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Clinical outcomes with canagliflozin according to baseline body mass index: results from post hoc analyses of the CANVAS Program

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Abstract

Aims: Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce several cardiovascular risk factors, including plasma glucose, blood pressure, albuminuria and body weight. Long-term treatment lowers risks of cardiovascular and renal events. The objective of this post hoc analysis was to determine the effects of canagliflozin treatment versus placebo on clinical outcomes in relation to body mass index (BMI).

Materials and methods: The CANVAS Program randomized 10 142 participants with type 2 diabetes to canagliflozin or placebo. These analyses tested the consistency of canagliflozin treatment effects across BMI levels for cardiovascular, renal, safety and body weight outcomes in three groups defined by baseline BMI: <25, 25-<30 and ≥30 kg/m^2.

Results: In total, 10 128 participants with baseline BMI measurements were included. There were 966 participants with BMI <25 kg/m^2, 3153 with BMI 25-<30 kg/m^2 and 6009 with BMI ≥30 kg/m^2. Mean percent body weight reduction with canagliflozin compared with placebo was greater at 12 months [−2.77% (95% confidence interval (CI): −2.95, −2.59)] than at 3 months [−1.72% (95% CI: −1.83, −1.62)]. The hazard ratios (HRs) for canagliflozin compared with placebo control for the composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke were 1.03 (95% CI: 0.66, 1.59) in participants with BMI <25 kg/m^2, 0.97 (0.76, 1.23) with BMI 25-<30 kg/m^2 and 0.79 (0.67, 0.93) with BMI ≥30 kg/m^2 (*P* for heterogeneity = 0.55). The effects of canagliflozin on each component of the composite were also similar across BMI subgroups, as were effects on heart failure and renal outcomes (*P* for heterogeneity ≥0.19). The effects on safety outcomes were also broadly similar.

Conclusions: Canagliflozin improved cardiovascular and renal outcomes consistently across patients with a broad range of BMI levels.

1 | INTRODUCTION

Both type 2 diabetes and obesity are epidemics causing major global public health problems.[1] Excess body fat is a major contributor to the development of type 2 diabetes, as well as cardiovascular (CV) disease and premature death.[2-8] Given the benefits of weight loss in the prevention and treatment of type 2 diabetes,[9,10] weight management is recommended for patients with type 2 diabetes who are overweight or obese.[11] One of the more important considerations in deciding on an appropriate antihyperglycaemic agent is its effects on body weight.[11]

Sodium glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose levels by reducing the renal threshold for glucose and increasing urinary glucose excretion.[12] In addition, SGLT2 inhibitors improve other CV risk factors, including blood pressure (BP), albuminuria and body weight. Reductions in body weight may be achieved both through loss of calories and through natriuresis. Moderate and sustained reductions in body weight were observed in the EMPA-REG OUTCOME trial,[13,14] the CANVAS (CANagliflozin cardioVascular Assessment Study) Program[15,16] and the DECLARE-TIMI 58 trial.[17] The same trials demonstrated that SGLT2 inhibitors reduced the risk of CV and renal events. However, whether the effects of SGLT2 inhibitors on weight loss vary according to participant characteristics and whether the benefits of SGLT2 inhibitors differ among patients with differences in body mass index (BMI) are unknown.

The objectives of this post hoc analysis were to determine whether the effects of the SGLT2 inhibitor canagliflozin on CV outcomes, renal outcomes, body weight and safety indicators vary according to baseline BMI levels, using data from the CANVAS Program.

2 | MATERIALS AND METHODS

2.1 | Ethics

CANVAS and CANVAS-Renal (CANVAS-R; ClinicalTrials.gov registration numbers NCT01032629 and NCT01989754) were approved by the institutional review board for each centre, and all participants provided written informed consent. All procedures followed were in accordance with the Declaration of Helsinki 1964, as revised in 2013.

2.2 | Study design and participants

The CANVAS Program, comprising two similarly designed and conducted large-scale double-blind trials, CANVAS and CANVAS-R, assessed the CV and renal efficacy and safety of canagliflozin compared with placebo. A detailed description of the design and the main results of the CANVAS Program were previously published.[15,18] In brief, 10 142 participants with type 2 diabetes and a history or high risk of CV disease were enrolled from 667 centres in 30 countries. The individuals included men and women with type 2 diabetes [haemoglobin A1c (HbA1c) ≥7.0% and ≤10.5%] who were either ≥30 years of age with a history of symptomatic atherosclerotic CV disease or ≥50 years of age with ≥2 of the following risk factors for CV disease: duration of diabetes mellitus ≥10 years, systolic BP >140 mmHg while receiving ≥1 antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria or high-density lipoprotein cholesterol <1 mmol/L. Participants were required to have an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2 at entry, but there were no specific body weight-related inclusion criteria.

