scarce. It is important to compare this information, and also benchmark this against national registries in order to assess its usefulness for pharmacoepidemiological studies on cancer.

Objectives: To investigate sources of variation in the incidence of Cancer across routine EHR DBs in Europe, using a standardized methodology.

Methods: We used six EHR DBs from Spain-ES (BI-FAP), the United Kingdom-UK (THIN and CPRD), the Netherlands-NL (Mondriaan: AHC and NPCRD), and Denmark-DK (National registrations of patients-NRP). Cancer incidences were calculated for the whole population between 2003 and 2008 and were stratified by sex, age and type of cancer (breast, prostate and colon). Overall incidence rates were age and sex standardized to the European 2008 reference population.

Results: The initially observed variation in cancer incidence decreased after standardization and ranged for any cancer from 25.2/10,000 in the NL (NPCRD) in 2004, to 71.5/10,000 in the DK (NRP) in 2008. The incidence of cancer increased in DK and doubled in NPCRD between 2003 and 2008, but decreased in BI-FAP and THIN. Cancer incidence was higher for women in all DBs, except for BIFAP and AHC. In 2008, the incidence of breast cancer was the highest in the NPCRD (37.6/10,000) and the lowest in BIFAP (9.1/10,000), while the incidence of prostate cancer was the highest in DK (15.9/10,000). No major differences were observed between countries regarding colon cancer.

Conclusions: The incidence of cancer as measured in six routine EHR DBs differed between the four European countries using a standard methodology, despite the convergence seen after standardization for age and sex. Overall cancer incidence increased over time for most of the European countries, except for Spain. From our analysis we can infer that incidences are in line with the European cancer registries available.

577. Identifying Drug-Safety Signals in Electronic Health Records: An Evaluation of Automated Case-Detection Algorithms with Different Sensitivity and Specificity

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Background: Recent studies have shown the feasibility of using automated machine-learning methods to generate case-detection algorithms using both structured data and un-structured free-text in electronic health records (EHRs). An advantage of such automated methods over manual methods is that they allow generation of several variants of a case-detection algorithm with different sensitivity and specificity levels.

Objectives: To evaluate automatically generated case-detection algorithms with different levels of sensitivity and specificity in their ability to identify drug-safety signals in EHRs.

Methods: A training set of 3,988 patients was created by searching the IPCI (Integrated Primary Care Information) database for ICPC codes and keywords related to acute renal failure. The set was manually annotated by two medical doctors. A rule learning algorithm was used on the training set to generate several case-detection algorithms with different levels of sensitivity and specificity as measured on the training set using cross-validation. For a reference set of positive and negative control drug-outcome pairs the relative risks were computed using an incidence rate ratio (IRR) adjusted for age and sex, and using a self-controlled case series (SCCS) analysis. For every case-detection algorithm we then computed the area under the receiver operating characteristics curve (AUC) by varying the relative risk threshold and comparing it with the reference set.

Results: The sensitivity of automatically generated case-detection algorithms varied from 0.71 to 0.90, with corresponding specificity varying from 0.89 to 0.43. When using the IRR, the AUCs varied from 0.49 to 0.79. For SCCS, the AUCs varied from 0.44 to 0.76. We observed that case-detection algorithms with high sensitivity lead to identification of more drug-safety signals in EHRs.

Conclusions: Several automated case-detection algorithms with different sensitivity and specificity levels were evaluated. However, further experiments are needed to validate the association between algorithms with high sensitivity and more drug-safety signals in EHRs.

578. Standard Method for Assessment of Electronic Health Record (EHR) Data Sources for Pharmacoepidemiology

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Background: Selecting the correct data source for conducting medical research is essential and challenging. This is particularly true for the selection of an electronic health records (EHR) data source. We developed a method to rate the extent to which an EHR data source can be used for epidemiological research, to guide data source selection.

Objectives: To quantify the viability for conducting epidemiological research in eight EHR-based healthcare data sources.

Methods: We assembled a 47-question survey to assess available data elements and data types based on the needs of epidemiological studies. We then completed the survey for EHR data source from eight healthcare institutions, including three large regional academic systems, two large national healthcare systems, and one large regional community healthcare system; as well as two national healthcare databases. Answers to the survey were categorized 'yes' or 'no', with the 'no' category encompassing 'unknown' responses. Viability of conducting research was determined by percentage of 'yes' responses for each data source.

Results: The crude mean for 'Yes' responses was 87.5% across all institutions, with scores ranging from 100% to 70% viability (Institutions randomly represented by letters A–H): A. 100%, B. 96%, C. 89%, D. 79%, E. 70%, F. 91%, G. 98%, H. 77%.

Conclusions: Although all institutions examined allowed for acceptable levels of viability in conducting epidemiological research, heterogeneity of viability suggests that vigilant data source selection is necessary.

579. Risk of Fracture with Thiazolidinediones: An Individual Patient Data Meta-Analysis

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Background: Observational studies have provided contrasting results regarding sex difference and the type of fractures for users of thiazolidinediones (TZDs). This may be due to differences in study designs, study populations, the recording of fractures, and other potential causes of bias.

Objectives: (1) to compare patient characteristics of TZD users and the occurrence of fractures across three different healthcare registries, (2) to estimate the risk of fracture with TZDs in three different healthcare registries, using exactly the same study design, (3) to perform an individual patient data meta-analysis of these studies.

Methods: Population-based cohort studies were performed utilizing the British Clinical Practice Research Datalink (CPRD), the Dutch PHARMO Record Linkage System and the Danish National Databases. In all three databases, the exposed cohort consisted of all

patients (aged 18+) with at least one prescription of antidiabetic (AD) medication (GPRD: n = 196,024, PHARMO: n = 123,452, Denmark: n = 180,049). Cox proportional hazards models were used to estimate hazard ratios (HRs) of fracture with TZD use, using a time-dependent design. This was done in every database separately and we combined all records in an individual patient data meta-analysis.

Results: The proportion of patients who were prescribed a TZD was lower in Denmark (4.2%) than in the CPRD (19.5%) and PHARMO (12.2%). Incidence rates of fracture were much higher in Denmark than in the CPRD and PHARMO. In all three registries, the risk of fracture was increased for women who were exposed to TZDs: HR 1.5 [1.4–1.6] in CPRD, HR 1.4 [1.2–1.6] in PHARMO and HR 1.2 [1.0–1.4] in Denmark. Combining the data in an individual patient data meta-analysis resulted, for women, in a 1.4-fold increased risk of any fracture for current TZD users vs. other AD drug users (HR 1.4 [1.3–1.5]). For men, there was no increased fracture risk. Risks were increased for fractures of the radius/ulna, humerus, tibia/fibula, ankle and foot, but not for hip/femur or vertebral fractures.

Conclusions: We consistently found a 1.2- to 1.5-fold increased risk of fractures for women using TZDs, but not for men, across three different healthcare registries.

580. Using Natural Language Processing To Identify US Veterans with Binge Eating Disorder

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Background: Binge eating disorder (BED) does not have a specific ICD-9 diagnosis code but is included under the non-specific code for 'eating disorder, not otherwise specified' (EDNOS).

Objectives: Identify patients with clinician-diagnosed BED in the Department of Veterans Affairs (VA) healthcare system and compare the baseline characteristics to patients with an EDNOS diagnosis without BED (EDNOS-only).

Methods: A natural language processing (NLP) tool was developed to identify patients with clinician-diagnosed BED using narrative clinic notes from electronic medical records. Researchers manually reviewed 1,000 records to assess the tool's ability to correctly identify patients with BED. Patients with a diagnosis of EDNOS were identified separately by ICD-9 code. Adult veterans with BED or EDNOS between 2000 and 2011 were included if they had ≥ 1 year of activity before and after index date (defined as the first mention of BED or diagnosis of EDNOS), BMI measurement on index date (± 60 days), and no diagnosis for other eating disorders. Baseline characteristics were compared between groups using t-tests and chi-square tests as appropriate with a p-value < 0.05 considered significant.

Results: From the national VA system, the NLP tool was run on 193,450 clinic notes that contained a mention of binge eating in order to identify patients with a confirmed BED diagnosis. NLP classification accuracy was 91.8% compared to human review. The study included 593 patients identified by NLP to have a confirmed BED diagnosis and 1,354 patients with EDNOS-only that met all eligibility criteria. For BED and EDNOS-only patients, mean (SD) for age was 48.7 (10.3) and 49.8 (12.5) years (p = 0.04) and mean for BMI was 40.2 (9.9) and 37.0 (11.2) kg/m^2 (p < 0.001), respectively. More BED patients were male (72.2% vs. 62.8%, p < 0.001) and fewer were white (71.2% vs. 75.6%, p = 0.06) compared to EDNOS-only.

Conclusions: Though there is no ICD-9 diagnosis code for BED, we were able to identify patients with BED in the VA system using NLP with > 90% accuracy. Compared to EDNOS-only, BED patients tended to be younger, more obese, and were more likely to be male. Future work will include further analysis of these cohorts.

581. Validity of the Duration of Inhaled Corticosteroid Prescription and the Number of Allowed Refills Recorded in Québec Databases

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Background: Adherence is a major issue in asthma and the Quebec claims database have been widely used to measure it. However, the duration of the prescription (Rx) and the number of allowed refills, database variables used to measure adherence, have never been validated.

Objectives: To validate the duration of inhaled corticosteroid (ICS) Rx and the number of allowed refills recorded in Quebec databases against the duration of ICS Rx and allowed refills written on the Rx sheet.

Methods: We selected a representative sample of 390 Rx of ICS dispensed in 40 pharmacies in Quebec to patients aged 18–44 years old. The duration of the ICS Rx and the number of allowed refills were collected from the patient's pharmacy electronic record (PER) [data electronically transferred to the database] and compared with the information written on the Rx sheet. From both sources of data, the number of days covered by the Rx (number of refills × duration) was calculated. The concordance between the PER and the Rx sheet was estimated using intraclass correlation coefficients (ICC) for the number of allowed refills and the number of covered days. We also calculated the percentage of agreement between the duration of the Rx recorded in the PER and the one calculated using the dosage written on the Rx sheet.

Results: In our sample, 53% of the Rx were for Flovent®, 16% Symbicort®, 13% Advair®, 11% Pulmicort®, 5% Alvesco® and 2% Qvar®. The level of agreement for the duration of the Rx was 62.9%. According to the ICS molecule dispensed, the agreement varied from to 0% to 83.3%. The ICC for the number of refills between the PER and the Rx sheet was 0.97 (95% CI: 0.97–0.98), while it was 0.91 (0.89–0.93) for the number of days covered.

Conclusions: The level of concordance was very high for the number of refills and the number of days covered, and moderate for the duration of the Rx. We are developing an algorithm based on the molecule and the formulation to improve the validity of the duration of the Rx recorded in the PER. We also plan to perform the same analyses among patients aged 0–17 and 45–65 years.

582. A New Method To Get Fast Patient Reported Outcomes Data from Primary Care in the UK for Patients With Atrial Fibrillation (AF) in the Health Improvement Network (THIN)

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Background: A study to assess AF symptom burden and health related quality of life (HRQOL) aimed to recruit 500 newly diagnosed AF patients and 500 matched controls using THIN data. Patient recruitment using precollected primary care data offers advantages, so response rates and completeness of disease classification were quantified.

Objectives: To quantify GP and patient recruitment rates and completeness of AF classification for newly diagnosed AF patients and controls.

Methods: Cases of newly diagnosed AF and matched controls were identified as soon as data were received from practices (usually within 1 week of diagnosis). GPs were contacted by THIN staff and asked to confirm patient eligibility and AF type. GPs then invited eligible patients to participate, thus maintaining anonymity. Patients were asked to complete HRQOL questionnaires at enrolment, 6 and 12 months. GPs received payment for completing questionnaires but patients were not incentivised. Response rates were calculated and AF classification analysed.

Results: GP response rate was 82% (3,632/4,412), providing 2,383 eligible patients. Response rate was slightly higher for controls than AF patients, 54% (615/1,144) vs. 47% (586/1,239), giving an overall patient response rate of 50% (1,201/2,383). Within 18 months, this method successfully recruited beyond the necessary sample size (516 matched case–control pairs). GPs classified AF type for 63% of AF patients (114 permanent, 51 persistent and 158 paroxysmal).

Conclusions: GP and patient response rates were high, despite the long-term commitment to the study, allowing successful recruitment. AF type is usually assigned in hospital but GPs were able to provide AF type for many patients. Using THIN data, differences between patient responders and non-responders can be investigated to assess any potential bias. Newly diagnosed AF patients for whom clinical information is already available can be quickly identified for potential recruitment. Large numbers of newly diagnosed patients can be recruited and followed up in an efficient and cost-effective way.

583. Methods to Link a U.S Arthritis Cohort With Medicare Administrative Claims Data

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Background: Linkages between clinical and administrative data may provide a valuable resource for pharmacoepidemiologic and health services research.

Objectives: To describe methods and validity of a linkage between a de-identified national arthritis registry and U.S. Medicare data.

Methods: Data from 2006 to 2010 for rheumatoid arthritis (RA) patients in the Consortium of Rheumatology Researchers of North America (CORRONA) was linked to Medicare (100% sample selected using ICD-9 codes). Deterministic linkage was performed using birth year, sex, provider identification number, and U.S. state of the CORRONA site. Medicare data was restricted to claims from rheumatology or with an RA diagnosis. Visit dates from CORRONA were matched to Medicare visit dates. At least 1 visit date was required to match exactly. If a CORRONA participant had an all-visit match to > 1 Medicare beneficiary, unique matches selected to be the beneficiary with the greatest number of matched CORRONA visits. In the event of ties, the participant was considered not matched. A fuzzy match was done for CORRONA participants without any all-visit match allowing date mismatches of ± 4 days. Linkage accuracy was evaluated in a sub-cohort with full date of birth [DOB]; exact match on full DOB was used as a gold standard.

Results: CORRONA participants with self-reported Medicare coverage at any time (n = 12,220) were identified to be matched to 103,549 Medicare beneficiaries with arthritis treated by CORRONA physicians. A total of 9,484 CORRONA participants matched exactly on at least 1 visit, and 5,918 matched uniquely on all visits. For these participants, linkage accuracy was 98% for patients with > 2 matched visits, 97% for patients with exactly 2 matched visits, and 78% for those with exactly 1 matched visit. Patients who uniquely linked with > 2 visits with allowance of up to 4 days mismatch between visit dates were linked with 85% accuracy.

Conclusions: A novel linkage between a natioanl de-identified outpatient arthritis registry and U.S. Medicare claims data on multiple non-unique identifiers appears both feasible and valid.

584. Multiple Database Approach for Study of Associations Between Frequently Used Drugs and Community-Acquired Pneumonia

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Background: The association between community-acquired pneumonia (CAP) and commonly used drugs such as statins, ACE-inhibitors (ACE-I), and proton pump inhibitors (PPI) has been extensively studied in different settings and populations with often conflicting results. The origin of this heterogeneity is unknown and unravelling its nature is important for clinical interpretation of these pharmacoepidemiological (PE) results.

Objectives: To explore sources of heterogeneity in the association between CAP and use of ACE-I, statins, and PPIs by using the same methods in a multi-database study in multiple settings.

Methods: We used data from the TI PHARMA Mondriaan project providing access to various healthcare databases from hospitals, general practices (GP), and pharmacies. Ten different case-control sets in five different populations derived from both general practitioner (GP) and hospital data have been generated (2004–2010). Patients and controls were matched on age, gender, and index year. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between the three drug classes of interest and CAP. Crude associations were adjusted for comorbidity and drug use (semi-adjusted; common variables in all sets), and for all available confounders (fully adjusted).

Results: In total, data of 38,742 cases and 118,019 controls have been studied. The mean age of the hospitalised patients was 63 years and 46–61 years for the GP patients. For statin use and pneumonia risk the semi-adjusted OR varied from 0.82 to 1.38. A comparable range was observed for ACE-I and PPI use with ORs of 1.02–1.61 and 1.29–2.69, respectively. Overall, the associations were stronger for hospitalised CAP patients matched to population controls vs. GP CAP patients matched to population controls. Furthermore, prevalence of drug exposure was higher when assessed based on dispensing data vs. prescription data.

Conclusions: Associations between statin, ACE-I, and PPI use and CAP risk were influenced by sampling population and data source and may explain the large heterogeneity observed between previous observational PE studies.

585. Antiepileptic Drug Use in Seven Electronic Health Record Databases in Europe: A Methodological Comparison

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Background: The annual prevalence of antiepileptic drug (AED) prescribing reported in the literature differs considerably among European countries; this may be due to differences in type of data sources, time periods, population distributions, and methodology.

Objectives: To assess the prevalence of AED prescribing across seven European routine health care databases in Spain, Denmark, the Netherlands, the UK, and Germany using standardised methodology and to investigate sources of variation.

Methods: We used data from the Spanish Base de Datos para la Investigación Farmacoepidemiologica en Atencion Primaria (BIFAP), the Danish national registries, the Dutch Mondriaan project (AHC, NPCRD), The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD) from the UK, and the German Bavarian claims database (KVB). Analyses on annual prevalence of AEDs over the study period of 2001–2009 were stratified by sex, age, and AED type ('old' vs. 'new' depending registration year for marketing). Overall prevalences were standardised to the European 2008 reference population.

Results: Prevalence of any AED varied from 79 per 10,000 persons in the Netherlands to 147 per 10,000 persons in Spain in 2001. After standardisation this range decreased to 88 per 10,000 persons in the Netherlands to 144 per 10,000 in Spain and Denmark. In all databases prevalence increased yearly since 2001 with 6% in Denmark to 15% in Spain. This increase could be entirely attributed to an increase in prescribing of 'new' AEDs. AED use increased with age for both females and males up to ages of 80–89 years-old and tended to be somewhat higher in females between 40 and 70 years-old. We did not find differences across databases in the number of AEDs concomitantly used.

Conclusions: During the study period of 2001–2009, AED prescribing increased in all five EU countries which was mainly due to newer AEDs. Using a standardised methodology showed consistent trends across databases and countries over time. Differences in age and sex distribution explained part of the variation between countries.

586. Comparison of Seven Electronic Healthcare Databases in EU Countries Using a Standardized Methodology; A Descriptive Study on the Exposure to Calcium-Channel Blockers (CCBs)

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Background: Information on prevalence of CCB prescribing is scarce in the literature and differs considerably among European countries due to differences in type of data sources, time periods, population distributions, and methodology used.

Objectives: To measure and investigate sources of variation in prevalence of CCB prescribing across seven European routine health care databases using a standardised methodology.

Methods: We used seven electronic health record databases from Spain (BIFAP), the United Kingdom (UK; THIN, CPRD), Netherlands (Mondriaan AHC, NPCRD), Denmark (national prescription registry), and Germany (Bavarian Claims). Analyses on annual prevalence of CCBs (2001–2008) were stratified by sex, age, and CCB class ('with vascular effects' or 'with mainly direct cardiac effects'). Overall prevalences were age/sex-standardised to the European 2008 reference population.

Results: For vascular CCBs the variation in prevalence decreased after standardisation and varied from 192 per 10,000 persons (Netherlands, NPCRD) to 393 per 10,000 in the UK (THIN) in 2001. Except for Spain, the prevalence of vascular CCBs increased from 2001 to 2009 by 47%/year (Netherlands, AHC) to 89%/year (Denmark). Cardiac CCB use was lower, 87 per 10,000 (NPCRD) to 154 (AHC) in 2001 and then decreased in all databases by 4.5%/year (UK, THIN) to 42%/year (Denmark) in 2009. Any CCB use was negligible up to age 40 and increased for both sexes up to 2,739 per 10,000 at age 80–89 years in BIFAP.

Conclusions: We showed that from 2001 to 2009, the prevalence of CCB prescribing differs in five EU countries using a standard methodology, despite the convergence seen after standardisation to a reference population. Overall findings show that prescribing of CCBs with direct cardiac effects decreased whereas, except in Spain, CCBs with vascular effects increased.

587. Estimating Time-Specific Propensity Scores: A Case Study of the Effectiveness of Inhaled Long-Acting Beta-Agonists on Asthma Exacerbations

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Background: Propensity scores (PS) are increasingly used in observational studies of medication use. Typically, PS are estimated over the entire study period without consideration of the potential effect of changing patterns of the included variables over time.

Objectives: This study sought to compare PS estimated using the entire study period (conventional PS) and PS estimated for specific time periods (time-specific PS), and to determine whether there are differences in observed treatment effects using these two approaches.

Methods: We conducted a retrospective analysis using a claim database from the United States. Asthmatic patients aged 5–24 years who received an asthma controller medication during 1997–2008 were included. Exposed patients were those who received an inhaled long-acting beta-2 agonist (LABA). PS were estimated by conventional and time-specific approaches. The conventional approach used the entire time period to estimate a PS for each patient. The time-specific approach divided the study period into 1 year periods and estimated PS separately for each period by including patients with index dates during that period. Thus, each individual in the dataset had two PS estimated. A paired t-test was used to compare PS between approaches. Both PS approaches were used to estimate the adjusted hazard ratio (HR) for asthma exacerbations using a multivariate Cox proportional hazard model.

Results: A total of 288,518 patients with an average age of 11.9 ± 5.8 years were included. The difference between conventional and time-specific PS in each time period ranged from −0.097 to 0.220 (p < 0.05). The adjusted HR of conventional PS-matched cohort was 1.28 (95% confidence interval (CI); 1.26–1.31) for asthma exacerbations, while the estimate for the time-specific PS-matched cohort was 1.29 (95%CI; 1.27–1.32).

Conclusions: When focused on a specific year, there was a difference between PS estimated using the entire study period vs. those estimated specifically for that year. However, in this case study, there was minimal effect of time-specific PS on the observed treatment effects compared to conventional PS approaches.

588. Development and Validation of a Claims-Based Algorithm to Identify Urinary Retention in Patients Receiving Antiepileptic Drugs

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Background: Urinary retention (UR) involves a constellation of symptoms and extensive differential diagnoses, leading to possible misclassified cases based on claims data.

Objectives: To develop a claims-based definitional algorithm (ALGM) for identifying UR in antiepileptic drug (AED) users, and refine and validate the ALGM in medical records.

Methods: Claims data from the HealthCore Integrated Research DatabaseSM in 2008–2011 were used to identify AED patients (pts) with UR based on three ALGMs: (1) UR ICD-9 diagnosis (Dx) code (e,g,, bladder atony/paralysis, neurogenic bladder, urine retention, 596.4x, 596.53–596.54, 788.2x); (2) UR ICD-9 Dx code + a procedure code for catheterization; 3) ICD-9 Dx code for non-specific UR-related symptoms (e.g., splitting, slowing, hesitancy of urination, 788.41, 788.43, 788.61–788.65). Medical chart data for a random sample of 50 pts satisfying ≥ 1 of the ALGMs (pooled ALGM) were abstracted and reviewed by urologists. Positive predictive values (PPVs) and 95% confidence intervals (CIs) for the individual and pooled ALGMs were computed using the Wilson score method. Physician chart adjudication forms were reviewed to identify rules for ALGM refinement.

Results: PPV for the pooled ALGM was 72% (57–83%). PPV for ALGM #1 was subpar at 70% (46–87%). PPV for ALGM #2 was high at 95% (73–100%), while PPV for ALGM #3 was poor at 30% (8–65%). Based on physician notes, exclusion diagnoses were added to ALGM #1 to remove pts with neurogenic bladder (596.54) plus urinary incontinence (625.6, 788.3x, 788.91), and incomplete bladder emptying (788.21) plus cystitis (595). PPV of revised ALGM # 1 was increased to 82% (56–95%). Physician notes for ALGM # 3 did not yield systematic patterns. Given the low PPV, this ALGM was removed. The finalized pooled ALGM (revised ALGM #1 and ALGM #2) yielded a PPV of 89% (74–97%), a substantial improvement from that for the original ALGMs.

Conclusions: UR claims ALGM developed in this study demonstrated a PPV of near 90%. Further validation of the UR ALGM using more medical records is warranted. A robust definitional claims ALGM for UR will enable the assessment of UR among AED pts in real-world settings.

589. Determining Multiple Sclerosis Subtype from Electronic Medical Records

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Background: Multiple sclerosis (MS) is a central nervous system disease that causes a range of symptoms as nerve signals are disrupted by scarring and demyelination. MS is classified into subtypes depending on the patterns of cognitive or physical impairment progression: relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), or progressive relapsing (PRMS). The subtype is important in managing the disease and determining appropriate treatment. ICD-9 codes are uninformative about MS subtype, which increases the difficulty of studying the effects of subtype on disease.

Objectives: We sought to use progress notes and other clinical text in the electronic medical record to identify MS subtype using natural language processing (NLP) techniques.

Methods: Patients with at least two ICD-9 codes for MS in 1999–2010 were identified from EMR in the Department of Veterans Affairs. Clinical experts were interviewed for possible keywords and phrases denoting MS subtype. For each patient, EMR clinical notes since the first MS diagnosis date were searched by NLP for these keywords and phrases. Presence of subtype-related keywords and phrases were automatically analyzed by NLP in context to remove mentions that were negated ('not relapsing-remitting') or unrelated to MS ('RR' meaning respiratory rate). One thousand mentions of MS subtype were validated and all records of 137 patients were reviewed for missed mentions.

Results: There were 7,756 MS patients identified by ICD-9 code. MS subtype was identified for 2,854 (35%) patients with 1,836 (64%) having just 1 subtype: 1,118 (39%) RRMS, 561 (20%) PPMS, 854 (30%) SPMS, and 68 (2%) PRMS. 747 (26%) patients had two subtypes, the most common being 459 (16%)

patients with RRMS followed by SPMS. Two hundred and thirteen (7%) had three subtypes and 58 (2%) had four subtypes. Specificity of subtype identification was 93.8% and positive predictive value was 96.4%.

Conclusions: Subtype was documented for only one third of MS patients and NLP accurately identified these cases. Multiple documented subtypes is consistent with disease progression. The most common misidentification was due to ambiguity while clinicians were trying to determine subtype.

590. Characterization of Patients with ANCA-Associated Vasculitis by Subtype in the Veterans Affairs Database

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Background: Antineutrophil cytoplasmic antibody (ANCA)-Associated Vasculitis (AAV) is composed of three subtypes; granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS). Characterization of AAV subtypes is challenging due to lack of clear distinction between the different disorders, case capture, and case ascertainment. Thus, data on patient demographics and comorbidities are currently lacking.

Objectives: To characterize the demographics and comorbidities of AAV patients by subtype.

Methods: The Department of Veterans Affairs (VA) has a robust electronic health record (EHR) database containing over 20 million patients. Natural language processing (NLP) was applied to identify patients with AAV subtypes between 1999 and 2011.1 Patient demographics and comorbidities (by ICD-9 code) were captured and analyzed for each subtype. A comorbidity was defined as at least one record of an ICD-9 diagnostic code during the 180 days after and including the index date (first AAV subtype diagnosis).

Results: Three hundred and eighty-seven patients were identified as having GPA (5.2% female, mean age 63 years), 327 with MPA (4.0%, 66 years) and 656 with CSS (7.5%, 62 years). The majority of patients had at least one recorded comorbidity (94–97%). The most common comorbidities for GPA were hypertension (44.6%), hyperlipidemia (22.8%), diabetes (20.0%), COPD (18.0%), and anemia (15.7%); MPA,

hypertension (60.9%), anemia (33.6%), hyperlipidemia (23.9%), diabetes (23.6%), and acute renal failure (22.9%); CSS, hypertension (45.3%), COPD (31.4%), asthma (30.6%), diabetes (20.3%), and hyperlipidemia (19.8%).

Conclusions: This study, which applies NLP methodology to the VA database, provides a unique opportunity to identify and characterize AAV subtypes. The prevalence of CSS in the cohort was higher than expected. Hypertension was the most common comorbidity amongst the three subtypes. Awareness of the clinical burden among patients with AAV may help improve the standard of care for these patients.

Reference: 1. DuVall, et al. Using NLP of EHR to Identify Patients with AAV in the VA.(abbr) ISPE 28th Conference; August 2012.

591. Analyzing Database Studies with Many Outcomes or Co-Morbidities: Using SAS® to Dynamically Generate Analytic Programs from Case Definitions Stored in Excel®

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Background: Studies using insurance claims or electronic medical records databases rely on complex combinations of diagnosis, procedure, and medication codes to identify comorbidities and disease outcomes. Developing multiple coding algorithms is requires clinical and epidemiologic expertise and familiarity with coding systems. Programming algorithms can be time-consuming and can introduce errors.

Objectives: Improve efficiency and accuracy of database analyses.

Methods: Codes used to define comorbities and outcomes can be assembled and stored in an Excel workbook external to the analytic programming, which typically uses SAS®. The Excel workbook can then be read into SAS, transformed to SAS format, and dynamically converted into SAS programming statements required to identify patients with the comorbidities and outcomes of interest.

Results: We conducted a psoriasis cohort study using a disease definition Excel workbook to illustrate the process of storing different disease definition components in Excel and generating SAS programming statements directly from these definitions. The psoriasis study included multiple algorithms comprising combinations of diagnosis, procedure and medication codes for

approximately 70 baseline comorbidities and disease outcomes. The comorbidity and outcome definitions and all of the components of the definitions were stored in an Excel workbook. The information contained in the Excel workbook was used to dynamically generate the SAS code required to create patient-level analytic datasets and to generate the study results.

Conclusions: Storing disease definitions external to the SAS analytic programs has multiple benefits. By storing codes in Excel, non-programmers can create, review, and modify disease definitions without knowledge of SAS programming. In addition, SAS programs don't need to be updated whenever disease definitions are modified, and programs reflect the most current version of the disease definitions. Disease definitions can be assembled external to SAS programming and incorporated directly into SAS programs improving efficiency and accuracy of database analyses.

592. Study Designs in Pharmacoepidemiologic Studies on Electronic Healthcare Databases: A Systematic Review

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Background: Observational studies are widely used in the real life pharmacoepidemiologic studies. Several designs are available, such as cohort (C), case–control (CC), or case-only (CO) designs. Recommendations on their use in medical products (MP) safety monitoring on electronic healthcare (EH) databases (DB) have been recently published.

Objectives: We aimed at describing study designs used in pharmacoepidemiologic studies on EHDB, whether they fit the recent recommendations, and how frequent are the situations in which CO could have been applied.

Methods: We searched Medline for articles published in the second part of 2011. Terms referring to (1) EHDB, (2) effect of MP, and (3) observational designs, were combined. Two independent readers collected data using a standardized extraction form, focusing on designs, exposures (EXP) and events (EV) characteristics. Situations in which CO could have been applied must combine an intermittent or acute EXP, an abrupt onset or recurrent EV, and a rare EV.

Results: We analysed the data of 94 papers. Of these, 48 (51%) used data of administrative DB, 19 (20%) of pharmacy records, and 16 (17%) of primary care records. Safety was assessed in 49 (52%) papers, effec-

tiveness in others. Study designs used were 67 (71%) C, 25 (27%) CC, and 2 (2%) CO study design. EXP was intermittent or acute in 16 (24%) C and 4 (16%) CC. EV had an abrupt onset in 56 (83%) C and 11 (44%) CC. One CO study assessed the risk of an EV with insidious onset related to an intermittent EXP; the other, the risk of an EV with an abrupt onset related to a sustained EXP. A rare or intermittent EV was reported in 75 (80%) studies. Overall, the EXP was classified as intermittent or acute, with a rare or recurrent EV with an abrupt onset, in 7 (7.5%), all of them using a C design. These are situations in which the key assumptions of CO designs are fulfilled.

Conclusions: Cohort study is the most common design employed in pharmacoepidemiology on EHDB. CO designs are rarely applied; in fact fulfilment of key assumptions for CO is somewhat rare (7.5%). However, a small potential for increasing in their use may be expected.

593. Potential for Early Pharmacoepidemiologic Studies and Monitoring Intake of a Biologic Treatment Using an Electronic Health Records Database Prior to Assigned J-Code

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Background: Pharmacoepidemiologic studies of newly approved treatments using claims databases can be challenging because of the time after approval before a specific billing J-code is released. Electronic Health Records (EHR) do not require billing codes in order to document treatment with a biologic medicine, and thus potentially provide information about the use of new treatments earlier than claims. Tocilizumab is a biologic approved for treatment of Rheumatoid Arthritis patients with inadequate response to a Disease-Modifying Anti-Rheumatic Drug. Though first approved 1 November 2010, the J-code was not issued until 1 January 2011.

Objectives: To estimate the capability to document tocilizumab treatment between EHR and healthcare claims databases to determine the potential for early pharmacoepidemiologic study and intake monitoring.

Methods: Patients treated with tocilizumab were identified in the GE Centricity (GE) EHR and Truven

Health MarketScan (MarketScan) healthcare claims databases (GE: tocilizumab; MarketScan: J3262). This cohort was narrowed to patients with a diagnosis of RA and age ≥ 18 years at the index date (first documented tocilizumab record). Patients with a tocilizumab record prior to the U.S. approval date were excluded. The time from approval to the first documented tocilizumab record was calculated.

Results: In GE, 709 patients had a medication record for tocilizumab and 567 patients (82.1% females, mean age 56.2 years SD 12.7) met all inclusion criteria. In MarketScan, 718 patients had a tocilizumab billing code and 688 patients (83.3% females, mean age 54.9 years SD 12.5) met all inclusion criteria. The first tocilizumab record in GE was documented 24 days after approval and 203 patients (35.8%) had a tocilizumab record by the time of the J-code release date (J3262 – 1 January 2011, 355 days after approval). The first tocilizumab J-code in MarketScan was documented 355 days after the approval date.

Conclusions: These results demonstrate that EHRs allow for earlier identification of patients on biologic treatments, which supports earlier pharmacoepidemiologic studies and intake monitoring.

594. Utilization of New Diagnosis Codes for Basal Cell Carcinoma in two Large Nationwide EHR Databases

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Background: Basal cell (BCC) and squamous cell (SCC) carcinomas are the most common skin cancers in the US and are classified as non-melanoma skin cancers (NMSC). Historically no specific ICD-9 codes existed to distinguish between NMSC types. Rather, they were grouped under diagnosis (Dx) codes 173.x, the 4th digit indicating the general tumor location. In October 2011, the 4-digit NMSC ICD-9 codes were expanded to 5 digits, the 5th digit distinguishing between BCC (1), SCC (2), unspecified type (0), or other specified type (9).

Objectives: To assess the utilization of new NMSC diagnosis ICD-9 codes 173.xx from two large national electronic health record (EHR) databases.

Methods: All occurrences of old (173.x) and new (173.xx) NMSC diagnosis codes were identified across the national Veterans Affairs (VA) and GE Centricity (GE) EHR databases in the 6-months before and after the new codes release date (10/1/2011). These results

were grouped by month, specific code, and physician specialty. Transition from the former codes to new codes was assessed.

Results: A total of 110,416 VA, and 33,483 GE NMSC codes were documented between 10/1/2011 and 3/31/2012. Although both 4-digit and 5-digit codes were documented in the VA in 10/2011, all codes after 10/2011 were 5-digit codes. In GE, 66.0% of NMSC documented in the 5 months after 10/2011 used 5-digit codes, while 34.0% continued using 4-digit codes. The new BCC code (173.x1) accounted for most of the 5-digit codes documented (55.3% VA, 58.8% GE), followed by SCC codes (29.3% VA, 30.6% GE). The majority of new NMSC codes were documented by specialty care physicians, primarily dermatologists.

Conclusions: Use of new NMSC codes provides improved specificity in identifying NMSC subtypes. The VA is a single large integrated healthcare system that demonstrated a complete transition to the new 5-digit NMSC codes within 1 month of release. In contrast, the GE database encompasses multiple healthcare groups, each adopting the new codes at various times. When conducting pharmacoepidemiologic studies, it is important to consider variability in healthcare institutions' adoption of new diagnosis codes.

595. Potentially Missing Prescription Medication Claims in Administrative Databases: Angioedema Prior to New Angiotensin Receptor Blocker Use

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Background: Many new user studies in administrative claims databases rely on a first billing claim to identify medication initiation. However physician samples, low-cost generic medications, and out-of-pocket payment may prevent billing claims for common medications from being submitted to payers. Angioedema is a common adverse event of angiotensin-converting enzyme inhibitors (ACEi), that typically would result in a switch to an angiotensin receptor blocker (ARB).

Objectives: We estimated the proportion of missing claims for prior ACEi use in ARB initiators using the measured incidence of angioedema in all new ACEi users and known ACEi-ARB switchers to estimate percentage of missing ACEi claims.

Methods: We identified new users of ARBs and thiazide diuretics as well as a general population sample identified at outpatient office visits in a large commercial and Medicare supplementary insurance database. We calculated the rate of angioedema prior to ARB initiation in all ARB users, and then in known ACEi-

ARB switchers. Using a range of estimates of the baseline rate of angioedema in non-ACEi users from the general population or new thiazide initiators, we estimated expected proportions of former ACEi users among new ARB users, and compared the expected values to our observed population.

Results: We identified 1,050,681 new ARB initiators; 373,004 (35.5%) had claims for ACEi use in the prior 6 months. The pre-ARB initiation angioedema incidence was 0.40% in the whole sample, and 0.84% in the ACEi-ARB switchers. Estimates of angioedema incidence in non-ACEi users ranged from 0.04% in the general population to 0.13% prior to thiazide diuretic initiatiors. Pre-initiation angioedema was observed in 0.15% of ARB users without observed prior ACEi use. Estimates of missing ACEi claims range from 1.7% to 9.0%.

Conclusions: Up to 9% of pharmacy dispensing claims for ACEi may be missing in administrative claims datasets–this estimate similar to other estimates of missing medication information. Studies implementing the new user design relying on a first observed claim should consider study design modifications to ensure new use.

596. Sensitivity Analysis of Methods for Active Surveillance of Acute Myocardial Infarction Using Electronic Databases

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Background: Validity of conclusions from observational studies depends heavily on design and analytic decisions.

Objectives: To explore the impact of design/analysis decisions on balance metrics and risk estimates using databases for active surveillance of marketed drugs.

Methods: Using the Mini-Sentinel protocol for the Active Surveillance of acute myocardial infarction (AMI) in Association with Use of Anti-Diabetic Agents as a template, we defined cohorts of new users of Metformin (M) and second-generation Sulfonylureas (S), baseline covariates and AMI events using three definitions of washout and baseline periods. We assessed covariate balance and risk estimates using cumulative data in quarterly analyses with two propensity score (PS) matching and one stratification methods and Cox regression.

Results: Extending washout from 183 to 365 days decreased new users from 27,420 to 25,675. A 365-day baseline identified 78 more patients with possible gestational diabetes and 2% more smokers than a 183-day baseline. Matching all cumulative patients tended to produce smaller absolute standardized mean differences in covariates than matching only new patients each quarter. For analyses with 365 days for both washout and baseline, all hazard ratio (HR) CIs contained 1. With either of 183 days, HRs tended to 'signal', more so with matching only new patients each quarter. With 365-day washout and 183-day baseline, HRs based on matching only new patients each quarter 'signaled' in June and September 2009, 2.2–2.4 (1.1, 4.9) for both calipers, while HRs based on matching all cumulative patients 'signaled' (same magnitude) only in September 2009 for caliper 25%. In PS stratification, PS trimming improved balance whereas stratifying PS further into deciles did not. HRs were similar to those from PS matching.

Conclusions: Longer durations of washout and baseline may enhance the classification of new users and better capture comorbidities but at reduced sample size. Matching all cumulative patients offered better balance than matching only new patients each quarter. PS matching achieved better balance than PS stratification but with only half the sample size.

597. Development and Validation of an Acute Liver Failure (ALF) Risk Prediction Model for Patients with Drug-Induced Hepatitis (DIH)

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Background: Few data have evaluated the ability of clinical and laboratory variables measured at the time of DIH diagnosis to predict the development of ALF.

Objectives: To derive and internally validate a prognostic model to classify DIH patients by risk of progression to ALF using separate cut-off points for clinical and research purposes.

Methods: We conducted a retrospective cohort study among Kaiser Permanente Northern California (KPNC) members with an ICD-9 diagnosis of DIH (toxic hepatitis [573.3] or drug-induced liver disorder [573.8]) and no pre-existing liver disease between 2004 and 2010. ALF was confirmed by medical record review. We used logistic regression to evaluate the predictive ability of clinical and laboratory variables recorded at DIH diagnosis and selected the model with the highest discriminatory ability. For clinical use, we required $\geq$ 90% sensitivity and selected the cut-off with the highest specificity. For research purposes, we required $\geq$ 90% specificity and identified the cut-off with the highest sensitivity. Internal validation was performed by using a bootstrapping approach. For each bootstrap sample, we compared the model's performance to Hy's Law.

Results: Among 15,479 eligible KPNC members, 23 (0.2%) developed ALF. A risk prediction model comprised of sex, aspartate aminotransferase (AST), and total bilirubin had the highest discrimination (area under the ROC curve, 0.89; 95% CI, 0.78–0.97). The model with the clinical cut-off had a sensitivity of 0.91 (0.71–0.99) and specificity of 0.83 (0.82–0.84). The model with the research cut-off had a specificity of 0.94 (0.93–0.95) and sensitivity of 0.64 (0.41–0.83). Internal validation showed little decrease in discrimination using either cut-off. In direct comparisons using bootstrap samples, our cut-offs were four to five times more likely than Hy's Law to have higher sensitivity and specificity.

Conclusions: A risk prediction model with sex, AST, and total bilirubin identified patients with DIH who are at increased risk of ALF with both high sensitivity for clinical use and high specificity for research purposes.

598. Validity of Diagnostic Codes to Identify Cases of Severe Acute Liver Injury in the U.S. Food and Drug Administration's Mini-Sentinel Distributed Database

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Background: The validity of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify diagnoses of severe acute liver injury (SALI) is not well known.

Objectives: To examine the positive predictive values (PPVs) of hospital ICD-9-CM diagnoses in identifying SALI among health plan members in the Mini-Sentinel Distributed Database (MSDD) for patients without liver/biliary disease and for those with chronic liver disease (CLD).

Methods: We selected random samples of members (149 without liver/biliary disease; 75 with CLD) with a principal hospital diagnosis suggestive of SALI (ICD-9-CM 570, 572.2, 572.4, 572.8, 573.3, 573.8, or V42.7) in the MSDD (2009–2010). Medical records were reviewed by hepatologists to confirm SALI events. PPVs of codes and code combinations for confirmed SALI were determined by CLD status.

Results: Among 105 members with available records and no liver/biliary disease, SALI was confirmed in 26 (PPV, 24.7%; 95% CI, 16.9–34.1%). Combined hospital diagnoses of acute hepatic necrosis (570) and liver disease sequelae (572.8) had high PPV (100%; 95% CI, 59.0–100%) and identified 7/26 (26.9%) events. Among 46 CLD members with available records, SALI was confirmed in 19 (PPV, 41.3%; 95% CI, 27.0–56.8%). Acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a

PPV of 83.3% (95% CI, 51.6–97.9%) and identified 10/19 (52.6%) events.

Conclusions: Most individual hospital ICD-9-CM diagnoses had low PPV for confirmed SALI events. Select code combinations had high PPV but did not capture all events.

599. Developing Acute Coronary Syndrome Disease Cohorts Using Primary and Secondary Care Database Linkages

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Background: More complete patient disease cohorts can be created by joining primary and secondary care records. Creation of a patient cohort of Acute Coronary Syndrome (ACS) using the Clinical Practice Research Datalink (CPRD) and the Hospital Episode Statistics (HES) database from the UK highlights the benefits of combining these distinct medical record sources.

Objectives: Compare the demographic characteristics, comorbidities, concomitant medications and follow-up duration in three ACS cohorts developed using the CPRD and the HES databases (CPRD, HES and CPRD-HES linked) for the period 2000–2010.

Methods: Inclusion Criteria: A medical record of unstable angina or acute myocardial infarction (ACS) and linkable records between the two databases. The index date was first ACS occurrence within the CPRD or HES data. Baseline information was taken from the 12 months prior to the index date in CPRD or all available information in HES prior to the index admission. The CPRD-HES ACS cohort used records in HES between the HESstart and HESend (start and end of research quality HES data, respectively) dates and CPRD records 180 days prior to and after the HESstart and HESend dates.

Results: The CPRD-HES cohort captured the most ACS patients (153,686) followed by the HES cohort (152,975) and the CPRD cohort (14,306). The CPRD-HES linked cohort captured a higher prevalence of baseline comorbidities for example Hypertension (19.8%) and Diabetes (13%), compared to the CPRD cohort (Hypertension 6.6%, Diabetes 10.3%) and HES cohort (Hypertension 13.9%, Diabetes 6.3%). The linked cohort captured ethnicity which was not available in CPRD, and smoking, alcohol and prescription information that were missing entirely in HES. The CPRD cohort had the longest mean follow-up duration (12.3 years) followed by CPRD-HES (10.6 years) and HES (8.6 years).

Conclusions: The linkage increased the number of risk factors, comorbidities and provided prescription information that was not available in HES or CPRD data alone resulting in an enriched ACS disease cohort.

600. Distinguishing Incident and Prevalent Diabetes in an Electronic Medical Record Database

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Background: The risk of diabetes mellitus (DM)-associated complications increases with longer DM duration. Use of Electronic Medical Records (EMR) to assess DM duration relies on accurate identification of patients with newly diagnosed DM.

Objectives: To distinguish incident from prevalent DM and test this classification by examining the association between incident and prevalent DM with common outcomes associated with longer duration of DM.

Methods: Incidence rates (IRs) of DM were measured in 3-month intervals through 36 months after registration in The Health Improvement Network (THIN) database. We used Joinpoint regression to identify the point at which a statistically significant change in the trend of IRs occurred. Further analyses used this point to distinguish those likely to have incident (n = 50,315) vs. prevalent (n = 28,337) DM diagnoses. Incident and prevalent cohorts were compared using Cox regression for the following end points: all-cause mortality, cardiovascular disease (CVD), diabetic retinopathy (DR), diabetic nephropathy (DNP), and diabetic neuropathy (DN). Analyses were adjusted for potential confounders including age, sex, smoking, hyperlipidemia, hypertension, and calendar year.

Results: For patients registering in THIN practices with Vision software, trends in IRs of DM plateaued 9 months after registration (p = 0.02). All cause-mortality was increased (HR 1.61, 95% CI 1.53–1.70) among patients diagnosed with DM prior to 9 months following registration (prevalent DM) compared to those diagnosed after 9 months following registration (incident DM). Similarly, the risk of DM-related complications was higher in DM patients classified as prevalent relative to incident [CVD, HR 2.23 (2.08–2.40); DR, HR 1.31 (1.24–1.38); DNP, HR 2.30 (1.95–2.72); DN, HR 1.28 (1.16–1.41)].

Conclusions: Incidence rates of newly diagnosed DM decrease to a plateau by 9 months following registration. When conducting studies in an EMR database,

failure to exclude patients with a first diagnosis of DM within 9 months of registration can lead to exaggerated associations of outcomes related to the duration of diabetes.

601. A Novel Process for the Identification, Development and Assessment of Database Coding Algorithms for Five Psychiatric Conditions

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Background: Definitions of health outcomes and comorbidities applied in electronic healthcare database studies often lack rigor and consistency across the pharmacoepidemiology scientific community.

Objectives: This study describes a method for defining high-quality coding algorithms for a set of five psychiatric clinical conditions.

Methods: Coding algorithms for five psychiatric conditions including generalized anxiety disorder (GAD), bipolar disorder (BD), depressive disorder (DD), schizophrenia type (ST) and post-traumatic stress disorder (PTSD) were developed. The process for developing coding algorithms encompasses several steps. First, a literature review was conducted to identify existing coding algorithms for each condition using published database studies. Concurrently, a certified clinical coding expert independently recommended codes for inclusion. Codes identified from the literature and/or the coding expert were then reviewed by a general physician and a psychiatrist. Each physician was instructed to provide comments on the validity of each algorithm identified as well as recommendations to refine the algorithms.

Results: Across the five psychiatric conditions, 19 papers were retrieved for this study. Of these 19, five studies provided information for GAD, five studies for BD, four studies for DD, four studies for ST, and four studies for PTSD. These papers were reviewed by clinicians and 'optimal' algorithms were identified. Prevalence for each condition was calculated in a claims database (using the optimal algorithms) and benchmarked against published estimates from large scale epidemiologic studies. Full results for the defined 'optimal' algorithms and comparison of prevalence rates will be presented at ICPE.

Conclusions: This approach used the most recent peer-reviewed literature and coupled it with expert insight from ICD-9 reimbursement, clinical and epidemiologi-

cal expertise. The result is an evidence-based preferred list of coding algorithms for five psychiatric conditions for use in conducting research using administrative claims data.

602. A Novel Process for the Identification, Development and Assessment of Database Coding Algorithms for Six Cardiovascular Conditions

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Background: Definitions of health outcomes and comorbidities applied in electronic healthcare database studies often lack rigor and consistency across the pharmacoepidemiology scientific community.

Objectives: This study describes a method for defining high-quality coding algorithms for a set of six cardiovascular clinical conditions.

Methods: Coding algorithms for six cardiovascular conditions including congestive heart failure (CHF), myocardial infarction (MI), stroke (S), transient ischemic attack (TIA), deep vein thrombosis (DVT) and pulmonary embolism (PE) were developed. The process for developing coding algorithms encompasses several steps. First, a literature review was conducted to identify existing coding algorithms for each condition using published database studies. Concurrently, a certified clinical coding expert independently recommended codes for inclusion. Codes identified from the literature and/or the coding expert were then reviewed by a general physician and a cardiologist. Each physician was instructed to provide comments on the validity of each algorithm identified as well as recommendations to refine the algorithms.

Results: Across the six cardiovascular conditions, 64 papers were retrieved for this study. Among these papers performance characteristics of the algorithms (sensitivity, specificity, positive predictive value, etc.) were provided in three studies for CHF, one for MI, two for S, one for TIA, two for DVT, and one for PE. These papers were reviewed by clinicians and 'optimal' algorithms were identified. Incidence rates for each condition were calculated in a claims database (using the optimal algorithms) and benchmarked against published rates from large scale epidemiologic studies. Full results for the defined 'optimal' algorithms and comparison of incidence rates will be presented at ICPE.

Conclusions: This approach used the most recent peer-reviewed literature and coupled it with expert insight

from ICD-9 reimbursement, clinical and epidemiological expertise. The result is an evidence-based preferred list of coding algorithms for six cardiovascular conditions for use in conducting research using administrative claims data.

603. Identifying Causes of Death in a Large Cohort of Asthma Patients

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Background: A large multisite collaboration examined asthma mortality using data from 10 large health insurers/data partners. A cohort of 994,627 patients aged ≥ 4 years fulfilling a claims definition of persistent asthma were followed for fact and cause of death via linkage to the US National Death Index (NDI). NDI linkage results may include multiple matches per patient, with the most likely match usually selected by manual review. An automated algorithm (AA) was used to process the NDI results due to the large number of patients and need for a standard method that could be applied by 10 separate data sites to select the most likely match. The AA, based on one used widely by US cancer registries, uses varying combinations and completeness of patient identifiers.

Objectives: To determine the level of agreement between the AA and the NDI most likely matches and to characterize the causes of death in this cohort of asthma patients.

Methods: Each data partner submitted patient identifiers to the NDI for linkage to determine fact and cause of death using a common selection procedure that screened for up to 2 years after the last claim. The level of agreement between the AA-defined most likely match and the NDI most likely match was derived. Causes of death were tabulated.

Results: Deaths totaled 31,931 in the 618,870 persons submitted to the NDI. The most common underlying cause of death (UCOD) was chronic obstructive pulmonary disease, then lung cancer and heart disease. Of 18,553 deaths identified during follow-up, asthma was listed among causes of death on the death certificate in 5.1% of deaths and was the UCOD in 1.5% of deaths. Over 30% of patients submitted to the NDI had at least one possible match returned. The AA-defined most likely match agreed with the NDI best match more than 99% of the time, regardless of whether the patient vital status was known at the time of NDI linkage.

Conclusions: The application of a standard but more liberal AA provided an efficient way to assess many potential NDI matches but did not yield a meaningful increase in the number of additional deaths identified over the NDI's best match. Asthma as the UCOD was rare in this cohort of asthma patients.

604. Decision Rules for Microbiologically-Evaluable Complicated Urinary Tract Infection in an Electronic Medical Record-Linked Administrative Database

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Background: Informative data on microbiologically-evaluable (ME) complicated urinary tract infections (cUTI) typically arise from clinical trials. In two retrospective studies, ICD-9 case validation of hospitalized acute pyelonephritis, a subset of cUTI, had a positive predictive value of 80–82%; ME populations were not reported.

Objectives: To identify and categorize ME cUTI in hospitalized adults using electronic medical record-linked administrative data (EMR-LAD).

Methods: Retrospective cohort study of hospitalized adults with cUTI identified for years 2008–2010 in the Cerner Infectious Diseases Hospital Events Database (Health Facts®, Cerner Corp, Kansas City, MO). Case inclusion criteria were ≥ 18 years old with (1) ≥ 1 ICD-9 code for acute pyelonephritis or infection with a complicating diagnostic or procedure code, (2) a urine culture (UC) report, and (3) ≥ 1 antimicrobial prescription. Index UC was the 1st date/time stamped report; if result null or not mapped, the 2nd UC report (if available) was identified. An algorithm was created to identify uropathogens based on specimen source and site; pathogen groups were Gram-negative (GN), Gram-positive (GP), yeast (Y), contaminants (C), quantity not sufficient (QNS), and other (O). Susceptibility data were evaluated to identify multidrug resistance (MDR) in Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, and enterococci.

Results: The cohort comprised 7,810 adults, 3,801 (49%) of whom had acute pyelonephritis, 37% were ≥ 75 years old, and 60% were female. In ME cUTI subjects (69%, N = 5,387), 6,250 uropathogens included 3,849 GN, 1,078 GP, 165 Y, 557 C, 552 QNS, 49 O; MDR was identified in 207/2,701 (8%)

Enterobacteriaceae, 33/267 (12%) *P. aeruginosa*, and 5/16 (31%) *A. baumannii*; 87/147 (59%) *S. aureus* were MRSA and 67/547 (12%) enterococci were VRE.

Conclusions: These decision rules for ME cUTI in an EMR-LAD enable assessment of treatment patterns and outcomes for pathogen-specific infections in real-world settings as well as inform the planning of future cUTI clinical trials.

605. An Assessment of How the Outputs from Signal Detection Can Be Effected by Variation of Database Profile by Analysing Adverse Events Reports of FDA and PMDA Received in 2010

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Background: A statistical approach to analyzing cumulative ADE reports on these databases has been encouraged by regulatory authorities in the 21st century. The differences between the Japanese Adverse Drug Event Report database (JADER) (which became publically available in April 2012) and FDA Adverse Event Reporting System (FAERS) has not been previously assessed.

Objectives: To understand the profiles of two major ICH regional databases and how that impacts signal detection to better understand potential pitfalls in assessment and help avoid future misinterpretation.

Methods: This study examined the variables in three ADE data sources in 2010: cases of JADER (JP), Japanese cases extracted from FAERS (F-JP) and US cases from FAERS (F-US). By using BCPNN as signal detection, IC-2SD > 0 for threshold was applied to each data source, then evaluation was performed on the results of BCPNN of three common drugs that were frequently reported as the main suspect drug to JADER and FAERS.

Results: JP, F-JP and F-US have 31,747 (M = 50, F = 48, NA = 2 [%]), 18,182 (45, 45, 10) and 348,295

(31, 56, 13) cases respectively. The average of number of ADEs per case was 1.56 (SD = 1.29, max = 37), 3.33 (3.48, 62) and 3.0 (3.68, 127), in addition, differences in the type of reported MedDRA Preferred Terms (PT) were observed. Etanercept, Infliximab and Paroxetine were selected for signal detection. Eight percent to 18% of total PTs of ADE cases were signaled; Etanercept as an example, the ratio of signaled PTs were 14%, 9% 11% respectively in JP, F-JP and F-US, and 88 PTs were commonly observed. Only herpes zoster [PT 10019974] was commonly detected (JP IC = 1.95 IC-2SD = 0.82, F-JP 2.04 1.02, F-US 1.46 1.19).

Conclusions: Three main data sources generated quite different results using BCPNN. Discrepancies among three data sources, such as types of PTs and drugs reported and average number of ADEs per case were potential causes for this. This may be due to different reporting rules in Japan and USA. This study used data in 2010 only and trending using long term data could harmonise signal analysis to allow for these differences.

606. Validation of a Multiple Myeloma Algorithm in Administrative Data

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Background: The ability to assess outcomes among patients with hematologic malignancies in large administrative databases is contingent upon accurately identifying these patients. Currently, there are no published algorithms that identify valid cases of multiple myeloma (MM) in administrative data.

Objectives: Evaluate algorithms to use with administrative data to identify valid cases of MM.

Methods: Identified patients ≥ 18 years of age with ≥ 1 International Classification of Diseases, 9th revision (ICD-9) code for MM (203.0x) in the Henry Ford Health System from 1/1/2005 to 2/28/2011. Tested multiple algorithms to identify MM patients and compared the results to morphologically confirmed MM patients identified in a tumor registry whose data are included in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.

Results: Identified 1,432 patients with a mean age of 65.9 (std. deviation 13.9) and 49% (N = 706) were

female. A one-part algorithm used: ≥ 2 ICD-9 codes for MM at least 30 days apart; the positive predictive value (PPV) was 56% (95% confidence interval (CI); 0.51–0.62) and the sensitivity was 93% (95% CI; 0.89–0.96). A two-part algorithm used: Part A: ≥ 2 ICD-9 codes for MM–And–(≥ 1 procedure code for bone marrow aspirate, biopsy, or interpretation–Or–≥ 1 procedure code for two of the following tests: assay of gammagloblulins, immunofixation procedure, serum protein electrophoresis, or skeletal survey); Part B: ≥ 2 ICD-9 codes for MM 5 to 90 days after the procedures identified in part A. The PPV was 86% (95% CI; 0.80–0.90) and the sensitivity was 79% (95% CI; 0.73–0.84).

Conclusions: The potential to identify cases of MM using administrative data seems promising. To achieve a reasonable predictive value, a sequence of ICD-9 codes in combination with procedure codes followed by ICD-9 codes for MM within a specific time window is required. Further analyses are underway at a different study site to validate this algorithm.

607. Multiple Imputation of Missing Data in Longitudinal Electronic Health Records

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Background: Electronic Health Records (EHR) are increasingly used for pharmacoepidemiological studies. However, data on health indicators and laboratory results are often not recorded on a regular basis.

Objectives: To compare results of using different approaches to deal with missing health indicator data in longitudinal EHR.

Methods: Using data from The Health Improvement Network (THIN), UK primary care database and simulated data we evaluated biases and precision of estimates of using complete case, standard multiple imputation (MI) using baseline information, and the new twofold FCS imputation algorithm that accounts for the longitudinal data structure of EHR. As an example we designed a 'simple' time-to-event model where we evaluated associations of socio-demographics and health indicators (blood pressure, weight, height, cholesterol and smoking) measured in the baseline year with cardiovascular events, and estimated effects with standard errors. This provided a mixture of continuous and categorical variables, posing additional challenges to MI algorithms. For the simulation study up to 70% of the data were made missing in any given year.

Results: Few individuals have complete and regular records of health indicators in UK primary care. MI of missing health indicators in EHR improves the precision of effect estimates in comparison with complete case analysis. Precision was improved further by using the twofold FCS imputation algorithm. The simulations suggested that under certain circumstances the twofold FCS imputation may retain information much better than MI at baseline or complete case analysis equivalent to increasing the effective sample size from 240 to 600 in a study of 1,000 participants.

Conclusions: Both standard MI and twofold MI of longitudinal EHR give more precise estimates in subsequent analyses compared to complete case analysis. Twofold MI maximises the use of data available, with the gain relative to baseline MI depending on the strength of correlations within and between variables. Using this approach also increases plausibility of the missing at random assumption by using repeated measures over time of variables whose baseline values may be missing.

608. Projection Methods Using Oncology Electronic Health Records To Produce Nationally Representative Estimates

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Background: Electronic health records (EHR) are increasingly used in clinical practice. A proprietary EHR database, the Oncology Services Comprehensive Electronic Records (OSCER) database, was established in 2004 for epidemiologic and outcomes research of pharmaceutical products. OSCER is a data warehouse with > 550,000 patient records from 78 community-based or hospital-affiliated outpatient oncology practices in the United States.

Objectives: A projection methodology was developed for OSCER to estimate prevalence and drug utilization of cancer patients actively treated in oncology clinics.

Methods: The projection system simultaneously estimates relationships between key data elements and projects these estimates to the entire US population utilizing patient EHR HIPAA compliant data fields

from OSCER linked to prescription (Rx) and medical office claims data. Rx and medical office claims are projected by tumor type and treatment regimen. The claims totals are then used to create factors to project the EHR sample to the US population. These factors are used to project patients by tumor, stage, regimen, line, and lab values that are nationally representative of treated cancer patients.

Results: The projection methodology provides estimates of the 1-year period prevalence of patients treated in oncology practices in the US. Projection estimates are comparable to SEER (Surveillance, Epidemiology, and End Results program) for the top four major cancers (Howlader 2011; Mariotto 2011): breast (2422915), prostate (2173205), colorectal (959289), and lung (590685) cancer in 2010. Discrepancies identified between SEER and projected prevalence from OSCER are explained in part by the number of patients who are not treated or no longer actively treated (eg, remission) with no recorded visit to an oncology clinic.

Conclusions: We developed methods to estimate prevalence and number of patients treated with specific drug therapies by cancer type and stage of disease at the US population level through linkage of patient level EHR data to health insurance claims. This OSCER projection system has the potential to improve and expedite business forecasts and pharmacoepidemiology studies.

609. The Identification of Incident Cancers in UK Primary Care Databases: A Systematic Review

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Background: Many studies have utilised UK primary care databases such as the General Practice Research Database (GPRD), or The Health Improvement Network (THIN) to investigate associations between drug use and cancer risk. However, methods used to identify cancer cases are not well described.

Objectives: To systematically review methods utilised by studies to identify incident cancers of the breast, colorectum, and prostate in a UK primary care database setting.

Methods: Medline and Embase were searched for abstracts (1980–2012) using key words such as 'can-

cer', 'primary care', and 'database'; and related synonyms. Methodological data were extracted from the manuscripts: database utilised, cancer outcome(s), codelist creation methods, case inclusion/exclusion criteria, and validation methods. Codelist questionnaires, and requests for study codelists were also sent to authors of included studies.

Results: Sixty-nine relevant studies were identified: 53 GPRD; seven THIN; one GPRD + THIN; and eight QRESEARCH studies. 21/69 studies examined > 1 cancer type: breast (n = 41), colorectal (n = 42), and prostate (n = 22). Overall, 21 study codelists were received. All 21 studies included codes indicating malignant tumours, however other cancer related codes included by the 21 studies varied: codes of malignant morphologies (n = 10), neoplasms of uncertain behaviour (n = 15), non-invasive tumours (n = 16), and benign tumours (n = 4). 42/69 studies required ≥ 1 cancer diagnosis code for case inclusion, while 27 required confirmatory evidence of diagnosis such as related surgery, though only 16 of these specified the exact evidence required.

Conclusions: Codelists used to identify cancer outcomes in primary care databases appeared to vary between studies, and were not readily accessible. Two main divisions of case definitions were apparent among the studies: the majority requiring only cancer diagnosis codes, whereas other studies needed additional confirmatory evidence of diagnosis. Transparent reporting of codelist creation methods, and improved accessibility of study codelists are needed. Moreover, it is unknown whether this apparent variation in methods actually lead to different results when applied to study questions.

610. A Remote Research Environment for Collaborative Drug Safety Studies: The OCTOPUS Infrastructure

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Background: In recent years the recognition that drug safety studies should be conducted across countries and/or databases in a collaborative manner has increased considerably. These large projects federate the available databases using local anonymization and aggregation methods. To achieve a successful and sustainable collaboration database custodians in such distributed networks should be more than just data suppliers. As most of the custodians reside in research institutes analytical tasks should be distributed as well.

Objectives: To develop a secured infrastructure that accommodates pooled analyses for distributed collaborative drug safety studies.

Methods: We developed OCTOPUS, a remote research environment that provides secured access to pooled and aggregated data. The infrastructure offers several analytical tools, word processing software, and utilities. It can host multiple research projects, each with its own secured area to share data and results. Procedures have been developed to ensure data protection and secure file transfer from and to the collaborating partners.

Results: OCTOPUS is currently used in various European and global drug and vaccine safety projects. It allows for distributed analyses, shared quality control, data archiving and rotating principle investigatorship.

Conclusions: The need for collaborative pharmacoepidemiological studies requires the development of infrastructures that facilitates collaboration, and optimizes efficiency while profiting from distributed, specialized expertise. The OCTOPUS remote research environment is a socio technological framework that has proven its value in various projects. It stimulates geographically dispersed research groups to collaborate and has resulted in consortia that where engaged in all the phases of the drug safety research. Moreover, it allowed for task distribution and division of responsibilities. The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 241679 – the ARITMO project.

611. Time Trends in Prevalence of Inhaled Long-Acting beta-2-Adrenoceptor Agonist Prescribing – A Comparison of Seven European Electronic Health Record Databases

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Background: Inhaled long-acting beta-2-adrenoceptor agonists (LABA) are frequently used in patients suffering from asthma and chronic obstructive pulmonary disease (COPD). For evaluation of real-life data, drug consumption studies are needed but results might be widely influenced due to methodological differences in particular regarding inter-country comparisons.

Objectives: This study aims to compare the LABA prescribing in the general population and specifically in patients suffering from asthma and/or COPD in five European countries.

Methods: Crude and age- and sex-standardized (European 2008 reference population) annual period prevalence rates per 10,000 persons were calculated for the period 2002–2009 based on seven European electronic health record databases (Denmark, Germany, Spain, the Netherlands (2), and the United Kingdom (2)). Stratification by sex, age, and indication were performed for the annual period prevalence rates.

Results: In all databases, we observed an increase in LABA prescriptions during the study period for the general population and for patients suffering from asthma and/or COPD. In 2008, the highest standardized period prevalence was observed in the Dutch Mondriaan–AHC and the Spanish BIFAP database (443.3 and 395.5 per 10,000 persons), and the lowest in the German Bavarian Claims and Dutch Mondriaan–NPRCD database (278.7 and 290.6 per 10,000 persons). Prevalence rates for LABA increased with age and were highest in patients over 70 years. Patients with a combined diagnosis of asthma and COPD had higher prevalence rates of LABA compared to patients with a single diagnosis of asthma or COPD. The proportion of patients with one inhaled LABA prescription only ranged from 14% (UK databases) to 35% (Spanish BIFAP database) in 2008 in the general population.

Conclusions: By using a standardized protocol, we demonstrated inter- and intra-country differences in LABA prescriptions. A general increase of LABA prescriptions during the study period was observed in all databases. This research received support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

612. A Detection Algorithm for Statin-Induced Myopathy Using Electronic Medical Records

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Background: The utility of electronic medical records (EMRs) for pharmacovigilance (PV) has been highly anticipated, because analysis using appropriately selected EMRs enables accurate evaluation of adverse drug event (ADE) frequencies and thus promotes appropriate regulatory actions. As one of the clinically important ADEs, statin-induced myopathy (SIM) has been widely reported, but pharmacoepidemiological methodology for detecting this ADE with high predictability has not yet been established.

Objectives: The current study aimed to develop a detection algorithm highly specific for SIM using EMRs.

Methods: We collected EMRs on prescriptions, laboratory tests, diagnoses and medical practices from the hospital information system of Kobe University Hospital (Japan) for a total of 5,109 patients who received prescription of statins (atorvastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin and fluvastatin) from April 2006 to March 2009. Our developed algorithm for extracting SIM-suspected patients consisted of three steps: (1) event detection: increase of creatine kinase (CK) and subsequent statin discontinuation, (2) filtration by exclusion factors (disease diagnosis/medical practices), and (3) judgment on the time course of CK values (baseline, event and recovery). A causal relationship between the event and statin prescription (probable/possible/unlikely) was judged by experienced pharmacists' review of patient medical charts. The utility of the current algorithm was assessed with positive predictive value (PPV).

Results: Among 5,109 statin-treated patients, five SIM-suspected subjects were identified by the current algorithm at a frequency of 0.1%. Review of the medical charts revealed that the causality of statin use for SIM for all five suspected patients were judged as 'Likely (probable/possible)'; thus, PPV was estimated as 100% (95% confidential interval: 56.6–100%).

Conclusions: We successfully developed a detection algorithm for SIM with high PPV. Further study is needed to confirm the utility of the current algorithm and its applicability to PV in a larger population.

613. Test Data in General Practice Are Not Missing at Random – Can We Identify When They Are?

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Background: Data on the recording of diagnostic tests and test results in general practice databases are likely to be missing not at random (MNAR). The use of such data will introduce selection bias into studies of diagnostic test accuracy. Restriction of study populations to patients in practices where test data are likely to be missing at random (MAR) may allow for valid studies of diagnostic test data; however identification of such patients has not been pursued to date.

Objectives: As part of a study of the diagnostic accuracy of rheumatoid factor (RF) testing in general practice, we sought to evaluate to what extent laboratory test results appeared to be MNAR in the UK CPRD between 2000 and 2008. We also sought to develop a method to determine where tests and test results in a practice appeared to be MNAR.

Methods: The distribution of test records and test result recording (positive/negative/missing) in the CPRD was investigated in practices within calendar years, and the proportion of missing data and ratio of positive to negative results calculated. The distribution of these statistics was compared to that reported in studies with relatively complete RF test data in order to identify periods during which recording appeared consistent with data being MNAR.

Results: We identified 178,461 RF tests in 1,782 eligible practices-years. Thirty-three percent of these had missing test results, 14% had a positive and 53% had a negative result. In 491 practice-years, 100% of tests had an associated result recorded. In 19.6% of these more than 1 in every 5 test results were positive, a ratio consistent with test records being MNAR. Among the 1,291 practice-years in which some test results were missing, 34.7% had a distribution of test results consistent with test results being MNAR. Excluding practice-years with data considered MNAR, and imputing missing results in practices where test results were MAR, yielded a dataset of 119,713 RF tests.

Conclusions: The recording of RF tests and results in the UK CPRD is incomplete, with data being MNAR in many practices. It is possible to identify episodes of practice data in which test recording appears consistent with unbiased recording of tests and test results.

614. Harmonisation of Event Definitions across Electronic Healthcare Databases; Pancreatic and Bladder Cancer as a Case Study

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Background: Differences in clinical setting, coding practices and coding dictionaries may limit the comparability of event rates estimated in different electronic healthcare databases.

Objectives: As part of the Safety Evaluation of Adverse Reaction in Diabetes (SAFEGUARD) project we sought to harmonise the operational definitions of pancreatic cancer (PC) and bladder cancer (BC) across nine inpatient and/or outpatient databases based in the UK, Spain, Netherlands, Germany, Italy and the USA and to compare the event rates obtained using these definitions to incidence rates in cancer registries.

Methods: Clinical definitions for PC and BC were defined and UMLS concepts related to the diseases were identified. Using these, investigators developed algorithms identifying the occurrence of PC and BC in their local data source. The harmony of these operational definitions was investigated through algorithm review and through the comparison of population-based event rates (number of first recorded events/ 100,000 person years) between databases and against the GLOBOCAN national cancer registry incidence rates in each database's respective country.

Results: We identified 96,666 BC events in 240,845,193 person years and 37,721 PC events in 241,241,693 person years. Initial review of algorithms and event rates revealed differences in disease definitions across databases, such as the inclusion/non-inclusion of carcinoma in-situ cases. Revision of the algorithms produced age standardised event rates (SER) ranging from 4.3 to 50.2 for PC and from 8.3 to 182.2 for BC. SER for PC in three of the databases were considerably higher than their respective national GLOBOCAN rates while SER for BC were considerably higher in four databases. Amongst the remaining databases, rates compared relatively well with their respective national GLOBOCAN figures; on average the SER of PC was 0.1 lower than the GLOBOCAN rate while the SER of BC was 6.3 higher.

Conclusions: Harmonisation of operational definitions improved internal and external comparability of event rates in many of the databases, however further work is needed to understand the remaining sources of heterogeneity.

615. Validation of Mortality Information in the German Pharmacoepidemiological Research Database (GePaRD)

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Background: Large electronic healthcare databases are increasingly being used for pharmacoepidemiological research; however, these databases need validation, since the data are not collected for research purposes.

Objectives: To validate information on mortality within the German Pharmacoepidemiological Research Database (GePaRD).

Methods: In GePaRD, information on death was available in core and hospitalization data of three statutory health insurances (SHIs) for the years 2004–2006. For each year, crude all-cause mortality rates overall and stratified by age group and sex as well as age-standardized rates of all-cause mortality, the rate of premature deaths (death at < 65 years) and the proportion of inpatient deaths among all deaths were calculated. Results were compared to the corresponding mortality indicators from the Federal Statistical Office in Germany (FSOG). For patients who died in

hospital, the date of death was compared to that recorded in the core data.

Results: The study populations comprised about 5–6 million insured per year. Stratified crude rates as well as age standardized rates of all-cause mortality and the rate of premature deaths in GePaRD were lower, but displayed similar patterns to data of the FSOG. Nearly all hospital deaths (~99%) were recorded in core data and in ~97% the date of death matched the date of death in core data. The proportion of inpatient deaths among all deaths by age group and sex and the rate of premature deaths were in good accordance with the data of the FSOG.

Conclusions: The high internal validity of data for patients who died in the hospital and the agreement in the proportion of hospital deaths among all deaths suggest a valid coding of mortality information in GePaRD. Lower mortality in comparison to the data from the FSOG can be explained by socio-demographic characteristics of the participating SHIs.

616. Harmonization of Outcome Extraction for Ischemic and Hemorrhagic Stroke Across Data Sources in the SAFEGUARD Project

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Background: In the EU-funded project 'Safety evaluation of adverse drug reactions in diabetes' (SAFEGUARD) information of several healthcare databases (DBs) from Europe and the USA will be analyzed. An important step prior to initiating multidatabase observational safety studies is the harmonization of the definitions and the extraction of outcomes in all DBs to avoid inconsistencies among them.

Objectives: To assess the comparability of incidence rates (IRs) of ischemic (IS) and hemorrhagic stroke (HS) diagnoses across DBs involved the SAFEGUARD project.

Methods: Nine population cohorts were extracted without any exclusion criteria from eight European and one US DB: Italy (HSD/Lombardy/Puglia), UK (CPRD), Spain (BIFAP), Netherlands (IPCI, PHARMO), Germany (GePaRD) and US (Medicare). The study period comprised the years from 1999 and 2012 depending on data availability of each DB. Terminology mapping was used to harmonize the codes for IS and HS events in different coding systems: ICD-9 (Lombardy, Puglia, PHARMO, HSD and Medicare), ICD-10-GM (GePaRD), READ (CPRD) and ICPC (IPCI and BIFAP). Three DBs (IPCI/BIFAP/HSD) also used free-text algorithms for case identification. Data was extracted locally from each DB and processed using standardized software (Jerboa) to obtain IRs (stratified by age and sex) and standardized IRs (SIR) (WHO population) per 100,000 person years (PY) for each DB.

Results: Overall, we detected 296,927 incident IS events and 69,094 incident HS events during 240,141,028 PYs and 241,067,032 PYs, respectively in the study period. Compared to the other DBs, SIR for IS was substantially lower in one DB and higher in another DB for both IS and HS. In the remaining DBs, SIRs for IS and HS ranged from 44.0–112.0 and 10.4–22.9 per 100,000 PYs, respectively with similar patterns of age- and sex-specific IRs.

Conclusions: Outcome harmonization of IS and HS is crucial to detect inconsistencies between DBs. Observed variations among DBs might be explained by different background incidences and characteristics of source populations, and different coding systems. Further harmonization efforts are required.

617. Identification of Seizures Among Adults and Children Following Influenza Vaccination Using Health Insurance Claims Data

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Background: Post-licensure surveillance of adverse events following vaccination often relies on electronic healthcare data to detect and evaluate safety signals. The accuracy of seizure-related diagnosis codes in

identifying true incident seizures in vaccine studies are influenced by factors such as clinical diagnostic setting and age. As most post-vaccination seizure studies have focused on pediatric populations, more information is needed on how well seizure can be identified in adults using algorithms that rely on electronic healthcare data.

Objectives: To validate an algorithm for identification of seizure events in adults and children within an administrative claims database against medical records from a large, commercially-insured United States (US) population. This validation study was part of a safety study of influenza vaccination during the 2009–2010 and 2010–2011 seasons.

Methods: Adults and children receiving influenza vaccination were drawn from a claims database of a large US healthcare insurer. Potential seizure events were identified with an algorithm comprising of ICD-9 diagnosis codes associated with an emergency department (ED) visit or hospitalization within pre-specified risk windows following vaccination. Seizure events were confirmed by medical record review. The positive predictive value (PPV) of the algorithm was estimated.

Results: Review confirmed 77 of 82 potential seizure events in the ED setting (PPV = 93.9%, 95% confidence interval [CI]: 86.3–98.0%) and 36 of 94 potential seizure events in the inpatient setting (PPV = 38.3%, 95% CI: 28.5–48.9%). The PPVs varied by age within the ED setting (98.2%, 95% CI: 90.5–100.0% in < 7 years; 76.9%, 95% CI: 46.2–95.0% in 7–24 years; 92.3%, 95% CI: 64.0–99.8% in ≥ 25 years) and within the inpatient setting (64.7%, 95% CI: 38.3–85.8% in < 7 years; 33.3%, 95% CI: 9.9–65.1% in 7–24 years; 32.3%, 95% CI: 21.2–45.1% in ≥ 25 years).

Conclusions: Our algorithm for identification of seizure events had a high level of accuracy in the emergency department setting in young children and older adults and a lower, but acceptable, level of accuracy in older children and young adults.

618. When Follow-Up Time Cannot Be Assigned: Chronic Kidney Disease and It's Diagnosis

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Background: Chronic Kidney Disease (CKD) is important in pharmaco-epidemiology. It is studied as outcome for drug nephrotoxicity and as effect-modifier. The KDIGO Clinical Practice Guideline states that abnormalities should be present > 3 months before CKD can be diagnosed. Because measurements are not performed systematically, studying CKD in observational studies might be challenging.

Objectives: To study the impact of the requirement that at least two abnormal kidney functions > 3 months apart should be present on the prevalence and incidence rates of CKD estimated from a retrospective cohort study in a dynamic population.

Methods: Data on > 1 million subjects were available from the Integrated Primary Care Information database, containing complete electronic medical records gathered by general practitioners. The incidence and prevalence of CKD were based on (1) an increased urine albumin to urine creatinine ratio (ACR), (2) a decreased estimated Glomerular Filtration Rate (eGFR), or (3) explicit statement in the medical record. A diagnosis was considered 'possible' based on a single abnormal measurement and 'definite' based on two abnormal measurements > 3 months apart.

Results: A total of 784,563 adult subjects, with 1,379,097 eGFR measurements and 178,425 ACR measurements were available. The overall CKD incidence rate in adults for a possible diagnosis was 1,213 per 100,000 person-years and 6.7% of the adult population had a prevalent diagnosis of CKD. For a definite diagnosis these were 489 per 100,000 person-years and 5.1%. In patients with an incident definite diagnosis confirmation of the first abnormal measurement was obtained after a median 301 days (Interquartile range 148–444 days).

Conclusions: In daily practice repeat measurement after a first abnormal kidney function measurement is performed later than the 3 months required by the guideline, resulting in an underestimation of CKD from electronic health care data when using the strict definition. A diagnosis based on a single measurement might be valid too, if abnormal measurements shortly followed by hospitalization or a repeat measurement with improvement, more likely compatible with acute kidney injury, are excluded.

619. Spending with Infliximab vs. Disease-Modifying Anti-Rheumatic Drugs for Rheumatoid Arthritis Treatment in SUS, from 2003 to 2006

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune incapacitating disease, which causes economic impacts for patients and for society. Pharmacological treatment includes the use of biological agents, such as infliximab (IFX), which are indicated for patients who have failed treatment with therapeutic disease-modifying anti-rheumatic drugs (DMARD). These medicines are available in Brazil through the Unified Health System (SUS).

Objectives: The aim of this study was to characterize the profile of users and related expenses with IFX and DMARD for RA treatment in SUS.

Methods: We constructed a cohort from 2003 to 2006 from databases of the Outpatient Information System databases of SUS. Analyzes were stratified by clinical and socio-demographic characteristics. We calculated the average monthly expenses for each individual follow-up year and the factors that influenced it. The costs were converted to real (BRL) to U.S. dollars (USD) using the index of purchasing power parity of the World Bank, which 1 USD corresponded to 1.71 BRL. We used SPSS 17.0 to the statistical analysis.

Results: The cohort consisted of 26,228 patients, mostly female, between 40 and 59 years, residing in Southeast and diagnosed with Felty's syndrome. Medicines for RA totalized USD 43,453,852.15, of which infliximab accounted for 70% of the value. The median monthly spending per capita was USD 2,026.92 for patients using IFX compared to USD 84.12 for patients treated with DMARD. The monthly spending for individual patients using IFX was higher for males, with RA complications diagnosis and residents in regions Midwest and Southeast. The number of patients seen by SUS followed the concentration of rheumatologists/capita and Human Development Index of the municipality of residence.

Conclusions: Drug treatment for RA was the main expense in SUS, with high economic impact due to IFX. Sex, diagnosis, age and region of residence were factors that influenced spending.

620. Statins and the Risk of Herpes Zoster: A Population-Based Cohort Study

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Background: Herpes zoster is a common illness caused by reactivation of latent varicella-zoster virus infection. The incidence increases with age, from 2 per 1,000 patient-years among individuals < 50 years of age to over 10 per 1,000 person-years in those 70 years of age and older. Statins are widely used lipid-lowering drugs with immunomodulatory properties which may favour reactivation of latent varicella-zoster virus.

Objectives: To compare the risk of herpes zoster in older patients receiving statins with that of non-users of these drugs.

Methods: We conducted a population-based retrospective cohort study of all Ontario residents aged 66 years or older using administrative healthcare databases between April 1, 1997 and March 31, 2010. We used propensity-score matching to ensure comparability in measured confounders between patients initiating continuous statin therapy and non-users of these drugs. The primary outcome was a new diagnosis of herpes zoster, defined as a physician visit, emergency department visit, or hospitalization for herpes zoster, or the receipt of a prescription for either valaciclovir of famciclovir. All individuals were followed for up to 2-years from their index date until the occurrence of the outcome, death, statin discontinuation, or end of the study period. We used Cox proportional hazards regression to examine the association of statin use and herpes zoster.

Results: Over our study period, we matched 494,651 individuals newly exposed to statins to an equal number of untreated individuals with highly similar baseline characteristics. In our primary analysis, the rate of herpes zoster was higher among users of statins relative to non-users of these drugs (13.25 vs. 11.71 per 1,000 person-years, respectively; hazard ratio 1.13, 95% CI 1.10–1.17). The attributable fraction of exposed individuals was 11.6%. In a test of specificity, no association was found between statin use and knee arthroplasty (hazard ratio 1.04, 95% CI 0.99–1.09).

Conclusions: Our findings suggest that, among older patients, statins are associated with a small but significantly increased risk of herpes zoster.

621. Assessing the Completeness and Quality of Saudi Adverse Event Reporting System (SAERS)

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Background: The Saudi Adverse Event Reporting System (SAERS) is a part of the Saudi Food & Drug Authority Pharmacovigilance system for monitoring the safety of medications. SAERS includes adverse events from pharmaceutical companies as well as healthcare professionals and patients. The completeness and the accuracy of data sent to the SAERS are very important to be assessed.

Objectives: The objective of the study was to assess the completeness and quality of reports in the SAERS database.

Methods: Reports that have been received during the period of December 2009 until June 2012 in the SAERS were reviewed. The completeness was assessed by reviewing the components of the adverse drug reaction (ADR) form and how many of these fields were filled. For quality, the type and the quantity of the information in the fields that was filled by the reporter were reviewed. A descriptive analyses of to evaluate the completeness of the SAERS components (ADRs form components) were carried out. The Statistical Package for Social Science (SPSS) Software for Windows,Version 20.0 was used to perform these analyses.

Results: There were 14,783 reports during the period of December 2009 until June 2012. Number of reports jump from 439 to 14,783 reports in 2009 and 2012, respectively. Majority of these reports were spontaneous reports. The information related to the drug and adverse event were almost complete, 99.4% and 98.4% reports; respectively. As patient demographic data and for gender field, 90% of the reports have it filled, while 67% of reports include the age information. Majority of reports include the outcome information (80%). However, there are other fields that don't often filled such as action taken and dechallenge information. The most reported drug class was tumor necrosis factor

inhibitors (6.5%). While events involving the respiratory organ system was the most reported event (4.5%).

Conclusions: This is the first study assessing the completeness and quality of SAERS. SAERS showed an increasing tendency of reporting over time. Although the system is considered new, it has a high number of reports and based on the results of this study, it is relatively considered of a good quality of data.

622. Strengthening Pharmacovigilance Capabilities in Canada by Using MedDRA Coding and Medical Case Review in Parallel to Classify Reports of Adverse Events Following Immunization Received by the Public Health Agency of Canada

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Background: The Canadian Adverse Events Following Immunization Surveillance System(CAEFISS) collects Adverse Events Following Immunization (AEFI) reports. The majority come from public health professionals. Reports are MedDRA (Medical Dictionary for Regulatory Activities) coded. A new medical case review (MCR) process was added in 2011 to classify reports by severity and main reason for reporting.

Objectives: To demonstrate the relative contribution of MedDRA and MCR processes to national pharmacovigilance activities.

Methods: AEFI reports received in 2011–2012 were coded in MedDRA. In parallel, the MCR assigned a primary reason for reporting and severity classification (Serious/High/Moderate/Low Impact). Serious classification is based on international definition. The other classifications were developed using aspects of health care utilization, impact on daily activities, and treatment. The contributions of MedDRA coding and MCR in our vaccine pharmacovigilance activities were assessed.

Results: MedDRA allowed for signal detection using disproportionate reporting analysis and facilitated response to requests on specific events. The granularity of MedDRA permitted thorough description of signs and symptoms. Results of MCR facilitated rapid summation of the types and severity of AEFIs, and identification of reporting trends as well as any changes in these trends. The MCR process also enabled prioritization for selective analyses and signal investigation.

Conclusions: Pharmacovigilance activities are enhanced when both MedDRA coding and MCR are used. MCR process ensured review of individual reports by a health care professional providing timely preliminary

assessment of signals when needed. MCR classification is closely aligned with the national report form enabling feedback to Public Health authorities, Health Professionals and the Public regarding the safety profile of vaccines in Canada. Depending on the nature of the request and requestor, results of both processes can be used to provide meaningful feedback, thus increasing the flexibility of CAEFISS.

623. Evaluation of a Standardised MedDRA Query (SMQ) in Administrative and Electronic Medical Record (EMR) Databases

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Background: Semi-automated analytical products, such as SAEfetyWorks® (SW), provide access to various databases via a common data vocabulary. In SW, source data for conditions are represented by ICD-9 codes which have been mapped to MedDRA from data provided by the Unified Medical Language System (UMLS). It is critical to understand MedDRA with regards to its application in drug safety research using administrative data.

Objectives: This study was designed to evaluate the completeness of the data dictionary mapping to a MedDRA SMQ in a semi-automated analysis tool.

Methods: A literature search in PubMed was conducted to identify ICD-9 codes that corresponded with the MedDRA preferred terms (PT) that comprise the SMQ for biliary disorders. Each PT along with the words ICD-9, administrative, claims, hospital or electronic were searched. ICD-9 and CPT dictionaries were also reviewed. A list of ICD-9 and CPT codes was created based upon search results. Administrative claims and EMR databases were analyzed for the number of patients with a biliary SMQ diagnosis based on the UMLS mapping and were compared to the results from comprehensive search strategy (CSS). The databases interrogated in this analysis were GE Centricity (GE), PharMetrics (PM) and MarketScan Commercial Claims (CCMC).

Results: The difference between the number of patients identified by the comprehensive search strategy and the UMLS mapped SMQ was $\leq 1\%$. 381,749; 1,424,253; and 2,854,681 patients were identified based on the UMLS mapped SMQ for biliary disorders in GE, PM and CCMC databases, respectively. The CSS identified 384,593; 1,434,757; and 2,886,532 patients, respectively. ICD-9 procedure codes were rarely or never used in GE or PM and CPT codes were more common than ICD-9 procedure codes in CCMC.

Conclusions: The UMLS mapping of ICD-9 to MedDRA PTs within the biliary SMQ provided excellent consistency with the comprehensive search strategy. Due to the large number of PTs in a typical SMQ these results are likely generalizable to other SMQs. Neither ICD-9 nor CPT procedure codes were mapped by UMLS; however the impact was limited due to the broad nature of the SMQ.

624. Risk Identification in Healthcare Records – Comparison to Epidemiological Studies

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There is increased interest in healthcare records for broad risk identification. This requires a generic analytical framework that works for a variety of drugs and adverse drug reactions, while being robust to data quality problems. Unlike confirmatory studies, the analytical design cannot be carefully optimized for a pre-specified hypothesis of interest.

Objectives: To evaluate the performance of a calibrated self-controlled cohort (CSCC) analysis in a generic implementation against published epidemiological studies in the same database.

Methods: The CSCC implementation was used to identify increased rates of medical events after drug prescriptions in The Health Improvement Network (THIN) database. Comparison was made to previously published epidemiological studies based on THIN and discrepancies were reviewed and classified. An assessment of the selected epidemiological studies was performed.

Results: Among 235 published studies on THIN, our literature review identified 13 studies of possible adverse drug reactions, listing a total of 56 evaluated drug-adverse reaction pairs. The CSCC highlighted 13 of the 27 associations identified by the studies (sensitivity 0.48), together with an additional four that had not been highlighted by the studies (positive predictive value 0.86). Explanations for the 14 false negatives include lack of power as CSCC analysis was performed on a more granular level of individual drugs

and medical events, and increased rates of the medical event in the control period due to other drugs. Others may reflect the tentative nature of the published epidemiological findings. Possible explanations for false positives include protopathic biases and channeling effects. Their identification requires clinical and epidemiological expertise and can be facilitated by the review of the associated temporal patterns.

Conclusions: We identified reasons for and against concordance between CSCC and the studies. Accurate assessment of method performance requires: clinically relevant groupings of dugs and medical events plus evaluation of multiple methodologies.

625. Safety Signal Surveillance Study of Adverse Events of Special Interest for Intradermal Influenza Vaccine Using THIN Database

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Background: Intradermal influenza (IDflu) vaccine has been indicated for active immunization against flu disease in adults aged ≥ 18 years in the UK since 2010. To monitor early safety signals for IDflu, we initiated an ongoing post-licensure safety surveillance study.

Objectives: The objective of the study was to monitor the incidence of adverse events of special interest (AESIs) following IDflu vaccination in adults in the UK.

Methods: The crude incidence rates of the AESIs, i.e. vasculitis including polymyalgia rheumatica (PMR), convulsions, encephalomyelitis, Guillain-Barre Syndrome, neuritis, severe allergic reaction, and thrombocytopenia were calculated in patients who had IDflu vaccination using THIN data from 01/09/2010 to 31/01/2012 and compared to intramuscular influenza (IMflu) vaccine and no influenza vaccine groups. Cases of AESIs were defined using Read Codes reported during the 42 days following vaccination except for convulsions (2 days) and severe allergic reaction (3 days). Follow up was censored at time of AESI, death, disenrollment from health practice, end of study period or risk window. The entry date was the date of flu vaccination or 1 September 2010 (or 1 year after the beginning of enrollment if it occurred later) for those not receiving flu vaccine.

Results: Among 12,086 IDflu vaccinees the only AESI observed was vasculitis (six PMR and one non-PMR cases). The incidence rate of vasculitis including PMR was 396.4 per 100,000 person-years (95%CI, 159.4–

816.7) for IDflu, 341.8 (95%CI, 314.1–371.2) for IMflu, and 36.2 (95%CI, 34.2–38.3) for no flu groups. For IDflu, the PMR cases were elderly patients and had no information on vascular involvement.

Conclusions: The incidence rate for vasculitis (primarily PMR) was about the same in IDflu and IMflu groups, but higher than no flu vaccine group. Given the limited number of cases, uncontrolled confounding factors, and lack of support from other data sources, these results should be interpreted with caution. Monitoring should continue to further assess the IDflu vaccine AESI (labeled for IMflu) in context of the benefits.

626. Withdrawn by Author.

627. Development of an Algorithm for Detecting Heparin-Induced Thrombocytopenia and Assessment of the Risk Factors Using a Medical Information Database

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Background: A new era of pharmacovigilance is coming using the electronic medical information data systems that are widely spread in most hospitals in Japan.

Objectives: To promote pharmacovigilance activities using a medical information database (MID), we aimed to develop and validate a novel algorithm for detecting heparin-induced thrombocytopenia (HIT), and to assess possible risk factors for HIT.

Methods: This study was performed using a standardized MID in University Hospital of Hamamatsu University School of Medicine (Shizuoka, Japan) which covers health records of approximately 200 thousand patients. Patients who were treated with unfractionated heparin (UFH) together with proper platelet count testing from 1st April 2008 through 31st March 2012 at the Hospital were included. Patients receiving anti-cancer drug therapy within 4 weeks before the UFH administration were excluded. We developed a HIT detection algorithm based on the time-course information of platelet count and the diagnostic information

to exclude pseudo-HIT. Definite diagnoses of HIT were made from medical record review by a skilled hematologist, and algorithm performance was assessed using positive predictive value (PPV). Possible risk factors for HIT development were evaluated by multivariate logistic regression analysis.

Results: The current algorithm detected 47 patients with suspected HIT in the source population (n = 2,875). Of these, 41 were identified as definitive HIT after the medical record review. The PPV for the algorithm was 87.2% (95% CI: 74.8–94.0%), and the frequency of definitive HIT was 1.4%. Longer-term treatment (more than 3 days) was identified as a risk factor for HIT, with an odds ratio of 5.38 (95% CI: 2.35–12.32) for definitive HIT.

Conclusions: We successfully developed a novel, high PPV detection algorithm for HIT, and identified possible risk factor for HIT. Our results support the utility of MIDs for improving pharmacovigilance and related scientific research.

628. Positive Predictive Value of ICD-10 Discharge Diagnoses of Infection Among Cancer Patients in Denmark

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Background: Infections are serious complications of neoplasms and antineoplastic treatments. Validating infection diagnoses recorded in administrative databases is important for use of these databases in pharmacovigilance studies.

Objectives: To estimate the positive predictive value (PPV) of primary hospital discharge diagnoses of infection in the Danish National Registry of Patients (DNRP) among cancer patients; and to estimate PPV for discharge diagnoses of infections of special interest: pneumonia, skin infection, and sepsis.

Methods: This validation study was conducted in northern Denmark, an area of about 580,000 residents. We identified patients with a primary diagnosis of infection in the DNRP from 2006 to 2010, who had a history of solid tumor within 5 years of the potential infection. We randomly sampled 272 patients, including at least 40 patients with each of the infections of special interest to ensure adequate PPV precision. Medical chart review was used as the reference standard. Presence and type of infection was confirmed or ruled out based on an assessment by clinicians blinded

to the recorded infection diagnosis. The overall PPV was estimated with and without requiring agreement on type of infection. A PPV was also estimated for each infection of special interest.

Results: Two hundred and sixty-six (98%) medical charts were available for review. Median age at infection diagnosis was 67 years (quartiles: 59–76); median length of hospital stay was 6 days (quartiles: 3–11). Presence of any infection was confirmed in 261 of the sampled patients, for an overall PPV of 98.1% (95% confidence interval [CI]: 95.9–99.3). Requiring agreement on infection type, by level of affected organ system, lowered the overall PPV to 77.4% (95% CI: 72.1–82.2). For skin infection, pneumonia and sepsis, PPVs (95% CI) were 79.0% (64.2–89.6), 92.5% (85.8–96.6) and 82.2% (69.2–91.2), respectively.

Conclusions: Diagnoses of infection in the DNPR have a high degree of validity overall and for the three studied infections of special interest making the DNRP a reliable source for pharmacovigilance studies focused on infections.

629. Incidence of Opioid Intoxications in Patients with or Without Alcohol Related Disorders Treated with High-Potency Opioid Analgesics in 2004–2009

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Background: In November 2010, the European Medicines Agency's Committee for Medicinal Products for Human Use completed a review of the safety and effectiveness of slow release oral high-potency opioids (HPO) based on the concern that some of these controlled-release systems may be unstable when co-ingested with alcohol resulting in a too quick release of the active substance.

Objectives: To estimate incidence rates (IRs) of opioid intoxications (OIs) in patients with or without alcohol related disorders (ARD) treated with HPO analgesics.

Methods: Data were obtained from the German Pharmacoepidemiological Research Database (GePaRD) including over 17 million insurants. Analyses were based on a cohort of patients receiving at least one HPO prescription in the years 2004 to 2009. For these patients prescriptions of high- and low-potency opioids during time in cohort were assessed and the durations of treatment estimated. Patients were classified as having ARD, if they had a respective diagnosis or medical treatment. OI was defined as a hospitalization for opioid intoxication or related events. IRs with 95% confidence intervals (CIs) were calculated.

Results: Of 308,268 HPO users, < 1% (0.6%) had an OI, resulting in an overall IR of 340.4 per 100,000 person years (95% CI: 325.5–355.7). ARD was found in 5.4% of patients. IRs were highest in patients receiving concomitant high- and low-potency opioid therapy or concomitant slow and quick release HPO, respectively. Regarding slow release HPOs including patches, exposure to morphine was associated with the highest risk, followed by transdermal fentanyl. ARD increased the overall IR for slow release HPO by a factor of 1.5. Orally applied products showed higher increases than transdermal patches.

Conclusions: Our study found the IR of OI to be substantially higher in patients with ARD compared to those without. Against the background of increasing opioid consumption and given the high percentage of patients with ARD in our cohort of HPO users, careful and responsible opioid prescribing and monitoring is highly important.

630. Quantitative Analysis of Gender Based Risk in Macrolide-Related QT Prolongation and Cardiovascular Events

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Background: Use of macrolides has been associated with the risk of QT interval prolongation (QTP), predisposing patients to serious arrhythmias such as Torsades de pointes (TdP), ventricular tachycardia and sudden death. Women are at greater risk of developing drug-induced QTP, but few studies have quantified sex differences in the risk of macrolide-related QTP and subsequent cardiovascular (CV) events.

Objectives: To estimate the risks of macrolide-related QTP and CV events by gender.

Methods: We reviewed FDA's Adverse Event Reporting System (AERS) database to retrieve U.S. reports on FDA approved macrolides (azithromycin, clarithromycin, erythromycin and Telithromycin) from July 2005 through June 2012. Reports missing gender and duplicates were removed. Cases were defined as the reports with (1) the QTP-specific MedDRA Preferred Terms (PTs) 'ELECTROCARDIOGRAM QT INTERVAL ABNORMAL', 'ELECTROCARDIO-GRAM QT PROLONGED,' and 'LONG QT SYN-DROME' or (2) TdP/QTP Standardised MedDRA Query (SMQ) PTs for CV events; non-cases were of other reactions. The Odds Ratios (OR) with 95% confidence intervals (95% CI) were calculated by Mantel-Haenszel estimation.

Results: We reviewed 2,264,514 reports from the AERS database and identified 5,878 macrolide reports: 727 Erythromycin, 896 Clarithromycin, 2,315 Azithromycin and 1,940 Telithromycin. There were 3,977 macrolide reports (68%) submitted by women and 1901 (0.32%) by men. The QTP-specific search identified 23 cases: 18 (78.3%) cases for women and 5 (21.7%) for men. The SMQ search retrieved 228 cases: 160 (70.2%) for women and 68(29.8%) for men. For QTP search, OR was 1.72 (95% CI: 0.639–4.651, p = 0.276)) and for TdP/QTP SMQ search 1.13 (95% CI: 0.846–1.509, p = 0.407); both suggested increased risk of QTP and CV events for women compared to men.

Conclusions: Our findings confirmed the female gender as a risk factor for QTP and CV events among US macrolide users. Quantitative results of this study can inform prescribers in safe, gender-specific selection of antibiotics.

631. Influence of Computing Power for Time-Dependent Analysis in Large Cohorts Using SAS

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Background: Analysing data from observational studies where patients switch exposure during follow-up requires the use of survival analysis models which incorporate time-dependent covariates. Such analyses are computationally complex and processing time is prohibitive with large healthcare databases. SAS (Cary, NC, USA) is widely used to perform these analyses.

Objectives: To define the best hardware and SAS configuration to do time-dependent analyses and establish the feasibility of doing these on large datasets.

Methods: Four computers were used; A:2core 2.3 GHz, B:4core 1.9 MHz C:32core 2.3Mhz and D:8core 2.4Mhz. Two computers (C & D) were then optimised according to SAS advice and internal tests. Code was used to create a repeatable random SAS dataset, with up to 10 years follow-up, a time dependent variables updated on a daily basis, a population of 10,000 and 30 covariates. A time-dependant Cox Proportional Hazards model was run using the PHREG procedure in SAS 9.3. Average processing times were calculated against standard hardware and SAS configurations. Iterations were run adjusting hardware and software in search of the best processing

times. Utilising the optimised system, feasibility was assessed by creating a table with various cohort and covariate ranges.

Results: Average Run-times were:

A:(n = 1) 948mins
B:(n = 3) 95mins
C:(n = 4) 119 min, optimised 41mins (65.1% improvement)
D:(n = 3) 52 min optimised 36 min (29.3% improvement)

Feasibility testing identified a comfort zone curve between 200,000 patients with two covariates and 100,000 with four covariates. Further increments to co-variates or patients took prohibitively long (> 5 weeks).

Conclusions: The fastest hardware did not produce the best results. Most gains were achieved through optimisation of SAS options. Using SAS to run time-dependent Cox model for cohort studies is achievable while limiting file sizes. Running against larger cohorts is impractical. Until SAS can utilise the hardware, specifically greater multicore processing with PHREG, such analyses will remain difficult. In the short term, other study designs such as nested case control studies must be used.

632. Adverse Drug Reaction Reports of Patients and Healthcare Professionals; How Different Are They?

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Background: Changes in the European pharmacovigilance legislation make it possible for patients of all European member states to report concerns regarding drugs directly to the national reporting centre for adverse drug reactions (ADRs). Despite a number of studies that have been conducted on patients as reporters in pharmacovigilance, typical characteristics of patients' ADR reports compared to those of healthcare professionals (HCPs) are unclear.

Objectives: To explore the differences in reported information between patients' and HCPs' ADR reports.

Methods: A retrospective study among 200 anonymised patients' and HCPs' ADR reports. Reports were rendered anonymous and rated using a list of objective (for example start date of the ADR) and subjective (for example the impact of the ADR) elements of information that could be important considering ADR reporting. A two-side Pearson's Chi-square test (p < 0.05) was used to detect statistically significant differences in the number of reported elements of information.

Results: The reported information between patients' and HCPs' reports is broadly consistent. However, differences were found in both objective and subjective elements of information; HCPs had a higher score for objective and patients for subjective elements. Elements of information that were more often reported by patients: outcome ADR, detailed description, course of ADR, impact the ADR on the patient's daily of life, severity, patient's weight and height, patient's thoughts about causality, and contact with or between HCPs. Elements of information that were more often reported by HCPs: seriousness, registration number for drugs, dosage, route of administration, pharmaceutical form, other suspect drugs, medical history, and diagnosis confirmed with test results.

Conclusions: Although the reported information is generally comparable, patients' reports are more focused on the impact of the reported ADRs, whereas reports from HCPs provide more diagnosis related information.

633. Hallucinations: A Case/Noncase Study in the French PharmacoVigilance Database

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Background: Hallucinations are sensory perceptions which occur without external stimuli. Hallucinations accompany certain neuropsychiatric disorders, such as schizophrenia, they also can be induced by drugs.

Objectives: To evaluate putative associations between exposure to medications and the occurrence of hallucinations on the French Pharmacovigilance System Database.

Methods: We used the case/noncase method in the French PharmacoVigilance Database (FPVD). Cases were all the observations with the LLT term 'perception disturbances', which included all types of hallucination, registered into the FPVD from January 1985 to 2013. Noncases were all other reports. Parkinson disease therapies were used as positive controls. Data were expressed as odds ratio (OR) with their 95% confidence intervals.

Results: Among the 469,181 reports of adverse effects recorded between 1985 and 2013, 0.9% (4,087) are

hallucinations. For about 50% (2,158) of these cases, these hallucinations were experimented by patient older than 65 years old. For about 10% (364), child of < 15 years are involved. A statistically significant OR was found with several medications included Parkinson disease therapies such as rasagiline (OR 18.1 [95% CI 10.7–30.7]) but also with zolpidem (OR 13.2 [95% CI 11.5–15.2]), methylphenidate (OR 8.6 [95%CI 5.2–14.3]) and baclofene(OR 4.4 [95%CI 2.7–7.2]). An increased risk of hallucinations was also observed with non central nervous system drugs, including ertapenem (OR 21.1 [95%CI 12.2–36.7]), voriconazole (OR 13.1 [95%CI 10.3–16.7]), valacyclovir (OR 8.6 [95%CI 6.5–11.4]), oseltamivir (OR 7.5 [95%CI 4.5–12.5]), mefloquine (OR 6.0 [95%CI 4.3–8.3]), ciprofloxacin (OR 3.8 [95%CI 3.1–4.6]) and omeprazole (OR 2.1 [95%CI 1.7–2.7]).

