Different eGFR Decline Thresholds and Renal Effects of Canagliflozin: Data from the CANVAS Program

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ABSTRACT

Background Traditionally, clinical trials evaluating effects of a new therapy with creatinine-based renal end points use doubling of serum creatinine (equivalent to a 57% eGFR reduction), requiring large sample sizes.

Methods To assess whether eGFR declines <57% could detect canagliflozin’s effects on renal outcomes, we conducted a post hoc study comparing effects of canagliflozin versus placebo on composite renal outcomes using sustained 57%, 50%, 40%, or 30% eGFR reductions in conjunction with ESKD and renal death. Because canagliflozin causes an acute reversible hemodynamic decline 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 on the basis of 57%, 50%, 40%, or 30% eGFR reduction, respectively, during a mean follow-up of 188 weeks. Compared with a 57% eGFR reduction (risk ratio [RR], 0.51; 95% confidence interval [95% CI], 0.34 to 0.77), the effect sizes were progressively attenuated when using 50% (RR, 0.61; 95% CI, 0.45 to 0.83), 40% (RR, 0.70; 95% CI, 0.57 to 0.86), or 30% (RR, 0.81; 95% CI, 0.71 to 0.93) eGFR reductions. In analyses that 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. Estimated sample sizes for studies on the basis of lesser eGFR reductions were much reduced by controlling for this early hemodynamic effect.

Conclusions Declines in eGFR <57% may provide robust estimates of canagliflozin’s effects on renal outcomes if the analysis controls for the drug’s acute hemodynamic effect.

Clinical Trial registry name and registration number: CANagliflozin cardioVascular Assessment Study (CANVAS), NCT01032629 and CANVAS-R, NCT01989754.

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 end points responsive to therapy are required. Doubling of serum creatinine (sCr), which is equivalent to a 57% reduction in eGFR, is an established end point that is highly predictive of ESKD.6 However, because 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

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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 renoprotective 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 end points (e.g., a 30% or a 40% eGFR reduction) to evaluate the renoprotective effects of the treatments, particularly those with no acute hemodynamic effect.\(^6,8\) This strategy has been tested previously\(^1,2\) 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 it has been infrequently validated beyond the original dataset used to support these outcomes. Although a number of clinical trials have recently used lesser eGFR decline thresholds as alternative renal end points,\(^3,6,8,11\) these end points vary in definition of the threshold used (30%, 40%, or 50% eGFR reduction) as well as whether sustained and unsustained reductions were used. Further characterization of the benefits and challenges of these novel end points and their various definitions is therefore required.

Canagliflozin is a sodium glucose cotransporter 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, BP, and body weight in people with type 2 diabetes.\(^1,8,19\) In the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, which consisted of two parallel trials (CANVAS and CANVAS-Renal [CANVAS-R]),\(^1,13\) canagliflozin was associated with a 43% reduction in the risk of the composite renal outcome on the basis of sustained doubling of sCr, ESKD, and renal death (hazard ratio, 0.53; 95% confidence interval [95% CI], 0.33 to 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, which was 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 it 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 demonstrates similar effects of canagliflozin compared with 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.
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 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. 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, or eGFR<15 ml/min per 1.73 m² 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 effect 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 end point adjudication committee that was blinded to group allocation. 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 with those assigned to placebo, as expected. 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 5 participants 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/) after 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.

**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 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 on the basis of 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), glycated hemoglobin (<8% or ≥8%), eGFR (<60 or ≥60 ml/min per 1.73 m²), 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 a 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 per 1.73 m². To evaluate individual benefit of canagliflozin versus placebo on the composite renal outcomes, the number of participants who needed to be treated (NNT) to prevent one event over 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 (0.02%) participants without a baseline sCr measurement. eGFR reductions were calculated using all available follow-up data and assumed that missing data were missing at random. All analyses were conducted using Stata/MP, version 15 (Stata Corporation, College Station, TX). A two-sided P value <0.05 was considered statistically significant.

RESULTS

Participant Characteristics
A total of 10,142 participants were randomized and recruited to the intention-to-treat 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 men, mean (SD) eGFR was 76.5 (20.5) ml/min per 1.73 m², and median urinary albumin-creatinine ratio was 12.3 (interquartile range, 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 on the basis of 57%, 50%, 40%, and 30% reductions in eGFR, respectively, whereas 21 (0.2%) participants developed ESKD or renal death.

