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Sitagliptin and cardiovascular outcomes in diabetic patients with chronic kidney disease and acute myocardial infarction: A nationwide cohort study

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ABSTRACT

Background: The cardiovascular safety and efficacy of sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, in type 2 diabetic patients with chronic kidney disease (CKD) after acute myocardial infarction (AMI) are unclear.
Methods: We analyzed data from the Taiwan National Health Insurance Research Database between March 1st, 2009 and December 31st, 2011. A total of 1025 AMI patients with diabetes with chronic kidney disease were selected as the study cohort. The study evaluated the cardiovascular safety and efficacy of sitagliptin by comparing 205 subjects (20%) who use sitagliptin to 820 matched subjects (80%) who do not. The primary outcomes included myocardial infarction, ischemic stroke or cardiovascular death.
Results: Primary composite outcomes occurred in 54 patients in the sitagliptin group (26.3%) and in 164 patients in the comparison group (20.0%) (HR, 1.32; 95% CI, 0.97–1.79; $P = 0.079$) during the mean follow-up of 1.02 years ($SD = 0.71$ years). The sitagliptin group had similar risks of ischemic stroke, all-cause mortality or hospitalization for heart failure (HF) compared to the non-sitagliptin group ($P = 0.938$, 0.523 and 0.795 respectively). However, sitagliptin use was associated with increased risks of recurrent myocardial infarction (HR, 1.73; 95% CI, 1.15–2.58; $P = 0.008$) and percutaneous coronary revascularization (HR, 1.43; 95% CI, 1.04–1.95; $P = 0.026$).
Conclusions: Among type 2 diabetic patients with CKD after AMI, the use of sitagliptin was not associated with an increased risk of cardiovascular death, ischemic stroke or hospitalization for HF but was associated with increased risks of recurrent MI and percutaneous coronary revascularization.

1. Introduction

Type 2 diabetes mellitus (T2DM) is strongly associated with the risk of major cardiovascular complications [1] with a two-fold higher mortality rate when compared to individuals without diabetes mellitus [2]. Among the T2DM patients, chronic kidney disease (CKD) is a predominant independent risk factor for increased cardiovascular-related disease and death compared to those with normal renal function [3]. Improved glycemic control is associated with a reduction in renal events, including onset of or worsening of nephropathy and development of microalbuminuria or macro-albuminuria [4,5]. However, clinical randomized trials have not shown the macrovascular risk reduction in intensive glycemic control [5,6]. Concerns regarding adverse cardiovascular outcomes remain.

Apart from unclear cardiovascular risk reduction benefits, anti-hyperglycemic treatment options for patients with T2DM and CKD are limited due to safety and tolerability issues [7]. Metformin is the most common anti-hyperglycemic agent but is contraindicated in T2DM patients with a creatinine clearance of <60 ml/min. Sulfonylureas are alternative treatment options; however, sulfonylureas are associated with an increased risk of hypoglycemia and weight gain [8,9]. Thiazolidinediones are related to edema, fluid retention and increased risk of cardiovascular events [10], which may limit the use of thiazolidinediones in patients with CKD. Therefore, a safe and tolerable anti-hyperglycemic agent with significant efficacy is in demand for the CKD population.

Sitagliptin is the first approved DPP-4 inhibitor with anti-hyperglycemic effects that enhances the incretin axis [11]. A number of

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recent studies revealed a decrease risk of adverse cardiovascular events in subjects treated with sitagliptin [12]. However, other studies suggest neutral effect on cardiovascular outcomes [13,14]. Conversely, some studies found that sitagliptin attenuates endothelial function with significantly reduced flow-mediated vasodilatation [15] and the loss of DPP4 activity is related to a prothrombogenic status of endothelial cells [16]. As a result, there is ongoing debate about the cardiovascular benefits and potential risks of the medication. Furthermore, past clinical studies usually excluded patients with severe renal insufficiency or end stage renal disease (ESRD) on hemodialysis, and therefore the efficacy and safety of these agents were not well characterized in these populations.

Sitagliptin has been licensed for use in patients with CKD and ESRD on hemodialysis. Few studies suggest that the medication is effective and well tolerated in patients with T2DM with moderate to severe chronic renal insufficiency [17] or in patients with ESRD on hemodialysis [18]. However, these studies were not designed with cardiovascular outcomes as the primary endpoints and were of short duration.

Given the current controversy surrounding the safety of DPP-4 inhibitors and limited clinical outcome data, we designed this study to evaluate the safety of sitagliptin with respect to cardiovascular outcomes in patients with T2DM and CKD who are at very high cardiovascular risk—patients with acute myocardial infarction.

