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The costs of developing a medicine are increasing yet the potential target populations are decreasing. Innovative medicines are treating previously untreatable diseases but there is still huge unmet medical need. The costs to the health care systems of providing these innovative treatments are rapidly becoming unsustainable for even the richest countries. For a patient to get access to a medicine, several different decisions need to be made by different stakeholders including regulators, payers, physicians and the patient themselves. The evidence required for these decisions is different but is not always being provided so decision makers have to make important decisions based on incomplete information. This is not in anyone's best interests. We need to change how we approach drug development and how we can deal with uncertainty.

101 Drug safety signal detection in regional healthcare database using the tree-based scan statistic and comparison to 3 other statistical methods

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Objectives: To evaluate the relative performance of Tree-based Scan Statistic (TreeScan), crude cohort study, Bayesian confidence propagation neural network (BCPNN) and Gamma Poisson Shrinker (GPS) for detecting statins-related adverse events (AEs) in electronic healthcare database.

Methods: Patients older than 18 years old with a diagnosis of hypertension in Yinzhou healthcare database from 2010 to 2016 were included in our study. We identified statin users according to the prescription information of out/in-patient. The AEs were defined by using the ICD-10 codes of out/in-patient diagnosis. We established a set of reference signals to better evaluate the performance of the method. Then the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, youden index and AUC of methods were calculated for evaluation. Moreover, our study compared the evaluation indicators of 4 signal detection methods. For AUC, we tested the statistical significance of the difference between the areas under two curves with the method of DeLong. In sensitivity study, we compared these 4 methods in 2 different situations, including new-user cohort and propensity score matched (PSM) cohort.

Results: The sensitivities of TreeScan, BCPNN and GPS were same (69%) and larger than crude cohort (46%). The specificity, PPV, NPV, accuracy, youden index of TreeScan were the largest in 4 methods, 82%, 31%, 96%, 81%, 52%, respectively. And AUC of TreeScan (0.75, 95%CI: 0.62-0.89) was significantly larger than other 3 methods. In new-user cohort and PSM cohort, the results remained consistent in original cohort. The AUC of TreeScan were 0.79 (95%CI: 0.65-0.93) and 0.77(95%CI: 0.64-0.92), which was significantly larger than other 3 methods, respectively.

Conclusion: TreeScan performs better than crude cohort, BCPNN, and GPS. It is proposed as a complement for other signal detection methods in drug safety active surveillance.

102 Adverse reaction signal detection for statins in regional healthcare database using tree-based scan statistic method

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Objective: To apply tree-based scan statistic (TreeScan) method for detecting adverse effect signals of statins and evaluate the performance of TreeScan.

Methods: Our study used Yinzhou healthcare database in Ningbo city from 2010 to 2016. Patients older than 18 years old with diagnosis of hypertension were included. We identified statin users according to the prescription information of out/in-patient. The AEs were defined through using the ICD-10 codes of out/in-patient diagnosis. We first detect the safety signals of statins by using the TreeScan method. In order to better evaluate the performance of the method, we established a set of reference signals by referring to a set of ICD-10 codes to identify AEs. Gold standard of these signals was constructed by searching of publish Meta-analysis and systematic reviews and package inserts of statins. By comparing the signals to reference signals, we could compute measures of diagnostic test, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, youden index and AUC.

Results: A total of 224,187 patients were finally enrolled and divided into two groups (85,758 statin users and 138,429 nonusers). We built a reference set of 126 AEs (ICD-10) including 13 positive signals and 113 negative signals. TreeScan generated 30 positive signals ($P < 0.05$), and 9 of them were known adverse effects. The sensitivity, specificity, PPV, NPV, accuracy, youden index and AUC were 69%, 82%, 31%, 96%, 81%, 52%, 75%, respectively.

Conclusion: TreeScan can be successfully applied as a signal detection method in drug safety surveillance, simultaneously evaluating small and large number of potential AEs (subsets of diagnosis codes) and adjusting for multiple testing inherent in many overlapping groups evaluated. Comparative evaluation study should be conducted to further evaluate its performance and explore its proper application condition.

103 Novel HLA genotype subclass clustering methods to characterize liver toxicity phenotype

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Aim/Objective: To validate methods identifying representative liver toxicity subclasses using unsupervised machine learning methods based on HLA Class I & Class II genotype.

Methods: Drug Induced Liver Injury (DILI) cases included in a previous European study (from EUDRAGENE (105 individuals), DILIGEN (208 individuals) and Spanish DILI Registry (54 individuals) datasets), totalling 367 individuals with 165 due to amoxicillin-clavulanate exposure. DILI cases were included with causality score greater than possible (Roussel Uclaf Causality Assessment Method score >3), (1) and independently reviewed by an adjudication board. Clinical characteristics of these cases and methods used for genotyping, supplemented with high resolution genotyping within the MHC region for HLA-A, -B, -DRB1, -DQA1, and -DQB1 have been described in detail previously. Preliminary analyses examined HLA class I and class II genetic associations with DILI phenotype data (liver injury type). To reduce the dimension of the genotype data, we selected the top-ranked 1000 GWAS SNPs associated with co-amoxiclav DILI, mapped to HLA class I and class II genotypes, using SNPedia. Using the DILI phenotypes and the HLA genotypes as constraints, we applied Agglomerative Hierarchical Clustering to the genotype data to discover groups of samples with the least phenotype conflict (i.e. best data fit).

Results: The HLA-DILI phenotypes that associated with the groups of samples confirmed the subclasses of HLA variants previously associated with co-amoxiclav DILI. We were able to replicate the top associated Class I HLA-A*0201 and Class II HLA-DRB1*1501-DQB1*0602 associated genotypes. We were also able to extract novel HLA signatures for cholestatic, hepatocellular and mixed sub phenotypes of liver injury.

Conclusion: Our methods can identify phenotypic clusters which characterise immunological co-amoxiclav DILI signatures with good validity and identify new signatures which characterise molecular disease DILI sub-phenotypes.

104 Multiple imputation and clinico-serological models to predict human papilloma virus (HPV) status in oropharyngeal carcinoma: an alternative when tissue is unavailable

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Aim: In epidemiological studies, determination of human papilloma virus (HPV) in oropharyngeal squamous cell carcinoma (OPSCC) may depend on the availability of clinical testing, and/or tumor tissue access. We aimed to identify alternative methods for estimating HPV status to improve the quality of such datasets.

Method: We developed multi-modal prediction models for HPV status and prognosis by combining both clinico-epidemiologic variables and either serological multiplex assays of HPV or multiple imputation of HPV status. Sensitivity, specificity and accuracy between these methods and either p16 immunostaining or survival were assessed.

Result: When comparing to a reference of tumor tissue p16 immunostaining in 783 OPC patients, the model incorporating a composite of 20 HPV serological antibodies and clinical factors (c-index: 0.96) performed better than using this composite HPV serology (c-index: 0.92) or imputation (c-index: 0.86) alone. However, the model containing a single HPV 16E6 antibody combined with clinical variables performed extremely well (c-index: 0.95). When defining HPV status by composite HPV, HPV 16E6 serology, multiple imputation, or through p16 immunostaining, each of these definitions demonstrated improved overall and progression-free survival in HPV-positive OPC patients, when compared to HPV-negative patients (adjusted hazard ratios between 0.25 and 0.63).

Conclusion: Our study strongly suggests that when blood samples are available, a model that utilizes a single HPV 16E6 antibody combined with several clinical features has excellent performance characteristics to estimate HPV status. When no blood or tumor tissue is available, multiple imputation remains a viable, but suboptimal option.

105 Impact of administration schedules on high-dose methotrexate medication in osteosarcoma: a systematic review and meta-analysis

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Objective: To systematically review the impact of administration schedules on high-dose methotrexate medication in patients with osteosarcoma.

Methods: Databases including MEDLINE, EMBASE, Clinical Trials.gov, China National Knowledge Infrastructure (CNKI), WANFANG Data, and Chinese Science and Technology Journal Database (CBM) were searched from inception to March 2018. Two reviewers independently screened records to identify eligible studies, extracted data and assessed their qualities under Newcastle-Ottawa scale (NOS) or MINORS (methodological index for non-randomized studies).

