Canagliflozin Reduces Renal-related Adverse Events in Type 2 Diabetes and Chronic Kidney Disease: Results From the Randomized CREDENCE Trial

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Abstract

Rationale and Objective: Canagliflozin reduced the risk of kidney failure and related outcomes in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) in the CREDENCE trial. This analysis examines the incidence of renal-related adverse events (AEs) during treatment with canagliflozin.

Study Design: CREDENCE was a randomized, double-blind, placebo-controlled, multicenter, international trial.

Setting and Participants: CREDENCE enrolled 4,401 participants with T2DM, CKD, and urinary albumin:creatinine ratio >300-5000mg/g.

Interventions: Participants were randomly assigned to receive canagliflozin 100mg/day or placebo.

Outcomes: Rates of renal-related AEs were analyzed using an on-treatment approach, overall and by screening estimated glomerular filtration rate (eGFR) strata (30-<45, 45-<60, and 60-<90 mL/min/1.73m^2).

Results: Canagliflozin was associated with a reduction in the overall incidence rate of renal-related AEs (60.2 vs 84.0 per 1,000 patient-years; hazard ratio [HR]: 0.71 [95% confidence interval (CI): 0.61, 0.82]; *P*<0.001), with consistent results for serious renal-related AEs (HR: 0.72 [95% CI: 0.51, 1.00]; *P*=0.05) and acute kidney injury (AKI; HR: 0.85 [95% CI: 0.64, 1.13]; *P*=0.3). The rates of renal-related AEs were lower with canagliflozin relative to placebo across the 3 eGFR strata (HRs of 0.73, 0.60, and 0.81 for eGFR 30-<45, 45-<60, and 60-<90 mL/min/1.73m^2, respectively; *P*-interaction=0.3), with similar results for AKI (*P*-interaction=0.9). Full recovery of kidney function within 30 days after an AKI event occurred

more frequently with canagliflozin versus placebo (53.1% vs 35.4%; odds ratio: 2.2 [95% CI: 1.0, 4.7]; *P*=0.04).

Limitations: Renal-related AEs including AKI were investigator reported and collected without central adjudication, biomarkers of AKI and structural tubular damage were not measured, and creatinine data after an AKI event were not available in all participants.

Conclusion: Canagliflozin compared to placebo was associated with a reduced incidence of serious and non-serious renal-related AEs in patients with T2DM and CKD. These results highlight the renal safety of canagliflozin.

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Trial Registration: The CREDENCE trial was registered at ClinicalTrials.gov with identifier number NCT02065791

Index words: Canagliflozin, SGLT2 inhibitor, renal-related adverse events, drug safety

Plain language summary:

Canagliflozin is safe for the kidneys in people with type 2 diabetes and chronic kidney disease

Canagliflozin reduced the risk of kidney failure and slowed the progression of kidney disease in people with type 2 diabetes and chronic kidney disease in the CREDENCE trial. This analysis examined kidney-related safety in the overall population and in subgroups based on kidney function. Results show that canagliflozin is safe for the kidneys, with fewer kidney-related safety events, even in patients with more severe kidney disease at the start of the trial. Among patients

who developed acute kidney injury during the trial, there were fewer who died or required dialysis in the canagliflozin versus placebo group. These data support the positive benefit-risk profile of canagliflozin in the high-risk population of people with type 2 diabetes and chronic kidney disease.

Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors are a relatively new class of oral glucose-lowering agents that have been shown to decrease the risks of major cardiovascular and heart failure outcomes in large cardiovascular safety trials.[1-3] These trials also demonstrated that SGLT2 inhibitors slow the progression of estimated glomerular filtration rate (eGFR) decline over time. While the cardiovascular safety of SGLT2 inhibitors has been well established, the risks for acute declines in kidney function are still debated, with the label of SGLT2 inhibitors including warnings around increased risk of acute kidney injury (AKI). These warnings are derived from postmarketing surveillance data that suggested increased risk of AKI among patients with type 2 diabetes mellitus (T2DM) and preserved kidney function.[4]

The cardiovascular safety trials with SGLT2 inhibitors enrolled patients with mostly normal kidney function in whom the incidence of AKI is low. The CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial was designed to establish the long-term efficacy and safety of canagliflozin in preventing kidney and cardiovascular outcomes in patients with T2DM and chronic kidney disease (CKD).[5] The trial demonstrated that canagliflozin markedly reduced kidney and cardiovascular events.[6] Since both diabetes and reduced kidney function are independent risk factors for AKI,[7] it is important to understand the effects of canagliflozin on kidney safety outcomes, including AKI, in the CREDENCE population in order to guide best clinical practice. We therefore conducted a post hoc analysis of the CREDENCE trial to investigate the effect of canagliflozin on kidney safety outcomes and examined the incidence, predictors, and consequences of AKI during placebo and canagliflozin treatment.

Methods

Study design and participants

Kidney safety outcomes were examined in this post hoc analysis of the CREDENCE trial, a randomized, double-blind, placebo-controlled, multicenter, international trial. The study design and the primary results have been published previously.[5, 6] The protocol was approved by the ethics committees at each site. All the participants provided written informed consent. In brief, CREDENCE participants were ≥30 years of age with a diagnosis of T2DM, glycated hemoglobin (HbA1c) between 6.5% and 12.0%, screening eGFR between 30 and 90 mL/min/1.73 m^2, and urinary albumin:creatinine ratio (UACR) between 300 and 5000 mg/g (>33.9-565.6 mg/mmol). All participants were receiving treatment with a stable maximum labeled or tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for ≥4 weeks prior to randomization. Exclusion criteria included nondiabetic kidney disease, type 1 diabetes mellitus (T1DM), and prior treatment of kidney disease with immunosuppression or a history of kidney replacement therapy. CREDENCE was an event-driven randomized controlled trial and the planned treatment period was dependent on the observed accrual rate and event rate. The event rate in the placebo arm was expected to be 7.5% which led to an estimated 27 months recruitment period and 33 months follow-up period.[5]

Randomization and study treatment

Eligible participants were randomly assigned to receive either daily treatment with oral canagliflozin 100 mg or matching placebo. Study treatment was continued until the commencement of dialysis, receipt of a kidney transplant, occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy, or study completion.

Outcomes

The primary outcome of the current analysis was the first renal-related adverse events (AEs). Renal-related AEs were defined as the composite of investigator-reported AEs that were coded as primarily renal according to the *Medical Dictionary for Regulatory Activities* (MedDRA) terminology. AEs coded as primarily renal included "Anuria," "Azotemia," "blood creatinine increase," "blood urea increase," "glomerular filtration decrease," "nephropathy toxic," "renal impairment," "renal failure," and "AKI." The first ~~R~~renal-related serious adverse events was an additional endpoint for the present study. The first ~~A~~AKI was a prespecified AE of interest and a third outcome in this study. Other renal-related AEs as described above were not prespecified AEs of interest and none of these were adjudicated by a separate endpoint committee. A table with MedDRA terminology used to summarize the renal-related adverse events is shown in **Table S1**. We also examined renal-related serious AEs, which were defined as renal-related AEs that were life threatening or led to unplanned hospitalization, prolonged hospitalization, or death.

To determine the validity of investigator reported AKI events, we analyzed the effect of canagliflozin compared to placebo on a 40% eGFR decline endpoint that occurred between two subsequent study visits. We choose a 40% eGFR decline because it is equivalent to 50% increase in serum creatinine (or 1.5 times increase in serum creatinine) from baseline which is consistent with the KDIGO definition of stage 1 AKI.

Recovery of kidney function 30 days after AKI was another exploratory outcome and was assessed using change in eGFR from the last eGFR measurement before AKI until the eGFR measurement within 30 days after the AKI event. Participants with on-treatment eGFR follow-up values on record within 30 days of the reported AKI event (n=97) were included in this analysis.

We defined a change in eGFR from the pre-AKI level of <-20% as no recovery, -20 to <0% as partial recovery, and ≥0% as full recovery. Dialysis and all-cause mortality 30 days after AKI was a final outcome in this study.

Investigators reported all potential renal endpoints for the study as adverse events. These events were submitted for adjudication by an independent event adjudication committee. Several of the terms used to report potential renal endpoints were also included in the preferred term listing used to identify renal-related adverse events (for example blood creatinine increased and GFR decreased). In order to account for this potential over-reporting of renal-related safety events, we performed an additional analysis excluding renal-related adverse events that were confirmed to be primary study endpoints (i.e. sustained doubling of serum creatinine, end-stage kidney disease or renal death).

Statistical analysis

Analyses were performed using the on-treatment data set, which included all events up through 30 days of the last dose of study medication in accordance with the statistical analysis plan. ~~Cox proportional hazard regression was performed~~We fitted cause specific hazard models (using Cox proportional hazards regression) to assess treatment effects of canagliflozin versus placebo to the first relevant AE. Cox models were stratified by eGFR categories defined at the screening visit. Subgroup analyses by patient's demographics, laboratory measurements, and concomitant medication use at baseline were performed, and tests for homogeneity of treatment effects across subgroups were performed by adding interaction terms to the relevant Cox models. The proportional hazards assumption was assessed by inspection of the log-cumulative hazard function of each treatment group and by including an interaction term between treatment

assignment and time as a time-varying covariate in the Cox regression models (**Fig S1A and S1B**). The log-cumulative hazard function revealed some degree of non-parallelism during the first months of the trial and the *P* value for the interaction term between treatment assignment and time was statistically significant for the renal-related AE endpoint. We subsequently fitted a piece-wise Royston and Parmar regression model that demonstrated a rapid decrease in the time-dependent hazard ratio (HR) in the first few weeks of the trial with the confidence bands of the time dependent HR largely overlapping the hazard ratio of the Cox model and therefore present the HR of the Cox models for all outcomes (**Fig S1C and S1D)**. We performed various sensitivity analyses. First we repeated our analyses using the intention-to-treat population which included all randomized patients. Second, we performed a competing risk analysis using the method described by Fine and Gray with the renal-related AE as the outcome event and mortality as a competing risk.

