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ORIGINAL ARTICLE

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Canagliflozin and atrial fibrillation in type 2 diabetes mellitus: A secondary analysis from the CANVAS Program and CREDENCE trial and meta-analysis

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Abstract

Aim: To assess the effects of canagliflozin on the incidence of atrial fibrillation/atrial flutter (AF/AFL) and other key cardiorenal outcomes in a pooled analysis of the CANVAS and CREDENCE trials.

Materials and Methods: Participants with type 2 diabetes and high risk of cardiovascular disease or chronic kidney disease were included and randomly assigned to canagliflozin or placebo. We explored the effects of canagliflozin on the incidence of first AF/AFL events and AF/AFL-related complications (ischaemic stroke/transient ischaemic attack/hospitalization for heart failure). Major adverse cardiovascular events and a renal-specific outcome by baseline AF/AFL status were analysed using Cox regression models.

Results: Overall, 354 participants experienced a first AF/AFL event. Canagliflozin had no detectable effect on AF/AFL (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.67-1.02) compared with placebo. Subgroup analysis, however, suggested a

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possible reduction in AF/AFL in those with no AF/AFL history (HR 0.78, 95% CI 0.62-0.99). Canagliflozin was also associated with a reduction in AF/AFL-related complications (HR 0.74, 95% CI 0.65-0.86). There was no evidence of treatment heterogeneity by baseline AF/AFL history for other key cardiorenal outcomes (all $P_{interaction} > 0.14$). Meta-analysis of five sodium-glucose cotransporter-2 (SGLT2) inhibitor trials demonstrated a 19% reduction in AF/AFL events with active treatment (HR 0.81, 95% CI 0.72-0.92).

Conclusions: Overall, a significant effect of canagliflozin on the incidence of AF/AFL events could not be shown, however, a possible reduction in AF/AFL events in those with no prior history requires further investigation. Meta-analysis suggests SGLT2 inhibition reduces AF/AFL incidence.

1 | INTRODUCTION

Type 2 diabetes (T2D) is a prominent public health problem, with a global prevalence of more than 460 million people[1] that is projected to increase to approximately 600 million by 2040.[1] It is associated with an increased risk of atrial fibrillation (AF) and atrial flutter (AFL),[2,3] the most commonly sustained arrhythmia in clinical practice, that in turn increases an individual's risk of embolic stroke, heart failure (HF) and cardiovascular (CV) death. The coexistence of both T2D and AF/AFL further increases an individual's risk of death and hospitalization.[4] Reducing the incidence of AF/AFL in people with T2D is therefore an important public health priority.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of oral hypoglycaemic medication that work by inhibiting the reabsorption of glucose in the early proximal renal tubule.[5] Large-scale clinical trials have shown that SGLT2 inhibitors can significantly reduce the risk of certain CV and kidney events, including major adverse CV events (MACE), hospitalization for HF, kidney failure and CV death, in participants with T2D, chronic kidney disease (CKD)[6,7] and HF.[6,8-13] However, they have not been shown to consistently reduce the risk of stroke.[14]

The effect of SGLT2 inhibitors on the incidence of AF/AFL is unclear. To date, no event-driven randomized trial has assessed the effect of SGLT2 inhibitors on AF/AFL as a prespecified endpoint. A post hoc analysis from the DECLARE-TIMI 58 trial found that the SGLT2 inhibitor dapagliflozin reduced the risk of AF/AFL by 19%.[15] Conversely, secondary analyses from the EMPA-REG Outcome trial have suggested no reduction in AF/AFL incidence with empagliflozin treatment.[16] Subsequent meta-analyses have suggested that the use of SGLT2 inhibitors was associated with a 19% reduction in the serious adverse events (SAEs) of AF/AFL compared to placebo, however, they have also raised the possibility that the reduction in AF/AFL could be isolated to dapagliflozin rather than being a SGLT2 inhibitor class effect.[16]

In these analyses, we explored the effects of canagliflozin on AF/AFL incidence. We also assessed whether there was heterogeneity of treatment effect on key CV and renal outcomes by baseline AF/AFL status in participants with T2D from the combined CANVAS Program (CANagliflozin CardioVascular Assessment Study: CANVAS,[17] and CANagliflozin cardioVascular Assessment Study-Renal:CANVAS-R[18]) and the CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).[19]

2 | MATERIALS AND METHODS

This was a pooled individual participant data meta-analysis from the CANVAS Program (CANVAS and CANVAS-R) and the CREDENCE trial. In brief, both studies were randomized, double-blind, placebo-controlled, multicentre trials. The CANVAS Program is composed of the CANVAS and CANVAS-R trials, which defined the effects of canagliflozin on CV, renal and safety outcomes in 10 142 participants with T2D and either established CV disease or at high CV risk, followed for a mean of 188 weeks at 667 sites in 30 countries.[13] The CREDENCE trial assessed the effect of canagliflozin on the primary composite outcome of end-stage kidney disease, a doubling of the serum creatinine level, or death from kidney disease in 4401 participants with T2D and CKD over a mean of 109 weeks at 690 sites in 34 countries.[6] All trial protocols were approved by the ethics committees at each site (ClinicalTrials.gov NCT01032629, NCT01989754 and NCT02065791), and were consistent with the principles outlined in the Declaration of Helsinki. All participants provided written informed consent. The study design, characteristics of participants, randomized treatment, and the main results of the CANVAS Program[13,17,18,20] and CREDENCE[6,19] trial have been published previously.

2.1 | Participants

The CANVAS Program enrolled men and women with T2D (glycated haemoglobin [HbA1c] ≥53 mmol/mol and ≤91 mmol/mol and estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.73 m^2), and aged ≥30 years with a history of symptomatic atherosclerotic vascular disease or aged ≥50 years with two or more risk factors for CV disease.[13] The definitions of baseline AF or AFL were identified in the

trial database of medical history using the Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms of "atrial fibrillation" or "atrial flutter".

Participants in the CREDENCE trial were men and women with T2D (HbA1c ≥48 mmol/mol and ≤108mmol/mol), CKD (eGFR ≥30 to <90 mL/min/1.73 m^2) and albuminuria (urine albumin-to-creatinine ratio [UACR] >300 to ≤5000 mg/g).[19] A history of AF/AFL at baseline was also identified in the trial database of medical history using the MedDRA preferred terms of "atrial fibrillation" or "atrial flutter".

