Oral Abstracts

01 Ten year trends of adverse drug reactions in residents of Jiangsu Province of China, 2010-2019

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Aims: To examine change in incidence rates of adverse drug reaction (ADR) in Jiangsu Province of China with a catchment population of 80 million.

Methods: We extracted data from the regulatory spontaneous ADR reporting system in Jiangsu and estimated age-adjusted incidence rates of ADR between 1st July 2010 and 30th June 2019, and rates by patient characteristics, severe incidents, major clinical condition groups, and main therapeutic medication groups that induced the adverse reaction. We used the percent change annualised estimator to evaluate trends over time.

Results: A total of 943,480 confirmed incidents were reported in Jiangsu residents. The age-adjusted rates of ADR incidents significantly increased by 17.1% per annum in the first 4 years and remain little changed for the last 5 years by -0.1% per annum, with severe incidents demonstrating a similar pattern (an increase of 30.4% up to July 2014 and decrease of 0.5% since then). Reduction in ADR rates was also observed since July 2014 for some clinical condition groups such as coronary heart diseases (decrease of 28.2% per annum), in comparison with a subtle increase of 2.2% in patients with malignant neoplasms. Noteworthy, we observed a monotonic increase of diabetes-related ADRs over 9 years (an increase of 13.6% per annum). Children aged under 15 years accounted for 11.7% of all ADR incidents, with the age-adjusted rate increasing from 86 in 2010-11 to 127 per 100,000 Jiangsu residents in 2018-19, demonstrating an annual increase of 4.2% (95%CI: 1.1-7.4%). Antibiotics (19.5%) were the most common medications contributing to ADR incidents, demonstrating a recent decrease of 3.6% although not statistically significant.

Conclusions: ADRs remain a population health challenge despite the overall upwards trend has turned since July 2014. The findings call for continuing efforts in ADR prevention in China, especially among vulnerable populations such as children and diabetic patients.

02 Incidence of nephrotoxicity associated Tenofovir disoproxil fumarate (TDF) in HIV-infected /AIDs patients at Rajavithi Hospital

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Objective: To determine the incidence of nephrotoxicity associated Tenofovir disoproxil fumarate (TDF) in HIV-infected /AIDs patients and to determine relational risk factors with nephrotoxicity from TDF.

Materials and Methods: A retrospective cohort study was conducted among HIV-infected /AIDs patients at Rajavithi Hospital. All patients who used TDF in a first time from January 1, 2015 to December 31, 2018. The eGFR were evaluated at baseline and will be followed up until December 31, 2019 or when nephrotoxicity occurs.

Result: Six hundred and seventy five patients in this study, mean age 33.6+ 10.32 years, a median of CD4 cell count 233 cell/mm3 (IQR 1-1213) and a median of BMI 21.1 kg/m2 (IQR 13.22-31.25). Five hundred and ten cases (75.6%) were male. Three hundred and ninety eight cases (58.9%) were medical benefits are social security. Decreasing in eGFR from baseline more than 25% had 35 cases (5.19%). Age (adjusted odds ratio, 1.05; 95% CI, 1.01 to 1.08), medical benefits of pay by yourself (adjusted odds ratio, 4.17; 95% CI, 1.26 to 13.73) and foreign workers (adjusted odds ratio, 3.74; 95% CI, 1.17 to 11.93) Underlying disease hypertension (adjusted odds ratio, 5.37; 95% CI, 1.65 to 17.50) thalassemia (adjusted odds ratio, 32.86; 95% CI, 1.85 to 583.20), chronic kidney disease (adjusted odds ratio, 17.28; 95% CI, 3.54 to 84.36) patients significantly were associated with > 25% decreasing in eGFR (p-value <0.05)

Conclusion: The incidence of declined kidney function in the patients receiving TDF treatment regimens was around 5.19%. Clinicians should be adviced to have intensive renal function monitoring by calculating eGFR levels at baseline and during follow up with TDF use. Further study with a control group and long-term follow-up closely is needed.

03 Drugs inducing myalgic encephalomyelitis/chronic fatigue syndrome: A pharmacovigilance study using FDA adverse event reporting system (FAERS)

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Aim/Objective: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, debilitating illness that involves inflammation of the brain and has an unknown aetiology. The association of drugs causing this syndrome has not been explored and identified. This study aimed to recognize drugs that have the potential to cause Chronic Fatigue Syndrome by using the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: The case/non-case retrospective observational study design was used to analyze and retrieve data from the FDA database. We queried the adverse event reports made to the database between July 1, 2004, and March 31, 2021, for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. Patient characteristics and outcomes were assessed. The data mining algorithms used were Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR). A value of ROR-1.96SE>1 (SE-standard error), PRR≥2 were considered as positive signal strength. Open Vigil was used for data extraction and curation.

Results: A total of 2169 ME/CSF cases were attributed to drugs during the study period. The majority of these were designated as serious reactions, including death, hospitalization, disability, and other life-threatening outcomes. Several drugs of different classes had the highest signals of inducing ME/CSF, specifically: Isotretinoin (PRR: 107.31; ROR: 108.01), Rofecoxib (PRR: 43.642; ROR: 43.766), Doxycycline (PRR: 11.59; ROR: 11.603), Metolazone (PRR: 36.79; ROR: 36.91), Azithromycin (PRR: 6.02; ROR: 6.02), Ciprofloxacin (PRR: 9.67; ROR: 9.681), Ethinyl Estradiol (PRR: 6.109; ROR: 6.111) and Sertraline (PRR: 4.279; ROR: 4.28).

Conclusion: Our results suggested the possibility that drugs have a crucial role in the aetiology of Chronic Fatigue Syndrome. These findings strengthen the role of timely pharmacovigilance to detect post-marketing signals through FAERS and other real-world data, by which clinicians can assess early and monitor the potential drugs which can induce Chronic Fatigue Syndrome/Myalgic Encephalomyelitis.

Keywords: Pharmacovigilance, FAERS, Chronic Fatigue Syndrome

04 Adverse outcomes after partner bereavement in people with reduced kidney function: Parallel cohort studies in England and Denmark

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Objective: To investigate whether partner bereavement is associated with adverse cardiovascular (CVD) and kidney-related events in people with reduced kidney function.

Methods: We conducted two parallel matched cohort studies using linked routinely collected health data in England (Clinical Practice Research Datalink, Hospital Episode Statistics, and Office of National Statistics, 1998-2018) and Denmark (Danish National Patient, Prescription and Education Registries and the Civil Registration System, 1997-2016). Bereaved people with reduced kidney function (estimated glomerular filtration rate (eGFR) <60mL/min/1.73m2 (England) or hospital-coded chronic kidney disease (Denmark)) and non-bereaved people with reduced kidney function similarly defined were matched on age, sex, general practice (England), and county of residence (Denmark) and followed-up from the bereavement date of the exposed person. Our main outcomes were CVD or acute kidney injury (AKI) hospitalization, or death. We used multivariable Cox regression to calculate hazard ratios (HR) adjusted for potential confounders.

Results: We identified 19,820 (England) and 5,408 (Denmark) bereaved individuals and matched them with 134,828 (England) and 35,741 (Denmark) non-bereaved individuals. Among the bereaved, the hospitalization rates were 31.7 (95%-CI: 30.5-32.9) in England and 78.8 (95%-CI: 74.9-82.9) in Denmark for CVD; 13.2 (95%-CI: 12.5-14.0) in England and 11.2 (95%-CI: 9.9-12.7) in Denmark for AKI; and the rates of death were 70.2 (95%-CI: 68.5-72.0) in England and 126.4 (95%-CI: 121.8-131.1) in Denmark. After adjusting for confounders, we found increased rates of CVD (England, HR 1.06 [95%-CI: 1.01-1.12]; Denmark, HR 1.10 [95%-CI: 1.04-1.17]), of AKI (England, HR 1.20 [95%-CI: 1.10-1.31]; Denmark HR 1.36 [95%-CI: 1.17-1.58]), and of death (England, HR 1.10 [95%-CI: 1.05-1.14]; Denmark HR 1.20 [95%-CI: 1.15-1.25]) in bereaved compared with non-bereaved people.

Conclusion: Partner bereavement is associated with an increased rate of CVD and AKI hospitalization, and death in people with reduced kidney function. Additional supportive care for this at-risk population may help prevent serious adverse events.

05 New method for reducing bias in estimated associations of time-varying drug exposures with imprecisely timed adverse events

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Aim/Objective: Many adverse drug events (ADEs), e.g. cancers or cognitive impairment, can be diagnosed only during medical visits, so it can only be established that they occurred at some time between two consecutive visits. Methods developed to analyze such interval-censored outcomes [1] do not handle time-varying exposures (TVEs), which are essential to account for variations in drug use in population-based pharmacoepidemiology studies [2]. We developed and validated a new method for estimating associations between TVEs and interval-censored ADEs.

