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SPECIAL ISSUE ARTICLE

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An overview of the CANVAS Program and CREDENCE trial: The primary outcomes and key clinical implications for those managing patients with type 2 diabetes

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Abstract

Aims: To provide an overview of the primary outcomes and key clinical implications of the CANVAS Program and CREDENCE trial, which were event-driven, double-blind randomized controlled trials that established the efficacy and safety of canagliflozin in those with type 2 diabetes (T2D) and high cardiovascular risk (CV) or albuminuric chronic kidney disease (CKD).

Methods and Results: The CANVAS programme (CANVAS and CANVAS-R trials) randomized 10 142 people with T2D and high CV risk to canagliflozin or placebo and followed them for a median of 126 weeks. The primary efficacy outcome was met, with canagliflozin treatment associated with a 14% reduction in major adverse CV events (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75 to 0.97; $p < 0.001$) as compared to placebo. The CREDENCE trial randomized 4401 individuals with T2D and albuminuric CKD to canagliflozin or placebo and followed them for 109 weeks. The CREDENCE trial also met its primary endpoint; canagliflozin treatment was associated with a 30% reduction in the composite of kidney failure, sustained doubling of serum creatinine level, or death from kidney or CV causes (HR 0.70, 95% CI 0.59 to 0.82; $p < 0.001$). Substantial reductions in hospitalization for heart failure (CANVAS: HR 0.67, 95% CI 0.52 to 0.87; CREDENCE: HR 0.61, 95% CI 0.47 to 0.80) and other key CV and kidney outcomes were also identified. Relative clinical benefits were consistent across subgroups defined by baseline age, sex, kidney function and history of CV disease but absolute benefits were greatest in those at highest baseline risk. Total serious adverse

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events were less common with canagliflozin treatment. Concerns about amputation and fracture risk observed in the CANVAS Program were not seen in CREDENCE and appear to have been spurious chance findings.

Conclusion: Canagliflozin reduced important CV, kidney and mortality outcomes in those with T2D and high CV risk or CKD across diverse patient groups, with a good safety profile. Taken together with the other sodium-glucose cotransporter-2 inhibitor CV and renal outcomes trials, these landmark findings have changed the treatment landscape for patients worldwide.

KEYWORDS
antidiabetic drug, cardiovascular disease, Canagliflozin, clinical trial, SGLT2 inhibitor, randomized trial

1 | INTRODUCTION

The first sodium-glucose cotransporter 2 (SGLT2) inhibitor, canagliflozin, was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency in 2013 as an oral hypoglycaemic agent for the treatment of type 2 diabetes (T2D).[1–3] Shortly after, in 2017, Neal et al. published the primary cardiovascular (CV) outcomes from the CANVAS Program (CANVAS and CANVAS-R trials) in the *New England Journal of Medicine*.[4] This was the second CV outcome trial for the SGLT2 inhibitor drug class and the first to establish the CV efficacy and safety of canagliflozin in those with T2D. It was followed 2 years later by the CREDENCE trial, the first SGLT2 inhibitor renal outcome trial, which demonstrated the benefits of canagliflozin for kidney outcomes in those with T2D and chronic kidney disease (CKD).[5]

Collectively, the CANVAS Program and the CREDENCE trial demonstrated that canagliflozin reduced important CV, renal and mortality outcomes. These included major adverse CV events (MACE), a composite of hospitalization for heart failure (HHF) and CV death, and end-stage kidney failure or kidney death in those with T2D with or without CKD.[4,5] These trials, alongside the EMPA-REG OUTCOME trial (published in 2015) of empagliflozin[6] and the DECLARE-TIMI trial (published in 2019) of dapagliflozin[7] changed the clinical outlook for those with T2D and CV disease. Further, following the publication of the CREDENCE trial, the EMPA-KIDNEY trial (published in 2023) of empagliflozin[8] and the DAPA-CKD trial (published in 2020) of dapagliflozin[9] confirmed the reno-protective benefits of SGLT2 inhibitors in CKD regardless of underlying diabetes status.

Type 2 diabetes affects >400 million worldwide and is a major risk factor for the development of CV disease.[10] Yet, prior to these landmark trials, clinicians had no hypoglycaemic agents for which there was definitive evidence of improved CV outcomes. Worldwide, CKD affects 800 million people, with T2D and hypertension accounting for 85% of recent growth in CKD.[10–13] Despite this large disease burden, it had been almost two decades since a new therapy had been identified that improved kidney outcomes in people with CKD. Preventing CV disease is another key goal for patients with CKD since they have a very high lifetime risk of CV disease as compared to the general population—only 10% of persons with diabetes and CKD reach kidney failure but many more will experience a major CV event.[12] This reflects the very high dual risks of CV death, due to both heart failure and atherosclerotic CV disease in the CKD population.[14,15]

