The effects of canagliflozin on gout in type 2 diabetes: a post hoc analysis of the CANVAS Program

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ABSTRACT

Background

Sodium glucose co-transporter 2 inhibitors reduce serum urate levels. In a *post hoc* analysis, we investigated the effect of canagliflozin compared to placebo on gout in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

Methods

The CANVAS Program randomly assigned 10,142 participants with type 2 diabetes to canagliflozin or placebo. Gout events were defined as an adverse event attributed to gout flare or commencement of a drug specifically for gout. The effects of canagliflozin compared to placebo were estimated by calculating the hazard ratio (HR) and 95% confidence interval (CI).

Findings

At baseline, mean age was 63 years, 36% were female, mean serum urate levels were 5.9 mg/dL and 5% had a history of gout. Mean follow-up was 3.6 years and mean serum urate levels were on average -0.39 mg/dL (95% CI, -0.43 to -0.36) lower in those treated with canagliflozin compared to placebo, equating to a 6.7% reduction in serum urate. During follow-up, there were 80 individuals who reported an episode of gout flare and 147 who commenced a drug for gout. The occurrence of gout flare or the need for treatment for gout was lower in those treated with canagliflozin compared to placebo (HR 0.53, 95% CI, 0.40 to 0.71). The proportional reduction for gout flare adverse events of 0.64 (95% CI, 0.41 to 0.99) was similar in size to that for commencement of a drug for gout 0.52 (95% CI, 0.38 to 0.72).

Interpretation

In this *post hoc* analysis, canagliflozin reduced serum urate levels and there is evidence to suggest that canagliflozin also reduced events related to gout flare amongst patients with type 2 diabetes.

Funding

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Trial registration

ClinicalTrials.gov identifiers, NCT01032629 (first posted December 15, 2008) and NCT01989754 (first posted November 21, 2013)

Keywords: SGLT2 inhibitor, canagliflozin, gout, urate, hyperuricemia

Research in context

Evidence before this study

Elevated levels of serum urate are associated with gout, and precipitated urate crystals around the joints can trigger an inflammatory response leading to acute gout flare. The sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin has been shown to reduce the risks of serious cardio-renal complications and reduce serum urate in patients with type 2 diabetes, but effects on gout flare are unknown.

Added value of this study

Canagliflozin treatment lowered serum urate levels and appeared to also reduce the risk of gout flare compared with placebo. The approximate halving in gout flare is greater than would be anticipated for the moderate reduction in serum urate and was comparable to that of other well-established preventative therapies.

Implications of all the available evidence

Canagliflozin may be of benefit to people with gout or at high risk for gout, and a definitive trial that investigates effects on gout flare is warranted.

INTRODUCTION

Gout is the most common form of inflammatory arthritis and occurs as a result of elevation of serum urate and a propensity to mount an inflammatory response to precipitated urate crystals. The deposition of urate crystals around the joints and the release of crystals into the joint space initiates an inflammatory cascade causing acute gout flare that typically endures for one to two weeks. The prevalence of gout ranges widely around the world but it affects between 2% and 4% of adults in higher-income countries,[1] with hyperuricemia affecting about a quarter of the population.[2]

Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, increases urinary glucose excretion and improves glycemic control, blood pressure, albuminuria, and weight control in patients with type 2 diabetes mellitus. Canagliflozin has been shown to decrease the risks of cardiovascular disease, heart failure, and kidney disease in large-scale randomized trials.[3,4] Treatment with canagliflozin reduces serum urate in patients with type 2 diabetes,[5] with similar effects observed for other SGLT2 inhibitors.[6] Whether SGLT2 inhibitors protect against gout is, however, unknown and exploration of this question was the motivation for this investigation. The specific goal of these *post hoc* analyses of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program was to determine the effects of treatment with canagliflozin on the risk of gout flare.

METHODS

The CANVAS Program integrated data from two randomized, double-blind, placebo-controlled trials of canagliflozin therapy. The study design and main findings have been published elsewhere.[7] Briefly, two similarly designed and conducted trials, CANVAS and CANVAS-Renal (CANVAS-R), were designed to assess the cardiovascular and renal safety and efficacy of canagliflozin compared with placebo. The primary outcome for the CANVAS program was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. A total of 667 centers in 30 countries were involved in

the two trials that were scheduled for joint closeout and analysis when at least 688 cardiovascular events had occurred. This was achieved in February 2017. The trial protocols and statistical analysis plans were published along with the primary CANVAS Program article.[3] All patients provided written informed consent, and the protocols for the two trials were approved by the ethics committee at each site. The trials were registered at ClinicalTrials.gov (identifiers: NCT01032629, NCT01989754).

Participants

Participants included in the CANVAS Program were individuals with type 2 diabetes mellitus, who were also required to be either 30 years of age or older with a history of symptomatic atherosclerotic cardiovascular disease, or 50 years of age or older with at least two cardiovascular risk factors (duration of diabetes mellitus of 10 years or more, systolic blood pressure above 140 mmHg while on at least one antihypertensive agent, current smoker, microalbuminuria, macroalbuminuria, or a high-density lipoprotein cholesterol level below 1 mmol/L). All participants were required to have an estimated glomerular filtration rate (eGFR) at entry of more than 30 mL/min/1.73 m^2. A history of gout at baseline was defined on the basis of either (1) a diagnosis of gout being recorded in the trial record, (2) a gout episode occurring during screening or run-in, or (3) a drug for the management of gout being included in the baseline medication record (allopurinol, benzbromarone, colchicine, febuxostat, or probenecid).

Randomization and masking

After a 2-week, single-blind, placebo run-in period, participants were randomized centrally through an interactive web response system using a computer-generated randomization schedule prepared by the study sponsor using randomly permuted blocks. Participants in CANVAS were assigned in a 1:1:1 ratio to canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo, and participants in CANVAS-R were randomly assigned in a 1:1 ratio to canagliflozin or matching placebo, administered first at a dose of 100 mg daily with optional up-titration to 300 mg from week 13 (average dose was 211 mg). Both participants and investigators were masked to individual treatment allocations until

the completion of the study. Use of other background therapy for glycemic management, treatment of heart failure, other risk factor control, and the management of gout were according to best practices instituted in line with local guidelines.

Data collection and follow-up

Face-to-face follow-up was conducted at three visits during the first year and at 6-month intervals thereafter, with telephone follow-up at 3-month intervals between face-to-face assessments. Every follow-up included inquiry about primary outcomes, secondary outcomes, serious adverse events, and adverse events of special interest. Adverse events were coded using MedDRA definitions and data collection was done using RAVE. In addition, all non-serious adverse events were collected in the first stage of the CANVAS trial prior to initial marketing approval for canagliflozin. Serum urate levels were measured at baseline, weeks 6, 18, 39, 52, and every 26 weeks after to a maximum of week 364 in CANVAS and at week 13, 26, and every 26 weeks after to a maximum of week 156 in CANVAS-R. Concomitant medication use during follow-up, including medications for the management of gout, was recorded every 3 months.

