Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease: Insights from the CREDENCE Trial

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ABSTRACT

Background

People with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) experience a high burden of hypertension but the magnitude and consistency of blood pressure (BP) lowering with canagliflozin in this population is uncertain. Whether the effects of canagliflozin on kidney and cardiovascular outcomes vary by baseline BP or BP lowering therapy is also unknown.

Methods

The CREDENCE trial randomized people with T2DM and CKD to canagliflozin or placebo. Post-hoc, we investigated the effect of canagliflozin on systolic BP across subgroups defined by baseline systolic BP, number of BP lowering drug classes, and history of apparent treatment-resistant hypertension (BP ≥130/80 mmHg while receiving ≥3 classes of BP lowering drugs, including a diuretic). We also assessed whether effects on clinical outcomes differed across these subgroups.

Results

The trial included 4,401 participants of whom 3,361 (76.4%) had baseline systolic BP ≥130 mmHg, and 1371 (31.2%) had resistant hypertension. By week 3, canagliflozin reduced systolic BP by 3.50mmHg (95% CI, -4.27 to -2.72), an effect maintained over the duration of the trial, with similar reductions across BP and BP lowering therapy subgroups (all P-interaction ≥0.05). Canagliflozin also reduced the need for initiation of additional BP lowering agents during the trial (HR 0.68, 95% CI 0.61-0.75). The effect of canagliflozin on kidney failure, doubling of serum creatinine, or death due to kidney or cardiovascular disease

(HR 0.70, 95% CI 0.59-0.82) was consistent across BP and BP lowering therapy subgroups (all P-interaction ≥0.35), as were effects on other key kidney, cardiovascular and safety outcomes.

Conclusions

In people with T2DM and CKD, canagliflozin lowers systolic BP across all BP defined subgroups and reduces the need for additional BP lowering agents. These findings support use of canagliflozin for end-organ protection and as an adjunct BP lowering therapy in people with CKD.

Clinical Trial Registration: URL: https://clinicaltrials.gov. Unique Identifier: NCT02065791.

Key Words: Canagliflozin, SGLT2 inhibitors, blood pressure, hypertension, chronic kidney disease

Clinical perspective

What is new?

- Treatment with the SGLT2 inhibitor canagliflozin results in early and sustained reductions in systolic blood pressure in people with type 2 diabetes and chronic kidney disease, regardless of baseline blood pressure, number of blood pressure lowering agents, and history of apparent treatment-resistant hypertension
- Canagliflozin improves blood pressure control and reduces the need for additional blood pressure lowering agents
- Kidney and cardiovascular protection with canagliflozin is similar irrespective of baseline blood pressure, number of blood pressure lowering agents, and history of apparent treatment-resistant hypertension

What are the clinical implications?

- People with type 2 diabetes and chronic kidney disease experience a very high burden of hypertension
- The blood pressure lowering effect of canagliflozin occurs early and is sustained in the long-term, the magnitude of which is comparable to low dose hydrochlorothiazide
- Canagliflozin could be considered as an adjunct blood pressure lowering agent in addition to its kidney and cardiovascular protective effects

Introduction

Hypertension is a major risk factor for cardiovascular events and progression of kidney disease and occurs commonly in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).[1-3] Blood pressure (BP) lowering is an important strategy for reducing cardiovascular risk and is a cornerstone management approach in these individuals. However achieving optimal BP control in people with T2DM and CKD is challenging, and the prevalence of resistant hypertension, requirement for multiple BP lowering therapies and risk of treatment related adverse events are high.[4]

Canagliflozin is a glucose-lowering agent of the sodium-glucose cotransporter 2 (SGLT2) inhibitor class, which has been shown to lower BP in people with T2DM and normal kidney function.[5, 6] Canagliflozin and other SGLT2 inhibitors act by blocking the reuptake of sodium and glucose in the proximal tubule.[7] The resulting natriuresis and osmotic diuresis has been suggested to contribute to reductions in intravascular volume and systolic BP of approximately 3-5mmHg,[7] although other mechanisms may also contribute.[8]

In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Trial, canagliflozin reduced the risk of kidney failure and of hospitalization for heart failure in patients with T2DM and CKD by 30 and 40% respectively.[9] While canagliflozin also lowered systolic BP, the magnitude and consistency of this effect across different levels of baseline systolic BP, number of BP lowering drug classes, and in patients with and without apparent treatment-resistant hypertension, is unclear.

Whether the effects of canagliflozin on kidney, cardiovascular and safety outcomes vary across these subgroups is also uncertain.

We therefore undertook a post-hoc analysis of the CREDENCE trial to assess the BP effects of canagliflozin and to examined the effects of canagliflozin on kidney, cardiovascular and safety outcomes across a number of BP defined subgroups.

Methods

Data availability

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

Study design and participants

Detailed methods and the statistical analysis plan for the CREDENCE trial have been published previously.[9, 10] Briefly, CREDENCE was a multi-center, event-driven, double-blind, randomized controlled trial, which was the first trial designed to assess the effect of canagliflozin on kidney, cardiovascular, and safety outcomes in people with T2DM and established CKD. The trial was conducted in 695 sites across 34 countries. Local institutional ethics committees approved the trial protocol at each site and all participants provided written informed consent.

The trial included participants aged 30 years and older with T2DM, a glycated hemoglobin (HbA1c) of 6.5 to 12.0% and CKD, which was defined as an estimated glomerular filtration rate (eGFR) of 30 to <90 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio (UACR) >300 to 5000 mg/g. All participants were required to be receiving maximum tolerated or labelled dose of renin angiotensin system (RAS) blockade for at least 4 weeks prior to randomization. Key exclusion criteria included non-diabetic kidney disease or type 1 diabetes, treatment with immunosuppression for previous kidney disease, current use of a mineralocorticoid receptor antagonist, or a history of dialysis or kidney transplantation. People with uncontrolled hypertension (systolic BP ≥180 and/or diastolic BP ≥100 mmHg) two weeks prior to randomization were also excluded.

Randomization and follow-up procedures

All eligible patients underwent a two-week, single blind, placebo run-in period before being randomized to either canagliflozin 100 mg, or matching placebo once daily. Randomization was performed centrally based on a computer-generated randomization schedule, using randomly permuted blocks stratified by pre-randomization eGFR (30 to <45, 45 to <60, 60 to <90 mL/min/1.73m^2). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate eGFR.

After randomization, study visits were conducted at weeks 3, 13, and 26 and then alternated between clinic and telephone follow-up at 13-week intervals thereafter. BP was measured at

baseline and at each clinic visit by local investigators after blood collection for laboratory tests. As mandated in the study protocol, 3 consecutive BP measurements were taken at intervals of at least 1 minute apart, and the average of the 3 readings was recorded. The same arm was to be used for BP measurements in each individual participant for the duration of the study. If BP was measured manually, it was recommended that it was measured by the same individual using the same equipment, if possible, at each visit to reduce variability.

The background use of other BP lowering therapies was guided by best practice in accordance with local guidelines. All participants, care providers, investigators and outcome assessors were blinded to randomized treatment allocation until the end of the trial.

Participant subgroups

We assessed the magnitude and consistency of systolic BP lowering with canagliflozin, as well as effects on kidney, cardiovascular and safety outcomes according to baseline systolic BP, number of BP lowering drug classes, and history of apparent treatment-resistant hypertension. Effects on systolic BP were also assessed across age, sex, race, HbA1c, eGFR and UACR subgroups. Baseline systolic BP was categorized as <130, 130-<140, 140-<150 and ≥150 mmHg. BP lowering therapies were organized into the following categories: RAS blockade; calcium channel blockers; beta-blockers; diuretics; peripherally acting antiadrenergic agents; centrally acting antiadrenergic agents; and direct acting vasodilators. Resistant hypertension was defined as systolic BP ≥130 and/or diastolic BP ≥80mmHg while receiving ≥3 classes of BP lowering drugs including a diuretic.[11]

Outcomes

Definitions for all outcomes in the CREDENCE trial have been reported previously.[9] The primary outcome of the trial was a composite of kidney failure (chronic dialysis, transplantation or sustained eGFR <15 mL/min/1.73m^2), sustained doubling of the serum creatinine, or death due to kidney or cardiovascular disease. In this post-hoc analysis, we also assessed the effect of canagliflozin versus placebo on a range on BP outcomes including the likelihood of achieving a >5 mmHg reduction in systolic BP by week 3, systolic BP over time (from baseline to week 3 and over the duration of the trial), achievement of BP targets and new initiation of BP lowering agents.

Other pre-specified kidney outcomes were: kidney failure, doubling of serum creatinine, or death due to kidney disease; kidney failure or death due to kidney or cardiovascular disease; kidney failure or death due to kidney disease; and kidney failure. Dialysis, kidney transplantation, or death due to kidney disease was assessed post-hoc.

A number of pre-specified cardiovascular outcomes were also assessed, including: cardiovascular death or hospitalization for heart failure; cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; hospitalization for heart failure; cardiovascular death; and death from any cause.

Pre-specified safety outcomes in this analysis included any serious adverse event; volume

depletion; acute kidney injury; kidney-related adverse events; amputation; and fracture. The definition of volume depletion was pre-specified in the statistical analysis plan and included the following investigator reported Medical Dictionary for Regulatory Activities (MedDRA) terms: BP decreased, dehydration, dizziness postural, hypotension, hypovolemia, orthostatic hypotension, presyncope, syncope, and urine output decreased.

Statistical analysis

Characteristics of participants stratified by baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension were compared using chi-square and ANOVA tests for categorical and continuous variables, respectively.

Post-hoc, we assessed the effect of canagliflozin on systolic BP over two time periods, from baseline to week 3 and over the duration of the trial, using two complementary approaches. We used a linear model to assess the change in systolic BP from baseline to week 3, with adjustment for baseline values and screening eGFR category. The effect of canagliflozin on systolic BP over the duration of the trial was analyzed using mixed-effect models for repeated measurements that included all post-baseline data up to week 182, assuming an unstructured covariance with covariates including baseline value, treatment allocation, screening eGFR category and trial visit, as has been done previously.[12] The consistency of BP lowering across different subgroups was assessed with the addition of treatment by subgroup interaction terms to the relevant model. Analyses of change in systolic BP were based on-treatment analyses using complete data, as pre-specified in the statistical analysis plan and to be consistent with

the primary trial report.[9]

To further explore the BP effects of canagliflozin we performed a range of additional post-hoc analyses. To explore which participants might experience greater early reductions in systolic BP, we used logistic regression to assess the probability of achieving a reduction in systolic BP of >5 mmHg at week 3 with canagliflozin versus placebo, overall and across participant subgroups. We described the proportion of participants achieving a systolic BP <130 mmHg at each study visit from week 3 to week 182. We also assessed the effect of canagliflozin on new initiation of BP lowering agents post-randomization using Cox regression, with event time measured until new initiation of BP lowering therapy or last trial contact date.

The effects of canagliflozin on all kidney and cardiovascular outcomes were assessed using Cox regression models stratified by screening eGFR using an intention-to-treat approach. Heterogeneity in treatment effects across subgroups was assessed using likelihood ratio tests to compare models with and without interaction terms, with no correction for multiple comparisons. We further assessed for any interaction between randomized treatment and systolic BP fitted continuously. We performed sensitivity analyses for the main kidney and cardiovascular outcomes adjusting for the competing risk of death using the Fine and Gray method.[13] For these outcomes, we also provided a descriptive assessment of the percentage of the randomized treatment effect removed with adjustment for change in BP from baseline to week 3, as was done previously in the CREDENCE trial.[14] For each outcome, the percentage

of the treatment effect explained was expressed using the equation: 100% x([HR – $HR^{adjusted}$]/[HR-1]).

For amputation and fracture outcomes, time-to event analyses included all participants who received ≥1 dose of canagliflozin or placebo and had an event at any time during follow-up. For all other safety outcomes, as pre-specified in the statistical analysis plan, on-treatment analysis was conducted based on events that occurred in participants who had an adverse outcome while they were receiving canagliflozin or placebo, or ≤30 days after discontinuation of randomized treatment.

All analyses were performed using SAS version 9.4.

Results

The CREDENCE trial included 4401 randomized participants with T2DM and CKD (mean age 63 years, BP 140/78 mmHg, eGFR 56 mL/min/1.73m^2, and median UACR 927 mg/g) who were followed for a median of 2.6 years. The trial was stopped early based on the advice of the Data Monitoring Committee after achieving prespecified efficacy criteria at a scheduled interim analysis. 4361 participants (99.1%) completed the study; 13 (0.6%) and 9 (0.4%) participants in the canagliflozin and placebo arms respectively were lost to follow-up.