Cox proportional hazard regression analyses were performed within the canagliflozin or placebo group separately to assess baseline characteristics associated with renal-related safety outcomes. Factors associated with the occurrence of AKI were collected during the trial and summarized by treatment groups. In addition, dialysis and death outcomes 30 days after AKI were collected and summarized by treatment group. In a sensitivity analyses we summarized these events 90 days after AKI since, according the Kidney Disease Improving Global Outcomes nomenclature, AKI can be defined by presence of up to 3 months. Ordinal logistic regression analysis was performed to assess the odds of recovery after AKI. We compared full recovery versus partial or no recovery (in pairs) between the canagliflozin and placebo groups. The Brant test to assess the proportional odds assumption was not violated (P=0.70). All analyses were performed in Stata version 15 (StataCorp LLC, College Station, Texas).

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

Effects of canagliflozin compared to placebo on renal-related AEs

The CREDENCE trial randomized 4401 participants, of whom 4397 received ≥1 dose of randomized treatment: 2197 assigned to placebo, 2200 assigned to canagliflozin (**Fig S2**). During a mean follow-up of 2.1 (standard deviation [SD]: 0.9) years, renal-related AEs were recorded in 678 participants; 388 participants (17.7%; event rate 8.4 per 100 patient-years) in the placebo group and 290 participants (13.2%; event rate 6.0 per 100 patient-years) in the canagliflozin group (HR: 0.71, 95% confidence interval [CI]: 0.61, 0.82; $P<0.001$). However, the impact of canagliflozin on renal-related AEs was not constant over the follow-up period. During the first months after randomization, a report of a renal-related AE was more likely to be received for participants assigned to canagliflozin than those assigned to placebo (**Fig 1A**). The increase in these events primarily represented investigator-reported increases in serum creatinine or decreases in eGFR. This early increase in frequency of reported events was apparent only early in the study; at 12 months, the Kaplan-Meier curves crossed and the risk of renal-related AEs was higher in the placebo group. The Kaplan-Meier curves continued to diverge throughout the remainder of follow-up (**Fig 1A**). Sensitivity analyses demonstrated that the results were very

similar in the intention-to-treat population (**Fig S3**). Additionally, accounting for the competing risk of mortality did not alter our findings; the effect size for the renal-related AE and AKI endpoints were virtually identical (HR 0.72 [95% CI: 0.6, 0.83] and 0.86 [95% CI: 0.64, 1.14], respectively).

Renal-related AEs comprise a range of different investigator-reported AEs. The effects of canagliflozin compared to placebo were consistent for the different components of the composite renal-related AE, with no evidence that canagliflozin increased the risk of any of the individual components (**Fig 2**). A subgroup analysis was performed to identify potential subgroups at higher risk of renal-related AEs during canagliflozin treatment. As shown in **Fig 3**, there was no evidence that the effect of canagliflozin on renal-related AEs varied by any baseline participant characteristics (all *P* homogeneity>0.2). However, an exception was baseline UACR, where the reduction in risk associated with randomization to canagliflozin was progressively larger in subgroups with higher UACR. Similar results were observed in an additional analysis excluding events that were confirmed to be renal endpoints for the trial (**Table S2)**.

Effect of canagliflozin on renal-related serious AEs and AKI

Overall, renal-related serious AEs occurred in 82 participants (3.7%; event rate 1.7 per 100 patient-years) in the placebo group and 61 participants (2.8%; event rate 1.2 per 100 patient-years) in the canagliflozin group (HR: 0.72 [95% CI: 0.51, 1.00]; *P*=0.05; **Fig 1B**). Ninety-eight participants (4.5%; event rate 2.0 per 100 patient-years) in the placebo group and 86 (3.9%; event rate 1.7 per 100 patient-years) in the canagliflozin group experienced a reported AKI event (HR: 0.85 [95% CI: 0.64, 1.13]; *P*=0.3; **Fig 1C**). The proportion of patients with renal-related serious AEs or AKI events was similar between treatment groups during the first months of

follow-up. However, after 12 months, the Kaplan-Meier curves started to separate, with fewer events reported in the canagliflozin treatment arm (**Fig 1B** and **Fig 1C**). AKI related serious AEs occurred in 50 participants (2.3%; event rate 1.0 per 100 patient-years) in the placebo group and 41 participants (1.9%; event rate 0.8 per 100 patient-years) in the canagliflozin group (HR: 0.79 [95%CI: 0.52, 1.19] *P*=0.26). Effects of canagliflozin on renal-related serious AEs and AKI were consistent across participant subgroups with a trend for a larger benefit of canagliflozin in higher UACR subgroups (**Fig S4** and **Fig S5**). The majority of renal-related serious AEs were AEs requiring hospitalizations (**Table S3**).

A 40% eGFR decline between two subsequent study visits occurred in 191 participants (8.7%; event rate 4.0 per 100 patient-years) in the canagliflozin group and in 216 participants (9.8%; event rate 3.5 per 100 patient-years) in the placebo group (HR: 0.87 [95% CI: 0.72, 1.06]). This HR is consistent with the HR for investigator reported AKI events.

Association of baseline participant characteristics with renal-related AEs and AKI

Participants who experienced a renal-related AE were younger; more likely to be black or African American; had a longer duration of diabetes; had a lower eGFR; and had higher systolic blood pressure, UACR, triglycerides, and total cholesterol level, as well as were more likely to be treated with insulin or diuretics (**Table 1**). Generally similar differences in baseline characteristics were observed when the canagliflozin and placebo group were separately analyzed (**Table 1**).

In observational analyses in the canagliflozin group, multivariable modeling revealed that at trial commencement younger age, male sex, black or African-American race, lower eGFR, higher UACR, and insulin and diuretic treatment were independently associated with a higher

risk of renal-related AEs (**Table 2**). Similar baseline participant characteristics were associated with AKI, with the exception of age, UACR, and insulin and diuretic treatment (**Table 2**). When the placebo group was analyzed, patient characteristics similar to those in the canagliflozin group were associated with these AEs (**Table S4**).

Incidence and outcomes after AKI events

During follow-up, 212 AKI events were recorded in 184 participants; 114 AKI events in 98 participants in the placebo group and 98 events in 86 participants in the canagliflozin group. Nineteen participants experienced multiple AKI events during follow-up. Main factors associated with AKI both in the canagliflozin and placebo groups were dehydration/hypovolemia and septic shock; **Table 3**). In about half of patients in both groups, study medication was continued after an AKI event (**Table 3**). Study medication was stopped temporarily or permanently at the time of the event in 24.5% and 8.2% of patients in the placebo group, respectively, and 29.1% and 7.0%, respectively, in the canagliflozin group (**Table 3**). An AE of volume depletion within 30 days before the AKI event was recorded by investigators in 15 patients (11 patients in the canagliflozin group and 4 patients in the placebo group [P=0.03]). ACE-inhibitors or ARBs were used in 100 patients before the AKI event. These agents were discontinued in 51 patients within 30 days after the AKI event (20 patients in the canagliflozin group and 31 patients in the placebo group). Diuretic treatment was initiated within 30 days before the AKI event in 14 patients (4 patients in the canagliflozin group and 10 patients in the placebo group [P=0.2]).

Outcomes after an AKI event are shown in **Fig 4**. Serum creatinine data after 30 days after AKI were available in 97 patients (48 in the placebo group and 49 in the canagliflozin

group). Not only did canagliflozin cause less AKI than placebo, patients assigned to canagliflozin were also more likely to recover. Full recovery of kidney function occurred in 53.1% of patients in the canagliflozin group versus 35.4% in the placebo group (odds ratio: 2.2 [95% CI: 1.0, 4.7]; *P*=0.04), whilst no recovery of kidney function was more frequently observed in the placebo group (35.4%) compared to the canagliflozin group (18.4%; odds ratio: 0.46 [95% CI: 0.21, 0.97]; *P*=0.04).

The proportion of participants requiring dialysis within 30 days after the AKI event was 16.3% in the placebo group compared to 10.5% in the canagliflozin group (*P*=0.3). The proportion of patients who died within 30 days after an AKI event was 10.2% and 7.0% in the placebo and canagliflozin groups, respectively (*P*=0.5). Results were similar in a sensitivity analysis that considered outcomes within 90 days after the AKI event (**Table S5**).

Discussion

This post hoc analysis from the CREDENCE trial showed that treatment with canagliflozin was associated with a decreased risk of renal-related safety outcomes, including AKI, in high-risk patients with T2DM and CKD. Not only was canagliflozin associated with a reduced incidence of AKI, 30-day outcomes after an AKI event also favored the canagliflozin group, with fewer patients requiring dialysis compared to the placebo group. These data underscore the positive benefit-risk profile of canagliflozin and support evolving practice guidelines recommending the use of SGLT2 inhibitors in patients with T2DM and CKD.