Conclusions: This pharmacoepidemiological study describes an association between drugs and hallucinations. This relationship involves not only some already suspected drugs but also other drugs less known to induce such an adverse drug reaction. Despite the mandatory limits of this kind of study, these data represent a PharmacoVigilance signal.

634. Leveraging Multiple EHR Databases in Parallel as an Innovative Means for Active Postmarketing Hepatotoxicity Monitoring in Oncology Patients

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Background: Pazopanib was approved in 2009 for advanced renal cell carcinoma (RCC). During clinical development, liver chemistry (LC) abnormalities and adverse hepatic events were observed, leading to a boxed warning for hepatotoxicity and detailed label prescriber guidelines for liver monitoring.

Objectives: To ensure patient safety, we designed a 4-year epidemiologic sequential cohort study, nested in three electronic health records databases, to assess real-world prescriber compliance with liver monitoring label guidelines, and to quantify the hepatic safety of pazopanib in clinical practice.

Methods: To accrue sufficient numbers of patients, given the low incidence of RCC, treatable population, and rare outcome of drug-induced liver injury (DILI), parallel epidemiologic analyses are being conducted with data from a U.S. national healthcare system, oncology community practices, and a Dutch network of healthcare records. A common surveillance protocol is implemented by a central coordinating center to ensure consistent methodology across databases. Summary statistics from each cohort reflecting cumulatively accrued patients are aggregated at regular intervals, and reported to regulatory agencies. LC elevations and possible Hy's Law cases are identified through laboratory data. Possible drug-induced liver failure cases are flagged via a screening algorithm. An adjudication committee of hepatologists reviews abstracted chart information for final determination of drug-associated causality using methods established by the DILI Network.

Conclusions: The design of observational safety studies in oncology is challenging due to limitations in longitudinal data sources that contain tumor histology, clinical characteristics, laboratory data, in- and outpatient encounters and procedures, and oral and IV medications. The methodological hurdles are compounded by uncommon cancers, small drug population sizes, and rare outcomes. This innovative study illustrates one approach to circumventing these limitations while still achieving timely and robust results that inform patient safety for a newly approved oncology medication.

635. Incidence of Cardiovascular Events in the Real World Population of Cancer Patients with Solid Tumors

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Background: Data on the incidence of cardiovascular (CV) events in cancer patients with solid tumors are important in order to differentiate whether an observed incidence of CV events is associated with an oncology treatment or an effect of the cancer itself. However, these data are limited.

Objectives: To estimate the incidence of specific CV events among cancer patients diagnosed with solid tumors who were not treated with tyrosine kinase inhibitors (TKIs) or drugs with similar mechanism of action.

Methods: *Design*: A population-based cohort study of Kaiser Permanente Northern California (KPNC) members. *Setting*: KPNC is an integrated health program with 3.2 million members comprising ~30% of the insured population in 14 Northern California counties. *Exposure*: Cancer registry diagnosis (1997–2009) of any solid tumor excluding non-melanoma skin cancer. A prespecified subgroup analyses included 10 specific cancers of interest, including renal, colorectal, and lung cancers. *Main outcome measures*: Acute coronary

syndrome (ACS), heart failure, ischemic stroke, hemorrhagic stroke, cardiac arrest, hypertension (HTN), deep venous thrombosis, pulmonary embolus, and CV death. *Statistical analysis*: The incidence rate (IR) of each outcome was measured as the rate of events per 1,000 person years (PY) occurring at any time after the cancer diagnosis reported with 95% confidence intervals (CI).

Results: Of ~160,000 patients were included in the cohort (mean age = 62.2 years, 54% female, and 74% White). Patients received varied cancer treatments at baseline. HTN occurred most commonly among all patients with the IR (per 1,000 PY) ranging from 28.5 (95%CI:25.4–32.1) for renal cell carcinoma to 43.4 (95% CI: 40.0–46.9) for NSCLC. The IR of each CV endpoint varied across cancer types; the IR of ACS ranged from 6.5 (95% CI: 6.2–6.9) in breast cancer patients to 20.7 (95% CI: 18.3–23.3) in renal cancer patients to 48.1 in SCLC patients (95% CI: 38.9–59.3). In general, the highest rate of each CV endpoint was observed among lung cancer patients.

Conclusions: This large, community based population study of cancer patients provides important epidemiologic data on the incidence of CV events by type of cancer.

636. Cause of Death Recording in the Health Improvement Network (THIN) UK Data Among the Afloat Study Population (n = 56,508)

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Background: Cause of death (COD) recording in UK general practices is dependent on several factors including reporting to the general practitioner, relevance and expectedness of the information, medicolegal influences and local recording practices. The AFLOAT study assessed health outcomes, including death, among atrial fibrillation (AF; N = 9,418) and matched control patients (N = 47,090) aged ≥ 40 years in The Health Improvement Network (THIN). Within 2 years of index date, 9.6% (N = 5,428) of the study population had died.

Objectives: To assess the distribution of COD recording in THIN among the AFLOAT study population.

Methods: COD was sourced from coded and free-text information in THIN. COD recording was assessed across cohorts, genders, age groups and practice sizes. Differences in proportions of recorded COD were investigated using chi-squared tests.

Results: From coded and free-text information, COD was available for 45.6% (N = 2,474) of patients who died. There was no evidence at the 5% level to suggest that the amount of COD recording differed between cohorts (p = 0.642) or gender (p = 0.602). However, there was evidence that recording differed across age groups (p = 0.012); the proportion of patients with COD recorded in each age group ranged from 41.3% (60–69 years) to 47.8% (80–89 years). There was evidence of a linear trend between COD recording and age (p = 0.018). The proportion with COD recorded in each practice size category ranged from 41.3% (small practices; 1,000–8,000 patients) to 49.0% (large practices; 12,000–30,000 patients). There was evidence that the amount of COD recording differed across practice sizes (p < 0.001) and there was a linear trend between COD recording and practice size (p < 0.001).

Conclusions: Approximately half of patients who died during the 2 year follow-up period had a recorded COD in THIN. COD was generally recorded more often in the older age groups and larger practices. To minimise bias, differences in COD recording should be considered when designing and interpreting studies which use COD information. Further research will evaluate access to death certificates in this population to supplement COD information.

637. Data Elements in Inpatient Databases To Enhance Safety and Health Outcomes Research

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Background: The type of health services rendered to inpatients (INPT) differs markedly from outpatients; IV drug administration, major surgeries and ICU stays are unique INPT services that change hourly or daily. Access to INPT data provides details of acute care often on conditions unique to INPT setting.

Objectives: To profile categories and granularity of INPT data.

Methods: Databases (DB) with INPT data were identified by reviewing 200 population healthcare DB profiles in B.R.I.D.G.E. TO DATA® (www.bridgetodata.org). Spontaneous reporting systems (SRS) were excluded due to generally high variability in data quality; DBs without diagnosis, drug or procedure data were excluded. The remainder were assessed for demographic & clinical data elements. DBs with data obtainable via linkage or request were retained.

Results: A total of 114/200 DBs profiled in B.R.I.D.G.E. had INPT data. Excluded were 12 SRS & 40 DBs missing diagnosis, drug or procedure data.

The remaining 62 INPT DBs consisted of (nonmutually exclusive) 42 longitudinal, two national surveillance, two cross-sectional & one hospital discharge DB and 21 registries. Fifty-five DBs with INPT data also had outpatient data. Of the 42 longitudinal DBs, only 13 captured *daily* medical events, such as drugs, procedures, physical exams, disease severity, medical services (e.g., dialysis, oxygen therapy) and special care (e.g., hospice care, rehab). Treatment data often had time of drug administration, department-specific medications (e.g., IV drugs, anesthesia, chemo) and drugs prescribed at discharge. The other DBs with INPT data provided summaries of events, e.g., admission/discharge diagnoses, procedures. Lifestyle information was often available (40) but type of data varied. Access to medical records (26) or linkage to other DBs (39) was frequently possible.

Conclusions: The pattern of hospital care is described by data elements unique to inpatient settings. Select INPT DBs with daily clinical data offer valuable information on acute treatment, diagnostic tests, drugs & procedures. This study highlights the types and details of INPT data that can provide detailed insight into safety & outcomes studies.

638. Prevalence, Selected Co-Morbidities and Systemic Therapies in a U.S. Population-Based Cutaneous Psoriasis Cohort

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Background: Data on the prevalence of and systemic therapies for cutaneous psoriasis in the United States are limited.

Objectives: To determine prevalence of, systemic treatments for, and selected co-morbidities in psoriasis patients with skin manifestations using a U.S. electronic medical records (EMR) deidentified dataset.

Methods: We created a cohort of patients with a skin psoriasis diagnosis [ICD-9 696.1] among the total population affiliated with integrated delivery network (IDN) providers, and that had at least 1 year of follow-up in the Humedica dataset between 2007 and March 2012. Systemic agents [methotrexate, TNF inhibitors, cyclosporine, acitretin] for psoriasis treatment, and selected infections and malignancies were identified. The prevalence of psoriasis, selected co-morbid infections and malignancies were estimated and compared with published data.

Results: Among 1,868,100 patients at IDNs, 17,568 (0.94%) psoriasis patients with median age of 55 years

were followed for an average of 2.4 years. Systemic therapy for psoriasis was prescribed in 5.2% of psoriasis patients [methotrexate (3.0%), TNF inhibitors (2.2%), cyclosporine (0.3%) or acitretin (0.6%)]. Bacterial sepsis (2.8%), invasive fungal infection (0.4%) and tuberculosis (0.2%) were documented. Specific causes of bacterial sepsis included *Staphylococci* (30.2%), *Streptococci* (7.3%), *E. coli* (6.9%), *Pseudomonas* (2.2%), and *Klebsiella* (2.0%); and 17.0% of bacterial sepsis patients had 2–9 bacterial sepsis episodes. In the psoriasis population, the cumulative incidence of selected cancers included prostate cancer (5.0%), breast cancer (2.3%), lymphoma (1.4%), lung cancer (1.2%), leukemia (0.5%), colon cancer (1.1%), melanoma (0.9%), and squamous skin cancer (0.5%).

Conclusions: The prevalence of psoriasis and cumulative incidence of systemic infections and malignancies were largely consistent with data from other population-based cohorts, mostly from Europe. Five percent of this cohort received systemic therapy for psoriasis. Identification of specific causes of bacterial sepsis in cutaneous psoriasis patients can better inform their medical care.

639. The Risk of Tetrazepam to Induce Severe Cutaneous Adverse Reactions

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Background: Severe cutaneous adverse reactions (SCAR) include different types of reactions. Blistering conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening with high mortality and long lasting sequelae in survivors. In drug reaction with eosinophilia and systemic symptoms (DRESS) the skin eruption is accompanied by organ involvement. Acute generalized exanthematous pustulosis (AGEP) is characterized by acute onset, but a shorter and rather benign course. Different drugs were identified to have an increased risk to induce these reactions. Recently, tetrazepam was suggested to be one of them.

Objectives: To determine the risk of tetrazepam to induce the different types of SCAR.

Methods: The international Registry of SCAR to Drugs and Collection of Biological Samples (RegiSCAR)

started to ascertain all potential cases of SJS/TEN, DRESS and AGEP in 2003. All cases are clinically evaluated using a consensus definition or scoring system published previously. Cases validated as probable or definite were checked for exposure to tetrazepam within 2 weeks and start of use within 8 weeks before the index-day, i.e. the onset of the reaction determined according to specific rules. The algorithm for assessment of drug causality in SJS/TEN (ALDEN) was applied to exposed cases of SJS/TEN.

Results: Of more than 2,500 cases (ca. 1,790 potential SJS/TEN, 440 DRESS, 340 l AGEP) in the Regi-SCAR-database, 1,732 with complete medication history are validated as probable or definite. Thirty cases were at some point exposed to tetrazepam, 19/25 SJS/TEN-cases in the relevant time period (0–13 day; < 8 weeks). In 14/19 cases ALDEN was applied and revealed a probable causality for tetrazepam in one case, a possible causality in five cases and an unlikely causality in eight cases, for which other culprit drugs were identified. One of two DRESS-cases was exposed to tetrazepam in the relevant time period and 2/3 AGEP-cases respectively. The DRESS- and the two AGEP-cases could be explained by drugs known to have a high risk for either reaction.

Conclusions: These results do not suggest a high risk of tetrazepam to induce SCAR. Further surveillance is necessary to finally evaluate the risk of tetrazepam.

640. Total Mortality Rates across Multiple Databases: Benchmarking Results from a Distributed Data Network – The SAFEGUARD Project

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Background: In order to assess the association between diabetes drug exposure and select disease outcomes including total mortality, a network of European data sources has been established. This network, named the Safety Evaluation of Adverse Reaction in Diabetes (SAFEGUARD), has applied common definitions to identify a range of patient outcomes of interest to the study of medications for treating type 2 diabetes.

Objectives: To estimate mortality rates across the data sources involved in the SAFEGUARD project.

Methods: Mortality data from seven data sources representing the Netherlands (IPCI, PHARMO), Italy (SISR Lombardy, SISR Puglia), UK (CPRD), Spain (BIFAP), and Germany (BIPS) were combined. Each data source covers time ranging from 1999 to 2012 depending on data availability. Data were extracted locally using consistent definitions that were tailored to meet unique features of each data source, and were processed using the same standardized software (JERBOA) running at each site. The processed output from each site represented a tabulation of overall mortality within pre-defined age and sex strata.

Results: The average mortality rates (per 100,000 person-years) combining the data sources were approximately 400 (ages 45–54), 1,000 (ages 55–64), 2,000 (ages 65–74), and 6,000 (ages 75–84). Total mortality incidence varied by as much as two-fold from the highest to the lowest data source within age and sex strata. The age and sex-specific all-cause mortality was consistent with an external mortality reference.

Conclusions: The SAFEGUARD project will evaluate mortality across different data sources. Descriptive analysis of seven of the included databases provides a mechanism by which distributed data sources can arrive at harmonized mortality incidence.

641. Hepatitis C Virus Genotype Coinfection and Distribution in Different Regions of Mexico

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Background: Prevalence of Chronic infection by Hepatitis C has been reported in 1.4% of Mexican adults, being genotype 1 the most prevalent. No research has been done so far to describe if the presence of co-infection by different HCV genotypes is present and to what extend, nor a geographical distribution.

Objectives: To describe the presence and distribution of Hepatitis C Virus genotype coinfection in Mexican Patients.

Methods: As part of several active surveillance studies in Mexico, from 2003 to 2011, we were able to identify patients with chronic hepatitis C (n = 14,843), who signed an informed consent and provided blood to identify HCV viral load by RT-PCR (Roche Cobas Amplicor-Taqman) and HCV Genotype by LIPA (Bayer Versant). Regionalization of Mexico was utilized to study the geographic distribution of HCV coinfection genotypes. Simple and relative frequencies of HCV genotypes distribution were performed as well as their geographical distribution along the country, with special focus on HCV Genotype coinfection.

Results: HCV genotype 1 infection was present in 72.36% of patients. Only 63 patients (0.43%) were identified as carrying a coinfection by two genotypes. No patients were identified carrying three or more HCV genotype coinfection. The most common coinfection was with genotype 1 and 2 (48%) following by genotype 1 and 4 (33%) and Genotype 1 and 3 (5%). Regional variations were identified: 50% of coinfection 1 and 2 occur in the central part of the country, and 42% in the northern states, in contras, 71% of confections 1 and 4 were present in the northern states, with just 14% in the central part of the country. Of interest is that in the southern part of the country, very few confections (just two cases of coinfection 1 and 4) were identified.

Conclusions: Genotype 1 was found in in 72.36% of studied patients, and its geographic distribution was not homogeneous thorough the country. The presence of HCV genotypes coinfection was identified though is a rare occurrence. The larger number of coinfection in the northern and central states might be secondary of the use of IVU drugs, practice that is not common in any other part of the country.

characteristics associated with serum phosphate levels following initiation of HD.

Methods: Medical records of 47,742 patients new to HD who were attending outpatient dialysis centers in the USA were analyzed. Monthly mean serum phosphate levels measured over a 6-month period (months 4–9 of HD) were assigned to one of three strata: high (> 5.5 mg/dL); target (3.5–5.5 mg/dL); and low (< 3.5 mg/dL). Patients were classified into one of six serum phosphate variability groups: consistently high (CH); target-to-high (TH); low-to-high (LH); consistently target (CT); low-to-target (LT); and consistently low (CL).

Results: The phosphate variability group distribution was: CT, 15.3% (n = 7,301); CH, 10.5% (n = 5,001); TH, 51.3% (n = 24,469); LH, 9.2% (n = 4,371); LT, 13.6% (n = 6,469); CL, 0.3% (n = 131). Compared with the CT group, the CH, TH, and LH groups had significantly (p < 0.001) higher mean baseline serum phosphate and iPTH levels, were significantly younger and had a significantly lower comorbidity index, while the LT and CL groups had significantly lower baseline serum phosphate and iPTH levels, were significantly older, and had a significantly higher comorbidity index. Compared with the CT group, baseline phosphate binder usage was significantly higher in the CH and TH groups, and significantly lower in the LH, LT, and CL groups. Overall, phosphate binder usage was 35% at baseline and 52% at the end of the study.

Conclusions: Age, comorbidity, baseline serum phosphate and iPTH levels were strongly associated with serum phosphate levels after initiation of HD. Only 15% of patients (CT group) maintained serum phosphate levels within the target range, despite the low rates of phosphate binder usage observed. These results suggest that early use of phosphate binders could improve the management of hyperphosphatemia in patients with ESRD who are new to HD.

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642. Serum Phosphate Variability and Phosphate Binder Usage in Patients New to Hemodialysis

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Background: In patients with end-stage renal disease (ESRD), hyperphosphatemia is associated with increased all-cause mortality.

Objectives: To carry out a retrospective analysis of variability in serum phosphate levels in patients new to hemodialysis (HD) in order to identify baseline patient

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643. Pharmacogenomics in Primary Care: Expanding Our Understanding with Deliberations

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Background: Pharmacogenomics (PGx), the study of the influence of genetic factors on drug response, is key to personalized medicine. One in four primary care patients is prescribed drugs with adverse reactions that may be due to genetic variability. Obtaining public

views before widespread implementation may identify issues that are specific to primary care.

Objectives: To describe critical ethical issues for primary care PGx.

Methods: Deliberative consultations were conducted in Montreal, Canada from May 2010 to January 2011. Health professionals, patients and stakeholders participated in individual 1.5-h deliberative sessions. A sample took part in two mixed sessions. Descriptive thematic analysis was used to identify critical themes.

Results: The commercialization of PGx and risk of discrimination were the main issues highlighted for all groups. Other common issues were insurance and employment implications of PGx results, the discovery of 'incidental' findings, and access, ownership, privacy and confidentiality of PGx data. Possible benefits identified were improved patient outcomes, efficiency and quality of care. Uncertainties regarding the logistics of PGx, such as timing, frequency and cost of testing as well as who would perform the tests, were discussed. Patients and health professionals were further concerned about the accessibility, cost of testing and the management burden associated with clinical use. Health professionals felt they needed additional training and decision aids or guidelines. They also questioned how PGx would challenge their duty to treat patients labeled as 'non-responders', particularly if no other treatment options are available. Most stakeholders agreed that further research must be conducted to demonstrate the cost-effectiveness of PGx, although consensus was reached on its potential for cost benefits related to decreasing the rate of adverse drug events. The final recommendation was that all issues should be included in a publicly deliberated, national ethical guideline.

Conclusions: Critical themes expanded upon existing ethical concerns and increased our understanding of the range of topics that need to be addressed to optimize primary care PGx.

644. CARING: Tumour Characteristics of Diabetic and Non-Diabetic Breast Cancer Patients

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Background: Epidemiological studies have associated diabetes mellitus to an increased breast cancer (BC) risk, which might be related to insulin exposure. The mechanisms by which diabetes mellitus and insulin may promote BC development and progression are established using in vitro and in vivo models. However, data for human BC including whether diabetics develop specific breast cancer subtypes is lacking.

Objectives: To determine whether diabetic BC patients have specific BC characteristics compared to non-diabetic BC patients.

Methods: Patients were identified through the Danish Breast Cancer Group and a random selection was made in strata of age groups $\leq$ and $>$ 50 years (1:1) at BC diagnoses and diabetes/non-diabetes (2:1) by the Aarhus University Hospital, in order to select a target population of around 600 patients. Additional selection criteria were: availability of tumour tissue blocks and patient core information, no other history of cancer, no adjuvant treatment prior to surgery, availability of data on medication use $\geq$ 5 years prior to tumour diagnosis and for diabetics a diagnosis with diabetes mellitus $\geq$ 1 year prior to BC diagnosis. The proportion of bilateral and multifocal tumours was studied and tested whether there was a difference between diabetic and non-diabetic patients using a Chi-squared test.

Results: Of 43,701 women with incident BC between 2000 and 2010 were identified, of whom 3,047 had diabetes. Among 691 selected patients, 660 had tissue available. 1.8% (n = 8) of the diabetic patients (n = 450) had synchronous bilateral tumours- and 4.0% (n = 18) had multifocal tumours, similar to respectively 1.9% (n = 4) and 4.8% (n = 10) among non-diabetics (n = 210, p = 0.90).

Conclusions: Although the crude analysis suggests no differences in the proportion of bilateral or multifocal tumours between diabetic and non-diabetic BC

patients, planned in-depth analyses on additional patient characteristics will provide insight in the robustness of these results. Future analysis will also focus in more detail on differences in tumour subtypes (immunohistochemical markers and DNA profiles) and survival results.

645. Genetic Association Between Variants in Genes for sPLA2 and Cardiovascular Biomarkers

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Background: Secretory phospholipase A2 (sPLA2) is suggested to be important for atherosclerosis and may represent a novel target for atherosclerosis and associated cardiovascular diseases.

Objectives: To investigate the association of genetic variants in the genes for sPLA2 with cardiovascular biomarkers.

Methods: The study population was derived from JUPITER (Justification for the Use of statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial. We limited the analysis to subjects of European ancestry. A total of 25 SNPs in $PLA2G2A$, 24 SNPs in $PLA2G3$, 46 SNPs in $PLA2G5$ and 4 SNPs in $PLA2G10$ for sPLA2 type IIA, III, V and X were examined. Outcomes were (1) baseline measurements for LDL-C, HDL-C, CRP, ApoA1, ApoB, ApoB/ApoA1, TG and (2) absolute change and percentage change in LDL-C after 12 months of rosuvastatin or placebo therapy. Absolute change was defined as the difference between 12-month and baseline values and percentage change as the absolute change divided by the baseline value. Analysis used linear regression. Models were adjusted for age, sex, BMI, smoking status, geographical region and measures of sub-European stratification. For baseline analysis, both the rosuvastatin and placebo groups were included in the analysis (n = 8,749). For LDL change analysis, patients non-compliant with study medication based on pill count were excluded, and the rosuvastatin (N = 3,534 compliant) and placebo (N = 3,512 compliant) groups were analyzed separately.

Results: For $PLA2G3$, nominal association was seen for multiple SNPs to baseline LDL-C (nine of 24 SNPs) and two other SNPs to HDL and ApoA1, but not to ApoB, ApoB/ApoA1, CRP or TG. No clear association was seen for $PLA2G2A$, $PLA2G5$ or $PLA2G10$ with any baseline markers. For the change phenotype, no association was found for any of the four genes with either absolute or percentage change in LDL-C after rosuvastatin or placebo treatment.

Conclusions: Genetic variants in $PLA2G3$ for sPLA2 type III were associated with baseline LDL-C, HDL-C and ApoA1.

646. Interactions of Human Papillomavirus and Host Genetic Polymorphisms in Carcinogenesis: A Systematic Review and Meta-Analysis

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Background: Oncogenic human papillomavirus (HPV) and host genetic polymorphisms (HGP) are independently associated with carcinogenesis. These HGPs should be investigated as they may impact on treatment and vaccine effectiveness.

Objectives: The purpose of this study was to review systematically the literature for HPV-HGP associations in carcinogenesis.

Methods: The systematic literature review evaluated studies of HPV-HGP relationships in any non-skin cancer. P53 meta-analyses were performed to evaluate the interaction of the P53-Arg72Pro polymorphism and HPV in head and neck cancer (HNC) risk. Odds ratios and measures of heterogeneity were evaluated using RevMan 5.1.

Results: The most common analysis was risk of cervical cancer by HGP, followed by HNC risk. P53-Arg72Pro was the most commonly studied HGP, followed by others in the P53 pathway. The Pro/− genotype was associated with higher risk of HNC (OR 3.84 [2.93–5.04], p < 0.0001), but no interaction with HPV was detected (pint = 0.14) using a meta-analytic approach. HPV-positive subsets, joint-effects models comparing only extreme HPV-HGP groups, and case-series were the most commonly utilized study designs. A smaller subset of studies assessed initiation of carcinogenesis (comparing pre-neoplasia to healthy individuals) and disease progression (comparing cancer to pre-neoplasia). All allelotyping studies were conducted in cervical cancer risk.

Conclusions: Interaction analyses, the gold standard, were rarely used analytic approaches due to limited

sample sizes. Instead, surrogate study designs were utilized, but not all designs provided comparator groups and were therefore rife with potentially dangerous assumptions. In the era of personalized medicine, host-environment interactions may provide the framework for targeted therapy.

647. Breast and Colorectal Cancer Patients Decision Making for Pharmacogenomic Diagnostics

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Background: Patient acceptance of the use of pharmacogenomic diagnostics is one key challenge to the future implementation of personalized medicine. However, little is known about how patients will make decisions to accept the use of genomic diagnostics for personalized medicine.

Objectives: To better understand and determine breast and colorectal cancer patients decision-making strategies and the trade-offs they make in deciding about characteristics of molecular genomic diagnostics for breast and colorectal cancer.

Methods: We surveyed a nationally representative sample of 300 breast and colorectal cancer patients using a Web-administered previously developed Patient Preferences for Personalized Medicine survey instrument. Eligibility criteria included patients aged 18 and older, with either breast or colorectal cancer, but not other cancers, able to communicate in English, and providing informed consent to respond to the questionnaire.

Results: Among breast cancer patients, 21% were knowledgeable about genetic expression profiling, another 15% had heard of it, but were unsure of what it meant, 18% were aware of Oncotype DX, and 13% stated that Oncotype DX had been included as part of their treatment. In contrast, 15% of colorectal cancer patients had heard of KRAS mutation testing, but claimed to be uncertain of what it meant. The probability of either false positive or false negative results was ranked high as a potential barrier by both breast and colorectal patients. However, 78.6% of breast cancer patients ranked the possibility of a false negative test result leading to under-treatment higher than the chance of a false positive which may lead to over-treatment (68%). This finding contrasted with the views of colorectal cancer patients who ranked the chance of a false positive as being of greater concern than a false negative (72.8% vs. 63%). Cancer patients seek a test accuracy rate of 90% or higher.

Conclusions: This study provides insights into the relative weight that breast and colorectal cancer patients place on various aspects of molecular genomic diagnostics, and the trade-offs they are willing to make among attributes of such tests.

648. Cholesteryl Ester Transfer Protein (CETP) Polymorphisms, Statin Use, and Their Impact on Cholesterol Levels and Cardiovascular Events

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Background: The association of variants in the CETP gene with efficacy of statins has been subject of debate, but most studies investigated a common non-functional variant. Three CETP variants were found to directly influence mRNA expression and RNA splicing, and to affect HDL-cholesterol (HDLc) levels and the risk of myocardial infarction (MI).

Objectives: To determine whether three functional CETP variants influence statin efficacy in modifying cholesterol levels and preventing MI.

Methods: For all analyses, only participants of European ancestry were selected. Three studies (population study Go-DARTS and randomized controlled trials PREVEND-IT and JUPITER, totaling 11,021 individuals) were included in a meta-analysis to investigate the variants' effect on achieved cholesterol levels. Linear regression was used to investigate the relation between CETP genotypes and achieved HDLc, LDL-cholesterol (LDLc) and total cholesterol levels during statin treatment. Results were pooled assuming random effects and using inverse variance weighting. Five studies, totaling 16,570 individuals, were included in a meta-analysis to assess the interaction between CETP genotypes and statin response in protecting against MI: GoDARTS, PREVEND, PREVEND-IT, MI-registry FAST-MI and population based case-control study UCP. Results from logistic regression models with statin*SNP interaction terms were pooled, assuming random effects and using inverse variance weighting.

Results: The enhancer SNP rs3764261 significantly increased HDLc by 0.02 mmol/L per T allele (95% CI 0.02–0.03, $p = 6E-05$) during statin use, and had no effect on achieved LDLc. Rs3764261 also showed an interaction with statin use on MI outcome (interaction-OR = 1.19 per T allele; 95% CI 1.01–1.40, $p = 0.04$). The SNPs influencing splicing (rs5883 and rs9930761) did not modify statin efficacy on treated cholesterol levels or MI.

Conclusions: Focusing on functional CETP variants, we showed that, during statin treatment, HDLc increased more in carriers of the rs3764261 T variant. This effect was accompanied by a reduced protection against MI by statins when compared to non-carriers.

649. Racial Differences Affect Patients Willingness in Providing Additional Biospecimens for Pharmacogenomic Testing

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Background: Pharmacogenomic testing (PGT) is important in maximizing drug efficacy and safety. More and more anti-cancer agents require associated biomarker testing for funding reimbursement. Sociocultural differences may affect attitudes towards re-biopsy, obtaining additional blood, or utilizing existing tumour samples for the purposes of biomarker testing.

Objectives: To describe the differences in factors affecting patient willingness to provide different types of biospecimens for PGT by race.

Methods: Seven hundred and ninety English-speaking adult clinic patients of all races were interviewed from the Princess Margaret Cancer Centre (Toronto, Canada) using a standardized hypothetical questionnaire assessing patient preferences and willingness to provide biological samples (blood or biopsy). Analysis utilized SAS v.9.3.

Results: Seventy-seven percent were Caucasian and 23% non-Caucasian (12% Asian, 5% African, 1% Middle Eastern, 1% Hispanic, and 5% other), with a median age of 58 years; half were women. Both Caucasians and non-Caucasians agreed that additional tests would be beneficial to their health (75%, $p > 0.05$). Caucasians who thought that additional tests would beneficial, that providing new blood tests were not distressing, and who understood genetic testing, were more agreeable to providing new blood samples (adjusted OR 2.60, 2.99, 2.95, and 2.47, respectively; $p < 0.05$); whereas non-Caucasians who found additional blood tests distressing, and preferred utilization of existing tumor samples over additional blood samples (adjusted OR 1.97, 2.52, respectively; $p < 0.05$).

Conclusions: Caucasian patients were more willing to provide a new blood sample for PGT, whereas non-Caucasian patients preferred utilizing the existing tumor and no additional blood sampling. Racial disparities in utilization of molecularly targeted drugs in cancer patients may be affected by socio-cultural attitudes.

650. Patient Willingness To Provide Different Types of Biological Samples for Pharmacogenomic Testing

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Background: More and more targeted anti-cancer agents require associated biological testing. Cetuximab and KRAS mutations, and Gefitinib and EGFR mutations are current examples. In many advanced cancer patients, the original samples are too small for such testing, and additional biopsies and/or blood may be necessary to complete a pharmacogenomic testing (PGT) profile. PGT can maximize drug efficacy and safety. However, willingness of patients provide extra samples may be a barrier to use of these anti-cancer agents.

Objectives: To determine the willingness of patients to obtaining additional specimens for PGT.

Methods: Seven hundred and ninety English-speaking adult patients from the Princess Margaret Cancer Centre (Toronto, Canada) were interviewed with a standardized hypothetical questionnaire. Patients represented a wide distribution of adult solid and hematological disease sites. Study endpoints included patient preferences and willingness to provide samples (new blood, new biopsy, or pre-existing tumor) on a 5-point Likert scale. Analysis utilized SAS v.9.3.

Results: Patients were 49% female; 77% Caucasian/12% Asian; median age 58 years; and 67% had completed high school. Median household income was evenly trichotomized at $50 K and $100 K. Despite 33% being uncomfortable with the level of their knowledge about PGT, 75% agreed that additional tests would be beneficial. Patient willingness to provide new samples was 88% for blood and 53% for biopsy, while 27% preferred existing tumor samples to be used in lieu of additional blood samples. Willingness to provide biopsy sample was associated with gender (adjusted OR 1.72; $p < 0.05$) and age (adjusted OR 1.02; $p < 0.05$), where, with year age increment, older patients were more willing to have an extra biopsy than younger individuals.

Conclusions: Patients were more willing to provide a new blood than biopsy sample for PGT. Despite the majority agreeing to the potential benefit of additional sampling, only half were willing to provide a new biopsy. Patient uptake of PGT and use of targeted drugs associated with a biomarker may be improved with enhanced patient education and increased efforts to accommodate preferences by developing blood-based biomarkers.

651. Effect of BRM Promoter Polymorphisms on Survival Outcomes of Platinum-Treated Advanced Non-Small Cell Lung Cancer (NSCLC) Patients

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Background: BRM, a key ATPase subunit of the SWI/SNF chromatin remodeling complex, is a putative tumor susceptibility gene in NSCLC. Loss of BRM expression occurs in 15% of NSCLC, and is associated with adverse outcome. Two BRM promoter insertion variants (BRM-741 and BRM-1321) result in epigenetic silencing of BRM through recruitment of histone deacetylases. Individuals carrying both homozygous BRM variants have doubled lung cancer risk. Pharmacological reversal of these epigenetic changes is a viable therapeutic strategy.

Objectives: To investigate the association between BRM promoter variants and survival outcomes of platinum-treated stage III–IV NSCLC patients.

Methods: Three hundred and eighty-seven platinum-treated stage III–IV NSCLC patients from the Princess Margaret Cancer Centre were genotyped for the BRM promoter variants using Taqman. Primary study end points were overall (OS) and progression-free survival (PFS). Association of BRM variants and OS & PFS were assessed using Cox proportional hazard models adjusted for prognostic variables.

Results: Of the patients, 73% were Caucasian, 55% male, median age 60 years, 47% stage IV, and 67% adenoca. Median OS was 2 years; median follow up, 3.9 years. The frequency of homozygosity was BRM-741, 18%; BRM-1321, 17%; both, 10%. Homozygous variants of BRM-741 were strongly associated with worse OS (adjusted HR [aHR] 1.7 [95% CI: 1.2–2.5; $p = 0.004$]) and PFS (aHR 1.5 [1.1–2.1; $p = 0.02$]) compared to the wild types. The homozygous variants of BRM-1321 were also associated with adverse OS (aHR 1.5 [1.1–2.2; $p = 0.02$]), with a non-significant trend toward shorter PFS (aHR 1.3 [0.9–1.7; $p = 0.18$]). Individuals carrying both homozygous BRM variants had a significantly worse OS (aHR 1.9

[1.2–3.1; p = 0.007]) and PFS (aHR 1.5 [1.0–2.4; p = 0.047]).

Conclusions: The same two homozygous BRM promoter variants that are associated with increased risk of NSCLC are also strongly associated with adverse survival in this cohort of platinum-treated stage III–IV NSCLC patients. Results are being validated in a clinical trial dataset which will better elucidate the significance of these BRM promoter variants in platinum-treated NSCLC patients.

652. Polymorphisms of Organic Cation Transporter1 (OCT1) in Indonesian Cancer Patients

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Background: Organic Cation Transporter1 (OCT1), encoded by SLC22A1, was known as the highly polymorphism of polyspesific transporter. In Caucasian, some of the studies found that the genetic variability of OCT1 might alter the drug response, such as metformin, imatinib, levodopa and 5-Hydroxytriptamine Receptor Antagonist (5-HTRA) drugs. However, the study of this gene variability in Asian is still sparse.

Objectives: This study was aimed to know the variability of OCT1 gene in Indonesian Cancer patients, which may predict the 5-HTRA drugs response.

Methods: The SNPs of OCT 1 were selected from the study of Tzvetkov et al; rs12208357, rs55918055, rs34130495, rs34059508 and unknown rs number (amino acid substitution methionine420-to-deletion methionine). The deoxyribonucleic acid (DNA) was extracted from saliva samples of 202 Indonesian cancer patients. Genotypes were established using Taqman assays and analysed on ABI 7500 realtime PCR System from Applied Biosystems according to manufacture's protocol of allelic discrimination.

Results: Contradictively to the previous findings in the Caucasian cancer patients, there were no genetic variations found in the Indonesian cancer patients according to the four SNPs included in this study and only 1.5% heterozygous were found in the Met420del. However, this finding is consistent with the previous studies in Japannese and Chinnese population.

Conclusions: The further study is warranted to do the sequencing analysis which could find the most possible variants in Indonesian cancer patients. The individualized therapy should be started in Indonesia, since many previous findings showed that the genetic variability of gene encoding proteins which have roles in drug transportation, metabolism and disposition could alter the drug responses.

653. The Opportunities and Challenges of Generating Evidence on Medical Device Associated Biomarkers and Implementing the Biomarker-Based Regulatory Research Applications

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Background: In order for the FDA to enhance evidence-based decisions in the coming era of personalized medicine, there is a need to implement reliable biomarkers for medical product performance.

Objectives: Unlike a well-established role of drug biomarkers, the current biomedical research lacks data on device-related biomarkers. To address the existing gap, we intend to use novel data sources and bioinformatics tools and develop an innovative approach to discovery of biomarkers for device safety and efficacy.

Methods: We are performing a study on cross-species biomarkers for Ventilation-Associated Pneumonia (VAP) and Lung Injury (VALI), using GEO/NCBI open-source 'omics database, *in silico* study design, and an innovative analytical algorithm based on GenePattern (the Broad Institute) and Ingenuity Pathway Analysis (IPA). The expected results will be juxtaposed to the epidemiological and clinical data on ventilation outcomes available from sources such as AHRQ.

Results: The GEO queries have identified animal models representative of target endpoints and mechanisms underlying the effects of ventilation. GenePattern-IPA analysis has shown the potential to yield signatures for the safe window of ventilation avoiding both injury zones of baro/volutrauma and atelectotrauma. We explored biological and clinical relevance of VALI/VAP-biomarkers by linking them to the lung pathophysiology and assessing their detectability in biofluids. The subsequent integration of biomarkers with clinical data could help stratify patients based on their outcomes and identify the risk groups for whom certain ventilation settings may represent less effective and tolerable options.

Conclusions: The final results will provide better insights into the basis of ventilation-related adverse events. Prospective case-control studies will be needed to validate *in silico* identified biomarkers and to develop the biomarker-based clinical and regulatory applications. The implementation of biomarkers is expected to refine the recommendations on ventilation

procedure and settings, and thereby enhance the efficacy and safety of ventilatory devices.

654. Evaluation of the Effect of SNPs in *CYP3A4* and *CYP4F2* on the Stable Phenprocoumon and Acenocoumarol Maintenance Dose

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Background: Coumarin derivatives are effective medications for the treatment and prevention of thromboembolic events. However, they have a small therapeutic window and there is a large variability in anticoagulant response. Single nucleotide polymorphisms in *CYP2C9* and *VKORC1* explain approximately 40% of the coumarin dose variation.

Objectives: To investigate the effects of two polymorphisms in *CYP3A4* and one polymorphism in *CYP4F2* on the stable phenprocoumon and acenocoumarol maintenance dose.

Methods: The Pre-EU-PACT cohort (551 phenprocoumon and 372 acenocoumarol users) was used to investigate the effect of *CYP3A4*1B*, *CYP3A4*22* and *CYP4F2 V433M* genotypes on the acenocoumarol and phenprocoumon maintenance dose. Unadjusted and adjusted mean coumarin maintenance dose differences were calculated and compared for each genotype using linear regression. The Committee Medical Ethics Leiden approved the study protocol and procedures were in accordance with the Helsinki Declaration.

Results: For phenprocoumon, a significant increase in the maintenance dose of 0.13 mg/day was found for patients carrying one variant *CYP4F2* allele (n = 185) if compared to wild type patients (2.17 mg/day, n = 325), and an even larger increase was found for patients carrying two *CYP4F2* variant alleles (n = 41): plus 0.24 mg/day, trend-test p = 0.003. For *CYP3A4*22*, a marginally significant effect (p = 0.05) was found on the phenprocoumon dose: mean dose for wild type patients was 2.25 mg/day (n = 496) and for patients carrying 1 variant allele −0.18 mg/day (n = 54), while no significant effect of *CYP3A4*1B* variant alleles was found. For acenocoumarol, no significant effects on the maintenance dose were found for both *CYP4F2* and *CYP3A4* variant alleles, although the trend for *CYP4F2* was comparable to the significant trend observed for phenprocoumon.

Conclusions: Genetic variations in *CYP4F2* appear to marginally increase the stable phenprocoumon maintenance dose. The same trend, although not significant, was found for acenocoumarol. No statistically significant effect was observed for *CYP3A4* genotypes for both phenprocoumon and acenocoumarol.

655. Associations Between Overall Survival and Response to Standard of Care and Biomarker Status in Ovarian Cancer Patients Using an Observational Tumor-Linked Database

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Background: To date, the Merck-Moffitt Collaboration (MMC) database is the largest US tumor bio-bank linked to longitudinal clinical data. As of December 2012, the database contains a total of 24,798 tumors with molecular profiling and clinical data from 18,992 Total Cancer Care™ patients (pts).

Objectives: To obtain measures of treatment (tx) response of ovarian cancer (OvCa) pts receiving first-line platinum therapy (PLT) and to identify associations between overall survival (OS) and folate receptor (FOLR) mRNA expression levels by tx response.

Methods: We identified newly diagnosed OvCa pts receiving a platinum-containing therapy as first-line tx. End of progression-free time occurred at one of the following dates after PLT: (1) first occurrence of new lesion, (2) growth of identified lesion, or (3) change of tx due to progression. Tx response categories were defined as refractory (progression during the first 4 months of PLT), resistant (progression within 6 months after cessation of PLT), partially sensitive (progression 6–12 months after cessation of PLT), and sensitive (progression > 12 months after cessation of PLT) and were correlated with OS. Associations between quartiles of FOLR mRNA expression levels and OS were evaluated using clinical data linked to molecular profiling data.

Results: A total of 625 OvCa pts were identified. Of these, 180 received PLT as their first tx. Distribution of tx response was refractory (n = 12), resistant (n = 26), partially sensitive (n = 20), sensitive (n = 84), and no progression (n = 38). Median OS of refractory pts was lowest at 1.5 months with other groups having similar survival (approximately 4 months). While there

was not a statistically significant association between FOLR mRNA expression and OS (logrank test, p-value = 0.07), differential trends in this association by tx response were observed.

Conclusions: The MMC database is an observational data source that may be used to capture real-world clinical and health outcomes in cancer patients. Further investigation of the association between OS and FOLR mRNA expression by tx response in OvCa pts receiving first-line PLT is warranted.

656. Influence of Genetic and Non-Genetic Factors on the Plasma Concentrations of the Clopidogrel Metabolite (SR26334) Among Chinese Patients

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Background: Genetic variation involved in the absorption and metabolism of clopidogrel as well as in its antiplatelet effect may explain its response variability.Studies have associated dysfunction of CYP2C19 alleles with an increased cardiovascular risk. In spite of genetic factor, clinical and pharmacokinetic factors may also contribute to this wide variability in response. Determination of the SR26334 has been used to monitor the therapeutic drug in clopidogrel-treated patients and to characterize the anti-platelet action of clopidogrel.

Objectives: The objective of this study was to investigate the contribution of genetic polymorphism of cytochrome P450 2C19 gene (CYP2C19) and non-genetic factors to clopidogrel in Chinese patients by using the plasma concentrations of SR26334 as a surrogate.

Methods: A total of 150 patients who received clopidogrel therapy were enrolled in this study. Genotyping was carried out to identify the alleles of CYP2C19*2 and CYP2C19*3 by using PCR-based restriction enzyme tests. The plasma concentrations of SR26334 were determined using a rapid LC method with UV detection.

Results: CYP2C19 genotyping showed that 68 patients were extensive metabolizers (EMs), 68 were ntermediate metabolizers (IMs) and 14 were poor metabolizers (PMs).Multiple linear regression models incorporating genetic polymorphism of CYP2C19 and non-genetic factors, such as blood collection time, smoking status and clopidogrel doses were developed, and explained up to 63.1% of the total variation (adjusted R^2 of 0.631) in the plasma concentrations of SR26334 in Chinese patients.

Conclusions: Blood collection time, smoking status, genetic polymorphism of CYP2C19 and clopidogrel doses were found to affect the plasma concentrations of SR26334 significantly.

657. Cost-Effectiveness of Pharmacogenetic-Guided Dosing of Phenprocoumon in Atrial Fibrillation

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Background: Genotyping patients for polymorphisms in the *CYP2C9* gene, encoding for the main metabolizing enzyme, cytochrome P450 2C9 (CYP2C9), and the *VKORC1* gene, encoding for the target enzyme Vitamin K epoxide reductase multiprotein complex 1 (VKORC1) helps to predict the required coumarin dose prior to treatment initiation.

Objectives: To investigate the cost-effectiveness of pharmacogenetic-guided phenprocoumon dosing vs. standard anticoagulation care, in Dutch patients with atrial fibrillation.

Methods: Using a decision-analytic Markov model we estimated the incremental effectiveness (in quality-adjusted life-years, QALYs) and cost-effectiveness of pharmacogenetic-guided phenprocoumon therapy vs. standard care. Time spent in different international normalized ratio (INR) ranges was used to estimate the risk of thromboembolic and bleeding events. The quality of life of patients in different health states was derived from literature. Costs were determined from a third-party payer perspective and a lifetime horizon was used. Additionally, sensitivity analyses for a selection of variables were performed.

Results: Compared with standard care, the pharmacogenetic-guided dosing strategy increased the QALYs only very slightly (2 days) and increased costs by €15. The incremental cost-effectiveness ratio was €2658 per QALY gained. In sensitivity analyses, the cost of genotyping had the largest influence on the cost-effectiveness ratio. In a probabilistic sensitivity analysis, the incremental costs of genotype-guided dosing were < €20,000 per QALY gained in 78.2% of the simulations.

Conclusions: Pharmacogenetic-guided dosing of phenprocoumon has the potential to increase health slightly and may be able to achieve this in a cost-effective way. Because of the many uncertainties in for example the costs of the genetic test or the effectiveness of genotyping, it is too early to conclude whether or not patients starting phenprocoumon should be genotyped.

658. Beat-to-Beat Variability of the QT Interval: A Systematic Review

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Background: Drug use is a common cause of certain cardiac arrhythmias, such as Torsades de Pointes (TdP). Nowadays, prolongation of the heart-rate corrected QT interval (QTc) is used to predict the risk for these arrhythmias following use of certain drugs. However, QTc alone does not accurately predict this risk. Increased repolarization instability, as measured by beat-to-beat variability of the QT interval, has been suggested as a necessary condition to produce the arrhythmogenic response. Two markers of repolarization instability on the electrocardiogram have been proposed as predictors for drug-induced arrhythmia risk: QT variability index (QTVI) and short term variability of the QT interval (STVqt).

Objectives: To give an up-to-date overview of the literature on QTVI and STVqt research, and to assess whether these markers are promising for further research into drug-induced arrhythmia.

Methods: We performed a systematic review of available literature on QTVI and STVqt following the PRISMA guidelines. We searched PubMed and Embase for articles reporting on short term variability and beat-to-beat variability of QT interval and QT variability index. Study selection and data extraction were performed by two individual reviewers.

Results: A total of 297 articles were found, the majority regarding QTVI. Most described studies in animals or in small human datasets only. QTVI and STVqt were mostly determined semi-automatically. QTVI has mainly been studied in cardiac and psychiatric disease and tended to be higher in patients compared to controls. A higher STVqt predicted certain drug-induced TdP more accurately than QTc.

Conclusions: The number of studies on QTVI and STVqt increased substantially over the past years. QTVI and STVqt seem to be better markers for the risk of certain drug-induced arrhythmias than QTc prolongation alone. However, substantial high-quality evidence is lacking. Further research into these markers is needed to define their role in the prediction of drug-induced arrhythmia and cardiac mortality.

659. Iatrogenic Aluminum and General Intelligence of Moroccan Children

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Background: Aluminum is a neurotoxic present in numerous sources such as air, food, household materials, water, cosmetics and drugs. Once entirely absorbed in gastrointestinal tract, it could impair neurocognitive performances.

Objectives: The evaluation of the general intelligence among Moroccan schooled children (aged 6–8 years) living in the low basin's Sebou River (North-West of Morocco) and the study of the possible relationship between this neurocognitive faculty and the consumption of iatrogenic aluminum.

Methods: A cross-sectional study is conducted among 129 school-aged children living in the urban, periurban and rural region of the low basin's Sebou River (N-W of Morocco). The children suffering from cranial traumatism or neurologic disease are excluded. General intelligence is measured by Raven's Standard Progressive Matrices (RSPM). The consumption of iatrogenic aluminum and the quality of children's live are evaluated by the questionnaire. Statistical analyses are realized by ANOVA 1, LSD and Pearson correlation coefficient.

Results: The obtained results show that the best scores of general intelligence are registered among the urban and rural children ($p < 0.01$). Moreover, significant correlations between performances in RSPM ($p < 0.05$) and consumption of iatrogenic aluminum are also found.

Conclusions: The children's intelligence appears in connection with iatrogenic aluminum consumption; however, several factors (environmental, psychological, socio-economical, and nutritional factors) could influence this performance. So, a deeper investigation is needed for studying all these factors.

660. Exploration of Defined Daily Dose and Days of Therapy in Paediatrics and ob-gyn – A Descriptive Analysis of Antifungals

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Background: Antimicrobial stewardship programs are put in place to optimize antimicrobial use and to reduce the emergence of drug resistance.

Objectives: To calculate Defined Daily Doses (DDD) and Days of Therapy (DOT) per 1,000 patient-days (1,000 PD) for antifungals in paediatrics and ob-gyn.

Methods: Design: Retrospective, transversal, descriptive study.

Setting: Centre hospitalier universitaire Sainte-Justine, a Canadian mother-child teaching hospital.

Exposures: All inpatients being exposed to at least one of the four following antifungals (e.g. fluconazole, caspofungin, voriconazole and posaconazole). during three distinct financial year (e.g. 2001/02, 2005/06 and 2010/11). Were excluded antibiotics and antivirals and amphotericin-b like antifungals (e.g. amphotericine B deoxycholate, amphotericine B liposomal) as there are only one DDD proposed for all amphothericin B formulations by World Health Organisation.

Main outcome measures: DDD/1,000 PD and DOT/1,000 PD

Statistical analysis: Data were extracted from pharmacy information systems and admission, departures and transfer (ADT) for analysis. Patients' orders were matched to patient care units and ADT workload data to calculate ratios. Mean dose per kg for five weight intervals were calculated for each antifungal.

Results: DDD/1,000 PD went from nine in 2001/02, to 30 in 2005/06 and 41 in 2010/11. DOT/1,000 PD went from 14 in 2000/01, to 40 in 2005/06 to 59 in 2010/11. Most of the increase is related to the use of fluconazole that went from 14 DOT/1,000 PD in 2000/01 to 31 in 2005/06 to 49 in 2010/11, due to a higher proportion of tertiary care and protocol changes in hematology-oncology. No significant change was noted for dose regimen. While DOT/1,000 PD are preferred to DDD/1,000 PD in paediatrics, both can be useful to monitor drug use trends within a hospital during a period of time.

Conclusions: There is an important increase in the use of antifungals in a teaching mother-child hospital. The increase is mainly related to the use of fluconazole in hematology-oncology. Both DDD/1,000 PD and DOT/1,000 PD can be useful to compare the use of antifungals in paediatrics.

661. Exploration of Defined Daily Dose and Days of Therapy in Paediatrics and ob-gyn – A Descriptive Analysis of Antivirals

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Background: Antimicrobial stewardship programs are put in place to optimize antimicrobial use and to reduce the emergence of drug resistance.

Objectives: To calculate Defined Daily Doses (DDD) and Days of Therapy (DOT) per 1,000 patient-days (1,000 PD) for antivirals in paediatrics and ob-gyn.

Methods: Retrospective, transversal, descriptive study.

Setting: Centre hospitalier universitaire Sainte-Justine, a Canadian mother-child teaching hospital.

Exposures: All inpatients being exposed to at least one of the eight following antivirals (e.g. acyclovir, cidofovir, famciclovir, foscarnet, ganciclovir, oseltamivir, valacyclovir, valganciclovir) during three distinct financial year (e.g. 2001/02, 2005/06 and 2010/11). Were excluded antibiotics, antifungals and ribavirin.

Main outcome measures: DDD/1,000 PD and DOT/1,000 PD.

Statistical analysis: Data were extracted from pharmacy information systems and admission, departures and transfer (ADT) for analysis. Patients' orders were matched to patient care units and ADT workload data to calculate ratios. Mean dose per kg for five weight intervals were calculated for each antiviral.

Results: DDD/1,000 PD went from 7.23 in 2001/02, to 12.6 in 2005/06 and 23.7 in 2010/11. DOT/1,000 PD went from 22.04 in 2000/01, to 34 in 2005/06 to 38.8 in 2010/11. Most of the increase is related to the use of famciclovir that went from 1 DOT/1,000 PD in 2000/01 to four in 2005/06 to 15 in 2010/11, due to a higher proportion of tertiary care and protocol changes in hematology-oncology. No significant change was noted for dose regimen. No significant change was noted for dose regimen. While DOT/1,000 PD are preferred to DDD/1,000 PD in paediatrics, both can be useful to monitor drug use trends within a hospital during a period of time.

Conclusions: There is an important increase in the use of antivirals in a teaching mother-child hospital. The increase is mainly related to the use of famciclovir in hematology-oncology. Both DDD/1,000 PD and DOT/1,000 PD can be useful to compare the use of antivirals in paediatrics.

662. Trends in Oral Antidiabetic Medication Use Among Children and Adolescents: 2003–2010

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Background: The prevalence of type 2 diabetes mellitus (T2DM) among pediatric patients has been rising during the last decade, largely attributable to the obesity epidemic. Awareness has increased but the actual trends in use of oral antidiabetics is not well documented.

Objectives: To examine the yearly incidence in the use of oral antidiabetic medications indicated for T2DM including biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors/meglitinides/dipeptidy peptidase-4, and combination treatments among children and adolescents.

Methods: We identified a cohort of pediatrics aged 8–18 with at least 3 months continuous enrollment within the years 2003–2010 from a large US insurance claims database. Patients with a diagnosis of polycystic ovary syndrome or T1DM were excluded. The incidence of new oral antidiabetic use was examined by year as well as within strata of gender, age, and geographic region.

Results: The overall incidence for oral antidiabetics from 2003 to 2010 was 1.85 per 10,000 persons (95% CI: 1.81–1.89 per 10,000). The incidence from 2003 to 2010 almost tripled among this population from 0.86 per 10,000 children (95% CI: 0.75–0.97 per 10,000) to 2.20 per 10,000 children (95% CI: 2.09–2.31 per 10,000), respectively. Prescription patterns by gender showed higher rates for females than males consistently through the years. The highest rates for all years were for the 16–18 age group. Biguanides were the most widely used class of medications although other classes including sulfonylureas and thiazolidinediones saw a steady proportion of usage as well. The South consistently had the highest prescription rates amongst all US regions.

Conclusions: We observed a nearly threefold increase in the incidence of new use of prescription oral antidiabetics as well as significant off-label usage of these drugs among children and adolescents from 2003 to 2010. More data on the comparative effectiveness of safety of these drugs in children is needed.

663. Obesity and Metabolic Abnormalities in Antipsychotic Exposed Youth

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Background: The association of metabolic abnormalities with second generation antipsychotics in youth is known, but is poorly understood in real-world settings. The North Carolina Division of Medical Assistance (DMA) developed the Antipsychotics-Keeping It Documented for Safety (A + KIDS) registry. The A + KIDS program encourages prescribers to report data on medication, dose, height, weight, and metabolic labs. The registry provides a unique opportunity to examine long-term, population-level effects of antipsychotics on obesity and metabolic derangements.

Objectives: Our objective is to describe the prevalence of obesity and metabolic derangements and examine possible risk factors for these conditions in the A + KIDS population.

Methods: Antipsychotic registrations from 4/01/2011 to 2/08/2013 were linked to the NC Medicaid eligibility file. Standard definitions for overweight, obesity, and metabolic laboratory derangements were used to characterize the population. Possible risk factors for metabolic abnormalities including demographic factors, and medication exposure factors were explored through stratification and bivariate analysis. Weekly registry updates will allow the analysis to reflect up to date information prior to the scientific conference.

Results: At the time of this analysis 18,687 unique patients were in the registry. BMI, lipid, and blood glucose data were available for 63.2%, 13.1%, and 13.8% of patients, respectively. Overall obesity prevalence was 27.2% and 29.8% among adolescents. The prevalence of total cholesterol ≥ 200 mg/dL was 10.9%, LDL ≥ 130 mg/dL was 10.8%, HDL < 50 mg/dL was 26.4%, and 12.2% for fasting blood glucose ≥ 100 mg/dL. Adolescent age, Hispanic race, and

female sex were most strongly associated with obesity prevalence. An updated analysis will include results regarding weight change and medication related risk factors.

Conclusions: This report adds to knowledge that antipsychotic exposed youth are a subpopulation vulnerable to metabolic problems. The identification of at-risk subgroups has strong practice implications. Next steps will involve a more complex analysis of risk factors for metabolic abnormalities including longer term exposure and polypharmacy exposure.

664. Analgesic and Psychiatric Co-Medication in Commercially Insured Pediatric Inflammatory Bowel Disease Patients

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Background: Individuals with inflammatory bowel disease (IBD) are treated with multiple medications to manage disease symptoms and common sequalae such as pain and psychiatric comorbidity. The potential for drug interactions is of concern, as is the potential for long-term medication use in children.

Objectives: Our aims were to characterize the prevalence and predictors of non-IBD medication use in a pediatric IBD population and compare drug use among children with and without IBD.

Methods: This cross-sectional study included children aged ≤ 18 years in the Thomson Reuters MarketScan Commercial Claims and Encounters database with continuous enrollment during 2009–2010 (n = 6,075,571). IBD patients were identified through diagnosis codes and IBD medication dispensings (n = 5,383) and matched on age, sex, and region to five children without IBD (n = 26,915). We estimated the prevalence of dispensed prescriptions for (1) narcotic analgesics, (2) non-narcotic analgesics, (3) anxiolytics, hypnotics, and sedatives and (4) antidepressants. Prevalence odds ratios (POR) and 95% confidence intervals (95% CI) comparing drug use by IBD status and evaluating predictors of medication use were estimated by logistic regression.

Results: Analgesic and psychiatric drug use was common among children with IBD (narcotic analgesics:

31%; non-narcotic analgesics: 5%; anxiolytics, hypnotics, and sedatives: 6%; antidepressants: 11%). Children with IBD were more likely to have a prescription for each drug group and had twice the prevalence odds of taking anxiolytics, hypnotics, and sedatives (POR 2.1, 95% CI 1.8–2.4) and antidepressants (POR 2.1, 95% CI 1.9–2.3) than those without IBD. Among pediatric IBD patients, analgesic and psychiatric drug use increased substantially with age and healthcare utilization. Except for narcotics, prescriptions were more common among girls with IBD than boys.

Conclusions: Analgesic and psychiatric drug use is common among pediatric IBD patients. Co-medication and the resulting potential for drug interactions have important implications for treatment in this pediatric patient population.

665. Description of Psychoactive Drug Utilization in Newly Diagnosed Patients with Pervasive Development Disorder in the Province of Quebec

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Background: A number of medication surveys conducted in the U.S. have demonstrated a high level of psychotropic drug usage in patients diagnosed with pervasive development disorder (PDD). Medication use is of interest as not many products are approved for treatment in autism, especially in children.

Objectives: Describe psychoactive drug utilization in subjects newly diagnosed with PDD in the Quebec province.

Methods: A cohort study was built by using RAMQ and Med-Echo databases for subjects having a new PDD diagnosis (ICD-9 codes: 299.0–299.9) between January 1998 and December 2010. Cohort entry date was the date of a first diagnosis confirmed by the absence of PDD diagnosis in the previous 2 years. Patients aged of 26 years or more at the index date were excluded as well as those not covered by the RAMQ drug plan in the year preceding the index date. Descriptive analyses of patient characteristics were done at cohort entry and drug use profiles were done the year prior to, and within the 3 years following diagnosis.

Results: A cohort of 4,684 subjects was identified; 78% of patients were male and the age ranges were as follows: 41.9% (1–5 years), 31.2% (6–12 years), 12.3% (13–17 years), 14.7% (18–25 years). Prior to being diagnosed with PDD, 35% received at least one psychoactive drug. Methylphenidate was most common in

6–12 year olds (36%) whereas antipsychotics were most common in the 13–17 year old group (28.6%) and in the adult population (51.7%). Antipsychotic use was also present in younger children: 5.7% in 1–5 year olds and 23% in 6–12 year olds, 1 year after diagnosis. Antipsychotic, antidepressant and anticonvulsant usage increased in the 3 years following diagnosis, and also with age.

Conclusions: Prior to PDD diagnosis, more than a third of the patients were on psychotropic medications, a practice that continued and increased after diagnosis. Psychoactive drug utilization is high and could be of concern if used to compensate for limited access to other treatment modalities such as educational and allied health therapies.

666. Increasing Utilization of Proton Pump Inhibitors in Children: A Cohort Study in Three European Countries

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Background: The use of proton pump inhibitors (PPIs) as gastro-acid suppressing drug has been increasing over recent years and has replaced the use of histamine-2-receptor antagonists (H2RAs) for a large amount in adults. Little is known on the extent of the use of these drugs in children and adolescents and whether there are geographical differences.

Objectives: To describe prescription patterns of PPIs and H2RAs in children and adolescents in three European countries and to study the proportion of PPI prescriptions over time.

Methods: A retrospective population-based study was conducted using data from three primary care electronic healthcare databases in the Netherlands, Italy, and Spain in the period 2001–2008. Annual prevalence of use for PPIs and H2RAs was calculated (number of users per 1,000 person years [PY]) and stratified by country, calendar-time, age and sex. The proportion of PPI prescriptions vs. H2RA prescriptions was calculated and linear regression analyses were applied.

Results: The overall prevalence of H2RAs was lowest in Italy with 2.1 users/1,000 PY (95% CI 2.0–2.1), followed by 3.3 users/1,000 PY (95% CI 3.1–3.5) in the Netherlands, and 3.9 users/1,000 PY (3.8–4.0) in Spain. Also the prevalence of PPIs was lowest in Italy at 1.2 users/1,000 PY (1.1–1.3), followed by the Netherlands (4.1 [3.8–4.5]) and Spain (8.5 [8.3–8.7]). During the study period the proportion of PPI prescriptions compared to H2RA prescriptions increased in all three countries; from 41.1% to 56.6% in the Netherlands ($R^2 = 0.401$; p = 0.09), from 24.6% to 48.6% in Italy ($R^2 = 0.910$; p < 0.001) and from 48.8% to 75.6% in Spain ($R^2 = 0.985$; p < 0.001). The increase of PPI prescribing pertaining to H2RA prescribing was highest in the older children and most prominent in Spain and Italy.

Conclusions: Between 2001 and 2008 PPI use in children and adolescents increased and replaced H2RA prescriptions, especially in the older children. There is a need for long term follow up studies in children to assess long term safety of PPI use.

667. Pediatric Pharmacoepidemiology Safety Study with Long-Term Use of Sertraline: The SPRITES Study

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Background: Since only approximately 25% of approved drugs are licensed for pediatric use, pharmacoepidemiology studies are crucial to inform the safe use of drugs in pediatric clinical care. As part of a regulatory referral, we are committed to conducting a long-term pediatric study to assess sertraline's effects on cognitive, emotional, physical and pubertal development. Owing to these research challenges, we assessed the feasibility of this request using the most scientifically robust and operationally efficient study design.

Objectives: To describe design features of the Sertraline Pediatric RegIstry for The Evaluation of Safety (SPRITES).

Methods: Significant design challenges included: (1) Identification of sufficient number of pts treated in psychiatric outpt care and examined across important

developmental milestones; (2) Developmental, cognitive and behavioral endpoints not well-defined; small changes may have a long latency period requiring ongoing surveillance; (3) Pediatric pts treated with sertraline may have co-occurring conditions or use other medications that could confound valid assessment of exposure-outcome relationship.

Results: We designed a 3-year prospective cohort study (n = 900 sertraline-exp/unexp (psychotherapy alone) pts ages 6–14 years) identified from among outpt sites in the US including those in the Child and Adolescent Psychiatry Trials Network (CAPTN). Pts are enrolled over 2 years and followed during peak maturation to assess changes in cognitive, emotional, physical and pubertal development. To minimize confounding, pts are restricted to a homogenous sample, potential confounders are regularly collected, and marginal structural models will be used. Exposure is assessed by dose and duration, and endpoints are measured bi-annually using simple, validated psychometric tests. SPRITES includes routine collection of non/serious adverse events and the Columbia Suicide Severity Rating Scale for suicide assessment. Study enrollment began in April 2012 and to date, 96 pts have been enrolled.

Conclusions: SPRITES is among the first observational study to monitor the long-term safety of sertraline in outpt pediatric clinical care.

668. Using PMSI Database To Identify Adverse Drug Reactions in a Pediatric University Hospital

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Background: Spontaneous notifications of adverse drug reactions (ADRs) suffer from under-reporting especially in children. The combination of different sources of data (spontaneous reporting or computerized medical databases) could improve ADRs notifications in pediatric hospitals.

Objectives: The aim of the present study was to identify ADRs using computerised hospital database Programme de Médicalisation des Systèmes d'Information (PMSI), to compare them to spontaneous notifications and to estimate the total number of ADRs occurring during the study period.

Methods: The study was conducted from January 2008 to December 2011. We selected 135 ICD-10 codes (10th International Classification of Diseases) related to an ADR. Hospitalization summaries of each patient were read to check out if there was mention of the ADR. All spontaneous ADRs which occurred during the study period in the Children University Hospital of Toulouse were selected. The capture-recapture method was applied to estimate the total number of ADRs.

Results: We retained 60 reports from the PMSI database and 200 from the FPVDB. Mean age of children was 8.0 years for PMSI and 7.2 years for FPVDB. The rate of 'serious' ADRs was higher in PMSI reports (74.6% vs. 38.9%, p < 0.0001). The most frequent ADRs reported were: 'Musculoskeletal and connective tissue disorders' (12.4%) and 'Nervous system disorders' (11.3%) for PMSI database and 'Skin and subcutaneous tissue disorders' (22.4%) and 'General disorders and administration site conditions' (17.5%) for FPVDB. The most frequently suspected drugs were 'antineoplastic and immunomodulating agents' (31.1%), and 'nervous system drugs' (16.7%) for PMSI database and 'antiinfectives for systemic use' (38.2%) and 'antineoplastic and immunomodulating agents' (22.2%) for FPVDB. Twenty-nine common cases were found from both databases, giving an estimated number of ADRs of 703 [95% confidence interval (CI) 507, 899].

Conclusions: Using PMSI database can improve the detection of ADRs. These results also show that, compared to spontaneous notifications, use of PMSI could provide additional knowledge of ADRs in children and underline the importance of this application in routine practice.

669. Teething Symptoms and Their Evolution over Time: Data Collected from Parents

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Background: There is currently no existing consensus regarding the symptoms attributable to teeth development. The symptoms vary from child to child. Because of these different experiences, parents and physicians often disagree as to the symptoms of teething and the pain associated.

Objectives: The objectives of this study were to describe teething symptoms and evaluate their evolution overtime from a parents' perspective.

Methods: This prospective observational study was conducted with pediatricians, who enrolled 597 children. Parents were asked to fill out a diary to collect symptoms evolution during 7 days following the baseline visit (n = 412). The symptoms' evolution described by parents were analysed at baseline and at day 7.

Results: For the 412 children where data was available from both physicians and parents, the median age was 8 months, 58.5% were male and for 49.8% of them it was the first teething experience. The average number of symptoms observed by the pediatricians at the inclusion visit was 4.9 (average), with almost all experiencing one or more buco-dental and systemic symptoms (96.6% and 94.3% respectively). The buco-dental symptoms evolution was as follows for baseline vs. day 7: gum tumefaction 80.5% vs. 59.6%, drooling 70.3% vs. 49.6%, gum erythema 41.4% vs. 26.5%. Other symptoms were collected such as: Diarrhea 39.3% vs. 19.7, diaper rash 50.2% vs. 27.9% appetite diminution 32.5% vs. 12.3% and fever (≥ 38°C) 14.6% vs. 3.1%. Unusual behaviors were also noted by parents and considered as imputable to teething: agitation/irritability 67.1% vs. 31.7%, weeping 59.8% vs. 26.8% and sleep disorder 55.1% 26.3%.No statistical correlation between symptoms duration and treatments group were shown.

Conclusions: Teething symptoms vary from a child to another, however most parents agree that those symptoms that occurred around the time of teething are imputable to this natural process.

670. Treatment of Teething Symptoms: Evaluation of Parent's Compliance to Pediatricians Prescriptions

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Background: Despite the availability of medications indicated for teething, there is no existing consensus regarding the symptoms attributable to teeth development and guidelines for their treatment.

Objectives: The objectives of this study were to describe teething symptoms, treatment management by pediatricians and evaluate parents' usage of the treatments prescribed.

Methods: A total of 161 pediatricians agreed to participate in this prospective observational study and filled out case reports form. Parents were also asked to fill out a diary to collect symptoms and delivered treatments. A full set of medical and treatment data recorded by the physicians and the parents were available for 412 children.

Results: For children included in the study, the median age was 8 months, 58.5% were male and for 49.8% of them it was their first teething experience. The average number of symptoms observed by the pediatricians at the inclusion visit was 4.9 with almost all experiencing one or more buco-dental and systemic symptoms (96.6% and 94.3% respectively). For the

412 children for who a full set of data was available, parents administered the treatment prescribed by the physician in 81.8%% of the cases for the oral solution CAMILIA, 75.4% for teething gels alone and 54.1% for the association of both. Paediatricians recommended giving oral pain reliever, in 64.5% of the cases this treatment has been administered by the parents regardless of the indicated teething treatments. 13.3% of the children didn't receive the treatment prescribed. The main reasons were: The symptoms decreased/disappeared (n = 36), the treatment had been forgotten (n = 10) or a non-pharmacological treatment was enough (n = 7). At the end of the follow-up, 80.7% of parents reported that they were satisfied/very satisfied by the treatment prescribed by the paediatrician.

Conclusions: The results highlighted that the parents are overall administering the treatments prescribed and following pediatricians' guidance.

671. Prescription Patterns and Treatment Adherence of Asthma Controller Therapies in Children in a Dutch Primary Care Database

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Background: Asthma is the most common chronic disease amongst children. The Global Initiative for Asthma (GINA) guidelines recommend a stepwise treatment approach, adjusted in a continuous cycle, driven by the patient's asthma control level. There are different asthma controller therapies, need to be taken daily to control asthma symptoms. Nevertheless, it is often reported that adherence to prescribed asthma controller therapy is suboptimal.

Objectives: To evaluate prescription patterns and treatment adherence (Medication Possession Rate = MPR) of asthma controller therapies in Dutch children, stratified by age, gender and calendar year.

Methods: Observational cohort study with data from the IPCI (integrated primary care information) database, a Dutch primary care database containing the complete medical records of more than 176,500 children. All children with physician diagnosed asthma, aged 5–18 years between 2000–2012, were identified. For these children, we retrieved all prescriptions of asthma drugs from the database and calculated the prevalence of use per 100 patient years (PY), stratified

by age and gender. In addition, we calculated the Medication Possession Rate (MPR).

Results: We identified an asthma cohort of 14,304 children (prevalence 8%) with 34,000 PY of follow-up (58% boys). Short-acting beta-agonists (37/100 PY) and inhaled corticosteroids (ICS) (30/100 PY) had been prescribed most frequently. Between the ages of 5 and 13 years, the prevalence of use of asthma drugs was similar in girls and boys. After the age of 13 years, the prevalence was higher in girls than in boys. The MPR was highest for leukotrien antagonist (median 49.8 [IQR 36]), comparable for long acting beta-agonist (LABA) and fixed combination therapies containing ICS + LABA (medians 39.3 [IQR 52] and 45.2 [IQR 44] respectively) and lowest for ICS and ipratropiumbromide (median 24.6 [IQR 30] and 22.7 [IQR 42]).

Conclusions: We showed that in Dutch pediatric primary care monotherapy with ICS was the most prescribed controller therapy. Also in Dutch children, treatment adherence was low, especially for ICS.

672. Prevalence and Patterns of Anti-Infective Medication Use in Children with Type 1 Diabetes Mellitus

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Background: Antiinfective medications are among the most commonly used classes of medicines in patients with Type1 Diabetes Mellitus (T1DM). Quantitative data of the prevalence and patterns of use of these drugs in children with T1DM are limited.

Objectives: To determine prevalence and patterns of antiinfective drug use in T1DM children in the Netherlands.

Methods: A population-based cohort study was conducted in the Dutch PHARMO Record Linkage System that comprises community pharmacy dispensing records linked to hospital admissions. All patients (< 19 year) with at least two insulin prescriptions between January 1999 and December 2009 (T1DM cohort) and a four times larger reference cohort with the same age and sex distribution, but without antidiabetic prescriptions were identified from PHARMO. Both cohorts were followed from the index date (first insulin prescription date) for 4 years. The period prevalence of antiinfective drug use (antibacterials, antimycotics, antimycobacterials, antivirals, and antifungals) in T1DM and reference cohorts was calculated by dividing the number of patients with at least one antiinfective prescription by the number of patients available in the cohort during the follow up time. Prevalence in the T1DM cohort was stratified by sex and age (0–5, 6–12, and 13–18 years) and year of follow up.

Results: A total number of 925 T1DM patients and 3,591 children in the reference cohort (49.3% females, mean age 10.1 years) met the inclusion criteria. The period prevalence of antiinfective drug use in T1DM was significantly higher than in the reference cohort with 63% vs. 53% (p = 0.000). Female T1DM patients had a higher prevalence of antiinfective use with 66% vs. 59% in male T1DM (p = 0.024). Zero to 5 year old T1DM patients had the highest prevalence of antiinfective use with 77%, this number was followed by 64% in 13–18 year and 56% in 6–12 year (p = 0.000). The highest prevalence was observed in the T1DM patients in the first year of diabetes with 35.5%.

Conclusions: T1DM children consume antiinfective medications significantly more than a reference cohort. There were differences in the prevalence of antiinfective drug use in different genders and age groups.

673. Medication Use and Disease History as Risk Factors for the Clinical Manifestation of Type 1 Diabetes Mellitus

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Background: Prior to the clinical presentation of type 1 diabetes mellitus (T1DM) there is a highly variable asymptomatic period of beta-cell destruction. It is not well known what triggers T1DM to become a clinically overt disease.

Objectives: To identify triggering factors for the occurrence of T1DM focusing on disease history and medication use.

Methods: A population-based case-control study was conducted in the Dutch PHARMO Record Linkage System that comprises community pharmacy dispensing records linked to hospital admissions. Patients younger than 25 years with at least two insulin prescriptions between 1999 and 2009, and a four times larger control group with the same age and sex distribution, but without antidiabetic prescriptions were included. Cases were compared to controls with regard to hospital admissions for 21 different diseases (based on ICD-9 codes) and medication use (based on ATC codes) 1 year prior to the clinical manifestation of T1DM using conditional logistic regression analysis. Effect modification by age and sex was explored.

Results: A total number of 1,133 cases and 4,512 controls (51.7% male, mean age 11.9 years) met the inclusion criteria. T1DM was significantly associated with a prior history of neoplasms, cystic fibrosis, anemia, mental disorders, pneumonia, and disease of digestive system with ORs of 12.3, 52.0, 5.3, 8.0, 4.0, and 2.5, respectively. Drugs in the following ATC groups 'alimentary tract and metabolism', 'blood and blood forming organs', 'systemic hormonal preparations', 'antiinfectives for systemic use', and 'nervous system' were significantly associated with increased risk of T1DM, with ORs of 1.5, 2.2, 2.4, 1.3, and 1.3, respectively. No effect modification by age and sex was found.

Conclusions: This population-based study showed that a diverse group of diseases and drug exposures were associated with T1DM becoming clinically overt. Further research is necessary to evaluate the causality of these relations and the involved mechanisms.

674. Demographic and Clinical Characteristics Prior to Clozapine Initiation in Early Onset Schizophrenia: A Study Based on the Danish Population-Based Registers

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Background: Early Onset Schizophrenia (EOS) is a severe variant of the adult onset disorder characterized by poor treatment response. Although the efficacy of clozapine (clz) for treatment-resistant EOS is well documented, it is still being prescribed infrequently.

Objectives: To identify demographic and clinical drivers for clozapine prescription in EOS.

Methods: The data were extracted from the Danish population-based medical and socio-demographic registries. From this unbiased population, we identified cases with a first diagnosis of schizophrenia (ICD-10: F20.0) between December 31, 1994 and December 31, 2006 with disease onset prior the 18th birthday (EOS) and followed their antipsychotic prescription history until 2010.

Results: Of the 661 EOS cases, 108 (median age at first clz prescription: 16.86 years, min 13.45; max: 17.96; 48 males) had been prescribed clozapine at least once after hospital discharge after a median time of 898 days (d) (25% percentile [p25]: 312.5 d, 75% percentile [p75]: 2,053 d). The median number of previously prescribed antipsychotics other than clozapine was 2.5 (p25:1; p75:5). EOS patients prescribed clozapine did not differ from the remaining cases in terms of their sex distribution or their clinical characteristics including the mean duration of the first hospital admission at EOS onset and the duration between schizophrenia onset and first antipsychotic prescribed (p-values > 0.5).

Conclusions: Basic clinical and demographic characteristics could not identify predictors of clozapine initiation in this sample. In our future work we aim to explore whether additional socio-demographic variables or regional prescribing biases influence clozapine initiation in EOS.

675. Maternal Smoking in Early Pregnancy Increases Risk of Childhood Overweight

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Background: Maternal smoking in pregnancy is a well-established risk factor for poor perinatal outcomes, however, the impact on childhood development is not well defined.

Objectives: We aimed to investigate the association between maternal smoking during pregnancy and childhood overweight at 4- to 5-years of age.

Methods: A retrospective cohort study using linked records from the Women's and Children's Health Network in South Australia. Women delivering a singleton, live-born infant between January 2000 and December 2005 were included (n = 22,615), while those with unknown smoking status were excluded (n = 823). Data were available from 7,658 (35%) on child height and weight at 4- to 5-years of age: of these 78% (5,961) were from women who were non-smokers, 18% (1,400) from women who smoked throughout pregnancy and 4% (297) from women who quit during early pregnancy.

Childhood overweight was defined as a BMI > 85th percentile, based on age and sex. Rates of overweight were compared using a generalised linear model, yielding prevalence ratios (PRs) and 95% confidence intervals).

Results: Compared to infants of women who were non-smokers, or quit smoking, smoking throughout pregnancy significantly reduced birth weight (−300 g; p < 0.01). Despite this birth weight disparity between smokers and those who quit, both groups had equivalent and significantly increased adjusted prevalence ratios (aPR) of children being overweight at age 4- to 5-years relative to children of non-smokers (Smokers: aPR 1.22; 95% CI 1.11–1.35; Quit smoking aPR 1.23; 95% CI 1.02–1.48). A significant dose response relationship was observed between average number of cigarettes smoked/day during pregnancy and the prevalence of childhood overweight.

Conclusions: Any maternal smoking in pregnancy, even if mothers quit during early pregnancy, may increase the risk of children becoming overweight by 4- to 5-years of age. These data may provide further support for promoting smoking cessation before rather than during early pregnancy.

676. Second Immunization Against Measles, Mumps, Rubella with MMRV, MMR or MMR + V

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Background: Evidence suggests an increased risk of febrile convulsions (FC) in children receiving 1st dose vaccination against measles, mumps, rubella, varicella (MMRV) compared to children receiving MMR or MMR and V vaccine separately (MMR + V). A 2nd immunization is recommended at 4–6 years in the US and at 15–23 months in Germany. Population-based data on 2nd dose immunization patterns in Germany and subsequent FC risk is limited.

Objectives: To describe 2nd dose immunization patterns in Germany. Estimations of the risk of FC after a 2nd dose of MMRV compared to MMR or MMR + V are currently undergoing usual quality control procedures and therefore not yet presented.

Methods: We performed a cohort study based on claims data from four German statutory health insurance providers (SHIs) covering > 17 million insurants throughout Germany. All insurants born from 2006 to 2008 with a 2nd dose of MMRV, MMR or MMR + V were included. FC was defined as hospitalization with a diagnosis of FC in absence of concurrent neurological conditions. Descriptive analyses of the cohort population were conducted. Adjusted (age, sex, history of FC) odds ratios (ORs) with 95% confidence intervals (CIs) will be estimated by logistic regression to compare MMRV with MMR and MMR + V in risk intervals (RI) 0–4, 5–12, 13–30 and 0–30 days after immunization.

Results: The cohort included 164,596 children. MMR was administered to 101,775, MMR + V to 10,914 and MMRV to 51,907 children for 2nd immunization. Most children (51.4%) were vaccinated in the recommended age-range, while 23.8% had < 15 and 24.8% had > 23 months at vaccination. MMR-vaccinated children were older (median: 19 vs. 16 months in MMR + V- and MMRV-vaccinated children) and with comparable frequency had a history of FC (1.6% vs. 1.3% vs. 1.3%, respectively). Adjusted ORs for each RI will be presented.

Conclusions: Preliminary results of this study show that the immunization patterns in Germany regarding a 2nd immunization against MMR and V only partly meet the present national recommendations. Sufficient data is available to provide estimates for the risk of FC in relevant RIs.

677. Trends in Prevalence of Antibacterial Drug Use Among Dutch Children from 2005 Until 2010

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Background: Systemic antibacterials are frequently used by children.

Objectives: To assess trends in prevalence of antibacterial drug use among Dutch children from 2005 until 2010.

Methods: The PHARMO Database Network, containing amongst others outpatient pharmacy dispensing data of approximately 3.2 million inhabitants in the Netherlands, was used for this study. For every year in the study period 2005–2010, the number of children aged 0–18 years with any dispensing of systemic antibacterials and per subtype was counted and extrapolated to the Netherlands, standardized for age and gender. Prevalence of use was reported per 10,000 children and was stratified by calendar year, age group (< 2 years: infants and toddlers, 2–11 years: children, 12–18 years: adolescents) and gender.

Results: The prevalence of antibacterial drug use decreased 1.1-fold among infants and toddlers (from 2,231 to 2,041 per 10,000), decreased 1.3-fold among children (from 1,979 to 1,564 per 10,000), but remained constant among adolescents (1,193 per

10,000). A decrease of use was mainly observed in the most prevalent types; penicillins with extended spectrum and macrolides. However, also trimethoprim and derivatives were less frequently used, especially among female adolescents (from 163 to 92 per 10,000). Prevalence of beta-lactamase resistant penicillins increased from 2 to 29 per 10,000 among infants and toddlers and from 44 to 77 per 10,000 among children. An increase in nitrofuran derivatives was observed among female children (from 38 to 100 per 10,000) and female adolescents (from 267 to 413 per 10,000).

Conclusions: This study provides an extensive overview of trends in antibacterial drug use among children in the Netherlands. An overall decrease of use was observed, while an increase was observed for nitrofuran derivatives and beta-lactamase resistant penicillins.

678. Characteristics and Determinants of Palivizumab Use in the Netherlands

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Background: Respiratory Syncytial virus (RSV) is the leading cause of respiratory tract infections. Efficacy of Palivizumab in reducing RSV related hospitalizations has been proven in preterm born infants and children with congenital heart disease (CHD) or bronchopulmonary dysplasia (BPD). However, the high costs of Palivizumab may limit its use.

Objectives: To describe the characteristics of Palivizumab users in the Netherlands and assess the determinants of receiving Palivizumab among infants with an indication according to the label.

Methods: Data for this study were obtained by linking the PHARMO Database Network, which includes detailed information on drug dispensing and hospitalization histories, and The Netherlands Perinatal Registry, including perinatal medical case records. From this linked cohort, all infants born between April 1st 1999 and March 31st 2007 were selected and characteristics of those receiving Palivizumab were described. Among infants with an indication to receive Palivizumab (i.e. born < 35 weeks, CHD or BPD), recipients were compared with non-recipients and determinants of receiving Palivizumab were examined using logistic regression analyses.

Results: Among the 3,321 infants with an indication to receive Palivizumab, only 15% were recipients. The majority was born < 32 weeks of gestation and mean age at first use was 3.1 months. The strongest predictor of receiving Palivizumab was being born < 32 weeks (OR 49.1; 95% CI 31.5–76.4). However, among the infants born < 32 weeks, still 50% did not receive Palivuzmab. Subanalyses among this group showed that the likelihood of receiving Palivizumab was higher for infants born in later years, having respiratory distress syndrome or being hospitalized in the RSV season.

Conclusions: In the Netherlands, Palivizumab is mostly prescribed to infants born < 32 weeks, which is according to Dutch guidelines. Use has increased over the years. However, not all children addressed in the label indication are receiving Palivizumab.

679. Trends in Prevalence of Drug Use Among Dutch Children from 2005 Until 2010

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Background: There has been growing attention for over-medicalization of children.

Objectives: We examined trends in outpatient drug use among children in the Netherlands from 2005 until 2010.

Methods: The PHARMO Database Network, containing amongst others outpatient pharmacy dispensing data of approximately 3.2 million inhabitants in the Netherlands, was used for this study. For every year in the study period 2005–2010, the number of children aged 0–18 with a dispensing for any drug and per anatomical group was counted and extrapolated to the Netherlands, standardized for age and gender. Prevalence of use was reported per 10,000 children and was stratified by calendar year and age group.

Results: In all age groups, drug use increased between 2005 and 2008, but has been descending since. The highest increase was found among adolescents (12–18 years): drug use increased from 4,910/10,000 in 2005 to 5,496/10,000 in 2008, but declined to 5,378/10,000 in 2010. Among infants and toddlers (< 2 years), use of dermatologicals, anti-infectives, respiratory drugs and drugs acting on the alimentary tract increased between 2005 and 2008. Since 2008, the largest decrease was found for anti-infectives and respiratory drugs (−236 and −136/10,000, respectively). Among children (2–11 years), use of dermato-

logicals, neurologicals and drugs acting on the alimentary tract increased between 2005 and 2008, while use of anti-infectives decreased (−192/10,000). Between 2008 and 2010, use of anti-infectives kept decreasing (−224/10,000). Among adolescents, drug use increased for all anatomical groups between 2005 and 2008, with the highest increase for drugs acting on the alimentary tract, respiratory drugs, dermatologicals and neurologicals. Between 2008 and 2010, use of neurologicals and drugs acting on the alimentary tract kept increasing, while use of anti-infectives decreased (−138/10,000).

Conclusions: Drug use increased between 2005 and 2008, especially among adolescents, but has been descending since. A substantial increase in use was observed for drugs acting on the alimentary tract, dermatologicals and neurologicals, while the use of anti-infectives decreased over time.

680. Prevalence of Childhood Asthma and Asthma-Related Health Services Utilization in the Province of British Columbia, Canada

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Background: Recently, an increase in childhood asthma prevalence has been reported, associated with an increase use of health service utilization. The province of British Columbia, due to extension, diverse ethnic background, and healthcare system is an ideal location to explore asthma prevalence trends over time.

Objectives: To determine the prevalence of childhood asthma, as well as asthma-related health service utilization over a 13-year study period.

Methods: A cohort of asthma patients between 0 and 18 years was identified using a linked provincial database containing fee-for-service physician billing records, hospital inpatient separation abstracts, and a prescription drug purchase records from 1996 to 2009 for 1.9 million BC respiratory patients. Using a validated asthma case definition, which included 1 hospitalization or two physician visits or three asthma medication dispensing in 1 year, we were able to identify asthma prevalence and its trend over time. In addition, we were able to identify physician visits, ED service visits and hospitalization related to this disease.

Results: Prevalence of asthma in the province has remained steady in the past 13 years, with annual values from 2.24% to 2.51%. Decreasing trends of health service use were found. In particular, compared to 1996 where 6,705 ED visits were identified, annual asthma related ED visits have decreased significantly from 1998 (5,972 visit) onwards (in 2009, 1,855 visits). The number of physician visits shows a non-significant decrease trend from 1996 (46,194 physician visits) to 2009 (32,918 physician visits). Finally, compared to 1996 where 578 hospitalizations were identified, annual hospitalization rates have decreased significantly from 2000 (537 hospitalizations) onwards (on 2009, just 274 hospitalizations).

Conclusions: We were able to identify a stable trend in prevalence and incidence in childhood asthma, with a decrease in asthma related health service utilization. Further research is necessary to identify the intervention(s) responsible for this decrease in asthma health services utilization over this time period.

681. Drug-Induced Adverse Reactions Via Breastfeeding: A Study in the French Pharmacovigilance Database

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Background: It is well-established that most of drugs were excreted into breast milk and thus also available to the infant. The effects on the infant, of many drugs taken by the mother are unknown.

Objectives: To describe Adverse Drug Reactions (ADRs) registered in the French Pharmacovigilance Database.

Methods: All spontaneous reports of ADRs in breastfed infants recorded by the 31 French Regional Pharmacovigilance centres in the National Pharmacovigilance database were investigated.

Results: Between January 1985 and June 2011, 174 ADRs in breastfed infant were notified to the French network of PharmacoVigilance. Median age was 49.0 ± 66.7 days. Mean weight (3863.9 ± 1326.9 g) and length (49.4 ± 3.0 cm) of infants were lower than in the French general population. The most often reported ADRs were nervous system disorders (28.6%), followed by gastrointestinal disorders (20.3%) and skin and subcutaneous tissue disorders

(6.5%). Sixty-five (37.4%) ADRs were considered as serious. Most frequently suspected drugs were nervous system drugs, mainly antiepileptics, benzodiazepines and opioid analgesics. Drugs more often suspected in serious ADRS were dextropropoxyphene (respiratory distress, apnea…), ketoprofene (renal and digestive adverse effects…), lamotrigine, hydroxyzine and clonazepam.

Conclusions: Some drug classes such as opioids and antiepileptics drugs, NSAIDs and benzodiazepines, which produced adverse effects in the infant, should be used, when necessary, with great care.

682. Misuse of Short Courses of Oral Glucocorticoids in Children: A Prospective Observational Study

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Background: Short courses of oral glucocorticoids (SCOG) appear to be frequently prescribed to children in spite of a definite iatrogenic potential, and uncertainty about the action mechanism the dose and the duration of treatments.

Objectives: To evaluate the validity of the use of SCOG in children according to current practice guidelines and to describe the adverse effects induced.

Methods: A prospective observational study was conducted between 7/2010 and 6/2011, including children under the age of 18, receiving a SCOG at the time of their admission to the paediatric emergency department of a university hospital. Data for evaluating the validity of the therapeutic indications of the SCOG being taken by the children according to current practice guidelines and the adverse effects observed were collected using a questionnaire and the patients' medical file.

Results: Altogether 100 children aged 4.8 ± 4.0 years (1 month–17 years) were included. During the 12 months prior to admission, 56% had received an oral corticotherapy. The main indication of oral glucocorticoids was lower respiratory tract disease (71%). In fact, 61% of the SCOG were prescribed for therapeutic indications not validated by current practice guidelines. The most frequent indications were acute cough (42%), acute bronchiolitis (16%) and acute bronchitis (8%). SCOG self-medication was encountered in 7% of the cases. The incidence of adverse effects was 38%; they were principally neuro-psychiatric disorders (65%).

Conclusions: Systematic use of SCOG cannot be recommended for children in a number of conditions due to insufficient proof of their efficiency and relative harmlessness. However, in this study, the most frequent misuses concerned conditions for which practice guidelines exist, formally advising against the use of oral glucocorticoids. In light of this information it appears essential to emphasize the practice of evidence-based medicine and patient education, in order to reduce unnecessary exposure of children to the potential adverse effects of oral glucocorticoids.

683. Distribution and Development of Co-Morbidities in Pediatric Patients with ADHD

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Background: Co-morbidities complicate the treatment regimens as well as require more specialized care in pediatric patients with attention deficit hyperactivity disorder (ADHD). There is a need to study the distribution and development of co-morbidities in this population.

Objectives: To determine the prevalence and development of mental co-morbidities in pediatric patients with ADHD.

Methods: This is a cross-sectional study in 29 US states Medicaid fee-for-service programs from 1999 to 2006 including youth ≤ 18 years with ≥ 2 ADHD outpatient claims. ADHD was defined to persist from first outpatient claim to the last with an extension of 1 year. Duration of 12 co-morbidities of interest was based on published literature: adjustment disorder (3 months), anxiety (3), autism (life-long [L]), bipolar disorder (L), depression (3), eating/elimination/sleep disorders (3), intellectual disabilities (L), learning disorders (3), oppositional defiant disorder/conduct disorder (ODD/CD) (L), schizophrenia (L), substance abuse (3) and tics/Tourette syndrome (L). The percentage of person-days with specific co-morbidity or combinations is reported. Survival analysis was used to describe the development of co-morbidities after the period with ADHD, stratified by age of ADHD onset.

Results: We identified 1,408,338 patients with at least one period of ADHD, totaling 1,260,892,319 days of follow up. The percentages of person days with 0, 1, 2, 3 and ≥ 4 co-morbidities were 61.4%, 25.8%, 9.0%,

2.8% and 1.0%, respectively. ODD/CD, learning disorder, adjustment disorder, depression and bipolar disorder were the most common co-morbidities. The median time of developing the first co-morbidity regardless of type was 714 days (95% CI 705, 724). ADHD onset at young age was associated with early development of learning disorder (mean survival time, for age < 10 and ≥ 11 years: 2,516, 2,276 days) while with late development of depression (2,530, 2,231) and substance abuse (2,849, 2,593).

Conclusions: Patients with ADHD have at least one mental co-morbidity in about 40% of the time of follow-up, stressing the importance of safety and efficacy data that include co-morbidities and co-therapy. Comorbidity pattern vary across age groups.

684. Influence of Drug Prescription Status in Pediatric Adverse Drug Reaction: Review of Spontaneous Reports Registered to the PharmacoVigilance by a Regional PharmacoVigilance Center

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Background: The large use of nonprescription drugs in pediatric population suggests that they are not dangerous. However, safety evaluation of these drugs in children is scarce.

Objectives: The aim of the present study was to analyze spontaneous reported Adverse Drug Reactions (ADRs) in children during a 26-year period and to describe their profile in terms of drug prescription status involved.

Methods: A retrospective analysis of pediatrics ADRs (< 18 years) reports, registered into the French PharmacoVigilance Database (FPVD) between January 1985 and December 2011 by Midi-Pyrenees PharmacoVigilance Center, was performed. The ADRs profile according to drugs prescription status was analyzed with respect to age, gender, category of ADRs, seriousness and suspected drugs. For cases involving prescription and nonprescription drugs, we retained the prescription status of the drug with the highest imputability. We excluded cases that involved different prescription status drugs with the same imputability.

Results: A total of 2,017 cases concerning 3,171 ADRs were identified and included in the study. The number of notifications increased gradually since 26 years (two in 1985 and 117 in 2011). The median age was 9 years [1 day–18 years]. A total of 1,038 cases concerned boys (51.4%). Among the 2,017 cases, we retained 1,906 notifications. Nonprescription drugs were

involved in 440 notifications (23.1%) represented by only nine drugs (n = 350; 79.5%): ibuprofen (n = 60; 13.6%) and hepatitis B vaccine (n = 51; 11.6%). In both groups, the most ADRs reported were 'Skin and subcutaneous tissue disorders' (n = 739; 23.6%) and 'General disorders and administration site conditions' (n = 471; 14.9%). The ADRs were serious in 35.9% for prescription drugs and in 32.6% for nonprescription drugs.

Conclusions: This study shows that nonprescription drugs, considered as safe, were responsible for 23.1% of ADRs reported in children to the Midi-Pyrénées PharmacoVigilance Center. About third of them were serious. These results highlight the need for vigilant surveillance of nonprescription drugs in children especially ibuprofen.

685. Analysis of Method To Capture Adverse Events in Neonates and Children in Tertiary Care Pediatric Hospitals

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Background: The U.S. legislation in the 1990s encouraging pediatric study development resulted in more pediatric efficacy studies submitted to FDA. Small sample sizes in pediatric drug trials mean greater reliance on postmarketing (PM) safety assessments. FDA receives limited PM safety and use data on young children, especially infants.

Objectives: (1) Pilot study of a new approach to pediatric post-marketing safety studying Proton Pump Inhibitors (PPIs) and Octreotide. (2) Assess impact of the type of product studied on the quality of data obtained using this data collection tool.

Methods: *Design:* Convenience sample (four hospitals, infants < 1 year, PPIs) (five hospitals, children < 7 years, Octreotide), retrospective data collection, paper questionnaires. Time frame:1/2011–10/2011,

PPIs; 1/2007–12/2010, Octreotide. *Setting:* U.S. tertiary care pediatric hospitals/centers. *Exposure:* Octreotide or PPIs. *Main outcome measures:* Mortality, other adverse events, compare data collected on PPIs with that on Octreotide. *Statistical analysis:* Statistical analysis descriptive: convenience sample with no control group.

Results: Patients studied received Octreotide (N = 222) or PPIs (N = 155). Subjects were 48% Female, Octreotide, 49% Female PPIs. Median birth weight of those that used Octreotide was 3.2 kg, PPIs 2.4 kg. Mortality in patients that used Octreotide 53/222 (24%), was higher than PPI 2/155 (1.29%). Top indications for Octreotide use (N = 193/222) were severe hypoglycemia (103), chylothorax (46), gastrointestinal bleeding (23), inhibition of retinal neovascularization (18). Top indications for PPI use (N = 116/155) were gastroesophageal reflux disease (56), maintenance of healing from erosive esophagitis (9), and ulcer prophylaxis (9). Nonfatal serious adverse events (N > 2) are reported below: PPIs- CNS problems (4). Octreotide-bradycardia (4), hypotension (4), hypoglycemia (3).

Conclusions: Octreotide patients were more ill with higher mortality than PPI patients. The available data from chart abstraction were more complete on the children that used Octreotide. Future directions include setting up query systems in these or other hospitals for medical product safety.

686. Antipsychotic Use for Youth with ADHD and Psychiatric Comorbidities

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Background: Antipsychotic use is increasing among youth with attention deficit-hyperactivity disorder (ADHD). However, no studies have examined whether antipsychotic treatment is mediated by comorbid conditions, like mood disorders, or used solely as 'off-label' treatment for ADHD.

Objectives: This study (1) compares antipsychotic use between youth with ADHD only vs. ADHD and internalizing and/or externalizing disorders, and (2) tests the mediating effect of a comorbid mood disorder on antipsychotic use among youth with ADHD.

Methods: Retrospective data from 2010 to 2011 child welfare administrative records and mental health and pharmacy Medicaid claims were used to identify youth in foster care aged 19 or younger who had two or more visits for ADHD. Using ICD-9 diagnostic codes, youth were classified into four mutually exclusive groups: (1) ADHD only, (2) ADHD + internalizing disorders, (3) ADHD + externalizing disorders, and (4) ADHD + both internalizing/externalizing disorders. Bivariable and multivariable logistic regression assessed the association between ADHD group and bipolar or mood disorder (i.e. mood disorder) on antipsychotic use.

Results: The 1,211 youth with ADHD were mostly aged 10–19 (72.2%), African-American (90.7%), and male (64%). Over one-third (39%) received an antipsychotic and 45% had a mood disorder. Among antipsychotic users, 15% had ADHD only. Over half (54%) of youth with ADHD + both internalizing/externalizing disorders received antipsychotics compared with 39%, 37%, and 31% with internalizing, externalizing, or ADHD only, respectively (p < 0.001). A mood disorder was more likely for youth with ADHD + both internalizing/externalizing disorder (72%) than the other groups (48%-internalizing; 41%-externalizing; 27%-no comorbidity; p < 0.001). Adjusting for demographic covariates, ADHD with or without comorbidities was not significantly associated with antipsychotic use. Having a mood disorder was associated with a 4-fold increase (95% CI = 3.0–5.4) in the odds of receiving an antipsychotic.

Conclusions: While most antipsychotic users had ADHD and an additional comorbidity, 15% of these users did not have coexisting disorder that supports such treatment.

687. Medication Administration Errors Among Paediatric Nurses in Lagos Public Hospitals: An Opinion Survey

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Background: Medication errors are a global problem with an increasing magnitude in both developed and developing countries. There is paucity of data on paediatric medicine administration error in developing countries.

Objectives: To investigate the incidence, nature of and factors contributing towards medicine administration errors among paediatric nurses working in public hospitals in Lagos, Nigeria.

Methods: A confidential, self-reporting questionnaire was administered to 75 nurses working in public hospitals in Lagos to obtain information on different aspects of medication administration errors.

Results: Fifty nurses responded to give a response rate of 66.7%. All the participants were females with a mean ± SD age of 35.3 ± 10.7 years. Thirty two (64%) had committed at least one medication error over the course of their career. Dose calculation error (24; 48%) and wrong timing of medicine administration (20; 40%) were the medication errors frequently committed by the participants. The consequences of the errors included shock (23; 46%), restlessness (21; 42%), disorientation (11; 22%), and respiratory depression (10; 20%). Increased workload (26; 52%) and not double checking medicine doses (12; 24%) were the major causes of the errors. Only 15 (30%) nurses had reported medication errors to their superiors. Fear of intimidation, retribution or being punished (11; 22%) and lack of policies in place to report medication errors (13; 26%) were the two major barriers to reporting medication errors. Half (50%) of the nurses indicated that policies were available in their work places to prevent medication errors.

Conclusions: Medication errors were frequently committed by the participants and resulted in some inconsequential effects, morbidity and deaths. Appropriate measures should be implemented to prevent future occurrence of medication errors.

688. Creating a Reference Set for Comparing Data Mining Methods and Evaluating Database Performance in Children – The GRiP Project

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Background: Given the increasing need for evidence on medicines' safety in children the Global Research in Pediatrics (GRIP) – Network of excellence aims to develop pediatric specific methods for safety signal detection in spontaneous reporting and electronic health care databases. Comparison of methods requires the use of a 'gold standard' set of true associations and no associations.

Objectives: To create a reference set ('gold standard') of drug-event combinations, considered as 'True Positive' (TP) or 'True Negative' (TN) associations.

Methods: (1) Drug selection based on frequency of use in children, global use, age and setting specific use (2) Adverse event selection based on reported adverse drug reactions in children, seriousness and specificity (3) Creation of cross-table of 'drug-adverse event' combinations. Information retrieval on unique drug-event associations was achieved via: (i) Review of Summary of Product Characteristics (SPC) and Micromedex (ii) Review of results from (i) using information in published literature. Drug-event combinations with discordant information in SPC and Micromedex were excluded. Concordant information yielded a 'possible TP' or 'possible TN', with each subjected to literature validation. For selected drugs, controlled vocabulary terms were identified in Embase (Emtree) and Medline (MeSH). The list of terms were examined and for each literature database, this was combined with free text to form the final search string. Adverse events were likewise translated.

Results: Thirty-nine drugs were selected including: nine antibacterials, three anti-retrovirals, four nervous system drugs, three antineoplastic/immunomodulating drugs, and three sex hormones. Sixteen adverse events were selected including: (1) Fixed drug eruption/ Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis (2) Aplastic anemia (3) Suicide (4) Thromboembolism (5) Anaphylactic shock (6) Acute Renal failure (7) Drug-Induced Liver Injury (8) Sudden Infant Death Syndrome.

Conclusions: This research shows how a much needed reference set that can be used for testing of signal detection methods in pediatrics can be created.

689. Use of SSRIs Among Children: A Danish Drug Use Study

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Background: The use of selective serotonin reuptake inhibitors (SSRIs) in children has been much debated in the past decade. Issues on efficacy and adverse reactions, such as suicide-related behavior, have sparked warnings and guidelines from several regulatory

authorities. Yet, the patterns of SSRI utilization among the pediatric population in Denmark have not been examined before.

Objectives: To provide a detailed study of SSRI utilization patterns among all children living in Denmark in 1995–2011.

Methods: A nationwide drug utilization study among all children aged 5–17 years living in Denmark between January 1, 1995 and December 31, 2011. On average, 838,000 children of this age resided in Denmark during the study period. We obtained data from the Danish National Prescription Database to estimate the incidence and prevalence of SSRI use by calendar year, children's age and gender, as well as treatment duration and concurrent use of other psychotropic drugs.

Results: We identified a total of 23,547 children (5–17 years) using SSRIs during the study period, filling a total of 170,356 prescriptions. Sertraline was most the commonly used substance over the entire period (64,595 fillings). The prevalence of SSRI use treatment was relatively low among young children (5–11 years) throughout the study period (< 0.6 per 1,000 children). Among adolescents (12–17 years) the prevalence rose significantly, especially among adolescent girls (from 0.3 to 8.4 per 1,000 children). The incidence of SSRI use followed a similar pattern as the prevalence. Until age 13, boys used SSRIs more commonly than girls, but thereafter the prevalence ratio between genders was reversed. SSRI users had a large concomitant use of other psychotropic drugs, especially concerning psychostimulants (e.g. 33% among boys aged 5–11) and antipsychotics (e.g. 28% among boys aged 5–11). Adolescents tended to cease treatment earlier than younger children (median 386–395 vs. 522–545 days).

Conclusions: Use of SSRIs has increased dramatically among adolescents in Denmark in 1995–2011, but was limited among younger children. The use of SSRIs should be closely monitored in the future.

