

The effect of canagliflozin on amputation risk in the CANVAS Program and the CREDENCE trial

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ABSTRACT

Background

The SGLT2 inhibitor canagliflozin was associated with increased amputation risk in the CANVAS Program but not in CREDENCE. We explored possible explanations for these differences in amputation risk.

Methods

Patient characteristics associated with amputation risk were assessed in univariable and multivariable regression models and compared between studies. Effects of canagliflozin on amputation risk were determined from proportional hazards models and compared between studies, between subgroups, and for a range of amputation outcomes. Effects over time were explored by plotting cumulative event curves.

Findings

In the CANVAS Program (n=10,142; median follow-up 2·4y) and CREDENCE trial (n=4401; median follow-up 2·5y), 2·3% and 5·3% of participants, respectively, reported baseline amputation history. Key differences at baseline were the proportions with nephropathy (CREDENCE higher, 100% vs 17·5%) and cardiovascular disease (CANVAS Program higher, 66% vs 50%). There were 133 amputations in CREDENCE (3·0% annual event rate) and 187 amputations in CANVAS (1·8% annual event rate), with a prior amputation being the strongest predictor of future amputation in both groups. Effects of canagliflozin on amputation risk were significantly different between trials ($p_{\text{heterogeneity}} 0·02$, $I^2=82\%$), but this was not explained by participant or trial differences. There was no evidence that foot disease management protocols instituted during CREDENCE ameliorated amputation risk.

Interpretation

We identified no explanation for the difference in amputation risk between CREDENCE and the CANVAS Program. In the context of null effects of SGLT2 inhibition on amputation in CREDENCE and all other large trials, there is a possibility that the finding in CANVAS was the result of chance.

Funding

Janssen Research & Development, LLC

RESEARCH IN CONTEXT

Evidence before this study

In the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, the sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin reduced the risk of cardiovascular and renal events in participants with type 2 diabetes, but there was an almost two-fold increased risk of amputation. This risk was not anticipated based on the known mechanisms of action of SGLT2 inhibitors, and no such risk has been observed in large-scale randomised trials of other SGLT2 inhibitors testing empagliflozin and dapagliflozin. Furthermore, canagliflozin did not increase the risk of amputations in the subsequent Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, despite these participants being at a higher risk for this outcome. While a previous analysis of the CANVAS Program failed to identify a clear explanation for the observed risk of amputations, possible explanations for the discrepancy in amputation risk between the CANVAS Program and the CREDENCE trial have not been explored in detail.

Added value of this study

This joint analysis of the CANVAS Program and the CREDENCE trial, using individual participant data, did not identify a mechanism for the amputation risk observed in the CANVAS Program, nor did it provide a pathophysiological explanation as to why no similar risk was observed in CREDENCE. The predictors of amputation were similar in both datasets and were anticipated based on previous epidemiological data. There was no evidence that differences in participant characteristics between the trials explained the differences in amputation risk, nor was there any interaction between demographic, clinical, laboratory, or medication variables and treatment effect in the pooled dataset. Notably, there was no evidence that difference in follow-up affected amputation risk, or that the protocol amendment addressing foot care that was implemented during CREDENCE explained the null effect on amputations in that trial.

Implications of all the available evidence

Despite a comprehensive set of analyses, no explanation for the divergent effect on amputations between the CANVAS Program and the CREDENCE trial was identified. In the absence of any increased risk of amputation in other SGLT2 inhibitor trials, including a further large study of canagliflozin, these results increase the possibility that the findings of the CANVAS Program, while extreme, were the result of chance.

BACKGROUND

Sodium glucose co-transporter 2 (SGLT2) inhibitors provide clear cardiovascular and renal benefits in a broad range of patients with type 2 diabetes.¹⁻⁵ These medications have an excellent safety profile, with total serious adverse events reduced in all completed large trials. The key safety concern to date has been an increased risk of amputation observed in the CANVAS Program of canagliflozin (hazard ratio [HR] 1.97; 95% confidence interval [CI] 1.41, 2.75),^{2,6} though an amputation risk has not been identified in the other four large placebo-controlled randomised trials of SGLT2 inhibition completed to date.^{1,3,4,7} This includes the CREDENCE trial, a second large outcome study of canagliflozin, in which the HR for amputation was 1.11 (95% CI 0.79, 1.56).⁴ Extensive exploration of the CANVAS Program data identified no explanation for the increased risk of amputation, and there remains no explanation for why canagliflozin or any SGLT2 inhibitor should cause an increased risk of amputation.⁶ The goal of these analyses was to determine whether there was an explanation for why the effects of canagliflozin on amputation risk vary between the CANVAS Program and CREDENCE.

METHODS

This analysis combined data from the CANVAS Program and CREDENCE trial. The CANVAS Program is composed of the CANVAS and CANVAS-Renal (CANVAS-R) trials, which defined the initial cardiovascular safety and efficacy of canagliflozin compared with placebo in 10,142 participants. It was done in 667 centres across 30 countries.² CREDENCE was a placebo-controlled trial of canagliflozin that was undertaken subsequently in 4401 patients with type 2 diabetes and nephropathy at 690 sites in 34 countries. CREDENCE proved a beneficial effect of canagliflozin on the primary composite outcome of end-stage kidney disease, doubling of serum creatinine, or death due to a renal or cardiovascular cause.⁴ All trials were approved by the ethics committees at every site, and all participants provided written informed consent. All procedures were in accordance with the Helsinki Declaration of 1964, as revised in 2013. A detailed description of study design, characteristics of participants, randomised treatment, and the main results of the CANVAS Program⁸⁻¹¹ and CREDENCE trial^{4,12} have been published previously.

Participants

Participants in the CANVAS Program were men and women with type 2 diabetes mellitus and HbA1c $\geq 7.0\%$ and $\leq 10.5\%$. Those enrolled were aged ≥ 30 years with a history of symptomatic atherosclerotic cardiovascular disease (CVD; which included prior amputation) or aged ≥ 50 years with ≥ 2 CVD risk factors.² The presence of amputation or peripheral arterial disease (PAD) history at baseline was based upon physician reporting, with no requirement for specific clinical evaluation or imaging.⁶

Participants in the CREDENCE trial were men and women with type 2 diabetes, chronic kidney disease (eGFR 30 to <90 mL/min/1.73m²) and albuminuria (urine albumin:creatinine ratio >300 to 5,000mg/g). There was a prespecified plan to include approximately 60% of participants with a baseline eGFR 30 to <60 mL/min/1.73m².¹² As with the CANVAS Program, a history of amputation or PAD at baseline was based on physician reporting. A history of atraumatic amputation was added as an exclusion to participation in CREDENCE through a protocol update (Amendment INT-5) implemented about three-quarters of the way through enrollment (06 May 2016) once the amputation risk in the CANVAS Program was identified.

