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Cardiovascular safety of evogliptin dual and triple therapy in patients with type 2 diabetes: a nationwide cohort study

Sohee Park,[1,2,3] Han Eol Jeong,[1,4] In-Sun Oh [ID] ,[1,5,6] Sangmo Hong [ID] ,[7] Sung Hoon Yu,[7] Chang Beom Lee,[7] Ju-Young Shin [ID] [1,4,8]

For numbered affiliations see end of article.

Correspondence to
Professor Ju-Young Shin;
shin.jy@skku.edu

ABSTRACT

Objective To investigate the risk of cardiovascular events associated with commonly used dual and triple therapies of evogliptin, a recently introduced dipeptidyl peptidase-4 inhibitor (DPP4i), for managing type 2 diabetes in routine clinical practice.

Design A retrospective cohort study.

Setting Korean Health Insurance Review and Assessment database.

Participants Patients who initiated metformin-based dual therapy and metformin+sulfonylurea-based triple therapy in South Korea from 2014 to 2018.

Interventions Initiation of combination therapy with evogliptin.

Primary and secondary outcome measures Hazards of cardiovascular events, a composite endpoint of myocardial infarction, heart failure and cerebrovascular events, and its individual components. Cox proportional hazards model with propensity score-based inverse probability of treatment weighting were used to estimate HRs and 95% CIs.

Results From the dual and triple therapy cohorts, 5830 metformin+evogliptin users and 2198 metformin+sulfonylurea+evogliptin users were identified, respectively. Metformin+evogliptin users, as compared with metformin+non-DPP4i, had a 29% reduced risk of cardiovascular events (HR 0.71, 95% CI 0.62 to 0.82); HRs for individual outcomes were cerebrovascular events (0.71, 95% CI 0.53 to 0.95), heart failure (0.70, 95% CI 0.59 to 0.82), myocardial infarction (0.89, 95% CI 0.60 to 1.31). Metformin+sulfonylurea+evogliptin users, compared with metformin+sulfonylurea+non-DPP4i, had a 24% reduced risk of cardiovascular events (0.76, 95% CI 0.59 to 0.97); HRs for individual outcomes were myocardial infarction (0.57, 95% CI 0.27 to 1.19), heart failure (0.74, 95% CI 0.55 to 1.01), cerebrovascular events (0.96, 95% CI 0.61 to 1.51).

Conclusions These findings suggest that dual or triple therapies of evogliptin for the management of type 2 diabetes in routine clinical practice present no cardiovascular harms, but could alternatively offer cardiovascular benefits in this patient population.

INTRODUCTION

Cardiovascular events in patients with type 2 diabetes should be closely monitored, considering the paradigm shift in the treatment

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A nationwide healthcare database with minimal exclusion criteria makes our findings generalisable to real-world patients with type 2 diabetes receiving combination oral antidiabetic drug therapies.

⇒ The large sample size allowed for accurate estimation of treatment effects for rare outcomes, including myocardial infarction, with sufficient statistical power.

⇒ Residual confounding from unaccounted or unmeasured confounders is possible because of the inherent nature of observational studies.

⇒ Laboratory or lifestyle data of haemoglobin A1c, body mass index, blood pressure, smoking status and cholesterol were unavailable for assessment from the Health Insurance Review and Assessment Service database.

of type 2 diabetes.[1–3] With this concern, the cardiovascular safety of dipeptidyl peptidase-4 inhibitor (DPP4i), individually and as a class, has been investigated in several cardiovascular outcome trials and observational cohort studies.[4–6] While prior studies have established the cardiovascular safety of DPP4is, they suggested the possibility that individual DPP4is may likely have different cardiovascular safety profiles in clinical use owing to their molecular heterogeneity and binding modes[7]; for example, saxagliptin and alogliptin have been associated with potential risk of heart failure (HF).[8] To date, a total of nine DPP4is are used in South Korea. However, limited evidence on the cardiovascular safety of relatively new agents, and the growing use of combination therapy of DPP4is leads to difficulty in clinical decision-making.[9]

Evogliptin is a relatively novel DPP4i that received its first global approval in 2015.[10 11] Although a previous observational study has established the cardiovascular safety of evogliptin[12] combination therapy with other antidiabetics warrants further investigation. In two randomised

clinical trials of evogliptin as a combination therapy with metformin (MET), cardiovascular-related adverse events were reported; however, formal causal assessments were lacking. One trial reported that 0.9% of patients in the evogliptin group experienced unstable angina,[13] whereas another trial reported that 6.5% of patients experienced dyslipidaemia.[14] However, these trials were underpowered to evaluate any clinically meaningful incidence of cardiovascular events. Furthermore, one observational study found that evogliptin as a combination therapy with MET was not associated with cardiovascular events when compared with MET+glimepiride.[12] However, to our knowledge, no study has examined the cardiovascular safety of evogliptin as a triple therapy. Hence, more evidence is needed, given the prevalent use of evogliptin in patients with type 2 diabetes as dual and triple therapies. Therefore, this study was aimed to assess the cardiovascular safety of evogliptin, when used as dual and triple therapy for type 2 diabetes management by using a nationwide healthcare database of South Korea.