Results: Totally 5 studies were included, 4 cohort studies of which were high quality (average NOS score of 7.75 points) and 1 non-randomized controlled trial of which was moderate quality (MINORS score of 18 points). The meta-analyses indicated the dose of 8 g/m² was superior to 10 g/m² in lowering the plasma concentration at 0h (MD=-249.4, 95%CI= [-308.14, -190.67]) and 72h (MD=-0.05, 95%CI= [-0.06, -0.03]) post-methotrexate, and the incidence of liver toxicity (OR=0.60, 95%CI= [0.41, 0.88]). The qualitative analyses suggested that the dose of 8 g/m² was superior to 10 g/m² in significantly reducing the risk of leukopenia (OR=0.05, 95%CI= [0.00, 0.66]) and thrombocytopenia (OR=0.02, 95%CI= [0.00, 0.48]). In terms of infusion time, the plasma concentration at 24h post-methotrexate was higher when the infusion time was 2h (MD=1.54, 95%CI= [0.32, 2.76]) or 4h (MD=0.54, 95%CI= [0.17, 0.91]), compared to 6h.

Conclusion: When high-dose methotrexate is prescribed to treat osteosarcoma, lower dose can achieve lower plasma concentration post-methotrexate and is safer, but the efficacy may not differ significantly. Shorter infusion time leads to higher plasma concentration at 24h post-methotrexate and may achieve better efficacy. However, the number of studies included in this systematic review and evidences for quantitative synthesis is limited. Well-designed and large-scale studies in osteosarcoma are still required to verify the conclusions.

106 Post-marketing Safety Surveillance and Evaluation of Moxifloxacin Based on a Computer-assisted Adverse Drug Reaction Alarm and Assessment System

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Objective: To examine the post-marketing safety of moxifloxacin, identify the potential risk factors, and ensure its clinical safety based on a computer-assisted adverse drug reaction alarm and assessment system.

Methods: The data of inpatients using moxifloxacin were extracted and analyzed with a Computer-assisted Adverse Drug Reaction Alarm and Assessment System (CADRAAS) developed by ourselves. CADRAAS is based on multiple-trigger and text-recognition models for automated detection of Adverse Drug Reactions (ADRs). Multiple-trigger models use quantitative changes in laboratory test results as triggering parameters, such as liver function, platelet count, hemoglobin level. Text-recognition models use common ADR terms, such as rash or pruritus as keywords, to scan electronic records of inpatients for related ADRs. Incidence of moxifloxacin-related ADRs was respectively calculated. Nested case-control study was conducted to evaluate the risk factors of moxifloxacin-related adverse skin reactions.

Results: 12930 cases were automatically detected based on multiple-trigger models in 6 hospitals. The incidence of liver impairment, thrombopenia, anemia, and leukopenia was respectively 3.88%, 0.49%, 2.21% and 0.95%. 7774 cases were automatically detected based on text-recognition models. The incidence of adverse skin reactions and anaphylactic shock was respectively 0.53% and 0.015%. Severe ADRs do not happen. The multivariate logistic regression analysis showed that alcohol consumption was associated with moxifloxacin-related adverse skin reactions (OR: 5.968; 95% CI: 1.213-29.371).

Conclusion: Moxifloxacin was well tolerated in the general population. Our system can finish the automated detection of moxifloxacin-related ADRs with high speed and efficiency. It is very promising in active pharmacovigilance.

107 Pharmacoepidemiology of prokinetic agents

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Prokinetic agents is one of the most commonly used drugs in clinic. Through the past decades, they show promising future in the treatment of gastrointestinal diseases, such as dyspepsia, gastroesophageal reflux disease, constipation and so on. Here, we review the pharmacoepidemiology of some representative drugs, including metoclopramide, domperidone, cisapride, mosapride and itopride. We review their distribution of usage, efficacy in clinical practice, and also pay attention to their safety.

108 Birth cohort effect of varicella infection before and after introducing varicella vaccination, South Korea, 2002-2017

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Objective: We used a series of birth cohorts to assess the effectiveness of varicella vaccination before and after its introduction in National Immunization Program

Methods: To evaluate the effect of varicella vaccination in different birth cohorts, we calculated the incidence and cumulative incidence rate of varicella in each birth cohort according to age. Varicella cases were identified based on the time of the first diagnosis for each individual in National Health Insurance Service claims data, contains information on the whole population of South Korea, which includes information regarding medical utilization, diagnoses of patients based on the International Classification of Disease, 10th revision (ICD-10), prescription records, and patients' characteristics. The number of claimed cases with a diagnosis of varicella (ICD-10: B01) was evaluated by age. The incidence rate was calculated as the number of varicella claims according to age divided by the number of births in each birth cohort. Because life-long protective immunity develops after varicella infection, the cumulative incidence rate was calculated by dividing the cumulative number of varicella claims (the total varicella claims from previous ages) by the number of births in each birth cohort.

Results: The incidence rate in children aged 4 to 6 years, the age at which varicella infection is most common, decreased to about one third in the birth cohort born after 2009 compared to those born before 2005. Approximately 27% of all babies born before 2005 were diagnosed as varicella at least once before 6 years of age. However, the cumulative incidence rate of varicella infection among children born after 2009 was approximately 11%.

Conclusion: The varicella incidence in post-vaccination birth cohorts was reduced compared with that of pre-vaccination birth cohorts. Further well designed epidemiologic studies are needed to assess the true effectiveness of varicella vaccination.

109 Incidence rates of health outcomes of interest among Chinese children exposed to selected vaccines: a population based retrospective cohort study

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Aim/Objective: To estimate incidence rates (IRs) of health outcomes of interest (HOI) among 0-2 year-old children exposed to vaccines of interests in China.

Methods: This retrospective cohort study used a population-based electronic health record (EHR) database in Yinzhou district of Ningbo, China. Children of 0-2 years old receiving at least one dose of oral poliomyelitis vaccine (OPV), Diphtheria, Tetanus, Pertussis (DPT), Haemophilus influenzae type b vaccine (Hib), or PANTAXIM recorded in the EHR database between January 1, 2012 and March 31, 2017 were included in the study. Yinzhou EHR database consists of complete immunization records and healthcare data of all children from hospitals and community health centers in the district and from only children's hospital in Ningbo. Eight HOIs (i.e. anaphylaxis, febrile seizures, seizures, wheezing/asthma, apnea, Kawasaki disease, urticaria/angioedema, Guillain-Barré syndrome) were identified using the International classification of diseases, tenth revision (ICD-10) codes. IRs per 100,000 person-days at risk and per 100,000 doses and their 95% confidence intervals were calculated during the 0-7 days and 0-30 days post-vaccination.

Results: A total of 220,422 eligible children was identified. No case of apnea, Kawasaki disease, and Guillain-Barré syndrome was observed within 30 days post vaccination. During 0-7 days post-vaccination of the four vaccines of interest, the IRs of anaphylaxis, febrile seizures, seizures, urticaria/angioedema and wheezing/asthma ranged from 0 to 0.19, 0 to 0.72, 0.16 to 0.98, 2.06 to 3.73, and 5.90 to 9.64 per 100,000 person days, respectively; and 0 to 0.92, 0 to 1.84, 0.19 to 4.59, 1.87 to 42.27, and 0.56 to 17.46 per 100,000 doses, respectively.

Conclusion: IRs of some HOIs identified by ICD 10 codes in Yinzhou EHR were comparable with that in the literature while IRs of other HOIs were not due to differences in study designs and study populations. Future studies should consider medical chart review for validating HOIs.

110 Prescription patterns of antidiabetic medications during pregnancy in South Korea, 2006-2013

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Aim/Objective: Complications and their medications are important for pregnant women, but medication researches on pregnancy are lacking. We aimed to describe prescription patterns of antidiabetic medications during pregnancy in outpatients setting.

Methods: We conducted a drug utilization study using the Korean National Health Insurance Service database. Pregnant women were defined as those who experienced delivery between 2006 and 2013. Pregnancy period was defined as 273 days prior to the delivery date, where seven days prior to delivery were excluded from analysis. Trimesters were categorized as first (280-191 days prior to delivery) and second/third (190-8 days prior to delivery). Study drugs were all antidiabetic medications (ATC code A10), including recommended (human insulin, insulin lispro, etc.) and non-recommended medications (all oral antidiabetic medications: metformin, sulfonylurea, etc.) during pregnancy. Prescription patterns were analyzed by calendar year, maternal age and drug class. We conducted Mantel-Haenszel chi-square test to determine the statistical significance of trends in medication use.

