Cardiovascular and Renal Outcomes with Canagliflozin in Patients with Peripheral Artery Disease: Data from the CANVAS program and CREDENCE trials

Short Title: Canagliflozin use in Peripheral Arterial Disease.

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ABSTRACT

Aims

Patients with type 2 diabetes mellitus (T2D) and PAD have a markedly elevated risk of macrovascular events and death. The sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin has well-established cardiorenal benefits but net effects in patients with PAD remain uncertain. We sought to define the proportional and absolute benefits of canagliflozin in those with and without peripheral arterial disease (PAD).

Materials and Methods

We pooled individual participant data from the CANVAS Program (n=10,142) and CREDENCE trial (n=4,401). In this post hoc analysis, the main outcomes of interest were major adverse cardiovascular events (MACE: non-fatal MI, non-fatal stroke or CV death), kidney outcomes, and extended MALE (major adverse limb events). Cox proportional hazards models were used to assess canagliflozin treatment effects in those with and without PAD. Absolute risk reductions per 1000 patients treated for 2.5 years were estimated using Poisson regression.

Results

Of 14,543 participants, 3,159 (21.7%) had PAD at baseline. In patients with PAD, canagliflozin reduced MACE (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.62-0.92), with similar relative benefits for other cardiovascular and kidney outcomes in participants with or without PAD at baseline (all $P_{interaction} > 0.268$). There was no increase in the relative risk of extended MALE events with canagliflozin, irrespective of baseline PAD history ($P_{interaction} > 0.864$). Absolute benefits of canagliflozin were greater in those with PAD.

Conclusions

Patients with T2D and PAD derived similar relative cardiorenal benefits from canagliflozin treatment but higher absolute benefits compared to those without PAD, with no increase in MALE.

INTRODUCTION

Peripheral artery disease (PAD) is a common form of cardiovascular (CV) disease,[1-3] but is often under-diagnosed and sub-optimally managed. Patients with type 2 diabetes mellitus (T2D) and concomitant PAD have a very high risk of macrovascular events and death.[1, 4-6] This risk is at least as large as those with established coronary artery disease.[7] Moreover, their risk of cardiac failure remains elevated even after adjusting for other CV risk factors.[8] In spite of this risk, PAD registries have shown that the use of CV risk factor modifying agents is suboptimal in this group.[9, 10]

Sodium glucose co-transporter 2 (SGLT2) inhibitors have been demonstrated to reduce cardiovascular events, prevent progression of kidney disease and reduce mortality in a broad range of patients with T2D including those with established atherosclerotic cardiovascular disease, chronic kidney disease and heart failure.[11-17] In the CANVAS Program and CREDENCE Trial canagliflozin reduced major adverse cardiac events (MACE), hospitalization for heart failure (HHF), and kidney disease in those with T2D and high CV risk or albuminuric kidney disease.[14-16] An increased risk of amputation was observed in the CANVAS Program[14] but not in the CREDENCE trial[15] and not with other SGLT2 inhibitors.[17, 18]

The proportional benefits and risks of the SGLT2 inhibitor drug class appear to be consistent across a broad range of patient groups.[14, 15, 17, 18] For example, a recent *post hoc* analysis from DECLARE-TIMI 58 suggested consistent relative benefits with dapagliflozin treatment irrespective of PAD history, with no increase in serious adverse events.[19] However, the amputation finding in the CANVAS Program[14] has raised uncertainty about the benefit to risk ratio of canagliflozin in patients with PAD already at greater baseline risk of vascular and limb events.[20,21] Accordingly, we sought to define the proportional and absolute effects of

canagliflozin versus placebo for the prevention of complications in T2D in those with and without PAD at baseline.

MATERIALS AND METHODS

We performed an individual patient data (IPD) analysis of the CANVAS Program and CREDENCE trial. The design of the CANVAS Program (CANVAS and CANVAS-R) and the CREDENCE trial have been published previously.[22-24] In brief, the CANVAS Program includes two randomized, double-blind placebo-controlled trials of canagliflozin in participants with T2D at elevated cardiovascular risk.[14] The CREDENCE trial was a randomized, double-blind placebo-controlled trial enrolling participants with T2D and albuminuric chronic kidney disease.[15]

Participants

The CANVAS Program enrolled individuals with T2D and eGFR > 30ml/min/1.73m^2. Participants were either ≥ 30years of age with a CV disease history or ≥ 50years of age with ≥ 2 risk factors for CV disease. CREDENCE enrolled individuals with T2D and chronic kidney disease as defined by eGFR 30-90ml/min/1.73m^2 and urine albumin/creatinine ratio of > 300-5000mg/g. All participants in CREDENCE were ≥ 30 years of age and were receiving a stable dose of angiotensin receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor for 4 weeks pre-randomisation. All participants provided informed consent, and ethics approval was obtained at all participating centres.

Randomization, Treatment and Follow up

Randomization was done following a 2-week single-blinded run-in period. CANVAS participants were assigned a 1:1:1 randomisation to canagliflozin 300mg, 100mg or matched placebo. CANVAS-R participants were assigned to canagliflozin 100mg up titrated to a maximum 300mg at week 13 versus matched placebo in a 1:1 fashion. CREDENCE participants were randomised 1:1 to receive canagliflozin 100mg or matched placebo. All participants, investigators and care providers were blinded to the study drug throughout the trial periods. Other therapy for glycaemic control and risk management was continued or instituted as per best practice in line with guideline-based care. Follow up was via face-to-face visits at least once every 6 months, with additional telephone follow-up made between each face-to-face appointment. At each follow-up, efficacy and safety events were recorded. All participants receiving any of the above dosing regimens were included in this subgroup analysis.

Outcomes

The primary outcome for the CANVAS Program was major adverse cardiac events (MACE) and, for the CREDENCE trial, was the composite of kidney failure (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of < 15 ml per minute per 1.73m^2), doubling of the serum creatinine, or death due to kidney or cardiovascular disease. In this current analysis, the main outcomes of interest were: MACE (non-fatal MI, non-fatal stroke or cardiovascular death) and its individual components, hospitalization for heart failure (HHF), cardiovascular death, all-cause mortality, a composite kidney outcome (doubling of serum creatinine, kidney failure or death due to kidney disease) and a cardiorenal composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular disease), and a composite HHF and cardiovascular death.

We also assessed a novel PAD composite outcome: 'Extended Major Adverse Limb Events' (extended MALE) including acute and chronic limb ischaemia, thrombosis and arterial restenosis. This was determined through all adverse events (AEs) collected as per protocols of both trials.[14 25] Again, these AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Coded events include: peripheral arterial occlusive disease, peripheral artery occlusion, peripheral artery stenosis, peripheral ischemia, peripheral vascular disorder, peripheral artery thrombosis, peripheral pulse decreased, peripheral restenosis and peripheral embolism or thrombosis.

The presence of PAD at study baseline was based on physician reporting without requirement for specific clinical evaluation or imaging.[26] The definition of PAD is not inclusive of cerebrovascular disease, but specific to lower extremity disease. In the CREDENCE trial a late protocol amendment was made (Amendment INT-5) to exclude participants from the trial if they had a history of atraumatic amputation within 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.[25] This occurred as a response to the increased amputation risk identified in the CANVAS Program.[14]

Safety outcomes assessed included total adverse events, amputation, fractures, total kidney-related adverse events, acute kidney injury, hyperkalaemia, diabetic ketoacidosis, volume depletion, osmotic diuresis, hypoglycaemia, urinary tract infection and mycotic genital infections.

Statistical Analysis

Baseline characteristics were compared overall for each trial as well as between participants who had PAD at baseline and those who did not. Categorical variables are presented as participant numbers and percentages with differences evaluated by Chi-square test. Continuous variables are presented as means (standard deviations) or medians (interquartile ranges) with differences assessed by a *t* test, a Wilcoxon two-sample test or a Van Elteren test.

