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Cardiorenal protective effects of canagliflozin in CREDENCE according to glucose lowering

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ABSTRACT

Introduction Relationships between glycemic-lowering effects of sodium glucose co-transporter 2 inhibitors and impact on kidney and cardiovascular outcomes are uncertain.

Research design and methods We analyzed 4395 individuals with prebaseline and postbaseline hemoglobin A1c (HbA1c) randomized to canagliflozin (n=2193) or placebo (n=2202) in The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial. Effects on HbA1c were assessed using mixed models. Mediation of treatment effects by achieved glycemic control was analyzed using proportional hazards regression with and without adjustment for achieved HbA1c. End points included combined kidney or cardiovascular death, end-stage kidney disease or doubling of serum creatinine (primary trial outcome), and individual end point components.

Results HbA1c lowering was modified by baseline estimated glomerular filtration rate (eGFR). For baseline eGFR 60–90, 45–59, and 30–44 mL/min/1.73 m^2, overall HbA1c (canagliflozin vs placebo) decreased by −0.24%, −0.14%, and −0.08% respectively and likelihood of >0.5% decrease in HbA1c decreased with ORs of 1.47 (95% CI 1.27 to 1.67), 1.12 (0.94 to 1.33) and 0.99 (0.83 to 1.18), respectively. Adjustment for postbaseline HbA1c marginally attenuated canagliflozin effects on primary and kidney composite outcomes: unadjusted HR 0.67 (95% CI 0.57 to 0.80) and 0.66 (95% CI 0.53 to 0.81); adjusted for week 13 HbA1c, HR 0.71 (95% CI 0.060 to 0.84) and 0.68 (95% CI 0.55 to 0.83). Results adjusted for time-varying HbA1c or HbA1c as a cubic spline were similar and consistent with preserved clinical benefits across a range of excellent and poor glycemic control.

Conclusions The glycemic effects of canagliflozin are attenuated at lower eGFR but effects on kidney and cardiac end points are preserved. Non-glycemic effects may be primarily responsible for the kidney and cardioprotective benefits of canagliflozin.22

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sodium glucose co-transporter 2 (SLGT2) inhibitors improve cardiorenal outcomes in type 2 diabetes. The mechanisms of protection, although thought to extend beyond glycemic control, are not fully understood.

WHAT THIS STUDY ADDS

⇒ In this post hoc analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial, we demonstrate that the clinical benefits associated with randomization to canagliflozin as compared with placebo were independent of the initial hemoglobin A1c (HbA1c), the extent of early reduction in HbA1c, and the time-averaged HbA1c during the study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future exploration of the cardiorenal benefits of SGLT2 inhibitors in patients with type 2 diabetes should focus on non-glycemic mechanisms of action.

INTRODUCTION

Sodium glucose co-transporter 2 (SGLT2) inhibitors lower the kidney threshold for glucose reabsorption, thereby increasing urinary sodium and glucose excretion. This results in improved glucose control which may result in modest body weight reduction in patients with type 2 diabetes mellitus (T2DM).[1] In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, canagliflozin significantly reduced the risk of kidney failure and cardiovascular events in participants with T2DM and chronic kidney disease (CKD).[2 3] These benefits were seen across the range of baseline hemoglobin A1c (HbA1c) levels,[4] but whether reductions in risk of cardiorenal outcomes are associated with on-treatment reductions in HbA1c have not previously been explored in the context of

Table 1 Baseline characteristics of the study population according to median HbA1c at 13 weeks

Variable	Week 13 HbA1c <7.7%			Week 13 HbA1c ≥7.7		
	All n=2036	Placebo n=912	Canagliflozin n=1124	All n=2162	Placebo n=1187	Canagliflozin n=975
Demographics						
Age (years)	63.4 (9.5)	63.6 (9.4)	63.2 (9.6)	62.4 (8.8)	62.7 (9.0)	62.1 (8.6)
Female	588 (28.9)	264 (28.9)	324 (28.8)	830 (38.4)	429 (36.1)	401 (41.1)
Race						
White	1332 (65.4)	577 (63.3)	755 (67.2)	1469 (67.9)	803 (67.6)	666 (68.3)
Black	95 (4.7)	44 (4.8)	51 (4.5)	116 (5.4)	61 (5.1)	55 (5.6)
Asian	437 (21.5)	212 (23.2)	225 (20.0)	400 (18.5)	222 (18.7)	178 (18.3)
Other or unknown	172 (8.4)	79 (8.7)	93 (8.3)	177 (8.2)	101 (8.5)	76 (7.8)
Comorbidities						
Hypertension	1967 (96.6)	879 (96.4)	1088 (96.8)	2097 (97.0)	1154 (97.2)	943 (96.7)
Heart failure	289 (14.2)	131 (14.4)	158 (14.1)	336 (15.5)	183 (15.4)	153 (15.7)
Cardiovascular disease	328 (16.1)	171 (18.8)	157 (14.0)	345 (16.0)	176 (14.8)	169 (17.3)
Duration of diabetes (years)	15.2 (8.7)	15.8 (8.9)	14.7 (8.6)	16.3 (8.4)	16.2 (8.2)	16.5 (8.6)
Blood pressure and labs						
Systolic BP (mm Hg)	139.8 (15.6)	140.0 (15.6)	139.6 (15.7)	140.4 (15.6)	140.7 (15.6)	140.0 (15.6)
Diastolic BP (mm Hg)	78.1 (9.4)	77.7 (9.4)	78.4 (9.3)	78.6 (9.3)	79.0 (9.3)	78.1 (9.4)
HbA1c (%)	7.5 (0.9)	7.4 (0.9)	7.5 (0.9)	9.0 (1.2)	8.9 (1.3)	9.1 (1.2)
eGFR (mL/min/1.73 m^2)	55.5 (16.2)	55.5 (16.3)	55.6 (16.2)	57.1 (16.6)	57.0 (16.7)	57.2 (16.4)
UACR (mg/g)	1385 (1118)	1425 (1157)	1354 (1084)	1454 (1143)	1423 (1106)	1492 (1186)

BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; UACR, urinary albumin to creatinine ratio.

CKD. Reductions in HbA1c-lowering efficacy of SGLT2 at low estimated glomerular filtration rate (eGFR) underlie the relatively high eGFR cut-offs for the initial labelled indications for marketed SGLT2 inhibitors in the USA.[5–8] However, large outcomes trials[3 9 10] have now led to widespread use of SGLT2 inhibitors in the setting of CKD despite remaining uncertainty regarding mediation of the cardiovascular and kidney benefits by improvement in glycemic control. The objective of this analysis was to quantify differences in the time-varying glycemic effects of canagliflozin in the CREDENCE trial according to baseline kidney function and to assess the extent to which reductions in HbA1c during the trial were associated with kidney and cardiovascular outcome benefits.

METHODS

Cohort

The design and primary outcomes of CREDENCE have been reported previously.[2 3] Briefly, CREDENCE was a double-blind, randomized controlled trial. Individuals with diabetes and CKD were randomized to canagliflozin 100 mg/day or placebo until trial completion, death, initiation of dialysis, kidney transplantation, an event of diabetic ketoacidosis, pregnancy, or use of prohibited therapy. Key inclusion criteria included diabetes, eGFR of 30 to <90 mL/min/1.73 m,^{2} urinary albumin-to-creatinine ratio >300 up to 5000 mg/g and HbA1c ≥6.5% to ≤12.0%. Treatment with a maximum-labelled/tolerated dose of ACE inhibitor or angiotensin receptor blocker (ARB) for ≥4 weeks prior to randomization was required.

Glycemia and eGFR assessment

HbA1c was measured centrally at screening, baseline, week 13, week 26, week 52, and every 26 weeks thereafter. Serum creatinine (with eGFR assessment) was measured centrally at screening, during run-in, week 3, week 13, week 26, week 52, week 78, and every 26 weeks thereafter.

Outcomes

We analyzed glycemic control at each protocol-specified assessment of HbA1c as well as mean changes over time. In addition to looking at mean changes in HbA1c, we looked at two binary definitions of glycemic effect: (a) >0.5% decrease in HbA1c, the threshold considered to represent moderate glucose-lowering efficacy in the American Diabetes Association and European Association for the Study of Diabetes guidelines[11 12] and (b) >0.3%, which has been used by the US Food and Drug Administration (FDA) as a threshold for a minimal clinically meaningful reduction in HbA1c.[13]

