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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

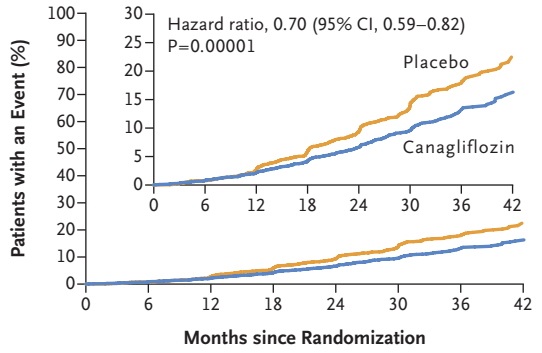
Rates of adverse events and serious adverse events were similar overall in the canagliflozin group and the placebo group (Table 2, and Tables S4 and S5 in the Supplementary Appendix). There was no significant difference in the risk of lower-limb amputation, with rates of 12.3 versus 11.2 per 1000 patient-years 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).

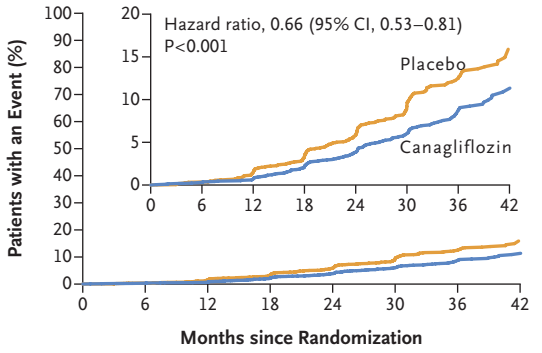
The least-squares mean (±SE) change in the estimated GFR slope was less in the canagliflozin group than in the placebo group (–3.19±0.15 vs. –4.71±0.15 ml per minute per 1.73 m^2 per year), for a between-group difference of 1.52 ml per minute per 1.73 m^2 per year (95% CI, 1.11 to 1.93) (Fig. 3B). During 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



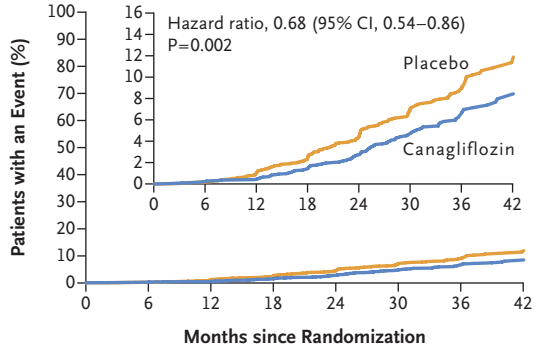
No. at Risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

B Renal-Specific Composite Outcome



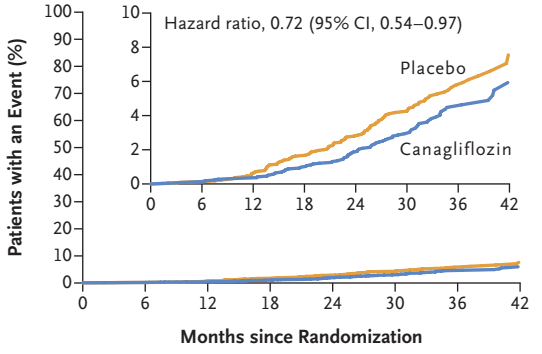
No. at Risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

C End-Stage Kidney Disease



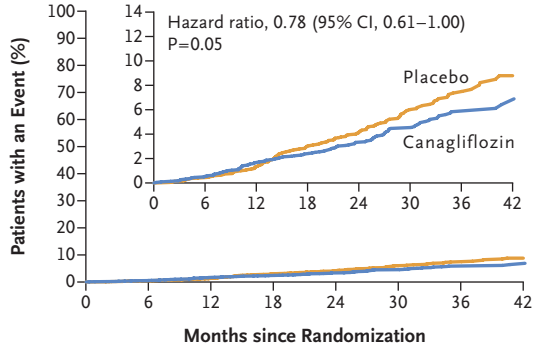
No. at Risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

D Dialysis, Kidney Transplantation, or Renal Death



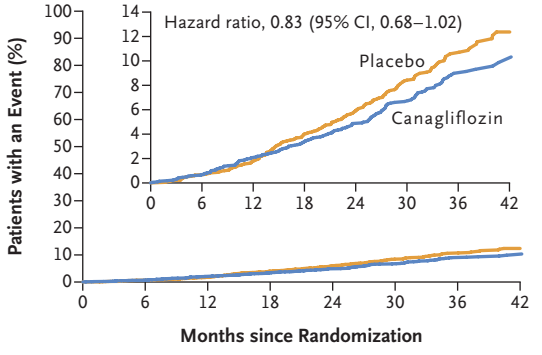
No. at Risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

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)	

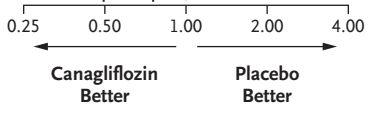


Figure 2. Subgroup Analysis, According to Estimated Glomerular Filtration Rate (GFR) at Screening and Albuminuria at Baseline.

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.

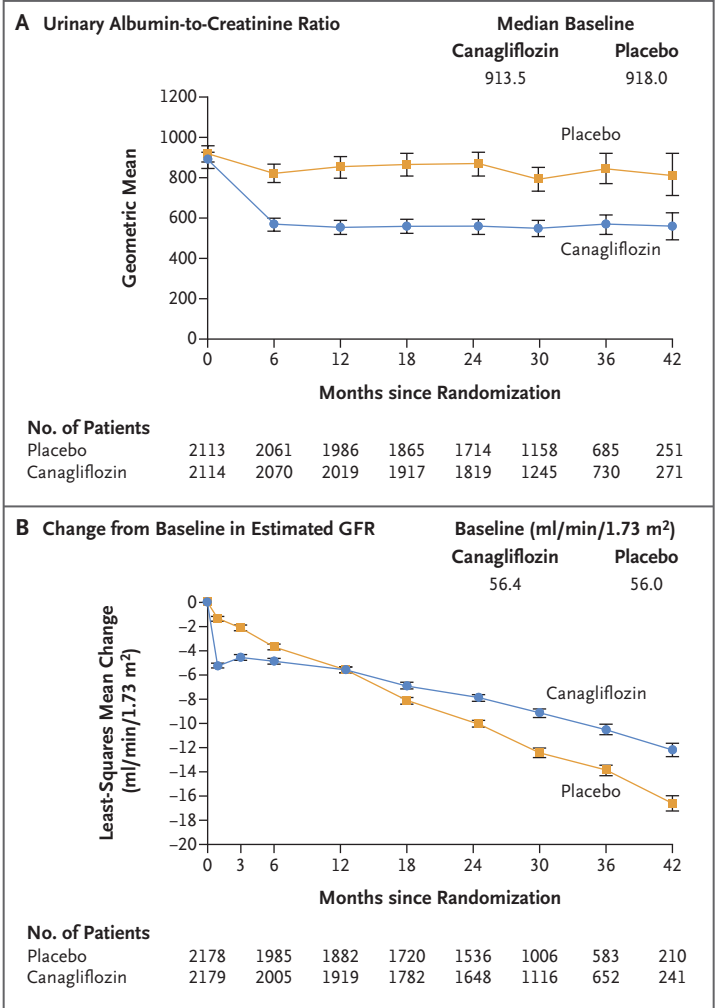


Figure 3. Effects on Albuminuria and Estimated GFR.