In the CREDENCE trial, renal-related safety outcomes occurred more frequently in the first few months, but after 12 months occurred more frequently in those assigned to placebo. Over the entire trial duration, the frequency of renal-related safety outcomes was significantly

lower in the canagliflozin group. Canagliflozin and other SGLT2 inhibitors cause an acute dip in eGFR, which is reversible after treatment discontinuation. Prior studies in patients with T1DM and T2DM have shown that the acute dip in eGFR reflects a reduction in intraglomerular pressure and reflects the hemodynamic mechanism of action of this drug class.[8-10] AKI is defined in clinical practice guidelines by a similar rise in serum creatinine as the increase in serum creatinine that can be expected at initiation of renal protective interventions such as SGLT2 inhibitors and renin-angiotensin-aldosterone system (RAAS) inhibitors.[11] This makes it challenging to distinguish a reversible beneficial fall in eGFR at initiation of these interventions from AKI. The higher frequency of renal-related AEs and AKI during the early stage of the trial may be a reflection of investigator response to the acute dip in eGFR. Additionally, the majority of the reported AKI events from clinical practice that led to warnings around increased risk of AKI occurred within 4 weeks after SGLT2 initiation and could also be a reflection of the acute dip in eGFR.[4]

While there were initial concerns about the long-term renal safety of SGLT2 inhibitors in patients with T2DM and CKD, these new findings from the CREDENCE trial provides evidence that, during prolonged treatment, canagliflozin decreases the risks of renal-related serious AEs or AKI. We believe that practitioners may be reassured by these analyses that support treatment with canagliflozin in accordance with the approaches of the CREDENCE trial. These approaches included continued treatment with canagliflozin until participants received maintenance dialysis or a kidney transplantation. Investigators were reminded of principles for the investigation and management of an acute decline in eGFR consistent with National Institute for Health and Care Excellence guidelines,[12] including repeat eGFR measurement, identification and management of precipitating conditions, and the evaluation and management of hypotension or hypovolemia

(including adjustment of blood pressure medications and/or diuretics). We believe that it is prudent to follow these principles, including evaluation and anticipation of situations of reduced renal perfusion and volume depletion, which may occur in the setting of gastrointestinal volume loss or elective surgery. In these circumstances, advice on "sick day rules" and temporarily withholding SGLT2 inhibitor treatment (using an approach similar to that used for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) could be considered.

The finding that AKI events were not increased, and may actually occur less frequently, in the canagliflozin group is consistent with prior cardiovascular outcome trials in patients with T2DM and preserved kidney function.[13] The mechanisms are not completely understood, but it has been proposed that SGLT2 inhibition decreases the high oxygen demand of the proximal tubule to reabsorb sodium and glucose. As a result, the workload of the proximal tubule and susceptibility to hypoxia, which is often present in diabetes and an important determinant of progressive renal function loss in experimental models, decreases. This renders the proximal tubule less susceptible to damage and can improve tubular cell structural integrity and possibly function.[14] A few randomized placebo-controlled studies have reported that SGLT2 inhibitors reduce urinary kidney injury molecule-1 levels, providing further clinical evidence of the direct protective effects of SGLT2 inhibitors on the proximal tubule.[15] Based on these data, AKI is a prespecified exploratory outcome in the DAPA-CKD and EMPA-KIDNEY trials in patients with CKD.[16, 17] These trials, along with CREDENCE and other mechanistic studies, will help to further characterize the renal safety profile.

The careful data collection and reporting in the CREDENCE trial allowed us to assess predisposing factors associated with AKI as well as outcomes after AKI events. The finding that dehydration or volume depletion events was the most frequently occurring predisposing factor is

consistent with findings from the VA NEPHRON D trial in patients with type 2 diabetes and CKD.[18] Although not statistically significant, fewer patients required dialysis or died in the canagliflozin group compared to the placebo group during the 30 days following an AKI event. An explanation for this finding could be that AKI observed during canagliflozin treatment is predominantly hemodynamically mediated AKI without structural renal damage, which results in better outcomes. This is analogous to findings from the VA NEPHRON D trial, where dual RAAS blockade led to a higher incidence of AKI but a lower rate of subsequent kidney and mortality outcomes, suggesting that the AKI during dual RAAS treatment is mainly hemodynamically mediated.[18]

Effects of canagliflozin on renal-related AEs and AKI were consistent in various participant subgroups. The risk reductions for renal safety outcomes and AKI achieved with canagliflozin were proportionally higher in the subgroup of participants with nephrotic range albuminuria. This is clinically relevant as these patients were at the highest risk of these AEs. As a result of their higher risk and larger proportional benefits, the absolute benefits of canagliflozin to prevent renal safety outcomes was highest in participants with nephrotic range albuminuria. Although effects of SGLT2 inhibitors on renal-related AEs and AKI were generally consistent in various subgroups, when the canagliflozin and placebo treatment groups were analyzed separately, similar patient subgroups were associated with renal safety outcomes, including black or African American patients and those with higher albuminuria and lower eGFR. These data are in line with previous studies, and careful monitoring for AKI in these patients is recommended regardless of whether they receive SGLT2 inhibitors.[7]

The current findings should be interpreted in the context of the limitations of this analysis. Firstly, renal-related AEs including AKI were investigator reported and collected

variably without central adjudication or confirmation with biomarkers of AKI measured in a central laboratory. This may have resulted in "noise" in the reported effect sizes and less robust exploration of modifying factors. However, the effect sizes for investigator reported AKI events were consistent with a post-hoc defined eGFR based endpoint of 40% eGFR decline between two subsequent study visits supporting the validity of the results. Secondly, biomarkers of AKI and structural tubular damage, such as kidney injury molecular-1 or interleukin-18, were not measured during the trial, which precluded differentiation between potential hemodynamically induced AKI without structural tubular damage and events with tubular damage. Thirdly, creatinine data within 30 days after an AKI event were not available in all participants, leading to potential bias. In addition, recovery of AKI was defined in a subset of patients and defined by postrandomization characteristics that were influenced by canagliflozin itself and which may bias the reported odds ratio for recovery of AKI. However, since AKI was less frequently reported in the canagliflozin group compared to the placebo group, this has likely led to an underestimation of the effect of canagliflozin for recovery of AKI.

In conclusion, canagliflozin compared to placebo treatment was associated with a lower incidence of serious and non-serious renal-related AEs, including AKI, in patients with T2DM and CKD. These data highlight the renal safety of canagliflozin in this population.

Author contributions

Data analysis: MO, JL, GLDT; data interpretation: all authors; study design and conduct: HJLH, MO, HZ, RA, GC, DMC, JC, DdZ, GLDT, AL, BN, VP, DCW, YY, MJJ. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions

pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Conflicts of interest

HJLH has served as a consultant for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Chinook, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi-Tanabe, CSL Pharma, and Retrophin and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen.

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HZ has received consulting and travel fees from Janssen for the role as a member of the CREDENCE Steering Committee.

JL is a full-time employee of the George Institute for Global Health.

RA has received research funding from GlaxoSmithKline; has received personal fees from Akebia, Bayer, Johnson & Johnson, Boehringer Ingelheim, Takeda, Daiichi Sankyo, Amgen, AstraZeneca, Sanofi, Celgene, Reata, Relypsa, GlaxoSmithKline, Gilead, ER Squibb and Sons, Fresenius, Ironwood Pharmaceuticals, Otsuka, OPKO, and Eli Lilly; and has served as associate editor of the *American Journal of Nephrology* and *Nephrology, Dialysis, and Transplantation* and as an author on *UpToDate*.

GC is a full-time employee of Janssen Research & Development, LLC.

DMC has received fees paid by Janssen Pharmaceuticals to the Baim Institute for work on the CREDENCE trial Steering Committee and as scientific lead; and received salary support from the Baim Institute for this work through October 2018. After that time, he received consulting fees from Baim. He has consulted for Amgen, AstraZeneca, Medtronic/Covidien, ZOLL, Fresenius, Daiichi Sankyo, Douglas and London, Eli Lilly, Merck, Gilead, GlaxoSmithKline, and Novo Nordisk; has served on data safety and monitoring boards for AstraZeneca; has served on a CEC for Merck and PLC Medical; and has received research support from Amgen, Bioporto, and Medtronic.

JC is a full-time employee of Janssen Research & Development, LLC.

DdZ has served on advisory boards and/or as a 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.

GLDT is a full-time employee of the George Institute for Global Health.

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

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YY is a full-time employee of Janssen Research & Development, LLC.

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Data sharing statement

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.

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Fig S3. Effects of canagliflozin versus placebo on (A) renal-related AEs and (B) AKI (intention-to-treat).*

Fig S4. Risk of renal-related serious AEs with canagliflozin compared with placebo in participants defined by characteristics at baseline.

Fig S5. Risk of AKI with canagliflozin compared with placebo in participant subgroups defined by characteristics at baseline.

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Table 1. Baseline Characteristics of the Study Participants With or Without Any Renal-related AEs Stratified by Treatment

Characteristic	Total			Canagliflozin			Placebo		
	Yes	**No**	***P***	**Yes**	**No**	***P***	**Yes**	**No**	***P***
N	678	3719		290	1910		388	1809	
Age, mean (SD), years	62 (10)	63 (9)	<0.001	62 (10)	63 (9)	0.005	62 (10)	63 (9)	0.02
Men, n (%)	470 (69)	2435 (65)	0.05	197 (68)	1242 (65)	0.3	273 (70)	1193 (66)	0.09
Race,* n (%)									
White	400 (59)	2528 (68)	<0.001	180 (62)	2528 (68)	0.03	220 (57)	1222 (68)	<0.001
Black or African American	64 (9)	159 (4)	<0.001	32 (11)	159 (4)	<0.001	32 (8)	80 (4)	0.002
Asian	149 (22)	728 (20)	0.15	56 (19)	728 (20)	0.9	93 (24)	359 (20)	0.07
Other	65 (10)	304 (8)		22 (8)	304 (8)		43 (11)	148 (8)	
Current smoker, n (%)	90 (13)	549 (15)	0.31	42 (14)	299 (16)	0.6	48 (12)	250 (14)	0.5
History of hypertension, n (%)	662 (98)	3594 (97)	0.17	286 (99)	1843 (96)	0.06	376 (97)	1751 (97)	0.9

