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RESEARCH LETTER

# Cardiovascular and kidney outcomes with canagliflozin according to type 2 diabetes treatment targets at baseline: Data from the CANVAS programme and CREDENCE

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## 1 | BACKGROUND

Management of type 2 diabetes mellitus (T2DM), a progressive metabolic disorder associated with substantial cardiovascular (CV) and kidney complications, includes risk factor optimization of glucose, blood pressure (BP) and lipids. Although there may be minor differences between guidance, treatment targets recommended by international clinical practice guidelines include maintaining glycated haemoglobin (HbA1c) ≤7.0% (with individual adaptation), BP <130/80 mmHg and low-density lipoprotein cholesterol (LDL-C) <2 mmol/L (<77 mg/dl), along with an annual evaluation of urinary albumin/creatinine ratio (UACR) to assess CV and kidney risk.[1-4]

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The sodium-glucose co-transporter 2 inhibitor class showed improvements in CV and kidney outcomes in patients with T2DM in CV outcome trials.[3] Canagliflozin reduced the risk of CV outcomes, including major adverse CV events (MACE; CV death, non-fatal myocardial infarction and non-fatal stroke), a composite of hospitalization for heart failure (HHF) or CV death (HHF/CV death) and kidney outcomes in patients with T2DM and high CV risk [CANagliflozin cardioVascular Assessment Study (CANVAS) programme][5] and in patients with diabetic nephropathy [Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial].[6] Consequently, treatment guidelines now recommend sodium-glucose co-transporter 2 inhibitors for reducing the risk of CV and kidney events in patients with T2DM.[1-4] As patients have varying control over their CV risk factors, it is important to know whether the clinical benefits of canagliflozin extend across the spectrum of attained treatment targets. This post-hoc analysis assessed the effects of canagliflozin versus placebo on CV and kidney outcomes in patients with T2DM and high CV risk, and/or chronic kidney disease according to baseline treatment target achievement and risk factors.

## 2 | METHODS

### 2.1 | Study design and participants

This post-hoc analysis is an integrated, pooled, patient-level, meta-analysis from the CANVAS programme and CREDENCE. The CANVAS programme comprised two multicentre, double-blind, placebo-controlled, randomized trials: CANVAS and CANVAS-R.[5,7] Eligible participants had T2DM (HbA1c ≥7.0% and ≤10.5%) and an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m$^2$ and were either aged ≥30 years with a history of symptomatic atherosclerotic CV disease or aged ≥50 years with ≥2 CV disease risk factors.[5,7] CREDENCE included participants with T2DM (HbA1c ≥6.5% and ≤12.0%), an eGFR of 30 to <90 ml/min/1.73m$^2$, and a UACR of >33.9 to ≤565.6 mg/mmol (>300 to ≤5000 mg/g).[6,8] Participants in all studies were randomized to canagliflozin or placebo. Participants had similar characteristics, with some differences related to inclusion criteria. In the CANVAS programme, 18% of participants had a history of nephropathy, ~20% had an eGFR <60 ml/min/1.73m$^2$, and 70% had normoalbuminuria at baseline.[5,9] In contrast, all CREDENCE participants had advanced nephropathy at baseline.[6] Lastly, 66% of CANVAS programme participants had established CV disease versus 50% in CREDENCE.

### 2.2 | Outcomes and analyses

This post-hoc analysis of the CANVAS programme and CREDENCE trial included participants who were randomized to canagliflozin or placebo and had values for all selected treatment targets.[5,6] Categorical variables are represented as percentages, and continuous variables are represented as mean (standard deviation) or median (interquartile range). The effects of canagliflozin versus placebo were examined for the time to the first occurrence of MACE, the composite of HHF/CV death, and the kidney composite of end-stage kidney disease (ESKD) or doubling of serum creatinine (dSCr). Patients were categorized by treatment target achievement and number of target levels achieved

