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Effects of canagliflozin on myocardial infarction: a *post hoc* analysis of the CANVAS programme and CREDENCE trial

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Aims Given the benefits of sodium glucose co-transporter 2 inhibition (SGLT2i) in protecting against heart failure in diabetic patients, we sought to explore the potential impact of SGLT2i on the clinical features of patients presenting with myocardial infarction (MI) through a *post hoc* analysis of CANVAS Programme and CREDENCE trial.

Methods and results Individuals with type 2 diabetes and history or high risk of cardiovascular disease (CANVAS Programme) or type 2 diabetes and chronic kidney disease (CREDENCE) were included. The intervention was canagliflozin 100 or 300 mg (combined in the analysis) or placebo. MI events were adjudicated as ST-elevation myocardial infarction (STEMI), non-STEMI, and type 1 MI or type 2 MI. A total of 421 first MI events in the CANVAS Programme and 178 first MI events in the CREDENCE trial were recorded (83 fatal, 128 STEMI, 431 non-STEMI, and 40 unknown). No benefit of canagliflozin compared with placebo on time to first MI event was observed [hazard ratio (HR) 0.89; 95% confidence interval (CI) 0.75, 1.05]. Canagliflozin was associated with lower risk for non-STEMI (HR 0.78; 95% CI 0.65, 0.95) but suggested a possible increase in STEMI (HR 1.55; 95% CI 1.06, 2.27), with no difference in risk of type 1 or type 2 MI. There was no change in fatal MI (HR 1.22, 95% CI 0.78, 1.93).

Conclusion Canagliflozin was not associated with a reduction in overall MI in the pooled CANVAS Programme and CREDENCE trial population. The possible differential effect on STEMI and Non-STEMI observed in the CANVAS cohort warrants further investigation.

Trial registration ClinicalTrials.gov identifiers: NCT01032629, NCT01989754, and NCT02065791.

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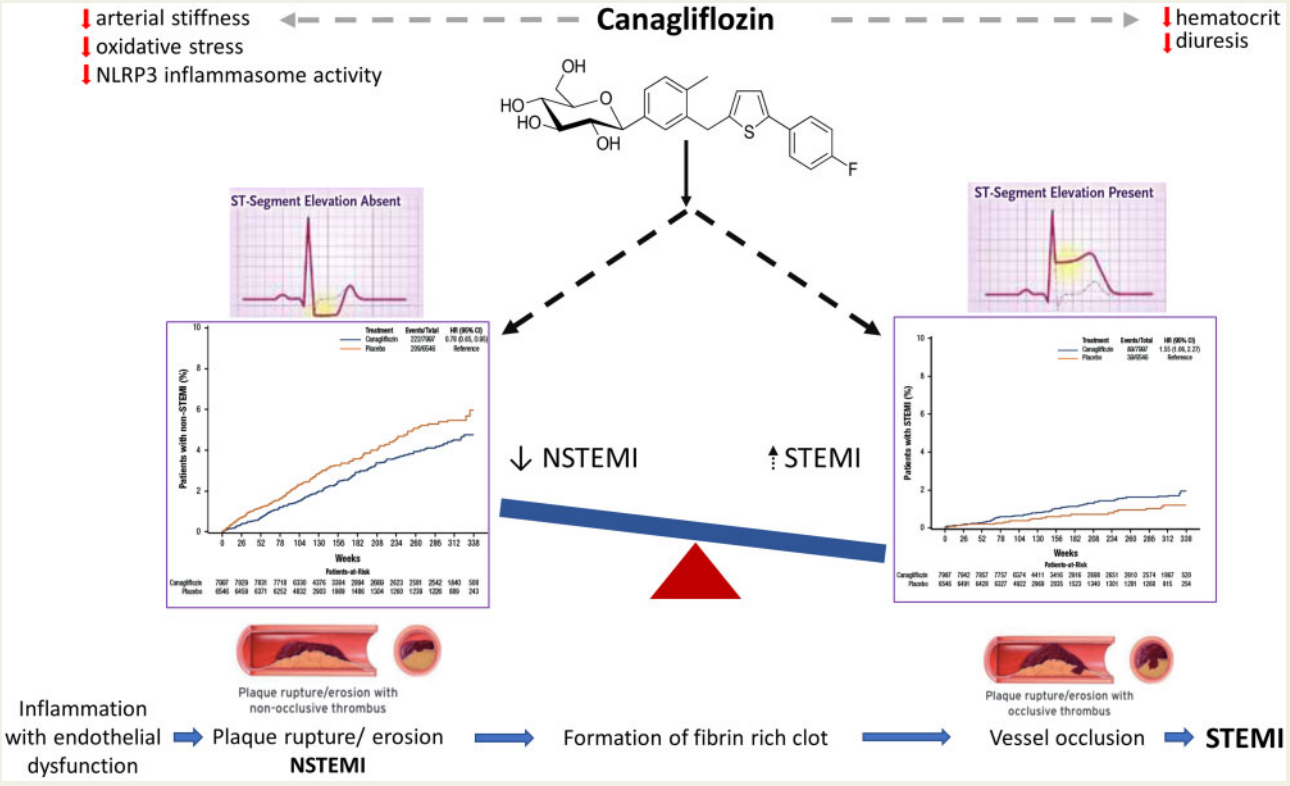
Graphical Abstract



Keywords Canagliflozin • Type 2 diabetes • Heart failure • Randomized trial • SGLT2 inhibitor

1. Introduction

An increased risk of atherosclerosis and myocardial infarction (MI) contributes to morbidity and mortality in patients with type 2 diabetes mellitus.[1–3] Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the risks of major adverse cardiovascular events and heart failure (HF) in individual trials, with evidence of possible protection against MI suggested by meta-analyses of the trials.[4] The pathogenesis of MI involves an interplay between the endothelium, inflammatory cells, and thrombogenic factors in the blood,[5–7] as well as direct myocardial effects, and therapy may differentially impact MI subtypes depending on the principal pathophysiology. Whether effects of SGLT2 inhibition are similar across MI subtypes is unknown, and the current study used the combined data from the CANVAS Programme[8] and the CREDENCE trial[9] to explore this question. Effects of canagliflozin vs. placebo were estimated for all MI [ST-elevation MI (STEMI), non-STEMI; and Type 1 MI and Type 2 MI] and fatal MI. Effects of canagliflozin on event severity and recurrent events were also examined.

2. Methods

The study used an individual patient data meta-analysis from the CANVAS Programme and CREDENCE trial. The design and main results of the CANVAS Programme[8,10–12] and the CREDENCE trial[9] have been published. In brief, the CANVAS Programme, comprising the integrated analysis of two similarly designed and conducted trials [CANVAS and CANVAS-Renal (CANVAS-R)], was designed to assess the cardiovascular and renal safety and efficacy of canagliflozin compared with placebo. CREDENCE was a placebo-controlled trial of canagliflozin in 4401 patients with type 2 diabetes and kidney disease. The protocols of both studies were approved by the local ethical committee at each site prior to recruitment. All the patients provided written informed consent including the use of patient data. The two studies were both conducted according to the ethical principles of the Declaration of Helsinki.

