



ORIGINAL ARTICLE

The effect of empagliflozin on the total burden of cardiovascular and hospitalization events in the Asian and non-Asian populations of the EMPA-REG OUTCOME trial of patients with type 2 diabetes and cardiovascular disease

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Abstract

Aims: The sodium-glucose co-transporter 2 inhibitor empagliflozin reduced the total burden of cardiovascular, mortality, and all-cause hospitalization events, including first and recurrent events, in EMPA-REG OUTCOME participants with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease (ASCVD). We investigated the effect of empagliflozin on the total burden of cardiovascular and hospitalization events in Asian participants.

Materials and methods: Participants were randomized to empagliflozin 10 mg, 25 mg or placebo plus standard of care. The primary and key secondary outcomes were the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke and the primary outcome plus hospitalization for unstable angina, respectively. The effect of pooled empagliflozin versus placebo on total (first plus recurrent) cardiovascular and hospitalization events was analysed using a negative binomial model that preserves randomization and accounts for within-patient correlation of multiple events. We analysed Asian versus non-Asian EMPA-REG OUTCOME population subgroups post hoc.

Results: Among 1517 Asian participants, empagliflozin reduced the relative risk of total events of the primary outcome by 39% versus placebo [rate ratio (95% confidence interval): 0.61 (0.43, 0.89)], the key secondary outcome by 33% [0.67 (0.48, 0.93)], the composite of cardiovascular death (excluding fatal stroke) and hospitalization for heart failure by 43% [0.57 (0.33, 0.996)], and all-cause hospitalization by 21% [0.79 (0.65, 0.97)]. The effects of empagliflozin were consistent between Asian and non-Asian populations (treatment-by-subgroup interaction $p > .05$).

Conclusions: Empagliflozin reduced the total burden of cardiovascular and hospitalization events in Asian and non-Asian EMPA-REG OUTCOME participants with T2D and established ASCVD, consistent with the overall trial population.

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KEYWORDS

cardiovascular disease, antidiabetic drug, clinical trial, empagliflozin, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

In 2019, 35.1% (163 million) of global adult cases of diabetes were in the Western Pacific region (including Japan and China).¹ This region had the highest number of deaths because of diabetes (1.3 million) among all of the International Diabetes Federation regions, and the number of cases is expected to increase to 212 million by 2045, with the majority being type 2 diabetes (T2D).¹

The Asian T2D population typically differs from T2D populations in the rest of the world in terms of pathophysiology of T2D, lifestyle (e.g. diet) and other disease-related factors, including genetic background and cardiovascular (CV) risk. For instance, Asian populations have lower insulin secretion because of greater pancreatic beta-cell dysfunction and higher visceral adiposity, and develop T2D at lower body mass index (BMI) ranges compared with Western populations.^{2,3}

CV disease is a major cause of premature mortality in people with diabetes, including in Asian populations.⁴ A recent multinational cohort study, including countries in Europe and Asia, found that heart failure (HF) is a frequent manifestation in T2D and is associated with an increased risk of mortality.⁵ Studies also showed that the presence of T2D increases the risk of all-cause hospitalization.⁶⁻⁸ With some variations among regions and countries, Asian populations often show different CV disease risk profiles, such as an increased risk of stroke^{2,9,10} and a lower risk of coronary heart disease, compared with Western populations.^{11,12} Furthermore, according to 2019 data, 35% of CV deaths were from stroke in Southeast Asia, versus 24% and 27% in Europe and America, respectively.¹² Some Asian countries, including China, India, Indonesia and Japan, are among the 10 countries with the highest levels of CV disease deaths globally⁹ and, as in other populations, a residual CV risk remains in the Asian population despite use of standard of care therapies for CV prevention.^{9,11-14}

Currently, there is an unmet need for effective therapies that reduce the residual risk of T2D complications in the Asian population.^{9,11-16} The highly selective sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin has been shown to be well tolerated, improve glycaemic control, reduce body weight and reduce blood pressure in pooled analyses of Asian and East Asian patients, consistent with other populations.^{17,18} In time-to-first event analyses of the EMPA-REG OUTCOME trial, empagliflozin was shown to reduce the risk of first events of the primary outcome of 3-point major adverse CV events (a composite of CV death, non-fatal myocardial infarction [MI], and non-fatal stroke) by 14%, as well as CV mortality by 38% and hospitalization for HF (HHF) by 35% in patients with T2D with established atherosclerotic CV disease from 42 countries across the globe.¹⁹ First events of the key secondary outcome of 4-point major adverse CV events (3-point major adverse CV events plus hospitalization for unstable angina) were not significantly reduced with

empagliflozin.¹⁹ In subsequent time-to-first event analyses of Asian EMPA-REG OUTCOME participants, the effects of empagliflozin on CV outcomes were shown to be consistent with the overall population (*p*-values for interaction by race >.05).²⁰ The adverse event profile of empagliflozin in Asian patients was also similar to the overall trial population.²⁰

Time-to-first event analyses are the gold standard for evaluation of clinical outcomes trials, but do not capture effects on the total morbidity burden experienced by patients and underestimate the net impact of effective interventions on healthcare resource utilization. Therefore, analysis of total (first plus recurrent) events is emerging as an important complement to traditional analytical methods.²¹ In previous total-versus-first-event analyses, a numerically greater treatment effect with empagliflozin was observed in the overall EMPA-REG OUTCOME trial population.²² For example, with empagliflozin versus placebo, a 17% relative risk reduction in total events of all-cause hospitalization was observed compared with 12% for first events only; a similar pattern was observed with a number of other CV outcomes.²²

A previous large-scale randomized clinical trial of the alpha-glucosidase inhibitor, acarbose, in 6522 Chinese participants with impaired glucose tolerance and without T2D (the 'ACE' trial) reported data on recurrent HF events.²³ However, to our knowledge, except for a study of metformin versus glipizide in 304 Chinese patients with T2D and coronary artery disease,²⁴ randomized clinical trials assessing the effect of T2D medications on total CV events including recurrent events in Asian populations with T2D are currently scarce.

We assessed the effect of empagliflozin on total (first plus recurrent) CV and hospitalization events in Asian versus non-Asian participants of the EMPA-REG OUTCOME trial.

