Renal, Cardiovascular, and Safety Outcomes of Canagliflozin By Baseline Kidney Function: A Secondary Analysis of the CREDENCE Randomized Trial

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Significance statement

CREDENCE demonstrated canagliflozin reduces the risk of cardiovascular and renal events in people with type 2 diabetes and substantial albuminuria. It was not clear whether the benefits of canagliflozin would be safely preserved in people with reduced eGFR. The relative benefits of canagliflozin for renal and cardiovascular outcomes appeared consistent among people with initial eGFR 30-<45, 45-<60, and 60-<90mL/min/1.73m^2. Absolute benefit for renal outcomes was greater in people with initial eGFR <60mL/min/1.73m^2. Safety outcomes were generally consistent among eGFR subgroups. Canagliflozin led to an acute eGFR drop followed by relative stabilization of eGFR loss across subgroups. The benefits and safety of canagliflozin are apparent across the eGFR range, not least of which was in those initiating treatment with eGFR 30-<45mL/min/1.73m^2.

Abstract

Background

Canagliflozin reduced renal and cardiovascular events in people with type 2 diabetes in CREDENCE. We assessed efficacy and safety of canagliflozin by initial estimated glomerular filtration rate (eGFR).

Methods

CREDENCE randomly assigned 4401 participants with eGFR 30-<90mL/min/1.73m^2 and substantial albuminuria to canagliflozin 100mg or placebo. We used Cox proportional hazards regression to analyze effects on renal and cardiovascular efficacy and safety outcomes within screening eGFR subgroups (30-<45, 45-<60, and 60-<90mL/min/1.73m^2) and linear mixed effects models to analyze the effects on eGFR slope.

Results

At screening, 1313 (30%), 1279 (29%), and 1809 (41%) participants had eGFR 30-<45, 45-<60 and 60-<90mL/min/1.73m^2. The relative benefits of canagliflozin for renal and cardiovascular outcomes appeared consistent among eGFR subgroups (all P-interaction >0.11), while absolute benefits for renal outcomes were greater in the lower eGFR subgroups, who were at greater risk. The lack of impact on serious adverse events, amputations, and fractures appeared consistent among eGFR subgroups. Canagliflozin led to an acute eGFR drop followed by relative stabilization of eGFR loss in all subgroups. Among those with eGFR 30-<45mL/min/1.73m^2, canagliflozin led to an initial drop of 2.03 mL/min/1.73m^2 (95% CI 1.34-2.73). Thereafter, the decline in eGFR was slower in the canagliflozin versus placebo group (–1.72±0.20 vs –4.33±0.20mL/min/1.73m^2; between-group difference 2.61mL/min/1.73m^2 [95% CI 2.06-3.16]).

Conclusions

In CREDENCE, canagliflozin safely reduced the risk of renal and cardiovascular events with consistent results across eGFR subgroups, including those initiating treatment with eGFR 30-<45mL/min/1.73m^2. Absolute benefits for renal outcomes were greatest in lower eGFR subgroups.

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Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors were developed as glucose-lowering agents for people with type 2 diabetes mellitus. Their physiological effect is exerted by inhibition of SGLT2 proteins on the luminal surface of proximal tubular cells, which they reach by filtration at the glomerulus.[1] There they inhibit the reabsorption of sodium and glucose from the renal tubule resulting in enhanced urinary sodium and glucose excretion. It is clear the effect of SGLT2 inhibitors on glucose lowering is attenuated at reduced estimated glomerular filtration rate (eGFR) levels,[2] and as a consequence, it has been hypothesized that the impact of SGLT2 inhibitors on clinical benefit would likewise be attenuated at a lower eGFR. The original regulatory indications restricted the use of SGLT2 inhibitors to a lower eGFR limit of 45 or 60 mL/min/1.73m^2 because of reduced efficacy in lowering blood glucose below these levels.[3-6]

Despite the attenuation of efficacy in lowering blood glucose in patients with impaired renal function, interest in studying canagliflozin for renal protective effects in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial was based on findings from early glycemic control studies in which favorable effects on lowering urinary albumin:creatinine ratio (UACR) and preserving eGFR were observed.[7, 8] The acute, modest decline in eGFR that was observed in previous studies attenuated over time and was consistent with a hemodynamically-mediated effect reminiscent of those seen with angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) therapy.[9] The strong association of albuminuria with clinical renal outcomes and the concept that these agents might lower intraglomerular pressure led to the hypothesis that they may protect against the progression of diabetic kidney disease, including in people with lower eGFR, potentially independent of the glucose lowering effect. The CREDENCE trial was designed to evaluate the benefits of canagliflozin on the risk of kidney failure and cardiovascular events, while also assessing safety, in people with type 2 diabetes at high risk of kidney disease progression.

Canagliflozin safely reduced renal and cardiovascular events in the CREDENCE population overall.[10] In this secondary analysis of the CREDENCE trial, we investigated whether the effects of canagliflozin on clinically important kidney, cardiovascular, and safety outcomes were consistent across the broad range of included eGFR, including in the lower eGFR range of 30 to 45 mL/min/1.73m^2 where glucose effects are minimal.

Methods

The CREDENCE study design[11] has been published previously. In brief, CREDENCE was a randomized, double-blind, placebo-controlled, multicenter clinical trial assessing the impact of canagliflozin on clinically important renal, cardiovascular, and safety outcomes in people with type 2 diabetes and chronic kidney disease.

Study participants

Eligible participants were ≥30 years of age with type 2 diabetes mellitus, a glycated hemoglobin (HbA1c) level of 6.5%-12.0%, an eGFR of 30-<90 mL/min/1.73m^2, UACR >300-5,000mg/g [>33.9-565.6 mg/mmol]) and treatment with a stable maximum labeled or tolerated dose of ACEi or ARB for ≥4 weeks prior to randomization. By design, approximately 60% of participants were to have a screening eGFR 30-<60 mL/min/1.73m^2. Exclusion criteria included nondiabetic kidney disease, type 1 diabetes mellitus, and prior treatment of kidney disease with immunosuppression or a history of renal replacement therapy.

Randomization, ~~and~~ study treatment and eGFR categories

Participants were randomized to receive oral canagliflozin 100 mg daily or matching placebo. The protocol stipulated that study treatment be continued until the commencement of dialysis, receipt of a kidney transplant, occurrence of diabetic ketoacidosis, pregnancy, or receipt of disallowed therapy or study conclusion.

Eligibility criteria for the study included an eGFR of 30-90 mL/min/1.73m^2. After screening, participants either proceeded to a 2-week single-blind placebo run-in or underwent an extended screening if required for various reasons including completing at least 4 weeks on a stable dose of renin-angiotensin blockade. Participants who did not proceed directly to the 2-week run-in period had a repeat eGFR measurement at the beginning of the run-in period. The most proximate eGFR measurement (eg, screening or Week –2) to baseline was deemed the 'screening' eGFR and was used to stratify randomization in the categories of 30-<45, 45-<60, and 60-<90 mL/min/1.73m^2. On the day of randomization an additional, baseline measurement of eGFR was performed. Background treatment intensification for glycemic management and cardiovascular protection according to practice guidelines was recommended.

