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DRUG SAFETY

Comparative cardiovascular risks of dipeptidyl peptidase 4 inhibitors with other second- and third-line antidiabetic drugs in patients with type 2 diabetes

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Keywords cardiovascular diseases, dipeptidyl peptidase 4 inhibitors, hypoglycaemia, type 2 diabetes

AIMS

Dipeptidyl peptidase 4 inhibitors (DPP4is) are suggested as a second- and third-line antidiabetic treatment for type 2 diabetes. Previous studies assessed only the cardiovascular effects of DPP4is as a second-line treatment, included sulphonylurea as the only comparator, and yielded inconclusive results on the risk of heart failure. The present study therefore evaluated the comparative cardiovascular risks of DPP4is with other second- and third-line antidiabetic drugs.

METHODS

Based on a large nationwide diabetic cohort, 113 051 patients with type 2 diabetes newly on metformin-based dual or triple therapy were identified in 2009–2011 and followed until 2013, or death if this occurred sooner. Primary interest targeted hospitalizations for ischaemic stroke, myocardial infarction and heart failure. Secondary outcomes were hypoglycaemia and all-cause mortality. Cox proportional hazards models were performed to assess time-to-event hazard ratio between propensity score-matched antidiabetic treatment groups.

RESULTS

DPP4is as a second-line add-on to metformin had a significantly lower stroke risk [hazard ratio (HR) 0.817 (95% confidence interval 0.687, 0.971)] and all-cause mortality [HR 0.825 (0.687, 0.992)] than those for sulphonylurea. DPP4is as a third-line add-on to metformin and sulphonylurea combined dual therapy had a significantly lower risk for stroke [HR 0.826 (0.740, 0.923)] and all-cause mortality [HR 0.784 (0.701, 0.878)] than those for acarbose, and significantly lower risks for stroke [HR 0.653 (0.542, 0.786)], heart failure [HR 0.721 (0.568, 0.917)] and all-cause mortality [HR 0.689 (0.594, 0.703)] than those for meglitinide.

CONCLUSIONS

DPP4is as a second- or third-line add-on treatment provided cardiovascular benefits and posed no increased risks for heart failure, hypoglycaemia or death.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dipeptidyl peptidase 4 inhibitors (DPP4is) are recommended as a second- and third-line add-on treatment with other antidiabetic drugs. With their high price, DPP4is are commonly prescribed as a third-line add-on to combination therapy with metformin and suphonylurea for those with inadequate glycaemic control.
- Current evidence suggests only that DPP4is have cardiovascular effects as a second-line treatment, describing their relative effects compared with sulphonylurea, and yields inconclusive results on the risk of heart failure.
- In April 2016, the Food and Drug Administration in the United States warned of the potential increased risk of heart failure with use of DPP4is, and suggested that a longitudinal evaluation be carried out.

WHAT THIS STUDY ADDS

- This large population-based longitudinal study confirms previous evidence of the cardiovascular benefits of DPP4is as a second-line add-on treatment to metformin and adds evidence about the favourable cardiovascular outcomes of DPP4is as a third-line add-on treatment to the metformin and sulphonylurea dual regimen.
- The use of DPP4is as a second- or third-line treatment provides cardiovascular benefits, reduces all-cause mortality and poses no increased risk of heart failure or hypoglycaemia over those of other antidiabetic drugs (i.e. acarbose, meglitinide and thiazolidinediones).
- DPP4is as a second- or third-line treatment in type 2 diabetes patients who have inadequate glycaemic control under metformin monotherapy might alter the future risks of developing cardiovascular diseases.

Tables of Links

TARGETS
Enzymes [2]
Dipeptidyl peptidase 4

LIGANDS
Metformin
Acarbose

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

With the growing prevalence of type 2 diabetes mellitus (T2DM) worldwide, this disease now contributes considerably to morbidity and mortality [3, 4]. Cardiovascular diseases (CVDs) are the leading causes of mortality in patients with T2DM [5]. Antidiabetic drugs are used to improve glycaemic control and to help to reduce further the risk of developing CVDs [6]. Dipeptidyl peptidase 4 inhibitors (DPP4is), newly available antidiabetic drugs, are recommended as second- and third-line add-on treatment to other antidiabetic drugs [7]. With their high price, DPP4is are commonly prescribed as a third-line add-on for those with inadequate glycaemic control on combination therapy with metformin (Met) and sulphonylurea (SU). In addition to improved glycaemic control, glucagon-like peptide-1 (GLP-1)-induced myocardial protection has been proposed for cardiovascular protection by DPP4is [8]. As a second-line add-on therapy to metformin, DPP4is were associated with a lower risk for major adverse cardiovascular events (MACEs) [9–14] and all-cause mortality [12, 15] compared with SU. In addition, a large observational study of 127 555 T2DM patients in Italy showed a significantly lower risk of heart failure (HF) with use of DPP4is as compared with SU [14] However, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial [16] and a recent large observational study from the US [17] found an increased risk of HF with DPP4is. A recent study by Ou *et al.* [18], based on the 2009–2013 Taiwan National Health Insurance Research Database (NHIRD), showed that, compared with users of a combination of Met and SU (Met + SU), Met + DPP4i users had significantly lowered risks for all-cause mortality, stroke, and hypoglycaemia, but there was no effect on the risks for myocardial infarction (MI) and HF [18]. However, most previous studies have focused only on DPP4is as a second-line add-on [12, 15, 18–20], included SU as the sole comparator [12, 15, 18, 20] and assessed only hypoglycaemia as a safety endpoint [18]. No studies study has assessed the cardiovascular outcomes of DPP4is as a third-line treatment. In addition, although DPP4is appear to provide cardiovascular benefits (i.e. a low risk for MACEs [9–14, 20] and stroke [18]), previous study findings on the HF risk with use of DPP4is have been inconsistent [16–19, 21]. In April 2016, the US Food and Drug Administration (FDA) warned of the potentially increased risk of HF with the use of two DPP4i drugs – saxagliptin and alogliptin – and urged healthcare professionals and patients to report cardiovascular events involving DPP4is [22]. However, Taiwan's FDA has no regulatory labelling on DPP4is with regard to their potentially elevated risk of HF. This is, in part, because of a lack of local data to confirm this safety concern in the Taiwanese population, which highlights the need for research in this area.

Against this background, the present study sought to utilize a nationwide longitudinal cohort of diabetic patients to conduct a comprehensive evaluation on cardiovascular risks and safety issues (i.e. hypoglycaemia) with the use of DPP4is, compared with other second- and third-line antidiabetic treatments, including SU, meglitinide (MEG), thiazolidinediones (TZD) and acarbose.

Materials and methods

The Institutional Review Board (IRB) of the National Cheng Kung University Hospital approved the study before commencement (A-ER-103-298). Patients' informed consents were waived by the IRB because the study was retrospective and based on secondary data (i.e. the NHIRD), in which people had been de-identified.

