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Empagliflozin and Kidney Function Decline in Patients with Type 2 Diabetes: A Slope Analysis from the EMPA-REG OUTCOME Trial

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ABSTRACT

Background Empagliflozin slowed the progression of CKD in patients with type 2 diabetes and cardiovascular disease in the EMPA-REG OUTCOME Trial. In a prespecified statistical approach, we assessed treatment differences in kidney function by analyzing slopes of eGFR changes.

Methods Participants (n=7020) were randomized (1:1:1) to empagliflozin 10 mg/d, empagliflozin 25 mg/d, or placebo added to standard of care. We calculated eGFR slopes using random-intercept/random-coefficient models for prespecified study periods: treatment initiation (baseline to week 4), chronic maintenance treatment (week 4 to last value on treatment), and post-treatment (last value on treatment to follow-up).

Results Compared with placebo, empagliflozin was associated with uniform shifts in individual eGFR slopes across all periods. On treatment initiation, adjusted mean slope (eGFR change per week, ml/min per 1.73 m^2) decreased with empagliflozin (−0.77; 95% confidence interval, −0.83 to −0.71; placebo: 0.01; 95% confidence interval, −0.08 to 0.10; P<0.001). However, annual mean slope (ml/min per 1.73 m^2 per year) did not decline with empagliflozin during chronic treatment (empagliflozin: 0.23; 95% confidence interval, 0.05 to 0.40; placebo: −1.46; 95% confidence interval, −1.74 to −1.17; P<0.001). After drug cessation, the adjusted mean eGFR slope (ml/min per 1.73 m^2 per week) increased and mean eGFR returned toward baseline level only in the empagliflozin group (0.56; 95% confidence interval, 0.49 to 0.62; placebo −0.02; 95% confidence interval, −0.12 to 0.08; P<0.001). Results were consistent across patient subgroups at higher CKD risk.

Conclusions The hemodynamic effects of empagliflozin, associated with reduction in intraglomerular pressure, may contribute to long-term preservation of kidney function.

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The prevalence of diabetic kidney disease continues to rise and is predicted to affect 200 million people around the world by 2040.[1] Although improved glycemic control and widespread use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have contributed to an improved prognosis for patients with diabetic kidney disease, their renal and cardiovascular risks remain high, underscoring the need for novel therapeutic interventions.

Empagliflozin, a selective sodium glucose cotransporter 2 (SGLT2) inhibitor, has been shown to reduce hyperglycemia, BP, and body weight in patients with type 2 diabetes.[2,3] In the EMPA-REG OUTCOME Trial, empagliflozin markedly decreased the risk of clinically important cardiovascular

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events (in particular, the risk of cardiovascular death), and in further hypothesis-generating analyses, it delayed the progression of CKD in people with type 2 diabetes and established cardiovascular disease.[4,5]

The beneficial kidney effects associated with empagliflozin are thought to be mediated by various mechanisms, including restoration of tubuloglomerular feedback leading to a reduction in intraglomerular pressure and hyperfiltration.[6] Both conditions are considered core components of the pathophysiology contributing to progression of diabetic as well as nondiabetic CKD.[7] In a previous mechanistic study comprising individuals with type 1 diabetes, empagliflozin was shown to reduce glomerular hyperfiltration, likely by reducing intraglomerular pressure.[8,9] Reductions in intraglomerular pressure, as shown by agents blocking the renin-angiotensin system, are frequently accompanied by a hemodynamic acute decrease in GFR, which is reversible after treatment cessation. Previous studies in patients with type 2 diabetes at various stages of CKD have shown that empagliflozin decreased eGFR by approximately 2–4 ml/min per 1.73 m^2 during the first weeks of treatment followed by a return to baseline values after treatment cessation.[10,11]

The EMPA-REG OUTCOME Trial yields a large, well characterized, and prospectively followed cohort. This provides an opportunity to more precisely understand the clinical effects of empagliflozin in patients with concomitant CKD[12] as well as delineate differences in the rate of change in kidney function over time (*i.e.*, eGFR slope) during the acute (treatment initiation), chronic maintenance, and post-treatment (follow-up) phases with empagliflozin in a range of patients with type 2 diabetes, and a previous report has provided the first results.[5] In this manuscript, we provide additional in-depth assessments of the prespecified analysis of eGFR slopes from the EMPA-REG OUTCOME Trial. We aimed to specifically investigate the consistency and clinical relevance of the effect of empagliflozin on acute changes in eGFR after treatment initiation, eGFR slopes during chronic maintenance treatment, and eGFR changes after study drug discontinuation. These analyses were performed in the overall trial population and then, within specific subgroups of individuals at higher risk of progressive CKD.

Significance Statement

Empagliflozin, a selective sodium glucose cotransporter 2 inhibitor, is indicated to improve glycemic control and reduce the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease. Hypothesis-generating results from the EMPA-REG OUTCOME Trial suggest that empagliflozin slows the progression of CKD. This manuscript presents the prespecified eGFR slope analysis from the trial, in which we evaluated changes in kidney function over time. Our results support a hemodynamic effect of empagliflozin, which may lead to reductions in intraglomerular pressure. During chronic maintenance treatment, this glomerular response to empagliflozin may translate into long-term preservation of kidney function. Our data add to the evidence of the utility of slope analysis as an emerging end point of CKD progression in clinical research.

METHODS

Design of the EMPA-REG OUTCOME Trial

As described in detail previously,[4,13] the EMPA-REG OUTCOME Trial (ClinicalTrials.gov identifier: NCT01131676) was a double-blind, placebo-controlled, multinational trial in which adults with type 2 diabetes, glycated hemoglobin A1c (HbA1c) ≥7%, and established cardiovascular disease were randomized in a 1:1:1 ratio to empagliflozin 10 mg, empagliflozin 25 mg, or placebo, all added to background standard of care. Background glucose-lowering therapy was to remain unchanged for the first 12 weeks, after which investigators were encouraged to adjust glucose-lowering therapy to achieve glycemic control according to local guidelines. Moreover, investigators were encouraged to treat other cardiovascular risk factors to the standard of care according to local guidelines.

Patients were required to have an eGFR of ≥30 ml/min per 1.73 m^2 (on the basis of the Modification of Diet in Renal Disease study [MDRD] formula) at screening. Patients attended the clinic at the following prespecified study visits: screening; baseline; weeks 4, 12, 16, 28, 40, and 52; every 14 weeks until treatment stopped (due to either end of study or discontinuation of study drug); and a final visit approximately 30 days after treatment cessation.[13] Serum creatinine and urinary albumin-to-creatinine ratio (UACR) were measured by a central laboratory using standardized procedures.[14] Serum creatinine was used to calculate eGFR using the MDRD equation. The primary outcome of the trial was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and results have been reported previously.[4]

Analyses

A mixed model for repeated measurements, which includes time points of the prescheduled measurements as fixed effects, was fitted to provide a descriptive presentation of the adjusted mean eGFR over time for empagliflozin and placebo groups. The model included "baseline HbA1c" and "baseline eGFR" as linear covariates and "geographic region," "baseline body mass index," "the last week that a patient could have had an eGFR measurement," "treatment," "visit," "interaction between visit and treatment," "interaction between the baseline HbA1c and visit," and "interaction between the baseline eGFR and visit" as fixed effects. An unstructured covariance matrix was used to account for serial correlation.

For the slope analysis reported here, the main prespecified efficacy outcome was the average rate of change of eGFR per year during the trial period when patients received stable treatment with study drug (week 4 until treatment cessation; *i.e.*, the chronic maintenance treatment period), and results are expressed as annual changes in eGFR. In addition, the average rate of change in eGFR per week in the first 4 weeks after starting treatment was assessed (*i.e.*, treatment initiation period) as well as that in the 30 days after stopping treatment

(*i.e.*, post-treatment cessation period). Changes in eGFR per week or year, further referred to as eGFR slope, were obtained using random coefficient models. Assessment of eGFR slope in the overall population was a prespecified analysis of the trial; *post hoc* analyses were also conducted in relevant subgroups at higher risk for CKD progression defined by baseline eGFR, UACR, race, BP, age, and HbA1c levels. For the overall population, the models included the following factors: "treatment," "baseline body mass index," and "geographic region" as fixed classification effects and "baseline HbA1c," "time," and "interaction of treatment by time" as linear covariates. Intercepts and slopes over time were allowed to vary randomly between patients by including the patient and time as random effects. Histogram plots of fitted individual eGFR slopes were provided for each period by treatment. For the subgroup analysis, the models additionally included the fixed factor for the subgroup as well as terms for treatment by subgroup interaction and treatment by subgroup by time interaction. Because empagliflozin was previously shown to exert an acute hemodynamic effect, eGFR slopes were separately calculated for three prespecified study periods: treatment initiation effects from baseline to week 4, chronic maintenance treatment effects from week 4 to last value on treatment, and post-treatment effects from last value on treatment to follow-up (planned to be approximately 30 days after cessation of treatment). For the first two time periods, only on-treatment data before stopping the blinded study drug was used, because it was expected that eGFR would increase after empagliflozin treatment was stopped. For the chronic maintenance treatment period, a uniform treatment effect was defined by a consistent shift of the distribution of individual eGFR slopes for empagliflozin compared with the distribution of individual eGFR slopes for placebo.[15] Thus, consistent changes across the population would be denoted by equally symmetric curves, such that the individual changes in eGFR are consistent in not only their directionality but also, their size. For the chronic maintenance treatment period, SDs of the empagliflozin and placebo arms were derived, and homogeneity was tested by the Levene test. These SDs reflect a combination of the variation in the true slopes and the variation in the estimated slopes relative to the true slopes. An additional sensitivity analysis for the chronic maintenance treatment period applied the random-intercept/random-coefficient model using log-transformed eGFR data. Significance was determined on the basis of an α-level of 0.05 without correction for multiple testing. Additional details of the eGFR slopes analyses are in Supplemental Material.