Outcomes

Li J extracted data from a copy of the study database held by the George Institute in Sydney, Australia. Serum urate concentrations were measured in samples by a single central laboratory using Roche modular and Cobas analyzers (Roche, Mannheim, Germany). We used two approaches to identify suspected gout flare following prior reports.[8] First we searched the adverse events database for records including permutations of the term 'gout' (gout, gouty arthritis, and gouty tophus). Second, we searched the concomitant medications database for recorded post-randomization prescription of a medication used for the long-term management of gout (allopurinol, benzbromarone, febuxostat, or probenecid) or the management of acute gout flare (colchicine, non-steroidal anti-inflammatory agents, or corticosteroids). A gout event based upon the commencement of a drug for the long-term management of gout (new gout medication) was defined only if there was no documented use of a

drug for the long-term management of gout in the record of concomitant medications made at baseline. A gout flare event based upon the commencement of a drug for acute management of gout was defined if the drug was colchicine (which is used infrequently for other indications) or if there was a note indicating specifically that the prescription was for gout flare management (non-steroidal anti-inflammatory agents and corticosteroids). Separately, we also searched the adverse events database for records including permutations of the word 'hyperuricemia' and for permutations of the word 'urolithiasis.'

The outcomes assessed for these analyses were (1) a composite based upon the occurrence of either an adverse event attributed to gout flare or the commencement of a drug for gout; (2) gout flare events alone; (3) commencement of a drug for gout events alone; and (4) hyperuricemia (which included events with the terms 'hyperuricemia,' 'increased blood serum urate,' or 'hyperuricosuria' not included in the other analyses). Finally, we also reported effects on urolithiasis.

Statistical analysis

Since this was a *post hoc* analysis there was no power calculation done *a priori*. However, a study of 10,142 individuals with equal randomization that records 182 events has about 80% power (two-sided alpha=0.05) to detect a 37% or greater reduction in the relative risk ratio of gout flare.

All analyses were done using the full CANVAS Program data to assess the effects of canagliflozin versus placebo on outcomes of interest. The exception to this was investigation of the effects of the 100 mg versus 300 mg doses of canagliflozin on serum urate levels and the subgroup analyses for aspirin and losartan that were done in the CANVAS trial participants alone (n=4,330). All analyses were done according to the principle of intention-to-treat and there was no imputation for missing data.

The effects of canagliflozin versus placebo on serum urate concentrations over time were determined using mixed linear models. All analyses were done using the combined trial datasets as specified in

the main trial statistical analysis plan with stratification by study.[7,9] Effects were determined overall and for subsets of patients defined by age, sex, history of gout, baseline serum urate levels, body mass index, glycated hemoglobin, eGFR, and baseline use of a drug therapy for gout. The effects of canagliflozin versus placebo on gout events were estimated from a Kaplan-Meier analysis with Cox proportional hazard models used to determine a hazard ratio (HR) and 95% confidence intervals (CIs). Analyses included terms for randomized treatment and trial (CANVAS vs CANVAS-R).[7] Potential modifying effects of age, sex, history of gout, baseline serum urate levels, body mass index, glycated hemoglobin, eGFR, and baseline allopurinol, aspirin, diuretic, losartan, or metformin use were investigated by including interaction terms in the Cox models. Secondary analyses that allowed for the assessment of multiple events within an individual were estimated using Anderson-Gill modeling. Analyses were done using SAS version 9.4. Nominal P values were calculated for effects of canagliflozin versus placebo and interaction P values were calculated to test for effects between subgroups. In both cases, P values of less than 0.05 were regarded as significant. Main analyses were repeated using the safety dataset and with adjustment for competing risks with no substantive impact on the findings in either case (Supplementary Tables 1-3).

Role of the funding source

This study is sponsored by Janssen Research & Development, LLC, who funded the trial. The sponsor was involved in the study design, the writing of the report, and the decision to submit the article for publication. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

A total of 7693 patients were screened between December 2009 and March 2011 for CANVAS and 7801 patients were screened between January 2014 and May 2015 for CANVAS-R. There were 10,142 patients randomly assigned to canagliflozin (n=5,795) or placebo (n=4,347) that were included in the

main analyses (Figure S1 and Table 1). Participant follow-up extended to a maximum of 7.1 years with a mean of 3.6 years and a median of 2.4 years. There were 471 participants with a history of gout at baseline: 366 with gout recorded in the medical record, 5 with a gout event occurring during the run-in period, and 217 with use of a medication for gout at or prior to baseline (allopurinol therapy was recorded at baseline in 204 participants and colchicine in 16, but none commenced the study using benzbromarone, febuxostat, or probenecid). Participant characteristics were well balanced across randomized groups (Table 1).

Effects of canagliflozin on serum urate levels

Baseline median serum urate concentrations were similar for the canagliflozin group and the placebo group but were higher in men than women, older compared to younger participants, those with a history of gout, those using allopurinol or diuretics, and those with higher body mass index, lower glycated hemoglobin, or lower eGFR (Table 2). The serum urate level fell immediately after commencing drug therapy (week 6) and remained lower in the canagliflozin group compared with the placebo group throughout follow-up (Figure S2). Mean serum urate levels were on average -0.39 mg/dL (95% CI, -0.43 to -0.36) lower in those treated with canagliflozin compared to placebo equating to a 6.7% reduction in serum urate. Amongst the 4,330 CANVAS participants randomized to different doses, there were comparable effects of the 300 mg dose versus placebo -0.46 mg/dL (95% CI, -0.52 to -0.40) and the 100 mg dose versus placebo -0.47 mg/dL (95% CI, -0.53 to -0.42; 7.9% reduction vs 8.4% reduction, P interaction = 0.354). Proportional reductions in serum urate levels were greater in older individuals, women, and those with a higher baseline body mass index, a lower baseline glycated hemoglobin, a shorter duration of diabetes, a lower urinary albumin:creatinine ratio, and a higher eGFR (Table 2). Amongst those with a starting serum urate level >6.0 mg/dL the proportions with a serum urate level <6.0 mg/dL at final follow-up were 36.3% in those assigned canagliflozin and 24.1% in those assigned placebo.

Effects of canagliflozin on gout

During follow-up 80 participants had a gout flare and 147 commenced a drug for gout. A further 75 had an event ascribed to hyperuricemia. Many of these individuals had more than one event or events of different types and in total there were 125 gout flare, 171 commencements of a drug for gout, and 79 hyperuricemia events recorded during the study.

