Effects of canagliflozin in reducing albuminuria and eGFR decline depend on the degree of glycemic control: A post-hoc analysis of the CREDENCE trial

Sjoukje van der Hoek MD[1], Niels Jongs PhD[1], Megumi Oshima MD PhD[2,3], Brendon L. Neuen[3], MBBS; J. Stevens PhD[1], Vlado Perkovic MD PhD[4], Adeera Levin MD[5], Kenneth W. Mahaffey MD,[6] Carol Pollock, MBBS[7], Tom Greene PhD[8], David C. Wheeler MD[9], Meg J. Jardine, MBBS, MD[10,] Hiddo J.L. Heerspink PhD[1,3]

[1] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center, Groningen, the Netherlands.

[2]Department of Nephrology and Laboratory Medicine, Kanazawa University, Japan

[3]The George Institute for Global Health, Sydney, NSW, Australia

[4]Faculty of Medicine & Health, University New South Wales, Sydney, Australia

[5]Division of Nephrology, University of British Columbia, Vancouver, BC, Canada;

[6]Stanford University School of Medicine, Stanford, CA, USA

[7]Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Royal North Shore Hospital, St Leonards, NSW, Australia;

[8] Division of Biostatistics, Department of Population Health Sciences, University of Utah Health, Salt Lake City, UT, USA

[9]Department of Renal Medicine, University College London, London, UK

[10] NHMRC Clinical Trials Centre, The University of Sydney, Sydney, New South Wales, Australia

Corresponding author:
Hiddo J.L. Heerspink
Department of Clinical pharmacy & pharmacology
University of Groningen, University Medical Center

Hanzeplein 1, 9713 GZ Groningen
The Netherlands
Tel: +3150-3617859
E-mail: h.j.lambers.heerspink@umcg.nl

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Abstract

Background and objectives

In the CREDENCE trial, the sodium glucose co-transporter 2 inhibitor (SGLT2i) canagliflozin improved kidney and cardiovascular outcomes and reduced the rate of estimated glomerular filtration decline (eGFR slope) in patients with type 2 diabetes and chronic kidney disease (CKD). In other clinical trials of patients with CKD or heart failure, the protective effects of SGLT2i on eGFR slope were greater in participants with versus participants without type 2 diabetes. This post-hoc analysis of the CREDENCE trial assessed whether the effects of canagliflozin on eGFR slope varied according patient subgroups by baseline HbA1c.

Design, setting, participants and measurements

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

Results

The annual difference in total eGFR slope was 1.52 mL/min/1.73m^2 (95% CI 1.11 to 1.93) slower in participants randomized to canagliflozin compared to placebo. The rate of eGFR decline was faster in those with poorer glycemic control. The mean difference in total eGFR slope between canagliflozin and placebo was greater in participants with poorer baseline glycemic control (difference in eGFR slope of 0.39, 1.36, 2.60, 1.63 mL/min/1.73m^2 for Hba1c subgroups 6.5-7.0%, 7.0-8.0%, 8.0-10.0%, 10.0-12.0%, respectively; P-interaction=0.010). The mean difference in change from baseline in UACR between participants randomized to canagliflozin and placebo was smaller in patients with baseline HbA1c 6.5– 7.0 (-17.4% [95% -28.4, -4.7] compared to those with an HbA1c 7.0-12% (-32.4% [95%CI -36.6, -28.0]; p-interaction 0.03) .

Conclusions

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

Introduction

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

Recent large clinical trials have assessed the impact of interventions on a composite outcome that usually includes well established kidney endpoints such as a sustained reductions in eGFR, kidney failure or death due to kidney failure (1,2,9,10). Drug effects on clinical kidney endpoints are determined by the number of patients reaching these endpoints, that is, in clinical trials of CKD progression, the patients with the fastest rate of progression. The rate of decline in kidney function (determined from the slope of estimated glomerular filtration rate (eGFR) over time) and change in albuminuria are established surrogate endpoints for kidney failure in clinical trials (10–12). Assessing effects based on eGFR slope provides an estimate of the effect of the intervention in all patients, including both slow and fast progressors. Statistical power for subgroup analyses is therefore typically greater for eGFR slope compared to clinical endpoints.

Recent analyses of large kidney and cardiovascular outcome trials showed that the effects of SGLT2 inhibitors on eGFR slope are more pronounced in patients with type 2 diabetes compared to those without diabetes (13–16). In addition, in patients with CKD without diabetes, the effect of SGLT2 inhibition on albuminuria is smaller compared to patients with type 2 diabetes (17,18), suggesting that the degree of glycemic control may modify the effect of these agents on kidney surrogate endpoints. Whether the dependency of these effects on

HbA1c can be detected in an exclusively type 2 diabetes population with varying degrees of glycemic control is unknown.

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

Methods

Study design and participants

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

Participants

Adults with type 2 diabetes and HbA1c of 6.5-12%, estimated glomerular filtration rate (eGFR) 30–90 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio (UACR) 300–5000 mg/g were eligible for participation. All participants were required to be treated with a stable maximally-tolerated dose of RAAS inhibitor (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]) for ≥4 weeks unless medically contraindicated. Key exclusion criteria included documented diagnosis of type 1 diabetes, treatment with immunosuppressive agents

for kidney disease, and a history of dialysis or kidney transplantation. A complete list of inclusion and exclusion criteria and the trial protocol has been previously published (19).

