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Cardiovascular outcomes of vildagliptin in patients with type 2 diabetes mellitus after acute coronary syndrome or acute ischemic stroke

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Keywords
Cardiovascular outcome, Type 2 diabetes mellitus, Vildagliptin

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ABSTRACT

Aims/Introduction: The cardiovascular (CV) outcomes of vildagliptin – a dipeptidyl peptidase-4 inhibitor – in patients with type 2 diabetes mellitus after acute coronary syndrome or acute ischemic stroke are unclear.

Materials and Methods: We analyzed data from the Taiwan National Health Insurance Research Database on 3,750 type 2 diabetes mellitus patients with acute coronary syndrome or acute ischemic stroke within 3 months between 1 August 2011 and 31 December 2013. Clinical outcomes were evaluated by comparing 1,250 participants receiving vildagliptin with 2,500 propensity score-matched participants. The primary composite outcome included CV death, non-fatal myocardial infarction and non-fatal stroke.

Results: The primary composite outcome occurred in 122 patients (9.8%) in the vildagliptin group and 263 patients (10.5%) in the control group (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.72–1.11) with a mean follow-up period of 9.9 months. No significant between-group differences were observed for CV death (HR 0.93, 95% CI 0.56–1.52), non-fatal myocardial infarction (HR 0.79, 95% CI 0.46–1.36) and non-fatal stroke (HR 0.96, 95% CI 0.74–1.24). The vildagliptin group was at similar risks of hospitalization for heart failure (HF) or coronary intervention to the control group (P = 0.312 and 0.430, respectively). For patients with HF at baseline, the risk of hospitalization for HF was similar between the vildagliptin and control groups (HR 1.04, 95% CI 0.57–1.88).

Conclusions: Among patients with type 2 diabetes mellitus after a recent acute coronary syndrome or acute ischemic stroke, treatment with vildagliptin was not associated with increased risks of CV death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for HF.

INTRODUCTION

Type 2 diabetes mellitus is associated with a marked increase in the risk of cardiovascular (CV) complications[1], with twofold excess risks of coronary heart disease, ischemic stroke and mortality compared with people without diabetes[2,3]. Among patients with type 2 diabetes mellitus, those with both diabetes and prior myocardial infarction (MI) or ischemic stroke are at particularly high risk of further CV events[4,5]. Ideally, any antidiabetes treatment should lower the risks of adverse events related to CV diseases, or at least not increase it. Based on this concern, in 2008, the US Food and Drug Administration (FDA) issued guidelines of specific requirements for CV safety assessment before and after approval of new antidiabetic agents[6].

Dipeptidyl peptidase-4 (DPP-4) inhibitors, including saxagliptin, alogliptin, sitagliptin, linagliptin and vildagliptin, are used to

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treat type 2 diabetes mellitus by blocking the degradation of endogenous glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide; such blockage leads to increased insulin secretion and suppression of glucagon secretion. Four previous CV outcome trials of DPP-4 inhibitors of saxagliptin (SAVOR-TIMI-53), alogliptin (EXAMINE), sitagliptin (TECOS) and linagliptin (CARMELINA) suggested no increased risks of CV death, MI or stroke with short-term use (median follow-up period of 1.5–3 years)[7–10]. Vildagliptin is the only one of these five kinds of DPP-4 inhibitors that lacks established or ongoing randomized controlled trials for CV outcomes and is not approved for use in the USA. Two large meta-analyses of pooled data from phase III and phase IV vildagliptin studies and a recent large European multidatabase observational cohort study suggested that vildagliptin was not associated with an increased risk of major adverse CV events in a broad spectrum of population[11–13]. However, these studies were not specifically designed to examine the effect of vildagliptin on patients with very high CV risks who suffered from a recent acute coronary syndrome (ACS) or acute ischemic stroke (AIS) within 3 months. In addition, many phase III and phase IV studies excluded patients who suffered from ACS or AIS 3–6 months before the enrollment. Furthermore, the limitation of meta-analysis might lead to mishandling in the analysis because of the diversity in study populations. For example, the famously harmful result from a large meta-analysis of the effect of rosiglitazone on MI is different from the results of two clinical trials that showed a neutral effect on MI[14–16]. Therefore, the FDA eliminated the prescribing and dispensing restrictions for rosiglitazone on 25 November 2013[17].

Given the unclear CV effect of vildagliptin on type 2 diabetes mellitus patients with a recent ACS or AIS, especially for Asian patients in the real world, we used data from Taiwan's National Health Insurance Research Database (NHIRD) to carry out a nationwide cohort study to evaluate the CV safety of vildagliptin in patients with type 2 diabetes mellitus after a recent ACS or AIS within 3 months.

METHODS

Data source

Taiwan's National Health Insurance program covers the medical needs of approximately 99% of its 23 million inhabitants. The NHIRD is managed by the National Health Research Institutes, and contains inpatient and outpatient data including date of birth, sex, diagnosis codes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes), drug prescriptions, surgical procedures, admission dates, hospitalizations, discharge dates and expenditure. The accuracy of disease diagnoses in NHIRD data has been validated[18–22]. The information and records of the patients analyzed in the present study were de-identified before analysis to protect their privacy and ensure patient anonymity. This study was approved by the institutional review board of Chang Gung Memorial Hospital.

Study cohort identification

We identified 1,802,707 patients with diagnoses of type 2 diabetes mellitus (ICD-9-CM code 250, excluding type 1 diabetes mellitus) between 1 August 2011 and 31 December 2013. Only patients with type 2 diabetes mellitus who were hospitalized for ACS (ICD-9-CM codes 410, 411.1 and 411.8) or AIS (ICD-9-CM codes 433–435) were included for analysis. After relevant exclusion, 28,220 patients with type 2 diabetes mellitus aged ≥40 years who had recent ACS or AIS within 3 months were eligible for inclusion in our study cohort (Figure 1). The index date was defined as the discharge date on which the patient was admitted for ACS or AIS. The follow-up period was based on the index hospitalization date to the date of death or 31 December 2013.

Vildagliptin exposure

Information on prescriptions for vildagliptin was extracted from NHIRD prescription data. Patients with type 2 diabetes mellitus after ACS or AIS were divided into a vildagliptin group and non-vildagliptin group (control group) according to the type of oral hypoglycemic agent received within 30 days of the index date. Patients who received incretin-based therapies (other DPP-4 inhibitors or glucagon-like peptide-1 receptor agonists) before the index date or within 30 days of the index date were excluded from the study to avoid interference (Figure 1). DPP-4 inhibitor exposure was defined in our previous work[23].

Ascertainment of type 2 diabetes mellitus and primary outcome

Diagnoses of type 2 diabetes mellitus were validated based on ICD-9-CM codes, where at least four outpatient visits corresponded to an accuracy of 95.7%[22]. Prescription of oral hypoglycemic agents corresponded to an accuracy of 99%. We identified patients with type 2 diabetes mellitus based on diagnosis code and oral hypoglycemic agents. The primary outcome was a composite end-point of CV death, non-fatal MI and non-fatal stroke. The diagnosis codes of ACS and AIS have been validated in previous NHIRD studies that have obtained high positive predictive values (≥95%)[19–21]. The definition of CV death met the criteria of the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials drafted by the FDA.