The risk of gout flare or the commencement of a drug for gout (n=182) was lower in those using canagliflozin compared to placebo (4.1 vs 6.6 patients per 1000 patient-years) with a corresponding HR of 0.53 (95% CI, 0.40 to 0.71; P<0.001; Figures 1 and 2). There was no evidence of differences for this outcome across subgroups defined by baseline age, sex, serum urate, history of gout, allopurinol use, aspirin use, diuretic use, metformin use, losartan use, body mass index, glycated hemoglobin, or eGFR (all P interaction >0.138; Figure 3). The estimates for gout flare alone (2.0 vs 2.6 patients per 1000 patient-years, HR 0.64, 95% CI, 0.41 to 0.99; P=0.046) and commencement of a drug for gout alone (3.3 vs 5.4 patients per 1000 patient-years, HR 0.52, 95% CI, 0.38 to 0.72; P<0.001) were broadly comparable. There was also a reduction in the risk of other events attributed to hyperuricemia (n=75, 1.8 vs 2.5 patients per 1000 patient-years, HR 0.59, 95% CI, 0.37 to 0.93; P=0.023). Findings based upon analyses that included recurrent events were comparable to the main results except with tighter confidence intervals and smaller P values (Figure 2). There was no increased risk of gouty flares after initiating treatment either overall, in patients with gout, or in patients with elevated baseline serum urate (Figures 1, S3, and S4).

Within CANVAS, the effects on the composite outcome of gout flare or the commencement of a medication for gout were HR 0.51 (95% CI, 0.35 to 0.75) for the 100 mg dose versus placebo and HR 0.55 (95% CI, 0.38 to 0.80) for the 300 mg dose versus placebo (P interaction=0.731).

There were 117 events identified that were attributed to urolithiasis and the HR for canagliflozin versus placebo was 0.83 (95% CI, 0.57 to 1.21).

DISCUSSION

Patients with diabetes and an elevated risk of cardiovascular disease treated with canagliflozin had lower levels of serum urate and a lower risk of gout flare. While these analyses are *post hoc*, the high statistical significance of the findings, the consistency of the data across a range of gout-related endpoints, and the comparability of findings across patient groups make it unlikely that this finding is due to chance or bias. These data suggest a possible protective effect for gout from an agent used for the management of diabetes and, if confirmed in dedicated prospective studies, would provide a rationale for the selective use of canagliflozin among people with type 2 diabetes who have gout or are at high risk for gout. The data also raise the question as to whether canagliflozin may be an effective treatment for gout amongst patients without diabetes, which might be another future area for investigation.

Our analyses benefitted from a large sample size, rigorous conduct of the trial, and the substantial number of gout events recorded. Gout was not, however, a prespecified endpoint and was captured as part of routine adverse event reporting during the trial. The MedDRA coding system is imprecise and less sensitive and specific for some outcomes than others. It is likely that some gout flare events will have been missed and some misclassified, but there is no reason to expect that such errors will have occurred differentially across active and placebo groups. The estimated HRs should not be biased by missed events, and misclassification of events typically leads to under-estimation of treatment effects in randomized trials. Absolute rates of gout flare events in the two groups, and the precise nature of the gout events that were recorded are, however, uncertain because gout was not a prespecified outcome with clearly defined criteria for reporting. Likewise, data about the reasons for the prescription of concomitant medicines during the trial were limited and it is likely that some

prescriptions have gone unreported. It is also possible that some of the recorded prescriptions of preventative medicines will have been for hyperuricemia in the absence of an acute gouty flare. The content of this report is also limited by the post hoc nature of the investigation, which increases the risk of chance findings resulting from the multiple analyses done. P-values are nominal and all conclusions should be viewed as hypothesis generating.

The expression of SGLT2 is predominantly in the kidney, though isoforms have also been detected in the small intestine, liver, brain, prostate, and testis.[10,11] SGLT2 inhibition lowers serum urate levels through effects of glycosuria on the glucose transporter 9 isoform 2 (GLUT9b) in the proximal renal tubule.[12] Increased concentration of glucose in the renal proximal tubule results in competition with urate for the facilitative GLUT9b hexose/urate transporter, which reduces urate reabsorption and may provide an explanation for lower levels of serum urate in patients with less well controlled diabetes. The magnitude of the effect of canagliflozin on serum urate observed in the CANVAS Program was small (6.7% mean reduction) compared to that previously reported for canagliflozin (13% mean reduction)[5] and substantially less than is typically achieved with allopurinol or febuxostat (30%-50% reductions).[13]

The large protective effect for gout observed with canagliflozin in the CANVAS Program, despite small reductions in serum urate levels, suggests the possibility of protective mechanisms beyond uric acid lowering. Canakinumab achieved a similar effect on the risk of gout flare (HR 0.48, CI, 0.36 to 0.63) without affecting serum uric acid levels, and the effects of fenofibrate on gout flare (HR 0.48, CI, 0.37 to 0.60) were obtained with a reduction in serum urate levels about twice that observed for canagliflozin, but only half as great as that typically achieved with allopurinol or febuxostat. The anti-inflammatory effects of canakinumab are presumed to be the mechanism by which that agent afforded protection against gout flare.[14] Canagliflozin has been shown in human studies to reduce levels of TNFR1 and IL-6 suggesting beneficial effects on the inflamsome.[15] While data describing

changes in high-sensitivity C-reactive protein and other inflammatory markers with canagliflozin in humans are scarce a number of reports, from animals studies indicate broader effects on inflammatory cytokine and chemokine concentrations.[16] Effects on interleukin-1β have also been demonstrated for several other SGLT2 inhibitors.[17-19]

Arhalofenate, initially developed as an insulin sensitizing agent for use in type 2 diabetes, was noted early in Phase 2 development to reduce serum urate levels by 14-24% and a potential role in the management of gout has been explored.[20] A trial done in patients with gout showed a 16-17% reduction in serum urate levels with reductions in interleukin-1β, the cytokine that is key to triggering gout flare.[21,22] Definitive effects of canagliflozin on interleukin-1β in humans remain to be proved but indirect effects on interleukin-1β stimulated cytokine and chemokine secretion in human cells have been reported[23] and animal models have showed reduction in interleukin-1β with SGLT2 inhibition.[24]

Anticipated associations of serum urate levels with baseline patient characteristics were observed.[25-28] There were marginally greater proportional reductions in serum urate with canagliflozin therapy amongst older patients and those with higher baseline body mass index, who also had higher levels of baseline serum urate. Substantially greater proportional reductions in serum urate levels amongst those with preserved renal function were anticipated given the renal mechanism of action[29] but the reason for the greater reductions in serum urate amongst women is unclear. A greater reduction in serum urate amongst those with lower glycated hemoglobin levels has been observed previously,[30] and while the explanation for this is unclear, hyperinsulinemia may be part of the explantion.[31] In no instances were there different effects of canagliflozin compared to placebo on gout outcomes across patient subgroups, which could reflect a predominant mechanism of action independent of serum urate lowering, or the limited statistical power to detect such differences. While losartan, diuretic, and allopurinol therapy are all known to have effects on serum urate levels,[32] there were no observed

interactions of canagliflozin with concomitant use of these agents for either serum urate levels or gout events.

