

Healthcare resource utilization in patients treated with empagliflozin in East Asia

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Keywords

Asia, Health resources, Sodium-glucose co-transporter 2 inhibitors

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ABSTRACT

Aims/Introduction: We investigated the utilization of healthcare resources in patients with type 2 diabetes treated with empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, versus dipeptidyl peptidase-4 (DPP-4) inhibitors in clinical practice in Japan, South Korea, and Taiwan.

Materials and Methods: We analyzed the Japanese Medical Data Vision database (December 2014–April 2018), the South Korean National Health Information Database, and the Taiwanese National Health Insurance claims database (both May 2016–December 2017). Patients with type 2 diabetes starting empagliflozin, 10 or 25 mg, or a DPP-4 inhibitor were matched 1:1 via propensity scores (PS). We compared inpatient care needs, emergency room (ER) visits, and outpatient visits between the treatment groups using Poisson regression and Cox proportional hazards models, pooled across countries by random-effects meta-analysis.

Results: We identified 28,712 pairs of PS-matched patients; the mean follow-up was 5.7–6.8 months. Empagliflozin-treated patients had a 27% lower risk of all-cause hospitalization compared with DPP-4 inhibitor-treated patients (rate ratio [RR] 0.73, 95% CI 0.67–0.79), and 23% reduced risk for first hospitalization (hazard ratio 0.77, 95% CI 0.73–0.81). The risk for an ER visit was 12% lower with empagliflozin than with DPP-4 inhibitors (RR 0.88, 95% CI 0.83–0.94) while the risk for outpatient visit was 4% lower (RR 0.96, 95% CI 0.96–0.97). These findings were generally consistent across countries, regardless of baseline cardiovascular disease, and in the subgroup starting empagliflozin with the 10 mg dose.

Conclusions: Empagliflozin treatment was associated with lower inpatient care needs and other healthcare resource utilization than DPP-4 inhibitors in routine clinical practice in East Asia in this study.

INTRODUCTION

Asia is becoming the epicenter of the global diabetes epidemic. The Western Pacific region (including East Asia) currently has

an estimated 163 million people with diabetes (35% of all global cases), the vast majority of whom have type 2 diabetes¹. This patient population is expected to increase to approximately 212 million by 2045¹. Type 2 diabetes generally imposes a substantial burden on healthcare systems globally as it results in a high demand for healthcare resources and high associated costs^{1–4}, and East Asia is no exception^{5–13}. Hospital inpatient care is the

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largest component of medical expenditure in type 2 diabetes, with one study estimating that hospitalization accounted for 43% of total medical costs¹⁴. People with type 2 diabetes often require more inpatient care than those without the disease due to the high burden of diabetic comorbidities and complications. A recent, large study in the Asia-Pacific region that explored the impact of diabetes on hospitalization found that individuals with diabetes were significantly more likely to have a hospitalization (for any reason) than those without this disease and spent significantly more days in hospital¹⁵.

Empagliflozin is a selective inhibitor of the sodium-glucose co-transporter-2 (SGLT2) protein¹⁶ that is widely approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. In the landmark EMPA-REG OUTCOME trial, empagliflozin reduced cardiorenal events and all-cause hospitalizations in patients with type 2 diabetes and established cardiovascular disease (CVD)^{17,18}. In pooled analyses of Asian patients from clinical trials, including East Asians, empagliflozin monotherapy or add-on therapy improved glycemic control, reduced body weight and blood pressure, and was well tolerated^{19,20}. Furthermore, subgroup analyses of EMPA-REG OUTCOME suggest that the reduction in cardiorenal events and the need for inpatient care with empagliflozin in the overall trial cohort was consistent in the subgroup of Asian patients^{21–23}.

The EMPagliflozin CompaRative EffectIveness and SafEty (EMPRISE) study program included non-interventional studies of the effectiveness, safety, healthcare utilization, and cost of empagliflozin in routine clinical practice in patients with type 2 diabetes in East Asia, Europe, and the United States (US)²⁴. In the US study, interim analyses showed that patients treated with empagliflozin had a lower rate of healthcare utilization including all-cause hospitalization, emergency visits, and inpatient days than those treated with dipeptidyl peptidase-4 (DPP-4) inhibitors²⁵.

The EMPRISE East Asia study included patients treated with empagliflozin or DPP-4 inhibitors in Japan, South Korea, and Taiwan. In this study, empagliflozin treatment was associated with a significantly reduced risk for all-cause mortality, hospitalization for heart failure (HHF), and end-stage renal disease compared with treatment with DPP-4 inhibitors²⁶.

In the present analysis of EMPRISE East Asia, we aimed to evaluate inpatient care needs and other healthcare resource utilization in patients with type 2 diabetes treated with empagliflozin versus DPP-4 inhibitors in routine clinical practice in Japan, South Korea, and Taiwan.

METHODS

Study design and patient population

The overall design of the EMPRISE East Asia study has been reported previously²⁶. In brief, patients with type 2 diabetes starting empagliflozin, 10 mg or 25 mg, or a DPP-4 inhibitor for the first time were identified from the Medical Data Vision

(MDV) database in Japan (from December 2014 to April 2018), the National Health Information Database (NHID) of the National Health Insurance Service in South Korea (May 2016–December 2017), and the National Health Insurance claims database in Taiwan (also May 2016–December 2017). The MDV database includes over 25 million patients from over 400 acute care hospitals in Japan, whereas the NHID in South Korea and the National Health Insurance claims database in Taiwan are both national claims databases.

