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ORIGINAL RESEARCH ARTICLE

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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et al

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.

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The full author list is available on page 748.

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Sources of Funding, see page 749

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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.[1] Sodium glucose cotransporter 2 (SGLT2) inhibitors have been shown to be noninferior to placebo[2] or superior to placebo[3,4] 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.[4]

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).[5] 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.[2–4] Effects on renal and heart failure outcomes showed consistent benefit in both primary and secondary prevention groups.[5]

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.[6] 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.[7] 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.[6,8] 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).[6,8] 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.[6] 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.[6,8]

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.[6] 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.[6] 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.[9] 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.[6]

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.[6]

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

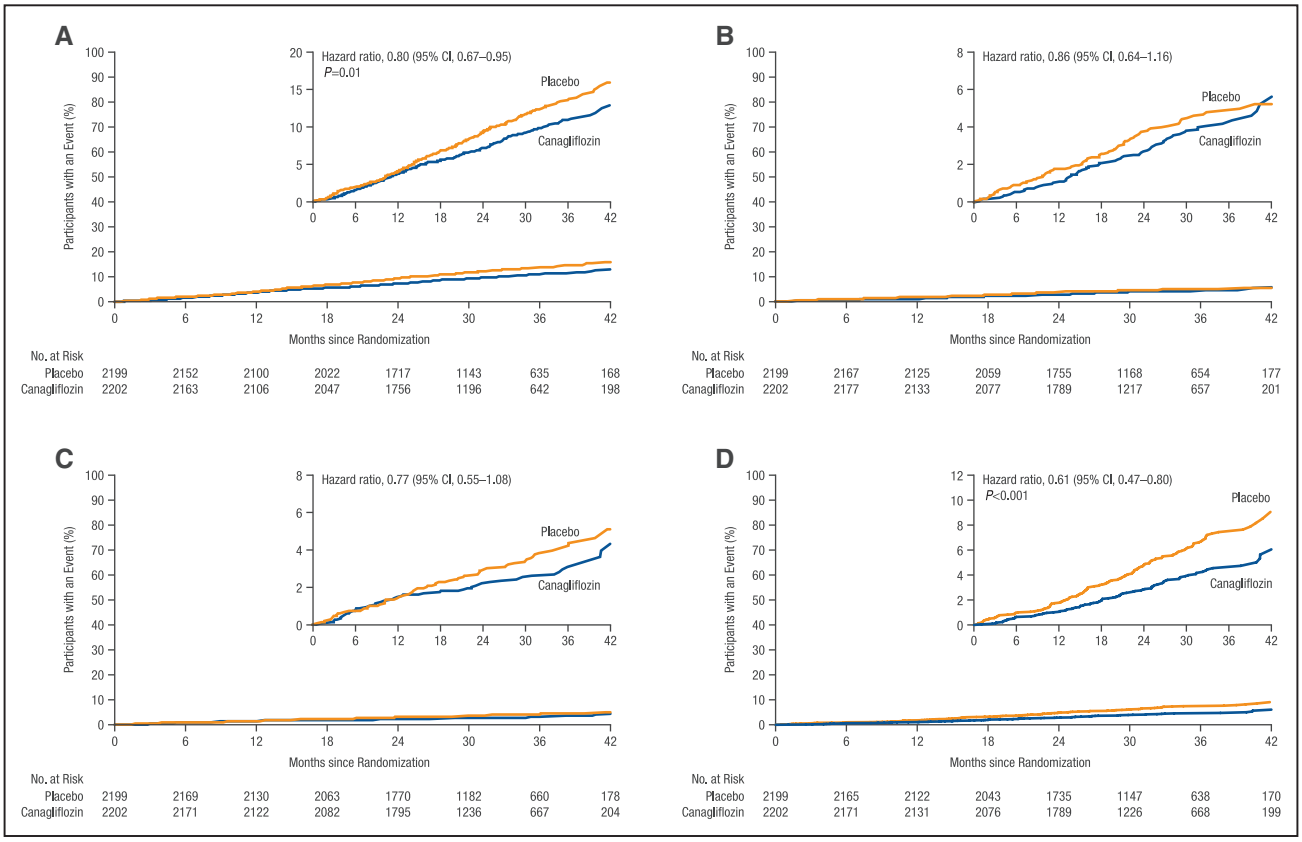


Figure 1. Effects of canagliflozin on cardiovascular outcomes in the overall population.
A, Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. **B**, Fatal or nonfatal myocardial infarction. **C**, Fatal or nonfatal stroke. **D**, Hospitalization for heart failure.

