Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus

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Context: Canagliflozin is a sodium glucose cotransporter 2 inhibitor developed to treat type 2 diabetes mellitus (T2DM).

Objective: The purpose of this study was to describe the effects of canagliflozin on bone fracture risk.

Design and Setting: This was a randomized phase 3 study in patients with T2DM.

Patients and Interventions: Canagliflozin doses of 100 and 300 mg were evaluated in the overall population of patients from 9 placebo- and active-controlled studies (N = 10 194), as well as in separate analyses of a single trial enriched with patients with a prior history/risk of cardiovascular disease (ie, the CANagliflozin cardioVascular Assessment Study [CANVAS]; N = 4327) and a pooled population of 8 non-CANVAS studies (N = 5867).

Outcome Measures: The incidence of adjudicated fracture adverse events (AEs), fall-related AEs, and volume depletion–related AEs was assessed.

Results: The incidence of fractures was similar with canagliflozin (1.7%) and noncanagliflozin (1.5%) in the pooled non-CANVAS studies. In CANVAS, a significant increase in fractures was seen with canagliflozin (4.0%) vs placebo (2.6%) that was balanced between the upper and lower limbs. The incidence of fractures was higher with canagliflozin (2.7%) vs noncanagliflozin (1.9%) in the overall population, which was driven by the increase of fractures in CANVAS. The incidence of reported fall-related AEs was low, but significantly higher with canagliflozin in CANVAS, potentially related to volume depletion–related AEs, but not significantly different in the pooled non-CANVAS studies and the overall population.

Conclusions: Fracture risk was increased with canagliflozin treatment, driven by CANVAS patients, who were older, with a prior history/risk of cardiovascular disease, and with lower baseline estimated glomerular filtration rate and higher baseline diuretic use. The increase in fractures may be mediated by falls; however, the cause of increased fracture risk with canagliflozin is unknown. (***J Clin Endocrinol Metab*** **101: 157–166, 2016)**

Patients with type 2 diabetes mellitus (T2DM) are at increased risk of fracture, and this risk increases further with advancing age (1–3). Comprehensive meta-analyses report an increased risk of hip fractures in patients with T2DM (4, 5). Several factors may contribute to this elevated fracture risk, including antihyperglycemic

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Abbreviations: AE, adverse event; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CANVAS, CANagliflozin cardioVascular Assessment Study; CI, confidence interval; β-CTX, collagen type 1 β-carboxy-telopeptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; HR, hazard ratio; SGLT2, sodium glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

and blood pressure (BP)–lowering treatments, and diabetes complications that might increase fall risk (eg, hypoglycemic events, peripheral and autonomic neuropathy, neuromuscular impairment, nephropathy, and retinopathy) (1, 6).

Canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor developed for the treatment of adults with T2DM (7–17), lowers plasma glucose by increasing urinary glucose excretion (18). Canagliflozin has demonstrated glycemic efficacy and reductions in body weight and BP and was generally well tolerated across a broad range of patients with T2DM (8–17). More adverse events (AEs) related to volume depletion (eg, orthostatic hypotension and postural dizziness) and osmotic diuresis (eg, increased frequency and volume of urination, thirst, and dry mouth) were observed soon after initiation of canagliflozin treatment.

As reported in a separate article in this issue, results from a phase 3 study in older patients aged 55 to 80 years with T2DM demonstrated that canagliflozin was associated with a small but statistically significant reduction in bone mineral density (BMD) at the total hip (but not at other skeletal sites) over 104 weeks and increases in the bone turnover markers serum collagen type 1 β-carboxytelopeptide (β-CTX), a resorption marker, and osteocalcin, a formation marker (19). Previous studies have demonstrated a link between weight loss, decreased estradiol levels, increased bone turnover, and decreases in BMD, possibly due to decreased estrogen production (20–24); weight loss and reductions in serum estradiol levels were seen in women treated with canagliflozin (19), which may explain the increases in bone turnover and decreases in total hip BMD observed with canagliflozin treatment.

To assess the effects of canagliflozin on bone fracture risk in patients with T2DM, the incidence of fracture AEs and spontaneously reported AEs of falls was assessed in an analysis of data from 9 placebo- and active-controlled studies that included a broad range of patients with T2DM, including patients with elevated cardiovascular (CV) risk, older patients, and patients with moderate renal impairment.