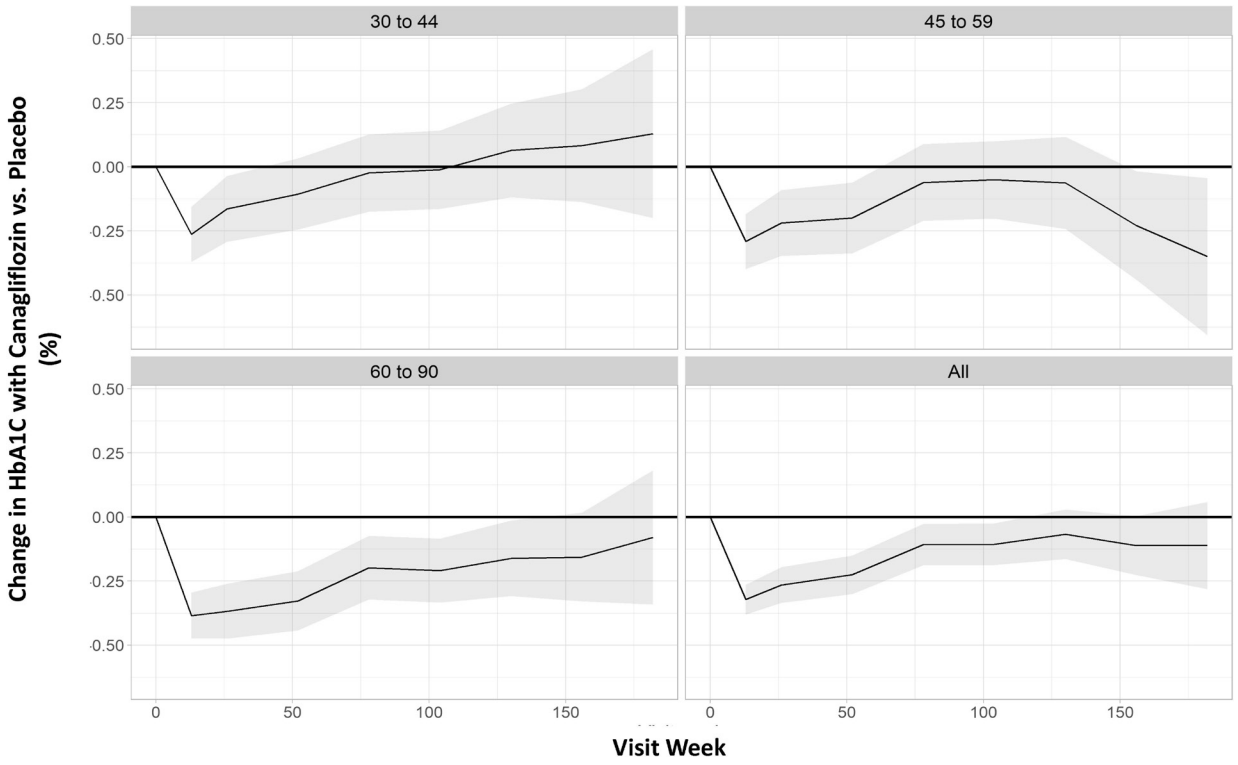

Figure 1 Treatment effect on hemoglobin A1c (HbA1c) with canagliflozin compared with placebo according to study week and estimated glomerular filtration rate (eGFR) stratum. Negative values favor canagliflozin. eGFR categories in mL/min/1.73 m^2; 95% CIs are demarcated by grey shading. P<0.001 for overall treatment effect. P=0.04 for difference in treatment effect according to eGFR stratum. P=0.57 for difference in treatment effect by eGFR and visit-week.

Clinical end points were based on the primary and secondary trial outcomes and included the primary trial end point, which was combined end-stage kidney disease (ESKD, dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), doubling of the serum creatinine level, or death from kidney or cardiovascular causes. Secondary end points were drawn from the prespecified secondary end points of the trial and include ESKD, doubling of serum creatinine, the combination of hospitalized heart failure and cardiovascular death, a renal composite end point which included the kidney-specific components of the primary end point, and major adverse cardiovascular events which included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalized heart failure, and hospitalized unstable angina.

Statistical analysis

Baseline characteristics and HbA1c values at individual time-points are presented according to their distribution as mean±SD, median (IQR) or n (%). Treatment effects on HbA1c were assessed using linear mixed models (LMM) with an unstructured covariance structure and with the main effects of treatment, time, baseline eGFR status, and baseline HbA1c. We additionally assessed two-way interactions between time and (a) treatment, (b) baseline HbA1c value, and (c) baseline eGFR status; and a three-way interaction between eGFR status, treatment, and time. The inclusion of the interaction terms in LMM adjusts for data with a missing-at-random structure for these variables. Treatment effects on binary glycemic outcomes used analogous generalized linear mixed models (with a logistic link function) and a Toeplitz covariance structure.[14] Analogous methods were used to analyze effect modification on HbA1c lowering at 13 weeks according to use of non-SGLT2 inhibitor diabetes therapies at baseline.

To assess mediation of clinical benefits of canagliflozin compared with placebo by treatment-related changes in HbA1c, we used Cox proportional hazards models for time to each type of event with and without adjustment for HbA1c. HbA1c was analyzed according to the value at week 13, as a time-varying variable, or as time-varying cubic spline. To facilitate comparisons across models, a complete case-approach including only those observations without missing HbA1c values was used in these analyses. In addition, we assessed effect-modification according to the achieved HbA1c at week 13 with HbA1c defined dichotomously as a moderate change or minimally significant change. To better understand the role of other diabetes treatments, we repeated the analyses for the primary trial outcome and the kidney composite outcome according to the use of background diabetes therapies. Proportional hazards assumptions were checked graphically with cumulative sums of Martingale residuals.[15] Analyses were done in SAS/R V.9.4 (Cary, North Carolina, USA). Given the post hoc,