Covariates and secondary outcomes

Comorbidities at baseline were identified based on ICD-9-CM diagnosis codes within 1 year before the index date (Table S1). History of event (i.e., MI) was detected based on inpatient diagnosis codes before the index date, which could be tracked back to 1997. The baseline medication catchment period was defined as medications prescribed within 30 days of the index date. Other CV outcomes of interest included hospitalization for heart failure (HF), percutaneous coronary intervention and coronary artery bypass grafting. Patients with HF at baseline were re-matched to evaluate the risk of hospitalization for HF

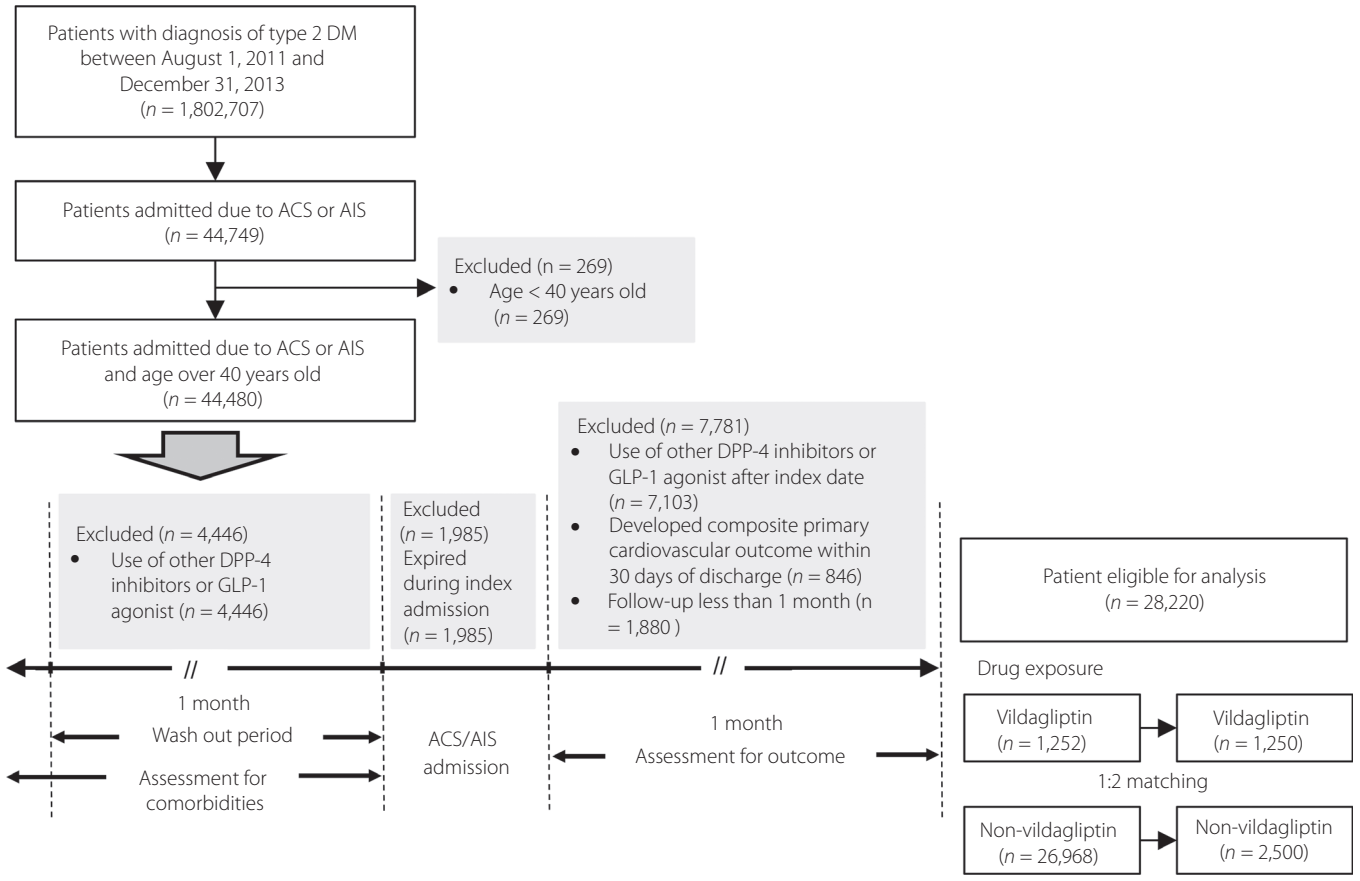


Figure 1 | Inclusion schema of the study patients. ACS, acute coronary syndrome; AIS, acute ischemic stroke; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

for further evaluation. The safety outcomes were acute pancreatitis, acute hepatitis, risk of hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, de novo dialysis and newly diagnosed malignancy. The inpatient diagnosis code of HF has high accuracy (positive predictive value 99%)[18]. Secondary outcomes were reported in our previous work[23].

Statistical analysis

To mitigate potential selection bias when comparing treatment effects in the vildagliptin and control groups, we matched each patient in the vildagliptin cohort with two patients in the control group by propensity score matching (PSM). The propensity score was the predicted probability of being in the vildagliptin group based on the covariate values in the logistic regression. The covariates were patient characteristics, baseline comorbidities, medications prescribed (listed in Table 1) and the index date. PSM was processed using a greedy nearest neighbor algorithm with a caliper of 0.2 times the standard deviation of the propensity score logit. Matching quality was analyzed using the absolute value of the standardized mean difference between the groups after matching, where a value <0.1 represented negligible difference between the groups.

We compared the risks of fatal outcomes (i.e., CV death, all-cause mortality and the primary composite outcome) between the groups by using Cox proportional hazards models. The risks of other time-to-event outcomes in the two groups were compared using a Fine and Gray subdistribution hazard model that considered death a competing risk. Matching pairs were stratified in both the Cox and the Fine and Gray models. The unadjusted cumulative event rate of the primary composite outcome was calculated and plotted. The cumulative incidence of hospitalization for HF was generated and plotted using a subdistribution cumulative incidence function. The study group (vildagliptin vs non-vildagliptin) was the only explanatory variable in the survival analyses.

A subgroup analysis was carried out to determine whether the hazard ratios (HRs) of composite CV outcomes for the vildagliptin and control groups were similar in the prespecified subgroups. A two-sided *P*-value <0.05 was considered statistically significant, and no adjustment for multiple testing (multiplicity) was made in the present study. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA), including the procedures of *psmatch* for PSM, *phreg*

Table 1 | Characteristics of the study patients before and after propensity score matching

