Empagliflozin and Cardiovascular Outcomes in Asian Patients With Type 2 Diabetes and Established Cardiovascular Disease
— Results From EMPA-REG OUTCOME® —

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Background: In the EMPA-REG OUTCOME® trial, empagliflozin added to standard of care reduced the risk of 3-point major adverse cardiovascular (CV) events (3-point MACE: composite of CV death, non-fatal myocardial infarction, or non-fatal stroke) by 14%, CV death by 38%, hospitalization for heart failure by 35%, and all-cause mortality by 32% in patients with type 2 diabetes (T2DM) and established CV disease. We investigated the effects of empagliflozin in patients of Asian race.

Methods and Results: Patients were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Of 7,020 patients treated, 1,517 (21.6%) were of Asian race. The reduction in 3-point MACE in Asian patients was consistent with the overall population: 3-point MACE occurred in 79/1,006 patients (7.9%) in the pooled empagliflozin group vs. 58/511 patients (11.4%) in the placebo group (hazard ratio: 0.68 [95% confidence interval: 0.48–0.95], P-value for treatment by race interaction (Asian, White, Black/African-American): 0.0872). The effects of empagliflozin on the components of MACE, all-cause mortality, and heart failure outcomes in Asian patients were consistent with the overall population (P-values for interaction by race >0.05). The adverse event profile of empagliflozin in Asian patients was similar to the overall trial population.

Conclusions: Reductions in the risk of CV outcomes and mortality with empagliflozin in Asian patients with T2DM and established CV disease were consistent with the overall trial population.

Key Words: Diabetes mellitus; Mortality; Race; Sodium-glucose cotransporter 2; Treatment outcomes

The prevalence of diabetes differs between races and between countries.[1,2] In 2015, 37% of adults with diabetes (153 million people) lived in the Western Pacific region and this region saw the highest number of deaths from diabetes (1.9 million) of all the regions studied by the International Diabetes Federation.[1] Diabetes tends to develop at a younger age in Asian populations compared with White populations, and Asian patients with type 2 diabetes (T2DM) are at higher risk of microvascular and macrovascular complications than White patients.[3,4]

Empagliflozin is a potent and highly selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2) used in the treatment of T2DM. In the EMPA-REG OUTCOME® trial in patients with T2DM and established cardiovascular (CV) disease, empagliflozin added to standard of care reduced the risk of the primary composite outcome of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (3-point major adverse CV events [3-point MACE])

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by 14%, CV death by 38%, all-cause mortality by 32%, and hospitalization for heart failure (HF) by 35% vs. placebo; there was no significant difference in the risk of MI or stroke with empagliflozin vs. placebo.[5,6] Of 7,020 patients treated in EMPA-REG OUTCOME®, 21.6% were of Asian race and 19.2% were from countries in Asia (Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, Thailand). Here we report the effect of empagliflozin on CV outcomes in the subgroup of patients of Asian race in EMPA-REG OUTCOME®.

Methods

Study Design
The design of the EMPA-REG OUTCOME® trial has been

described.[5,7] Patients in the trial had T2DM (with HbA1c 7.0–9.0% for drug-naive patients and 7.0–10.0% for those on stable glucose-lowering therapy), established CV disease, and estimated glomerular filtration rate (eGFR; according to the Modification of Diet in Renal Disease [MDRD] equation) $\geq 30\,mL/min/1.73\,m^2$. Patients were asked to select their race based on the following options: White, Asian, Black/African-American, American Indian or Native Alaskan, or Native Hawaiian or other Pacific Islander. Participants were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care. Throughout the trial (or after week 12 for glucose-lowering medications), investigators were encouraged to treat CV risk factors to achieve optimal standard of care according to local guidelines. The trial was to continue until ≥691 patients experienced an adjudicated event included in the primary outcome (3-point MACE). Patients who prematurely discontinued study medication continued to be followed for ascertainment of CV outcomes and vital status.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at every participating center. All patients provided written informed consent before study entry.

Outcomes

Definitions of the major clinical outcomes in EMPA-REG OUTCOME® have been published.[5,7] CV outcome events and deaths were prospectively adjudicated by Clinical Events committees (for cardiac and neurological events).[7] Adverse events (AEs) were reported by investigators based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA).