Data Sharing

The sponsor of the EMPA-REG OUTCOME Trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries *via* the Clinical Study Data Request website (https://www.clinicalstudydatarequest.com).

RESULTS

Patient Disposition

A total of 7020 patients were randomized between September 2010 and April 2013 and received at least one dose of study drug (placebo: n=2333; empagliflozin 10 mg: n=2345; empagliflozin 25 mg: n=2342) at 590 sites in 42 countries. The median duration of treatment was 2.6 years, and the median observation time was 3.1 years. Overall, 97.0% of patients completed the study, and final vital status was available for 99.2%; 683, 555, and 542 patients treated with placebo, empagliflozin 10 mg, or empagliflozin 25 mg, respectively, prematurely discontinued trial medication (*i.e.*, 25.4% of the total trial population), and reasons for premature discontinuation of study drug have been reported.[4]

Baseline Characteristics

At baseline, clinical characteristics and concomitant medications were similar between the placebo and empagliflozin groups as reported previously.[4] Baseline eGFR measurements were available for the majority of patients (missing only for two patients in the empagliflozin 25 mg group). More than one quarter (n=1819; 25.9%) of the patients had eGFR<60 ml/min per 1.73 m^2 at baseline (1249 [17.8%] with eGFR=45–59 ml/min per 1.73 m^2 [CKD stage 3A]; 543 [7.7%] with eGFR=30–44 ml/min per 1.73 m^2 [CKD stage 3B]), and 40.0% (n=2782) had prevalent albuminuria (microalbuminuria [UACR=30–300 mg/g]: 2013 [28.9%]; macroalbuminuria [UACR>300 mg/g]: 769 [11.0%]). Nearly one third (n=2250; 32.1%) had prevalent kidney disease defined as eGFR<60 ml/min per 1.73 m^2 and/or macroalbuminuria. Overall, 95% of patients were taking antihypertensive therapies at baseline, most commonly ACE inhibitors or ARBs (80.7%), β-blockers (64.9%), and diuretics (43.2%).

Empagliflozin Is Associated with Consistent Shifts in Individual eGFR Slopes

Adjusted mean eGFR values over time for the pooled empagliflozin and placebo groups are shown in Figure 1 on the basis of a mixed model for repeated measurements. In the next step, we calculated the estimated individual patient slopes on the basis of prespecified random coefficient models to assess the distribution of individual eGFR slopes. As shown in Figure 2, the effect of empagliflozin was considered to show a consistent shift across the distribution of individual eGFR changes compared with the rate of individual eGFR changes in the placebo group, and this finding was evident during all three prespecified periods. Hence, compared with placebo treatment, the distribution of individual eGFR slopes in the pooled empagliflozin group shifted leftward during treatment initiation (baseline to week 4), indicating a reduction in mean eGFR, but thereafter, it shifted rightward during both chronic maintenance treatment (week 4 to last value on treatment) and follow-up (last value on treatment to follow-up), indicating a period of slower loss of kidney function followed

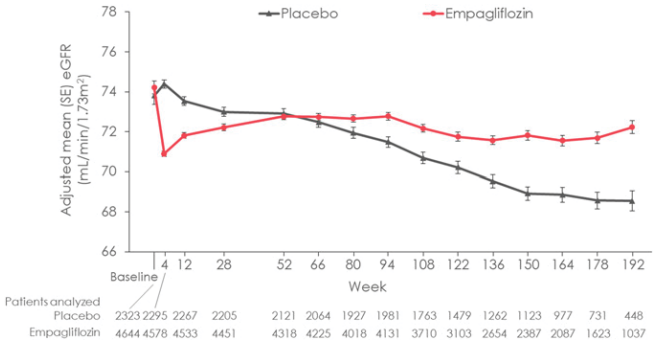

Figure 1. eGFR over time was different between empagliflozin and placebo in the EMPA-REG OUTCOME Trial in type 2 diabetes mellitus patients. eGFR is according to Modification of Diet in Renal Disease formula. Prespecified mixed model repeated measures analysis in patients treated with one or more doses of study drug who had a baseline measurement and at least one postbaseline measurement. Measurements obtained during study drug intake were used in this analysis. SE, SEM.

by an increase in mean eGFR, respectively. The changes in mean eGFR during the chronic maintenance treatment period (*i.e.*, the most clinically relevant period) are considered uniform, because the SDs in the placebo and empagliflozin arms were similar (1.51 versus 1.65 ml/min per 1.73 m^2, respectively; ratio, 0.9169). Testing for homogeneity by the Levene test did not reveal evidence that the SDs of the two treatment arms were significantly different (P=0.06). Results from the sensitivity analysis using log eGFR provided similar results (SDs in placebo and empagliflozin arms: 0.029 versus 0.029 ml/min per 1.73 m^2, respectively; ratio, 1.0266; Levene test P=0.71). In an additional sensitivity analysis, the distribution of individual eGFR slopes with the two doses of empagliflozin (10 and 25 mg) was considered to also reflect a consistent shift across all three prespecified study periods, confirming the overall consistency of the individual doses with the pooled analyses (Supplemental Figure 1).

Empagliflozin Slows the Annual Decline in eGFR Assessed by Mean eGFR Slopes

Adjusted mean eGFR slopes over the three prespecified study periods are shown in Figure 3A. During the treatment initiation phase, the weekly mean adjusted eGFR significantly declined in the empagliflozin group compared with the placebo group (Figure 3B). Thereafter, the annual adjusted change in mean eGFR during the chronic maintenance treatment period was not further reduced in the empagliflozin group (+0.23 ml/min per year per 1.73 m^2; 95% confidence interval, 0.05 to 0.40) and declined in the placebo group (−1.46 ml/min per year per 1.73 m^2; 95% confidence interval, −1.74 to −1.17; P<0.001 for empagliflozin versus placebo) (Figure 3B). The study included a post-treatment follow-up period, with eGFR measurements performed at approximately 30 days after the end of study drug intake. During this phase, the weekly adjusted mean eGFR change significantly increased in the empagliflozin group and overall returned toward mean baseline eGFR levels, with little change seen in the placebo group (Figure 3B). Notably, mean eGFR slope results with empagliflozin 10 mg and empagliflozin 25 mg were overall consistent with the pooled analyses across all three study periods (Supplemental Figure 2).

Mean eGFR Slopes in Subgroups of Patients at Higher Risk for Progressive CKD

In patients with prevalent CKD at baseline, mean slopes depicting weekly/annual changes in eGFR during the treatment initiation period, the chronic maintenance treatment period, and the postdrug cessation period for empagliflozin (pooled) and placebo are shown in Figure 4A. Differences in mean adjusted annual eGFR slope rates during chronic therapy were in favor of empagliflozin compared with placebo, with no significant difference between patients with or without prevalent CKD at baseline (Figure 5), and these results were overall consistent with the effects observed in the overall study

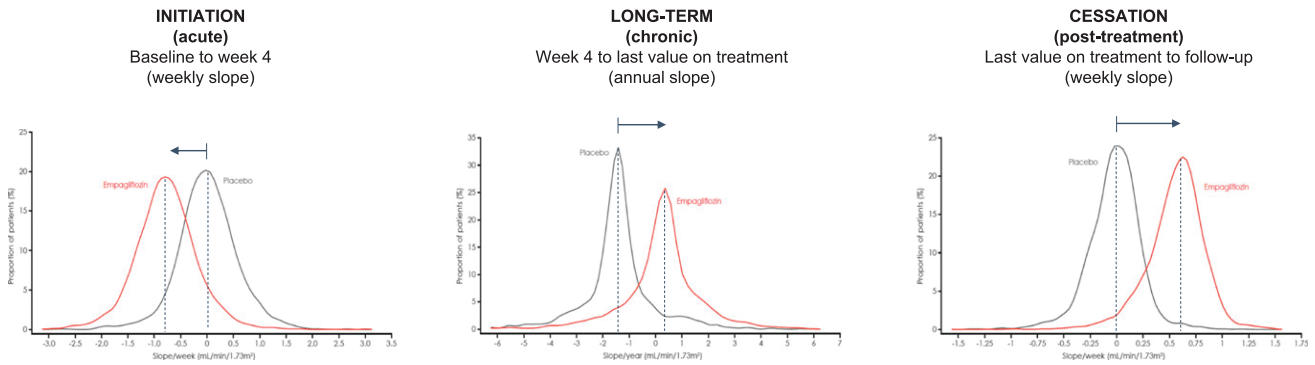

Figure 2. Empagliflozin showed a uniform shift across the distribution of individual eGFR changes compared with placebo. Overall population, pooled empagliflozin groups. Distribution of individual eGFR slopes over three prespecified study periods. The shape and symmetry of the curves during chronic maintenance treatment (annual slope) reflect a uniform shift in individual eGFR changes with empagliflozin. Individual slopes represent the individual patient's average change in eGFR (Modification of Diet in Renal Disease) per week (for initiation and cessation) and per year (for chronic maintenance treatment) for prespecified study periods assessed using random-intercept/random-coefficient models.