Post hoc efficacy analyses were based upon the integrated datasets from the CANVAS Program and the CREDENCE trial using an intention-to-treat method between patients allocated to canagliflozin versus placebo. Analyses assessed the time to the occurrence of the first event with hazard ratios (HRs) and 95% confidence intervals (CIs) obtained from Cox proportional hazards models with stratification according to trial (CANVAS, CANVAS-R or CREDENCE) and baseline history of cardiovascular disease. Multivariable models were additionally adjusted for baseline characteristics that were different between those with and without PAD at baseline(age, gender, race, diabetes duration, history of heart failure, history of coronary disease, history of cerebral disease, history of microvascular disease, history of amputation, baseline diastolic blood pressure, baseline HbA1c, baseline lipid, baseline eGFR, baseline UACR, and medications including insulin, sulfonylurea, metformin, DPP-4 inhibitor, statin, antithrombotic and diuretic). Annualized incidence rates per 1000 patient-years of follow-up were calculated for all outcomes. Heterogeneity of the treatment effect across subgroups defined by baseline PAD status was examined by including a subgroup-by-treatment interaction term in the relevant model with no adjustment for multiplicity. A two-sided P-value of < 0.05 for the interaction term was deemed likely to reflect a difference beyond chance.

For safety outcomes, as was pre-specified in the original trial protocols, on-treatment analyses were performed using events that occurred among subjects who had a safety outcome while they were receiving canagliflozin or placebo, or within 30-day after discontinuation of canagliflozin or placebo. The exception was for amputation and fracture outcomes, where analyses included participants who received at least one dose of canagliflozin or placebo and had an event at any time during follow-up.

Absolute risk reductions per 1,000 patients treated over 2.5 years on cardiorenal outcomes were estimated between canagliflozin and placebo-treated participants using Poisson regression analysis with the assumption of constant annual event probabilities as previously described.[27, 28]

Analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC, USA) and SAS Enterprise Guide Version 7.1 (SAS Institute) and STATA software Version 15.1 (Stata Corp).

RESULTS

Baseline characteristics

In total, 14,543 patients were enrolled in the CANVAS Program (n=10142) and CREDENCE trial (n=4401), of which 3159 (21.7%) participants had PAD at baseline (Table 1). Participants with PAD in the CANVAS Program and CREDENCE Trial were older and more likely to be white, have a longer duration of T2D, and have established HF, microvascular disease, cerebrovascular disease and amputation history (all $P < 0.0001$, Table 1 and Supplementary Table 1). Participants with PAD also had poorer cardiovascular risk factor control (including LDL, systolic blood pressure and HbA1C). Participants with PAD had a lower eGFR [mean (SD): 68.9 (23.1) vs 70.7 (21.6) ml/ min/1.73 m^2, $P = 0.0001$] and higher UACR [median

(interquartile range): 60.4 (9.8 – 704.0) vs 29.4 (8.1 – 484.0), *P* < 0.0001]. Those with PAD had an increased likelihood of insulin, antithrombotic and diuretic medication use (all *P* < 0.0001, Table 1).

Relative Benefits of Canagliflozin in those with PAD

The cumulative incidence of MACE, cardiovascular death or hospitalization for heart failure, and all-cause mortality was substantially higher in participants with PAD compared to those without PAD (Figure 1).

Canagliflozin reduced the risk of MACE by 17% in the overall population (HR 0.83, 95% CI 0.75 - 0.93), with consistent benefits irrespective of PAD at baseline (PAD: HR 0.76, 95% CI 0.62 - 0.92 and without PAD: HR 0.86, 95% CI 0.76 - 0.98;Figure 1 and 2). Canagliflozin reduced the risk of hospitalization for heart failure or cardiovascular death in the overall population by 26% (HR 0.74, 95% CI 0.66 - 0.84), again with consistent benefits irrespective of PAD at baseline (HR 0.69, 95% CI 0.56 - 0.86 vs. HR 0.76, 95% CI 0.66 - 0.88, P interaction = 0.415; Figure 1,2). Canagliflozin also reduced all-cause mortality by 15% in the overall population, with similar benefits irrespective of PAD status (P interaction= 0.320); Figure 1). Consistent relative effects were also observed for a range of other cardiovascular outcomes regardless of PAD at baseline (Figure 2).

Kidney outcomes were also consistently improved with canagliflozin with a 29% relative risk reduction in the composite kidney outcome in those with PAD versus 39% in those without PAD (HR 0.71, 95% CI 0.49 - 1.03 vs. HR 0.61, 95% CI 0.49 - 0.76, P interaction = 0.502; Figure 2). Estimates of relative effects and heterogeneity by PAD subgroups for the cardiovascular and kidney outcomes were unchanged in adjusted models (Supplementary Table 2).

Absolute benefits of canagliflozin in those with and without PAD at baseline

For every 1000 patients treated over 2.5 years, canagliflozin was estimated to prevent 33 MACE events in participants with PAD (95% CI -56, -9) as compared to 11 in those without PAD (95% CI -20, -2) (Figure 3). Similarly, treatment with canagliflozin was estimated to prevent 35 HHF/CV death events in participants with PAD (95% CI -56, -15) versus 14 in those without PAD (95% CI -21, -6). Greater absolute benefits were also seen in those with established PAD for CV death with prevention of 16 CV deaths (95% CI -32, 0) and 22 all cause deaths (95% CI -41,-3) compared to prevention of 4 CV deaths (95% CI -10,1) and 6 all cause deaths (95% CI -13,1) in those without PAD. Absolute benefits were similar for the composite kidney outcome in those with and without PAD (Figure 3).

Safety of canagliflozin in those with and without PAD at baseline

Canagliflozin treatment was associated with a reduction in total serious adverse events in those with (HR 0.85; 95% CI 0.76 - 0.95) and without (HR 0.93; 95% CI 0.87 - 1.00) PAD at baseline (P interaction = 0.257) (Table 2). In absolute terms, there were 79 fewer serious adverse events per 1000 patients treated with canagliflozin over 2.5 years in the PAD group (95% CI -136, -19) compared to 30 fewer in those without a history of PAD (95% CI -54, -7). A reduction in kidney-related adverse events was also seen with canagliflozin irrespective of PAD at baseline (HR 0.81; 95% CI 0.72 - 0.92; P interaction = 0.223).

There was no difference in the proportional risk of amputation by baseline PAD status (P interaction = 0.313) but there was an overall increased risk of amputation with canagliflozin (HR 1.50; 95% CI 1.19 - 1.89). This was due to the increase seen in the CANVAS Program (HR

1·97; 95% CI 1·41 - 2·75) though there was no effect observed in the CREDENCE trial (HR 1·11; 95% CI 0·79 - 1·55) and there was no evidence of heterogeneity of amputation risk by baseline PAD status in either study (both P interaction > 0.29).[29]

Canagliflozin did not affect the risk of the extended MALE outcome in the overall cohort, or in those with PAD (HR 1.09; 95% CI 0.82 - 1.46) or those without PAD (HR 1.22; 95% CI 0.91 - 1.64); P interaction for PAD subgroups = 0.864 (Table 2). When the trials were studied separately there was an increased risk of extended MALE in the overall CANVAS Program cohort (HR 1.37; 95% CI 1.05 - 1.81) with no difference between those with and without PAD at baseline (P interaction = 0.068). There was no increase in the risk of MALE in the CREDENCE trial (HR 0.94 95% CI 0.68 - 1.30) irrespective of PAD status at baseline (P interaction 0.376) (Table 2).

An increase in diabetic ketoacidosis (HR 3.94; 95% CI 1.5-10.36) was identified in the entire cohort, with no evidence of different effects in those with established PAD; P interaction = 0.792 (Table 2). There was an increase in genital mycotic infections in both male and females identified (HR 3.97; 95% CI 3.09 - 5.10 and HR 3.92; 95% CI 2.76 - 5.56 respectively; both P interaction > 0.446) in the entire cohort, with no evidence of heterogeneity by PAD subgroups (Supplementary Table 3).

DISCUSSION

In this *post hoc* analysis of individual patient data from the CANVAS Program and the CREDENCE trial, canagliflozin consistently reduced the proportional risk of key cardiovascular and kidney outcomes, irrespective of the presence or absence of PAD at baseline. Furthermore, because participants with PAD were at much greater risk of

cardiovascular events and death, absolute risk reductions with canagliflozin were larger for these individuals with no increase in total serious adverse events and no evidence that those with established PAD were at a higher risk of peripheral arterial disease events from treatment with canagliflozin. These data indicate safety and efficacy of canagliflozin in patients with PAD, a very high-risk group, who stand to gain significant benefit from this treatment.

