BACKGROUND: Canagliflozin reduces the risk of kidney failure in patients with type 2 diabetes mellitus and chronic kidney disease, but effects on specific cardiovascular outcomes are uncertain, as are effects in people without previous cardiovascular disease (primary prevention).

METHODS: In CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation), 4401 participants with type 2 diabetes mellitus and chronic kidney disease were randomly assigned to canagliflozin or placebo on a background of optimized standard of care.

RESULTS: Primary prevention participants (n=2181, 49.6%) were younger (61 versus 65 years), were more often female (37% versus 31%), and had shorter duration of diabetes mellitus (15 years versus 16 years) compared with secondary prevention participants (n=2220, 50.4%). Canagliflozin reduced the risk of major cardiovascular events overall (hazard ratio [HR], 0.80 [95% CI, 0.67–0.95]; P=0.01), with consistent reductions in both the primary (HR, 0.68 [95% CI, 0.49–0.94]) and secondary (HR, 0.85 [95% CI, 0.69–1.06]) prevention groups (P for interaction=0.25). Effects were also similar for the components of the composite including cardiovascular death (HR, 0.78 [95% CI, 0.61–1.00]), nonfatal myocardial infarction (HR, 0.81 [95% CI, 0.59–1.10]), and nonfatal stroke (HR, 0.80 [95% CI, 0.56–1.15]). The risk of the primary composite renal outcome and the composite of cardiovascular death or hospitalization for heart failure were also consistently reduced in both the primary and secondary prevention groups (P for interaction >0.5 for each outcome).

CONCLUSIONS: Canagliflozin significantly reduced major cardiovascular events and kidney failure in patients with type 2 diabetes mellitus and chronic kidney disease, including in participants who did not have previous cardiovascular disease.

**Clinical Perspective**

**What Is New?**

- Previous studies and a systematic review have indicated that the effects of sodium glucose cotransporter 2 inhibition are uncertain in people without previous cardiovascular disease (primary prevention).
- The CREDENCE trial (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) enrolled participants with and without previous cardiovascular disease.
- These analyses demonstrate robust and consistent reductions in cardiovascular and renal outcomes in participants with and without previous cardiovascular disease, with no increased risk of fractures or amputations.

**What Are the Clinical Implications?**

- These data support the initiation of canagliflozin in a much broader patient population with type 2 diabetes mellitus, including those with glycated hemoglobin as low as 6.5% and patients with estimated glomerular filtration rate between 30 and 45 mL·min⁻¹·1.73 m⁻², with expected reductions in renal and cardiovascular outcomes.

Patients with type 2 diabetes mellitus and chronic kidney disease are at increased risk of cardiovascular events. Sodium glucose cotransporter 2 (SGLT2) inhibitors have been shown to be noninferior to placebo or superior to placebo in reducing cardiovascular outcomes, including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, in patients with type 2 diabetes mellitus. In addition, cardiovascular death or hospitalization for heart failure has been reduced with canagliflozin compared with placebo.

A systematic review of 3 large cardiovascular outcome trials in participants with type 2 diabetes mellitus showed that SGLT2 inhibition reduced the risk of cardiovascular death, myocardial infarction, or stroke by 11% (hazard ratio [HR], 0.89 [95% CI, 0.83–0.96]; P=0.0014). However, this effect was restricted to a 14% reduction in patients with established cardiovascular disease (HR, 0.86 [95% CI, 0.80–0.93]), with no difference observed in patients without previous cardiovascular disease but with multiple risk factors for cardiovascular disease (HR, 1.00 [95% CI, 0.87–1.16]; P for interaction=0.0501). Directionally different effects on stroke have also been reported from previous trials, as have varying magnitudes of benefit for cardiovascular death. Effects on renal and heart failure outcomes showed consistent benefit in both primary and secondary prevention groups.

The CREDENCE trial (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) showed that canagliflozin prevented renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and chronic kidney disease. Although participants with and without cardiovascular disease were enrolled, it is expected that the presence of chronic kidney disease would result in high cardiovascular risk in the primary prevention cohort as well, so the effects on major cardiovascular events in this population are of particular interest. This article describes detailed analyses of individual cardiovascular outcomes and looks at effects on a range of outcomes in participants with and especially without known cardiovascular disease from the CREDENCE trial.

