Kidney, Cardiovascular, and Safety Outcomes of Canagliflozin According to Baseline Albuminuria: A CREDENCE Secondary Analysis

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Running headline: Canagliflozin effects in UACR subgroups

Abstract

Background and objectives

The kidney protective effects of renin-angiotensin system inhibitors are greater in people with higher levels of albuminuria at treatment initiation. Whether this applies to sodium glucose co-transporter 2 (SGLT2) inhibitors is uncertain, particularly in patients with a very high urine albumin-to-creatinine ratio (UACR ≥3000 mg/g). We examined the association between baseline UACR and the effects of the SGLT2 inhibitor, canagliflozin, on efficacy and safety outcomes in the CREDENCE randomised controlled trial.

Design, setting, participants, and measurements

CREDENCE enrolled 4401 participants with type 2 diabetes, an estimated Glomerular Filtration Rate 30-<90 mL/min/1.73^2 and UACR >300-5000 mg/g. Using Cox proportional hazards regression, we examined the relative and absolute effects of canagliflozin on kidney, cardiovascular and safety outcomes according to a baseline UACR of ≤1000 mg/g (*n*=2348), >1000-<3000 mg/g (*n*=1547) and ≥3000 mg/g (*n*=506). In addition, we examined the effects of canagliflozin on UACR itself, eGFR slope and the intermediate outcomes of glycated hemoglobin, body weight and systolic blood pressure.

Results

Overall, higher UACR was associated with higher rates of kidney and cardiovascular events. Canagliflozin reduced efficacy outcomes for all UACR levels, with no evidence that relative benefits varied between levels. Absolute risk reductions for kidney outcomes were greater in participants with higher baseline albuminuria; the number of primary composite events prevented across ascending UACR categories were 17 (95% confidence interval 3-38), 45 (9-81) and 119 (35-202) per 1000 treated participants over 2.6 years (P-heterogeneity=0.02). Rates of kidney-related adverse events were lower with canagliflozin, with a greater relative reduction in higher UACR categories.

Conclusions

Canagliflozin safely reduces kidney and cardiovascular events in people with type 2 diabetes and severely increased albuminuria. In this population, the relative kidney benefits were consistent over a range of albuminuria levels, with greatest absolute benefit in those with a UACR ≥3000 mg/g.

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Key words: SGLT2 inhibitors, canagliflozin, chronic kidney disease progression, albuminuria, randomized controlled trials, Cardiovascular System

Introduction

Agents that offer kidney protection often have greater relative benefits in those with higher albuminuria (or proteinuria) at treatment initiation. For example, the protective effect of renin-angiotensin system (RAS) inhibitors on the progression of chronic kidney disease (CKD) is modified by baseline proteinuria in people with[1,2] and without[3,4] diabetes. Similarly, the relative benefits of tolvaptan, a vasopressin v2 receptor antagonist, on eGFR decline in people with autosomal-dominant polycystic kidney disease increases with baseline albuminuria.[5] The relationship between albuminuria and treatment effects in these studies was demonstrated in populations with normal-to-moderate albuminuria. Whether this holds true at very high levels (including nephrotic-range) and whether albuminuria modifies the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors are unclear.

Prior to the demonstration of their benefits for kidney and cardiovascular outcomes[6,7], it was clear that SGLT2 inhibitors reduced albuminuria in patients with type 2 diabetes.[8] Albuminuria is a strong predictor of kidney disease progression and cardiovascular disease[9-11] and, together with eGFR, is the foundation for the Kidney Disease: Improving Global Outcomes (KDIGO) kidney disease risk classification system.[9,12] Consequently, people with higher albuminuria might derive greater absolute benefit from albuminuria-lowering treatments.

SGLT2 inhibitors prevent kidney and cardiovascular events in people with type 2 diabetes.[13-16] In the kidney outcome trial, CREDENCE, canagliflozin reduced the risk of the primary composite outcome of kidney failure, a doubling of serum creatinine, or kidney or cardiovascular death by 30% (HR 0.70, 95%CI 0.59-0.82). Canagliflozin also reduced the risk of numerous kidney- and cardiovascular-specific outcomes (e.g. kidney failure and the composite outcome of myocardial infarction, stroke or cardiovascular death).