Patients with PAD constitute a large proportion of patients with T2D and have markedly elevated risks of cardiovascular diseases in many different populations.[30-36] Furthermore, those with PAD exhibit an excess in CV and all-cause mortality risk as compared to those without PAD, even after adjusting for concomitant coronary artery disease, cerebrovascular disease and other CV risk factors.[1, 6, 34] The greater absolute risk reductions in the PAD cohort observed with SGLT2 inhibition has also been observed with other cardioprotective therapies, for example with antiplatelet treatment.[37]

SGLT2 inhibitors are very effective at reducing hospitalisation for heart failure (HHF) in those with[14, 18] and without T2D.[12, 13] Heart failure is prevalent in PAD patients and increased about 2-fold as compared to age and sex matched individuals without PAD.[8, 38] Risk factors for heart failure such as T2D, hypertension, dyslipidaemia and smoking, cluster in PAD patients[38] though the risk of HF in PAD typically remains elevated even after adjusting for concomitant risks.[39] It may be that worsening cardiorespiratory fitness, consequent upon reduced exercise tolerance, result in greater functional decline and increased risks of HHF.[40] Prevention of heart failure is thus an important priority in this patient group. The large

proportional and absolute benefits observed here further strengthen the case for SGLT2 inhibition in those with PAD.

Patients with PAD also have a greater risk of progressive kidney disease[19] and the prevalence of PAD is higher in more advanced stages of CKD.[41] In this analysis, we demonstrated similar baseline risk of a composite kidney outcome across those with and without PAD at baseline, with consistent relative and absolute reductions in the composite kidney outcome with canagliflozin treatment in those subgroups.[42]

The clear benefits reported here are broadly consistent with a recent secondary analysis from the DECLARE-TIMI 58 trial,[19] where dapagliflozin was demonstrated to reduce CV death, HHF and progression of kidney disease in those with T2D, irrespective of PAD status at baseline. This study had similar inclusion criteria to the CANVAS Program. It reported a baseline PAD history of 6% as compared to 21.7% in this current analysis and similar follow up times (median 4.2 years in DAPA-TIMI-58, 2.4 years in CANVAS Program and 2.5 years in CREDENCE trial). In all studies, consistent relative benefits were identified with greater absolute benefits for CV outcomes in those with established PAD.[14,15,19] Taken together, these data indicate that the systematic use of SGLT2 inhibition amongst patients with PAD will significantly improve clinical outcomes.

A robust assessment of the safety of SGLT2 therapy in patients with PAD is of importance given concerns about a possible increased risk of amputation with canagliflozin in the CANVAS Program.[14] The absence of any increased amputation risk in the CREDENCE trial[29] or any other study of an SGLT2 inhibitor,[17, 18] alongside a failure to identify a mechanism for causation of elevated amputation risk with SGLT2 inhibition, recently resulted in the FDA removing their black box amputation risk warning from canagliflozin.[43] Supporting this,

previous analyses by this group[29] identified no trial procedures, participant characteristics or biological reason to explain the elevated amputation risk seen in the CANVAS Program, leading to the possibility that this may have been a chance finding. Corresponding null findings for the 'extended MALE' outcome in the present analyses, also seen in the DECLARE-TIMI 58 trial analysis [19] for MALE and amputation with dapagliflozin treatment by PAD subgroup, provide further reassurance about safety of SGLT2 inhibitors in those with and without a history of PAD.

The absolute benefits of canagliflozin in those with established PAD are substantial with greater benefits for MACE, CV death, HF hospitalisations and all-cause mortality, with the number needed to treat more than halved in those with PAD compared to those without PAD. Coupled with fewer total serious adverse events in the canagliflozin group, this suggest significant net clinical benefit will be achieved in the PAD population.

This *post hoc* subgroup analysis from the CANVAS Program and CREDENCE trial benefits from the rigorous design and conduct of the contributing trials, a large population with (over 3000 individuals) with PAD at study entry, and a long follow up period. It was not, however, powered to detect differences in those with and without PAD and small or moderate sized differences in effects between subgroups may have been missed. These findings should therefore be interpreted as exploratory and hypothesis generating.

Conclusion

Canagliflozin treatment consistently reduced the proportional risks of cardiovascular and kidney outcomes irrespective of PAD status at baseline, with no relative increase in total serious adverse events or major adverse limb events in those with or without PAD. Absolute risk reductions for cardiovascular outcomes with canagliflozin were greater in those with

established PAD. These findings demonstrate the therapeutic importance and safety of the SGLT2 inhibitor canagliflozin in patients with T2D and PAD.

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Table 1. Baseline Characteristics of participants by PAD at baseline in the Pooled CANVAS Program[a] and CREDENCE Trial.

	Participants with PAD			Participants without PAD			*P-Value (total with PAD vs total without PAD)*
	Canagliflozin (n=1707)	Placebo (n=1452)	Total (n=3159)	Canagliflozin (n=6290)	Placebo (n=5094)	Total (n=11384)	
Age, years, mean (SD)	63.8 (8.8)	63.9 (8.7)	63.8 (8.7)	62.9 (8.5)	63.2 (8.5)	63.1 (8.5)	< 0.0001
Male, no. (%)	1161 (68.0)	936 (64.5)	2097 (66.4)	4038 (64.2)	3281 (64.4)	7319 (64.3)	0.030
Race, no. (%)							< 0.0001
White	1434 (84.0)	1214 (83.7)	2648 (83.9)	4561 (72.6)	3666 (72.0)	8227 (72.3)	
Asian	90 (5.3)	85 (5.9)	175 (5.5)	1112 (17.7)	874 (17.2)	1986 (17.5)	
Black	86 (5.0)	77 (5.3)	163 (5.2)	202 (3.2)	195 (3.8)	397 (3.5)	
Other[b]	97 (5.7)	74 (5.1)	171 (5.4)	410 (6.5)	357 (7.0)	767 (6.7)	
Current smoker, no. (%)	306 (17.9)	240 (16.5)	546 (17.3)	1055 (16.8)	844 (16.6)	1899 (16.7)	0.421
Hypertension, no. (%)	1562 (91.5)	1335 (91.9)	2897 (91.7)	5757 (91.5)	4731 (92.9)	10488 (92.1)	0.437
Duration of diabetes, years, mean (SD)	14.8 (8.6)	15.5 (8.7)	15.1 (8.7)	13.8 (7.9)	14.2 (8.0)	14.0 (7.9)	< 0.0001
Heart failure, no. (%)	394 (23.1)	342 (23.6)	736 (23.3)	738 (11.7)	639 (12.5)	1377 (12.1)	< 0.0001
MI, no. (%)	408 (23.9)	334 (23.0)	742 (23.5)	1467 (23.3)	1189 (23.3)	2656 (23.3)	0.853
Microvascular disease, %							
Retinopathy	641 (37.6)	586 (40.4)	1227 (38.8)	1497 (23.8)	1287 (25.3)	2784 (24.5)	< 0.0001
Nephropathy	834 (48.9)	746 (51.4)	1580 (50.0)	2362 (37.6)	2233 (43.8)	4595 (40.4)	< 0.0001
Neuropathy	968 (56.7)	817 (56.3)	1785 (56.5)	1896 (30.1)	1576 (30.9)	3472 (30.5)	< 0.0001
Atherosclerotic vascular disease, no. (%)[c]							
Coronary	888 (52.0)	762 (51.4)	1650 (52.2)	2999 (47.7)	2385 (46.8)	5384 (47.3)	< 0.0001
Cerebrovascular	463 (27.1)	358 (24.7)	821 (26.0)	992 (15.8)	845 (16.6)	1837 (16.1)	< 0.0001
Any	1707 (100)	1452 (100)	3159 (100)	3533 (56.2)	2852 (56.0)	6385 (56.1)	< 0.0001
Fracture, no. (%)	371 (21.7)	284 (19.6)	655 (20.7)	1266 (20.1)	1004 (19.7)	2270 (19.9)	0.325
Amputation, no. (%)	255 (14.9)	217 (14.9)	472 (14.9)	0 (0)	0 (0)	0 (0)	< 0.0001
BMI, kg/m^2, mean (SD)	31.7 (5.6)	31.8 (5.9)	31.7 (5.7)	31.8 (6.1)	31.7 (6.1)	31.8 (6.1)	0.639
SBP, mmHg, mean (SD)	137.9 (15.7)	138.5 (16.4)	138.1 (16.0)	137.2 (15.8)	137.9 (15.6)	137.5 (15.7)	0.049

