Relative and Absolute Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories: Findings From the CANVAS Program

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Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories

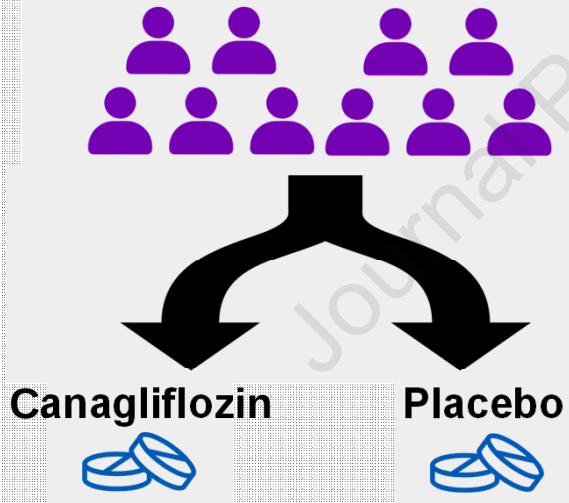
Design

CANVAS Program
Double-blind, placebo-controlled randomized trial

667 centers
30 countries

Population

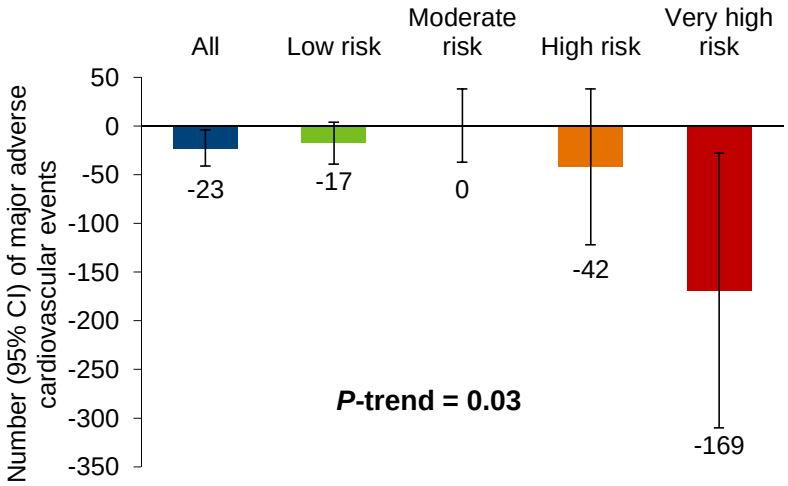
10,142 people with T2DM and eGFR ≥ 30 mL/min/1.73 m²
at high cardiovascular risk



Results

Major adverse cardiovascular events prevented per 1,000 patients treated over 5 years

KDIGO Risk Classification



CONCLUSION: Absolute risk reductions for cardiovascular disease with canagliflozin are likely greater for individuals at higher KDIGO risk.

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Relative and Absolute Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories: Findings From the CANVAS Program

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Abstract

Rationale & Objective: Canagliflozin reduces the risk of cardiovascular and kidney outcomes in type 2 diabetes. This study aimed to assess the relative and absolute effects of canagliflozin on clinical outcomes across different Kidney Disease: Improving Global Outcomes (KDIGO) risk categories based on estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (UACR.

Study Design: Post-hoc analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program.

Settings & Participants: The CANVAS Program randomized 10,142 participants with type 2 diabetes at high cardiovascular risk and an eGFR of ≥30 mL/min/1.73 m^2 to canagliflozin or placebo.

Intervention(s): Canagliflozin or matching placebo.

Outcomes: The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, with a set of other cardiovascular and kidney pre-specified outcomes.

Results: Of 10,142 participants, 10,031 (98.9%) had available baseline eGFR and UACR data. The proportions of participants in low-, moderate-, high-, and very high-risk categories were 58.6%, 25.8%, 10.6%, and 5.0%, respectively. The relative effect of canagliflozin on the primary outcome (HR 0.86, 95% CI 0.75-0.97) was consistent across KDIGO risk categories (*P*-trend=0.21), with similar results for other cardiovascular and kidney outcomes. Absolute reductions in the primary outcome were greater within higher KDIGO risk categories (*P*-trend=0.03) with a similar pattern of effect for the composite of cardiovascular death or hospitalization for heart failure (*P*-trend=0.06) and for chronic eGFR slope (*P*-trend=0.04).

Limitations: Predominantly a low kidney risk population, relatively few participants in higher KDIGO risk categories, and exclusion of individuals with eGFR <30 mL/min/1.73 m^2.

Conclusions: While the relative effects of canagliflozin are similar across KDIGO risk categories, absolute risk reductions are likely greater for individuals at higher KDIGO risk. The KDIGO classification system may be able to identify individuals who might derive greater benefits for end-organ protection from treatment with canagliflozin.

Funding: This post hoc analysis was not funded. The original CANVAS Program trials were funded by Janssen Research & Development, LLC and were conducted as a collaboration between the funder, an academic steering committee, and an academic research organization, George Clinical.

Trial registration: The original trials of the CANVAS Program were registered at ClinicalTrials.gov with study numbers NCT01032629 and NCT01989754.