Subjects and Methods

Patients and study design

Analyses were performed using data from studies with scheduled exposures to canagliflozin 100 or 300 mg for 1 year or longer from 9 placebo- and active-controlled, randomized, double-blind, phase 3 studies (Table 1), including interim results from the ongoing placebo-controlled CANagliflozin cardioVascular Assessment Study (CANVAS) in patients with a history of or high risk for CV disease on a background of standard care for the treatment of T2DM (50% treated with insulin and 47% treated with a sulfonylurea) (25). For the fracture analyses presented in this article, a cutoff date of May 2013 was used to

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Pooled Non-CANVAS Studies (N = 5867): Non-CANA (n = 2199); CANA 100 mg (n = 1647); CANA 300 mg (n = 2021)	CANVAS (N = 4327): Placebo (n = 1441); CANA 100 mg (n = 1445); CANA 300 mg (n = 1441)	Overall Population (N = 10 194): Non-CANA (n = 3640); CANA 100 mg (n = 3092); CANA 300 mg (n = 3462)
Sex			
Male	3055 (52.1)	2860 (66.1)	5915 (58.0)
Female	2812 (47.9)	1467 (33.9)	4279 (42.0)
Age, y	57.6 ± 9.8	62.4 ± 8.0	59.6 ± 9.4
≥75 y	219 (3.7)	290 (6.7)	509 (5.0)
Race			
White	4165 (71.0)	3177 (73.4)	7342 (72.0)
Black or African American	342 (5.8)	104 (2.4)	447 (4.4)
Asian	831 (14.2)	795 (18.4)	1626 (16.0)
Other[a]	529 (9.0)	251 (5.8)	779 (7.6)
HbA_{1c}, %	7.9 ± 0.9	8.2 ± 0.9	8.0 ± 0.9
FPG, mg/dL (mmol/L)	165.8 ± 41.4 (9.2 ± 2.3)	167.6 ± 46.8 (9.3 ± 2.6)	165.8 ± 43.2 (9.2 ± 2.4)
Body weight, kg	88.5 ± 20.9	91.1 ± 21.3	89.6 ± 21.1
BMI, kg/m^2	31.7 ± 6.0	32.1 ± 6.2	31.9 ± 6.1
Duration of T2DM, y	8.4 ± 6.6	13.4 ± 7.5	10.5 ± 7.4
Microvascular complications[b]	1468 (25.0)	1914 (44.2)	3386 (33.2)
eGFR, mL/min/1.73 m^2	85.0 ± 21.2	77.2 ± 18.9	81.7 ± 20.6
<60 mL/min/1.73 m^2	553 (9.4)	711 (16.4)	1265 (12.4)
Use of loop diuretics	226 (3.9)	499 (11.5)	725 (7.1)
Prior CV history	555 (9.5)	2470 (57.1)	3025 (29.7)

Abbreviation: CANA, canagliflozin. Data are means ± SD or n (%).

[a] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, not reported, other, and unknown.

[b] Includes neuropathy, nephropathy, and retinopathy.

support a request for additional analyses from health authorities. No CV event data from the ongoing CANVAS study were unblinded using this data cutoff. In addition to CANVAS, studies included in the pooled dataset were of canagliflozin as monotherapy, as a add-on to metformin, as an add-on to metformin plus a sulfonylurea, and as an add-on to metformin plus pioglitazone. The analysis also included placebo-controlled studies in older patients (aged 55–80 years) on a background of standard care for treatment of T2DM (33% receiving insulin and 49% receiving a sulfonylurea) (26) and in patients with moderate renal impairment (baseline estimated glomerular filtration rate [eGFR] of ≥30 to <50 mL/min/1.73 m^2) on a background of standard care for treatment of T2DM (74% receiving insulin and 31% receiving a sulfonylurea) (12). For the 8 non-CANVAS studies, data through each study's completion are presented. Overall, 6 studies were placebo controlled and 3 were active controlled (1 vs glimepiride and 2 vs sitagliptin). Of note, glimepiride and sitagliptin have not been shown to increase fracture risk in patients with T2DM (27, 28). The study design details have been reported previously for the individual studies included in this pooled dataset (8–11, 13, 15–17, 25). This analysis included some patients for whom the drug may not be indicated, including those with eGFR of 30 to <45 mL/min/1.73 m^2. Analyses were also performed in the pooled, non-CANVAS studies and in CANVAS alone. The analyses of fractures in all 9 studies pooled, and separately by non-CANVAS and CANVAS, were a consequence of the canagliflozin program independent data monitoring committee, which identified to Janssen an increased risk of fractures primarily driven by CANVAS.

The key inclusion criteria for the studies are summarized in Supplemental Table 1. Patients enrolled in CANVAS must have had a prior history of a CV event (eg, myocardial infarction or stroke) or ≥2 risk factors for a future CV event. In addition, patients were required to have inadequately controlled T2DM at screening, a baseline hemoglobin A_{1c} (HbA_{1c}) of ≥7.0% and ≤10.5%, an eGFR of ≥30 mL/min/1.73 m^2, and a fasting plasma glucose (FPG) of <270 mg/dL (15 mmol/L). In most non-CANVAS studies, patients must have had inadequately controlled T2DM at screening, a baseline HbA_{1c} of ≥7.0% and ≤10.5%, and an FPG of <270 mg/dL (15 mmol/L). Common exclusion criteria across the studies included a history of type 1 diabetes and severe renal impairment. The details of randomization and blinding and glycemic rescue therapy have been reported separately for the individual studies in each dataset (8, 10, 11, 15–17, 25).

All studies were conducted in accordance with the ethical principles that comply with the Declaration of Helsinki and are consistent with good clinical practices and applicable regulatory requirements. The study protocols and amendments were approved by institutional review boards and independent ethics committees at participating institutions. All patients provided written informed consent before participation.