2.2 | Randomization, treatment and follow-up

The CANVAS participants were randomized (1:1:1) to receive canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo, and the CANVAS-R participants were randomized (1:1) to receive canagliflozin 100 mg with optional uptitration to 300 mg from Week 13 or matching placebo. CREDENCE participants were randomized (1:1) to canagliflozin 100 mg or placebo, with stratification by screening eGFR category (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2). Participants and all staff were masked to individual treatment assignments until the completion of the study. Use of other background therapy for glycaemic management, the treatment of anticoagulation and other control of risk factors were instituted according to best practices consistent with local guidelines. In the CREDENCE trial, participants were required to be receiving maximally tolerated renin-angiotensin system blockade at entry.

After randomization, face-to-face follow-up was scheduled at least once every 6 months thereafter, with an additional telephone follow-up made between face-to-face assessments in the CANVAS Program and CREDENCE trial. Every follow-up included inquiry about primary and secondary outcome events and SAEs. Electrocardiogram (ECG) was recorded annually in the CANVAS trial. The UACR was measured every 26 weeks in CANVAS-R and at Week 12 and then annually in the CANVAS trial. Measurement of serum creatinine with eGFR was performed at least every 26 weeks in both trials. Participants who prematurely discontinued the trial regimen continued scheduled follow-up whenever possible, with extended efforts made to obtain full outcome data for all participants during the final follow-up window. For CREDENCE, urinary albumin and urinary creatinine were measured in single urine specimens from the first morning void at baseline, Week 26, and every 26 weeks thereafter.[21]

2.3 | Outcomes

The primary outcome in the CANVAS Program was MACE and in the CREDENCE trial it was the composite outcome of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an eGFR of <15 mL/min/1.73m^2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline sustained for at least 30 days according to central laboratory assessment, or death from renal or CV disease.

In the current post hoc analyses, the primary outcome of interest was time to first AF/AFL event, which was identified by search of the adverse event dataset in the CANVAS Program, and the CREDENCE trial used the MedDRA preferred terms "atrial fibrillation" and "atrial flutter". Secondary outcomes included AF/AFL-related complications, defined as a composite of ischaemic stroke/transient ischaemic attack (TIA) or hospitalization for HF, as these are common or serious complications of AF/AFL. Key CV and renal outcomes including MACE and renal-specific composite outcomes by AF/AFL subgroups were also assessed.

An Endpoint Adjudication Committee adjudicated all renal and CV outcomes in the CANVAS Program and CREDENCE trial. History of AF/AFL (either paroxysmal, persistent, or permanent AF, and/or AFL) was reported by local investigators in the electronic case report. Baseline ECGs were not mandated by the study protocol and were not available in both studies.

2.4 | Statistical analysis

We used individual patient-level data from the CANVAS Program and the CREDENCE trial with an intention-to-treat approach to compare all participants assigned to canagliflozin with those assigned to placebo. Participant characteristics were compared overall and for each trial, for participants who had AF/AFL at baseline and for participants who did not. Categorical variables were summarized as the number of participants with corresponding percentages. Continuous variables were summarized as the mean and standard deviation or median and interquartile ranges if the data were skewed. Baseline characteristics were compared using a chi-squared or generalized Cochran–Mantel–Haenszel test for categorical variables, a *t*-test for continuous normally distributed variables, and a Wilcoxon two-sample test for continuous variables with a skewed distribution. For these and all subsequent statistical tests, a P value < 0.05 was deemed likely to reflect differences beyond chance.

The effects of canagliflozin (doses combined) compared to placebo on AF/AFL, AF/AFL-related complications and other key outcomes were estimated by combining the CANVAS Program and CREDENCE trial datasets using an intention-to-treat approach, with stratification by trial. Annualized incidence rates per 1000 patient-years of follow-up were calculated for all outcomes in addition to hazard ratios (HRs) and 95% confidence intervals (CIs) determined from Cox regression models, with and without adjustment for multiple testing.

For all outcome analyses, we tested the homogeneity of treatment effects across the two groups with or without AF/AFL at baseline, P values for heterogeneity across groups were obtained by adding AF/AFL as a covariate and a term for AF/AFL-by-treatment interaction in the Cox regression model. For safety outcomes, an on-treatment analysis was performed using a similar approach to that used in previous analyses.[6,13,22] Analyses were performed using SAS

TABLE 1 Baseline characteristics of participant by history of atrial fibrillation/atrial flutter at baseline in the CANVAS Program and the CREDENCE trial

