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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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ABSTRACT

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

METHODS

In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.

RESULTS

The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.

CONCLUSIONS

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.)

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*A complete list of the CREDENCE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

The increasing prevalence of type 2 diabetes during recent decades[1] is the primary factor accounting for the substantial global increase in end-stage kidney disease. Currently, more than 3 million people worldwide are estimated to be receiving treatment for kidney failure, with predictions that the number will increase to more than 5 million by 2035.[2] The only currently approved treatment for renoprotection in patients with type 2 diabetes is renin–angiotensin system blockade, which was first shown to be effective 18 years ago.[3,4]

Inhibitors of sodium–glucose cotransporter 2 (SGLT2) were developed to lower blood glucose levels in patients with type 2 diabetes. In several trials designed to meet regulatory requirements for cardiovascular safety, investigators found reductions in cardiovascular events with SGLT2 inhibitors.[5-7] Secondary and exploratory analyses of these trials suggested that SGLT2 inhibition might improve renal outcomes; however, some uncertainty persisted, since relatively few patients reached end-stage kidney disease and the trial patients were at low risk for kidney failure.[7-9] We designed the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial to assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric chronic kidney disease.

Methods

Trial Design and Oversight

Details regarding the design of this randomized, double-blind, placebo-controlled, multicenter clinical trial have been published previously.[10] The protocol (available with the full text of this article at NEJM.org) was reviewed by relevant regulatory authorities and ethics committees responsible for each trial site. The trial was sponsored by Janssen Research and Development as a collaboration between the sponsor, an academic-led steering committee, and an academic research organization, George Clinical, with operational implementation by IQVIA, a contract research organization. Technical editorial assistance provided by MedErgy was funded by the sponsor.

Members of the steering committee designed the trial, supervised its conduct, and were responsible for reporting the results. Analyses were performed by the sponsor and independently confirmed at George Clinical with the use of original data. The first and last authors drafted the first version of the manuscript, and all the authors contributed to revisions. The decision to submit the manuscript for publication was made jointly by all the authors, who vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Patients were eligible if they were at least 30 years of age and had type 2 diabetes, with a glycated hemoglobin level of 6.5 to 12.0% (6.5 to 10.5% in Germany, according to a country amendment). They were also required to have chronic kidney disease, defined as an estimated glomerular filtration rate (GFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (urinary albumin-to-creatinine ratio, >300 to 5000, with albumin measured in milligrams and creatinine in grams), as measured in a central laboratory. There was a prespecified plan to include approximately 60% of patients with an estimated GFR of 30 to <60 ml per minute per 1.73 m^2.

All the patients were required to be receiving a stable dose of an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker for at least 4 weeks before randomization; a stable dose was considered to be either the maximum labeled dose or a dose not associated with unacceptable side effects. Dual-agent treatment with an angiotensin-converting–enzyme inhibitor and an angiotensin-receptor blocker, a direct renin inhibitor, or a mineralocorticoid-receptor antagonist was not allowed.

Patients who had suspected nondiabetic kidney disease or type 1 diabetes, had been treated with immunosuppression for kidney disease, or had a history of dialysis or kidney transplantation were excluded. Full inclusion and exclusion criteria are described in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

Trial Procedures

The patients were prescreened to determine the estimated GFR and urinary albumin-to-creatinine ratio by medical-chart review or prospective laboratory assessment. The patients who met the eligibility criteria at screening were included in a

2-week, single-blind, placebo run-in period and were eligible for randomization if they had received at least 80% of single-blind placebo during the run-in period.

The patients were randomly assigned in a double-blind fashion (1:1) to receive either canagliflozin (100 mg orally once daily) or matching placebo with the use of randomly permuted blocks, with stratification according to the category of estimated GFR (30 to <45 ml, 45 to <60 ml, or 60 to <90 ml per minute per 1.73 m^2) at screening. The administration of canagliflozin or placebo was to be continued until trial completion, initiation of dialysis, kidney transplantation, occurrence of diabetic ketoacidosis, pregnancy, or receipt of a disallowed therapy.

