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Please cite this article as: Oshima M, Jardine MJ, Agarwal R, Bakris G, Cannon CP, Charytan DM, de Zeeuw D, Edwards R, Greene T, Levin A, Lim SK, Mahaffey KW, Neal B, Pollock C, Rosenthal N, Wheeler DC, Zhang H, Zinman B, Perkovic V, Heerspink H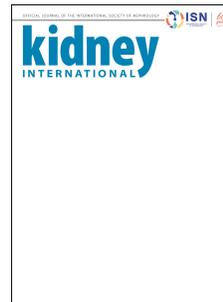JL, Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice., *Kidney International* (2021), doi: https://doi.org/10.1016/j.kint.2020.10.042.

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Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice.

Patients

Post-hoc analysis of the CREDENCE trial
N=4289

Canagliflozin

Placebo

Acute change in eGFR at week 3

Acute eGFR drop >10%

Acute modest eGFR drop >0% to 10%

Acute eGFR increase ≥0%

Results

Similar long-term eGFR trajectory

Canagliflozin   Placebo

(mL/min/1.73 m²/year)

Similar safety profile

Canagliflozin Placebo

Any adverse events
Acute eGFR drop
Acute modest eGFR drop
Acute eGFR increase

Any renal related events
Acute eGFR drop
Acute modest eGFR drop
Acute eGFR increase

0.5 1.0 2.0 0.5 1.0 2.0
Hazard ratio

CONCLUSION:

Long-term eGFR trajectories and overall and renal safety profiles were similar among subgroups of an acute drop in eGFR.

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[QUERY TO AUTHOR: title and abstract rewritten by Editorial Office – not subject to change]
Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice.

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Abstract

Canagliflozin slows the progression of chronic kidney disease in patients with type 2 diabetes and induces a reversible acute drop in estimated glomerular filtration rate (eGFR), believed to be a hemodynamic effect. Predictors of the initial drop and its association with long-term eGFR trajectories and safety outcomes are unknown. To assess this, we performed a post-hoc analysis of 4289 participants in the CREDENCE trial with type 2 diabetes and chronic kidney disease equally split into treatment and placebo groups who had eGFR measured at both baseline and week three. The eGFR was categorized at week three as greater than a 10% decline; between 0 and 10% decline; and no decline. Long-term eGFR trajectories and safety outcomes were estimated in each category of acute eGFR change by linear mixed effects models and Cox regression after adjustment for baseline characteristics and medications use. Significantly more participants in the canagliflozin (45%) compared to the placebo (21%) group experienced an acute drop in eGFR over 10%. An over 30% drop occurred infrequently (4% of participants with canagliflozin and 2% with placebo). The odds ratio for a drop in eGFR over 10% with canagliflozin compared to placebo was significant at 3.03 (95% confidence interval 2.65, 3.47). Following the initial drop in eGFR, multivariable adjusted long-term eGFR trajectories, as well as overall and kidney safety profiles, in those treated with canagliflozin were similar across eGFR decline categories. Thus, although acute drops in eGFR over 10% occurred in nearly half of all participants following initiation of canagliflozin, the clinical benefit of canagliflozin was observed regardless. Additionally, safety outcomes were similar among subgroups of acute eGFR drop.

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Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT2) have been shown to reduce the risk of kidney and cardiovascular outcomes in people with type 2 diabetes. SGLT2 inhibitors increase distal tubular sodium and chloride delivery to the macula densa, which augments tubuloglomerular feedback causing reversal of afferent arteriolar vasodilatation. As a result, SGLT2 inhibitors cause an acute reduction in intraglomerular pressure and glomerular filtration rate (GFR).[1] Large cardiovascular outcome trials have demonstrated that the initial drop in eGFR following initiation of SGLT2 inhibition is followed by a stabilisation of long-term kidney function decline.[2-5] However, in clinical practice, an acute drop in eGFR may raise safety concerns that prevent clinicians from continuing SGLT2 inhibitors. A better characterisation of the acute drop in eGFR and its association with long-term eGFR trajectories and safety outcomes is required to support appropriate use of SGLT2 inhibitors in clinical practice.

We therefore performed a post-hoc analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial to determine the predictors of an acute eGFR decline following initiation of the SGLT2 inhibitor canagliflozin and its associations with long-term eGFR trajectories and safety outcomes.

Results

Effect of canagliflozin versus placebo on acute eGFR decline

Of the 4401 participants in the CREDENCE trial, 4289 individuals (97.5%) (2144 in the canagliflozin group and 2145 in the placebo group had eGFR measurements available at baseline and week 3 and were included in this analysis. All participants were using an ACE-inhibitor or an angiotensin receptor blocker (ARB) as required by the protocol. At week 3, the mean acute change in eGFR was -7.0% (standard error [SE] 0.4) and 0.3% (0.4) in the canagliflozin and placebo group, respectively (mean difference -7.3%, 95% CI -8.5 to -6.1; p <0.001). More participants in the canagliflozin (956 [45%]) than in the placebo (450 [21%]) group experienced an acute eGFR drop of >10% (p <0.001) (Table 1). An acute drop in

eGFR of greater than 30% was rare and occurred in only 89 (4.2%) and 39 (1.8%) participants in the canagliflozin and placebo group, respectively (p <0.001).

Predictors of acute drop in eGFR

In the canagliflozin group, participants with an acute drop in eGFR were more likely to be older, had a longer duration of diabetes, a higher body mass index, systolic blood pressure, and eGFR, and were more likely to use diuretics at baseline, while they were less likely to have heart failure (Table 1). In the placebo group, it was higher systolic blood pressure, eGFR, and UACR that predicted an acute drop in eGFR.

To identify participants particularly prone to experience a drop in eGFR >10% with canagliflozin rather than placebo we performed a logistic regression analyses to examine the consistency of effects of canagliflozin versus placebo on acute eGFR decline in subgroups defined by baseline characteristics. Overall, canagliflozin increased the likelihood of an acute eGFR drop >10% compared to placebo (odds ratios [OR] 3.03, 95% confidence interval [CI] 2.65, 3.47; p <0.001) (Figure 1). In subgroup analyses across various baseline participant characteristics, participants with a history of heart failure were less likely to experience an eGFR decline >10% following canagliflozin initiation relative to placebo (p interaction =0.04). The likelihood of an acute drop in eGFR of >10% with canagliflozin compared to placebo was similar across other subgroups defined by the eGFR category at screening (Figure 1). Other participant characteristics at baseline were also not associated with a higher likelihood of a drop in eGFR with canagliflozin compared to placebo. Finally, the effect of canagliflozin versus placebo on percentage change in eGFR during the first 3 weeks was also consistent across various subgroups defined by participant characteristics at baseline (Supplementary table 1).