2. Methods

2.1. Data source

We conducted a nationwide population-based cohort study using Taiwan's National Health Insurance Research Database (NHIRD), which consists of standard computerized claims documents submitted by medical institutions that seek reimbursement through the NHI program. The NHI program covers the medical needs for 99.19% of the population in Taiwan, a group of more than 25 million people. The accuracy and validity of NHIRD data are based on regular auditing of claims by the NHI Bureau [19]. False reimbursement claims result in substantial penalties. Minor infractions involve fines of 100 times the amount of the false claim, while serious infractions may result in the revocation of a physician's license or criminal charges. All clinical diagnoses were recorded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes. The information and records of patients were de-identified prior to analysis. This study was approved by the Ethics Institutional Review Board of Chang Gung Memorial Hospital.

2.2. Study group and cohort definition

We identified all patients in the NHIRD with T2DM (ICD-9-CM codes 250) between March 1st, 2009 and December 31st, 2011. Only T2DM patients with CKD (ICD-9-CM code 585) or ESRD on hemodialysis who were hospitalized for AMI (ICD-9-CM code 410) were included in our study (Fig. 1). The accuracy of using ICD-9 diagnosis codes to identify CKD or AMI in the claims database has been validated in previous studies [20–22]. The first hospitalizations throughout the study period were assigned as the indexed admission time. The follow-up period was based upon the index hospitalization to date of death, loss of follow-up, or until December 31st, 2011.

Sitagliptin exposure was based on computer-based prescription claims after the index date, and patients were classified into the sitagliptin group or non-sitagliptin comparison group. Patients who received a prescription of sitagliptin for 90 consecutive days following index discharge were defined as the sitagliptin group, while patients who did not receive sitagliptin were considered the comparison group. Sitagliptin dosages were given in according to Taiwan's National Health Insurance regulation. The dosages were 50 mg and 25 mg daily in patients with eGFR between 30 to 50 ml/min and below 30 ml/min, respectively.

Patients were excluded if they met any of the following criteria: (1) newly diagnosed T2DM; (2) age <40 years; (3) expired during index admission; (4) use of other DPP-4 inhibitors before or after the indexed hospitalization; and (5) major adverse cardiovascular events (defined as cardiovascular death, MI or ischemic stroke) within 30 days of discharge or (6) followed for less than 30 days after the indexed hospitalization.

2.3. Outcomes and covariate measurements

Baseline comorbidities were identified by ICD-9-CM diagnosis codes and medication during index hospitalization. Primary outcomes were composite events of cardiovascular death, MI or ischemic stroke (Fig. 2). Definitions of cardiovascular death meet the criteria of Standardized Definitions for End Point Events in Cardiovascular Trials draft by the Food and Drug Administration [23]. Death and causes of death were according to registry data of NHIRD [24]. Other secondary outcomes of interest were deaths of any cause, hospitalization for heart failure, coronary revascularization, pancreatitis, hypoglycemia, diabetic ketoacidosis or hyperosmolar hyperglycemic state.