Outcomes

The primary outcome for these analyses was the same as the primary trial[10]: the composite of end-stage kidney disease (chronic dialysis for ≥30 days, kidney transplantation, or eGFR <15 mL/min/1.73m^2 sustained for ≥30 days by central laboratory assessment), doubling of serum creatinine from baseline average of randomization and prerandomization value sustained for ≥30 days by central laboratory assessment, or death due to renal or cardiovascular disease. Secondary renal outcomes included the composite of end-stage kidney disease, doubling of serum creatinine, or renal death; end-stage kidney disease; doubling of serum creatinine; and the exploratory composite of initiation of renal replacement therapy (initiation of chronic dialysis for ≥30 days or receipt of a kidney transplant), or renal death. Other efficacy outcomes included the composite of cardiovascular death or hospitalization for heart failure; the composite of cardiovascular death, myocardial infarction, or stroke; hospitalization for heart failure; cardiovascular death; and the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina. Safety events were explored in the current analysis where there were at least 10 events per eGFR subgroup and included: all adverse events and serious adverse events, amputation, fracture, osmotic diuresis, and volume depletion. The renal and cardiovascular outcomes and selected safety outcomes were independently adjudicated.

Other outcomes for this study included eGFR slope measured as the acute change in eGFR from baseline to week 3 (acute slope), the annualized chronic change in eGFR from week 3 until end of treatment (chronic slope) and the annualized change in eGFR from baseline to week 130 (total slope). The eGFR slope analyses used on-treatment measures in order to avoid the expected distortions due to modifications of the hemodynamic effect that occur when study drug is discontinued. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the eGFR.

We also assessed the impact of canagliflozin on the intermediate outcomes of HbA1c, body weight, systolic blood pressure, and UACR.

Observational analysis of participants whose last on-treatment eGFR was lower than 30 mL/min/1.73m^2

In an observational analysis, in order to illustrate the course of participants within the study, we assessed outcomes in participants whose last on-treatment eGFR was below 30 mL/min/1.73m^2 for the time period from their first eGFR below 30 mL/min/1.73m^2 until end of study. The outcomes reported in this way were those specified in the hierarchical testing sequence of the protocol, namely: the primary composite endpoint; the composite of cardiovascular death or hospitalization for heart failure; the composite of cardiovascular death, myocardial infarction, or stroke; hospitalization for heart failure; the renal composite of doubling of serum creatinine, end-stage kidney disease or renal death; and cardiovascular death.

Statistical analysis

Analysis of the effects of canagliflozin on the primary outcome was prespecified in participants with screening eGFR categories of 30-<45, 45-<60, and 60-<90 mL/min/1.73m^2 using an intention-to-treat approach; analyses of other renal, cardiovascular, and safety outcomes by eGFR categories were post hoc. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all outcomes were estimated using a Cox proportional hazards regression model within each eGFR strata. We tested the heterogeneity of treatment effects across screening eGFR categories by adding eGFR categories as a covariable and an interaction term of treatment by eGFR categories to the relevant model. Annualized incidence rates were calculated per 1000 patient-years of follow-up. Absolute risk differences were calculated by subtracting the number of participants with an endpoint (per 1000 patients over follow-up) of placebo from those of canagliflozin. The heterogeneity of absolute risk reduction for CV or renal endpoints across screening eGFR subgroups was estimated using fixed effects meta-analysis. Linear mixed effects models for repeated measures were used to analyze changes in intermediate outcomes over time in the on-treatment analysis population (unless otherwise noted), assuming an unstructured covariance and adjusting for the baseline value, trial group, and trial visit. On-treatment eGFR slope was estimated using all central laboratory eGFR measurements from study Day 1 up to the last dose of the study medication plus 2 days. The effects of canagliflozin on the mean on-treatment eGFR slope were analysed by fitting a 2-slope mixed effects linear spline model (with a knot at Week 3) to eGFR values, with random intercept and random slopes for treatment. When the unstructured models failed to converge, a simplified model with a random intercept and a single random slope was used to account for the variation in eGFR trajectories across participants. The mean total slope was computed as a weighted combination of the acute and chronic slopes to reflect the mean rate of eGFR change to Week 130. We also provide a visual representation of the pattern of change in mean eGFR using a restricted maximum likelihood (REML) repeated measures approach. This analysis included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline eGFR and baseline eGFR-by-visit interaction. In the nonrandomized subgroup of participants defined by last on-treatment eGFR below 30 mL/min/1.73m^2, the number of participants with the first event occurred on and after the first eGFR <30 mL/min/1.73m^2 were summarized by treatment group for the renal and cardiovascular outcomes. Given the post hoc nature of many of the analyses, P values have been presented for descriptive rather than inferential purposes, without adjustment for multiplicity. All analyses were performed using SAS version 9.4.

Data availability

Data from this study will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been

approved by regulators in the United States and European Union and the study has been completed for 18 months.

Results

The CREDENCE trial randomized 4,401 participants with a median follow-up duration of 2.62 years (range 0.02-4.53 years) and was stopped for efficacy at the interim analysis on the advice of the Data Monitoring Committee. At baseline, participants had a mean age of 63 years, 34% were female, 67% were white, and 20% were Asian. The mean HbA1c was 8.3%, mean blood pressure was 140/78 mmHg, and 50% had a history of cardiovascular disease. The mean baseline eGFR was 56.2 mL/min/1.73m^2 and median UACR was 927 mg/g (105 mg/mmol).

There were 1313 (30%), 1279 (29%), and 1809 (41%) participants with a screening eGFR of 30-<45, 45-<60, and 60-<90 mL/min/1.73m^2, respectively (Supplementary Table 1). Baseline characteristics for participants within each eGFR category were balanced between the groups randomized to interventional treatment or placebo (Supplementary Table 1). Participants with lower baseline eGFR were numerically more likely to be older, have a longer duration of diabetes, have greater insulin and diuretic use, and have higher levels of albuminuria (Supplementary Table 1).

Renal Time to Event Outcomes

The effects of canagliflozin on the primary composite outcome of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death (HR 0.70, 95% CI 0.59-0.82) was consistent in all eGFR categories (P-interaction = 0.11) (Figure 1). Similarly, the effects of canagliflozin on the renal composite outcome of end-stage kidney disease, doubling of serum creatinine, or renal death (HR 0.66, 95% CI 0.53-0.81), as well as end-stage kidney disease, doubling of serum creatinine, the composite of initiation of renal replacement therapy or renal death were all consistent by baseline eGFR category, with no evidence that the results differed (all P-interaction >0.11). Canagliflozin separately reduced the primary composite (HR 0.75, 95% CI 0.59-0.95) and the renal specific composite (HR 0.71, 95% CI 0.53-0.94) in participants with screening eGFR 30-<45 mL/min/1.73m^2.

Cardiovascular Outcomes

Across eGFR subgroups, canagliflozin consistently reduced cardiovascular death or hospitalization for heart failure; the composite of cardiovascular death, myocardial infarction, or stroke; and hospitalized heart failure, with all P-values for interaction >0.25 (Figure 2). In particular, canagliflozin reduced the composite of cardiovascular death or hospitalization for heart failure (HR 0.69, 95% CI 0.50-0.94) in participants with screening eGFR 30-<45 mL/min/1.73m^2.

Safety

Canagliflozin led to fewer adverse events and serious adverse events overall, with consistent results across screening eGFR subgroups (P-interaction = 0.40 and 0.15, respectively; Figure 3). Rates of other adverse events including fractures and amputations were mostly not different among people randomized to canagliflozin or placebo overall, with consistent results across eGFR subgroups. The exceptions were volume depletion and osmotic diuresis events which were not more common with canagliflozin overall but with some evidence the effects differed among eGFR subgroups (P-interaction = 0.01 and 0.03, respectively). No unexpected safety signals were observed in patients with screening eGFR 30-<45 mL/min/1.73m^2.