History of heart failure, n (%)	111 (16)	541 (15)	0.22	46 (16)	283 (15)	0.6	65 (17)	258 (14)	0.2
Duration of diabetes, mean (SD), years	16.5 (8.8)	15.7 (8.6)	0.02	16.8 (9.2)	15.4 (8.6)	0.01	16.3 (8.6)	16.0 (8.6)	0.5
History of cardiovascular disease, n (%)	339 (50)	1879 (51)	0.80	146 (50)	966 (51)	0.9	193 (50)	913 (50)	0.8
History of amputation, n (%)	43 (6)	191 (5)	0.20	18 (6)	101 (5)	0.5	25 (6)	90 (5)	0.2
Body mass index, mean (SD), kg/m^2	32 (7)	31 (6)	0.14	32 (7)	31 (6)	0.02	31 (9)	31 (6)	0.9
Systolic blood pressure, mean (SD), mmHg	142 (17)	140 (15)	<0.001	141 (17)	140 (15)	0.05	143 (16)	140 (15)	<0.001
Diastolic blood pressure, mean (SD), mmHg	79 (10)	78 (9)	0.31	78 (10)	78 (9)	0.8	79 (10)	78 (9)	0.1
HbA1c, mean (SD), %	8.2 (1.3)	8.3 (1.3)	0.52	8.2 (1.3)	8.3 (1.3)	0.5	8.2 (1.3)	8.3 (1.3)	0.8
eGFR, mean (SD), mL/min/1.73 m^2	48 (16)	58 (18)	<0.001	48 (17)	58 (18)	<0.001	48 (16)	58 (18)	<0.001
UACR, median (IQR), mg/g	1642 (708-2971)	843 (444-1641)	<0.001	1341 (614-2675)	862 (447-1681)	<0.001	1716 (799-3163)	819 (440-1603)	<0.001

Total cholesterol, mean (SD), mmol/L	4.8 (1.4)	4.6 (1.3)	0.04	4.8 (1.5)	4.7 (1.3)	0.2	4.7 (1.3)	4.6 (1.3)	0.1
HDL cholesterol, mean (SD), mmol/L	1.1 (0.4)	1.2 (0.3)	0.65	1.1 (0.4)	1.2 (0.3)	0.5	1.2 (0.4)	1.1 (0.3)	0.9
LDL cholesterol, mean SD), mmol/L	2.5 (1.2)	2.5 (1.1)	0.22	2.6 (1.3)	2.5 (1.1)	0.3	2.5 (1.1)	2.5 (1.0)	0.4
Triglycerides, median (IQR), mmol/L	1.9 (1.4-2.8)	1.8 (1.3-2.6)	0.008	2.0 (1.4-2.9)	1.8 (1.3-2.6)	0.07	1.9 (1.4-2.8)	1.8 (1.3-2.6)	0.05
Drug therapy, n (%)									
Insulin	505 (74)	2377 (64)	<0.001	226 (78)	1225 (64)	<0.001	279 (72)	1152 (64)	0.002
Diuretic	391 (58)	1665 (45)	<0.001	168 (58)	857 (45)	<0.001	223 (57)	808 (5)	<0.001

AE, adverse event; SD, standard deviation; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration ratio, UACR, urinary albumin:creatinine ratio; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Race or ethnic group was reported by the patients. The designation “Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Table 2. Predictors of Renal-related AEs and AKI in the Canagliflozin Group

	Renal-related AEs				AKI			
	Univariable		Multivariable		Univariable		Multivariable	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age (per 10 years)	0.84	0.74, 0.95	0.77	0.67, 0.90	0.99	0.78, 1.25	0.87	0.66, 1.15
Men (vs. Women)	1.12	0.87, 1.43	1.40	1.07, 1.84	1.36	0.85, 2.18	1.51	0.90, 2.54
Race								
White	0.72	0.57, 0.92	1.03	0.65, 1.65	0.75	0.49, 1.17	1.29	0.46, 3.64
Black or African American	2.78	1.92, 4.01	2.21	1.25, 3.89	4.89	2.84, 8.41	5.15	1.67, 15.83
Asian	1.01	0.76, 1.36	1.13	0.68, 1.89	0.69	0.38, 1.28	1.38	0.44, 4.38
Current smoker (vs. non-smoker)	0.96	0.69, 1.33	1.11	0.79, 1.56	1.20	0.69, 2.09	1.49	0.84, 2.64
History of hypertension	2.28	0.85, 6.12	1.85	0.68, 5.05	NA	NA	NA	NA*
History of heart failure	1.09	0.79, 1.49	1.03	0.73, 1.45	1.54	0.91, 2.58	1.38	0.79, 2.41
Duration of diabetes (per 1 year)	1.02	1.00, 1.03	1.01	0.99, 1.03	1.03	1.00, 1.05	1.01	0.99, 1.04
History of cardiovascular disease	1.03	0.81, 1.29	1.00	0.78, 1.29	1.54	1.00, 2.38	1.33	0.83, 2.13
Body mass index (per 1 kg/m^2)	1.02	1.00, 1.04	1.02	0.99, 1.04	1.05	1.02, 1.09	1.05	1.02, 1.09

Systolic blood pressure (per 10 mmHg)	1.10	1.02, 1.18	1.08	0.99, 1.17	1.15	1.01, 1.31	1.19	1.03, 1.38
Diastolic blood pressure (per 10 mmHg)	1.00	0.88, 1.13	0.93	0.81, 1.07	0.89	0.71, 1.11	0.83	0.64, 1.07
HbA1c (per 1 %)	0.99	0.91, 1.09	0.96	0.87, 1.06	0.99	0.84, 1.17	0.94	0.78, 1.13
eGFR (per 5 mL/min/1.73 m^2)	0.85	0.82, 0.88	0.87	0.84, 0.91	0.84	0.78, 0.90	0.85	0.79, 0.92
UACR (per 1000 mg/g)	1.26	1.20, 1.33	1.21	1.14, 1.28	1.03	0.88, 1.20	0.99	0.85, 1.17
HDL cholesterol (per 1 mmol/L)	0.86	0.61, 1.20	0.96	0.67, 1.40	0.36	0.17, 0.76	0.41	0.18, 0.94
LDL cholesterol (per 1 mmol/L)	1.06	0.96, 1.18	1.09	0.98, 1.22	0.94	0.77, 1.15	1.04	0.84, 1.29
Triglycerides (per 1 mmol/L)	1.02	0.96, 1.09	1.01	0.94, 1.09	1.04	0.93, 1.16	1.01	0.88, 1.16
Drug therapy								
Insulin	1.99	1.51, 2.63	1.39	1.03, 1.88	2.11	1.25, 3.54	1.38	0.79, 2.41
Diuretic	1.61	1.27, 2.03	1.33	1.04, 1.70	1.31	0.86, 1.99	0.79	0.50, 1.26

AE, adverse event; AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*History of hypertension was not analyzed in the canagliflozin group since none of the participants in the canagliflozin group without a history of hypertension developed AKI.

Table 3. Outcomes After AKI Events

	Total	**Canagliflozin**	**Placebo**
AKI events (N)	212	98	114
Number of patients with AKI events, n (%)	184 (4.2)	86 (4.1)	98 (4.5)
Predisposing factors associated with AKI‡			
Dehydration/volume depletion	61 (33.2)	31 (36.0)	30 (30.6)
Diagnostic agent	3 (7.6)	2 (2.3)	1 (1.0)
Trauma	1 (0.5)	0 (0)	1 (1.0)
Cardiovascular event	35 (19.0)	15 (17.4)	20 (20.4)
Infection/septic shock	55 (29.9)	25 (29.1)	30 (30.6)
Perioperative	2 (1.1)	1 (1.2)	1 (1.0)
Other**	56 (30.4)	27 (31.4)	29 (29.6)
Drug action			
Drug interrupted, n (%)	49 (26.6)	25 (29.1)	24 (24.5)
Drug withdrawn, n (%)	14 (7.6)	6 (7.0)	8 (8.2)
Dose not changed, n (%)	89 (48.4)	42 (48.8)	47 (48.0)
Not applicable, n (%)	30 (16.3)	11 (12.8)	19 (19.4)
Unknown, n (%)	2 (1.1)	2 (2.3)	0 (0)
Recovery of kidney function			
Change in eGFR from pre- to 30 days post-AKI*			
<-20% (no recovery)	26 (26.8)	9 (18.4)	17 (35.4)
-20 to <0% (partial recovery)	28 (28.9)	14 (28.6)	14 (29.2)
≥0% (full recovery)	43 (44.3)	26 (53.1)	17 (35.4)

AKI event requiring dialysis, n (%)	25 (13.6)	9 (10.5)	16 (16.3)
AKI event requiring chronic dialysis, n (%)	6 (3.3)	2 (2.3)	4 (4.1)
Death within 30 days after AKI, n (%)	16 (8.7)	6 (7.0)	10 (10.2)