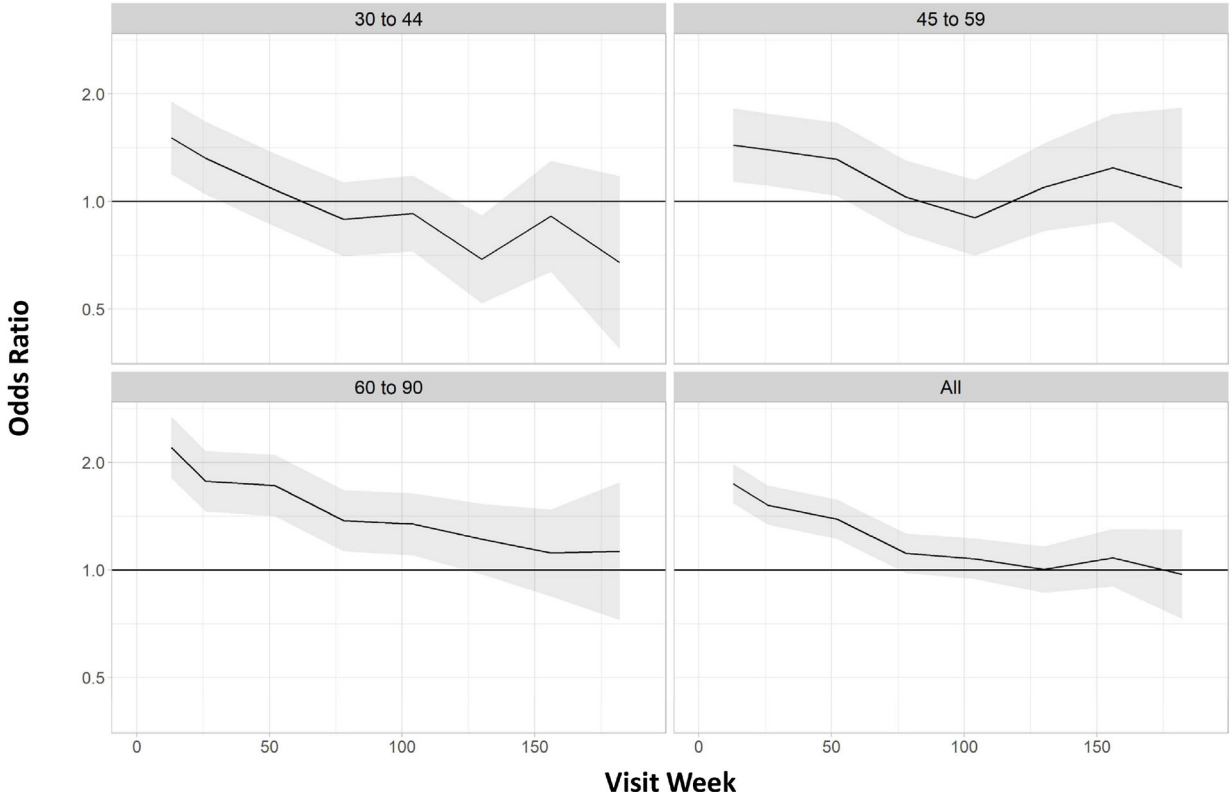

Figure 2 Odds of achieving at least at moderate reduction (>0.5%) in hemoglobin A1c (HbA1c) with canagliflozin compared with placebo according to study week and estimated glomerular filtration rate (eGFR) stratum. eGFR categories in mL/min/1.73 m^2; 95% CIs are demarcated by grey shading.

hypothesis-generating nature of the analyses, we did not correct for multiple comparisons.

RESULTS

Baseline characteristics of the study population

Baseline characteristics of individuals with an HbA1c below the median (mean HbA1c 7.5%±0.9%) were generally similar to those with HbA1c above the median at 13 weeks (mean HbA1c 9.0%±1.2%). However, individuals with better control at 13 weeks were marginally older (63 vs 62 years) and the proportion of women (29% vs 38%) and Black patients (4.7% vs 5.4%) was slightly lower in those with better control, whereas the proportion of Asian patients (22% vs 19%) was slightly higher (table 1). The duration of diabetes was shorter (15.2±8.7 vs 16.3±8.4 years) and eGFR was modestly lower (55.5±16.2 vs 57.1±16.6 mL/min/1.73 m^2).

Glycemic effects

Compared with placebo, canagliflozin was associated with an overall difference of −0.16% (95% CI −0.23 to −0.10) in HbA1c over the course of the study (figure 1). The overall difference in HbA1c compared with baseline was greater with canagliflozin compared with placebo at each time point, although CIs were consistent with a null effect at 130 weeks. There was significant effect modification by baseline eGFR category (p=0.04) with a mean decrease of −0.24% (95% CI −0.33 to −0.15) for individuals with eGFR of ≥60 mL/min/1.73 m^2, −0.14% (95% CI −0.24 to −0.04) for individuals with eGFR 45–59 mL/min/1.73 m^2, and −0.08% (95% CI −0.18 to 0.02) for individuals with eGFR 30–44 mL/min/1.73 m^2. Differences in HbA1c lowering between canagliflozin and placebo were most apparent early and tended to dissipate over the course of follow-up. Point estimates for the extent of lowering favored the canagliflozin group throughout follow-up except in the lowest eGFR group, in which the effects were attenuated and there was no evidence of differences between canagliflozin and placebo in late glycemic control. Observed changes in HbA1c for the placebo and canagliflozin group by study week are provided in online supplemental figure 1. There was no evidence of effect modification on glycemic effects at 13 weeks according to the use of non-SGLT2 diabetes medication at baseline (online supplemental table 1).

Results were similar when binary definitions of HbA1c lowering were used. The likelihood of achieving a greater than moderate decrease of HbA1c (>0.5%) with canagliflozin was significantly lower at lower baseline eGFR (p=0.001) with ORs of 1.47 (95% CI 1.27 to 1.67), 1.12 (0.94 to 1.33), and 0.99 (0.83 to 1.18) with eGFR of 60–90, 45–59, and 30–44 mL/min/1.73 m^2, respectively (figure 2, online supplemental table 2). Results were similar using the FDA definition for minimal significant change in HbA1c of 0.3%.