DBP, mmHg, mean (SD)	76.9 (9.6)	77.2 (9.7)	77.0 (9.7)	78.0 (9.5)	78.2 (9.6)	78.1 (9.5)	< 0.0001
HbA1c, %, mean (SD)	8.3 (1.1)	8.3 (1.1)	8.3 (1.1)	8.2 (1.1)	8.2 (1.1)	8.2 (1.1)	0.013
Cholesterol, mmol/L, mean (SD)							
Total	4.6 (1.3)	4.6 (1.3)	4.6 (1.3)	4.4 (1.2)	4.4 (1.2)	4.4 (1.2)	< 0.0001
LDL	2.4 (1.0)	2.5 (1.0)	2.4 (1.0)	2.3 (1.0)	2.3 (1.0)	2.3 (1.0)	< 0.0001
HDL	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	0.651
Triglycerides, mmol/L, mean (SD)	2.2 (1.7)	2.1 (1.6)	2.1 (1.6)	2.1 (1.3)	2.1 (1.6)	2.1 (1.4)	0.062
eGFR, mL/min/1.73 m^2, mean (SD)	69.1 (23.4)	68.7 (22.7)	68.9 (23.1)	71.6 (21.2)	69.6 (22.0)	70.7 (21.6)	0.0001
UACR, mg/g, median (IQR)[d]	47.7 (9.6, 600.0)	72.7 (10.3, 787.0)	60.4 (9.8, 704.0)	25.1 (7.9， 398.0)	37.5 (8.4, 599.0)	29.4 (8.1, 484.0)	< 0.0001[f]
Albuminuria, no (%)							< 0.0001[g]
Normal	766 (45.1)	603 (41.8)	1369 (43.6)	3262 (52.2)	2407 (47.7)	5669 (50.2)	
Microalbuminuria	347 (20.4)	263 (18.3)	610 (19.4)	1226 (19.6)	926 (18.3)	2152 (19.1)	
Macroalbuminuria	585 (34.5)	575 (39.9)	1160 (37.0)	1756 (28.1)	1718 (34.0)	3474 (30.8)	
Drug therapy, no. (%)							
Insulin	1070 (62.7)	929 (64.0)	1999 (63.3)	3272 (52.2)	2708 (53.2)	5980 (52.5)	< 0.0001
Sulfonylurea	583 (34.2)	481 (33.1)	1064 (33.7)	2557 (40.7)	2008 (39.4)	4565 (40.1)	< 0.0001
Metformin	1115 (65.3)	947 (65.2)	2062 (65.3)	4608 (73.3)	3700 (72.6)	8308 (73.0)	< 0.0001
GLP-1 receptor agonist	71 (4.2)	49 (3.4)	120 (3.8)	240 (3.8)	230 (4.5)	470 (4.1)	0.406
DPP-4 inhibitor	185 (10.8)	182 (12.5)	367 (11.6)	890 (14.1)	755 (14.8)	1645 (14.5)	< 0.0001
Statin	1239 (72.6)	1010 (69.6)	2249 (71.2)	4629 (73.6)	3758 (73.8)	8387 (73.7)	0.005
Antithrombotic[e]	1328 (77.8)	1097 (75.6)	2425 (76.8)	4249 (67.6)	3421 (67.2)	7670 (67.4)	< 0.0001
RAAS inhibitor	1475 (86.4)	1242 (85.5)	2717 (86.0)	5371 (85.4)	4423 (86.8)	9794 (86.0)	0.972
β-Blocker	839 (49.2)	745 (51.3)	1584 (50.1)	3083 (49.0)	2524 (49.5)	5607 (49.3)	0.377
Diuretic	833 (48.8)	688 (47.4)	1521 (48.1)	2729 (43.4)	2297 (45.1)	5026 (44.2)	< 0.0001

PAD, peripheral artery disease; MI, myocardial infarction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; UACR, urine albumin-to-creatinine ratio; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase 4.

a One participant was randomized at two different sites, and only the first randomization is included in the intention-to-treat analysis set.

b Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown.

c Some patients had more than one type of atherosclerotic vascular disease.

d Values for albuminuria categories calculated based on N of 4436 with diuretics and N of 5597 without diuretics and 10,033 for the total population for the CANVAS Program.

e Includes antiplatelets and anticoagulants.

f P value corresponds to Wilcoxon two-sample test.

g P value corresponds to Van Elteren test for no association.

Table 2. Key adverse events in participants by PAD at baseline in the Pooled CANVAS Program and/or CREDENCE Trial.

	Patients with an event per 1000 patient-years			
	Canagliflozin	Placebo	Hazard ratio (95% CI)	*P*-value Interaction
A. Key adverse Events				
Any serious adverse events				
Overall	138.94	161.38	0.92 (0.86-0.97)	
PAD	188.66	229.43	0.85 (0.76-0.95)	0.257
No PAD	127.50	145.35	0.93 (0.87-1.00)	
Amputations				
Overall	7.53	5.62	1.50 (1.19-1.89)	
PAD	25.21	20.02	1.37 (1.03-1.82)	0.313
No PAD	3.44	2.16	1.69 (1.12-2.54)	
Renal-related adverse events				
Overall	27.16	36.34	0.81 (0.72-0.92)	
PAD	54.00	68.81	0.90 (0.70-1.16)	0.223
No PAD	23.17	32.10	0.78 (0.67-0.90)	
Diabetic ketoacidosis				
Overall	0.91	0.26	3.94 (1.50-10.36)	
PAD	0.75	0.27	3.41 (0.37-31.38)	0.792
No PAD	0.94	0.26	4.19 (1.43-12.30)	
B. Extended major adverse limb events				
Combined dataset				
Overall	8.84	7.82	1.18 (0.96-1.44)	
PAD	23.96	20.90	1.09 (0.82-1.46)	0.864
No PAD	5.37	4.66	1.22 (0.91-1.64)	
CANVAS Program				
Overall	7.85	5.50	1.37 (1.05-1.81)	
PAD	23.27	19.59	1.08 (0.76-1.54)	0.068
No PAD	4.57	2.38	1.79 (1.15-2.77)	
CREDENCE Trial				
Overall	12.71	13.51	0.94 (0.68-1.30)	
PAD	26.01	23.45	1.11 (0.68-1.81)	0.376
No PAD	8.72	10.59	0.82 (0.54-1.27)	

PAD, peripheral artery disease; CI, confidence interval. Extended Major Adverse Limb Events *including reported adverse events due to peripheral arterial occlusive disease, peripheral artery occlusion, peripheral artery stenosis, peripheral ischemia, peripheral vascular disorder, peripheral artery thrombosis, peripheral pulse decreased, peripheral restenosis and peripheral embolism or thrombosis.

Figure legends

Figure 1. Rates of MACE, CV death or hospitalisation for HF, all-cause mortality in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

The hazard ratios and 95% confidence intervals were determined from the Cox proportional hazards models. The heterogeneity of the treatment effect across subgroups defined by baseline PAD status was examined by including a subgroup-by-treatment interaction term in the relevant model.
Abbreviations: MACE, major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; CV, cardiovascular; HF, heart failure; PAD, peripheral artery disease; CI, confidence interval.

Figure 2. Effects of canagliflozin on cardiovascular and renal outcomes in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

The relative effects of canagliflozin versus placebo on cardiovascular and renal outcomes were estimated by combining individual patient data of both trials with stratification for trial and history of cardiovascular disease. Hazard ratios and 95% confidence intervals were determined from the Cox proportional hazards models. The heterogeneity of the treatment effect across subgroups defined by baseline PAD status was examined by including a subgroup-by-treatment interaction term in the relevant model.
Abbreviations: PAD, peripheral artery disease; CI, confidence interval; MACE, major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; ESKD, end-stage kidney disease.