The date of the first prescription of empagliflozin or DPP-4 inhibitor was counted as the index date. This study included patients with ≥ 12 months of data prior to the index date who were aged ≥ 18 years at the index date, had a diagnosis of type 2 diabetes prior to the index date, and had not had a prescription for empagliflozin, another SGLT2 inhibitor, or a DPP-4 inhibitor in the 12 months prior to the index date. The diagnosis of type 2 diabetes was based on diagnostic codes using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) in Japan and Korea and both the 9th (ICD-9) and 10th revisions in Taiwan. Patients were excluded if they had a diagnosis of type 1 diabetes, secondary diabetes, gestational diabetes, or end-stage renal disease in the 12 months before the index date.

Patients were grouped into cohorts of new users of empagliflozin or DPP-4 inhibitors. These groups underwent 1:1 propensity-score matching, adjusting for 110–166 covariates. These covariates, which have been reported previously in detail²⁶, included characteristics related to baseline demographics, comorbidities (including those related to diabetes), medication, lifestyle factors, and prior healthcare resources utilization. Post-matching covariate balance between treatments was assessed for each covariate by the calculation of standardized difference; an absolute standardized difference of >0.1 between post-matching covariates was considered to be meaningful²⁷. Propensity score matching and assessment was re-done for analyses of baseline subgroups.

The EMPRISE East Asia study is registered on the European Union electronic register of Post-Authorisation Studies (EU PAS; register number EUPAS27606) and on ClinicalTrials.gov (identifier NCT03817463). The study was approved by local institutional review boards in each country. All patient data were de-identified.

Outcomes

In the current analysis, the following outcomes for healthcare resource utilization were investigated: (1) inpatient care, measured by all-cause hospitalizations, first hospitalizations, and duration of hospitalization (length of stay and total number of inpatient days); (2) emergency care, measured by emergency room (ER) visits; and (3) outpatient care, defined as outpatient visits (excluding ER visits). These outcomes were assessed by extracting information relating to inpatient and outpatient usage of healthcare resources (e.g. length of stay) from the study databases, including administrative codes (Table S1).

Follow-up for these outcomes started on the day after the index date and continued until one of the following events occurred: death, discontinuation of the initial drug, switch to another study drug (any SGLT2 inhibitor, any DPP-4 inhibitor), initiation of concomitant use with another study drug (any SGLT2 inhibitor, any DPP-4 inhibitor), or end of data availability.

Statistical analysis

Analyses of outcomes in patients were conducted according to the treatment they received, i.e. the ‘as-treated’ population. All-cause hospitalizations, outpatient visits (excluding ER visits), and ER visits were compared between the treatment groups using Poisson regression models, while first hospitalizations were evaluated using Cox proportional hazard models; in all analyses, the models were adjusted for any unbalanced covariates, which were assessed based on an absolute standardized difference of >0.1, as described above. Data from individual countries were pooled using random effects meta-analysis models; the *I*² index and Q test were used to measure heterogeneity, and the Z test was used to assess distribution.

Patients receiving the 10 mg dose of empagliflozin were also evaluated separately, as this is the dose strength predominantly used in Japan²⁸ and other Asian countries. In Japan and South Korea, patients were censored if they were titrated to a different empagliflozin dose; in Taiwan, patients starting empagliflozin 10 mg/day were considered to be part of that subgroup regardless of future dose adjustment.

RESULTS

Overall, 1,086,727 patients with type 2 diabetes were identified as having started empagliflozin or a DPP-4 inhibitor during the study period: 432,054 in Japan, 325,608 in South Korea, and 329,065 in Taiwan. The large majority of these patients had started DPP-4 inhibitors (Figure 1). From this cohort, 28,712 empagliflozin/DPP-4 inhibitor pairs of propensity score-matched patients were identified, including 5,592 pairs from Japan, 9,072 pairs from South Korea, and 14,048 pairs from Taiwan (Figure 1). Most of these patients started empagliflozin at the 10 mg dose: 5,432 (97.1%) in Japan, 7,760 (85.5%) in South Korea, and 8,339 (59.4%) in Taiwan. The mean follow-up time was 5.7 months in Japan, 6.8 months in South Korea, and 5.9 months in Taiwan (median of 3.2, 5.7, 4.2 months, respectively)²⁶.

Baseline characteristics were generally comparable between treatment groups following propensity scoring (Table 1, Table S2), as reported previously²⁶. However, the following variables were unbalanced (absolute standardized difference >0.1): past use of glucagon-like peptide-1 receptor agonists or second-generation sulfonylureas in Japan, and total pharmacy costs, total pharmacy costs for antidiabetic drugs, and total pharmacy costs for non-antidiabetic drugs in Taiwan (Table S2). To adjust for these differences, these variables