After randomization, trial visits were conducted at weeks 3, 13, and 26 and then alternated between telephone calls and in-clinic visits at 13-week intervals. Additional testing of blood at either the central or local laboratory and safety assessments were permitted at any time at the discretion of the investigators. The use of other background therapy for glycemic management and control of cardiovascular risk factors was recommended in accordance with local guidelines.

During the trial, an increased risk of lower limb amputation was identified in another trial of canagliflozin.[5] A protocol amendment for the present trial in May 2016 asked investigators to examine patients' feet at each trial visit and temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation.

OUTCOMES

The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline (average of randomization and prerandomization value) sustained for at least 30 days according to central laboratory assessment, or death from renal or cardiovascular disease.

Secondary outcomes that were planned for sequential hierarchical testing were specified in the following order: first, a composite of cardiovascular death or hospitalization for heart failure; second, a composite of cardiovascular death, myocardial infarction, or stroke; third, hospitalization for heart failure; fourth, a composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death; fifth, cardiovascular death; sixth, death from any cause; and seventh, a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or for unstable angina. All other efficacy outcomes were exploratory.

Safety evaluations included laboratory testing and assessments of adverse events. All renal and cardiovascular outcomes that were part of the primary and secondary outcomes, as well as key safety outcomes (fractures, pancreatitis, ketoacidosis, and renal-cell carcinoma), were adjudicated by independent adjudication committees whose members were unaware of trial-group assignments. (Details regarding trial outcomes are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

The trial was designed to be event-driven, with the enrollment of at least 4200 patients (844 events) required to provide a power of 90% to detect a risk of the primary outcome that was 20% lower in the canagliflozin group than in the placebo group at an alpha level of 0.045 after adjustment for one interim analysis. A single interim analysis was to be conducted by an independent data monitoring committee after the primary outcome had occurred in 405 patients. Prespecified stopping guidance that was provided to the data monitoring committee by the steering committee proposed possible recommendation of early cessation if clear evidence of benefit was observed for the primary outcome ($P<0.01$) and the composite of end-stage kidney disease or death from renal or cardiovascular causes ($P<0.025$), with consideration of the overall balance of risks and benefits.

In the intention-to-treat population, we used a stratified Cox proportional-hazards model to analyze the primary and secondary outcomes, according to the category of estimated GFR at screening. Data were censored on October 30, 2018, or the date of last known contact, which included the last trial visit (either in-clinic or telephone) or the date of alternative contact confirming that the patient was alive at the time of trial closure.

If the trial was to be stopped at the interim analysis, the significance level for the primary outcome would be determined by the alpha spend-

ing function (two-sided level of 0.022 for 585 events), and the secondary outcomes would be tested at a two-sided level of 0.038, to account for type I error inflation in the group sequential design. Subgroup analyses were assessed by tests for the interaction between the trial group and the subgroup in stratified Cox proportional-hazards models without adjustment for multiple testing. We used mixed models for repeated measures to analyze changes in intermediate outcomes over time in the on-treatment analysis population (unless otherwise noted), assuming an unstructured covariance and adjusting for the baseline value, trial group, category of estimated GFR at screening, trial visit, interaction between trial group and visit, and interaction between baseline value and visit. All available measurements were used with no distinction made for missing outcomes for patients who were alive and outcomes that were not observed because of death. Slope analyses regarding the estimated GFR for the acute phase (baseline to week 3), chronic phase (week 3 to end of treatment), and total slope through week 130 are described in the Supplementary Appendix.

We used the data set for all treated patients through 30 days after the last dose for the safety analyses (on-treatment analysis) and used the on-study analysis that included all treated patients through the end of the trial to evaluate selected adverse events, including cancer, amputation, and fracture.

We calculated the numbers of patients who needed to be treated to prevent one event during 2.5 years as the reciprocal of the between-group difference in cumulative incidence at 2.5 years on the basis of the Kaplan–Meier curve. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From March 2014 through May 2017, a total of 12,900 patients were screened and 4401 underwent randomization at 690 sites in 34 countries (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the patients were similar in the two groups (Table 1, and Tables S1 and S2 in the Supplementary Appendix).[10] The mean age was 63 years, and 33.9% of the patients were women. The mean glycated hemoglobin value was 8.3%, the mean estimated GFR was 56.2 ml per minute per 1.73 m^2, and the median urinary albumin-to-creatinine ratio was 927, with albumin measured in milligrams and creatinine in grams.