Procedures and measurements

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

Endpoints

The primary composite endpoint for CREDENCE was time to doubling of serum creatinine (confirmed by a second serum creatinine measurement after at least 28 days), onset of kidney failure (defined as maintenance dialysis for at least 28 days, kidney transplantation, or eGFR <15 mL/min/1.73m^2 confirmed by a second measurement after at least 28 days), or death from a kidney or cardiovascular cause. Secondary endpoints included: 1) time to a composite kidney endpoint of doubling of creatinine, kidney failure or death from kidney disease; 2) a composite

cardiovascular endpoint defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death; and 3) hospitalization for heart failure or cardiovascular death. The rate of kidney function decline (eGFR slope) and albuminuria was a pre-specified exploratory efficacy endpoint. All primary and secondary efficacy endpoints were adjudicated by a masked, independent Events Adjudication Committee.

Statistical analysis

Participant characteristics were summarized by baseline Hba1c (<7; 7 – 8%; 8-10%; >10%). Continuous variables are reported as mean (SD) or as median (IQR), and categorical variables as n (%).

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

The effect of canagliflozin compared with placebo on the rate of eGFR decline was also estimated in subgroups by baseline Hba1c, UACR and eGFR at screening. In these analyses all possible two-way and three-way interaction terms between the randomized treatment, subgroup indicator and two-slope linear spline in follow-up time were added to account for differences between subgroups in the effect of the treatment on the mean eGFR trajectory. We removed the stratification factor in subgroups by baseline eGFR to avoid redundant terms in our model. The acute change in eGFR was calculated as the mean change from baseline at week 3. The

chronic eGFR slope was calculated as the mean rate of change in eGFR from week 3 until last on -treatment visit and was expressed as change per year.

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

Cox proportional hazard regression was performed to assess the effect of canagliflozin compared to placebo on the clinical endpoints, yielding hazard ratios (HR) and 95% confidence intervals (95% CI) from model parameter coefficients and standard errors. We evaluated the primary and secondary efficacy endpoints in participants stratified by baseline HbA1c. We tested for heterogeneity of the canagliflozin treatment effect by including an interaction term between randomized treatment group and baseline HbA1c. We used R version 4.1.1 for statistical analyses (R Foundation, Vienna, Austria). P values of less than 0·05 were considered to indicate statistical significance.

Results

The CREDENCE trial randomized 4401 patients to receive either canagliflozin 100mg daily (n=2202) or placebo (n=2199) between March 2014 and May 2017. The trial was stopped early for efficacy based on a planned interim analysis with a median follow-up of 2.62 years (range 0.02 to 4.53).

At baseline, in the total trial population, the mean age was 63 years (SD 9.2), 33.9% of participants were women, mean eGFR was 56.2 mL/min per 1.73 m^2 (SD 18.2), median UACR was 927 mg/g (IQR 463–1833) and mean HbA1c was 8.3% (SD 1.3).There were 650 participants (14.8%) with a baseline HbA1c between 6.5 and 7%, 1406 (32.0%) with a HbA1c 7.0-<8.0%, 1849 (42.0%) with a HbA1c 8.0-<10.0 and 494 (11.2 %) with a HbA1c 10.0-12.0%.

Mean HbA1c levels in the four groups were 6.6% (SD 0.3), 7.4% (SD 0.3), 8.8% (SD 0.6) and 10.8% (SD 0.8) respectively (table 1).

Effects on eGFR slope

Canagliflozin caused an acute reduction in eGFR at week 3 with a mean reduction of -3.72 mL/min per 1.73 m² per year (SE 0.25) compared to -0.55 mL/min per 1.73 m² per year (SE 0.25) in the placebo group, resulting in a between-group difference of -3.17 mL/min per 1.73 m² per year (95% CI -3.87 to -2.47).Thereafter, the eGFR decline was attenuated in the canagliflozin group with a mean decline of -1.85 mL/min per 1.73 m² per year (SE 0.13) compared to -4.59 mL/min per 1.73 m² per year (SE 0.14) in the placebo group with a between-group difference of 2.74 mL/min per 1.73 m² per year (95% CI 2.37 to 3.11). Combining the acute and chronic effects, the total eGFR slope from baseline to end of treatment (week 130) was smaller in the canagliflozin group with -3.19 mL/min per 1.73 m² per year (SE 0.15) compared to -4.71 mL/min per 1.73 m² per year (SE 0.15) in the placebo group, resulting in a between-group difference of 1.52 mL/min per 1.73 m² per year (95% CI 1.11 to 1.93) (table 2).

When analyzing the total eGFR slope by baseline HbA1c subgroups, we observed that in patients with near-normal glycemic control (HbA1c 6.5 – 7.0%) those randomized to canagliflozin showed a 0.39 mL/min/1.73m^2 per year (95%CI -0.56 to 1.33) slower rate of eGFR decline from baseline when compared to placebo. This compared to a 1.82 mL/min/1.73m^2 per year (95%CI 1.40 to 2.25) difference in eGFR decline between treatment groups in those patients with higher Hba1c values (HbA1c 7.0 – 12.0%) (p-interaction 0.007; **figure 1^A and 1^B**). When stratifying the population into more granular HbA1c categories, in patient subgroups with higher baseline HbA1c values the rate of eGFR decline during follow-up was faster (table 2). The effect of canagliflozin compared to placebo on chronic and total eGFR slopes was larger in patients with higher baseline HbA1c ($p_{interaction}$=0.02 for chronic slope and $p_{interaction}$=0.01 for total slope; table 2). In addition, the between group differences in eGFR slope expressed as

percentage difference was progressively larger in higher baseline HbA1c subgroups (table 2). The decline in kidney function in both the placebo and the canagliflozin groups was larger with increasing baseline UACR. Partly as a result, the effect of canagliflozin on eGFR slope was also more pronounced in higher baseline UACR groups ($p_{interaction}$=0.04 for chronic slope and $p_{interaction}$=0.008 for total slope) (table 2).