	CANVAS Program		CREDENCE		Pooled CANVAS and CREDENCE			
	With AF/AFL (n = 613)	Without AF/AFL (n = 9529)	With AF/AFL (n = 273)	Without AF/AFL (n = 4128)	With AF/AFL (n = 886)	Without AF/AFL (n = 13 657)	Total (n = 14 543)	Total with AF/AFL vs. total without
Age, years, mean ± SD	68.0 ± 7.3	63.0 ± 8.2	67.7 ± 7.4	62.7 ± 9.2	67.9 ± 7.3	62.9 ± 8.5	63.2 ± 8.5	<0.0001
Female sex, n (%)	182 (29.7)	3451 (36.2)	61 (22.3)	1433 (34.7)	243 (27.4)	4884 (35.8)	5127 (35.3)	<0.0001
Race, n (%)								<0.0001
White	570 (93.0)	7374 (77.4)	223 (81.7)	2708 (65.6)	793 (89.5)	10 082 (73.8)	10 875 (74.8)	
Asian	15 (2.5)	1269 (13.3)	28 (10.3)	849 (20.6)	43 (4.9)	2118 (15.5)	2161 (14.9)	
Black	12 (2.0)	324 (3.4)	6 (2.2)	218 (5.3)	18 (2.0)	542 (4.0)	560 (3.9)	
Other	16 (2.6)	562 (5.9)	16 (5.9)	353 (8.6)	32 (3.6)	915 (6.7)	947 (6.5)	
Current smoker, n (%)	71 (11.6)	1735 (18.2)	35 (12.8)	604 (14.6)	106 (12.0)	2339 (17.1)	2445 (16.8)	<0.0001
Hypertension, n (%)	565(92.2)	8560 (89.8)	268 (98.2)	3992 (96.7)	833 (94.0)	12 552 (91.9)	1338 5(92.0)	0.0246
Duration of diabetes, years, mean ± SD	13.4 ± 8.0	13.6 ± 7.7	15.1 ± 8.5	15.8 ± 8.6	13.9 ± 8.2	14.2 ± 8.1	14.2 ± 8.1	0.2857
Microvascular disease								
Nephropathy, n (%)	128 (20.9)	1646 (17.3)	273 (100.0)	4128 (100.0)	401 (45.3)	5774 (42.3)	6175 (42.5)	0.0819
Retinopathy, n (%)	136 (22.2)	1993 (20.9)	104 (38.1)	1778 (43.1)	240 (27.1)	3771 (27.6)	4011 (27.6)	0.7351
Neuropathy, n (%)	197 (32.1)	2913 (30.6)	129 (47.3)	2018 (48.9)	326 (36.8)	4931 (36.1)	5257 (36.2)	0.6793
Atherosclerotic disease								
Coronary, n (%)	434 (70.8)	5287 (55.5)	143 (52.4)	1170 (28.3)	577 (65.1)	6457 (47.3)	7034 (48.4)	<0.0001
Cerebrovascular, n (%)	169 (27.6)	1789 (18.8)	70 (25.6)	630 (15.3)	239 (27.0)	2419 (17.7)	2658 (18.3)	<0.0001
Peripheral, n (%)	152 (24.8)	1961 (20.6)	72 (26.4)	974 (23.6)	224 (25.3)	2935 (21.5)	3159 (21.8)	0.008
Any, n (%)	505 (82.4)	6819 (71.6)	186 (68.1)	2034 (49.3)	691 (78.0)	8853 (64.8)	9544 (65.6)	<0.0001
CVD at entry, n (%)	461 (75.2)	6195 (65.0)	186 (68.1)	2034 (49.3)	647 (73.0)	8229 (60.3)	8876 (61.0)	<0.0001
HF, n (%)	211 (34.4)	1250 (13.1)	114 (41.8)	538 (13.0)	325 (36.7)	1788 (13.1)	2113 (14.5)	<0.0001
Amputation, n (%)	19 (3.1)	219 (2.3)	7 (2.6)	227 (5.5)	26 (2.9)	446 (3.3)	472 (3.3)	0.5898
BMI, kg/m^2, mean ± SD	33.4 ± 5.8	31.9 ± 5.9	33.2 ± 6.3	31.2 ± 6.1	33.4 ± 6.0	31.7 ± 6.0	31.8 ± 6.0	<0.0001
SBP, mmHg, mean ± SD	135.9 ± 16.1	136.7 ± 15.7	139.9 ± 15.6	140.0 ± 15.6	137.1 ± 16.1	137.7 ± 15.8	137.7 ± 15.8	0.2999
DBP, mmHg, mean ± SD	77.1 ± 10.1	77.7 ± 9.6	78.5 ± 10.1	78.3 ± 9.3	77.5 ± 10.1	77.9 ± 9.5	77.9 ± 9.6	0.2237
HbA1c, %, mean ± SD	8.2 ± 0.9	8.3 ± 0.9	8.1 ± 1.3	8.3 ± 1.3	8.2 ± 1.0	8.3 ± 1.1	8.3 ± 1.1	0.018
Cholesterol, mmol/L, mean ± SD								
Total	4.2 ± 1.1	4.4 ± 1.2	4.3 ± 1.2	4.7 ± 1.3	4.3 ± 1.1	4.5 ± 1.2	4.5 ± 1.2	<0.0001
HDL	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.0006
LDL	2.2 ± 0.9	2.3 ± 0.9	2.2 ± 0.9	2.5 ± 1.1	2.2 ± 0.9	2.4 ± 1.0	2.4 ± 1.0	<0.0001
LDL/HDL ratio	2.0 ± 0.9	2.0 ± 0.9	2.1 ± 1.0	2.3 ± 1.1	2.1 ± 0.9	2.1 ± 1.0	2.1 ± 1.0	0.0785

TABLE 1 (Continued)

	CANVAS Program		CREDENCE		Pooled CANVAS and CREDENCE			
	With AF/AFL (n = 613)	Without AF/AFL (n = 9529)	With AF/AFL (n = 273)	Without AF/AFL (n = 4128)	With AF/AFL (n = 886)	Without AF/AFL (n = 13 657)	Total (n = 14 543)	Total with AF/AFL vs. total without
Triglycerides, mmol/L, mean ± SD	2.0 ± 1.2	2.0 ± 1.4	2.2 ± 1.4	2.2 ± 1.6	2.0 ± 1.2	2.1 ± 1.5	2.1 ± 1.5	0.3275
eGFR, mL/min /1.73 m^2, mean ± SD	68.7 ± 17.9	77.0 ± 20.6	54.2 ± 17.5	56.3 ± 18.3	64.2 ± 19.0	70.7 ± 22.1	70.3 ± 22.0	<0.0001
UACR, mg/mmol, median (IQR)	16.5 (7.7-68.6)	12.1 (6.6-40.5)	795 (423-1601)	929 (465.5-1848.5)	55.7 (10.3-511.0)	32.4 (8.4-525.0)	33.3 (8.4-523.6)	<0.0001
Concomitant drug therapies, n (%)								
Insulin	326 (53.2)	4769 (50.1)	153 (56.0)	2731 (66.2)	479 (54.1)	7500 (54.9)	7979 (54.9)	0.6207
Metformin	421 (68.7)	7404 (77.7)	170 (62.3)	2375 (57.5)	591 (66.7)	9779 (71.6)	10 370 (71.3)	0.0018
Sulphonylureas	230 (37.5)	4131 (43.4)	95 (34.8)	1173 (28.4)	325 (36.7)	5304 (38.8)	5629 (38.7)	0.2018
GLP-1 receptor agonists	21 (3.4)	386 (4.1)	15 (5.5)	168 (4.1)	36 (4.1)	554 (4.1)	590 (4.1)	0.9922
DPP-4 inhibitors	82 (13.4)	1179 (12.4)	50 (18.3)	701 (17.0)	132 (14.9)	1880 (13.8)	2012 (13.8)	0.344
Loop diuretic	214 (34.9)	1094 (11.5)	105 (38.5)	850 (20.6)	319 (36.0)	1944 (14.2)	2263 (15.6)	<0.0001
Non-loop diuretic	187 (30.5)	2995 (31.4)	61 (22.3)	1041 (25.2)	248 (28.0)	4036 (29.6)	4284 (29.5)	0.3231
Calcium channel blocker	239 (39.0)	3204 (33.6)	153 (56.0)	1976 (47.9)	392 (44.2)	5180 (37.9)	5572 (38.3)	0.0002
RAS inhibitor	491 (80.1)	7625 (80.0)	273 (100.0)	4122 (99.9)	764 (86.2)	11 747 (86.0)	12 511 (86.0)	0.8575
β blocker	462 (75.4)	4959 (52.0)	191 (70.0)	1579 (38.3)	653 (73.7)	6538 (47.9)	7191 (49.5)	<0.0001
Statin	474 (77.3)	7126 (74,8)	208 (76.2)	2828 (68.5)	682 (77.0)	9954 (72.9)	10 636 (73.1)	0.0078
Antithrombotic	570 (93.0)	6901 (72.4)	243 (89.0)	2381 (57.7)	813 (91.8)	9282 (68.0)	10 095 (69.4)	<0.0001

