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Original article

Empagliflozin cardiovascular and renal effectiveness and safety compared to dipeptidyl peptidase-4 inhibitors across 11 countries in Europe and Asia: Results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study

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ABSTRACT

Background: Continued expansion of indications for sodium-glucose cotransporter-2 inhibitors increases importance of evaluating cardiovascular and kidney efficacy and safety of empagliflozin in patients with type 2 diabetes compared to similar therapies.
Methods: The EMPRISE Europe and Asia study is a non-interventional cohort study using data from 2014 –2019 in seven European (Denmark, Finland, Germany, Norway, Spain, Sweden, United Kingdom) and four Asian (Israel, Japan, South Korea, Taiwan) countries. Patients with type 2 diabetes initiating empagliflozin were 1:1 propensity score matched to patients initiating dipeptidyl peptidase-4 inhibitors. Primary endpoints included hospitalization for heart failure, all-cause mortality, myocardial infarction and stroke. Other cardiovascular, renal, and safety outcomes were examined.
Findings: Among 83,946 matched patient pairs, (0·7 years overall mean follow-up time), initiation of empagliflozin was associated with lower risk of hospitalization for heart failure compared to dipeptidyl peptidase-4 inhibitors (Hazard Ratio 0·70; 95% CI 0.60 to 0.83). Risks of all-cause mortality (0·55; 0·48 to 0·63), stroke (0·82; 0·71 to 0·96), and end-stage renal disease (0·43; 0·30 to 0·63) were lower and risk for myocardial infarction, bone fracture, severe hypoglycemia, and lower-limb amputation were similar between initiators of empagliflozin and dipeptidyl peptidase-4 inhibitors. Initiation of empagliflozin was associated with higher risk for diabetic ketoacidosis (1·97; 1·28 to 3·03) compared to dipeptidyl peptidase-4 inhibitors. Results were consistent across continents and regions.
Interpretation: Results from this EMPRISE Europe and Asia study complements previous clinical trials and real-world studies by providing further evidence of the beneficial cardiorenal effects and overall safety of empagliflozin compared to dipeptidyl peptidase-4 inhibitors.

Research in context

Evidence before this study

In 2015, the EMPA-REG OUTCOME® clinical trial showed cardio-protective effects of empagliflozin in patients with type 2 diabetes (T2D) and cardiovascular disease when added to standard care. To investigate both the cardiovascular and kidney effectiveness, and safety of empagliflozin initiation in a real-world, routine care setting, the United States EMPagliflozin compaRative effectIveness and SafEty study (EMPRISE US) was implemented using data from commercial and federal data sources. In EMRPISE US studies, initiation of empagliflozin was associated with a lower risk of hospitalization for heart failure (HHF), all-cause mortality (ACM), and a composite of myocardial infarction (MI), stroke and ACM when compared to dipeptidyl peptidase-4 inhibitors (DPP-4i). For safety outcomes, initiation of empagliflozin was associated with a lower risk of acute kidney injury, increased risk of diabetic ketoacidosis, and similar risk of lower-limb amputations and fractures in empagliflozin compared to DPP-4i. More recently, an extension of EMPRISE was implemented using routine care data from Europe and Asia to further expand investigation of the effectiveness and safety of empagliflozin into routine clinical practice settings.

Added value of this study

This EMPRISE Europe and Asia study builds upon previous evidence from clinical trials and real-world evidence (RWE) studies as one of the largest investigations of both cardiovascular and kidney effectiveness and safety of empagliflozin when compared to DPP-4is in routine clinical care settings. Starting out with a diverse population of 1·9 million persons with T2D initiating empagliflozin/sodium glucose cotransporter-2 inhibitor (SGLT-2i) or DPP-4i in eleven countries across two continents, this EMPRISE study is the first to report both safety and effectiveness outcomes in a single study that incorporates data from several diverse study populations.

Implications of all the available evidence

Results from RWE studies have shown beneficial cardiovascular and kidney effects of empagliflozin compared to DPP-4is. Most international treatment guidelines have recently been updated to recommend SGLT-2is and glucagon-like peptide-1 receptor agonists as effective therapies for patients with T2D due to their cardiovascular benefit in appropriate populations (i.e., patients with T2D with cardiovascular disease, high cardiovascular risk, heart failure, or kidney disease). These EMPRISE results support efforts to translate such treatment guidelines into clinical practice.

Introduction

Individuals with type 2 diabetes (T2D) are at high risk of multiple comorbidities, including cardiovascular (CV) and kidney disease [1]. Up to one-third of individuals with T2D experience adverse CV events, such as atherosclerosis, coronary heart disease, heart failure (HF), and stroke. Furthermore, CV events are the cause of death in 50% of individuals with T2D [1]. Kidney disease also affects 33% of individuals with T2D [2,3], which leads to higher risk of death [4]. The extensive CV and kidney comorbidities observed in individuals with T2D necessitate evaluation of the effectiveness and safety of available treatments to safely reduce CV and kidney risks in this population.

Empagliflozin is a selective sodium glucose cotransporter-2 inhibitor (SGLT-2i) that reduces hyperglycemia by decreasing the renal reabsorption of glucose, thereby increasing glucosuria [5]. The EMPA-REG OUTCOME® trial [6], the EMPEROR-Reduced trial [7,8], and the EMPEROR-Preserved trial [9] all demonstrated beneficial CV and kidney effects of empagliflozin among individuals with T2D and patients with HF with and without T2D. Although these studies have provided robust trial evidence, a need exists to evaluate the effectiveness and safety of empagliflozin in diverse real-world settings.

The initial EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study examined individuals with T2D using data from

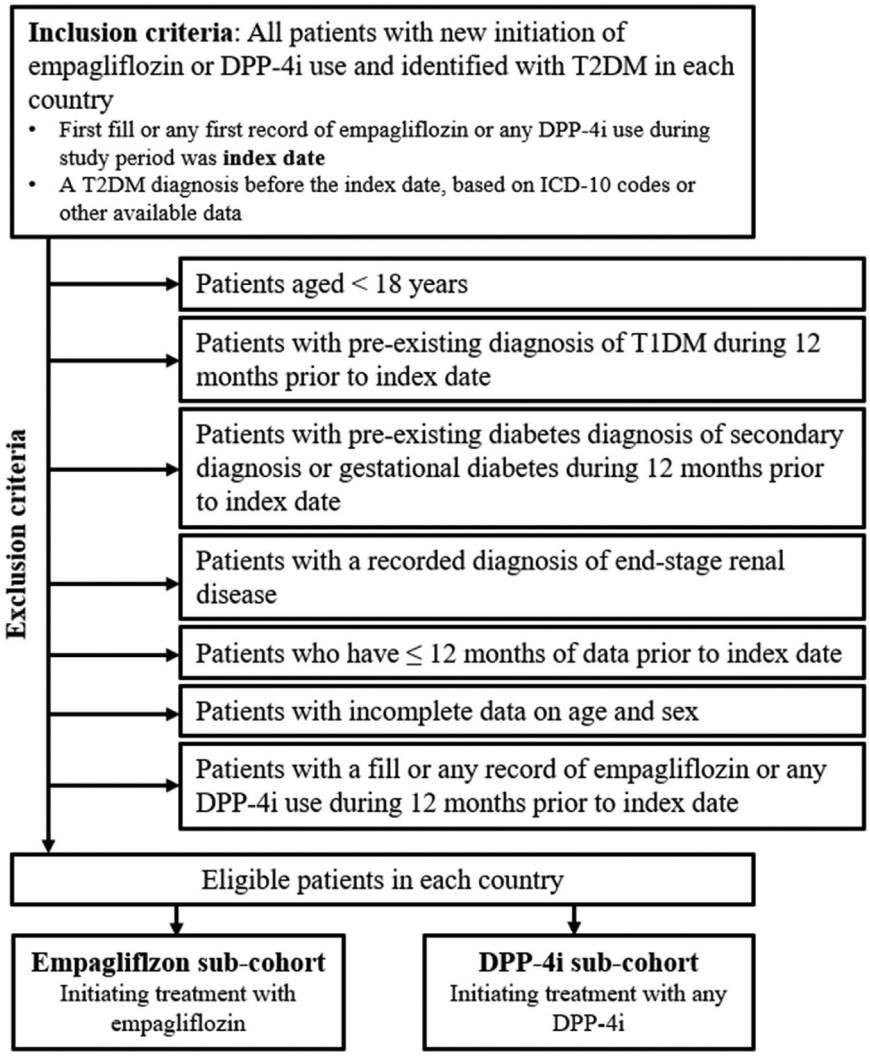

Fig. 1. Flowchart of inclusion and exclusion criteria

DPP-4i - Dipeptidyl peptidase-4 inhibitor; ICD-10 - International Statistical Classification of Diseases and Related Health Problems, 10th Revision; T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus.

routine care in the United States (US) and showed that empagliflozin in comparison with sitagliptin or other dipeptidyl peptidase-4 inhibitors (DPP-4i) was associated with lower risk of hospitalization for HF (HHF), all-cause mortality (ACM), a myocardial infarction (MI)/stroke/ACM composite, similar risk of MI/stroke, and a safety profile consistent with documented information [10–12]. The current study aimed to expand EMPRISE to several Asian and European countries and to focus on populations with diverse T2D pathophysiology [13]. This new EMPRISE study examined outcomes among individuals with T2D initiating empagliflozin or DPP-4i, evaluating the risk of HHF, ACM, atherosclerotic CV outcomes, kidney outcomes, and safety outcomes in routine clinical care.

Methods

Data sources

This non-interventional, multi-country cohort study used an active comparator, new-user design [14] to analyze secondary data from routine care settings in 11 countries from Europe (Denmark, Finland, Germany, Norway, Spain, Sweden, and UK) and Asia (Israel, and three East Asian countries Japan, South Korea, and Taiwan). Details on data sources are listed in *supplementary material, section a (see supplementary materials associated with this article on line).*

Study design and inclusion/exclusion criteria

Adults ≥ 18 years with T2D initiating empagliflozin or DPP-4i between May 2014 (i.e., the marketing authorization dates for empagliflozin) and end of data availability, which was no later than December 2018 (December 2019 for Germany) were identified. The index date was first date of any record of empagliflozin/DPP-4i use. Individuals with pre-existing type 1 diabetes, secondary diabetes, gestational diabetes, end-stage renal disease (ESRD), or any fill of empagliflozin or any DPP-4i in the 12 months prior to the index date (6 months prior for Germany) were excluded (DPP-4i - Dipeptidyl peptidase-4 inhibitor; ICD-10 - International Statistical Classification of Diseases and Related Health Problems, 10th Revision; T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus.

