Canagliflozin Reduces Kidney-Related Adverse Events in Type 2 Diabetes and CKD

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Canagliflozin and Kidney-Related Adverse Events in Type 2 Diabetes and CKD: Findings From the Randomized CREDENCE Trial

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Rationale & 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 (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial. This analysis of CREDENCE trial data examines the effect of canagliflozin on the incidence of kidney-related adverse events (AEs).

Study Design: A randomized, double-blind, placebo-controlled, multicenter international trial.

Setting & Participants: 4,401 trial participants with T2DM, CKD, and urinary albumin-creatinine ratio >300-5,000 mg/g.

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

Outcomes: Rates of kidney-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/1.73 m^2).

Results: Canagliflozin was associated with a reduction in the overall incidence rate of kidney-related AEs (60.2 vs 84.0 per 1,000 patient-years; hazard ratio [HR], 0.71 [95% CI, 0.61-0.82]; $P < 0.001$), with consistent results for serious kidney-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 kidney-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/1.73 m^2, respectively; $P = 0.3$ for interaction), with similar results for AKI ($P = 0.9$ for interaction). 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: Kidney-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 for all participants.

Conclusions: Compared with placebo, canagliflozin was associated with a reduced incidence of serious and nonserious kidney-related AEs in patients with T2DM and CKD. These results highlight the safety of canagliflozin with regard to adverse kidney-related AEs.

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

Visual Abstract online

Complete author and article information provided before references.

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Sodium/glucose cotransporter 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) decrease over time. Although the cardiovascular safety of SGLT2 inhibitors has been well established, the risks for acute declines in kidney function are still debated, with the labels of SGLT2 inhibitors including warnings regarding 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 of 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] Because diabetes and reduced kidney function are independent risk

PLAIN-LANGUAGE SUMMARY

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 trial population and in subgroups based on kidney function. Results show that canagliflozin is safe for the kidneys, with fewer kidney-related safety events, even among patients with more severe kidney disease at the start of the trial. Among patients in whom acute kidney injury developed during the trial, fewer in the canagliflozin group died or required dialysis compared with the 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.

factors for AKI,[7] it is important to understand the effects of canagliflozin on kidney safety outcomes, including AKI, in the CREDENCE population 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 committee at each site. All participants provided written informed consent. In brief, CREDENCE participants were ≥30 years of age with a diagnosis of T2DM, glycated hemoglobin A_{1c} concentration 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 5,000 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 inhibitor or angiotensin receptor blocker for ≥4 weeks before randomization. Exclusion criteria included nondiabetic kidney disease, type 1 diabetes mellitus, 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-month recruitment period and 33-month follow-up period.[5]

Randomization and Study Treatment

Eligible participants were randomly assigned to receive 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 present analysis was the first kidney-related adverse event (AE). Kidney-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* 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 kidney-related serious AE was an additional end point for the present study. The first AKI was a prespecified AE of interest and a third outcome in this study. Other kidney-related AEs as described above were not prespecified AEs of interest, and none of these were adjudicated by a separate end-point committee. *Medical Dictionary for Regulatory Activities* terminology used to summarize the kidney-related AEs is shown in Table S1. We also examined kidney-related serious AEs, which were defined as kidney-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 with placebo on a 40% eGFR decrease end point that occurred between 2 consecutive study visits. We choose a 40% eGFR decrease because it is equivalent to a 50% (or 1.5 times) increase in serum creatinine level from baseline, which is consistent with the KDIGO (Kidney Disease: Improving Global Outcomes) 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 estimate before AKI to the estimate 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 less than −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 end points for the study as AEs. These events were submitted for adjudication by an independent event adjudication committee. Several of the terms used to report potential renal end points were also included in the preferred term listing used to identify kidney-related AEs (eg, blood creatinine level increased and glomerular filtration rate decreased). To account for this potential overreporting of kidney-related

safety events, we performed an additional analysis excluding kidney-related AEs that were confirmed to be primary study end points (ie, sustained doubling of serum creatinine level, kidney failure requiring kidney replacement therapy, or death from kidney disease).