Characteristics	Before matching		SMD	After matching		SMD†
	Vildagliptin (*n* = 1,252)	Non-vildagliptin (*n* = 26,968)		Vildagliptin (*n* = 1,250)	Non-vildagliptin (*n* = 2,500)	
Index admission etiology						
Acute coronary syndrome	366 (29.2)	7,644 (28.3)	0.02	365 (29.2)	777 (31.1)	−0.04
Acute ischemic stroke	886 (70.8)	19,324 (71.7)	−0.02	885 (70.8)	1,723 (68.9)	0.04
Age at index date, years (mean ± SD)	68.3 ± 10.7	70.0 ± 11.0	−0.15	68.3 ± 10.7	67.9 ± 10.6	0.04
Age group						
40–64 years	486 (38.8)	9,165 (34.0)	0.10	485 (38.8)	1,028 (41.1)	−0.05
65–74 years	407 (32.5)	8,039 (29.8)	0.06	407 (32.6)	777 (31.1)	0.03
75–84 years	293 (23.4)	7,675 (28.5)	−0.12	292 (23.4)	582 (23.3)	<0.01
≥85 years	66 (5.3)	2,089 (7.7)	−0.10	66 (5.3)	113 (4.5)	0.04
Sex						
Male	721 (57.6)	15,678 (58.1)	−0.01	719 (57.5)	1,446 (57.8)	−0.01
Female	531 (42.4)	11,290 (41.9)	0.01	531 (42.5)	1,054 (42.2)	0.01
Type 2 diabetes mellitus duration, years (mean ± SD)	11.8 ± 3.8	11.4 ± 3.8	0.11	11.8 ± 3.8	11.7 ± 3.8	0.02
Type 2 diabetes mellitus duration group						
0–5 years	92 (7.3)	2,430 (9.0)	−0.06	92 (7.4)	202 (8.1)	−0.03
6–10 years	237 (18.9)	5,152 (19.1)	−0.01	237 (19.0)	454 (18.2)	0.02
11–15 years	709 (56.6)	16,113 (59.7)	−0.06	709 (56.7)	1,424 (57.0)	−0.01
≥16 years	214 (17.1)	3,273 (12.1)	0.14	212 (17.0)	420 (16.8)	0.01
Total no. HbA1c examinations in the previous year (mean ± SD)	2.8 ± 2.0	2.5 ± 2.1	0.10	2.8 ± 2.0	2.7 ± 3.1	0.02
History of event						
Previous ischemic stroke	291 (23.2)	7,159 (26.5)	−0.08	290 (23.2)	552 (22.1)	0.03
Old myocardial infarction	93 (7.4)	2,251 (8.3)	−0.03	93 (7.4)	193 (7.7)	−0.01
Heart failure	139 (11.1)	3,777 (14.0)	−0.09	138 (11.0)	303 (12.1)	−0.03
VTE: PE or DVT	12 (1.0)	358 (1.3)	−0.03	12 (1.0)	23 (0.9)	0.01
Comorbidity						
CKD						
None	863 (68.9)	18,568 (68.9)	<0.01	861 (68.9)	1,728 (69.1)	<0.01
Non-dialysis CKD	336 (26.8)	6,788 (25.2)	0.04	336 (26.9)	659 (26.4)	0.01
Dialysis	53 (4.2)	1,612 (6.0)	−0.08	53 (4.2)	113 (4.5)	−0.01
Ischemic heart disease	566 (45.2)	12,204 (45.3)	<0.01	564 (45.1)	1,174 (47.0)	−0.04
Gout	84 (6.7)	2,391 (8.9)	−0.08	84 (6.7)	181 (7.2)	−0.02
Atrial fibrillation	92 (7.3)	2,382 (8.8)	−0.06	91 (7.3)	197 (7.9)	−0.02
Peripheral arterial disease	86 (6.9)	1,612 (6.0)	0.04	85 (6.8)	165 (6.6)	0.01
Hypertension	990 (79.1)	21,872 (81.1)	−0.05	989 (79.1)	1,947 (77.9)	0.03
Dyslipidemia	558 (44.6)	10,851 (40.2)	0.09	558 (44.6)	1,129 (45.2)	−0.01
Chronic obstructive pulmonary disease	99 (7.9)	2,419 (9.0)	−0.04	99 (7.9)	200 (8.0)	<0.01
Malignancy	79 (6.3)	1,887 (7.0)	−0.03	78 (6.2)	152 (6.1)	<0.01
Cirrhosis	14 (1.1)	547 (2.0)	−0.07	14 (1.1)	34 (1.4)	−0.03
HBV infection	25 (2.0)	518 (1.9)	0.01	25 (2.0)	49 (2.0)	<0.01

Table 1 (*Continued*)

Characteristics	Before matching		SMD	After matching		SMD†
	Vildagliptin (*n* = 1,252)	Non-vildagliptin (*n* = 26,968)		Vildagliptin (*n* = 1,250)	Non-vildagliptin (*n* = 2,500)	
HCV infection	19 (1.5)	567 (2.1)	−0.05	19 (1.5)	30 (1.2)	0.03
Alcoholism	13 (1.0)	282 (1.0)	<0.01	13 (1.0)	28 (1.1)	−0.01
Autoimmune disease	25 (2.0)	419 (1.6)	0.03	25 (2.0)	62 (2.5)	−0.03
Previous coronary intervention	167 (13.3)	3,532 (13.1)		166 (13.3)	347 (13.9)	
Non-DM medication						
Aspirin	1,066 (85.1)	22,708 (84.2)	0.02	1,064 (85.1)	2,130 (85.2)	<0.01
Clopidogrel	504 (40.3)	10,335 (38.3)	0.04	502 (40.2)	1,031 (41.2)	−0.02
Warfarin	59 (4.7)	1,741 (6.5)	−0.08	59 (4.7)	109 (4.4)	0.01
NOAC	11 (0.9)	185 (0.7)	0.02	11 (0.9)	18 (0.7)	0.02
ACEI/ARB	840 (67.1)	17,007 (63.1)	0.08	838 (67.0)	1,665 (66.6)	0.01
β-Blocker	542 (43.3)	11,495 (42.6)	0.01	540 (43.2)	1,093 (43.7)	−0.01
CCB	599 (47.8)	14,270 (52.9)	−0.10	599 (47.9)	1,204 (48.2)	−0.01
Digoxin	64 (5.1)	1,575 (5.8)	−0.03	64 (5.1)	135 (5.4)	−0.01
Statin	653 (52.2)	12,316 (45.7)	0.13	652 (52.2)	1,311 (52.4)	<0.01
NSAIDs/Cox-2 Inhibitors	325 (26.0)	6,868 (25.5)	0.01	324 (25.9)	656 (26.2)	−0.01
Diuretics	235 (18.8)	5,621 (20.8)	−0.05	235 (18.8)	468 (18.7)	<0.01
Spironolactone	93 (7.4)	2,141 (7.9)	−0.02	92 (7.4)	182 (7.3)	<0.01
Fibrate	138 (11.0)	2,009 (7.4)	0.12	137 (11.0)	291 (11.6)	−0.02
Hypoglycemic drugs						
Biguanides	618 (49.4)	13,015 (48.3)	0.02	617 (49.4)	1,226 (49.0)	0.01
SU	674 (53.8)	11,199 (41.5)	0.25	672 (53.8)	1,331 (53.2)	0.01
Thiazolidinediones	102 (8.1)	1,363 (5.1)	0.12	101 (8.1)	210 (8.4)	−0.01
Alpha glucosidase inhibitors	218 (17.4)	3,333 (12.4)	0.14	217 (17.4)	438 (17.5)	<0.01
Non-SU insulin secretagogues (glinide)	189 (15.1)	3,694 (13.7)	0.04	187 (15.0)	386 (15.4)	−0.01
Insulin	637 (50.9)	12,288 (45.6)	0.11	635 (50.8)	1,268 (50.7)	<0.01

Data are presented as frequency and percentage or mean ± standard deviation. †An absolute value of standardized mean difference (SMD) of ≤0.1 indicates a negligible difference between the two groups. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; CKD, chronic kidney disease; DVT, deep vein thrombosis; HBV, hepatitis B virus; HCV, hepatitis C virus; NOAC, novel oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SD, standard deviation; SU, sulfonylurea.

for survival analyses and the macro of *%cif* for the cumulative incidence function.