690. Relative Age in Class and Stimulant Drug Utilization for ADHD

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Background: Recent studies have demonstrated that the youngest children in a class are up to twice as likely as their older classmates to be prescribed stimulants for ADHD.

Objectives: To investigate whether younger age in class is associated with an increased risk of being prescribed stimulants for ADHD among school-aged children in Denmark.

Methods: For all children in Denmark we obtained data from The Danish National Prescription Registry and the Danish Student Registry between July 1, 2000 and June 31, 2012. We estimated the prevalence proportion ratio (PPR) of receiving stimulant prescriptions between the youngest children in class (born in October-December) and the oldest in class (born in January-March). PPRs were stratified by study year, children's grade level, and gender. The main analysis was restricted to children in 1st through 6th grade (7–12 years), who started school on their age assigned grade level.

Results: We identified 932,032 eligible children for the main analysis, of which 246,596 (26.5%) were relatively young in class and 161,116 (17.3%) relatively old. Overall, 40% of those relatively young were delayed in school, i.e. did not attend school at their age assigned grade level, and were thus excluded from the main analyses. Over the study period, annual prevalence proportion of stimulant use from age 7 to 12 increased from 0.13 to 1.03 per 1,000 children among those relatively young and from 0.15 to 1.47 per 1,000 children among those relatively old in class. The average PPR over the entire study period, comparing the relatively youngest with the relatively oldest, was 1.08 (95% CI, 1.04–1.12). When including children not on their age assigned grade level, i.e. classifying children based on their age assigned school grade, the PPR was 1.09 (1.06–1.12).

Conclusions: Contrary to previous studies, we observed almost no relative age-effect on ADHD use among children in Denmark. This may be explained by a high proportion of relatively young children with delayed school entry, which may effectively serve as an alternative to investigating immature children for an ADHD diagnosis.

691. National Trends in Psychotropic Medications Prescribed for Pediatric Bipolar Disorder with and Without Comorbid Behavioral Disorders, 1999–2010

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Background: Increasing diagnosis of pediatric bipolar disease (PBD) has drawn attention in recent years. However, the recent trend in psychotropic medication use in PBD and the impact of comorbid disorders on its treatment is unknown.

Objectives: This study aims to assess (1) recent trends in PBD from a national probability sampled survey of physician office visit data and patterns of psychotropic medication usage among these youth; (2) the impact of comorbid behavioral conditions on psychotropic medication usage among PBD-diagnosed youth.

Methods: In a cross-sectional study, pediatric visits to office-based physician practices between 1999 and 2010 were analyzed using National Ambulatory Medical Care Survey data with population-weighted bivariate and multivariable methods. The dependent variables were PBD visit rates and psychotropic medications prescribed by year among visits with and without comorbid behavioral disorders.

Results: PBD prevalence was 0.41%, 0.59% and 0.39%, respectively, across three study time points. Antipsychotic (49.28–59.46%) and stimulant (33.99–39.28%) use significantly increased. When PBD visits were stratified by comorbid behavioral disorders, the adjusted odds of having a comorbid behavioral disorder was 3.7 (95% CI = 2.1, 6.3) times greater compared with PBD visits without comorbid behavioral disorder, 5.6 (95% CI = 2.8, 11.1) times greater in 2–9 year olds compared with older youth; and 2.9 (95% CI = 1.7, 5.0) times greater among males. While stimulants were the predominant class prescribed for PBD visits with comorbid behavioral disorder (> 70% vs. 10%), antidepressants were significantly greater in PBD visits without comorbid behavioral disorders (22% vs. 45%). Prescription of antipsychotics was high (> 62%) for PBD visits regardless of the presence of comorbid behavioral disorders. A trend was observed for concomitant use ≥ 2 drug classes in patients with behavior comorbid conditions (p < 0.06).

Conclusions: While the prevalence of PBD visits decreased in recent years in U.S. youth, behavioral conditions accompanying PBD visits were prominent, reflecting complex medication regimens with weak benefit-risk ratios.

692. Pediatric Exclusivity: Evolving Legislation and Novel Complexities Within Pediatric Therapeutic Development

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Background: Pediatric drug development has a long history of success and failures, yet there is still a lack of appropriately labeled pediatric drugs. Significant challenges to conducting pediatric clinical trials deter research. There is a great need for trials because pediatric metabolism and tolerability differences cannot be extracted from adult data. The Food and Drug Administration Modernization Act (FDAMA, 2007) established the exclusivity principle to correct this deficit. Sponsors receive a 6 month patent extension if pediatric clinical trials are conducted, encouraging increased knowledge of pediatric indications and dosing.

Objectives: To review pediatric exclusivity laws and provide recommendations for policy refinement.

Methods: Review of the current literature in PubMed, Pediatric Exclusivity drug listings, drug labeling, clinical trials, and postmarket safety studies.

Results: There are 192 drugs granted exclusivity through November of 2012. Hypertension is the most prevalent indication approved. Fewer drugs granted extension are aligned with epidemiological needs such as asthma, ADHD, and epilepsy. Studies do not necessarily address appropriate age groups, include studies with Phase IV signals, or study indications that are not relevant to pediatrics. Pediatric exclusivity includes 31 of the top 100 highest selling drugs. Patent extension is granted regardless of if the study results in updated labeling. The beneficial impact of the legislation is 425 studies have been completed providing increased knowledge in the conduct of pediatric clinical trials.

Conclusions: While more pediatric studies are conducted now, the granting of exclusivity is not based on the trial significantly contributing to enhanced pediatric treatment. Amendments are needed to promote studies approved under the law to meet these requirements: the clinical indication is relevant to the pediatrics; the childhood disease addressed represents a significant disease burden; the important age ranges are addressed; studies with a safety signal identified prior to initiation are terminated; and trials meeting endpoints and improving pediatric dosing may gain additional incentives.

693. Automated Information Retrieval for Constructing Evidence-Based Pediatric Formularies

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Background: Pediatric prescriptions are a challenge because data on drug safety and efficacy in children are limited. Pediatric formularies are developed to guide pediatricians but updating these formularies with the latest evidence from scientific literature is a manual, time-consuming and cumbersome process. To simplify and streamline this task, we developed an automated system that facilitates the process of evidence gathering from scientific literature, and we evaluated its performance on the Dutch pediatric formulary (Kinderformularium).

Objectives: To evaluate whether an automated information retrieval system can improve the manual process of extracting evidence for pediatric formulary creation.

Methods: Our system uses knowledge-based and rule-based components to extract 14 qualitative and quantitative attributes from scientific abstracts, such as drug, dosage and frequency. These attributes are then used to suggest and rank scientific literature that is relevant in formulary creation. We propose and evaluate several ways to improve evidence extraction, including the use of association rules and Medical Subject Headings.

Results: The system achieves an average F-score of 0.88 in extracting the 14 attributes from a human-annotated test corpus of 169 Medline abstracts. The ranked list of scientific literature retrieved by the system is substantially better than the results retrieved via Medline queries (Mean Average Precision 0.53 vs. 0.16) for drugs in the Kinderformularium.

Conclusions: The proposed system is fully automatic and can be effectively used to retrieve information for the construction of a pediatric formulary.

694. Results from a Registry To Monitor the Safety of Celecoxib and Other Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Juvenile Idiopathic Arthritis (JIA)

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Background: Little is known about the long-term safety of NSAIDs in children with JIA despite usage for > 30 years. Celecoxib (CELE), a selective COX-2 inhibitor, was approved for JIA in December 2006 by the US FDA with a condition to conduct the Safety in Idiopathic Arthritis: NSAIDs and Celebrex Evaluation Registry (SINCERE).

Objectives: To collect longer-term safety and developmental data on JIA patients (pts) treated with CELE or non-selective NSAIDs (nsNSAIDs) as utilized in routine clinical care.

Methods: This prospective observational multi-center US registry enrolled a cohort of JIA pts aged 2–17 years who were prescribed, not more than 6 months prior, either CELE or a nsNSAID. Concomitant medications, treatment switches, and discontinuations were permitted. Pediatric rheumatologists collected demographic, developmental, clinical, and safety information; quarterly for the first yr, and twice annually thereafter for a minimum of 2 year. The primary outcome was overall safety (serious and non-serious adverse events [SAEs and AEs]). Gastrointestinal and cardiovascular events were events of special interest (ESI). Results were analyzed using descriptive statistics.

Results: A total of 274 pts (219 nsNSAID/55 CELE) were followed for 410 pt-year of observation (PYO). At baseline, the CELE group was older, had numeri-

cally longer disease duration, higher median weight and height, and greater history of NSAID intolerance, consistent with the practice of using celecoxib as the 2nd or 3rd NSAID in JIA. A similar incidence of AEs occurred across groups (44, 53, and 50/100 PYO for nsNSAID, CELE, and off-NSAID [≥ 29 days after final dose] groups respectively). Two pts each on nsN-SAID and off-NSAID experienced ESI. Twelve pts experienced 18 SAEs; none were attributed to NSAID. Incidence rates (95% CI) of SAEs per 100 PYO were 3.4 (1.2, 5.6), 2.9 (0, 7.0), and 4.0 (0, 8.6) for the nsN-SAID, CELE, and off-NSAID cohorts respectively.

Conclusions: SINCERE is one of the largest JIA NSAID treatment cohorts to date and despite apparent confounding by indication, the results suggest no important differences in the safety profile of celecoxib and nsNSAIDs.

695. Results from a Novel and Proactive Program to Evaluate the Safety of Celecoxib in Juvenile Idiopathic Arthritis (JIA) Patients

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Background: Clinical trials evaluating NSAID use in JIA are unable to study rare or delayed safety effects as these trials are generally short-term; little information is available from voluntary postmarketing surveillance. The pediatric population and rare disease present additional scientific and operational challenges.

Objectives: To assess the safety of celecoxib via the Celebrex JIA Postmarketing Program.

Methods: This multidisciplinary program collects adverse events (AE) that may be associated with NSAID use in the JIA population. The four components are:

A multicenter, prospective observational registry (SINCERE: Safety in Idiopathic arthritis: NSAIDs and Celebrex Evaluation REgistry) to collect long-term safety and developmental data on JIA patients treated with celecoxib or nonselective (ns)NSAIDs as utilized in routine clinical care.

A de novo active surveillance (AS) program embedded within a physician network to ascertain the occurrence of serious AEs (SAEs) and important medical events (IMEs) in treated JIA patients, regardless of therapy.

A 6-week, open-label, randomized clinical trial to evaluate the short-term effects of treatment with celecoxib or naproxen on blood pressure in patients with JIA.

A panel of pediatric experts to semi-annually review SAEs generated from the above listed sources and (S) AEs from voluntary postmarketing surveillance.

Results: As of February 2013, the AS program and SINCERE are complete. SINCERE collected 410 person years (PY) of observation from 274 JIA patients; the incidence of SAEs overall was 2.9 per 100 PY, and was 3.4 per 100 PY for nsNSAIDs and 2.9 per 100 PY for celecoxib, despite greater disease severity and longer disease duration in the celecoxib group, suggesting confounding by indication. The AS program reported 1.27 SAEs and IMEs per 100 PY. Of 292 events, three were attributed to celecoxib and none were events of special interest.

Conclusions: The safety of celecoxib for JIA appears similar to nsNSAIDs. This comprehensive Celebrex JIA Postmarketing Program may serve as a model to proactively generate and monitor safety data in special populations such as children with JIA.

696. Comorbid Conditions and Drug Utilization of Pediatric-Onset Multiple Sclerosis Patients in a Large US Health-Claims Database

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Background: Pediatric-onset MS (POMS; prior to 18 years) is well recognized but relatively uncommon. As such, the epidemiology of POMS has rarely been studied, and information on co-morbid conditions and drug utilization are limited.

Objectives: To describe the demographic, comorbid conditions, and drug utilization among POMS patients in a sample of the insured US population.

Methods: POMS patients were selected from a large US insurance claims database from January 1, 2004 to June 31, 2011. POMS patients were defined as those with at least two or more ICD-9 codes for MS with an index claim before age 18. Controls were selected matched on year of birth, gender, time in the database, and pharmacy benefit eligibility. Comorbidities were classified using the Clinical Classification System (CCS) developed by the Agency for Health Research Quality (AHRQ) which groups ICD-9 codes into clini-

cal categories. Odds ratios (OR) and 95% confidence intervals comparing comorbidities in cases and controls were calculated. Medications were grouped into drug classes using the USC classification system.

Results: Among the 110,349 MS patients in the database, 916 (0.83%) were less than age 18 with a mean age of diagnosis of 14 years, and 59% were females. Common comorbid conditions in cases with increased odds compared to controls include: connective tissue disease (31%, OR: 5.5); headache, including migraines (28%, OR: 9.4); metabolic disorder (19%, OR: 4.8); diseases of the heart (17%, OR: 6.1); non-traumatic joint disorder (17%, OR: 2.3); and gastrointestinal disorder (17%, OR: 5.5). The majority of patients (90%) were not prescribed any MS disease modifying treatment.

Conclusions: POMS occurs in < 1% of the MS population but is associated with substantial comorbidity. The relative increase in comorbid conditions in this pediatric population merits further investigation.

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697. Evaluation of Long-Term Safety of Latanoprost in Pediatric Populations: Design and Rationale of an Ongoing Non-Interventional Cohort Study

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Background: Latanoprost is frequently used to reduce elevated intraocular pressure (IOP) in pediatric patients with glaucoma, but there is no published report on the long-term safety of latanoprost in pediatric populations.

Objectives: The study is designed to evaluate the potential long-term impact of latanoprost on ocular developmental and neurodegenerative diseases, pigmentation of the eye and corneal thickness in pediatric populations.

Methods: The primary endpoint is the best-corrected visual acuity (BCVA). Secondary endpoints include refractive error, horizontal corneal diameter, IOP, optic nerve changes, visual field, pigmentation changes of the eye and corneal thickness. At least 150 patients < 18 years of age with glaucoma or elevated IOP have been enrolled into one of the two groups with an approximate 1:1 ratio: latanoprost-treated group (continually treated with latanoprost for at least 1 month within 1 year prior to the baseline) or the non prostaglandin analogue (PGA)-treated group (not continu-

ally treated with PGAs for at least 1 month prior to the baseline and unlikely to be treated with PGAs during the study period). Enrollment is stratified by age: < 1, 1–< 5 and 5–< 18 years. At least 40 patients have been enrolled in each of the two older age groups. All patients will be treated and followed up as per routine medical practice for 3 years. The study has > 90% power to detect a 1-line difference on Snellen chart in BCVA change from baseline between two groups.

Results: This study design will address the main challenges in evaluation of long-term safety of latanoprost in pediatric populations, including the rarity of pediatric glaucoma (especially in the younger age groups), the selection of appropriate control groups and specific regulatory requirements. Study results will be available in 2016.

Conclusions: This study design will address scientific issues in evaluation of long-term safety of latanoprost in pediatric populations.

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698. Pediatric Information in Cough/Cold Medication Product Labeling

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Background: Reports of adverse events arising from cough/cold medication (CCM) use in pediatrics raised safety concerns. The adverse events were reported to be largely due to medication misuse (e.g. dosing errors) which is in part a result of inadequate product labeling and unstandardized measuring devices.

Objectives: To evaluate the provision of pediatric information on CCM products in Singapore, the provision and type of accompanying measuring device for liquid medications, and within-product consistency between labelled dosing instructions and markings on measuring devices.

Methods: A systematic search for CCM products registered in Singapore was conducted on the Singapore Health Sciences Authority online database, using active ingredients of antitussives, expectorants, mucolytics, antihistamines and decongestants as search terms. Proprietary CCM products available for retail sale in Singapore were included in the study. Information on the product labels, package inserts and measuring devices were evaluated using a self-developed criteria checklist. Descriptive statistics were generated to summarize the data.

Results: Among 58 proprietary CCM products evaluated, 30 (51.7%) were liquid preparations (oral: n = 22, 37.9%; nasal: n = 8, 13.8%), and 28 (48.3%)

were oral solid dosage forms. While all except one product provided pediatric labeling information (98.3%), 40.4% (23/57) of these products lacked dosing instructions for certain ages and 63.3% (19/30) of the liquid products lacked childproof cap/mechanism. Aside from three nasal spray products, the other 27 liquid products could be supplemented with a measuring device but only 14 (51.9%) were supplied with a measuring dropper (n = 6), spoon (n = 5) or cup (n = 3). Of the measuring devices that bear markings for different dose measurements (n = 9), all except one had markings consistent with labelled dosing instructions (88.9%) but more than half had superfluous markings (55.6%).

Conclusions: Inadequacies in pediatric dosing instructions, measuring devices for accurate dose measurements, and safety childproof features against accidental consumption, were identified in proprietary CCMs in Singapore. Medication safety can be improved with better product labeling.

699. Coverage for Services and Medicines in the Brazilian Unified Health Care System (SUS) – Evidence from a Household Survey

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Background: Previous research has suggested that SUS may be succeeding in providing free medical care, but not medicines, to the Brazilian population, thereby compromising the fulfillment of its premises of equity and comprehensiveness of care.

Objectives: To describe patterns and identify determinants for the access to medicines via SUS, investigating for regional variations across Brazil.

Methods: The 2008 Supplementary Wave on Health Care Access and Utilization of the Brazilian National Household Survey (PNAD), a nationally-representative cross-sectional sample of the non-institutionalized civilian population, was utilized. Logistic regression analyses were conducted to identify the effect of local, demographic and socioeconomic characteristics in the proportion of medicine prescriptions successfully obtained from SUS.

Results: A total of 391,886 individuals were interviewed; 14.24% sought medical care in the last 14 days. Consultations were obtained from SUS in 81.42% of cases, and medicines were prescribed in 51.85% of the time. 45.46% of prescriptions were obtained from SUS. Prescriptions were more likely to be obtained from SUS when they were issued in SUS-provided consultations (OR: 1.65, 95% CI: 1.57–1.73).

Older age, female gender, lower socioeconomic status, iliteracy and rural residence, but not race, were significantly and independently associated with higher odds of obtaining medicines from SUS. There was a large regional variation in the obtainment of medicines. States in the South and Southeast, the country's wealthiest regions, were associated with higher access to medicines (OR: 1.54, 95% CI: 1.36–1.74 and OR: 1.76, 95% CI: 1.53–2.02, respectively).

Conclusions: In Brazil, obtaining medicines from SUS is less frequent than obtaining medical services. Poor individuals in wealthy regions are currently the most likely to successfully obtain medicines from SUS. Regional characteristics must be taken into consideration alongside individual factors in order to inform improvements to equity and comprehensiveness of care in the Brazilian health care system.

700. Primary Non-Adherence in Portugal

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Background: Not filling a prescription – primary non-adherence – is the first step in medication non-adherence and represents an important public health problem. However it has not been studied in Portugal.

Objectives: The objective of this study was to determine the prevalence of primary non-adherence in the Portuguese National Health Service and identify factors associated with this behaviour.

Methods: We analyzed e-prescribing data available for the year 2009 in the Portuguese National Health Service. Of 26,815,143 electronic prescribing items of reimbursed medicines were compared with claims to determine filling. Electronic prescribing items were matched with filled claims by drug name and dosage. Multivariable logistic regression was used to identify characteristics associated with primary non-adherence. Variables related to the patient (gender and age), socioeconomic status, drug price, drug class and type of health service were included in the model.

Results: After applying the inclusion/exclusion criteria 26,815,143 electronic prescribing items remained eligible for the study purpose. Of these prescriptions 6,539,043 were never filled – primary non-adherence rate of 24.5%. Male patients were significantly less likely to have filled prescriptions. Pensioners with low income who have additional reimbursement of the drug price were more likely to have filled prescriptions. Prescriptions with origin in primary care were more likely to be filled than prescriptions with origin in hospital care. Brand medicines were slightly more likely to be filled.

Conclusions: More than 24% of prescriptions were never filled. Additional research is needed to explore other variables that may influence primary non-adherence and that can be subject of intervention.

701. Medication Related Problems in Cardio-Metabolic Disease Management in Sub-Saharan Africa: A Systematic Review

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Background: The burden of cardio-metabolic diseases is growing rapidly in Sub-Saharan Africa, but little is known about medication related problems in these patients.

Objectives: To review frequency and type of medication related problems in the management of diabetes and cardiovascular diseases in Sub-Saharan Africa.

Methods: We performed an electronic search of embase.com (MEDLINE and EMBASE), WHO library database (WHOLIS) and INRUD bibliography for original studies on medication related problems in patients with diabetes and cardiovascular diseases in Sub-Saharan Africa following PRISMA guidelines.

Results: A total of 40 relevant articles were included out of 4,097 studies. Most of the studies came from Nigeria (n = 25). Tertiary care (n = 21) was the most common setting and hypertension patients (n = 24) were studied frequently. Methods included cross-sectional surveys (n = 14) and retrospective reviews of case notes (n = 12). Non-adherence (n = 19) and inappropriate prescribing (n = 10) were studied most frequently. Medication non-adherence ranged between 15% and 59%. Reasons for non-adherence included: supply problems because of long distances, forgetting, side effects, illiteracy and high cost of drug therapy. Inappropriate prescribing was due to physicians not following treatment guidelines (e.g. underutilization of the most cost effective medication, inappropriate polypharmacy), not recording diagnoses, not prescribing by brand names as well as not considering drug–disease and drug–drug interactions.

Conclusions: Overall few studies are available outside Nigeria. Non-adherence seems to be a common problem in Sub-Sahara Africa as elsewhere, but some reasons are specific for resource restricted settings. More research is needed, especially on inappropriate prescribing and interventions which improve medication related problems.

702. Frequency and Risk Factors of Potentially Inappropriate Medications Use in a French Rural Elderly Population: Data from the AMI Cohort

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Background: Use of potentially inappropriate medications (PIM) is known to be associated with an increased risk of adverse events in elderly subjects. In France, few studies have been conducted to quantify the PIM use but, to our knowledge, none has focused on the rural population.

Objectives: To estimate the frequency of PIM use in a French rural elderly population and identify associated factors.

Methods: A cross-sectional study was performed using data collected through the AMI study, a cohort of 1,002 elders retired agricultural workers, living in Gironde (Southwestern France) and recruited from the Farmer Health Insurance rolls (Mutualité Sociale Agricole, MSA). Data on sociodemographic characteristics and health status were collected through standardized questionnaires and reimbursement claims from the MSA dataset. All subjects having at least one reimbursed drug in the 3 months prior to inclusion in the cohort (baseline interview) were included in this study. PIM use was evaluated using the Beers criteria (1997) adapted to the French medical practice. Factors associated with PIM use were identified using multivariate logistic regression.

Results: A total of 883 subjects were included (mean age: 76.5 years, 62.3% of men). Considering the overall Beers criteria, 44.1% of subjects had at least one reimbursement of PIM. The most frequent types of PIM reimbursed were propoxyphene (14.2%), cerebral vasodilators (13.0%), drugs with anticholinergic properties (12.2%) and long-acting benzodiazepines (8.0%). The PIM use was more frequent in women (OR [95% CI]) (1.5 [1.1–2.1]), subjects aged 75 years and over (1.6 [1.2–2.1]), subjects with at least five reimbursed drugs excluding PIM (1.8 [1.3–2.6]) and subjects suffering from depression (2.8 [1.8–4.5]).

Conclusions: The overall frequency and risk factors of PIM use found in this rural population were closed to those reported in a previous study conducted among French urban elders through the Three-City (3C)

study. However, use of analgesics containing propoxyphene and muscle relaxants was higher in the AMI cohort whereas use of cerebral vasodilators was higher in the 3C cohort.

703. Prescription Drug Use in the Last 12 Months of Life: Observations in a Cohort of Elderly Patients

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Background: The end-of-life is a period of high therapeutic burden. Concerns have been raised about the quality of prescribing practice during this period, particularly in relation to the appropriateness of drugs and the absence of effective palliative treatments.

Objectives: To examine the extent and nature of prescription drug use in the last 12 months of life according to cause of death.

Methods: Our cohort included Australian Government Department of Veterans' Affairs decedents (died 2005–2007) with full health care entitlements, who resided in New South Wales and were ≥ 65 years at death. ICD-10 codes (Australian Bureau of Statistics database) were used to determine underlying cause of death. We used dispensing claims (Repatriation Pharmaceutical Benefits Scheme) to examine the volume of drugs prescribed in the last 12 months of life and developed a schema to classify drugs as essential (cessation could lead to rapid decline e.g.epilepsy drugs), preventative/non-essential (e.g.statins, vitamins), symptom management (e.g.opioids), or short-term treatment (e.g.antibiotics).

Results: The six most common causes of death (cancer, COPD, heart failure, cerebrovascular disease, coronary heart disease and dementia) accounted for 72% (9,705/13,525) of decedents (61% were male; median age at death 86 years, range 65–109 years). Volume of drug use in the last 12 months of life varied by cause of death ranging from 52 drugs/person in dementia to 96 in COPD. Rates of drug use were highest in the last month of life across all causes of death, but the relative increase was largest for cancer patients largely due to the increase in drugs for symptom management (mainly opioids). We found little change in rates of essential drugs and small reductions in nonessential drugs.

Conclusions: Our results demonstrate that high volumes of drugs are used at life's end, many of these would be considered appropriate and necessary. However, there appears to be limited attempts to rationalize drug use or to reduce pill burden by de-prescribing potentially unnecessary long-term treatments.

704. Patterns of Testosterone Supplementation Initiation in US Men, 2000–2010

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Background: New formulations and delivery mechanisms, increased direct-to-consumer marketing, and wider recognition of natural declines in testosterone levels in older age and chronic disease may have contributed to wider use of testosterone supplementation therapy (TST), without strong evidence of benefit or assurance of safety in older men who are already at higher risk for morbidity and mortality.

Objectives: We describe the patterns of initiation of TST in US men during the years 2000–2010.

Methods: We identified adult males (ages 18+) with a billing claim for a testosterone laboratory measurement in US commercial and Medicare supplementary insurance claims databases and determined if TST was initiated within 30 days of the test. We also identified all initiators of TST without prior laboratory testing. We described patterns and trends of usage over the years 2000–2010 relative to baseline testosterone levels, age, and other clinical factors.

Results: We identified 873,949 men with testosterone measurements (lab results were available in 3% of the total sample, years 2007–2010), 14% of whom subsequently initiated a testosterone formulation. We additionally identified 134,005 TST initiators without a baseline lab test. TST use increased from 0.20% to 0.66% off all adult men initiating between 2000 and 2010. Among TST initiators with baseline lab values available (n = 26,123), 42% had a normal testosterone level, 2% had high levels, and 56% had reduced or low levels. Injection use decreased from 49% in 2000 to 37% in 2010, patch use decreased from 25% to 6%, with gel/jelly use increasing from 25% to 57%.

Conclusions: Testosterone supplementation has increased over the past decade, with dramatic shifts away from in-office injections to pharmacy-dispensed gels or patches. Many patients appear to initiate without baseline lab testing, and among those with lab measurements, many patients have normal testosterone levels prior to supplementation. Given widening use in spite of continued safety and efficacy questions, it is important to consider carefully the medical necessity of TST prior to initiation.

705. Prognostic Markers of Bone Metastases and Mortality Among Patients with Non-Metastatic Prostate Cancer Treated with Androgen Deprivation Therapy (ADT) in Denmark, 1997–2010

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Background: ADT is an effective but time-limited treatment of prostate cancer. Castration-resistant prostate cancer (CRPC) is defined by sequential rises in serum prostate-specific antigen (PSA) despite castration levels of androgens.

Objectives: We evaluated the incidence of CRPC and PSA doubling time (DT) as predictors of bone metastases (BM) and survival among prostate cancer patients treated with ADT.

Methods: This population-based cohort study set in northern Denmark linked data on hospital visits, cancer diagnosis, deaths, pathology reports, and laboratory tests. Among 9,518 men diagnosed with non-metastatic prostate cancer in 1997–2010, we identified men with ≥ 2 PSA measurements and treated with ADT (i.e. index date and defined as ≥ 6 months treatment with gonadotropin releasing hormone, orchiectomy, or castration-level serum testosterone). Follow-up was from ADT to BM, death, emigration, or 31 December 2011. We estimated the 5-year cumulative incidence proportion (CIP) of CPRC. For the time-varying value PSA DT (calculated using the latest three PSA measurements), we used Fine-Gray regression for competing risks to estimate crude subhazard ratios (subHR) for BM, and Cox regression to estimate crude mortality rate ratios (MRR).

Results: Our cohort included 2,494 ADT-treated patients with ≥ 2 PSA measurements. Their median age at ADT index date was 75 years and the median follow-up time was 3 years. One thousand seven hundred and eleven of the men developed CRPC, corresponding to a 5-year CIP of 80% (95% CI: 78–82). Among the CRPC patients, 1,665 had an episode of $0 < PSA\ DT \leq 6$ months during follow-up. In the entire cohort, men with $0 < PSA\ DT \leq 6$ months had an increased risk of BM (subHR 8.90 [7.0–11.3]) and death (MRR 6.45 [5.7–7.3] compared with men with PSA DT ≤ 0 months or PSA DT > 10 months.

Conclusions: Shorter PSA DT was a strong predictor of BM and death among non-metastatic prostate cancer patients treated with ADT. This study demonstrates the importance of PSA measured after ADT initiation in defining higher risk of these outcomes.

706. Black Women are at Increased Risk of Dose-Limiting Chemotherapy Induced Peripheral Neuropathy in Breast Cancer

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Background: Chemotherapy induced peripheral neuropathy (CIPN) is a potentially dose-limiting toxicity. Recent data from early stage breast cancer clinical trials have suggested that black women are at increased risk for CIPN symptoms.

Objectives: We examined whether black race was a risk factor for dose-limiting CIPN events in a general academic practice.

Methods: This retrospective cohort study included 260 women, (27.3% black) that received neoadjuvant or adjuvant paclitaxel for non-metastatic breast cancer. The primary outcome was a dose-limiting (DL) event (dose delay, dose reduction, or treatment discontinuation) attributed to CIPN (DL-CIPN). Cox proportional hazards models were used to analyze patient level and treatment level factors related to DL-CIPN. Survival time was represented by cumulative dose in milligrams of paclitaxel received. The final model included independent risk factors (p < 0.05) of DL-CIPN and confounders that when adjusted for altered the crude estimate by 10% or more.

Results: There were 39 DL-CIPN events; five were excluded from analyses for being a subsequent event. For the 34 DL-CIPN events, the median cumulative dose received at time of DL-CIPN event was 925 mg (range = 256–1,520 mg), which differed significantly (p < 0.001) from the 188 women who had no dose-limiting event of any cause (median = 1,272, range = 928–2,136 mg). Black race was the only statistically significant independent risk factor for DL-CIPN. Compared to whites, black women had a > 2-fold increased risk of DL-CIPN (HR = 2.29, 95% CI = 1.17–4.50). After adjusting for oncologist, menopausal status, obesity (BMI ≥ 30), and regimen (80 mg/m^2 weekly for 12

cycles vs. 175 mg/m^2 bi-weekly for four cycles) the risk of DL-CIPN for blacks compared to whites was HR = 3.35 (95% CI = 1.54–7.28).

Conclusions: Our findings contribute to the growing body of evidence that black race is associated with CIPN symptom onset and severity. Efforts to elucidate mechanisms, increase clinicians' awareness of the greater susceptibility of black women to CIPN, and the development of symptom management strategies, effective in ensuring adequate adherence to chemotherapy, are crucial.

707. Post-Diagnostic Use of Statins and the Prevention of Mortality and Metastasis in Patients with Prostate Cancer: Nested Case–Control Study

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Background: Statins have been of interest in its anti-tumour effects on a variety of cancers, including prostate cancer.

Objectives: To determine whether the post-diagnostic use of statins is associated with a decreased risk of prostate cancer mortality, distant metastasis, and all-cause mortality in patients with prostate cancer and to assess whether this association is modified by pre-diagnostic use of statins.

Methods: We conducted a population-based cohort study using nested case-control analyses. Data were obtained from four linked databases from the United Kingdom (UK): UK Cancer Registry, Clinical Practice Research Database, Hospital Episode Statistics database and Office of National Statistics. Participants included a cohort of 13,126 men newly-diagnosed with non-metastatic prostate cancer between April 1, 1998 and December 31, 2009, with follow up until October 1, 2012. Exposure was defined as use of statins after prostate cancer diagnosis. Conditional logistic regression was used to estimate RRs, along with 95% confidence intervals (CIs) for prostate cancer mortality, distant metastasis and all-cause mortality and the

effect modification by pre-diagnostic use of statins for the three outcomes.

Results: Use of statins after prostate diagnosis was associated with a decreased rate of prostate cancer mortality (RR: 0.79, 95% CI: 0.67–0.92). Use of statins was also associated with a decreased risk of distant metastasis and all-cause mortality (RR: 0.78, 95% CI: 0.66–0.92 and RR: 0.89, 95% CI: 0.80–0.99, respectively). Pre-diagnostic use of statins modified the association for all three outcomes, with strong risk reductions restricted to patients who used statins before diagnosis.

Conclusions: While the use of statins after diagnosis was associated with a decreased risk of all prostate cancer outcomes, these effects were mainly restricted to patients who also used statins before diagnosis, suggesting that statins may have stronger effects on carcinogenesis in early stages of cancer development.

708. Relative Risk of Bladder Cancer with Pioglitazone for Diabetes Mellitus: An Updated 8-Year Interim Report of a 10-Year Follow-Up Study

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Background: Pioglitazone is a PPAR-gamma agonist used to treat diabetes. Prior observational studies (including a prior interim analysis of this study) and a randomized trial have suggested an increased incidence of bladder cancer among patients treated for more than 2 years with pioglitazone. Here we report the results of an updated interim analysis.

Objectives: Examine the association between pioglitazone therapy and the risk of bladder cancer.

Methods: This cohort study includes 193,099 patients in the Kaiser Permanente Northern California Diabetes Registry who were age 40+ between 1997 and 2002. Those with prior bladder cancer were excluded. Ever use of pioglitazone and other classes of diabetes medications required filling 2+ prescriptions within 6 months. Ever use of each diabetes medication was treated as a time dependent variable. Cox regression generated hazard ratios (HR) compared pioglitazone use to non-pioglitazone use adjusted for age, sex, race-ethnicity, year of cohort entry, diabetes medications,

A1c, CHF, SES, renal function, other bladder conditions, history of prior cancers other than bladder cancer, and smoking. Follow-up was through 31 December 2010.

Results: Among 193,099 patients, 33,416 were treated with pioglitazone. There were 137 bladder cancers among pioglitazone treated and 952 bladder cancers among non-pioglitazone controls. Ever use of pioglitazone was not associated with an increased risk of bladder cancer (HR 1.07, 95% CI 0.87–1.30), with similar associations in men and women (test for interaction p = 0.35) and smokers and nonsmokers (test for interaction p = 0.79). In this updated 8-year interim analysis, we did not observe a statistically significant association with longer duration of therapy [< 1.5 years HR 0.78 (0.57–1.05); 1.5–4 years HR 1.15 (0.87–1.53); > 4 years HR 1.30 (0.91–1.86); test for trend p > 0.24].

Conclusions: Ever use of pioglitazone is not associated with an increased incidence of bladder cancer. The previously observed increased incidence with longer duration therapy was not observed in this 8-year interim analysis. The final analysis will include approximately two additional years of data.

709. Male Breast Cancer in Users of Finasteride and Dutasteride: A Case–Control Study

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Background: Beside alpha blockers, the 5α-reductase inhibitors finasteride and dutasteride are indicated for the treatment of lower urinary tract symptoms caused by benign prostate hyperplasia. In several case reports finasteride has been associated with male breast cancer.

Objectives: To quantify the risk for male breast cancer in users of finasteride and dutasteride.

Methods: A case-control study was conducted in the UK CPRD database among men aged 45 years and older. Cases were all men diagnosed with breast cancer during the period 1 January 1992 and 31 December 2011. Controls were matched to cases on age and GP practice in a ratio of 1: 10. Use of finasteride, dutasteride and alpha blockers was assessed prior to the diagnosis of breast cancer as was information on possible confounders (cirrhosis, gynaecomastia). Crude and adjusted odds ratios were estimated using conditional logistic regression analyses.

Results: Three hundred and ninety-eight cases were identified and matched to 3,930 controls. Ever use of finasteride or dutasteride was associated with a non-significant 25% crude increased risk of breast cancer compared to non-users (OR 1.25, 95% CI: 0.75–2.14). If 1–25 prescriptions had been issued in the 5 years before the index date, no significantly increased risk was observed (OR 1.19, 95% CI: 0.81–1.74). In contrast, men who had received 25–50 prescriptions during the 5 years preceding the index date a significant 84% increased risk compared to non-users (adj. 1.84, 95% CI: 1.07–3.20). Compared to men who used alpha blockers only the relative risk was 0.87 (95% CI 0.48–1.57).

Conclusions: Men who were frequently prescribed finasteride or dutasteride over a period of 5 years had an increased risk of breast cancer.

710. Use of Biguanides and the Risk of Colorectal Cancer

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Background: The biguanide metformin is the most frequently used drug in the management of type 2 diabetes mellitus (T2DM). Recently, observational studies have shown that metformin may be protective against the development of various types of malignancies. At present, the results for a protective effect are most convincing for breast cancer. For colorectal cancer, the results have been conflicting.

Objectives: To evaluate the risk of colorectal cancer in biguanide users compared with population-based non-diabetic controls and with users of other antidiabetic (AD) medication.

Methods: We conducted a population-based cohort study (1996–2007) utilizing the Danish National Health Registers. Oral antidiabetic drug users (n = 177,281) were matched 1:3 by year of birth and

sex to non-users. Cox proportional hazards models were used to estimate hazard ratios (HRs) of colorectal cancer. Time-dependent adjustments were made for age, co-morbidity, and drug use. First, the risk of colorectal cancer was estimated for never, current, recent and past users of biguanides compared with non-diabetic controls. Second, we compared the risk of colorectal cancer in current, recent and past users of biguanides with that in other AD drug users (never users of biguanides).

Results: Current biguanide users had a 1.2-fold increased risk of developing colorectal cancer as compared to non-diabetic controls (HR = 1.19, 95% CI = 1.08–1.30). For never, recent and past users of biguanides there was a 1.3–1.6-fold increased risk compared to non-diabetic controls. Current biguanide users had no increased risk of developing colorectal cancer as compared to users of other AD drugs (HR = 0.95, 95% CI = 0.87–1.04).

Conclusions: In our study, we did not find a protective effect of biguanides against the risk of developing colorectal cancer. There was a small increased risk compared to non-diabetic controls, but this is probably largely explained by the underlying disease (T2DM).

711. GRACE: A Validated Checklist for Identifying Robust Observational Studies of Comparative Effectiveness

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Background: Many consider observational studies too inherently biased to be able to contribute to decision making about the comparative effectiveness (CE) of medical diagnostics and treatments.

Objectives: To validate a set of broadly applicable screening questions for identifying observational CE studies of good enough quality for decision support because they are likely to produce reasonably accurate and unbiased effect estimates.

Methods: An 11-item checklist was developed through literature review and consultation with experts from ISPOR, ISPE, payer groups, private sector and academia. Item content covers four quality domains: comparability of subjects, information about the exposure or intervention, outcome measurement, and statistical analysis, which are metrics similar to those used in assessing observational study quality for systematic reviews. Checklist items were tested using studies of drugs, medical devices and medical proce-

dures. We focused on research quality, not applicability to any decision. A fundamental challenge was to find a gold standard against which to test checklist items. One hundred and thirteen volunteers from five continents each rated ≥ 3 articles (N = 280 assessments) from three validation sets of studies that (1) had quality assessments published in systematic reviews; (2) were assessed for quality by one of nine advisors from academic and payer groups, or (3) were assessed for quality by two of the nine advisors.

Results: Expert reviews uncovered an unsettling lack of agreement about what 'good' looks like, especially in situations that lacked context, with 52% concordance (five experts, 23 assessments). The single best performing checklist item, data quality for the primary outcome(s), scored ≥ 0.67 for positive predictive value in four of six samples and ≥ 0.67 for negative predictive values in all six samples. Another high scoring question, sensitivity analyses, had a positive predictive value ≥ 0.69 for in all six samples.

Conclusions: The usefulness of observational studies for CER depends heavily on the specific decision in question. In all cases, however, objective and valid outcomes are most important.

712. Control Treatments in Randomized Controlled Trials are Often Deemed not Acceptable in the Context of Care. The Example of Biologics in Rheumatoid Arthritis

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Background: According to the principle of equipoise the control treatment in a randomized controlled trial (RCT) should be the best proven treatment, if any, for the patient condition.

Objectives: To compare the willingness of physicians to include a patient in a RCT or to prescribe to the same patient in a usual care context the control treatment of the RCT.

Methods: We performed a randomized web-based survey of international physicians. For each of the 30 last RCT assessing biologics in rheumatoid arthritis (RA) recorded in the WHO International Clinical Trials Registry Platform, a synopsis of the RCT and three case-vignettes of fictive eligible patients were made. Corresponding author of recent articles in RA were invited by an e-mail, masking study hypothesis, to connect to a web site. After checking for eligibility (caring for RA patients and enrolling patients in RCT) they were randomly allocated to the Trial group or to the Care group. Physicians in the Trial group rated their willingness to enrol three fictive patients in the corresponding RCT. Physicians in the Care group rated their willingness to prescribe to three fictive patients the control treatment of the RCT they were derived from.

Results: Of the 1,779 physicians invited to participate, 262 (15%) connected to the web site and 151 were eligible and have been randomized between the Trial or Care group. For 63 (70%) fictive patients, physicians did not find appropriate in the context of care to prescribe the treatment corresponding to the control arm of the RCT the fictive patients were issued from. Acceptability of prescribing control treatment in a care context and of enrolment in a trial context was discordant in 62 (69%) fictive patients, weighted kappa coefficient is −0.08 (bootstrapped IC 95%: −0.18; 0.04).

Conclusions: The majority of physicians caring for RA patients do not found acceptable in a care context to prescribe the treatments given in control groups of RCT assessing biologics. The ethical requirement of equipoise seems to be violated and the scientific usefulness of these trials to make evidence-based decision in clinical practice is questionable.

713. Changing Patterns of Use of Osteoporosis (OP) Medications in the Years Post Launch: Implications for Comparative Effectiveness Research (CER)

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Background: Newly marketed drugs may be used by higher risk patients but over time are used in those with lower risk, decreasing confounding by indication.

Objectives: To examine predictors of first-time use of oral and injectable OP drugs and describe how these predictors change over time.

Methods: We identified women aged ≥ 55 years enrolled in a commercial insurance plan 2005–2010 with a new claim for an oral or injectable OP drug. A 12-month baseline period with no evidence of that OP drug was used to identify (1) new users and (2) predictors of OP use. Oral OP drugs were identified by National Drug Codes (NDC) and injectable drugs [zoledronic acid (ZOL), intravenous ibandronate (IVIB), teriparatide (TER)] were identified by NDC and Health Common Procedure Coding System codes. We estimated propensity scores (PS) for each participant to predict initiation of an injectable vs. an oral drug as a function of baseline covariates. Yearly PS frequency distributions by treatment group were estimated and c-statistics were calculated to compare overlap in PS distribution between treatments across years. For each injectable, odds ratios (OR) from the PS logistic regression models describing the association between covariates and initiation of injectable vs. oral drug were calculated.

Results: There were 19,266 new users of ZOL, 3,676 of IVIB, 13,935 of TER and 363,658 of oral OP. Injectable users were more likely to have prior fractures, to be older and to have more concomitant medications than new users of oral drugs. C-statistics suggested the models' predictive value decreased over time as did the association of several predictors with injectable drug use. In just 3 years on the market, association between prior OP fractures and the initiation of injectable vs. oral drugs decreased for TER (OR = 2.4, 95% CI 2.2–2.7 to OR = 1.8, 95% CI 1.7–2.0); IVIB (OR = 2.1, 95% CI 1.9–2.4 to OR = 1.2, 95% CI 1.1–1.3); and ZOL (OR = 1.7, 95% CI 1.5–1.8 to OR = 1.1, 95% CI 1.0–1.2).

Conclusions: Post launch, injectable OP drugs were used in the higher-risk patients. Over time, this use shifted to lower-risk patients.

714. Treatment Dynamics of Newly Marketed Drugs and Implications for Comparative Effectiveness Research

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Background: Clinicians and payors require rapid comparative effectiveness (CE) evidence generation to

inform treatment and coverage decisions for newly marketed drugs.

Objectives: To empirically assess treatment dynamics of new drugs shortly after marketing and their implications for the validity of CE research with frequently refreshed claims data.

Methods: We used claims data for Medicare beneficiaries in two US states to evaluate five CE examples beginning at market entry of the newer drug: (1) raloxifene vs. alendronate and fracture; (2) risedronate vs. alendronate and fracture; (3) simvastatin + ezetimibe fixed-dose combination [simvastatin + ezetimibe] vs. simvastatin alone and cardiovascular events; (4) rofecoxib vs. non-selective nonsteroidal anti-inflammatory drugs [ns-NSAIDs] and myocardial infarction; and (5) rofecoxib vs. ns-NSAIDS and gastrointestinal (GI) bleed. We examined the following drug use dynamics, which can complicate valid comparisons in the early marketing period: evolving utilization patterns; higher outcome risk among those treated with the new drugs; and prior treatment patterns that may indicate treatment resistance or intolerance. We replicated active CE monitoring with sequential matched cohort analyses and examined its ability to address these challenges had it been implemented at each drug's market entry.

Results: Uptake and utilization patterns of the new drugs varied markedly. Patients initiating the new drugs were more likely to have used other drugs for the same indication (28% for new drug users, 13% for comparators). Patients initiating rofecoxib had a higher predicted baseline risk of GI bleed than patients initiating ns-NSAIDs (0.8% vs. 0.6%). Patients initiating risedronate and alendronate had similar predicted baseline risks of fracture (4.3% vs. 4.4%), while those initiating raloxifene and simvastatin + ezetimibe had lower predicted risks of outcomes of interest relative to their active comparators. Sequential matched cohort analyses yielded results consistent with expectation for each example.

Conclusions: Treatment dynamics of new drugs vary considerably and unpredictably. Analyses that account for these dynamics can yield valid CE results.

715. Comparative Effectiveness of Pazopanib and Sunitinib in Renal Cell Carcinoma Using Real World Data

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Background: The COMPRAZ trial established similar effects in first-line treatment of metastatic renal cell carcinoma (mRCC) with pazopanib (PAZ) and sunitinib (SUN). The study also found improved quality of life (QoL) and fewer adverse events with PAZ compared to SUN.

Objectives: To compare the progression-free survival (PFS) and characteristics of mRCC patients prescribed either PAZ or SUN.

Methods: mRCC patients prescribed either PAZ or SUN were identified from the hospital cancer registry in the study period April 2005–November 2012. Survival time was calculated from the date PAZ or SUN was started until death/progression or censored until next appointment date. Data include clinical, treatment and demographic information. Data were analysed with descriptive statistics and Cox regression to calculate the hazard ratio (HR) adjusting for differences between groups.

Results: There were 494 mRCC patients identified receiving PAZ (113/494;23%) or SUN (381/494;77%). The median PFS was similar in each group (PAZ-14.5 vs. Sun-15.6 months), and found not significant when analysed by Cox regression (HR = 0.87, 95% CI 0.66–1.15). Significant differences between groups were found in mean age (PAZ-67 vs. SUN-65 years; $p = 0.04$) with more women > 70 years receiving PAZ (54% vs. SUN-37%) and younger men (< 70 years) receiving SUN (72% vs. PAZ-59%). Most mRCC patients had clear cell histology (79%) and treated with PAZ (91% vs. SUN-75%). More mRCC patients were treated with PAZ as first-line treatment then SUN (74% vs. 62%; $p = 0.02$). After controlling for these differences, the HR for survival did not changed significantly (HR = 0.84, 95% CI 0.62–1.12).

Conclusions: Our study confirms similar effectiveness comparing PAZ and SUN using real world clinical data. Although the study found differences in the risk profiles of the two groups, after controlling for these differences in the statistical model, there is still no significant difference between the drugs in terms of survival.

716. Comparative Effectiveness of Infliximab and Adalimumab for Crohn's Disease

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Background: Antibodies against tumor necrosis factor alpha (anti-TNF) are widely used in the treatment of Crohn's disease.

Objectives: This study compared the effectiveness of infliximab and adalimumab, the two most commonly used anti-TNF medications for Crohn's disease.

Methods: We conducted a retrospective cohort study utilizing United States Medicare data (2006–2010). Patients with Crohn's disease who were new users of infliximab or adalimumab after January 31, 2007 were included. Patients over age 85 and those with rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis were excluded. The primary outcome measures were persistence on therapy at week 26 without the need for surgery or glucocorticoids, time to surgery (including bowel resection, creation of an ostomy or surgical treatment of a perforation or abscess), and time to hospitalization for Crohn's disease. Multiple potential confounders were summarized in a propensity score. Logistic and Cox regression were used to compute odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI) adjusted for the propensity score quintile. Sensitivity analyses used alternative definitions of the outcomes, including persistence at week 52 and broader definitions of hospitalization and surgery.

Results: The cohort included 1,444 and 866 new users of infliximab and adalimumab, respectively. After 26 weeks, 49% of infliximab-treated patients remained on drug as compared to 47% of those treated with adalimumab (OR 0.99, 95% CI 0.81–1.20). Patients treated with infliximab had a numerically lower crude incidence rate of surgery than those treated with adalimumab, but this was not statistically significant (5.5 vs. 6.8 surgeries per 100 person-years, adjusted HR 0.79, 95% CI 0.60–1.05). Rates of hospitalization did not differ between the drugs (HR 0.88, 95% CI 0.72–1.07). The results were not appreciably different across a range of sensitivity analyses and in analyses stratified by use of glucocorticoids at the time of initiation of anti-TNF therapy.

Conclusions: We observed similar effectiveness of infliximab and adalimumab for Crohn's disease across three clinically important outcome measures.

717. Impact of Safety Warnings on the Use of Antipsychotics in the Elderly with Dementia in France

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Background: Following new safety information about antipsychotic (AP) use in the elderly with dementia, the French drug agency issued two main safety warnings about olanzapine and risperidone in March 2004 and about all APs in December 2008. Little is known about the impact of these warnings on AP use among the elderly.

Objectives: To assess the impact of safety warnings on AP use in the elderly with dementia.

Methods: Design: Quasi-experimental study. Setting: France, 2003–2011, subjects aged ≥ 65 in the EGB database (1/97th random sample of claims) insured by the main scheme of health insurance (covering 90% of the population). Exposures: Dementia was defined by ≥ 2 claims on a 12-month period for antidementia drugs, registration with chronic condition 'Alzheimer's disease and related diseases', or a hospitalization with ICD10 diagnostic codes in F00-F03 or G30. Outcomes: Monthly rates of AP use, defined daily dose (DDD), and shares by medication class and agent. Analysis: We used linear segmented regression models of AP use corrected for autocorrelation of errors to assess the impact of the two warnings, comparing three periods: January 3–February 4 (pre-warning period), March 4–November 8 (post-first warning), and December 8–December 11 (post-warnings).

Results: Between 2003 and 2011, 6,859 dementia patients were identified of whom 2,708 (39.5%) had any AP use. Mean monthly rates of AP use gradually decreased from 13.9% in 2003 to 10.0% in 2011. The warnings were not associated with any abrupt changes on rates of use or DDDs for overall APs. Use of first generation APs decreased while the use of second generation APs increased until 2004 and then leveled off to about 50% of overall AP use. The first warning coincided with a reduction in the rate of growth of risperidone use and drop in olanzapine use (+36% and −19% respectively between March 4 and March 5).

Mean dose of second generation APs showed a gradual decline unrelated to warnings.

Conclusions: Use of APs in elderly people with dementia decreased between 2003 and 2011 in France. The first warning which was limited to risperidone and olanzapine may have helped to stem the rate of growth in use of those drugs seen in the pre-warning period.

718. Impact of Over-the-Counter Restrictions on Antibiotic Usage in Brazil and Mexico in 2010

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Background: In Latin American countries over-the-counter (OTC) dispense of antibiotics is common. In 2010, both Mexico and Brazil implemented policies to enforce existing laws of restricting use of antibiotics only to patients presenting a prescription.

Objectives: To evaluate the impact of OTC restrictions on antibiotics usage in Brazil and Mexico in 2010.

Methods: Retail quarterly sales data in kilograms of oral and injectable antbiotics between 2007 and 2012 for Brazil and Mexico were obtained from IMS Health. The unit of analysis for antibiotics usage was the defined daily dose per 1,000 inhabitants per day (DDD/TID) according to the WHO ATC classification system. Interrupted time series analysis was conducted using antihypertensives as reference group to account for changes occurring independently of the OTC restrictions directed at antibiotics. To reduce the effect of (a) seasonality and (b) autocorrelation dummy variables and Prais-Winsten were used respectively. Homoscedasticity in the residuals was estimated and Levene's test was applied.

Results: Between 2007 and 2012 total antibiotics usage increased in Brazil (from 5.7 to 8.5 DDD/TID, +49.3%) and decreased in Mexico (10.5–7.5 DDD/TID, −29.2%). Interrupted time series analysis showed a change in level of consumption of −1.22 DDD/TID (p < 0.00) for Brazil and −1.08 DDD/TID (p < 0.00) for Mexico. In Brazil the penicillins, sulfonamides and macrolides consumption had a decrease of level after the intervention of 0.67 DDD/TID (p < 0.00), 0.34 (p = 0.014) and 0.408 (p = 0.011) respectively. While in Mexico it was found that only penicillins and sulfonamides had significant changes of level of −0.76

DDD/TID (p < 0.00) and −0.16 DDD/TID (p < 0.00).

Conclusions: Despite different overall usage patterns of antibiotics in Brazil and Mexico, the effect of the OTC restrictions on antibiotics usage was similar. In Brazil the trend of increase usage of antibiotics was tempered after the OTC restrictions, in Mexico the trend of decrease usage was boosted.

719. Impact of FDA Warnings on Long-Acting Beta Agonist Use in a State Medicaid Program

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Background: Long-acting beta agonists (LABAs) have been known to increase the risk of life-threatening asthma exacerbations for more than a decade. In February 2010, the US Food and Drug Administration (FDA) issued additional safety information about this risk and strengthened the boxed warning on all LABA containing products. The impact of these warnings on prescribing behavior is unknown.

Objectives: The objective of this study was to quantify changes in LABA utilization following the FDA's 2010 announcement and product label changes.

Methods: We used an interrupted time-series analyses to evaluate monthly LABA utilization over a 4 year period (20 months before and 28 months after the FDA warning) using state Medicaid administrative claims data. Changes in utilization were quantified as total prescription fills and incident fills in a rolling cohort of new users. Incident use was quantified overall and among a subgroup of those with a diagnosis of asthma.

Results: During the study period, 11,850 unique Medicaid beneficiaries had at least one incident fill for a LABA containing product. A diagnosis of asthma was present in 61% the of study sample. At baseline, there were 7.9 new LABA starts per 10,000 enrollees per month. In the 20 months prior to the FDA's warnings, trends in total fills, new starts, and new starts among those with asthma were statistically stable. Following the FDA's warning, the trend in utilization declined for all three measures: total fills (−0.04 fills/1,000 enrollees/month; p = 0.0007), incident fills (−0.07 starts/10,000 enrollees/month; p = 0.06), and incident fills among those with asthma (−0.08 starts/10,000 enrollees/month; p = 0.01). The decline in utilization was largest among those with asthma, culminating in a 44% (95% CI −63% to −25%) relative reduction in new starts by the last month of follow-up.

Conclusions: The FDA's strengthened warning was associated with significant declines in the trend of LABA fills and new starts in those with a diagnosis of asthma.

720. Patient Understanding of Drug Risk: Analysis of Medication Guide Assessments

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Background: Sponsor-conducted Medication Guide (MG) assessments have not been subject to systematic review and information is lacking on how the characteristics of MGs and MG assessments affect the major outcome of the MG assessment, the patients' knowledge of the primary drug risk.

Objectives: To conduct a systematic evaluation of MG assessments and identify determinants of (1) response rate in MG assessments, (2) reading rates of the MG, and (3) patient knowledge of the primary drug risk as evaluated by a MG assessment.

Methods: We analyzed MG assessment reports submitted to the FDA from September 2008 to June 2012. We investigated the relationship between a priori defined responder, drug and assessment characteristics and response rates, reading rates, and knowledge rates via univariate binomial linear models. A threshold of at least 80% patient understanding of the primary drug risk was defined as an acceptable knowledge rate.

Results: Sixty-six unique MG assessments met the inclusion criteria for the analysis. The mean response rate was 20.6% and about 80.5% of the survey responders reported receiving the MG, with a mean reading rate of 87.0%. Response rate increased in responders who completed the survey in person (67.2%) vs. not in person (17.3%). Reading rates decreased with each additional page of the MG, increasing proportion of prevalent users, and increasing mean age of the responders. The mean correct primary drug knowledge was 63.8%. Knowledge rate tended to increase with increasing proportion of responders and responders who reported reading the MG. Twenty MG assessments achieved the study's 80% knowledge threshold. Assessments that reached the 80% threshold showed little difference with regard to respondents' mean age, proportion of prevalent users, reading the MG, understanding the MG, offered counseling, and accepting counseling.

Conclusions: Only a minority of MG assessments showed a high level of knowledge, suggesting limitations in the effectiveness of MGs. The reasons for limited understanding across the assessments are not clear. Our analyses did not identify factors that independently predicted a knowledge rate of 80% or higher.

721. Development and Piloting of an 'Enhanced' Medication Guide Prototype

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Background: Medication Guides (MGs) are identified as an element in Risk Evaluation & Mitigation Strategies (REMS). However, abundant research suggests that they are ineffective in informing patients about the safe and appropriate use of specific drug products.

Objectives: To detail an empirically-based process for developing an improved version of a MG.

Methods: Two prototype versions of MGs were newly developed following health literacy best practices. These, combined with five other extant prototypes, were administered in six cognitive discussion groups (N = 47 participants); each session included (1) a brief structured interview, (2) a rating task to highlight preference rankings for the seven MGs through a pairwise comparisons, and (3) task-oriented discussion that included the desirable and detracting attributes for each MG.

Results: The results of the pairwise comparisons showed two of the Guide prototypes were clearly preferred by participants with one (FDA-based) prototype chosen 55% (138/235) of the time across all combinations and a second (Northwestern-AbbVie prototype) chosen 54% (127/235) of the time. Qualitative feedback showed preferences for bolding text, using text boxes, shading, bulleted lists to segment content, and easily accessible headers to aid in document navigation.

Conclusions: The two prototypes chosen most often via the rating task were also the most preferred in qualitative discussions. Common attributes that reflect plain language, patient-centered sequencing of content, and use of highly visible textual cues were clearly preferred. As follow-up, the two preferred prototypes were assessed in a cross-sectional, randomized controlled trial among 600 primary care patients with findings will be released in early Spring 2013.

722. Patient Comprehension of Risk Information in the ADVAIR® DISKUS® and SEREVENT® DISKUS® Medication Guides: A Cross-Sectional Study of Patients with Asthma or COPD

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Background: Medication Guides (MG) are mandatory when the Food and Drug Administration (FDA) determines that it is necessary for patients' safe and effective use of a medicine. However, MG effectiveness at patient risk communication requires evaluation.

Objectives: To assess patients' comprehension and reading behaviors of the safety messages found in the ADVAIR and SEREVENT MGs.

Methods: Four hundred and fifty-two adults who had self-reported asthma or COPD and prior controller medication use were identified in 10 market research centers. Patients read the ADVAIR MG (Cohort 1: n = 150 asthma, Cohort 3: n = 153 COPD) or SEREVENT MG (Cohort 2: n = 149 asthma). Structured interviews were conducted using comprehension methods for 12 unique scenario-based risk questions relating to safe use of these medications. Demographic characteristics, Rapid Estimate of Adult Literacy in Medicine (REALM) scores, and past MG reading behaviors were tabulated. Generalized estimating equations (GEE) for correlated binary data were used to identify factors associated with correct responses to risk questions, adjusting for age, race, gender, education, cohort, prior ADVAIR use, REALM, and insurance status.

Results: For 10 of the 12 individual risk questions, ≥ 75% of patients reported correct responses. Only health literacy was significantly associated with correct responses (OR = 1.18, 95% CI [1.02–1.05] per 1-pt increase in REALM, $p < 0.001$). Among patients w/ prior ADVAIR dispensings (n = 292), 40% reported reading the MG once, 41% read it > 1 but not every time, 16% had never read the MG, and 3% reported reading it every time it was received. Reasons for incorrect responses and inconsistent reading behaviors were both varied and informative for improving risk communication and MGs.

Conclusions: Comprehension of safety risks in the ADVAIR and SEREVENT MGs was adequate for most patients but comprehension decreased with decreasing health literacy. The on-going FDA/industry initiatives to improve effectiveness of patient communication materials, including MGs, should consider health literacy and reasons behind inconsistent reading behaviors. GSK-funded WEUSRTP4156.

723. Oral Glucocorticoids and the Risk of Incident Type II Diabetes Mellitus in Patients with Rheumatoid Arthritis, a Retrospective Cohort Study

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Background: Glucocorticoid (GC) therapy is used by more than one in two patients with Rheumatoid Arthritis (RA). GCs are effective but have side effects including Diabetes Mellitus (DM).

Objectives: To quantify the risk of incident type II DM in patients with RA treated with oral GCs, and its relationship with dose.

Methods: Adult patients with RA were identified from a large UK Clinical Practice Research Database (CPRD) during the study period 01/92–12/09. GC exposure from first code for RA was considered using several models including a time-varying binary indicator of ever or current use, current daily dose, average daily dose and cumulative dose. Incident DM was defined as a READ code for type II DM, at least two oral anti-diabetic prescriptions or abnormal blood results (blood sugar, HbA1C or glucose tolerance test). Incidence rates for type II DM were calculated for some pattern of GC exposure. Crude and adjusted Hazard Ratios (HR) were estimated using Cox regression.

Results: Of 23,736 adult RA patients were included. Seventy percent were female with a median age of 59 years (IQR 49–71). Median time at risk per patient was 5.39 years (Range: 0.003–18.0). Of 2,462 patients were diagnosed with type II DM during follow-up: incidence 14.0 events/1,000 person years (pyrs) in unexposed patients and 21.9 events/1,000 pyrs in time following GC exposure. The crude HR was 1.53 (95% CI 1.41–1.66) in ever GC users compared with non-use. After adjusting for all covariates, the HR reduced to 1.38 (95% CI 1.27–1.51). This equates to one additional case of DM per year for every 185 patients currently receiving GCs. Patients currently taking between 10 and 30 mg/day had an adjusted HR of 1.95 (95% CI 1.62–2.34) compared to non-use, equating to one additional case of DM for every 67 patients treated. A 5 mg increase in *average* daily dose was associated with a 32% increased risk (HR 1.32; 95% CI 1.26–1.39) suggesting prolonged exposure increased risk.

Conclusions: Oral GC therapy is a significant and clinically important risk factor for incident Type II DM in patients with RA. Screening for DM might be warranted in patients taking oral GC therapy.

724. Venous Thromboembolism in Users of a 24-Day Regimen of a Combined Oral Contraceptive Compared to Conventional 21-Day Regimens: Final Results from the INAS-OC Study

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Background: Fluctuations of serum hormone levels influence the cardiovascular risk associated with hormonal contraceptives. Shortening of the pill-free interval in combination with a progestin with a long half-life leads to less fluctuation of hormone levels and might have an impact on the incidence of venous thromboembolism (VTE) associated with oral contraceptives (OCs).

Objectives: To assess the risk of VTE associated with a 24-day drospirenone-containing contraceptive regimen (DRSP 24d). This is compared to established COCs in a study population that is representative of actual OC users.

Methods: The INternational Active Surveillance Study of women taking Oral Contraceptives (INAS-OC) was a prospective, controlled, non-interventional cohort study carried out in the USA and six European countries with three cohorts: DRSP 24d, DRSP 21d, Other OCs. New users of an OC (starters, switchers or restarters) were recruited by a network of prescribing physicians and contributed follow-up information for up to 5 years. All self-reported clinical outcomes of interest were validated by health care professionals. Primary clinical outcome of interest was VTE (deep venous thrombosis, pulmonary embolism). Data analysis was based on life-table methods. All analyses made allowance for confounding, using multivariate techniques such as Cox regression models.

Results: Results reported in this abstract are based on 185,623 woman-years (WY) of follow-up. Overall, 123 VTEs occurred in OC users (DRSP 24d: 18, DRSP 21d: 14, Other OCs: 91). The overall VTE incidence is 9.1/10,000 WY (95% CI: 7.6–10.9). For the three cohorts the VTE incidence is 7.3 (DRSP 24d), 9.4 (DRSP 21d) and 9.5 (Other OCs), respectively. The crude hazard ratio (HR) for DRSP 24d vs. Other OCs is 0.7 (95% CI: 0.4–1.2). Adjustment for age, BMI, duration of current OC use and family history of VTE lead to an adjusted HR of 0.8 (95% CI: 0.4–1.3). Final study results based on more than 200,000 WY will be presented at the meeting.

Conclusions: DRSP 24d, DRSP 21d and other OC use were associated with similar VTE risk during routine clinical use.

725. The Safety of Oral Contraceptives in Adolescents

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Background: Oral contraceptives (OCs) are widely used by healthy women below the age of 18. Female adolescents (age 12–17 years) are usually excluded in clinical studies of new OCs. The availability of data on rare serious adverse events (SAEs) associated with OC use in adolescents is sparse. Three large prospective active surveillance studies (EURAS-OC, TASC, INAS-OC) investigated new and established OCs under real-life conditions in which teenagers under age 18 could participate if their parents/guardians consented.

Objectives: To compare SAE incidence rates, contraceptive failure and return to fertility rates for teenage OC users (< 18) with those for young adult OC users (18–24).

Methods: EURAS-OC, TASC and INAS-OC were controlled, prospective, post-marketing, non-interventional cohort studies of new users under routine conditions of medical practice in nine European countries and the USA. New users of an OC (starters, switchers or restarters) were recruited by a network of prescribing physicians. Baseline survey and active follow-up were based on postal questionnaires, with validation of reported events by the women's treating physicians. A multifaceted 4-level follow-up procedure was established to ensure low loss to follow-up rates.

Results: More than 20,000 teenagers (approximately 15% of the study population) under the age of 18 were enrolled. Follow-up yielded more than 60,000 woman-years of observation. With the exception of appendicitis, mononucleosis, injuries and accidents, no significant differences between these teenagers and young women aged 18–24 were found. The incidence of causally unrelated SAEs (> 250/10,000 WY) was clearly higher than the incidence of SAEs that are potentially causally related with OC use (e.g., thromboembolism). The incidence of venous thromboembolism (2.4/10,000 WY) was statistically significantly lower than in women aged 18 or older. Contraceptive failure rates and return to fertility rates were very similar for adolescents and women aged 18–24.

Conclusions: OC use is safe and efficacious in adolescents. Results do not indicate a higher risk of serious adverse drug reactions, lower effectiveness or longer return to fertility in adolescents compared to young adult OC users.

726. Combined Oral Contraceptive and Venous Thromboembolism – Time Matters

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Background: Multiple studies have previously suggested an increased risk for venous thromboembolic events (deep vein thrombosis [DVT] and pulmonary embolism [PE]) associated with use of newer combined oral contraceptives (COCs).

Objectives: In women age 15–49, characterize the time-dependency of the relative risk for developing DVT and PE, comparing newer COCs (containing desogestrel and drospirenone) to older COCs (levonorgestrel and norethindrone).

Methods: We conducted a population-based cohort study using the MarketScan Research database. New courses of COCs were defined as ones where no other COCs were dispensed in the prior 12 months. We excluded women with HIV, cancer, coagulation disturbances and women treated with fertility drugs. Exposure to COCs containing desogestrel, drospirenone, levonorgestrel or norethindrone (of estrogen content < 50 μg) was estimated using dispensing data. Discontinuation was defined by either a drug-free interval of 29 days, or switching to another hormonal contraceptive. We censored women when they turned 50 years of age. We compared the risk for the first event of either hospitalization for DVT or PE, or outpatient encounter for DVT with dispensing of anti-coagulants. We analyzed each usage month separately (months counted from the COC initiation date) using crude Cox regression model.

Results: During 2007–2011, 1,181,630 new course of COC were identified. The median duration of a course was between 4.00 and 5.75 depending on type of COC. We found a double-peak pattern of the hazard ratio comparing the newer and older COCs. Significantly increased hazards of DVT and PE were observed between 3 and 7 months after initiation, followed by a nadir approaching the null. A second peak of hazard ratios was detected after 18 cycles of use. The second peak was not statistically significant, possibly due to small sample size from censoring).

Conclusions: We demonstrated an immediate (months 3–7 of use) and possibly delayed (after 18 months of use) serious harm associated with the newer COC compared to the older COC. These could represent different biological mechanism for DVT and PE in the newer COC users.

727. The Implications of 'Off-Label' Use in Primary Care in England: An Example from a Post-Marketing Cohort Study

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Background: Off label use is where a medicinal product is used for a medical purpose not in accordance with the authorised product information. As a result, real-life populations using a product 'off-label' could differ from Randomised Controlled Trial (RCT) populations. Modified Prescription-Event Monitoring (M-PEM) can systematically gather data on 'off-label' use and quantify it. In this example we examined Intrinsa®, a transdermal testosterone patch indicated for Hypoactive Sexual Desire Disorder (HSDD) in bilaterally oophorectomised and hysterectomised women receiving concomitant oestrogen.

Objectives: Describe utilisation of Intrinsa® and assess, where possible, if it is being used according to the authorised product information.

Methods: A M-PEM study was conducted. Patients identified from dispensed prescriptions issued by general practitioners (GPs) for Intrinsa® March 2007–August 2010. Questionnaires sent to GPs 6 months following 1st prescription for Intrinsa®, requesting drug utilisation information. Summary descriptive statistics calculated.

Results: Final cohort = 3,073 patients. Majority of patients were female (3,017, 98.2%), median age 50 years (IQR:44–55 years). Most commonly reported indication was HSDD in 2,324 females (77.0%). 43.5% females (n = 1,313) were reported to have been hysterectomised and bilaterally oophorectomised; 584 (19.4%) naturally menopausal and 184 pre menopausal. For 1,029 (34.1%) patients the GP specified that the patient was not using concomitant oestrogen. Overall, only 643 patients (20.9%) were being prescribed Intrinsa® according to the authorised product information.

Conclusions: In real-life, clinicians are prescribing some medicinal products outside the recommended terms of the licence, with only 20.9% of patients receiving Intrinsa® according to prescribing guidelines. This highlights that the real-life patient population using Intrinsa® may have a different risk profile to RCT patients. Evidence obtained solely from RCTs might not be relevant as a result, so evidence from post-marketing observational studies is important to ensure a product's safety and effectiveness in real-life use and will inform the risk management process.

728. Menopausal Hormone Therapy and Risks of Cardiovascular Events and Mortality in Female Statin Users – A Population Based Register Study

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Background: The risk for cardiovascular (CV) disease associated with menopausal hormone therapy (MHT) has in the past decade been a subject of continued discussion. Additionally, statin treatment as prevention of CV disease is common among middle-aged or older women. Knowledge regarding the impact of concurrent MHT and statin use on CV outcomes and mortality is limited.

Objectives: To study the effect of MHT on risk of CV outcomes and total mortality in female statin users.

Methods: All incident female statin users, ≥ 40 years of age, in Sweden, who filled a first statin prescription between 2006 and 2007, were enrolled in a cohort study entering 12 months after statin initiation. Information on dispensed drugs, comorbidity, CV events and total mortality was obtained from the national registers. MHT was defined as ≥ 2 dispensed prescriptions of estrogens used for symptoms related to menopause within 12 months after statin initiation. Those with one MHT dispensing were excluded (5%). Those without any previous CV event were considered using statins as primary prevention. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using multivariable Cox regression analysis, adjusting for age and CV related comorbidity.

Results: A total of 53,613 statin users were followed for a mean of 3.9 years, 9,454 (18%) on MHT and 44,159 (82%) untreated. Almost 55% of the women used statins as primary prevention. There was practically no difference in non-fatal CV events between those treated with MHT and untreated (HR 0.96, 95% CI 0.90–1.01). MHT was associated with a lower risk of CV death (HR 0.52, 95% CI 0.42–0.65) and total mortality (HR 0.65, 95% CI 0.58–0.72). A similar pattern was found for primary prevention.

Conclusions: There was no significant difference in non-fatal CVD events between female statin users with and without MHT. MHT was associated with a significant lower risk for CV death and total mortality. Uncontrolled confounding, such as lifestyle, disease severity and previous MHT may influence the results.

729. SSRI Use in Pregnancy: A Study in six European Databases

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Background: Use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has been associated with adverse pregnancy outcomes such as cardiac defects. It is not always clear which SSRIs are implicated and what the impact on prescribing should be.

Objectives: To evaluate utilisation patterns of SSRIs before, during and after pregnancy in six European databases.

Methods: A common protocol was implemented across six databases, two in Italy and the UK and one in each of Denmark and the Netherlands. All pregnancies between 2004 and 2009 were identified in each database. For those ending in a delivery, dispensed (Denmark, Italy, the Netherlands) or prescribed (UK) prescriptions for SSRIs issued in the year before, during, and the year after pregnancy were identified. Drug choice was evaluated over time using 3-month periods and prescribing patterns were compared between databases.

Results: SSRI use was much higher in the UK than in the other databases, with use being lowest in Denmark: overall, in the year leading up to pregnancy in the UK 8.7% of mothers were prescribed an SSRI compared with 3.9% in Denmark. During pregnancy, figures were more comparable with between 2.3% (Denmark) and 3.7%(UK) being dispensed/prescribed an SSRI during any pregnancy trimester and prescribing being lowest in the 2nd and 3rd trimesters in all databases. After pregnancy, SSRI prescribing increased rapidly in the UK compared with the other countries. Use was relatively stable over the study period except for in Denmark, where a steady increase in prescribing during pregnancy was observed from 1.6% to 3.1%. Fluoxetine and citalopram were the SSRIs of choice in the UK and Denmark whereas in Italy and the Netherlands paroxetine was more popular. In all countries, between 40.6%(Netherlands) and 47.1%(Italy) of women who discontinued SSRI use before or during

pregnancy did not restart after delivery; of those who did, the majority did so in the first 3–6 months.

Conclusions: There were clear differences in SSRI utilisation patterns in women of childbearing age across Europe. The differences between countries, especially in the time leading up to and after pregnancy raise questions regarding appropriateness of prescribing and the impact on breastfeeding.

730. Antidepressant Use Near Delivery Increases the Risk of Postpartum Hemorrhage

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Background: Serotonin reuptake inhibitor (SRI) antidepressant use is associated with an increased risk for gastrointestinal bleeding due to antiplatelet effects. It is unclear whether SRI use during pregnancy increases the risk for postpartum hemorrhage (PPH).

Objectives: To determine whether SRI or non-SRI use near delivery is associated with PPH.

Methods: We conducted a retrospective cohort study using 2000–2007 US Medicaid data. We identified 106,000 pregnant women with a mood or anxiety disorder diagnosis. Women were categorized into four mutually exclusive exposure groups using the dispensing date and days dispended from pharmacy records: current (delivery date), recent (1–30 days before delivery date), past (1–5 months before delivery date) and no exposure to antidepressants. We compared the risk for PPH by timing of exposure and by antidepressant class and type. Relative risks (RR), risk differences and 95% confidence intervals (CIs) were adjusted for PPH risk factors, mood/anxiety disorder severity indicators, other indications, and other medications.

Results: The risk of PPH was 2.8% among women with mood/anxiety disorders but no antidepressant exposure. Compared to no exposure, women with current SRI exposure had a 1.5-fold increased risk for PPH (CI: 1.3–1.6) and an excess risk of 1.3% (CI: 0.9–1.6); women with current non-SRI exposure had a 1.4-fold increased risk (CI: 1.1–1.8) and an excess risk of 1.0% (95% CI: 0.1–2.0). The RR for recent SRI exposure was 1.2 (CI: 1.0–1.4) and was 0.9 (CI: 0.8–1.1) for past exposure. The RRs for recent and past non-SRI exposure were 1.2 (CI: 0.8–1.7) and 1.3 (CI: 1.0–1.6). Current selective serotonin reuptake inhibitor (SSRI) monotherapy was associated with PPH (RR: 1.4, CI: 1.3–1.6), as was current serotonin-norepinephrine reuptake inhibitor (SNRI) (RR: 2.1, CI: 1.6–2.8) and tricyclic monotherapy (RR: 1.9, CI: 1.1–3.3). Current exposure to specific SSRI compounds (paroxetine, sertraline, fluoxetine, escitalopram, citalopram) and venlafaxine was significantly associated with PPH.

Conclusions: Exposure to SRI and non-SRI antidepressants, including SSRIs, SNRIs and tricyclics, near delivery was associated with a 1.4–2.1-fold increased risk for PPH.

731. In Utero Exposure to Antidepressant Drugs and Risk of Attention Deficit Hyperactivity Disorder (ADHD): A Nationwide Danish Cohort Study

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Background: Use of selective serotonin reuptake inhibitors (SSRIs) is increasing, also in pregnant women. Existing studies on in utero exposure to antidepressant drugs and long-term neurodevelopmental outcomes are sparse.

Objectives: To investigate whether in utero exposure to antidepressant drugs is associated with an increased risk of attention deficit hyperactivity disorder (ADHD).

Methods: We conducted a nationwide cohort study. From the Danish Medical Birth Registry we identified a cohort of 877,778 singletons born alive from 1996 to 2009 with follow-up through 2010. ADHD was defined as redemption of a prescription for ADHD medication or receipt of an ADHD hospital diagnosis identified in national registries. The unique personal civil registration number assigned to each Danish citizen permitted accurate linkage of the registries. We used Cox proportional-hazards regression to compute adjusted hazard ratios (aHR), comparing exposed children and children born by former users to unexposed children

born by never users. To assess the role of family-related factors (such as genetics and socioeconomic status) as potential confounders, we conducted a within-mother between-pregnancy analysis, a conditional logistic regression model, on a subpopulation of 813 children.

Results: In the cohort analysis children exposed to any antidepressants in utero had a greater risk of ADHD (aHR = 1.2 [95% CI: 1.1–1.4]) than unexposed children born to never users. We also found a higher risk of ADHD (aHR = 1.6 [95% CI: 1.5–1.7]) among children born to former users, compared with unexposed children born to never users. In the within-mother between-pregnancy analysis the adjusted odd ratio was 1.1 (95% CI: 0.5–2.3).

Conclusions: We found an increased risk of ADHD in children exposed in utero to antidepressants. The former user and within-mother between-pregnancy analysis indicated presence of confounding from family-related factors.

732. Antidepressant Use in Late Gestation and Breastfeeding Rates at Discharge from Hospital

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Background: Few studies have investigated breastfeeding outcomes among women taking antidepressants. Evidence suggests that these women may be less likely to initiate breastfeeding, potentially due to concerns regarding exposure through breast milk, but underlying maternal illness may also play an important role.

Objectives: To evaluate the association between antidepressant use in late gestation and breastfeeding outcomes.

Methods: A retrospective cohort study using linked records from the Women's and Children's Health Network in South Australia. This included electronic data from the Women's and Children's Hospital (WCH) Perinatal Statistics Collection and the WCH Hospital Pharmacy Dispensing Records. Women delivering live-born singleton between January 2001 and December 2008 were included (n = 32,662). The main outcome measure was the prevalence of breastfeeding at discharge from hospital following delivery. Logistic regression models were used to calculate ORs and 95% confidence intervals (CIs), adjusting for confounders identified *a priori*.

Results: Of eligible pregnant women, 575 received a dispensing for an antidepressant in late gestation (exposed), 1,373 did not receive a dispensing for an antidepressant but had a reported psychiatric illness during pregnancy (untreated psychiatric illness) and 30,714 did not receive a dispensing for an antidepressant and had no reported psychiatric illness during pregnancy (unexposed). Women exposed to an antidepressant were significantly less likely to be breastfeeding their infants at discharge from hospital compared to women who were unexposed (aOR 0.70; 95% CI 0.56–0.88), but no difference was observed when compared to women with an untreated psychiatric illness (aOR 0.89; 95% CI 0.68–1.16).

Conclusions: These results suggest that while women taking antidepressants appear to be less likely to initiate breastfeeding, this may be influenced by underlying maternal illness, rather than antidepressant use alone. Regardless of the cause, women taking antidepressants and women with a psychiatric illness may benefit from additional education and support to improve breastfeeding rates.

733. The Effect of Regulatory Advisories on Maternal Antidepressant Prescribing, 1995–2007: An Interrupted Time-Series Study of 228,876 Pregnancies

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Background: In late 2004, the U.S. FDA and Health Canada issued public health advisory warnings about the risk of perinatal complications with antidepressants. Little is known about the impact of these warnings on antidepressant prescribing during pregnancy.

Objectives: To assess whether antidepressant prescribing during pregnancy decreased following release of the 2004 U.S. and Canadian advisory warnings regarding perinatal complications with antidepressants.

Methods: We analyzed data from 228,876 singleton pregnancies among women, aged 15–44 years, who

were continuously enrolled in the Tennessee Medicaid program with full pharmacy benefits (1995–2007). Pregnancy exposure to antidepressants was determined through outpatient pharmacy dispensing files. Information on sociodemographic and clinical factors was obtained from enrollment files and linked birth certificate files. An interrupted time-series design with segmented regression analysis was used to quantify the impact of the advisory warnings (2002–2005).

Results: Antidepressant prescribing increased steadily from 1995 to 2001, followed by sharper increases from 2002–late 2004. Overall antidepressant prescribing prevalence was 34.51 prescriptions (95% CI 33.37–35.65) per 1,000 women in January 2002, and increased at a rate of 0.46 (95% CI 0.41–0.52) prescriptions per 1,000 women per month until the end of the pre-warning period (May 2004). During the post-warning period (October 2004–June 2005), antidepressant prescribing decreased by 1.48 (95% CI 1.62–1.35) prescriptions per 1,000 women per month. These trends were observed for both SSRI and non-SSRI antidepressants, although SSRI prescribing decreased at a greater rate.

Conclusions: The late 2004 release of public health advisory warnings about the risk of perinatal complications with SSRIs and other antidepressants in the U.S. and Canada was associated with a reversal of pre-advisory increases in antidepressant prescribing to pregnant women in Tennessee Medicaid, which suggests that the warnings were impactful on antidepressant prescribing to pregnant women.

734. Specific Selective Serotonin Reuptake Inhibitors (SSRIs) During Pregnancy and Major Cardiac Defects: A National US Cohort Study in Publicly-Insured Women

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Background: Considerable controversy remains regarding the potential teratogenicity of SSRIs. The main limitations of previous studies were insufficient sample size to assess specific SSRIs and specific malformations, and potential confounding by indication.

Objectives: We attempted to overcome these limitations using a large cohort of women with diagnosed depression to study the safety of SSRIs.

Methods: The source population included 935,040 women enrolled in Medicaid during 2000–2007. We examined the risk of all major cardiac defects, as well as right ventricular outflow obstruction (RVOO) and ventricular septal defects (VSD) in particular, associated with first trimester pharmacy dispensings of SSRIs. Claims-based outcomes were validated through medical record review, with positive predictive values between 75% and 85% that were non-differential for SSRI users and non-users. We restricted the cohort to women with depression and used propensity score adjustment to further control for depression severity and other potential confounders.

Results: During the first trimester, 46,792 (5.0%) women received SSRIs. The prevalence of cardiac malformations at birth was 1.65% among users and 1.28% among non-users. Associations for any cardiac defect were attenuated with increasing levels of covariate adjustment. For SSRIs overall, relative risks were 1.29 (95% CI, 1.20–1.39) unadjusted, 1.18 (1.08–1.29) depression-restricted, and 1.10 (1.00–1.22) restricted and fully-adjusted. For paroxetine, sertraline and fluoxetine, restricted and fully-adjusted relative risks were 0.99 (0.82–1.20), 1.11 (0.95–1.31), and 1.13 (0.95–1.35) respectively. No increased risk was observed for the previously hypothesized associations between paroxetine and RVOO (0.82, 0.49–1.36), or between sertraline and VSD (1.02, 0.75–1.37). Results were not substantially different when the estimated positive predicted values were used in sensitivity analyses.

Conclusions: After careful control for depression severity, and using a very large cohort, no meaningful increase in risk of specific cardiac defects was observed for the most commonly used SSRIs.

735. ARITMO Final Results: Prediction of the Arrhythmogenic Risk of Antihistamines, Antipsychotics and Anti-Infectives by Integration of Translational Evidence

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Background: Cardiac ventricular arrhythmia as a side effect of anti-arrhythmic and non-antiarrhythmic drugs has become a major pharmacological safety concern for the pharmaceutical industry and the health regulatory authorities. Since the recognition of the problem in the 1990s a number of blockbuster drugs have been withdrawn from the market because of reports of Torsade de Pointes (TdP) and sudden death or cardiac

death (SD or SCD). To avoid marketing of drugs that have torsadogenic potential, current guidelines (ICH E14, ICH 7SB) require a battery of preclinical and clinical tests that are sensitive but not specific and therefore may preclude potentially harmless drugs to be further developed. Several attempts have been made to list the drugs that are associated with QTc prolongation and cardiac arrhythmias, none is fulfilling so far. The ARITMO project was funded by the European Commission upon a request of the European Medicines Agency to develop prediction models for the arrhythmogenic risk of selected classes of drugs. The ARITMO consortium worked with common case definitions, a common drug list, common protocols and datasharing to allow for integration of evidence using a Dempster Shafer model.

Objectives: To demonstrate and discuss how ARITMO applied a novel model that allows for ranking of the arrhythmogenic potential of all anti-infectives, antihistamines and antipsychotics based on the integration of in silico, clinical, genetic, pharmacovigilance and epidemiological evidence.

Description:

(1) The workshop focus will be on the ARITMO methods and results.
(2) Introduction to the ARITMO approach
(3) State of the art: *in-vivo*, *in vitro* data, clinical trial and epidemiological data from the literature
(4) ECG markers of TdP risk
(5) HeRG affinities from experimental and predicted in-silico models
(6) TdP/SCD risk from AERS, EUDRAVIGILANCE and national pharmacovigilance data
(7) Evidence from pooled epidemiological studies on TdP/QTc prolongation
(8) Evidence from pooled epidemiological studies on VA/SCD risk
(9) Integration of evidence for clinical and regulatory decision making using Dempster Shafer Modelling.

736. Challenges in Studying Drug-Induced Liver Injury in Pharmacoepidemiology Data Sources

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Background: Drug-induced liver injury (DILI) accounts for 10% of all adverse drug reactions, is associated with morbidity, and can lead to acute liver failure, liver transplantation, and death. There are many challenges in studying DILI that must be addressed in order to conduct valid studies.

Objectives: (1) To provide an overview of the challenges in identifying DILI in epidemiologic studies and to discuss methods to ascertain severe liver injury and acute liver failure in electronic data sources; (2) To discuss methods to use electronic health records to confirm a drug as the cause of acute liver injury; and (3) To discuss the challenges in evaluating DILI in active safety surveillance. This symposium will benefit pharmacoepidemiologists seeking additional knowledge about the design, conduct, and analysis of studies of DILI.

Description: There are major challenges to identifying DILI in epidemiologic studies. In particular, severe liver injury and acute liver failure, two key endpoints in DILI studies, are difficult to ascertain and confirm in electronic data sources. Determination that a drug is the cause of acute liver injury within population-based databases also remains difficult. Finally, post-marketing surveillance of DILI remains a challenge in regulatory settings. This symposium will provide an overview of the methodologic challenges inherent in pharmacoepidemiologic studies of DILI and discuss ways to address these challenges. In the first talk, Dr. Lo Re will provide a brief overview of the methodologic challenges faced by researchers evaluating DILI. He will then discuss methods by which severe liver injury and acute liver failure could be validly ascertained in pharmacoepidemiology data sources. Dr. Cheetham will discuss methods to use data from electronic health records to confirm a drug as the cause of acute liver injury. Dr. Zornberg will discuss the challenges in evaluating DILI in the regulatory setting, particularly in active safety surveillance. We will conclude by engaging the membership through a panel discussion. This symposium will benefit researchers seeking additional expertise in the design and analysis of pharmacoepidemiologic studies of DILI.

737. Confounding's Ugly Little Sister: Measurement Bias in Pharmacoepidemiology

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Background: While methods to address confounding have received broad attention, the impact of measure-

ment bias and methods for remediation are often less appreciated. This workshop will introduce three approaches to address misclassification in three diverse datasets including registry, claims and electronic health record (EHR) data.

Objectives: This workshop focuses on introductory and intermediate level pharmacoepidemiologists with interest in measurement. Specific objectives include: (1) to review the impact of misclassification in various epidemiologic study designs, (2) to share real-world examples of differential and non-differential misclassification along with effective approaches for remediation.

Description: We will begin the workshop with an overview of misclassification bias, including a review of the effects of low sensitivity or specificity in various designs aimed at estimating relative risk. We will proceed with three examples of misclassification: (1) Non-differential misclassification in a claims-based analysis of risk for pituitary tumors; (2) differential misclassification in an EHR-based analysis of diabetogenic risk; and (3) differential misclassification in a registry-based analysis of lung function. For each example, we will interactively discuss approaches to remediate potential bias and share final results with and without remediation. Discussed approaches will include matching and imputation techniques.

738. Improving Consistency in Findings from Pharmacoepidemiological Studies: The IMI-PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Project

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Background: Pharmacoepidemiological (PE) research should provide consistent, reliable and reproducible results to contribute to the benefit-risk assessment of medicines. IMI-PROTECT aims to identify sources of methodological variations in PE studies using a common protocol and analysis plan across databases. In addition, differences by design, applied to a same drug-adverse event (AE) pair in different databases are examined. Results from PE studies will be evaluated on seven drug-AE pairs (i.e. (1) antibiotics and acute liver injury; (2) antidepressants and hip fracture; (3) benzodiazepines and hip fracture; (4) anticonvulsants and suicide/suicide attempts; (5) calcium channel blockers and malignancies; (6) inhaled long-acting $\beta2$ agonists and acute myocardial infarction; (7) a negative control study: antibiotics and acute myocardial infarction) conducted in eight European and one US electronic databases. These are: the UK (CPRD), UK (THIN), the Danish national registries, the Dutch Mondriaan project (NPCRD, AHC), the Spanish BIFAP, the German Bavarian Claims (KVB) database (only descriptive), PGRx and US InVision Datamart (formerly LabRx). In order to maintain the blinding of investigators from one another's results, these results will only be disclosed during the ICPE conference.

Objectives: To review and understand the methodological issues encountered in these studies and to draw conclusions about their relevance for future PE research.

Description: We will present data on association studies in the various databases using different designs with a focus on cohort, but also case-control, case-crossover, and self-controlled case series for some drug-AE pairs. The major methodological issues such as choice of study design, analytical methods to control for confounding, variation in operational definitions of exposure, outcome and confounders across databases with different coding systems will be discussed.

Program:

(1) Introduction to IMI-PROTECT WP2/WP6.
(2) Results from PE studies on drug-ae associations.
(3) Panel discussion.

739. Improving the Science of Regulatory Decision-Making – Advances in 2012/2013

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Background: Regulatory agencies and academic programs worldwide are paying increased attention to advancing regulatory science. In 2010, the NIH and FDA launched the Advancing Regulatory Science Initiative and in August, 2011, the FDA published 'Advancing Regulatory Science at FDA: A Strategic Plan'. In 2009 EMA launched a multinational collaboration, PROTECT. Most efforts to develop drug regulatory science address drug development and postmarketing benefit/risk assessment, but frequently fail to address how better data will be translated into decision making. The panel will address what impact these programs and specific initiatives, such as the FDA Sentinel efforts, the Observational Medical Outcomes Partnership (OMOP), the US health care reform legislation and the impact of comparative effectiveness findings (PCORI) have had on drug regulation and promotion?

Objectives:

(1) To understand the scope of current US and non-US efforts to improve regulatory science, particularly those that have been launched in the past 12 months.
(2) To discuss how these efforts are addressing scientific approaches to regulatory decision-making.
(3) To understand how scientific evidence, medical practice, patient preferences, economics, politics, the press, public opinion and other societal considerations affect regulatory decisions.
(4) To become familiar with possible scientific approaches to regulatory decision-making.

Description: In Barcelona, Drs. Dal Pan (FDA), Raine (MHRA), Leufkens (University of Utrecht), Avorn (Harvard) reviewed current efforts to improve regulatory science and to move beyond improving the prompt and efficient availability of reliabile scientific intelligence to addressing the question of advances in regulatory decision-making. Have the new initiatives, in the US, Europe and Asia improved the decision-making process? How have economic pressures, political pressures, societal preferences been integrated into regulatory decision-making? What are the major challenges we are currently facing and are there tools being developed to improve regulatory decision-making? This year, Dr. Songlin Xue (takeda) will summarize Asian initiatives.

740. Interpreting and Communicating Risk of Medications in Pregnancy, Using SSRIs as an Example

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Background: Often we consider publishing our research as the last step in the process. However, women considering pregnancy, women who are pregnant and health care providers caring for these women need to be able to interpret and use our research to make treatment decisions for their health and the infant's. We may consider ourselves to be scientists and not policy makers, but, if we do not clearly describe and interpret our results others will interpret it for us. This abstract is submitted on behalf of the Medications in Pregnancy SIG.

Objectives: To be aware of the challenges that health care providers, who care for women with chronic conditions such as depression, face. To learn how to write scientific manuscripts and press releases that are as helpful as possible for health care providers, the general public and policy makers.

Description: A moderator and four speakers will discuss the challenges of interpreting the scientific data that is out there. The first speaker will briefly discuss the existing literature on SSRIs and major birth defects, and the potential reasons for conflicting results, or conflicting interpretation of results. The second speaker will provide the clinical perspective of a provider who treats women with depression who might want to get pregnant or who already are pregnant. Someone from a teratogen information center will provide insight into what aspects of communication are important to inform and educate in a transparent way, for instance by using absolute risks. Someone from a regulatory agency will discuss what aspects of publications on medications in pregnancy are most important

to them as they regulate. Lastly a journalist will share with us what factors influence whether a paper will be considered for coverage in a media outlet and what information is useful for them to write their articles. Participants can be involved by providing specific examples and working together to come up with improved ways to present data.

741. Unlocking the Secrets of Free Text Through Natural Language Processing: An Introduction for Pharmacoepidemiologists

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Background: Many pharmacoepidemiologic studies rely on large electronic (administrative) databases, but for some variables, these data have poor accuracy. Manual medical record review can provide more accurate information but is expensive and time consuming. Automated tools to extract better information from electronic medical records (EMRs) could greatly improve accuracy and efficiency.

Objectives: (1) to introduce the audience to Natural Language Processing (NLP), including reviewing basic principles, tools, and terminology; (2) to present detailed examples of the use of NLP in clinical studies; and (3) to describe steps audience members can take to explore applying NLP themselves.

Description: First, Dr. Dublin will provide background and motivation for the symposium by reviewing challenges that arise in pharmacoepidemiologic studies, such as the need for outcome validation or better confounder measurement. Next, Dr. Solti will provide an overview of Natural Language Processing, including principles, tools and technologies. He will introduce some of the fundamental concepts of clinical NLP including text processing 'pipelines', the development of a 'gold standard', and methods for evaluating NLP tools' accuracy. He will also describe some widely used open source NLP software. The next two talks will focus on applications of NLP for clinical or epidemiologic research. Dr. Matheny will describe work using NLP to identify postoperative surgical complications from a comprehensive EMR (from US Veterans Health Administration medical centers). Next, Dr. Kors will demonstrate the use of machine learning to develop automatic case detection algorithms using

European EMR data. He will compare different machine learning approaches and show how the resulting algorithms can be tuned to meet specific study demands. Finally, Dr. Carrell will describe steps audience members can take to explore applying NLP in their own work. We will present strategies for developing NLP capacity in the local setting and also describe transportable NLP systems that require no special expertise from local users.

742. Association Between ABCB1/ABCC2 Polymorphisms and Anti-Epileptic Dosages in Ambulatory Elderly: Results from the Rotterdam Study

Raymond Noordam,[1,2] Nikkie Aarts,[1,2] Albert Hofman,[2] André G Uitterlinden,[1] Ron HN van Schaik,[3] Bruno H Stricker,[1,2] Loes E Visser.[1,2,4] *[1]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; [2]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, The Netherlands; [4]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands.*

Background: Polymorphisms in the ABCB1 (1236C>T, 2677G>T/A, 3435C>T) and ABCC2 (−24C>T, 1234G>A, 3972C>T) genes, which encode for multidrug efflux pumps, are associated with a less functional protein. This results in a lower efflux of several drugs, including anti-epileptic drugs, such as carbamazepine and phenytoin. However, studies were not able to demonstrate an association between the polymorphisms and the response to anti-epileptic drugs, which is likely due to an insufficient sample size and no consensus on how many months without a convulsion should be considered as a successful response.

Objectives: To assess the association between ABCB1 and ABCC2 gene polymorphisms and prescribed dosages of oral anti-epileptic drugs in a population-based study of ambulatory elderly.

Methods: Participants from the Rotterdam Study were included if they had more than five consecutive prescriptions for anticonvulsants and DNA was available (n = 217; 8,419 prescriptions). The study outcome was defined as the mean standardized dosage (ratio between prescribed daily dosage and the defined daily dosage; DDD) of all consecutive prescriptions using repeated measurement analysis, considering age and sex as confounders.

Results: ABCB1 homozygous T-T-T haplotype carriers were prescribed higher dosages than homozygous C-G-C haplotype carriers (standardized dosage: 0.47 vs. 0.36 DDD, respectively, p = 0.040). For the individual

polymorphisms, this association was observed for the 1236C>T (p = 0.018) and 2677G>T (p = 0.015) polymorphisms, but not for 3435C>T (p = 0.50). A stratified analysis showed an association for carbamazepine and phenytoin. No association was observed between ABCC2 gene polymorphisms and dosage.

Conclusions: Polymorphisms in ABCB1, but not ABCC2, were associated with a higher dosage (especially carbamazepine and phenytoin, both being ABCB1 substrates), which is indicative of a poorer drug response in the variant allele carriers. Although counterintuitive, these findings confirm the complex underlying biology of response to anticonvulsants.

743. Association Between Statin Therapy and Non-Alcoholic Fatty Liver Disease in a Large Population-Based Study

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Background: Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome. It is frequently associated with dyslipidemia and has been associated with the risk of cardiovascular disease (CVD), independent of the metabolic syndrome. Statin therapy is effective in the treatment of metabolic syndrome, but the effect and safety of statins in NAFLD is not well established.

Objectives: The objective was to study the association between statin therapy and the presence and severity of NAFLD, and elevated alanine aminotransferase (ALT) levels, in a large cross-sectional population-based study.

Methods: In the Rotterdam Study, a prospective population-based cohort study, we identified 2,578 subjects who underwent liver ultrasonography, and for whom statin prescription data were available. We used logistic regression models, and investigated the effect of both current and past use, and duration of use. The analyses were adjusted for age, sex, statin dose, total cholesterol level, alcohol consumption, metabolic syndrome, history of CVD, and use of fibrates or other cholesterol-lowering drugs.

Results: The prevalence of NAFLD was 35.3%. In total, 990 participants had ever used statin therapy (631 current users and 359 past users). In multivariable analyses, ever use of statin therapy was neither associated with NAFLD, nor with elevated serum ALT concentrations [OR 0.94, 95% CI 0.66–1.33 and OR 1.23, 95% CI 0.68–2.23, respectively]. However, current statin use for > 2 years was associated with a significantly lower prevalence of NAFLD [OR 0.44, 95% CI 0.21–0.96].

Conclusions: Within the Rotterdam study, more than 2 years current use of statin therapy was associated with a lower prevalence of NAFLD. No association was found with elevated serum ALT. The strength of this study compared with previous studies on this topic is that we were able to adjust the analyses for history of CVD, and to categorize use of statins according to duration and dose. Since the primary cause of death in NAFLD is CVD, prevention of CVD through lipid lowering treatment with statins should be an important aspect of treatment of NAFLD patients.

744. Hospital Readmissions: Using Drug Prescriptions as a Proxy for Severity-of-Illness

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Background: Many jurisdictions use hospital readmission models to financially penalize hospitals. These models rarely adjust for outpatient prescription drug use, which is an important proxy for severity-of-illness. Several authors have argued that omitting drug prescriptions may lead to the penalization of hospitals with well-controlled readmission risk.

Objectives: To determine how outpatient drug prescriptions at the time of hospital admission confound the effect of hospital care on all-cause readmissions.

Methods: We used a cohort of 252,316 patients over 65 years of age from a Quebec administrative database, who were discharged 619,274 times from 20 Montreal hospitals during 1996–2006. We fit a Cox proportional hazards model, using the time-to-readmission (to any Quebec hospital) as the dependent variable, and indicator variables for the 20 included Montreal hospitals. We controlled for age, sex, admission type (emergency and non-emergency), time of admission, discharge to a nursing home and admission diagnosis. We added indicator variables for the 1,000 prescription drugs and measured the change in the hazard ratios of the hospitals.

Results: In the model without prescription drugs, the hazard ratios of the hospitals varied from 0.86 to 1.10; 12 hospitals had significantly different hazards as compared to the reference hospital. After adding the pre-

scription drugs to the model, the associations between the hospitals and readmission remained unchanged, despite strong predictive effects of many drugs on readmissions. The area under the receiver-operating characteristic curve (AUC) of prediction of 30-day readmission was 0.64 for the model without drugs, and 0.66 for the model with drugs.

Conclusions: Our results suggest that while outpatient prescriptions at the time of admission are associated with hospital readmission, they do not significantly confound the effect of hospitals on readmission.

745. Use of Intermittent Androgen Deprivation Therapy in Prostate Cancer: A Population-Based Study

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Background: Androgen deprivation therapy (ADT) has been widely used as the primary treatment for metastatic prostate cancer (PCa) and is increasingly used as salvage therapy for recurrent PCa. International randomized clinical trials have shown that intermittent ADT (IADT) improves quality of life compared to continuous ADT (CADT). However, it remains unknown how IADT is used in general US practice and whether it is adopted differentially based on geographic region and characteristics of the patient and physician.

Objectives: To assess the utilization of and predictors associated with IADT adoption in general practice.

Methods: Using the U.S. SEER-Medicare database, we conducted a retrospective cohort study of men 66 and older who used ADT for treating their metastatic, recurrent, and localized PCa anytime during 2004–2009. IADT is defined as treatment with a gap longer than 3 months between scheduled ADT dates and with at least one PSA test or one physician visit during treatment gaps. Key predictors included patients' sociodemographics and clinical factors, and physician characteristics. We carried out generalized linear model analysis in modeling receipt of IADT to accounts for the clustering of patients treated within the same physicians.

Results: Among 11,304 PCa patients eligible for IADT, 50% and 37% of them used IADT and CADT, respectively; the remaining received single shot ADT. We found a trend of decreasing IADT utilization in recent years. Compared to Pacific regions, IADT was more adopted in East (odds ratio, OR = 1.61, 95% CI = 1.30, 1.99), Central (OR = 2.02, 95% CI = 1.61, 2.53) and Mountain (4.13, 95% CI = 2.59, 6.57) regions. IADT was less used by specialists who weren't urologists (OR = 0.41, 95% CI = 0.32, 0.52), and physicians who practiced longer than 30 years vs. shorter than 10 years (OR = 0.64, 95% CI = 0.44, 0.93).

Conclusions: Our data indicated significant geographic variation in IADT adoption. Physician characteristics, such as urology specialty and fewer years in practice, played a larger role than patients' sociodemographics and clinical factors in IADT receipt.

746. Psychopharmacological Medication Use in Nursing Home Residents with Delirium

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Background: Delirium is a prevalent and problematic condition among nursing home (NH) residents. Although antipsychotics (APs) effectively treat delirium, they are indicated for short duration, at lowest possible dose, and without concomitant use of other psychopharmacological medications (PPMs), especially those with anticholinergic properties. Suboptimal use of PPMs may increase risk of subsequent delirium episodes.

Objectives: To examine AP and other PPM use and quality in NH older adults diagnosed with delirium.

Methods: This cross-sectional study used a 5% random sample of 2007 Medicare claims data linked to Minimum Data Set files. Continuously enrolled beneficiaries were included if they stayed in NHs for > 100 days and were diagnosed with delirium but had no evidence of: chronic psychiatric conditions (schizophrenia-related conditions, psychosis, and mood disorders), or Alzheimer's disease related dementia (ADRD) plus behavioral symptoms. Dependent measures included prevalence of PPM use: 1) by therapeutic classes (APs, antidepressants [ADs], anxiolytics [AXs], sedative-hypnotics [SHs]); 2) by concomitant classes; 3) by adequacy of indication (defined by rele-

vant practice guidelines and literature); and, 4) among users with adequate indications, by annual days of use and modified standardized daily dose (mSDD), using a maximum recommended geriatric dose threshold.

Results: Residents with delirium (n = 21,620) were predominantly female (78%), white (86%), with a mean age of 85 years. Two-thirds (66%) of residents with delirium used ≥ 1 PPMs (AP = 21%, AD = 56%, SH = 8%, AX = 3%). Among PPM users, 29% used ≥ 2 PPM classes; combination AP and AD classes accounted for 65% of concomitant PPM use. The proportion of AD, AX, and SH users with adequate indications were 74%, 60%, and 32%, respectively. AP and AD users had high mean annual days of use (190.5 and 227.3 days). The majority of AP users (92%) met adequate dose criteria (mSDD ≤ 1).