Baseline characteristics

The number of participants with baseline systolic BP <130, 130-<140, 140-<150 and ≥150

mmHg was 1040 (23.6%), 1142 (25.9%), 1054 (23.9%) and 1165 (26.5%) respectively (Table 1). Participants with higher systolic BP at baseline were more likely to be older, have established macrovascular disease, higher body mass index and albuminuria (Table 1). Participants receiving greater numbers of BP lowering therapies and those with resistant hypertension were also more likely to be older, have a history of heart failure, longer duration of diabetes, established macrovascular disease, lower eGFR and higher albuminuria (Supplemental Table 1 and Supplemental Table 2).

Background use of BP lowering therapies

Almost all participants (*n*=4,395, 99.9%) were receiving RAS blockade at baseline, as mandated for entry into the trial. 2,129 (48.4%) were receiving a calcium channel blocker, 1,770 (40.2%) a beta blocker and 2,057 (46.7%) a diuretic (Supplemental Table 4). The proportion of participants receiving multiple classes of BP lowering therapies at baseline, and their combinations, is displayed in Supplemental Table 3. 3,394 participants (77.2%) were taking ≥2 classes of BP lowering therapies, the most common regimens being RAS blockade plus calcium channel blocker (12.5%) or RAS inhibitor plus diuretic (10.3%). 1,130 (25.7%). 901 (20.5%) participants were receiving 3 and 4 or more classes of BP lowering drugs respectively at baseline. The prevalence of apparent treatment-resistant hypertension at baseline was 31.4% (Supplemental Table 2). Baseline use and new initiation of BP lowering drugs by class of agent are summarized in Supplemental Table 4.

Change in systolic BP, predictors of BP response, and need for additional BP lowering agents

At week 3, canagliflozin-treated participants experienced a greater reduction in systolic BP than placebo-treated participants (-3.39 mmHg, SE 0.28 vs. 0.11 mmHg, SE 0.28; difference -3.50 mmHg, 95% CI, -4.27 to -2.72; Supplemental Table 5). This early reduction in systolic BP was similar across categories of baseline systolic BP, number of BP lowering drug classes, and in participants with and without resistant hypertension, as well as a number of other subgroups (P-interaction ≥0.10; Figure 1 and Supplementary Table 5).

Canagliflozin increased the likelihood of experiencing a >5mmHg reduction in systolic BP by week 3 (OR 1.45, 95% CI 1.28–1.64), with more canagliflozin-treated participants (868 [40.0%]) experiencing a >5mmHg reduction in systolic BP than placebo-treated participants (682 [31.4%]). The probability of a >5mmHg reduction in systolic BP with canagliflozin was similar across BP and BP lowering therapy subgroups and was consistent across a number of other baseline characteristics (all P-interaction ≥0.25; Table 2).

Reductions in systolic BP were sustained over the duration of the trial (mean difference -3.30mmHg, 95% CI, -3.87 to -2.73; Supplemental Table 5) The long-term BP lowering effects of canagliflozin were consistent across BP defined subgroups and other participant characteristics over the duration of the trial (Figure 1 and Supplemental Table 5). The proportion of participants who achieved a systolic BP <130 mmHg was consistently higher with canagliflozin compared to placebo throughout follow up (Figure 2).

During the trial, 627 (39.8%) participants in the canagliflozin arm and 836 (61.3%) in the

placebo arm were commenced on additional BP lowering agents. Canagliflozin significantly reduced the need for initiation of new BP lowering therapies (HR 0.68, 95% CI 0.61-0.75; Figure 3).

Kidney outcomes

Canagliflozin reduced the risk of the primary composite outcome of kidney failure, doubling of serum creatinine, or death due to kidney or cardiovascular disease by 30% (HR 0.70, 95% CI 0.59-0.82), with consistent effects across different levels of baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension (P-interaction ≥0.35; Figure 4). Effects on kidney failure, doubling of serum creatinine or death due to kidney disease (HR 0.66, 95% CI 0.53-0.81) and other kidney outcomes, including kidney failure alone, were also similar across all subgroups (Figure 4). Effects on other kidney outcomes, including dialysis, transplant or death due to kidney disease, are summarized in Supplemental Figure 1, with similar results observed in sensitivity analyses adjusting for the competing risk of death (Supplemental Table 6).

Cardiovascular outcomes

The effect of canagliflozin on cardiovascular death or hospitalization for heart failure (HR 0.69, 95% CI 0.57-0.83) was consistent regardless of baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension (all P-interaction ≥0.07; Figure 5). The effect on cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR 0.80, 95% CI 0.67-0.95) also did not vary across BP or BP therapy defined sugroups (all P-

interaction≥0.14). Results were consistent in sensitivity analyses adjusting for the competing risk of death (Supplemental Table 6). Canagliflozin reduced the risk of hospitalization for heart failure across BP therapy defined subgroups, with some evidence that the magnitude of benefit varied by baseline systolic BP (P-interaction=0.04; Figure 5). While the effect of canagliflozin on all-cause mortality appeared greater in people on fewer BP lowering agents (P-interaction=0.01); effects on this outcome as well as cardiovascular death were otherwise consistent across other BP defined subgroups (Supplemental Figure 2).

Proportion of treatment effects explained by change in systolic BP

Analyses of the proportion of treatment effects on key kidney and cardiovascular outcomes explained by change in systolic BP at week 3 are displayed in Supplemental Table 7. Reductions in systolic BP with canagliflozin explained 2.6% of the effect on the primary composite outcome, and 4.0% of the effect on the kidney-specific composite (doubling of serum creatinine, kidney failure or death due to kidney disease). The BP lowering effect of canagliflozin explain 5.9% of the effect on cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke and 0.7% of the effect on cardiovascular death or hospitalization for heart failure.

Safety outcomes

The risk of any serious adverse event (HR 0.87, 95% CI 0.79-0.97) was lower with canagliflozin compared to placebo, with no effect modification by baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension (P-

interaction>0.10; Figure 6). The effect of canagliflozin on volume depletion and on acute kidney injury also did not vary across these subgroups (all P-interaction>0.10; Figure 6). Effects on amputation, fracture and all kidney-related adverse events were also similar across subgroups (Supplemental Figure 3).

Discussion

In this post-hoc analysis of the CREDENCE trial, treatment with canagliflozin resulted in early and sustained reductions in BP irrespective of baseline systolic BP, number of BP lowering drug classes, and history of apparent treatment-resistant hypertension. The likelihood of experiencing a clinically significant reduction in BP by the first study visit was similar across a range of participant characteristics and BP defined subgroups. Importantly, canagliflozin treated participants were more likely to achieve a systolic BP <130 mmHg during the trial and less likely to require additional BP lowering agents. Finally, the kidney and cardiovascular protective effects canagliflozin were consistent across BP and BP therapy defined subgroups, with no interaction observed for volume depletion or acute kidney injury. Taken together, these results provide compelling evidence that canagliflozin could be considered as an adjunct BP lowering agent in people with T2DM and CKD, in addition to its kidney and cardiovascular protective effects.

Our findings build upon previous randomized studies that observed moderate reductions in BP with SGLT2 inhibition in people with T2DM and normal kidney function.[15] In the EMPA-REG BP trial, empagliflozin reduced mean 24-hour ambulatory systolic BP by approximately

3-4 mmHg after 12 weeks,[16] with consistent reductions irrespective of the number of background BP lowering drugs.[17] A meta-analysis of seven RCTs involving 2381 patients reported 24-hour average ambulatory BP reduction of 3.62/1.72 mmHg with SGLT2 inhibition, which was comparable to BP lowering seen with low-dose hydrochlorothiazide.[18] Similar findings with clinic BP have been reported in short-term trials of other SGLT2 inhibitors,[6, 19, 20] and the longer-term BP lowering effects of SGLT2 inhibitors in individuals with T2DM and relatively preserved kidney function have been demonstrated in large cardiovascular outcome trials.[5, 21, 22]

The CREDENCE population differs substantially from the populations of previous SGLT2 inhibitor trials. Because CREDENCE recruited individuals at high risk of kidney disease progression, the burden of elevated BP was substantially higher than in previous trials. All participants had severely increased albuminuria, almost 60% had a starting eGFR <60 mL/min/1.73m^2, and almost half were treated with three or more classes of BP lowering therapies. Compared to the general population, resistant hypertension is at least twice as common in people with CKD and becomes increasingly so as eGFR declines.[4] In the CRIC (Chronic Renal Insufficiency Cohort) study, approximately 40% of participants with established CKD had apparent treatment-resistant hypertension.[23] The pattern of use of BP lowering therapies and prevalence of resistant hypertension in CREDENCE is consistent with these data, and suggest that our findings are likely to be directly applicable to the routine care of patients with T2DM and CKD, where the burden of resistant hypertension and use of multiple BP lowering therapies is high.

In this regard, our observation that canagliflozin reduces the need for additional BP lowering agents is a finding that would be welcome to many people living with CKD, who identify medication burden as an important contributor to poorer quality of life. The need for fewer BP lowering agents over time in canagliflozin treated participants may reflect better preservation of vascular and kidney function with SGLT2 inhibition, which is supported by Mendelian randomization studies demonstrating a direct causal effect of higher kidney function on lower BP.[24]

The mechanisms by which canagliflozin and other SGLT2 inhibitors lower BP are likely multifactorial with differing contributing factors in people with and without CKD.[8, 25] An important distinction is that unlike other BP lowering agents,[26] there appears to be no association between baseline BP or dose of an SGLT2 inhibitor and the magnitude of BP reduction, an observation which we have extended to people with CKD.[18] For the most part, effects on BP have been attributed to natriuresis and osmotic diuresis, the premise of which is predicated on normal kidney function.

However, reductions in BP that are at least as large in people with CKD in the absence of significant glycosuria suggest that natriuresis may not be the sole mechanism for BP lowering in this population. While the glycosuric effect of SGLT2 inhibition diminishes substantially as kidney function declines, effects on systolic BP appear preserved across the spectrum of eGFR studied to date, including down to an eGFR <30 mL/min/1.73m^2.[27-29] This observation

is confirmed and strengthened by the CREDENCE data, which includes one of the largest number of participants with eGFR <45 mL/min/1.73m^2 of any SGLT2 inhibitor outcome trial to date.[30] The explanation for BP lowering with canagliflozin in people with CKD is not clear, but could be due to greater salt sensitivity in this population, augmented natriuresis in combination with other diuretics, or other mechanisms independent of natriuresis.

A number of natriuretic independent mechanisms for BP lowering with SGLT2 inhibitors have been proposed. Despite their effects on intravascular volume, BP lowering with SGLT2 inhibitors is not accompanied by a compensatory increase in heart rate.[31] One hypothesis is that these drugs reduce neurohormonal activation.[32] Recent experimental data showed that chemical denervation in a neurogenic hypertensive animal model reduced SGLT2 expression, and that dapagliflozin reduced norepinephrine levels in kidney tissue, providing evidence of crosstalk between SGLT2 inhibitors and sympatho-inhibition.[33] This is further supported by favorable effects on arterial stiffness, vascular resistance, and BP variability in human clinical trials.[34-36] The underlying mechanisms linking SGLT2 inhibition and neurohormonal activity are yet to be fully elucidated, but are likely be through multiple indirect effects and possibly effects mediated through the sympathetic nervous system.

Regardless of the underlying mechanisms, relatively modest reductions in BP with SGLT2 inhibition are unlikely to fully explain the substantial risk reductions in kidney failure and cardiovascular outcomes with these agents,[9, 37-39] a conclusion supported by the finding that less than 10% of treatment effects on kidney and cardiovascular outcomes were explained by

change in systolic BP.

The strength of this study lies in the high quality of data obtained from the CREDENCE trial, which was a large, well-conducted, randomized, double-blind, placebo-controlled trial. All kidney and cardiovascular outcomes were adjudicated by expert committees blinded to treatment allocation. The high burden of hypertension in the study population and use of multiple classes of BP lowering therapies allowed us to extend previous observations on the BP lowering effects of SGLT2 inhibition to the CKD population and assess the consistency and durability of this effect across a number of clinically important subgroups. The absence of any clear difference in risk of adverse outcomes across different levels of systolic BP, in particular volume depletion and acute kidney injury, is reassuring and underscores the safety of canagliflozin in patients with T2DM and CKD.