RESULTS

Patient characteristics

In total, 28,220 patients with type 2 diabetes mellitus who were admitted for ACS or AIS between 1 August 2011 and 31 December 2013 were eligible for the present study. Of those, 1,252 (4.4%) were prescribed vildagliptin. After application of PSM, 1,250 patients (33.3%) were in the vildagliptin group and 2,500 matched patients (66.7%) were in the control group (Figure 2). The mean follow-up period was 9.9 months (standard deviation 6.2 months), and the maximum follow-up duration was 2.4 years. The mean age of the patients at baseline was 68 years (standard deviation 10.7 years). After PSM, the absolute standardized mean difference values were <0.1, which indicated negligible differences in demographics, comorbidities and medications at baseline between the two groups (right panel of Table 1).

Cardiovascular outcomes

A primary composite outcome, namely CV death, non-fatal MI and non-fatal stroke, occurred in 122 patients (9.8%) in the vildagliptin group and 263 patients (10.5%) in the control group (HR 0.90, 95% confidence interval [CI] 0.72–1.11; Table 2; Figure 2). Regarding the individual composite outcome, vildagliptin users had risks of CV death (HR 0.93, 95% CI 0.56–1.52), non-fatal MI (HR 0.79, 95% CI 0.46–1.36) and non-fatal stroke (HR 0.96, 95% CI 0.74–1.24) similar to those in the control group (Table 2). Regarding secondary outcomes, no significant differences were observed in the risks of hospitalization for HF (HR 0.81, 95% CI 0.53–1.22; Figure 3), percutaneous coronary intervention (HR 1.16, 95% CI 0.89–1.50), coronary artery bypass grafting (HR 0.71, 95% CI 0.36–1.42) or all-cause mortality (HR 0.82, 95% CI 0.59–1.13) between the vildagliptin and control groups (Table 2).

Safety outcomes

The vildagliptin and control groups did not differ significantly in terms of incidence of acute hepatitis (0 vs 0.4%; P = not applicable), acute pancreatitis (0.2 vs 0.3%; $P = 0.840$), hypoglycemia (3.9 vs 3.4%; $P = 0.437$), diabetic ketoacidosis/hyperosmolar hyperglycemic state (1.7 vs 1.0%; $P = 0.057$), de novo dialysis (2.2 vs 2.8%; $P = 0.322$) or newly diagnosed malignancy (3.4 vs 2.4%; $P = 0.061$; Table 2).

Subgroup analysis

The subgroup analysis showed that vildagliptin had a similar effect on the primary composite outcome in the ACS and AIS cohorts (Figure 4). The effect of vildagliptin did not differ significantly in the subgroups of sex, age, type 2 diabetes mellitus duration, prior stroke, prior MI, HF, dialysis, ischemic heart disease, atrial fibrillation, hypertension, dyslipidemia, cirrhosis and percutaneous coronary intervention (Figure 4).

Outcomes of patients with HF at baseline

Of the 28,220 patients with type 2 diabetes mellitus who had recent ACS or AIS, 3,916 (13.9%) had a history of HF at baseline; of these, 139 were in the vildagliptin group and 3,777 were in the non-vildagliptin group (Table 1). We matched each patient with HF at baseline in the vildagliptin group with two patients with HF in the control group. After PSM, 133 patients with HF were in the vildagliptin group, and 266 matched participants were in the control group (Table 3). All clinical

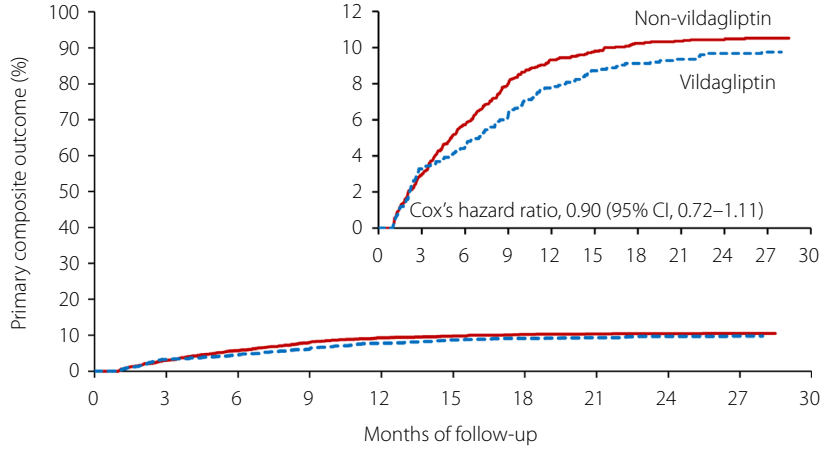


Figure 2 | Unadjusted event rates of the primary composite outcome, including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in the vildagliptin and non-vildagliptin groups. CI, confidence interval.

Table 2 | Clinical outcomes of the study cohorts after propensity score matching

Outcome	No. events (%)		Vildagliptin vs non-vildagliptin	*P*
	Vildagliptin (*n* = 1,250)	Non-vildagliptin (*n* = 2,500)	HR (95% CI)‡	
Primary composite outcome†	122 (9.8)	263 (10.5)	0.90 (0.72–1.11)	0.325
Components of primary outcome				
Non-fatal myocardial infarction	18 (1.4)	46 (1.8)	0.79 (0.46–1.36)	0.394
Non-fatal stroke	85 (6.8)	178 (7.1)	0.96 (0.74–1.24)	0.763
CV death	23 (1.8)	48 (1.9)	0.93 (0.56–1.52)	0.758
Other CV outcomes				
Myocardial infarction	19 (1.5)	55 (2.2)	0.70 (0.41–1.17)	0.172
Stroke	87 (7.0)	182 (7.3)	0.96 (0.75–1.24)	0.765
Hemorrhagic stroke	7 (0.6)	14 (0.6)	1.01 (0.41–2.51)	0.978
Ischemic stroke	81 (6.5)	172 (6.9)	0.95 (0.73–1.23)	0.692
All-cause mortality	52 (4.2)	123 (4.9)	0.82 (0.59–1.13)	0.215
Hospitalization for heart failure	31 (2.5)	77 (3.1)	0.81 (0.53–1.22)	0.312
Coronary intervention	98 (7.8)	179 (7.2)	1.10 (0.86–1.41)	0.430
Percutaneous coronary intervention	88 (7.0)	154 (6.2)	1.16 (0.89, 1.50)	0.281
Coronary artery bypass graft	11 (0.9)	31 (1.2)	0.71 (0.36–1.42)	0.333
Safety outcomes				
Hypoglycemia	49 (3.9)	86 (3.4)	1.15 (0.81–1.63)	0.437
DKA or HHS	21 (1.7)	24 (1.0)	1.77 (0.98–3.18)	0.057
Acute pancreatitis	3 (0.2)	7 (0.3)	0.87 (0.23–3.36)	0.840
De novo dialysis	28 (2.2)	71 (2.8)	0.80 (0.52–1.24)	0.322
Acute hepatitis	0 (0.0)	10 (0.4)	NA	–
New diagnosis malignancy	43 (3.4)	59 (2.4)	1.45 (0.98–2.15)	0.061
Bone fracture	28 (2.2)	53 (2.1)	1.07 (0.68–1.69)	0.768

†Any one of cardiovascular (CV) death, non-fatal myocardial infarction and non-fatal stroke. ‡Except for CV death, all-cause mortality and primary composite outcome, other time to event outcomes were estimated using Fine and Gray's subdistribution hazard model, which considered all-cause mortality as a competing risk. CI, confidence interval; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; HR, hazard ratio; MACE, major adverse cardiovascular event; NA, not applicable.