**METHODS**

**Data Availability**

Data from this study will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months.

**Study Design and Organization**

Details of the CREDENCE study design and the primary results have been published previously. CREDENCE was a randomized, double-blind, placebo-controlled, multicenter international clinical trial. The study was approved by the necessary regulatory authorities and ethics committees. The study was registered at ClinicalTrials.gov (https://www.clinicaltrials.gov; NCT02065791).

The trial was funded and sponsored by Janssen Research & Development, LLC and was an academic/industry collaboration with an academic-led Steering Committee (online-only Data Supplement) and an academic research group, George Clinical. Analyses were performed by the sponsor and independently confirmed at George Clinical with the use of original data. The first author drafted the manuscript. All authors contributed to revisions and agreed to submit the paper.

**Participants**

The criteria for inclusion and exclusion have been previously published (online-only Data Supplement). In brief, participants were eligible if they were ≥30 years of age, had a clinical diagnosis of type 2 diabetes mellitus with a glycated hemoglobin level of 6.5% to 12.0%, and had chronic kidney disease, with an estimated glomerular filtration rate (eGFR; calculated with the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] formula) of 30 to <90 mL·min⁻¹·1.73 m⁻² and albuminuria (urine albumin:creatinine ratio of >300 to 5000 mg/g [>33.9–565.6 mg/mmol]). All participants were to be on stable maximum tolerated labeled daily dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks before randomization. Treatment with dual angiotensin-converting enzyme inhibitor and...
angiotensin receptor blocker, direct renin inhibitor, or mineralocorticoid receptor antagonist at the time of enrollment was not allowed. Classification of primary or secondary prevention was based on cardiovascular medical histories collected by investigators during the screening period. Participants were classified as belonging to the secondary prevention cohort if they had a history of coronary, cerebrovascular, or peripheral vascular disease. All other participants were classified as belonging to the primary prevention cohort. All participants provided informed consent.

Study Procedures
Participants were randomly assigned in double-blind fashion (1:1) to canagliflozin 100 mg daily or matching placebo with stratification by screening eGFR categories (30–<45, 45–<60, and 60–<90 mL min⁻¹.1.73 m⁻²). After randomization, study visits were conducted at weeks 3, 13, and 26 and then alternated between telephone calls and in-clinic visits at 13-week intervals.

Outcomes
The efficacy outcomes for these analyses included those in the prespecified hierarchical testing sequence detailed previously. All deaths, cardiovascular events, and renal outcomes, as well as all suspected pancreatitis, fractures, renal cell carcinoma, and diabetic ketoacidosis events, were reviewed by adjudication committees blinded to therapy. The definitions used for the clinical events have been published previously.

Statistical Analyses
The study was stopped early on the basis of the recommendations of the independent data monitoring committee. Details of the stopping criteria and other statistical considerations have been reported previously. Analyses of the primary and secondary outcomes were planned for hierarchical testing, with subgroup analyses for the primary outcome prespecified in both cohorts. Additional analyses are post hoc. All analyses of the effects of canagliflozin compared with placebo on cardiovascular and renal outcomes were based on the intention-to-treat principle using all follow-up time for all randomized participants. Renal, cardiovascular, mortality, and safety outcomes were analyzed with a stratified Cox proportional hazards regression model, according to the eGFR category at screening. HRs and 95% CIs were estimated for participants assigned to canagliflozin versus participants assigned to placebo separately for the primary and secondary prevention cohorts, and P values are shown for outcomes that were significantly reduced according to the original hierarchical testing strategy. The HRs for cardiovascular disease and kidney disease outcomes comparing the placebo groups in the secondary prevention cohort versus the primary prevention cohort were calculated to remove potential confounding effects of canagliflozin treatment and to estimate the relative risk as part of the natural disease course. Subgroup analyses within each prevention cohort were assessed by tests for the multiplicative interaction term between the randomized treatment group and the subgroup in stratified Cox proportional hazards models without adjustment for multiple testing. Safety outcomes were analyzed with an on-treatment approach (based on patient time and events accrued while on study drug or within 30 days of study drug discontinuation) except for fracture, cancer, and amputation events, which were assessed using all follow-up time.