Our findings should be interpreted in light of some limitations. This was a post-hoc analysis and was not specifically designed to assess BP lowering effects in individual subgroups or effects on clinical outcomes in each category of systolic BP. The reported interaction P values were not adjusted for multiple comparisons and should be interpreted appropriately. Because the mediation analyses were observational without adjustment for confounders between change in systolic BP and clinical outcomes, estimates of the proportion of treatment effects explained by reductions in systolic BP should be interpreted as a measure of association and thus causality cannot be directly inferred. Fully automated oscillometric devices and 24-hour ambulatory blood pressure monitoring, which may provide more acute measurement of BP,[40]

were not mandated in the study protocol; however, otherwise detailed instructions on measurement technique, the large number of participants, repeated measurements, and relatively long duration of follow-up reduces the potential impact of measurement error on these results.

Conclusion

In people with T2DM and CKD, canagliflozin lowers systolic blood pressure across all blood pressure defined subgroups and reduced the need for additional blood pressure lowering agents. These findings support use of canagliflozin for end-organ protection and as an adjunct blood pressure lowering therapy in people with CKD.

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A.E. Schutte serves on a Scientific Advisory Board for Abbott, has received grant support from Boehringer-Ingelheim and Pfizer, and received speaker honoraria from Omron, Servier, Novartis and Takeda. She is the President of the International Society of Hypertension, 2018-2020.

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Medical.

D. de Zeeuw reports serving on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, Mitsubishi Tanabe; serving on Steering Committees and/or as a speaker for AbbVie and Janssen; and serving on Data Safety and Monitoring Committees for Bayer.

A. Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); is on the data safety and monitoring board for NIDDK, Kidney Precision Medicine, University of Washington Kidney Research Institute Scientific Advisory Committee; and is funded by the 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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All other authors have nothing to disclose.

Supplemental Materials

Online-only Tables 1 - 7

Online-only Figures 1 - 3

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Table 1. Characteristics of participants with systolic BP < 130, 130-<140, 140-<150, ≥150mmHg at baseline.

	SBP < 130mmHg (N=1040)	SBP 130-<140mmHg (N=1142)	SBP 140-<150mmHg (N=1054)	SBP ≥ 150mmHg (N=1165)
Age, years, mean(SD)	61.6(9.7)	62.5(9.1)	63.3(8.9)	64.2(8.9)
Sex, No.(%)				
Male	669(64.3)	776(68.0)	710(67.4)	752(64.6)
Female	371(35.7)	366(32.0)	344(32.6)	413(35.4)
Race, No.(%)				
White	668(64.2)	771(67.5)	734(69.6)	758(65.1)
Black or African American	49(4.7)	55(4.8)	42(4.0)	78(6.7)
Asian	228(21.9)	235(20.6)	206(19.5)	208(17.9)
Native Hawaiian or other Pacific Islander	7(0.7)	6(0.5)	7(0.7)	5(0.4)
American Indian or Alaska Native	19(1.8)	19(1.7)	16(1.5)	24(2.1)
Multiple	17(1.6)	10(0.9)	16(1.5)	21(1.8)
Other*	52(5.0)	46(4.0)	33(3.1)	71(6.1)
Region, No.(%)				
North America	334(28.3)	316(26.7)	242(20.5)	290(24.5)
Central/South America	209(22.2)	233(24.8)	230(24.4)	269(28.6)
Europe	153(17.7)	176(20.4)	236(27.3)	299(34.6)
Rest of the world	344(24.3)	417(29.5)	346(24.5)	307(21.7)
Current smoker, No.(%)	165(15.9)	174(15.2)	151(14.3)	149(12.8)
History of heart failure, No.(%)	135(13.0)	193(16.9)	165(15.7)	159(13.7)
Duration of diabetes, years, mean(SD)	15.8(9.1)	15.3(8.0)	15.7(8.7)	16.3(8.7)
BP lowering drug therapy, No.(%)				
RAS inhibitor	1037(99.7)	1140(99.8)	1053(99.9)	1165(100.0)
Beta blocker	369(35.5)	443(38.8)	420(39.9)	538(46.2)
Calcium channel blocker	387(37.2)	512(44.8)	560(53.1)	670(57.5)
Diuretic	418(40.2)	486(42.6)	499(47.3)	654(56.1)
Peripherally acting antiadrenergic agents	47(4.5)	68(6.0)	67(6.4)	120(10.3)

Centrally acting antiadrenergic agents	38(3.7)	55(4.8)	67(6.4)	88(7.6)
Vasodilator	13(1.3)	24(2.1)	10(1.0)	35(3.0)
Atherosclerotic vascular disease history, No.(%) †				
Coronary	304(29.2)	337(29.5)	326(30.9)	346(29.7)
Cerebrovascular	153(14.7)	167(14.6)	176(16.7)	204(17.5)
Peripheral	219(21.1)	273(23.9)	259(24.6)	295(25.3)
CV disease history, No.(%)	495(47.6)	574(50.3)	559(53.0)	592(50.8)
Microvascular disease history, No.(%)				
Retinopathy	392(37.7)	500(43.8)	463(43.9)	527(45.2)
Neuropathy	489(47.0)	567(49.7)	521(49.4)	570(48.9)
History of amputation, No.(%)	49(4.7)	56(4.9)	59(5.6)	70(6.0)
Body mass index, Kg/m^2, mean(SD)	30.7(6.4)	31.2(6.0)	31.6(6.0)	31.8(6.3)
Systolic BP, mmHg, mean(SD)	120.1(7.1)	134.5(3.0)	143.7(3.0)	159.8(8.5)
Diastolic BP, mmHg, mean(SD)	72.7(8.5)	77.8(8.2)	80.0(8.2)	82.3(9.6)
HbA1c, %, mean(SD)	8.3(1.3)	8.3(1.3)	8.2(1.3)	8.3(1.3)
eGFR, ml/min/1.73m^2, mean(SD)	56.4(18.9)	57.3(18.6)	56.3(17.8)	54.8(17.6)
UACR, mg/g, median(IQR)	729.0(385.0,1521.5)	831.5(450.0,1688.0)	929.0(496.0,1783.0)	1142.0(566.0,2307.0)

BP indicates blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; HbA1c, glycohemoglobin; IQR, interquartile range; RAS, renin angiotensin system; SD, standard deviation; and UACR, urinary albumin/creatinine ratio.

* Includes other, unknown, and not reported.

† Some participants had ≥1 type of atherosclerotic disease.

Table 2. Probability of experiencing a >5mmHg reduction in systolic BP at week 3 with canagliflozin versus placebo by participant characteristics, BP and BP lowering therapy subgroups.

	Canagliflozin n/N (%)	Placebo n/N (%)	Odds ratio (95 % CI)	P-interaction
Total population	868/2172 (40)	682/2169 (31)	1.45 (1.28–1.64)	
Age (years)				0.43
<55	172/397 (43)	116/383 (30)	1.76 (1.31–2.36)	
55-<65	309/784 (39)	241/754 (32)	1.38 (1.12–1.71)	
65-<75	309/784 (39)	250/809 (31)	1.45 (1.18–1.79)	
≥75	78/207 (38)	75/223 (34)	1.19 (0.80–1.77)	
Sex				0.25
Male	577/1421 (41)	447/1447 (31)	1.53 (1.31–1.78)	
Female	291/751 (39)	235/722 (33)	1.31 (1.06–1.62)	
Baseline systolic BP (mmHg)				0.92
<130	88/514 (17)	61/507 (12)	1.51 (1.06–2.15)	
130-<140	181/574 (32)	132/552 (24)	1.47 (1.13–1.91)	
140-<150	239/524 (46)	180/517 (35)	1.57 (1.22–2.02)	
≥150	360/560 (64)	309/593 (52)	1.65 (1.31–2.10)	
Number of BP lowering drug classes				0.90
None or one	178/479 (37)	154/514 (30)	1.38 (1.06–1.80)	
Two	280/706 (40)	194/636 (31)	1.50 (1.19–1.88)	
Three or more	410/987 (42)	334/1019 (33)	1.46 (1.21–1.75)	
Resistant hypertension				0.84
Yes	307/665 (46)	253/692 (37)	1.49 (1.20–1.85)	
No	561/1507 (37)	429/1477 (29)	1.45 (1.24–1.69)	
Screening eGFR (ml/min/1.73m^2)				0.30
30-<45	279/646 (43)	207/647 (32)	1.62 (1.29–2.03)	
45-<60	250/631 (40)	217/633 (34)	1.26 (1.00–1.58)	
60-<90	339/895 (38)	258/889 (29)	1.49 (1.22–1.82)	
Screening UACR (mg/g)				0.62
≤1000	448/1172 (38)	349/1145 (30)	1.41 (1.19–1.68)	
>1000	420/1000 (42)	333/1024 (33)	1.50 (1.25–1.80)	
Baseline HbA1c (%)				0.47
<7	123/317 (39)	103/321 (32)	1.34 (0.97–1.86)	
7-<8	280/692 (40)	214/693 (31)	1.52 (1.22–1.90)	
8-<9	206/548 (38)	188/582 (32)	1.26 (0.99–1.61)	
≥9	259/614 (42)	177/572 (31)	1.63 (1.28–2.07)	

Figure Legends

Figure 1. Changes in systolic BP with canagliflozin versus placebo (A) from baseline to week 3 and (B) over the duration of the trial according to baseline systolic BP, number of classes of BP lowering drug classes, and history of resistant hypertension.

BP: blood pressure.

Figure 2. Proportion of participants achieving a systolic BP <130 mmHg at each study visit during the trial. BP: blood pressure.

Figure 3. Effect of canagliflozin on initiation of additional BP lowering agents during the trial. BP: blood pressure.

Figure 4. Effect of canagliflozin on kidney outcomes according to baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension.

SBP: systolic blood pressure; KIDNEY FAILURE: end-stage kidney disease; HR: hazard ratio; CI: confidence interval.

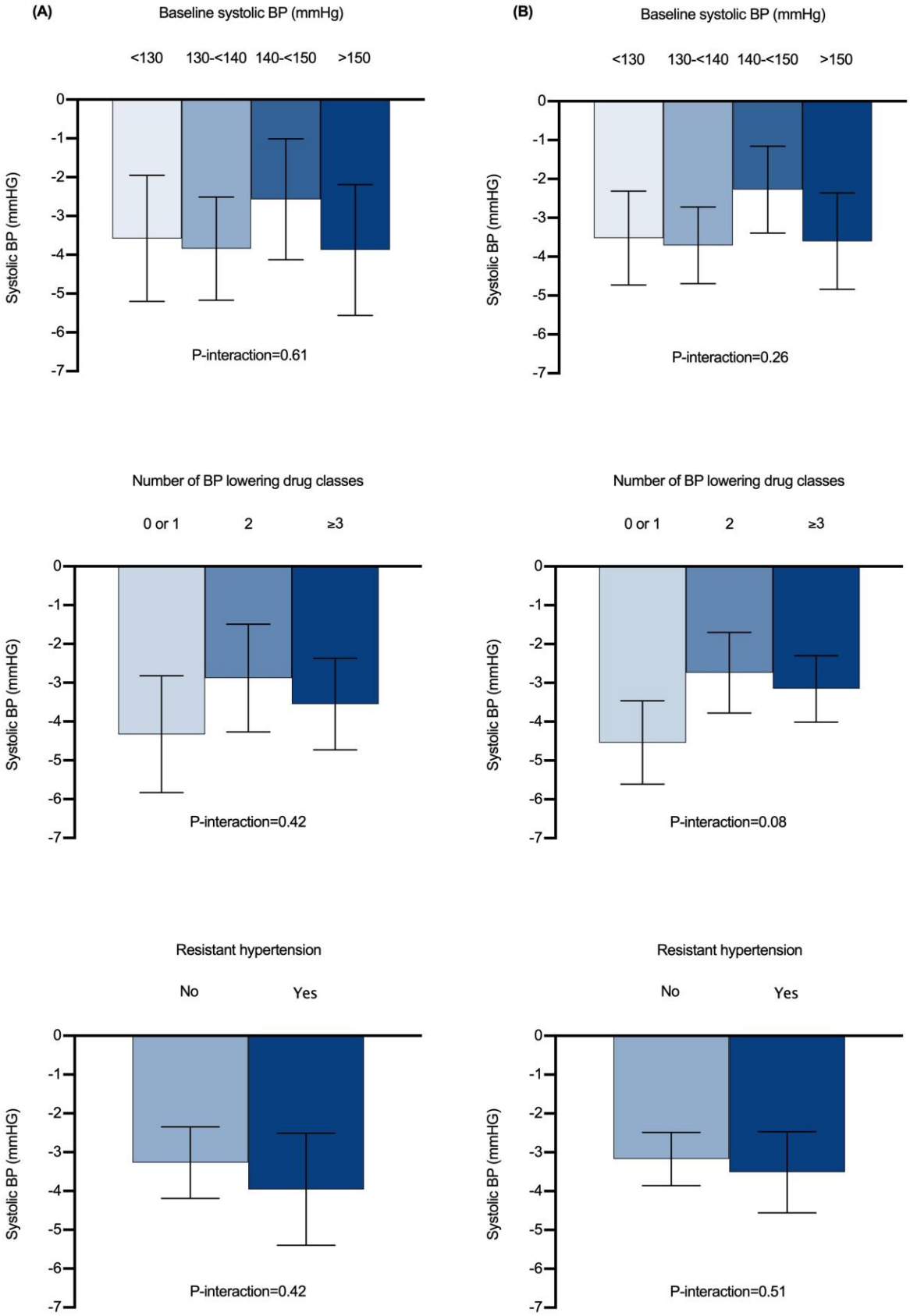
Figure 5. Effect of canagliflozin on cardiovascular outcomes according to baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension.