The requisite number of primary outcome events to trigger the interim analysis were accrued by July 2018. The data monitoring committee advised the steering committee members that the prespecified efficacy criteria for early cessation had been achieved and recommended that the trial be stopped. The trial leadership accepted this recommendation, the patients were recalled for final visits, and the trial was concluded.

At the trial conclusion at a median follow-up of 2.62 years (range, 0.02 to 4.53), 1201 patients (27.3%) in the two groups had discontinued therapy (Table S3 and Figs. S1 and S2 in the Supplementary Appendix); the rate of adherence to the trial regimen was 84% during follow-up. A total of 4361 patients (99.1%) were either alive with follow-up at the end of the trial or had died before the final follow-up visit. Consent was withdrawn by 16 patients (0.4%), and vital status was ascertained for all but 6 patients (4395 [99.9%]).

EFFECT ON THE PRIMARY OUTCOME AND RENAL COMPONENTS

The event rate of the primary composite outcome of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death was significantly lower in the canagliflozin group than in the placebo group (43.2 and 61.2 per 1000 patient-years, respectively), which resulted in a 30% lower relative risk (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001) (Table 2 and Fig. 1A). The effects were consistent across regions and other prespecified subgroups (Fig. 2, and Fig. S3 in the Supplementary Appendix) and for the components of end-stage kidney disease (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002) (Table 2 and Fig. 1C). The effects were also consistent across renal components, including the doubling of the serum creatinine level (hazard ratio, 0.60; 95% CI, 0.48 to 0.76; P<0.001) (Table 2) and the exploratory outcome of dialysis, kidney transplantation, or renal death (hazard ratio, 0.72; 95% CI, 0.54 to 0.97) (Table 2 and Fig. 1D). Nearly identical results were shown in sensitivity analyses that included imputation of missing

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Canagliflozin (N=2202)	Placebo (N=2199)	All Patients (N=4401)
Age — yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex — no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group — no. (%)†			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker — no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension — no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure — no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes — yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease — no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation — no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body-mass index‡	31.4±6.2	31.3±6.2	31.3±6.2
Blood pressure — mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin — %	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR — ml/min/1.73 m^2§	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)¶	923 (459–1794)	931 (473–1868)	927 (463–1833)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race or ethnic group was reported by the patients. The designation "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The baseline estimated glomerular filtration rate (GFR) was missing for one patient in the canagliflozin group.
¶ The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

data (hazard ratio, 0.69; 95% CI, 0.59 to 0.82) or that were adjusted for competing risks (hazard ratio, 0.70; 95% CI, 0.59 to 0.82).

SECONDARY AND EXPLORATORY OUTCOMES

Patients in the canagliflozin group also had a lower risk of several secondary outcomes tested in a hierarchical fashion (Table 2), including the composites of cardiovascular death or hospitalization for heart failure (hazard ratio, 0.69; 95% CI, 0.57 to 0.83; P<0.001), cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01), and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). The relative risk of the composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death was lower by 34% in the canagliflozin group (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001) (Table 2 and Fig. 1B).

There was no significant between-group difference in the risk of cardiovascular death (hazard ratio, 0.78; 95% CI, 0.61 to 1.00; P=0.05) (Table 2 and Fig. 1E), so the differences in all subsequent outcomes in the hierarchical testing sequence were not formally tested. The hazard ratio for death from any cause was 0.83 (95% CI, 0.68 to 1.02) (Table 2 and Fig. 1F); for the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina, the hazard ratio was 0.74 (95% CI, 0.63 to 0.86) (Table 2).