2.1 Participants

CANVAS Programme participants had type 2 diabetes mellitus [glycated haemoglobin (HbA1c) ≥7.0% and ≤10.5% and estimated glomerular filtration rate (eGFR) >0 mL/min/1.73m^2]. Participants were either aged ≥30 years with a history of symptomatic atherosclerotic cardiovascular disease, or aged ≥50 years with ≥2 risk factors for cardiovascular disease. CREDENCE participants had type 2 diabetes, eGFR 30 to <90 mL/min/1.73 m^2, and urine albumin: creatinine ratio (UACR) >300–5000 mg/g.

2.2 Randomization, treatment, and follow-up

CANVAS participants were randomized (1:1:1) to canagliflozin 300 mg, canagliflozin 100 mg, or placebo, and CANVAS-R participants were

randomized (1:1) to canagliflozin or placebo, at an initial dose of 100 mg daily with optional up titration to 300 mg from Week 13. CREDENCE participants were randomized (1:1) to canagliflozin 100 mg or placebo, with stratification by screening eGFR categories (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2).

Participants and all study and sponsor staff were masked to individual treatment allocations. Background glycaemic and cardiovascular therapies were managed according to best practice. Face-to-face follow-up occurred at least once every 6 months after randomization with alternating telephone follow-up between face-to-face assessments. As MI event subtypes were not pre-specified target outcomes, the total corresponding data related to this *post hoc* analysis were not completely available.

2.3 Outcomes

Outcomes of interest for these analyses were time to first (i) all MI; (ii) fatal MI; (iii) MI subtypes [STEMI, non-STEMI, and unknown MI (uMI)]; (iv) Type 1 MI and Type 2 MI. All MI events were assessed by a blinded endpoint adjudication committee using the same pre-specified set of criteria for diagnosis that were broadly consistent across the CANVAS Programme[8] and the CREDENCE trial.[9] In the CREDENCE trial, MI subtype (fatal/non-fatal; STEMI/non-STEMI; Type 1/Type 2) was recorded by the adjudication committee according to standard criteria (Supplementary material online, *Table S1*).[9,13,14] In the CANVAS Programme, the same detailed MI features were obtained by secondary review of the documentation used for endpoint adjudication (G.F., J.Y., J.L., and P.J.L.). Presence of LV dysfunction was extracted by secondary review of the adjudication package, but was only available for participants in the CANVAS Programme, and only when clinically documented. Assessment was based upon reports of LV function made within 30 days of the MI event, and definitions of LV dysfunction were based upon the lowest reported ejection fraction. The occurrence of complications within 30 days of the MI was determined from review of the endpoint packages for the CANVAS Programme and from review of adverse event reports in the CANVAS Programme and the CREDENCE trial. Cardiogenic shock was defined by hemodynamic criteria: systolic blood pressure <90 mmHg for at least 30 min, or vasopressors required to achieve a blood pressure >90 mmHg with clinical evidence of impaired organ perfusion, pulmonary congestion, or both.

2.4 Statistical analysis

Categorical variables were summarized as the number of patients 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 χ^2 or generalized Cochran–Mantel–Haenszel test for categorical variables, a *t*-test for continuous normally distributed variables, and a Wilcoxon 2-sample test for continuous variables with a skewed distribution. Univariable and multivariable models were fitted to determine the baseline participant characteristics associated with the risk of MI and the risk of different subtypes of MI (STEMI vs. non-STEMI). Baseline participant characteristics associated with MI risk were assessed using proportional hazards models in the combined data from the CANVAS Programme and CREDENCE trial. Univariate associations were determined for candidate MI risk factors independent of treatment assignment; those risks with significant univariate associations [95% confidence intervals (CIs) did not cross unity] were included in a single multivariate model that also included randomized treatment.

The effects of canagliflozin (doses combined) compared to placebo on MI, MI subtypes (STEMI, non-STEMI, and uMI; Type 1 MI and Type 2 MI), and MI associated with complications were estimated by combining the CANVAS Programme and CREDENCE trial datasets and undertaking individual participant data meta-analyses using an intention-to-treat approach with stratification for trial. Annualized incidence rates per 1000 patient-years of follow-up were calculated for all outcomes in addition to hazard ratios (HRs) and 95% CI determined from Cox regression models. Given that all analyses were *post hoc*, we have calculated CIs but not *P*-values for effect estimates. The constancy of effects across the trials was evaluated by assessing the percentage of variability across the pooled estimates attributable to heterogeneity beyond chance using the I^2 statistic and also by calculating the *P*-value for heterogeneity via the Q 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 heterogeneity beyond chance. A *P*-value for heterogeneity of <0.05 was considered to show significant heterogeneity, >0.1 was interpreted as no evidence of heterogeneity, and values between 0.05 and 0.10 were considered to demonstrate borderline heterogeneity.[15,16] Analyses were performed using SAS version 9.2, SAS Enterprise Guide version 7.1. There was no imputation for missing data.

3. Results

3.1 Baseline characteristics

There were 14 543 patients in the integrated CANVAS Programme and CREDENCE trial. Over a median of 2.5 years, a total of 599 (4.1%) patients experienced an MI (first event during study). In 83 patients, this MI was fatal (Supplementary material online, *Figure S1*). Of the total MI (first MI for each participant), 128 were STEMIs, 431 were non-STEMIs, and 40 were undetermined uMIs. Baseline characteristics of the CANVAS Programme[8] and CREDENCE trial[9] were generally similar except that, by design, the entire CREDENCE cohort compared with the CANVAS Programme cohort had more participants with microvascular disease (nephropathy, neuropathy, and retinopathy all *P*<0.001) with UACR>300 mg/g (100% vs. 5%; *P* < 0.001), and a greater proportion of participants had reduced eGFR in the CREDENCE trial compared to the CANVAS Programme (60% vs. 21%). Conversely, there were more secondary prevention patients in the CANVAS Programme vs. CREDENCE trial (66% vs. 50%). Baseline HF history was similar between trials (15%).

Table 1 presents baseline characteristics of participants who did and did not have MI during follow-up in the combined CANVAS Programme and CREDENCE trial data. Those who experienced an MI were older (mean age 64.5±8.5 vs. 63.2±8.5 years), more likely to be male (73.0% vs. 64.4%), and more frequently had pre-existing cardiovascular disease (79.0% vs. 60.3%), previous MI (38.6% vs. 22.7%) or peripheral arterial disease (27.0% vs. 21.5%). They also displayed a higher mean systolic blood pressure (140.5±17.9 vs. 137.5±15.7 mmHg) and a lower eGFR (66.4±21.2 vs. 70.5±22.0 mL/min/1.73 m^2). Baseline diuretic, beta blocker, calcium channel blocker, statin, and antithrombotic use were higher in those who experienced an MI. Baseline insulin therapy was more frequent in those with an MI, while metformin and dipeptidyl peptidase-4 inhibitor use was lower. Male sex, pre-existing cardiac disease, systolic blood pressure, eGFR, UACR, and insulin therapy at baseline

Table 1 Baseline characteristics of participants who did or did not suffer MI during follow-up in the combined data from the CANVAS Programme and the CREDENCE trial