SBP: systolic blood pressure; HR: hazard ratio; CI: confidence interval.

Figure 6. Effect of canagliflozin on key safety outcomes according to baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension.

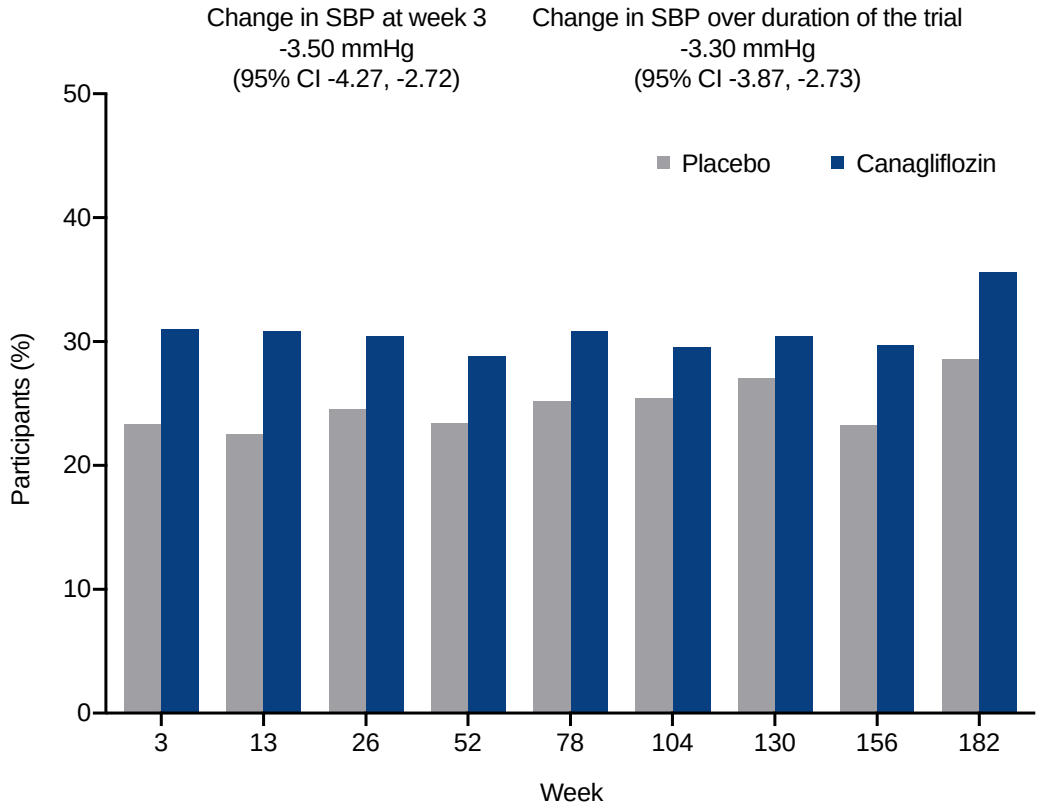
SBP: systolic blood pressure; HR: hazard ratio; CI: confidence interval. Volume depletion included the following MedDRA terms: BP decreased, dehydration, dizziness postural, hypotension, hypovolemia, orthostatic hypotension, presyncope, syncope, and urine output decreased.

Figure 1.



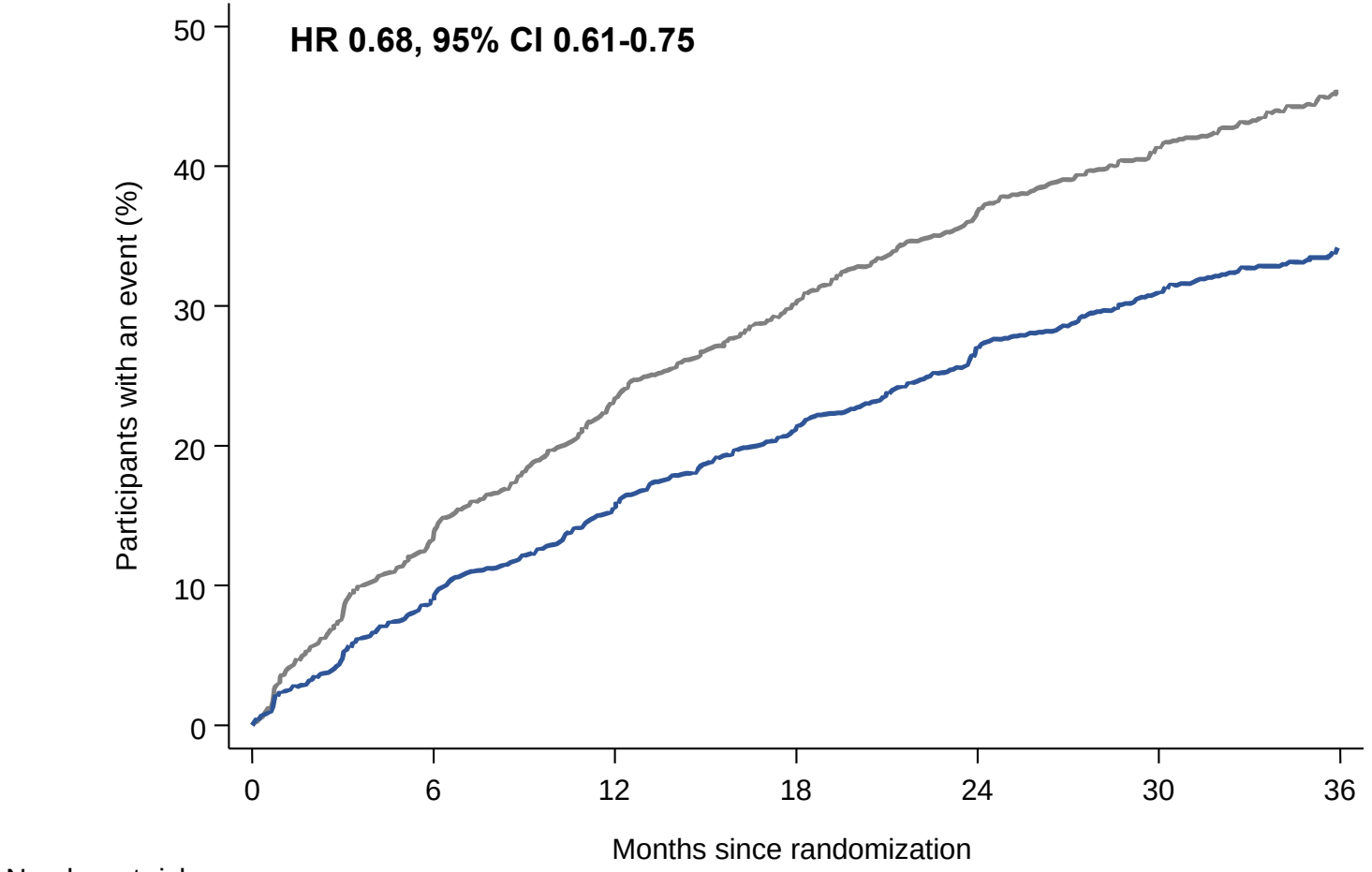
BP: blood pressure. Error bars represent 95% confidence intervals for the placebo subtracted difference in systolic BP across BP defined subgroups

Figure 2.



Participants (n)									
Canagliflozin	2172	2141	2096	2047	1962	1842	1261	731	264
Placebo	2169	2131	2096	2027	1923	1766	1187	682	245

Figure 3.



Number at risk							
Placebo	2199	1803	1514	1293	964	562	289
Canaglfilozin	2202	1897	1672	1483	1135	721	357

Figure 4.