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system; SBP, systolic blood pressure; UACR, urine albumin creatinine ratio.

version 9.2, SAS Enterprise Guide version 7.1 and Stata version 12.0. There was no imputation for missing data.

2.5 | Meta-analysis

We also performed an updated meta-analysis of clinical (CV or renal) outcome trials to assess the effects of the SGLT2 inhibitor drug class on AF/AFL outcomes. We followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement[23] except for protocol registration. Our current studies as well as the DECLARE-TIMI 58[15] and DAPA-HF[24] studies were the only clinical outcome trials to report AF/AFL events and thus were included. Study-level data on AF/AFL were extracted separately. Summary HRs with 95% CIs were generated by using the random-effects model. The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was evaluated using the I^2 statistic and by calculating the *P* value for heterogeneity. I^2 statistics of 25%, 50% and 75% were regarded as low, moderate and high likelihood of differences beyond chance, respectively.

3 | RESULTS

3.1 | Baseline characteristics

There were 14 543 participants in the pooled dataset of the CANVAS Program and CREDENCE trial. Overall, 10 011 participants (36%) were female, with a mean age of 63 (±8.5) years and a median follow-up of 2.5 years.

Whilst the trial populations were similar with respect to many characteristics there were some salient differences largely reflective of their different inclusion criteria. In CREDENCE all participants had CKD at baseline as compared to 18% of participants in the CANVAS Program

with nephropathy and 20% of participants with eGFR <60 mL/min/1.73m^2.[6,13,25] Furthermore, 66% had established CV disease in the CANVAS Program and 50% in CREDENCE. (Table 1).

Overall, 886 participants (6.1%) had a history of AF/AFL at study baseline in the CANVAS Program and CREDENCE trial. Those who had AF/AFL at baseline were older (mean age 67.9 ± 7.3 vs. 62.9 ± 8.5 years) and were more likely to be male (72.6% vs. 64.2%), to be of White race (89.5% vs. 73.8%), to have pre-existing atherosclerotic disease (78.0% vs. 64.8%), and to have a history of hypertension (94.0% vs 91.9%). Regarding baseline markers of CV risk, those who had AF/AFL at baseline had a higher body mass index (BMI; 33.4 ± 6.0 vs. 31.7 ± 6.0 kg/m^2) and a higher UACR (55.7 vs. 32.4 mg/mmol) than those who had no AF/AFL history. They were also more likely to be taking loop diuretics (36.0% vs. 14.2%), calcium channel blockers (44.2% vs. 37.9%), β blockers (73.7% vs. 47.9%), statins (77.0% vs. 72.9%), or any antithrombotic (91.8% vs. 68.0%) at baseline as compared to those with no AF/AFL history (Table 1). There were no differences in terms of baseline anticoagulant use by randomized treatment group in the CANVAS Program and CREDENCE trial (Table S3).

3.2 | Effects of canagliflozin on AF/AFL and AF/AFL-related complications

A total of 354 participants (2.4%) experienced a first AF/AFL event during the trial (193 vs. 161 events, 6.9 vs. 8.3 events per 1000 patient-years for the canagliflozin and placebo group, respectively). Of those, 61 (17.2%) had a history of AF/AFL at baseline and 293 (82.8%) had no history of AF/AFL. There was no clear effect on the incidence of AF/AFL with canagliflozin treatment in the overall cohort (HR 0.82, 95% CI 0.67-1.02), however, it was possibly reduced in those without a history of AF/AFL (HR 0.78, 95% CI 0.62-0.99). Results remain unchanged after adjustment for baseline age, gender, BMI, HbA1c, eGFR and UACR (AF/AFL subgroups $P_{interaction} = 0.23$). These findings were largely consistent across the CANVAS Program and CREDENCE trial ($I^2 = 0\%$, $P_{interaction} = 0.591$ for AF/AFL primary outcome; Table 2).

Canagliflozin was associated with a reduction of AF/AFL-related complications (composite of ischaemic stroke/transient ischaemic attack or hospitalization for HF) by 26% (HR 0.74, 95% CI 0.65-0.86). This was consistent across those with and without established AF/AFL ($P_{heterogeneity} = 0.96$), which may suggest the benefit is unrelated to coexistent AF/AFL. Canagliflozin did not reduce the risk of ischaemic stroke/TIA in those with a history of AF/AFL (HR 0.61, 95% CI 0.31-1.17) or those without ($P_{heterogeneity} = 0.14$; Figure 1).

