University of Groningen

Effects of Canagliflozin in Patients with Baseline eGFR

Bakris, George; Oshima, Megumi; Mahaffey, Kenneth W; Agarwal, Rajiv; Cannon, Christopher P; Capuano, George; Charytan, David M; de Zeeuw, Dick; Edwards, Robert; Greene, Tom

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Link to publication in University of Groningen/UMCG research database

Effects of Canagliflozin in Patients with Baseline eGFR <30 ml/min per 1.73 m²
Subgroup Analysis of the Randomized CREDENCE Trial

George Bakris,[1] Megumi Oshima ,[2,3] Kenneth W. Mahaffey,[4] Rajiv Agarwal,[5] Christopher P. Cannon,[6] George Capuano,[7] David M. Charytan ,[8,9] Dick de Zeeuw,[10] Robert Edwards,[7] Tom Greene,[11] Hiddo J.L. Heerspink,[2,10] Adeera Levin,[12] Bruce Neal,[2,13,14] Richard Oh,[7] Carol Pollock,[15] Norman Rosenthal,[7] David C. Wheeler,[2,16] Hong Zhang,[17] Bernard Zinman,[18] Meg J. Jardine,[2,19] and Vlado Perkovic[2,20]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence:
Dr. George L. Bakris, ASH Comprehensive Hypertension Center, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Chicago Medicine, 5841 S Maryland Avenue, Chicago, IL 60637. Email: gbakris@gmail.com

Abstract

Background and objectives The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated that the sodium glucose cotransporter 2 (SGLT2) inhibitor canagliflozin reduced the risk of kidney failure and cardiovascular events in participants with type 2 diabetes mellitus and CKD. Little is known about the use of SGLT2 inhibitors in patients with eGFR <30 ml/min per 1.73 m². The participants in the CREDENCE study had type 2 diabetes mellitus, a urinary albumin-creatinine ratio >300–5000 mg/g, and an eGFR of 30 to <90 ml/min per 1.73 m² at screening. This *post hoc* analysis evaluated participants with eGFR <30 ml/min per 1.73 m² at randomization.

Design, setting, participants, & measurements Effects of eGFR slope through week 130 were analyzed using a piecewise, linear, mixed-effects model. Efficacy was analyzed in the intention-to-treat population, on the basis of Cox proportional hazard models, and safety was analyzed in the on-treatment population. At randomization (an average of 29 days after screening), 174 of 4401 (4%) participants had an eGFR <30 ml/min per 1.73 m² (mean [SD] eGFR, 26 [3] ml/min per 1.73 m²).

Results From weeks 3 to 130, there was a 66% difference in the mean rate of eGFR decline with canagliflozin versus placebo (mean slopes, −1.30 versus −3.83 ml/min per 1.73 m² per year; difference, −2.54 ml/min per 1.73 m² per year; 95% confidence interval [CI], 0.90 to 4.17). Effects of canagliflozin on kidney, cardiovascular, and mortality outcomes were consistent for those with eGFR <30 and ≥30 ml/min per 1.73 m² (all *P* interaction >0.20). The estimate for kidney failure in participants with eGFR <30 ml/min per 1.73 m² (hazard ratio, 0.67; 95% CI, 0.35 to 1.27) was similar to those with eGFR ≥30 ml/min per 1.73 m² (hazard ratio, 0.70; 95% CI, 0.54 to 0.91; *P* interaction=0.80). There was no imbalance in the rate of kidney-related adverse events or AKI associated with canagliflozin between participants with eGFR <30 and ≥30 ml/min per 1.73 m² (all *P* interaction >0.12).

Conclusions This *post hoc* analysis suggests canagliflozin slowed progression of kidney disease, without increasing AKI, even in participants with eGFR <30 ml/min per 1.73 m².

Introduction

Diabetes is the leading cause of kidney failure; approximately one in four adults with diabetes will develop persistent albuminuria and/or persistent declines in eGFR (1). Despite the risk of kidney failure in people with type 2 diabetes, treatment options to slow nephropathy progression are limited (2,3). Sodium glucose cotransporter 2 (SGLT2) inhibitors, which were originally developed to help control blood glucose levels in people with type 2 diabetes, have been shown to reduce the risk of cardiovascular events, including major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death) and hospitalization for heart failure, in patients with type 2 diabetes and high cardiovascular risk in

cardiovascular outcomes trials (4). Results from these trials also suggested SGLT2 inhibition slows progression to kidney failure, but the low risk of kidney disease of these study cohorts led to a small number of kidney-related events across trials (4). Until recently, there were limited data on the use of SGLT2 inhibitors in patients with compromised kidney function, and there were few treatment options for this patient population with low eGFR and high risk of developing kidney failure.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study was a dedicated kidney outcomes trial that demonstrated that the SGLT2 inhibitor canagliflozin significantly reduces the risk of

kidney failure and cardiovascular events in participants with type 2 diabetes and CKD (5,6). On the basis of data from the CREDENCE trial, the US Food and Drug Administration approved canagliflozin for reducing the risk of kidney failure, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria (7). The US prescribing information for canagliflozin was also updated to allow continuation of 100 mg canagliflozin in patients already receiving therapy whose eGFR falls below 30 ml/min per 1.73 m² with a urinary albumin-creatinine ratio (UACR) >300 mg/g until initiation of dialysis or kidney transplantation, reflecting the form of the CREDENCE trial intervention (7,8). Despite this, the potential kidney and cardiovascular benefits of canagliflozin in patients with advanced CKD (eGFR <30 ml/min per 1.73 m²) have not been reported. This article describes the efficacy and safety of canagliflozin in a *post hoc* subgroup analysis of CREDENCE trial participants with eGFR <30 ml/min per 1.73 m² at randomization.