2.3 | Randomized treatment and follow-up

After a 2-week, single-blind, placebo run-in period, participants in CANVAS were randomly assigned in a 1:1:1 ratio to receive once-daily canagliflozin 100 mg, canagliflozin 300 mg or placebo, while participants in CANVAS-R were randomly assigned in a 1:1 ratio to receive once-daily canagliflozin 100 mg or matching placebo, with an optional uptitration to 300 mg starting at week 13, through a central web-based system with the use of a computer-generated randomization schedule with randomly permuted blocks. Participants were required to have stable background glucose-lowering therapy for 8 weeks before screening and wherever possible to persist with this treatment regimen unchanged for the first 18 weeks after randomization in CANVAS.[19] Beyond 18 weeks in CANVAS and throughout CANVAS-R, background drug treatments for glucose control were at the discretion of the responsible investigator, with the exception of SGLT2 inhibitors.[19,20] All participants and trial staff were blinded to individual treatment allocations until the end of the trial. Participants were followed at least three times in the first year and at 6-month intervals thereafter until the end of the study, with telephone follow-up between face-to-face assessments.

2.4 | Body mass index

BMI was calculated from height and body weight. For this analysis, participants were classified into three groups based on BMI at baseline: <25, 25-<30 and ≥30 kg/m^2. Only participants with baseline BMI measurements were included in this analysis.

2.5 | Outcomes

The primary outcome for the CANVAS Program was a composite of death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke. Secondary outcomes included death from CV causes, fatal or non-fatal MI, fatal or non-fatal stroke, hospitalization for heart failure and a composite renal outcome of 40% decrease in eGFR, end-stage kidney disease or renal death. This analysis also assessed effects on the intermediate outcomes, including HbA1c, systolic BP, body weight, urine albumin/creatinine ratio (UACR) and eGFR. In addition, the effects on key safety outcomes were determined. Safety outcomes included adverse events coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of the database lock.[15] Both serious and non-serious adverse events were collected for the CANVAS trial until early 2014, as mandated by the US Food and Drug Administration and other regulatory bodies for initial approval of canagliflozin.

TABLE 1 Characteristics of study participants at registration according to baseline BMI levels

	BMI <25 kg/m^2 (N = 966)	BMI 25-<30 kg/m^2 (N = 3153)	BMI ≥30 kg/m^2 (N = 6009)	*P* for trend
Age, years (mean ± SD)	64.0 ± 8.9	63.9 ± 8.5	62.8 ± 8.0	<0.001
Sex, n (%)				<0.001
Female	328 (33.95)	980 (31.1)	2319 (38.6)	
Male	638 (66.05)	2173 (68.9)	3690 (61.4)	
Race, n (%)				<0.001[a]
White	443 (45.9)	2273 (72.1)	5220 (86.9)	
Asian	404 (41.8)	590 (18.7)	288 (4.8)	
Black or African American	32 (3.3)	82 (2.6)	219 (3.6)	
Other[b]	87 (9.0)	208 (6.6)	282 (4.7)	
Current smoker, n (%)	193 (20.0)	595 (18.9)	1017 (16.9)	0.003
History of hypertension, n (%)	782 (81.0)	2749 (87.2)	5580 (92.9)	<0.001
History of heart failure, n (%)	87 (9.0)	381 (12.1)	992 (16.5)	<0.001
Duration of diabetes, years (mean ± SD)	14.2 ± 8.3	13.6 ± 7.7	13.4 ± 7.7	0.004
Drug therapy, n (%)				
Insulin	359 (37.2)	1383 (43.9)	3346 (55.7)	<0.001
Sulphonylurea	562 (58.2)	1513 (48.0)	2280 (37.9)	<0.001
Metformin	725 (75.1)	2426 (76.9)	4665 (77.6)	0.09
GLP-1 receptor agonist	4 (0.4)	68 (2.2)	333 (5.5)	<0.001
DPP-4 inhibitor	130 (13.5)	427 (13.5)	702 (11.7)	0.01
Statin	662 (68.5)	2317 (73.5)	4608 (76.7)	<0.001
Antithrombotic	690 (71.4)	2293 (72.7)	4476 (74.5)	0.01
RAAS inhibitor	671 (69.5)	2400 (76.1)	5033 (83.8)	<0.001
Beta-blocker	392 (40.6)	1559 (49.4)	3466 (57.7)	<0.001
Diuretic	267 (27.6)	1108 (35.1)	3109 (51.7)	<0.001
Microvascular disease history, n (%)				
Retinopathy	179 (18.6)	634 (20.1)	1314 (21.9)	0.005
Nephropathy	159 (16.5)	503 (16.0)	1110 (18.5)	0.007
Neuropathy	250 (25.9)	867 (27.5)	1990 (33.1)	<0.001
Atherosclerotic vascular disease[c]				
Coronary	494 (51.1)	1795 (56.9)	3423 (57.0)	0.01
Cerebrovascular	162 (16.8)	607 (19.3)	1186 (19.7)	0.06
Peripheral	184 (19.1)	668 (21.2)	1258 (20.9)	0.39
Any	675 (69.9)	2294 (72.8)	4344 (72.3)	0.35
CV disease history, n (%)[d]	642 (66.5)	2113 (67.0)	3890 (64.7)	0.06
History of amputation, n (%)	25 (2.6)	62 (2.0)	149 (2.5)	0.52
BMI, kg/m^2 (mean ± SD)	23.1 ± 1.5	27.7 ± 1.4	35.6 ± 4.7	<0.001
Systolic BP, mmHg (mean ± SD)	133.6 ± 16.9	135.4 ± 15.8	137.8 ± 15.4	<0.001
Diastolic BP, mmHg (mean ± SD)	75.8 ± 9.1	77.1 ± 9.4	78.3 ± 9.8	<0.001
HbA1c, % (mean ± SD)	8.2 ± 1.0	8.2 ± 0.9	8.3 ± 0.9	0.01
Total cholesterol, mmol/L (mean ± SD)	4.30 ± 1.12	4.35 ± 1.13	4.38 ± 1.17	0.06
Triglycerides, mmol/L (mean ± SD)	1.62 ± 1.17	1.91 ± 1.32	2.15 ± 1.48	<0.001
HDL-C, mmol/L (mean ± SD)	1.25 ± 0.35	1.19 ± 0.32	1.16 ± 0.30	<0.001
LDL-C, mmol/L (mean ± SD)	2.33 ± 0.92	2.31 ± 0.93	2.28 ± 0.94	0.051
LDL-C/HDL-C ratio (mean ± SD)	1.97 ± 0.89	2.04 ± 0.92	2.06 ± 0.93	0.008