Initiation of chronic urate-lowering therapy with allopurinol or febuxostat can lead to an increased frequency of gout flares in the short term[33-35] and uricosuric medications can increase the risk of renal stones. We observed neither with canagliflozin therapy. This may be attributable to the limited reduction in serum urate achieved with canagliflozin, alongside possible direct anti-inflammatory effects. Canagliflozin also decreases urinary pH,[36] which is associated with urolithiasis,[37] though higher urine volumes resulting from canagliflozin therapy may have moderated any associated risk.

In summary, canagliflozin reduced serum urate levels, with evidence also suggesting a possible reduction in gout flare events amongst patients with type 2 diabetes mellitus.

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Transparency statement: B. Neal (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of

the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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

Authorship: The Steering Committee designed the CANVAS Program in conjunction with the Sponsor. This *post hoc* analysis was conceived by J. Li, B. Neal, V. Perkovic and Z. Zhou. J. Li and Z. Zhou did the statistical analyses with review by a Sponsor statistician. J. Li, S.V. Badve, Z. Zhou, A. Rodgers, R. Day, R. Oh, and M. Lee contributed to the data analysis and data interpretation. V. Perkovic, D. de Zeeuw, K.W. Mahaffey, G. Fulcher, D.R. Matthews, and B. Neal contributed to the study design and conduct and data interpretation. J. Li and B. Neal wrote the first draft of the paper, had full access to the study design information, and had final responsibility for the decision to submit for publication. All authors provided input into subsequent drafts and approved the final version for submission. B. Neal attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interest

J. Li is a full-time employee of the George Institute.

S.V. Badve, A. Rodgers, and R. Day have nothing to disclose.

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Table 1. Baseline participant characteristics of all 10,142 randomized participants

	Canagliflozin (n=5795)	Placebo (n=4347)
Age, years (mean, SD)	63.2±8.3	63.4±8.2
Female (%)	35.1	36.7
Race (%)		
White	77.8	79.0
Asian	13.4	11.7
Black	3.0	3.7
Other	5.8	5.6
Current smoker (%)	17.6	18.1
Hypertension (%)	89.5	90.6
Duration of diabetes, years (mean, SD)	13.5±7.7	13.7±7.8
Retinopathy (%)	20.8	21.3
Nephropathy (%)	17.2	17.9
Neuropathy (%)	30.8	30.4
Gout (%)	4.5	4.8
Coronary disease (%)	55.8	57.2
Heart failure (%)	13.9	15.1
Cerebrovascular disease (%)	19.2	19.4
Peripheral vascular disease (%)	20.3	21.6
Body mass index, kg/m^2 (mean, SD)	31.9±5.9	32.0±6.0
Serum urate, mg/dL (mean, SD)*	5.9 ± 1.6	5.9 ± 1.6
Serum urate >6 mg/dL (%)	41.3	41.4

Serum urate >7 mg/dL (%)	20.9	21.6
Systolic blood pressure, mmHg (mean, SD)	136.4±15.8	136.9±15.8
Diastolic blood pressure, mmHg (mean, SD)	77.6±9.6	77.8±9.7
Glycated hemoglobin, % (mean, SD)	8.2±0.9	8.2±0.9
Total cholesterol, mmol/L (mean, SD)	4.4±1.1	4.4±1.2
HDL cholesterol, mmol/L (mean, SD)	1.2±0.3	1.2±0.3
LDL cholesterol, mmol/L (mean, SD)	2.3±0.9	2.3±0.9
Triglycerides, mmol/L (mean, SD)	2.0±1.3	2.0±1.5
eGFR, mL/min/1.73 m² (mean, SD)	76.7±20.3	76.2±20.8
UACR <30 mg/g (%)[†]	69.9	69.8
UACR 30-300 mg/g (%)[†]	23.0	22.0
UACR >300 mg/g (%)[†]	7.1	8.2
Allopurinol (%)	2.2	1.8
Antithrombotic (%)	73.1	74.4
Anti-platelet except heparin[‡]	67.6	69.2
Aspirin (%)[‡]	60.5	63.2
Diuretic (%)	43.8	45.0
Losartan (%)[‡]	10.4	10.9
Metformin (%)	76.7	77.7

eGFR=estimated glomerular filtration rate; HDL=high density lipoprotein; LDL=low density lipoprotein; SD=standard deviation; CANVAS=CANagliflozin cardioVascular Assessment Study.

*****2 participants did not have baseline serum urate measurements.

[†]109 participants did not have baseline urinary albumin measurements.

[‡]Data for aspirin and losartan use were available for CANVAS only.

Table 2. Effects of canagliflozin on serum urate levels overall in the 10,140 randomized participants with measurements and in participant subgroups defined by baseline characteristics.

