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Effects of empagliflozin on markers of liver steatosis and fibrosis and their relationship to cardiorenal outcomes

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Abstract

Aims: Empagliflozin treatment reduced liver fat in small type 2 diabetes cohorts. This post-hoc study evaluated effects of empagliflozin on risk for non-alcoholic fatty liver disease-related steatosis and fibrosis, as well as the relationship between risk categories and cardiorenal outcomes in the randomized, placebo-controlled EMPA-REG OUTCOME trial.

Materials and methods: EMPA-REG OUTCOME treated 7020 people with type 2 diabetes and cardiovascular disease with 10/25 mg/day empagliflozin or placebo. For this analysis, the Dallas steatosis index, hepatic steatosis index, non-alcoholic fatty liver disease fibrosis score and Fibrosis-4 score were calculated to assess steatosis and fibrosis risk. Changes from baseline in scores were examined by mixed model repeated measures and their associations with cardiorenal outcomes and mortality by Cox regression.

Results: At baseline, 73% and 84% of participants had high steatosis risk by Dallas steatosis index and hepatic steatosis index, whereas 23% and 4% had a high risk of advanced fibrosis by non-alcoholic fatty liver disease fibrosis score and Fibrosis-4 score. Percentages of people at high steatosis risk slightly decreased with empagliflozin only, whereas empagliflozin did not improve percentages of individuals at high fibrosis risk over time compared with placebo. The high risk of advanced fibrosis at baseline related to higher risk for cardiovascular events. Effects of empagliflozin on cardiorenal and all-cause mortality outcomes were consistent across all risk groups.

Conclusions: Empagliflozin may reduce steatosis but not fibrosis risk in individuals with type 2 diabetes and cardiovascular disease. The improvements in cardiorenal outcomes and mortality associated with empagliflozin therapy appear to be independent of steatosis and fibrosis risk.

KEYWORDS
antidiabetic drug, clinical trial, liver, SGLT2 inhibitor

1 | INTRODUCTION

People with type 2 diabetes are prone to develop non-alcoholic fatty liver disease (NAFLD).[1] Type 2 diabetes further accelerates NAFLD progression from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.[2] Moreover, NAFLD associates with an increased risk of cardiovascular diseases, including cardiomyopathy and certain cardiac arrhythmias, thereby contributing to the excess morbidity and mortality in people with both type 2 diabetes and NAFLD.[2]

Hepatic fibrosis is a strong predictor of NAFLD-related mortality[2] and clinically relevant advanced fibrosis stages, F3 and F4, can be present in up to 20% of persons with NAFLD and type 2 diabetes.[1] While the 'gold-standard' diagnosis of fibrosis still requires liver biopsy,[2] several imaging methods have been introduced including vibration-controlled transient elastography or magnetic resonance elastography. These methods are mostly restricted to use in specialized centres[3] as they require specific technical equipment, qualified and trained personal, making them difficult to perform in large multinational clinical trials involving hundreds of study sites. Thus, non-invasive indices calculated from demographic, anthropometric and laboratory parameters provide an opportunity to estimate the prevalence and effects of interventions on liver fibrosis in large cohorts.[3] In addition, hepatic steatosis, the primary criterium of NAFLD diagnosis, may be estimated by non-invasive indices.[4,5]

Sodium glucose co-transporter 2 inhibitors are associated with a modest weight loss and improved cardiovascular and renal outcomes.[6,7] Recent small-scale randomized controlled trials have shown that empagliflozin also improved hepatic steatosis and beneficial effects of empagliflozin on histological components including fibrosis were suggested from an uncontrolled pilot trial.[6] The underlying mechanisms remain largely unknown; however, apart from weight loss, they may even include improvement of adipose tissue function with amelioration of local inflammation and/or oxidative stress.[8,9]

The present study examined the effects of empagliflozin treatment in a large cohort of persons with type 2 diabetes with established cardiovascular disease (a) on indices of hepatic steatosis and fibrosis, (b) on glycaemia and body weight, as well as (c) on cardiorenal outcomes and all-cause mortality in groups at different steatosis and fibrosis risk. Finally, this analysis addressed the question whether baseline steatosis and fibrosis risk scores are associated with the incidence of cardiorenal events in this patient population. To this end, an exploratory post-hoc analysis was performed in the EMPA-REG OUTCOME study, previously showing lower rates of cardiovascular events and deaths from any cause with empagliflozin at a median observation time of 3.1 years.[7]

2 | MATERIALS AND METHODS

2.1 | Study design

The design of EMPA-REG OUTCOME has been previously decribed.[7] Adult individuals with type 2 diabetes and established cardiovascular disease were included; elevated liver enzymes >3× upper limit of normal were exclusion criteria (see Supporting Information for further details).

The main objective of this post-hoc analysis was to compare the effects of empagliflozin and placebo on Dallas steatosis index (DSI)[10] and hepatic steatosis index (HSI)[11] as well as on NAFLD fibrosis score (NFS) and Fibrosis-4 score (FIB-4) (see Supporting Information for calculations and cut-offs).

2.2 | Calculations and statistical analysis

The present post-hoc analyses of the randomized clinical trial EMPA-REG OUTCOME were performed on the modified intention-to-treat population, including all randomized participants, who received ≥1 dose of the study drug. The effects on risk scores as well as glycated haemoglobin (HbA1c) and weight were evaluated using a mixed-effect model repeated measurement model, which included baseline HbA1c and baseline of score (or weight) as linear covariates and their interaction with visit in addition to baseline estimated glomerular filtration rate (Modification of Diet in Renal Disease Study) category, geographical region and baseline body mass index category. Treatment, subgroup (if applicable) and visit were also entered as fixed effects as well as all two- and three-way interactions thereof. In addition, the model included a fixed categorical effect for 'time of randomization' to account for each patient's theoretical ability to 'reach' certain weeks in this study arising from the study design. Because of small group sizes, participants at baseline intermediate and high risk (based on FIB-4) were pooled for analysis of time courses of parameters in FIB-4 low and high fibrosis risk categories and HSI low and intermediate risk categories were combined for all subsequent analyses. All time to first event analyses were performed with multivariate Cox regression models that included terms for sex, baseline age, estimated glomerular filtration rate, body mass index, HbA1c, geographical region, subgroup, and treatment × subgroup interaction. Continuous baseline characteristics of fibrosis and steatosis risk groups are given as mean ± standard deviation, categorical variables as number and proportions. All other data are expressed as adjusted means (95% confidence interval) or adjusted means ± standard error. As this was a post-hoc exploratory study, no adjustments for multiple comparisons/outcomes were performed. Statistical significant differences were indicated at $p < .05$. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Baseline characteristics of the whole cohort and different steatosis and fibrosis risk groups

