

ORIGINAL RESEARCH ARTICLE

Variation in Association Between Thiazolidinediones and Heart Failure Across Ethnic Groups: Retrospective analysis of Large Healthcare Claims Databases in Six Countries

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Abstract

Introduction The prevalence of polymorphisms among the metabolising enzymes and pharmacodynamic receptors relevant for the thiazolidinediones differs by ethnic group, a factor that may modify risk of adverse drug events.

Objective The aim of the study was to determine if the risk of oedema or heart failure associated with the thiazolidinediones varies in populations in Australia, Canada, Hong Kong, Japan, Korea and Taiwan.

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Methods Sequence symmetry analyses were undertaken to investigate the risk of peripheral oedema, as measured by incident furosemide dispensing, and risk of hospitalisations for heart failure. Results were pooled, with Australia and Canada representing predominantly Caucasian population and all other countries contributing to Asian population estimates.

Results Pooled estimates of risk for furosemide initiation in the Caucasian populations were significantly increased for pioglitazone [adjusted sequence ratio (ASR) 1.47; 95 % confidence interval (CI) 1.14–1.91] and rosiglitazone (ASR 1.65; 95 % CI 1.58–1.72), while in the Asian populations, the pooled risk estimates were lower (ASR 1.11; 95 % CI 0.93–1.32 and ASR 1.21; 95 % CI 1.01–1.45 for pioglitazone and rosiglitazone, respectively). Results for

Key Points

No increased risk of either peripheral oedema or heart failure hospitalisation was found for pioglitazone in the Asian population, while, in the predominantly Caucasian population, pioglitazone was associated with a 47 % increased risk of oedema and an 88 % increased risk of hospitalisation for heart failure.

The risk of oedema and heart failure associated with rosiglitazone was generally lower in the Asian population than in the Caucasian population.

Our results highlight the need for regulatory agencies to consider differences in response to medicines by ethnicity and for more research to determine the incidence of adverse events across ethnic groups.

hospitalisation for heart failure showed a similar trend, with elevated risk in the Australian data (ASR 1.88; 95 % CI 1.01–3.5 and ASR 1.25; 95 % CI 0.76–2.05 for pioglitazone and rosiglitazone, respectively), while no increased risk was found in the pooled results for the Asian populations.

Conclusion The risk of both oedema and heart failure with thiazolidinediones was higher in predominantly Caucasian countries than in the Asian countries assessed. Assessment of adverse events by ethnicity may support safer medicine use.

1 Introduction

Meta-analytic evidence from randomised controlled trials shows that the thiazolidinediones rosiglitazone and pioglitazone are associated with heart failure and oedema [1–3]. Rosiglitazone appears to have a higher risk of heart failure than pioglitazone [4, 5]. A meta-analysis of comparative, observational studies (12 cohort studies and four case–control studies) found a 22 % [pooled odds ratio 1.22; 95 % confidence interval (CI) 1.14–1.31] increased risk for heart failure with rosiglitazone compared with pioglitazone on the basis of data from eight studies [5]. Another meta-analysis, limited to cohort studies only, reported similar results [4]. In both meta-analyses, all but one of the included studies were undertaken in the USA, Canada or the UK, with the remaining study from Taiwan [4, 5].

It is important to assess the safety of the thiazolidinediones across all ethnic groups as there is the potential for the adverse event profile to differ. In vitro studies show pioglitazone is metabolized by the polymorphic enzymes *CYP2C8* and to a lesser extent *CYP3A4* [6], while rosiglitazone is metabolised by *CYP2C9* and *CYP2C8* [7]. The prevalence of *CYP2C8* genotypes varies across ethnic groups, with one report finding a *CYP2C8*3* allele frequency of 9 % in Caucasians and 2 % in Asians [8] and another showing up to 17 % in Southern European populations and none in the Japanese population [9]. A novel *CYP2C8* variant, *CYP2C8*11* was not found in Caucasians or African Americans, but was found in up to 1 % of Vietnamese [10]. *CYP2C8*11* was found to increase clearance of rosiglitazone [10]. The presence of the *CYP2C8*3* allele has also been shown to increase the clearance of rosiglitazone [11] and pioglitazone [12] and to affect glycaemic control [13]. Reactive metabolites of the thiazolidinediones have been linked to liver toxicity [14], and so may have the potential to influence other adverse events; however, we located no publications reporting their contribution to adverse cardiac events.

