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Effects on Clinical Outcomes of Adding Dipeptidyl Peptidase-4 Inhibitors Versus Sulfonylureas to Metformin Therapy in Patients With Type 2 Diabetes Mellitus

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Background: Recent studies concluded that dipeptidyl peptidase-4 (DPP-4) inhibitors provide glycemic control but also raised concerns about the risk for heart failure in patients with type 2 diabetes mellitus (T2DM). However, large-scale studies of the effects on cardiovascular outcomes of adding DPP-4 inhibitors versus sulfonylureas to metformin therapy remain scarce.

Objective: To compare clinical outcomes of adding DPP-4 inhibitors versus sulfonylureas to metformin therapy in patients with T2DM.

Design: Nationwide study using Taiwan's National Health Insurance Research Database.

Setting: Taiwan.

Patients: All patients with T2DM aged 20 years or older between 2009 and 2012. A total of 10 089 propensity score–matched pairs of DPP-4 inhibitor users and sulfonylurea users were examined.

Measurements: Cox models with exposure to sulfonylureas and DPP-4 inhibitors included as time-varying covariates were used to compare outcomes. The following outcomes were considered: all-cause mortality, major adverse cardiovascular events (MACEs) (including ischemic stroke and myocardial infarction), hospitalization for heart failure, and hypoglycemia. Patients were followed until death or 31 December 2013.

Results: DPP-4 inhibitors were associated with lower risks for all-cause death (hazard ratio [HR], 0.63 [95% CI, 0.55 to 0.72]), MACEs (HR, 0.68 [CI, 0.55 to 0.83]), ischemic stroke (HR, 0.64 [CI, 0.51 to 0.81]), and hypoglycemia (HR, 0.43 [CI, 0.33 to 0.56]) compared with sulfonylureas as add-on therapy to metformin but had no effect on risks for myocardial infarction and hospitalization for heart failure.

Limitation: Observational study design.

Conclusion: Compared with sulfonylureas, DPP-4 inhibitors were associated with lower risks for all-cause death, MACEs, ischemic stroke, and hypoglycemia when used as add-ons to metformin therapy.

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Data from the Framingham Heart Study suggest that type 2 diabetes mellitus (T2DM) is associated with a 2- to 3-fold increased risk for cardiovascular disease (1, 2). Since 2008, the U.S. Food and Drug Administration and the European Medicines Agency have required premarketing and postmarketing demonstrations of the cardiovascular safety of new antidiabetic therapies (3). Many glucose-lowering therapies with various mechanisms of action are available. The current guidelines of the American Diabetes Association and the European Association for the Study of Diabetes recommend metformin as the optimal first-line drug (4, 5). Because diabetes is a progressive disease, many patients do not achieve target glycemic control after initiating metformin therapy. However, the choice of a second-line drug is unclear.

Results of previous studies have suggested that sulfonylureas, the medications most commonly prescribed as add-ons to metformin therapy, may increase cardiovascular risks (6–8). Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new pharmacologic class of drugs for treatment of T2DM, improve glycemic control by increasing incretin levels (9–12). Incretins (gut-derived peptides) exert antidiabetic effects by stimulating insulin secretion in a glucose-dependent manner (13, 14). In several clinical studies, DPP-4 inhibitors plus metformin achieved similar glucose control with a lower risk for hypoglycemia than sulfonylureas plus metformin (15–17). An understanding of the effects of these therapies on cardiovascular risk may provide additional useful information to inform the choice of second-line therapy for patients with T2DM. At present, however, clinical evidence showing the comparative effects of adding DPP-4 inhibitors and sulfonylureas to metformin therapy on all-cause mortality and major adverse cardiovascular events (MACEs) is scarce (15, 18). Recently, the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) study raised concerns about an increased risk for heart failure in patients with T2DM treated with DPP-4 inhibitors (19). Most previous studies have not examined this outcome.

Given the limited comparative data on these 2 oral hypoglycemic agents as second-line therapies, we performed a propensity score–matched study using Tai-

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Editorial comment 1

EDITORS' NOTES

Context

Studies have suggested that treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors is associated with increased risk for heart failure in patients with type 2 diabetes mellitus (T2DM).

Contribution

In a large study of DPP-4 inhibitors or sulfonylureas added to metformin for treatment of T2DM, risks for myocardial infarction and hospitalization for heart failure with DPP-4 inhibitors were similar to those with sulfonylureas, but risks for all-cause death, major adverse cardiovascular events, ischemic stroke, and hypoglycemia were lower with DPP-4 inhibitors.

Caution

Possibility of unmeasured confounding.

Implication

This study provides additional evidence on the comparative effects of DPP-4 inhibitors and sulfonylureas as add-ons to metformin.

wan's National Health Insurance Research Database (NHIRD) to compare all-cause mortality and the occurrence of MACEs (including ischemic stroke and myocardial infarction), hospitalization for heart failure, and hypoglycemia among patients with T2DM treated with DPP-4 inhibitors or sulfonylureas as add-ons to metformin therapy.

METHODS

Data Source

Taiwan initiated the National Health Insurance (NHI) program in 1995 to provide universal health coverage for its citizens. This program is among the largest and most comprehensive medical coverage systems in the world; it covers outpatient care, emergency department care, hospital care, dental services, medical examinations, laboratory tests, drug prescriptions, and interventional procedures. Because enrollment is mandatory, 98.4% of Taiwan's approximately 22.96 million citizens were enrolled as of 2007. Data for this study were obtained from the NHIRD, which was released for research purposes by Taiwan's National Health Research Institutes. For the current study, we used the Longitudinal Cohort of Diabetes Patients data set, which has been validated by the National Health Research Institutes for research purposes (20). This database, which represents most of the population of diabetic patients in Taiwan, consists of deidentified secondary data from a random sample of 120 000 patients with diabetes diagnoses taken each year since 1999. Although encryption and deidentification prevent the direct linking of patients' original information for privacy purposes, information for each patient is linked using a unique identification number in the NHIRD. Diseases were defined using diagnosis codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Design

This population-based observational cohort study aimed to investigate the association of DPP-4 inhibitors and sulfonylureas administered in addition to metformin therapy and the risk for all-cause death, MACEs, hospitalization for heart failure, and hypoglycemia in patients with T2DM. The study included all patients aged 20 years or older with a diagnosis of diabetes between March 2009 (when DPP-4 inhibitors became available in Taiwan) and June 2012. Incident metformin users who had not previously used any other oral hypoglycemic agents were identified and considered to be enrolled in the study cohort on the date that they subsequently filled a prescription for a DPP-4 inhibitor or sulfonylurea. The index date was defined as the first day of DPP-4 inhibitor or sulfonylurea use. We excluded patients who were using other nonstudy hypoglycemic agents for diabetes control between the first day of metformin prescription and the index date. We selected patients who were adherent to metformin by excluding those who were not using it on the date of sulfonylurea or DPP-4 inhibitor prescription or during the previous 90 days (**Appendix Figure**, available at www.annals.org) (6).

For patients using sulfonylureas and DPP-4 inhibitors, we extracted data on demographic variables, diagnosis and procedure codes, and drug prescriptions for the period from March 2009 to December 2013. We analyzed sociodemographic data (including age, sex, and monthly income), index year, urbanization level (4 levels, with level 1 referring to urban areas and level 4 referring to rural areas), hospital level (4 levels, with level 1 referring to medical centers and level 4 referring to local medical clinics), Charlson Comorbidity Index (CCI) score (21), adapted Diabetes Complications Severity Index (aDCSI) score (22–24), and other comorbidities known to be risk factors for MACEs. Concomitant receipt of other medications (including α-blockers, angiotensin-converting enzyme inhibitors, angiotensin II–receptor blockers, β-blockers, calcium-channel blockers, diuretics, other antihypertensive drugs, aspirin, clopidogrel, ticlopidine, cilostazol, warfarin, steroids, nitrates, nonsteroidal anti-inflammatory drugs, proton-pump inhibitors, statins, and selective serotonin reuptake inhibitors) that could be a confounding factor in the analysis of hypoglycemia and MACEs was also taken into consideration.