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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REFERENCES

1. International Diabetes Federation. IDF diabetes atlas. 8th ed. Brussels: International Diabetes Federation, 2017.
2. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet 2015;385:1975-82.
3. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
4. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
5. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
6. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
7. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
8. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691-704.
9. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34.
10. Jardine MJ, Mahaffey KW, Neal B, et al. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. Am J Nephrol 2017;46:462-72.
11. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587-97.
12. Brenner BM, Ballermann BJ, Gunning ME, Zeidel ML. Diverse biological actions of atrial natriuretic peptide. Physiol Rev 1990;70:665-99.
13. Ortola FV, Ballermann BJ, Anderson S, Mendez RE, Brenner BM. Elevated plasma atrial natriuretic peptide levels in diabetic rats: potential mediator of hyperfiltration. J Clin Invest 1987;80:670-4.
14. Sternlicht H, Bakris GL. Blood pressure lowering and sodium-glucose co-transporter 2 inhibitors (SGLT2i): more than osmotic diuresis. Curr Hypertens Rep 2019;21(2):12.
15. Esterline RL, Vaag A, Oscarsson J, Vora J. Mechanisms in endocrinology — SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? Eur J Endocrinol 2018;178(4):R113-R125.
16. Chakraborty S, Galla S, Cheng X, et al. Salt-responsive metabolite, β-hydroxybutyrate, attenuates hypertension. Cell Rep 2018;25(3):677-689.e4.
17. Schutten JC, Joosten MM, de Borst MH, Bakker SJL. Magnesium and blood pressure: a physiology-based approach. Adv Chronic Kidney Dis 2018;25:244-50.
18. Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. Circulation 2018;138:458-68.
19. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. Eur Heart J 2016;37:1526-34.
20. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. Diabetes Care 2018;41(1):e4-e5.
21. Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. BMJ 2012;344:e3863.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Supplementary Appendix

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Inclusion and Exclusion Criteria

Inclusion Criteria at Screening Visit

1. Man or woman ≥30 years-old with a clinical diagnosis of type 2 diabetes mellitus (T2DM).
2. Glycated hemoglobin (HbA1c) ≥6.5% to ≤12.0%, (≥6.5% to ≤10.5% in Germany).
3. Estimated glomerular filtration rate (eGFR) ≥30 to <90 mL/min/1.73 m^2 (as determined using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation).

   Note*:* An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (i.e., eGFR ≥30 to <60 mL/min/1.73 m^2; first category):CKD Stage 2 (i.e., eGFR ≥60 to <90 mL/min/1.73 m^2; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, entry of subjects with Stage 2 CKD (i.e., eGFR ≥60 to <90 mL/min/1.73 m^2) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.
4. Urinary albumin:creatinine ratio (UACR) >300 mg/g to ≤5000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol).
5. All subjects must be on a stable maximum tolerated labeled daily dose of ACEi or ARB for at least 4 weeks prior to randomization.

   Note: A maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is defined as the maximum approved labeled dose for diabetic nephropathy (for agents with an approved indication for diabetic nephropathy in patients with T2DM, i.e., losartan and irbesartan) or the maximum approved dose for hypertension (for agents without an approved indication for diabetic nephropathy), unless side effects or adverse events limit the use of the maximum approved dose. For subjects who are not

on a maximum labeled daily dose of an ACEi or ARB, investigators will be required to document why a higher dose should not be used.

6. Women must be:

   - postmenopausal, defined as
     - >45 years of age with amenorrhea for at least 18 months, or
     - >45 years of age with amenorrhea for at least 6 months and <18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or
   - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), or otherwise be incapable of pregnancy, or
   - heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, and consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, or
   - not heterosexually active.

   Note: Subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.

7. Women of childbearing potential (i.e., those subjects who do not meet the postmenopausal definition above), regardless of age, must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations.

Note: A serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations.

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.
9. Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Each subject must also sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

Inclusion Criterion for Randomization

10. Subjects must have ≥80% compliance (by pill count) with single-blind placebo.

Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-related/Metabolic

1. History of diabetic ketoacidosis or type 1 diabetes mellitus (T1DM).

2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

3. Known medical history or clinical evidence suggesting nondiabetic renal disease.

4. Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant.

Note: Subjects with a history of treated childhood renal disease, without sequelae, may participate.

5. Uncontrolled hypertension (systolic blood pressure [BP] ≥180 and/or diastolic BP ≥100 mmHg) by Week –2.

Note: Subjects not fulfilling BP criteria at the initial screening visit may have their BP-lowering medication regimen adjusted, followed by re-evaluation up to the Week –2 run-in period (the ACEi or ARB regimen must be stable for at least 4 weeks before Day 1 to be eligible).

6. Blood potassium level >5.5 mmol/L during screening.

Note: Subjects in whom hyperkalemia was associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, or mineralocorticoid receptor antagonists (MRAs; e.g., spironolactone or eplerenone), who have been withdrawn from these drugs, and in whom usage of these drugs is not indicated in the view of the treating physician, may be included in the study.

7. Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomization, or a revascularization procedure is planned during the trial.

8. Current or history of heart failure of New York Heart Association (NYHA) class IV cardiac disease (The Criteria Committee of the NYHA).

9. Electrocardiogram (ECG) findings within 12 weeks before randomization that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance).

Gastrointestinal

10. Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis).

Laboratory

11. Alanine aminotransferase (ALT) levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.

Other Conditions

12. History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

13. History of human immunodeficiency virus (HIV) antibody positive.

14. Major surgery within 12 weeks before randomization, or has not fully recovered from surgery.

15. Any condition that in the opinion of the investigator or sponsor's medical monitor would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments.

16. History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening (added May 5, 2016).

Medications/Therapies

17. Combination use of an ACEi and ARB.

18. Use of an MRA or a direct renin inhibitor (DRI).

Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with an MRA or DRI during screening. Subjects who are off therapy with an MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrollment.

19. Current use of a sodium glucose co-transporter 2 (SGLT2) inhibitor (within 12 weeks prior to randomization).

20. Current participation in another canagliflozin study or previously exposed to canagliflozin in a prior canagliflozin study.

21. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.

22. Received an active investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks before Day 1/baseline.

General

23. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.

24. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since the time of the initial screening visit. Before randomization, subjects whose clinical status changes after screening such that they now meet an exclusion criterion should be excluded from participation.

Safety Analyses

Adverse events (AEs)	All AEs will be collected and coded using the *Medical Dictionary for Regulatory Activities* (*MedDRA*) from randomization until 30 days after the last date of blinded study medication
AEs of interest	All malignancies, renal cell carcinoma, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (e.g., angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious AEs of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, diabetic ketoacidosis (and related AEs including ketoacidosis, metabolic acidosis, or acidosis), amputation, and pregnancy
Hypoglycemia	All episodes of hypoglycemia (both symptomatic and asymptomatic) are recorded on a dedicated hypoglycemia electronic case report form (eCRF)
Safety laboratory tests	Chemistry, hematology, urinalysis
Physical examination	Pulse, blood pressure, weight

Primary Endpoint Criteria

End-stage Kidney Disease (ESKD)

In the absence of universally accepted guidelines that define the onset of ESKD, the following definitions have been developed to identify and adjudicate ESKD events:

1. Diagnosis

Worsening uremia in patients progressing from chronic kidney disease (CKD) to ESKD causes characteristic symptoms which require renal replacement therapy (RRT) in the form of dialysis or transplantation. The requirement of ongoing RRT establishes the diagnosis of ESKD. In some cases, the diagnosis can be made in the absence of RRT when certain criteria are fulfilled:

- Kidney Transplantation: Definitive RRT prescribed when uremic symptoms have already occurred, or are anticipated to occur, due to the progression of irreversible CKD. Death during the transplant surgery will be considered kidney transplantation.
- Chronic Dialysis: ESKD will be diagnosed if dialysis is performed for ≥30 days and is not subsequently known to recover. Indications for dialysis are indicated in Section 2 below.
- Dialysis Not Administered: In cases where dialysis is not available or not administered due to futility or subject refusal, the diagnosis of ESKD will require a sustained estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2 (by CKD Epidemiology Collaboration [CKD-EPI] formula and confirmed by repeat central laboratory measure at 30 days or more of the initial onset).