Baseline characteristics

Up to 182 variables describing baseline characteristics were collected during a period of 12+ months prior to index date (6 months

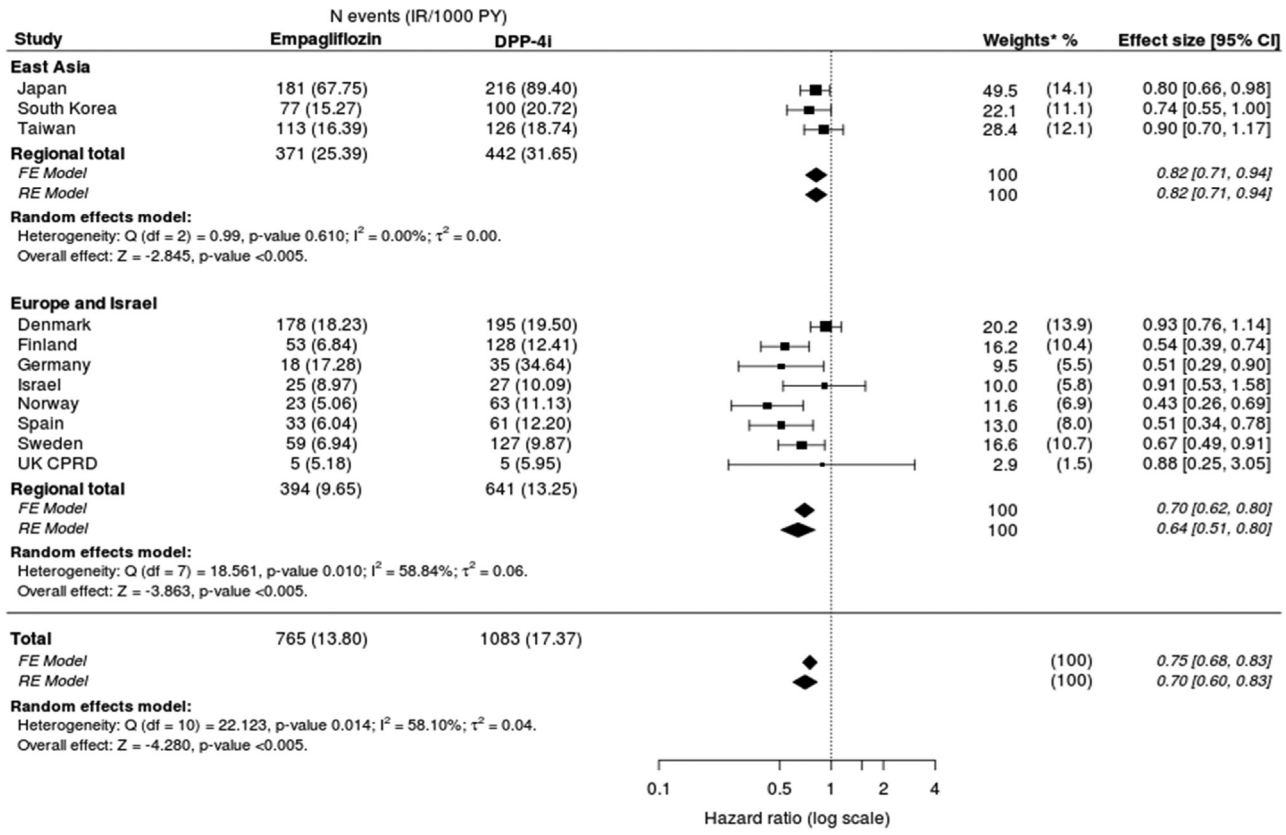

Fig. 2. Hazard ratios for hospitalization for heart failure in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

* Weights: The weights in parentheses represent the countries' weight with all countries included in the meta-analysis. The weights presented without parentheses correspond to the countries' weight when included only in the regional meta-analysis.

Results presented utilized the As-Treated analytic approach with 100% grace period prior to censoring for medication discontinuation. The HHF definition used any hospitalization with an associated heart failure diagnosis code (Japan, South Korea, Taiwan); heart failure as primary diagnosis associated with hospital admission (Denmark, Finland, Germany, Norway, Sweden); diagnosis of heart failure in any position of hospitalization (Israel, UK CPRD); any heart failure diagnosis associated with healthcare encounters, including hospitalizations, specialist outpatient, and primary care encounters (Spain) .

Studies with insufficient numbers of events for reporting or for analysis in either of the study group are omitted from the analysis. Numbers <5 are not shown due to data protection but are included in meta-analysis. If values <5 exist, total number of events and incidence rates are presented as intervals.

prior for Germany) and the variables included information on sex, age, comorbidities, drug exposure, and laboratory values. These baseline variables were included in propensity score (PS) modeling to match patient characteristics across groups of individuals initiating empagliflozin or DPP-4i in each individual country. The number of baseline characteristics included in the PS modeling varied among the countries due to variation in the data sources. Details on selected baseline characteristics are provided in *supplementary material, section b (see supplementary materials associated with this article on line).*

Follow-up and censoring

An as-treated (AT) approach to drug exposure was used in the main analyses. Follow-up began the day after initiation of the study drugs (index date) and ended on the first occurrence of any of the following: the date of an effectiveness/safety outcome, discontinuation of the initial drug, switch to or add on any other study drug, death, or end of data availability. In case of discontinuation, a grace period of 100% of the duration of the most recent fill/supply was included in the exposure period to account for uncertainty related to actual drug use patterns.

A sensitivity analysis was performed using an intention-to-treat (ITT) approach, where the exposure was assumed to continue until date of an effectiveness outcome, death, or end of data availability (whichever came first) to account for the possibility that the primary effectiveness outcomes associated with drug exposure might have manifested after drug discontinuation. In two additional sensitivity analyses using the AT approach, the length of the grace period was changed to 30 days and 90 days, respectively, instead of a grace period of 100% of the duration of the most recent fill/supply.

For analysis of safety outcomes, a risk window of 30 days was added to the grace periods connecting drug supplies to extend the period of exposure to the drug after discontinuation to account for the potential lag in the occurrence of a safety outcome. In a sensitivity analysis of safety outcomes, the length of the risk window was changed to 14 and 90 days even if some of the safety outcomes can present themselves rather quickly, i.e., diabetic ketoacidosis (DKA), severe hypoglycemia (SH), and acute kidney injury (AKI) requiring dialysis. Additional details are described in *supplementary material, section c (see supplementary materials associated with this article on line).*

Outcomes

Four primary effectiveness outcomes (HHF, ACM, MI, stroke), and five secondary outcomes (CV mortality; coronary revascularization procedures; two composite outcomes [a) HHF + CV mortality, (b) MI, stroke, and CV mortality (i.e., 3-point major adverse cardiovascular events (MACE)]; and ESRD were examined. Secondary outcomes also

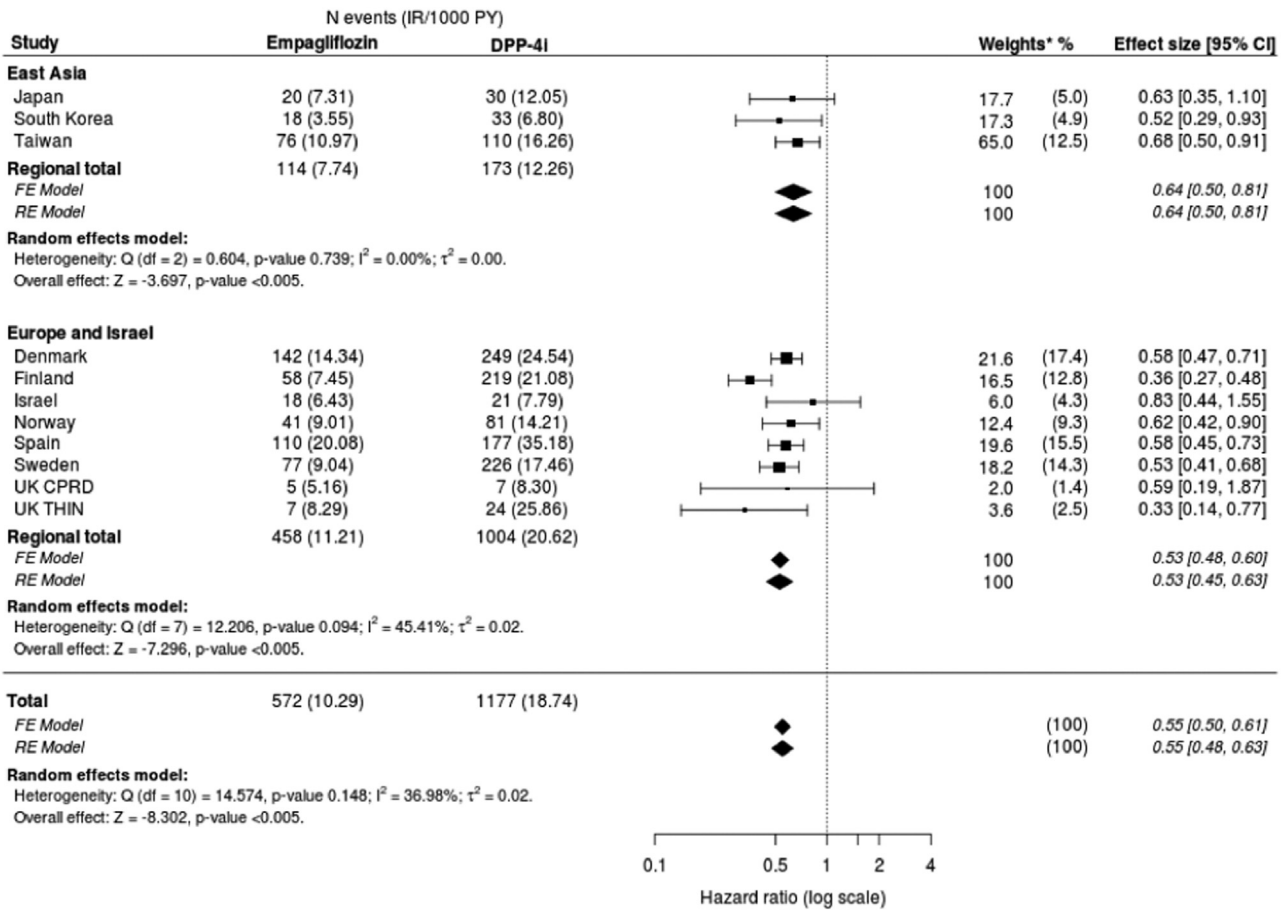

Fig. 3. Hazard ratios for all-cause mortality in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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included five safety outcomes (bone fracture, DKA, SH, lower-limb amputation (LLA), and AKI requiring dialysis).