Conclusions: Persistent and high use of APs and other PPMs runs contrary to recommended treatment guidelines for delirium in older adults. Findings suggest the need to further investigate the temporality of delirium relative to AP and other PPM exposure and duration.

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747. Prescribing Patterns of Anti-Epileptic Drugs for Seizure Prevention after Stroke in the Elderly

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Background: Stroke is the most common cause of acquired epilepsy in the elderly. Anti-epileptic drugs (AEDs) are recommended for post-stroke epilepsy, but evidence is scant with regard to when to use prophylactic treatment regimen (primary vs. secondary) and which AED to choose (newer AEDs, e.g. lamotrigine, have been shown to have a better safety profile in the elderly). Prescribing practices remain unclear in routine care of patients with stroke at strong risk of seizures.

Objectives: To describe prescribing patterns of AED therapy for post-stroke seizure prevention in the elderly.

Methods: We identified a cohort of Medicare beneficiaries ≥ 65 years old who experienced an ischemic or hemorrhagic stroke during 1995–2008, and had no AED treatment or recorded seizure diagnosis in the 6 months prior to stroke. AED initiators for the primary prevention of post-stroke seizures were patients who initiated an AED within 30 days after stroke and had no prior seizure diagnosis. AED initiators for secondary prevention initiated an AED within 30 days following a post-stroke seizure. Post-stroke seizures were classified into early seizures (occurring within the first week after stroke) and late seizures (between 1 week and 2 years after stroke).

Results: We identified 70,035 patients who had an ischemic stroke and 10,714 who had a hemorrhagic stroke during 1995–2008. Among those experiencing an ischemic stroke, 0.6% initiated an AED for the primary prevention of seizures, 9.2% initiated an AED after an early seizure (262 out of 2,861 patients), and 10.1% initiated an AED after a late seizure (505 out of 5,010). Among the patients experiencing a hemorrhagic stroke, 2.7% initiated an AED for primary prevention of seizures, 11% initiated an AED after an early seizure (100 out of 906), and 9.5% initiated an AED after a late seizure (132 out of 1,394). Phenytoin was the most commonly prescribed AED, independent of stroke type and prophylactic regimen.

Conclusions: AEDs are infrequently prescribed in the elderly even in the setting of a seizure occurring after a stroke. Phenytoin, an older AED, is the most commonly prescribed agent during the time period studied.

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748. Transparency in Data Preparation for Drug Exposure Using the Clinical Practice Research Datalink and Sensitivity of Results to Various Assumptions

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Background: Pharmacoepidemiological analyses of large population datasets require raw medication data to be converted into a drug matrix with temporally contiguous lines of coded data listing all changes in drug exposure. This data preparation requires many assumptions, yet no agreed algorithms exist and data preparation remains opaque. This would be problematic if different assumptions in data preparation generate different results in analyses.

Objectives: The study aim was to test the sensitivity of results to a range of possible assumptions in data preparation, using the example of the association between oral glucocorticoid (GC) therapy and incident Diabetes Mellitus (DM).

Methods: In a retrospective cohort design, the Clinical Practice Research Datalink (CPRD) was used to identify adult patients with RA during the study period January 92–December 9. Multiple decision nodes were

identified for defining stop dates and prescription dosage. This abstract focuses on three decision nodes: (1) selecting stop date from three different available stop date options, (2) handling missing stop dates (ignore prescription or various estimations of stop date), and (3) dealing with overlapping prescription periods (ignore or append overlap). One drug matrix was generated for each possible pathway through the three decision nodes. Rate Ratios (RR) for incident DM were calculated using Poisson regression for each resultant drug matrix.

Results: Of 32,763 RA patients with 192,488 person-years follow-up were included. Of 14,796 individuals were ever exposed to oral GCs and 3,319 patients developed incident DM. Twelve different matrices were developed based on all permutations of assumptions at the three decision nodes. The RR for ever GC use compared to non-use ranged from 1.17 (95% CI 0.85–1.60) to 3.68 (95% CI 0.52–26.1). This equates to a range in absolute risk from one additional case of DM per year for every 24 patients to one in every 370 patients exposed.

Conclusions: Results are highly sensitive to assumptions of data preparation. Transparency in data preparation is required in addition to clear reporting of cohort generation and analysis methods.

749. Automated Use of Electronic Health Record Text Data To Improve Validity in Pharmacoepidemiology Studies

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Background: Most pharmacoepidemiology studies are carried out with highly-structured information. Electronic health records (EHRs) offer a rich source of clinical data stored in notes and other unstructured text, but it is challenging to extract meaning from this data.

Objectives: To evaluate whether confounding adjustment via an automated, semantically-neutral approach to using the free-text information in EHRs would improve validity of pharmacoepidemiology studies.

Methods: We hypothesized that certain phrases occurring in patients' unstructured EHR data may serve as useful predictors of baseline health status. We created a cohort of 9,906 commercially-insured patients who initiated statin therapy. We linked clinical and other notes from a regional EHR exchange to patients' administrative claims. We noted all 2-word phrases that occurred in the EHR and created dichotomous variables indicating presence of each phrase for each patient. We used used the high-dimensional propensity score algorithm to identify those phrases that had the strongest association with exposure and outcome. We selected the 500 phrases, diagnosis codes, procedure codes, and drugs that most resembled confounders, and entered these variables into a propensity score (PS) predicting high- vs. normal-intensity statin initiation. We used the PS to adjust for confounding in a study of myocardial infarction within 180 days.

Results: The selected phrases indicated both good and poor health: well taken, within normal, breast exam, mildly enlarged. We observed a crude odds ratio (OR) of 2.19 (95% CI 1.71, 2.80). The OR decreased to 2.03 (1.59, 2.60) with age and sex adjustment. Adjusting for certain pre-defined variables, the OR decreased to 1.21 (0.86, 1.71); adding two-word phrase adjustment moved the OR further downward to 0.96 (0.66, 1.41). The monotonic decrease toward the null is compatible with RCT findings.

Conclusions: Though residual bias may have remained, adjusting for phrases observed in a patient's EHR provided an improvement in confounding adjustment. The confounders identified included markers for healthy users, a group that is typically difficult to identify in administrative data.

750. Quantifying the Role of Stroke as an Intermediate on the Causal Pathway from Antipsychotic Use to Death in Older Adults

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Background: Observational studies in older adults show higher mortality for first-generation antipsychotics (FGAs) than second-generation antipsychotics (SGAs). Some studies report higher risk of stroke for FGAs than SGAs. However, the extent to which stroke explains the differential mortality between FGAs and SGAs is unclear.

Objectives: To quantify how much stroke contributes to the differential mortality between FGAs and SGAs in older adults.

Methods: A cohort of 9,885 FGA and 21,228 SGA new users age 65 or older, who were concurrently enrolled in Medicare and statewide pharmacy assistance programs in New Jersey or Pennsylvania between 1994 and 2005, were followed for incident ischemic or hemorrhagic stroke until death for up to 6 months after antipsychotic initiation. We estimated natural direct and indirect effects of antipsychotic type on mortality through stroke using the risk ratio (RR) scale; we also calculated the percent of the mortality difference that was mediated by stroke using the risk difference (RD) scale. We corrected for potential misclassification of our claims-based stroke definition using a maximum likelihood approach and predictive value weighting, and conducted a sensitivity analysis for a potential unmeasured binary confounder of the stroke-mortality relationship.

Results: FGAs showed marginally higher risk for stroke (RR = 1.18; 95% confidence interval [CI] 0.93, 1.50) and mortality (RR = 1.14; 95% CI 1.06, 1.23) as compared to SGAs, but stroke explained little (2.7%) of the observed difference in mortality. The indirect effect was null (RR = 1.00; 95% CI 1.00, 1.01), and the direct effect was similar to the total effect of antipsychotic type (FGA vs. SGA) on mortality (RR = 1.15; 95% CI 1.09, 1.22). A downward bias from an unmeasured confounder was unlikely, and correction for potential measurement error in the claims-based definition of stroke did not qualitatively change the results.

Conclusions: These results suggest that the difference in mortality between FGA and SGA users develops mostly through pathways that do not involve stroke. Studies with better stroke and confounder ascertainment would help confirm this finding.

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751. Acute Kidney Injury in Statin Initiators: Treatment Effect Heterogeneity over the Propensity Score Distribution

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Background: Statins are widely used for preventing cardiovascular events, but recent reports suggest they may increase the risk of renal injury. The lack of a comparable active treatment complicates non-experimental studies of statins.

Objectives: We investigated the risk of acute kidney injury (AKI) in statin initiators vs. non-users in a large, US claims database, years 2000–2010.

Methods: We identified adult (ages 18+) statin initiators in pharmacy claims and a comparison group of non-users at outpatient physician visits. Patients were followed for 1 year for diagnosis codes of AKI or renal failure. Rates of AKI were compared in statin users vs. non-users with Cox-proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI). We estimated the propensity score (PS) and plotted PS distributions by treatment. HR were estimated in 50 strata of the PS, as well as in the whole sample using trimmed inverse probability of treatment weighting (IPTW), and in a PS-matched sample.

Results: We identified 4,146,506 eligible statin users and 4,033,800 non-users. Users and non-users had AKI incidences of 0.9% and 0.3%, respectively. Multivariable models yielded HR = 0.97 (95% CI: 0.94–0.99), while PS methods yielded more protective estimates–matched HR = 0.79 (95% CI: 0.76–0.81), IPTW HR = 0.76 (95% CI: 0.73–0.79). We noted considerable non-overlap in the PS distributions by treatment group (c = 0.90) and extreme IPTW weights. Treatment effect heterogeneity was observed over the PS distribution, with elevated HRs observed at the tails of the PS distribution in those treated contrary to prediction. Age restriction and stratification improved PS overlap and gave more homogeneous estimates: ages 40–64, matched HR = 0.82 (95% CI: 0.78–0.87); ages ≥ 65, HR = 0.66 (95% CI: 0.63–0.69). Further stratification into disease subgroups yielded similar, stable estimates.

Conclusions: As a class, statins were not associated with an increased risk of AKI. Yet, substantial treatment effect heterogeneity was observed along the PS distribution. Restriction to clinically relevant, more homogeneous groups yielded better PS matching and more stable estimates with PS methods.

752. A Multivariable-Adjusted Rapid Assessment of the Association Between Zoledronic Acid and Myocardial Infarction

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Background: A randomized trial published in November 2012 demonstrated the efficacy of zoledronic acid in reducing fracture risk in men. However, 1.5% of patients in the zoledronic acid group experienced myocardial infarction (MI) vs. 0.3% among placebo-treated patients (RR, 4.68; 95% CI, 1.02–21.55).

Objectives: To rapidly assess the association between zoledronic acid and MI using a previously developed modular program.

Methods: We applied the module to 2006–2011 data from a large US commercial claims database. We used the program to identify new users of zoledronic acid, new users of other bisphosphonates, and pre-specified MI risk factors as well as potential confounders identified by the high-dimensional propensity score (Hd-PS) algorithm in a pre-treatment baseline period. The program PS-matched patients in the two groups, followed them for hospitalization for MI in the 365 days following treatment initiation, and estimated hazard ratios (HR) and 95% confidence intervals (CIs). We separately compared zoledronic acid initiators to initiators of all bisphosphonates and to initiators of intravenous (IV) bisphosphonates only. We also conducted analyses among males and females separately.

Results: We identified 7,830 eligible new users of zoledronic acid and 150,650 bisphosphonate initiators, of whom 4,278 (3%) initiated an IV bisphosphonate. Zoledronic acid initiators tended to have a higher degree of comorbidity burden. In crude analyses, we observed a hazard ratio (HR) for MI of 2.06 (95% CI, 1.45–2.92) comparing zoledronic acid to all bisphosphonates and 1.16 (95% CI, 0.64–2.10) in comparison to IV bisphosphonates. In 1:1 Hd-PS matched analyses, we observed an HR of 1.35 (95% CI, 0.76–2.41) comparing zoledronic acid to all bisphosphonates and an HR of 0.81 (95% CI, 0.32–2.03) in the IV comparison. Results were similar among males and females.

Conclusions: In this rapid assessment, we did not observe a meaningfully increased risk of MI among initiators of zoledronic acid vs. other bisphosphonates. Although a doubling of risk cannot be ruled out, the nearly five-fold increase observed in the trial could not be reproduced.

753. Marginal Structural Model (MSM) To Estimate Joint Effect of Osteoporosis (OP) Medications on Serious Infection Using Claims Data

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Background: Women with postmenopausal osteoporosis (PMO) tend to switch treatments over time. Thus estimation of the joint effect of consecutive OP medications can be biased by time-varying (TV) confounders if they are influenced by earlier treatment and affect subsequent treatment and outcome. MSM is a useful tool to adjust for such confounding.

Objectives: To estimate the joint effect of consecutive treatment with bisphosphonate (BP) and other OP medications on incidence of serious infection in women with PMO.

Methods: Women 55+ years old, who had diagnosis or treatment related to OP were identified from the MarketScan database (2004–2011) and followed for incident serious infection by diagnosis codes. Time-fixed (TF) covariates were assessed at the start of follow-up while TV covariates were updated prior to starting, switching or ending OP treatment, being censored or diagnosis of fragility fracture, considered a potentially major TV confounder. The stabilized weight (SW) was estimated based on the probability of treatment and being uncensored given previous treatment, and TV and TF covariates. Causal effect of BP or other OP medications on serious infection was estimated by covariate-adjusted Cox models and MSM weighted by the SW.

Results: A total of 164,377 cases of serious infection were identified from 795,368 patient-years. The incidence rate ratio (IRR) and 95% confidence interval (CI) comparing treatment with BP and other OP medications to no treatment was 1.01 (0.99–1.03) and 1.06 (1.02–1.11), respectively, in the Cox model adjusting for TF covariates; and was 1.12 (1.10–1.14) and 1.17 (1.12–1.22), respectively, after adjusting for TF and TV covariates. In MSM, the IRR (95% CI) was 0.99 (0.98–1.01) for BP and 1.05 (1.01–1.10) for other OP medications. Sensitivity analyses with SW calculated using the most recent updates generated similar results.

Conclusions: The association of BP and other OP medications with the incidence of serious infection in the Cox model adjusting for TV covariates was attenuated in MSM, suggesting the presence of TV confounding which cannot be addressed by regular covariate adjustment.

754. Does Drug Treatment for Attention Deficit/Hyperactivity Disorder (ADHD) Prevent Injuries Among Children with ADHD?

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Background: Children with attention deficit / hyperactivity disorder (ADHD) have a higher risk of accidents and injuries compared to children without ADHD. Methylphenidate (MPH) and atomoxetine (ATX) are widely used to reduce the symptoms of ADHD, but it remains unclear if they can decrease the risk of injuries.

Objectives: To investigate whether the use of MPH or ATX reduces the risk of injuries among children with ADHD using the case-crossover (CCOD) and self-controlled case series design (SCCSD).

Methods: We used the German Pharmacoepidemiological Research Database (GePaRD) to identify incident cases of ADHD among children aged 3–17 years in 2005–2007. Among all ADHD children, we identified those with an inpatient injury diagnosis (classified by the Injury Mortality Diagnosis Matrix) subsequent to their first ADHD diagnosis up to the end of follow up (December 2008). For the CCOD, exposure to MPH and ATX was assessed at the time of hospitalization with an injury diagnosis and at the control time point 90 days prior to the hospitalization. For the SCCSD, the time dependent exposure was assessed between the initial ADHD diagnosis and the end of follow up. Conditional logistic regression was used to calculate odds ratios (ORs) in the CCOD. Methods described by Whitaker et al. were used for the SCCSD analysis. In additional analyses, we restricted the sample to children with brain injuries only.

Results: Among 37,650 ADHD children, 2,186 had received an injury diagnosis. The ORs of experiencing an injury under MPH or ATX use were 0.86 (95% CI: 0.73–1.02) in the SCCSD and 0.98 (95% CI: 0.76–1.28) in the COOD. When we restricted the outcomes to brain injuries only, the risk for injury was reduced under MPH or ATX in the SCCSD (OR: 0.66; 95% CI: 0.49–0.91), but not in the CCOD (OR: 0.98; 95% CI: 0.75–1.29.).

Conclusions: No preventive effect of ADHD drugs on injuries in ADHD children was observed overall, but there was a preventive effect regarding the risk of brain injuries in the SCCSD. Different estimates from SCCSD and CCOD might be explained by the inability to control for exposure trends in the CCOD.

755. Instrumental Variable Analysis of ADHD Treatment and Serious Adverse Events

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Background: A dearth of evidence exists on the association between treatment for Attention-Deficit-Hyperactivity-Disorder (ADHD) and serious adverse events (SAE). A strong correlation between birth month and treatment provides an opportunity to study SAEs using instrumental variable (IV) analysis.

Objectives: To estimate SAE risk associated with ADHD treatment and to assess the value of IV analysis to adjust for confounding in ADHD populations.

Methods: We performed a fixed cohort study in the U.S. MarketScan database. Exposed patients were children 6–18 years of age between 2007 and 2011, diagnosed with ADHD and treated with a stimulant. The control group consisted of the siblings of the treated patients. Follow-up for treated patients began the day after they started their stimulant. Controls were assigned the same follow-up start dates as their siblings. We estimated the one-year risk difference for SAEs (defined as an emergency admission to hospital for any reason). IV analysis was used to adjust for confounding factors using two-stage ordinary least squares regression. First and second stage models also included additional covariates for age, sex and geographic region. The analysis was repeated using two IVs: quarter of birth (modeled as a categorical variable), and month of birth (modeled as 11 binary variables).

Results: Our study included 141,266 ADHD-treated patients and 191,286 sibling controls, among whom there were 1,382 events and 902 events, respectively. The crude one-year risk difference was 5.07 events per 1,000 patients (95% CI 4.50–5.64). Adjustment for age, sex and geographic region did not appreciably alter the risk difference. The IV adjusted risk differences were 3.75 per 1,000 when birth quarter served as the instrument (95% CI −14.73 to 22.22), and −2.66 per 1,000 when birth month was used (95% CI −21.2 to 15.90).

Conclusions: ADHD patients in our study population were are at significantly greater risk of SAEs than their siblings. IV analysis lacked sufficient power to estimate a precise adjusted risk difference, but adjusted point estimates were closer to the null, suggesting that some or all of the eleveated crude risk was attributable to unmeasured confounding.

756. Prenatal Exposure to Acid-Suppressive Drugs and the Risk of Allergic Diseases in the Offspring: A Cohort Study

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Background: Recent studies have reported an increased risk for the development of asthma in children after prenatal exposure to acid suppressive drugs. Allergic diseases often develop simultaneously so associations can also be present for allergic rhinitis and atopic dermatitis.

Objectives: To assess the associations between the use of acid suppressive medication during pregnancy and the development of allergic diseases in children.

Methods: Using a linked mother-infant subset of the University Groningen prescription database IADB.nl we conducted a pregnancy cohort study among 33,536 children born between 1995 and 2011, with a maximum follow-up of 8 years. Maternal exposure was defined as ≥ 1 dispensed prescriptions for Proton Pump Inhibitors (PPIs) and/or Histamine 2-antagonists (H2As) during pregnancy. Children were considered to have a drug-treated allergic disease if they received either ≥ 2 prescriptions for ointments containing steroids or calcineurin-inhibitors (atopic dermatitis), ≥ 2 prescriptions for inhaled steroids (asthma) or ≥ 2 prescriptions for nasal steroids (allergic rhinitis) in 12 months. Clustered Cox proportional hazard regression was used to estimate crude and adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI).

Results: A total of 489 (1.5%) children were exposed to PPIs or H2As during pregnancy. The aHR for the development of any allergic disease was 1.37 (95% CI: 1.14–1.66) for children exposed to PPIs or H2As. Prenatal exposure to PPIs and /or H2As was associated with atopic dermatitis, asthma and allergic rhinitis with aHRs of 1.32 (95% CI 1.06–1.64), 1.57 (95% CI 1.20–2.05) and 2.40 (95% CI 1.42–4.04), respectively. Risks were elevated for the development of two or more (aHR 2.13, 95% CI: 1.43–3.19) and three allergic diseases (aHR 5.18, 95% CI: 2.16–12.42) in exposed children.

Conclusions: Prenatal exposure to PPIs and H2As appeared associated with an increased risk of allergic diseases in the offspring, especially with the development of multiple allergic diseases. The benefit-risk balance of these drugs should be reconsidered in pregnancy.

757. Development and Validation of an Algorithm To Ascertain Non-Hospitalized Suicide Attempts Using Administrative Claims Data

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Background: The validity of pharmacoepidemiologic studies conducted through administrative databases relies in part on the validity of outpatient diagnoses (ICD-9). Non-hospitalized suicide attempt is largely underascertained in the Quebec databases (RAMQ), partly due to the under-utilization of E-codes and potential misclassification with non-intentional injuries. With evolving health care practices, most children and adolescents who attempt suicide are not hospitalized. Consequently, it is necessary to develop reliable methods of case ascertainment.

Objectives: To develop and validate an algorithm for the ascertainment of non-hospitalized suicide attempts in youth using the claims databases of Quebec (RAMQ).

Methods: The development cohort consisted of 30 known cases of suicide attempt (age < 18), who visited the emergency department (ED) of the two Montreal paediatric hospitals without being admitted. An a priori algorithm was developed, through pattern recognition of the care pathway (medical services, diagnostic codes, psychiatric consults, and location of services). The algorithm was then validated in a sample of 53 cases of suicide attempt and 82 cases of non-intentional injuries (year 2007–2008). Algorithms were developed using multivariate regression models and regression tree analysis. Measures of sensitivity and specificity were obtained to classify the performance of the algorithms.

Results: The a priori algorithm consisted of the presence of a billing claim with a location of service at the ED in addition to a diagnostic code corresponding to a trauma within 2 days of ED visit (sensitivity 98.1% and specificity 14.2%). Using regression tree analysis, we were able to improve the specificity of the algorithm by adding a component of psychiatric consult or a psychiatric diagnosis within 2 days or the ED visit (sensitivity 69.8% and specificity 97.6%).

Conclusions: For studies requiring high specificity, such as case-control studies, the algorithm developed using the regression tree would be preferable.

758. Potential for Selection Bias in the Context of a Restriction Drug Access Program: The Case of Atomoxetine in Quebec, Canada

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Background: Occurrence of side-effects when exposed to first line drugs is a common criterion for reimbursement of a drug with restrictive access. Patients answering this criterion are likely to be at higher risk for side-effects and may bias results obtained within observational studies.

Objectives: To assess the frequency of cardiovascular outpatient visits amongst children exposed to atomoxetine in the context of a restrictive drug access plan.

Methods: We conducted two nested case-control studies. The first was nested within a cohort of children de novo users of methylphenidate, amphetamines or atomoxetine covered by the Quebec (Canada) public drug insurance plan between January 2001 and October 2010 (FULL cohort). The second case-control study was nested within a sub-cohort of de novo atomoxetine users with no cardiovascular events prior to the first dispensing of atomoxetine (ATO-NOPCV). The main outcome measure was an outpatient visit to a pediatrician, cardiologist or an internist for a cardiovascular reason (hereby defined as a cardiovascular outpatient visit) identified by physician billing codes. Cases were matched on sex, age and date of entry within the cohorts ($\pm$ 30 days) to up to 10 controls. Patients with an active dispensation of atomoxetine at the index date were considered exposed to atomoxetine. Conditional logistic regressions were used to calculate conditional odd ratios (OR).

Results: The FULL cohort comprised 38,495 patients. Among these patients, 3,595 (9.3%) had no prior cardiovascular events and were included within the ATO-NOPCV sub-cohort. Odds of cardiovascular outpatient visits in patients exposed to atomoxetine decreased from OR = 2.80 (95% CI: 2.07–3.78) within the FULL cohort to OR = 0.82 (95% CI: 0.52–1.28) within the ATO-NOPCV sub-cohort.

Conclusions: Reimbursement policies need to be considered when conducting observational studies. Had we not considered these policies, we would have incorrectly identified atomoxetine as a major risk factor for cardiovascular outpatient visits.

759. Pediatric Drug Safety Surveillance in FDA-AERS, a Description of Adverse Events: A GRiP Study

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Background: Individual case safety reports (ICSRs) are a cornerstone in drug safety surveillance. Information on the safety of drugs used in children is crucial but so far existing and readily available datasources from spontaneous reporting databases are underused.

Objectives: Therefore we studied characteristics of pediatric ICSRs reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS).

Methods: Public available ICSRs reported in children (0–18 years) to AERS were downloaded from the FDA-website for the period January 2004–December 2011. Characteristics of these ICSRs, including the reported drugs and events, were described and stratified by age-groups.

Results: We included 106,122 pediatric ICSRs (55% boys) (58% USA) with a median of one drug [range 0–157] and three events [1–94] per ICSR. Mean age was 9.1 years. Ninety percent was submitted through expedited (15-days) (65%) or periodic reporting (25%) and 10% by non-manufacturers. The proportion and type of pediatric ICSRs reported were relatively stable over time. Most commonly reported drug classes by decreasing frequency were 'neurological' (58%), 'antineoplastic' (32%) and 'anti-infectives' (25%). Most commonly reported system organ classes were 'general' (13%), 'nervous system' (12%) and 'psychiatric' (11%). Duration of use could be calculated for 19.7% of the reported drugs, of which 14.5% concerned drugs being used long-term (> 6 months).

Conclusions: Knowledge on the distribution of the drug classes and events within AERS is a key first step in developing pediatric specific methods for drug safety surveillance. Analysis of the reported drugs indicate disproportionate safety reporting of neurological/psychiatric and antineoplastic agents.

760. Suicide-Related Events in Young People Following Prescription of SSRIs and Other Antidepressants: A Self-Controlled Case Series Analysis

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Background: Concerns have been raised about a possible association between antidepressants and suicide-related behavior in young people. Therefore, treatment of young people with selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine has been discouraged by the UK drug authority since 2003, while other regulators have issued a warning for all antidepressant types. The evidence for the risk of suicide-related behavior has been inconsistent.

Objectives: We aimed to examine the temporal association between SSRI and tricyclic antidepressant (TCA) prescriptions and suicidal behavior in children.

Methods: We used a self-controlled case series design among 81 young people aged 10–18 years with a record of completed suicide, 1,496 with a recorded suicide attempt, 1,178 with suicidal ideation and 2,361 with intentional self-harm. We used electronic health records from 479 general practices in The Health Improvement Network (THIN) UK primary care database from 1995 to 2009 and compared Incidence Rate Ratios (IRRs) before, during and after an antidepressant prescription was recorded.

Results: For attempted suicide, suicidal ideation or intentional self-harm, IRRs were similar for the time the person was prescribed either SSRIs or TCAs: IRRs increased during pre-exposure, peaked on prescription day, were stable up to the fourth prescription-week, and decreased after prescriptions stopped. For both types of antidepressants, IRRs were lower or similar to pre-exposure levels during the period of prescription. For SSRIs, there was an increase in the IRR for completed suicide on the day of prescription (N = 5; IRR = 42.5, 95% CI: 4.5–403.4), and during the fourth week of SSRI prescription (N = 2; IRR = 11.3, 95% CI: 1.1–115.6).

Conclusions: Overall, there are no systematic differences between the association of TCAs and SSRIs with incidence risk ratios for attempted suicide, suicidal ideation or intentional self-harm. Moreover, apart from the day of prescription, rates were not statistically significantly different from pre-exposure levels. The pattern of death from suicide for SSRIs was similar to that found in non-fatal suicide-related behavior.

761. Drug Synergism of Non-Selective NSAIDs, Coxibs and Low-Dose Aspirin on the Risk of Upper Gastrointestinal Bleeding: A Self-Controlled Case Series Analysis

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Background: Concomitant use of NSAIDs and low-dose aspirin (LDA) increases the risk of upper gastrointestinal bleeding (UGIB). Though clinical guidelines suggest to avoid certain drug combinations, little is known about the magnitude of interaction.

Objectives: To estimate the magnitude of interaction between non-selective (ns)NSAIDs, coxibs, LDA with other drugs (i.e., steroids).

Methods: A self-controlled case series was performed using data from seven population-based European databases. UGIB cases were identified with ICD-9th CM, ICD-10 or ICPC codes. Drug exposure was classified into mutually exclusive groups by the ATC system. Incidence rate ratios (IRRs) (with 95% CIs) of UGIB during exposure were derived by Poisson regression modeling. Interaction was measured on additive (by Relative Excess Risk due to Interaction; RERI with 95% CI) and multiplicative scale.

Results: In total 114,835 UGIB cases, with corresponding follow-up of 930,888 person-years, were analyzed. Monotherapy with nsNSAIDs showed a higher IRR than for coxibs or LDA (IRR 4.3; 2.9 and 3.1, respectively). The IRR was highest for concomitant use of nsNSAIDs and steroids (IRR 12.8; 95% CI: 11.2–14.7), which also showed the highest additive interaction (RERI 5.5; 95% CI: 3.7–7.3). The IRR for nsNSAIDs and aldosterone antagonists was 11.0 (95% CI 8.6–14.0; RERI 4.5; 95% CI: 1.8–7.1). Selective serotonin re-uptake inhibitors (SSRIs) and anticoagulants combined with either nsNSAIDs, coxibs or LDA

increased the risk of UGIB significantly and also to a greater extent than expected based on the sum of the individual drugs (RERI 1.6;1.9 and 0.5 for SSRIs and 2.4;0.1 and 1.9 for anticoagulants, respectively).

Conclusions: Concomitant use of SSRIs with nsNSA-IDs, coxibs or LDA significantly increases the risk of UGIB up to seven-fold. Concomitant use of steroids, anticoagulants or antiplatelets with nsNSAIDs or LDA, but not with coxibs, increased the risk of UGIB. These increased risks were greater than the sum of the risks of individual drugs. This knowledge is clinically relevant and can help clinicians in tailoring therapy to minimize UGIB adverse events.

762. An Application of Multivariate Self-Case Control Series Method for Active Drug Safety Surveillance in an UK EMR

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Background: Literature on the application of the Multivariate Self-Case Control Series (MSCCS) method and its feasibility for active surveillance is limited and primarily focused on US databases.

Objectives: To test the MSCCS method using UK THIN Database in the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM); assess and compare the performance of MSCCS to Univariate SCCS (USCCS) method.

Methods: The MSCCS model accounts for the presence of multiple drugs and potential drug interactions during the observation period. SAS codes and parameter settings of both SCCS methods provided by OMOP were applied to the THIN CDM. Drug and health outcome of interests predefined by OMOP were used as exposures and outcomes. The OMOP reference set of 53 drug-outcome pairs (nine positive and 44 negative control pairs) was used as a 'Ground Truth' for method assessment.

Results: MSCCS highlighted seven out of nine pairs of the true associations, five with statistical significance. Thirty six true negative pairs out of 44 negative controls were identified. MSCCS offered lower sensitivity (56% vs. 78%) but better specificity (82% vs. 59%) than USCCS. While the negative predictive value was the same (90% vs. 90%), the positive predictive value was stronger for MSCCS (38% vs. 21%). For both methods, the results varied by the selection of risk period and the majority of false positive pairs (63% – MSCCS vs. 70% – USCCS) had RR < 2. Changing parameters from first to all occurrences had minimal impact on the results for both methods. MSCCS was

more sensitive to the selection of precision setting but not to the choice of exposed start date (day 1 vs. day 0). MSCCS was more computational intensive (≥ 6 times to complete a run) than USCCS and had more stringent system requirements to ensure tractability.

Conclusions: MSCCS scores, though imperfect, were more predictive of true associations than USCCS scores, with similar negative predictive values. There was some performance variability based on choice of parameters. For both methods, a RR < 2 led to a higher risk for false positives. Further research to understand MSCCS' performance characteristics across other databases are needed.

763. 'First-Wave' Exposure-Trend Bias in Self-Controlled (SC) Study Designs for Active Safety Monitoring of Newly Marketed Medications

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Background: Methodological issues in using large healthcare databases for rapid, active safety surveillance of newly marketed medical products are advancing. Issues with use of SC designs for this purpose are not fully understood.

Objectives: We conducted example studies to illustrate potential bias related to population-level time trends in active safety surveillance of newly marketed medications using a case-crossover (CCO) design and examined the utility of the case-time control (CTC) design to reduce such bias.

Methods: Using 2000–2006 Medicaid Analytic eXtract data, we performed 'active surveillance' by estimating sequential exposure odds ratios (E-OR) for four new drugs within this time frame (telithromycin, daptomycin, valdecoxib, and aripiprazole) with different durations of normal use. The outcomes of interest were acute hepatotoxicity and myocardial infarction. We compared sequential E-OR from CCO analyses, odds ratios for population level exposure time-trends (PT-OR) estimated in age-, sex-, calendar time-matched control persons, and adjusted odds ratios (A-OR) from CTC analyses, where A-OR = E-OR /PT-OR.

Results: In the first CCO analysis 6 months after telithromycin market entry, the E-OR for acute hepatotoxicity was 4.3 and dropped to 1.6 by the 9th quarter. The PT-OR for telithromycin among matched controls started at 2.9 and declined to 1.1 by the 9th quarter while the A-OR's started at 1.4 and ended at 1.3.

Qualitatively similar results were observed with the other drugs. The decline of PT-OR among matched controls to near-null values continued at the 15th quarter for aripiprazole, consistent with longer average duration of use.

Conclusions: In CCO without appropriate exposure-time trend adjustment, initial E-OR's can be strongly upward biased among first wave users of a new drug. By examining patterns of PT-OR decline after market entry of diverse drugs, benchmarks for different types of drugs might be established that enable SC designs to be useful in active safety surveillance. CTC can adjust for observed population level time-trends following market entry.

764. A Standardized Modular Program Using Self-Controlled (SC) Methods for Semi-Automated Safety Monitoring

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Background: Regulatory agencies are developing distributed electronic healthcare data networks comprising millions of covered lives to facilitate rapid medical product safety assessment. Modular programs allow participating organizations to quickly and easily run standardized analyses. For SC methods, assessment of exposure time-trends is particularly important.

Objectives: To develop and test a modular SAS program for use with the Mini-Sentinel Common Data Model (MS-CDM) that conducts case-crossover (CCO) analyses, provides options for alternative exposure-time adjustment strategies, and outputs results and diagnostics.

Methods: The program can adjust for population level exposure-time trends (P-ET) with case-time control (CTC) analyses or prognosis related exposure-trends (I-ET) with case-case time-control (CCTC) analyses. Using 2000–2006 Medicaid Analytic eXtract data converted to MS-CDM (N > 80 million), we mimicked real-time monitoring for three drugs introduced to market during this time period (telithromycin, valdecoxib, aripiprazole); outcome was acute hepatotoxicity for telithromycin and myocardial infarction for valdecoxib and aripiprazole.

Results: The output includes odds ratios (OR) with bootstrapped confidence intervals for CCO, CTC, and CCTC as well as ORs for population and prognosis exposure time-trends. In the initial monitoring periods following market entry, the CCO OR for each new drug suggested strong associations with increased risk of the respective outcomes (OR = 4.3, 12.0, 3.0). Diagnostics indicated that the dominant source of time-trend bias during the initial monitoring periods was P-ET (OR = 2.9, 4.3, 3.9). CTC analyses adjusting for P-ET in CCO ORs produced estimates more consistent with expectation in initial monitoring periods (OR = 1.4, 2.8, 0.8). For the selected examples, I-ET was a relatively weak source of bias (OR = 1.4, 0.8, 1.3).

Conclusions: Standardized modular code using SC methods can be implemented quickly and easily in a distributed data network. SC analyses with diagnostics and methods to adjust for time-trend biases can be used to rapidly detect safety signals in new medical products.

765. Self-Control Tree Scan Data Mining for Vaccine Adverse Events

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Background: Post-market drug and vaccine safety surveillance is important to detect adverse events too rare to find in clinical trials. Data mining methods are useful to screen many diagnostic codes for unexpected safety issues in the absence of specific safety concerns.

Objectives: The tree-based scan statistic is a data mining method that simultaneously evaluates a hierarchical system of both specific and broad diagnosis definitions. Self-control methods are widely used in vaccine safety studies, as they adjust for between person confounders. To minimize the number of false signals while evaluating thousands of overlapping disease outcome definitions, we present the novel development of a self-control tree-based scan statistic.

Methods: We used a 1–28 day post vaccination risk window and a 29–56 day post-vaccination control window. Under the null hypothesis, any disease outcome is equally likely to occur in either window. Statistical significance is calculated by generating random data sets under the null hypothesis, calculating a maximum likelihood, and adjusting for the multiple testing inherent in the many disease outcomes evaluated. The new method was tested by evaluating adverse events after MMRV vaccination. Electronic data was obtained

from six health insurance plans. In addition to the 1–28 day risk window, we also evaluated 0, 1–2, 7–10 and 8–21 day risk windows.

Results: There were 108,891 and 119,276 doses of MMRV given to 1–2 and 4–6 year olds, respectively, resulting in a total of 4,809 and 2,983 post-vaccination diagnostic events. With the 1–28 day risk window, there were only statistical signals for seizures and a variety of skin conditions (e.g. hives) among children aged 1–2 years. For the 4–6 year old children, all statistical signals were for different skin conditions. These findings are consistent with the known safety profile for MMRV.

Conclusions: The self-control tree-scan statistic detected several known adverse effects following MMRV vaccine, with no additional statistical signals. It is a promising data mining method for vaccine safety surveillance, and it could potentially be useful for drugs as well.

766. Persistence to Cardiovascular Treatment in Patients with Acute Coronary Syndrome

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Background: Recommended treatment for secondary prevention of acute coronary syndrome (ACS) is lifetime treatment with four therapeutic classes (BASI): betablockers, antiplatelet agents, statins or other lipid-lowering agents and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. How is this followed in real life?

Objectives: Describe use and persistence to secondary prevention therapies recommended after first occurrence of ACS.

Methods: Database study of patients with first registration for ACS from 2004 to 2007 in the 1/97 permanent random sample of the French national healthcare insurance database (Echantillon Généraliste de Bénéficiaires, EGB). Patients were identified using the long-term disease classification system (Affection de Longue Durée, ALD), resulting in full healthcare benefits coverage. The drugs of interest were the four BASI therapeutic classes. Persistence was assessed only for patients with three or four BASI classes dispensed during the 2 months following the registration for ACS. Non-persistence was defined by a gap of more than 42 days between two treatment periods. The follow-up period was 24 months after the registration for ACS.

Results: Of 2,157 patients with an incident ACS registration, 920 (42.7%) had at least one dispensation of all four BASI classes and 719 (33.3%) of three BASI classes. Persistence to treatment at 24 months was 56.6% for patients with four BASI and 56.3% for patients with three BASI. Non-persistence was greatest with beta-blockers followed by statins or other lipid-lowering agents, similarly in patients with either three or four BASI classes at inclusion.

Conclusions: Seventy-six percent of ACS patients had at least three of the four BASI drugs at inclusion, but only 43% all four, and the persistence to these treatments was sub-optimal. There is no significant difference between persistence to treatment for patients with three BASI or with four BASI. The treatments most commonly discontinued were those with the most contraindication and side effects.

767. Persistence with Statin Therapy: Does the Level of Lipid Values Influence Medication-Taking Behaviour?

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Background: Although many predictors of statin adherence have been studied, the ability to explain medication-taking behavior remains poor. There are reasons to believe that therapy adherence may be related to the patient's risk of a cardiovascular event.

Objectives: To study the effect of level of low-density lipoprotein cholesterol (LDL-C) values at baseline on statin therapy discontinuation.

Methods: A population-based cohort study was conducted using Swedish registers. Incident statin users aged 20 years of age or older who purchased a statin between July 1, 2006 and June 30, 2007 and who had a measurement of LDL-C during 6 months before the index date were identified. The cohort was classified according to the LDL-C values at baseline (< 3.5, 3.5–3.9, 4.0–4.9 and $\geq$ 5.0 mmol/L). The cohort was followed until June 30, 2009, censoring at hospitalization, migration and death. Discontinuation was defined as a gap in treatment > 90 days. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using multivariable Cox regression analysis adjusting for potential confounders (gender, age, education, income, prescriber's work place, health care center, country of birth, county of residence). Analyses were stratified by primary and secondary prevention.

Results: A total of 35,264 patients were enrolled in the cohort of which 59.2% (20,872) were treated as pri-

mary and 14,392 (40.8%) as secondary prevention. The level of LDL-C at baseline was significantly associated with statin therapy discontinuation in subjects treated for primary prevention. Compared to patients with low LDL-C values, those with higher LDL-C values had a lower risk of discontinuing the therapy (< 3.5 mmol/L, reference; 3.5–3.9 mmol/L HR 0.89 CI 95% 0.83–0.96; 4.0–4.9 mmol/L HR 0.89, CI 95% 0.84–0.95; ≥ 5.0 mmol/L HR 0.83, CI 95% 0.77–0.89). No association was found between LDL-C values at baseline and statin discontinuation in secondary prevention.

Conclusions: The findings from this study suggest that high level of LDL-C values at baseline improve statin adherence in primary prevention but not in secondary prevention.

768. Relationship between Adherence to Preventive Therapies and Mortality Post-Acute Myocardial Infarction (AMI): Examining the 80% Cutpoint

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Background: Poor medication adherence to preventive therapies following AMI has been shown to increase the risk of mortality. Researchers often dichotomize adherence at 80%, despite little supporting evidence. Previous research has studied the association between adherence and mortality following AMI without examining a dose-response relationship or controlling for healthy user bias.

Objectives: To examine whether a dose-response relationship exists between adherence and mortality and the appropriateness of an 80% cutpoint in secondary AMI prevention.

Methods: Using 2007–2009 Medicare claims, this retrospective study used a 100% cohort of Part D beneficiaries ≥ 65 years hospitalized for AMI in 2008 who were discharged to home and survived 180 days post-discharge. Users of angiotensin-enzyme-inhibitors (ACE-Is)/angiotensin receptor blockers (ARBs), beta-blockers or statins were examined. Cox proportional hazards regression modeled the relationship between 180-day adherence and subsequent mortality during the follow-up period until death or censoring on 12/31/2009. Each model adjusted for baseline sociodemographic and clinical covariates, use of the other preventive agents, and 180-day calcium channel blocker (CCB) adherence. CCBs have little demonstrated effect on mortality; thus, adjusting for CCB adherence should reduce healthy user bias.

Results: Of 11,165 patients using ≥ 1 preventive therapy and CCBs within 30 days post-discharge, 14–15% died depending on therapy group in the follow-up period. The adjusted hazard ratios (95% CI), including CCB adherence, for risk of death in adherers compared to non-adherers defined by the 80% cutoff were 0.81 (0.71–0.93), 0.88 (0.78–1.00), and 0.91 (0.79–1.04) for ACEI/ARBs, beta-blockers, and statins, respectively. Adjustment by CCB adherence significantly moved the hazard ratio closer to the null. Adherence by quintiles and continuous measures followed a more complicated dose-response relationship than the 80% cutpoint.

Conclusions: This study suggests the relationship between medication adherence and outcomes may not be adequately captured by the 80% cutoff often used in adherence literature.

769. Did HEDIS Get it Right? Evaluating the Quality of a Quality Measure

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Background: In 2007 the National Committee of Quality Assurance introduced a new Healthcare Effectiveness Data and Information Set (HEDIS) measure assessing the 'persistence of beta-blocker treatment after a heart attack' that classifies patients as adherent if they have ≥ 135 days covered during the 180 days after myocardial infarction (MI). There are many alternative ways in which this quality measure may have been specified.

Objectives: We sought to evaluate whether the chosen HEDIS measure was optimal.

Methods: We assembled a retrospective cohort of 8,672 post-MI patients ≥ 35 years old and calculated beta-blocker adherence during the180 days after discharge using several measures: having ≥ 135, ≥ 144 and ≥ 180 treatment days covered, receiving ≥ 3 and ≥ 6 prescriptions, and having gaps in therapy of ≥ 0, ≥ 15, and ≥ 30 days. We also assessed adherence over the first 90 days post-discharge: having 72 days (80%) treatment days covered and having a gap of ≥ 15 days. All of the evaluated measures were binary and categorized patients as adherent or not. We assessed the strength of the association between each measure and a composite outcome (readmission for major vascular event or death within 181–365 days after discharge) using

multivariable Cox models. We compared the predictive capacity of each adherence definition model to one that did not contain adherence by computing a change in C-statistics and a continuous net reclassification improvement index (NRI).

Results: Adherence was associated with clinical outcome reductions, with hazard ratios ranging from 0.72 (95% CI: 0.53–0.98) to 0.86 (95% CI: 0.76–0.96), in all of the measures except one. While none of the adherence measures, including the HEDIS definition, significantly changed the C-statistic relative to a model that did not include adherence, having 72 days covered during the first 90 days post-discharge had the greatest change in NRI (correctly reclassifying 12% of cases and 16% of non-cases; NRI 28%, 95 CI 22–38%) and was superior to the HEDIS and the other measures evaluated.

Conclusions: We identified an adherence measure with better predictive ability and shorter assessment period than that definition selected by HEDIS to measure beta-blocker use after MI.

770. Quantitative Risk-Benefit Analysis of Oral Anticoagulants in Patients with Atrial Fibrillation

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Background: Warfarin is commonly used to lower the risk of stroke in patients who have atrial fibrillation, while it has dangerous side effects or interactions that could place patients at risk of bleeding. New oral anticoagulants, including apixaban and dabigatran, have been developed as the other potential choices to prevent the occurrence of stroke.

Objectives: This study aims to conjointly evaluate the therapeutic efficacy and safety of the above new medications and warfarin to assist decision making of prescribing and reimbursement.

Methods: A decision model was created to compare the risk-benefit of the aforementioned medications. Using published meta-analysis data, we performed a probabilistic Monte Carlo simulation to estimate the joint distribution of each type of efficacy (including prevention of all strokes, ischemic stroke and hemorrhagic stroke) and safety (including major bleeding, intracranial bleeding and gastrointestinal bleeding). The incremental risk-benefit ratios (ICBRs) were calculated, and the results were illustrated by incremental risk–benefit planes. To account for differential risk preferences across patients, the results were also illustrated using risk–benefit acceptability curves and net-benefit curves.

Results: To prevent the occurrence of all strokes, when risk was defined as having major bleeding or gastroin-

testinal bleeding, warfarin was dominated by apixaban (ICBR = −0.39 and −0.30 respectively); dabigatran showed increasing risk and benefit as compared to apixaban (ICBR = 3.22 and 2.22 respectively). Dabigatran dominated warfarin and apixaban when risk was defined as having intracranial bleeding (ICBR = −0.86 and −0.04 respectively).

Conclusions: The overall results generally indicate that the new oral anticoagulants might be preferred over warfarin. Selecting appropriate medicines according to both patient's condition and the risk-benefit feature of medicine is suggested in order to achieve better treatment goals.

771. Risk of Stroke after Herpes Zoster Infection – A Self-Controlled Case-Series Analysis

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Background: Varicella-zoster-virus (VZV) vasculopathy is a severe complication of a herpes zoster (HZ) infection which may lead to transient ischemic attacks, aneurysm, subarachnoid hemorrhage and possibly ischemic and hemorrhagic stroke. Epidemiological data on the association of HZ and stroke are important for burden of HZ disease studies and the assessment of VZV vaccine effectiveness.

Objectives: To assess increase in risk of stroke after HZ infection.

Methods: This study was based on data of three statutory health insurance providers from the German Pharmacoepidemiological Research Database (GePaRD), and based on a cohort of insurants who were prior to cohort entry continuously insured for 12 months without a diagnosis of HZ. The increase in risk of stroke after HZ infection was estimated using a self-controlled case-series method. For the main analysis a combined endpoint of hemorrhagic, ischemic and unspecified stroke was defined. In secondary analyses, the sub-entities hemorrhagic and ischemic stroke were examined separately. Observation period was from January 1st, 2005 to December 31st, 2009 and the observation time of each individual was subdivided into risk and control periods as well as into age intervals. Risk periods were defined as the time from beginning until the end of a HZ infection episode plus 3 months. A log-linear Poisson model was fitted to estimate relative incidences (RI) for stroke. Sensitivity analyses regarding the length of risk periods, potentially time-variant confounders and the impact of case

fatality were performed to examine the robustness of the results with respect to violations of the assumptions.

Results: During the observation period 88,576 strokes were observed. Eight hundred and forty-eight events occurred during the risk periods (total person time 3,240 person-years) and 87,728 during the control periods (364,690 person-years). The estimated relative incidence was 1.12 (95% CI 1.03–1.21) which indicates a slightly increased risk of stroke after HZ infection.

Conclusions: The risk of stroke after HZ infection was slightly increased compared to control periods. Time-invariant confounders were controlled for by using a self-controlled method based on within-person comparisons.

772. Use of a Common Data Model to Meaningfully Compare Patients Diagnosed with and Treated for Depression Among Disparate Databases

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Background: Use of a Common Data Model (CDM) to standardize data format and assumptions facilitates consistent and efficient application of research methods across disparate data sources, producing meaningfully comparable results.

Objectives: This study compared patient and treatment characteristics for patients diagnosed with depression in 2008–2009 across multiple distributed observational databases after source data was transformed into a CDM format.

Methods: Patients with newly diagnosed depression were identified from five distributed Claims (Commercial and Gov't) and Electronic Health Record (EHR) databases, comprising nearly 300 million patients previously transformed into CDM format. Using a CDM analysis module, patient and treatment characteristics for anti-depressant drug classes (e.g. SSRI, SNRI, TCA, MAOI, Other) were examined and treatment patterns were analyzed 365 days following initial treatment.

Results: Across databases 1–2% of patients met depression study criteria. Mean age (34–43) and gender (63–78% female) varied by database with youngest and most female in Gov't Claims. Treated patients varied by database with 61–83% treated sometime after first diagnosis and 9–30% within the first 60 days. In both cases EHR had highest% treated. SSRI's were prescribed most often (72–75%) and MAOIs least ($\leq 0.02\%$) in treatments occurring w/in 60 days after diagnosis. Patients who continued treatment for at least 365 days varied by database type: Gov't Claims (5%), Commercial Claims (14–15%), EHR (32%). Discontinuation was consistent across Claims (65–69%) with EHR lower (46%). Switching was consistent (12–14%) and augmentation was consistent across all (7–8%) except Gov't Claims (13%). Analyses were complete in < 2 days.

Conclusions: Databases record data in different ways, to different degrees, for different reasons. Use of a CDM enforces transparent application of standardized rules once during data prep. rather than separately at analysis time. Consistent application of transformation rules and analysis modules enables results to be meaningfully compared across disparate data and highlights differences that may be important for interpretation.

773. Generic vs. Branded Bupropion: Hindsight Using Administrative Data

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Background: In December 2006 Budeprion XL 300MG, a generic version of Wellbutrin XL 300MG, was approved by the FDA based on bioequivalence studies of the 150MG product. Subsequently, the FDA received reports of recurrent depression for patients switching from Wellbutrin to Budeprion. As a result, the FDA requested Budeprion's manufacturer (Teva) conduct a follow-up study to evaluate these concerns. Teva abandoned this effort in late 2011 citing inadequate recruitment. In October 2012 the FDA determined, from clinical data, that 300MG Budeprion was not bioequivalent with Wellbutrin and requested Budeprion's withdrawal.

Objectives: To determine whether differences in bioequivalence could have been detected in administrative

claims using product discontinuation as a proxy for treatment failure.

Methods: We constructed a retrospective cohort within TruvenHealth MarketScan Commercial Claims. Adults (18–64 years) initiating 300MG bupropion XL (brand or generic) from July 2007 to December 2011 and who were continuously insured for 180 days prior to initiation were included. We used inverse probability of treatment weighting to balance pre-treatment characteristics. Cox Proportional Hazards models compared time to discontinuation (2+ months without 80% of days covered following a month with ≥ 80% coverage) between branded and generic products. We censored person-time at discontinuation, insurance coverage loss or December 31, 2011.

Results: There were 8,633 Wellbutrin initiators, 75,642 Budeprion initiators and 144,872 other generic bupropion initiators over the study period. Groups were balanced on measured covariates after propensity score weighting. Average time to discontinuation was 5 months among Wellbutrin initiators and 4 months among Budeprion initiators (HR: 1.14, 95% CI: 1.11–1.16). Differences in time to discontinuation between Wellbutrin initiators and other generic bupropion initiators were small (HR: 0.96, 95% CI: 0.94–0.98).

Conclusions: Administrative databases offer the potential to detect possible differences in bioequivalence in specific settings, potentially shortening time to market withdrawal of non-equivalent pharmaceutical products.

774. Use of Varenicline vs. Bupropion and Risk of Psychiatric Adverse Events

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Background: Psychiatric adverse events following initiation of varenicline, a drug used for smoking cessation, have been reported to passive drug safety surveillance systems.

Objectives: To investigate whether varenicline use was associated with increased risk of psychiatric adverse events, compared with another drug used for smoking cessation, bupropion.

Methods: We conducted a register-based cohort study in Denmark, 2007–2010, comparing new users of varenicline and bupropion in unmatched and 1:1 propensity score-matched analyses. Using Cox regression, we estimated the hazard ratio (HR) for any psychiatric adverse event (emergency department visit or inpatient admission with a psychiatric diagnosis) within 30 days following treatment initiation.

Results: In unmatched analyses, there were 106 (0.18%) psychiatric adverse events among 59,790 varenicline users (rate 22 events per 1,000 person-years), compared with 46 (0.26%) events among 17,936 bupropion users (rate 31 per 1,000); the HR was 0.69 (95% CI 0.49–0.98). In propensity score-matched analyses, 39 (0.22%) events occurred among 17,935 varenicline users (rate 27 per 1,000), compared with 46 (0.26%) events among 17,935 bupropion users (rate 31 per 1,000); varenicline was not associated with increased risk of psychiatric adverse events (HR 0.85, 95% CI 0.55–1.30). The overall rate of psychiatric adverse events was substantially higher among participants with a history of psychiatric disorder than in patients without such history; the risk associated with varenicline did not differ significantly by history of psychiatric disorder.

Conclusions: The risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission was not significantly higher with varenicline use compared with bupropion. These findings should be interpreted considering the design of the study, which compared the relative risk of psychiatric events between users of varenicline, and users of another drug with an identical treatment indication, bupropion. As such, they may provide evidence in the context of the clinical situation when a treatment choice between these two drugs for smoking cessation is considered.

775. Is Childhood Attention-Deficit (Hyperactivity) Disorder Associated with Atopic Diseases and Skin Infections? A Matched Case–Control Study Using the GPRD

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Background: Data to support the hypothesis of a relationship between ADHD and allergies are conflicting.

Objectives: To assess whether children with ADHD are more likely to have a history of atopic disorders, skin infections and medical prescriptions than children without ADHD.

Methods: We conducted a nested case-control study among boys using the United Kingdom General Practitioner Practice Database (GPRD). Cases were defined as children with firsttime diagnosis of ADHD who were treated with methylphenidate. Four controls

that had neither ADHD nor ADHD-drug prescriptions in their medical records were matched to each case on age and general practice. Conditional logistic regression analyses to obtain independent odds ratios and corresponding 95% confidence intervals and p-values.

Results: We identified 884 boys with a first-time diagnosis of drug-treated ADHD and 3,536 controls. The independent odds ratios adjusted for age and presence of low birth weight or preterm delivery were 1.4 (95% confidence interval 1.2–1.7, p < 0.0001) for a medical history of asthma, 1.5 (1.3–1.9, p < 0.0001) for impetigo and 1.5 (1.3–1.7, p < 0.0001) for any antihistamine drug prescriptions. Other exposures that were more common in cases than controls, though not independently were cow's milk intolerance, and any prescription from the drug categories anti-asthmatics, respiratory corticosteroids, topical steroids, antibacterials or antifungals.

Conclusions: Despite possible limitations inherent to observational studies, this study lends support to the emerging evidence that childhood ADHD is associated with atopic diseases and impetigo. Further interdisciplinary research is needed to understand the underlying mechanisms and to evaluate targeted preventive, diagnostic, and therapeutic interventions.

776. Factors Associated to Antidepressant Initiation After the Diagnosis of Amyotrophic Lateral Sclerosis: A Population-Based Cohort Study in Friuli Venezia Giulia, Italy

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Background: In Amyotrophic Lateral Sclerosis (ALS), a rare fatal neurodegenerative disease, estimated prevalence of antidepressants (AD) use is 38%.

Objectives: To assess factors associated to the initiation of AD use after the diagnosis of ALS.

Methods: A population-based incidence study ascertained ALS cases in FVG from 2001 to 2009 through multiple sources, including hospitalization database, archives of the Neurology Departments and of the regional chapter of the Italian ALS association (AIS-LA). ALS diagnosis was validated through medical chart review and date of diagnosis (ID) was established. For confirmed cases we extracted from the FVG outpatient prescription database, through a unique personal identifier, prescriptions from 2000 to 2011. We identified all prescriptions for AD (N06A) from 1 year before ID to the earliest of date of death or December 31, 2011. New users were defined as those cases that at the time of ALS diagnosis had not had any prescription for AD in the prior year. Cox proportional hazard regression was used to estimate hazard ratio (HR) and 95% confidence interval (95% CI) for AD treatment initiation. The model included sex, age at ALS diagnosis (< 68 years, ≥ 68) and type of onset (bulbar and mixed, spinal).

Results: Of 262 confirmed ALS cases (50.4% men, median age at diagnosis 68 years), 69 (26.3%) were users of AD in the year prior to ID. New users after ALS diagnosis were 100 (38.2%) and the most prescribed AD were SSRIs (59.5% of AD prescriptions). Paroxetine was the most frequent SSRI (32.7%), followed by Citalopram (24.7%) and Sertraline (24.2%). Tricyclic AD (of which 99% Amitriptyline) accounted for 31.7% of AD prescriptions. In new users women had HR = 1.3 (95% CI 0.9–2.1), the cases with age < 68 years at diagnosis HR = 1.8 (95% CI 1.1–2.8) and those with bulbar and mixed onset HR = 1.3 (95% CI 0.8–2.0).

Conclusions: Use of AD is frequent before diagnosis, and ALS has often an insidious onset. In new users female sex, younger age at diagnosis and bulbar involvement at onset are associated with a slight increased risk of initiating AD after ALS diagnosis.

777. Neighborhood Material and Social Deprivation and Use of Antidepressants in Depression

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Background: The Quebec's public drug plan aims to provide to residents equal access to medication. One would therefore assume that access of individuals suffering from depression to antidepressants (AD) and to guideline-recommended 1st-line (GR1) AD would not differ according to their material and social deprivation level.

Objectives: Among individuals suffering from depression who are the most materially and socially deprived and those who are the least deprived: to describe the proportion exposed to ADs in the 365 days following diagnosis; and among the latter, to describe the proportion who obtained a GR1 AD as the initial prescription.

Methods: Using Quebec administrative health data, we conducted a cohort study including individuals aged ≥ 18 years, newly diagnosed with depression between 1997/01/01 and 2006/12/31 and enrolled in the public drug plan 1 year before and 2 years following depression diagnosis. Neighborhood material and social deprivation were measured using indices built and validated using the Quebec population. Individuals in the 1st and 5th quintiles were the least and most deprived, respectively. Individuals were considered exposed to an AD if they obtained such a drug in the 365 days following diagnosis. GR1 ADs were those proposed by the Canadian Network for Mood and Anxiety Treatments. Difference in proportions between the most and the least deprived groups was tested using 95% confidence intervals (CI).

Results: Out of 100,485 individuals included, 65,479 (65%) were exposed to an AD in the year following diagnosis. Among the least (n = 2,001) and the most (n = 7,057) materially and socially deprived groups, 63.6% (95% CI = 60.8–66.4) and 64.7% (63.21–66.2) were exposed to an AD, respectively. Among the 65,479 exposed to an AD, 58,226 (89%) obtained a GR1 AD as the initial prescription. The proportion of individuals initially exposed to a GR1 AD was 88.4% (83.6–93.2) in the least deprived group (n = 1,272) and 87.3% (84.8–89.8) in the most deprived one (n = 4,562).

Conclusions: Results suggest that the Quebec drug plan is achieving its goal as access to AD or GR1 AD treatment does not differ between the most and the least deprived groups.

778. An Algorithm To Predict Biologic DMARD Use in the THIN Database

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Background: The Health Improvement Network (THIN) database with data collected from General Practitioners (GP) are limited in their capabilities to capture therapies prescribed by specialists, including biologic disease modifying antirheumatic drugs (bDMARD), except on the rare occasion that bDMARD drugs were prescribed by GPs.

Objectives: To develop and evaluate an algorithm to predict bDMARD use in the THIN database.

Methods: We identified 409 bDMARD users in the database according to the drug codes. Of 2,123 patients with rheumatoid arthritis but no record of bDMARD prescriptions were randomly selected. Patients were divided into two equal groups, one for algorithm development and one for algorithm testing. With the first group, logistic regression was performed on the following variables: (1) discontinued prescription of methotrexate, (2) renal and hepatic AE associated with MTX, (3) adding other non-biologics DMARDs to MTX, (4) dose reduction of MTX, (5) adding 2nd non-bDMARD to the treatment regimen (MTX or none MTX), and (6) referral to rheumatologist. A score to predict bDMARD use was then calculated based on the coefficients of the model.

Results: Factors (1), (3), (4), (5) and (6) were found to be significant predictors of bDMARDs use. Using a ROC curve to determine a predictive score that maximize sensitivity and specificity, 0.1347 was set as cut point to differentiate bDMARD users and non-users. When testing the algorithm against actual bDMARD use identified by the prescriptions of the drugs, sensitivity was 0.66, specificity 0.73, positive predictive value (PPV) 0.32, and negative predictive value (NPV) 0.92.

Conclusions: We found that in the THIN database, clinical factors can be used as significant predictors of bDMARD use. The algorithm provided good sensitivity, specificity, and NPV, but low PPV. This may be because some actual bDMARD users in the database were classified as non-users because of missing data from specialists. As a further step, free text fields and questionnaires completed by patients and GPs could be queried to obtain bDMARD prescriptions from specialists, and the confirm bDMARD use status could be used as a better 'gold standard' to improve the predictive qualities of the algorithm.

779. Narcolepsy and H1N1 Vaccination in France: A Case–Control Sub-Analysis Focusing on the Risk of Narcolepsy with Cataplexy

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Background: Following the 2009 scandinavian signal of narcolepsy with Pandemrix H1N1 vaccine, a multinational case-control study coordinated by the VAESCO consortium was launched, to which France contributed with the Narcoflu-VF study. Despite the signal was mostly based on narcolepsy with cataplexy (NC) cases, this study main objective was to evaluate this potential risk for all-type narcolepsy.

Objectives: To study the association between NC and H1N1 vaccination.

Methods: For Narcoflu-VF, patients with narcolepsy diagnosed between October 2009 and April 2011 were included from 14 French sleep centres. Date of diagnosis constituted the main index date. Up to four controls (recruited within case' hospitals or a healthy volunteer's database) were matched to cases according to age, sex, and location. Information on medical history, past infections, and vaccinations was collected through phone interviews. The sub-analysis presented considered only NC cases and their matched controls. Using conditional logistic regression, association between NC and H1N1 vaccination was estimated in the whole population, by age (< 18 or ≥ 18 years), and

by time period (before or from July 2010) to study a potential media effect.

Results: Eighty-five NC cases were included, of which 23 were excluded because of incomplete index date. Of the remaining 62 NC cases, 59 (64% of men, 57.6% < 18 years) could be matched with 135 controls. H1N1 vaccination was associated with NC with an Odds Ratio (OR) of 5.5 (95% CI 2.5–12.0) in the whole population. This was 6.5 (2.1–19.9) in subjects < 18 years and 4.7 (1.6–13.9) in those aged 18 and over. Association was not significant in the pre-mediatisation period (OR 2.8; 0.8–10.5). Sensitivity analyses considering referral date for sleep testing, and first symptoms onset date as index dates found similar results, but significant for all time-periods.

Conclusions: H1N1 vaccination was associated with an increased risk of NC in both children and adults. The association in adults, only found in France, should be further investigated. Due to limited sample size, studying risk for individual H1N1vaccines was not possible.

780. Prevalence and Risk Factors for Prehypertension and Hypertension Moroccan Patients

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Background: Studies detailing prevalence of prehypertension and hypertension in Morocco are meager.

Objectives: The objective of this study is to determine the risk factors associated with prehypertension and hypertension.

Methods: This is a prospective study in November 2010 and February 2012, concerning 940 patients with essential hypertension followed in the outpatient of cardiology, at the city of Rabat. Men and women, over 25 years of age were included. Dietitian administered questionnaire followed physician evaluation, examination and blood pressure measurement. Diagnosis for prehypertension (BP 130–139/85–89 mmHg) and hypertension (BP ≥ 140/90 mmHg) were based on European Society of Cardiology criteria.

Results: Prevalence of prehypertension and hypertension, respectively, was significantly greater in urban (W 31.5; 31.9%; M 35.1; 35.5%) compared to rural (W 30.0; 29.1%; M 34.7; 35.6%). Subjects with prehypertension and hypertension were older, with higher BMI, central obesity and of sedentary behavior. They had higher salt, with greater oral contraceptive usage (W). Multivariable logistic regression analysis, revealed strong positive associations of hypertension with age, central obesity, BMI, sedentary lifestyle, salt and oral contraceptive usage (W). Fruit, vegetable and legume intake showed inverse associations, tobacco intake showed none. One in four with hypertension was aware of their diagnosis and of those receiving treatment, one in three exhibited control.

Conclusions: There is little awareness that prehypertension and hypertension are public health issues in Morocco. Ageing population, central obesity, sedentary lifestyle, excessive salt, lower fruit, vegetable and legumes intake increases risk for blood pressure elevation.

781. Differences Between Hypertensive and Normotensive Women Attended in Primary Care in Morocco

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Background: Hypertensive heart disease is the important cause of death associated with high blood pressure.

Objectives: The aim is to know the differences in cardiovascular risk factors, target organ damage, associated cardiovascular disease and cardiovascular risk between hypertensive (HT) and normotensive (NT) women attended in primare care.

Methods: A descriptive, cross-sectional and multicenter study between November 2010 and February 2012. Population: Random selection of women with age between 45 and 75 years attended in primare care. The following variables were analyzed: associated cardiovascular risk factors (CVRF): hypertension, diabetes, dyslipidemia, smoke and obesity; target organ damage (TOD): left ventricular hypertrophy (LVH) by electro-cardiography, decrease of glomerular filtration rate (GFR), microalbuminuria and slight increase in plasma creatinine; and cardiovascular or renal disease (CVD): stroke, coronary heart disease, heart failure, peripheral vascular disease and renal disease. Cardiovascular risk (CVR) was stratified according to ESC-ESH 2009 guidelines.

Results: Nine hundred and three women were selected, mean age 59.6 ± 8 years; 412 (45.6%) were hypertensive. In HT women systolic blood pressure was 138 ± 14 vs. 124.8 ± 14 mmHg in NT; diastolic blood pressure was 81.6 ± 9 vs. 75.8 ± 8 mmHg; Prevalence of CVRF in HT respect NT were: obesity 44.7% vs. 18.9% (OR 3.45; IC 95%: 2.56–4.65, p < 0.001); dyslipidemia 48.8% vs. 35.8% (OR 1.70; IC 95%: 1.30–2.22, p < 0.001); diabetes 21.8% vs. 6.1% (OR 4.29; IC 95%: 2.77–6.64, p < 0.001) and smoke 10.2% vs. 17.7% (OR 0.52; IC 95%: 0.35–0.78, p = 0.001). TOD was more prevalent in HT than NT: 27.3% vs. 9.4% (OR 3.60; IC 95%: 2.42–5.36, p < 0.001), and decrease of glomerular filtration rate 18.2% vs. 7.5% (OR 2.73; IC 95%: 1.79–4.14, p < 0.001). CVD was present in 14.8% of HT and 4.7% in NT (OR 3.53; IC 95%: 2.14–5.82, p < 0.001). CVR high or very high was 65.3% in HT and 26.9% in NT (OR 5.11; IC 95%: 3.84–6.80, p < 0.001).

Conclusions: Half of women between 45 and 75 years attended in primare care were hypertensive and respect normotensive women they had high prevalence of others cardiovascular risk factors, target organ damage.

782. Trends in the Antimicrobial Susceptibility of Bacteremias Over the Past Decade: A Regional Antibiogram of the ESKAPE Pathogens

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Background: Bacteremias are associated with negative clinical outcomes and high mortality rates. Such infections are extremely difficult to treat, particularly as antibiotic resistance rates change, potentially leading to the administration of inappropriate empiric therapies.

Objectives: To develop and evaluate a 10-year regional antibiogram of ESKAPE pathogens from blood cultures: *Enterococcus faecium* and *faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* (*Escherichia coli*, *Proteus mirabilis*).

Methods: Our regional antibiogram included blood culture and antibiotic susceptibility data from five Veterans Affairs hospitals in New England between 2002 and 2011. We calculated isolate counts, ranges in percent susceptibility, and modeled yearly percent change in susceptibility (generalized linear mixed models) for all bug and drug combinations.

Results: Over the 10 year study period, 4,063 unique ESKAPE isolates were included from blood culture sites. Gram-negative organisms represented 33% of the isolates (n = 1,354). For *Acinetobacter* (n = 52), amikacin susceptibility decreased 68% annually (p = 0.03). Significant (p < 0.01) yearly percent decreases in susceptibility to gentamicin (GENT) (15%), ampicillin/sulbactam (10%), trimethoprim/sulfamethoxazole (TMP/SMX) 9%, and ciprofloxacin (15%) were observed in *E. coli* (n = 812). GENT susceptibility improved by 15% (p < 0.01) annually in *P. aeruginosa* (n = 289). For *S. aureus* (n = 1,624), susceptibility increased significantly (p < 0.01) each year by 6.5% for oxacillin, 31% for TMP/SMX, 16% for tetracycline, and 28% for vancomycin.

Conclusions: Our study identified significant changes in resistance among bacteremias caused by the ESKAPE pathogens. Lower resistance (i.e. higher susceptibility rates) among the gram-positives, particularly the reduction in *S. aureus* blood cultures demonstrating oxacillin resistance (MRSA), may be attributed to infection control and stewardship programs. Of concern was the observed increase in resistance among the gram-negatives, providing additional evidence of a growing public health crisis.

783. Antibiotic Resistance and Differences by Culture Site in *Staphylococcus aureus*

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Background: Reduced susceptibility to antibiotics and the emergence of resistant strains of bacteria have become a serious problem in the recent past due to overuse and misuse of these drugs.

Objectives: To compare antibiotic resistance in *S. aureus* by infection site over a ten-year period.

Methods: We assessed culture data from five acute care facilities of the Veterans Affairs New England Healthcare System between 2002 and 2011. *S. aureus* cultures from the blood (invasive) or urine (non-invasive) were included. Resistance trends against nine antibiotics were evaluated: ciprofloxacin (CIP), clindamycin (CLI), gentamicin, (GEN), linezolid (LZD), oxacillin (OXA), penicillin (PEN), tetracycline, (TET), trimethoprim/sulfamethoxazole (SXT), and vancomycin (VAN). Percent resistance was compared by culture site using the Wilcoxon Mann–Whitney test and over time using generalized linear mixed models. Statistical significance was set at p < 0.05.

Results: Overall, 7,173 unique *S. aureus* cultures were included in our study (blood 1,624, urine 5,549). Resistance rates varied significantly by culture site for CIP, CLI, GEN, OXA, PEN, TET, and VAN. Significant modeled annual percent decreases in resistance were observed for CIP (urine 8.5%), CLI (urine 15.4%), GEN (blood 30.4%, urine 13.0%), OXA (blood 6.5%, urine 5.4%), TET (blood 16.6%, urine 14.9%), SXT (blood 30.9%, urine 25.7%), and VAN (blood 27.7%). Alternatively, resistance to penicillin increased significantly for blood cultures (5.7%), but not urine (1.1%).

Conclusions: Significant decreases were observed in antibiotic resistance over time. These decreases were consistent between invasive and non-invasive culture sites.

784. Identification and Treatment of Recurrent Ovarian Cancer in a Large Administrative Claims Database

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Background: The majority of women with ovarian cancer are diagnosed with stage III or IV disease, and many will have a recurrence.

Objectives: To identify and describe treated recurrences in women with ovarian and fallopian tube cancer.

Methods: Adult women in a large US-based administrative claims database (2001–2011) were identified as having ovarian and fallopian tube cancer using ICD-9-CM codes. To classify women as having incident cancer, they were required to have ≥ 1 year of continuous enrollment and have no claims with cancer diagnosis codes or chemotherapy treatment in the year prior to the first cancer claim. For this analysis, we included women who had both surgery and platinum-based chemotherapy as their initial treatment. Treated recurrences were identified by gaps in chemotherapy treatment, and were divided into subgroups by treatment-free intervals: 12+ months, 6–12 months, and 3–6 months. For each recurrence subgroup, we described treatments received.

Results: Of the 3,408 women identified with ovarian cancer, the median age at diagnosis was approximately

59 years (range: 18–100), > 30% of women had metastatic disease at diagnosis, and 9% had chemotherapy before surgery. Follow-up ranged from a median of < 2 years for women diagnosed in the latter time periods to almost 3 years in the earlier periods. Recurrences treated with a > 3 month gap in treatment were identified in 943 patients, with 36% being treatment-free for 12+ months, 33% between 6 and 12 months, and 30% between 3 and 6 months. For patients with recurrence after 12+ months, the majority of treatments were platinum-based with platinum /paclitaxel being the most common (29%). In the 6–12 month treatment-free group, platinum/paclitaxel was used less frequently (15%) and single agent chemotherapies, such as doxorubicin, gemcitabine, topotecan and paclitaxel, were more common than in the 12+ month group.

Conclusions: We found that for women with recurrent ovarian cancer, platinum-based chemotherapy regimens were most common in women who had a treatment-free interval of 12+ months, and less common in women with treatment-free intervals of < 12 months.

785. Management of Depression in Taiwan: Unmet Needs in Advanced Pancreatic Cancer Patients?

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Background: Although depression is one of the strongest determinants of health related quality of life, it is likely to be under-reported by patient and under-diagnosed by physicians. The information on the management of depression in pancreatic cancer patients in Taiwan is not yet available, studies using the National Health Insurance Research Database (NHIRD) may help to understand how depression is diagnosed and treated in these patients.

Objectives: To assess the clinical management of depression and prescription patterns of anti-depressants.

Methods: Firstly, a cross sectional study was conducted in a tertiary referral center. All advanced pancreatic cancer patients from September 2012 to January 2013 were invited. To assess depression, the pharmacist interviewed patients by two stem questions (2Q), which is recommended by Depression in Cancer Care Consensus Group. Clinicians also independently evaluated if these patients had depression. Secondly, to explore the nationwide scenario, we examined the prescribing patterns of anti-depressants in pancreatic cancer patients using a 1-million randomly sampled beneficiaries' data in 2010 from Taiwan's NHIRD. We further confirmed the diagnose of pancreatic cancer with the Registry for Catastrophic Illness Patient Database, a subpart of the NHIRD.) The prevalence of depression (ICD9-CM-code: 293.83, 296.2, 296.3, 300.4, 309, 309.1, 309.28, 311) and utilization of depressants (ATC-code: N06A) were estimated.

Results: Among 49 eligible patients, 31 (63.3%, 95% CI = 48.3–76.6%) were diagnosed as depression by clinicians, while 41 (83.7%, 95% CI = 70.3–92.7%) identified by 2Q. None of the patients were taking or prescribed depressants at the time of interview. With NHIRD, in 87 pancreatic cancer patients, 5 (5.8%, 95% CI = 1.9–12.9%) were recorded with depression, and 16 (18.4%, 95% CI = 10.9–28.1%) were prescribed with anti-depressants. Four depressive pancreatic cancer patients were prescribed with anti-depressant(s).

Conclusions: Our findings suggest that remarkable discrepancies between clinical observation and database findings indeed existed. Unmet needs of depression management in patients with pancreatic cancer require further investigation.

786. Developing a Model for Type 2 Diabetes Mellitus Medication Use Prevalence at Local Level

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Background: Socio-economic profile, demographic composition and access to care are important predictors of local health and health care use. How such predictors are associated with medication use at local level is unknown, but knowledge is essential to improve efficiency of preventive programs in risk areas.

Objectives: We explored spatial patterns of type 2 diabetes mellitus (T2DM) medication use at local level and determined its association with local demographic, socio-economic and access to care variables.

Methods: Using the University of Groningen pharmacy database IADB.nl, we estimated the five-year prevalence of T2DM medication use (2005–2009) in persons aged 45+ at four-digit postal code level for two Dutch

areas, totaling 141 postal code areas. Statistics Netherlands supplied data on potential predictor variables. We used empirical Bayes smoothing to deal with the small sample problem. We composed variables for socio-economic profile, ageing and access to care and estimated first an overall multiple linear regression model followed by two models for each separate geographical area.

Results: Socioeconomic profile, ageing and access to care were all significant predictors for T2DM medication use in the model incorporating both areas. In our first area (Groningen-Veendam) the smoothed prevalence of T2DM medication use ranged from 5.0% to 24.3%. Access to care and socio-economic profile were statistically significant predictors in this area. In the second area (Zwolle-Kampen-Noordoostpolder) smoothed prevalence ranged from 6.2% to 20.2%. Here, socioeconomic profile and ageing were significant predictors. The discriminative value of the model was higher in our first area (adjusted R-squared 0.41 compared to 0.25 in the second area). The unstandardized coefficients pertaining to the three composite predictors were similar in all three models, indicating that the relations with T2DM are roughly stable across space.

Conclusions: Our results demonstrate the importance of socio-economic profile, ageing and access to care variables for explaining and projecting local health care use for type 2 diabetes mellitus.

787. Depression and Anxiety Diagnoses and Treatment in Hemophilia Patients: A US Claims Database Study

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Background: Published reports found that hemophilia A or B patients report anxiety and/or depression with corroborating scores on validated screening tools. Epidemiologic data on the prevalence of a clinical diagnosis of anxiety or depression and the prescribing of relevant medications in hemophilia patients is limited.

Objectives: In a US claims database, determine the prevalence of depression and anxiety diagnoses and use of anti-anxiety and anti-depression medications in the hemophilia A and B population and in matched controls.

Methods: Subjects derived from a US claims database spanning 2004–2010. Hemophilia cases were defined as having ICD-9 code 286.0 or 286.1 and receiving factor VIII or factor IX replacement. Two controls matched on age, gender, follow-up time, and health insurance benefits were selected for each case, resulting in 1,498

hemophilia cases and 2,996 controls. Frequencies, odds ratios (OR), and 95% confidence intervals (CI) are presented.

Results: The mean age of study subjects was 22 years, with 69% under 31 years. Mean follow-up time in the database was 38 months. 7.5% of hemophilia cases were diagnosed with anxiety and 7.0% with depression compared with 7.8% and 5.8% respectively in controls. Among all hemophilia cases, irrespective of anxiety or depression diagnosis, 11% received anti-anxiety medications compared to 7% of all controls (OR = 1.7, 95% CI 1.4–2.1), and 14% received anti-depressant medications compared with 9.7% of controls (OR = 1.5, 95% CI 1.2–1.8). Hemophilia patients older than 30 years were twice as likely to have a diagnosis of depression, but equally as likely to receive anti-depressants compared to those 30 years or less.

Conclusions: Hemophilia A and B patients received diagnoses of anxiety and depression with similar frequency to controls. Anti-anxiety and anti-depressant medication use was more common in hemophilia patients than in controls. These diagnoses and medications were prevalent in < 15% of a young hemophilia population over an average 3 year time span, consistent with a recent report in children which utilized a psychiatric screening tool but lower than observed in a study in older patients.

788. Baclofen for Alcohol Dependence in France: Incidence of Treated Patients and Patterns of Prescribing

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Background: Recently, baclofen has been widely promoted in alcohol dependence in France.

Objectives: To estimate incidence of baclofen prescription for alcohol dependence in France from 2007 to 2011, and to describe patterns of prescribing and prescribers.

Methods: Design: Cohort study including all patients starting baclofen between 01/01/2007 and 31/12/2011 with at least a second dispensing in the next 120 days. Incident status was required (no reimbursement of baclofen 1 year before the inclusion). Setting: a representative sample of the French beneficiaries of the national health insurance scheme: the Échantillon Généraliste de Bénéficiaires EGB database. Exposures: Patients were classified in two groups: 'neurologic'

group defined as at least one of the following criteria: (1) health insurance coverage for chronic conditions: stroke, paraplegia, multiple sclerosis and serious central or medullary neurologic condition (2) other chronic conditions in which baclofen could be prescribed for spasticity (3) reimbursements of antispastic drugs (4) hospitalization for a neurologic condition. We assumed that all the remaining patients were treated for alcohol dependence, defining the 'alcohol' group. Main outcome measures: incidence.

Results: Among the 670 included patients, 241 were in the 'neurologic' group and 429 in the 'alcohol' group, giving an incidence increasing for the 'alcohol' group from 2007 (7/105 person-year) to 2011 (22/105 person-year). By contrast, this incidence remained stable for the 'neurologic' group (9/105 person-year in 2007 to 7/105 person-year in 2011). Demographic characteristics were similar (mean age 54 ± 18 years, 50.0% of men). Initial prescriber was a general practitioner for 347 patients (80.9%) in the 'alcohol' group vs. 201 patients (83.4%) in the 'neurologic' group (p = 0.045), a psychiatrist for 32 (7.5%) vs. 0 (0.0%) (p < 0.001), a neurologist for 17 (4.0%) vs. 26 (10.8%) (p < 0.001) and a gastroenterologist for 5 (1.2%) vs. 0 (0.0%) (p = 0.166).

Conclusions: Use of baclofen for alcohol dependence might be threefold in comparison with neurologic indication.

789. Background Rates of Anaphylaxis in General and Allergic Populations

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Background: Allergic rhinitis (AR) is the most common allergic disease. Allergen immunotherapy (AI) is the only available treatment that modifies the allergic process instead of just suppressing symptoms, but it is associated with rare anaphylaxis. Monitoring new therapies for anaphylaxis signals requires knowledge of population-specific background incidence, but few estimates are available.

Objectives: To estimate the incidence rate (IR) of anaphylaxis in general and allergic populations.

Methods: This retrospective cohort study used administrative claims data from the HealthCore Integrated Research Database[SM] for members age ≥ 5 years. Cohorts included (1) patients with neither AR nor AI

(non-allergic cohort), (2) AR patients unexposed to AI (AR cohort), and (3) AI patients with or without AR. We identified anaphylaxis based on a revision of the Harduar-Morano algorithms. The IR of anaphylaxis was defined as the number of events in the study population divided by person-years (PY) at-risk. Patients could contribute > 1 event.

Results: There were 6,717,911 non-allergic, 3,237,972 AR, and 352,219 AI patients in the study. The IR of anaphylaxis per 10,000 PY was 2.5 (95% CI: 2.4–2.6) for the non-allergic cohort and ranged from 13.8 (95% CI: 13.6–14.1, AR cohort) to 36.0 (95% CI: 34.8–37.2, AI cohort) in the allergic groups. There were 14,081 (0.1%) patients with ≥ 1 anaphylaxis event; 1,122 (8.0%) had multiple events. Emergency department or inpatient encounters accounted for 69.7% of events in the non-allergic cohort, but only 39.1% and 32.5% in the AR and AI cohorts, respectively. Of the 3,331 events in the AI cohort, 39.0% occurred on the same day as AI administration. Incidence of anaphylaxis was consistently higher for patients with a history of anaphylaxis or asthma in the baseline period.

Conclusions: The claims-based results suggest that anaphylaxis rates are higher among allergic patients, especially those receiving AI. However, the high proportion of events presenting in outpatient settings suggests that the reported rates may be overestimated. Validation of the Harduar-Morano algorithms based on medical records adjudication, now underway, will better inform our understanding of these findings.

790. Parkinson's Disease and Risk of Retinal Degeneration

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Background: The basic epidemiologic features of retinal degeneration (RD) in Parkinson's disease (PD) patients are poorly understood.

Objectives: To estimate the incidence rate and adjusted relative risk of RD in incident PD vs. non-PD patients. Also, to assess the role of potential risk factors in the development of RD in PD patients.

Methods: A retrospective, population-based database cohort study in incident PD patients (cohort entry date [CED] between July 1999 and June 2009) and a cohort of patients free of PD 1:1 matched for age, sex, CED, and practice was conducted using information from the Clinical Practice Research Datalink (CPRD) in the United Kingdom. Patients with < 3 years of registration prior to CED were excluded. Crude incidence rate (IR) of RD with its 95% confidence interval (CI) was

calculated assuming a Poisson distribution. Cox proportional hazards regression models were used to assess the Hazard Ratio (HR) of the associations, adjusting for potential confounders.

Results: There were 128 cases of RD among the 6,990 incident PD patients and 203 among the non-PD controls. The IR of RD per 1,000 person-years was 4.3 (95% CI = 3.6–5.1) in PD patients and 5.7 (95% CI = 5.0–6.5) in the non-PD cohort. IR increased with increasing age. The crude IR ratio of RD in PD patients compared to non-PD patients was 0.75 (95% CI = 0.59–0.94). PD patients treated with dopaminergics showed a decreased risk of developing RD (HR = 0.74, 95% CI = 0.58–0.94) compared to non-PD patients. Untreated PD was not associated with a decreased risk of RD (HR = 0.96, 95% CI = 0.63–1.46). In PD patients, untreated and treated diabetes were associated with a HR of developing RD (other than diabetic retinopathy and diabetic macular edema) of 2.27 (95% CI = 1.08–4.74) and 1.35 (95% CI = 0.74–2.46), respectively. On the other hand, hypertension was not significantly associated with a modified risk of RD in PD patients (HR = 1.15, 95% CI = 0.80–1.65). Both diabetes and hypertension were considered as time-dependent variables.

Conclusions: PD patients appeared to be at a lower risk of developing RD than the general population of the same age and sex. This decreased risk was mostly dependent on treatment with dopaminergics.

791. Incidence Rates of Pneumonia in Solid Tumor Cancer Patients in the UK

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Background: Pneumonia may be caused by various bacterial, viral, fungal, or other agents, and represents the leading infectious cause of death in cancer patients (pts). The Health Improvement Network (THIN) is a research database of electronic medical records entered by general practices in the UK, which provides large sample size and long follow-up.

Objectives: The primary objective was to estimate incidence rates of pneumonia among pts with solid malignant tumors compared to noncancer patients.

Methods: For this retrospective matched cohort study, incident solid tumor pts (excluding basal and squamous cell carcinoma) identified between January 1986 and March 2008 were matched 5:1 to non-cancer pts

with the same age, sex, general practice, and enrollment period. Pts with a diagnosis of solid tumor were followed from the first date of diagnosis of solid tumor through the first occurrence of pneumonia, death, or loss to follow-up. Matched cancer-free pts were followed from the date of solid tumor diagnosis of their matched cancer patient through the same endpoints as above.

Results: Among 122,815 incident solid tumor pts (representing 401,794 person-years) and 613,814 matched non-cancer pts (3.0 million person-years), we identified 3,292 and 13,524 pneumonia cases, respectively. Incidence rates of all-cause pneumonia per 10,000 person-years (95% confidence intervals) were thus 82 (79–85) and 46 (45–46), respectively (Incident Rate Ratio (IRR) = 1.8 [1.7–1.9]). Among solid tumor cancer pts, the incidence rate of bacterial and viral pneumonia was 9.3 (8.4–10.3) and 5.4 (5.1–5.6), respectively. The IRR for bacterial and viral pneumonia among cancer pts, relative to noncancer pts, was 1.7 (1.6–1.9) and 1.8 (1.3–2.5), respectively.

Conclusions: Results suggest that pts diagnosed with solid tumors are nearly twice as likely to develop pneumonia as non-cancer pts. As expected, the incidence of bacterial pneumonia is higher than that of viral pneumonia. Analysis of additional pts characteristics and cancer type will provide insight into the increased risk of pneumonia in this patient population.

792. Contextualization of Safety Endpoints in a Rheumatoid Arthritis (RA) Development Program: Collaboration with the Consortium of Rheumatology of North American Registry (CORRONA)

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Background: Epidemiologic data are needed throughout the product's life cycle to contextualize potential safety issues particularly when interpretation of adverse events (AEs) is not feasible within clinical trial data (i.e., insufficient statistical power, lack of active comparator, paucity of quality published data).

Objectives: To develop a standing cohort of patients with RA with similar characteristics (i.e., demographics and disease severity) to patients within the tofacitinib global Phase 2, Phase 3 and long-term extension RA studies.

Methods: Pfizer Inc., collaborated with the CORRONA registry to establish three unique cohorts of patients to query for safety contextualization: (1) all patients with RA, (2) patients with moderate-to-severe

RA (operationalized as ≥ 4 Joint Count and ACR functional class of I, II or II) and (3) patients with moderate-to-severe RA treated with methotrexate (MTX). The primary outcomes of interest included serious infections, malignancies and cardiovascular endpoints as reported by physicians. To calculate the rate of each safety event, the number of incident events was divided by the total person-years of observation within the eligible RA cohort. Within each cohort, age and gender specific rates were estimated.

Results: A total of 22,625 adult patients with RA with at least one followup visit were identified within the registry. When disease severity was considered the sample size was reduced to 9,739, approximately 70% of whom were treated with MTX. Overall, the background rate of safety events was higher among the cohort of patients with moderate-to-severe disease relative to the total RA population and among patients who were ≥ 65 years of age (vs. < 65).

Conclusions: Without contextualization, it is difficult to derive meaningful conclusions regarding the rate of AEs in sponsored trials. The results of this collaboration illustrated key risk factors for future feasibility assessments for post-marketing studies, and rapid regulatory query responses.

793. Sickle Cell Disease Prevalence in a Large US Administrative Claims Database

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Background: Given the absence of a reliable surveillance system, the true prevalence of sickle cell disease (SCD) in the United States remains unknown. Administrative claims data represent a potential resource for estimating SCD prevalence.

Objectives: The purpose of this study is to examine the feasibility of estimating SCD prevalence in the United States using a large, administrative claims database.

Methods: The Truven MarketScan® database (Commercial, Medicare, and Medicaid) was used to calculate the annual prevalence of SCD for each year between January 1, 2007 and December 31, 2011. To be eligible for this study, individuals must have had a minimum of 334 days of enrollment for the year of the calculation. Cases of SCD were identified as persons with one inpatient claim or two outpatient claims at least 30 days apart containing a diagnosis of SCD (ICD-9-CM codes 282.41, 282.42, or 282.6x). Because SCD is a chronic disease, individuals with a qualifying diagnosis of sickle cell disease were automatically iden-

tified as having SCD in each subsequent year of enrollment. Final prevalence estimates were expressed per 100,000.

Results: Prevalence of sickle cell disease increased during the study period from 34.76 in 2007 to 38.64 in 2011. For each year of the study, prevalence of the disease was greater in females relative to males. The highest prevalence of SCD was observed among the Medicaid population (184.62 in 2007 to 227.08 in 2011).

Conclusions: The prevalence of SCD observed in this study was comparable to the unadjusted prevalences derived from studies using birth cohort data, and is slightly higher compared to estimates adjusted for early mortality. Insurance claims data represent a potential alternative resource for estimating the prevalence of sickle cell disease in the United States.

794. Statin Therapy is Associated with Decreased Risk of First Intracerebral Hemorrhage and Reduced 30-Day Fatality: Results of a Nationwide Observational Study Including 7,696 Cases and 14,670 Controls

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Background: Statin therapy prevents vascular events, but an increased risk of intracerebral hemorrhage (ICH) has been reported.

Objectives: We assessed the hypothesis that statin therapy was associated with increased risk of ICH and increased mortality after ICH.

Methods: Using data from comprehensive national registers in 2006–2009, we identified 7,696 cases with first-event ICH in the Swedish Stroke Register and 14,670 sex- and age-matched stroke-free controls in the Swedish Population Register. Drug therapy at the time of ICH was identified through the Swedish Drug Prescription Register. The risk of ICH with statins was estimated using conditional logistic regression, adjusted for explanatory factors, such as hypertension, diabetes, and use of antithrombotic therapy. We investigated the association between statins and 30-day mortality among the 7,696 ICH-cases using logistic regression analyses, adjusted for age and sex in addition to the other explanatory factors.

Results: Statins were used by 1,276 (16.6%) of the ICH-cases and by 2,552 (17.4%) of the controls. The crude and adjusted odds ratios (OR) of ICH with statins were 0.94 (95% CI, 0.87–1.02) and 0.70 (95% CI,

0.64–0.76), respectively. The 1,276 ICH-cases with statins at stroke onset were 2 years older, more often men and had more risk factors for stroke than the 6,420 ICH-cases without stroke therapy. In the crude model, statins were not associated with decreased risk of 30-day mortality (1.13; 95% CI, 0.99–1.29). But in the adjusted model, statins were associated with reduced likelihood of death at 30 days (OR 0.80; 95% CI 0.69–0.94).

Conclusions: This nationwide study demonstrates an association between statin therapy and decreased risk of ICH and short-term mortality. Given the widespread use of statin therapy in prevention of coronary heart disease, these findings are reassuring even though randomized trials of statin therapy in secondary stroke prevention still is required.

795. Demographics of the Patient Population Recruited into the Febuxostat vs. Allopurinol Streamlined Trial (FAST)

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Background: Gout is one of the most common inflammatory joint diseases and incidence is rising worldwide. Gout has traditionally been thought of as affecting older males but incidence in women and younger patients is rising. Patients with gout are known to have increased cardiovascular risk. The Febuxostat vs. Allopurinol Streamlined Trial (FAST) is evaluating the long term cardiovascular safety of febuxostat compared with allopurinol in patients with gout.

Objectives: To report patient demographics for the first 400 patients randomised into FAST.

Methods: Patients in Scotland, England and Denmark are identified through a search of their primary care provider's patient database. Patients over the age of 60 who have a diagnosis of gout for which they are prescribed allopurinol and who have at least one additional cardiovascular risk factor are eligible for inclusion. Before randomisation all patients have their urate control with allopurinol optimised aiming for serum urate levels < 357 μmol/L.

Results: Of the first 400 patients randomised into FAST, 25% are in Denmark, 19% in England and 56% in Scotland. Eighty-five percent of patients are male. Median age is 69 years [IQR 65–75]. Median BMI is 31 [IQR 28–34]. Eight percent are current smokers, 61% are former smokers, 76% consume alcohol on a regular basis (median 14 units per week [IQR 7–28]), 81% are hypertensive, 68% have a history of raised cholesterol, 26% are diabetic, 25% have a history of ischaemic heart disease, 16% have renal impairment and 6% have a history of stroke. Mean baseline urate level was 335 μmol/L (SD 78.6). Sixty-four percent of patients had urate levels < 357 μmol/L at baseline. Median dose of allopurinol at screening was 300 mg daily [IQR 100–300] with maximum prescribed dose of 600 mg daily.

Conclusions: Patients enrolled in FAST are predominantly male and obese with significant additional cardiovascular risk factors. Urate lowering therapy was sub-optimal in around one third of patients. This patient cohort is known to be at high risk of cardiovascular events therefore firmly establishing the cardiovascular safety of urate lowering therapies is paramount in long term management of these patients.

796. Prevalence of Treated Gout in Scotland, England and Denmark and Summary of Recruitment into the Febuxostat vs. Allopurinol Streamlined Trial (FAST)

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Background: Prevalence of gout is increasing worldwide and in the UK is estimated to be 1.4% in the general population rising to 6% in the over 65 age group. Around a third of gout patients in the UK receive urate lowering therapy, most commonly in the form of allopurinol. FAST is a clinical trial evaluating the long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with gout. Patients are recruited into FAST from primary care giving an opportunity to examine the epidemiology of this common condition.

Objectives: To assess prevalence of treated gout in the over 60 age group in Scotland, England and Denmark and to review the recruitment of this population into FAST.

Methods: Patients are identified through a search of their primary care provider's patient database. Patients eligible for inclusion are over the age of 60, have a diagnosis of gout for which they are prescribed allopurinol and at least one additional cardiovascular risk factor. If there are no contra-indications, suitable

patients are invited for a screening visit. Data is presented by region referring to Scotland, England and Denmark respectively.

Results: A total of 178 GP practices have been searched to date (74, 39 and 65) and full data is available for 731,872 patients (367,217, 264,309 and 100,346). Patients meeting the baseline inclusion criteria (> 60 years, prescribed allopurinol for gout and one additional CV risk factor) comprised 0.59%, 0.41% and 0.52% respectively of the total practice population. For the over 60 population 2.7% in Scotland and 2% in England met the inclusion criteria. For recruitment into FAST, of those meeting the baseline criteria 12.7%, 18.0% and 20.8% agreed to attend for screening and of those screened 68.2%, 38.1% and 56.5% were finally randomised into the trial.

Conclusions: Recruitment into the FAST study has shown that prevalence of treated gout in the over 60 age group is broadly in line with known epidemiological surveys in the UK and Denmark. Recruiting into clinical trials remains difficult with poor uptake from eligible patients.

797. Healthcare Utilization and Treatment Patterns for Patients (pts) with Gastric Cancer (GC) in China

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Background: GC is the third most common cancer in China with approximately 0.3 million deaths and 0.4 million new cases annually.

Objectives: To describe treatment patterns and survival for GC pts, and to assess treatment outcomes and associated factors including health insurance coverage, gastric-intestinal disease, clinical comorbidities and family genetic or demographic factors.

Methods: A retrospective cohort study was conducted. Primary data sources were medical records collected from multiple major Shanghai medical centers with timeframe of January 2004–March 2010. Treatment outcomes included 'improvement' and 'recovery or cure' (as documented in the pts' record), and death. Classical logistic regression and COX proportional hazard regression analysis were performed to assess the relationship between health outcomes and associated factors.

Results: A total of 2,249 GC pts were identified with mean age 65.9% and 36% female. Average follow-up was 26.3 months since GC index date (1st GC diagnosis date). During the study period, 518 (23%) pts died. GC treatments included surgical procedure (28%), radiation (2%), chemotherapy (14%), and traditional Chinese medicine/herbal regimens (21%). Major chemotherapy included 5-FU, cisplatin, etoposide, leucovorin, mitomycin, oxaliplatin, and semustine. From multivariable models, pts more likely to achieve recovery or cure were those who received surgical procedures (OR = 15.0, 95% CI 11.3–19.9), radiation (OR = 2.4, 95% CI 1.2–4.9), any chemotherapy (OR = 2.7, 95% CI 1.9–3.9), and were covered by public health insurance (OR = 3.5, 95% CI 2.3–5.3) or collaborative insurance (OR = 3.5, 95% CI 2.1–5.8). Higher risk of mortality was significantly associated with key factors like advanced age (OR = 1.0, 95% CI 1.0–1.0), late-stage cancer (OR = 9.8, 95% CI 5.1–19.0), and liver disease (OR = 1.9, 95% CI 1.4–2.6). A lower risk of mortality was associated with surgical procedure treatment (OR = 0.6, 95% CI 0.5–0.7) and chemotherapy (OR = 0.6, 95% CI 0.4–0.9).

Conclusions: Multiple treatment regimens for GC are available in China. Surgical procedure, chemotherapy, TCM/herbal, and health insurance coverage are associated with positive treatment outcome and survival duration.

798. Risk of Seizures Among Patients with Schizophrenia as Compared to the General Population in the Clinical Practice Research Datalink (CPRD)

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Background: The risk of seizures is not well characterized in patients with schizophrenia, furthermore it is not clear how this risk relates to antipsychotic use.

Objectives: To estimate the risk of seizures in patients with schizophrenia in the Clinical Practice Research Datalink (CPRD) relative to the general population. To estimate the risk of seizures in patients with schizophrenia treated with antipsychotics relative to untreated patients.

Methods: A cohort study was conducted using available CPRD data up to July 2012 and included patients with a diagnosis of schizophrenia (treated and untreated with antipsychotics). The outcome of interest was an incident seizure event on or after the diagnosis of schizophrenia. The schizophrenia cohort was matched 1:3 on age and sex to a reference general population cohort. Baseline characteristics were calculated

for each cohort. Adjusted hazard ratios (HRs) along with 95% confidence intervals (95% CI) were estimated.

Results: Of 30,759 patients were identified in the schizophrenia cohort. The HR for seizures in the schizophrenia cohort relative to the general population was 1.45 (95% CI = 1.27–1.67) after controlling for baseline, current medications and comorbidities. The HR for seizures among patients not treated with antipsychotics relative to those treated with antipsychotics was 1.78 (95% CI = 1.44–2.19).

Conclusions: These results suggest that there is an increased risk of seizures among patients with schizophrenia relative to the general population. Additionally, there is an increased risk of seizures among patients not treated with antipsychotics relative to those treated with antipsychotics. These results suggest a potential association between the underlying disease of schizophrenia and the risk of seizures.

799. CARING: Does Subgroup Analysis by Gender Modify the Potential Association Between Diabetes Mellitus and Cancer? A Meta-Analysis

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Background: As part of the CARING project a systematic review and a meta-analysis on the association between cancer and diabetes mellitus (DM) was conducted.

Objectives: To examine if male or female gender influence the association between DM and cancer.

Methods: A systematic review and meta-analysis was performed according to the PRISMA guidelines. The systematic literature search included Pubmed, Embase, Cinahl, Bibliotek.dk, Cochrane library, Web of Science and Svemed+ with the search terms: 'Diabetes mellitus', 'Neoplasms', 'Prospective study' and 'Risk of cancer'. Odds ratios, relative risks, risk ratios, hazard ratios, prevalence ratios, incidence ratios and standardized incidence ratios were used in the pooled analysis. Statistical analysis was performed using random effects

models if appropriate and direct comparison of estimates.

Results: A total 1,785 records were screened by title and abstract and 253 records were assessed by full text for inclusion, of which 195 records fulfilled the criteria for the meta-analysis. Subgroup analyses were performed by gender. Significant increased risk of cancer at all sites was observed for females (RR = 1.18, 95% CI [1.11–1.27], 11 records), but not for males (RR = 1.10 [0.82–1.47], 12 records). Overall an increased risk of colon, liver, pancreas and kidney cancers appeared in both genders. Although there appear to be differences in the relative risk for esophagus (male: RR = 1.15 [0.74–1.79], female: RR = 1.59 [0.51–4.89]) and kidney cancer (male: RR = 1.31 [1.05–1.63], female: RR = 1.8 [1.59–2.03]) between sexes, only kidney cancer reached statistical significance (p = 0.01).

Conclusions: The risk of cancer in diabetes seems not to be modified by gender. Seemingly, women with diabetes have an increased risk of cancer at all sites, which is not apparent among males. The risk of cancer at some specific sites is increased in diabetics, but male and female estimates do not differ significantly. The increased overall risk among females may be due to gender specific cancers such as breast, endometrial and ovary cancer.

800. CARING: Diabetes Mellitus and Risk of Cancer – A Systematic Review and Meta-Analysis

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Background: Patients suffering from diabetes mellitus (DM) may experience an increased risk of cancer, but results are conflicting.

Objectives: To examine the association between DM and cancer by a meta-analysis.

Methods: A systematic review and meta-analysis was performed according to the PRISMA guidelines. The systematic literature search included Pubmed, Embase, Cinahl, Bibliotek.dk, Cochrane library, Web of Science

and Svemed+ with the search terms: 'Diabetes mellitus', 'Neoplasms', 'Prospective study' and 'Risk of cancer'. Odds ratios, relative risks, risk ratios, hazard ratios, prevalence ratios, incidence ratios and standardized incidence ratios were used in the pooled analysis. Statistical analysis was performed using random effects models.

Results: A total of 1,785 records were screened by title and abstract and 253 records were subsequently assessed by full text, of which 195 records fulfilled the criteria for the systematic review. The cancer types studied showed significant heterogeneity across studies by Chi-square-test. Compared to non-diabetic controls, DM patients had an increased risk of any cancer (RR = 1.14, 95% CI [1.01–1.28], 26 records). Diabetics seemed especially at risk of liver (RR = 2.27, [1.86–2.78], 47 records), pancreas (RR = 2.21 [1.86–2.62], 47 records) and endometrial cancer (RR = 1.9, [1.67–2.16], 24 records), although an increased risk was also seen for biliary tract, stomach, colon, rectum, kidney, bladder, breast and thyroid gland cancer. In contrast, DM patients appeared to experience a decreased risk for prostate cancer (RR = 0.87 [0.81–0.93], 44 records).

Conclusions: DM patients were at higher risk of cancer than non-diabetics, especially digestive tract cancers and hormone/related cancers (breast, endometrial). However, an apparent protective effect against prostate cancer was present. The observed effects could be due to confounding by factors not adequately adjusted for in the studies like obesity.

801. Burden of Human Respiratory Syncytial Virus (RSV) Infection

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Background: Human RSV causes upper and lower respiratory tract infections (URTI/LRTI) among people of all ages. It is the most common cause of LRTI in children.

Objectives: To review the age-specific incidence of RSV infection and associated hospitalization rates in healthy adults and children.

Methods: A systematic search was conducted in PubMed and relevant websites to identify RSV incidence and hospitalization literature published between 1992 and 2012 in English, French, Spanish, Italian, and German. The most relevant global studies, particularly ones from the US and Europe were identified and their bibliographies screened. Only population-based and prospective cohort studies linked to census or population data were selected.