Analyses of fracture and fall AEs

Data for patients from each study who received ≥1 dose of the study drug were included in the analyses. The analysis of fracture AEs included all fractures occurring at any time postrandomization, regardless of the timing of the last dose of study medication; similar results were seen in the on-treatment analysis of fracture AEs (data on file). Fracture AEs were analyzed in the 9 studies individually, including CANVAS alone, as well as in the pooled non-CANVAS studies and the overall population. Assessments were performed at the scheduled week 52 completion for 6 studies and at the scheduled week 104 completion for 2 studies, and a cutoff date of May 31, 2013, was used for the ongoing CANVAS study (median duration of treatment exposure of ~2.4 years). A separate assessment of fracture AEs was performed for the 2 non-CANVAS studies with a scheduled 104-week duration (ie, add-on to metformin vs glimepiride [drugs not known to have effects on bone (29)] and the study in older adults with T2DM). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. All fracture AEs were adjudicated by an independent blinded committee to confirm that events were fractures and to determine the fracture location. Fracture AEs were also evaluated in subgroups based on sex (male or female), baseline age (<65 and ≥65 years), duration of T2DM (<10 and ≥10 years), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and prior fracture history (yes or no) in CANVAS and in the overall population. The estimation of HRs and 95% CIs was derived separately for each subgroup. The homogeneity assessment was conducted by adding a covariate for the subgroup and the corresponding treatment-by-subgroup interaction using the Cox proportional hazards model. Interaction P values of <.10 were interpreted as a strong signal for a difference in the treatment effect between subgroups. A statistical assessment of fracture AEs was also performed by comparing the pooled non-CANVAS studies vs CANVAS alone using data from the first 52 weeks posttreatment, as most non-CANVAS studies were 52 weeks in duration. A sensitivity analysis excluding fractures in the hand, foot, skull, and face was also performed for CANVAS.

Fall AEs were captured by verbatim reports that used a term indicative of a fall (eg, "fall," "falling," "fell," or "collapse," but excluding events not possibly related to a physical fall, such as "hair falling out") and were analyzed in the pooled non-CANVAS studies, CANVAS, and the overall population. Fall AEs were not prespecified events of interest and were not prospectively collected. Incidence was based on the number of patients with at least 1 fracture or fall AE and not the total number of events.

Results

Patient disposition and baseline characteristics

Baseline characteristics for the 3 analyses are summarized in Table 1 and Supplemental Tables 2 to 4. In the pooled non-CANVAS studies, the mean age was 57.6 years, body mass index (BMI) was 31.7 kg/m^2, HbA_{1c} was 7.9%, and duration of T2DM was 8.4 years; nearly 10% and 25% of patients had a prior history of CV events and microvascular complications, respectively. In CANVAS, the mean age was older (62.4 years, $P < .001$ vs pooled non-CANVAS), BMI was higher (32.1 kg/m^2, $P = .004$ vs pooled non-CANVAS), HbA_{1c} was higher (8.2%, $P < .001$ vs pooled non-CANVAS), and duration of T2DM was longer (13.4 years, $P < .001$ vs pooled non-CANVAS); approximately 60% and 44% of patients had prior CV history and microvascular complications, re-

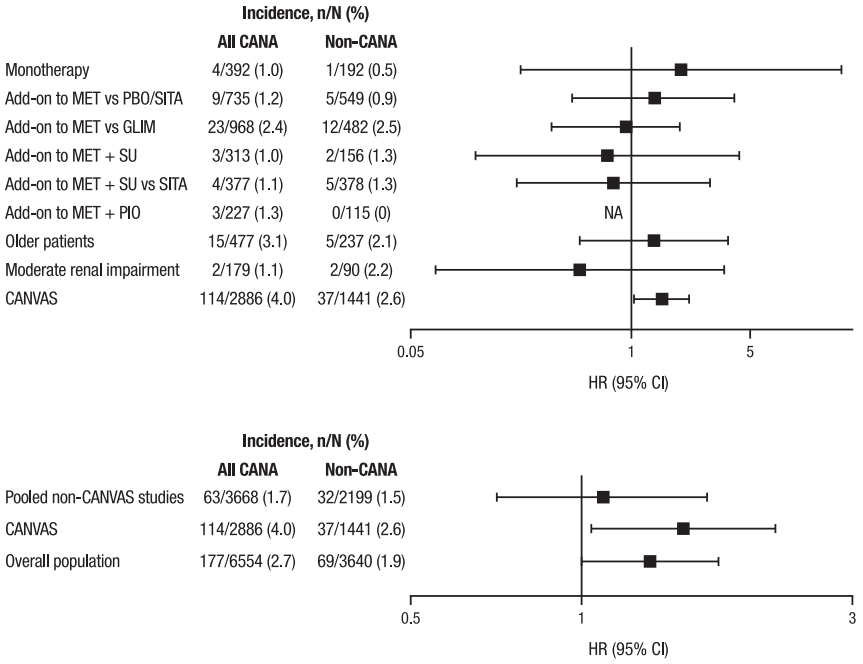

Figure 1. HRs (95% CIs) for pooled canagliflozin 100 and 300 mg vs noncanagliflozin in the incidence of fracture AEs in the 9 individual studies, the pooled non-CANVAS studies, CANVAS, and the overall population. CANA, canagliflozin; MET, metformin; PBO, placebo; SITA, sitagliptin; GLIM, glimepiride; SU, sulfonylurea; PIO, pioglitazone; NA, not assessed.