2. Onset of ESKD

The mode of onset of ESKD will be adjudicated into the following categories:

- Chronic progression.
- Acute deterioration, diagnosed when the decline in kidney function is sudden and acute kidney injury is superimposed on CKD, resulting in RRT.

3. Confirmation of ESKD

- In cases where RRT is given in the form of dialysis, the patient will be contacted at 90 days after the initiation of dialysis to document if dialysis is continuing.
- If the patient recovers renal function (defined as patient taken off dialysis because the physician evaluates that patient has enough renal function to live independently), the diagnosis of ESKD will be rescinded.
- If the patient is known to have received dialysis for >30 days but <90 days, and not known to recover, ESKD will be confirmed. The reason for the unavailability of information beyond 30 days should be clearly documented by the investigator.
- If dialysis was initiated, but not continued for 30 days due to death, futility of therapy, or transplantation, the patient will be considered to have reached ESKD. In this situation, the reason for discontinuation of dialysis should be clearly documented by the investigator.

4. Date of ESKD

- If an event is adjudicated as ESKD due to kidney transplantation, the date of the transplantation will be the date of the event if transplantation was the first form of RRT given.
- If an event is adjudicated as ESKD due to initiation of dialysis, the date when dialysis was initiated will be the date of the event.

- In cases where dialysis is unavailable, or not administered, the date of ESKD will be when eGFR falls below 15 mL/min/1.73 m^2. If a confirmatory central laboratory value cannot be collected due to death, and there is no evidence of acute kidney injury, the date of the event will be the date in which eGFR falls below 15 mL/min/1.73 m^2. If local and central laboratory tests are collected on the same day, the central laboratory value overrules the local laboratory value. Information around the presence or absence of symptoms of uremia will also be collected for all patients meeting the ESKD endpoint; however, this will not affect the final adjudication decision, which will be based on the primary definition of ESKD as described in Sections 1 to 4 above.
- Symptomatic Uremia: Symptomatic uremia is diagnosed in the presence of the uremic syndrome, which is a constellation of signs and symptom involving several different systems, including:
    - General: Pruritus, dry skin, fatigue, anhedonia;
    - Metabolic: Deterioration in nutritional status, recent significant weight loss, electrolyte or acid-base disturbances (severe hyperkalemia or severe acidosis);
    - Gastrointestinal: Nausea, vomiting;
    - Neurological: Neuropathy, encephalopathy, psychiatric disturbances, seizures;
    - Volume overload, including difficult-to-control or accelerated hypertension;
    - Bleeding diathesis not attributable to other causes;
    - Pleuritis or pericarditis of uremic origin or other;
    - Severe hyperparathyroidism.
- Advanced Asymptomatic Uremia: The initiation of dialysis is generally performed when eGFR declines to <15 mL/min/1.73 m^2 on a subjective basis in anticipation of development of uremic symptoms. If no symptoms are documented for initiation of dialysis, asymptomatic uremia will be diagnosed. In the minority of patients who exhibit no symptoms even at very low eGFR

values (such as <8 mL/min/1.73 m^2), however are initiated RRT in the view of benefits of therapy, the diagnosis will be of advanced asymptomatic uremia.

Doubling of Serum Creatinine

Doubling of serum creatinine will be defined as a ≥2-fold increase in serum creatinine from the baseline assessment that persists for ≥30 days and is not thought to be due to reversible cause.

The baseline serum creatinine, as determined by averaging the 2 values closest to randomization, will be used to compare subsequent values and determine if doubling of serum creatinine has occurred.

Both central serum creatinine values and local laboratory values may be used to calculate the increase in serum creatinine. The investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. The event will be adjudicated positively once the initial doubling of serum creatinine via local or central laboratory results has been confirmed by the central laboratory at ≥30 days, and if the process is determined to be irreversible.

If a confirmatory central laboratory value cannot be collected due to death or dialyses and there is no evidence of acute kidney injury, the event will be adjudicated positively.

The date of the event will be the date on which the creatinine first doubled. If central and local laboratory tests are collected on the same day, the central laboratory value overrules the local laboratory value.

Death

All deaths will be reviewed by the adjudicators to determine the cause of death, which will be classified as either renal death, cardiovascular (CV) death, or non-CV death.

Renal Death

Renal death refers to deaths in patients who have reached ESKD who die prior to initiating RRT and no other cause of death is adjudicated. This may occur in the situations where either the patient refuses RRT or both the physician and the patient consider RRT futile and believe that the patients' current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. This may also occur in situations where dialysis is not available. These events are classified as renal death when death occurs following refusal of dialysis AND no other cause of death is adjudicated. When a more specific cause of death is adjudicated, such as sepsis or trauma, the more specific cause will be designated as the primary cause of death.

CV Death

CV death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

1. Death due to acute MI refers to a death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after an MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note

that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days of the MI, it will be considered a death due to MI.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden cardiac death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

   - Death witnessed and occurring without new or worsening symptoms;
   - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI;
   - Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review);
   - Death after unsuccessful resuscitation from cardiac arrest;
   - Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology; or

- Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

Unless additional information suggests an alternate specific cause of death (e.g., death due to other CV causes), if a patient is seen alive ≤24 hours of being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. Death due to HF refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology. Deaths due to HF can have various etiologies, including single or recurrent MI, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

4. Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to CV procedures refers to death caused by the immediate complications of a cardiac procedure.

6. Death due to CV hemorrhage refers to death related to hemorrhage such as a nonstroke intracranial hemorrhage, nonprocedural or nontraumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death due to other CV causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Definition of Non-CV Death

Non-CV death is defined as any death that is not thought to be due to a CV cause. The following is a suggested list of non-CV causes of death:

- Pulmonary;
- Gastrointestinal;
- Hepatobiliary;
- Pancreatic;
- Infection (includes sepsis);
- Noninfectious (e.g., systemic inflammatory response syndrome [SIRS]);
- Hemorrhage that is neither CV bleeding nor a stroke;
- Non-CV procedure or surgery;
- Trauma;
- Suicide;
- Nonprescription drug reaction or overdose;
- Prescription drug reaction or overdose;
- Neurological (non-CV);
- Malignancy; or
- Other non-CV, specify:

Definition of Undetermined Cause of Death

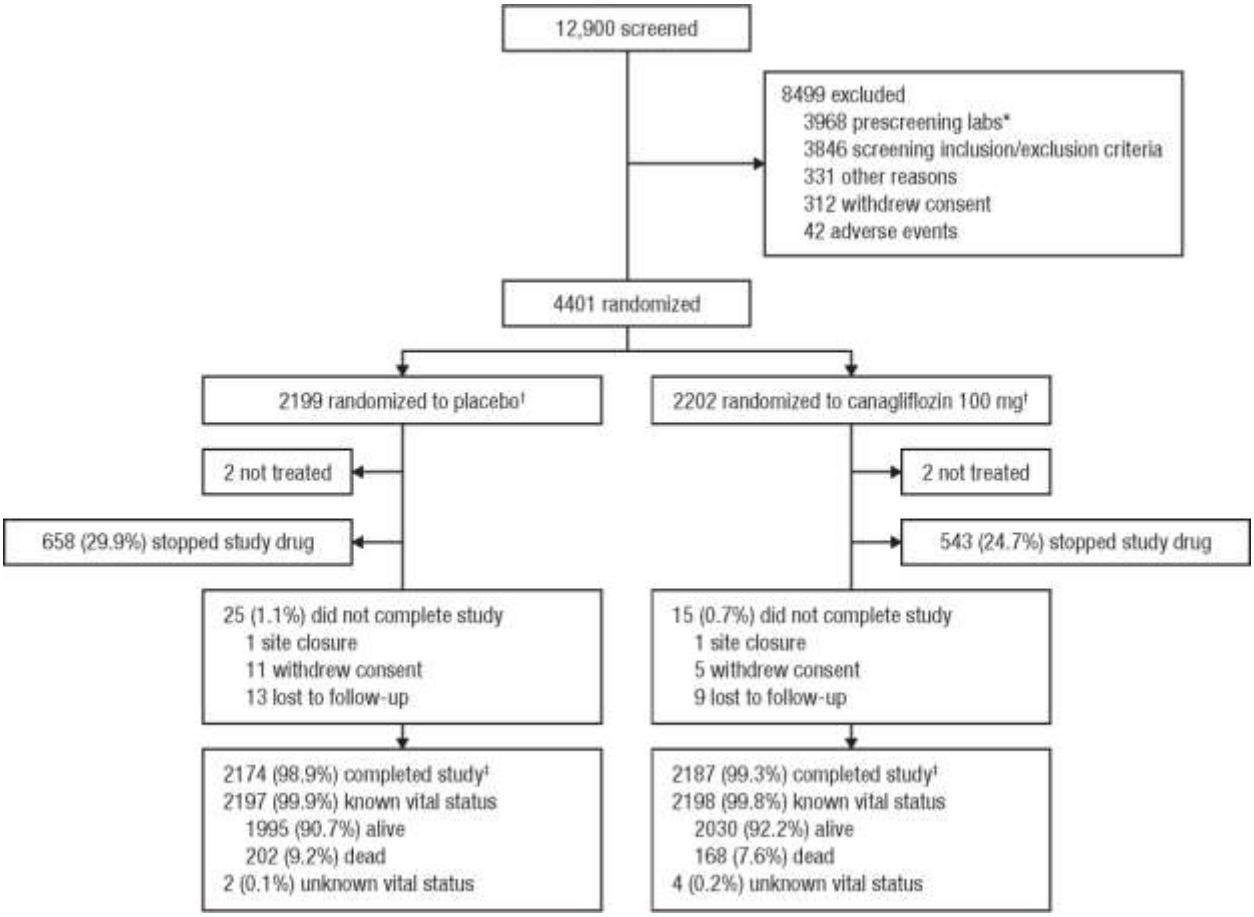
Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail

to assign the cause of death. This category of death should be avoided as much as possible and should only apply to a minimal number of patients.

Estimated Glomerular Filtration Rate (eGFR) Slope Analyses

The on-treatment eGFR slope for the acute and chronic phase was analyzed using a two-slope model with a knot at week 3, including the fixed effects of treatment, baseline eGFR, screening eGFR strata, continuous time, time spline (one knot at Week 3), with two-way interactions of treatment by time, treatment by time spline, eGFR strata by time, eGFR strata by time spline, and the random effects of intercept, time and time spline. Total slope at week 130 was calculated as a linear contrast of the acute and chronic phases based on the two-slope model.

Figure S1. Study flow diagram.

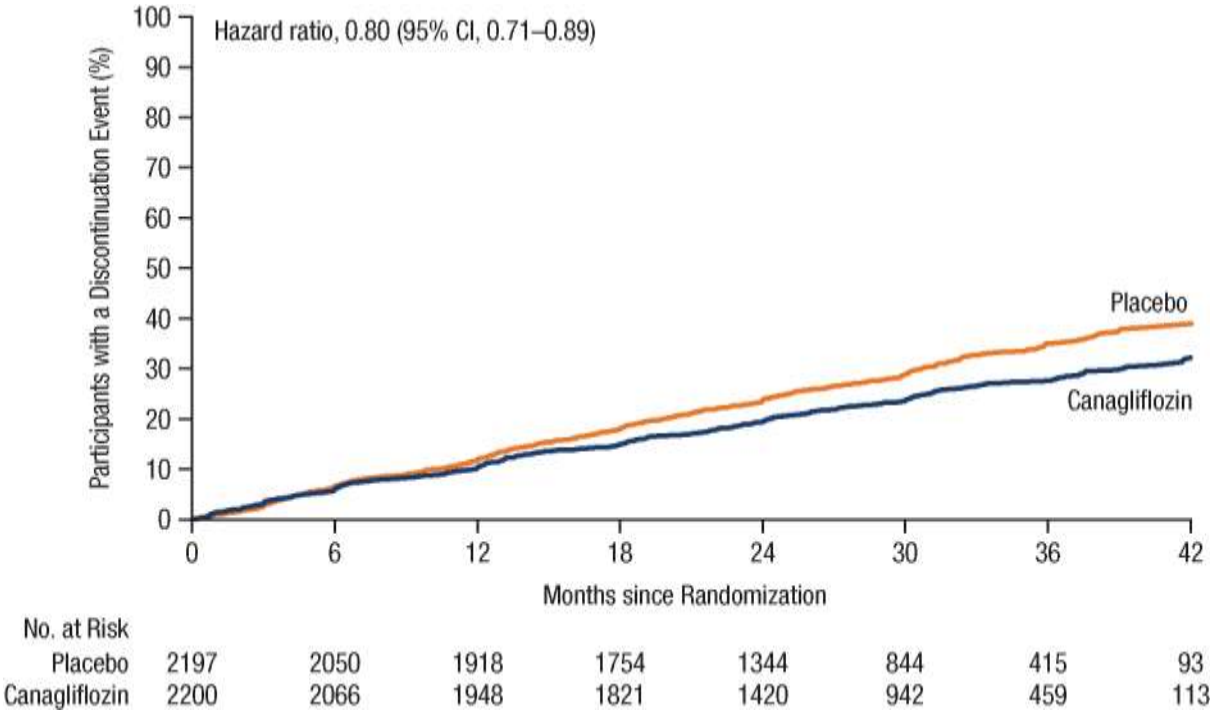


*Includes failed prescreening of estimated glomerular filtration rate and/or proteinuria/albuminuria.

†All randomized participants were in the intent-to-treat population; participants who did not receive study drug were excluded from the on-treatment and on-study analysis sets.