The CREDENCE trial recruited participants with severely increased albuminuria (UACR >300-5000 mg/g), including >500 with nephrotic-range albuminuria who were already stabilized on RAS blockade. In this population of people at high risk of progressive kidney and cardiovascular disease, we assessed the relative and absolute effects of canagliflozin according to baseline UACR.

Methods

CREDENCE was an event-driven, double-blind, randomised controlled trial whose design and main results have been previously described.[15,17] Ethical approval was obtained at each participating site prior to commencement of recruitment. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

Participants and albuminuria assessment

Trial eligibility criteria were designed to recruit participants at high risk of progression of diabetic kidney disease. Participants were aged ≥30 years with type 2 diabetes, a glycated hemoglobin (HbA1c) level of 6.5%-12.0%, an eGFR of 30-<90 mL/min/1.73m^2 (calculated using the CKD Epidemiology Collaboration formula)[18] and a UACR of >300-5000 mg/g. Key exclusion criteria included nondiabetic kidney disease, type 1 diabetes, and prior treatment of kidney disease with immunosuppression or kidney replacement therapy (KRT). Treatment with a stable maximum-labeled/tolerated dose of ACE inhibitor or angiotensin receptor blocker (ARB) for ≥4 weeks prior to randomization was required.

In CREDENCE, albuminuria was assessed at multiple timepoints. First, to be eligible for screening, participants were required to have a UACR >300 mg/g (>33.9 mg/mmol) or equivalent, confirmed by a local laboratory result within 6 months of screening. At screening, a UACR of >300-5000 mg/g (>33.9-565.6 mg/mmol) on central laboratory measurement was required. Third, albuminuria was measured

at randomisation through a central laboratory, but, notably, this was not used to judge eligibility. Thus, participants with a UACR <300 mg/g by randomisation could be enrolled.

Participants were randomized in a 1:1 ratio to receive double-blinded oral canagliflozin 100 mg or placebo daily until initiation of KRT (dialysis or kidney transplantation), occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy or study end.

Outcomes

The efficacy outcomes for the current analyses were the same as those reported for the overall trial.[15] All efficacy outcomes and selected safety outcomes were independently adjudicated by blinded expert committees.

The primary outcome was the composite of kidney failure (initiation of dialysis for ≥30 days, kidney transplantation, or eGFR <15 mL/min/1.73m^2 sustained for ≥30 days by central laboratory assessment), a doubling of serum creatinine from baseline (average of randomization and pre-randomization value) sustained for ≥30 days by central laboratory assessment, or death due to kidney or cardiovascular disease. Secondary kidney and cardiovascular efficacy outcomes are shown in Table 1.

Safety outcomes with ≥10 events in each albuminuria subgroup were examined, and included all kidney-related adverse events combined, acute kidney injury (AKI), volume depletion, hyperkalemia, urinary tract infections (UTI) and hypoglycemia (Table 1). Similar to other CREDENCE analyses, kidney-related adverse events were defined as those that were coded as primarily involving the kidney according to *Medical Dictionary for Regulatory Activities* (MedDRA) terminology and which were investigator-reported (Table 1).

Percentage and absolute change in albuminuria was calculated as the difference between baseline UACR and the average of all UACR measurements to Week 182. eGFR slope was assessed as the acute change in eGFR from baseline to Week 3 (acute slope), the annualized change in eGFR from Week 3 until treatment end (chronic slope) and the annualized change in eGFR from baseline to Week 130 (total slope). Finally, we assessed the intermediate outcomes of HbA1c, body weight and systolic blood pressure.

Statistical analysis

The effects of canagliflozin were analyzed according to the baseline UACR categories ≤1000, >1000-<3000 and ≥3000 mg/g. These broadly equate to a urine protein-to-creatinine ratio of ≤1920 mg/g, >1920-<5000 mg/g and ≥5000 mg/g, albeit with some uncertainty around these values (http://ckdpcrisk.org/pcr2acr/, accessed on 24 July2020).[19] Baseline UACR was used in the present analysis as it represents the pre-treatment measurement at which all participants had been treated with a stable dose of maximally-tolerated ACE inhibitor/ARB.