Data source

We utilized the Longitudinal Cohort of Diabetes Patients (LHDB) 1996–2013 from the NHIRD. Taiwan's NHIRD is population based and derived from the claims data from the National Health Insurance (NHI) programme, a mandatory-enrolment, single-payment system that covers over 99% of Taiwan's population [23]. The LHDB is a valid national dataset that consists of a random sample of 120 000 de-identified all diabetes incident cases from each calendar year, who were tracked back to 1996 and followed up to 2013 to establish a longitudinal cohort. The LHDB is most representative of Taiwan's diabetic population and provides a research opportunity to evaluate the long-term health outcomes of patients.

Cohort

From the LHDB, we selected patients aged ≥20 years with a diagnosis of T2DM [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) = 250.0X-250.9X, where X = 0 or 2] during 2009–11. Study subjects treated with two and three antidiabetic drugs were classified into dual and triple therapy cohorts, respectively. Pharmacotherapy for T2DM is typically based on a stepped-up scheme, where patients begin with monotherapy, then dual and triple therapy, and finally rely on a combination injectable therapy (e.g., Met+DPP4i+insulin) [24]. More add-on drugs imply more severe diabetes cases. So, patients treated with dual therapy are likely to be different from those on triple therapy. With this in mind, we stratified patients by the number of antidiabetic drugs they were on (i.e. dual or triple) and analysed them separately.

For the dual therapy cohort, we first selected the cases with stable use of Met. Stable Met users were defined as those who had more than three consecutive Met refills during 2009–2011 and any gaps between two consecutive refills of fewer than 30 days. The definition of 'three consecutive refills' was applied because, for a chronic disease population such as diabetes in Taiwan, when a patient has had three or more consecutive refills on a certain medication, he or she is considered to be stable on this treatment and likely to continue with it. This criterion has been used in previous diabetes studies to define the stable use of antidiabetic medications [25–27]. The date of the first claim for addition of the second-line antidiabetic drug to Met in 2009–2011 was defined as the index date. Patients with a history of dual antidiabetic therapy at 180 days before the index date were excluded, to ensure that only new dual therapy users during 2009–2011 were included. For the triple therapy cohort, we first assessed the pattern of Met-based triple regimens. We found that Met and SU (Met + SU) combination regimens, including Met + SU + DDP4i, Met + SU + acarbose (ACA), Met + SU+ TZDs, and Met + SU + MEG, were most commonly prescribed. We therefore selected the cases on Met + SU-based triple therapies in the analysis. We first identified stable Met + SU combination users in 2009–2011 (i.e. the patients who had been stable on a combination regimen of Met + SU during 2009–2011). As mentioned above, 'stable' use was defined as ' more than three consecutive refills on a Met + SU combination regimen during 2009–2011 and any gaps between two consecutive refills of fewer than 30 days'. The date of the first claim for addition of a third-line antidiabetic treatment to the Met + SU regimen in 2009–2011 was then defined as the index date. We excluded those with a history of triple therapy before the index date (naïve to the third-line add-on drug in the 180 days prior to the index date), so only new triple therapy users during 2009–2011 were included.

Exposure to antidiabetic drugs

Medication utilization was identified in the NHIRD. The Anatomical Therapeutic Chemical (ATC) Classification System was used for classification of the active ingredients of drugs. Dual therapy users were classified into five mutually exclusive groups according to the first second-line add-on antidiabetic drug to Met in 2009–2011, including SU, DPP4is, TZDs, ACA and MEG. Triple therapy users were classified into four mutually exclusive groups according to the first third-line add-on antidiabetic drug to the Met + SU dual regimen during 2009–2011, including DPP4is, TZDs, ACA and MEG. As the main interest of the present study was to assess the comparative effects between DPP4is and other oral antidiabetic agents (OADs), insulin use was not analysed. The clinical use/placement of DPP4is in Taiwan is likely to be comparable with that of OADs rather than insulin. Prescribers there are likely to make a selection between DPP4is and other OADs, but not insulin, in treating diabetes. A previous study in the Taiwanese population with T2DM showed that the patients treated with insulin had already used 2.7 ± 0.7 OADs before insulin treatment [28]. Insulin therapy in Taiwan is often administered to patients with acute medical conditions or treatment failure of three OADs on their maximum doses. Therefore, insulin users are likely to be those with advanced diabetes who required more intensive glycaemic control (i.e. using insulin) compared with those with OADs only. Insulin users at baseline may be clinically different from those with OADs, and the inclusion of these insulin users may have confounded our findings. Therefore, the potential effect of exposure to insulin was not analysed in the present study. When using observational data, propensity score (PS) matching is commonly used to reduce the bias due to a lack of distribution overlap

and that due to different density weighting [29]. A PS is generally defined as the probability of study participants receiving a treatment based on observed characteristics [30]. PS and matching algorithm allow scholars to reconstruct counterfactuals using observation data and to estimate the causal effect [31]. In the present study, we adapted the PS matching using the nearest neighbour approach without replacement within a caliper of 0.025 on the PSs at a fixed ratio of 1:1 [30], to match the two comparison treatment groups (i.e. Met + SU *vs*. Met + DPP4i). A previous study on variables selection for PS suggested that it is preferable to include either the variables that affect the outcome or those that affect both treatment selection and the outcome [32]. The PSs were computed by using a logistic regression model, where treatment status (i.e. receipt of Met + SU *vs*. Met + DPP4i) was a dependent variable and there was a list of independent variables which were considered to be associated with the selection of OAD and cardiovascular outcomes of interest, including demographics (i.e. age, gender), comorbidity history [hypertension, hyperlipidaemia, coronary artery disease (CAD), a composites score – Charlson comorbidity index [33]], diabetic complications (measured via the adapted diabetes complication severity index [34]), CVD history (stroke, MI, HF),and CVD medication history (α-blockers, β-blockers, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), antiplatelet agents, anticoagulants, diuretics, digoxin, and nitrates). For dual therapies, the Met + SU group served as a reference group for PS matching because this combination is the most conventional and commonly used regimen [25]. As Met + SU + DPP4i is the most commonly prescribed triple regimen in patients receiving triple therapy in Taiwan [25], we selected, in PS matching, patients with the Met + SU + DPP4i to form three study groups that has PS distributions comparable to each of the three triple therapy groups (i.e. Met + SU + TZDs, Met + SU + ACA and Met + SU + MEG).

Study outcomes

The primary outcomes of interest were MACEs [a composite outcome of nonfatal hospitalizations for ischaemic stroke (ICD-9: 430–438), MI (ICD-9: 410, 412) and HF (ICD-9: 428)] and individual CVD components (i.e. nonfatal stroke, MI and HF). The safety endpoint was an emergency room visit or hospitalization for hypoglycaemia (ICD-9: 250.8, 251.0, 251.1, 251.2). Mortality status was ascertained from inpatient files from the NHIRD, which indicate if the patient expired during the hospitalization (coded as '4'), if the patient was in the acute stage of their illness when discharged (coded as 'A'), or if the patient was discharged against medical advice (coded as '5'), which mostly occurs in Taiwan when there is no further effective treatment for sustaining life and the patient and/or the family wishes to bring the patient home for comfort. Additionally, we used the disenrollment records from the NHIRD registration files of beneficiaries to confirm mortality. As NHI enrolment is mandatory for all residents of Taiwan, the most common reason that can allow disenrollment is death. A previous validation study in Taiwan indicated that the death records in the NHIRD were in high accordance with those in the catastrophic illness registry (CIR) and the in-hospital electronic medical records (EMR) [35]. The CIR and EMR both had death records and thus served as a gold standard in the validation study [35].

