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BRIEF REPORT

WILEY

The effects of canagliflozin on heart failure and cardiovascular death by baseline participant characteristics: Analysis of the CREDENCE trial

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Abstract

Heart failure is prevalent in those with type 2 diabetes and chronic kidney disease, and is associated with significant mortality and morbidity. In the CREDENCE trial, canagliflozin reduced the risk of hospitalization for heart failure (HHF) or cardiovascular (CV) death by 31%. In the current analysis we sought to determine whether the effect of canagliflozin on HHF/CV death differed in subgroups defined by key baseline participant characteristics. Cox regression models were used to estimate hazard ratios and 95% confidence intervals. Canagliflozin was associated with a reduction in the relative risk of HHF/CV death regardless of age, sex, history of heart failure or

CV disease, and the use of loop diuretics or glucagon-like peptide-1 receptor agonists (all $p_{\text{interaction}} > .114$). The absolute benefit of canagliflozin was greater in those at highest baseline risk, such as those with CV disease (50 fewer events/1000 patients treated over 2.5 years vs. 20 fewer events in those without CV disease) or advanced kidney disease (estimated glomerular filtration rate [eGFR] 30–45 mL/min/1.73m²: 61 events prevented/1000 patients treated over 2.5 years vs. 23 events in eGFR 60–90 mL/min/1.73m²). Canagliflozin consistently reduces the proportional risk of HHF/CV death across a broad range of subgroups with greater absolute benefits in those at highest baseline risk.

KEYWORDS

antidiabetic drug

1 | INTRODUCTION

There are over 400 million adults with type 2 diabetes (T2D) globally, and this is projected to increase to 600 million by 2050.¹ T2D is the leading cause of chronic kidney disease (CKD), with over 40% of those with T2D developing CKD.¹ Not only is heart failure prevalent in both these conditions, but the co-existence of both T2D and CKD with heart failure is associated with increased hospitalization rates and reduced survival.²

In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, the sodium-glucose co-transporter-2 (SGLT2) inhibitor canagliflozin reduced the risk of the primary composite outcome of endstage kidney disease, doubling of serum creatinine, or renal or cardiovascular (CV) death, compared with placebo in patients with T2D and CKD.³ Canagliflozin also reduced the risk of secondary renal and CV events, including the composite of hospitalization for heart failure (HHF) or CV death by 31% (HR 0.69, 95% CI 0.57, 0.83; $p < .001$). The objective of this analysis was to determine whether the effect of canagliflozin on the composite of HHF/CV death differs in subgroups defined by key baseline participant characteristics that are associated with incident heart failure and its attendant complications.

2 | METHODS

The CREDENCE trial was an event-driven, double-blind, randomized control trial assessing the effect of canagliflozin on kidney, CV and safety outcomes in participants with T2D and CKD.³ The trial included participants with T2D aged 30 years and older, an HbA1c level of 6.5% to 12.0%, and CKD, which was defined as an estimated glomerular filtration rate (eGFR) of 30 to less than 90 mL/min/1.73m² and a urinary albumin-to-creatinine ratio (UACR) of more than 300 to 5000 mg/g. All participants were required to be receiving a maximum tolerated labelled dose of renin angiotensin system blockade for at least 4 weeks prior to randomization. Participants were randomized to either canagliflozin 100 mg, or matching placebo once daily, and were stratified by prerandomisation eGFR (30 to <45, 45 to <60, 60 to

<90 mL/min/1.73m²). Follow-up occurred at weeks 3, 13 and 26 and then alternated between clinic and telephone follow-up at 13-week intervals thereafter. The detailed protocol and statistical plan have been published previously.⁴

In the current analysis, we analysed the effect of canagliflozin on HHF/CV death in the overall population and in subgroups based on the following baseline characteristics: age (<65 or ≥65 years); sex (male or female); race (White, Asian, Black, other); history of CV disease (yes or no); history of heart failure (none, yes, New York Heart Association [NYHA] class I, II or III); history of hypertension (yes or no); history of atrial fibrillation (yes or no); eGFR category (30 to <45, 45 to <60, or 60 to 90 mL/min/1.73m²); UACR category (≤1000 or >1000 mg/g); baseline HbA1c category (<8% or ≥8%); body mass index category (≤25, 25–<30, ≥30 kg/m²); duration of diabetes (≤10, >10 years); use of diuretics (yes or no); use of glucagon-like peptide-1 (GLP-1) receptor agonists (yes or no); and use of metformin (yes or no). Use of metformin was considered an important category given that most T2D guidelines currently recommend SGLT2 inhibitor therapy as an add-on to metformin.⁵ History of CV disease was defined as a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular or peripheral).³