Of the 7020 participants who were treated with empagliflozin or placebo, 6927 and 7018 had data available to derive DSI and HSI, respectively, and 6970 and 6972, respectively, had data to derive NFS

TABLE 1 Baseline characteristics of DSI-, HSI-, NFS-, FIB-4-categorized steatosis and fibrosis risk groups

	Low risk	Intermediate	High risk
DSI			
Total n	253	1616	5058
Males, n (%)	201 (79.4)	1209 (74.8)	3546 (70.1)
Race, n (%)			
White	137 (54.2)	949 (58.7)	3920 (77.5)
Asian	69 (27.3)	509 (31.5)	928 (18.3)
Black/African American	46 (18.2)	150 (9.3)	156 (3.1)
Other	1 (0.4)	8 (0.5)	54 (1.1)
Age, years; mean ± SD	65.9 ± 9.0	65.1 ± 8.9	62.4 ± 8.4
Body mass index, kg/m^2; mean ± SD	23.9 ± 2.4	26.7 ± 3.9	32.2 ± 4.8
>10 years since T2D diabetes, n (%)	169 (66.8)	1055 (65.3)	2736 (54.1)
Glycated haemoglobin, %; mean ± SD	7.9 ± 0.9	8.0 ± 0.8	8.1 ± 0.9
Baseline insulin use, n (%)	102 (40.3)	715 (44.2)	2520 (49.8)
eGFR, ml/min/1.73 m^2; mean ± SD	79.3 ± 22.4	73.7 ± 21.3	73.9 ± 21.4
Hypertension, n (%)	199 (78.7)	1398 (86.5)	4738 (93.7)
CAD, n (%)	180 (71.1)	1222 (75.6)	3836 (75.8)
his			
Total n	89	1010	5919
Males, n (%)	66 (74.2)	803 (79.5)	4146 (70.0)
Race, n (%)			
White	27 (45.2)	470 (46.5)	4583 (77.4)
Asian	61 (68.5)	495 (49.0)	960 (16.2)
Black/African American	1 (1.1)	40 (4.0)	316 (5.3)
Other	0 (0)	5 (0.5)	59 (1.0)
Age, years; mean ± SD	67.2 ± 8.3	65.5 ± 8.7	62.7 ± 8.6
Body mass index, kg/m^2; mean ± SD	20.5 ± 1.7	24.2 ± 1.9	31.9 ± 4.7
>10 years since T2D diabetes, n (%)	57 (64.0)	645 (63.9)	3307 (55.9)
Glycated haemoglobin, %; mean ± SD	7.88 ± 0.94	7.94 ± 0.81	8.10 ± 0.85
Baseline insulin use, n (%)	29 (32.6)	359 (35.5)	2998 (50.7)
eGFR, mL/min/1.73 m^2; mean ± SD	73.4 ± 22.9	71.5 ± 20.5	74.5 ± 21.5
Hypertension, n (%)	71 (79.8)	862 (85.3)	5484 (92.7)
CAD, n (%)	59 (66.3)	760 (75.2)	4488 (75.8)
NFS			
Total n	809	4562	1599
Males, n (%)	493 (60.9)	3312 (72.6)	1175 (73.5)
Race, n (%)			
White	375 (46.4)	3278 (71.9)	1395 (87.2)
Asian	368 (45.5)	1015 (22.2)	119 (7.4)
Black/African American	55 (6.8)	231 (5.1)	69 (4.3)
Other	11 (1.3)	38 (0.8)	16 (1.0)
Age, years; mean ± SD	56.2 ± 8.4	62.6 ± 8.0	68.2 ± 7.4
Body mass index, kg/m^2; mean ± SD	27.04 ± 4.12	30.06 ± 4.74	34.07 ± 5.33
>10 years since T2D diabetes, n (%)	374 (46.2)	2541 (55.7)	1071 (67.0)
Glycated haemoglobin, %; mean ± SD	8.18 ± 0.87	8.07 ± 0.85	8.02 ± 0.84
Baseline insulin use, n (%)	316 (39.1)	2110 (46.3)	939 (58.7)
eGFR, mL/min/1.73 m^2; mean ± SD	80.5 ± 24.0	75.4 ± 21.0	66.9 ± 19.5

(Continues)

TABLE 1 (Continued)

	Low risk	Intermediate	High risk
Hypertension, n (%)	692 (85.5)	4162 (91.2)	1519 (95.0)
CAD, n (%)	512 (63.3)	3440 (75.4)	1319 (82.5)
FIB-4			
Total n	3505	3161	306
Males, n (%)	2334 (66.6)	2406 (76.1)	241 (78.8)
Race, n (%)			
White	2421 (69.1)	2384 (75.4)	244 (79.7)
Asian	811 (23.1)	636 (20.1)	56 (18.3)
Black/African American	236 (6.7)	114 (3.6)	5 (1.6)
Other	37 (1.1)	27 (0.8)	1 (0.3)
Age, years; means ± SD	59.5 ± 8.1	66.5 ± 7.5	69.8 ± 7.8
Body mass index, kg/m^2; mean ± SD	30.76 ± 5.28	30.51 ± 5.20	30.33 ± 5.44
>10 years since T2D diabetes, n (%)	1832 (52.3)	1945 (61.5)	210 (68.6)
Glycated haemoglobin, %; mean ± SD	8.15 ± 0.87	8.00 ± 0.82	7.96 ± 0.79
Baseline insulin use, n (%)	1670 (47.6)	1535 (48.6)	161 (52.6)
eGFR, mL/min/1.73 m^2; mean ± SD	77.9 ± 22.1	70.7 ± 19.9	64.8 ± 19.5
Hypertension, n (%)	3179 (90.7)	2920 (92.4)	276 (90.2)
CAD, n (%)	2487 (71.0)	2516 (79.6)	270 (88.2)

