

Canagliflozin and Renal Outcomes in Type 2 Diabetes: Data From the CANVAS Randomised Clinical Trial Program

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Research in Context

Evidence before this study

Sodium glucose co-transporter 2 (SGLT2) inhibitors such as canagliflozin reduce glucose levels, blood pressure, body weight and albuminuria in patients with type 2 diabetes, all of which suggest they might have protective effects on the kidney. The analyses of effects on the exploratory renal outcomes from the EMPA-REG OUTCOME trial suggested that empagliflozin-treated participants with established cardiovascular disease had slower decline in kidney function, and a reduced risk of a composite outcome comprising end-stage kidney disease (ESKD) or doubling in creatinine, although these outcomes were not adjudicated in that trial. The CANagliflozin cardioVascular Assessment Study (CANVAS) Program recently reported that canagliflozin prevents major cardiovascular events, and the results of exploratory analyses on adjudicated renal outcomes demonstrated a reduced risk of adverse kidney outcomes, based on a composite endpoint of sustained 40% reduction in eGFR, ESKD or renal death. The effects of canagliflozin on a comprehensive range of kidney outcomes are therefore of interest in better defining the effects of canagliflozin and SGLT2 inhibitors on kidney function in diabetes.

Added value of this study

This pre-specified exploratory analysis of the CANVAS Program showed that canagliflozin reduced the risk of sustained major kidney outcomes (doubling of creatinine, ESKD or renal death) in participants with type 2 diabetes at high cardiovascular risk (with and without established cardiovascular disease). It also found that kidney function declined progressively in placebo-treated participants, but was stabilised in participants treated with canagliflozin, and that albumin loss in the urine was reduced. The results were consistent across subgroups of participants, and renal adverse event rates were not increased.

Implications of all the available evidence

These data show clear evidence of substantial kidney protection in participants with type 2 diabetes at high cardiovascular risk treated with canagliflozin. These results, while consistent with those reported for empagliflozin, provide additional support for the growing evidence that SGLT2 inhibitors such as canagliflozin can play an important role slowing the progression of diabetic kidney disease, given

renal outcomes were both confirmed and adjudicated in this trial. Further studies are required to assess whether canagliflozin can delay time to kidney failure in patients with established kidney disease.

ABSTRACT

Background

In the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, canagliflozin reduced the rates of major adverse cardiovascular events and suggested a renal benefit in patients with type 2 diabetes at high risk for cardiovascular events compared to placebo. The results of a pre-specified exploratory analysis of canagliflozin's long-term effects on a comprehensive range of sustained and adjudicated renal outcomes are reported.

Methods

The CANVAS Program consists of two double-blind, randomised trials assessing canagliflozin compared to placebo in participants with type 2 diabetes at high cardiovascular risk. Pre-specified outcomes reported here include the composite of sustained, adjudicated doubling in serum creatinine, end-stage kidney disease (ESKD), or renal death, as well as individual components of this outcome, annual eGFR loss, and changes in urinary albumin:creatinine ratio (UACR).

Findings

A total of 10 142 participants (baseline mean eGFR 76.5 mL/min/1.73 m², median UACR 12.3 mg/g, 80% receiving renin-angiotensin system blockade) were randomised. The composite of sustained doubled creatinine, ESKD, or renal death occurred less frequently in the canagliflozin group compared to placebo (hazard ratio 0.53, 95% confidence interval [CI] 0.33–0.84), with consistent findings in pre-specified patient subgroups. Annual eGFR decline was slower (slope difference 1.2 mL/min/1.73 m²/year, 95% CI 1.0–1.4) and mean UACR was 18% lower (95% CI 16%–20%) in participants treated with canagliflozin compared to placebo. Rates of renal adverse events were comparable in both groups.

Interpretation

In a pre-specified exploratory analysis, canagliflozin was associated with a reduced risk of sustained loss of kidney function, attenuated eGFR decline, and lower albuminuria supporting a possible renoprotective effect in people with diabetes.

Funding

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Trial registration

ClinicalTrials.gov identifiers, NCT01032629 and NCT01989754

INTRODUCTION

Type 2 diabetes is the most common cause of kidney failure in many countries¹ and the number of people receiving renal replacement therapy for kidney failure globally is projected to increase from 2.6 million in 2010 to >5 million people in 2030.² Control of risk factors, including glucose,³⁻⁵ blood pressure (BP),⁶⁻⁸ and albuminuria,⁹ is the focus of attempts to protect kidney function, alongside renin-angiotensin system (RAS) blockade.^{10,11} Residual risk nonetheless remains high, and several novel interventions targeting kidney disease have recently proved unsuccessful.¹²⁻¹⁵

Sodium glucose co-transporter 2 (SGLT2) inhibitors lower glucose, BP, and body weight in people with type 2 diabetes, and also alter intrarenal haemodynamics in hyperfiltering individuals with type 1 diabetes,¹⁶ although effects on glycaemia and body weight are attenuated in people with reduced kidney function.¹⁷ The CANagliflozin cardioVascular Assessment Study (CANVAS) Program consists of two parallel trials (CANVAS and CANVAS-R [renal]).¹⁸ The CANVAS Program demonstrated cardiovascular safety, and reported 14% lower rates of cardiovascular events among canagliflozin- compared to placebo-treated participants.¹⁸ In pre-specified, exploratory analyses outside the formal hypothesis testing sequence (Figure S1), canagliflozin was also associated with a 27% reduction in the likelihood of progression of albuminuria and a 70% higher likelihood of regression of albuminuria. In addition, there were 40% lower rates of a composite renal outcome comprised of sustained and adjudicated 40% reductions in estimated glomerular filtration rate (eGFR), ESKD or renal death.¹⁸ Exploratory analyses of the EMPA-REG OUTCOME study have recently reported that the SGLT2 inhibitor empagliflozin also has potential benefits on renal outcomes, although these were not adjudicated in that trial.¹⁹

Collectively, these data suggest that SGLT2 inhibitors might have renoprotective efficacy, but regulatory decisions and guidelines have previously required benefits to be demonstrated for 'harder' endpoints based on doubling in creatinine, with central adjudication. While a sustained doubling of serum creatinine is undoubtedly an important endpoint, given that it reflects a loss of 57% of kidney function (eGFR), the rate of kidney function decline in conditions like type 2 diabetes is often

moderate. Clinical trials therefore require very long follow-up duration and/or extremely large numbers of participants to accumulate an adequate number of events in broad populations of participants, which can impact feasibility and has therefore generated an increasing interest in using lesser changes in eGFR as an alternative outcome.

In order to address this challenge, a workshop convened by the US National Kidney Foundation and the US Food and Drug Administration in collaboration with academic researchers proposed that a sustained 40% reduction in eGFR could be a reasonable replacement for doubling of serum creatinine, but trials using this outcome have not yet led to treatment indications by regulatory authorities. As such, there is great interest in the magnitude and consistency of effects of canagliflozin on a range of renal outcomes from the CANVAS Program,

We report here analyses assessing the effects of canagliflozin on a comprehensive range of pre-specified, adjudicated, exploratory renal outcomes across the CANVAS Program.²⁰

METHODS

Study design and participants

The CANVAS Program integrates two directly comparable randomised, placebo-controlled trials, CANVAS and CANVAS-R (Renal), that have been described in detail previously,²⁰⁻²² with primary safety and efficacy results reported.¹⁸ In brief, the CANVAS trial was designed to meet the US Food and Drug Administration guidance for registration of new glucose lowering agents,²³ as part of a meta-analysis of all studies that led to the registration of this agent. In consultation with regulatory agencies, a second comparable trial (CANVAS-R) was initiated post-approval in order to allow the upper bound of the 95% confidence interval (CI) for the noninferiority hazard ratio (HR) for cardiovascular events to be less than 1·3 in an integrated analysis of CANVAS/CANVAS-R. As part of the design of this trial, plans were made for renal-specific analyses to be undertaken across the CANVAS Program. The details of the cardiovascular and renal analysis plans were finalised prior to data lock and have been published.²⁰⁻²²

The main entry criteria for the trials were identical.^{18,21,22} People with type 2 diabetes and HbA1c $\geq 7.0\%$ and $\leq 10.5\%$ (≥ 53 and ≤ 91 mmol/mol) who were aged ≥ 30 years and had a history of symptomatic atherosclerotic vascular disease, or who were aged ≥ 50 years and had ≥ 2 pre-specified cardiovascular risk factors,^{21,22} which could include elevated urinary albumin:creatinine ratio (UACR), were eligible to participate. Individuals with an eGFR < 30 mL/min/1.73 m² were excluded, but there were no other kidney-related eligibility criteria.

Randomisation and masking

Participants entered a 2-week, single-blind, placebo run-in period designed to ensure potential participants were able to comply with study procedures and to identify immediate non-compliers. Central randomisation was performed using an interactive web response system, based on a computer-generated randomisation schedule prepared by the study sponsor using randomly permuted blocks.

Participants in CANVAS were randomly assigned (1:1:1) to once-daily canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo. Participants in CANVAS-R were randomly assigned (1:1) to once-daily canagliflozin or matching placebo at an initial dose of 100 mg daily with optional up-titration to 300 mg or matching placebo initiating at week 13. Participants and all study staff were blinded to treatment allocations until study completion. Investigators and sites were encouraged to use local best-practice guidelines for other glycaemic management and background therapies, including RAS blockade.

Procedures

Post-randomisation, face-to-face follow-up was scheduled for 3 times in the first year and at 6-month intervals thereafter, with alternating telephone follow-up between face-to-face assessments. UACR was measured every 26 weeks in CANVAS-R, and at week 12 and then annually in CANVAS. Serum creatinine measurement with estimation of GFR was undertaken in a central laboratory using the Jaffe method with rate blanking,²⁴ and was performed at least 3 times in the first year after randomisation, and then every 26 weeks. Off-treatment serum creatinine measurements approximately 30 days after

cessation of randomised treatment were collected in participants enrolled in CANVAS-R. Adverse events (AEs), including information about kidney outcomes (eg, need for renal replacement therapy), were assessed at every visit. Individuals who prematurely discontinued study treatment were encouraged to continue scheduled follow-up wherever possible.

Outcomes

A number of composite kidney outcomes were pre-specified, the components of which were adjudicated by a blinded renal Endpoint Adjudication Committee (Supplementary Appendix). These included the composite of sustained doubling of serum creatinine (sent for adjudication if sustained for two consecutive measures ≥ 30 days apart, or occurring on the last available measurement), end-stage kidney disease (ESKD; defined as the composite of maintenance dialysis sustained for at least 30 days, renal transplantation, or a sustained eGFR < 15 mL/min/1.73 m²) and renal death (defined as participant death with a proximate renal cause). As doubling of serum creatinine is a relatively late end-point reflecting a 57% reduction in eGFR, and lower thresholds of eGFR decline have been proposed as being clinically important and potentially acceptable endpoints from a regulatory perspective,²⁵⁻²⁷ additional pre-specified outcomes included the composite of sustained 40% reduction in eGFR, ESKD, or renal death, as well as the composite of each of these outcomes combined with either cardiovascular death or new-onset macroalbuminuria. For each composite, time to the first event was counted, with any subsequent events disregarded. Each of the components of the composite outcomes are also separately reported, and the outcomes are defined in detail in the Supplementary Appendix.

Other pre-specified renal outcomes included albuminuria- and creatinine-based outcomes (eGFR slope, change in urinary albumin levels, new-onset micro- or macroalbuminuria analysed jointly and separately). GFR was estimated (eGFR) using the Modification of Diet in Renal Disease equation,²⁸ based on centrally measured serum creatinine collected at routine study visits. Albuminuria was measured in first morning void urine specimens and calculated as the UACR. Changes in albuminuria with canagliflozin were calculated as the ratio of the geometric mean of post-randomisation UACR

measures compared with placebo. New-onset albuminuria was defined as the development of micro- or macroalbuminuria in participants with baseline normoalbuminuria. Normoalbuminuria was defined as UACR <30 mg/g. New-onset microalbuminuria was defined as the development of a UACR $\geq$ 30 mg/g to $\leq$ 300 mg/g in participants with baseline normoalbuminuria, and where the UACR increased by $\geq$ 30% from baseline. New-onset macroalbuminuria was defined as the development of a UACR >300 mg/g in participants with baseline normo- or microalbuminuria, and where the UACR increased by $\geq$ 30% from baseline.

Renal-related serious AEs were captured throughout both trials, and all AEs (regardless of seriousness) were also collected in CANVAS until early 2014. Kidney-related safety outcomes included any (serious and non-serious) renal-related AEs (collected from CANVAS until January 2014) or serious AEs and AEs leading to study drug discontinuation (collected throughout both trials), including acute kidney injury (AKI), and were evaluated based on incidence of preferred term, using a standard narrow *Medical Dictionary for Regulatory Activities (MedDRA)* query. Hyperkalaemia was evaluated using the *MedDRA* preferred terms hyperkalaemia and increased blood potassium.

