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Published in:
Clinical journal of the American Society of Nephrology : CJASN

DOI:
10.2215/CJN.0000000000000161

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Glycemic Control and Effects of Canagliflozin in Reducing Albuminuria and eGFR

A *Post Hoc* Analysis of the CREDENCE Trial

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Abstract

Background In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin improved kidney and cardiovascular outcomes and reduced the rate of estimated glomerular filtration decline (eGFR slope) in patients with type 2 diabetes and CKD. In other clinical trials of patients with CKD or heart failure, the protective effects of SGLT2 inhibitors on eGFR slope were greater in participants with versus participants without type 2 diabetes. This *post hoc* analysis of the CREDENCE trial assessed whether the effects of canagliflozin on eGFR slope varied according to patient subgroups by baseline glycated hemoglobin A1c (HbA1c).

Methods CREDENCE (ClinicalTrials.gov [NCT02065791]) was a randomized controlled trial in adults with type 2 diabetes with an HbA1c of 6.5%–12.0%, an eGFR of 30–90 ml/min per 1.73 m^2, and a urinary albumin-to-creatinine ratio of 300–5000 mg/g. Participants were randomly assigned to canagliflozin 100 mg once daily or placebo. We studied the effect of canagliflozin on eGFR slope using linear mixed-effects models.

Results The annual difference in total eGFR slope was 1.52 ml/min per 1.73 m^2 (95% confidence interval [CI], 1.11 to 1.93) slower in participants randomized to canagliflozin compared with placebo. The rate of eGFR decline was faster in those with poorer baseline glycemic control. The mean difference in total eGFR slope between canagliflozin and placebo was greater in participants with poorer baseline glycemic control (difference in eGFR slope of 0.39, 1.36, 2.60, 1.63 ml/min per 1.73 m^2 for HbA1c subgroups 6.5%–7.0%, 7.0%–8.0%, 8.0%–10.0%, 10.0%–12.0%, respectively; $P_{interaction} = 0.010$). The mean difference in change from baseline in urinary albumin-to-creatinine ratio between participants randomized to canagliflozin and placebo was smaller in patients with baseline HbA1c 6.5%–7.0% (−17% [95% CI, −28 to −5]) compared with those with an HbA1c of 7.0%–12% (−32% [95% CI, −40 to −28]; $P_{interaction} = 0.03$).

Conclusions The effect of canagliflozin on eGFR slope in patients with type 2 diabetes and CKD was more pronounced in patients with higher baseline HbA1c, partly because of the more rapid decline in kidney function in these individuals.

Clinical Trial registry name and registration number: Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE), NCT02065791

CJASN 18: 748–758, 2023. doi: https://doi.org/10.2215/CJN.0000000000000161

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce the risk of heart failure and slow progression of kidney function decline in patients with type 2 diabetes and CKD.[1–4] These beneficial effects seem to be unrelated to improvements in glycemic control and are likely mediated by reductions in glomerular hyperfiltration, along with multiple other direct cellular and metabolic effects. These glucose-independent effects, which are associated with long-term preservation of kidney function, may also explain why SGLT2 inhibitors reduced the risk of major kidney outcomes in patients with CKD, irrespective of disease etiology.[5–8]

Recent large clinical trials have assessed the effect of interventions on a composite outcome that usually includes well-established kidney end points, such as a sustained reduction in estimated glomerular filtration rate (eGFR), kidney failure, or death due to kidney failure.[1,2,9,10] Drug effects on clinical kidney end points are determined by the number of patients reaching these end points, that is, in clinical trials of

CKD progression, the patients with the fastest rate of progression. The rate of decline in kidney function (determined from the slope of eGFR over time) and change in albuminuria are established surrogate end points for kidney failure in clinical trials.[10–12] Assessing effects based on eGFR slope provides an estimate of the effect of the intervention in all patients, including both slow and fast progressors. Statistical power for subgroup analyses is, therefore, typically greater for eGFR slope compared with clinical end points.

Recent analyses of large kidney and cardiovascular outcome trials showed that the effects of SGLT2 inhibitors on eGFR slope are more pronounced in patients with type 2 diabetes compared with those without diabetes.[13–16] In addition, in patients with CKD without diabetes, the effect of SGLT2 inhibition on albuminuria is smaller compared with patients with type 2 diabetes,[17,18] suggesting that the degree of glycemic control may modify the effect of these agents on kidney surrogate end points. Whether the dependency of these effects on glycated hemoglobin A1c (HbA1c) can be detected in an exclusively type 2 diabetes population with varying degrees of glycemic control is unknown.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial assessed the effects of canagliflozin on outcomes in a type 2 diabetes population with CKD and albuminuria and showed significantly lower rates of kidney failure and cardiovascular events compared with placebo.[1] We performed a *post hoc* analysis of the CREDENCE trial to investigate whether baseline HbA1c modifies the effects of canagliflozin compared with placebo on eGFR slope and changes in urinary albumin-to-creatinine ratio (UACR).

Methods

Study Design and Participants

CREDENCE was a randomized, double-blinded, placebo-controlled, multicenter clinical trial; studies describing the trial design, baseline characteristics, and primary results have been previously published.[19] The trial was conducted at 690 sites in 34 countries from March 2014 through 2018. The CREDENCE trial was conducted according to the principles of the Declaration of Helsinki and was registered with ClinicalTrials.gov (NCT02065791). Ethics committees at all participating centers approved the protocol, and all participants provided informed consent.