Statistics

Our primary analysis was performed as an 'intent-to-treat' analysis, where all patients were followed from the index date until death, withdrawal from the NHI programme or the end of 2013 – whichever came first. The crude incidence rate of events (i.e. CVD) was calculated as the total number of events over the follow-up period, divided by person-years at risk. The person-years at risk was defined as the sum of patients from the index date (i.e. the start date of dual or triple therapy) to the diagnosis of the first event, dropout from the NHI programme, death, or 31 December 2013, whichever came first. Cox proportional hazards regression was applied to evaluate the time to event between two matched groups. The graph of the log[−log(survival)] *vs*. the log of survival time graph (using the PROC LIFETEST function in SAS, SAS® software, version 9.4 SAS Institute, Cary, NC, USA) resulted in parallel curves, implying that the variables in the Cox model satisfied the proportional hazard assumption [36]. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed. Subgroup analyses were conducted for the patients with or without a history of CVD (including stroke, MI, HF and CAD). Several sensitivity analyses were conducted. First, we modified the PS-matching ratio to 4:1 (controls to cases). Typically, increasing the number of matched controls up to a ratio of about 4/1 improves the power of the study. However, such a rise is not linear; beyond a ratio of about 4/1 [37], there is little improvement in the power of the results beyond that of increasing the number of controls [38]. Boosting the ratio of controls to cases affects the confidence interval (the precision of the results) and increases the power of the study to find an association [39]. Secondly, we added Met persistent use (medication possession ratio, MPR $\geq$ 0.7) as one of inclusion criteria in the follow-up, to eliminate the potential bias of non-Met adherence. Thirdly, we applied 'on treated' analysis, where patients were censored (the observation was ended) at 90 days after they were switched to another antidiabetic drug or had one added on, or discontinued treatment. Fourthly, we adjusted for potential competing causes of death in the Cox model analyses by using Fine and Gray's method [40, 41]. A P value of <0.05 was considered statistically significant. SAS version 9.4 was utilized for analysis.

Results

A total of 113 051 patients with T2DM newly on metformin-based therapies (68 967 dual therapy users, 44 084 triple therapy users) were identified (Figure 1). Among patients on dual therapy, Met + SU users accounted for the majority of patients (76.8%), following by Met + DPP4i users (9.0%). For triple therapies, Met + SU-based triple regimens accounted for the majority of patients (n = 42 662, 96.77%), with most patients

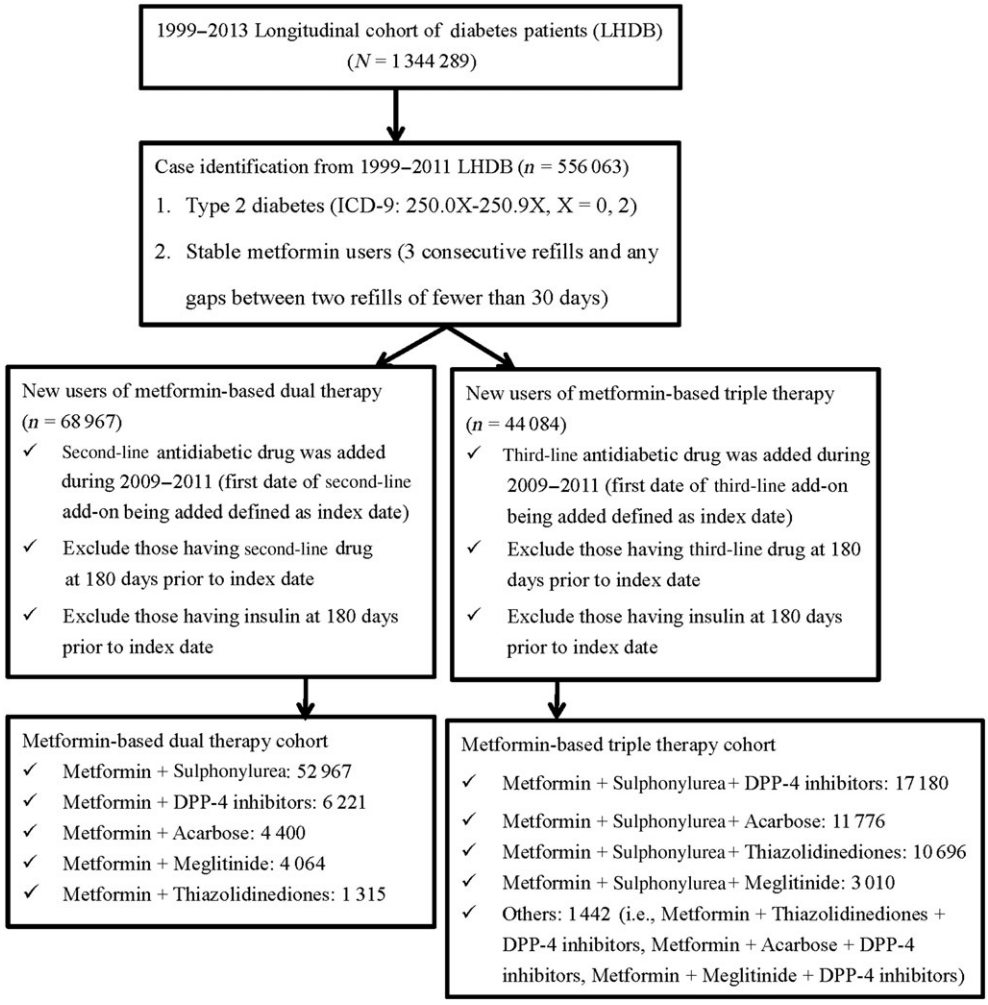

Figure 1
Flow chart of case selectionDPP-4, dipeptidyl peptidase 4; ICD-9, International Classification of Diseases, Ninth Revision

prescribed a DPP4i as a third-line add-on (40.27%), followed by ACA (27.60%). Table 1 shows the characteristics of the patients in the two matched dual therapy regimens. After matching, the Met + SU group had higher percentages of patients with a history of hyperlipidaemia and using an ACEI/ARB compared with the Met + DPP4i group. As shown in Table 2, there was no significant difference in patients' baseline characteristics between the two matched triple regimen user groups. After PS matching, the Met + DPP4i group had lower crude rates of MACEs, stroke, MI, death, and hypoglycemia compared with their matched Met + SU referents (Table 3). In addition, the Met + SU + DPP4i group had lower crude rates of MACEs, stroke, AMI, death and hypoglycaemia compared with their matched Met + SU + ACA or Met + SU + MEG referents. Tables 4 and 5 present the results from Cox model analyses of the comparative risks for CVD, all-cause mortality and hypoglycaemia between the two matched dual regimens and between the two matched triple regimens, respectively. In the analyses that compared the dual therapy cohort, the Cox model also controlled for differences in patients' characteristics between the two matched groups (as shown in Table 1) as covariates. As there was no statistical difference in patients' characteristics between the two matched triple regimen groups (Table 2), the Cox model analyses for the triple regimens did not control for any covariates (only treatment status – e.g. receipt of Met + SU + DPP4i vs. Met + SU + TZDs in the model). Table 4 and Figure 2 indicate that, compared with Met + SU referents, only Met + DPP4i users had significantly lower risks for MACEs, stroke, all-cause mortality and hypoglycaemia. Table 5 and Figure 3 show that Met + SU + DPP4i users had significantly lowered risks for MACEs, stroke and all-cause mortality compared with their matched Met + SU + ACA referents. Met + SU + DPP4i users also had lower risks for MACEs, stroke, HF, all-cause mortality and hypoglycaemia compared with their matched Met + SU + MEG referents. Subgroup analysis of patients with and without a history of CVD in dual and triple therapy cohorts also showed consistent trends (Tables 4 and 5). The sensitivity analyses for dual and triple therapies

