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ORIGINAL ARTICLE

Empagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in routine care in East Asia: Results from the EMPRISE study

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ABSTRACT

Aims/Introduction: The EMPA-REG OUTCOME® trial demonstrated benefits of empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), on cardiovascular, renal outcomes and all-cause mortality in patients with type 2 diabetes and established cardiovascular disease. The EMPRISE study program evaluates how these effects translate in a broad population of patients with type 2 diabetes in routine clinical care across countries.

Materials and Methods: The study included patients ≥18 years with type 2 diabetes initiating empagliflozin or any dipeptidyl peptidase-4 inhibitors (DPP-4i) from large administrative databases in Japan, South Korea, and Taiwan. Propensity score-matched (1:1) 'as-treated' analyses comparing the risk of cardiovascular outcomes and all-cause mortality between empagliflozin and DPP-4i use were performed in each country. Pooled hazard ratios (pHR) with 95% confidence intervals (CI) were computed using random effects meta-analysis models comparing both empagliflozin and SGLT2i with DPP-4i use, respectively. Intention-to-treat and subgroup analyses in patients with/without cardiovascular disease and in patients receiving 10 mg empagliflozin were performed.

Results: The study included 28,712 and 70,233 matched patient pairs for empagliflozin/DPP-4i and SGLT2i/DPP-4i analyses, respectively. The risk of composite outcomes including (i) hospitalization for heart failure (HHF) and all-cause mortality was lower with empagliflozin (pHR 0.76, 95% CI 0.67–0.86) and SGLT2i (0.71, 0.65–0.77); (ii) combined myocardial infarction, stroke, and all-cause mortality was also lower with empagliflozin (0.74, 0.61–0.88) and SGLT2i (0.69, 0.60–0.78) compared to DPP-4i. The intention-to-treat and three subgroup analyses were consistent with results of the main analyses.

Conclusions: The results suggest that both empagliflozin and SGLT2i compared with DPP-4i are associated with a lower risk of cardiovascular events and all-cause mortality in routine clinical care in East Asia.

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†See Appendix S1S1.
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INTRODUCTION

The burden of the diabetes is growing in East Asia regions. In 2017, 37% of the global diabetes population lived in the Western Pacific Region (WPR)[1]; and projections from the International Diabetes Federation estimate that 212 million adults will be living with diabetes in the WPR by 2045[2]. Some large-scale studies showed that the leading cause of death was malignant neoplasm, which was more common than cardiovascular diseases in East Asian patients with diabetes[3-5]. However, cardiovascular deaths significantly increased in the East Asia region due to population aging[6]. A large pooled analysis of more than one million participants from Asian cohorts consisting of mostly (90%) East Asian populations demonstrated that cardiovascular disease is one of the major causes of premature mortality in people with diabetes[7].

With the introduction of the class of sodium-glucose cotransporter 2 inhibitors (SGLT2i), the results from the EMPA-REG OUTCOME® trial[8] have since been complemented and reinforced by other studies and in addition to antihyperglycemic effects have also demonstrated cardio-renal protective effects[9,10].

The EMpagliflozin CompaRative Effectiveness and SafEty (EMPRISE) study has conducted non-interventional studies of the effectiveness, safety, healthcare utilization, and cost of care of empagliflozin and comparator drugs in routine clinical practice in patients with type 2 diabetes in 11 countries in East Asia and Europe (EU PAS register number EUPAS27606), and also in the United States (US). The results from both the US and East Asia study showed that compared with sitagliptin/dipeptidyl peptidase-4 inhibitors (DPP-4i), initiation of empagliflozin was associated with a decrease in the risk of hospitalization for heart failure (HHF) in patients both with and without a history of cardiovascular disease[11,12]. In addition, empagliflozin was also associated with a lower risk of all-cause mortality (ACM) compared with DPP-4i in the EMPRISE East Asia[12].

To complement the evidence from EMPRISE studies in the USA[11] and East Asia[12], this study set out primarily to evaluate the risk of two composite outcomes: (i) hospitalization for heart failure and all-cause mortality, and (ii) myocardial infarction (MI), stroke, and all-cause mortality in addition to hospitalization for heart failure and all-cause mortality in East Asia in patients intiating empagliflozin compared with DPP-4i , as well as in patients intiating SGLT2i compared with DPP-4i. Additional individual outcomes of myocardial infarction, stroke, and coronary revascularization procedures were included in the analyses along with subgroup analyses.

MATERIALS AND METHODS

Study design

This was a retrospective cohort study based on administrative data in three East Asian countries: Japan, South Korea, and Taiwan[12]. Patients with type 2 diabetes newly initiating treatment with empagliflozin, any SGLT2i (canagliflozin, dapagliflozin, or empagliflozin), or any DPP-4i were analyzed separately in each country. After the country-level analyses, meta-analyses were performed. Main analyses used an 'as-treated' approach comparing empagliflozin use with DPP-4i use. A similar approach compared any SGLT2i use with DPP-4i use. Sensitivity analyses of empagliflozin vs DPP-4i used (i) an intention-to-treat (ITT) approach and, analyzed (ii) sub-populations of patients with and without cardiovascular history, and (iii) patients who initiated empagliflozin 10 mg.

Setting and data sources

The study period was 2014–2018 in Japan, 2016–2017 in South Korea, and 2016–2017 in Taiwan[12]. All variables were obtained from the following data sources: Medical Data Vision database in Japan[13], National Health Insurance Service database in South Korea[14], and National Health Insurance database, Death Registry, and Registry for Catastrophic Illness Patients in Taiwan[15]. The data sources from South Korea and Taiwan were nationwide, including information on inpatient and outpatient care. The Japanese data source covered acute phase hospitals data for 25.6 million people. Further details about the data sources are available in Appendix S2.

