Using a population-wide healthcare database to capture drug-related serious adverse events

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Uncommon adverse effects may not be detected in clinical trials conducted for the registration of new drugs

- Limited sample size
- Limited observation period
- Idiosyncratic reactions

Conventional ways of detecting rare adverse effects

- Large outcome studies (e.g. new drugs for diabetes)
- Long-term follow-up studies
- Phase 4 studies
- US Risk Evaluation and Management Strategy (REMS)
- EU Risk Management Plan (RMP)
- Reports from doctors (UK yellow card)
- Reports from professionals, consumers and manufacturers (FDA Adverse Event Reporting System)
- Registries
- Case controls studies and meta-analysis

Computerised patient data

- Opportunities
  - Big data (many patients, many variables)
  - Linkage of databases
  - Longitudinal
  - Real world unselected patients
- Challenges
  - Analyzable data
  - Accuracy
  - Missing data
  - Validity
  - Confounding
  - Ethical considerations
  - Generalisability to other populations

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Increased risk of sleep apnoea among primary headache disorders: a nationwide population-based longitudinal study

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ABSTRACT

Background Primary headache disorders (PHDs) are associated with sleep problems. It is suggested that headache and sleep disorder share anatomical and physiological characteristics. We hypothesised that patients with PHDs were exposed to a great risk for developing sleep apnoea (SA).

Methods In this retrospective longitudinal study, the data obtained from the Longitudinal Health Insurance Database in Taiwan were analysed. The study included 1346 patients with PHDs who were initially diagnosed and 5348 patients who were randomly selected and age/sex matched with the study group as controls. PHDs, SA, comorbidities and other confounding factors were defined based on International Classification of Diseases, Ninth Revision, Clinical Modification. Cox proportional hazards regressions were employed to examine adjusted HRs after adjusting with confounding factors.

Results Our data revealed that patients with PHDs had a higher risk (HR 2.17, 95% CI 1.259 to 3.739, p<0.05) to develop SA compared with matched cohorts, whereas patients with migraine exhibited a high risk (HR 2.553, 95% CI 1.460 to 4.395, p<0.01). The results showed that patients with PHDs aged 18–44 exhibited highest risk of developing SA. In addition, males with PHDs exhibited an HR 3.159 (95% CI 1.479 to 6.749, p<0.01) for developing SA, respectively. The impact of PHDs on SA risk was progressively increased by various follow-up time intervals.

Conclusion Our results suggest that PHDs are linked to an increased risk for SA with sex-dependent and time-dependent characteristics.

INTRODUCTION

Primary headache disorders (PHDs) are considered as chronic disabling illness, which are characterised by repeated exacerbation and unidentifiable causes. They are of global health concern due to their high prevalence and impact on productivity and quality of life in the sufferers. The association between headache and sleep has been known to be bidirectional. It is observed in many primary headache including migraine, tension-type headache (TTH) and cluster headache.[1–5] Sleep disturbances have been shown to be a trigger for migraine attacks. Recent research has reported that the sleep disturbance was positively associated with TTH.[6] It has been reported that patients with cluster headache suffer from sleep-disordered breathing.[7 8] Although the cause-and-effect relationship between primary headache and sleep disorder has been recognised for many decades, the understanding of actual mechanism underlying PHDs and sleep disorder is still sketchy.

Sleep apnoea (SA), a respiratory disturbance during sleep, has gained increasing attention for its increased global prevalence and consequent deteriorations.[9 10] The disorders have been associated with various health problems including cardiovascular, metabolic and psychiatric disorder. SA has been associated with different degrees of headache.[11] Obstructive SA is known to worsen primary headaches such as migraine and TTH.[4 12] Cluster headache has been associated with SA syndrome during active cluster episode.[13] SA has been shown to be associated with chronic pain.[14 15] On the other hand, a recent study has reported that there is no clear relationship between migraine and obstructive SA in the general population.[16] It has been shown that the presence and severity of SA have no influence on presence and attack frequency of TTH.[17] However, the association between PHDs and SA remains controversial.

It is suggested that headache and sleep share a close relationship, showing a dense anatomical and physiological overlap in the central nervous system. The aim of the present study was to investigate the relationship between PHDs and SA in the general population. In addition, we hypothesised that patients with PHDs had increased risk for developing all type SA using data from the National Health Insurance Research Database (NHIRD).