Treatment effect was analysed using Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with subgroup by treatment interaction terms added to test for heterogeneity. Absolute risk differences were estimated by subtracting the incidence rates (per 1000 patient-years) of placebo from those of canagliflozin and multiplying by 2.5 years, and similarly for CIs by multiplying the lower and upper CIs.

3 | RESULTS

In the overall cohort the mean (SD) age of participants was 63 (9.3) years, 34% were female, 15% had a history of heart failure and 50% a history of CV disease at study baseline. These characteristics were well balanced across randomized groups. Those who experienced a HHF/CV death event during the trial were older (aged 65.3 vs. 62.8 years; $p < .001$) than those who did not, and were more probable to have a history of heart failure (26.9% vs. 13.5%; $p < .001$), CV disease

(65.3% vs. 48.8%; $p < .001$) or atrial fibrillation (9.7% vs. 4.8%; $p < .001$). They also had a higher UACR (1265 vs. 884 mg/g; $p < .001$), HbA1c (8.4% vs. 8.2%; $p = .004$), systolic blood pressure (141.8 vs. 139.8 mmHg; $p = .01$) and lower eGFR (51.8 vs. 55.0 mL/min/m²; $p < .001$) at study baseline than participants who did not experience an event (Table 1).

Canagliflozin treatment was associated with a reduction in the composite outcome of HHF/CV death in those with T2D and CKD regardless of age ($p_{\text{interaction}} = .509$), sex ($p_{\text{interaction}} = .747$), history of heart failure ($p_{\text{interaction}} = .236$) or history of CV disease ($p_{\text{interaction}} = .566$). The benefits of active treatment were also evident irrespective of baseline eGFR ($p_{\text{interaction}} = .567$), UACR ($p_{\text{interaction}} = .590$) and the use of loop diuretics ($p_{\text{interaction}} = .246$), GLP-1 receptor agonists ($p_{\text{interaction}} = .585$) or metformin ($p_{\text{interaction}} = .557$). These results were consistent, although not separately significant in all subgroups (Figure 1).

The background risk of a HHF/CV death event was increased in those with a history of CV disease (60.3 vs. 30.7 events/1000 patient-years), a history of heart failure (78.5 vs. 40.1 events/1000 patient-years), lower eGFR (64.0 for eGFR 30–45 mL/min/1.73m² vs. 34.1 events/100 patient-years for eGFR 60–90 mL/min/1.73m²), and those with a higher UACR (58.0 vs. 34.8 events/100 patient-years, for UACR > 1000 vs. ≤1000 mg/g, respectively) as reflected by the event rates in the placebo arm. Accordingly, the absolute benefits of canagliflozin in these groups was greater than in those with a lower background risk. For example, in participants with established CV disease, treatment with canagliflozin resulted in 50 fewer events (95% CI –80, –21) per 1000 patients treated over 2.5 years versus 20 events (95% CI –42, 1.2) in those without CV disease (Figure 1).

4 | DISCUSSION

People with T2D and CKD in the CREDENCE trial experienced 45 HHF/CV death events per 1000 patient-years. This is more than double the event rates seen in the CANVAS Program, a population of T2D patients most of whom did not have established CKD (21 events per 1000 patient years).⁶ In this high-risk group we showed that canagliflozin, in addition to standard of care, consistently reduced the relative risk of the prespecified secondary outcome of HHF/CV death, regardless of baseline participant characteristics such as age, sex or co-morbidities. These findings are consistent with the results of other large event-driven SGLT2 inhibitor trials in T2D populations, including trials of empagliflozin (EMPA-REG outcome trial), canagliflozin (CANVAS) and dapagliflozin (DECLARE TIMI-58 trial).^{7,8} The exception is the recently published VERTIS CV trial in T2D with established CV disease, which did suggest a possible greater reduction in HHF with ertugliflozin treatment in those with an eGFR of less than 60 mL/min/1.73m², albuminuria and those on diuretics.⁹ These consistent benefits, however, have not previously been confirmed in those with diabetic kidney disease. These data support the use of canagliflozin in people with diabetes and kidney disease, unless contraindicated, to prevent heart failure morbidity or CV death.