Figure 3. Absolute risk reductions per 1000 patients treated over 2.5 years in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

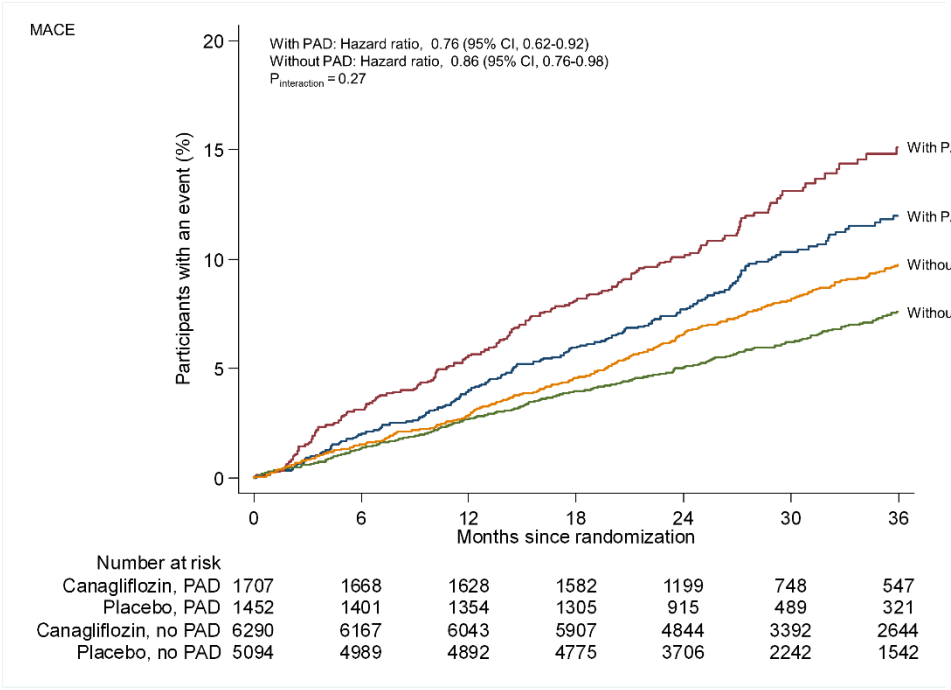
Absolute benefits and risks per 1,000 participants over 2.5 years with canagliflozin versus placebo in the overall population and in participant subgroups defined by PAD at baseline.
Abbreviations: PAD, peripheral artery disease; CI, confidence interval; MACE, major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; 2xScr, doubling of serum creatinine; ESKD, end-stage kidney disease.

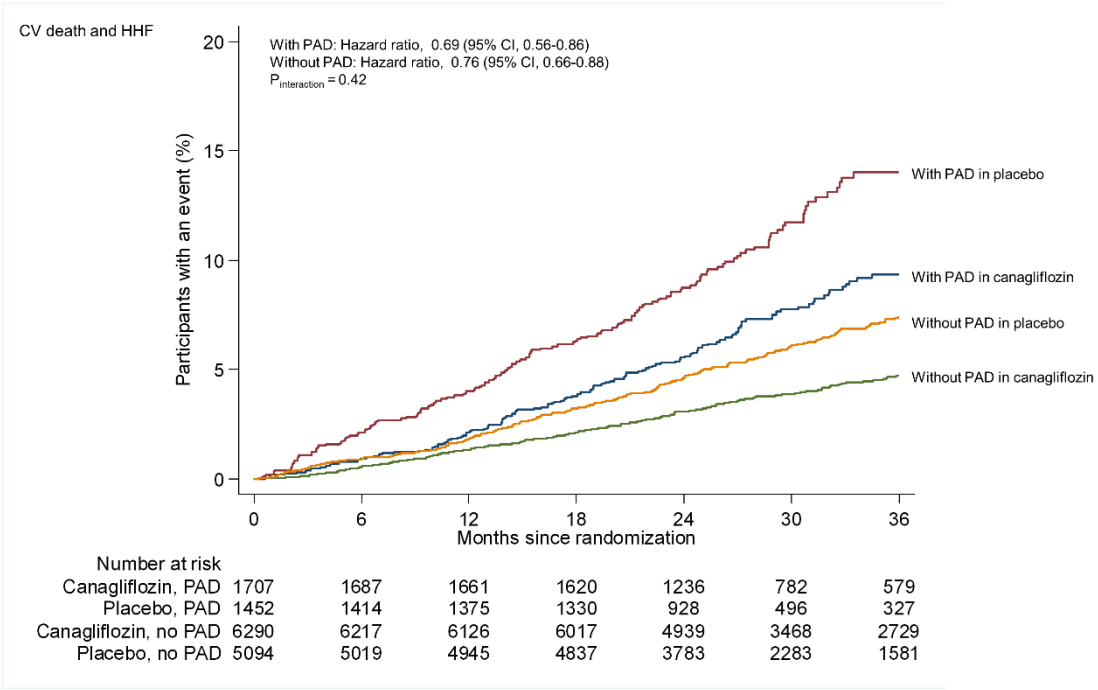
Supplementary Figure 1. Absolute risk reduction in adverse events by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

Absolute benefits and risks per 1,000 participants over 2.5 years with canagliflozin versus placebo in adverse events in the overall population and defined by PAD at baseline.

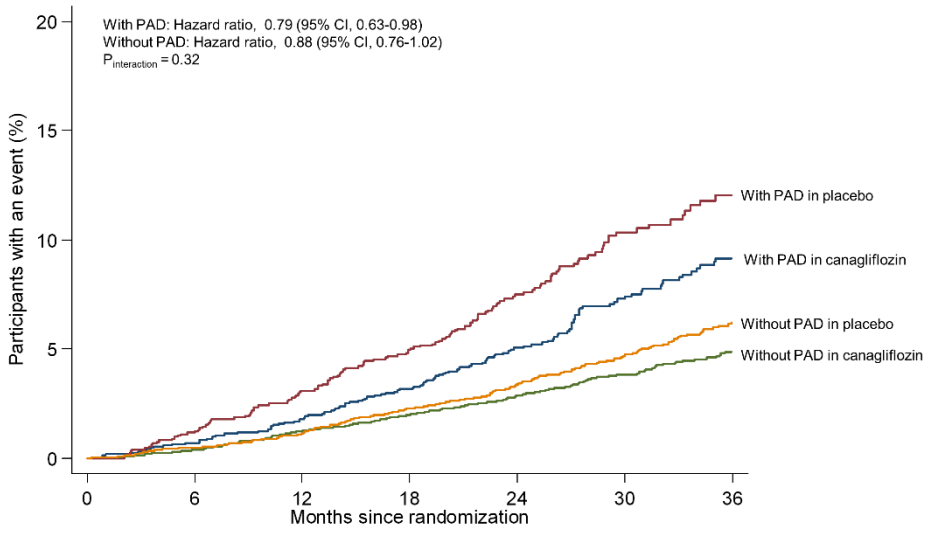
Abbreviations: PAD, peripheral artery disease; CI, confidence interval

Figure 1. Rates of MACE, CV death or hospitalisation for HF, all-cause mortality in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.





