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Review

Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: A common comorbidity associated with severe complications

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ABSTRACT

Patients with type 2 diabetes mellitus (T2DM) are exposed to non-alcoholic fatty liver disease (NAFLD), a comorbidity associated with cardiovascular disease and chronic kidney disease, and which may progress to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. Sodium–glucose cotransporter type-2 (SGLT2) inhibitors are glucose-lowering agents that improve glucose control while promoting weight loss and lowering serum uric acid levels. These agents may exert cardiovascular and renal protection in T2DM patients with established cardiovascular disease. Recent findings from both randomized controlled trials and open-label studies have also shown that SGLT2 inhibitors are able to reduce fatty liver content, as assessed by different imaging techniques, and improve biological markers of NAFLD, especially serum liver enzymes, in patients with T2DM. In addition, there are emerging data to suggest a mechanism beyond the reduction of hyperglycaemia and body weight, and a potential role for the decrease in low-grade inflammation and oxidative stress associated with SGLT2 inhibitor therapy. This positive effect of SGLT2 inhibitors on NAFLD complements their already well-known effects on cardiovascular and chronic kidney diseases.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common finding in obese people with insulin resistance, especially patients with type 2 diabetes mellitus (T2DM) [1]. It can also progress to non-alcoholic steatohepatitis (NASH) and, ultimately, fibrosis and cirrhosis, which means that prevention is becoming a crucial challenge [2,3]. Because of the current epidemics of both obesity and T2DM, the prevalence of NAFLD is likely to increase, thereby potentially resulting in tremendous clinical and social economic burdens [4]. Moreover, recent data have shown that NAFLD is not only confined to liver-related morbidity and mortality, but should also be considered a multisystemic disease [5]. Indeed, it is now recognized that NAFLD increases the risks of both cardiovascular disease (CVD) and chronic kidney disease (CKD) [5,6], while the role of low-grade inflammation appears crucial in all three comorbidities, a finding that may be targeted by some glucose-lowering agents [7]. Oxidative stress is also considered an important factor in producing the lethal hepatocyte injury associated with NAFLD [8]. According to recent evidence, sodium–glucose cotransporter type-2 (SGLT2) inhibitors can reduce systemic and tissue low-grade inflammation [9], and improve oxidative stress by either amelioration of free-radical generation or potentiation of cellular antioxidative capacity [10].

The current guidelines are consistent with key elements in the management of NAFLD, yet still reflect significant differences on certain critical points [11]. There is still no approved pharmacotherapy for patients with NAFLD and NASH [2], although numerous pharmacological strategies have been evaluated in clinical studies or are currently in development [3,12]. Data on the effects of antidiabetic medications in NAFLD and NASH are limited and sometimes conflicting [13–15]. Non-significant effects have been reported with insulin, metformin, sulphonylureas and dipeptidyl peptidase (DPP)-4 inhibitors, whereas positive effects have been demonstrated with thiazolidinediones and glucagon-like peptide (GLP)-1 receptor agonists [13–15]. SGLT2 inhibitors have shown some efficacy in early preliminary experimental and clinical studies focused on NAFLD [12,13,16] and, considering their positive impact on cardiovascular events [17] and renal outcomes [18], they also occupy an increasing role in the management of T2DM [19]. In this context, their effects on NAFLD have raised growing interest and certainly call for further investigation.

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The present narrative review aims to analyze the available data demonstrating the possible positive effects of SGLT2 inhibitors on NAFLD as determined by either imaging techniques to assess liver fat content and fibrosis or by biological markers of liver steatosis.

Methods

To identify relevant studies, an extensive literature search of MEDLINE and EMBASE was performed from January 2014 to December 2018, using the terms 'SGLT2 inhibitor' or 'gliflozin' combined with 'fatty liver' or 'NAFLD' or 'NASH'. A further search was performed using the generic names of the SGLT2 inhibitors commercially available worldwide or in Japan, specifically, 'canagliflozin', 'dapagliflozin', 'empagliflozin', 'ertugliflozin', 'ipragliflozin', 'luseogliflozin' and 'tofogliflozin'. No language restrictions were imposed. Reference lists of original studies, narrative reviews, previous systematic reviews and meta-analyses were also carefully examined.

Two types of populations were analyzed: patients with poorly controlled T2DM (but not screened for NAFLD) who had participated in large randomized controlled trials (RCTs); and patients with T2DM who had been selected specifically because of the presence of NAFLD. The latter diagnosis was made by the detection of either significant steatosis, using imaging techniques [ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI)] [20–24], or significantly elevated levels of serum liver enzymes [alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)] [24,25] or, more rarely, liver biopsy [26].

The T2DM patients had participated in RCTs in which liver function was generally analyzed as a secondary endpoint in post-hoc analyses [27–29], but also as a primary endpoint in more recent trials [22,23]. Some data were also derived from open, non-controlled studies mostly performed in Asia. The effects of SGLT2 inhibitors on NAFLD were investigated with the three compounds commercially available in the US and most European countries, namely, canagliflozin, dapagliflozin and empagliflozin, although numerous studies have also been performed with SGLT2 inhibitors marketed in Japan, namely, ipragliflozin, luseogliflozin and tofogliflozin. These studies compared the effects of SGLT2 inhibitors *vs* either placebo or other glucose-lowering agents (active controls) on NAFLD markers; the latter comparisons allow the detection of effects on NAFLD independently of improved glucose control.

Non-invasive tests are now widely used in routine clinical practice to assess steatosis and fibrosis, and have been included in national and international guidelines [30]. Available studies with SGLT2 inhibitors have also used different complementary approaches to assess both the presence and severity of NAFLD [2,31]. Almost all of them used clinical chemistry and serum liver enzymes (ALT, AST, GGT) as indirect markers of steatosis. A fatty liver index may also be used to identify patients with hepatic steatosis: while it cannot accurately predict liver fat content [32], it has nevertheless been used in some studies with SGLT2 inhibitors [33,34]. Additionally, an index of fibrosis severity (FIB-4), derived from biological and clinical measurements [35], has been used in different RCTs to assess the efficacy of SGLT2 inhibitors on liver function [20,21,24,36].

