Observational Study

Medicine®

OPEN

Cardiovascular risk of sitagliptin in ischemic stroke patients with type 2 diabetes and chronic kidney disease

A nationwide cohort study

Chung-Yu Liang, MD[a,b], Dong-Yi Chen, MD[c], Chun-Tai Mao, MD[a,b], I-Chang Hsieh, MD[c], Ming-Jui Hung, MD, PhD[a,b], Chao-Hung Wang, MD, PhD[a,b], Ming-Shien Wen, MD[c], Wen-Jin Cherng, MD[c], Tien-Hsing Chen, MD[a,b,*]

Abstract

Limited data are available about the cardiovascular (CV) safety and efficacy of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, in ischemic stroke patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). Ischemic stroke patients with T2DM and CKD were selected from the Taiwan National Health Insurance Research Database (NHIRD) from March 1, 2009 to December 31, 2011. A total of 1375 patients were divided into 2 age- and gender-matched groups: patients who received sitagliptin (n = 275; 20%) and those who did not (n = 1,100). Primary major adverse cardiac and cerebrovascular events (MACCE), including ischemic stroke, hemorrhagic stroke, myocardial infarction (MI), or CV death, were evaluated. During a mean 1.07-year follow-up period, 45 patients (16.4%) in the sitagliptin group and 165 patients (15.0%) in the comparison group developed MACCEs (Hazard ratio [HR] 1.05; 95% confidence interval [CI], 0.75–1.45). Compared to the non-sitagliptin group, the sitagliptin group had a similar risk of ischemic stroke (HR 0.82; 95% CI, 0.51–1.32.), hemorrhagic stroke (HR 1.50; 95% CI, 0.58–3.82), MI (HR 1.14; 95% CI, 0.49–2.65), and CV mortality (HR 1.06; 95% CI, 0.61–1.85). The use of sitagliptin in recent ischemic stroke patients with T2DM and CKD was not associated with increased or decreased risk of adverse CV events.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BBB = blood brain barrier, CKD = chronic kidney disease, CV = cardiovascular, DKA = diabetic ketoacidosis, DPP-4 = dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, GLP-1 = glucagon-like peptide 1, HHS = Hyperosmolar hyperglycemic state, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, MI = myocardial infarction, NA = not applicable, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PCI = percutaneous coronary intervention, PSM = propensity score method, T2DM = type 2 diabetes mellitus, TZD = thiazolidinedione.

Keywords: chronic kidney disease, dipeptidyl peptidase 4 (DPP-4) inhibitor, ischemic stroke, sitagliptin

1. Introduction

Patients diagnosed with type 2 diabetes mellitus (T2DM) have a higher risk of cardiovascular (CV) events with double of the risk of ischemic stroke compared to those without diabetes.[1] Acute stroke can also lead to abnormalities in glucose metabolism that can result in poor clinical outcomes.[2] Patients with acute ischemic stroke who have a history of DM are associated with a higher incidence of mortality than those who have yet to develop DM.[3] Nonetheless, strategies for blood sugar control during acute stroke vary. Hyperglycemia has been found to be associated with poor outcomes in large vessel infarction or cortical infarction,[4,5] but moderate hyperglycemia is also reported to be associated with favorable outcomes in patients with lacunar infarction.[6] Intensive glucose control in acute stroke has been suggested based on previous experience and implemented in the intensive-care unit (ICU),[7] but was found to be associated with severe hypoglycemia and event-related poorer outcomes.[8] Therefore, controversies still exist about the benefits of anti-hyperglycemic treatment for patients after acute ischemic stroke.

Sitagliptin is the first approved dipeptidyl peptidase-4 (DPP-4) inhibitor with antihyperglycemic effects provided by enhancing the availability of incretin hormones.[9] Results of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) Study suggested that sitagliptin did not increase the risk of major adverse CV events among patients with type 2 diabetes and established CV disease.[10] However, that study excluded patients with estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2 of body-surface area who may have experienced more CV events after acute ischemic stroke. Our previous

Editor: Elena Cecilia Rosca.

Chung-Yu Liang and Dong-Yi Chen: These authors contributed equally to this study.

The authors report no relationships that could be construed as a conflict of interest.

[a] Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung, [b] Chang Gung University College of Medicine, Taoyuan, [c] Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou, Taiwan.

[*] Correspondence: Tien-Hsing Chen, No. 222, Maijin Road, Keelung City 204, Taiwan (e-mail: skyheart0826@gmail.com).

Medicine (2018) 97:52(e13844)

Received: 25 September 2018 / Received in final form: 31 October 2018 / Accepted: 5 December 2018

http://dx.doi.org/10.1097/MD.0000000000013844

study,[11] which comprised patients with chronic kidney disease (CKD) who were precluded from participating in TECOS, has also demonstrated that sitagliptin was associated with a neutral CV effect in T2DM with recent ischemic stroke, but those with end stage renal disease (ESRD) receiving renal replacement therapy were excluded. Therefore, only limited published data are available for evaluating the safety and efficacy of sitagliptin among acute ischemic stroke patients with T2DM and CKD (with or without renal replacement therapy). The CV risk associated with sitagliptin in the CKD patient group remains unclear in the real-world clinical setting. As a result, we conducted this population-based cohort study using data from the NHIRD of Taiwan to investigate the CV outcomes of sitagliptin in patients with ischemic stroke and CKD.