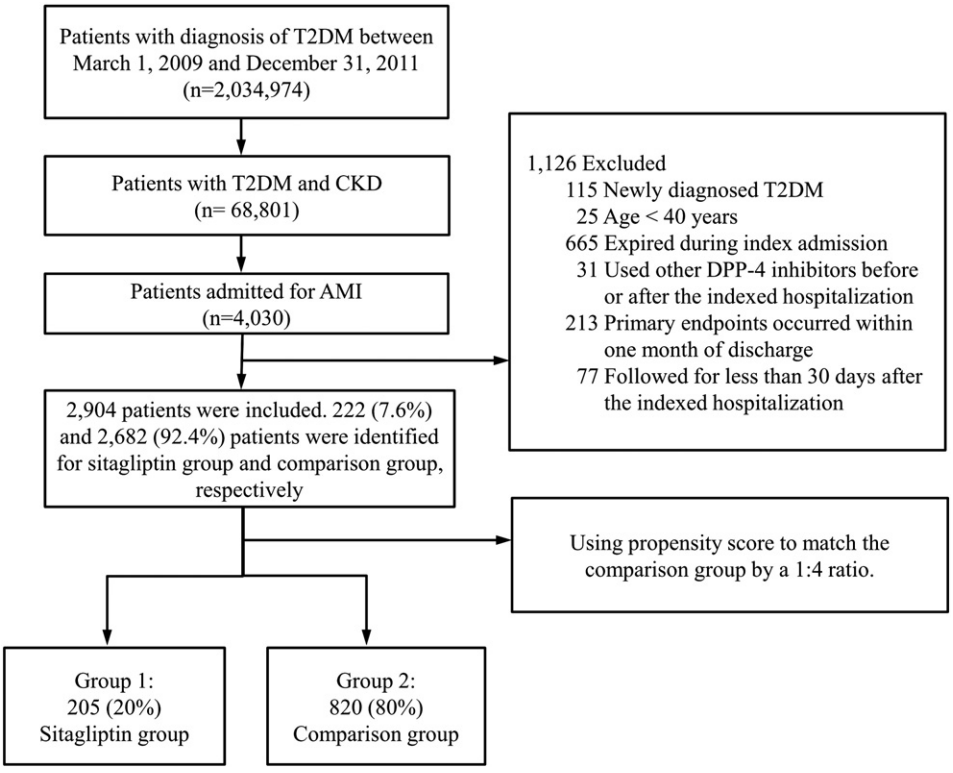

Fig. 1. Flowchart of inclusion. Individuals with T2DM and CKD hospitalized with a diagnosis of AMI were included in our analysis after relevant exclusions (T2DM = type 2 diabetes mellitus, CKD = chronic kidney disease, AMI = acute myocardial infarction, DPP-4 = dipeptidyl peptidase 4).

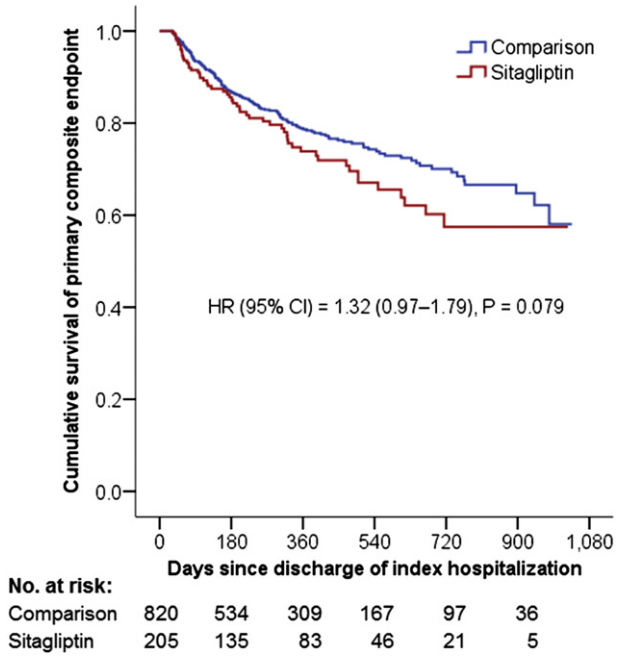

Fig. 2. Cumulative Kaplan–Meier survival estimates of the time to primary composite endpoint. The primary end point was a composite of myocardial infarction, ischemic stroke, or cardiovascular death. No significant differences in the primary composite outcomes were observed between the two study groups after a median 1.02-year follow-up.

2.4. Statistical analysis

We matched the comparison cohort with sitagliptin groups by a 1:4 ratio in terms of patient's characteristics, baseline comorbidities, medication prescribed 90 days since indexed hospitalization (listed in Table 1), and index year and month by using propensity score. The matching procedure was performed by using NCSS 2007 (Number Cruncher Statistical System, Limited Liability Company, Kaysville, Utah).

Clinical characteristics between study groups (sitagliptin and comparison groups) were compared by chi-square test for categorical variables and by independent sample t-test for continuous variables. The difference of time to the first occurrence of a predefined primary or secondary outcome after index hospitalization between study groups was made by Cox proportional hazard models, with adjustment of the propensity score. The Cox models were then performed with stratification according to the status of end-stage renal disease (ESRD) at baseline. The survival rates of predefined period (i.e. 3 months, 1 year and complete course) for each study group were estimated and depicted by the Kaplan–Meier method. All data analysis was conducted using SPSS software version 15 (SPSS Inc., Chicago, Illinois).

Table 1
Baseline clinical characteristics of the study patients.

Characteristics	Sitagliptin ($n = 205$)	Comparison ($n = 820$)	P
Age (yrs)	68.5 ± 10.1	68.8 ± 11.0	0.693
Age ≧75 years	60 (29.3)	257 (31.3)	0.566
Gender			0.827
Male	111 (54.1)	437 (53.3)	
Female	94 (45.9)	383 (46.7)	
Previous myocardial infarction	16 (7.8)	56 (6.8)	0.625
Previous cerebral vascular accident	47 (22.9)	188 (22.9)	1.000
Comorbidity			
Neuropathy	42 (20.5)	139 (17.0)	0.235
Retinopathy	27 (13.2)	108 (13.2)	1.000
Coronary artery disease	150 (73.2)	608 (74.1)	0.776
Chronic obstructive pulmonary disease	47 (22.9)	177 (21.6)	0.678
End stage renal disease	104 (50.7)	412 (50.2)	0.901
Peripheral arterial disease	14 (6.8)	69 (8.4)	0.457
Hypertension	190 (92.7)	761 (92.8)	0.952
Heart failure	99 (48.3)	391 (47.7)	0.876
Dyslipidemia	103 (50.2)	434 (52.9)	0.491
Malignancy	17 (8.3)	54 (6.6)	0.389
Previous PCI	115 (56.1)	474 (57.8)	0.658
Follow-up days	382 ± 256	370 ± 261	0.550

Values are mean ± SD or n (%); PCI = percutaneous coronary intervention.