Interestingly, some studies have added imaging techniques to assess hepatic fat content. Changes in liver fat can be measured using the MRI-derived proton density fat fraction (MRI-PDFF), a robust and quantitative biomarker of hepatic steatosis corresponding to intracellular fat accumulation in hepatocytes [22,23]. This technique is considered the most appropriate non-invasive endpoint for steatosis reduction in clinical trials and assessments of therapy response [37]. Alternatively, CT scans have been performed to assess the liver/spleen attenuation ratio as an indirect marker of NAFLD (the lower the ratio, the higher the degree of NAFLD) [38] in some trials focused on SGLT2 inhibitors [20,21], while other studies have used transient elastography (FibroScan®) [24], a technique that assesses liver fat and fibrosis using non-invasive measurements of liver stiffness and controlled attenuation parameters [30,39,40].

However, liver biopsy is still considered the gold-standard method, as it provides the most detailed pictures of NAFLD, NASH and fibrosis [2,31], although it is increasingly being replaced by non-invasive tests in clinical practice [30]. Indeed, only one pilot study has used liver biopsy to evaluate the effects of an SGLT2 inhibitor on NAFLD/NASH [41].

Results

Imaging techniques: changes in liver fat content

MRI-PDFF was used in two recent RCTs and two open-label studies carried out in T2DM patients with NAFLD. Dapagliflozin 10 mg as monotherapy reduced liver fat content by 13% compared with a placebo after 12 weeks [22] (Table 1), whereas combined treatment with dapagliflozin plus omega-3 (*n*-3) carboxylic acids further reduced liver fat content (−21% with combined therapy vs. −13% with dapagliflozin monotherapy) [22]. In the Effect of Empagliflozin on Liver Fat Content in Patients with Type 2 Diabetes (E-LIFT) open-label study [23], T2DM patients with NAFLD were randomly assigned to either empagliflozin 10 mg added to standard treatment for T2DM or standard treatment without empagliflozin (control group). Empagliflozin was significantly more potent in reducing liver fat (MRI-PDFF mean difference between empagliflozin and control groups at 20 weeks: −4.0%; $P < 0.0001$; Table 1) [23].

Similar results were reported in a single-arm pilot study to assess the effects of canagliflozin in patients with both T2DM and NAFLD. Hepatic fat fraction was reduced by 32% from baseline after 6 months, a significant reduction that was maintained at 12 months ($P < 0.0005$ and $P < 0.005$, respectively; Table 1) [42]. Comparable findings were observed with luseogliflozin in an open-label trial that showed a reduction in hepatic fat content of 27% after 24 weeks of therapy [43] (Table 2).

Another indirect marker of a decreased liver fat content can be derived from a significant increase in the liver/spleen attenuation ratio assessed by CT. A greater change was observed with an SGLT2 inhibitor in a 24-week RCT comparing dapagliflozin with other glucose-lowering agents [36] (Table 1)). In two other head-to-head studies, SGLT2 inhibitors were compared with metformin on the one hand, and with pioglitazone on the other. After 6 months, luseogliflozin 2.5 mg showed a greater decrease in liver fat content compared with metformin 1500 mg daily, which was associated with no significant improvement [21]. In addition, in the luseogliflozin group, a significant correlation was observed between changes in liver fat content and reduced serum ALT levels [21]. Interestingly, ipragliflozin 50 mg was associated with a significant improvement in liver fat content of a similar amplitude as with pioglitazone 15–30 mg/day after 24 weeks [20] (Table 2). In addition, in the ipragliflozin group, a significant correlation was also observed between changes in liver/spleen ratio as a marker of steatosis (together with ALT and GGT) and body weight, whereas no such correlation was seen in the pioglitazone group [20].

In all studies, some weight loss and, when body composition was assessed, decreases in fat mass and visceral adipose tissue were noted in patients treated with SGLT2 inhibitors compared with those receiving other antidiabetic agents [20–22,24,27].

Table 1
Effects of the three sodium–glucose cotransporter-2 (SGLT2) inhibitors available in Europe and the US vs. placebo (or no treatment in non-controlled open studies) on liver enzymes and liver fat content in patients with type 2 diabetes.