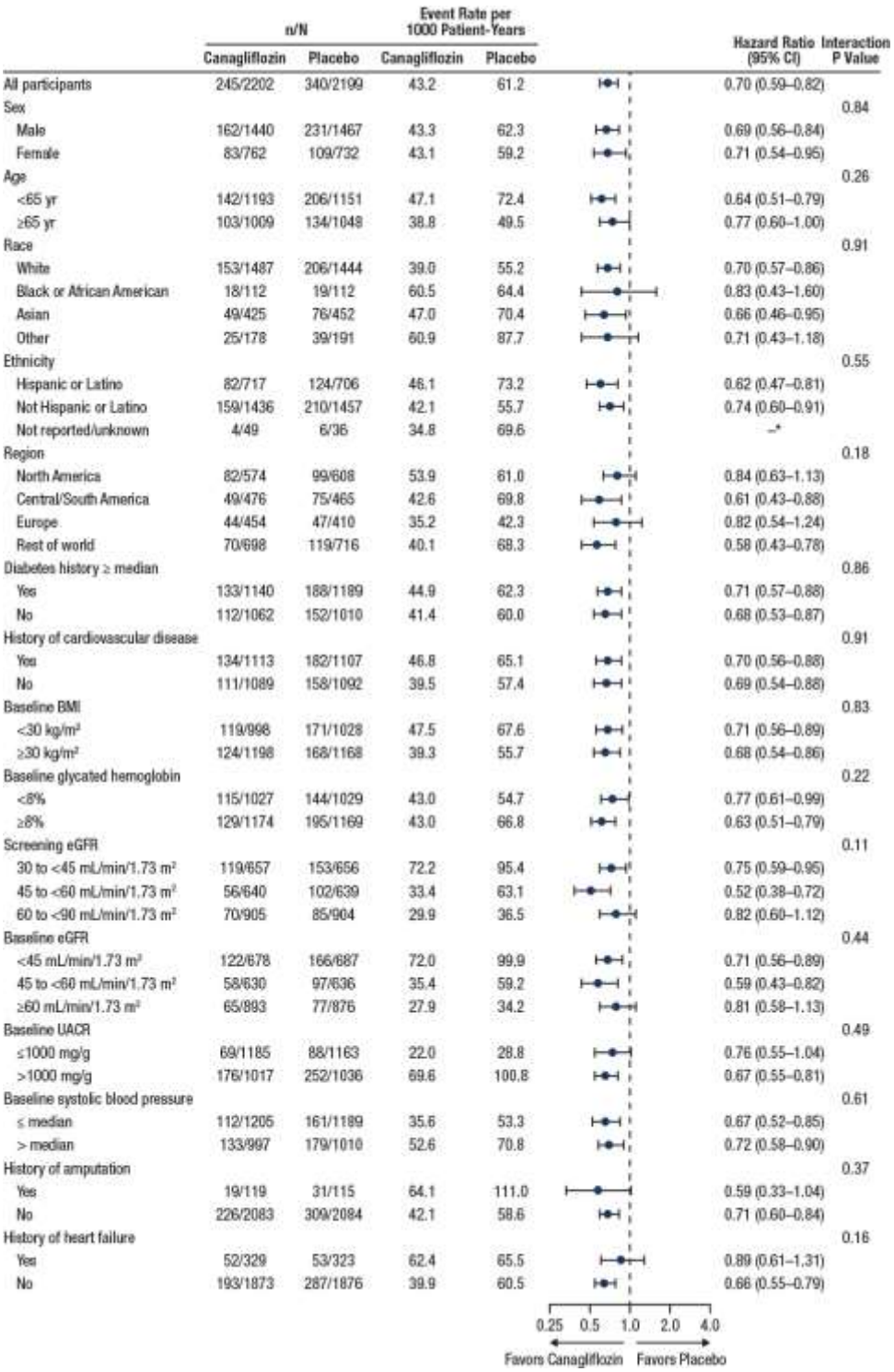
‡Defined as having been followed until a time point between the announcement of the end of study and the end of study, or if the subject had died prior.

Figure S2. Discontinuation from randomized treatment in CREDENCE.



No. at Risk								
Placebo	2197	2050	1918	1754	1344	844	415	93
Canagliflozin	2200	2066	1948	1821	1420	942	459	113

Figure S3. Subgroup analysis of the primary composite endpoint.*



	n/N		Event Rate per 1000 Patient-Years		Hazard Ratio (95% CI)	Interaction P Value
	Canagliflozin	Placebo	Canagliflozin	Placebo		
All participants	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	
Sex						0.84
Male	162/1440	231/1467	43.3	62.3	0.69 (0.56–0.84)	
Female	83/762	109/732	43.1	59.2	0.71 (0.54–0.95)	
Age						0.26
<65 yr	142/1193	206/1151	47.1	72.4	0.64 (0.51–0.79)	
≥65 yr	103/1009	134/1048	38.8	49.5	0.77 (0.60–1.00)	
Race						0.91
White	153/1487	206/1444	39.0	55.2	0.70 (0.57–0.86)	
Black or African American	18/112	19/112	60.5	64.4	0.83 (0.43–1.60)	
Asian	49/425	76/452	47.0	70.4	0.66 (0.46–0.95)	
Other	25/178	39/191	60.9	87.7	0.71 (0.43–1.18)	
Ethnicity						0.55
Hispanic or Latino	82/717	124/706	46.1	73.2	0.62 (0.47–0.81)	
Not Hispanic or Latino	159/1436	210/1457	42.1	55.7	0.74 (0.60–0.91)	
Not reported/unknown	4/49	6/36	34.8	69.6	–*	
Region						0.18
North America	82/574	99/608	53.9	61.0	0.84 (0.63–1.13)	
Central/South America	49/476	75/465	42.6	69.8	0.61 (0.43–0.88)	
Europe	44/454	47/410	35.2	42.3	0.82 (0.54–1.24)	
Rest of world	70/698	119/716	40.1	68.3	0.58 (0.43–0.78)	
Diabetes history ≥ median						0.86
Yes	133/1140	188/1189	44.9	62.3	0.71 (0.57–0.88)	
No	112/1062	152/1010	41.4	60.0	0.68 (0.53–0.87)	
History of cardiovascular disease						0.91
Yes	134/1113	182/1107	46.8	65.1	0.70 (0.56–0.88)	
No	111/1089	158/1092	39.5	57.4	0.69 (0.54–0.88)	
Baseline BMI						0.83
<30 kg/m²	119/998	171/1028	47.5	67.6	0.71 (0.56–0.89)	
≥30 kg/m²	124/1198	168/1168	39.3	55.7	0.68 (0.54–0.86)	
Baseline glycated hemoglobin						0.22
<8%	115/1027	144/1029	43.0	54.7	0.77 (0.61–0.99)	
≥8%	129/1174	195/1169	43.0	66.8	0.63 (0.51–0.79)	
Screening eGFR						0.11
30 to <45 mL/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 mL/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 mL/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline eGFR						0.44
<45 mL/min/1.73 m²	122/678	166/687	72.0	99.9	0.71 (0.56–0.89)	
45 to <60 mL/min/1.73 m²	58/630	97/636	35.4	59.2	0.59 (0.43–0.82)	
≥60 mL/min/1.73 m²	65/893	77/876	27.9	34.2	0.81 (0.58–1.13)	
Baseline UACR						0.49
≤1000 mg/g	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000 mg/g	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Baseline systolic blood pressure						0.61
≤ median	112/1205	161/1189	35.6	53.3	0.67 (0.52–0.85)	
> median	133/997	179/1010	52.6	70.8	0.72 (0.58–0.90)	
History of amputation						0.37
Yes	19/119	31/115	64.1	111.0	0.59 (0.33–1.04)	
No	226/2083	309/2084	42.1	58.6	0.71 (0.60–0.84)	
History of heart failure						0.16
Yes	52/329	53/323	62.4	65.5	0.89 (0.61–1.31)	
No	193/1873	287/1876	39.9	60.5	0.66 (0.55–0.79)	