Table 1

Baseline patient characteristics of metformin-based dual regimen users

Dual therapy cohort	Before PS matching	After PS matching							
	Met + SU (n = 52 967)	Met + DPP4i (n = 5980)	1:1 matched Met + SU	Met + TZDs (n = 1315)	1:1 matched Met + SU	Met + ACA (n = 4386)	1:1 matched Met + SU	Met + MEG (n = 4050)	1:1 matched Met + SU
Person-years (mean)	–	3.20	3.42	3.62	3.40	3.32	3.37	3.25	3.30
Age (mean ± SD)	55.7 ± 12.3	57.2 ± 12.5	57.1 ± 12.4	57.6 ± 12.0	58.1 ± 12.7	58.1 ± 13.0	58.3 ± 12.3	59.1 ± 13.5	59.3 ± 12.7
Male (%)	57.41%	52.41%	51.76%	54.90%	52.32%	52.19%	50.71%	56.0%	55.2%
Comorbidity history									
Hypertension (%)	51.86	57.41	58.91	61.90	62.89	59.69	61.88*	58.00	58.90
Hyperlipidaemia (%)	44.57	55.74	57.99*	59.70	62.66	55.65	58.76**	47.01	48.12
Stroke (%)	6.54	8.24	8.55	7.76	8.14	9.03	9.26	12.41	13.01
Heart failure (%)	2.29	2.64	3.04	1.90	2.51	2.55	2.80	4.32	4.50
CAD (%)	10.63	15.64	16.51	13.46	14.98	17.76	18.56	15.20	16.51
CCI (mean ± SD)	2.9 ± 1.0	3.0 ± 1.5	3.1 ± 1.5	3.0 ± 1.4	3.1 ± 1.5	3.2 ± 1.5	3.3 ± 1.7	3.4 ± 1.8	3.4 ± 1.8
aDCSI (mean ± SD)	0.6 ± 1.1	0.8 ± 1.3	0.8 ± 1.4	0.7 ± 1.2	0.8 ± 1.3	0.8 ± 1.3	0.9 ± 1.4	0.9 ± 1.5	1.0 ± 1.6
Diabetes duration (years)	1.5 ± 2.6	4.1 ± 3.4	4.2 ± 3.5	4.0 ± 3.4	4.0 ± 3.6	3.5 ± 3.3	3.5 ± 3.5	3.2 ± 3.4	3.2 ± 3.5
Metformin duration (years) (mean ± SD)	0.6 ± 1.5	2.7 ± 2.6	2.6 ± 2.8	2.6 ± 2.7	2.4 ± 2.9	2.2 ± 2.6	2.1 ± 2.7	1.9 ± 2.6	1.9 ± 2.7
Medication history									
α-blocker (%)	2.49	3.16	2.99	3.95	3.80	3.40	3.29	3.70	3.57
β-blocker (%)	16.52	18.60	19.85	19.24	18.40	20.77	21.66	17.51	18.41
Diuretics (%)	12.96	10.84	11.09	12.62	11.94	14.59	15.48	15.02	15.52
CCB (%)	26.97	29.15	29.73	35.82	36.58	34.22	35.23	32.41	32.80
AECI/ARB (%)	28.66	43.48	45.38*	46.08	49.05	41.81	43.87	36.80	37.73
Lipid-lowering agent (%)	29.77	47.61	49.30	50.42	55.29*	43.37	47.20***	34.24	35.92
Antiplatelet agent (%)	19.04	29.16	29.62	32.02	32.78	30.37	32.12	27.10	27.72
Nitrates (%)	2.52	4.83	5.30	3.73	4.11	4.79	4.90	3.83	4.31
Anticoagulant (%)	0.51	0.97	1.07	0.91	0.99	0.66	0.75	0.81	0.70
Digoxin (%)	1.29	1.49	1.77	1.14	0.91	1.28	1.39	2.32	2.41

Baseline patient characteristics were measured 1 year prior to the second-line antidiabetic drug being added (index date). Diabetes duration: from diabetes diagnosis to the beginning of dual antidiabetic therapy

ACA, acarbose; ACEI/ARB, angiotensin II-converting enzyme inhibitor/angiotensin receptor blocker; aDCSI, adapted diabetes complication severity index; CAD, coronary artery diseases; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; DPP4i, dipeptidyl peptidase-4 inhibitor; MEG, meglitinide; Met, metformin; PS matching, propensity score 1:1 matching using the nearest neighbour technique; SD, standard deviation SU, sulphonylurea; TZD, thiazolidinedione

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

yielded results similar to those of the primary analysis (Tables S1 and S2).

Discussion

This was the largest population-based longitudinal cohort study comprehensively to evaluate the risks for cardiovascular events, hypoglycaemia and all-cause mortality with use of DPP4is compared with other second- and third-line antidiabetic drugs. We found that DPP4is as an add-on (second- or third-line) treatment to metformin yielded positive effects on cardiovascular outcomes and posed no increased risks for hypoglycaemia or death, compared with other conventional antidiabetic treatments. Our subgroup analyses further differentiated the effect of DPP4is for patients with and without a history of CVD, which eliminated potential bias from pre-existing CVD conditions