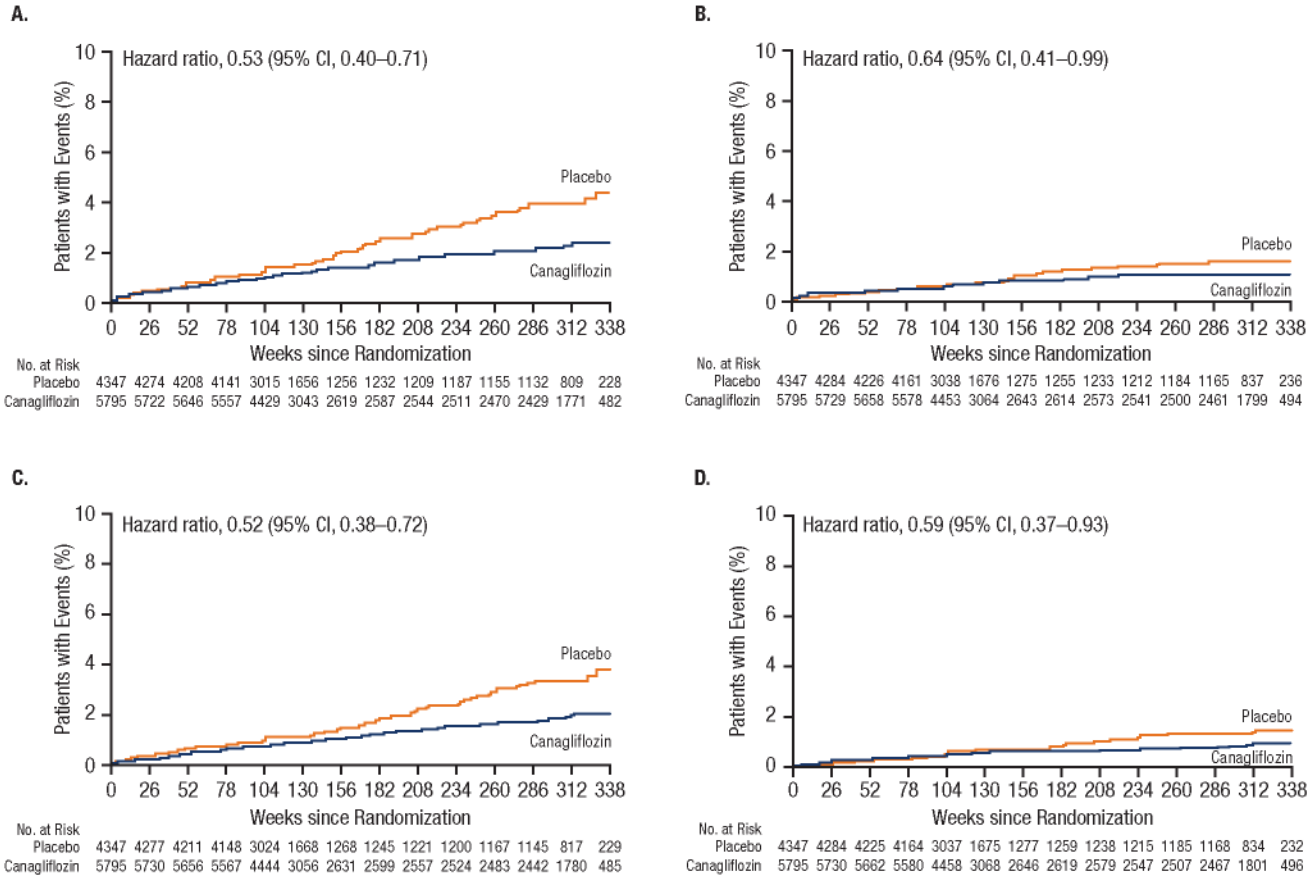
	Mean (SD) at baseline (mg/dL)		Mean (SD) difference during follow-up (mg/dL)	Percent difference during follow-up (%)	P interaction for percent differences
	Canagliflozin	Placebo			
All participants	5.85 (1.59)	5.88 (1.63)	-0.39 (-0.43, -0.36)	-6.7 (-7.3, -6.0)	
Age					
<65 years	5.73 (1.56)	5.76 (1.61)	-0.36 (-0.40, -0.31)	-6.1 (-6.9, -5.2)	0.026
≥65 years	6.01 (1.61)	6.02 (1.65)	-0.44 (-0.49, -0.38)	-7.4 (-8.3, -6.5)	
Sex					
Male	6.01 (1.56)	6.05 (1.61)	-0.34 (-0.38, -0.30)	-5.4 (-6.1, -4.6)	<0.001
Female	5.56 (1.59)	5.59 (1.64)	-0.49 (-0.55, -0.44)	-9.1 (-10.2, -8.1)	
Serum urate					
>6 mg/dL	7.35 (1.12)	7.42 (1.18)	-0.52 (-0.58, -0.46)	-7.1 (-8.0, -6.3)	0.076
≤6 mg/dL	4.80 (0.84)	4.80 (0.85)	-0.30 (-0.34, -0.26)	-6.3 (-7.2, -5.4)	
>7 mg/dL	8.17 (1.02)	8.25 (1.08)	-0.57 (-0.66, -0.48)	-7.0 (-8.1, -5.9)	0.332
≤7 mg/dL	5.24 (1.05)	5.23 (1.05)	-0.35 (-0.38, -0.31)	-6.5 (-7.3, -5.8)	
History of gout					
Yes	6.50 (1.91)	6.82 (1.88)	-0.68 (-0.86, -0.49)	-9.1 (-12.1, -6.0)	0.128
No	5.82 (1.56)	5.83 (1.61)	-0.38 (-0.41, -0.34)	-6.5 (-7.2, -5.9)	
Allopurinol					
Yes	6.02 (1.72)	6.41 (1.73)	-0.51 (-0.79, -0.24)	-6.7 (-11.9, -1.5)	0.964
No	5.85 (1.58)	5.87 (1.63)	-0.39 (-0.42, -0.35)	-6.7 (-7.3, -6.0)	
Aspirin*					

Yes	5.90 (1.56)	5.91 (1.66)	-0.44 (-0.51, -0.37)	-7.5 (-8.7, -6.3)	0.105
No	5.76 (1.54)	5.79 (1.64)	-0.52 (-0.60, -0.43)	-9.2 (-10.7, -7.6)	
Diuretic					
Yes	6.37 (1.68)	6.39 (1.74)	-0.45 (-0.51, -0.39)	-7.2 (-8.1, -6.3)	0.172
No	5.45 (1.38)	5.47 (1.41)	-0.34 (-0.39, -0.30)	-6.2 (-7.1, -5.4)	
Losartan*					
Yes	5.62 (1.38)	5.72 (1.59)	-0.40 (-0.56, -0.24)	-7.5 (-10.5, -4.5)	0.701
No	5.87 (1.57)	5.88 (1.66)	-0.47 (-0.53, -0.42)	-8.2 (-9.2, -7.2)	
Metformin					
Yes	5.79 (1.53)	5.81 (1.55)	-0.39 (-0.43, -0.35)	-6.6 (-7.3, -5.9)	0.929
No	6.06 (1.75)	6.13 (1.86)	-0.40 (-0.48, -0.32)	-6.7 (-8.1, -5.4)	
Body mass index					
<30 kg/m^2	5.53 (1.53)	5.54 (1.52)	-0.32 (-0.37, -0.27)	-5.8 (-6.7, -4.8)	0.015
≥30 kg/m^2	6.08 (1.59)	6.12 (1.66)	-0.44 (-0.49, -0.40)	-7.3 (-8.1, -6.5)	
Glycated hemoglobin					
<8%	6.05 (1.57)	6.04 (1.58)	-0.54 (-0.59, -0.49)	-9.1 (-9.9, -8.2)	<0.001
≥8%	5.70 (1.59)	5.75 (1.66)	-0.27 (-0.32, -0.23)	-4.9 (-5.7, -4.0)	
Diabetes duration					
≤12 years	5.78 (1.57)	5.80 (1.62)	-0.45 (-0.50, -0.40)	-7.7 (-8.6, -6.8)	0.001
>12 years	5.92 (1.60)	5.96 (1.65)	-0.34 (-0.38, -0.29)	-5.7 (-6.5, -4.9)	
eGFR					
<60 mL/min/1.73 m^2	6.88 (1.78)	7.02 (1.81)	-0.30 (-0.39, -0.22)	-4.0 (-5.3, -2.6)	<0.001
≥60 mL/min/1.73 m^2	5.61 (1.43)	5.57 (1.43)	-0.41 (-0.45, -0.38)	-7.3 (-8.0, -6.6)	
Urinary albumin:creatinine ratio					
<30 mg/g	5.73 (1.55)	5.72 (1.57)	-0.45 (-0.49, -0.41)	-7.8 (-8.5, -7.0)	<0.001
30-300 mg/g	6.04 (1.63)	6.19 (1.67)	-0.28 (-0.36, -0.21)	-4.4 (-5.7, -3.1)	
>300 mg/g	6.42 (1.61)	6.43 (1.79)	-0.21 (-0.34, -0.07)	-3.3 (-5.5, -1.1)	

BMI=body mass index; eGFR=estimated glomerular filtration rate; SD=standard deviation; CANVAS=CANagliflozin cardioVascular Assessment Study. 10,140 participants had a baseline serum uric

acid measurement and 9992 participants had at least one measurement after baseline. *In CANVAS only.