While the relative benefits from canagliflozin treatment were consistent across patient subgroups, absolute benefits were greater in those at highest baseline risk, namely, those with macroalbuminuria, lower eGFR, established CV disease and those taking loop diuretics. For example, those with a UACR of more than 1000 mg/g experienced 58 events per 1000 patient-years in the placebo arm; however, canagliflozin therapy resulted in an absolute risk reduction of 39 events per 1000 patients treated over 2.5 years. Those with a UACR of less than 1000 mg/g had a smaller absolute risk difference of 30 events per 1000 patients over 2.5 years.

In patients with CKD, avoiding heart failure events is vital. Heart failure is not only highly prevalent in CKD, but the severity of kidney dysfunction increases the mortality risk in heart failure patients.^{2,10} Further, loss of kidney function has been shown to accelerate after HHF.¹¹ The complex interplay between T2D and heart failure is also highly relevant: not only is T2D a risk factor for the development of heart failure, but it is an independent predictor of heart failure prognosis. This is probably related to the increased prevalence of coronary heart disease, left ventricular hypertrophy, and systolic and diastolic left ventricular dysfunction in T2D,¹² pathologies that are further exacerbated by the presence of CKD, making the combination of diabetes and CKD complex and high risk. In addition to the robust evidence from T2D trials, the recently published DAPA-CKD trial showed that SGLT2 inhibition reduced HHF/CV death in a CKD population by 29%, irrespective of T2D status, with no increase in serious adverse events.¹³ This provides further certainty about the important role of SGLT2 inhibitors to prevent HHF in people with CKD.

Our subgroup analysis should provide confidence to clinicians when prescribing canagliflozin in their patients, given the clear signal of benefit across a broad spectrum of age, sex, kidney function and CV disease history. One common clinical concern is the lack of treatment options and risk of adverse treatment effects when managing elderly T2D patients and those with advanced CKD.¹⁴ The current analysis shows that canagliflozin benefits are preserved as kidney function declines and when renally acting medications such as loop diuretics are being used. These results, coupled with the previously published safety profile,³ suggest that age and established CKD should not be barriers to the prescription of SGLT2 inhibition.

The mechanisms responsible for the heart failure reduction seen with SGLT2 inhibition are probably complex and are hypothesized to extend beyond glycosuria, diuresis and natriuresis. These include improving myocardial performance through favourable alterations in ventricular loading conditions (reduction in preload and afterload), reduced myocardial wall stress promoting cardiac remodeling, and improvement in vascular function and blood pressure control. There is also emerging evidence to suggest that SGLT2 inhibitors may promote improvements in myocardial metabolism and energy utilization, potentially by increasing production of the ketone body B-hydroxybutyrate. Additional hypotheses include possible direct actions on the myocardial Na⁺/H⁺

TABLE 1 Baseline characteristics stratified by the presence of a hospitalization for heart failure (HHF)/cardiovascular (CV) death event during follow-up