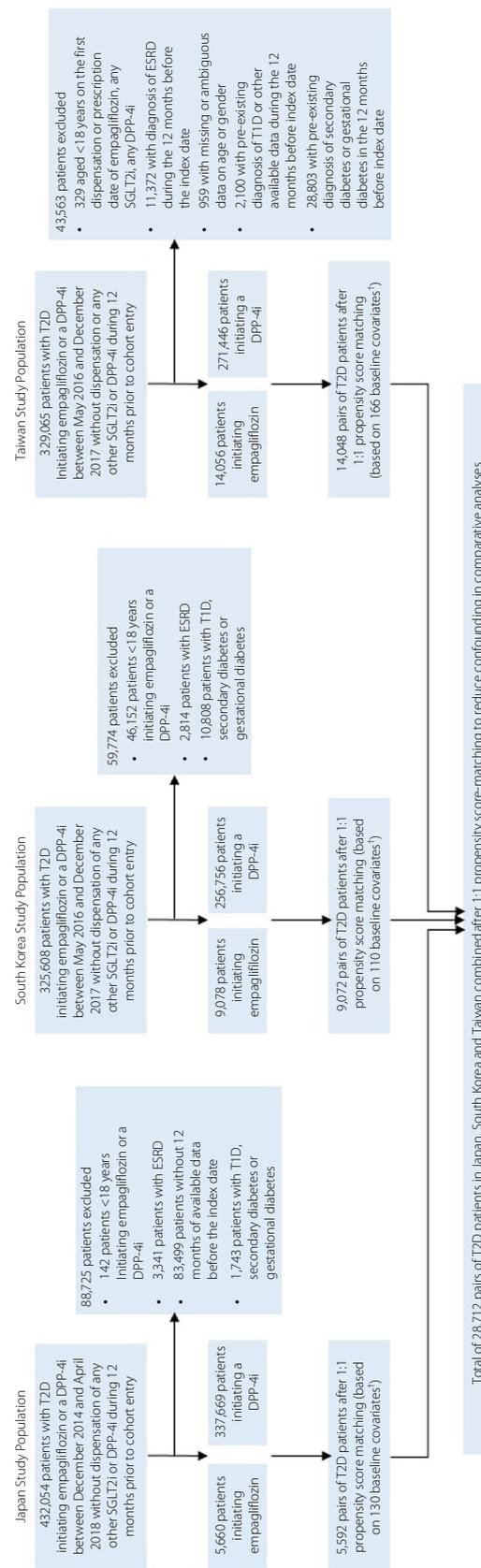


Figure 1 | Flow chart of overall study population of empagliflozin versus DPP-4 inhibitors. †Covariates with insufficient numbers not included. DPP-4i, dipeptidyl peptidase-4 inhibitor; ESRD, end-stage renal disease; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Based on: Cardiovascular and renal effectiveness of empagliflozin in routine care in East Asia: Results from the EMPRISE East Asia study. Seino et al. *Endocrinology, Diabetes & Metabolism*. Volume 4/Issue 1. ©2020 The Authors. <https://onlinelibrary.wiley.com/doi/10.1002/edm2.183>. Article made available under Creative Commons Attribution license CC-BY: <https://creativecommons.org/licenses/by/4.0/>.

were included in the statistical models for the evaluation of outcomes. The mean age at drug initiation was 55.9–59.3 years, and 24.4–40.5% of patients were elderly across the three countries (17.3–26.8% aged 65–74 years, 7.1–13.7% aged ≥ 75 years). The burden of comorbidities was generally low (e.g. stroke: 4.5–6.1% of patients; chronic kidney disease: 1.6–5.6%), with the exception of ischemic heart disease which was present in 19.9–32.4% of patients across countries. All-cause hospitalization and the number of hospital days and emergency department visits were higher at baseline in Japan than in the other two countries, most likely due to the MDV database containing data only from acute care hospitals in Japan. Sitagliptin was the most common DPP-4 inhibitor index drug at baseline, as reported previously (Table S3)²⁶.

Inpatient care need

The rates of first hospitalization and all-cause hospitalization were markedly higher in patients with CVD at baseline than in those without CVD in all three countries (Figure 2). Treatment with empagliflozin was associated with a 23% lower risk for first hospitalization compared with treatment with DPP-4 inhibitors: hazard ratio 0.77, 95% confidence interval (CI) 0.73–0.81 (Figure 2a). This risk reduction was consistent across Japan (24%), South Korea (25%), and Taiwan (20%), as well as in patients with (19%) and without (20%) CVD (Figure 2a). Similarly, empagliflozin was associated with a 27% lower risk for all-cause hospitalization compared with DPP-4 inhibitors: rate ratio (RR) 0.73, 95% CI 0.67–0.79 (Figure 2b). This risk reduction was consistent across Japan (31%), South Korea (30%) and Taiwan (21%), as well as in patients with (23%) and without (20%) CVD (Figure 2b). Thus, the lower risk of hospitalization was consistent in the empagliflozin group compared with the DPP-4 inhibitor group irrespective of first events, all events (including recurrent events), and the presence or absence of CVD.

The number of inpatient days was lower in patients initiating empagliflozin compared with DPP-4 inhibitors in all three countries. The mean (standard deviation) length of stay in patients with at least one hospitalization was 13.38 (18.57) days in the empagliflozin group compared with 15.52 (22.94) days in the DPP-4 inhibitor group in Japan, 10.00 (16.86) days and 12.89 (29.96) days, respectively, in South Korea, and 9.73 (15.06) days and 12.26 (23.83) days, respectively, in Taiwan (Table 2). Similar trends were seen in the subgroups of patients with and without CVD at baseline (Table S4).

Emergency care need

Despite patients in South Korea and Taiwan having similar baseline characteristics, the rate of ER visits was higher in Taiwan; it was also higher in patients with CVD than in those without CVD in both countries (Figure 3). The rate of ER visits appeared to be much lower in Japan. Overall, treatment with empagliflozin was associated with a 12% reduction in risk for an ER visit, compared with treatment with DPP-4 inhibitors

(RR 0.88, 95% CI 0.83–0.94), which was consistent across countries (10%, 9% and 14% in Japan, South Korea and Taiwan, respectively).