2. Methods

2.1. Data source

Data for this national cohort study were retrieved from the NHIRD, which consists of standard computerized claims data submitted by medical institutions that seek reimbursement through the NHI program. The NHI program offers comprehensive medical care for more than 23 million residents, representing more than 99% of the population of Taiwan. Previous studies have described the NHIRD in detail and the accuracy of its diagnostic data has been validated.[12–16] The information and records of the patients were de-identified prior to analysis to protect their privacy and ensure patient anonymity, therefore informed consent was waived. The study protocol was reviewed and approved by the Ethics Institutional Review Board of Chang Gung Memorial Hospital, and this work was supported by grants from the Chang Gung Memorial Hospital, Taiwan (CGRPG2F0011, CLRPG2C0024, and CLRPG2G0081).

2.2. Study group and cohort definition

A total of 5479 T2DM patients with CKD were identified who were admitted for acute ischemic stroke between March 1, 2009 and December 31, 2011. Ischemic stroke and CKD were identified using the International Classification of Diseases (the 9th Revision) Clinical Modification [ICD-9-CM] codes 433 to 435 and 585 registered by the clinician respectively. The accuracy of diagnosis for T2DM, acute ischemic stroke, and CKD have been validated in previous NHIRD studies.[12–16] A flowchart of the inclusion of the study cohort is shown in Figure 1. The patients were divided into two study groups, sitagliptin users (n = 311) and non-sitagliptin users (n = 4,206). Patients who received a prescription of sitagliptin for 90 consecutive days following index discharge were defined as the sitagliptin group, whereas patients who did not receive sitagliptin were considered the comparison cohort. The index hospitalization was defined as the index date when the patient was admitted for ischemic stroke. The follow-up period was defined as from the index date to the date of event occurrence,

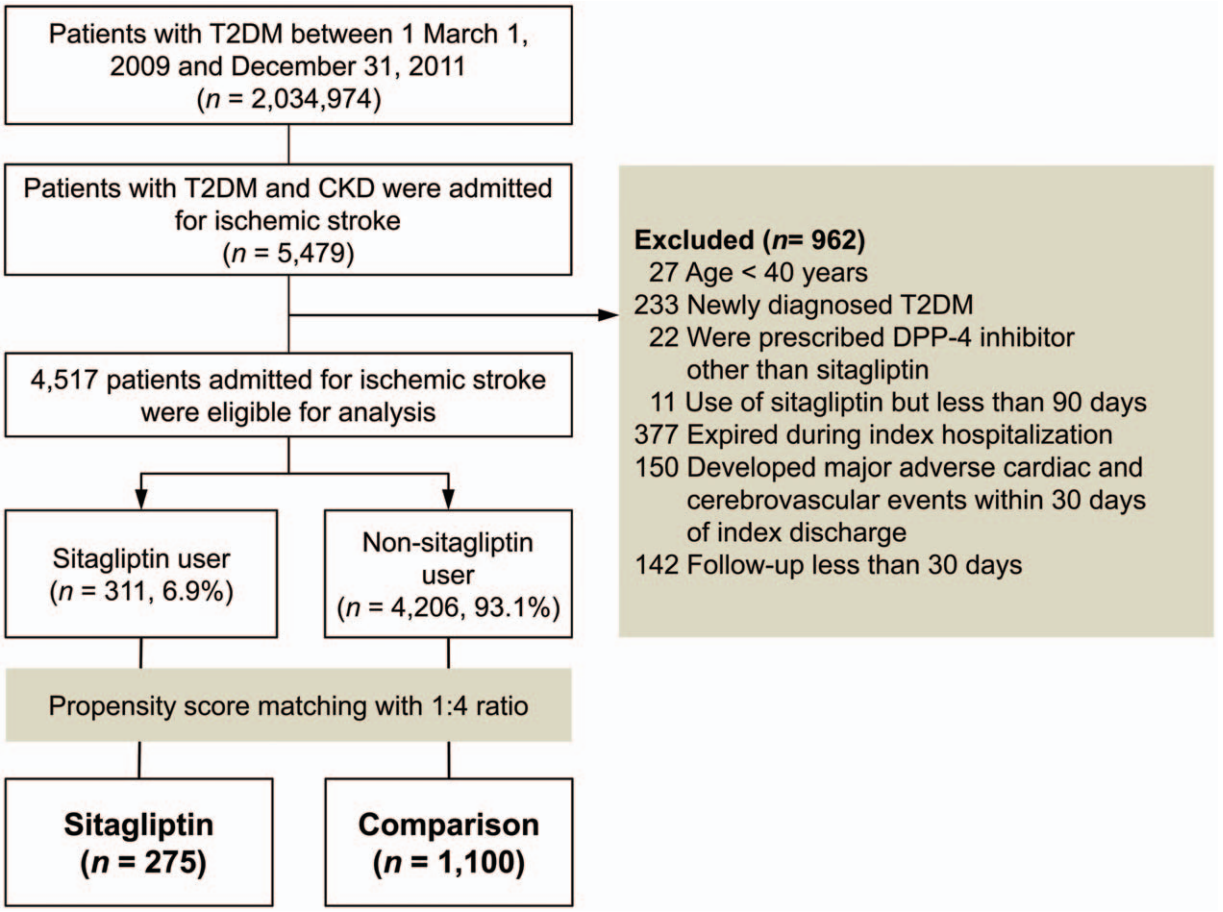


Figure 1. Inclusion and exclusion of the study patients.

death or until the end of the study period (December 31, 2011), whichever occurred first.