MATERIALS AND METHODS

Database

This retrospective study analysed the data obtained from Longitudinal Health Insurance Database (LHID) released by the Taiwan National Health Research Institute. LHID contains all original claims data of 1 million beneficiaries, randomly sampled from the registry for Beneficiaries of NHIRD covering more than 99.5% of Taiwan population. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was employed for coding diagnosis by the National Health Insurance programme. The data in the LHID were de-identified and therefore the signed informed consent of participants was waived.

Clinical Data Analysis and Reporting System (CDARS)

- The is an electronic health records system of the Hong Kong Hospital Authority.
- Serious events, such as deaths, strokes and heart attacks, are captured with good accuracy.

Clinical Data Analysis and Reporting System (CDARS)

- The system records patient data from 42 hospitals and institutions, 47 specialist outpatient clinics, and 73 general outpatient clinics.
- The data include demographics, deaths, hospital admissions and discharges, outpatient visits, drug records, diagnoses, procedures, and laboratory tests
- Patient records are anonymized to protect patient identity.
- CDARS had been extensively used for conducting large population-based studies. Data validity has been shown to be high for a variety of diagnoses, including AF (positive predictive value [PPV]=95%), ischemic stroke (PPV=90%), intracranial haemorrhage (ICH) (PPV=95%), and gastrointestinal bleeding (GIB) (PPV=100%).

How CEDARS can be used to answer clinically-relevant questions quickly

- Stroke Incidence in Hong Kong After Recall of Contaminated Generic Valsartan
- Patients with nonvalvular atrial fibrillation treated with dual antiplatelet therapy versus oral anticoagulants
- Diuretic-induced hypokalaemia
- Vancomycin-induced acute kidney injury in Hong Kong in 2012-2016

Stroke Incidence in Hong Kong After Recall of Contaminated Generic Valsartan

SLY Chan, MF Tsoi, TT Cheung & BMY Cheung

Background

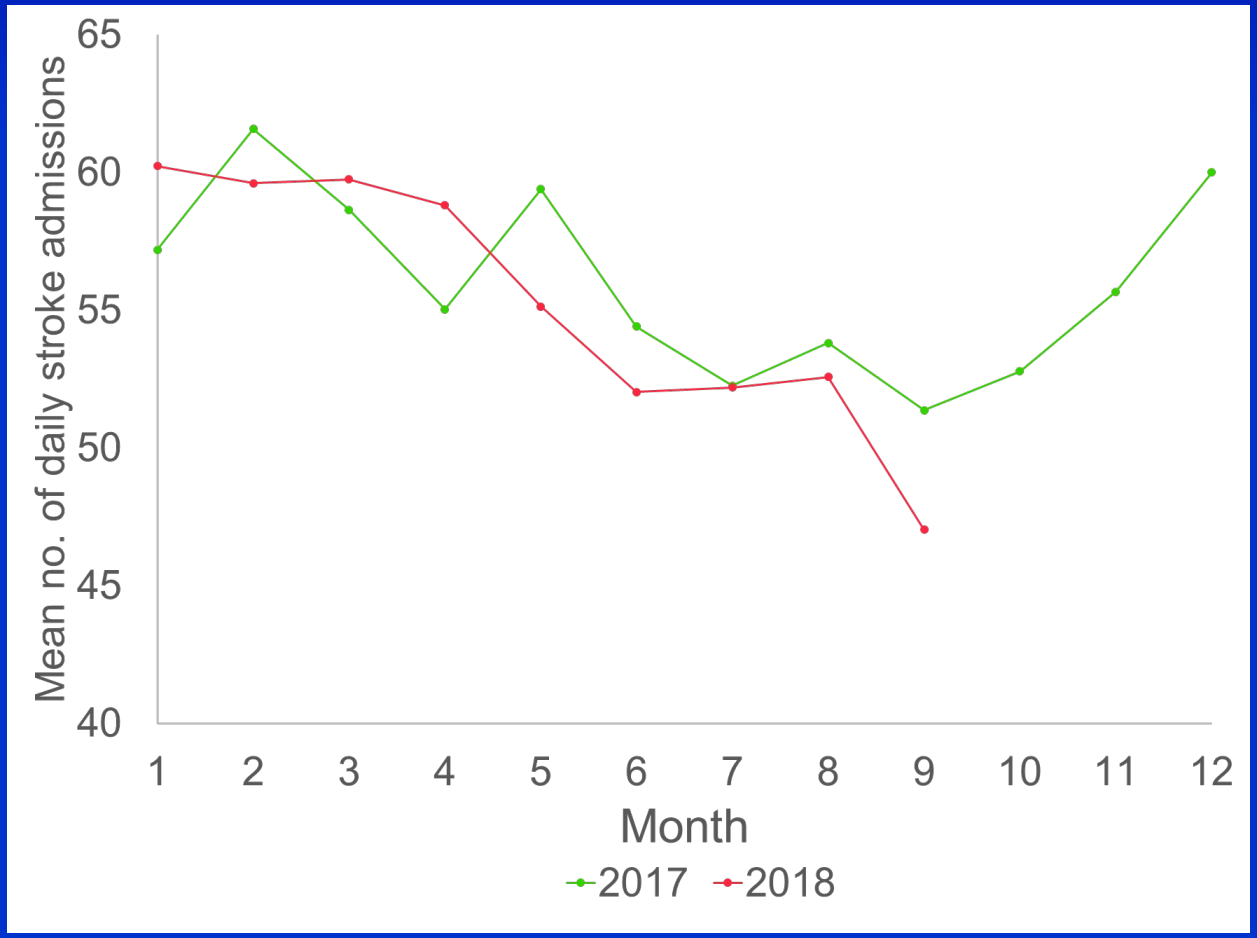
- The Department of Health of Hong Kong made an announcement, with press release, to the medical profession and the public, on 6 July 2018.
- Recall of five generic valsartan products suspected to be contaminated by nitrosodimethylamine
- 30,000 patients were affected
- As strokes could be caused by sudden cessation of antihypertensive treatment and news about contaminated drugs can trigger the cessation of other medications, we investigated the incidence of strokes among Hospital Authority (HA) patients before and after the recall of the contaminated valsartan

