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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

BACKGROUND

METHODS

RESULTS

CONCLUSIONS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South Wales Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at vperkovic@georgeinstitute.org.au.

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

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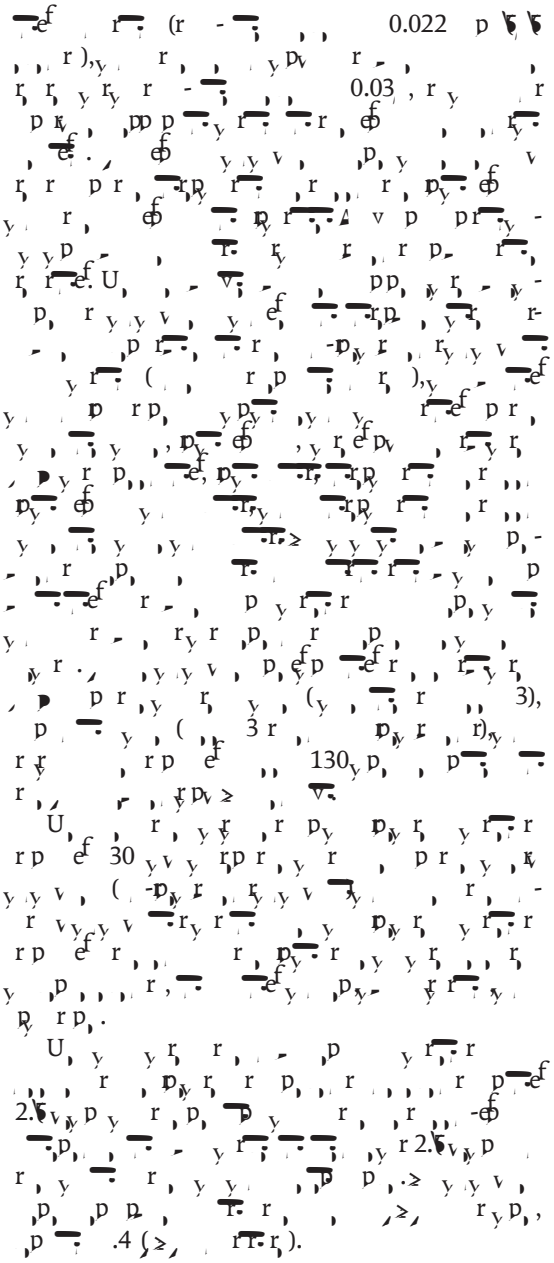
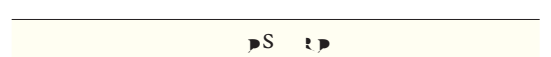
A Quick Take is available at NEJM.org

TRIAL DESIGN AND OVERSIGHT

PATIENTS

TRIAL PROCEDURES





PATIENTS

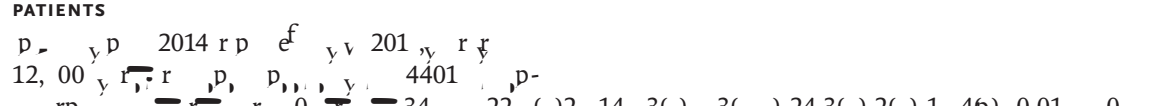


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

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.

SECONDARY AND EXPLORATORY OUTCOMES

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

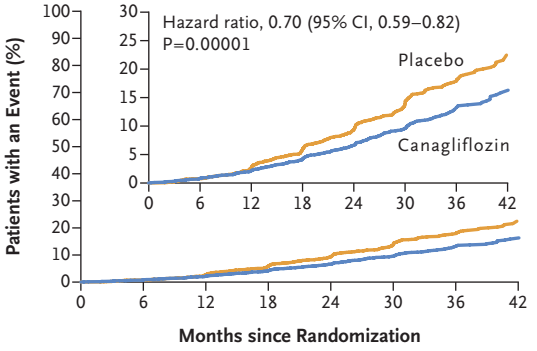
Acute pancreatitis	5/2200	2/2197	1.0	0.4	NA	NA
Hyperkalemia¶	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)	NA
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)	NA
Diabetic ketoacidosis‖	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA

* 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

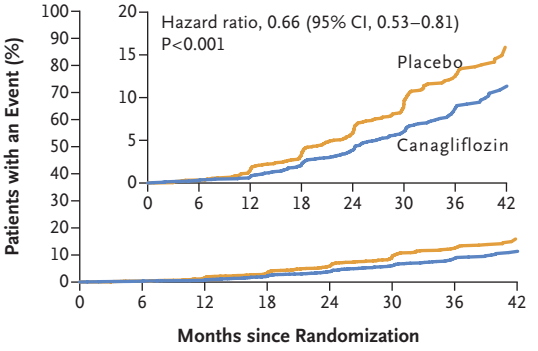
EFFECT ON INTERMEDIATE OUTCOMES

A Primary Composite Outcome



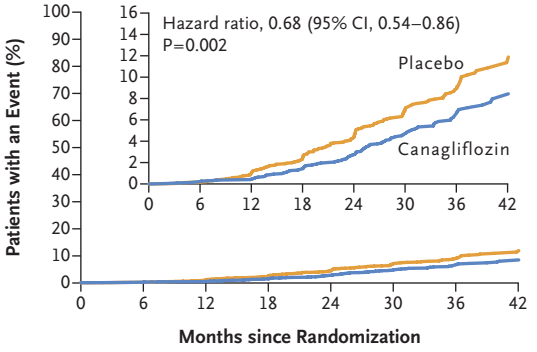
No. at Risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

B Renal-Specific Composite Outcome



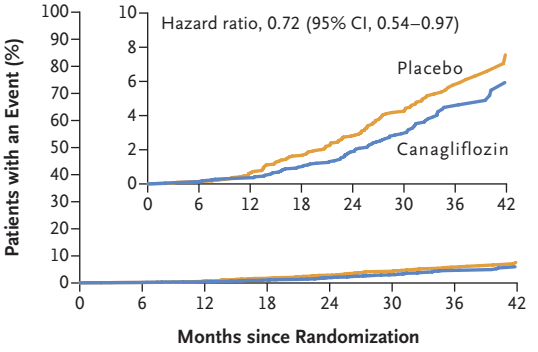
No. at Risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

C End-Stage Kidney Disease



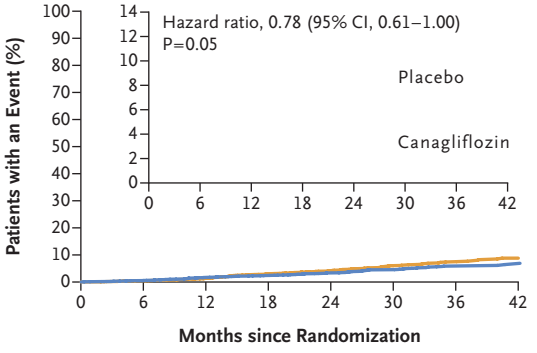
No. at Risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

D Dialysis, Kidney Transplantation, or Renal Death



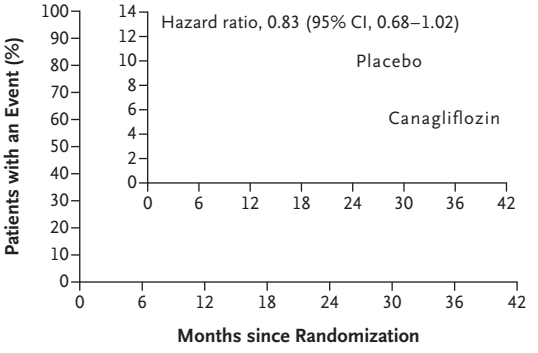
No. at Risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

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.

p y p 2. 4 p r p 1. 3 2
p v y p (5% , 2.3 r 3.11).