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 1. Baseline Demographic and Disease Characteristics of Primary and Secondary Prevention Cohorts in CREDENCE*

Characteristic	Primary Prevention			Secondary Prevention		
	Canagliflozin (n=1089)	Placebo (n=1092)	Total (n=2181)	Canagliflozin (n=1113)	Placebo (n=1107)	Total (n=2220)
Age, y	61.1±9.7	61.7±9.4	61.4±9.6	64.6±8.2	64.6±8.9	64.6±8.6
Female sex, n (%)	405 (37.2)	394 (36.1)	799 (36.6)	357 (32.1)	338 (30.5)	695 (31.3)
Race, n (%)						
White	646 (59.3)	640 (58.6)	1286 (59.0)	841 (75.6)	804 (72.6)	1645 (74.1)
Black or African American	58 (5.3)	63 (5.8)	121 (5.5)	54 (4.9)	49 (4.4)	103 (4.6)
Asian	265 (24.3)	268 (24.5)	533 (24.4)	160 (14.4)	184 (16.6)	344 (15.5)
Other†‡	120 (11.0)	121 (11.1)	241 (11.0)	58 (5.2)	70 (6.3)	128 (5.8)
Region, n (%)						
North America	325 (29.8)	337 (30.9)	662 (30.4)	249 (22.4)	271 (24.5)	520 (23.4)
Central/South America	235 (21.6)	254 (23.3)	489 (22.4)	241 (21.7)	211 (19.1)	452 (20.4)
Europe	186 (17.1)	177 (16.2)	363 (16.6)	268 (24.1)	233 (21.0)	501 (22.6)
Rest of the world	343 (31.5)	324 (29.7)	667 (30.6)	355 (31.9)	392 (35.4)	747 (33.6)
Ethnicity, n (%)‡						
Hispanic/Latino	415 (38.1)	430 (39.4)	845 (38.7)	302 (27.1)	276 (24.9)	578 (26.0)
Not Hispanic/Latino	639 (58.7)	637 (58.3)	1276 (58.5)	797 (71.6)	820 (74.1)	1617 (72.8)
Not reported/unknown	35 (3.2)	25 (2.3)	60 (2.8)	14 (1.3)	11 (1.0)	25 (1.1)
Current smoker, n (%)	172 (15.8)	143 (13.1)	315 (14.4)	169 (15.2)	155 (14.0)	324 (14.6)
History of hypertension, n (%)	1046 (96.1)	1048 (96.0)	2094 (96.0)	1085 (97.5)	1081 (97.7)	2166 (97.6)
History of heart failure, n (%)	63 (5.8)	58 (5.3)	121 (5.5)	266 (23.9)	265 (23.9)	531 (23.9)
History of myocardial infarction, n (%)	0	0	0	215 (19.3)	227 (20.5)	442 (19.9)
History of stroke, n (%)	0	0	0	225 (20.2)	233 (21.0)	458 (20.6)
Duration of diabetes mellitus, y	14.8±8.4	15.5±8.4	15.2±8.4	16.3±8.9	16.5±8.7	16.4±8.8
Drug therapy, n (%)						
Insulin	691 (63.5)	681 (62.4)	1372 (62.9)	761 (68.4)	751 (67.8)	1512 (68.1)
Sulfonylurea	309 (28.4)	337 (30.9)	646 (29.6)	303 (27.2)	319 (28.8)	622 (28.0)
Metformin	670 (61.5)	662 (60.6)	1332 (61.1)	606 (54.4)	607 (54.8)	1213 (54.6)
GLP-1 receptor agonist	40 (3.7)	49 (4.5)	89 (4.1)	49 (4.4)	45 (4.1)	94 (4.2)
DPP-4 inhibitor	211 (19.4)	211 (19.3)	422 (19.3)	167 (15.0)	162 (14.6)	329 (14.8)
Statin	708 (65.0)	684 (62.6)	1392 (63.8)	830 (74.6)	814 (73.5)	1644 (74.1)
Antithrombotic§	477 (43.8)	453 (41.5)	930 (42.6)	864 (77.6)	830 (75.0)	1694 (76.3)
RAAS inhibitor	1089 (100)	1088 (99.6)	2177 (99.8)	1112 (99.9)	1106 (99.9)	2218 (99.9)
β-blocker	331 (30.4)	316 (28.9)	647 (29.7)	552 (49.6)	571 (51.6)	1123 (50.6)
Diuretic	458 (42.1)	471 (43.1)	929 (42.6)	568 (51.0)	560 (50.6)	1128 (50.8)
Microvascular disease history, n (%)						
Retinopathy	407 (37.4)	425 (38.9)	832 (38.1)	528 (47.4)	522 (47.2)	1050 (47.3)
Neuropathy	430 (39.5)	443 (40.6)	873 (40.0)	647 (58.1)	627 (56.6)	1274 (57.4)
History of amputation, n (%)	0	0	0	119 (10.7)	115 (10.4)	234 (10.5)
Body mass index, kg/m^2	31.2±6.4	31.0±6.3	31.1±6.3	31.6±6.0	31.6±6.1	31.6±6.0
Systolic blood pressure, mm Hg	139.0±15.9	139.8±15.9	139.4±15.9	140.6±15.2	140.5±15.4	140.5±15.3
Diastolic blood pressure, mm Hg	79.0±9.2	78.5±9.5	78.8±9.4	77.5±9.4	78.2±9.3	77.8±9.3
Glycated hemoglobin, %	8.2±1.3	8.3±1.3	8.3±1.3	8.3±1.3	8.3±1.3	8.3±1.3
Cholesterol, mg/dL (mmol/L)						
Total	182.9±51.1 (4.7±1.3)	180.7±48.8 (4.7±1.3)	181.8±50.0 (4.7±1.3)	178.9±51.5 (4.6±1.3)	178.9±50.6 (4.6±1.3)	178.9±51.1 (4.6±1.3)