Outpatient care

The rate of outpatient visits was higher in patients with CVD compared with those without CVD in all three countries (Figure 4). There was a small (4%) but significant overall reduction in the risk for outpatient visits in patients receiving empagliflozin compared with those receiving DPP-4 inhibitors (RR 0.96, 95% CI 0.96–0.97), which was consistent across countries and in patients with and without baseline CVD.

10 mg dose of empagliflozin

In the subgroup of patients receiving the 10 mg dose of empagliflozin 1:1 propensity-score matched to individuals receiving DPP-4 inhibitors, the risks of first hospitalization (overall HR 0.79, 95% CI 0.73–0.85), all-cause hospitalization (overall RR 0.75, 95% CI 0.70–0.79), and ER visit (overall RR 0.85, 95% CI 0.79–0.92) were all significantly lower with empagliflozin in all three countries (Figures S1 and S2). The risk of an outpatient visit was significantly lower in Japan (RR 0.94, 95% CI 0.92–0.95) and numerically lower in South Korea (RR 0.99, 95% CI 0.98–1.00) and Taiwan (RR 0.96, 95% CI 0.92–1.00) (Figure S3).

DISCUSSION

The burden of diabetes care in East Asia, in terms of healthcare resource utilization and cost, is growing due to the high prevalence of patients with type 2 diabetes in the region¹. Given this increasing burden, we assessed the impact of empagliflozin on the utilization of healthcare resources in East Asian patients with type 2 diabetes in routine clinical practice. In this analysis, treatment with empagliflozin was associated with significant reductions in inpatient care needs, ER visits, and outpatient visits, compared with treatment with DPP-4 inhibitors. The reductions in healthcare resource utilization by East Asian patients with type 2 diabetes treated with empagliflozin were evident shortly after treatment initiation and were generally consistent across Japan, South Korea, and Taiwan irrespective of healthcare system and clinical practices; they were also comparable in patients with and without baseline CVD, underscoring that the lower need for inpatient care in empagliflozin-treated patients was evident even in those without CVD.

These findings from East Asia are consistent with the reduced healthcare resource utilization associated with empagliflozin observed in patients with type 2 diabetes in the US compared with DPP-4 inhibitors specifically²⁵ or other glucose-lowering drugs generally²⁹, as well as the EMPA-REG OUTCOME clinical trial, which found that empagliflozin reduced all-cause hospitalizations in patients with type 2 diabetes and CVD, including Asians^{18,23}. In the EMPA-REG OUTCOME

Table 1 | Selected baseline clinical and demographic characteristics

Characteristic	Japan		South Korea		Taiwan				
	Empagliflozin (n = 5,592)	DPP-4 inhibitor (n = 5,592)	ASD	Empagliflozin (n = 9,072)	DPP-4 inhibitor (n = 9,072)	ASD	Empagliflozin (n = 14,048)	DPP-4 inhibitor (n = 14,048)	ASD
Age, years, mean (SD)	59.28 (13.80)	59.33 (13.96)	0.00	55.96 (12.52)	55.91 (12.72)	0.00	56.92 (12.56)	56.74 (13.18)	0.01
65–74 years	1,458 (26.07)	1,501 (26.84)	n/a	1,570 (17.31)	1,585 (17.47)	n/a	2,708 (19.28)	2,593 (18.46)	n/a
≥75 years	751 (13.43)	764 (13.66)	n/a	646 (7.12)	645 (7.11)	n/a	1,004 (7.15)	1,151 (8.19)	n/a
Female	1,845 (32.99)	1,813 (32.42)	0.01	3,900 (42.99)	3,987 (43.95)	0.02	5,883 (41.88)	5,854 (41.67)	0.00
Cardiovascular disease [†]	2,150 (38.45)	2,182 (39.02)	n/a	3,985 (43.93)	3,939 (43.42)	n/a	3,892 (27.71)	3,903 (27.78)	n/a
Ischemic heart disease	1,813 (32.42)	1,789 (31.99)	0.01	1,965 (21.66)	1,979 (21.81)	0.00	2,806 (19.97)	2,796 (19.90)	0.00
Old myocardial infarction	396 (7.08)	379 (6.78)	0.01	134 (1.48)	146 (1.61)	0.01	189 (1.35)	208 (1.48)	0.01
Acute myocardial infarction	383 (6.85)	410 (7.33)	0.02	327 (3.60)	333 (3.67)	0.00	390 (2.78)	365 (2.60)	0.01
Any stroke	342 (6.12)	342 (6.12)	0.00	542 (5.97)	560 (6.17)	0.01	627 (4.46)	647 (4.61)	0.01
Diabetic retinopathy	819 (14.65)	738 (13.20)	0.04	1,791 (19.74)	1,760 (19.40)	0.01	1,364 (9.71)	1,347 (9.59)	0.00
Diabetic nephropathy	432 (7.73)	423 (7.56)	0.01	1,294 (14.26)	1,310 (14.44)	0.01	2,754 (19.60)	2,721 (19.37)	0.01
Chronic kidney disease	248 (4.43)	274 (4.90)	0.02	144 (1.59)	150 (1.65)	0.01	790 (5.62)	767 (5.46)	0.01
Diabetic neuropathy	175 (3.13)	196 (3.51)	0.02	1,522 (16.78)	1,497 (16.50)	0.01	942 (6.71)	946 (6.73)	0.00
Combined Comorbidity	1.19 (1.83)	1.15 (1.73)	0.02	0.35 (1.03)	0.32 (1.02)	0.03	0.69 (1.36)	0.69 (1.4)	0.00
Index, mean (SD)	10.98 (9.86)	10.67 (9.55)	0.03	7.11 (4.73)	7.23 (4.82)	0.03	22.45 (14.57)	22.64 (15.12)	0.01
Number of distinct medication prescriptions, mean (SD)	8.08 (1.84)	7.97 (1.81)	0.06	n/a	n/a	n/a	n/a	n/a	n/a
HbA1c, % mean (SD)	2,575 (46.05)	2,648 (47.35)	0.03	1,888 (20.81)	2,002 (22.07)	0.03	1,998 (14.22)	1,981 (14.10)	0.00
All-cause hospitalizations (in 12 months prior to index date)	1.22 (0.62)	1.19 (0.59)	0.05	0.35 (1.00)	0.40 (1.15)	0.04	0.21 (0.70)	0.20 (0.66)	0.01
Number of all-cause hospital admissions, mean (SD)	10.91 (14.97)	11.22 (14.13)	0.02	2.71 (14.53)	3.21 (17.12)	0.03	1.40 (8.04)	1.41 (6.98)	0.00
Number of emergency department visits, mean (SD)	2.13 (3.53)	2.22 (3.37)	0.03	0.18 (0.65)	0.19 (0.76)	0.01	0.42 (1.07)	0.42 (0.97)	0.00

