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Clinical Research Article

Canagliflozin and Metabolic Associated Fatty Liver Disease in Patients With Diabetes Mellitus: New Insights From CANVAS

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Abstract

Context: Metabolic dysfunction–associated fatty liver disease (MAFLD) is highly prevalent among patients with type 2 diabetes mellitus (T2DM); however, there is still no approved pharmacological treatment. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have been suggested to beneficially modify liver-related outcomes in patients with diabetes.

Objective: We aimed to investigate the effects of the SGLT-2 inhibitor canagliflozin on liver-related outcomes in patients with advanced T2DM and high cardiovascular risk.

Methods: We performed a secondary post hoc analysis of 2 large double-blind randomized controlled trials, CANVAS (NCT01032629) and CANVAS-R (NCT01989754), which included patients with T2DM and high cardiovascular risk who were randomized to receive either canagliflozin or placebo once daily. The primary endpoint was a composite of improvement of alanine aminotransferase (ALT) levels >30% or normalization of ALT levels. Secondary endpoints included change in noninvasive tests of fibrosis and weight reduction of >10%.

Results: In total, 10 131 patients were included, with a median follow-up of 2.4 years (mean age 62 years; mean duration of diabetes 13.5 years; 64.2% male). Of those patients, 8967 (88.5%) had MAFLD according to hepatic steatosis index and 2599 (25.7%) exhibited elevated liver biochemistry at baseline. The primary composite endpoint occurred in 35.2% of patients receiving canagliflozin and in 26.4% with placebo (adjusted odds ratio [*a*OR] 1.51; 95% CI, 1.38-1.64; $P < .001$). Canagliflozin led to improvements in some noninvasive tests of fibrosis (NFS, APRI, FNI). Significant weight reduction of >10% (within 6 years) was achieved in 12.7% with canagliflozin compared to 4.1% with placebo (*a*OR 3.45; 95% CI, 2.91-4.10; $P < .001$).

Conclusion: In patients with T2DM, treatment with canagliflozin vs placebo resulted in improvements in liver biochemistry and metabolism and might beneficially affect liver fibrosis.

Key Words: SGLT-2 inhibitor, nonalcoholic fatty liver disease, metabolic associated fatty liver disease, diabetes, alanine aminotransferase, noninvasive tests of fibrosis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST to Platelet Ratio Index; BMI, body mass index; FIB-4, Fibrosis-4; FNI, Fibrotic NASH Index; HbA1c, glycated hemoglobin; MAFLD, metabolic associated fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD Fibrosis Score; OR, odds ratio; SGLT-2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

Metabolic associated fatty liver disease (MAFLD) is highly prevalent among patients with type 2 diabetes mellitus (T2DM) (1) and it has been shown that patients with T2DM are at high risk of progression to steatohepatitis (NASH), higher stages of fibrosis, and eventually cirrhosis (2). With the global obesity pandemic, MAFLD has evolved to the leading cause of chronic liver disease at a global scale (3) and is rapidly becoming a leading cause for end-stage liver disease and consequently for liver transplantation (4). However, evidence suggests that MAFLD not only increases the risk for liver-related morbidity and mortality (5), but also for cardiovascular disease (6) and chronic kidney disease (7). Despite an increasing burden of disease, no pharmacotherapy has yet been approved (8). The current cornerstones of therapy focus on lifestyle interventions to encourage weight loss and treatment of coexisting metabolic conditions (9, 10).

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are modern antidiabetic drugs that increase urinary glucose excretion and thereby lead to improved glycemia, reduced blood pressure and body weight (11, 12) as well as improved

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cardiovascular and renal outcomes (13). In addition, in early preliminary experimental and clinical studies, they have been shown to reduce oxidative stress, systemic and tissue low-grade inflammation (14), and to reduce fatty liver content (15, 16). Due to these multifaceted effects, SGLT-2 inhibitors have been proposed as promising novel treatment for MAFLD; however, individual high-quality data from large randomized controlled trials are still scarce.

In this secondary analysis of 2 large randomized controlled outcome trials, we aimed at investigating the effects of the SGLT-2 inhibitor canagliflozin on liver-related outcomes in patients with advanced T2DM and high cardiovascular risk.

Methods

Study Design and Participants

This is a secondary analysis of 2 randomized, placebo-controlled, double-blind, multicenter trials: CANVAS (NCT01032629) and CANVAS-R (NCT01989754) involving patients with T2DM and high cardiovascular risk. Full details of the trial designs and results have been published previously (11). In brief, adult patients from 667 centers in 30 countries worldwide with T2DM (glycated hemoglobin level, ≥ 7.0% and ≤10.5%) and age ≥30 years with a history of symptomatic atherosclerotic cardiovascular disease, or age ≥50 years with at least 2 risk factors for cardiovascular disease, were randomized to either receive canagliflozin or placebo once daily in addition to their established antidiabetic treatment, respectively. In the CANVAS trial programs, alcohol consumption was not defined as exclusion criterion; therefore, we used the new nomenclature "metabolic dysfunction–associated fatty liver disease" (MAFLD) which includes all patients with evidence of fatty liver disease in addition to one of the following 3 features: overweight/obesity, T2DM, or metabolic dysregulation irrespective of other underlying chronic liver diseases.