Figure 1. Effects of canagliflozin on (a) gout flare or the commencement of a drug for gout, (b) gout flare alone, (c) commencement of a drug for gout, and (d) hyperuricemia, in all 10,142 randomized participants.



CI=confidence interval; HR=hazard ratio.

Figure 2. Effects of canagliflozin on events attributable to gout in 10,142 randomized participants.

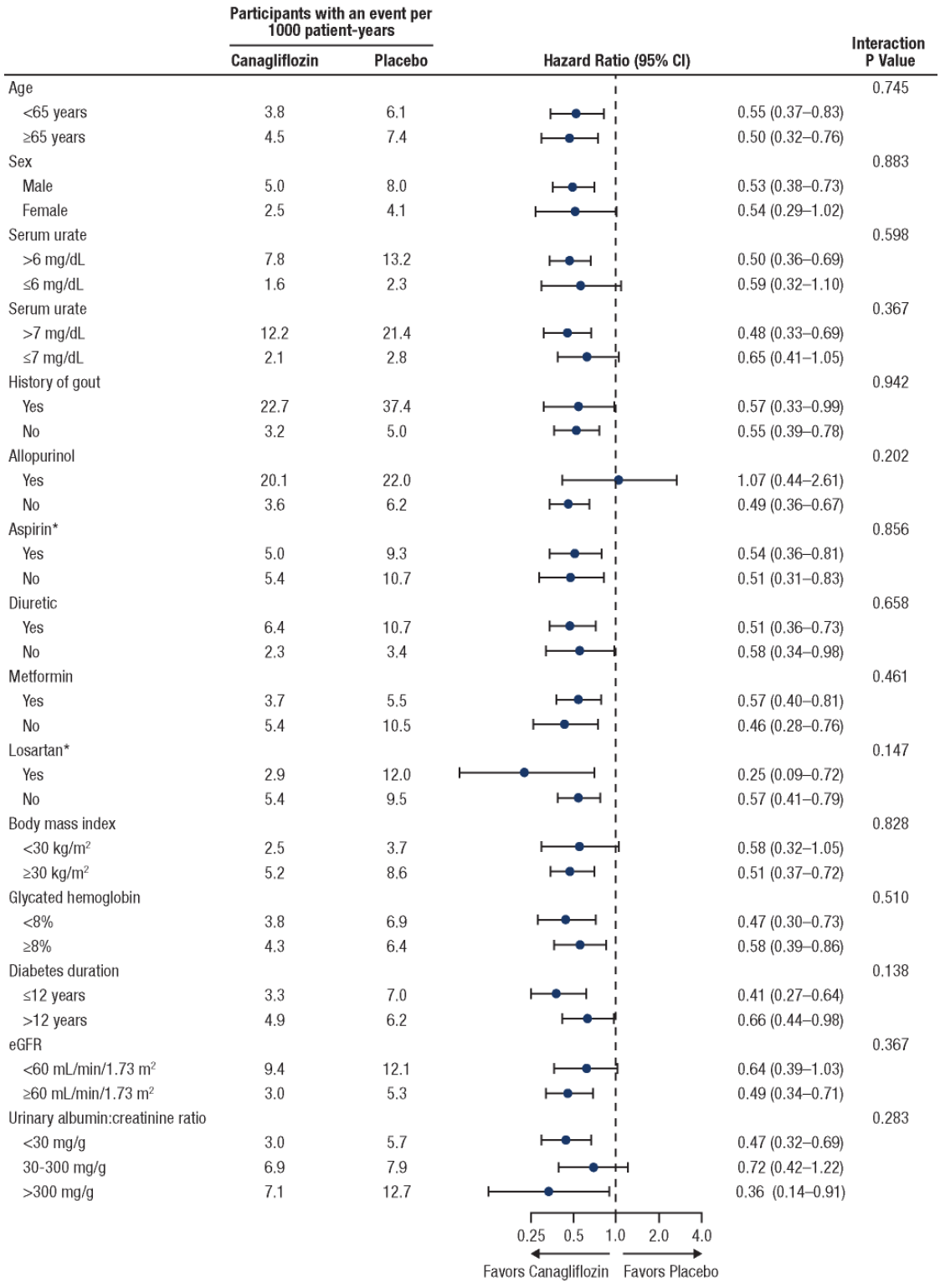
	Number of participants with an event	Participants with an event per 1000 patient-years		Hazard Ratio (95% CI)	Nominal P Value
		Canagliflozin	Placebo		
First event*					
Gout or commencement of a drug for gout	182	4.1	6.6	0.53 (0.40–0.71)	<0.001
Gout	80	2.0	2.6	0.64 (0.41–0.99)	0.046
Commencement of a drug for gout	147	3.3	5.4	0.52 (0.38–0.72)	<0.001
Hyperuricemia	75	1.8	2.5	0.59 (0.37–0.93)	0.023
First and recurrent events†					
Gout or commencement of a drug for gout	256	5.6	9.0	0.51 (0.40–0.66)	<0.001
Gout	125	2.8	4.3	0.54 (0.38–0.76)	0.001
Commencement of a drug for gout	171	3.8	5.9	0.55 (0.40–0.74)	<0.001
Hyperuricemia	79	1.9	2.6	0.59 (0.38–0.91)	0.018

CI=confidence interval; HR=hazard ratio.

*First event is first event during follow-up.

†First and recurrent events are first and subsequent events during follow-up with recurrent events defined on the basis of occurring at least 2 weeks apart.

Figure 3. Effects of canagliflozin on gout or the commencement of a drug for gout in all 10,142 randomized participant in participant subgroups defined by baseline characteristics