**TABLE 1** Baseline achievement of treatment targets and number of targets achieved

| | Canagliflozin ($n$ = 7941) | Placebo ($n$ = 6491) | Total ($n$ = 14 432) | $p$ Value |
|---|---|---|---|---|
| Treatment target, $n$ (%) | | | | |
| HbA1c ≤7.0% | | | | .729 |
| Goal met | 830 (10) | 690 (11) | 1520 (11) | |
| Goal not met | 7111 (90) | 5801 (89) | 12 912 (89) | |
| LDL-C <2 mmol/L (<77 mg/dl) | | | | .18 |
| Goal met | 3380 (43) | 2691 (41) | 6071 (42) | |
| Goal not met | 4561 (57) | 3800 (59) | 8361 (58) | |
| BP <130/80 mmHg | | | | .036 |
| Goal met | 1898 (24) | 1455 (22) | 3353 (23) | |
| Goal not met | 6043 (76) | 5036 (78) | 11 079 (77) | |
| UACR <2 mg/mmol (<18 mg/g) | | | | <.001 |
| Goal met | 3449 (43) | 2568 (40) | 6017 (42) | |
| Goal not met | 4492 (57) | 3923 (60) | 8415 (58) | |
| Number of targets achieved | | | | |
| 0 | 1939 (24.4) | 1744 (26.9) | 3683 (25.5) | |
| 1 | 3228 (40.6) | 2623 (40.4) | 5851 (40.5) | |
| 2 | 2053 (25.9) | 1627 (25.1) | 3680 (25.5) | .001 |
| 3 | 661 (8.3) | 461 (7.1) | 1122 (7.8) | |
| 4 | 60 (0.8) | 36 (0.6) | 96 (0.7) | |

Abbreviations: BP, blood pressure; HbA1c, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin/creatinine ratio.

(0, 1, 2, and 3 or 4) at baseline. The targets were defined as: HbA1c ≤7.0%, LDL-C <2 mmol/L (<77 mg/dl), BP <130/80 mmHg, or UACR <2 mg/mmol (18 mg/g).

Hazard ratios and 95% confidence intervals for each outcome were estimated using Cox regression models stratified by the achievement of treatment targets and, in separate models, by the number of targets achieved at baseline. Interaction *p* values were calculated by including the treatment group by achievement of treatment targets and treatment group by number of targets achieved at baseline in the model.

A two-sided $p < .05$ for the interaction term was deemed probable to reflect a difference beyond chance. This post hoc analysis is not intended for inference, so no type 1 error adjustments were made. Thus, *p* values are descriptive only. Analyses were performed using SAS version 9.4 (SAS Institute).

## 3 | RESULTS

### 3.1 | Baseline characteristics

The pooled analysis included 14 543 participants from the CANVAS programme ($n = 10\,142$) and CREDENCE trial ($n = 4401$), with mean (SD) baseline HbA1c of 8.3% (1.1), LDL-C of 2.4 (1.0) mmol/L [92.8 (38.7) mg/dl], and BP of 138/78 (16/10) mmHg, and median (range) baseline UACR of 3.8 (1.0–59.2) mg/mmol [33.6 (8.9–523.9) mg/g].

At baseline, 3683 (26%) participants had achieved no treatment targets, 5851 (41%) had achieved one, 3680 (25%) had achieved two, and 1218 (8%) had achieved three or four targets (Table 1). In addition, 8415 (58%) participants had a UACR >2 mg/mmol.

### 3.2 | Effects of canagliflozin on key cardiovascular and kidney outcomes

Regardless of whether baseline targets were met or UACR was elevated, canagliflozin consistently reduced the risk of MACE, HHF/CV death, and ESKD/dSCr versus placebo (Figure 1). Among participants who experienced a CV event and did not achieve HbA1c, LDL-C or BP targets or a reduction in UACR, canagliflozin still reduced CV risk (all *p* interaction ≥.38). The beneficial effects of canagliflozin on ESKD/dSCr were observed irrespective of achievement of HbA1c, LDL-C and BP baseline targets (all *p* interaction ≥.45). Canagliflozin reduced kidney events similarly as to whether UACR was elevated (>2 mg/mmol), and reduced CV outcomes with