Treatment discontinuation

Among these 4289 participants, none discontinued their assigned treatment during the first 3 weeks of the trial. After week 3, 519 (24.2%) in the canagliflozin and 629 (29.3%) in the

placebo group discontinued their assigned treatment during follow-up. There was no statistically significant difference in number of participants who discontinued therapy across categories of an acute eGFR change in each treatment group (Table 2). Discontinuation rates were also similar within the canagliflozin group when finer categories of eGFR decline thresholds were used (Supplementary table 2).

Long-term eGFR trajectories

Compared to the placebo group, the annual decline in eGFR in the canagliflozin group was smaller in each category of an acute change in eGFR. After multivariable adjustment, the annual change in eGFR from week 13 to the last available measurements among participants receiving canagliflozin with an acute eGFR drop >10% was similar as compared with those receiving canagliflozin that experienced an acute modest drop between 0 to 10% or increase in eGFR (p = 0.11; Figure 2A). In the few participants with an acute drop in eGFR >30% after canagliflozin initiation long-term eGFR trajectory was similar as compared to the main analyses (Supplementary figure 1). Within the placebo group there was no statistically significant difference in an annual change in eGFR across categories of an acute change in eGFR (p = 0.09; Figure 2B). Further adjustment for acute changes in eGFR did not alter these findings. In a subgroup analysis, the long-term eGFR trajectories within the canagliflozin group were similar as compared to the main analysis in each subgroup of eGFR at screening (Supplementary table 3). The only exception was the subgroup with eGFR between 30 and 45 mL/min/1.73 m^2. In this subgroup participants with a drop in eGFR had a significantly slower rate of eGFR decline during long-term follow-up compared to participants with an increase in eGFR (Supplementary table 3).

Safety outcomes during acute and chronic phases

During the first 3 weeks, the percentage of participants experiencing an adverse event was similar between the canagliflozin and placebo groups except for renal related adverse events (Supplementary table 4). Renal related adverse events were more frequently

reported in those who experienced an acute eGFR drop of >10% with canagliflozin than placebo.

During the chronic phase after week 3, the event rates for each safety outcome were lower in the canagliflozin compared to placebo group regardless of the acute change in eGFR category (Figure 3). Within the canagliflozin and placebo groups separately, the event rates and multivariable adjusted hazard ratios for overall and serious adverse events, overall and serious renal related adverse events, acute kidney injury, and hyperkalemia did not differ across categories of an acute change in eGFR (Figure 3). When finer categories of eGFR decline thresholds were used, results were generally similar with the exception that in the subgroup of participants with an acute drop of >30% using canagliflozin the overall adverse events (multivariable adjusted hazard ratio 1.34 [95%CI 1.05, 1.72]) and renal related adverse events rates (multivariable adjusted hazard ratio 2.15 [95%CI 1.28, 3.60]) were higher compared to participants with an acute increase in eGFR using canagliflozin (Supplementary figure 2). Similar findings were observed across screening eGFR subgroups (Supplementary table 5). In an additional analysis using the predicted likelihood of an acute eGFR drop >10%, the effects of canagliflozin relative to placebo on adverse events were consistent regardless of a likelihood of an eGFR drop >10% above or below the median (p for interaction >0.51) (Supplementary table 6).

Discussion

In this post-hoc analysis of the CREDENCE trial we demonstrated that an initial drop in eGFR in response to canagliflozin is common but a larger drop of 30% in eGFR was a rare event. We also demonstrated that the long-term eGFR trajectories as well as overall and renal safety profiles during canagliflozin treatment were similar regardless of the initial eGFR drop except when it unusually exceeded 30%, when adverse events and renal related adverse events were reported more frequently. These data suggest that an acute decrease in eGFR up to 30% can be tolerated after treatment initiation with canagliflozin.

Understanding which patients with diabetes and CKD are more likely to experience an acute drop in eGFR upon SGLT2 inhibitors initiation is important to guide best use of SGLT2 inhibitors in clinical practice. Observational analyses done in just those assigned to canagliflozin identified older age, higher systolic blood pressure, higher eGFR, absence of heart failure, and use of diuretic treatment as predictors of an acute fall in eGFR. Acute drops in eGFR also occurred in some placebo group participants, which is likely explained by the large biological variability of eGFR and the phenomenon of regression of the mean.[6] The participant characteristics associated with an acute drop in eGFR in the placebo group were higher systolic blood pressure, eGFR, and UACR. In the randomised comparison between canagliflozin and placebo it was only a history of heart failure that predicted acute drop in eGFR with those with a history of heart failure less likely to experience an acute eGFR drop of at least 10%. We note that the interaction p-value for this comparison was of borderline statistical significance and not adjusted for multiple testing and the results should thus be cautiously interpreted, but it is possible that improvements in cardiac output following SGLT2 inhibition increase glomerular filtration and decreases the likelihood of a drop in GFR.

The likelihood of experiencing a greater than 10% decline in eGFR following canagliflozin was consistent regardless of the starting eGFR level. It should be noted that in the current analyses the initial decline in eGFR was expressed as percentage decline and the absolute acute eGFR decline was smaller at lower compared to higher eGFR as previously reported.[7] Additionally, among participants in the lowest eGFR category at screening, the long-term rate of eGFR decline was also less in participants with an acute eGFR decline compared to those with an increase. Taken together, we believe that practitioners may be reassured by these data that in conjunction with the renal and cardiac benefits seen across the eGFR spectrum of 30-90 ml/min/1.73m^2 support initiation of canagliflozin in patients with eGFR between 30 and 45 mL/min/1.73 m^2.

