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

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

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ABSTRACT

Background

The magnitude and consistency of blood pressure (BP) lowering with canagliflozin in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) is uncertain. Whether the effects of canagliflozin on kidney and cardiovascular outcomes vary by baseline BP or BP lowering therapy is also unknown.

Methods

CREDENCE randomized 4,401 participants with T2DM and CKD to canagliflozin or placebo. We investigated the effect of canagliflozin on systolic BP according to baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension (BP ≥140/90 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 2,219 (50.4%) had baseline systolic BP ≥140 mmHg, and 962 (21.9%) had resistant hypertension. By week 3, canagliflozin reduced systolic BP by 3.48mmHg (95% CI, -4.25 to -2.70) with similar effects irrespective of baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension (all P-interaction ≥0.40). BP reductions were maintained for all subgroups over the duration of the trial. The effect of canagliflozin on the primary outcome of end-stage kidney disease, 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 kidney, cardiovascular and safety

outcomes.

Conclusions

Treatment with canagliflozin results in early and sustained reductions in systolic BP of a similar magnitude regardless of baseline systolic BP, number of concomitant BP lowering drugs, or history of resistant hypertension. These findings support use of canagliflozin for end-organ protection and as an adjunct BP lowering agent in people with T2DM and CKD.

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

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

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 end-stage kidney disease (ESKD) 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 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 magnitude and consistency of systolic BP lowering with canagliflozin according to baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension. We also examined the effects of canagliflozin on kidney, cardiovascular and safety outcomes across these subgroups.

Methods

Study design and participants

Detailed methods and the statistical analysis plan for the CREDENCE trial have been published previously.[10, 11] 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 labeled 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, 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 canaglfilozin, as well as effects on kidney, cardiovascular and safety outcomes according to baseline systolic BP, number of BP lowering drug classes, and history of 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 ≥140 and/or diastolic BP ≥90mmHg while receiving ≥3 classes of BP lowering drugs including a diuretic.[12]

Outcomes

Definitions for all outcomes in the CREDENCE trial have been reported previously.[9] The primary outcome was a composite of ESKD, sustained doubling of the serum creatinine, or death due to kidney or cardiovascular disease. In this analysis, we also assessed the effect of

canagliflozin versus placebo on systolic BP over 2 time periods: from baseline to week 3, and over the duration of the trial (baseline to week 182).

Other prespecified kidney outcomes were: ESKD, doubling of serum creatinine, or death due to kidney disease; ESKD or death due to kidney or cardiovascular disease; ESKD or death due to kidney disease; and ESKD. 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 Activies (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-squared and ANOVA tests for categorical and continuous variables, respectively.

The effect of canagliflozin on systolic BP at week 3 and 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 and adjusting for a pre-defined set of covariates: the baseline value, treatment allocation, category of eGFR at screening, trial visit, interaction between treatment allocation and visit, and interaction between baseline value and visit.

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. Effect modification by 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. Annualized incidence rates were calculated per 1000 patient-years of follow-up.

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.

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 3). The proportion of participants receiving multiple classes of BP lowering therapies at baseline, and their combinations, is displayed in Table 2. 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 resistant hypertension at baseline was 21.9% (Supplemental Table 2). Baseline use and new initiation of BP lowering drugs by class of agent are summarized in Supplemental Table 3.

Effect on systolic BP

The reduction in systolic BP at week 3 in the overall trial population was larger in canagliflozin treated participants (-3.27 mm Hg, SE 0.28 mm Hg) than placebo treated participants (0.20 mm Hg, SE 0.28 mm Hg; mean difference -3.48mmHg, 95% CI, -4.25 to -2.70; Supplemental Table 4). 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 4).

By week 3, canagliflozin reduced systolic BP with similar effects across categories of baseline systolic BP, number of BP lowering drug classes, and in participants with and without resistant hypertension (P-interaction ≥0.45; Figure 1). The magnitude of effect was

similarly consistent across these subgroups over the duration of the trial (Figure 1). Reductions in systolic BP over both time periods were observed across a number of other participant subgroups (Supplemental Table 4).