Statistical Analysis

Analyses were performed using the on-treatment data set, which included all events through 30 days of the last dose of study medication in accordance with the statistical analysis plan. We fitted cause-specific hazard models (using Cox proportional hazards regression) to assess treatment effects of canagliflozin versus placebo on the first relevant AE. Cox models were stratified by eGFR categories defined at the screening visit. Subgroup analyses by patient demographic characteristics, 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 S1). The log–cumulative hazard function revealed some degree of nonparallelism 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 kidney-related AE end point. 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 HR of the Cox model, and we therefore present the HR of the Cox models for all outcomes (Fig S1). 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 kidney-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 kidney-related safety outcomes. Factors associated with the occurrence of AKI were collected during the trial and summarized by treatment group. In addition, dialysis and death outcomes 30 days after AKI were collected and summarized by treatment group. In a sensitivity analysis, we summarized these events 90 days after AKI because, according to KDIGO nomenclature, AKI can be defined as present for as long as 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 with Stata software, version 15 (StataCorp).

Results

Effects of Canagliflozin Compared With Placebo on Kidney-Related AEs

The CREDENCE trial randomized 4,401 participants, of whom 4,397 received ≥1 dose of randomized treatment: 2,197 assigned to placebo and 2,200 assigned to canagliflozin (Fig S2). During a mean follow-up of 2.1 ± 0.9 (standard deviation) years, kidney-related AEs were recorded in 678 participants: 388 (17.7%; event rate, 8.4 per 100 patient-years) in the placebo group and 290 (13.2%; event rate, 6.0 per 100 patient-years) in the canagliflozin group (HR, 0.71 [95% CI, 0.61-0.82]; $P < 0.001$). However, the impact of canagliflozin on kidney-related AEs was not constant during the follow-up period. During the first months after randomization, a report of a kidney-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 kidney-related AEs became 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 sizes for the kidney-related AE and AKI end points were virtually identical (HRs of 0.72 [95% CI, 0.60-0.83] and 0.86 [95% CI, 0.64-1.14], respectively).

Kidney-related AEs comprise a range of different investigator-reported AEs. The effects of canagliflozin versus placebo were consistent for the different components of the composite kidney-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 kidney-related AEs during canagliflozin treatment. As shown in Fig 3, there was no evidence that the effect of canagliflozin on kidney-related AEs varied by any baseline participant characteristic (all $P > 0.2$ for homogeneity). However, an exception was baseline UACR, for which 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 end points for the trial (Table S2).