Methods

- Patients who had stroke episodes were identified in the Clinical Data Analysis and Report System (CDARS).
- Inclusion Criteria:
  - stroke episodes occurring from 7 July to 10 October 2018 (3/12 after announcement of contamination)
  - stroke episodes occurring from 7 July to 10 October 2017 (control period)
- Demographic variables, concomitant medications, vital status and causes of deaths were obtained from CDARS.
- ICD-9 codes 430, 431, 433.01, 433.11, 433.21, 433.81, 433.91, 434.01, 434.11, 434.91, 435.9, 436 were used as the working definition of acute stroke in this study

	No. of hospitalized admissions due to stroke	
	Mean±SD	Median (Max-Min)
Year 2017		
7/7/2017 – 10/10/2017	52±10	52 (24-71)
7/7/2017 – 4/8/2017	54±10	54 (24-71)
Year 2018		
7/7/2018 – 10/10/2018	51±11.5	51 (25-75)
7/7/2018 – 4/8/2018	54±10.7	54 (31-75)

Monthly stroke admissions in 2017 and 2018



Conclusions

- There was no increase in the number of stroke admissions into Hong Kong Hospital Authority hospitals following the drug recall
- Withdrawal and replacement of generic valsartan products were well managed

Thromboembolic, bleeding, and mortality risks among patients with nonvalvular atrial fibrillation treated with dual antiplatelet therapy versus oral anticoagulants: A population-based study
Lau et al. Heart Rhythm 2019