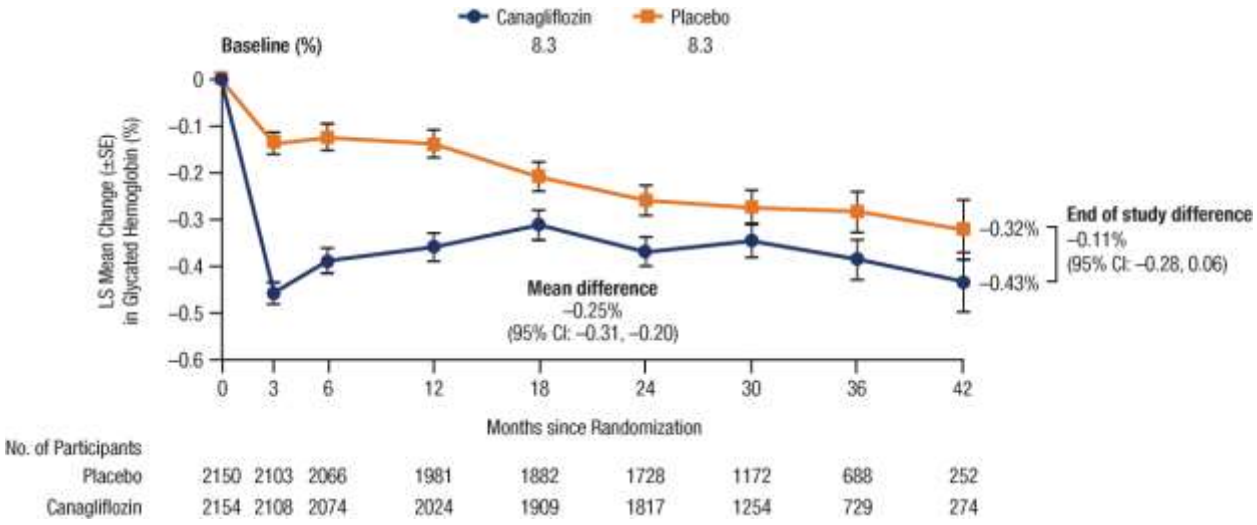
CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio.

*Subgroup analysis was conducted when the total number of events was greater than 10 for both treatment groups (canagliflozin group and placebo) and there was at least 1 event in both groups.

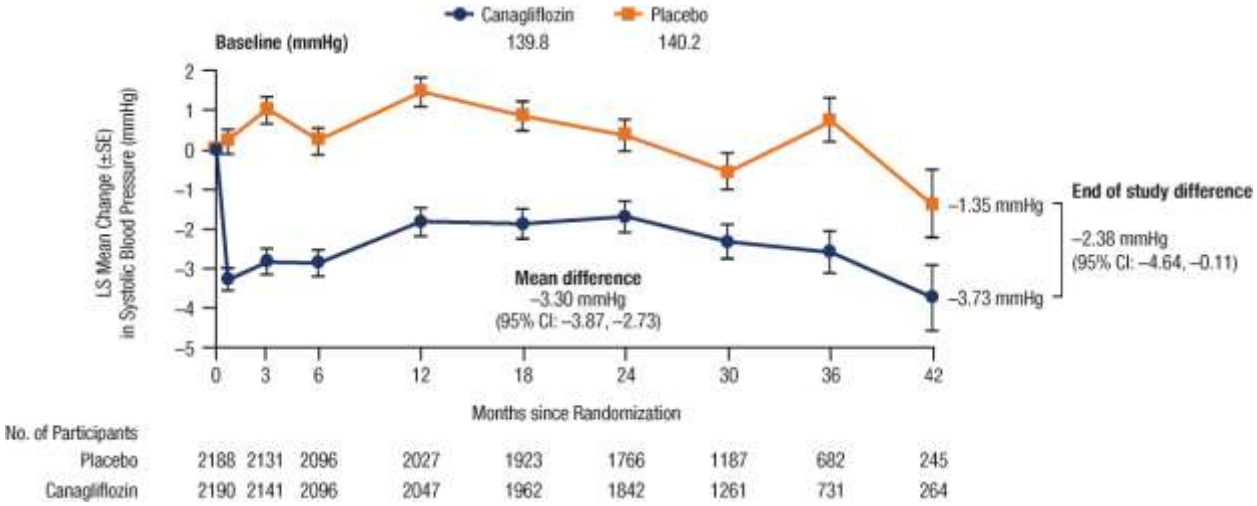
P values are based on the test of subgroup by treatment interaction in a stratified Cox proportional hazard model, without adjustment for multiple testing.

