Empagliflozin and kidney outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: Results from the EMPA-REG OUTCOME® trial

Takashi Kadowaki1*, Masaomi Nangaku1, Stefan Hantel2, Tomoo Okamura3, Maximilian von Eynatten4, Christoph Wanner5, Audrey Koitka-Weber4,5,6

1Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, 2Boehringer Ingelheim International GmbH, Biberach, Germany, 3Nippon Boehringer Ingelheim Co., Ltd, Tokyo, Japan, 4Boehringer Ingelheim International GmbH, Ingelheim, Germany, 5Department of Medicine, Würzburg University Clinic, Würzburg, Germany, and 6Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Keywords
Diabetic kidney disease, Empagliflozin, Type 2 diabetes mellitus

ABSTRACT
Aims/Introduction: In the EMPA-REG OUTCOME® trial, empagliflozin added to standard of care improved clinically relevant kidney outcomes by 39%, slowed progression of chronic kidney disease, and reduced albuminuria in patients with type 2 diabetes and established cardiovascular disease. This exploratory analysis investigated the effects of empagliflozin on the kidneys in Asian patients.

Materials and Methods: Participants in the EMPA-REG OUTCOME® trial were randomized (1:1:1) to empagliflozin 10 mg, 25 mg or a placebo. In patients of Asian race, we analyzed incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of renal-replacement therapy or renal death) and its components, estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio changes, and renal safety.

Results: Of 7,020 treated patients, 1,517 (26.1%) were Asian. In this subgroup, consistent with the overall trial population, empagliflozin reduced the risk of incident or worsening nephropathy (hazard ratio 0.64, 95% confidence interval 0.49–0.83), progression to macroalbuminuria (hazard ratio 0.64, 95% confidence interval 0.49–0.85) and the composite of doubling of serum creatinine, initiation of renal-replacement therapy or renal death (hazard ratio 0.48, 95% confidence interval 0.25–0.92). Furthermore, empagliflozin-treated participants showed slower eGFR decline versus placebo, and showed rapid urine albumin-to-creatinine ratio reduction at week 12, maintained through week 164, with effects most pronounced in those with baseline microalbuminuria or macroalbuminuria. The kidney safety profile of empagliflozin in the Asian subgroup was similar to the overall trial population.

Conclusions: In Asian patients from the EMPA-REG OUTCOME® trial, empagliflozin improved kidney outcomes, slowed eGFR decline and lowered albuminuria versus placebo, consistent with the overall trial population findings.

INTRODUCTION
Type 2 diabetes mellitus is frequently perceived as a disease of the Western world, and while it is widely known that the incidence of diabetes in Asian countries is predicted to increase over the coming years, it is less often recognized that the incidence is in fact already high throughout the Asian region. For example, in 2017 the International Diabetes Federation estimated that >100 million people in China had diabetes, as did >80 million people in Southeast Asia1. Together, more than half the number of people with diabetes worldwide were from Asian countries1.
Certainly, these statistics are partially explained by the large populations of these countries, but the epidemiology and pathophysiology of diabetes also vary between racial and ethnic groups\textsuperscript{2–10}. Asian patients with type 2 diabetes mellitus are more likely to be diagnosed at a relatively young age (approximately 20% are diagnosed before they are aged 40 years\textsuperscript{11} and are at higher risk for complications than patients with late-onset type 2 diabetes mellitus\textsuperscript{12}. Among type 2 diabetes mellitus complications, cardiovascular (CV) disease is often the focus of attention, but microvascular complications are also of critical importance, and approximately 50% of type 2 diabetes mellitus patients worldwide will develop diabetic kidney disease (DKD) during their lifetime\textsuperscript{13,14}. An increasing body of evidence suggests that Asian individuals with type 2 diabetes mellitus are at greater risk of DKD than other racial groups\textsuperscript{6–9,15–19}.

Unfortunately, options to prevent or treat DKD are limited; currently available treatment involves control of blood glucose and blood pressure along with renin–angiotensin–aldosterone system inhibition, and encouraging smoking cessation. However, patients receiving the current standard of care remain at increased risk of clinical kidney and CV events, and premature death\textsuperscript{12,20,21}. Given the pressing need for additional treatments, there has been extensive interest in possible kidney benefits of the type 2 diabetes mellitus drugs known as sodium–glucose cotransporter 2 (SGLT2) inhibitors\textsuperscript{22,23}.