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m^2	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53–0.81)	<0.001
Death from any cause	168/2202	201/2199	29.0	35.0	0.83 (0.68–1.02)	NA
Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273/2202	361/2199	49.4	66.9	0.74 (0.63–0.86)	NA
End-stage kidney disease, renal death, or cardiovascular death†	214/2202	287/2199	37.6	51.2	0.73 (0.61–0.87)	NA
Dialysis, kidney transplantation, or renal death†	78/2202	105/2199	13.6	18.6	0.72 (0.54–0.97)	NA
Safety‡						NA
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA

Acute pancreatitis	5/2200	2/2197	1.0	0.4	NA	NA
Hyperkalemia¶	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)	NA
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)	NA
Diabetic ketoacidosis‖	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA

* NA denotes not applicable because P values are reported only for outcomes that were included in the hierarchical-testing strategy and hazard ratios and 95% confidence intervals (CI) are reported only for outcomes with more than 10 events.
† This outcome was exploratory.
‡ The numbers of amputation, fracture, and cancer events were determined in the on-study population, whereas the other safety events were determined in the on-treatment population. The analyses for fracture, renal-cell carcinoma, acute pancreatitis, and diabetic ketoacidosis were based on confirmed and adjudicated results.
§ The diagnosis of breast cancer was established only in women.
¶ Adverse events of hyperkalemia were spontaneously reported by the investigator. The definition of hyperkalemia includes the preferred terms of "hyperkalemia" and "blood potassium increased" in the *Medical Dictionary for Regulatory Activities*.
‖ All potential ketone-related events were adjudicated for diabetic ketoacidosis by an independent adjudication committee on the basis of clinical presentation and predefined biochemical measures.

EFFECTS ON SAFETY OUTCOMES

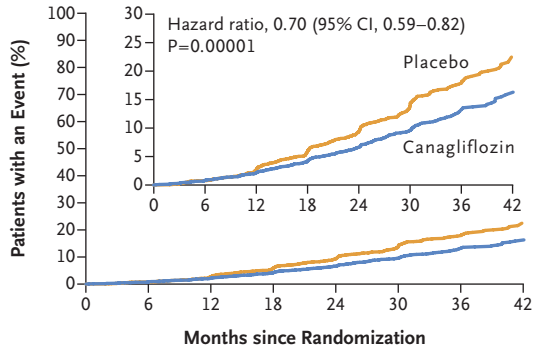
Rates of adverse events and serious adverse events were similar overall in the canagliflozin group and the placebo group (Table 2, and Tables S4 and S5 in the Supplementary Appendix). There was no significant difference in the risk of lower-limb amputation, with rates of 12.3 versus 11.2 per 1000 patient-years in the canagliflozin group and the placebo group, respectively (hazard ratio, 1.11; 95% CI, 0.79 to 1.56). Rates of fracture were also similar in the two groups (hazard ratio, 0.98; 95% CI, 0.70 to 1.37). Rates of diabetic ketoacidosis were low but higher in the canagliflozin group than in the placebo group (2.2 vs. 0.2 per 1000 patient-years) (Table S6 in the Supplementary Appendix).

EFFECT ON INTERMEDIATE OUTCOMES

For glycated hemoglobin, the least-squares mean level at 13 weeks was lower in the canagliflozin group than in the placebo group by 0.31 percentage points (95% CI, 0.26 to 0.37), and the between-group difference narrowed thereafter, with an overall mean difference in the reduction throughout the trial of 0.25 percentage points (95% CI, 0.20 to 0.31) (Fig. S4 in the Supplementary Appendix). On average, levels were lower in the canagliflozin group for systolic blood pressure (by 3.30 mm Hg; 95% CI, 2.73 to 3.87), diastolic blood pressure (by 0.95 mm Hg; 95% CI, 0.61 to 1.28), and body weight (by 0.80 kg; 95% CI, 0.69 to 0.92). The geometric mean of the urinary albumin-to-creatinine ratio was lower by 31% (95% CI, 26 to 35) on average during follow-up in the canagliflozin group (Fig. 3A).

