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Early Change in Albuminuria with Canagliflozin Predicts Kidney and Cardiovascular Outcomes: A *Post Hoc* Analysis from the CREDENCE Trial

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ABSTRACT

Background The association between early changes in albuminuria and kidney and cardiovascular events is primarily based on trials of renin-angiotensin system blockade. It is unclear whether this association occurs with sodium-glucose cotransporter 2 inhibition.

Methods The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial enrolled 4401 patients with type 2 diabetes and CKD (urinary albumin-creatinine ratio [UACR] >300 mg/g). This *post hoc* analysis assessed canagliflozin's effect on albuminuria and how early change in albuminuria (baseline to week 26) is associated with the primary kidney outcome (ESKD, doubling of serum creatinine, or kidney death), major adverse cardiovascular events, and hospitalization for heart failure or cardiovascular death.

Results Complete data for early change in albuminuria and other covariates were available for 3836 (87.2%) participants in the CREDENCE trial. Compared with placebo, canagliflozin lowered UACR by 31% (95% confidence interval [95% CI], 27% to 36%) at week 26, and significantly increased the likelihood of achieving a 30% reduction in UACR (odds ratio, 2.69; 95% CI, 2.35 to 3.07). Each 30% decrease in UACR over the first 26 weeks was independently associated with a lower hazard for the primary kidney outcome (hazard ratio [HR], 0.71; 95% CI, 0.67 to 0.76; $P<0.001$), major adverse cardiovascular events (HR, 0.92; 95% CI, 0.88 to 0.96; $P<0.001$), and hospitalization for heart failure or cardiovascular death (HR, 0.86; 95% CI, 0.81 to 0.90; $P<0.001$). Residual albuminuria levels at week 26 remained a strong independent risk factor for kidney and cardiovascular events, overall and in each treatment arm.

Conclusions In people with type 2 diabetes and CKD, use of canagliflozin results in early, sustained reductions in albuminuria, which were independently associated with long-term kidney and cardiovascular outcomes.

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Micro- or macroalbuminuria are present in approximately 25% of individuals with type 2 diabetes and are strong independent risk markers of cardiovascular and kidney disease.[1,2] Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a cornerstone in the treatment of patients with type 2 diabetes and reduces the risks of kidney failure and cardiovascular outcomes. *Post hoc* analyses from clinical trials of RAAS inhibitors have

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consistently shown that the magnitude of albuminuria reduction during the first months of treatment is associated with a degree of risk reduction for kidney and cardiovascular outcomes.[3–6] These data support the monitoring of albuminuria to inform kidney and cardiovascular prognosis, and suggest that albuminuria may be an independent target for treatment. However, whether or not early changes in albuminuria are associated with kidney and cardiovascular outcomes with interventions that do not modulate the RAAS is uncertain.

The sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin was originally developed as an oral glucose-lowering agent. Early clinical trials demonstrated that canagliflozin also decreased albuminuria and slowed the rate of kidney function decline, independent of its glycemic effects.[7,8] These findings supported the design of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, which demonstrated that canagliflozin reduces the risks of kidney failure and cardiovascular outcomes in patients with type 2 diabetes and CKD.[9]

In this *post hoc* analysis of the CREDENCE trial, we investigated whether an early change in albuminuria after treatment with canagliflozin is associated with long-term cardiovascular and kidney outcomes, and whether this association is independent of the early change in other cardiovascular risk factors.

Significance Statement

Studies of renin-angiotensin system inhibitors have consistently shown that the magnitude of albuminuria reduction during the first months of treatment is associated with risk reduction for kidney and cardiovascular outcomes. Whether or not the association between early changes in albuminuria and these outcomes also occurs with sodium-glucose cotransporter 2 (SGLT2) inhibition is unclear. This *post hoc* analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated that, in people with type 2 diabetes and CKD, treatment with the SGLT2 inhibitor canagliflozin results in an early and sustained reduction in albuminuria. It also shows that early changes in albuminuria were independently associated with long-term kidney and cardiovascular outcomes. These findings highlight the importance of monitoring albuminuria during canagliflozin treatment to assess kidney and cardiovascular prognosis.

METHODS

Patients and Study Design

CREDENCE was a multicenter, double-blind, placebo-controlled, randomized trial evaluating the effects of canagliflozin on kidney and cardiovascular outcomes in patients with type 2 diabetes and CKD. The design of the trial and primary outcomes have been published previously.[9,10] In brief, 4401 individuals underwent randomization at 690 sites in 34 countries between March 2014 and May 2017. Patients were eligible if they were ≥30 years of age; had type 2 diabetes, with a glycated hemoglobin A1c (HbA1c) level between 6.5% and 12.0%; and CKD, defined as an eGFR of 30 to <90 ml/min per 1.73 m^2 and a urinary albumin-creatinine ratio (UACR) of between 300 and 5000 mg/g (>33.9–565.6 mg/mmol). All participants were required to be receiving the maximum tolerated or labeled dose of RAAS inhibitors for at least 4 weeks before randomization.

Participants were randomized to receive 100 mg canagliflozin daily, or matching placebo, using randomly permuted blocks with stratification by screening eGFR categories (30 to <45, 45 to <60, and 60 to <90 ml/min per 1.73 m^2). The use of other background therapy for glycemic management and control of cardiovascular risk factors were recommended in accordance with local guidelines. The median follow-up period was 2.6 years until the last trial visits (either in clinic or *via* telephone), which occurred by October 30, 2018. Local institutional ethics committees approved the trial protocols at each site. All participants provided written informed consent. The trial was conducted according to the principles outlined in the Declaration of Helsinki. CREDENCE is registered with clinicaltrials.gov (NCT02065791).

This secondary analysis of the CREDENCE trial was conducted *post hoc* and was not prespecified as part of the original statistical analysis plan.

Albuminuria Assessments

Urinary albumin and urinary creatinine were measured in single urine specimens from the first morning void at baseline, week 26, and every 26 weeks thereafter (Supplemental Figure 1). Urine albumin concentration was divided by the urine creatinine concentration to correct for hydration status. Albuminuria was thus expressed as UACR. Early change in UACR was defined as the percentage change in UACR from baseline to week 26. The 26-week exposure window was chosen because it was the first time point at which follow-up UACR measurements were available, and prior studies have shown that the UACR-lowering effect of canagliflozin is fully present at that time point.[8,11]

Outcomes

The primary kidney outcome for this study was defined as a composite of ESKD (defined as dialysis for at least 30 days, kidney transplantation, or an eGFR of <15 ml/min per 1.73 m^2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline (average of randomization and prerandomization values) sustained for at least 30 days according to central laboratory assessment, or kidney death. The primary cardiovascular outcomes for this *post hoc* analysis were major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, and a composite of hospitalization for heart failure or cardiovascular death (HHF/CV death). All kidney and cardiovascular outcomes were adjudicated by an independent, blinded, endpoint adjudication committee using predefined and rigorous endpoint definitions.