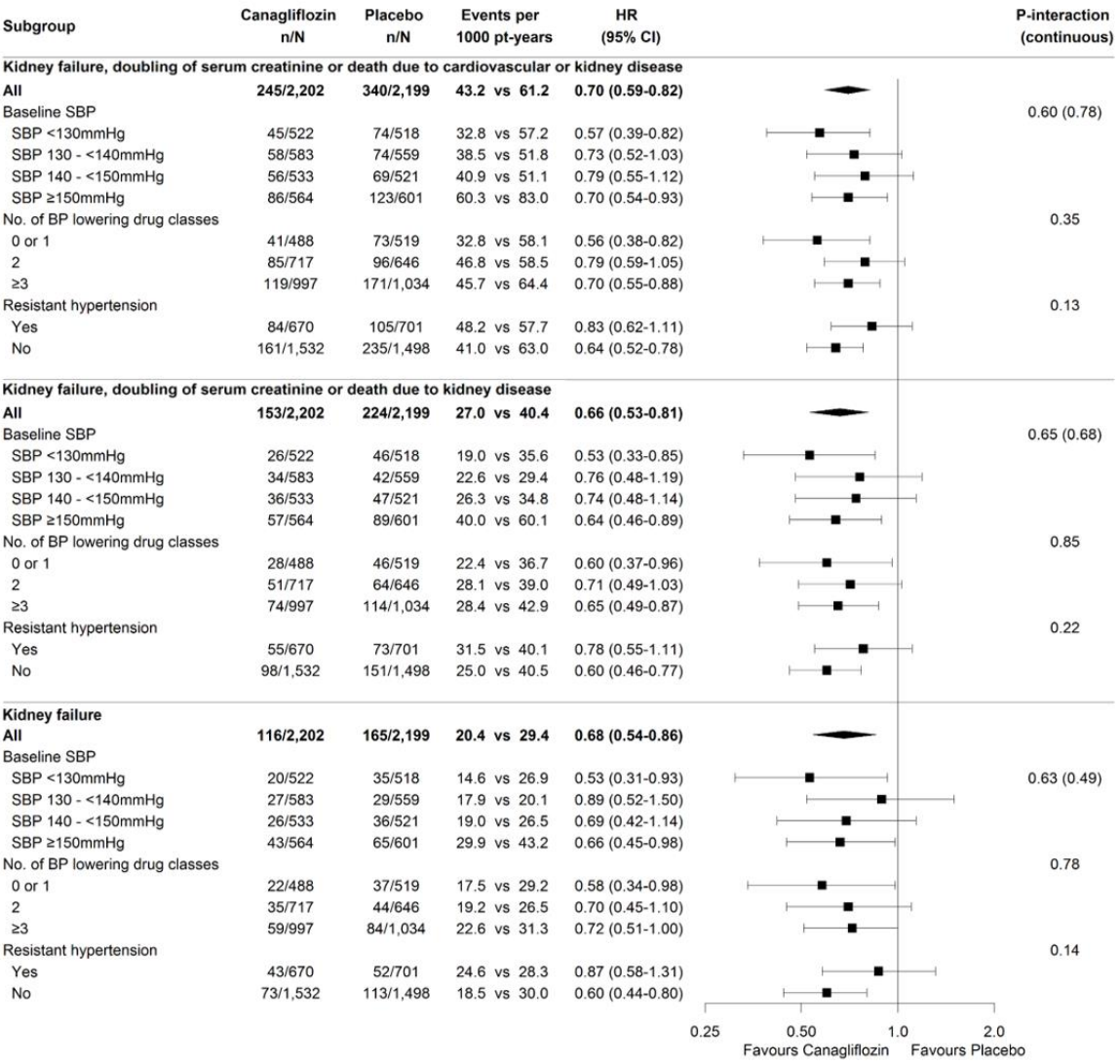

Subgroup
Canagliflozin n/N
Placebo n/N
Events per 1000 pt-years
HR (95% CI)
P-interaction (continuous)
Kidney failure, doubling of serum creatinine or death due to cardiovascular or kidney disease
All 245/2,202 340/2,199 43.2 vs 61.2 0.70 (0.59-0.82)
Baseline SBP 0.60 (0.78)
SBP <130mmHg 45/522 74/518 32.8 vs 57.2 0.57 (0.39-0.82)
SBP 130 - <140mmHg 58/583 74/559 38.5 vs 51.8 0.73 (0.52-1.03)
SBP 140 - <150mmHg 56/533 69/521 40.9 vs 51.1 0.79 (0.55-1.12)
SBP ≥150mmHg 86/564 123/601 60.3 vs 83.0 0.70 (0.54-0.93)
No. of BP lowering drug classes 0.35
0 or 1 41/488 73/519 32.8 vs 58.1 0.56 (0.38-0.82)
2 85/717 96/646 46.8 vs 58.5 0.79 (0.59-1.05)
≥3 119/997 171/1,034 45.7 vs 64.4 0.70 (0.55-0.88)
Resistant hypertension 0.13
Yes 84/670 105/701 48.2 vs 57.7 0.83 (0.62-1.11)
No 161/1,532 235/1,498 41.0 vs 63.0 0.64 (0.52-0.78)
Kidney failure, doubling of serum creatinine or death due to kidney disease
All 153/2,202 224/2,199 27.0 vs 40.4 0.66 (0.53-0.81)
Baseline SBP 0.65 (0.68)
SBP <130mmHg 26/522 46/518 19.0 vs 35.6 0.53 (0.33-0.85)
SBP 130 - <140mmHg 34/583 42/559 22.6 vs 29.4 0.76 (0.48-1.19)
SBP 140 - <150mmHg 36/533 47/521 26.3 vs 34.8 0.74 (0.48-1.14)
SBP ≥150mmHg 57/564 89/601 40.0 vs 60.1 0.64 (0.46-0.89)
No. of BP lowering drug classes 0.85
0 or 1 28/488 46/519 22.4 vs 36.7 0.60 (0.37-0.96)
2 51/717 64/646 28.1 vs 39.0 0.71 (0.49-1.03)
≥3 74/997 114/1,034 28.4 vs 42.9 0.65 (0.49-0.87)
Resistant hypertension 0.22
Yes 55/670 73/701 31.5 vs 40.1 0.78 (0.55-1.11)
No 98/1,532 151/1,498 25.0 vs 40.5 0.60 (0.46-0.77)
Kidney failure
All 116/2,202 165/2,199 20.4 vs 29.4 0.68 (0.54-0.86)
Baseline SBP
SBP <130mmHg 20/522 35/518 14.6 vs 26.9 0.53 (0.31-0.93) 0.63 (0.49)
SBP 130 - <140mmHg 27/583 29/559 17.9 vs 20.1 0.89 (0.52-1.50)
SBP 140 - <150mmHg 26/533 36/521 19.0 vs 26.5 0.69 (0.42-1.14)
SBP ≥150mmHg 43/564 65/601 29.9 vs 43.2 0.66 (0.45-0.98)
No. of BP lowering drug classes 0.78
0 or 1 22/488 37/519 17.5 vs 29.2 0.58 (0.34-0.98)
2 35/717 44/646 19.2 vs 26.5 0.70 (0.45-1.10)
≥3 59/997 84/1,034 22.6 vs 31.3 0.72 (0.51-1.00)
Resistant hypertension 0.14
Yes 43/670 52/701 24.6 vs 28.3 0.87 (0.58-1.31)
No 73/1,532 113/1,498 18.5 vs 30.0 0.60 (0.44-0.80)
0.25
0.50
1.0
2.0
Favours Canagliflozin
Favours Placebo

Figure 5.

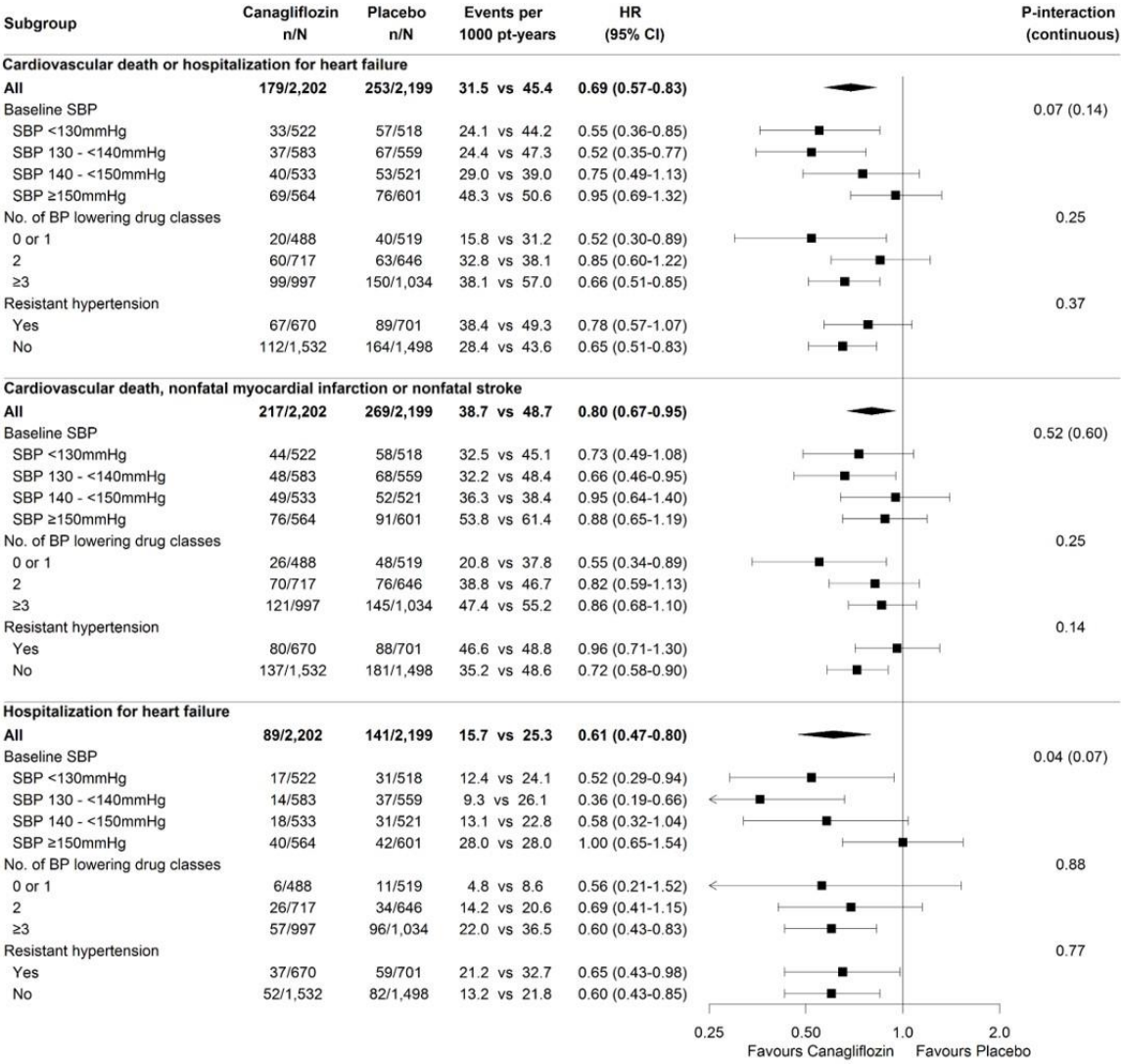
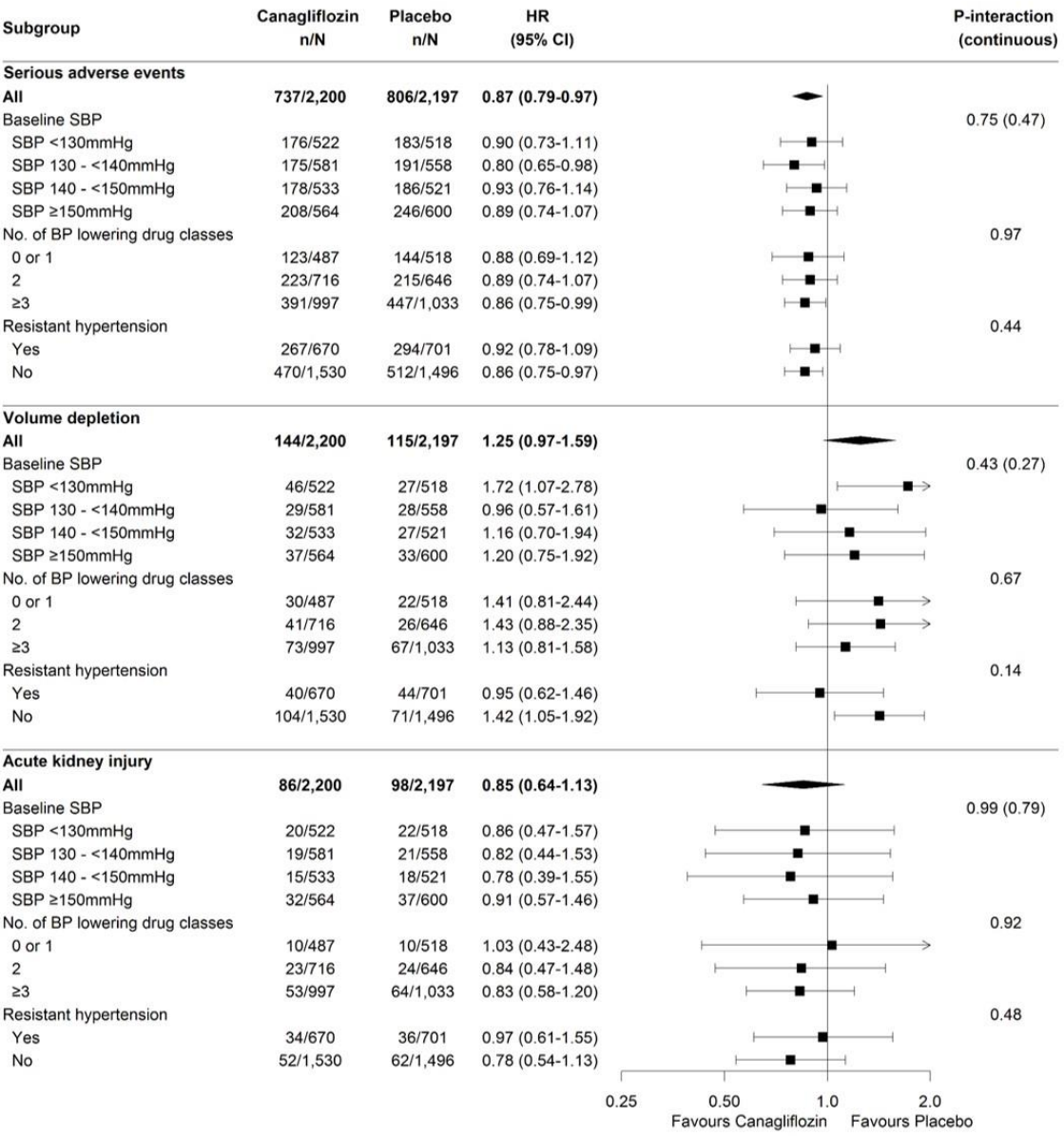