We analyzed the following CV/mortality outcomes in the subgroup of patients of Asian race: 3-point MACE, 4-point MACE (composite of CV death, non-fatal MI, non-fatal

Table 1. Baseline Characteristics of Asian Patients			
	Placebo (n=511)	Empagliflozin 10 mg (n=505)	Empagliflozin 25 mg (n=501)
Age, years	60.7±9.4	61.1±8.8	61.1±9.4
<65	340 (66.5)	328 (65.0)	321 (64.1)
≥65	171 (33.5)	177 (35.0)	180 (35.9)
Male	379 (74.2)	369 (73.1)	370 (73.9)
Region			
Asia*	450 (88.1)	445 (88.1)	450 (89.8)
Other	61 (11.9)	60 (11.9)	51 (10.2)
HbA1c, %†	8.09±0.86	8.06±0.85	8.05±0.83
Time since diagnosis of T2DM, years			
≤1	19 (3.7)	25 (5.0)	20 (4.0)
>1 to 5	91 (17.8)	88 (17.4)	110 (22.0)
>5 to 10	149 (29.2)	115 (22.8)	118 (23.6)
>10	252 (49.3)	277 (54.9)	253 (50.5)
Weight, kg	70.7±13.2	71.1±13.6	70.5±13.2
Body mass index, kg/m²	26.6±3.9	26.8±4.2	26.5±4.0
<25	184 (36.0)	184 (36.4)	174 (34.7)
≥25	327 (64.0)	321 (63.6)	327 (65.3)
Waist circumference, cm‡	94.2±9.9	94.2±10.3	93.3±10.2
eGFR, mL/min/1.73 m² (MDRD)	73.6±21.8	74.3±22.4	73.8±21.0
≥90	104 (20.4)	117 (23.2)	121 (24.2)
60 to <90	275 (53.8)	253 (50.1)	250 (49.9)
<60	132 (25.8)	135 (26.7)	130 (25.9)
LDL-cholesterol, mg/dL§	86.0±38.2	86.0±37.9	84.3±34.4
HDL-cholesterol, mg/dL§	45.7±11.9	46.7±11.6	46.9±12.1
Systolic blood pressure, mmHg	132.7±17.1	133.5±16.7	132.6±17.1
Diastolic blood pressure, mmHg	75.7±10.0	76.0±9.4	75.7±9.8
Cardiovascular disease	507 (99.2)	503 (99.6)	495 (98.8)
CAD¶	392 (76.7)	391 (77.4)	389 (77.6)
Multivessel CAD	284 (55.6)	277 (54.9)	279 (55.7)
History of myocardial infarction	209 (40.9)	210 (41.6)	201 (40.1)
History of stroke	122 (23.9)	138 (27.3)	118 (23.6)
Coronary artery bypass graft	78 (15.3)	94 (18.6)	97 (19.4)
Single-vessel CAD	53 (10.4)	58 (11.5)	49 (9.8)
Peripheral artery disease	59 (11.5)	38 (7.5)	49 (9.8)

(**Table 1** continued the next page.)

	Placebo (n=511)	Empagliflozin 10 mg (n=505)	Empagliflozin 25 mg (n=501)
Cardiac failure[‖]	25 (4.9)	24 (4.8)	28 (5.6)
Glucose-lowering therapies			
Medication taken alone or in combination			
Metformin	388 (75.9)	395 (78.2)	378 (75.4)
Sulfonylureas	339 (66.3)	299 (59.2)	314 (62.7)
Insulin	151 (29.5)	171 (33.9)	148 (29.5)
Dipeptidyl peptidase-4 inhibitors	78 (15.3)	76 (15.0)	67 (13.4)
Thiazolidinediones	29 (5.7)	26 (5.1)	31 (6.2)
Glucagon-like peptide-1 agonists	4 (0.8)	0	3 (0.6)
Monotherapy	119 (23.3)	118 (23.4)	120 (24.0)
Dual therapy	247 (48.3)	231 (45.7)	234 (46.7)
Antihypertensive therapies	476 (93.2)	472 (93.5)	463 (92.4)
ACE inhibitors/ARBs	361 (70.6)	367 (72.7)	362 (72.3)
β-blockers	298 (58.3)	301 (59.6)	293 (58.5)
Diuretics	135 (26.4)	139 (27.5)	130 (25.9)
Calcium-channel blockers	189 (37.0)	191 (37.8)	190 (37.9)
Mineralocorticoid receptor antagonists	15 (2.9)	29 (5.7)	26 (5.2)
Lipid-lowering drugs	412 (80.6)	421 (83.4)	409 (81.6)
Statins	398 (77.9)	406 (80.4)	393 (78.4)
Fibrates	37 (7.2)	31 (6.1)	38 (7.6)
Ezetimibe	12 (2.3)	13 (2.6)	15 (3.0)
Niacin	4 (0.8)	4 (0.8)	1 (0.2)
Other	16 (3.1)	15 (3.0)	16 (3.2)
Anticoagulants and antiplatelets	477 (93.3)	459 (90.9)	451 (90.0)
Acetylsalicylic acid	440 (86.1)	423 (83.8)	428 (85.4)
Clopidogrel	96 (18.8)	85 (16.8)	75 (15.0)
Vitamin K antagonists	11 (2.2)	13 (2.6)	10 (2.0)