Variable	Participants with HHF/CV death			Participants without HHF/CV death			p value (event vs. no event)
	Canagliflozin (n = 179)	Placebo (n = 253)	Total (n = 432)	Canagliflozin (n = 2023)	Placebo (n = 1946)	Total (n = 3969)	
Age, years, mean (SD)	65.3 (8.5)	65.2 (8.3)	65.3 (8.3)	62.7 (9.2)	62.9 (9.3)	62.8 (9.3)	<.001
Female, n (%)	62 (34.6%)	81 (32.0%)	143 (33.1%)	700 (34.6%)	651 (33.5%)	1351 (34.0%)	.696
Race, n (%)							
White	121 (67.6%)	174 (68.8%)	295 (68.3%)	1366 (67.5%)	1270 (65.3%)	2636 (66.4%)	.047
Asian	27 (15.1%)	47 (18.6%)	74 (17.1%)	398 (19.7%)	405 (20.8%)	803 (20.2%)	
Black or African American	14 (7.8%)	18 (7.1%)	32 (7.4%)	98 (4.8%)	94 (4.8%)	192 (4.8%)	
Other	17 (9.5%)	14 (5.5%)	31 (7.2%)	161 (8.0%)	177 (9.1%)	338 (8.5%)	
Current smoker, n (%)	18 (10.1%)	42 (16.6%)	60 (13.9%)	323 (16.0%)	256 (13.2%)	579 (14.6%)	.695
History of hypertension, n (%)	174 (97.2%)	245 (96.8%)	419 (97.0%)	1957 (96.7%)	1884 (96.8%)	3841 (96.8%)	.809
Duration of diabetes, years, mean (SD)	17.1 (9.5)	16.0 (8.5)	16.4 (8.9)	15.4 (8.6)	16.0 (8.6)	15.7 (8.6)	.091
Microvascular disease history, n (%)							
Retinopathy	78 (43.6%)	113 (44.7%)	191 (44.2%)	857 (42.4%)	834 (42.9%)	1691 (42.6%)	.521
Neuropathy	95 (53.1%)	139 (54.9%)	234 (54.2%)	982 (48.5%)	931 (47.8%)	1913 (48.2%)	.018
Atherosclerotic vascular disease history, n (%)							
Coronary	68 (38.0%)	109 (43.1%)	177 (41.0%)	585 (28.9%)	551 (28.3%)	1136 (28.6%)	<.001
Cerebrovascular	34 (19.0%)	51 (20.2%)	85 (19.7%)	308 (15.2%)	307 (15.8%)	615 (15.5%)	.024
Peripheral	66 (36.9%)	98 (38.7%)	164 (38.0%)	465 (23.0%)	417 (21.4%)	882 (22.2%)	<.001
CV disease history, n (%)	115 (64.2%)	167 (66.0%)	282 (65.3%)	998 (49.3%)	940 (48.3%)	1938 (48.8%)	<.001
History of atrial fibrillation, n (%)	20 (11.2%)	22 (8.7%)	42 (9.7%)	93 (4.6%)	97 (5.0%)	190 (4.8%)	<.001
History of amputation, n (%)	13 (7.3%)	31 (12.3%)	44 (10.2%)	106 (5.2%)	84 (4.3%)	190 (4.8%)	<.001
Body mass index, kg/m ² , mean (SD)	31.9 (6.6)	32.3 (7.0)	32.2 (6.8)	31.3 (6.1)	31.2 (6.1)	31.2 (6.1)	.010
Systolic blood pressure, mmHg, mean (SD)	142.9 (16.3)	141.0 (16.7)	141.8 (16.5)	139.5 (15.5)	140.1 (15.5)	139.8 (15.5)	.010
Diastolic blood pressure, mmHg, mean (SD)	77.7 (10.5)	76.8 (9.4)	77.2 (9.8)	78.3 (9.3)	78.6 (9.4)	78.4 (9.3)	.009
HbA1c, %, mean (SD)	8.5 (1.4)	8.4 (1.4)	8.4 (1.4)	8.3 (1.3)	8.2 (1.3)	8.2 (1.3)	.004
LDL cholesterol, mmol/L, mean (SD)	2.6 (1.2)	2.6 (1.1)	2.6 (1.1)	2.3 (1.7, 3.1)	2.3 (1.7, 3.1)	2.3 (1.7, 3.1)	.056
LDL/HDL cholesterol ratio, mean (SD)	2.4 (1.2)	2.4 (1.1)	2.4 (1.2)	2.1 (1.5, 2.9)	2.1 (1.5, 2.8)	2.1 (1.5, 2.8)	.023
	52.7 (18.2)	51.2 (16.9)	51.8 (17.4)	55.0 (42.0, 70.0)	55.0 (42.0, 69.0)	55.0 (42.0, 70.0)	<.001

TABLE 1 (Continued)