3. Results

3.1. Study patients

From March 2009 through December 2011, a total of 1025 patients diagnosed with T2DM and CKD who were hospitalized for AMI were identified for our study cohort. Of those, 205 patients (20%) were in the sitagliptin group and 820 matched patients (80%) in the comparison group. The mean age for the overall cohort was 68.7 years (SD = 10.8 years). The mean follow-up period was 1.02 years (SD = 0.71 years), and the maximum follow-up time was 2.83 years. The two study groups were well balanced with respect to baseline characteristics, comorbidities and non-study medications. The patients with ESRD accounted for 50.7% of the sitagliptin group and 50.2% in the comparison group (Table 1). The use of drugs for cardiovascular disease and T2DM were well matched in both groups (Table 2).

3.2. Cardiovascular outcomes

The events of composite primary outcome occurred in 54 patients (26.3%) in the sitagliptin group and in 164 patients (20.0%) in the comparison group (HR, 1.32; 95% CI, 0.97–1.79; $P = 0.079$) (Table 3). Except for those of MI, no significant differences in the individual composite endpoints were observed between the two study groups. In contrast, the incidence rate of MI was significantly higher for patients treated with sitagliptin within 1-year (13.7% vs. 8.4%; HR, 1.62; 95% CI, 1.05–2.52), and complete course (16.6% vs. 9.6%; HR, 1.73; 95% CI, 1.15–2.58) periods as compared with the comparison patients (Table 3; Fig. 3A).

In terms of secondary outcomes, patients treated with sitagliptin had similar risk for all-cause mortality or HF with HRs of 0.90 (95% CI, 0.67–1.23) and 0.94 (95% CI, 0.62–1.45) respectively, compared to nonusers of sitagliptin (Table 4). However, the incidence rate of percutaneous coronary revascularization was significantly higher for patients treated with sitagliptin (HR, 1.43; 95% CI, 1.04–1.95). The result of subgroup analysis revealed that sitagliptin users were associated with an increased risk of MI in the ESRD subgroup (21.2% vs. 10.0%; HR, 2.24; 95% CI, 1.34–3.77; $P = 0.002$) but not in the non-ESRD subgroup (11.9% vs. 9.3%; HR, 1.23; 95% CI, 0.64–2.36; $P = 0.533$) (Fig. 4A–B). In addition, higher risk of coronary revascularization was noted in the ESRD subgroup (31.7% vs. 18.2%; HR, 1.90; 95% CI, 1.26–2.86; $P = 0.002$) when compared to the non-ESRD subgroup (19.8% vs. 18.6%; HR, 1.02; 95% CI, 0.62–1.68; $P = 0.927$) (Fig. 5).

Table 2
Proportions of patients receiving nonstudy medications.

Medication after enrollment	Sitagliptin ($n = 205$)	Comparison ($n = 820$)	P
Cardiovascular disease medication			
ACEI or ARB	116 (56.6)	441 (53.8)	0.471
Aspirin	161 (78.5)	633 (77.2)	0.681
Clopidogrel	179 (87.3)	715 (87.2)	0.963
Beta-blockers	124 (60.5)	487 (59.4)	0.775
Calcium-channel blockers	100 (48.8)	407 (49.6)	0.827
Diuretics	96 (46.8)	376 (45.9)	0.802
Statins	106 (51.7)	438 (53.4)	0.661
T2DM medication			
Insulin	76 (37.1)	319 (38.9)	0.630
TZD	10 (4.9)	32 (3.9)	0.529
Sulfonylurea	87 (42.4)	324 (39.5)	0.444

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; TZD = thiazolidinedione; and T2DM = type 2 diabetes mellitus.

Table 3
Primary outcomes in various follow-up periods.

Outcome	Number of event (%)		Sitagliptin vs. comparison	
	Sitagliptin	Comparison	HR (95% CI)[a]	*P*
3 month follow-up				
Myocardial infarction	13 (6.3)	29 (3.5)	1.78 (0.93–3.43)	0.084
Ischemic stroke	1 (0.5)	3 (0.4)	1.32 (0.14–12.73)	0.808
Cardiovascular death	6 (2.9)	20 (2.4)	1.20 (0.48–2.98)	0.700
Primary composite endpoint[b]	17 (8.3)	51 (6.2)	1.34 (0.77–2.32)	0.299
1 year follow-up				
Myocardial infarction	28 (13.7)	69 (8.4)	1.62 (1.05–2.52)	0.031
Ischemic stroke	4 (2.0)	18 (2.2)	0.86 (0.29–2.53)	0.779
Cardiovascular death	23 (11.2)	66 (8.0)	1.38 (0.86–2.21)	0.186
Primary composite endpoint[b]	43 (21.0)	136 (16.6)	1.26 (0.90–1.78)	0.180
All course				
Myocardial infarction	34 (16.6)	79 (9.6)	1.73 (1.15–2.58)	0.008
Ischemic stroke	6 (2.9)	22 (2.7)	1.04 (0.42–2.56)	0.938
Cardiovascular death	30 (14.6)	87 (10.6)	1.36 (0.89–2.05)	0.151
Primary composite endpoint[b]	54 (26.3)	164 (20.0)	1.32 (0.97–1.79)	0.079

[a] Adjusted for propensity score.
[b] Anyone of myocardial infarction, ischemic stroke, or cardiovascular death.