Statistical methods

In each country, individuals initiating empagliflozin were PS matched (1:1 ratio using the nearest-neighbor algorithm) with individuals initiating any DPP-4i. Standardized mean differences for each covariate were calculated to assess post-matching balance between the empagliflozin and DPP-4i groups.

Incidence rates (IR) (events per person-years (PY)) with corresponding 95% confidence intervals (CI) were calculated for each patient cohort separately. The UK cohort consisted of two data sources that could not be pooled resulting in 2-point estimates for UK populations, where available. Hazard ratios (HR) with 95% CI were estimated by Cox regression for all effectiveness and safety outcomes with time since initiation of empagliflozin/DPP-4i as time scale. HRs were estimated using models adjusted for all unbalanced baseline PS-variables separately in each country.

Aggregate country-level results were pooled using random effect meta-analysis models [15] of effectiveness and safety outcomes in new users of empagliflozin compared to new users of DPP-4i. Measures of the extent of the heterogeneity were assessed (I^2, τ^2, χ^2 test). The standard errors of the study-specific estimates were adjusted to incorporate a measure of the extent of heterogeneity among the effects observed in the different countries.

Description of the statistical software used are provided in *supplementary material, section d (see supplementary materials associated with this article on line).*

Results

Participants

Out of 1,878,317 individuals with T2D that initiated empagliflozin, any SGLT-2i, or any DPP-4i with no prescriptions/fills/dispensation of these drugs during 12 months prior to index date (6-months for Germany), a total of 85,244 pairs of individuals initiating empagliflozin and DPP-4i were PS-matched. The largest number of matched pairs were from Sweden, Taiwan, and Finland (15,785, 14,048, and 11,801, respectively). The smallest number from Germany and UK cohorts (839 and 2200, respectively). Patient attrition flowcharts with numbers of pairs for individual countries by treatment cohort are provided in *supplementary material, section e (see supplementary materials associated with this article on line).*

In the matched pairs, mean age ranged between 56 and 65 years across countries, with lower mean age in the East Asian populations (*supplementary material, section b; see supplementary materials associated with this article on line*). The proportion of women was consistent

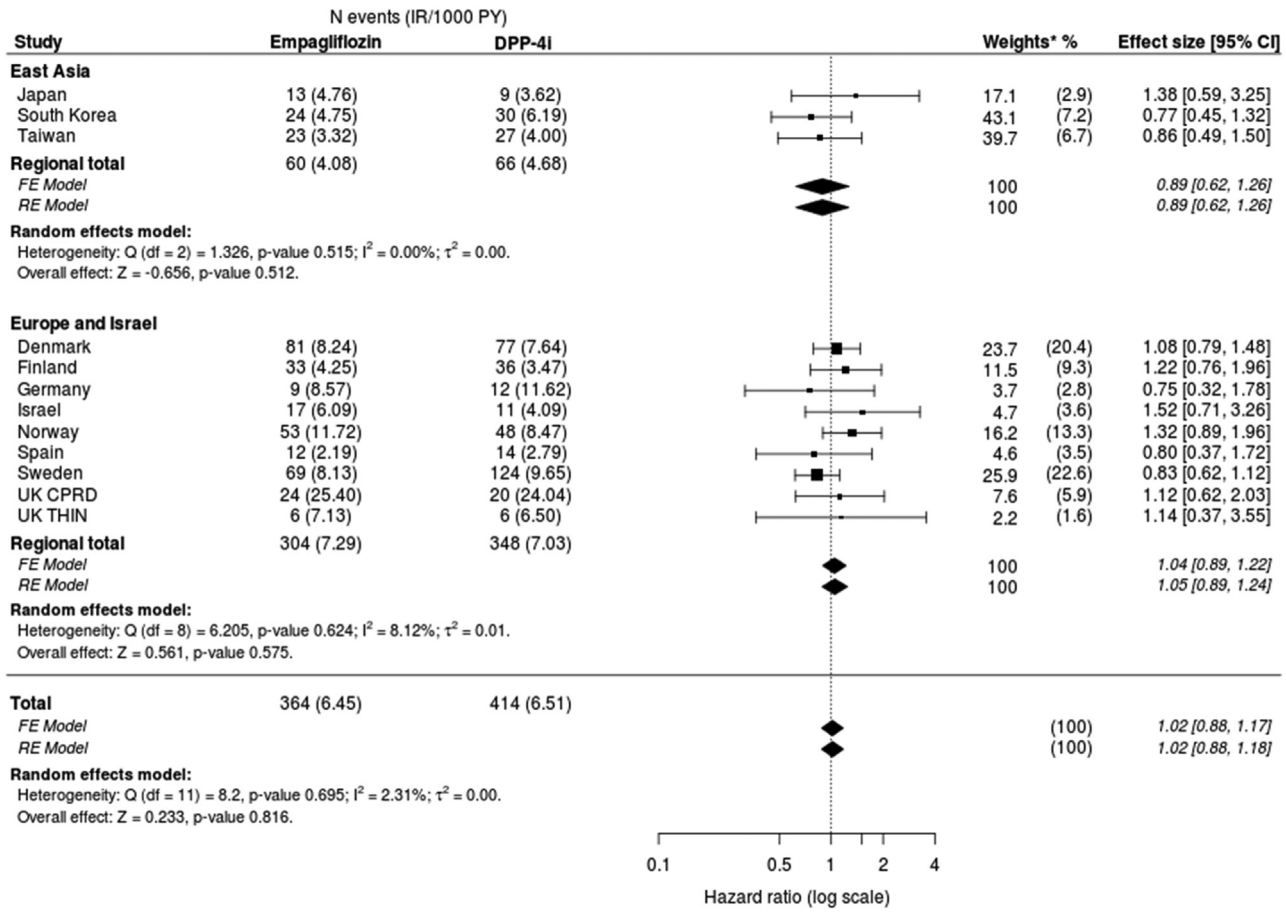

Fig. 4. Hazard ratios for myocardial infarction in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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across countries (ranging from 33% in Japan to 43% in South Korea). At baseline, individuals were exposed to between 1·2 and 2·6 glucose-lowering drugs (range of means across countries). The proportion of new users of glucose-lowering drugs at baseline was highest in Japan (43%) and South Korea (26%), followed by Israel (12%). The proportion of individuals on insulin or with concomitant initiation of insulin at baseline ranged between 2% and 32% across countries. The comorbidity status of the individuals at baseline also varied by country, e.g., hypertension was prevalent among more than 80% of the German individuals, but among only 6% of Norwegian individuals. Congestive HF was observed in 27% in the Japanese cohort at baseline but was present in as few as 3% and 8% of individuals in other countries. Prevalence of ischemic heart disease at baseline ranged between 2% and 32% across the 11 countries, with the highest prevalence in Japan (32%). Proportion of individuals with chronic kidney disease at baseline varied between too few to report and 6% (Taiwan) (Fig. 1).

Outcomes

Analyses of outcomes were based on 117,768 PY of follow-up among 83,946 pairs of individuals with an overall average follow-up time of 0·7 year (~256 days). For some analyses, not all countries contributed data, which is shown in Figs. 2–15. Results from the main analyses indicate that initiation of empagliflozin was associated with a 30% lower risk of HHF (HR: 0·70; 95% CI: 0·60 to 0·83) (Fig. 2) compared to DPP-4i. The risk of ACM was 45% lower in empagliflozin (0·55; 0·48 to 0·63) compared to DPP-4i (Germany not included) (Fig. 3). There was no difference in risk of MI between new users of empagliflozin and new users of DPP-4i (1·02; 0·88 to 1·18) (Fig. 4) yet empagliflozin was associated with an 18% lower risk of stroke (0·82; 0·71 to 0·96) compared to DPP-4i (Fig. 5).

For secondary effectiveness outcomes, data for some outcomes were not systematically available in all 11 countries (*supplementary material, section f; see supplementary materials associated with this article on line)*. Based on data from the five reporting countries (Taiwan, Finland, Norway, Sweden, and UK CPRD), empagliflozin was associated with 41% (0·59; 0·42 to 0·84) lower risk for CV mortality compared to DPP-4i (Fig. 6). The incidence of coronary revascularization procedures was not different between initiators of empagliflozin and DPP-4i (0·93; 0·79 to 1·09) (Spain not included) (Fig. 7). There was a 46% lower risk of the composite outcome HHF + CV mortality associated with use of empagliflozin compared to DPP-4i (0·54; 0·46 to 0·64) (Fig. 8) based on data from the four countries with available data (Finland, Norway, Sweden, UK CPRD). Among these same four countries and Taiwan, no difference in risk of MACE (0·95; 0·81 to 1·11) was observed between empagliflozin and DPP-4i (Fig. 9). Based on patient data from eight countries (Denmark, Finland, Germany, Israel, Japan, Norway, Sweden, and Taiwan), risk of ESRD was 57% lower in the empagliflozin sub-cohort (0·43; 0·30 to 0·63) compared