All participants provided written informed consent. The conduct of the trials adhered to the Declaration of Helsinki and Good Clinical Practice Guidelines (17), and ethical committees of all participating hospitals approved the studies before patient recruitment. The studies were designed and conducted by the sponsor in collaboration with the principal investigators. The sponsor collected the data and monitored study conduct.

Procedures

Eligible patients underwent a 2-week, open-label, placebo run-in period in which background glucose-lowering therapy was unchanged. Participants in the CANVAS trial were randomly assigned to receive canagliflozin at a dose of 100 mg or 300 mg, or to receive matching placebo (1:1:1 ratio). Participants in the CANVAS-R trial were randomly assigned to receive canagliflozin at a dose of 100 mg, with an optional increase to 300 mg from week 13, or to receive matching placebo (1:1 ratio). Follow-up visits, including clinical examination and blood tests, were performed in 3 visits during the first year (week 13, 26, and 52) and at 6-month intervals thereafter.

Outcomes

The primary objectives of CANVAS and CANVAS-R were to evaluate the effects of canagliflozin treatment on cardiovascular and renal endpoints. In this secondary post hoc analysis, the primary aim was to evaluate liver-related outcomes. The primary endpoint was a composite of the proportion of patients achieving a clinically significant reduction in alanine aminotransferase (ALT) levels or achieving ALT normalization (ALT ≤30 IU/L). A reduction in ALT levels of more than 30% was deemed clinically significant (18). Secondary endpoints included clinically significant reduction of ALT levels, ALT normalization, and proportion of patients with progression to severe fibrosis or cirrhosis (F3 or F4) according to validated noninvasive fibrosis scoring systems (19): NAFLD Fibrosis Score (NFS) (20), Fibrosis-4 (Fib-4) (21), AST to Platelet Ratio Index (APRI) (22), and Fibrotic NASH Index (FNI) (23). In addition, we assessed the proportion of patients with reduction in body weight of more than 5% or 10%, respectively; as well as the proportion of patients achieving optimal glycemic control (glycated hemoglobin [HbA1c] < 7.0%), and good blood pressure control (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg).

Statistical Analysis

Descriptive statistics were used to summarize differences in demographic and baseline characteristics among study groups. Baseline demographics were stratified according to presence of MAFLD as assessed by the hepatic steatosis index (24, 25). The used cutoff (hepatic steatosis index >36) has previously been validated in patients with T2DM as compared with steatosis detection via ultrasound (26). Continuous variables were given as mean ± SD, and categorical variables as numbers (percentage). For comparative analyses, data from both canagliflozin dose groups (100 and 300 mg) were pooled. For the main outcome measures, crude and multivariable adjusted estimates of the effect size and corresponding 95% CI were determined using linear or logistic regression, as appropriate. All multivariable models were adjusted for the same variables: randomized treatment, age, gender, race, body mass index (BMI), smoking status, hypertension, hyperlipidemia, heart failure, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, coronary heart disease, peripheral artery disease, cerebrovascular disease, chronic kidney disease, hepatopathy, and liver steatosis. For analyses on the secondary endpoint ALT normalization, patients with ALT ≤30 IU/L were excluded.

All tests were two-sided, $P < .05$ was considered significant with two-sided 95% CI. All statistical analyses were performed using STATA version 15.1 (StataCorp, College Station, TX, USA).

Results

Patient Characteristics

This study integrates data from 2 trials (CANVAS and CANVAS-R) involving a total of 10 142 participants with T2DM and high cardiovascular risk. Liver-related parameters were available for 10 131 patients (99.9% of all included patients; canagliflozin, n = 5787; placebo, n = 4344). Baseline characteristics stratified by the existence of MAFLD are shown in Table 1 and by treatment in Supplementary Table S1 (27). Participants had a mean age of 62 years, 35.8% were female, and the mean duration of diabetes was 13.5 years. The median follow-up was 2.4 years (126.1 weeks). Most patients were obese (6048; 59.7%) with a mean BMI among participants of 32 kg/m^2 and a mean HbA1c of 8.2%.