Variable	Participants with HFF/CV death		Participants without HHF/CV death			p value (event vs. no event)	
	Canagliflozin (n = 179)	Placebo (n = 253)	Total (n = 432)	Canagliflozin (n = 2023)	Placebo (n = 1946)		Total (n = 3969)
eGFR, mL/min/1.73 m ² , mean (SD)							
UACR, median (IQR)	1288.0 (563.0, 2660.0)	1239.0 (598.0, 2669.0)	1265.0 (579.0, 2663.5)	883.0 (450.0, 1759.0)	886.5 (453.0, 1784.0)	884.0 (452.0, 1766.0)	<.001
NYHA							
No HF	124 (69.3%)	192 (75.9%)	316 (73.1%)	1749 (86.5%)	1684 (86.5%)	3433 (86.5%)	<.001
NYHA I	17 (9.5%)	20 (7.9%)	37 (8.6%)	89 (4.4%)	78 (4.0%)	167 (4.2%)	
NYHA II	25 (14.0%)	29 (11.5%)	54 (12.5%)	154 (7.6%)	151 (7.8%)	305 (7.7%)	
NYHA III	9 (5.0%)	9 (3.6%)	18 (4.2%)	23 (1.1%)	29 (1.5%)	52 (1.3%)	
Unknown	4 (2.2%)	3 (1.2%)	7 (1.6%)	8 (0.4%)	4 (0.2%)	12 (0.3%)	
Concomitant drug therapies, n (%)							
Diuretic	97 (54.2%)	139 (54.9%)	236 (54.6%)	929 (45.9%)	892 (45.8%)	1821 (45.9%)	<.001
Loop diuretic	55 (30.7%)	88 (34.8%)	143 (33.1%)	424 (21.0%)	388 (19.9%)	812 (20.5%)	<.001
Beta blocker	93 (52.0%)	133 (52.6%)	226 (52.3%)	790 (39.1%)	754 (38.7%)	1544 (38.9%)	<.001
Statin	126 (70.4%)	177 (70.0%)	303 (70.1%)	1412 (69.8%)	1321 (67.9%)	2733 (68.9%)	.585
Antithrombotic	122 (68.2%)	173 (68.4%)	295 (68.3%)	1219 (60.3%)	1110 (57.0%)	2329 (58.7%)	<.001
Insulin	146 (81.6%)	186 (73.5%)	332 (76.9%)	1306 (64.6%)	1246 (64.0%)	2552 (64.3%)	<.001
Metformin	93 (52.0%)	126 (49.8%)	219 (50.7%)	1183 (58.5%)	1143 (58.7%)	2326 (58.6%)	.002
Sulphonylurea	41 (22.9%)	70 (27.7%)	111 (25.7%)	571 (28.2%)	586 (30.1%)	1157 (29.2%)	.132
Thiazolidinedione	2 (1.1%)	2 (0.8%)	4 (0.9%)	69 (3.4%)	63 (3.2%)	132 (3.3%)	.006
Calcium channel blocker	95 (53.1%)	137 (54.2%)	232 (53.7%)	956 (47.3%)	941 (48.4%)	1897 (47.8%)	.020
Dipeptidyl peptidase-4 inhibitor	18 (10.1%)	41 (16.2%)	59 (13.7%)	360 (17.8%)	332 (17.1%)	692 (17.4%)	.048
Glucagon-like peptide-1 receptor agonist	9 (5.0%)	11 (4.3%)	20 (4.6%)	80 (4.0%)	83 (4.3%)	163 (4.1%)	.605

Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; UACR, urine albumin creatinine ratio.
CV disease history was defined as a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular or peripheral).

FIGURE 1 The relative and absolute effects of canagliflozin on the composite of hospitalization for heart failure (HHF)/cardiovascular (CV) death by key baseline characteristics. eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; UACR, urine albumin creatinine ratio

exchanger, thereby increasing mitochondrial calcium levels; and reduced cardiac fibrosis via attenuated TGF- β 1 fibroblast activation.^{12,15} These latter hypotheses are plausible but preliminary/speculative in nature and require further confirmation.

These analyses are post hoc and examine underpowered subgroups, which increases the risk that the play of chance impacts upon the results. It is also possible that real differences between subgroups may have been missed. The findings are thus exploratory and should be interpreted in this context.

In conclusion, patients with co-existent diabetes and CKD are at a high risk of a HHF/CV death event, and canagliflozin consistently reduces the proportional risk of these events across a broad range of subgroups. The absolute benefit of canagliflozin is greater in those at highest risk, such as those with a history of CV disease or advanced kidney disease.