The effect of canagliflozin versus placebo on early change in albuminuria was calculated from baseline to week 26. For the association between early change in UACR and clinical outcomes, participants were followed from week 26 until the first of the study outcomes, death, or the end of follow-up.

Statistical Analyses

For these analyses, we used 30% thresholds to define change in UACR for several reasons. Large-scale meta-analyses of observational studies have demonstrated that 30% changes in UACR are strongly associated with kidney outcomes.[12] Collaborative meta-analyses sponsored by regulatory agencies have also demonstrated that randomized treatment effects on UACR of at least 30% also correlate strongly with treatment effects on clinical kidney outcomes, particularly in individuals with UACR >30 mg/g at baseline.[13] In addition, 30% change in UACR has been used in a randomized trial to identify responders and has been approved by the US Food and Drug Administration as a threshold to define treatment response.[14] Changes in UACR were expressed as a percentage to focus on relative changes and to enable the assessment of change in UACR across a range of baseline levels of UACR.

We summarized baseline characteristics of participants according to categories of early change in UACR. Continuous variables were reported as means with SDs for variables with approximately symmetric distributions. Results for variables with skewed distributions were presented as median and interquartile range and were transformed into natural logarithms before analysis. Linear trends across categories of an early change in UACR were tested by linear or logistic regression analysis, as appropriate.

We evaluated the effect of canagliflozin compared with placebo on early change in UACR in three complementary analyses. First, we assessed the effect of canagliflozin versus placebo on geometric mean percentage reduction in UACR from baseline to week 26 by analysis of covariance, using treatment as factor and baseline UACR as covariate. Second, we calculated the odds ratio (OR) for achieving a >30% reduction in UACR or a ≥30% increase in UACR at week 26 by logistic regression. Third, we assessed the effect of canagliflozin compared with placebo on the odds of achieving a progression or regression in UACR stage by logistic regression. For this analysis, progression in UACR stage was defined as the development of nephrotic range albuminuria (UACR ≥3000 mg/g), accompanied by an increase in UACR of ≥30% from baseline. Patients (n=411) with UACR ≥3000 mg/g at baseline were excluded from this analysis. Regression in UACR stage was defined as a transition from macroalbuminuria (UACR ≥300 mg/g) to normo- or microalbuminuria (UACR <300 mg/g), or from microalbuminuria (UACR 30 to <300 mg/g) to normoalbuminuria (UACR <30 mg/g), accompanied by a decrease in UACR of >30% from baseline. Patients (n=29) with UACR <30 mg/g at baseline were excluded from this analysis.

We analyzed the association between early change in UACR (fitted categorically and continuously) with kidney and cardiovascular outcomes using Cox proportional hazard regression. When early change in UACR was fitted continuously, hazard ratios (HRs) were expressed per 30% reduction in UACR and adjusted for baseline covariates (including age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic BP, HbA1c, eGFR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, RAAS inhibitor use, randomized treatment [canagliflozin or placebo], and log-transformed UACR) and percentage changes in HbA1c, body weight, systolic BP, and eGFR at week 26. We also analyzed early change in UACR categorically with categories defined as a >30% reduction, a 0% to ≤30% reduction (minor decrease), a 0% to <30% increase (minor increase), and a ≥30% increase. In this analysis, we used a minor increase in UACR (0% to <30%) as reference and adjusted for the same covariates as described previously. Linear trends across categories of early change in UACR were tested by fitting the exposure as an ordinal variable in the relevant model. In sensitivity analyses, missing values of UACR at week 26 and other covariates were imputed using multiple imputation.

To further assess the associations between an early progression or regression of UACR and subsequent risks of kidney and cardiovascular outcomes, we performed Cox regression to estimate HRs for kidney and cardiovascular outcomes in participants who experienced an early transition in UACR stage (as defined previously) compared with those who did not. Cox models were adjusted for the same covariates as described above.

For each outcome, we provide a descriptive assessment of the percentage of the treatment effect, which is removed by statistical adjustment for change in log-transformed UACR values from baseline to week 26. Log-transformed baseline UACR was included as a covariate to the model to minimize the effect of regression to the mean. For each outcome, the percentage of the treatment effect explained was expressed using the equation: $100\% \times \left(\left[HR - HR_{adjusted} \right] / \left[HR - 1 \right] \right)$.[15] Because we did not control confounding between change in UACR and outcomes, estimates of the percentage of treatment effect explained should be interpreted as a measure of association, which may or may not reflect the portion of the treatment effects mediated through UACR.

Finally, to further examine the associations between UACR at week 26 (*i.e.*, residual UACR) and kidney and cardiovascular risk, we estimated the HRs across categories of UACR at week 26 (≤300, >300 to ≤1000, >1000 to ≤3000, and >3000 mg/g) separately in the placebo and canagliflozin treatment arms. We used the lowest UACR category in the placebo arm as a common reference for the other categories and adjusted models for the following baseline covariates: age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic BP, HbA1c, eGFR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, RAAS inhibitor use, randomized treatment (canagliflozin or placebo), and log-transformed UACR. All analyses were performed in Stata version 15.

RESULTS

Study Population

Of 4401 participants in the CREDENCE trial, 205 were excluded because they did not have data available at week 26, and 78 patients were excluded because they experienced a kidney or cardiovascular outcome before week 26. After further exclusion of 282 participants with missing laboratory values, the final study cohort in this analysis consisted of 3836 participants (Supplemental Figure 2).

Effect of Canagliflozin on UACR

Overall, canagliflozin, compared with placebo, reduced geometric mean UACR at 26 weeks by 31% (95% CI, 27% to 36%). Canagliflozin increased the odds of experiencing a >30% reduction in UACR (OR, 2.69; 95% CI, 2.35 to 3.07; $P<0.001$), and decreased the odds of a ≥30% increase in UACR (OR, 0.41; 95% CI, 0.36 to 0.48; $P<0.001$) at week 26. Treatment with canagliflozin also reduced the risk of progression in UACR stage at week 26 from non-nephrotic to nephrotic-range albuminuria (OR, 0.52; 95% CI, 0.41 to 0.66; Figure 1A). Additionally, canagliflozin increased the likelihood of achieving regression in UACR stage (from macroalbuminuria to micro- or normoalbuminuria) compared with placebo (OR, 1.85; 95% CI, 1.55 to 2.22; Figure 1B). However, at the individual level, there was a large variation in UACR change from baseline to week 26 among individual participants, both in the placebo and canagliflozin group (Figure 2).

