Received: 10 March 2023 | Revised: 22 March 2023 | Accepted: 23 March 2023

DOI: 10.1111/dom.15065

RESEARCH LETTER

WILEY

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

Tae Won Yi MD[1,2] | Michelle M.Y. Wong MD[2] | Brendon L. Neuen MD[1,3] | Clare Arnott MD[1,4,5,6] | Paul Poirier MD[7] | Jochen Seufert PhD[8] | April Slee PhD[9] | Wally Rapattoni MSc[10] | Fernando G. Ang PhD[10] | David C. Wheeler MD[1,11] | Kenneth W. Mahaffey MD[12] | Vlado Perkovic MD[1,3,4] | Adeera Levin MD[2]

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

[2]Division of Nephrology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[3]Royal North Shore Hospital, Sydney, New South Wales, Australia

[4]Faculty of Medicine, UNSW Sydney, Sydney, New South Wales, Australia

[5]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

[6]Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

[7]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec City, Québec, Canada

[8]Division of Endocrinology and Diabetology, Department of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[9]New Arch Consulting, Seattle, Washington, USA

[10]Janssen, Inc., Toronto, Ontario, Canada

[11]Centre for Nephrology, University College London, London, UK

[12]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

Correspondence
Adeera Levin, MD, Division of Nephrology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.
Email: alevin@providencehealth.bc.ca

Funding information
Janssen Research & Development, LLC and Janssen Inc.

KEYWORDS: canagliflozin, cardiovascular disease, SGLT2 inhibitor, type 2 diabetes

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

TABLE 1 Baseline characteristics of patients with CKD (no PAD) and CKD with PAD

	CKD (no PAD)				CKD with PAD			
	Full cohort		PSM cohort		Full cohort		PSM cohort	
	Canagliflozin ($n = 1792$)	Placebo ($n = 1722$)	Canagliflozin ($n = 1605$)	Placebo ($n = 1605$)	Canagliflozin ($n = 626$)	Placebo ($n = 508$)	Canagliflozin ($n = 483$)	Placebo ($n = 483$)
Mean age, y	65	65	65	65	66	66	66	66
Female, %	38	38	38	38	36	35	35	35
Mean duration of diabetes, y	16	16	16	16	17	17	17	17
History of CV disease, %	50	48	49	49	95	97	98	97
History of hypertension, %	97	98	98	98	98	98	98	98
History of heart failure, %	14	13	14	14	23	25	24	25
Mean HbA1c, %	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2
SBP, mmHg	139	139	139	139	140	139	139	139
DBP, mmHg	77	77	77	77	76	76	76	76
Mean eGFR, mL/min/1.73m^2	46	46	46	46	46	45	46	45
Median UACR, mg/mmol (mg/g)	44 (388)	53 (464)	46 (408)	48 (421)	50 (439)	56 (499)	52 (460)	51 (453)
Insulin use, %	65	63	65	63	73		75	73

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.

canagliflozin, including lowering the risk of the primary composite CV outcome and three-point major adverse CV events (MACE; CV death, non-fatal myocardial infarction and non-fatal stroke) by 14% in the overall cohort and 18% in patients with established CVD.[4] 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, Barraclough 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 arterial 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.

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/1.73m^2. 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).

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/1.73m^2 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/1.73m^2, 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/1.73m^2. CREDENCE participants were randomized to canagliflozin 100 mg or placebo.