We compared the distribution of eGFR changes in patients randomized to canagliflozin and placebo during the acute and chronic phases. During the first 3 weeks the canagliflozin group showed a uniformly larger reduction in eGFR compared to placebo, with a uniform shift in the distribution of eGFR changes to the left without a change in the variability (SDs of acute eGFR slopes in the canagliflozin and placebo groups 5.2 vs 5.1mL/min/1·73m^2 per 3 weeks respectively; **figure 2A**). During the chronic phase, the annual rate of eGFR change was slower in the canagliflozin group, and the variability of eGFR declines was somewhat reduced as indicated by the smaller standard deviation and the contraction of the left end of the distribution towards the right (SDs of the slopes in the canagliflozin and placebo groups 8.9 vs. 9.9 mL/min/1·73m^2/year, respectively; ratio 0·9; F-value 31; p<0.001 **figure 2B**).

Effects on UACR

Canagliflozin resulted in a lowering of the geometric mean of the urinary albumin-to-creatinine ratio of 30.7% (95% CI 26.5-34.6) compared to placebo. This effect was less pronounced in patients with near-normal glycemic control compared to those with higher HbA1c (**figure 1C)**. Patients with lower baseline UACR levels had a larger proportional UACR reduction (p interaction 0.04; **figure 3**).

Effects on kidney and cardiovascular outcomes by baseline HbA1c

Randomization to canagliflozin resulted in similar risk reductions of the primary composite outcome, composite outcome of end stage kidney disease, doubling of serum creatinine or renal

death, end stage kidney disease, composite outcome of cardiovascular death, myocardial infarction or stroke and composite outcome of cardiovascular death or hospitalization for heart failure regardless of baseline HbA1c (all p-interaction>0.3; **figure 4**).

Discussion

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

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

distribution of the eGFR slopes during chronic treatment). Thus, the effect of canagliflozin on eGFR slope in all patients (both fast and slow progressors) is primarily driven by fast progressors. Thus, the effect modification by baseline HbA1c for the eGFR slope endpoint may be explained at least partly by a more rapid loss of kidney function in those with poorer glycemic control as we observed that patients with near-normal Hba1c values at randomization had a lesser eGFR decline during follow-up compared to patients with higher Hba1c values. These results may also explain why in patients without diabetes and normoalbuminuria participating in the EMPA-KIDNEY trial, empagliflozin did not reduce the rate of kidney decline and kidney endpoints (8)

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

Our slope analyses are in keeping with results from other clinical trials with SGLT2 inhibitors (13,18). An analysis in patients with CKD participating in the DAPA-CKD trial reported that the effect of dapagliflozin on eGFR slope was greater in the subgroup of patients with type 2 diabetes (67% of the participants) compared to those without type 2 diabetes (18). Additionally, the benefit of dapagliflozin in attenuating eGFR slope was more pronounced in patients with higher HbA1c and more extensive albuminuria, consistent with our results from CREDENCE. The results of our post-hoc analysis are also consistent with data from the EMPAREG-Outcome trial that reported more pronounced effects of the SGLT2 inhibitor

empagliflozin on eGFR slope in patients with type 2 diabetes and established cardiovascular disease (14). Analyses of clinical trials in patients with heart failure also show similar results (5,6,15). In the DAPA-HF, EMPEROR-Reduced and EMPEROR Preserved trials, dapagliflozin and empagliflozin improved chronic eGFR slope with a larger effect in patients with type 2 diabetes compared to patients without diabetes.

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

Although the effects of canagliflozin in slowing the decline in eGFR were attenuated in patients with near-normal glycemia at baseline, it is important to emphasize that the benefits of canagliflozin on cardiovascular and heart failure endpoints was consistent irrespective of the degree of glycemic control. Since cardiovascular endpoints occur frequently in patients with diabetes and CKD, our data indicate that despite the effect of canagliflozin on eGFR decline

was more pronounced in patients with higher HbA1c and albuminuria, those with a slower decline in kidney function still derive cardiovascular benefit from canagliflozin.

The limitations of this study include the absence of eGFR measurements after discontinuation of canagliflozin to confirm the reversibility in the acute change in eGFR. However, the CANVAS-R trial demonstrated that 4 weeks after canagliflozin treatment the initial dip in eGFR was completely reversible (25). Secondly, this was a post-hoc analysis and may be prone to chance findings. Finally, the follow-up period of the CREDENCE trial was much shorter than the period during which most patients are treated in clinical practice. The relatively short timeframe of the trial precludes assessment of canagliflozin on kidney function in slow progressors who may derive benefit during a longer follow-up.

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

Disclosures:

SvdH, MO, NJ and JS report no diclosures

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Contribution

SvdH, NJ, MO and HJLH had full access to all data and final responsibility for the decision to submit for publication. VP AL TG KWM CP DCW MJJ HJLH contributed in the design and conduct of the CREDENCE trial. SvdH and HJLH wrote the first draft of the manuscript. NJ and MO analyzed the data. All authors reviewed the manuscript, contributed with revisions, and provided approval for the final version for submission.