Data are n (%) or mean ± SD in patients treated with ≥1 dose of study drug. *Participating countries from Asia: Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, Thailand. †Placebo, n=511; empagliflozin 10 mg, n=504; empagliflozin 25 mg, n=501. ‡Placebo, n=508; empagliflozin 10 mg, n=502; empagliflozin 25 mg, n=500. §Placebo, n=509; empagliflozin 10 mg, n=502; empagliflozin 25 mg, n=495. ¶Defined as any of the components of history of myocardial infarction, coronary artery bypass graft, multivessel CAD, single-vessel CAD. ‖Based on narrow standardized MedDRA query 'cardiac failure'. ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; T2DM, type 2 diabetes mellitus.

stroke, or hospitalization for unstable angina), CV death, all-cause mortality, fatal or non-fatal stroke, non-fatal stroke, fatal or non-fatal MI, non-fatal MI, hospitalization for HF, composite of HF hospitalization or CV death. Subgroup analyses were conducted to investigate the consistency between the treatment effects on these outcomes observed in the Asian subgroup and the treatment effects in the other races (White, Black/African-American, other). In addition, we analyzed changes in HbA1c, weight, systolic and diastolic blood pressure, heart rate, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, uric acid, and eGFR (according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation). AEs reported during treatment or within 7 days of the last intake of study drug and further clinical laboratory measurements were analyzed descriptively. CV outcomes were also assessed in patients from the East Asian region (Hong Kong, Japan, Korea, Taiwan), all of whom were of Asian race.

Statistical Analysis

Analyses were conducted following a modified intent-to-treat approach in patients treated with ≥1 dose of study drug (treated set). Treatment group differences across sub-groups of race in the risk of CV outcomes and all-cause mortality were assessed using Cox proportional hazards models with treatment, age, sex, baseline body mass index (BMI), baseline HbA1c, baseline eGFR, region, race, and treatment by race interaction as factors. Cumulative incidence function estimates of 3-point MACE and CV death were corrected for death as a competing risk. Kaplan-Meier estimates are presented for all-cause mortality. Because of the declining numbers of patients at risk, cumulative incidence and Kaplan-Meier plots have been truncated at 48 months.