spectively. In the overall population, the mean age was 59.6 years, BMI was 31.9 kg/m^2, HbA_{1c} was 8.0%, and duration of T2DM was 10.5 years. The incidence of pioglitazone use in the overall population was approximately 7% and balanced across treatment groups. Nearly one-third of patients had a prior history of CV events, and one-third had microvascular complications (ie, nephropathy, neuropathy, and retinopathy).

In the pooled non-CANVAS studies, mean drug exposures were 64, 59, and 56 weeks with canagliflozin 100 and 300 mg and noncanagliflozin, respectively, whereas in CANVAS the mean exposure was longer (116, 114, and 109 weeks with canagliflozin 100 and 300 mg and placebo, respectively). For the overall population, mean drug exposures were 88, 82, and 77 weeks with canagliflozin 100 and 300 mg and noncanagliflozin, respectively.

Incidence of fracture AEs

The incidence of fracture AEs by study, along with the HRs and 95% CIs, is shown in Figure 1. In the pooled non-CANVAS studies, there was no evidence of a difference in the incidence of fracture AEs in the pooled canagliflozin group vs noncanagliflozin (1.7% vs 1.5%, respectively), with a similar incidence in the canagliflozin 100 and 300 mg groups (1.6% and 1.8%, respectively) (Figure 1 and Table 2). Two of the 8 non-CANVAS studies were of 2 years' duration. In the pooled 2-year studies, the incidence of fractures was similar in the pooled canagliflozin group vs noncanagliflozin group (2.6% vs 2.4%, respectively), with a similar incidence in the canagliflozin 100 and 300 mg groups (2.3% and 2.9%, respectively) (Table 2). The time-to-event Kaplan-Meier curves with canagliflozin 100 and 300 mg in the pooled non-CANVAS studies over 52 weeks and in the pooled 2-year studies over 104 weeks are shown in Supplemental Figure 1.

In CANVAS, the incidence of adjudicated fracture AEs was statistically significantly higher in the pooled canagliflozin group vs placebo group (4.0% vs 2.6%, respectively), with a similar incidence in the canagliflozin 100 and 300 mg groups (3.9% and 4.0%, respectively) (Figure 1 and Table 2). More fracture AEs occurred with canagliflozin vs placebo starting early (ie, within the first few weeks) after initiation of treatment, with a continued rate of increase in each group observed over 104 weeks (Figure 2 and Supplemental Figure 2). The incidence of fracture AEs at week 52 in the pooled canagliflozin and placebo groups was 2.0% and 1.4%, respectively (Supplemental Table 5). The HRs (95% CIs) for fractures with canagliflozin at week 52, the minimum scheduled follow-up time for all studies included in this analysis, were 1.44 (0.87–2.39) in CANVAS and 0.80 (0.49–1.29) in the pooled non-CANVAS studies ($P = .11$ for the test of subgroup homogeneity).

In CANVAS, the incidence of lower (1.7%) and upper (1.6%) limb fractures in the pooled canagliflozin group was increased compared with those for placebo (1.2% for lower limbs and 1.1% for upper limbs), with a similar incidence in the canagliflozin 100 and 300 mg groups of fractures in the lower limbs (1.5% and 1.8%, respectively) and upper limbs (1.7% and 1.5%, respectively) (Table 3). The incidence of fractures at other sites (eg, spine and thoracic cage) is shown in Table 3. None of the differences in fractures with canagliflozin vs placebo at individual sites met statistical significance. A sensitivity analysis excluding fractures in the hand, foot, skull, and face (ie, fracture locations not associated with osteoporosis or skeletal fragility) showed that the incidence of fractures was no longer statistically significantly higher with canagliflozin (Supplemental Table 6). The incidence of fractures was increased with canagliflozin vs placebo across subgroups based on sex, age, duration of T2DM, baseline eGFR, and prior fracture history (Figure 3). As was ex-