Kidney outcomes

Canagliflozin reduced the risk of the primary composite outcome of ESKD, 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 2). Effects on ESKD, doubling of serum creatinine or death due to kidney disease (HR 0.70, 95% CI 0.59-0.82) and other kidney outcomes, including ESKD alone, were also similar across all subgroups (Figure 2). Effects on other kidney outcomes, including dialysis, transplant or death due to kidney disease, are summarized in Supplemental Figure 1.

Cardiovascular outcomes

The effect of canagliflozin on the composite of 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 3). The effect on cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR 0.80, 95% CI 0.67-0.95) did not vary by baseline systolic BP or number of BP lowering drug classes (P-interaction= 0.52 and 0.25, respectively), although there was some evidence that the magnitude of benefit varied by history of resistant

hypertension (P-interaction=0.04; Figure 3). Effects on other cardiovascular and mortality outcomes are summarized in Supplemental Figure 2.

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 4). 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 4). 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 resistant hypertension. Moreover, the kidney and cardiovascular benefits of canagliflozin did not vary across these subgroups, and there was no impact on risk of volume depletion or acute kidney injury. The magnitude and consistency of BP lowering observed with canagliflozin provides compelling evidence that it 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.[13] In the EMPA-REG BP trial, empagliflozin reduced mean 24 hour ambulatory systolic BP by approximately 3-4 mmHg after 12 weeks,[14] with consistent reductions irrespective of the number of background BP lowering drugs.[15] Similar findings have been reported in short-term trials of other SGLT2 inhibitors,[6, 16, 17] 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, 18, 19]

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.[20] 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.

The mechanism by which canagliflozin and other SGLT2 inhibitors lower BP is likely multifactorial with differing contributing factors in people with and without CKD.[8, 21] An important distinction is that unlike other BP lowering agents,[22] there appears to be no association between baseline values and the magnitude of BP reduction, an observation which we have extended to people with CKD. 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 is not 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.[23-25] This observation is confirmed and strengthened by the CREDENCE data, which includes the largest number of participants with eGFR <45 mL/min/1.73m^2 of any SGLT2 inhibitor outcome trial to date.[26] 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.[27] One hypothesis is that these drugs reduce neurohormonal activation.[28] 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.[29] This is further supported by favorable effects on arterial stiffness, vascular resistance, and BP variability in human clinical trials.[30-32] 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.

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. Fully automated oscillometric devices, which may provide more acute measurement of BP,[33] 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

Treatment with canagliflozin results in early and sustained reductions in systolic BP of a similar magnitude regardless of baseline systolic BP, number of concomitant BP lowering drugs, or history of resistant hypertension. These data support the use of canagliflozin for end-organ protection and as an adjunct BP lowering therapy in people with T2DM and CKD.

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Supplemental Materials

Online-only Tables 1 - 4

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. Number of BP lowering drug classes and their combinations at baseline

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.

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. 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; ESKD: end-stage kidney disease; HR: hazard ratio; CI: confidence interval.

