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 albuminuria and the effects of the SGLT2 inhibitor, canagliflozin, on efficacy and safety outcomes in the CREDENCE randomised 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 (all P-heterogeneity>0.17). 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% CI 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 (P-heterogeneity=0.003).

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 are 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 clinical trial

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 inhibitors (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 the rate of 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 levels of albuminuria. Whether the effect holds true at very high levels (including nephrotic range) and whether baseline albuminuria modifies the treatment effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors are not clear.

Prior to the demonstration of their benefits for patient-level kidney and cardiovascular outcomes[6,7], it was clear that SGLT2 inhibitors produced a reduction in 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 the eGFR, is the foundation for the Kidney Disease: Improving Global Outcomes (KDIGO) kidney disease risk classification system.[9,12] Consequently, people with higher albuminuria levels might derive greater absolute benefit from albuminuria-lowering treatments such as SGLT2 inhibitors.

SGLT2 inhibitors prevent cardiovascular and kidney events in people with T2DM.[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 separately 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 more than 500 in the nephrotic range 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

The CREDENCE trial was an event-driven, double-blind, randomised controlled trial whose design and main results have been previously described.[15,17]

Participants and albuminuria assessment

In brief, trial eligibility criteria were designed to ensure that the recruited population were at high risk of progression of diabetic kidney disease. Study participants were aged ≥30 years with T2DM, a glycated hemoglobin (HbA1c) level of 6.5%-12.0%, an eGFR of 30-<90 mL/min/1.73m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula)[18] and a UACR of >300-5000 mg/g. Key exclusion criteria included nondiabetic kidney disease, type 1 diabetes mellitus, and prior treatment of kidney disease with immunosuppression or kidney replacement therapy (KRT). Treatment with a stable maximum-labeled or 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, eligibility criteria required a UACR of >300-5000 mg/g (>33.9-565.6 mg/mmol) on central laboratory measurement. Third, albuminuria was measured at randomisation visit 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 kidney, cardiovascular and mortality outcomes and selected safety outcomes were independently adjudicated by expert committees blinded to treatment allocation.

The primary outcome was the composite of kidney failure (initiation of dialysis for ≥30 days, kidney transplantation, or an 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 according to central laboratory assessment, or death due to kidney disease or cardiovascular disease.

Secondary kidney-related efficacy outcomes for the current analyses (and for the overall trial) were the composite of kidney failure, a doubling of serum creatinine or kidney death, the composite of kidney failure or kidney death, and the composite of KRT initiation (dialysis for ≥30 days or kidney transplantation) or kidney death. The individual kidney outcomes of kidney failure and doubling of serum creatinine were also assessed, as was the composite of kidney failure, kidney death, or cardiovascular death. Secondary cardiovascular outcomes included the composite of cardiovascular death or hospitalization for heart failure; the major adverse cardiovascular events (MACE) composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke; the individual outcomes of hospitalization for heart failure, cardiovascular death and death from any cause; and the

cardiovascular composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina.

Safety outcomes for which there were at least 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.

Outcomes for the current study included percentage and absolute reduction in albuminuria and change in eGFR over time. Change in albuminuria was the difference between baseline and the average of all UACR measurements to Week 182. Changes in eGFR slope were assessed as the acute change in eGFR from baseline to Week 3 (acute slope), the annualized change in eGFR from Week 3 until end of treatment (chronic slope) and the annualized change in eGFR from baseline to Week 130 (total slope). Finally, we assessed the effect of canagliflozin on 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 to capture a range of albuminuria levels. 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 albuminuria 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 ACEi/ARB for ≥4 weeks.

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 the screening eGFR categories (30-<45, 45-<60, and 60-<90 mL/min/1.73m^2). The heterogeneity of relative effects across different UACR subgroups was assessed by including UACR category 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. For the efficacy outcomes, the heterogeneity in absolute risk reduction was estimated using a fixed-effect meta-analysis incorporating a chi-squared test for heterogeneity.

To assess the relative effect of canagliflozin on albuminuria, a linear mixed effects model for repeated measures was used to analyze the percentage change in log-transformed UACR over time in the overall ITT population and by UACR subgroup, with treatment as the explanatory variable and adjusting for baseline UACR (log-transformed) and trial visit. Time was included as a categorical factor such that the geometric means were modelled for each follow-up visit separately. The residuals from the mean model were assumed to have an unstructured covariance matrix. A similar approach was used for the continuous intermediate outcomes of HbA1c, body weight and systolic blood pressure.