Participants

Adults with type 2 diabetes and an HbA1c of 6.5%–12%, eGFR 30–90 ml/min per 1.73 m^2, and UACR 300–5000 mg/g were eligible for participation. All participants were required to be treated with a stable maximally tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks unless medically contraindicated. Key exclusion criteria included documented diagnosis of type 1 diabetes, treatment with immunosuppressive agents for kidney disease, and a history of dialysis or kidney transplantation. A complete list of inclusion and exclusion criteria and the trial protocol have been previously published.[19]

Procedures and Measurements

Eligible participants started with a 2-week single-blinded placebo run-in period to assess adherence to study medications. Participants who had received at least 80% of study medication were randomly assigned to canagliflozin 100 mg once daily or matching placebo. Randomization was stratified by eGFR (30 to <45 ml, 45 to <60 ml, or 60 to <90 ml/min per 1.73 m^2). We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration and incorporated a term for self-reported race (Black versus non-Black). Participants and all study personnel (except the Independent Data Monitoring Committee) were masked to treatment allocation. After randomization, in-person study visits were performed after 3 weeks, 3 and 6 months, and at 6-month intervals thereafter. At each follow-up visit, study personnel recorded vital signs; obtained blood and urine samples; and recorded information on potential study end points, adverse events, concomitant therapies, and study drug adherence. Clinical chemistry parameters, including HbA1c, urinary albumin, and creatinine, were measured at baseline and at 6-month intervals thereafter, HbA1c also after 13 weeks, and serum creatinine additionally after 3 and 13 weeks, in a central laboratory.

End Points

The primary composite end point for CREDENCE was time to doubling of serum creatinine (confirmed by a second serum creatinine measurement after at least 28 days), onset of kidney failure (defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 ml/min per 1.73 m^2 confirmed by a second measurement after at least 28 days), or death from a kidney or cardiovascular cause. Secondary end points included (*1*) time to a composite kidney end point of doubling of creatinine, kidney failure, or death from kidney disease; (*2*) a composite cardiovascular end point defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; and (*3*) hospitalization for heart failure or cardiovascular death. The rate of kidney function decline (eGFR slope) and albuminuria was a prespecified exploratory efficacy end point. All primary and secondary efficacy end points were adjudicated by a masked, independent events adjudication committee.

Statistical Analyses

Participant characteristics were summarized by baseline HbA1c (<7; 7%–8%; 8%–10%; >10%). Continuous variables are reported as mean (SD) or as median (interquartile range [IQR]) and categorical variables as *n* (%).

The effect of canagliflozin on the mean on-treatment eGFR slope was analyzed using a two-slope mixed-effects linear spline model with a knot at 21 days and correlated random intercepts and slopes for each participant over time (unstructured covariance matrix). eGFR measurements after treatment discontinuation were excluded from slope analyses to avoid bias in the eGFR slope estimates resulting from hemodynamic changes in eGFR after canagliflozin discontinuation. For the overall population, the model included fixed effects for treatment, randomization stratification factors (eGFR at

screening), a two-slope linear spline in follow-up time as a continuous variable, and interactions for treatment with the two-slope linear spline terms.

The effect of canagliflozin compared with placebo on the rate of eGFR decline was also estimated in subgroups by baseline HbA1c, UACR, and eGFR at screening. In these analyses, all possible two-way and three-way interaction terms between the randomized treatment, the subgroup indicator, and the two-slope linear spline in follow-up time were added to account for differences between subgroups in the effect of the treatment on the mean eGFR trajectory. We removed the stratification factor in subgroups by baseline eGFR to avoid redundant terms in our model. The acute change in eGFR was calculated as the mean change from baseline at week 3. The chronic eGFR slope was calculated as the mean rate of change in eGFR from week 3 until the last on-treatment visit and was expressed as change per year.

The distribution among individuals in the acute change in eGFR and chronic slope was graphically represented by kernel density curves for the best linear unbiased predictions for the acute and chronic eGFR slopes under the two slope mixed-effects models.

Cox proportional hazard regression was performed to assess the effect of canagliflozin compared with placebo on the clinical end points, yielding hazard ratios and 95% confidence intervals (95% CIs) from model parameter coefficients and standard errors. We evaluated the primary and secondary efficacy end points in participants stratified by baseline HbA1c. We tested for heterogeneity of the canagliflozin treatment effect by including an interaction term between the randomized treatment group and baseline HbA1c. We used R version 4.1.1 for statistical analyses (R Foundation, Vienna, Austria). P values < 0.05 were considered to indicate statistical significance.

Results

The CREDENCE trial randomized 4401 patients to receive either canagliflozin 100 mg daily (n=2202) or placebo (n=2199) between March 2014 and May 2017. The trial was stopped early for efficacy based on a planned interim analysis with a median follow-up of 2.62 years (IQR, 2.11–3.09). Efficacy analyses were conducted in 4399 participants because two participants had missing HbA1c values.

At baseline, in the total trial population, the mean age was 63 years (SD 9); 34% of participants were women; mean eGFR was 56 ml/min per 1.73 m^2 (SD 18); median UACR was 927 mg/g (IQR, 463–1833); and mean HbA1c was 8.3% (SD 1.3). There were 650 participants (15%) with a baseline HbA1c between 6.5 and 7%, 1406 (32%) with a HbA1c of 7.0 to <8.0%, 1849 (42%) with a HbA1c of 8.0 to <10.0%, and 494 (11%) with a HbA1c of 10.0%–12.0%. Mean HbA1c levels in the four groups were 6.6% (SD 0.3), 7.4% (SD 0.3), 8.8% (SD 0.6), and 10.8% (SD 0.8), respectively (Table 1).