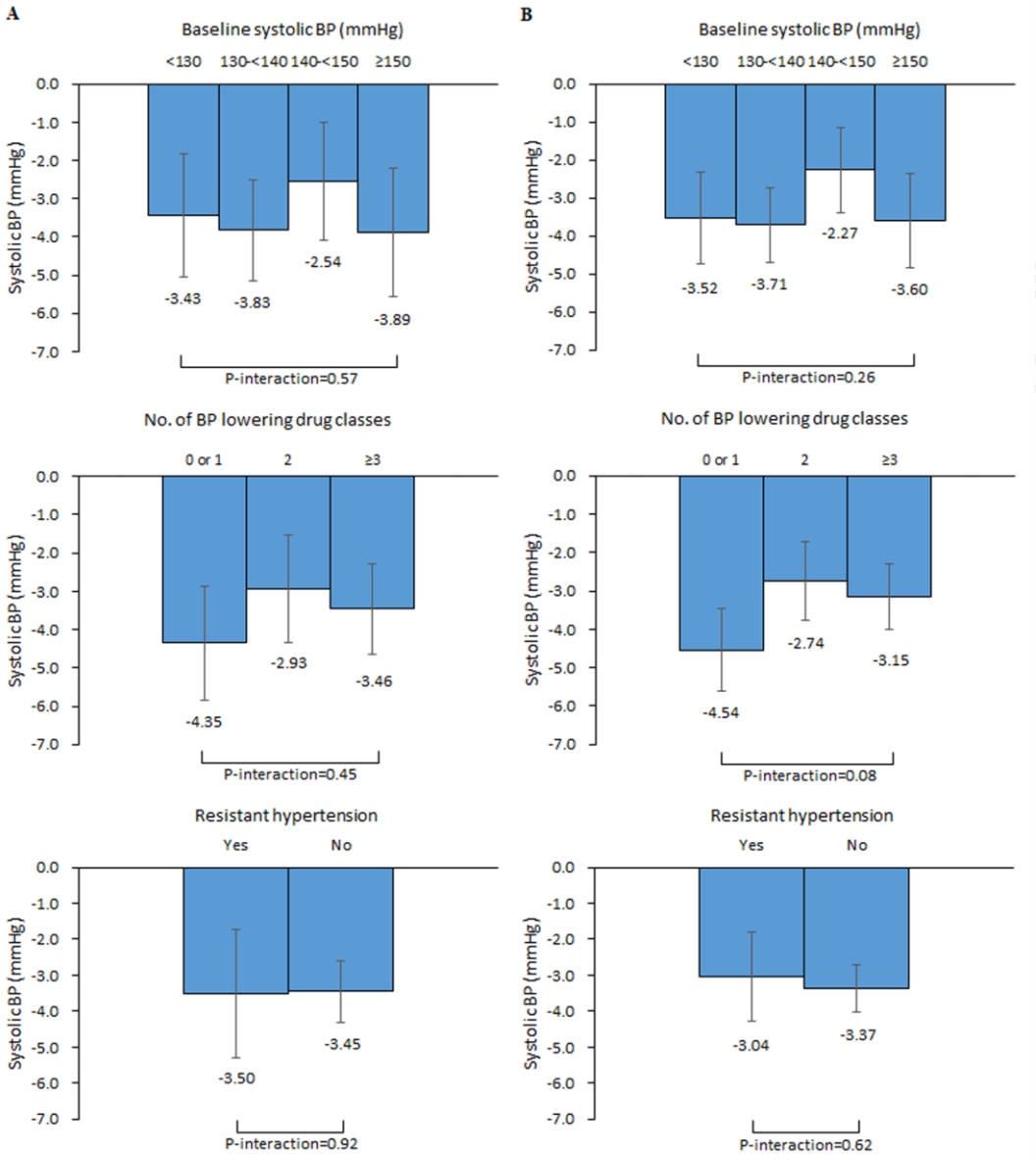
Figure 3. Effect of canagliflozin on cardiovascular outcomes according to baseline systolic BP, number of BP lowering drug classes, and history of resistant hypertension.

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

Figure 4. 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.


A
Baseline systolic BP (mmHg)
<130
130-<140
140-<150
≥150
Systolic BP (mmHg)
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-3.43
-3.83
-2.54
-3.89
P-interaction=0.57
No. of BP lowering drug classes
0 or 1
2
≥3
-4.35
-2.93
-3.46
P-interaction=0.45
Resistant hypertension
Yes
No
-3.50
-3.45
P-interaction=0.92
B
Baseline systolic BP (mmHg)
<130
130-<140
140-<150
≥150
-3.52
-3.71
-2.27
-3.60
P-interaction=0.26
No. of BP lowering drug classes
0 or 1
2
≥3
-4.54
-2.74
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P-interaction=0.08
Resistant hypertension
Yes
No
-3.04
-3.37
P-interaction=0.62

Figure 2.