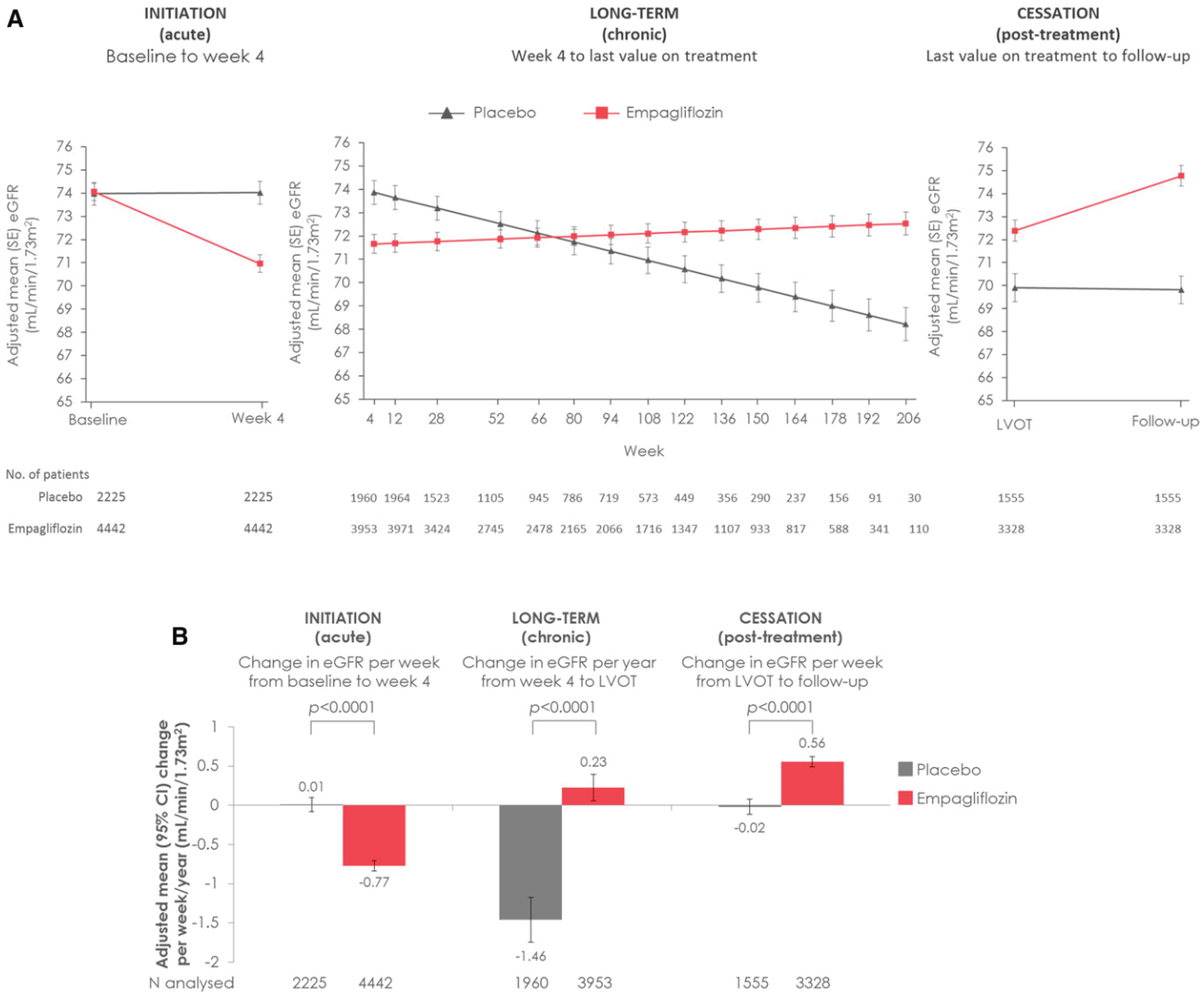

Figure 3. Empagliflozin slowed the annual decline in eGFR assessed by mean eGFR slopes based on random-intercept/random-coefficient models. Overall population, pooled empagliflozin groups. (A) Adjusted mean eGFR over prespecified study periods. (B) Change in eGFR per week or year during prespecified study periods. All patients were treated with one or more doses of study drug. Adjusted mean slopes represent the average change in eGFR (Modification of Diet in Renal Disease) per week (for initiation and cessation) and per year (for chronic maintenance treatment) for prespecified study periods. 95% CI, 95% confidence interval; LVOT, last value on treatment.

population. Detailed mean eGFR slope results for prevalent CKD subgroups across all three prespecified study periods are depicted in Supplemental Figure 3A. In addition, differences in weekly mean eGFR slope rates for empagliflozin versus placebo were consistent in patients with and without prevalent CKD during both the initiation and cessation time periods (Supplemental Figure 4).

A similar pattern of adjusted mean eGFR weekly/annual slopes during the initiation, chronic maintenance treatment, and cessation periods for empagliflozin and placebo was seen in further analyses for subgroups on the basis of baseline UACR (Figure 4B), race (Figure 4C), BP (Figure 4D), age (Figure 4E), and baseline HbA1c (Figure 4F). As with the overall patient population, adjusted mean annual eGFR slope rates during chronic therapy were stable with empagliflozin compared with a decline in placebo in most of the subgroups, and they were smaller with empagliflozin compared with placebo in all subgroups (Figure 5). Notably, we identified potential heterogeneity in the treatment effect of empagliflozin during chronic treatment maintenance for two at-risk patient subgroups: the placebo-corrected numerical treatment effect of empagliflozin on slowing annual decline in eGFR seemed to be larger in patients with macroalbuminuria or increased BP levels compared with patients with lower levels of albuminuria or BP at baseline (P values for interaction <0.001 and <0.02, respectively) (Figure 5). Further detailed mean eGFR slopes

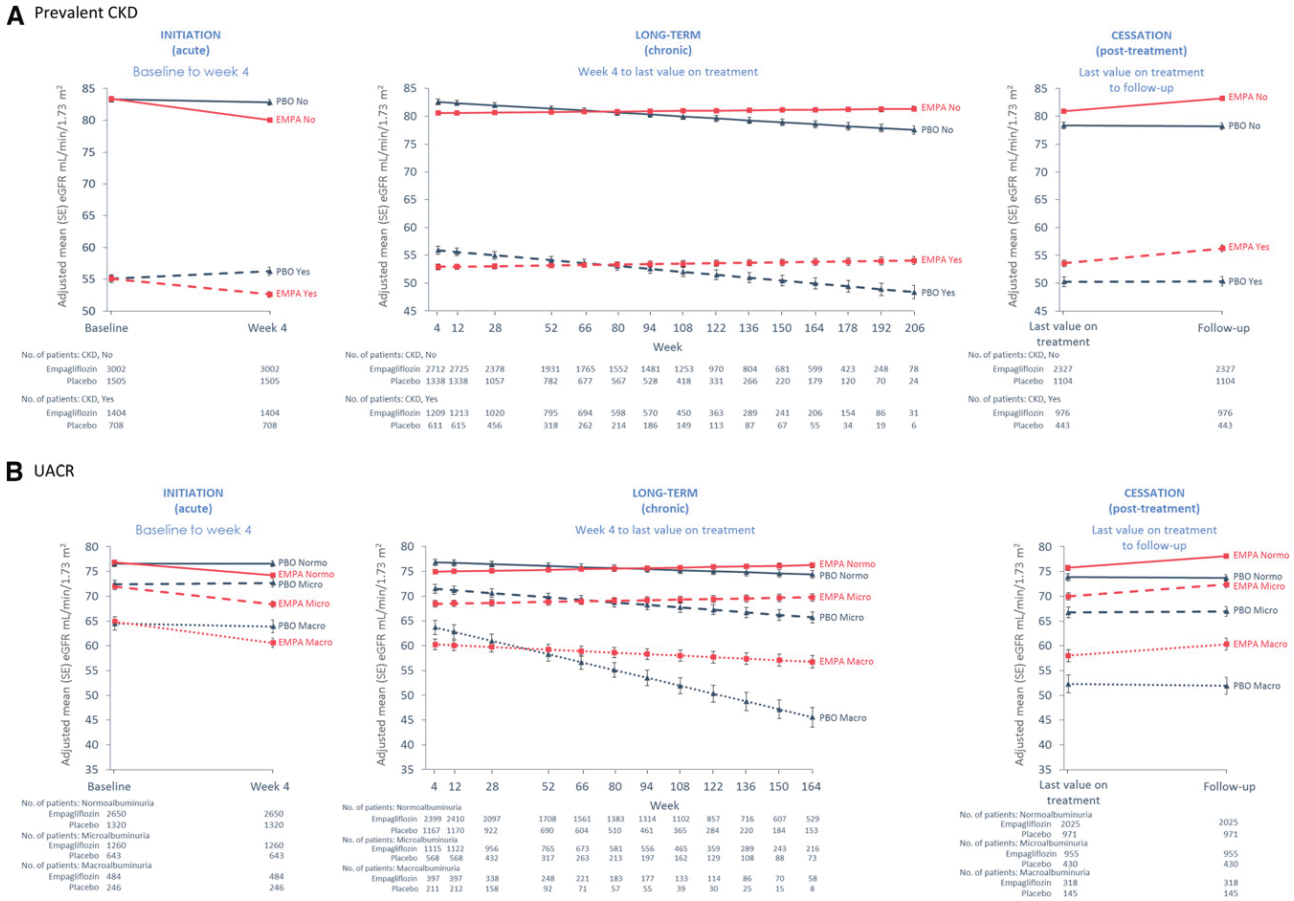

Figure 4. Empagliflozin slowed the annual decline in eGFR in patient subgroups at higher risk for CKD progression assessed by mean eGFR slopes based on random-intercept/random-coefficient models. Adjusted mean eGFR across subgroups on the basis of baseline characteristics for (A) prevalent CKD, (B) urinary albumin-to-creatinine ratio (UACR), (C) race, (D) BP, (E) age, and (F) glycated hemoglobin A1c (HbA1c). DBP, diastolic BP; EMPA, empagliflozin; PBO, placebo; SBP, systolic BP; SE, SEM.

data for the patient subgroups across all three prespecified study periods are depicted in Supplemental Figure 3, B–F.