The prevalence of the *CYP2C9* genotype also varies across ethnic groups, with *CYP2C9*1* present in 60 % in

the Caucasian population compared with 93 % in the Japanese, 92 % in the Chinese, 91 % in the Korean and 91 % in other Asian populations [15]. *CYP2C9*2* is present in up to 19 % of Caucasian populations; however, it is virtually non-existent in East Asian populations [9]. *CYP2C9*3* variants are also more common in Caucasian populations than in East Asian populations [9]. These large variations might have the potential to impact on the metabolism and effect of rosiglitazone.

Further, there is the potential for pharmacodynamic-based variation in response to the thiazolidinediones across ethnic groups. Thiazolidinediones are thought to exert their action by binding to peroxisome proliferator-activated receptor-gamma [16]. This receptor also has variants, with the *Pro 12Ala* polymorphism thought to reduce transcriptional activity [17]. This polymorphism has been shown to affect risk of type 2 diabetes, glucose control and lipid profiles [18–20]. Variation in the prevalence of this polymorphism occurs across ethnic groups, with a prevalence of 4 % in the Japanese population [19] and 14 % in the Danish population [18]. Another gene, the adiponectin (*ADIPOQ*), has also been reported to be associated with thiazolidinediones response. Treated with pioglitazone, type 2 diabetes mellitus (T2DM) patients with the *ADIPOQ C-11377 CC* genotype were associated with a significantly smaller reduction in glycated haemoglobin (HbA_{1c}) compared with the minor G allele carriers [21]. In rosiglitazone therapy, *ADIPOQ C-11377 CC* genotype T2DM patients had a greater reduction in fasting plasma glucose compared with the CG and GG genotypes carriers [22].

Collectively, these polymorphic variations, which vary in prevalence across ethnic groups, affect both pharmacokinetic and pharmacodynamic responses to the thiazolidinediones and have been shown to affect hypoglycaemic response to the medicines. The variations may also affect the prevalence of adverse events across populations; however, this has not been the focus of studies to date. Given the ongoing concerns about risk of heart failure and oedema with the thiazolidinediones, the purpose of this study was to determine if the risk of heart failure and oedema associated with the thiazolidinediones (i.e. rosiglitazone and pioglitazone) varied between populations located in Asia, Australia and Canada.

2 Methods

In order to study whether the risk of heart failure and oedema with thiazolidinediones differed between ethnic groups, we performed a study among member groups of the Asian PharmacoEpidemiology Network (AsPEN) [23]. AsPEN provides a mechanism to support the conduct of

cross-country pharmacoepidemiologic research to facilitate prompt detection and communication of emerging safety issues between countries. The AsPEN participants in this study were based in Australia, Hong Kong, Japan, Korea and Taiwan. The datasets included the Australian Government Department of Veterans' Affairs healthcare claims database (Australia) (2005–2010), the Australian Government Drug Utilisation Subcommittee dataset (2005–2009), the Clinical Data Analysis and Reporting System (Hong Kong) (2008–2012), the Japan Medical Data Centre insurance claims database (2005–2010), the Hamamatsu Medical University Database (Japan) (1999–2010), the Korea Health Insurance Review and Assessment Service database (HIRA DB) (Korea) (2006–2008), and the National Health Insurance Research Database (Taiwan) (2002–2008). The Australian dataset contains prescription and hospital claims records for all veterans and their dependents in Australia (approximately 300,000) and represents a predominantly elderly cohort. The Hong Kong dataset is a national electronic healthcare record of public hospitals and their ambulatory clinics, covering over 7 million persons. The Japanese dataset represents a privately insured population of approximately 300,000; an adult working population and their dependents. The Hamamatsu Medical University Database is a hospital records database covering approximately 200,000 persons. The Korean data are from the national insurance data and include the entire population of approximately 50 million persons. The Taiwanese dataset is also a national insurance dataset covering 23 million persons, and a random sample of 1 million persons was included in this study [23]. All these datasets encompass patient-level dispensing data, which include the following: a patient identifier, patient demographics, date of medicine supply, medicine dispensed, quantity and strength. Medicines are mapped from individual country-specific codes to the WHO Anatomical Therapeutic Chemical (ATC) classification codes [24]. Patient-level hospital datasets are also available, which include a patient identifier, patient demographics, date of admission and discharge, primary diagnoses, secondary diagnoses, and procedures undertaken during admission. Diagnoses are coded according to the International Classification of Diseases (ICD) 9th or 10th edition [25]. In addition to these datasets, we also used the national prescription dispensing dataset from Australia. This patient-level dataset includes all prescriptions reimbursed under Australia's national health insurance for pharmaceuticals and covers a population of 23 million persons. The Canadian Institute for Health Information (CIHI)'s National Prescription Drug Utilization Information System (NPDUIS) (2000–2012) was used to enable comparisons between Australia and Canada, countries thought to have populations of similar ethnic mix. NPDUIS contains public drug claims data from seven jurisdictions in Canada. Patient-linked