Analyses of eGFR slope were conducted using on-treatment eGFR measurements only. This was to avoid the expected distortions from modifications of the hemodynamic effect following the cessation of study drug. On-treatment eGFR measurements comprised all those available between Day 1 and the last dose of study medication plus 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 eGFR slope (acute, chronic and total) 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. The pattern of 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 has been made in these analyses. Importantly, given the post-hoc nature of many of the 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 years).[15] Overall, participants had a median UACR of 927 mg/g (105 mg/mmol) at baseline. 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 1). 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 was higher among participants with higher levels of albuminuria compared to those with lower levels, whilst the opposite was true for the proportion of Caucasian patients. Higher UACR subgroups were also more likely to be using glucose-lowering regimens that reflect higher severity of diabetes (i.e. more receiving insulin and fewer receiving a sulphonylurea or biguanide), and have more microvascular disease, higher blood pressure and lower eGFR, compared to lower UACR subgroups (Table 1).

Higher baseline albuminuria was consistently associated with a higher rate of kidney and cardiovascular events in both the placebo and canagliflozin groups during follow-up (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 hospitalised heart failure event, 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 across the subgroups 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 initiation of kidney replacement therapy (KRT) 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).

However, for almost all kidney outcomes, the absolute benefit appeared 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 the P-heterogeneity was 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 (Supplementary Tables 1 and 2), the relative benefits were 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), the MACE composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, the risk of hospitalisation for heart failure, and the extended cardiovascular composite of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for heart failure or hospitalization for 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 greater levels of albuminuria 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). The opposite was true for the absolute reduction in albuminuria, 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

There was an acute drop in eGFR with the commencement of canagliflozin that 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 albuminuria category (P-heterogeneity=0.04) although not in a linear fashion (Supplementary Table 3). The absolute reduction in chronic eGFR loss was 2.31 (1.88, 2.73), 3.29 (2.67,3.91) and 2.49 (1.00, 3.99) mL/min/1.73m^2/year in those with baseline UACR of ≤1000 mg/g, >1000-<3000 mg/g and ≥3000 mg/g, respectively. Those with baseline UACR ≥3000 mg/g assigned to placebo had the fastest decline in 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 participants assigned to placebo, safety outcomes included kidney-related adverse events (79 patients with an event per 1000 patient-years), followed by hypoglycemia (49 patients per 1000 patient-years) and UTIs (45 patients per 1000 patient-years) (Figure 1 and Supplementary Table 4). 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 these 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 compared to placebo. Across all intermediate outcomes, the largest reductions were observed in those in the lowest UACR category (≤1000 mg/g).

Discussion

In the CREDENCE trial, canagliflozin produced better kidney outcomes and prevented kidney-related adverse events in adults with T2DM at high risk of kidney disease progression.[15] The relative benefit was consistent across all levels of baseline albuminuria, including those in the nephrotic range. However, Individuals with albuminuria ≥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 albuminuria ≥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).

Our findings provide confidence in the association of high-range albuminuria with increasing risk. Current understanding of albuminuria-related risk is grounded in studies of people with more moderate levels of albuminuria than seen in the CREDENCE study. 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] 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 itself. The canagliflozin-induced relative reduction in albuminuria appeared less marked in those with baseline albuminuria ≥3000 mg/g than in those with lower levels of albuminuria. Not surprisingly, absolute reductions were lower in those with UACR ≤1000 mg/g than in those with higher levels of albuminuria. 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 recruited, and require confirmation in other trials enrolling people with nephrotic-range albuminuria. They raise the possibility that SGTL2 inhibitors might confer kidney protection in patients with T2DM through mechanisms independent of albuminuria reduction.

This study has several strengths, many of which relate to the design of the original trial. CREDENCE recruited people with severely increased albuminuria despite a maximum RAS blockade, providing the ability to test the effect of canagliflozin on diverse outcomes 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, these findings are limited to people with albuminuria and diabetes with the extent of any generalisability to non-diabetic kidney disease remaining unknown at present, with future trials awaited.[26,27] CREDENCE was stopped early on grounds of clear efficacy for the primary endpoint. This may have limited power to assess the impact of canagliflozin on secondary and safety endpoints. Finally, this study was a post-hoc analysis of the original trial and therefore not specifically designed to test treatment effects in the three subgroups. The reported P-heterogeneity values must therefore be interpreted with caution.