Table 1. Patient characteristics according to baseline HbA1c subgroups[a]

Characteristic	HbA1c (%)			
	6.5–7.0	7.0 to <8.0	8.0 to <10.0	≥10.0 to <12.0
N[b]	650	1406	1849	494
Age, yr	64 (9)	64 (9)	62 (9)	61 (9)
Male, *n* (%)	475 (73)	966 (69)	1212 (66)	252 (51)
Race, *n* (%)				
Asian	158 (24)	289 (21)	336 (18)	94 (19)
Black	29 (5)	63 (5)	105 (6)	27 (6)
Other[c]	56 (9)	104 (7)	160 (9)	49 (10)
White	407 (63)	950 (68)	1248 (68)	324 (66)
Current smoker, *n* (%)	85 (13)	224 (16)	279 (15)	51 (10)
Duration of diabetes, yr	15 (9)	16 (9)	16 (9)	15 (8)
History of hypertension, *n* (%)	631 (97)	1353 (96)	1796 (97)	478 (97)
History of heart failure, *n* (%)	75 (12)	208 (15)	284 (15)	84 (17)
History of cardiovascular disease, *n* (%)	322 (50)	693 (49)	958 (52)	246 (50)
Diabetic retinopathy, *n* (%)	240 (37)	590 (42)	844 (46)	208 (42)
Body mass index, kg/m^2	30.8 (6.4)	31.1 (6.0)	31.7 (6.1)	31.5 (6.5)
Systolic BP, mm Hg	140 (16)	140 (15)	140 (16)	139 (16)
Diastolic BP, mm Hg	78 (9)	78 (10)	79 (9)	79 (9)
HbA1c, %	6.6 (0.3)	7.4 (0.3)	8.8 (0.6)	10.8 (0.8)
Total cholesterol, mg/dl	174 (46)	174 (46)	182 (50)	201 (58)
Triglycerides, mg/dl	168 (115)	186 (115)	204 (151)	248 (195)
eGFR, ml/min per 1.73 m^2[d]	54 (17)	55 (18)	57 (18)	60 (20)
UACR, mg/g, median (IQR)	860 (438–1790)	937 (469–1778)	927 (474–1837)	967 (452–2058)
Insulin, *n* (%)	314 (48)	847 (60)	1358 (73)	365 (74)
Diuretic, *n* (%)	290 (45)	676 (48)	888 (48)	202 (41)

HbA1c, glycated hemoglobin A1c; UACR, urinary albumin-to-creatinine ratio; IQR, interquartile range.
[a]Data are mean (SD) unless otherwise indicated.
[b]Two randomized participants had missing baseline HbA1c values and were excluded from the analysis.
[c]Includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.
[d]Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Effects on eGFR Slope

Canagliflozin caused an acute reduction in eGFR at week 3 with a mean reduction of −3.72 ml/min per 1.73 m^2 per year (standard error of the mean [SEM] 0.25) compared with −0.55 ml/min per 1.73 m^2 per year (SEM 0.25) in the placebo group, resulting in a between-group difference of −3.17 ml/min per 1.73 m^2 per year (95% CI, −3.87 to −2.47). Thereafter, the eGFR decline was attenuated in the canagliflozin group with a mean decline of −1.85 ml/min per 1.73 m^2 per year (SEM 0.13) compared with −4.59 ml/min per 1.73 m^2 per year (SEM 0.14) in the placebo group, with a between-group difference of 2.74 ml/min per 1.73 m^2 per year (95% CI, 2.37 to 3.11). Combining the acute and chronic effects, the total eGFR slope from baseline to the end of treatment (week 130) was smaller in the canagliflozin group with −3.19 ml/min per 1.73 m^2 per year (SEM 0.15) compared with −4.71 ml/min per 1.73 m^2 per year (SEM 0.15) in the placebo group, resulting in a between-group difference of 1.52 ml/min per 1.73 m^2 per year (95% CI, 1.11 to 1.93) (Table 2).

When analyzing the total eGFR slope by baseline HbA1c subgroups, we observed that in patients with near-normal glycemic control (HbA1c 6.5%–7.0%), those randomized to canagliflozin showed a 0.39–ml/min per 1.73 m^2 per year (95% CI, −0.56 to 1.33) slower rate of eGFR decline from baseline when compared with placebo. This compared with a 1.82–ml/min per 1.73 m^2 per year (95% CI, 1.40 to 2.25) difference in eGFR decline between treatment groups in those patients with higher baseline HbA1c values (HbA1c 7.0%–12.0%) ($P_{interaction}$ = 0.007; Figure 1, A and B). When stratifying the population into more granular HbA1c categories at baseline, in patient subgroups with higher HbA1c values, the rate of eGFR decline during follow-up was faster (Table 2). The effect of canagliflozin compared with placebo on chronic and total eGFR slopes was larger in patients with higher baseline HbA1c ($P_{interaction}$ = 0.02 for chronic slope and $P_{interaction}$ = 0.01 for total slope; Table 2). In addition, the between-group differences in eGFR slope expressed as percentage difference were progressively larger in higher baseline HbA1c subgroups (Table 2). The decline in kidney function in both the placebo and canagliflozin groups was larger with increasing baseline UACR. Partly as a result, the effect of canagliflozin on eGFR slope was also more pronounced in higher baseline UACR groups ($P_{interaction}$ = 0.04 for chronic slope and $P_{interaction}$ = 0.008 for total slope) (Table 2). The effects of canagliflozin on eGFR slope were consistent by diabetes duration and diabetic retinopathy status at baseline (Supplemental Table 1).

We compared the distribution of eGFR changes in patients randomized to canagliflozin and placebo during the acute and chronic phases. During the first 3 weeks, the canagliflozin group showed a uniformly larger reduction in eGFR compared with placebo, with a uniform shift in the distribution of eGFR changes to the left without a change in variability (SDs of acute eGFR slopes in the canagliflozin and placebo groups 5.3 versus 5.1 ml/min per 1.73 m^2 per 3 weeks, respectively; Figure 2A). During the chronic phase, the annual rate of eGFR change was slower in the canagliflozin group, and the variability of eGFR decline was somewhat reduced as indicated by the smaller SD and by the contraction of the left end of the distribution toward the right (SDs of the slopes in the canagliflozin and placebo groups 8.9 versus 9.9 ml/min per 1.73 m^2 per year, respectively; ratio 0.9; F-value 31; $P < 0.001$; Figure 2B).

Effects on UACR

Canagliflozin resulted in a lowering of the geometric mean of the UACR of 31% (95% CI, 27 to 35) compared with placebo. This effect was less pronounced in patients with near-normal glycemic control compared with those with higher HbA1c (Figure 1C). Patients with lower baseline UACR levels had a larger proportional UACR reduction ($P_{interaction}$ = 0.04; Figure 3).