	No MI (*n*=13 944)	MI[a] (*n*=599)	*P*-value MI vs. no MI	MI[a](*n*=599)			
				STEMI[a] (*n*=128)	Non-STEMI[a] (*n*=431)	uMI[a] (*n*=40)	*P*-value STEMI vs. non-STEMI
Age, years, mean (SD)	63.2 (8.5)	64.5 (8.5)	<0.001	62.4 (9.0)	65.2 (8.3)	63.8 (7.7)	0.001
Male, *N* (%)	8979 (64.4)	437 (73.0)	<0.001	94 (73.4)	311 (72.2)	32 (80.0)	0.776
Current smoker, *N* (%)	2341 (16.8)	104 (17.4)	0.715	24 (18.8)	70 (16.2)	10 (25.0)	0.505
Hypertension, *N* (%)	12 830 (92.0)	555 (92.7)	0.569	118 (92.2)	398 (92.3)	39 (97.5)	0.954
Duration of diabetes, years, mean (SD)	14.2 (8.1)	14.8 (8.5)	0.068	13.3 (8.7)	15.2 (8.2)	15.8 (9.5)	0.024
Microvascular disease, *N* (%)							
Retinopathy	3821 (27.4)	190 (31.7)	0.021	31 (24.2)	141 (32.7)	18 (45.0)	0.067
Nephropathy	5910 (42.4)	265 (44.2)	0.368	45 (35.2)	199 (46.2)	21 (52.5)	0.027
Neuropathy	5017 (36.0)	240 (40.1)	0.042	41 (32.0)	176 (40.8)	23 (57.5)	0.073
Cardiovascular disease, *N* (%)	8403 (60.3)	473 (79.0)	<0.001	94 (73.4)	346 (80.3)	33 (82.5)	0.097
Coronary disease	6629 (47.5)	405 (67.6)	<0.001	80 (62.5)	299 (69.4)	26 (65.0)	0.144
Prior MI	3167 (22.7)	231 (38.6)	<0.001	56 (43.8)	161 (37.4)	14 (35.0)	0.192
Heart failure	2025 (14.5)	88 (14.7)	0.909	16 (12.5)	66 (15.3)	6 (15.0)	0.430
Coronary revascularization	3893 (27.9)	256 (42.7)	<0.001	48 (37.5)	191 (44.3)	17 (42.5)	0.171
Cerebrovascular disease	2539 (18.2)	119 (19.9)	0.304	24 (18.8)	88 (20.4)	7 (17.5)	0.679
Peripheral arterial disease	2997 (21.5)	162 (27.0)	0.001	27 (21.1)	123 (28.5)	12 (30.0)	0.095
Prior amputation	447 (3.2)	25 (4.2)	0.191	2 (1.6)	21 (4.9)	2 (5.0)	0.098
Body mass index, kg/m^2, mean (SD)	31.7 (6.0)	32.2 (5.8)	0.054	31.4 (5.5)	32.6 (5.9)	30.9 (5.5)	0.050
SBP, mmHg, mean (SD)	137.5 (15.7)	140.5 (17.9)	<0.001	138.9 (15.8)	141.0 (18.4)	140.0 (18.7)	0.237
DBP, mmHg, mean (SD)	77.9 (9.6)	76.9 (10.0)	0.011	77.8 (9.4)	76.5 (10.1)	78.3 (10.5)	0.176
Glycated haemoglobin, %, mean (SD)	8.3 (1.1)	8.3 (1.1)	0.108	8.3 (1.1)	8.3 (1.0)	8.6 (1.2)	0.832
Total cholesterol, mmol/L, mean (SD)	4.4 (1.2)	4.5 (1.3)	0.250	4.7 (1.3)	4.4 (1.2)	4.6 (1.4)	0.026
Triglycerides, mmol/L, median (IQR)	1.7 (1.3, 2.4)	1.8 (1.2, 2.6)	0.116	1.9 (1.4, 2.6)	1.8 (1.2, 2.6)	1.5 (1.2, 2.7)	0.141
LDL cholesterol, mmol/L, mean (SD)	2.4 (1.0)	2.4 (1.0)	0.200	2.6 (1.1)	2.3 (1.0)	2.5 (0.9)	0.008
HDL cholesterol, mmol/L, mean (SD)	1.2 (0.3)	1.1 (0.3)	0.117	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)	0.475
eGFR, mL/min/1.73 m^2, mean (SD)	70.5 (22.0)	66.4 (21.2)	<0.001	70.5 (19.6)	65.5 (21.4)	63.4 (22.4)	0.018
Urinary albumin: creatinine ratio, mg/g, median (IQR)	32.9 (8.4, 518.0)	45.6 (9.3, 657.5)	0.050	32.3 (8.0, 190.6)	47.0 (9.3, 726.7)	277.1 (18.8, 1460.0)	0.016
Medication use, *N* (%)							
Diuretic	6236 (44.7)	311 (51.9)	0.001	61 (47.7)	222 (51.5)	28 (70.0)	0.444
Loop diuretic	2138 (15.3)	125 (20.9)	<0.001	17 (13.3)	95 (22.0)	13 (32.5)	0.297
RAAS inhibitor	11 995 (86.0)	516 (86.1)	0.933	106 (82.8)	372 (86.3)	38 (95.0)	0.324
Beta blocker	6818 (48.9)	373 (62.3)	<0.001	77 (60.2)	271 (62.9)	25 (62.5)	0.577
Calcium channel blocker	5310 (38.1)	262 (43.7)	0.005	48 (37.5)	196 (45.5)	18 (45.0)	0.110
Statin	10 168 (72.9)	468 (78.1)	<0.001	88 (68.8)	350 (81.2)	30 (75.0)	0.003
Antithrombotic[b]	9617 (69.0)	478 (79.8)	<0.001	95 (74.2)	353 (81.9)	30 (75.0)	0.056
Insulin	7595 (54.5)	384 (64.1)	<0.001	64 (50.0)	296 (68.7)	24 (60.0)	<0.001

Continued

Table 1 *Continued*

	No MI (n=13 944)	MI[a] (n=599)	*P*-value MI vs. no MI	MI[a](n=599)			
				STEMI[a] (n=128)	Non-STEMI[a] (n=431)	uMI[a] (n=40)	*P*-value STEMI vs. non-STEMI
Metformin	9986 (71.6)	384 (64.1)	<0.001	88 (68.8)	271 (62.9)	25 (62.5)	0.224
Sulfonylurea	5422 (38.9)	207 (34.6)	0.033	50 (39.1)	142 (32.9)	15 (37.5)	0.201
Thiazolidinedione	604 (4.3)	24 (4.0)	0.702	6 (4.7)	18 (4.2)	0 (0)	0.802
GLP-1 receptor agonist	565 (4.1)	25 (4.2)	0.883	4 (3.1)	19 (4.4)	2 (5.0)	0.521
DPP-4 inhibitor	1949 (14.0)	63 (10.5)	0.016	14 (10.9)	46 (10.7)	3 (7.5)	0.932

Baseline characteristics were compared using χ^2 test for categorical variables and *t*-test for continuous normally distributed variables, and a Wilcoxon 2-sample test for continuous variables with a skewed distribution.
DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure; SD, standard deviation.
[a]Only time to the first MI events were included analyses.
[b]Includes antiplatelets and anticoagulants.

were significant predictors of MI on univariate and multivariate analysis (*Table 2*).