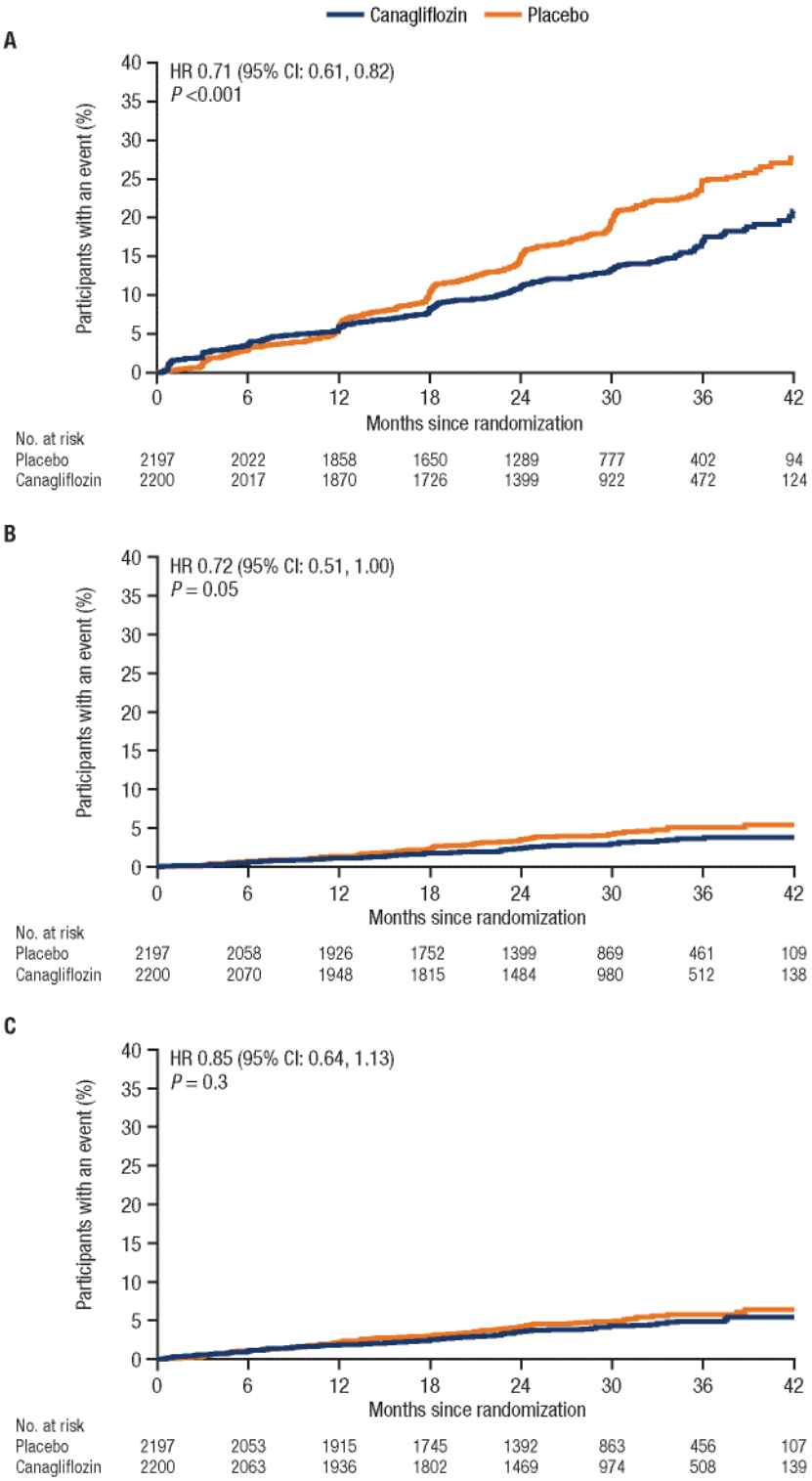
AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

*Other includes for example antibiotic use (gentamycin / vancomycin), pneumonia, choledocholithiasis/acute pancreatitis, respiratory depression, chronic obstructive pulmonary disease

**Data available in 97 patients with serum creatinine recorded within 30 days after the AKI event: 49 in the canagliflozin group and 48 in the placebo group.

‡ Numbers do not add up since more than one predisposing factor could be reported per patient.

Figure 1. Effects of canagliflozin compared with placebo on the risk of **(A)** any renal-related AEs, **(B)** renal-related serious AEs, and **(C)** AKI. *

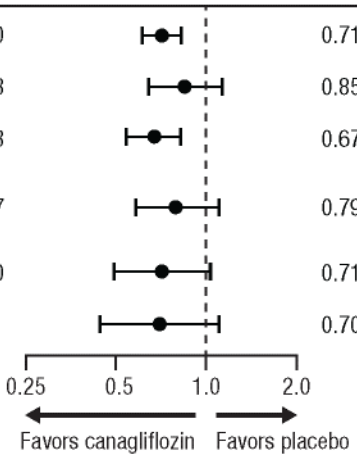


AE, adverse event; AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*On-treatment analyses were performed from baseline until 30 days after the last date of study drug. Hazard ratios were estimated using Cox models that were stratified by screening eGFR subgroup.

Figure 2. Effects of canagliflozin compared with placebo on the risk of renal-related AEs according to preferred term, as reported by investigators.

	Participants with an event		Participants with an event per 1000 patient-years			
	Canagliflozin	Placebo	Canagliflozin	Placebo	HR (95% CI)*	*P* value
Any renal-related AEs	290	388	60.2	84.0	0.71 (0.61, 0.82)	<0.001
AKI	86	98	17.2	20.3	0.85 (0.64, 1.13)	0.3
Blood creatinine increased	144	203	28.9	42.3	0.67 (0.54, 0.82)	<0.001
Glomerular filtration rate decreased	68	81	13.5	16.7	0.79 (0.58, 1.10)	0.2
Renal impairment	50	68	10.0	14.0	0.71 (0.49, 1.03)	0.07
Other†	32	44	6.3	9.0	0.70 (0.44, 1.10)	0.1

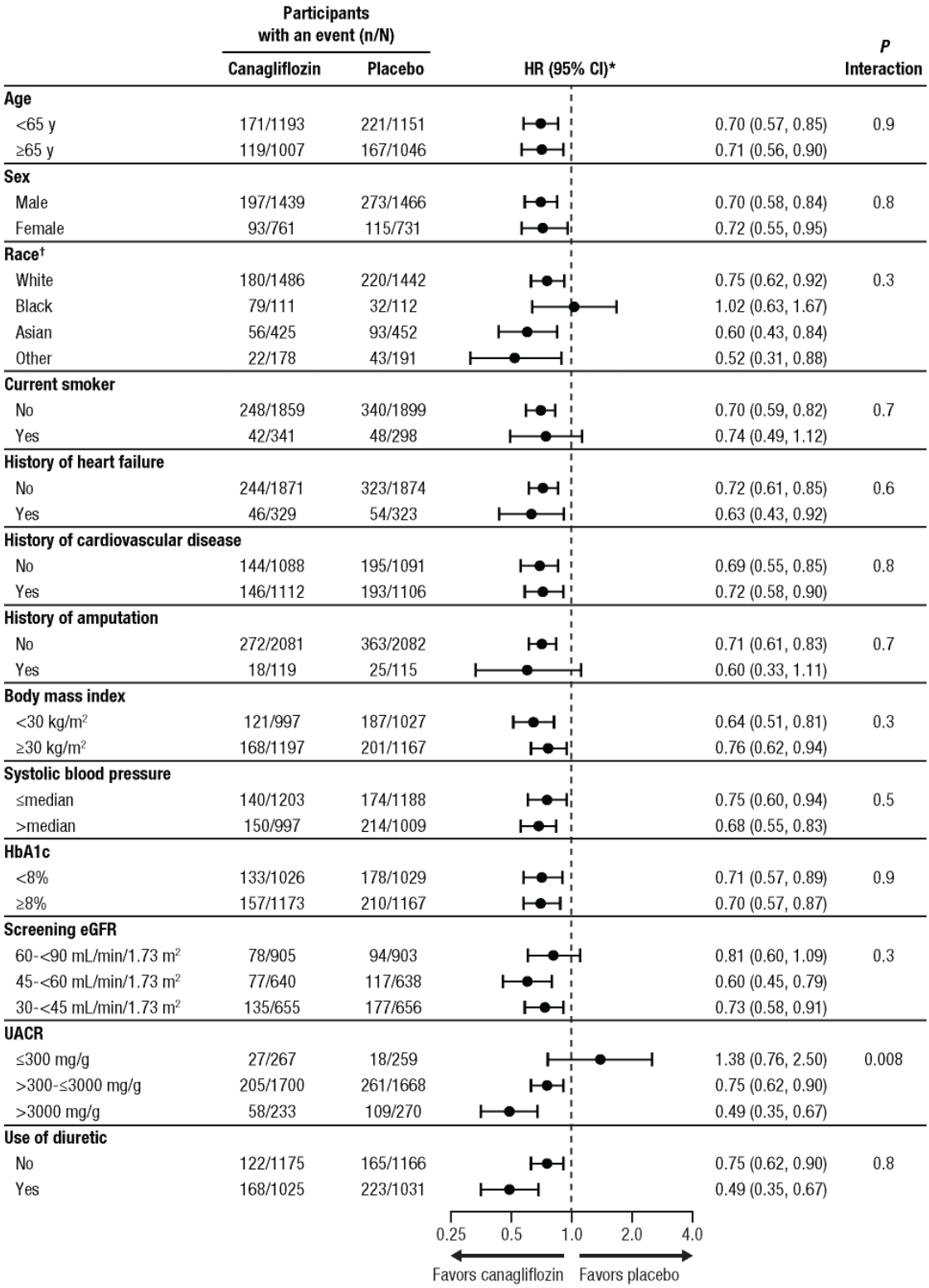


AE, adverse event; HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

*On-treatment analyses were performed from baseline until 30 days after the last date of study drug. Hazard ratios were estimated using Cox models that were stratified by screening eGFR subgroup.

†Other category includes anuria, azotemia, blood urea increase, nephropathy toxic, oliguria, and renal failure.

Figure 3. Risk of renal-related AEs with canagliflozin compared with placebo in participant subgroups defined by characteristics at baseline.