Keywords: Canagliflozin, Cardiovascular outcomes, KDIGO, Kidney outcomes, SGLT2 inhibitor

Plain language summary:

Canagliflozin reduces the risk of cardiovascular and kidney outcomes in patients with type 2 diabetes. This post-hoc analysis of the Phase 3, randomized, placebo-controlled Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (n=10,142) assessed the effect of canagliflozin on these outcomes in participants with different levels of risk for chronic kidney disease, defined by the Kidney Disease: Improving Global Outcomes (KDIGO) classification based on estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (UACR). The relative effects of canagliflozin on cardiovascular and kidney outcomes were similar across KDIGO risk categories, but absolute risk reductions were likely greater for individuals within higher risk KDIGO categories. The KDIGO classification system may be able to be used to identify individuals who would derive greater benefits for end-organ protection from treatment with canagliflozin.

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of glucose-lowering agents that have been shown to reduce the risk of cardiovascular events in several large cardiovascular outcome trials.[1-3] Recently, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated that the SGLT2 inhibitor canagliflozin reduces the risk of kidney failure and cardiovascular events in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).[4]

Lower estimated glomerular filtration rate (eGFR) and higher urinary albumin:creatinine ratio (UACR) independently predict kidney and cardiovascular events and all-cause mortality.[5-7] The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Classification of CKD incorporates both eGFR and UACR into a 2-dimensional framework to stratify individuals according to their risk of a range of adverse outcomes, including cardiovascular events, acute kidney injury, end-stage kidney disease (ESKD), and mortality.[8] The KDIGO classification system has played an important role in improving understanding of the epidemiology of CKD, as well as assessing severity and predicting adverse outcomes for individuals.

The CREDENCE trial recruited participants with severely increased albuminuria (UACR >300 mg/g) and approximately 60% had an eGFR <60 mL/min/1.73 m^2 at baseline; as a result, the majority of participants were very high risk according to the KDIGO classification system. It is unclear whether the relative benefits for kidney and cardiovascular outcomes observed in the CREDENCE trial are generalizable to individuals in earlier stages of CKD, as defined by the KDIGO classification system, and whether the KDIGO classification of CKD can be used to estimate absolute risk reductions, identify those who might benefit most from treatment and therefore support decision making in routine clinical practice.

We undertook a post hoc analysis of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program to assess whether the relative effects of canagliflozin on cardiovascular, kidney, and safety outcomes varied by KDIGO risk categories, and to determine any absolute differences in treatment effect across subgroups.

Methods

Trial design and participants

The CANVAS Program comprised 2 parallel, randomized, double-blind, placebo-controlled trials (CANVAS [NCT01032639] and CANVAS-R (NCT01989754) in which individuals with T2DM and an eGFR ≥30 mL/min/1.73 m^2 who had, or were at high risk of cardiovascular disease were randomized to canagliflozin or placebo. Detailed study methods and statistical analysis plan for the integrated analysis and reporting of the CANVAS Program have been previously published and are available online.[2, 9] The protocols were approved by the ethics committees at each site. All the participants provided written informed consent.

Randomization and follow-up

Randomization was performed centrally through a web-based response system. All participants, care providers, investigators, and outcome assessors were blinded to treatment allocations until the end of the trials.

After randomization, face-to-face follow-up was scheduled ≥3 times in the first year and then alternated between face-to-face and telephone follow-up at 6 monthly intervals thereafter. Adverse event assessment was performed at each study visit. Other glycemic and cardiovascular risk factor management, including renin-angiotensin system blockade, was guided by best practice in accordance with local guidelines.

KDIGO classification

We categorized participants with eGFR and UACR measurements at baseline into 4 risk categories according to the KDIGO classification system[8]: low risk (eGFR ≥60 mL/min/1.73 m^2 and UACR <30 mg/g), moderate risk (eGFR 45-<60 mL/min/1.73 m^2 and UACR <30 mg/g, or eGFR ≥60 mL/min/1.73 m^2 and UACR 30-300 mg/g), high risk (eGFR 30-<45 mL/min/1.73 m^2 and UACR <30 mg/g, eGFR 45-<60 mL/min/1.73 m^2 and UACR 30-300 mg/g, or eGFR ≥60 mL/min/1.73 m^2 and UACR >300 mg/g), and very high risk (eGFR <30 mL/min/1.73 m^2 with any UACR, eGFR 30-<45 mL/min/1.73 m^2 and UACR ≥30 mg/g, or eGFR 45-<60 mL/min/1.73 m^2 and UACR >300 mg/g).

Outcomes

Definitions for all outcomes in the CANVAS Program have been published.[2] The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Other cardiovascular outcomes included cardiovascular death or hospitalization for heart failure, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and fatal or nonfatal heart failure. We assessed two kidney outcomes: (1) sustained 40% decline in eGFR, ESKD, or death due to kidney disease and (2) sustained 40% decline in eGFR, ESKD, or death due to cardiovascular or kidney disease (i.e. a composite cardio-renal outcome similar to the primary outcome in CREDENCE). To further assess the effect of canagliflozin on progression of kidney disease, we also assessed a continuous kidney outcome, eGFR slope, defined as the annual mean difference in eGFR between canagliflozin and placebo during acute and chronic treatment periods. Serum creatinine collected at study visits was centrally measured, and eGFR was calculated using the Modification of Diet in Renal Disease equation.