Participants

All patients with a new initiation of study drugs were identified separately in each country during the corresponding study periods (Figure 1). New initiation was defined as not having any SGLT2i or DPP-4i use during the preceding 12 months. The date of the new initiation of a study drug was defined as the index date (ID). All patients were required to have a diagnosis of type 2 diabetes recorded before the index date. Patients were excluded if they were <18 years at index date; diagnosed with type 1 diabetes, secondary diabetes, gestational diabetes or end-stage renal disease during the 12 months before the index date; had <12 months of data available before index date; or had incomplete data on age or sex at index date. The eligibility criteria are defined in more detail in Table S1. Patients were grouped into cohorts of new users of empagliflozin, any SGLT2i, or DPP-4i. The study population included both patients with and without cardiovascular diseases[8].

Follow-up time

The follow-up started on day 1 after the index date. End of follow-up for both the 'as-treated' and intention-to-treat approach was defined as the first occurrence of any of the following events: occurrence of the outcome being studied, death, or end of patient data availability. End of follow-up in the analyses of any SGLT2i use vs DDP-4i use followed the same rules. The following changes in use of the initial drug: discontinuation of the initial drug, switch to another study drug (any SGLT2i or any DPP-4i), initiating concomitant use of empagliflozin and a DPP-4i or a SGLT2i and a DDP-4i, or initiating concomitant use of two SGLT2i or two DPP-4i also led to end of follow-up in the 'as-treated' approach. Change of dose was not a censoring event.

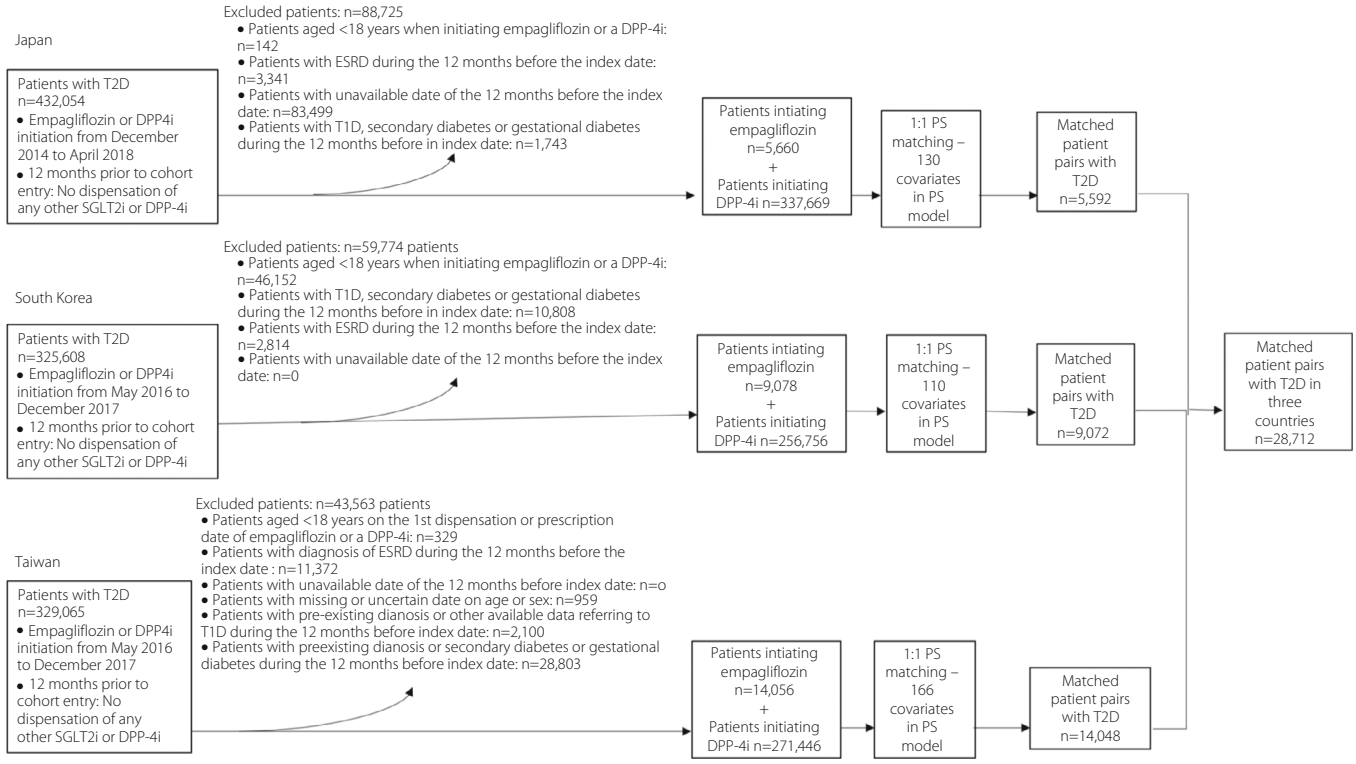

Figure 1 | Flow chart for cohorts for analyses of empagliflozin vs DPP-4i. DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; PS, propensity score; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

Data sources, variables, and measurements

Drug use, based on the Anatomical Therapeutic Chemical (ATC) classification system, was identified from prescription records in Japan and in South Korea and from records of dispensed drugs in Taiwan (Table S1). All prescribed/dispensed drugs during the study periods were considered. The duration of the drug exposure and date of treatment discontinuation were defined separately in each country based on the information available from prescription/dispensing records and dosages. Drug use was assumed to begin on the date of a prescription. A supply, indicating the duration of exposure after a prescription, was defined for each prescription based on the days' supply variable. The duration of the supply was derived from the dispensed amount and the daily dose, or the days' supply variable (if available). A grace period (GP) of 100% of the calculated duration of drug exposure was applied to address the uncertainty of the actual duration of exposure[16], except for Taiwan where a grace period of a maximum of 10 days was accepted before treatment was considered discontinued. Further, drug exposures overlapping in time were handled by shifting the subsequent exposure by a maximum of 14 days. Periods of overlapping supplies and grace periods were combined into exposure periods.