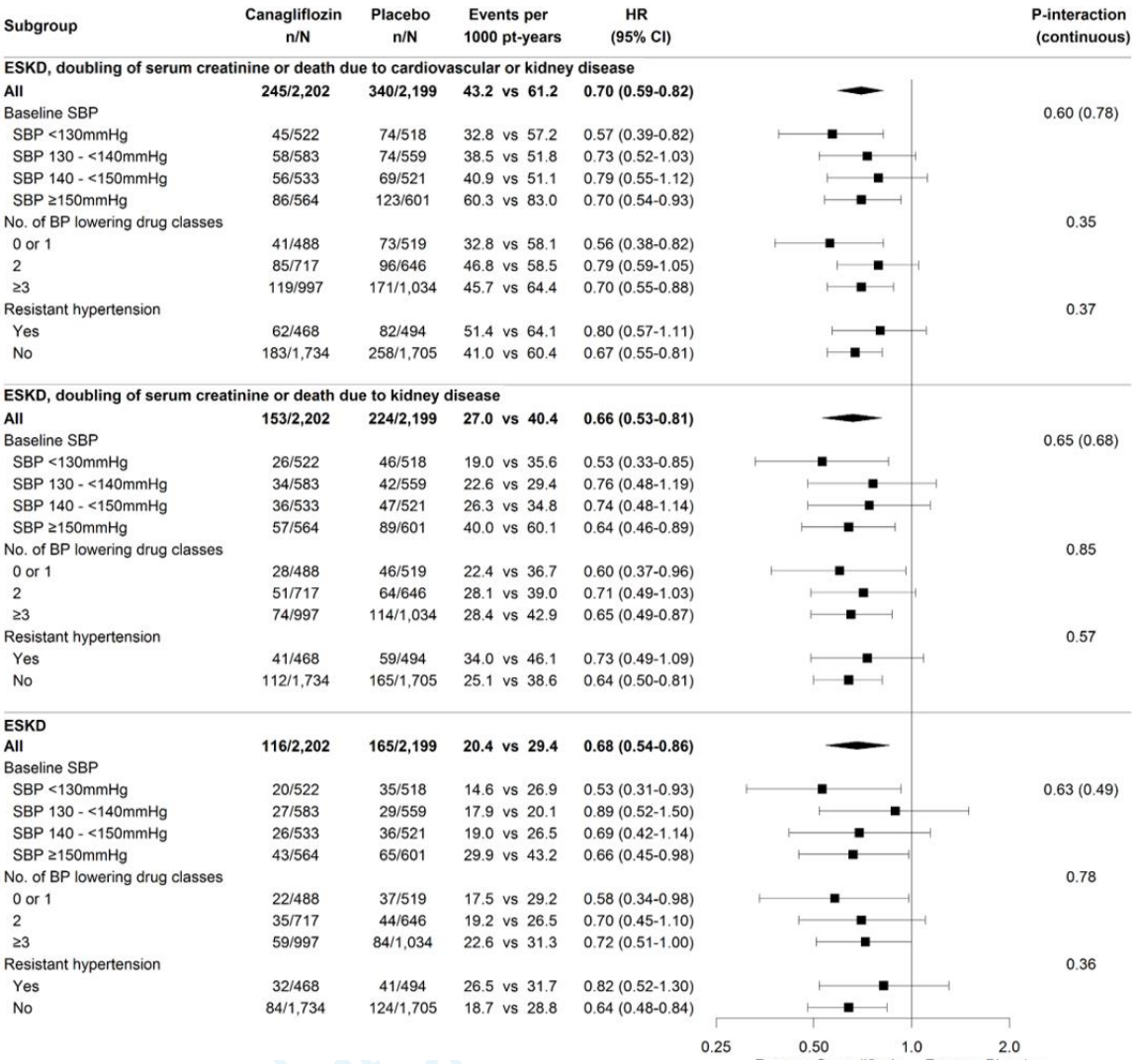

Figure 3.