All-cause mortality



Number at risk							
Canagliflozin, PAD	1707	1695	1677	1648	1263	803	595
Placebo, PAD	1452	1435	1407	1379	979	537	362
Canagliflozin, no PAD	6290	6260	6201	6149	5090	3600	2846
Placebo, no PAD	5094	5066	5029	4963	3919	2399	1670

Figure 2. Effects of canagliflozin on cardiovascular and renal outcomes in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

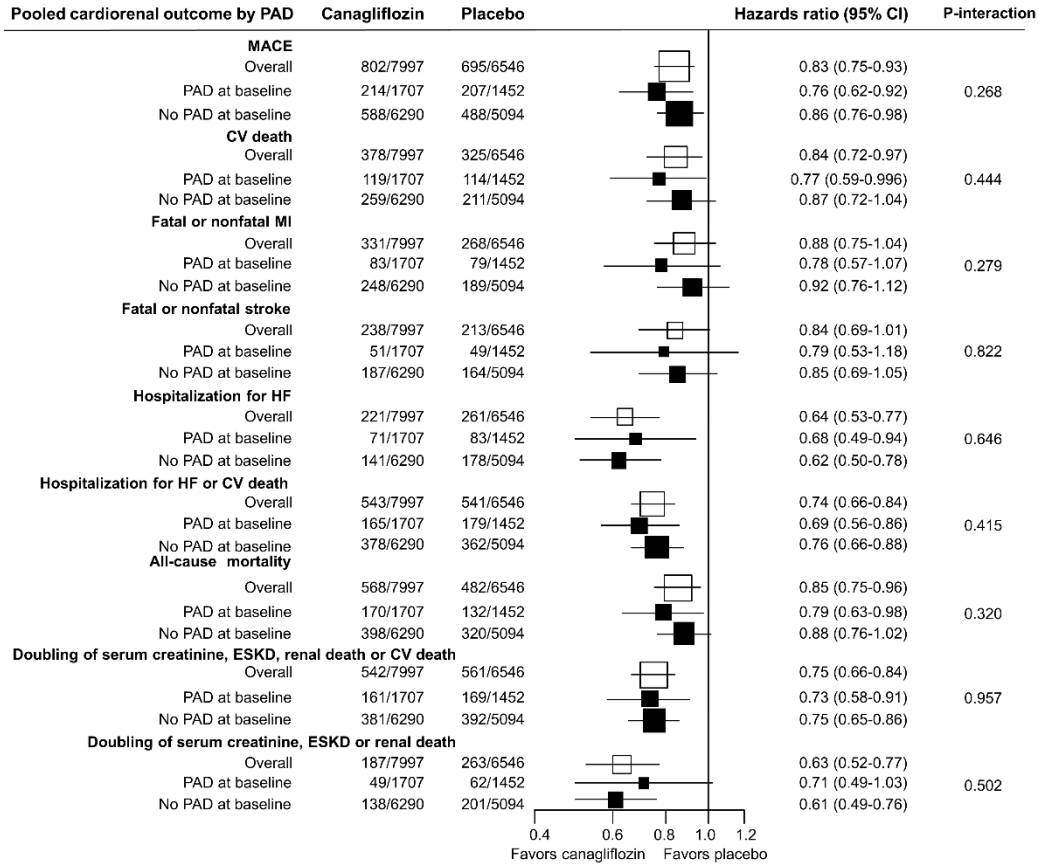
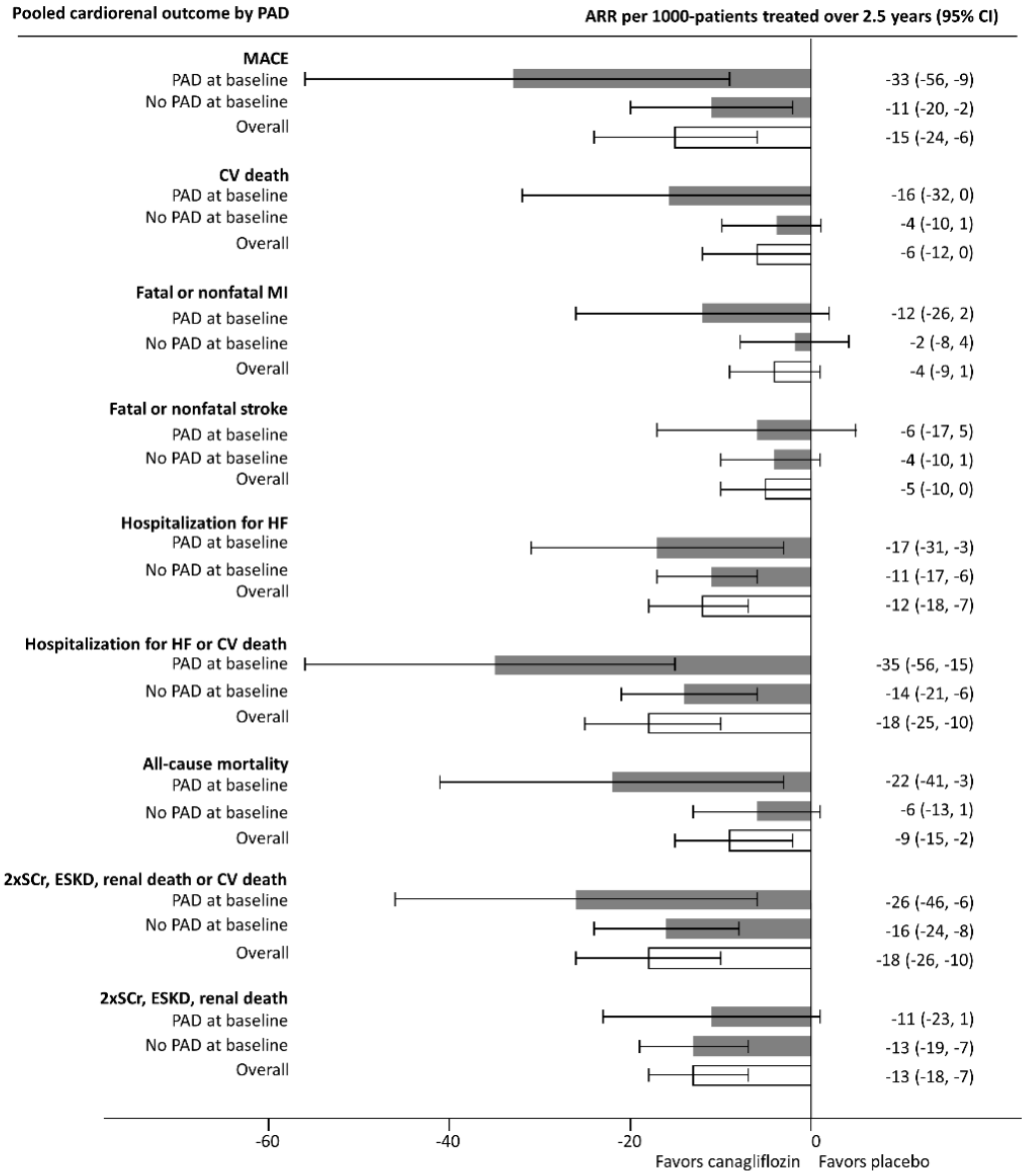


Figure 3. Absolute risk reductions per 1000 patients treated over 2.5 years in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.



Supplementary Table 1. Baseline Characteristics of participants by PAD at baseline in the CANVAS Program or the CREDENCE Trial.