Association between UACR Change and Kidney and Cardiovascular Outcomes

Characteristics of participants stratified according to change in UACR from baseline to week 26 are displayed in Table 1. A reduction in UACR of >30% was observed in 1551 (40.4%) participants, a minor reduction between 0% and ≤30% in 742 (19.3%), a minor increase between 0% and <30% in 473 (12.3%), and a ≥30% increase was observed in 1070 (27.9%) participants. Patients with a decrease in UACR were older; had a higher baseline UACR, BP, and eGFR; were more likely to be female; and to be diagnosed with heart failure. They were also more likely to be allocated to canagliflozin treatment (Table 1).

Over a median follow-up of 2.2 years (interquartile range, 1.7–2.6), 324 (8.4%) kidney, 349 (9.1%) MACE, and 317 (8.3%) HHF/CV death outcomes were observed. We observed log-linear associations between early change in UACR with kidney and cardiovascular outcomes, such that each 30% decrease in UACR over the first 26 weeks was independently associated with an average 29% lower hazard for the kidney (HR, 0.71; 95% CI, 0.67 to 0.76; $P<0.001$), 8% lower hazard for the MACE (HR, 0.92; 95% CI, 0.88 to 0.96; $P<0.001$), and 14% lower hazard for the HHF/CV death (HR, 0.86; 95% CI, 0.81 to 0.90; $P<0.001$) outcome. A similar association was observed for HHF alone (Supplemental Figure 3). The risk relationship between the early change in UACR and clinical outcomes was log linear, with a steeper risk gradient for the kidney than for cardiovascular outcomes, as displayed in Figure 3 and Supplemental Table 1. When canagliflozin- and placebo-assigned patients were analyzed separately, the relationship between early change in UACR and risk of kidney and cardiovascular outcomes was significant in both treatment arms, with a stronger risk relationship for the kidney outcome in the canagliflozin group (Table 2). The association between early change in UACR and kidney outcome was stronger in patients with lower eGFR and higher UACR (Table 2). In contrast, the associations between early change in UACR and cardiovascular outcomes were consistent across baseline UACR and eGFR subgroups (P interaction>0.38). Results were similar in sensitivity analyses using multiple imputation to account for missing values (Supplemental Table 2).

We subsequently analyzed whether a transition in UACR stage during the first 26 weeks was associated with kidney and cardiovascular outcomes. Progression of UACR to nephrotic-range albuminuria was associated with a significantly higher risk for the kidney and HHF/CV death outcome, after adjusting for baseline covariates and week 26 changes in HbA1c, body weight, systolic BP, and eGFR (Figure 4). Conversely, regression in UACR stage during the first 6 months was associated with a lower risk of MACE and HHF/CV death outcomes (Figure 4).

The results of the analysis assessing the proportion of the treatment effect explained by UACR change on kidney and cardiovascular protection with canagliflozin are displayed in Table 3. UACR lowering from baseline to week 26 explained 47.5% of the effect on the primary kidney outcome, 36.1% of the effect on the MACE outcome, and 41.0% of the effect on the HHF/CV death outcome.

Association between Residual UACR and Kidney and Cardiovascular Outcomes

Finally, we assessed the relationship between the residual UACR level at week 26 and kidney and cardiovascular outcomes. As expected, more patients in the canagliflozin, compared with placebo, group were categorized into lower UACR categories at week 26 (Figure 5). Nevertheless, UACR remained >1000 mg/g in 643 (33.2%) patients in the canagliflozin arm at week 26 versus 883 (46.5%) in the placebo arm ($P<0.001$). We observed a strong association between residual UACR at week 26 with kidney and cardiovascular outcomes (Figure 6). The association between week 26 UACR and outcomes was present irrespective of randomized treatment allocation. The canagliflozin and placebo groups completely overlapped, indicating that residual UACR levels after treatment with canagliflozin were associated with similar kidney and cardiovascular risk as the (unchanged) UACR level in participants treated with placebo.

DISCUSSION

The recognized association between early change in albuminuria and kidney and cardiovascular events in people with and

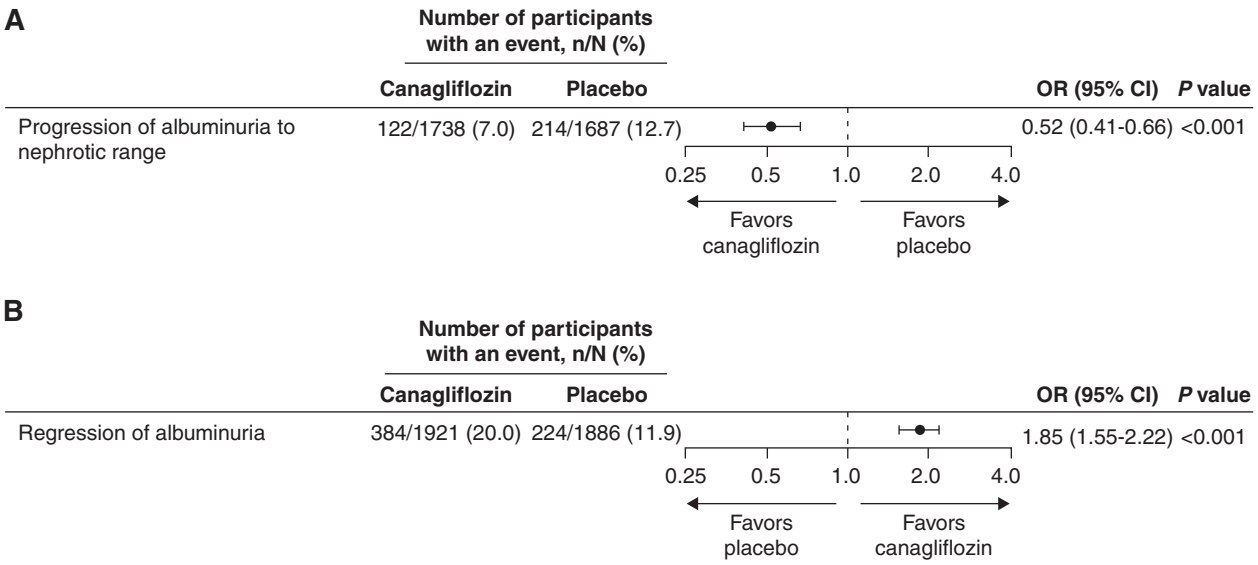

Figure 1. By week 26, canagliflozin lowered the odds of progression to nephrotic range albuminuria (Panel A) and increased the odds of regression of albuminuria (Panel B). Canaglifozin decreased the odds of a ≥30% increase in albuminuria (OR, 0.41; 95% CI, 0.36 to 0.48; $P<0.001$) and increased the odds of experiencing a >30% reduction in albuminuria (OR, 2.69; 95% CI, 2.35 to 3.07; $P<0.001$).

without type 2 diabetes or CKD is largely based on interventions that inhibit the RAAS. This study extends these findings by demonstrating that albuminuria reductions during the first months of treatment with the SGLT2 inhibitor canagliflozin are associated with a reduced risk of kidney and cardiovascular outcomes in people with type 2 diabetes mellitus and CKD, independent of baseline and of early changes in cardiovascular risk markers. Furthermore, we observed that, despite early and sustained reductions in albuminuria with canagliflozin, levels of residual albuminuria remained a strong predictor of kidney and cardiovascular events. Taken together, these data highlight the importance of monitoring albuminuria during canagliflozin treatment to assess kidney and cardiovascular prognosis.