RESEARCH DESIGN AND METHODS

Data source

This study used the data extracted from Health Insurance Review and Assessment Service (HIRA) database of South Korea between 1 January 2014 and 31 December 2018. The HIRA database contains longitudinal health insurance claims data on diagnoses, prescribed drugs, procedures, dates of hospitalisations and ambulatory care utilisation from the entire Korean population of approximately 50 million, owing to the universal healthcare system of South Korea.[15] All personal identifiers were replaced with de-identifiable codes. Diagnoses were coded using the International Classification of Diseases (ICD-10), and prescribed drugs were coded based on the domestic National Drug Chemical codes that were mapped to the Anatomical Therapeutic Chemical classification codes. Diagnoses recorded in the HIRA database were found to have an overall positive predictive value of 82.4%.[16]

Study population

We identified a base cohort of patients newly prescribed MET for type 2 diabetes (ICD-10: E11–E14) between 1 January 2015 and 31 December 2016. Base cohort entry was defined as the date of the first MET prescription. We excluded patients prescribed any antidiabetics in the previous year of base cohort entry, patients aged <20 years at base cohort entry and women with polycystic ovarian syndrome (ICD-10: E28.2) prior to base cohort entry because MET is also indicated for this condition.

We identified two study cohorts from the base cohort: (1) patients who initiated dual oral antidiabetic drug (OAD) therapy after 1 March 2016 (dual therapy cohort) and (2) patients who initiated triple OAD therapy after 1 March 2016 (triple therapy cohort); study cohort entry was defined after 1 March 2016 because reimbursement

of evogliptin was initiated on this date in South Korea. The index date for dual and triple therapy cohorts was defined as the date of prescription for the first dual and triple OAD therapy, respectively. We excluded patients with a history of cardiovascular events (myocardial infarction [MI], HF and cerebrovascular events) within 180 days prior to the index date. Patients meeting the eligibility criteria were followed-up from the index date until the earliest outcome occurrence, in-hospital death, or the end of the study period (31 December 2018) (online supplemental figure S1).

Exposure

The most widely prescribed dual and triple OAD regimens of evogliptin were defined as the exposure group of interest (online supplemental tables S2 and S3): a combination of MET and evogliptin (MET+evogliptin; 97.05%) from the dual therapy cohort, and combination of MET, sulfonylurea (SU) and evogliptin (MET+SU+evogliptin; 81.53%) from the triple therapy cohort. We did not investigate the less commonly used regimens because of insufficient power. The reference group in the dual therapy cohort was defined as patients who initiated MET+non-DPP4i (SU, thiazolidinedione (TZD), α-glucosidase inhibitors (AGI), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and meglitinides (MEG)), whereas the reference group in the triple therapy cohort was defined as patients who initiated MET+SU+non-DPP4i (TZD, AGI, SGLT2i and MEG).

As we aimed to compare the comparative cardiovascular safety among OADs, non-oral agents (eg, insulin and glucagon-like peptidase-1 receptor agonists) were not included in the analysis. In support, according to 2018 report by the Korea Diabetes Association, 82.3% of patients with type 2 diabetes were treated with OADs, including >70% patients receiving combination therapy of ≥2 OADs and 26.1% receiving triple therapy in 2016.[17]

Outcome

The primary outcome was incident hospitalisation or visit to an emergency department for a cardiovascular event, a composite endpoint comprising MI (ICD-10: I21), HF (I50) and cerebrovascular events (I60–I66, G45). The secondary outcomes were the individual components (MI, HF and cerebrovascular events) of the primary composite outcome. Diagnoses recorded in the HIRA database had an overall positive predictive value of 82.4%.[16]