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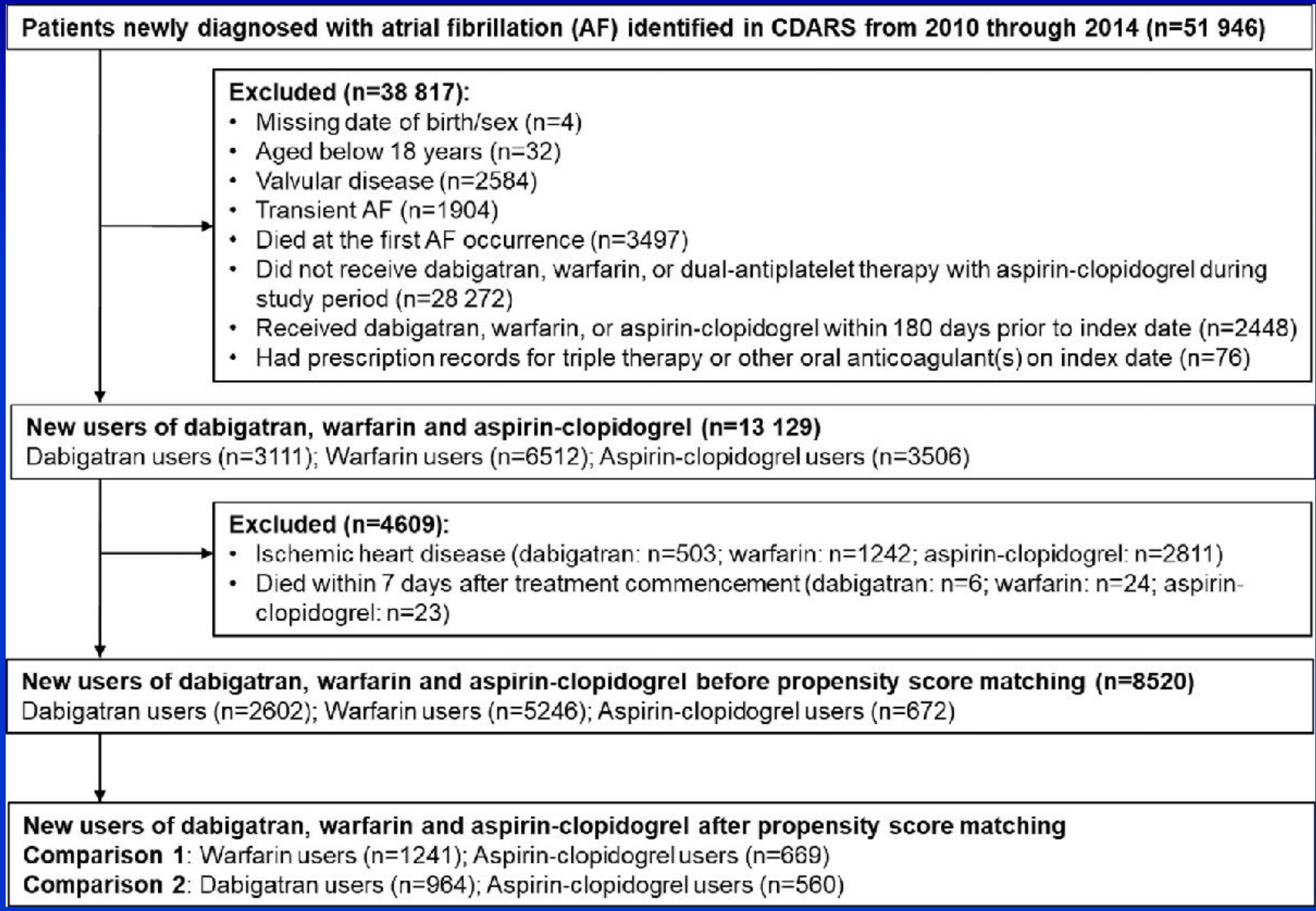
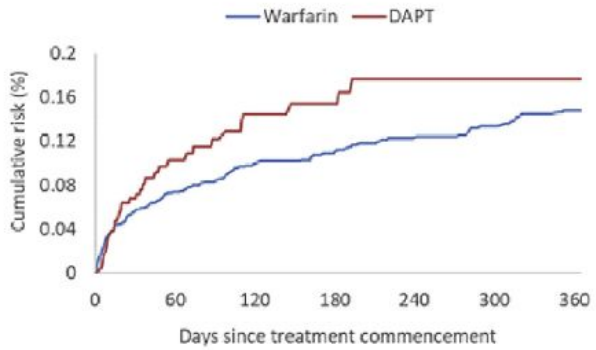
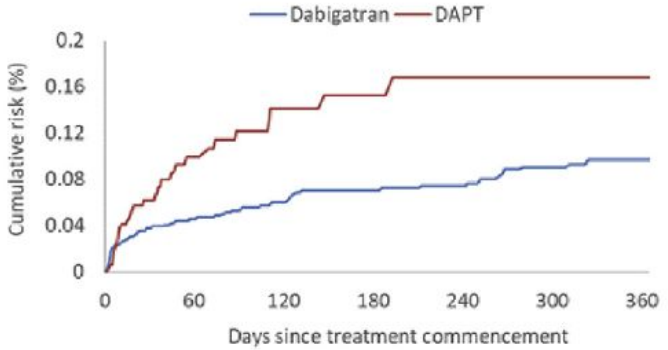
Thromboembolic, bleeding, and mortality risks among patients with nonvalvular atrial fibrillation treated with dual antiplatelet therapy versus oral anticoagulants