Randomised Treatment

Participants in CANVAS were randomised (1:1:1) to receive canagliflozin 300mg, canagliflozin 100mg, or matching placebo, whereas participants in CANVAS-R were randomised (1:1) to receive canagliflozin or matching placebo (initially 100mg with optional uptitration to 300mg). All participants in CREDENCE were randomised (1:1) to canagliflozin 100mg or placebo.

Follow-up

Participants in the CANVAS Program and CREDENCE trial were scheduled for face-to-face follow-up at least once every 6 months, with an additional telephone follow-up made between each face-to-face appointment. Serious adverse events were assessed at all follow-up occasions in both cases. Amputations were initially recorded by the investigators using the standard electronic case record forms for the capture of adverse events and/or diagnostic and therapeutic procedures. In May 2016, following notification of the amputation safety signal, a dedicated case report form was created to ensure systematic and standardised data collection for amputation events in the CANVAS Program and CREDENCE trial. Investigators were required to complete the dedicated amputation case report form for every new event, as well as retrospectively for every amputation event already recorded, which occurred post randomization. Additionally, participant case records and the associated pharmacovigilance database were searched using the text strings ‘ampu’, ‘remov’, ‘resection’, ‘necrosectomy’, ‘disarticulation’, ‘exarticulation’, ‘BKA’, and ‘AKA’ to identify any additional possible amputation events. Information regarding date, location (right or left, toes, trans-metatarsal, ankle, below knee or above knee, other), and aetiology of amputation (traumatic or atraumatic, infectious, chronic, or acute ischaemic) was recorded for all trials. Amputation events occurring at any time point prior to final follow-up, for all randomised participants regardless of whether the participant remained on the study drug, were captured.

Outcomes

In these secondary analyses, the main outcome was all atraumatic lower extremity amputations. Separate reporting was done for all major atraumatic lower extremity amputations (at or above ankle) and all minor atraumatic lower extremity amputations (below ankle).

Statistical Analysis

Participant characteristics were compared overall for each trial, for patients who experienced amputation during follow-up and for patients who did not. Prevalence and levels of risk factors were presented as proportions or means, with differences evaluated using chi-square tests for categorical variables and *t* tests for continuous variables. For these and all subsequent statistical tests, $p < 0.05$ was deemed likely to reflect differences beyond chance, though all results were interpreted in light of the multiple comparisons made.

The associations of baseline participant characteristics with amputation risk were assessed separately for the CANVAS Program and CREDENCE trial using proportional hazards models with HRs and 95% CIs estimated. First, univariable associations were determined for each candidate risk factor, and then those risk factors with significant univariable associations were included in a single multivariable model. Where a single risk was assessed using multiple measures (eg, glucose and HbA1c were both measures of glycaemia), the risk with the greatest HR was carried forward for inclusion in the multivariate modelling. To determine whether there were differences in the associations of baseline risk factors with amputation

between the CANVAS Program and CREDENCE trial, univariable models were fit with trial×risk factor interaction terms included.

The effects of canagliflozin on amputation risk were assessed separately for the CANVAS Program and CREDENCE trial using proportional hazards models to obtain HRs and 95% CIs for each. A test of proportional hazards was used to examine the evolution of the treatment effects over time. Differences in the effects of canagliflozin between the CANVAS Program and CREDENCE trial were quantified by fitting a trial×treatment interaction term. The constancy of effects was also evaluated by assessing the percentage of variability across the pooled estimates attributable to heterogeneity beyond chance using the I^2 statistic. An I^2 statistic of 0%-25% was considered to reflect a low likelihood, 26%-75% a moderate likelihood, and 76%-100% a high likelihood of differences beyond chance.

Evidence for modification of the effects of canagliflozin on amputation risk by baseline participant characteristics were also explored separately for each trial and in the combined dataset by fitting proportional hazards models that included treatment, baseline characteristic, and treatment×baseline characteristic interaction terms.

A landmark analysis was done to assess the effect of the CREDENCE trial protocol change on the risk of amputation observed in the trial. Briefly, this was achieved by estimating the effects of canagliflozin on amputation risk using all participant time and events up to the date that the protocol change was implemented, and then repeating the analysis using only the participant time and events after the date of the protocol change. The HRs and CIs obtained before and after the protocol change were compared. A sensitivity analysis was also done using a date 2 months after the protocol change to allow for any lag in implementation effects.

We also did a fragility analysis to better understand the robustness of the finding.¹³ Amputation events were sequentially added to the placebo group, and the HRs, CIs, and p-values recalculated until the p-value became nonsignificant. In addition, since randomisation ratios were unequal, we also repeated the process by subtracting events from the control group.

Analyses were performed using SAS version 9·2 (SAS Institute, Cary, NC, USA), SAS Enterprise Guide version 7·1 (SAS Institute), and STATA version 13·1 (StataCorp, College Station, TX, USA).

RESULTS

There were 10,142 participants in the CANVAS Program, of which 10,134 (>99%) received ≥1 dose of randomised treatment, and there were 4401 participants in CREDENCE of which 4397 (>99%) received ≥1 dose of randomised treatment. Median follow-up was 2·4 years in the CANVAS Program and 2·5 years in CREDENCE. The CREDENCE trial was stopped early in October 2018 for canagliflozin benefit at a prespecified interim analysis on the guidance of the Independent Data and Safety Monitoring Committee.

Participant Characteristics

CANVAS Program participants were 35·8% female, with a mean age 63·3 years, and CREDENCE trial participants were 33·9% female, with a mean age 63·0 years (Table 1). Participant characteristics exhibited multiple statistical differences between the two trials, reflecting the large sample sizes, but trial populations were mostly similar. Key exceptions

were CVD history at baseline (65·6% in the CANVAS Program versus 50·4% in CREDENCE) and chronic kidney disease at baseline (17·5% nephropathy and 20·1% eGFR <60 mL/min/1·73m² in the CANVAS Program versus 100·0% nephropathy and 59·8% eGFR <60 mL/min/1·73m² in CREDENCE). In the CANVAS Program, 2·3% of patients had a history of amputation at trial entry versus 5·3% in CREDENCE.

Characteristics of patients who experienced amputation and association between baseline characteristics and amputation risk

There were 187 (1·8%) patients in the CANVAS Program (140 in the canagliflozin group, 47 in the placebo group) who had an amputation during follow-up (Table 1), with an absolute event rate of 6·3 versus 3·4 per 1000 patient-years in the canagliflozin- and placebo-treated arms, respectively. In CREDENCE, there were 133 (3·0%) patients with an amputation (70 in the canagliflozin group, 63 in the placebo group), with absolute event rates of 12·3 versus 11·2 per 1000 patient-years in the canagliflozin- and placebo-treated arms, respectively. In both trials, those who experienced an amputation were more likely to be male, have pre-existing atherosclerotic disease, have a microvascular complication of diabetes, and have a history of amputation. With respect to baseline markers of cardiovascular risk, those who experienced an amputation displayed a higher body mass index, systolic blood pressure, HbA1c, and serum LDL than those who didn't. They were also more likely to be taking insulin, loop diuretics, β blockers, and aspirin at entry to the trial. There were no large differences in the baseline characteristics of those who did and did not experience amputation between the CANVAS Program and CREDENCE trial (Table 1).