Table 1. Baseline characteristics of included patients

	Total N = 10 131	MAFLD unlikely N = 1164	MAFLD N = 8967	*P* value
General characteristics				
Age, years	62 (8.0)	64 (9.0)	61 (8.0)	<.001
Sex				
Female	3631 (35.8%)	270 (23.2%)	3361 (37.5%)	<.001
Male	6500 (64.2%)	894 (76.8%)	5606 (62.5%)	
Race/ethnicity				
White	7933 (78.3%)	618 (53.1%)	7315 (81.6%)	<.001
Asian	1284 (12.7%)	405 (34.8%)	879 (9.8%)	
Black	336 (3.3%)	36 (3.1%)	300 (3.3%)	
Other	578 (5.7%)	105 (9.0%)	473 (5.3%)	
Body weight kg	90.2 (20.2)	67.5 (10.5)	93.1 (19.3)	<.001
Body mass index				
Underweight (BMI 15-19.9)	39 (0.4%)	39 (3.4%)	0 (0.0%)	<.001
Normal weight (BMI 20-24.9)	901 (8.9%)	681 (58.5%)	220 (2.5%)	
Overweight (BMI 25-29.9)	3143 (31.0%)	442 (38.0%)	2701 (30.1%)	
Obesity class I (BMI 30-34.9)	3332 (32.9%)	2 (0.2%)	3330 (37.1%)	
Obesity class II (BMI 35-39.9)	1773 (17.5%)	0 (0.0%)	1773 (19.8%)	
Obesity class III (BMI ≥40)	943 (9.3%)	0 (0.0%)	943 (10.5%)	
Systolic blood pressure, mmHg	137 (15.8)	134 (16.5)	137 (15.6)	<.001
Diastolic blood pressure, mmHg	78 (9.7)	76 (9.4)	78 (9.7)	<.001
Smoker	1804 (17.8%)	248 (21.3%)	1556 (17.4%)	<.001
Comorbidities (%)				
Hypertension	9105 (89.9%)	967 (83.1%)	8138 (90.8%)	<.001
Hyperlipidemia	7046 (69.5%)	712 (61.2%)	6334 (70.6%)	<.001
Heart failure	1430 (14.1%)	112 (9.6%)	1318 (14.7%)	<.001
Diabetic nephropathy	1958 (19.3%)	224 (19.2%)	1734 (19.3%)	.94
Diabetic neuropathy	2802 (27.7%)	279 (24.0%)	2523 (28.1%)	.003
Diabetic retinopathy	91 (0.9%)	5 (0.4%)	86 (1.0%)	.07
Coronary heart disease	1221 (12.1%)	122 (10.5%)	1099 (12.3%)	.08
Peripheral artery disease	1457 (14.4%)	166 (14.3%)	1291 (14.4%)	.90
Cerebrovascular disease	1444 (14.3%)	162 (13.9%)	1282 (14.3%)	.73
Chronic kidney disease	288 (2.8%)	36 (3.1%)	252 (2.8%)	.59
Hepatopathy	28 (0.3%)	6 (0.5%)	22 (0.2%)	.099
Steatosis	731 (7.2%)	45 (3.9%)	686 (7.7%)	<.001
Laboratory values				
HbA1c, %	8.2 (0.9)	8.2 (0.9)	8.3 (0.9)	<.001
Triglycerides, mmol/L	2.0 (1.4)	1.6 (1.3)	2.1 (1.4)	<.001
LDL cholesterol, mmol/L	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	.74
HDL cholesterol, mmol/L	1.2 (0.3)	1.2 (0.4)	1.2 (0.3)	<.001
eGFR, mL/min/1.73 m^2	76 (20.0)	76 (22.0)	77 (20.0)	.13
ALT, IU/L	26 (14.0)	19 (13.0)	27 (14.0)	<.001
AST, IU/L	23 (11.0)	22 (18.0)	23 (10.0)	.03
GGT, IU/L	38 (44.0)	30 (48.0)	39 (42.9)	<.001
ALP, IU/L	77 (25.0)	77 (26.0)	77 (25.0)	.99
Bilirubin, μmol/L	9 (4.0)	9 (4.0)	9 (4.0)	.002
Albumin, g/L	41.4 (3.1)	41.6 (3.5)	41.3 (3.1)	.02
Noninvasive scores (%)				
NFS				
Advanced fibrosis (≥F3)	2265 (22.4%)	143 (12.3%)	2122 (23.7%)	<.001
Indeterminate	6436 (63.5%)	739 (63.5%)	5697 (63.5%)	.98

(*continued*)

Table 1. Continued

	Total N = 10 131	MAFLD unlikely N = 1164	MAFLD N = 8967	*P* value
No advanced fibrosis (<F3)	1430 (14.1%)	282 (24.2%)	1148 (12.8%)	<.001
FIB-4				
Advanced fibrosis (≥F3)	273 (2.7%)	58 (5.0%)	215 (2.4%)	<.001
Indeterminate	3362 (33.2%)	509 (43.7%)	2853 (31.8%)	<.001
No advanced fibrosis (<F3)	6496 (64.1%)	597 (51.3%)	5899 (65.8%)	<.001
APRI				
Cirrhosis (F4)	47 (0.5%)	9 (0.8%)	38 (0.4%)	.099
Indeterminate	1273 (12.6%)	109 (9.4%)	1164 (13.0%)	<.001
No cirrhosis (<F4)	8811 (87.0%)	1046 (89.9%)	7765 (86.6%)	.002
FNI				
Fibrosis	4470 (44.1%)	402 (34.5%)	4068 (45.4%)	<.001
Indeterminate	4868 (48.1%)	624 (53.6%)	4244 (47.3%)	<.001
No fibrosis	793 (7.8%)	138 (11.9%)	655 (7.3%)	<.001

Data are presented as n (%) or mean (SD). MAFLD was diagnosed using hepatic steatosis index >36. Rule-in cutoffs for advanced fibrosis: NFS >0.675, FIB-4 > 2.67, FNI >0.33, and for cirrhosis APRI >1.5. Rule-out cutoffs for advanced fibrosis: NFS < −1.455, FIB-4 < 1.3, FNI <0.1, and for cirrhosis APRI <0.5. Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio; AST, aspartate aminotransferase; FIB-4, Fibrosis-4; FNI, Fibrotic NASH Index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic associated fatty liver disease; NFS, NAFLD Fibrosis Score.

The majority of patients (n = 8967; 88.5%) had MAFLD according to the hepatic steatosis index; however, at baseline merely 7.2% of patients were known to have liver steatosis and 0.3% had a previous diagnosis of unspecified hepatopathy. Among those with MAFLD, the proportions of patients from White ethnic background was significantly higher (81.6% vs 53.1%, $P < .001$), while patients with Asian ethnicity were significantly less represented (9.8% vs 34.8%, $P < .001$). While HbA1c values were almost identical (8.3% vs 8.2%), patients with MAFLD had higher blood pressure values and were more frequently diagnosed with hypertension, hyperlipidemia, and heart failure (Table 1).

