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Effects of DPP-4 inhibitors on cardiovascular outcomes in patients with type 2 diabetes and end-stage renal disease☆

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ABSTRACT

Background: Recent clinical trials have evaluated the cardiovascular outcomes of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes mellitus (T2DM), but those with end-stage renal disease (ESRD) were ineligible for participation in these trials. We aimed to characterize the impact of DPP-4 inhibitors on major adverse cardiovascular events (MACEs) in patients with T2DM and ESRD undergoing chronic dialysis.
Methods: This nationwide observational study utilized data from 3556 patients aged ≥20 years with T2DM and ESRD who initiated treatment with DPP-4 inhibitors between 1 March 2009 and 31 June 2013, retrieved from Taiwan's National Health Insurance Research Database. Each DPP-4 inhibitor user was matched to a non-user control subject using propensity scores. The primary outcomes were all-cause mortality and MACEs (ischemic stroke and myocardial infarction). The secondary outcomes were hospitalization for heart failure and hypoglycemia. All subjects were followed until death or 31 December 2013.
Results: Compared with non-users, DPP-4 inhibitor users had lower risks of all-cause mortality (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.39–0.47), MACEs (HR 0.76, 95% CI 0.65–0.90), and ischemic stroke (HR 0.77, 95% CI 0.61–0.97); the risks of myocardial infarction and hospitalization for heart failure and hypoglycemia did not differ. This treatment effect remained consistent in subgroup analyses according to age, sex, comorbidities, dialysis modality, and insulin use.
Conclusions: In this nationwide ESRD cohort, DPP-4 inhibitor use was associated with reduced risks of all-cause mortality and ischemic stroke.

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common cause of end-stage renal disease (ESRD) worldwide [1]. Treatment options to achieve glycemic control are very limited for patients with T2DM and ESRD because most anti-diabetic drugs are excreted primarily by the kidney. Insulin therapy appears to be most suitable in this population, but its benefits are usually offset by poor tolerance in real practice for frequent monitoring of glucose level and dosage adjustment, which may increase the risk of hypoglycemia.

Although recent guidelines [2] have loosened the prohibition on metformin use for patients with estimated glomerular filtration rates (eGFR) >30 mL/min/1.73 m^2, serious concerns about metformin-associated lactate acidosis or death remain for patients with eGFR <15 mL/min/1.73 m^2 [3]. Compared with other insulin secretagogues, such as sulfonylurea (only glipizide and gliclazide are recommended for the ESRD population) and meglitinides, which are associated with increased risk of hypoglycemia, and thiazolidinediones, which may promote fluid overload, dipeptidyl peptidase-4 (DPP-4) inhibitors, novel incretin-based anti-diabetic drugs, stimulate insulin secretion by increasing incretin levels in a glucose-dependent manner. They thus appear to be a safe and effective treatment option for this population [4–6].

However, little is known about long-term outcomes in patients with T2DM and ESRD treated with DPP-4 inhibitors. Recent randomized

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controlled trials (RCTs), including the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial [7], the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial [8], and the Trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin (TECOS) [9], have focused on the cardiovascular safety of DPP-4 inhibitors in patients with diabetes and cardiovascular disease. They showed no increase in the occurrence of major adverse cardiovascular events (MACEs) in DPP-4 inhibitor users compared with controls, despite the controversy about the risk of heart failure. However, patients with T2DM and ESRD were excluded from these RCTs. Few studies have investigated DPP-4 inhibitor use in this specific population, and they have had small samples, short follow-up periods, and no hard endpoint [4,10]. To address this gap in knowledge, we conducted a nationwide, propensity score–matched, population-based cohort study involving patients with T2DM and ESRD initiating DPP-4 inhibitors to characterize subsequent MACE outcomes.

2. Materials and methods

2.1. Data source

Using Taiwan's National Health Insurance Research Database (NHIRD), we retrieved all medical records of patients with T2DM and ESRD undergoing chronic dialysis in Taiwan. The national health insurance (NHI) program offers comprehensive medical care coverage to more than 99% of the country's population of 23 million inhabitants. Taiwan's National Health Research Institutes released the NHIRD for research purposes, with data encrypted to protect privacy. This database contains all information on outpatient consultations, hospitalizations, procedures, and prescriptions recorded within the NHI system. We have described the NHIRD in detail in previous works [11–14]. Several scientific research papers examining populations with T2DM or ESRD using validated data from the NHIRD have been published (http://nhird.nhri.org.tw/en/Research.html) [13,15,16]. Disease diagnoses registered in the NHIRD are classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Institutional Review Board of Taipei City Hospital exempted this study from full review (TCHIRB-1030407-W) because anonymous patient records were retrieved from the NHIRD.