Table 2 Risk of primary composite end point and secondary kidney and cardiovascular end points with canagliflozin (n=2099) compared with placebo (n=2099) with and without adjustment for postbaseline HbA1c (total n=4198)

Outcome	Model	HR (95% CI)
Primary composite	Unadjusted	0.67 (0.57 to 0.80)
	Week 13 HbA1c	0.71 (0.60 to 0.84)
	Time-varying HbA1c	0.68 (0.57 to 0.80)
	Time-varying HbA1c spline	0.68 (0.58 to 0.81)
Kidney composite	Unadjusted	0.66 (0.53 to 0.81)
	Week 13 HbA1c	0.68 (0.55 to 0.84)
	Time-varying HbA1c	0.65 (0.53 to 0.81)
	Time-varying HbA1c spline	0.66 (0.54 to 0.81)
Cardiovascular death and heart failure hospitalization	Unadjusted	0.66 (0.54 to 0.81)
	Week 13 HbA1c	0.70 (0.57 to 0.85)
	Time-varying HbA1c	0.66 (0.54 to 0.81)
	Time-varying HbA1c spline	0.67 (0.55 to 0.82)
Doubling of creatinine	Unadjusted	0.59 (0.46 to 0.74)
	Week 13 HbA1c	0.60 (0.48 to 0.76)
	Time-varying HbA1c	0.58 (0.46 to 0.74)
	Time-varying HbA1c spline	0.59 (0.46 to 0.74)
ESKD	Unadjusted	0.69 (0.54 to 0.88)
	Unadjusted	0.70 (0.55 to 0.90)
	Week 13 HbA1c	0.68 (0.54 to 0.87)
	Time-varying HbA1c	0.70 (0.55 to 0.89)
Cardiovascular death	Unadjusted	0.73 (0.56 to 0.95)
	Week 13 HbA1c	0.78 (0.60 to 1.01)
	Time-varying HbA1c	0.74 (0.57 to 0.96)
	Time-varying HbA1c spline	0.75 (0.58 to 0.97)
Major adverse cardiovascular events	Unadjusted	0.79 (0.65 to 0.95)
	Week 13 HbA1c	0.83 (0.69 to 1.01)
	Time-varying HbA1c	0.81 (0.67 to 0.97)
	Time-varying HbA1c spline	0.81 (0.67 to 0.97)

ESKD, end-stage kidney disease; HbA1c, hemoglobin A1c.

Cardiovascular and kidney outcomes

As previously reported, compared with placebo, canagliflozin was associated with a reduced risk of the primary outcome, the kidney composite outcome, and the cardiovascular composite outcome of cardiovascular death or heart failure hospitalization.[3] Adjustment for postbaseline HbA1c had no detectable effect on the HR for the primary composite outcome (table 2): unadjusted (HR 0.67, 95% CI 0.57 to 0.80); adjusted for week 13 HbA1c (HR 0.71, 95% CI 0.60 to 0.84); adjusted for time-varying HbA1c (HR 0.68, 95% CI 0.57 to 0.80), and adjusted for time-varying HbA1c as a cubic-spline (HR 0.68, 95% CI 0.58 to 0.81). For the kidney composite, unadjusted estimates (HR 0.66, 95% CI 0.53 to 0.81) and estimates adjusted for week 13 HbA1c (HR 0.68, 95% CI 0.55 to 0.84), continuous (linear) time-varying HbA1c (HR 0.65, 95% CI 0.53 to 0.81), and time-varying HbA1c as a cubic spline (HR 0.66, 95% CI 0.54 to 0.81) were also similar. Qualitatively similar results were seen for other kidney and cardiovascular outcomes. Reductions in risk for the primary and kidney composites were similar regardless of background diabetes therapy (online supplemental table 3).

In analyses of time-varying HbA1c as a cubic spline, we assessed the risk of events according to the achieved time-varying HbA1c during follow-up. Estimates of risk were consistent with relatively uniform risks of the primary outcome for time-varying HbA1c values between 6% and 11% in models adjusting for use of canagliflozin or placebo with the exception of MACE, for which an increase in risk was apparent at lower achieved HbA1c (figure 3). Likewise, relative risk reduction was similar regardless of whether change in HbA1c at week 13 met the criteria for a moderate or minimally significant HbA1c change (online supplemental table 4, $Pi_{nteraction} \geq 0.39$).

DISCUSSION

In this post hoc analysis of the CREDENCE study, we demonstrated that the glycemic effects of canagliflozin were modified by baseline eGFR, with a progressively lesser reduction and lower likelihood of achieving a >0.5% decrease in HbA1c across CKD stages G1-2 (eGFR >60 mL/min/1.73 m^2), stage G3A (eGFR 45–60 mL/min/1.73 m^2), and stage 3B (eGFR 30–44 mL/min/1.73 m^2). Looking at the impact of HbA1c reduction on end points during the trial, there was no evidence that adjustment for the postbaseline change in HbA1c reduction (assessed at week 13) led to an attenuation in the effect of canagliflozin on the primary composite outcome or on secondary kidney and cardiovascular outcomes. Similar results were observed when we used a time-varying adjustment that took into account the level of glycemic control throughout the study period.