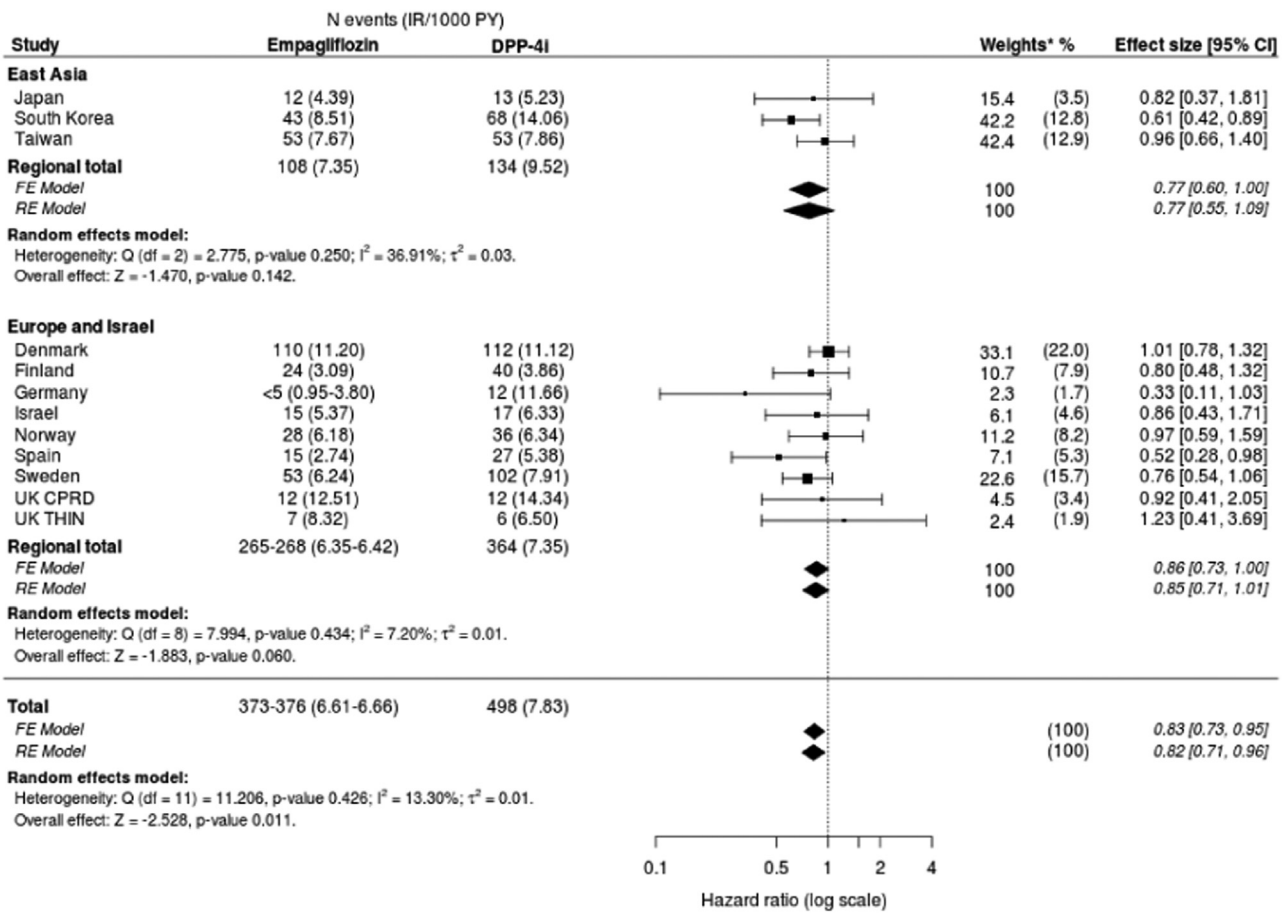

Fig. 5. Hazard ratios for stroke in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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to DPP-4i (Fig. 10). The remaining three countries (South Korea, Spain, and UK) had no observed events of ESRD among the examined patient pairs.

For three out of five safety outcomes (bone fracture (0·89; 0·77 to 1·02), SH (0·95; 0·75 to 1·20), and LLA (0·78; 0·52 to 1·17)), no differences in risk were observed between empagliflozin and DPP-4i (Fig. 11 (all 11 countries), Fig. 13 (all 11 countries), Fig. 14 (Finland and Spain not included), respectively). Among the 12 country-specific HRs for bone fracture (two point-estimates for UK due to the CPRD and THIN data sources), eight were in favor of empagliflozin and four were in favor of any DPP-4i which led to an overall neutral HR in the meta-analysis (Fig. 11). Events of DKA were reported in six countries (Denmark, Finland, Sweden, Japan, South Korea, and Taiwan) with IR below 3/1000 PY; however, a higher risk was observed among initiators of empagliflozin (1·97; 1·28 to 3·03) compared to DPP-4i (Fig. 12). For SH, Taiwan exhibited the highest IR (28·6 to 37·7/1000 PY) and was the only country with lower risk in users of empagliflozin compared to DPP-4i (0·76; 0·64 to 0·90) (Fig. 13). IR for LLA were < 2/1000 PY in all countries except Germany where reported IR of 11·5 and 15·6/1000 PY were observed, resulting overall in no differences in risk for LLA between individuals initiating empagliflozin compared to DPP-4i (Fig. 14). For AKI requiring dialysis (reported for Denmark, Finland, Spain, South Korea, and Taiwan), there was inter-country variation of the IR between 0·1–12·7/1000 PY with an overall 44% lower risk among individuals initiating empagliflozin compared to DPP-4i (0·56; 0·38 to 0·82) (Fig. 15).

In all sensitivity analyses (ITT approach; the AT approach with an alternate grace period of 30 and 90 days), results were consistent with results from the main analyses (*supplementary material, section f; Figs. 7 and 18; see supplementary materials associated with this article on line*). Despite higher average follow-up time of 1·2 years in the ITT analytic approach, the direction and magnitude of findings were similar to results from the main AT analyses. Similar results were also observed in sensitivity analyses with differing lengths of time for grace periods. With an alternative length of the risk window of 90 days, instead of 30 days, the HRs were consistent with the main analyses (*supplementary material, section f, Figs. 20, 22, 24, 26, 28; see supplementary materials associated with this article on line*). Similarly, with an alternative length of the risk window of 14 days, the HRs were also consistent with the main analyses (*supplementary material, section f; Figs. 19, 21, 23, 25, 27; see supplementary materials associated with this article on line*).

Discussion

This EMPRISE study utilized routine clinical practice data from 11 countries (*supplementary material, section g; see supplementary materials associated with this article on line)* and focused on individuals

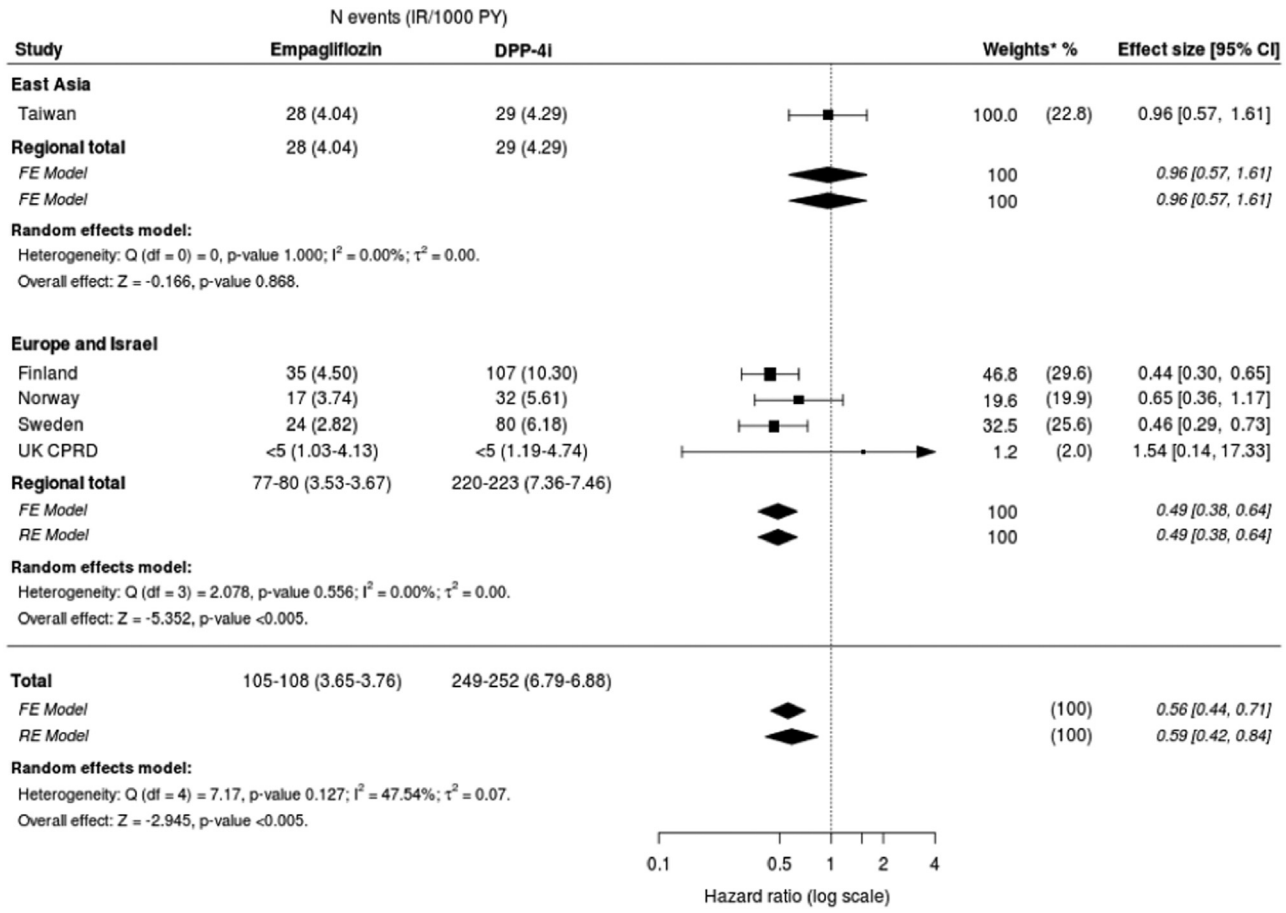

Fig. 6. Hazard ratios for cardiovascular mortality in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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with T2D initiating empagliflozin or DPP-4i during the years 2014–2019. Its results demonstrate that initiation of empagliflozin when compared to DPP-4i is associated with both a lower risk for cardiovascular and kidney outcomes and has a safety profile consistent with that documented in previous observational studies [12] and clinical trials [6].

In addition to consistency with trial evidence, these findings also complement the previous EMPRISE US study results [10–12] and address the evidence gap surrounding other RWE of the cardiovascular effects of the SGLT-2i drug class by demonstrating in routine clinical care settings that initiation of the individual SGLT-2i empagliflozin is specifically associated with lower risk of HHF, ACM, stroke, and ESRD when compared to DPP-4i. Despite observed benefit of empagliflozin on most primary outcomes, no differences in risk for MI were observed across study groups, which is a finding consistent with results from the EMPA-REG OUTCOME® trial [6,8,16] and EMPRISE US studies [10–12].These EMPRISE safety results were also similar to previous trial reports in that no difference in risk for bone fractures, SH, and LLAs were observed when compared to DPP-4i. Despite the low rates of DKA observed across EMPRISE sites, individuals initiating empagliflozin were nearly twice as likely to experience DKA, which is a finding consistent with the already existing knowledge from epidemiological studies about DKA in relation to SGLT-2 inhibitor use in patients with T2D [17,18].