| | Number of participants with an event (n/N) | | Number of participants with an event per 1000 participant-years | | HR (95% CI) | Interaction *P* value |
|---|---|---|---|---|---|---|
| | Canagliflozin | Placebo | Canagliflozin | Placebo | | |
| **MACE** | | | | | | |
| HbA1c ≤7.0% | | | | | | |
| Yes | 72/830 | 56/690 | 25.9 | 27.9 | 0.94 (0.66, 1.33) | 0.38 |
| No | 723/7111 | 635/5801 | 29.7 | 37.6 | 0.80 (0.71, 0.89) | |
| LDL-C <2 mmol/L (<77 mg/dL) | | | | | | |
| Yes | 294/3380 | 250/2691 | 25.2 | 31.4 | 0.81 (0.68, 0.96) | 0.97 |
| No | 501/4561 | 441/3800 | 32.4 | 40.3 | 0.81 (0.71, 0.92) | |
| BP <130/80 mmHg | | | | | | |
| Yes | 172/1898 | 145/1455 | 25.1 | 33.9 | 0.75 (0.60, 0.93) | 0.41 |
| No | 623/6043 | 546/5036 | 30.7 | 37.3 | 0.83 (0.74, 0.93) | |
| UACR <2 mg/mmol (<18 mg/g) | | | | | | |
| Yes | 285/3449 | 212/2568 | 21.3 | 26.0 | 0.82 (0.69, 0.98) | 0.90 |
| No | 510/4492 | 479/3923 | 37.0 | 44.5 | 0.83 (0.73, 0.94) | |
| **HHF or CV death** | | | | | | |
| HbA1c ≤7.0% | | | | | | |
| Yes | 48/830 | 56/690 | 16.9 | 27.6 | 0.61 (0.42, 0.90) | 0.51 |
| No | 492/7111 | 483/5801 | 19.7 | 28.0 | 0.70 (0.62, 0.80) | |
| LDL-C <2 mmol/L (<77 mg/dL) | | | | | | |
| Yes | 210/3380 | 194/2691 | 17.6 | 24.0 | 0.73 (0.60, 0.89) | 0.49 |
| No | 330/4561 | 345/3800 | 20.7 | 30.8 | 0.67 (0.58, 0.78) | |
| BP <130/80 mmHg | | | | | | |
| Yes | 128/1898 | 114/1455 | 18.4 | 26.2 | 0.70 (0.55, 0.90) | 0.93 |
| No | 412/6043 | 425/5036 | 19.7 | 28.5 | 0.69 (0.61, 0.80) | |
| UACR <2 mg/mmol (<18 mg/g) | | | | | | |
| Yes | 149/3449 | 118/2568 | 10.8 | 14.1 | 0.76 (0.59, 0.97) | 0.65 |
| No | 391/4492 | 421/3923 | 27.7 | 38.6 | 0.71 (0.62, 0.82) | |
| **ESKD or dSCr** | | | | | | |
| HbA1c ≤7.0% | | | | | | |
| Yes | 32/830 | 47/690 | 11.3 | 23.2 | 0.50 (0.32, 0.78) | 0.91 |
| No | 155/7111 | 212/5801 | 6.2 | 12.2 | 0.51 (0.42, 0.63) | |
| LDL-C <2 mmol/L (<77 mg/dL) | | | | | | |
| Yes | 55/3380 | 78/2691 | 4.6 | 9.6 | 0.49 (0.34, 0.69) | 0.73 |
| No | 132/4561 | 181/3800 | 8.3 | 16.1 | 0.52 (0.42, 0.65) | |
| BP <130/80 mmHg | | | | | | |
| Yes | 28/1898 | 41/1455 | 4.0 | 9.3 | 0.43 (0.27, 0.70) | 0.45 |
| No | 159/6043 | 218/5036 | 7.6 | 14.6 | 0.53 (0.43, 0.65) | |
| UACR <2 mg/mmol (<18 mg/g) | | | | | | |
| Yes | 5/3449 | 8/2568 | 0.4 | 0.9 | 0.38 (0.12, 1.15) | 0.50 |
| No | 182/4492 | 251/3923 | 12.8 | 23.0 | 0.56 (0.46, 0.68) | |

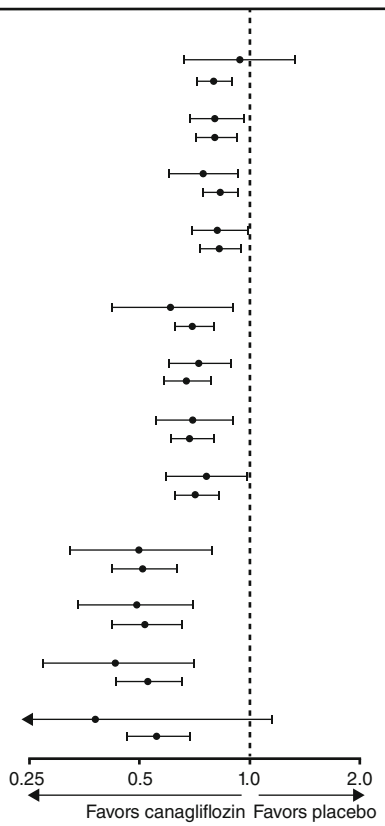


**FIGURE 1** Effects of canagliflozin versus placebo on CV and kidney events by T2DM treatment targets achieved at baseline. BP, blood pressure; CI, confidence interval; CV, cardiovascular; dSCr, doubling of serum creatinine; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; T2DM, type 2 diabetes mellitus; UACR, urinary albumin/creatinine ratio.

elevated or normal UACR, at baseline. Furthermore, the number of uncontrolled targets at baseline did not impact the beneficial effect of canagliflozin on CV and kidney outcomes (all $p$ interaction ≥.17; Figure S1).