Results: Of 1,773 publications identified, 68 studies were included. Data on RSV incidence among healthy subjects was limited (n = 5 studies for adults; 10 for children). In adults, RSV was detected in 4–18% of healthy individuals tested (US, UK). Older age and co-morbidities increased the risk of RSV infection. In the pediatric population, RSV incidence was highest among infants < 1 year compared to older children (43,500–86,900 vs. 11,000–22,650/100,000 children < 5 years; Australia). RSV infection peaked in winter except for tropical regions where peak incidence was reported between the summer and early fall. RSV hospitalization data was found in six and 33 studies for adults and children, respectively. In the adult population, RSV accounted for 6.1% of all hospital admissions due to acute respiratory illnesses (URTI/LRTI rate: 10–110/100,000; US, UK, Canada). In children < 1 year, RSV accounted for 8.2% of all respiratory admissions (URTI/LRTI rate: 638–1,290/100,000; Spain, US). The annual rate of acute RSV-associated LRTI admissions was 4,500–19,136/100,000 in this age group. These rates were highest among newborns and decreased with age (19,136/100,000 babies ≤ 5 months vs. 188/100,000 children < 5 years).

Conclusions: RSV is a common respiratory infection associated with significant morbidity in both children and adults. Understanding the incidence and associated resource use is fundamental to research investments in vaccine development.

802. Out-of-Pocket Prescription Drug Expenditures Among the Korean Elderly: Who is Vulnerable to Cost Burden?

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Background: In Asia, most elderly people lived with their children in the past, but nowadays substantial proportion of them lived alone. The lack of social security combined with the change in living arrangement may result in less medical treatment for the elderly. Out-of-Pocket (OOP) payments for prescription drugs are important for chronic disease for elderly people.

Objectives: The study aimed to investigate the association between living arrangement and the presence of

chronic disease and the impact of living arrangement for OOP payments for prescription drugs in the elderly.

Methods: The data obtained from the 2008 Korea-Health-Panel-Survey (KHPS) data. Chronic diseases diagnosed by doctor were self-reported by respondents. The annual OOP payments for prescription drugs expenses were defined as total amount paid per person during 1 year in 2008. Living arrangement was divided into living alone, only with spouse, and living with adults. The logistic regression was used to investigate the chronic disease and living arrangement. Relationship of living arrangement to OOP payments for prescription drugs was analyzed using a generalized linear model with a log link function and gamma distribution.

Results: A total of 2,342 elderly participated in our study. The percentage of elderly people lived alone, with a spouse only, and lived with adults were 14.5%, 48.3%, and 37.2%, respectively. Living alone elderly people had 2.75 OR (95% CI = 1.70–4.43) for having chronic diseases when compared with elderly people lived with adults after adjustments. The elderly lived alone had trends of having less OOP payments for prescription drugs (Cost Ratio = 0.82, 95% CI = 0.70–0.97).

Conclusions: The elderly lived alone have higher probability of having chronic disease but, they spent less on OOP payments for prescription drug. Appropriate prescription drug use is important for elderly persons with chronic disease not only for health outcome but also for quality of life. Further study should be needed to explain the mechanism why living arrangement affected the presence of chronic disease and OOP payments for prescription drugs.

803. Long-Term Follow Up of Concomitant Medication Use in Type 2 Diabetes Patients: A Cohort Study

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Background: Concomitant disease and associated drug use is frequent in patients with type 2 diabetes mellitus. However, data on longitudinal changes in the prevalence of co-medication in such patients is limited.

Objectives: To assess changes in the prevalence of concomitant medication use in patients with type 2 diabetes before and after initiation with oral antidiabetic agents (OAD).

Methods: A cohort study was performed among new users of OAD aged ≥ 35 years, who were enrolled in the Diabetes Care System (DCS) in the Dutch region of West-Friesland (200,000 inhabitants). Patients receiving care from the DCS were linked to drug dispensing data obtained from 15 community pharmacies and two dispensing general practices in the region. The study period was between 1998 and 2007. The prevalence of medication use was assessed up to 10 years before and after initiation of OAD. Drugs evaluated included cardiovascular (CV) drugs and statins, but also included a range of non-CV drugs like antidepressants, antipsychotics, benzodiazepines, antibiotics, NSAIDs, respiratory medication and proton pump inhibitors.

Results: We identified 2,933 incident users of OAD (51.9% men, mean age 61 years). The prevalence of drug use gradually increased with time for nearly any type of medication. However, the initiation of OAD triggered a shift in the prevalence of CV drug use. In the year prior to initiation, 58.7% of the patients used CV drugs, which increased to 73.9% in the first year after. Renin angiotensin aldosterone system inhibitors and statins attributed most to this increase. Also, the proportion of patients using more than one CV drug increased steadily over time. Stratification according to age and sex showed similar patterns with this shift being more pronounced in younger patients and men. The prevalence of non-CV medication use increased steadily, mostly due to a rise in the use of antibiotics, drugs for gastroesophageal reflux disease and eye medication.

Conclusions: The increase in concomitant medication use in patients with type 2 diabetes was mostly attributable to an increase of cardiovascular medication according to guidelines aimed at prevention of cardiovascular disease.

804. Case-Mix in General Practice in Italy: Score Development and Validation

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Background: General Practitioners are traditionally funded by the healthcare authorities on the bases of

mean age and gender of their patients. Potential differences in case-mix (i.e., combination of morbidities in individual patients) are not adequately taken into account.

Objectives: To develop and validate the Italian Health Search Morbidity index (HSM-index) with which to adjust the absorption of healthcare costs for comorbidity burden. Thus, case-mix-adjusted comparisons among expenditures of regional healthcare authorities might be carried out.

Methods: We used a cohort of 879,471 individuals (447,204 and 432,267 formed the development and the validation sample, respectively) belonging to Health Search Database – CSD (HSD), between January, 1, 2008 and December, 31, 2010. The response variable was the total costs (transformed on the logarithmic scale) which comprised drug prescriptions, specialists' visits, laboratory tests, and other diagnostic procedures. In addition to age and gender, each covariate (i.e., concurrent disease) was retained in a multi-level model with random intercept (patients and local health authorities were the levels) whether it was statistically significantly ($p < 0.05$) associated to increased or decreased costs. The estimated coefficients were summed up to create the HSM-index for individual patients, and categorized in deciles. The score was therefore implemented in a regression linear model to compute its explained variance (R2) in terms of cost estimation. Costs were compared among Italian regions by adjusting for the national HSM-index.

Results: The distribution of HSM-index was skewed with a median of 4.99 (maximum value: 11.56; minimum value 2.95). The average yearly cost per patient was € 407.90. The index explained 48.6% of the variability for the overall patient-related costs which varied ± 11% in relation to crude costs, when Italian regions were compared each other by adjusting for case-mix.

Conclusions: The HSM-index is an effective tool to adjust the patients-related costs for their case-mix.

805. An Efficient Way To Estimate Disease Prevalence Rates by Extrapolation of Data from Several Small Studies

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Background: For decades, Russian healthcare statistics were focused at efficient reporting on infectious diseases and major severe conditions (e.g. stroke), while the accuracy of reporting on many chronic conditions (such as diabetes or COPD), and less 'socially important' conditions (e.g. headache or allergic rhinitis) left much to

desire. Sometimes diagnostic criteria differed significantly across various regions, resulting in a lack of comparability (e.g. multiple sclerosis prevalence rates across the regions [Boyko AN, et al, 2008]). One of approaches to obtain more accurate estimation of disease prevalence in Russia is extrapolation of the data of smaller studies in several regions, paying attention to possible confounding factors, such as gender, age, etc.

Objectives: To derive prevalence rates for certain conditions from several local Russian studies and compare obtained estimates to official Russian statistics and the data reported in a large cross-sectional survey.

Methods: The selected conditions were depression (Akarachkova ES., Vershinina SV., 2010), insomnia and restless legs syndrome (Romanova et al., 2007), and allergic rhinitis (Emelyanov et al., 2002). The local studies were conducted on population from 299 to 4,224 patients, representing large cities in the European part of Russia. The cross-sectional survey (National Health and Wellness Survey, NHWS) was conducted by Kantar Health in Russia in 2011 on 10,039 adults living in urban areas.

Results: For most conditions absolute differences of prevalence rates in gender subgroups across local studies and NHWS data did not exceed ± 2% (Vietri J et al, 2012). Only depression prevalence in men and overall prevalence of allergic rhinitis according to NHWS were higher than it was reported in local studies: by 7% and 5.1% respectively. Officially reported prevalence rates were available for some conditions, they turned out to be several times lower than the data derived from both local studies and NHWS.

Conclusions: When official health statistics are not available or considered to be inaccurate, extrapolating data from several smaller studies may be efficient for conditions where such studies are available.

806. Rheumatoid Arthritis (RA) in Quebec: Baseline Demographics, Co-Morbidity and Physician Use in an Incident Sample of Provincial Drug Plan Beneficiaries

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Background: RA is a chronic condition that involves long-term drug therapy. Accordingly, many studies attempt to assess the comparative effectiveness or safety of alternative treatments in RA. To properly interpret pharmacoepidemiological analyses in this

population, we require a good understanding of baseline demographics, co-morbidity and health care use.

Objectives: To describe baseline characteristics of incident RA cases, who are insured by public (RAMQ) drug insurance in Quebec, in 2002–2008.

Methods: We used physician billing data to ascertain potential RA cases, based on at least one ICD9 code 714. We considered 'confirmed' RA cases as those with a rheumatology billing code diagnosis or those with > 2 physician visits coding for RA. We excluded subjects with evidence (multiple billing diagnoses) for systemic lupus, myositis, scleroderma, Sjogrens, or ankylosing spondylitis. To define incident RA, we excluded subjects with RA billing diagnoses prior (i.e. 1989–2001). We restricted our analysis to Quebec residents covered by the public drug plan and aged 65+. We present descriptive statistics, of demographics variables, Charlson co-morbidity scores, and physician use.

Results: Applying our criteria, we identified 20,033 new RA cases across 2002–2008. Most RA cases (65.6%) were female, from urban areas (79.9%) and the mean age was 74.6 years (SD = 6.5). Among these incident RA patients, 16.7% were heavy users of health care (> 20 physician visits in 1 year), and the mean Charlson co-morbidity score was 1.6, SD = 2.1. Females were more likely than males to be heavy users of health care but Charlson co-morbidity score was higher in men than in women.

Conclusions: Among new-onset RA cases covered by the Quebec public drug plan, many have evidence of co-morbidity, and a significant percent are heavy users of health care, even at this early stage. Since these factors are often correlated with drug use, and long-term adverse outcomes of potential interest, they should be carefully considered in all pharmacoepidemiological analyses in RA.

807. Multiple Sclerosis Subtypes and Infections Resulting in a Hospitalization in the Veterans Health Administration

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Background: Infections can lead to relapse or exacerbation of symptoms in patients with multiple sclerosis (MS), an autoimmune inflammatory demyelinating disease of the central nervous system.

Objectives: This study is the first to evaluate the association between MS subtypes and the risk of infection.

Methods: We identified patients with an MS diagnosis who sought care in the US Veterans Health Administration (VHA) system from 1999 to 2010. Each MS patient was matched to four non-MS patients on age and sex. MS subtype was identified from narrative clinic notes using natural language processing. Cox Proportional Hazards regression models were developed to assess the influence of MS subtypes on serious infections (an infection listed as an admitting diagnosis in VHA inpatient records) according to relevant ICD-9 codes. These multivariable regression models controlled for demographic characteristics, comorbid conditions, drug exposures, disability status, and healthcare utilization.

Results: Our analysis cohort included 7,743 MS and 30,972 non-MS patients. Mean (SD) age was 53.8 (13.4) years and 80.7% were male. Of the 2,728 (35.2%) MS patients with an identified MS subtype, relapsing remitting (n = 1,815, 23.4%), progressive (including primary and secondary progressive) (n = 886, 11.4%), and progressive relapsing (n = 27, 0.3%) were the most common. Compared to non-MS patients, regression models revealed a higher risk of serious infection in MS patients with progressive (HR = 3.06, 95% CI = 2.56–3.65), progressive relapsing (HR = 3.79, 95% CI = 1.22–11.78), and unknown (HR = 1.37, 95% CI = 1.21–1.56), but not for relapsing remitting (HR = 0.77, 95% CI = 0.57–1.04) subtype. In addition, an elevated risk of serious respiratory (HR = 2.34, 95% CI = 1.64–3.34), urinary tract (HR = 9.21, 95% CI = 6.82–12.43), skin and soft tissue (HR = 6.39, 95% CI = 1.37–29.78), and sepsis (HR = 7.37, 95% CI = 4.01–13.53) infections was seen in progressive MS patients.

Conclusions: VHA MS patients with progressive, progressive relapsing, and unknown subtype are more likely than non-MS patients to be hospitalized due to infection. Future work should identify strategies for reducing these costly complications.

808. Exacerbation Recurrence Rates in Patients with Moderate to Very Severe COPD in the Netherlands: A Real-Life Study

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Background: Chronic obstructive pulmonary disease (COPD) and acute exacerbations of COPD (AE-COPD) are both important public health problems. Rates of (severe) AECOPDs are well studied, but less is known about the rate of severe infective AECOPDs.

Objectives: To compare rates of different types of AE-COPDs including infective ones among patients with different severities of COPD.

Methods: Data for this study was obtained from the PHARMO Database Network, which includes drug dispensing records from pharmacies, hospitalization records and detailed information from general practitioners. Patients with moderate to very severe COPD (GOLD II-III-IV) and a moderate or severe AECOPD between 2000 and 2010 were included in the study. Moderate and severe AECOPDs were defined by drug use and respiratory hospitalizations respectively. Presence of an infectious agent in severe AECOPDs was based on discharge diagnoses. Patients were followed from the first AECOPD to end of registration in PHARMO, death, or end of study period, whichever occurred first. During follow-up, all recurrent AE-COPDs were counted and characterized. Recurrence rates were compared between patient groups (GOLD III vs. GOLD II and GOLD IV vs. GOLD III) using negative binominal regression, because of overdispersion, and adjusting for confounders.

Results: Of 886 patients in the study, 52% had GOLD II, 34% GOLD III and 14% GOLD IV. The overall AECOPD recurrence rate per person year increased from 0.6 for patients with GOLD II to 1.1 for patients with GOLD III and 1.3 for patients with GOLD IV. The rate of severe AECOPD was 0.06, 0.14 and 0.17 for patients with GOLD II, GOLD III and GOLD IV, respectively. For severe infective AECOPDs, the rate was 0.05, 0.11 and 0.11, respectively. The difference in overall recurrence rate between patients with GOLD III and patients with GOLD II was significant (adjusted rate ratio 1.77, 95% CI 1.45–2.17). These patients were also more likely to have moderate, severe and severe infective AECOPDs than patients with GOLD II.

Conclusions: AECOPD recurrence rates are nearly two times higher among patients with severe and very severe COPD compared to patients with moderate COPD.

809. Incidence of Colorectal Cancer in Association with Diagnosed Hypertension

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Background: There is limited evidence that hypertension (HTN) is associated with an increased risk of colorectal cancer (CRC). The CRC risk has been shown though to be higher in overweight/obese persons and in individuals with type 2 diabetes mellitus (T2DM).

Objectives: To assess incidence and risk of CRC in HTN vs. non-HTN patients and the combined effect of HTN with T2DM and body mass index.

Methods: Retrospective cohort study in the UK Clinical Practice Research Datalink (CPRD) in patients with incident HTN (cohort entry date [CED] between January 1994 and June 2010) aged 18–79 years. A comparison group without diagnosed HTN was 1:1 matched for age, sex, practice, CED, and years of history in the CPRD prior to CED. Patients with a history of cancer, HIV/AIDS, anti-retroviral drug prescriptions, alcoholism, < 3 years of medical history prior to CED and/or with a CRC diagnosis within the 1st year of follow-up were excluded. Patients were followed from CED until a recorded CRC, death, age 80 years, occurrence of an exclusion criterion, medical record ended, or end of study period. Crude CRC incidence rates (IRs) and 95% confidence intervals (CIs) were calculated. Hazard ratios (HRs) were estimated using Cox regression models adjusted for potential confounders.

Results: Among 288,045 patients each in the HTN and the non-HTN group, 2,509 were newly diagnosed with CRC. IRs per 100,000 person-years were 83 (95% CI

79–88) for HTN, and 113 (107–119) for non-HTN patients. IRs increased with increasing age, were higher in males than females, and highest in T2DM and overweight/obese patients. IRs were higher in patients with T2DM than without. HR of CRC for HTN compared to non-HTN patients was 0.7 (0.7–0.8). Overweight/obese HTN patients with T2DM had a HR of 1.1 (0.9–1.4), overweight/obese non-HTN patients with T2DM had a HR of 1.5 (1.1–2.0), both compared to normal weight, non-HTN patients without T2DM. In HTN patients, the HR for overweight/obese with T2DM vs. normal weight patients without T2DM was 1.7 (1.3–2.1).

Conclusions: The study provides evidence that the CRC risk for HTN patients was not higher than for non-HTN patients. The effects of obesity and/or T2DM on CRC risk seem to be stronger than the effect of HTN.

810. Incidence of Food-Induced Anaphylaxis; a Retrospective Population Cohort Study in the UK Clinical Practice Research Datalink (CPRD)

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Background: Specific information on epidemiology of food-induced anaphylaxis (FIA) and recurrent FIA (RFIA) is limited in the literature, although is the most common cause of anaphylaxis in children and the third cause of anaphylaxis in adults.

Objectives: To estimate incidence rates of 1st FIA and RFIA in children and adults in a general population from the UK.

Methods: A retrospective population cohort study was conducted using data from the UK Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) linkage. All patients eligible for HES from 1st April 1997 through 31st October 2011, and with at least 6 months of medical history prior to the cohort entry date (CED) were included. Patients with a record of anaphylactic shock of any cause prior to CED were excluded. The cohort was followed-up from CED until 1st FIA or end of registration. The subgroup of 1st FIA patients was followed-up from 1st FIA until RFIA or end of registration. Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated for 1st FIA and RFIA.

Results: Among 5,228,013 eligible patients, 753 had a 1st FIA, 381 were adults and 502 were children. The cumulative incidence (CumI) was 14.4 per 100,000 persons and the IR (95% CI) was 2.3 (2.2, 2.5) per 100,000 person-years (PY) overall, 1.6 in adults and in children IR was 6.6 in younger than 6 years and 2.9 in other ages. Among patients with a 1st FIA episode, 144 had a RFIA, representing a CumI of 19.12% and an IR of 3.3 (2.8–4.0) per 100 PY. In adults the IR of RFIA was 3.2 and in children the IR was 4.7 in younger than 6 and 2.0 in other ages. There were 87 cases of first peanut-induced anaphylaxis (PIA) and the IR was 0.27 (0.22, 0.33) per 100,000 PY, being 0.14 in adults, 0.43 in children aged 6–17 years and 0.92 in younger than 6 years. Overall IR of recurrece of PIA was 7.6 (5.2–11.2) per 100 PY, 8.7 in adults, 9.3 in children 6–17 years old and 5.1 in children younger than 6 years.

Conclusions: The incidence of both 1st FIA and RFIA reported in this study was similar to the those reported in the literature. The highest incidence rates of 1st FIA, RFIA were found among patients 5 years old or younger.

811. Trends in Incidence Rates (IR) of Hip/Femur Fractures in Five European Countries: A Comparison Using Electronic Health Care Records (e-HCR)

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Background: Hip fractures represent a major public health challenge in developed countries and Europe holds an important share of this disease worldwide. Although there are many studies, direct cross-national comparisons using a common methodology are scarce.

Objectives: We aimed to estimate the IR of hip/femur fractures across five European countries using e-HCR databases (DB) and comparing IR and trends from 2003 to 2009.

Methods: A descriptive study on the incidence of hip/femur fractures was performed within seven DB from Denmark (national prescription registry), the Netherlands (Mondriaan AHC, NPCRD), Germany (Bavarian Claims), Spain (BIFAP) and the UK (THIN, CPRD), based on the same protocol. Yearly IR of hip/femur fractures were calculated for the general population and for those aged ≥ 50 years. Trends over time were evaluated using linear regression analysis for both crude and standardized IR, and annual change was expressed as a percentage using the first year as reference.

Results: Sex and age standardized IR were similar for the UK, the NL and Spanish DBs over the study period, ranging from 7 to 10 per 10,000 person-years for the general population and 15–25 for those aged ≥ 50 years; the German Bavarian Claims DB showed slightly higher IR (about 13 and 30), whereas the Danish DB yielded IR twofold higher (19 and 50, correspondingly). IR increased exponentially with age in both sexes, and the IR ratio female:male was ≥ 2 for patients aged ≥ 70–79 years in most DBs. Statistically significant trends in the standardized IR over time were only shown for the CPRD (UK) (+0.9% per year; $p < 0.01$) and the Danish DB (-1.4% per year; $p < 0.01$) for the general population.

Conclusions: Standardized IR of hip/femur fractures were similar in most countries and remained stable over the study period. Denmark presented the highest IR and showed a consistent, though moderate, decline over time. Despite efforts made to prevent this condition, we have not observed a general decline in Europe.

812. Patient Preferences for Antihypertensive Medications in General Practice

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Background: Hypertension is a public health problem in Mexico City. More than 17 million people older than 35 years of age are at risk of hypertension, 65% did not know their diagnosis and only one third of patients take their medications as directed.

Objectives: To determine patient preferences for antihypertensive medications in General Practice.

Methods: A cross-sectional study using General Practices was designed. Adult consecutive patients with diagnosis of hypertension and users of at least one antihypertensive medication were included. The study was approved by the Ethics Committee of the Institution. Each patient filled out a questionnaire and data were captured by an independent assistant.

Results: There were 200 hypertensive patients with mean age of 54.5 ± 10 years, 72% were married and had an average income of < 400 dollars per month. The mean systolic and diastolic blood pressure was 136 ± 4.6 and 94 ± 4.9 mmHg, respectively. All patients had medical insurance and their medications were free. Seventy-two percent of patients were satisfied with the nursing services and 83% with medical care. A third of patients believed that hypertension was curable, 40% measured their blood pressure regularly at home and in 67% hypertension changed their lives. A third of patients take their medications regularly. The calcium-channel blockers were the most frequently used medications and 17% used alternative medicine. Approximately 80% of patients would like to receive more information related to hypertension.

Conclusions: Despite of access to antihypertensive medications and medical care, Mexican hypertensive patients have poor adherence rates to medications and a high percentage do not measure their blood pressure regularly. Results suggest that culturally-adapted educational interventions will be beneficial for this population.

813. Incidence of Giant Cell Arteritis in Clinical Practice Research Datalink and Cumulative Use of Prednisolone in Patients Treated for GCA

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Background: Giant cell arteritis (GCA) is an inflammatory disease of unknown origin in the elderly. High-dose corticosteroids are the mainstay of therapy. The corticosteroid prednisolone is widely used as treatment for patients with GCA.

Objectives: To establish the incidence of GCA, with and without corticosteroid treatment, and to establish the cumulative use of prednisolone in patients with diagnoses of GCA.

Methods: The data source was Clinical Practice Research Datalink in the United Kingdom. The denominator population consisted of patients enrolled for at least 12 months between January 1, 2000, and December 31, 2011. Selection criteria for the GCA cohort were: at least one record of a READ diagnostic term for GCA; at least 50 years of age; at least one prescription for an oral or a systemic corticosteroid within 6 months of first GCA record; at least one prescription for prednisolone at or after the first GCA record. To evaluate the incidence of GCA, patients with any record of GCA before the end of the first 6 months of available history were excluded because this was considered prevalent. Incidence was defined as rate of first occurrence of GCA/10,000 person-years (PY) in the overall population.

Results: A total of 5,283 patients fulfilled GCA selection criteria (incidence 1.12/10,000 PY); 4,671 (88.4%) of these also received corticosteroid treatment (incidence 0.99/10,000 PY). About 4,655 of 4,671 (99.7%) corticosteroid-treated patients had been prescribed prednisolone, with a median number of 20 prescriptions and a median cumulative dose of 6,700 mg prednisolone. In the group with at least 24 months of follow-up history available (n = 3,074), the median number of prescriptions was 28, and the median cumulative dose was 8,238 mg prednisolone; 199 (6.5%) had a cumulative prednisolone dose of 25,000 mg or higher.

Conclusions: At an incidence of 1/10,000, GCA is relatively uncommon. Overall, patients with GCA in the United Kingdom are treated with high cumulative doses of prednisolone.

814. Thromboembolic Events Among Older Ovarian Cancer Patients: A SEER-Medicare Analysis

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Background: The incidence of venous and arterial thromboembolic events (TEs) among ovarian cancer (OC) patients is poorly described in the literature.

Objectives: Due to the impact of these comorbidities on treatment choice, quality of life, and survival, it is important to quantify the scope of TE risk after OC diagnosis in order to offer patients optimal care.

Methods: SEER-Medicare linked data (1991–2005) was utilized for this retrospective cohort analysis of OC patients. This database combines two large, population-based, geographically diverse U.S. data sources, providing detailed information about older persons (≥ 65 years). The main goal of this study was to estimate and describe the incidence of arterial thromboembolic events (ATEs: transient ischemic attack (TIA), ischemic stroke (IS), myocardial infarction (MI), unstable angina (UA)) and venous thromboembolic events (VTEs: deep vein thrombosis (DVT), pulmonary embolism (PE), other thromboembolic events (OTE)) after OC diagnosis. The total follow-up time was 1 year after diagnosis.

Results: There were 13,250 OC patients in this analysis. VTE incidence rates ranged from 63.5/1,000 (PE) to 233/1,000 (DVT); ATE incidence rates ranged from 51/1,000 (MI) to 92/1,000 (TIA). Regardless of type of TE, over 60% of TEs were observed in the first 90 days after OC diagnosis. The most common TE was DVT; 15.2% of OC patients (n = 2,013) experienced DVT after OC diagnosis with an incidence rate of 233/1,000. The rate of DVTs was twice as high among black (419/1,000) vs. white (225/1,000) OC patients and DVT rates increased with higher stage (stage I: 133/1,000, stage IV: 247/1,000). The rate of PEs was 3.3 times higher in stage IV vs. stage I cancers. Patients with a recent history of a TE had substantially higher rates of the same TE after OC diagnosis when compared to those without a recent history (unadjusted rate ratios ranged from 5.2 to 14.6).

Conclusions: TEs are common and serious co-morbidities that should be closely monitored in older OC patients, particularly during the first 90 days after diagnosis. High risk subgroups include black patients, those with a recent history of a TE, and those with advanced cancer stage.

815. The Burden Imposed by Atopic Dermatitis on Families: Creation of a Specific Questionnaire

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Background: The notion of individual burden, associated with the disease, has been introduced recently to determine the 'disability' caused by the pathology in the broadest sense of the word (psychological, social, economic, physical).

Methods: The ABS questionnaire (Atopy Burden Score Q) consists of 19 items, structured around five components. It was distributed to a random sample of families consulting at the Necker Hospital, staying at the Avène Hydrotherapy Center, and members of the patient association. The ABS was accompanied by SF12 and PGWBI, to confirm internal and external validation, and by the PO-SCORAD to assess the level of severity.

Results: Fifty-eight Q were considered evaluable. Fifty-one percent of the AD children were girls. The PO-SCORAD established the level of severity of the AD: 14%, 50% and 36% of children had mild, moderate or severe AD respectively. Internal validity was measured by Cronbach's alpha, which is equal to 0.81, reflecting a good homogeneity of the 19 items. The mean PGWBI score is 51.82 ± 14.28. The score reflecting the most important deterioration is found among parents of children with severe atopy. In contrast, the scores associated with moderate and mild atopy are not correlated with severity. Families' QoL, measured using the SF12, revealed no deterioration in the physical component. The ABS score is correlated with the scores of the Q used, thus confirming external validity. The mean score calculated from the ABS is 48.17 ± 18.36. The score increases with the severity of the AD. A statistically significant difference is observed between the three severity groups, i.e. mild, moderate and severe, with scores of 30.63, 42.55 and 62.62 respectively.

Conclusions: The internal and external validity of our Q were confirmed. ABS is correlated with the severity of AD. Hence, we have a short, easy-to-use, validated tool for assessing the burden imposed by atopy on families. This is currently being done as part of a program aimed at evaluating the therapeutic education and treatment of children in hydrotherapy centers. Following cultural and linguistic validation, the ABS is now available in US English, Spanish, German and Italian.

816. Hemangioma Family Burden: Creation of a Specific Questionnaire

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Background: The notion of individual burden, associated with the disease, has been introduced recently to determine the 'disability' caused by the pathology in the broadest sense of the word (psychological, social, economic, physical.

Objectives: The aim of our study is to develop a specific questionnaire for assessing the burden on families of children with HI.

Methods: A 'Hemangioma Family Burden' questionnaire (HFB) consisting of 22 items, The score increases with the heaviness of the burden. It was distributed (to families consulting at the Necker Hospital and at the Pellegrin Children's Hospital) accompanied by two validated quality-of-life questionnaires (SF12 and PGWBI) to obtain internal and external validation.

Results: Fifty-eight evaluable Q were returned. One parent from each family described how they perceived the effects of the disease, which led to the creation of six severity groups, paired together for size reasons: 'not very far-reaching' and 'somewhat far-reaching'; 'quite far-reaching' and 'far-reaching'; 'very far-reaching' and 'extremely far-reaching'. Internal validity was measured by Cronbach's alpha, which is equal to 0.95, reflecting a good homogeneity of the 22 Q items. The mean scores of the physical and mental components are 54.93 ± 5.12 and 40.49 ± 11.28 respectively. Hence, the HFB score is correlated with these two components, thus confirming external validity. The mean score calculated from the HFB is 23.42 ± 19.93. The score increases with the 'severity score' of the parents. In fact, a statistically significant difference is observed between the three severity groups: 5.28 ± 6.8 for those reporting the smallest extent to 41.0 ± 18.71 for those reporting the greatest extent, and 27.7 ± 16.96 for a moderate extent. This confirms the sensitivity of the HFB.

Conclusions: During the evaluation, internal and external validity were confirmed. The HFB is correlated with the extent felt by parents, a feeling deemed relevant because it is often the cause of consultation and demand for treatment. We now have an easy-to-use, validated IH tool for assessing the disability caused. Following cultural and linguistic validation, the HFB is now available in US English, Spanish, German and Italian.

817. Burden of Chronic Kidney Disease

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Background: Chronic Kidney Disease (CKD) is important in pharmaco-epidemiology. It is studied as outcome for drug nephrotoxicity and as effect-modifier. Most population-based studies on the epidemiology of CKD have a cross-sectional design and, except for end-stage renal disease, limited information on incidence is available. The relation between incidence and prevalence of a chronic disease as CKD might be influenced by a differential risk on mortality and disease progression.

Objectives: To estimate incidence and prevalence of CKD using electronic medical records as gathered by general practitioners.

Methods: Data on more than 1 million subjects were available from the Integrated Primary Care Information (IPCI) project, containing complete electronic medical records gathered by general practioners. CKD was based on (1) an increased urine albumin to urine creatinine ratio (ACR), (2) a decreased estimated Glomerular Filtration Rate (eGFR), or (3) explicit statement of CKD in the medical record. The outcome CKD was analyzed overall and for stages 1–5 as provided by the KDIGO 2012 Clinical Practice Guideline separately. Results were stratified by sex, 5 year age groups, and diabetes.

Results: In 784,563 adult subjects a total of 1,379,097 eGFR measurements and 178,425 ACR measurements were available. The incidence rate of CKD in adults was 1,213 per 100,000 person-years, and 6.7% of the adult population had a prevalent diagnosis of CKD. The incidence rate increased with age and was the highest in patients with diabetes, with an overall incidence of 25,000 per 100,000 person-years, with a prevalence of more than 75% in the highest risk category. For stage G1 of CKD -especially in those with diabetes- prevalence decreased with advancing age, despite an increase in incidence rate.

Conclusions: This is the first study to report incidence rates of CKD for an entire adult population for stage G1-5 of CKD, stratified by sex, 5-year age groups and diabetes mellitus. Differences between incidence and prevalence for stage G1 of CKD were observed, possibly due to a more rapid decline in eGFR with reclassification to prevalent stage G3 of CKD. This study demonstrates that CKD affects many, especially at older age and patients with diabetes.

818. A Decision Aid for Initiating a Registry Study

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Background: As health care stakeholders consider registries as a source of real-world data to support decision-making, well designed patient registries may provide insights into product effectiveness, safety, and quality of care, and typically provide data on populations not included in clinical trials.

Objectives: To develop a decision aid that provides practical and methodologic guidance with respect to initiation of a new patient registry for an identified research aim(s).

Methods: A targeted literature review that included published guides to planning and conducting registry studies including textbook chapters and AHRQ-funded methods reviews was conducted. From the review, a set of 'decision points' for whether to implement a registry and whether existing registries or data sources can be leveraged as well as key considerations that would drive the decisions were identified.

Results: Considerations regarding study purposes that lend themselves to being addressed by a registry included, whether the purpose or features of the research question warrant a randomized design or an observational study approach. Factors that determined suitability of existing registries and/or existing data sources for implementation of a registry were enumerated and a flowchart following from the considerations and leading to one of five decisions was created. The decisions are: (1) an RCT may be required to meet this evidence need, (2) an existing registry has been identified that can meet this evidence need, (3) a new registry utilizing prospective data collection is recommended to meet this evidence need, (4) a new hybrid registry combing use of existing data sources with prospective data collection is recommended to meet this evidence need, and (5) a new registry can be conducted using existing data sources to meet this evidence need.

Conclusions: The authors developed a tool for navigating the considerations that may lead to a decision to

initiate a randomized clinical trial rather than a registry, to leverage an existing registry to address a new research question, or to initiate a new registry using existing data, new data collection, or a combination of the two.

819. Overview of the Clinical and Economic Burden of Prostate Cancer in the U.S. Veteran Population

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Background: Prostate cancer is the most common form of cancer in American males, with nationwide incidence of 154.8/100,000 males, based on cases from 2005 to 2009. This research focuses on current clinical and economic characteristics of US Department of Veterans Affairs (VA) beneficiaries diagnosed with prostate cancer.

Objectives: Evaluate the demographic characteristics and monthly all-cause healthcare resource utilization incurred by VA-eligible prostate cancer patients.

Methods: A retrospective database analysis was performed using Veterans Health Administration data from October 1, 2007 through September 30, 2011. Eligible veteran beneficiaries were men with ≥ 1 International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code claims for malignant neoplasm of prostate (185.xx). Descriptive statistics were calculated as means $\pm$ standard deviation (SD) to measure resource use and costs.

Results: The largest proportion of prostate cancer patients resided in the Southern US region in 2011 (34.85%). Common comorbid conditions included hypertension (n = 131,790, 59.24%) and any tumor or other malignancy (n = 106,803, 48.01%). The average number of medical admissions totaled 0.18 (SD = 0.67) for the 10.78% of patients with inpatient visits, 0.07 (SD = 0.45) for those with emergency room (ER) (4.10%), 12.86 (SD = 14.52) for physician office (99.89%) and 13.73 (SD = 15.30) for patients with outpatient visits (99.91%). Healthcare utilization translated to average monthly costs of $3,721 (SD = $22,184) for inpatient, $18 (SD = $175) for ER, $5,012 (SD = $8,693) for physician office, and $5,385 (SD = $9,417) for outpatient visits.

Conclusions: Frequent outpatient resource use in over 99% of veterans diagnosed with prostate cancer led to considerable monthly costs. If resource use remained constant throughout the year, annual outpatient costs would total $60,144 for physician office and $64,620 for outpatient visits. Treatment is likely complicated

by the presence of comorbid conditions as well. Further research could help determine how these characteristics in VA patients currently compare to prostate cancer patients in other U.S. health care settings.

820. Longitudinal Patterns of Complications of Cystic Fibrosis (CF): An Analysis of a Claims Database in the United States

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Background: CF is an inherited disease with complications that develop throughout the patient's life.

Objectives: To quantify CF complications by age and examine trends in prevalence over 3 years in a claims database.

Methods: We retrospectively analyzed medical and pharmacy claims from the Optum Research and Impact National Benchmark databases (2004–2009). CF patients were identified by: ≥ 1 inpatient CF claim (ICD9 277.0×); or ≥ 2 outpatient CF claims; or for patients aged 6–45 years, ≥ 1 CF claim plus ≥ 1 pharmacy fills for dornase alfa. Complications were defined by diagnosis/procedure codes and filled prescriptions. Prevalences of complications during Year 1 were stratified by age group (0–5, 6–10, 11–17, and 18+ years). Prevalences of complications were calculated for each follow-up year (1, 2, and 3) for patients with 3+ years in database. McNemar's test was used to compare complications by follow-up year.

Results: The CF cohort included 5,019 patients with 1+ years of follow-up. The CF complications identified during Year 1 that increased with age included *Pseudomonas aeruginosa* infection, bronchiectasis, diabetes, and depression; where the prevalence (%) for patients aged 0–5 years was 28, 4, < 1, and < 1 and was higher for patients aged 18+ years with 62, 27, 26, and 22, respectively. By age, prevalence (%) of chronic sinusitis increased from 12 (0–5 years) to 33 (6–10 years) and then decreased to 32 (11–17 years) and 24 (18+ years). Among 1,804 patients with 3+ years of follow-up, trends in prevalence (%) for Year 1 vs. Year 3 were increasing for diabetes (16.7 vs. 18.9, p = 0.001) and depression (13.7 vs. 16.6, p < 0.001). Despite differences by age, the prevalence of *Pseudomonas aeruginosa* (57.5 vs. 58.2, p = 0.560), bronchiectasis (20.2 vs. 21.9, p = 0.093), and chronic sinusitis (25.6 vs. 27.7, p = 0.065) did not vary significantly from Year 1 to Year 3.

Conclusions: Longitudinal patterns for CF complications were identified. The prevalence of some CF com-

plications increased by age and had an increasing trend over 3 years (diabetes, depression) while others increased only by age (*Pseudomonas aeruginosa* infection, bronchiectasis).

822. Assessing Saudi National Guard Hospital Anticoagulation Management Services after Enhancing the Direct Involvement of Clinical Pharmacist in Patient Care Using Electronic Referral System – A Pilot Study

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Background: New intervention, Anticoagulation Management Module, has been implemented to facilitate clinical pharmacist intervention in early stage of anticoagulant prescribing for admitted patients, in which the clinical pharmacist received an electronic official consultation request from patient's medical consulting team to initiate and mange Warfarin therapy.

Objectives: -To explore the impact of the early clinical pharmacist intervention with patients on anticoagulants after adopting new electronic system.

Methods: Crosse sectional observational design used to compare the impact of the intervention. Historical data from chart review was utilized as baseline control for the comparison. Adult patients 18 years or older admitted to Medical Ward in Riyadh hospital. Patients admitted on July- December 2011 had been included on the study as control and patients admitted after the implementation of the intervention on January 2012 were included on the study. The outcome measures are; (1) Time needed to stabilize INR within the therapeutic range. (2) Percentage of treated patients within the therapeutic INR level from first time of dosing.

Results: The results based on currently collected data in this interim analysis. Only data for 23 patients' pre intervention group and 17 post intervention group had been collected. The time needed to stabilize INR has shown differences between both group, the interventional group need on average less 2 days than the control group to be stabilized (3.5 [SD = 2.43] days vs. 5.46 [SD = 3.96]). 34.7% of control group did not research the therapeutic group while only 11.7 on the interventional group.

Conclusions: An improvement on the time needed to stabilize the INR theraputic level has been detected on the interventional group; furthermore, this preliminary data analysis shows this new intervention has potential to reduced percentage of patients who are not within INR therapeutic level in early stage of treatment. This interim results are not conclusive since there are many limitations related to sample size and potential seasonal variability.

823. Cost and Utilization Trends of Antiemetic Drug in US Using Medicaid Database, 1991–2011

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Background: Antiemetic is a drug that is effective against vomiting and nausea which are considered one of most common symptoms that a lot of patients complain of.

Objectives: The objective of this study is to calculate price trends for individual antiemetic and to describe the trends of utilization and spending on antiemetic drugs in the U.S. Medicaid program.

Methods: A retrospective descriptive analysis was performed using data from the Medicaid database from 1991 through second quarter 2011. We extracted the utilization and expenditure data from the national Medicaid pharmacy files collected by the Centers for Medicare & Medicaid Services. Study drugs include antihistamines (cyclizine, dimenhydrinate, buclizine), steroids (dexamethasone, methylprednisolone), dopamine antagonists (droperidol, ondansetron, granisetron, palonosetron). Total prescriptions reimbursed by Medicaid and total reimbursement cost were calculated by adding the data for each antiemetic identified by its NDC. The Annual totals of reimbursement per-prescription were calculated as annual total reimbursement divided by Annual total number of prescriptions.

Results: The total number of prescriptions which paid by' Medicaid was increased from $339,822 in 1991 to $1.0 million in second quarter of 2011. The data shows 80% decrease in antiemetic utilization in 1999. The drug Ondansetron has increasing trends after 2006 up to about 70% in the first quarter of 2011. The price was in increasing rate until 2011. About 100% increase in the price of generic Zofran. The average of reimbursement per prescription has increased from $15.22 in 1991 to $36.90 in 2011.

Conclusions: In the light of this study, more studies are needed to create antiemetic guidelines that would help to improve efficacy, increase the patients compliance, and decrease the antiemetic costs.

824. Co-Prescription of Gastroprotective Agents in Patients Taking Non-Selective NSAIDs or COX-2 Selective Inhibitors: A Hospital Based Retrospective Study

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Background: Non Selective NSAIDs and COX-2 selective inhibitors (COXIBs) have been associated with an increased risk of upper GI complications, in particular when risk factors are present. Previous studies have shown that 20% to 40% of patients requiring NSAIDs are concomitantly prescribed gastroprotective agents (GPA).

Objectives: To evaluate prevalence and factors associated with of co-prescription of GPAs and non-selective NSAIDs or COXIBs in General Hospital, Yogyakarta, Indonesia.

Methods: A cohort retrospective study was done using Hospital Medical Record Database. All osteoarthritis and rheumatoid arthritis patients aged 35 years or older who had received at least one prescription during 2009–2011 for non-selective NSAIDs and/or COXIBs were included. GPA use was defined as receipt of any GPA prescription between the fill date of NSAID prescription and 90 of days of supply. GPAs included PPIs, H2-receptor antagonists, and misoprostol.

Results: Total 1,860 patients used at least one NSAIDs or COXIBs were analysed. Mean of NSAIDs prescription were 4.4 ± 1.5 per patient/year. Among chronic users, 60% were treated with non-selective NSAIDs and 40% with COXIBs, while for new users were prescribed to 96% and 4%, respectively. GPAs were prescribed to 44.3% NSAIDs and COXIBs users, and higher on NSAIDs compare to COXIBs (43.1% vs. 25.8%). H2 antagonist and PPIs were prescribed to 78.5% and 17.3, respectively. Elderly, combination of NSAIDs or COXIB, use of antiplatelet or corticosteroid and history of GI complications were received more co-prescription GPA, with RR (95% CI) 1.28 (1.05–1.55), 1.49 (1.14–1.94), 1.50 (1.18–1.91), 1.65 (1.10–2.47) and 3.60 (2.79–4.66), respectivley. Chronic use and higher dosage were not associated with co-prescription of GPAs.

Conclusions: Co-prescription of GPAs in patients taking non-selective NSAIDs or COXIBs were lower. Non-selective NSAIDs were more prescribed GPA compare to COXIBs. Elderly, combination use of NSAIDs or COXIB, the use of antiplatelet agent, corticosteroid and history of GI complications were factors associated with co-prescription of GPAs.

825. Drug Utilization of Patients Admitted with Conditions Wholly Attributable to Alcohol in Friuli Venezia Giulia, Italy

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Background: Alcohol consumption is the second health risk factor in Friuli Venezia Giulia (FVG), Italy, due to high consumption and prevalence of conditions attributable to alcohol.

Objectives: To compare outpatient drug utilization between patients admitted to the hospital for conditions wholly attributable to alcohol and a hospital control group.

Methods: For its 1.2 million resident FVG maintains computerized information on outpatient prescriptions and hospital admissions linked by a unique personal identifier. This study is a secondary analysis of an existing data set including all residents in FVG who were ever prescribed reimbursed NSAIDs prescription medications between 1 January 2001 and 31 December 2008. A case of hospital admission was attributed wholly to alcohol according to ICD-CM-9 discharge codes definitions by CDC. Controls were all other subjects hospitalized for conditions not attributable to alcohol. To evaluate the association between alcohol-related conditions and outpatient utilization of major categories of medications, we compared prescriptions among cases and controls and estimated the odds ratio (OR) and its 95% confidence interval (95% CI) using unconditional logistic regression adjusted for age, sex and duration of observation in the study. Since utilization pre- and post-admission was very consistent only pre-admission results are presented.

Results: Cases were 686, controls 235,987. Cases were directly associated with disulfiram (OR = 20.9; 95% CI: 11.3–35.5), antipsychotics (OR = 1.9; 95% CI: 1.3–2.9), SSRIs (OR = 1.3; 95% CI: 1.0–1.7) and diuretics (OR = 1.6; 95% CI: 1.3–2.0). Inverse associations were found with lipid modifying agents (OR = 0.5; 95% CI: 0.4–0.7) but also cardiac glycosides, stimulants, and antiarrhythmics; aspirin; anticoagulants; and antihypertensive drugs.

Conclusions: This drug utilization exploratory analysis using a population-based public-use data set suggests that alcohol-related problems in this high-risk population might be monitored regarding impact of anti abuse drugs and about possible effects of interaction with medications.

826. User and Treatment Characteristics of Oral Contraceptives in the European Union

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Background: Since their introduction, oral contraceptives have evolved, with modifications of hormone doses and combinations, dosage regimes and administration schedules. OCs are widely used by women with varying health status.

Objectives: As a basis for future safety evaluations of oral contraceptive (OC) use in Europe, current user and treatment characteristics were assessed in four European healthcare databases.

Methods: A descriptive retrospective database study was performed over 2009–2010 in GP databases from the Netherlands (IPCI), UK (THIN) and Italy (HSD) and linked pharmacy dispensing and hospital admission data from the Netherlands (PHARMO). Study follow-up started at the first OC prescription in 2009–2010 (users), 1 year after database entry or at January 1, 2009. Health indicators at start of follow-up included BMI and previous diagnosis of, or use of drugs for selected chronic conditions. Also, previous diagnoses of deep vein thrombosis, pulmonary embolism, cerebrovascular disease, myocardial infarction, breast cancer and cervical cancer were assessed. Treatment characteristics of OC included history of use, type of OC (chemical substance) used during 2009–2010 and switches or discontinuations.

Results: Among 4.9 million women, 14% had OC prescribed in 2009–2010. In the Netherlands and UK, 12–16% and in Italy 6% had a record of OC use. The prevalence of OC recorded prescription at January 1, 2010 was 81 per 1,000 women of all ages and 271 per 1,000 women aged 15–24, a much lower figure than what is recorded by surveys, probably due to switches between use and non-use and to reimbursement and/or prescription policies that reduce recording in GP databases. Among the non-users in 2009–2010, up to 22% had a history of OC recorded use. Little differences in health indicators were found between users and non-users in the databases where the information was available.

Conclusions: Trends in health among European women in general also apply to OC users. However, OC use is not registered very well in healthcare databases which limits the possibilities of pharmacovigilance. Distribution channels and reimbursement policies vary, as well as recording in the databases.

827. Characteristics of Selective Serotonin Re-Uptake Inhibitor (SSRI) Initiators 1999–2009

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Background: In recent years antidepressant use has increased and characteristics of antidepressant initiators may have changed.

Objectives: Describe characteristics of SSRI initiators to determine if changes exist over time.

Methods: The PharMetrics Claims Database was used to identify a cohort of SSRI initiators (360 days without prior antidepressant prescription) with an index SSRI prescription (Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram, or Fluvoxamine) between January 1, 1999 and December 31, 2009. Analyses were conducted in all initiators and in the subset with a depression diagnosis (≥ 1 diagnosis in 360 days prior to SSRI initiation). Covariates, assessed using claims from 360 days prior to SSRI initiation, included demographics, depression severity indicators, suicide attempts, psychiatric/non-psychiatric conditions, and healthcare utilization.

Results: Overall, 965,601 patients fit study inclusion criteria. Proportion of initiators with a depression diagnosis code fluctuated without a clear pattern (range: 30–44%) but remained fairly stable in the later portion of the study period (38–35% 2006–2009). The proportion of initiators with an anxiety diagnosis code increased substantially from 1999 (10%) to 2009 (26%) while proportion of males rose slightly (32–36%). Initiators with no other prescriptions generally varied between 7% and 8%. In patients with a diagnosis of depression, the proportion with a primary inpatient diagnosis stayed low over the 11 year period (3.7% in 1999, 1.8% in 2003, 3.0% in 2009) and the proportion with only one outpatient depression code increased (23%, 1999; 19%, 2000 to 43%, 2007–2009). Proportion with a prior suicide attempt more than doubled from 1999 (0.26%) to 2009 (0.68%) in initiators with a depression diagnosis. The proportion of specific SSRI type prescribed each year varied but the

major variations were evident in initiators with and without a depression diagnosis.

Conclusions: We observed variability over time in the prevalence of the indication of SSRI initiation in claims data. Variations could be attributed to changes in SSRI indications, off-label uses, and coding practices.

828. The Medical Management and Expenditure of Dry Eye Syndrome in Taiwan

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Background: Dry eye is a common complaint in patients encountered by ophthalmologists, which may result from the inflammatory response and can occur in the absence of systemic disease. However, the management of dry eye syndrome in real setting warrants assessment but remains lacking in Taiwan.

Objectives: This study aimed to evaluate the current management and annual medical expenditure of dry eye in real world setting in Taiwan.

Methods: This retrospective cohort study was conducted using Taiwan's National Health Insurance claims sampled database. Patients had any diagnosis of dry eye syndrome (including Sjögren syndrome (SS), Keratoconjunctivitis sicca, and tear film insufficiency) during 2006–2009 were enrolled. We evaluated the treatment strategy by extracting the prescription of ophthalmological solution within 30 days after index date. We classified the treatment into five categories, that is artificial tear substitute only, corticosteroid only, artificial tear substitute combined with corticosteroid, use any ophthalmologicals or no use of ophthalmological solution as above mentioned. Annual expenditure was calculated from 1 year after index date and categorized as ophthalmology-related and others.

Results: 35,534 patients had dry eye diagnosis during 2006–2009. The proportion of primary SS, secondary SS, and tear film insufficiency were 0.3%, 1.8% and 97.9%, respectively. The prevalence of dry eye syndrome increased from 0.58% to 0.92% on yearly basis, but the incidence was consistent. Overall, 73% of patients receiving artificial tears, of which 47% of them (6,333 patients) combined with corticosteroid. Only 1,143 patients (3.2%) had received treatment for 1 year, mostly of them were discontinued after 30 days. Regarding the medical expenditure related to ophthalmology, the annual cost for dry eye among SS patients were significantly higher than those without SS. In contrast, ophthalmology-related drug cost was similar between primary SS and secondary SS, but the drug cost with regard to non-ophthalmology for secondary SS was nearly two times than that for primary SS.

Conclusions: Our finding suggests that the short-term artificial tears are the first choice to relieve dry eye symptom, and nearly half of them are combined with corticosteroid. The medical expenditure increased dramatically once the systemic disease is involved.

829. Prevalence of Aliskiren Use among Patients with Hypertensive Diabetes in Taiwan: A Nationwide Population-Based Study

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Background: Aliskiren is an orally administered, non-peptide direct renin inhibitor indicated for the management of hypertension. It was effective in controlling blood pressure as monotherapy and in combination with other antihypertensive drugs. Aliskiren was reimbursed by the Taiwan's National Health Insurance since February 2010.

Objectives: To estimate the 11-month prevalence of aliskiren use among patients with hypertensive diabetes.

Methods: A cross-sectional survey was implemented using National Health Insurance Research Database between February 2010 and December 2010. Adult outpatients who had diagnoses of diabetes and hypertension and who had concurrent anti-diabetic and anti-hypertensive drug claim were identified. Drugs were identified and classified by the National Drug Code and the Anatomic Therapeutic Chemical code. Results are stated as percentages or means and standard deviations. All statistical analyses were conducted using the SAS 9.2 statistical software.

Results: During the 11-month period, a total of 10,543 outpatient visits met the study criteria. Of these, there were 21 patients prescribed aliskiren. The mean age of the aliskiren user was 65.1 ± 11.7 years; 52.38% were males. The estimated 11-month prevalence of aliskiren use is 0.2%. Among aliskiren user, there were seven

patients (33.3%) receiving concurrently angiotensin receptor blockers; there were 14 patients (66.7%) prescribed as combination therapy.

Conclusions: The results of the present study can provide related information about aliskiren used in patients with hypertension and diabetes in Taiwan. It is still must be concerned in future regarding contraindications to its use.

830. Characteristics of Incident Statins Users in Maccabi Healthcare Services 2000–2010

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Background: The Israeli health care system provides universal healthcare cover, including pharmaceuticals, so statins have been widely available. However, updated distribution of statin use and associated cardiovascular outcomes in the country are scarce.

Objectives: To analyze the pharmacoepidemiology of statins in Maccabi Healthcare Services (MHS), a 2 million member HMO in Israel during the first decade of the 21st century.

Methods:

Design: Observational, retrospective database study.

Settings: The automated database of MHS, the second largest health maintenance organization in Israel.

Exposure: Statins dispensed through pharmacies in the 2000–2010 period.

Main outcome measures: Utilization was expressed in the number of packages for each form of each drug by each manufacturer. Incident patients were those patients who had not been on a statin therapy regimen since January 1, 2000 and who received their first statin prescription in the year under consideration.

Statistical analysis: Following methods previously described, we calculated the mean proportion of days covered (PDC) by dividing the quantity of statins dispensed by the total interval from index date to disenrollment from MHS, death, or December 31, 2010 whichever occurred first.

Results: We were able to retrieve 266,977 patients from the database who had received at least one prescription for a statin during the study period (mean age:55 years). The number of incident patients peaked at 2006 and age at first statin dropped from 58.5 years in 2000 to 54.5 in 2010. Total LDL-cholesterol and triglycerides at first statins dropped from 168 mg/dL and 205 mg/dL to 154 and 169 mg/dL in 2010. Secondary prevention patients comprised 25% of incident patients in 2000 and only 10% in 2010. PDC in the first year of use remained similar throughout the study period (approx. 55%).

Conclusions: During the study period, incident statins users are characterized by declining age and number of other risk factors for cardiovascular diseases. No improvement in adherence during first year of use has been noted.

831. Adherence and Persistence with Type 2 Diabetes (T2DM) Medications: Saxagliptin, Sulfonylureas (SU), Thiazolidinediones (TZD), and Glucagon-Like Peptide 1 (GLP-1) Agonists

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Background: Adherence to diabetes medications is important for maintaining glycemic control and has been shown to reduce the complications of diabetes.

Objectives: Compare adherence and persistence among patients initiating non-insulin antidiabetic drugs. Determine other factors that affect adherence and persistence.

Methods: Adults with T2DM who initiated saxagliptin (a DPP-4 enzyme inhibitor), a GLP-1agonist (except extended-release), a sulfonylurea (SU), or a thiazolidinedione (TZD) during 08/01/2009–01/31/2011 were selected from a US healthcare claims database. Patients had no prescriptions for the index drug class during the year prior to initiation. Patients were followed for 1 year to assess adherence (proportion of days covered [PDC]) and persistence (time to discontinuation) on the initial study drug. Comparisons of the proportion adherent (PDC ≥ 80%) were adjusted using logistic regression. Hazard ratios for discontinuation were adjusted using proportional hazards regression.

Results: 8,383 saxagliptin, 13,908 GLP-1 agonist, 65,709 SU, and 29,702 TZD patients qualified. The proportion adherent was higher (p < 0.001) for saxagliptin (57.4%) than for GLP-1agonist (33.7%), SU (46.5%), or TZD (43.8%). The adjusted odds ratios (95% confidence intervals) for being adherent compared with saxagliptin were: GLP-1agonist 0.40 (0.37–0.42), SU 0.49 (0.46–0.52), TZD 0.54 (0.51–0.57). The adjusted hazard ratios for discontinuation compared with saxagliptin were: GLP-1agonist 1.71 (1.64–1.78), SU 1.63 (1.56–1.71), and TZD 1.55 (1.49–1.61). Other

factors associated with better adherence and longer persistence included male gender, older age group (compared with 55–64 years), mail order use, and renal impairment. Adherence and persistence with the study drug were lessened with higher patient drug cost-sharing and in patients who had other diabetes drugs in their regimen in addition to the study drug.

Conclusions: Among patients in a US claims database, adherence was better and persistence was longer for saxagliptin as compared with GLP-1 agonists, SUs, or TZDs.

832. Metastatic Castration-Resistant Prostate Cancer: Treatment Pathway and Associated Cost in Canada

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Background: Prostate cancer (PCa) is the most common cancer and the 3rd leading cause of cancer mortality in Canadian men. Men dying of prostate cancer do so after failing castration. The management of this disease phase is complex and the associated drug treatments costly.

Objectives: The objective of this study was to estimate the cost of drug treatments of metastatic castration-resistant prostate cancer (mCRPC), in the context of the latest evidence-based approach.

Methods: Two Markov models with Monte-Carlo microsimulations were developed in order to simulate the management of the disease and to estimate the cost of drug treatments in mCRPC, as per Quebec's public healthcare system, and the latest drug developments. The models include additional lines of treatment after docetaxel (i.e. abiraterone or cabazitaxel). The drug exposure and survival were based on clinical trial results and clinical practice guidelines found in literature review. All costs were assigned in Canadian dollars ($). Only direct drug costs were estimated.

Results: The mean cost of mCRPC drug treatments over an average period of 27.6 months was estimated at $36,207 (95% Confidence Interval: $35,679–$36,816) per patient. Over the mCRPC period, the luteinizing hormone releasing hormone agonists (LH-RH) prescribed to maintain castrate testosterone accounted for 28% of the total medication cost, whereas denosumab prescribed to decrease bone-related events accounted for 41%, respectively. When patients receive cabazitaxel in sequence after abiraterone and docetaxel, the mCRPC medications cost increases by 43%.

Conclusions: Our study estimates the direct drug costs associated with mCRPC treatments in the Canadian health system. The total cost of medications for the treatment of each annual cohort of 4,100 mCRPC patients is estimated at $ 148.5 million. Other emerging therapies may become part of the spectrum of mCRPC treatment in the near future, and potentially add to the costs. Perhaps decreasing the use of LH-RH therapies during mCRPC phase can result in potential savings to assist in covering the costs of life-prolonging novel systemic treatments.

833. Influence of Life-Saving Drugs Use before Acute MI and during Acute MI Phase on Mortality: LISS (Lyubertsy Infarct Survival Study) Registry Data

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Background: Significant progress has been achieved in ischemic heart disease treatment in last decades. However, it is well known that life-saving drugs use is not adequate.

Objectives: To asses the real use of cardiovascular (CV) drugs before reference acute MI (myocardial infarction) and in-hospital therapy and to evaluate its influence on short-term and long- term mortality.

Methods: The study was performed using registry data of acute MI of Lubertsy district of Moscow region. All clinical cases of patients (pts) with acute MI subsequently admitted to three hospitals between 01.01.2005 and 31.12.2007 were analyzed (n = 1,133). During hospitalization 172 (15.2%) pts died, 961 were discharged. Mortality follow up study was performed with median time 1.6 years [1,0;2,4]. During follow-up period 191 deaths occured, 83.2% of them were caused by CV diseases. Continuous data were expressed as mean ± SD. Cox regression model was used to establish prognostic predictive variables (age-, sex- adjusted) after hospital discharge. The probability of survival was calculated using the Kaplan-Meier method.

Results: Before reference acute MI 68,5% of pts had CHD, 24,2% survived acute MI previously, 12.9% had congestive heart failure, 12.9% had atrial fibrillation, 76.5% had arterial hypertension. Only 16% pts before reverence acute MI received antiplatelet agents, 2% received statins, 13%- diuretics, 21% beta-blockers, 36%- ACE inhibitors. Significant positive impact of beta-blockers and ACE-inhibitors use before acute

MI on short-term prognosis (hospital mortality) was shown: for beta-blockers RR = 0.54 (95% CI) (0.36; 0.82), p = 0.004, and for ACE inhibitors RR = 0.71 (0.51; 0.99), p = 0,04. Moreover, these agents showed positive influence on long-term life prognosis: RR = 0.61 (0.41; 0.90), p = 0.01 and RR = 0.67 (0.49; 0.93), p = 0.02 respectively. Among therapy administrated in acute reference MI phase, thrombolisis, aspirin and BB demostrated significant positive effect on long-term prognosis (RR 0.42, 0.65 and 0.58, respectively).

Conclusions: Inadequate use of life-saving drugs in pts with high risk of MI can partly explain high mortality rates.

834. Differences in Use of Pharmacologic Smoking Cessation Aids between Lung and Other Cancer Patients

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Background: Use of smoking aids may differ between patients with lung vs. other cancers, in part because of the long established link between smoking and lung cancer risk. To better develop smoking cessation programs for cancer patients, a greater understanding of these patterns is needed.

Objectives: To identify whether differences in usage patterns of pharmacologic smoking cessation aids (i.e., nicotine replacement therapy [NRT], bupropion, varenicline) exist between lung and non-lung cancer patients and to identify any socio-demographic or clinico-pathological factors associated with these usage differences.

Methods: 738 lung cancer patients and 539 patients with other cancers (breast, gastrointestinal, genitourinary-gynecological, hematological and other) were surveyed at Princess Margaret Hospital (Toronto, Canada) between 2010 and 2012 with respect to their smoking history and cessation aid usage. Multivariate logistic regression models evaluated the association between socio-demographic, smoking, and clinico-pathological variables with use of smoking cessation aids in these two groups, adjusted for significant covariates.

Results: Among the 269 (36%) lung cancer and 85 (16%) non-lung cancer patients who were smoking at diagnosis: 42% and 19% used NRT, 13% and 35% used bupropion and 10% and 19% used varenicline, respectively. Lung cancer patients were less likely to use bupropion (adjusted odds ratio, aOR = 0.52, 95% CI [0.27–1.03]) and varenicline (aOR = 0.53 [0.27–1.04]), but were more likely to use NRT (aOR = 3.12 [1.60–6.06]), when compared to patients with other cancers. Among lung cancer patients, older individuals were less likely to have used bupropion (OR = 0.94 [0.91–0.98]). Among patients with other cancers, visiting their family doctor recently was associated with lower use of NRT (OR = 0.11 [0.01–0.93]), while patients with greater pack years of exposure were more likely to use varenicline (OR = 1.04 [1.01–1.06]).

Conclusions: Patterns and predictors of utilization of pharmacologic smoking cessation aids are different in lung vs. other cancers. Smoking cessation programs targeting cancer patients should use this information to tailor management strategies accordingly.

835. Patient Activation by DTCA Influences Primary Care Physicians' Prescriptions of Celebrex for Osteoarthritis

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Background: DTCA aims to 'activate' patients to request specific medication from physicians.

Objectives: Assess if primary care physicians (PCPs) alter prescribing patterns in response to specific requests from activated patients.

Methods: We performed a factorial experiment in which PCPs viewed clinically authentic videos of 'patients' presenting with knee osteoarthritis (OA). The patients were played by professional actors who differed by sex, race (white, Black, Hispanic) and SES (higher, lower). 192 US PCPs were recruited. In half of vignettes the patient was 'activated' and asked: 'I've seen ads for Celebrex and it looks just like what I need…I really want to try that.' The non activated patients requested help but not specific medications. Vignettes were balanced on sex, race and SES. PCPs were balanced by sex and experience. After viewing

the video, PCPs completed a questionnaire indicating the treatment(s) they would likely order. We used multivariate ANOVA models to examine the association between patient characteristics and PCP prescribing choices.

Results: 53% of PCPs seeing an active request reported that they would prescribe celecoxib, compared to 24% of PCPs without active request (p < 0.0001). PCPs seeing an active request were less likely to report that they would prescribe a non-selective NSAID (29%) than PCPs seeing a celecoxib request (42%; p = 0.06). PCPs seeing an active request for celecoxib chose any NSAID for 82% of vignettes, compared to 66% of PCPs without active request (p = 0.004). The associations between active request and prescribing patterns were not influenced by patient characteristics (gender, race, SES) or PCP characteristics (gender, experience).

Conclusions: PCPs seeing an activated request for celecoxib were more than twice as likely to prescribe it compared to PCPs seeing a non-activated patient with identical history; they were also more likely to prescribe any NSAID. Given the higher price, increased risk of cardiovascular toxicity and similar efficacy of celecoxib compared to non-selective NSAIDs, these findings suggest that some types of patient activation may increase health care costs and compromise appropriateness of prescribing.

836. Pharmacy-Based Interventions To Reduce Primary Medication Non-Adherence

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Background: Medication non-adherence can cause morbidity and mortality. Primary non-adherence occurs when patients do not fill a first prescription for new medication.

Objectives: Evaluate two pharmacy interventions to reduce primary non-adherence to cardiovascular (CV) medications.

Methods: In 2007 CVS pharmacies began automated calls to patients who had not picked up new prescriptions in 3 or 7 days. In 2009 pharmacists and technicians began live calls to patients who had not picked up prescriptions in 8 days. A 1–2% random sample of patients served as controls. We used CVS-Caremark claims to identify the rate at which prescriptions for CV medications were not filled in 30 days.

Results: The automated population included 852,629 patients (9,282 control) and 1.2 million prescriptions (13,179 control). The live intervention included 121,155 patients (2,976 control) and 139,502 prescriptions (3,407 control). The groups were balanced by age, gender, and prior prescription use. For the automated intervention, the rate of unfilled prescriptions was 4.2% in the intervention group and 4.5% in the control group (p > 0.1). The live intervention was used in a group that had not filled prescriptions after 8 days and had higher rates of primary non-adherence. The rate of unfilled prescriptions was 36.9% in the intervention group and 41.7% in the control group, a difference of 4.8% (p < 0.0001). The difference for antihypertensives was 6.9% (p < 0.0001) but for statins was only 0.5% (p > 0.1).

Conclusions: Automated calls to patients had no effect on primary medication adherence. Live calls to patients at high risk for primary non-adherence significantly increased primary adherence to CV medications, although many patients still did not fill their prescriptions. The findings were driven by improved antihypertensive adherence, with no effect on statin adherence. Our findings indicate that 20 live calls from the pharmacy would be needed for one new filled prescription, or 15 calls per prescription filled if the results were limited to antihypertensives. Future analyses of long-term adherence and clinical outcomes will be needed to assess the cost-effectiveness of these interventions for pharmacies or health systems.

837. Experience of Using Gout Flare Prophylaxis in the FAST Trial

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Background: Initiation, increase or change of urate lowering therapy in patients with gout is associated with acute gout attacks. FAST (Febuxostat vs. Allopurinol Streamline Trial) is a large safety trial that optimises patients' allopurinol dose before randomisation to febuxostat or allopurinol. The protocol offers all patients prophylaxis against gout flares. There is sparse evidence supporting such regimens.

Objectives: To describe the use of gout flare prophylaxis regimens amongst UK recruited patients in FAST.

Methods: Patients are supplied with one of the following regimens depending on their co-prescribed medi-

cation and renal function: colchicine 0.5 mg *bd* or *od*, naproxen 500 mg *bd* or 250 mg *bd*, diclofenac 50 mg *td* or *bd*, or meloxicam 15 mg *od* or 7.5 mg *od*. This is supplied for 6-months following any increase in urate lowering therapy. All NSAID prophylaxis has gastroprotection with omeprazole or ranitidine. Patients already receiving therapy sufficient for gout flare prophylaxis are not offered further therapy. Patients can decline prophylaxis, and may switch regimens or stop completely if desired. We describe the initial prophylaxis supplied to patients receiving 2 or more supplies of trial medication and how this changed with time.

Results: As of February 2013, 269 UK-patients enrolled in FAST had received 2 or more supplies of study medication. Of these 30 (11.2%) refused or did not need prophylaxis at baseline, 193 (71.7%) received colchicine 0.5 mg *bd*, 44 (16.4%) received colchicine 0.5 mg *od*, 1 (0.3%) received naproxen 500 mg *bd* and 1 (0.3%) received diclofenac 50 mg *td*. Of those initially started on colchicine 0.5 mg *bd*, 128 (71.3%) continued with it, 38 (19.7%) reduced their dose, 20 (10.4%) stopped prophylaxis & 7 (3.6%) switched to NSAIDs. Of those initially started on colchicine *od*, 37 (84.1%) continued with it and 7 (15.9%) stopped prophylaxis. Patients commonly cited gastrointestinal disturbance as a reason for reducing or stopping colchicine.

Conclusions: The use of gout flare prophylaxis in patients enrolled in the FAST trial has been well tolerated. Despite this a substantial minority of patients have opted to reduce their dose of colchicine or stop prophylaxis completely because of side effects.

838. Adherence to Cardiovascular Drugs in Urban and Farmers Elders in the 3C and AMI Cohorts

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Background: Reduction of the risk of coronary heart disease needs a good adherence to cardiovascular (CV) drugs. It may vary according to sociodemographic characteristics.

Objectives: To assess and compare adherence to CV drugs in elderly urban- or rural dwelling men.

Methods: Men (+65 years) included in the 3C (living in Bordeaux) and AMI (farmers living in rural areas) cohorts were selected. From drug reimbursement data, adherence was studied among men with at least one CV drug reimbursement, ie: Vit. K antagonists (VKA), Anti-platelet agents (AA), Antiarrhytmics (AR), Organic Nitrates (ON), Diuretics (DIU), Beta-Blockers (BB), Calcium Channel Blockers (CCB), Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARB), Statins (STA). A subject was adherent if, over the year following the first CV drug reimbursement date, the Medication Possession Ratio (MPR) was $\geq$ 80% without a gap (> 70 days) between two reimbursements. Adherence was described and compared for each group. To consider differences between the groups (e.g. cognitive status, number of non-CV drugs), for classes with sufficient frequency (AA, DIU, BB, CCB, ACI, ARB, STA), a propensity score was used.

Results: A total of 821 elderly men were identified (469 urban and 352 farmers). Between both groups, adherence was comparable, and, except for VKA, was over 50%. For VKA, adherence was 42.3% in the urban group vs. 49.3% in the farmers group (pnadj = 0.67). It was 67.1% vs. 74.6% for AA (padj = 0.64), 53.7% vs. 60.9% for AR (padj = 0.42), 59.3% vs. 54.6% for ON (padj = 0.66), 68.5% vs. 73.9% for DIU (padj = 0.41), 67.9% vs. 74.8% for BB (padj = 0.18), 87.1% vs. 75.9% for CCB (padj = 0.04), 71.5% vs. 82.5% for ACEi (padj = 0.40), 79.2% vs. 70.8% for ARB (padj = 0.11), and 65.3% vs. 69.1% for STA (padj = 0.79).

Conclusions: Adherence to CV drugs was not different between elderly urban-dwelling men and elderly men retired farmers. However, adherence was not optimal, in particular for VKA. This may be explained by the frequent dose adaptation of VKA that may limit the frequency of prescription renewals and thus lower the MPR. For the other CV drugs, indication and better safety profile may account for higher level of adherence.

839. The Effect of the Financial Crisis in the Use of Psychotropics Drugs in Portugal

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Background: Consumption of psychotropic drugs increased in the last decade in Portugal. Since 2011 Portugal is under an EU/IMF bailout programme, which introduced severe wage cuts and increased unemployment rate. The social and financial crisis may

have a negative effect in mental health with a consequent increase in psychotropic drug use, but this effect remains unstudied.

Objectives: To analyze psychotropic utilization and expenditure trends in a national level and determine if there were changes in consumption trend as a consequence of the economic and social crisis or other policy measures in the pharmaceutical sector.

Methods: Monthly data was collected from 2000 to 2012. Data collection refers to psychotropic prescribed and dispensed in outpatient care in the National Health Service (NHS). Psychotropic drugs include anxiolytics, antidepressants and antipsychotic and correspond to the following ATC index 2012 codes: N05A; N05B; N06A and N06CA. Main outcome measure was the Defined Daily Dose (DDD) per 1,000 inhabitants per day (DID). Dummy variables representing the implementation of the memorandum of understanding and other policy measures were used in order to determine their effects on the time series. Statistical analysis was performed using SPSS 20.0.

Results: Psychotropic utilization has been increasing over the last 10 years exceeding 200 DID in 2012. The increase was mainly due to Antipsychotics and Antidepressants. Benzodizepines presented high levels of consumption, which remains a problematic issue, but the trend remained stable. The model did not show a statistical significant ($p > 0.05$) change in the level of consumption, expressed in DID, due to the financial crisis.

Conclusions: The financial and social crisis did not have an effect on the use of these drugs. Howeever it remains to be studied if this is due to lack of access to medical care.

840. Use of NSAIDs with Increased Risk of Cardiovascular Events in Low and Middle Income Countries

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are extremely widely used and some have been shown to increase the risk of heart attack and stroke. The rates of cardiovascular disease are rising rapidly in low and middle income countries.

Objectives: High risk NSAIDs (e.g. etoricoxib, diclofenac) should be avoided in patients at increased risk of cardiovascular events. To determine if this was the case in practice, we studied the inclusion of NSAIDs on Essential Medicines Lists (EMLs) and analysed NSAID sales data in low-, middle- and high-income countries.

Methods: Data on the relative risk (RR) of cardiovascular events with individual NSAIDs were derived from meta-analyses of randomised trials and controlled observational studies. Listing of individual NSAIDs on EMLs was obtained from the World Health Organisation. NSAID sales or prescription data for 15 low, middle, and high income countries were obtained from Intercontinental Medical Statistics Health or national prescription pricing audit (in the case of England).

Results: Three drugs (rofecoxib, diclofenac, etoricoxib) ranked consistently high on cardiovascular risk. Naproxen had the lowest risk. Diclofenac was listed on 74 national EMLs, naproxen on just 27. Rofecoxib use was not documented in any country. Diclofenac and etoricoxib accounted for one third of total NSAID usage across the 15 countries (median 33.2%, range 14.7–58.7%). This did not vary between low and high income countries. Diclofenac was by far the most commonly used NSAID, with a market share close to that of the next three most popular drugs combined. Naproxen had an average market share of < 10%.

Conclusions: Listing of NSAIDs on national EMLs should take account of cardiovascular risk, with preference given to low risk drugs. Diclofenac has a very similar cardiovascular risk to rofecoxib, which was withdrawn from worldwide markets owing to cardiovascular toxicity. Diclofenac should be removed from EMLs and its marketing status worldwide should be reviewed.

841. Interactive Medication Reconciliation by Secure Messaging

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Background: Adverse drug events (ADE) are the most common of all healthcare associated adverse events. Transitions between inpatient and ambulatory care and insufficient monitoring have been identified as a preventable and ameliorable cause of ADE.

Objectives: We examined the impact of secure messaging for medication reconciliation following hospital discharge.

Methods: We enrolled 60 patients. Eligible patients were instructed on the use of secure messaging and given a $50 cash incentive. An interactive medication reconciliation template, modeled after AHRQ

resources, was developed by the research team. Medication reconciliation of discharge medication lists were facilitated by the study pharmacist and sent to the patient via secure message within 72 h of discharge. Information about the frequency and severity of clinically important medication errors and potential ADEs was collected from sent and received messages. We conducted bivariate analysis to determine individual characteristics associated with medication errors and potential ADEs.

Results: We observed a total of 127 clinically important medication errors, 108 of which were found in 51 patient discharges and 26 of which were observed in participant responses. In bivariate analysis, clinically important medication errors were significantly more likely to be observed among patients taking > 5 medications and those with a hospital length of stay longer than the median of 4 days (p < 0.05). A total of 23 potential ADEs were identified among 15 participants. Potential ADEs were significantly more common among patients with > 5 medications (p = 0.03) and in those with a longer length of hospitalization (p = 0.02) in bivariate analysis.

Conclusions: Secure messaging for medication reconciliation among patients post-discharge is feasible and may be a valuable tool to improve ambulatory medication safety. Clinically important medication errors and potential ADEs were common and occurred more frequently in patients taking more medications and in those with a longer hospital stay.

842. A Tablet a Day or a Tablet a Week – Does It Affect Refill Adherence to Bisphosphonates in Sweden?

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Background: The effectiveness of oral bisphosphonates in reducing the risk of osteoporotic fractures is compromised by low adherence and poor persistence. To improve adherence, tablets which can be taken once weekly have been developed.

Objectives: To examine the impact on methods and assumptions applied when estimating refill adherence in the Swedish Prescribed Drug Register (SPDR) with a focus on patients using bisphosphonates with different dosing regimens.

Methods: In the SPDR 13,312 new users of bisphosphonates (18–85 years) were identified between 1 July 2006 and 30 June 2007 and were followed for a maximum of 2 years. The patients were categorised into groups based on dosing regimen: one tablet daily, one tablet weekly, switching between these regimens and other regimens. Refill adherence was estimated on persistent patients with the CMA (Continuous measure of Medication Acquisition) and the maximum gap methods. Persistence was defined as the number of days from the first prescription until the end of duration of the last prescription with a grace period of 60 days.

Results: The majority of the patients (93%, n = 12,419) used one tablet weekly. No differences in adherence were observed between the groups in the main analysis using either method. The sensitivity analyses performed had similar effects on adherence irrespective of the dosing regimen and method used. However, patients on one tablet weekly were significantly more adherent compared with patients on one tablet daily, using CMA, when the study population was restricted to patients aged 60–85 years (99% vs. 97%), when disregarding hospitalisations (99% vs. 97%) and when the length of the grace period, in the persistence analyses, was 45 days (100% vs. 99%).

Conclusions: The methods used and the assumptions applied have an impact on whether patients in Sweden on one tablet weekly are assessed as more adherent to bisphosphonates than patients on one tablet daily.

843. Up-Titration of Allopurinol in the Febuxostat vs. Allopurinol Streamlined Trial (FAST)

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Background: Gout is a common condition and reducing urate levels is key to preventing flares and complications. Gout patients are often sub-optimally controlled with urate lowering therapy. FAST is a clinical trial evaluating the long term cardiovascular safety

of febuxostat in comparison with allopurinol in gout patients and provides an opportunity to assess gout management in this study population.

Objectives: To review baseline urate levels and the up-titration of allopurinol required to achieve EULAR (European League Against Rheumatism) recommended urate targets for the first 400 patients randomised into FAST.

Methods: FAST is recruiting from primary care in England, Scotland and Denmark. Patients are over the age of 60, prescribed allopurinol for gout and have at least one additional cardiovascular risk factor. After screening their allopurinol dose is titrated up in 100 mg increments to achieve the EULAR recommended urate target of <357 μmol/L (< 6 mg/dL). Once urate levels are at target, patients are randomised to receive either febuxostat or allopurinol and followed up for a minimum of 3 years.

Results: At screening 255 of the 400 randomised patients had a urate level < 357 μmol/L and 145 patients (36%) required up-titration of allopurinol. Scotland had 60% patients at target, England 67% and Denmark 69%. For those requiring up-titration mean urate was 421 μmol/L (SD 44.5). Median allopurinol dose prescribed was 100 mg daily [IQR 100–200 mg], compared with a median dose of 300 mg daily [IQR 200–300 mg] in those at target. The median number of up titrations required was 1 (range 1–5) with 64% of patients achieving urate targets after one up-titration. Mean fall in urate after one up-titration was 69 μmol/L. More patients requiring multiple up-titrations were male (92% vs. 81%, p < 0.01) but there were no differences in age, BMI or renal function.

Conclusions: Gout is often sub-optimally managed and 36% of patients in FAST were not controlled to target urate levels at baseline. Up-titration of allopurinol is effective and the majority of patients achieved target urate levels with a single up-titration.

844. Withdrawn by Author.

845. Development of Prescription Quality Indicators among Diabetic Patients in Taiwan

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Background: Diabetes mellitus has become an important public health challenge as the number of diabetic patients will continue to rise in the next decade. Meanwhile, there has been an increasing complexity of medical treatment for diabetic patients.

Objectives: The prescription quality of anti-diabetic, anti-hypertensive, and lipid-lower agents among patients with diabetes needed to be examined.

Methods: We did a literature review on the published practice guidelines about anti-diabetic, anti-hypertensive, and lipid-lower agents therapeutic recommendations for patients with diabetes. A multidisiplinary panel of seven experts examined these indicators using RAND/UCLA appropriateness methodology. Furthermore, we analyzed data from a nationwide pay-for-performance program for diabetes care in Taiwan to evaluate the trends in prescription quality in 2006–2010.

Results: For appropriate use, four indicators included porportion of oral anti-diabetic drug initiators in type 2 diabetes patients receiving metformin rose from 53% to 70%; patients with two consecutive A1c ≥ 9.0% receiving insulin therapy rose from 26% to 42%; patients with two consecutive LDL ≥ 130 mg/dL receiving statin therapy rose from 31% to 36%; patients with microalbuminuria receiving ACE inhibitors or ARBs therapy rose from 44% to 50%. For inappropriate use, two indicators included porportion of diabetic patients with two consecutive creatinine ≥ 2.0 mg/dL receiving metformin decreased from 27% to 17%; diabetes patients receiving TZD remained around 2%. For undertreatment, decreased from 23% to 16% patients with MPR < 0.8. For overtreatment, decreased from 3% to 2% patients with MPR > 1.2. For cost, three indicators included porportion of anti-diabetic prescriptions that included generic drugs slightly rose from 79% to 82%; statin prescriptions that included generic drugs was around 40–43%; ACEi among ACEi or ARBs prescriptions decreased from 54% to 36%.

Conclusions: In general, the prescription quality of anti-diabetic, anti-hypertensive, and lipid-lower agents has improved among diabetic patients in Taiwan. However, we found that there were possible statin underprescription and ARBs overprescription, which may need further evaluation.

846. Comparison of ATC/DDD Utilization Data of Nervous System Medications with Potential for Abuse and/or Dependence in Bulgaria

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Background: European studies on drug utilization have showed that medicines consumption levels can vary

significantly between countries. Different factors affect drug consumption across countries.

Objectives: To investigate the consumption of selected medicines with potential for abuse and/or dependence in Bulgaria over 8 years time-period and to analyze these estimations with regard to clarify tendencies in drug utilization.

Methods: Observational retrospective study of the Bulgarian Ministry of Health database of medicines with potential for abuse and/or dependence from 2002 to 2009 in DDDs/1000 inh/day and analysis of these estimations were performed.

Results: The decrease in ATC code N for an 8-year period is 93%. The most prescribed products on ATC level 2 are psycholeptics. The most prescribed medicinal products on level 2 are psycholeptics (N05) and analgesics (N02), on level 3 – hypnotics and sedatives (N05C) and opioids (N02A), on level 4 – barbiturates, plain (N05CA) and other opioids (N02AX). There is a significant increase in the DDDs/1000inh/day for the benzodiazepine derivates (N03AE) – from 0.054 in 2002 to 0.93 in 2009 and for drugs used in opioid dependence (N07BC) – from 0.1 in 2002 to 1.25 in 2009. The overall decrease is due to reduced consumption in ATC code N05B by 42%, i.e. 7.08 DDDs/1000 inh/day in 2002 to 4.55 DDDs/1000 inh/day in 2007 and N05C by 99% – from 222.79 DDDs/1000 inh/day in 2002 to 0.15 DDDs/1000 inh/day in 2009. The comparison between and within the levels showed major discrepancies and fluctuations throughout the years.

Conclusions: Our findings provoke necessity to investigate key factors influencing drug use, strengthening data-base and regional and international comparisons. They should be an object to future studies.

847. Methotrexate and Anti-TNF Drug Use in Seniors with New-Onset Rheumatoid Arthritis (RA) in Quebec

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Background: RA is a potentially disabling condition that generally requires long-term drug therapy, with a variety of agents. Methotrexate (MTX) is considered one cornerstone therapy for RA. Biologic therapies, including anti-Tumor Necrosis Factor (anti-TNF) drugs, have been available for RA in Quebec since 2002.

Objectives: To describe MTX and anti-TNF use in Quebec seniors with incident RA, from 2002 to 2008.

Methods: We used physician billing data to ascertain potential RA cases, based on at least one ICD9 code 714. We considered 'confirmed' RA cases as those with a rheumatology billing code diagnosis or those with > 2 physician visits coding for RA. We excluded subjects with evidence (multiple billing diagnoses) for lupus, myositis, scleroderma, Sjogrens, or ankylosing spondylitis. To define incident RA, we excluded subjects with RA billing diagnoses prior (i.e. 1989–2001). We restricted our analysis to those aged 65 or over and fully insured by the provincial drug plan. Frequencies were used to describe MTX and anti-TNF use, stratified by sex and whether or not the patients had been seen by a rheumatologist at any time point.

Results: We identified 20,033 seniors with new-onset RA across 2002–2008, with average length of follow-up of 3.1 years. Most of them (65.6%) were female and the mean age was 74.6 years (SD = 6.5). During the follow-up period, 39.3% of patients had at least one rheumatology visit, 15.1% were on MTX and 0.8% were dispensed an anti-TNF agent at least once. The frequency of use of these two drugs was similar for men and women, but those who had at least one rheumatology visit were more likely (28.9%) to be dispensed MTX than those who had not seen a rheumatologist in the period (6.3%). A similar trend was seen for anti-TNF drug use (1.8% vs. 0.2%). A limitation of our work was that it did not consider other disease-modifying agents used in RA.

Conclusions: In our sample of seniors with new-onset RA, MTX and anti-TNF drug use was similar among men and women, but was much more likely to occur in patients who had been seen by a rheumatologist. This again emphasizes access to a rheumatologist as an apparent key determinant to use of these agents in seniors with RA.

848. What Attitudes Could Influence Antibiotic Dispensing without Prescription?

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Background: Excessive and inappropriate use of antibiotics, are attributed to inadequate prescription and self-medication with antibiotics obtained from leftovers from previous courses or self-medication with antibiotics dispensed in pharmacies without prescription.

Objectives: The aim of this study was to identify attitudes of community pharmacists to microbial resistances and antibiotic use, and, to assess the influence of these attitudes on propensity to dispense antibiotics without prescription.

Methods: Population studied included all pharmacists working in community pharmacies in an area of the Nomenclature of Territorial Units for Statistics (NUT) II for Portugal, defined by the Centre Regional Health Administration (ARS-C). A structured questionnaire, about pharmacists' attitudes related to antibiotic dispensing process was constructed after review of published studies and after performed a qualitative study designed in North Regional Health Administration (ARS-N), with pharmacists' focus group sessions. After validation, questionnaire was sent to 1197 pharmacists, by post mail, with a pre-filled envelope, to facilitate response, and the offer of a pencil. To increase the response rate, questionnaire has been sent four times at an interval of 4 weeks between each transmission, to non-respondents. Logistic regression was used to determine the propensity to dispense without prescription odds ratio (OR) for a change in exposure for each attitude.

Results: 770 pharmacists answered to the questionnaire with response rate near of 65%. It was identified three attitudes that could influence propensity of dispense antibiotics without prescription: complacence, responsibility of others and fear/precaution. Responsibility of others was attributed to patients or to health system.

Highest OR was observed for complacence (95% CI: OR 1,449; p < 0.0001).

Conclusions: Results from this study are very important to a understand pharmacists' attitudes that could influence antibiotic dispensing process and design tailored interventions to improve antibiotic use.

849. Assessing Physician Knowledge and Attitudes Regarding Antibiotic Prescribing and Microbial Resistances

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Background: Misprescription of antibiotics has been related with the development of antimicrobial resistances worldwide, which represents a life-threatening concern. Considering the main role of physicians in this field, it is essential to assess their knowledge and attitudes regarding antibiotic prescribing and resistances.

Objectives: The aim is to characterize primary care physicians' knowledge and attitudes regarding antibiotic prescribing and resistances.

Methods: It was conducted a transversal study in the Center Regional Health Administration (ARS-C) of Portugal, including all physicians working in primary care facilities of the National Health System (n = 1097). A validated, reply-paid, self-administered questionnaire was used to assess (1) attitudes and knowledge about antibiotic prescribing and resistances, (2) preferential sources of knowledge used and (3) sociodemographic and clinical practice information.

Results: The response rate was 43% (n = 473). Regarding sociodemographic characteristics, the mean age was 52.55 years, 53% (n = 249) were female, 77% (n = 362) only work at the National Health System and 22% (n = 103) also work at private settings. All participants were General Practitioners and 66% (n = 312) also work in the emergency department.

Regarding the attitudes assessed, physicians recognize that responsibility of others (health care system, scientific investigation or other professionals) could influence the prescription process. For the group of statements regarding the usefulness of some sources of knowledge, we obtained a Cronbach's alpha of 0.730. The sources of knowledge classified as being preferential were clinical practice guidelines, previous clinical experience, continuous education courses and the contribution of peers or others medical specialist.

Conclusions: Physicians recognize that there are some factors (as previous clinical practice or the responsibility of others) that influence antibiotic prescribing. Accordingly, these factors that influence primary care physicians' clinical practice should be considered to design multidisciplinary and more effective interventions to improve antibiotic prescription.

850. Validity and Reliability of a Questionnaire To Assess Knowledge and Attitudes Regarding Antibiotic Prescribing and Resistances

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Background: Misprescription of antibiotics has resulted in the development of bacterial resistances worldwide. To assess factors underlying physician antibiotic prescribing behavior, it is essential to develop valid and reliable instruments.

Objectives: To develop and validate a questionnaire designed to assess physicians' knowledge and attitudes about antibiotic prescribing and resistances, and the usefulness of some sources of knowledge.

Methods: The questionnaire was developed based on the literature review and it was designed to assess physicians' knowledge and attitudes about antibiotic prescribing and resistances. The development and validation process included two different stages: (1) content and face validation, which included the evaluation by expertise panels; and (2) the reliability analysis, to evaluate the internal consistency (Cronbach's alpha – α) and the reproducibility (Intraclass Correlation Coefficient –

ICC) of the questionnaire. To evaluate the questionnaire reliability, a pilot study was conducted at the Regional Health Administration of North, using the test-retest method, on a sample of 30 hospital care physicians and 30 primary care physicians.

Results: Content validity, which included the evaluation of professionals concepts used, and face validity, that assess the linguistic and interpretative terms in the statements, resulted in 28 changes of the questionnaire. About the reliability analysis, all ICC values obtained were, at least, fair to good for both groups of physicians studied (ICC > 0.4). About the internal consistency, Cronbach's alpha values obtained were satisfactory for both groups of physicians studied (Hospital care physicians: $\alpha = 0.783$; Primary Care Physicians: $\alpha = 0.770$).

Conclusions: Our results sustain this questionnaire as a valid and reliable tool to assess physicians' knowledge and attitudes regarding antibiotic prescribing and resistance. As a future perspective, it is essential to use this questionnaire in a larger sample to understand and improve rational antibiotic prescribing and to develop interventions aimed to improve antibiotic use.

851. Variation in Nursing Home Antipsychotic Use across Psychiatric Consultant Providers

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Background: Inappropriate antipsychotic prescribing in nursing homes (NH) is a well-documented and multifaceted problem, but the of influence of the psychiatric consultant provider is unclear.

Objectives: To examine variation in NH antipsychotic prescribing across psychiatric consultant providers.

Methods :

Design and Setting: Cross-sectional study of 60 NHs in Connecticut participating in a cluster randomized controlled trial. We used October 2009-September 2010 baseline data (Minimum Data Set, Nursing Home Compare, prescription dispensings) linked to survey data on psychiatric consultant providers.

Exposure: Psychiatric consultant provider for each NH.

Main outcome variable: Facility-level prevalence of atypical antipsychotic use.

Statistical Analysis: We calculated annual means and interquartile ranges [IQR] of atypical antipsychotic prescribing of NHs served by each psychiatric consultant provider and arrayed the providers from lowest to highest prevalence. Generalized linear models were used to predict mean antipsychotic prescribing for each psychiatry group adjusting for facilities' profit status, quality, staffing, and patient case-mix (age, sex and schizophrenia diagnosis). Observed vs. predicted antipsychotic prescribing levels were compared for each psychiatry group.

Results: We identified seven psychiatry groups serving 60 NHs (range: 3–27 NHs per psychiatry group). Overall mean antipsychotic prescribing for all 60 NHs was 19.2% (SD 8.1, IQR 14.0%, 21.8%). Across psychiatry groups, the mean prevalence of atypical antipsychotic prescribing ranged from a low of 12.2% (SD 5.8) to a high of 26.4% (SD 3.6). Among the psychiatry group with the highest ranked prescribing levels, all NHs had mean prescribing levels exceeding the overall study mean, while all NHs serviced by the two lowest ranked psychiatry groups had levels below the overall study mean. Comparison of observed vs. predicted prescribing revealed these differences remained after adjustment for facility-level differences in staffing, quality and patient case-mix.

Conclusions: NH antipsychotic prescribing levels vary considerably by the psychiatric consultant provider, even after adjusting for patient case-mix and facility staffing.

852. Do Antidepressant Drug Treatments Increase the Probability of Receiving an Antipsychotic Treatment in General Population?

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Background: An antidepressant drug treatment (ADT) may be associated with adverse effects such as manic switch or mood swings, which may lead to prescription of sedative treatment, particularly antipsychotic drugs.

Objectives: To assess whether the prescription of ADT is subsequently associated with an increased probability of prescription of an antipsychotic treatment and to estimate the temporal trends of this outcome.

Methods: A nested case-control study was carried out in a cohort of persons initiating a new ADT registered in the national insurance database (n = 28,145). Cases were defined as subjects receiving a new antipsychotic treatment. The date of first dispensing was the index date. They were matched to four controls who did not receive any antipsychotic drug until the index date. Multivariate logistic regression analyses were performed to assess the association between the first dispensing of antipsychotic and the presence of an antidepressant treatment during at least 2 weeks in the 4 weeks prior to index date. The time trends of the first dispensing of antipsychotic drug were assessed according to antidepressant treatment duration before index date.

Results: 2558 subjects (9.1%) received an new antipsychotic drug over the follow up. After adjustment for gender, age, chronic disease status, welfare benefit, specialty of the ADT prescriber, co-prescription of other psychotropic drugs, a new antipsychotic dispensing was associated with exposure to ADT in the previous 4 weeks (OR 1.42; IC95% 1.29–1.58; p 0.0001). For 2.3% patients, there was no chronologic relationship between antipsychotic dispensing and ADT. For 3.7% patients, the antipsychotic dispensing was concomitant to the ADT initiation and for 3.1%, it occurred after at least 14 days of antidepressant treatment.

Conclusions: The dispensing of ADT increases the risk of receiving an antipsychotic treatment, which may be a proxy for manic switch, in the general population. Whatever the motivation, the initiation of an antipsychotic during an antidepressant treatment may be a proxy for a severe or complicated depression and it happened in nearly one out of 10 patients.

853. Withdrawn by Author.

854. Trends in the Use of Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs in the General U.S. Population

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Background: In addition to aspirin's effect on preventing cardiovascular disease (CVD), recent studies also suggest that regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin might reduce cancer risk, cancer metastasis, and cancer mortality.

Objectives: The objective of this study was to describe trends in the prevalence of regular aspirin and other nonsteroidal anti-inflammatory drug (NSAID) use

among adults in the U.S. during 2005 and 2010, and to identify characteristics of regular users.

Methods: Data from the 2005 and 2010 National Health Interview Survey (NHIS) were analyzed to estimate the prevalence of regular use of aspirin and other NSAIDs among U.S. adults aged 18 years and older. Frequency calculations were conducted taking into consideration the complex, multistage sample design that involved stratification, clustering, and oversampling of specific population groups. Data from 2005 NHIS were age-adjusted to the 2010 NHIS population. The differences between these years were then tested using the chi square test. Results were stratified by demographics and self-reported medical conditions and extrapolated to provide U.S. population estimates.

Results: In 2010, around 43 million adults (19.0%) took aspirin at least three times per week for more than 3 months (i.e., regular users), and more than 29 million adults (12.1%) were regular users of NSAIDs other than aspirin. Compared with 2005, this was an overall increase of 57% in aspirin use and 41% in NSAID use. These increases were consistent across the strata of age, sex, race, and selected medical conditions, including cardiovascular disease (CVD), arthritis, peptic ulcers, cancer, and headache, except for Asian Americans.

Conclusions: Large increases in both aspirin and NSAIDs other than aspirin were observed over a 5 year period. The increase may be the result of increasing media attention reporting that regular aspirin use lowers the risk of CVD and related deaths, and may also prevent cancer. Moreover, safety concerns related to alternative medications such as acetaminophen and selective COX-2 inhibitors may influence users of these drugs to switch to aspirin and other NSAIDs.

855. Ectopic Pregnancies under IUD Use: Interim Results from the EURAS-IUD Study

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Background: Intrauterine devices (IUDs) are a well-accepted and widely-used method of contraception and have shown high contraceptive efficacy in clinical trials. The absolute risk of ectopic pregnancies associated with IUDs has been insufficiently investigated. It is also unknown whether the perforation rate is higher with levonorgestrel-releasing IUDs (LNG IUD) than with copper IUDs.

Objectives: The primary objective of the analysis is to determine the rate of ectopic pregnancies in women using IUDs and describe associated complications.

Methods: Large, controlled, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: levonorgestrel (LNG) IUDs and copper IUDs. In total, more than 60,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden) were recruited. The study started in 2006, follow-up will end in 2013. Both women and their treating physicians receive a single follow-up 12 months after enrolment. All patient-reported outcomes of interest are validated by the women's treating physicians.

Results: In October 2012, 61,380 women were enrolled (70.1% using LNG-IUDs, 29.9% using copper IUDs). One-year follow-up data were already available for 37,184 LNG and 15,561 copper IUD users. Women in the LNG IUD cohort were slightly older (37.4 years vs. 33.3 years). A total of 69 contraceptive failures have been reported (13 LNG IUD, 56 copper IUD), of which 15 were ectopic (5 LNG IUD, 10 copper IUD). This translates into an ectopic pregnancy rate per 100 WYs of 0.01 (95% CI: 0.00–0.03) and 0.07 (95% CI: 0.03–0.13) for LNG and copper IUD users, respectively. The corresponding incidence rate ratio (IRR) for LNG IUD vs. copper IUD was 0.19 (95% CI; 0.05–0.62). The respective IRR for women below the age of 30 and women 30 years and above are 0.20 (95% CI: 0.02–1.78) and 0.21 (95% CI:0.06–0.75). Updated results will be presented at the ISPE meeting.

Conclusions: The contraceptive failure rate was low for both cohorts. LNG IUD users tended to have a lower ectopic pregnancy rate compared with copper IUD users. Physicians should have a high index of suspicion for extra-uterine gravida if they suspect a pregnancy under IUD use.

856. Cost-Minimization Analysis of Treatment of Mild-To-Moderate Hypertension in Morocco

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Background: Hypertension is a highly prevalent risk factor for cardiovascular disease (CVD), which affects approximately 50 million Morrocan's. The outcome data from several clinical trials and meta-analyses

prove that new and old classes of antihypertensive drugs provide similar reductions of cardiovascular morbidity and mortality.

Objectives: The purpose of this study was to compare the costs associated with the prescription of first-line antihypertensive agents in Morocco.

Methods: A cost minimization analysis was performed. A decision analysis model was developed to compare the five alternative interventions: chlorthalidone, propranolol, amlodipine, enalapril and losartan. The evaluation of the cost of managing mild to- moderate hypertension includes the cost of drug therapy, monitoring, treating side-effects, poor compliance and switching. All costs were calculated from a health system's perspective, in 2012 $US. The time horizon was 3 years.

Results: The total cost to achieve and maintain hypertension control in Morocco setting was $279.42, $308.79, $367.36, $297.69 and $347.57 for chlorthalidone, propranolol, amlodipine, enalapril and losartan respectively. The drug acquisition cost was 27.24%, 51.38%, 58.38%, 47.93%, and 61.45% respectively. Sensitivity analysis tested the effect of modifying the prices of the antihypertensive agents and laboratory monitoring, the doses of the alternative drugs and the compliance rate on the economic endpoints and confirmed the superiority of chlorthalidone.

Conclusions: In patients with mild-to-moderate hypertension in Morocco, treatment costs to prevent CVD are much lower with chlorthalidone than with the other first-line antihypertensive agents.

857. Cost-Utility Analysis of Antihypertensive Medications in Morocco: A Decision Analysis

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Background: Many drugs are available for control of hypertension and its sequels in Morocco but some are not affordable for majority of the populace. This serious pharmacoeconomic question has to be answered by the nation's health economists.

Objectives: The objective of this study was to evaluate the cost-effectiveness of drugs from four classes of antihypertensive medications commonly used in Morocco in management of hypertension without compelling indication to use a particular antihypertensive drug.

Methods: The study employed decision analytic modeling. Interventions were obtained from a meta-analysis. The Markov process model calculated clinical outcomes and costs during a life cycle of 3 years of 1000 hypertensive patients stratified by three cardiovascular risk groups, under the alternative intervention scenarios. Quality adjusted life year (QALY) was used to quantify clinical outcome. The average cost of treatment for the 1000 patient was tracked over the Markov cycle model of the alternative interventions and results were presented in 2013 USD. Probabilistic cost-effectiveness analysis was performed using Monte Carlo simulation, and results presented as cost-effectiveness acceptability frontiers. Expected value of perfect information (EVPI) and expected value of parameter perfect information (EVPPI) analyses were also conducted for the hypothetical population.

Results: Thiazide diuretic was the most cost-effective option across the three cardiovascular risk groups. Calcium channel blocker was the second best for Moderate risk and high risk with a willingness to pay of at least 2000$/QALY. The result was robust since it was insensitive to the parameters alteration.

Conclusions: The result of this study showed that thiazide diuretic followed by calcium channel blocker could be a feasible strategy in order to ensure that patients in Morocco with hypertension are better controlled.

858. Cost-Effectiveness of Angiotensin Receptor Blockers in Moroccan Patients with Hypertension

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Background: Hypertension is a known independent risk factor for cardiovascular diseases. Cardiovascular diseases result in an enormous burden to society, both in

terms of health and costing. Therefore, health gains and related cost-savings achieved by optimizing antihypertensive treatment is important.

Objectives: The aim of this study was to estimate the cost-effectiveness of treating patients with hypertension in Morocco with angiotensin II receptor blockers (ARBs).

Methods: Our analysis comprised estimation of the cost-effectiveness comparing blood pressure lowering of olmesartan, losartan, valsartan and irbesartan; blood pressures at 8 weeks were inserted in the Framingham risk functions to estimate cardiovascular complications, using an national health economic model.

Results: After 8 weeks, the analysis showed that with olmesartan vs. losartan, valsartan, and irbesartan a statistically significant larger decrease in blood pressure was achieved (11.5 vs. 8.2, 7.9, and 9.9 mmHg [p < 0.05], respectively). Furthermore, olmesartan resulted in most complications averted. Cost-effectiveness for olmesartan, losartan, valsartan, and irbesartan was estimated at €272.7, €191.3, €287.4, and €395.9 per cardiovascular complication averted, respectively. Pharmacy data showed that trial-dosing at 1 'Defined Daily Dose' (DDD) was not found in practice. On average, losartan, valsartan and irbesartan were consequently dosed above 1 DDD varying from 1.19 to 1.38 DDD, whereas olmesartan was dosed at 0.88 DDD and thus presenting (relatively) lower costs.

Conclusions: Olmesartan was estimated to be the most cost-effective option of the four ARBs. However, due to differences found in within-trial vs. daily practice dosing and absence of effectiveness data from daily practice, confirmation is needed from further prospective studies comparing ARBs based on comparable blood pressure control including cardiovascular hard endpoints.

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859. Cost-Effectiveness of Intermittent Preventive Treatment in Pregnancy (IPTp) with Sulfadoxine-Pyrimethamine in the Light Increasing Resistance

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Background: Intermittent Preventive Treatment in pregnancy with sulphadoxine-pyrimethamine (IPTp-SP) has been efficacious but there is now increasing resistance of Plasmodium falciparum to IPTp-SP. There is need to determine the level of resistance at which IPT-SP would cease to be cost-effective. Such question could be addressed using standardized modeling framework to provide estimates of SP's cost-effectivenss at different level of resistance compared to other alternative drugs used for prevention of malaria in pregnancy.

Objectives: This study aimed to determine the point of resistance at which IPTp-SP ceases to be cost-effective with reference to weekly chloroquine chemoprophylaxis.

Methods: A decision tree was developed to model the research question with the assumption that 1,000 women in their first pregnancy received each preventive intervention. Costing was based on a societal perspective and included items such as drug cost, cost of antenatal clinic (ANC) programme and the cost of losing a neonate. Outcome of antimalarial prophylaxis was represented using effective reduction in neonatal mortality rate (NNMR) and calculated using an established equation. Probabilistic sensitivity analysis was used to capture uncertainty surrounding each variable.

Results: At the current level of resistance, IPTp-SP is a cost-effective option for prevention of malaria infection in pregnant women. However, if resistance to SP increases by 10%, weekly chloroquine chemoprophylaxis will be a more cost-effective option to use in preventing malaria in pregnancy.

Conclusions: This study provides criteria which could guide health decision makers in their choice of antimalarial prevention strategy in pregnancy in the light of dwindling efficacy of SP.

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860. Risk of Venous Thromboembolism Complications Associated with Recurrent Venous Thromboembolism

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Background: Venous thromboembolism (VTE) increases the risk of developing several complications, including recurrent VTE.

Objectives: This study quantifies the long-term risk of complications associated with the development of an index recurrent VTE.

Methods: An analysis of healthcare insurance claims from the Ingenix IMPACT database was conducted. Between 01/2004 and 09/2008, subjects aged ≥ 18 years on the date of first recurrent VTE diagnosis requiring

hospitalization (index recurrent deep vein thrombosis [DVT], pulmonary embolism [PE], or both) with ≥ 12 months of baseline observation prior to the index recurrent VTE were matched 1:1 with control VTE patients without recurrence, based on exact matching factors and propensity scores. The risk of developing thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency for up to 1 year after the index recurrent VTE event was compared between the recurrent VTE and the VTE control group.