The outcomes of interest in this study included both composite (i) hospitalization for heart failure and all-cause mortality, and (ii) myocardial infarction, stroke, and all-cause mortality, and individual, hospitalization for heart failure, all-cause mortality, myocardial infarction, stroke, and coronary revascularization procedures outcomes. Outcomes were defined based on codes from the 9th (Taiwan only) and 10th revision of International Classification of Diseases (ICD), and disease codes in Japan in cases where ICD was not detailed enough. Code lists for each outcome are given in Tables S2 and S3.

These covariates included sociodemographic characteristics, lifestyle variables, diabetes complications, comorbidities, laboratory values, prior or concomitant use of other antidiabetic drugs, prior use of other drugs, healthcare resource utilization, and healthcare cost. Sociodemographic characteristics and lifestyle variables were measured at index date, whereas the other covariates were measured from the 12 months before the index date (inclusive).

Statistical methods

Empagliflozin use was compared with DPP-4i use in the main analyses, separately in each country. The main analyses were performed with an 'as-treated' approach to drug exposure in which all reasons for ending the follow-up were applicable. Sensitivity analyses were performed using an intention-to-treat approach in which empagliflozin use was compared with DPP-4i use, but follow-up was not censored at changes in drug use.

Three subgroups based on the 'as-treated' approach were investigated separately: (i) patients with previous cardiovascular diseases, (ii) patients without previous cardiovascular diseases, and (iii) patients initiating empagliflozin 10 mg.

In addition, analyses comparing the risk of all outcomes between any SGLT2i use and DPP-4i use were performed to investigate if the observations related to use of empagliflozin represent class effects.

Confounding was minimized with 1:1 propensity score (PS) matching considering all covariates. The propensity score was estimated with logistic regression. For Japan, South Korea and Taiwan, respectively, 130, 110, and 166 covariates were included in the PS model for comparison of empagliflozin use and DPP-4i use. Pairwise propensity score models were applied separately for the comparison between empagliflozin use and DPP-4i use, and any SGLT2i use and DPP-4i use. The nearest-neighbor algorithm, with calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score, was used in the matching. During the matching procedure, matched patients from the DPP-4i group were removed from the pool of eligible patients for future pairs. Thus, matching was performed without replacement, as inference becomes more complex when matching with replacement, because the matched controls are no longer independent[17]. The matching process was evaluated by observing the absolute standardized differences (ASD), and in the case of non-balance (ASD > 0.1)[18], the covariate was used in adjusting the outcome model[12]. Identification of the subgroups was done using the main study population before matching. After identifying each of the subgroups for patients initiating empagliflozin, the 1:1 propensity score matching was re-performed.

All outcomes were analyzed using a Cox proportional hazards regression model and the results were reported with hazard ratio (HR) and 95% confidence interval (CI). Each country reported hazard ratios with standard errors, and random effects meta-analysis model was used to pool the country-specific results after heterogeneity test was performed.

RESULTS

Participants

In total, 1,086,727 patients initiating empagliflozin or DPP-4i use without previous SGLT2i or DPP-4i use were identified in Japan, South Korea, and Taiwan during the study period (Figure 1). The main study population consisted of 28,712 empagliflozin/DPP-4i PS-matched patient pairs in total from the countries (5,592, 9,072, and 14,048 pairs in Japan, South Korea, and Taiwan, respectively) after applying the eligibility criteria. For the additional analyses of patients initiating any SGLT2i vs DPP-4i use, a total of 70,233 patient pairs were PS-matched (Figure S1).

Baseline characteristics

Most covariates were balanced after the propensity score matching, as indicated by the ASD values <0.1 (Table 1). Non-balanced variables included in Cox outcome models were for Japan: past use of glucagon-like peptide-1 receptor agonists and past use of second generation sulfonylureas; for Taiwan: total pharmacy costs, total pharmacy costs for antidiabetic drugs, and total pharmacy costs for non-antidiabetic drugs, and no non-balanced variables for South Korea. The median age among empagliflozin users in all countries was 56–60 years and the median age among DPP-4i users was 56–61 years. The majority of empagliflozin users (57.0–67.0%) and DPP-4i users (56.1–67.6%) were male. A history of cardiovascular diseases was found among 39%, 44%, and 28% of Japanese, South Korean, and Taiwanese patients, respectively. A minority of the study patients were diagnosed with diabetic complications (retinopathy, neuropathy, nephropathy). All Taiwanese patients had previously received a prescription for a glucose lowering drug (ATC codes A10A+A10B, excluding SGLT2i and DPP-4i) (Table 1), whereas the corresponding proportion was lower in Japan (21–22%). Most patients in South Korea (84–85%) used an antidiabetic drug other than SGLT2i and DPP-4i at ID. Most patients (59–97%) initiated empagliflozin treatment with 10 mg in accordance with prescribing information. Previous use of cardiovascular drugs varied between the countries: angiotensin II receptor blockers varied between 32% (Japan) and 52% (Taiwan), and use of statins ranged between 38% (Japan) and 68% (South Korea).

The average follow-up in the main analyses was 6.1 months among all patients initiating treatment with empagliflozin (varying from 5.8 months in Japan to 6.7 months in South Korea) and 5.9 months among all patients initiating treatment with a DPP-4i (varying from 5.4 months in Japan to 6.4 months in South Korea).

Comparison of empagliflozin vs DPP-4i

The risk of the composite outcome including hospitalization for heart failure and all-cause mortality (pooled HR [pHR] 0.76, 95% CI 0.67–0.86), and the composite outcome including myocardial infarction, stroke, and all-cause mortality (pHR 0.74, 95% CI 0.61–0.88) was lower for empagliflozin compared with DDP-4i (Table 2).