References

1. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu P-L, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE TRIAL Investigators: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 380: 2295–2306, 2019 10.1056/nejmoa1811744
2. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde A-M, Wheeler DC: Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 383: 1436–1446, 2020 10.1056/nejmoa2024816
3. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, Barrett TD, Weidner-Wells M, Deng H, Matthews DR, Neal B: Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 6: 691–704, 2018 10.1016/S2213-8587(18)30141-4
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373: 2117–28, 2015 10.1056/NEJMoa1504720
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi D-J, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca H-P, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde M-F, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators: Cardiovascular and Renal Outcomes

with Empagliflozin in Heart Failure. *N Engl J Med* 383: 1413–1424, 2020 10.1056/nejmoa2022190

6. McMurray JJ v, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde A-M; DAPA-HF Trial Committees and Investigators: Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 381: 1995–2008, 2019 10.1056/NEJMoa1911303
7. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–La Rocca H-P, Choi D-J, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone S v., Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators: Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 385: 1451–1461, 2021 10.1056/nejmoa2107038
8. EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, Sammons E, Zhu D, Hill M, Stevens W, Wallendszus K, Brenner S, Cheung AK, Liu Z-H, Li J, Hooi LS, Liu W, Kadowaki T, Nangaku M, Levin A, Cherney D, Maggioni AP, Pontremoli R, Deo R, Goto S, Rossello X, Tuttle KR, Steubl D, Petrini M, Massey D, Eilbracht J, Brueckmann M, Landray MJ, Baigent C, Haynes R: Empagliflozin in Patients with Chronic Kidney Disease [published online ahead of print Nov 4, 2022]. *N Engl J Med* 2022 10.1056/NEJMoa2204233

9. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G: Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med* 383: 2219–2229, 2020 10.1056/NEJMoa2025845

10. Heerspink HJL, Greene T, Tighiouart H, Gansevoort RT, Coresh J, Simon AL, Mao Chan T, Fan Hou F, Lewis JB, Locatelli F, Praga M, Paolo Schena F, Levey AS, Inker LA; Chronic Kidney Disease Epidemiology Collaboration: Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol* 7: 128–167, 2019 10.1016/S2213-8587(18)30314-0

11. Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, Simon AL, Ying J, Beck GJ, Wanner C, Floege J, Li PK-T, Perkovic V, Vonesh EF, Greene T: GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-Analysis of Treatment Effects of Randomized Controlled Trials. *J Am Soc Nephrol* 30: 1735–1745, 2019 10.1681/ASN.2019010007

12. Greene T, Ying J, Vonesh EF, Tighiouart H, Levey AS, Coresh J, Herrick JS, Imai E, Jafar TH, Maes BD, Perrone RD, del Vecchio L, Wetzels JFM, Heerspink HJL, Inker LA: Performance of GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Statistical Simulation. *J Am Soc Nephrol* 30: 1756–1769, 2019 10.1681/ASN.2019010009

13. Heerspink HJL, Jongs N, Chertow GM, Langkilde AM, McMurray JJ v, Correa-Rotter R, Rossing P, Sjöström CD, Stefansson BV, Toto RD, Wheeler DC, Greene T; DAPA-CKD Trial Committees and Investigators: Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 9: 743–754, 2021 10.1016/S2213-8587(21)00242-4

14. Wanner C, Heerspink HJL, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, Hantel S, Woerle HJ, Broedl UC, von Eynatten M, Groop PH: Empagliflozin and kidney function decline in patients with type 2 diabetes: A slope analysis from the EMPA-REG OUTCOME trial. *J Am Soc Nephrol* 29: 2755–2769, 2018 10.1681/ASN.2018010103

15. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, Komajda M, Miller A, Pehrson S, Teerlink JR, Schnaidt S, Zeller C, Schnee JM, Anker SD: Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. *Circulation* 144: 1284–1294, 2021 10.1161/circulationaha.121.056824

16. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, Chopra V, Boer RA de, Desai AS, Ge J, Kitakaze M, Merkley B, O'Meara E, Shou M, Tereshchenko S, Verma S, Vinh PN, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Bengtsson O, Langkilde AM, Sjöstrand M, McMurray JJV: Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. *Circulation* 143: 298, 2021 10.1161/CIRCULATIONAHA.120.050391

17. Cherney DZI, Dekkers CCJ, Barbour SJ, Cattran D, Abdul Gafor AH, Greasley PJ, Laverman GD, Lim SK, di Tanna GL, Reich HN, Vervloet MG, Wong MG, Gansevoort RT, Heerspink HJL: Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. *Lancet Diabetes Endocrinol* 8: 582–593, 2020 10.1016/S2213-8587(20)30162-5

18. Jongs N, Greene T, Chertow GM, McMurray JJ v, Langkilde AM, Correa-Rotter R, Rossing P, Sjöström CD, Stefansson BV, Toto RD, Wheeler DC, Heerspink HJL; DAPA-CKD Trial Committees and Investigators: Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a

prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 9: 755–766, 2021 10.1016/s2213-8587(21)00243-6

19. Jardine MJ, Mahaffey KW, Neal B, Agarwal R, Bakris GL, Brenner BM, Bull S, Cannon CP, Charytan DM, de Zeeuw D, Edwards R, Greene T, Heerspink HJL, Levin A, Pollock C, Wheeler DC, Xie J, Zhang H, Zinman B, Desai M, Perkovic V; CREDENCE study investigators: The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics. *Am J Nephrol* 46: 462–472, 2017 10.1159/000484633
20. Grams ME, Sang Y, Ballew SH, Matsushita K, Astor BC, Carrero JJ, Chang AR, Inker LA, Kenealy T, Kovesdy CP, Lee BJ, Levin A, Naimark D, Pena MJ, Schold JD, Shalev V, Wetzels JFM, Woodward M, Gansevoort RT, Levey AS, Coresh J: Evaluating Glomerular Filtration Rate Slope as a Surrogate End Point for ESKD in Clinical Trials: An Individual Participant Meta-Analysis of Observational Data. *J Am Soc Nephrol* 30: 1746–1755, 2019 10.1681/ASN.2019010008
21. Jardine M, Zhou Z, Lambers Heerspink HJ, Hockham C, Li Q, Agarwal R, Bakris GL, Cannon CP, Charytan DM, Greene T, Levin A, Li J-W, Neuen BL, Neal B, Oh R, Oshima M, Pollock C, Wheeler DC, de Zeeuw D, Zhang H, Zinman B, Mahaffey KW, Perkovic V: Kidney, Cardiovascular, and Safety Outcomes of Canagliflozin according to Baseline Albuminuria. *Clin J Am Soc Nephrol* 16: 384–395, 2021 10.2215/CJN.15260920
22. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, Wanner C: Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 5: 610–621, 2017 10.1016/S2213-8587(17)30182-1
23. Oshima M, Jardine MJ, Agarwal R, Bakris G, Cannon CP, Charytan DM, de Zeeuw D, Edwards R, Greene T, Levin A, Lim SK, Mahaffey KW, Neal B, Pollock C, Rosenthal N,