Regression models (Table 2) identified multiple anticipated baseline characteristics associated with the risk of amputation, including a history of prior amputation or CVD, male sex, HbA1c >8%, and microvascular disease. Previous amputation was the most powerful predictor of subsequent amputation. There was some evidence that the associations for these risks varied between the CANVAS Program and CREDENCE trial for smoking, albuminuria, and prior amputation. Current smoking was not significantly associated with amputation risk in either study, but the point estimate of effect in the CANVAS Program (HR 1·11; 95% CI 0·77, 1·59) was directionally different from that observed in CREDENCE (HR 0·59; 95% CI 0·32, 1·06), with *p* heterogeneity of 0·03. For both albuminuria and prior amputation, there were positive associations with amputation risk, but both were stronger in the CANVAS Program versus CREDENCE, with *p* heterogeneity of 0·04 and 0·01, respectively. In all cases, the strengths of association were more comparable in the multivariable analyses. The baseline variable for which there was strongest evidence of a difference in effect between the CANVAS Program and CREDENCE trial was randomisation to canagliflozin, with the difference between trials persisting in the multivariable analyses (*p* for heterogeneity 0·02).

Canagliflozin and amputation risk

Cox regression analyses identified differences between the effects of canagliflozin on the risk of amputation in the CANVAS Program (HR 1·97; 95% CI 1·41, 2·75) and CREDENCE trial (HR 1·11; 95% CI 0·79, 1·55), with *p* heterogeneity of 0·02 and an *I*² of 82% (Figure 1). There was no overall increase in the risk of major amputation (HR 1·18; 95% CI 0·78, 1·78), but there was a difference between trials (*p* heterogeneity 0·03; *I*² = 80%) resulting from an increased risk in the CANVAS Program but not CREDENCE. There was an overall increased risk in minor amputation (HR 1·51; 95% CI 1·14, 2·00) with moderate evidence of differences between studies (*p* heterogeneity 0·07; *I*² = 70%), with adverse effects in the CANVAS Program but not in CREDENCE. Both the 100mg and 300mg doses of canagliflozin were associated with an increase in amputation risk in the CANVAS trial, but

there was no increased risk with the 100mg dose in CREDENCE. Within the CANVAS trial, where there was randomisation to canagliflozin 100mg versus 300mg, the risk of amputation with the 100mg versus 300mg dose was not different (HR 1.11; 95% CI 0.75, 1.67). Cumulative event curves for all amputation, minor amputation, and major amputation in the CANVAS Program and CREDENCE are shown in Figure 2.

An analysis of patient subgroups was performed to determine whether there were interactions of baseline participant characteristic with the effects of canagliflozin that might explain the amputation risk in the CANVAS Program or the difference in amputation risk between the CANVAS Program and CREDENCE trial. These subgroups comprised multiple measures, including age, sex, baseline medical history, physical assessments, biological markers, and medications. There was no evidence that the effect of canagliflozin on amputation risk was driven by any participant characteristic, with all p interaction values but one being nonsignificant in the CANVAS Program, CREDENCE, and the combined trial datasets. The one exception was baseline use of antithrombotic therapy in the CANVAS Program where those who were not taking antithrombotics at baseline had a greater risk of amputation than those who were (p interaction 0.03; Table 3).

Effects of the protocol update on amputation risk in the CREDENCE trial

The CREDENCE trial protocol update instigated by the reported adverse effect of canagliflozin on amputation in the CANVAS Program was implemented on 6 May 2016. Following the protocol update, there were 130 participants (3.0%) recorded as permanently discontinuing study drug for reasons related to amputation risk: 20 due to a perceived risk and 110 as a result of a lower limb adverse event.

A landmark analysis identified no increase in amputation risk in those treated with canagliflozin versus placebo prior to the protocol change or after the protocol change (HR 1.03; 95% CI 0.70, 1.54 versus HR 1.34; 95% CI 0.69, 2.66), with no statistical evidence of a difference in effect before and after the protocol amendment (p interaction 0.51; Figure 3). This conclusion was unchanged if the landmark analysis was repeated for a date two months later.

Fragility analysis findings

The HR for amputation in the CANVAS Program became nonsignificant (1.29; 95% CI 1.00, 1.67; p=0.055) if the number of events in the placebo group was increased by 32, from 47 to 79 while holding the number of events in the active group constant. Correspondingly, it was necessary to decrease the number of events in the active group by 43, from 140 to 97, to achieve a nonsignificant HR for amputation (1.28; 95% CI 0.99, 1.65; p=0.058).

DISCUSSION

Extensive investigation of the joint CANVAS Program and CREDENCE trial datasets has confirmed differences in amputation risk between the trials but failed to identify biologically or clinically plausible reasons for the amputation risk observed in the CANVAS Program.⁶ Nor has it been possible to provide an explanation for why the effect of canagliflozin on amputation risk varies between the two datasets. In particular, there was no evidence that the main difference between the studies, the proportions of patients with nephropathy and the proportions of patients with established CVD, were reasons for the observed variation in effects on amputation risk. In addition, the analyses were unable to identify any impact of canagliflozin dose or the protocol amendment implemented in the CREDENCE trial designed to minimise amputation risk on the differences observed between the CANVAS Program and

the CREDENCE trial. While it remains possible that some unidentified factor has resulted in the differences in the effects of canagliflozin on amputation risk between the CANVAS Program and the CREDENCE trial, there is a possibility that the CANVAS amputation finding may have occurred due to chance.

It was not surprising that the differences in baseline characteristics between the CANVAS Program and the CREDENCE trial failed to explain the variation in amputation risk between the studies. There is no biological rationale for an interaction of CVD history or chronic kidney disease with the effect of canagliflozin on amputation risk, but the question warranted specific investigation as the most widely postulated explanation for the differences observed. It is of note that detailed prior analyses of the CANVAS Program data did not identify any effect of these or other participant characteristics on amputation risk, and also that overall statistically significant amputation risks were absent in all other trials of SGLT2 inhibitors.^{1,3,7} There have been some secondary analyses of participant subsets in other trials that have identified numeric imbalances in amputation risk for particular subgroups,¹⁴⁻¹⁷ but no clear pattern has emerged and the robustness of those observations is uncertain.