The direct effects of the SGLT2 outcome trials on clinical care pathways have been profound. Both T2D and CKD guidelines have changed worldwide to include SGLT2 inhibitors in their treatment algorithms.[16,17] For example, since 2021, the American Diabetes Association has recommended SGLT2 inhibitors in those with established atherosclerotic CV disease or CKD 'irrespective of A1C levels' to 'reduce the risk of major adverse CV events and heart failure hospitalisation'.[18] Further highlighting their importance, SGLT2 inhibitors were listed on the World Health Organization essential medicines list in 2021.[19]

In this review, we outline the relative and absolute benefits of canagliflozin across important patient subgroups included in the CANVAS Program and CREDENCE trial. We also discuss safety concerns and risk across patient subgroups. Finally, we outline how these trials, and others in the class, have changed patient care pathways and clinical outcomes.

2 | THE CANVAS PROGRAM: THE CANVAS AND CANVAS-R TRIALS

2.1 | Trial design, participants and randomization

The CANVAS Program comprised the CANVAS (CANagliflozin cardioVascular Assessment Study) trial and the CANVAS-Renal trial, in a total of 10 142 people with T2D and high CV risk. Both were event-driven, double-blind, placebo-controlled randomized trials designed to assess the CV safety, CV efficacy and broader tolerability of canagliflozin. The CANVAS trial was initiated in 2009 for the evaluation of CV outcomes. Interim data from the CANVAS trial were unmasked and used to obtain initial FDA approval of canagliflozin in 2013. CANVAS-Renal was then commenced in 2014 to meet the sample size to test for CV outcomes and to assess for albuminuria.[4] The CANVAS Program enrolled men and women with T2D and glycated haemoglobin (HbA1c) ≥7.0% (53 mmol/mol) and ≤10.5% (91.3 mmol/mol), age ≥ 30 years with a history of symptomatic atherosclerotic CV disease or age ≥ 50 years with ≥2 CV disease risk factors. Participants in CANVAS were randomized (1:1:1) to receive canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo, whereas participants in

CANVAS-R were randomized (1:1) to receive canagliflozin or matching placebo (initially 100 mg with optional uptitration to 300 mg from Week 13). The mean follow-up was 188 weeks across 667 sites in 30 countries. The primary outcome was MACE (a composite of CV death, nonfatal stroke and nonfatal myocardial infarction). All major CV events, renal outcomes, deaths, and selected safety outcomes, were reviewed by endpoint adjudication committees[4,20] (ClinicalTrials.gov NCT01032629, NCT01989754).

The baseline characteristics of the CANVAS Program participants are outlined in Table 1; their mean age was 63 years, 36% were female, 66% had a history of CV disease, the mean estimated glomerular filtration rate (eGFR) was 77 mL/min/1.73 m^2 and the mean duration of T2D was 13.5 years. These were well balanced across randomization arms.[4]

2.2 | Efficacy outcomes

Canagliflozin reduced important composite CV, kidney and mortality outcomes.[21] The primary outcome was met in this trial, with canagliflozin treatment associated with a 14% reduction in MACE (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75 to 0.97; $p < 0.001$) as compared to placebo (Figure 1). Point estimates for the individual components of this composite primary outcome were less than 1 but were not separately significant, with the upper bounds of CIs crossing unity. A 33% reduction in HHF was demonstrated with canagliflozin treatment (HR 0.67, 95% CI 0.52 to 0.87) as well as a 40% reduction (HR 0.60, 95% CI 0.47 to 0.77) in the kidney composite outcome comprising a 40% reduction in eGFR, need for renal replacement therapy or renal death. There was no clear effect of canagliflozin on all-cause

TABLE 1 Baseline characteristics.

Characteristic	CANVAS ($n = 4330$)	CANVAS-R ($n = 5812$)	CREDENCE ($n = 4401$)
Age, years, mean (SD)	62.4 (8.0)	64.0 (8.4)	63.0 (9.2)
Women, *n* (%)	1469 (33.9)	2164 (37.2)	1494 (33.9)
Duration of diabetes, years, mean (SD)	13.4 (7.5)	13.7 (7.9)	15.8 (8.6)
Cardiovascular disease, *n* (%)	2549 (58.9)	4107 (70.7)	2220 (50.4)
Heart failure, *n* (%)	515 (11.9)	946 (16.3)	652 (14.8)
SBP, mmHg, mean (SD)	136.3 (15.7)	136.9 (15.8)	140.0 (15.6)
HbA1c, %, mean (SD)	8.2 (0.9)	8.3 (0.9)	8.3 (1.3)
eGFR mL/min/1.73 m^2, mean (SD)	77.2 (18.9)	75.9 (21.6)	56.2 (18.2)
Median albumin-to-creatinine ratio (IQR)	11.9 (6.6, 36.4)	12.6 (6.7, 46.7)	927.0 (463.0, 1833.0)
RAS blockade use, *n* (%)	3490 (80.6)	4626 (79.6)	4395 (99.9)
Statin use, *n* (%)	3131 (72.3)	4469 (76.9)	3036 (69.0)

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range; RAS, renin-angiotensin system; SBP, systolic blood pressure.