Figure S4. Effects on intermediate outcomes (ITT).*

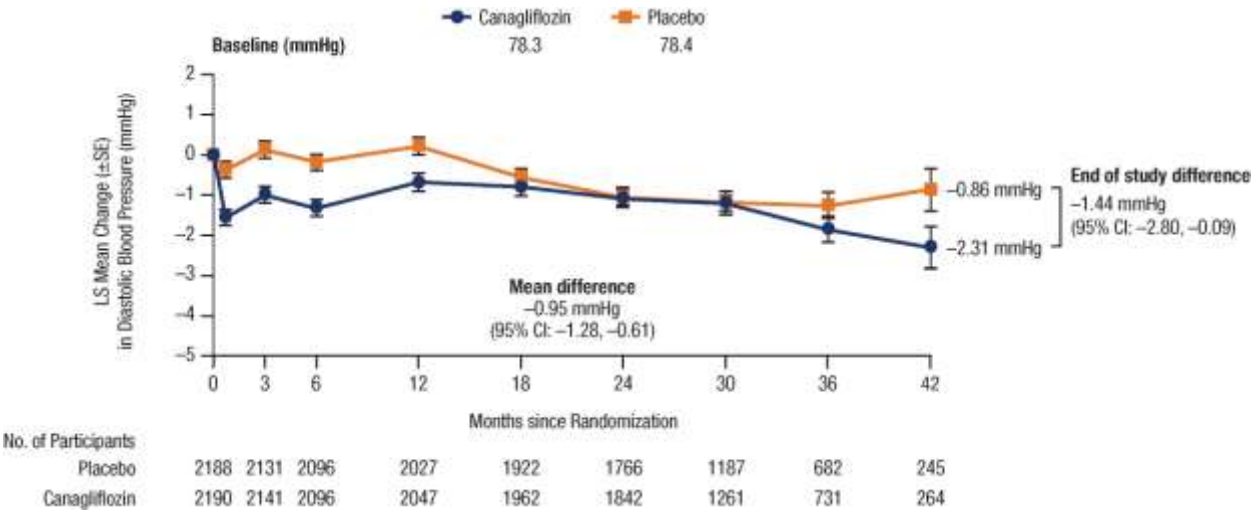
A) Glycated hemoglobin



B) Systolic blood pressure

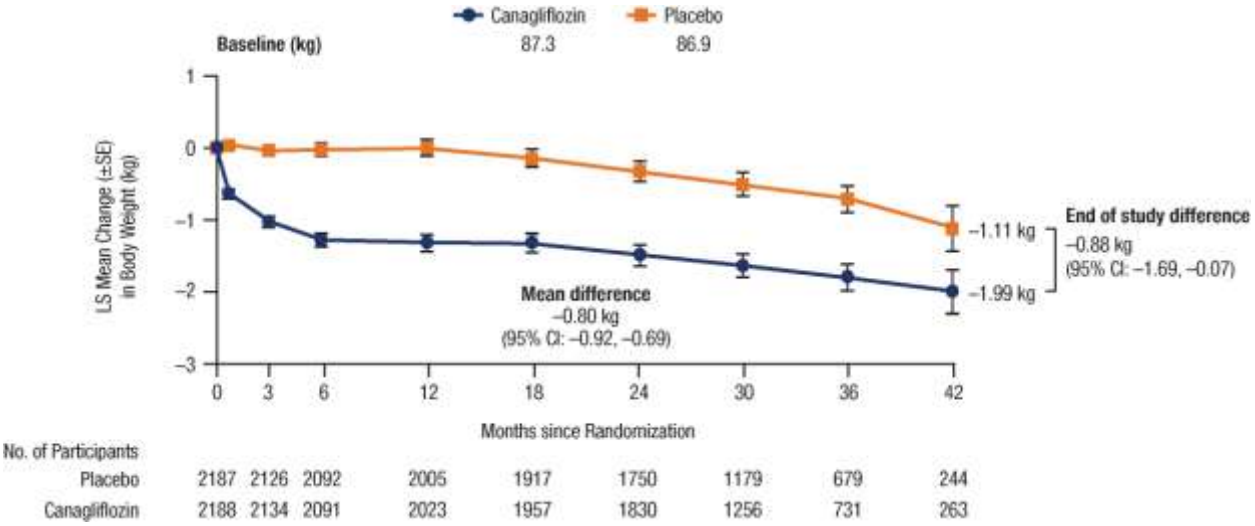


C) Diastolic blood pressure



No. of Participants									
Placebo	2188	2131	2096	2027	1922	1766	1187	682	245
Canagliflozin	2190	2141	2096	2047	1962	1842	1261	731	264

D) Body weight



No. of Participants									
Placebo	2187	2126	2092	2005	1917	1750	1179	679	244
Canagliflozin	2188	2134	2091	2023	1957	1830	1256	731	263

ITT, intention-to-treat; LS, least square; SE, standard error.

*Mean differences shown are based on the on-treatment analysis.

Table S1. Detailed Baseline Demographic and Disease Characteristics by Randomized Groups*

Characteristic	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (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—no. (%)			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black or African American	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)
Region—no. (%)			
North America	574 (26.1)	608 (27.6)	1182 (26.9)
Central/South America	476 (21.6)	465 (21.1)	941 (21.4)
Europe	454 (20.6)	410 (18.6)	864 (19.6)
Rest of the world	698 (31.7)	716 (32.6)	1414 (32.1)
Current smoker—no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
History of hypertension—no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
History of 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
Drug therapy—no. (%)			
Insulin	1452 (65.9)	1432 (65.1)	2884 (65.5)
Sulfonylurea	612 (27.8)	656 (29.8)	1268 (28.8)
Biguanides	1276 (57.9)	1269 (57.7)	2545 (57.8)
GLP-1 receptor agonist	89 (4.0)	94 (4.3)	183 (4.2)

DPP-4 inhibitor	378 (17.2)	373 (17.0)	751 (17.1)
Statin	1538 (69.8)	1498 (68.1)	3036 (69.0)
Antithrombotic‡	1341 (60.9)	1283 (58.3)	2624 (59.6)
RAAS inhibitor	2201 (>99.9)	2194 (99.8)	4395 (99.9)
Beta blocker	883 (40.1)	887 (40.3)	1770 (40.2)
Diuretic	1026 (46.6)	1031 (46.9)	2057 (46.7)
Microvascular disease history—no. (%)			
Retinopathy	935 (42.5)	947 (43.1)	1882 (42.8)
Nephropathy	2202 (100)	2199 (100)	4401 (100)
Neuropathy	1077 (48.9)	1070 (48.7)	2147 (48.8)
Atherosclerotic vascular disease history—no. (%)‖			
Coronary	653 (29.7)	660 (30.0)	1313 (29.8)
Cerebrovascular	342 (15.5)	358 (16.3)	700 (15.9)
Peripheral	531 (24.1)	515 (23.4)	1046 (23.8)
Cardiovascular disease history—no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
History of amputation—no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body mass index—kg/m^2	31.4 ± 6.2	31.3 ± 6.2	31.3 ± 6.2
Systolic blood pressure—mmHg	139.8 ± 15.6	140.2 ± 15.6	140.0 ± 15.6
Diastolic blood pressure—mmHg	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
Cholesterol—mg/dL (mmol/L)			
Total	180.9 ± 51.3 (4.7 ± 1.3)	179.8 ± 49.7 (4.6 ± 1.3)	180.4 ± 50.5 (4.7 ± 1.3)
Triglycerides	198.8 ± 140.5	197.0 ± 148.1	197.9 ± 144.4

	(2.2 ± 1.6)	(2.2 ± 1.7)	(2.2 ± 1.6)
HDL cholesterol	44.5 ± 13.8	44.5 ± 13.1	44.5 ± 13.4
	(1.2 ± 0.4)	(1.2 ± 0.3)	(1.2 ± 0.3)
LDL cholesterol	97.0 ± 42.7	95.9 ± 39.9	96.4 ± 41.3
	(2.5 ± 1.1)	(2.5 ± 1.0)	(2.5 ± 1.1)
Ratio of LDL to HDL	2.3 ± 1.1	2.3 ± 1.0	2.3 ± 1.1
eGFR—mL/min/1.73 m^2[¶]	56.3 ± 18.2	56.0 ± 18.3	56.2 ± 18.2
eGFR ≥90 mL/min/1.73 m^2—no. (%)	105 (4.8)	106 (4.8)	211 (4.8)
eGFR ≥60 to <90 mL/min/1.73 m^2—no. (%)	788 (35.8)	770 (35.0)	1558 (35.4)
eGFR ≥45 to <60 mL/min/1.73 m^2—no. (%)	630 (28.6)	636 (28.9)	1266 (28.8)
eGFR ≥30 to <45 mL/min/1.73 m^2—no. (%)	594 (27.0)	597 (27.1)	1191 (27.1)
eGFR ≥15 to <30 mL/min/1.73 m^2—no. (%)	83 (3.8)	89 (4.0)	172 (3.9)
eGFR <15 mL/min/1.73 m^2—no. (%)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Median urine albumin:creatinine ratio (IQR)—mg/g	923.0	931.0	927.0
	(459-1794)	(473-1868)	(463-1833)
Normoalbuminuria—no. (%)[#]	16 (0.7)	15 (0.7)	31 (0.7)
Microalbuminuria—no. (%)[#]	251 (11.4)	245 (11.1)	496 (11.3)
Nephrotic range macroalbuminuria—no. (%)**	233 (10.6)	270 (12.3)	503 (11.4)
Non-nephrotic range macroalbuminuria—no. (%)[††]	1702 (77.3)	1669 (75.9)	3371 (76.6)

SD, standard deviation; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

*Plus–minus values are means ±SD.

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

[‡]Includes anticoagulation and antiplatelet agents, including aspirin.

[||]Some participants had ≥1 type of atherosclerotic disease.

[¶]Values for baseline eGFR categories calculated based on N of 2201 for canagliflozin, 2199 for placebo, and 4400 for the total population.

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

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

[††]Non-nephrotic range macroalbuminuria is defined as urine albumin:creatinine ratio >300 mg/g and ≤3000 mg/g.