Materials and Methods

Study Design

CREDENCE (ClinicalTrials.gov identifier, NCT02065791) was a randomized, double-blind, placebo-controlled, multicenter, international trial, the details of which have been published previously (5,6). This *post hoc* analysis examined efficacy and safety outcomes in patients with eGFR <30 ml/min per 1.73 m² at randomization. Although participants were enrolled in the study on the basis of an eGFR of 30 to <90 ml/min per 1.73 m² at screening, some patients' eGFR values changed by the time of randomization, such that the recorded eGFR measurement was <30 ml/min per 1.73 m² by the time of randomization assessment.

Study Participants

Eligible participants were ≥30 years of age with type 2 diabetes, glycated hemoglobin (HbA1c) of 6.5%–12.0%, screening eGFR of 30 to <90 ml/min per 1.73 m², and UACR of >300–5000 mg/g (>33.9–565.6 mg/mmol), and were receiving treatment with a stable maximum labeled or tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks before randomization. Exclusion criteria included nondiabetic kidney disease, type 1 diabetes mellitus, and prior treatment of kidney disease with immunosuppression or a history of KRT.

Randomization and Study Treatment

Participants were randomized to receive 100 mg oral canagliflozin daily or matching placebo. The protocol stipulated that study treatment be continued until the commencement of dialysis, receipt of a kidney transplant, occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy, or study conclusion (5,6). Background treatment intensification for glycemic management and cardiovascular protection according to practice guidelines was recommended.

Outcomes

This *post hoc* analysis assessed the following intermediate outcomes: change from baseline in HbA1c, systolic BP, UACR, and eGFR. In addition, eGFR change was assessed and measured as the acute change in eGFR from baseline to week 3 (6), the annualized chronic change in eGFR from week 3 until the end of treatment, and the total annualized change in eGFR from baseline to week 130.

Efficacy analyses were the same as those identified in the primary study and included the effects of canagliflozin on the primary composite outcome of kidney failure, doubling of serum creatinine, or kidney or cardiovascular death (5,6). Other efficacy outcomes included the effects of canagliflozin on cardiovascular death; the composite of cardiovascular death or hospitalization for heart failure; the composite of cardiovascular death, myocardial infarction, or stroke; hospitalization for heart failure; the composite of kidney failure, doubling of serum creatinine, or kidney death; kidney failure; and the composite of dialysis, kidney transplantation, or kidney death. Safety analyses included assessments of adverse events.

Statistical Analyses

Changes in HbA1c and systolic BP over time were analyzed using a mixed-effects model for repeated measures, which included data up to week 182, assuming an unstructured covariance and adjusting for baseline value, treatment, trial visit, and interactions of treatment by visit and baseline value by visit. Due to the highly skewed distribution of UACR data, UACR was log transformed and the geometric mean of postbaseline UACR was estimated using a similar model. The geometric mean ratio was used to calculate the reduction in postrandomization UACR for canagliflozin compared with placebo.

On-treatment eGFR slope was estimated using a piecewise, linear, mixed-effects model with a knot at week 3, including the fixed effects of treatment, randomization eGFR, continuous time, and a linear spline in follow-up time, with a knot at week 3, with interactions of treatment with the time spline terms. The model also included random intercepts, initial slopes (before week 3), and long-term slopes (after week 3) to account for variation in trajectories across participants. When the full model failed to converge, a simplified model with a single random slope was used. The effects of canagliflozin on mean total slope through week 130 were computed as a weighted combination of the estimated effects on the initial and long-term slopes.

Kidney, cardiovascular, and mortality outcomes were analyzed in the intention-to-treat population, on the basis of Cox proportional hazard models in participants with randomization eGFR <30 and ≥30 ml/min per 1.73 m². Safety outcomes were analyzed in all treated participants through 30 days after the last dose (on treatment). The interaction of treatment effects between participants with randomization eGFR <30 and ≥30 ml/min per 1.73 m² was tested by adding eGFR category as a covariable and an interaction term of treatment by eGFR categories to the Cox model. Hazard ratios (HRs) and 95% confidence intervals (CIs) for canagliflozin versus placebo were estimated. Due to the *post hoc* nature of this analysis, only nominal *P* values were reported.

Ethics

Local institutional ethics committees approved the trial protocols at each site. All participants provided written

informed consent. The trial was conducted according to the principles outlined in the Declaration of Helsinki.

Results
Patients
A total of 4401 participants were randomized to canagliflozin or placebo in the CREDENCE trial, with a median follow-up duration of 2.62 (interquartile range, 2.11–3.09) years.

At the time of screening, when eligibility for the trial on the basis of eGFR was assessed, all participants had an eGFR between 30 and <90 ml/min per 1.73 m^2. However, by the time of randomization (an average of 29 days later), 174 (4%) participants had an eGFR <30 ml/min per 1.73 m^2, but were still eligible for the trial as per the study protocol. The mean (SD) eGFR for these 174 participants was 35 (7) ml/min per 1.73 m^2 at screening, and 26 (3) ml/min per 1.73 m^2 at randomization. The distribution of eGFR values among participants with randomization eGFR <30 ml/min per 1.73 m^2 is shown in Supplemental Figure 1. Median (interquartile range) time between screening and randomization measurement was comparable for patients with eGFR <30 and ≥30 ml/min per 1.73 m^2 (29 [24–36] and 29 [23–36] days, respectively), with no notable differences between treatment groups. Most patients (>88%) had their randomization assessment between 3 and 8 weeks after screening. However, a higher proportion of patients with eGFR <30 ml/min per 1.73 m^2 had randomization measurements >8 weeks after screening compared with patients with eGFR ≥30 ml/min per 1.73 m^2 (13 of 174 [7%] versus 156 of 4226 [4%] patients; P interaction=0.01) (Supplemental Table 1).