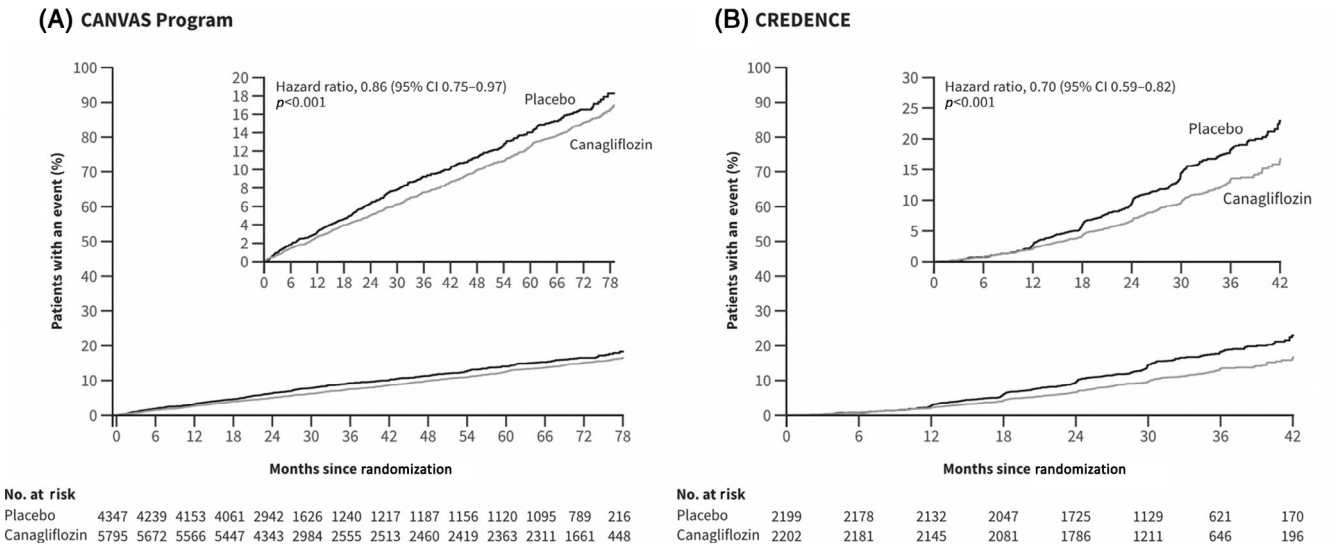

FIGURE 1 Primary Outcomes in the CANVAS Program and CREDENCE trial. CI, confidence interval.

	Events/patients (%)		Event rate per 100 patient years		
Hospitalization for heart failure or cardiovascular death					
CANVAS Program	364/5795 (6.3)	288/4347 (6.6)	16.3	20.8	0.78 (0.67-0.91)
CREDENCE	179/2202 (8.1)	253/2199 (11.5)	31.5	45.4	0.69 (0.57-0.83)
Pooled	543/7997 (6.8)	541/6546 (8.3)	19.3	27.8	0.74 (0.66-0.84)
Hospitalization for heart failure					
CANVAS Program	123/5795 (2.1)	120/4347 (2.8)	5.5	8.7	0.67 (0.52-0.87)
CREDENCE	89/2202 (4.0)	141/2199 (6.4)	15.7	25.3	0.61 (0.47-0.80)
Pooled	212/7997 (2.7)	261/6546 (4.0)	7.6	13.5	0.64 (0.54-0.77)
Cardiovascular death					
CANVAS Program	268/5795 (4.6)	185/4347 (4.3)	11.6	12.8	0.87 (0.72-1.06)
CREDENCE	110/2202 (5.0)	140/2199 (6.4)	19.0	24.4	0.78 (0.61-1.00)
Pooled	378/7997 (4.7)	325/6546 (5.0)	13.1	16.1	0.84 (0.72-0.98)
Major adverse cardiovascular event					
CANVAS Program	585/5795 (10.1)	426/4347 (9.8)	26.9	31.5	0.86 (0.75-0.97)
CREDENCE	217/2202 (9.9)	269/2199 (12.2)	38.7	48.7	0.80 (0.67-0.95)
Pooled	802/7997 (10.0)	695/6546 (10.6)	29.3	36.5	0.84 (0.76-0.93)
Doubling of serum creatinine, kidney failure, or death due to kidney failure					
CANVAS Program	34/5795 (0.6)	39/4347 (0.9)	1.5	2.8	0.53 (0.33-0.84)
CREDENCE	153/2202 (6.9)	224/2199 (10.2)	27.0	40.4	0.66 (0.53-0.81)
Pooled	187/7997 (2.3)	263/6546 (4.0)	6.6	13.5	0.63 (0.53-0.77)
Doubling of serum creatinine					
CANVAS Program	27/5795 (0.5)	33/4347 (0.8)	1.2	2.4	0.50 (0.30-0.84)
CREDENCE	118/2202 (5.4)	188/2199 (8.5)	20.7	33.8	0.60 (0.48-0.76)
Pooled	145/7997 (1.8)	221/6546 (3.4)	5.1	11.3	0.58 (0.47-0.72)
Kidney failure or death due to kidney failure					
CANVAS Program	10/5795 (0.2)	11/4347 (0.3)	0.4	0.8	0.55 (0.23-1.32)
CREDENCE	118/2202 (5.4)	166/2199 (7.5)	20.7	29.6	0.69 (0.54-0.87)
Pooled	128/7997 (1.6)	177/6546 (2.7)	4.5	9.0	0.68 (0.54-0.86)
All-cause mortality					
CANVAS Program	400/5795 (6.9)	281/4347 (6.5)	17.3	19.5	0.87 (0.74-1.01)
CREDENCE	168/2202 (7.6)	201/2199 (9.1)	29.0	35.0	0.83 (0.68-1.02)
Pooled	568/7997 (7.1)	482/6546 (7.4)	19.7	23.9	0.85 (0.75-0.97)