PROJECTED ESTIMATED EFFECTS

M r p p y y r r r y r
e 1000 y r r p p p y r p 2.5
v y p r p p y r r r -
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p y r p p y p y p y p y r
p 4 p y r r r y y -
e f e f r y r y e f (-
p r p y r , 22 5% , 15 r 3),
e 3 p r p y r -
r e f v y e f r p -
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r (, 43 5% , 2 r 121).
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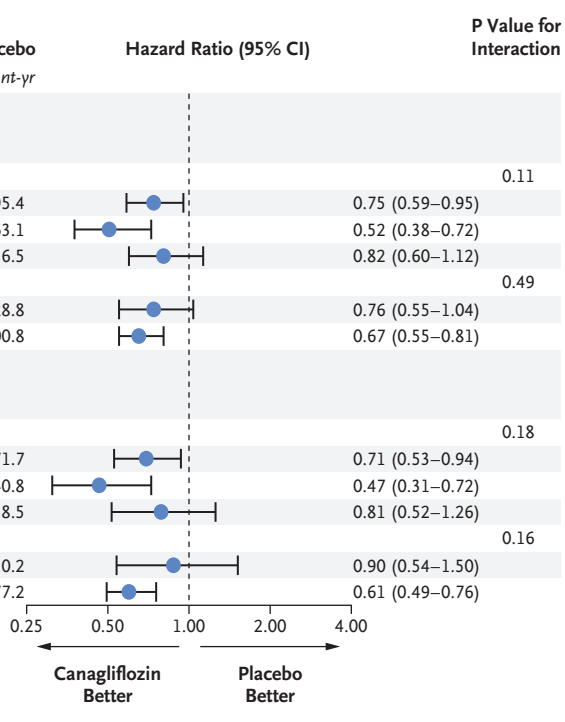

Figure 2. Subgroup Analysis, According to Estimated Glomerular Filtration Rate (GFR) at Screening and Albuminuria at Baseline.

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.

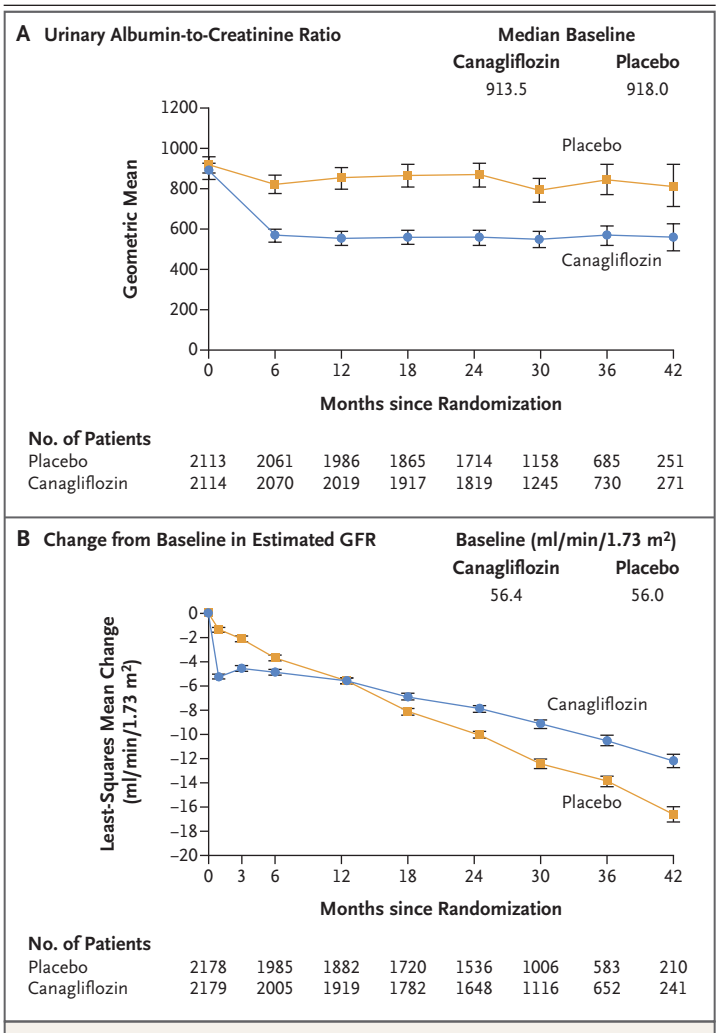

Figure 3. Effects on Albuminuria and Estimated GFR.

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 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.

APPENDIX

REFERENCES

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