Different eGFR decline thresholds and the renal effects of canagliflozin: data from the CANVAS Program

Megumi Oshima,[1,2] Bruce Neal,[1,3,4] Tadashi Toyama,[2] Toshiaki Ohkuma,[1] Qiang Li,[1] Dick de Zeeuw,[5] Hiddo J.L. Heerspink,[1,5] Kenneth W. Mahaffey,[6] Gregory Fulcher,[7] William Canovatchel,[8] David R. Matthews,[9] Vlado Perkovic[1]

[1]Department of Renal and Metabolic, The George Institute for Global Health, UNSW Sydney, Sydney, Australia; [2]Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan; [3]The Charles Perkins Centre, University of Sydney, Sydney, Australia; [4]Imperial College London, London, UK; [5]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [6]Stanford University School of Medicine, Stanford, CA, USA; [7]Royal North Shore Hospital, Sydney, Australia; [8] Janssen Global Services, LLC, Raritan, NJ, USA; [9]Harris Manchester College, University of Oxford, Oxford, UK.

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Corresponding author

Vlado Perkovic

The George Institute for Global Health

UNSW Sydney

Level 5, 1 King St.

Newtown NSW 2042

Australia

Telephone: +61 2 8052 4300

Fax: +61 2 8052 4301

Email: vlado.perkovic@unsw.edu.au

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Significance statement

Traditionally, the effects of new therapies on renal outcome is tested using doubling of serum creatinine (≈57% eGFR reduction) as an endpoint, requiring large clinical trials. The use of lesser eGFR reductions has been proposed, but few studies have evaluated their reliability. In this post hoc study of the CANVAS Program, use of 50%, 40%, and 30% eGFR reductions resulted in a greater number of observed events compared to 57%. Observed effect sizes for canagliflozin versus placebo were attenuated when lesser eGFR reductions were used, most likely due to the acute effect of SGLT2 inhibition on eGFR. These data support the consideration of lesser eGFR decline thresholds for the evaluation of SGLT2 inhibitors, if the acute effect is controlled for.

Abstract

Background

Traditionally, creatinine-based renal endpoints use doubling of serum creatinine (equivalent to a 57% estimated glomerular filtration rate [eGFR] reduction) requiring large clinical trials. We assessed whether lesser eGFR declines could detect the effects of canagliflozin on renal outcomes observed in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program to reduce the sample size required in clinical trials.

Methods

This post hoc study compared the effects of canagliflozin versus placebo on the composite renal outcomes that used sustained 57%, 50%, 40%, or 30% eGFR reductions, in conjunction with end-stage kidney disease and renal death. Because canagliflozin causes an acute reversible hemodynamic fall in eGFR, we made estimates using all eGFR values, as well as estimates that excluded early measures of eGFR influenced by the acute hemodynamic effect.

Results

Among the 10,142 participants, 93 (0.9%), 161 (1.6%), 352 (3.5%), and 800 (7.9%) participants recorded renal outcomes based upon a 57%, 50%, 40%, or 30% eGFR reduction, respectively, during mean follow-up of 188 weeks. Compared to a 57% eGFR reduction (risk ratio 0.51 [95% CI 0.34–0.77]), the effect sizes were progressively attenuated when using 50% (0.61 [0.45–0.83]), 40% (0.70 [0.57–0.86]), or 30% (0.81 [0.71–0.93]) eGFR reductions. In analyses controlled for the acute hemodynamic fall in eGFR, effect sizes were comparable regardless of whether a 57%, 50%, 40%, or 30% eGFR reduction was used.

Conclusions

Declines in eGFR less than 57% may provide robust estimates of the effects of canagliflozin on renal outcomes, if the acute effect is controlled for.

Introduction

Type 2 diabetes remains the most common cause of kidney failure throughout the world,[1, 2] although a growing number of treatments have been shown to improve prognosis.[3–5] Further effective treatments are needed and, in order to define their efficacy in clinical trials, clinically meaningful endpoints responsive to therapy are required. Doubling of serum creatinine (sCr), which is equivalent to a 57% reduction in estimated glomerular filtration rate (eGFR), is an established endpoint that is highly predictive of end-stage kidney disease (ESKD).[6] However, as the rate of decline in kidney function is typically moderate in many people, particularly in the earlier stages of type 2 diabetes,[7] the use of a 57% eGFR reduction in clinical trials in patients with type 2 diabetes requires large sample sizes to accumulate an adequate number of events, which can limit the feasibility of these studies. To overcome this issue and encourage development of new reno-protective therapy, a workshop convened by the US National Kidney Foundation (NKF) and the US Food and Drug Administration (FDA) proposed the utility of lesser eGFR decline thresholds as alternative renal endpoints (e.g., a 30% or a 40% eGFR reduction) to evaluate the reno-protective effects of the treatments, particularly with no acute hemodynamic effect.[6, 8, 9-12] This strategy has been tested previously[8] and can potentially increase the number of events and thus statistical power, which may result in a decrease in sample size and follow-up duration as well as trial cost, but has been infrequently validated beyond the original dataset used to support these outcomes. While a number of clinical trials have recently used lesser eGFR decline thresholds as alternative renal endpoints,[13–17] these endpoints vary in definition of the threshold used (30%, 40%, or 50% eGFR reductions) as well as whether sustained and unsustained reductions were used. Further characterization of the benefits and challenges of these novel endpoints, and their various definitions, is therefore required.

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed as a glucose-lowering agent in patients with type 2 diabetes. SGLT2 inhibitors promote urinary glucose excretion and alter intrarenal hemodynamics, leading to improvement in blood glucose, blood pressure, and body weight in people with type 2 diabetes.[18, 19] In the CANagliflozin cardioVascular

Assessment Study (CANVAS) Program, which consisted of two parallel trials (CANVAS and CANVAS-R),[1, 13] canagliflozin was associated with a 43% reduction in the risk of the composite renal outcome based upon sustained doubling of sCr, ESKD, and renal death (hazard ratio 0.53 [95% confidence interval (CI) 0.33–0.84]) in participants with type 2 diabetes and a history or high risk of cardiovascular disease. These effects were consistent across baseline participant characteristics, including kidney function and albuminuria,[20, 21] suggesting that SGLT2 inhibitors have potential renal benefits. These benefits have recently been confirmed prospectively in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, conducted in a population of individuals at very high renal risk, who had type 2 diabetes and established kidney disease.[4] Canagliflozin use is associated with an acute reversible fall in eGFR followed by the stabilization of kidney function and is an example of a treatment in which the use of lesser eGFR decline thresholds is of uncertain value.

We performed a post hoc analysis of data from the CANVAS Program to determine whether use of lesser eGFR decline thresholds demonstrate similar effects of canagliflozin, compared to the usual 57% eGFR reduction. In addition, as SGLT2 inhibitors typically induce an acute hemodynamic fall in eGFR soon after their initiation,[19, 20] we assessed whether this acute effect of canagliflozin influenced use of lesser eGFR decline thresholds.

Methods

Study design and participants

The CANVAS Program comprised two multicenter, double-blind, placebo-controlled, randomized trials, CANVAS and CANVAS-R, conducted in comparable populations and designed to collectively assess the cardiovascular safety and efficacy of canagliflozin, as well as its effect on renal and adverse outcomes, in participants with type 2 diabetes and a history or high risk of cardiovascular disease. A detailed description of the design has been published previously.[13, 22, 23] In brief, a total of 10,142 individuals were recruited from 667 centers in 30 countries: 4330 in CANVAS between December 2009 and March 2011 and 5812 in CANVAS-R between January

2014 and May 2015. Both trials were scheduled for joint close out and analysis when at least 688 cardiovascular events had occurred, and the last randomized participant had undergone at least 78 weeks of follow-up; this occurred in February 2017.

The main inclusion criteria for both trials were identical and included participants with type 2 diabetes mellitus (glycated hemoglobin [HbA1c] ≥7.0% and ≤10.5%) who were either ≥30 years old with established atherosclerotic vascular disease or ≥50 years old with two or more cardiovascular risk factors.[13, 22, 23] These risk factors included duration of diabetes of at least 10 years; systolic blood pressure >140 mmHg while receiving one or more antihypertensive agents; current smoking; microalbuminuria or macroalbuminuria; or high-density lipoprotein cholesterol level <1 mmol/L. Participants with a baseline eGFR <30 mL/min/1.73 m^2 were excluded.