Statistical analysis

For categorical outcomes, HRs and 95% CIs were estimated by the principle of intention-to-treat using Cox regression models, with stratification by trial and adjustment for baseline albuminuria level or eGFR as appropriate. Subgroup analyses were undertaken for pre-defined patient categories. As the primary aim of the CANVAS Program was to demonstrate cardiovascular safety and efficacy, the pre-specified renal outcomes assessed here were either outside the formal analysis sequence, or were not reached in the testing hierarchy, thus nominal effect estimates are provided.¹⁸ Unless otherwise specified, efficacy analyses are reported for the full integrated dataset that includes all randomised participants in the CANVAS Program (the CANVAS and CANVAS-R trials), and for both canagliflozin doses combined compared to placebo.

The average rate of change in eGFR over time and the differences between treatment arms were assessed via a piecewise linear mixed effect model in two time periods: baseline to week 13, week 13 to last available measure during the trial period, using an intention-to-treat approach. The model included fixed effect terms for treatment and study, with linear covariates of time and time-by-treatment interaction. The intercept and time were included as random effects to allow variation between patients. A similar model was used to assess effects using an on-treatment approach, which included data up to two days after the discontinuation of study medication. The 30 days post-discontinuation of randomised therapy measure of creatinine in the CANVAS-R trial was used to assess changes in eGFR independent of the acute and reversible haemodynamic effects of canagliflozin.

A linear mixed effects model was fit to the logarithm of UACR and included treatment, logarithm of baseline UACR value, visit, study, treatment-by-visit interaction, and logarithm of baseline UACR value by visit interaction as fixed effects. The percentage of treatment difference relative to placebo was calculated by taking the antilogarithm of the estimated coefficient for the treatment group and subtracting 1, and then multiplying by 100 to provide percentage differences between groups. Albuminuria levels below the limit of detection were assigned the values of the lower detectable limit, with sensitivity analyses undertaken by excluding these values.

To evaluate the impact of changes in HbA1c on renal efficacy of canagliflozin relative to placebo, a two-stage modeling approach was applied.²⁹ In the first stage, the longitudinal data of effect on HbA1c before development of a renal outcome were fit with a linear mixed model including treatment, study, baseline value of HbA1c, and the continuous covariates of time and time by treatment interaction. Intercept and time were included as random effects. The fit trajectory function of the endpoint was then included in the separate Cox models of renal composite endpoints as a time-varying covariate. The mixed effect model of UACR was also adjusted for the fit values of change in HbA1c from stage one modeling to understand the benefit of canagliflozin beyond glycemic control.

An on-treatment analysis for safety outcomes (i.e. patients who received ≥ 1 dose of study drug up to 30 days after study drug discontinuation) was done, as an on-treatment analysis was likely to be a more conservative approach than an intention-to-treat analysis in this context. Some serious AEs (cancer, fracture, amputation and diabetic ketoacidosis) were collected and included in analyses regardless of timing in order to capture any longer-term effects of canagliflozin.

Analyses were performed using SAS version 9.2. The studies are registered with ClinicalTrials.gov, identifiers NCT01032629 and NCT01989754.

Role of the funding source

The trials were sponsored by Janssen and conducted as a collaboration between Janssen, an academic Steering Committee, and an Academic Research Organization, George Clinical. The sponsor was involved in the study design, collection, analysis, and interpretation of the data, and the writing of the report. Analyses were undertaken independently by the Sponsor, and independently replicated and results confirmed by a statistician at George Clinical. Any discrepancies were resolved by discussion. The manuscript was drafted by the first author with all authors participating in subsequent revisions. The authors had full access to the data, made final decisions about content and submission for publication, and vouch for the accuracy and completeness of the analyses. The corresponding author had full access to all of the data and the final responsibility to submit for publication. The trials were approved by the ethics committees at each site and all participants provided written informed consent.

RESULTS

The CANVAS Program screened 15 494 people (December 2009-March 2011 for CANVAS and January 2014-May 2015 for CANVAS-R²⁰⁻²²), among whom 10 142 participants were randomised across 2 trials: CANVAS (4330 participants) and CANVAS-R (5812 participants; Figure S2).

Reasons for screen failures are shown in Figure S2, and included 64 people who did not comply with the placebo during the run-in phase. Mean follow-up was 188 weeks (296 weeks in CANVAS and 108 weeks in CANVAS-R). At baseline, median UACR was 12.3 mg/g; microalbuminuria was

present in 22·6% of participants and macroalbuminuria was present in 7·6% of participants. Baseline mean eGFR was 76·5 mL/min/1·73 m²; 24·4% of participants had an eGFR $\geq$ 90 mL/min/1·73 m²; 55·5% between 60 and <90 mL/min/1·73 m²; and 19·8% between 30 and <60 mL/min/1·73 m², including 5·2% with an eGFR <45 mL/min/1·73 m².

Baseline characteristics were well balanced across randomised groups (Table 1), including when categorised by baseline eGFR. Baseline characteristics by study have been reported previously¹⁸ and renal characteristics by study are summarised in Table S1. Compared to participants with normal kidney function, those with reduced kidney function were, on average, older, more likely to be female, have a longer diabetes duration, have established microvascular or macrovascular disease, and be treated with insulin and cardiovascular protective therapies.

At baseline, 80·2% and 79·8% of participants in the canagliflozin and placebo groups, respectively, were receiving RAS blockade, with an additional 4·0% and 3·9% of participants, respectively, having this therapy added to their treatment regimen during follow-up.

Effects on major kidney outcomes

The composite outcome of sustained doubling in serum creatinine, ESKD, or renal death occurred less frequently with canagliflozin compared to placebo (1·5 vs 2·8/1000 patient-years; HR 0·53, 95% CI 0·33–0·84; Figures 1A and 2).

Lower rates were also observed in canagliflozin-treated participants when either new-onset macroalbuminuria (HR 0·58, 95% CI 0·50–0·67) or cardiovascular death (HR 0·82, 95% CI 0·68–0·97) was added to this composite outcome (Figure 2). For each of these outcomes, substituting the sustained doubling of creatinine with sustained 40% reduction in eGFR resulted in more events and greater precision with similar point estimates of effect (Figure 2).

Few individuals experienced sustained ESKD or renal death during the trials, given that participants were generally at low renal risk overall, and event rates were not clearly different between canagliflozin and placebo (0.4 vs 0.8/1000 patient-years, HR 0.56, 95% CI 0.23–1.32; Figure 2).

Effects on composites containing either sustained doubling of serum creatinine or 40% reductions in eGFR were comparably lower among canagliflozin-treated participants across subgroups for both outcomes (Figure 3). These effects were also similar after adjustment for changes in HbA1c (Table S2). Analyses by dose from the CANVAS trial alone suggest that the 100 mg and 300 mg doses had similar effects on these outcomes (Table S3).

Effects on estimated glomerular filtration

Overall change in eGFR

Mean eGFR over time is shown in Figure 1B. From baseline to the final available measurements for each participant, the mean change in eGFR in placebo-treated participants from baseline to the last available eGFR was -3.9 ± 0.2 mL/min/1.73 m², compared to -1.8 ± 0.2 mL/min/1.73 m² in canagliflozin-treated participants (mean difference 2.0 mL/min/1.73 m², 95% CI 1.5–2.6). Among participants who completed study treatment and were re-evaluated approximately 30 days after treatment discontinuation (per the CANVAS-R protocol), mean change in eGFR from baseline to the last available measurements during the off-treatment period was 2.6 mL/min/1.73 m² higher (95% CI 1.8–3.4, Figure 1C) in the canagliflozin-compared to placebo-treated participants.

Effects on eGFR slope

The differences in eGFR slopes between treatment groups varied throughout follow-up due in part to an acute haemodynamic change on eGFR upon initiation of treatment (Figure 1B). From baseline to week 13, the placebo-treated group had an adjusted mean $\pm$ standard error GFR acute decrease of -0.7 ± 0.2 mL/min/1.73 m², whereas canagliflozin-treated participants had a decrease of -3.1 ± 0.1 mL/min/1.73 m² (difference between canagliflozin and placebo of -2.4 ± 0.2 mL/min/1.73 m²; 95% CI -2.8 to -2.0 mL/min/1.73 m²). From week 13 to last available measurements during the trial

(median of 20·9 months overall, 67·5 months for CANVAS and 16·7 months for CANVAS-R), participants randomised to placebo had a mean annual long-term decline of $-0·9 \pm 0·1$ mL/min/1·73 m²/year whereas those randomised to canagliflozin experienced a stabilisation of kidney function, with a mean annual long-term increase of $0·3 \pm 0·1$ mL/min/1·73 m²/year (difference $1·2 \pm 0·1$ mL/min/1·73 m²/year, 95% CI 1·0–1·4 mL/min/1·73 m²/year), using intention-to-treat based analyses. Similar results were observed using on-treatment measurements ($-0·8 \pm 0·1$ mL/min/1·73 m²/year with placebo versus $0·3 \pm 0·1$ mL/min/1·73 m²/year with canagliflozin (difference $1·1 \pm 0·1$ mL/min/1·73 m²/year; 95% CI 0·9–1·3 mL/min/1·73 m²/year). Results were also similar in participants with baseline eGFR above and below 60 mL/min/1·73 m² (Table S4), and those who were and were not treated with RAS blockade at baseline (Table S5). The treatment effects of canagliflozin on the rate of eGFR decline after 13 weeks were greatest in participants with baseline macroalbuminuria ($3·0$ mL/min/1·73 m²/year, 95% CI 2·0–4·0) compared to those with microalbuminuria ($1·0$ mL/min/1·73 m²/year, 95% CI 0·6–1·4) or normoalbuminuria ($1·1$ mL/min/1·73 m²/year, 95% CI 0·9–1·2; Table S6). Effects were also comparable across CANVAS and CANVAS-R (Table S7).

Effects on albuminuria

Overall, patients treated with canagliflozin had an 18% lower level of albuminuria during follow-up (95% CI 16%–20%, Figure 4A). The difference in albuminuria compared to placebo was 9% (95% CI 7%–12%), 34% (95% CI 29%–38%) and 36% (95% CI 28%–43%) in patients with normo-, micro-, and macroalbuminuria at baseline, respectively (Figure 4B–4D), although average albuminuria levels increased over time in both groups. Albuminuria reductions remained significant after adjustment for HbA1c changes over time (14% lower [95% CI 12%–16%]; Table S8).

Among participants with normoalbuminuria at baseline, new-onset albuminuria (micro- or macro-) occurred less frequently in participants randomised to canagliflozin compared to placebo (100·4 vs 130·8/1000 patient-years, HR 0·80, 95% CI 0·73–0·88). Lower rates of new-onset microalbuminuria were observed among participants with normoalbuminuria at baseline randomised to canagliflozin

(96.7 vs 127.3/1000 patient-years; HR 0.80, 95% CI 0.73–0.87, Figure 4E); rates of new-onset macroalbuminuria among participants with normo- or microalbuminuria at baseline were also lower (15.1 vs 27.6/1000 patient-years; HR 0.58, 95% CI 0.50–0.68; Figure 4F) among the canagliflozin group compared to placebo.

Safety outcomes

The total number of renal-related serious AEs was not different with canagliflozin versus placebo (2.5 vs 3.3/1000 patient-years; HR 0.76, 95% CI 0.49–1.19). Rates of serious AEs due to AKI (1.6 vs 2.5/1000 patient-years; HR 0.66, 95% CI 0.39–1.11) or hyperkalaemia (0.4 vs 0.6/1000 patient-years; HR 0.75, 95% CI 0.27–2.11) were also not different (Figure S3). Rates of all serious and non-serious renal AEs (collected in CANVAS participants prior to January 2014) were also not different with canagliflozin versus placebo (20.3 vs 17.8/1000 patient-years; HR 1.16, 95% CI 0.86–1.56). In the CANVAS trial, no differences were found for either AKI (3.0 vs 4.2/1000 patient-years; HR 0.72, 95% CI 0.38–1.39) or hyperkalaemia (7.0 vs 4.5/1000 patient-years; HR 1.60, 95% CI 0.92–2.81). The increased risk of amputation was consistent in people with baseline eGFR levels above and below 60 mL/min/1.73m² (HR 1.91 [95% CI 1.29–2.83] vs 2.17 [95% CI 1.14–4.10], respectively), as was the risk of fracture (HR 1.29 [95% CI 1.04–1.61] vs 1.18 [95% CI 0.80–1.73], respectively).