Results: The recurrent VTE and VTE cohorts (8,001 subjects in each group) were well-matched with respect to age, gender, comorbidities, and VTE risk factors distributions. The absolute risks of developing thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency were 7.1%, 4.4%, 1.5%, 5.3%, 1.4%, and 7.2% for the recurrent VTE group and 2.5%, 1.3%, 0.8%, 2.0%, 0.9%, and 3.8% for the VTE group, respectively. The corresponding risk ratios indicated that the risk of developing any complications was significantly higher for the recurrent VTE group compared to the VTE group (risk ratio [95% CI]: thrombocytopenia: 2.8 [2.4–3.3], superficial venous thrombosis: 3.3 [2.7–4.1], venous ulcer: 1.9 [1.4–2.6], pulmonary hypertension: 2.7 [2.2–3.2], stasis dermatitis: 1.5 [1.1–2.0], and venous insufficiency: 1.9 [1.6–2.2], all p-values < 0.01).

Conclusions: In this large matched-cohort study, recurrent VTE patients had significantly higher risk of complications compared to VTE control patients.

861. The Medicines Benefits Package of National Health Insurance Fund in Sudan [NHIF] The Access, Effectiveness and Use

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Background: The irrational use of medicines has become a common problem worldwide. More than 50% of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients fail to take medicines correctly. Inequitable access to medicines in Sudan has been a big problem during the last 20 years. The role of implementation of NHIFin 1995 in improving the access to medicines and the comprehensiveness of the medicines benefits package was not assessed.

Objectives: To describe the development of NHIF medicines benefits package since 1995 and assess medicines availability and expenditure by pharmacological groups.

Methods:

Design: Retrospective descriptive study.

Setting and study population: The annual consumption reports of NHIF, Sudan of the years from 2002 to 2012 and the NHIF medicines lists updates of 2003, 2006 and 2012. Outcome measure (s): the Number of new medicines included in each update, percentage of medicines coverage (% of medicines available out of the total NHIF list), the pattern of medicines expenditure by pharmacological group.

Results: The medicines benefits package was increased from 280 in 1995 to 350 in 2003 and 513 in 2006 and to 595 in 2012. The cost of medicines was reduced from 65% (of the total medical services expenditure) in 2003 into 40% in 2005 due to implementation of pooled procurement policy but the antibacterials represents 30% of the total medicines cost (28–32%) during the last 10 years while the percentage of prescriptions with antibacterials was 65% (2010). The medicines coverage was 86%.

Conclusions: Although the NHIF medicines benefits package is regularly updated and it includes varieties of essential medicines from the different pharmacological categories and for different levels of care, but there is irrational use of medicines and there is a need to develop and implement clinical guidelines. This study reflects the urgent need for a well-designed study to measure the role of NHIF in improving the access and use of Medicines.

862. Validity and Reliability of Indonesian Version of ST George Respiratory Questionnaire in Tuberculosis Patients

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Background: Indonesia is on the 4th rank of the highest tuberculosis burden in the world. Even we have a good achievement in case detection rate and success of treatment in tuberculosis, but still have 450,000 of new cases and 64,000 of mortality cases every year. The long duration of treatment could affect patients' quality of life, probably because of the side effects, physiological and social impact.

Objectives: This study is aimed to develop the reliability and validity of Indonesian version of St George Respiratory questionnaire (SQRQ).

Methods: We recruited 50 newly diagnosed tuberculosis patientsin the respiratory disease center and public health centers in Yogyakarta. The SGRQ was 'self-administered' questionnaire. The reliability was analyzed by cronbach's α coefficient and the validity were analyzed for known group and construct validity. The floor and ceiling effects were observed to analyze the distribution of patients' response.

Results: There were 24 female and 26 male tuberculosis patients. The average age of female patients was 35.75 (SD: 15.65), while male patients was 40.96 (SD: 17.45). The reliability of the activity and impact domains were excellent, withthe value of cronbach's α coefficients were ≥ 0.8. All of the questions had no floor and ceiling effects. According to the patients' gender, there was no significant difference between the score of three domains. The eight questions of symptom domain met the criteria of construct validity, which were the value of correlation coefficients with symptom domain were ≥ 0.4 and each of the questions were more associated with symptom domain than other domain. Only question number 11 did not meet the criteria of construct validity. The value of correlation coefficient with activity domain was ≤ 0.4 and this question was more associated with symptom domain. The questions number 30 and 45–49 did not meet the construct validity as well, because they were more related with activity symptom than impact symptom.

Conclusions: The Indonesian version of SGRQ met the reliability and validity criteria, except for the impact symptoms in construct validity.

863. Prescription Audit of Indian Elderly Ambulatory Patients Using WHO Prescribing Indicators

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Background: Studies on the characterization of prescription among Indian elderly are limited in literature.

Objectives: This study, therefore, aimed to evaluate the prescription pattern specifically among Indian elderly patients using WHO prescribing indicators.

Methods: Prescriptions of 4005 outpatients, age 60 years or above, were evaluated prospectively using WHO prescribing core indicators.

Results: The average age (±SEM) of patients was 68.28 ± 0.11 years. On an average, each patient had 2.01 ± 0.01 diagnoses & was prescribed 6.45 ± 0.04 drugs. The most common disorder was 'Diseases of circulatory system'. The patients were prescribed an average of 6.45 ± 0.04 medications. Over half of the patients (57.9%) received more than five medications concurrently. The percentage of drugs prescribed by generic name was only 0.8%. Antibiotic usage was 13% while 7.3% of patients were prescribed injections. The percentage of drugs prescribed from National List of Essential Medicines 2003 was 66% of the drugs prescribed.

Conclusions: The minimal prescription of antimicrobials and injections coupled with higher prescriptions from essential drug list is a very positive reflection of good prescribing among elderly outpatients. This, to the best of our knowledge, is the first set of results on prescribing in a sample of 4,005 Indian outpatients.

864. Withdrawn by Author.

865. Community Pharmacists' Knowledge, Behaviors and Experiences about Adverse Drug Reactions Reporting in Saudi Arabia

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Background: Adverse drug reaction is one of the most common causes of morbidity and mortality in community settings.

Objectives: To assess community pharmacists' (CPs) knowledge, behaviors and experiences towards adverse drug reactions (ADRs) reporting in Saudi Arabia.

Methods: A cross-sectional survey was conducted using a validated self-administered questionnaire delivered to convenience sample of 104 CPs working in Riyadh, Saudi Arabia. A descriptive data analysis was performed using the Statistical Package for Social Science (SPSS) Software for Windows, (Version 20.0).

Results: The survey was distributed to 147 CPs of whom 104 responded to the survey (Response rate [70.7%]). The mean age of the participants was 29 years old, majority of the respondents had graduated with a bachelorette degree 101 (98.1%) and working in chain pharmacies 68 (66.7%). Only 23

respondents (22.1%) had mentioned that they are familiar with ADRs reporting process, with only 21 respondents (20.2%) know that pharmacists can submit ADRs online. Majority of the participants, 90 (86.5%) had never reported ADRs. Reasons for not reporting ADRs most commonly include: lack of awareness about the method of reporting 45.9%, and misconception that reporting ADRs is the duty of physician and hospital pharmacists 16.6%. The most common approach perceived by community pharmacist to manage patients suffering from ADRs was to refer him/her to a physician 80(76.9%).

Conclusions: Majority of community pharmacist in Riyadh have poor knowledge of ADRs reporting process. Stakeholders should take necessary steps to urgently design interventional programs to increase the knowledge and awareness of pharmacist about ADRs reporting process.

866. Association of Anti-TNF-α Agents and Fractures in Rheumatoid Arthritis Patients

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Background: Tumor necrosis factor alpha (TNF-α) inhibitors are essential elements of treatment for rheumatoid arthritis (RA), however whether the TNF-α inhibitors reduced the risk of fractures remained unclear.

Objectives: To evaluate influence of TNF-α inhibitors on risk of fracture.

Methods: We conducted a retrospective cohort study using the Korean Health Insurance Review & Assessment Service databases covering all Korean RA patients for 2006–2010. RA patients were defined as those with at least two prescriptions involving disease modifying anti-rheumatic drugs (DMARDs) which were initiated after Jan 2007 under the diagnosis of RA (ICD-10: M05, M06). Patients with prescription of cyclophosphamide or diagnosis of cancers, renal failures, liver failures, and organ transplantation were excluded. Patients were categorized into TNF-α inhibitors user and non-biologic DMARD combination users. We identified diseases and medications which were related as risk factor of fractures and considered them as possible confounders. Patients were enrolled and followed from the index date to the day of the death, or the occurrence of outcomes, or 31 December 2010 whichever came first. Outcomes were hip fractures (S72), forearm fractures (S52), upper arm fractures (S42), and pelvis and L-spine fractures (S32). Incidence rates and their 95% confidence intervals were presented, and the incidence rate ratios were calculated using Cox proportional hazard model.

Results: Among 1,760 RA patients treated with TNF-α inhibitors, 34 fractures occurred during 3,116 person-year of follow-up, which resulted in the incidence rate of 10.90 per 1,000 person-year. For 18,783 patients with non-biologic DMARD combination therapy, 566 fractures occurred during 38,943 person-year, which was equivalent to the incidence rate of 14.53 per 1,000 person-year. The crude incidence rate ratio (IRR) was 0.75 (95% CI:0.53–1.06), and adjusted IRR was 1.38 (95% CI:0.95–2.00). Adjusted IRRs were remained consistent regardless of the sex, and menopausal status.

Conclusions: TNF-α inhibitor did not show significant reduction in the risk of fracture.

867. Impact of Influenza Vaccination on Risk of Myocardial Infarction, Pneumonia, and Death in Elderly Patients Surviving Intensive Care: A Cohort Study

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Background: While influenza vaccination has been associated with decreased morbidity and mortality in the general elderly population, no data exist on its potential impact on complications and mortality following critical illness.

Objectives: To examine the impact of influenza vaccination on the 6-month risk of myocardial infarction (MI), pneumonia, and death after surviving a hospitalization with an intensive care unit (ICU) admission.

Methods: We conducted this population-based cohort study from 2005 to 2011 using population-based medical databases covering Northern Denmark. We identified all ICU patients aged 65 + years who survived to hospital discharge and followed them for up to 6 months. Exposure was defined as receipt of the current season's influenza vaccination, identified by reimbursements. Covariates included preadmission medication, comorbidity, urbanization, marital status, admission diagnosis, seasonality, length of stay, and ICU treatments. We estimated the 6-month cumulative risk of MI and pneumonia, accounting for competing risk by death, and the 6-month mortality risk. Event rates were compared by means of hazard ratios (HRs) with 95% confidence intervals (CIs) computed from a

Cox regression model adjusted for covariates. Analyses were repeated after propensity-score (PS) matching.

Results: We identified 20,324 ICU survivors, of whom 9,031 (44.4%) were vaccinated. Vaccinated patients were older, received more medication, and had more comorbidity, but had similar reasons for admission and proportion receiving organ supportive ICU treatments. The risk of MI within 6 months was 1.0% in vaccinated and 1.2% in non-vaccinated patients (adjusted HR(aHR) = 0.75; 95% CI: 0.57–0.99). The risk of pneumonia was 5.7% in vaccinated vs. 5.0% in non-vaccinated patients (aHR = 0.98; 95% CI: 0.86–1.11). The 6-month mortality risk was 12.9% vs. 12.3% (aHR = 0.93; 0.85–1.00). The estimates increased slightly in the PS matched analysis.

Conclusions: Among ICU survivors, preadmission influenza vaccination was associated with decreased risk of myocardial infarction and death, but not with occurrence of pneumonia.

868. Occurrence of Hemolytic Reactions (HRs) on the Same Day as Immune Globulin (IG) Product Administrations during 2008–2012

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Background: Hemolytic reactions (HRs) are rare but serious, adverse events that can occur following immune globulin (IG) use.

Objectives: To estimate risk of HRs on the same day as IG product administration among IG product users.

Methods: A retrospective cohort study was conducted using health insurance claims from the HealthCore Integrated Research Database (HIRD^SM). The cohort included individuals exposed to intravenous and subcutaneous IG products from January 2008 through June 2012. IG product exposures were identified by HCPCS codes, and HRs were assessed as a composite outcome based on the presence of ICD-9-CM diagnosis codes. Unadjusted same-day HR rates (per 1,000 persons exposed) were estimated overall, and by year, age, gender, and specific IG products. Multivariable analysis is underway to control for confounding and assess potential risk factors.

Results: Of 14,944 persons exposed, 159 (10.6 per 1,000 persons) had claims evidence of HRs on the same-day as IG exposure. Crude HR rates (per 1,000)

for 2008, 2009, 2010, 2011 and 2012 were 9.0, 4.7, 5.3, 5.7, and 3.4 respectively. When stratified by age groups, HR rates (per 1,000) were 13.7 for under 15 years of age, 7.2 for 15–44 years, 8.4 for 45–64 years, and 16.4 for 65 years and older. The same-day HR rates (per 1,000) varied by gender, with 9.2 for females and 12.3 for males. The non-zero HR rates (per 1,000) also varied for different IG products from 5.1 to 18.4, with the lowest rate for Vivaglobin.

Conclusions: The study showed a potential variation in the risk of HRs among IG users by age, gender, and products administered. Results suggested higher risk of the same-day HRs among the very young and the elderly, as well as for specific IG products. Variations may potentially be explained by product dosages, rates and routes of administration, as well as by other predisposing factors that warrant further research including multivariable analyses.

869. Patient Reported Health Outcomes from Well-Controlled Trials of Biologic Therapies: A Systematic Review

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Background: Whether clinically efficacious biologic therapies routinely achieve meaningful improvements in patients' experience of disease is unknown.

Objectives: To summarize the magnitude of patient reported physical and mental health benefits achieved with efficacious biologic therapies as measured by the Medical Outcomes Study short-form 36 (SF-36), the most widely used measure of functional health and wellbeing.

Methods: We performed a systematic review of randomized, double-blind, placebo-controlled trials of biologic therapies. PubMed and supplemental sources were queried from 1/1/1995 to 12/31/2011 for publications documenting significant clinical endpoint improvements and full SF-36 score reports by treatment group. We evaluated standardized SF-36 physical and mental component score (PCS, MCS) changes by treatment arm and net of placebo. Scores were compared vs. minimum important difference (MID) thresholds of 3 and 5 points (equivalent to 0.3 and 0.5 SD units, respectively).

Results: The search returned 805 publications, 35 of which were well-controlled, adequately documented, trials of a biologic therapy. Therapies targeted rheumatoid arthritis (n = 9), psoriasis (n = 8), inflammatory bowel disease (n = 5), psoriatic arthritis (n = 4),

multiple sclerosis (n = 3), ankylosing spondylitis (n = 3), neurological conditions (n = 2), and anemia (n = 1). Median sample size was 375 (IQR:264–652). For treatment arms, median PCS improvement was 6.6 points (IQR: 3.2–9.3); MCS median improvement 4.1 (IQR: 2.7–6.3). Mean treatment arm improvements met 3 point threshold for MID in 29/35 (83%) of trials and 5 point MID threshold in 26/35 (74%). After subtracting placebo arm treatment effects, median net of placebo PCS change was 4.6 (IQR: 2.3–5.8) and median MCS change 2.8 (IQR: 1.7–3.8). Mean net of placebo changes met 3 point MID thresholds in 27/35 (77%) of trials and 5 point thresholds 17/35 (49%).

Conclusions: Biologic therapies that improved clinical markers of disease activity robustly improved SF-36 functional health and well-being measures, improving how patients feel and what they are able to do in daily life, in over three quarters of well-controlled trials.

870. Risk of Lymphoma in Rheumatoid Arthritis (RA) Patients Treated with Certolizumab Pegol (CZP) Compared to World and US General Populations

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Background: It is widely accepted that patients with RA have an increased risk of lymphoma compared to the general population. Findings from 10 European cohort studies and one study in the United States noted standardized incidence ratios (SIR) for lymphoma ranging from 1.2 to 24.1, indicating heterogeneity but a consistent excess in lymphoma incidence in RA populations compared to general population referents. Clinical studies have also shown an increased risk of lymphoma with anti-tumor necrosis factor (TNF) usage compared to placebo. CZP, as an anti-TNF, has been evaluated for the risk of lymphoma in RA population since 2007.

Objectives: To calculate SIRs for lymphoma in RA population treated with CZP compared to general populations in the world and US.

Methods: SIRs compared the observed number of lymphoma cases from CZP clinical studies to the expected number based on general population referents. Expected values were calculated by applying age and gender stratified incidence rates from GLOBOCAN 2008 representing the world general population and SEER 2005–2009 representing the US general population to the age and gender stratified patient years (PY) of CZP exposure as of 30 Nov 2011 from 14 clinical studies.

Results: Five lymphoma cases have been identified among 4,049 RA subjects exposed to CZP representing a total of 9,277 PY at risk. The expected number of lymphoma cases using GLOBOCAN 2008 as the referent population is 1.84 resulting in an SIR of 2.72 (95% CI: 0.88, 6.34). The expected number of lymphoma cases using SEER 2005–2009 as the referent population is 2.76 resulting in an SIR of 1.81 (95% CI: 0.59, 4.23). The confidence interval around both estimates is large given sample size limitations and rareness of the event.

Conclusions: These results suggest an excess risk of lymphoma in RA patients treated with CZP compared to the general populations. Further, the results are consistent with literature suggesting that patients with RA and those treated with anti-TNFs as part of clinical trials have an increased risk of lymphoma.

871. Withdrawn by Author.

872. Evaluation of Protective Effect of TNF-α Inhibitors Against Ischemic Stroke in Patients with Rheumatoid Arthritis

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Background: Use of tumor necrosis factor alpha (TNF-α) inhibitors in rheumatoid arthritis (RA) may reduce risk of ischemic stroke, however this beneficial effect of TNF-α inhibitors was not quantitatively evaluated in Korean population yet.

Objectives: To evaluate reduction of ischemic stroke by TNF-α inhibitors among Korean RA patients.

Methods: A retrospective cohort study was conducted using the Korean Health Insurance Review & Assessment Service databases during the year 2006–2010. RA was defined as 2 or more prescriptions of disease modifying anti-rheumatic drugs (DMARDs) after 2007 with the diagnosis of RA (ICD-10: M05, M06). RA Patients with TNF-α inhibitors or non-biologic DMARD combination were included after exclusion of those with prescription of cyclophosphamide, diagnosis of cancers, renal failures, liver failures, and organ transplantation. The ischemic stroke was defined as the admission claim of an ischemic stroke (I63). The date of the first claim for the admission was defined as the date of occurrence of the outcome. A total of 17,759 RA patients were followed from the index date

to the occurrence of ischemic stroke, or the day of death, or 31 December 2010. The incidence rate ratios adjusting for possible risk factors were calculated using Cox proportional hazard model.

Results: Among 1,313 RA patients treated with TNF-α inhibitors, four events occurred during 2,267 person-year of follow-up, which resulted in the incidence rate of 1.76 per 1,000 person-year. For 16,746 patients with non-biologic DMARD combination therapy, 123 ischemic stroke occurred during 35,067 person-year, which was equivalent to the incidence rate of 3.51 per 1,000 person-year. The adjusted incidence rate ratio (aIRR) was 0.62 (95% CI:0.22–1.72). Adjusted IRR for female was 0.81 (95% CI: 0.25–2.70), male 0.32 (95% CI: 0.04–2.45).

Conclusions: TNF-α inhibitor showed tendency of reduction of ischemic stroke, however it was not statistically significant.

873. Effectiveness of the Pandemic H1N1 Influenza Vaccines in Preventing Hospitalization for Influenza and Pneumonia: A Population-Based Case-Control Study

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Background: The pandemic H1N1 (pH1N1) vaccines were effective in preventing laboratory-confirmed influenza during the 2009 pandemic, but their effectiveness in preventing hospitalization is not clear.

Objectives: We evaluated the effectiveness of these vaccines in preventing hospitalization due to influenza or pneumonia (I&P) using the laboratory and administrative databases of Manitoba Health.

Methods: In this population-based case-control study, individuals hospitalized in Manitoba with I&P during the pandemic's second wave (N = 1,812) were matched on age, gender and region to five controls who had not been admitted to hospital (N = 9,060). Information on seasonal or pH1N1 vaccine receipt, comorbidities, and health care utilization in the previous 5 years was obtained from Manitoba Health's administrative databases. Odds ratios for the association between receipt of pH1N1 vaccine and hospitalization with I&P were estimated using conditional logistic regression. Analyses were repeated separately for the subset of cases that had laboratory-confirmed pH1N1 infection.

Results: Adjusting for matching variables, income, comorbidity, immune status and receipt of antivirals, antibiotics and other vaccines, the adjuvanted H1N1 vaccine was 39% (95%CI 24–51%) effective in preventing hospitalization due to I&P when vaccination occurred ≥ 14 days before index date. Adjusting for the same variables, the adjuvanted H1N1 vaccine was 96% (95% CI 61–100%) effective in preventing hospitalization with laboratory-confirmed influenza. Effectiveness was lower among older (≥ 55 years) individuals and among those with immunocompromising conditions. There was also evidence that the H1N1 vaccine might be less effective among those who had received the 2009/10 TIV.

Conclusions: The adjuvanted H1N1 vaccine used during Manitoba's H1N1 mass vaccination campaign was moderately effective against hospitalization due to influenza and pneumonia and particularly effective against hospitalization due to laboratory-confirmed influenza, especially among children and younger adults.

874. Hospitalization and Skilled Nursing Care are Predictors of Influenza Vaccination: Evidence of Confounding by Frailty

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Background: Non-experimental studies of preventive medications, such as vaccinations, can suffer from the healthy-user bias, because treated patients may be healthier than untreated patients. Indicators of health status and frailty suitable for attenuating this bias may be identifiable in healthcare utilization data.

Objectives: To examine the association of recent hospitalization and skilled nursing care and the receipt of influenza vaccination in patients with end-stage renal disease.

Methods: Using the United States Renal Data System, we constructed population-based, cohorts of adult, hemodialysis patients each year between 1999 and 2005. Cox proportional hazards models controlling for demographic and baseline health status variables, were used to examine the association between time-fixed and time-varying variables and vaccination status.

Results: There were more than 100,000 patients in each cohort. Vaccination coverage increased from 47% in 1999 to 60% in 2005, and most doses of vaccine were

given by the end of October. Patients with any length of hospitalization were less likely to be vaccinated, however the association was stronger in patients with longer stays (15–25 days: HR = 0.64 [95% CI: 0.62–0.65]; 26–30 days: HR = 0.40 [0.38–0.42]). Patients with any length of skilled nursing care of more than 1 day had similar estimates; these patients were also less likely to be vaccinated (26–30 days HR = 0.66 [0.64–0.69]).

Conclusions: Patients with recent, long-term hospitalizations or skilled nursing stays were less likely to receive an influenza vaccination, suggesting evidence of the healthy-user effect. These variables can often be identified in administrative claims data and could be used to account for bias in studies of preventive services in patients on dialysis.

875. Feasibility Evaluation for a Rituximab (RTX) Utilization Study To Be Conducted in Infusion Centers

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Background: Automated clinical databases are an important data source for drug utilization studies but often they do not capture prescriptions for drugs such as biological agents and other data sources are required. We describe how a feasibility evaluation (FE) was designed and implemented for a drug utilization study (DUS) of RTX, a biological agent approved for the treatment of rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, and administered in specialized infusion centers (ICs). There is some evidence of RTX use in additional conditions, e.g. systemic lupus erythematosus, but the extent of this use is unclear. RTX prescriptions are usually not captured in hospital or population prescription databases.

Objectives: The FE goal was to evaluate if a single study conducted in ICs across five European countries (France, Germany, Italy, Spain, and The UK) could achieve the following operational goals: to collect estimates of treated patients by clinical indication; to learn about counseling practices and workflow at the ICs; to assess the feasibility of conducting both a medical record abstraction to characterize clinical use and a patient self-administered survey to evaluate the counseling practices at the ICs.

Methods: A feasibility questionnaire was sent to a total of 65 ICs and 30 completed it (overall response rate, 46%; range by country, 22–75%).

Results: Results were heterogeneous across the five countries regarding response rates of ICs, number of eligible patients, ICs characteristics, clinical use of RTX, and infusion waiting times. Countries were more homogeneous regarding ICs operations and counseling practices, availability of variables for chart abstraction, infusion duration, and interest to participate in the future study.

Conclusions: In conclusion, DUSs can be performed when usual data sources are not available but it is recommended to conduct FEs to guide the study design and confirm feasibility, especially when the study is conducted in several countries with different health care systems and prescribing practices.

876. Risk of Guillain-Barré Syndrome Following Adjuvanted Pandemic Influenza A (H1N1) 2009 Vaccination: Self-Controlled Case Series Study in Germany

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Background: The increased risk of Guillain-Barré syndrome (GBS) after the 1976 swine influenza vaccination in the United States raised concerns that the pandemic swine influenza vaccines of 2009 might also be associated with GBS. In Germany, the influenza A (H1N1) vaccination campaign started at the end of October 2009, almost exclusively using an inactivated, monovalent, AS03-adjuvanted vaccine (Pandemrix).

Objectives: A prospective, epidemiologic study was conducted by the Paul-Ehrlich-Institut (PEI), the German national competent authority responsible for vaccines, to assess whether the 2009 pandemic influenza A (H1N1) vaccination in Germany impacts the risk of GBS and its variant Fisher syndrome (FS).

Methods: Potential cases of GBS/FS were reported by 351 participating hospitals throughout Germany (227 neurologic and 124 pediatric hospitals) using a standardized reporting form. The self-controlled case series (SCCS) methodology was applied to all GBS/FS cases fulfilling the Brighton Collaboration (BC) case definition (levels 1–3 of diagnostic certainty) with symptom onset between November 1, 2009 and September 30, 2010 reported until end of December 2010.

Results: Out of 676 GBS/FS reports, in 30 cases GBS/FS (BC-levels 1–3) occurred within 150 days following

influenza A(H1N1) vaccination. The relative incidence of GBS/FS within the primary risk period (days 5–42 post vaccination) compared to the control period (days 43–150 post vaccination) was 4.65 (95% CI, 2.17–9.98). Similar results were found when stratifying for infections within 3 weeks prior to onset of GBS/FS, and when excluding cases with additional seasonal influenza vaccination. The result of temporally adjusted analyses supported the primary finding of an increased relative incidence of GBS/FS following influenza A(H1N1) vaccination.

Conclusions: The results indicate an increased risk of GBS/FS in temporal association with pandemic influenza A(H1N1) vaccination in Germany.

877. Immune Globulins (IGs) and Risk for Thrombotic Adverse Events (TEs) during 2008–2012 Study Period

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Background: Thrombotic events (TEs) are uncommon but serious, adverse events that can occur following administration of immune globulin (IG) products.

Objectives: To assess the risk of same-day TE occurrence following exposure to various IG products.

Methods: A retrospective administrative claims-based cohort study of individuals exposed to IG products during January 2008 through June 2012 was conducted using HealthCore's Integrated Research Database (HIRD[SM]). IG products were identified by recorded Healthcare Common Procedure Coding System (HCPCS) codes, and TEs were ascertained via ICD-9-CM diagnosis codes. Crude same-day TE rates (per 1,000 persons exposed) were estimated overall and by specific IG products, age, and gender.

Results: Of 14,944 individuals exposed to IG products, 233 (15.6 per 1,000 persons exposed) had claims evidence of TE on the same-day as the IG exposure. The crude TE rates (per 1,000) for 2008, 2009, 2010, 2011, and 2012 were 9.8, 6.4, 9.6, 10.9, and 5.5 respectively. The TE rates (per 1,000) among males and females were 16.1 and 15.1, respectively. The TE rates (per 1,000) were 7.5 for those under 15 years of age, 9.5 for those 15–44 years, 17.6 for those 45–64 years, and 21.0 for those 65 years and older. Unadjusted same-day TE rates (per 1,000) ranged from 7.3 to 142.9 for different IG products, with the lowest TE rate for Hizentra.

Conclusions: The study shows potentially elevated TE rates for specific products and suggests increasing same-day TE risk with older age groups. Overall, the analysis suggests that TE rates among IG users may vary by age, gender, and specific IG products used. There is a need for further multivariable regression analyses to control for potential confounders and further identify recipient risk factors.

878. Characterization of Patients with Rheumatoid Arthritis Treated with Rituximab or Tocilizumab in Post-Marketing Patient Registries

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Background: Prospective, observational disease registries such as the Anti-Rheumatic Therapy In Sweden (ARTIS), British Society of Rheumatology Biologics Register (BSRBR), and Rheumatoid Arthritis – Observation of Biologic Therapy (RABBIT) provide a unique opportunity to collect long-term pharmacovigilance data for risk management of first-in-class biopharmaceuticals rituximab (RTX) and tocilizumab (TCZ) in the post-marketing setting.

Objectives: To characterize baseline data for RTX and TCZ patients with rheumatoid arthritis (RA) enrolled in ARTIS, BSRBR, and RABBIT.

Methods: ARTIS, BSRBR, and RABBIT collect data on the incidence of adverse events of interest (serious/non-serious), mortality, and pregnancy outcomes using a standardised reporting form (Manchester Template) which provides summary of patient characteristics and incidence rates of safety events in biannual pharmacovigilance reports. Baseline characteristics for RTX and TCZ cohorts are presented from each registry and compared with control cohorts of patients on other biologic or non-biologic disease-modifying antirheumatic drugs.

Results: As of end-2012, a total of 1631 RTX and 300 TCZ patients were enrolled in BSRBR (patient-years [pt-yrs] follow-up, 2,870 and 246, respectively), ARTIS (2,936 RTX 8,177 pt-yrs, 1,019 TCZ 1,580 pt-yrs), and RABBIT (1,206 RTX 3,212 pt-yrs, 560 TCZ 1,408 pt-yrs). RTX and TCZ-treated patients with RA are generally older, have more severe disease at baseline than control cohorts, and the majority were on prior biologic therapies. Baseline characteristics of enrolled RTX and TCZ patients will be presented.

Conclusions: Data from prospective, observational patient registries show differences in baseline charac-

teristics of RTX and TCZ treated patients in comparison with control cohorts. Future analysis will compare incidence rates adjusted for differences in baseline characteristics between RTX, TCZ, and comparator cohorts.

879. Exacerbation of Herpes Zoster Ophthalmicus (HZO) Following Zoster Vaccine, Live, Attenuated [Oka/Merck]: A Case Series

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Background: One vaccine is authorized for the prevention of herpes zoster in persons 50 years of age or older: zoster vaccine, live, attenuated [Oka/Merck]. Overall efficacy is estimated as 51%. Zoster vaccine has not been studied in persons who have previously experienced an episode of herpes zoster. A Canadian (index) case of exacerbation of HZO post zoster vaccine was brought to the attention of the Health portfolio.

Objectives: To examine the potential association between recurrence of HZO and zoster vaccine administration, in patients with a prior history of HZO. To remind health professionals of the importance of reporting adverse events following immunization.

Methods: This is a case series. The following searches were conducted: Canada Vigilance database (January 1-December 31, 2012), World Health Organization (WHO) database (to December 2, 2012), Pubmed (to January 28, 2013). At Health Canada's request, the Market Authorization Holder (MAH) also conducted a search of their database to August 31, 2011. Causality assessment was conducted using the WHO algorithm for vaccine.

Results: The searches, together with the index case, retrieved a total of seven reports. Causality was assessed as unlikely in 1 and possible in 6. Of the possible reports, one patient had immune deficiency (a contraindication to vaccination), one had symptoms more consistent with neurotrophic keratitis, (a long-term complication of acute HZO), two were on low dose steroids at the time of vaccination and two were quiescent off of medication for HZO at time of vaccination. Proposed mechanisms include ocular auto-inoculation of live attenuated virus, and vaccine induced increase in cell-mediated immunity directed towards viral antigens within the eye.

Conclusions: There is insufficient information to confirm or refute a potential association between vaccination with zoster vaccine and an exacerbation or recurrence of HZO post-vaccination. The benefit/risk of zoster vaccine for the prevention of herpes zoster in subjects over age 50 continues to be positive. The adverse event of HZO will be an adverse drug reaction of special interest in the Periodic Safety Update Reports provided by the MAH.

880. Population Characteristics, Treatment Patterns and Medical Events in Patients with Psoriatic Arthritis

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Background: The association of comorbidities and psoriatic arthritis (PsA) is limited to a few small studies. We employ a large US database to study selected drug treatment patterns and medical events in PsA.

Objectives: To describe the demographics, treatments, and prevalence of medical events in patients with PsA using administrative claims data.

Methods: This retrospective study of Marketscan data included patients with ≥ 2 claims having a diagnosis (index event) of PsA (ICD-9 code 696.0) between 7/1/2006 and 12/31/2009, with no other inflammatory rheumatic conditions, and 24 months of follow-up. Drug therapy was assessed for topical agents, disease-modifying antirheumatic drugs (DMARDs), biologics, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-malarials, antibiotics, and corticosteroids. Medical events assessed were opportunistic infections, upper respiratory tract infection (URTI), malignancy, cardiovascular (CV), and psychiatric events. Cross-tab analysis and univariate statistics explored relationships among demographics, medical events, and drug therapy.

Results: In this database, of 3,874 patients meeting the PsA criteria, 53.5% were female, with a mean age of approximately 50 years. Post-index (24 months) treatments included topical and systemic corticosteroids (51.8% and 49.2% respectively), DMARDs (50.1%), anti-TNF agents (45.9%), topical agents (28.8%) and NSAIDs (21.6%). Medical event prevalence included CV (44.0%), URTI (26.3%), malignancy (15.6%), psychiatric (13.7%), and opportunistic infections (8.6%). The most prevalent opportunistic infections were candidiasis (47.4%), herpes simplex (21.6%), varicella zoster (12.0%), and human papilloma virus (8.4%). The most common medical conditions associated with anti-TNF therapy included hypertension (47.0%), URTI (27.5%), skin cancer (16.3%), and depression (15.5%).

Conclusions: In a US claims database, patients with PsA had a high use of corticosteroids, DMARDs, and anti-TNF agents. The prevalence of opportunistic infections, as well as cardiovascular, respiratory tract infection, malignancy, and psychiatric medical conditions are reported.

881. Comparative Risks of Recurrent Hospitalized Infection Associated with Biologics in RA Patients at High Risk

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Background: Serious infections are an important concern for patients with rheumatoid arthritis (RA) treated with biologics. Insufficient data guide the optimal treatment in this high risk population.

Objectives: To compare the subsequent risk of hospitalized infections associated with specific biologics among RA patients previously hospitalized for infection while receiving anti-TNF therapy.

Methods: Using Medicare data from 2006 to 2010 for 100% of beneficiaries with RA, we identified patients who were hospitalized with infection while on anti-TNFs and and who had US Medicare fee-for-service and prescription drug coverage in the 6 months before the hospitalization discharge and throughout follow up. Follow-up began 60 days after discharge and ended at the time of next infection, loss of coverage or after 18 months. We determined biologic exposure on each person-day and treated exposure as time varying. Confounding was controlled through a person-specific infection risk score that was separately derived among new users of anti-TNF and non-biologic DMARDs. We calculated the subsequent incidence rate of hospitalized infection for each biologic and used cluster adjusted Cox regression to evaluate the association between various biologics and subsequent infection, controlling for infection risk score decile.

Results: During follow-up we identified 13,772 person-years of exposure to biologics; of this time 5% was on abatacept, 2% on rituximab and 93% on anti-TNFs, including 23% on etanercept, 18% on adalimumab and 52% on infliximab. Abatacept users had the lowest crude incidence rate of subsequent hospitalized infection, and etanercept users had the highest. After adjusting for infection risk score decile and the original anti-TNF, abatacept (hazard ratio (HR): 0.80, 95% CI: 0.68–0.95) and etanercept (HR: 0.84, 95% CI: 0.74–0.96) users had significantly lower risks of infection compared to infliximab users.

Conclusions: Among RA patients at high risk for recurrent serious infection who experienced a hospitalized infection while on anti-TNFs, abatacept and etanercept appear to be associated with the lowest risk of subsequent infection among the commonly prescribed biologics.

882. Identification of Newly Approved Medications Using Non-Specific Drug Codes in Medicare Administrative Claims Data: Tocilizumab as a Case Study

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Background: After licensure in the US, parenterally administered medications are typically identified using non-specific drug codes, with the same codes being assigned to multiple new agents. Accurately identifying these medications is critical to research on the safety and effectiveness of new therapies. Methods to identify medications prior to assignment of specific drug codes have not been well described.

Objectives: To describe a generalized approach using non-specific drug codes to identify parenteral therapies in Medicare claims and to assess the ability of that approach to identify tocilizumab (TCZ), a new biologic agent approved in 2010 in the US.

Methods: We used 2008 to 2010 Medicare data for a cohort of patients with rheumatoid arthritis for algorithm development. Our claims-based algorithm classified non-specific drug codes identified in this time frame based upon: (1) ICD9 diagnosis codes; (2) unit values (i.e. dose); (3) codes for infusion or injection procedures on the same day; and, (4) observed and expected unit price and total allowed reimbursement amounts. We assessed algorithm performance by determining the number of claims classified as TCZ before and after the licensure of this agent. We used 2010 Medicare data linked to a large arthritis registry to assess the external validity of the algorithm.

Results: Of 472,803 claims with non-specific drug codes in our cohort, 9,762 claims satisfied the algorithm for TCZ; 74.3% of 9,762 claims were classified as TCZ by exact unit price or allowed amount, 4.4% by units unique for TCZ; 21.3% by diagnosis code and minimal deviation from allowed unit price or total allowed amount. Among preliminarily identified TCZ claims,

5% occurred prior to its licensure date and 95% after. The algorithm demonstrated good performance characteristics in the arthritis registry that included 2,161 enrollees with 34 known TCZ users: sensitivity 94% (95% CI 80–99), specificity 100% (99–100) and PPV 97% (84–100).

Conclusions: A claims-based algorithm can be used to accurately identify newly approved biologics administered parenterally prior to the assignment of a specific drug code.

883. Sex-Specific Association between Antidepressant Drug Use and Body Mass Index in Ambulatory Elderly: Results from the Rotterdam Study

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Background: Most evidence on antidepressant-induced weight gain is from clinical trials, which are not able to disentangle whether weight gain was caused by a relief of depressive symptoms or by the antidepressant drug itself.

Objectives: This study aimed to investigate the association between antidepressant drug use and body mass index (BMI) in a population-based study comprising ambulatory elderly. Furthermore, we assessed whether the association was modified by sex or by antidepressant drugs with a high receptor affinity.

Methods: Participants from the Rotterdam Study with information on BMI and depressive symptoms (Center of Epidemiologic Studies Depression scale or CES-D) were included in this study (n = 7,017; 16,333 measurements). Outcomes were defined as mean BMI and mean change in BMI between consecutive center visits. Data on antidepressant use were obtained from pharmacy records. All analyses were performed using repeated measurements with non-users as a reference group, considering concomitant use of anti-psychotic drugs and depressive symptoms as confounders. Results were additionally analyzed, stratified by sex and individual drugs.

Results: Compared to non-users (N = 15,784 measurements), users of SSRIs (N = 288 measurements) had a higher mean BMI (difference: 0.3 kg/m^2; p-value = 0.037) and a larger change in BMI between consecutive center visits (difference: $+0.46 \text{ kg/m}^2$ change; p-value < 0.001), but this was not shown for other antidepressant drug classes. The association between SSRIs and BMI was only observed in females and not in males (p for SSRIs*sex interaction = 0.066 and 0.008, respectively for BMI and BMI change). Stratification on individual SSRIs showed only a statistically significant association for paroxetine (N = 188 measurements).

Conclusions: In women, use of SSRIs was associated with a higher BMI compared to non-users. This association was only statistically significant for paroxetine, the SSRI with the highest receptor affinity. The difference in SSRI-induced weight gain between males and females might be explained by the difference in serotonergic signaling.

884. Strengthening Vaccine Lot Safety Surveillance

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Background: Controlling diseases with vaccines relies crucially on ensuring their safety. Despite stringent manufacturing controls, historical examples of production batch problems compel continuous close surveillance for contamination or other issues. However, safety surveillance of vaccine lots depends on spontaneous reports that often lack lot information, despite the 1986 U.S. National Childhood Vaccine Injury Act (NCVIA) requirement for detailed vaccination records.

Objectives: Enhance the value of safety case reports by improving vaccine lot data quality and completeness.

Methods: MedImmune analyzed accumulated safety case reports and developed a pilot project to check lot identifiers and intervals from distribution to vaccination in new case reports of safety concerns for its live attenuated influenza vaccine (LAIV).

Results: From 2003 to 2011, 7.2% of reported LAIV lots were not valid, and 43.4% of case reports had no lot identifier. Because LAIV has a short dating period (18 weeks), we examined case reports with valid lots and vaccination dates > 18 weeks after the lots' release dates but not coded for administration of expired product. Approximately 10% more reports had expired vaccine administrations than recognized by reporters. The pilot lot validation project detected an average of 1.77 discrepancies per week, facilitating data entry checks and focused follow-up for corrections.

Conclusions: To maximize the information value in spontaneous reports, vaccine manufacturers and regulatory authorities could implement lot data validation

for incoming case reports of suspected side effects or any other communications about specific vaccine lots. Manufacturers could validate lots in their reports, while FDA and CDC could validate lots in direct reports to the Vaccine Adverse Event Reporting System (VAERS). However, because the most frequent lot data deficiency is complete absence of identifiers, we also suggest that public health authorities and manufacturers could expand awareness of the NCVIA's requirements and the availability of lot details in provider records, so that reporters could more consistently supply vaccine lot identifiers.

885. Development of Safety Concerns within RMPs after Approval: A Cohort Study of Biologicals

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Background: Risk management plans (RMPs) form an integral part of the regulatory approval of new drugs in Europe. The RMP details all safety concerns and associated pharmacovigilance activities, facilitating post-approval knowledge increase. The process of knowledge incorporation in the RMP during a medicine's life cycle is currently unknown, and requires study.

Objectives: To explore the development of RMPs of biologicals after approval, by quantifying changes in safety concerns over time, and analyzing reasons for change.

Methods: For a cohort of 17 biologicals (approved 11/'05 – 12/'09) initial RMPs and subsequent updates until 12/'12 were retrieved from EMA. Information on baseline safety concerns and associated pharmacovigilance activities was extracted from initial RMPs and follow-up information from RMP updates. In RMPs safety concerns are classified as *identified risks*, *potential risks*, and *missing information* (e.g. use in children). Incidence rates of transitions between these three classes, additions after approval and 'omissions' (issue resolved or sufficiently studied) were calculated.

Results: The median number of safety concerns was 15 (range: 7–23) per product at approval: 3 identified and six potential risks, and five missing information. Median follow-up was 59 months per product, involving a median of eight RMP updates. During follow-up, 43/ 251 (3/49 identified risks, 29/99 potential risks, 11/103 missing information) of the concerns changed (0.045/ year overall, and 0.014/year, 0.084/year, 0.027/year for respective concerns). Among the 43 changes, 20 concerned omissions (three identified and nine potential risks, eight missing information), resulting from completion of committed studies (9/20) or other studies (3/ 20), no new data (4/20), or unknown (4/20). 59 concerns were newly added (21 identified and 23 potential risks, 15 missing information), originating from studies (20/59), spontaneous reports (10/59), new indications (9/59), or other/combination (20/59).

Conclusions: The observed development of RMPs after approval supports their role in a medicine's life cycle. Five years post-approval, the emphasis seems to be on newly emerged concerns, rather than on changes in baseline concerns.

886. Recent Trends in Medication Usage for the Treatment of Juvenile Idiopathic Arthritis in the U.S. and the Influence of TNF Inhibitors

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Background: The pharmacologic management of JIA has changed dramatically since the advent of TNF inhibitors (TNFi).

Objectives: Using claims from the last 7 years from a large commercial U.S. health insurer, we investigated medication use in JIA by calendar year and among individuals before and after new TNFi use.

Methods: We identified children < 17 years old with ≥ 1 physician diagnosis code for JIA. Use of TNFi, methotrexate (MTX), NSAIDs, and oral glucocorticoids (GC) was determined. Changes in medication usage over time were evaluated with Cochran-Armitage test for trend. New TNFi users were defined by no receipt of any TNFi in the 6 months immediately prior to starting TNFi and a minimum of 6 months of follow-up. Among prevalent users of NSAIDs and GC, we used paired *t*-tests to compare the number of filled prescriptions for NSAIDs and the cumulative mean daily GC dose in the 6 months before and after new TNFi use.

Results: We identified 3,531 unique individuals with JIA. The proportion of patients receiving TNFi increased from 8.0% in 2005 to 21.9% in 2011 (p < 0.0001), and the proportion of MTX users increased from 18.2% to 23.1% (p = 0.02). The proportion of NSAIDs users (50.3% in 2005) and GC users (19.4% in 2005) was relatively unchanged (p = 0.11; p = 0.10, respectively). We identified 269 new TNFi

users. Among 152 prevalent NSAID users, the number of prescriptions decreased in the 6 months following new TNFi (mean 2.89 before vs. 2.02 after; p < 0.0001). Among 103 prevalent GC users, the mean daily GC dose was reduced in the 6 months following new TNFi (mean decrease 3.1 mg/day; p = 0.0002). Many new TNFi users (147/269; 55%) had not filled a MTX prescription in the previous 6 months, and only 12% (17/147) of these used MTX in the 6 months following new TNFi. Overall, 39% (105/269) had any concurrent MTX use in the 6 months following new TNFi use.

Conclusions: TNFi use in the treatment of JIA has increased 2–3 fold over the last 7 years with a concurrent smaller increase in MTX use. New use of TNFi was associated with a reduction in NSAID and GC use. The data suggest that TNFi may be replacing, rather than complementing, MTX in many patients.

887. Autoimmune, Neurologic, and Venous Thromboembolic Adverse Events Following Administration of a Quadrivalent HPV Vaccine to Adolescent Girls in Denmark and Sweden

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Background: The introduction of a new vaccine will invariably put focus not only on its effectiveness but also on its safety.

Objectives: To assess the risk of serious adverse events after quadrivalent human papillomavirus (qHPV) vaccination.

Methods :

Design: Register-based cohort study, October, 2006, through December, 2010.

Setting: Denmark and Sweden. Participants: 997,585 girls aged 10–17 years, among whom 296,827 received a total of 696,419 qHPV vaccine doses.

Main outcome measure: Incident autoimmune, neurologic, and venous thromboembolic events (53 different outcomes) up to 180 days after each vaccine dose. Only events with at least five vaccine-exposed cases were considered for further assessment. Poisson regression was used to estimate age-, country-, and calendar year-adjusted rate ratios (RRs), comparing vaccinated and unvaccinated girls.

Results: Among the 53 outcomes, at least five vaccine-exposed cases occurred in 29 and these were analyzed

further. Whereas the RRs for 20 of 23 autoimmune events were not significantly increased, qHPV vaccine exposure was significantly associated with Behcet's syndrome, Raynaud's disease, and type 1 diabetes. Each of these three outcomes fulfilled only 1 of 3 predefined signal strengthening criteria; the pattern of distribution in time following vaccination was random for all three; and the RRs for these outcomes in the time period from day 181 following vaccination were similar to the RRs in the primary risk period. The RRs for five neurologic events were not significantly increased and there were inverse associations with epilepsy (RR 0.65, 95% CI 0.53–0.79) and paralysis (RR 0.55, 95% CI 0.34–0.88). There was no association between qHPV vaccine exposure and venous thromboembolism (RR 0.85, 95% CI 0.54–1.34).

Conclusions: This cohort study found no evidence supporting associations between qHPV vaccine exposure and autoimmune, neurologic, and venous thromboembolic adverse events. Although associations for three autoimmune events were initially observed, on further assessment, these were weak and not temporally related to vaccine exposure.

888. A Novel Approach to Assessing the Real-World Effectiveness of the Human Papillomavirus Vaccine: The Regression Discontinuity Design

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Background: The Regression Discontinuity Design (RDD) is a quasi-experimental, instrumental variable-based technique used to assess the impact of policy changes; it may also have valuable applications in pharmacoepidemiology.

Objectives: To test the assumptions of the RDD and determine whether it is an appropriate approach to evaluating the effectiveness of the quadrivalent human papillomavirus (HPV) vaccine on health outcomes.

Methods: Using Ontario administrative health and immunization databases, we identified a population-based cohort of girls in Grade 8 in 2003/04–2010/11. Exposure was categorized based on eligibility for free HPV vaccination (2003/04–2006/07 vs. 2007/08–2010/11) and actual vaccine receipt (0 vs. ≥ 1 dose). A continuous instrumental variable (−48 to 47) was created using birth month and year. Since −48 to −1 represented the unexposed cohort and 0–47 the exposed, December 1993 (instrument = −1) and January 1994 (instrument = 0) defined the eligibility cut-off. Baseline

characteristics (e.g., socio-demographics, vaccination history) of groups were compared, and the probability of vaccination was calculated and graphed, stratified by instrument.

Results: Based on data from 21 of the 36 immunization databases, we identified a cohort of 155,999 unexposed and 145,177 exposed girls (N = 301,176). Exposure cohorts were similar across factors like age, urban/rural status, and previous receipt of mandatory and optional vaccines, indicating groups are balanced on factors other than program exposure. A difference in income quintile was observed (p < 0.01), but is not expected when all 36 databases are used. A bar graph of the probability of vaccine receipt by instrumental variable confirmed two additional assumptions of the RDD were met – there was discontinuity in exposure at the cut-off (4.6% vs. 45.8%) and there were no discontinuities at locations other than the cut-off.

Conclusions: The RDD is suitable for use in this context. Applying this design to our large population-based cohort will allow us to assess the real-world impact of this vaccine on outcomes like anogenital warts and cervical dysplasia while minimizing confounding bias.

889. Applicability of the Brighton Collaboration Case Definition for Seizure after Immunization in Active and Enhanced Passive Surveillance in Canada

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Background: The Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) receives reports through active surveillance via the Immunization Monitoring Program ACTive (IMPACT) for selected AEFI leading to hospitalization and via passive surveillance enhanced by targeted reporting. As an AEFI of public health importance, seizure has always been an IMPACT target and included on the national reporting form. The Brighton Collaboration Case Definitions (BCCD) have been adopted by CAEFISS as the national case definitions but their applicability to active and passive surveillance has not been fully assessed.

Objectives: To evaluate data completeness and applicability of the BCCD for generalized seizure to AEFI reports collected through active surveillance (IMPACT) and enhanced passive surveillance (non-IMPACT).

Methods: This was a retrospective review of reports to CAEFISS (1998–2011) coded as seizure in children aged < 2 years. The case definition was BCCD level 1, 2 or 3 (at least history of unconsciousness and generalized motor manifestations). Physician-diagnosed generalized seizure not meeting the BCCD was designated level 4. Partial seizures were excluded from this analysis. The effects of reporting source, severity (serious = hospitalized > 24 h) and year (1998–2008 vs. 2009–2011) were assessed by stratified analysis.

Results: Of 1225 seizure reports analyzed, 375 were from IMPACT and 850 were from non-IMPACT sources. 240 (20%) cases met BCCD level 1, 2 or 3 including 121/574 (21%) serious and 119/651 (18%) non-serious cases (p = 0.2). Use of reporting forms capturing level of consciousness and motor manifestations (2009–2011) was associated with increases in cases meeting the BCCD (50% vs. 13% IMPACT, p < 0.001; 30% vs. 14% non-IMPACT, p < 0.001). Among reports from 2009 to 2011, level of consciousness was unavailable in 51% and motor manifestations were unavailable in 32%.

Conclusions: A minority of seizure reports met the BCCD. Eliciting level of consciousness and motor manifestations may increase the number of cases meeting the BCCD but this information is not always available in the source records.

890. Life-Style Characteristics of Elderly Persons Who Receive Seasonal Influenza Vaccination

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Background: Influenza vaccination has been associated with a range of positive outcomes in observational studies. It has been debated if these findings are at least in part due to healthy user bias. Seasonal influenza vaccination is recommended and provided free-of-charge to all persons aged 65+ years in Denmark. Few studies have provided data if elderly persons who receive influenza vaccination are actually more or less healthy than those who do not receive vaccination.

Objectives: To examine differences in life-style factors in elderly persons with and without receipt of influenza vaccine.

Methods: We conducted a cross-sectional study in the Central Denmark Region among elderly persons aged 65 years and older who received and returned a questionnaire as a part of a population-based Danish survey conducted in 2006. Data on receipt of influenza vaccination within +/− 6 month of the survey date was obtained from the Danish National Health Service Register. The prevalence of different life-style factors among influenza-vaccinated and unvaccinated persons was examined and compared by age- and sex-standardized prevalence ratios (PRs).

Results: We identified 4,250 elderly persons aged 65+ years, of whom 1,726 (40.6%) received current season's influenza vaccination. There was no major difference in the proportion of current smokers (17.4% vs. 19.0%; PR = 0.94, 95% CI: 0.82–1.07), while more vaccinated people were former smokers (53.5% vs. 47.0%, PR = 1.11, 95% CI: 1.04–1.18). There were no major differences in the prevalence of obesity (BMI $\geq$ 30: 15.1% vs. 14.3%; PR = 1.09, 95% CI: 0.94–1.26), dietary habits (unhealthy diet: 12.1% vs. 13.2%; PR = 0.91, 95% CI: 0.77–1.07), or excessive alcohol consumption (14.4% vs. 15.1%; 95% CI: 1.02, 95% CI: 0.88–1.19). Vaccinated persons were less likely to perform regular exercise (33.6% vs. 39.3%; PR = 0.87, 95% CI: 0.80–0.95).

Conclusions: We found no evidence of a particularly healthy life-style among elderly people who receive influenza vaccination. Life-style factors are therefore unlikely to be a major confounder in studies of influenza vaccination outcomes within a homogenous health-care system in Denmark.

891. Impact of Censoring at or Truncating Risk Time of Hospitalizations on the Effect Measure of the Association between Antiepileptic Drugs and Suicide Attempt

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Background: In observational pharmacoepidemiological studies prescription data is frequently used, which generally do not include inpatient medication information. This case of missing data is only seldom considered and censoring patients at first hospitalization requires this to be an independent censoring event.

Objectives: To evaluate the scope of the problem of hospitalizations on exposure status and the impact of censoring on estimates of the association between antiepileptic drug (AED) use and suicide attempts.

Methods: We performed a register based cohort study including 25% of the Danish population with all incident users of AEDs between 1/7-1996 and 16/12-2006. Further we used Cox analysis of suicide attempt comparing treatment status of AEDs, with adjustment for treatment indications and other treatment-related variables.

Results: We identified 26,916 hospitalizations (unrelated to outcome) among 43,069 incident users of AEDs. 5.16, 11.49 or 21.33% of patients were hospitalized within 10, 30 or 90 days, respectively, after the index date (the first AED prescription). Time spent in hospital accounted for 1.77% and 46.65%, respectively, of 159,065 person years. Comparing treatment status, the hazard rate ratios (HRR) estimate of suicide attempt was increased by 28% and by 31% when censoring after one overnight stay or 3 days at the hospital, respectively. The HRR increased by 5% if the periods of hospitalization were omitted, while keeping the follow-up time after discharge.

Conclusions: Censoring at first hospitalization changed estimates of increased risk of suicide among AED patients. This indicates that hospitalizations are not independent censoring events, and hence they should not simply be ignored when studying the risk of suicide in these patients.

893. Clinical Characteristics, Quality Measure Attainment, and Diabetes-Related Healthcare Costs in Patients with Type 2 Diabetes Mellitus (T2DM) Receiving Metformin (MET) and Sulfonylurea (SU)

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Background: Management of T2DM, particularly in elderly patients, might be challenging due to complex comorbidities and decline in functional status.

Objectives: This study examined the clinical characteristics of patients with T2DM and an elderly subgroup. Additionally, attainment of quality goals and its correlation with diabetes-related costs were assessed.

Methods: Health insurance claims and electronic medical records from 14,532 adults with T2DM (2007–2011) were used to identify a sample receiving MET+SU. The index date was defined as the first

dispensing of MET+SU after 6 months of eligibility. Clinical characteristics were assessed during baseline and quality measure attainment, defined as no values above specific thresholds (HbA1c < 8%, BMI < 30 kg/m^2, BP < 140/90 mmHg, LDL-C < 100 mg/dL), was evaluated during a 12-month landmark period after the index date. Association between quality measure attainment and diabetes-related costs, calculated after the landmark period, was evaluated using non-parametric bootstrap methods adjusting for imbalance in baseline characteristics between cohorts.

Results: 2,044 patients (mean age: 67 years; female: 46%), including 1,283 (62.8%) patients ≥ 65 years, were identified. Baseline comorbidities included cardiovascular disease (all patients: 25.5%; ≥ 65 years: 33.4%), congestive heart failure (5.9%; 8.1%), hypertension (66.5%; 74.2%), hyperlipidemia (73.9%; 78.1%), and neuropathy (16.0%; 20.2%). The proportions meeting quality goals were: 82.9% (≥ 65 years: 88.2%) for HbA1c, 34.4% (42.1%) for BMI, 31.6% (27.7%) for BP, and 68.2% (73.3%) for LDL-C. Quality measure attainment was associated with significantly lower diabetes-related costs per-patient per-year (adjusted mean cost differences: -$1,445 for HbA1c; -$1,218 for BMI; -$2,029 for HbA1c and BMI; all p < 0.05) compared to non-attainment.

Conclusions: This study highlights the high incidence of comorbidities and potential financial benefits of attaining T2DM quality outcomes in a population treated with MET+SU.

894. Evaluation of the Efficacy and Safety of Bitherapy on Moroccan Patients Treated from Hepatitis C

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Background: In Morocco studies estimate a prevalence of HCV to 3.5% for the whole population, and 5% for the age group between 45 and 75 years. According to these results, the number of patients with HCV in Morocco reached 300,000 and only 15,000 patients treated.

Objectives: The aim of this work is to findout the efficacy and safety of treatment with interferon alfa-2a and ribavirin in Moroccan patients suffrring from hepatitis C and identify factors associated with treatment response.

Methods: This is a retrospective study conducted between February and August 2012 in the regions of Casablanca, El Jadida, Mohammedia, Khouribgua, Beni Mellal, Safi; concerning clinical, paraclinical and therapeutic data collected from patients suffering from hepatitis C and treated over a period of 24 weeks (genotype 2, 3, 4) or 48 weeks (genotype 1).

Results: At the end of the study, 143 patients were followed up. The average age was 58.1 years. The sex ratio M/F was 0.90. Genotype 1 was observed in 63 patients (43.4%), genotype 2 in 59 patients (41.3%). The positive response was observed in 73 patients (51.4), relapse in 42 patients (29.4%) and negative response in 28 patients (19.5%). 14 patients stopped their treatment (9.8%). The main side effects were asthenia (88.8%), metabolic and liver complications: the hepatocellular carcinoma, cirrhosis, graft cases, leukopenia, acute anemia (4.9%). In multivariate analysis, the associated factor with healing was discontinuation of treatment (p = 0.005 OR = 12.2 95% CI [−60.705 2.482]. Predictive Values of a Positive Response at week 12 were: 83, 01% for genotype 1 and 95% for genotype 2. Predictive Values of Negative Response at week 12 were: 59.25% for genotype 1 and 33.33% for genotype 2.

Conclusions: Discontinuations constitute a significant risk to the success of the treatment, improving treatment outcomes of hepatitis C depends on the continuity of the treatment itself, compliance with protocols and patient education.

895. Correlates of Nonmedical Use of ADHD-Type Stimulants vs. Nonmedical Use of Other Stimulants in a U.S. National Sample

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Background: ADHD stimulants have the highest abuse potential among the legally approved drugs, but few studies focus on nonmedical use of ADHD stimulants.

Objectives: To compare sociodemographic characteristics, mental health status, deviant behaviors, and other substance use in nonmedical ADHD stimulant users and other stimulant users.

Methods: Using data from the 2009–2011 National Survey on Drug Use and Health (NSDUH), 11,370

individuals reporting nonmedical use of ADHD stimulants and 4,732 reporting nonmedical use of other stimulants were compared. Data were analyzed via binary logistic regressions adjusting for sociodemographics.

Results: Compared to other stimulant users, nonmedical ADHD stimulant users were more likely to be male, young, white, never married, from lower income families, unemployed, and to have some college education. Among adults, nonmedical ADHD stimulant users were more likely to use marijuana, cocaine, heroin, hallucinogens, ecstasy, prescription opioids, tranquilizers, and sedatives, while adolescents were only more likely to use marijuana, hallucinogens, ecstasy, tranquilizers, and alcohol, compared to other stimulant users. Adult nonmedical ADHD stimulant users (vs. other stimulant users) were more likely to have past-year major depression (aOR = 1.4[1.1,1.7]) and to receive mental health treatment (aOR = 1.3[1.1, 1.5]), while adolescent users showed lower likelihood of major depression (aOR = 0.5[0.3, 0.8]) as compared to other stimulant users. Adolescent ADHD stimulant users were more likely to engage in deviant behaviors than other stimulant users, including being arrested and booked (aOR = 2.8[1.7, 4.8]), selling illegal drugs (aOR = 3.2 [2.0, 5.1]), stealing (aOR = 2.3[1.5, 3.6]), and attacking others (aOR = 1.67[1.1, 2.5]), while adult ADHD stimulant users were only more likely than their other stimulant user counterparts to sell illegal drugs.

Conclusions: This study provides evidence that nonmedical ADHD stimulant users have different substance use, mental health and deviant behavior profiles as compared to other stimulant users. The findings have implications for policy aimed at curbing nonmedical use of prescription stimulants.

896. High Use of Opioids in Patients with Dementia

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Background: Several studies have shown that patients with dementia receive less analgesic medication than their cognitively intact peers, but recently published studies have suggested that this pattern might be changing.

Objectives: We investigated the prevalent use of analgesics, using data from the Danish prescription database, comparing home dwelling and institutionalized elderly with and without dementia.

Methods: We used individual-level data from national Danish registers to investigate the use of opioids (ATC code: N02A) in the Danish elderly population over 65 years old. The Danish Prescription database covers all prescription medication bought from 1995 and forward. We compared the use of opioids in 2010 in patients who had been diagnosed with dementia with elderly not diagnosed with dementia. Home living and institutionalized subjects were assessed separately.

Results: Of 860,784 elderly Danish residents, 34,045 had been diagnosed with dementia between 01.01.2000 and 31.12.2009. Of home dwelling patients with dementia, 27.3% filled a prescription for an opioid in 2010, compared with 16.8% of individuals at home without dementia (p < 0.0001). Of institutionalized patients with dementia, 37.8% filled a prescription for an opioid, compared with an even higher prevalence in institutionalized patients without dementia (42.9%, p < 0.0001). In all elderly, use of long-acting opioids, i.e. fentanyl (5.9%) and buprenorphin (9.1%), was significantly higher in patients with dementia compared with elderly without dementia (1.3%, and 1.5%, respectively). For institutionalized patients the use of fentanyl were comparable in patients with and without dementia (appr. 8%), but patients with dementia used more buprenorphin (12.4% vs. 9.2%).

Conclusions: In Denmark, home living patients with dementia receive significantly more opioids than elderly without dementia, which is contrary to previously published studies. Institutionalized elderly's use of opioids is very high irrespective of dementia, though higher in those without dementia. The increased use of long-acting opioids in the most fragile of the elderly (ie. patients with dementia and/or nursing home residents) is concerning and needs to be further investigated.

897. Withdrawn by Author.

898. Combination Antihypertensive Therapy in Older Americans

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Background: Over 50 million Americans have hypertension–an important risk factor for cardiovascular

morbidity and mortality. Yet little is known about patterns of antihypertensive usage in older patients in 'real world' settings.

Objectives: To describe new users of antihypertensive therapy and identify predictors of combo initiation among older Americans.

Methods: We used Medicare claims (2007–2010) to identify a cohort of new users of antihypertensives. Eligible new users were ≥ 66 at initiation, continuously enrolled in Parts A/B for ≥ 1 year prior, and had no claims for antihypertensives in the prior 6 months. Patients with a claim for a second antihypertensive class within 15 days after index date were defined as combo initiators. Prevalence ratios (PR) and 95% confidence intervals (CI) for initiating combo vs. monotherapy were estimated by multivariable Poisson regression. Candidate predictors included gender, age, race, prescriber characteristics, comorbidities and co-medications.

Results: In preliminary results through 2009, we identified 343,189 new users, 21.5% of whom initiated combo therapy. The two most prevalent combos were ACEI+THZ (5.0%) and ACEI+BB (5.0%). Compared to monotherapy, combo initiators were younger (75.7 year [SD = 7.5] vs. 76.6 year [SD = 8.1]), more likely to be African-American (13.5 vs. 7.7%), and more likely to have had a recent myocardial infarction (5.0 vs. 1.5%), but less likely to be taking other medications (52.4 vs. 66.2%). Being African-American (female [1.57, 1.50–1.63], male [1.51, 1.45–1.59]), taking other medications (0.79 per drug, 0.77–0.81), having unstable angina (1.24, 1.19–1.28) or chronic heart failure (1.30, 1.27–1.33) were moderate predictors. Atrial fibrillation (0.91, 0.88–0.93) and diabetes (1.08, 1.06–1.10) were weak predictors. Patients with chronic kidney disease were equally likely to use combo or monotherapy (1.00, 0.97–1.03).

Conclusions: In this population-based analysis of older Americans, 1 in 5 new users of antihypertensives start treatment with combination therapy with the most frequent combination being ACEI+THZ. In the absence of blood pressure data, the strongest predictors of combination vs. monotherapy were African-American race and number of co-medications.

899. Validaton of a Cohort of New Users of Oral Antidiabetic Agents Free of Microvascular Complications in the RAMQ Database

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Background: Statistics on diabetes and its complications are well monitored through the Chronic Disease Surveillance System in Canada. However, data on drug usage, particularly among new users of Oral Antidiabetic Agents are limited.

Objectives: To validate a cohort of new Oral Antidiabetic users free of reported microvascular complications by comparing the baseline characteristics of the population with statistics from the Chronic Disease Surveillance System and other published data in Canada.

Methods: We identified new users of at least one Oral Antidiabetic between 2000 and 2009 using Quebec administrative data (RAMQ). New use was defined as a pharmacy claim for any Oral Antidiabetic following 24 Antidiabetic-free months of plan eligibility. Patients were included if they were aged between 45 and 85 years of age and were free of reported microvascular outcomes (retinopathy, end-stage renal failure or neuropathic complication). Characteristics of patients and determinants of microvascular endpoints were presented as proportions for categorical variables and as means with standard deviation (SD) for continuous variables.

Results: Among the 122,100 patients who initiated an Antidiabetic, 50% were men and 14% received social assistance; mean age was 67(10) years and 52% had a cardiovascular disease (30% ischemic heart disease, 7% cerebrovascular disease, 6% peripheral arterial disease, 9% heart failure, 13% at least two heart complications). Cardiovascular risks include dyslipidemia and hypertension, which were reported in respectively 58% and 76% of users. 8900 patients (7%) had chronic kidney disease. Metformin accounted for 79% of all initial prescriptions while sulfonylureas accounted for 12%. In the year prior to the index date, the mean number of hospitalizations was 0.3(0.7), 7(7) visits to a physician, and patients filled 7(5) prescriptions.

Conclusions: Our data confirm that our cohort of new users of oral antidiabetics free of reported microvascular complications show a similar profile to other Canadian Diabetic patients. Our approach will further assess the effect of adherence to oral antidiabetic agents on the occurrence of microvascular endpoints.

900. Pharmaco-Epidemiological Study of Treatment Resistant Schizophrenia and Clozapine Treatment

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Background: Approximately 30% of patients with schizophrenia (SZ) are considered to be treatment resistant, i.e. not responding to first-line antipsychotic (AP) treatment. Clozapine (CLZ) is recommended in treatment resistant schizophrenia (TRS), but is considered to be underused, probably due to the fear of severe side effects and the inconvenience of mandatory regular blood monitoring. However, little is known about predictors which could identify patients with TRS, i.e. eligible for treatment with CLZ.

Objectives: To determine base-line predictors of TRS and investigate the association of known risk factors of SZ and TRS.

Methods: Population-based register study using Danish register data on patients newly diagnosed with SZ from 1995 to 2006 and information on AP prescriptions from 1995 to 2010. TRS is defined using prescription data as (1) CLZ initiation, or (2) eligibility for CLZ, defined according to treatment guidelines as first event of either initiating CLZ or a fourth different AP. Logistic regression analysis of TRS within 4 years of follow-up is performed to identify factors predictive of TRS.

Results: Of all SZ (n = 12,087) patients 12.4% filled a prescription for CLZ, 21.4% received a fourth different AP prescription (not CLZ), resulting in 31.4% with TRS defined as 2). Female gender was associated with increased CLZ treatment, OR = 1.3 (95% CI: 1.1–1.5), as well as admission to psychiatric hospital and paranoid subtype at first SZ diagnosis. Age at onset and calendar year of diagnosis were both associated with decreased odds per year. A family history (parents or siblings) of SZ was not found to be significantly associated with CLZ treatment, OR = 0.8 (95% CI: 0.6–1.1). Results of the analyses including all the mentioned factors were basically the same.

Conclusions: The analysis using Danish prescription data indicate that CLZ is prescribed less than recommended. Several factors observable at first diagnosis were found to be significantly associated with TRS (in terms of CLZ initiation). No significant association was found between a family history of SZ and CLZ initiation.

901. Trends of Utilization of and Spending on Anti-Tuberculosis Medications in the United States Medicaid Program from 1991 to 2011

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Background: Tuberculosis (TB) is a serious infectious disease which affects the respiratory system. In 2011, 10,521 new TB cases were reported in the U.S. The anti-TB drug class contains both first- and second-line treatments, with the first-line regimen considered the skeleton of TB eradication.

Objectives: The purpose of the current study was to describe the trends in utilization of and spending on anti-TB drugs generally and individual anti-TB medications in the U.S. Medicaid Program.

Methods: A retrospective, descriptive analysis was conducted to examine the trends in utilization of and spending on anti-TB medications, using the national Medicaid pharmacy files from 1991 quarter 1 through 2011 quarter 2. Study drugs included isoniazid, rifampin, pyrazinamide, and ethambutol (first-line therapies); and cycloserine, kanamycin, streptomycin, amikacin, capreomycin, moxifloxacin, rifater, rifamate, thioamides, paser, rifapentine and rifabutin (second-line therapies). Quarterly prescription numbers and reimbursement amounts were calculated over time by summing data for individual drug products. The quarterly per-prescription reimbursement as a proxy for drug price was computed for each drug.

Results: Total Medicaid utilization of anti-TB drugs rose by 43% from 151,344 in 1991 to 216,271 in 2011. Utilization of the first-line drugs increased from 47,348 in 1991 to 65,482 in 1993, stayed at this level for 4 years, and then decreased to an average of 43,245 per year. Medicaid reimbursement for anti-TB medications increased 246% ($6.5 million to $22.4 million) between 1991 and 2011. Prices for second-line drugs were higher than those for traditional drugs due to absence of generic availability for the newer drugs. In 2011, reimbursement for second-line agents was 10 times that for first-line therapies.

Conclusions: Utilization of anti-TB drugs was closely related to disease incidence. The rise in spending on second-line agents may be due to increased usage for other indications along with rising prices. An effective management program for anti-TB drug prescribing might be helpful for Medicaid.

902. Prescription Patterns of Antihypertensives in a Community-Health Center in Mexico City. A Drug Utilization Study

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Background: Hypertension prevalence has increased in Mexico during the last few years; in parallel, antihypertensive consumption has similarly increased. The adequacy of this consumption to the existing prevalence of hypertension and to current guidelines is unknown.

Objectives: To learn the pattern of antihypertensive prescription and to compare it with official recommendations.

Methods: A survey was carried out in a community-health center in Mexico City. Medical records were searched to identify those corresponding to patients diagnosed of this condition during the year 2012. All relevant information was retrieved with particular attention to medication patterns. Consumption patterns were then compared to current recommendations included in the official guidelines (*Guia de Práctica Clínica. Diagnóstico y Tratamiento de la Hipertensión Arterial en el Primer Nivel de Atención*).

Results: A total of 102 records of interest were identified; mean age of patients was 61 years (age range, 32–89; women, 69.6%). Of them, 96 patients received some medication for hypertension. Patients younger than 55 years-old (n = 30) were treated mostly with angiotensin-converting-enzyme inhibitors, the recommended ones; for those patients being 55 years or older (n = 66), thiazides or calcium antagonists, the recommended medications, were not the most used.

Conclusions: The patterns of consumption do not fully correspond with those recommended in the official guidelines in Mexico. There is a need for an educational intervention directed to health professionals and patients.

903. Glucocorticoid-Induced Osteoporosis Management: A Systematic Review

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Background: Glucocorticoid (GC) therapy is commonly prescribed to reduce inflammation, pain and morbidity in patients with inflammatory arthritis, inflammatory bowel disease, chronic lung disease and severe dermatologic reactions. However, prolonged use of oral GC-therapy is the most common cause of secondary osteoporosis. Fracture risk increases within 3 months of starting daily oral GC therapy, and 30–50% of adults treated with long-term oral GCs experience a fracture. Clinical practice guidelines recommend that all patients starting oral GC therapy $\geq$ 3 months receive bone mineral density (BMD) testing and/or osteoporosis treatment.

Objectives: To identify the proportion of long-term oral GC users ($\geq$ 3 months) receiving osteoporosis management (BMD test and osteoporosis treatment).

Methods: We completed a systematic search of MEDLINE to identify all English language articles that examined GC-induced osteoporosis management. Review articles, intervention studies, and studies identifying only treatment without BMD testing were excluded. Study methods and outcomes (BMD testing and osteoporosis treatment) were abstracted and summarized by calendar year and geographic location.

Results: We identified 23 eligible papers published between 1999 and 2012: 15 studies were completed in North America, three in Europe, and five in other regions. Heterogeneity in methods used to define long-term GC exposure and patient populations precluded the direct comparison of results between countries, by practice site, or over time. However, 70% of studies identified BMD testing and osteoporosis treatment rates < 40%, 35% to 43% of studies reported rates < 20%, and little evidence suggested any increase in osteoporosis management over time.

Conclusions: Despite consistent recommendations across clinical practice guidelines to target osteoporosis prevention at the onset of GC-therapy, osteoporosis management among long-term GC-users is low with little evidence that rates are improving. This represents a missed opportunity for fracture prevention among chronically ill patients requiring prolonged GC-therapy. Targeted interventions are needed to help reduce the burden of fracture-related morbidity associated with GC-induced osteoporosis.

904. The Prescribing of Simvastatin in the UK – A Drug Utilisation Study in the Clinical Practice Research Datalink (CPRD)

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Background: Statins are used in the prevention and treatment of cardiovascular disease. The SEARCH trial found that 80 mg simvastatin provided little additional benefit compared to 20 mg. As a result the MHRA is reviewing the risk benefit balance of high dose simvastatin. This DUS was conducted to characterise the population and evaluate patterns of use.

Objectives: To compare time to first high-intensity dose simvastatin from first simvastatin therapy among users for primary prevention and secondary treatment.

Methods: Data on patients aged 40–99 years initiating simvastatin 2007–2011 were extracted from the CPRD. Those registered for a year with no prior record of a statin were considered new users. Secondary treatment was assumed when there was a previous cardiovascular disease diagnosis, with primary prevention assumed otherwise. High intensity statins were defined as those with greater cholesterol lowering activity than simvastatin 40 mg according to NICE guidelines (> 40 mg simvastatin, > 10 mg atorvastatin, > 40 mg fluvastatin and > 5 mg rosuvastatin). Time from initiating simvastatin therapy to first high-intensity simvastatin was measured using a subdistribution competing-risks hazard regression model.

Results: 199,594 patients initiated simvastatin, 39% for primary prevention. 0.27% started on a high intensity dose. 1.62% of patients switched to high-intensity simvastatin, 11% experienced a competing risk event (death, switch to another high-intensity statin or statin discontinuation) with 87.19% censored. Secondary treatment was associated with a decreased incidence of high-intensity simvastatin-use; SHR = 0.79, 95% CI: (0.74,0.85) p < 0.0001. Controlling for age and gender attenuated the association; SHR = 0.95, 95% CI: (0.88,1.02) p = 0.127.

Conclusions: The incidence of high-intensity simvastatin use is low. Secondary treatment was associated with a higher rate compared to use for primary prevention. After adjusting for age and gender the association was attenuated, as secondary prevention users were older on average than primary prevention users. Further analyses will focus on reasons for dose-switching and outcomes associated with high-intensity statins.

905. Provider Contact and Antidepressant Fills Prior to Suicide Attempt: A Retrospective Case Series of 32,000 Attempters

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Background: It has been estimated that 45% of suicide completers have contact with a primary care provider (PCP) within 30 days of their death, and 19% have contact with a mental health provider (MHP). Health care provider contact and medications filled prior to a suicide attempt, however, are not well understood.

Objectives: To estimate the prevalence of primary care and mental health provider contacts and antidepressant (AD) fills prior to suicide attempts.

Methods: We identified a retrospective case series of suicide attempters from the IMS LifeLink Health Plan Claims Database, a large source of longitudinal health care claims in the US. The data included paid medical and pharmacy claims from 1999 to 2008. We included patients with at least one diagnosis code indicating a suicide attempt and at least 180 days of continuous health plan eligibility prior to the attempt. We estimated the proportion of attempters with PCP and MHP contacts and the proportion with an AD fill within 180 days before their first attempt.

Results: We identified 32,249 patients age 5–89 years with a suicide attempt (average age 30 years, 34% male). Half (54%) had a mental health diagnosis within 180 days before their attempt. Most (74%) saw a PCP during the same time period, while 38% saw a MHP (20% had no PCP or MHP contact). Within 30 days before their attempt, 54% had contact with a PCP or MHP (41% PCP, 27% MHP). Nearly 40% of attempters filled at least one AD during the 180 days prior to their attempt. Prevalence of provider contact was high among the 60% who did not fill an AD: 65% had contact with a PCP during 180 days prior, 22% with a MHP.

Conclusions: This study found a high prevalence of PCP contact during the 180 days prior to a suicide attempt, double the frequency of MHP contact. Health care providers may more closely monitor patients taking an AD due to the possible increased suicide risk associated with the medication. In the current study, however, PCP contact was frequent even among patients not receiving an AD. These data further support primary care as an opportunity to identify and intervene with suicidal patients.

906. The Effect of Adherence on Treatment Change among HIV/AIDS Patients at the Korle-Bu Teaching Hospital in Ghana

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Background: Antiretroviral therapy (ART) is the mainstay in the management of HIV/AIDS. A level of at least 95% adherence has been found to be beneficial among HIV/AIDS patients. Low adherence may lead to treatment failure or may be the result of side effects. Both may subsequently lead to treatment change.

Objectives: To evaluate the effect of adherence on ART change.

Methods: Data for this matched case control study were extracted from available written clinical and pharmacy records and the electronic database at the Korle-Bu Teaching Hospital. Cases comprised all those ($\geq$ 15 years) starting first line ART for at least 1 month between 1/1/2004 and 31/12/2009 who experienced a first change in therapy. Controls (who did not change treatment) were matched one-to-one to cases on date of start ART +/−15 days. Adherence was determined using the proportion of days covered (PDC) approach and poor adherence was defined as PDC levels below 95%. Measures of effect were calculated using conditional logistic regression. A variable was described as a possible confounder if it was associated with the outcome with a $p < 0.2$.

Results: The 298 cases and 298 matched controls were similar in all baseline characteristics except initial body mass index ($p = 0.048$) and WHO staging of HIV ($p = 0.047$). Among cases 20.1% (60/298) changed to second line therapy whilst the others changed to other first line treatments. Overall, 11.2% of controls compared to 20.1% of cases had adherence levels below 95% (crude odds ratio (OR) 2.35, 95% CI 1.33–4.15, $p < 0.0001$). After adjusting for all possible confounders adherence levels below 95% was about three and half times (ORadj = 3.45 [95% CI 1.22–9.77]) as likely to lead to a treatment change compared to levels higher than or equal to 95%.

Conclusions: Although over 4 out of 5 cases and controls adhered to treatment, the fact that poor adherence is associated with over three times the likelihood of switching calls for concern, especially in the light of second-line treatment costs. Because of the high HIV/AIDS burden in sub-Saharan Africa more work needs to be done to improve adherence to antiretroviral therapy.

907. A Pregabalin Drug Utilization Study Report

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Background: Based on a number of case reports from some European countries, the European Medicines Agency (EMA) requested that Pfizer conduct a Drug Utilization Study (DUS) to evaluate potential for abuse of pregabalin.

Objectives: To evaluate prescribing patterns for pregabalin and assess the proportion of pregabalin patients with a substance abuse history.

Methods: This descriptive, retrospective DUS examined prescribing patterns of pregabalin from The Health Improvement Network (THIN) in the United Kingdom (UK). Diagnoses served as a proxy for the European Union approved pregabalin indications of epilepsy, neuropathic pain (NP), and generalized anxiety disorder (GAD). Patients without a diagnosis code corresponding to an approved pregabalin indication were categorised as 'other'. Substance abuse history was defined via diagnostic codes or medications used to treat abuse of alcohol, tobacco, prescription medications, or illegal substances.

Results: A total of 18,951 patients in the THIN database were prescribed pregabalin between September 2004 and July 2009. The median age was 58 years and 40% were male. The mean average daily dose (ADD) prescribed was: 244 mg/day for epilepsy, 235 mg/day for NP, 209 mg/day for GAD and 204 mg/day for other diagnoses. There were 136 (1%) patients prescribed an ADD over 600 mg (the maximum labeled dose) and 18% of them (25/136) had a recorded history of substance abuse. The proportions by diagnosis were epilepsy 6% (8/136), NP 26% (35/136), GAD 16% (22/136), and 'other' 58% (79/136). Approximately 14% (2,587/18,951) of all patients had a recorded history of substance abuse.

Conclusions: Data from the THIN (UK) database suggest that prescribed pregabalin doses were generally appropriate based on diagnosis. Fourteen percent of all patients had a recorded history of substance abuse. A small proportion (1%) of patients were prescribed high doses (more than the labeled maximum daily dose) and of those, < 1 in 5 patients also had a recorded history of substance abuse.

908. Trends in Antibacterial Use in a German Intensive Care Unit (ICU)

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Background: Antibacterial therapy requires constant surveillance in all settings to guide interventions for minimization of resistance development. This includes prescribing intensities and time trends from ICUs where both infection and resistance prevalence is high but individual level data are rarely available.

Objectives: To determine intensity and time trends of antibacterial use in a surgical ICU.

Methods: We analyzed demographic and antibacterial administration data from the electronic medical records from the 26-bed surgical ICU of a tertiary care hospital in Mannheim, Germany, from 04/2006 to 10/2011. For our Poisson models we defined a treatment day as a record of one or more doses of a specific antibacterial in a calendar day in a patient. A calendar day could represent > 1 treatment days in case of antibacterial switch or combination therapy. Admission and discharge days were counted as complete patient days. Antibacterial classes were also separately analyzed.

Results: During 13,553 ICU admissions with 57,792 patient days, antibacterials were administered during 4,215 admissions (31.1%) with 33,085 treatment days. Adjusted for monthly variation, we observed an increase in treatment days for all antibacterials by 38.2% (rate ratio comparing 2011–2006, 95% confidence interval (CI) 20.2–58.9%). The corresponding adjusted average annual increase was 8.7% (95% CI 6.1–11.3%). This increase varied for antibacterial classes and was strongest for quinolones (23.6%, 95% CI 16.7–30.9%) that on average were administered in 11.0% (95% CI 9.8–12.4%) of patient days with a maximum of 17.3% (95% CI 14.5–20.7%, 1390 treatment days) in 2011.

Conclusions: The observed increase in treatment days may be due to changes in patient characteristics. It could represent an increase in antibacterial combination therapy or exposed patient days. The latter is supported by the trend in quinolones, a class known to be associated with antibiotic resistance. These unfavorable changes in quinolone use may result from more frequent treatment initiation locally, or from treatment continuation reflecting increased utilization in referring wards or external centers impacting our utilization patterns, which should be investigated.

909. Trends in Prevalent and Incident Use of Blood Glucose-Lowering Agents in Norway: No Increase in Incidence 2006–2011

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Background: Numerous studies show that the prevalence of diabetes is increasing in most countries.

Objectives: Describe time trends in prevalent and incident use of blood glucose-lowering drugs in all age groups in Norway during 2005–2011.

Methods: The Norwegian Prescription Database contains all prescriptions dispensed from all pharmacies covering the entire population (4.9 million). All individuals having blood glucose-lowering drugs in the study period were retrieved. Prevalence and incidence rates of use of all blood glucose-lowering drugs (ATC code A10), insulins and analogues (A10A) and non-insulins (A10B) were calculated. A reference period of 24 months without dispensed blood glucose-lowering drugs was used to define new users. Influence of age, gender and period were modelled using Poisson regression. Mean population from Statistics Norway was used in the calculations.

Results: The overall 1-year prevalence of blood glucose-lowering drugs use in Norway increased from 2.5% in 2005 to 3.2% in 2011. Among users of non-insulins, the 1-year prevalence increased from 1.8% to 2.5%. The number of new users of non-insulins decreased significantly from 2010 to 2011. In the patient group receiving insulin only, the 1-year prevalence and the incidence rate were both stable in the period 2006–2010.

Conclusions: The proportion of the Norwegian population using blood glucose-lowering drugs other than insulins increased during 2005–2011. The interpretation of this finding is an increase in drug-treated Type 2 Diabetes. Interestingly, the number of new users of non-insulins decreased significantly from 2010 to 2011. The prevalence and incidence of insulin use only, were stable during the study period suggesting no increase in Type 1 Diabetes.

910. Prevalence, Incidence, Treatment Patterns and Mortality in Patients with Acute Coronary Syndrome in France from 2004 to 2009

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Background: Few epidemiologic data on the evolution of prevalence and incidence of acute coronary syndrome (ACS) and treatment patterns for secondary prevention of ACS are available in France.

Objectives: Estimate the evolution from 2004 to 2009 of the prevalence, incidence, treatment patterns and mortality of ACS in France.

Methods: Repeated cross-sectional study from 2004 to 2009 in the 1/97 permanent random sample of the French national healthcare insurance database (Echantillon Généraliste de Bénéficiaires, EGB). Patients were identified using the long-term disease classification system (Affection de Longue Durée, ALD) resulting in full healthcare benefits coverage. The drugs of interest were the four therapeutic classes recommended in the secondary prevention after occurrence of ACS: betablockers, antiplatelet agents, statins or other lipid-lowering agents (LLA), and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). The prevalence and incidence of ACS, the mortality of patients with ACS and the exposure to these drug classes was assessed for each year from 2004 to 2009.

Results: A total of 9 622 ACS patients were identified from 2004 to 2009 resulting in an estimated national prevalence of 868,493–1,029,573 patients. During this period, incidence changed from 71 238 to 79 671 per year. Overall exposure to the four therapeutic classes increased from 2004 to 2009: 61.1% to 66.3% of patients had at least one dispensation of betablockers, 72.2% to 79.5% of antiplatelet agents, 74.0% to 82.2% of statins or other LLA and 51.6% to 64.7% of ACEI or ARB. The overall mortality varied from 3.5% in 2004 to 4.1% in 2009, related to increasing population age over time.

Conclusions: Exposure to secondary prevention in prevalent patients recorded with ACS identified from registration for full healthcare benefits coverage, seems suboptimal but improving over the study period.

911. Clinical Provider Perceptions of Intentional Medication Discontinuation

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Background: While medication adherence and medication reconciliation receive considerable attention, there has been less focus on intentional, proactive *discontinuation* of medications that may no longer be necessary or whose benefits no longer outweigh associated risks.

Objectives: To identify clinical provider beliefs and attitudes associated with medication discontinuation.

Methods: We conducted 45–60 min semi-structured qualitative interviews with 20 Primary Care providers at two Veterans Affairs (VA) Medical Centers. Providers discussed perceptions of medication management, polypharmacy and clinical decision making related to discontinuation. Transcribed interviews were analyzed based on the principles of grounded theory.

Results: Study participants had varying years of clinical experience and mixed exposure to prior practice in non-VA settings. We identified five domains that affected how clinical providers make and act upon decisions to discontinue medication: (1) Polypharmacy – perceptions of its definition, prevalence and importance; (2) Understanding of the patient – developed relationships, established trust and open communication enabled better understanding of patients' knowledge of and adherence to their medications, establishing a foundation upon which decisions could be based; (3) Clinical reasoning and decision making – the rationale and professional jurisdiction that support medication discontinuation; (4) Clinical practice activities – actions required in patient care, often requiring providers to multitask or feel time pressures; and (5) Structural factors such as personnel (e.g., provider roles and care-team composition), system (e.g., coordination across multiple providers and locations) and information technologies.

Conclusions: Clinicians express a wide variety of opinions and viewpoints related to medication management decisions, and especially discontinuation. In order to develop and implement effective interventions that improve prescribing practices, whether targeted at the clinician or organization of care delivery, additional

research is needed on the full range of attitudes and beliefs harbored by clinical providers as well as the environments in which they practice.

912. Prevalence of Antibiotic Use: A Methodological Comparison across Various European Health Care Data Sources

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Background: There is widespread concern about possible increases in antibiotic use but comparative data from different European countries on levels of use are lacking.

Objectives: This study was designed to measure and understand the variation in antibiotic utilization across seven European health care databases from Denmark, Germany, the Netherlands, Spain and the United Kingdom between 2004 and 2009.

Methods: Descriptive analyses were stratified by gender, age and type of antibiotic. Separate analyses were performed to measure the most common underlying indications leading to the prescription of an antibiotic agent.

Results: The average yearly period prevalence of antibiotic use between 2004 and 2009 varied from 15 (Netherlands) to 30 (Spain) users per 100 patients, whilst the overall number of prescriptions for antibiotic agents increased. A higher prevalence of antibiotic use by females, the very young (0–9 years) and old (80+) was consistently observed in all databases. The lowest point prevalence was recorded in June and September and ranged from 0.51 (Netherlands) to 1.47 (UK) per 100 patients per day. Twelve (Netherlands) to 49 (Spain) percent of all users were diagnosed with a respiratory tract infection and the most common type of antibiotic drug class in every database were penicillins.

Conclusions: Using identical methodology in all 7 EU databases to assess antibiotic use allowed us to compare drug usage patterns across Europe. Our results contribute quantitatively to the overall understanding of the pattern of use of antibiotic agents in different EU countries.

913. Variation in 12-Lead Electrocardiography for Chest Pain Patients Transported in North Carolina by Emergency Medical Service

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Background: Prehospital 12-lead electrocardiography (ECG) is critical to timely ST-Elevated Myocardial Infarction (STEMI) care; however, its use remains inconsistent. Previous studies to identify reasons for failure to obtain a prehospital ECG have generally only focused on individual Emergency Medical Services (EMS) systems in urban areas.

Objectives: To identify patient, geographic, and EMS agency-related factors associated with performing a pre-hospital ECG across the state of North Carolina (NC).

Methods: A cohort of emergency transports occurring between 1/1/2008 and 11/29/2010 consisting of patients at least 30 years of age with a pre-hospital chief complaint of chest pain was identified from the NC Pre-hospital Medical Information System (PreMIS). Age, gender, race, pulse rate, blood pressure, transport time, time of day, day of week, year of service, highest EMS crew certification, agency type, rural status, EMS system ECG capability, and health referral region were

assessed for association with ECG utilization. The relative risk of ECG utilization was estimated for each factor individually and adjusting for demographic factors.

Results: Among 3.1 million EMS encounters, 134,350 patient transports met study criteria. From 2008 to 2010, a pre-hospital ECG was performed in 82,311 (61%) of chest pain transports; utilization increased from 55% in 2008 to 65% in 2010 (trend p < 0.001). Utilization by health referral region ranged from 22.9% to 74.2% and was lowest in rural areas. The certification-level of the EMS provider and system-level ECG equipment availability were the strongest predictors of ECG utilization. Persons in an ambulance with a Paramedic were significantly more likely to receive a pre-hospital ECG than ambulances without one (RR 2.15, 95% CI 1.55, 2.99). Other factors had near null or insignificant relative risks.

Conclusions: Across a large geographic area prehospital ECG use increased over a 2 year period in North Carolina, although large gaps in quality still remain. Increasing capability to perform a prehospital ECG in rural areas and improving EMS certification training levels appear to be the most promising areas for improvement.

914. Audit of Dabigatran Use at a Canadian Tertiary Care Centre

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Background: Real-world use of dabigatran, a direct thrombin inhibitor shown to prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF), has revealed reports of serious bleeding events, lack of an effective reversal agent, and use beyond the approved indication.

Objectives: To determine the appropriateness of dabigatran use at a 3-site tertiary care centre following its addition to the hospital formulary in June 2011.

Methods: We conducted a retrospective chart review of patients prescribed dabigatran from August to October 2011. Descriptive statistics were used to summarize the indication for use, adherence to hospital prescribing restrictions (prevention of stroke in patients with NVAF and creatinine clearance (CrCl) > 30 mL/min), dosing, drug interactions, documentation of stroke and bleeding risks, and reasons for treatment interruptions.

Results: We identified 80 patients (87 admissions) taking dabigatran, either newly initiated in hospital or receiving it prior to admission. Ten patients (13 admissions) were not continued on it in hospital. Of the remaining 70 patients (74 admissions), 87% were receiving dabigatran for NVAF or atrial flutter in patients with CrCl > 30 mL/min. The remaining nine admissions did not meet prescribing restrictions due to the presence of valvular disease, absence of atrial fibrillation, or impaired renal function. Most patients were dosed appropriately for their age (93%), however, 48% were on concomitant interacting medications. Overall rates of stroke and bleeding risk documentation were low (40% and 16%, respectively), with stroke risk assessment for patients newly initiated on dabigatran in hospital being moderately higher (56%). A total of 55 treatment interruptions were recorded in 87 admissions, of which three included hospitalization for major gastrointestinal bleeding.

Conclusions: Dabigatran is appropriately prescribed in the majority of patients for the indication of NVAF and CrCl > 30 mL/min at this tertiary care centre. Greater consideration to potential drug interactions and improved documentation of stroke and bleeding risks are warranted.

915. Development of Evidence Based Medication Related Indicators of Potentially Preventable Hospitalisations

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Background: Between 2% and 3% of all hospital admissions are medication-related and half have been considered to be potentially preventable. Indicators of potentially preventable hospitalisations have been adopted widely internationally as a measure of health system performance, however few assess appropriate processes of care around medication use, that if followed may prevent hospitalisation.

Objectives: To develop and validate evidence-based medication related indicators of potentially preventable hospitalisations.

Methods: A modified RAND Appropriateness method was used for the development of medication-related indicators of potentially preventable hospitalisations, which included literature review, the strength of supporting evidence summarised, an initial face and con-

tent validity by an expert panel, followed by an independent assessment of indicators by an expert clinical panel across various disciplines, using an online survey. Analysis of ratings was performed on the four key elements of preventability; the medication-related problem must be recognisable, the adverse outcomes foreseeable, and the causes and outcomes identifiable and controllable.

Results: A total of 48 potential indicators across all major disease groupings were developed based on level III evidence or greater, that were independently assessed by 78 expert clinicians (22.1% response rate). The expert panel considered 29 of these (60.4%) sufficiently valid. Of these 21 (72.4%) were based on level I evidence.

Conclusions: This study provides a set of face and content validated indicators of medication-related potentially preventable hospitalisations, linking suboptimal processes of care and medication use with subsequent hospitalisation. Further analysis is required to establish operational validity in a population-based sample, using an administrative health database. Implementation of these indicators within routine monitoring of healthcare systems will highlight those conditions where hospitalisations could potentially be avoided through improved medication management.

916. Incidence in Use of Carotid Artery Stenting in Taiwan, 2005–2009: A Nationwide Study

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Background: Carotid artery stenosis is the critical factor of stroke. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) was the common procedure to treat carotid artery stenosis and prevent stroke. Despite the efficacy of CEA and CAS is still controversy. The utilization of CAS in Taiwan with population based insurance data didn't well document.

Objectives: To describe the use of carotid artery stenting in Taiwan from 2005 through 2009 using National Health Insurance Database.

Methods: We conducted a multiple retrospective cross-sectional study and enroll patients who aged 20 years or older and hospitalized for carotid artery stenting from 2005 to 2009. We calculated age- and sex-adjusted incidence rates of carotid artery stenting and used outpatient and inpatient database to identify patient characteristics and comorbidites prior to hospitalization.

Results: A total of 2,341 persons (0.14‰) had at least one hospitalization because of carotid artery stenting in 2005–2009. The age- and sex-adjusted incidence rates of carotid artery stenting was 2.08 per 100,000 persons (95% CI, 1.86–2.30) in 2005, and increased with year, to 3.12 per 100,000 persons (95% CI, 2.85–3.39) in 2009. Overall, the mean age was 71.24 years old in 2005–2009 and male about 81.2%. Comorbidity prior to hospitalization, diabetes was accounting for 40.5% to 44.3%, hypertension about 86.9% to 88.7%, hyperlipidemia about 49.1% to 59%. And medical center was most of patients hospitalized because of carotid artery stenting (75–84.3%) in 2005–2009.

Conclusions: With claims data, the use of carotid artery stenting (CAS) is increasing in 2005–2009 in Taiwan. In order to understand rational use and to monitor outcome and safety, the national surveillance system need to establish.

917. Medication-Related Problems of Elders in Long-Term Care Facilities in Taipei in Taiwan

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Background: Long-term care is now a significant concern in the aging society. The elders may suffer from medication-related problems while taking multiple medicines for chronic diseases. For this reason, it is necessary to provide pharmaceutical care in long term care (LTC)services.

Objectives: The aim of this survey was to find out the facts of inappropriate medication use, medication-taking behaviour of elders in LTC facilities, and evaluate the efficiency of pharmaceutical care services.

Methods: The study was a cross-sectional survey. Samples included two groups of people, residents aged 65 or above and health care professionals in LTC facilities in Taipei city. Data were collected by three different modules of questionnaires, which were designed for specific respondents including residents, and care takers. The contents of questionnaires were composed by the demographics of residents, the personal information of care takers, the medication assessment of residents, and the medication regulation assessment in facilities. Questionnaires were taken twice at an interval of 1 month. Data were statistically analysed by using SPSS Statistics 19.0 computer software.

Results: There were 1,480 effective questionnaires from 51 LTC facilities. The pharmacists intervention were

the major factors decreased the rate of inappropriate medication use in older adults (listed in Beers Criteria) from 70.3% to 47.3% (p < 0.001), the rate of drug-drug interaction, and medication needed to monitor clinical laboratory data and therapeutic index also had been reduced by 25.4% and 38.5% (from 67.2% to 41.8%, p < 0.001; from 82.7% to 44.2%, p < 0.001). The pharmacists had also resolved major problems of medication management in facilities included inadequate classification and management of medical waste, and storage of medication inappropriate temperature and humidity.

Conclusions: Pharmacists can provide adequate pharmaceutical care services, reduce the risk of inappropriate medication and improve the quality of medical therapy. A continuous long-term pharmaceutical service can enhance the medication safety for elders and facilitates, and improve the quality of the long-term residential care services.

918. Pattern of Use and Costs of Osteoporosis Drugs in an Italian Sub-Population: Data from ARNO Observatory

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Background: Osteoporosis represents a condition of high epidemiological prevalence and with a strong impact on the social welfare, on prevention and on pharmaceutical costs.

Objectives: To describe prevalence and to evaluate pattern of use and sanitary costs of patients treated with osteoporosis drugs in ARNO Observatory.

Methods: Prescriptions of patients who received osteoporosis drugs in 2011 from 29 Italian Local Health Units (LHU) were selected from ARNO Observatory. Prescription pattern and co-medications were analyzed during this period. A group without osteoporosis drugs, matched for age, gender and LHU was compared to the studied population to evaluate different sanitary burden of care.

Results: Of the 5,313,167 subjects over 40 years, 185,489 (prevalence 3.5%) were treated with osteoporosis drugs. The prevalence rate, as expected, is higher in female than male (6.1% vs. 0.1%) with a modal value on 70–79 years for female. Of studied patients, 81.3% received bisphosphonates, 1.2% parathyroid hormone, 0.9% SERMs, 20.9% strontium ranelatum. A considerable percentage (24.8%) didn't received vitamin D supplements in association. More prescribed

drugs to patients with osteoporosis than control group (p < 0.01), expression of higher comorbidity, were corticosteroids (+70%), nervous system drugs (+42%), PPI (+33%), antiinflammatory and antiasthmatics (+26%), while the less prescribed were lipid modifying agents (−33%) and other cardiovascular drugs (−6%). Average yearly cost/patient was 2,329€ most of all not directly related to osteoporosis. Compared to control group, patients with osteoporosis were more frequently hospitalized, beyond fractures, for arthritis (+99%, p < 0.01) and chronic bronchitis (+52%, p < 0.01). Less than 50% of patients controlled their serum calcium levels in the last 3 years, 32% performed a densitometry and less than a fifth a radiography.

Conclusions: In a large community setting of osteoporotic patients, the lack of supplement of vitamin D undermines the effectiveness of the specific pharmacological treatment. Despite low diagnostic approach, patients cost as much to the National Health System especially due to their frequent co-morbidities.

919. Polypharmacy among Medicaid Recipients with Inflammatory Bowel Disease

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Background: Polypharmacy increases the risk of drug interactions and is of growing concern in the chronically ill, including individuals with inflammatory bowel disease (IBD). IBD patients are prescribed multiple medications to manage disease as well as to treat comorbidities, which may be more common in the Medicaid population.

Objectives: We aimed to characterize the prevalence and predictors of non-IBD medication use among Medicaid recipients and to compare drug use among individuals with and without IBD.

Methods: This cross-sectional study includes members of the Thomson Reuters MarketScan Multi-State Medicaid database with continuous enrollment during 2009–2010 (n = 1,934,298). IBD patients were identified through diagnosis codes and IBD medication dispensings (n = 2,727) and matched on age and sex to five individuals without IBD (n = 13,635). We estimated the prevalence of dispensed prescriptions for

analgesics (narcotics; non-narcotics), psychiatric drugs (anxiolytics, hypnotics, and sedatives; antidepressants), and broad drug classes defined by the Anatomic Therapeutic Classification system. Predictors of non-IBD medication use and comparisons of drug use by IBD status were evaluated using chi-square tests and logistic regression.

Results: The prevalence of medication use was higher among IBD patients than the general Medicaid population for nearly every drug class examined. Notably, analgesic and psychiatric medication prevalence was significantly higher among individuals with IBD compared to those without (narcotic analgesics: 73% vs. 56%; non-narcotic analgesics: 40% vs. 32%; anxiolytics, hypnotics, and sedatives: 42% vs. 28%; and antidepressants: 52% vs. 38%; $p < 0.0001$ for all comparisons). Middle age, female gender, gastrointestinal surgery, Crohn's disease, and increasing number of inpatient, outpatient, and prescription events were significant predictors of all four drug classes among IBD patients; associations were strongest for narcotic analgesics.

Conclusions: Patients with IBD in this study had increased medication use, particularly of analgesic and psychiatric drugs. IBD providers should be aware of polypharmacy and its potential for drug interactions.

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920. Prevalence and Correlates of Polypharmacy among Men and Women with Mental Illness in Brazil: PESSOAS Project

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Background: Pharmacological intervention is one of the main strategies for treatment of patients with mental illness (PMI), exposing this population to the risk of polypharmacy. There are few studies on the magnitude and correlates of polypharmacy among PMI.

Objectives: To evaluate the prevalence and correlates of polypharmacy among PMI in Brazil, stratified by sex.

Methods: National study of 2,475 adult (18+ years old) psychiatric patients under hospital or outpatient care in Brazil. Sociodemographic, clinical and behavioral data were obtained through face-to-face interviews and medical charts. Polypharmacy was defined as the use of five or more drugs, psychotropic or not. Odds ratios (OR) were estimated by logistic regression to assess the independent correlates of polyphamacy with 95% confidence intervals (CI).

Results: The use of any psychotropic drugs was recorded in 2377 (96.0%) patients, 1218 (95.4%) among women and 1159 (96.7%) among men. Polypharmacy was recorded in 270 (22.0%) women and 281 (24.0%) men ($p > 0.05$). Correlates of polypharmacy were similar among men and women. There was a higher proportion of polypharmacy among those hospitalized in both sexes [Women: OR (IC) = 2.16 (1.56; 2.98); Men: 2.04 (1.53; 2.73)]. Lower proportion of polypharmacy occurred among women with anxiety and depression diagnoses [0.43 (0.25; 0.73)] and men with substances use disorder [0.43 (0.23; 0.78)].

Conclusions: There was a high prevalence of both, medication use and polypharmacy, among PMI in this national study in Brazil. There was no sex difference in either prevalence or correlates of polypharmacy in this population. The type of care (hospital or outpatient) and the diagnosis were correlated with polypharmacy in this population.

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921. Utilization Patterns of Cabergoline for Prolactin Reduction in Europe Following the Strengthening of Prescribing Information – The SUCRE Study

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Background: In 2008, as part of an Article 31 referral, the Committee for Medicinal Products for Human Use (CHMP) concluded that strengthening of prescribing information was needed for ergot dopamine agonists for maximum daily dose, second-line use, and need for serial echocardiography. Market holders were also required to assess adherence to and effectiveness of changes to prescribing information.