Association of Baseline Characteristics With Impaired ALT Levels

In total, 2599 patients (25.7%) presented with ALT levels >30 IU/L. ALT levels were negatively correlated with age, with highest values in patients aged <50 years (29.6 IU/L, SD 15.4) and lowest among patients aged >70 years (21.2 IU/L, SD 10.0) (Supplementary Table S2 (27)). When compared with female patients, male sex was associated with higher ALT levels at baseline (between-group difference 3.5 IU/L; 95% CI, 2.95 to 4.07; $P < .001$). Among ethnicities, Black patients had the lowest ALT levels (21.3 IU/L, SD 11.8), while highest levels were seen in White patients (26.0 IU/L, SD 14.1) (between-group difference −4.4 IU/L; 95% CI, −5.84 to −2.87; $P < .001$). There was a correlation of ALT concentration and BMI, with the highest values among patients with BMI >35 kg/m^2. Patients with known liver steatosis had higher ALT levels when compared to those without steatosis (between-group difference 3.9 IU/L; 95% CI, 2.90 to 4.96; $P < .001$). In the small fraction of patients with prior diagnosis of hepatopathy, ALT levels were at mean 12.2 IU/L higher when compared to patients without the diagnosis (95% CI, 7.27 to 17.18; $P < .001$).

Primary and Secondary Endpoints

In patients receiving canagliflozin, a rapid and sustained reduction in ALT and AST levels was observed, while in patients receiving placebo liver biochemistry remained unchanged (Fig. 1). The primary composite endpoint of clinically significant improvement or normalization in ALT was reached by a higher proportion of patients receiving canagliflozin (2037/5787; 35.2%) compared with placebo (1146/4344; 26.4%), resulting in an adjusted odds ratio (*a*OR) of 1.51 (95% CI, 1.38 to 1.64; $P < .001$) (Fig. 2A and Table 2). The secondary endpoint of improvement in ALT levels by more than 30% was reached by 31.7% of patients receiving canagliflozin, compared to 22.3% with placebo (*a*OR 1.61; 95% CI, 1.47 to 1.76; $P < .001$; Fig. 2B). Normalization of initially elevated ALT levels was achieved in 69.5% of patients with canagliflozin vs 57.5% of patients randomized to placebo (*a*OR 1.71; 95% CI, 1.44 to 2.03; $P < .001$; Fig. 2C). Within 6 years after randomization, a reduction in body weight by more than 5% but less than 10% was achieved by 38.8% in the canagliflozin group vs 16.3% in the placebo group (*a*OR 3.24; 95% CI, 2.94 to 3.58; $P < .001$). Likewise, a significantly larger proportion of patients receiving canagliflozin (12.7%) achieved weight loss of more than 10%, compared with 4.1% of patients receiving placebo (*a*OR 3.45; 95% CI, 2.91 to 4.10; $P < .001$) (Fig. 2D). Higher proportions of patients receiving canagliflozin vs placebo (34.0% vs 17.7%) achieved optimal glycemic control of HbA1c < 7.0% (*a*OR 2.51; 95% CI, 2.27 to 2.78; $P < .001$) as well as good blood pressure control (34.2% vs 24.6%) (*a*OR 1.64; 95% CI, 1.49 to 1.81; $P < .001$) (Table 2).

Noninvasive Tests of Fibrosis

At baseline, advanced fibrosis (stage ≥F3) could be ruled out in 14.1% of patients according to NFS. In contrast, according to FIB-4, advanced fibrosis could be ruled out in the majority of patients (64.1%) (Table 1). Treatment with canagliflozin vs