References	Patients	Duration (weeks)	Treatment	n	HbA_{1c} (%)	Body weight (kg)	ALT (U/L)	AST (U/L)	GGT (U/L)	FIB-4 index	MRI-PDFF (liver content)
Randomized controlled trials											
Eriksson et al. 2018 [22]	NAFLD	12	Dapagliflozin 10 mg	19	7.38→6.75 $P < 0.05$	90.3→87.9 $P < 0.05$	67→53 $P < 0.05$	52→45 $P < 0.05$	97→89 $P < 0.05$	NA	17.3→15.1 $P < 0.05$
			Placebo	19	7.44→7.35 P = NS	92.9→92.6 P = NS	57→54 P = NA	49→47 P = NA	54→50 P = NA	NA	15.1→14.5 NS
Kuchay et al. 2018 [23]	NAFLD	20	Empagliflozin 10 mg	22	9.0→7.2 $P < 0.001$	80.8→77.5 P = 0.001	64.3→49.7 P = 0.001	44.6→36.2 P = 0.040	65.8→50.9 P = 0.002	NA	16.2→11.3 $P < 0.0001$
			Placebo (+ adjusted OADs)[a]	20	9.1→7.1 $P < 0.0001$	81.1→79.5 P = 0.022	65.3→61.6 P = NA	45.3→44.6 P = NA	63.9→60.0 P = NA	NA	16.4→15.5 P = 0.054
Sattar et al. 2018 [28]	All (four RCTs)	24	Empagliflozin 10 or 25 mg	1652	NA	NA	28.2→23.6 $P < 0.0001$	23.0→21.0 $P < 0.0001$	NA	NA	NA
			Placebo	825	NA	NA	28.4→27.0 P = NA	23.1→22.5 P = NA	NA	NA	NA
Sattar et al. 2018 [28]	All (ERO)	164	Empagliflozin 10 or 25 mg	4611	8.07→≈7.65 P = NA	86.6→≈84.6 P = NA	25.5→22.5 P = 0.004	22.5→21.3 P = 0.107	NA	NA	NA
			Placebo	2313	8.08→≈8.10 P = NA	86.2→≈85.7 P = NA	26.2→24.4 P = NA	22.9→22.4 P = NA	NA	NA	NA
Leiter et al. 2016 [29]	All (four RCTs)	26	Canagliflozin 100 mg	833	8.00→7.15 $P < 0.001$	89.7→87.2 $P < 0.001$	27.8→24.2 P = NA	23.0→21.5 P = NA	37.5→33.6 P = NA	NA	NA
			Canagliflozin 300 mg	834	8.00→6.94 $P < 0.001$	88.5→85.4 $P < 0.001$	28.6→23.4 P = NA	23.7→21.2 P = NA	39.5→32.5 P = NA	NA	NA
			Placebo	646	8.00→7.87 P = NA	89.2→88.7 P = NA	27.6→27.4 P = NA	22.9→23.3 P = NA	38.8→41.8 P = NA	NA	NA
Open non-controlled studies											
Tobita et al. 2017 [26]	NASH[b]	24	Dapagliflozin 5 mg	16	7.4→6.8 $P < 0.01$	79.6→75.8 $P < 0.01$	59→30 $P < 0.01$	52→26 $P < 0.01$	64→33 $P < 0.01$	NA	NA
Inoue et al. 2018 [42]	NAFLD	52	Canagliflozin 100 mg	20	8.7→7.7 P = 0.0051	83.6→80.7 P = 0.0007	80.0→59.0 P = 0.009	52→43 P = 0.017	132→92 P = 0.0008	1.20→1.15 P = 0.24	17.6→12.1 P = 0.0013
Itani et al. 2018 [46]	NAFLD	26	Canagliflozin 100 mg	35	7.45→6.36 $P < 0.05$	73.3→69.6 $P < 0.05$	74.2→40.4 $P < 0.05$	45.5→28.6 $P < 0.05$	80.6→56.2 $P < 0.05$	1.42→1.23 $P < 0.05$	NA
Lee et al. 2018 [51]	All	26	Dapagliflozin/empagliflozin	69/46	8.56→7.55 $P < 0.001$	81.1→79.5 $P < 0.001$	40.3→29.0 $P < 0.001$	28.2→23.1 $P < 0.001$	NA	NA	NA

Results are expressed as changes before→after treatment.
ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; FIB-4: Fibrosis-4 (liver); MRI-PDFF: proton density fat fraction on magnetic resonance imaging; NAFLD: non-alcoholic fatty liver disease; NA: not available; NS: not significant; OADs: oral antidiabetic drugs; RCTs: randomized controlled trials; NASH: non-alcoholic steatohepatitis; ERO: BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME).
[a] Adjusted to maintain glycaemic equipoise in both treatment groups so that changes in glycaemic parameters had no effect on liver fat.
[b] Confirmed by percutaneous liver biopsy.

Table 2
Effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors available in Japan vs other oral glucose-lowering agents as controls (or no add-on treatment in non-controlled open studies) on liver enzymes and indicators of fatty liver content and fibrosis in patients with type 2 diabetes.

References	Patients	Duratin (weeks)	Treatment	*n*	HbA_{1c} (%)	Body weight (kg)	ALT (U/L)	AST (U/L)	GGT (U/L)	FIB-4 index	CT (liver/ spleen ratio)
Randomized controlled trials											
Ito et al. 2017 [20]	NAFLD	24	Ipragliflozin 50 mg	30	8.52→7.57 $P < 0.05$	79.6→76.7 $P < 0.05$	57.4→38.2 $P < 0.05$	39.7→27.3 $P < 0.05$	62.8→44.0 $P < 0.05$	2.12→1.61 $P < 0.05$	0.78→0.98 $P < 0.05$
			Pioglitazone 15–30 mg	31	8.28→7.07 $P < 0.05$	76.7→77.6 $P \leq 0.05$	53.1→36.8 $P < 0.05$	43.3→32.4 $P < 0.05$	71.6→48.8 $P < 0.05$	2.06→1.70 $P < 0.05$	0.72→0.94 $P < 0.05$
Shibuya et al. 2018 [21]	NAFLD	26	Luseogliflozin 2.5 mg	16	7.8→6.5 $P = 0.002$	74.0→71.6 $P = 0.002$	49.5→31.0 P = NA	NA	NA	NA	0.907→1.033 $P = 0.0008$
			Metformin 1500 mg	16	7.4→7.3 $P = 0.36$	72.7→72.8 $P = 0.65$	39.0→39.0 P = NA	NA	NA	NA	0.991→0.851 $P = 0.017$
Open non-controlled studies											
Takase et al. 2017 [33]	All	16	Ipragliflozin 50 mg	21	7.7→7.3 $P = 0.0052$	77.3→74.5 $P < 0.0001$	45.3→37.4 $P = 0.0063$	35.5→32.6 $P = 0.2952$	63.1→49.4 $P = 0.0537$	NA	NA
Ohta et al. 2017 [47]	All	24	Ipragliflozin 50 mg	20	8.2→6.9 $P < 0.001$	82.2→78.7 $P < 0.001$	52.5→29.0 $P < 0.001$	36.9→22.4 $P < 0.001$	NA	NA	IHL: 29.0→17.7 $P < 0.001$
Miyake et al. 2018 [48]	NAFLD (biopsy)	24	Ipragliflozin 50 mg	12	7.65→7.20 $P = 0.003$	67.8→66.4 $P < 0.001$	68.5→36.5 $P = 0.016$	74.0→39.5 $P = 0.003$	64.0→31.0 $P = 0.011$	NA	NA
Miyake et al. 2018 [48]	NAFLD (echo-graphy)	24	Ipragliflozin 50 mg	31	8.0→6.9 $P < 0.001$	82.0→80.6 $P < 0.001$	55.0→36.5 $P = 0.016$	34.5→24.0 $P = 0.003$	43.5→29.0 $P = 0.141$	NA	NA
Tabuchi et al. 2018 [34]	All	12	Ipragliflozin 50 mg	8633	8.11→7.40 $P < 0.05$[a]	78.6→76.3 $P < 0.05$[a]	38.6→32.7 $P < 0.05$	30.4→27.0 $P < 0.05$	59.4→50.1 $P < 0.05$	NA	NA
Tabuchi et al. 2018 [34]	NALFD	12	Ipragliflozin 50 mg	3239			53.9→43.3 $P < 0.05$	39.0→32.5 $P < 0.05$	75.6→60.9 $P < 0.05$	NA	NA
Ohki et al. 2016 [49]	NAFLD	48	Ipragliflozin 50 mg	24	8.4→7.6 $P < 0.01$	84.8→81.7 $P < 0.01$	62→38 $P < 0.01$	37→28 $P = 0.03$	75→60 $P = 0.03$	1.75→1.39 $P = 0.04$	NA
Sumida et al. 2019 [43]	NAFLD	24	Luseogliflozin 2.5 mg	40	7.29→7.00 $P = 0.002$	75.6→74.2 $P < 0.001$	54.7→42.4 $P < 0.001$	40.7→31.9 $P < 0.001$	62.4→48.2 $P = 0.003$	1.63→1.52 $P = 0.17$	MRI-HFF: 21.5→15.7 $P < 0.001$
Kusunoki et al. 2016 [25]	No NAFLD	24	Luseogliflozin 2.5 mg	54	6.9→6.9 P = NS	77.6→75.7 $P <$ 0.01	20→20 P = NA	19→19 P = NA	26→26 P = NA	NA	NA
	NAFLD			25	7.2→6.8 P = NS	83.7→81.7 $P < 0.01$	53→35 P = NA	42→30 P = NA	89→69 P = NA	NA	NA
Matsuba et al. 2018 [50]	All	12	Luseogliflozin 2.5 mg	14	8.24→7.19 $P < 0.001$	Δ: −2.87 $P < 0.001$	31.4→22.9 $P < 0.05$	23.4→20.4 P = NS	56.1→30.1 $P < 0.05$	NA	NA