Objectives: To examine utilization patterns of cabergoline for prolactin reduction following the strengthening of prescribing information.

Methods: A cohort study was conducted of incident and prevalent users of cabergoline identified before and after strengthening of prescribing information in

2008, between 1/1/2006 and 12/1/2011 from four healthcare databases in Netherlands (Integrated Primary Care Information – IPCI); United Kingdom (The Health Information Network -THIN), Italy (Health Search Database -HSD-Thales) and Denmark (healthcare registries) representing 28 million person-years (py). Incidence and prevalence rates of cabergoline use for prolactin reduction were calculated by calendar year and gender.

Results: Full results for SUCRE are not yet available. Based on interim results for three of four databases, incidence and prevalence of cabergoline use for prolactin reduction declined after strengthening of prescribing information. Usage was highest in HSD-Thales where incidence declined from 2.45 to 2.19 per 10,000 py from 2006 to 2010, and the majority of users were female. From 2006 to 2010, prevalence of cabergoline use declined from 3.26 to 3.02 per 10,000 py in HSD-Thales. In Denmark, from 2006 to 2010, incidence and prevalence rose slightly from 1.67 to 1.86 from 1.67 to 1.95 per 10,000 py, respectively.

Conclusions: While utilization of cabergoline for prolactin reduction declined in HSD –Thales, THIN and IPCI after strengthening of prescribing information, small increases in incidence and prevalence of use were observed in the Danish healthcare registries. Among the four databases studied, the majority of the prescribing for prolactin reduction occurred in HSD-Thales and the majority of users were female.

922. Withdrawn by Author.

923. Preliminary Results of the Impact of the Use of Pillbox on the Stabilization of the INR among Patients Initiating Warfarin Treatment from a Prospective Cohort

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Background: Warfarin, a widely prescribed oral anticoagulant, is well known to have a narrow therapeutic range. Many studies confirmed that the adherence helps to achieve a stabilization of the INR, but little data is available on the impact of the use of a pillbox.

Objectives: To evaluate the association between the use of a pillbox in patients initiating warfarin therapy and the stabilization of the INR.

Methods: This study was based on a prospective cohort of new warfarin-users whose objectives are to assess the genetic, clinical and environmental risks associated with the effectiveness and safety of warfarin. Demographic and clinical data were collected among a subgroup of 265 patients who began the treatment between May 1st, 2010 and Oct. 1st, 2011 at one of 15 hospitals in the province of Quebec. They were followed-up each 3 months during 6–12 months. Our outcomes were the% of time in therapeutic range (TTR), time to achieve stabilization and adherence reported by the patient. Multivariate linear model was used with adjustment for age, sex, BMI, comorbidities, prior MI and stroke, alcohol and cigarettes use.

Results: 45.6%, 54.8%, 61.3% and 64.2% of patients used a pillbox at 3, 6, 9 and 12 months respectively. Approximately 75% of these patients prepared their own pillbox. No significant association was found between the use of a pillbox and TTR for each period of follow-up ($p > 0.05$). There was no significant association either between the use of a pillbox and time to achieve stabilization ($p = 0.115$) and adherence for period of follow-up ($p > 0.05$). Finally, using a pillbox prepared specifically by the pharmacist is negatively associated with the TTR (-0.122; 95%CI; -0.24 to -0.08) during the first 3 months of the treatment when compared to the non-users.

Conclusions: Preliminary results suggest that there are no significant differences between users and non-users of a pillbox on the measured endpoints. However, a sensibility analysis suggests that using a pillbox prepared by a pharmacist may have negative impact on the TTR. Additional analysis including comedication and genetics factors are on going.

924. Validity of Self-Reported Regimen of Dose by Patient Initiating Warfarin Treatment: Population-Based Study

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Background: Warfarin is an oral anticoagulant used for the prevention of thrombosis, but it has a narrow therapeutics index. Therefore, many dose adjustments may be necessary to achieve a therapeutic INR. The dose of warfarin is important to establish an association between clinical and safety outcomes and the exposure.

Objectives: To evaluate the convergent validity of the weekly dose of warfarin as reported by the patient compared to the weekly prescribed dose.

Methods: This study was based on a prospective cohort of new warfarin-users whose objectives are to assess the genetic, clinical and environmental risks associated with the effectiveness and safety of warfarin. Demographic and clinical data were collected on a subgroup of 219 patients who began the treatment between May 1st, 2010 and Oct. 31st, 2011 at the Montreal Heart Institute. They were followed-up each 3 months for a year. The primary outcome is the concordance between the reported and prescribed weekly dose of warfarin (established when the reported dose equals to 95% to 105% of the prescribed dose). The secondary outcome is the difference between the means of reported and prescribed warfarin weekly doses. A t-test and a Pearson correlation are used for the secondary outcome and a generalized mixed linear model with repeated measures is used for the primary outcome.

Results: Patients had a mean age of 67.7, 58.9% of them were men and 70.3% had atrial fibrillation. Overall, there was no significant difference between the means of reported and prescribed warfarin weekly dose (Pearson coefficient = 0.969, p = 0.544). However, we observed that the correlation was weak at 3 months for patients in the low dose group and in the high dose group (Pearson coefficient = 0.806 and 0.829, respectively). Mixed linear model analysis detected no association between the covariates and the concordance.

Conclusions: This study confirms the convergent validity between the reported and the prescribed dose of warfarin among new users during the first 12 months of the treatment. It is therefore possible to use the reported dose to evaluate the association between the exposure to warfarin and clinical and safety outcomes.

925. Withdrawn by Author.

926. Patient's Views on Multi-Dose Dispensed Medicines

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Background: Medication errors and non-adherence to the prescribed drugs constitute patient suffering and is a high cost burden. Multi-dose dispensed medicines (MDDM) from the pharmacies have been introduced to facilitate patients handling of the prescribed medicines. However, evidence are missing.

Objectives: To investigate patients' experiences of MDDM with regard to adherence and medication safety.

Methods :

Design: In Sweden about 30,000 individuals (the majority patients aged > 75 years) with MDDM, manage their medicine handling by themselves. A questionnaire was construed to illuminate medication handling and effects of MDDM with respect to medication safety.

Setting: A systematic sample was drawn from a frame with all Swedish municipalities including all patients outside nursing homes without assistance from primary care nurse resulting in ~14% of the Swedish municipalities with in total 5,343 patients population.

Main outcome measures: Patients' experiences of MDDM from the pharmacies with regard to adherence and medication safety.

Results: 1570 returned questionnaires were included, corresponding to a response rate of ~33%. The majority of the patients, 56%, had received MDDM for more than 2 years and > 90% collected their MDDM every second week at the pharmacy. However, 57% wanted to go to the pharmacy less often. 46%, handled their medications without assistance, whereas 38% had assistance (a relative), 20% with reminders on when to take the medications and ~15% to open

the MDDM sachets. 90% of patients answered that the MDDMs helped them to take the correct dose of the medications, that they were satisfied to have MDDM and felt secure with the MDDM-sachets. However, 30% reported they forgot to take the medications and that MDDM sachets did not improve their ability to remember to take the medicines.

Conclusions: Patients express that they feel secure with MDDM and helps them to take the correct dose of the prescribed medications. However, many patients answered that MDDM did not help them to remember to take their medications.

927. Impact of Regulatory Warnings on Concomitant Use of Oxycodone and Macrolide Antibiotics

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Background: Oxycodone, an opioid analgesic marketed in the U.S. to treat moderate to severe pain, can cause potentially fatal respiratory depression when used in conjunction with other medications that inhibit the metabolism of cytochrome P450 3A4 enzymes. In June 2001, the US Food and Drug Administration (FDA) issued a 'black box' warning against concomitant use of oxycodone and macrolide antibiotics, which are potent cytochrome P450 3A4 inhibitors.

Objectives: To determine if the oxycodone label change was associated with reductions in potentially dangerous co-prescribing of oxycodone and macrolide antibiotics among patients enrolled in the Tennessee Medicaid program.

Methods: The authors used data from the Tennessee Medicaid Research database from 1996 to 2004 to conduct an interrupted time series analysis using segmented regression analysis of the impact of the June 2001 label change on concomitant use of oxycodone and macrolide antibiotics.

Results: After adjusting for secular trends, concomitant use of oxycodone and macrolide antibiotics continued to increase at a rate of 0.91 (95% confidence interval = 0.72, 1.09; p < 0.001) per 100,000 enrollees per month in the post-intervention period. Concomitant use of oxycodone and amoxicillin, a potential replacement medication for macrolide antibiotics, continued

to increase at a rate of 2.23 (95% confidence interval = 1.59, 2.87; p < 0.001) per 100,000 enrollees per month in the post-intervention period.

Conclusions: Potentially dangerous concomitant use of oxycodone and macrolide antibiotics continued to increase after the FDA's 2001 regulatory action.

928. Dispensing Pattern of Blood Glucose-Lowering Drugs in New Diabetic Patients in Real Practice

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Background: The rising prevalence and incidence of blood glucose-lowering drug use is considerably attributable to the progressive aging and increasing obesity. Evidence about antidiabetics use in European countries with high risk are limited.

Objectives: To assess the dispensing pattern of blood glucose-lowering therapy and the characteristics of the naïve users in Southern Italy.

Methods: Several claims data of Caserta Local Health Unit (LHU), a province of Southern Italy with 1 million of residents, were combined: (1) drugs routinely dispensed to the patients and paid for by the national health system, (2) drugs directly supplied to patients by LHU, and (3) drugs supplied by hospitals through local pharmacies. People who received at least one dispensing of antidiabetics between January 2009-December 2012 were identified. Prevalence of use and incidence of new treatments (per 1000 inhabitants with 95% CI) were calculated for each year and stratified by group therapy. Sub-analyses by age and co-medication therapy were performed.

Results: Overall, the 1-year prevalence of anti-diabetics use increased from 62.6 (CI 95% 62.1–63.1)/1000 inhabitants in 2009–63.7 (62.2–64.3) in 2011 whereas a light decrease was observed in 2012 (62.3; 61.8–62.8) likely due to the revision of reimbursement criteria. Accordingly, the incidence of new users of anti-diabetics increased from 12.4/1,000 inhabitants (12.2–12.6) in

2010–13.4 (13.4–13.7) in 2011, followed by a progressive decrease to 10.6 (10.4–10.8) in 2012. Metformin was the first choice treatment for new diabetic users followed by sulfonylureas and their combinations, although their use is slightly decreased on 2012, likely due to reimbursement rules. Overall, among 27,661 new users of antidiabetics more than 30% received a concomitant dispensing of anti-hypertensives (26.6%) and other cardiovascular agents (6.3%), followed by lipid modifying agents (19.3%).

Conclusions: This is a good example of management of multiple claims databases to evaluate dispensing trends to diabetic patients. According to the guidelines, the use of metformin and sulfonylureas, as either monotherapy or in combination, is the first choice for the initial treatment.

929. Intervention To Reduce Adverse Outcomes among Older Adults Discharged from Skilled Nursing Facilities to Home

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Background: Older adults are often transferred from hospitals to skilled nursing facilities (SNFs) for post-acute care or rehabilitation. Patients may be at risk for adverse outcomes after SNF discharges, but little research has focused on this period.

Objectives: To assess the impact of an alert system on the rates of adverse outcomes among older adults discharged from SNFs to home.

Methods: Within a multispecialty group practice, we tracked 30-day re-hospitalizations after SNF discharges during an intervention that provided discharge alerts to primary care physicians. We compared them to discharges from the pre-intervention period matched on age, gender and SNF. For the first 100 discharges during the intervention period and their matches, we performed chart reviews to identify adverse drug events (ADEs). Multivariate analyses controlled for age, gender and intervention status.

Results: During the intervention period, we matched 313 SNF discharges to 313 previous discharges. There was a slight reduction in the rate of 30-day re-hospitalization (30% vs. 31%, adjusted RR 1.06 (95% CI 0.76, 1.49); RD 1.04). Within the ADE study, 30% of the discharges during the intervention period and 30% of matched discharges had ADEs within 45 days. Among the 83 ADEs identified, 28% were deemed preventable; 69% resulted in symptom duration more than 1 day; 69% occurred within the first 14 days after discharge. This was a highly vulnerable population: mean age 82.5 (standard deviation (SD) 6.7); mean number of prescribed medications 11.9 (SD 8); 17% had Charlson Comorbidity Scores of 4 or greater. Common clinical conditions included myocardial infarction (24%), heart failure (22%), COPD (23%), and major depression (28%). Patients with Charlson Scores of 4 or greater were more likely to experience an ADE than those with lower scores (adjusted OR 2.5 (CI 1.2, 5.5), RD 0.21).

Conclusions: Simply providing alerts when these vulnerable patients are discharged from SNFs is not sufficient to lower rates of adverse outcomes. Further research is required to track trajectories and identify additional points for interventions.

930. Continuation Rates of Long-Acting Reversible Contraceptives: A UK Primary Care Study

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Background: Limited data are available on the continuation rates of long-acting reversible contraceptives (LARCs) in the UK.

Objectives: To determine the continuation rates and method switching profiles of women using LARCs in the UK, using The Health Improvement Network (THIN) database.

Methods: Women in THIN aged 18–44 years between January 2004 and January 2011, registered with their primary care physician for at least 5 years, and with a computerized prescription history of at least 1 year, were included. The LARC methods examined were: copper intrauterine devices (Cu-IUDs), the levonorgestrel-releasing intrauterine system (LNG-IUS), progestogen-only implants and progestogen-only injections. Using computer algorithms, the database was searched for the specific Read and MULTILEX codes. New LARC users were identified and followed until there was a record indicating termination of use, or the study period ended. The follow-up period

was 6 years for users of Cu-IUDs and the LNG-IUS, 4 years for users of progestogen-only implants and 1 year for users of progestogen-only injections. Women were considered to have terminated use if a code indicative of discontinuation, or insertion of a replacement device, was recorded. Manual review of computerized profiles demonstrated the validity of this approach.

Results: The proportion of women who discontinued use during the same year of administration was 7.5% for Cu-IUDs, 10.6% for the LNG-IUS, 13.2% for progestogen-only implants and 54.4% for progestogen-only injections. After the follow-up period, 56.9% of Cu-IUD users, 51.7% of LNG-IUS users and 68.9% of progestogen-only implant users were recorded as having discontinued use of that method. By the end of the study, a higher proportion of Cu-IUD and LNG-IUS users (21.1% and 18.6%, respectively) undertook re-administration of the same method than progestogen-only implant users (10.7%).

Conclusions: Over the follow-up period, the cumulative discontinuation rate was highest for users of progestogen-only implants and lowest for users of intrauterine devices. Re-administration of the same contraceptive method was more common for users of intrauterine devices than for users of progestogen-only implants.

931. Antiretroviral Outpatient Drug Utilization in Portugal (2007–2012)

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Background: HIV infection remains a major public health problem in Europe. Portugal has one of the highest rates of AIDS cases (2.8 cases per 100,000 population) comparing with 28 European Countries (rate of 0.9). If HIV infection is adequately controlled, there is a potential for minimizing AIDS morbidity and mortality in Portugal.

Objectives: The objectives of this study are: (1) to analyse the trend in the use and expenditure of antiretroviral drugs in Portugal and (2) to compare drug utilization patterns at regional and national level.

Methods: Data refers to the drugs prescribed and dispensed in hospital pharmacies, from 1st January 2007 to 31st December 2012. Data was expressed in Defined Daily Dose (DDD) per 1000 inhabitants per day (DHD) and DDDs were assigned in accordance with ATC 2012. For fixed associations it was assigned the sum of the DDDs of isolated products. It was collected for each hospital the number of patients receiving antiretroviral drugs in the hospital pharmacy in the year 2011. Drug indicators (DDD per patient, Cost per DDD, Cost per Patient) were compared between

group of hospitals (hospitals with more than 1000 patients; between 500 and 999 and between 200 and 499 patients).

Results: Use of antiretroviral drugs increased from 4,1 DDD per 1000 inhabitants Day in 2007–6,1 DHD in 2012, an increase of 47%. Considering the patients that received HIV medicines in hospital pharmacies the median average of DDD per day is 3, which is in accordance with the majority of the therapeutic schemes which include an association of three substances. In 2007, the most used drug was Lamivudine+Zidovudine but it presented a major decrease during the study period. On the other hand, Entricitabine+Tenofovir and Efavirenz, both in two pill or one pill scheme, presented a major increase and it was, in 2012, the most used combination in HIV treatment In Portugal. There were no significant differences (p > 0.05) between groups of hospitals in relation to the three studied indicators.

Conclusions: Changes in antiretroviral drug use are in accordance with Portuguese guidelines. However hospitals differed in relation to the preferred scheme and the substances included in each hospital formulary.

932. Development of Two Patient Decision Aids To Increase Inhaled Corticosteroids Use in Asthma

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Background: Although inhaled corticosteroids (ICS) improve quality of life and lung function, and reduce hospitalizations in patients with asthma, many do not take ICS regularly, as the Canadian asthma guidelines recommend. Based on the Ottawa Decision Support Framework and the International Patient Decision Aid Standards, we have drafted two patient decision aids (PtDAs) to address the underuse of ICS.

Objectives: We sought to check the acceptability of our PtDAs with key stakeholders – health profession-

als, and patients facing the decision to use ICS to optimize asthma control.

Methods: From 2012-11-05 to 2013-02-12, we performed a qualitative assessment of our PtDAs. We recruited asthma educators through an asthma network. By convenience sampling, we recruited patients – aged 18–65 years, having a diagnosis of asthma in their medical report – at the outpatient asthma clinic and research center of a tertiary care center. We asked participants to read one or other of our PtDAs, provided consecutively according to availability. We asked them to fill the self-administered Ottawa Hospital Research Institute Acceptability Questionnaire, which rated the presentation/amount of information, balance in presentation, and usefulness of the PtDAs, and provided us with feedback to refine them. Participants assessed successive versions of our PtDAs, and were recruited until no new themes emerge from the gathered feedback.

Results: Eleven out of the 17 invited educators and all the 20 invited patients filled our questionnaire. Throughout acceptability testing, participants mostly judged our PtDAs acceptable in presentation/amount of information, balanced, and useful in helping patients decide on pharmacotherapy. From the gathered feedback, we redrafted five successive versions of one PtDA and 3 of the other. The seven participants who assessed one or other of the last version of our PtDAs did not comment on what they dislike about it and on suggestions to improve it. We then approved our PtDAs.

Conclusions: We have refined our two PtDAs according to key stakeholders' acceptability assessment. We will pilot-test our refined PtDAs to explore whether they may increase ICS use, as recommended by guidelines.

933. Metabolic Risk and Screening in CMHC Patients Starting SGAs in MO Medicaid

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Background: Persons receiving second-generation antipsychotics (SGA) are at risk for development of obesity-related cardiometabolic diseases.

Objectives: We evaluated differences in baseline metabolic risk & metabolic screening between individuals receiving treatment at Community Mental Health Centers (CMHCs) compared to those who never received treatment from a CMHC.

Methods: Data included MO Medicaid claims from 9,475 individuals with an index SGA prescription claim between 8/2009 and 4/2010. Diagnoses were identified by ICD-9-CM codes in claims data during 12 months preceding the index date. Metabolic risk factors were defined by American Diabetes Association criteria & included age, race, diabetes, lipid metabolism disorder, hypertension or heart disease. Baseline metabolic screening was defined by a CPT code for any glucose or lipid screening 12 months before the index SGA prescription. We compared CMHC and non-CMHC patients using chi-square and *t*-tests.

Results: We found 37% of oral SGA starters in MO Medicaid received treatment at a CMHC. CMHC and non-CMHC patients were demographically similar – 77% were white, 20% black and 2.5% other/unknown; 57% were female. CMHC patients had significantly higher percentage of serious mental illness including schizophrenia, major depression & bipolar disorder. A significantly greater percentage of CMHC patients were screened for metabolic disease at baseline compared to non-CMHC patients: 32.2% vs. 27.2% for glucose, 12.7% vs. 9.1% for lipids & 11.9% vs. 8.4% for both glucose and lipids (all $p < 0.01$). CMHC patients had more prevalent diabetes (11.7% vs. 10.4%, $p < 0.05$) & lipid disorders (13.2% vs. 11.2%, $p < 0.05$). A greater percentage of non-diabetic CMHC patients had risk factors for metabolic disease with 24.6% having 2 or more ADA risk factors. Between group differences in hypertension or heart disease were not observed.

Conclusions: CMHC-treated patients beginning an oral SGA received baseline screening for metabolic disease with greater frequency than non-CMHC patients. Screening frequency was low overall, but is appropriately higher in CMHC patients, who have more metabolic disease at baseline & greater psychiatric comorbidity.

934. Medicine Safety Issues from within Hospital Distribution of Medicines

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Background: Medicine safety is a priority for governments. In Australian hospitals the distribution to, and storage of, selected regularly required medicines spe-

cific to each ward (imprest), is a common practice. Nurses administer these medicines based on information in the patients medicines chart. It is a high risk area for medication misadventure.

Objectives: To determine the safety and quality of the imprest system in two wards in a 415 bed Australian tertiary hospital. To implement any needed changes to the improve medication safety within the imprest system.

Methods: A Drug Utilisation Review (DUR) of distribution and storage of medicines in two acute care psychiatric wards (32 beds) using seven key requirements of Society of Hospital Pharmacists of Australia's (SHPA) Distribution of Medications Guidelines as the gold standard. Results were discussed with all staff and changes implemented.

Results: 141 imprest unique medicines were approved for these wards; the review found 240 unique medicines available for use. These extra medications were procured through incorrect pathways and remained on the ward due to poor stock management. 4713 not required and 855 out of date items were found and discarded or returned to the hospital's pharmacy. Medicines were neither stored alphabetically by generic name, nor separated by dose forms: e.g. solid, liquid, injectable. Consequently needed medicines could not be quickly identified in a safe manner. This was corrected. Patient's own medications (POM) bought into the wards had no uniform place for storage. Consequently accurate medication reconciliations on admission and discharge could not be completed. High risk practices for non-imprest medications were in place e.g. multiple strengths of one medication being stored together increasing the risk of an incorrect strength being administered. Best practice in line with the SHPA guidelines, and systems which carry the lowest error rate, have now been integrated into this setting.

Conclusions: Regular ward specific DURs of hospitals' imprest systems are necessary to improve medication safety and reduce medication wastage.

935. The Effect of Non-Dihydropyridine Calcium Channel Blocker Therapy among Patients with Supraventricular Tachyarrhythmias Hospitalized for Systolic Heart Failure

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Background: Non-dihydropyridine calcium channel blockers (NDHP CCBs) are used for heart rate control among patients with supraventricular tachyarrhyth-

mias. However, clinical guidelines advise against their use among systolic heart failure (HF) patients given safety concerns from studies conducted before widespread use of ACE-inhibitors and beta-blockers in HF.

Objectives: To evaluate the effect of NDHP CCB receipt at discharge on clinical outcomes among patients with supraventricular tachyarrhythmias hospitalized for systolic HF.

Methods: Patients with left ventricular ejection fraction < 40% and a history of atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachyarrhythmias hospitalized for HF at a Veterans Affairs Medical Center between 2003 and 2007 were identified. We propensity-matched patients who received diltiazem or verapamil at discharge with up to three controls. Cox proportional hazards models were used to evaluate the association between NDHP CCB use at discharge, all-cause mortality and HF rehospitalization at 6 months. The Kaplan–Meier method and log-rank test were used to compare survival.

Results: Among 8,691 patients who met study inclusion criteria, 5.4% were prescribed a NDHP CCB at discharge. Concomitant ACE-inhibitor or angiotensin-receptor blocker use was 79% and beta-blocker use was 61%. Among 1,785 matched patients, NDHP CCB recipients had a 24% lower risk of all-cause mortality at 6 months compared with patients who did not receive any CCB at discharge (hazard ratio [HR] 0.76; 95% CI: 0.57–1.00; log-rank p = 0.035). HF rehospitalization did not differ at 6 months (HR, 0.98; 95% CI: 0.81–1.19; log-rank p = 0.66).

Conclusions: In this study of veterans with supraventricular tachyarrhythmias hospitalized for systolic HF, among whom concomitant therapy with renin-angiotensin inhibitors and beta-blockers was common, receipt of a NDHP CCB at discharge was associated with a lower risk of mortality at 6 months and was not associated with HF rehospitalization. NDHP CCBs appear to be safe and potentially beneficial when used in conjunction with current guideline-recommended HF therapies.

936. Prevalence and Potential Preventability of Adverse Drug Events – A Population-Based Medical Record Study of 4,995 Adults

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Background: Adverse drug events (ADEs) are common and often preventable among hospitalised patients, but the extent and potential preventability of ADEs in the entire healthcare is largely unknown.

Objectives: To estimate the 3-month prevalence of ADEs and the preventability of ADEs among the adult general public in Sweden, and to identify drug classes and organ systems associated with ADEs.

Methods: A random sample of 5,025 adult residents in the county council of Ostergotland in Sweden in 2008 was drawn from the national population register. Public, private, outpatient and inpatient medical records were reviewed retrospectively in a stepwise manner, complemented with register data on dispensed drugs. ADEs, including adverse drug reactions (ADRs), subtherapeutic effects of drug therapy (STEs), drug dependence and abuse, drug intoxications from overdose, and morbidity due to drug-related untreated indication, were detected during a 3-month study period, and their preventability assessed.

Results: Among 4,995 adults with accessible medical records, the prevalence of ADEs was 11.9% (95% CI, 11.0–12.2%), and for preventable ADEs 5.6% (95% CI, 4.9–6.2%). Of the ADE categories, ADRs (6.8%; 95% CI, 6.1–7.5%) and STEs (6.4%; 95% CI, 5.7–7.1%) were the most prevalent. The preventability of ADEs was 38.8% (35.8–41.9%), but varied by ADE category and was higher for serious ADEs (55.9%; 95% CI, 45.8–66.0%). Nervous system and cardiovascular drugs were the groups most frequently associated with all and preventable ADEs, with varying drugs by ADE category. ADRs and preventable ADRs affected frequently the gastrointestinal and central nervous systems, while STEs and preventable STEs were dominated by hypertension and hyperglycemia.

Conclusions: The prevalence of ADEs and preventable ADEs among the adult general public supports developing preventive strategies in the entire health system. Describing the ADE categories separately appears to enrich characterising ADEs. Because all and preventable ADEs were similar and the most common ADE drugs were frequently dispensed, system-level prevention may be more advantageous than targeting preventive strategies to specific ADEs.

937. Use of Pharmaceutical and Non-Pharmaceutical Complementary and Alternative Medicine in Cancer Patients

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Background: Cancer patients often supplement treatment with anti-cancer and supportive care agents with complementary and alternative medicine (CAM). Some CAM can reduce toxicity of traditional medicine, while others can interfere with efficacy or toxicity of drug therapy.

Objectives: To determine the prevalence of pharmaceutical (P) and non-pharmaceutical (NP) CAM use in adult patients with a wide range of cancers, and find socio-demographic/behavioural/pathologic factors associated with CAM use.

Methods: 523 eligible patients diagnosed with a range of malignancies were surveyed at Princess Margaret Hospital (Toronto). Exploratory multivariate regression identified factors associated with CAM use.

Results: 42% used CAM after diagnosis (35%, NP-CAM; 22%, P-CAM). P-CAM agents typically included herbal and Eastern medications, vitamins at super-biologic doses, and non-prescription supplements. Factors significantly associated with CAM use after diagnosis included CAM use before diagnosis (adjusted odds ratio, aOR = 11.2, 95% [6.9–18.0]) and conventional therapy that was multimodal (e.g. chemoradiation with surgery; aOR = 2.9 [1.6–5.0]). Breast and gynecological patients were more likely to use CAM than lung/thorax/thyroid or skin (aOR = 2.6 [1.2–5.3]), gastrointestinal/genitourinary (aOR = 2.13 [1.2–4.0]) and head and neck or hematological (aOR = 1.8 [1.0–3.3]) patients. Income over $80,000 (aOR = 1.9 [1.1–3.1]) and completing some level of post-secondary education (aOR = 1.7 [1.1–2.7]) were associated with greater use of CAM. Female gender and Asian ethnicity were associated with CAM use in univariate analysis, but not in multivariate models. No associations were observed between CAM use and cancer stage, intent of treatment (curative vs. palliative),

performance status, smoking or diet variables, or overall Charlson comorbidity index scores.

Conclusions: CAM use is more likely in patients with higher income, more education, three or more treatment modalities or in patients diagnosed with breast or gynecological cancers. Prior CAM use was the strongest factor associated with CAM use after diagnosis.

938. Use of Prescription Weight-Loss Drugs in the United States, 1993–2011

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Background: Pharmacologic treatment options can aid in efforts to combat obesity. However, several weight-loss agents have been withdrawn from the U.S. market for safety reasons; the latest was sibutramine, withdrawn in 2010. Two new prescription weight-loss drugs were approved in 2012.

Objectives: To examine national trends in prescription antiobesity drug use in the United States, and to describe characteristics of users and patterns of use, including duration of use and concomitant use of prescription weight-loss drugs.

Methods: National drug use estimates for 1993–2011 were extracted from IMS Health Vector One® National, and patient characteristics for 2008–2011 from Vector One® Total Patient Tracker and Encuity Research, LLC. Physician Drug & Diagnosis Audit®. The Source Healthcare Analytics Source Lx® database was used to examine duration of anti-obesity drug use for 2002–2011 with a sensitivity analysis in the IMS LifeLink® database.

Results: In 2011, approximately 2.74 million patients used antiobesity drugs, predominantly phentermine (2.43 million patients). The use of prescription orlistat and sibutramine was relatively uncommon. Eighty-five percent of users were female, 62% were between the ages of 17 and 44, and 3.5% of antiobesity drug occurrences were in patients with body mass index < 25 kg/m². Duration of use was generally short and most patients only had one episode of use during the observation period. The longest episode of use was 30 days or shorter in 47% to 58% of patients. Approximately one quarter of patients used anti-obesity drugs for longer than 90 days and only 1.3% to 4.2% for longer than 1 year. Concomitant use of two or more prescription weight-loss drugs was generally uncommon, although phentermine was dispensed during 13% to 16% of benzphetamine, diethylpropion, or phendimetrazine episodes of use.

Conclusions: Phentermine dominated the prescription weight-loss market in terms of users and dispensings. Although recommended limits on duration of use for phentermine and other amphetamine congeners ('a few weeks') were often exceeded, duration of use of all prescription antiobesity drugs was generally short.

939. Factors Associated with Utilization of Saxagliptin in the US and UK

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Background: Patterns and determinants of saxagliptin (saxa) use among type 2 DM patients in real-world settings are unknown.

Objectives: To place into context studies of the effects of the drug we sought to: (1) compare characteristics between patients with type 2 DM who are initiators of saxa and those who are initiators of oral antidiabetic drugs (OADs) in classes other than dipeptidyl peptidase-4 inhibitors (DPP4i), and (2) identify factors associated with saxagliptin initiation.

Methods: We conducted separate cross-sectional studies in the HealthCore Integrated Research Database

(HIRDSM) in the US and the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) in the UK. Eligible patients were: ≥ 18 years old; newly prescribed saxa or other OAD (excluding DPP4i); and enrolled for ≥ 180 days prior to the new prescription. OAD users were matched on age, sex, and region. Conditional logistic regression was used to determine adjusted odds ratios (OR) of factors associated with saxa vs. other OADs.

Results: Among new initiators of saxa (n = 2,213) or other OADs (matched; n = 22,130) in HIRDSM, ≥ 2 hemoglobin A1c measurements (OR, 2.24; 1.93–2.61); prior OAD use (OR, 6.04; 5.43–6.72); diagnoses of allergic rhinitis (OR, 1.32; 1.07–1.63), hyperlipidemia (OR, 1.19; 1.06–1.34), and hypertension (OR, 1.17; 1.04–1.31); and use of ACE inhibitors (OR, 1.19; 1.03–1.38) were associated with saxa use. Among new initiators of saxa (n = 742) or other OADs (n = 7,398) in CPRD, prior OAD use (OR, 16.13; 12.19–21.35); diagnoses of COPD (OR, 1.52; 1.17–1.99), CVD (OR, 1.37; 1.06–1.79) and peripheral neuropathy (OR, 4.46; 2.01–9.94); and use of angiotensin receptor blockers (OR, 1.32; 1.03–1.70) and antihyperlipidemic agents (OR, 1.36; 1.08–1.72) were associated with saxa use. Among new initiators of saxa (n = 655) or other OADs (n = 6,391) in THIN, prior OAD use (OR, 17.41; 12.83–23.64); diagnoses of COPD (OR, 1.63; 1.22–2.19) and peripheral vascular disease (OR, 2.96; 1.26–6.93); and use of beta-blockers (OR, 1.30; 1.03–1.64); and antihyperlipidemic agents (OR, 1.36; 1.07–1.74) were associated with saxa.

Conclusions: These findings suggest saxa was used in patients with more complex clinical presentation.

940. Withdrawn by Author.

941. Antipsychotic and Antidepressant Use and Mortality among Nursing Home Residents with Alzheimer's Disease and Related Dementias

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Background: Antipsychotics (APs) and antidepressants (ADs) are widely used to control psychiatric and behavioral symptoms in nursing home (NH) residents with Alzheimer's disease and related dementias (ADRD). Despite growing evidence that suboptimal use of these agents places NH residents at increased risk for mortality, there is little consensus on the utility of APs and ADs in managing cognitive impairment.

Objectives: Controlling for behavioral symptoms (physical, verbal, and socially inappropriate behaviors), this study assesses the association of AP and AD exposure with mortality in NH residents with ADRD.

Methods: This retrospective cohort study used a 5% random sample of the 2007–2009 Medicare administrative and prescription drug claims linked to Minimum Data Set 2.0 files. Beneficiaries were included if they had: (1) evidence of a NH stay ≥ 101 days (index date); (2) an ADRD diagnosis at baseline (12 months pre-index) or during the drug exposure period (6 months post-index); and (3) survived and retained Medicare enrollment during post-index period. Beneficiaries with severe mental illness (schizophrenia, psychosis, mood disorders) were excluded. All-cause mortality associated with AP and AD exposure was assessed in the follow-up period using Cox proportional hazards models.

Results: The cohort (n = 35,782) had a mean age of 83 years and was mostly female (79.9%). AP and AD prevalence was 28.3% and 58.3%. Compared to AP nonusers, AP users were more likely to have a delirium diagnosis (44.4% vs. 33.8%, p < 0.001) and behavioral symptoms (23.9% vs. 10.9%, p < 0.001). Similar patterns were observed between AD users and nonusers. AP use was not associated with mortality. AD users had a lower mortality risk (adjusted relative risk [aRR] = 0.94, p < 0.001) compared to nonusers; statistical significance remained after control for AP use (aRR = 0.94, p < 0.001).

Conclusions: Findings suggest AP exposure alone does not affect mortality outcomes; however, further work to examine quality of prescribing by indication, dose, and duration should be conducted. As well, the use and quality of ADs in this population warrants further exploration.

942. Prevalence of Use of Benzodiazepines and Related Drugs in Seven European Databases: A Cross-National Descriptive Study from the PROTECT-EU Project

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Background: Benzodiazepines use has been a matter of concern worldwide. Although many drug utilization studies have been published, only a few were designed for direct cross-national comparison.

Objectives: This study aims at describing and comparing benzodiazepines use and trends in five European countries. Additionally, the use of benzodiazepine-related drugs ('Z-drugs') was evaluated.

Methods: We calculated crude and standardized prevalence rates of drug use by calendar year from 2001 to 2009, in seven European health care electronic databases (DB). We also calculated age and sex specific prevalence rates and the distribution by benzodiazepine-anxiolytics (N05BA), benzodiazepine-hypnotics (N05CD) and benzodiazepine-related drugs (N05CF). Indication and number of prescriptions issued in 2008 were also examined.

Results: The age- and sex-standardized prevalence of use in 2008 was highest in BIFAP, Spanish DB (1,598 per 10,000 p-y) whereas Bavarian Claims, German DB (477 per 10,000 p-y) yielded the lowest. Prevalence in the Spanish DB increased over the study period, while a decreased was showed in the Danish, Bavarian and Dutch-NPCRD, and remained stable in the two UK DB and the Dutch-AHC DB. Use of anxiolytics outweighed that of hypnotics in the Spanish, Dutch and Bavarian DB, but the reverse was shown in the UK and Denmark. In people over 50 years of age, prevalence rates were consistently twofold higher in women than in men in all DB. In 2008, the percentage of patients with ≥ 4 four prescriptions ranged from 16% to 46%.

Conclusions: This study shows that analysing drug utilization in different DB according to a common protocol is feasible and valuable. Moreover it adds up to the knowledge of the real prescribing/dispensing patterns of these drugs in primary care. International comparisons are desirable as they may play an important role in pharmacovigilance.

943. Epidemiologic Measures of Drug Use: Antiepileptic Drugs, Benzodiazepines, and Antidepressants in Four European Countries

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Background: The proportion of a population using a particular drug over a period or a point in time provides basic information for drug utilisation studies.

Objectives: To calculate the exposed population to several groups of drugs in Denmark (DK), Norway (NO), Sweden (SE), and The Netherlands (NL), for year 2009.

Methods: We downloaded drug consumption data according to the Anatomic-Therapeutic-Chemical (ATC) classification version 2012: antiepileptics (N03A), benzodiazepine hypnotics, sedatives and anxiolytics (N05BA/N05CD), and antidepressants (N06A). We calculated defined daily doses (DDD)/1000 inhabitants/day (DID) or therapeutic intensity, and 1-year prevalence, defined as at least one filled prescription during 2009. For completeness, we give average mean age and percentage of female users for DK, NO and SE.

Results: One-year prevalence (‰) of N03A, was 20.8, 20.8, 19.9, and 16.3; DID was 13.5, 13.1, 6.5, 8.2 in DK, NO, SE and NL, respectively. Mean age was 52.7 years, 55% women. For N05BA, 1-year prevalence (‰) was 38.5, 54.1, 38.4, and 14.3; DID was 12.3, 17.9, 12.0, and 5.6 in DK, NO, SE and NL, respectively. For N05CD, 1-year prevalence (‰) was 7.8, 9.2, 5.9, and 7.9; DID was 5.3, 6.3, 4.3, and 3.2 in DK, NO, SE, and NL, respectively. Mean age was 63.4 years, 62% women. For N06A, 1-year prevalence (‰) was 80.2, 60.5, 80.0, 55.3; in DID 77.0, 51.6, 71.2, 30.6, in DK, NO, SE, NL, respectively. Mean age 54.8, 65.4% women. For all these groups of drugs, 1-year prevalence rates were higher than DID. Thus, users consumed less than the assumed 1DDD/day. Overall drug consumption is much lower in NL.

Conclusions: Results in DID and period prevalence give an overview of the population exposed to a drug. Both measures have their pitfalls. One-year prevalence mixes prevalent with new users and may overestimate drug use. DID is subject to the differences between prescribed and defined daily doses.

944. Educational Intervention and Knowledge Assessment in Patients on Oral Anticoagulant Treatment

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Background: Educational interventions (EI) addressed to patients under vitamin K antagonists (VKA) treatment lack patients' knowledge assessment, before and after the intervention.

Objectives: Knowledge assessment about oral anticoagulant medication with a validated questionnaire before and after EI addressed to patients attending an anticoagulation clinic.

Methods: Adult Spanish-speaking literate patients on acenocoumarin or warfarin treatment from an anticoagulation clinic at a second level hospital in Mexico City were invited to an EI, which comprised a 75 min lecture and a 75 min questions-and-answers session. Patients received printed information. Knowledge was measured with a validated, 87 closed items questionnaire. Group 1: 33 patients who attended the EI; group 2: 29 patients who did not show up to the EI. Knowledge assessment in group 1 was performed before and 3–6 weeks after EI; group 2 also filled the questionnaire twice. Exposures to questionnaire were at least 1 month apart. Outcome measures were questionnaires overall correct answers and correct answers minus wrong answers before and after an EI. Descriptive statistics and t tests were obtained.

Results: Group 1. Before EI: correct answers mean: 52.1, SD ± 12.4; correct minus wrong answers mean: 38.9, SD ± 14.6; after EI: correct answers mean: 67.7, SD ± 7.9 p = 0.003; correct minus wrong answers mean: 57.4, SD ± 11.8, p = 0.017. Group 2: first questionnaire: correct answers mean: 55, SD ± 13.3; correct minus wrong answers mean: 41, SD ± 15.5, second questionnaire: correct answers mean: 58 SD ± 12.4, p = 0.034; correct minus wrong answers mean: 44.5, SD ± 12.4, p = 0.009. Second questionnaires correct answers means and correct answers minus wrong answers means in group 1 vs. group 2 were different, p < 0.001. Percentage increase in second questionnaire, group 1: correct answers 18.7%, correct answers minus wrong answers, 22%; group 2: correct answers 3.45%, correct answers minus wrong answers: 4%.

Conclusions: Results suggest that all patients under anticoagulant treatment should receive an EI and that knowledge should always be assessed.

945. Time Series Methods Applied in Drug Utilization Research: A Systematic Review

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Background: Time series analysis is a quasi-experimental research design often used to estimate the effects of health care interventions.

Objectives: To systematically examine the trends and applications of time series methods applied in drug utilization research.

Methods: We completed a systematic search of MEDLINE to identify all English language articles that employed time series analysis in drug utilization research. Studies that examined the impact of government or media advisories, clinical practice guidelines, or formulary interventions on drug utilization were eligible. We tabulated the number of publications by year and type (methodological contribution, review paper, or empirical application) and summarized the methods used in empirical applications overall and by publication year.

Results: Of 1,454 unique articles identified, 99 drug utilization research studies were eligible: 3 methodological contributions, 26 review papers, and 70 empirical applications. The first article was published in 1987. All review papers and 91% of empirical applications were published after the year 2000. Of the 65 empirical applications that studied a single intervention, 62% examined formulary changes, 29% examined government and media advisories, and 9% examined guideline changes. Of the 62 articles that reported statistical methods, segmented regression analysis (55%), autoregressive integrated moving average (ARIMA) models (29%), and linear regression (11%) were most commonly applied. Autocorrelation was investigated in 66% of all studies, 40% accounted for seasonality, and 13% accounted for stationarity. Few studies executed forecasting (29%) or used a comparison group (29%).

Conclusions: Use of time series analysis in drug utilization research has increased rapidly since the year 2000. It is recommended that analyses account for autocorrelation, seasonality, and stationarity, yet few studies report these considerations. As the application of time series analysis continues to increase, it is important to develop standards of practice to properly assess intervention impacts on drug utilization.

946. Drug Use Pattern of Rivaroxaban in Germany

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Background: Rivaroxaban is an orally active, highly selective direct factor Xa inhibitor which has been approved for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery in Germany in 2008. Subsequently approval was gained in 2011 for the indications prevention of stroke in patients with atrial fibrillation and treatment of deep vein thrombosis.

Objectives: To describe the use of rivaroxaban in Germany during a time period in which approval was limited to the orthopaedic indication.

Methods: Source of data for this drug utilization study was one of the four statutory health insurance providers included in the German Pharmacoepidemiological Research Database (GePaRD), which provided data on about 7 million insurants throughout Germany. Analyses were based on a cohort of rivaroxaban users from October 2008 to December 2009 and encompassed potential indications for rivaroxaban use, duration of treatment, and co-prescribing of potentially interacting drugs as stated in the German Summary of Product Characteristics (SPC). Potential indications were assessed based on predefined algorithms and included also those not approved during the study period.

Results: During the study period 425 rivaroxaban users were identified contributing 440 treatment periods. For more than 82% of these episodes labelled indications could be determined. Rivaroxaban treatment durations exceeded recommendations as stated in the SPC in 95% of the episodes following elective knee replacement whereas rivaroxaban use after elective hip surgery was found to be longer than recommended in 56%. Prescribing of potentially interacting medication was rare except for non-steroidal anti-inflammatory drugs.

Conclusions: Our study did not identify important off-label use of rivaroxaban except for treatment duration which was particularly longer in patients with elective knee surgery. This prolonged treatment duration might

result from other guidelines which recommend extended thromboprophylaxis also after knee surgery. Prescribing of co-medications was mainly plausible comprising drugs used to reduce post-operative pain and included none of the drugs not recommended for concomitant use.

947. Withdrawn by Author.

948. Urinary Incontinence: A Poorly Recognised Adverse Effect of Medicines

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Background: Urinary incontinence is an under reported adverse effect of many medicines. Most observational studies which show an association between medicines and urinary incontinence have methodological limitations; including cross-sectional design, difficulty in controlling for confounding by indication and lack of information regarding existing incontinence prior to medicine exposure. Few studies have reported the risk of incident incontinence associated with medicines.

Objectives: To identify the risk of incident urinary incontinence associated with commonly used medicines.

Methods: Prescription sequence symmetry analyses (PSSA) were undertaken using administrative claims data from the Australian Government Department of Veterans' Affairs, between 1 January 2001 and 31 December 2008. PSSA assessed asymmetry in the distribution of incident dispensing of medicines reported to be associated with urinary incontinence (prazosin, diuretics, calcium channel blockers (CCBs), ACE inhibitors, angiotensin receptor blockers (ARBs), HRT, levodopa, antipsychotics, sedatives, SSRIs, venlafaxine, anticholinesterases) before and after incident dispensing of oxybutynin (to treat urinary incontinence). Crude and adjusted sequence ratios (ASR) with 95% confidence intervals were calculated.

Results: Significant associations between initiation of CCBs, ACEI, ARBs, hypnotic/sedatives and SSRIs and subsequent initiation of oxybutynin were found. ASRs ranged from 1.12 (1.03–1.23) for SSRIs to 1.61 (1.27–2.03) for verapamil. Amongst female patients, there was increased risk of initiation of oxybutynin following prazosin (ASR 1.85 (1.61–2.13) and conjugated-oestrogen initiation (ASR 1.73 (1.22–2.45). PSSA showed no significant association between initiation of levodopa, venlafaxine or anticholinesterases and subsequent initiation of oxybutynin.

Conclusions: Our study has highlighted the potential for initiation of commonly used medicines to be associated with subsequent initiation of oxybutynin to treat urinary incontinence. Increased awareness of the potential for medicines to contribute to urinary incontinence is required.

949. Trends in the Use of Non-Benzodiazepine Sleep-Aid Medications in the United States, 1996–2010

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Background: During the past decade, several non-benzodiazepine (non-BZD) sleep-aid medications have been developed and marketed for the treatment of insomnia. However, concerns have been raised about their safety, especially in older adults. Little is known regarding the extent of the use of these medicines in the United States.

Objectives: To examine temporal trends in prescribing for non-BZD sleep-aid medications from 1996 to 2010, and to assess differences in these trends across patient groups.

Methods: We used data from 409,667 patient visits in the US from the National Ambulatory Medical Care Survey (years: 1996–2010) to assess prescription trends for three non-BZD sleep-aid medications: zolpidem, zaleplon and eszopiclone. To test for trends over time, we used logistic regression with time as the predictor and patient visits where a non-BZD was prescribed as the outcome. Analyses were controlled for age, gender and race, and interaction terms of these covariates with time were included in models to test for differences in temporal trends across different demographic groups.

Results: The proportion of patient visits resulting in a prescription for a non-BZD increased from 0.2% in 1996 to 1.7% in 2010. After adjustment for age, gender, and race, there was almost a 9-fold increase in the odds of a patient visit where non-BZDs were prescribed from 1996 to 2010 (adjusted odds ratio [AOR] = 8.93, 95% Confidence Interval [CI] = 7.21–11.05, p < 0.001). There was no evidence for interaction of time with age, gender, or race. Similar increases were observed even among visits by patients aged

≥ 65 years (from 0.3% to 2.5%; AOR = 8.92, 95% CI = 6.32–12.59, p < 0.001).

Conclusions: Between 1996 and 2010, there was approximately a 9-fold increase in prescription of non-BZD sleep-aid medications, with little variation in trend across the different age, gender and racial groups. The rapid growth in prescription of non-BZD sleep-aid medications calls for greater attention to the possible adverse health effects of these medications in community settings, especially among the elderly who may be more vulnerable to these effects.

950. Sex-Based Differences in the Use of Evidence-Based Treatment for Heart Failure in Québec

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Background: Canadian treatment guidelines for heart failure (HF) recommend for both men and women an evidence-based treatment (EBT) made of a combination of a beta-blocker (BB) and either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker, or of a BB and hydralazine plus isosorbide dinitrate. Results of past studies suggest that women with HF are more likely than men to underuse ACEi. However, little is known about sex differences in the use of the EBT.

Objectives: To measure the association between sex and the use of EBT in the 60 months following HF diagnosis.

Methods: In a cohort study using Quebec administrative health data, we assessed the use of EBT among Drug Plan covered subjects aged 18+ who had a 1st diagnosis of HF between 2000 and 2009. Subjects were followed from the 1st HF diagnosis until December 31, 2009, loss of eligibility to the drug plan or death whichever came first. EBT users were those who had at least one active claim for drugs qualifying as an EBT at HF diagnosis and at the 6th, 12th, 36th and 60th month diagnosis anniversary. Adjusted 60-month period prevalence ratios (APR) with 95% confidence intervals (CI) were performed using Working-Poisson Regression. Ratios were adjusted for socio-demographic characteristics, comorbidities and health services use. To control for the potential modifying effect of suffering from ischemic heart disease (IHD) on the use of EBT, analyses were stratified according to a history or not of IHD in the year prior to HF diagnosis.

Results: 52.5% of the 167 010 individuals included in the cohort were female. In the 60-month period following the HF diagnosis, men were slightly more likely than women to use EBT [(APR 1.01; 1.00–1.01) and (APR 1.04; 95% CI 1.03–1.05) in IHD subjects and in those free of IHD, respectively)].

Conclusions: Results suggest a sex-based difference in the use of EBT by individuals suffering from HF, although this difference might not be clinically significant.

951. Optimizing Medication Use among Patients with Advanced Alzheimer Disease in Long-Term Care – A Scoping Review

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Background: Seniors with advanced Alzheimer disease (AD) in nursing homes receive medications for a mean of 21 health complaints, increasing risks of adverse events. Symptoms like agitation, depression, constipation or pain may be adverse events from medications intended as preventive strategies. With progress of ADR care shifts from preventive to palliative, and medications need to be reviewed, adjusted or discontinued. Research is limited on which previously indicated medications for such patients do not benefit them anymore. Evidence is limited on interventions to review, adjust or discontinue medications for these patients.

Objectives: A scoping review of the literature was performed to answer the questions:

(1) Which medications may be considered inappropriate for patients with advanced AD?
(2) Which criteria allow judging medication appropriateness in this population?
(3) Which interventions exist to optimize medication use in this population?

Methods: We used guidance from the National Institute for Health and Clinical Excellence, followed a framework by Arksey and Levac and identified all published and grey literature of evidence on inappropriate medication use among patients with advanced

ADR in English, French, German or Dutch. The information on medication criteria or interventions was extracted, its quality reviewed and a knowledge synthesis produced. A rigorous and transparent methodology was used and documented.

Results: The search identified 6,186 hits; 356 remained relevant after double screening and 78 articles underwent data extraction. Quality assessment left 40 articles; 25 intervention studies were retrieved, eight of which focused on psychoactive medications, with mostly positive results; 17 studies addressed medications in general with specialist, pharmacist, or multidisciplinary interventions including decision-aids, leading to small but significant reductions in potentially inappropriate medications, adverse events or medication load, with improved or sustained morbidity and mortality.

Conclusions: Different, particularly multidisciplinary interventions show promise to improve medication appropriateness and burden among these vulnerable patients.

952. Patterns of Relapse and Associated Cost Burden in Schizophrenia Patients Receiving Atypical Antipsychotics

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Background: Most patients with schizophrenia experience a chronic course of the disease with many relapses, often characterized by exacerbation of psychoses and frequent rehospitalizations, which are associated with significant cost burden.

Objectives: To identify relapse in schizophrenia and the main cost drivers of relapse using a claims-based algorithm.

Methods: Multistate Medicaid data (1997–2010) were used to identify adults with schizophrenia receiving atypical antipsychotics (AAPs). The first schizophrenia diagnosis following AAP initiation was defined as the index date. Baseline weekly cost was assessed during the 12 months before the index date, and weekly costs were calculated for $\geq$ 2 years post index. An algorithm was developed to identify relapse episodes based on weeks associated with high cost increase from baseline and high absolute weekly cost. Resource use and costs of relapsers during baseline and relapse episodes were compared using incidence rate ratios (IRRs) and bootstrap methods. No adjustment was made for multiplicity.

Results: 9,793 relapsers were identified, with a mean of nine relapse episodes per patient. Duration of relapse episodes decreased over time, with a mean (median) duration of 34(4) weeks for the first and 8 (1) weeks for remaining episodes. Compared with baseline, resource utilization during relapse episodes was significantly greater in pharmacy, outpatient, and institutional visits (hospitalizations and emergency room visits), with IRRs ranging from 1.9 to 2.4 (all p < 0.0001). Correspondingly, relapse was associated with a mean (95% CI) cost increase of $2,459($2,384–$2,539)–nearly six times larger than mean (median) weekly baseline maintenance cost of $425($148). Institutional visits characterized most (53%) of the relapse episode incremental costs, with hospitalizations (excluding mental institute inpatient admissions) representing 36%.

Conclusions: Relapses in schizophrenia patients were associated with cost on average six times higher than the median maintenance costs. Institutional visits characterized most of the cost increase.

953. Meta-Analysis of the Efficacy and Safety of Bortezomib (BTZ) Retreatment in Patients (pts) with Multiple Myeloma (MM)

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Background: BTZ is administered for a finite course; thus, MM pts may remain sensitive to BTZ-based therapy at relapse.

Objectives: We conducted a meta-analysis to assess efficacy and safety of BTZ-based retreatment in studies of pts with relapsed (rel) and/or refractory (ref) MM.

Methods: The proportion of BTZ-ref pts was identified where available. Other prognostic factors were extracted and used in weighted stratified analyses of TTP, PFS, and OS. Random-effect pooled estimates were calculated for ORR ($\geq$ PR) and rates of common AEs.

Results: Twenty-three studies (N = 1,051 pts) were identified. BTZ was given IV in all studies. Retreatment comprised BTZ $\pm$ dex in four studies and BTZ-based combination therapy in 19. BTZ-ref pts were included in 11 studies; six studies included only rel pts.

Across studies with data available, pooled, weighted average ORR was 39% (95% CI: 31–47) and median TTP, PFS, and OS were 7.5, 5.8, and 16.6 months. Stratified univariate analyses showed outcomes were generally consistent across groups while pts with ≤ 4 prior therapies and rel (but not ref) pts had higher ORRs of 43% and 57%, respectively. By random-effects meta-regression analysis, compared to ref pts, rel pts were associated with a higher ORR by 28–41 percentage points. The most common grade 3/4 AEs were thrombocytopenia (35%), neutropenia (15%), anemia (14%), pneumonia (10%), and peripheral neuropathy (3%).

Conclusions: Based on these findings, BTZ retreatment is efficacious and well tolerated in rel pts. In an era of new and emerging treatment options, these data indicate BTZ retreatment continues to be a highly effective option in previously treated pts.

954. Sociodemographic Correlates of Glucosamine/ Chondroitin Use over 4 Years in the National Osteoarthritis Initiative

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Background: Studies of cross-sectional correlates of glucosamine/chondroitin (GLU/CHON) exist, but descriptions of longitudinal use of glucosamine/chondroitin are scant.

Objectives: We identified correlates of longitudinal use of glucosamine/chondroitin among participants with radiographically confirmed osteoarthritis of the knee.

Methods: The Osteoarthritis Initiative identified persons with radiographic tibiofemoral knee OA in at least one knee at baseline. We included 2,114 participants who completed five assessments over 4 years. Trained interviewers asked 'During the past 6 months, did you use chondroitin for joint pain or arthritis?' and 'During the past 6 months, did you use glucosamine for joint pain or arthritis?' The vast majority used both. Correlates of GLU/CHON treatment for OA considered included sociodemographic indicators, measures of health related quality of life, and clinical indices of knee OA. Polytomous logistic regression provided adjusted odds ratio estimates (aOR) and 95% confidence intervals (CI).

Results: Forty-five percent reported use of GLU/ CHON on any assessment, with 32% reporting use at one to four times, and 13% at all assessments. Blacks relative to non-Hispanic Whites were less likely to use GLU/CHON for any number of assessments ($aOR_{use\ 5\ times}$: 0.13; [95% CI: 0.06–0.28]). Participants reporting graduate level education relative to those with < high school education had increased odds of GLU/CHON use on multiple assessments ($aOR_{use\ 5\ times}$: 1.69; [95% CI: 1.02–2.80]). Participants reporting conventional medication use at baseline (e.g. over the counter and prescription pain medications) were more likely to report use of GLU/CHON at every assessment (aOR: 1.64; 95% CI: 1.19–2.26).

Conclusions: Patients suffering from knee OA seek complementary and alternative medicine treatments. GLU/CHON therapies are commonly used to treat joint and arthritis pain among persons with knee OA, but its use over time wanes. Factors associated with continued use may be more associated with sociodemographic factors, rather than disease severity and effectiveness of treatments.

955. Potentially Inappropriate Medications in the Elderly with Alzheimer's Disease and Related Dementia

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Background: Alzheimer's disease and other dementia are mainly encountered in the elderly, who use numerous medications. Some of these drugs may be considered as potentially inappropriate if their benefit/risk ratio is not judged favourable in this frail and old population.

Objectives: To assess the prevalence and the risk factors of potentially inappropriate medications (PIM) use in the elderly with Alzheimer's disease and related dementia.

Methods: A cross-sectional observational multicentre study was conducted from 1/2009 to 6/2011 in six metropolitan regions and 1 over-sea region of France.

Patients with dementia aged 75 years and more, treated with cholinesterase inhibitors or memantine were included. They were selected according to a representative sample based on their usual dwelling place (home or institution). Socio-demographic data, history, drugs given were registered. PIM use was estimated using the French PIM list (Eur J Clin Pharmacol 2007; 63:725–31).

Results: 594 subjects were included; 63.6% living at home and 36.4% in institution. Mean age was 84.2 ± 5.0 years [75–99] and 73.7% of subjects were women. Mean MMSE was 16.9 ± 6.0 [0–29]; 74.9% of the patients suffered from Alzheimer's disease. The mean number of drugs (6.6 ± 2.8) and the PIM use prevalence (44.6% [95%CI: 40.6–48.7%]) were not significantly different between the metropolitan (44.1%) and the overseas areas (51.1%). The most often used PIM were (87.5%): benzodiazepines, association of psychotropics, cerebral vasodilators, association of anticholinesterasics and anticholinergics. The risk factors of PIM use were polymedication (OR = 4.0, 95%CI: 2.5–6.4), life in institution (OR = 1.9, 95%CI: 1.3–2.7) and being a woman (OR = 1.5, 95%CI: 1.0–2.2).

Conclusions: The use of PIM is high in the French population of patients with Alzheimer's disease and related dementia. These drugs should be used cautiously in these patients as they could aggravate memory and dementia.

956. Withdrawn by Author.

957. Predictors of Non-Vaccination Against Human Papillomavirus among US Women Aged 18–26: Data from the 2010 National Health Interview Survey

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Background: HPV vaccination is routinely recommended for young adult women aged 18–26 regardless of previous sexual activity or history of HPV-related disease. As of 2010, only 21% of US women had received ≥ 1 doses of HPV vaccine.

Objectives: To examine demographic, health service utilization, knowledge, and economic predictors of HPV non-vaccination and develop a predictive model of non-vaccination.

Methods :

Design: Retrospective cohort study.

Setting: The National Health Interview Survey (NHIS) is a nationally representative sample and a primary public health surveillance source for adult vaccine coverage. Participants (N = 27,157) were asked whether they had 'ever received the HPV shot or vaccine?' Only females aged 18–26 who answered yes or no (N = 1,866) were included in the study. Main outcome measures

Self-reported receipt of ≥ 1 doses of HPV vaccine [1 = no (not vaccinated), 0 = yes (vaccinated)].

Statistical analysis: Descriptive statistical analyses, univariate procedures, and multivariate logistic regression.

Results: Receipt of HPV vaccine was reported by 21.86% of women. Eight variables were retained for the final model (age aOR = 2.98, 95% CI = 2.04, 4.37; marriage aOR = 1.88, 95% CI = 1.09, 3.24; live birth in the past 5 years aOR = 2.73, 95% CI = 1.72, 4.31, current birth control use aOR = 0.46, 95% CI = 1.73, 4.31; region aOR = 0.48, 95% CI = 0.30, 0.75; health insurance coverage aOR = 1.88, 95% CI = 1.18, 2.98; flu shot receipt aOR = 0.34, 95% CI = 0.23, 0.50; tetanus shot receipt aOR = 0.42, 95% CI = 0.27, 0.65). This model showed good fit to the data (Hosmer-Lemeshow chi-square = 5.26(8); p = 0.72; max rescaled R-square = 0.26; c statistic = 0.79).

Conclusions: Six years after the approval of the HPV vaccine, uptake among adult women remains low. These findings show that older age, being married, having children, living in the southern US, and not receiving other preventive health vaccines or services are associated with non-vaccination. These findings identify a subgroup of women who might benefit from targeted vaccine promotion campaigns and clinical interventions to increase vaccine uptake.

958. Factors Associated with Compliance with Inhaled Corticosteroids in Asthma

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Background: Suboptimal compliance with inhaled corticosteroids (ICS), the main asthma controller medication, is common and recognized as a cause of poor asthma control. Understanding the factors associated with this suboptimal compliance is important to implement effective interventions to improve asthma control.

Objectives: To measure ICS compliance, among people aged from 12 to 45 years with moderate to severe asthma and to identify factors associated with compliance with ICS.

Methods: We conducted a cross-sectional study among people reporting the use of ICS during the baseline interview of the RESPIRE study carried in the province of Quebec, Canada. Compliance with ICS was measured using the medication possession ratio (MPR, i.e. the sum of day's supply/365) using pharmacy prescription fill data for the year preceding the interview. Participants with a MPR > 75% were considered to be compliant. A total of 46 potential factors of compliance with ICS were pre-identified using the PRECEDE model and measured during telephone interviews. They included predisposing, enabling, reinforcing and behavioural factors. To identify factors associated with ICS compliance, we built a multivariate logistic regression model using a manual stepwise procedure. Odds ratios (OR) were estimated with their 95% confidence interval (CI).

Results: Of the 319 participants who reported using ICS, 29 (9.1%) were compliant (median MPR = 16.4%). Participants less likely to be compliant with their ICS were women vs. men (OR = 0.43; 95%CI: 0.18–0.99) and those perceiving no risk of dying if drugs were not taken as prescribed vs. those perceiving a moderate to very high risk (OR = 0.43; 95%CI: 0.19–0.98). On the other hand, participants with very low or low family income and those who reported using ≥ 3 asthma drugs were more likely to be compliant than those with a high family income (OR = 6.36; 95%CI: 1.43–28.22) and those reporting one or two asthma drugs (OR = 4.24; 95%CI: 1.71–10.49), respectively.

Conclusions: Compliance with ICS was very poor in these individuals with moderate to severe asthma. Knowledge of the factors associated with ICS compliance could help to develop future interventions to improve asthma control.

959. Withdrawn by Author.

960. Effect of Computerized Clinical Decision Support on Appropriate Laboratory Monitoring of Medications

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Background: Monitoring medications with laboratory testing to assess efficacy or toxicity is often not performed.

Objectives: To determine the effect of computerized clinical decision support (CCDS) on adherence to recommended lab monitoring.

Methods: A randomized controlled trial of 11 primary care practices (6 intervention, 5 control; 17 clinicians) using an electronic health record with CCDS alert capability. Baseline period: 6/1/10–5/31/11 and intervention period: 6/23/11–12/22/11. There were 32 target medications, each requiring 1–6 distinct lab tests for monitoring. At the time when one of these meds was prescribed, the CCDS determined if the indicated lab test(s) was done in the preceding 365 days and alerted the clinician if not. Primary outcome was the proportion of meds with appropriate lab monitoring, defined as completion of all indicated labs from 365 days before to 14 days after the prescription. Patient factors included age, sex, number of encounters and number of target meds during the time period.

Results: In the baseline period, 10,541 unique patient-medication encounters occurred in control practices and 10,244 in intervention practices; in the intervention period, there were 9,535 and 8,066 in control and intervention practices, respectively. At baseline, practices were similar on many measured factors (e.g., mean age 60 ± 14 years in control practices vs. 60 ± 15 years in intervention practices); however, some differences were apparent (e.g., mean number of visits 6.6 in control practices vs. 4.5 in intervention practices). In the baseline period, the primary outcome occurred for 70.7% of meds in control practices and 79.4% in intervention practices compared to complete monitoring for 62.4% of meds in control practices and 77.7% in intervention practices during the intervention period. For meds requiring ≥ 3 lab tests (n = 555) at most 17.7% had complete monitoring.

Conclusions: Adherence to recommended lab monitoring decreased over time in both groups, although less pronounced in the intervention practices, suggesting some effectiveness. Interventions may need to extend

beyond clinicians to improve the complex practice of laboratory monitoring of medications.

962. Profiling Chronic Opioid Use for Non-Cancer Pain in the United States

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Background: Opioids are prescribed to ~90% of US patients with chronic pain. Treatment options for opioid-induced constipation (OIC), the most prevalent side-effect, are expanding beyond over-the-counter laxatives. Profiling opioid users can help frame questions related to benefit or safety in those receiving treatment options for OIC.

Objectives: To describe patient characteristics, treatment patterns, and healthcare use (HCU) among patients newly initiating opioid therapy.

Methods: Patients ≥ 18 years of age with ≥ 1 prescription (first fill is index date) for opioids during 1/1/2007–12/31/2011 were identified in the HealthCore Integrated Research Environment. Patients were required to have ≥ 30 days continuous opioid exposure. Patients with prior opioid use or a cancer diagnosis during the pre-index period were excluded. Opioid exposure was stratified by exposure length (30–182 vs. ≥ 183 days) and index opioid type (weak vs. strong). Patients were followed until the latter of exposure or study window end dates. All analyses were descriptive. Variables of interest included patient demographics, prescribing physician type, concomitant disease and drug use, HCU, index opioid characteristics, and opioid treatment patterns.

Results: Of all enrollees, ~5.8 million (27%) were dispensed an opioid of which 257,602 (4%) were chronic users. Mean age was 51, 52% were female and 58% utilized a preferred provider organization. The majority (84%) indexed on weak opioids. The most indexed weak and strong opioids were hydrocodone (51%) and oxycodone (16%) respectively. The most common pain conditions observed were arthritis (50%) and low back pain (19%). Notable comorbidities include cardiovascular diseases (46%), diabetes (14%), anxiety (8%) and substance abuse (7%). During opioid use, 16% of patients were hospitalized and 18% had an emergency room visit which is consistent with what was observed prior to opioid exposure. Additional results stratified by exposure length and index opioid type will be presented.

Conclusions: Chronic opioid users displayed high morbidity and HCU. Similar results were observed for patient characteristics, treatment patterns, and HCU across strata for exposure length and index opioid type.

963. Does Weight Status Affect Antibiotic Prescribing Patterns?

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Background: Obesity is a risk factor for infection and antibiotic (Ab) resistance. Although physicians are prescribing Abs more frequently to obese patients, it is not clear whether there is variation in the type of Ab selected and indication with weight status.

Objectives: To describe the oral Ab prescribing patterns and the most common infection types in the community by weight.

Methods: A descriptive population study using administrative health data linked to the 1992 and 1998 provincial health survey was conducted. Participants were normal to obese weight, aged 20–79 years, and received at least one oral Ab from the survey date to December 2005. Weight group was determined using Body mass index (BMI) with WHO cut-offs for normal, excess and obese. BMI was calculated using corrected self-reported height and weight. Data on all dispensed Abs were obtained from the prescription claims. The ICD-9 codes for infections were retrieved from the medical service claims. Frequency distributions for categorical variables were calculated.

Results: 39.0% and 21.4% of the study sample (N = 6,179) were overweight and obese, respectively. Penicillins (35%) and macrolides (18%) were the most commonly prescribed Ab classes. Cephalosporins were used more frequently in obese vs. non-obese patients (13.9% vs. 11.9%). Clarithromycin (8.9% vs. 7.7%), cloxacillin (5.9% vs. 5.4%) and cefuroxime (4.4% vs. 3.8%) were prescribed more often to excess weight patients than normal weight. The most common Ab indications were upper respiratory tract infections (normal 33.5%; overweight 28%; obese 28.3%). Lower respiratory tract infections were more frequent for overweight (26.9%) and obese individuals (24.6%) than for normal weight (20.9%). Skin and soft tissue

infections were more prevalent among the excess weight groups (overweight 15.3%; obese 14.7%) compared to normal weights (12.9%).

Conclusions: There was little variability in the prescribing patterns of oral Ab classes and medications between weight groups. Despite the higher prevalence of resistance in obese patients, broad-spectrum Ab prescribing is still widespread and primary care physicians are not selecting alternative Ab regimens.

964. Profile of Use of Anti-Tumor Necrosis Factor (Anti-TNF) Agents and Disease Modifying Anti Rheumatic Drugs (DMARD) in Ankylosing Spondylitis Patients in a Brazilian Healthcare Database

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Background: Anti-TNF agents represent therapeutic options for patients with ankylosing spondylitis (AS) who failed with non-steroidal anti-inflammatory drugs. DMARD are prescribed for patients with peripheral arthritis. These medicines were included in the pharmaceutical assistance program of Brazilian National Health System (SUS) in March 2010.

Objectives: To describe the pattern of use of anti-TNF drugs and DMARD among AS patients in Minas Gerais state, Brazil.

Methods: We developed a retrospective cohort of AS patients using data from the APAC/SIA, an administrative database that provides information on high cost procedures, and the SIH, a hospital database. Both databases are related to procedures of the SUS. We applied probabilistic record linkage to match registers issued to the same patient. We included all individuals aged over 18 years-old who had a first pharmacy claim for a prescription of adalimumab, infliximab, etanercept, methotrexate or sulfasalazine during March 2010 through March 2011. We described the demographic characteristics of patients and the frequency of medicines dispensed. We used the Database Management System mysql 5.5.29-0ubuntu0.12.04.1 for the analysis.

Results: We identified 240 AS patients and 979 pharmacy claims. Over 70% were male and the mean age was 41.0 years-old (SD 12.2). Approximately 46% were between 20 and 39 years-old. Almost 33% of the patients started the AS treatment with etanercept, 30.8% with adalimumab and 8.8% with infliximab. Sulfasalazine was the only DMARD (27.5%) used. The majority of patients used only anti-TNF agents (71.7%) or only DMARD (25.4%). Three patients were hospitalized during this period with the diagnostic of juvenile ankylosing spondylitis, unspecified myositis and unspecified coxarthrosis.

Conclusions: Probabilistic record linkage method was effective for linkage of APAC/SIA and SIH data. As would be expected in a cohort of patients with AS, subjects were young with a male to female ratio of 2:1, and the majority of patients used anti-TNF drugs instead of DMARD.

965. Bladder Antimuscarinics Use in Veterans Affairs Community Living Centers

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Background: No recent study evaluated initiation and the magnitude of bladder antimuscarinics (BAM) use in the Veterans Affairs (VA) nursing homes, known as Community Living Centers (CLC).

Objectives: To evaluate utilization and predictors of BAM initiation for urinary incontinence management in the VA CLC.

Methods: The study employed multiple VA data sources (Minimum Data Set [MDS], inpatient, outpatient, and pharmacy administrative files). We assembled a retrospective cohort that included individuals 65 years and older admitted for long-term care (> 90 days) in any of the VA CLC between October 1, 2002 and September 30, 2009. BAM use included immediate- or extended-

release products (oxybutynin chloride, tolterodine, darifenacin, solifenacin, trospium, hyoscyamine, dicyclomine, or flavoxate). Exposure to a BAM was identified from pharmacy data. Based on the BAM use prior to CLC admission and the first dispensing date after CLC admission, users were classified as incident, prevalent, or former users. We constructed a logistic regression model to identify patient characteristics predicting BAM initiation compared to non-use.

Results: BAMs were used by 9.8% of the residents 65 years and older admitted for long-term care; 44% (1,195) were new users. All but 53 received nonselective immediate release preparations, predominantly oxybutynin chloride (75%). For new users, mean BAM use was 161.48 days (median = 49 days). Predictors of BAM initiation included demographic characteristics, bladder and bowel continence status, comorbidities, other medication use, cognitive performance and functional status. Women (odds ratio [OR] = 2.11; 95% CI: 1.54–2.88) and those with an indwelling catheter (OR = 3; 95% CI: 2.55–3.54) were more likely to start BAM treatment. Cognitive impairment (OR = 0.71; 95% CI: 0.53–0.95) and limited mobility (OR = 0.98; 95% CI: 0.97–0.99) decreased the odds of BAM initiation. New-users had less comorbidity burden, but used more medications and had a higher anticholinergic load.

Conclusions: Our results suggest treatment selection based on overall health status or patient tolerability (fewer adverse effects with previous medication could increase the chance of getting a new drug).

966. Practice Pattern Changes in Small Dialysis Organizations Following 25% Phase-In v 100% Opt-In to the Dialysis Capitated Payment System

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Background: On Jan 1, 2011, to increase cost-efficiency in care, the end-stage renal disease (ESRD) prospective payment system (PPS) was implemented by the Centers for Medicare & Medicaid Services, initiating a bundled payment for dialysis drugs and services that were previously independently reimbursed. Under PPS, dialysis facilities could choose to opt-in 100% or 25% per year over 4 years.

Objectives: Analyses by opt-in status may be useful in understanding the effects of a systemic policy shift. Herein we describe practice changes in 25% v 100% opt-in facilities in a representative sample of small dialysis organizations (SDOs) that may be more sus-

ceptible than larger organizations to the financial pressures exerted by the PPS.

Methods: Data are from the Study to Evaluate the PPS Impact on SDOs (STEPPS), a prospective observational cohort study of US patients receiving dialysis. Clinical care data between baseline (Q4 2010) and Q4 2011 are described.

Results: Ten facilities (pt N = 314) and 39 facilities (pt N = 1,639) opted-in 25% and 100%, respectively. At baseline, patients enrolled in 25% and 100% facilities were generally balanced across demographic, lab, and most co-morbidity characteristics. However, fewer patients at 100% (v 25%) opt-in facilities were black (22% v 32%). Between baseline and 1 year post-bundle, changes in both use of treatments and resulting lab values were generally larger in 100% v 25% facilities. Declines in mean epoetin alfa dose were greater (20% v 11%); vitamin D use, including route of administration, changed (intravenous [IV]: 22% decrease v 2% increase; oral-activated: 127% v 181% increase); but IV iron use changed little. Mean hemoglobin decreased (5% v 1%), median ferritin levels increased (32% v 14%), and median parathyroid hormone level changes were directionally different (32% increase v 4% decrease).

Conclusions: A facility's decision to opt-in 100% v 25% (per year) appears to have affected its use of commonly used renal medications. The clinical effects of practice changes under a bundled payment system merits further investigation.

967. Usage Patterns of 'OTC' vs. 'Prescription' NSAIDs in France

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Background: Most risks of NSAIDs are dose and duration-dependent, related to their pharmacological properties. Risks measured for prescription strength (POM) NSAID may not apply to OTC-strength (OTC) NSAIDs. However most prescription or healthcare reimbursement databases do not include data on OTC NSAIDs usage. In France OTC NSAIDs are reimbursed if prescribed, which represents over 70% of OTC NSAIDs sales.

Objectives: To describe and compare the users and usage patterns of OTC and POM NSAIDs, from a national representative reimbursement database.

Methods: We queried EGB, the French national Healthcare system database 1/97 representative sample, over 2009–2010, for usage patterns in OTC and prescription NSAIDs users. At the time the National healthcare systems databases covered about 80% of the French population.

Results: In EGB, 229,477 of 526,108 subjects had at least 1 NSAID dispensation over 2 years; 44,484 patients (19.4%) were dispensed OTC NSAIDs only, 121,208 (52.8%) prescription only. OTC users were younger (39.9 vs. 47.4 years old) and more often female (57% vs. 53%). OTC patients were dispensed on average 15 Defined Daily Doses (DDD) over 2 years, vs. 53 DDD for prescription users; 93% OTC vs. 60% POM bought fewer than 30 DDD over 2 years, and 1.5% OTC vs. 12% POM bought at least 90 DDD. Chronic comorbidities were found in 19% OTC users vs. 28% POM users; 24% vs. 37% had 1 or more dispensations of a cardiovascular drug at any time over the 2 years.

Conclusions: Risks derived from clinical trials where patients use more than 90 DDD apply to 12% only of prescription-strength NSAIDs, and fewer than 1.5% of OTC Users. Risks derived from population studies of prescription NSAIDs would probably not apply to OTC NSAIDs.

968. The Enigma of Appropriate Antimicrobial Use: A Model Antimicrobial Stewardship Program (ASP)

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Background: Antimicrobial resistance is one of the greatest public health threats worldwide. ASPs promote appropriate antimicrobial utilization and play a key role in the fight against drug resistance.

Objectives: To describe the development and interventions of a formal ASP at a small teaching hospital.

Methods: We formed an ASP team of attending and fellow infectious disease (ID) physicians, a clinical ID pharmacist and fellow, and pharmacy residents and students. The team utilized a prospective audit approach reviewing all antimicrobial use daily for appropriateness. The pharmacy fellow, residents, and students reviewed patient (pt) charts and identified interventions. All interventions were discussed with the ID physicians and ID pharmacist. Verbal communica-

tion and/or written notes were used to make final recommendations. Pharmacy members followed-up on interventions and documented results. Differences between pts receiving ASP interventions (INT) were compared to those with no intervention (NO INT) using the χ^2, fisher's exact, and *t*-tests as appropriate.

Results: We reviewed 437 pts from Sept 2012 to Feb 2013. These pts were 96% male and 93% white, with a mean age of 71. Interventions were made in 32% of pts. No significant differences were observed between INT and NO INT pts with respect to age, sex, race, or admission unit. The mean time spent per pt chart review was longer for INT vs. NO INT pts (23 vs. 17 min p < 0.001). Pts in the INT group were more likely than the NO INT group to be treated with vancomycin (50% vs. 36% p < 0.001) or piperacillin/tazobactam (45% vs. 38% p < 0.001) for pneumonia (36% vs. 26% p = 0.03) or skin infections (28% vs. 16% p = 0.004). INT pts had a longer mean length of stay compared to NO INT pts (9 vs. 5 days p < 0.001). The intervention acceptance rate was 74%. The most common interventions were drug optimization (21%), antibiotic discontinuation (21%), IV to PO (20%), vancomycin dosing/monitoring (20%), and de-escalation (9%).

Conclusions: Using a team approach with prospective audit and feedback, our model of a formal ASP effectively monitored antibiotic utilization in a small teaching hospital which ultimately improved appropriate antimicrobial use.

969. Identifying Older Adults with Major Depressive Disorder from Medicare Current Beneficiary Survey Data

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Background: Major depression in older adults is generally underdiagnosed and undertreated. Underreporting of the disease in claims data limits the accuracy of algorithms to identify the disease. As administrative claims data has been frequently used for quality measures and improvement, it is important to develop and validate the methods to identify older adults with depression and those who received care.

Objectives: To describe the validity of the methods for depression identification in older Medicare population.

Methods: We conducted a large nationally representative cross-sectional study using Medicare Current Beneficiary Survey from 2006 to 2008. We screened community dwelling older beneficiaries with depression using validated self-report Patient Health Questionnaire 2 (PHQ-2) scale. We then identified depression according to the three definitions: (1) International

Classification of Disease, Ninth Revision (ICD-9) codes of 296.2, 296.3, 300.4, 309.0, 309.1, 298.0, and 311; (2) prescribed medication records with antidepressants; and (3) ICD-9 diagnoses or use of antidepressant medications. We estimated sensitivity and specificity of each defined algorithm compared with the depression identification made with PHQ-2.

Results: The prevalence of depression varied with the algorithms: 9.6% with PHQ-2, 4.3% with ICD-9 diagnoses, 19.8% with antidepressant use, and 20.8% with ICD-9 diagnoses/medication use. When using PHQ-2 as the gold standard, ICD-9 diagnoses showed 11.9% (95% Confidence Interval [CI], 10.4–13.7) of sensitivity and 91.2% (95% CI, 90.7–91.6) of specificity. However, sensitivity for antidepressant use was 41.5% (95% CI, 39.1–44.0), while specificity was 93.0% (95% CI, 92.6–93.5). When combining antidepressant use into ICD-9 identification, sensitivity (43.8%; 95% CI, 41.4–46.3) and specificity (93.2%; 95% CI, 92.8–93.6) were slightly increased.

Conclusions: The study documented variation in sensitivity for depression identification, implying using Medicare claims to identify depressed patients may result in underestimation of the depression. In order to improve the accuracy of depression identification, researcher may consider using multiple types of claims.

970. Patterns of Antibiotic Use and Dose Adjustment in Patients with Chronic Kidney Disease at Kenyatta National Hospital, Kenya

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Background: The presence of reduced kidney function in any patient alters drug disposition. This alteration necessitates appropriate individualization of drug therapy to avoid unnecessary drug accumulation and adverse drug effects.

Objectives: The objective of the study was to determine the patterns of antibiotic use and dose adjustment practices in patients with chronic kidney disease at Kenyatta National Hospital.

Methods: The study was a retrospective cross sectional study. Data was collected on antibiotic prescriptions and renal function parameters between, January, 2006 and December, 2010. The antibiotic dosage for systemic administration, which ought to have been adapted depending on renal function, was determined from the dosing guideline for adult patients with chronic kidney disease and this was compared with the prescribed dosages to determine the appropriateness of the prescribed doses. Chronic kidney disease patients, with antibiotic prescription and aged 18 years and above during the time of antibiotic prescription were eligible for the study. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease four variable equation. Data analysis was done using STATA version 9 statistical software. Data was subjected to descriptive, confounding and logistic regression analysis.

Results: Ceftriaxone and co-amoxiclav were the most frequently prescribed antibiotics. Dose adjustment was indicated in 59.9% of antibiotic prescriptions; however appropriate adjustment was only done in 27.7% (95% CI 23.18–32.23) of the prescriptions. The most important risk factor for inappropriate dose adjustment was the severity of renal disease. Co-amoxiclav was the least frequenyly adjusted antibiotic with only 8.5% appropriate adjustment whereas, vancomycin had the highest prevalence of correct dose adjustment at 69.7% of the prescriptions that required adjustment. Over dosage was the most common dosing error.

Conclusions: Antibiotic dose adjustment in patients with chronic kidney disease was often overlooked. Strategies to improve prescribing need to be developed and implemented to enhance rational prescribing of antibiotics.

971. Geographic Variation of Chronic Opioid Use in Fibromyalgia

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Background: Opioid use for the treatment of chronic nonmalignant pain has increased drastically over the past decade. Although no evidence of efficacy exists supporting the treatment of fibromyalgia syndrome (FM) with chronic opioid therapy a large number of these patients receive this therapy. Geographic variation in the use of opioids has been demonstrated in the past, but no studies examining variation of chronic opioid use exist.

Objectives: This study answers two research questions. First, to what extent does geographic variation between states for chronic opioid utilization in patients with FM exist? Second, what association between contextual and structural factors and the rate of chronic opioid use at the state level is seen?

Methods: Using a large, nationally representative dataset of commercially insured individuals we examined both the extent of geographic variation and factors associated with variation of chronic opioid use among FM patients across states. Characteristics examined include: gender, disease prevalence, physician prevalence, illicit drug use, and the prescence of a prescription monitoring program (PMP) in addition to other contextual and structural characteristics.

Results: The analysis included 245,758 FM patients, 11.3% received chronic opioid therapy. There was a fivefold difference between states with the lowest rate of use (~4%) and those with the highest (~%20). The wCOV was 36.2%. Percent female and prior illicit opioid use rates were associated with higher rates of chronic opioid use while FM and physician prevalence were associated with lower rates. PMP presence was not significantly correlated.

Conclusions: Geographic variation in chronic opioid use among FM patients exists at rates similar to those seen in other studies examining opioid use. This large level of geographic variation suggests that the prescribing decision is not based solely on physician-patient interaction, but also on contextual and structural factors at the state level. The level of physician and condition prevalence suggest that information dissemination and peer-to-peer interaction may play a key role in adopting evidence based medicine for the treatment of patients suffering from FM and related conditions.

972. Medical and Mechanical Prophylaxis for Venous Thromboembolism after Total Hip and Knee Replacement

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Background: Venous thromboembolism (VTE) after total hip (THR) and knee replacement (TKR) is a frequent complication (10–30%). Prophylactic therapy significantly reduces the risk of symptomatic VTE within 3 months of surgery (1–10%). A variety of options are recommended including medical and mechanical prophylaxis, but current evidence is unclear about the optimal strategy, and prescribing patterns are not well explored.

Objectives: To describe current postoperative regimens for VTE prophylaxis after THR or TKR.

Methods: We identified a cohort of patients who had THR or TKR from the Premiere Perspective Comparative Database during 2007–2011. A minimum hospital stay of 2 days post-surgery was required. We excluded patients with atrial fibrillation, concomitant hip or knee fracture or malignancy, or a severe postoperative bleeding. VTE prophylaxis was identified within 48 h postoperatively and classified into subcutaneous unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, warfarin, mechanical therapy (graduated compression stockings or intermittent pneumatic compression device), combinations of these regimens, and no treatment with any of these therapeutic strategies. Patients receiving VTE treatment doses vs. preventative doses of parenteral anticoagulants were excluded. New oral anticoagulants, i.e. dabigatran or rivarixaban, were not considered as their use was negligible during the study period.

Results: We identified 297,028 patients who underwent either THR or TKR during 2007–2011. Among those, 379 received treatment with UFH (0.1%), 61,194 with LMWH (20.6%), 20,517 with fondaparinux (6.9%), 124,493 with warfarin (41.9%), 2,090 with mechanical therapy (0.7%), 20,430 with LMWH/warfarin (6.9%), and 5.9% with other combinations of the above therapies. 50,425 patients (17.0%) received no treatment with any of these therapeutic strategies.

Conclusions: Warfarin, followed by LMWH, was the most commonly prescribed strategy for VTE prophylaxis after THR or TKR. A considerable number of patients received no postoperative VTE prophylactic treatment. The heterogeneity with respect to practice suggests the need for comparative effectiveness research.

973. Drug Utilization and Safety Evaluations: Lessons Learned from International Multi-National Retrospective Chart Review Study Applications

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Background: Increasingly, to meet marketing authorization and risk management data needs, regulators are requiring real world prescription pattern data including empirical off label-use. In the absence of suitable databases, chart review studies can result in robust datasets appropriate for evaluations of drug utilization and safety outcomes.

Objectives: Delineate design and operational issues/challenges associated with the application of chart

review methodology to drug utilization and safety studies.

Methods: Design and operational parameters of four recent chart review studies of clinical outcomes and/or drug utilization and safety conducted in Canada, the United States and Europe have been summarized. Opportunities, challenges and lessons learned are delineated in detail.

Results: All studies were post authorization safety studies and all but one of these studies was mandated by the FDA or EMA. The therapeutic areas varied across the studies including renal, cardiovascular and intensive care populations. Sample size varied from as low as 100 patients to more than 2000 patients and the number of countries and sites varied from 1–5 and 12–375 respectively. Across studies, key challenges included determining eligibility and study periods that permit evaluations of recent care patterns while allowing sufficient follow-up time; design and local implementation of case identification and sampling frame methodologies; and safety reporting in the context of retrospective chart data. The studies evaluating inappropriate or off-label use required careful attention to protocol language to minimize response bias, as well as a carefully executed operational plan for the identification of prescribers and the collection of data from prescribers over time.

Conclusions: Though challenging to implement, retrospective chart reviews are increasingly necessary to address drug utilization and safety related research questions. A series of multi-national chart review case studies with diverse research objectives highlight common design and operational challenges that can be anticipated and overcome.

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974. Non-Prescription Medicines -The Missing Pieces of the Drug Utilization Puzzle

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Background: It is well known the medication utilization increases with age. Medication utilization among elderly nursing home residents is well studied, however most studies focus on exploration of prescribed medicines and do not include non-prescription or complementary medication utilization.

Objectives: The aim of this study was to explore utilization of medications that are available with out a prescription in an elderly nursing home cohort.

Methods: A cross sectional survey of medication use in residents (n = 2,585) from 26 aged care facilities in the greater Sydney region was conduced. Between 30 June 2009 and 31 July 2010. The data source used was pharmacy supply records containing both prescription and non-prescription medications. Medications were classified using the ATC classification and non-prescription status was determined for each product based on the current Australian legislation.

Results: Non-prescription medicines were used by the majority of residents in the study population (90.68%, n = 2,344). Most residents used multiple non-prescription products during the 12-month period with a median of four different non-prescription products per resident used in the study period. The main non-prescription products used were paracetamol, laxatives, calcium and vitamin D containing preparations.

Conclusions: Use of medicines available without a prescription was high in the aged care setting and should be included in drug utilization studies. A number of potential quality use of medicine issues are raised given the main non-prescription agents used and the indications they may be used for which may include both prescription and non prescription medicines in optimal management. Any assessment of prescribing quality should take both prescribed and non-prescribed medications into consideration.

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975. Medication Characteristics and Disparities in the Underuse of Prescription Medications among Chronically Ill Adults in the U.S.

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Background: Little is known about the relationship between medication characteristics and the underuse of prescription medications among chronically ill adults in the U.S., particularly in the context of disparities in underuse.

Objectives: The objective of this study was to examine social disparities in the underuse of preventative (e.g. antihypertensives) and symptomatic-relief (e.g. analgesics) prescription medications among U.S. adults with chronic conditions.

Methods: Prescription medication data from the National Health and Nutrition Examination Survey (NHANES) 2009–2010, a nationally representative cross-sectional health examination survey, were examined for persons aged $\geq$ 18 years. A total of 1,700 respondents had multiple chronic conditions for which a symptomatic and a preventative prescription medica-

tion were both clinically indicated constitute our sample.

Results: Overall, 48.5% of adults with multiple chronic conditions used both symptomatic-relief and preventative medications. The underuse of symptomatic-relief medications was significantly more common than the underuse of preventative medications (16.4% vs. 3.8%, respectively; p < 0.05). In addition, dissimilar to preventative medications, there were social disparities in the underuse of symptomatic medications. Blacks and Hispanics with multiple chronic conditions were significantly (p < 0.05) less likely to use symptomatic medications (19.5% and 18.4%, respectively) than Whites (14.5%). In addition, the underuse of symptomatic medications was more common in men in comparison to women (19.2% vs. 14.2%, respectively; p-value < 0.05). These disparities persist after accounting for differences in drug coverage, age, education and polypharmacy.

Conclusions: These results suggest widespread underuse of prescription medications that provide symptomatic relief for common chronic conditions such as asthma and arthritis among the U.S. adult population. Social disparities in the underuse of symptomatic medications may contribute to the documented disparities in associated health outcomes. Efforts to reduce disparities may need to consider medication characteristics, such as clinical effects.

976. Sulfonylurea Use Associated with Higher Emergency Room Utilization among Elderly Patients with Type 2 Diabetes

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Background: Emergency hospitalizations related to adverse events due to prescription medications are common and pose a significant economic burden on the US healthcare system. Recent evidence among the US elderly population suggests that drugs used to manage type 2 diabetes account for almost one-fourth of such hospitalizations which are often associated with hypoglycemia. However, it is not yet known whether sulfonylureas (SU), commonly prescribed oral anti-hyperglycemic agents known to cause hypoglycemia, are associated with increased risk of emergency hospitalizations compared to other oral drugs.

Objectives: To evaluate the association between SU and emergency room (ER) use among eldely patients with type 2 diabetes.

Methods: We conducted a retrospective study using the pharmacy and medical claim information in Market-

Scan® (2009–2010) to evaluate this association. The analysis included 36,460 elderly patients aged ≥ 65 years on SU monotherapy and 1:1 propensity score matched group of patients on monotherapy with other oral agents (insulin users excluded).

Results: The mean number of ER visits among SU users was 0.65 compared to 0.55 among non-users (p < 0.0001) during the 1 year follow-up period. In conditional logistic regression model, conditional on propensity to use SU and accounting for potential confounders (age, gender, type of health insurance, geographic region, history of CVD, stroke, pharmacologically treated hypertension and dyslipidemia, and use of benzodiazepines and anti-convulsant therapy), the ORs comparing SU users vs. non-users were 1.10 (95% CI: 1.06–1.41) for 1 ER visit and 1.27 (95% CI: 1.21–1.33) for ≥ 2 ER visits. When specifically comparing SU vs. metformin monotherapy, these adjusted ORs were 1.14 (95% CI: 1.09–1.19) for 1 ER visit and 1.37 (95% CI: 1.30–1.44) ≥ 2 ER visits.

Conclusions: These results suggest that elderly patients with diabetes on SU are more likely to have ER visits compared to those using other oral agents. Further research should confirm this finding and consider evaluation of factors associated with ER utilization among SU users.

977. Lack of Therapeutic Efficacy on Type 2 Diabetic Patients Treated with Glibenclamide and Metformin in Mexico City

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Background: Through HbA1c determination, an official study (ENSANUT, 2006) revealed that only 5.3% of diagnosed diabetic patients in Mexico were properly controlled. The study also revealed that 94.65% of diagnosed diabetic patients were uncontrolled even under medical treatment.

Objectives: Our goal is to find out whether a Mexico City population sample of type 2 diabetic patients is similar or different to the rest of the Mexican population on its therapeutic response to the most used oral antidiabetic drugs in the country.

Methods: We present a cross-sectional, observational and descriptive study in a sample of type 2 diabetic patients. We studied three groups according to applied drug treatment: glibenclamide (GLIB), metformin

(METF) or both, and a control group managed with lifestyle changes only. We reviewed medical records of a diabetes clinic at a primary level health center in Mexico City. Patients were treated by physicians at the aforementioned diabetes clinic, according to a Mexican government protocol (Diagnöstico y tratamiento de la diabetes mellitus tipo 2. México: Instituto Mexicano del Seguro Social, 2012). We performed ANOVA and *t* Student's test on all groups.

Results: The HbA1c mean among all groups was: GLIB 7.33 ± 0.42, METF 7.81 ± 0.37, both 8.67 ± 0.38, lifestyle change 9.44 ± 1.19. Fasting plasma glucose mean was: GLIB 100 ± 24.3, METF 155.6 ± 9.23, both 187.2 ± 10.7, lifestyle change 175 ± 35.8. Statistically significant differences between groups were not found.

Conclusions: Preliminary results in this population sample correspond to the ones described by ENSA-NUT 2006. Even though blood glucose levels in the glibenclamide treated group were acceptable, HbA1c levels were no different respect to the other groups. We think that the absence of statistically significant differences is due to the reduced sample size (N = 57).

978. Performance of Three Brands of Drug Interaction Programs for Use in Geriatrics

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Background: Elderly patients are vulnerable to drug interactions because of age-related physiologic changes, an increased risk for disease associated with aging, and the consequent increase in medication use. Preventing adverse drug interactions is a relevant strategy to optimize the geriatric pharmacotherapy. Drug interaction screening programs (DISCP) has recently gained attention as a valuable tool to detect drug interactions and therefore support rational prescribing. There are great variability among DISCP regarding their ability to correctly identify drug interactions and classify their severity and clinical significance.

Objectives: To evaluate DISCP and determine their accuracy in identifying drug-drug interactions that may occur in geriatric.

Methods: DISCP were identified through a bibliographic search. The programs' sensitivity, specificity, positive and negative predictive values were determined to assess their accuracy in detecting drug-drug interactions. The accuracy of those software programs was determined using 100 clinically important interactions and 100 clinically unimportant interactions. Stockley's Drug Interactions 8th edition was employed as the gold standard in the identification of drug-drug interaction.

Results: The programs studied were: Drug Interaction Checker (DIC), Drug-Reax (DR) and Lexi–Interact (LI). LIC presented the highest sensitivity (0.93) and DR showed the lowest (0.86). Regarding specificity, 0.86 was found to DR and 0.65 to LI and 0.66 to DIC. The DR's positive predictive value (0.86) was higher than values presented by DIC and LI (0.73). DR and DIC had the lowest (0.86) and the highest (0.90) negative predictive values, respectively.

Conclusions: DR seems to be the most appropriate DISCP to identify drug-drug interactions in geriatrics because of its balance between sensitivity and specificity. The use of a quality program can help the healthcare team to detect and manage drug interactions in elderly patients, contributing to the rational use of drugs.

979. Agreement among Published Explicit Criteria for Inappropriate Medications in Elderly People

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Background: Pharmacoterapy is a fundamental component of the care of elderly people. Inappropriate prescribing is highly prevalent in older people and it is an important issue on concern. Implicit and explicit criteria help to guide medication use in older people and to measure the quality of prescribing. Explicit criteria provide a list of drugs and other prescribing indicators. Due to the need for better prescribing in elderly patients, several explicit criteria have been published.

Objectives: To evaluate the agreement among the lists of drugs and prescribing indicators presented by explicit criteria used to guide prescribing in elderly patients.

Methods: The drug and prescribing indicators presented by 12 lists of published explicit criteria were all compared, and each of these lists was compared to that provided on Beers 2012 list for potentially inappropriate medication use in older people. A kappa coefficient was used to calculate the agreement among the lists.

Results: A total of 384 prescribing indicators were listed encompassing 339 drugs. Only amitriptyline was common in the 12 list. Other drugs common to 10 or more lists were clonidine, diazepam, indometacin and methyldopa. The global Fleiss' kappa was 0.104. The best Cohen′s kappa coefficient were 0.4210 (Priscus list and the Austrian consensus list) and 0.4170 (Japanese

Beers criteria for inappropriate medication use in elderly patients and the list of potentially inappropriate drugs for Korean elderly). The Korean list showed the best concordance with Beers 2012 (Cohen′s kappa 0.2550).

Conclusions: Slight agreement was found among the lists of explicit criteria. Regional drug availability, economic considerations, the methodology used in the development of the criteria and clinical practice patterns can explain the poor agreement. The incorporation of evidence and the adoption of a method to classify potentially inappropriate medicines according to drug classes instead of the current approach which includes individual drugs would result in higher transnational usability and better concordance.

980. Evaluation of Drug Interaction Screening Programs in Oncology

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Background: Drug interactions in cancer patients are an issue on concern. These interactions may be frequently identified, specially because cancer patients receive multiple medications concurrently with complex antineoplasic regimens. Nowadays, several commercial drug interaction screening programs (DISCP) are available. However, there is wide variability among DISCP regarding their ability to correctly identify drug interactions and classify their severity and clinical significance.

Objectives: To evaluate DISCP and determine their accuracy in identifying drug interactions that may occur in oncology.

Methods: DISCP were identified through a bibliographic search. The programs' sensitivity, specificity, positive and negative predictive values were determined to assess their accuracy in detecting drug interactions. The accuracy of the software programs identified was determined using 100 clinically important interactions and 100 clinically unimportant interactions. Stockley's Drug Interactions 8th edition was employed as the gold standard in the identification of drug-drug interaction.

Results: The DISCP included in the study were: Drug Interaction Checker (DIC), Drug-Reax (DR) and Lexi-Interact (LI). The programs were very similar in sensitivity (0.48–0.58) and negative predictive values (0.61–0.65). DR displayed the highest specificity (0.89) and LI showed the lowest (0.78). Regarding positive predictive values, the results were 0.81 for DR, 0.74 for DIC and 0.73 for LI.

Conclusions: Considering the safety of medication use, the low sensitivity is more clinically important than the low specificity. Not identifying a drug interaction impedes planning interventions to avoid or minimize a clinically important drug adverse event. Due to the poor sensitivity, the three programs have not achieved the minimum quality to be used in the healthcare process in oncology. This study reinforces that these programs should be improved to ensure the rational use of drugs and the quality of patient care.

981. INN Mandatory Prescription in Portugal Mainland

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Background: Portugal recently implemented the INN (International Nonproprietary Name) mandatory prescription. This legislation makes it compulsory for physicians at all levels of the system, both public and private, to prescribe by INN instead of a specific product or brand. This intends to increase the use of generic medicines and the less costly available product.

Objectives: To characterize the prescription and dispensing after this measure implementation. To determine the impact for the National Health System and patients due to this policy change. To establish a relation with the use of generics.

Methods: Data collection refers to prescriptions in ambulatory care to the population covered by the NHS, since the introduction of INN prescription on the 1st June 2012. Other relevant time periods were also considered. Descriptive statistical analysis and Pearson Correlations were performed.

Results: With the INN prescription, pharmacies must have three of the five medicines with the lowest price in the homogeneous group set for Reference Price System. From these they are obliged to dispense the cheapest one. As a result, NHS expenditure decreased more than 12% and patient's expenditure reduced almost 20%. Accessibility was maintained and packages even registered an increase. INN prescriptions reached 92% of total prescriptions. Of these 30% were changed due to patient option for another product (generic or not). At this point only < 5% prescriptions are prescribed manually (with no possibility for INN). This policy definitely had an impact in the generics volume market share, which registered a 5% increase and is now situated in 37%. Statistical relation for this was significant at p < 0.1.

Conclusions: Despite the few months after the implementation and still with a transition period going on INN mandatory prescription already shows some

results. The main ones related to a decrease in medicines achieving costs. Competitive mechanism between products is now more visible in order to be at the cheapest group thus reducing prices. Generics increase was statistical significant. Some other countries also implemented recently INN mandatory prescription so future studies should establish a cross-national comparison.

982. Antimicrobial Utilization in Hospital and Primary Care in Portugal Mainland

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Background: Portugal is one of the European countries with higher use of antimicrobials. However, this use is decreasing in the last few years. Several reasons may be behind this, namely new guidelines, campaigns or a more rational prescription and use among other factors.

Objectives: To analyze antimicrobial utilization and expenditure trends, both in hospital and primary care. To identify utilization patterns within each different subgroups or regions and to determine the impact of latest clinical guidelines and policy changes in the sector.

Methods: Data collection refers to antimicrobials prescribed and dispensed in ambulatory care to the population covered by the NHS, from 2000 to 2012 and in hospital care from 2007 and 2012. Main outcome measure was the Defined Daily Dose /1000 inhabitants/day (DID) according to ATC Index 2013. Statistical methods were applied such as Pearson Correlations, ANOVA procedures and regression intervention models.

Results: Antimicrobial utilization has been decreasing over the years, both in hospital and primary care. In primary care antimicrobial use actually stands for < 25 DID. We can address the existing reduction to tetracyclines and cephalosporins, these last with < 10% of total antimicrobial use achieving the target established in the National Health Plan. Antimicrobial utilization also revealed distinct patterns when concerning geographical regions. In hospital care, despite the overall reduction, carbapenems utilization is rising 5% (meropenem). A statistical significant relation ($p < 0.08$) was established when assessing the impact of recent policy changes.

Conclusions: Use of antimicrobials is decreasing in the last few years. Some policy changes such the use of generics, reimbursement and prices were associated with changes in volume and expenditure trends. However, the impact of new guidelines for antimicrobial use that were published in 2011, was not statistical significant yet.

983. Prognostic Value of Chronic Anxiety and Depression and Utilization of Anti-Depressant Medication in Patients with Coronary Heart Disease

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Background: Symptoms of depression and anxiety determine prognosis of patients with coronary heart disease (CHD). Less clear is the prognostic value of persistence or changes of symptoms and utilization of specific anti-depressive medication.

Objectives: We evaluated the association of 1-year persistence or changes of anxiety and depressive symptoms with cardiovascular disease (CVD)-events during long-term follow-up and in addition, assessed the utilization of anti-depressive medication.

Methods: Prospective cohort study in stable CHD patients. Anxiety and depression at baseline and at 1 year follow-up were evaluated with the Hospital Anxiety and Depression Scale (HADS). Cardiovascular disease (CVD)-events were determined during a 10 year follow-up. A Cox-proportional hazard model was used to determine the association of 1 year changes of symptoms of anxiety and depression on secondary CVD-events.

Results: Of the 1,034 patients with CHD 10.4% showed an improvement, 20.6% a worsening, and 4.0% a persistently increased anxiety symptoms score (the resp. proportions for depressive symptoms were 7.4%, 15.1%, and 3.0%). One-year changes in anxiety symptoms were not associated with CVD events (n = 152). However, 1-year changes of depressive symptoms were (p trend < 0.05 after adjustment for covariates; patients with worsening of depressive symptoms had an HR of 1.79 (95% CI 1.17–2.74) compared to patients with a normal score. The utilization of anti-depressive medication in the overall population was 2% (95% CI 1.2–2.9%) and 3.1% (95% CI 2.0–4.2%) at baseline and 1 year follow-up. Prevalence increased with increasing symptom score and reached 6.7% in subjects with a worsening score and 21.9% in subjects with a persistently increased depressive score.

Conclusions: The study supports an important role of symptoms of depression for long-term prognosis of patients with CHD and suggests that treatment prevalence may still point to an area of an unmet medical need.

984. Association between Bronchodilator Treatment and Myocardial Infarction in COPD Patients: A Structured Assessment of Systematic Reviews and Meta-Analyses

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Background: For the treatment of the chronic obstructive pulmonary disease (COPD) beta-2-adrenoceptor agonists (B2A) and muscarinic antagonists (MA) are frequently used drugs. In numerous studies, association of B2A or MA usage and cardiovascular events were evaluated but results are conflicting, in particular for 'myocardial infarction' (MI).

Objectives: This review aims to summarize the current state of research concerning the association between inhaled B2A or MA and MI for the treatment of COPD patients.