Participants underwent a 2-week, single-blind, placebo run-in period before randomization. Participants in CANVAS were randomly assigned in a 1:1:1 ratio to receive canagliflozin 100 mg daily, canagliflozin 300 mg daily, or matching placebo, while participants in CANVAS-R were randomly assigned in a 1:1 ratio to receive canagliflozin 100 mg daily or matching placebo, with an optional increase to 300 mg or matching placebo daily starting from Week 13.

The trials are registered with ClinicalTrials.gov, numbers NCT01032629 (CANVAS) and NCT01989754 (CANVAS-R). Local institutional ethics committees approved the trial protocols at each site. All participants provided written informed consent. Both trials were conducted according to the principles outlined in the Declaration of Helsinki.

Study visits and measurements

After randomization, three face-to-face follow-up sessions were scheduled in the first year, with additional sessions scheduled at 6-month intervals thereafter, which alternated between telephone follow-up and face-to-face assessments. The measurement of sCr was done in a central laboratory by use of the Jaffe method with rate blanking[24] at least three times in the first year after randomization, and every 26 weeks thereafter. eGFR was estimated by use of the Modification of

Diet in Renal Disease equation.[25] Investigators and sites were encouraged to use local best-practice guidelines for other glycemic management and background therapies.

Outcomes

For this study, we defined the primary outcomes as the composite of various eGFR reductions (57%, 50%, 40%, and 30%), ESKD (defined as the composite of maintenance dialysis that was sustained for ≥30 days, renal transplantation, or eGFR <15 mL/min/1.73 m^2 that was sustained for ≥30 days), or renal death (defined as participant death with a proximate renal cause). These primary outcomes required eGFR reductions that were sustained for two consecutive measurements ≥30 days apart unless the reduction was identified on the last available measurement during follow-up.

To assess the impact of requiring sustained reductions, additional analyses were performed (1) after excluding those events where the outcome was defined on the last available measurement and not confirmed as sustained, and (2) including all reductions whether sustained or not. ESKD and renal death were prespecified in the study protocols and adjudicated by a renal endpoint adjudication committee that was blinded to group allocation.[13, 22, 23] Although the prespecified kidney outcome for the main trial included doubling of sCr and a 40% eGFR reduction that were adjudicated, this study did not use these adjudicated eGFR reductions to allow more direct comparability between the various eGFR decline thresholds.

Analysis using eGFR at Week 6/13 as baseline

Participants assigned to canagliflozin had an acute fall in eGFR during the first weeks after randomization compared to those assigned to placebo,[20] as expected.[19] Because this early hemodynamic decline might confound the analyses, we did subsidiary investigations in which we assigned the first on-treatment, postrandomization measure of eGFR as the baseline value. This measure was made at Week 6 postrandomization in CANVAS and Week 13 in CANVAS-R. We used off-treatment measurements at Week 0 in those assigned to placebo in both trials

(Supplemental Figure 1). After excluding participants in the canagliflozin group who missed sCr measurement after Week 6/13 (*N*=80, including five patients who died before Week 6/13), 10,062 participants were included.

Data sharing information

Data from the CANVAS Program 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 have been approved by regulators in the United States and European Union and the study has been completed for 18 months. The trial protocols and statistical analysis plans were published along with the primary CANVAS Program manuscript.[13]

Statistical analyses

Analyses are reported for the full integrated dataset that includes all randomly assigned participants in the CANVAS Program using the intention-to-treat (ITT) approach for both canagliflozin doses combined versus placebo.

The treatment effects of canagliflozin were assessed by using Kaplan-Meier analyses and log-rank tests, in which time to the first event was counted, with any subsequent events disregarded. Because the proportional hazards assumption did not hold for the eGFR reductions other than 57% that were used in this study by testing based upon the scaled Schoenfeld residuals, we estimated risk ratios (RRs) and 95% CIs for the composite renal outcomes using log-binomial regression models adjusted for baseline eGFR and trial (CANVAS or CANVAS-R). Annualized incidence rates in the canagliflozin and placebo groups were calculated separately per 1000 patient-years of follow-up. Subgroup analyses were undertaken for baseline participant categories including trial (CANVAS or CANVAS-R), age (<65 or ≥65 years), sex, race (White, Asian, or other), HbA1c (<8 or ≥8%), eGFR (<60 or ≥60 mL/min/1.73 m^2), and albuminuria (<30 or ≥30 mg/g). The interaction between subgroups was tested by adding interaction terms between the treatment and subgroups to the model.

Indicative comparative sample sizes required to demonstrate the effects of canagliflozin on the composite renal outcomes were calculated retrospectively using the observed results for event rates and RRs and assuming follow-up duration of 5 years (two-sided α=0.05 and 90% power). Dropout rates were not considered for the sample size calculation. Required sample sizes were also estimated for participants with baseline eGFR of ≥60 and <60 mL/min/1.73 m^2. To evaluate individual benefit of canagliflozin versus placebo on the composite renal outcomes, the number of patients who needed to be treated to prevent 1 event during 5 years was calculated as the reciprocal of the difference between the event rates at 5 years in the canagliflozin and placebo groups.

There were two participants (0.02%) without a baseline sCr measurement. eGFR reductions were calculated using all available follow-up data and assumed that missing data was missing at random. All analyses were conducted using Stata/MP, version 15 (Stata Corporation, College Station, TX, USA). A two-sided *P* value <0.05 was considered statistically significant.

Results

Participants characteristics

A total of 10,142 participants were randomized and recruited to the ITT population, including 4347 in the placebo group and 5795 in the canagliflozin group; among those, 9734 participants (96.0%) completed the trial. As previously described,[13, 20] at baseline, mean (SD) age was 63.3 (8.3) years, 64.2% were male, mean (SD) eGFR was 76.5 (20.5) mL/min/1.73 m^2, and median urinary albumin:creatinine ratio (UACR) (interquartile range) was 12.3 (6.7–42.1) mg/g (Supplemental Table 1). Baseline characteristics for participants were well balanced across randomized treatment groups.[13, 20]

Treatment effects on composite renal outcomes

During the mean (SD) follow-up of 188 (106) weeks (296 [74] weeks in CANVAS and 108 [20] weeks in CANVAS-R), 93 (0.9%), 161 (1.6%), 352 (3.5%), and 800 (7.9%) participants in the total

population developed an outcome based upon 57%, 50%, 40%, and 30% reductions in eGFR, respectively, while 21 (0.2%) participants developed ESKD or renal death.

Canagliflozin significantly decreased the risk of the primary outcome based upon 57%, 50%, 40%, and 30% eGFR reductions compared with placebo (all log-rank tests *P* <0.001, Figure 1). As shown in Figure 2, the event rate for the primary outcome based upon 57%, 50%, 40%, and 30% eGFR reductions was lower with canagliflozin than with placebo; the events occurred in 1.9 versus 3.7, 3.6 versus 5.8, 8.2 versus 12.3, and 20.3 versus 26.5 participants per 1000 patient-years, respectively. The effect size of canagliflozin on the composite of a 57% eGFR reduction, ESKD, and renal death (RR 0.51 [95% CI 0.34–0.77]) was similar to the composite of ESKD and renal death (0.56 [0.24–1.32]). However, the effect size was progressively attenuated when a 57% eGFR reduction was replaced by a 50% (RR 0.61 [95% CI 0.45–0.83]), 40% (0.70 [0.57–0.86]), or 30% eGFR reduction (0.81 [0.71–0.93]). Similar effect sizes were observed after excluding eGFR reductions made on the last available measurement for which evidence of a sustained decline was not available, although the event rate was reduced by approximately half. When all reductions were included, the proportional effect estimates were decreased further, and effect estimates for canagliflozin versus placebo were no longer significant; although the event rates nearly doubled.