	CANVAS Program[a]				**CREDENCE Trial**			
	PAD (n=2113)	No PAD (n=8029)	All (N=10142)	*P* Value[b]	PAD (n=1046)	No PAD (n=3355)	All (N=4401)	*P* Value[c]
Age, years, mean (SD)	63.8 (8.8)	63.2 (8.1)	63.3 (8.3)	0.0014	63.8 (8.6)	62.8 (9.4)	63.0 (9.2)	0.0010
Male, no. (%)	1373 (65.0)	5136 (64.0)	6509 (64.2)	0.3887	724 (69.2)	2183 (65.1)	2907 (66.1)	0.013
Race, no. (%)				<0.0001[h]				< 0.0001
White	1826 (86.4)	6118 (76.2)	7944 (78.3)		822 (78.6)	2109 (62.9)	2931 (66.6)	
Asian	76 (3.6)	1208 (15.0)	1284 (12.7)		99 (9.5)	778 (23.2)	877 (19.9)	
Black	113 (5.3)	223 (2.8)	336 (3.3)		50 (4.8)	174 (5.2)	224 (5.1)	
Other[d]	98 (4.6)	480 (6.0)	578 (5.7)		75 (7.2)	294 (8.8)	369 (8.4)	
Current smoker, no. (%)	377 (17.8)	1429 (17.8)	1806 (17.8)	0.9591	169 (16.2)	470 (14.0)	639 (14.5)	0.085
Hypertension, no. (%)	1882 (89.1)	7243 (90.2)	9125 (90.0)	0.1197	1015 (97.0)	3245 (96.7)	4260 (96.8)	0.614
Duration of diabetes, years, mean (SD)	14.3 (8.5)	13.4 (7.5)	13.5 (7.8)	< 0.0001	16.9 (8.7)	15.4 (8.6)	15.8 (8.6)	< 0.0001
Heart failure, no. (%)	489 (23.1)	972 (12.1)	1461 (14.4)	< 0.0001	247 (23.6)	405 (12.1)	652 (14.8)	< 0.0001
MI, no. (%)	583 (27.6)	2373 (29.6)	2956 (29.1)	0.0771	159 (15.2)	283 (8.4)	442 (10.0)	< 0.0001
Microvascular disease, %								
Retinopathy	673 (31.9)	1456 (18.1)	2129 (21.0)	< 0.0001	554 (53.0)	1328 (40.0)	1882 (42.8)	< 0.0001
Nephropathy	534 (25.3)	1240 (15.4)	1774 (17.5)	< 0.0001	1046 (100)	3355 (100)	4401 (100)	-
Neuropathy	1082 (51.2)	2028 (25.3)	3110 (30.7)	< 0.0001	7.3 (67.2)	1444 (43.0)	2147 (48.8)	< 0.0001
Atherosclerotic vascular disease, no. (%)[e]								
Coronary	1225 (58.0)	4496 (56.0)	5721 (56.4)	0.1029	425 (40.6)	888 (26.5)	1313 (29.8)	< 0.0001
Cerebrovascular	578 (27.4)	1380 (17.2)	1958 (19.3)	< 0.0001	243 (23.2)	457 (13.6)	700 (15.9)	< 0.0001
Any	2113 (100.0)	5211 (64.9)	7324 (72.2)	< 0.0001	1046 (100)	1174 (34.5)	2220 (50.4)	< 0.0001
Fracture, no. (%)	464 (22.0)	1751 (21.8)	2215 (21.8)	0.8813	191 (18.3)	519 (15.5)	710 (16.1)	0.032
Amputation, no. (%)	238 (11.3)	0 (0)	238 (2.3)	< 0.0001	234 (22.4)	0 (0)	234 (5.3)	< 0.0001
BMI, kg/m^2, mean (SD)	31.8 (5.6)	32.0 (6.0)	32.0 (5.9)	0.1856	31.5 (6.0)	31.3 (6.2)	31.3 (6.2)	0.1900
SBP, mmHg, mean (SD)	136.7 (16.3)	136.6 (15.6)	136.6 (15.8)	0.9348	141.1 (15.1)	139.6 (15.8)	140.0 (15.6)	0.007
DBP, mmHg, mean (SD)	76.7 (9.8)	78.0 (9.6)	77.7 (9.7)	< 0.0001	77.7 (9.4)	78.5 (9.3)	78.3 (9.4)	0.011
HbA1c, %, mean (SD)	8.3 (0.9)	8.2 (0.9)	8.2 (0.9)	0.0052	8.3 (1.3)	8.3 (1.3)	8.3 (1.3)	0.527

Cholesterol, mmol/L, mean (SD)								
Total	4.5 (1.3)	4.3 (1.1)	4.4 (1.2)	< 0.0001	4.7 (1.3)	4.7 (1.3)	4.7 (1.3)	0.421
LDL	2.4 (1.0)	2.3 (0.9)	2.3 (0.9)	< 0.0001	2.5 (1.1)	2.5 (1.1)	2.5 (1.1)	0.154
HDL	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	0.2801	1.1 (0.3)	1.2 (0.4)	1.2 (0.3)	0.628
Triglycerides, mmol/L, mean (SD)	2.1 (1.6)	2.0 (1.4)	2.0 (1.4)	0.0189	2.2 (1.6)	2.2 (1.6)	2.2 (1.6)	0.632
eGFR, mL/min/1.73 m^2, mean (SD)	75.7 (22.2)	76.7 (20.0)	76.5 (20.5)	0.0751	55.3 (18.3)	56.5 (18.2)	56.2 (18.2)	0.061
UACR, mg/g, median (IQR)[f]	14.5 (7.1, 62.0)	11.8 (6.5, 38.4)	12.3 (6.7, 42.1)	<0.0001[h]	957.0 (491.0, 1949.0)	917.0 (459.0, 1790.0)	927.0 (463.3, 1833.0)	0.077[h]
Albuminuria, no (%)				0.0759[i]				0.197[i]
Normal	1363 (65.1)	5644 (71.1)	7007 (69.8)		6 (0.6)	25 (0.8)	31 (0.7)	
Microalbuminuria	503 (24.0)	1763 (22.2)	2266 (22.6)		107 (10.2)	389 (11.6)	496 (11.3)	
Macroalbuminuria	227 (10.9)	533 (6.7)	760(7.6)		933 (89.2)	2941 (87.7)	3874 (88.0)	
Drug therapy, no. (%)								
Insulin	1214 (57.5)	3881 (48.3)	5095 (50.2)	< 0.0001	785 (75.1)	2099 (62.6)	2884 (65.5)	< 0.0001
Sulfonylurea	830 (39.3)	3531 (44.0)	4361 (43.0)	0.0001	234 (22.4)	1034 (30.8)	1268 (28.8)	< 0.0001
Metformin	1516 (71.7)	6309 (78.6)	7825 (77.2)	< 0.0001	546 52.2)	1999 (59.6)	2545 (57.8)	< 0.0001
GLP-1 receptor agonist	69 (3.3)	338 (4.2)	407 (4.0)	0.0491	51 (4.9)	132 (3.9)	183 (4.2)	0.183
DPP-4 inhibitor	244 (11.5)	1017 (12.7)	1261 (12.4)	0.1654	123 (11.8)	628 (18.7)	751 (17.1)	< 0.0001
Statin	1499 (70.9)	6101 (76.0)	7600 (74.9)	< 0.0001	750 (71.7)	2286 (68.1)	3036 (69.0)	0.030
Antithrombotic[g]	1657 (78.4)	5814 (72.4)	7471 (73.6)	< 0.0001	768 (73.4)	1856 (55.3)	2624 (59.6)	< 0.0001
RAAS inhibitor	1672 (79.1)	6444 (80.3)	8116 (80.0)	0.2478	1045 (99.9)	3350 99.9)	4395 (99.9)	0.683
β-Blocker	1125 (53.2)	4296 (53.5)	5421 (53.5)	0.8285	459 (43.9)	1311 (39.1)	1770 (40.2)	0.006
Diuretic	993 (47.0)	3497 (43.6)	4490 (44.3)	0.0046	528 (50.5)	1529 (45.6)	2057 (46.7)	0.006

PAD, peripheral artery disease; MI, myocardial infarction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; UACR, urine albumin-to-creatinine ratio; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase 4.

a One participant was randomized at two different sites, and only the first randomization is included in the intention-to-treat analysis set.

b P value for comparison between total participants with PAD and total participants without PAD at baseline in the CANVAS Program.

c P value for comparison between total participants with PAD and total participants without PAD at baseline in the CREDENCE Trial.

d Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown.

e Some patients had more than one type of atherosclerotic vascular disease.

f Values for albuminuria categories calculated based on N of 2093 with PAD and N of 7940 without PAD and 10,033 for the total population for the CANVAS Program.

g Includes antiplatelets and anticoagulants.

h P value corresponds to Wilcoxon two-sample test.

i P value corresponds to Van Elteren test for no association.