Methods: We adapted the Simulation Extrapolation (SIMEX) methodology [3] to time-to-event analyses of associations between TVEs and imprecisely timed ADEs. It involves (i) artificially extending the time between visits (lag) to estimate how this affects estimated regression coefficients; and (ii) extrapolating this relationship to the hypothetical case with lag=0, when exact ADE times are known. In simulations, we compared SIMEX-corrected estimates versus conventional estimates obtained by imputing event times at the end or midpoint of the interval between the relevant visits. The method was applied in a population-based study of the association between cumulative duration of hydrochlorothiazide use and non-melanoma skin cancer (NMSC).

Results: In simulations, our SIMEX-corrected estimates reduced the bias (by about 75%-90%) and root mean squared errors (by 25%-60%) relative to conventional estimates, which often yielded relative bias >25% to the null. The advantages of our method increased with more events. In the hydrochlorothiazide study, the mean time between visits when NMSC could be diagnosed was 7.6 months. SIMEX-corrected estimates suggested stronger association (HR=1.38 (1.15-1.69) for each additional year of hydrochlorothiazide use) than conventional analyses (HR=1.29 (1.10-1.50)).

Conclusion: Our new SIMEX-based method improves the accuracy of estimated associations between TVEs and imprecisely timed ADEs.

[1] Lindsay, Ryan. Stat Med 1998;17:219-238.
[2] Pazzagli et al. PDS 2018;27:148-160.
[3] Cook, Stefanski. JASA 1994;89:1314-1328.

Keywords: Methods, Time-varying exposures, Timing of events, Simulations

06 Discovering adverse events of medical devices through natural language processing and machine learning

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Aim: To develop a methodology for detecting adverse events from medical devices using professional- and self-report text data, through natural language processing (NLP) techniques and statistical machine learning.

Methods: We applied NLP techniques to identify patterns between medical devices, adverse events, and patient behaviour. We performed a case study using text reports involving mesh implants from the publicly available Database of Adverse Event Notifications (DAEN) managed by the Australian Therapeutic Goods Administration (TGA). We used hierarchical clustering to extract clusters of reports detailing adverse effects. Having validated this approach, we applied it to other device categories using a much larger corpus of reports, from the Food and Drug Administration 's Manufacturer and User Facility Device Experience (MAUDE) database. We again extracted clusters of reports detailing adverse effects, and filtered these to search for associations with particular activities and manufacturers.

Results: We examined 410 unique reports involving mesh implants from 22 different manufacturers in the TGA dataset and found clear interrelationships between various physical activities, device manufacturers and adverse events. For mesh products, 310 reports (75.6%) mention pain, and 46 (11.2%) mention sexual intercourse, with a clear relationship existing between co-occurences of the two. From 3,002,144 reports in the MAUDE dataset, we found clear relationships between activities without need for statistical supervision, and which we stratified by device manufacturer and type of adverse event.

Conclusion: In this analysis we explored the use of NLP techniques to automate and scale-up the extraction of information from unstructured text data to help understand relationships between adverse events and related events experienced by patients with respect to different devices. This is likely to have important implications for enhancing time to adverse event discovery of medical devices and has potential application in other unstructured data such as social media posts and electronic medical records.

07 Ten year change in coronary heart disease management and outcome in Malaysia

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Objective: Coronary heart disease (CHD) remains the leading cause of deaths in most countries, including Malaysia. This study was aimed to investigate the 10-year change in CHD trends in Malaysia, including the utilisation of coronary intervention, pharmacotherapies and its outcome.

Method: The Malaysian National Cardiovascular Database-Acute Coronary Syndrome (NCVD-ACS) registry was used for this observational, retrospective study. Patients over 20 years old admitted with ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina in the year 2008 (n=2793) and year 2017 (n=20,750) were identified. The changes in demographic presentation, coronary intervention, uptake of pharmacotherapies and death at discharge and 1-year were examined.

Results: CHD admission increased almost 7-fold in 2017 compared to 2008 ($p<0.001$). Men presenting with CHD have increased by 3% ($p<0.001$), with a 3% reduction ($p<0.001$) in women in the same period. Cardiac catheterisation procedure has increased from 17% in 2008 to 39% in 2017 ($p<0.001$) with greater number percutaneous coronary intervention (PCI) performed (13% in 2008, 27% in 2017 ($p<0.001$)). The rate of coronary artery bypass graft (CABG) remained less than 2%. A significant increment was observed in in-hospital cardiac intervention, namely antiplatelets ($p<0.001$) and anticoagulants ($p<0.001$) within the 10-years. In 2017, aspirin is already near the maximum with 96% administration. ACEi/ARB rate of prescription, however, has shown significant decreases in prescribing ($p<0.001$). The 1-year death outcome for the year 2008 was at 18.3% and dropped significantly to 16.6% in 2017 ($p<0.05$).

Conclusion: Significant improvement in coronary intervention, pharmacotherapies such as antiplatelets and anticoagulants, and mortality outcomes were observed in Malaysia when comparing two-time points in 10 years. Increased uptake of coronary intervention such as PCI should be targeted to produce a greater decline in mortality in the next decade.

Keywords: Cardiovascular Disease, Mortality, Intervention, Pharmacotherapies.

08 Medication regimen complexity, medication burden and adherence among primary care patients with type-2 diabetes mellitus: A retrospective analysis

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Introduction: Type 2 diabetes (T2DM) patients with comorbidities often require multiple medications with potentially complex regimes to achieve or maintain their glycaemic control. This could increase the medication burden and placed them at potential risk of poor medication adherence, medication interaction or inappropriate medication use.

Objective: This study examined the effect of medication regimen complexity, medication burden and medication adherence on glycaemic control among patients with T2DM.

Method: We used pharmacy dispensing data of 2696 eligible patients with T2DM from selected public primary care clinics in Malaysia. Treatment profiles for all chronic medications (patient-level) and diabetes medications (diabetes-specific) were quantified during the period preceding the latest HbA1c measurement between January 2018 and May 2019. Regimen complexity was proxied by the validated Medication Regimen Complexity Index (MRCI) tool while adherence was calculated as Proportion Days Covered (PDC) over a fixed time interval. Multivariable logistic regression analysis was used to estimate adjusted odds ratio and 95% confidence interval for the association between MRCI, medication burden and medication adherence with glycaemic control.

Results: Overall, mean (±SD) age was 60.4 (±10.8), 62.9% were female, 85.8% had hypertension, 74.6% had hyperlipidaemia and 34.5% were categorised as having good glycaemic control (HbA1c ≤7%). Mean medication count was 4.8 (±1.7) for all chronic medications, with a mean 1.3 (±0.7) for anti-diabetic medication. Overall mean scores of patient-level MRCI and diabetes-specific MRCI were 15.1 (±4.9) and 7.9 (±3.0) respectively. High MRCI, medication count of ≥5 and poor medication adherence were associated with lower likelihood of achieving HbA1c ≤7%.

Conclusion: High complexity, medication burden and low medication adherence have negative effects on glycaemic control among patients with T2DM. These findings indicate the need to identify patients with complex management regimens so that targets for intervention can be taken in order to improve adherence and achieve optimum outcomes.

09 Association between dual or triple oral antidiabetic therapy involving evogliptin and cardiovascular events in T2DM patients: A nationwide cohort study

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Aim/Objective: To assess the association between dual or triple oral antidiabetic drug (OAD) therapy involving evogliptin and the risk of cardiovascular events among patients with type 2 diabetes mellitus.

Methods: We conducted a population-based cohort study using South Korea's healthcare database (2014-2018). We identified two separate cohorts of patients who newly initiated dual or triple OAD therapy. Exposure was assessed using an intention-to-treat approach, with the index date defined as the date of initiating dual or triple OAD therapy between Mar 2016 and Jun 2018. The primary outcome was defined as a hospital admission or emergency department visit for cardiovascular events (myocardial infarction [MI], heart failure [HF], cerebrovascular diseases); secondary outcomes were the individual components. Cox proportional hazards model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the risk of cardiovascular events associated with evogliptin as dual or triple therapy, compared with OADs other than dipeptidyl peptidase-4 inhibitors (DPP4i).

Results: Of 218,296 and 95,851 dual and triple OAD therapy initiators, 6,007 and 2,696 involved evogliptin, respectively. Use of metformin+evogliptin, compared with metformin+non-DPP4i OAD, showed reduced risks of cardiovascular events (HR 0.71, 95% CI 0.62–0.82), HF (HR 0.70, 95% CI 0.59-0.82), and cerebrovascular disease (HR 0.71, 95% CI 0.53-0.95), but showed statistically non-significant findings for MI (HR 0.89, 95% CI 0.60-1.31). Although the risk of cardiovascular events was also decreased with metformin+sulfonylurea+evogliptin (HR 0.76, 95% CI 0.59-0.97), when compared with metformin+sulfonylurea+non-DPP4i OAD, statistically non-significant findings were observed for MI (HR 0.57, 95% CI 0.27-1.19), HF (HR 0.74, 95% CI 0.55-1.01), and cerebrovascular disease (HR 0.96, 95% CI 0.61-1.51).