The pattern of treatment effects of canagliflozin on the primary outcomes were generally consistent across baseline participant categories including baseline eGFR and albuminuria with moderate heterogeneity (Supplemental Figure 2).

Treatment effects controlling for acute hemodynamic effects

Calculating the effects of canagliflozin versus placebo on the composite renal outcomes using Week 6/13 eGFR data as baseline for the canagliflozin group (to remove the impact of the acute hemodynamic fall in eGFR associated with the use of canagliflozin) meant that the attenuation of effect associated with using lesser eGFR reductions in the composite renal outcome was mostly removed; RRs (95% CI) were 0.38 (0.24–0.60) when a 57% eGFR reduction was used in the composite renal outcome, 0.44 (0.31–0.62) when a 50% eGFR reduction was used, 0.43 (0.33–

0.54) when a 40% eGFR reduction was used, and 0.49 (0.42–0.57) when a 30% eGFR reduction was used (Figure 3). After excluding eGFR reductions based upon the last available measurement, event rates fell as before, but stronger estimated effect sizes were observed for all eGFR decline thresholds. When all reductions were included, the effect sizes were smaller but still significant for every eGFR decline threshold. Similar treatment effects of canagliflozin on the primary outcomes were observed between participants with baseline eGFR of ≥60 and <60 mL/min/1.73 m^2 (all *P* for interaction >0.4, Supplemental Figure 3).

Required sample sizes

Figure 4 and Supplemental Table 2 show the required sample sizes for demonstrating a range of effect sizes for the composite renal outcome. For the primary analytic approach based upon using all baseline and follow-up measurements, lowering the eGFR decline threshold from a 57% reduction to a 30% reduction had little effect on the sample size required. Requiring sustained reductions (Figure 4A, diamond-shaped data points) required smaller sample sizes across all eGFR decline thresholds compared to estimates that also included eGFR reductions detected at the last visit for which a sustained effect could not be confirmed (Figure 4A, circular data points) or both sustained and unsustained reductions (Figure 4A, triangular data points).

The use of on-treatment baseline data for canagliflozin, which removes the confounding impact of the acute hemodynamic effects of canagliflozin on eGFR (Figure 4B), greatly decreased required sample sizes regardless of the persistence of the reduction in eGFR; using a 30% eGFR reduction within the composite renal outcome and including all reductions rather than any other strategy.

Patients with baseline eGFR of ≥60 mL/min/1.73 m^2 required smaller sample sizes across all eGFR decline thresholds compared to patients with eGFR of <60 mL/min/1.73 m^2 when all baseline and follow-up measurements were used (Supplemental Figure 4A and Supplemental Table 3A). When on-treatment baseline values were used for the canagliflozin group, required

sample sizes decreased to the similar extent among patients with eGFR of ≥60 and <60 mL/min/1.73 m^2 (Supplemental Figure 4B and Supplemental Table 3B).

Numbers needed to treat

The number of participants who needed to be treated for 5 years was 111 (95% CI 81–173) when a 57% eGFR reduction was used in the composite renal outcome, and progressively decreased when 50% (88 [64–140]), 40% (50 [38–71]), and 30% (32 [25–46]) eGFR reductions were used (Supplemental Table 4). When the acute hemodynamic effects were controlled for, the smaller number was observed across all eGFR decline thresholds; 14 (95% CI 13–16) patients were needed to be treated for 5 years to prevent 1 composite event of a 30% eGFR reduction, ESKD, or renal death.

Discussion

In this study, we assessed the treatment effects of canagliflozin versus placebo on different eGFR decline thresholds, definitions, and study designs in people with type 2 diabetes, using the data from the CANVAS Program. Canagliflozin significantly decreased the risk of the composite renal outcome based upon 57%, 50%, 40%, and 30% eGFR reductions, compared with placebo. Compared to a 57% eGFR reduction, use of lesser eGFR decline thresholds resulted in a greater number of observed events, but under standard analytic approaches, the effect sizes were attenuated when lesser eGFR decline thresholds were incorporated into the composite renal outcome. The estimated sample size to be required in clinical trials was thus not affected by lesser eGFR decline thresholds.

The pattern of attenuation of the treatment effects shown in this study was consistent with a previous study[8] and meta-analysis[6, 9, 11] that assessed the treatment effects of various interventions. These studies suggested that agents with a substantial acute hemodynamic effect on eGFR may not be suitable for study with trials using endpoints based on lesser eGFR decline thresholds.[6, 8, 9, 11] SGLT2 inhibitors induce an acute hemodynamic effect on eGFR soon after

initiation, regardless of baseline kidney function,[18, 27] and this was indeed observed in the CANVAS Program, though canagliflozin subsequently slowed down the rate of eGFR decline during follow-up.[20] Similar patterns were observed in clinical trials using other SGLT2 inhibitors such as empagliflozin and dapagliflozin.[27–29]

We found that use of sustained reductions in eGFR showed stronger treatment effects across all eGFR decline thresholds, compared to when all eGFR reductions were used, whether sustained or not. Similarly, according to the previous meta-analysis from 37 randomized controlled trials[6] in which eGFR reductions were confirmed at the next available visit (a median of 3.2 months after the initial visit), use of unconfirmed endpoints resulted in 10% to 50% more events but underestimated treatment effects compared to confirmed endpoints. This observation is consistent with a simulation study addressing this issue.[11] Unsustained eGFR reductions are more likely to capture fluctuations in eGFR caused by acute kidney injury, dehydration, measurement error, and acute treatment effects, rather than true declines in kidney function. The inclusion of such events in analyses designed to assess treatment effects introduces noise, and this biases effect estimates toward the null. These results support the utility of confirming eGFR reductions with consecutive measurements, which was the recommendation made by the NKF/FDA workshop addressing this question.[9]

In this study, we also assessed whether the use of different baseline measures of eGFR might reduce possible confounding caused by the acute reversible hemodynamic effect of canagliflozin treatment. In a prospective trial this might be done by having a short active run-in period prior to randomization, which then generates both on-treatment and off-treatment baseline measures for each participant. The postrandomization values could then be compared to the relevant baseline to judge whether an outcome has occurred; for example, people randomized to canagliflozin would have subsequent eGFR levels compared to those at the end of the active run-in period, whereas those randomized to placebo could be compared to the eGFR measurement prior to the run-in period. In addition, a short follow-up after discontinuation of treatment at the end

of the trial might be considered in this design to test whether the acute hemodynamic fall in eGFR is reversible after long-term treatment.

While there is a potential additional risk of bias resulting from temporally separated baseline measures for the groups, this can be minimized by keeping the run-in period short. While CANVAS did not have an active run-in period, we retrospectively assessed the potential value of this approach by calculating eGFR reductions from postrandomization measurements made at Week 6/13 of follow-up in the canagliflozin group. We found that this approach almost entirely removed the attenuation of effect estimates otherwise associated with including lesser declines in eGFR within the composite renal outcome. We also found that the estimates of treatment effect using this approach appeared less susceptible to noise from random fluctuation, such that the results remained clear even when all reductions, not just sustained reductions, were used. This approach is thus likely to reduce expense and time necessary to confirm eGFR reductions, which will have significant cost implication.

Currently established renal endpoints based upon a 57% eGFR reduction require large clinical trials, which may discourage the development of new treatments for kidney diseases.[9] We demonstrated that use of a sustained 40% eGFR reduction would greatly decrease sample size requirements compared to a 57% eGFR reduction, if on-treatment baseline values were used for the canagliflozin group, regardless of persistence of the eGFR decline. The number needed to treat similarly decreased when lesser eGFR decline thresholds were used, indicating the greater benefit of canagliflozin versus placebo to individual patients. These results reflect primarily the impact of the much greater number of events available to assess the same effect size on the outcome of interest. Our study suggests that use of a 30% eGFR reduction may be a reasonable alternative endpoint for assessing renal effects in clinical trials of SGLT2 inhibitors, particularly in the earlier stages of type 2 diabetes and chronic kidney disease, if the effect of the acute hemodynamic decline in eGFR is controlled for (Figure 5). Likewise, the data suggest that use of a 30% eGFR reduction would be reasonable for the evaluation of other reno-protective drugs in which acute eGFR effects are not a feature.