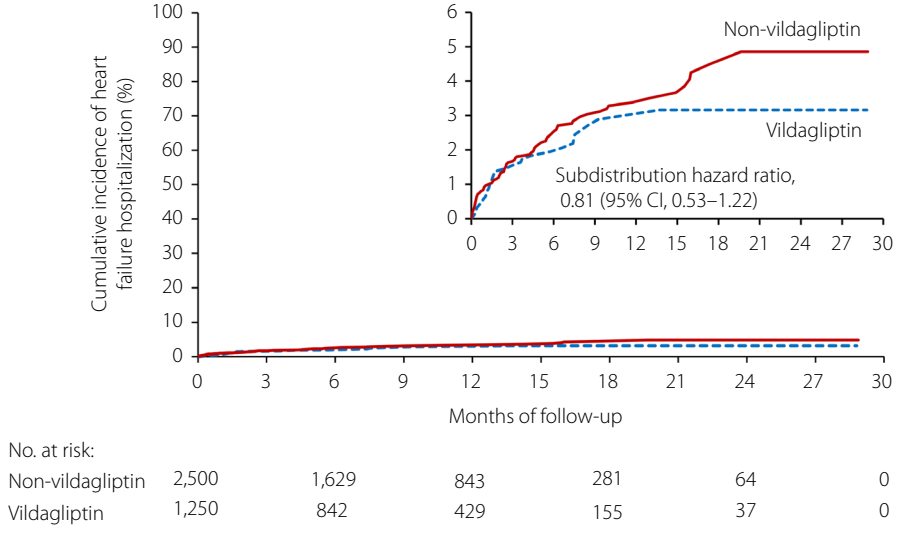
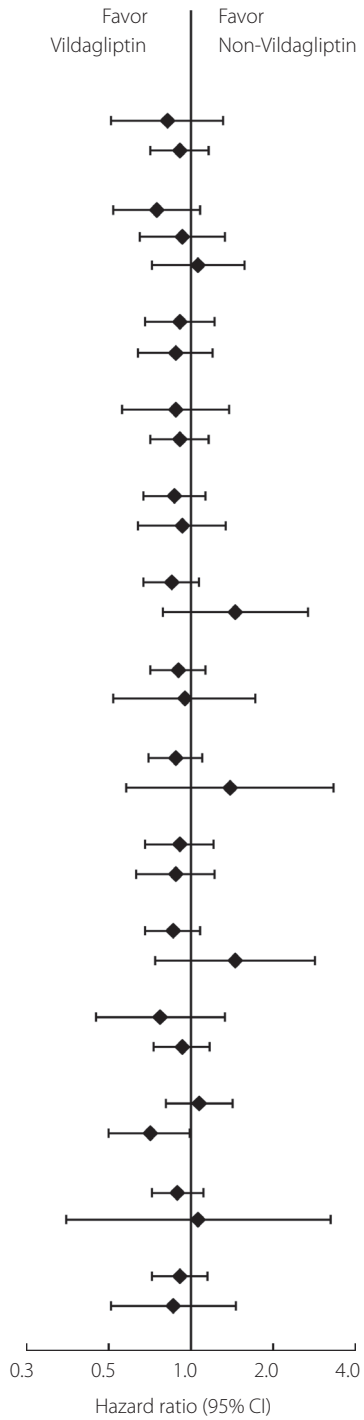


Figure 3 | Cumulative incidence of hospitalizations for heart failure in the vildagliptin and non-vildagliptin groups in the whole cohort. CI, confidence interval.



	Event (%)		Vildagliptin vs. Non-vildagliptin HR (95% CI)	*P* value for interaction
	Vildagliptin	Non-Vildagliptin		
Index admission etiology				0.708
Acute coronary syndrome	24 (6.6)	63 (8.1)	0.82 (0.51, 1.31)	
Acute ischemic stroke	98 (11.1)	200 (11.6)	0.91 (0.71, 1.16)	
Age				0.438
< 65 years	39 (8.0)	108 (10.5)	0.75 (0.52, 1.08)	
65-74 years	44 (10.8)	87 (11.2)	0.93 (0.65, 1.33)	
≥ 75 years	39 (10.9)	68 (9.8)	1.06 (0.72, 1.57)	
Gender				0.860
Male	65 (9.0)	142 (9.8)	0.91 (0.68, 1.22)	
Female	57 (10.7)	121 (11.5)	0.88 (0.64, 1.20)	
T2DM duration				0.905
< 10 years	28 (8.5)	60 (9.2)	0.88 (0.56, 1.38)	
≥ 10 years	94 (10.2)	203 (11.0)	0.91 (0.71, 1.16)	
Previous ischemic stroke				0.772
No	79 (8.2)	183 (9.4)	0.87 (0.67, 1.13)	
Yes	43 (14.8)	80 (14.5)	0.93 (0.64, 1.34)	
Old myocardial infarction				0.107
No	105 (9.1)	237 (10.3)	0.85 (0.67, 1.07)	
Yes	17 (18.3)	26 (13.5)	1.45 (0.79, 2.68)	
Heart failure				0.880
No	107 (9.6)	225 (10.2)	0.90 (0.71, 1.13)	
Yes	15 (10.9)	38 (12.5)	0.95 (0.52, 1.72)	
Dialysis				0.314
No	114 (9.5)	249 (10.4)	0.88 (0.70, 1.10)	
Yes	8 (15.1)	14 (12.4)	1.39 (0.58, 3.32)	
Ischemic heart disease				0.880
No	71 (10.3)	144 (10.9)	0.91 (0.68, 1.21)	
Yes	51 (9.0)	119 (10.1)	0.88 (0.63, 1.22)	
Atrial fibrillation				0.143
No	108 (9.3)	241 (10.5)	0.86 (0.68, 1.08)	
Yes	14 (15.4)	22 (11.2)	1.45 (0.74, 2.84)	
Hypertension				0.543
No	18 (6.9)	44 (8.0)	0.77 (0.45, 1.33)	
Yes	104 (10.5)	219 (11.2)	0.93 (0.73, 1.17)	
Dyslipidemia				0.063
No	77 (11.1)	137 (10.0)	1.07 (0.81, 1.42)	
Yes	45 (8.1)	126 (11.2)	0.71 (0.50, 0.99)	
Cirrhosis				0.767
No	117 (9.8)	255 (10.6)	0.89 (0.72, 1.11)	
Yes	5 (9.6)	8 (8.6)	1.06 (0.35, 3.24)	
Previous coronary				0.870
No	102 (9.4)	218 (10.1)	0.91 (0.72, 1.15)	
Yes	20 (12.0)	45 (13.0)	0.86 (0.51, 1.46)	

Figure 4 | Subgroup analysis of the primary composite outcome. CI, confidence interval; HR, hazard ratio; T2DM, type 2 diabetes mellitus.

characteristics were well balanced between the groups, except that patients aged ≥85 years, those with ischemic heart disease and those with dyslipidemia were slightly higher in the vildagliptin group (standardized mean difference 0.10, 0.11 and 0.10, respectively; Table 3). For patients with HF at baseline, no significant differences were observed between the vildagliptin and control groups in terms of the risk of primary composite outcome (11.3 vs 13.5%, HR 0.83, 95% CI 0.45–1.51) or hospitalization for HF (12.0 vs 12.0%, HR 1.04, 95% CI 0.57–1.88; Table 4; Figure 5).