Wheeler DC, Zhang H, Zinman B, Perkovic V, Heerspink HJL: Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice. *Kidney Int* 99: 999–1009, 2021 10.1016/j.kint.2020.10.042

24. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI: Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation* 134: 752–772, 2016 10.1161/CIRCULATIONAHA.116.021887

25. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, Barrett TD, Weidner-Wells M, Deng H, Matthews DR, Neal B: Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 6: 691–704, 2018 10.1016/S2213-8587(18)30141-4

Table 1: Patient characteristics according to baseline HbA1c subgroups*

	HbA1c (%)			
	6.5-7.0	**7.0-<8.0**	**8.0-<10.0**	**≥10.0-<12.0**
N†	650	1406	1849	494
Age, y	64.1 (9.3)	64.0 (9.4)	62.4 (9.0)	60.9 (8.9)
Male, n (%)	475 (73.1)	966 (68.7)	1212 (65.5)	252 (51.0)
Race, n (%)				
Asian	158 (24.3)	289 (20.6)	336 (18.2)	94 (19.0)
Black or African American	29 (4.5)	63 (4.5)	105 (5.7)	27 (5.5)
Other‡	56 (8.6)	104 (7.4)	160 (8.7)	49 (9.9)
White	407 (62.6)	950 (67.6)	1248 (67.5)	324 (65.6)
Current smoker, n (%)	85 (13.1)	224 (15.9)	279 (15.1)	51 (10.3)
Duration of diabetes, y	14.7 (9.1)	15.8 (8.7)	16.4 (8.6)	14.9 (7.8)
History of hypertension, n (%)	631 (97.1)	1353 (96.2)	1796 (97.1)	478 (96.8)
History of heart failure, n (%)	75 (11.5)	208 (14.8)	284 (15.4)	84 (17.0)
History of cardiovascular disease, n (%)	322 (49.5)	693 (49.3)	958 (51.8)	246 (49.8)
Body mass index, kg/m^2	30.8 (6.4)	31.1 (6.0)	31.7 (6.1)	31.5 (6.5)
Systolic BP, mmHg,	140.3 (15.7)	140.0 (15.3)	140.2 (15.7)	138.8 (16.0)
Diastolic BP, mmHg	77.7 (9.3)	78.2 (9.6)	78.5 (9.2)	78.9 (9.2)
HbA1c, %	6.6 (0.3)	7.4 (0.3)	8.8 (0.6)	10.8 (0.8)
Total cholesterol, mmol/L	4.5 (1.2)	4.5 (1.2)	4.7 (1.3)	5.2 (1.5)
Triglycerides, mmol/L	1.9 (1.3)	2.1 (1.3)	2.3 (1.7)	2.8 (2.2)
eGFR, mL/min/1.73 m$^{2\|\|}$	53.5 (17.4)	54.8 (17.9)	57.2 (18.2)	59.8 (19.6)
UACR, mg/g, median (IQR)	860 (438,1790)	937 (469, 1778)	927 (474, 1837)	967 (452, 2058)
Insulin, n (%)	314 (48.3)	847 (60.2)	1358 (73.4)	365 (73.9)
Diuretic, n (%)	290 (44.6)	676 (48.1)	888 (48.0)	202 (40.9)

BP, blood pressure; SD, standard deviation; UACR, urinary albumin:creatinine ratio. *Data are mean (SD) unless otherwise indicated. †Two randomized participants had missing baseline HbA1c values and were excluded from the analysis. ‡Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported. ||Calculated using the CKD-EPI (CKD Epidemiology Collaboration) equation.