Supplementary Table 2. Unadjusted and adjusted effects of canagliflozin on cardiovascular and kidney outcomes in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

	Unadjusted HR (95% CI)	*P* value for heterogeneity	Adjusted HR (95% CI)	*P* value for heterogeneity
MACE				
Overall	0.83 (0.75-0.93)			
PAD	0.76 (0.62-0.92)	0.27	0.73 (0.60-0.89)	0.19
No PAD	0.86 (0.76-0.98)		0.86 (0.76-0.97)	
Cardiovascular death				
Overall	0.84 (0.72-0.97)			
PAD	0.77 (0.59-0.996)	0.44	0.76 (0.58-0.99)	0.44
No PAD	0.87 (0.72-1.04)		0.87 (0.72-1.04)	
Fatal or nonfatal MI				
Overall	0.88 (0.75-1.04)			
PAD	0.78 (0.57-1.07)	0.28	0.77 (0.56-1.06)	0.23
No PAD	0.92 (0.76-1.12)		0.93 (0.76-1.13)	
Fatal or nonfatal stroke				
Overall	0.84 (0.69-1.01)			
PAD	0.79 (0.53-1.18)	0.82	0.74 (0.49-1.11)	0.71
No PAD	0.89 (0.69-1.05)		0.84 (0.68-1.05)	
Hospitalization for HF				
Overall	0.64 (0.53-0.77)			
PAD	0.68 (0.49-0.94)	0.65	0.64 (0.46-0.89)	0.91
No PAD	0.62 (0.50-0.78)		0.64 (0.51-0.80)	
Hospitalization for HF or cardiovascular death				
Overall	0.74 (0.66-0.84)			
PAD	0.69 (0.56-0.86)	0.42	0.67 (0.53-0.83)	0.20
No PAD	0.76 (0.66-0.88)		0.77 (0.66-0.89)	
All-cause mortality				
Overall	0.85 (0.75-0.96)			
PAD	0.79 (0.63-0.98)	0.32	0.79 (0.63-0.99)	0.25
No PAD	0.88 (0.76-1.02)		0.88 (0.76-1.03)	
Doubling of serum creatinine, ESKD, renal death or cardiovascular death				
Overall	0.75 (0.66-0.84)			
PAD	0.73 (0.58-0.91)	0.96	0.70 (0.56-0.88)	0.57
No PAD	0.75 (0.65-0.86)		0.76 (0.66-0.88)	
Doubling of serum creatinine, ESKD, renal death				
Overall	0.63 (0.52-0.77)			
PAD	0.71 (0.49-1.03)	0.50	0.69 (0.47-1.02)	0.88
No PAD	0.61 (0.49-0.76)		0.63 (0.51-0.79)	

Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, with stratification according to trial and history of cardiovascular disease. Adjusted hazard ratios were adjusted variables including age, gender, race, diabetes duration, history of heart failure, history of coronary disease, history of cerebral disease, history of microvascular disease, history of amputation, baseline diastolic blood pressure, baseline HbA1c, baseline lipid, baseline eGFR, baseline UACR, and medications including insulin, sulfonylurea, metformin, DPP-4 inhibitor, statin, antithrombotic and diuretic.

Abbreviations: MACE, major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; MI, myocardial infarction; HF, heart failure; ESKD, end-stage kidney disease.

Supplementary Table 3. Adverse events in participants by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial.

	Patients with an event per 1000 patient-years			
	Canagliflozin	Placebo	Hazard ratio (95% CI)	*P*-value Interaction
Any serious adverse events				
Overall	138.94	161.38	0.92 (0.86-0.97)	
PAD	188.66	229.43	0.85 (0.76-0.95)	0.257
No PAD	127.50	145.35	0.93 (0.87-1.00)	
Amputations				
Overall	7.53	5.62	1.50 (1.19-1.89)	
PAD	25.21	20.02	1.37 (1.03-1.82)	0.313
No PAD	3.44	2.16	1.69 (1.12-2.54)	
Fractures				
Overall	14.65	11.98	1.19 (1.01-1.40)	
PAD	15.03	13.31	1.06 (0.74-1.52)	0.561
No PAD	14.56	11.64	1.21 (1.01-1.46)	
Renal-related adverse events				
Overall	27.16	36.34	0.81 (0.72-0.92)	
PAD	54.00	68.81	0.90 (0.70-1.16)	0.223
No PAD	23.17	32.10	0.78 (0.67-0.90)	
Acute kidney injury				
Overall	6.83	9.97	0.79 (0.62-1.01)	
PAD	11.30	10.84	1.16 (0.73-1.84)	0.064
No PAD	5.68	9.73	0.67 (0.50-0.90)	
Hyperkalemia				
Overall	11.58	15.18	0.86 (0.71-1.05)	
PAD	15.73	17.86	0.90 (0.62-1.32)	0.702
No PAD	15.51	14.46	0.85 (0.68-1.06)	
Diabetic ketoacidosis				
Overall	0.91	0.26	3.94 (1.50-10.36)	
PAD	0.75	0.27	3.41 (0.37-31.38)	0.792
No PAD	0.94	0.26	4.19 (1.43-12.30)	
Volume depletion				
Overall	21.10	15.51	1.29 (1.09-1.54)	0.237
PAD	26.33	15.48	1.51 (1.06-2.17)	
No PAD	19.76	15.52	1.23 (1.01-1.49)	
Osmotic diuresis				
Overall	18.80	6.68	2.22 (1.76-2.80)	
PAD	14.79	6.13	1.87 (1.09-3.21)	0.467
No PAD	19.85	6.82	2.30 (1.78-2.98)	
Hypoglycemia				
Overall	37.10	32.22	1.03 (0.91-1.17)	
PAD	37.68	28.51	1.14 (0.86-1.52)	0.395
No PAD	36.95	33.24	1.01 (0.88-1.16)	
Urinary tract infection				
Overall	34.36	29.44	1.09 (0.96-1.24)	
PAD	29.82	28.53	0.96 (0.72-1.29)	0.300
No PAD	35.55	29.69	1.12 (0.97-1.30)	
Male genital mycotic infection				

Overall	28.71	7.02	3.97 (3.09-5.10)	
PAD	24.48	4.76	4.67 (2.39-9.09)	0.446
No PAD	29.82	7.59	3.86 (2.94-5.06)	
Female genital mycotic infection				
Overall	38.77	7.65	3.92 (2.76-5.56)	
PAD	22.11	3.83	4.43 (1.53-12.83)	0.738
No PAD	42.74	8.70	3.84 (2.65-5.57)	

PAD, peripheral artery disease; CI, confidence interval.

Supplementary Table 4. Effects of canagliflozin on major cardiovascular and kidney endpoints in participants by PAD at baseline in the CANVAS, CANVAS-R and CREDENCE Trial.

	Hazard ratio (95% CI)	*P* value for heterogeneity
MACE		
CANVAS	0.88 (0.75-1.03)	
PAD	0.73 (0.52-1.02)	0.23
No PAD	0.92 (0.77-1.10)	
CANVAS-R	0.82 (0.66-1.01)	
PAD	0.77 (0.52-1.16)	0.74
No PAD	0.84 (0.65-1.07)	
CREDENCE	0.80 (0.67-0.95)	
PAD	0.76 (0.57-1.02)	0.79
No PAD	0.81 (0.65-1.01)	
Hospitalization for HF or cardiovascular death		
CANVAS	0.82 (0.67-0.99)	
PAD	0.71 (0.48-1.06)	0.43
No PAD	0.85 (0.67-1.06)	
CANVAS-R	0.72 (0.55-0.94)	
PAD	0.82 (0.53-1.29)	0.47
No PAD	0.67 (0.48-0.93)	
CREDENCE	0.69 (0.57-0.83)	
PAD	0.62 (0.45-0.84)	0.44
No PAD	0.73 (0.57-0.93)	
All-cause mortality		
CANVAS	0.84 (0.70-1.01)	
PAD	0.77 (0.52-1.12)	0.60
No PAD	0.86 (0.69-1.06)	
CANVAS-R	0.92 (0.70-1.21)	
PAD	0.76 (0.48-1.21)	0.27
No PAD	1.03 (0.73-1.46)	
CREDENCE	0.83 (0.68-1.02)	
PAD	0.81 (0.58-1.13)	0.93
No PAD	0.83 (0.64-1.08)	
Doubling of serum creatinine, ESKD, renal death or cardiovascular death		
CANVAS	0.80 (0.65-0.99)	
PAD	0.67 (0.44-1.02)	0.37
No PAD	0.83 (0.65-1.06)	
CANVAS-R	0.86 (0.62-1.18)	
PAD	0.86 (0.50-1.47)	0.96
No PAD	0.86 (0.58-1.28)	
CREDENCE	0.70 (0.59-0.82)	
PAD	0.69 (0.52-0.93)	1.00
No PAD	0.69 (0.57-0.85)	

Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, with stratification according to trial and history of cardiovascular disease.

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; HF, heart failure; ESKD, end-stage kidney disease.

Supplementary Figure 1. Absolute risk reduction in adverse events by PAD at baseline in the Pooled CANVAS Program and CREDENCE Trial