Data are n (%) unless stated otherwise. ASD, absolute standardized difference; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; n/a, not available; SD, standard deviation. [†]History of myocardial infarction, unstable angina, coronary atherosclerosis, and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease or surgery, or lower-extremity amputation.

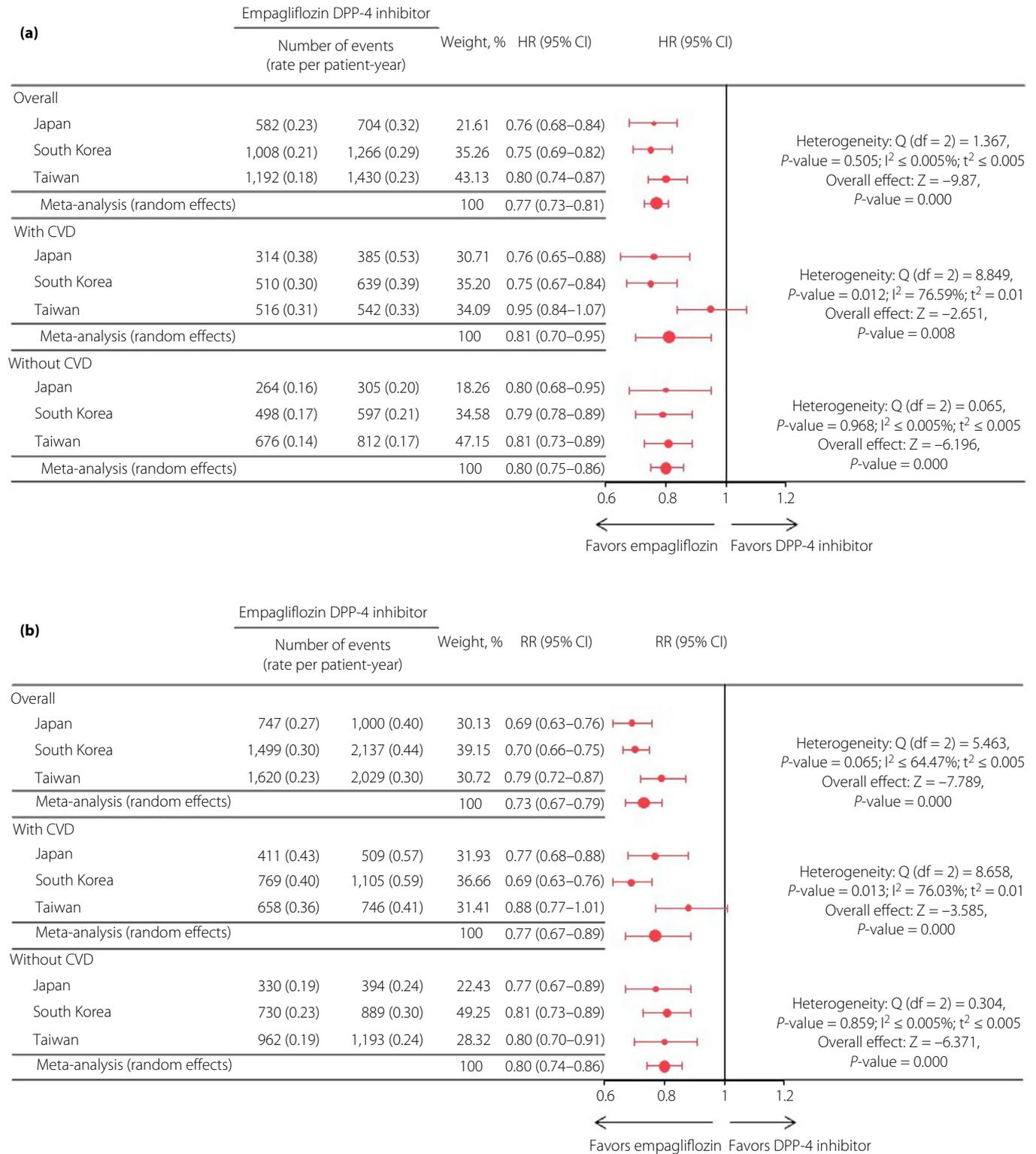


Figure 2 | Risk of (a) first hospitalization and (b) all-cause hospitalization in 1:1 propensity score-matched patients. CI, confidence interval; CVD, cardiovascular disease; df, degrees of freedom; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; RR, rate ratio.