The results of our study demonstrate that acute declines in eGFR up to 30% after initiation of canagliflozin treatment would not be a reason to discontinue treatment - eGFR

trajectories during chronic treatment with canagliflozin were consistent within the canagliflozin group and significantly better than placebo regardless of the initial eGFR change. Moreover, safety outcomes within canagliflozin-treated subjects were consistent regardless of the initial eGFR change. Acute drops in eGFR greater than 30% were rare but were associated with a higher likelihood of adverse events during prolonged treatment that should prompt careful monitoring. This 30% eGFR threshold is close to the 30% serum creatinine increase, equivalent to a 27% eGFR decline, deemed tolerable upon initiation of renin-angiotensin-aldosterone system (RAAS) inhibition in light of the long-term kidney protective effects of these agents.[8, 9] We note that although a greater than 30% drop in eGFR with canagliflozin was associated with a higher risk of adverse events we cannot answer the question whether reducing the dose or discontinuing canagliflozin would attenuate this increased risk given the nature of the data available to us.

During the first 3 weeks of the trial renal related adverse events were more frequently reported among individuals with an acute drop in eGFR. Renal related adverse events comprise a range of different investigator reported events, which include decreases in eGFR and increases in serum creatinine. The higher frequency during the early stage of the trial may be a reflection of investigator response to the acute drop in eGFR.

Rather than being interpreted as an adverse event, prior studies in patients with CKD with or without diabetes treated with ACE inhibitors or ARBs demonstrated that an acute drop in eGFR is associated with long-term preservation of kidney function, supporting the concept that the acute decline in eGFR is of hemodynamic origin and reflects a reduction in intra-glomerular pressure that is associated with long-term kidney preservation.[10-13] However, this pattern could not be replicated in other studies with ACE-inhibitors or ARBs nor in our trial.[14,12, 15, 16] It should be noted that the subgroup of participants with an acute drop in eGFR comprised participants with a canagliflozin induced acute (reversible) drop in eGFR as well as participants with pre-existing progressive kidney function loss in whom eGFR will likely continue to decline during the chronic phase of the trial thereby diluting the association. This complicates assessment and interpretation of the relationship between an acute drop in

eGFR and long-term kidney function. A better characterization of the eGFR decline prior to initiation of SGLT2 treatment would help in future studies to distinguish the acute hemodynamic drop in eGFR from progressive kidney function loss.

The strengths of our study include the large number and diverse groups of participants, the sequential measurements of eGFR during the CREDENCE trial, and the ability to adjust for multiple important risk factors. However, our study has several limitations. First, as our study cohort was derived from a clinical trial of patients with type 2 diabetes and chronic kidney disease, the results may limit generalisability to broader populations. Second, the analyses according to the acute change in eGFR were no longer randomized. Although we adjusted the analyses for differences in participant characteristics across drop in eGFR categories, residual confounding cannot be excluded. In addition, eGFR was not measured after treatment discontinuation. We therefore could not establish whether the acute drop in eGFR is reversible after treatment discontinuation. However, in patients with type 2 diabetes with established cardiovascular disease or cardiovascular risk factors it has been shown that eGFR is completely reversible 30 days after canagliflozin discontinuation[2]. Finally, serum creatinine was measured with the Jaffe method which is more susceptible to interferences than the enzymatic methods.[17]In addition, within-individual variability in eGFR is high.[6] Both factors may have led to misclassifications and limit the precision of the results.

In conclusion, although acute drops in eGFR >10% occurred in nearly half of all participants following initiation of canagliflozin, the benefit of canagliflozin compared with placebo was observed regardless of the acute eGFR decline. Safety outcomes were also similar among subgroups of initial drop in eGFR. Considering the beneficial effects of canagliflozin on renal and cardiovascular outcomes in patients with type 2 diabetes and CKD, our data suggest that an acute drop in eGFR of no more than 30% following canagliflozin initiation may be no reason for safety concern, but close monitoring of kidney function remains essential.

Methods

Study design and participants

We performed a post-hoc observational analysis from the CREDENCE trial
(ClinicalTrials.gov no. NCT02065791) which was a multicenter, double-blind, placebo-
controlled, randomized trial evaluating the effects of canagliflozin on renal outcomes in
subjects with type 2 diabetes and chronic kidney disease. The design of the trial and primary
outcomes have been published previously.[3, 18] In brief, a total of 4401 individuals underwent
randomization at 690 sites in 34 countries between March 2014 and May 2017. Participants
were eligible if they were ≥30 years of age and had type 2 diabetes, with a glycated
haemoglobin (HbA1c) level of 6.5 to 12.0%. They were also required to have chronic kidney
disease, defined as eGFR of 30 to <90 ml/min/1.73 m^2 and urinary albumin-to-creatinine
ratio (UACR) of >300 to 5000 mg/g (>33.9 to 565.6 mg/mmol). All the participants were to
receive a stable dose of RAAS inhibitors for at least 4 weeks before randomization.

Participants were randomized to receive canagliflozin 100 mg daily or matching
placebo using randomly permuted blocks with stratification by screening eGFR categories
(30-<45, 45-<60, and 60-<90 mL/min/1.73 m^2). The use of other background therapy for
glycaemic management and control of cardiovascular risk factors were recommended in
accordance with local guidelines. The median follow-up period was 2.6 years until the last
trial visits (either in-clinic or telephone) which occurred by October 30, 2018. 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.

Category of an acute change in eGFR

Serum creatinine was measured in a central laboratory by use of the Jaffe method with rate
blanking at randomization, week 3, week 13, week 26, and every 26 weeks thereafter, as
published previously.[3, 18] eGFR was calculated using the Chronic Kidney Disease
Epidemiology Collaboration (CKD-EPI) formula.[19]

For the current observational analysis we included all participants with eGFR measurements at baseline and week 3 (Supplementary figure 3). The acute change in eGFR was defined as the percentage change in eGFR at week 3. The 3-week period was chosen because it was the first time point at which follow-up eGFR measurements were available and prior studies have shown that the acute effect of SGLT2 inhibitors on eGFR are fully present after 2 to 3 weeks.[20, 21] Participants were categorized by percentage decline in eGFR at week 3: greater than 10% decline (defined as acute eGFR drop); between 0 and 10% decline (acute modest eGFR drop); and no decline (acute eGFR increase). These cut offs were chosen post-hoc with the aim of providing easily understandable thresholds and approximately equal sample sizes for each category. In an additional analysis, we used finer categories of acute change in eGFR: >30% decrease, >20 to 30% decrease, >10 to 20% decrease, >0 to 10% decrease, or ≥0% increase. Since these subgroups were defined by a post-randomization variable (eGFR), these subgroups do not allow for randomized comparison.

