RESEARCH LETTER

Effects of canagliflozin on cardiovascular and kidney events in patients with chronic kidney disease with and without peripheral arterial disease: Integrated analysis from the CANVAS Program and CREDENCE trial

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1 | BACKGROUND

Global prevalence of diabetes in 2021 was ~537 million adults and is projected to rise to 783.2 million in 2045.1 Type 2 diabetes (T2D) is commonly associated with cardiovascular (CV) risk factors and co-morbidities, including chronic kidney disease (CKD), CV disease (CVD) and peripheral arterial disease (PAD).2 PAD is an independent predictor of CV and cerebrovascular events, with greater incidence in patients with versus those without T2D.3 Canagliflozin, a sodium-glucose co-transporter-2 inhibitor, reduced the risk of CV and kidney events in patients with T2D and high CV risk or nephropathy in the CANVAS Program and CREDENCE trial, respectively.4,5 The CANVAS Program showed significant benefits of

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canagliflozin, including lowering the risk of the primary composite CV outcome and three-point major adverse CV events (MACE; CV death, nonfatal myocardial infarction and non-fatal stroke) by 14% in the overall cohort and 18% in patients with established CVD.\(^6\) CREDENCE showed a 30% reduction in the primary outcome of end-stage kidney disease (ESKD), doubling of serum creatinine (dSCR), or death from renal or CV causes with canagliflozin in participants with T2D and albuminuric CKD.\(^5\)

Additionally, canagliflozin has been associated with a risk of amputation in the CANVAS Program but not CREDENCE; however, no explanation for this finding has been uncovered.\(^6\) Recently, Barralouagh et al. conducted an individual patient data analysis of the CANVAS Program and CREDENCE that reported the proportional and absolute benefits of canagliflozin in patients who have T2D with and without PAD, and examined a novel PAD composite outcome of extended major adverse limb events (MALE), including acute and chronic limb ischaemia, thrombosis and arteriolar restenosis.\(^7\) To further investigate this subgroup of high-risk participants, the present pooled analysis assessed the efficacy of canagliflozin in patients who have CKD with and without PAD at baseline.

<table>
<thead>
<tr>
<th>TABLE 1 Baseline characteristics of patients with CKD (no PAD) and CKD with PAD</th>
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<tr>
<td><strong>CKD (no PAD)</strong></td>
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<td>Mean duration of diabetes, y</td>
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<td>History of heart failure, %</td>
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<td>Mean HbA1c, %</td>
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<td>DBP, mmHg</td>
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<tr>
<td>Mean eGFR, mL/min/1.73m²</td>
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<tr>
<td>Median UACR, mg/mmol (mg/g)</td>
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<td>Insulin use, %</td>
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Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease; PSM, propensity score matching; SBP, systolic blood pressure; UACR, urine albumin-creatinine ratio.

The CANVAS Program consisted of two double-blind, placebo-controlled, randomized, multicentre trials, CANVAS and CANVAS-R.\(^4\) Eligible participants had T2D (HbA1c ≥ 7.0% and ≤ 10.5%), an eGFR of 30 mL/min/1.73m² or higher and were either aged at least 30 years with a history of symptomatic atherosclerotic CVD or at least 50 years with at least CVD risk factors (i.e. T2D duration ≥ 10 y, systolic blood pressure > 140 mmHg on ≥ 1 medication, current smoker, microalbuminuria [urine albumin-creatinine ratio (UACR) 30-300 mg/g] or macroalbuminuria [UACR ≥ 300 mg/g], or high-density lipoprotein cholesterol < 1 mmol/L). CANVAS Program participants were randomized to canagliflozin 100 mg, canagliflozin 300 mg or placebo.

CREDENCE was a randomized, double-blind, placebo-controlled, multicentre trial that investigated the safety and efficacy of canagliflozin in participants with T2D and albuminuric CKD, an eGFR of 30 to less than 90 mL/min/1.73m², and a UACR of more than 300 to 5000 mg/g (33.9-565 mg/mmol).\(^5\) All participants were established on the maximum labelled or tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for 4 or more weeks prior to randomization. To assess the impact of canagliflozin on the progression of CKD, ~60% of participants had stage 3 CKD with an eGFR of 30 to 60 mL/min/1.73m². CREDENCE participants were randomized to canagliflozin 100 mg or placebo.

2 | METHODS

This post hoc analysis integrated individual pooled data from the CANVAS Program and CREDENCE trial. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m². PAD was defined based on investigator classification on the electronic case report form without requirement for specific clinical evaluation or imaging. PAD excluded cerebrovascular disease and was specific to lower extremity disease. Propensity score matching (PSM) analysis balanced patient demographics and baseline clinical characteristics between groups to address potential residual confounding (Data S1).

3 | RESULTS

Of the 14 543 participants in the pooled population, 3514 had CKD without PAD (canagliflozin, n = 1792; placebo, n = 1722; mean eGFR, 46 mL/min/1.73m²; mean age, 65 years; symptomatic CVD history, 49%; insulin use, 64%), and 1156 had CKD and PAD.
The present analysis examined individual pooled data from the CANVAS Program and CREDEENCE trial in participants with CKD with or without PAD at baseline. In these high-risk participants, canagliflozin reduced the risk of MACE benefit with canagliflozin in individuals with T2D, CKD and PAD translates into an ARR of 0.51 (0.33, 0.79) between groups (P interaction > .20 for all outcomes; Figure 1B). The outcomes were similar between the full and PSM cohorts.