Abbreviations: CAD, coronary artery disease; DSI, Dallas steatosis index; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4; HSI, hepatic steatosis index; NFS, non-alcoholic fatty liver disease fibrosis score; T2D, type 2 diabetes.

and FIB-4 at baseline. According to the DSI, 5058 of 6927 (73%) participants were categorized at high steatosis risk at baseline, whereas for HSI, 5919 of 7018 (84%) participants were at high steatosis risk. Regarding fibrosis indices, 1599 of 6970 (23%) and 306 of 6972 (4%) participants were at risk of advanced fibrosis by NFS and FIB-4, respectively. Steatosis and fibrosis risk at baseline were further calculated by other established indices. Percentages of participants grouped at high steatosis risk were between 72% and 87%, whereas the percentage of participants at high risk of advanced fibrosis ranged from 1% to 69% (Table S1). Stratifying participants by NFS, FIB-4 and HSI, but not DSI, revealed more frequent insulin use and higher incidence of coronary artery disease in groups at high risk compared with those at low risk (Table 1).

3.2 | Empagliflozin-mediated changes of Dallas steatosis index, hepatic steatosis index, non-alcoholic fatty liver disease fibrosis score and Fibrosis-4 categories over time

At baseline, percentages of participants in the different DSI risk categories were comparable for empagliflozin and placebo. Over time, percentages remained largely unchanged for placebo whereas the percentage of participants at high steatosis risk dropped with empagliflozin from 73 at baseline to 66%, 67% and 67% at 52, 108 and 164 weeks, respectively (Figure 1A). The changes from baseline category to week 52 category and further on are visualized in Figure S1. In the empagliflozin group, more participants improved than worsened comparing baseline category to week 52 category, which was also observed for placebo although to a less extent. After week 52, this effect was attenuated in both groups.

Baseline percentages of participants in the different HSI risk groups were comparable for empagliflozin and placebo. Over time, numbers remained largely unchanged for placebo whereas the percentage of people at high steatosis risk dropped with empagliflozin from 84% at baseline to 77%, 78% and 77% at 52, 108 and 164 weeks, respectively (Figure 1B). Figure S2 shows that more participants improved than worsened compared with the baseline category with empagliflozin at 52 weeks and less prominent with placebo. After week 52, this effect was attenuated in both groups and no further improvements were observed thereafter in both groups.

Baseline percentages of participants in different NFS risk groups of advanced fibrosis were comparable for empagliflozin and placebo with only little variation throughout the course of the study (Figure 1C). After week 52, the percentage of people in the high-risk category was slightly increased in both groups Figure S3).

At baseline and thereafter, the percentages of participants in low-, intermediate- and high-FIB-4 risk groups were comparable for empagliflozin and placebo with only minimal changes over time (Figure 1D). After week 52, percentages of persons in the intermediate- and high-risk categories were increased in both groups (Figure S4).

Changes from baseline in the respective indices are depicted in Figure S5.

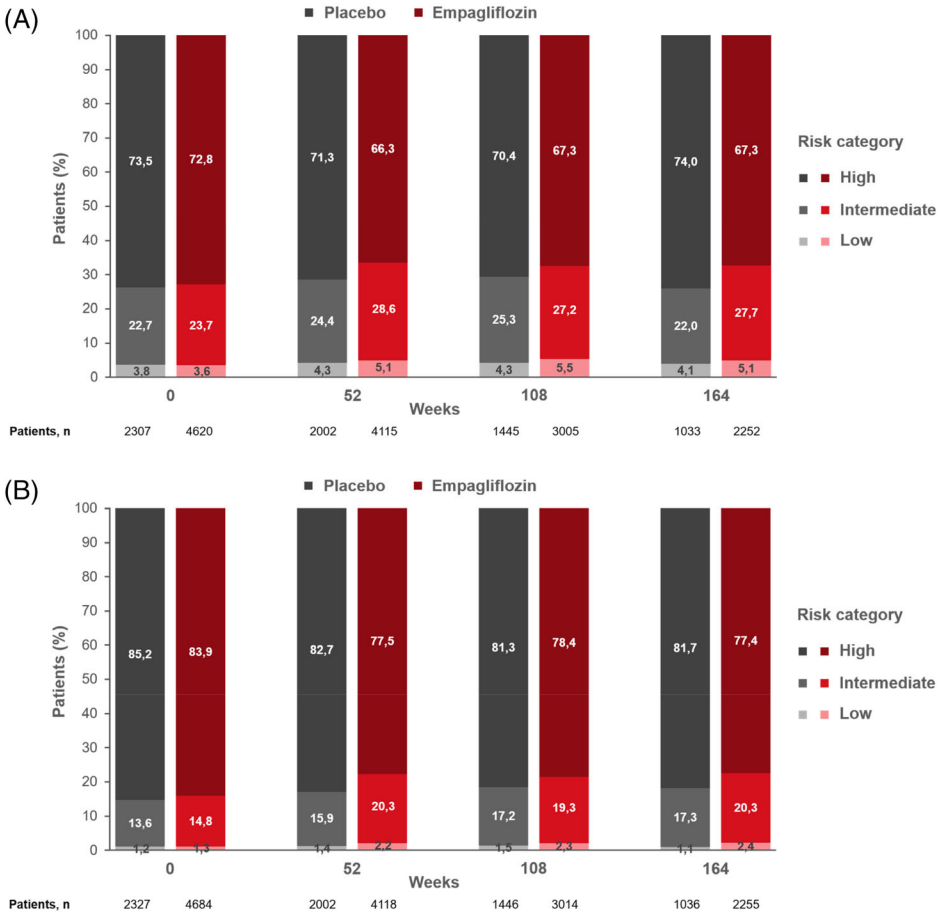


FIGURE 1 Percentage of patients in low/intermediate/high-risk categories by (A) Dallas steatosis index, (B) hepatic steatosis index, (C) non-alcoholic fatty liver disease fibrosis score and (D) Fibrosis-4 at 0, 52, 108 and 164 weeks of treatment

3.3 | Effects of empagliflozin on body weight and glycated haemoglobin in different risk categories

Across all derived steatosis and fibrosis risk groups, empagliflozin reduced body weight as compared with placebo at most time points (Figure S6). HbA1c decreased with empagliflozin compared with placebo at most time points in steatosis and at all time points in fibrosis risk groups (Figure S7).