Potential confounders

We assessed age and sex on the index date and duration of diabetes by estimating the time period from base cohort entry (incident MET monotherapy) to the index date (incident dual or triple OAD therapy). We estimated the Charlson Comorbidity Index score within 180 days prior to the index date.[18] Comorbidities and diabetes-related complications (hypertension, dyslipidaemia, chronic obstructive pulmonary disease, hypoglycaemia, retinopathy, neuropathy,
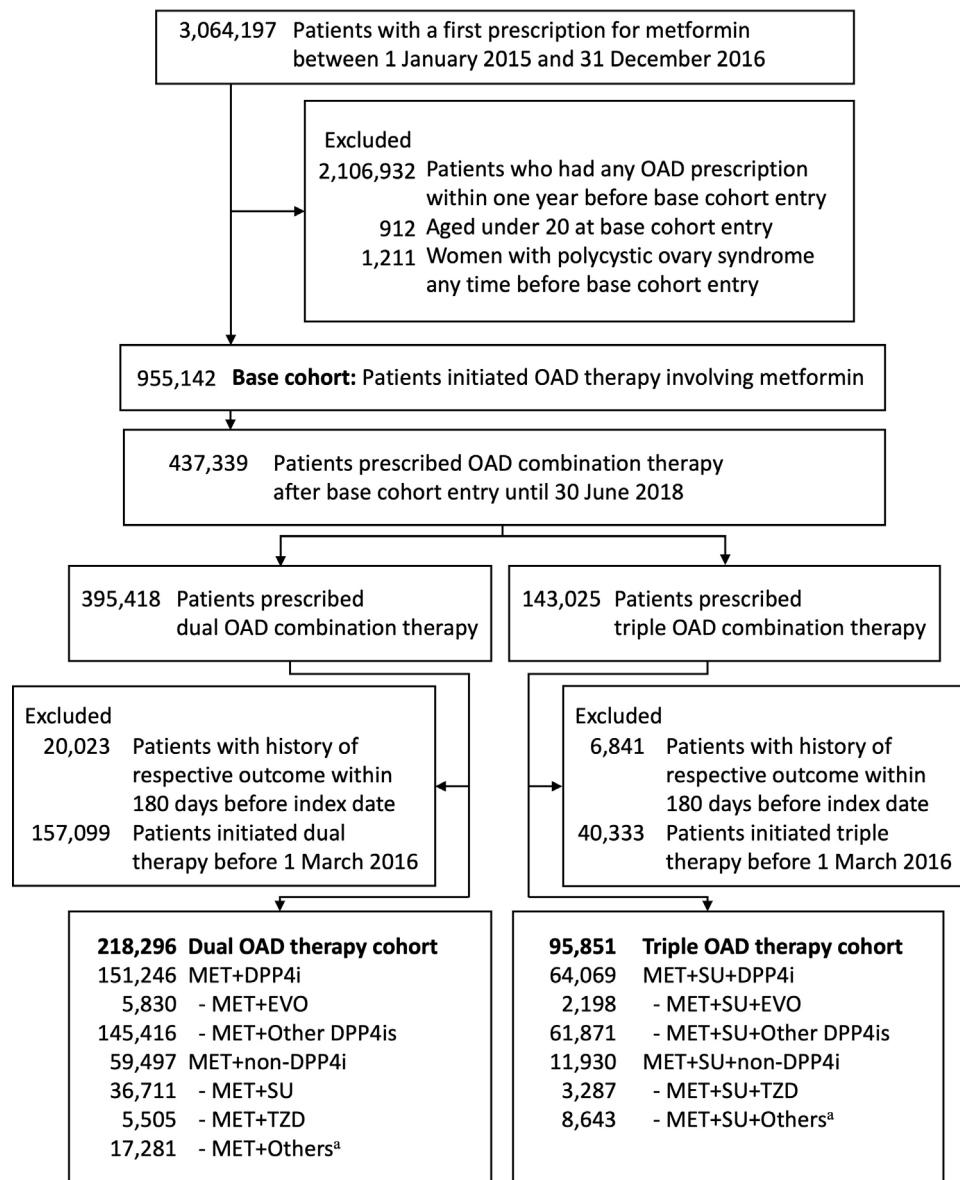
Figure 1 Flow chart showing the inclusion and exclusion criteria for the study patients. †Others include α-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors and meglitinides. Note: The reimbursement of evogliptin was initiated on 1 March 2016. DPP4i, dipeptidyl peptidase-4 inhibitor; EVO, evogliptin; MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea; TZD, thiazolidinedione.

nephropathy and peripheral vascular disease) and use of comedications (ACE inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, diuretics, nitrates, digoxin, acetylsalicylic acid, other antiplatelet drugs, warfarin, other anticoagulants and statins) were also assessed within the 180-day period before the index date (online supplemental table S1).

Statistical analyses

Patients' baseline characteristics were described as counts with proportions for categorical variables and mean with standard deviations (SDs) for continuous variables. The standardised mean difference (SMD) was used to compare baseline characteristics between groups, with an absolute SMD estimate >0.1 indicating a significant imbalance. Propensity score methods were not used in this study as our study included patients with type 2 diabetes at similar stages of the disease in both dual and triple therapy cohorts; patients are therefore believed to have similar demographic and clinical characteristics and disease severity.

Cumulative incidence curves were plotted for the primary composite outcome of each exposure group and evaluated for any differences among curves at all time points using the Gray's test.[19] We estimated incidence rates per 1000 person-years with 95% CI for study outcomes, based on the Poisson distribution. We used the Cox proportional hazards regression model for each study outcome to estimate the HR with 95% CI, where the model was adjusted for all potential confounders.

Furthermore, we investigated the potential effect modification by age (20–44, 45–64, ≥65 years) and sex.

We repeated the main analysis for other individual DPP4is approved in South Korea, including alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin and vildagliptin as an ancillary analysis.

All analyses were conducted using the SAS Enterprise Guide V.6.1 (SAS Institute, Cary, North Carolina, USA).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Among 955 142 patients newly prescribed MET between 2015 and 2016 (base cohort), 218 296 and 95 851 patients initiated the dual and triple OAD therapy after 1 March 2016, respectively (figure 1). There were 151 246 MET+DPP4i users (including 5830 patients who used evogliptin) and 59 497 MET+non-DPP4i users from the dual therapy cohort, and 64 069 MET+SU+DPP4i users (including 2198 patients who used evogliptin) and 11 930 MET+SU+non-DPP4i users from the triple therapy cohort (figure 1). Combination regimens of MET+DPP4i and MET+SU+DPP4i were the most commonly prescribed in their respective cohorts (online supplemental tables S2 and S3).