Conclusion: Use of evogliptin in combination with metformin as dual therapy or with metformin and sulfonylurea as triple therapy was associated with a decreased risk of cardiovascular events, compared with dual or triple therapy of non-DPP4i OAD.

10 Risk for diabetic macular edema with sodium glucose cotransporter 2 inhibitors in type 2 diabetes patients: Cohort study in Taiwan

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Aim: To investigate risk of diabetic macular edema (DME) from sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes mellitus (T2DM).

Methods: We conducted a retrospective cohort study by analyzing a large multi-institutional electronic medical records database in Taiwan. We included adult patients with T2DM without DME newly receiving SGLT2 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) during 2016-2018. We used propensity score with inverse probability of treatment weighting to generate comparable groups. Study outcome was the incident DME determined by clinical diagnosis in outpatient visits or admissions. We followed patients from the index date to DME occurrence, last clinical visit, patient death, or December 31st, 2020. We performed Cox proportional hazards regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the risk of DME.

Results: We included 9,986 SGLT2 inhibitor new users [mean age: 59.6yrs (SD 12.1), HbA1c: 8.6% (IQR 7.7-9.6), eGFR: 89.1ml/min/1.73m2 (IQR 71.4-108.7), UACR: 26.1mg/g (IQR 9.7-117.6)] and 1,067 GLP-1 RA new users [mean age: 58.4yrs (SD 41.5), HbA1c: 8.8% (IQR 8.0-9.8), eGFR: 91.6ml/min/1.73m2 (IQR 68.6-114.0), UACR: 37.6mg/g (IQR 11.1-153.2)] with similar baseline characteristics. Lower DME risks were observed among patients newly receiving SGLT2 inhibitors (7.9 / 1,000 person-years), compared to those receiving GLP-1 RAs (10.7 / 1,000 person-years) with an HR of 0.75 (95% CI: 0.64-0.88).

Conclusions: Our findings suggested SGLT2 inhibitors were associated with lower risks of DME in T2DM patients in clinical practice, compared to GLP-1 RAs. Future studies are necessary to confirm this observation.

11 Signal detection of metformin-statins drug drug interactions using the Korea Adverse Event Reporting System Database

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Aim/objective: As cardiovascular disease in diabetic patients has emerged as a significant clinical problem, prophylactic statin use has increased. However, the information on drug interaction between metformin, the first therapy in diabetes, and statins is insufficient. Therefore, we aimed to detect potential drug-drug interactions (DDI) of the concomitant use of metformin and statins using the Korea adverse event reporting system (KAERS) database.

Methods: We used the KAERS database from 2015 to 2019. We used the Ω shrinkage measure model and χ2 statistics model to detect potential interaction signals and set the criteria for detecting DDI with metformin and statins. Ω shrinkage, which suggests Ω 025>0 as thresholds from the frequentist and Bayesian approaches, and χ2 statistics model that detects signals when χ >2. When at least one of the three indicators was satisfied, it was considered as a signal. Detected signals were reviewed in the drug labels in Korea.

Results: Of the 2,372,236 total drug-AE pairs, 8,207 pairs of metformin-AEs, 26,607 pairs of statin-AEs, and 545 pairs of metformin-statin-AE were included. For DDI, forty two signals based on WHO-ART preferred terms (PTs), such as urticaria and vitiligo, were detected, which met at least one index criteria. Skin and appendages disorders (26 PTs), categorized based on system organ classes (SOC), were the most detected signals, followed by the musculo-skeletal system disorders (8 PTs). Among the 8 cases that satisfying all three indicators, dermatitis fungal, hypertrichosis, melanosis, and nail disorder were not listed in the Korean drug label.

Conclusions: We detected and compared potential signals for DDI associated with metformin and statins, some of which were not listed in the drug. Further studies could be considered to confirm the association.

Keywords: Drug-drug interactions; Metformin; Statin; KAERS

12 Effectiveness and safety evaluation of SGLT-2i in patients with type 2 diabetes mellitus: A systematic review and network meta-analysis

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Objective: To conduct network meta-analysis for multiple outcome indicators to evaluate the efficacy and safety of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with type 2 diabetes (T2DM).

Methods: Medline, Embase, Cochrane Library and Clinical Trials were searched from inception through September 2019 for randomized controlled trials (RCTs) assessed the efficacy and safety of SGLT-2i versus placebo or other anti-diabetic drugs among patients with T2DM. Odds ratio (OR) or mean difference (MD) with 95%CIs were estimated through network meta-analysis.

Results: A total of 239 RCTs with a research duration of 12 weeks or more were included, and 11 clinical outcome evaluation indicators were determined, including: glycosylated hemoglobin, body weight, total cholesterol, hypoglycemia, and hypotension, urinary tract infection, etc. The SGLT-2i drugs we were concerned about include: canagliflozin, dapagliflozin, ipragliflozin, empagliflozin, and all other listed drugs. Dapagliflozin is not as effective as canagliflozin in reducing glycosylated hemoglobin (MD=1.32%, 95% CI (0.51,2.14)) and weight reduction (MD=5.41 kg, 95% CI (3.16,7.66)). However, it reduces body weight (MD=-3.87 kg,95%CI (-4.97, -2.77)), reduces systolic blood pressure (MD= -6.26 mmHg,95%CI (-10.04,-2.49)), and the risk of hypoglycemia (OR= 0.22,95%CI (0.12,0.42)) and other aspects are better than insulin glargine, and better than sitagliptin in reducing systolic blood pressure (MD= -3.74 mmHg,95%CI (-7.30, -0.18)). The risk of urinary tract infection caused by dapagliflozin was higher than that of insulin glargine (OR= 8.80, 95% CI (1.01, 76.76)). For other outcome indicators, there was no statistically significant difference between dapagliflozin and sitagliptin, pioglitazone, metformin, insulin glargine and other hypoglycemic drugs.

Conclusion: Compared with hypoglycemic drugs such as canagliflozin, sitagliptin, and insulin glargine, dapagliflozin outperforms in reducing body weight, systolic blood pressure, and reducing the risk of hypoglycemia, but it may cause higher risk of urinary tract infection than insulin glargine.

Keywords: SGLT-2 inhibitors; anti-diabetic drugs; type 2 diabetes mellitus, network meta-analysis

13 Estimating vaccine effectiveness using real-world data: Causal structural considerations and advances in Targeted Learning

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Objective: When studying vaccine effectiveness using observational data, it is essential to consider the data generation process (DGP) that likely generated the observed data. Advances in machine learning (ML)-based causal inference, particularly Targeted Learning (TL), allow us to estimate the relevant part of the DGP needed to evaluate the target parameter directly. The advantages of the TL approach include a larger predictor space to draw upon and reduced potential for model misspecification. However, we find situations, such as when sampling amounts to conditioning on a potential collider, where a balance of ML-based approaches and directed acyclic graphs (DAG) consideration of the DGP work together to support proper effect estimation.

This study uses a counterfactual-based simulation of a realistic vaccine/infection DGP to evaluate traditional and ML-based estimation methods across varying sampling schemes to assess sources of and potential remedies for bias.

Methods: We used agent-based modeling to simulate a cohort of patients using causal structural (Bayesian network) models. These models incorporate a counterfactual framework with node(s) for health beliefs and protective behaviors and a potential collider for observation, e.g., data available in electronic health records (EHR). We then employed varying enhanced sampling approaches to simulate how this cohort might present to a healthcare system, e.g., higher sampling from vaccinated and infected individuals. Finally, we estimate vaccine effectiveness (VE) using semiparametric Cox models and TL and compare results.

Results: Cox proportional hazards models performed similarly to TL models (in % bias) when both models were correctly specified. And both sets of models have bias introduced when conditioning (filtering) on the potential collider.

Conclusion: It is important to understand the DGP and allow it to inform study design, regardless of the analytic approach. Knowing the likely directionality of residual confounding via simulation can help inform bounded answers, e.g., lower bound of real-world effectiveness.

14 Post-marketing surveillance study on influenza vaccine using the disproportional analysis and tree-based scan statistic

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Aim/Objective: Concerns on the safety monitoring of influenza vaccine have been raised due to increased infectious disease and the expansion of the National Immunization Program. We aimed to detect safety signals of influenza vaccine using various signal detection algorithms (SDAs) and compare the performance of SDAs.