(*Continued*)

Table 1. Continued

Characteristic	Primary Prevention			Secondary Prevention		
	Canagliflozin (n=1089)	Placebo (n=1092)	Total (n=2181)	Canagliflozin (n=1113)	Placebo (n=1107)	Total (n=2220)
Triglycerides	199.0±139.7 (2.2±1.6)	194.1±138.0 (2.2±1.6)	196.6±138.8 (2.2±1.6)	198.5±141.4 (2.2±1.6)	199.9±157.5 (2.3±1.8)	199.2±149.6 (2.2±1.7)
HDL cholesterol	45.2±15.0 (1.2±0.4)	44.6±13.4 (1.2±0.3)	44.9±14.3 (1.2±0.4)	43.8±12.4 (1.1±0.3)	44.3±12.7 (1.1±0.3)	44.0±12.5 (1.1±0.3)
LDL cholesterol	98.2±43.2 (2.5±1.1)	97.0±38.8 (2.5±1.0)	97.6±41.0 (2.5±1.1)	95.8±42.1 (2.5±1.1)	94.9±41.0 (2.5±1.1)	95.3±41.6 (2.5±1.1)
Ratio of LDL to HDL	2.3±1.2	2.3±1.1	2.3±1.1	2.3±1.1	2.2±1.0	2.3±1.0
eGFR, mL·min^{-1}·1.73 m^{-2}‖	57.1±18.7	56.6±18.4	56.8±18.5	55.6±17.6	55.5±18.2	55.5±17.9
eGFR ≥90 mL·min^{-1}·1.73 m^{-2}, n (%)	56 (5.1)	57 (5.2)	113 (5.2)	49 (4.4)	49 (4.4)	98 (4.4)
eGFR ≥60–<90 mL·min^{-1}·1.73 m^{-2}, n (%)	407 (37.4)	392 (35.9)	799 (36.6)	381 (34.3)	378 (34.1)	759 (34.2)
eGFR ≥45–<60 mL·min^{-1}·1.73 m^{-2}, n (%)	294 (27.0)	321 (29.4)	615 (28.2)	336 (30.2)	315 (28.5)	651 (29.3)
eGFR ≥30–<45 mL·min^{-1}·1.73 m^{-2}, n (%)	289 (26.5)	277 (25.4)	566 (26.0)	305 (27.4)	320 (28.9)	625 (28.2)
eGFR ≥15–<30 mL·min^{-1}·1.73 m^{-2}, n (%)	43 (3.9)	45 (4.1)	88 (4.0)	40 (3.6)	44 (4.0)	84 (3.8)
eGFR <15 mL·min^{-1}·1.73 m^{-2}, n (%)	0	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Median urine albumin:creatinine ratio (IQR), mg/g	956 (446–1820)	937 (456–1850)	943 (450–1841)	883 (477–1790)	928 (493–1898)	903 (484–1827)
Normoalbuminuria, n (%)¶	10 (0.9)	8 (0.7)	18 (0.8)	6 (0.5)	7 (0.6)	13 (0.6)
Microalbuminuria, n (%)¶	124 (11.4)	134 (12.3)	258 (11.8)	127 (11.4)	111 (10.0)	238 (10.7)
Nonnephrotic-range macroalbuminuria, n (%)#	841 (77.2)	824 (75.5)	1665 (76.3)	861 (77.4)	845 (76.3)	1706 (76.8)
Nephrotic-range macroalbuminuria, n (%)**	114 (10.5)	126 (11.5)	240 (11.0)	119 (10.7)	144 (13.0)	263 (11.8)

CREDENCE indicates Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; and RAAS, renin angiotensin aldosterone system.