MET+evogliptin users were older (mean age 56.0 (SD 11.7) years) than MET+non-DPP4i users (mean age 54.1 (SD 12.6) years; SMD 0.162) and had a higher proportion of dyslipidaemia (40.9% vs 35.9%; SMD 0.104) and use of statins (48.9% vs 43.5%; SMD 0.107) in the dual therapy cohort. In the triple therapy cohort, MET+SU+evogliptin users were older (mean age 52.9 (SD 12.0) years) than MET+SU+non-DPP4i users (mean age 50.1 (SD 12.3) years; SMD 0.228) and had a shorter duration of diabetes (mean 354.0 (SD 319.5) vs mean 431.3 (SD 326.4) days; SMD −0.239) and lower proportion of β-blocker use (7.9% vs 11.3%; SMD −0.118). The baseline characteristics of MET+DPP4i and MET+SU+DPP4i were similar to those of MET+evogliptin and MET+SU+evogliptin, respectively (table 1).

The incidence of cardiovascular events was significantly lower in MET+evogliptin (Gray's p value<0.001) and MET+DPP4i (p=0.006) than in MET+non-DPP4i in the dual therapy cohort. Moreover, the cumulative incidence plots for cardiovascular events showed no significant differences in the triple therapy cohort: MET+SU+non-DPP4i versus MET+SU+evogliptin (p=0.074) and MET+SU+DPP4i (p=0.117) (figure 2).

In the dual therapy cohort, the use of MET+evogliptin as compared with MET+non-DPP4i was associated with reduced risks of cardiovascular events (HR 0.71, 95% CI 0.62 to 0.82; p<0.001), HF (HR 0.70, 95% CI 0.59 to 0.82; p<0.001) and cerebrovascular events (HR 0.71, 95% CI 0.53 to 0.95; p=0.021), but showed a statistically non-significant association for MI (HR 0.89, 95% CI 0.60 to 1.30; p=0.543). Moreover, the use of MET+DPP4i was consistent with a decreased risk of cardiovascular events (HR 0.91, 95% CI 0.87 to 0.95; p<0.001) and HF (HR 0.88, 95% CI 0.84 to 0.93; p<0.001); however, a statistically non-significant association for MI (HR 0.91, 95% CI 0.80 to 1.04; p=0.160) and cerebrovascular events (HR 0.95, 95% CI 0.87 to 1.04; p=0.304) was observed. In addition, the use of MET+SU+evogliptin as compared with MET+SU+non-DPP4i was associated with a reduced risk of cardiovascular events (HR 0.76, 95% CI 0.59 to 0.97; p=0.027); however, MET+SU+DPP4i showed a statistically non-significant association (HR 1.01, 95% CI 0.92 to 1.12; p=0.781). For all individual components of the primary outcome as secondary outcomes, both MET+SU+evogliptin and MET+SU+DPP4i, as compared with MET+SU+non-DPP4i, showed a statistically non-significant association (table 2). Trends of individual DPP4is other than evogliptin were similar to the main analysis (online supplemental tables S4 and S5).

Age-stratified and sex-stratified analyses revealed no significant effect modification regarding the risk of cardiovascular events and its individual components associated with MET+evogliptin and MET+DPP4i when compared with MET+non-DPP4i (online supplemental tables S6 and S7). In contrast, a significant effect modification by sex was observed for the risk of cardiovascular events when comparing MET+SU+evogliptin versus MET+SU+non-DPP4i (men: HR 0.67, 95% CI 0.49 to 0.93; women: HR 1.16, 95% CI 0.79 to 1.71; p-for-interaction=0.040). Moreover, there was also significant effect modification by age for the risk of HF associated with MET+SU+DPP4i versus MET+SU+non-DPP4i (20–44 years old: HR 0.74, 95% CI 0.51 to 1.08; 45–64 years old: HR 1.18, 95% CI 1.00 to 1.41; ≥65 years old: HR 0.97, 95% CI 0.80 to 1.19; p-for-interaction=0.039; online supplemental tables S8 and S9).

CONCLUSIONS

This population-based cohort study examined the risk of cardiovascular events associated with the use of evogliptin either as dual or triple therapy with other OAD(s). The use of MET+evogliptin and MET+SU+evogliptin was associated with reduced risks of cardiovascular events (29% and 24%, respectively) as compared with MET+non-DPP4i and MET+SU+non-DPP4i. Moreover, MET+evogliptin was associated with a significantly decreased risk of HF and cerebrovascular events compared with MET+non-DPP4i in the dual therapy cohort.