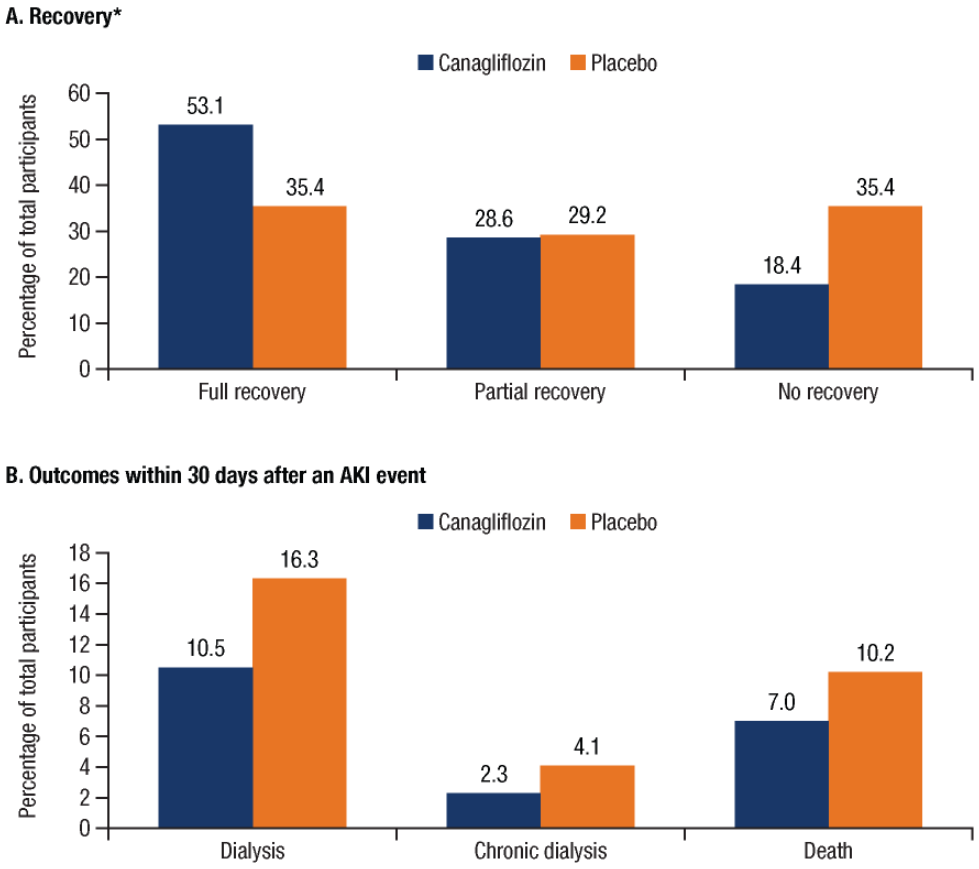


AE, adverse event; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration ratio; UACR, urinary albumin:creatinine ratio.

*On-treatment analyses are performed from baseline until 30 days after the last date of study drug. Cox models were stratified by screening eGFR subgroup.

[†]Race was reported by the patients. The designation “Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Figure 4. Outcomes after AKI events.



AKI, acute kidney injury; eGFR, estimate glomerular filtration rate.

*Data available in 97 participants in whom serum creatinine data were available within 30 days after the event: 49 in the canagliflozin group and 49 in the placebo group.

Full recovery defined as change in eGFR from the pre-AKI level of ≥0%; partial recovery as -20 to <0% change; no recovery as <-20% change in eGFR from the pre-AKI level. Dialysis, defined as any dialysis recorded in the database, and chronic dialysis were study endpoints adjudicated by the independent event adjudication committee.

Figure Legends

Figure 1. Effects of canagliflozin compared with placebo on the risk of **(A)** any renal-related AEs, **(B)** renal-related serious AEs, and **(C)** AKI.*

AE, adverse event; AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*On-treatment analyses were performed from baseline until 30 days after the last date of study drug. Hazard ratios were estimated using Cox models that were stratified by screening eGFR subgroup.

Figure 2. Effects of canagliflozin compared with placebo on the risk of renal-related AEs according to preferred term, as reported by investigators.

AE, adverse event; HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

*On-treatment analyses were performed from baseline until 30 days after the last date of study drug. Hazard ratios were estimated using Cox models that were stratified by screening eGFR subgroup.

[†]Other category includes anuria, azotemia, blood urea increase, nephropathy toxic, oliguria, and renal failure.

Figure 3. Risk of renal-related AEs with canagliflozin compared with placebo in participant subgroups defined by characteristics at baseline.

AE, adverse event; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration ratio; UACR, urinary albumin:creatinine ratio.

*On-treatment analyses are performed from baseline until 30 days after the last date of study drug. Cox models were stratified by screening eGFR subgroup.

[†]Race was reported by the patients. The designation "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Figure 4. Outcomes after AKI events.

AKI, acute kidney injury; eGFR, estimate glomerular filtration rate.

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Table S1. MedDRA Terminology Used to Summarize Renal-related Adverse Events. Terms in bold Signify Events That Were Reported in the CREDENCE Trial

Acute kidney injury
Acute phosphate nephropathy
Acute prerenal failure
Anuria
Azotemia
Blood creatinine increased
Blood urea increased
Continuous hemodiafiltration
Dialysis
Glomerular filtration rate decreased
Hemodialysis
Hemofiltration
Hypercreatininemia
Hyponatriuria
Neonatal anuria

Nephritis
Nephropathy toxic
Oliguria
Peritoneal dialysis
Prerenal failure
Renal failure
Renal failure acute
Renal failure neonatal
Renal impairment
Renal impairment neonatal

Table S2. Effects of Canagliflozin Compared With Placebo on the Risk of Renal-related AEs According to Preferred Term After Excluding Renal-related AEs Confirmed as a Study Endpoint.

	Participants with an event (%)		**Participants with an event per 1000 patient-years**	
	Canagliflozin	Placebo	Canagliflozin	Placebo
Any renal-related AE	232 (10.5)	283 (12.9)	45.7	57.7
AKI	84 (3.8)	94 (4.3)	16.6	19.2
Blood creatinine increased	75 (3.4)	82 (3.7)	14.8	16.7
eGFR decreased	42 (1.9)	48 (2.2)	8.3	9.8
Renal impairment	47 (2.1)	62 (12.6)	9.3	12.6

Table S3. Reasons of Serious Renal-related Adverse Events

	Total	Canagliflozin	Placebo
Renal-related serious adverse events (N)	143	61	82
Reasons			
Required hospitalization, N (%)	87 (60.8)	35 (57.4)	52 (63.4)
Prolong hospitalization, N (%)	32 (22.4)	17 (27.9)	15 (18.3)
Persistence or significant disability, N (%)	9 (6.3)	2 (3.3)	7 (8.5)
Life threatening, N (%)	31 (21.7)	12 (19.7)	19 (23.2)
Death, N (%)	14 (9.8)	6 (9.8)	8 (9.8)
Unknown, N (%)	2 (1.4)	0 (0)	2 (2.4)

Table S4. Predictors of Renal-related AEs and AKI in the Placebo Group

	Renal related AEs				AKI			
	Univariable		Multivariable		Univariable		Multivariable	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age (per 10 years)	0.87	0.78, 0.97	0.88	0.77, 0.99	1.15	0.92, 1.44	1.13	0.87, 1.46
Men (vs women)	1.19	0.96, 1.48	1.36	1.07, 1.73	1.13	0.74, 1.74	1.33	0.83, 2.13
Race								
White	0.64	0.52, 0.78	0.65	0.46, 0.92	0.62	0.41, 0.92	0.51	0.26, 1.01
Black or African American	1.91	1.33, 2.74	1.49	0.93, 2.38	2.55	1.36, 4.78	1.37	0.57, 3.28
Asian	1.23	0.97, 1.55	0.82	0.57, 1.20	1.11	0.69, 1.78	1.99	0.47, 2.11
Current smoker (vs nonsmoker)	0.91	0.67, 1.23	0.98	0.72, 1.33	1.20	0.69, 2.09	1.38	0.78, 2.42
History of hypertension	1.05	0.59, 1.86	0.70	0.39, 1.26	3.24	0.45, 23.2	1.86	0.25, 13.54
History of heart failure	1.14	0.87, 1.48	1.19	0.89, 1.60	1.61	1.00, 2.59	1.86	1.11, 3.14
Duration of diabetes (years)	1.00	0.99, 1.02	1.00	0.98, 1.02	1.02	0.99, 1.04	1.01	0.98, 1.03
History of cardiovascular disease	0.96	0.79, 1.17	0.91	0.73, 1.12	1.06	0.71, 1.58	0.88	0.57, 1.34
Body mass index (kg/m^2)	1.00	0.98, 1.02	1.00	0.98, 1.02	1.07	1.04, 1.10	1.07	1.04, 1.10

Systolic blood pressure (per 10 mmHg)	1.15	1.07, 1.22	1.11	1.03, 1.20	1.17	1.03, 1.33	1.14	0.98, 1.31
Diastolic blood pressure (per 10 mmHg)	1.09	0.98, 1.22	0.93	0.82, 1.06	0.88	0.72, 1.09	0.84	0.66, 1.07
HbA1c (per 1 %)	1.01	0.94, 1.09	1.01	0.94, 1.10	0.94	0.81, 1.10	0.97	0.82, 1.16
eGFR (per 5 mL/min/1.73 m^2)	0.84	0.82, 0.87	0.85	0.82, 0.88	0.85	0.79, 0,90	0.87	0.81, 0.93
UACR (per 1,000 mg/g)	1.40	1.34, 1.47	1.41	1.33, 1.49	1.22	1.09, 1.38	1.23	1.07, 1.41
HDL cholesterol (mmol/l)	0.97	0.72, 1.31	1.14	0.83, 1.57	0.81	0.44, 1.50	1.09	0.56, 2.11
LDL cholesterol (mmol/l)	1.07	0.97, 1.18	1.05	0.95, 1.17	0.83	0.67, 1.02	0.88	0.70, 1.12
Triglycerides (mmol/l)	1.03	0.97, 1.08	1.01	0.95, 1.08	1.01	0.90, 1.13	1.00	0.88, 1.15
Drug therapy								
Insulin	1.50	1.20, 1.87	1.16	0.91, 1.47	2.39	1.45, 3.94	1.71	1.00, 2.92
Diuretic	1.59	1.30, 1.94	1.34	1.08, 1.67	1.67	1.12, 2.50	1.71	1.00, 2.92