*Plus-minus values are mean±SD.

†Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

‡Percentages may not total 100.0% because of rounding.

§Includes anticoagulation and antiplatelet agents, including aspirin.

‖Values for baseline eGFR categories calculated on the basis of n=2219 for the total secondary prevention cohort (1112 in the canagliflozin group and 1107 in the placebo group).

¶Eligibility was based on screening urine albumin:creatinine ratio >300 to ≤5000 mg/g.

#Nonnephrotic-range macroalbuminuria is defined as urine albumin:creatinine ratio >300 and ≤3000 mg/g.

**Nephrotic-range macroalbuminuria is defined as urine albumin:creatinine ratio >3000 mg/g.

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.[6] 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.

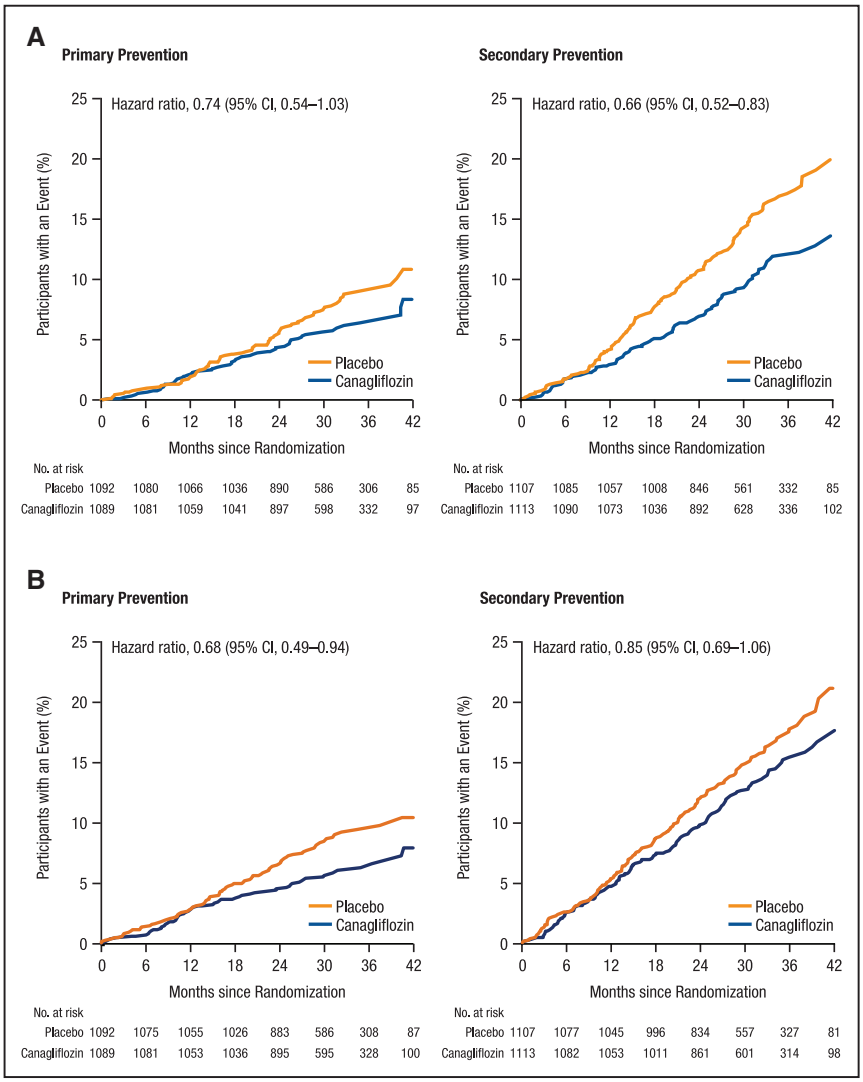
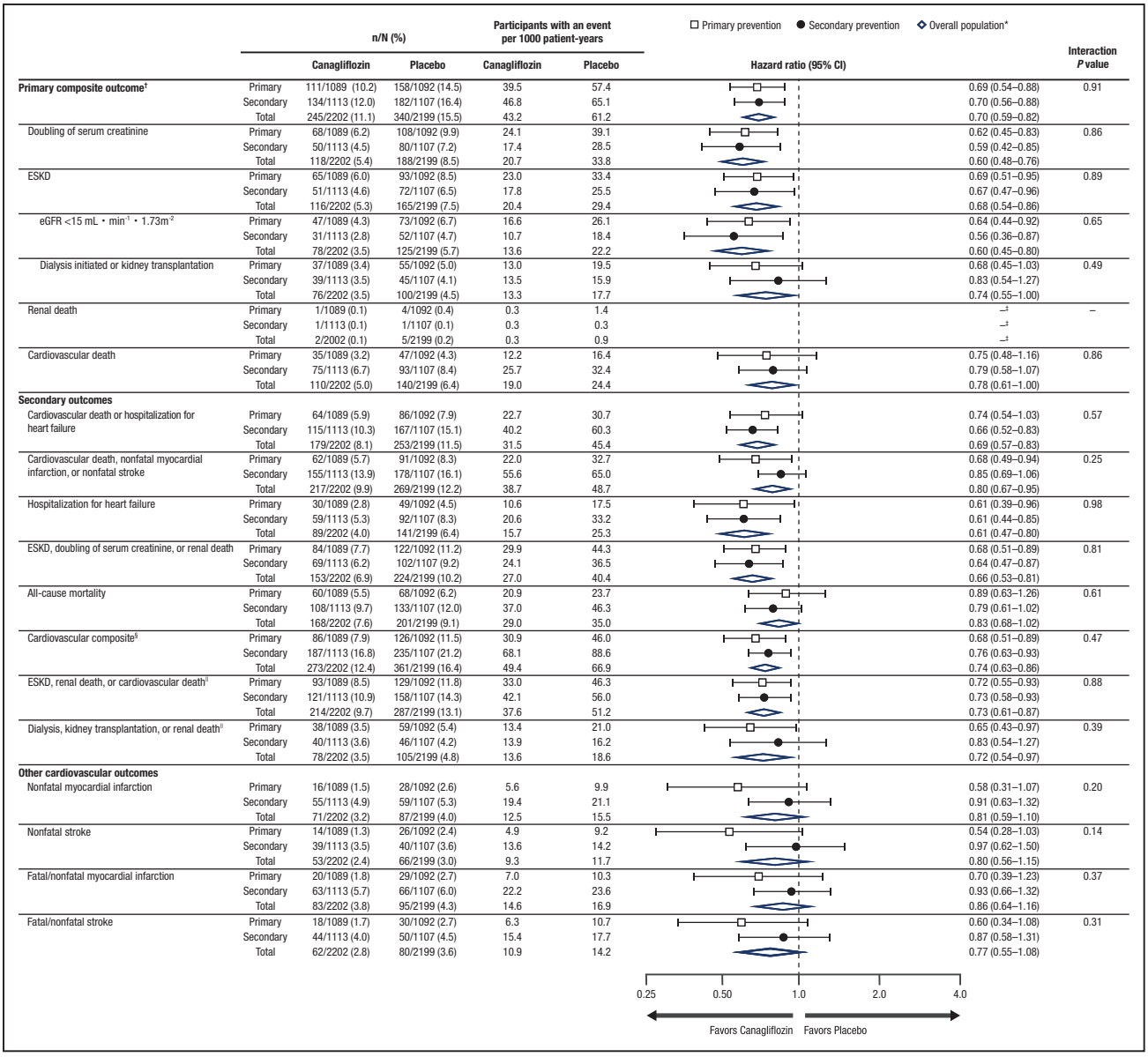