Our findings were consistent with the studies that assessed the cardiovascular safety of DPP4is as MET-based dual OAD therapy.[20–25] A meta-analysis of randomised clinical trials and observational studies found a reduced risk of cardiovascular events associated with MET+DPP4i (pooled relative risk 0.71, 95% CI 0.56 to 0.90) compared with MET+SU.[21] Moreover, recent observational studies from Denmark[20] (HR 0.71, 95% CI 0.62 to 0.81) and

Table 1 Baseline characteristics of metformin-based dual oral antidiabetic therapy and metformin+sulfonylurea-based triple oral antidiabetic therapy users

Characteristics,* n (%)	Metformin-based dual OAD therapy			Metformin+sulfonylurea-based triple oral antidiabetic therapy		
	MET+EVO (n=5830)	MET+DPP4i (n=151246)	MET+non-DPP4i (n=59497)	MET+SU+EVO (n=2198)	MET+SU+DPP4i (n=64069)	MET+SU+non-DPP4i (n=11930)
Age, years						
Mean±SD	56.0±11.7†	55.1±12.0	54.1±12.6	52.9±12.0†	52.3±12.0†	50.1±12.3
20–44	960† (16.5)	28533 (18.9)	13381 (22.5)	533† (24.3)	16 579† (25.9)	3929 (32.9)
45–64	3490 (60.0)	89494 (59.2)	34033 (57.2)	1291 (58.7)	37274 (58.2)	6543 (54.8)
≥65	1380 (23.7)	33219 (22.0)	12083 (20.3)	374 (17.0)	10216 (16.0)	1458 (12.2)
Sex						
Female	2299 (39.4)	58177 (38.5)	23141 (38.9)	750 (34.1)	21 674 (33.8)	4298 (36.0)
Male	3531 (60.6)	93069 (61.5)	36356 (61.1)	1448 (65.9)	42 395 (66.2)	7632 (64.0)
Duration of diabetes prevalence, days						
Mean±SD	223.5±279.1	248.6±290.6	249.9±292.1	354.0±319.5†	329.5±330.0†	431.3±326.4
Charlson Comorbidity Index						
Mean±SD	0.7±1.1	0.7±1.2	0.7±1.2	0.7±1.0	0.7±1.1	0.7±1.1
0	3750 (64.3)	94663 (62.6)	37199 (62.5)	1381 (62.8)	38684 (60.4)	7117 (60.0)
1	859 (14.7)	24374 (16.1)	9751 (16.4)	385 (17.5)	11995 (18.7)	2461 (20.6)
2	884 (15.2)	22595 (14.9)	8776 (14.8)	306 (13.9)	8922 (13.9)	1628 (13.7)
≥3	337 (5.8)	9614 (6.4)	3771 (6.3)	126 (5.7)	4468 (7.0)	724 (6.1)
Comorbidities						
Hypertension	2679 (46.0)	62280 (41.2)	25150 (42.3)	845 (38.4)	23221 (36.2)	4597 (38.5)
Dyslipidaemia	2,386† (40.9)	60029 (39.7)	21346 (35.9)	878 (40.0)	25439 (39.7)	4744 (39.8)
COPD	42 (0.7)	1489 (1.0)	522 (0.9)	14 (0.6)	524 (0.8)	98 (0.8)
Hypoglycaemia	0 (0.0)	3 (0.0)	2 (0.0)	0 (0.0)	3 (0.0)	0 (0.0)
Diabetes-related complication						
Retinopathy	261 (4.5)	6624 (4.4)	2434 (4.1)	81 (3.7)	2651 (4.1)	496 (4.2)
Neuropathy	98 (1.7)	2847 (1.9)	1151 (1.9)	35 (1.6)	1267 (2.0)	228 (1.9)
Nephropathy	20 (0.3)	1082 (0.7)	320 (0.5)	12 (0.6)	449 (0.7)	63 (0.5)
Peripheral vascular disease	25 (0.4)	762 (0.5)	313 (0.5)	13 (0.6)	429 (0.7)	78 (0.7)
Medications						
ACEi/ARB	2351 (40.3)	56187 (37.2)	22231 (37.4)	783 (35.6)	22313 (34.8)	4587 (38.5)
Beta-blocker	612 (10.5)	16925 (11.2)	6916 (11.6)	173† (7.9)	6370 (9.9)	1353 (11.3)
CCB	1850 (31.7)	46077 (30.5)	18671 (31.4)	569 (25.9)	17268 (27.0)	3469 (29.1)

Continued

Table 1 Continued

Characteristics,* n (%)	Metformin-based dual OAD therapy						Metformin+sulfonylurea-based triple OAD therapy					
	MET+EVO (n=5830)		MET+DPP4i (n=151 246)		MET+non-DPP4i (n=59 497)		MET+SU+EVO (n=2198)		MET+SU+DPP4i (n=64 069)		MET+SU+non-DPP4i (n=11 930)	
Diuretics	1111	(19.1)	27 092	(17.9)	11 287	(19.0)	339	(15.4)	10 558	(16.5)	2087	(17.5)
Nitrate	87	(1.5)	3724	(2.5)	1264	(2.1)	26	(1.2)	1295	(2.0)	259	(2.2)
Digoxin	26	(0.5)	961	(0.6)	364	(0.6)	14	(0.6)	444	(0.7)	73	(0.6)
Acetylsalicylic acid	797	(13.7)	20 828	(13.8)	7779	(13.1)	234	(10.7)	7876	(12.3)	1458	(12.2)
Other antiplatelet drugs	764	(13.1)	20 684	(13.7)	7922	(13.3)	271	(12.3)	8575	(13.4)	1741	(14.6)
Warfarin	22	(0.4)	602	(0.4)	169	(0.3)	6	(0.3)	194	(0.3)	27	(0.2)
Other anticoagulants	110	(1.9)	5001	(3.3)	1639	(2.8)	41	(1.9)	2162	(3.4)	321	(2.7)
Statins	2,849†	(48.9)	73 034	(48.3)	25 901	(43.5)	1059	(48.2)	31 451	(49.1)	6318	(53.0)