hospital datasets at the national level were not available for inclusion in the analyses for Australia or Canada.

We used sequence symmetry analysis (SSA), a signal detection method for adverse drug events utilising administrative claims data [26], to assess the association between the thiazolidinediones and oedema or heart failure across countries. The method has been validated against adverse events identified in randomised controlled trials and against negative controls from product information of unrelated products [27]. The method has also been validated in a simulation study [28]. The method has been shown to have a similar performance to signal detection methods used with spontaneous adverse drug reaction reports [29], and the method has been shown to provide timely signals for cardiovascular events with the thiazolidinediones [30]. The AsPEN initiative works on a distributive network model [31] that requires participants to create a common minimum dataset including (1) a unique patient identifier; (2) a variable to identify the medicine dispensed based on the WHO standard ATC code; and (3) a variable to identify the date of medicine supply; and when using hospital datasets (4) a variable to identify the date of admission and (5) a variable to identify the primary diagnosis of interest based on the ICD code. The co-ordinating centre for this study, the University of South Australia, developed the statistical analysis code as a stand-alone SAS program for execution by each participant in their home institution. The SAS program used global macro variables, which required participants to enter the variable names used in their datasets rather than forcing the creation of a data file with common data variable names. This approach eliminates a complex programming burden for participants and overcomes barriers due to language and disparate data structures. Participants executed the SAS code, and a standardised file of summary results was returned to the co-ordinating centre for collation. These standardised files included graphics of the number of people dispensed the study medicines each month (prevalent population), the number of people starting study medicines each month (incident population), and the results of the SSA, including the graphics showing temporal sequences.

Pioglitazone and rosiglitazone were available in all countries with the exception of Japan, where rosiglitazone only was available. Outcomes assessed were:

1. The first dispensing of furosemide (ATC code C03CA01) as an indicator medicine for oedema (furosemide is also used in exacerbations of heart failure).
2. The first hospital admission with a primary diagnosis of heart failure (ICD 10 codes I50 or ICD 9 code 428) as the indicator of heart failure, where hospital data were available.

We also included analyses for each outcome with metformin (ATC code A10BA02). Metformin served as a marker of the background rate of cardiovascular adverse events associated with initiation of medicines for diabetes, as some people will have established cardiovascular disease at the time of first commencing therapy for diabetes.

In the SSA method, the dates of incident dispensing of rosiglitazone, pioglitazone, metformin, and furosemide and hospitalisation for heart failure were determined for each individual patient. All incident dispensings that occurred within 1 year of each other for the same person were included in the analysis. We excluded patients who initiated any of the study medicines in the first year of data coverage in any dataset to ensure we limited the analyses to incident users. The crude sequence ratio (SR) was calculated by dividing the number of persons with furosemide initiated after rosiglitazone initiation with the number of persons with furosemide initiated prior to rosiglitazone. The SR estimates the incidence rate ratio of the event in exposed compared with non-exposed person-time. The SSA method uses a within-person design, making it robust towards confounders that are stable over time [26]; however, it is sensitive to prescribing trends over time. Therefore, a null-effect SR was calculated to adjust for temporal trends. The null-effect SR is the expected SR in the absence of a causal association, given the incident medicine use and events in the background population. A description of the formula used for this value is provided elsewhere [32]. An adjusted SR was obtained by dividing the crude SR by the null-effect SR, and 95 % CIs were calculated [32]. The same analyses were undertaken for the other medicines and the hospitalisation outcome. The SSAs were restricted to sequences of incident dispensings or sequences of dispensings and hospitalisations within 12 months of each other to limit the effect of age and other potential time-varying covariates on the probability of exposure and outcome. Moreover, a 12-month period has better specificity and positive predictive value compared with shorter periods [27]. Results were pooled according to countries predominant ethnic mix; thus Japan, Hong Kong, Korea and Taiwan were pooled for the Asian cohort, with Canada and Australia contributing to the Caucasian cohort. Pooled estimates were obtained with a random effect model, using the generic inverse variance method [33].