Effects on eGFR slope

Canagliflozin led to an acute drop in eGFR at Week 3 that was significant in every eGFR subgroup (all P <0.001) although the drop was least in those with screening eGFR 30-<45 mL/min/1.73m^2/year (P

heterogeneity = 0.02; Figure 4; Table 1). Thereafter, the eGFR of those randomized to placebo declined by 4.59 mL/min/1.73m^2/year with similar declines seen in all eGFR categories. Canagliflozin led to a slower eGFR decline in every eGFR category compared with placebo (all P <0.001), with no evidence the benefit differed among eGFR subgroups (P heterogeneity = 0.65; Table 1). Canagliflozin improved total slope, the combined impact of the acute effect and chronic change in slope from baseline to Week 130, overall and in every eGFR subgroup (all P <0.001) with no evidence the effect varied between eGFR subgroups (P heterogeneity = 0.71; Table 1).

In those with an eGFR of 30-<45mL/min/1.73m^2, the group closest to a threshold for dialysis initiation, canagliflozin led to an acute drop in eGFR of 2.03 (95% CI 1.34-2.73) mL/min/1.73m^2 followed by an attenuation in eGFR decline of 2.61 (95% CI 2.06-3.16) mL/min/1.73m^2/year compared with those receiving placebo (mean decline [SD] 1.85 [0.13] in those assigned to canagliflozin compared with 4.59 [0.14] in those assigned to placebo).

Absolute effects of canagliflozin

While the relative benefits of canagliflozin compared with placebo were generally consistent among the eGFR subgroups, the absolute benefits were greater in those with lower screening eGFR subgroups (all P heterogeneity <0.03) for all renal outcomes other than dialysis, transplantation or renal death where the effects were consistent across subgroups (P heterogeneity = 0.06; Figure 1). The absolute benefits for cardiovascular events did not clearly differ among eGFR subgroups except for the composite of cardiovascular death or hospitalized heart failure, where there was borderline evidence the absolute benefits were greater in lower screening eGFR subgroups (P heterogeneity = 0.096; Figure 2)

Effect on intermediate outcomes

Canagliflozin reduced HbA1c, blood pressure, body weight, and albuminuria compared to placebo in participants across screening eGFR subgroups (Figure 5 and Supplementary Table 2). The glucose lowering effect of canagliflozin was numerically less and reductions in blood pressure were numerically greater in participants with lower initial eGFR compared with placebo, whereas reductions in body weight and albuminuria were similar across subgroups.

Experience of those experiencing last on-treatment eGFR below 30 mL/min/1.73m^2

In the CREDENCE trial, a substantial number of participants experienced an eGFR below 30 mL/min/1.73m^2. For the subgroup of participants who ended with an on-treatment eGFR below 30mL/min/1.73m^2 (N=929; canagliflozin, n=417; placebo, n=512), mean follow-up to the first eGFR below 30 mL/min/1.73m^2 was 12.9 months (canagliflozin, 11.7 months; placebo, 13.8 months) while mean follow-up thereafter was 19.3 months (canagliflozin, 20.5 months; placebo 18.4 months). The relative number of events occurring after eGFR first fell below 30/ml/min/1.73m^2 in the canagliflozin and placebo arms appeared similar to the trial overall (Supplementary Table 3). Because these analyses concern comparisons according to a postrandomization event (eGFR falling below 30 mL/min/1.73m^2), they are not randomized and should be regarded as exploratory, but may be useful to illustrate the course of participants within the study.

Discussion

Canagliflozin consistently and safely prevented renal and cardiovascular events in participants with substantial albuminuria across eGFR categories of 30-<45, 45-<60 and 60-<90 mL/min/1.73m^2. These benefits were attained on the background of universal renin-angiotensin system blockade use. While the relative benefits were consistent across eGFR categories, increasingly higher event rates were observed for both renal and cardiovascular events as eGFR levels declined, with greater absolute

benefits in the lower eGFR subgroups. The beneficial effect of canagliflozin on the occurrence of clinical events was reinforced by the observed reduction in the chronic rate of renal functional decline, which was reduced by more than 50% in all three subgroups. In particular, canagliflozin attenuated the chronic decline in eGFR over time by 60% and 65% in those with initial eGFR 30-<45 and 45-<60 mL/min/1.73m^2, respectively. Reassuringly, there was no excess of major safety concerns in participants with eGFR 30-<45 mL/min/1.73m^2, while observational analyses did not suggest differences in benefits as eGFR declined below 30 mL/min/1.73m^2. Together, these findings make a compelling case for commencing canagliflozin in people with eGFR between 30 and 90 mL/min/1.73m^2 and substantial albuminuria, and supporting the continuation of therapy below this threshold.

The effects of canagliflozin compared with placebo on intermediate outcomes were broadly consistent with those seen in previous studies. As expected, the glucose-lowering efficacy of canagliflozin was attenuated in patients with worsening renal function. However, the reductions in albuminuria, body weight and blood pressure were generally similar across eGFR subgroups. The initial acute drop in eGFR seen in CREDENCE is a well-established response to canagliflozin treatment initiation[8] and, together with the subsequent attenuation of eGFR decline is consistent with reductions in intraglomerular pressure being a plausible contributing mechanism to renal protection.[13-15] Other potential mechanisms for renoprotection are being actively studied.[16-18] The data strongly suggest a glucose independent mechanism of renal and cardiovascular benefit in CREDENCE.

Despite continuing uncertainty regarding the relative importance of several potential mechanisms, CREDENCE has established clear benefit for clinical renal outcomes.[10] The important novel finding that kidney and cardiac protection is preserved in those in whom treatment is started with an eGFR between 30 and 45 mL/min/1.73m^2 provides further insights into the potential mechanism of action. The finding of clinical benefits for important outcomes despite reduced effects on glycemic control raises important questions on whether these agents benefit kidney disease outcomes in nondiabetic settings. Ongoing trials recruiting people with nondiabetic kidney disease are likely to yield important further insights.[19-21]

Similarly, the benefits of SGLT2 inhibitors for preventing heart failure hospitalizations in participants with predominantly preserved kidney function has been established in three large cardiovascular outcome trials,[22-24] despite uncertainty on the precise mechanisms of heart failure mitigation. These agents do have a natriuretic effect which is reflected in early reductions in blood pressure and weight, and is a potentially contributor to the early benefits for heart failure hospitalization. However, the benefits continue to accumulate over time, despite stabilization of volume status. The CREDENCE trial has confirmed the absolute benefits for preventing heart failure hospitalizations are greater in those with lower eGFR levels who are at greater risk of heart failure events.

An important aspect of CREDENCE among the trials of SGLT2 inhibitors is that treatment was deliberately continued regardless of the eGFR falling below 30 mL/min/1.73m^2. We provide observational reports of the events occurring once eGFR fell below 30 mL/min/1.73m^2 in those whose eGFR remained below 30 mL/min/1.73m^2 at end of treatment, in analyses that are limited by their dependence on an outcome that occurs well after randomization. The ongoing DIAMOND[21] and DAPA-CKD trials[19] are recruiting participants with eGFR down to 25 mL/min/1.73m^2 while the EMPA-Kidney trial[20] includes those with an eGFR down to 20 mL/min/1.73m^2. Together these trials will provide evidence of the impact of SGLT2 inhibitors in people with lower commencement eGFR levels. In the meantime, the consistency overall between our exploratory reports and the overall CREDENCE findings provide reassurance there is no reason to dismiss the CREDENCE protocolized

approach of continuing treatment until the commencement of chronic dialysis or receipt of a renal transplant.