Methods: We conducted a vaccine safety surveillance study using the Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database (KIDS-KD) between 2005 and 2019. Safety signals for influenza vaccine and its subtypes (quadrivalent influenza vaccines (QIVs) versus trivalent influenza vaccines (TIVs), and cell-based versus egg-based influenza vaccines) were detected following SDAs: disproportionality analysis (DA) comprising of proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC); tree-based scan statistic (TSS). The performance of each algorithm was evaluated based on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and the area under the curve (AUC).

Results: Compared to the other vaccines, several safety signals such as injection site pain, anaphylactic reaction, neuritis, and narcolepsy were detected with influenza vaccine by all of four SDAs. Injection site local reactions were reported more frequently with QIVs than TIVs. In contrast, systemic reactions and central & peripheral nervous system disorders were detected as signals with TIVs compared to QIVs. Injection site pain, and somnolence were detected in cell-based influenza vaccines. Systemic reactions and paralysis were detected in egg-based influenza vaccines. In the performance evaluation of SDAs, TSS showed the highest values at sensitivity, PPV, accuracy and AUC. IC demonstrated the highest specificity.

Conclusion: QIVs and TIVs showed different signal information, but the number of detected signals was less with QIVs. Signal detection performance varies according among SDAs. Although TSS showed balanced performance, complimentary use of SDAs would be beneficial when the large noise due to false positive is expected.

15 Detecting signals for interaction between MMR vaccine and varicella vaccine using Korea Adverse Event Reporting System

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Aim/Objective: Measles, mumps, and rubella (MMR) vaccine and varicella vaccine are often administered simultaneously. Both are given at 12-15 months of age. However, safety issues regarding concomitant vaccination are being raised. There are few studies on such issues. The objective of this study was to detect signals for potential interactions between MMR and varicella vaccines using Korea Adverse Event Reporting System (KAERS).

Methods: Adverse events (AEs) reported for vaccines, including MMR and varicella vaccines, were obtaeind from the KAERS database from 2015 to 2019. Potential signals for interactions between vaccines were detected applying Ω shrinkage measure and χ2 statistics model. The former suggested Ω025 > 0 as a threshold from frequentist and Bayesian approaches. The latter detected signals at χ > 2. If one or more of three indices were met, it was identified as a signal. All detected signals were reviewed to determine whether these signals corresponded to known AEs from each drug label in Korea and Micromedex®.

Results: A total of 23,328 vaccine-related reports, including 70 on MMR vaccine only, 35 on varicella vaccine only, and 174 on their co-vaccination were included in this study. A total of 26 signals were detected for the interaction between the two vaccines. Among them, 12 signals met all three indices of nervousness, somnolence, and eating disorder. Seven signals, including stridor, concussion, and fracture, were not known AEs for any vaccine. AEs reported in previous studies regarding the safety of simultaneous administration of both vaccines, such as purpura, cerebral disorder, rash, vomiting, and diarrhoea, were detected in this study

Conclusion: We detected signals for the potential interactions between MMR and varicella vaccines when administered simultaneously. However, further investigations using other databases and additional monitoring are needed to confirm our findings.

Keywords: KAERS database, vaccine interaction, MMR vaccine, varicella vaccine

16 Data mining for adverse events of influenza vaccine in the elderly cancer patients using self-controlled tree-temporal scan statistic analysis

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Aim/Objective: Both cancer patients and the elderly are at high risk of flu complications, so influenza vaccination is recommended. We aimed to evaluate potential adverse events (AEs) following influenza vaccination in elderly cancer patients using the self-controlled tree-temporal scan statistic method.

Methods: Using a large-linked database of Korea Disease Control and Prevention Agency vaccination data and the National Health Insurance Service claims data, we identified cancer patients aged ≥65 who received flu vaccines during 2016/2017 and 2017/2018 seasons. Cancer patients were defined as those diagnosed with cancer (ICD-10: C00-C97) at least one inpatient or ≥3 outpatient claims for a year prior to vaccination. We included any outcomes occurring on 1–84 days post-vaccination and evaluated all risk windows, which started 1–28 days and ended 2-42 days. The patients diagnosed with same disease during a year before vaccination were excluded. The tree-temporal scan statistic was applied to identify statistically significant clustering within the hierarchy of ICD-10. The term 'set' was used to classify signal groups sharing the second tree level.

Results: This study included 431,276 doses of flu vaccine (2016/2017: 208,938 doses; 2017/2018: 222,338 doses). We detected signals for 2 sets: rickettsioses on 6-38 days (14 [6-38 days] vs. 0 events [1-5 and 39-84 days], p=0.004) and other dorsopathies on 1-15 days (197 [1-15 days] vs. 563 events [16-84 days], p=0.032). Dorsopathy is a known AE of influenza vaccine. However, rickettsioses were not listed on the label. No signals were found when analyzed by flu season.

Conclusion: Few signals were detected in elderly cancer patients. Rickettsioses, not on the label, might be a new signal, but considering that it mostly occurs in autumn, the possibility of seasonality could not be ruled out. Therefore, influenza vaccination could be more recommended in patients with cancer.

Key words: influenza vaccine, elderly, cancer patients, data mining

17 The spontaneous reports of anaphylaxis following immunization in Korea

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Objective: Anaphylaxis, an acute hypersensitivity reaction through multiple organ systems, is rare but may be life-threatening adverse events following immunization (AEFIs). The incidence risk of anaphylaxis varies by characteristics of vaccine or patient such as type, adjuvant, stabilizer, and disease history. In Korea, information on overall reporting patterns of anaphylaxis by various vaccine types and reporting characteristics is deficient. We aimed to identify the patterns and characteristics associated with spontaneous reports of anaphylaxis following immunization.

Methods: The spontaneous reports of AEFIs between January 2011 and December 2019 were retrieved from Korea adverse event reporting system database (KIDS-KD). The anaphylaxis was defined using World Health Organization Adverse Reaction Terminology (WHO-ART) based on the case definition of the Council for International Organizations of Medical Sciences and Brighton collaboration. Vaccines were defined using Anatomical Therapeutic Chemical code, and the vaccine type was categorized into viral- and bacterial-vaccines. We performed a descriptive analysis of reporting characteristics including age, sex and seriousness.

Results: A total of 39,195 spontaneous reports on vaccines with 130,006 vaccine-AEs pairs were identified between 2011 and 2019 in Korea. The majority of reported cases were aged between 2 months and 23 months (30.3%;39,370 reports) and 75,107 reports (57.8%) were female. Among total of 85,550 reports (65.8%) for viral-vaccines and 45,594 reports (35.1%) for bacterial-vaccines, number of anaphylaxis reports were 144 (0.2%) and 35 (0.1%), respectively. Among the viral-vaccines with anaphylaxis, 69 reports (48.6%) were egg-based influenza vaccines, of which 35 reports (50.7%) were serious. Of the reports for bacterial-vaccines, 12 reports (34.3%) were in pneumococcal vaccines and 51.4% (7 reports) were serious.

Conclusion: The number of reports on anaphylaxis was higher in viral-vaccines than bacteria-vaccines, especially egg-based influenza vaccine showed the highest proportion with the number of reports and seriousness, which could be associated with adjuvant or stabilizer.

Keywords: vaccine; anaphylaxis

18 Differential demographic and clinical characteristics between MMR vaccinated and unvaccinated children in South Korea: A nationwide study

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Aim/Objective: In the context of recent measles outbreaks, substantial factors associated with MMR unvaccination need to be clarified. This study aimed to identify differential demographic and clinical characteristics between MMR vaccinated and unvaccinated groups.

Methods: We used a large-linked database to identify children born between 2008 and 2016 by combining data from the Korea Immunization Registry Information System and National Health Information database. MMR vaccination status was ascertained up to age of 2 years to define MMR vaccinated and unvaccinated groups. We excluded children who died within 2-year of birth or received MMR vaccine out-of-schedule (i.e., 1st dose beyond 2-year of birth). Socioeconomic status such as residence type, insurance type, and household income level were assessed at the date of MMR vaccination, and comorbid conditions and healthcare utilizations were assessed 12-month period prior to date of MMR vaccination. To identify factors associated with MMR unvaccination, we conducted multivariate logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Of 3,973,253 children included in our study, 3,897,579 (98.1%) received and 75,674 (1.9%) did not receive MMR vaccine. Compared with MMR vaccinated group, underutilization of healthcare resources was more notable in MMR unvaccinated group (number of outpatient visit [5.73±12.1 vs. 25.8±17.06]; days hospitalized [1.69±14.5 vs. 2.32±6.90]). Children were less likely to receive MMR vaccine if they were born with congenital anomaly (OR 2.12; 95% CI 1.90-2.36), never admitted to intensive care unit (1.88; 1.78-1.98), or never visited emergency room (3.57; 3.53-3.72). Parental factors such as low household income level (3.66; 3.58-3.74), self-employed health insurance (7.34; 7.21-7.46), or residing in metropolitan area (1.44; 1.41-1.46) were more likely to be observed in the MMR unvaccinated group.