Outcomes and follow-up

The outcome for this study was the on-treatment eGFR slope which was defined as the annual rate of change in eGFR based on all on-treatment eGFR measurements from week 13 to the last available measurements. Investigator reported safety outcomes included any adverse events, any serious adverse events, (serious) renal-related adverse events, acute kidney injury, and hyperkalemia. The definition of hyperkalemia includes the preferred terms of "hyperkalemia" and "blood potassium increased" according the Medical Dictionary for Regulatory Activities. Number of events were counted separately for the acute phase (from baseline to week 3) and for the chronic phase (from week 3 through 30 days after the last dose for the safety analyses) of the trial. Participants were followed from the end of the acute phase until the first of the study outcomes, death, or the end of follow-up (Supplementary figure 2).

Statistical analyses

The on-treatment population, defined as all participants who took at least 1 dose of study medication, was used for our analysis. We summarised baseline characteristics according to categories of an acute change in eGFR in the canagliflozin and placebo group. Continuous variables were reported as means with SDs for variables with approximately symmetrical distributions. Results for variables with skewed distributions were presented as median and interquartile range (IQR) and were transformed into natural logarithms before analysis. Linear trends across categories of an acute change in eGFR in each treatment group were tested by linear regression analysis and logistic regression analysis, as appropriate.

For assessment of predictors of acute eGFR declines following canagliflozin initiation, logistic regression models were used to estimate the univariate ORs and their corresponding 95% CIs of canagliflozin versus placebo for the risk of an acute eGFR drop >10% in the overall population and across the following baseline participant subgroups: age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, history of cardiovascular disease, body mass index, systolic blood pressure, HbA1c, screening eGFR, UACR, and use of insulin and diuretic. A test for interaction across subgroups was performed by adding an interaction term between categorical values of each respective subgroup and treatment assignment in the logistic regression models. We also estimated the effects of canagliflozin versus placebo on an acute change in eGFR during the first 3 weeks across baseline participant subgroup using mixed effects models which were adjusted for baseline eGFR and treatment.

The on-treatment eGFR slope was analyzed by mixed effects model with random slopes and random intercepts. The model was adjusted for categories of acute change in eGFR, time, an interaction term for acute change in eGFR category by time as well as the following baseline covariates and an interaction term between these covariates and time: age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic blood pressure, HbA1c, eGFR, log-transformed UACR, high density lipoprotein cholesterol,

low density lipoprotein cholesterol, log-transformed triglycerides, and use of diuretic and RAAS inhibitor. The linearity assumption was verified by visual inspection of the long-term eGFR trajectory.

Cox proportional hazard regression was performed to estimate the hazard ratio for safety outcomes according to categories of an acute change in eGFR. Safety outcomes that occurred within 3 weeks after randomization were excluded and follow-up time was calculated from the week 3 serum creatinine measurement until 30 days after the last administration of study medication. The models used an acute increase in eGFR as reference and were adjusted for baseline covariates as described above. Homogeneity of treatment effects were tested by adding an interaction term between treatment assignment and category of an acute change in eGFR as a continuous variable in the Cox regression models. The proportional hazards assumption was confirmed by including an interaction term between the acute change in eGFR category and time as a time-varying covariate in the Cox regression models. In an additional analysis, we predicted the likelihood of an acute eGFR drop >10% for each participant in the canagliflozin group using a logistic regression model based on the following baseline covariates: age, sex, history of heart failure, duration of diabetes, body mass index, systolic blood pressure, eGFR, log-transformed UACR, and use of diuretic. These covariates were selected since they were significantly different across categories in drop in eGFR. Using the logistic regression model we calculated the probability of a drop in eGFR >10% for each participant in the canagliflozin and placebo group. We finally stratified the population by median probability of drop in eGFR >10% and assessed the effects of canagliflozin versus placebo on adverse events among participants above and below the median likelihood of eGFR drop more than 10%.

To assess the impact of baseline eGFR, we estimated the long-term eGFR slope and safety outcomes according to screening eGFR categories (30-<45, 45-<60, and 60-<90 mL/min/1.73 m^2). All analyses were conducted using Stata, version 15 (Stata Corporation, College Station, TX, USA). A two-sided p value <0.05 was considered statistically significant.

Data Availability

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

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D. de Zeeuw reports serving on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, Mitsubishi Tanabe; serving on steering committees and/or as a speaker for AbbVie and Janssen; and serving on data safety and monitoring committees for Bayer.

Acknowledgements

References

1. Heerspink HJ, Perkins BA, Fitchett DH, *et al.* Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation* 2016; **134:** 752-772.

2. 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.

3. Perkovic V, Jardine MJ, Neal B, *et al.* Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; **380:** 2295-2306.

4. Wanner C, Inzucchi SE, Lachin JM, *et al.* Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016; **375:** 323-334.

5. Mosenzon O, Wiviott SD, Cahn A, *et al.* Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol* 2019; **7:** 606-617.

6. Waikar SS, Rebholz CM, Zheng Z, *et al.* Biological Variability of Estimated GFR and Albuminuria in CKD. *Am J Kidney Dis* 2018; **72:** 538-546.

7. Jardine MJ, Zhou Z, Mahaffey KW, *et al.* Renal, Cardiovascular, and Safety Outcomes of Canagliflozin by Baseline Kidney Function: A Secondary Analysis of the CREDENCE Randomized Trial. *J Am Soc Nephrol* 2020; **31:** 1128-1139.

8. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000; **160:** 685-693.

9. Hirsch S, Hirsch J, Bhatt U, *et al.* Tolerating increases in the serum creatinine following aggressive treatment of chronic kidney disease, hypertension and proteinuria: pre-renal success. *Am J Nephrol* 2012; **36:** 430-437.

10. Apperloo AJ, de Zeeuw D, de Jong PE. Short-term antiproteinuric response to antihypertensive treatment predicts long-term GFR decline in patients with non-diabetic renal disease. *Kidney Int Suppl* 1994; **45:** S174-178.

11. Holtkamp FA, de Zeeuw D, Thomas MC, *et al.* An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* 2011; **80:** 282-287.