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CONFLICT OF INTEREST

CA is supported by an NHMRC/MRFF Priority Investigator Grant and a NSW Health EMCR Grant. She is an employee of the George Institute for Global Health. JL has nothing to declare. CPC has received research grants from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Merck, Janssen and Takeda; and has received consulting fees from Aegerion, Alnylam, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Corvidia, GlaxoSmithKline, Innovent, Eisai, Eli Lilly, Kowa, Merck, Pfizer, Regeneron and Sanofi. DZ reports serving on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma and Mitsubishi Tanabe; serving on Steering Committees and/or as a speaker for AbbVie and Janssen; and serving on Data Safety and Monitoring Committees for Bayer. BLN is supported by an NHMRC Postgraduate Scholarship. He has received travel support from Janssen and consultancy fees from

Bayer for steering committee membership, with all fees paid to his institution. HJLH 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. DC has served on clinical events committees or data safety and monitoring boards for PLC Medical, AstraZeneca, Allena Pharmaceuticals, and Merck; served on steering committees for Zoll Medical and Janssen Pharmaceuticals; and reported consulting fees or travel fees from Daichi Sankyo, Fresenius, and Medtronic/Covidien, NovoNordisk, Gilead, Merck, and Amgen, and fees related to service on the steering committee for the kidney outcome trial of an SGLT2 inhibitor (canagliflozin; CREDENCE, NCT02065791). AA has nothing to disclose. MH has received grant support from the World Heart Federation via Boehringer Ingelheim and Novartis; the American Heart Association, Verily and AstraZeneca; and the American Medical Association for work unrelated to this paper. GAF reports receiving research support from the co-funded National Health and Medical Research Council and Heart Foundation (Australia) Practitioner Fellowship and the Heart Research Australia, and compensation from Janssen for serving on the Adjudication Panel of the CANVAS Program. GB works for The University of Chicago Medicine. He is a Consultant for Merck, Bayer, Vascular Dynamics, KBP Biosciences, Ionis, Alnylam and Astra Zeneca. He has research support and is on the Steering committee of trials for Bayer and Vascular Dynamics. He is the Editor of the *American Journal of Nephrology*. TIC has received funding paid by Janssen Pharmaceuticals to Stanford University for serving as a national leader for CREDENCE; has served as a consultant for Bayer, Janssen Pharmaceuticals, Novo Nordisk, Fresenius Medical Care, Tricida, Gilead and AstraZeneca; and has received grant support from Satellite Healthcare, the American Heart Association and the National Institutes of Health. KF has nothing to disclose. NR is an employee of Janssen Research & Development. BZ is a consultant for Janssen, Eli Lilly, Boehringer Ingelheim, Eli Lilly and Novo Nordisk. MJJ is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Amgen, Baxter, CSL, Eli Lilly, Gambro and MSD; has served on advisory boards sponsored by Akebia, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, MSD and Vifor; serves on Steering Committee for trials sponsored by CSL and Janssen; serves on a Steering Committee for an investigator-initiated trial with funding support from Dimerix; has spoken at scientific meetings sponsored by Janssen, Amgen, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution. VP has received fees for Advisory Boards, Steering Committee roles, or Scientific Presentations from Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Vifor and Tricida. BN is supported by an Australian National Health and Medical Research Council Principal Research Fellowship; holds a research grant for this study from Janssen; and has held research grants for other large-scale CV outcome trials from Roche, Servier and Merck Schering Plough; and his institution has received

consultancy, honoraria or travel support for contributions he has made to advisory boards and/or the continuing medical education programmes of Abbott, Janssen, Novartis, Pfizer, Roche and Servier. KWM's financial disclosures can be viewed at <http://med.stanford.edu/profiles/kenneth-mahaffey>.

AUTHOR CONTRIBUTIONS

C. Arnott, J Li, B Neal and K Mahaffey contributed to the design, analysis and conduct of the study and the interpretation of the data. C Cannon, D de Zeeuw, B Neuen, H Heerspink, D Charytan, A Agarwal, M Huffman, G Figtree, G Bakris, T Chang, K Feng, N Rosenthal, B Zinman, M Jardine and V Perkovic contributed to conduct of the study and the interpretation of the data. C Arnott, B Neal and K Mahaffey had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14386>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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