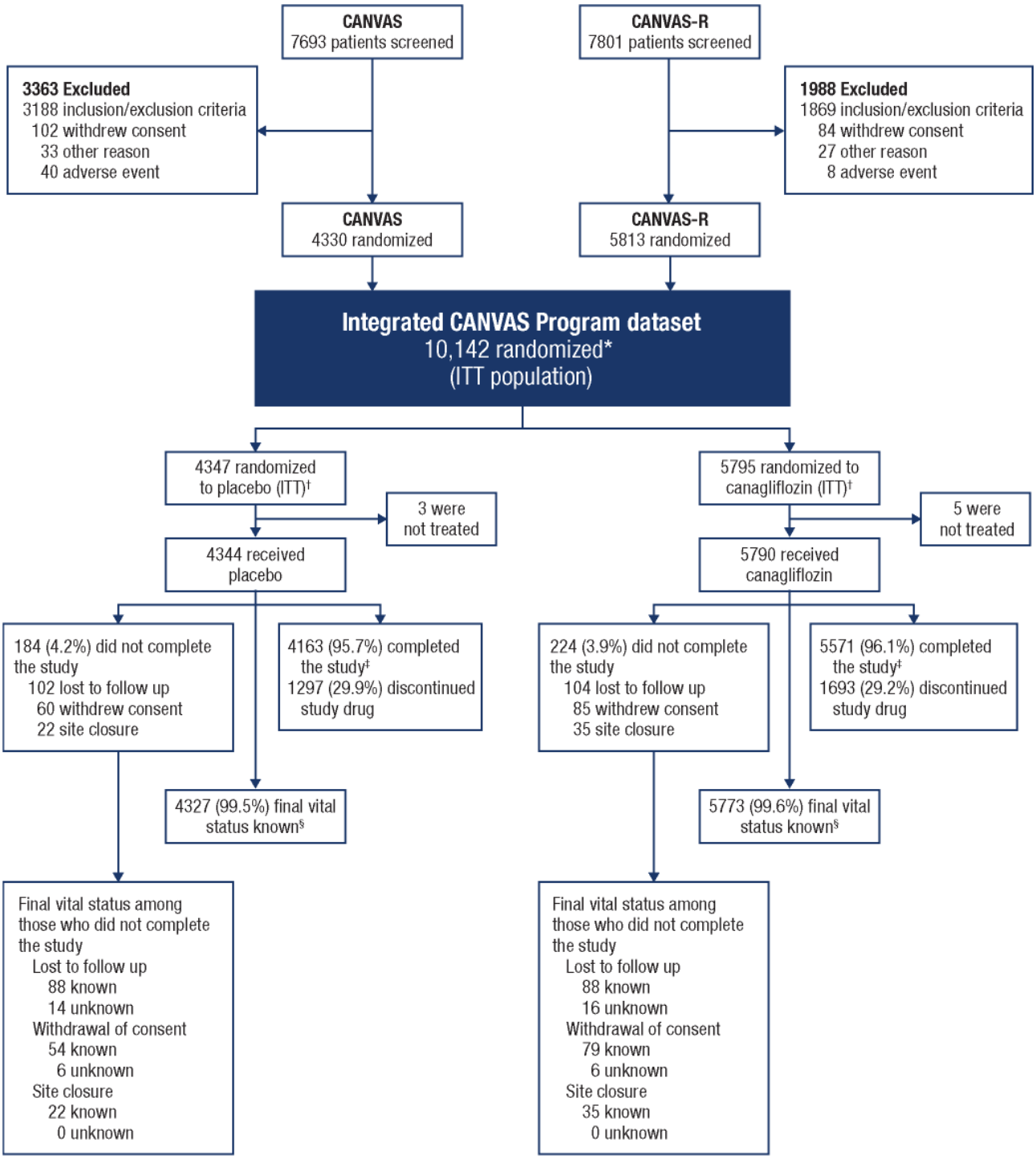


CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio.

*In CANVAS only

SUPPLEMENTARY MATERIAL

Figure S1. Trial flow chart



ITT, intent-to-treat.

*One patient was randomized at 2 different sites and therefore the second randomized 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.

Figure S2. Effects of canagliflozin on serum urate in 10,140 randomized participants with one or more serum urate measurements.

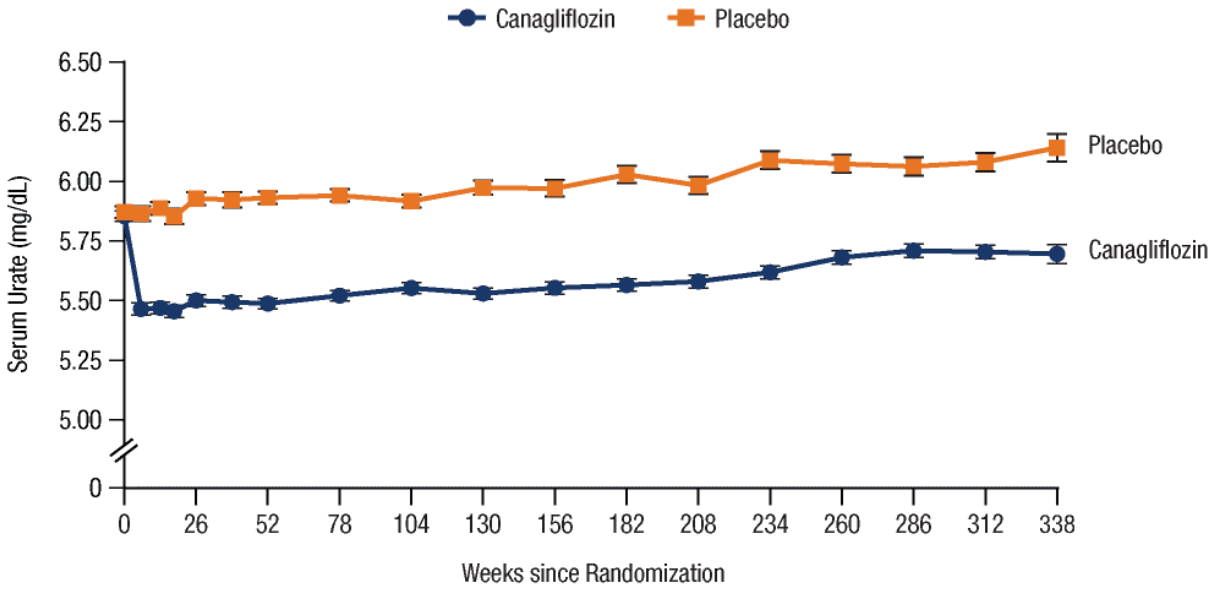


Figure S3. Effects of canagliflozin versus placebo on the risk of gout or the commencement of a drug for gout in 4190 patients with elevated serum urate (>6 mg/dL) at baseline throughout follow-up (main figure) and during first year of follow-up (inset).