Previous SGLT2 inhibitor trials have shown consistent effects on kidney and cardiovascular outcomes across different levels of albuminuria,[28-30] however these trials included very 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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D. de Zeeuw has served on advisory boards and/or as speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi-Tanabe; has served on steering committees and/or as a speaker for AbbVie and Janssen; and has served on Data Safety and Monitoring Committees for Bayer.

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Q. Li, C. Hockham, J-W Li have no conflicts of interest to declare.

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Table 1. Baseline characteristics of participants by 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; RAAS, renin angiotensin aldosterone 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 of <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]

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 total eGFR slope (Baseline to Week 130) by baseline uACR.

Figure 1. Relative and absolute effects of canagliflozin on kidney outcomes and kidney-related adverse events by baseline uACR. ***<<Note to authors, revised figure including kidney failure outcome in development to be added prior to resubmission>>***

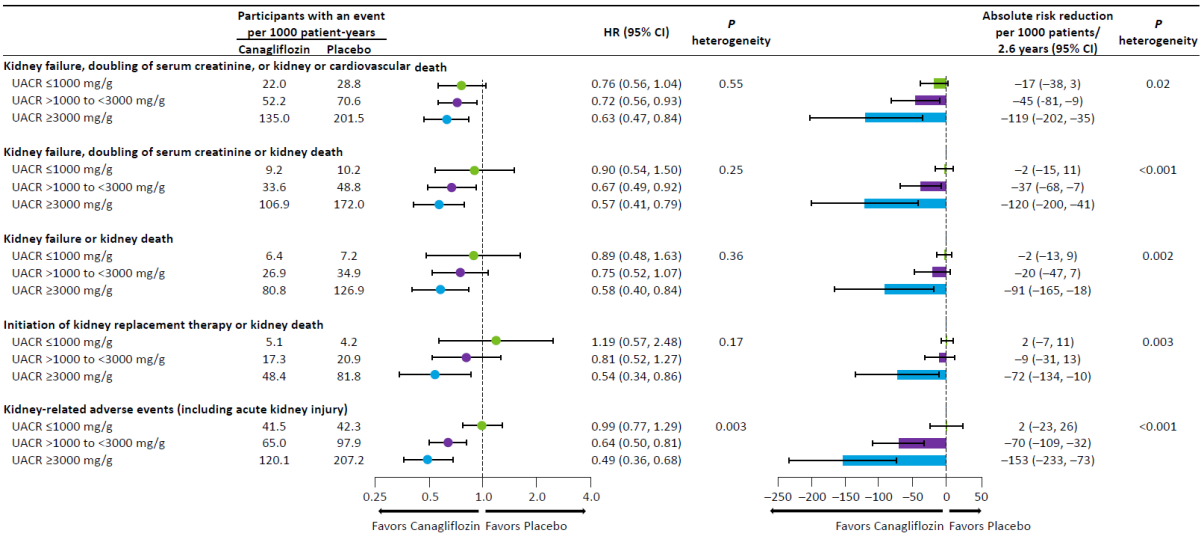


Figure 2. Relative and absolute effects of canagliflozin on cardiovascular and mortality outcomes by baseline uACR. ***<<Note to authors, revised figure removing 'All' data in development to be added prior to resubmission>>***