3.3 | Effects of canagliflozin on key CV outcomes

In the pooled dataset, canagliflozin was associated with a reduction in hospitalization for HF (HR 0.64, 95% CI 0.53-0.77), with no evidence of significant difference in treatment effect by AF/AFL subgroup

TABLE 2 Unadjusted and adjusted effects of canagliflozin on the first atrial fibrillation/atrial flutter event in the CANVAS Program and the CREDENCE trial

	Participants with an event, n/N		Participants with an event per 1000 patient-years		Unadjusted HR (95% CI)	*P* interaction	Adjusted HR (95% CI)	*P* interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo				
All	193/7997	161/6546	6.9	8.3	0.82 (0.67, 1.02)		0.83 (0.67, 1.02)	
With AF/AFL	37/483	24/403	25.2	22.3	1.13 (0.67, 1.90)	.19	1.10 (0.65, 1.87)	.23
Without AF/AFL	156/7514	137/6143	5.9	7.5	0.77 (0.61, 0.98)		0.78 (0.62, 0.99)	
CANVAS program	143/5795	96/4347	6.5	7.0	0.86 (0.66, 1.12)		0.85 (0.65, 1.10)	
With AF/AFL	27/351	20/262	23.9	27.7	0.87 (0.48, 1.56)	.73	0.83 (0.46, 1.51)	.63
Without AF/AFL	116/5444	76/4085	5.5	5.8	0.85 (0.64, 1.14)		0.85 (0.64, 1.15)	
CREDENCE	50/2202	65/2199	8.8	11.5	0.76 (0.53, 1.10)		0.79 (0.55, 1.14)	
With AF/AFL	10/132	4/141	29.8	11.3	2.87 (0.88, 9.36)	.02	2.84 (0.85, 9.42)	.02
Without AF/AFL	40/2070	61/2058	7.5	11.6	0.64 (0.43, 0.96)		0.67 (0.45, 0.997)	

Note: HRs and 95% CIs were estimated with the use of Cox regression models, with stratification according to study. Adjusted HRs were adjusted for variables including age, gender, baseline body mass index, baseline glycated haemoglobin, baseline estimated glomerular filtration rate and baseline urine albumin-creatinine ratio.

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval; HR, hazard ratio.

Subgroup	Canagliflozin n/N	Placebo	Canagliflozin Events per 1000 patient-years	Placebo	HR (95% CI)	P value for heterogeneity
MACE						
All	**802/7997**	**695/6546**	**29.3**	**36.5**	**0.84(0.75,0.93)**	**0.66**
With AF/AFL	90/483	75/403	60.1	69.4	0.92(0.67,1.25)	
Without AF/AFL	712/7514	620/6143	27.6	34.5	0.83(0.74,0.92)	
CV death						
All	**378/7997**	**325/6546**	**13.1**	**16.1**	**0.84(0.72,0.97)**	**0.65**
With AF/AFL	56/483	46/403	35.3	39.8	0.90(0.60,1.33)	
Without AF/AFL	322/7514	279/6143	11.8	14.7	0.83(0.70,0.98)	
Nonfatal MI						
All	**378/7997**	**325/6546**	**13.1**	**16.1**	**0.84(0.70,0.99)**	**0.20**
With AF/AFL	56/483	46/403	35.3	39.8	1.40(0.72,2.73)	
Without AF/AFL	322/7514	279/6143	11.8	14.7	0.80(0.67,0.96)	
Nonfatal stroke						
All	**211/7997**	**182/6546**	**7.6**	**9.4**	**0.87(0.71,1.06)**	**0.14**
With AF/AFL	16/483	22/403	10.5	20.1	0.58(0.30,1.12)	
Without AF/AFL	195/7514	160/6143	7.4	8.7	0.90(0.73,1.12)	
AF/AFL-related outcomes						
All	**399/7997**	**412/6546**	**14.3**	**21.2**	**0.74(0.65,0.86)**	**0.96**
With AF/AFL	51/483	57/403	33.6	52.1	0.74(0.50,1.09)	
Without AF/AFL	348/7514	355/6143	13.2	19.4	0.75(0.65,0.87)	
Ischemia stroke/TIA						
All	**201/7997**	**163/6546**	**7.2**	**8.4**	**0.93(0.75,1.14)**	**0.14**
With AF/AFL	16/483	21/403	10.5	19.1	0.61(0.31,1.17)	
Without AF/AFL	185/7514	142/6143	7.0	7.7	0.97(0.78,1.21)	
Hospitalization for HF						
All	**212/7997**	**261/6546**	**7.6**	**13.5**	**0.64(0.53,0.77)**	**0.31**
With AF/AFL	38/483	38/403	25.2	35.6	0.73(0.46,1.16)	
Without AF/AFL	174/7514	223/6143	6.6	12.2	0.62(0.51,0.76)	
CV death or Hospitalization for HF						
All	**543/7997**	**541/6546**	**19.3**	**27.8**	**0.74(0.66,0.84)**	**0.51**
With AF/AFL	86/483	79/403	56.7	73.7	0.79(0.58,1.08)	
Without AF/AFL	457/7514	462/6143	17.2	25.2	0.73(0.64,0.83)	
Renal composite						
All	**187/7997**	**263/6546**	**6.6**	**13.5**	**0.63(0.53,0.77)**	**0.40**
With AF/AFL	9/483	9/403	5.8	8.1	0.87(0.34,2.24)	
Without AF/AFL	178/7514	254/6143	6.7	13.8	0.63(0.52,0.76)	
ESKD						
All	**126/7997**	**173/6546**	**4.5**	**8.8**	**0.69(0.55,0.87)**	**0.37**
With AF/AFL	6/483	5/403	3.8	4.5	0.36(0.19,3.98)	
Without AF/AFL	120/7514	168/6143	4.5	9.1	0.68(0.53,0.85)	
Doubling of serum creatinine level						
All	**145/7997**	**221/6546**	**5.1**	**11.3**	**0.59(0.47,0.72)**	**0.62**
With AF/AFL	5/483	6/403	3.2	5.4	0.68(0.20,2.34)	
Without AF/AFL	140/7514	215/6143	5.3	11.7	0.58(0.47,0.72)	
Renal death						
All	**2/7997**	**8/6546**	**0.1**	**0.4**	**0.21(0.04,1.00)**	**NA**
With AF/AFL	0/483	1/403	0	0.9	NA	
Without AF/AFL	2/7514	7/6143	0.1	0.4	0.24(0.05,1.16)	
All-cause mortality						
All	**568/7997**	**482/6546**	**19.7**	**23.9**	**0.85(0.75,0.96)**	**0.50**
With AF/AFL	77/483	61/403	48.6	52.7	0.94(0.67,1.32)	
Without AF/AFL	491/7514	421/6143	18.0	22.2	0.84(0.74,0.96)	