DISCUSSION

The CANVAS Program demonstrated that patients at high cardiovascular risk with mostly well preserved kidney function had improvements in a range of renal function parameters when treated with canagliflozin. Along with lower levels of albuminuria and a reduced likelihood of developing micro- or macroalbuminuria, canagliflozin-treated participants also experienced a stabilisation in kidney function measured by change in eGFR over time and by slope of eGFR decline, which translated into fewer participants experiencing a sustained reduction in kidney function.

These analyses show consistent results on a broad range of renal outcomes, including those used by regulators, guidelines, and clinicians to define renoprotection, and therefore provide strong support for

the hypothesis that canagliflozin has clinically relevant renal benefits for patients. The breadth and consistency of these findings add substantially to the strength of the conclusions that can be drawn from the limited renal outcome data provided in the original CANVAS Program report.¹⁸ The robustness of these exploratory renal protection findings is further supported by the magnitude of the differences between canagliflozin and placebo arms, and the consistency of the protection across multiple different pre-specified, sustained, and adjudicated renal endpoints. In the recently reported renal data from the EMPA-REG OUTCOME trial,¹⁹ similar benefits of empagliflozin on GFR slope and composite renal outcomes including doubling of serum creatinine, ESKD, and renal death were reported, further strengthening the likelihood that SGLT2 inhibitors have important benefits for the kidney. While kidney outcomes were not confirmed or adjudicated during the EMPA-REG OUTCOME trial,³⁰ subsequent analyses have shown similar results based upon retrospectively confirmed events.³¹ On this background, the clear effects on pre-specified, prospectively confirmed, and adjudicated endpoints in the CANVAS Program greatly increase the likelihood that SGLT2 inhibition will have a future role in kidney protection amongst patients with type 2 diabetes.

Several mechanisms may contribute to renoprotection with SGLT2 inhibitors. Improved glycaemic control was found to reduce the risk of ESKD in the ADVANCE trial,^{5,32} though this has not been a consistent finding.⁴ Head-to-head studies against sulphonylureas have also shown stabilisation of eGFR in participants treated with SGLT2 inhibitors, whereas it declined progressively in those randomised to sulphonylureas.³³ Furthermore, the renal benefits were similar after adjustment for effects on HbA1c, making it very unlikely that the renal effects are glucose dependent. BP lowering may also be an important contributor but the renal effects of intensive BP control have also been somewhat inconsistent.^{8,34} The acute effects on eGFR suggest that intraglomerular pressure is reduced by SGLT2 inhibitors, which may be due to inhibition of tubuloglomerular feedback and afferent arteriolar vasoconstriction.¹⁶ This mechanism is complementary to that of RAS blockade, and its role is supported by short-term data in patients with type 1 diabetes treated with empagliflozin demonstrating attenuated renal hyperfiltration by affecting tubuloglomerular feedback. Although untested in patients with type 2 diabetes, a similar mechanism is expected.¹⁶ Finally, recent studies of

other classes of glucose-lowering agents have either shown no consistent effect on kidney outcomes (dipeptidyl peptidase-4 [DPP-4] inhibitors),^{35,36} or have shown benefits for albuminuria based outcomes and eGFR slope, but not for ESKD or doubling of serum creatinine (liraglutide, a glucagon-like peptide-1 [GLP-1] receptor agonist).³⁷ Overall, the available data suggest that the large apparent benefits for the kidney are likely to be predominantly due to the specific renal effects of SGLT2 inhibitors, and can be achieved on top of RAS blockade.

The CANVAS Program renal analyses benefit from the large size, long duration, strong design, rigorous conduct and the pre-specification, confirmation, and adjudication of renal outcomes. Patients were well managed according to contemporary guidelines, although glycaemic control did not achieve guideline targets on average, highlighting the need for better glucose-lowering therapies. The major limitation of this and prior reports is the paucity of the clinically important kidney outcomes of ESKD and renal death (21 events in total) or doubling of serum creatinine (60 events), due in large part to the recruitment of participants with high cardiovascular risk but overall with mostly normal kidney function and therefore relatively low renal risk. Future research aiming to better define people at high risk of rapid loss of kidney function should be a priority. Regulatory agencies have routinely and reasonably prioritised ESKD and renal death over albuminuria- or creatinine-based outcomes, and it is unlikely that the exploratory analyses from the CANVAS Program or the EMPA-REG OUTCOME trial will lead to the granting of a treatment indication for the prevention of kidney disease on the label of SGLT2 inhibitors. The ongoing Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE, NCT02065791) trial will define whether the albuminuria- and creatinine-based effects observed with canagliflozin translate into clinically important renal benefits in individuals with type 2 diabetes. To the best of our knowledge, CREDENCE will be the first dedicated renal outcome trial using an SGLT2 inhibitor, and will provide more data about effects in people with established kidney disease, including those with reduced kidney function, since most participants have eGFR <60 mL/min/1.73 m² and all have macroalbuminuria despite maximally tolerated RAS blockade. Further trials with dapagliflozin³⁸ and empagliflozin³⁹ will also look at renal effects in both diabetic and non-diabetic chronic kidney

disease. Further analyses assessing delay in onset time of albuminuria progression are planned, but have not yet been conducted. While pre-specified, the renal outcomes reported for the CANVAS Program are outside the formal hypothesis testing sequence and thus exploratory¹⁸ and the large number of analyses and relatively few outcomes increases the risk of false positive findings, though the broad concordance of the data and consistency with other SGLT2 inhibitor trials strengthens the conclusion of renoprotection in people with diabetes.

Conclusions

Canagliflozin reduced the risk of sustained decline in kidney function, lowered albuminuria excretion, and attenuated eGFR decline. These results suggest canagliflozin may have an important role in reducing the burden of kidney disease in people with diabetes.

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Declaration of interests

VP reports receiving research support from the Australian National Health and Medical Research Council (Senior Research Fellowship and Program Grant); serving on Steering Committees for AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen and Pfizer; and serving on advisory boards and/or speaking at scientific meetings for AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier and Vitae with all honoraria paid to his employer. DdZ reports serving on advisory boards and/or as a speaker for AbbVie, Astellas, Eli Lilly, Fresenius, Janssen, Boehringer Ingelheim, Bayer and Mitsubishi-Tanabe with all consultancy honoraria paid to his institution. KWM reports receiving research support from Afferent, Amgen, AstraZeneca, Daiichi, Ferring, Google (Verily), Janssen, Medtronic, Merck, Novartis, Sanofi and St. Jude; serving as a consultant (including continuing medical education [CME]) for Ablynx, AstraZeneca, BAROnova, Bio2 Medical, Boehringer Ingelheim, Bristol-Myers Squibb, Cardiometabolic Health Congress, Cubist, Eli Lilly, Elsevier, Epson, GlaxoSmithKline, Janssen, Merck, Mt. Sinai, Myokardia, Novartis, Oculeve, Portola, Radiometer, Springer Publishing, The Medicines Company, Theravance, Vindico and WebMD; and having equity in BioPrint Fitness. GF reports receiving research support from Novo Nordisk and serving on advisory boards and as a consultant for Janssen, Novo Nordisk, Boehringer Ingelheim and Merck Sharp and Dohme. NE, WS, TDB, MW, and HD report being full-time employees of Janssen Research & Development, LLC, and holding stock in Johnson & Johnson. DRM reports receiving research support from Janssen; serving on advisory boards and as a consultant for Novo Nordisk, Novartis, Sanofi-Aventis, Janssen and Servier; and giving lectures for Novo Nordisk, Servier, Sanofi-Aventis, Novartis, Janssen, Mitsubishi Tanabe and Aché Laboratories. BN reports receiving research support from the Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen, Roche, Servier and Merck Schering Plough; and serving on advisory boards and/or involvement in CME programs for Abbott, Janssen, Novartis, Pfizer, Roche and Servier with any consultancy, honoraria or travel support paid to his institution. No other potential conflicts of interest relevant to this article are reported.

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FIGURE LEGENDS

Figure 1. Effects of canagliflozin compared to placebo on a) composite of doubling of creatinine, ESKD, or renal death across the CANVAS Program, b) eGFR over time across the CANVAS Program, c) eGFR over time and after a median of 30 days off-treatment in the CANVAS-R study

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

For the composite renal outcome, time to the first event type was counted.

Figure 2. Effects of canagliflozin on major renal outcomes

CI, confidence interval; dSCr, doubling serum creatinine; ESKD, end-stage kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

For each composite and individual outcome, time to the first event of that type was counted, and any subsequent events were disregarded. 40% reduction in eGFR and doubling of creatinine were required to be sustained, defined as being present on at least 2 consecutive measurements more than 30 days apart. ESKD defined as the composite of maintenance dialysis sustained for at least 30 days, renal transplantation or a sustained eGFR $<15 \text{ mL/min/1.73 m}^2$, and adjudicated by an expert committee. Renal death defined as death where the proximate cause was renal as defined by the endpoint adjudication committee. There were only 3 renal deaths, all in the placebo group.

Figure 3. Subgroup analyses for the composite of doubling of serum creatinine, ESKD, or renal death and the composite of 40% reduction in eGFR, ESKD, or renal death

ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, cardiovascular; RAS, renin-angiotensin system.

Test of treatment by subgroup interaction was conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups.

Figure 4. Effects of canagliflozin versus placebo on UACR in a) all participants; participants with baseline b) normoalbuminuria, c) microalbuminuria and d) macroalbuminuria; e) new-onset microalbuminuria in participants with normoalbuminuria at baseline; and f) new-onset macroalbuminuria in participants with normo- or microalbuminuria at baseline

UACR, urinary albumin:creatinine ratio; CI, confidence interval.

Table 1. Baseline characteristics for the CANVAS Program by baseline eGFR

	eGFR <60 mL/min/1.73 m ²			eGFR ≥60 mL/min/1.73 m ²		
	Canagliflozin	Placebo	Total	Canagliflozin	Placebo	Total
	(n = 1110)	(n = 929)	(N = 2039)	(n = 4684)	(n = 3417)	(N = 8101)
Age, years, mean (SD)	67·6 (7·8)	67·6 (7·6)	67·6 (7·7)	62·1 (8·0)	62·3 (8·0)	62·2 (8·0)
Sex, No. (%)						
Male	659 (59·4)	527 (56·7)	1186 (58·2)	3100 (66·2)	2222 (65·0)	5322 (65·7)
Female	451 (40·6)	402 (43·3)	853 (41·8)	1584 (33·8)	1195 (35·0)	2779 (34·3)
Race, No. (%)						
White	907 (81·7)	766 (82·5)	1673 (82·1)	3600 (76·9)	2669 (78·1)	6269 (77·4)
Asian	118 (10·6)	98 (10·5)	216 (10·6)	659 (14·1)	409 (12·0)	1068 (13·2)
Black or African American	27 (2·4)	19 (2·0)	46 (2·3)	149 (3·2)	141 (4·1)	290 (3·6)
Other ^a	58 (5·2)	46 (5·0)	104 (5·1)	276 (5·9)	198 (5·8)	474 (5·9)
Current smoker, No. (%)	120 (10·8)	106 (11·4)	226 (11·1)	900 (19·2)	680 (19·9)	1580 (19·5)
History of hypertension, No. (%)	1043 (94·0)	885 (95·3)	1928 (94·6)	4144 (88·5)	3051 (89·3)	7195 (88·8)
History of heart failure, No. (%)	200 (18·0)	164 (17·7)	364 (17·9)	603 (12·9)	493 (14·4)	1096 (13·5)
Duration of diabetes, years, mean (SD)	16·1 (8·4)	15·7 (8·2)	15·9 (8·3)	12·8 (7·4)	13·1 (7·6)	13·0 (7·5)