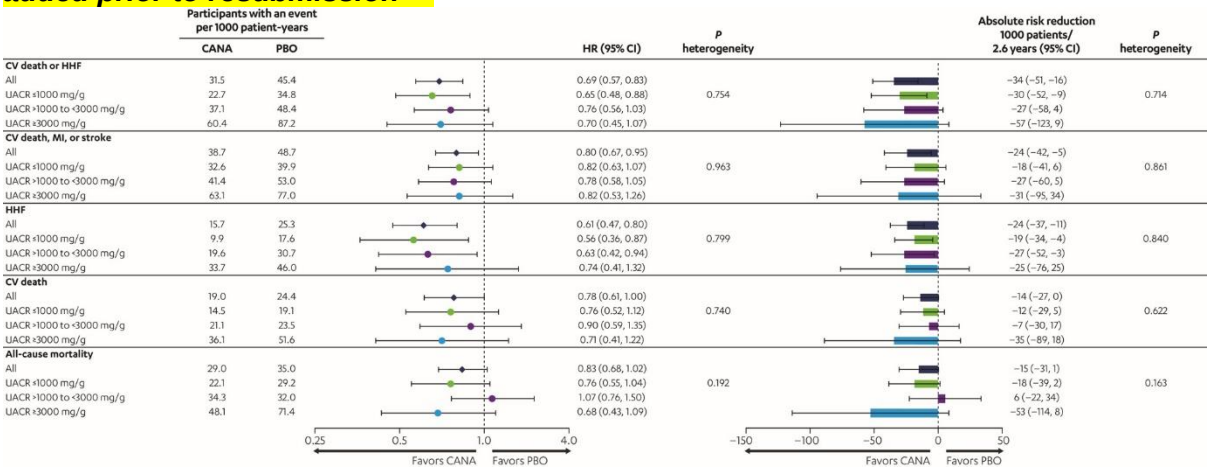
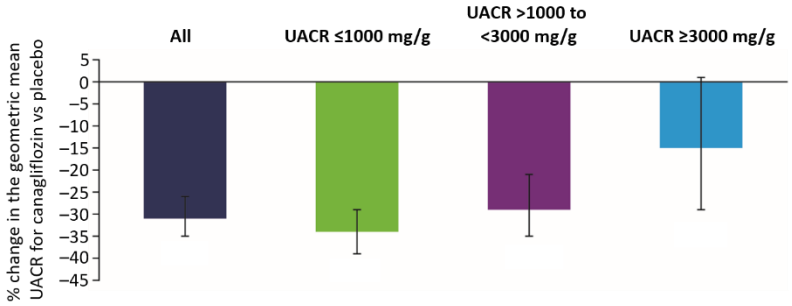


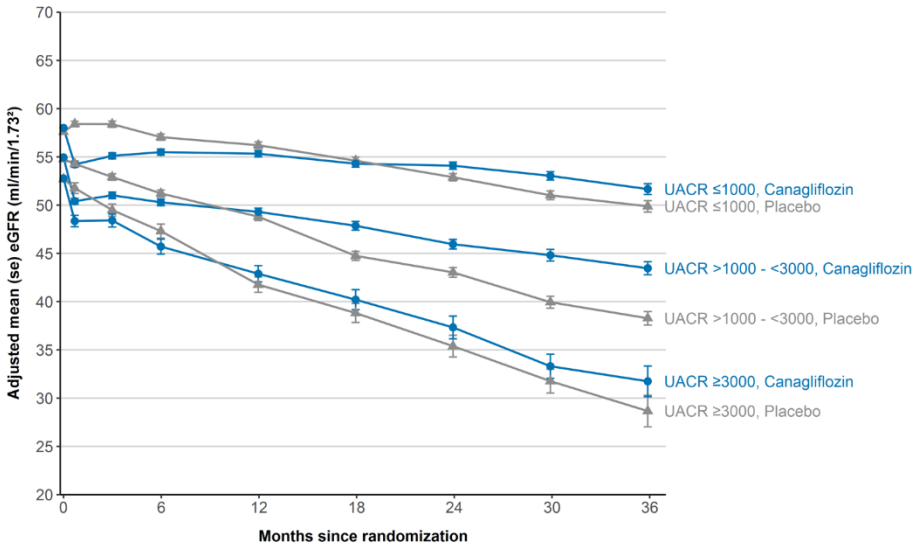
Figure 3. Effect of canagliflozin on albuminuria reduction by baseline uACR.



					P-het	P-trend
No. of participants	4401	2348	1547	506		
Median baseline albuminuria (mg/g)	927(463-1833)	489(321-693)	1630(1254-2167)	3893(3407-4765)		
Relative reduction in albuminuria (%)†	31(26-35)	35(29-39)	29(21-35)	14(-2-28)	0.03	0.01
Absolute reduction in albuminuria (mg/g)‡	239.5(207.0-270.2)	162.9(137.9-186.0)	355.2 (263.3-438.5)	340.9 (-51.2-669.0)		

†Percentage change in the geometric mean of canagliflozin relative to placebo. Heterogeneity was estimated by fitting an interaction term to a linear mixed effects model for repeated measures
‡Absolute change in the geometric mean of canagliflozin relative to placebo.

Figure 4. Effects of canagliflozin on total eGFR slope (Baseline to Week 130) by baseline uACR.