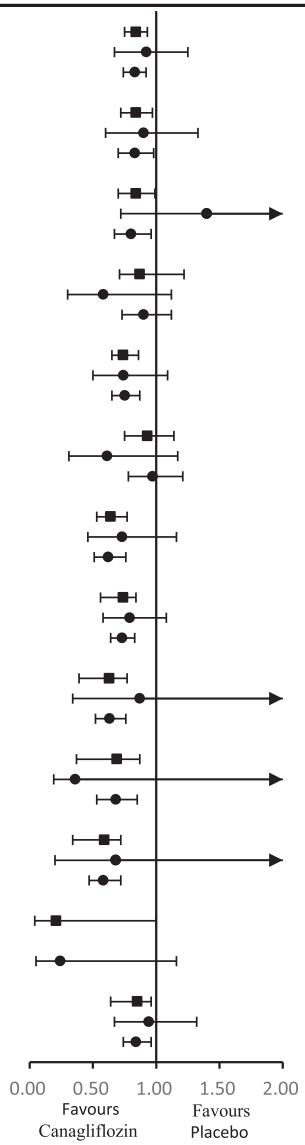

FIGURE 1 Effects of canagliflozin on cardiovascular (CV) and renal outcomes in participants by atrial fibrillation (AF)/atrial flutter (AFL) at baseline in the pooled CANVAS Program and CREDENCE trial. Hazard ratio (HR) and 95% confidence intervals (CIs) were estimated with the use of Cox regression models, with treatment as the explanatory variable and stratification by study. *P* values for the interaction of treatment by subgroup are based on the Cox regression models, including treatment, AF/AFL at baseline, and their interaction variable. AF/AFL-related outcomes indicates a composite of ischaemic stroke/transient ischaemic attack or hospitalization for heart failure (HF), renal composite indicates a composite of end-stage kidney disease (ESKD; dialysis, transplantation, or a sustained estimated glomerular filtration rate of <15 mL per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes. MACE, major adverse cardiovascular events; MI, myocardial infarction

($P_{heterogeneity}$ = 0.31). Similarly, there was no heterogeneity of treatment effect by AF/AFL subgroups for the outcome of MACE (AF/AFL group: HR 0.92, 95% CI 0.67-1.25; No AF/AFL group: HR 0.83; 95% CI 0.74-0.92; $P_{heterogeneity}$ = 0.66), nonfatal myocardial infarction (AF/AFL group: HR 1.40; 95% CI 0.72-2.73; No AF/AFL group: HR 0.80; 95% CI 0.67, 0.96; $P_{heterogeneity}$ = 0.20) and CV death (AF/AFL group: HR 0.90, 95% CI 0.60-1.33; No AF/AFL group: HR 0.83, 95% CI 0.70-0.98; $P_{heterogeneity}$ = 0.65).

Compared with placebo, canagliflozin was associated with significantly lower risks of the renal-specific composite (HR 0.63, 95% CI 0.53-0.77), end-stage kidney disease (HR 0.69, 95% CI 0.55-0.87), doubling of serum creatinine level (HR 0.59, 95% CI 0.47-0.72), and all-cause mortality (HR 0.85, 95% CI 0.75-0.96). These findings were not separately significant in those with a history of AF/AFL; however, subgroup analyses suggest consistent effects irrespective of AF/AFL history (all *P* for interaction >0.14; Figure 1).

	Number of participants with an event	Canagliflozin Events per 1000	Placebo patient-years	HR(95% CI)	*P* value for heterogeneity
All serious adverse events					
All	**4820**	**138.9**	**161.4**	**0.91(0.86,0.96)**	**0.78**
With AF/AFL	432	253.7	298.3	0.87(0.72,1.06)	
Without AF/AFL	4388	133.2	154.2	0.91(0.86,0.97)	
Adverse events leading to discontin					
All	**1578**	**39.5**	**40.8**	**1.04(0.94,1.15)**	**0.18**
With AF/AFL	140	58.6	75.5	0.83(0.59,1.17)	
Without AF/AFL	1438	38.4	38.8	1.06(0.95,1.18)	
Amputation					
All	**320**	**7.5**	**5.6**	**1.49(1.18,1.89)**	**0.49**
With AF/AFL	24	9.1	9	1.11(0.49,2.52)	
Without AF/AFL	296	7.4	5.4	1.53(1.20,1.95)	
All Fractures					
All	**631**	**14.7**	**12.0**	**1.19(1.01,1.40)**	**0.24**
With AF/AFL	44	20.9	11.8	1.61(0.83,3.11)	
Without AF/AFL	587	14.3	12.0	1.16(0.98,1.38)	
Serious renal-related adverse events					
All	**226**	**4.6**	**7.4**	**0.73(0.56,0.96)**	**0.90**
With AF/AFL	23	8.7	13.7	0.76(0.33,1.79)	
Without AF/AFL	203	4.3	7.0	0.74(0.56,0.97)	
Serious acute kidney injury					
All	**242**	**5**	**7.8**	**0.80(0.62,1.03)**	**0.34**
With AF/AFL	29	12.8	14.9	1.09(0.51,2.31)	
Without AF/AFL	213	4.5	7.4	0.77(0.59,1.01)	
Serious hyperkalaemia					
All	**357**	**6.8**	**11.7**	**0.80(0.65,0.99)**	**NA**
With AF/AFL	23	8.7	13.7	0.92(0.40,2.11)	
Without AF/AFL	324	6.7	11.6	0.80(0.64,0.99)	
Hypoglycaemia*					
All	**1016**	**52.8**	**52.2**	**1.02(0.90,1.16)**	**0.79**
With AF/AFL	43	41.8	37.9	1.09(0.58,2.02)	
Without AF/AFL	973	53.5	53.1	1.02(0.89,1.16)	
Urinary tract infection*					
All	**909**	**46.3**	**44.2**	**1.09(0.95,1.25)**	**0.03**
With AF/AFL	58	68.2	35.5	1.87(1.04,3.35)	
Without AF/AFL	58	45.1	44.7	1.05(0.92,1.21)	
Female mycotic genital infection*					
All	**228**	**50.4**	**11.2**	**3.69(2.53,5.40)**	**0.87**
With AF/AFL	9	44.4	8.4	4.34(0.54,35.0)	
Without AF/AFL	219	50.7	11.3	3.66(2.49,5.40)	
Male mycotic genital infection*					
All	**487**	**28.7**	**7**	**3.98(3.10,5.12)**	**NA**
With AF/AFL	30	35	0	NA	
Without AF/AFL	457	28.3	7.5	3.69(2.87,4.75)	