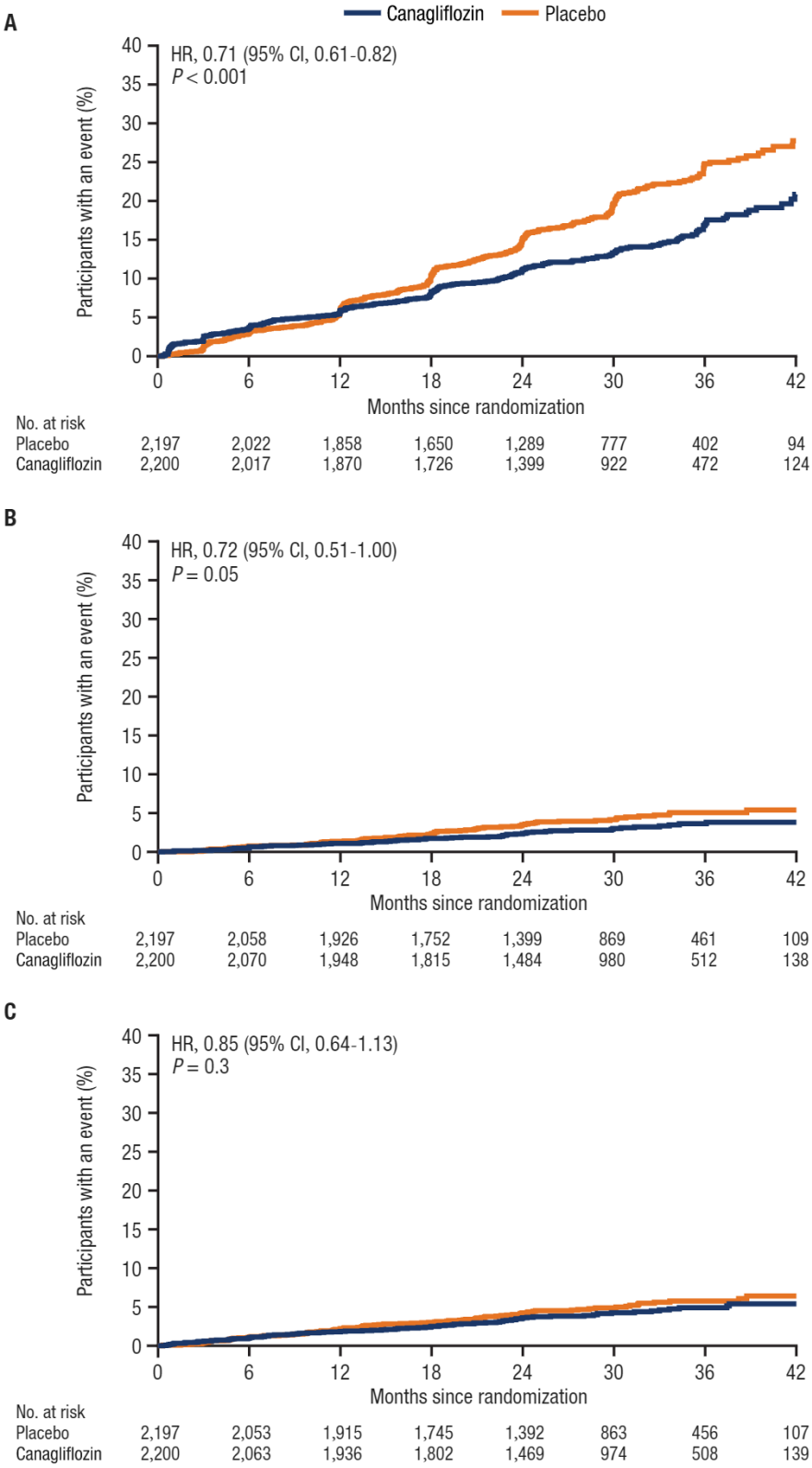

Figure 1. Effects of canagliflozin compared with placebo on the risk of (A) any kidney-related adverse events (AEs), (B) kidney-related serious AEs, and (C) acute kidney injury (AKI). On-treatment analyses were performed from baseline until 30 days after the last date of study drug. Hazard ratios (HRs) were estimated using Cox models that were stratified by screening estimated glomerular filtration rate (eGFR) subgroup.

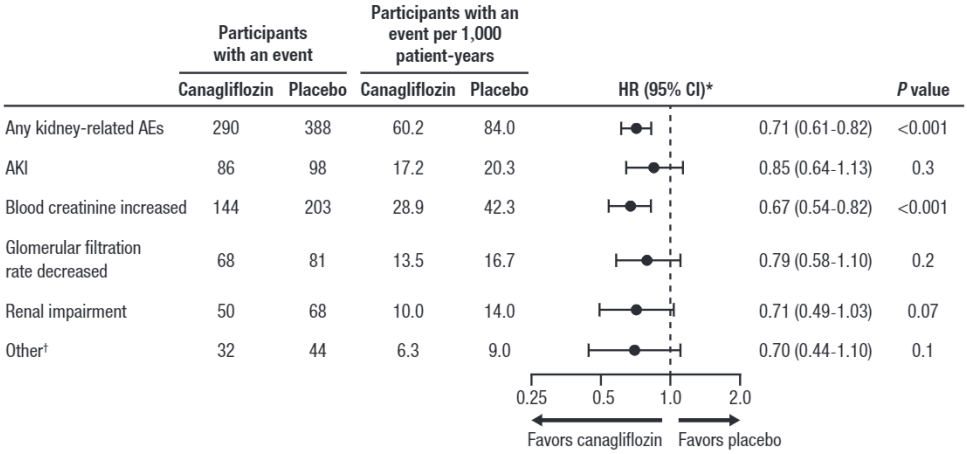

Figure 2. Effects of canagliflozin compared with placebo on the risk of kidney-related adverse events (AEs) according to preferred term, as reported by investigators. *On-treatment analyses were performed from baseline until 30 days after the last date of study drug. Hazard ratios (HRs) were estimated using Cox models that were stratified by screening estimated glomerular filtration rate (eGFR) subgroup. †"Other" category includes anuria, azotemia, blood urea increase, nephropathy toxic, oliguria, and renal failure. Abbreviation: AKI, acute kidney injury.