AE, adverse event; AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

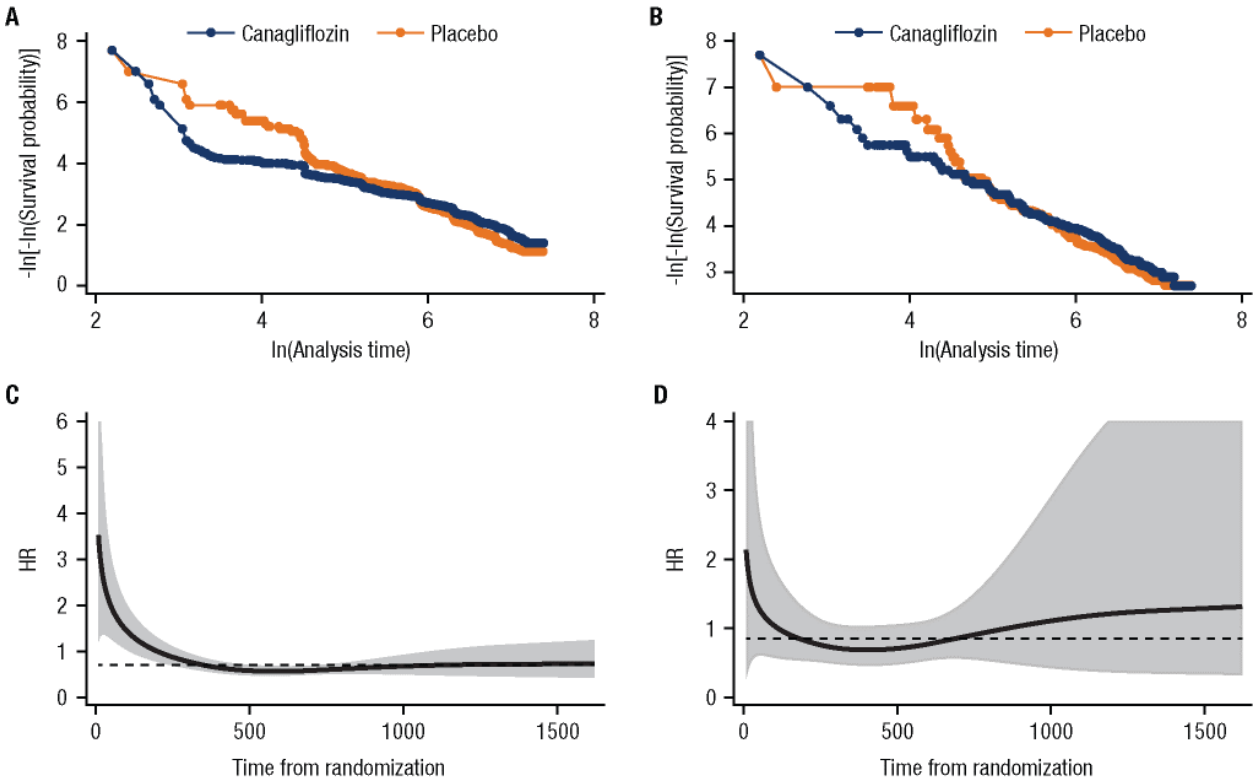
Table S5. Recovery of kidney function by day 90 and dialysis or death outcomes within 90 Days after AKI events

	Total	Canagliflozin	Placebo
<-20% (no recovery)	26 (26.8)	9 (20.9)	17 (40.5)
-20 to <0% (partial recovery)	24 (28.9)	12 (27.9)	12 (28.6)
≥0% (full recovery)	35 (44.3)	22 (51.2)	13 (31.0)
AKI event requiring dialysis, n (%)	28 (15.2)	11 (12.8)	17 (17.3)
AKI event requiring chronic dialysis, n (%)	7 (3.8)	3 (3.5)	4 (4.1)
Death within 90 days after AKI, n (%)	24 (13.0)	9 (10.5)	15 (15.3)

eGFR data for recovery in kidney function by day 90 was available for 85 subjects.

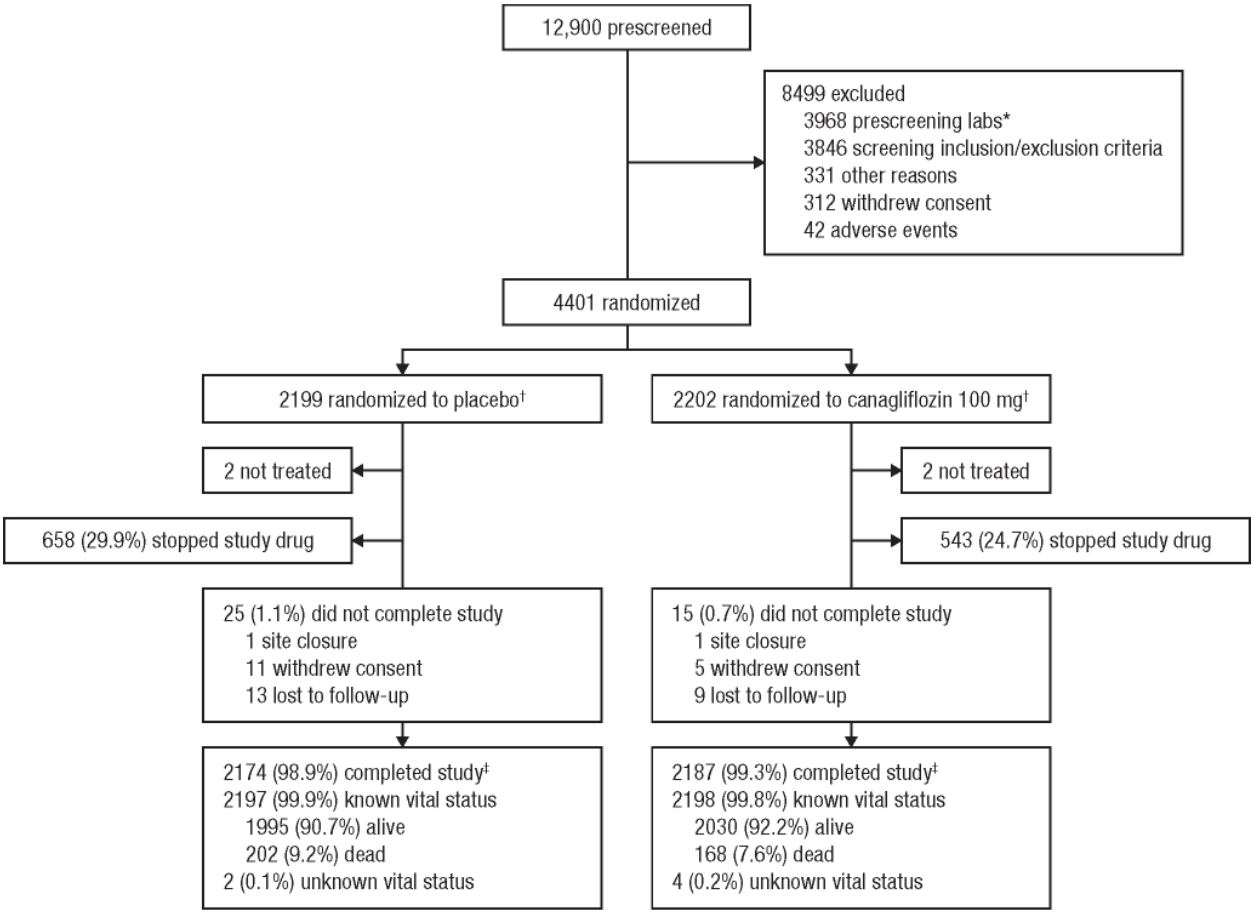
AKI, acute kidney.

Fig S1. Log cumulative hazard function for renal-related AEs (A) and for AKI (B); time dependent hazard ratio according piece-wise Royston and Parmar model for renal-related AEs (C) and for AKI (D).



AE, adverse event; AKI, acute kidney injury.

Fig S2. Study flow diagram.



*Includes failed prescreening of estimated glomerular filtration rate and/or proteinuria/albuminuria.

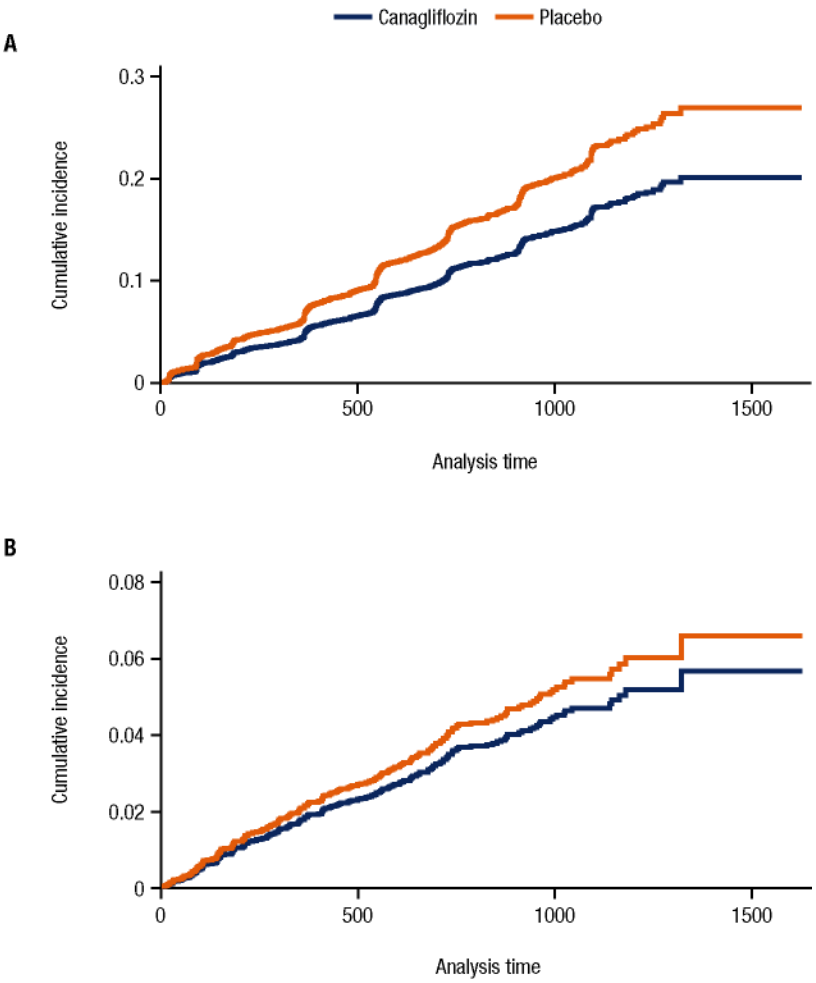
†All randomized participants were in the intent-to-treat population; participants who did not receive study drug were excluded from the on-treatment and on-study analysis sets.