Effects on Kidney and Cardiovascular Outcomes by Baseline HbA1c

Randomization to canagliflozin resulted in similar risk reductions of the primary composite outcome; composite outcome of kidney failure; doubling of serum creatinine or kidney death and kidney failure; composite outcome of cardiovascular death, myocardial infarction, or stroke; and composite outcome of cardiovascular death or hospitalization for heart failure, regardless of baseline HbA1c (all $P_{interaction} > 0.3$; Figure 4).

Discussion

Canagliflozin reduces the risk of kidney failure and cardiovascular events and slows the decline in eGFR in patients with type 2 diabetes and CKD who participated in the CREDENCE trial. In this study, we conducted additional analyses of the effect of canagliflozin on eGFR slope and albuminuria according to the degree of glycemic control at baseline. We found that the beneficial effect of canagliflozin in attenuating eGFR slope was present at all levels of glycemic control, but was more pronounced in patients with higher baseline HbA1c levels and albuminuria. Moreover, the albuminuria-lowering effect of canagliflozin was larger in patients with poorer glycemic control (HbA1c level of 7% or higher) compared with those with near-normal glycemic control (HbA1c 6.5% to <7.0%).

The finding that the effect of canagliflozin on eGFR slope was attenuated in patients with better glycemic control might be unexpected because canagliflozin consistently reduced kidney and cardiovascular end points, irrespective of the degree of baseline glycemic control, and because treatment effects on eGFR slope are strongly associated with treatment effects on kidney failure.[11,20] However, comparison of treatment effects on time to kidney failure is based on the rates at which patients reach these end points and have less statistical power to detect subgroup differences. In clinical trials, with an average follow-up duration of 2.5–3 years, treatment effect estimates depend primarily on patients with a fast decline of kidney function who reach the end point during the follow-up period of the clinical trial. By contrast, comparison of treatment effects on eGFR slope incorporates data on all randomized patients and thus includes both slow and fast progressors. We demonstrated that canagliflozin showed

Table 2. Effects of canagliflozin versus placebo on eGFR changes according to baseline participant subgroups

Characteristic		Acute Phase (Baseline to Week 3) eGFR Change (ml/min per 1.73 m^2)				Chronic Phase (Week 3 to the Last Available Measurement) Annual eGFR Change (ml/min per 1.73 m^2 per year)				Total Phase (Baseline to Week 130) Annual eGFR Change (ml/min per 1.73 m^2 per year)				Difference (%)
		Mean (SEM)		Difference (95% CI) SEM	*P* for Interaction	Mean (SEM)		Difference (95% CI) SEM	*P* for Interaction	Mean (SEM)		Difference (95% CI) SEM	*P* for Interaction	
		Canagliflozin	Placebo			Canagliflozin	Placebo			Canagliflozin	Placebo			
Overall		−3.72 (0.3)	−0.55 (0.3)	−3.17 (−3.87 to −2.47)		−1.85 (0.1)	−4.59 (0.1)	2.74 (2.37 to 3.11)		−3.19 (0.2)	−4.71 (0.2)	1.52 (1.11 to 1.93)		32
HbA1c, %	<7	−3.82 (0.4)	−0.50 (0.4)	−3.32 (−4.52 to −2.12)	0.87	−2.21 (0.3)	−3.98 (0.3)	1.77 (0.88 to 2.65)	0.02	−3.63 (0.3)	−4.02 (0.3)	0.39 (−0.56 to 1.33)	0.01	9
	7 to <8	−3.44 (0.3)	−0.65 (0.3)	−2.79 (−3.64 to −1.95)		−1.97 (0.2)	−4.38 (0.2)	2.41 (1.78 to 3.04)		−3.18 (0.2)	−4.54 (0.3)	1.36 (0.69 to 2.04)		30
	8 to <10	−3.51 (0.3)	−0.66 (0.3)	−2.85 (−3.62 to −2.08)		−1.61 (0.2)	−4.91 (0.2)	3.30 (2.74 to 3.86)		−2.91 (0.2)	−5.14 (0.2)	2.23 (1.63 to 2.83)		43
	≥10	−2.41 (0.6)	0.86 (0.6)	−3.27 (−4.99 to −1.55)		−2.92 (0.5)	−5.62 (0.4)	2.69 (1.43 to 3.96)		−3.49 (0.5)	−5.09 (0.5)	1.60 (0.30 to 2.91)		31
Screening eGFR, ml/min per 1.73 m^2	30 to <45	−2.45 (0.3)	−0.41 (0.3)	−2.03 (−2.73 to −1.34)	0.02	−1.72 (0.2)	−4.33 (0.2)	2.61 (2.06 to 3.16)	0.65	−2.56 (0.2)	−4.35 (0.2)	1.79 (1.20 to 2.38)	0.71	41
	45 to <60	−4.08 (0.3)	−0.64 (0.3)	−3.44 (−4.32 to −2.57)		−1.62 (0.2)	−4.58 (0.2)	2.97 (2.32 to 3.61)		−3.11 (0.3)	−4.76 (0.3)	1.65 (0.96 to 2.34)		35
	60 to <90	−3.66 (0.3)	−0.39 (0.3)	−3.27 (−4.17 to −2.37)		−2.32 (0.2)	−4.92 (0.2)	2.60 (1.97 to 3.32)		−3.61 (0.2)	−5.03 (0.2)	1.42 (0.75 to 2.09)		28
UACR, mg/g	≤1000	−3.15 (0.4)	0.45 (0.4)	−3.60 (−4.58 to −2.62)	0.44	−0.78 (0.2)	−3.09 (0.2)	2.31 (1.88 to 2.73)	0.04	−1.88 (0.2)	−2.79 (0.2)	0.91 (0.42 to 1.40)	0.008	33
	>1000 to <3000	−4.13 (0.4)	−1.29 (0.4)	−2.84 (−3.84 to −1.83)		−2.65 (0.2)	−5.94 (0.2)	3.29 (2.67 to 3.91)		−4.15 (0.2)	−6.37 (0.3)	2.23 (1.55 to 2.90)		35
	≥3000	−4.70 (0.8)	−2.26 (0.7)	−2.44 (−4.52 to −0.36)		−6.43 (0.6)	−8.92 (0.5)	2.49 (1.00 to 3.99)		−8.15 (0.6)	−9.68 (0.6)	1.53 (−0.11 to 3.17)		16