*Age and sex were assessed on the index date, and other baseline characteristics were assessed within 180 days prior to the index date.
†Absolute standardised difference >0.1, when non-DPP4i was used as a reference group.
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DPP4i, dipeptidyl peptidase-4 inhibitor; EVO, evogliptin; MET, metformin; OAD, oral antidiabetic drug; SD, standard deviation; SU, sulfonylurea.
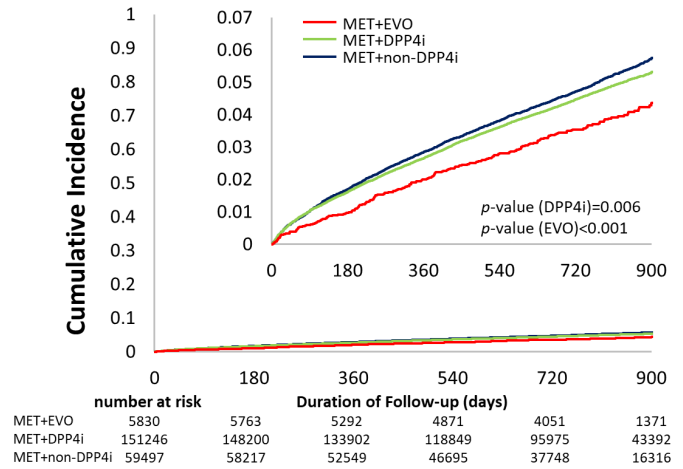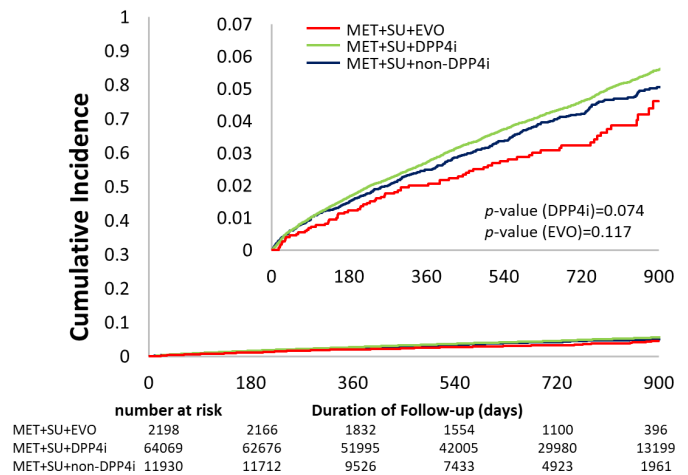
Figure 2 Cumulative incidence curves for cardiovascular events associated with evogliptin and dipeptidyl peptidase-4 inhibitor (DPP4i) compared with non-DPP4i oral antidiabetic drugs as metformin-based dual therapy and metformin+sulfonylurea-based triple therapy. EVO, evogliptin; MET, metformin; OAD, oral antidiabetic drugs; SU, sulfonylurea.

Taiwan[22] (HR 0.85, 95% CI 0.74 to 0.98) reported similar findings regarding the risk of cardiovascular events after the addition of DPP4is as compared with SU to MET monotherapy. However, two other previous studies are inconsistent with our findings.[26 27] Although there was a non-significant association between MET+DPP4i and cardiovascular events (HR 1.02, 95% CI 0.88 to 1.19) as compared with MET+SU,[26] this study used represented different time period (2015–2018 vs 2008–2013) and had an older study population (mean age 55 vs 62 years). Although another study also showed a non-significant effect for major adverse cardiovascular events (MACE) associated with MET+DPP4i (HR 0.52, 95% CI 0.13 to 2.10) compared with MET+SU,[27] this study lacked statistical power (114 patients treated with MET+DPP4i) and, thus, showed abnormally wide CI. These limitations result in complexity in performing direct comparisons with our

Table 2 Risk of cardiovascular events associated with evogliptin and dipeptidyl peptidase-4 inhibitor (DPP4i) compared with non-DPP4i oral antidiabetic drugs as metformin-based dual therapy and metformin+sulfonylurea-based triple therapy