12. Ohkuma T, Jun M, Rodgers A, *et al.* Acute Increases in Serum Creatinine After Starting Angiotensin-Converting Enzyme Inhibitor-Based Therapy and Effects of its Continuation on Major Clinical Outcomes in Type 2 Diabetes Mellitus. *Hypertension* 2019; **73:** 84-91.

13. Wright JT, Jr., Bakris G, Greene T*, et al.* Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; **288:** 2421-2431.

14. Evans M, Bain SC, Hogan S*, et al.* Irbesartan delays progression of nephropathy as measured by estimated glomerular filtration rate: post hoc analysis of the Irbesartan Diabetic Nephropathy Trial. *Nephrol Dial Transplant* 2012; **27:** 2255-2263.

15. Collard D, Brouwer TF, Olde Engberink RHG*, et al.* Initial Estimated Glomerular Filtration Rate Decline and Long-Term Renal Function During Intensive Antihypertensive Therapy: A Post Hoc Analysis of the SPRINT and ACCORD-BP Randomized Controlled Trials. *Hypertension* 2020; **75:** 1205-1212.

16. Clase CM, Barzilay J, Gao P*, et al.* Acute change in glomerular filtration rate with inhibition of the renin-angiotensin system does not predict subsequent renal and cardiovascular outcomes. *Kidney Int* 2017; **91:** 683-690.

17. Group. KDIGOKCW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter, Suppl* 2013; **3:** 1-150.

18. 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:** 462-472.

19. Levey AS, Stevens LA, Schmid CH*, et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150:** 604-612.

20. Pollock C, Stefansson B, Reyner D*, et al.* Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; **7:** 429-441.

21. Yale JF, Bakris G, Cariou B*, et al.* Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013; **15:** 463-473.

Figure legends

Figure 1: Odds ratios and 95% confidence intervals of canagliflozin versus placebo for the risk of an acute drop in eGFR (>10% per 3 weeks) across baseline participant subgroups.

Footnote to figure 1: Abbreviation: eGFR, estimated glomerular filtration ratio, UACR, urinary albumin-to-creatinine ratio; RAAS, renin angiotensin aldosterone system. Race or ethnic group was reported by the participants. The designation "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Figure 2: Adjusted mean (standard error) eGFR and annual changes in long-term eGFR trajectories (from week 13 to the last available measurements) in the (A) canagliflozin and (B) placebo groups according to an acute change in eGFR.

Footnote to figure 2: Abbreviation: eGFR, estimated glomerular filtration ratio. In the canagliflozin group those with an acute drop in eGFR had a significantly slower rate of eGFR from month 3 until the end of treatment compared to those with an acute increase in eGFR (p=0.037). In the canagliflozin group the mean differences in annual changes in eGFR between category of acute drop in eGFR >10% versus increase in eGFR was 0.58 (95%CI -0.04 to 1.20) ml/min/1.73m^2/year. The difference was 0.65 (95%CI -0.02 to 1.32) ml/min/1.73m^2 between the category of acute drop in eGFR between 0 and 10% versus increase in eGFR.

Figure 3: Adjusted hazard ratios and 95% confidence intervals for the risk of adverse events during follow-up according to an acute change in eGFR (per 3 weeks) in the canagliflozin and placebo groups**.**

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Footnote to figure 3: The adjusted hazard ratios compared those with an acute decrease in eGFR (<-10%) or an acute modest eGFR decrease (-10% to <0%) with those who had an acute increase in eGFR (≥0%). This comparison was made within the canagliflozin and placebo groups separately. On-treatment analyses are performed from week 3 through 30 days after the last date of study drug. Time to the first occurrence of adverse event after week 3 was analysed and the analyses were adjusted for the following baseline covariates: age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic blood pressure, diastolic blood pressure, HbA1c, eGFR, log-transformed UACR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, and use of diuretic and RAAS inhibitor. Renal related adverse events include acute kidney injury, anuria, azotemia, blood creatinine increased, blood urea increased, glomerular filtration ratio decreased, nephropathy toxic, oliguria, renal failure, and renal impairment. Hyperkalaemia was spontaneously reported by the investigator. The summary counts provided for the adverse event of hyperkalaemia include the MedDRA preferred terms of "hyperkalaemia" and "blood potassium increased."

Table 1: Baseline characteristics by treatment according to an acute change in eGFR per 3 weeks

Characteristic	Canagliflozin				Placebo			
	Acute eGFR drop (>10%)	Acute modest eGFR drop (>0 to 10%)	Acute eGFR increase (≥0%)	P for trend	Acute eGFR drop (>10%)	Acute modest eGFR drop (>0 to 10%)	Acute eGFR increase (≥0%)	P for trend
N (%)	956 (45)	600 (28)	588 (27)		450 (21)	646 (30)	1049 (49)	
Age (years; mean [SD])	63.3 (9.3)	62.7 (8.9)	62.1 (9.1)	0.01	62.7 (9.3)	63.6 (9.1)	62.9 (9.3)	0.90
Men (n [%])	635 (66)	398 (66)	375 (64)	0.32	288 (64)	445 (69)	699 (67)	0.52
Race or ethnic group (n [%])								
White	630 (66)	423 (71)	406 (69)		298 (66)	426 (66)	685 (65)	
Black or African American	51 (5)	28 (5)	28 (5)		21 (5)	32 (5)	54 (5)	
Asian	187 (20)	108 (18)	112 (19)		82 (18)	132 (20)	224 (21)	
Other	88 (9)	41 (7)	42 (7)		49 (11)	56 (9)	86 (8)	
Current smoker (n [%])	153 (16)	98 (16)	82 (14)	0.32	50 (11)	87 (13)	155 (15)	0.06
History of hypertension (n [%])	926 (97)	578 (96)	572 (97)	0.73	432 (96)	631 (98)	1012 (96)	0.93
History of heart failure (n [%])	127 (13)	86 (14)	107 (18)	0.01	73 (16)	94 (15)	147 (14)	0.29
Duration of diabetes (years; mean [SD])	16.0 (8.9)	15.4 (8.5)	15.0 (8.4)	0.03	16.2 (8.5)	16.1 (8.7)	15.8 (8.5)	0.37
History of cardiovascular disease (n [%])	477 (50)	304 (51)	303 (52)	0.53	220 (49)	312 (48)	548 (52)	0.15
History of amputation (n [%])	48 (5)	34 (6)	31 (6)	0.68	27 (6)	32 (5)	53 (5)	0.52
Body mass index (kg/m^2; mean [SD])	32 (6)	31 (6)	31 (6)	0.03	32 (6)	31 (6)	31 (6)	0.30
Systolic blood pressure (mmHg; mean [SD])	141 (16)	140 (15)	138 (15)	0.001	142 (17)	141 (15)	139 (15)	<0.001
Diastolic blood pressure (mmHg; mean [SD])	78 (9)	79 (10)	78 (9)	0.93	78 (9)	79 (9)	78 (10)	0.21
HbA1c (%; mean [SD])	8.2 (1.3)	8.2 (1.3)	8.4 (1.4)	0.11	8.3 (1.3)	8.3 (1.3)	8.3 (1.4)	0.97
eGFR (mL/min/1.73 m^2; mean [SD])	57.9 (18.1)	56.9 (18.2)	53.6 (18.1)	<0.001	58.1 (19.0)	58.9 (18.5)	53.3 (17.6)	<0.001