Our subgroup analyses by baseline eGFR found similar patterns of reduction in required sample sizes if on-treatment baseline values were used for the canagliflozin group. This was inconsistent with a previous simulation study, reporting that required sample size decreased with lesser eGFR decline thresholds when mean baseline eGFR was high (67.5 mL/min/1.73 m^2) but was stable across eGFR decline thresholds when mean baseline eGFR was low (27.5 mL/min/1.73 m^2).[Greene et al 2014] This inconsistency may be because the majority of the participants in the CANVAS program included patients with relatively high baseline eGFR (mean eGFR 76.5 [SD 20.5] mL/min/1.73 m^2) and only 554 participants (5.5% of total population) had baseline eGFR of <45 mL/min/1.73 m^2. Further investigation is needed for validating the utility of lesser eGFR declines in the cohort of the advanced stages of chronic kidney disease.

The key strength of this study is that the data were derived from a large, multicenter, randomized controlled trial program that was conducted to an extremely high standard with long duration of follow-up. The multiple measurements of sCr allowed comprehensive exploration of the effects of using sustained and unsustained eGFR reductions. However, our study has several limitations. First, the eGFR decline thresholds were not adjudicated and our exploratory analyses using the postrandomization eGFR measures as a substitute for notional on-treatment baseline values may be subject to bias. Second, lesser eGFR declines are subject to greater degrees of measurement error and are more likely to lead to false events. Even a small acute treatment effect can cause an increase in the rate of type 1 errors for a 30% or 40% eGFR declines,[Levey et al 2014][Greene et al 2014] which may lead to erroneous conclusions for benefits or harms of interventions. We recommend careful consideration of these alternative endpoints in the design of future clinical trials. Finally, our study cohort did not have much population with severe kidney dysfunction, which may limit generalizability to the advanced stages of type 2 diabetes and chronic kidney disease.

In conclusion, the use of lesser eGFR decline thresholds may offer a valid and highly cost-effective approach to identifying the reno-protective effect of SGLT2 inhibitors and other agents designed to protect kidney function. Further investigation in prospective trials is warranted.

Author contributions

M.O. and V.P. designed the study; M.O. performed the analyses under T.T., T.O., Q.L., and V.P.; all authors interpreted the data; M.O., V.P., and B.N. drafted the article; all authors revised it; all authors approved the final version of the manuscript; all authors agreed with the work.

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Supplemental Figure 1: The study design of our analysis.

Supplemental Figure 2: Subgroup analyses for the effects of canagliflozin versus placebo (risk ratios and 95% confidence CIs) on the composite renal outcomes using an eGFR reduction of either 57%, 50%, 40%, or 30%, plus end-stage kidney disease or renal death.

Supplemental Figure 3: Effects of canagliflozin versus placebo (risk ratios and 95% CIs) by baseline eGFR on the composite renal outcomes according to whether eGFR reductions were adjusted for the acute hemodynamic effect of canagliflozin.

Supplemental Figure 4: Required sample sizes by baseline eGFR for assessing treatment effects of canagliflozin on the composite renal outcomes when eGFR reductions were (A) uncontrolled for acute hemodynamic effects and (B) controlled for acute hemodynamic effects.

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Figure legends

Figure 1: Effects of canagliflozin versus placebo on the composite renal outcomes using an eGFR reduction of either (A) 57%, (B) 50%, (C) 40%, or (D) 30%, plus end-stage kidney disease or renal death.

ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; RR, risk ratio; CI, confidence interval.

eGFR decline was based upon reductions sustained for two consecutive measurements ≥30 days apart unless identified on the last available measurement. Log-rank test was used to assess the treatment effect of canagliflozin versus placebo.

Figure 2: Effects of canagliflozin versus placebo (risk ratios and 95% CIs) on the composite renal outcomes according to whether eGFR reductions were sustained or not.

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

The prespecified study outcome was based upon reductions that were sustained for two consecutive measurements ≥30 days apart or those identified on the last available measurement. Sustained reductions only were defined as reductions that were sustained for two consecutive measurements ≥30 days apart. All reductions were defined as sustained or unsustained reductions.

Figure 3: Effects of canagliflozin versus placebo (risk ratios and 95% CIs) on the composite renal outcomes according to whether eGFR reductions were adjusted for the acute hemodynamic effect of canagliflozin.

CI, confidence interval; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.

Sustained and unsustained reductions defined as above. Acute hemodynamic effects were controlled for by using first postbaseline eGFR measurements for those assigned to canagliflozin.

Figure 4: Required sample sizes for assessing treatment effects of canagliflozin on the composite renal outcomes when eGFR reductions were (A) uncontrolled for acute hemodynamic effects and (B) controlled for acute hemodynamic effects.

ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.

Effects of using prespecified definitions of eGFR decline (diamond-shaped data points), only sustained reductions in eGFR (circular data points) or all reductions sustained or unsustained (triangular data points).

Figure 5: Proposed design of a randomized clinical trial assessing the effects of a therapy with an acute effect on eGFR.

eGFR, estimated glomerular filtration rate.

Figure 1: Effects of canagliflozin versus placebo on the composite renal outcomes using an eGFR reduction of either (A) 57%, (B) 50%, (C) 40%, or (D) 30%, plus end-stage kidney disease or renal death.