(Continues)

TABLE 1 (Continued)

	BMI <25 kg/m^2 (N = 966)	BMI 25-<30 kg/m^2 (N = 3153)	BMI ≥30 kg/m^2 (N = 6009)	*P* for trend
eGFR, mL/min/1.73 m^2 (mean ± SD)	78.5 ± 22.2	77.1 ± 20.3	75.8 ± 20.3	<0.001
UACR, mg/g, median (IQR)	13.1 (7.2, 46.9)	11.6 (6.5, 34.2)	12.6 (6.6, 45.7)	0.77
Albuminuria				0.07[a]
Normoalbuminuria, n (%)	659 (68.5)	2265 (72.8)	4075 (68.6)	
Microalbuminuria, n (%)	213 (22.1)	634 (20.4)	1415 (23.8)	
Macroalbuminuria, n (%)	90 (9.4)	214 (6.9)	454 (7.6)	

Abbreviations: BMI, body mass index; BP, blood pressure; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; UACR, urinary albumin/creatinine ratio.

[a]*P* values for race and albuminuria were derived from the chi-squared test.

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

[c]Some participants had >1 type of atherosclerotic disease.

[d]As defined in the protocol.

Thereafter, following registration of the drug, only serious adverse events, adverse events leading to study drug discontinuation, and selected adverse events of interest were collected across the CANVAS Program. All major CV, renal and selected safety outcomes were adjudicated by central endpoint adjudication committees blinded to treatment allocation. Detailed definitions for the outcomes were previously published.[15]

2.6 | Statistical methods

Differences in baseline characteristics across BMI categories were tested by linear regression analysis or logistic regression analysis, as appropriate. Cox regression models were used to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for the primary and other CV and renal outcomes, with stratification according to trial and history of CV disease (for CV outcomes) and baseline eGFR level (<60 or ≥60 mL/min/1.73 m^2) as the exploratory variable (for the main renal outcome) using an intention-to-treat approach, for all canagliflozin groups combined versus placebo. Safety outcomes were analysed using an on-treatment approach (with data based on participants who had a safety outcome while they were receiving study drug, or within 30 days after discontinuation of study drug), except for amputation, fracture and diabetic ketoacidosis outcomes, where analyses included participants who received ≥1 dose of study drug and had an event at any time during follow-up. Annualized incidence rates were calculated per 1000 patient-years of follow-up. The effects of canagliflozin on continuous outcomes (HbA1c, systolic BP, body weight, eGFR) were calculated as mean change from baseline across the entire follow-up period. The average change in these continuous outcomes over time and the difference between canagliflozin and placebo (placebo-subtracted differences) were analysed using mixed-effects models for repeated measurements that included all the post-baseline data up to week 312, assuming that missing data were missing at random, and the covariates for study, visit, treatment and baseline values. UACR was log-transformed because of its skewed distribution, and the geometric mean of post-baseline UACR was estimated using a similar mixed-effects model. Changes in albuminuria were calculated as the ratio of the geometric mean of post-randomization UACR measures with canagliflozin compared with placebo. Early percentage change in body weight over 12/13 weeks or over 52 weeks and the difference between canagliflozin and placebo were also evaluated using linear regression analysis with study and treatment as covariates. Heterogeneity of treatment effect across subgroups defined by baseline BMI levels was tested by: (a) adding subgroup and a term for subgroup by treatment interaction to the relevant model, (b) testing for a linear trend across the subgroups and (c) including a treatment-by-BMI interaction term in the model. The global *P* values for heterogeneity across subgroups were obtained through the likelihood ratio test. Statistical analyses were performed with the SAS Enterprise Guide, version 7.11 (SAS Institute, Cary, North Carolina) and Stata software (release 13; StataCorp, College Station, Texas). A two-sided $P < 0.05$ was considered statistically significant. No adjustments for multiple statistical comparisons were made.