In the CREDENCE trial, we observed that changes in albuminuria during the first 6 months of treatment with canagliflozin are independently associated with long-term clinical outcomes, although change in albuminuria does vary widely among individual participants. The association between change in albuminuria and kidney outcomes was stronger than for cardiovascular outcomes. This reflects the central role of albuminuria as a risk factor for kidney events, whereas cardiovascular risk is determined by multiple other factors, including hyperglycemia and hyperlipidemia. The association between change in albuminuria and clinical outcomes was consistent for most subgroups. A notable exception was observed for baseline albuminuria, in which a larger reduction for the kidney end point was observed per 30% albuminuria reduction at higher baseline levels of albuminuria. The association between albuminuria and risk of kidney failure is log-log linear, and thus a 30% reduction in albuminuria is associated with a greater risk reduction in people with higher levels of albuminuria at baseline, which has also been demonstrated previously.[12]

The effect of canagliflozin on early change in albuminuria was robust in various analyses. Treatment with canagliflozin resulted in an early reduction in albuminuria when analyzed continuously or categorically. We observed that, even within 26 weeks, canagliflozin decreased the risk of progression to nephrotic-range albuminuria, and that an early transition in albuminuria stage confers important prognostic information. A regression in albuminuria stage during the first 26 weeks of the trial was associated with a lower kidney and cardiovascular risk, whereas a progression in albuminuria stage was associated with a higher risk. The strong and consistent association between an early albuminuria change and clinical outcomes,

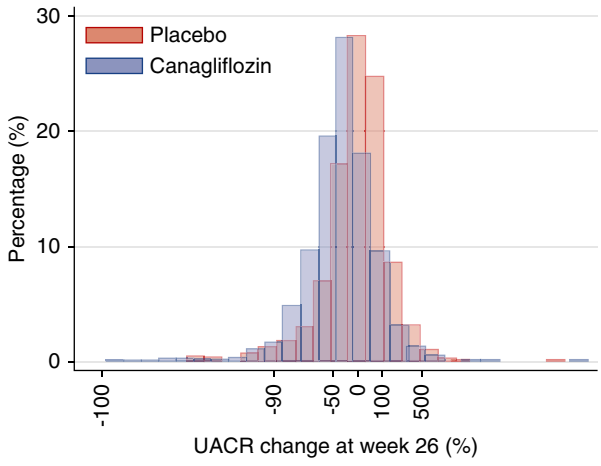

Figure 2. Canagliflozin lowered albuminuria by 31% (95% CI, 27% to 36%) at week 26. At an individual level, however, there was large variation in early change in albuminuria, both in canagliflozin- and placebo-treated participants.

Table 1. Baseline characteristics of participants by early change in albuminuria at week 26

Characteristics	Early Change in Albuminuria at Week 26				*P* Trend
	>30% Decrease	0% to ≤30% Decrease	0% to <30% Increase	≥30% Increase	
N (%)	1551 (40.4)	742 (19.3)	473 (12.3)	1070 (27.9)	
Change in % UACR at week 26, median (IQR)	−58.6 (−75.2 to −43.8)	−16.5 (−23.7 to −8.9)	13.9 (7.0 to 21.4)	81.8 (50.5 to 156.2)	<0.001
Baseline UACR (mg/g), median (IQR)	964 (507–1867)	1080 (537–2117)	874 (469–1807)	668 (358–1434)	<0.001
Baseline UACR, *n* (%)					<0.001
≤300 mg/g	147 (9.5)	60 (8.1)	56 (11.8)	203 (19.0)	
>300 to ≤1000 mg/g	655 (42.2)	291 (39.2)	206 (43.6)	476 (44.5)	
>1000 to ≤3000 mg/g	563 (36.3)	300 (40.4)	153 (32.3)	315 (29.4)	
>3000 mg/g	186 (12.0)	91 (12.3)	58 (12.3)	76 (7.1)	
Age, years	63.7 (8.8)	62.7 (9.4)	62.2 (9.4)	62.2 (9.1)	<0.001
Men, *n* (%)	945 (60.9)	521 (70.2)	329 (69.6)	737 (68.9)	<0.001
Race or ethnic group, *n* (%)					0.07
White	1064 (68.6)	478 (64.4)	295 (62.4)	697 (65.1)	
Black	76 (4.9)	30 (4.0)	21 (4.4)	59 (5.5)	
Asian	289 (18.6)	177 (23.9)	109 (23.0)	224 (20.9)	
Other	122 (7.9)	57 (7.7)	48 (10.1)	90 (8.4)	
Current smoker, *n* (%)	205 (13.2)	121 (16.3)	62 (13.1)	166 (15.5)	0.19
History of hypertension, *n* (%)	1499 (96.6)	720 (97.0)	458 (96.8)	1032 (96.4)	0.78
History of heart failure, *n* (%)	266 (17.2)	86 (11.6)	57 (12.1)	145 (13.6)	0.008
Duration of diabetes, yr	15.8 (8.7)	15.8 (8.9)	16.1 (8.6)	15.4 (8.2)	0.36
History of cardiovascular disease, *n* (%)	798 (51.5)	354 (47.7)	229 (48.4)	535 (50.0)	0.45
Body mass index, kg/m^2	31.3 (6.1)	31.1 (5.6)	31.1 (6.4)	31.3 (6.2)	0.93
Systolic blood pressure, mm Hg	140.5 (15.6)	140.3 (15.5)	140.1 (14.7)	138.4 (15.6)	0.001
Diastolic blood pressure, mm Hg	78.6 (9.3)	78.4 (9.2)	78.6 (9.3)	77.7 (9.6)	0.02
HbA1c, %	8.3 (1.3)	8.2 (1.3)	8.2 (1.3)	8.3 (1.3)	0.81
eGFR, ml/min per 1.73 m^2	57.6 (18.2)	55.4 (18.1)	56.2 (17.7)	55.7 (18.6)	0.02
Screening eGFR, *n* (%)					0.58
30 to <45 ml/min per 1.73 m^2	432 (27.9)	226 (30.5)	135 (28.5)	314 (29.4)	
45 to <60 ml/min per 1.73 m^2	452 (29.1)	224 (30.2)	147 (31.1)	299 (27.9)	
60 to <90 ml/min per 1.73 m^2	667 (43.0)	292 (39.4)	191 (40.4)	457 (42.7)	
Total cholesterol, mmol/L	4.7 (1.3)	4.7 (1.3)	4.6 (1.3)	4.6 (1.3)	0.03
HDL cholesterol, mmol/L	1.2 (0.4)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.31
LDL cholesterol, mmol/L	2.5 (1.1)	2.5 (1.1)	2.5 (1.0)	2.5 (1.0)	0.12
Triglycerides (mmol/L), median (IQR)	1.8 (1.3–2.7)	1.9 (1.4–2.7)	1.9 (1.4–2.7)	1.8 (1.3–2.5)	0.08
Insulin use, *n* (%)	1001 (64.5)	494 (66.6)	312 (66.0)	697 (65.1)	0.75
Diuretic use, *n* (%)	742 (47.8)	348 (46.9)	205 (43.3)	490 (45.8)	0.19
Randomized treatment					<0.001
Canagliflozin, *n* (%)	1006 (64.9)	377 (50.8)	179 (37.8)	374 (35.0)	
Placebo, *n* (%)	545 (35.1)	365 (49.2)	294 (62.2)	696 (65.0)	