Table 3 | Characteristics of the study patients who had a history of heart failure at baseline before and after propensity score matching

Characteristics	Before matching		SMD†	After matching		SMD†
	Vildagliptin (n = 139)	Non-vildagliptin (n = 3,777)		Vildagliptin (n = 133)	Non-vildagliptin (n = 266)	
Index admission etiology						
Acute coronary syndrome	63 (45.3)	1,688 (44.7)	0.01	62 (46.6)	124 (46.6)	0.00
Acute ischemic stroke	76 (54.7)	2,089 (55.3)	–0.01	71 (53.4)	142 (53.4)	0.00
Age at index date, years (mean ± SD)	71.6 ± 10.6	73.0 ± 10.9	–0.13	71.7 ± 10.7	71.7 ± 10.2	–0.01
Age group						
40–64 years	36 (25.9)	940 (24.9)	0.02	36 (27.1)	63 (23.7)	0.08
65–74 years	47 (33.8)	1,042 (27.6)	0.13	42 (31.6)	90 (33.8)	–0.05
75–84 years	42 (30.2)	1,298 (34.4)	–0.09	41 (30.8)	93 (35.0)	–0.09
≥85 years	14 (10.1)	497 (13.2)	–0.10	14 (10.5)	20 (7.5)	0.10
Sex						
Male	73 (52.5)	1,967 (52.1)	0.01	69 (51.9)	134 (50.4)	0.03
Female	66 (47.5)	1,810 (47.9)	–0.01	64 (48.1)	132 (49.6)	–0.03
Type 2 diabetes mellitus duration, years (mean ± SD)	12.6 ± 3.0	12.6 ± 3.0	0.02	12.7 ± 3.0	12.5 ± 3.4	0.06
Type 2 diabetes mellitus duration group						
0–5 years	3 (2.2)	121 (3.2)	–0.06	3 (2.3)	10 (3.8)	–0.09
6–10 years	21 (15.1)	491 (13.0)	0.06	19 (14.3)	41 (15.4)	–0.03
11–15 years	86 (61.9)	2,559 (67.8)	–0.12	82 (61.7)	162 (60.9)	0.02
≥16 years	29 (20.9)	606 (16.0)	0.13	29 (21.8)	53 (19.9)	0.05
HbA1c examination in the previous year (mean ± SD)	2.8 ± 2.3	2.4 ± 2.0	0.16	2.8 ± 2.3	2.6 ± 2.2	0.09
History of event						
Previous ischemic stroke	35 (25.2)	1,359 (36.0)	–0.24	34 (25.6)	77 (28.9)	–0.07
Old myocardial infarction	33 (23.7)	1,004 (26.6)	–0.07	31 (23.3)	58 (21.8)	0.04
VTE: PE or DVT	1 (0.7)	121 (3.2)	–0.18	1 (0.8)	2 (0.8)	0.00
Comorbidity						
CKD						
None	51 (36.7)	1,719 (45.5)	–0.18	48 (36.1)	102 (38.3)	–0.05
Non-dialysis CKD	58 (41.7)	1,340 (35.5)	0.13	56 (42.1)	104 (39.1)	0.06
Dialysis	30 (21.6)	718 (19.0)	0.06	29 (21.8)	60 (22.6)	–0.02
Ischemic heart disease	107 (77.0)	2,753 (72.9)	0.09	105 (78.9)	197 (74.1)	0.11
Gout	15 (10.8)	419 (11.1)	–0.01	15 (11.3)	25 (9.4)	0.06
Atrial fibrillation	29 (20.9)	777 (20.6)	0.01	26 (19.5)	50 (18.8)	0.02
Peripheral arterial disease	25 (18.0)	414 (11.0)	0.20	22 (16.5)	47 (17.7)	–0.03
Hypertension	121 (87.1)	3,322 (88.0)	–0.03	119 (89.5)	234 (88.0)	0.05
Dyslipidemia	61 (43.9)	1,594 (42.2)	0.03	59 (44.4)	105 (39.5)	0.10
Chronic obstructive pulmonary disease	22 (15.8)	626 (16.6)	–0.02	21 (15.8)	42 (15.8)	0.00
Malignancy	9 (6.5)	295 (7.8)	–0.05	8 (6.0)	13 (4.9)	0.05
Cirrhosis	1 (0.7)	97 (2.6)	–0.15	1 (0.8)	3 (1.1)	–0.03
HBV	3 (2.2)	46 (1.2)	0.08	3 (2.3)	8 (3.0)	–0.04
HCV	4 (2.9)	74 (2.0)	0.06	3 (2.3)	8 (3.0)	–0.04

Table 3 (*Continued*)

Characteristics	Before matching		SMD†	After matching		SMD†
	Vildagliptin (*n* = 139)	Non-vildagliptin (*n* = 3,777)		Vildagliptin (*n* = 133)	Non-vildagliptin (*n* = 266)	
Alcoholism	2 (1.4)	17 (0.5)	0.09	1 (0.8)	2 (0.8)	0.00
Autoimmune disease	7 (5.0)	71 (1.9)	0.17	6 (4.5)	13 (4.9)	–0.02
Previous coronary intervention	58 (41.7)	1,386 (36.7)	0.10	55 (41.4)	98 (36.8)	0.09
Non-DM medication						
Aspirin	110 (79.1)	3,011 (79.7)	–0.01	105 (78.9)	212 (79.7)	–0.02
Clopidogrel	84 (60.4)	2,035 (53.9)	0.13	81 (60.9)	153 (57.5)	0.07
Warfarin	11 (7.9)	448 (11.9)	–0.13	11 (8.3)	16 (6.0)	0.09
NOAC	3 (2.2)	51 (1.4)	0.06	2 (1.5)	5 (1.9)	–0.03
ACEI/ARB	92 (66.2)	2,420 (64.1)	0.04	88 (66.2)	172 (64.7)	0.03
β-Blocker	82 (59.0)	1,989 (52.7)	0.13	79 (59.4)	149 (56.0)	0.07
CCB	70 (50.4)	2,145 (56.8)	–0.13	69 (51.9)	132 (49.6)	0.05
Digoxin	22 (15.8)	603 (16.0)	–0.01	21 (15.8)	42 (15.8)	0.00
Statin	70 (50.4)	1,623 (43.0)	0.15	68 (51.1)	124 (46.6)	0.09
NSAIDs/Cox-2 inhibitors	34 (24.5)	897 (23.7)	0.02	32 (24.1)	63 (23.7)	0.01
Diuretics	60 (43.2)	1,679 (44.5)	–0.03	56 (42.1)	110 (41.4)	0.01
Spironolactone	25 (18.0)	694 (18.4)	–0.01	25 (18.8)	40 (15.0)	0.10
Fibrate	10 (7.2)	233 (6.2)	0.04	9 (6.8)	23 (8.6)	–0.07
Hypoglycemic drugs						
Biguanides	42 (30.2)	1,071 (28.4)	0.04	39 (29.3)	82 (30.8)	–0.03
SU	65 (46.8)	1,204 (31.9)	0.31	59 (44.4)	124 (46.6)	–0.04
Thiazolidinediones	8 (5.8)	118 (3.1)	0.13	6 (4.5)	14 (5.3)	–0.04
Alpha glucosidase inhibitors	29 (20.9)	456 (12.1)	0.24	26 (19.5)	56 (21.1)	–0.04
Non-SU insulin secretagogues (glinide)	41 (29.5)	797 (21.1)	0.19	40 (30.1)	79 (29.7)	0.01
Insulin	78 (56.1)	2,231 (59.1)	–0.06	75 (56.4)	147 (55.3)	0.02