2 | MATERIALS AND METHODS

2.1 | Trial design

In the EMPA-REG OUTCOME trial, patients with T2D, haemoglobin A1c (HbA1c) 7%-10%, established CV disease typically of atherosclerotic origin (MI, stroke, coronary artery disease, peripheral artery disease), and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m² were randomized 1:1:1 to empagliflozin 10 mg, 25 mg, or placebo. EMPA-REG OUTCOME was designed as a non-inferiority trial of empagliflozin (pooled 10 mg and 25 mg doses) versus placebo, in accordance with regulatory guidance to assess the CV safety of glucose-lowering drugs, with superiority hierarchically assessed.¹⁹ Participants were asked to select their race based on the following options: White, Asian, black/African American, American Indian or Native Alaskan, and Native Hawaiian or other Pacific Islander.

Outcomes in those who selected 'Asian', and subsequently those who were also situated in East Asian countries (i.e. Hong Kong, Japan, Taiwan and Korea), were assessed post hoc.

2.2 | Outcomes

CV outcome events and deaths were prospectively adjudicated by two clinical events committees (one for cardiac events and the other for neurological events), as recommended by the Food and Drug Administration guidelines.²⁵ Hospitalizations were captured by adverse event reporting as adverse events leading to hospitalization [Medical Dictionary for Regulatory Activities (MedDRA), version 18.0]. The primary outcome of the trial was 3-point major adverse CV events and the key secondary outcome was 4-point major adverse CV events. Additional outcomes included: MI (fatal and non-fatal); main coronary outcome (MI and coronary revascularization); expanded coronary outcome (MI, coronary revascularization and hospitalization for unstable angina); coronary revascularization; hospitalization for unstable angina; stroke (fatal or non-fatal); transient ischaemic attack (TIA); the composite of stroke (fatal or non-fatal) and TIA; HHF; composite of CV death (excluding fatal stroke) and HHF; all-cause hospitalization; all-cause mortality; and CV death. Excluding mortality outcomes, all outcomes included fatal and non-fatal events.

Participants who prematurely discontinued a study drug or experienced a first outcome event were to be followed for ascertainment of (further) CV outcomes. Attempts were made to collect vital status information for any participant who was lost to follow-up, as allowed by local guidelines.

2.3 | Statistical methods

The empagliflozin groups (10 mg and 25 mg) were pooled, for comparison with placebo for analyses of all investigated outcomes. Analyses were repeated for the individual empagliflozin doses (10 mg and 25 mg) for the primary outcome of 3-point major adverse CV events. The analyses included all participants who received at least one dose of study drug (modified intention-to-treat population). We calculated confidence intervals (CIs) and *p*-values without adjustment for multiplicity. Occurrence of all events for each outcome were plotted over time using mean cumulative function plots (showing the cumulative average number of events per participant). The rate of total (first plus recurrent) events was analysed using a negative binomial model with CIs based on robust error variance estimators. The use of negative binomial regression for the analyses of total events in the overall population was pre-specified.²² Analyses of total events of 3-point major adverse CV events, MI, stroke and HHF in the overall population were pre-specified and total events analyses of other outcomes were selected post hoc.²² Asian versus non-Asian (determined by patient self-classified race) subgroup analyses of total events were conducted post hoc using a negative binomial model, including terms for age, sex, baseline HbA1c, baseline eGFR, region, baseline BMI and subgroup, as

well as a treatment-by-subgroup interaction term to investigate consistency between treatment effects on outcomes. Mortality events were analysed using a Poisson regression model including the same baseline factors.

Total events of all-cause hospitalization were assessed for the Asian and non-Asian subgroups using a Wei-Lin-Weissfeld (WLW) model time-to-event analysis²⁶ to produce estimated relative treatment effect hazard ratios (HRs) by order of event (1st, 2nd, 3rd events etc.), including a test of the consistency of treatment effect estimates across the individual order of sequential events. The WLW model otherwise included similar terms as the negative binomial model. The WLW analysis was conducted in the Asian and non-Asian subgroups separately.

Incidence rates of outcomes in the empagliflozin and placebo treatment groups are presented in the East Asian population for comparison with the Asian population.

As previously reported for the overall EMPA-REG OUTCOME population,²² we analysed baseline characteristics according to the number of events experienced by participants during the trial [i.e. 0, 1 and >1 event(s)] in the placebo group for the primary outcome of 3-point major adverse CV events, the main coronary outcome, HHF and all-cause hospitalization.

All analyses were performed at the nominal alpha level of .05 without correction for multiple hypothesis testing. All analyses were performed with SAS version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Patient demographics

In total, 7020 patients were randomized to receive empagliflozin 10 mg, 25 mg or placebo for a median of 2.6 years with 3.1 years of median follow-up. As previously reported, baseline characteristics were similar between treatment groups.¹⁹

In total, 1517 (21.6%) EMPA-REG OUTCOME trial participants identified as Asian, of whom 1345 were from countries in Asia (Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand). Table 1 shows the baseline demographics for Asian and non-Asian participants. At baseline, Asian participants had a lower mean weight and BMI, and a greater proportion with BMI <25 kg/m² compared with non-Asian participants (35.7% vs. 7.1%, respectively). Baseline use of diuretics, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers was lower in Asian compared with non-Asian participants. In addition, compared with non-Asian participants, a smaller proportion of Asian participants received glucose-lowering medications as monotherapy, a greater proportion used sulphonylureas, and a smaller proportion used insulin. A smaller proportion of Asian versus non-Asian participants had a history of peripheral artery disease, coronary artery bypass graft, MI or HF at baseline, and a greater proportion had a history of multivessel coronary artery disease. With these exceptions, baseline characteristics were balanced between the Asian and non-Asian populations; for example, the proportion of Asian participants with stroke was comparable with the non-Asian population. As previously reported,