Baseline characteristics and their association with the likelihood of an MI presenting as a STEMI vs. non-STEMI were also examined *(Table 2* and Supplementary material online, *Table S2*). On univariate analysis, the likelihood of presenting with a STEMI vs. non-STEMI was 44% lower for those on baseline statins (HR 0.56; 95% CI 0.38, 0.81) and 47% lower for those on baseline insulin (HR 0.53; 95% CI 0.37, 0.76). Baseline insulin use was the only factor that remained significant on multivariate analysis (HR 0.59; 95% CI 0.41, 0.85). With respect to continuous variables associated with an increased risk of STEMI compared to non-STEMI, total cholesterol (HR 1.26; 95% CI 1.09, 1.45) and LDL cholesterol levels (HR 1.38; 95% CI 1.17, 1.63) were significant on univariate analysis only.

3.2 The effects of canagliflozin on MI and MI subtypes

In the CANVAS Programme and CREDENCE trial, the pre-specified endpoint of CV death, non-fatal MI, and non-fatal stroke showed statistically significant reduction in risk with canagliflozin vs. placebo, with all three components, including non-fatal MI, contributing.[8,9] There was no clear effect of canagliflozin on MI overall (HR 0.89; 95% CI 0.75, 1.05) with comparable results for the CANVAS Programme (HR 0.89; 95% CI 0.73, 1.09) and the CREDENCE trial (HR 0.86; 95% CI 0.64, 1.16) and no heterogeneity between studies (I^2 =0%, *P* interaction =0.82; *Figure 1*).

With respect to MI subtypes, canagliflozin treatment was associated with a 22% lower rate of non-STEMI (HR 0.78; 95% CI 0.65, 0.95), with comparable effects in the CANVAS Programme and the CREDENCE trial (I^2 =0%, *P* interaction =0.34; *Figure 1*). STEMI risk was 55% higher in participants randomized to canagliflozin treatment in the pooled analysis (HR 1.55; 95% CI 1.06, 2.27), with some evidence of heterogeneity between the two studies (CANVAS Programme: HR 1.83; 95% CI 1.17, 2.86 compared to CREDENCE trial HR 0.84; 95% CI 0.38, 1.87; I^2 =67.6%, *P* interaction =0.09; *Figure 1*). There was no association of treatment allocation with the risk of uMI (HR 0.70; 95% CI 0.37, 1.31). Cumulative event curves for MI subtypes (STEMI and non-STEMI) in the pooled CANVAS Programme and the CREDENCE trial are presented in *Figure 2*. Canagliflozin treatment was not associated with significant differences in type 1 MI or type 2 MI (*Figure 3*).

No clear difference in hazard rates for fatal MI was observed between studies (HR 1.22; 95% CI 0.78, 1.93; I^2 =0%, *P* interaction = 0.90; *Figure 1*). Cumulative events for fatal MI in the CANVAS Programme and the CREDENCE trial are presented in *Figure 2*.

MI outcomes were assessed with respect to canagliflozin dose (100 vs. 300 mg) in CANVAS alone (Supplementary material online, *Figure S2*). The only outcome that varied by dose was STEMI, which occurred less frequently in participants assigned to canagliflozin 300 vs. 100 mg (HR 0.49; 95% CI 0.28, 0.84).

3.3 Clinical features of MI patients according to treatment

Despite interrogation of individual case files, consistency of data entry regarding cardiac enzymes and other clinical markers of clinical severity and complications were insufficient for detailed analysis. The limited data are presented in Supplementary material online, *Table S2*. There were no differences in systolic or diastolic blood pressure and heart rates at the time of MI presentation by treatment group. Mean (standard deviation) LVEF (*n*=171) was similar in the canagliflozin vs. placebo groups

Table 2 Baseline characteristics associated with risk of MI[a] and risk of STEMI[a] vs. non-STEMI[a] in the combined data from the CANVAS Programme and the CREDENCE trial

	MI vs. no MI		STEMI vs. Non-STEMI	
	Univariable HR (95% CI)	Multivariable HR (95% CI)	Univariable HR (95% CI)	Multivariable HR (95% CI)
Demographics				
Age (years older)	**1.02 (1.01, 1.03)**		0.98 (0.96, 1.00)	
Male	**1.43 (1.20, 1.72)**	**1.28 (1.06, 1.55)**	1.01 (0.68, 1.51)	
Current smoker (yes/no)	1.04 (0.85, 1.29)		1.29 (0.82, 2.01)	
Race				
White vs. non-White	1.12 (0.93, 1.35)		1.01 (0.65, 1.55)	
Asian vs. non-Asian	0.87 (0.69, 1.09)		1.29 (0.77, 2.13)	
Black vs. non-Black	1.09 (0.71, 1.66)		0.53 (0.13, 2.16)	
Region				
North America vs. others	**1.20 (1.00, 1.43)**		1.00 (0.68, 1.46)	
Central/South America vs. others	**0.57 (0.41, 0.79)**	**0.65 (0.45, 0.93)**	1.25 (0.50, 3.10)	
Europe vs. others	**1.23 (1.04, 1.46)**		0.94 (0.65, 1.38)	
Rest of world vs. others	0.84 (0.70, 1.00)		1.03 (0.70, 1.53)	
Hypertension (yes/no)	1.19 (0.87, 1.62)		1.07 (0.56, 2.06)	
Duration of diabetes (years greater)	**1.01 (1.00, 1.02)**		0.98 (0.96, 1.00)	
Microvascular disease (yes/no)				
Retinopathy	**1.28 (1.07, 1.52)**		0.84 (0.55, 1.28)	
Nephropathy	**1.33 (1.05, 1.68)**		1.01 (0.63, 1.64)	
Neuropathy	**1.21 (1.03, 1.43)**		0.92 (0.62, 1.36)	
Cardiovascular disease (yes/no)	**2.76 (2.26, 3.36)**	**1.79 (1.35, 2.37)**	0.72 (0.48, 1.07)	
Coronary disease	**2.44 (2.04, 2.90)**		0.74 (0.51, 1.07)	
Prior myocardial infarction	**2.34 (1.97, 2.77)**	**1.51 (1.24, 1.85)**	1.08 (0.75, 1.55)	
Heart failure	1.10 (0.88, 1.38)		0.80 (0.47, 1.36)	
Coronary revascularization	**2.13 (1.80, 2.51)**		0.75 (0.52, 1.08)	
Cerebrovascular disease	1.19 (0.97, 1.45)		0.99 (0.63, 1.54)	
Peripheral arterial disease	**1.51 (1.26, 1.81)**		1.08 (0.69, 1.68)	
Atrial fibrillation	1.41 (0.97, 2.06)		0.41 (0.13, 1.31)	
Amputation (yes/no)	1.44 (0.97, 2.16)		0.57 (0.14, 2.35)	
Laboratory and clinical variables				
Body mass index (1 kg/m^2 greater)	1.01 (1.00, 1.02)		**0.96 (0.93, 0.99)**	
SBP (1 mmHg greater)	**1.01 (1.01, 1.02)**	**1.02 (1.01, 1.02)**	1.00 (0.99, 1.01)	
DBP (1 mmHg greater)	**0.99 (0.98, 1.00)**	**0.99 (0.98, 1.00)**	1.02 (1.00, 1.03)	
Glycated haemoglobin (1% greater)	**1.09 (1.02, 1.18)**	**1.13 (1.04, 1.22)**	0.94 (0.79, 1.12)	
Total cholesterol (1 mmol/L greater)	1.05 (0.98, 1.12)		**1.26 (1.09, 1.45)**	
Triglycerides (1 mmol/L greater)	1.03 (0.98, 1.08)		1.02 (0.90, 1.15)	
LDL cholesterol (1 mmol/L greater)	1.07 (0.99, 1.16)		**1.38 (1.17, 1.63)**	
HDL cholesterol (1 mmol/L greater)	0.80 (0.62, 1.03)		0.97 (0.51, 1.83)	
eGFR (1 mL/min greater)	**0.99 (0.98, 0.99)**	**0.99 (0.99, 1.00)**	1.00 (0.99, 1.01)	
UACR (1 mg/g greater)	**1.00 (1.00, 1.00)**	**1.00 (1.00, 1.00)**	1.00 (1.00, 1.00)	
HCT (1% greater)	0.98 (0.97, 1.00)		1.02 (0.99, 1.06)	
Concomitant medications (yes/no)				
Diuretic	**1.32 (1.13, 1.55)**		0.87 (0.62, 1.24)	
Loop diuretic	**1.56 (1.28, 1.90)**		0.66 (0.39, 1.11)	
RAAS inhibitor	1.01 (0.79, 1.28)		0.86 (0.54, 1.39)	
Beta blocker	**1.77 (1.50, 2.09)**		0.75 (0.52, 1.08)	
Calcium channel blocker	**1.28 (1.09, 1.51)**		0.90 (0.62, 1.30)	
Statin	**1.33 (1.09, 1.61)**		**0.56 (0.38, 0.81)**	
Antithrombotic[b]	**1.82 (1.49, 2.22)**		0.67 (0.45, 1.00)	
Insulin	**1.52 (1.28, 1.80)**	**1.24 (1.01, 1.54)**	**0.53 (0.37, 0.76)**	**0.59 (0.41, 0.85)**
Metformin	**0.72 (0.61, 0.85)**		1.08 (0.74, 1.58)	