Results: A total of 66,734 deliveries were identified among 49,570 women, in which, 292 deliveries (0.44%) were prescribed with antidiabetic medication(s). Antidiabetic medication use during pregnancy increased from 0.22% in 2006 to 0.73% in 2013 (p -value < 0.001). We observed an increase in prevalence of antidiabetic medication use with maternal age; 0.23% at < 29 years, 0.51% at 30-39 years and 1.30% at > 40 years (p -value < 0.001). Of all prescriptions in the first trimester, the most common were insulin (42.8%), metformin (27.2%) and sulfonylureas (14.5%), while that of in the second/third trimester were insulin (90.0%).

Conclusions: Prevalent users of antidiabetic medications in Korea (0.44%) was lower than that in the USA (3.24%) and Europe (2.0%). We observed that non-recommended medications were more commonly prescribed in the first trimester than in second/third, which warrants the necessity of rational drug use in early period of pregnancy.

111 Developmental outcomes at age four following maternal antiepileptic use

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Objective: Determine whether maternal use of antiepileptic drugs (AEDs) in pregnancy is associated with developmental delay in children.

Methods: Retrospective database linking cohort study using the Pharmaceutical Collection (all community dispensed medicines), the National Minimum Dataset (hospital events) and the Before School Check (B4SC; nationwide childhood development assessment) databases. Encrypted individual identifiers were used to link infants exposed to AEDs during pregnancy between 2008 and 2012 to the B4SC assessments between 2012 and 2016.

Results: Between 2012 and 2016, 89% of all New Zealand four-year-olds had a B4SC ($n=287,572$). Of those, 606 children had a mother who had been dispensed one or more AEDs during pregnancy. 159 infants (20.8%) whose mother had been dispensed an AED did not have a recorded B4SC—poorer coverage than rest of the population. After adjusting for socioeconomic deprivation, gender and ethnicity, exposure to AEDs was associated with increased odds of being referred for further assessment in at least one of the measured childhood development domains (OR 1.7; 95% confidence interval 1.4 to 2.1; $p<0.001$). An increased risk of two or more significant developmental concerns (RR 1.4; 1.02, 1.99, $p=0.037$) and an increased risk (RR 2.1; 1.6, 2.8; $p<0.001$) of having a high Strengths and Difficulties Questionnaire (SDQ) score (≥ 17 - indicating emotional or behavioural concerns). Individually, sodium valproate and lamotrigine were associated with an increased risk of high SDQ scores (sodium valproate RR 2.8; 1.8, 4.4; $p<0.001$; lamotrigine RR 2.3; 1.3, 4.2; $p=0.005$). Children whose mothers' had been dispensed sodium valproate were nearly three times more likely to already be under specialist paediatric care (RR 2.9; 1.7, 5.0; $p<0.001$).

Conclusion: Maternal use of AEDs is associated with an increased risk of referral for developmental concerns at age four. Maternal AED use was particularly associated with concerns about emotional or behavioural development.

112 Infant antibiotic use increases the risk of childhood asthma

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Objective: Early life antibiotic use disrupts the developing microbiome and influences the developing immune system and the risk for childhood asthma. It is important to understand whether timing, frequency, and class of antibiotics play a role in the development of childhood asthma.

Methods: We conducted a population-based cohort study of 152,622 term, non-low birthweight, and otherwise healthy infants born 1995-2003 who were enrolled in the Tennessee Medicaid Program. Detailed information about infant antibiotic administration was captured. Asthma status was ascertained using asthma specific healthcare encounters and medications at age 6 years. The association between frequency, timing, and class of infant antibiotics and childhood asthma was assessed using multivariable logistic regression models adjusting for a priori selected covariates.

Results: Among 152,622 enrolled infants, 79% (120,973) received at least one course of antibiotics during infancy. Fourteen percent (20,984) developed asthma by age 6 years. Compared with children who did not receive any antibiotics, children with at least one course in infancy were more likely to be male, Caucasian, with urban residence, have bronchiolitis healthcare encounters during infancy, and have mothers who smoked during pregnancy. There was a significant dose response relationship between infant antibiotic courses and childhood asthma. For each additional course of antibiotics administered, there was a 19% increased relative odds of having asthma (Adjusted odds ratio: 1.19, 95% confidence interval: 1.18, 1.20). When limited to children who received at least one course of antibiotics, there was no significant relationship between infant age at and class of antibiotics and the risk of childhood asthma.

Conclusion: Frequent antibiotic use during infancy is associated with increased risk of childhood asthma in a dose dependent manner. The effect of timing and class of antibiotic is limited. We need to next understand how to protect infants who require antibiotics from the effects predisposing to asthma.

113 Comparative effect of four antimalarial treatments on haematocrit in children in Southwest of Nigeria

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Aim: It is often difficult in treated patient to disentangle disease from effect of drugs. Anaemia in malaria has both central (dyserythropoiesis) and peripheral causes (phagocytosis of both infected and uninfected erythrocytes and haemolysis). The aim of this study was carried out to compare change in haematocrit following four antimalarial treatments among children of microscopically confirmed *Plasmodium falciparum* infection.

Method: Relevant data were extracted from 313 case record forms of children aged 3-119 months enrolled in antimalarial clinical trials in Southwest Nigeria between 1998 and 2014. Symptoms compatible with acute uncomplicated malaria, parasite density of at least 1000/ μ L and absence of chronic illness or danger signs of severe malaria were enrolment criteria. Change in haematocrit level from base line through the treatment period and 28 days post treatment were compared among children treated with Artemether-Lumefantrine (82), Chloroquine (34), Artovaquone-Proguanil (41) and Artesunate-Amodiaquine (156).

Results: There were 169 males and 144 females and overall median age of the patients was 25 months. The mean difference (95% CI) in haematocrit among children were 4.7% (95% CI = 3.6, 5.8), 2.4% (95% CI = 0.5, 4.4), 4.4% (95% CI = 2.7, 6.0), and 3.8% (95% CI = 3.0, 4.7) for Artemether-Lumefantrine, Chloroquine, Artovaquone-Proguanil and Artesunate-Amodiaquine, respectively. Using the general lineal model, repeated measure analysis showed that there were significant difference in the mean haematocrit level over the 28 day follow up among the four treatment groups ($p = 0.020$) even after adjusting for sex and age and there were no significant interactions between covariates and haematocrit.

Conclusion: All children experienced increase in haematocrit after treatment and the changes differ among antimalarials.

114 Thromboembolism, Bleeding, and Mortality among Patients with Atrial Fibrillation Treated with Dual Antiplatelet Therapy versus Oral Anticoagulants: A Population-Based Study

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Objective: Current guidelines recommend oral anticoagulation therapy (OAC) for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). However, many patients refuse or are deemed inappropriate for OAC in clinical practice. Dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel is considered as an alternative to OAC, but there are limited clinical data comparing these treatments. The objective of this study was to compare the effectiveness and safety outcomes of DAPT and OAC in clinical practice.

Methods: Cohort study using a population-wide database of Hong Kong Hospital Authority. New patients with NVAF during 2010-2014 and prescribed DAPT or OAC (warfarin or dabigatran) were followed until July 31, 2016. Outcomes were thromboembolism, bleeding, and death. Propensity score (PS) matching at 1:2 ratio was used to select DAPT users with similar characteristics to OAC users, analyzed using Poisson regression.

Results: Among 51,946 new patients with AF, 8,520 users of OAC and DAPT were identified. The likelihood of receiving DAPT over OAC increased with older age and previous intracranial hemorrhage. Among DAPT users, the incidences of thromboembolism, death, and bleeding per 100 patient-years were 15.8, 17.6, and 5.1 respectively. When compared to DAPT users, PS-matched analyses indicated a lower incidence of thromboembolism and/or death among OAC users (incidence rate ratio [IRR]=0.32, 95% confidence interval [CI]=0.19-0.55 for dabigatran and IRR=0.58, 95%CI=0.36-0.95 for warfarin), with no significant differences in bleeding events.

Conclusion: DAPT users were at markedly increased risk of thromboembolism and death compared to OAC users. These findings indicate the need for improved stroke risk reduction strategies among patients taking DAPT and the opportunities of using OAC in high-risk groups to prevent more events.

115 Implementation of a novel design in evaluating oral anti-coagulant effectiveness and safety: a prevalent new user design study

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Aim: Implementing the prevalent new user design proposed by Suissa in 2017 to evaluate dabigatran in Taiwan with warfarin as comparator.