Sulfonylurea and DPP-4 Inhibitor Exposure

The exposures of interest were DPP-4 inhibitors (including sitagliptin, vildagliptin, and saxagliptin) and sulfonylureas (acetohexamide, chlorpropamide, tolazamide, tolbutamide, gliclazide, glimepiride, glipizide, gliquidone, glibornuride, or glyburide) added to metformin therapy. For each DPP-4 inhibitor or sulfonylurea prescription, detailed information on drug type, quantity, dose, dispensing date, and days of drug sup-

ply was collected. The period of exposure to each DPP-4 inhibitor or sulfonylurea was defined as extending from the day of prescription to the end of the last dispensed drug supply. In Taiwan, the NHI program allows for a refill prescription that is valid for 90 days with up to 3 refills (25, 26). Therefore, when a patient filled a prescription within 90 days after the previous one, he or she was considered to have received continuous therapy. An interval greater than 90 days between refills was categorized as discontinuation of therapy (27).

Outcomes

The following outcomes were considered: all-cause mortality, MACEs (a composite measure of hospitalization for ischemic stroke [ICD-9-CM code 433.x, 434.x, or 436] and myocardial infarction [ICD-9-CM code 410.x]), hospitalization for heart failure (ICD-9-CM code 428.x), and hospitalization for hypoglycemia (ICD-9-CM code 251.0x, 251.1x, or 251.2x). Patients were followed until death or the end of the study (31 December 2013), whichever occurred first.

Statistical Analysis

Descriptive statistics (means, SDs, and frequencies) were used to characterize the study population at baseline. We examined differences in baseline characteristics between DPP-4 inhibitor users and sulfonylurea users by using standardized mean differences. For each patient with T2DM, we calculated a propensity score for the likelihood of prescription of a DPP-4 inhibitor as an add-on to metformin therapy by using baseline covariates in a multivariate logistic regression model (**Appendix Table 1**, available at www.annals.org). We used the PSMatching macro in SAS to match each DPP-4 inhibitor user to 1 sulfonylurea user according to propensity score (calipers of width equal to 0.1 SD of the logit of the propensity score) based on nearest-neighbor matching without replacement (28). Cox regression models were used to evaluate the relative hazards of outcomes in the 2 study groups. We treated exposure to sulfonylureas and DPP-4 inhibitors as time-varying covariates (29). Patients were censored on the day that they added or switched to the opposite medication (DPP-4 inhibitor or sulfonylurea) or discontinued metformin therapy. Poisson distribution was used to compare the incidence rates of outcomes between groups. To assess the robustness of our results, we performed a sensitivity analysis using cancer as a negative control outcome (30, 31). We postulated that a different cancer risk between DPP-4 inhibitor users and sulfonylurea users would suggest the presence of uncontrolled confounding or some other bias during follow-up. In subgroup analyses, Cox regression was performed according to age, sex, CCI score, hypertension, chronic kidney disease, hospitalization for heart failure, myocardial infarction, and cerebrovascular disease. We also examined interactions in associations by using likelihood ratio tests.

SQL Server 2012 (Microsoft) was used for data linkage, processing, and sampling. Propensity scores were calculated using SAS, version 9.3 (SAS Institute). All other statistical analyses were conducted using Stata, version 13.0 (StataCorp). All 2-tailed *P* values less than 0.05 were considered statistically significant.

Role of the Funding Source

This research received no support from any funding agency in the public, commercial, or not-for-profit sector.

RESULTS

Characteristics of the Study Population

Among patients with T2DM who satisfied the study selection criteria before propensity score matching, DPP-4 inhibitor users were older and had longer diabetes durations, higher CCI and aDCSI scores, and more baseline comorbidities than sulfonylurea users. For the primary analyses, we created a propensity score–matched cohort of 10 089 pairs of sulfonylurea users and DPP-4 inhibitor users. After propensity score matching, baseline characteristics did not differ significantly between groups (**Table 1**). The distribution of DPP-4 inhibitor use and sulfonylurea use during follow-up is shown in **Appendix Table 2** (available at www.annals.org).

Outcomes

During the mean follow-up of 3.3 years (maximum, 4.8 years), a total of 563 (5.6%) DPP-4 inhibitor users and 4425 (7.3%) sulfonylurea users died of any cause. After propensity score matching, follow-up was similar between groups (mean, 2.8 years [SD, 1.0 year]). Users of DPP-4 inhibitors had lower risks for all-cause death (hazard ratio, [HR], 0.63 [95% CI, 0.55 to 0.72]) and MACEs (HR, 0.68 [CI, 0.55 to 0.83]) than sulfonylurea users. In further analyses, DPP-4 inhibitor users also had lower risks for ischemic stroke (HR, 0.64 [CI, 0.51 to 0.81]) and hypoglycemia (HR, 0.43 [CI, 0.33 to 0.56]). However, risks for myocardial infarction (HR, 0.75 [CI, 0.52 to 1.07]) and hospitalization for heart failure (HR, 0.78 [CI, 0.57 to 1.06]) were similar between groups (**Table 2**). Similar results were obtained for both cohorts before propensity score matching (**Appendix Table 3**, available at www.annals.org). Subgroup analyses produced results similar to those of the primary analyses (**Figures 1** to **4** and **Appendix Tables 4** to **7**, available at www.annals.org).

In the sensitivity analysis using cancer as a negative control outcome, we found no difference in cancer risk between DPP-4 inhibitor users and sulfonylurea users (HR, 0.88 [CI, 0.72 to 1.08]; $P = 0.24$) (**Appendix Table 8**, available at www.annals.org).

DISCUSSION

To our knowledge, this is the largest study comparing the effects on all-cause mortality and MACEs of DPP-4 inhibitors and sulfonylureas used as add-ons to metformin therapy. We found that the use of DPP-4 inhibitors as initial add-on therapy with metformin reduced the risks for all-cause death and MACEs compared with sulfonylurea use. In analyses of MACE