For all event-based outcomes, an intention-to-treat (ITT) approach was used. Annualized incidence rates were calculated per 1000 patient-years of follow-up. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards regression model, stratified by screening eGFR (30-<45, 45-<60, and 60-<90 mL/min/1.73m^2). The heterogeneity of relative effects across UACR subgroups was assessed by including UACR group as a model covariate, together with an interaction term for treatment and baseline UACR. To calculate absolute risk differences, the number of participants with an outcome (per 1000 patients over mean follow-up) in those assigned to canagliflozin was subtracted from the corresponding number in those assigned to placebo. The heterogeneity in absolute risk reduction was estimated using a fixed-effect meta-analysis with a chi-squared test.

To assess the relative effects of canagliflozin on albuminuria, HbA1c, body weight and systolic blood pressure, linear mixed effects models for repeated measures were used to analyze the percentage change in the outcome (log-transformed for UACR) over time. Models were adjusted for baseline value and trial visit. Time was included as a categorical factor such that the geometric means were modelled for each visit separately. The residuals from the mean model were assumed to have an unstructured covariance matrix.

eGFR slope analyses were conducted using on-treatment eGFR measurements only. This was to avoid the expected distortions from modifications of the hemodynamic effect following cessation of study drug. On-treatment eGFR measurements comprised all measurements available between Day 1 and the last dose of study medication (+2 days) from a central laboratory. To estimate the effects of canagliflozin on the mean eGFR slope, a 2-slope mixed effects linear spline model was fitted to eGFR measurements (with a knot at Week 3, the first post-randomisation eGFR measure), with a random intercept and random slopes for treatment. Similar to previous CREDENCE subgroup analyses,[20] the mean total slope was computed as a weighted combination of the acute and chronic slopes. Heterogeneity in the effect of canagliflozin on acute, chronic and total eGFR slope between UACR subgroups was estimated by comparing the subgroup-level effects using a chi-squared test with two degrees of freedom, accounting for the standard error in each subgroup. Change in mean eGFR according to treatment and baseline UACR is graphically presented using a restricted maximum likelihood (REML) repeated measures approach.

No adjustment for multiplicity of testing was made. Importantly, given the post-hoc nature of these analyses, the presented P values should be interpreted with caution and have been presented for descriptive rather than inferential purposes. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

The 4401 participants of the CREDENCE trial were followed for a median of 2.6 years (range 0.0-4.5).[15] Overall, median baseline UACR was 927 mg/g (105 mg/mmol). Around half (53%) had a baseline UACR ≤1000 mg/g, 35% had a UACR between >1000 and <3000 mg/g and 12% had a UACR ≥3000 mg/g (Table 2). Mean age was lower in patients with a higher baseline UACR compared to those with a lower UACR. The proportion of females and patients of Asian ethnicity were higher among participants with higher UACR compared to those with lower UACR, whilst the opposite was true for the proportion of Caucasian patients. Higher UACR subgroups were also more likely to be using glucose-lowering regimens reflecting higher diabetes severity (i.e. more receiving insulin and fewer receiving a sulphonylurea or biguanide), and more likely to have microvascular disease, higher blood pressure and lower eGFR, compared to lower UACR subgroups (Table 2).

Higher baseline UACR was consistently associated with a higher rate of kidney and cardiovascular events in both the placebo and canagliflozin groups (Figures 1-2, Supplementary Table 2). The rates at which participants with baseline UACR ≥3000 mg/g randomised to placebo experienced at least one event was 201.5 events per 1000 patient-years for the primary outcome and 126.9 events per 1000 patient-years for the composite of kidney failure or kidney death. The rates at which this same population experienced at least one cardiovascular or fatal event was 87.2 events per 1000 patient-years for the composite of cardiovascular death or hospitalisation for heart failure, 77.0 for the composite of cardiovascular death, myocardial infarction or stroke, and 71.4 for all-cause mortality.