Results are expressed as changes before→after treatment.
ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; FIB-4: fibrosis-4; CT: computed tomography; NAFLD: non-alcoholic fatty liver disease; NA: not available; IHL: intrahepatic lipid (assessed by proton magnetic resonance spectroscopy); MRI-HFF: hepatic fat fraction on magnetic resonance imaging; NS: not significant.
Δ: difference between end of study vs. baseline.
[a] Pooled data in Nakamura et al. 2018 cited by Tabuchi et al. 2018 [34].

Clinical chemistry: changes in serum liver enzymes

Numerous studies have used changes in serum liver enzymes (ALT, AST and sometimes GGT) as indirect markers of improved hepatic function with SGLT2 inhibitors in patients with T2DM with or without NAFLD at baseline. Compared with a placebo, positive results were reported with empagliflozin [23,28], dapagliflozin [22] and canagliflozin [29] (Table 3). In post-hoc analyses of large-scale phase-III RCTs, small yet significant reductions in serum liver enzymes were observed with SGLT2 inhibitors in non-selected patients with T2DM insufficiently controlled with their baseline therapies [28,29]. Of note, these enzyme reductions were more marked in T2DM patients specifically selected for having NAFLD, although these more recent RCTs were smaller in scale [22,23]. However, no imaging assessment of liver fat content was performed in the large placebo-controlled studies [28,29] whereas the two recent RCTs used MRI-PDFF measurements [22,23]. As already discussed, the main advantage of such dedicated trials is that they combine measurements of serum liver enzymes with measurements of liver fat content [22,23] (Table 1). Changes in the latter correlated significantly with changes in the former (GGT: $r = 0.53$, $P = 0.02$) [22].

Compared with metformin [20], glimepiride [27,28] and DPP-4 inhibitors [29], SGLT2 inhibitors (luseogliflozin, canagliflozin, empagliflozin) were associated with significant reductions in serum liver enzyme levels (mainly ALT) despite similar glucose control (Table 2 and Table 3). These results were confirmed in two studies comparing dapagliflozin with other glucose-lowering medications [24,36] (Table 3). Also, in a recent meta-analysis of 11 RCTs comparing canagliflozin with either placebo or an active control in a total of 6745 T2DM patients, canagliflozin 100 mg and 300 mg significantly ($P < 0.001$) decreased ALT (weighted mean difference: −11.7, 95% CI: −14.4, -8.9), AST (-7.5, 95% CI: −10.6, −4.4) and GGT (−15.2, 95% CI: −17.7, −12.6) after 26 and 52 weeks, with slightly greater reductions observed with canagliflozin 300 mg than with 100 mg, suggesting a dose–response effect [44]. Moreover, analyses of pooled data from four 26-week, placebo-controlled studies of canagliflozin 100 mg and 300 mg [29] (Table 1) and two 52-week, active-controlled studies of canagliflozin 300 mg *vs* sitagliptin 100 mg [29] (Table 3) revealed that canagliflozin produced improvements in liver function tests *vs* either placebo or sitagliptin treatment. According to the authors, these differential effects were fully explained by the combined effects of reductions in HbA_{1c} and body weight with canagliflozin [29].

In one retrospective open study, dapagliflozin resulted in significantly greater decreases in ALT and AST compared with either sitagliptin or linagliptin [45] (Table 3). Similar findings were reported when comparing the effects of empagliflozin on ALT and AST changes in studies where placebo (Table 1) or glimepiride (Table 3) were the controls [28]. Compared with pioglitazone, a compound with proven efficacy for reducing liver fat content in patients with T2DM and NAFLD [2,31], ipragliflozin exerted similar beneficial effects on glycaemic control and NAFLD biological markers in patients with T2DM complicated by NAFLD [20] (Table 2). Reductions in serum liver enzymes were also reported in a number of open-label studies from Japan with canagliflozin, ipragliflozin and luseogliflozin [25,26,33,34,42,43,46–50] and from China with dapagliflozin and empagliflozin [51] (Table 1 and Table 2).

Such reductions may appear relatively small, albeit statistically significant, when considering the entire T2DM population. However, many of the T2DM patients included in studies not specifically dedicated to NAFLD had normal serum enzyme levels at baseline, a population in which almost no reduction in such enzymes could be detected [25]. When the population was divided into tertiles according to baseline levels of ALT or AST, the decreases in serum liver enzymes observed with empagliflozin were consistently greater in the upper tertile subgroup [28]. Similarly, in a large cohort of Japanese T2DM patients, reductions in ALT, AST and GGT levels were more marked when the results were analyzed separately in patients with elevated serum liver enzyme levels at baseline and compared with levels in the overall population [34] (Table 2).