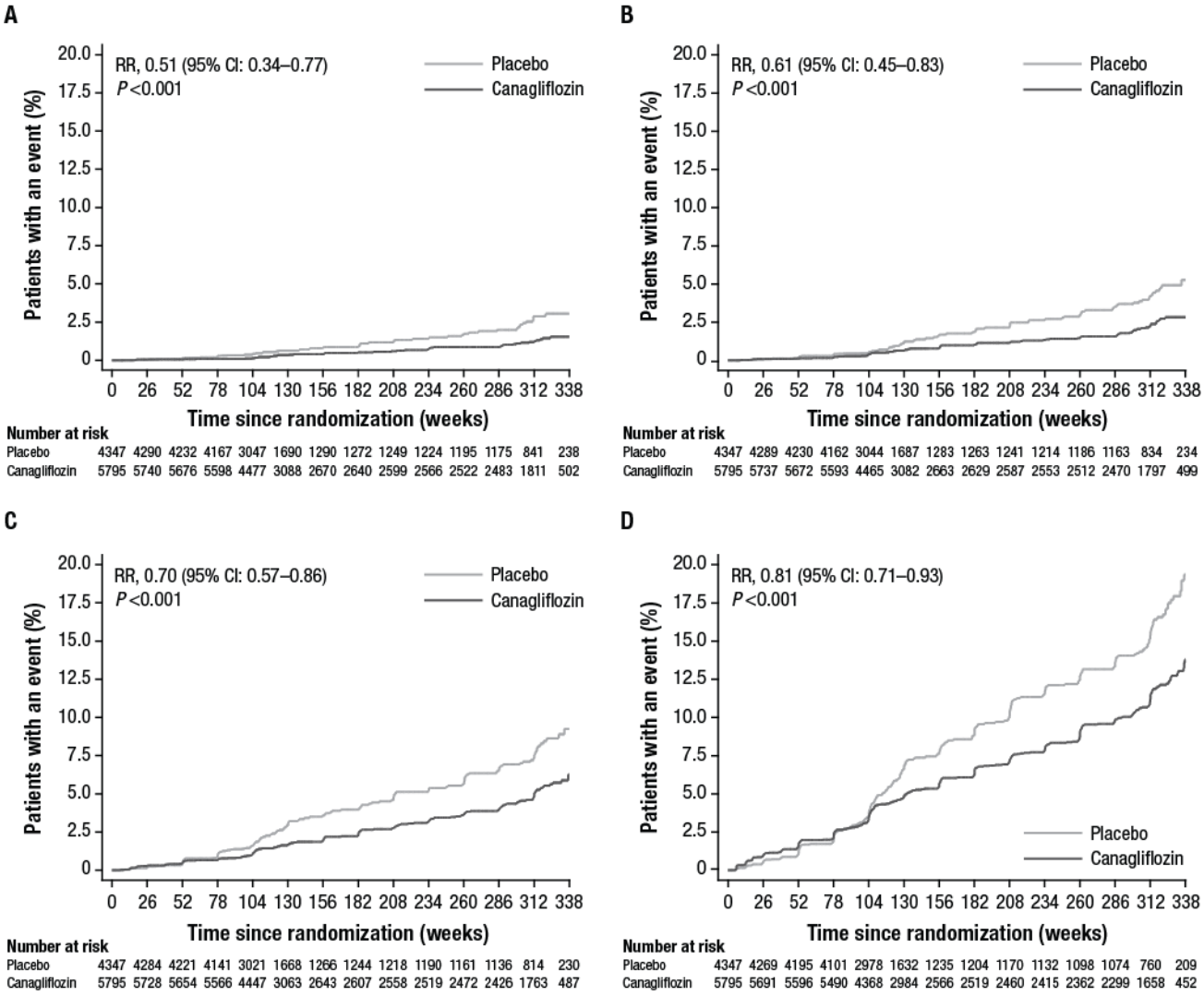

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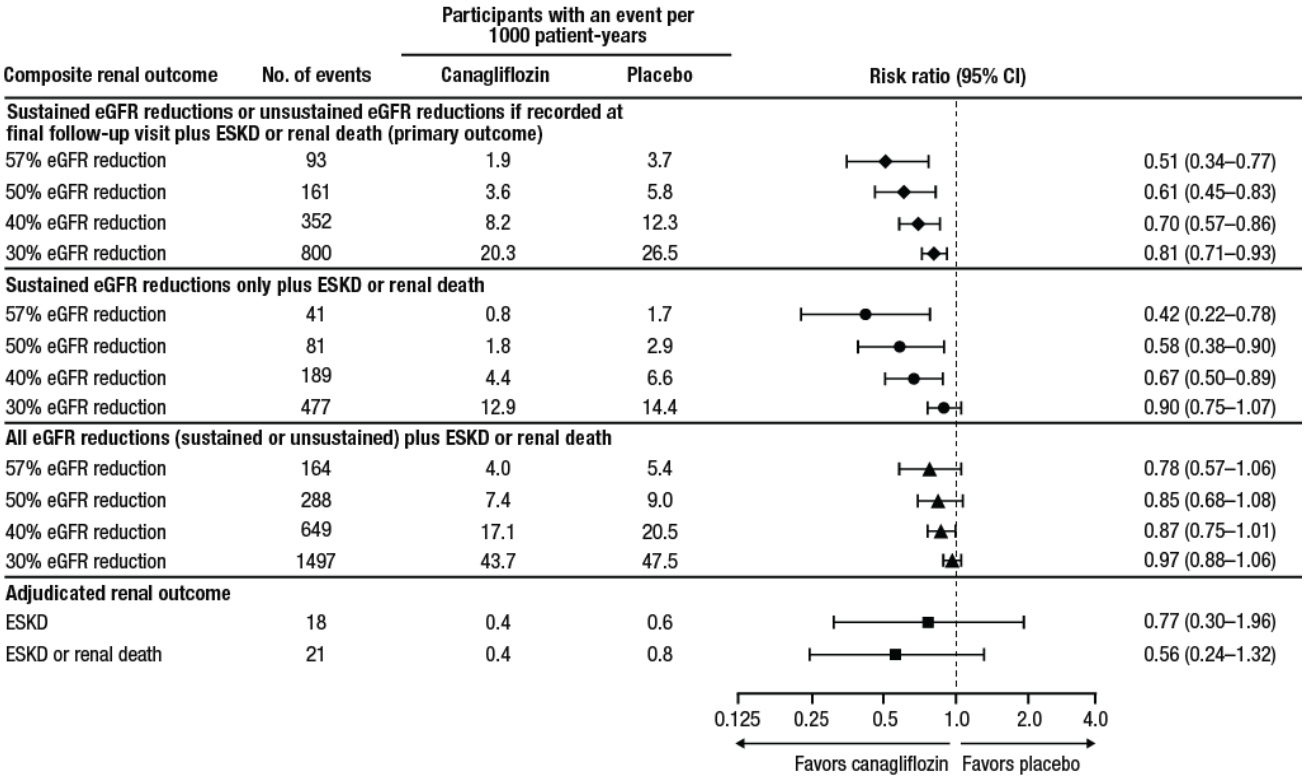
Figure 2: Effects of canagliflozin versus placebo (risk ratios and 95% CIs) on the composite renal outcomes according to whether reductions were sustained or not.



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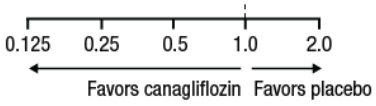
The prespecified study outcome was based upon reductions that were sustained for two consecutive measurements ≥30 days apart or those identified on the last available measurement. Sustained reductions only were defined as reductions that were sustained for two consecutive measurements ≥30 days apart. All reductions were defined as sustained or unsustained reductions.

Figure 3: Effects of canagliflozin versus placebo (risk ratios and 95% CIs) on the composite renal outcomes according to whether eGFR reductions were adjusted for the acute hemodynamic effect of canagliflozin.

Composite renal outcome	No. of events	Participants with an event per 1000 patient-years: Canagliflozin	Placebo	Risk ratio (95% CI)
Sustained eGFR reductions or unsustained eGFR reductions if recorded at final follow-up visit plus ESKD or renal death (primary outcome)				
57% eGFR reduction	81	1.4	3.7	0.38 (0.24–0.60)
50% eGFR reduction	137	2.6	5.8	0.44 (0.31–0.62)
40% eGFR reduction	279	5.2	12.3	0.43 (0.33–0.54)
30% eGFR reduction	618	12.4	26.5	0.49 (0.42–0.57)
Sustained eGFR reductions only plus ESKD or renal death				
57% eGFR reduction	36	0.6	1.7	0.27 (0.13–0.54)
50% eGFR reduction	63	1.0	2.9	0.31 (0.18–0.51)
40% eGFR reduction	144	2.5	6.6	0.35 (0.25–0.50)
30% eGFR reduction	328	6.3	14.4	0.42 (0.34–0.53)
All eGFR reductions (sustained or unsustained) plus ESKD or renal death				
57% eGFR reduction	135	2.8	5.4	0.55 (0.39–0.77)
50% eGFR reduction	230	5.0	9.0	0.57 (0.44–0.74)
40% eGFR reduction	493	10.3	20.5	0.52 (0.43–0.62)
30% eGFR reduction	1117	25.0	47.5	0.56 (0.50–0.63)
Adjudicated renal outcome				
ESKD	18	0.5	0.6	0.56 (0.22–1.46)
ESKD or renal death	21	0.5	0.8	0.41 (0.17–0.98)



CI, confidence interval; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.
Sustained and unsustained reductions defined as above. Acute hemodynamic effects were controlled for by using first postbaseline eGFR measurements for those assigned to canagliflozin.

Figure 4: Required sample sizes for assessing treatment effects of canagliflozin on the composite renal outcomes when eGFR reductions were (A) uncontrolled for acute hemodynamic effects and (B) controlled for acute hemodynamic effects.