3 | RESULTS

3.1 | Patient characteristics

Of the 10 142 patients who participated in the CANVAS Program, 10 128 (99.9%) had baseline BMI measurements and were included in this analysis. Baseline characteristics according to baseline BMI levels are shown in Table 1. Patients with higher BMI tended to smoke less but were more frequently white, or had a diagnosis of hypertension or heart failure; this group also reported greater use of multiple drug therapies for glucose control and CV disease prevention, but less sulphonylurea use. Patients with higher BMI had greater prevalence of retinopathy, nephropathy and neuropathy and had higher measured values of BP and triglyceride levels. Levels of high-density lipoprotein cholesterol and eGFR were lower among those with higher BMI. Baseline characteristics across canagliflozin and placebo groups in each BMI subgroup were generally well balanced.

3.2 | Cardiovascular and renal outcomes

Overall, canagliflozin significantly reduced the risk of the composite CV outcome [CV death, non-fatal MI or non-fatal stroke; HR 0.86 (95% CI: 0.75, 0.97); Figure 1] compared with placebo, with no significant heterogeneity across subgroups defined by baseline BMI. The HRs for canagliflozin compared with placebo were 1.03 (95% CI: 0.66, 1.59) in patients with BMI <25 kg/m^2, 0.97 (95% CI: 0.76, 1.23) in patients with BMI 25-<30 kg/m^2, and 0.79 (95% CI: 0.67, 0.93) in patients with BMI ≥30 kg/m^2 (*P* for heterogeneity = 0.55). This association was unchanged when patients with BMI ≥30 kg/m^2 were further split into those with BMI 30-<40 and ≥40 kg/m^2; HRs were 0.79 (95% CI: 0.66, 0.94) in the 5071 with BMI 30-<40 kg/m^2 and 0.82 (95% CI: 0.56, 1.20) in the 938 with BMI ≥40 kg/m^2 (*P* for heterogeneity = 0.72).