DISCUSSION

This study supports the hypothesis that empagliflozin treatment results in consistent shifts in individual patient eGFR slopes during the three prespecified study periods: a leftward shift (*i.e.*, eGFR decline relative to placebo) shortly after initiation (indicative of an acute hemodynamic response), a rightward shift (*i.e.*, slowing of eGFR loss relative to placebo) during chronic maintenance treatment (indicative of preserving kidney function), and a rightward shift (*i.e.*, increase in eGFR relative to placebo) shortly after drug cessation (indicative of a reversal of the renal hemodynamic effect—even after long-term drug intake). This dynamic eGFR slope pattern was also consistent across patients with an array of eGFRs in the trial and specifically across subgroups of patients at higher risk of CKD progression. Interestingly, we found an indication for a more pronounced effect of empagliflozin to slow kidney function decline in patients with prevalent macroalbuminuria or increased BP. Individuals with these clinical conditions are known to be at increased risk for rapid decline in kidney function, and our hypothesis-generating findings merit future clinical research. Further assessment of eGFR slope in patients with type 2 diabetes, albeit during shorter-term treatment and lacking a postdrug follow-up period, has previously been reported for another SGLT2 inhibitor, canagliflozin.[16]

Historically, doubling of serum creatinine level, which roughly equates to a 57% reduction in eGFR, has been used as an end point in clinical studies of kidney disease.[15,17,18] Use of this measure, however, necessitates lengthy follow-up and/or very large numbers of patients in clinical trials, because doubling of serum creatinine is a late manifestation of CKD progression. Consequently, much effort is being devoted to exploring novel alternative measures of kidney disease progression for use as a more effective metric of CKD progression. This initiative also aims to reduce complexity and logistical

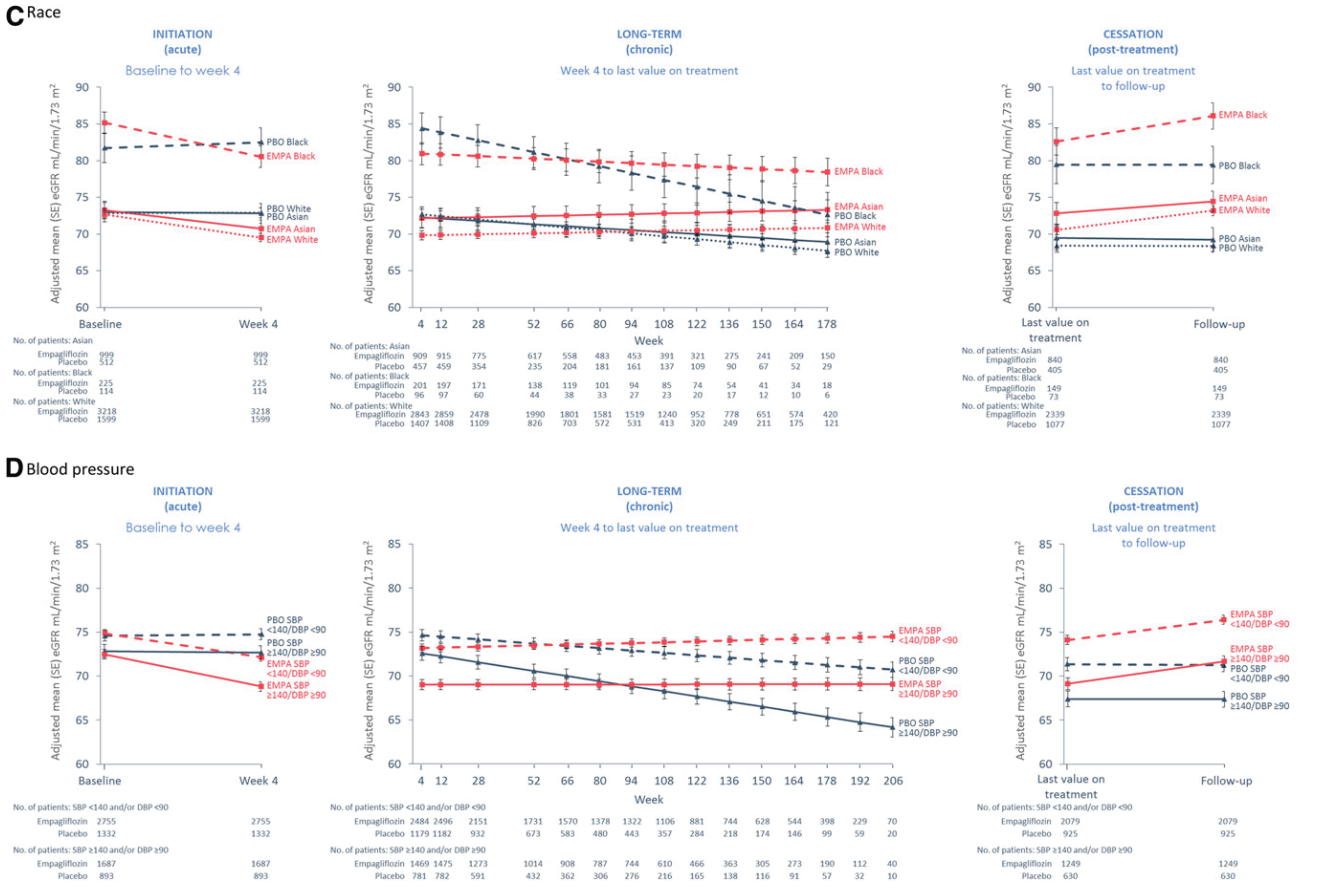

Figure 4. Continued.

burden for investigators and patients in clinical research as well as enable the study of individuals with earlier-stage CKD. One such potential alternative end point under discussion is the rate of change in kidney function over time (*i.e.*, eGFR slope).[15,19]

We propose that eGFR slopes may be considered as a surrogate end point for future clinical research in CKD/diabetic kidney disease under certain conditions where relevant prerequisites are fulfilled. First, a population in need of additional kidney-protective therapy (*e.g.*, individuals with a clinically meaningful decline in annual eGFR slope) has to be defined. Second, a clinically relevant treatment effect of the specific intervention (*e.g.*, a minimal expected slowing in annual GFR decline) should be prespecified. Third, the minimum duration of a chronic maintenance treatment effect should be ensured. For example, in the EMPA-REG OUTCOME Trial, such criteria apply to the subgroups of patients with prevalent CKD: a clinically relevant treatment effect with empagliflozin (compared with a clinically relevant annual decline in kidney function in the placebo group) accompanied by an appropriate duration for which the drug effect was maintained. Additional investigations are needed to clarify clinically relevant effect sizes and the minimal duration of chronic treatment effects for a range of drugs and conditions (including interventions with acute hemodynamic effects). Such investigations will help to standardize eGFR slope analysis in future clinical trials.

Our prespecified slope analysis of the EMPA-REG OUTCOME Trial shows that empagliflozin treatment was associated with a consistent shift in individual eGFR slopes (independent of the underlying rate of GFR change) during the three study periods, in particular showing evidence for homogeneity during the chronic maintenance treatment period (the most clinically relevant period). The latter phenomenon is referred to as a uniform treatment effect.[15,20] The alternative, where the effect of an intervention is stronger for faster-progressing patients than for slower-progressing patients, has been termed the proportional treatment effect model.[15,20] In this latter scenario, the treatment effect is proportional to the underlying rate of eGFR decline that would have been observed if no intervention was applied. If a proportional effect is present, using mean eGFR slope may be less advantageous compared with a dichotomous outcome (*e.g.*, a time to event analysis), because the treatment effect may be diluted by the inclusion of patients with less progressive disease. We consider that the consistent shifts in individual eGFR slope during the chronic maintenance treatment period observed in the