Within each prevention cohort, the number of patients who needed to be treated to prevent 1 event during 2.5 years was calculated as the reciprocal of the between-group difference in cumulative incidence at 2.5 years on the basis of the Kaplan–Meier curve. The 95% CIs for the numbers needed to treat (NNT) were calculated according to the method of Altman et al. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS
In CREDENCE, a total of 4401 participants were randomized in 34 countries. The mean follow-up was 2.62 years. Vital status was known for all but 6 participants (0.1%) at the end of the study.

Cardiovascular Outcomes
Cardiovascular outcomes by treatment assignment are shown for the overall population in Figure 1. Canagliflozin compared with placebo reduced the risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (9.9% versus 12.2%; HR, 0.80 [95% CI, 0.67–0.95]; P=0.01), with similar results for cardiovascular death (5.0% versus 6.4%; HR, 0.78 [95% CI, 0.61–1.00]), nonfatal myocardial infarction (3.2% versus 4.0%; HR, 0.81 [95% CI, 0.59–1.10]), and nonfatal stroke (2.4% versus 3.0%; HR, 0.80 [95% CI, 0.56–1.15]). Canagliflozin also lowered the risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or hospitalization for unstable angina (12.4% versus 16.4%; HR, 0.74 [95% CI, 0.63–0.86]). Canagliflozin reduced the risk of the composite of cardiovascular death or hospitalization for heart failure (8.1% versus 11.5%; HR, 0.69 [95% CI, 0.57–0.83]; P<0.001) and hospitalization for heart failure (4.0% versus 6.4%; HR, 0.61 [95% CI, 0.47–0.80]; P<0.001) in the overall population.

Primary and Secondary Prevention
Patient Characteristics
A total of 2181 participants (49.6%) had no history of documented cardiovascular disease at entry and were in the primary prevention group, and 2220 participants (50.4%) were in the secondary prevention group. The baseline demographics are shown in Table 1 for the primary and secondary prevention groups and by treatment assignment. Primary prevention participants were younger (61.4 years versus 64.6 years) and more often female (36.6% versus 31.3%) and Asian (24.4% versus 15.5%) with a shorter duration of diabetes mellitus (15.2 years versus 16.4 years) compared with
secondary prevention participants. Primary and secondary prevention participants had similar mean eGFR (56.8 mL·min\(^{-1} \cdot \text{m}^{-2}\) versus 55.5 mL·min\(^{-1} \cdot \text{m}^{-2}\)) and median urine albumin:creatinine ratio (943 mg/g versus 903 mg/g).

### Cardiovascular Outcomes by Primary and Secondary Prevention

In placebo-treated patients, cardiovascular death or hospitalization for heart failure occurred more frequently in the secondary prevention group compared with the primary prevention group (15.1% versus 7.9%; HR, 1.95 [95% CI, 1.51–2.53]), as did major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; 16.1% versus 8.3%; HR, 1.97 [95% CI, 1.53–2.54]).

The effects of the randomized treatment assignment on cardiovascular outcomes are shown for the primary and secondary prevention groups in Figures 2 and 3. Canagliflozin reduced major cardiovascular events, with a meaningful reduction in this outcome for the primary prevention group (HR, 0.68 [95% CI, 0.49–0.94]) that was consistent with the effect in the secondary prevention groups (HR, 0.85 [95% CI, 0.69–1.06]; \(P\) for interaction=0.25). Consistency in the effects was also observed across all other cardiovascular end points for both the primary and secondary prevention groups (all \(P\) for interaction >0.10).

### Renal Outcomes by Primary and Secondary Prevention

In placebo-treated patients, the risk of the primary end point (composite of end-stage kidney disease, doubling serum creatinine, or renal or cardiovascular death) was comparable between the secondary prevention group and the primary prevention group (16.4% versus 14.5%; HR, 1.11 [95% CI, 0.89–1.37]). The effects of the randomized treatment assignment on renal outcomes are shown for the primary and secondary prevention groups in Figure 3. Canagliflozin reduced renal outcomes, with no evidence of heterogeneity in the primary and secondary prevention groups. All interaction \(P\) values were not significant.