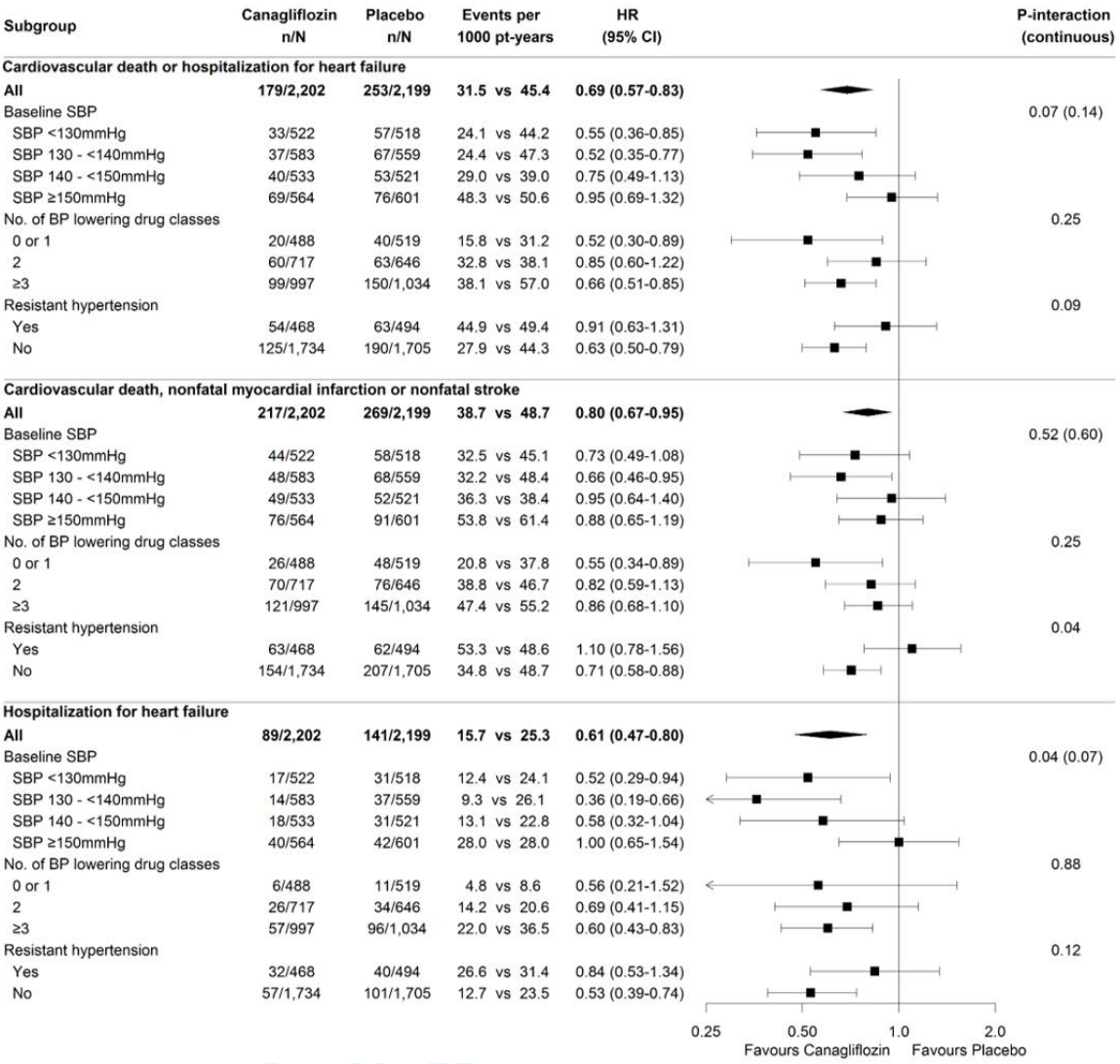

Figure 4.