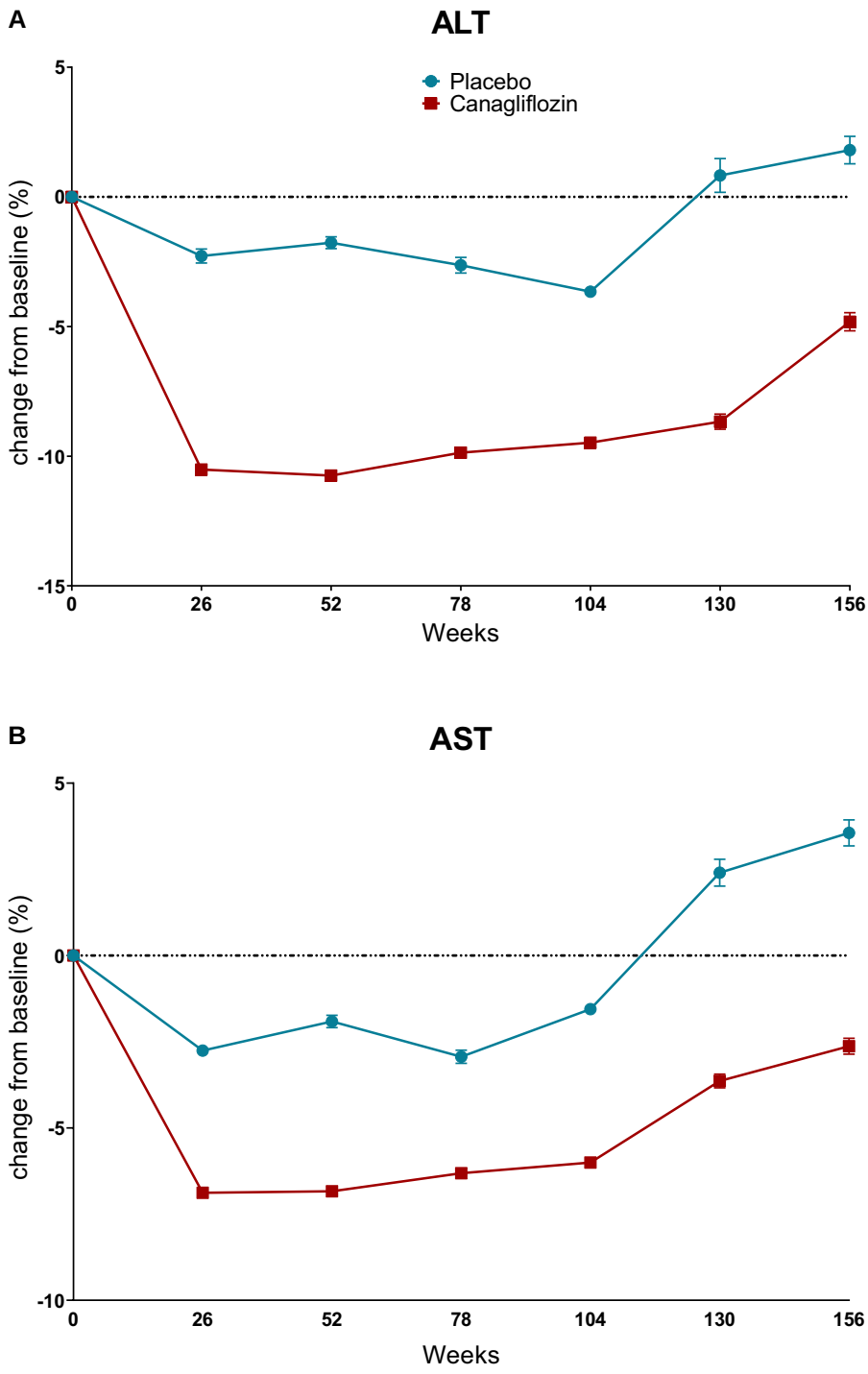

Figure 1. Effects of canagliflozin on liver function tests over time. Temporal dynamics of liver biochemistry: alanine aminotransferase, ALT (A) and aspartate aminotransferase, AST (B) in patients randomized to canagliflozin or placebo.

placebo led to significant reductions in absolute NFS values both at 1 year (between-group difference −0.049; 95% CI, −.077 to −.022; $P < .001$), and at 3 years after randomization (between-group difference −0.062; 95% CI, −.116 to −.008; $P = .002$) (Table 3). However, this did not result in a reduction of the proportion of patients categorized as having advanced fibrosis (Supplementary Fig. S1 (27)). Absolute values of FIB-4 scores were mostly unchanged over time in both groups without differences between the treatment groups (Table 3 and Supplementary Fig. S1 (27)). According to baseline APRI scores, 0.5% of patients were categorized with suspected cirrhosis. Treatment with canagliflozin vs placebo led to a significant reduction in absolute APRI values at 1 year (between-group difference −0.016; 95% CI, −.025 to −.007; $P = .001$), but not at 3 years after randomization (Table 3). According to the novel noninvasive score FNI, 44.1% of patients were ruled in to have fibrosis and 7.8% were ruled out (Table 1). Canagliflozin led to a significant reduction in absolute FNI scores at 1 year (between-group difference −0.082; 95% CI, −.089 to −.075; $P < .001$) and 3 years (between-group difference −0.054; 95% CI, −.067 to −.041; $P < .001$) (Table 3).