Conclusion: There were substantial factors associated with MMR unvaccination, underscoring a need to optimize targeted interventions tailored to the subset of children in South Korea.

Keywords: Measles; Measles-Mumps-Rubella vaccine; Vaccine uptake; Vaccine hesitancy

19 Prenatal exposure to psychotropic medications and the risk of seizure in children: A population-based cohort study

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Aim/Objective: The risk of seizure in children with prenatal antidepressant exposure remains unclear and controversial. We aimed to investigate the association between prenatal exposure to antidepressants and the risk of seizure in children.

Methods: We conducted a population-based retrospective cohort study with data from the Hong Kong Clinical Data Analysis and Reporting System. Pregnant women aged 15 to 50 years old who delivered a live birth between 2001 to 2015 were included. Children were followed up until 2016. Exposure was defined as antidepressant use during pregnancy. Pregnancy episodes with antipsychotics or lithium use and maternal history of epilepsy were removed. Hazard ratios (HRs) with a 95% confidence interval (CI) were evaluated to assess the association between prenatal exposure to antidepressant and seizure using propensity score fine-stratification weighting, Cox proportional hazards regression model, and sibling-matched analysis.

Findings: Among 414,058 mother-child pairs identified, 412,796 children were included in the analyses. 2,191 (0.53%) children were exposed to antidepressants during pregnancy. 18,478 (4.48%) children had a seizure diagnosis during follow-up (mean: 6.59 years). Children with prenatal antidepressant exposure were associated with an increased risk of seizure, compared to those without (weighted HR [wHR] 1.23, 95%CI 1.02-1.48). Similar associations were observed for infancy seizure, but not for neonatal seizure or perinatal seizure. However, increase in risk of seizure was also found when comparing children of mothers who had used antidepressants before but not during pregnancy with never users (wHR 1.29, 95%CI 1.13-1.49). Meanwhile, no significant difference in risk of seizure was observed between gestational users and sibling-matched gestational non-user (wHR 1.16, 95%CI 0.75-1.77).

Conclusion: The association between prenatal antidepressants exposure and the risk of seizure in children might be explained by confounders such as maternal psychiatric disorders. Pregnant women and clinicians should determine the risk-benefit balance of antidepressants use based on individual factors.

20 Associations between prenatal exposure to antipsychotics and birth and neurodevelopmental complications: A population-based cohort study

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Objective: To evaluate the association between prenatal exposure to antipsychotics and the risk of birth and neurodevelopmental problems.

Methods: This population-based cohort study included children born between 2001 and 2015 with follow-up through to 2019, as identified by the Hong Kong Clinical Data Analysis and Reporting System. Analyses controlling for pregnancy and maternal covariates with propensity score fine-stratification, as well as sibling comparisons, were applied to examine the associations between prenatal exposure to antipsychotics and preterm birth (<37 gestational weeks), small for gestational age (birth weight <2 standard deviations below the mean for gestational age), and first diagnosis of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children.

Results: The final cohorts included 333,749 pairs of mother-child records for ADHD analyses and 411,251 pairs for ASD/preterm birth/small for gestational age analyses. 13,196 children (3.95%) were diagnosed with ADHD (8.23% exposed vs 3.95% unexposed), 8,715 infants (2.12%) developed ASD (3.82% exposed vs 2.12% unexposed), 33,891 children were preterm (13.03% exposed vs 8.23% unexposed) and 7,009 offspring were small for gestational age (2.69% exposed vs 1.70% unexposed). After addressing potential covariates, the weighted hazard ratio (wHR) was 1.16 (95% confidence interval [CI]: 0.83-1.61) for ADHD and 1.06 (95% CI: 0.70-1.60) for ASD, while the weighted odds ratio (wOR) was 1.40 (95% CI: 1.13-1.75) for preterm birth and 1.36 (95% CI: 0.86-2.14) for small for gestational age. Sibling-matched analysis indicated no significant difference between prenatal exposure to antipsychotics and any of the outcomes.

Conclusions: No evidence supported prenatal exposure to antipsychotics increasing the risk of ADHD/ASD/preterm birth/small for gestational age. However, there may be confounding by indication for ADHD/ASD outcomes. These findings do not support a recommendation for women to stop their regular antipsychotic treatment during pregnancy based on potential harm of delivering an offspring with birth or neurodevelopmental complications.

21 Polymorphisms in the adrenergic neurotransmission pathway impact antidepressant response in depressed patients

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Aim: Mood disorders are a prevalent mental health disorder but understanding the mechanism of action for optimised treatment remains elusive. The adrenergic neurotransmission pathway presents an opportunity to determine whether genetic mutations impact antidepressant response.

Methods: 163 patients with major depressive disorders were used to establish treatment response using the Hamilton Depression Rating Scale (HAMD-17). Majority of the patients had never been treated with antidepressants previously during their entire life.

Patients were genotyped for 14 SNPs in ADRA1A, SLC6A2, ADRβ1, MAOA and COMT to determine the impact of adrenergic neurotransmission polymorphisms related in antidepressant response. Patients were treated mainly with SSRIs and TCAs. Clinical status was measured before initiation, after two weeks and after four weeks of antidepressant treatment. The difference in HAMD-17 scores between the measurement periods were assessed and defined as the outcome measure.

Multiple linear regression was conducted to determine the association between the genotypes and difference in HAMD-17 across the study period. Covariates of age, sex, antidepressant medication and depression diagnoses were included in the regression.

Results: Throughout the study HAMD-17 scores were measured at initiation (24.1 ± 4.9), at two weeks (12.9 ± 5.0) and at four weeks (5.1 ± 3.9) for each patient. The difference in HAMD-17 scores was found to be 11.2 ± 4.4 between initiation and two weeks, 7.8 ± 5.3 between two weeks and four weeks, and 19.0 ± 5.3 throughout the entire study.

SLC6A2 rs1532701 homozygous G Patients were associated with improved ΔHAMD-17 across week 2–4 and the entire study (B = 7.1, p = 0.002; B = 6.7, p = 0.013). Homozygous GA patients were further associated with improved ΔHAMD-17 compared to homozygous A patients at week 2–4 (B = 2.8, p = 0.023).

Conclusions: Limited polymorphisms in adrenergic neurotransmission genes were associated with antidepressant response in depressed patients.

22 Consumption and expenditure on monoclonal antibodies and Fc-fusion protein biologic medicines in Asia-Pacific regions

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Aim/Objective: Monoclonal antibody (mAb) and Fc-fusion protein (FcP) are highly effective therapeutic biologics. However, high costs can impede their affordability and accessibility. We aimed to analyze the consumption and expenditure trends in 15 Asia-Pacific regions (APAC) and three benchmark countries (UK, Canada, and USA).

Methods: We analysed 448 biologics products from IQVIA-MIDAS database between 2010 and 2020, 89% of which were indicated for cancer or autoimmune diseases. We classified them according to their targets of action: tumor necrosis factor (TNF, N=121), interleukin (IL, N=42), lymphocyte (N=91), programme death/ligand receptor (PD, N=15), endothelial growth factor (EGF, N=107) and tumor cell or selective immunosuppressants (N=21). For each year, we used standard units sold (SU per 1000 population) and manufacture level price (2017 US dollars) to evaluate the consumption (accessibility) and expenditure (affordability). Consumption and expenditure increase over time were estimated using compound annual growth rate (CAGR).

Results: In 2020, TNF accounted for the major market share in the three benchmark countries (41-57%) while EGF was predominantly used in APAC (15-60%). Between 2010 and 2020, there was increasing consumption trend for all regions' product classes with the greatest CAGR observed for PD (102%), followed by IL (68%). The average increasing rate of biologic medicines expenditure in lower-middle-income regions (21%) was greater than upper-middle (14%), high-income regions (13%) and benchmark countries (12%). Despite this, consumption of biologics was lower in lower-middle-income regions (0.47 SU per 1000 population) than in upper-middle-income regions (2.86), high-income regions (52.92) and benchmark countries (113.09). Consumption was significantly correlated with 2017 GDP per capita (Spearman's coefficient = 0.8; $p < 0.001$).

Conclusion: The uptake and healthcare spending on mAb and FcP biologics significantly increased in the last 11 years, however the accessibility and affordability of these medicines remain unequal and largely associated with the country income.

Keywords: mAb; Fc-fusion protein; biologic

23 Clinical and cost-saving effects of the Drug Utilization Review modernization project in inpatient and outpatient settings in Korea

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Aim/Objective: Korea's national health insurance authority introduced a drug utilization review (DUR) modernization pilot project in which health professionals provided follow-up services to monitor adverse drug events. The project was operated for 20 medical institutions between August and December 2019. We aimed to evaluate the effects of the project on clinical and economic outcomes.