Consistent with previous analyses, we separately reported all serious adverse events for the CANVAS Program along with serious or non-serious adverse events for the CANVAS trial alone due to differences in adverse event reporting between the trials.[10, 11]

Statistical analysis

Baseline characteristics for participants across KDIGO risk categories were compared using chi-square and ANOVA tests for categorical and continuous variables, respectively.

We assessed the relative effects of canagliflozin on cardiovascular, kidney, and safety outcomes overall and by baseline KDIGO risk categories using Cox regression and an intention to treat approach. Subgroup by treatment interaction terms were added to the relevant model to test for effect modification across subgroups. The *P*-trend values across KDIGO risk categories were obtained using likelihood ratio tests. Annualized incidence rates were calculated per 1000 patient-years of follow-up. Sensitivity analyses adjusting for competing risk of death were performed for these outcomes using the Fine and Gray method.[12]

We assessed the effect of canagliflozin on eGFR slope over the total study duration and separately during two time periods: from baseline to Week 13 (acute slope), and Week 13 to last available measure during the trial (chronic slope). Effects on eGFR slope were estimated by a piecewise linear mixed effect model using an intention-to-treat approach as previously described.[10, 11, 13] To assess trend in treatment effects on eGFR slope across subgroups, we performed the analysis separately for each subgroup, obtained estimated treatment effects and their standard errors (SEs), and compared the estimated effects between the subgroups while accounting for the estimated SE within each subgroup using a chi-square test with degrees of freedom equal to one less than the number of subgroups being compared.

For safety outcomes, on-treatment analysis was performed using only events that occurred amongst participants who had a safety outcome while they were receiving canagliflozin or placebo, or ≤30 days after discontinuation of randomized treatment. For amputation and fracture outcomes, analyses

included participants who received ≥1 dose of canagliflozin or placebo and had an event at any time during follow-up.

Absolute effects on key outcomes of interest per 1000 patients treated over 5 years and corresponding 95% CIs were estimated as the difference in incidence rates between canagliflozin and placebo treated participants using Poisson regression analysis with the assumption of constant annual event probabilities. Absolute risk reductions and 95% confidence intervals between treatment groups were obtained by the delta method after post-estimation from the Poisson regression model. To assess trend in absolute risk reductions across subgroups, we obtained estimated absolute treatment effects and their standard errors for each subgroup. We then compared the estimated effects across the ordered subgroups while accounting for the estimated SE within each subgroup using Chi-Square test with 1 degree of freedom.

Analyses were performed with SAS software, version 9.2, SAS Enterprise Guide, version 7.11, and STATA software, version 15.1.

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

Results

The CANVAS Program included 10,142 participants, of whom 10,031 (98.9%) had both eGFR and UACR measured at baseline. 9734 (96.0%) participants completed the trials with a mean follow-up of 188.2 weeks. The number of overall participants in low-, moderate-, high-, and very high-risk

categories at baseline was 5876 (58.6%), 2587 (25.8%), 1068 (10.6%), and 500 (5.0%), respectively (Figure 1).

Across progressively higher KDIGO risk categories, participants were more likely to be older, have a longer duration of diabetes, and have higher HbA1c (all P <0.0001; Table 1). They were also more likely to have a history of cardiovascular disease, heart failure, or microvascular complications (all P <0.0001). Baseline use of renin angiotensin system (RAS) blockade was high overall (80.0%) and in each KDIGO risk group (Table 1). Characteristics of participants randomized to canagliflozin and placebo were generally similar within each of the KDIGO risk categories (Table S1).

Cardiovascular outcomes

The relative effect of canagliflozin on cardiovascular outcomes across different KDIGO risk categories is displayed in Figure 2. In the overall population, canagliflozin reduced the risk of major adverse cardiovascular events (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75-0.97), cardiovascular death or hospitalization for heart failure (HR 0.78, 95% CI 0.67-0.91), and heart failure alone (HR 0.70, 95% CI 0.55-0.89), with consistent relative effects across KDIGO risk categories (all P-trend >0.20). Likewise, there was no significant interaction between relative treatment effect and KDIGO risk category for all other cardiovascular outcomes (all P-trend >0.20; Figure 2). Results were essentially unchanged in sensitivity analyses adjusted for the competing risk of death (Table S2).

Kidney outcomes

The effect of canagliflozin on 40% decline in eGFR, ESKD or death due to cardiovascular or kidney disease (HR 0.77, 95% CI 0.66-0.89) and the kidney-specific composite outcome excluding cardiovascular death (HR 0.60, 95 % CI 0.47-0.77) did not vary in a linear fashion across KDIGO

categories (P-trend=0.56 and 0.80, respectively). Results were similar in sensitivity analyses adjusted for the competing risk of death (Table S2).

The absolute effect of canagliflozin on eGFR slope varied across different time periods. Treatment with canagliflozin resulted in an acute fall in eGFR within the first 13 weeks that was similar across KDIGO risk categories (*P*-trend=0.58; Figure 3A). From Week 13 to the end of follow-up, the rate of decline in kidney function for placebo-treated participants increased across progressively higher KDIGO risk categories, and as a result, the absolute effect of canagliflozin on eGFR slope was greater in higher KDIGO risk categories (*P*-trend=0.04; Figure 3B). The annual placebo-subtracted differences for total eGFR slope across subgroups are displayed in Table S3.