Changes from baseline in HbA1c, weight, systolic and diastolic blood pressure, heart rate, LDL- and HDL-cholesterol, uric acid and eGFR were assessed using mixed model repeated measures analysis with baseline HbA1c and the baseline value for the endpoint in question as linear covariates, and baseline BMI, baseline eGFR (MDRD), region, the last week a patient could have had a measurement for the endpoint in question, treatment, visit, visit by treatment interaction, visit by race interaction, treatment by race interaction, treatment by visit by race interaction, visit by baseline HbA1c interaction, and visit by baseline value for the endpoint in question as fixed effects. All data from baseline to study end were considered for these analyses.
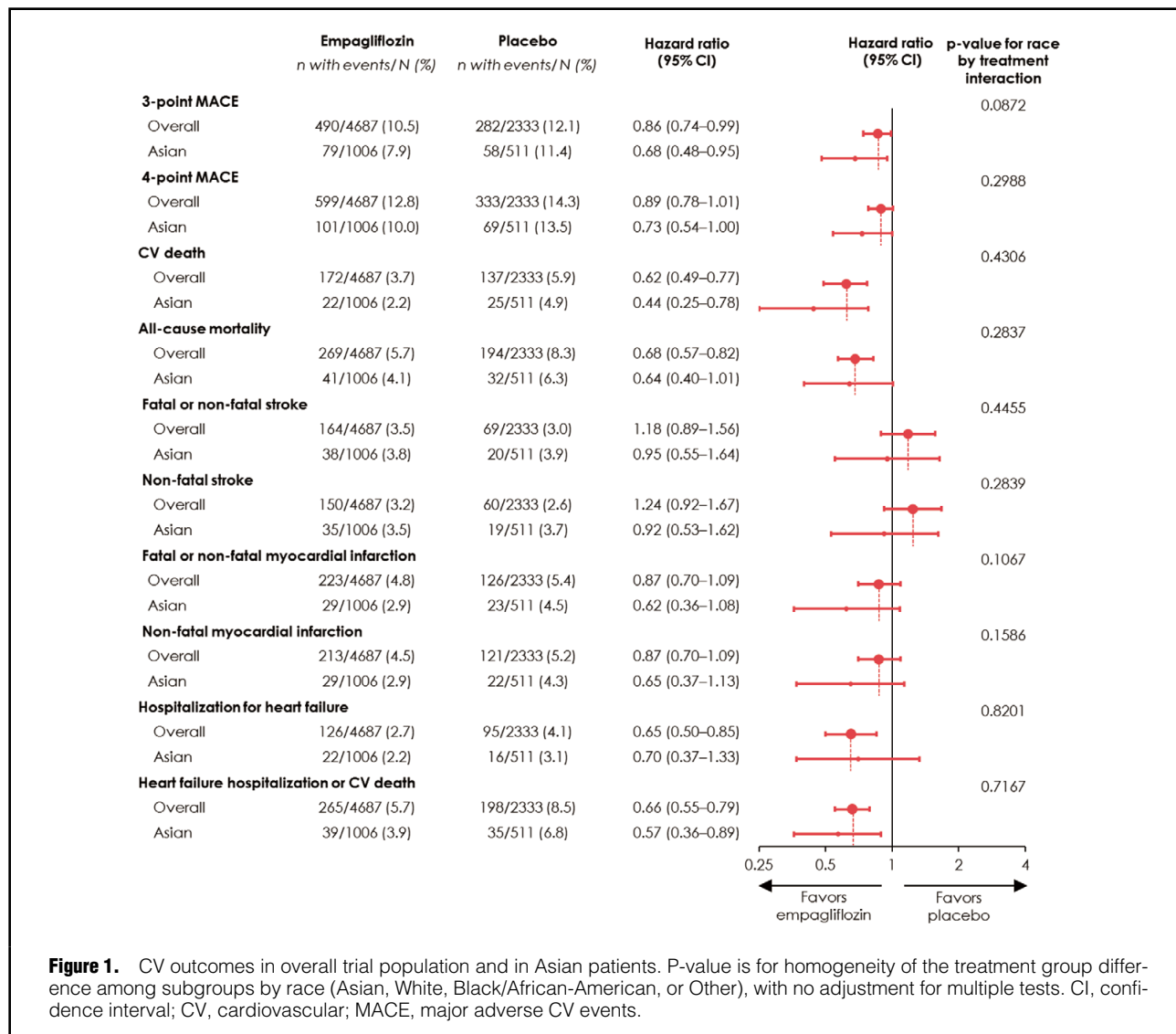
| | Empagliflozin | Placebo | Hazard ratio | Hazard ratio | p-value for race |
	n with events/ N (%)	n with events/ N (%)	(95% CI)	(95% CI)	by treatment interaction
3-point MACE					0.0872
Overall	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74–0.99)		
Asian	79/1006 (7.9)	58/511 (11.4)	0.68 (0.48–0.95)		
4-point MACE					0.2988
Overall	599/4687 (12.8)	333/2333 (14.3)	0.89 (0.78–1.01)		
Asian	101/1006 (10.0)	69/511 (13.5)	0.73 (0.54–1.00)		
CV death					0.4306
Overall	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49–0.77)		
Asian	22/1006 (2.2)	25/511 (4.9)	0.44 (0.25–0.78)		
All-cause mortality					0.2837
Overall	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57–0.82)		
Asian	41/1006 (4.1)	32/511 (6.3)	0.64 (0.40–1.01)		
Fatal or non-fatal stroke					0.4455
Overall	164/4687 (3.5)	69/2333 (3.0)	1.18 (0.89–1.56)		
Asian	38/1006 (3.8)	20/511 (3.9)	0.95 (0.55–1.64)		
Non-fatal stroke					0.2839
Overall	150/4687 (3.2)	60/2333 (2.6)	1.24 (0.92–1.67)		
Asian	35/1006 (3.5)	19/511 (3.7)	0.92 (0.53–1.62)		
Fatal or non-fatal myocardial infarction					0.1067
Overall	223/4687 (4.8)	126/2333 (5.4)	0.87 (0.70–1.09)		
Asian	29/1006 (2.9)	23/511 (4.5)	0.62 (0.36–1.08)		
Non-fatal myocardial infarction					0.1586
Overall	213/4687 (4.5)	121/2333 (5.2)	0.87 (0.70–1.09)		
Asian	29/1006 (2.9)	22/511 (4.3)	0.65 (0.37–1.13)		
Hospitalization for heart failure					0.8201
Overall	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50–0.85)		
Asian	22/1006 (2.2)	16/511 (3.1)	0.70 (0.37–1.33)		
Heart failure hospitalization or CV death					0.7167
Overall	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55–0.79)		
Asian	39/1006 (3.9)	35/511 (6.8)	0.57 (0.36–0.89)		

0.25   0.5   1   2   4

Favors empagliflozin ← | → Favors placebo

Figure 1. CV outcomes in overall trial population and in Asian patients. P-value is for homogeneity of the treatment group difference among subgroups by race (Asian, White, Black/African-American, or Other), with no adjustment for multiple tests. CI, confidence interval; CV, cardiovascular; MACE, major adverse CV events.

