Canagliflozin and Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus and Chronic Kidney Disease in Primary and Secondary Cardiovascular Prevention Groups Results From the Randomized CREDENCE Trial

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Canagliflozin and Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus and Chronic Kidney Disease in Primary and Secondary Cardiovascular Prevention Groups

Results From the Randomized CREDENCE Trial

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 studies 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 recommendation 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 CREDEENCE, 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⁻¹·1.73 m⁻² versus 55.5 mL·min⁻¹·1.73 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>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin (n=1089)</td>
<td>Placebo (n=1092)</td>
</tr>
<tr>
<td></td>
<td>Total (n=2181)</td>
<td>Canagliflozin (n=1113)</td>
</tr>
<tr>
<td></td>
<td>Total (n=2220)</td>
<td></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>265 (24.3)</td>
<td>268 (24.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>120 (11.0)</td>
<td>121 (11.1)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td>73 (9.2)</td>
<td>71 (6.5)</td>
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<tr>
<td>Hispanic/Latino</td>
<td>325 (29.8)</td>
<td>337 (30.9)</td>
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<tr>
<td>Not Hispanic/Latino</td>
<td>639 (58.7)</td>
<td>637 (58.3)</td>
</tr>
<tr>
<td>Not reported/unknown</td>
<td>35 (3.2)</td>
<td>25 (2.3)</td>
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<tr>
<td>Current smoker, n (%)</td>
<td>172 (15.8)</td>
<td>143 (13.1)</td>
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<tr>
<td>History of hypertension, n (%)</td>
<td>1046 (96.1)</td>
<td>1048 (96.0)</td>
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<tr>
<td>History of heart failure, n (%)</td>
<td>63 (5.8)</td>
<td>58 (5.3)</td>
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<tr>
<td>History of myocardial infarction, n (%)</td>
<td>0</td>
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<tr>
<td>History of stroke, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, y</td>
<td>14.8±8.4</td>
<td>15.5±8.4</td>
</tr>
<tr>
<td>Drug therapy, n (%)</td>
<td>691 (63.5)</td>
<td>681 (62.4)</td>
</tr>
<tr>
<td>Insulin</td>
<td>309 (28.4)</td>
<td>337 (30.9)</td>
</tr>
<tr>
<td>Metformin</td>
<td>670 (61.5)</td>
<td>662 (60.6)</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>40 (3.7)</td>
<td>49 (4.5)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>211 (19.4)</td>
<td>211 (19.3)</td>
</tr>
<tr>
<td>Statin</td>
<td>708 (65.0)</td>
<td>684 (62.6)</td>
</tr>
<tr>
<td>Microvascular disease history, n (%)</td>
<td>477 (43.8)</td>
<td>453 (41.5)</td>
</tr>
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<td>Non-smokers</td>
<td>331 (30.4)</td>
<td>316 (28.9)</td>
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<tr>
<td>Diuretics</td>
<td>458 (42.1)</td>
<td>471 (43.1)</td>
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<tr>
<td>History of amputation, 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>
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<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 (4.7±1.3)</td>
<td>180.7±48.8 (4.7±1.3)</td>
</tr>
</tbody>
</table>
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 I 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. 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]), 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 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.
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 m⁻². This high baseline risk may explain, in part, the benefits in the primary prevention group seen in CREDEENCE 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 CREDEENCE population was at higher risk for cardiovascular events compared with other SGLT2 inhibitor trials, given the targeted enrollment of high baseline risk may explain, in part, the benefits in the primary prevention group seen in CREDEENCE, regardless of the presence or absence of preexisting clinical characteristics, extent of diabetes mellitus, and renal function. The CREDEENCE population was at higher risk for cardiovascular events compared with other SGLT2 inhibitor trials, given the targeted enrollment of high baseline risk.
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 CREDEANCE 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**

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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.

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

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