Safety outcomes

The relative effects of canagliflozin on serious safety outcomes were similar across KDIGO risk categories (Figure 4). The risk of serious kidney-related adverse events, acute kidney injury, and hyperkalemia were not modified by KDIGO risk categories (all *P*-trend >0.15; Figure 4). The relative effect of canagliflozin on amputations was also not modified by KDIGO subgroups (*P*-trend=0.85; Figure 4). The relative effects of canagliflozin on serious and non-serious safety outcomes in the CANVAS trial alone are summarized in Figure S1. The risk of osmotic diuresis with canagliflozin attenuated across higher KDIGO risk categories (P-trend=0.01).

Absolute effects

The absolute risk reduction with canagliflozin for the primary cardiovascular outcome increased across higher KDIGO risk categories (*P*-trend=0.03; Figure 5). There was also some evidence that the absolute reduction in cardiovascular death or hospitalization for heart failure increased across higher KDIGO risk subgroups (*P*-trend=0.06). Point estimates for absolute effects on heart failure alone and kidney outcomes also increased across participants at higher KDIGO risk, however these

did not reach statistical significance (Figure 5). There was no evidence of an interaction for the absolute effect on amputations (*P*-trend=0.26; Figure 5).

Discussion

In this post hoc analysis of the CANVAS Program, we made two main observations. Firstly, the relative effects of canagliflozin on cardiovascular and kidney outcomes were broadly similar across KDIGO risk categories. Secondly, because the risk of these outcomes increased across progressively higher-risk subgroups, absolute risk reductions with canagliflozin for the primary outcome of major adverse cardiovascular events and the composite of cardiovascular death or hospitalization for heart failure increased in a graded and linear fashion across higher KDIGO risk categories. The absolute effect of canagliflozin on progression of kidney disease, as measured by chronic eGFR slope, also appeared to increase with higher KDIGO risk categories. These data suggest that the KDIGO classification of CKD can be used in clinical practice to identify people with T2DM in whom SGLT2 inhibition with canagliflozin is likely to result in the greatest treatment benefits.

It is somewhat unsurprising that we found that the relative effects of canagliflozin on cardiovascular and kidney outcomes were consistent across KDIGO risk categories. Secondary analyses of large-scale SGLT2 inhibitor trials have found no evidence of interaction between treatment and eGFR or albuminuria (within the range of values studied),[10, 11, 14, 15] a finding that has been reinforced in a recent meta-analysis of SGLT2 inhibitor cardiovascular and kidney outcome trials.[16] These findings contrasts with data on RAS blockade in non-diabetic kidney disease, where the relative benefits of angiotensin converting enzyme inhibitors increases with increasing albuminuria,[17] and statin therapy where the relative effects on cardiovascular outcomes attenuates with declining eGFR.[18]

While the KDIGO classification of CKD has been used to stratify the risk of adverse outcomes for individuals, it has very seldom been used to predict treatment response with SGLT2 inhibition or other commonly used cardioprotective therapies. We found that the KDIGO risk categories were useful in identifying participants in the CANVAS Program who were likely to derive greater absolute risk reductions for major adverse cardiovascular events and for cardiovascular death or hospitalization for heart failure. Point estimates for absolute risk reductions also appeared to increase across high KDIGO risk categories for hospitalization for heart failure alone and for the kidney-specific composite outcome, however these did not reach statistical significance, possibly due to the smaller number of events for these outcomes. For the continuous kidney outcome of chronic eGFR slope where there was much greater power to assess differences in absolute treatment effect, the effect of canagliflozin appeared to increase across higher KDIGO risk subgroups.

There are likely to be multiple mechanisms – independent of glucose-lowering – that contribute to the beneficial cardiovascular and kidney effects of SGLT2 inhibitors. SGLT2 inhibitors are thought to reduce intraglomerular pressure by restoring tubuloglomerular feedback.[19] The hemodynamic nature of the acute fall in eGFR with SGLT2 inhibitors is supported by off-treatment data demonstrating that the early 'dip' in eGFR is reversible on drug cessation.[10, 20] The mechanism by which SGLT2 inhibition reduce intraglomerular pressure is thought to be through increased distal sodium delivery to the macular densa and adenosine mediated afferent arteriole vasoconstriction, which has been demonstrated at a single nephron level in animal models and in people with type 1 diabetes with whole kidney hyperfiltration.[21, 22] More recent data in type 2 diabetes have raised the possibility that efferent arteriolar tone may also be affected.[23] Regardless, reductions in intraglomerular pressure, along with enhanced natriuresis, are likely to play an important role not only in protection against kidney failure but also in reducing the risk of heart failure, especially in patients with CKD where subclinical volume overload is highly prevalent.[24] A number of other potential mechanisms have also been suggested, including protective effects on the vascular

endothelium, anti-inflammatory actions, improvements in tubular oxygenation, and other direct cellular and metabolic effects.[25-27]

The validity of our findings is supported by the quality of data from the CANVAS Program clinical trials, which were conducted to a high standard with blinded outcome adjudication by expert committees. Approximately 80% of participants were treated with RAS blockade at baseline and use of other cardioprotective therapies was also high, demonstrating that the benefits of canagliflozin are achieved in addition to current standard of care. The use of continuous eGFR slope data provided additional explanatory power to investigate the kidney protective effects of canagliflozin across KDIGO risk categories, an approach which has also been employed for other major SGLT2 inhibitor trials, including CREDENCE.[11, 28]