The CREDENCE study was designed to examine the effect of canagliflozin on outcomes of people at risk of progression of diabetic kidney disease. As such, its strengths include the inclusion of people with substantial albuminuria (who are at high risk of both renal and cardiovascular events), stratified randomization by screening eGFR categories, so that a majority of participants had an eGFR of below 60 mL/min/1.73m^2 providing robust assessment of canagliflozin in people with reduced eGFR down to 30 mL/min/1.73m^2. In addition, renal events were carefully evaluated with central assessment of eGFR, requirement for chronic outcomes to be documented as sustained, and adjudication of renal and other important events. The findings may not be generalizable to people commencing treatment with an eGFR below 30 mL/min/1.73m^2. Similarly, the findings apply to those with substantial albuminuria, although the concordance of the results with those of the CANVAS Program in which most participants had no or minor levels of albuminuria is reassuring. The trial was stopped early on grounds of clear efficacy for the primary endpoint which may have limited the power to assess the impact on secondary and safety endpoints. The analyses reported for participants who ended treatment with an eGFR below 30 mL/min/1.73m^2 are reported according to randomization arm but, as this cohort is defined by a postrandomization event, they are confounded and subject to biases including survival bias and collider bias, and should be regarded purely as hypothesis-generating.

Canagliflozin safely prevents clinically important renal and cardiovascular events in people with diabetes, substantial albuminuria and an eGFR at commencement of treatment between 30 and 90 mL/min/1.73m^2. These effects appear consistent across eGFR categories with greater absolute benefits for renal endpoints in lower eGFR categories. They support the expansion of canagliflozin treatment initiation to those with eGFR 30-<45 mL/min/1.73m^2, and the general continuation of treatment until the initiation of dialysis or receipt of kidney transplant.

Author contributions

M.J. Jardine wrote the first draft of the paper, had full access to the study design information, and had final responsibility for the decision to submit for publication. Z. Zhou, M. Oshima, G.L. di Tanna, and T. Sun contributed to the analysis and interpretation of data. M.J. Jardine, K.W. Mahaffey, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, D. Charytan, D. de Zeeuw, T. Greene, H.J.L. Heerspink, A. Levin, B. Neal, C. Pollock, R. Qiu, D.C. Wheeler, H. Zhang, B. Zinman, N. Rosenthal, and V. Perkovic contributed to the design and conduct of the study and the interpretation of the data. H.S. Bajaj contributed to the conduct of the study and interpretation of the data. All authors provided input into subsequent drafts and approved the final version for submission. Technical editorial assistance was provided by Alaina Mitsch, PhD, and Kimberly Dittmar, PhD, of MedErgy, and was funded by Janssen Global Services, LLC. All authors reviewed and approved the manuscript.

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D. de Zeeuw has served on advisory boards and/or as speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi-Tanabe; has served on steering committees and/or as a speaker for AbbVie and Janssen; and has served on Data Safety and Monitoring Committees for Bayer.

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A. Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and is on the DSMB for NIDDK, Kidney Precision Medicine, University of Washington Kidney Research Institute Scientific Advisory Committee, as well as being funded by Canadian Institute of Health Research, and Kidney Foundation of Canada. She has received fees for time as CREDENCE National Coordinator from Janssen, directed to her academic team.

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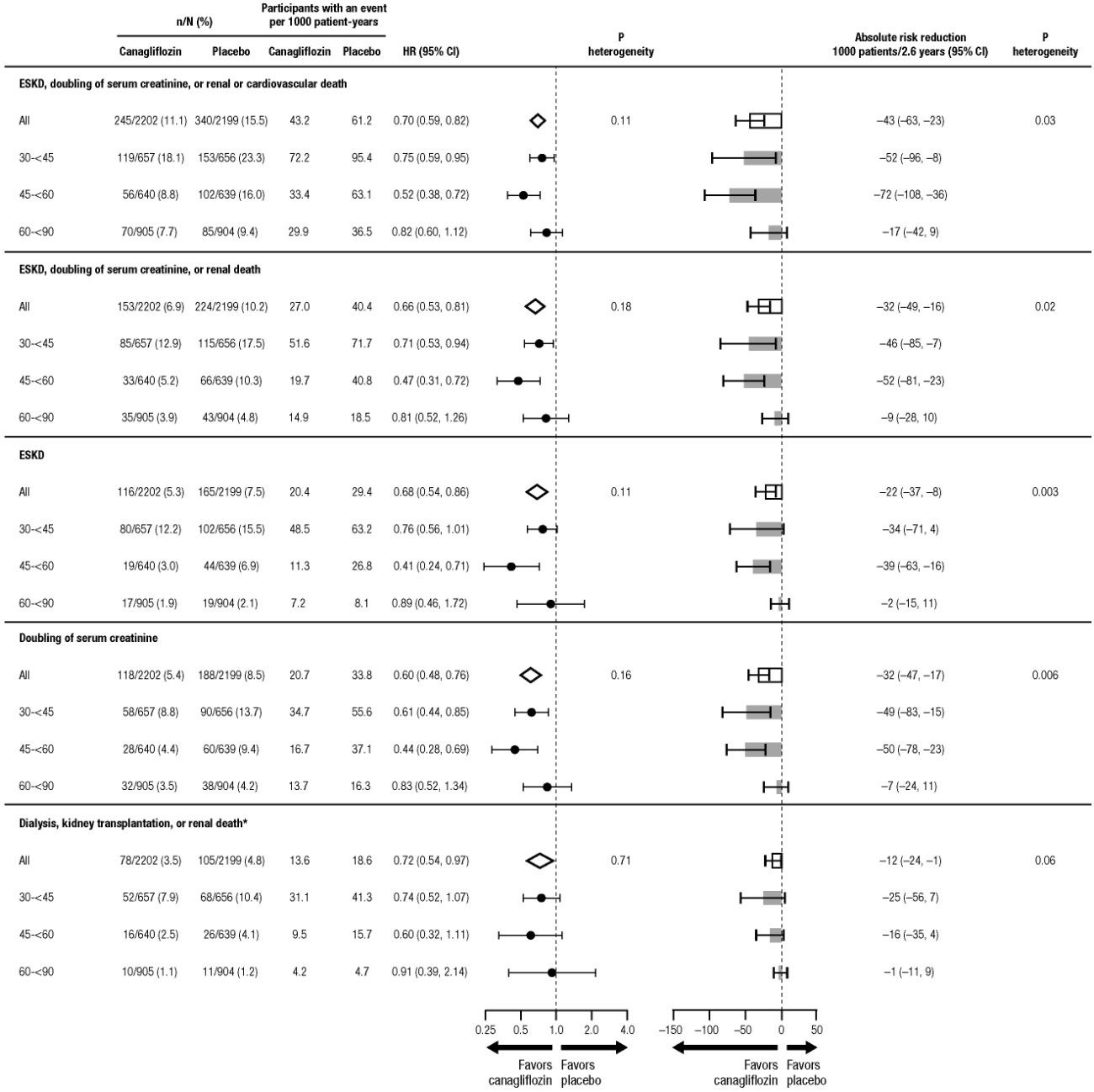
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Table 1. Effects of Canagliflozin on eGFR Slope by Screening eGFR