Table 2. Summary of Adjudicated Fracture AEs

	Non-CANA (Placebo and/or Active Control)	CANA 100 mg	CANA 300 mg	All CANA
Pooled non-CANVAS studies, n[a]	2199	1647	2021	3668
Fracture AE, n (%)	32 (1.5)	27 (1.6)	36 (1.8)	63 (1.7)
Incidence rate (/1000 patient-years)	11.4	11.6	13.4	12.5
Incidence rate (/100 patient-years)	1.14	1.16	1.34	1.25
HR vs all non-CANA (95% CI)		0.99 (0.59–1.66)	1.17 (0.73–1.88)	1.09 (0.71–1.66)
Pooled 2-year non-CANVAS studies, n	719	724	721	1445
Fracture AE, n (%)	17 (2.4)	17 (2.3)	21 (2.9)	38 (2.6)
Incidence rate (/1000 patient-years)	12.9	12.2	15.4	13.8
Incidence rate (/100 patient-years)	1.29	1.22	1.54	1.38
HR vs all non-CANA (95% CI)		0.94 (0.48–1.84)	1.19 (0.63–2.25)	1.06 (0.60–1.88)
CANVAS, n[b]	1441	1445	1441	2886
Fracture AE, n (%)	37 (2.6)	57 (3.9)	57 (4.0)	114 (4.0)
Incidence rate (/1000 patient-years)	10.8	16.3	16.4	16.3
Incidence rate (/100 patient-years)	1.08	1.63	1.64	1.63
HR vs all non-CANA (95% CI)		1.52 (1.00–2.30)	1.50 (0.99–2.27)	1.51 (1.04–2.19)
Overall population, n[c]	3640	3092	3462	6554
Fracture AE, n (%)[d]	69 (1.9)	84 (2.7)	93 (2.7)	177 (2.7)
Incidence rate (/1000 patient-years)	11.0	14.4	15.1	14.7
Incidence rate (/100 patient-years)	1.10	1.44	1.51	1.47
HR vs all non-CANA (95% CI)		1.28 (0.93–1.77)	1.34 (0.98–1.84)	1.32 (1.00–1.74)

Abbreviation: CANA, canagliflozin.

[a] Total drug exposure was 2018, 2282, and 2353 patient-years with canagliflozin 100 and 300 mg and noncanagliflozin, respectively.

[b] Total drug exposure was 3210, 3159, and 3022 patient-years with canagliflozin 100 and 300 mg and placebo, respectively.

[c] Total drug exposure was 5228, 5441, and 5375 patient-years with canagliflozin 100 and 300 mg and noncanagliflozin, respectively.

[d] Five patients with fracture AEs were receiving background pioglitazone therapy (1 patient with canagliflozin 100 mg, 3 patients with canagliflozin 300 mg, and 1 patient with noncanagliflozin).

pected, in both the canagliflozin and placebo groups, the fracture incidence was higher in women than in men and in patients with a prior fracture history than in those with no fracture history. However, none of the subgroup analyses showed a statistically significant increase in fracture risk with canagliflozin, and no single subgroup drove the increase in fracture risk (ie, none of the interaction *P* values were <.1).

In the overall population, the proportion of patients with fracture AEs was higher in the canagliflozin groups (100 and 300 mg combined) vs the noncanagliflozin groups (2.7% vs 1.9%, respectively), with the same incidence in the canagliflozin 100 and 300 mg groups (2.7%) (Figure 1 and Table 2). Fractures were primarily localized to the lower limbs (1.1% and 1.0% with pooled canagliflozin and noncanagliflozin, respectively) and upper limbs (1.1% and 0.7%, respectively), with a similar incidence in the canagliflozin 100 and 300 mg groups at both locations (Supplemental Table 7). The incidence of fractures was increased with canagliflozin vs noncanagliflozin across subgroups based on sex, age, duration of T2DM, baseline eGFR, and prior fracture history (Supplemental Figure 3). As in CANVAS, none of the subgroup analyses showed a statistically significant increase in fracture risk with canagliflozin, and no single subgroup drove the increased fracture risk observed in the overall population.

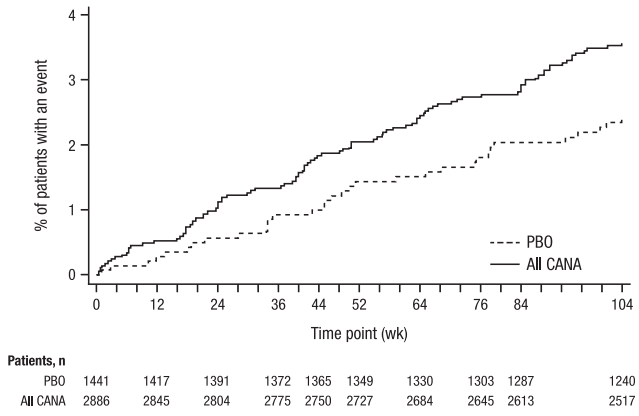

Figure 2. Kaplan-Meier plot of time to first adjudicated fracture AE in CANVAS. HR (95% CI) for all CANA vs PBO = 1.51 (1.04–2.19). PBO, placebo; CANA, canagliflozin.