Continued

Table 2 *Continued*

	MI vs. no MI		STEMI vs. Non-STEMI	
	Univariable HR (95% CI)	**Multivariable HR (95% CI)**	**Univariable HR (95% CI)**	**Multivariable HR (95% CI)**
Sulfonylurea	**0.78 (0.65, 0.92)**		1.08 (0.75, 1.55)	
Thiazolidinedione	0.72 (0.48, 1.08)		0.54 (0.22, 1.35)	
GLP-1 receptor agonist	1.14 (0.77, 1.71)		0.75 (0.27, 2.03)	
DPP-4 inhibitor	0.81 (0.62, 1.05)		1.27 (0.72, 2.23)	
Canagliflozin treatment (yes/no)	0.89 (0.75, 1.05)		**1.49 (1.02, 2.19)**	

Univariable and multivariable models were fitted to determine the baseline participant characteristics associated with the risk of MI and the risk of different subtypes of MI (STEMI vs. non-STEMI). Baseline participant characteristics associated with MI risk were assessed using proportional hazards models in the combined data from the CANVAS Programme and CREDENCE trial. Univariate associations were determined for candidate MI risk factors independent of treatment assignment; those risks with significant univariate associations (95% confidence intervals did not cross unity) were included in a single multivariate model that also included randomized treatment showed as bold values. The multivariate model included all characteristics with significant univariate associations. Only characteristics significant in the multivariate model are listed as bold values.

95% CI, 95% confidence interval; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HCT, haematocrit; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; UACR, urine albumin: creatinine ratio.

[a]Only time to the first MI events were included analyses.

[b]Includes antiplatelets and anticoagulants.

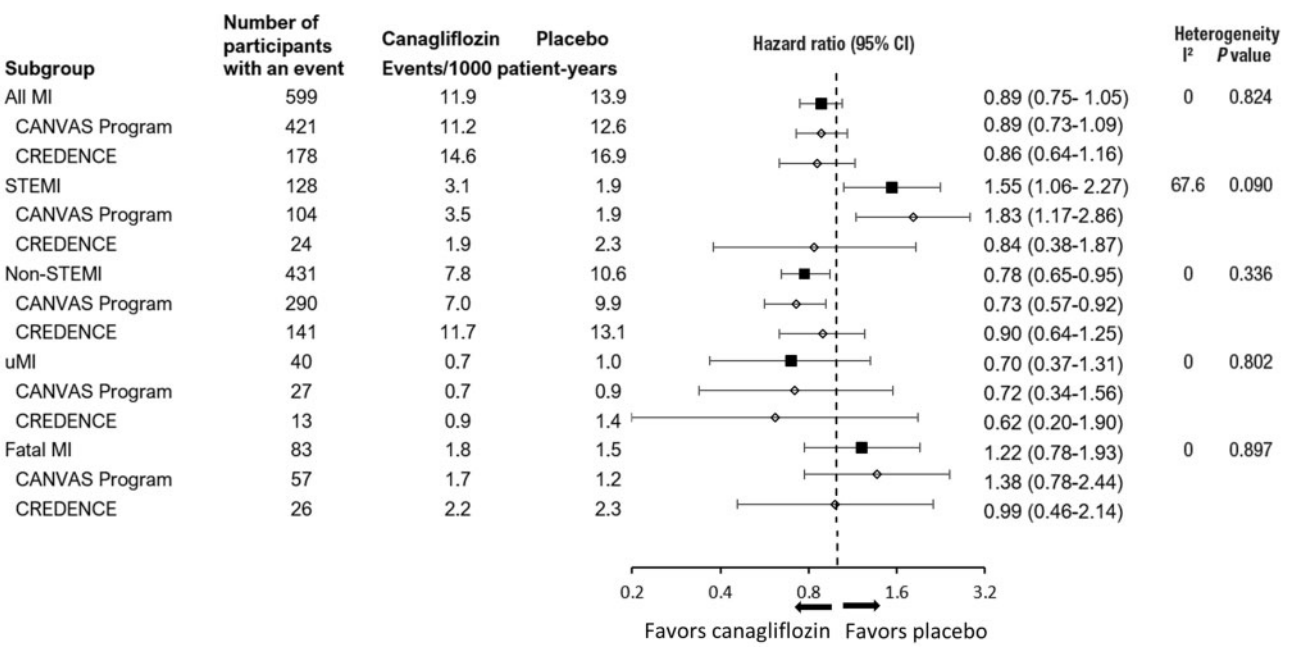


Figure 1 Effects of canagliflozin vs. placebo on MI subtypes for the participants in CANVAS Programme, CREDENCE trial, and overall. All 599 time to the first MI events were recorded (421 in the CANVAS Programme and 178 events in the CREDENCE trial). These included 128 STEMI, 431 non-STEMI, 40 uMI, and 83 fatal MI. The effects of canagliflozin (doses combined) compared to placebo on MI and MI subtypes were estimated by combining the CANVAS Programme and the CREDENCE trial datasets and undertaking individual participant data meta-analyses using an intention-to-treat approach with stratification for trial. Annualized incidence rates per 1000 patient-years of follow-up were calculated for all outcomes in addition to HRs and 95% CIs determined from Cox regression models. The constancy of effects across the trials was evaluated by assessing the percentage of variability across the pooled estimates attributable to heterogeneity beyond chance using the I^2 statistic and also by calculating the *P*-value for heterogeneity via the Q statistic. 95% CI, 95% confidence interval; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; uMI, unknown myocardial infarction.