Baseline characteristics for participants within the subgroup with eGFR <30 ml/min per 1.73 m^2 were balanced between the groups randomized to canagliflozin and placebo (Table 1).

In the overall trial, 25% of patients in the canagliflozin group and 30% of patients in the placebo group discontinued treatment for any reason, and a total of 12% and 13% of patients in the canagliflozin and placebo groups, respectively, discontinued due to an adverse event. There were no differences in effects of canagliflozin versus placebo on discontinuation between patients with eGFR <30 and ≥30 ml/min per 1.73 m^2 (P interaction >0.15; Figure 1).

Intermediate Outcomes
In the 174 patients with eGFR <30 ml/min per 1.73 m^2, there was no difference between the effect of canagliflozin and placebo on HbA1c over the study (difference in least squares mean change, −0.27%; 95% CI, −0.63 to 0.09). The effect of canagliflozin on systolic BP in patients with randomization eGFR <30 ml/min per 1.73 m^2 did not clearly differ compared with placebo over the study (difference in least squares mean change, −2.66 mm Hg; 95% CI, −6.18 to 0.86). In contrast, the geometric mean for UACR was 33% lower (95% CI, −49 to −10) during the study in patients treated with canagliflozin than in those in the placebo group (Figure 2A). No differences in the effects of canagliflozin on HbA1c, systolic BP, or UACR were observed between patients with eGFR <30 and ≥30 ml/min per 1.73 m^2 (P for heterogeneity=0.86, 0.66, and 1.0, respectively).

Mean eGFR in participants with eGFR <30 ml/min per 1.73 m^2 over the study is depicted in Figure 2B. The mean annual decline in eGFR from baseline to week 130 was slower in patients treated with canagliflozin compared with placebo (mean slopes of +0.03 versus −1.88 ml/min

---

Table 1. Baseline characteristics of participants with randomization eGFR <30 ml/min per 1.73 m^2

Characteristic[a]	Canagliflozin (n=84)	Placebo (n=90)	Total (n=174)
Age, yr	64 (10)	66 (9)	65 (10)
Male, n (%)	54 (64)	52 (58)	106 (61)
Race, n (%)			
White	55 (65)	59 (66)	114 (66)
Black	7 (8)	2 (2)	9 (5)
Asian	14 (17)	11 (12)	25 (14)
Other[b]	8 (10)	18 (20)	26 (15)
Current smoker, n (%)	9 (11)	14 (16)	23 (13)
History of hypertension, n (%)	82 (98)	89 (99)	171 (98)
History of heart failure, n (%)	9 (11)	14 (16)	23 (13)
Duration of diabetes, yr	17.5 (9.9)	16.6 (9.3)	17.0 (9.6)
History of cardiovascular disease, n (%)	41 (49)	45 (50)	86 (49)
History of amputation, n (%)	10 (12)	2 (2)	12 (7)
Body mass index, kg/m^2	32 (7)	31 (6)	32 (6)
Systolic BP, mm Hg	138 (16)	139 (17)	139 (16)
Diastolic BP, mm Hg	75 (9)	76 (11)	76 (10)
HbA1c, %	8.2 (1.3)	8.0 (1.1)	8.1 (1.2)
eGFR, ml/min per 1.73 m^2	26 (3)	27 (3)	26 (3)
UACR, mg/g, median (IQR)	1056 (459, 2525)	1153 (483, 2253)	1064 (464, 2376)

HbA1c, glycated hemoglobin; UACR, urinary albumin-creatinine ratio; IQR, interquartile range.
[a]Data are mean (SD) unless otherwise indicated.
[b]Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

	Number of participants who discontinued treatment, n/N (%)				P
	Canagliflozin	Placebo	HR (95% CI)		interaction
All discontinuations					
eGFR <30 ml/min per 1.73 m²	33/84 (39)	34/90 (38)		1.07 (0.66, 1.72)	0.25
eGFR ≥30 ml/min per 1.73 m²	510/2115 (24)	624/2107 (30)		0.78 (0.70, 0.88)	
Discontinuations due to an adverse event					
eGFR <30 ml/min per 1.73 m²	22/84 (26)	17/90 (19)		1.43 (0.76, 2.69)	0.15
eGFR ≥30 ml/min per 1.73 m²	241/2115 (11)	268/2107 (13)		0.86 (0.72, 1.02)	
Discontinuations due to personal reasons					
eGFR <30 ml/min per 1.73 m²	4/84 (5)	6/90 (7)		0.72 (0.20, 2.58)	0.87
eGFR ≥30 ml/min per 1.73 m²	160/2115 (8)	193/2107 (9)		0.80 (0.65, 0.98)	
Discontinuations due to dialysis or kidney transplant					
eGFR <30 ml/min per 1.73 m²	2/84 (2)	3/90 (3)		0.73 (0.12, 4.37)	0.88
eGFR ≥30 ml/min per 1.73 m²	16/2115 (0.8)	25/2107 (1)		0.60 (0.32, 1.13)	
Other discontinuations*					
eGFR <30 ml/min per 1.73 m²	5/84 (6)	8/90 (9)		0.69 (0.22, 2.10)	0.95
eGFR ≥30 ml/min per 1.73 m²	93/2115 (4)	138/2107 (7)		0.65 (0.50, 0.85)	

0.125 0.25 0.5 1.0 2.0 4.0

Favors canagliflozin ← → Favors placebo

Figure 1. | **There was no difference in discontinuation of treatment at eGFR <30 ml/min per 1.73 m² compared to eGFR >30 ml/min per 1.73 m².** *Other reasons include poor adherence, safety or tolerability, disallowed therapy, protocol violation, site closure, and other. 95% CI, 95% confidence interval; HR, hazard ratio.