Earlier marketing authorization for dapagliflozin and canagliflozin compared to empagliflozin [19–23] allowed examination of the cardio-protective effect of the SGLT-2i drug class at a time when empagliflozin was only recently available in clinical practice. Results from these large, multinational, RWE studies suggested the lower risk of HHF and death observed in SGLT-2is when compared to other glucose-lowering agents may be a class effect that extends to empagliflozin, although no direct examination of empagliflozin as an individual SGLT-2i was performed. Based on evidence from individuals across Western and Eastern countries, the CVD-REAL and CVD-REAL 2 studies demonstrated a lower risk of HHF, ACM, MI and stroke in a combined group of individuals using any of three SGLT-2is (dapagliflozin, canagliflozin, or empagliflozin) compared to other glucose lowering drugs [19,24]. Although empagliflozin was not examined individually in these studies, it was suggested that the benefits may carry forward to empagliflozin specifically. Furthermore, a meta-analysis of 14 similar RWE studies including 3.2 million individuals concluded that the SGLT-2i drug class has robust benefits on reducing MACE, ACM, HHF, MI, stroke, CVM, and HF regardless of a history of using other glucose-lowering drugs [25]. Despite the robust nature of this evidence, neither the cardiovascular effectiveness nor the safety of empagliflozin was specifically examined in these studies. This EMPRISE study is among the first to provide RWE from a diverse set of countries across two continents that supports existing evidence

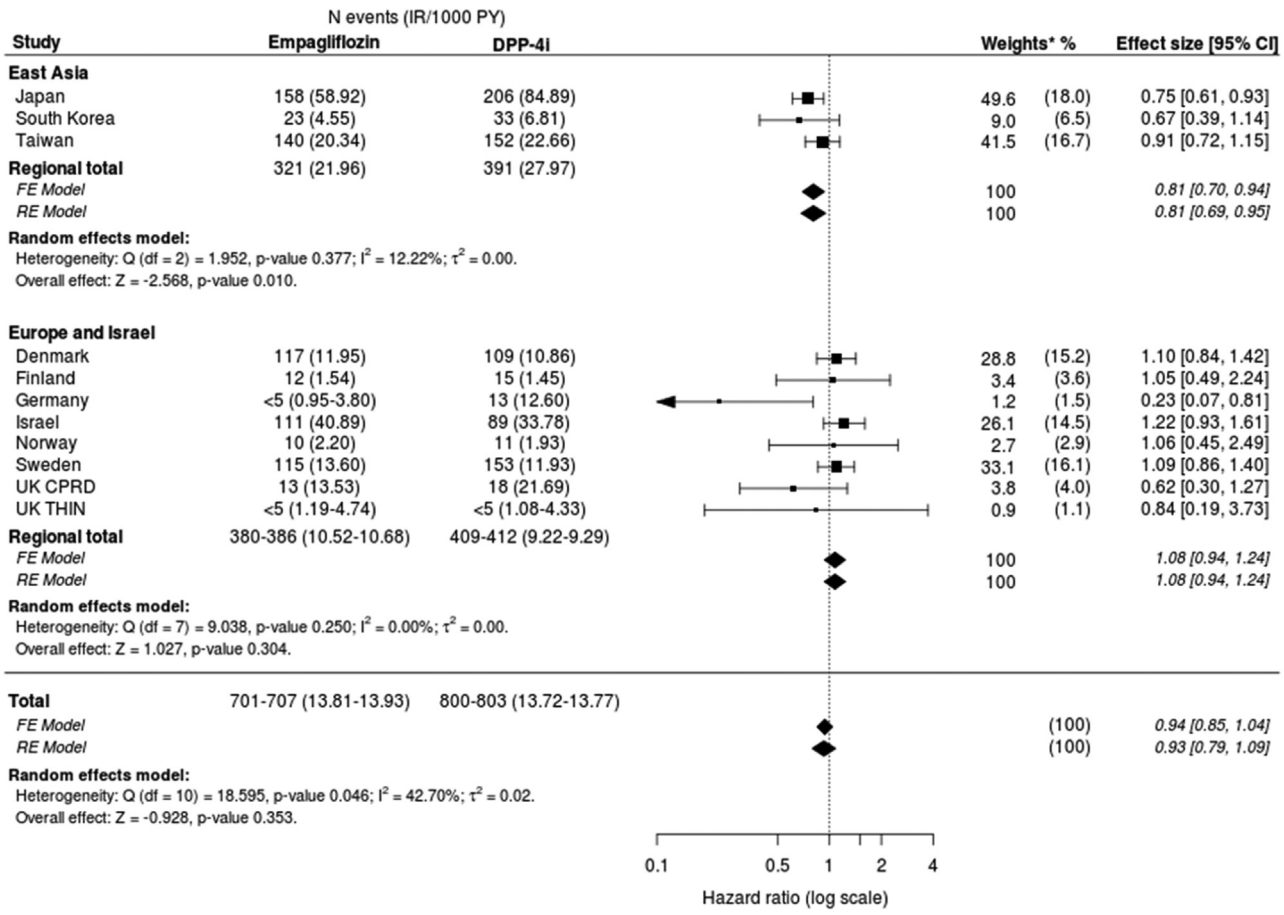

Fig. 7. Hazard ratios for coronary revascularization procedure in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

* Weights: The weights in parentheses represent the countries' weight with all countries included in the meta-analysis. The weights presented without parentheses correspond to the countries' weight when included only in the regional meta-analysis.

Results presented utilized the As-Treated analytic approach with 100% grace period prior to censoring for medication discontinuation.

Studies with insufficient numbers of events for reporting or for analysis in either of the study group are omitted from the analysis. Numbers <5 are not shown due to data protection but are included in meta-analysis. If values <5 exist, total number of events and incidence rates are presented as intervals.

[6,7,9] and further substantiates the cardiovascular and kidney benefit of empagliflozin when compared to DPP-4i. Moreover, results from this study also demonstrate that empagliflozin is safe with respect to bone fractures, SH, LLA [26], and AKI [27] and quantify the risk of DKA.

Strengths

The diverse patient population with T2D was selected from 11 countries and included 85,244 pairs of PS-matched individuals. These data complement and expands the representativeness of available clinical trial evidence for the cardiovascular and kidney effectiveness and safety of empagliflozin when compared to DPP-4i. The EMPRISE study methodology addressed many forms of potential bias that impact RWE studies. Specifically, the active comparator, new-user design and PS matching used in this study limited residual confounding. Additionally, immortal time bias was limited by initiating follow-up at the first drug prescription. In contrast to previous studies [19,22], the use of DPP-4i instead of a combined group of "other glucose-lowering treatments" as the comparator also decreased confounding by indication since DPP-4i users during the study period had a similar indication to drug use as individuals in the empagliflozin cohort.

Limitations

As with any observational study, the possibility for residual confounding remains despite mitigation approaches used. The level of population representativeness and data availability in the registers/databases used for this study varied across the eleven countries in EMPRISE. Several countries sourced data from nationwide health care registers and they were largely representative of the overall populations examined. Although most study sites in EMPRISE were in the outpatient primary care setting, some study sites included acute care (e.g., Japan) and specialty care (e.g., Germany) practices which likely resulted in patient populations with longer duration/more advanced T2D and greater prevalence rates of comorbidities (e.g., hypertension, HF). Such variations in healthcare settings across countries likely contributed to the wide variation observed in the prevalence of comorbidities in patient populations across EMPRISE sites. Also, differences may exist across the study countries regarding prescribing practices and approaches used for diagnostic coding. These country-level differences in the populations represented may explain the large variation in the high proportion of individuals with congestive HF, ischemic heart disease, or other comorbidities at baseline across regions. The data sources used for this EMPRISE study also varied in terms of completeness and availability of covariates to

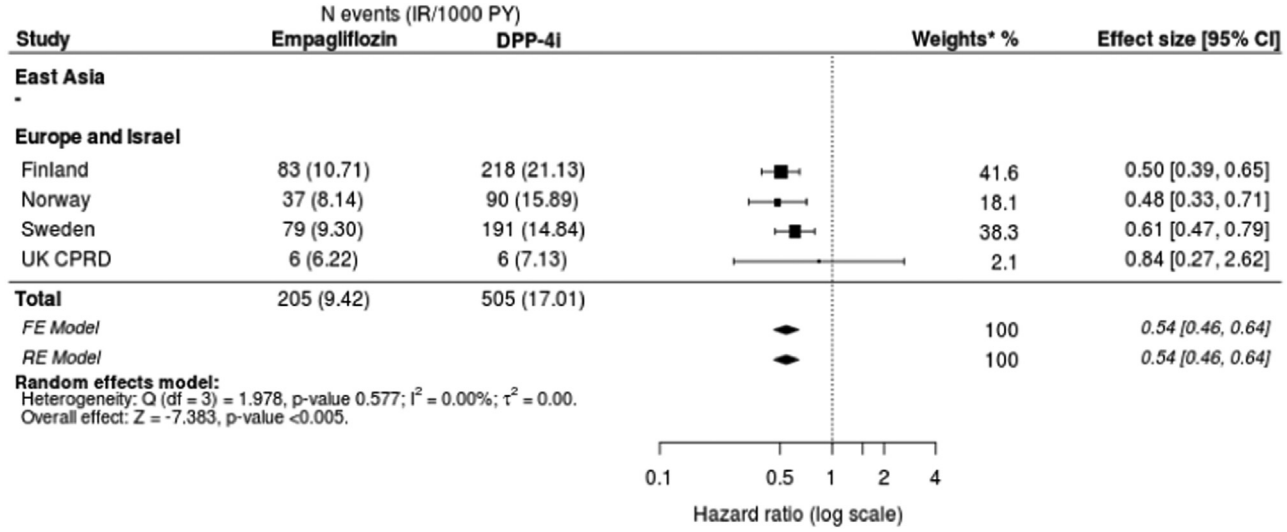

Fig. 8. Hazard ratios for composite outcome of hospitalization for heart failure or cardiovascular mortality in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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Results presented utilized the As-Treated analytic approach with 100% grace period prior to censoring for medication discontinuation. The HHF definition used any hospitalization with an associated heart failure diagnosis code (Japan, South Korea); heart failure as primary diagnosis associated with hospital admission (Denmark, Finland, Germany, Norway, Sweden); diagnosis of heart failure in any position of hospitalization (Israel, UK CPRD); any heart failure diagnosis associated with healthcare encounters, including hospitalizations, specialist outpatient, and primary care encounters (Spain).

Studies with insufficient numbers of events for reporting or for analysis in either of the study group are omitted from the analysis. Numbers <5 are not shown due to data protection but are included in meta-analysis. If values <5 exist, total number of events and incidence rates are presented as intervals.