3.3. Safety outcomes

The sitagliptin and comparison groups did not differ significantly with respect to the incidence of hypoglycemia (2.9% and 4.5%; $P = 0.288$). The incidence of diabetic ketoacidosis or hyperosmolar hyperglycemic state was also similar across the two study groups (0.5% and 1.3%; $P = 0.294$). There were no significant differences in the incidence of pancreatitis between two groups (Table 4).

4. Discussion

This was the first nationwide, population-based study to evaluate the clinical outcome of sitagliptin therapy in T2DM patients with CKD after AMI. Our study suggested that treatment with DPP-4 inhibitor sitagliptin resulted in similar rates of major cardiovascular events between these two groups of T2DM patients with CKD after recent AMI. However, the incidence rates of MI and percutaneous coronary revascularization were significantly higher for patients treated with sitagliptin. The increase in MI events is likely clinically relevant as there is a trend of a higher MI rate among the sitagliptin group after the three-month follow-up. There was a significant increased risk at the one-year follow-up, a risk that persisted until the end of the study. The risk resulted in a number needed to harm of 14.4. In the ESRD subgroup, treatment with sitagliptin was particularly associated with a 2.24-fold increased risk of MI and 1.90-fold increased risk of coronary revascularization. This may have an effect on the treatment options for diabetic patients with CKD and prior MI, especially in the ESRD group.

Our study included patients with considerably high cardiovascular risk as a result of T2DM with CKD and AMI. The primary composite cardiovascular event rates were more than 20% during the mean follow-up period of 1.02 years. To date, the cardiovascular outcomes of sitagliptin have not been consistent from different trials. Some studies revealed a decrease risk of adverse cardiovascular events [12] while others suggested a neutral effect on cardiovascular outcomes [13,14]. Different from these cardiovascular safety trials of DPP4-inhibitor performed on a major population of non-CKD subjects, all the patients in our study are the CKD subjects and ESRD patients account for 50.3% of the study population. Our study revealed that use of sitagliptin is associated with increased risks of recurrent MI and coronary revascularization among these high cardiovascular risk group patients.

In this study, the increase in MI and coronary revascularization events was predominantly associated with the ESRD subgroup. The