Canagliflozin significantly decreased the risk of the primary outcome on the basis of 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 on the basis of 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 to 0.77) was similar to the composite of ESKD and renal death (RR, 0.56; 95% CI, 0.24 to 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 to 0.83), 40% (RR, 0.70; 95% CI, 0.57 to 0.86), or 30% (RR, 0.81; 95% CI, 0.71 to 0.93) eGFR reduction. 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 was generally consistent across baseline participant categories, including baseline eGFR and albuminuria, though there was some evidence of heterogeneity for a few outcomes (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 effect 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% CIs) were 0.38 (0.24 to 0.60) when a 57% eGFR reduction was used in the composite renal outcome, 0.44 (0.31 to 0.62) when a 50% eGFR reduction was used, 0.43 (0.33 to 0.54) when a 40% eGFR reduction was used, and 0.49 (0.42 to 0.57) when a 30% eGFR reduction was used (Figure 3). After excluding eGFR reductions on the basis of 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 eGFRs of ≥60 and <60 ml/min per 1.73 m² (all P values for interaction >0.48) (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 on the basis of 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 with 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 effect 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; the smaller sample sizes were required when both sustained and unsustained lesser eGFR reductions were used within the composite renal outcome. Participants with baseline eGFR of ≥60 ml/min per 1.73 m² required smaller sample sizes across lesser eGFR reductions compared with participants with eGFR of
60 ml/min per 1.73 m² when all baseline and follow-up measurements were used (Supplemental Figure 4A, Supplemental Table 3A). When on-treatment baseline values were used for the canagliflozin group, required sample sizes decreased to a similar extent among participants with eGFR of $60 \text{ and } 60 \text{ ml/min per 1.73 m}²$ (Supplemental Figure 4B, Supplemental Table 3B).

**Numbers Needed to Treat**

The NNT for 5 years was 111 (95% CI, 81 to 173) when a 57% eGFR reduction was used in the composite renal outcome and progressively decreased when 50% (88; 95% CI, 64 to 140), 40% (50; 95% CI, 38 to 71), and 30% (32; 95% CI, 25 to 46) eGFR reductions were used (Supplemental Figure 4A, Supplemental Table 4A). After controlling for the acute hemodynamic effects, NNT decreased across all eGFR decline thresholds; when a 40% eGFR reduction was used, NNT decreased from 50 to 28 to prevent one composite renal event.

**DISCUSSION**

In this study, we assessed the effects of canagliflozin versus placebo on kidney outcomes defined by different eGFR decline thresholds and different possible study designs in people with type 2 diabetes using data from the CANVAS Program. Canagliflozin significantly decreased the risk of the composite renal outcome on the basis of 57%, 50%, 40%, and 30% eGFR reductions compared with placebo. Compared with 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 sizes required in clinical trials were not affected by use of lesser eGFR decline thresholds under this base model but were much reduced under a design in which the early hemodynamic effect of canagliflozin was controlled for.

The pattern of attenuation of the treatment effects shown in this study was consistent with a previous study and meta-analysis 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 end points on the basis of lesser eGFR decline thresholds. SGLT2 inhibitors induce an acute hemodynamic effect on eGFR soon after initiation, regardless of baseline kidney function, and this was indeed observed in the CANVAS Program, though canagliflozin subsequently slowed the rate of eGFR decline during follow-up. Similar patterns were observed in clinical trials using other SGLT2 inhibitors, such as empagliflozin and dapagliflozin.

We found that use of sustained reductions in eGFR resulted in stronger treatment effects across all eGFR decline thresholds compared with when all eGFR reductions were used, whether sustained or not. This parallels findings from a previous meta-analysis of 37 randomized, controlled trials in which eGFR reductions were confirmed at the next available visit (a median of 3.2 months after the initial visit), where use of unconfirmed end points resulted in 10%–50% more events but underestimated treatment effects compared with confirmed end points. This observation is also consistent with a simulation study addressing this issue. The reason for underestimation of effects is that unsustained eGFR reductions are more likely to capture fluctuations in eGFR caused by AKI, 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.