Myocardial infarction was the least frequently observed outcome, with 60 events among empagliflozin and 66 events among DPP-4i users in the three countries (Table 2). The event with the highest event count was the composite outcome including hospitalization for heart failure and all-cause mortality (458 events during empagliflozin use and 588 events during DPP-4i use in the countries) (Table 2). The pooled incidence rates (Table 2) indicated that most outcomes were less frequent among empagliflozin users in comparison with DPP-4i users. For example, the incidence rate of hospitalization for heart failure was 25.39 and 31.65 events/1,000 person-years among empagliflozin and DPP-4i users, respectively. Thus, empagliflozin use was associated with a lower risk of the separate cardiovascular outcomes: hospitalization for heart failure (pHR 0.82, 95% CI 0.71–0.94), all-cause mortality (pHR 0.64, 95% CI 0.50–0.81), and coronary revascularization procedures (pHR

Table 1 | Baseline characteristics in main analysis after propensity score matching

Characteristic	Japan			South Korea			Taiwan		
	Empagliflozin (*n* = 5,592)	DPP-4i (*n* = 5,592)	ASD†	Empagliflozin (*n* = 9,072)	DPP-4i (*n* = 9,072)	ASD†	Empagliflozin (*n* = 14,048)	DPP-4i (*n* = 14,048)	ASD†
Age (years)									
At ID, median (IQR)	60 (49.0–69.0)	61 (49.0–69.0)	0.00	56 (48.0–64.0)	56 (48.0–64.0)	0.00	57.67 (48.6–65.5)	57.29 (48.0–65.6)	0.00
Age (years), *n* (%)									
18–54	2,047 (36.6)	2,049 (36.6)		3,941 (43.4)	3,944 (43.5)		5,882 (41.9)	6,076 (43.3)	
55–64	1,336 (23.9)	1,278 (22.9)		2,915 (32.1)	2,898 (31.9)		4,454 (31.7)	4,228 (30.1)	
65–74	1,458 (26.1)	1,501 (26.8)		1,570 (17.3)	1,585 (17.5)		2,708 (19.3)	2,593 (18.5)	
75+	751 (13.4)	764 (13.7)		646 (7.1)	645 (7.1)		1,004 (7.1)	1,151 (8.2)	
Sex									
Male, *n* (%)	3,747 (67.0)	3,779 (67.6)	0.01	5,172 (57.0)	5,085 (56.1)	0.02	8,165 (58.1)	8,194 (58.3)	0.00
Calendar year of ID			0.00			0.01			0.01
2014, *n* (%)	NA	NA		NA	NA		NA	NA	
2015, *n* (%)	50 (0.9)	50 (0.9)		NA	NA		NA	NA	
2016, *n* (%)	1,344 (24.0)	1,342 (24.0)		2,241 (24.7)	2,218 (24.4)		4,826 (34.4)	4,786 (34.1)	
2017, *n* (%)	3,049 (54.5)	3,052 (54.6)		6,831 (75.3)	6,854 (75.6)		9,222 (65.6)	9,262 (65.9)	
2018, *n* (%)	1,149 (20.5)	1,148 (20.5)		NA	NA		NA	NA	
Selection of previous diseases (12 months before ID)‡									
Atrial fibrillation	530 (9.5)	584 (10.4)	0.03	271 (3.0)	292 (3.2)	0.01	310 (2.2)	341 (2.4)	0.01
CV history§	2,150 (38.5)	2,182 (39.0)	0.01	3,985 (43.9)	3,939 (43.4)	0.01	3,892 (27.7)	3,903 (27.8)	0.00
Congestive heart failure	1,520 (27.2)	1,562 (27.9)	0.02	707 (7.8)	704 (7.8)	0.00	863 (6.1)	895 (6.4)	0.01
Ischemic heart disease	1,813 (32.4)	1,789 (32.0)	0.01	1,965 (21.7)	1,979 (21.8)	0.00	2,806 (20.0)	2,796 (19.9)	0.00
MI (acute)‡	383 (6.8)	410 (7.3)	0.02	327 (3.6)	333 (3.7)	0.00	390 (2.8)	365 (2.6)	0.01
MI (old)‡	396 (7.1)	379 (6.8)	0.01	134 (1.5)	146 (1.6)	0.01	189 (1.3)	208 (1.5)	0.01
Stroke (ischemic)	184 (3.3)	177 (3.2)	0.01	460 (5.1)	456 (5.0)	0.00	504 (3.6)	529 (3.8)	0.01
Stroke (hemorrhagic)	39 (0.7)	37 (0.7)	0.00	64 (0.7)	76 (0.8)	0.02	142 (1.0)	147 (1.0)	0.00
Previous cardiac procedure‡	409 (7.3)	443 (7.9)	0.02	206 (2.3)	205 (2.3)	0.00	459 (3.3)	484 (3.4)	0.01
Chronic kidney disease	248 (4.4)	274 (4.9)	0.02	144 (1.6)	150 (1.7)	0.01	790 (5.6)	767 (5.5)	0.01
Diabetic retinopathy	819 (14.6)	738 (13.2)	0.04	1,791 (19.7)	1,760 (19.4)	0.01	1,364 (9.7)	1,347 (9.6)	0.00
Diabetic neuropathy	175 (3.1)	196 (3.5)	0.02	1,522 (16.8)	1,497 (16.5)	0.01	942 (6.7)	946 (6.7)	0.00
Diabetic nephropathy	432 (7.7)	423 (7.6)	0.01	1,294 (14.3)	1,310 (14.4)	0.01	2,754 (19.6)	2,721 (19.4)	0.01
Total number of distinct diagnosis codes, median (IQR)	8 (5.0–12.0)	8 (5.0–12.0)	NA	18 (11.0–27.0)	18 (12.0–27.0)	NA	2 (1.0–3.0)	2 (1.0–3.0)	NA
Description of baseline drug use									
Any other antidiabetic drugs¶††	1,233 (22.0)	1,160 (20.7)	0.06	7,732 (85.2)	7,627 (84.1)	0.02	14,048 (100.0)	14,048 (100.0)	0.00
Metformin‡‡	1,864 (33.3)	1,762 (31.5)	0.04	7,779 (85.7)	7,806 (86.0)	0.01	10,408 (74.1)	10,329 (73.5)	0.02
Sulfonylureas 2nd generation§§	567 (10.1)	386 (6.9)	0.12	3,365 (37.1)	3,326 (36.7)	0.00	5,013 (35.7)	5,022 (35.7)	0.00
Glucagon-like peptide-1 receptor agonists§§	673 (12.0)	501 (9.0)	0.10	39 (0.4)	31 (0.3)	0.01	272 (1.9)	221 (1.6)	0.03
Thiazolidinediones§§	345 (6.2)	268 (4.8)	0.06	915 (10.1)	914 (10.1)	0.00	2,340 (16.7)	2,379 (16.9)	0.01
Insulin§§	1,844 (33.0)	1,768 (31.6)	0.03	1,269 (14.0)	1,272 (14.0)	0.01	3,854 (27.4)	3,828 (27.2)	0.00
Alpha-glucosidase inhibitors§§	436 (7.8)	360 (6.4)	0.05	347 (3.8)	346 (3.8)	0.00	1,889 (13.4)	1,931 (13.7)	0.01