Effect of Canagliflozin on Kidney-Related Serious AEs and AKI

Overall, kidney-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 kidney-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 C). 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 = 0.3). Effects of canagliflozin on kidney-related serious AEs and AKI were consistent across participant subgroups, with a trend for a larger benefit of canagliflozin in higher UACR subgroups (Figs S4 and S5). The majority of kidney-related serious AEs were AEs requiring hospitalizations (Table S3).

A 40% eGFR decrease between 2 consecutive 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 Kidney-Related AEs and AKI

Participants who experienced a kidney-related AE were younger; more likely to be of Black race or African American; had a longer duration of diabetes; had a lower eGFR; had higher systolic blood pressure, UACR, triglyceride level, and total cholesterol level; and were more likely to be treated with insulin or diuretic agents (Table 1). Generally similar differences in baseline characteristics were observed when the canagliflozin and placebo groups 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 kidney-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. The main factors associated with AKI in the canagliflozin and placebo groups were dehydration/hypovolemia and septic shock (Table 3). In approximately half of patients in both groups, study medication was continued after an AKI event (Table 3). Study medication was stopped temporarily or

	Participants with an event (n/N)			*P* for interaction
	Canagliflozin	Placebo	HR (95% CI)*	
Age				
<65 y	171/1,193	221/1,151	0.70 (0.57-0.85)	0.9
≥65 y	119/1,007	167/1,046	0.71 (0.56-0.90)	
Sex				
Male	197/1,439	273/1,466	0.70 (0.58-0.84)	0.8
Female	93/761	115/731	0.72 (0.55-0.95)	
Race†				
White	180/1,486	220/1,442	0.75 (0.62-0.92)	0.3
Black or African American	79/111	32/112	1.02 (0.63-1.67)	
Asian	56/425	93/452	0.60 (0.43-0.84)	
Other	22/178	43/191	0.52 (0.31-0.88)	
Current smoker				
No	248/1,859	340/1,899	0.70 (0.59-0.82)	0.7
Yes	42/341	48/298	0.74 (0.49-1.12)	
History of heart failure				
No	244/1,871	323/1,874	0.72 (0.61-0.85)	0.6
Yes	46/329	54/323	0.63 (0.43-0.92)	
History of cardiovascular disease				
No	144/1,088	195/1,091	0.69 (0.55-0.85)	0.8
Yes	146/1,112	193/1,106	0.72 (0.58-0.90)	
History of amputation				
No	272/2,081	363/2,082	0.71 (0.61-0.83)	0.7
Yes	18/119	25/115	0.60 (0.33-1.11)	
Body mass index				
<30 kg/m²	121/997	187/1,027	0.64 (0.51-0.81)	0.3
≥30 kg/m²	168/1,197	201/1,167	0.76 (0.62-0.94)	
Systolic blood pressure				
≤median	140/1,203	174/1,188	0.75 (0.60-0.94)	0.5
>median	150/997	214/1,009	0.68 (0.55-0.83)	
HbA_{1c}				
<8%	133/1,026	178/1,029	0.71 (0.57-0.89)	0.9
≥8%	157/1,173	210/1,167	0.70 (0.57-0.87)	
Screening eGFR				
60-<90 mL/min/1.73 m²	78/905	94/903	0.81 (0.60-1.09)	0.3
45-<60 mL/min/1.73 m²	77/640	117/638	0.60 (0.45-0.79)	
30-<45 mL/min/1.73 m²	135/655	177/656	0.73 (0.58-0.91)	
UACR				
≤300 mg/g	27/267	18/259	1.38 (0.76-2.50)	0.008
>300-≤3,000 mg/g	205/1,700	261/1,668	0.75 (0.62-0.90)	
>3,000 mg/g	58/233	109/270	0.49 (0.35-0.67)	
Use of diuretic				
No	122/1,175	165/1,166	0.75 (0.62-0.90)	0.8
Yes	168/1,025	223/1,031	0.49 (0.35-0.67)	