	N Canagliflozin/Placebo	Canagliflozin	Placebo	Difference (95% CI)	P value	P-interaction
eGFR Change from baseline to Week 3 (mL/min/1.73 m^2)						
All (unstructured)	2179/2178	–3.72 (0.25)	–0.55 (0.25)	–3.17 (–3.87, –2.47)	<0.001	
eGFR 30-<45	645/648	–2.45 (0.25)	–0.41 (0.25)	–2.03 (–2.73, –1.34)	<0.001	0.02
eGFR 45-<60	635/635	–4.08 (0.32)	–0.64 (0.31)	–3.44 (–4.32, –2.57)	<0.001	
eGFR 60-<90	899/895	–3.66 (0.32)	–0.39 (0.33)	–3.27 (–4.17, –2.37)	<0.001	
Annual eGFR change from Week 3 to last available measurement (mL/min/1.73 m^2/year)						
All (unstructured)	2081/2095	–1.85 (0.13)	–4.59 (0.14)	2.74 (2.37, 3.11)	<0.001	
eGFR 30-<45	611/622	–1.72 (0.20)	–4.33 (0.20)	2.61 (2.06, 3.16)	<0.001	0.65
eGFR 45-<60	605/613	–1.62 (0.23)	–4.58 (0.24)	2.97 (2.32, 3.61)	<0.001	
eGFR 60-<90	865/860	–2.32 (0.23)	–4.92 (0.23)	2.60 (1.97, 3.23)	<0.001	
Annual eGFR change from baseline to Week 130 (mL/min/1.73 m^2/year)						
All (unstructured)	2179/2178	–3.19 (0.15)	–4.71 (0.15)	1.52 (1.11, 1.93)	<0.001	
eGFR 30-<45	645/648	–2.56 (0.21)	–4.35 (0.21)	1.79 (1.20, 2.38)	<0.001	0.71
eGFR 45-<60	635/635	–3.11 (0.25)	–4.76 (0.25)	1.65 (0.96, 2.34)	<0.001	
eGFR 60-<90	899/895	–3.61 (0.24)	–5.03 (0.24)	1.42 (0.75, 2.09)	<0.001	

eGFR, estimated glomerular filtration rate; CI, confidence interval.
Data in the columns of canagliflozin and placebo are mean (standard error).
The effects of canagliflozin on the mean on-treatment eGFR slope were analyzed using a 2-slope linear spline model for eGFR, with a knot at Week 3 to account for separate acute (baseline to Week 3) and chronic (Week 3 to end of treatment) slopes. The full model also included random intercepts, acute and chronic slopes. When the full model failed to converge, a simplified model with a random intercept and a single random slope was used. The mean total slope was computed as a weighted combination of the acute and chronic slopes to reflect the mean rate of eGFR change to Week 130.

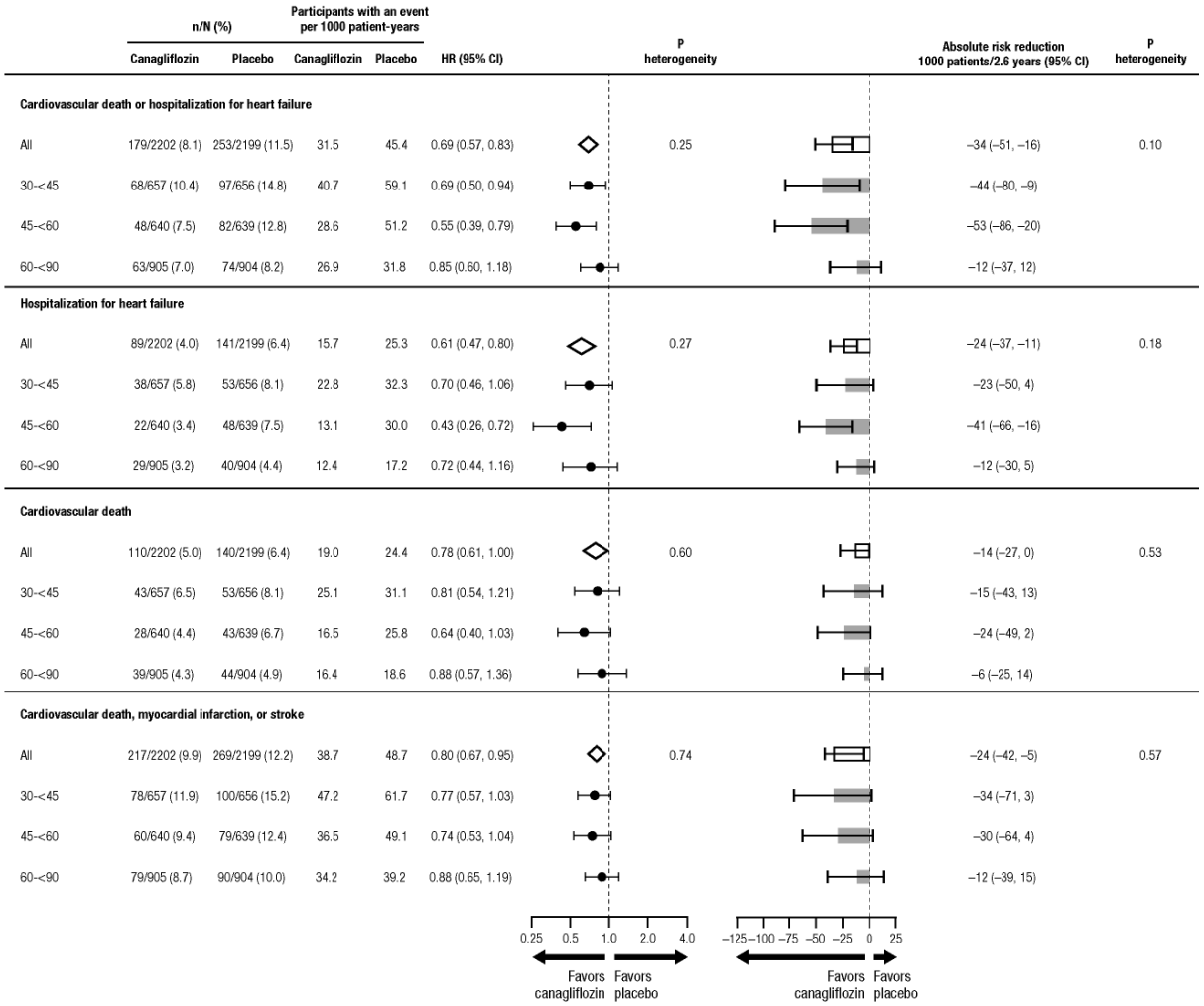
Figure 1. Effect of canagliflozin on renal outcomes by screening eGFR.



eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; ESKD, end-stage kidney disease.