Analysis of 3-point MACE, 4-point MACE, hospitalization for HF, the composite of HF hospitalization or CV death, AE summaries (including serious AEs), and AEs of special interest in Asian patients, and analysis of CV outcomes in East Asian patients, treated with empagliflozin vs. placebo were prespecified (both for the individual doses and the pooled empagliflozin group). The other analyses presented here were conducted post-hoc. All subgroup analyses were exploratory; statistical significance was concluded based on an alpha level of 0.05. Although the P-value for treatment by race interaction is provided for CV/mortality outcomes, point estimates and confidence intervals (CI) for treatment comparison are presented only for the Asian subgroup.

Results

Baseline Characteristics
A total of 1,517 of 7,020 patients (21.6%) identified themselves as of Asian race. The baseline characteristics of Asian patients were generally balanced between the placebo and empagliflozin groups (**Table 1**). Mean (SD) age was 61.0 (9.2) years, 73.7% were male, mean (SD) BMI was 26.6 (4.0) kg/m², mean (SD) HbA1c was 8.07 (0.85) %, mean (SD) eGFR was 73.9 (21.7) mL/min/1.73 m², 55.4% had multivessel coronary artery disease, 40.9% had a history of MI, 24.9% had a history of stroke, 17.7% had a coronary artery bypass graft, and 5.1% had cardiac failure. At baseline, 71.9% of Asian patients were on angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers, 58.8% were on β-blockers, and 26.6% were on diuretics.

CV Outcomes
In the overall patient population, there was a significantly lower risk of 3-point MACE (primary outcome) in the empagliflozin group (490/4,687 patients [10.5%]) than in the placebo group (282/2,333 patients [12.1%]) (hazard ratio: 0.86 [95.02% CI: 0.74–0.99]).[5] The reduction in 3-point MACE in Asian patients was consistent with the overall patient population: 3-point MACE occurred in 79/1,006 patients (7.9%) in the empagliflozin group vs. 58/511 patients

(11.4%) in the placebo group (hazard ratio: 0.68 [95% CI: 0.48–0.95], P-value for treatment by race interaction 0.0872) (**Figures 1,2A**). The secondary outcome, 4-point MACE, occurred in 101/1,006 Asian patients (10.0%) in the empagliflozin group vs. 69/511 Asian patients (13.5%) in the placebo group (hazard ratio: 0.73 [95% CI: 0.54–1.00]), consistent with the overall patient population (hazard ratio: 0.89 [95.02% CI: 0.78–1.01]) (P-value for treatment by race interaction 0.2988).

The effects of empagliflozin on components of 4-point MACE, all-cause mortality, and HF outcomes in Asian patients were consistent with the overall patient population (**Figure 1**). In Asian patients, the hazard ratio for CV death was 0.44 (95% CI: 0.25–0.78) and the hazard ratio for all-cause mortality was 0.64 (95% CI: 0.40–1.01), consistent with the hazard ratios in the overall patient population (CV death: 0.62 [95% CI: 0.49–0.77]; all-cause mortality: 0.68 [95% CI: 0.57–0.82]) (**Figures 1,2B,2C**). In Asian patients, there was no difference between empagliflozin and placebo in the risk of stroke (hazard ratio: 0.95 [95% CI: 0.55–1.64]) or MI (hazard ratio: 0.62 [95% CI: 0.36–1.08]), consistent with the overall patient population (hazard ratio for stroke: 1.18 [95% CI: 0.89–1.56]; hazard ratio for MI: 0.87 [95% CI: 0.70–1.09]) (**Figure 1**). There were reductions in the risks of hospitalization for HF and the composite of HF hospitalization or CV death in Asian patients (hazard ratio for hospitalization for HF: 0.70 [95% CI: 0.37–1.33]; hazard ratio for the composite of HF hospitalization or CV death: 0.57 [95% CI: 0.36–0.89]), which were consistent with the overall patient population (hazard ratio for hospitalization for HF: 0.65 [95% CI: 0.50–0.85]; hazard ratio for the composite of HF hospitalization or CV death: 0.66 [95% CI: 0.55–0.79]) (**Figure 1**).

In patients from East Asian countries (pooled empagliflozin, n=397; placebo, n=189), the effects of empagliflozin on CV outcomes were comparable with the Asian subgroup, as well as the overall trial population (**Table S1**).