As a class, SGLT2 inhibitors are now well established as a treatment option for type 2 diabetes mellitus, with clinical trials showing these agents provide effective reductions in glycated hemoglobin (HbA1c) in a wide range of patient groups. In patients with type 2 diabetes mellitus and established CV disease, SGLT2 inhibitors have shown significant reductions in the risk of macrovascular complications in dedicated CV outcome trials\textsuperscript{24,25}. In the Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME\textsuperscript{26}) trial, empagliflozin, a highly selective inhibitor of SGLT2, significantly reduced the risk of the primary outcome of three-point major adverse CV events (MACE; composite of CV death, non-fatal myocardial infarction or non-fatal stroke), driven by a 38% relative risk reduction in CV death, when added to standard care\textsuperscript{24}. Despite diminishing glucose-lowering efficacy with declining kidney function, improved CV outcomes with empagliflozin were also consistent across subgroups of patients by baseline kidney function or albuminuria\textsuperscript{26}.

Furthermore, in the EMPA-REG OUTCOME\textsuperscript{26} trial, kidney outcomes were among prespecified secondary end-points and, over the course of the study, empagliflozin was associated with lower rates of clinically relevant kidney outcomes versus placebo, as well as a slower decline in the estimated glomerular filtration rate (eGFR), and sustained reductions in the urine albumin-to-creatinine ratio (UACR)\textsuperscript{27,28}. Given the potential differences between Asian patients and other populations in disease etiology, subgroup analyses of EMPA-REG OUTCOME\textsuperscript{26} were prespecified; analysis of CV outcomes and mortality showed that risk reductions with empagliflozin were consistent between the overall trial population and Asian patients\textsuperscript{29}. We report a subgroup analysis of EMPA-REG OUTCOME\textsuperscript{26} assessing the effect of empagliflozin on kidney outcomes, eGFR and albuminuria in patients of Asian race.

**METHODS**

**Study Design**

The EMPA-REG OUTCOME\textsuperscript{26} study design and methods have been previously described\textsuperscript{24,30}. Key inclusion criteria were adults with type 2 diabetes mellitus (HbA1c 7.0–9.0% for drug-naive patients and 7.0–10.0% for patients receiving stable glucose-lowering treatment), body mass index ≤ 45 kg/m\textsuperscript{2}, established CV disease and eGFR ≥ 30 mL/min/1.73 m\textsuperscript{2}, according to the Modification of Diet in Renal Disease (MDRD) equation. Patients were randomized 1:1:1 to receive once-daily empagliflozin 10 mg, empagliflozin 25 mg or a placebo in addition to standard of care. The trial continued until at least 691 patients experienced an adjudicated event included in the primary outcome of three-point major adverse CV events.

Centers in 11 so-called Asian countries (Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan and Thailand) participated in the EMPA-REG OUTCOME\textsuperscript{26} trial, and are referred to subsequently as “Asian countries.” However, all patients of Asian race were included in this analysis, irrespective of their geographic location. Patients self-identified their race.

Serum creatinine and UACR were measured by a central laboratory at the following timepoints: the start of the placebo run-in period; randomization; weeks 4 (only serum creatinine), 12, 28 and 52; then every 14 weeks until the end-of-study visit; at the end-of-study visit; and 30 days after the end-of-study visit. At the same timepoints, except for week 4, urine dipstick was carried out locally. The timing of urine collection (e.g., first-morning void) was not specified. Events that were consistent with changes in albuminuria category (defined, for the purpose of this study, in accordance with the Kidney Disease Improving Global Outcomes categories\textsuperscript{31} as normoalbuminuria [UACR < 30 mg/g], microalbuminuria [UACR ≥ 30 to ≤ 300 mg/g] or macroalbuminuria [UACR > 300 mg/g]) were captured if any laboratory assessment fulfilled the criteria on one occasion\textsuperscript{28}. To calculate eGFR, the MDRD formula was used at baseline, and the Chronic Kidney Disease Epidemiology Collaboration formula was used for eGFR over time.

The trial was carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The protocol was approved by an independent ethics committee or institutional review board at each participating site, and all patients provided informed consent before study entry.