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

		Acute phase (baseline to week 3) eGFR change (ml/min/1.73 m^2)				Chronic phase (week 3 to the last available measurement) Annual eGFR change (ml/min/1.73 m^2/year)				Total phase (baseline to week 130) Annual eGFR change (ml/min/1.73 m^2/year)				
		Mean (SE)		Difference (95% CI) SE	P for interaction	Mean (SE)		Difference (95% CI) SE	P for interaction	Mean (SE)		Difference (95% CI) SE	P for interaction	Difference (%)
		Canagliflozin	Placebo			Canagliflozin	Placebo			Canagliflozin	Placebo			
Overall		-3.72 (0.3)	-0.55 (0.3)	-3.17 (-3.87, -2.47)		-1.85 (0.1)	-4.59 (0.1)	2.74 (2.37, 3.11)		-3.19 (0.2)	-4.71 (0.2)	1.52 (1.11, 1.93)		32.3
HbA1c (%)*	<7	-3.82 (0.4)	-0.50 (0.4)	-3.32 (-4.52, -2.12)	0.87	-2.21 (0.3)	-3.98 (0.3)	1.77 (0.88, 2.65)	0.02	-3.63 (0.3)	-4.02 (0.3)	0.39 (-0.56, 1.33)	0.01	9.1
	7-<8	-3.44 (0.3)	-0.65 (0.3)	-2.79 (-3.64, -1.95)		-1.97 (0.2)	-4.38 (0.2)	2.41 (1.78, 3.04)		-3.18 (0.2)	-4.54 (0.3)	1.36 (0.69, 2.04)		30.0
	8-<10	-3.51 (0.3)	-0.66 (0.3)	-2.85 (-3.62, -2.08)		-1.61 (0.2)	-4.91 (0.2)	3.30 (2.74, 3.86)		-2.91 (0.2)	-5.14 (0.2)	2.23 (1.63, 2.83)		43.4
	≥10	-2.41 (0.6)	0.86 (0.6)	-3.27 (-4.99, -1.55)		-2.92 (0.5)	-5.62 (0.4)	2.69 (1.43, 3.96)		-3.49 (0.5)	-5.09 (0.5)	1.60 (0.30, 2.91)		31.4
Screening	30-<45	-2.45 (0.3)	-0.41 (0.3)	-2.03 (-2.73, -1.34)	0.02	-1.72 (0.2)	-4.33 (0.2)	2.61 (2.06, 3.16)	0.65	-2.56 (0.2)	-4.35 (0.2)	1.79 (1.20, 2.38)	0.71	41.1
eGFR*	45-<60	-4.08 (0.3)	-0.64 (0.3)	-3.44 (-4.32, -2.57)		-1.62 (0.2)	-4.58 (0.2)	2.97 (2.32, 3.61)		-3.11 (0.3)	-4.76 (0.3)	1.65 (0.96, 2.34)		34.7
(mL/min/1.73 m^2)	60-<90	-3.66 (0.3)	-0.39 (0.3)	-3.27 (-4.17, -2.37)		-2.32 (0.2)	-4.92 (0.2)	2.60 (1.97, 3.32)		-3.61 (0.2)	-5.03 (0.2)	1.42 (0.75, 2.09)		28.2
UACR (mg/g)	≤1000	-3.15 (0.4)	0.45 (0.4)	-3.60 (-4.58, -2.62)	0.44	-0.78 (0.2)	-3.09 (0.2)	2.31 (1.88, 2.73)	0.04	-1.88 (0.2)	-2.79 (0.2)	0.91 (0.42, 1.40)	0.008	32.6
	>1000-<3000	-4.13 (0.4)	-1.29 (0.4)	-2.84 (-3.84, -1.83)		-2.65 (0.2)	-5.94 (0.2)	3.29 (2.67, 3.91)		-4.15 (0.2)	-6.37 (0.3)	2.23 (1.55, 2.90)		35.0
	≥3000	-4.70 (0.8)	-2.26 (0.7)	-2.44 (-4.52, -0.36)		-6.43 (0.6)	-8.92 (0.5)	2.49 (1.00, 3.99)		-8.15 (0.6)	-9.68 (0.6)	1.53 (-0.11, 3.17)		15.8

The effects of canagliflozin on on-treatment eGFR slope were analyzed using a piecewise, linear mixed effects model with a knot at week 3, including the fixed effects of treatment, baseline eGFR, continuous time, and time spline (one knot at Week 3), with two-way interactions of treatment by time and treatment by time spline, and the random effects of intercept, time and time spline. Compound symmetry was used to fit the covariance structures in the mixed effect models, as the model did not converge when unstructured was used.

Figure 1: Effects of canagliflozin compared to placebo on eGFR slope in patients with near-normal glycemic control (HbA1c 6.5-7.0%; Panel A) and poor glycemic control (HbA1c 7.0-12%; Panel B). Panel C shows the effect of canagliflozin on least square mean change from baseline in UACR in patients with near-normal and poor glycemic control