Glycemic Control

In Asian patients, at week 12, the adjusted mean differences in HbA1c between patients receiving empagliflozin (n=988) and placebo (n=503) were −0.48% (95% CI −0.57 to −0.40) for empagliflozin 10 mg and −0.64% (95% CI −0.73 to −0.55) for empagliflozin 25 mg (**Figure 3**). At week 94, the adjusted mean differences in HbA1c between Asian patients receiving empagliflozin (n=922) and placebo (n=463) were −0.44% (95% CI −0.57 to −0.30) for empagliflozin 10 mg and −0.53% (95% CI −0.66 to −0.40) for empagliflozin 25 mg. At week 206, the adjusted mean differences in HbA1c between Asian patients receiving empagliflozin (n=100) and placebo (n=40) were −0.15% (95% CI −0.46 to 0.15) for empagliflozin 10 mg and −0.49% (95% CI −0.80 to −0.19) for empagliflozin 25 mg. In Asian patients, the effects of empagliflozin on glycemic control were comparable with the overall trial population.

CV Risk Factors and Medications

Consistent with the overall trial population, in Asian patients, small reductions in weight, systolic blood pressure, diastolic blood pressure and uric acid, and small increases in LDL- and HDL-cholesterol, were observed with empagliflozin vs. placebo (**Figure S1**). There was no increase in heart rate.

Consistent with the overall results, a higher percentage of Asian patients in the placebo group received additional
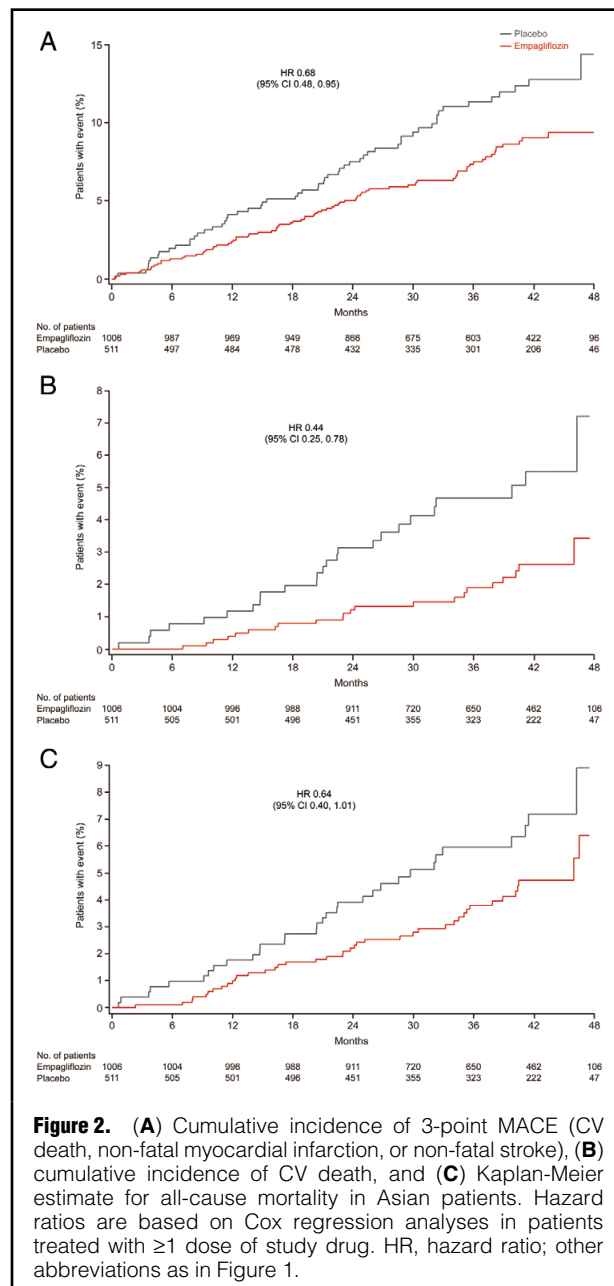

Figure 2. (**A**) Cumulative incidence of 3-point MACE (CV death, non-fatal myocardial infarction, or non-fatal stroke), (**B**) cumulative incidence of CV death, and (**C**) Kaplan-Meier estimate for all-cause mortality in Asian patients. Hazard ratios are based on Cox regression analyses in patients treated with ≥1 dose of study drug. HR, hazard ratio; other abbreviations as in Figure 1.
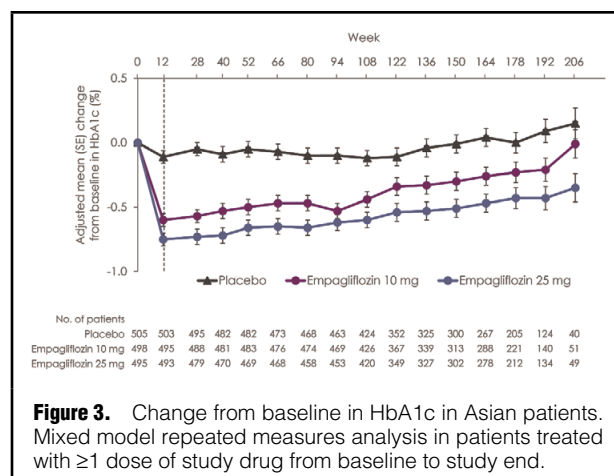

Figure 3. Change from baseline in HbA1c in Asian patients. Mixed model repeated measures analysis in patients treated with ≥1 dose of study drug from baseline to study end.