2.3. Exclusion criteria

Patients were excluded if they met any of the following criteria:

1. age <40 years;
2. newly diagnosed T2DM, which was defined as T2DM diagnosed during index hospitalization, which was done to ensure consistency in disease severity and duration among diabetic patients;
3. use of sitagliptin but less than 90 days, which was done to avoid carry-over effect;
4. received DPP-4 inhibitors other than sitagliptin before or after index hospitalization;
5. expired during index hospitalization or developed any composite major adverse cardiac and cerebrovascular event (MACCE) (defined as ischemic stroke, hemorrhagic stroke, myocardial infarction (MI) or CV death) within 30 days of discharge;
6. were followed for less than 30 days after the index hospitalization.

2.4. Study outcomes and covariate measurements

The baseline comorbidities were defined as least 2 outpatient claims or 1 hospitalization of ICD-9 diagnosis codes one year prior to the index date. A majority of these comorbidities based on ICD-9-CM codes have been validated previously.[15] Medications were defined as at least 2 outpatient prescriptions or 1 refilled prescription at pharmacies within 3 months after the index date. The primary outcome was defined as MACCEs. The study outcomes were required to be the same as the discharge diagnosis to avoid misclassification. CV death was defined according to the criteria of the Standardized Definitions for End Point Events in CV Trials published by the Food and Drug Administration (FDA).[17] Deaths were identified by the patients' withdrawal from NHI.[18] Other CV outcomes of interest were any stroke, death of any cause and admission due to heart failure. Diagnosis of heart failure was validated in a previous NHIRD study.[16] Indications for safety outcomes included acute pancreatitis, chronic pancreatitis, hypoglycemia, diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS).

2.5. Statistical analysis

To mitigate the treatment selection-bias, propensity score matching (PSM) was conducted in which 1 patient in the sitagliptin cohort was matched with 4 counterparts in the comparison cohort. The propensity score was the predicted probability of being treated with sitagliptin given the patient's covariates. Those covariates included patient's characteristics, baseline comorbidities, non-study medications, and the index date. The "greedy nearest neighbor" matching method was adopted and the caliper was set as 0.2 times standard deviation of the logit of the propensity score. The matching procedure was performed using the procedure of '*psmatch*' in SAS version 9.4 (SAS Institute, Cary, NC).

The clinical characteristics between the two study groups (sitagliptin and comparison groups) were compared by chi-square test for categorical variables and independent sample *t* test for continuous variables. Risk of time-to-event outcomes between the study groups was compared using the Cox proportional hazard model in which the study group was the only explanatory variable and the matching pairs were stratified. Unadjusted cumulative event rate of primary outcomes (recurrent ischemic stroke and MACCE) was calculated and plotted. Subgroup analysis was performed to determine whether the hazard ratio of primary outcomes for the sitagliptin and non-sitagliptin groups were similar in the pre-specified subgroups (age group, gender, atrial fibrillation, ESRD, and previous stroke). Statistical significance was set at 2-tailed $P < .05$ and no adjustment of multiple testing (multiplicity) was made in this study. All data analysis was conducted using IBM SPSS software version 22 (IBM SPSS Inc, Chicago, IL).

3. Results

3.1. Patients' characteristics

The data of a total of 275 sitagliptin-treated patients and 1100 non-sitagliptin treated patients admitted from March 1, 2009 through December 31, 2011, were eligible for data analysis. The mean age for the overall cohort was 69.2 years (standard deviation [SD] = 10.8 years). Approximately 40% of patients had previous strokes. The mean follow-up period was 1.07 years (SD = 0.73 years) and the maximal follow-up time was 2.83 years. After PSM, the two study groups were well balanced in all baseline characteristics, comorbidities, medications for T2DM and CV disease after discharge (Table 1).

Among all patients, 28.4% of the sitagliptin group and 26.6% of the non-sitagliptin group were ESRD patients receiving dialysis. Patients with atrial fibrillation accounted for 10.2% of patients in the sitagliptin group and 9.5% in the comparison group ($P = .749$). The CHADS2 score was 5.0 for the sitagliptin group and 5.0 for the comparison group, and CHA2DS2-VASc score was 6.8 for the sitagliptin group and 6.6 for the comparison group ($P = 0.797$ and 0.674). Prevalence of atrial fibrillation, CHA2DS2-VASc, and CHADS2 scores were also comparable between the two study groups.

3.2. CV outcomes

The primary outcome of MACCE occurred in 45 patients in the sitagliptin group (16.4%) and in 165 patients in the non-sitagliptin group (15.0%) (Hazard ratio [HR] 1.05; 95% confidence interval [CI] 0.75–1.45) at the last follow up. No significant differences in the MACCEs were detected between the 2 study groups at 3-month follow-up (HR 0.59; 95% CI 0.29–1.20), 1-year follow up (HR 0.92; 95% CI 0.63–1.35) and at the end of the study (Table 2). No significant differences were found in the individual composite endpoint of ischemic stroke (HR 0.82; 95% CI 0.51–1.32), hemorrhagic stroke (HR 1.50; 95% CI 0.58–3.82), MI (HR 1.14; 95% CI 0.49–2.65), or CV death (HR 1.06; 95% CI 0.61–1.85) between the sitagliptin and comparison groups (Table 3). Figure 2 illustrates the cumulative event rate of recurrent ischemic stroke and MACCE in both study groups during the follow-up period. It was observed that the group difference in the curves was trivial and the log-rank tests revealed non-significant difference between the groups ($P = .434$ for recurrent ischemic stroke and $P = .769$ for MACCE).