Assessment of falls

The frequency of reported falls was low. The incidence of AEs related to reported falls in the pooled non-CANVAS studies was 1.2%, 1.3%, and 1.1% with canagliflozin 100 and 300 mg and noncanagliflozin, respectively; HRs (95% CIs) with canagliflozin 100 and 300 mg vs noncanagliflozin were 0.84 (0.46, 1.54) and 1.13 (0.65, 1.96), respectively. In CANVAS, the incidence of AEs related to reported falls with canagliflozin 100 and 300 mg and placebo was 1.9%, 3.3%, and 1.5%, respectively;

Table 3. Summary of Adjudicated Fracture AEs by Anatomical Region (CANVAS)

	Placebo (n = 1441)	CANA 100 mg (n = 1445)	CANA 300 mg (n = 1441)	All CANA (n = 2886)
Upper limb fracture	16 (1.1)	24 (1.7)	22 (1.5)	46 (1.6)
Clavicle	1 (0.1)	0	2 (0.1)	2 (0.1)
Hand	5 (0.3)	9 (0.6)	7 (0.5)	16 (0.6)
Humerus	2 (0.1)	3 (0.2)	7 (0.5)	10 (0.3)
Radius	1 (0.1)	1 (0.1)	3 (0.2)	4 (0.1)
Ulna	0	2 (0.1)	0	2 (0.1)
Wrist	7 (0.5)	10 (0.7)	3 (0.2)	13 (0.5)
Incidence rate (/1000 patient-years)	4.6	6.8	6.2	6.5
Incidence rate (/100 patient-years)	0.46	0.68	0.62	0.65
HR vs all non-CANA (95% CI)		1.47 (0.78–2.77)	1.36 (0.71–2.59)	1.42 (0.80–2.50)
Lower limb fracture	17 (1.2)	22 (1.5)	26 (1.8)	48 (1.7)
Calcaneus	2 (0.1)	0	0	0
Ankle	5 (0.3)	5 (0.3)	10 (0.7)	15 (0.5)
Femur	0	1 (0.1)	1 (0.1)	2 (0.1)
Fibula	0	1 (0.1)	1 (0.1)	2 (0.1)
Foot	5 (0.3)	9 (0.6)	10 (0.7)	19 (0.7)
Hip	3 (0.2)	3 (0.2)	3 (0.2)	6 (0.2)
Patella	2 (0.1)	2 (0.1)	0	2 (0.1)
Tibia	2 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Incidence rate (/1000 patient-years)	4.9	6.2	7.4	6.8
Incidence rate (/100 patient-years)	0.49	0.62	0.74	0.68
HR vs all non-CANA (95% CI)		1.34 (0.71–2.56)	1.54 (0.82–2.88)	1.44 (0.82–2.54)
Pelvis fracture	2 (0.1)	1 (0.1)	0	1 (<0.1)
Incidence rate (/1000 patient-years)	0.6	0.3	0	0.1
Incidence rate (/100 patient-years)	0.06	0.03	0	0.01
HR vs all non-CANA (95% CI)		0.48 (0.04–5.32)	NA	0.24 (0.02–2.68)
Skull or facial bone fracture	0	0	3 (0.2)	3 (0.1)
Incidence rate (/1000 patient-years)	0	0	0.8	0.4
Incidence rate (/100 patient-years)	0	0	0.08	0.04
HR vs all non-CANA (95% CI)		NA	NA	NA
Spine fracture	1 (0.1)	4 (0.3)	2 (0.1)	6 (0.2)
Cervical	0	0	1 (0.1)	1 (<0.1)
Lumbar	0	2 (0.1)	0	2 (0.1)
Thoracic	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Incidence rate (/1000 patient-years)	0.3	1.1	0.6	0.8
Incidence rate (/100 patient-years)	0.03	0.11	0.06	0.08
HR vs all non-CANA (95% CI)		3.93 (0.44–35.16)	1.97 (0.18–21.76)	2.95 (0.36–24.53)
Thoracic cage fracture	3 (0.2)	7 (0.5)	7 (0.5)	14 (0.5)
Scapula	1 (0.1)	0	0	0
Incidence rate (/1000 patient-years)	0.9	2.0	2.0	2.0
Incidence rate (/100 patient-years)	0.09	0.20	0.20	0.20
HR vs all non-CANA (95% CI)		2.29 (0.59–8.86)	2.30 (0.59–8.89)	2.30 (0.66–7.99)

Abbreviations: CANA, canagliflozin; NA, not assessed. Data are n (%) unless otherwise indicated.

HRs (95% CI) with canagliflozin 100 and 300 mg vs placebo were 1.24 (0.71–2.17) and 2.12 (1.28–3.51), respectively. The incidence of AEs related to reported falls in the overall population was 1.5%, 2.1%, and 1.3%, with canagliflozin 100 and 300 mg and noncanagliflozin, respectively; HRs (95% CI) with canagliflozin 100 and 300 mg vs noncanagliflozin were 1.03 (0.69–1.55) and 1.60 (1.11–2.32), respectively.