‡Defined as having been followed until a time point between the announcement of the end of study and the end of study, or if the subject had died prior.

From *The New England Journal of Medicine*, V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H.

Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, “Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy,” 380, 2295-2306.

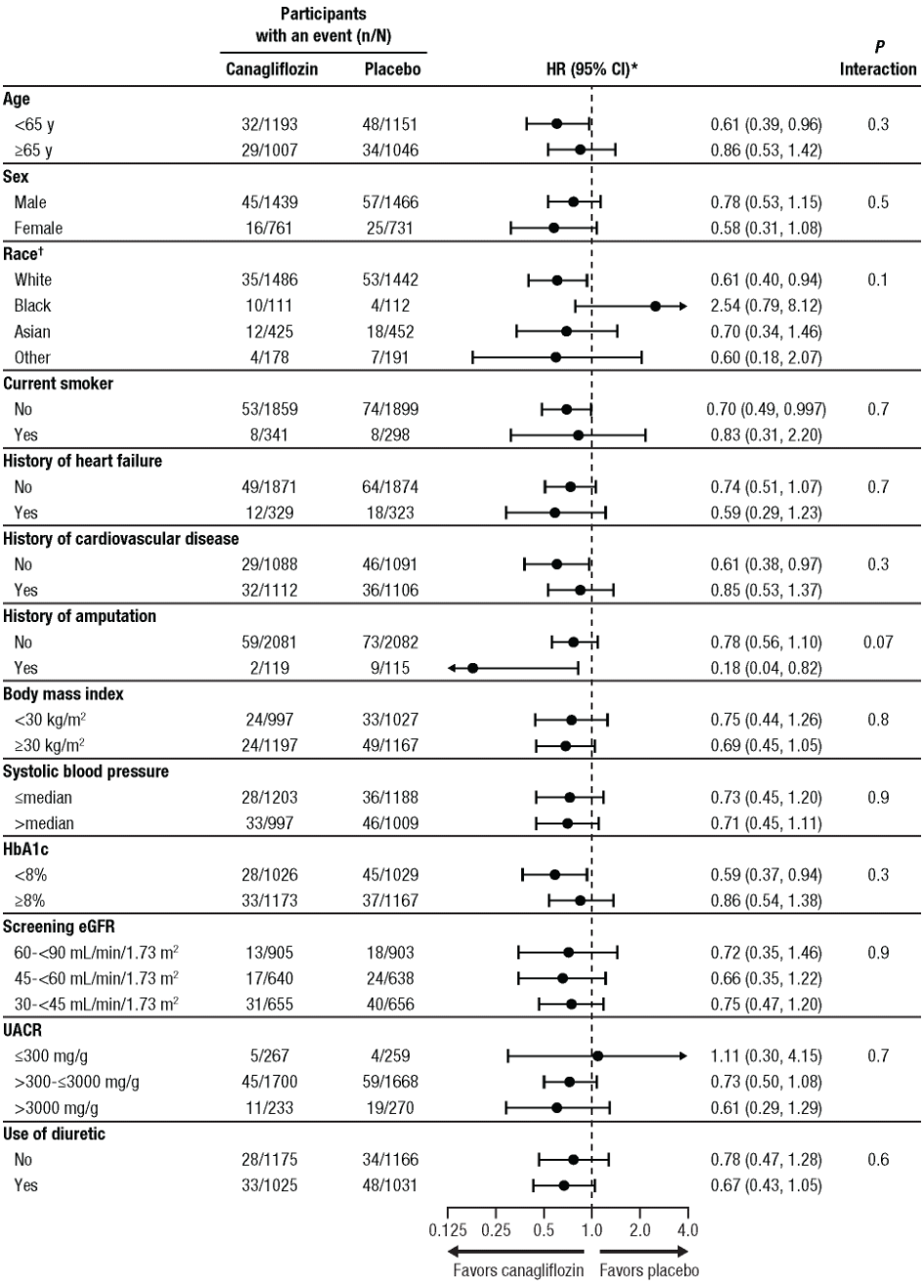
Fig S3. Effects of canagliflozin versus placebo on (A) renal-related AEs and (B) AKI (intention-to-treat).*



AE, adverse event; AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval.

*Intention-to-treat analyses were performed from baseline until the last study visit. Hazard ratios were estimated using Cox models which were stratified by screening eGFR subgroup.

Fig S4. Risk of renal-related serious AEs with canagliflozin compared with placebo in participants defined by characteristics at baseline.

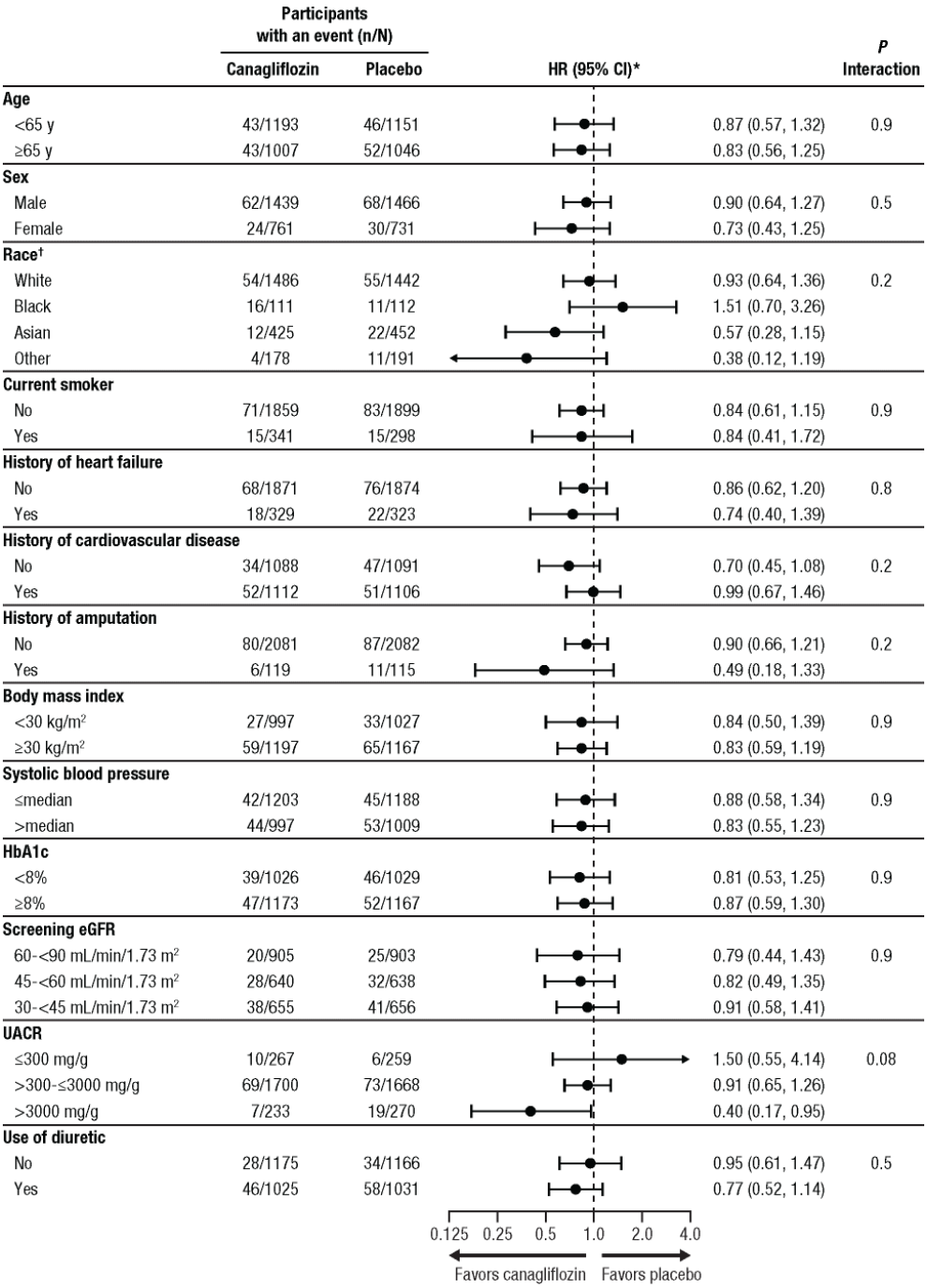


AE, adverse event; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration ratio; UACR, urinary albumin:creatinine ratio.

*On-treatment analyses are performed from baseline until 30 days after the last date of study drug. Cox models were stratified by screening eGFR subgroup.

†Race was reported by the patients. The designation “Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Fig S5. Risk of AKI with canagliflozin compared with placebo in participant subgroups defined by characteristics at baseline.



AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration ratio; UACR, urinary albumin:creatinine ratio.

*On-treatment analyses are performed from baseline until 30 days after the last date of study drug. Cox models were stratified by screening eGFR subgroup.

†Race was reported by the patients. The designation “Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.