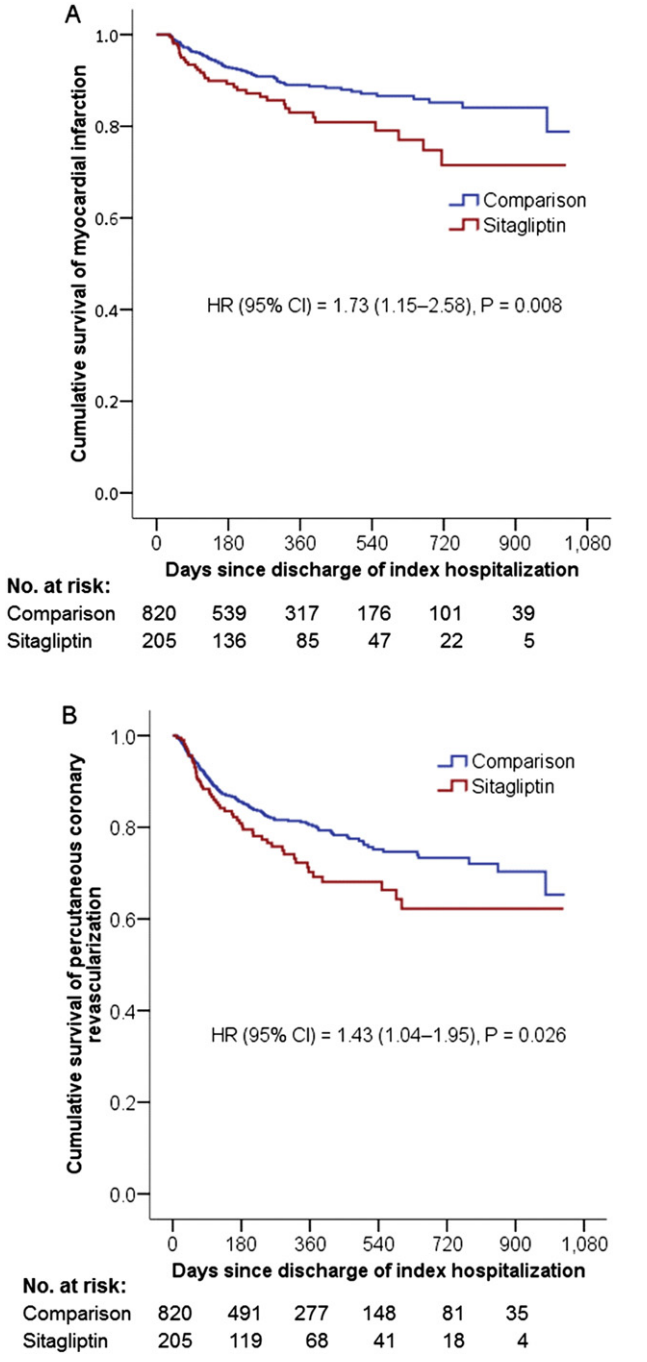

Fig. 3. Cumulative Kaplan–Meier survival estimates of the time to myocardial infarction (Panel A) or percutaneous coronary revascularization (Panel B). The incidence rates of myocardial infarction or percutaneous coronary revascularization were significantly higher for patients treated with sitagliptin compared to the comparison patients.

recently completed EXAMINE trial suggested that the DPP-4 inhibitor, alogliptin, did not increase the rate of major adverse cardiovascular events in patients with T2DM who had recent acute coronary syndrome [25]. Although ESRD patients were excluded from the EXAMINE study, the CKD subgroup analysis of this trial showed a trend of increased primary cardiovascular risk with the use of alogliptin in the moderate or severe renal impairment group (HR, 1.15; 95% CI, 0.91–1.46) when compared to the normal or mild impairment renal function group (HR, 0.84; 95% CI, 0.68–1.04) (the interaction with treatment *P* value = 0.046). Conversely, the SAVOR trial found that saxagliptin did not affect the rate of ischemic events, though the rate of hospitalization for heart failure increased [26]. No major cardiovascular event difference could be

Table 4
Secondary outcomes.

Outcome	Number of event (%)		Sitagliptin vs. comparison	
	Sitagliptin	Comparison	HR (95% CI)[a]	*P*
Other CV outcomes				
Death from any cause	50 (24.4)	218 (26.6)	0.90 (0.67–1.23)	0.523
Heart failure	26 (12.7)	106 (12.9)	0.94 (0.62–1.45)	0.795
Percutaneous coronary revascularization	53 (25.9)	151 (18.4)	1.43 (1.04–1.95)	0.026
Safety outcomes				
Any pancreatitis	0 (0.0)	2 (0.2)	N.A.	N.A.
Acute pancreatitis	0 (0.0)	2 (0.2)	N.A.	N.A.
Chronic pancreatitis	0 (0.0)	0 (0.0)	N.A.	N.A.
Hypoglycemia	6 (2.9)	37 (4.5)	0.63 (0.26–1.48)	0.288
DKA or HHS	1 (0.5)	11 (1.3)	0.33 (0.04–2.59)	0.294

CV = cardiovascular; NA = not applicable; DKA = diabetic ketoacidosis; and HHS = hyperosmolar hyperglycemic state.
[a] Adjusted for propensity score.

detected among different renal function groups of defined eGFR of >50, 30–50 or <30 ml/min/1.73 m^2.

Because of the controversy of cardiovascular effects of sitagliptin and also other DPP-4 inhibitors, further studies are required especially in patients with CKD to stratify the risk–benefit effect. Therefore, the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), a randomized, double-blind trial is essential for further evaluation for the safety of this drug [27]. This trial enrolled patients with established cardiovascular diseases; however, the trial excluded patients who had an eGFR of <30 ml/min/1.73 m^2. Therefore, it is improbable that the results of the TECOS trial will provide information about the safety of sitagliptin therapy in patients with advanced stage CKD or ESRD groups, which have especially high cardiovascular risk. Few other studies reported that sitagliptin was well tolerated in T2DM patients with moderate to severe chronic renal insufficiency [17] or even in ESRD on hemodialysis [18]. However, unlike our study, these studies did not specifically include individuals with recent AMI, and the studies did not designate cardiovascular outcomes as the primary endpoint. Therefore, our studies are currently the only evidence discussing this important issue about sitagliptin related cardiovascular outcome among the CKD population.

Finally, the precise mechanism of the increased MI among CKD population is unclear. There is still some dispute about the effect of sitagliptin on the vascular endothelial function. Although some studies revealed a decreased in inflammatory marker or cell adhesion molecules by sitagliptin [28,29], other studies reported that the loss of DPP4 activity was related to a prothrombogenic status of the coronary endothelial cells in MI patients [16]. Further study revealed that sitagliptin attenuated endothelial function with significantly reduced flow-mediated vasodilatation [15]. It is unclear if this prothrombogenic effect or reduced vasodilatation mechanism will amplify within the CKD population, especially for ESRD subjects, and thus associate with increased MI and coronary revascularization events. Therefore, further study of these implications is warranted to elucidate this issue.