Methods: National Health Insurance and mortality data for all 23.5 million residents from 2011 through 2015 were utilized. We created an incident non-valvular atrial fibrillation (AF) cohort and identified first dabigatran or warfarin prescriptions 30 days before or any time after the initial AF diagnosis. Dabigatran users comprised new users and switchers (from warfarin). Time and prescription-based exposure sets were developed to account for warfarin use before dabigatran initiation. Prescription, rather than individual patient, was the unique unit in the exposure sets. With one dabigatran prescription and one or more warfarin prescriptions in each exposure set, the sets were constructed in 6-month calendar blocks according to dabigatran new use or switching status and initiating date. A comparable warfarin prescription for the dabigatran prescription in each set was identified with propensity score matching, and the corresponding warfarin and dabigatran users were included for the final analyses. Outcomes of interest included intracranial hemorrhage, gastrointestinal bleeding, ischemic stroke and all-cause mortality. Cox proportional hazards models were used to estimate hazard ratios (HR).

Results: Prescriptions of 11,404 dabigatran initiators (23 % were switchers) and 21,495 warfarin users were included in exposure sets. Median follow-up duration was 0.9 year. Decreased risks of intracranial hemorrhage (HR: 0.5; 95% confidence interval [CI]: 0.39, 0.65) and all-cause mortality (HR: 0.58; 95% CI: 0.54, 0.63) were found among dabigatran users. No increased risk of gastrointestinal bleeding and similar stroke prevention effect were observed for dabigatran. No effect modification was observed between dabigatran new users and switchers.

Conclusion: In a population-based study with a design that accounted for prior drug use of the same class among users of a new drug, we found that dabigatran was associated with a lower risk of bleeding than warfarin among incident AF patients.

116 Prevalence, safety and effectiveness of oral anticoagulant use in people with and without dementia: a systematic review and meta-analysis

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Background: Differences in management and outcomes of oral anticoagulant (OAC) use may exist for people with and without dementia or cognitive impairment (CI).

Objective: To systematically review the prevalence and safety and effectiveness outcomes of OAC use in people with and without dementia or CI.

Methods: MEDLINE, EMBASE and CINAHL were searched for studies reporting prevalence or safety and effectiveness outcomes of OAC use for people with and without dementia, published between 2000 to September 2017. Study selection, data extraction and quality assessment were performed by two-reviewers.

Results: 27 studies met pre-specified inclusion criteria (21 prevalence studies, six outcomes studies). People with dementia had 52% lower odds of receiving OAC compared to people without dementia. Mean OAC prevalence was 32% for people with dementia, compared to 48% without dementia. There was no difference in the composite outcome of embolic events, myocardial infarction, and all-cause death between dementia and non-dementia groups (adjusted hazard ratio (HR) 0.72, 95% CI, 0.45-1.14, $p=0.155$). Bleeding rate was lower for people without dementia (HR 0.56, 95% CI, 0.37-0.85). Adverse warfarin events were more common for residents of long-term care with dementia (adjusted incidence rate ratio 1.48, 95% CI, 1.20-1.82). Community-dwelling people with dementia treated with warfarin had poorer anticoagulation control than those without dementia (mean time in therapeutic range (TTR) % \pm SD, 38 \pm 26 (dementia), 61 \pm 27 (no dementia), $p<0.0001$).

Conclusion: A lower proportion of people with dementia received oral anticoagulation compared with people without dementia. People with dementia had higher bleeding risk and poorer anticoagulation control when treated with warfarin.

117 Renal function change during bisphosphonate use in patients with chronic kidney disease

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Objectives: Oral bisphosphonates (BP) are contraindicated in patients with moderate-severe chronic kidney disease (CKD) partly due to concerns regarding their effects on renal function. The aim of this study was to assess the effect of BP use on CKD stage worsening and annual changes in estimated glomerular filtration rate (eGFR) over time.

Methods: Patients aged 40+ with an eGFR<45 in UK primary care (CPRD) linked to hospital records. Followed for up to 10 years. BP users censored 210 days after the last BP prescription. Unexposed patients could become exposed; 10-year follow up re-started. Users were matched to up to 5 non-users using propensity scores (PS), stratified by the number of years of follow-up. Cox regression was used to estimate the hazard ratio (HR) of stage worsening. The rates of annual eGFR changes were estimated by the slopes of a mixed effect model with cubic splines and an interaction between BP use and time.

Results: 31275 patients (6309 BP users) were included in the PS matched analyses. 3,978 (13%) patients moved to a later stage. The HR for BP users was 1.69 (95% confidence interval (CI): 1.58, 1.80). Annual eGFR changes were different for BP users and non-users, BP users had, on average, a lower eGFR for the first 7 years than non users. In the first three years, the mean eGFR increased at the rate of 2.58 (2.50, 2.66) and 0.91 (0.65, 1.17) mL/min/1.73 m² per year for non-users and users, respectively. They were followed by slow decline slopes of -0.80 (-0.89, -0.70) and -0.24 (-0.55, 0.08) per year. No significant difference in mean eGFR after 8 years.

Conclusion: BP use has a 70% higher likelihood of worsening in CKD stages. Further research is needed to understand the longitudinal changes in eGFR trajectories.

118 Trends and predictors of oral anticoagulant use in people with dementia and the general population of older adults in Australia

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Aim/Objective: People with dementia have lower rates of warfarin use for stroke prevention than people without dementia but no studies have reported rates of direct oral anticoagulant (DOAC) use. We investigated the incidence and prevalence of warfarin and DOAC use, and determined predictors for initiating DOACs and warfarin in people with dementia.

Methods: Data for up to 356,000 people aged ≥65 years from the Australian Pharmaceutical Benefits Scheme were analysed. The annual incidence and prevalence of warfarin and DOAC use from July 2013 to June 2017 were estimated using Poisson regression. Predictors of DOAC versus warfarin initiation were estimated using logistic regression. Stratified analyses were performed for the cohorts of people with dementia and the general population.

Results: The overall prevalence of oral anticoagulant use increased from 8% to 12% in people with dementia and 9% to 12% in the general population from 2013 to 2017. DOAC prevalence increased and warfarin prevalence decreased in each cohort. Warfarin incidence decreased by 40-60% in each cohort. DOAC incidence decreased during the first year but increased thereafter in each cohort. People aged ≥85 years had 20% lower odds of initiating DOACs in the general population and 35% higher odds of initiating DOACs in the dementia cohort than those aged 65-74 years. Women had 8% increased odds of initiating DOACs in the general population and 39% lower odds of initiating DOACs in the dementia cohort. Pain/inflammation and arrhythmias predicted DOAC initiation in each cohort. Cardiovascular diseases, gastric acid disorder, diabetes and end-stage renal disease were associated with lower odds of DOAC initiation in the general population.

Conclusion: There was a higher prevalence of anticoagulant use among people with dementia in 2016-2017 than in previous years. Clinicians were more likely to initiate DOACs than warfarin for people with dementia, particularly among those aged ≥85 years.

119 Use of falls risk medications in people at high and low falls risk in aged care services

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Aim/Objective: To explore the association between the risk of falling and the use of falls risk increasing drugs (FRIDs) in residents of aged care services.

Methods: A total of 383 residents from six aged care services in South Australia were included. Residents were categorised as being at low or high falls risk according to a modified validated algorithm. FRIDs comprised psychotropic medications and medications that can cause or worsen orthostatic hypotension. Inverse probability weighted multinomial logistic regression was used to estimate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the risk of falls and regular use of FRIDs. Covariates included age, sex, activities of daily living, frailty status, number of regular medications, comorbidities and nutritional status.

Results: The most prevalent regular FRIDs were antidepressants (48%), diuretics (43%) and renin-angiotensin system inhibitors (43%). In comparison, the prevalence of antipsychotics (9%) and sedative-hypnotics (14%) was low. The overall prevalence of psychotropic medications and medications that can cause or worsen orthostatic hypotension was similar in residents at high and low falls risk. However, residents at high falls risk had 1.75 times higher adjusted odds (95% CI 1.17-2.61) of using two or more psychotropic medications and 3.59 times higher adjusted odds (95% CI 2.27-5.69) of using two or more medications that can cause or worsen orthostatic hypotension.

Conclusion: Residents at high and low falls risk had a similar prevalence of FRIDs. While residents at high falls risk had a higher adjusted odds of using two or more FRIDs from each category, this was mainly attributable to antidepressant, cardiovascular and analgesic medications for which there were documented clinical indications. Clinicians appeared to have largely avoided psychotropic FRIDs that explicit criteria deem potentially inappropriate for residents at high falls risk.