3 Results

3.1 Oedema

With regards to the oedema outcome, there were significant associations between incident rosiglitazone use and incident furosemide dispensing in Australia and Canada, with

the pooled Australia–Canada estimate also significant [adjusted sequence ratio (ASR) 1.65; 95 % CI 1.58–1.72] (Fig. 1). Korea and Taiwan had similar point estimates, with only the result in Korea reaching statistical significance. These risk estimates were lower than Australia–Canada results (Fig. 1). There was a significant elevated risk in Hong Kong, which was of greater magnitude than the risk identified in the predominantly Caucasian populations. The pooled estimate for the Asian population was significant (ASR 1.21; 95 % CI 1.01–1.45), but the magnitude of the estimate was lower than the predominantly Caucasian population result.

For incident pioglitazone use, there was a significant association with incident furosemide dispensings within each predominantly Caucasian country and when the results were pooled (ASR 1.47; 95 % CI 1.14–1.91) (Fig. 2). In Japan, Korea and Taiwan, there was no significant association; however, results in Hong Kong were elevated. The pooled Asian population estimate was not significant (ASR 1.11; 95 % CI 0.93–1.32).

For incident metformin use, there was a significant association between metformin and incident furosemide dispensing in the pooled predominantly Caucasian population (ASR 1.26; 95 % CI 1.05–1.50) (Fig. 3); however, this was lower than the pioglitazone and rosiglitazone estimates. No significant association was found for metformin in the pooled Asian population (ASR 1.08; 95 % CI 0.95–1.22).

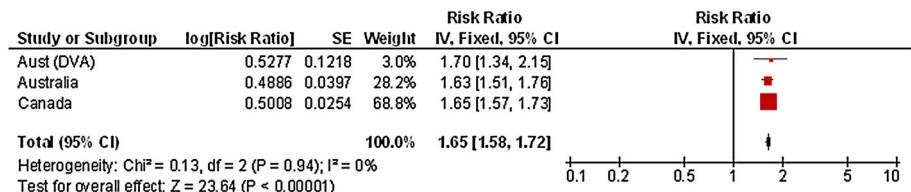
3.2 Heart Failure

The risk of hospitalisation for heart failure after rosiglitazone initiation was not significant in the Australian veteran population (ASR 1.25; 95 % CI 0.76–2.05). For pioglitazone, there was a significant association with heart failure hospitalisation (ASR 1.88; 95 % CI 1.01–3.5). There was no association between metformin use and hospitalisation for heart failure (ASR 1.11; 95 % CI 0.89–1.38).

No significant risk was observed for rosiglitazone use and heart failure hospitalisation in Taiwan; however, a significantly elevated risk was observed in Hong Kong (ASR 5.16; 95 % CI 1.53–17.35) and a slightly elevated risk in Korea (ASR 1.20; 95 % CI 1.01–1.42) (Fig. 4). The estimate for rosiglitazone and risk of hospitalisation for heart failure in the pooled Asian population was not significant (ASR 1.24; 95 % CI 0.84–1.83). For pioglitazone there were no significant associations in Japan, Korea or Taiwan, but there was for an increase in Hong Kong. No significant association was found when results were pooled (ASR 1.06; 95 % CI 0.79–1.43) (Fig. 4). No significant association was found in any Asian country or in the pooled analysis between metformin and heart failure hospitalisation (ASR 0.96; 95 % CI 0.89–1.04) (Fig. 4).