### Cardiovascular Outcomes Across Other Patient Subgroups

Figure 4 shows the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the overall population for subgroups defined by...
### Table 1. Baseline Demographic and Disease Characteristics of Primary and Secondary Prevention Cohorts in CREDENCE*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n=1089)</td>
<td>(n=1092)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total (n=2181)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Canagliflozin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=1113)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total (n=2220)</td>
</tr>
<tr>
<td>Age, y</td>
<td>61.1±9.7</td>
<td>61.7±9.4</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>405 (37.2)</td>
<td>394 (36.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>58 (5.3)</td>
<td>63 (5.8)</td>
</tr>
<tr>
<td>White</td>
<td>646 (59.3)</td>
<td>640 (58.6)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>58 (5.3)</td>
<td>63 (5.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>265 (24.3)</td>
<td>268 (24.5)</td>
</tr>
<tr>
<td>Other†‡</td>
<td>120 (11.0)</td>
<td>121 (11.1)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td>325 (29.8)</td>
<td>337 (30.9)</td>
</tr>
<tr>
<td>North America</td>
<td>235 (21.6)</td>
<td>254 (23.3)</td>
</tr>
<tr>
<td>Central/South America</td>
<td>186 (17.1)</td>
<td>177 (16.2)</td>
</tr>
<tr>
<td>Europe</td>
<td>343 (31.5)</td>
<td>324 (29.7)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>639 (58.7)</td>
<td>637 (58.3)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>35 (3.2)</td>
<td>25 (2.3)</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>172 (15.8)</td>
<td>143 (13.1)</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>63 (5.8)</td>
<td>58 (5.3)</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.2±6.4</td>
<td>31.0±6.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>139.0±15.9</td>
<td>139.8±15.9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>79.0±9.2</td>
<td>78.5±9.5</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>8.2±1.3</td>
<td>8.3±1.3</td>
</tr>
<tr>
<td>Cholesterol, mg/dl (mmol/L)</td>
<td>182.9±51.1</td>
<td>180.7±48.8</td>
</tr>
</tbody>
</table>

(Continued)
demographics, clinical history, and baseline laboratory values. The treatment effect with canagliflozin compared with placebo was consistent across subgroups, including across categories of renal function defined by eGFR and urine albumin:creatinine ratio. However, a borderline greater benefit was seen in people with a history of amputation compared with those without (P for interaction=0.06; all other interaction P>0.20).

Safety Outcomes

Figure 1 in the online-only Data Supplement shows the results for adverse events, serious adverse events, and other adverse events of interest for the primary and secondary prevention groups. No difference in fracture risk with canagliflozin (HR, 0.98 [95% CI, 0.70–1.37]) compared with placebo was observed in the overall population.8 Similar findings were seen in the primary and secondary prevention groups. Overall, no difference in amputation events was observed with canagliflozin compared with placebo (HR, 1.11 [95% CI, 0.79–1.56]),6 with no heterogeneity in the primary and secondary prevention groups.

Numbers Needed to Treat

Table 2 shows the number of participants who needed to be treated for 2.5 years to prevent 1 event, with 95% CIs shown only when they do not include 0. The NNT for end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death was 19 (95% CI, 12–40) in the primary and 26 (95% CI, 15–96) in the secondary prevention group. For cardiovascular death or hospitalization for heart failure, the NNT was 53 in the primary and 21 (95% CI, 13–47) in the secondary prevention group. For cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, the NNT was 36 (95% CI, 20–186) in the primary and 44 in the secondary prevention group.
DISCUSSION

The CREDENCE trial studied participants with type 2 diabetes mellitus and established chronic kidney disease, of whom half did not have known cardiovascular disease at study entry. In contrast to previous studies that have suggested reductions in major cardiovascular events with SGLT2 inhibitors only in participants with existing cardiovascular disease, canagliflozin reduced the risk of major cardiovascular events and renal outcomes in both the primary and secondary prevention groups. This finding suggests that canagliflozin can be effectively used for both primary and secondary prevention of major cardiovascular events in people with type 2 diabetes mellitus and chronic kidney disease and is the first antihyperglycemic drug to show benefit in a primary prevention group.