per 1.73 m² per year, respectively; placebo-subtracted difference, 1.91 ml/min per 1.73 m² per year; 95% CI, 0.18 to 3.64). The mean acute change in eGFR from baseline to week 3 was 3.26 ml/min per 1.73 m² with canagliflozin and 4.14 ml/min per 1.73 m² with placebo (placebo-subtracted difference, −0.88 ml/min per 1.73 m²; 95% CI, −3.16 to 1.39). From week 3 to the last measurement, there was a 66% difference in the mean rate of eGFR decline with canagliflozin compared with placebo (mean slopes of −1.30 versus −3.83 ml/min per 1.73 m² per year, respectively; placebo-subtracted difference, 2.54 ml/min per 1.73 m² per year; 95% CI, 0.90 to 4.17).

Kidney, Cardiovascular, and Mortality Outcomes

Despite a limited number of events in the subset of 174 participants with eGFR <30 ml/min per 1.73 m², the point estimates for the effects of canagliflozin on most kidney, cardiovascular, and mortality outcomes were generally consistent with those seen in patients with eGFR ≥30 ml/min per 1.73 m² (all P interaction >0.20; Figure 3). Treatment with canagliflozin reduced the risk of kidney failure in participants with eGFR ≥30 ml/min per 1.73 m² (HR, 0.70; 95% CI, 0.54 to 0.91) and the effects were consistent in participants with eGFR <30 ml/min per 1.73 m² (HR, 0.67; 95% CI, 0.35 to 1.27; P interaction=0.80).

Safety

Within the subgroup of patients with eGFR <30 ml/min per 1.73 m², those treated with canagliflozin had similar rates of adverse events, serious adverse events, hyperkalemia, and hypoglycemia compared with those treated with placebo. There was also no imbalance in the rate of kidney-related adverse events or AKI events with canagliflozin compared with placebo in this subgroup. In addition, there was no evidence of heterogeneity in the occurrence of adverse events between patients with eGFR <30 and ≥30 ml/min per 1.73 m² (all P interaction >0.12; Figure 4). The incidence of serious adverse events during on- and off-treatment periods is shown in Supplemental Table 2. Among patients with eGFR <30 ml/min per 1.73 m², the number of participants with a fracture (four in each group) or amputation (three with canagliflozin and one with placebo) was low between groups.

Discussion

In this *post hoc* analysis of participants in the CREDENCE trial with eGFR <30 ml/min per 1.73 m² at randomization, treatment with canagliflozin reduced albuminuria and the rate of eGFR decline compared with placebo. The effects of canagliflozin on kidney, cardiovascular, and mortality outcomes in participants with eGFR <30 ml/min per 1.73 m² appeared to be consistent with those seen in participants with eGFR ≥30 ml/min per 1.73 m² at randomization. There was no detectable increase in harmful effects, including kidney-related adverse events and AKI, with canagliflozin compared with placebo in participants with eGFR <30 ml/min per 1.73 m². These results support the use and continuation of SGLT2 inhibitor treatment, even in patients with eGFR <30 ml/min per 1.73 m², until the commencement of maintenance dialysis or receipt of a kidney transplant, and clinicians should consider this when discussing treatment options for patients with low eGFR.

A

Median baseline, mg/g

Canagliflozin 1056   Placebo 1153

Geometric mean UACR −33% (95% CI: −49, −10)

	0	26	52	78	104	130	156	182
Canagliflozin, n	80	76	75	67	63	45	29	9
Placebo, n	87	83	84	80	70	44	26	8