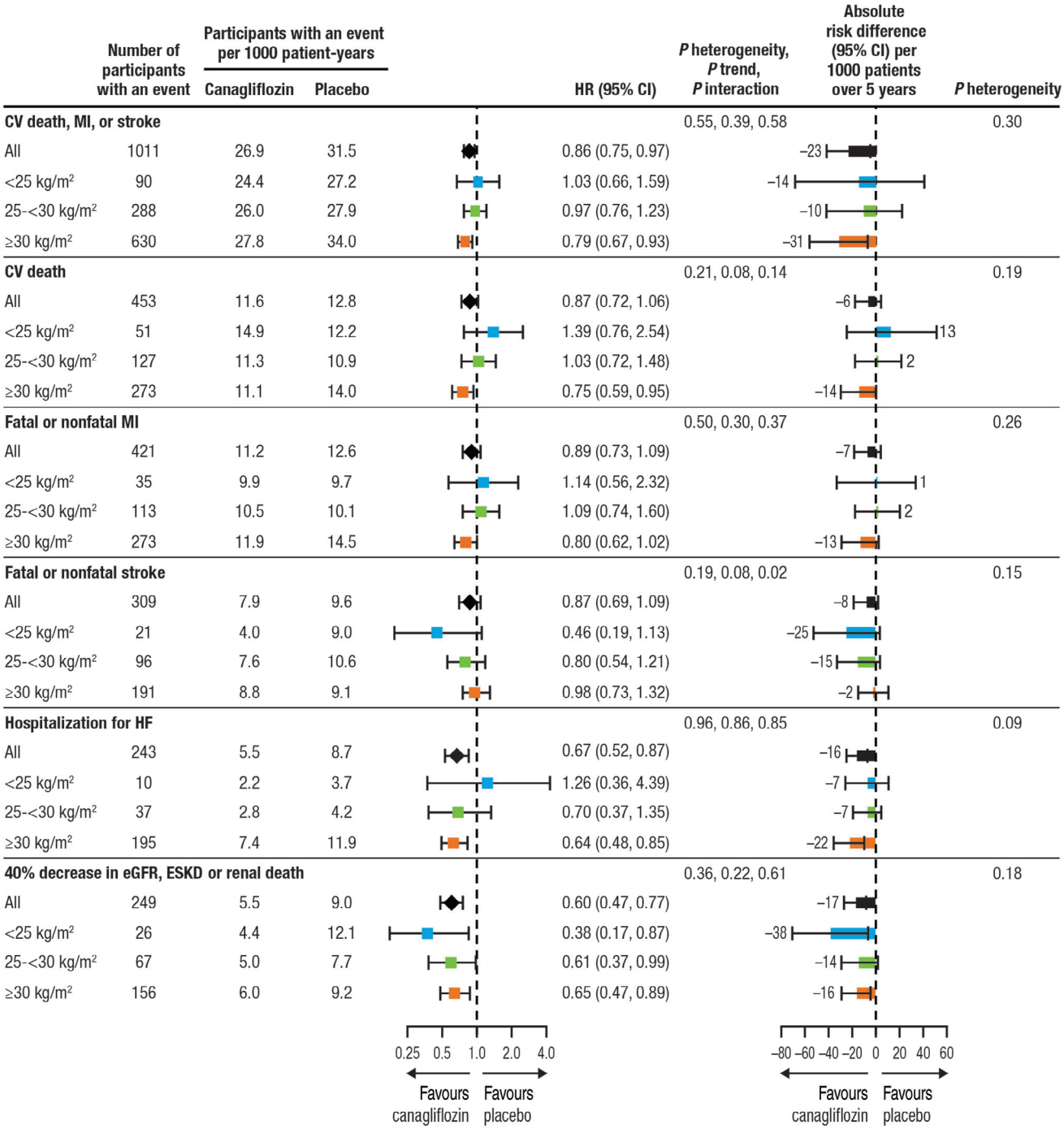

FIGURE 1 Effects of canagliflozin compared with placebo on CV and renal outcomes across the CANVAS Program according to baseline BMI levels. Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction

Furthermore, no heterogeneity in the effects was identified between Asian and non-Asian patients with BMI <25 kg/m^2 (*P* for heterogeneity = 0.86). The effect of canagliflozin was also consistent across BMI subgroups for deaths from CV causes, fatal or non-fatal MI, fatal or non-fatal stroke, hospitalization for heart failure and the composite renal outcome (all *P* for heterogeneity ≥0.19). When assessed as an interaction fitting baseline BMI as a continuous variable, significant heterogeneity was observed for fatal or non-fatal stroke (*P* for heterogeneity = 0.02) but not for any other outcome (all *P* for heterogeneity ≥0.14). Absolute risk reductions for CV and renal outcomes were also similar across BMI subgroups (*P* for heterogeneity ≥0.09; Figure 1).

3.3 | Intermediate markers

Irrespective of BMI, canagliflozin compared with placebo decreased HbA1c, systolic BP, UACR and eGFR. The placebo-subtracted mean differences in these intermediate markers were constant across BMI subgroups (all *P* for heterogeneity ≥0.09), except for body weight, where a greater absolute reduction in weight was observed among those with baseline BMI ≥30 kg/m^2 (*P* for heterogeneity <0.001; Figure 2). There were, however, no differences in effects across BMI subgroups if percentage weight loss was assessed (*P* for heterogeneity = 0.17).

The overall effects on percentage body weight varied substantially over time with canagliflozin use compared with placebo, resulting in a greater reduction at 12 months [−2.77% (95% CI: −2.95, −2.59); Figure S1 (see Supporting Information)] than at 3 months [−1.72% (95% CI: −1.83, −1.62)]. There was evidence that percentage weight reductions at 3 months were significantly greater with the 300 mg [−2.17% (95% CI: −2.35, −1.99)] compared with 100 mg [−1.67% (95% CI: −1.86, −1.49)] dose of canagliflozin (*P* <0.001 for the difference between the canagliflozin 100 mg and 300 mg groups in CANVAS). The same was true at 12 months for 300 mg [−3.28% (95% CI: −3.62, −2.95)] and for 100 mg [−2.54% (95% CI: −2.87, −2.21)] (*P* <0.001). At both time points there were greater percentage body weight reductions achieved among patients with no history of heart failure, and those using insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist but not a sulphonylurea (all *P* for trend <0.05). Effects at 3 months alone were also greater for those without a history of hypertension and those with a lower baseline HbA1c (all *P* for trend <0.05). Early effects according to baseline eGFR showed a lesser effect on body weight among those with eGFR 45-<60 mL/min/1.73 m^2 but comparable effects on those with either higher or lower levels of eGFR.

3.4 | Safety outcomes

The effects of canagliflozin on safety outcomes are shown in Figure 3 and Figure S2 (see Supporting Information). The risks of adverse events were consistent across the subgroups defined by baseline BMI (*P* for heterogeneity ≥0.15) with the exception of urinary tract infection (*P* for heterogeneity = 0.01), the risk for which appeared greater among patients with baseline BMI 25-<30 kg/m^2 but not among patients with baseline BMI <25 or ≥30 kg/m^2. This heterogeneity was not observed in the analyses using BMI as a continuous variable (*P* for interaction = 0.83).

4 | DISCUSSION

In this large-scale randomized, controlled trial of patients with type 2 diabetes, reductions in the risks of CV and renal events achieved with canagliflozin were consistent across subgroups defined by baseline BMI levels of <25, 25-<30 and ≥30 kg/m^2. Effects of canagliflozin on safety outcomes were also broadly similar across these subgroups. Overall, our findings suggest that CV and renal protective benefits of canagliflozin are not modified by baseline BMI levels, and further highlight the value of this therapy for CV disease prevention among obese, overweight and leaner patients.