120 Knowledge, attitudes and practices towards generic substitution: a cross-sectional study among endocrinologists in China

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Objectives: To evaluate the knowledge, attitudes and practices (KAP) of endocrinologists in China on the use of generics.

Methods: A cross-sectional nationwide online survey targeting endocrinologists from tertiary medical institutions in China was conducted. The survey was conducted using KAP questionnaire having (i) demographic data of the physicians, (ii) their knowledge about generic and originator, (iii) physicians' attitudes towards quality, safety and efficacy of generic medicines as well as generic substitution, (iv) prescribing behavior and concerns about issues prescribing generics. Descriptive statistical analysis and ordered logistic regression analysis were applied to identify risk factors associated with frequency of generic prescription.

Results: A total of 191 questionnaires out of 1500 were received, giving a final response rate of 14.6%. Of the respondents, 111 (58.1%) were female and 149 (78%) were postgraduate degree. The majority of the participants was in the age range of less than 50 years and comprised 72.3% of the respondents. Although more than half of the physicians had better generic-related knowledge, 70.2% believed that the quality of originator medicines is better than that of the generics as well as 65% had doubts about efficacy of generic medicines and 35.1% had doubts about their safety. Only 25.1% agreed with generic substitution. Of the respondents, 9.4% agreed that they 'always' write their prescriptions using originator product name whereas 57.6% do it 'usually'. Ordered logistic regression analysis identified age, concerns about the quality of the generics and cost of patient, and physicians' prescription experiences as independent risk factors for generic prescription frequency ($P < 0.05$).

Conclusions: The majority of the endocrinologists from tertiary medical institutions in China had negative perceptions about quality and the efficacy of generic medicines. This highlights the need for focused educational intervention and regulation prescribing behavior.

121 Treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?

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Aim: To determine the patterns and predictors of treatment initiation for type 2 diabetes mellitus (T2DM) in Australia, and whether treatment initiation is consistent with current clinical practice guidelines that recommend metformin monotherapy.

Methods: Individuals aged 18-99 years initiating medications for T2DM between July 2013 and November 2017 were identified from the 10% random sample of Pharmaceutical Benefits Scheme data. Individuals initiating insulin were excluded. Predictors included age, sex, year of initiation and comorbidities. Multinomial logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the predictors of initiating non-metformin monotherapy and combination therapy compared to metformin monotherapy.

Results: Of 62,976 people initiating T2DM medications, 54.8% were women and the mean age was 53.5 years. Overall, 87.8% initiated metformin monotherapy, 5.4% initiated non-metformin monotherapy and 6.7% initiated combination therapy. Of these, 54.5% initiated fixed-dose combinations. Age ≥ 80 versus < 30 years was associated with initiating non-metformin monotherapy (OR 11.0; 95%CI 8.68-14.0) and combination therapy (OR 3.58; 95%CI 2.88-4.46) compared to metformin monotherapy. Women were less likely to initiate non-metformin monotherapy (OR 0.81; 95%CI 0.75-0.87) and combination therapy (OR 0.56; 95%CI 0.52-0.60). Initiation on non-metformin compared to metformin monotherapy decreased over time. Congestive heart failure (OR 1.52; 95%CI 1.35-1.71) and cerebrovascular disease (OR 1.37; 95%CI 1.19-1.59) were associated with greater odds of initiating combination therapy. Increasing number of comorbidities up to five was associated with lower odds of initiating non-metformin monotherapy, while eight or more comorbidities was associated with higher odds. An increase in number of comorbidities was associated with lower odds of initiating combination therapy.

Conclusion: Less than 7% of individuals initiated treatment with ≥ 2 medications, suggesting treatment initiation is largely consistent with current clinical practice guidelines. Combination therapy was more common in individuals who were older, male and who had up to one comorbidity only.

122 Impact of a clinical pharmacist-led post-hospitalization care on clinical and humanistic outcomes among acute coronary syndrome patients: Randomized controlled study

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Objective: To assess the impact of clinical pharmacist-led post-hospitalization care on clinical outcomes, health related quality of life (HRQoL), medication adherence, and knowledge among patients with acute coronary syndrome (ACS).

Methods: A prospective randomized single blind parallel group study was conducted in Department of Cardiology of a tertiary care hospital over a period of one year. Patients diagnosed with ACS were included in the study during their discharge. After assessing the baseline HRQoL and knowledge about ACS, all patients were randomized into interventional and control groups by block randomization method. Interventional group were provided with patient information leaflets and followed over phone after 48 hours of discharge, on 7th and 15th day. On 30th (± 2) and 60th (± 2) day of discharge, home visits were made for medication reconciliation and for assessment of HRQoL, knowledge and medication adherence. Control patients were followed during out-patient department visits for all the assessments.

Results: Out of 384 ACS patients assessed for eligibility, 58 patients met the inclusion criteria and were randomized into interventional group (n=26) and control group (n=32). Two patients in each group re-admitted in coronary care unit due to ACS related problems, within a short period in control group compared to interventional group. Knowledge on ACS among the interventional group has been increased more significantly (p=0.001) than control group (p=0.01). There was a non-significant increase in HRQoL of patients in interventional group (5.14 to 5.42). Medication adherence was increased over period of time in interventional group.

Conclusion: Post-discharge follow-up by clinical pharmacist has been increased knowledge, HRQoL and medication adherence among patients with ACS.

123 Polypharmacy and risk factors in patients with myocardial infarction or stroke

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Aims: Polypharmacy is common in patients with cardiovascular disease (CVD), but data are limited on its patterns and potential risk factors. This study investigated the patterns of CV polypharmacy and assessed associated risk factors in patients with myocardial infarction (MI) or stroke.

Methods: This was a cross-sectional study conducted in 104,773 patients with the first diagnosis of CVD (54,078 patients with MI or angina, 50,695 patients with stroke or transient ischaemic attack (TIA)) aged ≥ 45 years in The Health Improvement Network (THIN) database from 2007 to 2016. The patterns (number and class) of CV polypharmacy were investigated based on the initial CV pharmacotherapy which was identified according to the CV drugs issued during 90 days after the first CVD. Patients who received at least one CV drug were included in the study. Multivariable logistic regression was used to assess the association of CV polypharmacy with the patient characteristics, CV risk factors and comorbidities.

Results: The mean age of the patients was 69.8 ± 11.8 years. The mean number of CV drugs was 3.69 (4.39 in MI/angina patients and 2.95 in stroke/TIA patients) with a range of 1-13. The proportion of patients who have 1-2, 3-4 and ≥ 5 drugs were 28.9%, 36.9% and 34.2%, respectively. The most commonly prescribed drugs were aspirin (55.5%), simvastatin (44.5%), clopidogrel (39.6%), bisoprolol (39.6%), ramipril (30.5%) and atorvastatin (27.2%). Gender (female: OR 0.72, 95%CI 0.70-0.74 vs. male), smoking status (current smoking: 1.29, 1.25-1.34 vs. never), body mass index (BMI) (obesity: 1.52, 1.47-1.59, overweight: 1.24, 1.20-1.29 vs. normal) and Charlson comorbidity index (index 5: 1.36, 1.22-1.50 vs index 0) were independently associated with polypharmacy (≥ 5 drugs).

Conclusion: The main factors associated with CV polypharmacy are gender, smoking status, BMI and multimorbidity.

124 Trends in hospitalised adverse drug events in New South Wales, Australia

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Aims: To examine trends in hospitalised adverse drug events (ADE) in New South Wales (NSW).

Methods: We extracted data from the NSW Admitted Patient Data Collection, a census of hospital separations. We estimated age-standardised rates of ADE-related hospitalisation between 2001 and 2014, and rates by patient characteristics, main therapeutic medication groups, and clinical condition groups that warranted the hospitalisation. We used the percent change annualised estimator to evaluate trends over time.

Results: A total of 315,274 ADE-related hospitalisations for acute care were identified. The age-standardised rates of ADE-related hospitalisations nearly doubled and increased by 6% (95%CI: 5-7%) per annum, with in-hospital death rate increase of 2%. Participants aged between 65 and 84 years accounted for nearly half of ADE-hospitalisations (46%), with age-adjusted rate increasing from 104 in 2001-02 to 189 per 100,000 NSW residents in 2013-14. Anticoagulants (14%) were the most common medications contributing to ADE-related hospitalisation, followed by opioid analgesics (10%).

Conclusions: ADE-related hospitalisation remains a population health burden with significant increase over time. The findings call for continuing efforts to prevent ADEs, especially among high risk populations such as older people.