**Outcomes**

Previously, the CV outcomes of the EMPA-REG OUTCOME\textsuperscript{26} trial have been reported in the overall trial population\textsuperscript{24,32,33}.
and in Asian patients. Kidney outcomes have been reported in detail for the overall trial population. Here, we analyzed post-hoc the following kidney outcomes in patients of Asian race: incident or worsening nephropathy (a composite of progression to macroalbuminuria, doubling of serum creatinine accompanied by an eGFR (MDRD) ≤45 mL/min/1.73 m², initiation of renal-replacement therapy or death from kidney disease); progression to microalbuminuria; and a composite of doubling of serum creatinine accompanied by an eGFR (MDRD) ≤45 mL/min/1.73 m², initiation of renal-replacement therapy or death from kidney disease. For the same outcomes, subgroup analyses were also carried out in patients from the East Asian region (patients from Hong Kong, Japan, Korea or Taiwan; all of whom were of Asian race). In addition, incident or worsening nephropathy was assessed in Asian patients by subgroup of baseline eGFR categories (<60 and ≥60 mL/min/1.73 m²).

Kidney function was measured using eGFR over time, as well as changes in eGFR from baseline to last value on treatment and to follow-up. UACR over time and changes from baseline to week 12 and 16 (median observation time) were analyzed by baseline UACR categories, as previously described for the overall trial population. Improvement or deterioration of UACR between defined UACR categories (normoalbuminuria, microalbuminuria and macroalbuminuria) was based on sustained measurements (≥2 consecutive measurements ≥4 weeks apart), and was determined as follows: time to new onset of sustained normoalbuminuria in patients with microalbuminuria at baseline; time to new onset of sustained normo- or microalbuminuria in patients with macroalbuminuria at baseline; time to new onset of sustained normo- or microalbuminuria in patients with macroalbuminuria at baseline; time to new onset of sustained macroalbuminuria in patients with normoalbuminuria at baseline; and time to new onset of sustained macroalbuminuria in patients with normoalbuminuria at baseline.

The safety results of Asian patients from the EMPA-REG OUTCOME trial have also been reported previously. We assessed additional safety measures relevant to kidney outcomes on the basis of adverse events (AEs) reported in subgroups by baseline eGFR categories (<60 and ≥60 mL/min/1.73 m²).

Statistical Analysis
All analyses were carried out in the treated set of patients who received one or more dose of the study drug (modified intention-to-treat approach) and compared the pooled empagliflozin groups (10 and 25 mg) versus placebo.

Baseline characteristics, background medications at baseline and introduced post-baseline, and AEs were presented by subgroups with baseline eGFR <60 or ≥60 mL/min/1.73 m².

Cox regression analyses for the overall trial population have been previously described. A Cox proportional hazards model was used to investigate the consistency of the treatment effects in the Asian subgroup and in the other races (White, Black/African American, Other). The results for the other races are not included in the present study, but were included in the model to allow calculation of the interaction P-value. Analyses by subgroup of eGFR used a similar model, with the addition of a factor for treatment by baseline eGFR (MDRD) interaction.

Changes in eGFR and UACR over time were evaluated using a mixed-model, repeated-measures analysis in patients who received one or more dose of the study drug, and had a baseline and post-baseline measurement. The eGFR analysis model included baseline HbA1c and eGFR (Chronic Kidney Disease Epidemiology Collaboration) as linear covariates, and region, baseline body mass index, the last week a patient could have had an eGFR measurement, treatment, visit, treatment-by-visit interaction, baseline HbA1c-by-visit interaction and baseline eGFR-by-visit interaction as fixed effects. For the analysis of patients of Asian race, the model also included race, visit-by-race interaction, treatment-by-race interaction and treatment-by-visit-by-race interaction as fixed effects. The UACR analysis model included baseline HbA1c as a linear covariate, and baseline eGFR category, region, baseline body mass index category, the last week a patient could have had a UACR measurement, treatment, visit, baseline UACR category, treatment-by-visit interaction, visit-by-baseline-UACR-category interaction, treatment-by-visit-by-baseline-UACR-category interaction and baseline HbA1c-by-visit interaction as fixed effects. UACR changes over time were analyzed by baseline UACR category (normoalbuminuria, microalbuminuria or macroalbuminuria). Kaplan-Meier estimates were generated for the time to first occurrence of kidney outcomes and UACR regression (improvement)/progression (deterioration); hazard ratios were determined by Cox regression analysis.

RESULTS
Patients
A total of 7,020 patients received one or more dose of the study drug during the EMPA-REG OUTCOME trial; of these, 1,517 (26.1%) were of Asian race. The median observation time in this subgroup was 3.3 years, similar to that of the overall trial population (3.1 years).