Figure 3. Risk of kidney-related adverse events (AEs) with canagliflozin compared with placebo in participant subgroups defined by characteristics at baseline. *On-treatment analyses are performed from baseline until 30 days after the last date of study drug. Cox models were stratified by screening estimated glomerular filtration rate (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. Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}; HR, hazard ratio; UACR, urinary albumin-creatinine ratio.

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 in the canagliflozin group and 4 in the placebo group; P = 0.03). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were used in 134 patients before the AKI event. These agents were discontinued in 62 patients within 30 days after the AKI event (28 in the canagliflozin group and 34 in the placebo group). In addition, 33 patients discontinued these agents within 30 days before the AKI event as a result of other events such as infections or planned hospitalizations (Table 3). Diuretic

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

	Total			Canagliflozin			Placebo		
Characteristic	**Yes**	**No**	***P***	**Yes**	**No**	***P***	**Yes**	**No**	***P***
No. of participants	678	3,719	–	290	1,910	–	388	1,809	–
Age, y	62 ± 10	63 ± 9	<0.001	62 ± 10	63 ± 9	0.005	62 ± 10	63 ± 9	0.02
Male sex	470 (69%)	2,435 (65%)	0.05	197 (68%)	1,242 (65%)	0.3	273 (70%)	1,193 (66%)	0.09
Race[a]									
White	400 (59%)	2,528 (68%)	<0.001	180 (62%)	2,528 (68%)	0.03	220 (57%)	1,222 (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%)	0.2	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	90 (13%)	549 (15%)	0.3	42 (14%)	299 (16%)	0.6	48 (12%)	250 (14%)	0.5
History of hypertension	662 (98%)	3,594 (97%)	0.2	286 (99%)	1,843 (96%)	0.06	376 (97%)	1,751 (97%)	0.9
History of heart failure	111 (16%)	541 (15%)	0.2	46 (16%)	283 (15%)	0.6	65 (17%)	258 (14%)	0.2
Duration of diabetes, y	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 CVD	339 (50%)	1,879 (51%)	0.8	146 (50%)	966 (51%)	0.9	193 (50%)	913 (50%)	0.8
History of amputation	43 (6%)	191 (5%)	0.2	18 (6%)	101 (5%)	0.5	25 (6%)	90 (5%)	0.2
Body mass index, kg/m^2	32 ± 7	31 ± 6	0.1	32 ± 7	31 ± 6	0.02	31 ± 9	31 ± 6	0.9
Systolic BP, mm Hg	142 ± 17	140 ± 15	<0.001	141 ± 17	140 ± 15	0.05	143 ± 16	140 ± 15	<0.001
Diastolic BP, mm Hg	79 ± 10	78 ± 9	0.3	78 ± 10	78 ± 9	0.8	79 ± 10	78 ± 9	0.1
HbA_{1c}, %	8.2 ± 1.3	8.3 ± 1.3	0.5	8.2 ± 1.3	8.3 ± 1.3	0.5	8.2 ± 1.3	8.3 ± 1.3	0.8
eGFR, 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, mg/g	1,642 [708-2,971]	843 [444-1,641]	<0.001	1,341 [614-2,675]	862 [447-1,681]	<0.001	1,716 [799-3,163]	819 [440-1,603]	<0.001
Total cholesterol, 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, mmol/L	1.1 ± 0.4	1.2 ± 0.3	0.7	1.1 ± 0.4	1.2 ± 0.3	0.5	1.2 ± 0.4	1.1 ± 0.3	0.9
LDL cholesterol, mmol/L	2.5 ± 1.2	2.5 ± 1.1	0.2	2.6 ± 1.3	2.5 ± 1.1	0.3	2.5 ± 1.1	2.5 ± 1.0	0.4
Triglycerides, 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									
Insulin	505 (74%)	2,377 (64%)	<0.001	226 (78%)	1,225 (64%)	<0.001	279 (72%)	1,152 (64%)	0.002
Diuretic	391 (58%)	1,665 (45%)	<0.001	168 (58%)	857 (45%)	<0.001	223 (57%)	808 (5%)	<0.001