No. of participants

UACR ≤1000 mg/g	Placebo	244	225	214	204	191	125	70
	Canagliflozin	251	230	222	210	206	154	84
UACR >1000 mg/g - <3000 mg/g	Placebo	1668	1512	1438	1321	1176	790	469
	Canagliflozin	1699	1553	1490	1386	1279	864	513
UACR ≥3000 mg/g	Placebo	270	234	215	180	155	84	40
	Canagliflozin	233	207	194	173	150	89	49

Beneficial Effects of Canagliflozin for Kidney, Cardiovascular, and Safety Outcomes Extend to People with High-Range Albuminuria.

SUPPLEMENTARY MATERIAL

Meg Jardine,[1,2] Zien Zhou,[1,3] Hiddo J.L. Heerspink,[1,4] Carinna Hockham,[1] Qiang Li,[1] Rajiv Agarwal,[5] George Bakris,[6] Christopher P. Cannon,[7] David M. Charytan,[8] Tom Greene,[9] Adeera Levin,[10] Jing-Wei Li,[1] Brendon L Nesuen,[1] Bruce Neal,[1,11,12] Richard Oh,[13] Megumi Oshima,[1] Carol Pollock,[14] David C. Wheeler,[1,15] Dick de Zeeuw,[4] Hong Zhang,[16] Bernard Zinman,[17] Kenneth W. Mahaffey,[18] Vlado Perkovic[1,19]

Supplementary Table 1. Relative and absolute effects of canagliflozin on additional kidney, cardiovascular and mortality outcomes in the overall CREDENCE cohort. These results have been previously published.[1]

	Participants with an event per 1000 patient-years		**Hazards Ratio (95% CI)**	**Absolute risk reduction 1000 patients/ 2.6 years (95% CI)**
	Canagliflozin	Placebo		
Kidney outcomes				
Kidney failure, doubling of serum creatinine, kidney death, or cardiovascular death	43.2	61.2	0.70 (0.59, 0.82)	-43 (-63, -23)
Kidney failure, doubling of serum creatinine, or kidney death	27.0	40.4	0.66 (0.53, 0.81)	-32 (-49, -16)
Kidney failure or kidney death	20.7	29.6	0.69 (0.54, 0.87)	-22 (-36, -7)
Initiation of kidney replacement therapy, or kidney death	13.6	18.6	0.72 (0.54, 0.97)	-12 (-24, -1)
Kidney failure	20.4	29.4	0.68 (0.54, 0.86)	-22 (-37, -8)
Kidney-related adverse events (including acute kidney injury)	57.1	79.1	0.71 (0.61, 0.82)	-45 (-66, -23)
Cardiovascular outcomes				
Cardiovascular death or hospitalization for heart failure	31.5	45.4	0.69 (0.57, 0.83)	-34 (-51, -16)
Cardiovascular death, myocardial infarction, or stroke	38.7	48.7	0.80 (0.67, 0.95)	-24 (-42, -5)
Hospitalization for heart failure	15.7	25.3	0.61 (0.47, 0.80)	-24 (-37, -11)
Cardiovascular death	19.0	24.4	0.78 (0.61, 1.00)	-14 (-27, 0)
All-cause mortality	29.0	35.0	0.83 (0.43, 1.09)	-15 (-31, 1)

Supplementary Table 2. Relative and absolute effects of canagliflozin on additional kidney, cardiovascular and mortality outcomes by baseline UACR.

	Participants with an event per 1000 patient-years		HR (95% CI)	P value	P-heterogeneity	Absolute risk reduction 1000 patients/ 2.6 years (95% CI)	P-heterogeneity
	Canagliflozin	Placebo					
Doubling of serum creatinine							
All	20.7	33.8	0.60 (0.48, 0.76)	<0.0001		-32 (-47, -17)	
UACR ≤1000 mg/g	5.4	7.5	0.71 (0.38, 1.32)	0.28	0.68	-5 (-16, 5)	<0.001
UACR >1000 to <3000 mg/g	26.5	41.4	0.62 (0.44, 0.88)	0.008		-37 (-65, -9)	
UACR ≥3000 mg/g	88.4	146.2	0.56 (0.39, 0.80)	0.001		-107 (-183, -32)	
Kidney failure, kidney death or cardiovascular death							
All	37.6	51.2	0.73 (0.61, 0.87)	<0.001		-33 (-52, -15)	
UACR ≤1000 mg/g	19.4	25.8	0.75 (0.54, 1.05)	0.10	0.59	-16 (-36, 3)	0.11
UACR >1000 to <3000 mg/g	45.9	57.0	0.79 (0.60, 1.04)	0.10		-28 (-61, 6)	
UACR ≥3000 mg/g	112.0	162.0	0.65 (0.47, 0.89)	0.008		-96 (-176, -16)	
Cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure or hospitalized unstable angina							
All	49.4	66.9	0.74 (0.63, 0.86)	<0.001		-40 (-61, -19)	
UACR ≤1000 mg/g	39.8	54.5	0.73 (0.58, 0.93)	0.01	0.95	-35 (-62, -9)	0.95
UACR >1000 to <3000 mg/g	53.9	73.2	0.74 (0.57, 0.95)	0.02		-43 (-79, -7)	
UACR ≥3000 mg/g	86.5	108.3	0.80 (0.55, 1.17)	0.25		-42 (-114, 31)	

