The Effects of Canagliflozin on Uric Acid and Gout in Patients With Type 2 Diabetes in the CANVAS Program

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INTRODUCTION

- 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 ~25% of the population²
- Gout has been shown to be independently associated with an increased risk of type 2 diabetes, and hyperuricemia has been linked to an increased risk of cardiovascular disease and chronic kidney disease progression^{3,4}; studies to determine whether lowering uric acid prevents cardiovascular and renal outcomes have been conducted⁵
- Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, has been shown to decrease the risk of cardiovascular disease, heart failure, and kidney disease in large-scale randomized trials^{6,7}
- Treatment with canagliflozin also reduces serum urate in patients with type 2 diabetes,⁸ with similar effects observed for other SGLT2 inhibitors⁹; however, it is unknown whether SGLT2 inhibitors protect against gout

OBJECTIVE

- To determine the effects of treatment with canagliflozin on serum urate levels and the risk of gout-related events in post hoc analyses of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program

METHODS

Study Design and Participants

- The CANVAS Program consisted of 2 multicenter, double-blind, placebo-controlled, randomized trials, CANVAS and CANVAS-R; the design, methods, and primary results of the CANVAS Program have been reported¹⁰⁻¹³
- Eligible participants had type 2 diabetes (HbA1c $\geq 7.0\%$ and $\leq 10.5\%$) and were either ≥ 30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or ≥ 50 years of age with ≥ 2 risk factors for cardiovascular disease
- A history of gout at baseline was defined on the basis of a diagnosis of gout being recorded in the trial record, a gout episode occurring during screening or run-in, or a drug for the management of gout or hyperuricemia being included in the baseline medication record (allopurinol, benzbromarone, colchicine, febuxostat, or probenecid)
- Participants in CANVAS were randomly assigned in a 1:1 ratio to canagliflozin 100 mg or 300 mg or matching placebo; participants in CANVAS-R were randomly assigned in a 1:1 ratio to canagliflozin 100 mg or matching placebo, with optional up-titration to canagliflozin 300 mg or matching placebo from Week 13
- Use of other background therapy for glycemic management, treatment of heart failure, and other risk factor control was according to best practices instituted in line with local guidelines

Outcomes

- Serum urate concentrations were measured in samples by a single central laboratory using Roche modular and Cobas analyzers (Roche, Mannheim, Germany)
- Suspected gout events were identified based on searches of the adverse event database for permutations of the term “gout” (gout, gouty arthritis, or gouty tophus) and searches of the concomitant medication databases for post-randomization prescription of a medication for the long-term management of gout (allopurinol, benzbromarone, febuxostat, or probenecid) or the management of acute gout (colchicine, nonsteroidal anti-inflammatory agents, or corticosteroids)
- Separate searches of the adverse events database for records including permutations of the word “hyperuricemia” and for permutations of the word “urolithiasis” were also conducted
- The following outcomes related to gout were assessed:
 - A composite based upon the occurrence of either an adverse event attributed to gout or the commencement of a drug for gout
 - Gout events alone
 - Commencement of a drug for gout events alone
 - Hyperuricemia (which included events with the terms “hyperuricemia,” “increased blood serum urate,” or “hyperuricosuria” not included in the other analyses)
 - Urolithiasis

Statistical Analyses

- Analyses were conducted using the integrated CANVAS Program data, except for comparisons of canagliflozin 100 mg and 300 mg, which were done in the CANVAS trial participants alone
- 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. Effects were determined overall and for key participant subgroups
- The effects of canagliflozin versus placebo on gout events were estimated from a Kaplan-Meier analysis, with Cox proportional hazard models used to determine hazard ratios (HRs) and 95% confidence intervals (CIs). Main analyses included terms for randomized treatment and trial (CANVAS vs CANVAS-R). Interaction terms were included in the Cox models to explore for possible modifying effects of age; sex; history of gout; baseline serum urate levels; body mass index; HbA1c; estimated glomerular filtration rate (eGFR); and use of allopurinol, aspirin, diuretic, losartan, or metformin at baseline
- Secondary analyses that allowed for the assessment of multiple events within an individual were estimated using Anderson-Gill modeling
- Nominal *P* values were calculated for effects of canagliflozin versus placebo, and interaction *P* values were used to test for effects between subgroups, with *P* values < 0.05 considered to be significant