Values for continuous variables given as mean ± standard deviation or median [interquartile range]; for categorical variables, as count (percentage). Abbreviations: AE, adverse event; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate, HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urinary albumin-creatinine ratio.
[a]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 Kidney-Related AEs and AKI in the Canagliflozin Group

	HR (95% CI) for Kidney-Related AEs		HR (95% CI) for AKI	
Predictor	Univariable	Multivariable	Univariable	Multivariable
Age (per 10 y)	0.84 (0.74-0.95)	0.77 (0.67-0.90)	0.99 (0.78-1.25)	0.87 (0.66-1.15)
Male sex	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 nonsmoker)	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[a]
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 y)	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 BP (per 10 mm Hg)	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 BP (per 10 mm Hg)	1.00 (0.88-1.13)	0.93 (0.81-1.07)	0.89 (0.71-1.11)	0.83 (0.64-1.07)
HbA_{1c} (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 1,000 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)

Abbreviations: AE, adverse event; AKI, acute kidney injury; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; UACR, urinary albumin-creatinine ratio.
[a]History of hypertension was not analyzed in the canagliflozin group because none of the participants in the canagliflozin group without a history of hypertension developed AKI.

treatment was initiated within 30 days before the AKI event in 14 patients (4 in the canagliflozin group and 10 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 receive 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), and a lack of recovery of kidney function was more frequently observed in the placebo group (35.4%) than in the canagliflozin group (18.4%; odds ratio, 0.46 [95% CI, 0.21-0.97]; P = 0.04).

The proportion of participants who required dialysis within 30 days after the AKI event was 16.3% in the placebo group, compared with 10.5% in the canagliflozin group (P = 0.3). The proportions of patients who died within 30 days after an AKI event were 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 kidney-related safety outcomes, including AKI, in patients at high risk 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 with 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, kidney-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 kidney-related safety outcomes was significantly lower in the canagliflozin group. Canagliflozin and other SGLT2 inhibitors cause an acute decrease in eGFR that is reversible after treatment discontinuation. Prior studies in patients with type 1 diabetes mellitus and T2DM have shown that the acute decrease in eGFR reflects a reduction in intraglomerular pressure and reflects the hemodynamic mechanism of action of this drug class.[8-10]

Table 3. Outcomes After AKI Events

Outcome	Total	Canagliflozin	Placebo
No. of AKI events	212	98	114
No. of participants with AKI events	184 (4.2%)	86 (4.1%)	98 (4.5%)
Predisposing factors associated with AKI[a]			
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	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[b]	56 (30.4%)	27 (31.4%)	29 (29.6%)
Drug action			
Drug interrupted	49 (26.6%)	25 (29.1%)	24 (24.5%)
Drug withdrawn	14 (7.6%)	6 (7.0%)	8 (8.2%)
Dose not changed	89 (48.4%)	42 (48.8%)	47 (48.0%)
Not applicable	30 (16.3%)	11 (12.8%)	19 (19.4%)
Unknown	2 (1.1%)	2 (2.3%)	0
Recovery of kidney function: ΔeGFR before vs 30 d after AKI[c]			
Less than −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	25 (13.6%)	9 (10.5%)	16 (16.3%)
Requiring maintenance dialysis	6 (3.3%)	2 (2.3%)	4 (4.1%)
Death ≤30 d after AKI	16 (8.7%)	6 (7.0%)	10 (10.2%)
RAAS inhibitor use			
Continued after AKI	72 (39.1%)	39 (45.3%)	33 (33.7%)
Discontinued ≤30 d after AKI	62 (33.7%)	28 (32.6%)	34 (34.7%)
Discontinued ≤30 d before AKI	33 (17.9%)	11 (12.8%)	22 (22.4%)
Discontinued >30 d before AKI	17 (9.2%)	8 (9.3%)	9 (9.2%)

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.
[a]Numbers do not add up because >1 predisposing factor could be reported per patient.
[b]Data available in 97 patients with serum creatinine level recorded ≤30 d after AKI event: 49 in the canagliflozin group and 48 in the placebo group.
[c]Includes, eg, antibiotic use (gentamycin/vancomycin), pneumonia, choledocholithiasis/acute pancreatitis, respiratory depression, chronic obstructive pulmonary disease.