Glycemia-independent effects of SGLT2 inhibition have been previously inferred from the study of cardiovascular and kidney benefits of canagliflozin that are observed despite a modest lowering of HbA1c when kidney function is impaired. Indeed, the mean decrease of 0.16% in HbA1c that we observed with canagliflozin compared with placebo

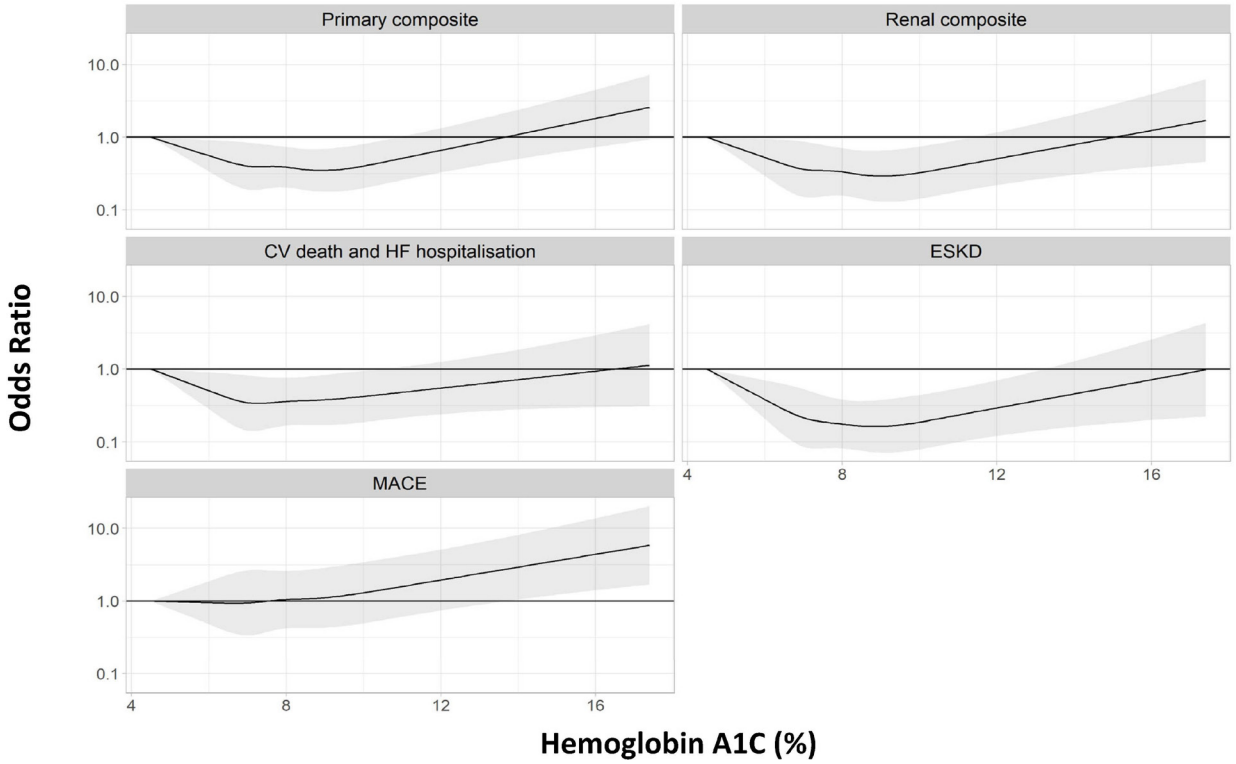

Figure 3 Risk of primary and secondary end points according to time-varying hemoglobin A1c (HbA1c) level (x-axis, minimum observed level as reference) adjusted for treatment with canagliflozin versus placebo. HRs for the primary composite, renal composite, combined cardiovascular (CV) death and hospitalization, and end-stage kidney disease (ESKD) are not suggestive of significant associations between achieved HbA1c and risk of cardiovascular or kidney events at high levels of time-varying HbA1c. For major adverse cardiovascular events (MACE), extremely elevated levels of time-varying HbA1c were associated with increased risk after adjusting for randomized therapy; 95% CI bands are shaded in grey. HF, heart failure.

in this analysis is considerably smaller than that seen in either short-term (approximately 0.7%–1.0%) or longer outcome trials (0.4%–0.6%).[16–20] We have already reported that baseline HbA1c level did not predict the impact of canagliflozin on study outcomes in the CREDENCE trial.[4] The current, analyses extend these findings by demonstrating that neither the initial HbA1c, the extent of initial reduction in HbA1c at 13 weeks, nor the time-averaged HbA1c during the whole study period, influenced the clinical benefits associated with randomization to canagliflozin as compared with placebo. Furthermore, reduction in cardiovascular and kidney risks were robust regardless of background diabetes therapies. These results therefore support the hypothesis that the cardiovascular and renoprotective effects of canagliflozin in this population of patients with both type 2 diabetes and CKD are largely independent of changes in glycemic status and suggest that non-glycemic mechanisms are operative. This analysis is consistent with findings from the CANagliflozin cardioVascular Assessment Study in which markers of glycemic control did not explain kidney outcomes in a mediation analysis, while albuminuria, hemoglobin, and hematocrit did, suggesting that anti-inflammatory effects, antifibrotic effects, effect on volume status, improvements in renal hypoxia, or other mechanisms of action are more important in explaining clinical benefits.[21] This conclusion is supported by a recent prespecified analysis of the DAPA-CKD study, which recruited 4304 participants with CKD of whom 738 had normoglycemia, 660 had prediabetes, and 2906 had type 2 diabetes at baseline. The effects of dapagliflozin on the primary outcome (a composite of doubling of serum creatinine, end-stage kidney disease, or death due to a renal or cardiovascular cause) were consistent in those with normoglycemia (HR 0.62 (95% CI 0.39 to 1.01)), prediabetes (HR 0.37 (0.21 to 0.66)), and type 2 diabetes (HR 0.64 (0.52 to 0.79)) with no effect modification on other outcomes (including all-cause mortality) when adjusted for baseline glycemic status.[22] This analysis, however, did not examine the impact of the level of glycemic control during the study on these clinical outcomes, although there were no differences in HbA1c between treatments arms in participants with normoglycemia or prediabetes at baseline. Trials of SGLT2 inhibitors in patients with heart failure have also indicated that the cardiovascular benefits of these drugs, particularly on hospitalization for worsening heart failure, are also observed in participants with heart failure and reduced ejection fraction who do not have type 2 diabetes at the time of randomization.[23 24]