Three large cardiovascular outcomes studies have previously reported results in primary and secondary prevention groups, and a systematic review of all 3 trials has been published. In those trials, the treatment benefit with SGLT2 inhibition compared with placebo in reducing cardiovascular outcomes was evident primarily in participants with established cardiovascular disease, with no benefit observed in those without known cardiovascular disease, although in the CANVAS Program (Canagliflozin Cardiovascular Assessment Study) there was no evidence of significant statistical heterogeneity in the treatment effect of canagliflozin compared with placebo in cardiovascular outcomes in primary and secondary prevention groups. In CREDENCE, a robust and consistent reduction in cardiovascular events and renal events was observed in both the primary and secondary prevention groups, suggesting that chronic kidney disease itself is a potent risk marker not only for cardiovascular events—the primary prevention group in CREDENCE was not at a low risk for cardiovascular events—but also for treatment benefit. The event rates for both cardiovascular and renal outcomes were generally similar or higher in CREDENCE than in the other trials as
expected because 50% had known cardiovascular disease and 60% had eGFR <60 mL·min⁻¹·1.73 m²⁻¹. This high baseline risk may explain, in part, the benefits in the primary prevention group seen in CREDENCE compared with the other studies.

Canagliflozin reduced major cardiovascular outcomes with consistency across the cardiovascular composites and individual component outcomes. This is similar to the findings of the CANVAS Program and suggests that clinicians can expect consistent reductions in the individual components of the composite major cardiovascular events outcome when using canagliflozin across broad patient populations defined by clinical characteristics, extent of diabetes mellitus, and renal function.

The CREDENCE population was at higher risk for cardiovascular events compared with previous SGLT2 inhibitor trials, given the targeted enrollment of participants with type 2 diabetes mellitus with established chronic kidney disease. As shown previously, the absolute and relative treatment effects of canagliflozin and other SGLT2 inhibitors were more robust for hospitalization for heart failure compared with atherosclerotic events, and these effects were consistent regardless of the presence or absence of preexisting cardiovascular disease across all completed studies.

Table 3. Effects of canagliflozin on renal and cardiovascular outcomes in the secondary and primary prevention cohorts.

eGFR indicates estimated glomerular filtration rate; and ESKD, end-stage kidney disease. *Diamonds represent the result of a single analysis of the full cohort.

Figure 3. Effects of canagliflozin on renal and cardiovascular outcomes in the secondary and primary prevention cohorts.

expected because 50% had known cardiovascular disease and 60% had eGFR <60 mL·min⁻¹·1.73 m²⁻¹. This high baseline risk may explain, in part, the benefits in the primary prevention group seen in CREDENCE compared with the other studies.

Canagliflozin reduced major cardiovascular outcomes with consistency across the cardiovascular composites and individual component outcomes. This is similar to the findings of the CANVAS Program and suggests that clinicians can expect consistent reductions in the individual components of the composite major cardiovascular events outcome when using canagliflozin across broad patient populations defined by clinical characteristics, extent of diabetes mellitus, and renal function.

The CREDENCE population was at higher risk for cardiovascular events compared with previous SGLT2 inhibitor trials, given the targeted enrollment of participants with type 2 diabetes mellitus with established chronic kidney disease. As shown previously, the absolute and relative treatment effects of canagliflozin and other SGLT2 inhibitors were more robust for hospitalization for heart failure compared with atherosclerotic events, and these effects were consistent regardless of the presence or absence of preexisting cardiovascular disease across all completed studies.

Table 3. Effects of canagliflozin on renal and cardiovascular outcomes in the secondary and primary prevention cohorts.

eGFR indicates estimated glomerular filtration rate; and ESKD, end-stage kidney disease. *Diamonds represent the result of a single analysis of the full cohort.

Figure 3. Effects of canagliflozin on renal and cardiovascular outcomes in the secondary and primary prevention cohorts.
including the present trial. Several mechanisms have been proposed to explain the effect of SGLT2 inhibitors on hospitalization for heart failure, including a natriuretic effect, improvement in blood pressure, lower weight, improved glucose levels, and altered myocardial energy metabolism. Further study is needed to better understand the mechanisms or to clarify the relative contribution of the effects on intermediaries and the impact on clinical outcomes.

These results have important clinical implications. First, clinicians considering treatment for cardiovascular and renal protection of patients like those enrolled in CREDENCE should do so regardless of whether there is known cardiovascular disease and can expect
in participants with type 2 diabetes mellitus and chronic kidney disease, canagliflozin reduced major cardiovascular events and renal outcomes across a broad spectrum of subgroups, including those without cardiovascular disease at baseline.