Drug therapy, No. (%)						
Insulin	682 (61·4)	562 (60·5)	1244 (61·0)	2208 (47·1)	1643 (48·1)	3851 (47·5)
Sulphonylurea	416 (37·5)	342 (36·8)	758 (37·2)	2111 (45·1)	1490 (43·6)	3601 (44·5)
Metformin	589 (53·1)	573 (61·7)	1162 (57·0)	3858 (82·4)	2805 (82·1)	6663 (82·2)
GLP-1 receptor agonist	40 (3·6)	43 (4·6)	83 (4·1)	182 (3·9)	142 (4·2)	324 (4·0)
DPP-4 inhibitor	131 (11·8)	152 (16·4)	283 (13·9)	566 (12·1)	412 (12·1)	978 (12·1)
Statin	876 (78·9)	714 (76·9)	1590 (78·0)	3454 (73·7)	2556 (74·8)	6010 (74·2)
Antithrombotic	889 (80·1)	730 (78·6)	1619 (79·4)	3347 (71·5)	2505 (73·3)	5852 (72·2)
RAS inhibitor	908 (81·8)	747 (80·4)	1655 (81·2)	3736 (79·8)	2723 (79·7)	6459 (79·7)
Beta blocker	674 (60·7)	601 (64·7)	1275 (62·5)	2365 (50·5)	1780 (52·1)	4145 (51·2)
Diuretic	662 (59·6)	560 (60·3)	1222 (59·9)	1874 (40·0)	1394 (40·8)	3268 (40·3)
Microvascular disease history, No. (%)						
Retinopathy	286 (25·8)	269 (29·0)	555 (27·2)	917 (19·6)	657 (19·2)	1574 (19·4)
Nephropathy	356 (32·1)	293 (31·5)	649 (31·8)	638 (13·6)	487 (14·3)	1125 (13·9)
Neuropathy	394 (35·5)	300 (32·3)	694 (34·0)	1393 (29·7)	1023 (29·9)	2416 (29·8)

Atherosclerotic vascular disease history, No. (%) ^b						
Coronary	621 (55.9)	515 (55.4)	1136 (55.7)	2398 (51.2)	1746 (51.1)	4144 (51.2)
Cerebrovascular	250 (22.5)	207 (22.3)	457 (22.4)	863 (18.4)	636 (18.6)	1499 (18.5)
Peripheral	289 (26.0)	216 (23.3)	505 (24.8)	887 (18.9)	721 (21.1)	1608 (19.8)
Any	816 (73.5)	681 (73.3)	1497 (73.4)	3160 (67.5)	2368 (69.3)	5528 (68.2)
CV disease history, No. (%) ^c	799 (72.0)	661 (71.2)	1460 (71.6)	2957 (63.1)	2238 (65.5)	5195 (64.1)
History of amputation, No. (%)	47 (4.2)	37 (4.0)	84 (4.1)	89 (1.9)	65 (1.9)	154 (1.9)
Body mass index, kg/m ² , mean (SD)	32.1 (5.9)	32.5 (6.2)	32.3 (6.0)	31.9 (5.9)	31.8 (5.9)	31.9 (5.9)
Systolic BP, mmHg, mean (SD)	137.3 (16.9)	137.7 (16.1)	137.5 (16.6)	136.2 (15.5)	136.7 (15.7)	136.4 (15.6)
Diastolic BP, mmHg, mean (SD)	75.6 (10.1)	75.4 (10.2)	75.5 (10.1)	78.1 (9.5)	78.4 (9.5)	78.2 (9.5)
Glycated haemoglobin, mean (SD)						
%	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
mmol/mol	67 (10.9)	67 (9.8)	67 (9.8)	66 (9.8)	66 (9.8)	66 (9.8)
Total cholesterol, mean (SD)						
mg/dL	170.2 (43.6)	168.1 (44.5)	169.2 (44.0)	167.9 (44.3)	169.1 (45.3)	168.4 (44.7)
mmol/L	4.4 (1.1)	4.4 (1.2)	4.4 (1.1)	4.3 (1.1)	4.4 (1.2)	4.4 (1.2)

Triglycerides, mean (SD)						
mg/dL	191·1 (122·0)	194·3 (117·5)	192·6 (120·0)	176·5 (117·2)	176·8 (139·1)	176·7 (126·9)
mmol/L	2·2 (1·4)	2·2 (1·3)	2·2 (1·4)	2·0 (1·3)	2·0 (1·6)	2·0 (1·4)
HDL-C, mean (SD)						
mg/dL	45·3 (13·0)	44·2 (11·6)	44·8 (12·4)	45·6 (12·3)	45·8 (11·8)	45·7 (12·1)
mmol/L	1·2 (0·3)	1·1 (0·3)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)
LDL-C, mean (SD)						
mg/dL	88·8 (36·1)	86·8 (36·4)	87·9 (36·2)	88·6 (36·1)	89·9 (36·1)	89·2 (36·1)
mmol/L	2·3 (0·9)	2·2 (0·9)	2·3 (0·9)	2·3 (0·9)	2·3 (0·9)	2·3 (0·9)
LDL-C:HDL-C ratio, mean (SD)	2·1 (1·0)	2·0 (0·9)	2·1 (0·9)	2·0 (0·9)	2·0 (0·9)	2·0 (0·9)
eGFR, mL/min/1·73 m ² , mean (SD)	49·2 (7·8)	49·0 (8·3)	49·1 (8·0)	83·2 (16·5)	83·6 (16·7)	83·4 (16·6)
UACR, median (IQR) ^d						
mg/g	21·5 (7·5–132·7)	21·7 (7·9–105·5)	21·6 (7·7–117·8)	11·5 (6·6–33·0)	11·1 (6·4–33·0)	11·3 (6·5–33·0)
mg/mmol	2·4 (0·9–15·0)	2·4 (0·9–11·9)	2·4 (0·9–13·3)	1·3 (0·7–3·7)	1·3 (0·7–3·7)	1·3 (0·7–3·7)
Normoalbuminuria, No. (%)	610 (55·5)	519 (56·6)	1129 (56·0)	3401 (73·3)	2475 (73·3)	5876 (73·3)
Microalbuminuria or macroalbuminuria, No. (%)	489 (44·5)	398 (43·4)	887 (44·0)	1239 (26·7)	900 (26·7)	2139 (26·7)

eGFR, estimated glomerular filtration rate; SD, standard deviation; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAS, renin-angiotensin system; CV, cardiovascular; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin:creatinine ratio; IQR, interquartile range.

^aIncludes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown.

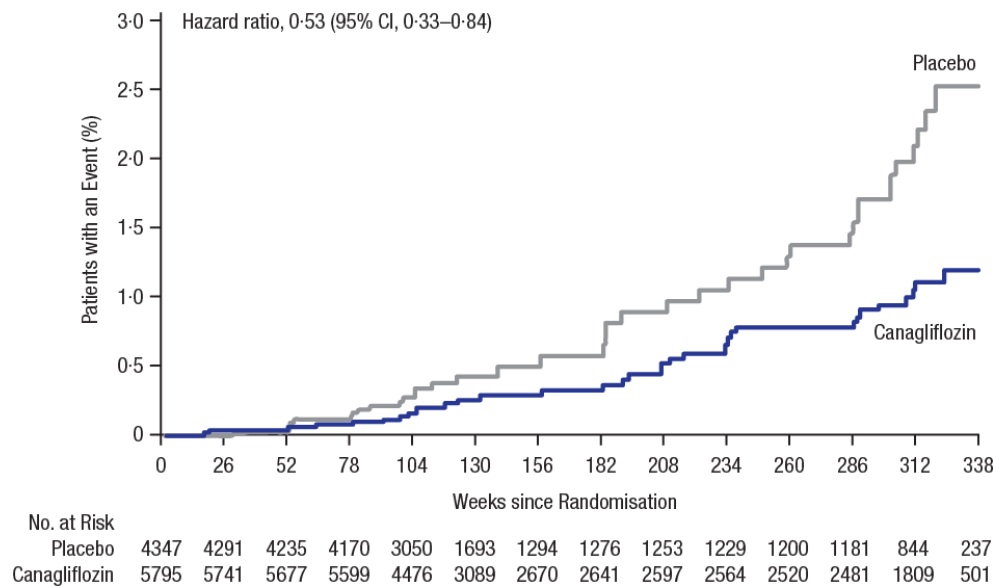
^bSome participants had ≥ 1 type of atherosclerotic disease.

^cAs defined in the protocol.

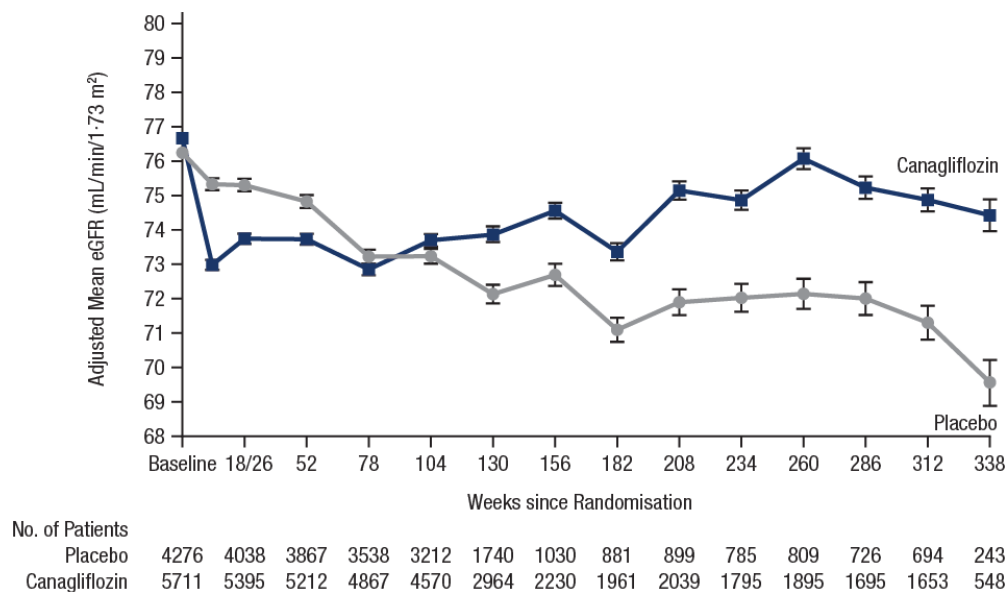
^dUACR measurements based on 1099 participants with canagliflozin, 917 participants with placebo, and 2016 participants total in the eGFR < 60 mL/min/1.73 m² subgroup and 4640 participants with canagliflozin, 3375 participants with placebo, and 8015 participants total in the eGFR ≥ 60 mL/min/1.73 m² subgroup.

Figure 1. Effects of canagliflozin compared to placebo on a) composite of doubling of creatinine, ESKD, or renal death across the CANVAS Program, b) eGFR over time across the CANVAS Program, c) eGFR over time and after a median of 30 days off-treatment in the CANVAS-R study

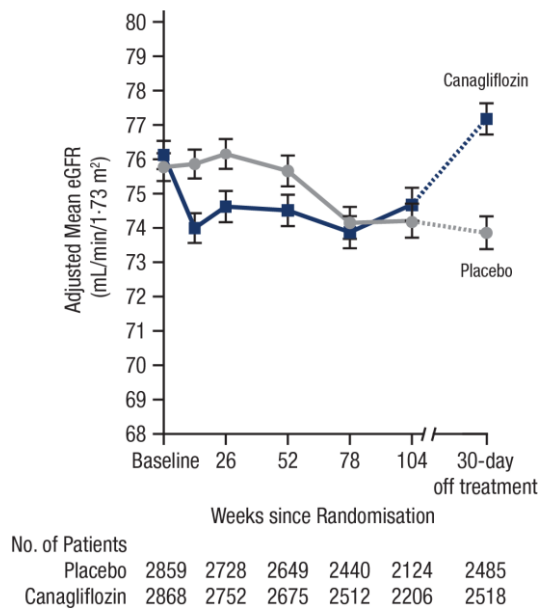
a)



b)



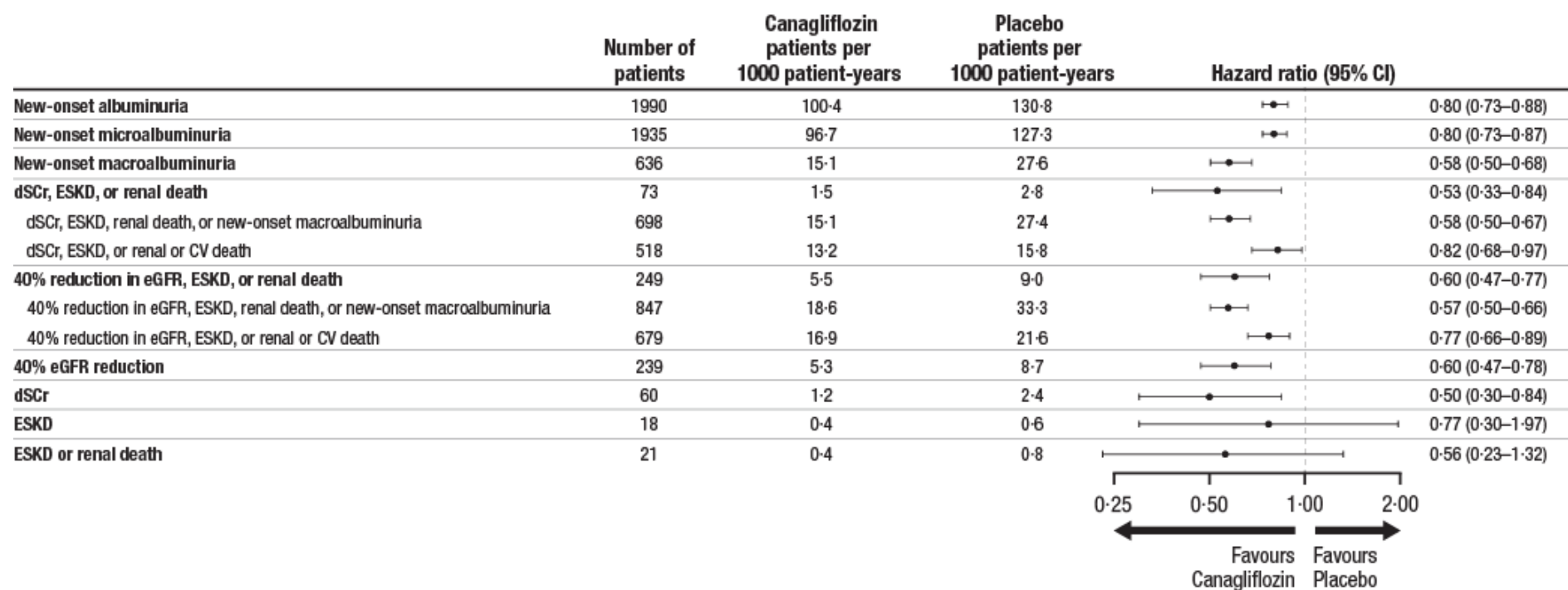
c)



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

For the composite renal outcome, time to the first event type was counted.