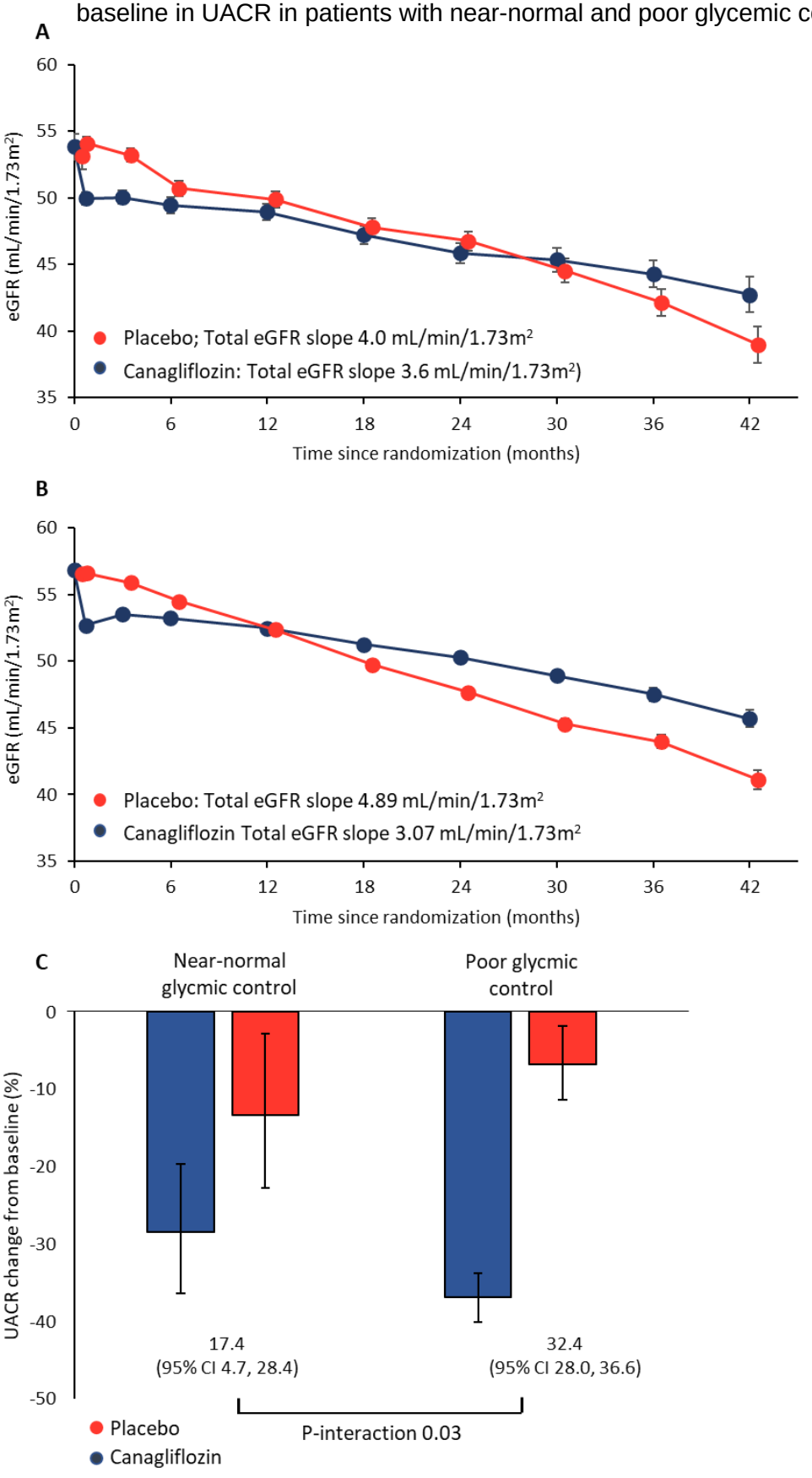
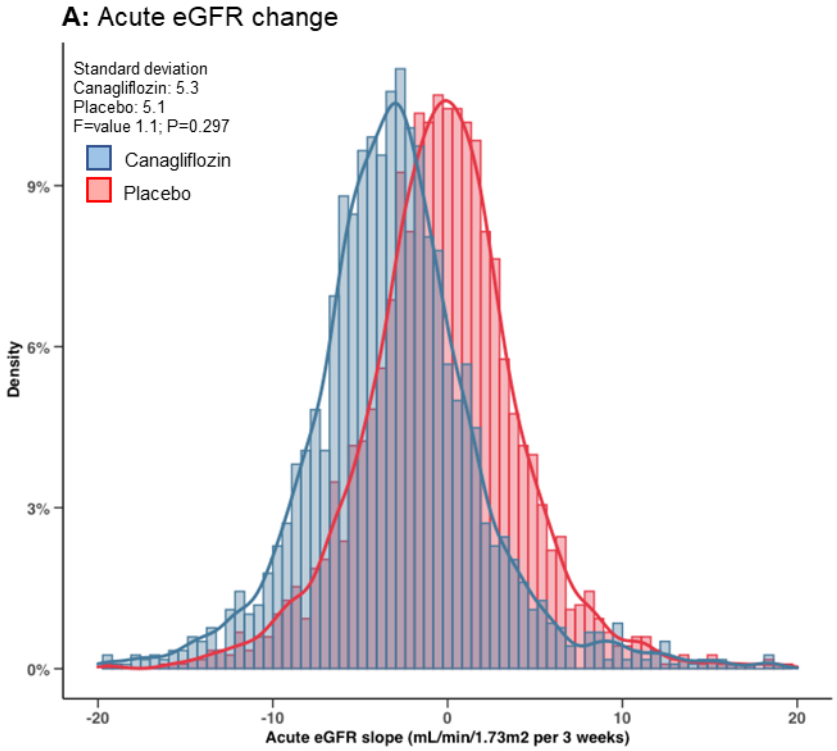


Figure 2: Distribution of eGFR changes in the acute phase (Panel A) and annual eGFR slope during the chronic treatment phase (Panel B) in the canagliflozin and placebo groups