It is also clear from these analyses that the protocol update in the CREDENCE trial mandating lower limb assessments and precluding individuals with prior amputation from inclusion in the study was not the reason for the absent risk of amputation—the relative risk of amputation with the use of canagliflozin compared to placebo was nonsignificant both before and after implementation of the protocol update and there was no evidence of a change in risk. A strategy of regular foot care for all patients using canagliflozin remains a reasonable practical recommendation, with consideration of interruption of therapy if a limb event threatens,⁶ but the available data do not provide strong evidence that this is a mechanism by which amputation is averted amongst patients using SGLT2 inhibitors.

Statistical power to detect an adverse effect of canagliflozin on amputation risk in CREDENCE was comparable to that in the CANVAS Program despite the smaller sample size and the shorter duration of follow-up. Overall absolute rates for amputation were higher in CREDENCE than in the CANVAS Program (3.0% versus 1.8% per annum), reflecting the greater vascular disease burden of participants at trial entry. Cumulative event curves for amputation separated early in the CANVAS Program and the shorter mean follow-up in CREDENCE do not explain why an amputation risk was observed in the CANVAS Program but not in the CREDENCE trial. Further, the equal randomisation ratio in CREDENCE enhanced statistical power compared to the CANVAS Program in which there were fewer participants assigned to placebo than to active therapy.

Non-randomised real-world datasets have not been able to resolve the uncertainty regarding the effects of canagliflozin on amputation risk, with a range of different findings reported. The EASEL study identified an increased risk of below-knee amputation risk in those using SGLT2 inhibitors that appeared to be primarily attributable to canagliflozin,¹⁸ but a subsequent US-based cohort of 73,024 individuals identified no increased risk in users of the drug.¹⁹ The OBSERVE-4D meta-analysis of observational datasets (including 142,800 patients using canagliflozin treatment) also failed to identify an increased risk of amputation.²⁰ A key challenge of these datasets is the high risk of confounding by indication for therapy, and the likelihood that such confounding will change over time as clinicians modify their practice based upon evolving reports about the benefits and risks of the class as a whole, and specific drugs in particular.

A mechanism by which SGLT2 inhibition with canagliflozin might confer an elevated risk of amputation remains unclear. Hypovolaemia resulting in haemoconcentration and hypoperfusion has been suggested as a possible pathological pathway, but every SGLT2 inhibitor produces such effects and it is only the CANVAS Program in which an adverse signal has been recorded. Furthermore, those on concomitant diuretics were not at a greater risk, as might be anticipated if this were the causal pathway. Prior to the reporting of CREDENCE, while no mechanism for the causation of amputation with canagliflozin could be identified, it was possible that there was some idiosyncratic canagliflozin-specific mechanism that caused the risk. Now, with different effects on amputation observed not just between studies using different drugs, but also between different studies of canagliflozin, the possible explanations for the increased risk of amputation in the CANVAS Program are further restricted.

The effect observed in the CANVAS Program was extreme and is statistically robust by standard measures. However, the divergent findings of the CANVAS Program compared to the CREDENCE trial and trials of other SGLT2 inhibitors increase the possibility that the CANVAS Program result was a chance observation. Counter to this argument is the observation that amputation risk appeared to be increased in both the CANVAS trial and the CANVAS-R trial, the two constituent studies that made up the CANVAS Program. Chance findings in large-scale outcome trials are increased by serial monitoring of data and, while unusual, can occur even when large numbers of individuals are included. Second trials that are able to address the compelling but not prespecified observations made in first studies can provide a useful test of the likely validity of the initial observation. The interaction observed for effects of cholesterylester transfer protein (CETP) inhibition on cardiovascular outcomes according to ADCY9 genotype reported from initial studies, for example, being recently refuted by a subsequent large-scale trial able to robustly test the hypothesis generated by the first.²¹

CONCLUSION

We identified no explanation for the difference in amputation risk between the CREDENCE trial and the CANVAS Program. There are now four completed large trials in addition to the CANVAS Program, none of which demonstrate an increased risk of amputation. Since these include a further large trial of canagliflozin, there is an increased possibility that the finding for the CANVAS Program, while extreme, was the result of chance. It remains possible that the effect of canagliflozin on amputation risk was real and additional data from ongoing trials of SGLT2 inhibitors will provide further insight into the likely explanation for the CANVAS Program observation.

Acknowledgements

The authors thank all investigators, study teams, and patients for participating in these studies. Technical editorial support was provided by Alaina Mitsch, PhD, of MedErgy, and was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

Declaration of interests

C. Arnott, Y. Huang, and G.L. Di Tanna are employees of the George Institute. B.L. Neuen is supported by an Australian National Health and Medical Research Council Postgraduate Scholarship and a University Postgraduate Award from the University of New South Wales; he has received travel support from Janssen. C.P. Cannon has received research grants from

Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Merck, Janssen, and Takeda; and has received consulting fees from Aegerion, Alnylam, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Corvidia, GlaxoSmithKline, Innovent, Eisai, Eli Lilly, Kowa, Merck, Pfizer, Regeneron, and Sanofi. R. Oh, G. Capuano, R. Edwards, M. Kavalam, and N. Rosenthal are full-time employees of Janssen Research & Development, LLC. V. Perkovic has received fees for Advisory Boards, Steering Committee roles, or Scientific Presentations from Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Vifor, and Tricida. M.J. Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Baxter, Amgen, Eli Lilly, and Merck Sharpe Dohme; serves on a Steering Committee sponsored by CSL, has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen; with any consultancy, honoraria, or travel support paid to her institution. K.W. Mahaffey has received research support from Afferent, Amgen, Apple, Inc, AstraZeneca, Cardiva Medical, Inc, Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health (NIH), Novartis, Sanofi, St. Jude, and Tenax; and has served as a consultant (speaker fees for CME events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and UCSF. B. Neal is supported by an Australian National Health and Medical Research Council Principal Research Fellowship; holds a research grant for this study from Janssen; and has held research grants for other large-scale cardiovascular outcome trials from Roche, Servier, and Merck Schering Plough; and his institution has received consultancy, honoraria, or travel support for contributions he has made to advisory boards and/or the continuing medical education programs of Abbott, Janssen, Novartis, Pfizer, Roche, and Servier.

Sources of funding

These studies were supported by Janssen Research & Development, LLC.

Role of the funding source

The sponsor was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Author contributions

C. Arnott, B. Neuen, C.P. Cannon, N. Rosenthal, V. Perkovic, M. Jardine, K.W. Mahaffey, and B. Neal contributed to the design and conduct of the study and the interpretation of the data. Y. Huang and G. Capuano contributed to the analysis and interpretation of data. G.L. Di Tanna, R. Oh, R. Edwards, and M. Kavalam contributed to the interpretation of the data. C. Arnott and B. Neal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Data from the CANVAS Program will be made available in the public domain via the Yale University Open Data Access Project (YODA; <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.