Data presented are mean (SD) unless otherwise indicated. Percentages may not total 100.0% due to rounding. IQR, interquartile range.

regardless of whether albuminuria is analyzed continuously or as a categoric transition, supports the utility of the Kidney Disease Improving Global Outcomes albuminuria categories for risk stratification and monitoring in routine clinical practice.[16]

Because canagliflozin significantly lowered albuminuria, and albuminuria changes were associated with kidney and cardiovascular events, we estimated the proportion of the effects of the randomized treatment on clinical outcomes that can be accounted for by statistical adjustment for early change in albuminuria. Because we did not control for potential confounding between albuminuria change and clinical outcomes, these analyses may or may not reflect the proportions of the treatment effect that is mediated through albuminuria. Nevertheless, we observed that reductions in albuminuria might explain close to 50% of the treatment effect on the primary kidney outcome. This finding extends previous work demonstrating that albuminuria lowering explained approximately half of the kidney-protective effect of the angiotensin receptor blocker losartan, and is consistent with recent data from the CANVAS Program.[3,17] Thus, our findings are similar to those previously observed with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, but achieved with an intervention that does not directly interfere in the RAAS.

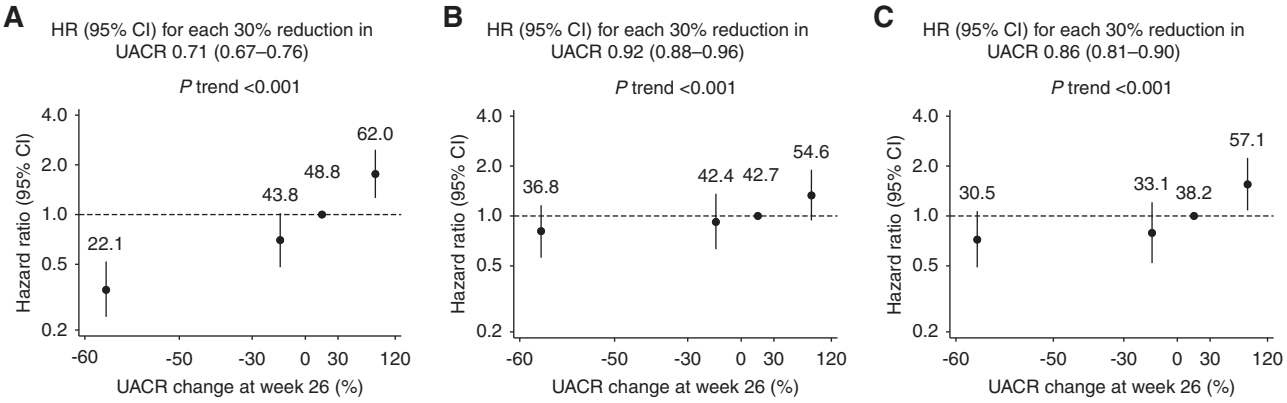

Figure 3. Early change in albuminuria at week 26 was independently associated with risk of (A) kidney composite outcome, (B) MACE, and (C) HHF/CV death. The numbers above each circle represent the event rates for each change in UACR category. Adjusted for baseline covariates (including age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic BP, HbA1c, eGFR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, RAAS inhibitor use, randomized treatment [canagliflozin or placebo], and log-transformed UACR) and percentage changes in HbA1c, body weight, systolic BP, and eGFR at week 26.

The mediating effect of albuminuria on kidney protection with canagliflozin may be attributed to reductions in intraglomerular pressure due to beneficial effects on afferent and/or efferent arteriolar tone.[18,19] Favorable direct and indirect effects on vascular endothelial and glycocalyx barrier function might also contribute to the observed kidney and/or cardiovascular benefits.[20]

Although canagliflozin substantially lowered albuminuria within 26 weeks, residual albuminuria remained high in a substantial proportion of participants treated with canagliflozin during the trial. The level of residual albuminuria in the canagliflozin treatment group displayed a similar association with clinical outcomes as the residual albuminuria in the placebo group. This underscores the need for additional therapies that further lower albuminuria to improve clinical outcomes for people with type 2 diabetes and CKD, especially those with very high levels of albuminuria. Various therapies that target other hormone systems or pathways of disease progression beyond SGLT2 transporters are currently in development and may be useful as an adjunct to SGLT2 inhibition.[21]