Methods: A comprehensive computer-based literature search was conducted in electronic databases (MEDLINE, Cochrane database) to identify meta-analyses or systematic reviews on the drug–adverse event pairs B2A or MA and MI. A combination of free text and MeSH terms was used. Results were limited to articles published in English between January 1946 and April 2012. Data were extracted by two independent reviewers using a standardized questionnaire. Finally, a quality assessment was performed for each included review.

Results: In total, 205 meta-analyses and systematic reviews were primarily identified. After the abstract and full text retrieval process 11 publications remained that were considered eligible for inclusion in this review. Most of the included reviews dealt with studies presenting a comparison between tiotropium vs. placebo (n = 5). In one meta-analysis only, inhaled anticholinergics significantly increased the risk of MI (2.0% vs. 1.6% for controls (placebo and active treatment – combined analysis), RR 1.52 [1.04–2.22]; Singh et al. JAMA 2008). In all other systematic reviews and meta-analyses, contradictory and non-significant results regarding MI risk were reported. The quality of the studies was acceptable; however, the main points of criticism were unclear definitions of the term 'adverse events' and missing severity classification.

Conclusions: Regarding meta-analyses and reviews assessed in our study, no clear evidence for an increased MI risk was found in patients receiving B2A or MA. This research received support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

985. Post Fracture Osteoporosis Care in Rheumatoid Arthritis (RA)

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Background: Factors such as a diagnosis of RA, a history of osteoporotic fracture after the age of 40, and the use of corticosteroids increase fracture risk. Studies conducted in RA revealed an overall sub-optimal management of osteoporosis, but none specifically examined care provided in a post fracture setting.

Objectives: To assess care provided for osteoporosis following a non-vertebral osteoporotic fracture in RA, and determine if practice has evolved since the publication of 2002 Canadian osteoporosis clinical practice guidelines.

Methods: This is a pre-post population based study using the Quebec health care databases (1998–2008). Included subjects were those with RA (ICD-9/10), aged $\geq$ 50 years, with a non-vertebral osteoporotic fracture (as per RAMQ validated algorithm), and no history of osteoporosis drug use. We defined two periods, pre and post 2002. After facture date, subjects were followed for 12 months. Provision of osteoporosis care was considered to have occurred if (1) a BMD test was performed (or had been performed in the year pre fracture) and/or (2) an antiresorptive drug (e.g. bisphosphonate) or hormone replacement therapy was initiated. Multivariable logistic regressions assessed the effect of factors on care provided. All analyses were conducted with SAS 9.2.

Results: A total of 1,279 subjects were included (pre: n = 602, post: n = 677). They were mainly women (77%) aged on average 74 (standard deviation, 10), and 40% had a fracture at a major site (femur, pelvis). The percentages of subjects who had documented care for osteoporosis was 37% and 44% (difference 8%, 95% CI, 2–12) in the pre and post periods, respectively. This improvement was driven by an increase in BMD testing. Over the two periods, the likelihood of receiving care for osteoporosis increased by 48% (OR = 1.48, 95% CI, 1.06–2.05). For each period, receiving care was more likely among those with a major fracture, females, those followed by a rheumatologist, and those taking oral corticosteroids.

Conclusions: Care following a fracture in RA has improved over our study period. This may be related to the 2002 Canadian osteoporosis clinical practice guidelines, or to other factors.

986. Rates of Non-Vertebral Osteoporotic Fractures in Rheumatoid Arthritis (RA) and Impact of Clinical Practice Guidelines for the Management of Osteoporosis

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Background: Osteoporosis is a common complication in RA resulting in fractures. In recent years, clinical practice guidelines for the management of osteoporosis, endorsed by the Osteoporosis Society of Canada, have been published, but their potential impact on fracture has not been appraised in RA.

Objectives: To identify the rates of non-vertebral osteoporotic fractures over time in RA patients aged ≥ 50 years and determine if a decrease was observed following the dissemination of the 2002 clinical practice guidelines.

Methods: This is a population based study using the physician billing claims and hospital discharge data (1998–2008) from the Quebec health care databases (RAMQ, MEDECHO). RA subjects aged ≥ 50 years were selected using recorded ICD-9/10 codes. A RAMQ validated algorithm identified non-vertebral osteoporotic fractures and age-standardized quarterly rates between 1998 and 2008 were calculated. The impact of the 2002 clinical practice guidelines was tested using a time series approach. An autoregressive integrated moving average (ARIMA) model was developed based on quarterly rates from 1998 to 2002 and then used to predict values from 2003 onward. Actual rates were then compared to forecasted ones. All analyses were conducted with SAS 9.2.

Results: The study population was predominantly female (70%) with a mean age of 70 (standard deviation, 9). Over the study period, the rates of all fractures ranged between 47/10,000 (Q1 1998) and 30/10,000 (Q2 2007). On average, the rates of fractures in women were twice as high as in men. The femur was the most common site. For both all fracture sites, and femoral fractures, the actual rates from 2003 onward fell within the rates projected by the ARIMA model and their 95% CI, indicating that the clinical practice guidelines did not translate into a reduction of fractures over our study time horizon.

Conclusions: Despite clinical practice guidelines to improve the management of osteoporosis in Canada, no impact on the rates of non-vertebral osteoporotic fractures could subsequently be observed in an older RA population.

987. Characteristics of Antipsychotic Dispensations after First Admission to a Long-Term Care Facility (LTCF) in Saskatchewan, Canada

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Background: Antipsychotics are used for the management of behavioral symptoms in dementia, but are associated with adverse events. LTCF admission is an opportunity for optimization of therapy, but requires detailed knowledge on antipsychotic utilization.

Objectives: To characterize antipsychotic dispensations after LTCF admission in Saskatchewan.

Methods: We defined a cohort of new LTCF residents ≥ 65 years first admitted between April 2002 and March 2011 from the Saskatchewan Health databases. Follow-up ended at first antipsychotic dispensation, exit from the facility, or 365 days after admission. We included individual-level and facility-level characteristics in our hierarchical Cox regression models. Prescriber information was also available from the databases.

Results: In our cohort of 25,419 newly admitted seniors, 7,311 (28.8%) were dispensed an antipsychotic during follow-up. Dispensation of antipsychotics in the year before LTCF admission was most strongly associated with time to dispensation after admission (adjusted HR for continuous use 7.6, 95% confidence interval 6.7–8.7, reference no use). 87.8% of dispensa-

tions were for atypical antipsychotics, mostly risperidone and quetiapine, 97.5% of dispensations were for oral administration. The last dispensation before and the first dispensation after admission were both issued from the same GP for 2,055 new residents, representing 28.1% of seniors with dispensations after admission.

Conclusions: Accounting for individual and facility characteristics, dispensation of antipsychotics before LTCF admission remains a strong predictor for dispensation after admission. Most seniors receive oral atypical agents. A considerable proportion of new residents receive antipsychotics from the same prescriber before and after admission suggesting these prescribers may be targeted by interventions to ensure their continuing use is appropriate.

988. Withdrawn by Author.

989. Sales Trends of Rosiglitazone and Pioglitazone after Safety Alert in Portugal (2002–2012)

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Background: Safety drug profile is not fully known before market authorization, besides pre-marketing studies being cautiously planned and implemented. Rosiglitazone (Rz) (A10BG02) and pioglitazone (Pz) (A10BG03) are antidiabetic drugs, used in type 2 diabetes mellitus.

Objectives: Our aim is to study Rz and Pz sales trends (January 2002-December 2012) and to analyze the influence of safety alerts (SA) of INFARMED (Portuguese National Authority of Medicines and Health Products, IP) in drug sales, in Portugal.

Methods: It was made a search about SA on INFARMED website and were selected SA on Rz drug. Pz and Rz sales data was provided from IMS Health Portugal and represent number of units sold for each drug and pharmaceutical presentation, by month, during the study period. It was calculated the DID (defined daily doses per 1,000 inhabitants per day). It was performed a statistical analysis using multiple regression and ANOVA tests (p-value < 0.05).

Results: It was found 4 SA on Rz: January 2006, May 2007, January 2008 and September 2010 (recommendation of market withdrawn). It is observed the trends on sales for short and long time after each of the alerts for Rz and Pz. For short periods immediately after alerts, there is a statistically significant decreasing of Rz sales trend. For long periods a trend of increasing on is statistically significant for all periods after alerts, except after 4th alert, where the increasing is not statistically significant. Pz presents a decrease on sales on short period after the first three alerts and a statistically significant increase on sales trends for short and long periods after the 4th alert.

Conclusions: It is expected a sales decrease after a SA on a drug. That is observed for Rz for the short periods immediately after alerts but the trend is not maintained during time. Pz sales seem to follow trends of Rz, probably because it belongs to the same group (A10BG). However, when Rz is withdraw from market, Pz sales increase, along with biguanides group (A10BA) which could be related with the fact that Pz and biguanides were the therapeutic alternative chosen by prescribers.

990. The Effect of a Training-Programme on Intravenous Preparation and Administration Errors in a Vietnamese Hospital

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Background: Medication safety has been a concern for decades worldwide, but there is still relatively little research about interventions to reduce medication administration errors in hospitals, especially in resource restricted settings such as Vietnam. Our large study on the frequency and type of medication errors in Vietnamese hospitals indicated that the highest risk was associated with intravenous medication administration.

Objectives: The objective of the study is to investigate the effect of intensive training on the frequency of

intravenous medication preparation and administration errors in an urban public hospital in Vietnam.

Methods: This is a controlled intervention study with a pre- and post-intervention measurement using direct observation method, carried out in two critical care units: Intensive care unit (ICU – intervention ward), and Post-Surgical unit (PSU – control ward). The intervention consisted of lectures plus practical ward-based teaching sessions, carried out by a clinical pharmacist and a nurse. In each ward, all intravenous doses prepared and administered by nurses were observed 12 h per day, on seven consecutive days, each period.

Results: A total of 1294 doses were observed, 718 in ICU and 576 in PSU. Error rate on the intervention ward decreased from 62.7% to 52.5% (p = 0.01); preparation errors including wrong dose, deteriorated drug, wrong technique of preparation decreased significantly (p < 0.05). On the control ward (PSU) there was no significant change in error rates (73.8% vs.73.1%, p = 0.85); almost all preparation error types were similar in both periods (p > 0.05), except for technique errors, which was increased from 15.5% to 25.9% (p < 0.05).

Conclusions: Intensive training showed a slight improvement in overall and specific error rates, particularly preparation errors. Further measures are needed to improve patient safety.

991. Errors in Medication Preparation and Administration in Vietnamese Hospitals

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Background: Errors in the medication use process in hospitals are common. Little is known about preparation and administration errors in resource-restricted settings, including Vietnam.

Objectives: We determined the frequency, type and severity of medication preparation and administration errors in two Vietnamese hospitals and identified associated factors.

Methods: This is a prospective study using an observation-based approach, carried out in two urban public hospitals. Four trained pharmacy students observed all drug preparations and administrations on six wards, 12 h per day on seven consecutive days. Severity of errors was judged by experts using a validated method. Multivariable logistic regression was performed to explore error-associated factors.

Results: In total, 2,122 out of 5,635 medications were erroneous. Error rate was 37.7% (95% confidence interval 36.4–38.9%). Most frequent errors involved administration technique, preparation technique, omission, and dose (53.1%, 32.6%, 5.0%, and 2.6%, respectively). Severity was judged to be moderate in 87.8% of the cases, followed by severe (8.8%), and minor errors (3.4%). Slightly lower medication errors were observed during afternoon round than at other times of the day (32.1% vs. 39.7%, p = 0.00). Higher error rates were observed for anti-infective drugs than for any other medication class (77.8% vs. 28.9%, p = 0.00). Medications with complex preparation procedures more likely involved errors than simple ones (58.1% vs. 24.7%, p = 0.00), and error rate of intravenous medications was higher than that of other medications (73.2% vs. 12.4%, p = 0.00).

Conclusions: This is one of the first large studies investigating medication errors in resource-restricted settings. In around a third of all medications potentially clinically relevant errors occurred, this is higher than in most other studies. Administration technique, preparation technique, and omission errors were most commonly encountered. Drug round, drug class, complexity of preparation, and administration route were error-related factors. Interventions focusing on intravenous medications with complex preparation procedure are needed to improve patient safety.

992. Effectiveness of Interventions by Community Pharmacists To Reduce Risk for Gastrointestinal Side Effects in NSAID Users

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Background: For users of nonsteroidal anti-inflammatory drugs (NSAIDs) at risk of gastrointestinal complications, preventive strategies are recommended.

Objectives: To evaluate the effect of pharmacists' interventions on improving safe NSAID-use.

Methods: In an observational study Dutch community pharmacists (IG) proposed safer NSAID-use during

February and June 2012 to a selection of their patients at risk. In July 2012 development of risk status of IG patients was compared to a cohort of all NSAID users in February at risk in remaining pharmacies (CG) by nationally collected dispensing data with multivariate logistic regression.

Results: 70 IG-pharmacists selected 468 NSAID users compared to 20,482 subjects in 1,672 CG-pharmacies. In IG compared to CG, NSAID related risk decreased by additional 3% (95% CI 0.94–1.00), corresponding with about 2,000 NSAID users in the Netherlands.

Conclusions: Pharmacists' interventions for safe NSAID-use resulted in a modest additional risk decrease.

993. Low Persistence with Oral Bisphosphonate Treatment in Portuguese Women with Postmenopausal Osteoporosis

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Background: Osteoporotic fractures are a major cause of morbidity & mortality. It is recognized that persistence to medication is crucial to reach optimal clinical outcomes. Availability of this real-world data in Portugal is lacking.

Objectives: To estimate the persistence level to oral bisphosphonates (OBP)-weekly alendronate, alendronate+cholecalciferol, weekly risedronate & monthly ibandronate-in women with postmenopausal osteoporosis (PMO) over 24 months from therapy initiation.

Methods: In this prospective observational cohort study, women ≥ 50 years with PMO with no PMO treatment within 6 months prior to study initiation were consecutively recruited through pharmacies (31 Jan to 30 Jul 2011). Data were collected at baseline during face-to-face interviews. Follow-up included

pharmacy records (refill dates & medication possession) & telephone-surveys for patients who agreed to be interviewed (cohort 2; all other subjects in cohort 1). Patients were classified as persistent if they refilled their prescription within 30 days after exhausting the time covered by their previous supply. For cohort 1, a 60-day grace period was used in sensitivity analysis. Log-rank tests were used to compare Kaplan-Meier curves of time to non-persistence.

Results: Of 427 women recruited with a mean (SD) age of 65.0(9.5) years, 380(89%) agreed to be interviewed (cohort 2) with 339 actually contacted. After 12 months follow-up, 9.4% (CI: 6.8–12.5%) of all subjects were persistent to OBP based on pharmacy records. Persistence rate in cohort 1 was 7.9% (CI: 2.1–19.1%) & in cohort 2 9.5% (CI: 6.8–12.8%). When self-reported, cohort 2 reported 33.1% (CI: 28.4–37.9%) persistence. When using a 60-day grace period, persistence in cohort 1 was 15.8% (CI: 6.5–28.9%). In cohort 2, 175 patients stopped taking their OBP medication. Common reasons for interruption include self-reported adverse event (28.6%), recommendation by physician (22.3%), making a pause from medication (16.0%).

Conclusions: Results at 12 months indicate a low level of persistence to OBP. Barriers and reasons leading to discontinuation of anti-PMO therapies should be addressed to promote adherence & consequently the level of anti-fracture protection.

994. Comparison of the Antidepressant Treatment Patterns in Younger and Older Adults Using the French Health Insurance Claims Database

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Background: Antidepressant drugs have been found underused in the older population relative to younger adults, particularly in the USA before Medicare part D. While treatment for depression appears influenced by health care systems, no study assessed the antidepressant use according to age in a universal health care system.

Objectives: To assess whether the patterns of antidepressant drug use differ between younger and older adults in a universal health care system.

Methods: A historical cohort study included 27,306 younger (under 65) and 7,747 older (65 +) adults, who were representative of the beneficiaries of the French national health care insurance and who initi-

ated a new antidepressant treatment. The outcomes of interest concerned the antidepressant use patterns during the first episode of antidepressant treatment over the 6-month follow-up: treatment duration, adherence to treatment assessed through the medication possession ratio, coprescription of other psychotropic drugs, switch or combination of antidepressant drugs. The impact of age on the use of antidepressant treatment was assessed using multivariate logistic regression models and Cox models.

Results: Older patients had a significantly longer average duration of treatment than younger adults (m = 135.4 days SD = 198.6 vs. m = 104.3 SD = 159.6; HR = 0.91 [0.88–0.93]). Furthermore, they had a higher probability of good adherence than younger adults when treatment was initiated by a general practitioner (23.36% vs. 16.70%; OR = 1.31 [1.22–1.41]), a hospital practitioner (OR = 1.76 [1.47–2.12]) or another specialist (OR = 1.85 [1.37–2.49]). The coprescription of psychotropic drugs was frequent in both groups (62.36% in older vs. 62.91% in younger) but decreased with older age in men (OR = 0.77; 95%CI [0.70–0.85]) and increased with older age in women (OR = 1.11 [1.04–1.19]). Combinations or switches of antidepressants were not associated with age.

Conclusions: Treatment duration and adherence were better in the older patients compared with younger. This favorable finding may be partly attributed to the French universal healthcare system.

995. Withdrawn by Author.

996. Trends in Buprenorphine and Methadone Sales and Utilization in the United States, 1997–2012

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Background: Despite buprenorphine's promise as a novel therapy for opioid dependence, little is known about its clinical adoption. We characterized trends in ambulatory use and sales of buprenorphine and methadone in the United States.

Objectives: To evaluate a retrospective drug utilization review program to reduce controlled substance use among individuals with high-risk utilization.

Methods: Cross-sectional analyses of buprenorphine and methadone utilization and sales using data from the IMS Health National Disease and Therapeutic Index, a nationally representative survey of ambulatory care (1997–2012), the IMS Health National Prescription Audit, reflecting retail, long-term care and mail-order pharmacy sales (2007–2011), and the IMS Health National Sales Perspective, capturing distribution of products from manufacturers to suppliers (2007–2011).

Results: Between 2003 and 2011, buprenorphine ambulatory treatment visits increased approximately 37%, reaching nearly 2 million treatment visits during 2011. During this period, the proportion of buprenorphine treatment visits accounted for by psychiatrists decreased from 92% to 37%. Two-thirds of 2011 treatment visits were for individuals 20–39 years of age, while 91% of these visits were for drug abuse or dependence and 90% involved the use of combination buprenorphine/naloxone rather than other buprenorphine products. Between January 2007 and December 2011, there were modest increases in retail pharmacy prescriptions for methadone, from approximately 325 to 375 thousand monthly prescriptions. By contrast, buprenorphine sales increased by an average of 40% annually during this period, from approximately 0.5 million during the first quarter of 2007 to 2.7 million during the last quarter of 2011. Despite these increases, methadone sales from manufacturers to distributors remained constant and four-fold greater than buprenorphine sales.

Conclusions: Since 2003, there has been a large increase in buprenorphine utilization. While the impact of increases in buprenorphine use on the epidemic of prescription opioid abuse remains to be examined, the increases reflect a substantial shift in the landscape of opioid dependence treatment.

997. Quality and Pattern of Use of Psychotherapeutic Agents in a Nigerian Referral Hospital

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Background: Recent studies have shown that worldwide psychotherapeutic drugs use is on the increase. However, data on the utilization of antipsychotic medications in developing economies are still inadequate.

Objectives: This study was aimed at evaluating the quality and use pattern of psychotherapeutic drugs among patients visiting a federally funded neuropsychiatric hospital in Nigeria.

Methods: This retrospective survey employed 500 prescriptions which were systematically sampled from out patient records in Federal Neuropsychiatric Hospital, Enugu, which serves the entire Eastern region. WHO prescribing and patient indicators were checked. Daily defined drug doses and costs were calculated as well as pattern of use over a six-quarter period between January 2008 and July 2009. Simple descriptive statistics and graphs were used to present outcome measures.

Results: Psychiatric patients were more of females (53.9%) and had a mean age of 39.4 years. With an average of 2.2 antipsychotic drugs per prescription, 75% were injections and 35.3% prescribed by brand names. Trihexylphenyl and Haloperidol were the only drugs within the DU90% and with the least cost per DDD (0.03–0.06USD/DDD). The utilization of the two drugs also increased within the 2-year period. Over 80% of the antipsychotic drug costs were high (0.07–5.6 USD/DDD). There was also an increase in prescription of psycholeptics and anticholinergics during the quarters under review.

Conclusions: With the increasing utilization and cost burden of psychotherapeutic agents, strategies to monitor and improve rational and cost effective prescribing should be adopted.

998. Characteristics Associated with Initiation of Intravenous vs. Subcutaneous Injection Tumor Necrosis Factor Inhibitors for Rheumatoid Arthritis Patients

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Background: Rheumatoid Arthritis (RA) is a chronic, systematic autoimmune disease primarily affecting synovial joints. RA prevalence among U.S. adults has been estimated at 1%, affecting 2.5 times as many women as men. Tumor necrosis factor inhibitors (TNF-i) and non-TNF biologics are the main treatment for RA.

Objectives: Examine the demographic and socioeconomic predictors associated with RA patients treated with intravenous (IV) vs. injectable TNF-i.

Methods: Patients with at least two RA diagnoses initiating infliximab, etanercept, adalimumab, and IV abatacept were selected from Medicare data (January 2006 – December 2009). The index date was the initial prescription or IV administration date. Logistic regression was used to identify demographic and socioeconomic variables associated with initiation of IV TNF-i (infliximab or IV abatacept) or subcutaneous injection (etanercept or adalimumab). Medications were also analyzed separately, using a multinomial logistic regression model. Demographic, clinical and socioeconomic status (SES) scores were controlled in the models.

Results: Patients age 65–69 were less likely to use IV treatment than those over age 80 (odds ratio [OR]: 0.59; $p < 0.0001$). Females were also less likely to be prescribed IV treatment (OR: 0.76; $p < 0.0001$). Patients with medium (OR: 1.46; $p < 0.0001$) and high SES scores (OR: 1.51; $p < 0.0001$) were more likely to initiate IV treatment compared to those with low SES scores. Using etanercept as the reference group for multinomial regression, female patients had a lower chance of switching to infliximab (OR: 0.73; $p < 0.0001$) and abatacept (OR: 0.76; $p < 0.0001$). Patients with an Elixhauser index score > 2 were more likely to be prescribed abatacept (OR: 1.45; $p < 0.0001$), but less likely to be prescribed infliximab (OR: 0.86; $p = 0.0023$). Patients with high SES scores were less likely to switch to adalimumab from etanercept.

Conclusions: Certain demographic and socioeconomic characteristics are associated with initial TNF treatment choices. Gender, SES, age, and Elixhauser index scores are significant variables in determining the treatment of choice.

999. Comparative Prevalence of Some Antipsychotic-Containing Drug Combinations in Geriatric Inpatients with Hospital-Acquired Pneumonia

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Background: Antipsychotic (AP) drug use has been reported to increase the risk of pneumonia in elderly people. Concomitant drug factors might increase this risk further.

Objectives: The aim of the study was to compare in AP-receiving elderly inpatients with or without hospital-acquired pneumonia the prevalence of benzodiazepine (BZ) and/or non-AP anticholinergic drug (ACh) coprescriptions that might increase the risk of pneumonia through sedation- or xerostomia-induced swallowing disorders.

Methods: 135 consecutive cases of hospital-acquired pneumonia in AP-receiving elderly patients (> 65 years) were recorded in the geriatric psychiatry wards of a 600-bed teaching hospital. Clinical data and drug regimens were extracted from the electronic medical records and compared with those from randomly selected 135 AP-receiving elderly inpatients without history of pneumonia in the same wards. The drug regimens analyzed were those ongoing at the time of pneumonia diagnosis for pneumonia patients (PP) or at the time of discharge for non-pneumonia patients (NPP).

Results: Mean age of patients was 77.4 in PP vs. 74.6 in NPP (p < 0.01). Proportion of patients with at least one chronic comorbidity was similar in the two patient groups (p = 0.20). The mean number of drugs per drug regimen was 6.0 in PP vs. 6.4 in NPP (p = 0.20). Frequency distribution of conventional or atypical AP treatments did not differ between the patient groups (p > 0.50). Prevalence of AP polypharmacy was higher in PP (16.3%) vs. NPP (6.7%, p = 0.013). Mean daily doses of risperidone, olanzapine, tiapride, and loxapine – the most frequently prescribed AP drugs – were similar in PP vs. NPP. Prevalence of AP therapy combined with either BZ or ACh was similar in PP (24% and 24.5%, respectively) and in NPP (32.5%, p = 0.14, and 23.5%, p = 0.88). Yet, combinations of BZ with ACh were two times more frequent in PP (23.5%) vs. NPP (11.8%, p = 0.01).

Conclusions: In this study, AP-receiving PP were older and more frequently treated with combinations of BZ and ACh drugs at the time of pneumonia diagnosis than AP-receiving NPP. Increased clinical surveillance of patients with such drug regimens might be appropriate.

1000. Benzodiazepine Use in the HIV-Infected Population

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Background: Patients living with HIV/AIDS struggle with mental illness, including anxiety and depression. Often this mental illness coexists with drug and alcohol dependence. Several studies have investigated the utilization of opiates in this population. However, little is known about the use or abuse of benzodiazepines (BZD), medications used primarily to treat anxiety.

Objectives: To evaluate the use of BZDs among HIV-infected patients enrolled in a commercially insured population.

Methods: We established a four state nationally representative, commercially insured, population-based cohort. Beneficiaries were included if they were between 19 and 64 years of age and had at least one healthcare claim in 2007 followed by a second claim in 2008 or 2009. Patients were considered HIV-positive if they had an HIV related claim in 2007 (ICD-9 code 042). We identified BZD use following enrollment in 2007 using national drug codes. Bivariate analyses examined the association between HIV-infection and benzodiazepine use. We used multivariate logistic regression models in the presence of baseline covariates to estimate adjusted odds ratios (OR) and associated 95% confidence intervals (CI).

Results: Overall there were 324,633 beneficiaries included in the sample, 723 were HIV-infected. Compared to the overall insured population, HIV patients were more likely to be male (80% vs. 44%), black (21% vs. 7%), and under the age of 50 (77% vs. 70%). HIV-infected patients were also more likely to have at least one prescription for a BZD compared to their uninfected counterparts (24% vs. 19%). Adjusted for other covariates, patients infected with HIV had 1.78 times the odds of filling a BZD prescription compared to their HIV-uninfected counterparts (OR: 1.78 95% CI: 1.50, 2.12).

Conclusions: Our results show that HIV-infected patients are more likely to fill a BZD prescription. Further research is needed to determine the implications of these observations.

1001. Assessment of Dronedarone Utilization Using US MarketScan Database

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Background: Dronedarone, an antiarrhythmic drug was approved in 2009 in the US in patients with a paroxysmal or persistent atrial fibrillation (AF). A drug utilization study using InVision DataMart® databases that was conducted previously has demonstrated labeling compliance and effectiveness of the REMS regarding worsening heart failure (HF). However the population aged 65+ in this database was under-represented. A study using MarketScan® database, which has a large Medicare population was conducted to confirm previous findings.

Objectives: To estimate the prevalence of dronedarone use in contraindicated patients with worsening or hos-

pitalization for HF within 1 month prior to dronedarone prescriptions, concomitant prescribing of contraindicated drugs, and recommended serum creatinine testing following dronedarone initiation among dronedarone users.

Methods: In this retrospective cohort study using MarketScan® data between July 20, 2009 and December 31, 2011, exposure was defined as one or more dronedarone prescriptions. Primary outcome measures were worsening or hospitalization for HF, concomitant prescribing of potent CYP3A4 inhibitors or QT-prolonging drugs, and serum creatinine testing.

Results: A total of 150,037 dronedarone prescriptions were filled by 31,408 patients, 86% of which had a diagnosis of AF at initiation of dronedarone or within 1 year before. Over 40% of patients were women and ~54% aged 65 or older. The prevalence of worsening or hospitalization for HF was 6.4% (95% CI 6.2–6.7%). The prevalence of concomitant prescribing of potent CYP3A4 inhibitors before and after dronedarone prescriptions was 2.0% (95% CI 1.8–2.1%) and 1.9% (95% CI 1.7–2.0%), respectively. The prevalence of concomitant prescribing of QT-prolonging drugs before and after dronedarone prescriptions was 10.0% (95% CI 9.7–10.4%) and 9.2% (95% CI 8.9–9.5%), respectively. Over 50% of patients had a creatinine test after initiation of dronedarone.

Conclusions: The results with a large population aged 65+ from MarketScan® database were similar to the previous findings from InVision DataMart® database. Dronedarone has mostly been used appropriately in compliance with the US Prescribing in the target populations.

1002. Time Trends in Assessment of Dronedarone Utilization in the US

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Background: Dronedarone utilization studies using InVision DataMart® database were conducted to assess compliance with prescribing information and the effectiveness of the REMS regarding contraindication for worsening heart failure (HF) on a yearly basis in the US. Dronedarone is an antiarrhythmic drug approved in 2009.

Objectives: To evaluate time trends for the prevalence of dronedarone use in contraindicated patients with worsening or hospitalization for HF within 1 month prior to dronedarone prescription, concomitant prescribing of contraindicated drugs, and recommended serum creatinine testing following dronedarone initiation among dronedarone users.

Methods: In this retrospective cohort study using InVision DataMart® database, exposure was defined as one or more dronedarone prescriptions. Time trends (Year1: 07/2009 to 06/2010, Year2: 07/2010 to 06/2011, Year3: 07/2011 to 03/2012) were assessed for unique patients identified in each time period for the following outcomes: worsening HF, prescribing of potent CYP3A4 inhibitors or QT-prolonging drugs, and serum creatinine testing.

Results: There were 2,675, 3,052 and 1,298 dronedarone users identified in year1, 2 and 3, respectively. Over 30% of patients were women and ~32% aged 65 or older. Approximately 93%, 89% and 84% of patients had a diagnosis of AF at initiation of dronedarone or within 1 year before in year 1, 2, and 3, respectively. The corresponding prevalence of worsening or hospitalization for HF was 4.8% (95% CI 4.0–5.6%), 4.8% (95% CI 4.1–5.6%), 3.7% (95% CI 2.7–4.7%). The corresponding yearly estimates of concomitant prescribing of potent CYP3A4 inhibitors and QT-prolonging drugs were 3.1% and 12.0%, 2.0% and 9.7%, and 1.2% and 7.2%. Over 63%, 56% and 33% of patients had serum creatinine test after dronedarone initiation in year 1, 2 and 3, respectively.

Conclusions: This trend analysis indicated that dronedarone use in contraindicated patients with worsening or hospitalization for HF was slightly decreased over time, and there was also a slight decrease in prescribing of potent CYP3A4 inhibitors or QT-prolonging drugs. It suggests that dronedarone has been used appropriately in compliance with the US Prescribing in the target populations.

1003. Withdrawn by Author.

1004. Trends in the Use of Guideline-Recommended Medication Treatment and In-Hospital Mortality of Patients with Acute Myocardial Infarction in China

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Background: Current practice guidelines recommend the routine use of several effective cardiac medications in the management of acute myocardial infarction (AMI). While in China, some previous studies have documented the underuse of these drugs early in the course of AMI.

Objectives: The objective of this study was to analyze temporal trends in the use of these medications and in-hospital mortality of patients with AMI in China.

Methods: We analyzed temporal trends in the use of aspirin, clopidogrel, β-Blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB), statins, and combinations thereof within 24 h at presentation of 4,714 AMI patients using a centralized data warehouse, which includes hospital information system (HIS) in 14 Chinese hospitals between 2005 and 2011. The association of these medications use with in-hospital mortality was also explored using hierarchical logistic regression.

Results: The use of guideline-recommended medications all increased over the study period, statins from 56.1% to 85.1%, clopidogrel from 59.7% to 87.7%, β-Blockers from 45.6% to 56.3%, ACEI/ARB from 46.1% to 56.1%, aspirin from 81.7% to 89.7%, and the combinations thereof increased from 24.6% to 35.1% (p < 0.001for all). Adjusted multifactor analyses showed that only the increasment of statins and clopidogrel had statistically significant, patients with advanced age, cancer and renal insufficiency were generally less likely to receive all these medications. The estimated in-hospital mortality decreased from 16.7% to 7.9% from 2005 to 2011(p < 0.001), After adjustment, the temporal trend was non-significant, the use of aspirin, clopidogrel, ACEI/ARB and statins significantly reduced in-hospital mortality, patients with advanced age, cancer and renal insufficiency had higher in-hospital mortality than their counterparts.

Conclusions: Use of guideline-recommended medications early in the course of AMI has generally increased between 2005 and 2011 in China. During this same time, there was a decrease in in-hospital mortality.

1005. Effects of Changing from Suboptimal to Optimal Asthma Regimens on Asthma-Related Health Services Utilization

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Background: Suboptimal use of asthma medications is common and has been associated with increased emergency department (ED) visits and hospital admissions for asthma exacerbations.

Objectives: To determine if changing from suboptimal to optimal regimens is associated with changes in asthma-related health services utilization over 13 years.

Methods: A cohort of 335,462 asthma patients between 5 and 55 years of age was identified using provincial health services utilization data, 1996–2009. Annual patient medication dispensings of short-acting bronchodilators (SABA) with or without ICS were categorized into optimal or suboptimal regimens based on the National Heart, Lung and Blood Institute Asthma Guidelines Expert Panel Report-3. A change from suboptimal to optimal regimen was defined as having ≥ 2 consecutive suboptimal regimen years followed by ≥ 2 consecutive optimal regimen years. The study outcomes included repeated ED visits and hospitalizations for asthma during the follow-up. Regimen optimality changes, study outcomes and measures of disease severity were all modeled as yearly-updated, time-dependent variables.

Results: Changing from suboptimal (2 years) to optimal regimens (2 years) was associated with a 50% reduction in the use of hospital services for asthma (hazard ratio (HR) 0.51, 95% confidence interval (CI) 0.39–0.67), and a 67% reduction in the use of ED services for asthma management (HR 0.33, 95% CI 0.30–0.36). With one additional optimal regimen year (2 years suboptimal followed by 3 years optimal), the use of hospital services decreased a further? 30% (HR 0.69, 95% CI 0.67–0.71); and the use of ED services for asthma decreased by 20% (HR 0.81, 95% CI 0.74–0.89).

Conclusions: Changing from suboptimal to optimal therapy results in significant reductions in health services utilization by patients with asthma. Patients with frequent prescribing and dispensing of SABA but without sufficient dispensing of ICS (suboptimal therapy) are likely to benefit from an increase in ICS use in terms of need for healthcare services. Findings suggest the need to for clinicians to reinforce the importance of close monitoring of their patients asthma drug therapy.

1006. Age and Sex Patterns of Drug Prescribing in a Defined American Population

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Background: Drug prescribing patterns may serve as indirect measures of the burden of diseases in a population. Prescribing patterns also vary considerably across geographic regions, and may serve as a proxy for health system performance.

Objectives: To describe age and sex patterns of drug prescribing in Olmsted County, MN. Prescription drugs are an important component of health care delivery, yet little is known about the prescribing patterns in the general population.

Methods: Population-based drug prescription records for the Olmsted County population in the year 2009 were obtained using the Rochester Epidemiology Project medical records-linkage system (n = 142,377). Drug prescriptions were classified using RxNorm codes and grouped using the National Drug File – Reference Terminology (NDF-RT).

Results: Overall, 68% of the population received a prescription for at least one group, 52% received two or more groups, and 21% received five or more groups. The most commonly prescribed drug groups in the entire population were penicillins and beta-lactam antimicrobials (17%), antidepressants (13%), opioid analgesics (12%), antilipemic agents (11%), and vaccines/toxoids (11%). However, prescribing patterns differed by age and sex. Vaccines/toxoids, penicillins and beta-lactam antimicrobials, and anti-asthmatic drugs were most commonly prescribed in boys and girls younger than 19 years. Antidepressants and opioid analgesics were most commonly prescribed in young and middle-aged adults. Cardiovascular drugs were most commonly prescribed in older adults. Women received more prescriptions than men for several groups of drugs, in particular for antidepressants. For several groups of drugs, the use increased with advancing age.

Conclusions: This study provides important baseline information for further pharmacoepidemiologic studies in this population.

1007. Trends in Antidepressant Prescribing: A Population-Based Study

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Background: Increase in antidepressant use is a cause for concern, mainly due to off-label use and safety in selected patient populations.

Objectives: To describe antidepressant (AD) prescribing trends between 2005 and 2011 in a defined US population.

Methods: We used the Rochester Epidemiology Project research infrastructure to identify written outpatient prescriptions for residents of Olmsted County, MN between 2005 and 2011. The prevalence of receiving at least one AD prescription was estimated by age and sex group for each year. The annual percent increase in the prevalence was estimated using negative binomial regression.

Results: The prevalence of receiving at least one AD prescription increased from 10.8% to 14.3% overall, and from 14.4% to 18.5% in females, and 7.0% to 9.8% in males. The largest increase was seen in the elderly (65+ years), from 14.6% to 23.1%. The annual percent increase was larger in 2008–2011 than in 2005–2007, and was mostly driven by increased AD prescriptions to the elderly.

Conclusions: Our data showed that AD prescribing continued increasing from 2005 to 2011, with a significant upward trend after 2007.

1008. Birth Cohort Confounds Effect Estimates of Guideline Changes on Prevalence of Statin Use in Diabetic Patients

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Background: In earlier research we found that birth cohort effects potentially confound effect estimates of

guideline changes on statin use. Conventional methods do not take the birth cohort dimension into account.

Objectives: We investigated whether including the birth cohort dimension in time series analysis leads to a more accurate estimation of the effect of a guideline change on the trend of statin use in diabetic patients.

Methods: Outpatient pharmacy data from a drug prescription database in the Netherlands (IADB.nl) were used to obtain the age- (30–85) and sex-specific number of users of statin per 1,000 diabetic patients (prevalence) per year from 1998 to 2011. The intervention took place in 2002 and targeted persons above age 70. Using likelihood ratio tests we compared an age-specified interrupted time series model which included the birth cohort dimension with one in which birth cohort was excluded.

Results: The model which included the birth cohort dimension had a significantly better fit to the data than the model which excluded birth cohort ($p < 0.001$). Both models found significant effects of the guideline change at age-group 70+ years and below 70 years ($p < 0.05$) but effect estimates differ. For ages below 70, the model estimated an increase in statin use among diabetics, but when cohort was included the estimated effect became stronger: 29.5% increase vs. 24% ($p < 0.05$). For ages above 70 an increase was also estimated, but now the model including birth cohort predicted smaller effect: 24.5% vs. 29.5% ($p = 0.09$). Both models found that, for both age groups, the increase in prevalence of statin use levels off from 2006 onwards ($p < 0.05$).

Conclusions: Birth cohort partially confounds the effect estimate of the guideline change on prevalence of statin use among diabetic patients. In order to come to more accurate estimations and better model fit, birth cohort should be included in the analysis.

1009. A Chart Review Methodology To Characterize Treatment Patterns and Clinical Outcomes in Patients with Multicentric Castleman's Disease

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Background: Little is known about usual care treatment patterns and associated outcomes in Multicentric Castleman Disease (MCD). Information on the management of this disease can inform clinical practice, treatment guidelines and elucidate areas of unmet medical need.

Objectives: The design and execution of a retrospective chart review study of patients with MCD are described, highlighting general methodological considerations for conducting chart review studies in rare diseases.

Methods: A multi-center, retrospective, chart review study of 59 MCD patients (61.0% male; mean age 53.3 ± 16.3 years) was conducted in two centers in the United States. All MCD cases within a defined eligibility period were identified. For eligible patients, medical record data were abstracted by site study staff; up to 6 months pre-index diagnosis date and up to 3 years of post-diagnosis. Anonymized data were recorded on paper case report forms (CRF) and entered into an electronic data capture (EDC) system.

Results: Key design challenges and lessons learned include: (1) site recruitment: limited number of participating treatment centers resulting in small study population; (2) CRF design: disease complexity and lack of published literature necessitated the involvement of MCD clinical experts with management knowledge (3) data abstraction: patients only seen at the site for a one-time consultation or second opinion resulting in minimal and missing data, making MCD diagnosis confirmation and eligibility criteria difficulty to confirm and underreporting of data and; (4) EDC system design: data from multiple clinical tests, exams and physicians visits were collected so the EDC system must permit large volumes of data with a validation plan to ensure quality data.

Conclusions: Acquisition of clinical outcomes, resource utilization and treatment pattern data through retrospective chart review study in a rare disease population such as MCD is challenging and requires an innovative approach, disease knowledge, and a sufficient treatment centers to optimize external validity.

1010. Using the RIFLE Classification System To Categorise Severity of Adverse Renal Events in a Prescription Event-Monitoring Study

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Background: Renal events (REs) range from minor changes in renal function tests (RFTs) up to acute renal failure (ARF). Categorising RE severity in drug safety studies may improve clinical relevance. In acute hospital care REs are considered on a spectrum of severity. The RIFLE classification system uses change in RFT from baseline to categorise severity and aid management.

Objectives: To investigate whether the application of the RIFLE classification system can improve discrimination of reported REs, within a Prescription Event-Monitoring (PEM) study of a direct renin inhibitor.

Methods: This study used an observational single exposure cohort design. Exposure data were collected from dispensed prescriptions issued by general practitioners (GPs) from Feb 2008 to Nov 2010. Outcome data were collected from questionnaires sent to GPs 6 months after each patient's first prescription. Drug relatedness assessments identified patients with REs probably or possibly related to the study drug. In these patients, reported baseline and event estimated glomerular filtration rate or creatinine were used to calculate change in RFT and apply a RIFLE category; Risk of renal injury (RiskRI), Renal Injury (RI), ARF, Renal Loss (RL), End Stage Kidney Disease (ESKD). The distribution of reported renal events was described.

Results: Of 6,385 patients in the final cohort, 24 patients had a reported RE probably or possibly related to study drug. Reports involved Renal Failure 16.7% (4/24) and RFT decline / renal impairment 83.3% (20/24). RIFLE categories; RiskRI 45.8% (11/24), RI 12.5%(3/24), ARF 16.7% (4/24). RFT decline (below lowest RIFLE criteria); 25.0% (6/24). Of the four patients reported as renal failure, three had suspected ARF by RIFLE and one had RFT decline. The 4th patient with ARF by RIFLE, was reported by GP as RFT decline.

Conclusions: GP reports of REs may not indicate severity. In this study, RIFLE suggested most REs were at less severe end of the spectrum. The forthcoming Acute Kidney Injury NICE guideline will disseminate RIFLE concepts. Further work is required to explore the validity of this tool, and application to other pharmacoepidemiological study designs.

1011. Latent Class Analysis: A New Approach To Characterize Psychotropic Drug Consumption

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Background: France has one of the highest recorded rates of psychotropic drug use (anxiolytics, hypnotics, antidepressants) compared to others countries and this constitutes a national public health problem. For pharmacodependence assessment, health authorities insist on the importance of obtaining quantitative information and developing appropriate methods, to evaluate the use of psychotropic drugs in real-life conditions. We used example of two hypnotic drugs: zolpidem and zopiclone.

Objectives: To characterize groups of users of zolpidem and zopiclone in real life conditions using a pharmaco-epidemiological methodology: latent class analysis (LCA).

Methods: Using the French health insurance database we selected non occasional users of zolpidem or zopiclone during a 6 months period. Six categorical variables were used to identify consumption behaviours: two variables were related to transgression behaviours (doctor shopping, pharmacy shopping), two variables were linked to severity of mental disorder (prescribing physicians, associated mental pathology) and two variables characterized the prescription (overconsumption, agreement with French practice guidelines). From these variables, LCA was applied to identify different subtypes of users for zolpidem and for zopiclone.

Results: A total of 25,168 non occasional users were included for zolpidem and 21,860 for zopiclone. Using LCA, four clinical subtypes of zolpidem users were identified: non problematic users, users with associations of hypnotics/anxiolytics, users with associated mental pathologies and compulsive users. Only three subgroups were identified for zopiclone users, LCA didn't discriminate a special class of compulsive users for this drug.

Conclusions: LCA is an original probabilistic method in this context. It allows (1) intra-class discrimination, by characterizing different subgroups of users and (2) inter-class discrimination, by defining a different number of groups for two drugs from the same therapeutic class.

1012. Assessing Quality in Systematic Reviews of Adverse Effects

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Background: Different tools assess the risk of bias in randomized clinical trials (RCT), observational studies (OS), and systematic reviews (SR). However, assessing the quality of studies included in systematic reviews of adverse effects is poor. Several factors specific to adverse effects need to be thoroughly considered as they may affect the quality of the studies included in a SR.

Objectives: To develop a checklist to assess the quality of included studies in SR of adverse effects.

Methods: Questions incorporating the following five domains were considered: (1) methods for study participants selection; (2) methods for measuring exposure and outcome variables; (3) design-specific sources of bias; (4) methods to control for confounding; and (5) statistical methods. Several items have been reproduced from other existing scales (Downs and Black, Cochrane risk of bias tool, AMSTAR) or published studies. The former aspects have also been adapted for secondary data source studies, frequently used in pharmacoepidemiological studies. Several questions refer to the quality of collecting information on adverse events in RCT of efficacy and OS.

Results: The final checklist contained 31 questions applicable to RCT, OS, and SR. It was divided into three parts. Part 1 referred to the definition and severity of a drug adverse effect, and the study design. Part 2 assessed methods for identifying adverse drug reactions/events, reporting frequency in RCT, and for attributing causality in both OS and RCT. Part 3 provided explanations for all questions and instructions to fill in the questionnaire. We propose to report the potential sources of bias for each included study.

Conclusions: This checklist allows assessing the quality of all types of epidemiologic studies that may be included in a systematic review of adverse effects. In addition, it contributes to the assessment of the methods used to detect an adverse event in RCT of efficacy. The checklist has not been validated yet.

1013. The Effect of Misclassification of the Outcome on the Relationship between an Increase in Anticholinergic Drug Burden and Memory Impairment in Older Adults

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Background: Data are conflicting with respect to estimates of association between anticholinergic drug use and cognitive impairment among older adults. Differences may be due to the method for classifying the outcome.

Objectives: Compared the effect of three different definitions of cognitive decline against a gold standard on the association between an increase in anticholinergic drug exposure and the rate of cognitive decline over 1 year.

Methods :

Design: A longitudinal cohort study.

Setting: Outpatient incontinence clinics, Montreal, CA.

Participants: 102 patients aged 60+ without dementia.

Exposure & outcome measures: Exposure was measured was using the Anticholinergic DBI. Progression from normal to a new mild neurocognitive disorder was determined using criteria from DSM-5. Three other definitions of cognitive decline applied: deterioration in the raw neuropsychological test scores from baseline to 1-year, the RCI, & a standardized regression based measure (SRB).

Statistical analysis: The sensitivity and specificity of each outcome against DSM-5 criteria, & ROC curves were compared. Estimates of association between drug exposure and cognitive decline were examined using logistic regression models for four classifications of the outcome.

Results: DSM-5 criteria identified 12 new cases of mild neurocognitive disorder over 1 year. The SRB method had the highest sensitivity (1.00) and the lowest specificity (0.03). The RCI had the lowest sensitivity (0.52) and the highest specificity (0.98). The raw change score

method demonstrated both low sensitivity (0.52) and low specificity (0.56). The area under the ROC curves was similar (range 0.40–0.53). Use of the SRB as a method of outcome ascertainment yielded a positive relationship between anticholinergic drug exposure and cognitive decline on the Trail B (OR 2.2; 95% CI-1.1–8.06). No associon with DSM-5 criteria, RCI and raw change scores.

Conclusions: Misclassification of the outcome using methods with high sensitivity and low specificity may result in spuriously positive associations between anti-cholinergic drug use and cognitive decline. Findings from ROC curves masked this effect.

1014. Comparison of Methods for the Estimation of Drug Prevalence in a Dynamic Cohort

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Background: Prevalence of drug use (PDU) is a frequently used measure in drug utilization studies. In drug safety studies, drug use is often employed as proxy for confounding co-morbidities. PDU is also important for the assessment of the public health impact of observed drug risks. Calculation of PDU is straightforward in cross-sectional studies. However, estimation of PDU is not as simple in the dynamic cohorts of claims databases.

Objectives: To compare approaches for estimation of PDU in dynamic cohorts.

Methods: Three approaches for estimation of PDU in dynamic cohorts will be presented and their assumptions will be discussed and compared:
1. Point prevalence at a fixed date, i.e. number of drug users (DU) at a certain date divided by the number of cohort members at this date.
2. Period prevalence, i.e. numbers of DU during a fixed period divided by the number of cohort members insured during this period.
3. Person time approach, i.e. number of DU during a fixed period divided by the person time accrued in this period.
  The application of these methods will be demonstrated using data of the German Pharmacoepidemiological Research Database (GePaRD) based on claims data from > 17 million insurants. PDU for several scenarios (e.g. short-/long-term use, seasonal effects) will be calculated and compared.

Results: All three approaches make (implicit) assumptions on the pattern of drug exposure and the dynamics of the cohort. This results in differences both in the numerator and the denominator of the PDU estimator

and hence in – sometimes considerable – differences in the estimated PDU. Point prevalences are sensitive to the choice of the date, period prevalences are sensitive to the definition of the denominator (i.e. inclusion of deaths) and the person time approach is sensitive to the dynamics of the cohort. The assumptions additionally lead to differences in characteristics of cohort members taken into account for prevalence estimation.

Conclusions: There is no best method for the estimation of PDU in a dynamic cohort. The method to use has to be chosen based on the characteristics of the drug (e.g. short-/long-term use) and the dynamics of the cohort, especially the dynamics of the exposed cohort.

1015. Utilization and Expenditure Trends for Anti-Allergic Agents in the Medicaid Program

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Background: Allergies are among the most common chronic conditions. About two thirds of the population have experienced allergic symptoms in their lives. In the U.S., the prevalence rate is estimated to be as high as 15%, representing 40–50 million individuals. Over half of the U.S. population has tested positive for one or more allergens.

Objectives: The objective of this study was to determine the utilization and expenditure trends for anti-allergic agents in the U.S. Medicaid program.

Methods: A retrospective, descriptive analysis was conducted. We extracted the utilization and expenditure data from the national Medicaid pharmacy files, which cover 1991 first quarter to 2011 second quarter. The study drugs included first-generation antihistamines (e.g. brompheneramine, chlorpheniramine, doxylamine, and pheniramine) and second-generation antihistamines (e.g. zelastine, cetirizine, desloratadine, levocertizine, and loratadine). The quarterly prescription numbers and reimbursement amounts were calculated over time by summing data for individual drug products. The uarterly per-prescription reimbursement as a proxy for drug price was computed for each study drug.

Results: The total number of prescriptions for anti-allergic drugs reached a peak of 18.7 million in 2003. The prescriptions for first-generation antihistamines dominated the market from 1991 to 1998, while the prescription market share for secondgeneration antihistamines increased from 12.84% in 1991 first quarter to 57.17% in 2011 second quarter. From 1991 to 2002, the total annual Medicaid expenditures for antihista-

mines grew from $87.7 million to $757.2 million, a rapid increase. The average annual per-prescription price of first-generation antihistamines fluctuated between $8 and $17, while the per-prescription price of second-generation antihistamines increased from $13 to $64 from 1991 to 2011.

Conclusions: Although the U.S. Medicaid Program encourages switching to over-the-counter medications when available, which may be outside of the study's database, utilization of and expenditures on anti-allergic medications have nevertheless risen substantially over the last two decades.

1016. Prospective Epidemiological Research on Functioning Outcomes Related to Major Depressive Disorder (PERFORM): Design and Characteristics of First 1,000 Patients

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Background: Major depressive disorder (MDD) ranks among diseases with the highest burden (Global Burden of Disease Study 2010). MDD affects daily functioning and work impairment. The patterns, mediators and modifiers of functional impairment are not completely understood.

Objectives: The main objectives of the study are to describe the functioning of patients with MDD and the factors that mediate and modify the functional impairment of patients. Here we report on the study design and the first 1,000 patients included.

Methods: PERFORM is a 2-year prospective cohort study conducted in France, the UK, Germany, Spain and Sweden. Outpatients were recruited from primary care or specialist practices. Inclusion criteria were: DSM-IV diagnosis of MDD, age 18–65 years, and initial or switched antidepressant treatment. Patients with schizophrenia, bipolar disorder, dementia, or other neurodegenerative disease were excluded. Patients were evaluated by the participating physicians with a sociodemographic and clinical questionnaire, the CGI-S, and the MADRS. Patients also completed the PHQ-9 for depression severity, the Sheehan Disability Scale (SDS) for functioning, the Work Productivity and Activity Impairment Questionnaire (WPAI-SHP) for absenteeism and presenteeism, and the PDQ-5 for perceived cognitive symptoms. Final sample size will be about 1,500 patients.

Results: The mean age of the first 947 patients recruited was 43.6 years and 73% were women. Two thirds (67%) were employed. More than half (58%) had a previous depressive episode, and 13% had attempted suicide in the past. MDD severity was moderate to severe as assessed by CGI-S (83%), MADRS (mean total score = 32.8) and PHQ-9 (mean total score = 17.7). Over 25% scored 16 or more on the PDQ-5 (very frequent cognitive symptoms). Overall functioning was impaired (mean SDS total score = 19.3), as were work (34% of work time lost) and overall activity (62% impairment) as assessed by the WPAI-SHP.

Conclusions: The preliminary results from this large European study showed that patients with MDD do experience important functional impairment.

1017. Case Series of Patients with Reported Renal Events in a Prescription Event-Monitoring (PEM) Study of Aliskiren

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Background: The direct renin inhibitor aliskiren (Rasilez[(R)]) was launched in the UK in Aug 2007 for essential hypertension. The SPC at market launch listed renal events (REs) as uncommon and reversible. In 2011 the ALTITUDE study was stopped due to events including REs. This case series is a post hoc analysis in response.

Objectives: To describe the characteristics of patients with renal events suspected to be related to aliskiren in a PEM study in England.

Methods: This study used an observational single exposure cohort design. Exposure data were collected from dispensed aliskiren prescriptions issued by general practitioners (GPs) from Feb 2008 to Nov 2010. Outcome data were collected from questionnaires sent to GPs 6 months after each patient's first prescription. Drug relatedness assessments were performed where relevant. Patients with REs probably or possibly related to aliskiren were categorised using reported laboratory values according to the RIFLE classification, (a spectrum of renal insults.) Characteristics of these patients were described.

Results: The final cohort consisted of 6385 patients of which 120 (1.9%), reported 183 REs; 78.1% (143/183) renal function test (RFT) decline, 21.9% (40/183) renal

failure. REs in 20.0% of the RE patients (24/120), were assessed as probably or possibly related to aliskiren. Reported characteristics of this subset: female 58.3% (14/24); median age 75 years (IQR 68–81); RIFLE categories (Acute Renal Failure (ARF) 16.7% (4/24), Renal Injury (RI) 12.5% (3/24), Risk of renal injury (Risk RI) 45.8% (11/24), RFT decline (below RIFLE) 25.0% (6/24); Chronic Kidney Disease (CKD) 79.2% (19/24); Diabetes Mellitus (DM) 62.5% (15/24); Concurrent ACE inhibitor (ACEi)/angiotensin blocker (ARB) use 45.8% (11/24). CKD, DM or ACEi/ARB use present in 95.8%(23/24). In 'Risk RI' and 'RFT decline' 100% (17/17) had CKD. In ARF 75.0% (3/4) had both DM and ACEi/ARB use.

Conclusions: REs were commonly reported but not always related to aliskiren. Where relatedness suspected, majority of ARF group, had DM and ACEi/ARB use, (as per ALTITUDE study). Majority with CKD were in less severe RE groups. Possibly RFTs were more closely monitored in CKD.

1018. Post-Authorization Surveys To Evaluate Physician Knowledge: Contract Research Organization (CRO) Evaluation Case Study

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Background: New EU legislation has increased the requirements for Post-Authorization Safety Studies (PASS). In particular, surveys are increasingly requested of drug manufacturers to measure effectiveness of risk minimization measures; however, recommendations are limited to ensuring external validity and maximized response rates. We give an example of a survey measuring prescribers' understanding of safety risks described in the summary of product characteristics for a new therapeutic agent. The protocol has two rounds of survey (six questions) with prescribers in seven EU countries.

Objectives: We evaluated CROs experienced in physician survey research or pharmacovigilance (PV).

Methods: CROs (n = 17) invited to submit proposals fit into 1 of 3 categories: (1) epidemiology, outcomes research (EPI), (2) clinical research (CR), and (3) market research (MR). An objective scorecard was developed and a cross-functional team participated in vendor evaluation.

Results: Proposals from 14 CROs were evaluated. Costs were higher for EPI (US$329K, 508K, 659K),

intermediate for CR ($298, 308K, 348K), and lowest for MR (median $209K; $58–259K; n = 8). MR had expertise in online research with adequate response rates and most had PV experience. EPI and CR had greater levels of PV experience, lower anticipated response rates, and limited focus on survey research with online methodologies. Anticipated response rates ranged from 5 to 15%, with higher rates associated with MR and lower rates with EPI and CR.

Conclusions: Manufacturers face substantial tradeoffs in their approach to conducting physician surveys. Different strategies to balance external validity and response rates could be implemented. MR vendors can offer more directed sampling of prescribers to maximize response rates, whereas EPI and CR focused on external validity using random sampling and multiple contact attempts but at a higher cost and lower response rates. Further guidance or standards for the design and conduct of non-interventional PASS would assist manufacturers in their decisions, particularly for survey designs, while increasing the odds of meeting the goals of authorities.

1019. Withdrawn by Author.

1020. Endotoxin-Associated Sterile Peritonitis Observational Study (e-STEPS): Safety Findings

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Background: From September to December 2010, a recall of peritoneal dialysis (PD) solutions (1 Dianeal and 2 Nutrineal lots) was initiated in Europe. These three recalled lots (manufactured at one site in Ireland) were related to elevated endotoxin levels and associated with increased sterile peritonitis (SP) spontaneous reports.

Objectives: Describe safety outcomes in PD patients with endotoxin-associated SP (e-SP), no peritonitis (NoP), and bacterial peritonitis (BP) over a 12-month period.

Methods: A post authorization safety study was conducted using a retrospective chart review study design in 12 European PD clinics (Germany, Hungary, Netherlands, Portugal, United Kingdom). e-SP and NoP patients used 1 of 3 recalled lots; BP patients used Baxter PD solutions in Viaflex containers from the same manufacturing site as the recalled lots. Safety data were collected up to 12 months pre/post index event. Safety was evaluated by assessing peritoneal

membrane function (i.e. dialysate/plasma creatinine [D/P Cr]), clinical outcomes and presentation/management of the index event. Statistics were mainly descriptive.

Results: Population included 127 patients (46 e-SP, 38 NoP, 43 BP). 50% were female and mean age was 64 ± 15 years. 95% were on continuous ambulatory PD at index event, 89% of patients had 1 or more serious adverse event (SAE); 393 SAEs were recorded overall. 89% of e-SP and 86% of BP patients recovered within 1 month of index event. Overall, 7% of patients died with no differences in fatality across cohorts. Within 12 months post index event and across cohorts, no significant differences were found in D/P Cr. Compared with e-SP and NoP cohorts, more BP patients permanently transferred to hemodialysis (HD) (37% vs. 8.7% e-SP and 0% NoP), developed peritonitis (51% vs. 17% e-SP and 13% NoP) and were hospitalized (61% vs. 41% e-SP and 40% NoP).

Conclusions: While majority of patients had 1 or more SAE, e-SP and NoP patients did not appear to have clinically meaningful long-term effects from recalled lot exposure on peritoneal membrane function or clinical outcomes; BP patients appeared to have more long-term clinical consequences.

1021. Using Forensic Toxicology Registers in Combination with Drug Dispensing Databases To Identify Prescription Drug Abuse: The Example of Tramadol

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Background: Non-therapeutic use of prescription drugs is an internationally recognized problem. To reduce the problem, early identification of drug abuse is critical. However, established methods are missing.

Objectives: To assess the proportion of individuals under investigation for driving under the influence of drugs (DUID), with a recent dispense of the drug identified in blood, for tramadol compared to other drugs with abuse potential, and to investigate differences between subjects with and without a recent drug dispense.

Methods: The study population included all subjects who underwent a forensic DUID investigation in Sweden 2006-07-01 – 2009-06-31, and who were identified with tramadol (t), flunitrazepam (f), diazepam (d), zo-lpidem (zd), zopiclone (zc), propoxyphene (pro), oxycodone (o) and/or pregabalin (pre) in blood. Results from toxicological analyses were linked to information on drug dispenses from the Swedish Prescribed Drug Register. A current drug dispense was defined as a dispense of the study drug within 12 months before the arrest date. For each drug, the proportion of subjects who had a recent drug dispense, was calculated. A significance test will show whether this difference is statistically significant. Potentially confounding factors, will be included in a stepwise forward multiple regression model, in which subjects with vs. without a recent drug dispense will be compared. p values < 0.05 are considered significant.

Results: A total of 2,260 individuals were included, of which 476 (21%) had tramadol in blood, 1893 (84%) were men and with a median age (range) of 34 (15–80) years. A recent dispense of the identified drug was found in 42%, with corresponding figures for each drug as follows: pre 83%, zd 79%, zc 70%, tl 60%, pro 53%, o 44%, d 26% and f 24%. These figures did not differ when using a cut-off of 6 months.

Conclusions: The proportion of subjects with a recent drug dispense, differs between drugs with varying dependence potential with a spectrum supported by the existing literature. This method may be used in the future to investigate non-therapeutic use of drugs with unknown abuse potential.

1022. Web Traffic: A New Tool in Pharmacovigilance?

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Background: An estimated 80% of internet users search for health information online making it the third most popular research online. Google defines trends as those searches with the highest amount of traffic. Google trends provide an index of the volume of Google queries by geographic location and category. Google flu trends are a sophisticated web-based tool detection of regional outbreaks of influenza, for example.

Objectives: The aim of this study was to analyse Google Trends data and their correlation with drug safety information.

Methods: During 1 week, 21 January to 27 January 2013, we analyzed the available data on Google trends. Requests have been made with the following keywords: methylphenidate, Ritaline®, Concerta®, pioglitazone, 'pilules' and side effects. We analyzed the data for the periods from 2004 to the data of the inquiry,

and the data corresponding to internet traffic last 3 months. We compared data between different countries and their evolution overtime. Regarding France, our research targeted regions and cities.

Results: For methylphenidate and its two trade marks, we observe significant differences. For Ritaline®, France (index 100) is ahead of connections, then for Canada (index 5) and USA (index 2). In France, the connections are the most frequent in the city of Montpellier (fifteenth French agglomeration). For Concerta®, the top three connecting countries are: Sweden (index 100), USA (index 96) and Canada (index 73). Under the heading methylphenidate, connecting ranking is as follows: United Stats (index 100), Canada (index 78) and South Africa (index 55). 'Pioglitazone' term has shown a peak in June 2011 (index 100). During the year 2012, index varies between 40 and 60. Web traffic is more important in India (index 100), USA (index 37), Canada (index 36). With the term 'pilules' corresponding to 'oral contraceptive pill', the top three connecting countries are: France (index 100), Morocco (index 47) and Canada (index 21).

Conclusions: Pharmacovigilance processes need to be innovative to use safety data from the pool of information generated from the internet. In the future, Pharmacovigilance should adapt to new technologies.

1023. Quantitative Evaluation of Metformin Safety Warning on Drug Utilization and Clinical Adverse Effect in Taiwan

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Background: Metformin, one of biguanide drugs, has been widely used for type 2 diabetes. Compared with phenformin, despite the low potential of lactic acidosis induced by metformin, the high mortality rate of it must be taken seriously. Recent studies have suggested that renal failure history and old patient are risk factors for lactic acidosis induced by metformin. To prevent the acidosis, the official announcement of safety warnings, metformin is not recommended to be prescribed for patients with renal failure history and elderly patient over the age of 80, was released by Taiwan FDA on December 23, 2008.

Objectives: This study aims to evaluate the impacts of the previous safety warning on drug utilization and clinical adverse effects.

Methods: Our data were drawn from the 2006 to 2010 Taiwan National Health Insurance Research Database, a nationally, population-based claims database. Using new-user research design and excluding patients who were only prescribed insulin, totally 355,713 new DM

cases were included in our data. An interrupted time series design and segmented regression models were used to estimate changes in monthly per capita prescribing rate of metformin and incidence rate of acidosis on new DM patients with renal failure history and new DM patients aged 80 years or older following the policy.

Results: The results show that there was no significant change in prescribing rate of metformin for new DM patients with renal failure history, while the prescribing rate for new elder DM patients decreased significantly by 10.02% (mainly trend change) at 12 months post-policy. In addition, the rates of acidosis on new DM patients with renal failure history and new DM patients aged 80 years or older significantly decreased by 2.49% and 55.73% (mainly level changes) at 12 months post-policy respectively.

Conclusions: This study reveals that the compliance with metformin safety warning was partially verified due to the reduction of drug utilization among elder patients. Furthermore, based on the declines of the rates of acidosis overtime, our results indicate that the safety warning policy fulfilled its main objectives.

1024. Observational Assessment of Safety in Seroquel (OASIS) – Design, Recruitment and Baseline Patient Characteristics

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Background: Prolonged-release quetiapine fumarate (Seroquel XL), a once-daily atypical antipsychotic, was launched in the UK in September 2008. The XL formulation was developed to improve tolerability and the administration of once daily dosing. OASIS was incorporated into the EU risk management plan to extend the post-authorisation safety knowledge in this area, with particular emphasis on safety during titration and at higher doses.

Objectives: The study was designed to examine the short-term safety and use (up to 12-weeks) of quetiapine XL, with quetiapine IR as a comparator, when prescribed by psychiatrists under normal conditions of use.

Methods: OASIS aimed to recruit 1500 patients with a clinical diagnosis of schizophrenia or bipolar mania, newly initiated on quetiapine XL or IR (750 each). Adult patients were recruited from over 50 NHS trusts throughout England over 3 years from December 2009 to December 2012. Questionnaires completed by study investigators collected baseline data on patients' demo-

graphics, medical history and planned dosage, and follow up information 12-weeks post index date to determine rate of events.

Results: A team of study facilitators established a cohort of psychiatrists in collaboration with the Mental Health Research Network. Patient recruitment increased over the 3 year period, with 26% of the total cohort recruited in the final 6 months. In March 2012, the Seroquel XL patent expired in the UK. 900 patients were recruited, less than the planned 1500. One explanation includes prescribing guidelines that encourage generic product use. Patients' baseline mean age was 40.2 years, with 56.1% female. Baseline evaluation indicates that fewer patients were recruited in the IR cohort than the XL, and fewer patients were prescribed higher doses than expected.

Conclusions: Important information on quetiapine XL utilisation and safety will still be obtained from OASIS, despite lower than planned recruitment. The influence of external factors such as prescribing guidelines and expert committee recommendations on cohort accrual are being explored.

1025. Trends in Utilization of Cabergoline for Neurological Indications in Four European Countries. Do Doctors Comply with Risk Minimization Activities Concerning Heart Valve Fibrosis? A Population-Based Analysis

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Background: Because of an increased risk of valvular heart disease, the European Medicines Agency (EMA) concluded in June 2008 that the dopamine agonists cabergoline and pergolide should be used for the neurological indication of Parkinson's disease (PD) only as second line therapy and only at a maximum dose of 3 mg per day.

Objectives: To investigate doctors' compliance with changes in prescribing guidelines for cabergoline for neurological indications in Europe.

Methods: We used longitudinal data of more than 10 mio people (28 mio person years) from four databases (THIN, HSD-THALES, IPCI, and Aarhus) from four European countries (UK, Italy, Netherlands, and Denmark). We calculated incidence and prevalence rates of cabergoline use for neurological indications by calendar year and sex. This was an interim analysis as part of an analysis requested by the EMA.

Results: In Italy, incidence rates of cabergoline use for neurological indications dropped from 2.3 per 10,000 person years in 2006 to 0.2 in 2008 and remained around 0.1 thereafter. In UK, incident usedropped from 0.2 in 2006 to around 0.1 thereafter. For Italy and UK, incident use did not differ between sexes. In Denmark, incident use for men was 0.1, 0.2, and 0.1 for the years 2008, 2009, and 2010, respectively, while for women it dropped from 0.1 in 2008 to zero thereafter. Incident use was zero over the entire study period in the Netherlands where cabergoline has never been approved for PD. Prevalent use was higher in females, but showed a similar pattern as incident use otherwise, and dropped to below 3 per 100,000 persons after 2008 for most databases. For UK (the database with daily dose), the percentage of cabergoline prescriptions at more than 3 mg per day decreased from 29% in 2007 to 18%, 17%, and 7% in 2008, 2009, and 2010, respectively.

Conclusions: After the warnings, cabergoline use for neurological indications decreased especially in Italy where utilization was relatively high in 2006. In UK, the only database with daily dose, use at more than 3 mg per day decreased.

1026. Why Are the Myelosuppression as Adverse Reactions of Linezolid Often Reported in Japan?

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Background: In Japan, linezolid (LZD) is reported to have a tendency to cause serious thrombocytopenia and anemia as adverse drug reactions in patients with renal dysfunction. These adverse reactions are often reported in Japan, but in the United States and European countries the frequencies of their occurrence are reported not to be high, those details are not clear. Clinical trial results also suggested that there is a possibility that the frequency of adverse reactions related to myelosuppression is higher in Japanese than in Western patients.

Objectives: In this study, we analyze the real world clinical data to explore factors involved in the onset of

hematopoietic disorders by LZD among Japanese patients.

Methods: This study involved all hospitalized patients treated with LZD injection at the National Hospital Organization Okayama Medical Center (609 beds) during the period from June 2006 to December 2011. The data of background factors including patient age, body weight, renal function, and duration of LZD administration, were analyzed by using descriptive statistical methods. Multivariate analysis was performed using frequencies of thrombocytopenia and anemia as outcomes.

Results: The mean age of patients treated with LZD was 71.6 ± 14.0 years and their mean body weight was 53.8 ± 12.6 kg, with about 50% of all patients being elderly (75 years $\leq$) or low-body weight (< 55 kg). A logistic regression analysis conducted as a form of multivariate analysis on the thrombocytopenia found the administration period at 10 days or more (OR8.3; 95% CI [3.2–24.5]) and estimated Glomerular Filtration Rate at < 50 mL (OR4.5; 95% CI [1.8–13.3]) to be significant. The analysis of subgroup consisting of elderly patients (75 years $\leq$) found increased risk of thrombocytopenia.

Conclusions: This study revealed that myelosuppression occurs frequently if given to patients with high risk, e.g., elderly, low-body weight, and renal dysfunction, however, it does not occur frequently during shorter duration of LZD administration. Further clinical studies considering the LZD pharmacokinetic data and multi-institutional joint research will be necessary to encourage more appropriate LZD usage.

1027. Antipsychotic Duration of Use among Medicaid-Insured Preschoolers, Young Children, and Adolescents

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Background: Over the last two decades, the increased use of antipsychotic medications, often for unlabeled indications, has been profound. However, patterns of antipsychotic use in relation to their duration by age group and psychiatric diagnosis among youth populations are lacking.

Objectives: The study aims to characterize antipsychotic medicated youth, and to assess differences in median duration of exposure to these agents, specifically by age group and psychiatric diagnoses among Medicaid-insured youth.

Methods: Using claims data from a mid-Atlantic state Medicaid program for youth aged 2–17 years with continuous enrollment in 2006, bivariate analyses, multivariable quantile and multinomial logistic regression models were employed. Study covariates included age groups [preschoolers (2–5 years); young children (6–12 years); adolescents (13–17 years)], psychiatric diagnostic groups, Medicaid-eligibility groups [TANF (very low family income), CHIP (low family income), SSI (disability), and foster care], gender, race/ethnicity, region, and other psychotropic medication use.

Results: The study population (N = 266,590) was predominantly African American (56%), aged 6–12 years (42.8%), and Medicaid-eligible by low family income. The prevalence of antipsychotic use was 3.4%. Youth with disruptive behavior or attention deficit hyperactivity disorders, and youth who were Medicaid-eligible through TANF or CHIP constituted the largest group of antipsychotic users, in particular for youth aged 12 years or younger. Compared to SSI-eligible youth, youth in foster care had significantly longer median durations of antipsychotic use across the age groups (preschoolers: 180 vs. 150 days; young children: 261 vs. 225 days; adolescents 245 vs. 221 days). Among antipsychotic users, bipolar disorder diagnosis increased with increasing age. However, among 2–5 year olds, youth diagnosed with bipolar disorder had the longest duration of antipsychotic use (203 median days).

Conclusions: Long term effectiveness, safety, and monitoring of antipsychotic medications in youth, particularly those diagnosed with externalizing behavior disorders are needed; and state Medicaid program oversight is warranted.

1028. Interaction of Age and Psychiatric Diagnosis on Antipsychotic Use among Publicly-Insured Youth with ADHD or Disruptive Behavior Disorders

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Background: Since the introduction of atypical antipsychotic medications, antipsychotic (ATP) use has expanded at a greater rate in youth than in adults and often for unlabeled indications, particularly for attention deficit hyperactivity disorder (ADHD) or disruptive disorders. No previous study has detailed the differential effect of age and comorbid psychiatric diagnosis on ATP use and its duration of use among publicly-insured youth with such behavioral disorders.

Objectives: The study aims to characterize annual ATP use and median duration of use among publicly-insured youth with ADHD or disruptive disorder, mainly by comorbid psychiatric diagnosis across age groups.

Methods: A cohort of youth with ADHD or disruptive disorder was identified using claims data from a mid-Atlantic state Medicaid program for youth aged 2–17 years with continuous enrollment in 2006. Bivariate analyses, age-stratified multivariable quantile and logistic regression models were employed. Study variables included age groups (2–5; 6–12; 13–17 years), psychiatric diagnosis, Medicaid-eligibility groups, gender, race/ethnicity, and region.

Results: The majority of the study population (N = 22,055) was African American, aged 6–12 years, and Medicaid-eligible by low family income. The annual prevalence of ATP use in this behavioral disorder cohort increased from 17.6% for 2–5 year-olds to 30.0% for 13–17 year-olds. Overall, median duration of ATP use was 189 days. Youth with comorbid bipolar disorder had significantly greater adjusted odds (AOR) of ATP use and greater adjusted median days of ATP exposure compared to youth without bipolar disorder, whereas these findings were most prominent for 2–5 year-olds (AOR:28.9; +76.5 median days). Depressive and anxiety disorders were also associated with greater ATP use, in particular for youth aged ≤ 12 years.

Conclusions: Antipsychotic use for ADHD or disruptive disorders was substantial regardless of age group. Comorbid psychiatric conditions, especially clinician-reported bipolar disorder for young children, increase the likelihood of ATP treatment. Clinical monitoring and Medicaid program oversight are warranted.

1029. Use of Glucagon-Like Peptide 1 Analogues and the Risk of Fracture in Type 2 Diabetes Patients

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Background: Although patients with Type 2 Diabetes Mellitus (T2DM) have an increased bone mineral density as compared to healthy patients, their risk of fracture is elevated. Anti-T2DM drugs such as thiazolidinediones have been associated with an increased fracture risk. In contrast, a meta-analysis of randomized controlled trials, that compared dipeptidyl peptidase-4 (DPP-4) inhibitors with other treatments and with placebo, showed a 40% reduced risk of fracture. DPP-4 inhibitors restrict degradation glucagon-like peptide-1 (GLP-1) which suggests that GLP-1 analogues may protect against fractures.

Objectives: To compare the risk of fracture in users of glucagon-like peptide-1 analogues (GLP-1As) with users of other antidiabetic drugs.

Methods: A retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD) (2007–2012), formerly known as the General Practice Research Database, was conducted. Non insulin antidiabetic drug (NIAD) users (N = 213.900), having at least one NIAD prescription since 2007 were selected. Cox proportional hazards models were used to estimate the hazard ratio's (HRs) of any fracture in users of GLP-1As vs. users of NIADs. Time-dependent adjustments were made for age, sex, body mass index, smoking, comorbidity and drug use.

Results: Compared with other NIAD users, current users of GLP-1As did not have an increased risk of fracture: adjusted (adj.) HR 1.05; 95% CI 0.87–1.27. Sex-stratified analyses did not show a different effect for men or women: adj. HR men 1.20; 95% CI 0.95–1.15, adj. HR women 1.12; 95% CI 0.92–1.37. Patients who had stopped taking GLP-1As for > 6 months had a 1.5-fold increased risk of fracture, adj. HR 1.50; 95% CI 1.14–1.97 while the risk was not elevated with recent users (those who had stopped taking the drug between 3 and 6 months), adj. HR 1.11; 95% CI 0.62–2.01.

Conclusions: Current use of GLP-1As was not associated with an increased risk of fracture. Our finding does not support the hypothesis that GLP-1 analogues may be a promising potential new treatment for osteoporosis.

1030. Withdrawn by Author.

1031. Withdrawn by Author.

1032. Utilization of Antipsychotic Medications in the Youth Population of Manitoba

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Background: Second-generation antipsychotics (SGAs) are not approved in Canada for use in children and adolescents (except aripiprazole). Serious safety concerns have been raised regarding the off-label use of these agents in young patients. While some Canadian administrative databases do not cover the entire population, Manitoba's Drug Prescription Information Network provides comprehensive information on all prescriptions dispensed in the province, which allows for accurate evaluation of medication use in youth.

Objectives: To assess utilization of antipsychotics in the youth population of the Canadian province of Manitoba.

Methods: Databases from the Population Health Research Data Repository at the Manitoba Centre of Health Policy were accessed to determine prevalent and incident use of antipsychotics in the youth population of Manitoba (0–19 years of age) during the time period 1996–2011. A cohort of incident users of SGAs (clozapine, risperidone, olanzapine, quetiapine, paliperidone, ziprasidone and aripiprazole) was stratified by sex and age group (0–6, 7–12, 13–19). Utilization of each SGA and most common indications were evaluated. Diagnoses of adverse events (diabetes, hypertension, arrhythmias and movement disorders) were also counted. Analyses were conducted with SAS statistical software.

Results: Prevalence of SGA use in the youth population of Manitoba increased from 2.3 to 9 per 1,000 between 2001 and 2011 while incidence increased from 1.2 to 2.7 per 1,000. Incidence rates were higher in males (0.8–1.5 per 1,000) than in females (0.3–1.1 per 1,000). The highest level of use was observed in the 13–19 group (49.4%). Risperidone was the most used agent (65.2%) followed by quetiapine (19.6%) and olanzapine (7.4%). The most common diagnosis was Attention Deficit Hyperactivity Disorder (56.8%) followed by Conduct Disorders (38%) and Mood Disorders (22.7%). Diabetes (1.9%), hypertension (2%), arrhythmias (1%) and movement disorders (1%) were reported in users following their first SGA prescription.

Conclusions: Increased SGA utilization was observed in the youth population of Manitoba. It is important to evaluate risks associated with antipsychotic therapy in young patients.

1033. Changes in Antibiotic Prescribing in Infants and Young Children in Denmark, 1999–2011

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Background: Antibiotics increase the prevalence of bacterial resistance at the population level and may be associated with asthma incidence. In 2007, the Institute for Rational Pharmacotherapy (IRF) in Denmark issued recommendations to all primary care physicians for treating children and adults with bacterial infections. These recommendations may have resulted in decreased antibiotic prescribing, especially among children.

Objectives: To describe changes in antibiotic prescribing in Denmark over time and to assess the potential impact of the IRF guidelines on prescription patterns among infants and young children.

Methods: We conducted an ecologic cross-sectional study of all antibiotic prescriptions filled in non-hospital settings in Denmark between 1999 and 2011, using data from the Danish Register of Medicinal Product Statistics (Statens Serum Institut, medstat.dk). We identified and grouped antibiotics according to their Anatomical Therapeutic Chemical (ATC) classification. We assessed prescribing of all antibiotics, broad- and narrow-spectrum antibiotics, amoxicillin, and phenoxymethylpenicillin in three populations in Denmark: (1) people of all ages, (2) children under 5 years of age and (3) infants only. For each ATC code or code group, we computed (1) the annual prevalence of people in Denmark with at least one prescription and (2) the annual volume of prescribed defined daily doses (DDD) per 1,000 inhabitant-days.

Results: Annual volume of filled antibiotic prescriptions increased markedly from 1999 to 2011 (12–18 DDD per 1,000 inhabitant-days). In infants and children, the prevalence of amoxicillin prescriptions increased, while phenoxymethylpenicillin and other narrow-spectrum antibiotic prescriptions decreased over the study period. From 2007 to 2009, antibiotic prescription prevalence decreased among infants (48% to 42%) and children (47% to 41%), but increased again in 2010.

Conclusions: The decrease in prevalence of antibiotic prescribing among infants and children after 2007 may have partially been due to the IRF recommendations. Different trajectories in the prevalence of broad- and narrow-spectrum antibiotics may cause concern about prescribing or resistance patterns.

1034. Incidence of Stimulant Augmentation among Children and Adolescents with Attention/Deficit Hyperactivity Disorder (ADHD) during 2010

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Background: The American Academy of Pediatrics Guidelines recommend against the use of off-label, adjunctive drug therapy for the treatment of ADHD. Despite off-label stimulant augmentation being well documented, there is little evidence to describe the incidence of such augmentation in the real-world setting.

Objectives: To estimate the incidence rate of stimulant augmentation for children and adolescents with ADHD during 2010.

Methods: Children (6–12) and adolescents (13–17) with ≥ 1 ADHD diagnosis and ≥ 1 stimulant fill during 2010 were identified from a large US commercial claims database. Stimulant augmentation (i.e. ≥ 30-day overlap of continuous medication supply between the augmenting agent and stimulant) was evaluated for 10 distinct psychotropic medication categories (atomoxetine, atypical antipsychotics [AAPs], bupropion, clonidine immediate release [IR], guanfacine IR, guanfacine extended release [XR], SNRIs, SSRIs, tricyclic antidepressants, and typical antipsychotics). Patients could augment with multiple different categories, but only once per category. Patients were ineligible to augment with a category if they had a fill from the category during the 90 days prior to stimulant initiation. The incidence rate was calculated for each category as the number of augmentations per 100 person years at risk [PYaR].

Results: A total of 89,535 children and 65,489 adolescents met all inclusion criteria. For children, the highest incidence rates of stimulant augmentation were observed for SSRIs (5.93 augmentations per 100 PYaR), guanfacine XR (5.84 per 100 PYaR), clonidine IR (5.05 per 100 PYaR), AAPs (4.56 per 100 PYaR), and guanfacine IR (2.47 per 100 PYaR). Among adolescents, the highest incidence rates were observed for SSRIs (12.44 per 100 PYaR), AAPs (5.89 per 100 PYaR), guanfacine XR (2.82 per 100 PYaR), clonidine IR (2.68 per 100 PYaR), and bupropion (2.14 per 100 PYaR).

Conclusions: The incidence rates of stimulant augmentation varied both among drug categories and between children and adolescents with ADHD. These incidence rates suggest that stimulant monotherapy may sometimes be insufficient for the treatment of ADHD.

1035. Use of Medication among Young People with Intellectual Disability in Quebec

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Background: Little is known about medication use among young people with intellectual disability (ID).

Objectives: To calculate the proportion of young people with ID who use medications. To describe the type of medications used. To identify factors associated with the use of psychotropic medication.

Methods: A population-based survey was conducted in 2010–2011 among 751 young people aged 0–24 years with either an autism-spectrum disorder or ID in the province of Quebec, Canada (TEDDIF, Gascon et al). Data was obtained using a structured telephone interview. Parents provided information on sociodemographics, their child's developmental characteristics, health issues and the use of social services. As for medication intake, parents answered the following questions: 'Does your child take one (or more) medication(s)? Which one(s)? Please specify the indication.' We then classified psychotropic medications into subgroups: antipsychotics, antidepressants, anxiolytics/ hypnotic, stimulants and mood stabilizers. We used descriptive statistics to calculate the proportion of medication users. Multivariate logistic regressions were performed to identify factors associated with the use of medication, yielding odds ratios (OR) and 95% CI.

Results: Among the 262 individuals with ID, 154 (59%) used at least one medication. A total of 108 (41%) individuals used non-psychotropic medications and 80 (31%) took psychotropic medications. Approximately one out of five used stimulants (19%). Anticonvulsives (17%) and thyroid hormones (12%) were also frequently used. Factors predicting the use of psychotropic medications included: challenging behaviors (OR: 2.87; 95% CI: 1.46–5.64), number of psychiatric diagnoses (4.39; 2.11–9.12) and a family context characterized by greater structural, social and economic difficulties (1.95; 1.06–3.58).

Conclusions: A significant proportion of young people with ID take medications. There is a need to better understand prescribing practices and to explore the reasons why dissimilar prescribing patterns exist for this particularly sensitive population.

1036. Use of Medication by Young People with Autism-Spectrum Disorders in Quebec

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Background: There is little evidence-based data on the use of medication in autism-spectrum disorders (ASD). Population-based information on the actual medication used also lacks for the province of Quebec.

Objectives: To calculate the proportion of young people with ASD who use medications. To describe the psychotropic medications used. To identify factors associated with the use of psychotropic medication.

Methods: A population-based survey was conducted in 2010–2011 among 751 young people aged 0–24 years with either an ASD or an intellectual disability in Quebec, Canada. Data was obtained using a structured telephone interview. Parents provided information on sociodemographics, their child's developmental characteristics, health issues and the use of social services. As for medication intake, parents answered the following questions: 'Does your child take one (or more) medication(s)? Which one(s)? Please specify the indication.' We then classified the psychotropic medicines into subgroups: antipsychotics, antidepressants, anxiolytics/hypnotic, stimulants and mood stabilizers. We calculated the proportion of medication users. Multivariate logistic regressions were then performed to identify factors associated with the use of psychotropic medications, yielding odds ratios (OR) and 95% confidence intervals (CI).

Results: Among the 489 individuals with ASD, 273 (56%) used at least one medication and 228 (47%) used psychotropic medications. About one third of these 489 individuals used stimulants (36%) and a fewer number used antipsychotics (13%), anxiolytics (7%) or antidepressants (5%). Factors associated with psychotropic medication use included: increased number of psychiatric diagnoses (OR = 3.02; 95%CI:2.09–4.38) and the presence of challenging behaviors (1.82;1.28–2.60), whereas increased adaptive behaviors (0.58;0.36–0.94) and a younger age (0.10; 0.03–0.35 [0–5 y vs. 18–25 y]) protected from such use.

Conclusions: Although little information supports the use of medication among young people with ASD, the proportion of psychotropic medication users is significant. There is a need to better understand prescribing patterns and ultimately generate recommendations to ensure optimal medication use.

1037. Persistent Antipsychotic Treatment and the Impact on Outpatient, Inpatient, and Emergency Department Services for Youth in Foster Care

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Background: Increased use of antipsychotic medication for children, and particularly youth in foster care, and mounting evidence of adverse metabolic effects has led to federal mandates for better monitoring and oversight. However, few longitudinal studies have examined persistence of antipsychotic treatment and associated mental health-related outcomes for youth in foster care.

Objectives: This study sought to a) characterize persistence of antipsychotic treatment among youth in foster care and b) examine the association between these patterns and mental health outpatient, inpatient, and emergency department (ED) services.

Methods: This retrospective study from 2010 to 2011 used child welfare administrative records and mental health and pharmacy Medicaid claims. Persistent use was defined as no more than three consecutive months without antipsychotic treatment during the study period. The dependent variables, measured over the 24-month study period, were number of: (1) outpatient; (2) inpatient; (3) ED services. Poisson regression models were used to examine the association between persistent antipsychotic treatment with each dependent variable, adjusting for age, gender, race/ethnicity, psychotherapy and days in foster care.

Results: Of the 511 youth who received antipsychotics, 195 (38.2%) had a persistent use. Compared to non-persistent antipsychotic users, the persistent antipsychotic users were more likely to be < 12 years old, male, and non-black. Persistent users were also more likely to have psychotherapy visits and to receive more than one antipsychotic concomitantly than non-persistent users. After adjusting for covariates, persistent antipsychotic users had rates of ED, hospital, and outpatient services that were 1.3, 1.6 and 1.3 times greater than rates of non-persistent antipsychotic users, respectively.

Conclusions: Persistent use of antipsychotic treatment may represent youth with severe impairment that is difficult to manage. Use of antipsychotics concomitantly among persistent users may have long-term safety concerns that require routine monitoring and oversight of clinical practice.

1038. Age-Related Emergency Department Reliance (EDR) and Healthcare Resource Utilization in Patients with Sickle Cell Disease (SCD)

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Background: For SCD patients, inadequate care during pediatric to adult transition may result in increased emergency department (ED) utilization. Emergency department reliance (EDR: total ED visits/total ambulatory [outpatient + ED] visits) identifies the proportion of ED visits in relation to all ambulatory visits.

Objectives: This study aimed at investigating age-related patterns of EDR and associated healthcare costs in SCD patients.

Methods: State Medicaid data from Florida, New Jersey, Missouri, Iowa, and Kansas were analyzed. Patients with ≥ 2 SCD diagnoses (ICD-9 282.6x) and ≥ 1 blood transfusion were included. Quarterly rates of EDR and SCD complication-related ED visits as well as healthcare costs were evaluated. Based on published thresholds, high EDR was defined as > 0.33. Regression analyses were used to assess risk factors for high EDR and calculate adjusted costs difference between patients with high vs. low EDR.

Results: 3,208 patients were identified; mean (SD) observation period was 6.5 (3.2) years. Mean ED visits/quarter increased from 0.76 to 2.23 between age 15 and 23, reaching a peak of 2.9 at age 36. The most common SCD complication-related ED visits were pain, infection, and pneumonia. EDR rose from 0.15 to 0.29 between age 15 and 23, and remained high thereafter. Patients were more likely to have high EDR during the post-transition period (≥ 18 years old, odds ratio [OR]: 2.38, $p < 0.001$) and when experiencing an SCD complication (OR: 4.18, $p < 0.001$). Patients with high EDR incurred higher inpatient and ED costs, resulting in higher total costs (high vs. low EDR, adjusted costs difference, OP: -\$285; IP: \$3,485; ED: \$120; Rx: -\$91; total: \$3,086, $p < 0.001$ for all).

Conclusions: Compared to children, SCD patients transitioning to adulthood relied more on ED for their care and those with high EDR incurred higher healthcare costs, highlighting the need to improve access to care for transitioning and adult SCD patients.

1039. Long-Acting Beta2-Adrenergic Agonists (LABA) Use in Pediatric and Adolescent Asthma Patients, 2003–2011

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Background: Concerns over the serious safety risks of Long-Acting Beta2-Adrenergic Agonists (LABA) in patients with asthma have led to various regulatory actions, including several Food and Drug Administration (FDA) advisory committee meetings and labeling changes for LABA products during 2003–2011. In February 2010, FDA recommended that LABAs be reserved for patients whose asthma cannot be adequately managed with asthma controller medications (ACMs); and pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid (ICS) should use a fixed-dose combination (FDC) of ICS and LABA.

Objectives: To monitor prescribing patterns for LABAs in pediatric and adolescent asthma patients, 2003–2011; and to describe changes for three distinct time periods: 2003–2004 (after 1st LABA labeling change), 2005–2009 (before-), and 2010–2011 (after-the most recent LABA labeling change).

Methods: Asthma patients 0–17 years-old with a new LABA prescription during 2003–2011 were extracted from IMS Health Plan Claims database. We estimated FDC- ICS/LABA and single-ingredient (SI) LABA use patterns over time; concomitant use of ACM and SI-LABA; and proportion of LABA initiators with prior ACM use.

Results: Of the 130,223 pediatric and adolescent asthma patients who initiated a LABA during the study period, the majority initiated a FDC-ICS/LABA product (96%). The proportion of SI-LABA initiators was small and declined in periods 1–3, (9, 4, and 2% respectively); and of SI-LABA initiators, the mean concomitant ratios with long-term ACMs were 50, 62, and 69%, for periods 1–3, respectively. Of the patients who initiated a LABA, the proportion of prior use of ACM was 38, 39, and 42% in periods 1–3, respectively.

Conclusions: The steady decline in the proportion of new users initiated on SI-LABA and increase in concomitant use with ACM is encouraging. Prior to initiating LABAs, the use of ACM has shown little change. Investigating the reasons for the low ACM use before LABA initiation may inform approaches to further improve adherence with the latest recommendations.

1040. Regional Variations in Complex Antipsychotic Medication Regimens in U.S. Foster Care Youth

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Background: Appropriate use of antipsychotics (ATP) for the treatment of children's mental health conditions is a major concern in the U.S. Compared to privately-insured youth, Medicaid enrollees are likely to have five-fold greater ATP use, raising safety concerns in the absence of sufficient efficacy data. Within the Medicaid population, government reports emphasize concern for antipsychotic use in foster care youth.

Objectives: This study aims (1) to characterize regional variations in the clinical and demographic characteristics of U.S. foster care youth with respect to their ATP use; and (2) among ATP users, to characterize complex ATP regimens and number of concomitant psychotropic medication classes.

Methods: National Medicaid Statistical Information System data for 2008 were organized for foster care youth with 12-months of continuous Medicaid enrollment. Bivariate and multivariable Poisson regression were employed to examine annual ATP use, concomitant ATP use, and counts of concomitant psychotropic medication classes, mainly by region and other characteristics. Episodes of concomitant ATP use with other psychotropic medication classes were defined by > 30 days of class overlap.

Results: Among 6 U.S. regions, ATP prevalence was highest in the Mid-Atlantic (16.3%) and lowest in the West-Pacific (9.1%). Youth aged 10–17 years and males had higher annual ATP use compared with their counterparts. While youth diagnosed with schizophrenia/other psychoses (81.0%) and bipolar disorder (77.1%) were the most frequent ATP users, youth with disruptive behavior and attention deficit hyperactivity disorder were by far the largest group of ATP users (N = 22,633, 53.7%). Among ATP-users, antidepressants (35.1%) and anticonvulsants (24.9%) were the most common medication classes used in combination with ATP. Further, one-quarter of these youth had complex regimens involving ATP with ≥ 2 other psychotropic medication classes.

Conclusions: Large proportions of foster care youth received ATPs for non-evidence based psychiatric conditions and in complex regimens with other psychotropic medications. The results support the need for ATP effectiveness and safety monitoring in these vulnerable U.S. youth.

1041. An Evaluation of Three Methods To Identify Adverse Event Signals Associated with Marketed Drugs and Devices

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Background: EBGM is a method of disproportionality analysis used to identify drug-event combinations occurring with greater than expected frequency compared to other drug-event combinations. Other methods are available that could work to complement the EBGM analysis and include the U-Chart and Increased Frequency calculation. The U-Chart is borrowed from the quality assurance profession and is a tool used to measure count-type data to see if a value has gone out of statistical control. It can be used for trending of safety reports and identifying events reported above the upper confidence level of the sales mean. It is useful for both drugs and devices. Increased Frequency is a calculation initially required by FDA for serious labeled drug reports but rescinded as a regulation in June 1997. It uses a critical value as a threshold for identifying increased frequency. The U-Chart and the Increased Frequency calculations are dependent on sales data used for denominator purposes while the EBGM is denominator independent.

Objectives: To determine if the EBGM, U-Chart, and Increased Frequency complement one another and result in greater sensitivity and/or specificity in safety signaling.

Methods: To test the usefulness of the three methods, one drug and two devices were selected for analysis. Two devices were chosen as representative of our company's surgical and vision care divisions. Inclusion criteria for all three classes of products included:

(1) each product had to be on the market for a minimum of 3 years
(2) for EBGM analysis, there must be an appropriate comparison group
(3) sales data for each product during the time periods analyzed must be available

For each product, two serious adverse events were selected. Each event was analyzed in three ways using three different methods.

Results: Preliminary data from one analysis suggests there may be usefulness in using all three methods in safety signaling; however, a larger sample size is needed for any conclusions to be made.

Conclusions: Early analysis suggests EBGM, U-Chart, and Increased Frequency calculation may be appropriate for safety signaling and trending. A more complete analysis will be presented at the time of the annual meeting.

1042. Long Acting Reversible Contraceptives and Female Sterilization in Medicaid Population, 1999–2009

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Background: Due to data collection issues it is difficult to evaluate national trends in use of long acting reversible contraceptives (LARC), laparoscopic sterilization (LS) and hysteroscopic sterilization (HS). LS has been available since the 1960s. HS was approved by FDA in 2002 so long term data is limited. Medicaid covers many LS, HS, and LARC procedures, providing an opportunity to analyze data on contraceptive use since 1999 using claims data opposed to population based surveys.

Objectives: To report the number of women in the Medicaid system undergoing sterilization and LARC; to compare volume of procedures over time and region; and to describe demographic characteristics of women undergoing these procedures.

Methods: This study used Parts A and B Medicaid fee for service claims data from 1999 to 2009. Beneficiaries who underwent sterilization and LARC procedures were identified by Current Procedural Terminology codes. Annual rates of each procedure and demographic trends were described.

Results: Intrauterine device claims grew from 18,543 in 1999 to 306,832 in 2009; subdermal implant claims grew from 305 in 2002 to 17,718 in 2009. In 1999, there were 77,259 LS claims, and 0 HS claims. From 1999 to 2009, claims for LS steadily grew until 2006 when they peaked at 103,551, then fell to 97,096 in 2009. Claims for HS started at 1,367 in 2005 and grew to 12,033 in 2009. 88% of women receiving an LARC implant were under age 30, compared to 79% of women receiving an IUD, 63% of women receiving LS and 50% of women undergoing HS. 51% of those receiving LARC were White. Among those undergoing interval LS, 61% were White and 38% non-White; among those undergoing postpartum LS, 49% were White and 50% non-White. Among women undergoing HS, 60% were White and 38% non-White. IUD's were more common in the West, LARC implants and LS were more common in the South, HS was more common in the Northeast and Midwest.

Conclusions: The rate of LARC and sterilization procedures, especially HS, in the Medicaid population has grown quickly. HS was more prevalent among women who were older, White and lived in the Northeast and Midwest.

1043. The Development of the Pelvic Floor Disorder Registry (PFDR)

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Background: Nearly one quarter of all women suffer from Pelvic Floor Disorders (PFD) which includes urinary/fecal incontinence, defecatory dysfunction, and pelvic organ prolapse (POP). In January 2012, the U.S Food and Drug Administration (FDA) mandated > 33 manufacturers of urogynecologic surgical mesh for POP to conduct post market surveillance studies due to reported safety and effectiveness concerns. To this end, multiple manufacturers, professional societies, research agencies and the FDA have worked collaboratively to develop a national registry to conduct mandated studies, develop the infrastructure to track patient outcomes and to grain greater scientific knowledge for all PFDs.

Objectives: To describe the objectives, infrastructure, governance, and development of the PFDR and challenges encountered.

Methods: The American Urogynecologic Society (AUGS) has actively engaged stakeholders from American College of Obstetrics and Gynecology (ACOG), the Society for Urodynamics and Female Urology (SUFU), American Urologic Association (AUA), Women's Health Registry Alliance, FDA, National Institute of Health (NIH), the medical device industry and participating providers. Three levels of participation to the registry have been created, all with unique Objectives

Level I- Universal Minimum Data Set, Level II- Expanded Data Set, and Level III- Specific Study Data Collection. Input and development of registry elements including data elements, data capture, registry con-

duct, research objectives, and study endpoints have been decided collaboratively by all stakeholders.

Results: Housed by AUGS, the PFDR has been designed as a national, multi-centered prospective cohort study of patients undergoing treatment for POP (with or without other PFDs) to evaluate the effectiveness, quality of life and safety associated with both surgical therapy and non-surgical management of POP. The first subjects are due to enroll in the PFDR is in early summer 2013.

Conclusions: Multiple stakeholders have been able to collaboratively work on the development of a robust national registry that will greatly benefit patients, the clinical community and satisfy regulatory mandates.

1044. Outcomes after Carotid Artery Stenting in Medicare Beneficiaries, 2005–2009

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Background: Peri-procedural complications and long-term outcomes following carotid artery stenting (CAS) have not been described in the Medicare population.

Objectives: To describe peri-procedural and long-term outcomes among Medicare patients undergoing CAS, overall and in subgroups defined by demographic and clinical characteristics.

Methods: Using the Centers for Medicare and Medicaid Services' (CMS) CAS Database (CAS-D) and Medicare data, we estimated peri-procedural mortality, stroke/transient ischemic attack (TIA), and myocardial infarction (MI) as well as long-term mortality and stroke/TIA among fee-for-service beneficiaries at least 66 years of age undergoing CAS between 2005 and 2009. We also investigated the association between outcomes and subgroups based on age, sex, race, National Coverage Determination indication, hospital admission type, and clinical trial participation.

Results: Of 23,174 patients eligible for Medicare and undergoing CAS (mean age: 76.3; male: 60.2%, white: 93.8%, high-surgical risk: 91.1%, symptomatic: 47.7%, severe carotid stenosis: 97.2%), crude 30-day mortality, stroke/TIA, and MI risks were 1.8% (95% confidence interval [CI]: 1.6–2.0), 3.4% (95% CI: 3.1–3.6%), and 2.5% (95% CI: 2.3–2.7%), respectively. Over a mean follow-up time of approximately 2 years, 36.5% (95% CI: 35.1–38.0) patients died and 10.4% had a new stroke/TIA (95% CI: 9.6–11.3). Older age, having high-surgical risk symptomatic carotid stenosis, and undergoing CAS during a non-elective hospital admission were associated with increased short- and long-term risk of mortality and stroke/TIA. Compared to landmark clinical trials, peri-proecdural mortality was 2–3 times higher in this study.

Conclusions: Real-world CAS patients were mostly high-surgical risk with high-grade stenosis while over 50% were asymptomatic. Older adults, patients at high-surgical risk with symptomatic stenosis, and patients undergoing non-elective CAS were at highest risk of peri-procedural complications and had worse long-term outcomes. Further studies are needed to understand the risks and benefits of CAS in real-world patients, who are different from trial patients in their characteristics and outcomes.

1045. Withdrawn by Author.

1046. The Development and Opportunities of a Transcatheter Aortic Valve Replacement Therapy (TVT) Registry

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Background: As a 1st of a kind medical device, trans-aortic valve replacement therapy (TVT) is indicated for transfemoral delivery in patients with severe aortic stenosis deemed to be inoperable or high risk for open aortic valve replacement. This was an opportunity to maximize research capabilities of a registry to track patient safety and real-world outcomes related to transcatheter aortic valve replacement (TAVR), and collaborate with multiple stakeholders from government to industry.

Objectives: To create a unique multifunctional registry that would serve as a postapproval study for a 1st of a kind medical devic, evaluate the feasibility of providing Medicare coverage by participating in the registry, and serve as a source of future research.

Methods: TAVR was approved by the FDA in 2011. As a condition of approval, the sponsor was to nest

data collection for mandated postapproval study in the TVT registry and to link the data to Centers for Medicare and Medicaid Services (CMS) for longterm follow-up. FDA, Society for Thoracic Surgeons, American College of Cardiology, CMS, and Edwards LifeSciences worked collaboratively to create the 1st registry to track patient safety and real-world outcomes related to TVT. The TVT Registry collects patient demographics, provider characteristics, history/ risk factors, cardiac/health status, adverse events, and patient outcomes. The team has also worked to garner CMS coverage for TAVR through patients' registry participation.

Results: Launched in 2012, the TVT Registry serves as a non-randomized, prospective postapproval study which monitors patient outcomes. The TVT Registry has been approved by CMS to meet the registry requirement outlined in the Medicare National Coverage Decision with Evidence Development on TAVR for both inoperable and high risk patients. It also serves as a platform for evaluating future transcatheter valve therapies.

Conclusions: Collaboration from multiple stakeholders has contributed to forming successful partnerships between federal agencies, academia, professional societies, and industry to create a registry which monitors the post-approval performance and facilitates approval of all newly approved devices.

1047. Cohort Profile of Privately Insured Working Adults Undergoing Total Hip Arthroplasty

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Background: Patients under the age of 65 are at an increased risk for many complications related to total hip arthroplasty (THA). However, evidence is limited regarding morbidity post THA procedure in this population.

Objectives: The objective of this study is to describe the demographic and clinical characteristics of a cohort consisting of privately insured patients under the age of 65 who received a THA procedure from 2003 to 2004.

Methods: The Marketscan Commercial Claims Database contains active employees, early retirees, recently unemployed (COBRA covered), and dependents covered by employer-sponsored insurance. Participants were entered into the study if they had a ICD-9-CM or CPT-4 code for primary THA after 6 months continuous coverage. Participants were excluded if enrolled in a HMO or PPO plan, had evidence of hip fracture, bone or metatstatic cancer, or infection of the hip prior to THA procedure. The study analyzed demographic, clinical, and profession related characteristics. Results are presented as means and percentages for continuous and categorical data, respectively.

Results: There were 8,313 participants included into the study with a THA procedure from 2003 to 2004. Each participant contributed an average of 615.89 member days over the 2 years. The primary diagnosis was osteoarthritis (85.5%) followed by rheumatoid arthritis (10.5%). Participants were not predominantly male or female (50.7% vs. 49.3%) and had an average age of 54 years. Of these participants, 232 (2.79%) had a revision of the THA during the study window. The average time to revision was 154.3 days.

Conclusions: We were successful in identifying a diverse population of THA patients that differs from those typically seen in claims database research. Future research will focus on how the unique aspects of this cohort contribute to the risk of revision in a younger, working population of osteoarthritis patients.