Our analysis of the CREDENCE dataset thus supports the hypothesis that non-glycemic mechanisms explain many of the benefits of canagliflozin, similar to other SGLT2 inhibitors, on cardiorenal outcomes. A number of alternative mechanisms have been proposed. For example, metabolic changes that result from glycosuria (even in

the absence of HbA1c reductions) may activate gluconeogenesis, ketogenesis and fatty acid oxidation, promoting autophagy (a process that allows cells to clear dysfunctional organelles). The consequences of autophagy could include reductions in oxidative stress which may in turn protect residual kidney (or myocardial) function.[25] Other pathways proposed to explain kidney protection include suppression of inflammation and fibrosis, mediated via inhibition of the renin-angiotensin-aldosterone system with consequent reductions in ischemia in the kidney.[26 27] Non-metabolic mechanisms involving changes in osmotic and non-osmotic sodium handling and intrarenal hemodynamic have also been proposed to explain the cardiovascular benefits of SGLT2 inhibitors.[28] Although the precise mechanism of clinical benefit have not been fully elucidated, the evolving clinical data support the use of SGLT2 inhibitors to improve cardiorenal end points in patients with both CKD and chronic heart disease.

There are a number of limitations to this post hoc analysis of the CREDENCE study. First, postrandomization data were incomplete—HbA1c was available in most (4198) participants at week 13 with a baseline HbA1c, and in 4125 participants at week 26 but only in 3990 at week 52, thus limiting our mediation analysis. Second, the CREDENCE study recruited patients with an eGFR >30 mL/min/1.73^2 and although 174 patients with an eGFR below this level were randomized (because of reductions in kidney function between the date of screen and randomization),[29] patients with stage 4 CKD were not well represented. Third, although our results support the hypothesis that the primary benefits of SGLT2 inhibition are derived from mechanisms other than improvement in glycemia, our study cannot prove causality since the decrease in HbA1c is a postrandomization variable with potential confounders and biases, some of which may not be adjusted for with the analytic approaches used. Lastly, variability in the precision of HbA1c measurement and the imperfect correlation of HbA1c with glucose lowering within individuals could have attenuated our power to detect mediation of the effects on clinical outcomes by the glucose-lowering effects of canagliflozin.

In conclusion, this post hoc analysis of the CREDENCE study demonstrates that in the context of CKD, although the glycemic effects of canagliflozin are attenuated at lower levels of eGFR, the clinical benefits on kidney and cardiovascular outcomes are preserved. Good glycemic control or a lack of reduction in HbA1c after starting canagliflozin in a patient with type 2 diabetes and CKD should not discourage ongoing use of the drug. Patients with good glycemic control and those who do not show HbA1c reductions on canagliflozin are still likely to gain renal and cardiovascular benefits from the medication.

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Competing interests DMC has personal fees or fees paid by Janssen Pharmaceuticals to the Baim Institute for work on the CREDENCE trial steering committee. He has received consulting fees from Amgen, CSL Behring, Eli Lilly, Fresenius, Gilead, Medtronic/Covidien, Merck, Novo Nordisk, Zoll, AstraZeneca, GlaxoSmithKline, PLC Medical, and Allena Pharmaceuticals, and has received research support from Medtronic and Amgen. KWM's financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. MJJ is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Amgen, Baxter, CSL, Eli Lilly, Gambro, and MSD; has served on advisory boards sponsored by Akebia, AstraZeneca, Baxter, Bayer, Boehringer Ingelheim (BI), MSD, and Vifor; serves on steering committee for trials sponsored by CSL and Janssen; serves on a steering committee for an investigator-initiated trial with funding support from Dimerix, spoken at scientific meetings sponsored by Janssen, Amgen, Roche, and Vifor; with any consultancy, honoraria, or travel support paid to her institution. CPC reports in calendar years 2020–2022: Research Grants from: Amgen, Better Therapeutics, BI, Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck, Novo Nordisk, Pfizer. Consulting fees from Aegerion/Amryt, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, BI, BMS, Eli Lilly, Janssen, Lexicon, Merck, Pfizer, Rhoshan, Sanofi. He serves on the Data and Safety Monitoring Boards for the Veteran's Administration, Applied Therapeutics, and Novo Nordisk. BN has received research grants and consulting fees from Janssen, all paid to his institution. HJLH has received honoraria for participation in steering committees or advisory boards from AstraZeneca, BI, Bayer, CSL Behring, Chinook, Gilead, Goldfinch, Janssen, Merck, Mitsubishi Tanabe, Mundipharma; Novartis, Novo Nordisk, and Travere Pharmaceuticals. His institution received research grants from AstraZeneca, AbbVie, Janssen, BI, and Novo Nordisk. RA was a member of the CREDENCE study steering committee and chair of its adjudication committee; is a member of the steering committees of FIDELIO/FIGARO (Bayer); INNOVATE/PROTECT (Akebia); AMBER (Relypsa/Vifor), and chairs a data safety monitoring board (Chinook). He also serves as a consultant for AstraZeneca, Bayer, BI, DiaMedica, Janssen, Merck, Reata, Relypsa, and Sanofi. GLB works for The University of Chicago Medicine. He is a consultant for Merck, Bayer, Vascular Dynamics, KBP Biosciences, Ionis, Alnylam, and AstraZeneca. He has research support and is on the steering committee of trials for Bayer and Vascular Dynamics. He is the editor of the *American Journal of Nephrology*. DdZ: advisory boards and/or speaker fees for Bayer, BI, Fresenius, Mitsubishi-Tanabe, Travere Pharmaceuticals; steering committees and/or speaker for AbbVie and Janssen; data safety and monitoring committees for Bayer. Honoraria paid to institution and consultant/speaker. AL serves as a scientific advisor to BI, AstraZeneca, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); is on the data safety and