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Table 1: Baseline Characteristics of Participant With and Without Amputation in the CANVAS Program and the CREDENCE Trial

	CANVAS Program		All	CREDENCE		All	P-value All CANVAS vs. all CREDENCE
	With amputation (n=187)	Without amputation (n=9947)		With amputation (n=133)	Without amputation (n=4264)		
Age, years, mean (SD)	62·0 (6·9)	63·3 (8·3)	63·3 (8·2)	60·7 (8·0)	63·1 (9·2)	63·0 (9·2)	0·05
Female sex, n (%)	32 (17·1)	3599 (36·2)	3631 (35·8)	28 (21·1)	1464 (34·3)	1492 (33·9)	0·03
Race, n (%)							
White	164 (87·7)	7774 (78·2)	7938 (78·3)	97 (72·9)	2831 (66·4)	2928 (66·6)	<0·0001
Asian	10 (5·3)	1274 (12·8)	1284 (12·7)	12 (9·0)	865 (20·3)	877 (19·9)	<0·0001
Black	3 (1·6)	332 (3·3)	335 (3·3)	6 (4·5)	217 (5·1)	223 (5·1)	<0·0001
Other	10 (5·3)	567 (5·7)	577 (5·7)	18 (13·5)	351 (8·2)	369 (8·4)	<0·0001
Current smoker, n (%)	36 (19·3)	1766 (17·8)	1802 (17·8)	12 (9·0)	627 (14·7)	639 (14·5)	<0·0001
Hypertension, n (%)	165 (88·2)	8953 (90·0)	9118 (90·0)	130 (97·7)	4126 (96·8)	4256 (96·8)	<0·0001
Duration of diabetes, years	16·3 (8·6)	13·5 (7·7)	13·5 (7·8)	16·7 (8·2)	15·8 (8·6)	15·8 (8·6)	<0·0001
Microvascular disease							
Nephropathy, n (%)	56 (29·9)	1716 (17·3)	1772 (17·5)	133 (100)	4246 (100)	4397 (100)	<0·0001
Retinopathy, n (%)	69 (36·9)	2058 (20·7)	2127 (21·0)	76 (57·1)	1806 (42·4)	1882 (42·8)	<0·0001
Neuropathy, n (%)	111 (59·4)	2998 (30·1)	3109 (30·7)	94 (70·7)	2049 (48·1)	2143 (48·7)	<0·0001
Atherosclerotic disease							
Coronary, n (%)	111 (59·4)	5606 (56·4)	5717 (56·4)	47 (35·3)	1265 (29·7)	1312 (29·8)	<0·0001
Cerebrovascular, n (%)	45 (24·1)	1911 (19·2)	1956 (19·3)	19 (14·3)	681 (16·0)	700 (15·9)	<0·0001
Peripheral, n (%)	113 (60·4)	1998 (20·1)	2111 (20·8)	95 (71·4)	949 (22·3)	1044 (23·7)	0·0001
Any, n (%)	172 (92·0)	7146 (71·8)	7318 (72·2)	110 (82·7)	2108 (49·4)	2218 (50·4)	<0·0001
CVD at entry, n (%)	154 (82·4)	6497 (65·3)	6651 (65·6)	110 (82·7)	2108 (49·4)	2218 (50·4)	<0·0001
Atrial fibrillation, n (%)	18 (9·6)	595 (6·0)	613 (6·0)				
Heart failure, n (%)	35 (18·7)	1424 (14·3)	1459 (14·4)	25 (18·8)	627 (14·7)	652 (14·8)	0·5
Amputation, n (%)	51 (27·3)	186 (1·9)	237 (2·34)	51 (38·3)	183 (4·3)	234 (5·3)	<0·0001
BMI, kg/m ² , mean (SD)	32·7 (6·1)	31·9 (5·9)	32·0 (5·9)	31·9 (7·1)	31·3 (6·1)	31·3 (6·2)	<0·0001
SBP, mmHg, mean (SD)	137·6	136·6	136·6	141·4	139·9	140·0	<0·0001
DBP, mmHg, mean (SD)	77·5 (9·6)	77·7 (9·7)	77·7 (9·7)	79·6 (8·8)	78·3 (9·4)	78·3 (9·4)	0·0005
HbA1c, %, mean (SD)	8·5 (0·9)	8·2 (0·9)	8·3 (1·0)	8·5 (1·3)	8·2 (1·3)	8·3 (1·3)	0·6
LDL cholesterol, mmol/L, mean	2·4 (1·0)	2·3 (0·9)	2·3 (0·9)	2·7 (1·1)	2·5 (1·1)	2·5 (1·1)	<0·0001
LDL/HDL cholesterol ratio, mean (SD)	2·1 (0·9)	2·0 (0·9)	2·0 (0·9)	2·6 (1·1)	2·3 (1·1)	2·3 (1·1)	<0·0001
eGFR, mL min ⁻¹ [1·73 m] ⁻² , mean (SD)	72·7 (19·6)	76·5 (20·5)	76·5 (20·5)	58·7 (20·2)	56·1 (18·2)	56·2 (18·2)	<0·0001
Micro- or macroalbuminuria, n (%)	95 (51·4)	2928 (29·7)	3023 (30·1)	133 (100)	4264 (100)	4397 (100)	<0·0001
UACR, mg/mmol, median (IQR)	3·73 (1·31, 17·1)	1·37 (0·75, 4·59)	1·39 (0·75, 4·76)	136·3 (69·7, 239·2)	104·0 (52·0, 204·3)	104·9 (52·4, 207·7)	<0·0001
Concomitant drug therapies, n (%)							
Insulin	131 (70·1)	4962 (49·9)	5093 (50·3)	100 (75·2)	2782 (65·2)	2882 (65·5)	<0·0001
Metformin	129 (69·0)	7691 (77·3)	7820 (77·2)	72 (54·1)	2471 (58·0)	2543 (57·8)	<0·0001
Sulphonylurea	69 (36·9)	4290 (43·1)	4359 (43·0)	35 (26·3)	1232 (28·9)	1267 (28·8)	<0·0001
GLP-1 receptor agonist	10 (5·3)	397 (4·0)	407 (4·0)	5 (3·8)	178 (4·2)	183 (4·2)	0·68
DPP-4 inhibitor	17 (9·1)	1244 (12·5)	1261 (12·4)	17 (12·8)	734 (17·2)	751 (17·1)	<0·0001
Loop diuretic	41 (21·9)	1267 (12·7)	1308 (12·9)	42 (31·6)	912 (21·4)	954 (21·7)	<0·0001
Non-loop diuretic	70 (37·4)	3576 (36·0)	3646 (36·0)	40 (30·1)	1230 (28·8)	1270 (28·9)	<0·0001
Calcium channel blocker	69 (36·9)	3374 (33·9)	3443 (34·0)	58 (43·6)	2071 (48·6)	2129 (48·4)	<0·0001
RAS inhibitor	148 (79·1)	7965 (80·1)	8113 (80·1)	133 (100)	4258 (99·9)	4391 (99·9)	<0·0001
β blocker	109 (58·3)	5311 (53·4)	5420 (53·5)	62 (46·6)	1707 (40·0)	1769 (40·2)	<0·0001
Statin	137 (73·3)	7459 (75·0)	7596 (75·0)	91 (68·4)	2943 (69·0)	3034 (69·0)	<0·0001
Aspirin	87 (46·5)	2862 (28·8)	2949 (29·1)	87 (65·4)	2362 (55·4)	2449 (55·7)	<0·0001
Other antithrombotic	65 (34·8)	4453 (44·8)	4518 (44·6)	5 (3·8)	167 (3·9)	172 (3·9)	<0·0001