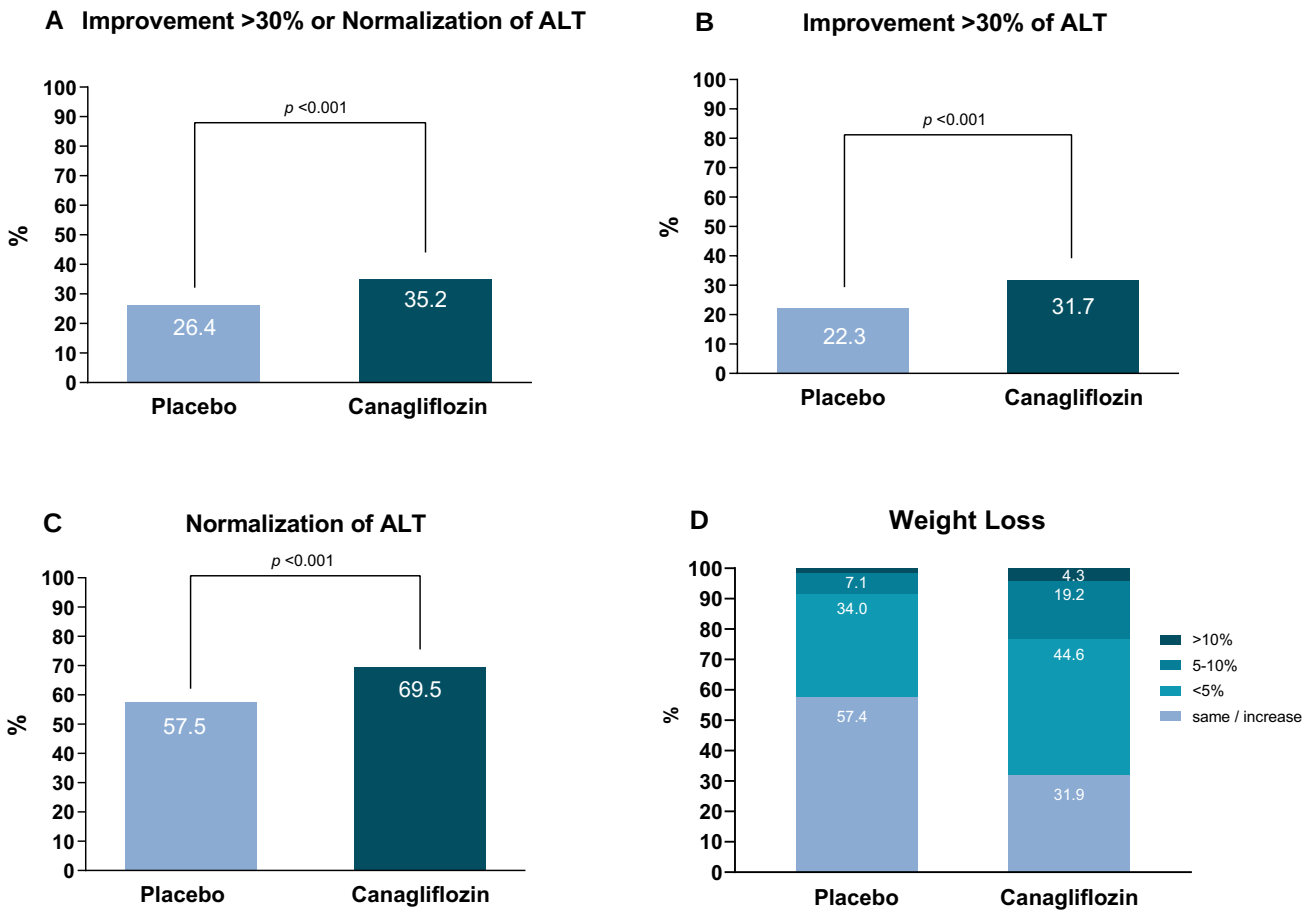

Figure 2. Primary and secondary outcomes. Endpoints up to 312 weeks after randomization are shown. The results of the combined primary endpoint show a significant superiority of canagliflozin compared with placebo (Panel A). Results on secondary endpoints show superiority of canagliflozin on improvement of ALT >30% (Panel B) and normalization of ALT (Panel C). Panel D shows weight loss achieved with canagliflozin compared with placebo at 1 year after randomization.

Differences in Effects Among Subgroups

All observed effects were broadly consistent across a wide range of prespecified subgroups (Supplementary Fig. S2 (27)). There was a significant difference in efficacy on the primary composite endpoint according to race, with less pronounced effects among patients from White ethnic background ($P_{\text{for heterogeneity}} = .001$). Furthermore, treatment effects with canagliflozin on the primary composite endpoint were more pronounced among patients without peripheral artery disease when compared to patients with that diagnosis. Secondary analyses according to improvement in HbA1c of 0.5% or more vs less than 0.5% at 1 year using an interaction term did not reveal any evidence of significant between-group difference ($P_{\text{for interaction}} > .05$). Likewise, subgroup analyses on body weight change (more than 5% vs less than 5% weight change at 1 year) did not reveal a subgroup difference ($P_{\text{for interaction}} > .05$).

Discussion

This is a secondary analysis of 2 large randomized, double-blind, placebo-controlled trials including more than ten thousand patients with long-standing diabetes and high cardiovascular risk. In this metabolically ill population, most patients had concomitant MAFLD and up to one-fifth were suspected to have advanced fibrosis. Treatment with the SGLT-2 inhibitor canagliflozin vs placebo in addition to the established antidiabetic regimen led to (i) significant weight reduction with improved blood pressure and glycemic control; (ii) a rapid and sustained improvement of liver biochemistry, which seemed to be independent from improvements in glycemic control or body weight; and (iii) reduced absolute scores in noninvasive tests of liver fibrosis.

This is the largest clinical trial, so far, investigating the effects of an SGLT-2 inhibitor on MAFLD in individuals with T2DM. Patients with long-standing T2DM and multiple cardiovascular risk factors are known to be at highest risk for the development of NASH (28, 29), of advanced stages of fibrosis (30), and to encounter adverse liver-related outcomes (31). These patients are characterized by high insulin resistance and chronic low-grade systemic inflammation, both of which are central pathophysiological mechanisms in the development of MAFLD-related adverse outcomes (32). Observational data suggest that, in patients with T2DM, the prevalence of MAFLD is approximately 67% (33). In our study population with a mean duration of diabetes of more than 10 years, the prevalence of MAFLD—estimated by hepatic steatosis index—was even higher at almost 90%, comparable with high prevalence previously described in morbidly obese patients (34). In contrast, elevated liver transaminases were found in around one-quarter of patients, underscoring the notion that altered liver biochemistry tests alone do not

