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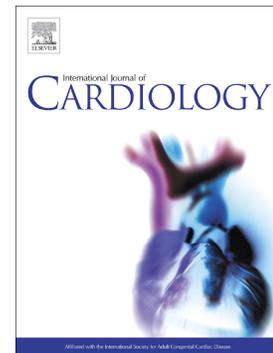
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The effects of combination canagliflozin and glucagon-like peptide-1 receptor agonist therapy on intermediate markers of cardiovascular risk in the CANVAS Program

Clare Arnott, MBBS, PhD[1-4,*] bneal@georgeinstitute.org.au; Brendon L. Neuen, MBBS (Hons), MSc[1]; Hiddo J.L. Heerspink, PharmD, PhD[2,5]; Gemma A. Figtree, MBBS, DPhil[1,4,6]; Mikhail Kosiborod, MD[7]; Carolyn S. Lam, MBBS, PhD[1,5,8]; Christopher P. Cannon, MD[9]; Norman Rosenthal, MD[10]; Wayne Shaw, DSL[10]; Kenneth W. Mahaffey, MD[11]; Meg J. Jardine, MBBS, PhD[1,2]; Vlado Perkovic, MBBS, PhD[1,2]; Bruce Neal, MB ChB, PhD[1,2]

[1]The George Institute for Global Health, UNSW Sydney, Sydney, Australia

[2]University of New South Wales, Sydney, Australia

[3]Royal Prince Alfred Hospital, Camperdown, Sydney, Australia

[4]Sydney Medical School, University of Sydney, Sydney, Australia

[5]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[6]Kolling Institute, Royal North Shore Hospital and University of Sydney, Sydney, Australia

[7]Saint Luke's Mid America Heart Institute, Kansas City, MO, USA

[8]National Heart Centre Singapore and Duke-National University Singapore

[9]Cardiovascular Division, Brigham and Women's Hospital and Baim Institute for Clinical Research, Boston, MA, USA

[10]Janssen Research & Development, LLC, Raritan, NJ, USA;

[11]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA.

[*]**Corresponding author at:** The George Institute for Global Health, Level 5, 1 King St, Newtown NSW 2042, Australia

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ABSTRACT

Background

Sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RA) reduce cardiovascular events, and improve intermediate markers of cardiometabolic health, in those with type 2 diabetes. We investigated these effects in the CANVAS Program.

Methods and Results

The CANVAS Program comprised 2 double-blind, randomized, placebo-controlled trials (CANVAS and CANVAS-R) done in patients with type 2 diabetes and elevated cardiovascular risk. Effects were estimated using mixed-effects models for continuous measures and Cox regression models for other outcomes. Randomized treatment by subgroup interaction terms were used to compare effects of canagliflozin versus placebo across subgroups defined by baseline use of GLP1-RA.

There were 10,142 participants, of whom 407 (4%) were using GLP1-RA therapy at baseline. Those using GLP1-RA at baseline were less likely to have a history of cardiovascular disease (60.4% vs 65.8%), had a longer duration of diabetes (15.2 vs 13.5 years) and a higher body mass index (BMI; 35.6 vs 31.8 kg/m^2) but were otherwise similar. There were greater reductions with canagliflozin versus placebo for HbA1c (–0.75% versus –0.58%; $P = 0.0091$), SBP (−6.26 versus −3.83 mmHg; $P = 0.0018$), and body weight (−3.79 versus −2.18 kg; $P < 0.0001$) in those on baseline GLP1-RA therapy. Effects across subgroups were similar for UACR ($P = 0.21$), eGFR slope ($P = 0.72$), major adverse cardiac events ($P = 0.94$) and total serious adverse events ($P = 0.74$).

Conclusions

There may be a synergistic effect of SGLT2 inhibition when used on a background of GLP1-RA for intermediate cardiometabolic markers.