Regarding other secondary outcomes, no statistically significant differences were found in the risks of heart failure admission (HR 1.12; 95% CI 0.59–2.14), or death from any cause (HR 0.78; 95% CI 0.55–1.10) between the 2 study groups. In terms of safety outcomes, no significant differences were found between

Table 1

Baseline demographic and clinical characteristics of study patients after propensity score matching.

Characteristics	Sitagliptin (n=275)	Comparison (n=1100)	P
Age (years)	69.3±10.8	69.1±10.9	0.822
Age≧75 years	94 (34.2)	365 (33.2)	0.753
Gender			0.744
Male	153 (55.6)	624 (56.7)	
Female	122 (44.4)	476 (43.3)	
Previous MI	19 (6.9)	89 (8.1)	0.515
Previous stroke			
Any*	114 (41.5)	483 (43.9)	0.463
Ischemic	92 (33.5)	387 (35.2)	0.591
Hemorrhage	12 (4.4)	50 (4.5)	0.897
Unspecified	53 (19.3)	221 (20.1)	0.761
Comorbidity			
ESRD	78 (28.4)	293 (26.6)	0.564
Neuropathy	86 (31.3)	358 (32.5)	0.686
Retinopathy	38 (13.8)	156 (14.2)	0.877
Coronary artery disease	82 (29.8)	335 (30.5)	0.837
Chronic obstructive pulmonary disease	54 (19.6)	214 (19.5)	0.946
Atrial fibrillation	28 (10.2)	105 (9.5)	0.749
$CHADS_2$ score†	5.0±0.9	5.0±0.9	0.797
CHA_2DS_2-VASc‡	6.8±1.4	6.6±1.4	0.674
Peripheral arterial disease	53 (19.3)	213 (19.4)	0.973
Hypertension	258 (93.8)	1,031 (93.7)	0.956
Heart failure	71 (25.8)	272 (24.7)	0.708
Dyslipidemia	143 (52.0)	566 (51.5)	0.871
Malignancy	22 (8.0)	85 (7.7)	0.880
Cirrhosis	7 (2.5)	29 (2.6)	0.933
Previous PCI	13 (4.7)	51 (4.6)	0.949
Previous carotid stenting	2 (0.7)	7 (0.6)	0.867
T2DM medication			
Insulin	87 (31.6)	360 (32.7)	0.730
Metformin	44 (16.0)	188 (17.1)	0.666
TZD	19 (6.9)	89 (8.1)	0.515
Sulfonylurea	120 (43.6)	462 (42.0)	0.623
CV disease medication			
Aspirin	173 (62.9)	683 (62.1)	0.802
Clopidogrel	138 (50.2)	542 (49.3)	0.787
Warfarin	13 (4.7)	46 (4.2)	0.690
Beta-blockers	103 (37.5)	400 (36.4)	0.737
ACEI or ARB	165 (60.0)	676 (61.5)	0.658
Calcium-channel blockers	148 (53.8)	615 (55.9)	0.533
Diuretics	85 (30.9)	344 (31.3)	0.907
Statins	103 (37.5)	408 (37.1)	0.911
Fibrate	27 (9.8)	113 (10.3)	0.824

Values are mean±SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, COPD = chronic obstructive pulmonary disease, ESRD = end stage renal disease, PCI = percutaneous coronary intervention, T2DM = Type 2 diabetes mellitus, TZD = thiazolidinedione.

* A discrepancy may exist between the sum of a subgroup and the total as a result of a single patient having had two or more strokes.

† The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.

‡ The CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category (female)].

Table 3

Secondary outcomes at the end of follow up.

Outcome	Number of events (%)		Sitagliptin *vs* Comparison	
	Sitagliptin (n=275)	Comparison (n=1100)	HR (95% CI)	P
Other CV outcomes				
Any stroke	27 (9.8)	121 (11.0)	0.85 (0.56–1.29)	0.438
Ischemic stroke	21 (7.6)	97 (8.8)	0.82 (0.51–1.32)	0.423
Hemorrhage stroke	6 (2.2)	16 (1.5)	1.50 (0.58–3.82)	0.401
MI	7 (2.5)	24 (2.2)	1.14 (0.49–2.65)	0.757
Non-fatal ischemic stroke	20 (7.3)	91 (8.3)	0.84 (0.52–1.36)	0.472
Non-fatal MI	6 (2.2)	20 (1.8)	1.17 (0.47–2.91)	0.735
CV death	16 (5.8)	59 (5.4)	1.06 (0.61–1.85)	0.824
Death from any cause	38 (13.8)	191 (17.4)	0.78 (0.55–1.10)	0.157
Heart failure	12 (4.4)	42 (3.8)	1.12 (0.59–2.14)	0.721
Safety outcomes				
Any pancreatitis	0 (0.0)	3 (0.3)	NA	NA
Acute pancreatitis	0 (0.0)	2 (0.2)	NA	NA
Chronic pancreatitis	0 (0.0)	1 (0.1)	NA	NA
Hypoglycemia	8 (2.9)	43 (3.9)	0.72 (0.34–1.53)	0.394
DKA or HHS	1 (0.4)	19 (1.7)	0.20 (0.03–1.53)	0.122