Overall baseline characteristics of the Asian patients have been reported previously and were generally balanced between the placebo and empagliflozin groups. At baseline, 71.9% of Asian patients were taking angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs), 58.8% were taking β-blockers, and 26.6% were taking diuretics. In addition, as observed in the overall trial population, loop diuretics were introduced in fewer Asian patients in the empagliflozin group than the placebo group during the study (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.47–0.91; Figure S1).

Baseline characteristics according to baseline eGFR <60 or ≥60 mL/min/1.73 m² are shown in Table S1, and baseline medications are shown in Table S2. As expected, patients with eGFR <60 mL/min/1.73 m² tended to be older, have a longer duration of type 2 diabetes mellitus, were more likely to have albuminuria and to receive diuretics. However, fewer
Empagliflozin-treated patients received diuretics (including loop diuretics) than those receiving a placebo (Table S2).

**Outcomes**

**Incident or Worsening Nephropathy**

For the Asian subgroup, event rates for kidney outcomes appeared higher than in the overall population (Figure 1), although this was not tested for statistical significance. The effects of empagliflozin on kidney outcomes in Asian patients were consistent with those in the overall trial population (Figures 1 and 2). Among the Asian subgroup, incident or worsening nephropathy occurred in 15.5% of patients in the empagliflozin group versus 21.8% of patients in the placebo group (HR 0.64, 95% CI 0.49–0.83), and the time to event followed a pattern consistent with the overall group (Figure 2a). Progression to macroalbuminuria occurred in 13.7% of patients in the empagliflozin group and in 19.3% of the placebo group (HR 0.64, 95% CI 0.49–0.85; Figures 1 and 2b). The composite of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m², initiation of renal-replacement therapy or death due to renal disease occurred in 1.8% of the empagliflozin group versus 3.6% of the placebo group (HR 0.48, 95% CI 0.25–0.92; Figures 1 and 2c).

Kidney outcomes in patients from the East Asian region were also consistent with the overall population (Table S3). Asian patients with an eGFR <60 mL/min/1.73 m² were more likely to experience adverse kidney outcomes than those with a baseline eGFR of ≥60 mL/min/1.73 m², but the beneficial effect of empagliflozin was consistent in both subgroups (Figure 3).

**Kidney Function Over Time**

Kidney function over time, based on eGFR measurements, is shown in Figure 4. In Asian patients treated with empagliflozin, eGFR values showed an initial short-term decline, after which values remained stable over 192 weeks; in placebo-treated patients, there was no short-term change, but eGFR values declined over long-term treatment (Figure 4a). The initial eGFR decrease in the empagliflozin group was reversed at the follow-up visit, which took place approximately 1 month (median 36 days) after cessation of the study drug (Figure 4b). At the post-treatment follow up, the adjusted mean difference from placebo in the change from baseline in eGFR with empagliflozin was +5.0 mL/min/1.73 m² (95% CI 3.7–6.3 mL/min/1.73 m²).

**UACR Changes**

Regardless of the baseline UACR category, treatment with empagliflozin resulted in a rapid reduction in UACR compared with placebo at week 12, which was maintained through week 164. The effect in Asian patients was consistent with the overall trial population (Table 1, Figure S2). Sustained improvement in albuminuria status was more common with empagliflozin than with placebo, and the effect in Asian patients was consistent with the overall trial population (Figure S3). Sustained deterioration in albuminuria status was more common.

| Empagliflozin | Placebo | Hazard ratio (95% CI) | Hazard ratio (95% CI) | P-value for race-by-treatment interaction |
|--------------|---------|-----------------------|-----------------------|------------------------------------------|
| n with event/N (%) | rate/1000 patient-yr | n with event/N (%) | rate/1000 patient-yr |                            |                            |                |                            |
| Incident or worsening nephropathy |          |                      |                      |                            |                            |                |                            |
| Overall | 525/4,124 (12.7) | 47.8 | 388/2,061 (18.8) | 76.0 | 0.61 (0.53, 0.70) |                            | 0.1945 |
| Asian | 134/865 (15.5) | 54.8 | 97/444 (21.8) | 82.6 | 0.64 (0.49, 0.83) |                            |                |
| Progression to macroalbuminuria |          |                      |                      |                            |                            |                |                            |
| Overall | 459/4,091 (11.2) | 41.8 | 330/2,033 (16.2) | 64.9 | 0.62 (0.54, 0.72) |                            | 0.1915 |
| Asian | 117/853 (13.7) | 48.3 | 84/435 (19.3) | 72.4 | 0.64 (0.49, 0.85) |                            |                |
| Doubling of serum creatinine (accompanied by eGFR ≤45 mL/min/1.73 m²), initiation of renal-replacement therapy or death due to renal disease |          |                      |                      |                            |                            |                |                            |
| Overall | 81/4,645 (1.7) | 6.3 | 71/2,323 (3.1) | 11.5 | 0.54 (0.40, 0.75) |                            | 0.7424 |
| Asian | 18/1,003 (1.8) | 6.1 | 18/507 (3.6) | 12.3 | 0.48 (0.25, 0.92) |                            |                |