SD: standard deviation; CVD: cardiovascular disease; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycosylated haemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urine albumin creatinine ratio; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; RAS: renin-angiotensin system.

Table 2: The Association of Baseline Characteristics With Amputation Risk

	CANVAS Program, HR (95% CI)		CREDENCE, HR (95% CI)		p interaction CANVAS Program vs CREDENCE
	Univariate	Multivariate	Univariate	Multivariate	
Demographics					
Male sex	2·63 (1·80, 3·85)	2·26 (1·53, 3·35)	1·92 (1·27, 2·92)	2·01 (1·30, 3·11)	0·27
Age (per 1 year older)	0·98 (0·97, 1·00)		0·97 (0·96, 0·99)	0·97 (0·96, 0·99)	0·17
Current smoker	1·11 (0·77, 1·59)		0·59 (0·32, 1·06)		0·03
Race					
White vs non-white	2·18 (1·41, 3·38)		1·31 (0·89, 1·92)		0·09
Asian vs non-Asian	0·32 (0·17, 0·61)	0·44 (0·23, 0·85)	0·41 (0·23, 0·74)		0·57
Black vs non-Black	0·59 (0·19, 1·86)		0·86 (0·38, 1·95)		0·60
Comorbidities					
Prior amputation	21·31 (15·40, 29·49)	16·27 (10·75, 24·63)	12·86 (9·06, 18·25)	14·50 (7·89, 26·65)	0·04
Peripheral vascular disease	2·51 (1·85, 3·41)	2·77 (1·93, 3·96)	2·26 (1·58, 3·25)	3·82 (2·11, 6·93)	0·66
Cardiovascular disease	2·85 (1·95, 4·16)	1·52 (1·01, 2·27)	4·83 (3·08, 7·57)		0·08
Hypertension	0·91 (0·58, 1·42)		1·36 (0·43, 4·29)		0·52
Heart failure	1·52 (1·05, 2·19)		1·35 (0·87, 2·09)		0·71
Microvascular disease					
Neuropathy	3·38 (2·52, 4·52)	1·86 (1·35, 2·56)	2·59 (1·78, 3·76)	1·59 (1·06, 2·38)	0·52
Nephropathy	2·18 (1·60, 2·99)		NA		
Retinopathy	2·27 (1·69, 3·06)		1·81 (1·29, 2·55)		
Albuminuria	2·65 (1·99, 3·54)	1·63 (1·20, 2·22)	1·52 (1·08, 2·14)	1·41 (1·00, 2·00)	0·01
Duration of diabetes mellitus	1·04 (1·03, 1·06)		1·01 (0·99, 1·03)		0·82
Concomitant medications					
Insulin	2·37 (1·73, 3·24)		1·64 (1·10, 2·43)		0·16
Sulphonylurea	0·72 (0·53, 0·97)		0·86 (0·58, 1·26)		0·59
Metformin	0·68 (0·50, 0·93)		0·85 (0·60, 1·19)		0·53
GLP-1 receptor antagonist	1·59 (0·84, 3·03)		0·86 (0·35, 2·10)		0·27
DPP-4	0·83 (0·50, 1·37)		0·69 (0·41, 1·15)		0·60
Diuretic	1·26 (0·95, 1·68)		1·41 (1·00, 1·98)	1·46 (1·02, 2·07)	0·71
Statin	0·94 (0·68, 1·30)		0·94 (0·65, 1·36)		0·96
Aspirin	1·34 (0·89, 2·03)		1·51 (1·05, 2·16)		0·67
Any antithrombotic	1·70 (1·04, 2·80)		0·97 (0·40, 2·36)		0·28
RAS inhibitor	0·93 (0·66, 1·33)		NA		
β blocker	1·28 (0·96, 1·71)		1·28 (0·91, 1·80)		1·0
Calcium channel blocker	1·17 (0·87, 1·57)		0·81 (0·58, 1·15)		0·31
Laboratory and clinical variables					
HbA1c (<8% vs ≥8%)	2·12 (1·54, 2·93)	1·99 (1·43, 2·76)	2·25 (1·54, 3·28)	2·04 (1·39, 3·00)	0·72
Haemoglobin (1 g/L greater)	1·00 (0·99, 1·01)		1·00 (0·99, 1·00)		1·0
eGFR (1 mL/min greater)	0·99 (0·98, 1·00)		1·01 (1·00, 1·02)		0·10
SBP (1 mmHg greater)	1·00 (1·00, 1·01)		1·01 (0·99, 1·02)		0·33
Haematocrit (1% greater)	1·00 (0·97, 1·04)		0·99 (0·96, 1·02)		0·65
BMI (1 kg/m ² greater)	1·02 (1·00, 1·04)		1·01 (0·99, 1·04)		0·68
LDL cholesterol (0·026 mmol/L greater)	1·08 (0·93, 1·26)		1·19 (1·03, 1·38)		0·53

HDL cholesterol (0·026 mmol/L greater)	0·74 (0·45, 1·19)		0·59 (0·34, 1·02)	0·49
Triglycerides (0·011 mmol/L greater)	1·07 (1·00, 1·15)		0·95 (0·84, 1·07)	0·66
Canagliflozin treatment	1·97 (1·41, 2·75)	1·82 (1·29, 2·56)	1·11 (0·79, 1·55)	0·02