Screening eGFR								
30-<45 (mL/min/1.73 m^2; n [%])	301 (31)	169 (28)	164 (28)		153 (34)	173 (27)	313 (30)	
45-<60 (mL/min/1.73 m^2; n [%])	290 (30)	176 (29)	157 (27)		123 (27)	199 (31)	306 (29)	
60-<90 (mL/min/1.73 m^2; n [%])	365 (38)	255 (43)	267 (45)		174 (39)	274 (42)	430 (41)	
UACR (mg/g; median [IQR])	923 (472–1794)	956 (468–1943)	878 (423–1728)	0.07	1079 (526–2170)	971 (496–1831)	834 (438–1784)	<0.001
Total cholesterol (mmol/l, mean [SD])	4.6 (1.3)	4.6 (1.3)	4.8 (1.4)	0.06	4.7 (1.2)	4.7 (1.2)	4.7 (1.3)	0.99
HDL cholesterol (mmol/l, mean [SD])	1.1 (0.3)	1.2 (0.4)	1.2 (0.4)	0.15	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	0.66
LDL cholesterol (mmol/l, mean [SD])	2.5 (1.1)	2.5 (1.1)	2.6 (1.1)	0.30	2.5 (1.0)	2.5 (1.0)	2.5 (1.1)	0.55
Triglycerides (mmol/l, median [IQR])	1.9 (1.3–2.7)	1.8 (1.3–2.7)	1.8 (1.4–2.6)	0.67	1.7 (1.3–2.6)	1.8 (1.3–2.8)	1.8 (1.3–2.6)	0.49
Drug therapy (n [%])								
Insulin	637 (67)	403 (67)	376 (64)	0.33	310 (69)	419 (65)	671 (64)	0.09
RAAS inhibitor	956 (100)	599 (100)	588 (100)	0.84	449 (100)	644 (100)	1047 (100)	0.82
Diuretic	479 (50)	271 (45)	254 (43)	0.01	233 (52)	284 (44)	494 (47)	0.24

SD, standard deviation; eGFR, estimated glomerular filtration ratio, UACR, urinary albumin-to-creatinine ratio; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAAS, renin angiotensin aldosterone system.
Race or ethnic group was reported by the participants. The designation "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Table 2: Discontinuation reasons according to an acute change in eGFR (per 3 weeks) in the canagliflozin and placebo groups

Participants, n (%)	Canagliflozin (n = 2144)	P	Placebo (n = 2145)	P
Total reasons				
All	519/2144 (24.2)		629/2145 (29.3)	
Acute eGFR drop (>10%)	247/956 (25.8)	0.13	144/450 (32.0)	0.25
Acute modest eGFR drop (>0 to 10%)	128/600 (21.3)		193/646 (29.9)	
Acute eGFR increase (≥0%)	144/588 (24.5)		292/1049 (27.8)	
Adverse event				
All	254/2144 (11.9)		273/2145 (12.7)	
Acute eGFR drop (>10%)	117/956 (12.2)	0.17	62/450 (13.8)	0.53
Acute modest eGFR drop (>0 to <10%)	59/600 (9.8)		86/646 (13.3)	
Acute eGFR increase (≥0%)	78/588 (13.3)		125/1049 (11.9)	
Personal reasons				
All	153/2144 (7.1)		188/2145 (8.8)	
Acute eGFR drop (>10%)	83/956 (8.7)	0.04	43/450 (9.6)	0.31
Acute modest eGFR drop (>0 to <10%)	33/600 (5.5)		63/646 (9.8)	
Acute eGFR increase (≥0%)	37/588 (6.3)		82/1049 (7.8)	
Dialysis or renal transplant				
All	18/2144 (0.8)		28/2145 (1.3)	
Acute eGFR drop (>10%)	7/956 (0.7)	0.74	9/450 (2.0)	0.34
Acute modest eGFR drop (>0 to <10%)	6/600 (1.0)		7/646 (1.1)	
Acute eGFR increase (≥0%)	5/588 (0.9)		12/1049 (1.1)	
Poor compliance				
All	14/2144 (0.7)		17/2145 (0.8)	
Acute eGFR drop (>10%)	6/956 (0.6)	0.75	4/450 (0.9)	0.22
Acute modest eGFR drop (>0 to <10%)	3/600 (0.5)		8/646 (1.2)	
Acute eGFR increase (≥0%)	5/588 (0.9)		5/1049 (0.5)	
Safety or tolerability				
All	13/2144 (0.6)		19/2145 (0.9)	
Acute eGFR drop (>10%)	4/956 (0.4)	0.33	2/450 (0.4)	0.39
Acute modest eGFR drop (>0 to <10%)	6/600 (1.0)		5/646 (0.8)	
Acute eGFR increase (≥0%)	3/588 (0.5)		12/1049 (1.1)	

Other*				
All	67/2144 (3.1)		104/2145 (4.9)	
Acute eGFR drop (>10%)	30/956 (3.1)	0.74	24/450 (5.3)	0.28
Acute modest eGFR drop (>0 to <10%)	21/600 (3.5)		24/646 (3.7)	
Acute eGFR increase (≥0%)	16/588 (2.7)		56/1049 (5.3)	

Difference across categories was tested using chi-square test.
*Other included disallowed therapy, protocol violation, site closure, and other reasons.