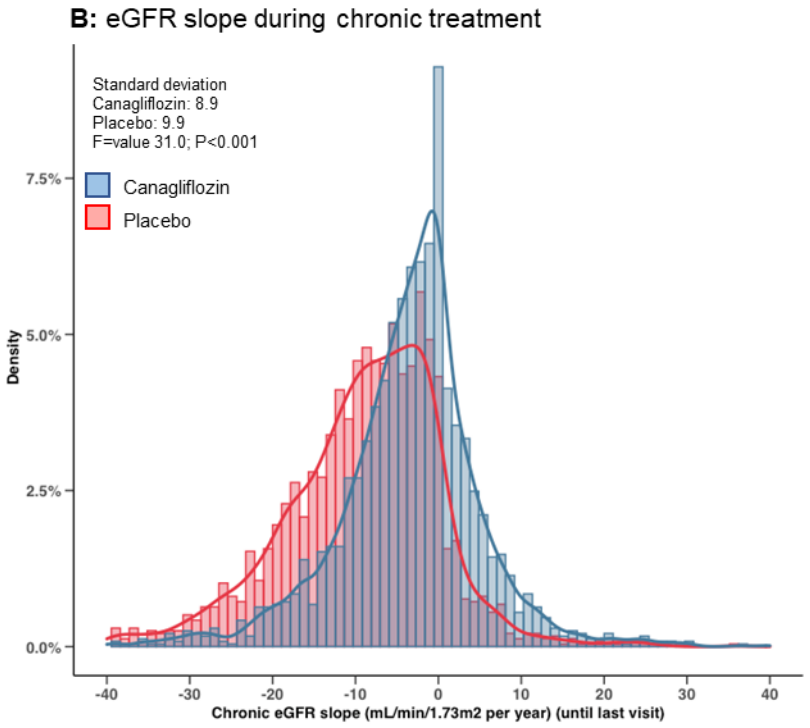
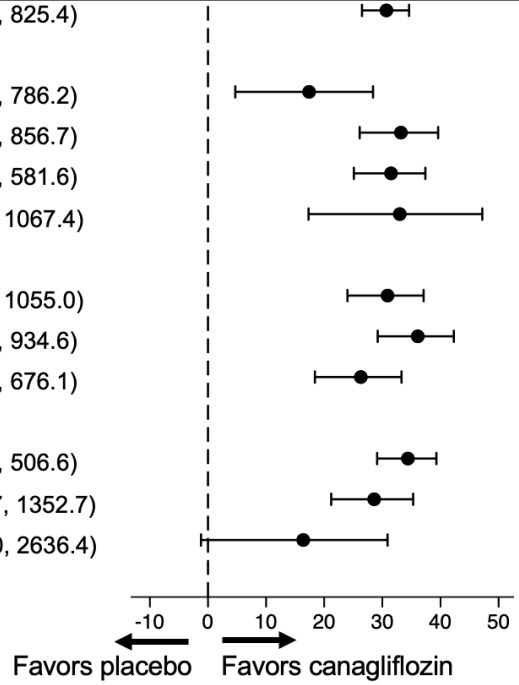


Figure 3: Effect of canagliflozin on UACR according to baseline participant subgroups

		Geometric mean UACR over time (mg/g [95% CI])			P for interaction
		Canagliflozin	Placebo	Difference (% [95% CI])	
Overall		546.3 (521.5, 572.3)	788.8 (751.9, 825.4)	30.7 (34.6, 26.5)	
HbA1c (%)					
	<7	579.0 (515.5, 650.4)	700.9 (624.9, 786.2)	17.4 (4.7, 28.4)	0.16
	7-<8	527.5 (486.3, 572.2)	789.5 (727.6, 856.7)	33.2 (26.1, 39.6)	
	8-<10	541.9 (504.9, 581.6)	791.9 (504.9, 581.6)	31.5 (25.1, 37.4)	
	≥10	791.2 (736.3, 850.2)	892.5 (746.3, 1067.4)	33.9 (17.3, 47.2)	
Screening eGFR (mL/min/1.73 m^2)					
	30-<45	674.1 (623.3, 729.0)	975.3 (901.7, 1055.0)	30.9 (24.0, 37.1)	0.13
	45-<60	550.7 (507.8, 597.2)	861.3 (793.8, 934.6)	36.1 (29.2, 42.3)	
	60-<90	460.8 (426.1, 498.3)	625.1 (577.9, 676.1)	26.3 (18.5, 33.3)	
UACR (mg/g)					
	≤1000	311.9 (292.9, 332.0)	475.6 (446.5, 506.6)	34.4 (29.1, 39.3)	0.04
	>1000-<3000	892.1 (824.9, 964.7)	1249.8 (1154.7, 1352.7)	28.6 (21.2, 35.3)	
	≥3000	1903.2 (1633.6, 2217.4)	2276.7 (1966.0, 2636.4)	16.4 (-1.2, 30.9)	



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

Figure 4: Effect of canagliflozin on primary and secondary outcomes according to baseline HbA1c

	N of participants with an event		Participants with an event per 1000 patient-years				
	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard ratio (95% CI)	P-value	P for interaction
Primary composite outcome							
<7	33	50	39.2	59.8	0.63 (0.41, 0.98)	0.04	0.49
7-<8	82	94	44.8	52.3	0.84 (0.63, 1.13)	0.26	
8-<10	96	142	39.4	61.0	0.63 (0.49, 0.82)	0.001	
≥10	33	53	58.7	89.4	0.67 (0.43, 1.04)	0.07	
ESKD, doubling of serum creatinine level, or death due to kidney failure							
<7	25	39	29.7	46.6	0.61 (0.37, 1.01)	0.06	0.37
7-<8	55	62	30.0	34.5	0.86 (0.60, 1.24)	0.42	
8-<10	53	88	21.7	37.8	0.56 (0.40, 0.79)	0.001	
≥10	20	35	35.6	59.0	0.63 (0.36, 1.08)	0.095	
ESKD							
<7	21	33	24.8	39.1	0.61 (0.35, 1.05)	0.07	0.73
7-<8	42	49	22.8	27.1	0.83 (0.55, 1.25)	0.38	
8-<10	39	57	15.9	24.2	0.64 (0.43, 0.97)	0.03	
≥10	14	26	24.8	43.3	0.60 (0.31, 1.15)	0.13	
CV death, myocardial infarction, or stroke							
<7	25	25	29.8	29.3	0.98 (0.56, 1.71)	0.93	0.82
7-<8	60	75	32.9	42.1	0.77 (0.55, 1.09)	0.14	
8-<10	101	127	42.2	55.2	0.76 (0.59, 0.99)	0.04	
≥10	30	41	54.4	69.3	0.81 (0.51, 1.31)	0.39	
HF hospitalization or CV death							
<7	18	31	21.1	36.7	0.56 (0.31, 1.01)	0.05	0.81
7-<8	55	71	29.9	39.4	0.74 (0.52, 1.06)	0.10	
8-<10	79	114	32.4	49.0	0.66 (0.49, 0.87)	0.004	
≥10	26	36	46.5	60.4	0.79 (0.48, 1.31)	0.36