Effects on composite indices of fatty liver and liver fibrosis

Two open studies of ipragliflozin showed that adding an SGLT2 inhibitor to standard glucose-lowering agents was able to significantly reduce fatty liver indices after 12–16 weeks of therapy from 70.1 to 60.3 ($P = 0.0009$) [33] and from 63.3 to 56.7 ($P < 0.05$) [34]. Using the FIB-4 index, a validated marker of liver fibrosis, several studies found no significant effects compared with baseline or other glucose-lowering agents [24,29]. Nevertheless, one study demonstrated a significant reduction in FIB-4 index with ipragliflozin at 24 weeks, similar to that observed with pioglitazone [20]. On the other hand, two open studies of canagliflozin reported divergent results without [42] and with [46] a significant reduction in FIB-4 after a follow-up of 52 weeks and 26 weeks, respectively. Open studies from Japan of luseogliflozin have reported mixed results with numerical but non-significant reductions in FIB-4 after 24 weeks [43], but significant decreases with ipragliflozin after 48 weeks [49]. The reasons for such discrepancies are unclear, although the patients' clinical characteristics and durations of follow-up may have varied from study to study.

Liver fibrosis assessed by transient elastography (FibroScan) revealed a numerical reduction of 15% ($P = 0.059$) after 24 weeks of dapagliflozin therapy while, concomitantly, a significant 8% reduction in liver steatosis was also observed ($P = 0.0424$). However, in the subgroup of T2DM patients with higher liver fibrosis scores, who also had higher ALT, AST and GGT serum levels, a significant 25% reduction was observed ($P = 0.0158$) [24].

Effects on biopsy-proven histopathological abnormalities

A prospective open-label study based on serial liver biopsies demonstrated that canagliflozin improved rates of hepatocyte steatosis and NAFLD activity scores at 24 weeks in all five participants, together with an improvement in histopathological findings [41]. The same researchers recently confirmed these results in nine T2DM patients with NAFLD, finding that after 24-week treatment with canagliflozin, stage scores of steatosis, lobular inflammation, ballooning and fibrosis all decreased by 78%, 33%, 22% and 33%, respectively, compared with pretreatment scores [52]. In 10 T2DM patients with biopsy-confirmed NASH classified as stage 1–3 fibrosis, significant improvements in several hepatic function/fibrosis markers, such as AST, FIB-4 index and FM-fibro index, were observed after 12 weeks of canagliflozin therapy [53]. In a case report of a 67-year-old woman with T2DM and NASH, administration of ipragliflozin improved her liver dysfunction both clinically (normalization of ALT) and histologically (marked improvement in steatosis, inflammation and ballooning) after 4 months of treatment. In addition, ultrasonography and CT showed a decrease in fatty deposits in her liver while two serum fibrosis markers, type IV collagen and hyaluronic acid, were also decreased after ipragliflozin therapy [54].

Discussion

Effects of SGLT2 inhibitors on NAFLD, CVD and CKD

NAFLD/NASH could be considered a 'forgotten' comorbidity of T2DM next to the well-known complications of micro- and

Table 3
Effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors available in Europe and US vs. other oral glucose-lowering agents (as controls) on liver enzymes and indicators of fatty liver content and fibrosis in patients with type 2 diabetes in randomized controlled trials.

References	Patients	Duration (weeks)	Treatment	*n*	HbA_{1c} (%)	Body weight (kg)	ALT (U/L)	AST (U/L)	GGT (U/L)	FIB-4 index	CT (liver/spleen ratio)
Randomized controlled trials											
Kurinami et al. 2018 [36]	All	26	Dapagliflozin 5 mg	28	7.6→6.7 $P < 0.01$	77.0→74.0 $P < 0.01$	26.5→19.0 $P < 0.01$	25.0→20.5 $P < 0.01$	34.0→23.0 $P < 0.05$	1.21→1.16 $P = 0.30$	0.96→1.07 $P < 0.01$
			Other OADs	27	7.7→6.9 $P < 0.01$	72.0→71.2 $P = 0.15$	21.0→20.0 $P = 0.85$	22.0→23.0 $P = 0.19$	36.0→31.0 $P = 0.27$	1.04→1.05 $P = 0.11$	1.08→1.10 $P = 0.02$
Shimizu et al. 2019 [24]	NAFLD	24	Dapagliflozin 5 mg	33	8.00→7.4 $P < 0.0001$	73.6→70.7 $P = 0.0004$	38.0→26.6 $P = 0.001$	28.0→27.5 $P = 0.0018$	47.0→27.0 $P = 0.0003$	1.32→1.27 $P = 0.7207$	NA
			Other OADs	24	7.7→7.0 $P = 0.14$	76.4→75.8 $P = 0.49$	33.0→32.0 $P = 0.4493$	29.8→27.4 $P = 0.3353$	37.5→32.0 $P = 0.0041$	1.11→1.17 $P = 0.9286$	NA
Cefalu et al. 2013 [27]	All	52	Canagliflozin 100 mg	483	7.80→6.98 $P < 0.0001$	86.8→83.1 $P < 0.0001$	29.8→26.8 $P = NA$	23.0→21.5 $P = NA$	37.5→33.6 $P = NA$	NA	NA
			Canagliflozin 300 mg	485	7.80→6.87 $P < 0.0001$	86.6→82.6 $P < 0.0001$	28.9→23.4 $P = NA$	23.7→21.2 $P = NA$	39.5→32.5 $P = NA$	NA	NA
			Glimepiride 1–8 mg	482	7.80→6.99 $P < 0.0001$	86.6→87.3 $P < 0.05$	29.2→27.4 $P = NA$	22.9→23.3 $P = NA$	38.8→41.8 $P = NA$	NA	NA
Sattar et al. 2018 [28]	All	164	Empagliflozin 25 mg	765	7.92→7.18 $P < 0.001$	82.5→79.4 $P < 0.001$	31.9→26.3 $P < 0.0001$	24.7→22.0 $P < 0.0001$	NA	NA	NA
			Glimepiride 1-4 mg	780	7.92→7.25 $P < 0.001$	83.0→84.4 $P < 0.05$	31.2→29.8 $P = NA$	25.0→25.3 $P = NA$	NA	NA	NA
Leiter et al. 2016 [29]	All	52 (two RCTs)	Canagliflozin 300 mg	722	8.00→7.07 $P < 0.001$	86.5→83.6 $P < 0.001$	29.0→25.9 $P = NA$	23.0→22.0 $P = NA$	39.5→34.8 $P = NA$	NA	NA
			Sitagliptin 100 mg	724	8.00→7.33 $P < 0.001$	88.6→88.2 $P = NS$	28.2→30.3 $P = NA$	22.8→24.7 $P = NA$	37.9→37.8 $P = NA$	NA	NA
Open non-controlled studies (retrospective)											
Choi et al. 2018 [45]	NAFLD	52	Dapagliflozin	50	8.3→7.7 $P < 0.05$	79.8→76.9 $P = 0.005$	51.9→30.8 $P = 0.008$ vs. DPP-4 inhibitors	36.3→24.9 $P = 0.077$ vs. DPP-4 inhibitors	NA	NA	NA
			DPP-4 inhibitors	52	7.4→7.2 $P = NS$	73.7→73.1 $P = NS$	49.6→40.1	35.6→29.6	NA	NA	NA