Table 2. Effects of canagliflozin on primary and secondary outcomes

	Placebo (n = 4344)	Canagliflozin (n = 5787)	Crude odds ratio (95% CI)	*P* value	Multivariable adjusted odds ratio (95% CI)	*P* value
Primary endpoint						
Clinically significant improvement of ALT or ALT normalization	1146 (26.4)	2037 (35.2)	1.52 (1.40–1.65)	<.001	1.51 (1.38–1.64)	<.001
Secondary endpoints						
Clinically significant improvement of ALT	968 (22.3)	1834 (31.7)	1.62 (1.48–1.77)	<.001	1.61 (1.47–1.76)	<.001
ALT normalization	584 (57.5)	1002 (69.5)	1.69 (1.43–2.00)	<.001	1.71 (1.44–2.03)	<.001
Weight reduction >5%	710 (16.3)	2243 (38.8)	3.24 (2.94–3.57)	<.001	3.24 (2.94–3.58)	<.001
Weight reduction >10%	176 (4.1)	735 (12.7)	3.45 (2.91–4.08)	<.001	3.45 (2.91–4.10)	<.001
Good blood pressure control	1068 (24.6)	1980 (34.2)	1.60 (1.46–1.74)	<.001	1.64 (1.49–1.81)	<.001
Good glycemic control	732 (17.7)	1869 (34.0)	2.40 (2.18–2.64)	<.001	2.51 (2.27–2.78)	<.001

Clinically significant improvement of ALT was defined as a reduction from baseline by more than 30%. Normalization of ALT was defined as a reduction from baseline to under 30 IU/L (patients with ALT ≤ 30 IU/L at baseline were excluded). Good blood pressure control was defined as blood pressure control below 140/90 mmHg. Good glycemic control was defined as reduction of HbA1c below 7.0% target. Abbreviation: ALT, alanine aminotransferase.

Table 3. Effects of canagliflozin on noninvasive tests of fibrosis

	Baseline	1 year	Change from baseline to 1 year (95% CI)	*P* value	3 years	Change from baseline to 3 years (95% CI)	*P* value
NFS							
Placebo	−0.187 (1.17)	−0.151 (1.18)	.052 (−.967, 1.109)		−0.267 (1.21)	.097 (−1.074, 1.141)	
Canagliflozin	−0.262 (1.18)	−0.257 (1.18)	.012 (−1.034, 1.025)		−0.371 (1.17)	.047 (−1.064, 1.192)	
Between-group difference	–	–	−.049 (−.077, −.022)	<.001	–	−.062 (−.116, −.008)	.002
FIB-4							
Placebo	1.262 (0.63)	1.262 (0.70)	.008 (−.536, .569)		1.249 (0.61)	.040 (−.562, .559)	
Canagliflozin	1.243 (0.78)	1.247 (0.59)	.009 (−.537, .551)		1.231 (0.62)	.060 (−.500, .599)	
Between-group difference	–	–	−.004 (−.024, 0.017)	.74	–	.009 (−.025, .044)	.60
APRI							
Placebo	0.339 (0.22)	0.336 (0.27)	−.002 (−.202, 0.202)		0.352 (0.28)	.012 (−.206, .250)	
Canagliflozin	0.343 (0.49)	0.322 (0.19)	−.022 (−.240, .167)		0.333 (0.22)	.004 (−.207, .207)	
Between-group difference	–	–	−.016 (−.025, −.007)	.001	–	−.011 (−.027, .005)	.17
FNI							
Placebo	0.346 (0.21)	0.325 (0.22)	−.019 (−.319, .291)		0.325 (0.22)	−.025 (−.348, .334)	
Canagliflozin	0.351 (0.21)	0.248 (0.18)	−.103 (−.421, .167)		0.272 (0.19)	−.080 (−.404, .211)	
Between-group difference	–	–	−.082 (−.089, −.075)	<.001	–	−.054 (−.067, −.041)	<.001

Abbreviations: APRI, AST to Platelet Ratio Index; FIB-4, Fibrosis-4; FNI, Fibrotic NASH Index; NFS, NAFLD Fibrosis Score.

qualify as diagnostic screening test for MAFLD. Of note, in CANVAS and CANVAS-R < 1% of patients had a prior diagnosis of liver disease at baseline. Hence, our data bring to light the huge diagnostic gap in patients with diabetes, who still do not routinely undergo screening for hepatic steatosis or stiffness in most health care systems (35), often resulting in late diagnosis of MAFLD at higher fibrosis stages or eventually at the stage of cirrhosis, when treatment strategies become more complex and longer lasting (36).

There is increasing evidence in favor of therapeutic value of SGLT-2 inhibitors as well as glucagon-like peptide 1 (GLP-1) agonists in MAFLD (37); however, most studies have the limitation of rather small sample sizes and/or short study durations (38). In line with previous small observational studies (39), we observed that treatment with canagliflozin vs placebo led to a rapid and sustained reduction of liver transaminases—even in patients with "normal" ALT levels at baseline. Serum transaminases have been shown to correlate with the risk of fibrosis progression, therefore sustained reduction or normalization can be considered a clinically meaningful endpoint (40). Indeed, previous studies with paired biopsies observed that, besides improvements in HbA1c, ALT normalization was one of the strongest predictors of fibrosis improvement compared with other biomarkers (41).

In our study, treatment with canagliflozin furthermore was associated with significantly improved body weight and glycemic and blood pressure control. In total, 23.5% of patients achieved a significant weight reduction of more than 5% total body weight and 4.3% even achieved more than 10% body weight reduction within 1 year of treatment.