Methods: We conducted difference-in-differences (DID) statistical methods using National Health Insurance claims data from the Health Insurance Review and Assessment Service (HIRA). We calculated the number of adverse drug events and allergic reactions as a clinical indicator and medical costs incurred to manage these events as an economic indicator. Each outcome measure was calculated for the 5-months period from August to December in 2018 and the same months in 2019 to consider the impact of seasonality. To select the control group, we considered institutional characteristics, such as region, type of medical care institution, number of beds, and number of physicians employed. We, then, calculated absolute and relative differences in each outcome measure. DID was defined as a difference in absolute differences between the intervention group and the control group.

Results: Overall, DID was -43 and -826 for the number of adverse drug events and allergic reactions and -$198,700 and $53,318 for medical costs in the inpatient and outpatient settings, respectively. For outpatients, the monthly number of adverse drug events and allergic drug reactions has grown higher for the control group than for the intervention group after the implementation of the pilot project.

Conclusion: Implementation of the DUR modernization pilot project with follow-up service lowered the number of adverse drug events and allergic reactions in the in- and outpatient setting. The project lowered medical costs incurred to manage these events in the inpatient setting only.

24 Global trends of polypharmacy in the elderly: A multinational population-based study

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Aim/Objective: Polypharmacy is a global issue in the aged population, and there is a substantial discrepancy in the prevalence of polypharmacy across countries due to differences in the healthcare system, prescribing behavior, or medication adherence. We aimed to compare global trends of polypharmacy in the elderly.

Methods: We conducted a multinational population-based study comprising four countries: Australia, South Korea, Taiwan, and the United Kingdom (UK). Study populations consisted of all individuals aged 65 years or older between Jan 1, 2003, and Dec 31, 2019, after excluding cancer patients. We defined polypharmacy as the use of ≥5 distinct medications concomitantly for a consecutive period of ≥60 days per year in an outpatient setting. We estimated annual prevalence of polypharmacy with 95% confidence intervals, and average annual percent change (AAPC) was calculated using a Poisson regression to assess the time trends. Stratified analyses were conducted by age-group and sex.

Results: A total of 1.56 million individuals were included in this study, and the prevalence of polypharmacy in 2015 varied across countries: Taiwan, 31.0%; South Korea, 27.1%; Australia, 19.5%; UK, 18.8%. The annual trends in polypharmacy increased over time in all countries except Australia (AAPC: South Korea, 6%; Taiwan, 2%, UK, 1%; Australia, -4%; p-value <0.05). Similar results were observed in sex- and age-stratified analyses; the magnitude of changes in annual trend increased with older age-group in South Korea and Taiwan (4% to 10.3% and 1.7% to 3.2%, respectively; p-value<0.05).

Conclusion: We found that the prevalence of polypharmacy was predominant in South Korea and Taiwan. Moreover, the annual trend increased over time in the Asian population, whereas decreasing or stable trend was found in Australia and UK. This result appears to be related to rapid societal aging and the increasing prevalence of chronic diseases in Asian countries.

Keywords: Polypharmacy, Drug Utilization, Multinational study

25 Association between proton pump inhibitors and dermatologic adverse events – A sequence symmetry analysis

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Aim/Objective: To investigate whether use of proton pump inhibitors (PPIs) is associated with subacute cutaneous lupus erythematosus (SCLE) and other adverse events (AEs) of dermatologic system.

Methods: Population-based claim data were collected from the National Health Insurance Database in Taiwan for the study. We first identified PPI incident users from 2005 to 2012 and further included those who had ever been firstly diagnosed with SCLE or other skin AEs within 6 months before or after the initiation of PPI. These skin AEs included a total of 28 prespecified events ranged from dermatitis, allergic reactions, vasculitis, and ulcers, etc., and were identified by ICD diagnostic codes. Then, we applied sequence symmetry analysis to analyze whether volume of prescription/diagnosis sequence with PPI followed by particular skin AEs is more than the reverse sequence. Background prescription rate of PPI was used to adjust the sequence ratio (SR).

Results: We identified 28,399 patients with different skin AEs within PPI initiation date +/- 6 months. PPI use might be related to occurrence of SCLE with results demonstrated increased adjusted SRs (aSR(95%CI) of 6-mon, 3-mon and 45-day were 1.41 (0.68-2.94), 2.10 (0.86-5.15) and 1.20 (0.36-3.92)) yet not significant due to limited case numbers. Other dermatologic AE revealed as a signal included chronic ulcer of skin (aSR(95%CI) of 6-mon, 3-mon and 45-day were 1.52 (1.37-1.68), 1.50 (1.32-1.70) and 1.31 (1.10-1.55)). Sensitivity analyses with time window of +/- 3-month and 45-day indicated additional signals of urticaria and rash.

Conclusion: PPI use might be associated with occurrence of SCLE, and its association requires larger size data or studies with more rigorous design to confirm. Other dermatologic AE found to be associated with PPI use included chronic skin ulcer, which could be detected as early as 45 days.

Keywords: PPI, adverse event, dermatologic, safety signal

26 Association between the pharmacological treatment of bipolar disorder and risk of trauma - self-controlled case series

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Objective: To investigate the association between different pharmacological agents and risk of trauma-related emergency room (ER) admissions among patients with bipolar disorder (BPD).

Method: We identified adult patients with BPD aged who were treated with either lithium, antipsychotics, valproate, lamotrigine or carbamazepine between 2001-2019 from the Hong Kong Clinical Data Analysis and Reporting System. Individuals who had incident episode of trauma-related ER admissions were included in the analysis. A self-controlled case series design was applied to control the time-invariant characteristics of patients. We divided the patient-time into 5 risk windows: absence of treatment (baseline), 30 days before the first treatment (pre-exposure), first 30 days of treatment, subsequent treatment and 30 days after the treatment (post-exposure). Relative incidence of trauma-related ER admissions at different risk periods were compared.

Results: Among 14021 patients with BPD, 5040 of them were treated with the pharmacological agents and had their first episode of trauma-related ER admission during the study period. An increased rate of trauma-related ER admissions was observed before the treatment started, with an incidence risk ratio (IRR) of 4.44 (95% CI 3.71-5.31). The IRR was dropped to 1.44 (95% CI 1.24-1.67) during the first 30 days of treatment before returning to baseline levels during the subsequent treatment period (IRR=0.97; 95% CI 0.88-1.06). Then IRR was risen to 1.34 (95% CI 1.09-1.66) during the post-exposure period. During subsequent treatment, the dual therapy of lithium and antipsychotics was associated with the reduced risk of trauma-related ER admissions (IRR=0.72; 95% CI 0.59-0.87) among all agents.

Conclusion: The incidence of trauma-related ER admissions was higher after treatment initiation but with a decreasing magnitude and then returned to baseline during continuous treatment. The observed re-growing risk of trauma-related ER admissions soon after treatment cessation implicated the importance that patients should not stop their treatment abruptly without doctors' advice.

27 Association between fluoroquinolone prescription and uveitis: A self-controlled case series

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Aim/Objective: In non-interventional studies fluoroquinolones have been associated with eye toxicity. However, there is concern over residual confounding. Our study aimed to investigate the association between fluoroquinolones and uveitis.

Methods: To eliminate time-invariant confounding we conducted a self-controlled case series using UK primary care data (CPRD GOLD). We included people with recorded incident uveitis and a prescription for either fluoroquinolone or a control exposure used for similar indications, cephalosporin, between April 1997 and June 2019. We used Poisson regression to estimate rate ratios comparing risk of uveitis in risk periods (30 days pre-treatment, day of initial prescription, days 1-29, 30-59, 60 until end of treatment episode) to baseline time, adjusting for calendar time and age.

Results: We included 7,249 eligible individuals (2,042 prescribed a fluoroquinolone only; 3,261 cephalosporin only; 1,946 both). There was little evidence of an association between fluoroquinolone use and uveitis at days 1-29 (adjusted rate ratio 1.23, 95% CI 0.95-1.58), days 30-59 (1.21, 95% CI 0.94-1.56), or days 60+ (0.84, 95% CI 0.50-1.45) following initial antibiotic prescription. There was weak evidence of an association between cephalosporin use and uveitis at days 1-29 (1.25, 95% CI 1.03-1.54), but no evidence at days 30-59 (1.03, 95% CI 0.83-1.28), or days 60+ (1.16, 95% CI 0.80-1.66). For both fluoroquinolone and cephalosporin use there was strong evidence of an association on day 0 (5.62, 95% CI 3.02-10.47; and 3.19, 95% CI 1.66-6.14 respectively).