Kidney Outcomes

The relative risk reduction for the primary composite outcome of kidney failure, doubling of serum creatinine or kidney or cardiovascular death (HR 0.70, 95% CI 0.59-0.82 in the primary analysis previously published; see Supplementary Table 1) was consistent across the baseline albuminuria

subgroups (P-heterogeneity=0.55). Similarly consistent effects were observed for all other kidney outcomes (all P heterogeneity>0.17), including the secondary kidney composite outcome of kidney failure, doubling of serum creatinine or kidney death (HR 0.66, 95% CI 0.53-0.81 in the primary analysis), the secondary kidney composite outcome of kidney failure or kidney death (HR 0.69, 95% CI 0.54-0.87 in the primary analysis), and the exploratory composite outcome of kidney replacement therapy (KRT) initiation or kidney death (HR 0.72, 95% CI 0.54-0.97 in the primary analysis) (Figure 1), the individually-assessed outcomes of kidney failure and doubling of serum creatinine, and the composite outcome of kidney failure or kidney or cardiovascular death (Supplementary Table 2).

For almost all kidney outcomes, the absolute benefit was greatest in the highest UACR category (≥3000 mg/g) (all P-heterogeneity <0.05, except for the composite of kidney failure or kidney or cardiovascular death, for which P-heterogeneity=0.11) (Figure 1 and Supplementary Table 2). For every 1000 patients with the highest level of baseline albuminuria treated over 2.6 years, canagliflozin would be expected to prevent 119 participants experiencing the primary composite outcome (number needed to treat [NNT] 9, 95% CI 5-29), 120 experiencing the composite of kidney failure, doubling of serum creatinine or kidney death (NNT 9, 95% 5-25), 91 experiencing kidney failure or kidney death (NNT 11, 95% CI 7-56), and 72 experiencing KRT initiation or kidney death (NNT 11, 95% CI 9-100) (Figure 1).

Cardiovascular Outcomes and All-Cause Death

For all cardiovascular outcomes where canagliflozin had an effect in the primary analyses (Supplementary Tables 1 and 2), the relative benefit was consistent across UACR subgroups (Figure 2 and Supplementary Table 2; all P heterogeneity>0.75). This included the composite of cardiovascular death or hospitalisation for heart failure (HR 0.69, 95% CI 0.57-0.83 in the primary analysis), MACE,, and the extended cardiovascular composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure or unstable angina (Figure 2 and Supplementary

Table 2). Canagliflozin did not reduce cardiovascular death or all-cause mortality in any of the UACR subgroups (Figure 2).

While the rates of cardiovascular events were higher in those groups with higher UACR at baseline, there were no clear differences in the absolute benefits of canagliflozin on cardiovascular outcomes across albuminuria categories (all P-heterogeneity>0.16) (Figure 2 and Supplementary Table 2).

Effects on UACR

Overall, canagliflozin reduced UACR by 31% (95% CI 26-35%), with an absolute reduction of 239.5 mg/g (95% CI 207.0-270.2 mg/g) (Figure 3). The relative reduction was higher in individuals with a lower baseline UACR (P-heterogeneity=0.03, Figure 3). However, the opposite was true for absolute albuminuria reduction, which was 162.9 mg/g (137.9-186.0 mg/g), 355.2 mg/g (263.3-438.5 mg/g) and 340.9 mg/g (-51.2-669.0 mg/g) in those with baseline UACR ≤1000 mg/g, >1000 and <3000 mg/g and ≥3000 mg/g, respectively.

Effects on eGFR slope

An acute drop in eGFR with treatment commencement was apparent and similar at Week 3 in every baseline albuminuria category (P-heterogeneity=0.44) (Figure 4 and Supplementary Table 3). Thereafter, canagliflozin attenuated annual eGFR decline in every albuminuria category, with some evidence that this protective effect varied by baseline UACR (P-heterogeneity=0.04) in a non-linear way (Supplementary Table 3). The absolute reduction in chronic eGFR slope was 2.31 (95% CI 1.88, 2.73), 3.29 (2.67,3.91) and 2.49 (1.00, 3.99) mL/min/1.73m^2/year in the three UACR subgroups, respectively. Those with baseline UACR ≥3000 mg/g assigned to placebo had the greatest chronic eGFR slope, with a loss of 8.92 (SE 0.53) mL/min/1.73m^2/year, which canagliflozin reduced by 28% to a loss of 6.43 (SE 0.55) mL/min/1.73m^2/year. Results were similar for total eGFR slope (to Week 130) (Supplementary Table 3).

Kidney Safety Outcomes

In the primary CREDENCE paper, canagliflozin reduced the risk of reported kidney-related adverse events overall (HR 0.71, 95% CI 0.61-0.82). Stratified by baseline UACR, the relative and absolute protective effects were greater in people with higher baseline albuminuria (P-heterogeneity=0.003 and <0.001 for relative and absolute effects, respectively) (Supplementary Table 4).