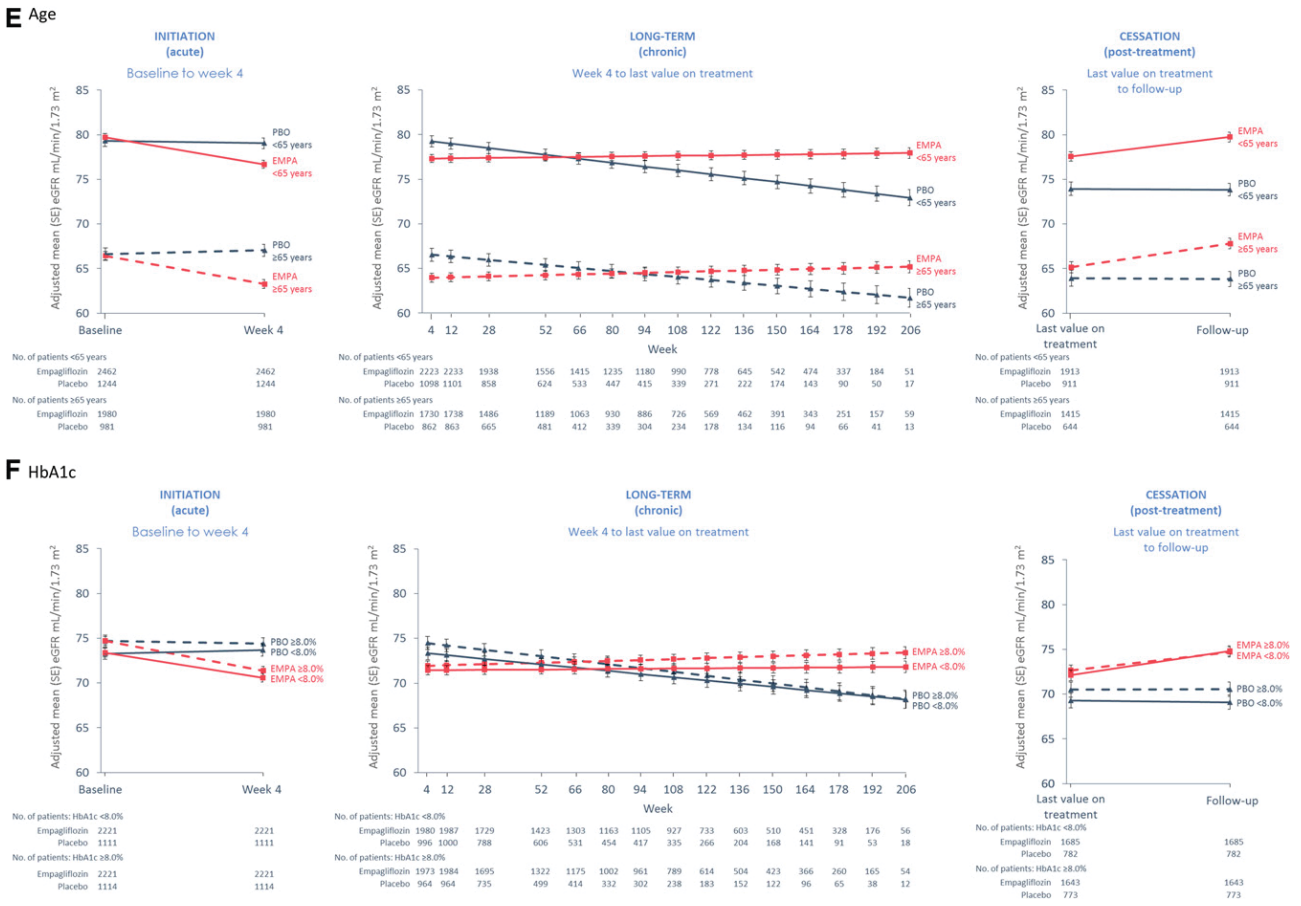

Figure 4. Continued.

EMPA-REG OUTCOME Trial are in line with the uniform treatment effects model, which supports the use of annual mean eGFR slope as a surrogate end point in future clinical trials with SGLT2 inhibitors.

Our results presented here have strengths and limitations. Analyses were prespecified and are considered of high internal validity, because eGFR slopes were assessed on the basis of recurrent standardized testing. This allowed for annual eGFR slope assessments on the basis of repeated measurements during the chronic maintenance treatment period; however, changes during the initiation and postdrug cessation periods were limited by two consecutive eGFR measurements and therefore, cannot definitively quantify the slope during these two phases. Our results are indicative of treatment effects of empagliflozin during active intake of study drug, because eGFR measurements after premature discontinuation of study drug were censored. This approach envisages determining the biologic effect of the drug; however, this methodology can also lead to potential selection bias of patients during the three prespecified study periods, and extrapolation of findings to the entire trial population has limitations. Moreover, direct comparisons between eGFR changes during the initiation and post-treatment periods should also be interpreted with caution. Nevertheless, the sample size of the overall population enabled the identification of meaningful numbers of patients at higher risk of progressive CKD, providing further confidence in the kidney effects of empagliflozin. Conversely, the EMPA-REG OUTCOME Trial was primarily designed as a cardiovascular trial, and eGFR$<$30 ml/min per 1.73 m^2 at screening was grounds for exclusion. Therefore, a limited number of definitive kidney outcomes were available to validate changes in eGFR slope against traditional kidney outcomes, such as doubling of serum creatinine and RRT. Hence, future studies are needed to explore the effect of empagliflozin and other SGLT2 inhibitors on kidney function decline in individuals at more advanced stages of CKD, including those without diabetes. A large kidney outcomes study of empagliflozin including patients with and without diabetes (the EMPA-KIDNEY Study) will start in 2018. Additional insights into the kidney effects of other SGLT2 inhibitors, including eGFR slope analyses, are expected to emerge from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial,[21] the Dapagliflozin Effect on CardiovascuLAR Events Thrombolysis in Myocardial Infarction Trial,[22] and the DAPA-CKD Trial (ClinicalTrials.gov: NCT03036150) involving canagliflozin or dapagliflozin.

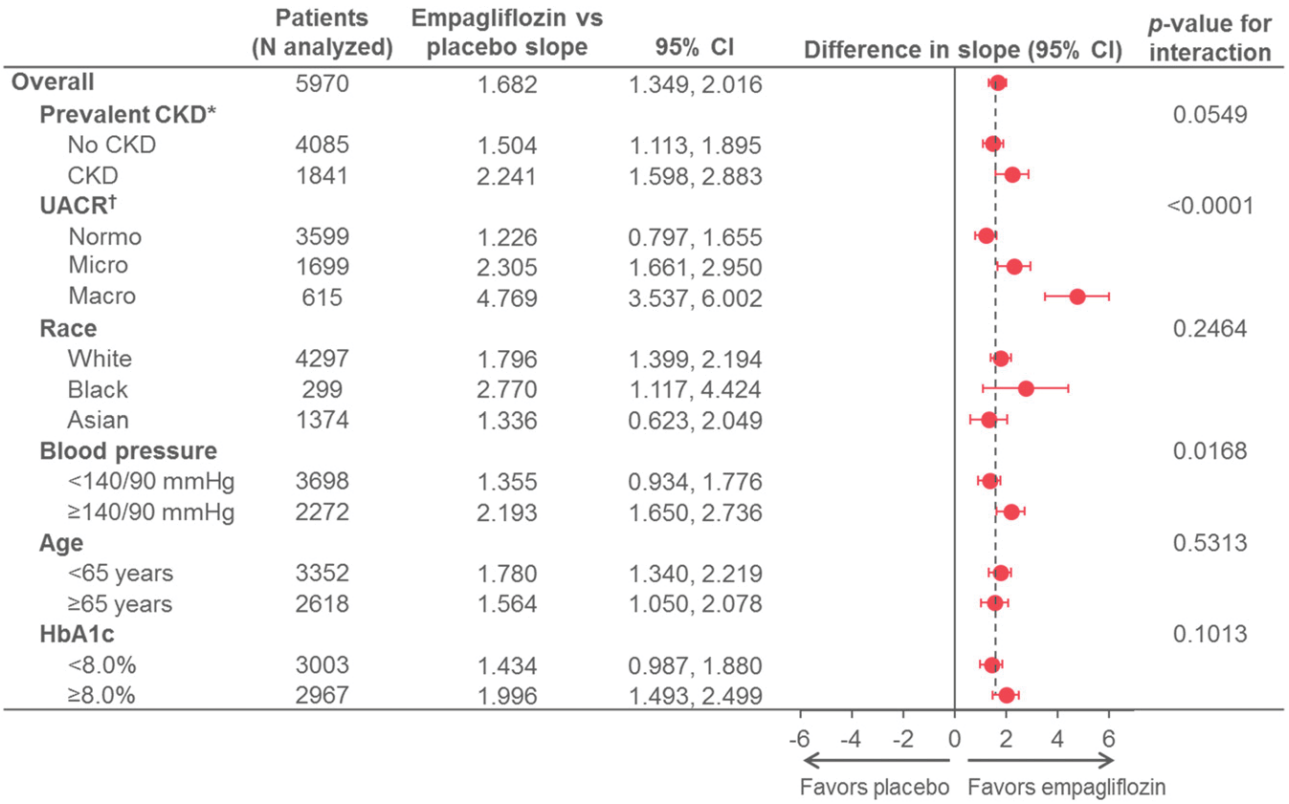

Figure 5. Annual changes in eGFR slope favored empagliflozin over placebo in the overall population and in subgroups. Differences in mean eGFR slopes (Modification of Diet in Renal Disease; milliliters per minute per 1.73 m^2) between empagliflozin and placebo during chronic treatment (week 4 to last value on treatment) in the treated set of the overall study population and patient subgroups. Measurements obtained during study drug intake were used. Differences depicted for individual data points between empagliflozin and placebo groups represent differences in the annual change in kidney function. Data were from a random-intercept/random-coefficient model. 95% CI, 95% confidence interval; HbA1c, glycated hemoglobin A1c. *Prevalent CKD was defined as eGFR<60 ml/min per 1.73 m^2 and/or macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] >300 mg/g). †Normo indicates normoalbuminuria (UACR<30 mg/g), micro indicates microalbuminuria (UACR=30–300 mg/g), macro indicates macroalbuminuria (UACR>300 mg/g).

Our comprehensive slope analysis shows that empagliflozin has the potential to significantly slow eGFR decline over a treatment period of approximately 3 years, including in patients at higher risk for progressive kidney disease. Moreover, empagliflozin slope patterns are indicative of a renal hemodynamic effect reminiscent of observations with ACE inhibitors or ARBs: an initial transient decline in eGFR followed by long-term slowing of kidney function loss.[23,24] After cessation of empagliflozin, eGFR slopes showed a swift upward trajectory toward baseline, suggestive of an immediate reversibility of the renal hemodynamic effect. Further studies may facilitate specific statistical models to assess the utility of slopes as an attractive surrogate end point of kidney disease progression in clinical research.

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SIGNIFICANCE STATEMENT

Empagliflozin, a selective sodium glucose cotransporter 2 inhibitor, is indicated to improve glycemic control and reduce the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease. Hypothesis-generating results from the EMPA-REG OUTCOME Trial suggest that empagliflozin slows the progression of CKD. This manuscript presents the prespecified eGFR slope analysis from the trial, in which we evaluated changes in kidney function over time. Our results support a hemodynamic effect of empagliflozin, which may lead to reductions in intraglomerular pressure. During chronic maintenance treatment, this glomerular response to empagliflozin may translate into long-term preservation of kidney function. Our data add to the evidence of the utility of slope analysis as an emerging end point of CKD progression in clinical research.