Table 2

Baseline patient characteristics of metformin-based triple regimen users

Triple therapy cohort	Before PS matching Met + SU + DPP4i (*n* = 17 180)	After PS matching Met + SU + DPP4i (*n* = 10 475)	1:1 matched Met + SU + TZDs	Met + SU + DPP4i (*n* = 11 248)	1:1 matched Met + SU + AC	Met + SU + DPP4i (*n* = 3008)	1:1 matched Met + SU + MG
Person-years (mean)	–	3.32	3.60	3.29	3.43	3.20	3.38
Age (mean ± SD)	57.7 ± 11.5	57.0 ± 11.1	56.9 ± 11.6	58.0 ± 11.9	58.0 ± 11.7	60.0 ± 12.3	59.6 ± 11.9
Male (%)	53.49	55.04	54.30	54.99	55.07	54.36	54.79
Comorbidity history							
Hypertension (%)	61.36	60.48	60.76	60.34	60.57	64.33	63.66
Hyperlipidaemia (%)	59.62	61.88	61.98	57.10	56.90	51.80	52.03
Stroke (%)	8.44	5.50	5.86	8.47	8.77	12.70	12.30
Heart failure (%)	2.65	1.56	1.57	2.70	2.78	4.69	4.26
CAD (%)	16.12	12.53	12.53	15.23	15.50	18.42	17.85
CCI (mean ± SD)	3.0 ± 1.4	3.0 ± 1.3	3.0 ± 1.4	3.1 ± 1.5	3.1 ± 1.5	3.5 ± 1.8	3.5 ± 1.9
aDCSI (mean ± SD)	1.0 ± 1.4	0.8 ± 1.2	0.8 ± 1.2	0.9 ± 1.5	0.9 ± 1.4	1.3 ± 2.0	1.3 ± 1.8
Diabetes duration (years)	6.1 ± 3.2	5.4 ± 3.2	5.4 ± 3.2	5.3 ± 3.3	5.3 ± 3.2	5.3 ± 3.2	5.2 ± 3.3
Metformin duration (years) (mean ± SD)	4.7 ± 3.0	4.1 ± 2.9	4.1 ± 2.9	3.9 ± 2.9	4.0 ± 2.8	3.9 ± 2.9	3.8 ± 2.8
SU duration (years) (mean ± SD)	5.1 ± 3.1	4.6 ± 3.1	4.6 ± 3.1	4.3 ± 3.1	4.4 ± 3.0	4.5 ± 3.1	4.4 ± 3.1
Medication history							
α-blocker (%)	3.86	2.91	2.90	3.81%	3.98	4.92	4.69
β-blocker (%)	20.27	18.00	17.66	19.64%	19.67	19.78	20.68
Diuretics (%)	13.45	14.34	14.57	15.50%	15.39	20.08	18.52
CCB (%)	34.51	36.04	35.70	36.43%	36.21	40.39	40.86
AECI/ARB (%)	53.29	45.20	45.03	46.96%	47.36	46.04	45.05

(*continues*)

Table 2
(Continued)

Triple therapy cohort	Before PS matching	After PS matching					
	Met + SU + DPP4i (n = 17 180)	Met + SU + DPP4i (n = 10 475)	1:1 matched Met + SU + TZDs	Met + SU + DPP4i (n = 11 248)	1:1 matched Met + SU + AC	Met + SU + DPP4i (n = 3008)	1:1 matched Met + SU + MG
Lipid-lowering agent (%)	55.06	52.69	52.49	48.95%	48.67	43.85	43.55
Antiplatelet agent (%)	34.33	29.15	29.11	32.41%	32.62	36.24	36.10
Nitrates (%)	4.89	2.60	2.80	4.19%	4.17	5.39	4.92
Anticoagulant (%)	0.87	0.45	0.47	0.67%	0.73	1.13	1.03
Digoxin (%)	1.70	1.24	1.31	1.77	1.80	2.13	1.96

Baseline patient characteristics were measured one year prior to the third-line antidiabetic drug being added (index date). No statistical difference in baseline patient characteristics between each type of triple regimen and their PS-matched referents. Diabetes duration: from diabetes diagnosis to the beginning of triple antidiabetic therapy

Baseline patient characteristics were measured 1 year prior to the second-line antidiabetic drug being added (index date). Diabetes duration: from diabetes diagnosis to the beginning of dual antidiabetic therapy

ACA, acarbose; ACEI/ARB, angiotensin II-converting enzyme inhibitor/angiotensin receptor blocker; aDCSI, adapted diabetes complication severity index; CAD, coronary artery diseases; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; DPP4i, dipeptidyl peptidase-4 inhibitor; MEG, meglitinide; Met, metformin; PS matching, propensity score 1:1 matching using the nearest neighbour technique; SD, standard deviation SU, sulphonylurea; TZD, thiazolidinedione

and provided an insight into the role of DPP4is for patients with and without a history of CVD, respectively.

Cardiovascular outcomes of DPP4is as a second-line add-on treatment

Our findings, based on real-world patients, support those of several randomized clinical trials, in which DPP4i use appeared not to be associated with increased CVD risks and mortality [16, 42–44]. In addition, our results are consistent with recent real-world-setting cohort studies showing favourable cardiovascular outcomes of DPP4is as a second-line antidiabetic treatment. Several cohort studies from Denmark [12], the US [11] and the UK [15] have shown that DPP4is as a second-line add-on drug to Met had a significantly lower MACE risk (including stroke and MI) than that associated with SU. However, two Taiwanese cohort studies of cardiovascular outcomes of DPP4is as a second-line add-on provided inconsistent results. The study by Cheng *et al*., based on the 2009–2011 NHIRD, showed that, compared with Met + SU users, there was a significantly lower risk of MI only in Met + MEG and Met + ACA users, but not in Met + DPP4i users [20]. Our study also assessed other dual regimens, but we did not observe the Met + ACA or Met + MEG regimen to provide better CVD benefits over the Met + SU regimen. The afore-mentioned difference might be explained by different follow-up periods, sample sizes and study methods. Cheng *et al*. [20] was limited by having a relatively shorter follow-up time (i.e. median follow-up for DPP4i users for MACEs: 0.59 years) and a more limited study sample (i.e. 2242 cases for DPP4i users), leading to lower rates of CVD events (i.e. crude rate of MACEs for DPP4i users: 0.16 per 1000 person-years) compared with those in the present study. In addition, we applied PS matching on patients' baseline diabetic severity to adjust for potential confounding by indication, but Cheng *et al*. [20] did not. A recent study by Ou *et al*. [18], based on the 2009–2013 NHIRD showed that, compared with PS-matched Met + SU referents, Met + DPP4i users had significantly lower all-cause mortality and stroke risk, but there was no significant effect on MI and HF risks. Our results regarding the comparison in cardiovascular outcomes between Met + DPP4i and Met + SU use are consistent with those of Ou *et al*. [18]. However, Ou *et al*. assessed only DPP4i and SU as second-line add-ons to metformin; they included no other antidiabetic drugs (e.g. TZDs) as add-ons. In addition, there were some differences in the inclusion criteria and patient characteristics between our study and that by Ou *et al*. Ou *et al*. used a 1-year longer time span for identifying study cases (2009–2012 in Ou *et al*. [18] *vs*. 2009–2011 in the present study). The stable Met user in the study by Ou *et al*. was defined by allowing a 90-day gap between two consecutive refills [18], whereas we used a more limited gap of 30 days or fewer, which was considered stricter. As such, our selected cases were likely to be the patients with more stable treatment and better health outcomes compared with those in the study by Ou *et al*. These differences may have resulted in a smaller sample size and less severe T2DM in the patients analysed in our study. Additionally, the prevalence of comorbidities in the study by Ou *et al*. [18] was higher than that

Table 3

Number and crude rate (per 1000 person-years) of MACEs, death, and hypoglycaemia according to each type of metformin-based dual and triple regimen user after propensity score matching