B

Mean baseline, ml/min per 1.73 m²

Canagliflozin 26   Placebo 27

	0 3 13	26	52	78	104	130	156	182
Canagliflozin, n	82 82 77	78	71	57	50	36	22	7
Placebo, n	89 88 85	81	76	65	59	33	21	8
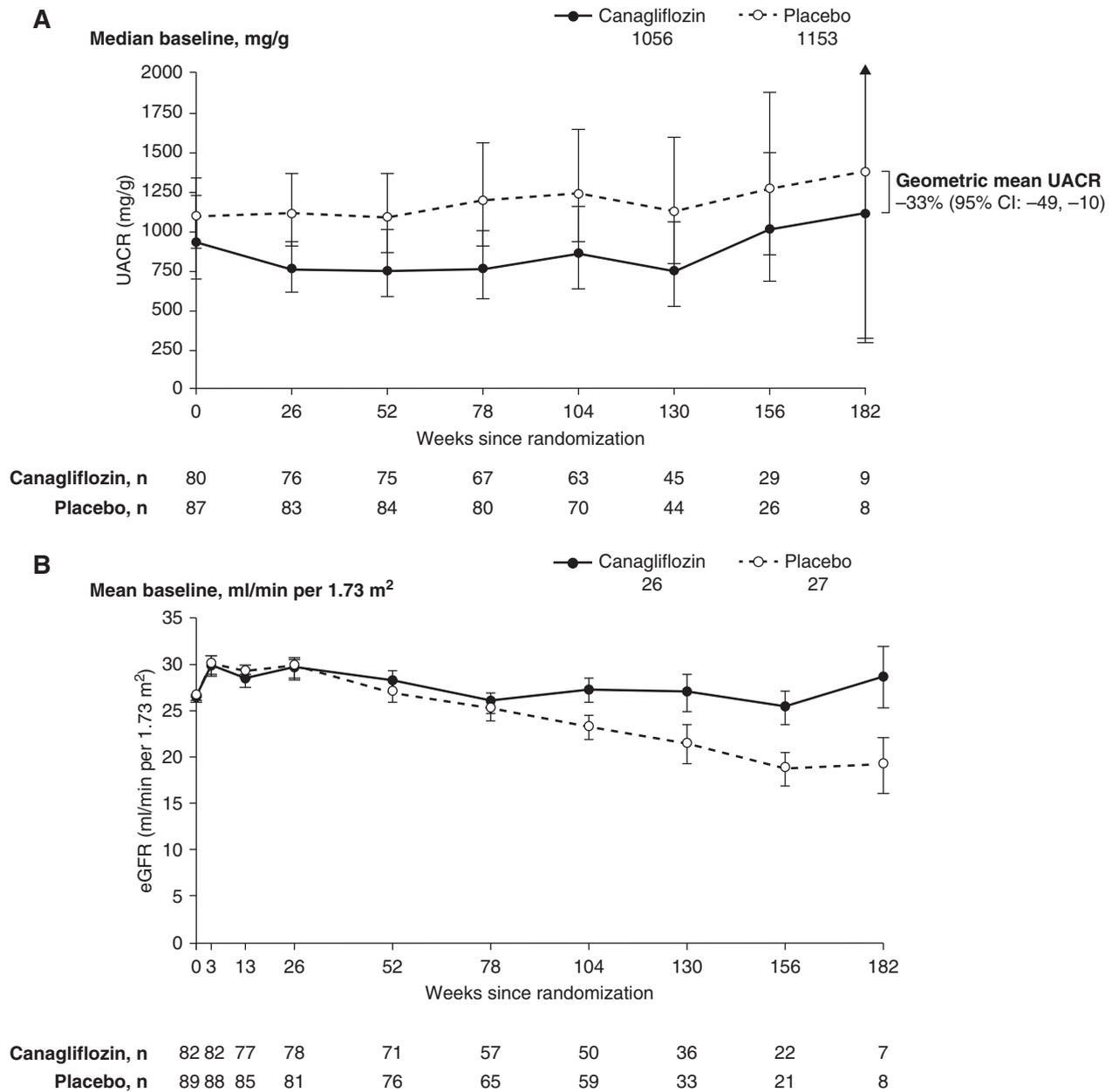
Figure 2. | **There was sustained reduction in albuminuria with a increased effect in acute GFR change with canagliflozin in participants with randomization eGFR <30 ml/min per 1.73 m².** Baseline levels of UACR (median) and eGFR (mean) are shown below the legend. Data are geometric mean ratio (95% CI) in (A). Data are mean (±SEM) in (B). UACR, urinary albumin-creatinine ratio.

Canagliflozin slowed the rate of eGFR decline in this subgroup of patients with eGFR <30 ml/min per 1.73 m². Unlike the overall population, there was no detectable initial acute drop in eGFR with canagliflozin in this subgroup, which is consistent with results of a subgroup analysis of patients with stage 3b and 4 CKD from another SGLT2 inhibitor study (9). There is no clear evidence that a reduction in intraglomerular pressure occurs at this stage of nephropathy with these agents (10), although recent data demonstrate BP reduction is similar in this advanced stage to that observed in early stages of nephropathy (11). Other factors, such as BP reduction, may have also contributed to the slowing of CKD. In addition, the requirement that the screening eGFR had to exceed 30 ml/min per 1.73 m² suggests some of the randomization eGFR values that were <30 ml/min per 1.73 m² probably resulted from random variation in patients whose typical eGFR was >30 ml/min per 1.73 m². Thus, an additional consideration is reversion to the mean because this cohort did have eGFR values just >30 ml/min per 1.73 m² at screening and <30 ml/min per 1.73 m² at randomization. Furthermore, most participants had eGFR levels between 20 and 30 ml/min per 1.73 m², so these results may not be generalizable to people with even lower eGFR levels.

Studies in animal models demonstrate SGLT2 inhibition results in sympathetic inhibition of kidney nerve function,

	Number of participants with an event		Participants with an event per 1000 patient-years				P interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo	HR (95% CI)		
Kidney failure, doubling of serum creatinine, or kidney or cardiovascular death							
eGFR <30 ml/min per 1.73 m^2	23	29	115.4	134.6		0.88 (0.51, 1.52)	0.48
eGFR ≥30 ml/min per 1.73 m^2	222	311	40.6	58.3		0.69 (0.58, 0.82)	
Cardiovascular death							
eGFR <30 ml/min per 1.73 m^2	8	8	37.4	33.7		1.10 (0.41, 2.93)	0.47
eGFR ≥30 ml/min per 1.73 m^2	102	132	18.3	24.0		0.76 (0.59, 0.99)	
Cardiovascular death or hospitalization for heart failure							
eGFR <30 ml/min per 1.73 m^2	14	14	67.9	61.2		1.12 (0.54, 2.36)	0.20
eGFR ≥30 ml/min per 1.73 m^2	165	239	30.1	44.8		0.67 (0.55, 0.82)	
Cardiovascular death, myocardial infarction, or stroke							
eGFR <30 ml/min per 1.73 m^2	13	14	63.8	61.9		1.04 (0.49, 2.20)	0.49
eGFR ≥30 ml/min per 1.73 m^2	204	255	37.8	48.1		0.78 (0.65, 0.94)	
Hospitalization for heart failure							
eGFR <30 ml/min per 1.73 m^2	6	8	29.2	35.0		0.84 (0.29, 2.43)	0.56
eGFR ≥30 ml/min per 1.73 m^2	83	133	15.1	24.9		0.61 (0.46, 0.80)	
Kidney failure, doubling of serum creatinine, or kidney death							
eGFR <30 ml/min per 1.73 m^2	17	25	85.6	116.0		0.76 (0.41, 1.40)	0.77
eGFR ≥30 ml/min per 1.73 m^2	136	199	24.9	37.3		0.66 (0.53, 0.82)	
Kidney failure							
eGFR <30 ml/min per 1.73 m^2	15	25	75.4	116.0		0.67 (0.35, 1.27)	0.80
eGFR ≥30 ml/min per 1.73 m^2	101	140	18.4	26.0		0.70 (0.54, 0.91)	
Dialysis, kidney transplantation, or kidney death							
eGFR <30 ml/min per 1.73 m^2	10	14	48.4	61.9		0.90 (0.39, 2.07)	0.87
eGFR ≥30 ml/min per 1.73 m^2	68	91	12.3	16.7		0.73 (0.53, 0.999)	