Higher BMI is associated with increased levels of circulating free fatty acids and greater accumulations of harmful visceral, hepatic, skeletal, intracardial and epicardial fat.[21-23] In particular, epicardial adipose tissue surrounding the heart generates pathogenic mechanical, endocrinological, immunological, paracrine and vasocrine signalling, all of which may contribute to heart failure—particularly heart failure with preserved ejection fraction.[24] Individuals with diabetes and higher baseline BMI may also have greater sodium and fluid retention and might achieve enhanced protection from SGLT2 inhibitor therapy because of the known natriuretic effects of the class. Therefore, there was a rationale for anticipating potentially greater effects of canagliflozin on clinical outcomes among patients with higher BMI at baseline.

The CANVAS Program findings of comparable effectiveness of SGLT2 inhibition for the prevention of CV and renal outcomes across BMI subgroups align with similar observations from the EMPA-REG OUTCOME trial[13] and the DECLARE-TIMI 58 trial.[17] Although small differences in protection between those with higher versus lower BMI may have gone undetected by these studies, these observations suggest that BMI level does not substantively modify the prevention of CV events by canagliflozin. The significant interaction observed for fatal or non-fatal stroke when BMI was fitted as a continuous variable may be a chance finding consequent upon the number of statistical tests conducted. Further studies focusing on relatively lean patients might better elucidate this issue. The evidence of benefit observed for the BMI category of <25 kg/m^2 may be of particular relevance to Asian populations, and while BMI may be an imperfect measure of adiposity among individuals of Asian ethnicity, there is an epidemic of obesity and type 2 diabetes in Asian populations, which occurs at relatively low BMI.[25,26] CV protection with SGLT2 inhibition at lower levels of BMI provides some reassurance about the likely impact of this drug class among Asians with type 2 diabetes irrespective of BMI.

The effects of canagliflozin on safety outcomes were also consistent across BMI subgroups. Canagliflozin increased the risks of amputation, genital infections, diabetic ketoacidosis, osmotic diuresis and volume depletion, but effects were not modified by baseline BMI. The