Subgroup
Canagliflozin n/N
Placebo n/N
Events per 1000 pt-years
HR (95% CI)
P-interaction (continuous)
Cardiovascular death or hospitalization for heart failure
All 179/2,202 253/2,199 31.5 vs 45.4 0.69 (0.57-0.83)
Baseline SBP 0.07 (0.14)
SBP <130mmHg 33/522 57/518 24.1 vs 44.2 0.55 (0.36-0.85)
SBP 130 - <140mmHg 37/583 67/559 24.4 vs 47.3 0.52 (0.35-0.77)
SBP 140 - <150mmHg 40/533 53/521 29.0 vs 39.0 0.75 (0.49-1.13)
SBP ≥150mmHg 69/564 76/601 48.3 vs 50.6 0.95 (0.69-1.32)
No. of BP lowering drug classes 0.25
0 or 1 20/488 40/519 15.8 vs 31.2 0.52 (0.30-0.89)
2 60/717 63/646 32.8 vs 38.1 0.85 (0.60-1.22)
≥3 99/997 150/1,034 38.1 vs 57.0 0.66 (0.51-0.85)
Resistant hypertension 0.37
Yes 67/670 89/701 38.4 vs 49.3 0.78 (0.57-1.07)
No 112/1,532 164/1,498 28.4 vs 43.6 0.65 (0.51-0.83)
Cardiovascular death, nonfatal myocardial infarction or nonfatal stroke
All 217/2,202 269/2,199 38.7 vs 48.7 0.80 (0.67-0.95)
Baseline SBP 0.52 (0.60)
SBP <130mmHg 44/522 58/518 32.5 vs 45.1 0.73 (0.49-1.08)
SBP 130 - <140mmHg 48/583 68/559 32.2 vs 48.4 0.66 (0.46-0.95)
SBP 140 - <150mmHg 49/533 52/521 36.3 vs 38.4 0.95 (0.64-1.40)
SBP ≥150mmHg 76/564 91/601 53.8 vs 61.4 0.88 (0.65-1.19)
No. of BP lowering drug classes 0.25
0 or 1 26/488 48/519 20.8 vs 37.8 0.55 (0.34-0.89)
2 70/717 76/646 38.8 vs 46.7 0.82 (0.59-1.13)
≥3 121/997 145/1,034 47.4 vs 55.2 0.86 (0.68-1.10)
Resistant hypertension 0.14
Yes 80/670 88/701 46.6 vs 48.8 0.96 (0.71-1.30)
No 137/1,532 181/1,498 35.2 vs 48.6 0.72 (0.58-0.90)
Hospitalization for heart failure
All 89/2,202 141/2,199 15.7 vs 25.3 0.61 (0.47-0.80)
Baseline SBP 0.04 (0.07)
SBP <130mmHg 17/522 31/518 12.4 vs 24.1 0.52 (0.29-0.94)
SBP 130 - <140mmHg 14/583 37/559 9.3 vs 26.1 0.36 (0.19-0.66)
SBP 140 - <150mmHg 18/533 31/521 13.1 vs 22.8 0.58 (0.32-1.04)
SBP ≥150mmHg 40/564 42/601 28.0 vs 28.0 1.00 (0.65-1.54)
No. of BP lowering drug classes 0.88
0 or 1 6/488 11/519 4.8 vs 8.6 0.56 (0.21-1.52)
2 26/717 34/646 14.2 vs 20.6 0.69 (0.41-1.15)
≥3 57/997 96/1,034 22.0 vs 36.5 0.60 (0.43-0.83)
Resistant hypertension 0.77
Yes 37/670 59/701 21.2 vs 32.7 0.65 (0.43-0.98)
No 52/1,532 82/1,498 13.2 vs 21.8 0.60 (0.43-0.85)
0.25
0.50
1.0
2.0
Favours Canagliflozin
Favours Placebo

Figure 6.


Subgroup
Canagliflozin n/N
Placebo n/N
HR (95% CI)
P-interaction (continuous)
Serious adverse events
All 737/2,200 806/2,197 0.87 (0.79-0.97)
Baseline SBP 0.75 (0.47)
SBP <130mmHg 176/522 183/518 0.90 (0.73-1.11)
SBP 130 - <140mmHg 175/581 191/558 0.80 (0.65-0.98)
SBP 140 - <150mmHg 178/533 186/521 0.93 (0.76-1.14)
SBP ≥150mmHg 208/564 246/600 0.89 (0.74-1.07)
No. of BP lowering drug classes 0.97
0 or 1 123/487 144/518 0.88 (0.69-1.12)
2 223/716 215/646 0.89 (0.74-1.07)
≥3 391/997 447/1,033 0.86 (0.75-0.99)
Resistant hypertension 0.44
Yes 267/670 294/701 0.92 (0.78-1.09)
No 470/1,530 512/1,496 0.86 (0.75-0.97)
Volume depletion
All 144/2,200 115/2,197 1.25 (0.97-1.59)
Baseline SBP 0.43 (0.27)
SBP <130mmHg 46/522 27/518 1.72 (1.07-2.78)
SBP 130 - <140mmHg 29/581 28/558 0.96 (0.57-1.61)
SBP 140 - <150mmHg 32/533 27/521 1.16 (0.70-1.94)
SBP ≥150mmHg 37/564 33/600 1.20 (0.75-1.92)
No. of BP lowering drug classes 0.67
0 or 1 30/487 22/518 1.41 (0.81-2.44)
2 41/716 26/646 1.43 (0.88-2.35)
≥3 73/997 67/1,033 1.13 (0.81-1.58)
Resistant hypertension 0.14
Yes 40/670 44/701 0.95 (0.62-1.46)
No 104/1,530 71/1,496 1.42 (1.05-1.92)
Acute kidney injury
All 86/2,200 98/2,197 0.85 (0.64-1.13)
Baseline SBP 0.99 (0.79)
SBP <130mmHg 20/522 22/518 0.86 (0.47-1.57)
SBP 130 - <140mmHg 19/581 21/558 0.82 (0.44-1.53)
SBP 140 - <150mmHg 15/533 18/521 0.78 (0.39-1.55)
SBP ≥150mmHg 32/564 37/600 0.91 (0.57-1.46)
No. of BP lowering drug classes 0.92
0 or 1 10/487 10/518 1.03 (0.43-2.48)
2 23/716 24/646 0.84 (0.47-1.48)
≥3 53/997 64/1,033 0.83 (0.58-1.20)
Resistant hypertension 0.48
Yes 34/670 36/701 0.97 (0.61-1.55)
No 52/1,530 62/1,496 0.78 (0.54-1.13)
0.25
0.50
1.0
2.0
Favours Canagliflozin
Favours Placebo

SUPPLEMENTAL MATERIALS

Supplemental Table 1. Characteristics of participants by number of BP lowering drug classes at baseline

	Zero or one (N=1007)	Two (N=1363)	Three or more (N=2031)
Age, years, mean(SD)	61.0(9.6)	62.5(9.3)	64.1(8.7)
Sex, No.(%)			
Male	647(64.3)	903(66.3)	1357(66.8)
Female	360(35.7)	460(33.7)	674(33.2)
Race, No.(%)			
White	655(65.0)	852(62.5)	1424(70.1)
Black or African American	22(2.2)	60(4.4)	142(7.0)
Asian	232(23.0)	339(24.9)	306(15.1)
Native Hawaiian or other Pacific Islander	7(0.7)	8(0.6)	10(0.5)
American Indian or Alaska Native	26(2.6)	25(1.8)	27(1.3)
Multiple	17(1.7)	18(1.3)	29(1.4)
Other*	48(4.8)	61(4.5)	93(4.6)
Region, No.(%)			
North America	276(23.4)	352(29.8)	554(46.8)
Central/South America	288(30.6)	281(29.9)	372(39.5)
Europe	78(9.0)	202(23.4)	584(67.6)
Rest of the world	365(25.8)	528(37.3)	521(36.9)
Current smoker, No.(%)	151(15.0)	223(16.4)	265(13.1)
History of heart failure, No.(%)	83(8.2)	180(13.2)	389(19.2)
Duration of diabetes, years, mean(SD)	14.8(8.5)	15.5(8.5)	16.4(8.7)
BP lowering drug therapy, No.(%)			
RAS inhibitor	1002(99.5)	1363(100.0)	2030(>99.9)
Beta blocker	0(0.0)	345(25.3)	1425(70.2)

Calcium channel blocker	0(0.0)	550(40.4)	1579(77.7)
Diuretic	0(0.0)	451(33.1)	1606(79.1)
Peripherally acting antiadrenergic agents	0(0.0)	10(0.7)	292(14.4)
Centrally acting antiadrenergic agents	0(0.0)	5(0.4)	243(12.0)
Vasodilator	0(0.0)	2(0.2)	80(3.9)
Atherosclerotic vascular disease history, No.(%) †			
Coronary	127(12.6)	380(27.9)	806(39.7)
Cerebrovascular	110(10.9)	217(15.9)	373(18.4)
Peripheral	213(21.2)	315(23.1)	518(25.5)
CV disease history, No.(%)	370(36.7)	667(48.9)	1183(58.3)
Microvascular disease history, No.(%)			
Retinopathy	410(40.7)	602(44.2)	870(42.8)
Neuropathy	467(46.4)	678(49.7)	1002(49.3)
History of amputation, No.(%)	56(5.6)	70(5.1)	108(5.3)
Body mass index, Kg/m^2, mean(SD)	29.2(5.3)	30.7(6.0)	32.8(6.3)
Systolic BP, mmHg, mean(SD)	135.5(14.7)	139.2(15.0)	142.8(15.9)
Diastolic BP, mmHg, mean(SD)	78.8(8.7)	78.6(9.2)	77.9(9.8)
HbA1c, %, mean(SD)	8.4(1.4)	8.3(1.3)	8.2(1.2)
eGFR, $ml/min/1.73m^2$, mean(SD)	61.2(18.6)	56.9(18.2)	53.2(17.5)
UACR, mg/g, median(IQR)	902.0(434.0, 1848.0)	909.0(483.0, 1778.0)	943.0(471.0, 1889.0)

BP indicates blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; HbA1c, glycohemoglobin; IQR, interquartile range; RAS, renin angiotensin system; SD, standard deviation; and UACR, urinary albumin/creatinine ratio.

* Includes other, unknown, and not reported.

† Some participants had ≥1 type of atherosclerotic disease.

Supplemental Table 2. Characteristics of patients with or without resistant hypertension at baseline

	Resistant hypertension (N=1371)	No resistant hypertension (N=3030)
Age, years, mean (SD)	64.1(8.7)	62.4(9.4)
Sex, No.(%)		
Male	913(66.6)	1994(65.8)
Female	458(33.4)	1036(34.2)
Race, No.(%)		
White	978(71.3)	1953(64.5)
Black or African American	95(6.9)	129(4.3)
Asian	186(13.6)	691(22.8)
Native Hawaiian or other Pacific Islander	4(0.3)	21(0.7)
American Indian or Alaska Native	19(1.4)	59(2.0)
Multiple	23(1.7)	41(1.4)
Other*	66(4.8)	136(4.5)
Region, No.(%)		
North America	361(26.3)	821(27.1)
Central/South America	272(19.8)	669(22.1)
Europe	410(29.9)	454(15.0)
Rest of the world	328(23.9)	1086(35.8)
Current smoker, No.(%)	168(12.3)	471(15.5)
History of heart failure, No.(%)	268(19.6)	384(12.7)
Duration of diabetes, years, mean (SD)	16.3(8.4)	15.5(8.7)
BP lowering drug therapy, No.(%)		
RAS inhibitor	1370(99.9)	3025(99.8)
Beta blocker	877(64.0)	893(29.5)
Calcium channel blocker	1031(75.2)	1098(36.2)
Diuretic	1371(100.0)	686(22.6)
Peripherally acting antiadrenergic agents	185(13.5)	117(3.9)
Centrally acting antiadrenergic agents	161(11.7)	87(2.9)
Vasodilator	51(3.7)	31(1.0)
Atherosclerotic vascular disease history, No.(%)†		
Coronary	525(38.3)	788(26.0)
Cerebrovascular	254(18.5)	446(14.7)
Peripheral	359(26.2)	687(22.7)
CV disease history, No.(%)	796(58.1)	1424(47.0)
Microvascular disease history, No.(%)		
Retinopathy	605(44.1)	1277(42.2)
Neuropathy	673(49.1)	1474(48.7)
History of amputation, No.(%)	75(5.5)	159(5.3)

Body mass index, Kg/m^2, mean (SD)	33.0(6.3)	30.6(6.0)
Systolic BP, mmHg, mean (SD)	146.8(13.4)	136.9(15.6)
Diastolic BP, mmHg, mean (SD)	79.5(9.1)	77.8(9.4)
HbA1c, %, mean (SD)	8.2(1.2)	8.3(1.3)
eGFR, $ml/min/1.73m^2$, mean(SD)	53.1(17.4)	57.6(18.5)
UACR, mg/g, median (IQR)	967.0(484.0, 1941.0)	884.0(456.0, 1797.0)

BP: blood pressure; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; HbA1c: glycated hemoglobin; IQR, interquartile range; RAS: renin angiotensin system; SD: standard deviation; UACR: urinary albumin/creatinine ratio.

* Includes other, unknown, and not reported.

† Some participants had ≥1 type of atherosclerotic disease.