KEY WORDS: SGLT2 inhibition; GLP1 receptor agonist; cardiovascular disease, type 2 diabetes

The effects of combination canagliflozin and glucagon-like peptide-1 receptor agonist therapy on intermediate markers of cardiovascular risk: a *post hoc* analysis from the CANVAS Program

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[1]The George Institute for Global Health, UNSW Sydney, Sydney, Australia; [2]University of New South Wales, Sydney, Australia; [3]Royal Prince Alfred Hospital, Camperdown, Sydney, Australia; [4]Sydney Medical School, University of Sydney, Sydney, Australia; [5]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [6]Kolling Institute, Royal North Shore Hospital and University of Sydney, Sydney, Australia; [7]Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; [8]National Heart Centre Singapore and Duke-National University Singapore; [9]Cardiovascular Division, Brigham and Women's Hospital and Baim Institute for Clinical Research, Boston, MA, USA; [10]Janssen Research & Development, LLC, Raritan, NJ, USA; [11]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA.

Corresponding author:

Clare Arnott

The George Institute for Global Health

Level 5, 1 King St

Newtown NSW 2042

Australia

Tel: +61 2 8052 4558

Email: bneal@georgeinstitute.org.au

Word Count: 1047

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The CANVAS Program comprised 2 double-blind, randomized, placebo-controlled trials (CANVAS and CANVAS-R) done in patients with type 2 diabetes and elevated cardiovascular risk. Effects were estimated using mixed-effects models for continuous measures and Cox regression models for other outcomes. Randomized treatment by subgroup interaction terms were used to compare effects of canagliflozin versus placebo across subgroups defined by baseline use of GLP1-RA.

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Conclusions

There may be a synergistic effect of SGLT2 inhibition when used on a background of GLP1-RA for intermediate cardiometabolic markers.

KEY WORDS: SGLT2 inhibition; GLP1 receptor agonist; cardiovascular disease, type 2 diabetes

INTRODUCTION

Sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RA) have been demonstrated to reduce cardiovascular events in those with type 2 diabetes mellitus (T2DM).[1,2] Both of these drug classes are known to reduce body weight, glycosylated hemoglobin (HbA1c), and other mediators of cardiometabolic health. Given their different mechanisms of action, there may be a benefit from combination therapy. We assessed the effects of canagliflozin in patients who were, and patients who were not, using GLP1-RA at baseline in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program.

METHODS

The CANVAS Program comprised 2 double-blind, randomized, placebo-controlled trials (CANVAS and CANVAS-R) that have been described previously.[3] Individuals with T2DM and HbA1c $\geq 7.0\%$ and $\leq 10.5\%$ who were either ≥ 30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or ≥ 50 years of age with ≥ 2 cardiovascular risk factors were included. Participants were randomized to canagliflozin or placebo, with other background glycaemic management and risk factor treatment as per best practice guidelines at each site. Self-reported use of GLP1-RA was recorded at baseline.

The primary outcome of the CANVAS Program was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. HbA1c, systolic blood pressure (SBP), body weight, urinary albumin:creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) were assessed as part of a range of intermediate markers prespecified for analysis.

We investigated the effects of canagliflozin versus placebo on these intermediate markers by baseline use of GLP1-RA using mixed-effects models for repeated measurements. Effects on long-term eGFR slope were assessed using piecewise linear mixed-effects models as previously described.[4] We determined effects of canagliflozin on the primary cardiovascular outcome by GLP1-RA subgroup using Cox regression models. The consistency of the effects of canagliflozin versus placebo across GLP1-RA subgroups was tested by adding randomized treatment by subgroup interaction terms to the models.

RESULTS

There were 10,142 participants in the CANVAS Program, of whom 407 (4%) were using GLP1-RA therapy at baseline; 4% of the canagliflozin treatment arm and 4% of placebo. The subgroups were similar in age, HbA1c level, blood pressure, and UACR, but those using GLP1-RA at baseline were less likely to be female (28.7% vs 36.1%), have a history of cardiovascular disease (60.4% vs 65.8%), or have a history of heart failure (6.4% vs 14.7%). Participants on GLP1-RA also had a longer duration of diabetes (15.2 vs 13.5 years) and a higher body mass index (BMI; 35.6 vs 31.8 kg/m^2). *(Table 1)* A similar number of participants in each study arm commenced GLP1-RA therapy during the study (138 in canagliflozin arm, 148 in placebo arm).