0.25 0.5 1.0 2.0 4.0

Favors canagliflozin ← → Favors placebo

Figure 3. | There was no difference in cardiovascular or kidney outcomes between those with eGFR <30 ml/min per 1.73 m^2 compared to those with eGFR >30 ml/min per 1.73 m^2.

and this may account for the glucose-independent effect of SGLT2 inhibition on BP (12). Therefore, the 3–4 mm Hg reduction in BP that results from SGLT2 inhibition may contribute, in some part, to renoprotection, similar to what was observed in the captopril trial, where a 4 mm Hg difference in BP contributed to slowed progression of diabetic nephropathy (13). The aforementioned denervation hypothesis is also consistent with results from the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure trial, which demonstrated the SGLT2 inhibitor dapagliflozin was beneficial in people without diabetes (14). The denervation hypothesis also aligns with the beneficial effects of canagliflozin observed in the subset of patients with eGFR <30 ml/min per 1.73 m^2, in whom some kidney and cardiovascular benefits are seen and are glucose independent. Additionally, the heterogeneity of effects on HbA1c, but not on other efficacy outcomes between eGFR subgroups (30 to <45, 45 to <60, and 60 to <90 ml/min per 1.73 m^2) further supports a glucose-independent mechanism of kidney and cardiovascular protection (8). Although other potential mechanisms for renoprotection are actively being studied (11,15–17), it is clear the albuminuria reduction seen in this subgroup

was similar to the overall population, and this is a well-accepted surrogate for renoprotection (18).

The conclusions that can be drawn from this nonprespecified-subgroup, *post hoc* analysis should be interpreted cautiously due to the limited statistical precision to robustly assess these outcomes due to the small sample size of this participant group.

The recently terminated Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial (19) and Effects of Dapagliflozin in Nondiabetic Patients With Proteinuria (DIAMOND) trial (20) recruited participants with eGFR down to 25 ml/min per 1.73 m^2, whereas the Study of Heart and Kidney Protection with Empagliflozin (EMPA-Kidney) trial (ClinicalTrials.gov Identifier: NCT03594110) includes those with an eGFR down to 20 ml/min per 1.73 m^2. Once available, data from these trials will provide additional insight into the effect of SGLT2 inhibitors in people with lower initial eGFR levels. Until the DIAMOND study is finished, we can say that dapagliflozin was safe and effective in people with eGFR down to 25 ml/min per 1.73 m^2 recruited for DAPA-CKD, and the consistent benefit of canagliflozin in the overall CREDENCE population and in patients with eGFR

	Number of participants with an event		Participants with an event per 1000 patient-years		HR (95% CI)		*P* interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo			
Any AE							
eGFR <30 ml/min per 1.73 m²	77	81	435.0	421.6		1.08 (0.79, 1.47)	0.17
eGFR ≥30 ml/min per 1.73 m²	1706	1779	348.3	377.6		0.87 (0.82, 0.93)	
Any serious AE							
eGFR <30 ml/min per 1.73 m²	37	40	209.0	208.2		1.03 (0.66, 1.61)	0.50
eGFR ≥30 ml/min per 1.73 m²	700	766	142.9	162.6		0.87 (0.79, 0.97)	
Hyperkalemia							
eGFR <30 ml/min per 1.73 m²	13	13	73.4	67.7		1.20 (0.55, 2.63)	0.43
eGFR ≥30 ml/min per 1.73 m²	138	168	28.2	35.7		0.79 (0.63, 0.99)	
Any kidney-related AE							
eGFR <30 ml/min per 1.73 m²	29	33	175.1	177.0		1.06 (0.64, 1.75)	0.12
eGFR ≥30 ml/min per 1.73 m²	261	355	53.3	75.3		0.69 (0.59, 0.81)	
AKI							
eGFR <30 ml/min per 1.73 m²	9	10	50.8	52.0		1.04 (0.42, 2.55)	0.70
eGFR ≥30 ml/min per 1.73 m²	77	88	15.7	18.7		0.84 (0.62, 1.14)	

0.25   0.5   1.0   2.0   4.0

Favors canagliflozin ← → Favors placebo

Figure 4. | **There was no difference in adverse events between those with eGFR <30 ml/min per 1.73 m² and >30 ml/min per 1.73 m².** AE, adverse event.

<30 ml/min per 1.73 m² at randomization suggests there is no reason to discontinue treatment until the commencement of maintenance dialysis or receipt of a kidney transplant, as stipulated in the CREDENCE protocol. Although there may be similar renoprotective effects in people with eGFR <30 ml/min per 1.73 m², we would not recommend initiating treatment with an SGLT2 inhibitor in people with eGFR <30 ml/min per 1.73 m² until results of the other pending studies are available.

Funding

Acknowledgments

Data Sharing Statement

Data from this study will be made available in the public domain *via* the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and the European Union and the study has been completed for 18 months.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.10140620/-/DCSupplemental.