5. Study limitations

There were several limitations to this study. First, we did not have personal information for our patients such as family history of cardiovascular disease, life style, body mass index or laboratory parameters including glycated hemoglobin levels. However, we were able to include a wide range of variables related to outcomes, including comorbidities and non-study medications, to make our two study groups well balanced. Second, the claims database did not include creatinine level, which is not routinely recorded in our database. Third, we assumed that patients properly adhered to their treatment medications in the claims data. Fourth, although ICD-10 came into use in World Health Organization Member States as from 1994, the clinical diagnoses in NHIRD were recorded according to ICD-9 codes during the period of 1997 to 2011. Finally, in our study, only a mean of 1.02 years and maximum of 2.83 years of follow-up were available in the NHIRD. Long-term studies are still needed to generate more information.

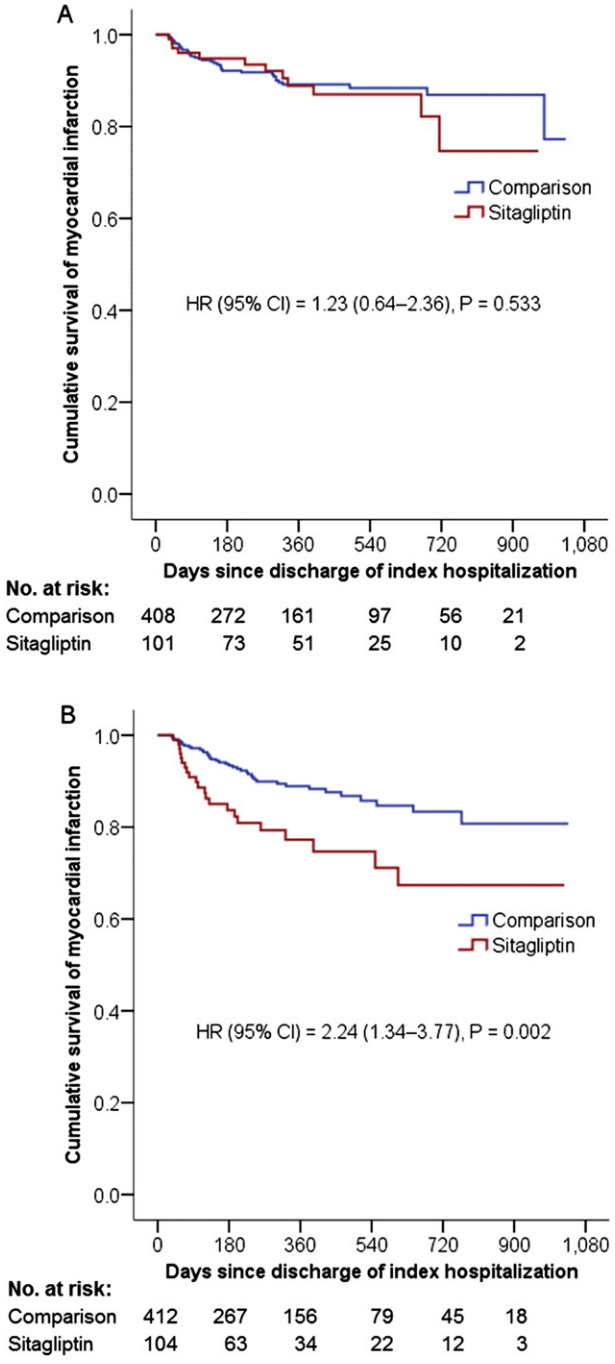

Fig. 4. Cumulative Kaplan–Meier survival estimates of the time to myocardial infarction (complete-course) stratified by ESRD: (A) without ESRD and (B) with ESRD. Sitagliptin users were associated with an increased risk of myocardial infarction in the ESRD subgroup (21.2% vs. 10.0%; HR, 2.24; 95% CI, 1.34–3.77; $P = 0.002$) but not in the non-ESRD subgroup (11.9% vs. 9.3%; HR, 1.23; 95% CI, 0.64–2.36; $P = 0.533$). The study group's interaction with ESRD was significant ($P < 0.05$).