Table 2 | Duration of hospitalization

	Japan		South Korea		Taiwan	
	Empagliflozin (<i>n</i> = 5,592)	DPP-4 inhibitor (<i>n</i> = 5,592)	Empagliflozin (<i>n</i> = 9,072)	DPP-4 inhibitor (<i>n</i> = 9,072)	Empagliflozin (<i>n</i> = 14,048)	DPP-4 inhibitor (<i>n</i> = 14,048)
Number of patients with hospital admissions [†]	582	704	1,008	1,266	1,192	1,430
Total number of inpatient days	7,788	10,926	10,078	16,313	11,604	17,537
Length of stay, days						
Mean (SD)	13.38 (18.57)	15.52 (22.94)	10.00 (16.86)	12.89 (29.96)	9.73 (15.06)	12.26 (23.83)
Median (Q1, Q3)	7 (3, 16)	8 (4, 17)	5 (2, 11)	6 (2, 13)	5 (3, 10)	6 (3, 12)
Total follow-up for all patients (patient-years)	2,734	2,488	5,064	4,855	6,927	6,764
Inpatient days as % of follow up, mean (SD)	1.23 (6.57)	1.51 (7.21)	0.75 (4.88)	1.4 (7.17)	0.76 (5.64)	1.07 (6.75)

DPP-4, dipeptidyl peptidase-4; Q, quartile; SD, standard deviation. [†]Post-baseline subgroup in which treatment groups were not re-matched by propensity scoring.

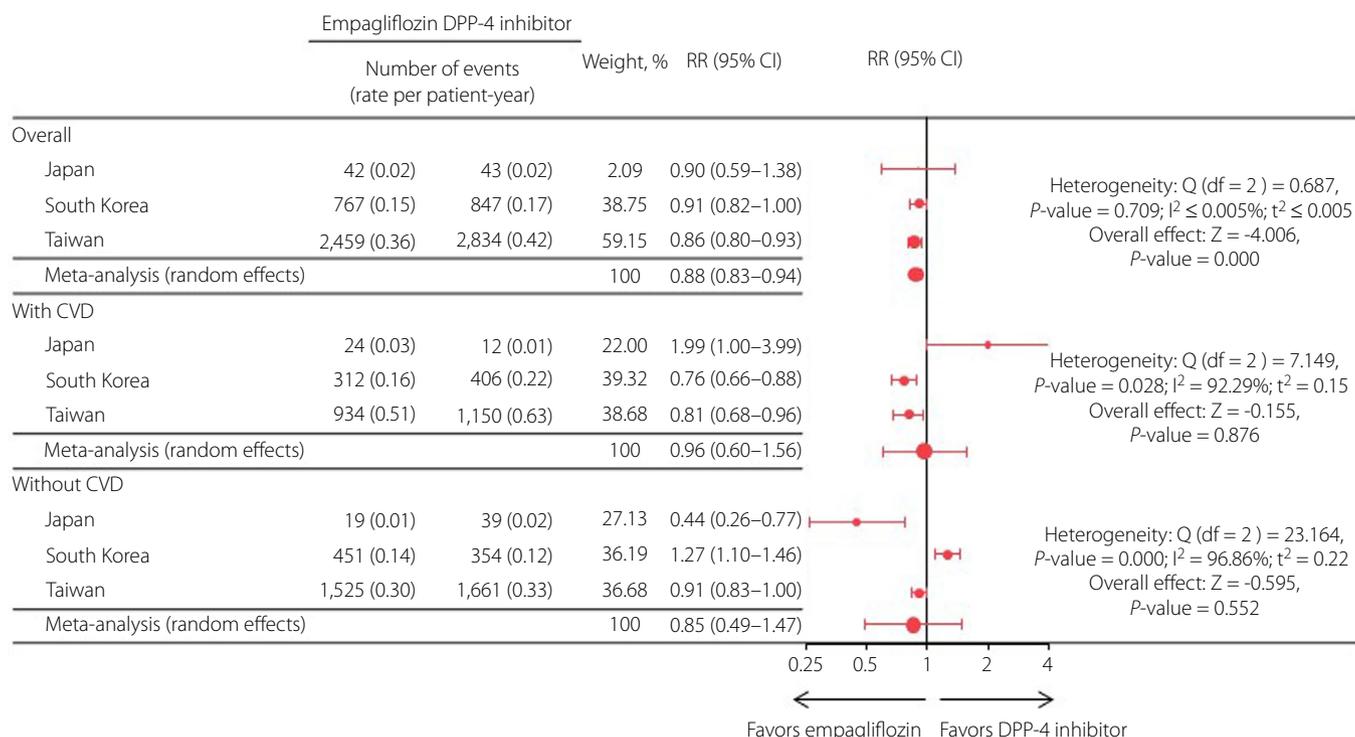


Figure 3 | Risk of emergency room visit in 1:1 propensity score-matched patients. CI, confidence interval; CVD, cardiovascular disease; *df*, degrees of freedom; DPP-4, dipeptidyl peptidase-4; RR, rate ratio.

trial, most types of hospital admissions were lower with empagliflozin compared with placebo, with prevention of HHF accounting for approximately 20% of the reduction in all-cause hospitalizations¹⁸. These data suggest favorable effects of empagliflozin on hospitalizations beyond those for heart failure and CVD even in routine clinical practice. More frequent

hospitalizations were found to be a strong predictor for frailty in community-dwelling geriatric patients³⁰; a reduction in the risk of hospitalizations with empagliflozin might therefore lead to benefit in elderly patients with type 2 diabetes.