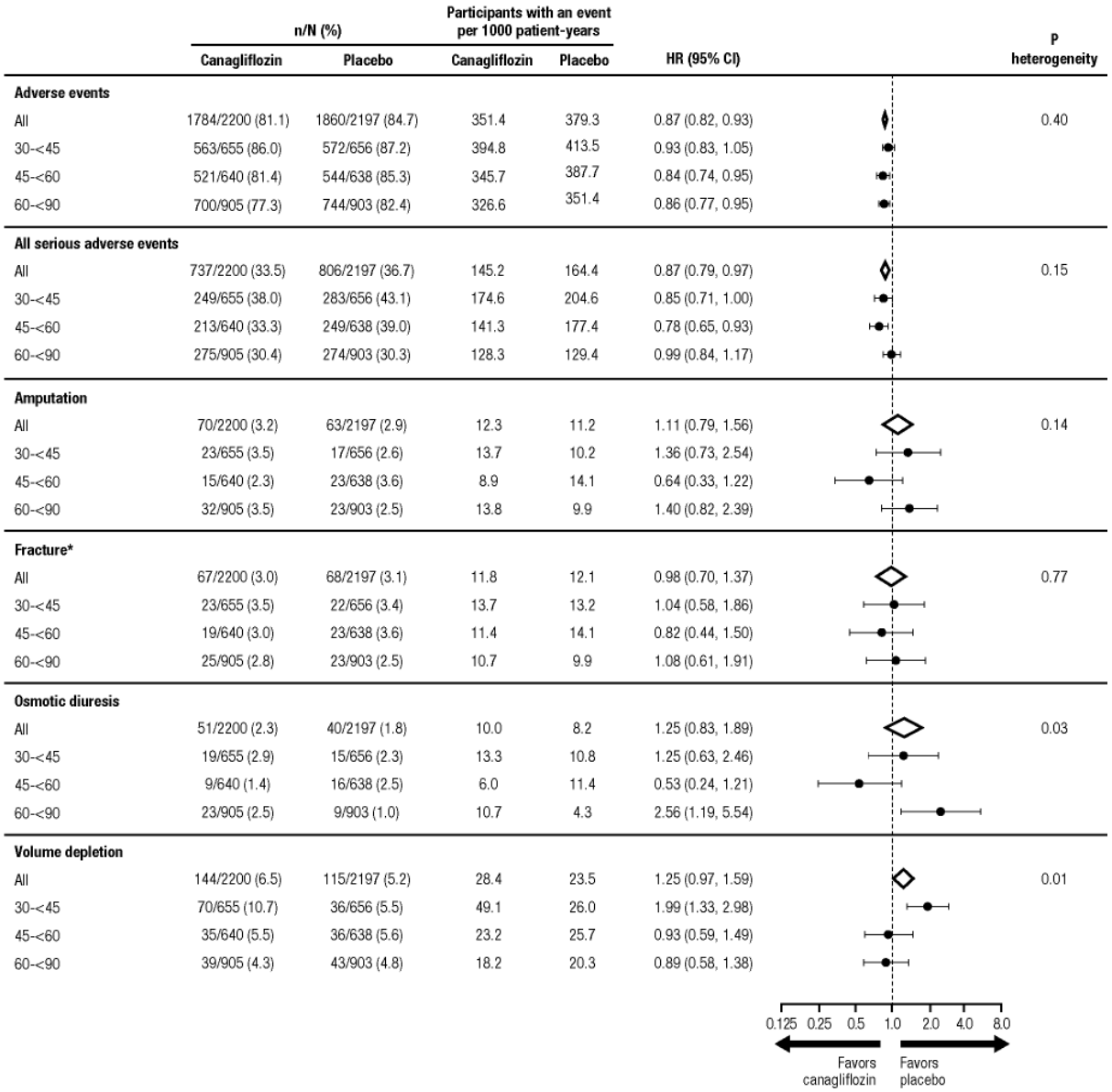
*This outcome was exploratory.

Figure 2. Effect of canagliflozin on cardiovascular outcomes by screening eGFR.



eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

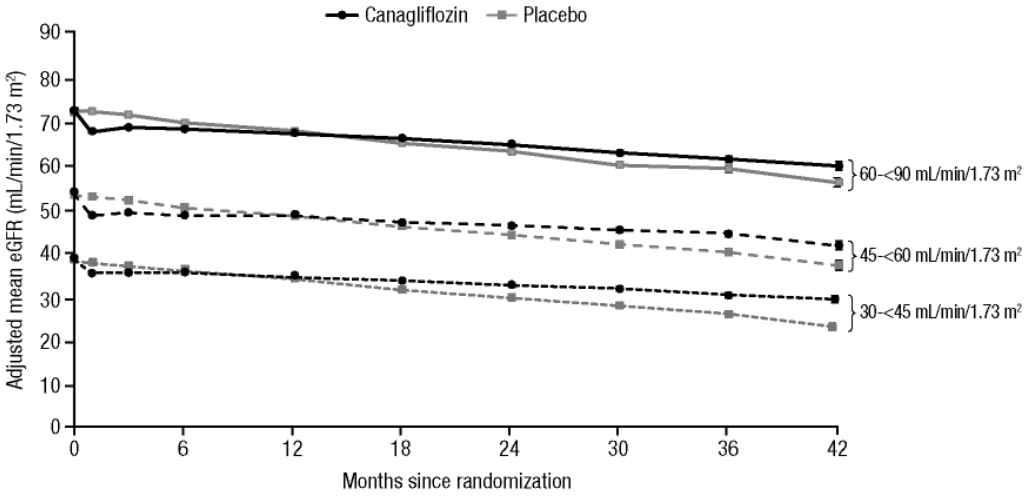
Figure 3. Effect of canagliflozin on safety outcomes by screening eGFR.



eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

*Based on confirmed and adjudicated results.

Figure 4. Effects of canagliflozin on eGFR change by screening eGFR subgroup.