Supplemental Table 1. Time between screening and randomization measurements.

Supplemental Table 2. Serious adverse events during on- and off-treatment.

Supplemental Figure 1. Distribution of eGFR at randomization in participants with randomization eGFR <30 ml/min per 1.73 m^2.

References

1. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH: Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA* 316: 602–610, 2016
2. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
3. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
4. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS: SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 393: 31–39, 2019
5. Jardine MJ, Mahaffey KW, Neal B, Agarwal R, Bakris GL, Brenner BM, Bull S, Cannon CP, Charytan DM, de Zeeuw D, Edwards R, Greene T, Heerspink HJL, Levin A, Pollock C, Wheeler DC, Xie J, Zhang H, Zinman B, Desai M, Perkovic V; CREDENCE study investigators: The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. *Am J Nephrol* 46: 462–472, 2017
6. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 380: 2295–2306, 2019
7. Janssen Pharmaceuticals: INVOKANA (canagliflozin) tablets, for oral use [package insert]. Titusville, NJ, 2019
8. Jardine MJ, Zhou Z, Mahaffey KW, Oshima M, Agarwal R, Bakris G, Bajaj HS, Bull S, Cannon CP, Charytan DM, de Zeeuw D, Luca di Tanna G, Greene T, Heerspink HJL, Levin A, Neal B, Pollock C, Qiu R, Sun T, Wheeler DC, Zhang H, Zinman B, Rosenthal N, Perkovic V; CREDENCE Study Investigators: Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: A secondary analysis of the CREDENCE randomized trial. *J Am Soc Nephrol* 31: 1128–1139, 2020
9. Dekkers CCJ, Wheeler DC, Sjöström CD, Stefansson BV, Cain V, Heerspink HJL: Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and stages 3b-4 chronic kidney disease. *Nephrol Dial Transplant* 33: 2005–2011, 2018
10. Picken M, Long J, Williamson GA, Polichnowski AJ: Progression of chronic kidney disease after acute kidney injury: Role of self-perpetuating versus hemodynamic-induced fibrosis. *Hypertension* 68: 921–928, 2016
11. Sternlicht H, Bakris GL: Blood pressure lowering and sodium-glucose co-transporter 2 inhibitors (SGLT2is): More than osmotic diuresis. *Curr Hypertens Rep* 21: 12, 2019
12. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, Arcambal A, Kiuchi MG, Head GA, Schlaich MP, Matthews VB: SGLT2 inhibitor–induced sympathoinhibition: A novel mechanism for cardiorenal protection. *JACC Basic Transl Sci* 5: 169–179, 2020
13. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
14. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators: Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 381: 1995–2008, 2019
15. Yaribeygi H, Katsiki N, Butler AE, Sahebkar A: Effects of antidiabetic drugs on NLRP3 inflammasome activity, with a focus on diabetic kidneys. *Drug Discov Today* 24: 256–262, 2019
16. Woods TC, Satou R, Miyata K, Katsurada A, Dugas CM, Klingenberg NC, Fonseca VA, Navar LG: Canagliflozin prevents intrarenal angiotensinogen augmentation and mitigates kidney injury and hypertension in mouse model of type 2 diabetes mellitus. *Am J Nephrol* 49: 331–342, 2019
17. Miyachi Y, Tsuchiya K, Shiba K, Mori K, Komiya C, Ogasawara N, Ogawa Y: A reduced M1-like/M2-like ratio of macrophages in healthy adipose tissue expansion during SGLT2 inhibition. *Sci Rep* 8: 16113, 2018
18. Levey AS, Gansevoort RT, Coresh J, Inker LA, Heerspink HL, Grams ME, Greene T, Tighiouart H, Matsushita K, Ballew SH, Sang Y, Vonesh E, Ying J, Manley T, de Zeeuw D, Eckardt KU, Levin A, Perkovic V, Zhang L, Willis K: Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: A scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis* 75: 84–104, 2020
19. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto R, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators: Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 383: 1436–1446, 2020
20. Cherney DZI, Dekkers CCJ, Barbour SJ, Cattran D, Gafor AHA, Greasley PJ, Laverman GD, Lim SK, Di Tanna GL, Reich HN, Vervloet MG, Wong MG, Gansevoort RT, Heerspink HJL; DIAMOND Investigators: Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): A randomised, double-blind, crossover trial. *Lancet Diabetes Endocrinol* 8: 582–593, 2020

AFFILIATIONS

[1]Department of Medicine, University of Chicago Medicine, Chicago, Illinois
[2]The George Institute for Global Health, University of New South Wales Sydney, Sydney, Australia
[3]Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan

[4]Department of Medicine, Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, California
[5]Indiana University School of Medicine and Veterans Affairs Medical Center, Indianapolis, Indiana
[6]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts
[7]Janssen Research & Development, LLC, Raritan, New Jersey
[8]Nephrology Division, New York University School of Medicine and New York University Langone Medical Center, New York, New York
[9]Baim Institute for Clinical Research, Boston, Massachusetts
[10]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[11]Division of Biostatistics, Department of Population Health Sciences, University of Utah, Salt Lake City, Utah
[12]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada
[13]Charles Perkins Centre, University of Sydney, Sydney, Australia
[14]Imperial College London, London, United Kingdom
[15]Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Royal North Shore Hospital, St Leonards, New South Wales, Australia
[16]Department of Renal Medicine, University College London Medical School, London, United Kingdom
[17]Renal Division, Peking University First Hospital, Beijing, China
[18]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[19]Concord Repatriation General Hospital, Sydney, Australia
[20]Royal North Shore Hospital, Sydney, Australia

Supplemental Material

Supplemental Table 1. Time Between Screening and Randomization Measurements

Supplemental Table 2. Serious Adverse Events during On- and Off-Treatment

Supplemental Figure 1. Distribution of eGFR at randomization in participants with randomization eGFR <30 mL/min/1.73 m^2.