The effects of canagliflozin on on-treatment eGFR slope were analyzed using a piecewise, linear mixed-effects model with a knot at week 3, including the fixed effects of treatment, baseline eGFR, continuous time, and time spline (one knot at week 3), with two-way interactions of treatment by time and treatment by time spline, and the random effects of intercept, time, and time spline. Compound symmetry was used to fit the covariance structures in the mixed effect models, as the model did not converge when unstructured was used. SEM, standard error of the mean; CI, confidence interval; HbA1c, glycated hemoglobin A1c; UACR, urinary albumin-to-creatinine ratio.

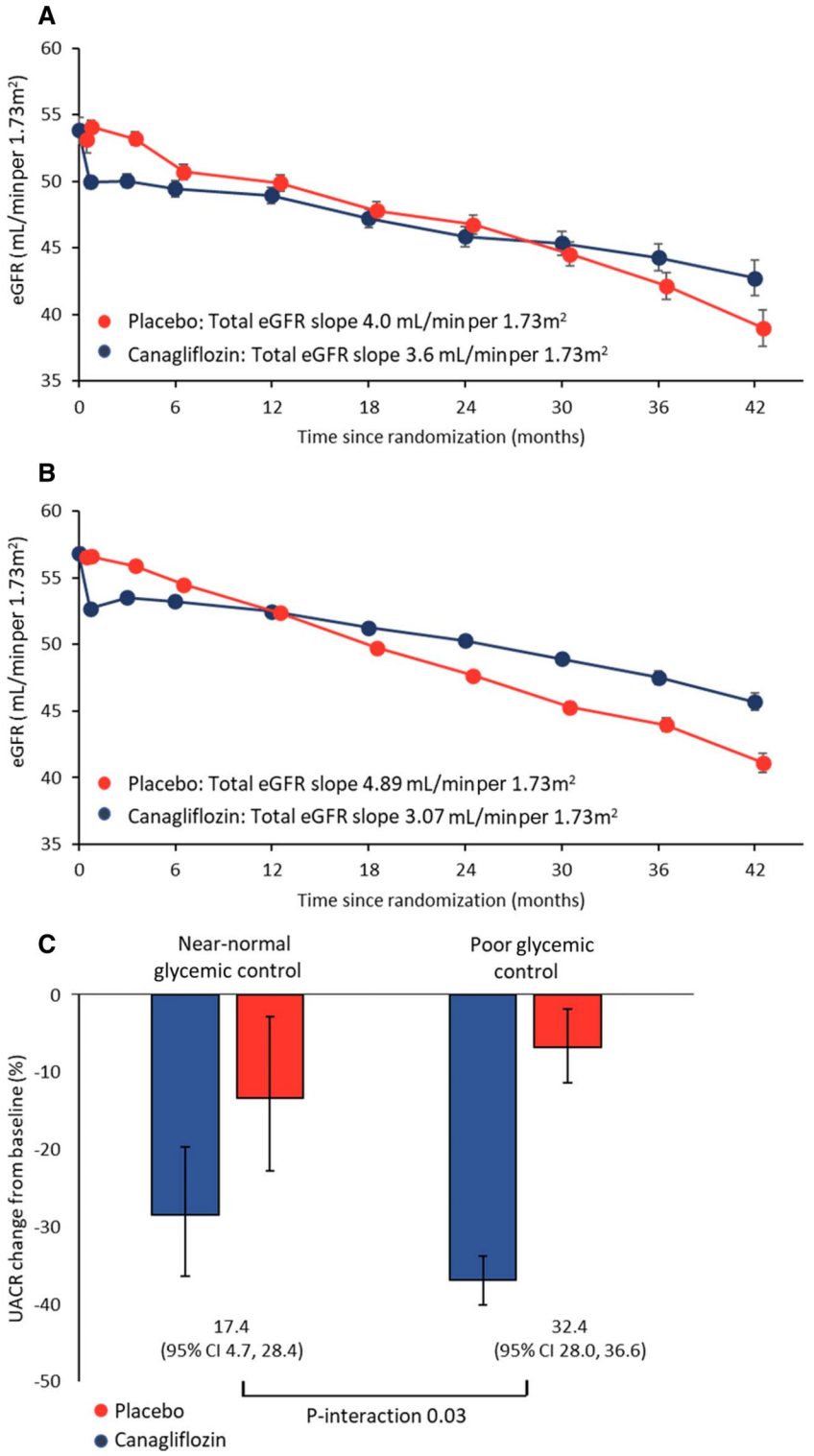


Figure 1. Effects of canagliflozin on eGFR slope and UACR change by baseline glycemic control. Effects of canagliflozin compared with placebo on eGFR slope in patients with near-normal glycemic control (HbA1c 6.5%–7.0%; A) and poor glycemic control (HbA1c 7.0%–12%; B). (C) The effect of canagliflozin on least squares mean change from baseline in UACR in patients with near-normal and poor glycemic control. CI, confidence interval; HbA1c, glycated hemoglobin A1c; UACR, urinary albumin-to-creatinine ratio. Figure 1 can be viewed in color online at www.cjasn.org.

a slightly greater treatment effect in fast progressors (as evidenced by a modest contraction of the left end of the distribution of the eGFR slopes during chronic treatment). Thus, the effect of canagliflozin on eGFR slope in all patients (both fast and slow progressors) is primarily driven by fast progressors. Thus, the effect modification by baseline