Table 1. (*Continued*)

Characteristic	Japan			South Korea			Taiwan		
	Empagliflozin (*n* = 5,592)	DPP-4i (*n* = 5,592)	ASD†	Empagliflozin (*n* = 9,072)	DPP-4i (*n* = 9,072)	ASD†	Empagliflozin (*n* = 14,048)	DPP-4i (*n* = 14,048)	ASD†
Angiotensin II receptor blockers	1,788 (32.0)	1,718 (30.7)	0.03	3,958 (43.6)	3,958 (43.6)	0.00	7,336 (52.2)	7,286 (51.9)	0.01
Beta-blockers	1,309 (23.4)	1,353 (24.2)	0.02	1,406 (15.5)	1,400 (15.4)	0.00	4,754 (33.8)	4,762 (33.9)	0.00
Calcium channel blockers	1,592 (28.5)	1,514 (27.1)	0.03	1,522 (16.8)	1,493 (16.5)	0.01	6,171 (43.9)	6,112 (43.5)	0.01
Nitrates	960 (17.2)	1,026 (18.3)	0.03	645 (7.1)	667 (7.4)	0.01	1,736 (12.40)	1,680 (12.0)	0.01
Statins	2,154 (38.5)	2,139 (38.3)	0.01	6,176 (68.1)	6,140 (67.7)	0.01	9,174 (65.3)	9,197 (65.5)	0.00
Antiplatelets	1,496 (26.8)	1,504 (26.9)	0.00	3,319 (36.6)	3,282 (36.2)	0.01	4,643 (33.1)	4,599 (32.7)	0.01
Initial dosage of empagliflozin									
Initiating treatment with empagliflozin 10 mg	5,432 (97.1)	NA	NA	7,760 (85.5)	NA	NA	8,339 (59.4)	NA	NA

More details on baseline characteristics are found in Table S2 in our previous publication.[12] †An ASD of a covariate of <0.1 between treatment groups in this study indicates a negligible difference in the mean or prevalence of the covariate. It was decided *a priori*, that if ASD > 0.1 existed for some covariates after matching, they would be used in post matching adjustments (i.e., the analyses would be adjusted for PS-variables with ASD >0.1). This turned out not to be the case. ‡The following conditions were considered: hypertension, hyperlipidemia, ischemic heart disease, myocardial infarction (acute or old), acute coronary syndrome or unstable angina, stable angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, other atherosclerosis, previous cardiac procedure, history of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), any stroke, ischemic stroke (with and without mention of cerebral infarction), hemorrhagic stroke, transient cerebral ischemia and related syndromes, other cerebrovascular disease, late effects of cerebrovascular disease, cerebrovascular procedure, CHF, peripheral vascular disease or surgery, atrial fibrillation, other cardiac dysrhythmia, cardiac conduction disorders, other cardiovascular disease, and edema. §Information on CV history was not used in the PS matching, but only used for defining subgroups. ¶Any other diabetes drug comprises the ATC group A10 excluding SGLT2i and DPP-4i. ††Definition in Japan: Prescription at index date or during 12 months prior with supply overlap with index date; Definition in South Korea: Prescription of any antidiabetic drugs in the index date; Definition in Taiwan: Prescription of any antidiabetic drugs during 365 days before the index date. ‡‡Fixed-dose combinations with metformin and the study drugs or other marketed SGLT2i or DPP-4i are excluded from the metformin group. Definition in Japan: At least one prescription of metformin 12 months prior to index date regardless of use at index date; Definition in South Korea and Taiwan: Metformin prescription in the index date or during 356 days before the index date. §§Definition in Japan: At least one prescription of drug 12 months prior to index date regardless of use at index date; Definition in South Korea: Prescription during 12 months prior to or at index date; Definition in Taiwan: Drug use during 365 days before the index date. ASD, absolute standardized difference; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; ID, index date; IQR, interquartile range; MI, myocardial infarction; NA, not applicable.

Table 2 | Country-level incidence rates and pooled hazard ratios for all outcomes in the main† analyses