In our study, the diagnostic performance of established noninvasive tests of fibrosis was highly heterogeneous. In

fact, according to NFS and FNI, the majority of patients would have to undergo further assessment of MAFLD severity, since these tests ruled out fibrosis only in a small proportion of patients. However, this was not the case with the FIB-4 score. This heterogeneity among noninvasive tests has been shown in previous studies involving patients with T2DM, in whom such tests seem to have poor diagnostic discrimination and often lead to unspecific and heterogenous results even with age-adjusted cutoffs (42). Recently, the use of sequential assessments using noninvasive tests has gained clinical relevance, since the large REGENERATE study has demonstrated that changes in noninvasive tests over time strongly correlated with histological changes of liver fibrosis (18). We observed statistically significant but rather small changes in NFS, APRI, and FNI scores at 1 and 3 years of treatment with canagliflozin when compared with placebo. In contrast to data also indicating an effect on FIB-4 scores (37), in our study FIB-4 remained largely stable.

These observations in noninvasive scores are in line with recent studies examining effects of SGLT-2 inhibitors on liver histology. In a small observational study investigating the effects of a 1-year treatment with canagliflozin in patients with T2DM, some histopathological improvements in markers of inflammation and fibrosis were observed in 6 out of 7 patients (43). A larger, 48-week, randomized, open-label, parallel-group trial involving patients with T2DM and biopsy-proven NAFLD (n = 40) confirmed significant improvements in both inflammation and fibrosis upon treatment with tofogliflozin. Most interestingly, gene expression profiling of liver tissue was performed, revealing that tofogliflozin effectively altered hepatic expression of genes involved in energy metabolism, inflammation, and fibrosis. In this study tofogliflozin was compared to glimepiride, which led to similar improvements of blood sugar control but without most of the effects on liver histology or gene expression, indicating that there may be direct effects on hepatocytes that go beyond glycemic control (44). Indeed, our results suggest that improvements in liver biochemistry were independent from glycemic control or body weight reduction, strengthening the hypothesis of possible direct effects of SGLT-2 inhibitors on the liver that need to be further explored in mechanistic studies.

SGLT-2 inhibitors have been shown to promote fasting-like metabolic changes, increasing fatty acid oxidation and ketone body formation via FGF21-dependent and -independent mechanisms (45). Multisystem effects of SGLT-2 inhibitors with their beneficial effects in heart failure and chronic kidney disease make them highly interesting since MAFLD is more and more seen as a multisystem disorder. NASH is increasingly considered an independent cardiovascular risk factor (46) and cardiovascular disease remains the most common cause of death in these patients (47). Furthermore, higher rates of chronic kidney disease are increasingly diagnosed in patients with MAFLD (7, 48). Given the paucity of large intervention studies assessing the effects of these novel glucose-lowering drugs on liver-related outcomes, our results should pave the ground for more studies in patients with NASH and/or MAFLD. This is especially relevant since it has been shown that the type of antidiabetic treatment may affect MAFLD-associated adverse events, such as the risk for the development of hepatocellular cancer (49).

Our findings should be interpreted in light of some limitations. The CANVAS and CANVAS-R trials were originally designed to investigate cardiovascular and renal outcomes in patients with T2DM and high cardiovascular risk (11). Therefore, the results should be seen as exploratory efficacy analyses. Second, although in previous studies improvements in noninvasive parameters have been associated with histologic response (18), future studies with paired liver biopsy are warranted to confirm and extend our results. Third, since only a small fraction of patients mirrored advanced fibrosis, possible antifibrotic effects were strongly underpowered and may be underestimated. Fourth, the CANVAS trials included diabetics only, therefore it remains unclear how MAFLD patients without diabetes would respond to canagliflozin. Finally, differences in the prevalence of MAFLD may be attributed to varying diagnostic accuracy of hepatic steatosis index across ethnicities (50). Strengths of the study include the randomized, placebo-controlled design, the well-characterized, large patient population with patients at high risk for MAFLD. Moreover, the median follow-up of more than 2 years is likely sufficient to capture meaningful changes in metabolism and fibrosis.

Conclusion

Our data demonstrate that SGLT-2 inhibitors are not only highly beneficial in the treatment of diabetes, heart failure, and chronic kidney disease, but also highly promising in the treatment of MAFLD. In addition to the known metabolic effects on glycemia and body weight, treatment with canagliflozin vs placebo significantly improved liver biochemistry and reduced scores of noninvasive tests of fibrosis independent from improvements in glycemic control or body weight. Given the established cardiovascular and renal benefits in patients with T2DM, SGLT-2 inhibitors could prove to be suitable and cost-effective pharmaceutical agents in the treatment of patients with MAFLD. Future studies are needed to investigate the evolution of liver histology upon SGLT-2 inhibitor treatment in both diabetic and nondiabetic patients.

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Author Contributions

A.B., E.R.C., and F.E. designed the study. A.B. and F.E. analyzed the data and were responsible for the decision to submit the manuscript. All authors provided substantial comments on drafts and approved the final report.

Disclosures

A.N.B., E.R.C., and M.H.H. have nothing to declare. F.E. has previously consulted for Boehringer Ingelheim. A.K. received an educational grant from Novo Nordisk.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Clinical Trial Information

ClinicalTrials.gov identification nos. NCT01032629 (CANVAS) and NCT01989754 (CANVAS-R)

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