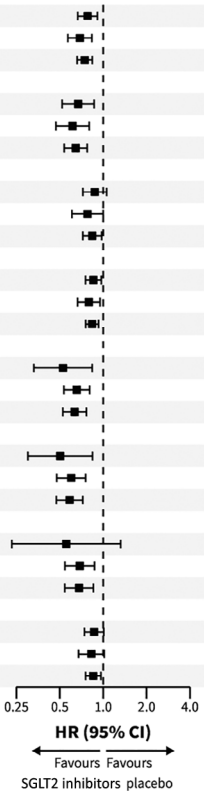

FIGURE 2 Key secondary outcomes across the CANVAS Program and CREDENCE trial. CI, confidence interval; HR, hazard ratio; SGLT2, sodium-glucose cotransporter-2.

(HR 0.87, 95% CI 0.74 to 1.01) or CV mortality (HR 0.87, 95% CI 0.72 to 1.06).[4] Other important secondary outcomes are shown in Figure 2.

Extensive subgroup analyses were reported in the publication for the primary outcome, with broadly consistent reductions in MACE observed irrespective of participant characteristics including age (< 65 years or ≥65 years), sex (male or female), race (White, Black, Asian, other), body mass index (BMI; <30 or ≥30 kg/m^2), duration of diabetes (<10 years or ≥10 years), HbA1c (<8% ≥ 8% [64 mmol/mol]), eGFR (30–60, 60–90 and ≥90 mL/min/1.73 m^2), history of heart failure and history of CV disease (all p heterogeneity >0.05).[4]

Canagliflozin also had important effects on intermediate markers of CV risk as compared to placebo. These included a mean difference in HbA1c of −0.58% (95% CI −0.61 to −0.56), a mean difference in systolic blood pressure of −3.93 mmHg (95% CI −4.30 to −3.56), a mean difference in diastolic blood pressure of −1.39 mmHg (95% CI −1.61 to −1.17) and a mean difference in body weight of −1.60 kg (95% CI −1.70 to −1.51; all $p < 0.001$).[4] All estimates with Cox regression were adjusted for baseline characteristics that included HbA1c, blood pressure and body weight.[4] Given the randomized nature of the trial, the groups were well balanced across study arms and thus not adjusted for intermediate markers of CV risk.

2.3 | Safety outcomes

Overall, serious adverse events were 7% less common in those randomized to canagliflozin than in those randomized to placebo (HR 0.93, 95% CI 0.87 to 1.00). Some serious adverse events of special interest were more common in the canagliflozin arm. These included apparently increased risks of lower limb amputation (HR 1.97, 95% CI 1.41 to 2.75), fracture (HR 1.26, 95% CI 1.04 to 1.52), genital infections (men: 34.9 vs. 10.8 events per 1000 patient years, $p < 0.001$; women: 68.8 vs. 17.5 events per 1000 patient years, $p < 0.001$) and volume depletion (26.0 vs. 18.5 events per 1000 patient years; $p < 0.009$). No increases in hypoglycaemia, urinary tract infection or acute kidney injury were identified. A small increase in ketoacidosis occurred with canagliflozin, but this was not statistically significant (0.6 vs 0.3 events per 1000 patient years; $p = 0.14$).[4]