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REFERENCES

1 Mudaliar S, Polidori D, Zambrowicz B, *et al*. Sodium-Glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. *Diabetes Care* 2015;38:2344–53.
2 Jardine MJ, Mahaffey KW, Neal B, *et al*. The canagliflozin and renal endpoints in diabetes with established nephropathy clinical evaluation (credence) study rationale, design, and baseline characteristics. *Am J Nephrol* 2018;46:462–72.
3 Jardine MJ, Mahaffey KW, Perkovic V. Canagliflozin and renal outcomes in diabetic nephropathy. reply. *N Engl J Med* 2019;381:1089–90.
4 Cannon CP, Perkovic V, Agarwal R, *et al*. Evaluating the effects of canagliflozin on cardiovascular and renal events in patients with type 2 diabetes mellitus and chronic kidney disease according to baseline HbA1c, including those with HbA1c < 7 %: results from the credence trial. Circulation 2020;141:407–10.
5 INVOKANA (canagliflozin) tablets, for oral use [article online]. 2018. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204042s027lbl.pdf
6 FARXIGA® (dapagliflozin) tablets, for oral use [article online]. 2018. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209091s000lbl.pdf
7 JARDIANCE® (empagliflozin) tablets, for oral use [article online]. 2018. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204629s018lbl.pdf
8 Kohan DE, Fioretto P, Tang W, *et al*. Long-Term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int* 2014;85:962–71.
9 Heerspink HJL, Stefánsson BV, Correa-Rotter R, *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436–46.
10 Herrington WG, Staplin N, Wanner C, *et al*. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;388:117–27.
11 American Diabetes A. 8. pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2018 . *Diabetes Care* 2018;41(Supplement_1):S73–85.
12 Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American diabetes association and the European association for the study of diabetes. *Diabetes Care* 2015;38:140–9.
13 Administration FaD. *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control; Draft Guidance for Industry; Availability*. Washington, DC: FDA, 2008: 1–34.
14 Generalized linear mixed models [article online]. 2003. Available: www.jstor.org/stable/4153190 [Accessed 23 Apr 2021].
15 Lin DY, Wei LJ, Ying Z. Checking the COX model with cumulative sums of martingale-based residuals. *Biometrika* 1993;80:557–72.
16 Stenlöf K, Cefalu WT, Kim K-A, *et al*. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013;15:372–82.
17 Kovacs CS, Seshiah V, Swallow R, *et al*. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 2014;16:147–58.
18 Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.
19 Wiviott SD, Raz I, Sabatine MS. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. reply. *N Engl J Med* 2019;380:1881–2.
20 Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–57.
21 Li J, Neal B, Perkovic V, *et al*. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney Int* 2020;98:769–77.
22 Persson F, Rossing P, Vart P, *et al*. Efficacy and safety of dapagliflozin by baseline glycemic status: a prespecified analysis from the DAPA-CKD trial. *Diabetes Care* 2021;44:1894–7.
23 Petrie MC, Verma S, Docherty KF, *et al*. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020;323:1353–68.
24 Anker SD, Butler J, Filippatos G, *et al*. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status. *Circulation* 2021;143:337–49.
25 Packer M. Role of impaired nutrient and oxygen deprivation signaling and deficient autophagic flux in diabetic CKD development: implications for understanding the effects of sodium-glucose cotransporter 2-inhibitors. *J Am Soc Nephrol* 2020;31:907–19.
26 Dekkers CCJ, Petrykiv S, Laverman GD, *et al*. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. *Diabetes Obes Metab* 2018;20:1988–93.
27 Woods TC, Satou R, Miyata K, *et al*. Canagliflozin prevents intrarenal angiotensinogen augmentation and mitigates kidney injury and hypertension in mouse model of type 2 diabetes mellitus. *Am J Nephrol* 2019;49:331–42.
28 Bjornstad P, Greasley PJ, Wheeler DC, *et al*. The potential roles of osmotic and nonosmotic sodium handling in mediating the effects of sodium-glucose cotransporter 2 inhibitors on heart failure. *J Card Fail* 2021;27:1447–55.
29 Bakris G, Oshima M, Mahaffey KW, *et al*. *Effects of Canagliflozin in Patients with Baseline eGFR*.