125 Characteristics of post-marketing observational studies in China: 2013-2018

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Objective: Characterize post-marketing observational studies registered in the Registry and Publicity Platform of Drug Clinical Trials from 2013 to 2018. The Platform was established by Center for Drug Evaluation, National Drug Administration of China (CNDA) in 2013 to help assure the information regarding clinical trial conduct is public and transparent.

Methods: The Platform was searched using 'observational studies', 'non-interventional studies', 'post-marketing', 'real-world' or 'epidemiology' and only kept one record if duplicated records were identified. Descriptive analyses were performed for the records from January 2013-4 June 2018.

Results: A total of 8478 studies were registered on the Platform until June 2018. The majority were early phase trials and only 50 (0.58%) post-marketing observational studies were identified, including nine studies in 2013, nine in 2014, 14 in 2015, eight in 2016, five in 2017 and five in 2018. Of the 50 studies, 39 were ongoing, ten completed and one on hold as of 4 June 2018. All were prospective design with primary data collection. The most common therapeutic area is oncology (N=11, 22.0%), followed by cardiovascular disease (N=5, 10%) and infectious diseases (N=5, 10%). Both safety and effectiveness were mentioned in study titles for 14 studies (28.0%), safety only for seven studies (14.0%), effectiveness only for two studies (4.0%), and neither safety nor effectiveness for 27 studies (54.0%). Of the 27 studies with title not mentioning either safety or effectiveness, observational study design was mentioned in five studies, post-marketing in eight studies. No information is available regarding study objective, sample size, follow-up period, comparators, and interim or final results.

Conclusions: The proportion of post-marketing observational studies registered on the Platform was very low with only limited information available to the public. All were prospective study design with primary data collection. It will help to improve the transparency of post-marketing observational studies if more study characteristics were recorded and made publicly available.

126 VALIDATE-J: a validation study of rheumatoid arthritis in Japanese claims data

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Background: Claims database research is new in Japan and few validation studies have been conducted. The validity of claims algorithms for rheumatoid arthritis (RA) is unknown in Japanese claims data.

Objectives: To provide initial results from VALIDATE-J: Validity of Algorithms in Large Databases: Infectious Diseases, Rheumatoid Arthritis and Tumor Evaluation in Japan.

Methods: US and Japanese investigators designed a multi-phased, multi-hospital, validation study of claims data for RA from 2 community teaching hospitals. Claims definitions were developed by the study team including Japanese rheumatologists: 1) >1 RA diagnosis (including suspect diagnosis) plus DMARDs or steroid within 1 month of diagnosis and 2) same as 1) but excluding suspect diagnosis. The gold standard was defined as physician diagnosis of RA in medical records. Trained chart abstractors collected information from medical records using a standardized form developed by study team. Positive predictive value (PPV) was calculated using the aforementioned gold standard.

Results: Negotiations and contracting required >1 year at 1 hospital and are ongoing in another. In one hospital, the claims-based algorithm identified 2247 cases using hospital claims data from 2012-2016. Among 2247 cases, 68% were female and mean age was 62 years. Using physician diagnosis of RA as the gold standard, based on abstracted information from 30 randomly sampled cases, PPV=75% (95% confidence interval (CI): 64.5%- 83.2%). In a subset excluding cases identified by 'suspect diagnosis of RA' in claims algorithm (n=68), PPV=86.7% (95% CI: 76.7%-92.9%). Among abstracted variables related to guideline-based criteria for RA, missing rates were 3.7% for CRP, 12.5% for disease duration, and 22.5% for serology.

Conclusions: The performance of a claims-based algorithm for RA had similar PPV to that reported in the US. As the Japan Pharmaceuticals and Medical Device Agency recently started encouraging validation studies to support the validity of database research, VALIDATE-J may set the standard.

127 Diagnosis- and external cause-based criteria to identify adverse drug reactions in hospital ICD-coded data

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Background: External-cause ICD codes are used commonly to ascertain adverse drug reaction (ADR) related hospitalisation. We quantified ascertainment of ADR-related hospitalisation using external-cause codes and additional ICD-based hospital diagnosis codes.

Methods: We reviewed the scientific literature to identify different ICD-based criteria for ADR-related hospitalisations, developed algorithms to capture ADRs based on candidate hospital ICD diagnoses and external-cause codes and incorporated previously published causality ratings estimating the probability that a specific diagnosis was ADR-related. We applied the algorithms to the NSW Admitted Patient Data Collection records of 45 and Up Study participants (2011-13).

Results: Of 493,442 hospitalisations among 267,153 study participants during 2011-13, 18.8% (n=92,953) had hospital diagnosis codes that were potentially ADR-related; 1.1% (n=5,305) had high/very high probability ADR-related diagnosis codes (causality ratings: A1 and A2); and 2.0% (n=10,039) had ADR-related external-cause codes. Overall, 2.2% (n=11,082) of cases were classified as including an ADR based hospitalisation on either external-cause codes or high/very high probability ADR-related diagnosis codes. Hence, adding high/very high probability ADR-related hospitalisation codes to standard external-cause codes alone increased the number of hospitalisations classified as having an ADR-related diagnosis by 10.4%. Only 6.7% of cases with high/very high probability ADR-related mental symptoms were captured by external-cause codes.

Conclusion: Selective use of high probability ADR-related hospital diagnosis codes in addition to external-cause codes yielded a modest increase in ADR detection, of potential clinical significance. Validated combinations of diagnosis codes could potentially further enhance capture.

128 Accuracy of molecular diagnostic tests for the detection of drug-resistant tuberculosis in China: a systematic review and meta-analysis

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Objective: This systematic review aimed to evaluate the accuracy of molecular diagnostics for the detection of resistance to first-line and second-line anti-tuberculosis (TB) drugs in Chinese patients.

Methods: Three English databases (EMBASE, PUBMED and the Cochrane Library) and four Chinese databases (CNKI, SinoMed, WanFang and VIP) were searched for eligible studies evaluating the accuracy of molecular diagnostic tests against drug susceptibility testing (DST). Two researchers independently screened literature according to the inclusion and exclusion criteria, extracted data and assessed study quality with QUADAS-2. Bivariate random-effects meta-analysis was conducted to pool the sensitivity and specificity by index test and drug resistance type with stata 14.0 and RevMan 5.2 software.

Results: This systematic review evaluated four TB molecular tests endorsed in China: Xpert assay, Line Probe assay, Genechip assay and MeltPro TB assay. A total of 71 articles were included, involving 159 studies. Comparing to DST reference standard, Xpert assay performed well in detecting rifampicin resistance, with the pooled sensitivity and specificity of 92% (89%, 94%) and 98% (97%, 99%), respectively. Line Probe assay was also an accurate method for rifampicin resistance detection with the pooled sensitivity of 91% (88%, 93%) and specificity of 98% (97%, 99%), but not for isoniazid and second-line drugs duo to lower sensitivity (less than 80%). The pooled sensitivities of Genechip for rifampicin, isoniazid and multi-drug resistance were 89% (85%, 91%), 79% (75%, 82%) and 79% (73%, 84%), respectively, and the pooled specificities were all more than 97%. Similarly, MeltPro TB assay had good sensitivity and specificity for first-line drugs resistance, varying from 87%-89% and 97%-98%, respectively, compared with that for second-line drugs (less than 80%).

Conclusions: These four molecular diagnostics are credible methods for rifampicin resistance detection with high overall accuracy, but they may not be an appropriate choice for other anti-TB drugs duo to low sensitivity.

129 Dipeptidyl peptidase-4 inhibitors and risk of inflammatory bowel disease among patients with T2D: a meta-analysis of randomized controlled trials

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Objective: Recent evidence suggests a possible association between dipeptidyl peptidase-4 inhibitor (DPP-4i) use and increased risk of inflammatory bowel disease (IBD). However, current evidence is inconclusive. This study aimed to evaluate the association between DPP-4i use and risk of IBD by performing a meta-analysis of all available randomized controlled trials (RCTs).

Methods: This meta-analysis is registered with PROSPERO (CRD number 42018095206). Eligible RCTs were identified by systematically searching electronic databases (PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov) from inception to April 28, 2018. The primary IBD outcome, which included Crohn's disease and ulcerative colitis, was identified using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0); unspecified colitis events were excluded. A Peto odds ratio (OR) with 95% confidence interval (CI) was used to calculate the pooled estimates.