There was no statistical evidence that the relative or absolute effect of canagliflozin, or lack thereof, on other safety outcomes varied according to baseline albuminuria (Supplementary Table 4).

Effects on Intermediate Outcomes

In the two lower UACR categories, reductions in mean HbA1c, mean body weight and mean systolic blood pressure were greater in the group treated with canagliflozin compared to the placebo-treated group (Supplementary Table 5). For the higher UACR category, only body weight was reduced by treatment with canagliflozin. Across all intermediate outcomes, the largest reductions were observed in those with a UACR ≤1000 mg/g.

Discussion

In the CREDENCE trial, canagliflozin produced better kidney outcomes in adults with type 2 diabetes at high risk of kidney disease progression.[15] In the present study, the relative benefit was consistent across all baseline albuminuria levels, including those in the nephrotic range. However, individuals with UACR ≥3000 mg/g, and therefore at greatest risk of progression of kidney disease, derived greater absolute benefit for kidney outcomes from canagliflozin during the median follow-up of 2.6 years. Canagliflozin also reduced a range of cardiovascular events, including hospitalisation for heart failure and MACE. For cardiovascular outcomes, both relative and absolute treatment effects were consistent

across the UACR categories. Canagliflozin appears safe for a range of albuminuria levels and, indeed, provided greater relative and absolute protection against kidney-related adverse events in those with a baseline UACR ≥3000 mg/g. The findings support the value of canagliflozin treatment for kidney and cardiovascular protection in people with diabetes and severely increased albuminuria levels (>300 mg/g).

The well-established association between albuminuria and the risk of CKD progression, kidney failure and AKI[10,11,21-23] is based on pooled analyses involving more than 1 million people, including >100,000 with diabetes.[24,25] These analyses form the rationale for classifications of the KDIGO CKD risk classification system, which grades albuminuria in categories of A1 (0-29 mg/g), A2 (30-299 mg/g) and A3 (≥300 mg/g).[9,24] Within these combined cohorts, mean albuminuria in those with available quantitative albuminuria measurements was around 17 mg/g, with only 2% of participants having a UACR ≥300 mg/g (or 2+ on dipstick),[24] which is more moderate than the albuminuria levels seen in CREDENCE. The CREDENCE cohort extends these analyses, providing capacity to examine kidney and cardiovascular risk in individuals with nephrotic-range albuminuria (≥3000 mg/g). Risk continues to increase well beyond UACR levels of 300 mg/g, most notably for kidney endpoints. Among placebo-treated participants, the rate of the composite outcome of kidney failure, doubling of serum creatinine or kidney death increased from 10.2 events per 1000 patient-years in those with baseline UACR ≤1000 mg/g to 172 events per 1000 patient-years in those with UACR ≥3000 mg/g. Cardiovascular risk also increased, although not as steeply, with, for example, rates of cardiovascular death rising from 19.1 deaths per 1000 patient-years in placebo-treated participants with UACR ≤1000 mg/g to 51.6 deaths per 1000 patient-years in those with UACR ≥3000 mg/g. The relative clinical kidney and cardiovascular benefit was as strong, and the absolute kidney benefit greater, in those with nephrotic-range albuminuria making this population a priority group for treatment.

We also examined the impact of canagliflozin on albuminuria. The relative reduction in albuminuria appeared less marked in those with baseline albuminuria ≥3000 mg/g than in those with lower UACR. Not surprisingly, absolute reductions were lower in those with UACR ≤1000 mg/g than in those with higher levels. It is possible that there are multiple causes of albuminuria in those with nephrotic-range albuminuria, not all of which may be amenable to the effects of SGLT2 inhibitors. These causes potentially include hemodynamic mechanisms, alternations in albuminuria handling, fixed structural injury, and others. These findings should be regarded as speculative given the relatively small number of participants with nephrotic-range albuminuria recruited, and require confirmation in other trials enrolling high-risk patients. Nevertheless, they raise the possibility that SGTL2 inhibitors confer kidney protection in patients with diabetes through mechanisms independent of albuminuria reduction.