Outcome	Country	Empagliflozin (n = 28,712) *N* events (IR per 1,000 person-years)	DPP-4i (n = 28,712) *N* events (IR per 1,000 person-years)	Pooled‡ HR (95% CI)	Heterogeneity test I^2 – Overall effect test
Composite outcome including HHF§ and ACM	Japan	193 (72.24)	239 (98.92)	0.76 (0.67, 0.86)	$I^2 \leq 0.005\%$
	South Korea	88 (17.45)	125 (25.90)		$Z = -4.423$
	Taiwan	177 (25.67)	224 (33.32)		P-value < 0.005
	Pooled	458 (31.35)	588 (42.1)		
Composite outcome including MI, stroke, and ACM	Japan	42 (15.39)	48 (19.31)	0.74 (0.61, 0.88)	$I^2 = 17.34\%$
	South Korea	79 (15.66)	123 (25.49)		$Z = -3.349$
	Taiwan	150 (21.73)	184 (27.31)		P-value < 0.005
	Pooled	271 (18.47)	355 (25.27)		
HHF§	Japan	181 (67.75)	216 (89.40)	0.82 (0.71, 0.94)	$I^2 \leq 0.005\%$
	South Korea	77 (15.27)	100 (20.72)		$Z = -2.845$
	Taiwan	113 (16.39)	126 (18.74)		P-value < 0.005
	Pooled	371 (25.39)	442 (31.65)		
ACM	Japan	20 (7.31)	30 (12.05)	0.64 (0.50, 0.81)	$I^2 \leq 0.005\%$
	South Korea	18 (3.55)	33 (6.80)		$Z = -3.697$
	Taiwan	76 (10.97)	110 (16.26)		P-value < 0.005
	Pooled	114 (7.74)	173 (12.26)		
MI	Japan	13 (4.76)	9 (3.62)	0.89 (0.62, 1.26)	$I^2 \leq 0.005\%$
	South Korea	24 (4.75)	30 (6.19)		$Z = -0.656$
	Taiwan	23 (3.32)	27 (4.00)		P-value = 0.512
	Pooled	60 (4.08)	66 (4.68)		
Stroke	Japan	12 (4.39)	13 (5.23)	0.77 (0.55, 1.09)	$I^2 = 36.91\%$
	South Korea	43 (8.51)	68 (14.06)		$Z = -1.47$
	Taiwan	53 (7.67)	53 (7.86)		P-value = 0.142
	Pooled	108 (7.35)	134 (9.52)		
Coronary revascularization procedure	Japan	158 (58.92)	206 (84.89)	0.81 (0.69, 0.95)	$I^2 = 12.22\%$
	South Korea	23 (4.55)	33 (6.81)		$Z = -2.568$
	Taiwan	140 (20.34)	152 (22.66)		P-value = 0.010
	Pooled	321 (21.96)	391 (27.97)		

†'As-treated' analyses, using a grace period of 100%. Empagliflozin was compared with DPP-4i. ‡Pooled HR from random effects meta-analysis model comparing empagliflozin with DPP-4i. §Defined as having heart failure diagnosis in any position of hospitalization. ACM, all-cause mortality; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalization for heart failure; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction.

0.81, 95% CI 0.69–0.95), in comparison with DPP-4i use (Table 2). No significant difference was observed in risk of stroke (pHR 0.77, 95% CI 0.55–1.09) with moderate heterogeneity (I^2 = 36.91%) or myocardial infarction (pHR 0.89, 95% CI 0.62–1.26) between empagliflozin use and DPP-4i use.

Comparison of SGLT2i vs DPP-4i

Similarly, SGLT2i use was associated with a lower risk of the composite outcomes (including HHF and ACM: pHR 0.71, 95% CI 0.65–0.77; including myocardial infarction, stroke, and ACM: pHR 0.69, 95% CI 0.60–0.78), and separate cardiovascular outcomes: hospitalization for heart failure (pHR 0.76, 95% CI 0.67–0.86) and all-cause mortality (pHR 0.60, 95% CI 0.51–0.70) in comparison with DPP-4i use (Table 3). Risk of myocardial infarction, stroke, or coronary revascularization procedures was not significantly lower for SGLT2i use compared with DPP-4i use (Table 3).

Sensitivity and subgroup analyses of empagliflozin vs DPP-4i

A lower risk for empagliflozin users vs DPP-4i users of the composite outcome including hospitalization for heart failure and all-cause mortality was observed in the intention-to-treat analyses (pHR 0.78, 95% CI 0.66–0.92), and in the patients with and without cardiovascular disease (pHR 0.82, 95% CI 0.72–0.94 and pHR 0.64, 95% CI 0.49–0.85, respectively), and in patients initiating 10 mg empagliflozin treatment (pHR 0.82,

Table 3 | Pooled incidence rates and pooled hazard ratios for all outcomes in the additional analyses[†] comparing SGLT2i users with DPP-4i users

Outcome	Country	SGLT2i (n = 70,233) N events (IR per 1,000 person-years)	DPP-4i (n = 70,233) N events (IR per 1,000 person-years)	Pooled[‡] HR (95% CI)	Heterogeneity test I^2 – Overall effect test
Composite outcome including HHF[§] and ACM	Japan	360 (52.42)	498 (74.39)	0.71 (0.65–0.77)	$I^2 \leq 0.005\%$
	South Korea	209 (15.12)	300 (22.94)		$Z = -7.962$
	Taiwan	348 (20.01)	414 (23.75)		P-value < 0.005
	Pooled	917 (24.08)	1,212 (32.58)		
Composite outcome including MI, stroke, and ACM	Japan	95 (13.64)	127 (18.55)	0.69 (0.60–0.78)	$I^2 = 34.11\%$
	South Korea	204 (14.75)	321 (24.59)		$Z = -5.561$
	Taiwan	305 (17.52)	414 (23.71)		P-value < 0.005
	Pooled	604 (15.81)	862 (23.07)		
HHF[§]	Japan	330 (48.05)	451 (67.37)	0.76 (0.67–0.86)	$I^2 = 31.47\%$
	South Korea	178 (12.87)	245 (18.74)		$Z = -4.534$
	Taiwan	225 (12.94)	259 (14.86)		P-value < 0.005
	Pooled	733 (19.25)	955 (25.67)		
ACM	Japan	43 (6.16)	61 (8.88)	0.60 (0.51–0.70)	$I^2 \leq 0.005\%$
	South Korea	41 (2.95)	65 (4.94)		$Z = -6.189$
	Taiwan	317 (18.16)	595 (33.96)		P-value < 0.005
	Pooled	401 (10.47)	721 (19.20)		
MI	Japan	28 (4.02)	22 (3.21)	0.82 (0.62–1.08)	$I^2 = 28.48\%$
	South Korea	70 (5.05)	86 (6.55)		$Z = -1.418$
	Taiwan	44 (2.52)	66 (3.77)		P-value = 0.156
	Pooled	142 (3.71)	174 (4.64)		
Stroke	Japan	26 (3.73)	50 (7.29)	0.69 (0.42–1.14)	$I^2 = 87.38\%$
	South Korea	107 (7.73)	187 (14.29)		$Z = -1.46$
	Taiwan	118 (6.77)	104 (5.97)		P-value = 0.144
	Pooled	251 (6.56)	341 (9.13)		
Coronary revascularization procedure	Japan	268 (38.88)	383 (56.99)	0.80 (0.59–1.07)	$I^2 = 85.03\%$
	South Korea	66 (4.77)	97 (7.39)		$Z = -1.495$
	Taiwan	296 (17.05)	280 (16.08)		P-value = 0.135
	Pooled	630 (16.54)	760 (20.40)		