There are some important limitations to consider when interpreting our findings. This was a post hoc subgroup analysis, and the trial was not designed to determine treatment effects in each of the KDIGO subgroups individually. The CANVAS Program included a relatively small proportion of participants in high or very high KDIGO risk categories, and therefore our analysis may be underpowered to detect differences in treatment effect across subgroups. Individuals with eGFR <30 mL/min/1.73 m^2 were excluded from the CANVAS Program (and other published SGLT2 inhibitor outcome trials) and thus it is uncertain whether these apply to those with move advanced kidney disease. Approximately two thirds of participants had established atherosclerotic cardiovascular disease at baseline, which may limit the generalizability of these findings to the broader diabetic kidney disease population; however, the effect of canagliflozin was not modified by history of atherosclerotic cardiovascular disease in CREDENCE, in which approximately half of participants did not have established atherosclerotic cardiovascular disease at baseline.[29] The reported tests for trend were not adjusted for multiple comparisons and are therefore susceptible to the play of chance. Accepting these limitations, our findings are consistent with comparable

analyses of the EMPA-REG OUTCOME trial[30, 31] and represent one of the largest analyses to date of the effects of SGLT2 inhibition across the spectrum of kidney and/or cardiovascular risk.

Upcoming trials enrolling participants with CKD include DAPA-CKD for dapagliflozin (NCT03036150), EMPA-KIDNEY for empagliflozin (NCT03594110), and SCORED for sotagliflozin, a combined SGLT1/SGLT2 inhibitor (NCT03315143). These trials will enrol participants with baseline eGFR as low as 20 mL/min/1.73 m^2, irrespective of albuminuria. Due to the proposed mechanism of kidney protection with these agents, both DAPA-CKD and EMPA-KIDNEY may also include participants with and without T2DM.[32, 33] Of note, DAPA-CKD has recently been stopped on advice of the data safety monitoring board due to overwhelming efficacy, raising the possibility that this class of drug may also slow the progression of non-diabetic kidney disease.

In summary, while the relative effects of canagliflozin on cardiovascular and kidney outcomes are similar across KDIGO risk categories, absolute risk reductions are greater in individuals at higher KDIGO risk. These findings support the use of the KDIGO classification system to identify people with T2DM who may derive the greatest benefits for end-organ protection with canagliflozin.

Supplementary Material

Figure S1. Relative effects of canagliflozin on safety outcomes collected in CANVAS alone in participant subgroups defined by baseline KDIGO risk category.
Table S1. Characteristics of canagliflozin- and placebo-treated participants by baseline KDIGO risk category.
Table S2. Relative effects of canagliflozin on cardiovascular and kidney outcomes in participant subgroups defined by baseline KDIGO risk category adjusted for competing risk of death.
Table S3. Absolute effect of canagliflozin versus placebo on total eGFR slope by baseline KDIGO risk category.

Article Information

Authors' Contributions: research idea and study design: BN, DRM, DdZ, KWM, GF, VP, DCW; data interpretation/analysis: BLN, TO, BN, DRM, DdZ, KWM, GF, JB, QL, MJJ, VP,

DCW; statistical analysis: TO, QL. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Characteristics of Participants by Baseline KDIGO Risk Categories

	Low risk (N=5876)	Moderate risk (N=2587)	High risk (N=1068)	Very high risk (N=500)
Age, years, mean (SD)	62.1 (8.0)	64.3 (8.2)	65.9 (8.5)	66.5 (8.2)
Sex, No. (%)				
Male	3744 (63.7)	1686 (65.2)	685 (64.1)	322 (64.4)
Female	2132 (36.3)	901 (34.8)	383 (35.9)	178 (35.6)
Race, No. (%)				
White	4569 (77.8)	2045 (79.0)	829 (77.6)	402 (80.4)
Asian	751 (12.8)	329 (12.7)	142 (13.3)	61 (12.2)
Black or African American	207 (3.5)	77 (3.0)	32 (3.0)	14 (2.8)
Other*	349 (5.9)	136 (5.3)	65 (6.1)	23 (4.6)
Current smoker, No. (%)†	1122 (19.1)	436 (16.9)	154 (14.4)	64 (12.8)
History of hypertension, No. (%)	5148 (87.6)	2386 (92.2)	1010 (94.6)	475 (95.0)
History of HF, No. (%)	760 (12.9)	396 (15.3)	186 (17.4)	93 (18.6)
Duration of diabetes, years, mean (SD)	12.7 (7.4)	14.1 (7.9)	15.7 (8.2)	16.9 (7.8)
Drug therapy, No. (%)				
Insulin	2633 (44.8)	1397 (54.0)	656 (61.4)	359 (71.8)
Sulphonylurea	2649 (45.1)	1109 (42.9)	406 (38.0)	160 (32.0)
Metformin	4810 (81.9)	2000 (77.3)	706 (66.1)	217 (43.4)
GLP-1 receptor agonist	236 (4.0)	93 (3.6)	50 (4.7)	23 (4.6)
DPP-4 inhibitor	710 (12.1)	312 (12.1)	153 (14.3)	73 (14.6)
Statin	4342 (73.9)	1950 (75.4)	837 (78.4)	396 (79.2)
Antithrombotic	4234 (72.1)	1944 (75.1)	830 (77.7)	392 (78.4)
RAAS inhibitor	4625 (78.7)	2114 (81.7)	885 (82.9)	397 (79.4)
Beta blocker	3015 (51.3)	1436 (55.5)	615 (57.6)	303 (60.6)
Diuretic	2265 (38.5)	1272 (49.2)	582 (54.5)	317 (63.4)
Microvascular disease history, No. (%)‡				
Retinopathy	1042 (17.7)	584 (22.6)	300 (28.1)	178 (35.7)
Neuropathy	1661 (28.3)	842 (32.5)	385 (36.0)	180 (36.0)
Atherosclerotic vascular disease history, No. (%)§				
Coronary	3281 (55.8)	1458 (56.4)	636 (59.6)	290 (58.0)
Cerebrovascular	1064 (18.1)	519 (20.1)	242 (22.7)	113 (22.6)
Peripheral	1102 (18.8)	559 (21.6)	286 (26.8)	146 (29.2)
Any				
CV disease history, No. (%)‖	3791 (64.5)	1695 (65.5)	747 (69.9)	358 (71.6)
History of amputation, No.	74 (1.3)	66 (2.6)	58 (5.4)	37 (7.4)