TABLE 1 Baseline demographics of the Asian and non-Asian populations

	Asian		Non-Asian		Total (N = 5502)
	Placebo (N = 511)	Pooled empagliflozin (N = 1006)	Placebo (N = 1822)	Pooled empagliflozin (N = 3680)	
Male, n (%)	379 (74.2)	739 (73.5)	1301 (71.4)	2596 (70.5)	3897 (70.8)
Age, years; n (%)					
<65	340 (66.5)	649 (64.5)	957 (52.5)	1946 (52.9)	2903 (52.8)
≥65	171 (33.5)	357 (35.5)	865 (47.5)	1734 (47.1)	2599 (47.2)
Age, years; mean ± SD	60.7 ± 9.4	61.1 ± 9.1	63.9 ± 8.5	63.7 ± 8.3	63.8 ± 8.4
Time since T2D diagnosis, years; n (%)					
≤1	19 (3.7)	45 (4.5)	33 (1.8)	83 (2.3)	116 (2.1)
>1 to 5	91 (17.8)	198 (19.7)	280 (15.4)	514 (14.0)	794 (14.4)
>5 to 10	149 (29.2)	233 (23.2)	422 (23.2)	942 (25.6)	1364 (24.8)
>10	252 (49.3)	530 (52.7)	1087 (59.7)	2141 (58.2)	3228 (58.7)
HbA1c, % ± SD	8.09 ± 0.86	8.06 ± 0.84	8.08 ± 0.84	8.07 ± 0.85	8.07 ± 0.85
Weight, kg; mean ± SD	70.73 ± 13.17	70.79 ± 13.36	91.08 ± 18.04	90.42 ± 17.96	90.63 ± 17.99
Body mass index, kg/m ² ; mean ± SD	26.60 ± 3.90	26.67 ± 4.08	31.80 ± 5.00	31.68 ± 5.04	31.72 ± 5.03
<25 kg/m ² ; n (%)	184 (36.0)	358 (35.6)	117 (6.4)	275 (7.5)	392 (7.1)
≥25 kg/m ² ; n (%)	327 (64.0)	648 (64.4)	1705 (93.6)	3405 (92.5)	5110 (92.9)
eGFR, mL/min/1.73 m ² ; mean ± SD	73.58 ± 21.75	74.05 ± 21.69	73.88 ± 20.85	74.19 ± 21.56	74.09 ± 21.33
<60 mL/min/1.73 m ² ; n (%)	132 (25.8)	265 (26.3)	475 (26.1)	947 (25.7)	1422 (25.8)
UACR, mg/g median (IQR)	23.87 (8.84, 101.66)	25.64 (8.84, 112.27)	15.91 (6.19, 67.63)	15.91 (6.19, 61.00)	15.91 (6.19, 62.76)
Microalbuminuria, n (%)	156 (30.5)	331 (32.9)	519 (28.5)	1006 (27.3)	1525 (27.7)
Macroalbuminuria, n (%)	70 (13.7)	141 (14.0)	190 (10.4)	368 (10.0)	558 (10.1)
Mean BP (systolic/diastolic), mmHg	132.7/75.7	133.0/75.9	136.6/77.1	135.9/76.8	136.1/76.9
Concomitant medications, n (%)					
Glucose-lowering therapies					
Metformin	388 (75.9)	773 (76.8)	1346 (73.9)	2685 (73.0)	4031 (73.3)
Sulphonylureas	339 (66.3)	613 (60.9)	653 (35.8)	1401 (38.1)	2054 (37.3)
Insulin	151 (29.5)	319 (31.7)	984 (54.0)	1932 (52.5)	2916 (53.0)
Dipeptidyl peptidase-4 inhibitors	78 (15.3)	143 (14.2)	189 (10.4)	386 (10.5)	575 (10.5)
Monotherapy	119 (23.3)	238 (23.7)	572 (31.4)	1142 (31.0)	1714 (31.2)

(Continues)

TABLE 1 (Continued)

	Asian		Non-Asian		Total (N = 5502)
	Placebo (N = 511)	Pooled empagliflozin (N = 1006)	Total (N = 1517)	Placebo (N = 1822)	
Dual therapy	247 (48.3)	465 (46.2)	712 (46.9)	901 (49.5)	1793 (48.7)
Antihypertensives	476 (93.2)	935 (92.9)	1411 (93.0)	1745 (95.8)	3510 (95.4)
Diuretics	135 (26.4)	269 (26.7)	404 (26.6)	853 (46.8)	1777 (48.3)
ACE inhibitors/ARBs	361 (70.6)	729 (72.5)	1090 (71.9)	1507 (82.7)	3068 (83.4)
Lipid-lowering	412 (80.6)	830 (82.5)	1242 (81.9)	1452 (79.7)	2989 (81.2)
Anticoagulants	477 (93.3)	910 (90.5)	1387 (91.4)	1613 (88.5)	3251 (88.3)
History of comorbidities, n (%)					
Peripheral artery disease	59 (11.5)	87 (8.6)	146 (9.6)	420 (23.1)	895 (24.3)
Coronary artery disease ^a	392 (76.7)	780 (77.5)	1172 (77.3)	1371 (75.2)	2764 (75.1)
Single vessel artery disease	53 (10.4)	107 (10.6)	160 (10.5)	185 (10.2)	391 (10.6)
Multivessel coronary artery disease	284 (55.6)	556 (55.3)	840 (55.4)	816 (44.8)	1623 (44.1)
Coronary artery bypass graft	78 (15.3)	191 (19.0)	269 (17.7)	485 (26.6)	984 (26.7)
Ischaemic or haemorrhagic stroke	122 (23.9)	256 (25.4)	378 (24.9)	431 (23.7)	828 (22.5)
Myocardial infarction	209 (40.9)	411 (40.9)	620 (40.9)	874 (48.0)	1778 (48.3)
Heart failure ^b	25 (4.9)	52 (5.2)	77 (5.1)	219 (12.0)	410 (11.1)

Note: Pooled empagliflozin group includes participants who received either 10 mg or 25 mg doses. Data are n (%) or mean \pm SD in patients treated with ≥ 1 dose of study drug. Participating countries from Asia: Hong Kong (n = 57), India (n = 163), Indonesia (n = 26), Japan (n = 83), Korea (n = 302), Malaysia (n = 221), Philippines (n = 188), Singapore (n = 23), Sri Lanka (n = 63), Taiwan (n = 144) and Thailand (n = 75). Microalbuminuria: UACR 30-300 mg/g; macroalbuminuria: UACR >300 mg/g.

Abbreviations: ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

^aComposite of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease and single vessel coronary artery disease.

^bBased on narrow standardized MedDRA query/cardiac failure¹, MeDRA version 18.0.