Fig. 1 Sequence symmetry analysis results for incident rosiglitazone use and risk of incident furosemide use. *Aust (DVA)* Australian Government Department of Veterans' Affairs healthcare claims database, *Australia* Australian Government Drug Utilisation Subcommittee dataset, *CI* confidence interval, *IV* inverse variance, *SE* standard error

Incident rosiglitazone and incident furosemide: Australian and Canadian populations



Incident rosiglitazone and incident furosemide: Asian populations

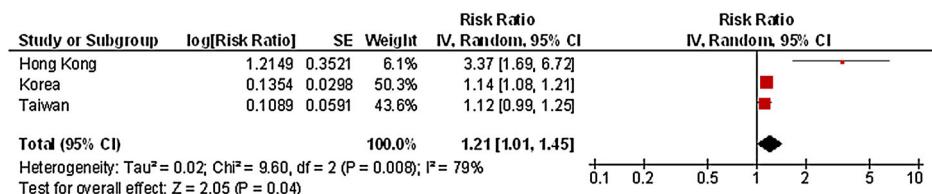
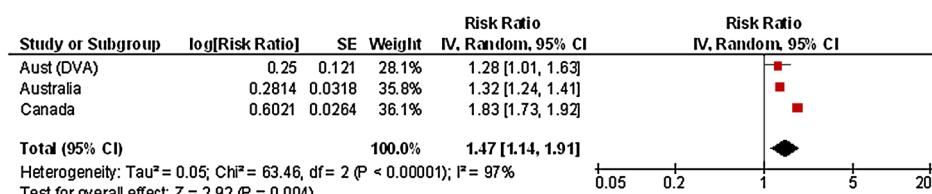
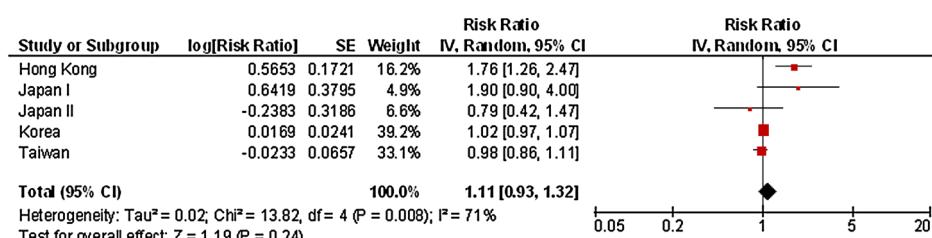


Fig. 2 Sequence symmetry analysis results for incident pioglitazone use and risk of incident furosemide use. *Aust (DVA)* Australian Government Department of Veterans' Affairs healthcare claims database, *Australia* Australian Government Drug Utilisation Subcommittee dataset, *CI* confidence interval, *Japan I* Japan Medical Data Centre insurance claims database, *Japan II* Hamamatsu Medical University Database, *IV* inverse variance, *SE* standard error

Incident pioglitazone and incident furosemide: Australian and Canadian populations



Incident pioglitazone and incident furosemide: Asian populations



4 Discussion

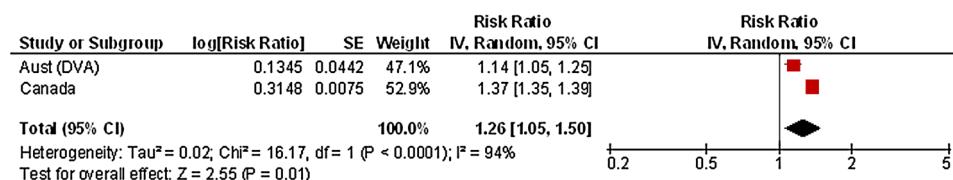
This is the first study to examine variation in the risk of oedema and heart failure associated with the thiazolidinediones by ethnic population. We found elevated risk for oedema, as indicated by furosemide dispensings, in the Australian and Canadian populations for both pioglitazone and rosiglitazone, results which are consistent with meta-analytic results from randomised controlled trials [1]. By

contrast, we found no elevated risk of oedema with pioglitazone in Korea, Taiwan or Japan, although the risk was elevated in the Hong Kong population. Results for rosiglitazone were elevated when estimates for the Asian population were pooled, but were lower than the pooled estimates for the Australian and Canadian populations for the same medicine.