Figure 2. Effects of canagliflozin on cardiovascular outcomes in the primary and secondary prevention cohorts.
A, Cardiovascular death and hospitalization for heart failure. **B**, Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

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,[5] 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,[3,4,10–12] and a systematic review of all 3 trials has been published.[5] 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.[12] 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



		n/N (%)		Participants with an event per 1000 patient-years		Hazard ratio (95% CI)	Interaction *P* value
		Canagliflozin	Placebo	Canagliflozin	Placebo		
Primary composite outcome†	Primary	111/1089 (10.2)	158/1092 (14.5)	39.5	57.4	0.69 (0.54–0.88)	0.91
	Secondary	134/1113 (12.0)	182/1107 (16.4)	46.8	65.1	0.70 (0.56–0.88)	
	Total	245/2202 (11.1)	340/2199 (15.5)	43.2	61.2	0.70 (0.59–0.82)	
Doubling of serum creatinine	Primary	68/1089 (6.2)	108/1092 (9.9)	24.1	39.1	0.62 (0.45–0.83)	0.86
	Secondary	50/1113 (4.5)	80/1107 (7.2)	17.4	28.5	0.59 (0.42–0.85)	
	Total	118/2202 (5.4)	188/2199 (8.5)	20.7	33.8	0.60 (0.48–0.76)	
ESKD	Primary	65/1089 (6.0)	93/1092 (8.5)	23.0	33.4	0.69 (0.51–0.95)	0.89
	Secondary	51/1113 (4.6)	72/1107 (6.5)	17.8	25.5	0.67 (0.47–0.96)	
	Total	116/2202 (5.3)	165/2199 (7.5)	20.4	29.4	0.68 (0.54–0.86)	
eGFR <15 mL · min^{-1} · 1.73m^{-2}	Primary	47/1089 (4.3)	73/1092 (6.7)	16.6	26.1	0.64 (0.44–0.92)	0.65
	Secondary	31/1113 (2.8)	52/1107 (4.7)	10.7	18.4	0.56 (0.36–0.87)	
	Total	78/2202 (3.5)	125/2199 (5.7)	13.6	22.2	0.60 (0.45–0.80)	
Dialysis initiated or kidney transplantation	Primary	37/1089 (3.4)	55/1092 (5.0)	13.0	19.5	0.68 (0.45–1.03)	0.49
	Secondary	39/1113 (3.5)	45/1107 (4.1)	13.5	15.9	0.83 (0.54–1.27)	
	Total	76/2202 (3.5)	100/2199 (4.5)	13.3	17.7	0.74 (0.55–1.00)	
Renal death	Primary	1/1089 (0.1)	4/1092 (0.4)	0.3	1.4	–‡	–
	Secondary	1/1113 (0.1)	1/1107 (0.1)	0.3	0.3	–‡	
	Total	2/2002 (0.1)	5/2199 (0.2)	0.3	0.9	–‡	
Cardiovascular death	Primary	35/1089 (3.2)	47/1092 (4.3)	12.2	16.4	0.75 (0.48–1.16)	0.86
	Secondary	75/1113 (6.7)	93/1107 (8.4)	25.7	32.4	0.79 (0.58–1.07)	
	Total	110/2202 (5.0)	140/2199 (6.4)	19.0	24.4	0.78 (0.61–1.00)	
Secondary outcomes							
Cardiovascular death or hospitalization for heart failure	Primary	64/1089 (5.9)	86/1092 (7.9)	22.7	30.7	0.74 (0.54–1.03)	0.57
	Secondary	115/1113 (10.3)	167/1107 (15.1)	40.2	60.3	0.66 (0.52–0.83)	
	Total	179/2202 (8.1)	253/2199 (11.5)	31.5	45.4	0.69 (0.57–0.83)	
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	Primary	62/1089 (5.7)	91/1092 (8.3)	22.0	32.7	0.68 (0.49–0.94)	0.25