Assessment of volume depletion–related AEs

An increase in volume depletion–related AEs was seen with canagliflozin 100 and 300 mg and noncanagliflozin in the non-CANVAS studies (2.6%, 3.1%, and 2.0%, respectively); HRs (95% CI) with canagliflozin 100 and 300 mg vs noncanagliflozin were 1.13 (0.74–1.73) and 1.45 (0.98–2.13), respectively. A larger dose-related increase in the incidence of volume depletion–related AEs was seen in CANVAS with canagliflozin 100 and 300 mg and placebo (5.3%, 6.9%, and 3.9%, respectively); HRs (95% CI) with canagliflozin 100 and 300 mg vs placebo were 1.32 (0.94–1.87) and 1.76 (1.27–2.44), respectively. The onset of volume depletion–related AEs was earlier with canagliflozin 300 mg in CANVAS (Supplemental Figure 4). It is important to note that no AEs of volume depletion (including syncope and presyncope) were reported in patients just before or within 30 days of experiencing fracture AEs.

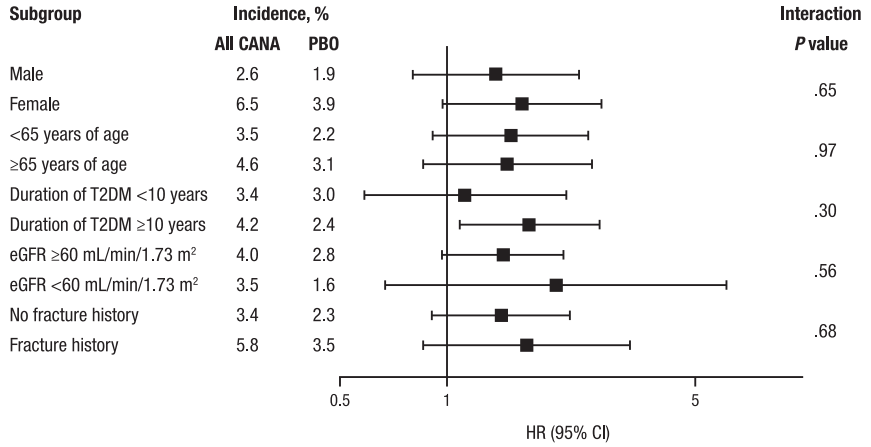

Figure 3. HRs (95% CIs) for canagliflozin 100 and 300 mg vs placebo in the incidence of fracture AEs by subgroup (CANVAS). CANA, canagliflozin; PBO, placebo.

Discussion

Overall, the incidence of fracture AEs was higher with canagliflozin vs noncanagliflozin in the broad population of patients with T2DM exposed to longer-term treatment. This increased fracture risk with canagliflozin was driven by the fracture AEs in CANVAS starting within the first few weeks after study drug initiation, with a continued rate of increase thereafter; however, no increase in fractures was observed in the pooled non-CANVAS studies over 52 weeks. In CANVAS, patients treated with canagliflozin had about 6 additional cases of fracture per 1000 patient-years compared to those of patients receiving placebo. The reason for the increased incidence of fractures with canagliflozin in 1 population of patients but not in another is unknown at this time and may be due to chance or may possibly be related to factors extrinsic to bone health, as described below. Additional data beyond 1 year of treatment exposure exist for the non-CANVAS population. In the 2 studies of 2 years' duration in the non-CANVAS population, an increased risk of fracture was not seen; however, the number of patients in this dataset was small.

As reported in a separate article in this issue, a study assessing the effects of canagliflozin on bone health found a small but statistically significant decrease in total hip BMD of unknown clinical significance, but no statistically significant change in BMD at other sites (ie, femoral neck, lumbar spine, and distal forearm) with canagliflozin over 104 weeks (19). The results of that study, in addition to the findings reported here, including the early onset of fractures and the increase in fractures observed only in a subset of the total phase 3 patient population with an elevated CV disease risk who were older and had lower eGFR and greater use of diuretics (CANVAS), suggest that the higher incidence of fractures may not be related to a direct effect of canagliflozin on bone health but rather to an external factor(s). Furthermore, SGLT2 is not found in bone or bone marrow (30), suggesting that a direct effect of canagliflozin on bone via SGLT2 inhibition is unlikely. In previous 12-week studies, canagliflozin was not associated with any meaningful changes in most biomarkers, including serum and urine calcium, serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and PTH, providing further evidence that canagliflozin does not directly affect bone health (7, 31). However, modest increases in β-CTX were seen with canagliflozin vs placebo in these studies, which may be related to body weight reduction with canagliflozin treatment (7, 31). In the study assessing bone health over 104 weeks (19), there were significant changes in β-CTX, estradiol, and osteocalcin at week 52; however, these biomarkers were not assessed in the CANVAS population in which the increase in fractures was observed and the exposure duration is longer. It is not known whether biomarkers in CANVAS would show a pattern similar to that of shorter-term studies. Small increases in serum phosphate have been observed with canagliflozin vs placebo in the CANVAS population (data on file). An analysis of postrandomization percent changes from baseline in the serum phosphate level revealed no differences in canagliflozin-treated patients with or without fractures (data on file). This finding suggests that there is no association between canagliflozin-associated serum phosphate increases and bone fractures.