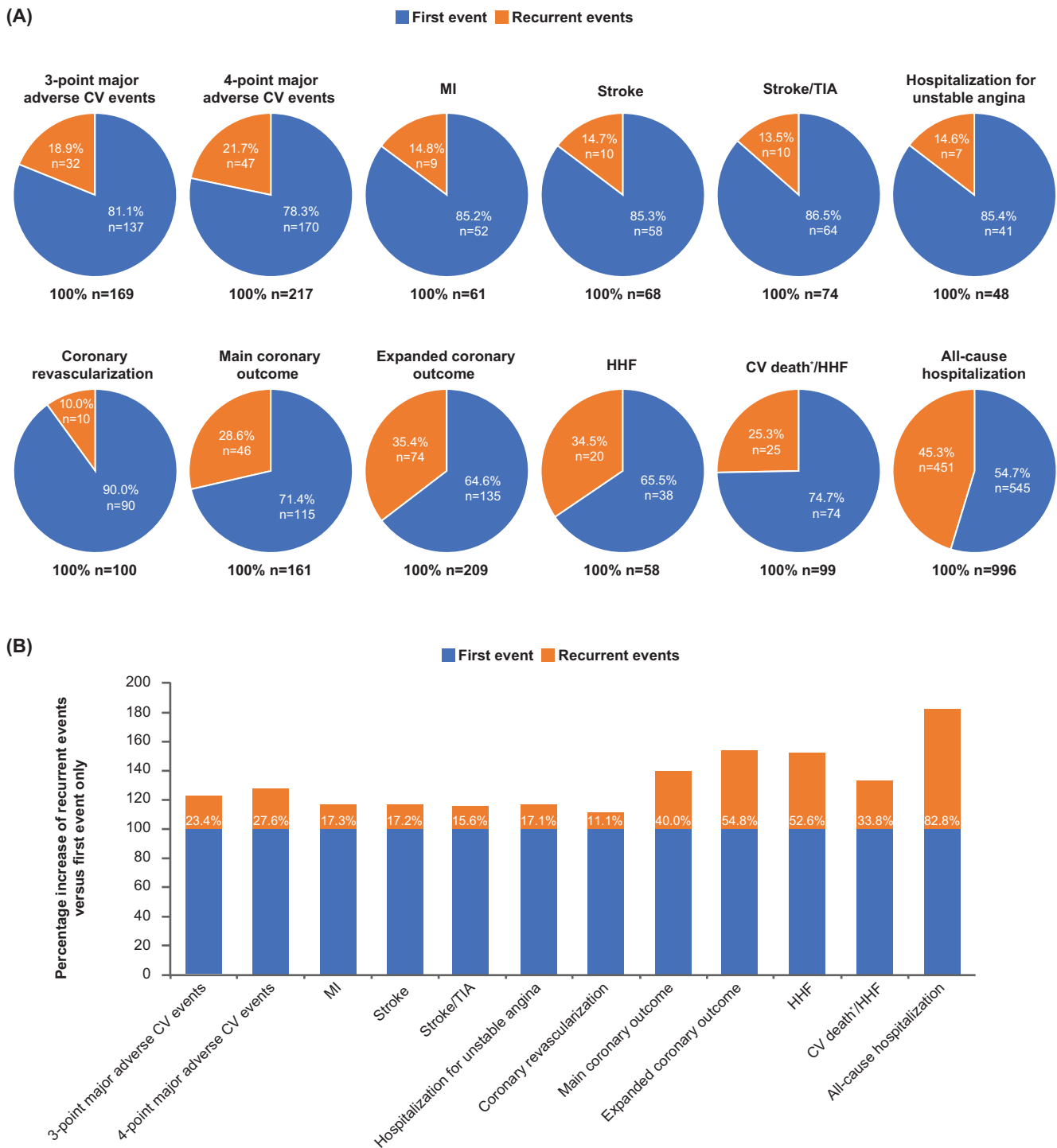


FIGURE 1 Among all Asian participants (N=1517), comprising the pooled empagliflozin 10 mg and 25 mg groups and placebo groups (A) the number and percentage of first versus recurrent events and (B) the percentage increase of recurrent events versus first events. Pooled empagliflozin group includes participants who received either 10 mg or 25 mg doses. Outcomes included fatal and non-fatal events. Participating countries from Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand. A, Number of total (first plus recurrent) events for all patients is set to 100.0%. Percentages of first events and of recurrent events relative to total events are provided. B, Proportion of first events for each outcome is set to 100.0% for all outcomes. Percentage numbers in the orange bars represent the percentage increase of recurrent events over first events for each outcome. 3-point major adverse CV events: composite of CV death, non-fatal MI and non-fatal stroke. 4-point major adverse CV events: 3-point major adverse CV events plus hospitalization for unstable angina. *Excluding fatal stroke. “n” represents number of events. Data represent the total population of Asian participants: N = 1517. CV, cardiovascular; HHF, hospitalization for heart failure; MI, myocardial infarction; TIA, transient ischaemic attack