Kidney Function Decline in Patients with Type 2 Diabetes:

A Slope Analysis from the EMPA-REG OUTCOME trial

Supplementary Material

Contents

Supplementary Statistical Information

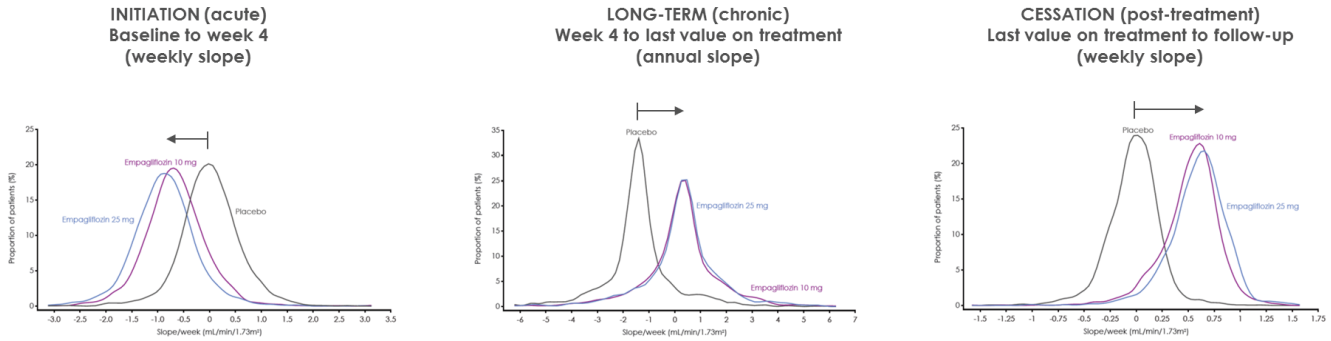
Analyses

Calculation of eGFR slopes for three pre-specified study periods: i) treatment initiation effects from baseline to week 4; chronic maintenance treatment effects from week 4 to last value on treatment; and post-treatment effects from last value on treatment to follow-up (planned to be approximately 30 days after cessation of treatment) was performed by applying a separate random coefficient model (with the factors as described in the Analyses Section of the main manuscript text) for each period. Patients were required to provide at least 2 measurements per study period to be included in the respective analysis. Hence, for the acute and post-treatment study periods patients were required to provide both the baseline and week 4 measurements, and the last value on treatment and follow-up measurements, respectively.

The analysis of the treatment-initiation period requires the assumption that any patients lost to follow-up or otherwise excluded were missing completely at random (MCAR). The analyses for the chronic maintenance and post-treatment periods require the assumption that any patients lost to follow-up or otherwise excluded prior to this specific study period were missing completely at random (MCAR). The analyses of the chronic maintenance treatment period additionally require that missing data occurring after the start of the chronic phase follow a missing at random (MAR) mechanism – this includes both missing data due to loss-to-follow-up and missing data resulting for artificial censoring when patients discontinued the study medication. The MAR assumption allows the probability of missing data to depend on the observed covariates and the observed values for eGFR, but not on the values of eGFR that were not observed.

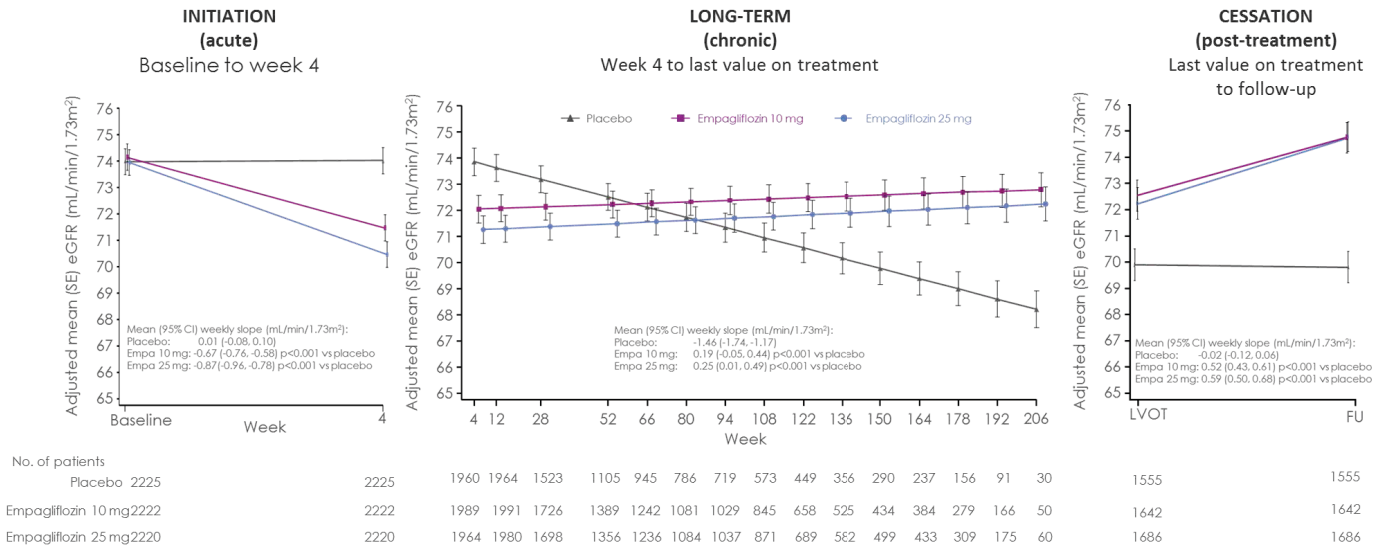
Supplementary Figure 1. Distribution of *individual* patient slopes

Overall population, individual empagliflozin dose groups. Distribution of *individual* eGFR slopes over pre-specified study periods reflect a consistent shift with both empagliflozin doses during all three periods. *Individual* slopes represent the individual patient's average change in eGFR (MDRD) per week (for initiation and cessation, respectively) and per year (for chronic maintenance treatment) for pre-specified study periods, assessed using random intercept, random coefficient models.



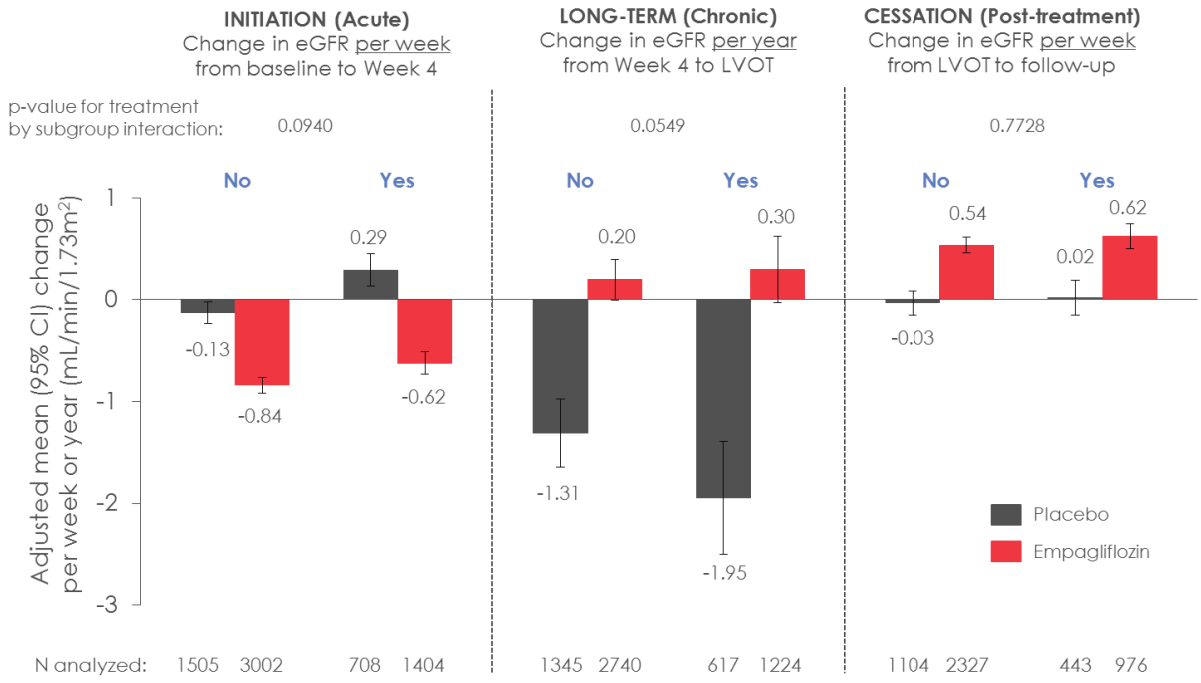
Supplementary Figure 2. eGFR over time based on random intercept, random coefficient models

Overall population, individual empagliflozin dose groups. Adjusted *mean* eGFR slopes over pre-specified study periods. *Mean* slopes represent the average change in eGFR (MDRD) per week (for initiation and cessation, respectively) and per year (for chronic maintenance treatment) for pre-specified study periods.