AKI is defined in clinical practice guidelines by an increase in serum creatinine level that is similar to the increase in serum creatinine level 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 decrease in eGFR at initiation of these interventions from AKI. The higher frequency of kidney-related AEs and AKI during the early stage of the trial may be a reflection of investigator response to the acute decrease in eGFR. Additionally, the majority of the reported AKI events from clinical practice that led to warnings about increased risk of AKI occurred within 4 weeks after SGLT2 initiation and could also be a reflection of the acute decrease in eGFR.[4]

Although 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 provide evidence that, during prolonged treatment, canagliflozin decreases the risks of kidney-related serious AEs or AKI. We believe 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 transplant. Investigators were reminded of principles for the investigation and management of an acute decrease in eGFR consistent with National Institute for Health and Care Excellence guidelines,[12] including repeat eGFR assessment, identification and management of precipitating conditions, and the evaluation and management of hypotension or hypovolemia (including adjustment of blood pressure medications and/or diuretic agents). We believe 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.

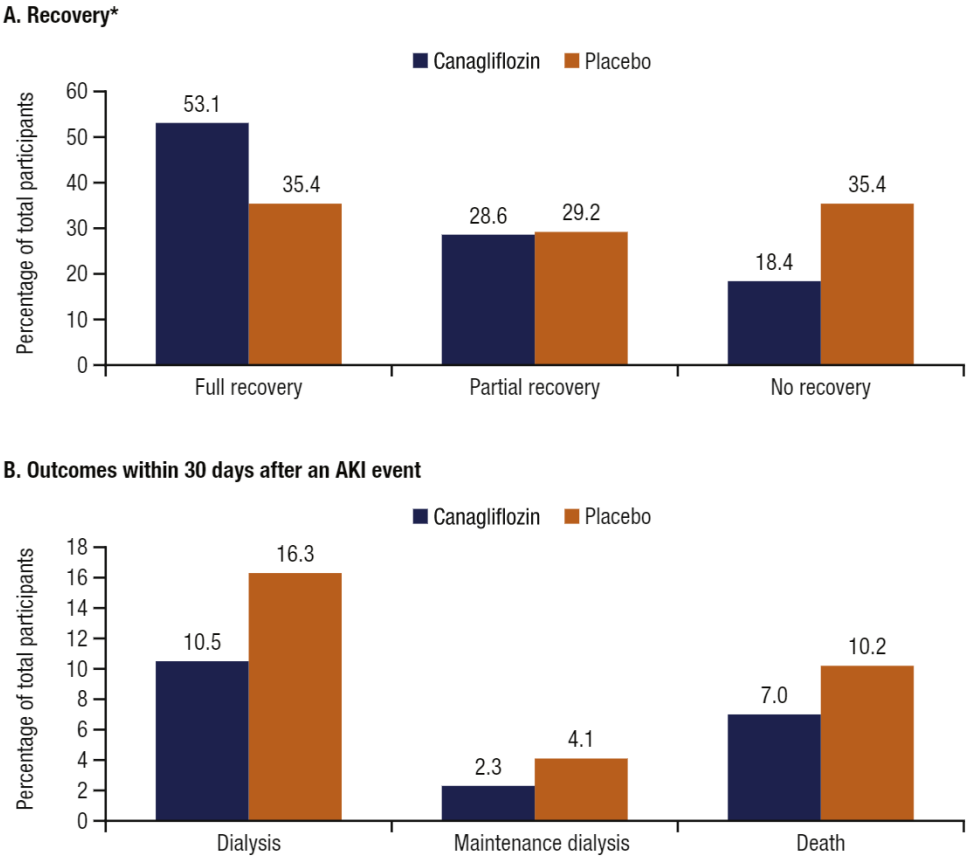

Figure 4. Outcomes after acute kidney injury (AKI) events. Full recovery was defined as change in estimated glomerular filtration rate (eGFR) from the pre-AKI level of ≥0%, partial recovery as −20% to <0% change, and no recovery as less than −20% change. Dialysis (defined as any dialysis recorded in the database) and maintenance dialysis were study end points adjudicated by the independent event adjudication committee. *Data were available in 97 participants in whom serum creatinine data were available within 30 days after the event: 49 in the canagliflozin group and 48 in the placebo group.