Supplemental Table 1. Time Between Screening and Randomization Measurements

	Canagliflozin	Placebo	Total
All			
Participants, n	2201	2199	4400
<3 weeks, n (%)	161 (7)	161 (7)	322 (7)
3 to 8 weeks, n (%)	1959 (89)	1950 (89)	3909 (89)
>8 weeks, n (%)	81 (4)	88 (4)	169 (4)
Randomization eGFR <30 mL/min/1.73 m^2			
Participants, n	84	90	174
<3 weeks, n (%)	4 (5)	3 (3)	7 (4)
3 to 8 weeks, n (%)	74 (88)	80 (89)	154 (89)
>8 weeks, n (%)	6 (7)	7 (8)	13 (7)
Randomization eGFR ≥30 mL/min/1.73 m^2			
Participants, n	2117	2109	4226
<3 weeks, n (%)	157 (7)	158 (7)	315 (7)
3 to 8 weeks, n (%)	1885 (89)	1870 (89)	3755 (89)
>8 weeks, n (%)	75 (4)	81 (4)	156 (4)

eGFR, estimated glomerular filtration rate.

Supplemental Table 2. Serious Adverse Events during On- and Off-Treatment

	Patients who continued the drug		Patients who discontinued the drug for reasons other than adverse event	
	Canagliflozin	Placebo	Canagliflozin	Placebo
On-treatment (until post-30 days after the last date of study drug)				
Patients with any SAE, n/N (%)				
Randomization eGFR <30 mL/min/1.73 m^2	16/51 (31)	22/56 (39)	5/11 (45)	8/17 (47)
Randomization eGFR ≥30 mL/min/1.73 m^2	466/1605 (29)	474/1483 (32)	89/269 (33)	115/356 (32)
Patients with a SAE per 1000 patient-years				
Randomization eGFR <30 mL/min/1.73 m^2	119.6	152.6	294.9	325.0
Randomization eGFR ≥30 mL/min/1.73 m^2	110.8	123.4	255.5	241.3
SAE episodes, n				
Randomization eGFR <30 mL/min/1.73 m^2	40	45	8	18
Randomization eGFR ≥30 mL/min/1.73 m^2	875	936	185	272
Days to the last date of drug, mean (SD)				

Randomization eGFR <30 mL/min/1.73 m²	957.9 (228.1)	940.2 (246.0)	563.0 (370.2)	528.8 (316.1)
Randomization eGFR ≥30 mL/min/1.73 m²	957.0 (236.3)	946.1 (235.5)	472.9 (313.8)	489.0 (313.3)

Off-treatment (after 30 days post the last date of study drug)

Patients with any SAE, n/N (%)

Randomization eGFR <30 mL/min/1.73 m²	2/51 (4)*	0	3/11 (27)	4/17 (24)
Randomization eGFR ≥30 mL/min/1.73 m²	10/1605 (0.6)†	8/1483 (0.5)†	59/269 (22)	96/356 (27)

Patients with a SAE per 1000 patient-years

Randomization eGFR <30 mL/min/1.73 m²	1002.1	0	259.7	189.0
Randomization eGFR ≥30 mL/min/1.73 m²	528.8	429.7	157.4	197.6

SAE episodes, n

Randomization eGFR <30 mL/min/1.73 m²	5	0	8	5
Randomization eGFR ≥30 mL/min/1.73 m²	28	12	180	266

Days after the last date of drug, mean (SD)

Randomization eGFR <30 mL/min/1.73 m²	14.3 (45.1)	3.8 (5.7)	383.5 (312.5)	454.6 (308.1)

Randomization eGFR ≥30 mL/min/1.73 m^2	4.3 (12.9)	4.6 (16.5)	508.9 (313.8)	498.5 (338.4)

Total (on- and off-treatment)

Patients with any SAE, n/N (%)

Randomization eGFR <30 mL/min/1.73 m^2	17/51 (33)	22/56 (39)	6/11 (55)	9/17 (53)
Randomization eGFR ≥30 mL/min/1.73 m^2	468/1605 (29)	476/1483 (32)	117/269 (43)	157/356 (44)

Patients with a SAE per 1000 patient-years

Randomization eGFR <30 mL/min/1.73 m^2	125.4	152.2	210.7	196.8
Randomization eGFR ≥30 mL/min/1.73 m^2	110.9	123.4	162.0	163.3

SAE episodes, n

Randomization eGFR <30 mL/min/1.73 m^2	45	45	16	23
Randomization eGFR ≥30 mL/min/1.73 m^2	903	948	366	539

Days during follow-up, mean (SD)

Randomization eGFR <30 mL/min/1.73 m^2	971.2 (213.7)	943.1 (246.8)	945.5 (396.7)	982.5 (215.5)
Randomization eGFR ≥30 mL/min/1.73 m^2	960.3 (235.1)	949.7 (234.9)	980.8 (259.1)	986.5 (257.8)

SAE, serious adverse event; eGFR, estimated glomerular filtration rate; SD, standard
deviation.

*2 patients with eGFR <30 mL/min/1.73 m^2 in the canagliflozin arm stopped the drug due to
a fatal SAE.

[†]10 and 8 patients with eGFR ≥30 mL/min/1.73 m^2 in the canagliflozin and placebo arms,
respectively, stopped the drug due to a fatal SAE.

Supplemental Figure 1. Distribution of eGFR at randomization in participants with randomization eGFR <30 mL/min/1.73 m^2.

eGFR, estimated glomerular filtration rate.