This analysis benefited from the rigorous methods of data collection and reporting in the CREDENCE trial. However, the results should be interpreted in the context of some limitations. This was a *post hoc* analysis with the inherent limitations of such an approach; as such, all reported *P* values were nominal in nature, and no correction for multiplicity was applied. The associations between early change in albuminuria and clinical outcomes are observational and, despite careful adjustment for potential confounders, residual confounding cannot be excluded. However, the strength and consistency of our findings with existing evidence from a range of other interventions suggests this is unlikely to materially alter our conclusions. It should also be noted that mediation analyses do not guarantee that albuminuria is directly on the pathway to progression of kidney disease and thus causality cannot be inferred. The question of whether individuals who do not achieve a reduction in albuminuria with canagliflozin still derive kidney and cardiovascular benefits could not be reliably answered in this study because these participants were defined postrandomization. Answering this question would require a separate randomized trial with either an active run-in period to identify participants who achieve an early reduction in albuminuria before randomization (such as in the ADVANCE trial) or leveraging an enrichment design, such as that used in the SONAR trial.[22,23] Albuminuria was measured in single urine samples from the first morning void. It is known that the day-to-day variability in urine samples from single first morning voids is larger than three consecutive first-morning-void samples collected on the same day.[24] This may explain, to some extent, the observed large variation in albuminuria changes in both the canagliflozin and placebo arms, suggesting that changes during canagliflozin treatment may not always necessarily indicate a treatment effect, but could also reflect—in part—random variation. Additionally, natural variability may have attenuated the strength of the association between change in albuminuria and kidney and cardiovascular outcomes. However, despite the use of single urine samples from the first morning void, a strong and highly significant association could still be detected. Finally, although CREDENCE was an international, multicenter randomized trial, approximately two-thirds of participants were White and some racial groups, such as Black, were underrepresented, which may have had an effect on the generalizability of our findings. However, there were no significant differences in the effects of canagliflozin on major kidney and cardiovascular outcomes across race subgroups.[9,25]

In conclusion, in people with type 2 diabetes and CKD, early reductions in albuminuria are associated with a reduction in risk of kidney and cardiovascular outcomes. Treatment with canagliflozin results in early and sustained reductions in albuminuria, which might explain a substantial proportion of

Table 2. HRs and 95% CIs of each 30% reduction in albuminuria at week 26 with the primary outcomes by baseline patient characteristics

Characteristic	Kidney Outcome			Cardiovascular Outcome			HHF/CV Death Outcome		
	N of Events/ Total	HR (95% CI)	*P* for Interaction	*N* of Events/ Total	HR (95% CI)	*P* for Interaction	*N* of Events/ Total	HR (95% CI)	*P* for Interaction
Overall		0.71 (0.67 to 0.76)			0.92 (0.88 to 0.96)			0.86 (0.81 to 0.90)	
Treatment									
Canagliflozin	130/1936	0.64 (0.58 to 0.71)	0.001	154/1936	0.93 (0.87 to 0.99)	0.78	132/1936	0.85 (0.79 to 0.93)	0.98
Placebo	194/1900	0.79 (0.72 to 0.86)		195/1900	0.91 (0.86 to 0.97)		185/1900	0.86 (0.80 to 0.92)	
Age (years)									
<65	227/2062	0.68 (0.62 to 0.74)	0.09	163/2062	0.94 (0.88 to 1.00)	0.83	141/2062	0.86 (0.79 to 0.93)	0.85
≥65	97/1774	0.75 (0.67 to 0.85)		186/1774	0.91 (0.85 to 0.97)		176/1774	0.86 (0.80 to 0.92)	
Sex									
Male	219/2532	0.66 (0.60 to 0.72)	0.05	242/2532	0.92 (0.86 to 0.97)	0.69	211/2532	0.86 (0.81 to 0.93)	0.72
Female	105/1304	0.80 (0.72 to 0.88)		107/1304	0.92 (0.86 to 0.99)		106/1304	0.85 (0.78 to 0.92)	
Screening eGFR (ml/min per 1.73 m^2)									
30 to <45	171/1107	0.69 (0.63 to 0.76)	0.02	121/1107	0.90 (0.82 to 0.98)	0.69	113/1107	0.85 (0.77 to 0.93)	0.63
45 to <60	87/1122	0.64 (0.54 to 0.74)		101/1122	0.93 (0.84 to 1.01)		97/1122	0.83 (0.75 to 0.92)	
60 to <90	66/1607	0.84 (0.73 to 0.96)		127/1607	0.94 (0.88 to 1.01)		107/1607	0.88 (0.81 to 0.96)	
UACR (mg/g)									
≤300	11/466	0.63 (0.42 to 0.93)	0.004	23/466	1.03 (0.89 to 1.20)	0.50	16/466	0.96 (0.80 to 1.16)	0.38
>300 to ≤1000	44/1628	0.84 (0.72 to 0.97)		145/1628	0.92 (0.85 to 0.99)		127/1628	0.87 (0.80 to 0.94)	
>1000 to ≤3000	141/1331	0.76 (0.69 to 0.85)		126/1331	0.92 (0.85 to 1.00)		118/1331	0.87 (0.80 to 0.96)	
>3000	128/411	0.59 (0.51 to 0.69)		55/411	0.88 (0.76 to 1.02)		56/411	0.77 (0.66 to 0.91)	

Adjusted for baseline covariates (including age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic blood pressure, HbA1c, eGFR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, RAAS inhibitor use, and log-transformed UACR) and percentage changes in HbA1c, body weight, systolic blood pressure, and eGFR at week 26. Interaction tests were performed by adding an interaction term between treatment assignment and categoric baseline factor to the relevant Cox models.