Supplementary material

Supplementary information is available at Kidney International's website

Supplementary Table 1: Effects of canagliflozin on an acute eGFR change across baseline participant subgroups

Abbreviations: eGFR, estimated glomerular filtration ratio, UACR, urinary albumin-to-creatinine ratio; RAAS, renin angiotensin aldosterone system.

Race or ethnic group was reported by patients. The designation "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Supplementary Table 2: Discontinuation reasons according to an acute change in eGFR (per 3 weeks) in the canagliflozin and placebo groups

Supplementary Table 3: Multivariable adjusted annual changes in eGFR for follow-up (from week 13 to the last available measurements) in the canagliflozin and placebo groups by screening eGFR

Supplementary Table 4: Number of participants with adverse events during the acute phase (from baseline to week 3) according to acute change in eGFR in the canagliflozin and placebo groups

Supplementary Table 5: Adjusted hazard ratios and 95% confidence intervals for the risk of adverse events during follow-up by baseline eGFR

On-treatment analyses are performed from week 3 through 30 days after the last date of study drug. Time to the first occurrence of adverse event after week 3 was analysed.

Baseline covariates include age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic blood pressure, HbA1c, eGFR, log-transformed UACR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, and use of diuretic and RAAS inhibitor.

Renal related adverse events include acute kidney injury, anuria, azotemia, blood creatinine increased, blood urea increased, glomerular filtration ratio decreased, nephropathy toxic, oliguria, renal failure, and renal impairment

Hyperkalaemia was spontaneously reported by the investigator. The summary counts provided for the adverse event of hyperkalaemia include the MedDRA preferred terms of "hyperkalaemia" and "blood potassium increased."

Supplementary Table 6: Hazard ratios and 95% confidence intervals for the effects of canagliflozin versus placebo on adverse events stratified by the medium likelihood of experiencing an acute drop in eGFR >10%.

Supplementary Figure 1: Adjusted mean (standard error) eGFR for follow-up (from week 13 to the last available measurements) in the participants with an acute eGFR decrease >30% after canagliflozin initiation

Supplementary Figure 2: Adjusted hazard ratios and 95% confidence intervals for the risk of adverse events during follow-up according to an acute change in eGFR (per 3 weeks) in the canagliflozin and placebo groups

On-treatment analyses are performed from week 3 through 30 days after the last date of study drug. Time to the first occurrence of adverse event after week 3 was analysed. Baseline covariates include age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic blood pressure, HbA1c, eGFR, log-transformed UACR, HDL

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cholesterol, LDL cholesterol, log-transformed triglycerides, and use of diuretic and RAAS inhibitor.

Renal related adverse events include acute kidney injury, anuria, azotemia, blood creatinine increased, blood urea increased, glomerular filtration ratio decreased, nephropathy toxic, oliguria, renal failure, and renal impairment

Hyperkalaemia was spontaneously reported by the investigator. The summary counts provided for the adverse event of hyperkalaemia include the MedDRA preferred terms of "hyperkalaemia" and "blood potassium increased."

Supplementary Figure 3: The study design of our analysis

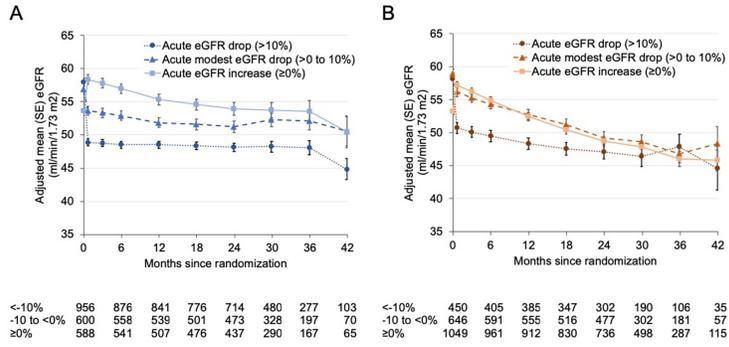Supplementary items are available on Kidney International's web site.

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	Number of participants with an event, n/N (%)			Odds ratio (95% CI)	*P* for interaction
	Canagliflozin	**Placebo**			
Overall	956/2144 (45)	450/2145 (21)		3.03 (2.65, 3.47)	NA
Age					
<55 years	166/394 (42)	91/379 (24)		2.30 (1.69, 3.14)	0.07
55-<65 years	339/773 (44)	149/751 (20)		3.16 (2.51, 3.97)	
65-<75 years	341/771 (44)	167/798 (21)		3.00 (2.40, 3.74)	
≥75 years	110/206 (53)	43/217 (20)		4.64 (3.01, 7.14)	
Sex					
Male	635/1408 (45)	288/1432 (20)		3.26 (2.76, 3.85)	0.14
Female	321/736 (44)	162/713 (23)		2.63 (2.09, 3.30)	
Race or ethnic group					
White	630/1459 (43)	298/1409 (21)		2.83 (2.40, 3.34)	0.45
Black	51/107 (48)	21/107 (20)		3.73 (2.03, 6.86)	
Asian	187/407 (46)	82/438 (19)		3.69 (2.71, 5.03)	
Other	88/171 (51)	49/191 (26)		3.07 (1.97, 4.78)	
Current smoker					
No	803/1811 (44)	400/1853 (22)		2.89 (2.50, 3.34)	0.09
Yes	153/333 (46)	50/292 (17)		4.11 (2.83, 5.97)	
History of hypertension					
No	30/68 (44)	18/70 (26)		2.28 (1.11, 4.68)	0.43
Yes	926/2076 (45)	432/2075 (21)		3.06 (2.67, 3.51)	
History of heart failure					
No	829/1824 (45)	377/1831 (21)		3.21 (2.78, 3.72)	0.04
Yes	127/320 (40)	73/314 (23)		2.17 (1.54, 3.07)	
History of cardiovascular disease					
No	479/1060 (45)	230/1065 (22)		2.99 (2.48, 3.62)	0.85
Yes	477/1084 (44)	220/1080 (20)		3.07 (2.54, 3.72)	
Body mass index					
<30 kg/m^2	419/967 (43)	205/995 (21)		2.95 (2.41, 3.60)	0.72
≥30 kg/m^2	534/1172 (46)	244/1147 (21)		3.10 (2.58, 3.72)	
Systolic blood pressure					
≤median	503/1173 (43)	233/1155 (20)		2.97 (2.47, 3.57)	0.73
>median	453/971 (47)	217/990 (22)		3.12 (2.56, 3.79)	
HbA1c					
<8%	459/995 (46)	207/1001 (21)		3.28 (2.70, 4.00)	0.28
≥8%	496/1148 (43)	242/1143 (21)		2.83 (2.36, 3.40)	
Screening eGFR					
30-<45 mL/min/1.73 m^2	365/887 (41)	174/878 (20)		2.87 (2.26, 3.65)	0.32
45-<60 mL/min/1.73 m^2	290/623 (47)	123/628 (20)		3.58 (2.78, 4.60)	
60-<90 mL/min/1.73 m^2	301/634 (47)	153/639 (24)		2.83 (2.29, 3.50)	
UACR					
<300 mg/g	95/264 (36)	50/253 (20)		2.28 (1.53, 3.40)	0.06
300-3000 mg/g	757/1651 (46)	330/1630 (20)		3.34 (2.86, 3.89)	
≥3000 mg/g	104/229 (45)	70/262 (27)		2.28 (1.56, 3.33)	
Use of insulin					
No	319/728 (44)	140/745 (19)		3.37 (2.66, 4.26)	0.28
Yes	637/1416 (45)	310/1400 (22)		2.88 (2.44, 3.39)	
Use of diuretic					
No	477/1140 (42)	217/1134 (19)		3.04 (2.52, 3.67)	0.99
Yes	479/1004 (48)	233/1011 (23)		3.05 (2.51, 3.69)	