- A cohort study using a population-wide database of the Hong Kong Hospital Authority (CDARS).
- New patients with AF from 2010–2014 who were prescribed DAPT or OAC (warfarin or dabigatran) were followed until July 31, 2016.
- Outcomes were thromboembolism, bleeding, and death.
- Propensity score (PS) matching at a ratio of 1:2 was used to select DAPT users with characteristics similar to those of OAC users, analyzed using Poisson regression.
- All observed baseline characteristics had standardized differences <0.1 after matching.

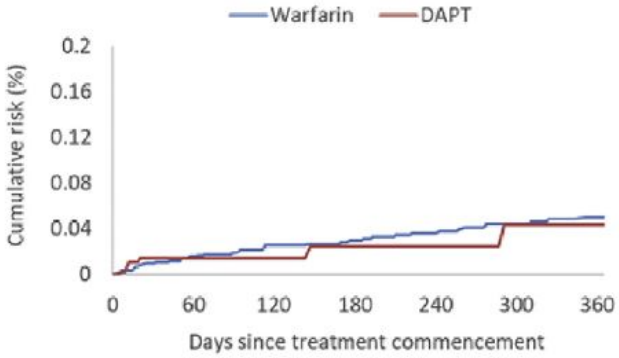

Patients newly diagnosed with atrial fibrillation (AF) identified in CDARS from 2010 through 2014 (n=51 946)
Excluded (n=38 817):
• Missing date of birth/sex (n=4)
• Aged below 18 years (n=32)
• Valvular disease (n=2584)
• Transient AF (n=1904)
• Died at the first AF occurrence (n=3497)
• Did not receive dabigatran, warfarin, or dual-antiplatelet therapy with aspirin-clopidogrel during study period (n=28 272)
• Received dabigatran, warfarin, or aspirin-clopidogrel within 180 days prior to index date (n=2448)
• Had prescription records for triple therapy or other oral anticoagulant(s) on index date (n=76)
New users of dabigatran, warfarin and aspirin-clopidogrel (n=13 129)
Dabigatran users (n=3111); Warfarin users (n=6512); Aspirin-clopidogrel users (n=3506)
Excluded (n=4609):
• Ischemic heart disease (dabigatran: n=503; warfarin: n=1242; aspirin-clopidogrel: n=2811)
• Died within 7 days after treatment commencement (dabigatran: n=6; warfarin: n=24; aspirin-clopidogrel: n=23)
New users of dabigatran, warfarin and aspirin-clopidogrel before propensity score matching (n=8520)
Dabigatran users (n=2602); Warfarin users (n=5246); Aspirin-clopidogrel users (n=672)
New users of dabigatran, warfarin and aspirin-clopidogrel after propensity score matching
Comparison 1: Warfarin users (n=1241); Aspirin-clopidogrel users (n=669)
Comparison 2: Dabigatran users (n=964); Aspirin-clopidogrel users (n=560)

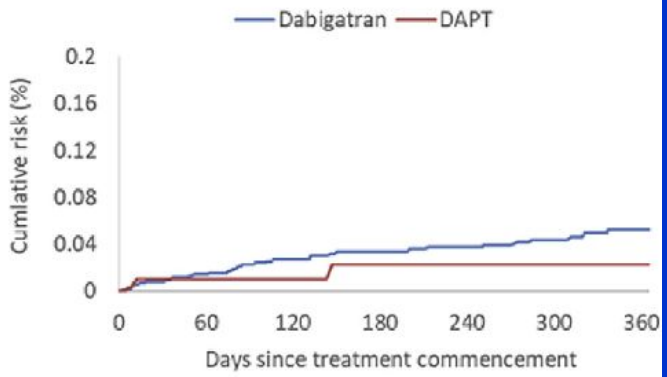
Effectiveness (composite of ischemic stroke, systematic emoblism, and death)