Table 2. Adverse Events in Asian Patients

	Placebo (n=511)	Empagliflozin 10 mg (n=505)	Empagliflozin 25 mg (n=501)
Adverse event	488 (95.5)	468 (92.7)	455 (90.8)
Serious adverse event	213 (41.7)	175 (34.7)	184 (36.7)
Death	23 (4.5)	12 (2.4)	17 (3.4)
Drug-related* adverse event	136 (26.6)	137 (27.1)	143 (28.5)
Adverse event leading to discontinuation	81 (15.9)	67 (13.3)	67 (13.4)
Event consistent with urinary tract infection†	95 (18.6)	93 (18.4)	85 (17.0)
Event consistent with genital infection‡	5 (1.0)	19 (3.8)	14 (2.8)
Confirmed hypoglycemic adverse event§	136 (26.6)	134 (26.5)	121 (24.2)
Acute renal failure¶	29 (5.7)	29 (5.7)	29 (5.8)
Event consistent with volume depletion‖	17 (3.3)	20 (4.0)	27 (5.4)
Bone fracture**	16 (3.1)	23 (4.6)	12 (2.4)
Thromboembolic event¶	5 (1.0)	2 (0.4)	2 (0.4)
Cancer	8 (1.6)	8 (1.6)	16 (3.2)
Diabetic ketoacidosis††	1 (0.2)	0	0

Data are n (%) of patients treated with ≥1 dose of study drug who reported ≥1 of the respective type of adverse event during treatment or within 7 days of the last intake of study drug, except for data on cancer, which are all events reported up to termination of the trial. *As reported by the investigator. †Based on 79 preferred MedDRA terms. ‡Based on 88 MedDRA preferred terms. §Plasma glucose level <70 mg/dL (3.9 mmol/L) and/or requiring assistance. ¶Based on 1 standardized MedDRA query. ‖Based on 8 MedDRA preferred terms. **Based on 62 MedDRA preferred terms. ††Based on 4 MedDRA preferred terms. MedDRA, Medical Dictionary for Regulatory Activities.

glucose-lowering medications (most commonly a dipeptidyl peptidase-4 inhibitor or insulin) and antihypertensive medications (including diuretics) during the trial, with no differences in the introduction of anticoagulants or lipid-lowering drugs post-baseline (**Tables S2,S3**).

Safety and Tolerability

The AE profile of empagliflozin in Asian patients was consistent with that observed in the overall trial population.[5] The percentages of Asian patients who had any AEs, serious AEs, or AEs leading to discontinuation of study drug were similar in the empagliflozin and placebo groups (**Table 2**). The proportions of patients with events consistent with genital infection (3.8%, 2.8% and 1.0% in the empagliflozin 10 mg, empagliflozin 25 mg and placebo groups, respectively) and volume depletion (4.0%, 5.4% and 3.3% in the empagliflozin 10 mg, empagliflozin 25 mg and placebo groups, respectively) were higher in patients treated with empagliflozin than placebo. Cancer was reported more frequently in patients treated with empagliflozin than placebo (1.6%, 3.2% and 1.6% in the empagliflozin 10 mg, empagliflozin 25 mg and placebo groups, respectively). The proportions of patients with events consistent with urinary tract infection, confirmed hypoglycemic AEs, acute renal failure, thromboembolic events, and bone fractures were similar in the empagliflozin and placebo groups. Diabetic ketoacidosis was reported in 1 patient treated with placebo and in none treated with empagliflozin.

Clinical laboratory parameters in Asian patients are shown in **Table S4**. No relevant changes in electrolytes were observed in any group. Hematocrit increased in patients treated with empagliflozin (mean±SD changes from baseline: 5.2±5.5% in the empagliflozin 10 mg group, 5.0±5.4% in the empagliflozin 25 mg group, 1.1±5.0% in the placebo group). In the empagliflozin group, there was an initial decrease in eGFR followed by an increase to near baseline levels (**Figure S1**).

Discussion

In the EMPA-REG OUTCOME® trial in patients with T2DM and established CV disease, empagliflozin given in addition to standard of care significantly reduced the risk of the primary outcome of 3-point MACE by 14%, driven by a 38% reduction in CV death.[5] Our new analyses demonstrate that the reductions in risk of CV and mortality outcomes were consistent between Asian patients and the overall trial population. An additional analysis showed that the reductions in risk of CV/mortality outcomes were consistent between patients from East Asian countries and the overall trial population; however, it should be noted that a statistical test for consistency was not performed, and the number of East Asian patients with CV events was small. As observed in the overall trial population, reductions in the risks of CV death and all-cause mortality in Asian patients occurred early and were maintained throughout the trial.