3 | CREDENCE TRIAL

3.1 | Trial design, participants and randomization

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial was a double-blind,

randomized, placebo-controlled trial of canagliflozin in those with both T2D and albuminuric CKD. The trial included participants with T2D aged 30 years or older, an HbA1c of 6.5% (48 mmol/mol) to 12.0% (108 mmol/mol), and CKD (defined as eGFR 30 to 89 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio [UACR] of >300 mg/g but < 5000 mg/g). Participants were recruited from 690 sites across 34 countries. There was a prespecified plan to include approximately 60% of participants with a baseline eGFR of 30 to 59 mL/min/1.73 m^2. All participants were required to be receiving a maximum tolerated dose of renin-angiotensin system (RAS) blockade for at least 4 weeks prior to randomization.[22] Participants were randomized (1:1) to canagliflozin 100 mg or placebo, with randomization stratified by screening eGFR category (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2). Follow-up was for a mean of 109 weeks. The primary composite outcome comprised end-stage kidney disease, doubling of serum creatinine level, or death from kidney or CV causes[5,22] (ClinicalTrials.gov NCT02065791).

The baseline characteristics of the CREDENCE trial participants are outlined in Table 1; the mean age was 63 years, 34% were female and the mean HbA1c was 8.3%. The mean eGFR at study commencement was 56.2 mL/min/1.73 m^2 and the median UACR was 927 mg/g.[5]

3.2 | Efficacy outcomes

This trial was terminated early for efficacy on the recommendation of the Data and Safety Monitoring Committee following a planned interim analysis. The primary outcome was met, with a 30% reduction in the relative risk of the primary composite outcome (HR 0.70, 95% CI 0.59 to 0.82; $p < 0.001$ [Figure 1]). Further, a 34% reduction in the secondary kidney outcome (end-stage kidney disease, doubling of serum creatinine, death from kidney disease) was seen with canagliflozin treatment (HR 0.66, 95% CI 0.53, 0.81) and a 20% reduction in MACE (HR 0.80, 95% CI 0.67 to 0.95) and a 39% reduction in HHF (HR 0.61, 95% CI 0.47 to 0.80 [Figure 2]). The effects of canagliflozin on the primary outcome and kidney composite outcomes were consistent across the prespecified subgroups defined by baseline kidney function (eGFR 20 to <45, 40 to <60 and 60 to <90 mL/min/1.73 m^2) and UACR (≤1000 or >1000 mg/g; all p for interaction >0.11).[5]

Based on the CREDENCE trial data, for the primary composite outcome, the number needed to treat to prevent an event was 22 (95% CI 15 to 38). The number needed to treat to prevent an HHF was 46 (95% CI 29 to 124).[5]

3.3 | Safety outcomes

As was seen in the CANVAS Program, total serious adverse events were reduced with canagliflozin treatment as compared to placebo (HR 0.87, 95% CI 0.79 to 0.97). Importantly, the relative risk of amputation was not increased (HR 1.11, 95% CI 0.79 to 1.56), nor was fracture risk (HR 0.98, 95% CI 0.70 to 1.37) and nor was the risk of acute kidney injury (HR 0.85, 95% CI 0.64 to 1.13). The relative risk of diabetic ketoacidosis was increased (HR 10.80, 95% CI 1.39 to 83.65) but very few events were observed—11 in the canagliflozin arm and one in the placebo arm—indicating that the absolute risk of diabetic ketoacidosis was low.[5]

4 | SECONDARY ANALYSES OF THE CANVAS PROGRAM AND CREDENCE TRIAL

Following publication of the primary outcome papers[4,5] several secondary analyses (separately and pooled) have been performed assessing the clinical benefits (relative and absolute) of canagliflozin across major patient subgroups, the safety profile, and the impact on intermediate markers of CV risk and surrogate markers of kidney function.[21,23–27] Pooled patient-level analyses combining both the CANVAS Program and CREDENCE trial data have consistently shown that canagliflozin reduces the relative risk of death, MACE, HHF and other key CV and renal outcomes[21] irrespective of a range of factors including BMI,[28] baseline diabetes treatment,[29] duration of T2D,[30] history of CV or peripheral vascular disease,[31] history of heart failure, baseline kidney function (as estimated by GFR or albuminuria)[32] or concomitant medications.[33] For example, all-cause mortality was reduced by 15% (HR 0.85, 95% CI 0.75–0.97) and CV death by 16% (HR 0.84, 95% CI 0.72–0.98) with canagliflozin treatment.[21] (Figure 1) Higher absolute benefits for these outcomes were identified for those at highest baseline risk.[21,23–25] Canagliflozin also reduced key adverse kidney outcomes, including development of end-stage kidney failure, need for renal replacement therapy, or kidney death, irrespective of baseline participant characteristics.[34]