Outcome	No. of Patients	No. of events	Person-years	IR* (95% CI)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Dual OAD therapy								
Cardiovascular events								
MET+EVO	5830	214	11862	18.0 (15.7 to 20.6)	0.74 (0.64 to 0.85)	<0.001	0.71 (0.62 to 0.82)	<0.001
MET+DPP4i	151246	6944	301541	23.0 (22.5 to 23.6)	0.94 (0.90 to 0.98)	0.006	0.91 (0.87 to 0.95)	<0.001
MET+non-DPP4i	59497	2890	118039	24.5 (23.6 to 25.4)	1.00 (reference)		1.00 (reference)	
Myocardial infarction								
MET+EVO	5830	28	12071	2.3 (1.5 to 3.4)	0.86 (0.59 to 1.27)	0.453	0.89 (0.60 to 1.31)	0.543
MET+DPP4i	151246	784	308964	2.5 (2.4 to 2.7)	0.94 (0.83 to 1.07)	0.369	0.91 (0.80 to 1.04)	0.160
MET+non-DPP4i	59497	326	121127	2.7 (2.4 to 3.0)	1.00 (reference)		1.00 (reference)	
Heart failure								
MET+EVO	5830	150	11937	12.6 (10.6 to 14.7)	0.73 (0.62 to 0.86)	<0.001	0.70 (0.59 to 0.82)	<0.001
MET+DPP4i	151246	4783	304106	15.7 (15.3 to 16.2)	0.92 (0.87 to 0.96)	<0.001	0.88 (0.84 to 0.93)	<0.001
MET+non-DPP4i	59497	2048	118987	17.2 (16.5 to 18.0)	1.00 (reference)		1.00 (reference)	
Cerebrovascular events								
MET+EVO	5830	49	12043	4.1 (3.0 to 5.4)	0.72 (0.54 to 0.97)	0.029	0.71 (0.53 to 0.95)	0.021
MET+DPP4i	151246	1715	307857	5.6 (5.3 to 5.8)	0.99 (0.91 to 1.09)	0.896	0.95 (0.87 to 1.04)	0.304
MET+non-DPP4i	59497	677	120739	5.6 (5.2 to 6.0)	1.00 (reference)		1.00 (reference)	
Triple OAD therapy								
Cardiovascular event								
MET+SU+EVO	2198	73	3982	18.3 (14.4 to 23.1)	0.82 (0.64 to 1.05)	0.118	0.76 (0.59 to 0.97)	0.027
MET+SU+DPP4i	64069	2774	113530	24.4 (23.5 to 25.4)	1.09 (0.99 to 1.21)	0.074	1.01 (0.92 to 1.12)	0.781
MET+SU+non-DPP4i	11930	457	20288	22.5 (20.5 to 24.7)	1.00 (reference)		1.00 (reference)	
Myocardial infarction								
MET+SU+EVO	2198	8	4050	2.0 (0.9 to 3.9)	0.59 (0.29 to 1.23)	0.162	0.57 (0.27 to 1.19)	0.134
MET+SU+DPP4i	64069	316	116281	2.7 (2.4 to 3.0)	0.82 (0.64 to 1.07)	0.146	0.79 (0.61 to 1.02)	0.071
MET+SU+non-DPP4i	11930	69	20728	3.3 (2.6 to 4.2)	1.00 (reference)		1.00 (reference)	
Heart failure								
MET+SU+EVO	2198	47	4011	11.7 (8.6 to 15.6)	0.83 (0.61 to 1.13)	0.242	0.74 (0.55 to 1.01)	0.061
MET+SU+DPP4i	64069	1889	114503	16.5 (15.8 to 17.3)	1.17 (1.03 to 1.32)	0.015	1.07 (0.94 to 1.21)	0.303
MET+SU+non-DPP4i	11930	292	20446	14.3 (12.7 to 16.0)	1.00 (reference)		1.00 (reference)	
Cerebrovascular events								
MET+SU+EVO	2198	23	4040	5.7 (3.6 to 8.5)	0.98 (0.63 to 1.53)	0.933	0.96 (0.61 to 1.51)	0.865
MET+SU+DPP4i	64069	710	115880	6.1 (5.7 to 6.6)	1.07 (0.88 to 1.29)	0.526	1.00 (0.82 to 1.21)	0.957
MET+SU+non-DPP4i	11930	120	20685	5.8 (4.8 to 6.9)	1.00 (reference)		1.00 (reference)	

*Per 1000 person-years.
DPP4i, dipeptidyl peptidase-4 inhibitor; EVO, evogliptin; IR, incidence rate; MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea.

findings. Thus, we reaffirmed the cardiovascular safety of DPP4is as a class when used as dual therapy with MET by showing comparable findings to those of prior studies and providing novel evidence that MET+evogliptin is associated with a decreased risk of cardiovascular events by a greater magnitude. However, to determine potential cardiovascular effect of evogliptin, dedicated prospective clinical trials in high-risk patient populations are warranted.

Contrary to the dual OAD therapy, there is limited evidence available on the cardiovascular safety of triple therapy.[20 22] Although Jensen *et al* observed a reduced risk of MACE associated with MET+SU+DPP4i (HR 0.39, 95% CI 0.22 to 0.67), the reference group in the study was MET+SU, allowing bias by comparing patients with type 2 diabetes those are likely to be at different stages or severity of the disease (triple vs dual therapy).[20] Additionally, one study found no risk of MACE associated with MET+SU+DPP4i as compared with MET+SU+TZD (HR 1.02, 95% CI 0.92 to 1.12),[22] similar to our study finding of non-significant association between risk of cardiovascular events and MET+SU+DPP4i compared with MET+SU+non-DPP4i (HR 1.01, 95% CI 0.92 to 1.12). Interestingly, although DPP4is as a class had a non-significant effect, the risk of cardiovascular events was reduced with MET+SU+evogliptin (HR 0.76, 95% CI 0.59 to 0.97), which might be attributable to the structural heterogeneity within drugs of DPP4i class leading to varying cardiovascular effects.[28] Therefore, our findings suggest that evogliptin as triple therapy with MET and SU can offer potential cardiovascular benefits to patients with type 2 diabetes, unlike MET+SU+DPP4i representing a non-significant association.