**Figure 1** | Kidney outcomes in the overall trial population and in Asian patients. Estimated glomerular filtration (eGFR) rate based on Modification of Diet in Renal Disease measurement. Cox regression analyses. 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. Races other than Asian are not shown, but were included in the model to allow calculation of the interaction P-value.
Figure 2 | Time to first kidney outcome events in the overall population and the subgroup of patients of Asian race. (a) Incident or worsening nephropathy. Progression to macroalbuminuria (urine albumin-to-creatinine ratio >300 mg/g), doubling of serum creatinine accompanied by estimated glomerular filtration rate (Modification of Diet in Renal Disease) ≤45 mL/min/1.73 m², initiation of renal-replacement therapy or death from renal disease. (b) Progression to macroalbuminuria. Urine albumin-to-creatinine ratio >300 mg/g. (c) Post-hoc kidney composite outcome. Doubling of serum creatinine accompanied by estimated glomerular filtration rate (Modification of Diet in Renal Disease) ≤45 mL/min/1.73 m², initiation of renal-replacement therapy or death due to renal disease. Kaplan–Meier estimates in patients treated with one or more dose of the study drug. Hazard ratio (HR) and 95% confidence interval (CI) based on a Cox regression model.
with placebo than with empagliflozin; again, Asian patients had results consistent with those of the overall trial population (Figure S4).

Safety
The safety profile of empagliflozin in the overall trial population and in Asian patients has been previously reported. Consistent with the known safety profile for empagliflozin, genital infections were reported more frequently than in patients in the placebo groups.

In Asian patients with eGFR < 60 mL/min/1.73 m², frequencies of serious AEs, drug-related AEs, and AEs leading to discontinuation were greater than in those with eGFR ≥ 60 mL/min/1.73 m²; however, frequencies were well balanced between the empagliflozin and placebo groups (Table S4). The frequencies of renal AEs consistent with acute renal failure, volume depletion, bone fractures, hyperkalemia and edema were higher in Asian patients with eGFR < 60 mL/min/1.73 m², but frequencies were similar between the empagliflozin and placebo groups (Table S4).

DISCUSSION
These analyses of kidney outcomes in Asian patients from EMPA-REG OUTCOME showed improvements with empagliflozin across the various outcomes studied, with results consistent with those of the overall trial population. As previously reported, in the overall trial population, empagliflozin in addition to standard of care was associated with lower rates of clinically relevant kidney outcomes, including a 39% reduction in the relative risk of incident or worsening nephropathy. In the subgroup of patients of Asian race, the corresponding risk reduction for incident or worsening nephropathy was 36%, and the components of progression to macroalbuminuria or the composite of doubling of serum creatinine, renal-replacement therapy, or death from renal disease. Kaplan–Meier estimates in patients treated with one or more dose of study drug. Hazard ratio (HR) and 95% confidence interval (CI) based on a Cox regression model.

Figure 3 | Time to first event of incident or worsening nephropathy in the subgroup of patients of Asian race, by subgroup of estimated glomerular filtration rate (eGFR) at baseline. Progression to macroalbuminuria (urine albumin-to-creatinine ratio > 300 mg/g), doubling of serum creatinine accompanied by eGFR (Modification of Diet in Renal Disease) ≤ 45 mL/min/1.73 m², initiation of renal replacement therapy or death from renal disease. Kaplan–Meier estimates in patients treated with one or more dose of study drug. Hazard ratio (HR) and 95% confidence interval (CI) based on a Cox regression model.
encourages investigators to treat all risk factors to the local standard of care, a number of patients received new prescriptions for medications that might also alter intrarenal hemodynamics, such as ACE inhibitors and ARBs, during the study. However, these were added in both the placebo and empagliflozin groups, and thus seem unlikely to have significantly impacted the present results.

Consistent with the overall study population, the benefits of empagliflozin on UACR were readily observed in Asian patients irrespective of baseline albuminuria status, although appeared of particular clinical relevance in patients with elevated urinary albumin levels at baseline.