Results: Of the 4,669 records retrieved from electronic databases, a total of 6 eligible RCTs, involving 41,509 patients and 9 IBD events, were included. The mean follow-up duration was 1.52 years. Overall, use of DPP-4i was not significantly associated with increased risk of IBD compared to control drugs (0.24% vs 0.19%; OR 1.15, 95% CI 0.31 to 4.29). Furthermore, subgroup analyses showed that DPP-4i were not significantly associated with an increased risk of IBD compared to placebo (involving 5 RCTs, OR 1.52, 95% CI 0.38 to 6.13). Moreover, our results were stable in terms of IBD risk when performing the sensitivity analysis by using the numbers of person-years (OR 1.01, 95% CI 0.30 to 3.44).

Conclusion: Our study did not support a significantly increased risk of IBD associated with DPP-4i use. However, the power of our study to evaluate the association was limited by the very low reported rates of IBD in RCTs. Population-based prospective studies and post-marketing surveillance are warranted to further investigate the IBD risk associated with DPP-4i.

130 Prescribing trend of pioglitazone after safety warning release in South Korea: a population-based interrupted time series study

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Aim: On June 10th, 2011, South Korea's Ministry of Food and Drug Safety issued a safety warning on pioglitazone and its risk of bladder cancer. The objective was to quantify the prevalence of pioglitazone users before and after the safety warning and evaluate the intervention's effects.

Methods: To estimate the proportion of pioglitazone and other antidiabetic drug users by using an interrupted time series design between 2008 and 2015 in South Korea, the National Health Insurance Service-National Sample Cohort database was used. Study drugs were pioglitazone and other antidiabetic drugs (rosiglitazone, sulfonylurea+metformin, DPP-4 inhibitors+GLP-1 analogues, and insulin analogues). Relative and absolute change in drug users were calculated with 95% confidence intervals (CI). To estimate the intervention's impact, monthly number of drug users among diabetic patients were presented by applying maximum likelihood estimation. Segmented regression was done to evaluate the effect of the intervention. The assumption of autocorrelation was assessed using Durbin-Watson (DW) statistics and seasonality was assessed using the Dickey-Fuller (DF) unit root test.

Results: There were in total, 82,459 diabetic patients and amongst them, 12,921 were pioglitazone users (15.67%). The relative change of pioglitazone was -12.44% (95% CI: -12.86%, -12.04%) and its absolute change was -1.67% (95% CI: -2.03%, -1.31%). The safety warning was associated with an immediate 2.63 decrease of pioglitazone users per 1,000 diabetic patients ($p \geq 0.05$). For pioglitazone's "Time" trend, only positive autocorrelation was present ($p > DW: 0.9994$), whereas seasonality was not (DF: $p < 0.05$). If the intervention had not been implemented, pioglitazone users would have shown a continuous increasing trend, reaching a proportion of 140 per 1,000 diabetic patients (double than that of observed).

Conclusion: The pioglitazone safety warning led to a moderate decrease in pioglitazone users. Despite the decrease, pioglitazone is still widely prescribed to diabetic patients, stressing the need to develop strategies to enhance drug safety.

131 Impact of incretin-based therapies on neurological manifestation among type 2 diabetes: a systematic review and network meta-analysis

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Background: As a new class of antidiabetic drugs, incretin-based therapies, including dipeptidyl peptidase-4 inhibitors (DPP-4i) and Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have led to concerns about symptoms which may lead to withdraw in patients with type 2 diabetes (T2DM), such as dizziness and headache.

Objective: To systematically evaluate the effect of incretin-based therapies on dizziness and headache in patients with T2DM.

Methods: Medline, Embase, the Cochrane library and clinical trial were searched from inception through June 23rd, 2017 to identify randomized clinical trials (RCTs) assessed the safety of DPP-4i or GLP-1 RAs versus placebo or other anti-diabetic drugs in T2DM. Network meta-analysis within a frequentist framework was performed to calculate odds ratios (ORs) for the incidence of dizziness and headache.

Results: 232 trials with 9 treatments and 146,195 patients were included, including 2 incretin-based therapies, placebo and 6 traditional anti-diabetic drugs (Metformin, Insulin, Sulfonylurea, Thiazolidinediones, alpha-Glucosidase inhibitor and Sodium-Glucose co-Transporter 2). Compared with insulin, thiazolidinediones and placebo, GLP-1 RAs significantly increased the incidence of dizziness (ranges of ORs: 1.40-1.92) and headache (ranges of ORs: 1.18-1.41). Meanwhile, compared with insulin, DPP-4i increased the risk of headache (OR: 1.22, 95%CI: 1.02-1.46) and dizziness (OR: 1.46, 95%CI: 1.05-2.03). DPP-4i seemed to have a lower risk of dizziness than GLP-1 RAs (OR: 0.76, 95%CI: 0.67-0.87). Ranking probability analysis indicated that GLP-1 RAs decreased the risk of dizziness and headache less among all 9 treatments with probability of 22.5% and 23.4%, while DPP-4i was 46.2% and 45.0%.

Conclusions: Incretin-based therapies seemed to be associated with increasing risk of dizziness and headache compared with insulin, thiazolidinediones and placebo.

132 Partner bereavement and risk of psoriasis: population-based cohort study in the United Kingdom

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Aim/Objective: Stress is commonly reported as important in the aetiology of psoriasis. However, epidemiological evidence is limited due to small sample sizes and difficulty measuring stress and recalling negative life events. We investigated the association between partner bereavement (an extreme life stressor) and psoriasis.

Methods: We conducted a matched cohort study using routinely collected healthcare data from the United Kingdom Clinical Practice Research Datalink and linked Hospital Episode Statistics. We identified couples in the same household of the opposite sex, with an age gap of ≤ 10 years and with no younger adults in the same household aged within 15 years of either of the couple. We excluded couples where both partners were < 40 years or ≥ 95 years, where any partner had a code indicating residence in a communal establishment, or households with > 10 members. Among eligible couples, up to 10 non-bereaved subjects were randomly matched by age, sex and general practice to each bereaved subject. We used stratified Cox regression to compute hazard ratios (HR) for first diagnosis of psoriasis during follow-up. We examined the association by time since bereavement (0–30 days, 0–90 days, 0–365 days, 0–1095 days) and plan to adjust for confounders.

Results: We included 167,292 bereaved subjects and 1,520,346 matched non-bereaved subjects. Their median age at cohort entry was 74 years and 66% were women. We found no evidence of association between partner bereavement and psoriasis (HR:1.01;95%CI:0.96–1.06) during the entire follow-up. Similarly, no statistically significant increase in relative risk of psoriasis was observed within 0–30 days (HR:1.03;95%CI:0.70–1.53), 0–90 days (HR:1.17;95%CI:0.94–1.45), 0–365 days (HR:1.06;95%CI:0.94–1.19), or 0–1095 days (HR:1.04;95%CI:0.97–1.12) after partner bereavement.

Conclusion: These preliminary findings did not support an association between partner bereavement and psoriasis. Further investigations including adjustment for lifestyle factors and exploring the effects of unforeseen partner death are planned.

133 Combined use of antidepressants or non-steroidal anti-inflammatory drugs and the risk of intracranial haemorrhage: a nationwide cohort study

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Aim/Objective: To define the risk of intracranial haemorrhage among users of 1) nonsteroidal anti-inflammatory drugs (NSAIDs) only, 2) antidepressants only, and 3) antidepressants and NSAIDs (antidepressants+NSAIDs).

Methods: We conducted a population-based cohort study of patients prescribed with either antidepressants or NSAIDs between January 2002 and December 2015 using data from the Korean National Health Insurance Service-National Sample Cohort database. Patients with first prescription of either antidepressants or NSAIDs (index date) between January 2003 and December 2015, were identified, where they had no history of receiving a prescription for either NSAID or antidepressant in the preceding year. Patients who had been diagnosed as having cerebrovascular diseases within a year before the index date were excluded. Outcome was defined as the time to first diagnosis with intracranial haemorrhage (ICD-10: I60-I62) after drug use. Multivariate Cox proportional hazards regression model was used to compare the risk of intracranial haemorrhage among users of 1) NSAIDs only, 2) antidepressants only, and 3) antidepressants+NSAIDs, by calculating hazard ratios (HR) and its 95% confidence interval (CI), where death was treated as a competing risk.