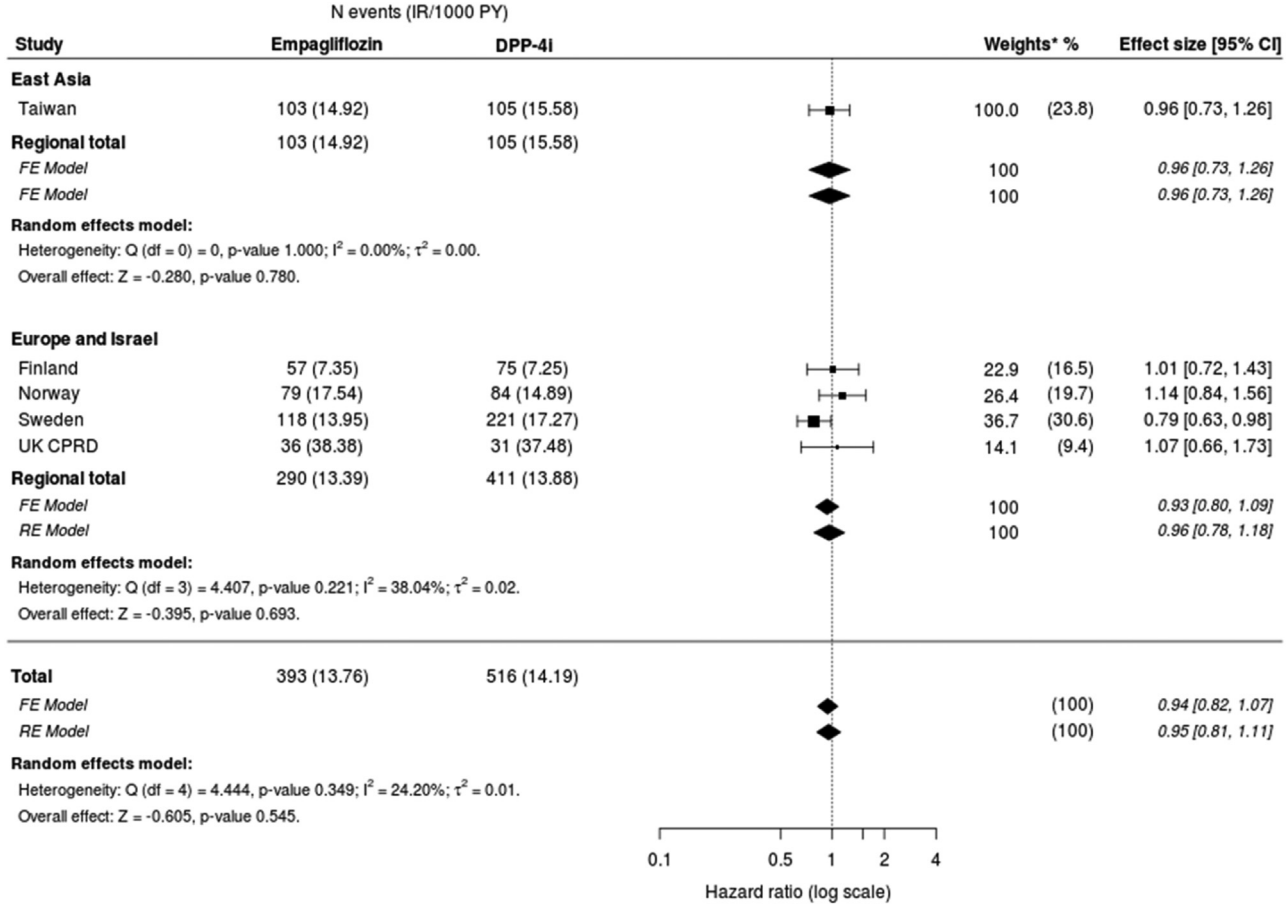

Fig. 9. Hazard ratios for 3-point major adverse cardiovascular events (MACE) in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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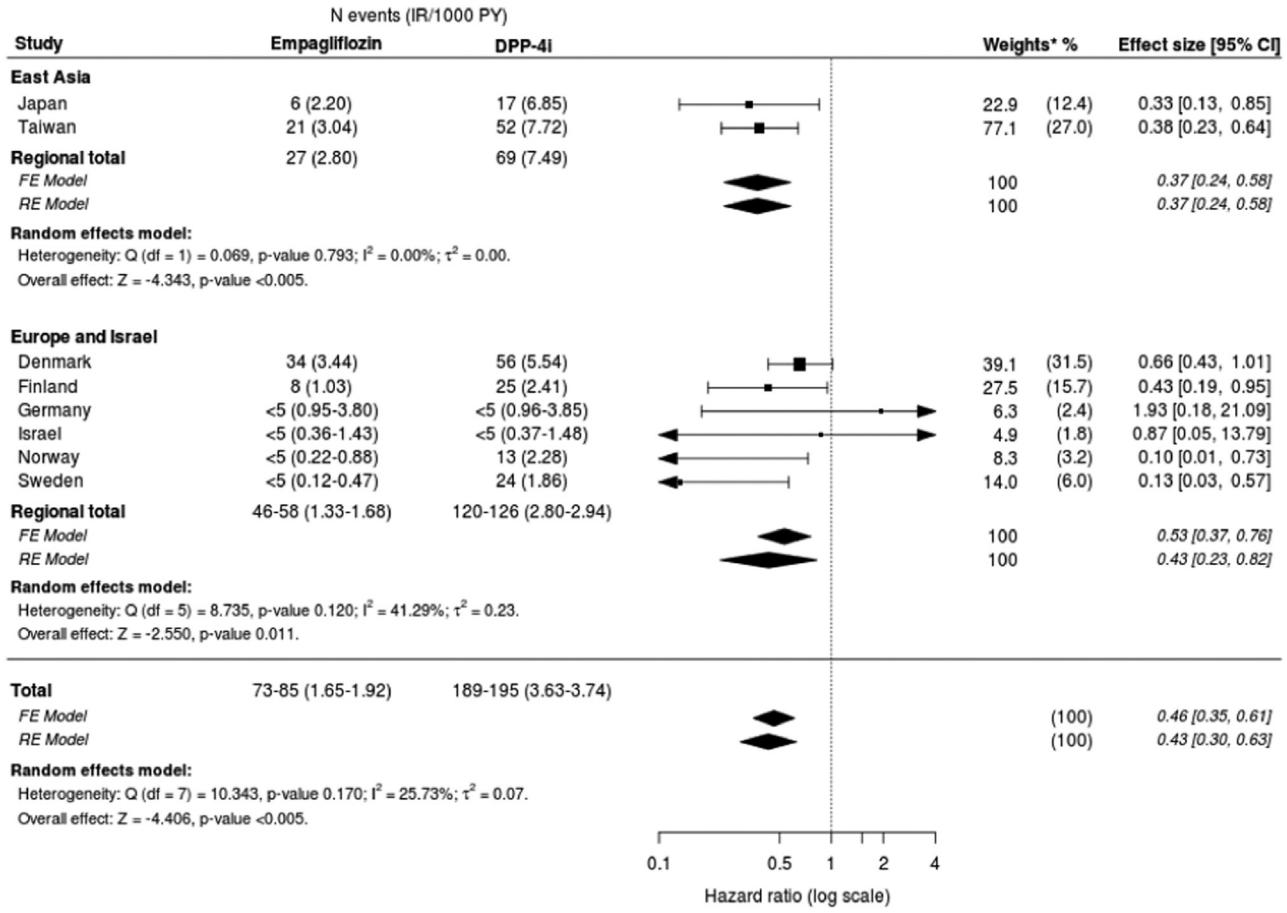

Fig. 10. Hazard ratios for end-stage renal disease in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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describe comorbidities and clinical health at inclusion, which may have influenced the ability to account for residual confounding.

Clinical implications

The recent expansion of the indication for empagliflozin to a broad range of individuals with HF across the spectrum of ejection fraction, together with the robust results from real world studies like EMPRISE in individuals with T2D, support the consideration of empagliflozin by prescribers as both a drug that can reduce hyperglycemia in individuals with T2D and as a treatment that reduces risk for cardiovascular events and prevents the progression of renal disease in individuals both with and without T2D.

Conclusions and perspectives of results

Results from RWE studies have shown beneficial cardiovascular and kidney effects of empagliflozin with no increased risk for safety outcomes except for a higher risk for DKA in individuals with T2D when compared to DDP-4i. Many international treatment guidelines have recently been updated to reflect SGLT-2is and glucagon-like peptide-1 receptor agonists as effective therapies regardless of metformin glycemic needs. These EMPRISE results support efforts to translate such treatment guidelines into clinical practice.

Contributors

Avraham Karasik, Daisuke Yabe, Dae Jung Kim, Kyong Hwa Ha, Anuradhaa Subramanian, Leo Niskanen, Fabian Hoti, Riho Klement, Soulmaz Fazeli Farsani, Elisabetta Patorno, Anouk Déruaz-Luyet, Moe H. Kyaw, Lisette Koeneman, and Júlio Núñez contributed to the design of the study.

Avraham Karasik, Stefanie Lanzinger, Elise Chia-Hui Tan, Daisuke Yabe, Dae Jung Kim, Cheli Melzer-Cohen, Kyong Hwa Ha, Francesco Zaccardi, Anuradhaa Subramanian, Leo Niskanen, Fabian Hoti, Riho Klement, Soulmaz Fazeli Farsani, Anouk Déruaz-Luyet, Moe H. Kyaw, Bendix Carstensen, Sigrun Halvorsen, and Júlio Núñez were responsible for data acquisitions, data management and statistical analyses in the respective countries. Fabian Hoti and Riho Klement were responsible for the meta-analyses.

All authors contributed to data interpretation and critical evaluation, participated in the drafting of the work and critical revision of the drafts. All authors approved the final version of the manuscript for publication. Soulmaz Fazeli Farsani had final responsibility for the decision to submit for publication.