No increase in the relative risk of serious adverse events (SAEs), kidney-related SAEs or lower limb amputation was observed with canagliflozin, regardless of baseline PAD status (P = .331; Table S1).

4 | CONCLUSIONS

The present analysis examined individual pooled data from the CANVAS Program and CREDEENCE trial in participants with CKD with or without PAD at baseline. In these high-risk participants, canagliflozin showed consistent CV and kidney benefits irrespective of PAD. The MACE benefit with canagliflozin in individuals with T2D, CKD and PAD translates into an ARR of 0.51 (0.33, 0.79) between groups (P interaction > .20 for all outcomes; Figure 1B). The outcomes were similar between the full and PSM cohorts.

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including inflammation, mineral-bone disease and other metabolic complications of CKD.\(^8,9\) The presence of both CKD and PAD confers a 2-fold higher risk of death than either condition alone.\(^8\) Our analysis of participants with baseline CKD with or without PAD shows the relative and absolute benefits conferred by canagliflozin on CV and kidney outcomes in this high-risk CV population. The rates of SAEs were lower with canagliflozin relative to placebo, with no increase in the rates of serious kidney-related AEs or lower limb amputation. Similarly, Barraclough et al. showed that canagliflozin consistently decreased the risk of major CV and kidney outcomes in patients with T2D, regardless of PAD status at baseline. Participants with PAD had higher risk for CV events and showed greater ARR with canagliflozin, without an increase in total SAEs.\(^7\) Furthermore, no increase in the relative risk of extended MAE was observed with canagliflozin, regardless of PAD status. Although this analysis did not assess extended MAE, the incidence of lower limb amputation was similar in both treatment groups—with or without PAD—thus extending the findings of Barraclough et al. to an even higher-risk subpopulation: those with T2D, CKD and PAD.

The strengths of this analysis include the diligent conduct and robust design of the randomized outcome trials; a cohort of individuals with T2D, CKD and PAD at baseline (>1100 participants); and a considerable follow-up period. However, this post hoc analysis was exploratory and not powered to detect differences between participants with and without PAD.

In conclusion, canagliflozin significantly reduced the risk of three-point MACE, the composite of HHF or CV death, dScr, ESKD, and the composite of ESKD or dScr in participants with T2D co-morbid with CKD, regardless of PAD history.

**AUTHOR CONTRIBUTIONS**

All authors had input into the final manuscript and critical review; First drafts were created by TWY and AL, with input from all; all authors had access to data and manuscript throughout the process.

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**FUNDING INFORMATION**

This study was sponsored by Janssen, Inc.

**CONFLICT OF INTEREST**

TWY has nothing to disclose. MMYW is a consultant for George Clinical; received honoraria for advisory board participation from AstraZeneca; and received research funding from Michael Smith Health Research BC. BLN received fees for travel support, advisory boards, scientific presentations and steering committee roles from AstraZeneca, Bayer, Boehringer Ingelheim, Cambridge Healthcare Research and Janssen, with all honoraria paid to his institution. CA received honoraria from Amgen; 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. PP received payment or honoraria for advisory boards or, continuing medical education from Abbott, Amgen, AstraZeneca, Bayer, Bausch Health, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics Inc., Janssen, Novartis, NovoNordisk, Sanofi and Servier. 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, GlaxoSmithKline, Intarcia, Ipsen, Janssen, LifeScan, MedScape, Merck Sharp and Dohme, Novartis, Novo Nordisk, Omniaimed, Pfizer, Roche, Sanofi, Servier, Takeda and Ypsomed. AS is an employee of New Arch Consulting and received funding from Janssen for this analysis. WR and FGA are employees of Janssen. 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. KWM’s disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. VP received fees for an advisory board, steering committee or scientific presentation from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chinox Therapeutics, CSL Vifor, Gilead, GlaxoSmithKline, Janssen, Medimmune, Mitsubishi-Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka and Traveo Therapeutics, Inc.; received speaker fees from Janssen; served on a data and safety monitoring committee for Dimerex; served on the board of directors for George Clinical, Garvan Institute, George Institute, Victor Chang Cardiac Research Institute, Ingham Institute and Mindgardens Neuroscience Network; and has stock in George Clinical. AL served as a scientific advisor to Boehringer Ingelheim, AstraZeneca, NIDDK, Occurx and Chinox Therapeutics; served on a data safety monitoring board or scientific committee for NIDDK, NIH, Kidney Precision Medicine, CURE consortium and the University of Washington Kidney Research Institute Scientific Advisory Committee; received research funding from CIHR, Kidney Foundation of Canada, GSK, AstraZeneca and Boehringer Ingelheim; and received fees for time as CREDENCE national coordinator from Janssen, directed to her academic team.

**DATA AVAILABILITY STATEMENT**

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at [https://www.janssen.com/clinical-trials/transparency](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](http://yoda.yale.edu).

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REFERENCES


SUPPORTING INFORMATION

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

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