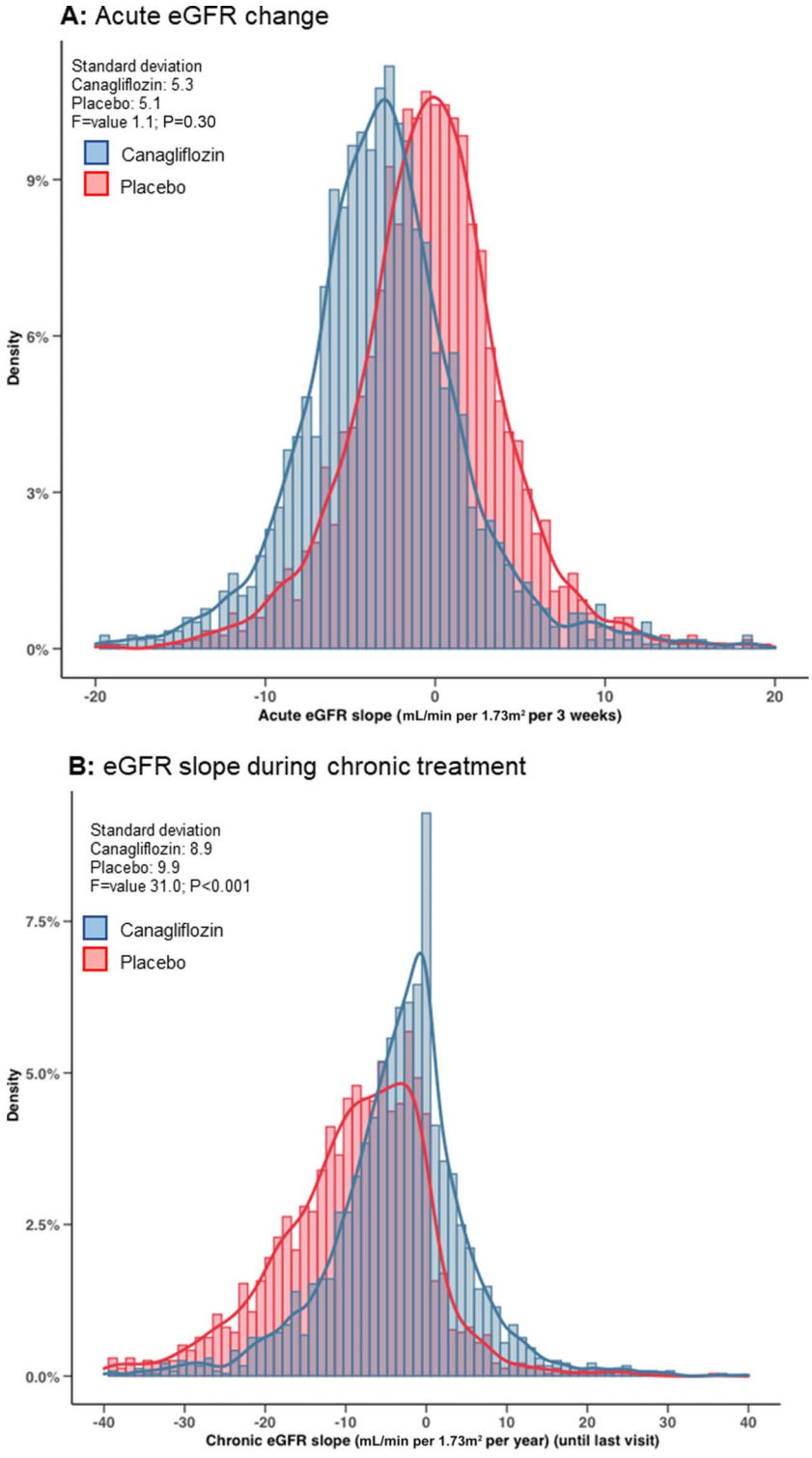
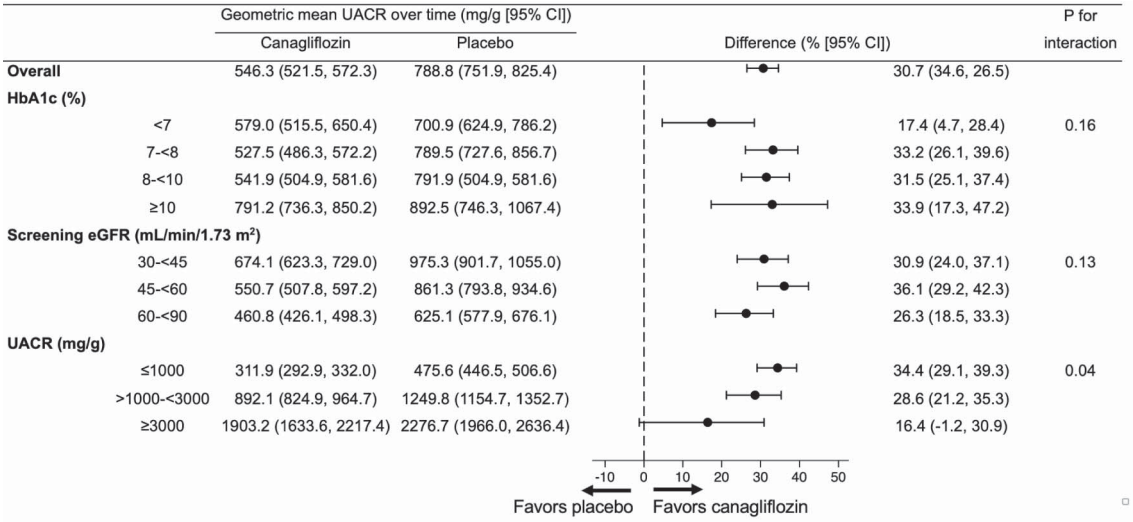


Figure 2. Distribution of eGFR changes. In the acute phase (A) and the annual eGFR slope during the chronic treatment phase (B) in the canagliflozin and placebo groups.