[†]'As-treated' analyses, using a grace period of 100%. SGLT2i was compared with DPP-4i. [‡]Pooled hazard ratio from random effects meta-analysis model comparing SGLT2i with DPP-4i. [§]Defined as having heart failure diagnosis in any position of hospitalization. ACM, all-cause mortality; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, broad definition for hospitalization for heart failure; HR, hazard ratio; IR, incidence rate per 1,000 person-years; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

95% CI 0.71–0.94) (Table 4) was in line with the main results (Table 2). Similarly, the results for the other composite outcome including myocardial infarction, stroke, and all-cause mortality were consistent across the analyses, including the intention-to-treat analyses (pHR 0.75, 95% CI 0.60–0.94) and the patients without cardiovascular disease (pHR 0.67, 95% CI 0.52–0.87) (Table 4). Similar to the main analyses, the hazard ratio estimates for myocardial infarction were statistically insignificant in all sensitivity analyses (Table 4). The risk of stroke for empagliflozin users was significantly lower in the intention-to-treat analyses and in patients initiating 10 mg empagliflozin treatment (Table 4). In the intention-to-treat analyses and in patients initiating 10 mg empagliflozin treatment, the risk of coronary revascularization procedure was significantly lower for users of empagliflozin (pHR 0.84, 95% CI 0.72–0.98 and pHR 0.76, 95% CI 0.62–0.92) (Table 4).

DISCUSSION

Cardiovascular disease is one of major causes of death in patients with diabetes and is predicted to increase in the East Asia region[7,19]. Given the increased importance of cardiovascular disease in the region we assessed the clinical effectiveness of empagliflozin on various cardiovascular outcomes in diverse patients with type 2 diabetes in East Asia. Our study showed that both empagliflozin and SGLT2i compared with DPP-4i are associated with a reduced risk of composite cardiovascular

Table 4 | Pooled incidence rates and pooled hazard ratios[†] for all outcomes in the sensitivity and subgroup analyses

Outcome	Empagliflozin *N* events (IR per 1,000 person-years)	DPP-4i *N* events (IR per 1,000 person-years)	Pooled[†] HR (95% CI)
Sensitivity analyses using an ITT approach[‡] (*n* = 28,712 matched patient pairs)			
Composite outcome including HHF[§] and ACM	791 (37.37)	1,033 (46.65)	0.78 (0.66–0.92)
Composite outcome including MI, stroke, and ACM	467 (21.86)	675 (30.12)	0.75 (0.60–0.94)
HHF[§]	600 (28.35)	724 (32.69)	0.85 (0.76–0.95)
ACM	253 (11.77)	386 (17.09)	0.72 (0.51 1.01)
MI	90 (4.20)	107 (4.75)	0.88 (0.66–1.17)
Stroke	153 (7.15)	221 (9.84)	0.72 (0.59–0.89)
Coronary revascularization procedure	469 (22.13)	570 (25.66)	0.84 (0.72–0.98)
Subgroup analyses[¶] among patients with CV history (9,485 matched patient pairs)			
Composite outcome including HHF[§] and ACM	369 (80.30)	465 (104.42)	0.82 (0.72–0.94)
Composite outcome including MI, stroke, and ACM	168 (35.98)	207 (45.55)	0.79 (0.62–1.00)
HHF[§]	320 (69.64)	394 (88.48)	0.82 (0.71–0.96)
ACM	73 (15.55)	98 (21.39)	0.82 (0.60–1.11)
MI	41 (8.75)	49 (10.74)	0.93 (0.61–1.42)
Stroke	61 (13.04)	67 (14.68)	0.69 (0.46–1.06)
Coronary revascularization procedure	267 (57.93)	325 (72.75)	0.83 (0.58–1.19)
Subgroup analyses[¶] among patients without CV history (19,220 matched patient pairs)			
Composite outcome including HHF[§] and ACM	87 (8.69)	135 (14.06)	0.64 (0.49–0.85)
Composite outcome including MI, stroke, and ACM	103 (10.30)	158 (16.48)	0.67 (0.52–0.87)
HHF[§]	49 (4.90)	66 (6.87)	0.72 (0.48–1.08)
ACM	41 (4.09)	74 (7.69)	0.60 (0.40–0.89)
MI	19 (1.90)	29 (3.02)	0.59 (0.32–1.11)
Stroke	47 (4.70)	62 (6.46)	0.78 (0.45–1.34)
Coronary revascularization procedure	53 (5.30)	70 (7.29)	0.71 (0.49–1.01)
Subgroup analyses[¶] among patients who initiate empagliflozin use with 10 mg (21,542 matched patient pairs)			
Composite outcome including HHF[§] and ACM	377 (34.72)	464 (44.04)	0.82 (0.71–0.94)
Composite outcome including MI, stroke, and ACM	208 (19.05)	253 (23.84)	0.82 (0.65–1.03)
HHF[§]	309 (28.46)	373 (35.40)	0.83 (0.70–0.99)
ACM	92 (8.40)	111 (10.41)	0.85 (0.64–1.12)
MI	51 (4.66)	51 (4.79)	1.14 (0.53–2.45)
Stroke	75 (6.86)	104 (9.78)	0.70 (0.52–0.95)
Coronary revascularization procedure[††]	170 (24.22)	225 (33.49)	0.76 (0.62–0.92)

[†]Pooled hazard ratio from random effects meta-analysis model comparing empagliflozin with DPP-4i. [‡]Intention-to-treat analyses. Empagliflozin was compared with DPP-4i. [§]Defined as having heart failure diagnosis in any position of hospitalization. [¶]As-treated analyses, using a grace period of 100%. Empagliflozin was compared with DPP-4i. [††]Results available from Japan and South Korea only. This analysis included 5,441 matched patient pairs. ACM, all-cause mortality; AT, as-treated; CI, confidence interval; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalization for heart failure; HR, hazard ratio; IR, incidence rate; ITT, intention-to-treat; MI, myocardial infarction.

outcomes: (i) hospitalization for heart failure and all-cause mortality, (ii) myocardial infarction, stroke, and all-cause mortality, and the individual outcomes of hospitalization for heart failure, all-cause mortality, and coronary revascularization procedure in routine clinical care. It is consistent with the EMPA-REG OUTCOME trial[8,20] and complement the trial in type 2 diabetes patients with or without history of cardiovascular disease in routine clinical care in East Asia. This study was consistent with the evidence related to empagliflozin having a lower risk of hospitalization for heart failure and all-cause mortality in comparison with DPP-4i use in patients with type 2 diabetes both with and without a history of cardiovascular disease in the USA[11].