(49.5±12% vs. 48.3±14%, $P = 0.65$). When all MI patients were considered, cardiogenic shock occurred more frequently with canagliflozin vs. placebo (8.1% vs. 2.3%, $P = 0.02$), but the number of events was small and the observation may have been driven by the higher proportion of STEMI. Of note, rates of revascularization and evidence-based medical management were low, but not significantly different between the treatment groups.

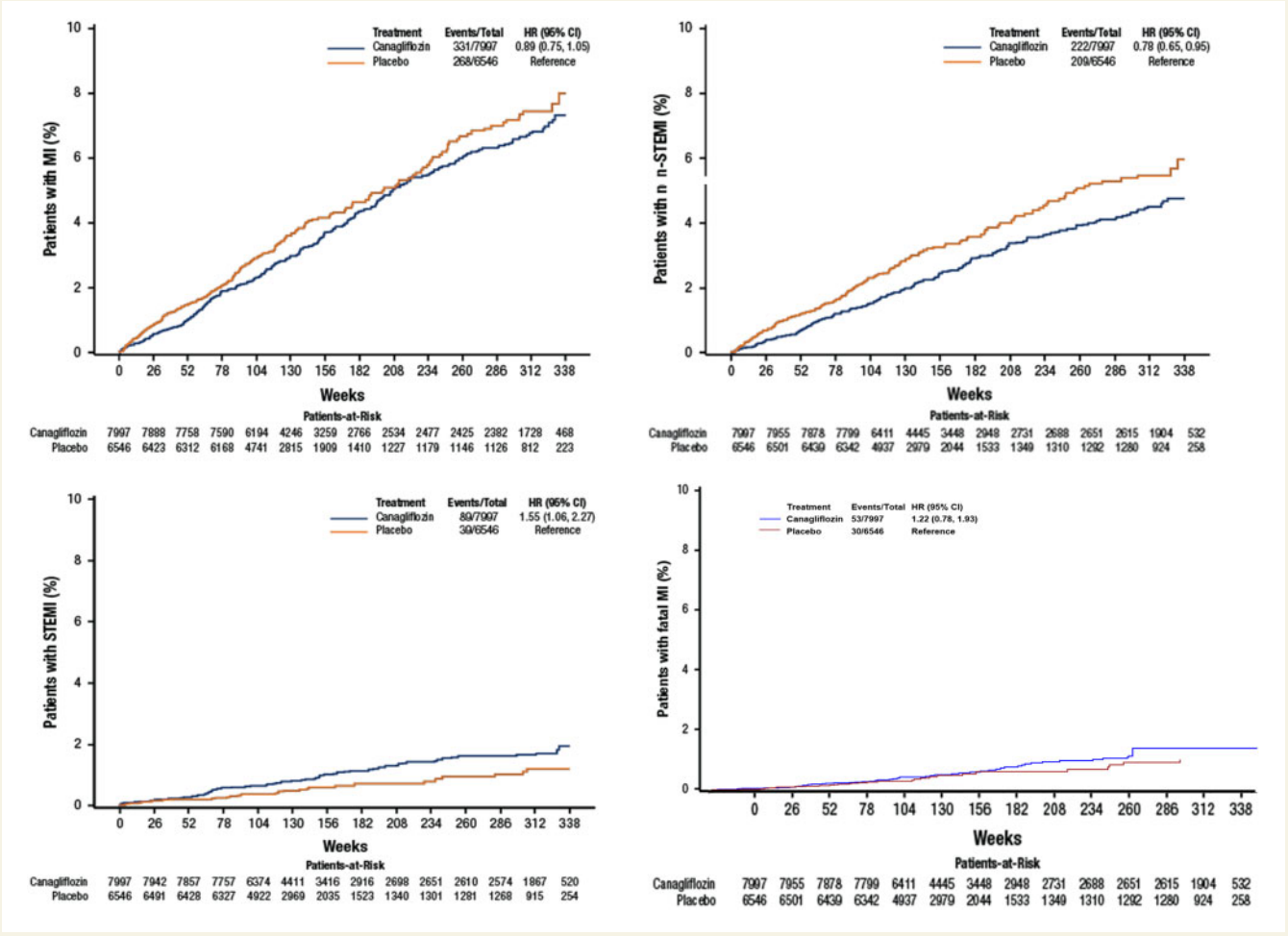


Figure 2 Cumulative event curves for all MI*, non-STEMI*, STEMI*, and fatal MI in the combined data from the CANVAS Programme and the CREDENCE trial. All 599 patients experienced the first MI (331 in canagliflozin and 268 in placebo), including 431 non-STEMI (222 in canagliflozin and 209 in placebo), 128 STEMI (89 in canagliflozin and 39 in placebo), and 83 fatal MI (53 in canagliflozin and 30 in placebo). The effects of canagliflozin (doses combined) compared to placebo on MI and MI subtypes were estimated by combining the CANVAS Programme and CREDENCE trial datasets and undertaking individual participant data meta-analyses using an intention-to-treat approach with stratification for trial. HRs and 95% CIs were determined from Cox regression models. 95% CI, 95% confidence interval; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; uMI, unknown myocardial infarction.

3.4 Effects of SGLT2 inhibition on recurrent HF events post-MI

Participants who experienced an MI from both treatment groups received similar in-hospital treatment, including evidence-based revascularization and prescription of discharge medications, including antiplatelets, renin–angiotensin–aldosterone system inhibitor, beta blockers, and statins (Supplementary material online, *Table S2*). We explored the association of canagliflozin treatment with events post-discharge, through to study completion in the CANVAS Programme. Treatment discontinuation after non-fatal MI in the CANVAS Programme was 19/374 (5.1%) while that in the CREDENCE trial was 2/158 (1.3%). Recurrent MI was observed in 49/374 patients (13.1%) who survived their initial first MI, with no difference for canagliflozin vs. placebo (14.9% vs. 10.7%, $P = 0.24$). Hospitalized HF occurred in 34/374 (9.1%) non-fatal MI patients, and was not significantly different with canagliflozin vs. placebo ($P = 0.51$) (*Table 3*).

4. Discussion

In patients with type 2 diabetes and high cardiovascular risk from the combined CANVAS Programme and CREDENCE trial, the rate of MI was substantial, impacting 1 in 20 patients within 2 years of follow-up; over 10% of the MIs were fatal. Canagliflozin did not reduce the risk of overall MI in the integrated dataset from the CANVAS Programme and CREDENCE trial. There was a possible directional difference in the effect of canagliflozin for non-STEMI vs. STEMI arising from the CANVAS Programme but not confirmed in the CREDENCE trial, with a significant protective effect of canagliflozin for non-STEMI, but an association with higher rates of STEMI. It is possible that these differences result from chance, supported by the moderate heterogeneity for the STEMI finding between the CANVAS Programme and CREDENCE trial.