Results are expressed as changes before→after treatment.
ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; FIB-4: fibrosis-4; CT: computed tomography; OADs: oral antidiabetic drugs; NAFLD: non-alcoholic fatty liver disease; NA: not available; RCTs: randomized controlled trials; DPP-4: dipeptidyl peptidase-4; NS: not significant.

macroangiopathy [55]. In recent years in patients with T2DM, the focus has mainly been on CVD and CKD, especially after the publication of large-scale prospective cardiovascular outcome trials also looking at the progression of renal disease as a secondary endpoint [17,56]. Indeed, there may be a close interrelationship between NAFLD/NASH, CVD and CKD [5,6]. In the Multi-Ethnic Study of Atherosclerosis (MESA), NAFLD was associated with increased inflammation and subclinical atherosclerosis as well as with coronary artery calcium scores independent of traditional risk factors, obesity and the metabolic syndrome [38]. In the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), the fatty liver index was able to predict incident CVD over a median 17-year follow-up of 1205 middle-aged men free of CVD at baseline [57]. In addition, a meta-analysis of nine observational studies found that NAFLD was associated with a nearly 40% increase in long-term risk of incident CKD [58], although caution is required before deciding causality, given the observational nature of the eligible studies.

Nevertheless, the fact that improvement/resolution of NAFLD has been associated with improved kidney function in some studies adds weight to the possibility of causality by suggesting that liver-focused treatments might be contributing to lowering the risk of extrahepatic complications such as CVD and CKD [6]. There is even promising evidence of the potential effect of some antidiabetic drugs on cardiometabolic outcomes for patients with NAFLD, which means that future studies need to address treatment of NAFLD not only for liver-related consequences, but also for cardiovascular and renal complications [59].

SGLT2 inhibitors have demonstrated cardiovascular [60] and renal [61] protection in T2DM patients with established CVD, while increasing evidence suggests that, beyond cardiovascular [17] and renal [18] protection, SGLT2 inhibitors may also be liver-protective by reducing liver fat content [62]. Consistent positive results have been observed with all three SGLT2 inhibitors commercially available worldwide (canagliflozin, dapagliflozin, empagliflozin; Tables 1 and 3); these favourable findings have also been confirmed with SGLT2 inhibitors in the Japanese marketplace (luseogliflozin and especially ipragliflozin; Table 2) [63]. Thus, this dataset argues for a class effect of SGLT2 inhibitors in NAFLD, as suggested by their effects on CVD and CKD [64]. However, as yet, no studies are available of the effects of ertugliflozin, a recently developed SGLT2 inhibitor [65], and sotagliflozin, a dual SGLT2–SGLT1 inhibitor [66], on markers of NAFLD in patients with T2DM.

Comparison with other glucose-lowering agents

SGLT2 inhibitors are associated with significant reductions in serum liver enzyme levels compared with various other oral glucose-lowering agents [24,36], including metformin [20], glimepiride [27,28] and DPP-4 inhibitors [29,45], despite similar glucose control. Regarding the first-line antidiabetic agent metformin [19], findings from the majority of studies using rodent models suggest that metformin may reduce liver fat accumulation, although data from human studies are less convincing [67]. While available findings on the effects of sulphonylureas on NAFLD in T2DM patients are scarce [13–15], an ongoing trial is currently comparing the effects of adding an SGLT2 inhibitor (tofogliflozin) and a sulphonylurea (glimepiride) as the third-line oral agent to metformin/DPP-4 inhibitor dual therapy on parameters related to liver function in T2DM patients [68]. Despite experimental observations suggesting that DPP-4 may play a role in chronic liver disease [69], DPP-4 inhibitors are not effective in reducing liver fat content in patients with T2DM and NAFLD, as demonstrated by a dedicated RCT comparing sitagliptin and a placebo [70].

Other glucose-lowering agents, such as thiazolidinediones (TZDs) and GLP-1 receptor agonists, have demonstrated an ability to reduce liver fat content and biological markers of NAFLD [13]. However, none has, as yet, received approval for the management of NAFLD in patients with T2DM [3,12]. TZDs (especially pioglitazone), which act as insulin-sensitizers, have shown positive results for NAFLD [71], including effects on fibrosis [72], and these glitazone effects were observed despite body weight gain, a change associated with a reduction in visceral adipose tissue in contrast to an increase in subcutaneous adipose tissue. Only one study has compared the effects of an SGLT2 inhibitor and a TZD in patients with T2DM and NAFLD [20]. Compared with pioglitazone, ipragliflozin exerted equally beneficial effects on NAFLD markers and glycaemic control (Table 2). However, ipragliflozin significantly reduced body weight ($P < 0.0001$), visceral fat area ($P = 0.0013$) and subcutaneous fat area ($P < 0.0001$) vs. pioglitazone, whereas the increase in serum adiponectin levels was greater ($P = 0.0009$) with the TZD than with the SGLT2 inhibitor [20].