To our best knowledge, only CVD-REAL2[21] and this EMPRISE East Asia study evaluated the impact of SGLT2i class on stroke and myocardial infarction compared with DPP-4i in East Asian countries in a real-world setting. More covariates were used for propensity score matching in EMPRISE East Asia compared to CVD-REAL2 (EMPRISE East Asia: 110–166 vs CVD-REAL2: 50). In this study, no difference in risk was

observed between empagliflozin/SGLT2i for stroke and myocardial infarction although some differences were observed in sensitivity analyses and between the three countries as shown in heterogeneity. The CVD-REAL2 study concluded the modest benefit of SGLT2i on stroke and myocardial infarction compared with DPP-4i in the overall population[21], however, the magnitude of hazard ratios for stroke and myocardial infarction differed across the three countries. These results from two independent studies suggest the benefit of SGLT2i on stroke and myocardial infarction is not conclusive, which contrasts with observations for hospitalization for heart failure and all-cause mortality which were consistent across all three countries[12,21,22].

Previous studies showed a poorer prognosis after coronary revascularization in patients with diabetes than without diabetes[23]. This EMPRISE study provides the first report which assessed coronary revascularization in East Asian patients with type 2 diabetes in real-world setting. In this study, empagliflozin was significantly associated with lower risk of coronary revascularization procedure compared with DPP-4i. SGLT2i showed a trend similar to empagliflozin for coronary revascularization procedure although it was not statistically significant.

As consistent with previous EMPRISE studies, the results were consistent between patients with or without history of cardiovascular disease. The results of the sensitivity analyses with the intention-to-treat approach were in line with the main analysis using the 'as-treated' approach indicating robustness of results, as an intention-to-treat approach will not censor noncompliant users and is expected to provide a more conservative estimate compared with the 'as-treated' approach. The results from 10 mg subgroup analyses were consistent with the main analyses since most patients initiated with empagliflozin 10 mg. The cardiovascular benefit was consistent between empagliflozin 10 and 25 mg in the EMPA-REG OUTCOME trial and confirmed with empagliflozin 10 mg in patients with chronic heart failure with reduced and preserved ejection fraction irrespective of diabetes status at baseline in the EMPEROR-Reduced and -Preserved trials[24,25], and in patients with chronic kidney disease in EMPA-KIDNEY trial[26].

This study used nationwide populations from three East Asian countries, with a total sample size of 28,712 and 70,233 paired patients in empagliflozin vs DPP-4i and SGLT2i vs DPP-4i, respectively. The study used administrative data, ensuring that the results represent routine clinical care. Further, unlike in the EMPA-REG OUTCOME trial, the study population in this study included both patients with and without previous cardiovascular disease. A strength of the study was to include sensitivity analyses to compare the effect of using an 'as-treated' approach compared with an intention-to-treat approach, and to investigate subgroups of patients with and without a history of cardiovascular disease. This study showed some variation in results from the three countries. It is most likely due to different populations among databases e.g., acute hospitals in Japan vs national database in South Korea and Taiwan. There are differences in healthcare system and patient management among the countries. It should be noted that extreme cases are excluded as a result of propensity score matching, which may reduce generalizability.

Confounding is a relevant concern in all observational studies. Drugs that are used in similar phases of type 2 diabetes[27-29](i.e., empagliflozin, other SGLT2i, and DPP-4i) were compared in this study to minimize confounding[29]. Risk for immortal time bias was also reduced with the new user design[31]. Further, a wide range of variables was available from administrative registers, enabling extensive confounding control with propensity score methodology. There are some potential limitations of this study that should be considered when interpreting results. Previous exposure to any antidiabetic drugs during 12 months prior to the index date was included as a variable in the propensity score matching but did not distinguish between dose or duration of drug exposure with risk of immortal time bias[32]. Furthermore, information on all relevant confounders was not available, such as the severity, duration of type 2 diabetes or glycated hemoglobin levels at the index date. This may have resulted in residual confounding. The follow-up period was relatively short (mean 5.7–6.8 months across the countries; median 3.2–5.7 months). Drug use information was based on records of prescribed or dispensed drugs and thus the actual adherence to drug use remains unknown.

The results of this study suggest an association between initiation of empagliflozin and a lower risk of the composite outcome of hospitalization for heart failure and all-cause mortality, and composite outcome of myocardial infarction, stroke, and all-cause mortality, and the individual outcomes of hospitalization for heart failure, all-cause mortality, coronary revascularization procedure when compared with DPP-4i among East Asian patients with type 2 diabetes. These results are in line with previous studies performed in other populations. The analyses of the class of SGLT2i compared with DPP-4i were similar to findings for analyses of empagliflozin. No substantial differences were observed in risk for examined outcomes between patients with or without history of cardiovascular disease.

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SUPPORTING INFORMATION

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

Figure S1 | Flowchart for cohorts for analyses of any SGLT2i vs DPP-4i.

Table S1 | Definitions used for eligibility criteria

Table S2 | Diagnoses used in outcome definitions

Table S3 | Procedures used to identify outcomes

Appendix S1 | EMPRISE East Asia study group composition.

Appendix S2 | Description of the data sources.