Table 1. Baseline Characteristics of Diabetic Patients

Characteristic	Before Propensity Score Matching			After Propensity Score Matching		
	DPP-4 Inhibitor User	Sulfonylurea User	Standardized Difference	DPP-4 Inhibitor User	Sulfonylurea User	Standardized Difference
Patients, *n*	10 131	60 209	–	10 089	10 089	–
Mean age (SD), *y*	57.9 (12.3)	56.7 (12.3)	0.097	57.9 (12.3)	57.8 (12.3)	0.005
Male, *n (%)*	5448 (53.7)	34 229 (56.8)	−0.062	5433 (53.9)	5449 (54.0)	−0.003
Index year, *n (%)*						
2009	1717 (16.9)	19 211 (31.9)	−0.354	1717 (17.0)	1717 (17.0)	0.000
2010	2795 (27.6)	23 197 (38.5)	−0.234	2795 (27.7)	2795 (27.7)	0.000
2011	3401 (33.6)	12 856 (21.4)	0.276	3399 (33.7)	3399 (33.7)	0.000
2012	2218 (21.9)	4945 (8.2)	0.390	2178 (21.6)	2178 (21.6)	0.000
Monthly income, *n (%)*						
Dependent	2644 (26)	15 462 (25.6)	0.010	2633 (26.1)	2574 (25.5)	0.013
<NT$19 100	1948 (19.2)	12 185 (20.2)	−0.025	1946 (19.3)	1965 (19.5)	−0.005
NT$19 100–NT$41 999	4119 (40.6)	26 842 (44.5)	−0.079	4107 (40.7)	4163 (41.3)	−0.011
≥NT$42 000	1420 (14)	5720 (9.5)	0.141	1403 (13.9)	1387 (13.7)	0.005
Urbanization level, *n (%)**						
1 (urban)	2998 (29.5)	18 127 (30.1)	−0.011	2977 (29.5)	3041 (30.1)	−0.014
2	6758 (66.7)	39 215 (65.1)	0.033	6737 (66.8)	6667 (66.1)	0.015
3	323 (3.1)	2371 (3.9)	−0.040	323 (3.2)	329 (3.3)	−0.003
4 (rural)	52 (0.5)	496 (0.8)	−0.038	52 (0.5)	52 (0.5)	0.000
Hospital level, n (%)						
1 (medical center)	2379 (23.5)	7467 (12.4)	0.292	2367 (23.5)	2358 (23.4)	0.002
2	3708 (36.6)	11 727 (19.5)	0.388	3684 (36.5)	3715 (36.8)	0.006
3	3178 (31.4)	13 567 (22.5)	0.200	3172 (31.4)	3149 (31.2)	0.005
4 (local medical clinic)	866 (8.5)	27 448 (45.6)	−0.917	866 (8.6)	867 (8.6)	0.000
Prescription by diabetes specialists, *n (%)*	1389 (13.7)	5781 (9.6)	0.128	1376 (13.6)	1417 (14.0)	−0.012
Outpatient visits to metabolism and endocrinology professionals in past year, *n (%)*						
0–5	8580 (84.6)	54 145 (89.9)	−0.158	8554 (84.8)	8569 (84.9)	−0.004
6–10	1192 (11.7)	4897 (8.1)	0.122	1179 (11.7)	1200 (11.9)	−0.006
11–15	298 (2.9)	862 (1.4)	0.103	295 (2.9)	259 (2.6)	0.022
<15	61 (0.6)	305 (0.5)	0.013	61 (0.6)	61 (0.6)	0.000
Charlson Comorbidity Index score, *n (%)*						
1	1577 (15.5)	12 435 (20.6)	−0.132	1846 (18.3)	1778 (17.6)	0.018
2	2018 (19.9)	13 418 (22.2)	−0.058	2144 (21.3)	2170 (21.5)	−0.006
3	1936 (19.1)	11 752 (19.5)	−0.010	1937 (19.2)	1973 (19.6)	−0.009
≥4	4600 (45.4)	22 604 (37.5)	0.160	4162 (41.3)	4168 (41.3)	−0.001
Median aDCSI score (IQR)†	1 (0–3)	1 (0–2)	0.170	1 (0–3)	1 (0–3)	−0.001
Mean duration of diabetes mellitus (SD), *mo*	51.0 (39.0)	36.8 (38.3)	0.366	50.8 (39.0)	50.8 (40.8)	0.001
Antihypertensive drug use, *n (%)*						
α-Blocker	168 (1.6)	846 (1.4)	0.021	168 (1.7)	176 (1.7)	−0.006
ACEI or ARB	2225 (21.9)	10 613 (17.6)	0.109	2206 (21.9)	2243 (22.2)	−0.009
β-Blocker	1134 (11.1)	6933 (11.5)	−0.010	1129 (11.2)	1117 (11.1)	0.004
Calcium-channel blocker	1995 (19.6)	12 782 (21.2)	−0.038	1989 (19.7)	2004 (19.9)	−0.004
Diuretic	678 (6.6)	4351 (7.2)	−0.021	676 (6.7)	696 (6.9)	−0.008
Other	60 (0.5)	649 (1)	−0.053	60 (0.6)	61 (0.6)	−0.001

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Table 1–Continued

Characteristic	Before Propensity Score Matching			After Propensity Score Matching		
	DPP-4 Inhibitor User	Sulfonylurea User	Standardized Difference	DPP-4 Inhibitor User	Sulfonylurea User	Standardized Difference
Other concomitant medications, *n* (%)						
Antiplatelet agent‡	1361 (13.4)	6547 (10.8)	0.078	1355 (13.4)	1351 (13.4)	0.001
Warfarin	58 (0.5)	209 (0.3)	0.033	56 (0.6)	68 (0.7)	−0.015
Steroid	468 (4.6)	3524 (5.8)	−0.055	467 (4.6)	469 (4.6)	−0.001
Nitrate	253 (2.4)	1190 (1.9)	0.035	251 (2.5)	252 (2.5)	−0.001
NSAID	1502 (14.8)	11 803 (19.6)	−0.127	1502 (14.9)	1504 (14.9)	−0.001
PPI	216 (2.1)	1062 (1.7)	0.027	215 (2.1)	206 (2.0)	0.006
Statin	1254 (12.3)	5370 (8.9)	0.112	1239 (12.3)	1245 (12.3)	−0.002
SSRI	102 (1)	601 (0.9)	0.001	101 (1.0)	102 (1.0)	−0.001
Comorbidities, *n* (%)						
Coronary artery disease	3664 (36.1)	17 988 (29.8)	0.134	3641 (36.1)	3612 (35.8)	0.006
Cerebrovascular disease	2111 (20.8)	10 180 (16.9)	0.101	2105 (20.9)	2127 (21.1)	−0.005
Myocardial infarction	408 (4)	1713 (2.8)	0.065	405 (4.0)	419 (4.2)	−0.007
Hypertension	7327 (72.3)	40 127 (66.6)	0.124	7288 (72.2)	7269 (72.0)	0.004
Heart failure	874 (8.6)	4574 (7.5)	0.038	872 (8.6)	878 (8.7)	−0.002
Peripheral vascular disease	480 (4.7)	2680 (4.4)	0.014	480 (4.8)	505 (5.0)	0.001
Peptic ulcer disease	2696 (26.6)	13 814 (22.9)	0.085	2688 (26.6)	2659 (26.4)	0.007
Chronic kidney disease	1147 (11.3)	6188 (10.2)	0.034	1140 (11.3)	1133 (11.2)	0.002
Liver disease	4043 (39.9)	22 658 (37.6)	0.047	4020 (39.8)	4016 (39.8)	0.001
Atrial fibrillation	290 (2.8)	1150 (1.9)	0.062	285 (2.8)	290 (2.9)	−0.003
Dyslipidemia	7574 (74.7)	39 283 (65.2)	0.209	7535 (74.7)	7545 (74.8)	−0.002
Valvular heart disease	957 (9.4)	4095 (6.8)	0.097	950 (9.4)	936 (9.3)	0.005
Cancer	1203 (11.8)	5536 (9.1)	0.087	1197 (11.9)	1196 (11.9)	0.000
Autoimmune disease	483 (4.7)	2127 (3.5)	0.062	478 (4.7)	466 (4.6)	0.006
Mean propensity score (SD)	0.26 (0.14)	0.12 (0.12)	1.060	0.26 (0.14)	0.26 (0.14)	0.000

ACEI = angiotensin-converting enzyme inhibitor; aDCSI = adapted Diabetes Complications Severity Index; ARB = angiotensin II–receptor blocker; DPP-4 = dipeptidyl peptidase-4; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; NT$ = new Taiwan dollars; PPI = proton-pump inhibitor; SSRI = selective serotonin reuptake inhibitor.
* Strata are from Taiwan National Health Research Institute publications.
† 13-point scale with 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic. Each category was assigned a score of 0 (no abnormality), 1 (some abnormality), or 2 (severe abnormality).
‡ Aspirin, clopidogrel, ticlopidine, or cilostazol.

components, DPP-4 inhibitors were associated with a lower risk for ischemic stroke but did not alter the risks for myocardial infarction and hospitalization for heart failure. Regarding adverse effects, DPP-4 inhibitors were associated with a lower risk for hypoglycemia than sulfonylureas.