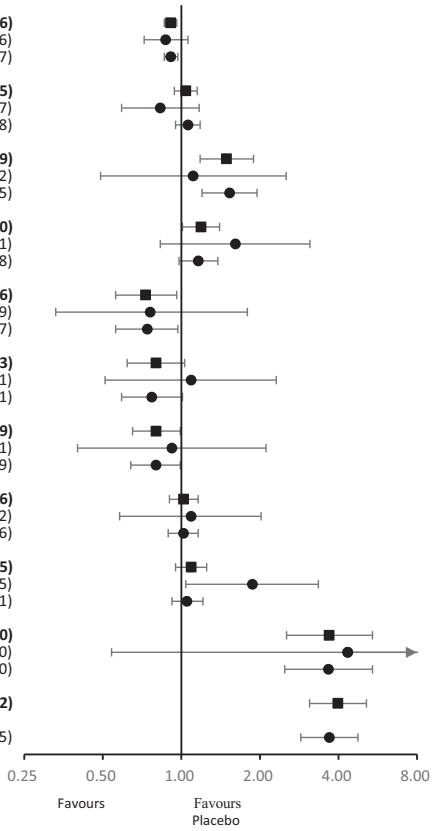

FIGURE 2 Adverse events in participants by atrial fibrillation (AF)/atrial flutter (AFL) at baseline in the pooled CANVAS Program and CREDENCE trial. Hazard ratio (HR) and 95% confidence intervals (CIs) were estimated with the use of Cox regression models, with treatment as the explanatory variable and stratification by study. *P* values for the interaction of treatment by subgroup are based on the Cox regression models, including treatment, AF/AFL at baseline, and their interaction variable. CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; NA, not applicable. *The annualized event rates are reported with data from CANVAS and CREDENCE up to January 7, 2014, because after this time, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected

Results remained unchanged after adjustment for age, gender, BMI, HbA1c, eGFR and UACR (Table S1).

3.4 | Safety outcomes

The risk of any SAE (HR 0.91, 95% CI 0.86-0.96) was lower with canagliflozin compared with placebo, with no effect modification by baseline AF/AFL ($P_{heterogeneity} = 0.78$). The effect of canagliflozin on serious renal-related adverse events (HR 0.73, 95% CI 0.56-0.96) did not vary across subgroups ($P_{heterogeneity} = 0.90$). Similarly, the effect on amputation, fracture and female mycotic genital infections were similar for AF/AFL subgroups. Urinary tract infections were increased with canagliflozin treatment only in those with a history of AF/AFL (HR 1.87, 95% CI 1.04-3.35; $P_{heterogeneity} = 0.03$ [Figure 2]).

3.5 | Meta-analysis of AF/AFL outcomes from available SGLT2 inhibitor trials

A meta-analysis including the CANVAS Program, CREDENCE trial, DECLARE-TIMI 58 and DAPA-HF demonstrated an overall reduction in the incidence of AF/AFL for all study participants (HR 0.81, 95% CI 0.72-0.92; $I^2 = 0.0\%$). This effect was also demonstrated in the subgroup of participants without a history of AF/AFL at study baseline (HR 0.80, 95% CI 0.70-0.92; $I^2 = 0.0\%$ [Figures S1 and S2]).

4 | DISCUSSION

In this pooled analysis from the CANVAS Program and CREDENCE trial we were not able to demonstrate a statistically significant reduction in overall AF/AFL incidence with canagliflozin treatment in those

with T2D and high risk of CV disease or CKD; however, AF/AFL was significantly reduced in those without a history of AF/AFL. Furthermore, canagliflozin did not reduce the risk of ischaemic stroke but did reduce the composite outcome of AF/AFL-related complications in those with a history of AF/AFL. Canagliflozin did reduce the risk of key CV events including MACE and hospitalization for HF irrespective of baseline AF/AFL history. Consistent benefits from canagliflozin treatment were identified for the renal outcomes across AF/AFL subgroups.

Type 2 diabetes and related comorbidities including hypertension, obesity, HF and CKD are strongly linked to an increased risk of AF/AFL. This is partly attributable to the promotion of atrial dilatation and fibrosis, which leads to the development of structural and electrical atrial remodelling, increasing the risk of AF/AFL.[26-28] Given that SGLT2 inhibitors modestly reduce blood pressure and body weight and improve glycaemic control, it has been hypothesized that SGLT2 inhibitors may reduce AF/AFL incidence in the high-risk populations.[29] SGLT2 inhibitors also provide cardioprotective effects by improving pre- and post-cardiac loading conditions, promoting efficient cardiac metabolism, ventricular remodelling, and potentially antiarrhythmic effects,[30] all of which could have a favourable impact on AF/AFL incidence and burden. Whilst no individual studies to date have been powered to assess the effect of SGLT2 inhibition on AF/AFL, a secondary analysis of DECLARE-TIMI 58 showed that dapagliflozin reduced the risk of AF/AFL events by 19% compared with placebo (264 vs. 325 events, 7.8 vs. 9.6 events per 1000 patient-years; HR 0.81, 95% CI 0.68-0.95).[15] The current pooled analysis, which included 14 543 participants with a median follow-up of 2.5 years, found a similar HR for AF/AFL; however, it was not statistically significant (193 vs. 161 events, 6.9 vs. 8.3 events per 1000 patient-years; HR 0.82, 95% CI 0.67-1.02). Whilst the current findings are not inconsistent with the DECLARE-TIMI 58 results, our lack of statistical significance needs to be explained. Patient populations did differ among the three studies, with CREDENCE participants having coexistent albuminuric CKD and T2D, whilst the CANVAS Program and DECLARE-TIMI 58 trial included participants with T2D and either established CV disease or high risk for CV disease. The key difference, however, may be the follow-up time. DECLARE-TIMI 58 followed participants for 4.2 years, as compared to only 2.5 years in the combined CANVAS Program and CREDENCE trial. This probably explains the smaller number of events observed in the current analysis, limiting our ability to identify reductions in AF/AFL. Supporting this, our broader meta-analysis of five SGLT2 inhibitor trials reporting on AF/AFL outcomes did identify a statistically significant reduction in AF/ALF events with active treatment.