The possible differential effect of canagliflozin on non-STEMI vs. STEMI was driven primarily by the CANVAS Programme, with moderate heterogeneity in the effect on non-STEMI vs. STEMI between the

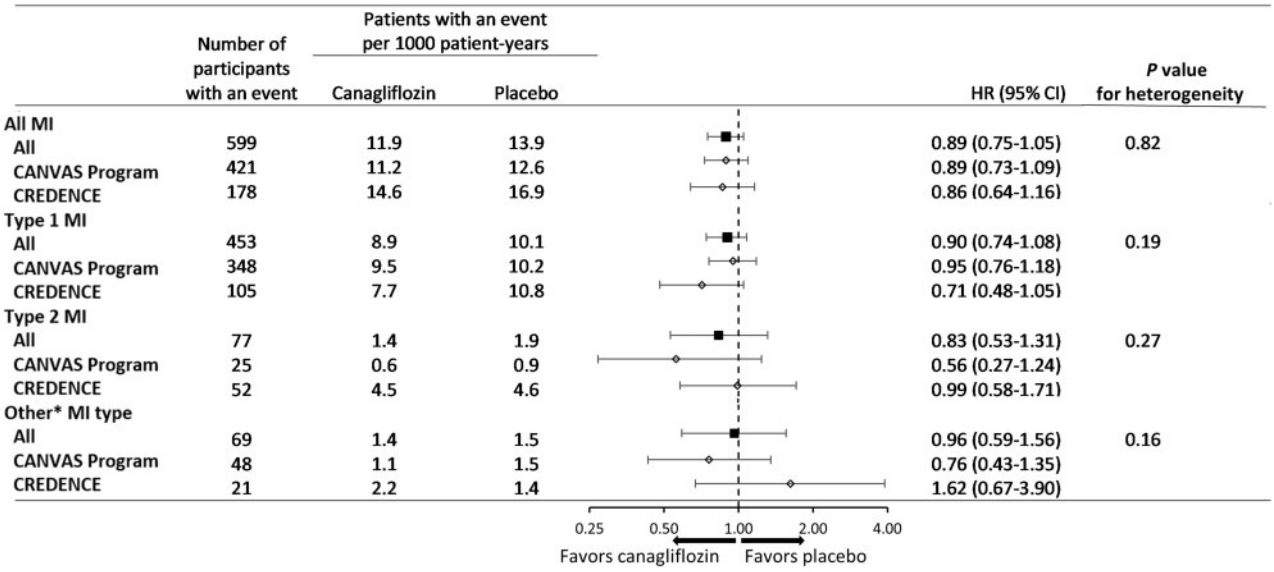


Figure 3 Effects of canagliflozin vs. placebo on all MI, type 1 MI, type 2 MI, other type MI in the combined data# from the CANVAS Programme and the CREDENCE trial. All 599 patients experienced the first MI, including 453 Type 1 MI (253 in canagliflozin and 200 in placebo), 77 Type 2 MI (39 in canagliflozin and 38 in placebo), and 69 other MI (39 in canagliflozin and 30 in placebo). The effects of canagliflozin (doses combined) compared to placebo on MI subtypes were estimated by combining the CANVAS Programme and CREDENCE trial datasets and undertaking individual participant data meta-analyses using an intention-to-treat approach with stratification for trial. HRs and 95% CIs were determined from Cox regression models. Other includes type 4 MI and unknown MI type. Only time to the first MI events were included analyses. 95% CI, 95% confidence interval; HR, hazard ratio; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 3 Post-discharge recurrent events of non-fatal MI participants in the CANVAS Programme by treatment group

Events, *N* (%)	Canagliflozin (*n*=215)	Placebo (*n*=159)	Non-fatal MI (*n*=374)	*P*-value canagliflozin vs. placebo
MI	32 (14.9)	17 (10.7)	49 (13.1)	0.24
HF	17 (7.9)	17 (10.7)	34 (9.1)	0.51
Stroke	8 (3.7)	6 (3.8)	14 (3.7)	0.86
Cardiovascular death	31 (14.4)	17 (10.7)	48 (12.8)	0.26
All-cause death	35 (16.3)	25 (15.7)	60 (16.0)	0.93

Compared by using a χ^2 test.
HF, heart failure; MI, myocardial infarction.

CANVAS Programme and CREDENCE trial. Whilst the trial populations were different at baseline with respect to proportion with cardiovascular disease history and UACR, neither characteristic was associated with higher STEMI risk. It is unlikely related to dose differences, given the observation in the CANVAS trial alone that the rate of STEMI was higher in the 100 vs. 300 mg group, but no increase in STEMI vs. non-STEMI was seen in CREDENCE trial, which exclusively prescribed canagliflozin 100 mg.

Whilst chance may be an explanation for the canagliflozin associated increase in STEMI observed in the CANVAS programme, and we have not confirmed a mechanism for our findings, we believe that the observations in this combined cohort of >14 000 patients may spur important research in the field if confirmed in validation studies. STEMI is typically associated with total vessel occlusion at the site of plaque rupture, resulting from more organized fibrin-rich clot, compared to a more platelet-dominated, non-occlusive picture for non-STEMI.[5,15] It is biologically plausible that a drug therapy could have differential effects on plaque progression and rupture, vs. thrombus formation once plaque rupture has occurred. This could shift the proportion of individuals that develop more organized fibrin-rich clots and differentially effect STEMI/non-STEMI presentations. A schematic illustration of possible mechanisms for divergent effects is provided in *Figure 4*. For example, although there was a trend towards overall reduction in MI in the canagliflozin group consistent with the meta-analysis data for the class, of the 421 participants who did suffer a fatal or non-fatal MI during the CANVAS Programme, the rate of STEMI was higher among individuals randomized to canagliflozin compared with placebo (32% vs. 15%, $P<0.001$), yet non-STEMI was lower (63% vs. 78%, $P<0.001$). There are currently no effects of canagliflozin on the clotting cascade described. However, the well-established effect of canagliflozin and other SGLT2 inhibitors in