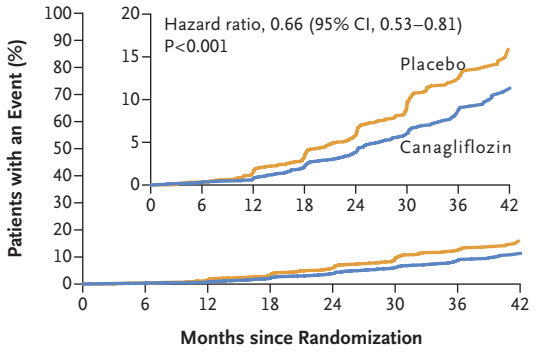
The least-squares mean (±SE) change in the estimated GFR slope was less in the canagliflozin group than in the placebo group (–3.19±0.15 vs. –4.71±0.15 ml per minute per 1.73 m^2 per year), for a between-group difference of 1.52 ml per minute per 1.73 m^2 per year (95% CI, 1.11 to 1.93) (Fig. 3B). During the first 3 weeks, there was a greater reduction in the estimated GFR in the canagliflozin group than in the placebo group (–3.72±0.25 vs. –0.55±0.25 ml per minute per 1.73 m^2), for a between-group difference of –3.17 ml per minute per 1.73 m^2 (95% CI, –3.87 to –2.47). Thereafter, the decline in the estimated GFR was slower in the canagliflozin group than in the placebo group (–1.85±0.13 vs. –4.59±0.14 ml per minute per 1.73 m^2 per year),

A Primary Composite Outcome



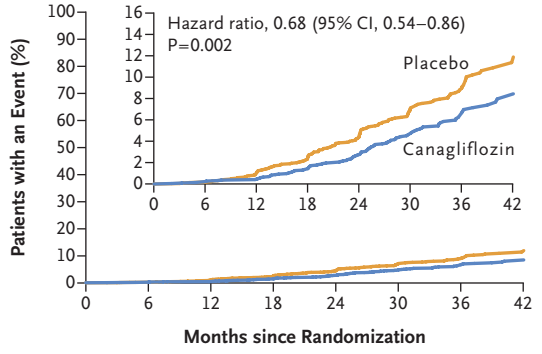
No. at Risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

B Renal-Specific Composite Outcome



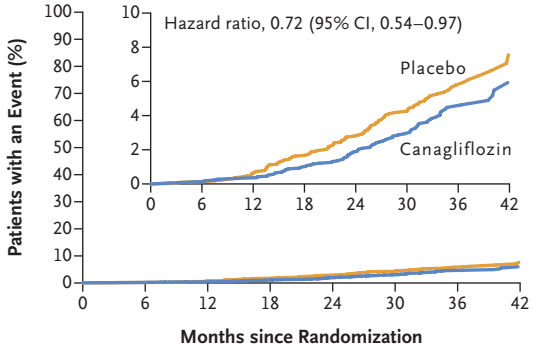
No. at Risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

C End-Stage Kidney Disease



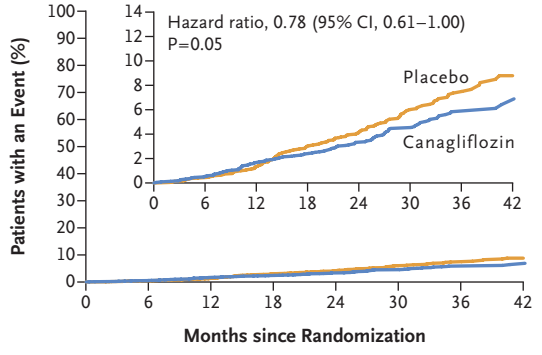
No. at Risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

D Dialysis, Kidney Transplantation, or Renal Death



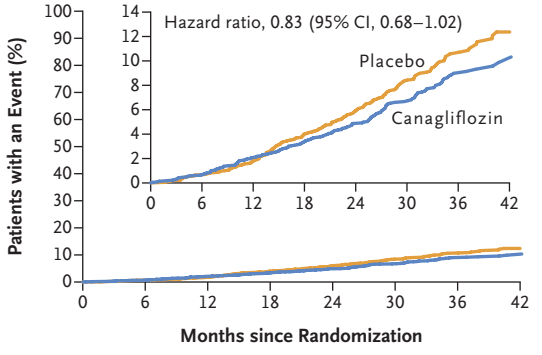
No. at Risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

E Death from Cardiovascular Cause



No. at Risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

F Death from Any Cause



No. at Risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

Figure 1 (facing page). Primary Composite, Renal, and Mortality Outcomes.