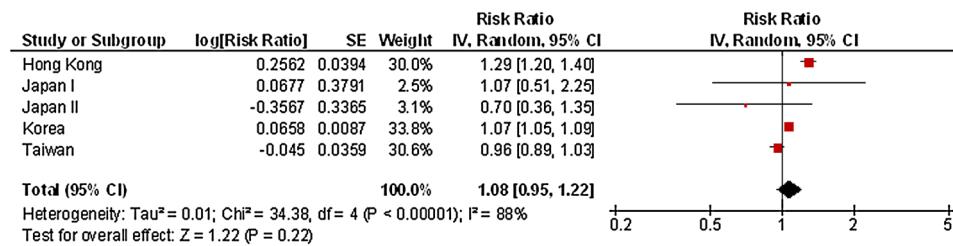
With regard to the risk of hospitalisation for heart failure, we only found elevated risk with rosiglitazone and

Fig. 3 Sequence symmetry analysis results for incident metformin use and risk of incident furosemide use. *Aust* (DVA) Australian Government Department of Veterans' Affairs healthcare claims database, *CI* confidence interval, *Japan I* Japan Medical Data Centre insurance claims database, *Japan II* Hamamatsu Medical University Database, *IV* inverse variance, *SE* standard error

Incident metformin and incident furosemide: Australian and Canadian populations



Incident metformin and incident furosemide: Asian populations



pioglitazone in the Hong Kong population, rosiglitazone in Korea and pioglitazone in the Australian veteran population. The limited sample size in Australia is likely to have reduced the study power for this endpoint for rosiglitazone. No significant risk of heart failure was found with pioglitazone in Korea, where a large sample size was available.

We used metformin and risk of dispensing for furosemide or a hospitalisation with a primary diagnosis of heart failure as indicators of the background rate of oedema and heart failure associated with diabetes diagnosis. We found that in the Australian and Canadian populations, the risk of oedema was higher with the thiazolidinediones compared with metformin; however, CIs did overlap. In the Asian populations, the risk of oedema with rosiglitazone was higher than that with metformin, while pioglitazone and metformin results were similar. The risk of hospitalisation for heart failure was similar among all three diabetes medicines for Korea and Taiwan, but elevated in Hong Kong for the thiazolidinediones compared with metformin. The underlying reason for the elevated risks of oedema and heart failure hospitalisation in Hong Kong is unclear; it may be that there are different treatment pathways in Hong Kong compared with the other Asian countries that influence these results.

The risk estimates in our study for oedema were higher for rosiglitazone than pioglitazone; by comparison, a published meta-analysis reported similar risk estimates between the two thiazolidinediones [1].

While not conclusive, our results are suggestive of a potential difference in risk of adverse events across countries, with slightly lower estimates in most Asian countries,

with the exception of Hong Kong, compared with Australia and Canada. Differences in the underlying prevalence of polymorphisms in both metabolising enzymes and pharmacodynamic receptors may have played a role; however, differences in other factors, including diet, physical activity or healthcare practice may also be contributors.

Our results highlight the need for regulatory agencies to consider differences in response to medicines by ethnic group and for more research to determine the incidence of adverse events across ethnic groups. Rosiglitazone was withdrawn from the European market in 2010 because of its adverse effect profile and has also been withdrawn from India, New Zealand, Hong Kong and South Africa; however, it is still available in Australia, the USA, Korea and Taiwan. If more research was undertaken to shed light on how adverse events varied by ethnicity, it may be that more nuanced regulatory responses, rather than whole-of-country withdrawal, could be developed.

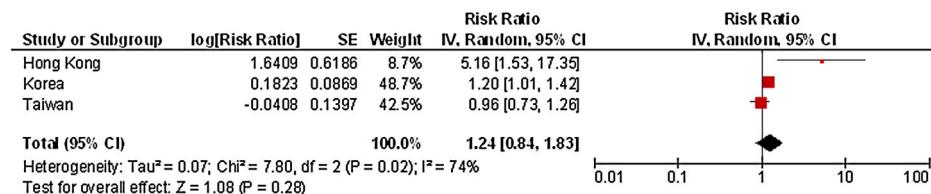
Our research study has several strengths, including the large populations under study. The total population from Australia and Canada was over 46 million; the total population from the Asian countries was over 80 million. We used standardised code and standardised data variables to avoid differences due to coding. We also used metformin as a marker of the background rate of adverse events associated with diabetes and medicine initiation. Limitations of our study include a lack of diagnostic information at the outpatient level in the majority of countries, and hence the reliance on furosemide as the proxy indicator for oedema. Furosemide is also used for the management of exacerbation of heart failure. Given both outcomes are