Odds ratio (95% CI): 1.0   2.0   4.0   8.0

eGFR, estimated glomerular filtration rate, UACR, urinary albumin-to-creatinine ratio; RAAS, renin angiotensin aldosterone system.
Race or ethnic group was reported by the participants. The designation "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

A

<-10%	956	876	841	776	714	480	277	103
-10 to <0%	600	558	539	501	473	328	197	70
≥0%	588	541	507	476	437	290	167	65

B

<-10%	450	405	385	347	302	190	106	35
-10 to <0%	646	591	555	516	477	302	181	57
≥0%	1049	961	912	830	736	498	287	115

eGFR, estimated glomerular filtration ratio.

	Canagliflozin					Placebo				
	Number of events	Participants with an event per 1000 patient-years		Hazard ratio (95% CI)	P for Interaction	Number of events	Participants with an event per 1000 patient-years		Hazard ratio (95% CI)	P for Interaction
Any adverse events										
Acute eGFR drop (>10%)	778	874.2		1.08 (0.96, 1.21)	0.30	390	1200.6		1.17 (1.03, 1.32)	0.05
Acute modest eGFR drop (>0% to 10%)	480	852.8		1.13 (0.99, 1.29)		525	959.6		0.97 (0.86, 1.08)	
Acute eGFR increase (≥0%)	454	763.7		1 (reference)		879	1008.0		1 (reference)	
Any serious adverse events										
Acute eGFR drop (>10%)	322	175.7		0.96 (0.80, 1.16)	0.80	169	215.6		1.16 (0.97, 1.40)	0.11
Acute modest eGFR drop (>0% to 10%)	188	158.8		0.91 (0.74, 1.11)		232	193.2		1.07 (0.91, 1.27)	
Acute eGFR increase (≥0%)	198	177.1		1 (reference)		379	192.5		1 (reference)	
Any renal related events										
Acute eGFR drop (>10%)	133	65.0		1.24 (0.92, 1.66)	0.08	90	100.4		1.26 (0.97, 1.64)	0.08
Acute modest eGFR drop (>0% to 10%)	61	45.6		0.77 (0.55, 1.09)		113	84.8		1.12 (0.88, 1.42)	
Acute eGFR increase (≥0%)	74	59.1		1 (reference)		173	78.9		1 (reference)	
Any serious renal related events										
Acute eGFR drop (>10%)	27	12.7		0.85 (0.47, 1.53)	0.73	17	18.1		1.05 (0.59, 1.87)	0.98
Acute modest eGFR drop (>0% to 10%)	10	7.2		0.41 (0.18, 0.89)		21	14.9		0.87 (0.51, 1.48)	
Acute eGFR increase (≥0%)	21	16.2		1 (reference)		40	17.4		1 (reference)	
Acute kidney injury										
Acute eGFR drop (>10%)	39	18.4		0.81 (0.49, 1.32)	0.59	21	22.5		1.14 (0.67, 1.93)	0.78
Acute modest eGFR drop (>0% to 10%)	12	8.7		0.34 (0.17, 0.69)		23	16.4		0.85 (0.51, 1.41)	
Acute eGFR increase (≥0%)	30	23.4		1 (reference)		46	20.1		1 (reference)	
Hyperkalemia										
Acute eGFR drop (>10%)	71	34.2		1.37 (0.90, 2.06)	0.10	33	36.4		1.04 (0.69, 1.56)	0.97
Acute modest eGFR drop (>0% to 10%)	35	25.8		0.97 (0.61, 1.57)		44	31.7		0.92 (0.64, 1.33)	
Acute eGFR increase (≥0%)	36	28.5		1 (reference)		90	40.4		1 (reference)	

0.25 0.5 1.0 2.0 4.0
Hazard ratio (95% CI)

0.25 0.5 1.0 2.0 4.0
Hazard ratio (95% CI)

The adjusted hazard ratios compared those with an acute eGFR drop (>10%) or an acute modest eGFR drop (>0% to 10%) with those who had an acute eGFR increase (≥0%). This comparison was made within the canagliflozin and placebo groups separately. On-treatment analyses are performed from week 3 through 30 days after the last date of study drug. Time to the first occurrence of adverse event after week 3 was analyzed and the analyses were adjusted for the following baseline covariates include age, sex, race or ethnic group, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body mass index, systolic blood pressure, HbA1c, eGFR, log-transformed UACR, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, and use of diuretic and RAAS inhibitor.
Renal related adverse events include acute kidney injury, anuria, azotemia, blood creatinine increased, blood urea increased, glomerular filtration ratio decreased, nephropathy toxic, oliguria, renal failure, and renal impairment.
Hyperkalemia was 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.