Metformin-based dual therapy cohort	Met + DPP4i (*n* = 5980) No. of events (crude rate)	1:1 matched Met + SU No. of events (crude rate)	Met + TZDs (*n* = 1315) No. of events (crude rate)	1:1 matched Met + SU No. of events (crude rate)	Met + ACA (*n* = 4368) No. of events (crude rate)	1:1 matched Met + SU No. of events (crude rate)	Met + MEG (*n* = 4050) No. of events (crude rate)	1:1 matched Met + SU No. of events (crude rate)
MACEs	373 (19.52)	464 (22.72)	98 (20.57)	109 (24.36)	353 (24.25)	380 (25.75)	457 (34.71)	412 (30.84)
Stroke	228 (11.77)	296 (14.28)	64 (13.30)	73 (16.11)	230 (15.59)	235 (15.62)	301 (22.42)	270 (19.85)
Heart failure	136 (6.96)	143 (6.79)	25 (5.10)	31 (6.75)	103 (6.85)	118 (7.72)	171 (12.46)	139 (10.00)
Myocardial infarction	69 (3.50)	95 (4.50)	19 (3.87)	17 (3.68)	55 (3.64)	73 (4.76)	61 (4.39)	72 (5.14)
Death	94 (10.53)	128 (11.84)	51 (10.33)	73 (15.70)	246 (16.20)	236 (15.23)	405 (28.94)	268 (18.98)
Hypoglycaemia	50 (2.54)	71 (3.36)	15 (3.06)	9 (1.94)	37 (2.45)	48 (3.12)	105 (7.59)	67 (4.79)

Metformin-based triple therapy cohort	Met + SU+ DPP4i (*n* = 10 475) No. of events (crude rate)	1:1 matched Met + SU+ TZDs No. of events (crude rate)	Met + SU+ DPP4i (*n* = 11 248) No. of events (crude rate)	1:1 matched Met + SU+ ACA No. of events (crude rate)	Met + SU + DPP4i (*n* = 3008) No. of events (crude rate)	1:1 matched Met + SU+ MEG No. of events (crude rate)
MACEs	739 (21.24)	785 (20.79)	947 (25.59)	1084 (28.08)	297 (30.79)	451 (44.39)
Stroke	447 (12.67)	520 (13.60)	567 (15.07)	707 (18.02)	183 (18.62)	290 (27.69)
Heart failure	257 (7.20)	249 (6.42)	349 (9.16)	349 (8.73)	114 (11.42)	165 (15.40)
Myocardial infarction	131 (3.65)	130 (3.33)	171 (4.46)	188 (4.67)	49 (4.86)	65 (5.95)
Death	446 (12.37)	470 (12.00)	545 (14.11)	687 (16.95)	200 (19.70)	331 (30.03)
Hypoglycaemia	178 (4.98)	211 (5.44)	215 (5.62)	264 (6.59)	76 (7.58)	142 (13.20)

ACA, acarbose; DPP4i, dipeptidyl peptidase-4 inhibitor, MEG, meglitinide; MACEs, major adverse cardiovascular events; Met, metformin; SU, sulphonylurea; TZDs; thiazolidinediones

Table 4

Comparative risks for cardiovascular diseases, all-cause mortality, and hypoglycaemia of metformin-based dual regimens, and subgroup analyses stratified by patients' CVD history

	Met + DPP4i (*n* = 5980) *vs.* 1:1 matched Met + SU (reference) HR (95% CI)			Met + TZDs (*n* = 1315) *vs.* 1:1 matched Met + SU (reference) HR (95% CI)			Met + ACA (*n* = 4368) *vs.* 1:1 matched Met + SU (reference) HR (95% CI)			Met + MEG (*n* = 4050)*vs.* 1:1 matched Met + SU (reference) HR (95% CI)		
	All patients (*n* = 11 960)	CVD history (*n* = 2758)	No CVD history (*n* = 9202)	All patients (*n* = 2630)	CVD history (*n* = 544)	No CVD history (*n* = 2086)	All patients (*n* = 8736)	CVD history (*n* = 2264)	No CVD history (*n* = 6508)	All patients (*n* = 81, 00)	CVD history (*n* = 2140)	No CVD history (*n* = 5952)
MACEs	**0.852** (0.743, 0.977)	**0.825** (0.686, 0.992)	0.929 (0.754, 1.146)	0.845 (0.643, 1.110)	0.921 (0.602, 1.409)	1.079 (0.735, 1.584)	0.940 (0.813, 1.087)	1.217 (1.000, 1.482)	1.014 (0.800, 1.287)	1.124 (0.984, 1.284)	1.185 (0.998, 1.407)	1.161 (0.933, 1443)
Stroke	**0.817** (0.687, 0.971)	0.812 (0.644, 1.024)	0.887 (0.677, 1164)	0.829 (0.593, 1.160)	0.893 (0.547, 1459)	1.014 (0.621, 1.655)	0.994 (0.829, 1.192)	1.227 (0.964, 1.562)	0.902 (0.674, 1.207)	1.128 (0.957, 1.329)	1.155 (0.938, 1.423)	1.090 (0.835, 1.423)
Heart failure	1.012 (0.800, 1.281)	0.896 (0.662, 1.213)	1.045 (0.725, 1.508)	0.759 (0.448, 1.286)	0.639 (0.261, 1.565)	1.067 (0.533, 2.139)	0.885 (0.680, 1.153)	1.060 (0.751, 1.497)	1.574 (0.942, 2.632)	1.245 (0.995, 1.557)	1.355 (1.023, 1.793)	1.495 (0.966, 2.243)
Myocardial infarction	0.785 (0.575, 1.073)	0.824 (0.532, 1.275)	0.917 (0.562, 1.496)	1.016 (0.528, 1.957)	0.598 (0.231, 1543)	1.769 (0.663, 4.719)	0.769 (0.542, 1.091)	1.158 (0.709, 1.892)	0.825 (0.458, 1.485)	0.851 (0.605, 1.196)	0.854 (0.551, 1.322)	1.210 (0.659, 2.223)
All-cause mortality	**0.825** (0.687, 0.992)	0.896 (0.678, 1.185)	0.799 (0.621, 1.028)	0.690 (0.482, 0.986)	0.992 (0.516, 1.907)	1.141 (0.693, 1.879)	1.051 (0.897, 1.257)	1.138 (0.869, 1.489)	1.081 (0.845, 1.383)	1.554 (1.331, 1.814)	1.961 (1.553, 2.476)	1.338 (1.085, 1.649)
Hypoglycaemia	**0.741** (0.516, 0.901)	**0.665** (0.574, 0.943)	**0.895** (0.659, 0.917)	1.603 (0.701, 3.664)	2.487 (0.482, 12.824)	1.198 (0.472, 3.037)	0.780 (0.508, 1.198)	0.833 (0.447, 1.553)	0.523 (0.301, 0.910)	1.581 (1.164, 2.148)	1.777 (1.115, 2.832)	1.531 (1.017, 2.304)

ACA, acarbose; CI, confidence interval; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase 4 inhibitor; HR, hazard ratio; MACEs, major adverse cardiovascular events; MEG, meglitinide; Met, metformin; SU, sulphonylurea; TZDs; thiazolidinediones. Bolded words in Tables refers the values which are statistically significant ($P < 0.05$).

in our study, which may explain the higher rate of death in the study by Ou *et al.* [18].