It may also be hard to detect a reduction in AF/AFL events in those with established AF (many of whom may have persistent AF), which might explain why we cannot detect a treatment effect in this subgroup.[31]

The current analysis did identify differences in AF/AFL incidence across the included trials. The incidence of first AF/AFL event was higher in participants without prior AF/AFL in the CREDENCE trial (11.6%) as compared to that in the CANVAS Program (5.8%). This is reflective of the different participant populations, with 100% of participants having diabetic nephropathy in the CREDENCE trial and only 19% in the CANVAS Program. Further, the median UACR in the CREDENCE trial (929 mg/mmol) was much higher than that in the CANVAS Program (12.1 mg/mmol). Reduced kidney function and the presence of albuminuria are well known to be strongly associated with the incidence of AF, independent of other risk factors,[32,33] and CREDENCE can thus be expected to be a higher risk population for the occurrence of AF/AFL.

Recent systematic reviews have further supported a possible protective role for SGLT2 inhibitors in AF/AFL. For example, in one meta-analysis of 38 335 participants from 16 randomized controlled trials (four trials used empagliflozin, six trials used canagliflozin and six trials used dapagliflozin),[34] SGLT2 inhibitors significantly reduced the incidence of reported AF/AFL by 24% (risk ratio 0.76, 95% CI 0.65-0.90; $P_{\text{heterogeneity}} = 0.93$, $I^2 = 0\%$). A finding which was consistent regardless of age, HbA1c, blood pressure and body weight. A subsequent larger meta-analysis of 33 randomized controlled trials including 66 685 participants suggested that use of SGLT2 inhibitors was associated with a 17% lower rate of SAEs of AF/AFL compared with placebo (risk ratio 0.83, 95% CI 0.71-0.96; $P_{heterogeneity} = 0.98$; $I^2 = 0\%$).[16] This beneficial effect on AF/AFL was mainly driven by the DECLARE-TIMI 58 trial, with a weight of 38% for the meta-analysis. After exclusion of the DECLARE-TIMI 58 trial, the reduction in AF/AFL incidence did not remain statistically significant (risk ratio 0.87, 95% CI 0.72-1.05). Whilst there was an absence of statistically significant benefit for canagliflozin, as was seen in the current pooled analysis, point estimates were consistently less than 1. This may indicate that the lack of benefit for this outcome is related to inadequate event numbers and/or incidence rate rather than a lack of clinical effect for canagliflozin. This is supported by one other meta-analysis that suggests the reduction in AF/AFL risk is a class effect rather than drug-specific.[35] The promising findings seen in the current study, coupled with our meta-analysis of SGLT2 inhibitor clinical outcome trials reporting AF/AFL outcomes, and data from other trials and meta-analyses, strongly support future studies prespecified and adequately powered to assess the effect of SGLT2 inhibitors on incidence of AF/AFL.

Ischaemic stroke/TIA, HF and CV death are key serious AF/AFL-related complications. In this study we did not demonstrate a statistically significant reduction in ischaemic stroke. Canagliflozin did, however, significantly reduce the risk of the composite AF/AFL-related complication outcome in those with a baseline history of AF/AFL, driven by a reduction in hospitalization for HF. These findings were consistent in those with no known baseline AF/AFL, which may indicate that this is not related to preventing AF/AFL-related events but rather reflective of the overall broad CV benefits of canagliflozin. This does, however, highlight the importance of a holistic approach to AF/AFL management that is not limited to rate/rhythm control and anticoagulation. In support of this, it has been recommended that an integrated care model be used for the clinical management of AF, including more attention to optimization of comorbidities and CV risk factors.[36-38]

The clear and large reduction in HF (and HF/CV death) seen with SGLT2 inhibitor treatment in participants with T2D has been reported in many previous trials, including the CANVAS Program and EMPA-REG OUTCOME trial, with benefits potentially greater in those with a history of HF or AF at baseline.[39,40] In our study, participants with AF/AFL at baseline had similar relative benefits to those with no history of AF/AFL, but higher event rates indicative of their elevated baseline risk and comorbidities (including higher rates of baseline HF). This emphasizes the potential benefit of using SGLT2 inhibitors in those with established AF/AFL who have a higher CV risk and thus who will derive the greatest absolute benefit.[40,41]

This post hoc pooled analysis of randomized, placebo-controlled trials has some limitations. Both the CANVAS Program and the CREDENCE trial report history of AF/AFL at baseline based on the patient's self-reported medical history, which might underestimate the number of participants with AF/AFL. Further, investigators did not report on whether individuals had a history of persistent or paroxysmal AF/AFL. AF/AFL events were not prespecified outcomes of the trial and routine ECGs were not performed, thus AF/AFL adverse events may be underestimated. This is a particular limitation in those with a history of AF/AFL in whom AF/AFL events would be less likely to be recorded as adverse events. Furthermore, due to relatively few AF/AFL events we have limited power to assure significant differences between groups with sufficient confidence.

In conclusion, overall, a significant effect of canagliflozin on the incidence of AF/AFL events could not be shown, but canagliflozin appeared to possibly reduce the incidence of AF/AFL in those without known AF/AFL. Further, meta-analysis suggests SGLT2 inhibition does reduce AF/AFL incidence.

The relative effects of canagliflozin on other key CV and renal outcomes was not modified by baseline AF/AFL history. These results suggest that canagliflozin can be used to safely prevent CV and renal outcomes in high-risk individuals with T2D, with a potential role in reducing AF/AFL events.

AUTHOR CONTRIBUTIONS

C. Li, J. Yu and C. Arnott contributed to the design of the analysis and interpretation of data. C. Li and C. Arnott wrote the first draft of the manuscript. All other authors contributed to the interpretation of data and subsequent manuscript draft, and approved the final manuscript for submission.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data from the CANVAS Program are available in the public domain via the Yale University Open Data Access Project (YODA; http://yoda.yale.edu/). Data from the CREDENCE trial 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 18months.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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