Among patients on background GLP1-RA therapy compared to those not using background GLP1-RA, those assigned canagliflozin versus placebo had a greater reduction in HbA1c (−0.75% versus −0.58%; $P_{interaction}$ = 0.0091), SBP (−6.26 versus −3.83 mmHg; $P_{interaction}$ = 0.0018), and body weight (−3.79 versus −2.18 kg; $P_{interaction}$ <0.0001). Whilst there was an overall reduction in the geometric mean of UACR and eGFR slope decline with canagliflozin compared to placebo, the effects on UACR (−18% versus −24%; $P_{interaction}$ = 0.21) and eGFR

slope (-1.25 versus -1.18 mL/min/1.73 m^2/year; $P_{interaction} = 0.72$) were comparable for those on pre-existing GLP1-RA and those not on GLP1-RA therapy. *(Figure 1)*

There were no differences in effects of canagliflozin on the primary cardiovascular outcome across the GLP1-RA subgroups (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.36 to 1.46 versus HR 0.86, 95% CI 0.76 to 0.98; $P_{interaction} = 0.94$), the composite adverse renal outcome (40% decline in eGFR, end-stage kidney disease or renal death) ($P_{interaction} = 0.43$) or total serious adverse events ($P_{interaction} = 0.74$). Findings were comparable in models adjusted for baseline age, SBP, HbA1c, BMI, history of cardiovascular disease, and history of heart failure.

DISCUSSION

In this post hoc analysis of the CANVAS Program, there was statistical heterogeneity in the effects of canagliflozin compared to placebo for some intermediate outcomes based on use of GLP1-RA therapy at baseline. The reductions in body weight, SBP, and HbA1c were greater in those on GLP1-RA therapy at baseline compared to those not on GLP1-RA at baseline, with no such differences observed for UACR or eGFR slope. No corresponding heterogeneity in the treatment effect of canagliflozin compared to placebo on the primary cardiovascular outcome according to baseline use of GLP1-RA was observed. However, while the analyses provided a good opportunity to compare effects between subgroups on the intermediate markers, the small number of patients using GLP1-RA at baseline limited statistical power for the comparison of effects on cardiovascular events.

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Evidence of a potential synergistic effect of SGLT2 inhibitors when used on a background of GLP1-RA has not been reported previously, though trial data describing the effects of this combination are limited.[5] The *Efficacy and Safety of Semaglutide Once-weekly Versus Placebo as add-on to SGLT-2i Subjects with Type 2 Diabetes Mellitus (SUSTAIN-9)*[6], *A Study of Dulaglutide in Participants with Type 2 Diabetes Mellitus (AWARD-10)*[7] and *Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once Weekly (DURATION-8)*[8] studies have demonstrated additive, but not multiplicative, effects of combination therapy on glycemic control and body weight reduction with good tolerability. These studies were, however, small and of relatively short duration. A recent meta-analysis of these three randomised controlled trials has reinforced the dual benefits of these medications on glycaemic parameters, and intermediate cardiovascular markers with tolerable safety profiles.[9]

Key limitations of this study need to be acknowledged. This is a post hoc analysis, and GLP1-RA therapy at baseline was not randomised, and those using versus not using GLP1-RA have different characteristics. Moreover, only 4% of participants in this study were taking GLP1-RA at study inclusion, and thus the subgroups being compared are unbalanced in size. This limits the power of these analysis to make conclusions on clinical endpoints. Finally, background use of cardiovascular risk factor medications were continued as per local guideline-directed best practice. It is possible that the differences in intermediate cardiovascular markers seen in this study are not solely due to randomized treatment or GLP1-RA status at baseline.