These results suggest the potential for empagliflozin to reduce the burden of early morbidity and mortality from DKD associated with Asian race in patients with type 2 diabetes mellitus. In the current analyses, event rates for kidney outcomes were higher in the Asian placebo subgroup than in the overall placebo group, supporting previous findings that Asians with type 2 diabetes mellitus have an elevated risk of progressive kidney disease. In Asian patients with type 2 diabetes mellitus, albuminuria has previously been reported to increase the risk of adverse kidney outcomes, and the magnitude of changes in proteinuria and protection of kidney function observed with empagliflozin in the present study might yield the potential to translate into clinical practice by delaying the need for dialysis by several years.

As previously reported, the overall safety profile of empagliflozin was similar in Asian patients and the overall trial population. Genital infections were relatively scarce in comparison with Western populations (approximately 3%, or half the rate). This might reflect improved hygiene measures in Asian populations, although this is hard to test. Our additional analyses in subgroups of Asian patients with eGFR above or below 60 mL/min/1.73 m² at baseline showed a greater likelihood of AEs in patients with reduced eGFR, whether they were assigned placebo or empagliflozin. A higher rate of AEs is expected in

Figure 4 | Changes in estimated glomerular filtration rate (eGFR according to Chronic Kidney Disease Epidemiology Collaboration) in Asian patients over the course of the study. (a) Mean eGFR over time (based on a mixed-model repeated-measures analysis in patients who received ≥1 dose of study drug, and had a baseline and post-baseline measurement using an observed cases approach, including values after study drug discontinuation). (b) eGFR at baseline, last value on treatment and follow up (ANOVA in patients treated with ≥1 dose of study drug who had a measurement at all three timepoints). CI, confidence interval; SE, standard error.
patients with impaired kidney function, and although no additional safety signal was noted with empagliflozin, these results highlight the need for individualized treatment approaches in populations with DKD. Edema appeared to be less frequent in patients taking empagliflozin, presumably related to its osmotic diuretic/natriuretic effect. Consistent with the overall study population, a lower proportion of Asian patients who received empagliflozin initiated loop diuretics during the study than in the group receiving placebo. The lower rate of introduction of loop diuretics in the empagliflozin group is consistent with the previously reported reduced incidence of hospitalization for heart failure.

The mechanism by which empagliflozin reduces the risk of clinically relevant kidney outcomes is likely multifactorial, with processes such as improvement in arterial stiffness, serum uric acid levels and tubulointerstitial hypoxia proposed, although the key contributor is thought to be lowering of intraglomerular pressure. This was not measured in the EMPA-REG OUTCOME trial, but a mechanistic study in patients with type 1 diabetes showed intraglomerular pressure reductions of 6–8 mmHg with empagliflozin. Reductions in glomerular hypertension are thought to result from increased sodium reaching the macula densa, restoring tubuloglomerular feedback, thus causing afferent arteriole vasomodulation. Taken together, the pattern of eGFR and UACR changes we observed suggest that empagliflozin-mediated hemodynamic effects on the kidney (associated with lowering of intraglomerular pressure) were likely the key contributor to the results in the subgroup of Asian patients, as it was for the overall population. This is of particular clinical relevance to Asian patients, as it is well known that many Asian diets include high-sodium consumption, often with insufficient potassium intake, an established contributor to high blood pressure. It is reported that racial groups differ in their levels of plasma renin activity, more salt-sensitive hypertension and ability to excrete a sodium load. Asian patients tend to be more responsive than other groups to antihypertensive agents affecting the renin–angiotensin–aldosterone system, such as ACE inhibitors and ARBs; for example, in Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL), ARB treatment reduced the risk of renal outcomes by 35% in Asians versus 16% in the overall trial population. These factors might have particular relevance for DKD, as abnormal renal sodium handling is a key mechanism in the development of kidney disease through hypertension and volume overload. Increased dietary salt intake has been repeatedly found to be associated with CV damage, and more recently, evidence has begun to emerge that patients with diabetes have increased tissue sodium content, suggesting total sodium content reduction as a potential therapeutic goal, which could partially explain why Asian

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patients could potentially be very responsive to such treatment approaches.

The EMPA-REG OUTCOME trial was a rigorously conducted study, and the multinational population has allowed additional analyses such as ours. One of the key strengths of our analyses was the broad grouping of patients of Asian race, including patients treated at centers elsewhere in the world. This suggests our results might be applicable across the range of patients of different Asian backgrounds, even though DKD etiology and pathophysiology might vary between groups. However, as patients who identified themselves as Asian were likely heterogeneous with regard to genetic, environmental and cultural factors relevant to kidney risk, additional studies in dedicated geographies could be of interest. Notably, East Asian patients might be at particularly increased risk; in our analyses, we were limited by a relatively small subgroup, but the results showed a trend towards consistent results with the overall group.