Supplementary Table 3. Effects of canagliflozin on eGFR slope (total, acute and chronic) by baseline UACR. The acute, chronic and total mean change in estimated Glomerular Filtration Rate (eGFR) and standard error (SE) in each treatment group (canagliflozin or placebo) according to UACR category are presented.

UACR categories	Canagliflozin		Placebo		Placebo-subtracted difference (95% CI)	P value‡	P-heterogeneity
	Mean (SE) eGFR change	P value†	Mean (SE) eGFR change	P value†			
Acute slope: eGFR Change from baseline to Week 3 (mL/min/1.73 m^2)							
≤1000 mg/g	-3.15 (0.35)	0.07	0.45 (0.36)	<0.001	-3.60 (-4.58, -2.62)	<0.001	0.44
>1000-<3000 mg/g	-4.13 (0.36)		-1.29 (0.36)		-2.84 (-3.84, -1.83)	<0.001	
≥3000 mg/g	-4.70 (0.77)		-2.26 (0.72)		-2.44 (-4.52, -0.36)	0.02	
Chronic slope: Annual eGFR change from Week 3 to last available measurement (mL/min/1.73 m^2/year)							
≤1000 mg/g	-0.78 (0.15)	<0.001	-3.09 (0.16)	<0.001	2.31 (1.88, 2.73)	<0.001	0.04
>1000-<3000 mg/g	-2.65 (0.22)		-5.94 (0.23)		3.29 (2.67, 3.91)	<0.001	
≥3000 mg/g	-6.43 (0.55)		-8.92 (0.53)		2.49 (1.00, 3.99)	0.001	
Total slope: Annual eGFR change from baseline to Week 130 (mL/min/1.73 m^2/year)							
≤1000 mg/g	-1.88 (0.17)	<0.001	-2.79 (0.18)	<0.001	0.91 (0.42, 1.40)	0.0003	0.008
>1000-<3000 mg/g	-4.15 (0.24)		-6.37 (0.25)		2.23 (1.55, 2.90)	<0.001	
≥3000 mg/g	-8.15 (0.60)		-9.68 (0.57)		1.53 (-0.11, 3.17)	0.07	

eGFR, estimated glomerular filtration rate; SE, standard error; CI, confidence interval.
The effects of canagliflozin on the mean on-treatment eGFR slope were analysed using a 2-slope linear spline model for mean eGFR, with a knot at Week 3 to account for separate acute (randomization to Week 3) and chronic (Week 3 to end of follow-up) slopes. The full model also included random intercepts, acute and chronic slopes. The mean total slope was computed as a weighted combination of the acute and chronic slopes to reflect the mean rate of eGFR change to Week 130.
†P value for comparison between UACR categories
‡P value for effect of canagliflozin on eGFR slope in each UACR category

Supplementary Table 4. Relative and absolute effects of canagliflozin on kidney safety outcomes by baseline UACR.