These new findings from the CANVAS Program warrant further investigation of the effects of SGLT2 inhibitors and GLP1-RA combination therapy in dedicated adequately powered

trials. Synergistic effects on blood pressure, HbA1c, and body weight may translate into important additional protection against cardiovascular outcomes.

DISCLOSURES

C. Arnott has nothing to declare.

B.L. Neuen is supported by an Australian National Health and Medical Research Council Postgraduate Scholarship and a University Postgraduate Award from the University of New South Wales; he has received travel support from Janssen.

H.J.L. Heerspink has served as a consultant for Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, and Mitsubishi-Tanabe; and has received grant support from Abbvie, AstraZeneca, Boehringer Ingelheim, and Janssen.

G.A. Figtree has received research support from the cofunded Australian National Health and Medical Research Council and Heart Foundation fellowship and Heart Research Australia; and has received compensation from Janssen for serving on the adjudication panel of the CANVAS Program.

M. Kosiborod has received research grants from AstraZeneca and Boehringer Ingelheim; has served as a consultant or on advisory boards for Amarin, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, Eli Lilly, GlaxoSmithKline, Glytec, Intarcia, Janssen, Merck (Diabetes), Novartis, Novo Nordisk, Sanofi, and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk.

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Table 1: Baseline characteristics stratified by baseline GLP1-RA use in the CANVAS Program

	No GLP1-RA (n=9735)	GLP1-RA (n=407)	P value
Age (years)	63.3 (8.3%)	62.6 (7.7%)	0.092
Female	3516 (36.1%)	117 (28.7%)	0.002
Current smoker	1751 (18.0%)	55 (13.5%)	0.021
Duration diabetes (years)	13.5 (7.8)	15.2 (7.0)	<0.0001
History of heart failure	1435 (14.7%)	26 (6.4%)	<0.0001
History of cardiovascular disease	6410 (65.8%)	246 (60.4%)	0.025
BMI (kg/m^2)	31.8 (5.9)	35.6 (6.3)	<0.0001
Systolic BP (mmHg)	136.6 (15.7)	137.0 (16.2)	0.630
Diastolic BP (mmHg)	77.7 (9.7)	77.5 (9.9)	0.710
HbA1C (%)	8.2 (0.9)	8.3 (0.9)	0.680
Total cholesterol (mmol/L)	4.4 (1.2)	4.0 (0.9)	<0.0001
eGFR (mL/min per 1.73m^2)	76.5 (20.5)	76.7 (20.9)	0.80
Albumin creatinine ratio (mg/g)	12.2 (6.7-41.8)	13.5 (6.5-48.8)	0.550

GLP1-RA: glucagon-like peptide-1 receptor agonist; BMI: body mass index; BP: blood pressure; HbA1C: glycosylated haemoglobin; eGFR: estimated glomerular filtration rate. Data are presented as mean (SD) or median (IQR) for continuous measures, and n(%) for categorical measures.