3.4 | Effects of empagliflozin on biochemical parameters included in different indices

Serum triglyceride levels slightly increased over time in the low and intermediate DSI group and were unchanged in the high DSI group, without any differences between empagliflozin and placebo in any DSI category (Table S2).

Platelet counts decreased more with empagliflozin compared with placebo in the NFS and FIB-4 low-risk categories at 52, 108 and 164 weeks, but increased in the respective high-risk categories over time, with a more prominent decrease and less prominent rise in the empagliflozin group, respectively, at most time points (Table S3ab).

Albumin levels slightly increased after dosing with empagliflozin compared with placebo in NFS intermediate- and high-risk categories and remained higher at most time points and all categories (Table S4).

3.5 | Cardiorenal outcomes in fibrosis and steatosis risk groups

For DSI and HSI, highest placebo incidence rates for cardiovascular and all-cause mortality were found in the low steatosis risk category, with statistically significant differences compared with the high steatosis risk category (Figure 2A,B, Table S5a).

Using both NFS and FIB-4 for stratification of fibrosis risk, the groups at high risk of advanced fibrosis had substantially higher incidence rates of cardiovascular death, first hospitalization because of heart failure, first hospitalization for heart failure or cardiovascular death as well as all-cause mortality compared with the respective groups at low risk of advanced fibrosis (Figure 2C,D, Table S5a). However, incidence rates of new onset or worsening of nephropathy showed a similar albeit attenuated pattern across risk categories by all four scores.

A similar pattern was observed in the empagliflozin group, although the differences in relative risks in low- versus intermediate-

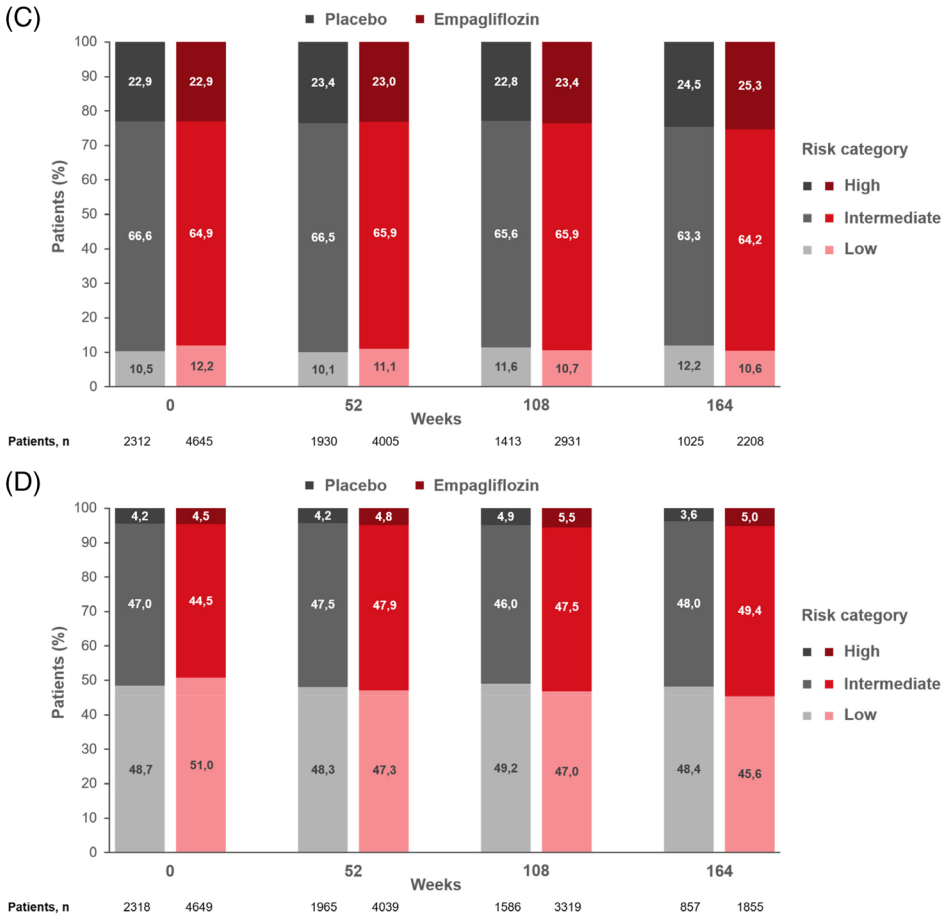


FIGURE 1 (Continued)

and high-risk categories did not reach statistical significance for most outcomes (Table S5b).

3.6 | Effects of empagliflozin on cardiorenal outcomes in groups at different risk of steatosis or fibrosis

Examining the treatment effects of empagliflozin versus placebo across the different steatosis and fibrosis risk groups showed consistent treatment effects on cardiorenal outcomes independent of steatosis or fibrosis category at baseline. Of note, for the combined endpoint of first hospitalization for heart failure or cardiovascular death, a quantitative interaction between DSI and treatment effect was observed, with all hazard ratios still reflecting a beneficial treatment effect, but of differing magnitude, for empagliflozin compared with placebo (Figure 2).