Supplemental Table 3. Number of BP lowering drug classes and their combinations

Participants, No.(%)	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (n = 4401)
1 BP lowering drug			
Total	**488(22.2)**	**514(23.4)**	**1002(22.8)**
RASI alone	488(22.2)	514(23.4)	1002(22.8)
2 BP lowering drugs			
Total	**717(32.6)**	**646(29.4)**	**1363(31.0)**
RASI + CCB	274(12.4)	276(12.6)	550(12.5)
RASI + beta blocker	190(8.6)	155(7.1)	345(7.8)
RASI + diuretic	246(11.2)	205(9.3)	451(10.3)
RASI + 1 other*	7(0.3)	10(0.5)	17(0.4)
3 BP lowering drugs			
Total	**574(26.1)**	**556(25.3)**	**1130(25.7)**
RASI + CCB + beta blocker	141(6.4)	144(6.6)	285(6.5)
RASI + CCB + diuretic	222(10.1)	205(9.3)	427(9.7)
RASI + beta blocker + diuretic	158(7.2)	160(7.3)	318(7.2)
RASI + CCB + 1 other*	26(1.2)	17(0.8)	43(1.0)
RASI + beta blocker + 1 other*	14(0.6)	9(0.4)	23(0.5)
RASI + diuretic + 1 other*	13(0.6)	20(0.9)	33(0.8)
RASI + 2 others*	0(0.0)	1(0.1)	1(<0.1)
≥ 4 BP lowering drugs			
Total	**423(19.2)**	**478(21.7)**	**901(20.5)**
RASI + CCB + beta blocker + diuretic	212(9.6)	238(10.8)	450(10.2)
RASI + CCB + beta blocker + diuretic + ≥ 1 other*	100(4.5)	108(4.9)	208(4.7)
RASI + CCB + beta blocker + ≥ 1 other*	34(1.5)	35(1.6)	69(1.6)
RASI + CCB + diuretic + ≥ 1 other*	40(1.8)	55(2.5)	95(2.2)
RASI + beta blocker + diuretic + ≥ 1 other*	32(1.5)	36(1.6)	68(1.6)
RASI + CCB + ≥ 2 others*	1(0.1)	0(0.0)	1(<0.1)
RASI + beta blocker + ≥ 2 others*	1(0.1)	2(0.1)	3(0.1)
RASI + diuretic + ≥ 2 others*	2(0.1)	4(0.2)	6(0.1)
CCB + beta blocker + diuretic + ≥ 1 other*	1(0.1)	0(0.0)	1(<0.1)

CCB; calcium channel blocker; RASI; renin angiotensin system inhibitor

* Includes peripherally acting antiadrenergic agents, centrally acting antiadrenergic agents and direct acting vasodilators.

Supplemental Table 4. Baseline use and new initiation of BP lowering drug therapy

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (n = 4401)
Baseline use			
RAS blockade	2201(>99.9)	2194(99.8)	4395(99.9)
Beta blocker	883(40.1)	887(40.3)	1770(40.2)
Calcium channel blocker	1051(47.7)	1078(49.0)	2129(48.4)
Diuretic	1026(46.6)	1031(46.9)	2057(46.7)
Peripherally acting antiadrenergic agents	140(6.4)	162(7.4)	302(6.9)
Centrally acting antiadrenergic agents	121(5.5)	127(5.8)	248(5.6)
Direct acting vasodilators	41(1.9)	41(1.9)	82(1.9)
New initiation			
RAS blockade	131(6.0)	160(7.3)	291(6.6)
Beta blocker	150(6.8)	207(9.4)	357(8.1)
Calcium channel blocker	195(8.9)	248(11.3)	443(10.1)
Diuretic	320(14.5)	474(21.6)	794(18.0)
Peripherally acting antiadrenergic agents	65(3.0)	85(3.9)	150(3.4)
Centrally acting antiadrenergic agents	33(1.5)	65(3.0)	98(2.2)
Direct acting vasodilators	34(1.5)	68(3.1)	102(2.3)

RAS: renin angiotensin system.

Supplemental Table 5. The least-squares mean change (±SE) in systolic BP and mean difference (95% CI) between canagliflozin and placebo by subgroups

	Baseline to week 3				Overall duration of the trial			
	Canagliflozin	Placebo	Difference	P-interaction	Canagliflozin	Placebo	Difference	P-interaction
Total population	-3.39 (0.28)	0.11 (0.28)	-3.50 (-4.27, -2.72)		-2.82 (0.22)	0.48 (0.23)	-3.30 (-3.87, -2.73)	
Age (years)				0.10				0.84
<55	-3.20(0.66)	0.46(0.68)	-3.66(-5.49, -1.84)		-1.83(0.52)	1.47(0.54)	-3.30(-4.62, -1.98)	
55-<65	-3.00(0.46)	0.36(0.46)	-3.36(-4.62, -2.10)		-2.11(0.37)	1.45(0.38)	-3.57(-4.51, -2.62)	
65-<75	-3.70(0.49)	-0.18(0.48)	-3.52(-4.85, -2.18)		-3.46(0.37)	-0.40(0.37)	-3.06(-4.02, -2.09)	
≥75	-3.83(0.90)	-0.51(0.86)	-3.33(-5.75, -0.91)		-4.57(0.75)	-1.53(0.72)	-3.04(-4.89, -1.18)	
Sex				0.11				0.34
Male	-3.64(0.34)	0.32(0.34)	-3.96(-4.90, -3.02)		-3.18(0.27)	0.30(0.27)	-3.49(-4.18, -2.79)	
Female	-2.90(0.49)	-0.26(0.50)	-2.63(-4.01, -1.26)		-2.03(0.40)	0.90(0.41)	-2.93(-3.94, -1.92)	
Baseline systolic BP (mmHg)				0.61				0.26
<130	4.93(0.59)	8.50(0.59)	-3.56(-5.19, -1.94)		7.87(0.46)	11.39(0.47)	-3.52(-4.73, -2.31)	
130-<140	-2.03(0.48)	1.80(0.49)	-3.83(-5.16, -2.50)		-0.71(0.40)	3.00(0.40)	-3.71(-4.69, -2.72)	
140-<150	-4.46(0.56)	-1.90(0.57)	-2.56(-4.12, -1.00)		-4.82(0.43)	-2.54(0.44)	-2.27(-3.39, -1.16)	
≥150	-11.03(0.62)	-7.16(0.60)	-3.86(-5.55, -2.18)		-12.97(0.49)	-9.37(0.48)	-3.60(-4.84, -2.36)	
Number of BP lowering drug classes				0.42				0.08
None or one	-3.77(0.57)	0.56(0.56)	-4.33(-5.83, -2.83)		-2.76(0.46)	1.78(0.45)	-4.54(-5.61, -3.46)	
Two	-2.82(0.49)	0.05(0.52)	-2.88(-4.27, -1.48)		-2.22(0.40)	0.52(0.42)	-2.74(-3.78, -1.70)	
Three or more	-3.66(0.43)	-0.11(0.42)	-3.55(-4.73, -2.37)		-3.31(0.34)	-0.15(0.33)	-3.15(-4.01, -2.30)	

Resistant hypertension				0.42				0.51
Yes	-5.75(0.53)	-1.79(0.52)	-3.96 (-5.40, -2.52)		-5.98(0.41)	-2.46(0.40)	-3.51(-4.56,-2.47)	
No	-2.33(0.33)	0.95(0.34)	-3.27 (-4.19, -2.35)		-1.37(0.27)	1.81(0.28)	-3.17(-3.86,-2.49)	
Screening eGFR (ml/min/1.73m^2)				0.54				0.34
30-<45	-3.59(0.55)	0.42(0.55)	-4.01(-5.54, -2.48)		-2.55(0.45)	1.14(0.45)	-3.69(-4.81, -2.57)	
45-<60	-3.31(0.54)	0.35(0.54)	-3.66(-5.17, -2.16)		-2.92(0.41)	0.56(0.42)	-3.48(-4.56, -2.39)	
60-<90	-3.39(0.40)	-0.41(0.40)	-2.98(-4.08, -1.88)		-3.13(0.32)	-0.25(0.32)	-2.88(-3.71, -2.06)	
Screening UACR (mg/g)				0.15				0.16
≤1000	-3.82(0.39)	0.24(0.39)	-4.06(-5.12, -3.00)		-3.22(0.31)	0.44(0.31)	-3.66(-4.45, -2.86)	
>1000	-3.05(0.41)	-0.13(0.41)	-2.92(-4.06, -1.79)		-2.45(0.32)	0.47(0.33)	-2.92(-3.74, -2.10)	
Baseline HbA1c (%)				0.44				0.30
<7	-3.46(0.72)	0.30(0.71)	-3.76(-5.75, -1.78)		-3.41(0.56)	0.65(0.56)	-4.05(-5.51, -2.59)	
7-<8	-3.29(0.50)	0.27(0.50)	-3.56(-4.94, -2.18)		-2.76(0.39)	0.31(0.40)	-3.06(-4.08, -2.05)	
8-<9	-2.80(0.56)	-0.41(0.55)	-2.40(-3.93, -0.87)		-3.14(0.43)	-0.56(0.43)	-2.58(-3.68, -1.49)	
≥9	-4.05(0.54)	0.10(0.56)	-4.14(-5.64, -2.65)		-2.24(0.44)	1.57(0.45)	-3.82(-4.93, -2.71)	

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

Supplemental Table 6. Effect of canagliflozin on kidney and cardiovascular outcomes adjusted for the competing risk of death

	N event	N censored	N competing event	HR (95% CI)	P-heterogeneity (continuous)
Kidney failure, doubling of serum creatinine or death due to cardiovascular or kidney disease					
All	**585**	**3726**	**90**	**0.70(0.59, 0.82)**	
Baseline SBP					0.59(0.75)
SBP <130mmHg	119	899	22	0.57(0.39, 0.82)	
SBP 130-<140mmHg	132	988	22	0.74(0.52, 1.04)	
SBP 140-<150mmHg	125	906	23	0.79(0.56, 1.12)	
SBP ≥150mmHg	209	933	23	0.70(0.53, 0.92)	
No. of BP lowering drug classes					0.38
0 or 1	114	877	16	0.56(0.39, 0.83)	
2	181	1153	29	0.79(0.59, 1.05)	
≥3	290	1696	45	0.70(0.55, 0.88)	
Resistant hypertension					0.15
Yes	189	1157	25	0.83(0.62, 1.10)	
No	396	2569	65	0.64(0.52, 0.78)	
Kidney failure, doubling of serum creatinine or death due to kidney disease					
All	**377**	**3726**	**298**	**0.66(0.54, 0.81)**	
Baseline SBP					0.66(0.68)
SBP <130mmHg	72	899	69	0.54(0.33, 0.86)	
SBP 130-<140mmHg	76	988	78	0.77(0.49, 1.20)	
SBP 140-<150mmHg	83	906	65	0.75(0.48, 1.15)	
SBP ≥150mmHg	146	933	86	0.64(0.46, 0.89)	
No. of BP lowering drug classes					0.88
0 or 1	74	877	56	0.62(0.39, 0.99)	
2	115	1153	95	0.71(0.50, 1.03)	
≥3	188	1696	147	0.65(0.49, 0.87)	
Resistant hypertension					0.26
Yes	128	1157	86	0.78(0.55, 1.10)	
No	249	2569	212	0.61(0.47, 0.78)	

Cardiovascular death or hospitalization for heart failure					
All	**432**	**3863**	**106**	**0.69(0.57, 0.84)**	
Baseline SBP					0.07(0.16)
SBP <130mmHg	90	924	26	0.55(0.36, 0.85)	
SBP 130-<140mmHg	104	1011	27	0.52(0.35, 0.77)	
SBP 140-<150mmHg	93	935	26	0.74(0.49, 1.12)	
SBP ≥150mmHg	145	993	27	0.95(0.69, 1.32)	
No. of BP lowering drug classes					0.27
0 or 1	60	922	25	0.52(0.31, 0.89)	
2	123	1207	33	0.85(0.60, 1.21)	
≥3	249	1734	48	0.66(0.51, 0.86)	
Resistant hypertension					0.37
Yes	156	1187	28	0.78(0.57, 1.07)	
No	276	2676	78	0.65(0.51, 0.83)	
Cardiovascular death, nonfatal myocardial infarction or nonfatal stroke					
All	**486**	**3811**	**104**	**0.80(0.66, 0.95)**	
Baseline SBP					0.53(0.62)
SBP <130mmHg	102	912	26	0.73(0.49, 1.08)	
SBP 130-<140mmHg	116	1001	25	0.66(0.46, 0.95)	
SBP 140-<150mmHg	101	925	28	0.94(0.64, 1.39)	
SBP ≥150mmHg	167	973	25	0.88(0.65, 1.18)	
No. of BP lowering drug classes					0.26
0 or 1	74	908	25	0.55(0.34, 0.89)	
2	146	1183	34	0.82(0.59, 1.13)	
≥3	266	1720	45	0.86(0.68, 1.10)	
Resistant hypertension					0.14
Yes	168	1176	27	0.96(0.71, 1.30)	
No	318	2635	77	0.72(0.58, 0.90)	