Furthermore, all patients enrolled in EMPA-REG OUTCOME had established CV disease and, as this significantly impacts the risk of future clinical events, the present results require confirmation in those without CV disease. Observational data from real-world studies might be useful here, and future trials of empagliflozin in patients with kidney disease should extend our understanding. In particular, the recently announced EMPA-KIDNEY study has been specifically designed to assess the effect of empagliflozin on clinical outcomes in people with established chronic kidney disease, with or without diabetes, receiving current standard of care. Key end-points will examine the most clinically relevant outcomes of kidney disease progression and CV mortality risk.

In summary, in the subgroup of Asian patients from the EMPA-REG OUTCOME trial, all of whom had type 2 diabetes mellitus and established CV disease, empagliflozin improved kidney outcomes, slowed kidney function loss and provided sustained improvements in albuminuria versus placebo, demonstrating results consistent with those reported for the overall trial population.

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DISCLOSURE
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REFERENCES
1. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. Available from: http://www.diabetesatlas.org/. Accessed January 15, 2018.
2. Gujral UP, Pradeepa R, Weber MB, et al. Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. Ann N Y Acad Sci 2013; 1281: 51–63.
3. Kodama K, Tojjar D, Yamada S, et al. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. Diabetes Care 2013; 36: 1789–1796.
4. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. J Diabetes Investig 2016; 7(Suppl 1): 102–109.
5. Yabe D, Seino Y, Fukushima M, et al. beta cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. Curr Diab Rep 2015; 15: 602.
6. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 2013; 1281: 64–91.
7. Shah A, Kanaya AM. Diabetes and associated complications in the South Asian population. Curr Cardiol Rep 2014; 16: 476.
8. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018; 14: 88–98.
9. Bakker LE, Sleddering MA, Schoones JW, et al. Pathogenesis of type 2 diabetes in South Asians. Eur J Endocrinol 2013; 169: R99–R114.
10. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. Lancet Diabetes Endocrinol 2015; 3: 1004–1016.
11. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. Lancet Diabetes Endocrinol 2014; 2: 935–943.
12. Chan JC, So WY, Yeung CY, et al. Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study. *Diabetes Care* 2009; 32: 977–982.

13. Mohammadi K, Woodward M, Marre M, et al. Comparative effects of microvascular and macrovascular disease on the risk of major outcomes in patients with type 2 diabetes. *Cardiovasc Diabetol* 2017; 16: 95.

14. Thomas MC, Cooper ME, Zimet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nat Rev Nephrol* 2016; 12: 73–81.

15. Gheith O, Farouk N, Nampoory N, et al. Diabetic kidney disease: world wide difference of prevalence and risk factors. *J NephroPharmacol* 2016; 5: 49–56.

16. Ali O, Mohiuddin A, Mathur R, et al. A cohort study on the rate of progression of diabetic chronic kidney disease in different ethnic groups. *BMJ Open* 2013; 3: e001855.

17. Dreyer G, Hull S, Mathur R, et al. Progression of chronic kidney disease in a multi-ethnic community cohort of patients with diabetes mellitus. *Diabet Med* 2013; 30: 956–963.

18. Clarke PM, Glasiou P, Patel A, et al. Event rates, hospital utilization, and costs associated with major complications of diabetes: a multicountry comparative analysis. *PLoS Med* 2010; 7: e1000236.

19. Parving HH, Lewis JB, Ravid M, et al. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. *Kidney Int* 2006; 69: 2057–2063.

20. Molitch ME, Adler AI, Flyvbjerg A, et al. Diabetic kidney disease: a clinical update from Kidney Disease: improving Global Outcomes. *Kidney Int* 2015; 87: 20–30.

21. Palsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. *Adv Chronic Kidney Dis* 2014; 21: 273–280.

22. Zou H, Zhou B, Xu G. SGLT2 inhibitors: a novel choice for the combination therapy in diabetic kidney disease. *Cardiovasc Diabetol* 2017; 16: 65.

23. van Bommel EJ, Muskiet MH, Tonneijck L, et al. SGLT2 inhibition in the diabetic kidney - from mechanisms to clinical outcome. *Clin J Am Soc Nephrol* 2017; 12: 700–710.

24. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.

25. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.

26. Wanner C, Lachin JM, Inzucchi SE, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation* 2018; 137: 119–129.

27. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334.

28. Cherney DZI, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017; 5: 610–621.

29. Kaku K, Lee J, Matthews M, et al. Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease - results from EMPA-REG OUTCOME®. *Circ J* 2017; 81: 227–234.

30. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol* 2014; 13: 102.

31. KDGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2017; 2017: 1–59.

32. Fitchett D, Inzucchi SE, Lachin JM, et al. Cardiovascular mortality reduction with empagliflozin in patients with type 2 diabetes and cardiovascular disease. *J Am Coll Cardiol* 2018; 71: 364–367.

33. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. *Eur Heart J* 2018; 39: 363–370.

34. Zinman B, Inzucchi SE, Lachin JM, et al. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. *Stroke* 2017; 48: 1218–1225.

35. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016; 37: 1526–1534.

36. Barbour SJ, Er L, Djurdjev O, et al. Differences in progression of CKD and mortality amongst Caucasian, Oriental Asian and South Asian CKD patients. *Nephrol Dial Transplant* 2010; 25: 3663–3672.

37. Wong LL, Kalantar-Zadeh K, Page V, et al. Insights from screening a racially and ethnically diverse population for chronic kidney disease. *Am J Nephrol* 2017; 45: 200–208.

38. Wada T, Haneda M, Furuichi K, et al. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. *Clin Exp Nephrol* 2014; 18: 613–620.

39. Takagi M, Babazono T, Uchigata Y. Differences in risk factors for the onset of albuminuria and decrease in glomerular filtration rate in people with Type 2 diabetes mellitus: implications for the pathogenesis of diabetic kidney disease. *Diabet Med* 2015; 32: 1354–1360.

40. Hu P, Zhou XH, Wen X, et al. Predictors of renal function decline in Chinese patients with type 2 diabetes mellitus.
and in a subgroup of normoalbuminuria: a retrospective cohort study. Diabetes Technol Ther 2016; 18: 635–643.
41. Sano M, Takei M, Shiraishi Y, et al. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. J Clin Med Res 2016; 8: 844–847.
42. Škrtić M, Yang GK, Perkins BA, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. Diabetologia 2014; 57: 2599–2602.
43. He FJ, MacGregor GA. Reducing population salt intake worldwide: from evidence to implementation. Prog Cardiovasc Dis 2010; 52: 363–382.
44. Tu W, Eckert GJ, Hannon TS, et al. Racial differences in sensitivity of blood pressure to aldosterone. Hypertension 2014; 63: 1212–1218.
45. Chan JC, Wat NM, So WY, et al. Renin angiotensin aldosterone system blockade and renal disease in patients with type 2 diabetes. An Asian perspective from the RENAAL Study. Diabetes Care 2004; 27: 874–879.
46. Kopp C, Linz P, Maier C, et al. Elevated tissue sodium deposition in patients with type 2 diabetes on hemodialysis detected by (23)Na magnetic resonance imaging. Kidney Int 2018; 93: 1191–1197.
47. Liu JJ, Lim SC, Yeoh LY, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with Type 2 diabetes. Diabet Med 2016; 33: 332–339.
48. Low S, Chi LS, Yeoh LY, et al. Long-term diabetes outcomes in multi-ethnic Asians living in Singapore. Diabetes Res Clin Pract 2016; 111: 83–92.
49. Boehringer Ingelheim and Eli Lilly and Company. Boehringer Ingelheim and Lilly announce an academic collaboration with University of Oxford to investigate the effects of empagliflozin in people with chronic kidney disease. [Press release 16 April 2018.] Available from https://www.boehringer-ingelheim.com/EMPA-KIDNEY Accessed April 17, 2018.

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

Table S1 | Baseline characteristics of Asian patients by baseline estimated glomerular filtration rate categories.
Table S2 | Selected medications at baseline and introduced post-baseline†.
Table S3 | Kidney outcomes in patients from the East Asian region.
Table S4 | Adverse events by baseline estimated glomerular filtration rate categories.
Figure S1 | Time to first introduction of loop diuretics post-baseline†.
Figure S2 | Urine albumin-to-creatinine ratio over time according to baseline albuminuria status in Asian patients.
Figure S3 | Improvement in albuminuria status in the overall trial population and in Asian patients.
Figure S4 | Deterioration in albuminuria status in the overall trial population and in Asian patients.