4 | DISCUSSION

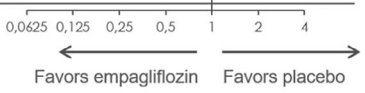
This post-hoc analysis of EMPA-REG OUTCOME suggests that empagliflozin (a) may improve steatosis risk as estimated by DSI and HSI, (b) does not reduce the risk of advanced fibrosis as calculated by NFS and FIB-4, (c) decreases glycaemia and body weight independent of steatosis and fibrosis risk, and (d) may confer consistent reduction of cardiorenal outcomes independent of steatosis and fibrosis risk category in people with type 2 diabetes when added to standard of care for about 3 years. Moreover, low- and high-risk fibrosis categories across all trial participants paralleled low and high risk for cardiovascular events and all-cause mortality.

Empagliflozin slightly reduced the percentages of participants in DSI and HSI high-risk categories over time when compared with placebo. In comparison, recent studies reported the effectiveness of 24-week empagliflozin treatment in the reduction of liver fat content, measured by ^{1}H magnetic resonance spectroscopy, when added to standard care or compared with placebo in individuals with type 2 diabetes.[8,12] However, fibrosis stage is the main prognostic factor in NAFLD.[13] An uncontrolled 24-week pilot trial provided first histological evidence that empagliflozin may reduce fibrosis in people with both type 2 diabetes and NASH.[14] A former analysis of EMPA-REG OUTCOME suggested improvements in serum transaminases [predominantly alanine aminotransferase (ALT)] with empagliflozin.[15] Of note, similar frequency and incidence of hepatic injury were reported for empagliflozin and placebo in clinical studies, but rare elevations in ALT and/or aspartate aminotransferase ≥5 times the upper normal

(A)

DSI

	Placebo		Empagliflozin				*p*-value for interaction
	n/N (%)	IR/1000 py	n/N (%)	IR/1000 py	HR (95% CI)	HR (95% CI)	
CV death							0.1145
No steatosis	11/88 (12.5)	43.8	7/165 (4.2)	14.6	0.32 (0.12, 0.81)		
Intermediate	43/523 (8.2)	28.9	43/1093 (3.9)	13.4	0.48 (0.31, 0.73)		
Steatosis	82/1696 (4.8)	16.5	117/3362 (3.5)	11.8	0.71 (0.54, 0.94)		
HHF							0.2641
No steatosis	3/88 (3.4)	12.5	3/165 (1.8)	6.4	NC		
Intermediate	23/523 (4.4)	15.9	25/1093 (2.3)	8.0	0.50 (0.28, 0.88)		
Steatosis	67/1696 (4.0)	13.9	96/3362 (2.9)	9.9	0.72 (0.53, 0.98)		
CV death or HHF*							0.0289
No steatosis	13/88 (14.8)	54.2	9/165	19.2	0.35 (0.15, 0.81)		
Intermediate	57/523 (10.9)	39.4	58/1093 (5.3)	18.6	0.47 (0.33, 0.68)		
Steatosis	125/1696 (7.4)	26.0	193/3362 (5.7)	20.0	0.77 (0.61, 0.96)		
All-cause mortality							0.4958
No steatosis	13/88 (14.8)	51.8	12/165 (7.3)	25.0	0.46 (0.21, 1.01)		
Intermediate	60/523 (11.5)	40.3	79/1093 (7.2)	24.6	0.62 (0.44, 0.87)		
Steatosis	120/1696 (7.1)	24.1	172/3362 (5.1)	17.3	0.72 (0.57, 0.91)		
Nephropathy							
No steatosis	15/74 (20.3)	81.5	18/143 (12.6)	48.5	0.52 (0.26, 1.04)		0.2332
Intermediate	74/451 (16.4)	64.8	130/956 (13.6)	50.9	0.77 (0.58, 1.02)		
Steatosis	292/1513 (19.3)	78.3	371/2962 (12.5)	47.0	0.58 (0.50, 0.68)		



(B)

HSI

	Placebo		Empagliflozin				*p*-value for interaction
	n/N (%)	IR/1000 py	n/N (%)	IR/1000 py	HR (95% CI)	HR (95% CI)	
CV death							0.0764
No / intermediate	35/345 (10.1)	35.2	32/754 (4.2)	14.3	0.42 (0.26, 0.68)		
Steatosis	102/1987 (5.1)	17.6	140/3932 (3.6)	12.1	0.69 (0.53, 0.88)		
HHF							0.7222
No / intermediate	10/345 (2.9)	10.3	16/754 (2.1)	7.3	0.75 (0.34, 1.65)		
Steatosis	85/1987 (4.3)	15.2	110/3932 (2.8)	9.8	0.64 (0.48, 0.85)		
CV death or HHF*							0.1292
No / intermediate	38/345 (11.0)	39.1	39/754 (5.2)	17.8	0.48 (0.30, 0.75)		
Steatosis	160/1987 (8.1)	28.6	226/3932 (5.7)	20.1	0.70 (0.57, 0.85)		
All-cause mortality							0.6115
No / intermediate	44/345 (12.8)	44.3	59/754 (7.8)	26.3	0.62 (0.42, 0.92)		
Steatosis	150/1987 (7.5)	25.9	210/3932 (5.3)	18.1	0.70 (0.57, 0.86)		
Nephropathy							0.6849
No / intermediate	68/298 (22.8)	92.0	95/641 (14.8)	54.9	0.57 (0.42, 0.78)		
Steatosis	320/1762 (18.2)	73.4	430/3483 (12.3)	46.4	0.62 (0.53, 0.71)		