(%)				
Body mass index, kg/m^2, mean (SD)	31.7 (5.8)	32.3 (6.1)	32.2 (6.0)	32.2 (6.2)
Systolic BP, mmHg, mean (SD)	134.8 (15.0)	138.4 (15.6)	139.6 (17.5)	142.5 (17.8)
Diastolic BP, mmHg, mean (SD)	77.8 (9.3)	77.8 (9.9)	77.0 (10.2)	76.8 (10.7)
Glycated hemoglobin, %, mean (SD)	8.2 (0.9)	8.3 (1.0)	8.4 (0.9)	8.5 (1.0)
Total cholesterol, mmol/L, mean (SD)	4.3 (1.1)	4.4 (1.1)	4.5 (1.3)	4.5 (1.2)
Triglycerides, mmol/L, mean (SD)	1.9 (1.3)	2.1 (1.5)	2.3 (1.6)	2.3 (1.6)
HDL-C, mmol/L, mean (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)
LDL-C, mmol/L, mean (SD)	2.3 (0.9)	2.3 (0.9)	2.3 (1.0)	2.3 (1.0)
LDL-C:HDL-C ratio, mean (SD)	2.0 (0.9)	2.1 (0.9)	2.1 (1.0)	2.2 (1.0)
eGFR, mL/min/1.73 m², mean (SD)	83.6 (16.4)	72.8 (19.9)	61.8 (20.4)	42.9 (8.9)
eGFR <60 mL/min/1.73 m², No. (%)	0 (0)	888 (34.3)	628 (58.8)	500 (100)
UACR, mg/g, median (IQR)	8.2 (5.7-13.2)	41.3 (13.1-84.3)	152.5 (37.0-526.7)	445.9 (121.9-1124.5)
UACR >300 mg/g, No. (%)	0 (0)	0 (0)	440 (41.2)	320 (64.0)

KDIGO, Kidney Disease: Improving Global Outcomes, SD, standard deviation; HF, heart failure; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system; CV, cardiovascular; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; IQR, interquartile range.

*Includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, multiple, other, and unknown.

†Three participants did not have smoking status recorded at baseline.

‡Two participants did not have retinopathy recorded at baseline.

§Some participants had >1 type of atherosclerotic disease.

‖As defined in the protocol.

FIGURE LEGENDS

Figure 1. KDIGO classification of CKD and proportion of canagliflozin and placebo treated participants in each KDIGO risk category.

CANVAS, CANagliflozin cardioVascular Assessment Study; KDIGO, Kidney Disease: Improving Global Outcomes.

Note: Differences in the proportion of participants randomized to canagliflozin and placebo were due to differences in randomization ratios in the CANVAS and CANVAS-R trials.

Figure 2. Relative effects of canagliflozin versus placebo on cardiovascular and kidney outcomes in participant subgroups defined by baseline KDIGO risk categories.

KDIGO, Kidney Disease: Improving Global Outcomes; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

Figure 3. Absolute effect of canagliflozin versus placebo on (A) acute change in eGFR and (B) chronic eGFR slope* in participant subgroups defined by baseline KDIGO risk categories.[†]

eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; CI, confidence interval; SE, standard error.

*Data are reported for Week 6 in CANVAS and Week 13 in CANVAS-R.