GLP-1 receptor agonists also have proven efficacy in reducing liver fat content in T2DM patients with NAFLD [2,31]. In a pooled analysis of six 26-week RCTs in the LEAD programme for T2DM patients not selected for having NAFLD, liraglutide 1.8 mg once daily improved liver enzymes, an effect that appears to be mediated by its dual action on weight loss and glycaemic control [73]. Similar positive findings were reported with the once-weekly GLP-1 receptor agonist dulaglutide in the AWARD programme [74]. Exenatide has also been shown to reduce liver fat content in obese patients with T2DM, an effect that seems to be mostly dependent on weight loss [75], while the positive effects of liraglutide on liver function and histopathology were confirmed in T2DM patients with NAFLD [76] and with NASH [77] in carefully controlled studies using liver biopsy.

Thus, the effects of GLP-1 receptor agonists on NAFLD markers are rather consistent, suggesting a class effect despite the heterogeneity of this pharmacological family [78]. However, this raises the question of how SGLT2 inhibitors compare with GLP-1 receptor agonists regarding their effects on fatty liver [79]. Moreover, to our knowledge, no RCT has assessed the effects of an SGLT2 inhibitor *vs* the incretin liraglutide. In a large observational study using the database of a Canadian diabetes registry, changes in serum levels of ALT, the most specific liver enzyme for NAFLD, were measured after a mean follow-up of 4.8 months in 3667 patients with T2DM who had canagliflozin, dapagliflozin, liraglutide or sitagliptin added to their diabetes treatments [80]. ALT levels were lower after treatment with SGLT2 inhibitors canagliflozin (−4.3 U/L) and dapagliflozin (−3.5 U/L) compared with incretins liraglutide (−2.1 U/L) and sitagliptin (-1.8 U/L), although all showed lower levels than in the controls ($P < 0.01$ vs. no added treatment). Of note, only the SGLT2 inhibitor treatment groups maintained significant ALT reductions vs. controls following multivariable adjustment and propensity score weighting. In fact, SGLT2 inhibitors (canagliflozin and dapagliflozin) resulted in weight- and HbA1c-independent lowering of ALT levels compared with incretins, with a dose–response relationship observed with higher baseline ALT levels [80].

Given these positive effects of SGLT2 inhibitors on NAFLD, and as also reported with TZDs and GLP-1 receptor agonists, it may be speculated that combining two drugs with proven efficacy might be even more powerful for improving liver function [81]. One review summarized the potential benefits of combined pioglitazone/empagliflozin therapy by preventing cardiovascular events in patients with T2DM [82], whereas empagliflozin 10 mg or 25 mg as add-on therapy to pioglitazone with or without metformin for 76 weeks led to sustained reductions in HbA_{1c} and weight compared with placebo in T2DM patients, although liver tests were not reported [83]. Several studies have already demonstrated that combining an SGLT2 inhibitor and GLP-1 receptor agonist can

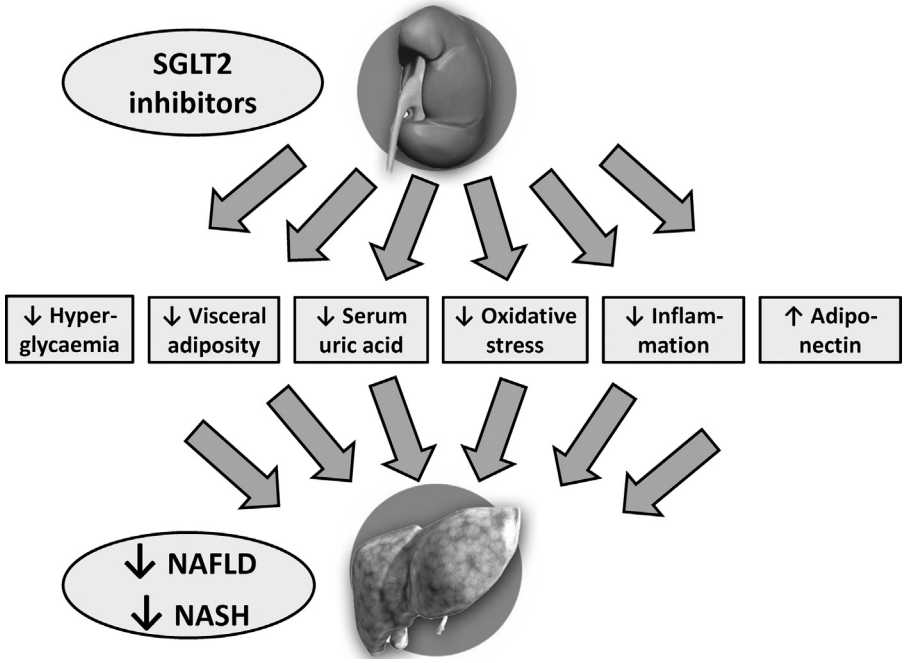

Fig. 1. Potential mechanisms contributing to improvement of fatty liver with sodium-glucose cotransporter-2 (SGLT2) inhibitor treatment. NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.

lead to better glucose control and greater weight loss [84,85]. Again, however, no specific data on liver function were reported in these investigations into the effects of dapagliflozin added to exenatide once weekly [84] or of luseogliflozin added to liraglutide [86]. Thus, further studies investigating the effects of combined therapy on NAFLD markers are awaited with considerable interest.

Mechanistic explanations

The mechanisms underlying the improvement of NAFLD with SGLT2 inhibitors remain largely unknown and, at present, can only be speculations (Fig. 1). SGLT2 inhibitors significantly lower fasting and postprandial hyperglycaemia [17], and decrease body weight and fat mass [87]. It is known that both chronic hyperglycaemia and excess adiposity are associated with NAFLD.