Compared with the overall trial population, Asian patients had lower mean weight and BMI; smaller proportions had peripheral artery disease, coronary artery bypass graft, or a history of MI; and greater proportions had multivessel coronary artery disease. However, baseline characteristics were balanced between treatment groups. It should be noted that the benefits of empagliflozin observed in EMPA-REG OUTCOME® occurred in patients with T2DM and established CV disease receiving multiple medicines with proven CV benefits, such as renin-angiotensin-aldosterone system inhibitors, statins, β-blockers, and acetylsalicylic acid. Similar proportions of patients were taking antihypertensive medications at baseline in the Asian subgroup compared with the overall trial population; use of diuretics and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers was lower in the Asian subgroup, but comparable between the empagliflozin and placebo groups.

Throughout the trial (and after week 12 for glucose-

lowering medications), investigators were encouraged to treat CV risk factors to achieve optimal standard of care according to local guidelines. Consistent with the overall trial population, a small reduction in HbA1c was observed in Asian patients treated with empagliflozin vs. placebo. Empagliflozin was also associated with weight loss: the effects of empagliflozin on weight in Asian patients in EMPA-REG OUTCOME® were similar to those observed in the overall trial population and in Asian patients who participated in previous phase III trials.[8] Reductions in weight with empagliflozin are mainly associated with reductions in visceral adiposity.[9,10] This may be particularly important in Asian patients, who have more visceral adiposity than Caucasians at any given BMI.[11] As observed in the overall trial population, empagliflozin reduced blood pressure in Asian patients, with no increase in heart rate.

The AE profile of empagliflozin in Asian patients was consistent with that reported in the overall trial population.[5] Events consistent with genital infection were more common in Asian patients treated with empagliflozin than with placebo. There was a slight imbalance in the proportion of Asian patients with events consistent with volume depletion between the placebo and empagliflozin groups, but the percentage of Asian patients with such events was low in all treatment groups, consistent with the overall population. Other AEs of special interest were reported in similar proportions of Asian patients treated with empagliflozin and placebo. There were no cases of diabetic ketoacidosis in Asian patients treated with empagliflozin. In the Asian subgroup, cancer events were reported in 8 (1.6%) patients, 16 (3.2%) patients and 8 (1.6%) patients in the empagliflozin 10 mg, empagliflozin 25 mg and placebo groups, respectively. In the overall trial population, no imbalance was observed between empagliflozin and placebo in the overall number of cancer events or in any specific subtype of cancer (data on file).

In EMPA-REG OUTCOME®, the reductions in risk of CV/mortality outcomes with empagliflozin occurred early, suggesting that the benefits were not primarily driven by an effect on atherosclerosis. The mechanisms behind the CV benefits of empagliflozin are believed to be multifactorial and may involve its effects on hyperglycemia, weight, visceral adiposity, uric acid, blood pressure, or arterial stiffness.[5,10,12] Recently, it was suggested that the CV benefits observed with empagliflozin in EMPA-REG OUTCOME® may be driven by hemodynamic and renal effects that are particularly beneficial in patients with cardiac dysfunction.[13] Empagliflozin has been shown to increase urinary glucose excretion and urine volume,[14,15] leading to a reduction in fluid volume that may reduce cardiac pre- and afterload. Further, the transient increase in sodium excretion that occurs with empagliflozin activates tubuloglomerular feedback mechanisms that result in a decrease in glomerular pressure,[16] addressing the maladaptive arteriolar responses seen in patients with T2DM.

These data support a reduction in CV outcomes and all-cause mortality in Asian patients with T2DM and established CV disease treated with empagliflozin in addition to standard of care. Limitations of these analyses include that patients who identified themselves as Asian based on the list of options provided for race were heterogeneous with respect to genetic, environmental, and cultural factors relevant to CV risk, and that the number of events in patients from East Asian countries was small.

Conclusion

Reductions in the risk of CV outcomes and all-cause mortality with empagliflozin vs. placebo were consistent between Asian patients and the overall patient population with T2DM and established CV disease in EMPA-REG OUTCOME®.

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Supplementary Files

Supplementary File 1

Figure S1. Weight, systolic and diastolic blood pressure, heart rate, low density and high density lipoprotein-cholesterol, uric acid and eGFR over time in Asian patients.

Table S1. CV outcomes in patients from the East Asian Region

Table S2. Glucose-lowering medications introduced post-baseline in Asian patients

Table S3. CV medications introduced post-baseline in Asian patients

Table S4. Clinical laboratory parameters in Asian patients

Please find supplementary file(s);
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