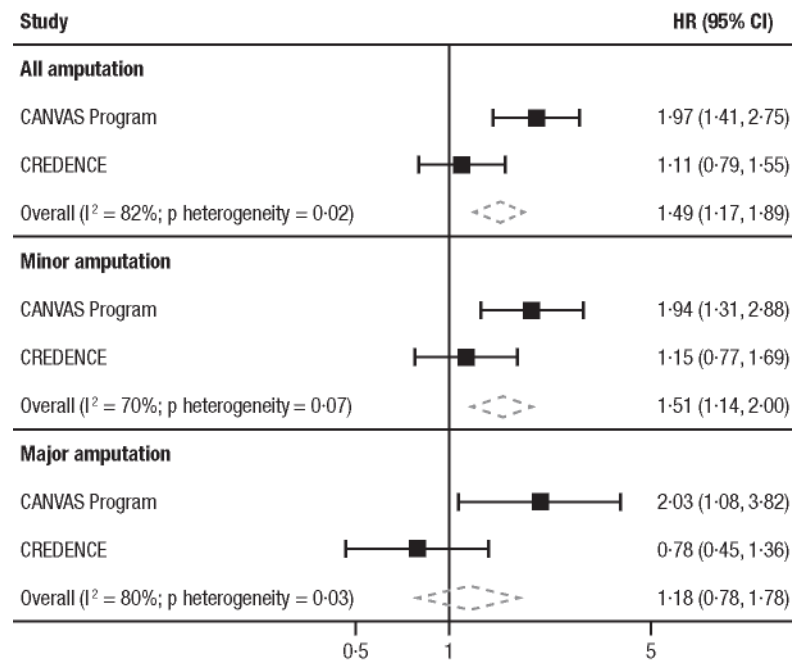
HR: hazard ratio; CI: confidence interval; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; RAS: renin-angiotensin system; HbA1c: glycosylated haemoglobin; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 3: Risk of Amputation With Canagliflozin Compared to Placebo in Participant Subgroups

	CANVAS Program	p inter- action	CREDENCE	p inter- action	Combined	p inter- action
Demographics						
Age <65 years	1.74 (1.16, 2.63)	0.37	1.01 (0.67, 1.52)	0.43	1.25 (0.94, 1.65)	0.17
Age ≥65 years	2.48 (1.39, 4.43)		1.39 (0.71, 2.43)		1.77 (1.18, 2.66)	
Male	1.77 (1.24, 2.53)	0.15	1.11 (0.76, 1.63)	0.99	1.34 (1.04, 1.73)	0.39
Female	3.50 (1.33, 9.16)		1.11 (0.53, 2.34)		1.75 (1.00, 3.02)	
Disease history						
CVD Yes	2.07 (1.43, 3.00)	0.63	1.11 (0.76, 1.61)	0.90	1.43 (1.11, 1.85)	0.74
CVD No	1.52 (0.70, 3.29)		1.09 (0.48, 2.47)		1.29 (0.74, 2.23)	
PVD Yes	1.39 (0.80, 2.40)	0.29	1.12 (0.75, 1.68)	0.77	1.32 (1.0, 1.76)	0.41
PVD No	2.34 (1.53, 3.58)		1.0 (0.53, 1.89)		1.62 (1.08, 2.43)	
Amputation Yes	2.15 (1.11, 4.19)	0.79	0.82 (0.47, 1.42)	0.22	1.19 (0.80, 1.77)	0.32
Amputation No	1.88 (1.27, 2.78)		1.28 (0.83, 1.98)		1.52 (1.15, 2.03)	
Nephropathy Yes	1.64 (0.91, 2.95)	0.58	1.11 (0.79, 1.56)	NA	1.22 (0.91, 1.63)	NA
Nephropathy No	2.13 (1.42, 3.20)		—		—	
Retinopathy Yes	1.87 (1.09, 3.20)	0.56	0.95 (0.61, 1.49)	0.31	1.25 (0.89, 1.76)	0.17
Retinopathy No	2.04 (1.33, 3.13)		1.36 (0.80, 2.30)		1.74 (1.25, 2.42)	
Neuropathy Yes	1.99 (1.28, 3.08)	0.80	1.34 (0.89, 2.02)	0.09	1.54 (1.15, 2.07)	0.36
Neuropathy No	1.91 (1.14, 3.21)		0.70 (0.37, 1.32)		1.23 (0.84, 1.79)	
Laboratory and clinical						
BMI <30 kg/m ²	2.03 (1.14, 3.60)	0.97	1.22 (0.74, 2.02)	0.61	1.39 (0.96, 2.02)	0.95
BMI ≥30 kg/m ²	1.93 (1.28, 2.92)		1.02 (0.64, 1.62)		1.41 (1.05, 1.90)	
Duration <10 years	1.19 (0.62, 2.29)	0.12	0.73 (0.31, 1.72)	0.30	0.96 (0.58, 1.60)	0.20
Duration ≥10 years	2.32 (1.57, 3.43)		1.20 (0.83, 1.74)		1.56 (1.20, 2.02)	
HbA1c <8%	1.83 (1.04, 3.21)	0.71	0.65 (0.34, 1.25)	0.06	0.96 (0.64, 1.47)	0.09
HbA1c ≥8%	2.00 (1.32, 3.03)		1.37 (0.91, 2.05)		1.64 (1.24, 2.18)	
eGFR <60 mL/min/1.73m ²	2.17 (1.14, 4.10)	0.79	1.16 (0.74, 1.82)	0.75	1.42 (1.03, 1.95)	0.98
eGFR ≥60 mL/min/1.73m ²	1.91 (1.29, 2.83)		1.04 (0.62, 1.74)		1.41 (1.09, 1.96)	
Concomitant medications						
Insulin Yes	1.83 (1.24, 2.71)	0.49	1.21 (0.81, 1.79)	0.36	1.42 (1.08, 1.87)	0.98
Insulin No	2.40 (1.26, 4.58)		0.84 (0.43, 1.68)		1.41 (0.91, 2.19)	
Metformin Yes	1.67 (1.13, 2.46)	0.13	0.94 (0.59, 1.49)	0.31	1.25 (0.94, 1.66)	0.18
Metformin No	3.04 (1.53, 6.04)		1.34 (0.81, 2.23)		1.75 (1.18, 2.59)	
Sulphonylurea Yes	1.75 (1.02, 3.02)	0.66	0.71 (0.36, 1.41)	0.14	1.15 (0.77, 1.71)	0.22
Sulphonylurea No	2.11 (1.38, 3.22)		1.29 (0.87, 1.93)		1.56 (1.18, 2.08)	
GLP-1 Yes	2.90 (0.61, 13.92)	0.57	4.52 (0.51, 40.5)	0.19	3.36 (0.95, 12.01)	0.17
GLP-1 No	1.93 (1.37, 2.71)		1.05 (0.75, 1.49)		1.36 (1.07, 1.72)	
DPP-4 Yes	1.59 (0.55, 4.57)	0.79	1.09 (0.42, 2.83)	0.90	1.26 (0.65, 2.59)	0.75
DPP-4 No	2.01 (1.41, 2.86)		1.11 (0.77, 1.60)		1.41 (1.11, 1.81)	
Statin Yes	1.91 (1.29, 2.82)	0.86	0.94 (0.63, 1.42)	0.17	1.32 (1.01, 1.73)	0.40
Statin No	2.13 (1.11, 4.11)		1.57 (0.85, 2.92)		1.65 (1.06, 2.57)	
Diuretic Yes	1.87 (1.17, 2.99)	0.78	0.96 (0.61, 1.51)	0.34	1.28 (0.93, 1.75)	0.38
Diuretic No	2.06 (1.28, 3.32)		1.34 (0.80, 2.24)		1.58 (1.12, 2.23)	
Antithrombotic Yes	1.66 (1.17, 2.37)	0.03	1.18 (0.78, 1.78)	0.51	1.36 (1.04, 1.77)	0.62
Antithrombotic No	6.38 (1.94, 20.91)		0.92 (0.50, 1.70)		1.57 (0.96, 2.51)	
β blocker Yes	1.69 (1.10, 2.59)	0.48	0.88 (0.54, 1.45)	0.21	1.25 (0.91, 1.71)	0.28
β blocker No	2.44 (1.42, 4.20)		1.35 (0.85, 2.17)		1.62 (1.14, 2.28)	
RAS Yes	2.00 (1.37, 2.93)	0.61	1.11 (0.79, 1.56)	NA	1.37 (1.07, 1.76)	NA
RAS No	1.86 (0.92, 3.78)		—		—	