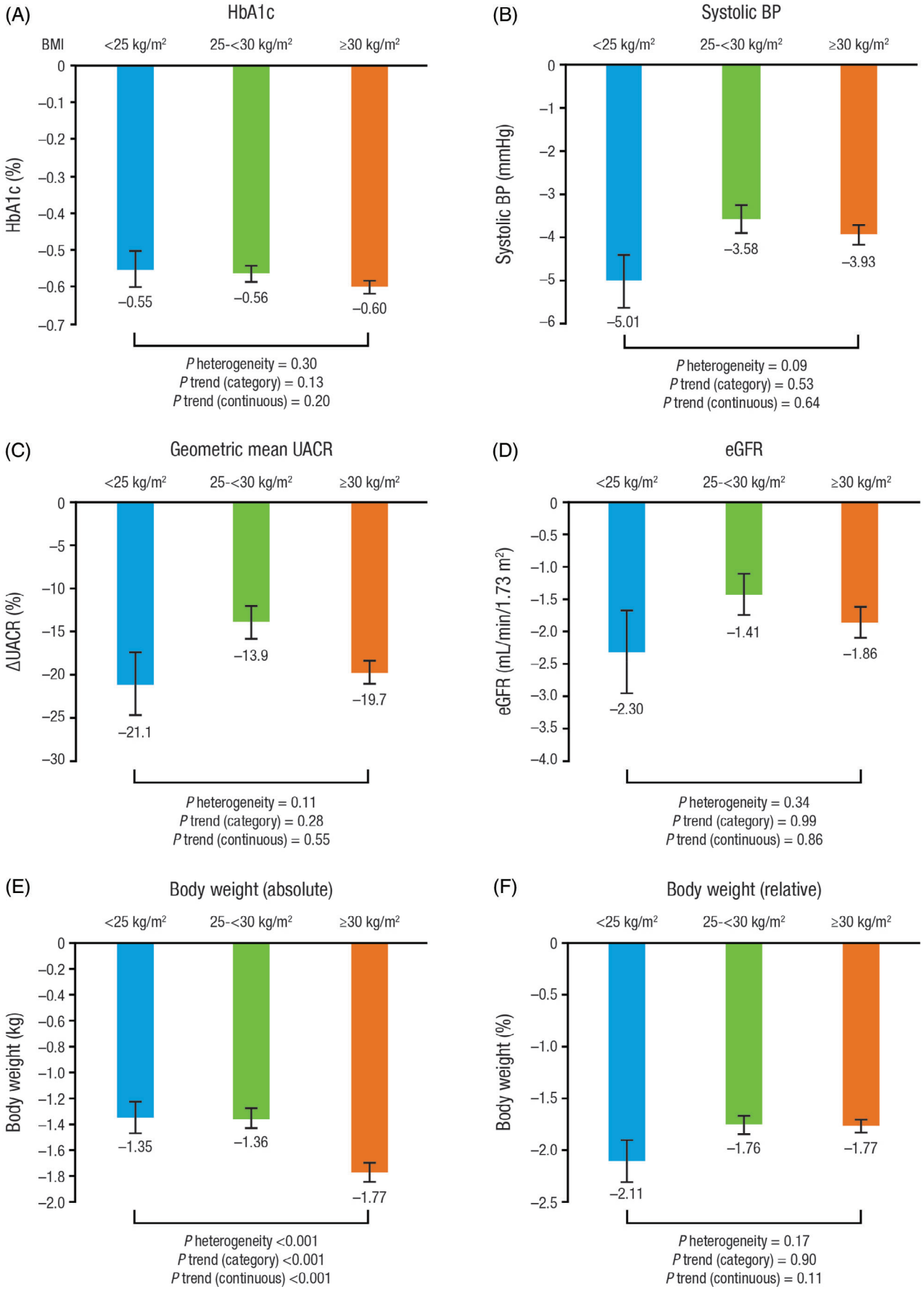

FIGURE 2 Effects of canagliflozin compared with placebo on intermediate markers of CV risk across the CANVAS Program according to baseline BMI levels. Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; UACR, urinary albumin/creatinine ratio

	Number of participants with an event	Participants with an event per 1000 patient-years		HR (95% CI)	*P* heterogeneity	*P* trend	*P* interaction
		Canagliflozin	Placebo				
All serious adverse events					0.77	0.59	0.62
All	3277	129.5	146.0	0.93 (0.87, 1.00)			
<25 kg/m²	291	118.9	124.9	1.08 (0.85, 1.38)			
25-<30 kg/m²	916	114.3	130.3	0.92 (0.81, 1.05)			
≥30 kg/m²	2064	139.3	158.2	0.91 (0.84, 1.00)			
Adverse events leading to discontinuation					0.26	0.14	0.87
All	1025	35.7	32.9	1.13 (0.99, 1.28)			
<25 kg/m²	105	36.4	38.1	1.01 (0.68, 1.52)			
25-<30 kg/m²	293	31.4	33.3	0.99 (0.78, 1.26)			
≥30 kg/m²	627	37.9	32.0	1.21 (1.03, 1.44)			
Amputation					0.69	0.76	0.45
All	187	6.3	3.4	1.97 (1.41, 2.75)			
<25 kg/m²	13	4.9	1.5	3.26 (0.71, 15.00)			
25-<30 kg/m²	50	5.3	3.3	1.82 (0.97, 3.39)			
≥30 kg/m²	124	7.0	3.7	1.93 (1.28, 2.92)			
Fracture					0.38	0.75	0.89
All	496	15.4	11.9	1.26 (1.04, 1.52)			
<25 kg/m²	50	14.7	13.7	1.14 (0.63, 2.06)			
25-<30 kg/m²	138	15.0	9.5	1.52 (1.05, 2.20)			
≥30 kg/m²	307	15.7	13.0	1.18 (0.93, 1.50)			
Infection of male genitalia					0.75	0.60	0.90
All	497	38.1	10.7	3.78 (2.95, 4.83)			
<25 kg/m²	31	23.6	4.2	5.70 (1.71, 18.95)			
25-<30 kg/m²	146	33.5	9.6	3.66 (2.34, 5.73)			
≥30 kg/m²	318	43.3	12.5	3.68 (2.72, 4.99)			
Venous thromboembolic events					0.45	0.64	0.21
All	52	1.7	1.9	0.88 (0.50, 1.55)			
<25 kg/m²	4	1.1	1.9	0.69 (0.09, 5.18)			
25-<30 kg/m²	12	1.6	0.9	1.60 (0.43, 5.96)			
≥30 kg/m²	36	1.8	2.4	0.76 (0.39, 1.49)			
Serious renal-related adverse events					0.15	0.02	0.046
All	83	2.5	3.3	0.76 (0.49, 1.19)			
<25 kg/m²	8	3.9	0.9	4.69 (0.56, 39.15)			
25-<30 kg/m²	14	1.6	1.4	1.00 (0.33, 3.03)			
≥30 kg/m²	61	2.8	4.6	0.60 (0.36, 1.00)			
Serious acute kidney injury					0.20	0.20	0.07
All	58	1.6	2.5	0.66 (0.39, 1.11)			
<25 kg/m²	4	2.2	0.0	–			
25-<30 kg/m²	7	0.9	0.6	1.54 (0.30, 8.09)			
≥30 kg/m²	47	1.9	3.9	0.50 (0.28, 0.90)			
Serious hyperkalemia					0.33	0.33	0.04
All	15	0.4	0.6	0.75 (0.27, 2.11)			
<25 kg/m²	2	1.1	0.0	–			
25-<30 kg/m²	3	0.4	0.3	1.19 (0.10, 13.61)			
≥30 kg/m²	9	0.3	0.9	0.32 (0.08, 1.29)			
Diabetic ketoacidosis					0.52	0.47	0.81
All	18	0.6	0.3	2.33 (0.76, 7.17)			
<25 kg/m²	5	1.3	1.5	1.05 (0.17, 6.62)			
25-<30 kg/m²	8	1.0	0.2	4.69 (0.57, 38.62)			
≥30 kg/m²	5	0.3	0.1	2.66 (0.29, 24.31)			

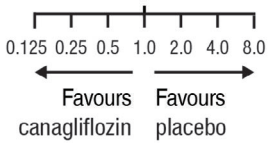

FIGURE 3 Effects of canagliflozin compared with placebo on safety outcomes across the CANVAS Program according to baseline BMI levels. Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio

heterogeneity observed for urinary tract infection appears to be attributable to chance, with no plausible explanation identified as to why there might be an increased risk among the BMI subgroup 25-<30 kg/m^2, but not among those with higher or lower BMI values.