Table S2. Baseline Use and New Initiation of Concomitant Antihyperglycemic Therapy (On Treatment)

	Baseline use			New Initiation		
Participants, n (%)	**Canagliflozin (n = 2200)**	**Placebo (n = 2197)**	**Total (N = 4397)**	**Canagliflozin (n = 2200)**	**Placebo (n = 2197)**	**Total (N = 4397)**
Alpha glucosidase inhibitors	66 (3.0)	73 (3.3)	139 (3.2)	10 (0.5)	16 (0.7)	26 (0.6)
Biguanides	1275 (58.0)	1268 (57.7)	2543 (57.8)	55 (2.5)	80 (3.6)	135 (3.1)
DPP-4 inhibitors	378 (17.2)	373 (17.0)	751 (17.1)	92 (4.2)	105 (4.8)	197 (4.5)
GLP-1 receptor agonists	89 (4.0)	94 (4.3)	183 (4.2)	54 (2.5)	57 (2.6)	111 (2.5)
Insulin	1451 (66.0)	1431 (65.1)	2882 (65.5)	98 (4.5)	132 (6.0)	230 (5.2)
Sulfonylurea	611 (27.8)	656 (29.9)	1267 (28.8)	61 (2.8)	95 (4.3)	156 (3.5)
Thiazolidinediones	71 (3.2)	65 (3.0)	136 (3.1)	21 (1.0)	30 (1.4)	51 (1.2)

Table S3. Reasons for Premature Discontinuation of Randomized Treatment

Participants, n (%)	Canagliflozin (n = 2200)	Placebo (n = 2197)
Any reason	543 (24.7)	658 (29.9)
Adverse event*	263 (12.0)	285 (13.0)
Personal reasons	164 (7.5)	199 (9.1)
Poor compliance	16 (0.7)	18 (0.8)
Safety or tolerability	13 (0.6)	19 (0.9)
Dialysis or renal transplant	18 (0.8)	28 (1.3)
Disallowed therapy	2 (0.1)	17 (0.8)
Protocol violation	3 (0.1)	3 (0.1)
Site closure	3 (0.1)	3 (0.1)
Other	61 (2.8)	86 (3.9)

*137 participants prematurely discontinued treatment due to an adverse event with a fatal outcome.

Table S4. Summary of Safety Results*

	n/N		Event rate per 1000 patient-years		
	Canagliflozin	**Placebo**	**Canagliflozin**	**Placebo**	**Hazard ratio (95% CI)†**
All adverse events	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)
All serious adverse events	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)
Serious adverse events related to study drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)
Fracture‡	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)
Cancer					
Renal cell carcinoma‡	1/2200	5/2197	0.2	0.9	–†
Breast§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)
Bladder	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)
Acute pancreatitis‡	5/2200	2/2200	1.0	0.4	–†

Hyperkalemia[¶]	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)
Diabetic ketoacidosis[‡, #]	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)
Osmotic diuresis	51/2200	40/2197	10.0	8.2	1.25 (0.83–1.89)
Volume depletion	144/2200	115/2197	28.4	23.5	1.25 (0.97–1.59)
Hypoglycemia	225/2200	240/2197	44.3	48.9	0.92 (0.77–1.11)
Urinary tract infection	245/2200	221/2197	48.3	45.1	1.08 (0.90–1.29)
Genital mycotic infection					
Male	28/1439	3/1466	8.4	0.9	9.30 (2.83–30.60)
Female	22/761	10/731	12.6	6.1	2.10 (1.00–4.45)
Hypersensitivity/cutaneous reactions	23/2200	30/2197	4.5	6.1	0.75 (0.44–1.30)
Hepatic injury	28/2200	32/2197	5.5	6.5	0.86 (0.52–1.43)
Renal-related adverse events (including acute kidney injury)	290/2200	388/2197	57.1	79.1	0.71 (0.61–0.82)

Photosensitivity	1/2200	1/2197	0.2	0.2	–[†]
Venous thromboembolism	21/2200	16/2197	4.1	3.3	1.28 (0.67–2.45)

CI, confidence interval.

*The numbers for amputation and fracture were based on the on-study analysis set, while the other safety endpoints were based on the on-treatment analysis set.

[†]Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

[‡]The analyses for fracture, renal cell carcinoma, acute pancreatitis, and diabetic ketoacidosis and were based on confirmed and adjudicated results.

[§]Includes female participants only.

[¶]Adverse events of hyperkalemia were spontaneously reported by the investigator. The summary counts provided for the adverse event of hyperkalemia include the MedDRA preferred terms of “hyperkalemia” and “blood potassium increased.”

[#]All potential ketone-related events were adjudicated for diabetic ketoacidosis by an independent adjudication committee based on clinical presentation and predefined biochemical parameters.

Table S5. Summary of Adverse Events by Body System or Organ Class

Body system or organ class, n (%)	Canagliflozin (n = 2200)	Placebo (n = 2197)
All adverse events	1784 (81.1)	1860 (84.7)
Blood and lymphatic system disorders	120 (5.5)	200 (9.1)
Cardiac disorders	300 (13.6)	393 (17.9)
Congenital, familial and genetic disorders	9 (0.4)	6 (0.3)
Ear and labyrinth disorders	77 (3.5)	77 (3.5)
Endocrine disorders	57 (2.6)	55 (2.5)
Eye disorders	234 (10.6)	257 (11.7)
Gastrointestinal disorders	463 (21.0)	475 (21.6)
General disorders and administration site conditions	288 (13.1)	382 (17.4)
Hepatobiliary disorders	70 (3.2)	74 (3.4)
Immune system disorders	22 (1.0)	20 (0.9)
Infections and infestations	932 (42.4)	1016 (46.2)
Injury, poisoning and procedural complications	307 (14.0)	304 (13.8)
Investigations	343 (15.6)	451 (20.5)
Metabolism and nutrition disorders	604 (27.5)	690 (31.4)
Musculoskeletal and connective tissue disorders	443 (20.1)	468 (21.3)

Neoplasms benign, malignant and unspecified (including cysts and polyps)	132 (6.0)	122 (5.6)
Nervous system disorders	396 (18.0)	419 (19.1)
Pregnancy, puerperium and perinatal conditions	2 (0.1)	0
Product issues	2 (0.1)	4 (0.2)
Psychiatric disorders	93 (4.2)	112 (5.1)
Renal and urinary disorders	339 (15.4)	423 (19.3)
Reproductive system and breast disorders	101 (4.6)	92 (4.2)
Respiratory, thoracic and mediastinal disorders	263 (12.0)	310 (14.1)
Skin and subcutaneous tissue disorders	313 (14.2)	324 (14.7)
Social circumstances	1 (<0.1)	1 (<0.1)
Surgical and medical procedures	0	1 (<0.1)
Vascular disorders	365 (16.6)	387 (17.6)

Table S6. Baseline Characteristics of Participants With Diabetic Ketoacidosis Adverse Events

	Participants with Diabetic Ketoacidosis* (n = 12)	All Participants (n = 4401)
Background insulin treatment—no. (%)	11 (91.7)	2884 (65.5)
Background metformin treatment—no. (%)	4 (33.3)	2545 (57.8)
Duration of diabetes—yr	23.8	15.8
Glycated hemoglobin—%	8.9	8.3
Glycated hemoglobin >10%—no. (%)	3 (25.0)	450 (10.2)
eGFR—mL/min/1.73 m^2	54.0	56.2
Screening eGFR ≥30 to <45 mL/min/1.73 m^2—no. (%)	7 (58.3)	1313 (29.8)
History of diabetic ketoacidosis	2 (16.7)	4 (0.1)

*****Precipitating factors (primarily recent or concurrent illness, recent reduction in insulin dose, or drugs affecting carbohydrate metabolism) were identified by the adjudication committee for 83% of cases (10 of 12 events) in the canagliflozin group and 100% (1 event) in the placebo group. With the exception of 1 case, concomitant blood glucose levels were >250 mg/dL (>13.9 mmol/L).