Many of the strengths of this study relate to the design of the original trial. CREDENCE recruited people with severely increased albuminuria despite a maximum-tolerated RAS blockade, providing the ability to test the effect of canagliflozin in people at very high kidney risk. In addition, kidney outcomes were independently adjudicated and eGFR and UACR assessed centrally. However, the trial did not include patients with screening albuminuria equivalent to the KDIGO Stages A1 and A2. Moreover, our findings are limited to people with diabetes and high kidney risk, with the extent of any generalisability to non-diabetic kidney disease still unknown. Future trials are awaited.[26,27] CREDENCE was stopped early on grounds of clear efficacy for the primary endpoint. This may limit the power to assess the impact of canagliflozin on secondary and safety outcomes.

Previous SGLT2 inhibitor trials have shown consistent effects on kidney and cardiovascular outcomes across different levels of albuminuria.[28-30] However, these trials included few participants with severely increased albuminuria. We extend this observation to individuals with nephrotic-range albuminuria who experienced similar relative, and greater absolute, kidney benefits from canagliflozin. The consistent relative benefit seen across all levels of baseline albuminuria in the CREDENCE[15] and

CANVAS trials[7,16] makes it reasonable to assume that absolute benefits would accrue in those at lower risk if followed for a longer time horizon, as would happen in clinical practice. Taken together, these findings provide treatment options for those with diabetes and nephrotic-range albuminuria. Ongoing SGLT2 inhibitor trials will provide complementary evidence for the effects of SGLT2 inhibitors on kidney and cardiovascular outcomes in those with non-diabetic albuminuria.[26,31,32]

Disclosures

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T. Greene has received consulting fees from Janssen, Durect, and Pfizer.

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

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Data Sharing Statement

De-identified individual-level data from this study, together with data dictionaries, 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, with no defined end date. The study protocol and statistical analysis plan are already in the public domain. All requests for data access will need to be made via the YODA Project. Data can be requested by any external researcher who submits a legitimate scientific proposal that promotes research which may advance science or lead to improvements in individual and public health and health care delivery. All proposals will be reviewed by the YODA Project. Once approved, data will be shared via a secure Safe Harbor platform. Requestors must sign a Data Use Agreement prior to receiving the data.

Supplementary Material Table of Contents

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Figure Legends

Figure 1. Relative and absolute effects of canagliflozin on kidney outcomes and kidney-related adverse events by baseline UACR.
Figure 2. Relative and absolute effects of canagliflozin on cardiovascular and mortality outcomes by baseline UACR.
Figure 3. Effect of canagliflozin on albuminuria reduction by baseline UACR.
Figure 4. Effects of canagliflozin on adjusted mean eGFR (Baseline to Week 130) by baseline UACR.

Table 1. Efficacy and safety endpoints of the CREDENCE study that are included in the present study. Table adapted from **Efficacy endpoints**	
Primary endpoint	Composite of kidney failure, a doubling of serum creatinine from baseline, or death due to kidney or cardiovascular disease
Secondary kidney endpoints	Composite of kidney failure, a doubling of serum creatinine or kidney death; Composite of kidney failure or kidney death; Composite of KRT initiation (dialysis for ≥30 days or kidney transplantation) or kidney death; Kidney failure; Doubling of serum creatinine; Composite of kidney failure, or kidney or cardiovascular death
Secondary cardiovascular endpoints	Composite of cardiovascular death or hospitalization for heart failure; Major adverse cardiovascular events (MACE) composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke; Hospitalization for heart failure; Cardiovascular death; Death from any cause; Composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina
Intermediate outcomes	Change in UACR; Acute, chronic and total eGFR slope; Change in HbA1c; Change in body weight; Change in systolic blood pressure;
Safety outcomes	
Kidney-related safety outcomes	Composite of acute kidney injury (AKI), anuria, azotemia, blood creatinine increased, blood urea increases, eGFR decreased, nephropathy toxic, renal failure, renal impairment; AKI
Other safety outcomes	Volume depletion; Hyperkalemia; Urinary tract infections (UTI); Hypoglycemia

Table 2. Baseline characteristics of participants in the CREDENCE trial, according to baseline UACR.