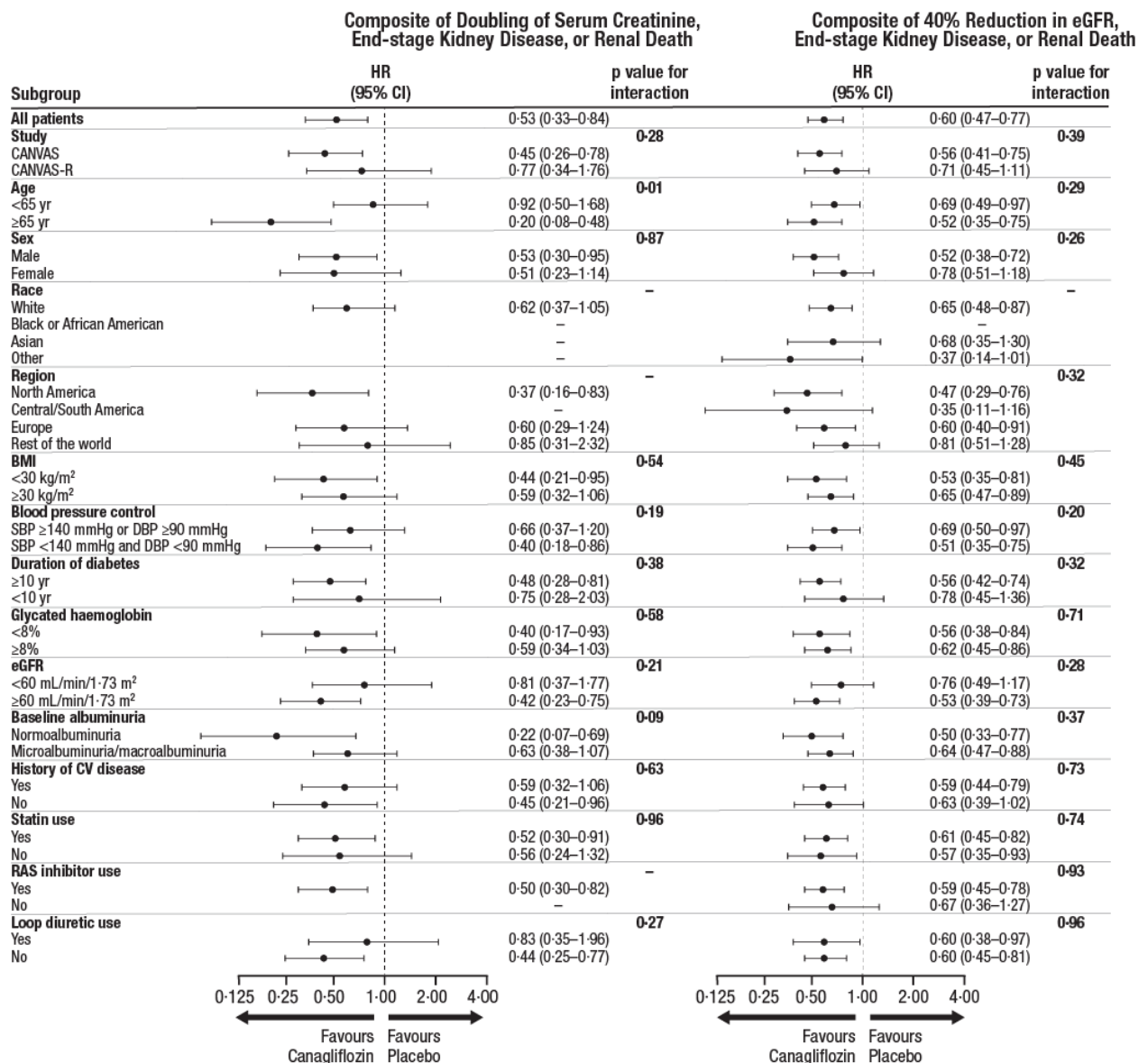
Figure 2. Effects of canagliflozin on renal outcomes



CI, confidence interval; dSCr, doubling serum creatinine; ESKD, end-stage kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

For each composite and individual outcome, time to the first event of that type was counted, and any subsequent events are disregarded. 40% reduction in eGFR and doubling of creatinine were required to be sustained, defined as being present on at least 2 consecutive measurements more than 30 days apart. ESKD defined as the composite of maintenance dialysis sustained for at least 30 days, renal transplantation or a sustained eGFR <15 mL/min/1.73 m², and adjudicated by an expert committee. Renal death defined as death where the proximate cause was renal as defined by the endpoint adjudication committee. There were only 3 renal deaths, all in the placebo group.

Figure 3. Subgroup analyses for the composite of doubling of serum creatinine, ESKD, or renal death and the composite of 40% reduction in eGFR, ESKD, or renal death

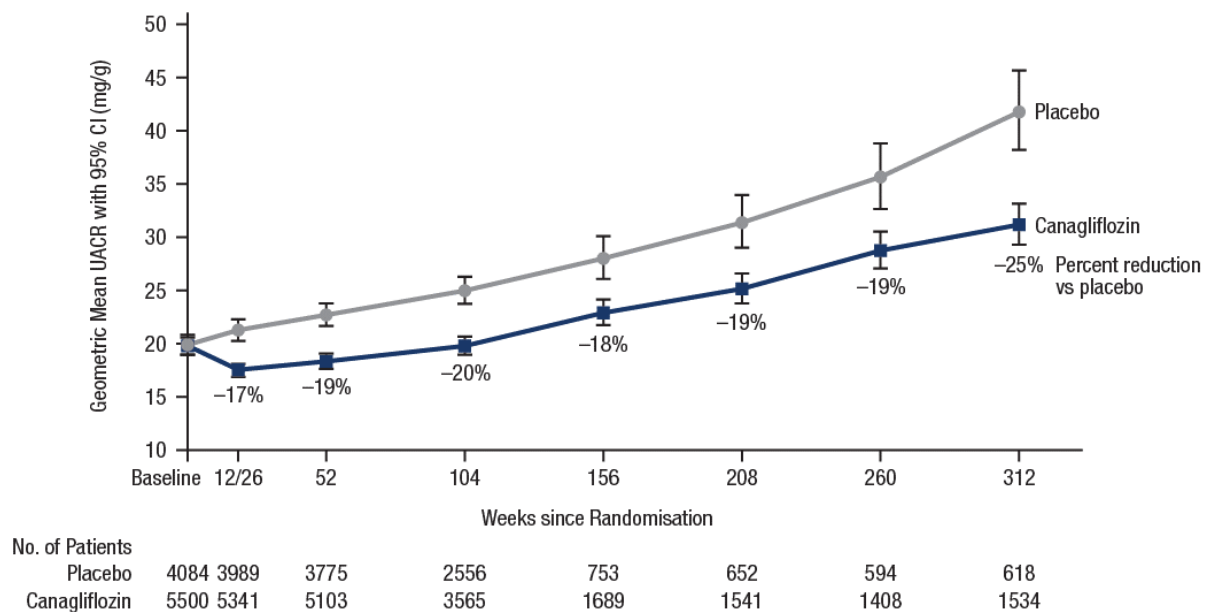


ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, cardiovascular; RAS, renin-angiotensin system.

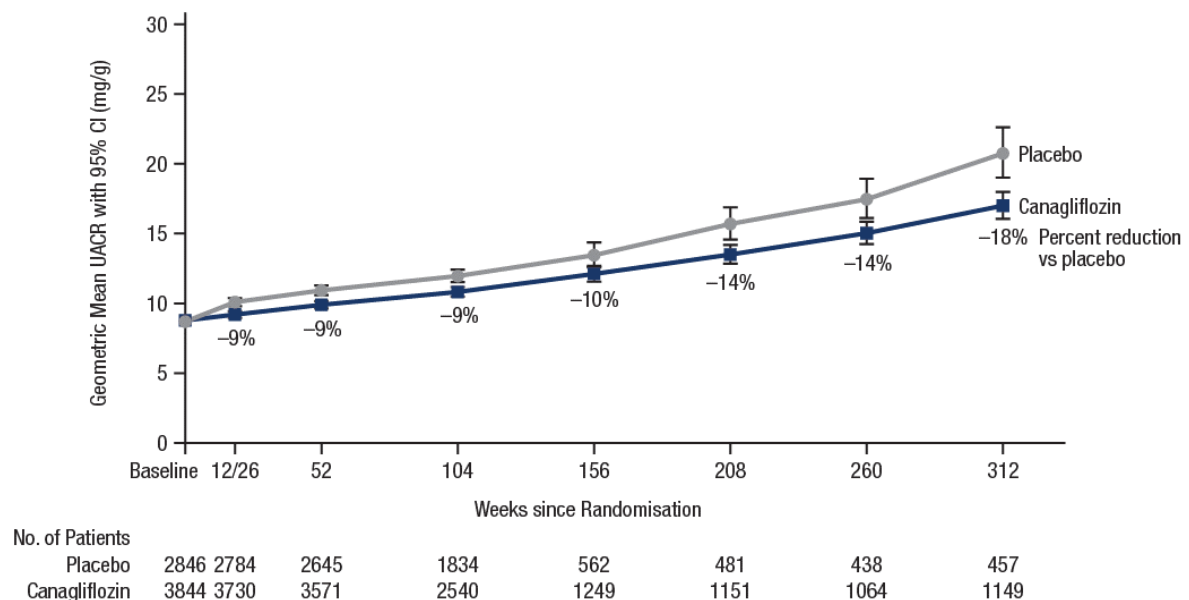
Test of treatment by subgroup interaction was conducted when the total number of events is greater than 10 for two treatment groups (all canagliflozin group and placebo) and at least 1 event in both groups.