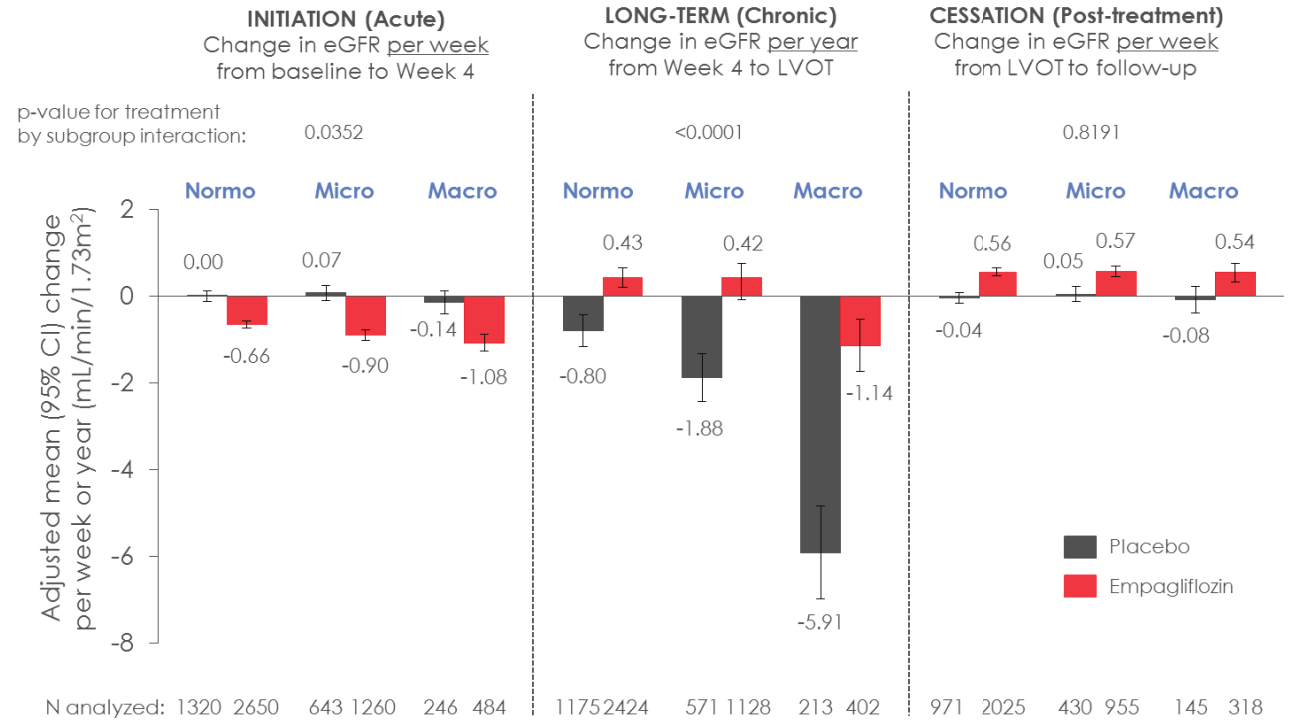


Supplementary Figure 3. *Mean* eGFR slopes during pre-specified study periods based on random intercept, random coefficient models in subgroups defined by baseline characteristics
(A) prevalent CKD, (B) UACR, (C) race, (D) blood pressure, (E) age, and (F) HbA1c. *Normo = normoalbuminuria (UACR <30 mg/g); micro = microalbuminuria (UACR 30−300 mg/g); macro = macroalbuminuria (UACR >300 mg/g). CKD, chronic kidney disease. LVOT, last value on treatment. N=number analyzed. SE, standard error.