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 kidney 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 (KIM-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 were the most frequent predisposing factor is consistent with findings from the VA NEPHRON D trial in patients with T2DM and CKD.[18] Although not statistically significant, fewer patients required dialysis or died in the canagliflozin group compared with 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 kidney damage, which results in better outcomes. This is analogous to findings from the VA NEPHRON D trial, in which dual RAAS blockade led to a higher incidence of AKI but a lower rate of subsequent kidney and mortality outcomes, suggesting that AKI during dual RAAS treatment is mainly hemodynamically mediated.[18]

Effects of canagliflozin on kidney-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 because 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 kidney-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 greater 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 present findings should be interpreted in the context of the limitations of this analysis. First, kidney-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 end point of a 40% eGFR decrease between 2 consecutive study visits, supporting the validity of the results. Second, biomarkers of AKI and structural tubular damage, such as KIM-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. Third, creatinine data within 30 days after an AKI event were not available in all participants, leading to potential bias. In addition, recovery from AKI was defined in a subset of patients and defined by postrandomization characteristics that were influenced by canagliflozin itself, which may bias the reported odds ratio for recovery from AKI. However, because AKI was less frequently reported in the canagliflozin group than in the placebo group, this has likely led to an underestimation of the effect of canagliflozin on recovery from AKI.

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

Supplementary Material

Supplementary File (PDF)

Figure S1: Log-cumulative hazard function and time-dependent HR according to piece-wise Royston and Parmar model for kidney-related AEs and AKI.

Figure S2: Study flow diagram.

Figure S3: Effects of canagliflozin versus placebo on kidney-related AEs and AKI (intention-to-treat analysis).

Figure S4: Risk of kidney-related serious AEs with canagliflozin compared with placebo in participant groups defined by baseline characteristics.

Figure S5: Risk of AKI with canagliflozin versus placebo in participant subgroups defined by characteristics at baseline.

Table S1: *Medical Dictionary for Regulatory Activities* terminology used to summarize kidney-related AEs.

Table S2: Effects of canagliflozin versus placebo on the risk of kidney-related AEs according to preferred term after excluding kidney-related AEs confirmed as a study end point.

Table S3: Reasons for serious kidney-related AEs.

Table S4: Predictors of kidney-related AEs and AKI in the placebo group.

Table S5: Outcomes within 90 days after AKI events.

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Data Sharing: Data from this study will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu) when 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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Canagliflozin and Kidney-Related Adverse Events in Type 2 Diabetes and CKD: Findings From the Randomized CREDENCE Trial

Design

CREDENCE
Multicenter, double-blind, placebo-controlled, randomized trial

690 centers
34 countries

Population

4,401 people with type 2 diabetes, CKD, and UACR >300-5,000 mg/g

Results

Canagliflozin reduces the risk of kidney-related adverse events

	Participants with an event per 1,000 patient-years		HR (95% CI)	*P* value
	Canagliflozin	Placebo		
Any kidney-related AEs	60.2	84.0	0.71 (0.61-0.82)	<0.001
AKI	17.2	20.3	0.85 (0.64-1.13)	0.3
Blood creatinine increased	28.9	42.3	0.67 (0.54-0.82)	<0.001
Glomerular filtration rate decreased	13.5	16.7	0.79 (0.58-1.10)	0.2
Renal impairment	10.0	14.0	0.71 (0.49-1.03)	0.07
Other	6.3	9.0	0.70 (0.44-1.10)	0.1

CONCLUSION: Canagliflozin decreased the incidence of kidney-related adverse events, highlighting the renal safety of canagliflozin in patients with type 2 diabetes and CKD.

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