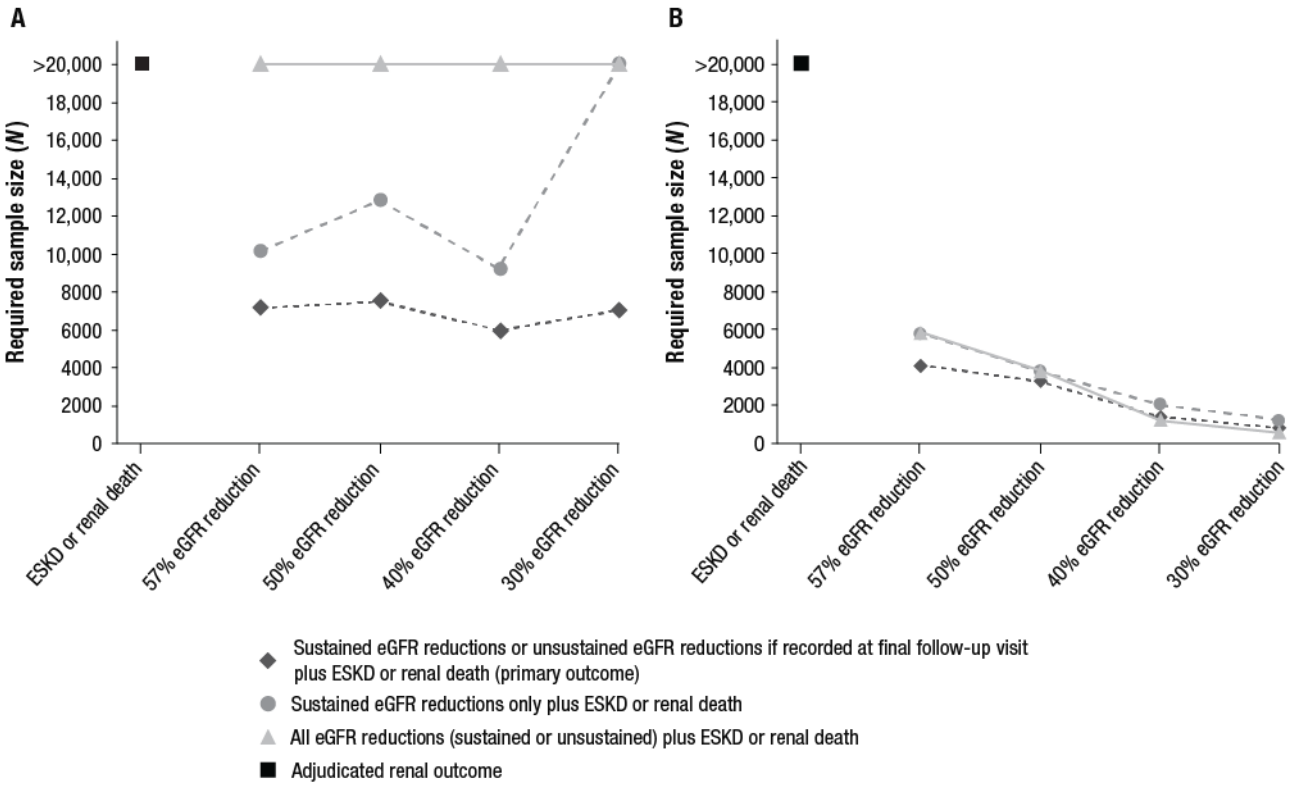


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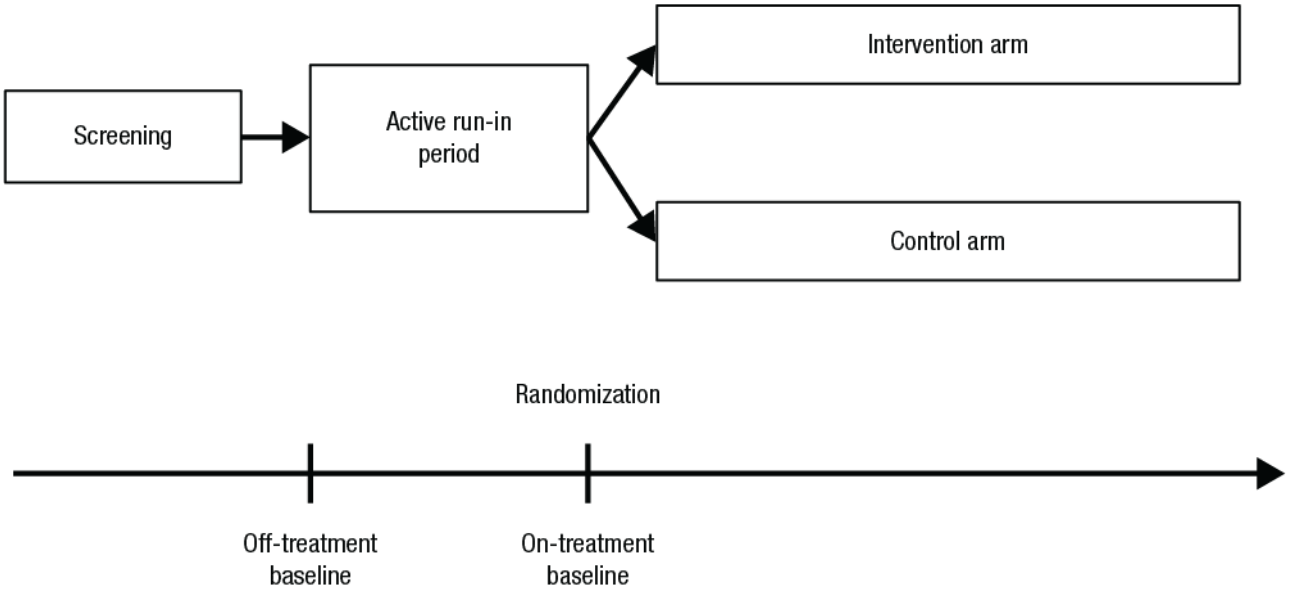
Figure 5: Proposed design of a randomized clinical trial assessing the effects of a therapy with an acute effect on eGFR.



eGFR, estimated glomerular filtration rate.

Supplementary Appendix

Supplemental Table 1: Baseline Characteristics in the CANVAS Program

Characteristic*	**Canagliflozin (*n*=5795)**	**Placebo (*n*=4347)**	**Total† (*n*=10,142)**
Age, y	63.2 (8.3)	63.4 (8.2)	63.3 (8.3)
Female, n (%)	2036 (35.1)	1597 (36.7)	3633 (35.8)
Race, n (%)‡			
White	4508 (77.8)	3436 (79.0)	7944 (78.3)
Asian	777 (13.4)	507 (11.7)	1284 (12.7)
Black	176 (3.0)	160 (3.7)	336 (3.3)
Other	334 (5.8)	244 (5.6)	578 (5.7)
Current smoker, n (%)	1020 (17.6)	786 (18.1)	1806 (17.8)
History of hypertension, n (%)	5188 (89.5)	3937 (90.6)	9125 (90.0)
History of heart failure, n (%)	803 (13.9)	658 (15.1)	1461 (14.4)
Duration of diabetes, y)	13.5 (7.7)	13.7 (7.8)	13.5 (7.8)
History of microvascular disease, n (%)			
Retinopathy	1203 (20.8)	926 (21.3)	2129 (21.0)
Nephropathy	994 (17.2)	780 (17.9)	1774 (17.5)
Neuropathy	1787 (30.8)	1323 (30.4)	3110 (30.7)
History of atherosclerotic vascular disease, n (%)§			
Coronary	3234 (55.8)	2487 (57.2)	5721 (56.4)
Cerebrovascular	1113 (19.2)	845 (19.4)	1958 (19.3)
Peripheral	1176 (20.3)	937 (21.6)	2113 (20.8)
Any	4127 (71.2)	3197 (73.5)	7324 (72.2)
History of cardiovascular disease, n (%)|	3756 (64.8)	2900 (66.7)	6656 (65.6)
History of amputation, n (%)	136 (2.3)	102 (2.3)	238 (2.3)
Body-mass index, kg/m^2	31.9 (5.9)	32.0 (6.0)	32.0 (5.9)
Systolic blood pressure, mmHg	136.4 (15.8)	136.9 (15.8)	136.6 (15.8)
Diastolic blood pressure, mmHg	77.6 (9.6)	77.8 (9.7)	77.7 (9.7)
Glycated hemoglobin, %	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
Cholesterol (mmol/L)			
Total	4.4 (1.1)	4.4 (1.2)	4.4 (1.2)
HDL	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
LDL	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)
Ratio of LDL to HDL	2.0 (0.9)	2.0 (0.9)	2.0 (0.9
Triglycerides, mmol/L	2.0 (1.3)	2.0 (1.5)	2.0 (1.4)
eGFR, mL/min/1.73 m^2	76.7 (20.3)	76.2 (20.8)	76.5 (20.5)
Median urinary albumin:creatinine ratio (mg/g Cr [interquartile range])	12.4 (6.71–40.9)	12.1 (6.57–43.9)	12.3 (6.65–42.1)

CANVAS, CANagliflozin cardioVascular Assessment Study; SD, standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; Cr, creatinine.
*Data are mean (SD) unless otherwise noted.
†One participant underwent randomization at two different sites; only the first randomization is included in the intention-to-treat analysis set.
‡Race was determined by investigator inquiry of the participant. Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple races, other races, and unknown.
§Some participants had more than one type of atherosclerotic disease.
|A history of cardiovascular disease was defined as a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular, or peripheral).