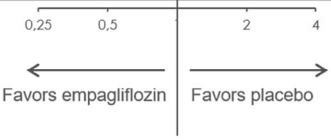


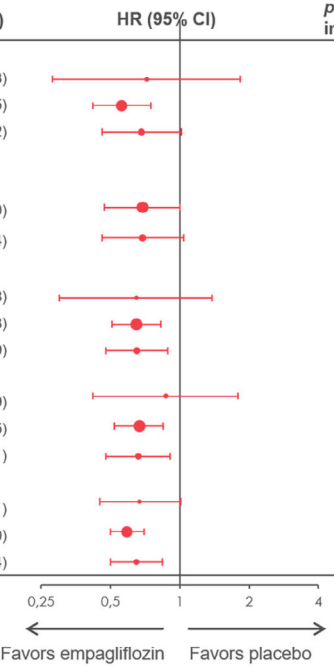
FIGURE 2 HR for empagliflozin versus placebo across different risk groups of (A) Dallas steatosis index (DSI), (B) hepatic steatosis index (HSI), (C) non-alcoholic fatty liver disease fibrosis score (NFS) and (D) Fibrosis-4 (FIB-4). The term "nephropathy" includes new onset or worsening of nephropathy. *Excluding fatal stroke. CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; IR, incidence rates; py, patient years

limit were found to be more frequent with empagliflozin treatment.[16] In the current analysis, we found no reduction in the number or percentage of people grouped at high risk of advanced fibrosis by NFS and FIB-4 with empagliflozin. However, a recent post-hoc analysis of DURATION-8 reported a small decrease in the proportions of participants at high risk for fibrosis by NFS and FIB-4 from baseline to 28 weeks in individuals with type 2 diabetes.[17] Furthermore, a real-word data analysis from people with type 2 diabetes who switched to sodium glucose co-transporter 2 inhibitor treatment also found the number of cases classified as advanced fibrosis by FIB-4 reduced after

(C)

NFS

	Placebo		Empagliflozin				*p*-value for interaction
	n/N (%)	IR/1000 py	n/N (%)	IR/1000 py	HR (95% CI)	HR (95% CI)	
CV death							0.6829
No fibrosis	7/243 (2.9)	9.6	12/566 (2.1)	7.0	0.72 (0.28, 1.83)		
Intermediate	88/1542 (5.7)	19.5	98/3020 (3.2)	11.0	0.56 (0.42, 0.75)		
Fibrosis	42/533 (7.9)	27.7	58/1066 (5.4)	18.7	0.68 (0.46, 1.02)		
HHF							0.9892
No fibrosis	7/243 (2.9)	9.8	5/566 (0.9)	3.0	NC		
Intermediate	47/1542 (3.0)	10.7	65/3020 (2.2)	7.5	0.69 (0.47, 1.00)		
Fibrosis	40/533 (7.5)	27.9	56/1066 (5.3)	18.9	0.69 (0.46, 1.04)		
CV death or HHF*							0.9997
No fibrosis	11/243 (4.5)	15.5	17/566 (3.0)	10.1	0.65 (0.30, 1.38)		
Intermediate	114/1542 (7.4)	26.0	149/3020 (4.9)	17.1	0.65 (0.51, 0.83)		
Fibrosis	72/533 (13.5)	50.2	96/1066 (9.0)	32.3	0.65 (0.48, 0.89)		
All-cause mortality							0.7764
No fibrosis	11/243 (4.5)	15.1	23/566 (4.1)	13.4	0.87 (0.42, 1.79)		
Intermediate	117/1542 (7.6)	26.0	156/3020 (5.2)	17.5	0.67 (0.52, 0.85)		
Fibrosis	65/533 (12.2)	42.9	86/1066 (8.1)	27.8	0.66 (0.48, 0.91)		
Nephropathy							0.7516
No fibrosis	37/213 (17.4)	66.5	63/503 (12.5)	46.0	0.67 (0.45, 1.01)		
Intermediate	254/1367 (18.6)	74.0	326/2688 (12.1)	45.4	0.59 (0.50, 0.70)		
Fibrosis	93/467 (19.9)	85.4	132/903 (14.6)	56.1	0.65 (0.50, 0.84)		



(D)

FIB-4

	Placebo		Empagliflozin				*p*-value for interaction
	n/N (%)	IR/1000 py	n/N (%)	IR/1000 py	HR (95% CI)	HR (95% CI)	
CV death							0.4435
No fibrosis	50/1130 (4.4)	15.0	75/2375 (3.2)	10.7	0.71 (0.50, 1.02)		
Intermediate	77/1091 (7.1)	24.4	79/2070 (3.8)	12.9	0.53 (0.38, 0.72)		
Fibrosis	10/99 (10.1)	35.9	14/207 (6.8)	23.2	0.67 (0.30, 1.50)		
HHF							0.3131
No fibrosis	31/1130 (2.7)	9.6	46/2375 (1.9)	6.7	0.71 (0.45, 1.11)		
Intermediate	52/1091 (4.8)	17.0	71/2070 (3.4)	12.0	0.70 (0.49, 1.00)		
Fibrosis	12/99 (12.1)	46.6	9/207 (4.3)	15.4	0.34 (0.15, 0.82)		
CV death or HHF*							0.3089
No fibrosis	71/1130 (6.3)	22.0	111/2375 (4.7)	16.2	0.74 (0.55, 1.00)		
Intermediate	108/1091 (9.9)	35.4	133/2070 (6.4)	22.4	0.63 (0.49, 0.81)		
Fibrosis	19/99 (19.2)	73.8	18/207 (8.7)	30.7	0.43 (0.23, 0.82)		
All-cause mortality							0.2903
No fibrosis	69/1130 (6.1)	20.8	117/2375 (4.9)	16.7	0.80 (0.60, 1.08)		
Intermediate	108/1091 (9.9)	34.2	124/2070 (6.0)	20.3	0.59 (0.45, 0.76)		
Fibrosis	16/99 (16.2)	57.5	24/207 (11.6)	39.7	0.71 (0.38, 1.33)		
Nephropathy							0.9288
No fibrosis	174/990 (17.6)	69.7	248/2088 (11.9)	44.5	0.62 (0.51, 0.75)		
Intermediate	193/969 (19.9)	81.4	248/1837 (13.5)	50.8	0.60 (0.50, 0.73)		
Fibrosis	18/89 (20.2)	86.4	25/169 (14.8)	55.4	0.68 (0.37, 1.24)		

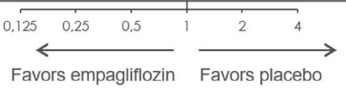


FIGURE 2 (Continued)

6 and 12 months.[18] At least in part, discrepancies in the different studies may be because of cohort characteristics. EMPA-REG OUTCOME included a type 2 diabetes collective with manifest cardiovascular disease, which often has progressive low-grade inflammation,[19,20] that may increase platelet count.[21] This effect may be counteracted by the previously reported anti-inflammatory effects of empagliflozin.[9] In EMPA-REG OUTCOME, platelet count, which is included in the denominator in FIB-4 and subtracted in NFS, was slightly lower with empagliflozin compared with placebo throughout the time of treatment and could contribute to the observed neutral

effect on fibrosis risk with empagliflozin. In contrast, serum albumin levels were higher with empagliflozin compared with placebo and may thereby contribute to lower NFS.