The incidence of AEs related to reported falls was low across treatment groups in the pooled non-CANVAS studies, in CANVAS, and in the overall population. It is important to note that reports of fall-related AEs were spontaneous and not actively collected; consequently, fall AEs were almost certainly underreported (32–34). A dose-related increase in volume depletion–related AEs was seen with canagliflozin, and volume depletion–related AEs occurred earlier with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo in CANVAS. Although volume depletion secondary to osmotic diuresis may increase the susceptibility to falls (35), and thus early fractures could be related to falls due to volume depletion AEs (eg, postural dizziness, orthostatic hypotension, and syncope) associated with canagliflozin treatment, it is not certain whether this occurred in the current analysis because data on falls were not systematically collected. An increase in fall-related fractures cannot be ruled out as a possible explanation for the increased fracture risk in the CANVAS population, as described below. A study of the SGLT2

inhibitor, dapagliflozin, showed an increased risk of fractures in patients with moderate renal impairment, a population in which dapagliflozin is not indicated (36); most patients in the dapagliflozin study who sustained a fracture also had higher rates of diabetic neuropathy and orthostatic hypotension. Thus, these patients may have been predisposed to falls (37). Consistent with this, a greater proportion of patients in CANVAS, who were at greater risk of fractures, had baseline microvascular complications (44%) than patients in the pooled non-CANVAS studies (25%). Furthermore, having a baseline eGFR of <60 mL/min/1.73 m^2 was found to be a risk factor for volume depletion–related AEs with canagliflozin, which may lead to falls (38). Canagliflozin is associated with an initial decrease in eGFR that stabilizes over time, consistent with the hemodynamic effects of canagliflozin treatment. The early decrease in renal function is not likely to be related to fracture risk as there was no significant difference in fracture risk among patients in CANVAS with baseline eGFR of <60 mL/min/1.73 m^2 vs those with baseline eGFR of ≥ 60 mL/min/1.73 m^2. Furthermore, canagliflozin was not associated with an increase in fractures in a separate study of patients with baseline eGFR of ≥ 30 and <50 mL/min/1.73 m^2 (26). Dapagliflozin, like canagliflozin, does not appear to be associated with increased fracture risk in the general population of patients with T2DM (37). Fracture data from long-term studies of other SGLT2 inhibitors in patients with increased CV risk are not yet available, so it is not clear whether the increase in fractures observed in this patient population is specific to canagliflozin or characteristic of all SGLT2 inhibitors.

Other studies associated hypertension and antihypertensive therapy with increased fracture risk. An observational study in patients ≥ 50 years of age showed an increased risk of hip fractures shortly after initiation of loop or thiazide diuretic therapy (39). A separate observational study showed a 43% increased risk of hip fractures in elderly patients immediately after beginning an antihypertensive treatment (35). Another study evaluating patients with T2DM being treated for hypertension reported contrasting results, however, and found that BP lowering was not associated with increased risk of falls or fractures (40). That study has some limitations, including a possible bias in the collection of fall data as it was not originally designed to assess fall or fracture risk, and the trial was not blinded to treatment assignment. Thus, the mechanism of BP lowering with canagliflozin treatment may provide a plausible potential explanation for the early increase in fall-related fractures in CANVAS.

One limitation of our current study is that the population was not specifically represented by high fracture risk patients (eg, patients with low BMD or prior fractures); therefore, fracture rates across the phase 3 program were modest and typical for a population with T2DM, but the study was not powered to detect significant differences across treatment arms. Another limitation was the post hoc analysis of data; multiple comparisons could increase the potential for false-positive results. The analysis included both placebo- and active-controlled studies, which complicates the analysis, although the active-controlled studies contributed a relatively small number of patients to the overall population and the active comparators included in these studies (glimepiride and sitagliptin) are not associated with increased risk of fracture. In addition, spine images were not routinely obtained to detect vertebral compression fractures that may not have been clinically apparent. The effects of canagliflozin on fractures continue to be monitored in ongoing studies, including CANVAS and a study to examine renal endpoints in patients with a history or risk of CV disease (CANVAS-R; ClinicalTrials.gov registration number NCT01989754), and in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; ClinicalTrials.gov registration number NCT02065791), a trial to assess whether canagliflozin reduces progression of diabetic nephropathy. Given that the current analysis was based on interim data from the ongoing CANVAS study, longer-term data will provide more definitive conclusions regarding fracture risk with canagliflozin treatment and will add to the understanding of the effects of canagliflozin on bone health.

In conclusion, canagliflozin was associated with an increased risk of fractures, primarily in the upper and lower extremities, that was driven by a significantly higher fracture rate in patients with elevated CV disease risk (CANVAS); patients in the pooled non-CANVAS studies did not have an increase in fractures with canagliflozin treatment. Although the cause of the increased fracture risk with canagliflozin is unknown, the small, inconsistent changes in total hip BMD (but not femoral neck, lumbar spine, or distal forearm BMD) observed with canagliflozin over 104 weeks and the fact that an early increase in fractures was observed in only a subgroup of patients treated with canagliflozin suggest that extrinsic factors related to canagliflozin, possibly related to falls or other indirect effects of canagliflozin on bone strength, may be a more likely explanation for this observed imbalance.

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