Panel A shows the primary composite outcome of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death in the canagliflozin group and the placebo group. Panel B shows the renal-specific composite outcome of end-stage kidney disease, doubling of serum creatinine level, or renal death. Panel C shows end-stage kidney disease, which was defined as the initiation of dialysis for at least 30 days, kidney transplantation, or an estimated glomerular filtration rate of less than 15 ml per minute per 1.73 m^2 of body-surface area that was sustained for at least 30 days, according to central laboratory assessment. Panel D shows the initiation of dialysis, kidney transplantation, or renal death, which was an exploratory outcome. Panel E shows death from cardiovascular causes, and Panel F death from any cause. The insets show the same data on an expanded y axis.

for a difference of 2.74 ml per minute per 1.73 m^2 per year (95% CI, 2.37 to 3.11).

PROJECTED ESTIMATED EFFECTS

On the basis of our trial data, we estimate that among 1000 patients in our trial treated for 2.5 years, the primary composite outcome of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death would occur in 47 fewer patients in the canagliflozin group than in the placebo group (number needed to treat [NNT], 22; 95% CI, 15 to 38), including 36 fewer composite renal outcomes of end-stage kidney disease, doubling of the serum creatinine level, or renal death (NNT, 28; 95% CI, 19 to 54) and 24 fewer end-stage kidney-disease events (NNT, 43; 95% CI, 26 to 121). Canagliflozin treatment would also prevent 22

Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m^2	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m^2	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m^2	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m^2	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m^2	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m^2	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	

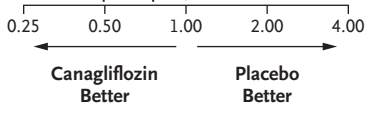


Figure 2. Subgroup Analysis, According to Estimated Glomerular Filtration Rate (GFR) at Screening and Albuminuria at Baseline.

Shown are the primary composite outcome and renal-specific composite outcome, according to the patients' estimated GFR at screening and urinary albumin-to-creatinine ratio (UACR) at baseline, in the canagliflozin group and the placebo group. The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams. CV denotes cardiovascular, and ESKD end-stage kidney disease.

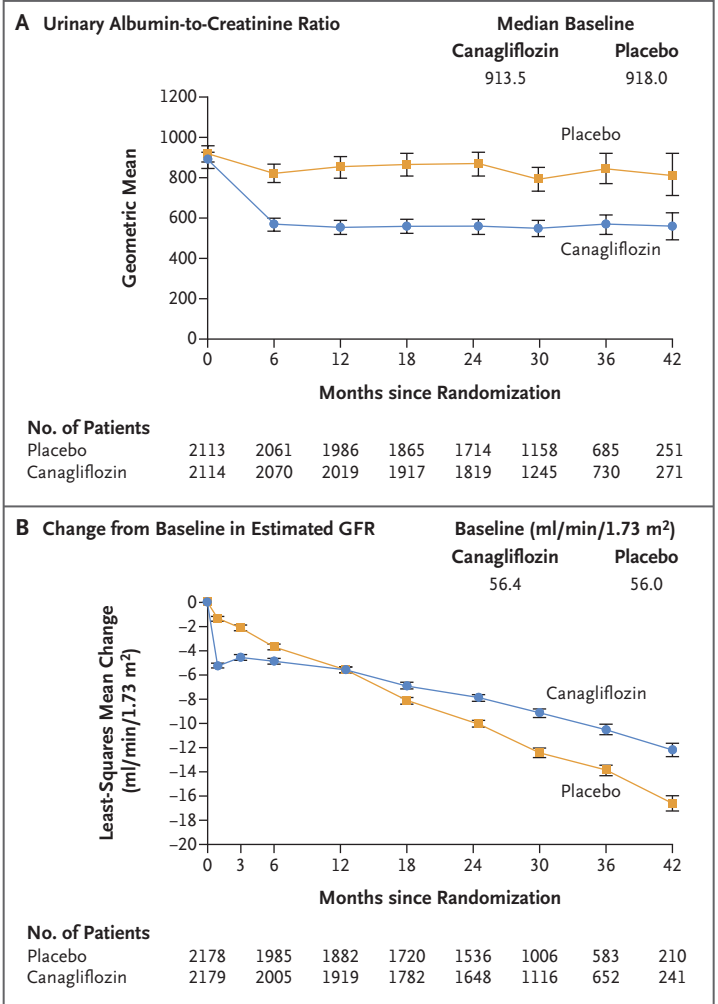


Figure 3. Effects on Albuminuria and Estimated GFR.