6. Conclusions

Among T2DM patients with CKD after AMI, sitagliptin use was not associated with an increased risk of cardiovascular death, ischemic stroke or heart failure hospitalizations. However, sitagliptin was associated with increased risks of recurrent MI and percutaneous coronary

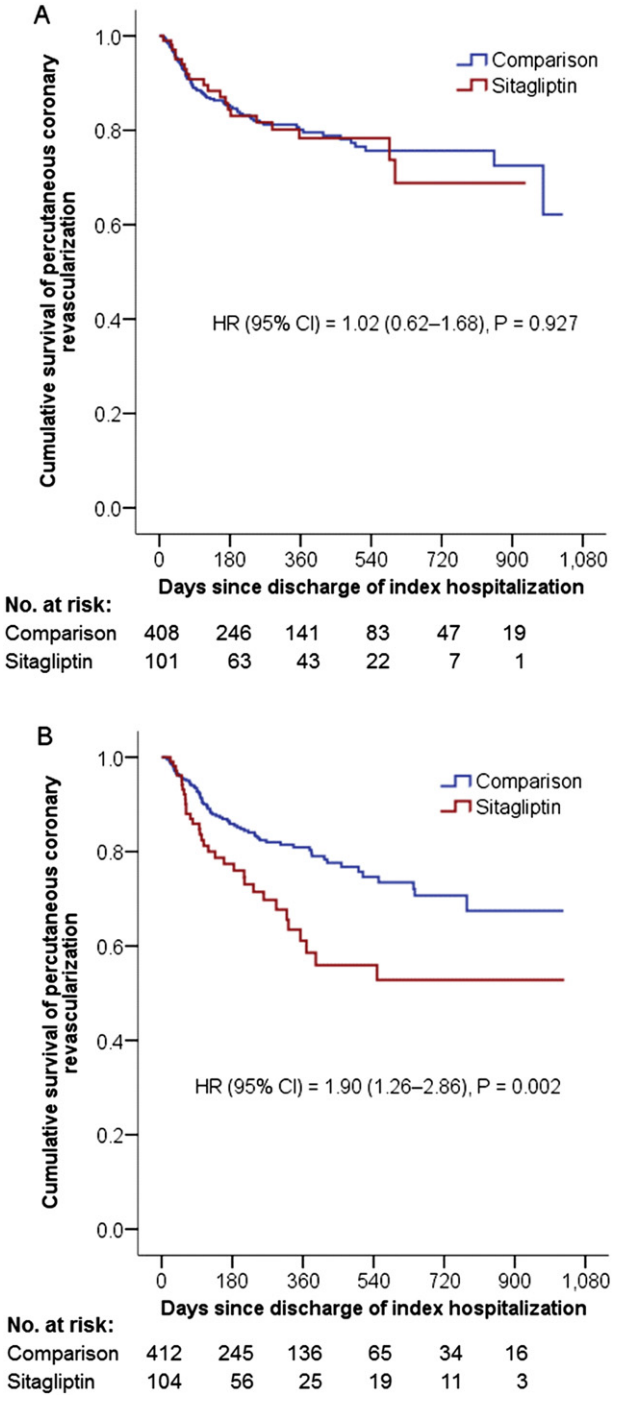

Fig. 5. Cumulative Kaplan–Meier survival estimates of the time to percutaneous coronary revascularization (complete-course) stratified by ESRD: (A) without ESRD and (B) with ESRD. Sitagliptin users were associated with an increased risk of percutaneous coronary revascularization in the ESRD subgroup (31.7% vs. 18.2%; HR, 1.90; 95% CI, 1.26–2.86, $P = 0.002$) but not in the non-ESRD subgroup (19.8% vs. 18.6%; HR, 1.02; 95% CI, 0.62–1.68, $P = 0.927$). The study group's interaction with ESRD was significant ($P < 0.05$).

revascularization throughout the nationwide cohort. These data could help clinicians weigh the benefits and potential risks of sitagliptin therapy in treating T2DM with CKD and AMI.

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Conflict of interest

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

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Appendix A. ICD-9-CM code used for diagnosis in the current study

Variable	Source	Code
Myocardial infarction	ICD-9 CM	410
Chronic kidney disease	ICD-9 CM	585
Ischemic stroke	ICD-9 CM	433–435
Neuropathy	ICD-9 CM	3572, 2496, and 2506
Retinopathy	ICD-9 CM	2505
Coronary artery disease	ICD-9 CM	413 and 4140
Chronic obstructive pulmonary disease	ICD-9 CM	490–496
Peripheral arterial disease	ICD-9 CM	440.0, 440.2x, 440.3x, 440.4, 440.9, 443.9, 444.2, 444.22, 444.8, 444.81, 445.0, 445.02, 250.7x, and 707.1x
Hypertension	ICD-9 CM	401–405
Heart failure	ICD-9 CM	428
Dyslipidemia	ICD-9 CM	272
Malignancy	ICD-9 CM	140–208
Acute pancreatitis	ICD-9 CM	5770
Chronic pancreatitis	ICD-9 CM	5771
Hypoglycemia	ICD-9 CM	2510, 2511, 2512, 2508, and 2498
DKA or HHS	ICD-9 CM	2501, 2502, and 2503

dx = diagnosis; DKA = diabetic ketoacidosis; and HHS = hyperosmolar hyperglycemic state.

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