Verification of the underlying data

Data was extracted, managed, curated, and analyzed locally. Aggregated data from all countries were pooled for the meta-

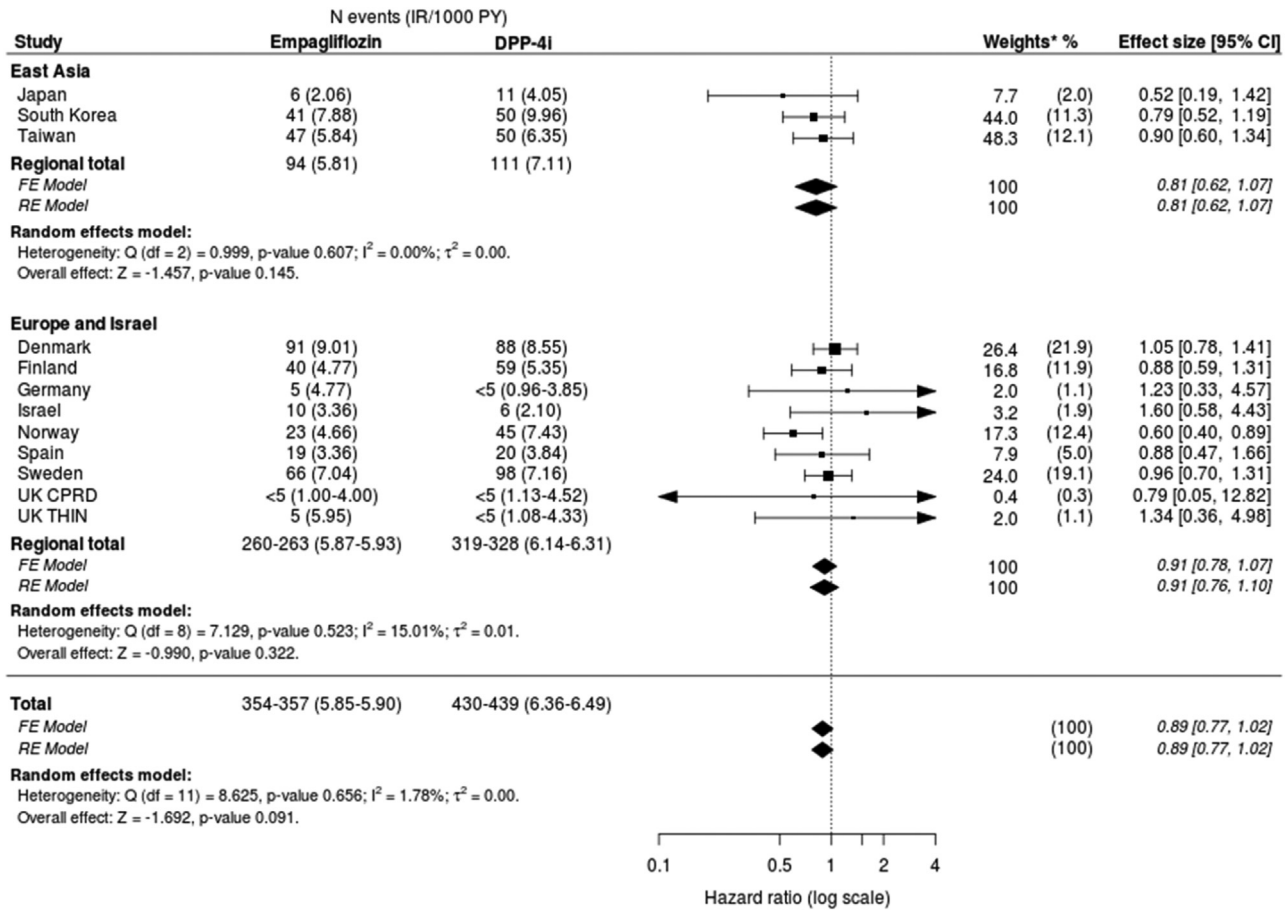

Fig. 11. Hazard ratios for bone fractures in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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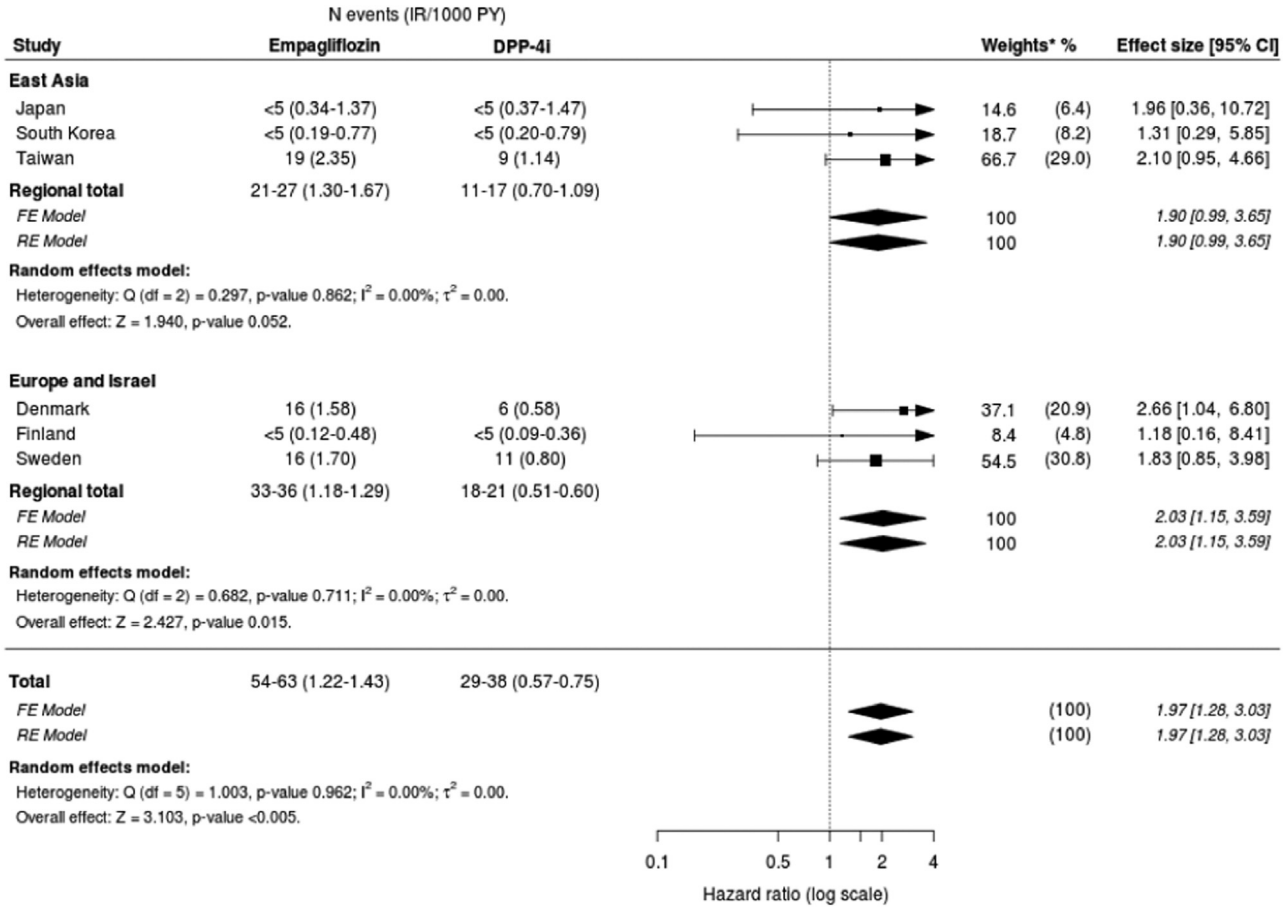

Fig. 12. Hazard ratios for diabetic ketoacidosis in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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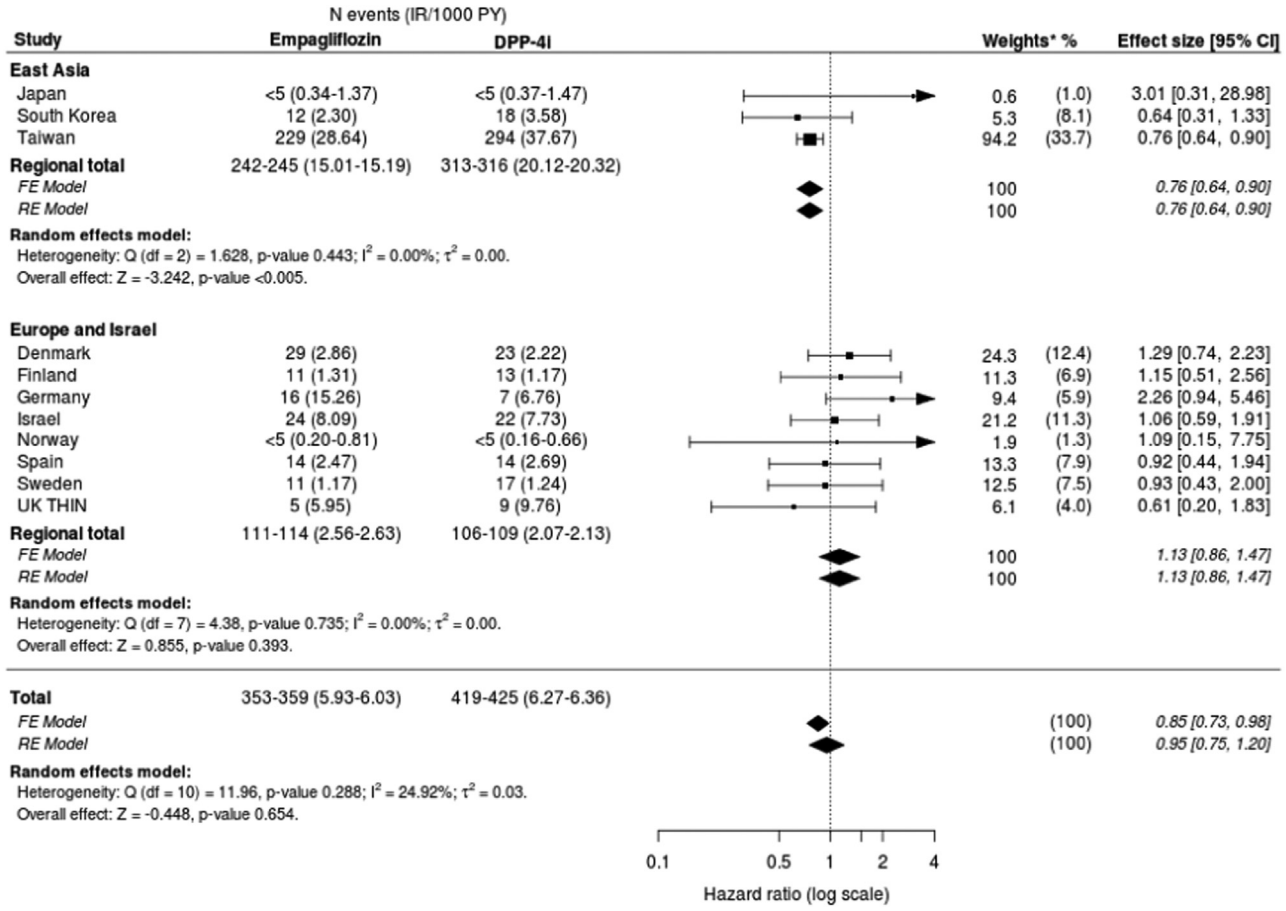