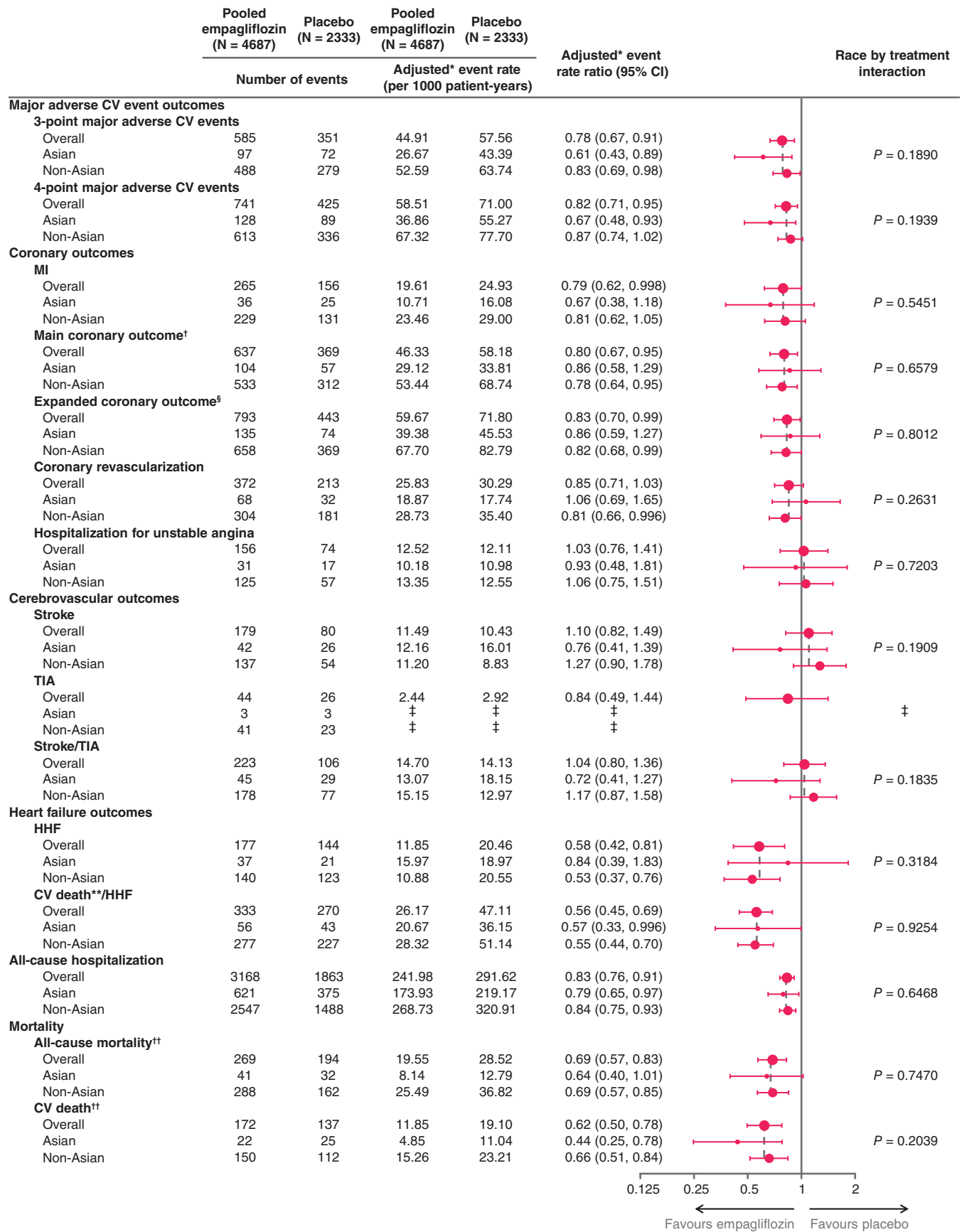


FIGURE 2 Legend on next page.

baseline characteristics were balanced between the treatment groups within Asian and non-Asian populations.²⁰

3.2 | Number of events

Among Asian participants, 137 (9.0%) experienced at least one event of the primary endpoint 3-point major adverse CV events, of whom 32 subsequently experienced a recurrent event (Figure 1A). The number of total (first plus recurrent) events of 3-point major adverse CV events was 169, equating to an increase in events of 23.4% versus first events only (Figure 1B). A substantially higher increase in total versus first events was observed with all-cause hospitalization, with an increase of 82.8% to, in total, 996 events. Similarly, an increased number of events with total versus first event analyses was observed with most measured outcomes, including CV death/HHF and stroke, with a 33.8% and 17.2% increase respectively.

3.3 | Baseline characteristics by number of events

The event rates of the placebo group were lower in the Asian versus the non-Asian subgroup for all CV, mortality and hospitalization outcomes measured, except for stroke outcomes (Figure 2). Among the Asian placebo group, those who experienced one or more event of all-cause hospitalization had a more adverse CV risk profile (e.g. higher age, higher systolic blood pressure, lower kidney function and higher frequency of albuminuria) compared with those who experienced no events (Table S2). For the primary outcome (3-point major adverse CV events), the main coronary outcome, and HHF, too few participants in the placebo group experienced >1 event overall and/or there were too few participants in the placebo group with events within each baseline factor (<15 participants) for any conclusions to be drawn (data not shown).

3.4 | CV, mortality and hospitalization event rates

The effect of empagliflozin in Asian participants was consistent with the non-Asian population and with the overall population for all CV and hospitalization outcomes analysed (interaction $p > .05$ for all outcomes; Figure 2).

In the Asian population, empagliflozin versus placebo significantly reduced the risk of total events of the primary outcome, 3-point major adverse CV events, by 39% [rate ratio (RR) (95% CI) 0.61 (0.43, 0.89)] with a consistent effect for the individual 10 mg and 25 mg empagliflozin doses, and the key secondary outcome, 4-point major adverse CV events, by 33% [0.67 (0.48, 0.93)] (Figures 2 and 3).

In the overall EMPA-REG OUTCOME trial population, based on total events, empagliflozin versus placebo significantly reduced the risk of MI by 21% [0.79 (0.62, 0.998)], the main coronary outcome by 20% [0.80 (0.67, 0.95)], and the expanded coronary outcome by 17% [0.83 (0.70, 0.99)] (Figure 2). No difference was observed between empagliflozin and placebo in the risk of stroke, TIA, and composite of stroke and TIA: 1.10 (0.82, 1.49), 0.84 (0.49, 1.44) and 1.04 (0.80, 1.36), respectively. The RR for total events of MI in the Asian population was directionally similar to observations in the overall population: 0.67 (0.38, 1.18) (interaction $p > .05$). Likewise, the RRs for total events of the main and expanded coronary outcomes in the Asian population were also directionally similar to those observed in the overall population (interaction $p > .05$). Consistent with the overall population, no difference in total events of stroke was observed between empagliflozin and placebo, RR (95% CI) 0.76 (0.41, 1.39) in the Asian population, nor for the composite of stroke and TIA, 0.72 (0.41, 1.27). For TIA alone, no model was produced in the Asian and non-Asian populations as fewer than two groups fulfilled the analysis requirements.

The risk of total events of HHF was reduced with empagliflozin versus placebo by 42% in the overall population [RR (95% CI) 0.58 (0.42, 0.81)]; total events of the composite of CV death and HHF by 44% [0.56 (0.45, 0.69)]; all-cause mortality by 31% [0.69 (0.57, 0.83)]; and CV death by 38% [0.62 (0.50, 0.78)]. Consistent with this, the risk of total events of the composite of CV death and HHF, all-cause mortality, and CV death were also reduced with empagliflozin versus placebo in the Asian population [0.57 (0.33, 0.996), 0.64 (0.40, 1.01) and 0.44 (0.25, 0.78), respectively]. A directionally similar effect on the risk of HHF was suggested in the Asian population: 0.84 (0.39, 1.83), consistent with the overall population (interaction $p > .05$).