	Secondary	155/1113 (13.9)	178/1107 (16.1)	55.6	65.0	0.85 (0.69–1.06)	
	Total	217/2202 (9.9)	269/2199 (12.2)	38.7	48.7	0.80 (0.67–0.95)	
Hospitalization for heart failure	Primary	30/1089 (2.8)	49/1092 (4.5)	10.6	17.5	0.61 (0.39–0.96)	0.98
	Secondary	59/1113 (5.3)	92/1107 (8.3)	20.6	33.2	0.61 (0.44–0.85)	
	Total	89/2202 (4.0)	141/2199 (6.4)	15.7	25.3	0.61 (0.47–0.80)	
ESKD, doubling of serum creatinine, or renal death	Primary	84/1089 (7.7)	122/1092 (11.2)	29.9	44.3	0.68 (0.51–0.89)	0.81
	Secondary	69/1113 (6.2)	102/1107 (9.2)	24.1	36.5	0.64 (0.47–0.87)	
	Total	153/2202 (6.9)	224/2199 (10.2)	27.0	40.4	0.66 (0.53–0.81)	
All-cause mortality	Primary	60/1089 (5.5)	68/1092 (6.2)	20.9	23.7	0.89 (0.63–1.26)	0.61
	Secondary	108/1113 (9.7)	133/1107 (12.0)	37.0	46.3	0.79 (0.61–1.02)	
	Total	168/2202 (7.6)	201/2199 (9.1)	29.0	35.0	0.83 (0.68–1.02)	
Cardiovascular composite§	Primary	86/1089 (7.9)	126/1092 (11.5)	30.9	46.0	0.68 (0.51–0.89)	0.47
	Secondary	187/1113 (16.8)	235/1107 (21.2)	68.1	88.6	0.76 (0.63–0.93)	
	Total	273/2202 (12.4)	361/2199 (16.4)	49.4	66.9	0.74 (0.63–0.86)	
ESKD, renal death, or cardiovascular death‖	Primary	93/1089 (8.5)	129/1092 (11.8)	33.0	46.3	0.72 (0.55–0.93)	0.88
	Secondary	121/1113 (10.9)	158/1107 (14.3)	42.1	56.0	0.73 (0.58–0.93)	
	Total	214/2202 (9.7)	287/2199 (13.1)	37.6	51.2	0.73 (0.61–0.87)	
Dialysis, kidney transplantation, or renal death‖	Primary	38/1089 (3.5)	59/1092 (5.4)	13.4	21.0	0.65 (0.43–0.97)	0.39
	Secondary	40/1113 (3.6)	46/1107 (4.2)	13.9	16.2	0.83 (0.54–1.27)	
	Total	78/2202 (3.5)	105/2199 (4.8)	13.6	18.6	0.72 (0.54–0.97)	
Other cardiovascular outcomes							
Nonfatal myocardial infarction	Primary	16/1089 (1.5)	28/1092 (2.6)	5.6	9.9	0.58 (0.31–1.07)	0.20
	Secondary	55/1113 (4.9)	59/1107 (5.3)	19.4	21.1	0.91 (0.63–1.32)	
	Total	71/2202 (3.2)	87/2199 (4.0)	12.5	15.5	0.81 (0.59–1.10)	
Nonfatal stroke	Primary	14/1089 (1.3)	26/1092 (2.4)	4.9	9.2	0.54 (0.28–1.03)	0.14
	Secondary	39/1113 (3.5)	40/1107 (3.6)	13.6	14.2	0.97 (0.62–1.50)	
	Total	53/2202 (2.4)	66/2199 (3.0)	9.3	11.7	0.80 (0.56–1.15)	
Fatal/nonfatal myocardial infarction	Primary	20/1089 (1.8)	29/1092 (2.7)	7.0	10.3	0.70 (0.39–1.23)	0.37
	Secondary	63/1113 (5.7)	66/1107 (6.0)	22.2	23.6	0.93 (0.66–1.32)	
	Total	83/2202 (3.8)	95/2199 (4.3)	14.6	16.9	0.86 (0.64–1.16)	
Fatal/nonfatal stroke	Primary	18/1089 (1.7)	30/1092 (2.7)	6.3	10.7	0.60 (0.34–1.08)	0.31
	Secondary	44/1113 (4.0)	50/1107 (4.5)	15.4	17.7	0.87 (0.58–1.31)	
	Total	62/2202 (2.8)	80/2199 (3.6)	10.9	14.2	0.77 (0.55–1.08)	