Results: The cohort was comprised of 642,881 study subjects, of which 638,791, 1,296 and 2,794 were users of NSAIDs only, antidepressants only, and antidepressants+NSAIDs, respectively. The incidence rate of intracranial haemorrhage per 1,000 person years were as follows: 0.71, 0.66, 2.11 for users of NSAIDs only, antidepressants only, and antidepressants+NSAIDs, respectively. The risk of intracranial haemorrhage during the entire study period was highest for antidepressants+NSAIDs users (adjusted HR 1.59, 95% CI: 1.23-2.06) with users of NSAIDs set as the reference group.

Conclusion: Combined use of antidepressants+NSAIDs, was associated with an increased risk of intracranial haemorrhage compared to use of NSAIDs alone.

134 Modelling the risks and benefits of antipsychotics in schizophrenia: Application of a novel regression-based risk-benefit approach

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Aim: Our aim was to apply a novel regression-based algorithm to understand the risk-benefit of antipsychotic (AP) drugs in the treatment of schizophrenia.

Methods: Patient data was sourced from the national prescription and hospitalization collections (2005-2016) maintained by the New Zealand Ministry of Health. The first date of first hospitalization for schizophrenia was defined as the index-date. Prescriptions dispensed and subsequent hospitalizations 1-90 days after the index date were captured. The benefit (B) of AP was modelled as the risk of re-hospitalization for schizophrenia “without” exposure. The risk (R) of AP was modelled as the risk of AP-related ADRs including myocarditis, neutropenia, neuroleptic malignant syndrome, dystonia, secondary parkinsonism, and incident diabetes “when exposed”. Risks were expressed as probability ratios, and the risk-benefit score (RBS) was calculated as the $\log(B/R)$. Probabilities required were calculated by multinomial logistic modelling, and the 95% confidence interval of RBS was derived using delta method.

Results: The combined use of clozapine and second-generation antipsychotics (SGA) had a favourable risk-benefit score (RBS = 12.23 [11.58-12.88]), and the increased probability of schizophrenia-related readmission without exposure largely exceeded the increased probability of experiencing any ADR when exposed. The combined use of all three APs, clozapine, first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA), also had a favourable risk-benefit score (RBS = 7.15 [6.06-8.24]). Combinations of SGA and FGA without clozapine, or combined use of clozapine and FGA, were all marginally ineffective, with a negative but close to zero RBS.

Conclusion: The observation that the combined use of clozapine and SGA has the highest effectiveness is congruent to real-world findings. This simple algorithm of risk-benefit evaluation has the potential for the development of a decision-making software to assist clinicians to optimize medication safety and improve post-marketing surveillance.

135 Incidence of all-cause, sudden death, and cardiovascular mortality among antipsychotic-treated patients with schizophrenia in Taiwan

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Aim/Objective: To assess and compare mortality rates for all-cause mortality, sudden death, and cardiovascular death among antipsychotic-treated patients with schizophrenia in Taiwan.

Methods: A retrospective cohort study design was used to assess the risk of mortality among antipsychotic-treated patients with schizophrenia. The study population was identified from the linkage of the Taiwan National Health Insurance (NHI) claims and National Register of Death databases from 2001–2015. Patients were hierarchically assigned to antipsychotic exposure monotherapy groups (new users of one month long acting injection [LAI] paliperidone palmitate (PP1M), other atypical LAIs [risperidone LAI], typical LAIs, atypical oral, and typical oral) or polypharmacy.

Results: After study inclusion and exclusion criteria were applied, a total of 68,354 antipsychotic-treated patients with schizophrenia were analyzed. There were 600 (0.87%) new users of PP1M monotherapy, 4,612 (6.75%) atypical LAI monotherapy, 8,753 (12.81%) typical LAI monotherapy, 44,654 (65.33%) atypical oral monotherapy, 9,546 (13.97%) typical oral monotherapy, 93 (0.14%) polypharmacy with any LAI, and 96 (0.14%) polypharmacy without any LAI patients. In time on drug analyses, overall all-cause mortality was 20.28 deaths per 1,000 population, sudden death was 2.76 per 1,000 population, and cardiovascular mortality was 0.71 per 1,000 population. Follow-up time ranged from 0.43 to 2.49 years. Incidence of mortality was highest among polypharmacy with any LAI patients and lowest among using PP1M monotherapy patients for all three death outcomes. Monotherapy patients treated with other atypical LAIs, typical LAIs, and atypical orals had similar incidences for each death outcome.

Conclusion: This study provides background incidence rates of mortality among antipsychotic-treated patients on various drug exposure groups in the Asia Pacific Region. Mortality rate patterns were similar among all death categories, were highest among polypharmacy with any LAI patients, and lowest among PP1M monotherapy patients.

136 Analysis of group-based trajectory model for sustained use of opioid analgesics in South Korea

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Aim/Objective: Consumption of prescription opioid analgesics has steadily increased in South Korea over the past decade. Our study is to examine the status and characteristics of patients prescribed with opioid analgesics.

Methods: We conducted a Group-Based Trajectory Modeling (GBTM) by using data from the National Health Insurance Service database of South Korea. Study population were outpatients prescribed opioid analgesics at least once in January 2009 and followed for 60 months until December 31, 2013. Study drugs included 16 opioids. The trajectory model was coded as a dichotomous variable where '1' was assigned for cases with an opioid prescribed duration of at least 80% each month, and '0' for otherwise. To verify the suitability of the model, Bayesian Information Criterion (BIC) was evaluated. Multinomial logistic regression was conducted to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) amongst fitted trajectory groups.

Results: Among 13,333 patients who were prescribed opioids, upon analysis of trajectory modeling, three trajectory groups were identified; high-sustained users (4.2%, n=555), early quitters (85.6%, n=11,410), and slow quitters (10.3%, n=1,368) (BIC=-75942.97). GBTM observed women (73.2%, n=406) and the elderly (70.1%, n=389) were more common in the high-sustained user group, compared to that of the early quitters (58.2%, n=6,644) and (29.7%, n=3,391), respectively. The aORs of high-sustained users, for depression, anxiety disorders, and sleep disorders were 5.60 (95% CI: 3.92-8.00), 2.51 (95% CI: 1.83-3.45), and 2.89 (95% CI: 2.067-4.042), respectively, when compared to early quitters. The results of high-sustained users and slow quitters were similar to the aforementioned with aORs of 2.17 (95% CI: 1.49-3.16), 1.42 (95% CI: 1.01-2.00), and 1.13 (95% CI: 0.80-1.60), respectively.

Conclusion: 4.2% of patients were identified as high-sustained users, and several factors were associated with sustained use of opioid analgesics. Patients are advised to be use opioids with careful attention.

137 Pharmaceutical opioid use and mortalities among older Australians

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Background: Australia is facing with an emerging opioid-related population health burden highlighted by recent multiple-fold increase in prescription opioid doses, subsidised prescription cost, and opioid-poisoning deaths among 3 million prescription users.

Aims: To investigate disproportionate burden of disease such as total mortality and hospitalisation in relation to prescription opioids use in older adults compared with general population in New South Wales of Australia.

Methods: The 45 and Up Study linked data were used to ascertain prescription opioid uses as well as deaths and hospitalisations in the study population. Poisson regression was used to estimate incidence rates for different outcomes; and model counted responses such as healthcare service utilisation. Cox proportional hazards models with robust variance estimation were used to estimate the hazard ratios of adverse outcomes in relation to time-varying opioid use patterns and doses, while adjusting for individual factors such as age, sex, alcohol, smoking, and comorbidities.

Results: Factors in relation to prescription opioid use included being younger, male, urban residents, with higher family income, and higher education attainment. Of common underlying causes of deaths, many were related to neoplasms; and its total mortality rate was significantly higher in prescription opioids users versus non-users (RR: 3.11, 95%CI: 2.93-3.30), followed by musculoskeletal conditions (1.96, 1.66-2.32), mental disorders (1.62, 1.45-1.80), respiratory diseases (1.60, 1.50-1.70), digestive diseases (1.56, 1.39-1.74). Injuries and poisoning were the leading causes of hospitalisation, with a 36% risk increase in prescription opioids users compared with non-users. The top 5 leading hospitalisation risk ratio was for infectious diseases (1.63, 1.56-1.69), musculoskeletal conditions (1.57, 1.53-1.62), respiratory diseases (1.55, 1.49-1.61), endocrine disorders (1.53, 1.48-1.58), and immune system diseases (1.52, 1.41-1.65). Further results will be presented at the conference.

Conclusion: In this large prospective study, prescription opioid use was associated with elevated risks of mortality and hospitalisations. The causality of this finding requires further analysis.