NAFLD closely associates with cardiorenal disease and risk is even increased in combined NAFLD and type 2 diabetes.[1] Patients grouped at high risk by either NFS or FIB-4 had higher placebo incidence rates of cardiovascular outcomes and all-cause mortality. While this observation may be expected, as age and/or serum albumin levels are included in the formulas,[22] several publications suggest that FIB-4 and/or NFS might be useful predictors of all-cause mortality in NAFLD with and without type 2 diabetes and thus help to improve risk stratification.[23-26] However, the relationship between risk scores and cardiorenal outcomes remains somewhat puzzling. Data from several cohorts as well as the present data show an association of FIB-4 and/or NFS high-risk categories with cardiovascular outcomes.[26,27] On the other hand, we did not observe an association of nephropathy with high-risk categories, in contrast to previous studies.[25,27] The differences in results may be at least partly because of cohort characteristics with different numbers of events. Moreover, smoking, baseline albuminuria, HbA1c, systolic blood pressure, glomerular filtration rate and haemoglobin concentrations were identified as determinants for progression of nephropathy in type 2 diabetes.[28] Thus, those risk factors may not be sufficiently reflected by fibrosis risk scores. Somewhat surprisingly, and although based on a low number of events, DSI and HSI identified individuals with low steatosis risk at highest incidence of cardiovascular and all-cause mortality endpoints. Of note, the degree of steatosis decreases during progression from advanced fibrosis to cirrhosis,[29] which might be an explanation of the observed results. Moreover, low body weight and thus (assumed) low liver fat as well as ALT values in the lower normal range were previously reported to associate with worse cardiovascular outcomes and mortality.[30] Of interest, advanced liver fibrosis (as measured by transient elastography) was identified as a risk marker and severe steatosis as a protective factor for cardiovascular complications and mortality in individuals with type 2 diabetes and NAFLD, which would support the present results.[31]

The present analysis further suggests that study participants in all steatosis and fibrosis risk categories profit similarly in relative terms from empagliflozin treatment in regard to cardiorenal outcome and all-cause mortality. Similarly, former analyses of the EMPA-REG OUTCOME study reported that cardiorenal treatment benefits with empagliflozin are consistent across age groups as well as underlying cardiovascular and heart failure risk.[32,33]

Major strengths of our analysis include the large number of enrolled participants, follow-up of more than 3 years, its placebo-controlled design and being the first to evaluate the effects of empagliflozin on risk of advanced fibrosis, metabolic parameters and cardiorenal outcomes dependent on steatosis and fibrosis category.

This analysis has also several limitations, as liver histology or imaging methods were not performed in the EMPA-REG OUTCOME. As with any clinical scoring system, the scores used herein merely imply the likelihood of but do not necessarily directly reflect the actual degree of steatosis or fibrosis. In addition, we cannot rule out other causes of fibrosis, as there was no defined assessment of alcohol intake and hepatitis serology foreseen in the trial protocol. This lack of data as well as the absence of records regarding liver-related clinical outcomes limits the interpretability and clinical significance of our data. However, as up to 20% of people with type 2 diabetes and NAFLD are predicted to have clinically relevant fibrosis,[1] NAFLD most likely represents the underlying cause in most cases.

In addition, the use of steatosis and fibrosis biomarkers has rarely been validated for assessment of longitudinal changes in these parameters in response to pharmacological treatment[34] and changes in the scores may also be driven by some components of the scores and not sufficiently reflect changes in liver tissue. Moreover, empagliflozin effects on hepatic fibrosis may not necessarily be detected by the indices even if present as one could assume that improvement of steatosis may also affect fibrosis in the long-term.[2,13] Of note, changes in NFS were previously associated with changes in liver fibrosis after 1 year of lifestyle intervention[35] suggesting a dynamic response to histological changes. Nevertheless, the current analyses do not support the beneficial effects of empagliflozin on hepatic fibrosis in type 2 diabetes.

In our post-hoc analyses, we did not adjust for multiple comparisons, as we considered them exploratory. Of note, this trial was not primarily powered to assess the cardiorenal effects of empagliflozin in different steatosis and fibrosis categories so that the differences in patient numbers of each risk category may limit interpretation of the obtained results. In addition, cohort size continuously dropped with time so that missing significances for scores between empagliflozin and placebo at later time points may rather result from loss of power than from time-dependent effects of empagliflozin itself.

NFS and FIB-4 were developed for assessment of fibrosis severity in NAFLD cohorts encompassing the whole clinical and histological liver disease spectrum. As our cohort was a preselected collective – because of the trial's inclusion and exclusion criteria,[7] liver-related findings from this study may be interpreted with caution and only adopt to patients with type 2 diabetes, cardiovascular disease and no or mild liver impairment.