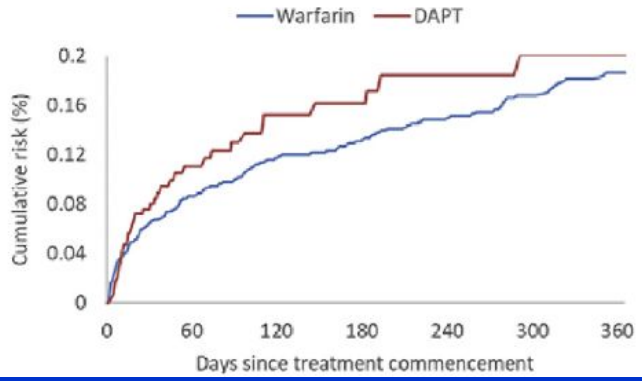


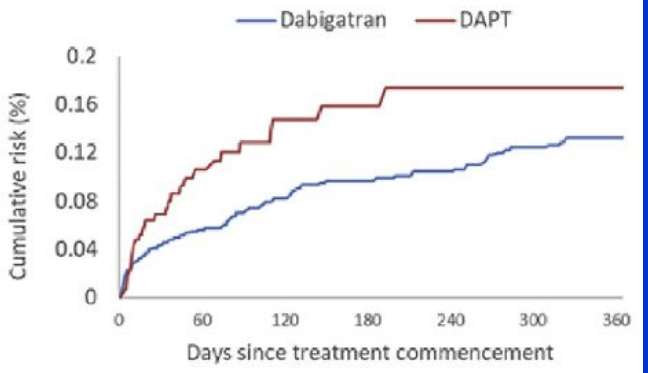
Safety (composite of intracranial hemorrhage and gastrointestinal bleeding)





Net benefit (composite of effectiveness and safety outcomes)





Conclusions

- DAPT users were at markedly increased risk for thromboembolism and death compared to OAC users.
- These findings indicate the need for improved stroke risk reduction strategies among patients taking DAPT
- OAC should be considered in high-risk groups

Diuretic-induced hypokalaemia

Prevalence and risk factors of hypokalemia among thiazide diuretics users in Hong Kong

V Tang et al.

- Hypertension affects ¼ of the population in Hong Kong (Population Health Survey 2014/15)
- Thiazide-type diuretics, mainly hydrochlorothiazide and indapamide, are commonly prescribed (Whelton et al. Hypertension 2017)
- 40% patients receiving diuretics experience hypokalaemia (Gennari et al. NEJM 1998)

Methods

- Patients who hospitalised for hypokalaemia from 2006 to 2017 were identified from the Clinical Data Analysis and Report System.
- Demographic variables, concomitant medications and RFT results were retrieved.
- Results were analysed using R version 3.4.3.


14574 hypokalaemia admissions in 2006-2017
4317 (29.6%) admissions associated with diuretics prescriptions
10257 (70.3%) admissions not associated with diuretics prescriptions
3974 (27.3%) admissions associated with prescriptions of 1 class of diuretics
333 (2.3%) admissions associated with prescriptions of 2 classes of diuretics
10 (0.07%) admissions associated with prescriptions of 3 classes of diuretics
2042 (14.0%) admissions associated with thiazide-type diuretics prescriptions
1538 (10.5%) admissions associated with indapamide prescriptions
1808 (12.4%) admissions associated with loop diuretics prescriptions
124 (0.9%) admissions associated with other diuretics prescriptions
191 (1.3%) admissions associated with prescriptions of loop and thiazide-type diuretics
135 (0.9%) admissions associated with prescriptions of loop and other diuretics
7 (0.05%) admissions associated with prescriptions of thiazide-type and other diuretics

Diuretic-induced hypokalaemia

- Not a major cause of hypokalaemia
- Good awareness of diuretic-induced hypokalaemia
- Indapamide, the most frequently-used diuretic for hypertension, accounted for 1562 (32.84%) of the 4757 cases of diuretic-induced hypokalaemia

Vancomycin-induced acute kidney injury in Hong Kong in 2012-2016

Qin et al.

- Vancomycin is known to induce acute kidney injury (AKI) but is often used in clinical practice for specific indications.
- Our aim was to study vancomycin-induced AKI in the real world.

Vancomycin-induced acute kidney injury in Hong Kong in 2012-2016

- Patients with vancomycin prescription and blood level measurement in 2012-2016 were identified using the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System. AKI was defined using KDIGO criteria.
- 1450 patients were identified as VIN from 12758 records in Hong Kong in 2012-2016.