Figure 1. The effect of canagliflozin treatment compared to placebo on HbA1c, SBP, body weight, and UACR in patients who were, and patients who were not, using GLP1-RA therapy at baseline in the CANVAS Program.
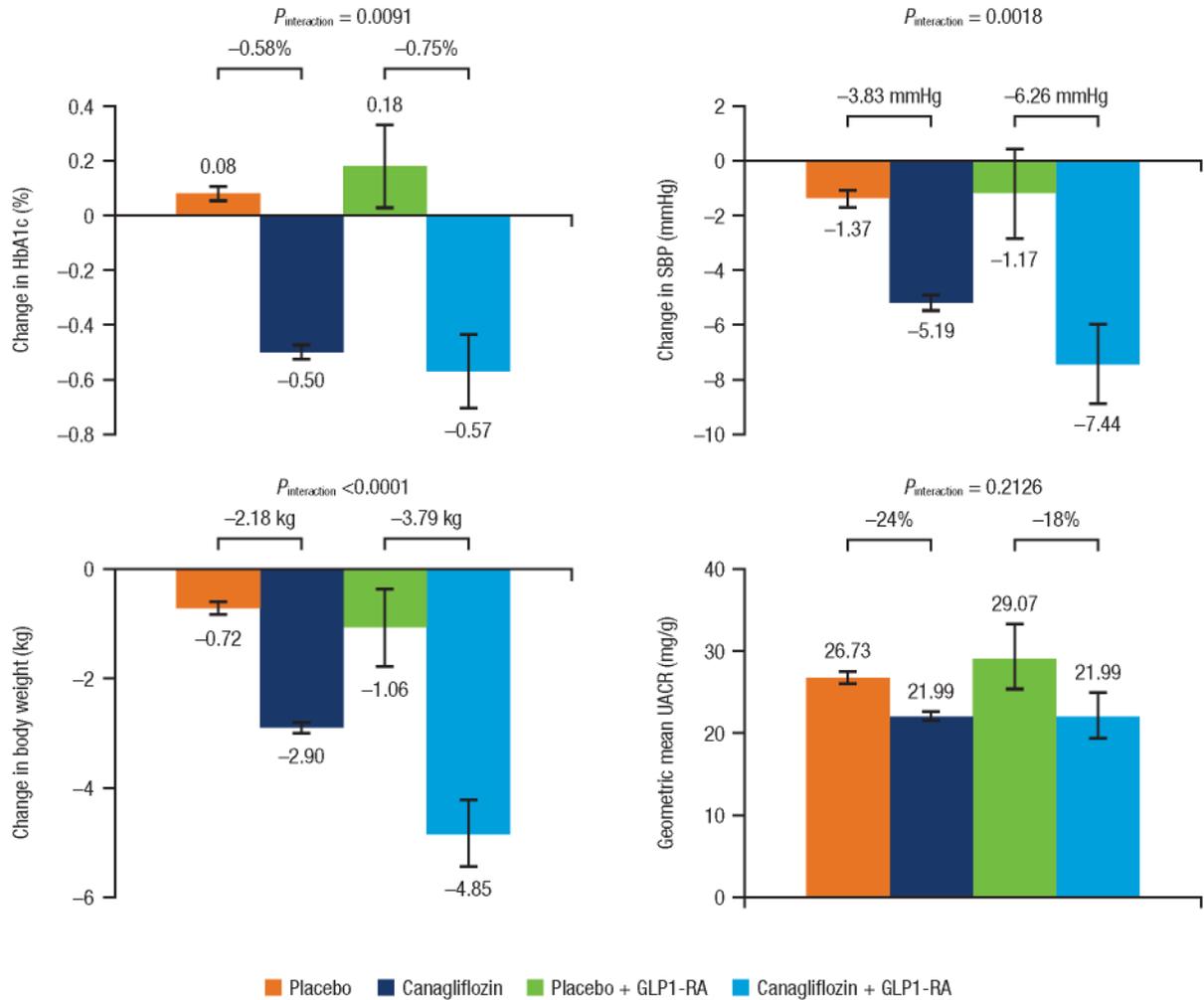
CANA, canagliflozin; GLP1-RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; UACR, urinary albumin:creatinine ratio.

AUTHOR CONTRIBUTION

CA, BLN, BN were involved with project conceptualisation, methodology, analysis, writing, editing and submission. HLL, GF, MK, CL, CC, NR, WS, KM, MJJ, VP were involved with project conceptualisation, writing and editing.

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HIGHLIGHTS

- In the CANVAS Program, 4% of participants were taking GLP1-RA therapy at baseline.
- Those on GLP1-RA at baseline had a greater reduction in HbA1C, SBP and body weight from canagliflozin therapy, as compared to those not on GLP1-RA.
- There was no difference in the effect of canagliflozin on MACE or composite adverse renal events between GLP1-RA subgroups.
- Those on GLP1-RA at baseline did not experience an increase in serious adverse events from canagliflozin therapy.