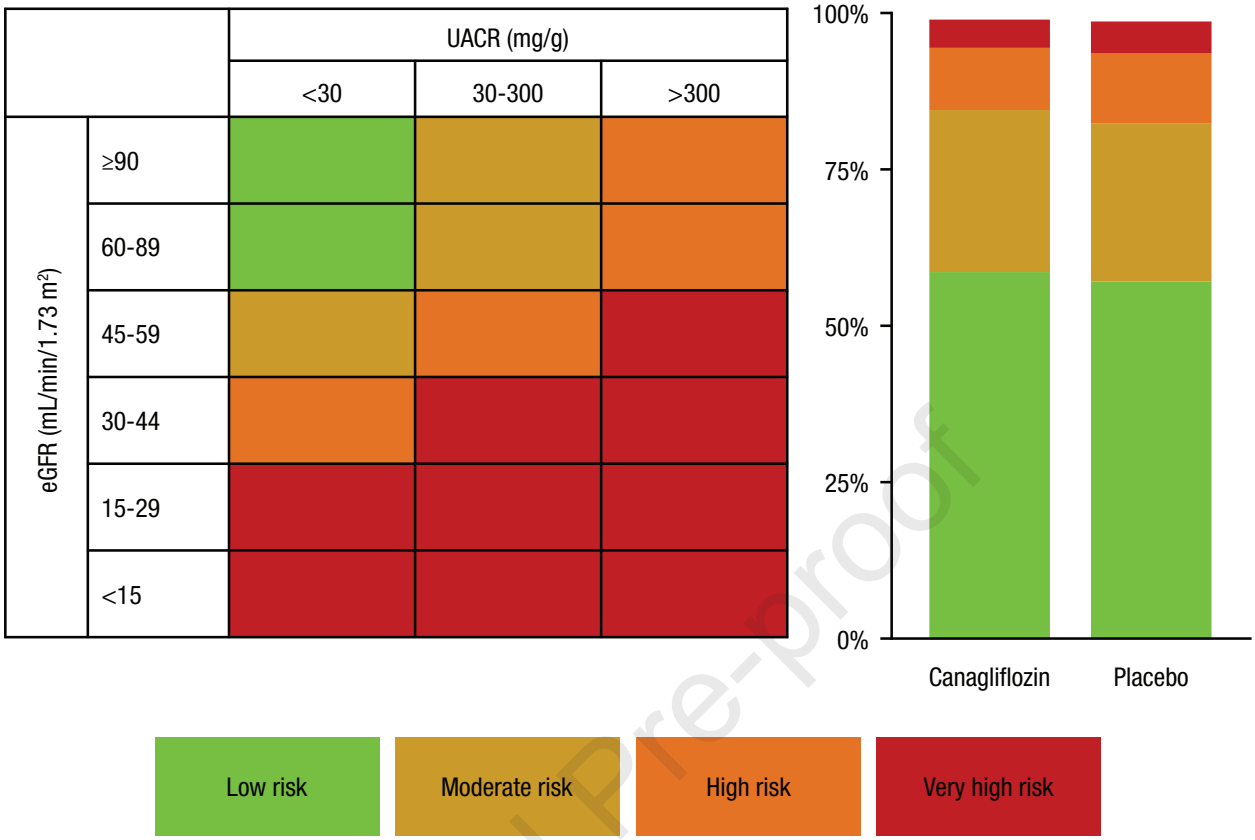
[†]eGFR values shown are mean ± SE.

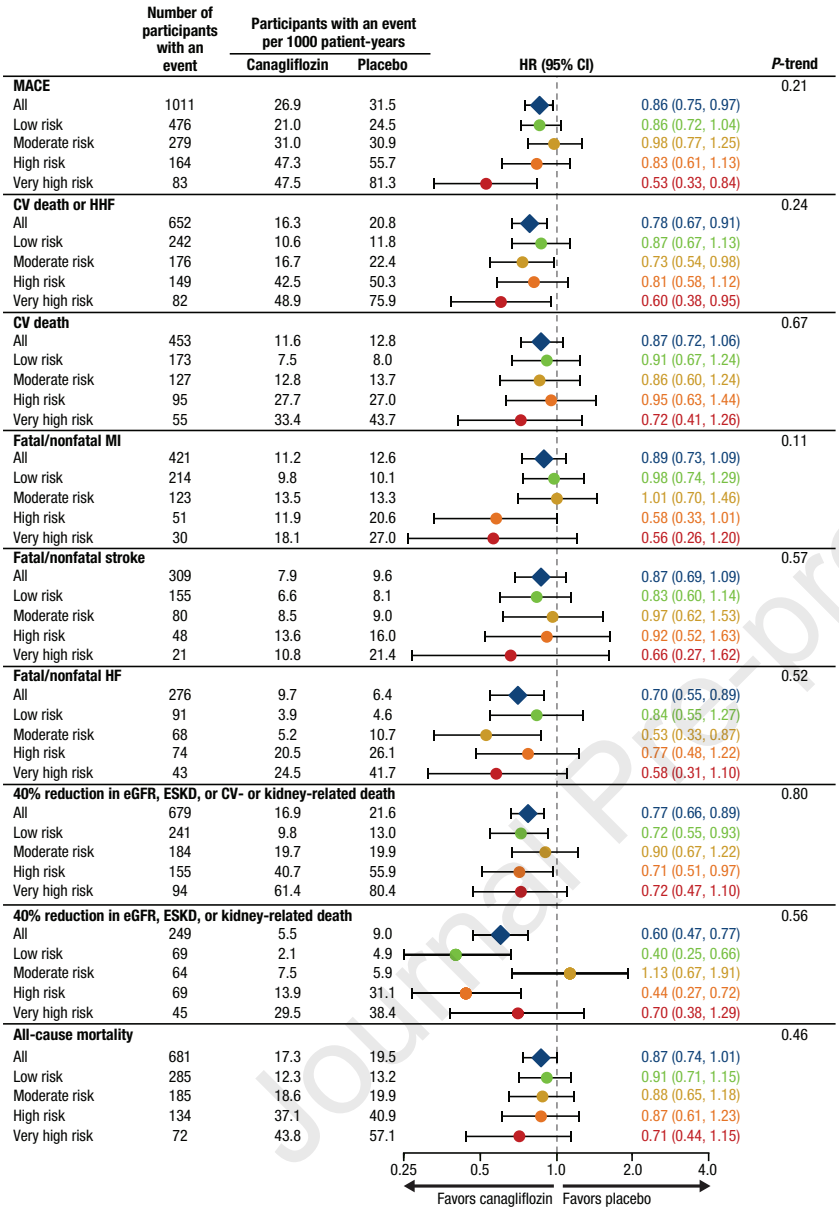
Figure 4. Relative effects of canagliflozin versus placebo on safety outcomes collected across the CANVAS Program in participant subgroups defined by baseline KDIGO risk categories.