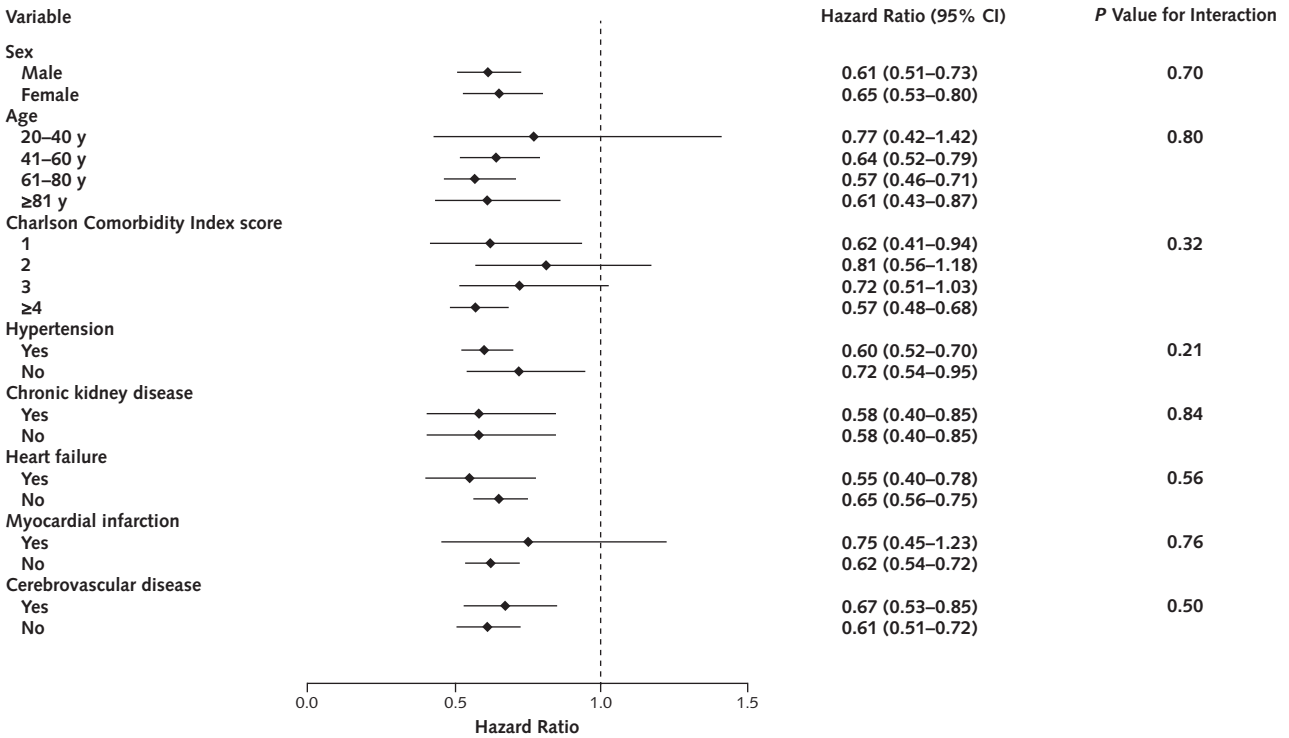
Previous clinical studies comparing the effects of DPP-4 inhibitors and sulfonylureas on MACE components have been largely inconclusive. In 2 meta-analyses (32, 33), DPP-4 inhibitors reduced the risk for adverse cardiovascular effects and nonfatal myocardial infarction compared with placebo and other oral hypoglycemic agents. In a subanalysis, Engel and colleagues (33) found that DPP-4 inhibitors were associated with a lower rate of cardiovascular events than sulfonylureas. Retrospective data from U.K. clinical practice research for 33 983 sulfonylurea users and 7864 DPP-4 inhibitor users revealed lower risks for all-cause death and MACEs in patients treated with DPP-4 inhibitors plus metformin than in those treated with sulfonylureas plus

Table 2. Incidence and Risks (After Propensity Score Matching) for All-Cause Death, Myocardial Infarction, Ischemic Stroke, Hospitalization for Heart Failure, and Hypoglycemia Among Metformin Users With Diabetes Mellitus Receiving Add-on DPP-4 Inhibitors or Sulfonylureas

Outcome	DPP-4 Inhibitor			Sulfonylurea			Crude	
	Events, *n*	Person-Years	Incidence Rate per 1000 Person-Years	Events, *n*	Person-Years	Incidence Rate per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value
All-cause death	366	20262	18.06	488	18179	26.84	0.63 (0.55–0.72)	<0.001
MACE*	209	20037	10.43	282	17913	15.74	0.68 (0.55–0.83)	<0.001
Myocardial infarction	69	20202	3.42	88	18085	4.87	0.75 (0.52–1.07)	0.109
Ischemic stroke	144	20096	7.17	203	18003	11.28	0.64 (0.51–0.81)	<0.001
Hospitalization for heart failure	100	20175	4.96	100	18086	5.53	0.78 (0.57–1.06)	0.108
Hypoglycemia	89	20151	4.42	170	18030	9.43	0.43 (0.33–0.56)	<0.001

DPP-4 = dipeptidyl peptidase-4; MACE = major adverse cardiovascular event.
* Myocardial infarction or ischemic stroke.

Figure 1. Subgroup analysis of effects of dipeptidyl peptidase-4 inhibitors vs. sulfonylureas on risk for all-cause death in patients with type 2 diabetes.



metformin (18). However, these researchers did not further explore MACE components (such as myocardial infarction, heart failure, and ischemic stroke), which were highly variable and heterogeneous in their sample. In addition, their results account only for combination therapy, rather than add-on treatment as in our study. In another randomized trial, Gallwitz and colleagues (15) examined MACEs as a secondary outcome and found that linagliptin was associated with significantly fewer events than glimepiride in patients for whom metformin provided inadequate glycemic control. Among MACE components, linagliptin was associated only with a lower risk for nonfatal stroke. However, the conclusions of that study may be limited by the small number of cardiovascular events (12 in the linagliptin group and 26 in the glimepiride group), the analysis of MACEs as a secondary outcome, and the omission of a measure of heart failure as an outcome.

Within this research context, our study was designed to evaluate MACEs as a primary outcome with a larger sample and longer follow-up. The results provide additional clinical evidence on the comparative effects of DPP-4 inhibitors and sulfonylureas as add-ons to metformin therapy. We found a lower risk for stroke in DPP-4 inhibitor users than in sulfonylurea users. In animal models, a DPP-4 inhibitor was found to protect against stroke in mice with T2DM; in contrast, a sulfonylurea had an antistroke effect only in healthy mice (34). However, the mechanism underlying the neuroprotective effects of DPP-4 inhibitors remains unknown. The increased expression of glucagon-like peptide-1 receptors on neurons and the decreased activation of microglial cells were noted after an ischemic insult, which might protect neurons against metabolic and oxidative stress and further limit infarction size. Activation of the incretin pathway in neurons by DPP-4 inhibitors may also promote proliferation and neuronal differentiation of neural precursor cells into neurons and provide cellular protection (35–37).