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/1.73m^2; mean age, 65 years; symptomatic CVD history, 49%; insulin use, 64%), and 1156 had CKD and PAD

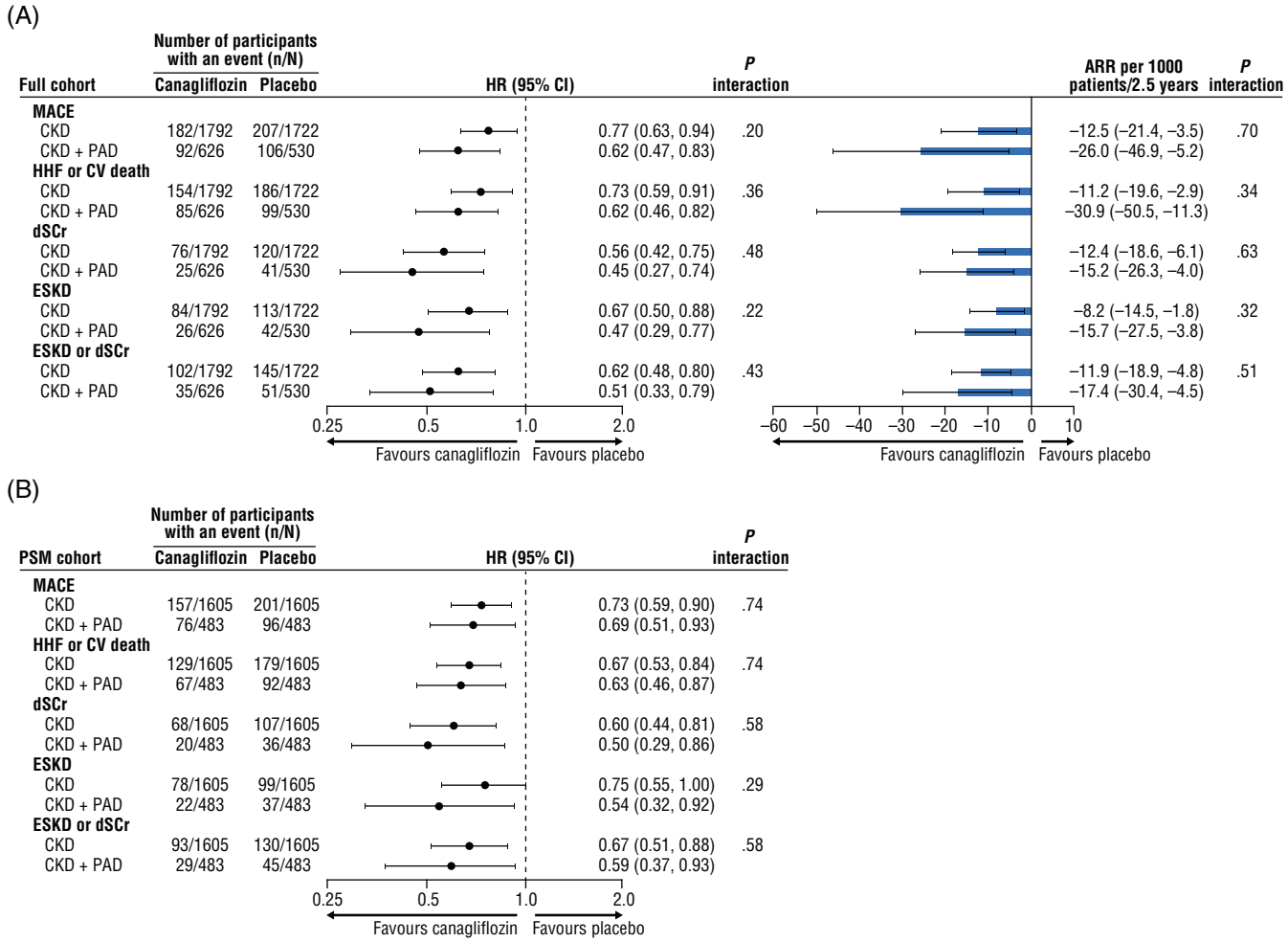

FIGURE 1 Effects of canagliflozin on CV and kidney outcomes by PAD status in A, The full cohort, and B, The PSM cohort. ARR, absolute risk reduction; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; dSCr, doubling of serum creatinine; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; PAD, peripheral arterial disease; PSM, propensity score matching

(canagliflozin, $n = 626$; placebo, $n = 530$; mean eGFR, 46 mL/min/1.73m^2; mean age, 66 years; symptomatic CVD history, 96%; insulin use, 74%) at baseline (Table 1).