CI = confidence interval, CV = cardiovascular, DKA = diabetic ketoacidosis, HHS = hyperosmolar hyperglycemic state, HR = hazard ratio, MI = myocardial infarction, NA = not applicable.

the 2 groups in the risks of hypoglycemia (2.9% and 3.9%; P=.394), DKA or HHS (0.4% and 1.7%; P=.122) (Table 3). In the subgroup analysis, no significant interactions (all P values >0.1) were found between the study groups by the pre-specified subgroups on recurrent ischemic stroke or MACCE (Fig. 3). It indicated that the observed neutral effect of sitagliptin was not significantly different across different levels of age group, gender, atrial fibrillation, ESRD and previous stroke.

4. Discussion

This population-based investigation evaluated the CV effects of sitagliptin with a specific focus on T2DM patients with recent ischemic stroke and CKD. Study results revealed that treatment with DPP-4 inhibitor sitagliptin resulted in similar rates of major cardiac and cerebrovascular events of ischemic stroke, hemorrhagic stroke, MI or CV death when compared with non-sitagliptin users in the cohort of T2DM patients with CKD and recent ischemic stroke. Secondary outcome analysis demonstrated no significant differences between the sitagliptin and comparison groups with regard to pancreatitis, hypoglycemia episodes, complications of hyperglycemia or all-cause mortality. Furthermore, the present study has shown that sitagliptin does not increase heart failure-related hospitalization events in patients with recent ischemic stroke and CKD who have higher CV risk and are susceptible to fluid overload.

Table 2

Primary MACCE* outcomes in various follow-up periods.

Outcome	Number of event (%)		Sitagliptin *vs* Comparison	
	Sitagliptin (n=275)	Comparison (n=1,100)	HR (95% CI)	P
3 month follow up	9 (3.3)	59 (5.4)	0.59 (0.29–1.20)	0.144
1 year follow up	33 (12.0)	137 (12.5)	0.92 (0.63–1.35)	0.666
At the end of follow up	45 (16.4)	165 (15.0)	1.05 (0.75–1.45)	0.791

CI = confidence interval, CV = cardiovascular HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction.

* Any one of ischemic stroke, hemorrhage stroke, myocardial infarction or CV death.