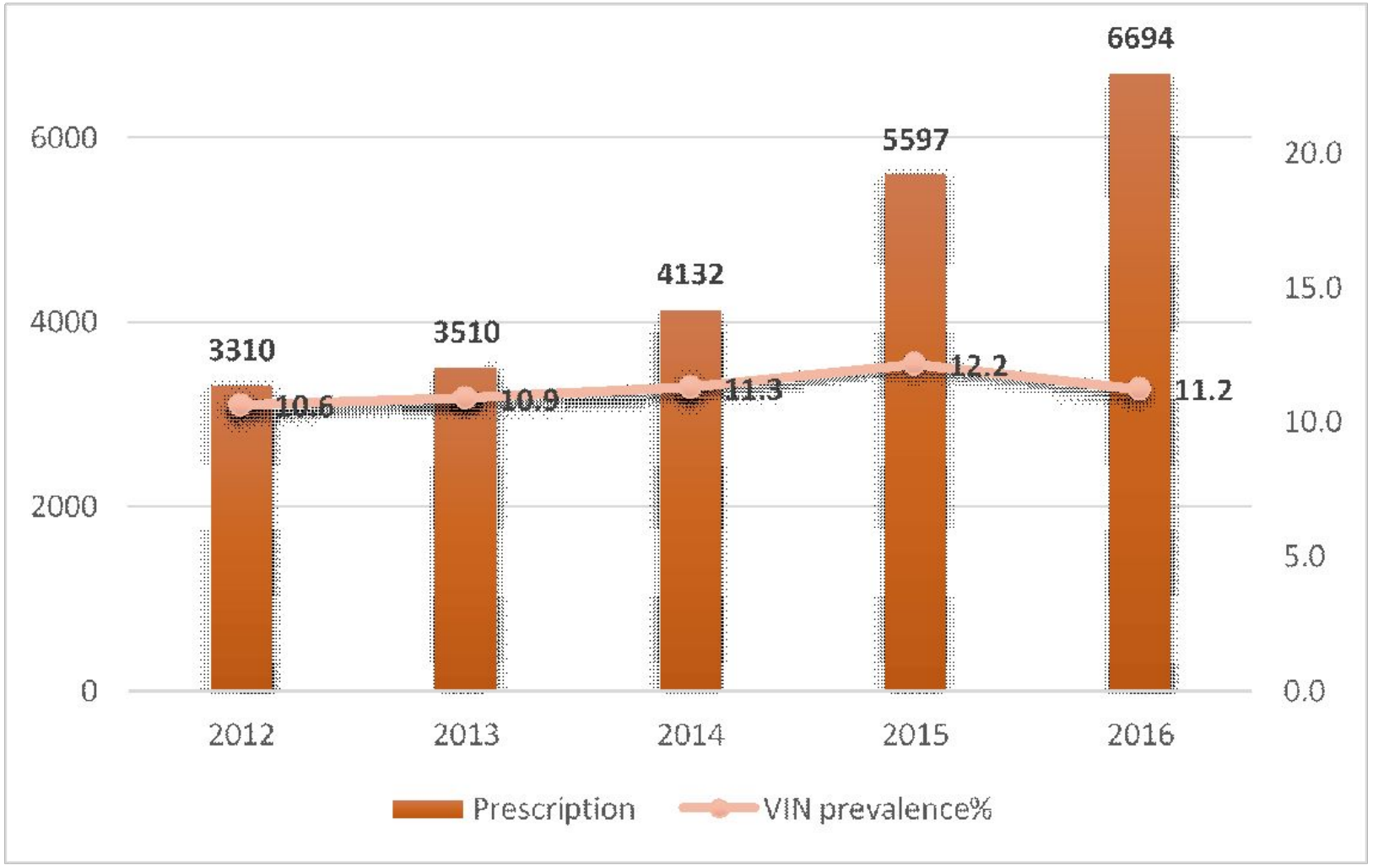


Figure 1 The prevalence of VIN and prescription of vancomycin from 2012 to 2016 in Hong Kong