2.2. Study cohort

The aim of this nationwide observational cohort study was to investigate associations between DPP-4 inhibitor use and the risks of mortality, MACEs, and adverse events (heart failure and hypoglycemia) in patients with T2DM and ESRD undergoing chronic dialysis. As DPP-4 inhibitors have become widely available in the Taiwanese market since March 2009, we identified all patients aged ≥ 20 years with ESRD undergoing chronic dialysis between 1 March 2009 and 31 June 2013. The NHIRD's catastrophic illness dataset was used to identify patients with ESRD (ICD-9-CM code 585). According to NHI rules, all patients with ESRD undergoing chronic dialysis can be registered in this dataset, and all co-payments for these patients are waived after strict verification by nephrology specialists supported by medical records, examination reports, and imaging studies. The DPP-4 inhibitor cohort included all patients with ESRD using the DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin, and linagliptin. For each DPP-4 inhibitor prescription, detailed information on drug type, quantity, dose, dispensing date, and days of drug supply was collected. The index date was the date of first DPP-4 inhibitor prescription after ESRD. Patients who had taken DPP-4 inhibitors within 90 days before cohort enrollment and renal transplant recipients were excluded. Patients who did not use DPP-4 inhibitors were included in the control cohort. Subjects in the control cohort were assigned the same index dates as corresponding patients in the DPP-4 inhibitor cohort. The mean adherence rate was measured by the proportion of DPP-4 inhibitor pill-days covered during the interval from the index date until death or 31 December 2013, whichever occurred first.

Table 1
Baseline characteristics of patients with Type 2 diabetes mellitus and end-stage renal disease.

	Before propensity score matching			Propensity score-matched		
Characteristics	DPP-4 Inhibitor User	DPP-4 Inhibitor Non-user	*Standardized difference*	DPP-4 Inhibitor User	DPP-4 Inhibitor Non-user	*Standardized difference*
Patients (no.)	3556	18,335		3375	3375	
Mean age (SD), years	60.8 (11.5)	66.2 (13.0)	−0.439	61.1 (11.5)	60.6 (12.2)	0.038
Gender (male)	1927 (54.2)	9818 (53.5)	0.013	1837 (54.4)	1849 (54.8)	−0.007
Charlson Comorbidity Index score, median (IQR)	10 (8–12)	11 (9–13)	−0.240	10 (9–12)	10 (8–12)	0.009
Adapted Diabetes Complications Severity Index score, median (IQR) †	6 (4–8)	6 (4–7)	0.182	6 (4–8)	6 (4–8)	0.010
Median (IQR) duration of end-stage renal disease, months	21 (6–55)	24 (6–67)	−0.111	21 (5–54)	19 (5–54)	0.028
Median (IQR) duration of diabetes mellitus, months	116 (78–141)	104 (59–137)	0.216	116 (78–142)	115 (79–143)	−0.034
Comorbidities						
Coronary artery disease	2223 (62.5)	12,270 (66.9)	−0.092	2117 (62.7)	2091 (62.0)	0.016
Cerebrovascular disease	1375 (38.7)	8522 (46.5)	−0.158	1323 (39.2)	1295 (38.4)	0.017
Myocardial infarction	424 (11.9)	2436 (13.3)	−0.041	409 (12.1)	414 (12.3)	−0.005
Hypertension	3508 (98.7)	17,886 (97.6)	0.081	3328 (98.6)	3330 (98.7)	−0.005
Heart failure	1743 (49.0)	9648 (52.6)	−0.072	1663 (49.3)	1608 (47.6)	0.033
Peripheral vascular disease	617 (17.4)	3501 (19.1)	−0.045	585 (17.3)	565 (16.7)	0.016
Peptic ulcer disease	2173 (61.1)	12,917 (70.4)	−0.198	2078 (61.6)	2028 (60.1)	0.030
Liver disease	1298 (36.5)	7709 (42.0)	−0.114	1244 (36.9)	1257 (37.2)	−0.008
Atrial fibrillation	229 (6.4)	1835 (10.0)	−0.130	221 (6.5)	202 (6.0)	0.023
Dyslipidemia	2849 (80.1)	12,672 (69.1)	0.255	2696 (79.9)	2726 (80.8)	−0.022
Valvular heart disease	561 (15.8)	4158 (22.7)	−0.176	539 (16.0)	530 (15.7)	0.007
Cancer	615 (17.3)	4449 (24.3)	−0.172	599 (17.7)	589 (17.5)	0.008
Autoimmune disease	169 (4.8)	1168 (6.4)	−0.071	163 (4.8)	168 (5.0)	−0.007
Propensity score, mean (SD)	0.29 (0.20)	0.14 (0.12)	0.950	0.27 (0.18)	0.27 (0.18)	0.000

All data are presented as *n* (%), except where otherwise indicated.
*Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.
†Adapted Diabetes Complications Severity Index is a 13-point scale from 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic, ranging from each complication. Each complication produced a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).
Abbreviations: DPP-4, dipeptidyl peptidase-4; SD, standard deviation; IQR, interquartile range;