3.5 | Causes of hospitalization

A 17% relative risk reduction with empagliflozin versus placebo in total events of all-cause hospitalization was observed in the overall population, which is consistent with our findings in the Asian

FIGURE 2 Comparison of pooled empagliflozin versus placebo total (first plus recurrent) events in Asian versus non-Asian participants. Pooled empagliflozin group includes participants who received either 10 mg or 25 mg doses. Outcomes included fatal and non-fatal events unless otherwise stated. The 3-point major adverse CV events event rate ratios (95% CI) for the individual empagliflozin doses versus placebo were 0.67 (0.44, 1.01) for empagliflozin 10 mg and 0.56 (0.35, 0.88) for empagliflozin 25 mg in the Asian population and 0.78 (0.64, 0.96) and 0.87 (0.71, 1.06), respectively, in the non-Asian population. Participating countries from Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand. *Negative binomial model used for the race subgroup analysis included age as a linear covariate and treatment, sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region, race (categorical) and treatment by race (categorical) interaction as fixed effects. †MI/coronary revascularization. ‡MI/coronary revascularization/hospitalization for unstable angina. ††There were fewer than 14 events in one subgroup, therefore no analysis was performed. **Excluding fatal stroke. †††Poisson regression model, including age as linear covariate, and sex, baseline HbA1c, baseline eGFR, geographical region, baseline body mass index, race (categorical) and treatment by race (categorical) interaction as fixed effects. BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalization for heart failure; MI, myocardial infarction; TIA, transient ischaemic attack

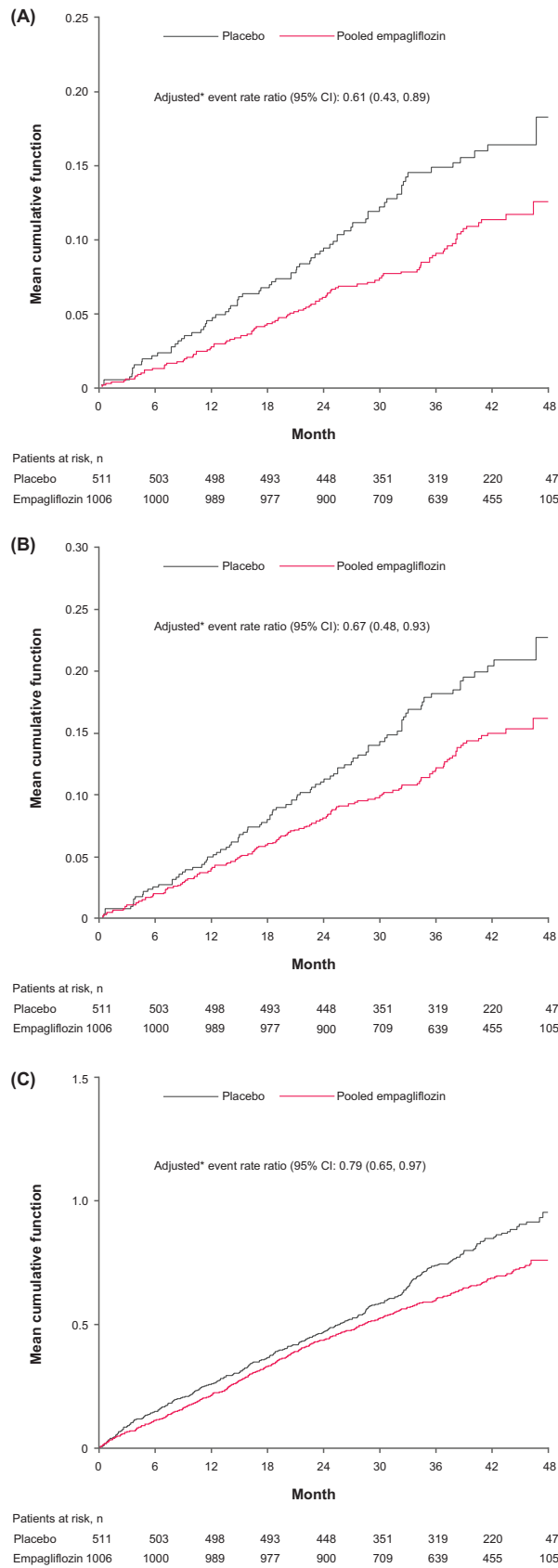


FIGURE 3 Legend on next page.

population [21% risk reduction, RR (95% CI) 0.79 (0.65, 0.97)] and in the non-Asian population. As previously reported, the most common reasons for hospitalization in the overall trial population (based on MedDRA System Organ Class terms) were cardiac disorders (13.7% of participants), infections and infestations (8.9%), and nervous system disorders (6.2%); with a consistently lower rate of events across most types of hospitalizations with empagliflozin versus placebo.²²

3.6 | All-cause hospitalization by order of events

WLW analyses of total events by the order of events (time to 1st, time to 2nd, time to 3rd event etc.) suggested that risk reductions with empagliflozin versus placebo were numerically larger with increasing order of events for all-cause hospitalization in the overall population, with a *p*-value for the test for consistency of the treatment effect across the order of events of .0256. A directionally similar trend was suggested in the Asian population and non-Asian populations; however, the test for consistency was only significant for the non-Asian subgroup (Asian: *p* = .1420; non-Asian: *p* = .0253; Figure 4).

3.7 | Effect of empagliflozin: East Asian population

The rate of events of investigated outcomes in the empagliflozin and placebo treatment groups for the East Asian population were generally comparable with the overall Asian population (Table S1).