Figure 4. Effects of canagliflozin versus placebo on UACR in a) all participants; participants with baseline b) normoalbuminuria, c) microalbuminuria and d) macroalbuminuria; e) new-onset microalbuminuria in participants with normoalbuminuria at baseline; and f) new-onset macroalbuminuria in participants with normo- or microalbuminuria at baseline

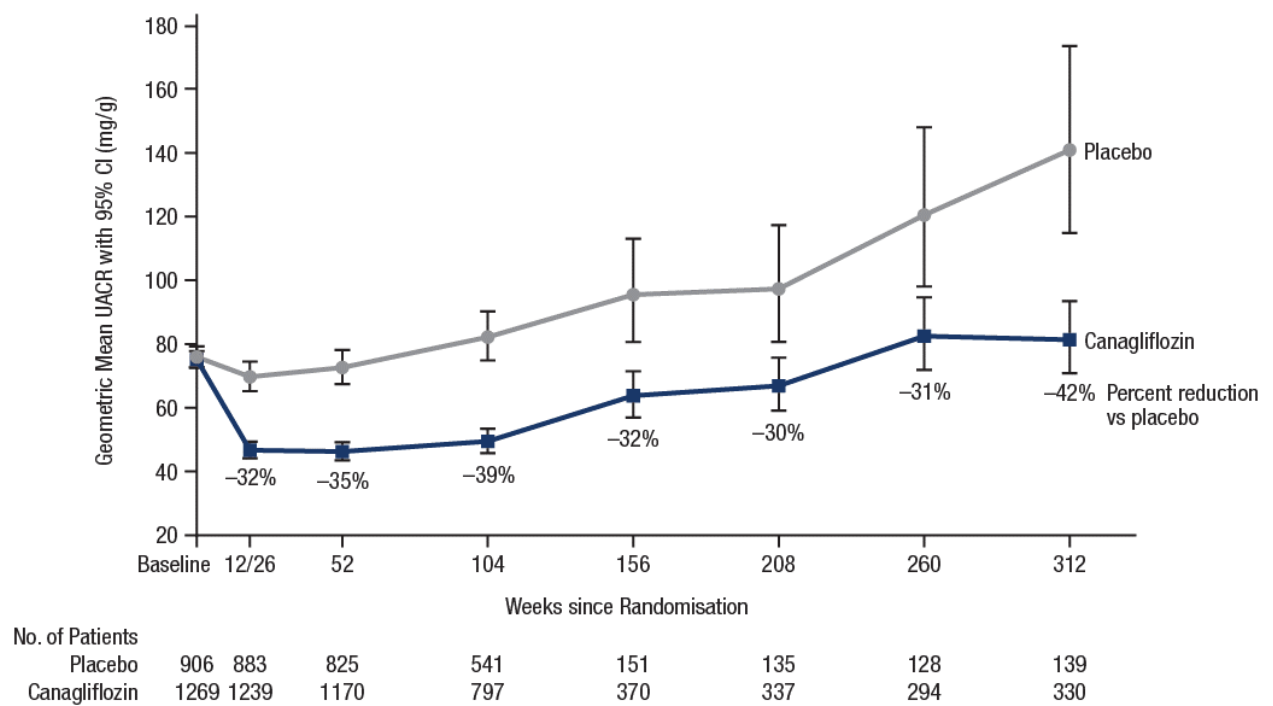
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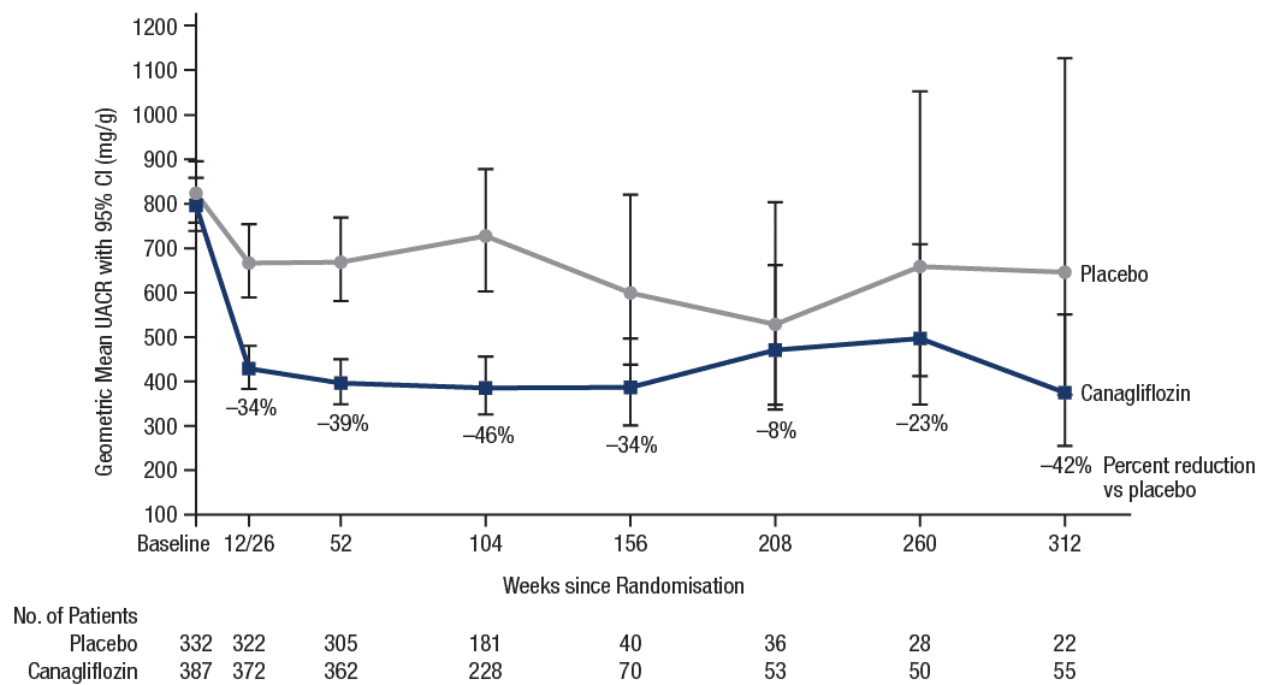
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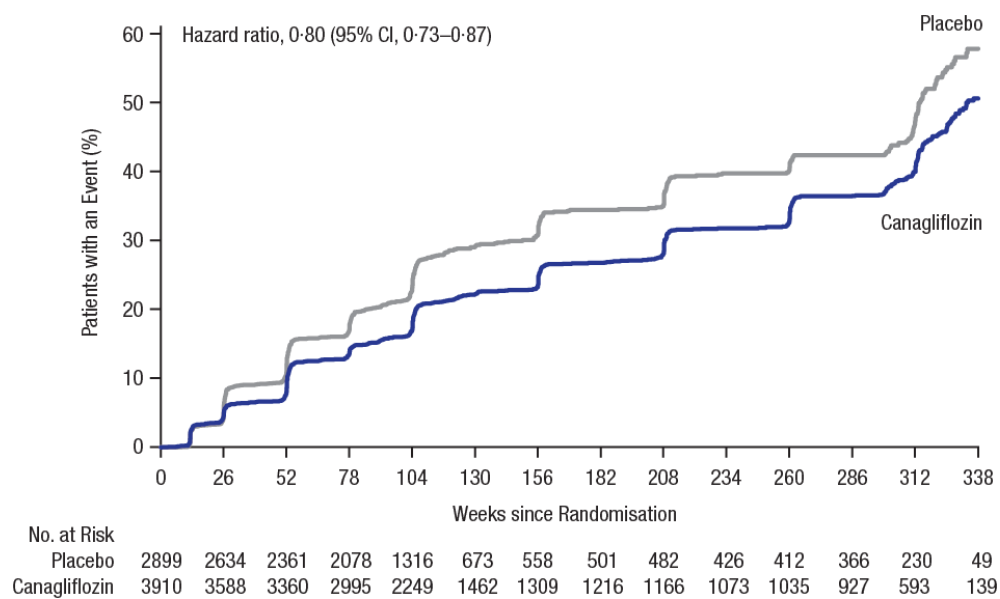
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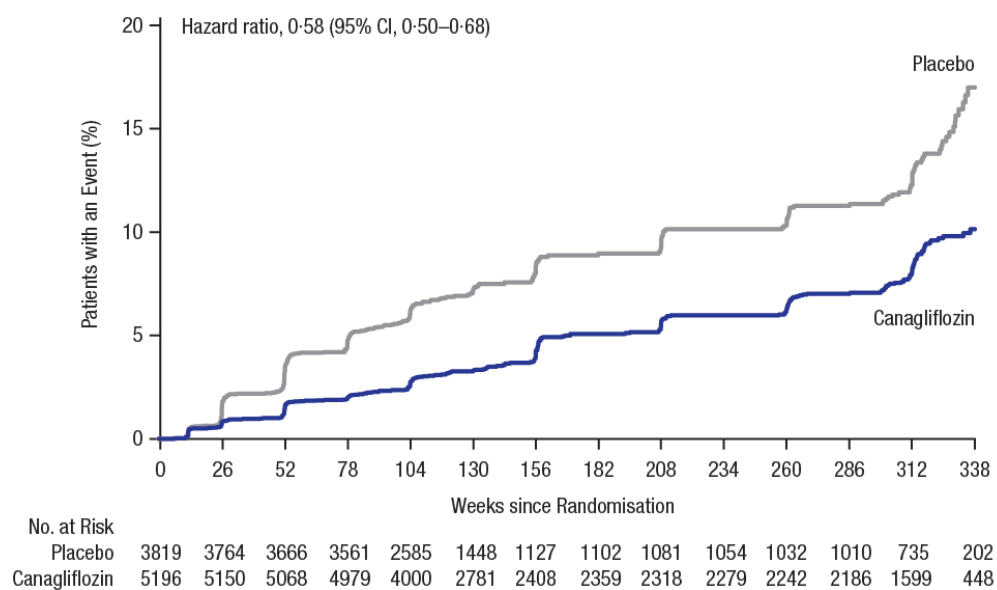
d)



e)



f)



UACR, urinary albumin:creatinine ratio; CI, confidence interval.

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CANVAS and CANVAS-R sites and investigators

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CANVAS Program renal outcome criteria

A. Renal endpoints

The renal endpoints of interest are:

- Progression of albuminuria;
- Regression of albuminuria;
- Renal composites:
 - 40% decrease in estimated glomerular filtration rate (eGFR), renal death, or requirement for renal replacement therapy;
 - Doubling of serum creatinine, renal death, or requirement for renal replacement therapy

Albuminuria

Urinary albumin:creatinine ratio (ACR) is used to assess albuminuria. Subjects will be classified as having normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR ≥30 mg/g and ≤300 mg/g), or macroalbuminuria (ACR >300 mg/g).

- **Albuminuria progression** is the development of microalbuminuria or macroalbuminuria in a subject with baseline normoalbuminuria or the development of macroalbuminuria in a subject with baseline microalbuminuria, accompanied by an ACR value increase of greater than or equal to 30% from baseline.
- **Albuminuria regression** is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary ACR value of greater than or equal to 30% from baseline.
- **The onset of events of albuminuria progression/regression** is based on the ACR measurements quantified by a central laboratory. The date of the progression/regression event will be defined as the visit date of the first urine sample for the potential progression/regression findings. Events based on ACR measurements were not adjudicated.

Renal Composites

The components of the renal composite endpoints, such as requirement for renal replacement therapy, 40% reduction in eGFR, and doubling of serum creatinine, identified by the investigators or the sponsor for meeting the criteria pre-specified in the charter will be sent to the independent Endpoint Adjudication Committee (EAC).

Requirement for Renal Replacement Therapy

In the absence of universally accepted guidelines that define the onset of end-stage kidney disease (ESKD), the following definitions have been developed to identify and adjudicate ESKD events.

1. Diagnosis

Worsening uremia in patients progressing from chronic kidney disease to ESKD causes characteristic symptoms that require renal replacement therapy in the form of dialysis or transplantation. The requirement of ongoing renal replacement therapy establishes the diagnosis of ESKD. In some cases, the diagnosis can be made in the absence of renal replacement therapy when certain criteria are fulfilled.

- **Kidney transplantation**
Definitive renal replacement therapy prescribed when uremic symptoms have already occurred, or are anticipated to occur, due to the progression of irreversible chronic kidney disease. Death during the transplant surgery will be considered kidney transplantation.
- **Chronic dialysis**
ESKD will be diagnosed if dialysis is performed for 30 days or more and is not subsequently known to recover. Indications for dialysis are indicated in section 2 below.
- **Dialysis not administered**
In cases where dialysis is not available or not administered due to futility or subject refusal, the diagnosis of ESKD will require sustained eGFR of <15 mL/min/1.73 m² (by CKD-EPI formula and confirmed by repeat central laboratory measure).

2. Onset of ESKD

The mode of onset of ESKD will be adjudicated into the following categories:

- Chronic progression
- Acute deterioration, diagnosed when the decline in kidney function is sudden and acute kidney injury is superimposed on chronic kidney disease resulting in renal replacement therapy.

3. Confirmation of ESKD

- If the patient recovers renal function, (defined as patient taken off dialysis because the physician evaluates that patient has enough renal function to live independently) the diagnosis of ESKD will be rescinded.
- If the patient is known to have received dialysis for >30 days but <90 days, and not known to recover, ESKD will be confirmed. The reason for the unavailability of information beyond 30 days should be clearly documented by the investigator.

If dialysis was initiated, but not continued for 30 days due to death, futility of therapy, or transplantation, the patient will be considered to have reached ESKD. In this situation, the reason for discontinuation of dialysis should be clearly documented by the investigator.

- If dialysis is known to have been continued for <30 days and there is no further information available about the event, the adjudicators will use their discretion in considering the event as an endpoint.

4. Date of ESKD

- If an event is adjudicated as ESKD due to kidney transplantation, the date of the transplantation will be the date of the event if transplantation was the first form of renal replacement therapy given.
- If an event is adjudicated as ESKD due to initiation of dialysis, the date when dialysis was initiated will be the date of the event.
- In cases where dialysis is not available or not administered due to futility or subject refusal, the date of ESKD will be when eGFR falls below 15 mL/min/1.73 m², as determined by central or local laboratory measurements.