Beyond the prespecified primary and secondary outcomes, both trials have provided a rich data source to better understand the effects of SGLT2 inhibition on a range of other outcomes, explore potential mechanisms of benefit, and better understand both T2D and CKD itself. For example, in the CREDENCE trial, canagliflozin reduced the risk of serious hyperkalaemia, a first-in-class observation, which was subsequently confirmed in large collaborative meta-analyses of other agents within the class.[27] Additionally, canagliflozin reduced the incidence of temporary or permanent discontinuation of RAS blockade in the CREDENCE trial.[35] Both findings have informed major guidelines and suggest that this class of agent more broadly might enable better use of other guideline-directed therapies to further improve cardio-renal outcomes in people with T2D. Improvements in anaemia,[36] reductions in use of blood pressure-lowering medications,[26] and effects on new-onset atrial fibrillation were also observed in secondary analyses of the CREDENCE trial.[37] Statistical mediation analyses[38] of the CANVAS Program provided novel insights into the potential mechanisms of the CV and kidney benefits of the drug class more generally, with a range of biomarker analyses also improving our understanding of CKD progression and how SGLT2 inhibition might reduce that risk.[39–41] Effects on haemoglobin, UACR, systolic blood pressure and serum urate combined have been shown to mediate three quarters of canagliflozin benefit on HHF/CV death in the CANVAS Program.[38] Similarly, in post hoc analysis of the CREDENCE trial, changes in haematocrit levels, haemoglobin levels, red

blood cell count and UACR mediated up to 85% of the renal benefits of canagliflozin.[42]

5 | AMPUTATION

The CANVAS Program led to significant concern with regard to a possible increased risk of amputation in a population already at high risk of adverse limb events. The increase in amputation risk was first observed by the Data and Safety Monitoring Committee during an interim analysis and appeared consistent across sex, age and other participant subgroups. Across the CANVAS Program (combined CANVAS and CANVAS-R), amputation risk was increased for both minor (HR 1.94, 95% CI, 1.31 to 2.88) and major amputation (HR 2.03, 95% CI 1.08 to 3.82). There was no significant difference in amputation risk across the individual trials included in the CANVAS Program: CANVAS (HR 2.12, 95% CI 1.34 to 3.38) and CANVAS-R (HR 1.80, 95% CI 1.10 to 2.93).[43] Such was the concern that canagliflozin received a 'boxed warning' from the FDA in 2017. However, the CREDENCE trial, did not find an increased risk of amputation (HR 1.11, 95% CI 0.79 to 1.55), minor amputation (HR 1.15, 95% CI 0.77 to 1.69) or major amputation (HR 0.78, 95% CI 0.45 to 1.36) in patients randomized to canagliflozin, despite having a larger proportion of patients with a previous history of amputation in the trial population compared to the CANVAS Program (5.3% vs. 2.3%).[5] The absence of harm in CREDENCE was observed across all participant subgroups, as well as before and after the protocol amendment.[43]

To further evaluate the divergent findings across the CANVAS Program and CREDENCE, a meta-analysis of the two trials was performed and, overall, amputation risk was not increased with canagliflozin although there was significant unexplained between-trial heterogeneity ($I^2 = 82\%$, p heterogeneity $= 0.018$).[43] Detailed analysis of both trials failed to identify a participant or trial factor to explain this heterogeneity.[43] Following much investigation and debate, as well as reference to the null findings for amputation in all the other completed trials of SGLT2 inhibitors,[44] chance was identified as the most likely explanation for the amputation signal identified in the CANVAS Program[43] (Figure 3). Real-world observational studies have not found increased risk of amputation with canagliflozin[45] in particular or with the SGLT2 inhibitors as a drug class.[46,47] In 2020, the FDA 'boxed warning' for amputation was removed from canagliflozin, although amputation is still listed as a warning. Clinical concern about amputation risk also appears to persist, with patients who have peripheral arterial disease frequently excluded from these medications.[48] This is despite the very large potential benefits that SGLT2 inhibitor treatment would confer for this very-high-risk patient population.[24]

6 | FRACTURE

A 26% increase in fracture risk with canagliflozin treatment was observed in the CANVAS Program (HR 1.26, 95% CI 1.04 to 1.52), an effect driven by an increased risk in the CANVAS trial (HR 1.55, 95% CI 1.21 to 1.97) but not CANVAS-R trial (HR 0.86, 95% CI 0.62 to 1.19); with significant between-trial heterogeneity (p interaction $= 0.005$).[4,44] In-depth analysis determined that the increased risk with canagliflozin was consistent across participant subgroups defined by age, sex, race, BMI, comorbidities and medication use.[44] Whilst attempts were made to explain a possible causal link between canagliflozin and fracture, including falls occurrence during the trial and other participant characteristics, nothing was identified.[44] Shortly thereafter, the CREDENCE trial reported no increase in fracture risk with canagliflozin treatment (HR 0.98, 95% CI 0.70, 1.37)[5] suggesting this was indeed a chance finding rather than true increase in risk.