Previous clinical trials evaluating the risk for heart failure in patients treated with DPP-4 inhibitors have produced mixed results; the recent SAVOR-TIMI 53 study (19) documented an unexpected association between hospitalization for heart failure and saxagliptin, but other randomized trials found no difference in the risk for heart failure between DPP-4 inhibitors and placebo (38, 39). Patients enrolled in the SAVOR-TIMI 53 study were randomly assigned to saxagliptin or placebo. The use of other hypoglycemic agents, such as sulfonylureas, should also be taken into consideration, given associations with a higher risk for hypoglycemia and possible risk for heart failure that may affect results. In our study, we found that this risk did not differ significantly between users of DPP-4 inhibitors and sulfonylureas as add-ons to metformin therapy. Because hypoglycemia may be associated with potentially harmful effects on mortality and the risk for cardiovascular

Figure 2. Subgroup analysis of effects of dipeptidyl peptidase-4 inhibitors vs. sulfonylureas on risk for myocardial infarction in patients with type 2 diabetes.

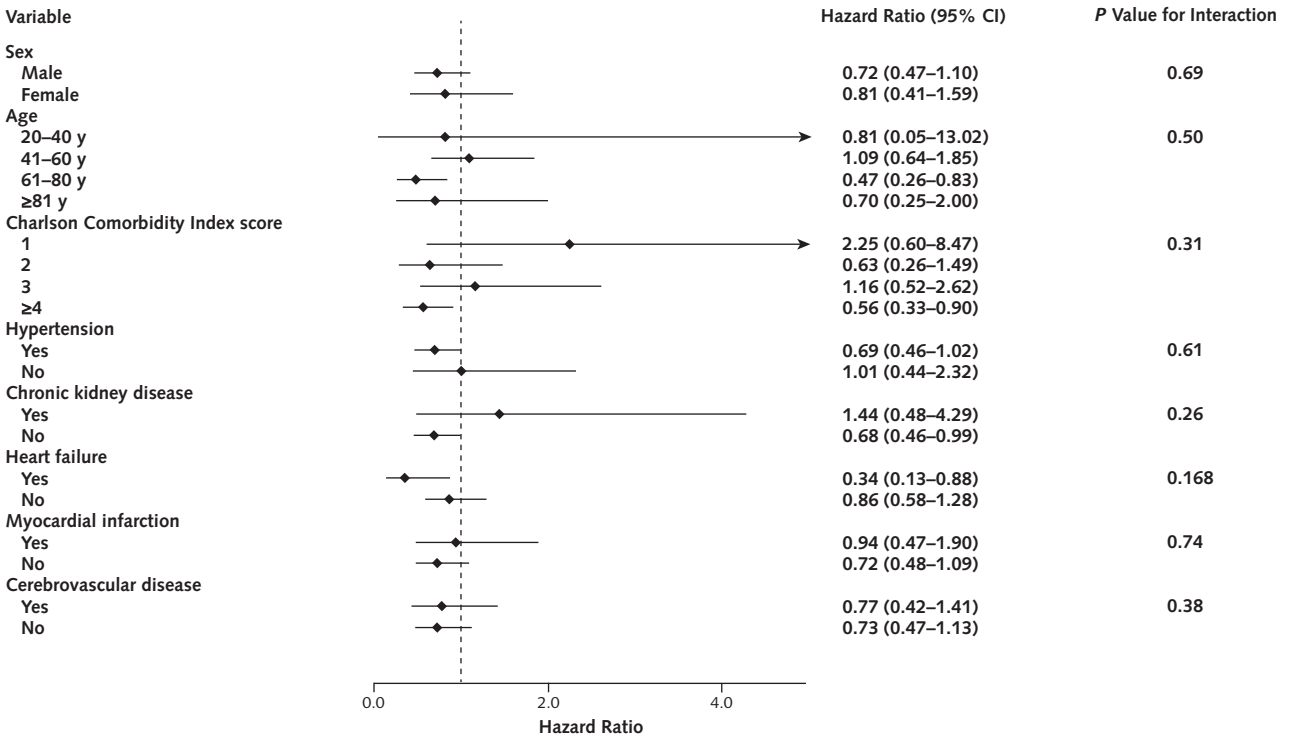


Figure 3. Subgroup analysis of effects of dipeptidyl peptidase-4 inhibitors vs. sulfonylureas on risk for ischemic stroke in patients with type 2 diabetes.

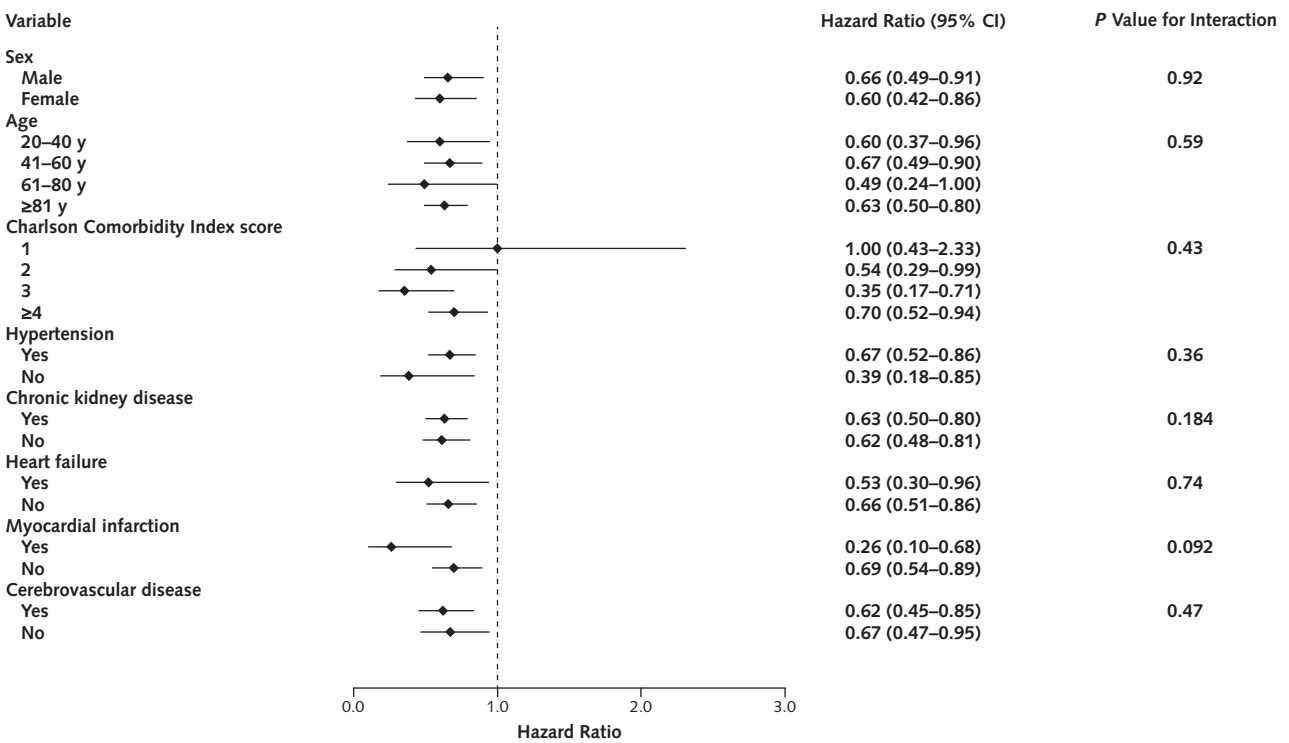
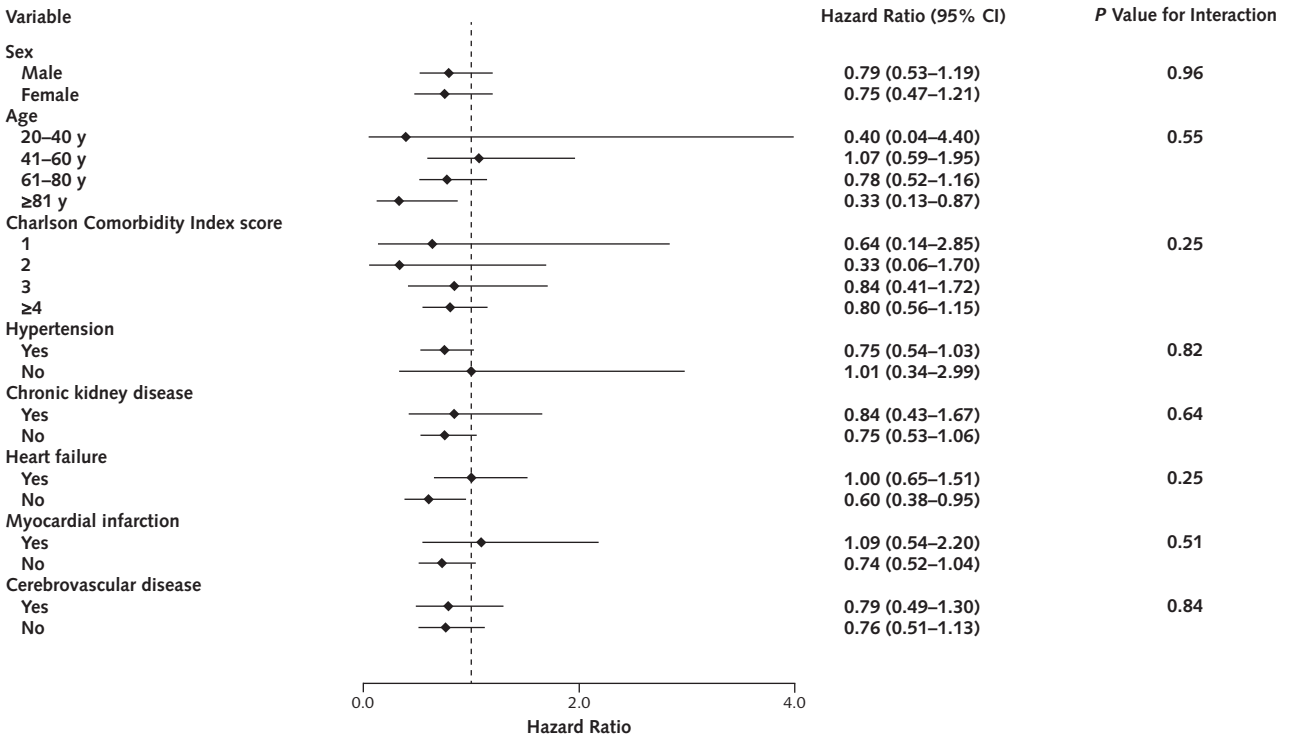