Cardiovascular outcomes of DPP4is as a third-line add-on treatment

Clinically, DPP4is commonly serve as a third-line treatment in countries such as Taiwan. The present study identified the most commonly used Met-based triple regimens, where the combination of Met + SU + DPP4i was the most prescribed. Our findings showed that DPP4i as a third-line add-on to initial Met + SU dual therapy provided cardiovascular benefits and lowered all-cause mortality over conventional antidiabetic drugs (i.e. ACA, MEG). Several studies have demonstrated that, compared with SU, DPP4is as a second-line add-on to Met are associated with a lower risk of stroke [12, 15, 17]. The present study of triple antidiabetic regimens further showed that DPP4is as a third-line add-on treatment to Met + SU-based therapy were associated with a significantly lower risk for stroke compared with ACA and MEG, and a nonstatistically significant trend towards being lower than that for the TDZs.

Several mechanisms have been proposed to explain the cardiovascular protective effects of DPP4is. These include GLP-1 endothelial effects (i.e. enhancement of endothelial function [45]); other, GLP-1-independent endothelial effects [46]; and a potential anti-inflammatory effect of GLP-1 via reducing C reactive protective protein levels [47]. Our results suggest that DPP4i use as a third-line add-on treatment might provide cardiovascular benefits over other antidiabetic drugs (e.g. ACA, MEG). Therefore, treatment decisions need to take the benefits and risks associated with antidiabetic drugs into consideration, with optimal treatment selected to alter CVD risks, especially for advanced T2DM patients (i.e. cases requiring triple therapies).

DPP4is and heart failure

The disruption of the neurohormonal regulatory mechanism has been hypothesized to explain the increased HF risk associated with DPP4i use [48]. Several studies have assessed the association between DPP4i use and HF risk, although the results appeared to be inconclusive. Previous randomized controlled trials [i.e. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) [16] and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) [21]] and a US cohort study of Met-based dual therapies [17] all showed an increased HF risk for DPP4i users, whereas the study by Kim *et al.* [11] found that DPP4i users (either on mono- or combination therapy) had a lower risk of HF than non-DPP4i users, which was consistent with a recent large observational study from Italy, indicating a significantly lower HF risk with DPP4is compared with SU [19]. In addition, the most recent placebo-controlled trial reported that sitagliptin use was not associated with an increased HF risk [44]. Consistent with previous observational studies [17, 19, 44], the present study did not find a significantly increased HF risk for Met + DPP4i users compared with Met + SU users. Additionally, we found that the patients taking a DPP4i as a third-line treatment had a significantly lower HF risk compared

Table 5

Comparative risks for cardiovascular diseases, all-cause mortality and hypoglycaemia of metformin-based triple regimens, and subgroup analyses stratified by patients' CVD history

	Met + SU + DPP4i[a] (*n* = 10 475) *vs.* 1:1 matched Met + SU + TZDs (reference) HR (95% CI)			Met + SU + DPP4i[a] (*n* = 11 248) *vs.* 1:1 matched Met + SU + ACA (reference) HR (95% CI)			Met + SU + DPP4i[a] (*n* = 3008) *vs.* 1:1 matched Met + SU + MEG (reference) HR (95% CI)		
	All patients (*n* = 20 950)	**CVD history[b] (*n* = 3710)**	**No CVD history[b] (*n* = 17 218)**	**All patients (*n* = 22 496)**	**CVD history (*n* = 5318)**	**No CVD history (*n* = 17 078)**	**All patients (*n* = 6016)**	**CVD history (*n* = 1768)**	**No CVD history (*n* = 4240)**
MACEs	1.016 (0.919, 1.124)	1.018 (0.867, 1.196)	0.963 (0.844, 1.098)	**0.902** (0.827, 0.984)	**0.875** (0.776, 0.987)	**0.885** (0.780, 0.992)	**0.676** (0.583, 0.783)	**0.696** (0.579, 0.837)	**0.737** (0.585, 0.928)
Stroke	0.924 (0.814, 1.049)	0.907 (0.742, 1.108)	0.933 (0.793, 1.099)	**0.826** (0.740, 0.923)	**0.822** (0.706, 0.957)	**0.807** (0.690, 0.943)	**0.653** (0.542, 0.786)	**0.669** (0.531, 0.843)	**0.721** (0.538, 0.967)
Heart failure	1.120 (0.940, 1.333)	1.172 (0.893, 1.537)	1.033 (0.818, 1.304)	1.037 (0.894, 1.203)	0.933 (0.766, 1.136)	1.178 (0.937, 1.482)	**0.721** (0.568, 0.917)	**0.694** (0.514, 0.938)	0.880 (0.601, 0.982)
Myocardial infarction	1.102 (0.864, 1.406)	1.374 (0.935, 2.017)	0.888 (0.643, 1.226)	0.954 (0.775, 1.174)	0.900 (0.684, 1.186)	0.858 (0.620, 1.188)	0.798 (0.551, 1.157)	0.930 (0.660, 1.623)	**0.778** (0.642, 0.946)
All-cause mortality	0.948 (0.833, 1.079)	**0.718** (0.559, 0.922)	0.963 (0.825, 1.125)	**0.784** (0.701, 0.878)	**0.708** (0.589, 0.851)	**0.788** (0.682, 0.911)	0.689 (0.594, 0.703)	0.645 (0.519, 0.708)	0.629 (0.597, 0.797)
Hypoglycaemia	0.911 (0.746, 1.113)	0.915 (0.628, 1.333)	0.885 (0.698, 1.122)	0.843 (0.704, 1.010)	0.973 (0.725, 1.307)	**0.748** (0.593, 0.942)	**0.757** (0.621, 0.836)	**0.784** (0.627, 0.871)	**0.757** (0.616, 0.801)

ACA, acarbose; CI, confidence interval; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase 4 inhibitor; HR, hazard ratio; MACEs, major adverse cardiovascular events; MEG, meglitinide; Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione

[a]In each subgroup (e.g. Met + SU + DPP4i and its matched Met + SU + TZDs), the Met + SU + DPP4i group served as comparator for its matched triple regimen (e.g. Met + SU + TZDs). Therefore, an HR less than 1 implies a lower risk of the event of interest (e.g. CVD) with the use of the Met + SU + DPP4i regimen

[b]A sum of 3710 (CVD history) and 17 218 (no CVD history) cases, adding up to 20 928, is not exactly equal to the initial total number of patients in this group (20 950). This is because, after the patients were stratified by CVD history, we conducted matching procedures for CVD history and non-CVD history groups, separately. A reduction in the number of patients after matching in these stratified subgroups occurred mainly because some cases (i.e. 22) were not matched to another reference case (i.e. we were unable to find a similar reference patient) after they had been classified into a specific subgroup (i.e. CVD history or non-CVD history group) and were then not included in the analyses.

Tables refers the values which are statistically significant ($P < 0.05$).