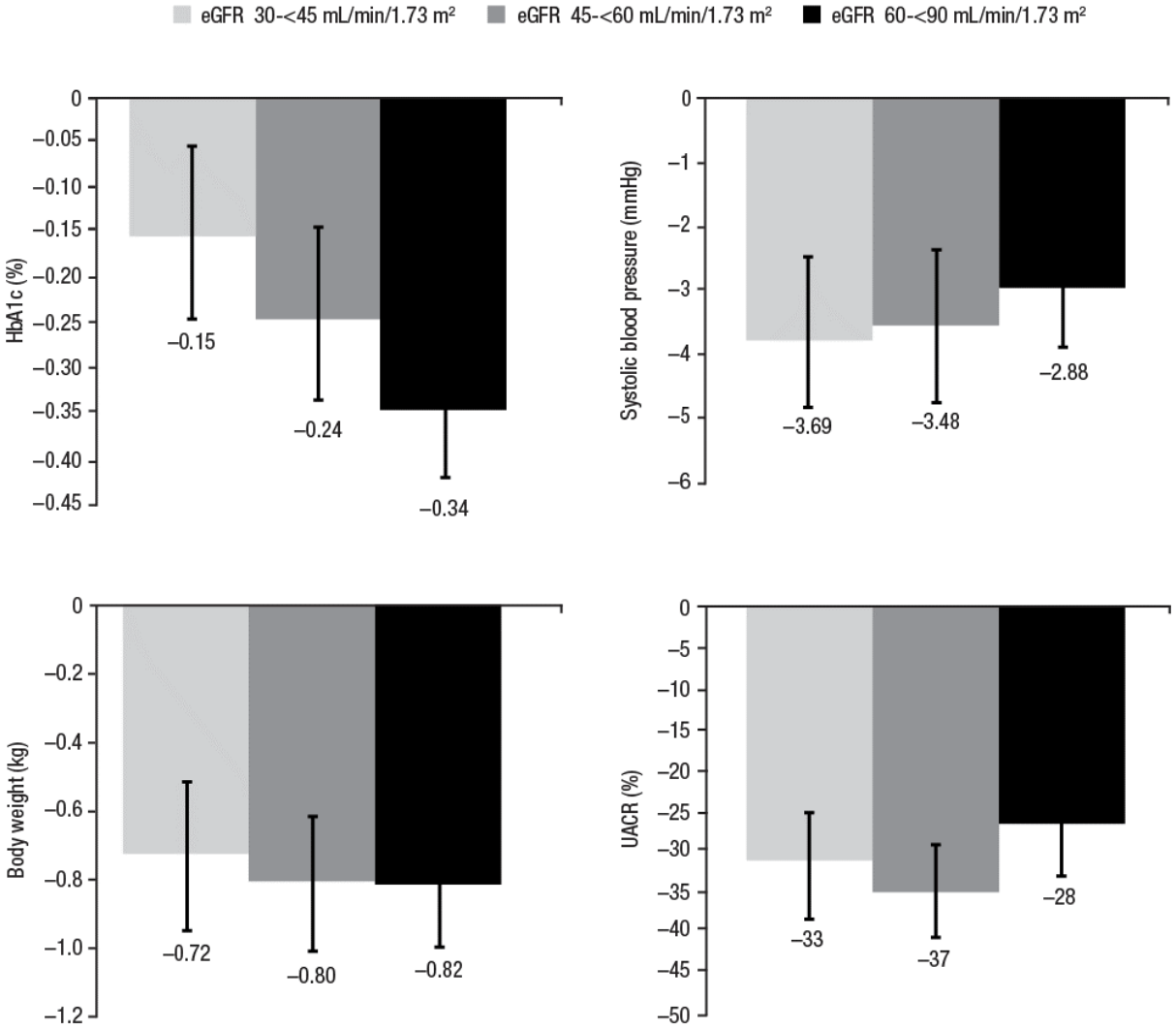
No. at risk

eGFR 60-<90	Canagliflozin	899	833	803	758	710	490	288	98
	Placebo	895	829	801	755	679	471	270	100
eGFR 45-<60	Canagliflozin	635	589	563	531	490	333	202	80
	Placebo	635	575	535	483	435	278	168	58
eGFR 30-<45	Canagliflozin	645	583	553	493	448	293	162	63
	Placebo	648	581	546	482	422	257	145	52

eGFR, estimated glomerular filtration rate.

The slope lines cross at the point corresponding to 14.3, 11.2 and 8.7 months for those with initial eGFR 60-<90 mL/min/1.73m^2, 45-<60 mL/min/1.73m^2 and 30-<45 mL/min/1.73m^2, respectively. The on-treatment eGFR includes all central laboratory eGFR measurements from study Day 1 up to the last dose plus 2 days. The change from baseline in eGFR was analyzed using a restricted maximum likelihood (REML) repeated measures approach.

Figure 5. Effects of canagliflozin on intermediate outcomes by screening eGFR.*



eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; CI, confidence interval.

*Data are placebo-subtracted mean difference (95% CI), except for UACR, where it is percent change in the geometric mean of canagliflozin relative to placebo.

Figure Legends

Figure 1. Effect of canagliflozin on renal outcomes by screening eGFR.

eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; ESKD, end-stage kidney disease.

*This outcome was exploratory.

Figure 2. Effect of canagliflozin on cardiovascular outcomes by screening eGFR.

eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

Figure 3. Effect of canagliflozin on safety outcomes by screening eGFR.

eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

*Based on confirmed and adjudicated results.

Figure 4. Effects of canagliflozin on eGFR change by screening eGFR subgroup.

eGFR, estimated glomerular filtration rate.

The slope lines cross at the point corresponding to 14.3, 11.2 and 8.7 months for those with initial eGFR 60-<90 mL/min/1.73m^2, 45-<60 mL/min/1.73m^2 and 30-<45 mL/min/1.73m^2, respectively. The on-treatment eGFR includes all central laboratory eGFR measurements from study Day 1 up to the last dose plus 2 days. The change from baseline in eGFR was analyzed using a restricted maximum likelihood (REML) repeated measures approach.

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Supplementary Table 1. Demographic and Clinical Characteristics by Screening eGFR

	eGFR 30-<45 mL/min/1.73 m^2		eGFR 45-<60 mL/min/1.73 m^2		eGFR 60-<90 mL/min/1.73 m^2	
Characteristic*	**Canagliflozin (N=657)**	**Placebo (N=656)**	**Canagliflozin (N=640)**	**Placebo (N=639)**	**Canagliflozin (N=905)**	**Placebo (N=904)**
Age, y	64.4 ± 9.3	64.9 ± 9.4	63.0 ± 9.1	62.9 ± 9.4	61.7 ± 8.9	62.1 ± 8.8
Female, n (%)	220 (33.5)	191 (29.1)	227 (35.5)	230 (36.0)	315 (34.8)	311 (34.4)
Race, n (%)						
White	426 (64.8)	413 (63.0)	432 (67.5)	411 (64.3)	629 (69.5)	620 (68.6)
Black or African American	36 (5.5)	28 (4.3)	34 (5.3)	36 (5.6)	42 (4.6)	48 (5.3)
Asian	131 (19.9)	145 (22.1)	133 (20.8)	140 (21.9)	161 (17.8)	167 (18.5)
Other[†]	64 (9.7)	70 (10.7)	41 (6.4)	52 (8.1)	73 (8.1)	69 (7.6)
Region, n (%)						
North America	202 (30.7)	189 (28.8)	150 (23.4)	203 (31.8)	222 (24.5)	216 (23.9)
Central/South America	121 (18.4)	127 (19.4)	140 (21.9)	118 (18.5)	215 (23.8)	220 (24.3)
Europe	144 (21.9)	142 (21.6)	151 (23.6)	104 (16.3)	159 (17.6)	164 (18.1)
Rest of the world	190 (28.9)	198 (30.2)	199 (31.1)	214 (33.5)	309 (34.1)	304 (33.6)
Current smoker, n (%)	87 (13.2)	74 (11.3)	80 (12.5)	84 (13.1)	174 (19.2)	140 (15.5)
History of hypertension, n (%)	639 (97.3)	642 (97.9)	620 (96.9)	617 (96.6)	872 (96.4)	870 (96.2)
History of heart failure, n (%)	109 (16.6)	90 (13.7)	88 (13.8)	91 (14.2)	132 (14.6)	142 (15.7)
Duration of diabetes, y	16.9 ± 9.3	17.2 ± 8.8	15.9 ± 8.8	16.3 ± 8.6	14.3 ± 7.9	14.9 ± 8.3
Drug therapy, n (%)						
Insulin	488 (74.3)	461 (70.3)	432 (67.5)	439 (68.7)	532 (58.8)	532 (58.8)
Sulfonylurea	160 (24.4)	182 (27.7)	166 (25.9)	175 (27.4)	286 (31.6)	299 (33.1)
Biguanides	214 (32.6)	233 (35.5)	383 (59.8)	365 (57.1)	679 (75.0)	671 (74.2)
GLP-1 receptor agonist	26 (4.0)	25 (3.8)	20 (3.1)	25 (3.9)	43 (4.8)	44 (4.9)
DPP-4 inhibitor	114 (17.4)	112 (17.1)	123 (19.2)	110 (17.2)	141 (15.6)	151 (16.7)
Statin	480 (73.1)	474 (72.3)	469 (73.3)	434 (67.9)	589 (65.1)	590 (65.3)
Antithrombotic[‡]	418 (63.6)	399 (60.8)	379 (59.2)	373 (58.4)	544 (60.1)	511 (56.5)
RAAS inhibitor	656 (99.8)	655 (99.8)	640 (100)	638 (99.8)	905 (100)	901 (99.7)
Beta blocker	303 (46.1)	319 (48.6)	262 (40.9)	259 (40.5)	318 (35.1)	309 (34.2)
Diuretic	352 (53.6)	366 (55.8)	303 (47.3)	303 (47.4)	371 (41.0)	362 (40.0)
Microvascular disease history, n (%)						