	Participants with an event per 1000 patient-years		HR (95% CI)	P value	P-heterogeneity	Absolute risk reduction 1000 patients/ 2.6 years (95% CI)	P-heterogeneity
	Canagliflozin	Placebo					
Acute kidney injury							
All	16.9	20.0	0.85 (0.64, 1.13)	0.27		-6 (-17, 6)	
UACR ≤1000 mg/g	15.8	15.2	1.05 (0.69, 1.61)	0.81	0.12	3 (-12, 18)	0.11
UACR >1000 to <3000 mg/g	19.4	22.5	0.85 (0.54, 1.36)	0.51		-6 (-27, 15)	
UACR ≥3000 mg/g	14.5	36.1	0.40 (0.17, 0.95)	0.04		-40 (-77, -3)	
Volume depletion							
All	28.4	23.5	1.25 (0.97, 1.59)	0.08		13 (-1, 27)	
UACR ≤1000 mg/g	28.2	23.8	1.23 (0.88, 1.70)	0.22	0.84	12 (-7, 32)	0.82
UACR >1000 to <3000 mg/g	30.2	23.1	1.34 (0.89, 2.03)	0.16		17 (-7, 40)	
UACR ≥3000 mg/g	22.8	22.8	1.01 (0.44, 2.29)	0.98		3 (-34, 39)	
Hyperkalemia							
All	29.7	36.9	0.80 (0.65, 1.00)	0.05		-14 (-29, 2)	
UACR ≤1000 mg/g	22.9	32.3	0.70 (0.51, 0.97)	0.03	0.46	-20 (-40, 0)	0.53
UACR >1000 to <3000 mg/g	34.8	40.3	0.86 (0.61, 1.21)	0.39		-11 (-39, 16)	
UACR ≥3000 mg/g	51.8	49.4	1.00 (0.58, 1.74)	1.00		11 (-42, 64)	
Urinary tract infection							
All	48.3	45.1	1.08 (0.90, 1.29)	0.42		11 (-7, 29)	
UACR ≤1000 mg/g	44.0	42.0	1.05 (0.81, 1.35)	0.72	0.93	8 (-16, 33)	0.90
UACR >1000 to <3000 mg/g	50.2	45.7	1.11 (0.82, 1.51)	0.50		12 (-19, 42)	
UACR ≥3000 mg/g	66.3	58.9	1.15 (0.70, 1.88)	0.58		23 (-35, 81)	
Hypoglycemia							
All	44.3	48.9	0.92 (0.77, 1.11)	0.39		-7 (-25, 11)	
UACR ≤1000 mg/g	45.4	45.7	1.03 (0.80, 1.32)	0.83	0.15	3 (-22, 28)	0.14
UACR >1000 to <3000 mg/g	41.1	55.8	0.73 (0.54, 0.99)	0.05		-31 (-62, 0)	
UACR ≥3000 mg/g	49.7	43.7	1.18 (0.67, 2.10)	0.57		18 (-33, 69)	

Supplementary Table 5. Effects of canagliflozin on the intermediate outcomes of HbA1c, body weight and systolic blood pressure by baseline UACR

	UACR ≤1000 mg/g		UACR >1000-<3000 mg/g		UACR ≥3000 mg/g	
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**	**Canagliflozin**	**Placebo**
HbA1c, %, n	1066	1060	846	847	239	241
Mean (SD) baseline	8.2 (1.2)	8.2 (1.3)	8.3 (1.3)	8.3 (1.3)	8.4 (1.5)	8.4 (1.3)
LS mean change (SE)	-0.42 (0.03)	-0.09 (0.03)	-0.43 (0.03)	-0.24 (0.03)	-0.39 (0.08)	-0.27 (0.08)
Difference vs placebo (95% CI)	-0.33 (-0.40, -0.26)		-0.18 (-0.26, -0.10)		-0.12 (-0.30, 0.06)	
Body weight, kg, n	1079	1072	850	852	247	249
Mean (SD) baseline	87.7 (20.3)	86.7 (20.3)	87.8 (21.3)	86.7 (20.6)	83.6 (20.1)	88.3 (22.4)
LS mean change (SE)	-1.34 (0.09)	-0.53 (0.09)	-0.92 (0.12)	-0.09 (0.11)	-0.87 (0.21)	-0.15 (0.21)
Difference vs placebo (95% CI)	-0.81 (-0.97, -0.66)		-0.84 (-1.02, -0.66)		-0.72 (-1.05, -0.38)	
Systolic blood pressure, mmHg, n	1081	1072	850	853	247	249
Mean (SD) baseline	138 (15)	139 (15)	141 (16)	141 (16)	141 (16)	144 (15)
LS mean change (SE)	-3.22 (0.31)	0.44 (0.31)	-2.75 (0.36)	0.67 (0.36)	-1.44 (0.74)	-0.55 (0.75)
Difference vs placebo (95% CI)	-3.66 (-4.45, -2.86)		-3.41 (-4.34, -2.49)		-0.90 (-2.67, 0.88)	

Reference

1. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019;380(24):2295-2306.