4 | DISCUSSION

Among the 1517 Asian participants (21.6%) in the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the relative risk of total (first plus recurrent) events of 3-point major adverse CV events by 39%, 4-point major adverse CV events by 33%, CV death/HHF composite by 43%, and all-cause hospitalization by 21%. These effects were consistent between the Asian, non-Asian (all interaction *p* > .05) and overall population, in line with previous time-to-first event analyses of EMPA-REG OUTCOME Asian participants.²⁰ Similarly, a recent meta-analysis of SGLT2 inhibitor clinical trials showed

that effects on HbA1c levels, fasting plasma glucose, body weight and systolic blood pressure were also consistent between Asian and non-Asian populations.²⁵

Because of the inclusion of recurrent events, the data in this analysis add substantial clinical information to the existing paucity of total events data for CV and hospitalization outcomes in Asian populations with T2D, who are known to be at high clinical risk. In this analysis of the EMPA-REG OUTCOME Asian population, the number of total events included was substantially greater than the number of events included in time-to-first event analyses for almost all outcomes measured. For example, there was a 23% increase in 3-point major adverse CV events and an 83% increase in all-cause hospitalization (169 vs. 137, and 996 vs. 545, respectively) when assessing total events versus first events only. The numerically higher event rates observed when analysing total versus first events only might be more representative of the known high residual risk of T2D complications and CV disease.^{9,11,12,14}

To our knowledge, except for a numerically lower rate of all-cause hospitalizations reported with sotagliflozin versus placebo in a relatively limited number of patients (in total, 13) with T2D after worsening HF from Korea,²⁷ the present study is the first to assess the effects of SGLT2 inhibitors on all-cause hospitalization of Asian participants with T2D from a randomized controlled trial. We found that the risk of all-cause hospitalization (which was the outcome with the largest number of events in both Asian and non-Asian populations: >900 events in the Asian population and >4000 events in the non-Asian population), was reduced by >20% in the Asian population [RR (95% CI) 0.79 (0.65, 0.97)], consistent with the non-Asian population, with broad implications for the total burden of disease. Moreover, a trend of increasing risk reduction of all-cause hospitalization with empagliflozin by increasing order of event (1st event, 2nd event, 3rd event etc.) was suggested in the Asian and non-Asian subgroups, in line with the more pronounced treatment effect with total versus first events previously observed in the overall EMPA-REG OUTCOME population.²² Significance in the test for consistency of effect size across the order of all-cause hospitalization events was only reached for the non-Asian population; however, this lack of statistical significance might be the result of relatively limited event numbers for higher orders of events in the Asian population.

FIGURE 3 Mean cumulative function curves of pooled empagliflozin versus placebo, including total (first plus recurrent) events in Asian participants, A, 3-Point major adverse CV events (primary endpoint), B, 4-Point major adverse CV events (key secondary endpoint), and C, All-cause hospitalization. Pooled empagliflozin group includes participants who received either 10 mg or 25 mg doses. Outcomes included fatal and non-fatal events. Participating countries from Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand. *Negative binomial model used for the race subgroup analysis included age as a linear covariate and treatment, sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region, race (categorical), and treatment by race (categorical) interaction as fixed effects. 3-point major adverse CV events is the composite of CV death, MI and stroke. 4-point major adverse CV events is the composite of CV death, MI, stroke and hospitalization for unstable angina. The mean cumulative function shows the population mean cumulative number of events up to time *t*. BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MI, myocardial infarction

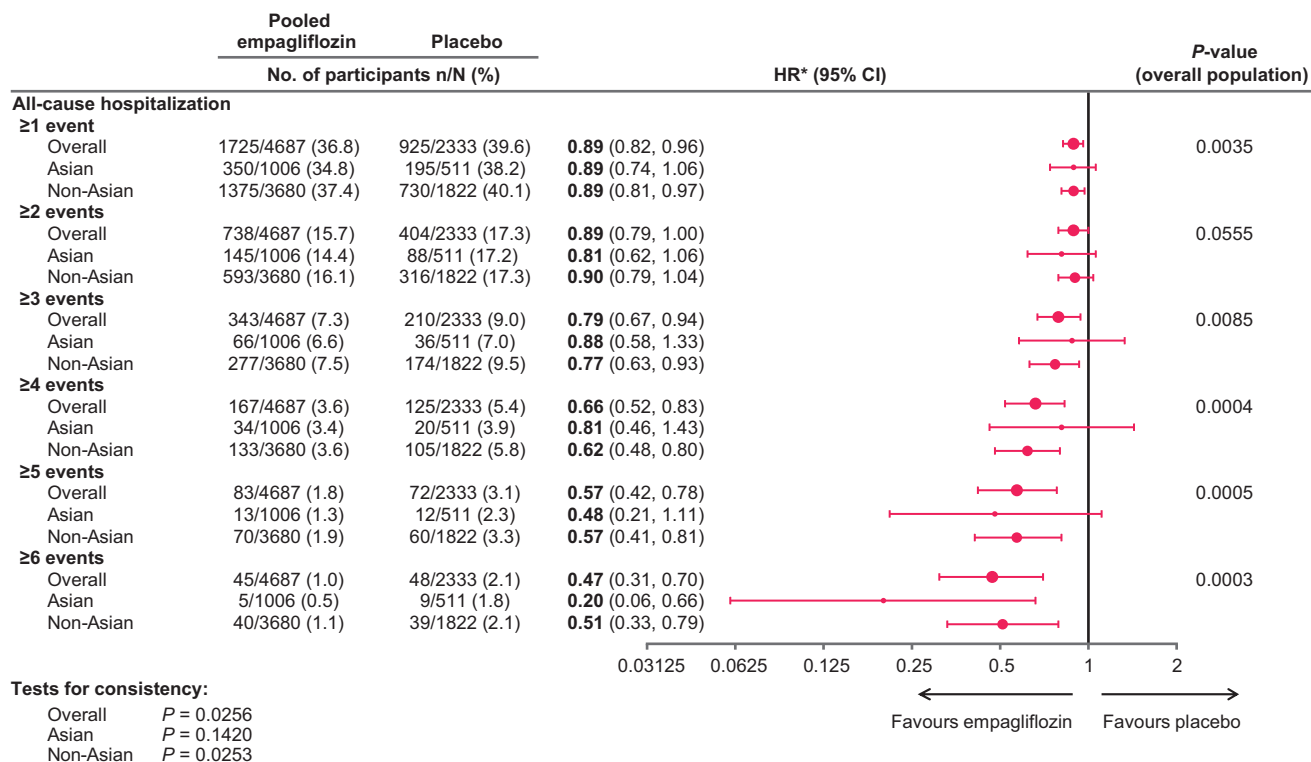


FIGURE 4 Comparison of pooled empagliflozin versus placebo time-to-event analyses of all-cause hospitalization by order of event according to the Wei-Lin-Weissfeld model. Pooled empagliflozin group includes participants who received either 10 mg or 25 mg doses. Outcomes included fatal and non-fatal events. n/N (%) represents 'n with event(s)'/total N' (%). Participating countries from Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand. Analysed population includes all participants who were given at least one dose of study drug. *Analysed as HR of empagliflozin versus placebo for time to event. HRs were adjusted using a Wei-Lin-Weissfeld model with factors for treatment, age, sex, baseline BMI, baseline HbA1c, baseline estimated glomerular filtration rate and geographical region; test for consistency (provided as a p -value) is the test for equality of ratios of empagliflozin versus placebo over the event count across all orders of events. Model and consistency test are applied in all participants and by race. CI, confidence interval; BMI, body mass index; HbA1c, glycated haemoglobin; HR, hazard ratio