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.
were used. This approach is thus likely to reduce expense and noise from randomization measurements made at week 6/13 of follow-up in the long-term treatment. Although CANVAS did not have an active run-in period, we retrospectively assessed the potential value of this approach by calculating eGFR reductions from postrandomization values could then be compared with the relevant baseline to judge whether an outcome has occurred; for example, people randomized to canagliflozin would have subsequent eGFR levels compared with those at the end of the active run-in period, whereas those randomized to placebo could be compared with 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.

Although 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. Although 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. Sustained and unsustained reductions are defined as in Figure 2. Acute hemodynamic effects were controlled for by using first postbaseline eGFR measurements for those assigned to canagliflozin.

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The attenuated effect associated with using lesser eGFR reductions in the composite renal outcome was mostly removed by controlling for the acute hemodynamic effects of canagliflozin. Sustained and unsustained reductions are defined as in Figure 2. Acute hemodynamic effects were controlled for by using first postbaseline eGFR measurements for those assigned to canagliflozin.

<table>
<thead>
<tr>
<th>Composite renal outcome</th>
<th>No. of events</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Risk ratio (95% CI)</th>
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<tbody>
<tr>
<td>Sustained eGFR reductions or unsustained eGFR reductions if recorded at final follow-up visit plus ESKD or renal death (primary outcome)</td>
<td>57% eGFR reduction</td>
<td>81</td>
<td>3.7</td>
<td>0.38 (0.24–0.60)</td>
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<td>50% eGFR reduction</td>
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<td>5.8</td>
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<td>40% eGFR reduction</td>
<td>279</td>
<td>12.3</td>
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<td>30% eGFR reduction</td>
<td>618</td>
<td>26.5</td>
<td>0.49 (0.42–0.57)</td>
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<tr>
<td>Sustained eGFR reductions only plus ESKD or renal death</td>
<td>57% eGFR reduction</td>
<td>36</td>
<td>1.7</td>
<td>0.27 (0.13–0.54)</td>
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<tr>
<td>50% eGFR reduction</td>
<td>63</td>
<td>2.9</td>
<td>0.31 (0.18–0.51)</td>
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<td>40% eGFR reduction</td>
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<td>0.35 (0.25–0.50)</td>
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<td>30% eGFR reduction</td>
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<td>14.4</td>
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<td>All eGFR reductions (sustained or unsustained) plus ESKD or renal death</td>
<td>57% eGFR reduction</td>
<td>135</td>
<td>5.4</td>
<td>0.55 (0.39–0.77)</td>
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<td>50% eGFR reduction</td>
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<td>9.0</td>
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<tr>
<td>40% eGFR reduction</td>
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<td>20.5</td>
<td>0.52 (0.43–0.62)</td>
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<tr>
<td>30% eGFR reduction</td>
<td>1117</td>
<td>47.5</td>
<td>0.56 (0.50–0.63)</td>
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<td>Adjudicated renal outcome</td>
<td>ESKD</td>
<td>18</td>
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<td>0.56 (0.22–1.46)</td>
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<tr>
<td>ESKD or renal death</td>
<td>21</td>
<td>0.8</td>
<td>0.41 (0.17–0.98)</td>
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</table>

Figure 3. The attenuation of effect associated with using lesser eGFR reductions in the composite renal outcome was mostly removed by controlling for the acute hemodynamic effects of canagliflozin. Sustained and unsustained reductions are defined as in Figure 2. Acute hemodynamic effects were controlled for by using first postbaseline eGFR measurements for those assigned to canagliflozin.
reporting that required sample size decreased with lesser eGFR decline thresholds when mean baseline eGFR was high (67.5 ml/min per 1.73 m²) but was stable across eGFR decline thresholds when mean baseline eGFR was low (27.5 ml/min per 1.73 m²). This inconsistency may be because the majority of the participants in the CANVAS Program had relatively high baseline eGFR (mean eGFR of 76.5 [SD = 20.5] ml/min per 1.73 m²), and only 554 participants (5.5% of total population) had baseline eGFR of <45 ml/min per 1.73 m². Further investigation is needed to validate the utility of lesser eGFR declines in a cohort with advanced stages of CKD.

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 a long duration of follow-up. The multiple measurements of sCr allowed comprehensive exploration of the effects of using sustained and unsustainable eGFR reductions. However, our study has several limitations. First, the eGFR decline thresholds were not adjudicated, and our exploratory analyses using the post-randomization eGFR measures as a substitute for notional on-treatment baseline values may be subject to bias. Second, lesser eGFR decline thresholds 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 decline, which may lead to erroneous conclusions for benefits or harms of interventions. We recommend careful consideration of these alternative end points in the design of future trials. Finally, our study cohort did not include many participants with severe kidney disease, which may limit generalizability to those with more advanced stages of type 2 diabetes and CKD.