Panel A shows the effects of canagliflozin and placebo on the urinary albumin-to-creatinine ratio in the intention-to-treat population. Panel B shows the change from the screening level in the estimated GFR in the on-treatment population. The I bars indicate the 95% confidence interval in Panel A and the standard error in Panel B. The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

hospitalizations for heart failure (NNT, 46; 95% CI, 29 to 124) and 25 composite events of cardiovascular death, myocardial infarction, or stroke (NNT, 40; 95% CI, 23 to 165).

DISCUSSION

In this trial, we found that patients with type 2 diabetes and chronic kidney disease who received canagliflozin had a lower risk of the primary composite outcome of end-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes than those who received placebo. Patients in the canagliflozin group also had a lower risk of end-stage kidney disease, hospitalization for heart failure, and the composite of cardiovascular death, myocardial infarction, or stroke. These results indicate that canagliflozin may be an effective treatment option for renal and cardiovascular protection in patients with type 2 diabetes with chronic kidney disease.

The observed benefits were obtained on a background of renin–angiotensin system blockade, the only approved renoprotective medications in type 2 diabetes, a factor that highlights the clinical significance of the findings. In contrast to completed cardiovascular outcome trials of SGLT2 inhibitors,[5-7] our trial included a population at high risk for kidney failure and had a primary outcome of major renal end points. In addition, we found that patients who received canagliflozin (including those who had a reduced estimated GFR at baseline) had a lower risk of the primary outcome overall than those in the placebo group, as well as less end-stage kidney disease. These findings were observed despite very modest between-group differences in blood glucose level, weight, and blood pressure and in contrast to previous concern about the initial acute reduction in the estimated GFR observed with SGLT2 inhibitors. This suggests that the mechanism of benefit is likely to be independent of glucose levels and may possibly stem from a reduction in intraglomerular pressure,[11-13] with other possible mechanisms presently being studied.[14-17]

Our trial population was also at high risk for cardiovascular outcomes, with cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure occurring in 13.8% of the population over a median of 2.62 years of follow-up. The significantly lower rates of cardiovascular outcomes, including the composite of cardiovascular death, myocardial infarction, or stroke, in the canagliflozin group in our trial are consistent with those observed with canagliflozin in the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program,[5] despite the smaller differences in glycemic control. The EMPA-REG OUTCOME trial also showed that empagliflozin was superior to placebo,[6] and the DECLARE–TIMI 58 (Dapagliflozin Effect on Car-

diovascular Events–Thrombolysis in Myocardial Infarction 58) trial showed that dapagliflozin was noninferior to placebo for this composite outcome.[7] The reduction in hospitalization for heart failure seen in our trial is consistent with results of other trials of SGLT2 inhibitors.[5-7,18,19]

The similar rates of amputation and fracture that we observed with canagliflozin and placebo are reassuring and consistent with trials of other SGLT2 inhibitors[6,7,20] but differ from the CANVAS Program findings.[5] Whether the increased risk of lower limb amputation in the CANVAS Program was due to differing trial populations or protocols or to chance remains unclear. The overall safety profile in our trial is otherwise consistent with the known adverse effects associated with canagliflozin.

This trial has certain limitations. First, the trial was stopped early at a planned interim analysis, which may have limited the power for some secondary outcomes and may increase the risk of overestimating effect sizes.[21] However, the precision of the effect and the consistency with the findings of previous large trials of SGLT2 inhibitors suggest that this limitation is unlikely to have a major effect on our findings. Second, we did not measure off-treatment estimated GFR levels among the patients who had completed the trial, so the differences in the estimated GFR values at the end of the trial are probably underestimations. Third, we excluded patients who had very advanced kidney disease (estimated GFR, <30 ml per minute per 1.73 m^2), nonalbuminuric or microalbuminuric disease, and kidney diseases believed to be due to conditions other than type 2 diabetes, so it is not known whether the findings can be generalized to such populations.

In conclusion, among patients with type 2 diabetes and kidney disease, those in the canagliflozin group had a lower risk of kidney failure and cardiovascular events than those in the placebo group at a median follow-up of 2.62 years.

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APPENDIX

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