The association between DPP4is and HF remains uncertain, as conflicting results have been reported in several randomised trials and observational studies.[29] The biological effects of DPP4i, including stimulation of cyclic adenosine monophosphate (cAMP) in cardiomyocytes and potentiation of stromal cell-derived factor-1, can possibly explain the associated elevated HF risk, by driving calcium overload affecting patients with reduced ejection fraction.[30–32] However, with no appropriate clinical consensus present on whether DPP4is used as combination therapy with other OAD(s) and its positive or negative contribution to the risk of HF, further investigations are needed. Available evidence on the risk of HF associated with DPP4i in combination with other OAD(s) are inconclusive. One study found that DPP4i users, either as monotherapy or dual therapy with MET, had a reduced risk of HF by 19% when compared with non-DPP4i initiators (HR 0.81, 95% CI 0.70 to 0.94).[33] Our findings were consistent by showing a significantly reduced risk of HF for MET+DPP4i (HR 0.88, 95% CI 0.84 to 0.93) and MET+evogliptin (HR 0.70, 95% CI 0.59 to 0.82), when compared with MET+non-DPP4i. Regarding triple OAD therapy, Ou *et al* reported no risk of HF associated with MET+SU+DPP4i (HR 1.12, 95% CI 0.94 to 1.33) when compared with MET+SU+TZD,[22] which was also

consistent with our finding for MET+SU+DPP4i (HR 1.07, 95% CI 0.94 to 1.21) and MET+SU+evogliptin (HR 0.74, 95% CI 0.55 to 1.01), as compared with MET+SU+non-DPP4i. Hence, our findings add to the existing literature that DPP4is as a class do not positively contribute to the risk of HF when used as dual therapy with MET or as triple therapy with MET+SU and present new real-world evidence that evogliptin has similar effects as other DPP4is.

The early separation of curves observed in our cumulative incidence curves (figure 2) raises questions about potential heterogeneity within the DPP4i class, which could contribute to differential cardiovascular effects. Recent evidence suggesting an attenuation effect of evogliptin on inflammation, fibrosis and calcification adds complexity to understanding its cardiovascular effects.[34] These findings emphasise the need for further research to elucidate the underlying mechanisms driving these differences.

Our study had several strengths. First, the selection of patients from a nationwide healthcare database with minimal exclusion criteria makes our findings generalisable to real-world patients with type 2 diabetes receiving combination OAD therapies. Second, the large sample size allowed for accurate estimation of treatment effects for rare outcomes, including MI, with sufficient statistical power. Third, we identified our study cohort as patients who newly initiated dual or triple OAD therapy from incident users of MET to improve comparison among those treated with combination OAD therapy owing to the inclusion of patients at similar stages of disease progression or severity and to avoid prevalent user bias.[35 36]

Our study had some limitations. First, laboratory or lifestyle data of haemoglobin A1c, body mass index, blood pressure, smoking status and cholesterol were unavailable for assessment from the HIRA database. However, we minimised residual confounding from such unmeasured covariates by adopting a new user design and adjusting for the duration of type 2 diabetes and various comorbidities and comedications. Second, the use of an intention-to-treat approach to ascertain exposure status could have led to potential exposure misclassification, which would have directed the effect estimate toward the null.[37] However, bias arising from this misclassification is likely to be minimal, as the maximum possible follow-up was 3 years; if any were present, it is likely to have been non-differential between exposure groups. Third, misclassification of diagnostic codes used to define the study outcomes was possible. However, any bias arising from this misclassification is likely to be minimal, as diagnostic codes recorded in the HIRA database were found to have an overall positive predictive value of 82.4% when compared with electronic medical records.[16] Moreover, we further minimised this bias by defining our outcomes as diagnoses that required hospital admission or were made in an emergency department. Furthermore, residual confounding from unaccounted or unmeasured

confounders is possible because of the inherent nature of observational studies.

This population-based cohort study using nationwide healthcare data from South Korea provides novel real-world evidence on the cardiovascular safety of evogliptin as either dual or triple therapy with MET and/or SU. It is important to note that our findings largely confirm previous research in this area, further supporting the cardiovascular safety profile of evogliptin in routine clinical practice. In addition to contributing to the growing body of evidence supporting the cardiovascular safety profile of DPP4is, findings from this study suggest that the combinations MET+evogliptin and MET+SU+evogliptin present no deleterious cardiovascular effects to patients with type 2 diabetes with inadequate glycaemic control after MET monotherapy and MET+SU dual therapy, but could alternatively offer potential cardiovascular benefits in this patient population.

Author affiliations
[1]School of Pharmacy, Sungkyunkwan University, Suwon, South Korea
[2]Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK
[3]Aston Pharmacy School, Aston University, Birmingham, UK
[4]Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea
[5]Departments of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[6]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada
[7]Division of Endocrinology and Metabolism, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, South Korea
[8]Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, South Korea

ORCID iDs
In-Sun Oh http://orcid.org/0000-0001-9878-4779
Sangmo Hong http://orcid.org/0000-0002-8535-0565
Ju-Young Shin http://orcid.org/0000-0003-1010-7525

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