RESULTS

Participants

- In the overall population, participant characteristics were well balanced between randomized groups (**Table 1**)
- There were 471 participants with a history of gout at baseline, including 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 or hyperuricemia at or prior to baseline

Table 1. Baseline Participant Characteristics in the CANVAS Program*		
	Canagliflozin (n = 5795)	Placebo (n = 4347)
Age, y	63.2 $\pm$ 8.3	63.4 $\pm$ 8.2
Female, %	35.1	36.7
Current smoker, %	17.6	18.1
Hypertension, %	89.5	90.6
Duration of diabetes, y	13.5 $\pm$ 7.7	13.7 $\pm$ 7.8
Body mass index, kg/m ²	31.9 $\pm$ 5.9	32.0 $\pm$ 6.0
HbA1c, %	8.2 $\pm$ 0.9	8.2 $\pm$ 0.9
eGFR, mL/min/1.73 m ²	76.7 $\pm$ 20.3	76.2 $\pm$ 20.8
Median (IQR) UACR, mg/g†	12.4 (6.7-40.9)	12.1 (6.6-43.9)
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
Gout, %	4.5	4.8
Serum urate, mg/dL*	5.9 $\pm$ 1.6	5.9 $\pm$ 1.6
Serum urate ≥ 6 mg/dL, %	41.3	41.4
Serum urate ≥ 7 mg/dL, %	20.9	21.6
Allopurinol, %	2.2	1.8
Antithrombotic, %	73.1	74.4
Antiplatelet, 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

IQR, interquartile range; UACR, urinary albumin:creatinine ratio; SD, standard deviation.
*Data are mean $\pm$ SD unless otherwise noted.
†109 participants did not have baseline urinary albumin measurements.
‡Participants did not have baseline serum urate measurements.
§Data for aspirin and losartan use were available for CANVAS only.

Effects of Canagliflozin on Serum Urate Levels

- The serum urate level fell immediately after commencing treatment with canagliflozin (Week 6) and remained lower compared with placebo throughout follow-up (**Figure 1**)
- 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 with placebo, equating to a 6.7% reduction in serum urate
- Among CANVAS participants (n = 4330), effects on serum urate levels were comparable between the 100 mg and 300 mg doses (placebo-subtracted differences of -0.47 mg/dL [95% CI, -0.53 to -0.42] and -0.46 mg/dL [95% CI, -0.52 to -0.40], respectively; *P* interaction = 0.354)
- Proportional reductions in serum urate levels were greater in older individuals (≥ 65 vs < 65 years); women; and those with a higher baseline body mass index (≥ 30 vs < 30 kg/m²), a lower baseline HbA1c ($< 8\%$ vs $\geq 8\%$), a shorter duration of diabetes (≤ 12 vs > 12 years), a lower UACR (< 30 vs 30 - 300 or > 300 mg/g), and a higher eGFR (≥ 60 vs < 60 mL/min/1.73 m²; all *P* interaction ≤ 0.026)

Figure 1. Effects of canagliflozin on serum urate.

Effects of Canagliflozin on Gout

- During follow-up, 80 participants had a gout event, 147 commenced a drug for gout, and 75 had an event ascribed to hyperuricemia
 - Many participants had > 1 event or events of different types, resulting in a total of 125 gout events, 171 commencements of a drug for gout, and 79 hyperuricemia events during the study
- The risk of gout or the commencement of a drug for gout was lower with canagliflozin compared with placebo (**Figure 2A**), with no evidence of differences across participant subgroups (all *P* interaction ≥ 0.138 ; **Figure 3**)
 - Comparable effects on this outcome were also seen with canagliflozin 100 mg and 300 mg versus placebo in CANVAS (HR, 0.51 [95% CI, 0.35 to 0.75] and HR, 0.55 [95% CI, 0.38 to 0.80], respectively; *P* interaction = 0.731)
- The risks of gout alone (**Figure 2B**), commencement of a drug for gout alone (**Figure 2C**), and hyperuricemia (**Figure 2D**) were also lower with canagliflozin compared with placebo
- Findings based upon analyses that included recurrent events were comparable to the main results except with tighter CIs and smaller *P* values (**Figure 4**)
- There were 117 events identified that were attributed to urolithiasis (HR, 0.83; 95% CI, 0.57 to 1.21 for canagliflozin vs placebo)

Figure 2. Effects of canagliflozin on (A) gout or the commencement of a drug for gout, (B) gout alone, (C) commencement of a drug for gout, and (D) hyperuricemia.