Fig. 13. Hazard ratios for severe hypoglycemia in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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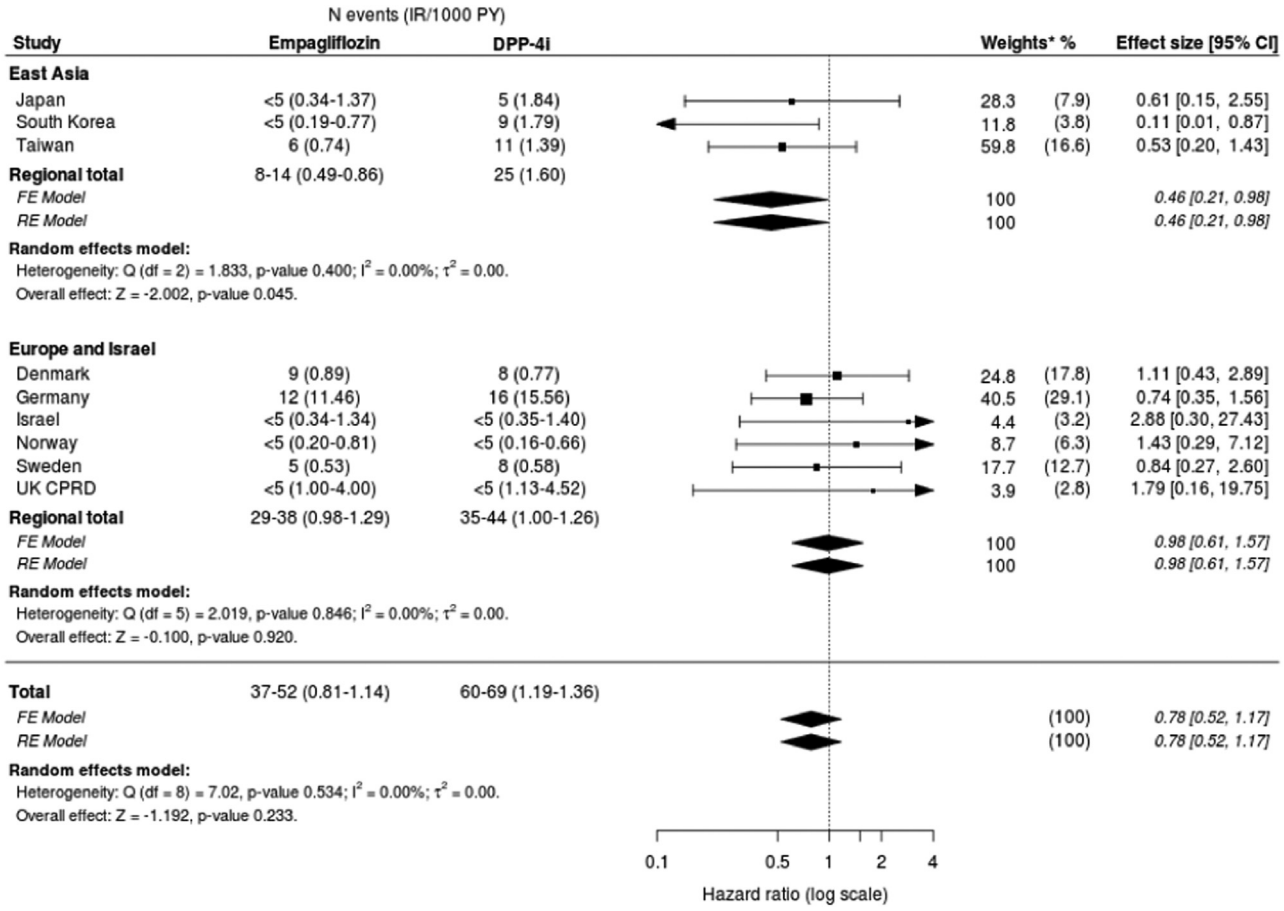

Fig. 14. Hazard ratios for lower-limb amputation in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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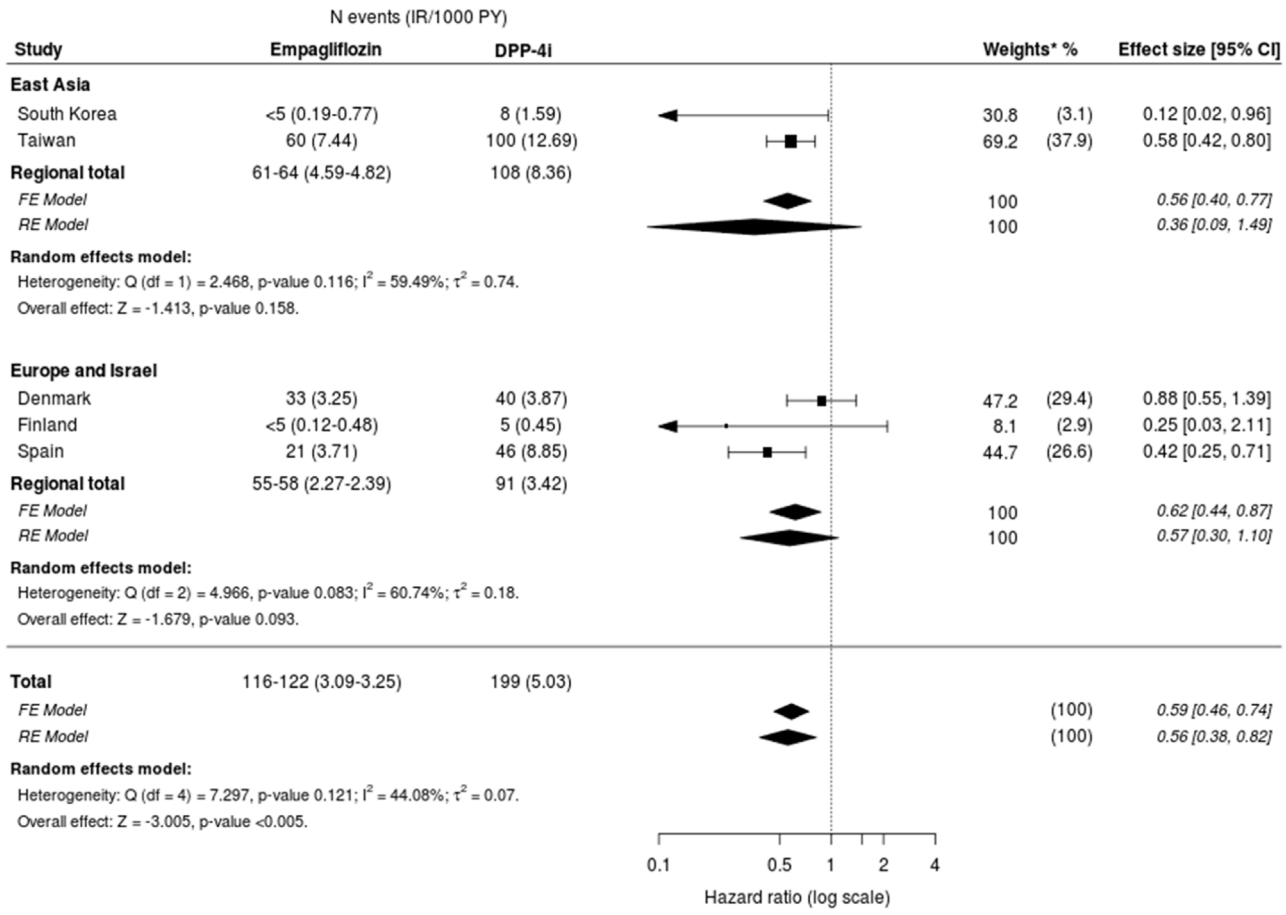

Fig. 15. Hazard ratios for acute kidney injury requiring dialysis in empagliflozin vs. DPP-4i

DPP-4i - Dipeptidyl peptidase-4 inhibitor; FE – Fixed effects; IR – Incidence rates; PY – Person-years; RE – Random effects; UK – United Kingdom.

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analyses by the IQVIA team. Riho Klement and Fabian Hoti verified the underlying aggregated data and had access to the aggregated data. In each country, the underlying data was verified by local principal investigators. They also undertook the task of curating the data from the country into a standardized format.

Data sharing statement

The data that support the findings of this study are available from third party data vendors. Data sharing by the study authors is not allowed under the current data use agreements.

This study used Korean NHIS-NSC data (NHIS-2022-1-455) made by National Health Insurance Service (NHIS). The authors declare no conflict of interest with NHIS.

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Declaration of Competing Interest

Avraham Karasik has received research grants and consulting fees from Boehringer Ingelheim; research grants from Astra Zeneca; research grants, consulting fees, and speaker fees from Novo Nordisk. Daisuke Yabe has received consulting/lecture fees from Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co. Ltd., and Takeda Pharmaceutical Company Limited, and grants from Arkray Inc., Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim, Ono Pharmaceutical Co. Ltd., Taisho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Company Limited, and Terumo Corporation. Dae Jung Kim has received grants support from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis Korea, Jeil Pharmaceutical, and Chong Kun Dang, speaker fees from Boehringer-Ingelheim, Novo Nordisk, Boryung, Hanmi, Novartis, Donga ST, Celltrion, AstraZeneca, and Dong Wha Pharmaceuticals. Wayne H—H Sheu has been 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, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Sanofi-Aventis, Takeda Pharmaceutical Company. Kamlesh Khunti has acted as a consultant, speaker or received consultation/lecture grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, and

Merck Sharp & Dohme, Boehringer Ingelheim, Bayer. Francesco Zaccardi has received speaker fees from Boehringer Ingelheim and Napp Pharmaceuticals. Thomas Nyström has received unrestricted grants from AstraZeneca and NovoNordisk and has been a national advisor of Abbot, Amgen, Novo Nordisk, Sanofi-Aventis, Eli Lilly, MSD, and Boehringer Ingelheim. Leo Niskanen has received speaker and consulting fees from Boehringer Ingelheim, MSD, AstraZeneca, and Sanofi, research grant to the institution, consulting fees, and speaker fees from Novo Nordisk. Majken Linnemann Jensen, Fabian Hoti, Riho Klement are employees of IQVIA and contracted by Boehringer Ingelheim to conduct the analyses. Soulmaz Fazeli Farsani, Anouk Déruaz-Luyet are employees of Boehringer Ingelheim International GmbH. Moe H Kyaw was employee of Boehringer Ingelheim. Lisette Koeneman is employee of Eli Lilly & Company and owns stock of Eli Lilly & Company. Dorte Vistisen has received research grants from Bayer A/S, Sanofi, Novo Nordisk A/S, and Boehringer Ingelheim. She holds shares in Novo Nordisk A/S. Sigrun Halvorsen has received speaker fees from Sanofi, Novartis, Boehringer Ingelheim, Bayer, Pfizer, and Bristol-Myers Squibb. Gisle Langslet has received consulting/lecture fees from Amgen, Sanofi, and Boehringer Ingelheim. Elisabetta Patorno has received a research grant from Boehringer Ingelheim. Julio Núñez reports personal fees from AstraZeneca, Novartis, Boehringer-Ingelheim, Eli Lilly, Rovi, Novo Nordisk, and Vifor Pharma (outside the submitted work). Stefanie Lanzinger, Reinhard W Holl, Elise Chia-Hui Tan, Cheli Melzer-Cohen, Kyong Hwa, Bendix Carstensen: None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2022.101418.

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