Globally, the direct and indirect costs of type 2 diabetes were estimated as \$US760 billion¹ and \$US1.31 trillion⁴ in 2019 and

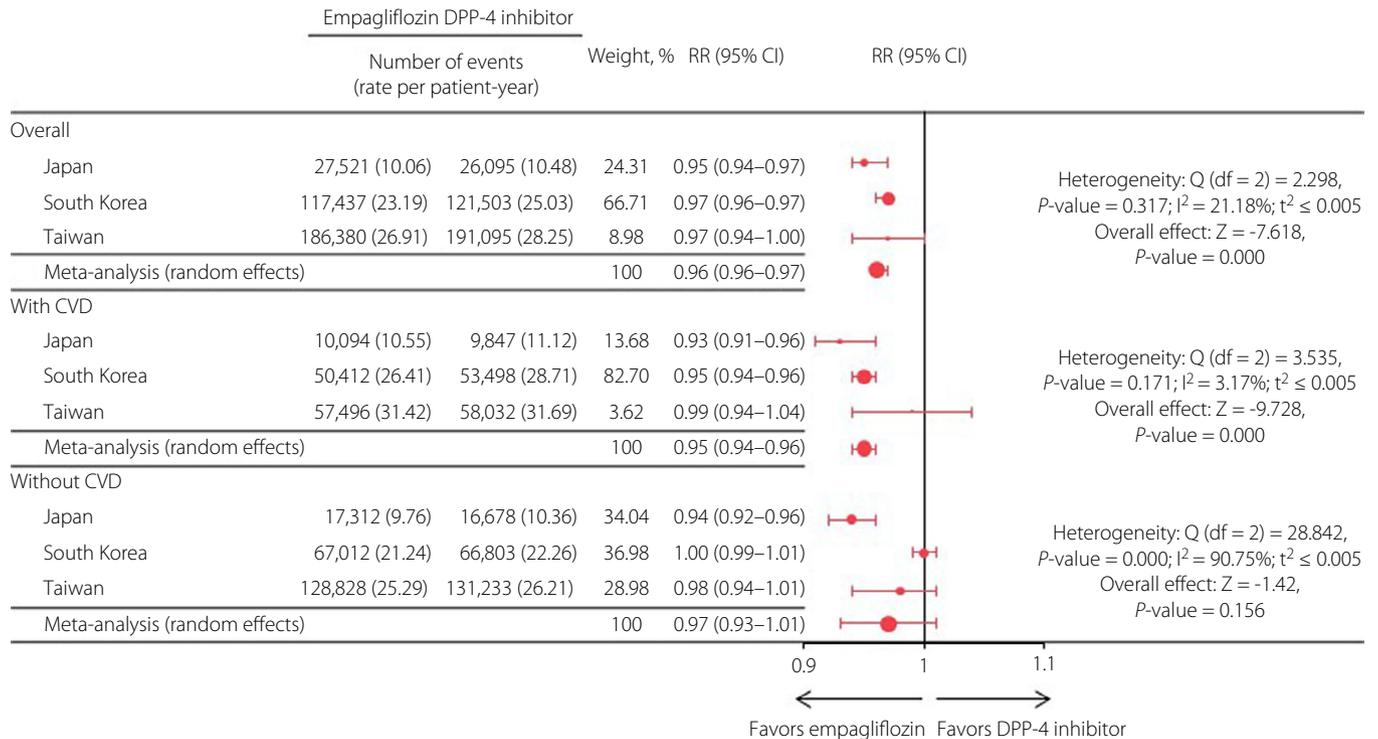


Figure 4 | Risk of outpatient visit (excluding emergency room visits) in 1:1 propensity score-matched patients. CI, confidence interval; CVD, cardiovascular disease; df, degrees of freedom; DPP-4, dipeptidyl peptidase-4; RR, rate ratio.

2015, respectively. Type 2 diabetes has also been shown to exert a substantial economic burden in Japan (medical costs for diabetes of 1206 billion yen [approximately \$US11 billion] in 2018⁵), South Korea (\$US18.3 billion in 2019¹³), and Taiwan (\$US2.96 billion in 2010, equivalent to approximately 0.8% of gross domestic product at that time⁹). Hospitalization was found to be one of the two largest contributors to direct costs of type 2 diabetes in economically developed countries³¹, which supports similar findings from the American Diabetes Association³. Cost-effectiveness modeling analyses suggest that empagliflozin is a highly cost-effective treatment in Japan³² and China^{33,34}. Given the economic burden of type 2 diabetes, the impact of empagliflozin on medical costs in routine clinical care will be analyzed for individual countries in the EMPRISE East Asia study.

This analysis from EMPRISE East Asia has several strengths, as well as some limitations. The study was designed to minimize confounding and time-related biases, and to also ensure balance between the treatment groups²⁴. The use of patient cohorts initiating empagliflozin or DPP-4 inhibitor for the first time reduces potential confounding by indication as well as time-related biases such as immortal time bias and time-lag bias^{35,36}. This analysis was also reflective of clinical practice in Japan, South Korea, and Taiwan. The use of DPP-4 inhibitors as a comparator was appropriate as an alternative treatment to empagliflozin in these countries as these drugs