Conclusion: We saw little evidence of an association between fluoroquinolones and uveitis except on the day of initial antibiotic prescription, which we anticipate may be an artefact of increased recording on the day of primary care appointment. Associations observed with fluoroquinolones and cephalosporins were of similar magnitude suggesting residual temporal confounding relating to underlying infection and health status as a potential explanation for non-null findings.

Keywords: uveitis, fluoroquinolones

28 Effectiveness and safety of low- and normal-dose direct oral anticoagulant estimated by the nationwide claims data in Japan

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Objective: Direct oral anticoagulant (DOAC) is often used at a low dose. We compared effectiveness and safety of low- vs normal-dose DOAC.

Methods: We used claims data of users of an oral anticoagulant (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) between April 2010 and March 2016 from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB Japan). We selected 944,766 subjects with a code of atrial fibrillation (AF) not specified as "valvular AF" before starting an oral anticoagulant after at least 1 year of non-use. The most frequent daily dose was "low " if it was 220 mg dabigatran, 10 mg rivaroxaban, 5 mg apixaban, and 30 mg edoxaban, and "normal " if it was 300 mg dabigatran, 15 mg rivaroxaban, 10 mg apixaban, and 60 mg edoxaban. We conducted 1:1 matching to have DOAC-warfarin pairs using propensity scores estimated from age, sex, 28 diagnoses, and 34 drugs. The outcomes for effectiveness and safety were the first admission for stroke/systemic embolism, and any bleeding, respectively. The Cox model was used to estimate hazard ratios (HRs) for outcomes of DOAC vs warfarin.

Results: Of 570,820 new users of DOAC, 328,048 (57.5%) used low- and 218,078 (38.2%) used normal-dose DOAC. Normal-dose users were younger (51.5 years old) and included more males (73.6%) than low-dose users (62.0 years old and 54.5% males). Without previous history of outcomes, HRs (95% Confidence Intervals) of low- and normal-dose DOAC were 0.61 (0.59-0.63) and 0.60(0.57-0.64) for effectiveness, 0.78 (0.76-0.80) and 0.79 (0.75-0.83) for safety. With previous history, they were 0.74 (0.72-0.75) and 0.90 (0.88-0.94) for effectiveness and 0.83(0.78-0.89) and 1.00 (0.88-1.14) for safety.

Conclusions: Our results are reassuring because low-dose DOAC showed effects not inferior to normal-dose DOAC. Further investigations are warranted to find patient characteristics suitable for low- vs normal-dose DOAC.

29 Assessing the effect of the “antipsychotics-antiparkinsonian agent” prescribing cascade on urinary retention

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Objective: Prescribing cascade (PC) occurs when an adverse drug reaction is mistaken as a new medical condition, and a new treatment is initiated to manage the problem. Previous studies have revealed the existence of “antipsychotics-Parkinsonism-antiparkinsonian agents” PC. Considering there might be additive anticholinergic effect, we aimed to evaluate the effect of this PC on urinary retention.

Methods: We performed a prescription sequence symmetry analysis using Taiwan’s National Health Insurance Database. Study population included new users of antipsychotics (AP) and urinary retention treatments (URT) during 2001-2012, and patients were further divided into those with and without a prescription of antiparkinsonian agents (PAR). We focused on trihexyphenidyl, biperiden, benztropine, and amantadine for PAR, alpha-1 blockers (alfuzosin, tamsulosin, silodosin, doxazosin, and terazosin) and bethanechol for URT. Patients with underlying Parkinson’s disease or benign prostatic hyperplasia were excluded to assure that PAR and URT were related to the PC. Sequence ratio (SR) was calculated for each drug pair (AP-URT, AP-PAR, and PAR-URT) to estimate the temporality of the prescriptions. We restricted the observation period to one year before and after the incident drug to reduce time-varying confounders.

Results: We identified 33,580 patients with a mean age of 66.7 (SD: 16.7). The adjusted SR and 95% confidence interval (CI) for AP-URT was 0.98 (0.93-1.02) in the study population, which turned out to be 2.04 (1.81-2.30) among patients who have used PAR and 0.85 (0.81-0.89) for those have not. The adjusted SRs and 95% CIs were 2.54 (2.24-2.87) for AP-PAR and 1.35 (1.21-1.50) for PAR-URT, which corresponded with previous studies.

Conclusion: Our finding suggested that the “antipsychotics-antiparkinsonian agents” prescribing cascade may account for downstream urinary retention. This highlights the importance of distinguishing between a new medical condition and an adverse drug reaction to avoid unnecessary treatments and outcomes.

Keywords: antipsychotics; antiparkinsonian agents; urinary retention; prescribing cascade

30 Risk of heart failure in Rheumatoid Arthritis patients treated with Tumour Necrosis Factor-α Inhibitors

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Objectives: To compare the risk of heart failure (HF) in rheumatoid arthritis (RA) patients treated with tumour necrosis factor-α inhibitors (TNFi) or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

Methods: We conducted a retrospective cohort study by analysing a multi-institutional electronic medical records database covering 1.3 million individuals (6% of Taiwan's population). We included RA patients aged 20 years and older who had treatment failure with at least 2 different csDMARD regimens and newly switched to another csDMARD regimen or TNFi from 2009-2019. We followed patients from initiation of the new therapies to the occurrence of hospitalization for heart failure (hHF), death, last clinical visit or December 31, 2020. We performed multivariable Cox proportional hazard models to compare TNFi and csDMARD groups for the risk of hHF, with adjustment for patients' characteristics.

Results: A total of 1,278 TNFi and 1,932 csDMARDs treated patients were identified, with 78% being females and having an average age of 55 (SD 13.28) years. The incidence rates of hHF for TNFi and csDMARD groups were 3.66 and 4.72 per 1,000 person-years, respectively (adjusted hazard ratio, aHR, 0.59; 95% CI 0.35-0.97), and the results remained consistent in patients both with an HF history (aHR 0.66; 95% CI 0.03-14.46) and without (aHR 0.49; 95% CI 0.27-0.89).

Conclusions: The findings suggest that those who switched to TNFi had a reduced risk of hHF, compared to those who switched to another csDMARD regimen.

Keywords: Rheumatoid arthritis, heart failure, TNFi, csDMARD

31 Time-to-mortality outcome for Remdesirvir and Favipiravir using in COVID-19 Patients: A systematic review and meta-analysis.

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Objective: Since the emerging pandemic of SARS-CoV-2, antivirals including Favipiravir and Remdesivir has been recommended to be repurposed for COVID-19. However, time-to- mortality outcome for these 2 antivirals have not been resulted. We aim to systematically accumulate mortality rate among COVID-19 patients who were given by Remdesivir and Favipiravir.

Methods: This systematic review and meta-analysis were reported in accordance with the Cochrane Library of Systematic Review. All original English research articles which addressed confirmed SARS−CoV-2 adult patients treating with Favipiravir or Remdesivir were included. We searched electronic database including PubMed, OVID(Medline), Web of Science, and Google Scholars up to 10 May 2021. We assessed the risk of bias of inclusive studies using Cochrane Collaboration criteria. All analyses were performed using Review Managers version 5.4 as well as R software 4.0.5, and the pooled hazard rate was calculated. Funnel plot techniques and Egger's regression test, as appropriate given their known limitations, were intended to assess publication bias. A totally of six studies were eligible to be included in our meta−analysis.

Results: Based on the cohort evidence, we found the COVID-19 patients who received Remdesivir had a lower mortality rate versus the comparative group (HR=0.71, 95%CI: 0.54-0.93; P=0.01) with statistical signifigance, whereas, the result from clinical trials reported a statistically insignificant finding (HR=0.82, 95%CI: 0.62-1.09; P=0.17). Favipiravir did not show the significant difference between two groups with regard to the overall mortality from a randomized clinical trial based on descriptive review.

Conclusion: Remdesivir possibly shows a beneficial effect in aspect of mortality rate among patients with moderate to severe COVID-19 based on cohort evidence. To minimize the potential bias, randomized double-blinded controlled trials or trial emulation using large observational data are highly recommended to increase the statistical power as well as the quality of evidence in meta-analysis.

Keywords: Remdesivir, Favipiravir, Time-to-mortality, COVID-19

32 Real world use of anticoagulation among hospitalized patients with COVID-19 in the United States

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Objectives: To describe the initial type and dose of an anticoagulant among hospitalized COVID-19 patients, inter-institutional variation of anticoagulant use, and the admission characteristics of patients.

Methods: Using the National COVID Cohort Collaborative, one of the largest US electronic healthcare record repositories for COVID-19 research, we created a cohort of hospitalized COVID-19 patients. We identified any users of an anticoagulant within 2 days of admission (enoxaparin, heparin, or direct oral anticoagulant [DOAC]). We then categorized the users into standard prophylaxis (SP), intermediate dose prophylaxis (ID), or treatment dose (TD). We described patients' characteristics and assessed the anticoagulant use by institution and bleeding risk factors.