Information around presence or absence of symptoms of uremia will also be collected, if available, for subjects meeting the ESKD endpoint; however this will not affect the final adjudication decision which will be based on the primary definition of ESKD as described in sections 1–4 above.

- Symptomatic uremia
Symptomatic uremia is diagnosed in the presence of the uremic syndrome, which is a constellation of signs and symptom involving several different systems, including:
 - General: Pruritus, dry skin, fatigue, anhedonia
 - Metabolic: Deterioration in nutritional status, recent significant weight loss, electrolyte or acid base disturbances (severe hyperkalemia or severe acidosis);
 - Gastrointestinal: Nausea, vomiting
 - Neurological: Neuropathy, encephalopathy, psychiatric disturbances, seizures;
 - Volume overload, including difficult-to-control or accelerated hypertension;
 - Bleeding diathesis not attributable to other causes;
 - Pleuritis or pericarditis of uremic origin or other;
 - Severe hyperparathyroidism.
- Advanced asymptomatic uremia
The initiation of dialysis is generally performed when eGFR declines to <15 mL/min/1.73 m² on a subjective basis in anticipation of development of uremic symptoms. If no symptoms are documented for initiation of dialysis, asymptomatic uremia will be diagnosed. In the minority of patients who exhibit no symptoms even at very low eGFR values (such as <8 mL/min/1.73 m²), but for whom renal replacement therapy is initiated in the view of benefits of therapy, the diagnosis will be of advanced asymptomatic uremia.

Doubling of Serum Creatinine and 40% Reduction in eGFR

Doubling of serum creatinine will be defined as a greater than or equal to 2-times increase in serum creatinine from the baseline assessment that persists for 30 days or more and is not thought to be due to reversible cause.

The baseline serum creatinine will be used to compare subsequent values and determine if doubling of serum creatinine has occurred.

A 40% reduction in eGFR will be defined as a greater than or equal to 40% reduction in eGFR from the baseline assessment that persists for 30 days or more and is not thought to be due to reversible cause

- The baseline eGFR will be used to compare subsequent values and determine if 40% reduction in eGFR has occurred.
- Both central serum creatinine and eGFR values and local lab values, if available, may be used to calculate the increase in serum creatinine or change in eGFR.
- Cases in which there is a single observation or there are not 2 consecutive observations of doubling of serum creatinine or 40% reduction in eGFR will not be submitted to the Renal EAC for adjudication.
- However, cases in which there is a single observation of doubling of serum creatinine or 40% reduction in eGFR at the last measurement during the studies will be submitted to the Renal EAC for adjudication.
- If a confirmatory central lab value cannot be collected due to death or dialyses and there is no evidence of acute kidney injury, the event will be adjudicated positively.
- It is assumed that as a matter of good general clinical practice, the investigator will make reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. The event will be adjudicated positively once the initial doubling of serum creatinine via local or central laboratory results has been confirmed at 30 days or more, and if the process is determined to be irreversible. The date of the event will be the date on which the creatinine first doubled.

B. Safety

Adverse events (AEs) will be coded using the latest version of the *Medical Dictionary for Regulatory Activities (MedDRA)* at the time of database lock.

CANVAS-R was started after the approval of canagliflozin. Since the safety profile of canagliflozin had been well established in the Phase 3 program, the AE collection in CANVAS-R was streamlined to include:

- Serious AEs;
- AEs that resulted in study drug discontinuation;
- All AEs (serious and nonserious) for selected AEs of interest.

After the approval of protocol amendment INT-6 (January 2014), the AE data collection in CANVAS was also streamlined in the same fashion as CANVAS-R.

Table S1. Renal Baseline Characteristics for the CANVAS Program by Study

	CANVAS			CANVAS-R		
	Canagliflozin	Placebo	Total	Canagliflozin	Placebo	Total
	(n = 2888)	(n = 1442)	(N = 4330)	(n = 2907)	(n = 2905)	(N = 5812)
eGFR, mL/min/1.73 m ² , mean (SD)	77.3 (18.6)	77.2 (19.4)	77.2 (18.9)	76.1 (21.8)	75.7 (21.5)	75.9 (21.6)
UACR, median (IQR)						
mg/g	11.9 (6.7–36.1)	12.0 (6.4–37.1)	11.9 (6.6–36.4)	13.1 (6.8–45.9)	12.2 (6.7–47.3)	12.6 (6.7–46.7)
mg/mmol	1.3 (0.8–4.1)	1.4 (0.7–4.2)	1.3 (0.7–4.1)	1.5 (0.8–5.2)	1.4 (0.8–5.4)	1.4 (0.8–5.3)
Normoalbuminuria, No. (%)	2067 (71.9)	1024 (71.3)	3091 (71.7)	1945 (67.8)	1971 (69.0)	3916 (68.4)
Microalbuminuria, No. (%)	652 (22.7)	316 (22.0)	968 (22.5)	670 (23.4)	628 (22.0)	1298 (22.7)
Macroalbuminuria, No. (%)	154 (5.4)	96 (6.7)	250 (5.8)	252 (8.8)	258 (9.0)	510 (8.8)

eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio.

Table S2. Adjusted Effects of Canagliflozin on Renal Composite Endpoints

		Canagliflozin effect on renal endpoints
Renal endpoints	Concomitant covariate	Hazard ratio (95% CI)
Doubling of serum creatinine renal composite	Treatment only	0·527 (0·331, 0·841)
	Adjusted for predicted change in HbA1c	0·426 (0·254, 0·714)
40% eGFR renal composite	Treatment only	0·601 (0·467, 0·773)
	Adjusted for predicted change in HbA1c	0·628 (0·474, 0·831)

CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table S3. Summary of Renal Outcomes in CANVAS Alone

	Number of patients	Patients per 1000 patient-years			Hazard ratio (95% CI)	
		Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Canagliflozin 100 mg vs placebo	Canagliflozin 300 mg vs placebo
Renal outcomes						
New-onset albuminuria	1113	99·1	86·5	110·2	0·90 (0·78-1·04)	0·79 (0·68-0·92)
New-onset microalbuminuria	1078	95·8	82·7	106·0	0·90 (0·78-1·04)	0·79 (0·68-0·91)
New-onset macroalbuminuria	365	14·9	14·5	21·1	0·72 (0·56-0·92)	0·69 (0·54-0·88)
Progression of albuminuria	1374	89·8	80·2	106·3	0·85 (0·75-0·97)	0·76 (0·66-0·86)
Regression of albuminuria	596	227·4	241·1	147·4	1·54 (1·25-1·89)	1·58 (1·28-1·94)
dSCr, ESKD, or renal death	50	1·6	1·3	3·3	0·48 (0·25-0·94)	0·40 (0·20-0·82)
dSCr, ESKD, renal death, or new-onset macroalbuminuria	405	15·2	14·4	22·2	0·69 (0·55-0·87)	0·64 (0·51-0·81)
dSCr, ESKD, or renal or CV death	366	13·9	13·6	17·3	0·82 (0·64-1·05)	0·78 (0·61-1·00)
40% reduction in eGFR, ESKD, or renal death	169	5·6	5·5	9·9	0·57 (0·40-0·82)	0·55 (0·38-0·79)
40% reduction in eGFR, ESKD, renal death, or new-onset macroalbuminuria	506	18·6	18·3	28·6	0·65 (0·53-0·81)	0·63 (0·51-0·78)
40% reduction in eGFR, ESKD, or renal or CV death	472	17·3	17·6	23·5	0·74 (0·60-0·93)	0·74 (0·60-0·92)

40% reduction in eGFR	161	5.5	5.1	9.4	0.59 (0.41-0.85)	0.54 (0.37-0.78)
dSCr	39	1.3	0.8	2.6	0.50 (0.24-1.03)	0.32 (0.14-0.75)
ESKD	13	0.4	0.6	0.6	0.61 (0.15-2.57)	0.96 (0.28-3.32)
ESKD or renal death	15	0.4	0.6	0.9	0.44 (0.11-1.69)	0.69 (0.22-2.16)

CI, confidence interval; dSCr, doubling serum creatinine; ESKD, end-stage kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

For each composite and individual outcome, time to the first event of that type was counted, and any subsequent events are disregarded. 40% reduction in eGFR and doubling of creatinine were required to be sustained, defined as being present on at least 2 consecutive measurements more than 30 days apart. ESKD defined as the composite of maintenance dialysis, renal transplantation or a sustained eGFR <15 mL/min/1.73 m², and adjudicated by an expert committee. Renal death defined as death where the proximate cause was renal as defined by the endpoint adjudication committee. There were only 3 renal deaths, all in the placebo group.

*Excludes data from CANVAS-R.

†Annualised incidence rates are reported through 7-Jan-2014 since after this time, only serious adverse events or adverse events leading to discontinuation were collected in CANVAS.

Table S4. Effects on eGFR Slope by Baseline eGFR*

	eGFR <60 mL/min/1.73 m ²			eGFR ≥60 mL/min/1.73 m ²			
	Canagliflozin	Placebo	Difference (95% CI)	Canagliflozin	Placebo	Difference (95% CI)	p value for interaction
Change from baseline to Week 6/13, mL/min/1.73 m ² †	-1.25 ± 0.26	1.58 ± 0.29	-2.83 (-3.58, -2.07)	-3.55 ± 0.15	-1.35 ± 0.18	-2.20 (-2.65, -1.75)	0.21
Annual change from Week 6/13 to last available measurement, mL/min/1.73 m ² /year	0.22 ± 0.12	-0.89 ± 0.15	1.11 (0.74, 1.48)	0.35 ± 0.06	-0.85 ± 0.08	1.20 (1.01, 1.38)	0.58

eGFR, estimated glomerular filtration rate; CI, confidence interval; SE, standard error.

*Data are mean ± SE.

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

Table S5. Effects on eGFR Slope by Baseline Use of RAS Agents*

	On RAS agent at baseline			Not on RAS agent at baseline			p value for interaction
	Canagliflozin	Placebo	Difference (95% CI)	Canagliflozin	Placebo	Difference (95% CI)	
Change from baseline to Week 6/13, mL/min/1.73 m ² †	-3.22 ± 0.14	-0.74 ± 0.17	-2.48 (-2.92, -2.04)	-2.71 ± 0.30	-0.66 ± 0.35	-2.06 (-2.97, -1.14)	0.39
Annual change from Week 6/13 to last available measurement, mL/min/1.73 m ² /year	0.28 ± 0.06	-0.89 ± 0.08	1.18 (0.99, 1.37)	0.52 ± 0.11	-0.67 ± 0.16	1.20 (0.82, 1.57)	0.96

eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; CI, confidence interval; SE, standard error.

*Data are mean ± SE.

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

Table S6. Effects on eGFR Slope by Baseline Albuminuria Status*

	Normoalbuminuria			Microalbuminuria			Macroalbuminuria		
	Canagliflozin	Placebo	Difference (95% CI)	Canagliflozin	Placebo	Difference (95% CI)	Canagliflozin	Placebo	Difference (95% CI)
Change from baseline to Week 6/13, mL/min/1.73 m ² [†]	-2.78 ± 0.16	-0.47 ± 0.18	-2.31 (-2.78, -1.84)	-3.55 ± 0.28	-1.05 ± 0.33	-2.50 (-3.35, -1.65) [‡]	-4.60 ± 0.48	-1.87 ± 0.53	-2.73 (-4.14, -1.33) [§]
Annual change from Week 6/13 to last available measurement, mL/min/1.73 m ² /year	0.59 ± 0.05	-0.47 ± 0.08	1.06 (0.88, 1.25)	-0.15 ± 0.11	-1.14 ± 0.15	0.99 (0.61, 1.36)	-1.76 ± 0.32	-4.77 ± 0.38	3.01 (2.03, 3.99) [¶]

eGFR, estimated glomerular filtration rate; CI, confidence interval; SE, standard error.

*Data are mean ± SE.

[†]Data are reported for Week 6 in CANVAS and Week 13 in CANVAS-R.

[‡]p value for interaction for microalbuminuria versus normoalbuminuria = 0.70.

[§]p value for interaction for macroalbuminuria versus microalbuminuria = 0.86; for macroalbuminuria versus normoalbuminuria = 0.66.

^{||}p value for interaction for microalbuminuria versus normoalbuminuria = 0.72.

[¶]p value for interaction for macroalbuminuria versus microalbuminuria and for macroalbuminuria versus normoalbuminuria <0.0001.