Figure 4. Subgroup analysis of effects of dipeptidyl peptidase-4 inhibitors vs. sulfonylureas on risk for hospitalization for heart failure in patients with type 2 diabetes.



events (40–42), the choice of oral hypoglycemic agent for patients with T2DM should be made with consideration of the risk for hypoglycemia and the patient's needs. Our study showed a reduced risk for hypoglycemia in DPP-4 inhibitor users compared with sulfonylurea users among patients with T2DM.

The primary strength of our study is the completeness of nationwide data from patients with T2DM using DPP-4 inhibitors or sulfonylureas in Taiwan. Because of the retrospective observational nature of the study, patients were matched and compared by using propensity scores to reduce confounding effects, and a time-varying analysis was performed. However, this study has several limitations. First, unmeasured confounding is the primary limitation inherent in the use of administrative data, although we used propensity score matching to control for patient characteristics in both cohorts. For example, the choice of sulfonylureas or DPP-4 inhibitors as second-line oral hypoglycemic agents for study participants was based on the decisions of physicians in charge, which may have caused selection bias. Second, information on indices of diabetes control, such as glycosylated hemoglobin, was lacking. However, the duration and severity (by aDCSI score) of T2DM were similar between study groups. In addition, patients who used oral hypoglycemic agents other than sulfonylureas or DPP-4 inhibitors after initiation of metformin therapy were excluded from the analyses. Third, the benefit of using a DPP-4 inhibitor as an add-on to metformin therapy in terms of the risk for future cardiovascular disease may manifest over a longer follow-up. Because DPP-4 inhibitors are a new class of oral hypoglycemic agents, additional long-term studies are needed to document their cardiovascular benefits.

The results of our study support the benefits of DPP-4 inhibitors as add-ons to metformin therapy in terms of a reduced risk for hypoglycemia compared with sulfonylureas. With respect to the clinical outcome of MACEs, we found that DPP-4 inhibitors reduced the risks for all-cause death and stroke but did not alter the risks for myocardial infarction and hospitalization for heart failure relative to sulfonylureas. This study adds to the clinical evidence for the evaluation of cardiovascular risk in patients with T2DM treated with sulfonylureas versus DPP-4 inhibitors after metformin.

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Note: Dr. Li and Dr. Yung-Tai Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer: This study was based in part on data from the NHIRD provided by the Bureau of National Health Insurance of the Department of Health and managed by the National Health Research Institutes. The conclusions presented in this study are those of the authors and do not necessarily reflect the views of the Bureau of National Health Insurance, the Department of Health, or the National Health Research Institutes.

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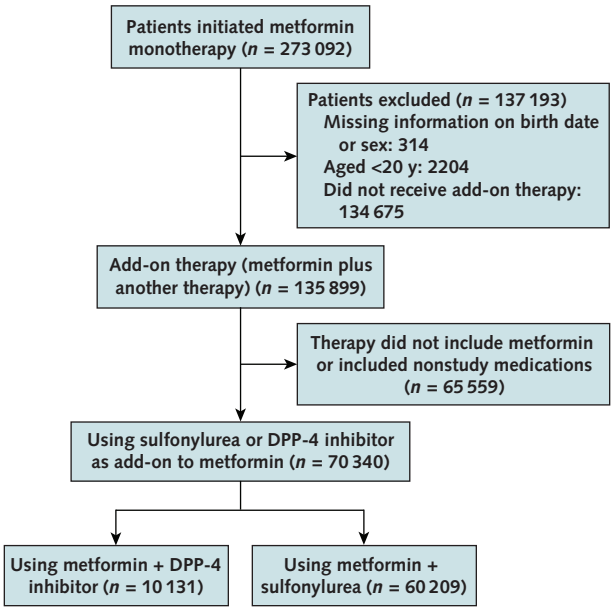
Appendix Figure. Study flow diagram.



DPP-4 = dipeptidyl peptidase-4.