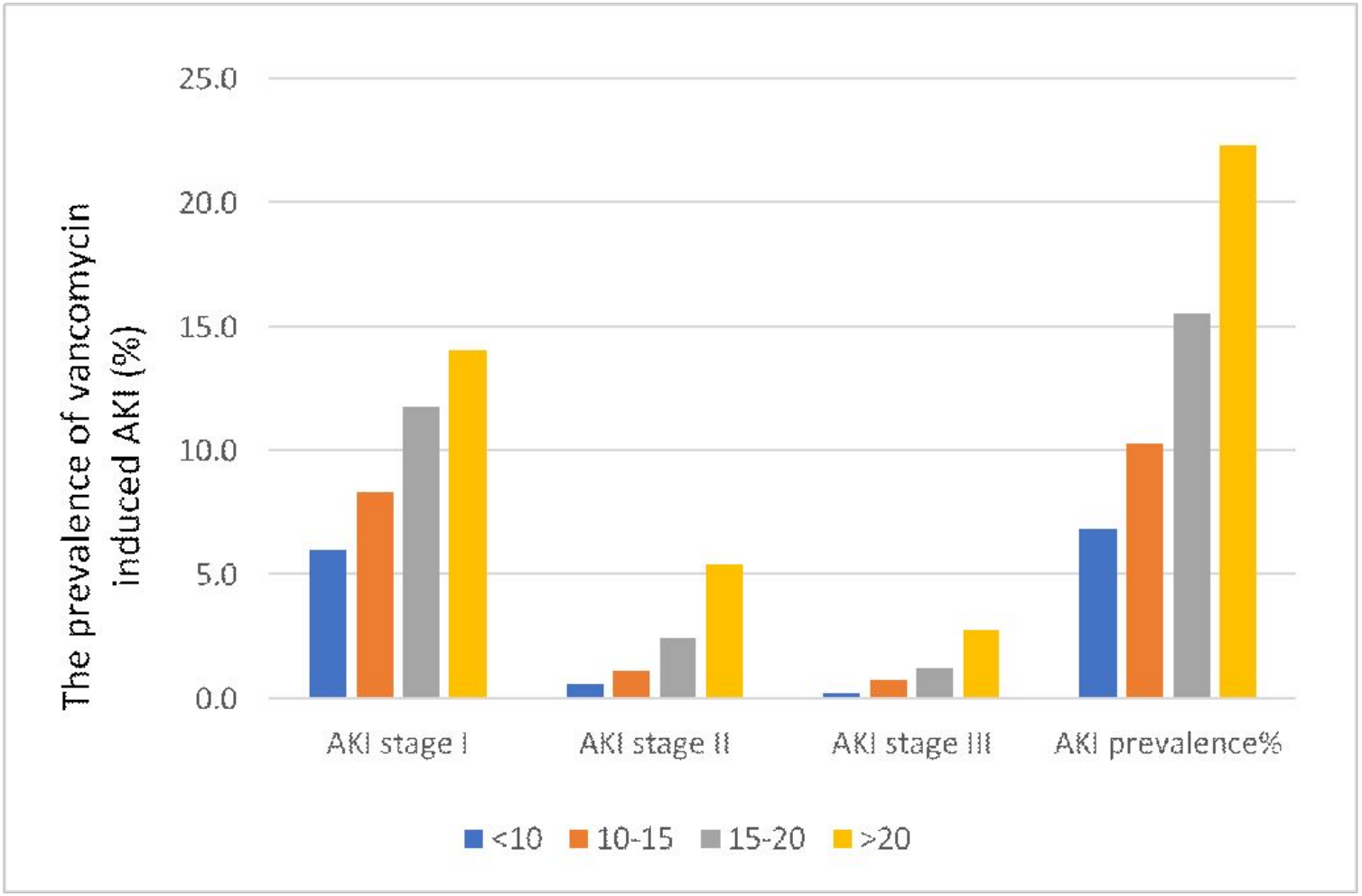


Figure 2 The prevalence of vancomycin induced AKI stratified by vancomycin level (mg/L) and AKI stage

Logistic regression showed that the following factors were associated with increased risk of AKI:

- older age group
- higher baseline creatinine
- serum trough vancomycin level
- respiratory failure
- chronic renal failure
- congestive heart failure
- concomitant diuretics
- piperacillin-tazobactam and meropenem prescription
- longer hospital stay

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- Vicka Tang, for the hypokalaemia study

Using a population-wide healthcare database to capture drug-related serious adverse events

Conclusions

- Large databases are useful for obtaining safety data on drugs
- Advantages include timeliness, large sample size and representativeness
- They complement information from randomised controlled trials, which remain the gold standard for efficacy data