Figure 3. Effects of canagliflozin on gout or the commencement of a drug for gout in participant subgroups.

	Participants with an event per 1000 patient-years		HR (95% CI)		Interaction P value
	Canagliflozin	Placebo			
Age					0.745
<65 y	3.8	6.1	0.55 (0.37-0.83)		
≥ 65 y	4.5	7.4	0.50 (0.32-0.76)		
Sex					0.883
Male	5.0	8.0	0.53 (0.38-0.73)		
Female	2.5	4.1	0.54 (0.29-1.02)		
Serum urate					0.598
≥ 6 mg/dL	7.8	13.2	0.50 (0.36-0.69)		
< 6 mg/dL	1.6	2.3	0.59 (0.32-1.10)		
Serum urate					0.367
≥ 7 mg/dL	12.2	21.4	0.48 (0.33-0.69)		
< 7 mg/dL	2.1	2.8	0.65 (0.41-1.05)		
History of gout					0.942
Yes	22.7	37.4	0.57 (0.33-0.99)		
No	3.2	5.0	0.55 (0.39-0.78)		
Allopurinol					0.202
Yes	20.1	22.0	1.07 (0.44-2.61)		
No	3.6	6.2	0.49 (0.36-0.67)		
Aspirin*					0.856
Yes	5.0	9.3	0.54 (0.36-0.81)		
No	5.4	10.7	0.51 (0.31-0.83)		
Diuretic					0.658
Yes	6.4	10.7	0.51 (0.36-0.73)		
No	2.3	3.4	0.58 (0.34-0.98)		
Metformin					0.461
Yes	3.7	5.5	0.57 (0.40-0.81)		
No	5.4	10.5	0.46 (0.28-0.76)		
Losartan*					0.147
Yes	2.9	12.0	0.25 (0.09-0.72)		
No	5.4	9.5	0.57 (0.41-0.79)		
Body mass index					0.828
< 30 kg/m ²	2.5	3.7	0.58 (0.32-1.05)		
≥ 30 kg/m ²	5.2	8.6	0.51 (0.37-0.72)		
HbA1c					0.510
$< 8\%$	3.8	6.9	0.47 (0.30-0.73)		
$\geq 8\%$	4.3	6.4	0.58 (0.39-0.86)		
Diabetes duration					0.138
≤ 12 y	3.3	7.0	0.41 (0.27-0.64)		
> 12 y	4.9	6.2	0.66 (0.44-0.98)		
eGFR					0.367
< 60 mL/min/1.73 m ²	9.4	12.1	0.64 (0.39-1.03)		
≥ 60 mL/min/1.73 m ²	3.0	5.3	0.49 (0.34-0.71)		
UACR					0.283
< 30 mg/g	3.0	5.7	0.47 (0.32-0.69)		
30-300 mg/g	6.9	7.9	0.72 (0.42-1.22)		
> 300 mg/g	7.1	12.7	0.36 (0.14-0.91)		

*In CANVAS only.

Figure 4. Effects of canagliflozin on events attributable to gout.

	Number of participants with an event	Participants with an event per 1000 patient-years		HR (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

0.25 0.5 1.0 2.0 4.0
Favors Canagliflozin Favors Placebo

*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 ≥ 2 weeks apart.

SUMMARY

- Canagliflozin reduced serum urate levels and gout-related events in patients with type 2 diabetes and an elevated risk of cardiovascular disease
- While these analyses are post hoc, the high statistical significance of the findings, the constancy of the data across a range of gout-related endpoints, and the comparability of findings across participant subgroups make it unlikely that this is a chance finding
- The large protective effect for gout achieved with canagliflozin, despite small reductions in serum urate levels, suggests the possibility of protective mechanisms beyond uric acid lowering

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