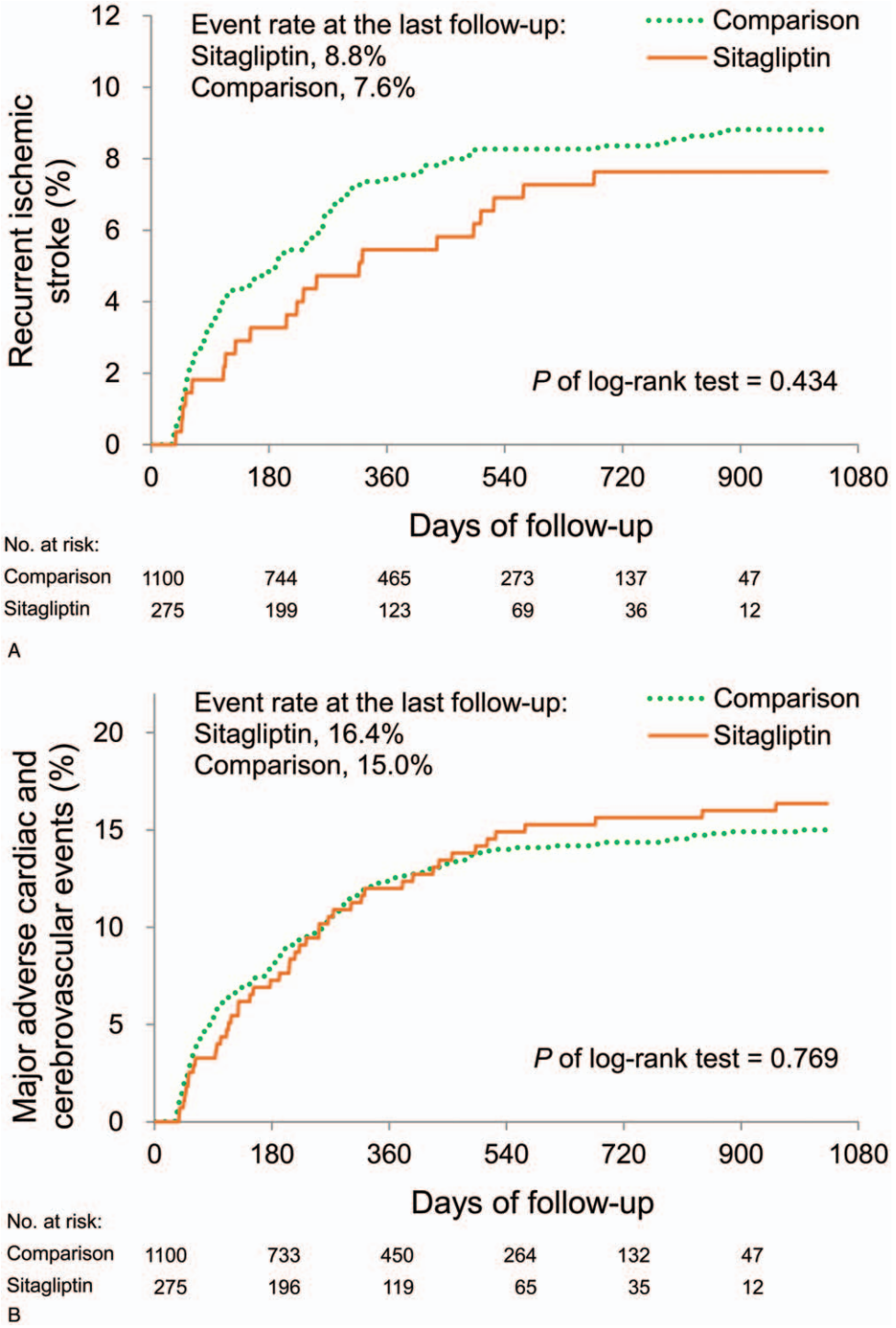
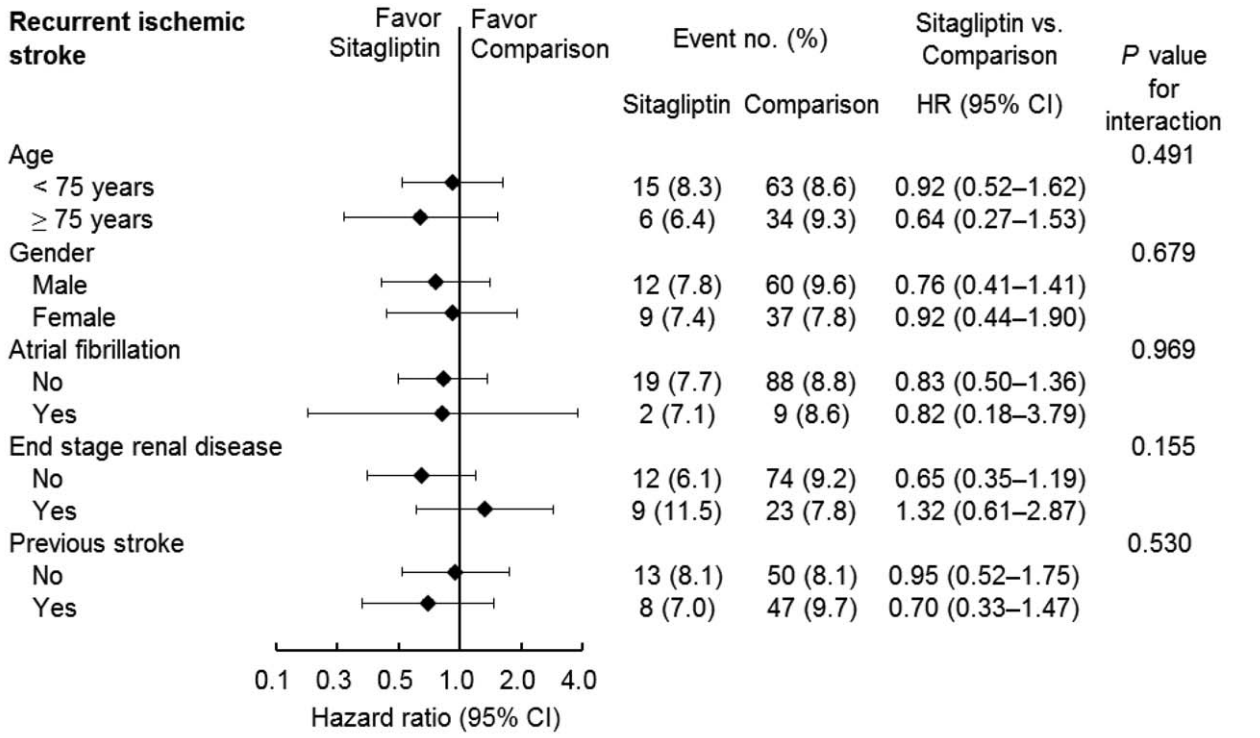


Figure 2. Unadjusted cumulative event rate of recurrent ischemic stroke (A) and MACCE (B) during the follow up. MACCE = major adverse cardiac and cerebrovascular events.

In the present study, the study population in which CV risk of sitagliptin was evaluated is different from that in the previous TECOS trial.[10] The TECOS trial enrolled patients with established CV diseases among which only 24.5% had prior cerebrovascular disease; however, all subjects included in the present study had experienced recent acute ischemic stroke. Furthermore, CKD patients were excluded in the TECOS trial. In contrast, all patients in the present study were CKD subjects among whom approximately one third had received renal replacement therapy. Sitagliptin has been licensed for use in CKD patients with or without dialysis. Patients with T2DM and CKD for whom sitagliptin was prescribed tend to be older and have more complications of DM and more comorbidities.[19] Thus, this high-risk group of patients is especially susceptible to safety and tolerability issues. Nonetheless, most of the current evidence reported in CV outcomes studies of DPP4-inhibitor was obtained