In those with CKD and PAD, canagliflozin reduced the risk of MACE (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.47, 0.83), the composite of hospitalization for heart failure (HHF) or CV death (HR, 0.62; 95% CI, 0.46, 0.82), dSCr (HR, 0.45; 95% CI, 0.27, 0.74), ESKD (HR, 0.47; 95% CI, 0.29, 0.77), and the composite of ESKD or dSCr (HR, 0.51; 95% CI, 0.33, 0.79; Figure 1A). There was no heterogeneity of effect or absolute risk reduction (ARR) with canagliflozin treatment between participants with and without PAD (*P* interaction > .20 for all outcomes).

After PSM, 3210 participants had CKD without PAD (mean eGFR, 46 mL/min/1.73m^2; symptomatic CVD history, 49%; insulin use, 64%), and 966 had CKD and PAD (mean eGFR, 46 mL/min/1.73m^2; symptomatic CVD history, 98%; insulin use, 74%), with equal numbers in the canagliflozin and placebo groups (Table 1). There was no heterogeneity of effect with canagliflozin 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 CREDENCE 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 −26.0 events/1000 patients over 2.5 years versus placebo.

PAD is present among 24% to 37% of those with CKD, with contributions from both traditional and non-traditional CV risk factors,

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 MALE was observed with canagliflozin, regardless of PAD status. Although this analysis did not assess extended MALE, 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 maunscript and critical review; First drafts were created by TWY and AL, with input from all; all authors had access to data and mansucript throughout the process.

ACKNOWLEDGEMENTS

This study was sponsored by Janssen, Inc. Medical writing support was provided by Kim Caldwell, PhD, of Lumanity Communications Inc., and was funded by Janssen, Inc. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. The CANVAS Program and CREDENCE trial were supported by Janssen Research & Development, LLC.

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, GI-Dynamics, GlaxoSmithKline, Intarcia, Ipsen, Janssen, LifeScan, MedScape, Merk Sharp and Dohme, Novartis, Novo Nordisk, Omniamed, 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, Chinook Therapeutics, CSL Vifor, Gilead, GlaxoSmithKline, Janssen, Medimmune, Mitsubishi-Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka and Travere Therapeutics, Inc.; received speaker fees from Janssen; served on a data and safety monitoring committee for Dimerix; 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, Occuryx and Chinook 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. 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.

ORCID

Brendon L. Neuen https://orcid.org/0000-0001-9276-8380
Clare Arnott https://orcid.org/0000-0001-9370-9913
Jochen Seufert https://orcid.org/0000-0001-5654-7310
Wally Rapattoni https://orcid.org/0000-0001-6400-982X
Adeera Levin https://orcid.org/0000-0003-2438-8401

REFERENCES

1. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119.
2. Nowakowska M, Zghebi SS, Ashcroft DM, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. *BMC Med*. 2019;17(1):145.
3. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol*. 2006;47(5):921-929.
4. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
5. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.
6. Arnott C, Huang Y, Neuen BL, et al. The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial. *Diabetes Obes Metab*. 2020;22(10):1753-1766.
7. Barraclough JY, Yu J, Figtree GA, et al. Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: data from the CANVAS program and CREDENCE trial. *Diabetes Obes Metab*. 2022;24(6):1072-1083.
8. Liew YP, Bartholomew JR, Demirjian S, Michaels J, Schreiber MJ Jr. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. *Clin J Am Soc Nephrol*. 2008;3(4):1084-1089.
9. Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;74(14):1823-1838.

SUPPORTING INFORMATION

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

How to cite this article: Yi TW, Wong MMY, Neuen BL, et al. 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. *Diabetes Obes Metab*. 2023;1-5. doi:10.1111/dom.15065