7 | CLINICAL IMPLICATIONS

The CANVAS Program and CREDENCE trial, alongside the other pivotal SGLT2 inhibitor trials, have offered compelling evidence of the composite CV, kidney and mortality benefits of this drug class in those with T2D and albuminuric CKD. These data have led to updates of T2D guidelines worldwide to incorporate SGLT2 inhibitors into treatment algorithms.[16,18,49,50] The importance of this cannot be underestimated, projections based on the CANVAS and CREDENCE trial suggest that canagliflozin could substantially extend survival free from kidney failure by approximately 12 years.[26] Economic analyses indicate that the addition of canagliflozin to standard care in patients with T2D and CKD is associated with net cost savings of up to $33 680 Canadian dollars over a patient's lifetime[51] and is largely driven by reduction in dialysis and progression to Stage 4 and 5 CKD.[52]

The introduction of SGLT2 inhibitors into clinical guidelines for T2D treatment represented the first move away from a 'gluco-centric' treatment algorithm, and emphasized the importance of the CV and kidney comorbidities of T2D. Current T2D guidelines recommend that SGLT2 inhibitors be considered as a first-line treatment option with metformin in all patients with T2D and comorbid atherosclerotic CV disease or CKD.[16,18,49,50] Recognizing the significant mortality, CV and CKD benefits of SGLT2 inhibitors, T2D treatment guidelines have also moved to recommending the substitution of other diabetes medications with SGLT2 inhibitors in patients with comorbid atherosclerotic CV disease or CKD even when glycaemic control (as measured by HbA1c) is within the recommended target range.[16]

Similarly, current CKD guidelines recommend the use of SGLT2 inhibitors as first-line drug therapy in patients with diabetes and CKD.[17] The KDIGO (Kidney Disease Improving Global Outcomes) guidelines now recommend SGLT2 inhibitor use in all patients with T2D and CKD if eGFR is >20 mL/min/1.73 m^2. Further groups prioritized for SGLT2 inhibitor use include patients with UACR > 200 mg/g and heart failure. In the management of T2D and CKD, SGLT2 inhibitor use should continue until patients progress to renal dialysis and transplantation.[17] SGLT2 inhibition is now viewed as a building block for CKD care and recommended for use concurrently with metformin, RAS blockade and statin therapy.

The barriers to implementation are, however, significant. Data from the United States suggest that fewer than 2% of patients with