Data are presented as the frequency and percentage or mean ± standard deviation. †An absolute value of standardized mean difference (SMD) of ≤0.1 indicates a negligible difference between the two groups. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; CKD, chronic kidney disease; DVT, deep vein thrombosis; HBV, hepatitis B virus; HCV, hepatitis C virus; NOAC, novel oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SD, standard deviation; SU, sulfonylurea.

Table 4 | Clinical outcomes of the study cohorts among the patients who had a history of heart failure at baseline

Outcome	No. events (%)		Vildagliptin vs non-vildagliptin	*P*
	Vildagliptin (*n* = 133)	Non-vildagliptin (*n* = 266)	HR (95% CI)‡	
Primary composite outcome†	15 (11.3)	36 (13.5)	0.83 (0.45–1.51)	0.537
Components of primary outcome				
Non-fatal myocardial infarction	2 (1.5)	7 (2.6)	0.61 (0.13–2.94)	0.535
Non-fatal stroke	10 (7.5)	16 (6.0)	1.30 (0.59–2.86)	0.517
CV death	4 (3.0)	17 (6.4)	0.47 (0.16–1.39)	0.172
Other CV outcomes				
Hospitalization for heart failure	16 (12.0)	32 (12.0)	1.04 (0.57–1.88)	0.900
Myocardial infarction	2 (1.5)	10 (3.8)	0.42 (0.09–1.92)	0.262
Stroke	10 (7.5)	19 (7.1)	1.08 (0.51–2.32)	0.838
Hemorrhagic stroke	0 (0.0)	4 (1.5)	NA	NA
Ischemic stroke	10 (7.5)	16 (6.0)	1.28 (0.58–2.82)	0.539
All-cause mortality	8 (6.0)	28 (10.5)	0.57 (0.26–1.26)	0.166
Coronary intervention (PCI or CABG)	11 (8.3)	28 (10.5)	0.81 (0.40–1.62)	0.546
PCI	10 (7.5)	26 (9.8)	0.80 (0.39–1.65)	0.539
CABG	1 (0.8)	3 (1.1)	0.68 (0.07–6.42)	0.736

†Any one of cardiovascular (CV) death, non-fatal myocardial infarction and non-fatal stroke. ‡Except for CV death, all-cause mortality and primary composite outcome, other time to event outcomes were estimated using Fine and Gray's subdistribution hazard model, which considered all-cause mortality as a competing risk. CABG, coronary artery bypass graft; CI, confidence interval; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; HR, hazard ratio; MACE, major adverse cardiovascular event; NA, not applicable; PCI, percutaneous coronary intervention.

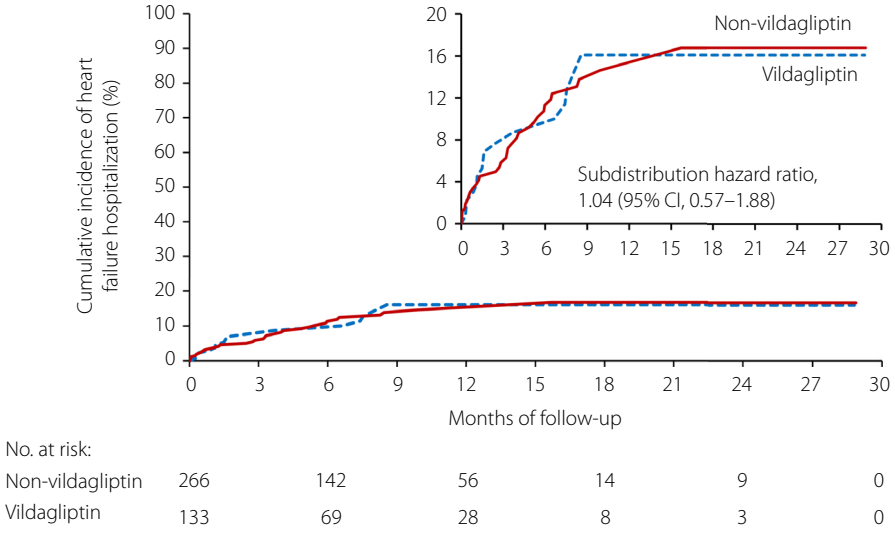


Figure 5 | Cumulative incidence of hospitalizations for heart failure in the vildagliptin and non-vildagliptin groups in patients with a history of heart failure. CI, confidence interval.

DISCUSSION

Although vildagliptin is available in >70 countries, including countries in the European Union, just four DPP-4 inhibitors (saxagliptin, alogliptin, sitagliptin and linagliptin) have been approved for type 2 diabetes mellitus treatment in the USA, because vildagliptin did not comply with the specific requirements for CV safety assessment issued by the FDA in December 2008[6,24]. In addition, post-marketing data regarding the safety of vildagliptin in patients with type 2 diabetes mellitus at very high CV risk who suffered from a recent ACS or AIS 3 months before the enrollment are limited. The present study was the first real-world cohort study based on a nationwide population to evaluate the CV outcomes of vildagliptin in type 2 diabetes mellitus patients after a recent ACS or AIS

within 3 months. The primary and secondary outcomes of the present study suggested that short-term use of vildagliptin in these patients with type 2 diabetes mellitus at very high CV risk were not associated with increased risks of CV death, non-fatal MI, non-fatal stroke, all-cause mortality or hospitalization for HF, and results were consistent in each subgroup analysis based on baseline characteristics. Therefore, the strength of our research is filling the gap in evidence for CV safety with respect to vildagliptin in these patients who tend to be vulnerable to the further major CV diseases over relatively short periods.

In terms of the primary composite outcome of CV death, non-fatal MI and non-fatal stroke, the results of the present study are consistent with four large-scale CV outcome trials of DPP-4 inhibitors (saxagliptin, alogliptin, sitagliptin and linagliptin), which exert neutral effects on CV death, MI and stroke[7–10]. Therefore, the present study showed consistency with previous meta-analysis results and similar 3-point major adverse CV events compared with other DPP-4 inhibitors, which means that no new CV safety signals were noted for CV death, MI or stroke with DPP-4 inhibitors.