Fig. 4 Sequence symmetry analysis results for incident diabetes medicine use and risk of incident heart failure hospitalisation: Asian countries. CI confidence interval, Japan I Japan Medical Data Centre insurance claims database, IV inverse variance, SE standard error

Rosiglitazone and heart failure hospitalisation: Australia (Canadian data unavailable)

Risk ratio, 95% CI
1.25; [0.76, 2.05}

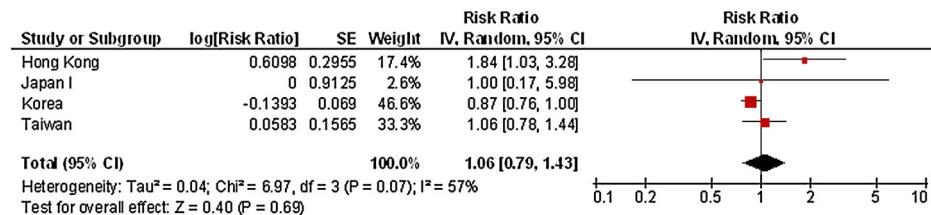
Rosiglitazone and heart failure hospitalisation: Asian countries



Pioglitazone and heart failure hospitalisation: Australia (Canadian data unavailable)

Risk ratio, 95% CI
1.88; [1.01, 3.5}

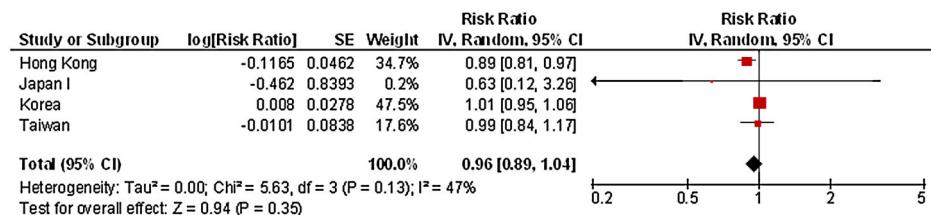
Pioglitazone and heart failure hospitalisation: Asian countries



Metformin and heart failure hospitalisation: Australia (Canadian data unavailable)

Risk ratio, 95% CI
1.11; [0.89, 1.38}

Metformin and heart failure hospitalisations: Asian countries



adverse events of the medicines of interest and the risk of each adverse event is likely to be proportional, this limitation should not affect the comparisons between countries. A second limitation is the lack of large datasets for the hospitalisation outcome in Canada and Australia, limiting

the strength of conclusions that could be drawn regarding the more serious outcome of heart failure hospitalisation. A third limitation is the differences in medications available in each country, resulting in the exclusion of some comparisons. A further limitation is that ethnic data were not

available, leading to a potential misclassification bias where the non-Caucasian population in Australia and Canada was pooled in the Caucasian population. The ethnic information, therefore, needs to be documented in healthcare claims datasets to facilitate the assessment of ethnic differences. Finally, we cannot exclude the possibility that some of the differences observed across countries may be due to differences in healthcare practice. However, the consistency of results in Japan, Korea and Taiwan suggests this impact, if real, is unlikely to be large.

5 Conclusion

Our multi-national study to assess differences in adverse events across the Asian and predominantly Caucasian ethnic populations is suggestive of differences in the incidence of oedema and heart failure by ethnic group, with risk estimates generally being lower in the Asian populations. While differences in environmental factors, including diet, physical activity or healthcare practice, may also be contributors, greater consideration to quantifying adverse events by ethnic group as part of regulatory assessment and post-marketing surveillance assessment is required.

Compliance with ethical standards

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Conflict of interest Elizabeth E. Roughead, Esther W. Chan, Nam-Kyong Choi, Michio Kimura, Tomomi Kimura, Kiyoshi Kubota, Edward Chia-Cheng Lai, Kenneth K.C. Man, Tuan A. Nguyen, Nobuhiro Ooba, Byung-Joo Park, Tsugumichi Sato, Ju-Young Shin, TongTong Wang, Jenna Griffiths, Ian C.K. Wong, Yea-Huei Kao Yang, and Nicole L. Pratt have no conflicts of interest that are directly relevant to the content of this study.

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