Appendix Table 1. Propensity Score Model Results of Probability of Dipeptidyl Peptidase-4 Inhibitor Prescription as Add-on to Metformin Therapy

Parameter	Estimate	Odds Ratio	95% CI		
			Lower	Upper	*P* Value
Age, per year	−0.00013	1	0.998	1.002	0.9096
Index year					
2009		1			
2010	0.3005	1.351	1.264	1.443	<0.0001
2011	0.9805	2.666	2.489	2.856	<0.0001
2012	1.6786	5.358	4.91	5.847	<0.0001
Index month					
January		1			
February	0.00406	1.004	0.885	1.139	0.9497
March	0.0923	1.097	0.981	1.226	0.1052
April	0.1193	1.127	1.006	1.262	0.039
May	0.2156	1.241	1.11	1.387	0.0001
June	0.2993	1.349	1.206	1.509	<0.0001
July	0.3241	1.383	1.223	1.563	<0.0001
August	0.3572	1.429	1.267	1.612	<0.0001
September	0.3372	1.401	1.241	1.582	<0.0001
October	0.4056	1.5	1.329	1.693	<0.0001
November	0.4338	1.543	1.37	1.739	<0.0001
December	0.5241	1.689	1.501	1.9	<0.0001
Male sex	−0.1846	0.831	0.792	0.873	<0.0001
Monthly income					
Dependent		1			
<NT$19 100	−0.0273	0.973	0.907	1.043	0.4434
NT$19 100–NT$41 999	0.0185	1.019	0.96	1.081	0.5424
≥NT$42 000	0.4048	1.499	1.379	1.629	<0.0001
Urbanization level*					
1 (urban)		1			
2	−0.0463	0.955	0.908	1.004	0.0727
3	−0.1108	0.895	0.785	1.021	0.0987
4 (rural)	−0.3167	0.729	0.537	0.989	0.0421
Hospital level					
1 (medical center)		1			
2	−0.0137	0.986	0.927	1.05	0.6653
3	−0.2982	0.742	0.697	0.791	<0.0001
4 (local medical clinic)	−2.3233	0.098	0.09	0.107	<0.0001
Prescription by diabetes specialists	−0.2009	0.818	0.753	0.889	<0.0001
Outpatient visits to metabolism and endocrinology professionals in past year					
0–5		1			
6–10	0.2981	1.347	1.239	1.465	<0.0001
11–15	0.6545	1.924	1.646	2.249	<0.0001
>15	0.5329	1.704	1.25	2.323	0.0008
Charlson Comorbidity Index score					
1		1			
2	0.0161	1.016	0.943	1.095	0.6721
3	0.0489	1.05	0.968	1.14	0.2414
≥4	0.0875	1.091	0.993	1.199	0.0682
aDCSI score†	0.0228	1.023	1.001	1.045	0.0366
Duration of diabetes mellitus, in months	0.00286	1.003	1.002	1.004	<0.0001
Antihypertensive drug use					
α-Blocker	0.0463	1.047	0.872	1.258	0.6209
ACEI or ARB	0.2283	1.257	1.175	1.343	<0.0001
β-Blocker	−0.0698	0.933	0.863	1.008	0.0783
Calcium-channel blocker	−0.2355	0.79	0.738	0.846	<0.0001
Diuretic	−0.0168	0.983	0.893	1.083	0.7327
Other	−0.2341	0.791	0.595	1.053	0.1084

Continued on following page

Appendix Table 1–Continued

Parameter	Estimate	Odds Ratio	95% CI		
			Lower	Upper	*P* Value
Other concomitant medications					
Antiplatelet agent‡	0.0177	1.018	0.94	1.102	0.6618
Warfarin	0.1119	1.118	0.809	1.546	0.4984
Steroid	−0.1866	0.83	0.746	0.923	0.0006
Nitrate	−0.0691	0.933	0.798	1.091	0.3862
NSAID	−0.2168	0.805	0.756	0.858	<0.0001
PPI	0.0571	1.059	0.9	1.245	0.4893
Statin	0.2374	1.268	1.176	1.367	<0.0001
SSRI	−0.0746	0.928	0.738	1.167	0.5224
Comorbidities					
Coronary artery disease	0.0547	1.056	0.995	1.121	0.0738
Cerebrovascular disease	−0.1248	0.883	0.821	0.948	0.0007
Myocardial infarction	−0.1071	0.898	0.791	1.021	0.0995
Hypertension	0.1171	1.124	1.062	1.191	<0.0001
Heart failure	−0.2321	0.793	0.72	0.873	<0.0001
Peripheral vascular disease	−0.0301	0.97	0.866	1.087	0.6038
Peptic ulcer disease	−0.0639	0.938	0.885	0.994	0.0312
Chronic kidney disease	−0.092	0.912	0.841	0.989	0.0267
Liver disease	−0.0189	0.981	0.93	1.035	0.4904
Atrial fibrillation	0.1053	1.111	0.954	1.294	0.1758
Dyslipidemia	0.277	1.319	1.25	1.392	<0.0001
Valvular heart disease	0.0718	1.074	0.988	1.169	0.0952
Cancer	0.0121	1.012	0.935	1.096	0.7652
Autoimmune disease	0.1122	1.119	1.001	1.251	0.0486

ACEI = angiotensin-converting enzyme inhibitor; aDCSI = adapted Diabetes Complications Severity Index; ARB = angiotensin II–receptor blocker; NSAID = nonsteroidal anti-inflammatory drug; NT$ = new Taiwan dollars; PPI = proton-pump inhibitor; SSRI = selective serotonin reuptake inhibitor.
* Strata are from Taiwan National Health Research Institute publications.
† 13-point scale with 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic. Each category was assigned a score of 0 (no abnormality), 1 (some abnormality), or 2 (severe abnormality).
‡ Aspirin, clopidogrel, ticlopidine, or cilostazol.

Appendix Table 2. Descriptive Statistics for Add-on Therapy During Follow-up

Variable	DPP-4 Inhibitor User	Sulfonylurea User
Continued using add-on at end of study, *n (%)**	5444 (53.7)	23 139 (38.4)
Mean duration (SD), *d*	980.7 (349.5)	1140.0 (398.2)
Median duration (IQR), *d*	923 (710–1224)	1184 (839–1451)
Switched from one of these add-ons to no add-on, *n (%)*	2675 (26.4)	24 126 (40.1)
Mean duration (SD), *d*	391.7 (279.2)	423.4 (296.8)
Median duration (IQR), *d*	328 (174–531)	359.5 (180–591)
Switched from one of these add-ons to another add-on, *n (%)*	1254 (12.4)	10 062 (16.7)
Mean duration (SD), *d*	296.8 (274.3)	277.4 (289.2)
Median duration (IQR), *d*	217 (84–427)	182 (42–416)
Switched from DPP-4 inhibitor to sulfonylurea or vice versa, *n (%)*	758 (7.5)	2882 (4.8)
Mean duration (SD), *d*	271.1 (262.3)	363.7 (328.9)
Median duration (IQR), *d*	189 (64–413)	277 (84–553)
Added add-on to DPP-4 inhibitor or sulfonylurea, *n (%)**	1488 (14.7)	11 520 (19.1)
Mean duration (SD), *d*	305.8 (289.9)	293.0 (318.9)
Median duration (IQR), *d*	216.5 (84–440.5)	175 (44–444)

DPP-4 = dipeptidyl peptidase-4; IQR = interquartile range.
* These 2 groups overlap.

Appendix Table 3. Incidence and Risks (Before Propensity Score Matching) for All-Cause Death, Myocardial Infarction, Ischemic Stroke, Hospitalization for Heart Failure, and Hypoglycemia Among Metformin Users With Diabetes Mellitus Receiving Add-on DPP-4 Inhibitors or Sulfonylureas

Outcome	DPP-4 Inhibitor			Sulfonylurea (Reference)			Crude		Adjusted for Propensity Score	
	Events, *n*	Person-Years	Incidence Rate per 1000 Person-Years	Events, *n*	Person-Years	Incidence Rate per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
All-cause death	365	20 314	17.67	1763	123 124	14.32	0.68 (0.61–0.76)	<0.001	0.64 (0.57–0.71)	<0.001
MACE*	211	20 086	10.50	1835	121 242	15.14	0.63 (0.54–0.74)	<0.001	0.69 (0.58–0.81)	<0.001
Myocardial infarction	69	20 253	3.41	504	122 613	4.11	0.78 (0.59–1.03)	0.079	0.87 (0.65–1.16)	0.338
Ischemic stroke	146	20 146	7.25	1381	121 722	11.35	0.58 (0.48–0.70)	<0.001	0.62 (0.51–0.75)	<0.001
Hospitalization for heart failure	100	20 226	4.94	557	122 470	4.55	0.86 (0.67–1.09)	0.205	0.81 (0.63–1.05)	0.112
Hypoglycemia	89	20 202	4.41	1135	121 951	9.31	0.38 (0.31–0.48)	<0.001	0.44 (0.35–0.55)	<0.001

DPP-4 = dipeptidyl peptidase-4; MACE = major adverse cardiovascular event.
* Myocardial infarction or ischemic stroke.