CANVAS, CANagliflozin cardioVascular Assessment Study; KDIGO, Kidney Disease: Improving Global Outcomes; HR, hazard ratio; CI, confidence interval.

Figure 5. Absolute benefits and risks per 1000 participants over 5 years with canagliflozin versus placebo in the overall population and in participant subgroups defined by baseline KDIGO risk categories.

KDIGO, Kidney Disease: Improving Global Outcomes; CI, confidence interval; MACE, major adverse cardiovascular event; HF, heart failure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.





	Number of participants with an event	Participants with an event per 1000 patient-years		HR (95% CI)	*P*-trend
		Canagliflozin	Placebo		
MACE					0.21
All	1011	26.9	31.5	0.86 (0.75, 0.97)	
Low risk	476	21.0	24.5	0.86 (0.72, 1.04)	
Moderate risk	279	31.0	30.9	0.98 (0.77, 1.25)	
High risk	164	47.3	55.7	0.83 (0.61, 1.13)	
Very high risk	83	47.5	81.3	0.53 (0.33, 0.84)	
CV death or HHF					0.24
All	652	16.3	20.8	0.78 (0.67, 0.91)	
Low risk	242	10.6	11.8	0.87 (0.67, 1.13)	
Moderate risk	176	16.7	22.4	0.73 (0.54, 0.98)	
High risk	149	42.5	50.3	0.81 (0.58, 1.12)	
Very high risk	82	48.9	75.9	0.60 (0.38, 0.95)	
CV death					0.67
All	453	11.6	12.8	0.87 (0.72, 1.06)	
Low risk	173	7.5	8.0	0.91 (0.67, 1.24)	
Moderate risk	127	12.8	13.7	0.86 (0.60, 1.24)	
High risk	95	27.7	27.0	0.95 (0.63, 1.44)	
Very high risk	55	33.4	43.7	0.72 (0.41, 1.26)	
Fatal/nonfatal MI					0.11
All	421	11.2	12.6	0.89 (0.73, 1.09)	
Low risk	214	9.8	10.1	0.98 (0.74, 1.29)	
Moderate risk	123	13.5	13.3	1.01 (0.70, 1.46)	
High risk	51	11.9	20.6	0.58 (0.33, 1.01)	
Very high risk	30	18.1	27.0	0.56 (0.26, 1.20)	
Fatal/nonfatal stroke					0.57
All	309	7.9	9.6	0.87 (0.69, 1.09)	
Low risk	155	6.6	8.1	0.83 (0.60, 1.14)	
Moderate risk	80	8.5	9.0	0.97 (0.62, 1.53)	
High risk	48	13.6	16.0	0.92 (0.52, 1.63)	
Very high risk	21	10.8	21.4	0.66 (0.27, 1.62)	
Fatal/nonfatal HF					0.52
All	276	9.7	6.4	0.70 (0.55, 0.89)	
Low risk	91	3.9	4.6	0.84 (0.55, 1.27)	
Moderate risk	68	5.2	10.7	0.53 (0.33, 0.87)	
High risk	74	20.5	26.1	0.77 (0.48, 1.22)	
Very high risk	43	24.5	41.7	0.58 (0.31, 1.10)	
40% reduction in eGFR, ESKD, or CV- or kidney-related death					0.80
All	679	16.9	21.6	0.77 (0.66, 0.89)	
Low risk	241	9.8	13.0	0.72 (0.55, 0.93)	
Moderate risk	184	19.7	19.9	0.90 (0.67, 1.22)	
High risk	155	40.7	55.9	0.71 (0.51, 0.97)	
Very high risk	94	61.4	80.4	0.72 (0.47, 1.10)	
40% reduction in eGFR, ESKD, or kidney-related death					0.56
All	249	5.5	9.0	0.60 (0.47, 0.77)	
Low risk	69	2.1	4.9	0.40 (0.25, 0.66)	
Moderate risk	64	7.5	5.9	1.13 (0.67, 1.91)	
High risk	69	13.9	31.1	0.44 (0.27, 0.72)	
Very high risk	45	29.5	38.4	0.70 (0.38, 1.29)	
All-cause mortality					0.46
All	681	17.3	19.5	0.87 (0.74, 1.01)	
Low risk	285	12.3	13.2	0.91 (0.71, 1.15)	
Moderate risk	185	18.6	19.9	0.88 (0.65, 1.18)	
High risk	134	37.1	40.9	0.87 (0.61, 1.23)	
Very high risk	72	43.8	57.1	0.71 (0.44, 1.15)