Results: Among 14,227 hospitalized COVID patients (60% male, mean age of 61, Charlson comorbidity index 2.7) from 6 institutions with harmonizable and detailed drug data, 10,874 (76%) received anticoagulation. Among those who received an anticoagulant, 8,865 (82%), 1,067 (9.7%), and 942 (8.7%) received enoxaparin, heparin, or a DOAC, respectively. Based on the initial dose and BMI, 7,784 (72%), 1384 (13%), and 1,706 (15%) were SP, ID, and TD, respectively. Among individuals on an anticoagulant and available lab data, an ID or TD anticoagulant was provided in presence of D-dimer greater than 1,000, INR >1.5, platelets <150,000, or platelets <100,000, 33%, 73%, 35%, and 34% of the time, respectfully. Among each institution, the use of any anticoagulant, SP and above SP ranged from 64%-84% (median 77%), 42%-69% (median 59%), and 10%-26% (median 18%), respectfully.

Conclusion: Our results support that the majority of patients hospitalized with COVID-19 receive an anticoagulant within 48 hours of admission and the most commonly used dose of anticoagulant is SD. Nevertheless, there is variation of anticoagulant use by institution. Our research will further characterize the use and risks of anticoagulation in COVID-19.

33 Role of oral anticoagulants in COVID-19 related outcomes: Two cohort studies

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Aim/Objectives: To investigate the association between OACs and COVID-19 outcomes among people with atrial fibrillation, using OpenSAFELY, a secure analytical platform.

Methods: On behalf of NHS England, we conducted two cohort studies using primary care data and pseudonymously-linked SARS-CoV-2 antigen testing data, hospital admissions, and death records from England. We used Cox regression to estimate HRs for COVID-19 outcomes comparing current OAC use versus non-use in those with CHA_2DS_2-VASc score of 2 in Study 1; and warfarin versus direct oral anticoagulant (DOAC) regardless of CHA_2DS_2-VASc score in Study 2. We accounted for age, sex, comorbidities, other medications and general practice in both studies.

Results: In Study 1, we observed no difference in risk of being tested for SARS-CoV-2 associated with current use (adjusted HR (aHR), 1.01, 95%CI, 0.96–1.05) versus non-use. We observed a lower risk of testing positive for SARS-CoV-2 (aHR, 0.73, 95%CI, 0.60–0.90), and COVID-19 deaths (aHR, 0.69, 95%CI, 0.49–0.97) associated with current use versus non-use. In Study 2, we observed a lower risk of COVID-19 deaths (aHR, 0.79, 95%CI, 0.76–0.83) associated with warfarin versus DOACs. Similar associations were found for all other outcomes.

Conclusions: Among those at low baseline stroke risk, people receiving OACs had a lower risk of receiving a positive COVID-19 test and severe COVID-19 outcomes than non-users; this might be explained by a causal effect of OACs in preventing severe COVID-19 outcomes or more cautious behaviours leading to reduced infection risk. There was no evidence of a harmful effect of warfarin on COVID-19 outcomes versus DOACs.

34 Pattern of drug utilization among hospitalized COVID-19 patients: A retrospective cross-sectional study in tertiary hospitals in Malaysia

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Objective: COVID-19 pandemic has severely burdened the health care system worldwide. This study aimed to investigate the drug utilization pattern among hospitalized COVID-19 patients in public hospitals in Malaysia.

Methods: This retrospective cross-sectional study was conducted from February 2020 to May 2021. All patients tested positive for COVID-19 and admitted to two public hospitals in East Coast Malaysia were included. Data on patients' age and gender, disease severity, comorbidities, drug treatment and length of hospital stay were extracted from medical and prescription records. Patients were stratified into stages based on the severity of their COVID infection. Stage 1 - 3 are classified as mild, stage 4 as moderate, and stage 5 as critical. Descriptive analysis was conducted using Stata software version 15.3.

Results: A total of 736 patients were included during the study period (62.4% males, mean ± standard deviation; age: 37.8 ± 19.3 years). The patients were classified as mild (97.4 %), moderate (2.5%), and critical (0.1%). Comorbidities were present in 31.3% COVID-19 patients, with hypertension being the most common (21.3%), followed by diabetes (12.8%), coronary heart disease (2%), and lung diseases (1.7%). Patients with COVID-19 received a variety of drug treatments including antivirals (15.4%), antibiotics (4.6%), chloroquine/hydroxychloroquine (12.4%) and corticosteroids (3.4%). The average length of hospitalization for all included patients was 9.9 ± 7.2 days.

Conclusion: The study found that COVID-19 patients were treated with various drug treatments, the majority of which were antiviral agents. This supportive care treatment is based on disease severity and there is currently no evidence to recommend a specific treatment for COVID-19. Future research is needed to evaluate drug utilization and its relevant clinical outcomes in COVID-19 patients.

Keywords: drug utilization pattern, hospitalized patients, COVID-19, Malaysia

35 Medication adherence of Vietnamese patients with chronic diseases during the COVID-19 pandemic

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Objectives: To determine the proportion of medication adherence in chronic disease patients and the association between patients' knowledge of COVID-19 prevention and medication adherence.

Methods: We conducted a cross-sectional study in some southern provinces of Vietnam. Medication adherence was measured using the General Medication Adherence Scale (GMAS), which was translated and validated in Vietnam. Patient knowledge of COVID-19 prevention was assessed using the 5K message of the Vietnam Ministry of Health (facemask, disinfection, distance, no gathering, health declaration). Multivariable regression was applied to determine the association between patients' characteristics and medication adherence.

Results: We included 1852 patients in the study. The majority of those were female (54.6%) and ≥60 years old (55.2%). Wearing facemasks (95.3%) and disinfecting (46.4%) were the most common prevention methods recognized by outpatients during follow-up visits. 57.6% of patients adhered to medications. Low and poor adherence were mostly due to patient behavior (7.6% and 2.4% respectively); in which, medication discontinuation due to experiencing undesirable effects was mostly recorded (6.6%). Patients who agreed that the COVID-19 pandemic obstructed treatment follow-up visits (OR=1.771; 95%CI=1.461-2.147; p<0.001), who recognized ≥2 methods of the 5K message (OR=1.422; 95%CI=1.173-1.725; p=0.001), who were employed (OR=1.677; 95%CI=1.251-2.248; p=0.001), who lived in urban areas (OR=1.336; 95%CI=1.090-1.637; p=0.005), who had education levels at high school or higher (OR=1.313; 95%CI=1.059-1.629; p=0.013), or who had ≤2 comorbidities (OR=1.293; 95%CI=1.044-1.600; p=0.019), were more likely to be adhered to medications.

Conclusions: The proportion of medication adherence of patients with chronic diseases was quite low in southern Vietnam during the COVID-19 pandemic. Patients who did not think the COVID-19 pandemic obstructed treatment follow-up visits or had poor knowledge of COVID-19 prevention were less likely to adhere to medications. Healthcare providers should pay more attention to these groups to achieve the treatment targets.

Key words: Medication adherence; COVID-19; GMAS; 5K; Vietnam.

36 Changes in antibiotic prescribing following COVID-19 restrictions: Lessons for post-pandemic antibiotic stewardship

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Aim: Public health responses to reduce SARS-CoV-2 transmission have profoundly affected the epidemiology and management of other infections. We examined the impact of COVID-19 restrictions on antibiotic dispensing in Australia.

Methods: We used national claims data to investigate antibiotic dispensing trends from November 2015 to October 2020 and whether changes reflected reductions in primary care consultations. We used interrupted time series analysis to quantify changes in monthly antibiotic dispensing and face-to-face and telehealth GP consultations and examined changes by recipient age, pharmacy State, and prescriber specialty.

Results: Over the study period, an estimated 19 921 370 people had 125 495 137 antibiotic dispensings, 71% prescribed by GPs. Following COVID-19 restrictions, we observed a sustained 36% (95% CI: 33% to 40%) reduction in antibiotic dispensings from April 2020. Antibiotics recommended for managing respiratory tract infections showed large reductions (range 51% to 69%), whereas those recommended for non-respiratory infections were unchanged. Dispensings prescribed by GPs decreased from 63.5 per 1000 population for April–October 2019 to 37.0 per 1000 for April–October 2020. Total GP consultation rates remained stable, but from April 2020, 31% of consultations were telehealth.

Conclusion: In a setting with a low COVID-19 incidence, restrictions were associated with a substantial reduction in community dispensings of antibiotics primarily used to treat respiratory infections, coincident with reported reductions in respiratory viral infections. Our findings are informative for post-pandemic antimicrobial stewardship and highlight the potential to reduce inappropriate prescribing by GPs and specialists for respiratory viral infections.