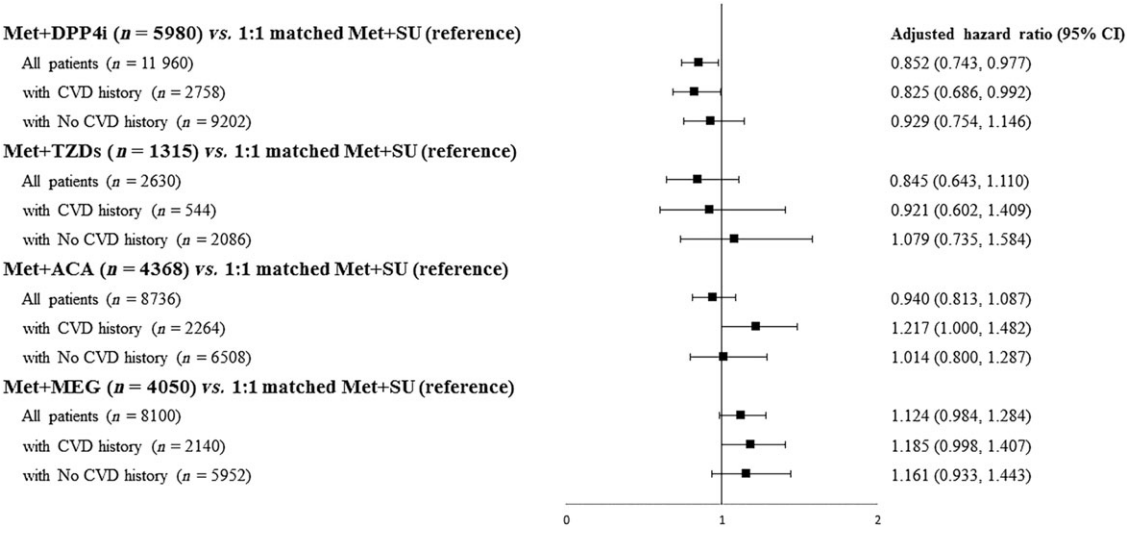

Figure 2

Comparative risks for major adverse cardiovascular events associated with metformin-based dual regimens. ACA, acarbose; CI, confidence interval; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; MEG, meglitinide; Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione

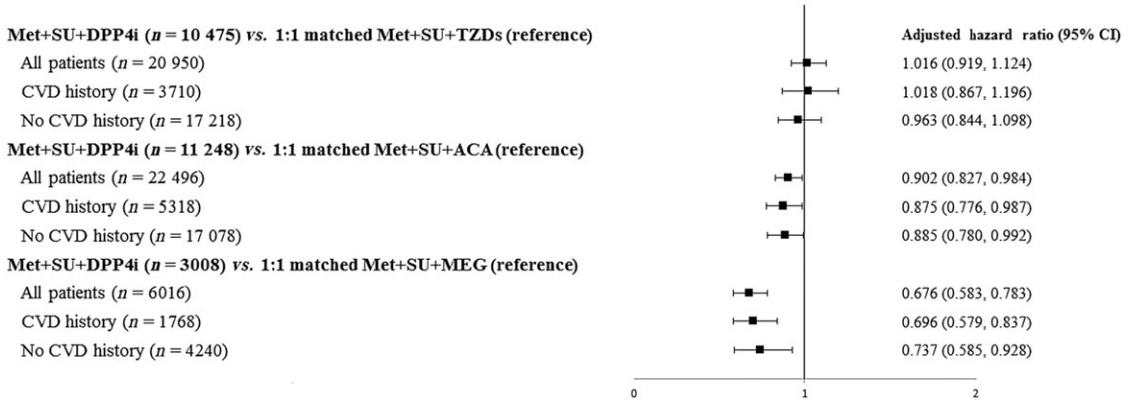

Figure 3

Comparative risks for major adverse cardiovascular events associated with metformin-based triple regimens. ACA, acarbose; CI, confidence interval; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; MEG, meglitinide; Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione

with those on a MEG add-on regimen. These results imply that DPP4is as a second- or third-line antidiabetic treatment might be superior to other add-ons (e.g. MEG) to alter the risk of HF for patients with T2DM.

Study limitations

First, we analysed only common combination triple regimens, which were Met + SU-based triple therapies. Future studies might analyse other combinations (e.g. SU + ACA + DPP4i) to confirm our findings. However, the combinations of treatment regimens analysed in the present study have accounted for the majority of antidiabetic drug utilization patterns in T2DM. Second, due to the nature of an observational study, a potential confounding by indication could not be eliminated. Although PS matching might mitigate this concern, potential residual confounding by incomplete adjustment for unmeasured bias (i.e. lifestyle risk factors, physicians' behaviours) for study outcomes may still exist. Third, identifying CVD outcomes from Taiwan's NHIRD might suffer from misclassification. However, previous validation studies for the identification of CVD events (e.g. MI [49] and stroke [50]) from the NHIRD showed high sensitivity and positive predictive values. Fourth, considering the Cox model that we utilized to examine the factors associated with 'time to event', the duration which a patient contributed to the analysis may vary by censored points. Study subjects would have different dosages and lengths of medication use, depending on censored points. However, the time-varying dosages and lengths of medication

use were not accounted for in our analyses. In addition, we did not further assess the dose–gradient relationship between medication use and CVD risk, mainly because not all study subjects had the same length of follow-up. Fifth, GLP-1 receptor agonists were only introduced into Taiwan's NHI formulary in 2011 (i.e. exenatide: May 2011, liraglutide: October 2012), and, thus, our study period (1999–2013) may not have been sufficiently long to capture its cardiovascular outcomes. In addition, in 2013, the utilization of and spending on GLP-1 agonists in Taiwan accounted for only 1.8% and 0.8% of total antidiabetic drugs, respectively [25]. In this regard, the present study may not have included a sufficient number of cases treated with GLP-1 agonists to be compared with other antidiabetic drugs, so GLP-1 agonists were not included in the analysis. Lastly, the study included only Taiwanese patients with T2DM. However, there is no apparent evidence indicating a difference in treatment efficacy regarding the use of DPP4is across ethnicities, so our study results may be applicable to other ethnicities and other health insurance settings. Moreover, as we also studied the role of DPP4is as a third-line add-on drug to Met + SU, such results may be beneficial for countries or healthcare settings in which a DPP4i is usually used in the later stages (i.e. as a third-line treatment) as a result of its higher price, compared with other antidiabetic drugs.

Conclusions

The present study confirms the previous evidence on the cardiovascular outcomes of DPP4is as a second-line treatment to Met and adds further evidence for the favourable clinical outcomes of DPP4is as a third-line add-on therapy. Additionally, our results suggest that DPP4is as a third-line treatment, in addition to their second-line role, might also provide cardiovascular benefits, reduce all-cause mortality and pose no increased risk for HF or hypoglycaemia compared with other antidiabetic drugs. Therefore, adding DPP4is as a second- or third-line treatment to T2DM patients with inadequate glycaemic control under Met monotherapy might alter future CVD risks.

Competing Interests

There are no competing interests to declare.

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Contributors

H.T.O. contributed substantially to the study concept and design, data acquisition, and analysis and interpretation of the data. K.C.C. contributed to data collection and the analysis. C.Y.L. and J.S.W. provided the clinical and statistical interpretation of the results. H.-T.O. wrote the first draft of the manuscript, and K.C.C., C.Y.L. and J.S.W. critically revised it. All authors gave approval for the publication of the final version.

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Supporting Information

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http://onlinelibrary.wiley.com/doi/10.1111/bcp.13241/suppinfo

Table S1 Sensitivity analyses for comparative effectiveness and safety of metformin-based dual therapy
Table S2 Sensitivity analyses for comparative effectiveness and safety of metformin-based triple therapy