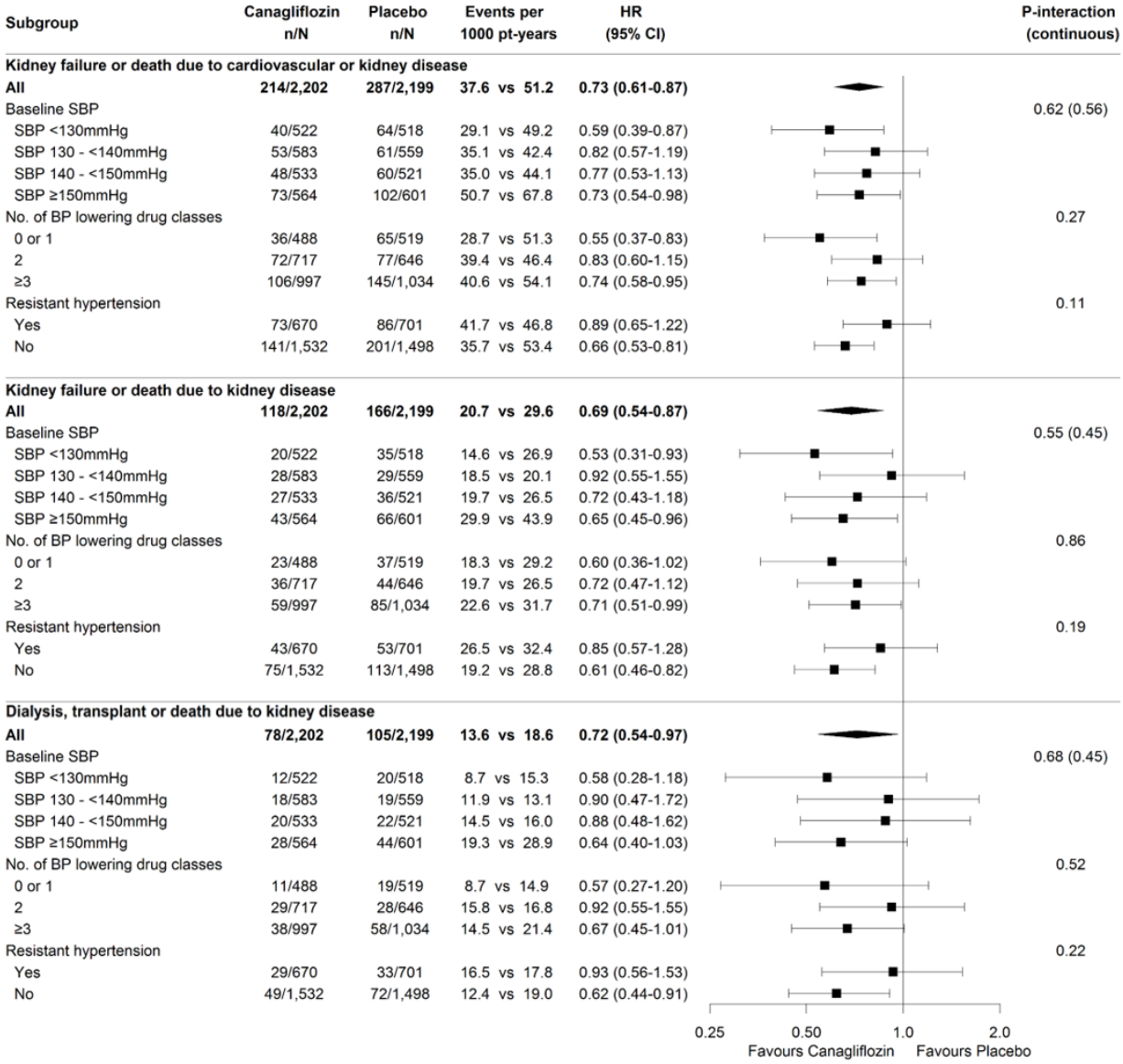
SBP: systolic blood pressure; BP: blood pressure; HR: hazard ratio; CI: confidence interval.

Supplemental Table 7. Assessment of the proportion of treatment effects explained by change in systolic BP at week 3

	HR control (95% CI)	HR adjusted (95% CI)	Proportion explained
Doubling of serum creatinine, kidney failure, or death due to kidney or CV disease	0.70 (0.59, 0.82)	0.70 (0.60, 0.83)	2.6%
Doubling of serum creatinine, kidney failure of death due to kidney disease	0.66 (0.53, 0.81)	0.67 (0.54, 0.83)	4.0%
Nonfatal myocardial infarction, nonfatal stroke or CV death	0.80 (0.67, 0.95)	0.81 (0.67, 0.97)	5.9%
Hospitalized heart failure or CV death	0.69 (0.57, 0.83)	0.69 (0.57, 0.84)	0.7%

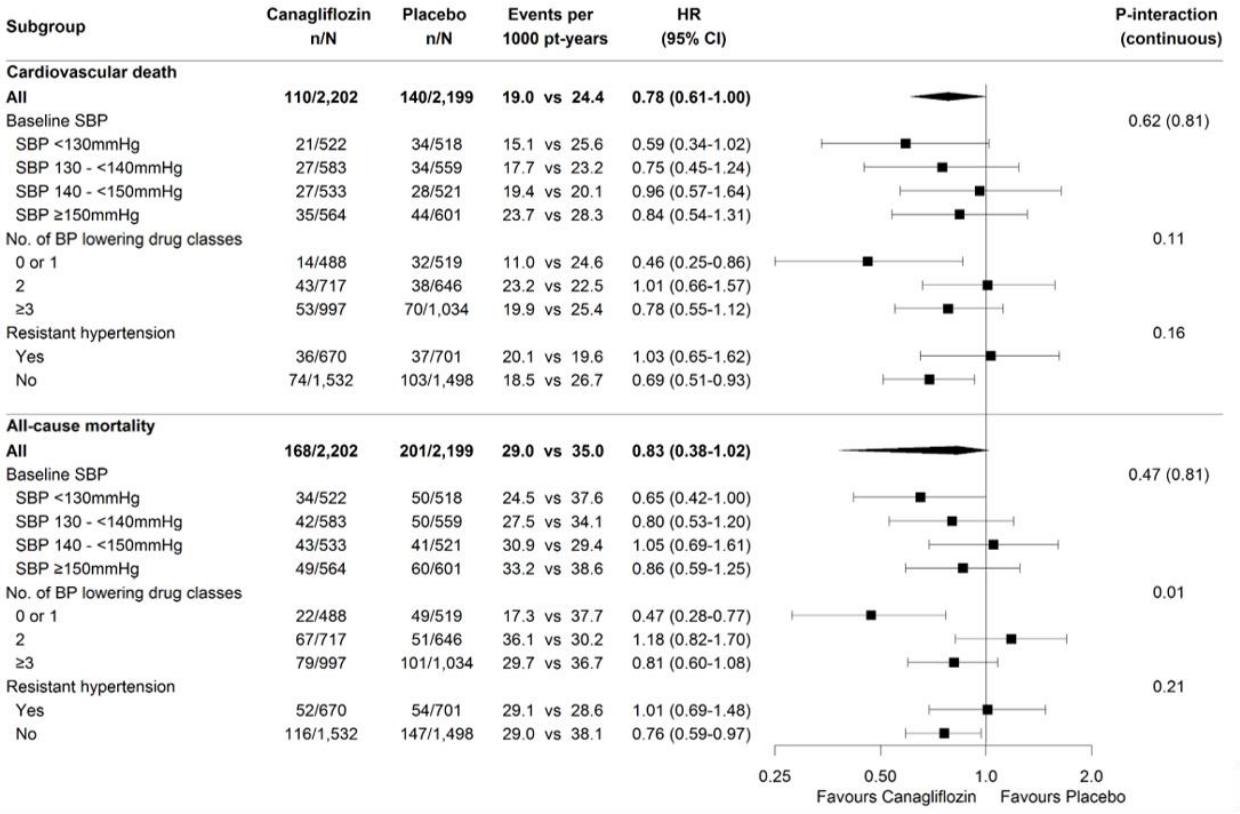
HR control reflects the HR for the comparison of canagliflozin versus placebo.
HR adjusted reflects the HR with further adjustment of the model for change in systolic blood pressure at week 3 and baseline value (to correct for potential regression to the mean)
% of treatment effect explained = 100* [(HRcontrol – HRadjusted) / (HRcontrol – 1)]

Supplemental Figure 1. Effect of canagliflozin on other kidney outcomes by baseline systolic blood pressure, number of blood pressure lowering drug classes, and history of resistant hypertension



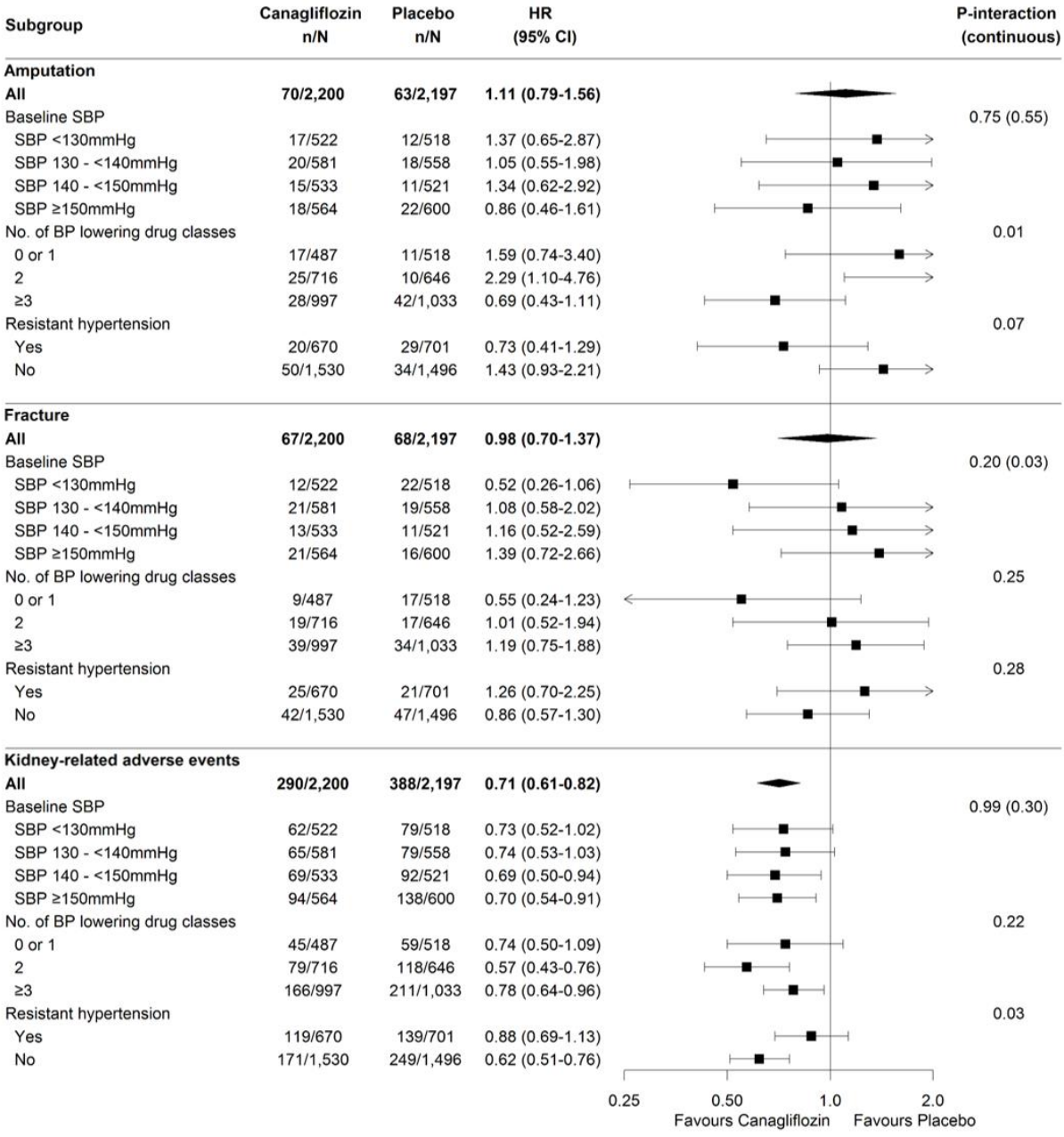
SBP: systolic blood pressure; BP: blood pressure.

Supplemental Figure 2. Effect of canagliflozin on cardiovascular and all-cause mortality by baseline systolic blood pressure, number of blood pressure lowering drug classes, and history of resistant hypertension



SBP: systolic blood pressure; BP: blood pressure.

Supplemental Figure 3. Effect of canagliflozin on amputation, fracture, and kidney related adverse events by baseline systolic blood pressure, number of blood pressure lowering drug classes, and history of resistant hypertension



SBP: systolic blood pressure; BP: blood pressure.