Characteristic	Baseline UACR (mg/g)		
	≤1000	>1000-<3000	≥3000
	n=2348 (53%)	*n*=1547 (35%)	*n*=506 (12%)
Age, y, mean (SD)	64 (9)	63 (9)	60 (9)
Female, n (%)	756 (32%)	534 (35%)	204 (40%)
Race, n (%)			
Asian	422 (18%)	331 (21%)	124 (25%)
Black or African American	138 (6.0%)	65 (4%)	21 (4%)
White	1,596 (68%)	1,018 (66%)	317 (63%)
Other[†]	192 (8%)	133 (9%)	44 (9%)
Region, n (%)			
North America	666 (28%)	381 (25%)	135 (27%)
Central/South America	523 (22%)	314 (20%)	104 (21%)
Europe	457 (20%)	328 (21%)	79 (16%)
Rest of the world	702 (30%)	524 (34%)	188 (37%)
Current smoker, n (%)	325 (14%)	242 (16%)	72 (14%)
History of hypertension, n (%)	2,273 (97%)	1,501 (97%)	486 (96%)
History of heart failure, n (%)	319 (14%)	247 (16%)	86 (17%)
Duration of diabetes, y	16 (9)	16 (9)	15 (8)
Drug therapy, n (%)			
Insulin	1,463 (62%)	1,057 (68%)	364 (72%)
Sulfonylurea	727 (31%)	427 (28%)	114 (23%)
Biguanide	1,433 (61%)	865 (56%)	247 (49%)
GLP-1 receptor agonist	108 (5%)	56 (5%)	19 (4%)
DPP-4 inhibitor	419 (18%)	267 (17%)	65 (13%)
Statin	1,628 (69%)	1,077 (70%)	331 (65%)
Antithrombotic[‡]	1,448 (62%)	915 (59%)	261 (52%)
RAS inhibitor	2,345 (100%)	1,545 (100%)	505 (100%)
Beta blocker	938 (340%)	631 (41%)	201 (40%)
Diuretic	913 (39%)	708 (46%)	261 (52%)
Microvascular disease history, n (%)			
Neuropathy	1,106 (47%)	765 (50%)	276 (55%)
Retinopathy	913 (39%)	708 (46%)	261 (52%)
History of cardiovascular disease, n (%)	1,198 (51%)	758 (49%)	264 (52%)
Body mass index, kg/m^2, mean (SD)[*]	31.4 (6.1)	31.3 (6.1)	31.2 (6.6)
Systolic blood pressure, mmHg, mean (SD)	138 (15)	142 (16)	143 (16)
Diastolic blood pressure, mmHg, mean (SD)	77 (9)	79 (9)	80 (9)
Glycated hemoglobin, %, mean (SD)	8.3 (1.3)	8.2 (1.3)	8.4 (1.5)

Triglycerides, mg/dL, mean (SD)[*]	186 (133)	204 (159)	221 (142)
Cholesterol, mg/dL, mean (SD)[*]	174 (46)	182 (50.3)	201 (58)
HDL cholesterol, mg/dL, mean (SD)[*]	43 (12)	46 (12)	46 (16)
LDL cholesterol, mg/dL, mean (SD)[*]	93 (39)	97 (39)	112 (50)
Ratio of LDL to HDL, mean (SD)[*]	2.2 (1.0)	2.3 (1.1)	2.6 (1.3)
eGFR, mL/min/1.73 m^2, mean (SD)	58 (18)	55 (18)	53 (18)
UACR, mg/g, median (IQR)[#]	489.0 (320.5-692.5)	1630.0 (1254.0-2167.0)	3893.0 (3408.0-4765.0)
UACR, mg/mmol, median (IQR)I[#]	55.3 (36.2-78.3)	184.2 (141.7-244.9)	439.9 (385.1-538.5)

eGFR, estimated Glomerular Filtration Rate; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAS, renin angiotensin system; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; IQR, interquartile range.

[†]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

[‡]Includes anticoagulation and antiplatelet agents, including aspirin.

[*]≤1% missing data

[#]Eligibility was based on a screening UACR of >300-5000 mg/g (33.9-565.6 mg/mmol). By baseline, 527 participants had a UACR <300mg/g, including 31 with normoalbuminuria (UACR <30 mg/g, or <3 mg/mmol) and 496 with microalbuminuria (UACR 30-300 mg/g, or 3-30 mg/mmol).[15]