The clinical profile of patients with T2D in the Asian population is known to differ from non-Asian populations.^{2,3} In particular, Asian patients with T2D tend to have a lower BMI compared with non-Asian patients, which is in line with the findings of the present study (mean baseline BMI: 26.64 versus 31.72 kg/m² in the Asian and non-Asian populations, respectively; Table 1). US studies have shown that people of South Asian heritage have the highest BMI-specific T2D prevalence among all ethnic groups.²⁸ However, reassuringly, a recent subgroup analysis of the EMPA-REG OUTCOME trial showed that the cardiorenal benefits of empagliflozin were consistent regardless of baseline BMI category, including among Asian participants.²⁹ Likewise, a recent rapid evidence assessment of glucose-lowering drugs reporting CV or kidney outcomes reported consistent cardiorenal effects between Asian and overall cohorts.³⁰

In the present study, among those treated with placebo, CV outcome event rates were lower in the Asian versus non-Asian populations, except for stroke, which was higher in the Asian population, consistent with previous studies.²⁰ This is in line with the known higher risk of stroke in the Asian population in comparison with Western populations.⁹⁻¹² Reassuringly, in the overall and Asian populations, our analyses showed no significant difference in the risk of total

events of the stroke-related outcomes with empagliflozin versus placebo.

Asian participants who received placebo and experienced one or multiple events of all-cause hospitalization tended to have a more adverse baseline CV risk profile than those who did not (Table S2), which is in line with the findings of a previous study investigating recurrent events in the overall EMPA-REG OUTCOME population.²² The suggested trend of increasing baseline CV risk profile with increasing number of events (0, 1 and >1) supports the relevance of investigating treatment effects on total events, including in the Asian population. As previously reported, placebo participants in the overall EMPA-REG OUTCOME population who experienced events of the primary outcome (3-point major adverse CV events), main coronary outcome, and HHF also tended to have a more adverse baseline CV risk profile compared with those who did not²²; however, in the Asian population, the number of participants with these outcomes within each baseline factor in the placebo group were too small to draw conclusions.

In the present analysis, we found that the rate of total (first plus recurrent) events in the empagliflozin and placebo treatment groups for the East Asian population were generally comparable with the

overall Asian population. Similar to our findings, in a real-world setting in Japan, Taiwan and South Korea, the EMPRISE East Asia observational cohort study found a lower risk of all-cause hospitalization [HR (95% CI) 0.73 (0.67, 0.79)] but no difference in the risk of stroke [0.77 (0.55, 1.09)] in those treated with empagliflozin versus those treated with dipeptidyl peptidase-4 inhibitors.^{31,32} The EMPRISE East Asia study also found a lower risk of HHF and all-cause mortality in patients treated with empagliflozin versus dipeptidyl peptidase-4 inhibitors [HR (95% CI), 0.82 (0.71, 0.94) and 0.64 (0.50, 0.81), respectively].^{31,32}

The strengths of this analysis include pre-specification of total event analyses for the statistical model and several outcomes in the overall population, including the primary outcome (3-point major adverse CV events), MI, stroke and HHF; however, all subgroup analyses were performed post hoc. All CV outcomes and deaths were centrally adjudicated by a blinded event committee. In addition, compared with existing evidence,²⁰ this analysis provides more statistically robust results by analysing events beyond the first occurrence. Other strengths of this analysis include: the use of statistical models that preserve randomization, accounting for within-patient correlation of multiple events and different follow-up times; over time plots supported a constant event rate; and we included both fatal and non-fatal events in the analyses.

A limitation of this post hoc analysis is that participants who identified themselves as Asian were heterogeneous with respect to genetic, environmental and cultural factors. Most Asian participants were from countries in Asia (1345 of 1517; 89%); therefore, the number of Asian participants who were not from Asian countries was too small for analysis. This is a possible limitation of the present study, as the impact of geographical location (Asia vs. not Asia) on the study outcomes in Asian participants is unknown. Another limitation is that the analyses were not adjusted for multiplicity. In addition, the EMPA-REG OUTCOME trial included patients with T2D and atherosclerotic CV disease followed for a median duration of 3.1 years, which might limit the generalizability of the findings of this analysis to other settings.

In conclusion, our data suggest relevant and sizeable clinical benefits of empagliflozin on the total burden of CV and hospitalization outcomes, including those associated with atherosclerosis and HF, in Asian patients with T2D and established atherosclerotic CV disease.

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CONFLICT OF INTERESTS

KK has acted in an advisory role for Astellas Pharma, Sanwa Kagaku Kenkyusho, Nippon Boehringer Ingelheim and Novo Nordisk Pharma, received honoraria or fees for promotional materials from Astellas Pharma, AstraZeneca, Daiichi Sankyo, MSD, Ono Pharmaceutical, Novo Nordisk Pharma, Nippon Boehringer Ingelheim, Taisho-Toyama Pharmaceutical, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma and Kowa Pharmaceutical, and received scholarships or donations from Nippon Boehringer Ingelheim, Taisho-Toyama Pharmaceutical, Mitsubishi Tanabe Pharma and Kowa Pharmaceutical. CW has received grants and served on steering committees for Boehringer Ingelheim, served on advisory boards for Boehringer Ingelheim, Merck Sharp & Dohme and Bayer, and received lecture fees from Boehringer Ingelheim, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, Mitsubishi and Bayer. SDA has received research support from Abbott Vascular and Vifor International, and personal fees from Boehringer Ingelheim, Bayer, AstraZeneca, Novartis, Vifor International, Impulse Dynamics, Respicardia and St Jude Medical. SP is a consultant for Boehringer Ingelheim. AY, MM and SSL are employees of Boehringer Ingelheim. SSL owns shares in Novo Nordisk and shares in dynamically traded investment funds, which might own stocks from pharmaceutical companies.

DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/> datasharing for further information.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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