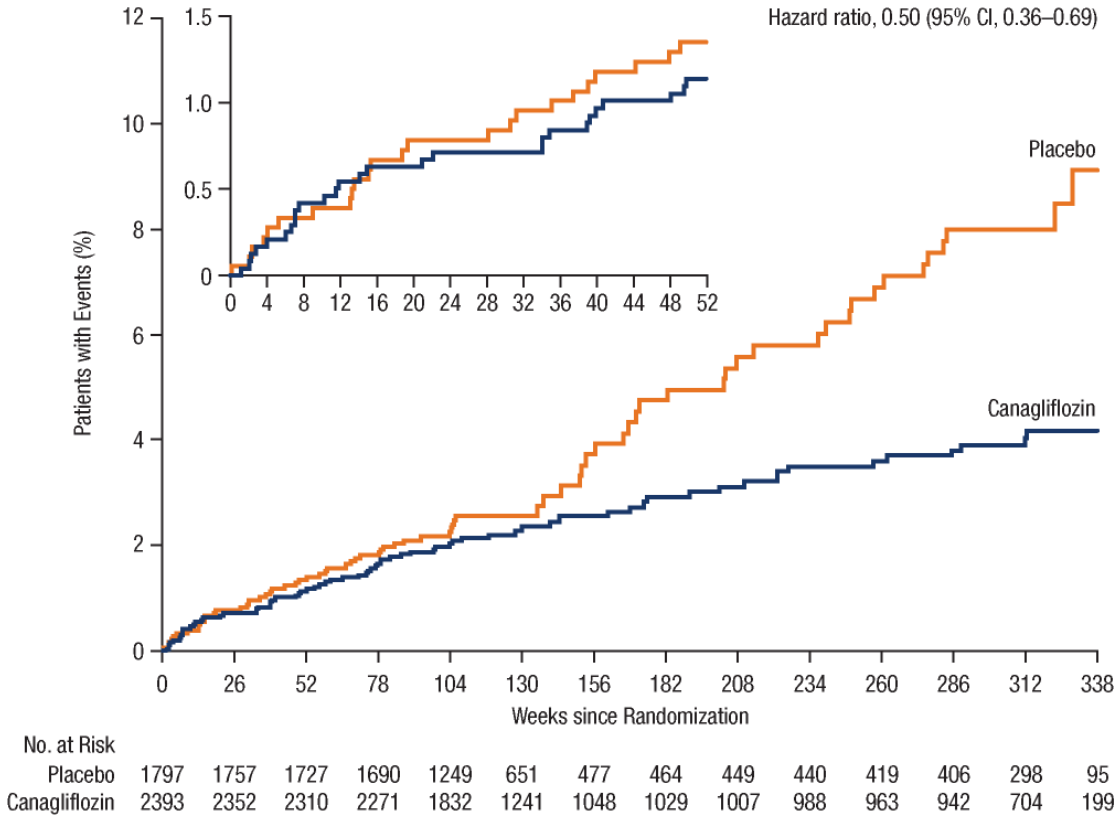


Figure S4. Effects of canagliflozin versus placebo on the risk of gout or the commencement of a drug for gout in 471 patients with gout at baseline throughout follow-up (main figure) and during first year of follow-up (inset).

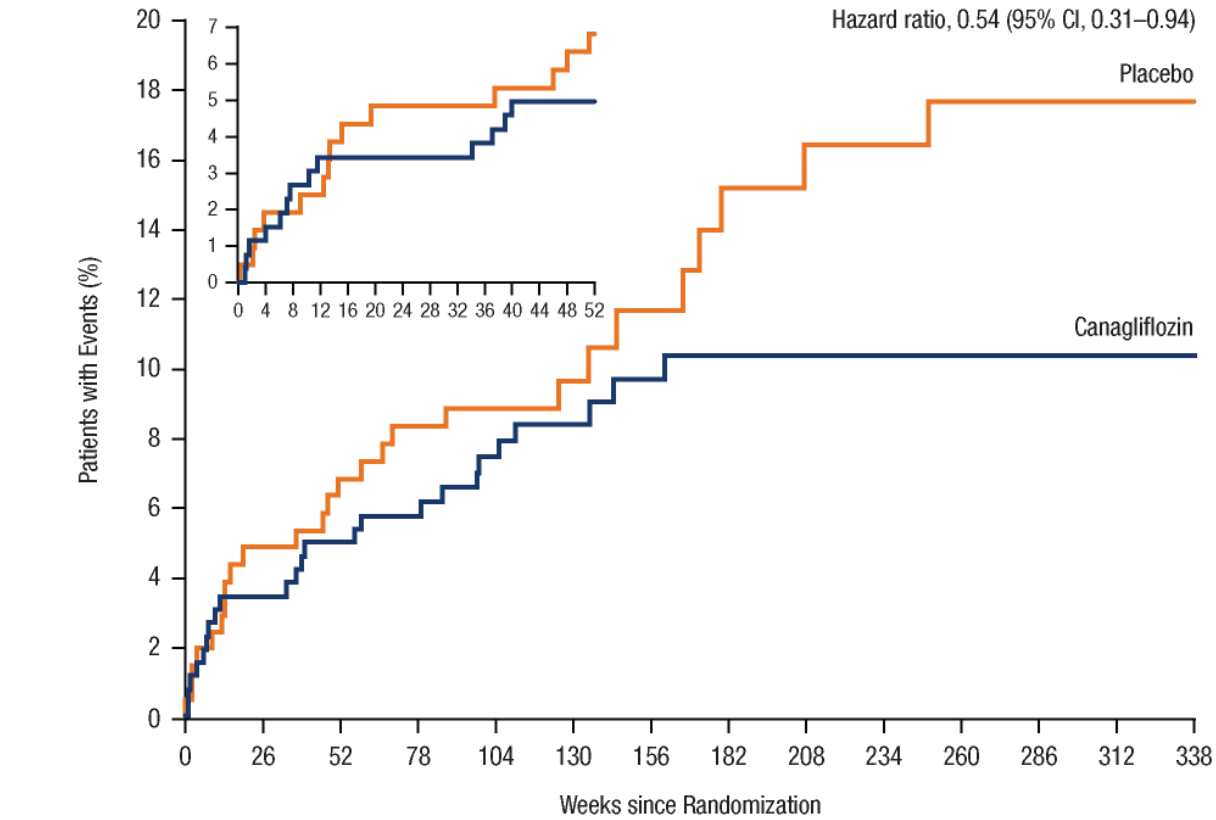


Table S1 Effects of canagliflozin on events attributable to gout with on-treatment analysis in 10,134 patients.

	Number of participants with event	Canagliflozin Rate (participants per 1000 patient-years)	Placebo Rate (participants per 1000 patient-years)	HR	95% CI	Nominal P-value
First event*						
Gout or the commencement of a drug for gout	166	4.6	7.2	0.52	(0.39, 0.71)	<0.001
Gout	74	2.3	2.8	0.66	(0.42, 1.06)	0.083
Commencement of a drug for gout	133	3.6	5.8	0.50	(0.36, 0.71)	<0.001
Hyperuricemia events	73	2.1	3.0	0.56	(0.36, 0.90)	0.015

Table S2 Effects of canagliflozin on events attributable to gout considering death as competing risk using Fine and Grays model.

	Number of participants with event	HR	95% CI	Nominal P-value
First event*				
Gout or the commencement of a drug for gout	182	0.53	(0.40, 0.72)	<0.001
Gout	80	0.64	(0.41, 1.01)	0.053
Commencement of a drug for gout	147	0.53	(0.38, 0.73)	<0.001
Hyperuricemia events	75	0.60	(0.38, 0.95)	0.028

Table S3. Effects of canagliflozin on serum urate levels overall in the 10,132 on-treatment participants with measurements.

	Mean (SD) at baseline (mg/dL)		Mean (SD) difference during follow-up (mg/dL)	Percent difference during follow-up (%)
	Canagliflozin	Placebo		
All participants	5.85 (1.59)	5.88 (1.63)	-0.41 (-0.44, -0.37)	-6.9 (-7.5, -6.3)