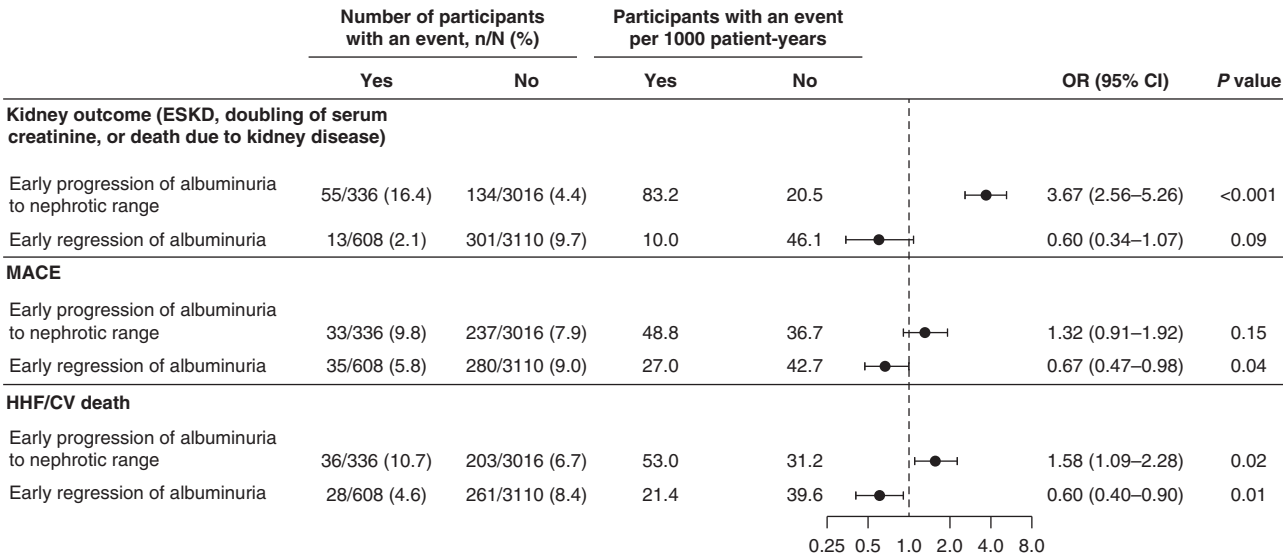

Figure 4. Early progression to nephrotic range albuminuria was associated with increased risk of the kidney outcome and HHF/CV death, while early regression of albuminuria was associated with a decreased risk of MACE and HHF/CV death. Early progression or regression of albuminuria is defined as the development of progression or regression of albuminuria before UACR measurements at week 26. Adjusted for baseline covariates (including age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic BP, HbA1c, eGFR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, RAAS inhibitor use, randomized treatment [canagliflozin or placebo], and log-transformed UACR) and percentage changes in HbA1c, body weight, systolic BP, and eGFR at week 26.

its kidney and cardiovascular protective effects. These findings underscore the importance of monitoring albuminuria during treatment with canagliflozin to inform kidney and cardiovascular prognosis.

DISCLOSURES

D. Charytan has received fees paid by Janssen Pharmaceuticals to the Baim Institute for work on the CREDENCE trial steering committee and as scientific lead, and has received salary support from the Baim Institute for this work through October 2018. After that time, he received consulting fees from Baim. He has consulted for Amgen, AstraZeneca, Medtronic/Covidien, Zoll, Fresenius, Daiichi Sankyo, Douglas and London, Eli Lilly, Merck, Gilead, and Novo Nordisk; has served on data safety and monitoring boards for AstraZeneca and Allena Pharmaceuticals; has served on a clinical endpoint committee for Merck and PLC Medical; has received research support from Amgen and Medtronic; has received grants from BioPorto; and has received personal fees from GlaxoSmithKline; outside the submitted work. L. De Nicola serves as a scientific advisor to Mundipharma, AstraZeneca, Astellas, and Vifor, and has received speaker fees for continuing medical education events by Mundipharma, AstraZeneca, Astellas and Vifor, outside the submitted work. D. de Zeeuw reports serving on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, Mitsubishi Tanabe, and Retrophin; serving on steering committees and/or as a speaker for AbbVie and Janssen; and serving on data safety and monitoring committees for Bayer; outside the submitted work. R. Edwards is a full-time employee of Janssen Research & Development, LLC. T. Greene reports personal fees from Durect, personal fees from Pfizer, and research support from AstraZeneca and Boehringer Ingelheim, outside the submitted work. He has received consulting fees from Janssen Research and Development LLC, during the conduct of the study. H. Heerspink is supported by a VIDI (917.15.306) grant from The Netherlands Organisation for Scientific Research; has served as a consultant for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, and Retrophin; has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen; and has received other from Novo Nordisk; outside the submitted work. M. Jardine 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 Baxter, Amgen, Eli Lilly, and Merck Sharp & Dohme; serves on a steering committee sponsored by CSL; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, and Vifor; has spoken at scientific meetings sponsored by Janssen and Amgen, with any consultancy, honoraria, or travel support paid to her institution; and reports other from AstraZeneca and other from Roche; outside the submitted work. She reports serving on the CREDENCE steering committee sponsored by Janssen Research & Development, LLC and to have spoken at scientific

Table 3. Assessment of the proportion of treatment effect explained by early change in albuminuria

Outcome	HR Control (95% CI)[a]	HR Adjusted (95% CI)[b]	Proportion Explained (%)[c]
Kidney outcome	0.62 (0.50 to 0.77)	0.80 (0.64 to 1.00)	47.5
Cardiovascular outcome	0.75 (0.61 to 0.92)	0.84 (0.68 to 1.04)	36.1
HHF/CV death	0.68 (0.55 to 0.84)	0.81 (0.65 to 1.01)	41.0

[a]HR control reflects the HR for the comparison of canagliflozin versus placebo.
[b]HR adjusted reflects the HR with further adjustment of the model for change in UACR at week 26 and baseline UACR (to correct for potential regression to the mean).
[c]Percentage of treatment effect explained = $100\times([HR_{control}-HR_{adjusted}]/[HR_{control}-1])$.

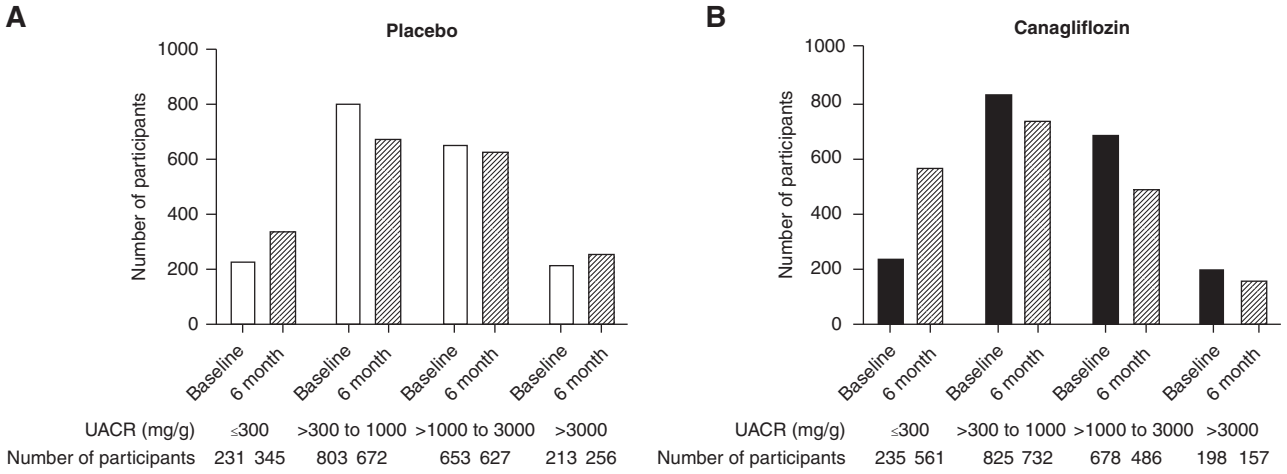

Figure 5. More participants treated with canagliozin, compared with placebo, were categorized into lower UACR categories at week 26. Number of participants in each category at baseline and month 6 are provided at the bottom.