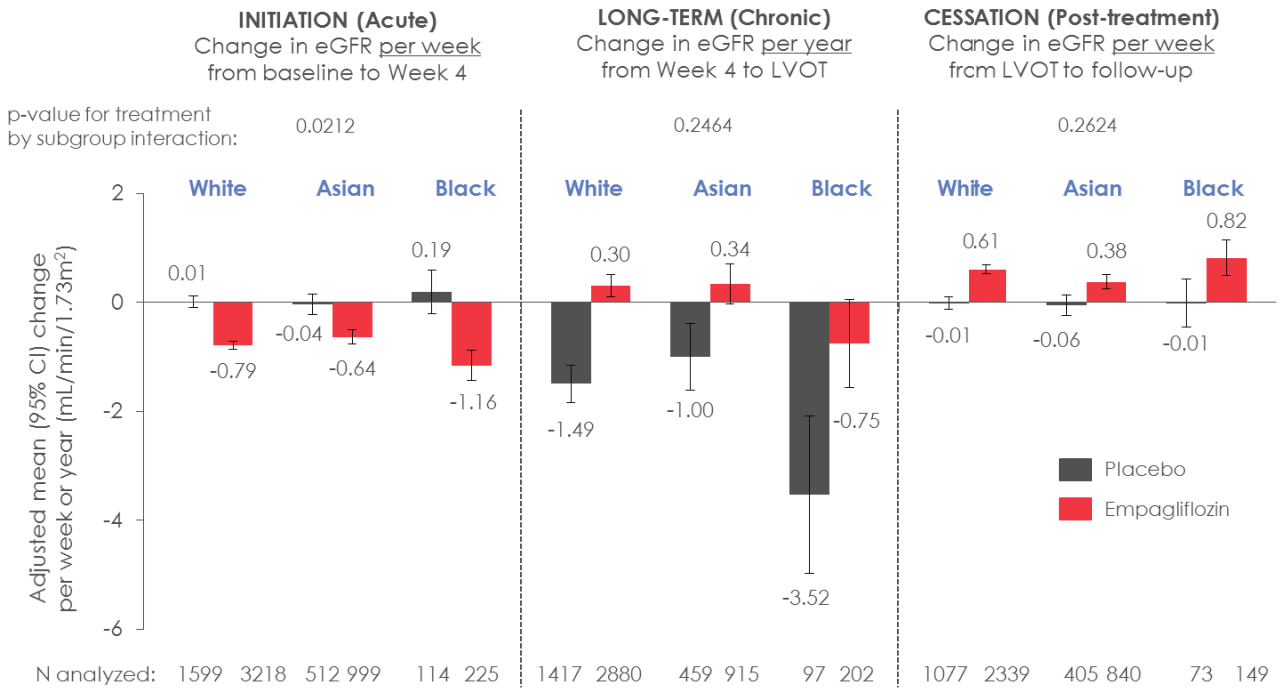
A. Prevalent CKD



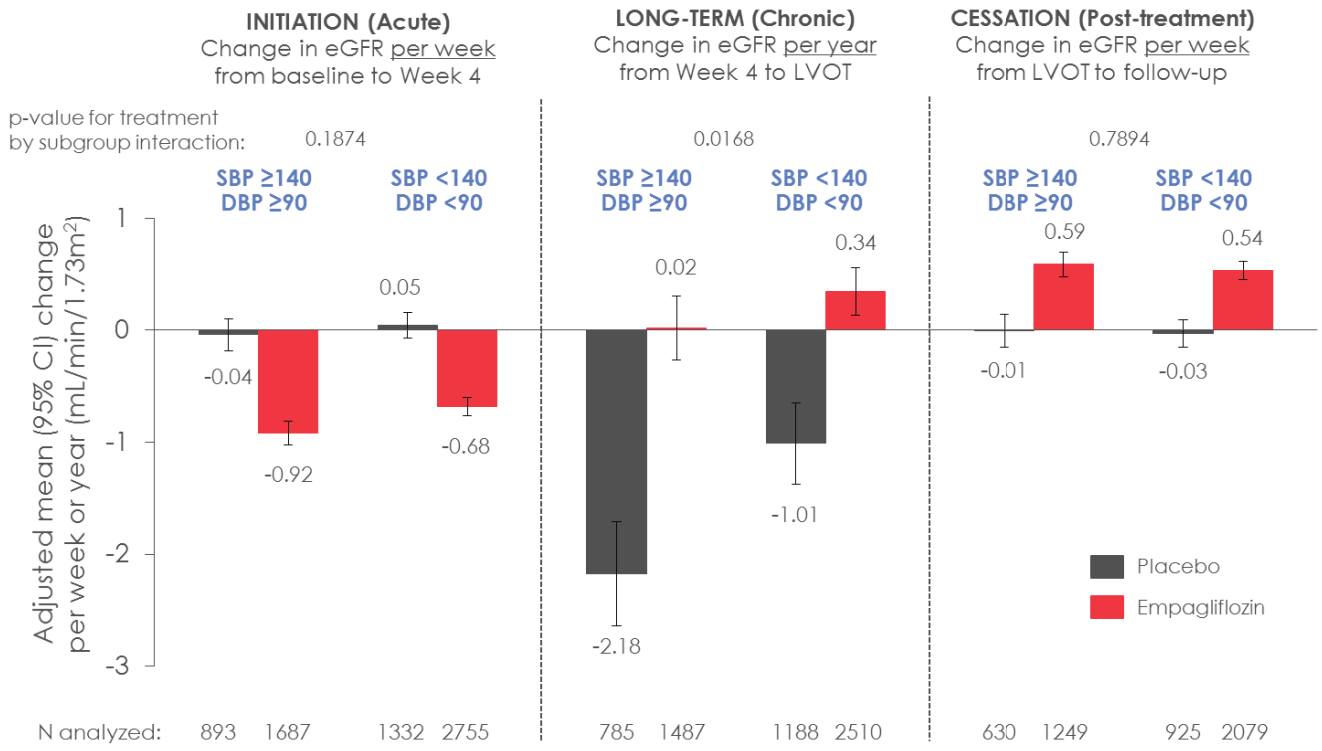
B. UACR*



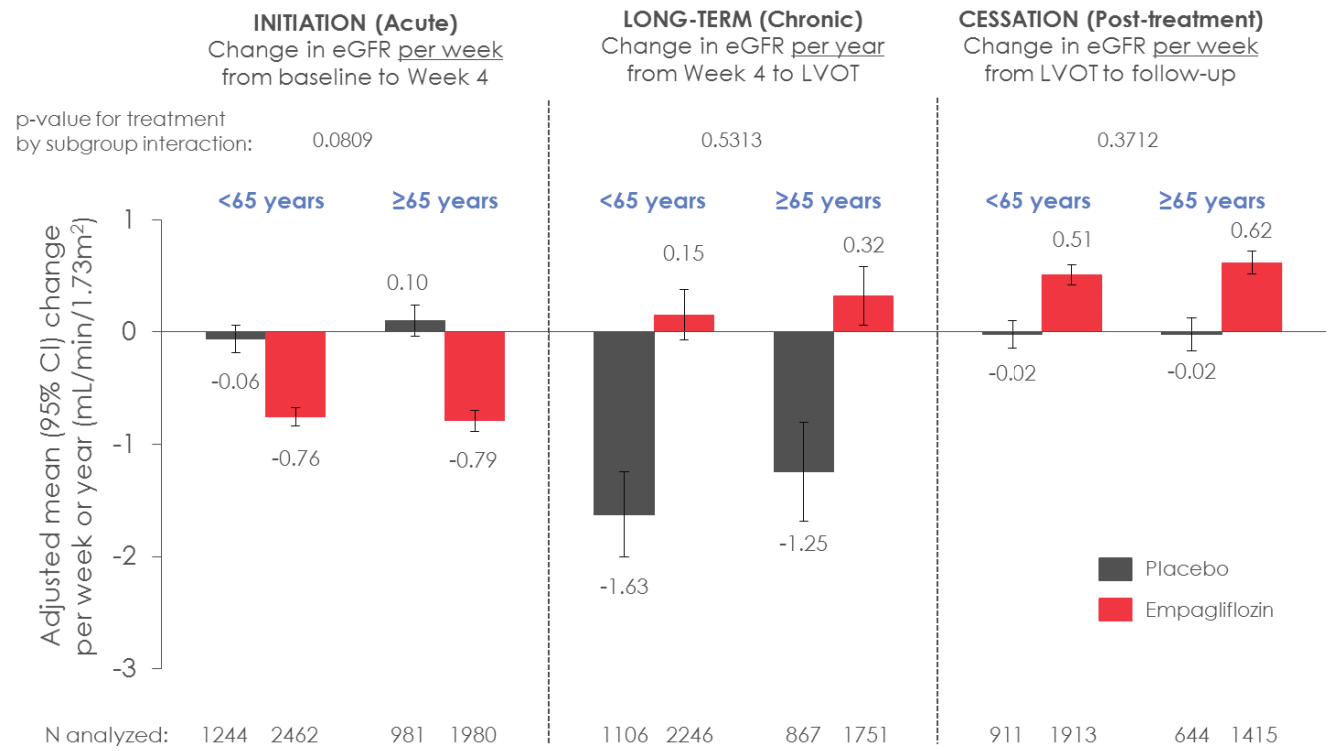
C. Race



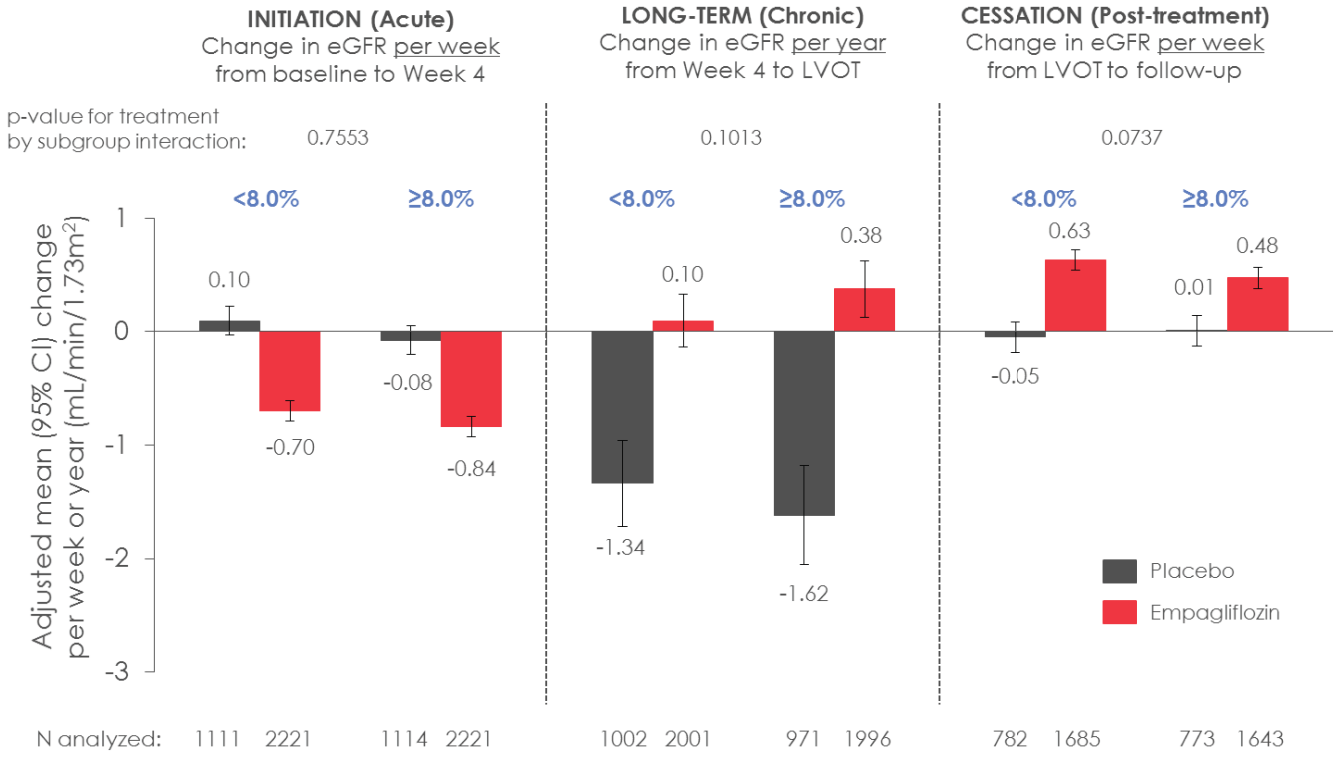
D. Blood pressure



E. Age



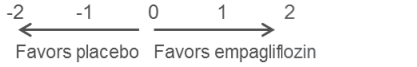
F. HbA1c



Supplementary Figure 4. Difference in the weekly change in renal function for empagliflozin or placebo groups
Differences in adjusted *mean* eGFR slopes (MDRD, ml/min/1.73m^2) between empagliflozin and placebo during (A) treatment initiation (baseline to week 4) and (B) treatment cessation (last value on treatment to follow-up) in the treated set of the overall study population and patient subgroups. Differences depicted for individual data points between empagliflozin and placebo groups represent weekly changes in renal function, respectively. Data from random intercept, random coefficient models. *Prevalent CKD was defined as eGFR <60 ml/min/1.73m^2 and/or macroalbuminuria (UACR >300 mg/g). †Normo = normoalbuminuria (UACR <30 mg/g); micro = microalbuminuria (UACR 30−300 mg/g); macro = macroalbuminuria (UACR >300 mg/g). CKD, prevalent chronic kidney disease; MDRD, Modification of Diet in Renal Disease; UACR, urinary albumin-to-creatinine ratio.

A. Baseline to week 4

	Patients (N analyzed)	Empagliflozin vs placebo slope	95% CI	*p*-value for interaction
Overall	6667	−0.781	−0.891, −0.671	
Prevalent CKD*				0.0940
No CKD	4507	−0.712	−0.846, −0.578	
CKD	2112	−0.914	−1.110, −0.719	
UACR†				0.0352
Normo	3970	−0.663	−0.806, −0.521	
Micro	1903	−0.970	−1.175, −0.765	
Macro	730	−0.933	−1.264, −0.603	
Race				0.0212
White	4817	−0.797	−0.927, −0.667	
Black	339	−1.352	−1.841, −0.864	
Asian	1511	−0.598	−0.830, −0.365	
Blood pressure				0.1874
<140/90 mmHg	4087	−0.726	−0.867, −0.584	
≥140/90 mmHg	2580	−0.877	−1.053, −0.702	
Age				0.0809
<65 years	3706	−0.694	−0.842, −0.546	
≥65 years	2961	−0.892	−1.058, −0.726	
HbA1c				0.7553
<8.0%	3332	−0.799	−0.954, −0.643	
≥8.0%	3335	−0.763	−0.919, −0.608	



B. Last value on treatment to follow-up

	Patients (N analyzed)	Empagliflozin vs placebo slope	95% CI	*p*-value for interaction
Overall	4883	0.576	0.460, 0.692	
Prevalent CKD*				0.7728
No CKD	3431	0.568	0.427, 0.708	
CKD	1419	0.605	0.394, 0.816	
UACR†				0.8191
Normo	2996	0.599	0.450, 0.748	
Micro	1385	0.520	0.302, 0.737	
Macro	463	0.618	0.249, 0.988	
Race				0.2624
White	3416	0.614	0.475, 0.754	
Black	222	0.827	0.283, 1.371	
Asian	1245	0.432	0.208, 0.657	
Blood pressure				0.7894
<140/90 mmHg	3004	0.564	0.413, 0.715	
≥140/90 mmHg	1879	0.596	0.414, 0.778	
Age				0.3712
<65 years	2824	0.530	0.378, 0.683	
≥65 years	2059	0.637	0.459, 0.816	
HbA1c				0.0737
<8.0%	2467	0.680	0.518, 0.842	
≥8.0%	2416	0.468	0.303, 0.634