Supplemental Table 2: Required Sample Sizes for Assessing Treatment Effects of Canagliflozin on the Composite Renal Outcomes When eGFR Reductions were (A) Uncontrolled for Acute Hemodynamic Effects and (B) Controlled for Acute Hemodynamic Effects

Composite renal outcome	A	B
Primary outcome (sustained eGFR reductions or unsustained eGFR reductions if recorded at final follow-up visit plus ESKD or renal death)		
57% eGFR reduction	7152	4116
50% eGFR reduction	7548	3272
40% eGFR reduction	5962	1410
30% eGFR reduction	7074	798
Sustained eGFR reductions only plus ESKD or renal death		
57% eGFR reduction	10164	5768
50% eGFR reduction	12860	3822
40% eGFR reduction	9242	2022
30% eGFR reduction	46812	1182
All eGFR reductions (sustained or unsustained) plus ESKD or renal death		
57% eGFR reduction	27772	5852
50% eGFR reduction	38552	3800
40% eGFR reduction	21220	1224
30% eGFR reduction	115474	588
Adjudicated renal outcome		
ESKD or renal death	41548	20958

ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.

Supplemental Table 3: Required Sample Sizes by Baseline eGFR for Assessing Treatment Effects of Canagliflozin on the Composite Renal Outcomes When eGFR Reductions were (A) Uncontrolled for Acute Hemodynamic Effects and (B) Controlled for Acute Hemodynamic Effects

Composite renal outcome	A	B
eGFR ≥60 mL/min/1.73 m^2		
Primary outcome (sustained eGFR reductions or unsustained eGFR reductions if recorded at final follow-up visit plus ESKD or renal death)		
57% eGFR reduction	5686	3468
50% eGFR reduction	5394	3078
40% eGFR reduction	5030	1436
30% eGFR reduction	4380	858
Adjudicated renal outcome		
ESKD or renal death	80748	31048
eGFR <60 mL/min/1.73 m^2		
Primary outcome (sustained eGFR reductions or unsustained eGFR reductions if recorded at final follow-up visit plus ESKD or renal death)		
57% eGFR reduction	21352	3292
50% eGFR reduction	79324	2384
40% eGFR reduction	14770	984
30% eGFR reduction	1168674	540
Adjudicated renal outcome		
ESKD or renal death	13908	7666

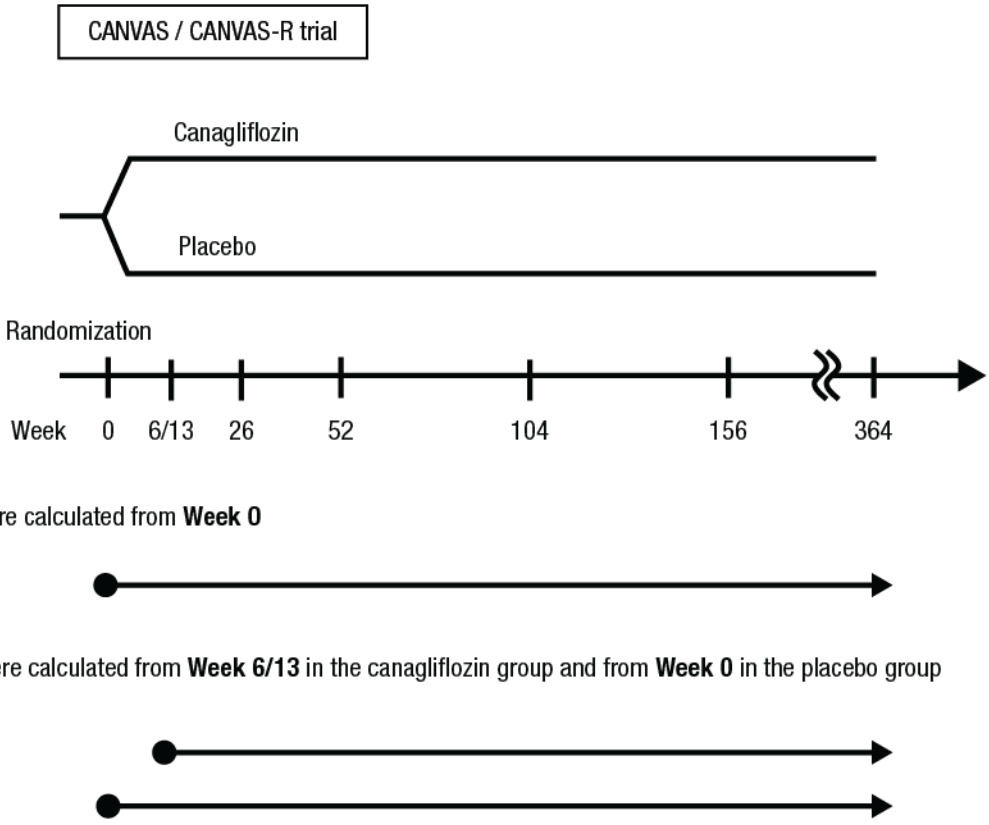
ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.

Supplemental Table 4: Number Needed to Treat (and 95% CI) for the Composite Renal Outcomes for 5 years when eGFR Reductions were (A) Uncontrolled for Acute Hemodynamic Effects and (B) Controlled for Acute Hemodynamic Effects

Composite renal outcome	A	B
Primary outcome (sustained eGFR reductions or unsustained eGFR reductions if recorded at final follow-up visit plus ESKD or renal death)		
57% eGFR reduction	111 (81–173)	89 (70–123)
50% eGFR reduction	88 (64–140)	63 (50–84)
40% eGFR reduction	50 (38–71)	28 (24–34)
30% eGFR reduction	32 (25–46)	14 (13–16)
Sustained eGFR reductions only plus ESKD or renal death		
57% eGFR reduction	208 (142–378)	172 (125–267)
50% eGFR reduction	172 (113–355)	105 (81–147)
40% eGFR reduction	92 (65–156)	49 (41–62)
30% eGFR reduction	132 (69–1637)	25 (21–29)
All eGFR reductions (sustained or unsustained) plus ESKD or renal death		
57% eGFR reduction	143 (89–356)	79 (60–114)
50% eGFR reduction	127 (75–414)	51 (40–68)
40% eGFR reduction	60 (40–-116)	20 (17–23)
30% eGFR reduction	53 (33–-139)	9 (8–10)
Adjudicated renal outcome		
ESKD or renal death	588 (302–6204)	667*