are generally prescribed at similar stages of type 2 diabetes disease severity (further reducing the chance of time-lag bias) and have similar costs, glycemic efficacy and low risk for hypoglycemia. The propensity-scoring methodology adjusted for more than 110 covariates, some of which – including baseline comorbidities and medication use – may be viewed as proxies for disease severity measures such as time since diagnosis. Propensity score models were re-done for analyses of baseline subgroups, as covariate balance is not automatically maintained in subgroups. Notably, most of the patients identified as initiating empagliflozin were retained after propensity-score matching (28,712/28,794 = 99.7%), which increases confidence that the final cohort was representative of clinical practice. Finally, the cardiorenal risk reduction associated with empagliflozin treatment in the same cohort of patients from Japan, South Korea and Taiwan was consistent with the cardiorenal benefit of empagliflozin seen in the EMPA-REG OUT-COME trial, as reported previously²⁶. However, despite efforts to minimize confounding and biases, residual confounding might still have been present. The follow-up period was also relatively short (mean 5.7–6.8 months across the countries; median 3.2–5.7 months), and we did not investigate reasons for all-cause hospitalizations. In addition, the competing risk of death was not considered in the analysis of first hospitalization; however, this is unlikely to have significantly affected those results, given the low number of deaths in the study

(287 patients [0.5% of the cohort]²⁶) and the similar risk reduction with empagliflozin for that outcome (23%) compared with all hospitalizations (27%). Comparison of the length of stay between treatment groups in patients with at least one hospitalization is limited by the fact that these were post-baseline subgroups that were not re-matched by propensity scoring. Furthermore, the study is limited by differences between the healthcare systems and databases in each country. Notably, the MDV database in Japan does not comprehensively record ER visits, as the code used for ER visits is not necessarily applied to all patients visiting the ER (some are coded to either the department of their personal doctor or the department they visit after the ER). This is probably why the rate of ER visits appeared to be much lower in Japan than South Korea and Taiwan, which may affect the generalizability of the Japanese ER data. Furthermore, it was not possible to evaluate adherence or persistence.

In conclusion, EMPRISE East Asia is one of the first studies of the effect of SGLT2 inhibitors on healthcare resource utilization in East Asian patients with type 2 diabetes in routine clinical practice. In this study, empagliflozin treatment was associated with lower rates of hospitalizations, outpatient visits, and ER visits than treatment with DPP-4 inhibitors. These results were consistent across Japan, South Korea, and Taiwan, and in patients with and without baseline CVD. Further research is needed to evaluate the implications of these findings on the costs of care.

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DISCLOSURE

W H-H Sheu reports being an advisor and/or speaker for AstraZeneca, Bayer HealthCare, Boehringer Ingelheim Pharmaceuticals, Daiichi-Sankyo, Eli Lilly and Company, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation,

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Approval date of registry and registration number of the study: EU PAS, register number EUPAS27606 (first registered January 21, 2019); ClinicalTrials.gov, identifier NCT03817463 (first registered January 25, 2019).

Animal studies: Not applicable.

DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to

relevant material, including participant-level clinical study data, as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (see Medical & Clinical Trials | Clinical Research | MyStudyWindow; <https://www.mystudywindow.com/msw/datasharing>). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Researchers should use the <https://vivli.org/> link to request access to study data and visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information (<https://www.mystudywindow.com/msw/datasharing>).

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SUPPORTING INFORMATION

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

Table S1 | Definition of healthcare resource utilization outcomes during the follow-up period

Table S2 | Baseline values of covariates after propensity-score matching. Reproduced from: Cardiovascular and renal effectiveness of empagliflozin in routine care in East Asia: Results from the EMPRISE East Asia study. Seino *et al.* *Endocrinology, Diabetes & Metabolism*. Volume 4/Issue 1. ©2020 The Authors. <https://onlinelibrary.wiley.com/doi/10.1002/edm2.183>. Article made available under Creative Commons Attribution license CC-BY: <https://creativecommons.org/licenses/by/4.0/>

Table S3 | DPP-4 inhibitor index drug at baseline. Reproduced from: Cardiovascular and renal effectiveness of empagliflozin in routine care in East Asia: Results from the EMPRISE East Asia study. Seino *et al.* *Endocrinology, Diabetes & Metabolism*. Volume 4/Issue 1. ©2020 The Authors. <https://onlinelibrary.wiley.com/doi/10.1002/edm2.183>. Article made available under Creative Commons Attribution license CC-BY: <https://creativecommons.org/licenses/by/4.0/>

Table S4 | Duration of hospitalization in patients with and without cardiovascular disease at baseline

Figure S1 | Risk of (a) first hospitalization and (b) all-cause hospitalization in 1:1 propensity score-matched patients in the empagliflozin 10 mg subgroup. In Japan and South Korea, patients were censored if titrated to a different empagliflozin dose; in Taiwan, patients initiating empagliflozin 10 mg/day were considered to be part of that subgroup regardless of future dose adjustment. CI, confidence interval; df, degrees of freedom; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; RR, rate ratio.

Figure S2 | Risk of emergency room visit in 1:1 propensity score-matched patients in the empagliflozin 10 mg subgroup. In Japan and South Korea, patients were censored if titrated to a different empagliflozin dose; in Taiwan, patients initiating empagliflozin 10 mg/day were considered to be part of that subgroup regardless of future dose adjustment. CI, confidence interval; df, degrees of freedom; DPP-4, dipeptidyl peptidase-4; RR, rate ratio.

Figure S3 | Risk of outpatient visit (excluding emergency room visits) in 1:1 propensity score-matched patients in the empagliflozin 10 mg subgroup. In Japan and South Korea, patients were censored if titrated to a different empagliflozin dose; in Taiwan, patients initiating empagliflozin 10 mg/day were considered to be part of that subgroup regardless of future dose adjustment. CI, confidence interval; df, degrees of freedom; DPP-4, dipeptidyl peptidase-4; RR, rate ratio.