Hospitalization for HF might not be a class effect of all DPP-4 inhibitors[25]. Increased risk of hospitalization for HF with two DPP-4 inhibitors (saxagliptin and alogliptin) was observed[7,26], and on 5 April 2016, the FDA recommended discontinuation of saxagliptin or alogliptin in patients with type 2 diabetes mellitus when any evidence of emerging HF is noticed[27]. By contrast, the present results showed that vildagliptin was not associated with an increased risk of HF compared with placebo treatment. Diabetes is a risk factor of HF that is independent of coronary artery disease and hypertension, and can cause cardiomyopathy[28]. According to the Framingham Heart Study, the risk of HF in patients with diabetes is 2.4-fold greater in men and fivefold greater in women than in the non-diabetic population[29–31]. For patients with type 2 diabetes mellitus, HF is highly prevalent, with more than one in five patients aged >65 years having HF[32,33]. Once patients with diabetes have HF, they tend to show lower survival than those without emerging HF; in one study, the corresponding mortality rates were 32.7 and 3.7% per year, respectively (HR 10.6)[32]. Therefore, HF risk evaluation should be considered when treating patients with diabetes, and especially when prescribing DPP-4 inhibitors.

The major predictors of hospitalization for HF are elevated in patients with brain natriuretic peptide, chronic kidney disease and especially those with a history of HF[34]. Vildagliptin has been reported to improve endothelium-dependent vasodilatation in type 2 diabetes mellitus patients[35]. Therefore, it is not clear whether the vasodilatation effect has benefit in type 2 diabetes mellitus patients with a previous history of HF. The recent small, randomized, placebo-controlled Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial evaluated vildagliptin use in 254 patients with type 2 diabetes mellitus and HF with reduced ejection fraction. That study showed that compared with placebo treatment, vildagliptin had no benefit, did not lead to increase HF-related hospitalization (13 vs 10 events, respectively; $P = 0.55$) and had a neutral effect on the left ventricular ejection fraction; however, vildagliptin could be associated with increasing left ventricular volumes of unknown cause[35]. Nevertheless, proportionally and statistically insignificant higher rates of death (8.6 vs 3.2%, respectively), CV death (5.5 vs 3.2%, respectively) and ACS (5.5 vs 2.4%, respectively) were observed in the vildagliptin group compared with the placebo group, but the overall number of these clinical events was low and the study in question was not powered to assess CV safety[25,35]. In fact, it should be noted that the VIVIDD study was not a conventional CV safety trial, but rather, focused on ventricular function, which could only be a surrogate end-point for HF. To investigate the clinical influence of vildagliptin on HF, we specifically reanalyzed our ACS or AIS study participants who had type 2 diabetes mellitus with HF at baseline ($n = 399$). Because type 2 diabetes mellitus patients with HF at baseline suffering from a recent ACI or AIS are uncommon clinically, the study number is small and is similar in the VIVIDD study ($n = 254$). For these patients with extremely high risk for CV, either observational cohort studies or randomized controlled trials are not always attainable to obtain a large number of patients because of the considerations of ethical issues, time and cost. The present results showed that vildagliptin was not associated with greater HF-related hospitalization (12 vs 12%) or major adverse clinical events (11.3 vs 13.5%) between the vildagliptin and control groups. Consequently, our findings could provide the clinical significance of CV safety of vildagliptin in patients with type 2 diabetes mellitus and established HF, which might complement the findings of the VIVIDD study. However, because of the small sample size, the present results could not be robust.

Patients with diabetes are at a twofold excess risk of ischemic stroke compared with those without diabetes[2]. DPP-4 inhibitors might have had neuroprotective effects in a mouse model of stroke through increased glucagon-like peptide-1 at the neuronal level of the brain[36]. In addition, the permeability of the blood–brain barrier could be increased by stroke-mediated damage; this might enhance the impact of DPP-4 inhibitors for neuroprotection, because these inhibitors do not cross the blood–brain barrier under normal conditions, and this restrains their effect on the central nervous system[37]. In a recent preclinical study, a neuroprotective effect of vildagliptin against cerebral ischemia in rats was observed[38]. In clinical trials, some data have suggested that linagliptin might have neuroprotective effects that could be associated with fewer stroke events when compared with glimepiride[39], although the results of the CARMELINA study showed a neutral effect on non-fatal stroke[10]. Therefore, the present study enrolled patients with type 2 diabetes mellitus with recent AIS as a portion of the study population to evaluate the potential anti-stroke efficacy of vildagliptin for patients with type 2 diabetes mellitus after AIS. The present results did not show a significant anti-stroke effect with vildagliptin treatment at the end of the follow-up period. Possible

explanations for this are described as follows. First, the results of animal experiments are not necessarily consistent with those of human studies. Second, the non-significant effect of vildagliptin on stroke in the present study is compatible with that in the CARMELINA study, because both studies are of DPP-4 inhibitors compared with other active comparators (using additional antihyperglycemic agents in the control group; not limited to using glimepiride) in order to diminish the difference in blood glucose. In contrast, in the aforementioned study carried out by Gallwitz *et al.*[39], the neuroprotective effect was noted in the specific condition when linagliptin was only compared with glimepiride.

Although the present study had the undeniable merit of identifying CV outcomes of vildagliptin in patients with type 2 diabetes mellitus after ACS or AIS, it also had some limitations. First, personal information of the study participants, such as smoking, lifestyle, family history of CV disease and laboratory parameters, including levels of glycated hemoglobin, lipid profile, blood pressure and body mass index, were not available in the registry data from NHIRD in Taiwan. Therefore, we included the total number of HbA1c examinations in the previous year, which could be a surrogate of the patient's medical compliance, duration of type 2 diabetes mellitus, the category of antihyperglycemic agents, diabetes-related complications to reduce the selection bias of type 2 diabetes mellitus severity at baseline, major comorbidities and medications for CV diseases with PSM to make our two study groups well-balanced when comparing treatment effects. Furthermore, because smoking is a potentially major confounding factor for CV outcomes, we used chronic obstructive pulmonary disease (COPD) as a proxy variable for smoking, because cigarette smoking is strongly associated with the prevalence of COPD and is a major factor in COPD[40]. Taiwan has a significant difference in smoking prevalence between men and women (40–50% in men and 3–4% in women)[41]. Therefore, by matching the COPD and sex variables between the two study groups, we mitigated the threat of this potential limitation[42]. Second, it remains unclear whether the findings of our present study are applicable to other ethnicities, because the study population is Taiwanese and unique. Third, due to our study design, risk factors for CV disease were only evaluated at baseline and not treated as time-dependent covariates. However, the dynamic change of these risk factors might not differ substantially in the vildagliptin and non-vildagliptin group. Despite this, we still suggest the further study should be recommended to take the consideration of time-varying risk factors. Finally, our present study had a mean of 9.9 months and maximum of 2.4 years of follow up, because vildagliptin has been available in Taiwan since 2012. In addition, according to the previous NHI regulations in Taiwan for data request, all data we have are to the date 31December 2013. A future study with a longer follow-up duration could yield more robust information to confirm the present findings. Despite these limitations, our real-world and nationwide population-based cohort study is still beneficial for answering uncertain questions without randomized controlled CV outcome trials of vildagliptin in patients with very high CV risks.

In summary, use of vildagliptin in patients with type 2 diabetes mellitus after a recent ACS or AIS within 3 months had similar effects on CV death, non-fatal MI and non-fatal stroke without increasing risks of hospitalization for HF, all-cause mortality, receipt of percutaneous coronary intervention and coronary artery bypass grafting. These findings could provide clinical physicians with real-world evidence supporting the use of vildagliptin as an antihyperglycemic agent for treatment of patients with type 2 diabetes mellitus and very high risk of further CV events.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | International Classification of Diseases, Ninth Revision, Clinical Modification codes used for diagnosis in the present study