**ARTICLE INFORMATION**

Received May 28, 2019; accepted June 12, 2019.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

The online-only Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.119.042007.

**Authors**

Kenneth W. Mahaffey, MD; Meg J. Jardine, MBBS, PhD; Severine Bompoint, BSc(stats); Christopher P. Cannon, MD; Bruce Neal, MB ChB, PhD; Hiddo J.L. Heerspink, PharmD, PhD; David M. Charytan, MD, MSc; Robert Edwards, MPH; Rajiv Agarwal, MD; George Bakris, MD; Scott Bull, PharmD; George Capuano, MD; Dick de Zeeuw, MD, PhD; Tom Greene, MD; Adeera Levin, MD; Carol Pollock, MBBS, PhD; Tao Sun, PhD; David C. Wheeler, MD; Yshai Yavin, MB ChB; Hong Zhang, MD, PhD; Bernard Zinman, MD; Norman Rosenthal, MD; Barry M. Brenner, MD; Vladko Perkovic, MBBS, PhD; On behalf of the CREDENCE Study Investigators. *

* A complete list of investigators is provided in the online-only Data Supplement.

**Correspondence**

Kenneth W. Mahaffey, MD, Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, 300 Pasteur Dr, Grant 5-102, Stanford, CA 94305. Email kenneth.mahaffey@stanford.edu

**Affiliations**

Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, CA (K.W.M.). George Institute for Global Health, University of New South Wales, Sydney, Australia (M.I.J., S.B., B.N., H.J.L.H., V.P.). Concord Repatriation General Hospital, Sydney, Australia (M.I.J.). Cardiovascular Division, Brigham & Women’s Hospital, Boston, MA (C.F.C.). Charles Perkins Centre, University of Sydney, Australia (B.N.). Imperial College London, UK (B.N.). Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, The Netherlands (H.J.L.H., D.d.Z.). Nephrology Division, NYU School of Medicine and NYU Langone Medical Center, New York (D.M.C.). Bairn Institute for Clinical Research, Boston, MA (D.M.C., C.F.C., B.M.B.). Janssen Research & Development, LLC, Raritan, NJ (R.E., S.B., G.C., T.S., Y.Y., N.R.). Indiana University School of Medicine and VA Medical Center, Indianapolis (R.A.). Department of Medicine, University of Chicago Medicine, IL (G.B.). Division of Biostatistics, Department of Population Health Sciences, University of Utah, Salt Lake City (T.G.). Division of Nephrology, University of British Columbia, Vancouver, Canada (A.L.). Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Royal North Shore Hospital, St. Leonards, NSW, Australia (C.P.). Department of Renal Medicine, UCL Medical School, London, UK (D.C.W.). Renal Division of Peking University First Hospital, Beijing, China (H.Z.). Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital, University of Toronto, ON, Canada (B.Z.). Renal Division and Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA (B.M.B.). Royal North Shore Hospital, Sydney, Australia (V.P.).

**Acknowledgments**

The authors thank all participants, investigators, and trial teams for their participation in the trial and the following people for their contributions to the statistical monitoring and analyses and the protocol development, safety monitoring, and operational implementation over the duration of the trial: Maria Ali, Jim Baldassare, Dainius Balis, William Canovatchel, Jun Chen, Pei-Ling Chu, Trokeen Cooke, Jag Craig, Jacki Danylyk, Mehul Desai, Lyndal Hones, Alan Jenkins, Mary Kavalam, Cha-Chi Lo, Xinchao Luo, Gary Meiningr, Rich Oh, Rose Qiu, Nicole Schmitt, DanielaSiebenkaess, Roger Simpson, Anna Temu, Payal Thakkar, Michele Wells, and Renata Yong. The Steering Committee designed the
study in conjunction with the sponsor. Dr Mahaffey wrote the first draft of the paper, had full access to the study design information, and had final responsibility for the decision to submit for publication. All authors provided input into subsequent drafts and approved the final version for submission. Editorial assistance for manuscript preparation was provided by Alaina Mitsch, PhD, and Kimberly Dittmar, PhD, of MedErgy, and was funded by Janssen Global Services, LLC. All authors reviewed and approved the manuscript.