Table S7. Effects on eGFR Slope by Study*

	CANVAS			CANVAS-R			p value for interaction
	Canagliflozin	Placebo	Difference (95% CI)	Canagliflozin	Placebo	Difference (95% CI)	
Change from baseline to Week 6/13, mL/min/1.73 m ² †	-4.15 ± 0.18	-2.65 ± 0.26	-1.50 (-2.12, -0.88)	-1.74 ± 0.19	0.47 ± 0.19	-2.20 (-2.73, -1.68)	0.11
Annual change from Week 6/13 to last available measurement, mL/min/1.73 m ² /year	0.44 ± 0.05	-0.71 ± 0.08	1.15 (0.96, 1.33)	-0.26 ± 0.14	-1.26 ± 0.15	1.01 (0.60, 1.41)	0.28

eGFR, estimated glomerular filtration rate; CI, confidence interval; SE, standard error.

*Data are mean ± SE.

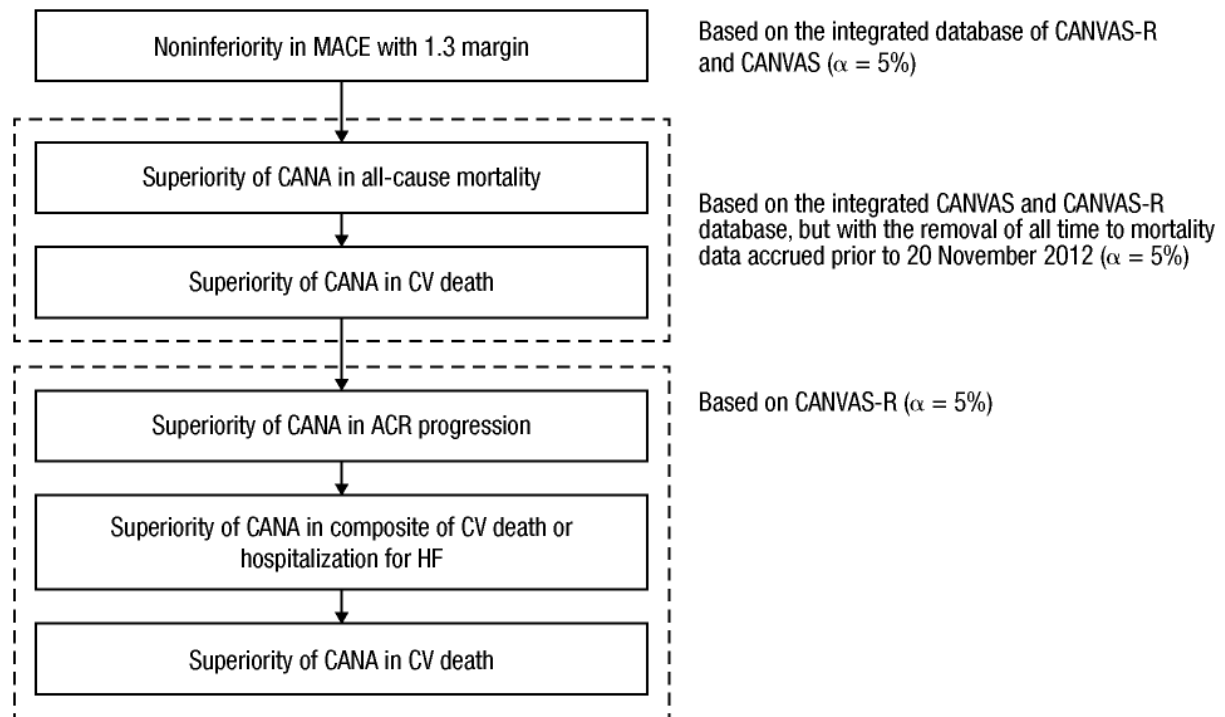
†Data are reported for Week 6 in CANVAS and Week 13 in CANVAS-R.

Table S8. Effect of Canagliflozin on UACR Reduction Over Time, After Adjustment for Longitudinal Hba1c Levels

Placebo			Canagliflozin		Canagliflozin vs placebo
Time point	N	GM (95% CI)	N	GM (95% CI)	GM ratio (95% CI)
Overall	3879	25·68 (25·00, 26·38)	5174	22·08 (21·57, 22·59)	0·86 (0·84, 0·88)
Week 26	3879	19·55 (19·09, 20·01)	5174	17·11 (16·77, 17·46)	0·88 (0·85, 0·90)
Week 52	3744	20·89 (20·34, 21·45)	5075	17·81 (17·42, 18·22)	0·85 (0·82, 0·88)
Week 104	2541	23·01 (22·24, 23·80)	3545	19·08 (18·55, 19·63)	0·83 (0·79, 0·87)
Week 156	749	25·77 (24·23, 27·41)	1677	21·82 (20·92, 22·77)	0·85 (0·79, 0·91)
Week 208	649	28·80 (26·88, 30·86)	1534	23·78 (22·71, 24·91)	0·83 (0·76, 0·90)
Week 260	590	32·77 (30·37, 35·36)	1398	26·96 (25·63, 28·36)	0·82 (0·75, 0·90)
Week 312	614	37·83 (34·89, 41·03)	1525	28·93 (27·43, 30·50)	0·76 (0·69, 0·84)

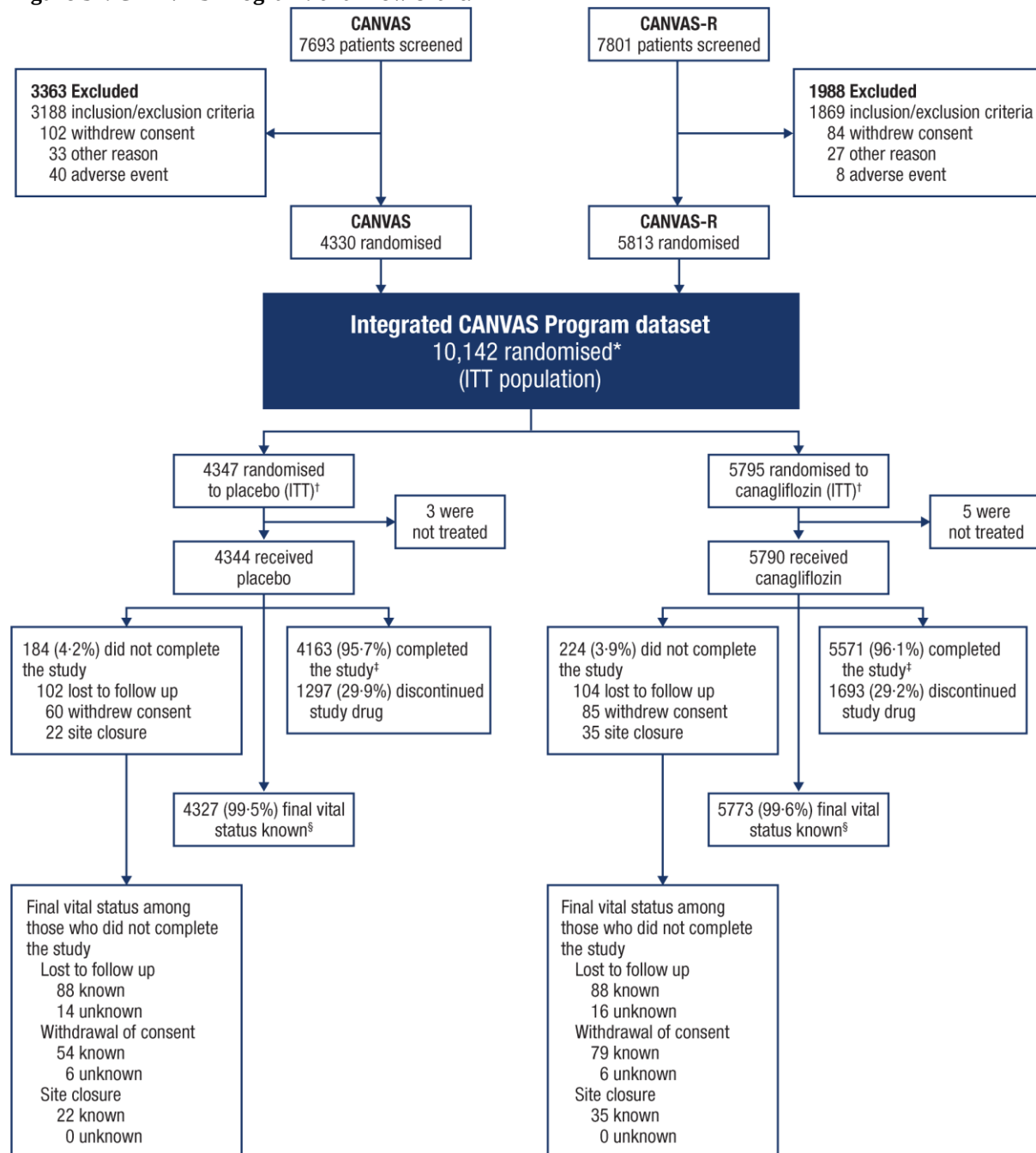
GM, geometric mean; CI, confidence interval.

Figure S1. Pre-specified hypothesis testing plan and results²⁰



MACE, major adverse cardiovascular events; CANA, canagliflozin; CV, cardiovascular; HF, heart failure. Reprinted from Neal B, et al. *Diabetes, Obesity and Metabolism*, Vol. 19, Issue 7, Pages 926-935 with permission from John Wiley & Sons © 2017.

Figure S2. CANVAS Program: trial flow chart.¹⁸



ITT, intent-to-treat.

*One patient was randomised at 2 different sites and therefore the second randomised ID was excluded from the ITT analysis set.

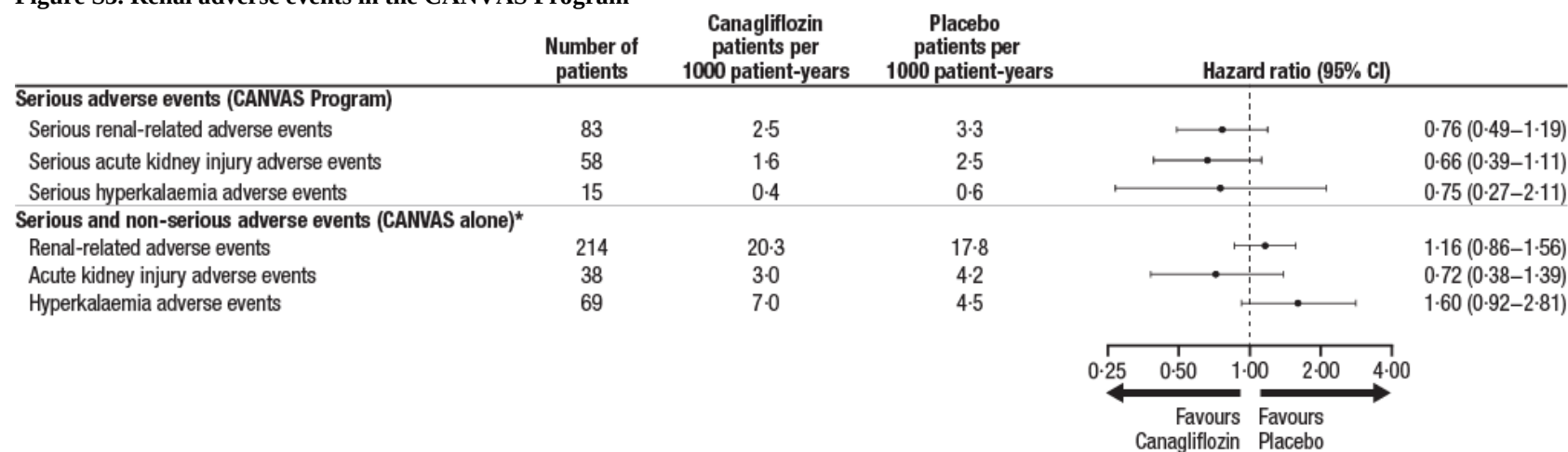
[†]Percentages calculated based on the ITT analysis set.

[‡]A patient is considered as having completed the study, regardless of whether the patient is on or off study drug, if the patient is followed until a time point between the notification of the trial end date (November 1, 2016) and the trial end date (February 23, 2017), or until the time of death for those who died prior to the trial end date.

[§]Including results from the search of public records.

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Figure S3. Renal adverse events in the CANVAS Program



CI, confidence interval.

*For these adverse events, the annualised incidence rate are reported based on the CANVAS study alone through 7-Jan-2014 since after this time, only serious adverse events or adverse events leading to discontinuation were collected. In the CANVAS-R study, only serious adverse events or adverse events leading to discontinuation were collected for these events. Due to the differences in collection methodology, an integrated analysis of these adverse events is not possible.