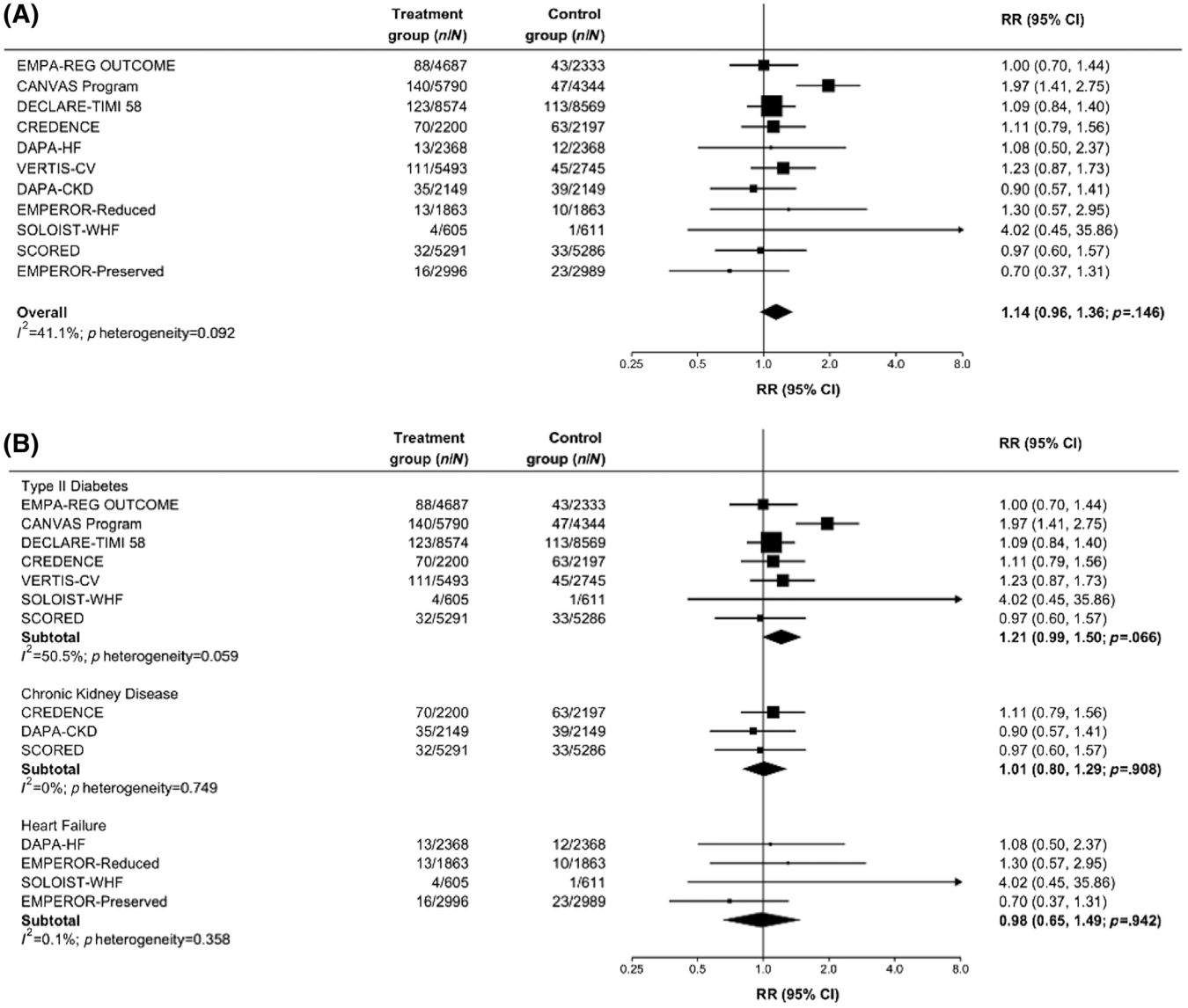

FIGURE 3 Amputation risk overall (A) and by trial population (B). Meta-analysis using hazard ratio (HR) and relative risk (RR) when HR unavailable. Performed using random-effects meta-analysis using R software. HR used: EMPA-REG Outcome, CANVAS, 58, CREDENCE. RR used: DAPA-HF, VERTIS-CV, DAPA-CKD, EMPEROR- Reduced, SOLOIST-WHF, SCORED, EMPEROR-Preserved. Reprinted with permission from: Arnott C, Fletcher RA and Neal B. Sodium Glucose Cotransporter 2 Inhibitors, Amputation Risk, and Fracture Risk. *Heart Fail Clin*. 2022;18:645–654.

T2D receive SGLT2 inhibitor therapy,[53] while in Europe, SGLT2 inhibitors make up only 4%–8% of T2D prescriptions.[54] Although SGLT2 inhibitor treatment is not indicated for all patients with T2D,[16] a large proportion with a compelling indication are not receiving this medication class. Barriers to prescription and access are complex and health system-specific but include cost, availability, physician misconceptions about the balance of benefits and risks, and prescribing inertia.[48]

Take-home messages for clinicians:

- Canagliflozin is an SGLT2 inhibitor that reduces the risk of MACE, HHF, progression of kidney disease, CV death, and all-cause mortality in those with T2D and high CV risk or albuminuric CKD;
- The relative benefits of canagliflozin are consistent across broad patient subgroups, with absolute benefits greater in those at highest baseline risk, such as those with established CV disease or with advanced CKD;
- Canagliflozin does not increase the risk of total serious adverse events;
- The initial signal of increased amputation risk with canagliflozin treatment in the CANVAS Program has not been confirmed in the CREDENCE trial or subsequent SGLT2 inhibitor trials and the 'black box' warning has been removed by the FDA;
- Canagliflozin reduces hyperkalaemia, thereby increasing the potential for the use of other guideline-directed therapies such as RAS blockers;

- Clinicians need to make a concerted effort to overcome the barriers limiting uptake of SGLT2 inhibitors for eligible patients given the highly favourable benefit–risk profile.

8 | CONCLUSIONS

The CANVAS Program and CREDENCE trial were pivotal trials establishing the CV, kidney and mortality benefits of canagliflozin in those with T2D and high CV risk or albuminuric CKD. Broad and consistent relative benefits have been identified across patient subgroups, with higher absolute benefits in those at elevated baseline risk. Canagliflozin has also been shown to have a highly favourable benefit–risk profile, with a clear reduction in total serious adverse events, and resolution of initial concerns about amputation risk. There remain, however, significant barriers to optimizing SGLT2 inhibitor use in at-risk patient groups. The trials have delivered key changes to global guidelines and care pathways but the full clinical benefits will only be realized with the widespread uptake anticipated by these recommendations.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interests to declare.

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DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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