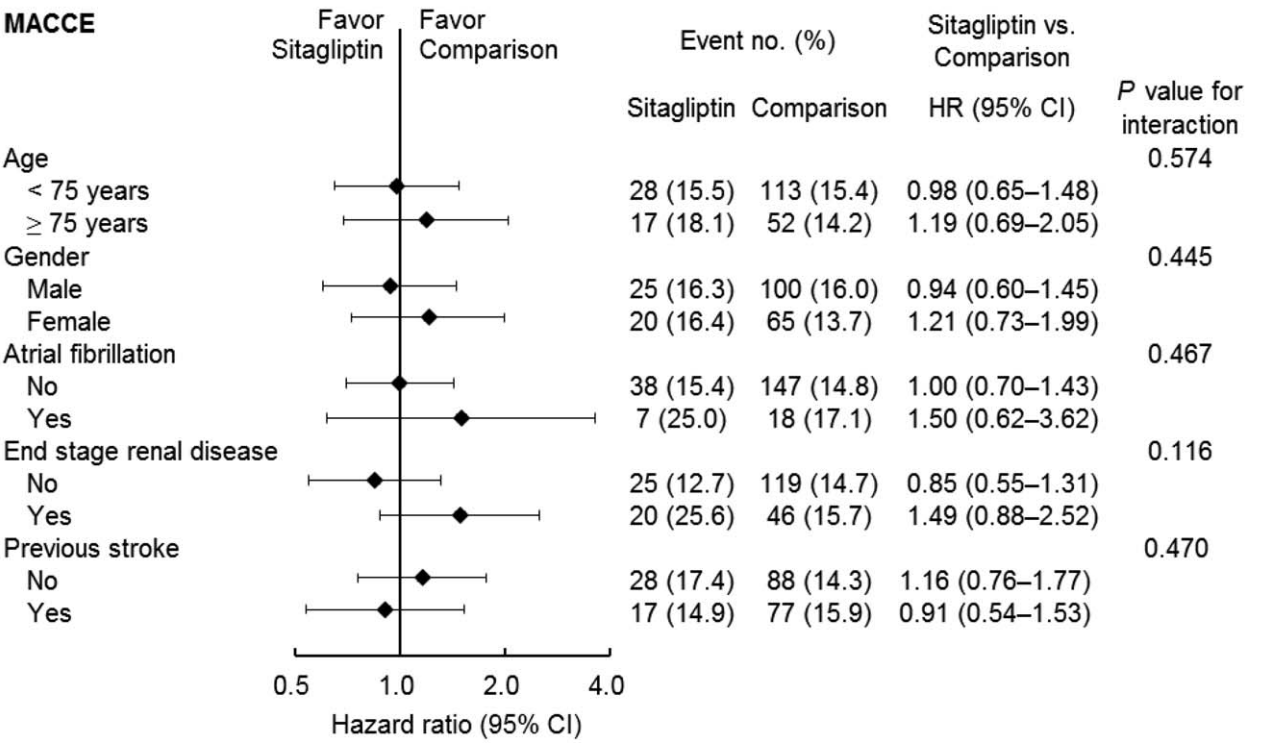


Figure 3. Pre-specified subgroup analysis of recurrent ischemic stroke (A) and MACCE (B). MACCE = major adverse cardiac and cerebrovascular events.

from major populations of non-CKD subjects (eGFR over 60 ml/min/1.73 m^2).[10,20,21] The present study examined only CKD subjects who had a recent episode of ischemic stroke hospitalization, placing the study cohort at a much higher risk than patients in other studies. With a mean follow-up period of 1.07 years, 14% of subjects in the present study developed a primary composite CV event. However, the study results demonstrated that use of sitagliptin is not associated with increased risk of CV events among these patients at high CV risk.

To date, there are only a limited number of studies on the effects of sitagliptin on acute ischemic stroke patients. An animal study has shown that sitagliptin attenuates transient cerebral

ischemia or reperfusion injury in diabetic rats.[22] Linagliptin, another form of DPP-4 inhibitor, was also found to be able to counteract stroke in diabetic mouse brain.[23] DPP-4 inhibitors do not have direct actions on the central nervous system because they cannot cross the blood brain barrier (BBB). Nonetheless, acute stroke-mediated BBB damage has been reported to increase permeability and it remains controversial whether this effect may exhibit the benefit of neuroprotection from sitagliptin. A previous study by our cardiology group in a majority of non-CKD patients addressed a neutral neuroprotective benefit of sitagliptin in acute ischemic stroke patients with type 2 DM.[11] Results of the present study demonstrated that sitagliptin is not associated with increased cerebrovascular risk, but it did not provide a neuroprotective benefit in acute ischemic stroke patients, regardless of whether patients were in the non-CKD or CKD population.

Interestingly, subgroup analysis in patients with ESRD and recent ischemic stroke suggested no significant differences in cardiac and cerebrovascular outcomes between sitagliptin users and a comparison group not receiving sitagliptin. However, in contrast, one previous study reported that DPP-4 inhibitors may improve ischemic stroke in patients with T2DM and ESRD.[24] The discrepancy between our results and those of that previous study may be related to differences in study populations and medications. In the previous study,[24] only about 40% of patients had a history of cerebrovascular disease, which is in contrast to the cohort in the present study in which all patients had recent ischemic stroke. Additionally, patients in the previous study took not only sitagliptin, but also other DPP-4 inhibitors, including vidaglipitin, sxagliptin, and linagliptin. The effect of reduced ischemic stroke in the previous study was derived primarily by the effect of saxagliptin rather than vildagliptin, sitagliptin or linagliptin. Therefore, in the subgroup analysis of the previous study, sitagliptin was not associated with fewer ischemic stroke events, which is also consistent with results of the present study.