Yet, the role of better glucose control in improving NAFLD remains unclear. In an open study of Chinese patients with T2DM (but not selected for having NAFLD), the amelioration of hepatic dysfunction, as assessed by significant reductions in ALT and AST, was mediated partly through alleviation of hyperglycaemia and possibly through improvement of insulin resistance independent of body weight changes [51]. However, better glucose control is not sufficient to significantly improve NAFLD, as revealed by the general lack of positive effects reported with metformin, DPP-4 inhibitors and insulin in patients with T2DM [13]. In a study comparing empagliflozin and a glucose-lowering therapy, both adjusted with the objective of maintaining glycaemic equipoise, a significant reduction in serum liver enzymes was observed with the SGLT2 inhibitor, but not in the controls, and a greater reduction in liver fat content, as assessed by MRI-PDFF, was noted in patients treated with empagliflozin compared with those using other glucose-lowering agents [23]. Similarly, in a study comparing canagliflozin with glimepiride, a slightly greater reduction in serum liver enzymes was observed with the former compared with the sulphonylurea, despite similar improvements in glucose control in both groups [27].

Body weight reduction has been reported to significantly reduce steatosis and serum liver enzymes in studies of bariatric surgery [88]. However, weight loss after bariatric surgery is much more marked than the rather modest weight reduction generally observed with SGLT2 inhibitors [89]. One study that showed significant reductions in ALT and GGT in patients with T2DM also reported significant reductions in HbA_{1c}, body weight and fat mass, associated with a significant improvement in insulin sensitivity [50]. This study also found a significant negative correlation between changes in insulin sensitivity index and body fat mass, although correlations with changes in serum liver enzymes were not tested [50].

One study of canagliflozin led to improvements in liver function tests *vs* either placebo or sitagliptin treatments that were fully explained by the combined effects of glycated haemoglobin (HbA_{1c}) and body weight decreases with the SGLT2 inhibitor [29]. However, in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), the ALT-lowering effect of empagliflozin vs. placebo considered independent of concomitant changes from baseline in HbA_{1c}, and body weight averaged 76.0% after both 24 weeks and 164 weeks [28]. In another study, improvement of liver dysfunction with ipragliflozin in patients with T2DM was seen irrespective of body weight loss [16] whereas, in a study using MRI assessment of liver fat content, no significant correlations between liver fat reduction and improvement in HbA1c or body weight were noted [23].

These observations suggest that the intervention of other, subtle mechanisms may be involved in NAFLD improvement with SGLT2 inhibitors. An experimental study in *db/db* mice showed that dapagliflozin not only corrrected hyperglycaemia, but also slowed the progression of diabetes-associated liver fibrosis (and glomerulosclerosis in kidneys) by improving hyperglycaemia-induced tissue inflammation and oxidative stress [90]. In a recent human study, in addition to a significant diminution of liver fat content, dapagliflozin reduced all measured serum biomarkers of hepatocyte injury, thereby suggesting less cellular damage and better

mitochondrial function or reduced endoplasmic reticulum stress associated with NAFLD [22]. Thus, the potential beneficial effects of SGLT2 inhibitors on low-grade inflammation and oxidative stress certainly merit further investigations, as recently discussed [9].

When a post-hoc exploratory analysis of a head-to-head study showing greater improvement of serum liver enzymes with canagliflozin *vs* glimepiride [27] also investigated selected adipokines, inflammatory biomarkers and chemokines in both treatment groups [91], the results indicated that canagliflozin decreased median serum leptin by 25% and median serum interleukin (IL)-6 by 22%, while significantly increasing median serum adiponectin by 17% vs. glimepiride. With canagliflozin, decreases in serum leptin correlated with changes in body weight, whereas increases in adiponectin and decreases in IL-6 were independent of changes in HbA_{1c}, weight or serum lipids [91]. Data on the association between NAFLD and circulating leptin and adiponectin levels are generally well established: leptin levels increase while adiponectin levels decrease, thereby increasing the severity of NAFLD [92].

Uric acid is associated with inflammatory biomarkers and induces inflammation by activating the nuclear factor (NF)-κB signalling pathway in HepG2 cells [93]. Increased serum uric acid levels are associated with CVD [94] and progression of CKD [95]. Interestingly, a relationship between high serum uric acid and risk of NAFLD has also been reported [96,97]. Thus, as SGLT2 inhibitors consistently reduce serum uric acid levels [98], it may be speculated that this effect could be contributing not only to better cardiovascular [17] and renal [18] prognoses, but also to improvement of NAFLD.

Conclusion

In addition to pioglitazone and liraglutide, SGLT2 inhibitors have also demonstrated favourable effects on NAFLD in T2DM patients, effects that arise largely beyond glucose-lowering activity, as they are more marked than those observed with sulphonylureas, DPP-4 inhibitors and even metformin in patients achieving similar glucose control. Yet, in contrast to those active comparators, SGLT2 inhibitors are able to reduce body weight, total fat mass and visceral adipose tissue, an additional effect that could contribute to reducing liver fat content and, thus, markers of NALFD. However, increasing evidence suggests that other mechanisms most probably play a role beyond effects on glycaemia and body weight. Anti-inflammatory effects and reduction of oxidative stress have been demonstrated in animal models and are worthy of further investigation in humans. The decrease of serum uric acid consistently associated with SGLT2 inhibitors may also have a positive role. If SGLT2 inhibitors, as with TZDs and GLP-1 receptor agonists, can reduce liver fat content in patients with T2DM and NAFLD, it may be speculated that their combined therapy might be even more effective, provided that the effects arise through different and potentially complementary mechanisms. This remains to be demonstrated in dedicated clinical RCTs of T2DM patients with severe NAFLD. Moreover, longer-term controlled studies need to confirm whether the improvement of NAFLD with SGLT2 inhibitors also avoids its progression to NASH and, ultimately, fibrosis and cirrhosis. Further research is now mandatory to progress this evolving field while focusing on NAFLD, an often forgotten complication of T2DM. In particular, larger RCTs with adequate liver endpoints for NAFLD and/or NASH are needed to definitively determine whether treatment with SGLT2 inhibitors improves NAFLD in patients with T2DM. In any case, even though SGLT2 inhibitors, as with any other glucose-lowering agents, are not yet confirmed to improve NAFLD, there is nevertheless growing evidence that they may confer liver protection as well as the already recognized cardiovascular and renal protection.

Disclosure of interest

A.J. Scheen has received lecturer/advisor/investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Servier. He has also worked as a clinical investigator in the EMPA-REG OUTCOME, CANVAS-R and DECLARE-TIMI 58 trials.

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