CVD: cardiovascular disease; PVD: peripheral vascular disease; NA: not available; BMI: body mass index; HbA1c: glycosylated haemoglobin; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; RAS: renin-angiotensin system.

Figure 1: Risk of Amputation by Type of Amputation in the CANVAS Program and the CREDENCE Trial



HR: hazard ratio; CI: confidence interval.

Figure 2: Cumulative Event Curves for Total, Major, and Minor Amputation in the CANVAS Program and the CREDENCE Trial

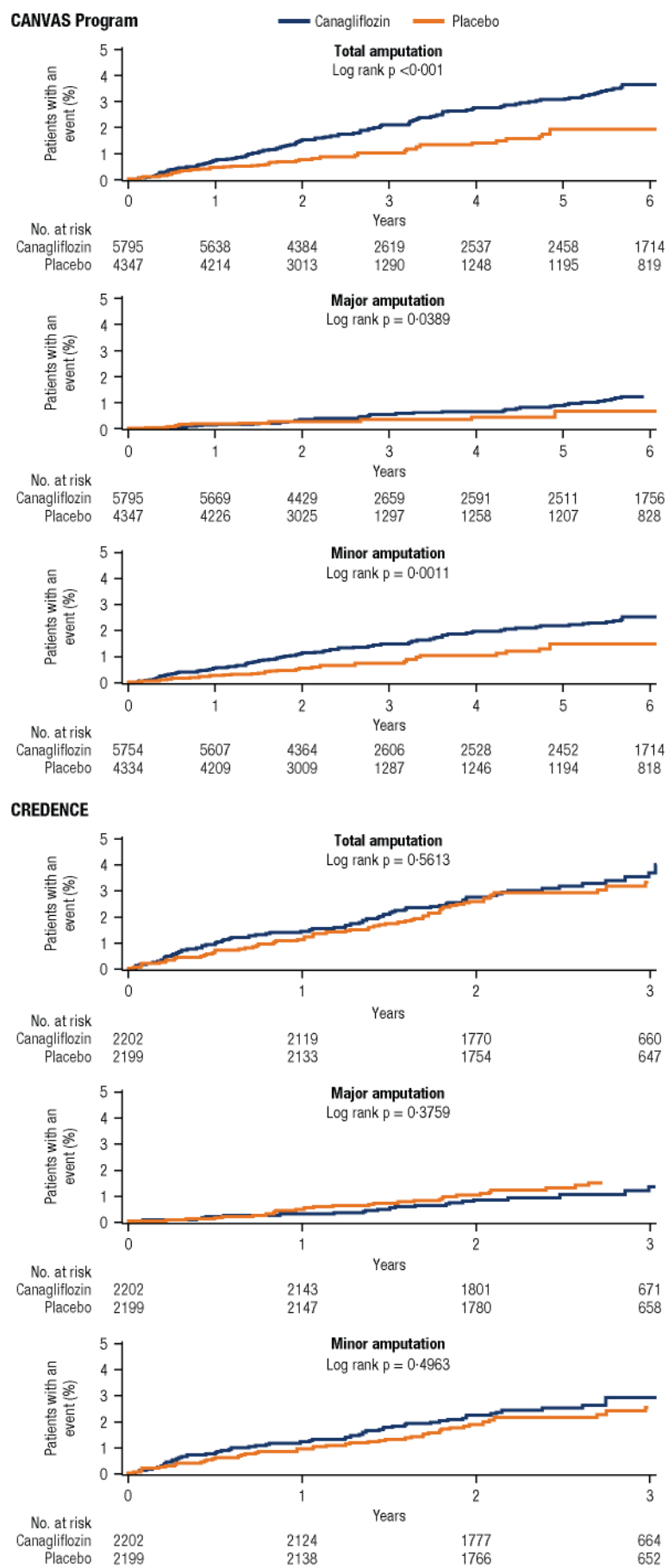
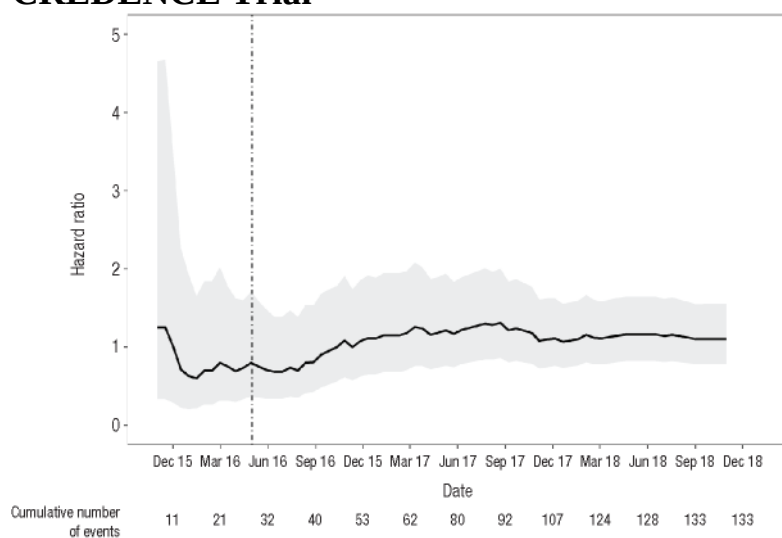


Figure 3: Continuous Total Amputation Hazard Ratio in the CREDENCE Trial



CI: confidence interval.

Hazard ratio (black line), 95% CI (shaded area), cumulative number of events (red line). Vertical dotted line denotes protocol change in May 2016.