HbA1c for the eGFR slope end point may be explained at least partly by a more rapid loss of kidney function in those with poorer glycemic control as we observed that patients with near-normal HbA1c values at randomization had a lesser eGFR decline during follow-up compared with patients with higher HbA1c values. These results may also explain why in patients without diabetes and normoalbuminuria participating in the EMPA-KIDNEY trial, empagliflozin did not reduce the rate of kidney decline and kidney end points.[8]



The change from baseline in intermediate outcomes was analyzed using a mixed effects model for repeated measures, which included the data up to week 182, assuming an unstructured covariance and adjusting for baseline value, treatment, trial visit, and interactions of treatment by visit and baseline value by visit.

Figure 3. Effect of canagliflozin on UACR according to baseline participant subgroups.

Decline in kidney function is markedly higher in patients with moderate-to-severe albuminuria compared with those with normal albuminuria. This was also observed in the CREDENCE trial where eGFR decline was at least three times higher in patients with albuminuria more than 3000 mg/g versus those less than 1000 mg/g. The effect of canagliflozin compared with placebo in reducing eGFR decline was more pronounced in those with higher albuminuria, these participants being the faster progressors. As reported before, the proportional but not absolute reduction in albuminuria was smaller in patients with higher levels of albuminuria at baseline.[21] This finding has not been observed in other trials with SGLT2 inhibitors.[18,22]

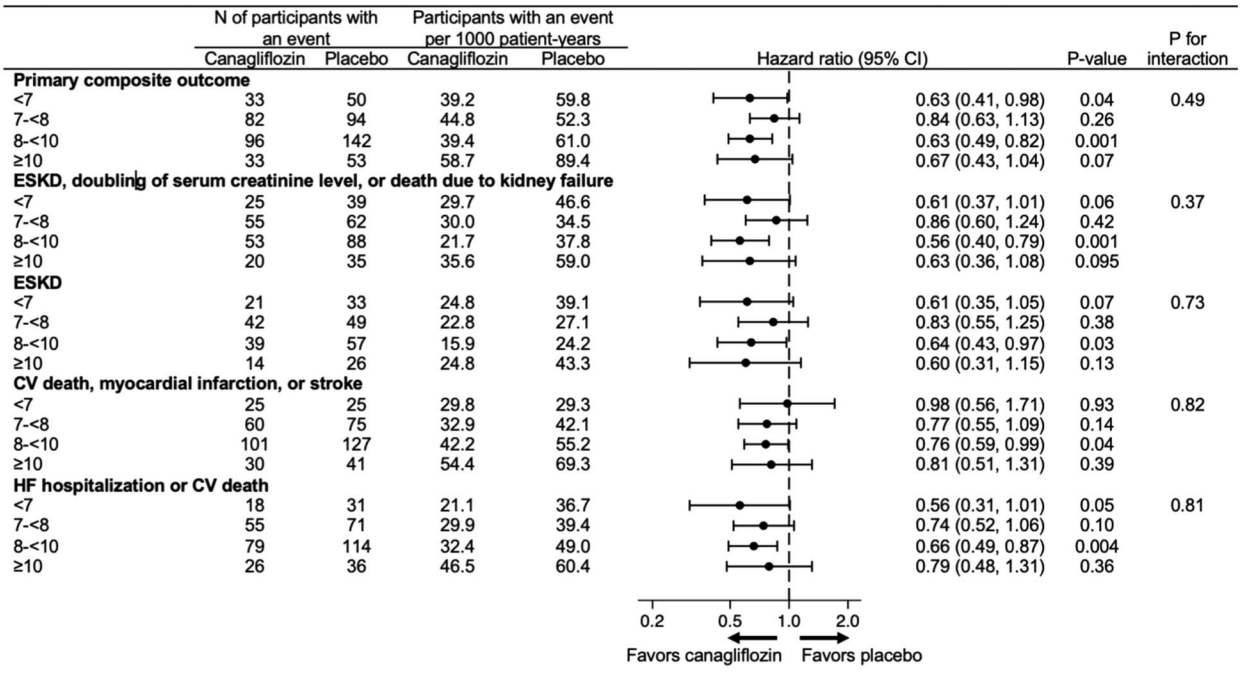


Figure 4. Effect of canagliflozin on primary and secondary outcomes according to baseline HbA1c. CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure.

Our slope analyses are in keeping with results from other clinical trials with SGLT2 inhibitors.[13,18] An analysis in patients with CKD participating in the Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial reported that the effect of dapagliflozin on eGFR slope was greater in the subgroup of patients with type 2 diabetes (67% of the participants) compared with those without type 2 diabetes.[18] In addition, the benefit of dapagliflozin in attenuating eGFR slope was more pronounced in patients with higher HbA1c and more extensive albuminuria, consistent with our results from CREDENCE. The results of our *post hoc* analysis are also consistent with data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) that reported more pronounced effects of the SGLT2 inhibitor empagliflozin on eGFR slope in patients with type 2 diabetes and established cardiovascular disease.[14] Analyses of clinical trials in patients with heart failure also show similar results.[5,6,15] In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure (EMPEROR)-Reduced, and EMPEROR-Preserved trials, dapagliflozin and empagliflozin improved the chronic eGFR slope with a larger effect in patients with type 2 diabetes compared with patients without diabetes.