meetings sponosred by Janssen Research & Development, LLC, during the conduct of the study. A. Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); is on the data safety and monitoring board for the NIDDK, Kidney Precision Medicine, University of Washington Kidney Research Institute Scientific Advisory Committee; is funded by the Canadian Institute of Health Research and Kidney Foundation of Canada, outside the submitted work; and has received fees for time as CREDENCE National Coordinator from Janssen, directed to her academic team, during the conduct of the study. J. Li is a full-time employee of the George Institute for Global Health. K. Mahaffey has received research support from Afferent, Amgen, Apple Inc., AstraZeneca, Cardiva Medical Inc., Daiichi Sankyo, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health (NIH), Novartis, Sanofi, St. Jude, and Tenax; has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol

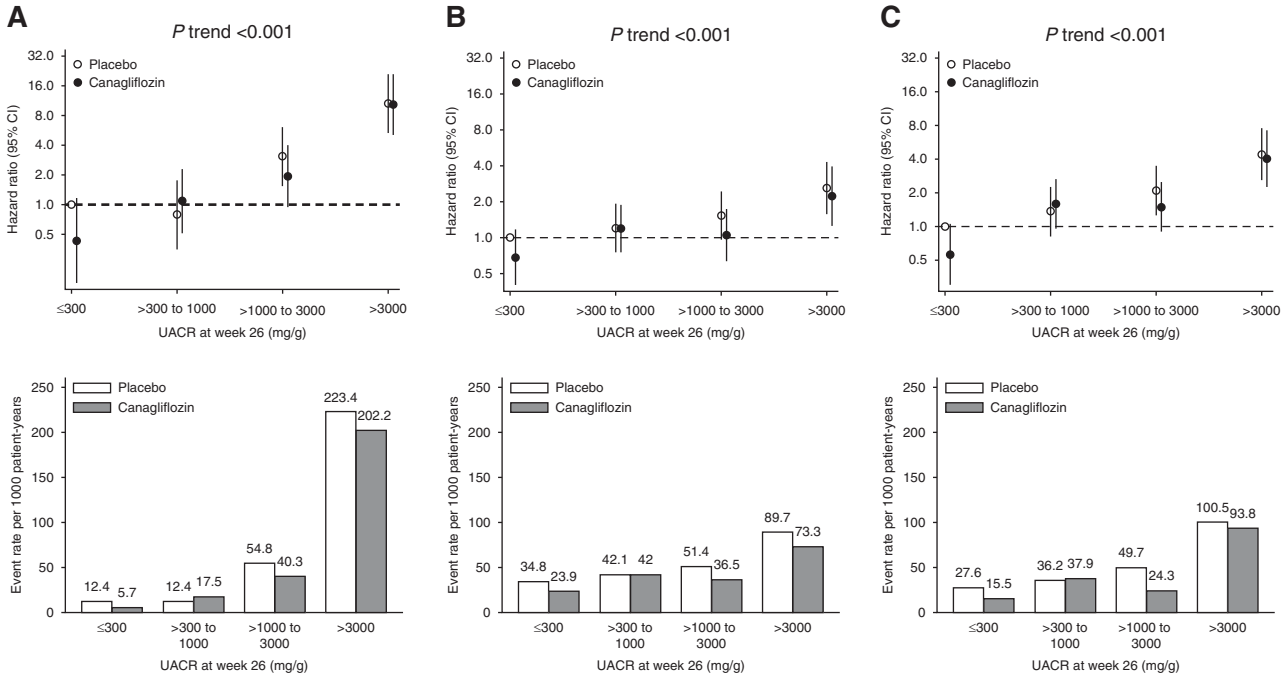

Figure 6. Residual albuminuria at week 26 was strongly associated with kidney and cardiovascular outcomes and was present irrespective of randomized treatment allocation. Associations of residual albuminuria at week 26 with (A) kidney composite outcome, (B) MACE outcome, and (C) HHF/CV death outcome in the canagliflozin and placebo groups. Adjusted for baseline covariates, including age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic BP, HbA1c, eGFR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, RAAS inhibitor use, randomized treatment (canagliflozin or placebo), and log-transformed UACR.

Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco; and has received personal fees from Abbott, Anthos, CSL Behring, Intermountain Health, Mount Sinai, Mundi Pharma, SmartMedics, and Theravance; outside the submitted work. B. Neuen is supported by an Australian National Health and Medical Research Council Postgraduate Scholarship and a University Postgraduate Award from the University of New South Wales, and he has received travel support from Janssen, outside the submitted work. M. Oshima is supported by the Japan Society for the Promotion of Science Program for Fostering Globally Talented Researchers. V. Perkovic has received fees for advisory boards, steering committee roles, or scientific presentations from AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsa, Retrophin, Sanofi, Servier, Vifor, and Tricida; has received personal fees from Vitae; and has received grants from the Australian National Health and Medical Research Council; outside the submitted work. C. Pollock has received honoraria for serving on advisory boards and as a speaker for Merck Sharp & Dohme, AstraZeneca, and Boehringer Ingelheim/Eli Lilly, and has received personal fees from Johnson and Johnson/Janssen Cilag and Novartis, outside the submitted work. N. Rosenthal is a full-time employee of Janssen Research & Development, LLC. D. Wheeler has received fees and travel funding from Janssen for his role as a member of the CREDENCE steering committee. He has also received fees for advisory boards, steering committee roles, or scientific presentations from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Mitsubishi, Mundipharma, Merck Sharp & Dohme, Napp, Ono Pharma, Reata, Tricida, and Vifor Fresenius, and he has received personal fees from Astellas, outside the submitted work. All remaining authors have nothing to disclose.

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H. Heerspink wrote the first draft of the paper, had full access to the study design information, and had final responsibility for the decision to submit for publication. M. Oshima, B. Neuen, and M. Jardine contributed to the analysis and interpretation of data. H. Heerspink, M. Oshima, and B. Neuen contributed to the design and conduct of the study and the interpretation of the data. All authors provided input into subsequent drafts and approved the final version for submission. All authors reviewed and approved the manuscript.

DATA SHARING STATEMENT

Data from this study will be made available in the public domain *via* the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and European Union, and the study has been completed for 18 months.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020050723/-/DCSupplemental.

Supplemental Figure 1. Study design of the analysis.

Supplemental Figure 2. Study design and identification of the study cohort.

Supplemental Figure 3. Associations of early changes in albuminuria at week 26 with HHF in the overall population.

Supplemental Table 1. Associations of early changes in albuminuria at week 26 with kidney composite outcome, MACE, and HHF/CV death in the overall population.

Supplemental Table 2. Sensitivity analysis of the associations of early changes in albuminuria at week 26 with kidney and cardiovascular outcomes in the overall population after missing values were imputed using multiple imputation.

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