Sources of Funding

This study is sponsored by Janssen Research & Development, LLC, which funded the trial. The sponsor was involved in the study design, the writing of the report, and the decision to submit the article for publication. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

Disclosures

All of the authors received research support and consulting fees from Janssen in relation to their roles on the Steering Committee of the CREDENCE trial. Dr Mahaffey has received research support from Affera, Amgen, Apple, Inc, Akebia, Bayer, Johnson & Johnson, Boehringer Ingelheim, Takeda, Daichi Sankyo, Johnson, Luitpold, Medtronic, Merck, National Institutes of Health, Novartis, Sanofi, St. Jude, and Tenax. Dr Mahaffey also has served as a consultant (speak- er fees for continuing medical education events only) for Abbott, Alnyx, As- traZeneca, Bain Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedEd, Medscape, Mitsubishi, Myk- ocardia, National Institutes of Health, Novartis, Novo Nordisk, Portola, Radiome- ter, Springer Publishing, University of California, San Francisco, and Merck. Dr Jardine 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 Gambro, Baxter, CSL, Amgen, Eli Lilly, and Merck; has served on advisory boards by Akebia, Bayer, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen, Amgen, and Roche, with any consultancy, honoraria, or travel support paid to her institution. Dr Neal 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 cardiovascular outcome trials from Roche, Servier, and Merck Schering Plough. His institution has received consultancy, honoraria, or travel support for contributions he has made to advisory boards or the continuing medical education programs of Abbott, Janssen, Novartis, Pfizer, Roche, and Servier. S. Bonpoint is a full-time employee of the George Institute for Global Health. Dr Heerspink has served as a consultant for Abbvie, Actel- las, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, and Mitsubishi-Tanabe and has received grant support from Abbvie, AstraZeneca, Boehringer Ingelheim, and Janssen. Dr Charytan has received fees paid by Jans- sen Pharmaceuticals to the Bain Institute for data monitoring committee work on CREDENCE trial Steering Committee and as scientific lead; he received salary support from the Bain Institute for this work through October 2018. After that time, he received consulting fees from Baim. He is also a consultant for Amgen, Medtronic/Covidien, Zoll, Fresenius, Daichi Sankyo, Douglas and London, and Eli Lilly; has served on Data and Monitoring boards for Akebia and AstraZeneca; and has served on the steering committee for the CREDENCE trial. Dr Pollock has received honoraria directed to her academic team. Dr Mahaffey has received research support and consulting fees from Afferent, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Corvidia, GlaxoSmithKline, Innoven, Eisai, Eli Lilly, Kowa, Merck, Pfizer, Regeneron, and Sanofi. Dr de Zeeuw has served on advisory boards or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi-Tanabe; has served on Steering Committees or as a speaker for Abbvie and Janssen; and has served on Data Safety and Monitoring Committees for Bayer. Dr Greene has received consulting fees from Janssen, Direx, and Pfizer. Dr Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and National Institute of Diabetes and Digestive and Kidney Diseases; is on the Data Safety Moni- toring Board for the National Institute of Diabetes and Digestive and Kidney Diseases, and Kidney Precision Medicine; is on the University of Washington Kidney Research Institute Scientific Advisory Committee; and is funded by Ca- nadian Institute of Health Research and Kidney Foundation of Canada. She has received fees for time as CREDENCE national coordinator from Janssen, directed to her academic team. Dr Pollock has received honoraria for serving on advisory boards and as a speaker for Merck Sharp and Dohme, AstraZen- eca, and Boehringer Ingelheim/Eli Lilly. Dr Wheeler has received consultancy fees from Agen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mitsubishi, Mundipharma, Napp, Ono Pharma, and Vifor Fresenius. Dr Zhang has received consulting fees from Janssen. Dr Zimman has served as a consultant for and received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp and Dohme, Novo Nordisk, and Sanofi and has received grant support from Boehringer Ingelheim, Novo Nordisk, and AstraZeneca. Dr Brenner has no pertinent disclosures aside from his involvement in this trial. Dr Perkovic has received fees for advisory boards, Steering Committee roles, or scientific presentations from Abbvie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Dimerex, Direx, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relpysa, Retrophin, Sanofi, Servier, Vifor, and Tricida.

REFERENCES


Circulation. 2019;140:739–750. doi: 10.1161/CIRCULATIONAHA.119.042007

August 27, 2019 749