4.1. Study limitations

Although the present study provides important information about sitagliptin use in fragile patients with recent ischemic stroke and CKD, several limitations must be noted. First, the severity of hypertension and diabetes are the major risk factors for recurrent stroke but the data about patients' blood pressure or blood glucose were not included in data from NHIRD. However, the use of anti-hypertensive and oral antidiabetic drugs was matched between the sitagliptin and comparison groups. Second, for the patients with CKD without dialysis, the stage of CKD could not be identified because patients' body weight and blood creatinine levels were not provided by NHIRD. Third, the NHIRD lacked laboratory information, including lipid profiles (eg, low-density lipoprotein, high-density lipoprotein, etc.), inflammatory factors such as high sensitivity C-reactive protein (hsCRP), and levels of N terminal pro B-type natriuretic peptide. Finally, our present study has a mean of 1.07 years and a maximum of 2.83 years of follow-up because of our available data of the NHIRD. A study with longer duration of follow-up in the future could give more robust information to confirm our finding.

5. Conclusions

Among T2DM patients with CKD after recent ischemic stroke, sitagliptin use was not associated with an increased risk of MI, CV death, ischemic stroke or hemorrhage stroke. Even in patients with ESRD, the use of sitagliptin did not increase composite cardiac-cerebrovascular events. Furthermore, use of sitaglipitin was not associated with increased risk of heart failure hospitalization even in patients with CKD who are more susceptible to fluid status. Therefore, sitaglipin use is safe in T2DM patients with recent ischemic stroke and CKD.

Acknowledgments

We thank Hsing-Fen Lin for statistical assistance.

Author contributions

Conceptualization: Chung-Yu Liang, Dong-Yi Chen, and Tien-Hsing Chen.
Methodology: Chung-Yu Liang, Dong-Yi Chen, Chun-Tai Mao, and Tien-Hsing Chen.
Supervision: I-Chang Hsieh, Ming-Jui Hung, Chao-Hung Wang, Ming-Shien Wen, Wen-Jin Cherng, and Tien-Hsing Chen.
Writing – original draft: Chung-Yu Liang and Dong-Yi Chen.
Writing – review & editing: Chun-Tai Mao.

References

[1] Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.
[2] Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426–32.
[3] Jia Q, Zhao X, Wang C, et al. Diabetes and poor outcomes within 6 months after acute ischemic stroke: the China National Stroke Registry. Stroke 2011;42:2758–62.
[4] Bruno A, Biller J, Adams HPJr, et al. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) investigators. Neurology 1999;52:280–4.
[5] Kruyt ND, Nys GM, van der Worp HB, et al. Hyperglycemia and cognitive outcome after ischemic stroke. J Neurol Sci 2008;270:141–7.
[6] Uyttenboogaart M, Koch MW, Stewart RE, et al. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. Brain 2007;130(Pt 6):1626–30.
[7] van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
[8] Kansagara D, Fu R, Freeman M, et al. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med 2011;154:268–82.
[9] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–705.
[10] Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42.
[11] Chen DY, Wang SH, Mao CT, et al. Sitagliptin After ischemic stroke in type 2 diabetic patients: a nationwide cohort study. Medicine (Baltimore) 2015;94:e1128.
[12] Lin CC, Lai MS, Syu CY, et al. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc 2005;104:157–63.
[13] Hsieh CY, Chen CH, Li CY, et al. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. J Formos Med Assoc 2015;114:254–9.
[14] Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–42.
[15] Wu CS, Lai MS, Gau SS, et al. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. PLoS One 2014;9:e112257.
[16] Cheng CL, Chien HC, Lee CH, et al. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. Int J Cardiol 2015;201:96–101.

[17] Hicks KA, Hung HMJ, Mahaffey KW, et al. for Standardized Data Collection for Cardiovascular Trials Initiative. Standardized definitions for end point events in cardiovascular trials. US Food and Drug Administration, 2010. http://www.clinpage.com/images/uploads/endpoint-defs_11-16-2010.pdf.
[18] Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906–14.
[19] Brodovicz KG, Chen Y, Liu Z, et al. Characterization of sitagliptin use in patients with type 2 diabetes and chronic kidney disease by cross-sectional analysis of a medical insurance claims database. Diabetes Ther 2015;6:627–34.
[20] Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet 2012;380:475–83.
[21] Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369:1317–26.
[22] El-Sahar AE, Safar MM, Zaki HF, et al. Sitagliptin attenuates transient cerebral ischemia/reperfusion injury in diabetic rats: implication of the oxidative-inflammatory-apoptotic pathway. Life Sci 2015;126:81–6.
[23] Darsalia V, Ortsater H, Olverling A, et al. The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride. Diabetes 2013;62:1289–96.
[24] Chan SY, Ou SM, Chen YT, et al. Effects of DPP-4 inhibitors on cardiovascular outcomes in patients with type 2 diabetes and end-stage renal disease. Int J Cardiol 2016;218:170–5.