Weight loss due to glycosuria is a unique characteristic of SGLT2 inhibitors[27] and, although not previously identified as a strong independent mediator of CV protection,[28] is clearly viewed as an important benefit by both patients and clinicians.[29] These analyses identified that percentage reductions in body weight with canagliflozin therapy were consistent across different initial levels of BMI. Greater weight loss was associated with several patient characteristics, including absence of a history of heart failure or hypertension, use of insulin, use of GLP-1 agonist and non-use of a sulphonylurea, but the mechanism for the greater percentage reduction in weight loss in these patients was not apparent. Similarly unclear was the reason why weight reductions in this study and a previous report[30] were greater among those with lower baseline HbA1c levels at 3 months—the opposite might have been anticipated, as renal excretion of glucose and calories with SGLT2 inhibition would be lower among those with well-controlled glycaemia.[31] The observed differences in weight reduction between eGFR subgroups were not linearly associated with renal function as might have been expected.[27] The greater effect of canagliflozin on weight at 12 months versus at 3 months probably reflects dual mechanisms of weight loss that are additive over time. Early reductions in body weight are likely to be driven primarily by fluid excretion resulting from the known natriuretic effects of the compound, with subsequent additional reduction in body weight attributable mostly to caloric loss and associated reduction in fat mass.[32]

The strengths of this analysis include the large and diverse patient population derived from an international, multicentre randomized trial conducted to a high standard, with a long duration of follow-up and rigorous adjudication of the main outcomes. It is of note that the conclusions about consistency of effects were not substantively different when assessed using measures of trend across either BMI categories or BMI fitted as a continuous variable. Limitations include the relatively small number of participants with BMI <25 kg/m^2, which reduced the statistical power to draw definite conclusions regarding treatment effects in leaner patients. In addition, the large number of statistical tests without correction for multiple comparisons may have resulted in spurious false-positive findings.

In conclusion, canagliflozin reduced the risk of CV and renal events in patients with type 2 diabetes, with consistent effects across subgroups defined by baseline BMI levels. However, the effects on body weight were different across patient subsets. These data indicate beneficial effects of canagliflozin in preventing CV and renal complications irrespective of the presence or absence of obesity.

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AUTHOR CONTRIBUTIONS

T.O. and L.V.G contributed to the analysis and interpretation of data. W.S. contributed to the design of the study. K.W.M, D.d.Z., D.R.M., V.P. and B.N. contributed to the design and conduct of the study and the interpretation of data. B.N. and D.R.M. were co-chairs of the CANVAS Program Steering Committee. T.O. and B.N. wrote the first draft of the manuscript, and all authors contributed to subsequent drafts and approved the final version for submission.

DATA AVAILABILITY

Data from the CANVAS Program will be made available in the public domain via the Yale University Open Data Access Project (YODA; http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in Europe and the USA and the study has been completed for 18 months.

CONFLICT OF INTEREST

T.O. is supported by the John Chalmers Clinical Research Fellowship of The George Institute for Global Health. L.V.G. has served on advisory boards and speakers bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Johnson & Johnson, Merck MSD, Novo Nordisk, Sanofi and Servier/Intarcia; and has received grant support from the EU (Hepadip & Resolve consortium) and National Research Funds. W.S. is a full-time employee of Janssen Research & Development, LLC. Disclosures for K.W.M. can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. D.d.Z. reports serving on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma and Mitsubishi Tanabe Pharma Corporation; serving on steering committees and/or as a speaker for AbbVie and Janssen; and serving on data safety and monitoring committees for Bayer. D.R.M. reports receiving research support from Janssen; serving on advisory boards and as a consultant for Novo Nordisk, Novartis, Sanofi-Aventis, Janssen and Servier; and giving lectures for Novo Nordisk, Servier, Sanofi-Aventis, Novartis and Janssen. V.P. reports receiving research support from the Australian National Health and Medical Research Council (Senior Research Fellowship and Program Grant); serving on Steering Committees for AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen and Pfizer; and serving on advisory boards and/or speaking at scientific meetings for AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier and Vitae with all honoraria paid to his employer. B.N. reports being supported by a National Health and Medical Research Council of Australia Principal Research Fellowship (APP1106947); serving on advisory boards and/or as consultant for Janssen, Merck Sharpe and Dohme and Mitsubishi Tanabe Pharma Corporation; and receiving lecture fees from Janssen, with any consultancy, honoraria or travel support paid to his institution.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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