Appendix Table 4. Subgroup Analysis of Risk for All-Cause Death Among Metformin Users With Diabetes Mellitus Receiving Add-on Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Characteristic	Hazard Ratio (95% CI)*	*P* Value	Interaction *P* Value
Sex			
Male	0.61 (0.51–0.73)	<0.001	0.700
Female	0.65 (0.53–0.80)	<0.001	
Age			
20–40 y	0.77 (0.42–1.42)	0.396	0.796
41–60 y	0.64 (0.52–0.79)	<0.001	
61–80 y	0.57 (0.46–0.71)	<0.001	
≥81 y	0.61 (0.43–0.87)	0.007	
Charlson Comorbidity Index score			
1	0.62 (0.41–0.94)	0.023	0.318
2	0.81 (0.56–1.18)	0.272	
3	0.72 (0.51–1.03)	0.070	
≥4	0.57 (0.48–0.68)	<0.001	
Hypertension			
Yes	0.60 (0.52–0.70)	<0.001	0.208
No	0.72 (0.54–0.95)	0.023	
Chronic kidney disease			
Yes	0.58 (0.40–0.85)	0.005	0.842
No	0.58 (0.40–0.85)	0.005	
Heart failure			
Yes	0.55 (0.40–0.78)	<0.001	0.561
No	0.65 (0.56–0.75)	<0.001	
Myocardial infarction			
Yes	0.75 (0.45–1.23)	0.250	0.761
No	0.62 (0.54–0.72)	<0.001	
Cerebrovascular disease			
Yes	0.67 (0.53–0.85)	0.001	0.501
No	0.61 (0.51–0.72)	<0.001	

* Adjusted for propensity score.

Appendix Table 5. Subgroup Analysis of Risk for Myocardial Infarction Among Metformin Users With Diabetes Mellitus Receiving Add-on Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Characteristic	Hazard Ratio (95% CI)*	*P* Value	Interaction *P* Value
Sex			
Male	0.72 (0.47–1.10)	0.125	0.690
Female	0.81 (0.41–1.59)	0.538	
Age			
20–40 y	0.81 (0.05–13.02)	0.8825	0.504
41–60 y	1.09 (0.64–1.85)	0.764	
61–80 y	0.47 (0.26–0.83)	0.010	
≥81 y	0.70 (0.25–2.00)	0.509	
Charlson Comorbidity Index score			
1	2.25 (0.60–8.47)	0.232	0.308
2	0.63 (0.26–1.49)	0.291	
3	1.16 (0.52–2.62)	0.717	
≥4	0.56 (0.33–0.90)	0.018	
Hypertension			
Yes	0.69 (0.46–1.02)	0.062	0.614
No	1.01 (0.44–2.32)	0.976	
Chronic kidney disease			
Yes	1.44 (0.48–4.29)	0.515	0.261
No	0.68 (0.46–0.99)	0.045	
Heart failure			
Yes	0.34 (0.13–0.88)	0.026	0.168
No	0.86 (0.58–1.28)	0.460	
Myocardial infarction			
Yes	0.94 (0.47–1.90)	0.866	0.744
No	0.72 (0.48–1.09)	0.119	
Cerebrovascular disease			
Yes	0.77 (0.42–1.41)	0.393	0.384
No	0.73 (0.47–1.13)	0.158	

* Adjusted for propensity score.

Appendix Table 6. Subgroup Analysis of Risk for Ischemic Stroke Among Metformin Users With Diabetes Mellitus Receiving Add-on Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Characteristic	Hazard Ratio (95% CI)*	*P* Value	Interaction *P* Value
Sex			
Male	0.66 (0.49–0.91)	0.010	0.917
Female	0.60 (0.42–0.86)	0.006	
Age			
20–40 y	0.60 (0.37–0.96)	0.032	0.590
41–60 y	0.67 (0.49–0.90)	0.009	
61–80 y	0.49 (0.24–1.00)	0.049	
≥81 y	0.63 (0.50–0.80)	<0.001	
Charlson Comorbidity Index score			
1	1.00 (0.43–2.33)	0.992	0.433
2	0.54 (0.29–0.99)	0.048	
3	0.35 (0.17–0.71)	0.004	
≥4	0.70 (0.52–0.94)	0.018	
Hypertension			
Yes	0.67 (0.52–0.86)	0.002	0.362
No	0.39 (0.18–0.85)	0.018	
Chronic kidney disease			
Yes	0.63 (0.50–0.80)	<0.001	0.184
No	0.62 (0.48–0.81)	<0.001	
Heart failure			
Yes	0.53 (0.30–0.96)	0.037	0.743
No	0.66 (0.51–0.86)	0.002	
Myocardial infarction			
Yes	0.26 (0.10–0.68)	0.006	0.092
No	0.69 (0.54–0.89)	0.003	
Cerebrovascular disease			
Yes	0.62 (0.45–0.85)	0.003	0.467
No	0.67 (0.47–0.95)	0.027	

* Adjusted for propensity score.

Appendix Table 7. Subgroup Analysis of Risk for Hospitalization for Heart Failure Among Metformin Users With Diabetes Mellitus Receiving Add-on Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Characteristic	Hazard Ratio (95% CI)*	*P* Value	Interaction *P* Value
Sex			
Male	0.79 (0.53–1.19)	0.257	0.962
Female	0.75 (0.47–1.21)	0.244	
Age			
20–40 y	0.40 (0.04–4.40)	0.453	0.545
41–60 y	1.07 (0.59–1.95)	0.827	
61–80 y	0.78 (0.52–1.16)	0.218	
≥81 y	0.33 (0.13–0.87)	0.026	
Charlson Comorbidity Index score			
1	0.64 (0.14–2.85)	0.555	0.245
2	0.33 (0.06–1.70)	0.186	
3	0.84 (0.41–1.72)	0.633	
≥4	0.80 (0.56–1.15)	0.221	
Hypertension			
Yes	0.75 (0.54–1.03)	0.078	0.824
No	1.01 (0.34–2.99)	0.991	
Chronic kidney disease			
Yes	0.84 (0.43–1.67)	0.621	0.642
No	0.75 (0.53–1.06)	0.102	
Heart failure			
Yes	1.00 (0.65–1.51)	0.983	0.254
No	0.60 (0.38–0.95)	0.031	
Myocardial infarction			
Yes	1.09 (0.54–2.20)	0.815	0.511
No	0.74 (0.52–1.04)	0.083	
Cerebrovascular disease			
Yes	0.79 (0.49–1.30)	0.358	0.842
No	0.76 (0.51–1.13)	0.180	

* Adjusted for propensity score.

Appendix Table 8. Risk for Cancer Among Metformin Users With Diabetes Mellitus Receiving Add-on Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Variable	Adjusted for Propensity Score	
	Hazard Ratio (95% CI)	*P* Value
Before propensity score matching (time-varying)	0.91 (0.77–1.07)	0.245
After propensity score matching (time-varying)	0.88 (0.72–1.08)	0.242