Figure 4. Required sample sizes were mostly not affected by use of lesser eGFR reductions (A panel) but were much decreased by controlling for the acute hemodynamic effects of canagliflozin (B panel). 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 unsustainable (triangular data points).

Figure 5. Proposed design of a randomized clinical trial assessing the effects of a therapy with an acute effect on eGFR. The acute effect of a therapy might be controlled by having a short active run-in period prior to randomization, which generates both on-treatment and off-treatment baseline eGFR measures for each participant; people randomized to the intervention arm would have subsequent eGFR levels compared with those at the end of the active run-in period, whereas those randomized to the control arm could be compared with the eGFR measurement prior to the run-in period.
In conclusion, the use of lesser eGFR decline thresholds may offer a valid and highly cost-effective approach to identifying the renoprotective effect of SGLT2 inhibitors and other agents designed to protect kidney function. Further investigation in prospective trials is warranted.

DISCLOSURES

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Dr. Megumi Oshima and Dr. Vlado Perkovic designed the study; Dr. Megumi Oshima performed the analyses under Dr. Qiang Li, Dr. Toshiaki Ohkuma, Dr. Vlado Perkovic, and Dr. Tadashi Toyama; Dr. William Canovatchel, Dr. Dick de Zeeuw, Dr. Greg Fulcher, Dr. Hiddo J. Lambers Heerspink, Dr. Qiang Li, Dr. Kenneth W. Mahaffey, Dr. David R. Matthews, Dr. Bruce Neal, Dr. Toshiaki Ohkuma, Dr. Megumi Oshima, Dr. Vlado Perkovic, and Dr. Tadashi Toyama interpreted the data; Dr. Bruce Neal, Dr. Megumi Oshima, and Dr. Vlado Perkovic drafted the article; Dr. William Canovatchel, Dr. Dick de Zeeuw, Dr. Greg Fulcher, Dr. Hiddo J. Lambers Heerspink, Dr. Qiang Li, Dr. Kenneth W. Mahaffey, Dr. David R. Matthews, Dr. Bruce Neal, Dr. Toshiaki Ohkuma, Dr. Megumi Oshima, Dr. Vlado Perkovic, and Dr. Tadashi Toyama approved the final version of the manuscript; Dr. William Canovatchel, Dr. Dick de Zeeuw, Dr. Greg Fulcher, Dr. Hiddo J. Lambers Heerspink, Dr. Qiang Li, Dr. Kenneth W. Mahaffey, Dr. David R. Matthews, Dr. Bruce Neal, Dr. Toshiaki Ohkuma, Dr. Megumi Oshima, Dr. Vlado Perkovic, and Dr. Tadashi Toyama had full access to all the data and had final responsibility for the decision to submit for publication.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019121312/-/DCSupplemental.

Supplemental Figure 1. The study design of our analysis.
Supplemental Figure 2. Subgroup analyses for the effects of canagliflozin versus placebo (RRs and 95% CIs) on the composite renal outcomes using either an eGFR reduction of 57%, 50%, 40%, or 30% plus ESKD or renal death.

Supplemental Figure 3. Effects of canagliflozin versus placebo (RRs and 95% CIs) by baseline eGFR on the composite renal outcomes with eGFR reductions 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 uncontrolled for acute hemodynamic effects and controlled for acute hemodynamic effects.

Supplemental Table 1. Baseline characteristics in the CANVAS Program.

Supplemental Table 2. Required sample sizes for assessing treatment effects of canagliflozin on the composite renal outcomes when eGFR reductions were uncontrolled for acute hemodynamic effects and controlled for acute hemodynamic effects.

Supplemental Table 3. Required sample sizes by baseline eGFR for assessing treatment effects of canagliflozin on the composite renal outcomes when eGFR reductions were uncontrolled for acute hemodynamic effects and controlled for acute hemodynamic effects.

Supplemental Table 4. Number needed to treat (and 95% CI) for the composite renal outcomes for 5 years when eGFR reductions were uncontrolled for acute hemodynamic effects and controlled for acute hemodynamic effects.

REFERENCES


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