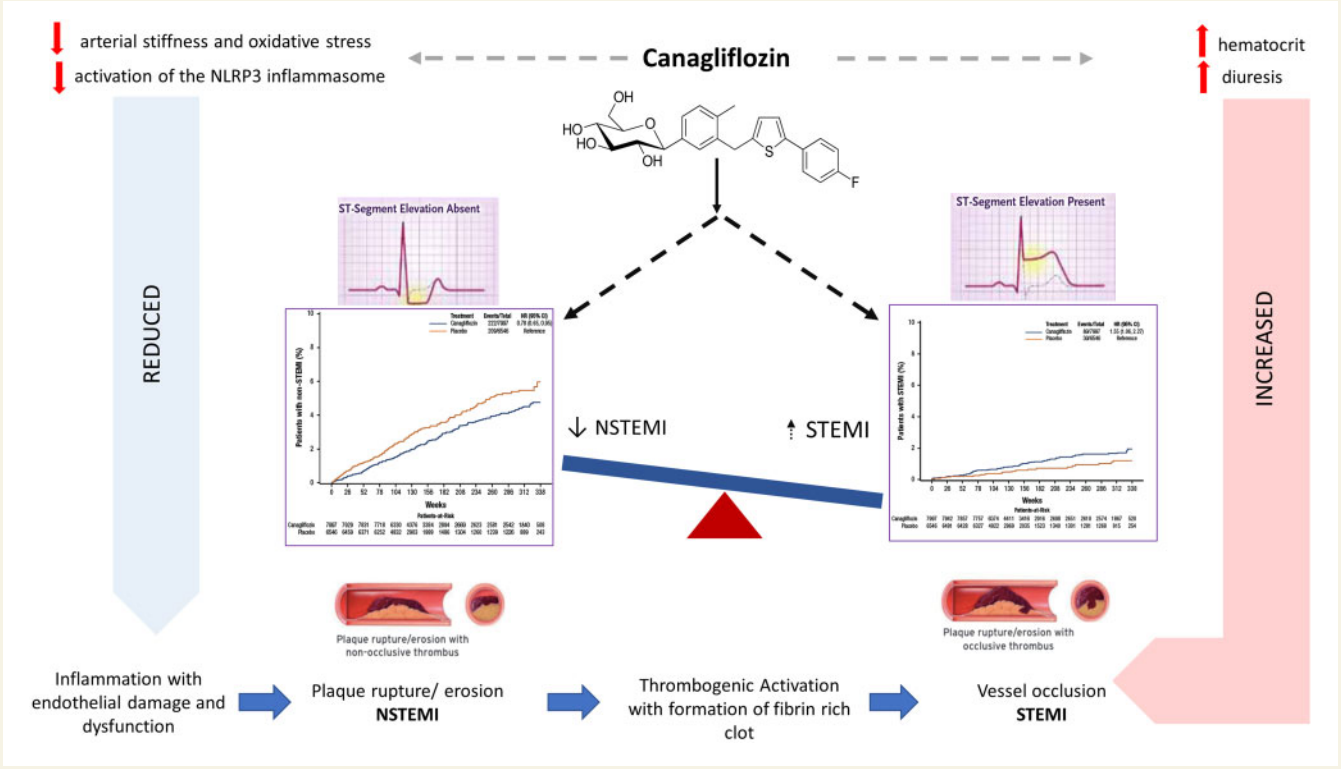


Figure 4 Schematic illustration of possible mechanisms for canagliflozin to reduce atherosclerotic plaque development and progression, but to increase the probability of organized fibrin clot and STEMI in the event of plaque rupture. The dotted arrow pointing up highlights the degree of certainty being less for the STEMI increase in association with canagliflozin than the decrease in STEMI, with the heterogeneity between the CANVAS Programme and the CREDENCE Trial. In regard to the possible biological mechanisms, previous studies had demonstrated that canagliflozin improves arterial stiffness,[22,23] decreases oxidative stress,[24] and activation of the NLRP3 inflammasome,[25] the fact may reduce the development and progression of atherosclerosis. In contrast, the known impact of canagliflozin on increasing haematocrit and the associated viscosity[26] may contribute to an increase susceptibility to organize the thrombus in the setting of plaque rupture.

increasing haematocrit makes an effect on clotting response to plaque rupture possible by potentially increasing viscosity in a low-flow state.[17–19] Previous studies have shown shortened bleeding time amongst individuals with elevated haematocrit levels.[20] In contrast, neither canagliflozin nor any other SGLT2 inhibitors have been associated with an increase in thrombotic stroke or venothrombotic disease.[4,8,9] Our findings highlight, however, the potential advantage of classifying MI as STEMI vs. non-STEMI at the time of adjudication in future clinical trials. It may also stimulate future mechanistic research to explore the potential effect of SGLT2 inhibition on clinical events involving thrombosis.

There is considerable interest regarding the potential benefits of SGLT2 inhibitors on LV remodelling post-MI, with studies designed to examine initiating therapy at or soon after an MI (NCT03087773, NCT03658031 and NCT03591991). The ability of our analysis to examine the potential impact of canagliflozin on LV remodelling and HF in individuals with type 2 diabetes who suffered an MI during participation in the CANVAS Programme was impacted by the disproportionate STEMI/non-STEMI ratio in the two treatment groups, and the incomplete nature of the LV functional data. Despite this, the higher incidence of STEMI in the treatment group in the CANVAS Programme but not in CREDENCE trial, normally expected to be associated with a larger infarct size and more substantial LV dysfunction than non-STEMI. There was no difference in ejection fraction between treatment and placebo groups in those who had available measures of LV systolic function. Despite the higher incidence of STEMI, there was also no difference in incidence of hospitalization for HF after discharge. The incomplete documentation of LV function in this study, coupled with an inability to definitively define the timing of LV impairment (pre or post-index MI), reduced the power to robustly address this issue, and overall, the findings do not preclude a potential beneficial effect on MI-related HF events. The prospective studies examining the impact of SGLT2 inhibitor therapy at, or soon after MI (NCT03087773, NCT03658031 and NCT03591991) on left ventricular remodelling remain of substantial interest.

The analyses performed in this study benefit from the rigorous design and conduct of the included studies, masked adjudication of MI events by an expert committee, and thorough assessment of each event to define STEMI, non-STEMI, and LV dysfunction.[21] Limitations include the retrospective *post hoc* approach of the analyses, limited power, the inability to classify some MIs, and the relatively few MI events for some subtypes. Furthermore, we share the challenge of many clinical trials related to the likely under-detection of silent MI, particularly relevant in the diabetic population. The adjudication committee identified only one silent MI in the CANVAS Programme and five in the CREDENCE trial, which is likely only a small proportion of silent MI events. There is no biological reason, however, that canagliflozin would have a differential effect on silent vs. clinically evident MIs and thus we do not think this limitation is likely to significantly affect overall findings. The overall poor management of MI

may make the findings less broadly applicable with only 44% receiving revascularization, a third not receiving a statin, and ~50% receiving neither angiotensin-II converting enzyme inhibitor/angiotensin II receptor blockers or beta blocker. Data were not available to determine whether LV impairment was present prior to MI but this should have been balanced between the randomly assigned groups and the absence of this information should not have biased estimates for effects of canagliflozin on MI with LV dysfunction. Incomplete data and ascertainment bias with respect to cardiac enzymes and other clinical markers of clinical severity at the time of MI are a further limitation in this current analysis. The unexpected differences in proportion of STEMI and non-STEMI in the treatment groups, and the known differences in myocardial injury and outcomes between the subtypes suggest that these results should be viewed with caution and should be considered hypothesis generating.

5. Conclusion

This individual patient data meta-analysis combining the CANVAS Programme and CREDENCE trial demonstrates no overall reduction in MI in those treated with canagliflozin, though statistical power was limited. The potential directionally different effect of canagliflozin on STEMI and non-STEMI observed in the CANVAS Programme, but not confirmed in CREDENCE trial, warrants further investigation.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Authors' contributions

J.Y., J.L., P.J.L., C.A., M.D.H., J.A.U., V.P., K.W.M., D.d.Z., G.F., D.R.M., W.S., B.N., and G.A.F. contributed to the design and conduct of the study and the interpretation of the data. J.Y., J.L., P.J.L., and G.A.F. contributed to the analysis and interpretation of data. J.Y., C.A., and G.A.F. drafted the manuscript. All authors critically revised the manuscript and gave final approval. J.Y. and G.A.F. 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. G.A.F. attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

Data from the CANVAS Programme 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 18 months.

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Translational perspective

Sodium glucose co-transporter 2 inhibitors (SGLT2i) protect against myocardial infarction (MI) and heart failure in those with type 2 diabetes. The effect of SGLT2i on MI subtypes, however, has not previously been evaluated. In this individual diabetic patient data meta-analysis of the CANVAS Programme and CREDENCE trial canagliflozin was associated with a reduction in non- STEMI but not STEMI. These data are important hypothesis generating information that will stimulate future mechanistic research to explore the potential effect of SGLT2 inhibition on thrombus formation in the setting of atherosclerotic plaque rupture.