The smaller albuminuria-lowering effect of canagliflozin that we observed in patients with near-normal glycemia has also been noted in other studies in patients with pre-diabetes or normal glycemia.[17,18] In a mechanistic study in patients without diabetes and CKD, dapagliflozin reduced UACR by 16% compared with placebo.[17] Likewise, in a *post hoc* analysis of the DAPA-CKD trial in patients without diabetes or pre-diabetes, dapagliflozin reduced albuminuria by 14% and 15%, respectively, compared with 35% in patients with type 2 diabetes.[18] Why the albuminuria lowering effect of SGLT2 inhibitors is attenuated in patients with near-normal or normal glycemic control is not completely understood. SGLT2 inhibitors exert a mild diuretic effect and reduce glomerular filtration, which is reversible directly after treatment cessation and is often referred to as the acute eGFR dip.[23] This suggests that SGLT2 inhibitors reduce intraglomerular pressure and thereby hyperfiltration.[24] A previous study demonstrated that the acute eGFR dip correlates with the reduction in albuminuria and suggested that the reduction in intraglomerular pressure on initiation of SGLT2 inhibition is attenuated in patients without type 2 diabetes, resulting in a smaller reduction in albuminuria.[18] However, in the CREDENCE trial, we did not observe a smaller acute eGFR dip in patients with near-normal glycemia.

Although the effects of canagliflozin in slowing the decline in eGFR were attenuated in patients with near-normal glycemia at baseline, it is important to emphasize that the benefits of canagliflozin on cardiovascular and heart failure end points was consistent, irrespective of the degree of glycemic control. Because cardiovascular end points occur frequently in patients with diabetes and CKD, our data indicate that despite the effect of canagliflozin on eGFR decline was more pronounced in patients with higher HbA1c and albuminuria, those with a slower decline in kidney function still derive cardiovascular benefit from canagliflozin.

The limitations of this study include the absence of eGFR measurements after discontinuation of canagliflozin to confirm the reversibility in the acute change in eGFR. However, the CANagliflozin cardioVascular Assessment Study–Renal (CANVAS-R) trial demonstrated that 4 weeks after canagliflozin treatment, the initial dip in eGFR was completely reversible.[3] Second, this was a *post hoc* analysis and may be prone to chance findings. Finally, the follow-up period of the CREDENCE trial was much shorter than the period during which most patients are treated in clinical practice. The relatively short time frame of the trial precludes assessment of canagliflozin on kidney function in slow progressors who may derive benefit during a longer follow-up.

In conclusion, the effect of canagliflozin in slowing the decline in kidney function in patients with type 2 diabetes and CKD is more pronounced in those with poorer baseline glycemic control and higher degrees of albuminuria, partly because of more rapid decline in kidney function in these individuals.

Disclosures

T. Greene reports consultancy for AstraZeneca, Durect, Invokana, Janssen Pharmaceuticals, Novartis, and Pfizer Inc and research funding from AstraZeneca, Boehringer Ingleheim, CSL, and Vertex. H.J.L. Heerspink reports ongoing consultancy agreements with AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly, Gilead, Janssen, Merck, Novartis, Novo Nordisk, and Travere Pharmaceuticals; has served as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly Gilead, Janssen, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, and Travere Pharmaceuticals; reports research funding from AbbVie, AstraZeneca, Boehringer Ingelheim, Janssen research support (grant funding directed to employer), and Novo Nordisk; receives lecture fees from AstraZeneca and Novo Nordisk; and was a member on the speakers bureau for AstraZeneca. M.J. Jardine reports employment with NHMRC Clinical Trials Centre, University of Sydney; is responsible for research projects that have received funding from Amgen, Baxter, CSL, Dimerix, Eli Lilly, Gambro, and MSD; reports research funding from Baxter, CSL, and Dimerix, with all payments to her institution; receives honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Cesas Medical, Janssen, Medscape, MSD, Occuryx, and Vifor and directs honoraria to clinical research programs; receives fees for advisory, steering committee, and/or scientific presentations from Akebia, Amgen, AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Cesas Linx, Chinook, CSL, Janssen, Medscape, MSD, Roche, and Vifor, with any consultancy, honoraria, or travel support paid to her institution; and reports advisory or leadership roles for Chinook, CSL, and Janssen and directs honoraria to clinical research programs. N. Jongs reports serving on the speakers bureau for AstraZeneca. A. Levin reports employment with BC Provincial Renal Agency and Providence Health Care; consultancy agreements with AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, GSK, Janssen, Kidney Foundation of Canada, NIH, Otsuka, and REATA; research funding from AstraZeneca, Boehringer Ingelheim, Canadian Institute of Health Research (CIHR), CITF (Canadian Immunology Task Force), GSK, Health Research BC,

Kidney Foundation of Canada, MOH BC, and Shared Care BC; honoraria from AstraZeneca, Bayer, GSK, Janssen, and NIH; advisory or leadership roles for AstraZeneca, Boehringer Ingelheim, CADTH, Chinook Therapeutics, CITF, GSK, KRESCENT (Kidney Research Scientist Core Education and National Training Program), NIDDK, REATA BC Renal (Exec Director), and Steering Committee Chair CURE Consortium; DSMB for NIDDK, Kidney Precision Medicine, U Washington Kidney Research Institute Scientific Advisory Committee; International Society of Nephrology Research Committee; and other interests or relationships as CREDENCE National Coordinator from Janssen—directed to her academic team, the Canadian Society of Nephrology, the DSMB Chair RESOLVE Trial (Australian Clinical Trial Network), the International Society of Nephrology, the Kidney Foundation of Canada Steering Committee ALIGN trial, and the NIDDK CURE Chair Steering Committee. K.W. 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Funding

The CREDENCE trial was funded by Janssen Research.

Acknowledgments

The authors thank all patients, investigators, and support teams for their time and participation in the CREDENCE trial.

SvdH, NJ, MO, and HJLH had full access to all data and final responsibility for the decision to submit for publication. VP, AL, TG, KWM, CP, DCW, MJJ, and HJLH contributed in the design and conduct of the CREDENCE trial.

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Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B754.

Supplemental Table 1. Effects of canagliflozin versus placebo on eGFR changes according to duration of diabetes and retinopathy.

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Received: November 17, 2022 **Accepted:** March 17, 2023
Published Online Ahead of Print: March 31, 2023

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