Retinopathy	300 (45.7)	296 (45.1)	282 (44.1)	272 (42.6)	353 (39.0)	379 (41.9)
Nephropathy	657 (100)	656 (100)	640 (100)	639 (100)	905 (100)	904 (100)
Neuropathy	328 (49.9)	310 (47.3)	299 (46.7)	328 (51.3)	450 (49.7)	432 (47.8)
History of cardiovascular disease, n (%)	345 (52.5)	338 (51.5)	325 (50.8)	326 (51.0)	443 (49.0)	443 (49.0)
Body mass index, kg/m^2	31.6 ± 6.3	31.1 ± 6.0	31.1 ± 5.8	31.4 ± 6.6	31.3 ± 6.3	31.4 ± 6.0
Systolic blood pressure, mmHg	141.4 ± 16.3	140.3 ± 16.6	139.0 ± 15.3	140.2 ± 15.9	139.2 ± 15.2	140.1 ± 14.7
Diastolic blood pressure, mmHg	77.4 ± 9.2	77.7 ± 9.8	77.8 ± 9.9	78.1 ± 9.4	79.2 ± 8.9	79.1 ± 9.0
HbA1c, %	8.2 ± 1.3	8.1 ± 1.3	8.2 ± 1.3	8.2 ± 1.3	8.4 ± 1.3	8.4 ± 1.4
Cholesterol, mmol/L						
Total	4.7 ± 1.3	4.5 ± 1.2	4.6 ± 1.3	4.7 ± 1.3	4.8 ± 1.3	4.7 ± 1.3
Triglycerides	2.3 ± 1.5	2.3 ± 1.7	2.3 ± 1.7	2.3 ± 1.6	2.2 ± 1.6	2.1 ± 1.7
HDL cholesterol	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.3
LDL cholesterol	2.5 ± 1.1	2.4 ± 1.0	2.4 ± 1.1	2.5 ± 1.1	2.6 ± 1.1	2.5 ± 1.0
Ratio of LDL to HDL	2.4 ± 1.1	2.2 ± 1.0	2.3 ± 1.1	2.3 ± 1.1	2.3 ± 1.1	2.3 ± 1.0
eGFR, mL/min/1.73 m^2[‖]	37.9 ± 9.0	37.5 ± 8.1	53.0 ± 10.4	52.5 ± 9.6	72.1 ± 12.8	71.9 ± 14.0
Median urine albumin:creatinine ratio (IQR), mg/g[#]	1116.0 (498.0-2283.0)	1065.0 (553.0-2343.0)	925.5 (464.5-1791.0)	936.0 (499.0-1868.0)	794.0 (425.0-1517.0)	792.5 (418.5-1587.0)
Median urine albumin:creatinine ratio (IQR), mg/mmol[#]	126.3 (56.3-258.3)	120.4 (62.5-264.8)	104.6 (52.5-202.6)	105.8 (56.5-211.3)	89.8 (48.1-171.5)	89.6 (47.3-179.5)

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IQR, interquartile range; SD, standard deviation.

*Plus-minus values are mean ± SD.

[†]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

[‡]Includes anticoagulation and antiplatelet agents, including aspirin.

[‖]One participant treated with canagliflozin in the screening eGFR 45-<60 mL/min/1.73m^2 subgroup was missing eGFR at baseline.

[#]Eligibility was based on screening urine albumin:creatinine ratio >300 mg/g to ≤5000 mg/g (33.9-<565.6 mg/mmol).

Supplementary Table 2. Effects of Canagliflozin on HbA1c, Body Weight, Systolic Blood Pressure and UACR According to Screening eGFR*

	eGFR 30-<45 mL/min/1.73 m^2		eGFR 45-<60 mL/min/1.73 m^2		eGFR 60-<90 mL/min/1.73 m^2	
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**	**Canagliflozin**	**Placebo**
HbA1c, %, n	620	631	618	619	877	877
Mean (SD) baseline	8.1 (1.3)	8.2 (1.3)	8.2 (1.3)	8.2 (1.3)	8.4 (1.3)	8.4 (1.4)
LS mean change (SE)	–0.37 (0.04)	–0.23 (0.04)	–0.36 (0.04)	–0.12 (0.04)	–0.49 (0.03)	–0.14 (0.03)
Difference vs placebo (95% CI)	–0.15 (–0.24, –0.05)		–0.24 (–0.33, –0.14)		–0.34 (–0.42, –0.26)	
Body weight, kg, n	646	648	634	634	899	893
Mean (SD) baseline	88.1 (20.6)	86.2 (19.9)	86.2 (19.5)	86.9 (22.0)	87.5 (21.6)	87.4 (20.3)
LS mean change (SE)	–1.07 (0.13)	–0.34 (0.13)	–1.11 (0.13)	–0.30 (0.13)	–1.21 (0.10)	–0.39 (0.10)
Difference vs placebo (95% CI)	–0.72 (–0.94, –0.51)		–0.80 (–1.00, –0.61)		–0.82 (–0.99, –0.65)	
Systolic blood pressure, mmHg, n	647	648	635	634	899	894
Mean (SD) baseline	141.5 (16.3)	140.2 (16.6)	139.0 (15.4)	140.2 (15.9)	139.2 (15.1)	140.2 (14.6)
LS mean change (SE)	–2.55 (0.45)	1.14 (0.45)	–2.92 (0.41)	0.56 (0.42)	–3.13 (0.32)	–0.25 (0.32)
Difference vs placebo (95% CI)	–3.69 (–4.81, –2.57)		–3.48 (–4.56, –2.39)		–2.88 (–3.71, –2.06)	
UACR, mg/g, n	598	603	604	598	860	854
Median baseline	1112.0	1057.0	905.5	902.5	774.0	789.0
Geometric mean (95% CI)	641.5 (592.0,695.2)	963.7 (889.1,1044.5)	530.0 (487.8, 575.8)	845.9 (777.8, 919.9)	447.8 (413.5, 485.1)	619.9 (572.2, 671.7)
Percent change in the geometric mean relative to placebo (95% CI)	33 (27; 40)		37 (31; 43)		28 (20; 35)	

UACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; SD, standard deviation; SE, standard error; CI, confidence interval.

*Linear mixed effects models for repeated measures were used to analyze changes in intermediate outcomes over time.

Supplementary Table 3. Number of Events in Participants Whose Final eGFR Was <30 mL/min/1.73m^2 From the Point Their eGFR First Fell Below 30 mL/min/1.73m^2

	Canagliflozin (n=417)	**Placebo (n=512)**
Primary composite endpoint	130	205
Composite of cardiovascular death or hospitalization for heart failure	46	73
Cardiovascular death, myocardial infarction, or stroke	46	66
Hospitalization for heart failure	23	40
Composite of doubling of serum creatinine, end-stage kidney disease, or renal death	111	181
Cardiovascular death	30	44
Mean (SD) follow-up period from eGFR <30 mL/min/1.73m^2 (months)	20.5 (13.30)	18.4 (11.99)

eGFR, estimated glomerular filtration rate.