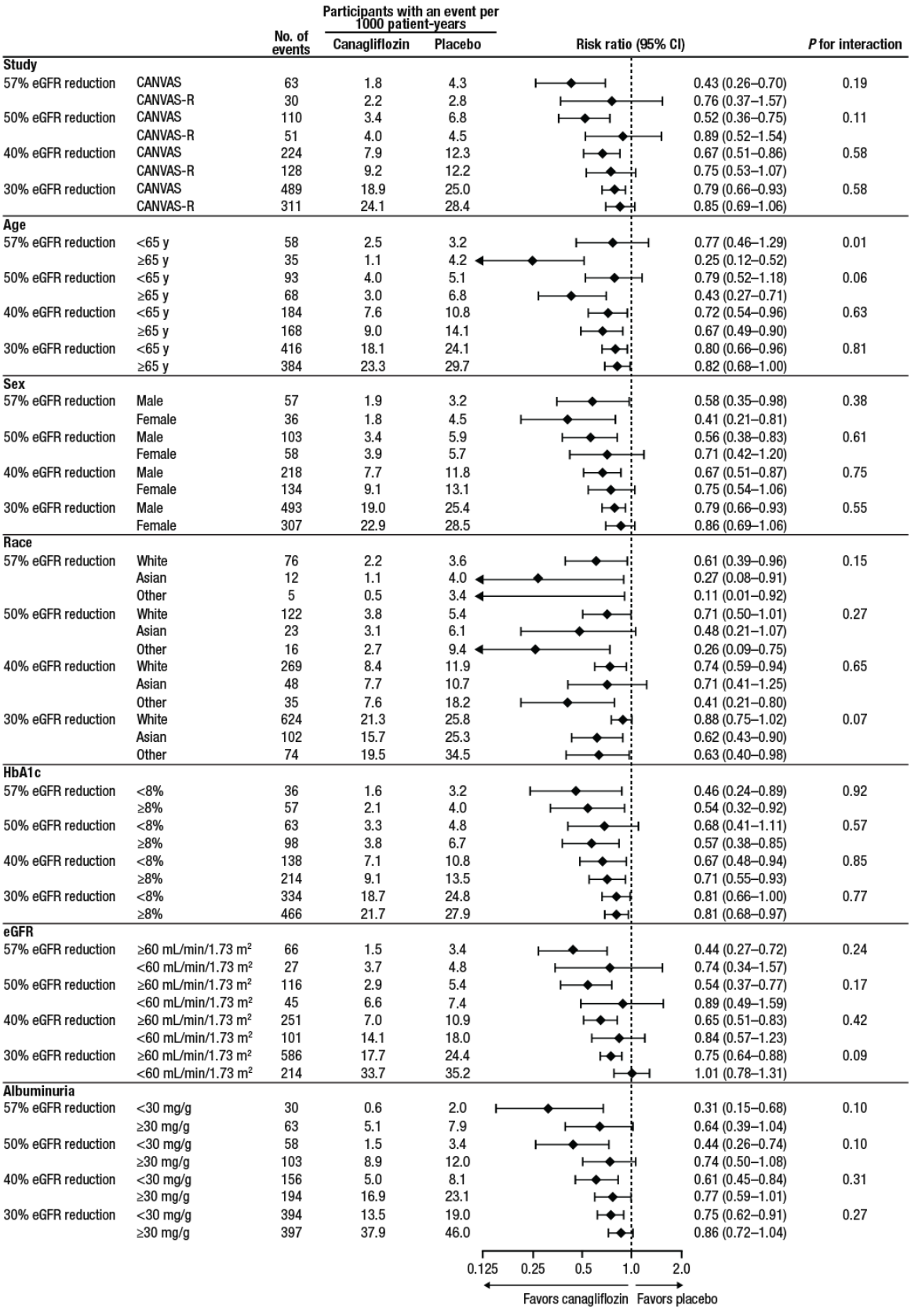
ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.
*The 95% CI for number needed to treat is not provided when the 95% CI includes 0.

Supplemental Figure 1: The study design of our analysis.



CANVAS, CANagliflozin cardioVscular Assessment Study; eGFR, estimated glomerular filtration rate.

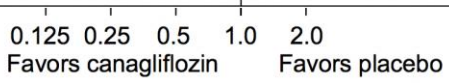
Supplemental Figure 2: Subgroup analyses for the effects of canagliflozin versus placebo (risk ratios and 95% CIs) on the composite renal outcomes using an eGFR reduction of either 57%, 50%, 40%, or 30%, plus end-stage kidney disease or renal death.



CI, confidence interval; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.
eGFR decline was based upon reductions sustained for two consecutive measurements ≥30 days apart unless identified on the last available measurement.

Supplemental Figure 3: Effects of canagliflozin versus placebo (risk ratios and 95% CIs) by baseline eGFR on the composite renal outcomes according to whether eGFR reductions were adjusted for the acute hemodynamic effect of canagliflozin.

		No. of events	Participants with an event per 1000 patient-years		Risk ratio (95% CI)	*P for interaction*
			Canagliflozin	Placebo		
57% eGFR reduction	eGFR ≥60	58	1.1	3.4	0.32 (0.18–0.56)	0.48
	eGFR <60	23	2.8	4.8	0.40 (0.18–0.89)	
50% eGFR reduction	eGFR ≥60	101	2.3	5.4	0.41 (0.27–0.62)	0.77
	eGFR <60	36	4.5	7.4	0.43 (0.22–0.81)	
40% eGFR reduction	eGFR ≥60	198	4.4	10.9	0.40 (0.30–0.54)	0.78
	eGFR <60	81	9.3	18.0	0.44 (0.29–0.67)	
30% eGFR reduction	eGFR ≥60	455	10.8	24.4	0.48 (0.40–0.58)	0.74
	eGFR <60	163	20.3	35.2	0.47 (0.35–0.63)	



CI, confidence interval; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.
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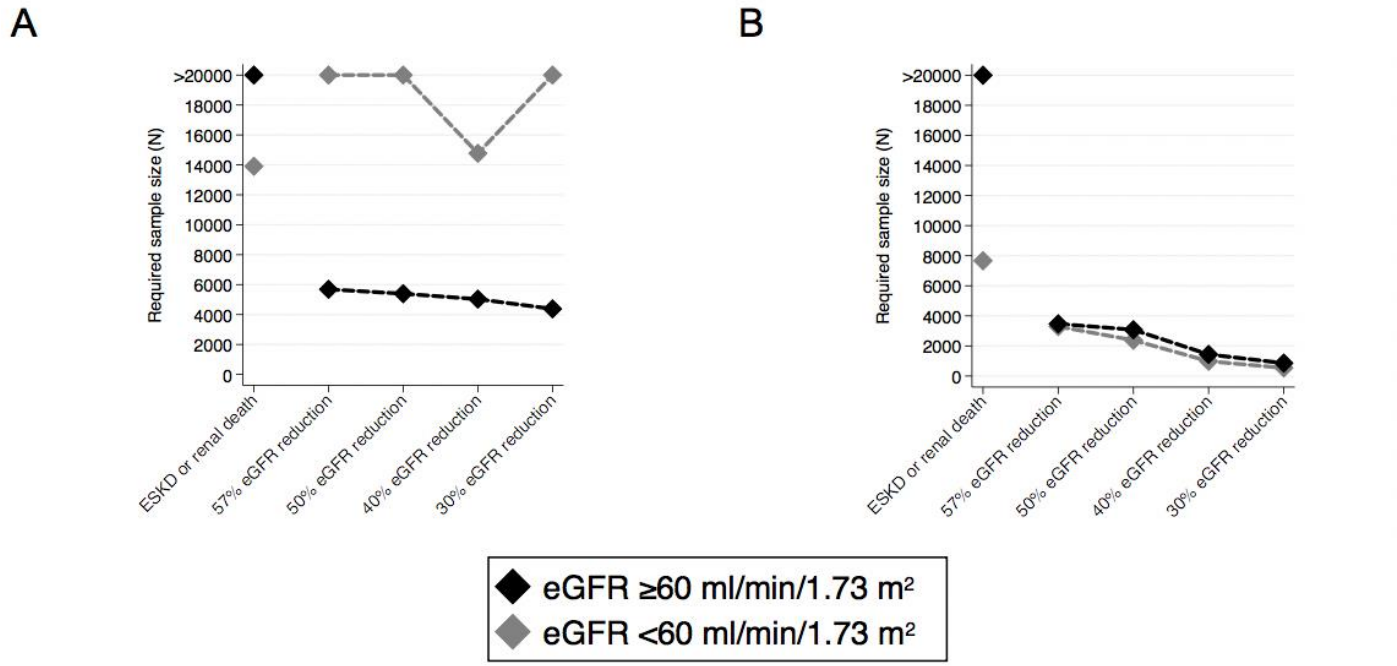
Supplemental Figure 4: Required sample sizes by baseline eGFR for assessing treatment effects of canagliflozin on the composite renal outcomes when eGFR reductions were (A) uncontrolled for acute hemodynamic effects and (B) controlled for acute hemodynamic effects.



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