## 4 | CONCLUSIONS

In this pooled analysis of the CANVAS programme and CREDENCE trial, participants with T2DM and high CV risk, and/or chronic kidney disease who were randomized to canagliflozin treatment showed consistent CV and kidney benefits versus placebo, regardless of whether T2DM-related or other CV-risk treatment targets were met at baseline.

Our findings highlight the importance of canagliflozin's protective effect on key CV and kidney outcomes irrespective of baseline risk factor control. This is particularly important in outpatient clinical settings where, despite best efforts, patients with T2DM may only achieve partial composite target goals.[10,11] The DM-SCAN study, which included primary care physician surveys and chart data from adults with T2DM, showed that 50%, 57% and 36% of patients achieved target levels of HbA1c, LDL-C and BP, respectively, with only 13% achieving all three targets.[10] Similarly, a low proportion of participants in the current analysis achieved the recommended treatment targets. Thus, our data show the benefits of canagliflozin for preventing cardiorenal complications in patients who have not yet achieved risk factor targets.

Strengths of this study include the multicentre, randomized, controlled trial designs, which were conducted to a high standard and with many participants. CV and kidney outcomes were pre-specified and adjudicated by expert committees. This analysis also has inherent limitations applicable to any post-hoc analysis of a randomized trial. The CANVAS programme and CREDENCE trial were not designed specifically to test outcomes in these subgroups, nor were there adjustments for multiple baseline test comparators. Thus, our findings should be considered exploratory. In addition, generalizability of the results may be limited to individuals with previous CV events, high CV risk or nephropathy, similar to the patients enrolled in the CANVAS programme and CREDENCE trial.

While control of CV and kidney risk factors in high-risk patients with T2DM is critical, this study showed that canagliflozin provides consistent CV and kidney benefits, regardless of whether treatment targets for these risk factors are met at baseline.

### AUTHOR CONTRIBUTIONS

MAT, SWT, WR, FGA, JS, BLN, CA, KWM and DCW contributed to the study design and data interpretation. AS performed the statistical analysis. MAT and VW drafted the manuscript, and the final version was critically revised and approved by all the authors.

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### CONFLICT OF INTEREST STATEMENT

MAT has received speakers bureau and advisory board fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk and Sanofi Genzyme. VW has received honoraria for speaking, advisory boards, and clinical research from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen and Novo Nordisk. SWT has received a KMH Clinic unrestricted grant and in-kind support for the Zero to Five study paid to Sunnybrook Research Institute; has received consulting fees from AstraZeneca paid to Sunnybrook Research Institute; has received payment or honoraria for lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Novartis, Novo Nordisk, Pfizer and Sanofi paid to the CHEP Plus education program; and has served as a volunteer for the American Hypertension Specialist Certification Program. AS is an employee of New Arch Consulting; and received funding from Janssen for this analysis. WR and FGA are employees of Janssen Inc. JS has received honoraria for talks and/or consultancy and/or research funding from Apitope, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GI-Dynamics, GlaxoSmithKline, Intarcia, Ipsen, Janssen, LifeScan, MedScape, Merck Sharp & Dohme, Novartis, Novo Nordisk, Omniamed, Pfizer, Roche, Sanofi, Servier, Takeda and Ypsomed. BLN has received fees for travel support, advisory boards, scientific presentations, and steering committee roles from AstraZeneca, Bayer, Boehringer and Ingelheim, Cambridge Healthcare Research and Janssen, with all honoraria paid to his institution. CA has received honoraria from Amgen; has received support from an NHMRC/MRFF Priority Fellowship and an NSW Health EMC Grant; and is an employee of The George Institute for Global Health. KWM's financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. DCW has received fees for advisory boards, committee work, educational activities, and scientific presentations form Amgen, Astellas, AstraZeneca (ongoing), Bayer, Boehringer Ingelheim, CSL Vifor, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Mundipharma, Tricida, and Zydus.

### DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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## SUPPORTING INFORMATION

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

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