Figure 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. †The primary composite outcome included ESKD, doubling of serum creatinine, or renal or cardiovascular death. ‡Hazard ratios and 95% CIs were calculated for outcomes with >10 events. §The cardiovascular composite outcome included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or hospitalization for unstable angina. ‖Exploratory outcome.

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 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[4] 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,[3,4,11] given the targeted enrollment of participants with type 2 diabetes mellitus with established chronic kidney disease. As shown previously,[5] 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,

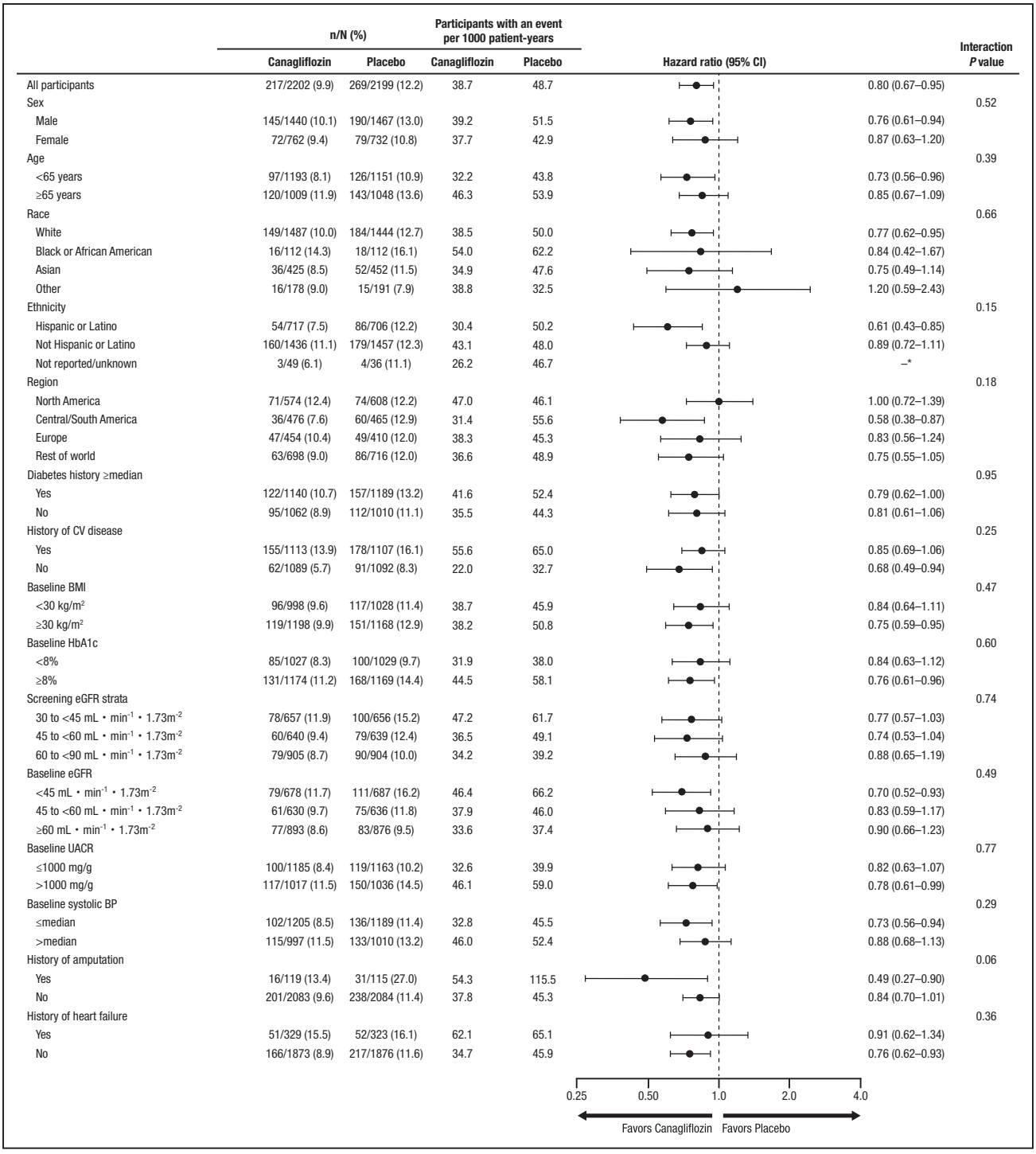


Figure 4. Effects of canagliflozin vs placebo on cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke across patient subgroups. BMI indicates body mass index; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; and UACR, urine albumin:creatinine ratio. *Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

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.[13] 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

Table 2. NNT for the Primary Composite Outcome and Select Cardiovascular Outcomes in the Primary and Secondary Prevention Cohorts and Overall Population

	NNT for 2.5 y (95% CI)		
	Primary Prevention	Secondary Prevention	Overall
End-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death	19 (12–40)	26 (15–96)	22 (15–38)
Cardiovascular death or hospitalization for heart failure	53*	21 (13–47)	29 (20–61)
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	36 (20–186)	44*	40 (23–165)

NNT indicates number needed to treat.

*The 95% CI for NNT is not provided when the 95% CI for absolute risk reduction at 2.5 years includes 0.

protection against major cardiovascular events even in those without preexisting cardiovascular disease. The NNT for cardiovascular outcomes ranged from 29 to 40 in the overall population, 36 to 53 in the primary prevention group, and 21 to 44 in the secondary prevention group. Second, canagliflozin is currently approved by the US Food and Drug Administration and other regulatory agencies for the prevention of cardiovascular outcomes in patients with eGFR >45 mL·min^{-1}·1.73 m^{-2}. Data from the CREDENCE trial, the first study of SGLT2 inhibitors dedicated to evaluate renal outcomes specifically in patients with diabetes mellitus with albuminuric nephropathy, support the initiation of canagliflozin in patients with eGFR as low as 30 mL·min^{-1}·1.73 m^{-2} and continuation until renal replacement therapy is initiated or side effects occur, which was the approach used in CREDENCE. The data also suggest benefit in patients with glycated hemoglobin as low as 6.5%, which is below the American Diabetes Association recommended target of 7.0% for most patients.[14] These robust results in CREDENCE were observed with an overall safety profile consistent with known side effects of canagliflozin and no significant difference in fractures or amputations.

These analyses have several limitations. The trial was not designed with adequate statistical power to evaluate outcomes in subgroups defined by known cardiovascular disease or in further subgroups defined by level of renal function. Although baseline characteristics were representative of the typical patient with type 2 diabetes mellitus and chronic kidney disease, the cardiovascular history was provided by site investigators after a review of available medical records or participant interviews; no formal assessment of cardiovascular disease was performed in participants at baseline. Some participants in the primary prevention group may have had cardiovascular disease that was not clinically evident.

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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