Furthermore, several laboratory parameters were not routinely measured in the trial so that the steatosis markers recommended for NAFLD screening in the current European guidelines[2] (fatty liver index, NAFLD liver fat score) could not be calculated. However, we calculated HSI and DSI for assessing steatosis risk in our cohort.[10,11] As the major limitation of DSI, there is still only one external validation study for this index, which was not focused on for type 2 diabetes.[36]

Of note, most steatosis and fibrosis indices are considered imperfect markers, as their variability is high and their positive predictive value in terms of NAFLD and NASH seems limited.[4,27,37,38] Furthermore, they have not been specifically developed for individuals with type 2 diabetes. Several studies even suggest that non-invasive tests may perform less well when applied to individuals with type 2 diabetes[37] and many of them include type 2 diabetes as a risk factor in their formulas.[38] In our study and previous reports, steatosis and fibrosis scores identified different proportions of people at high risk for steatosis or advanced fibrosis[27] so that results derived from a single index need to be interpreted with caution. Nevertheless, the 2020 American[39,40] and European guidelines on clinical management of

NAFLD[2] recommend using surrogate markers of steatosis and fibrosis for screening of patients at high risk of NAFLD, including patients with type 2 diabetes.[2]

In conclusion, empagliflozin may improve steatosis (DSI, HSI) but not fibrosis (NFS, FIB-4) risk in patients with type 2 diabetes and pre-existing cardiovascular disease. High-risk categories of fibrosis were associated with higher incidence of cardiovascular events. Empagliflozin further seemed to improve cardiorenal outcomes across all steatosis and fibrosis categories. With a lack of large-scale, prospective randomized placebo-controlled clinical trials, including imaging or histology for assessment of steatosis and fibrosis, this study adds relevant information on the potential effects of empagliflozin on NAFLD, and on the cardiorenal effects of empagliflozin in varying risk groups of patients with type 2 diabetes. Nevertheless, future research, including liver histology and/or imaging, is needed to assess better the potential benefits of empagliflozin treatment on fibrosis and its importance for clinical practice.

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CONFLICT OF INTEREST

SK has received research grants from the German Center for Diabetes Research (DZD e.V.) and the German Diabetes Society (DDG). APO is employee of Boehringer Ingelheim. BZ has received research grants awarded to his institution from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk, and honoraria from Janssen, Sanofi, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, and Merck Sharp & Dohme. CW reports honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Bayer and Sanofi. ES is employee of mainanalytics, contracted by Boehringer Ingelheim. NS has consulted for Amgen, Astrazeneca, Boehringer Ingelheim, Eli-Lilly, Hanmi, MSD, Novartis, Novo-Nordisk, Pfizer and Sanofi and received grant support from Astrazeneca, Boehringer Ingelheim, and Roche Diagnostics. SEI has received honoraria for lectures, advisory work and/or clinical trial leadership from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Merck, Lexicon, Esperion, vTv Therapeutics, Abbott and Pfizer. MR has served on scientific advisory boards or received speaker's honoraria for Allergan, Boehringer-Ingelheim Pharma, Bristol-Myers Squibb, Eli Lilly, Fishawack Group, Gilead Sciences, Novartis Pharma, Intercept Pharma, Inventiva, Novo Nordisk, Target NASH. He has been also a consultant for Terra Firma and involved with clinical trial research for Boehringer Ingelheim, Danone Nutricia Research and Sanofi-Aventis.

DATA AVAILABILITY STATEMENT

The sponsor of the study (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the following website (https://trials.boehringer-ingelheim.com/).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14670.

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REFERENCES

1. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. *Nat Rev Gastroenterol Hepatol*. 2017;14(1):32-42. doi:10.1038/nrgastro.2016.147
2. EASL-EASD-EASO. Clinical practice guidelines for the management of non-alcoholic fatty liver disease. *Diabetologia*. 2016;59(6):1121-1140. doi:10.1007/s00125-016-3902-y
3. EASL. Clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol*. 2021;75(3):659-689. doi:10.1016/j.jhep.2021.05.025
4. Kahl S, Straßburger K, Nowotny B, et al. Comparison of liver fat indices for the diagnosis of hepatic steatosis and insulin resistance. *PLoS One*. 2014;9(4):e94059. doi:10.1371/journal.pone.0094059
5. Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2014;40(10):1209-1222. doi:10.1111/apt.12963
6. Dewidar B, Kahl S, Pafili K, Roden M. Metabolic liver disease in diabetes - from mechanisms to clinical trials. *Metabolism*. 2020;111s:154299. doi:10.1016/j.metabol.2020.154299
7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
8. Kahl S, Gancheva S, Straßburger K, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. *Diabetes Care*. 2020;43(2):298-305. doi:10.2337/dc19-0641
9. Tsai KF, Chen YL, Chiou TT, et al. Emergence of SGLT2 inhibitors as powerful antioxidants in human diseases. *Antioxidants (Basel)*. 2021;10(8):1166. doi:10.3390/antiox10081166
10. McHenry S, Park Y, Browning JD, Sayuk G, Davidson NO. Dallas steatosis index identifies patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2020;18(9):2073-2080.e7. doi:10.1016/j.cgh.2020.01.020

11. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis*. 2010; 42(7):503-508. doi:10.1016/j.dld.2009.08.002
12. Kuchay MS, Krishan S, Mishra SK, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT trial). *Diabetes Care*. 2018;41(8):1801-1808. doi:10.2337/dc18-0165
13. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. *Gastroenterology*. 2018;155(2):443-457.e17. doi:10.1053/j.gastro.2018.04.034
14. Lai LL, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Empagliflozin for the treatment of nonalcoholic steatohepatitis in patients with type 2 diabetes mellitus. *Dig Dis Sci*. 2020;65(2):623-631. doi:10.1007/s10620-019-5477-1
15. Sattar N, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. *Diabetologia*. 2018;61(10):2155-2163. doi:10.1007/s00125-018-4702-3
16. Kinduryte Schorling O, Clark D, Zwiener I, Kaspers S, Lee J, Iliev H. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. *Adv Ther*. 2020;37(8):3463-3484. doi:10.1007/s12325-020-01329-7
17. Gastaldelli A, Repetto E, Guja C, et al. Exenatide and dapagliflozin combination improves markers of liver steatosis and fibrosis in patients with type 2 diabetes. *Diabetes Obes Metab*. 2020;22(3):393-403. doi:10.1111/dom.13907
18. Colosimo S, Ravaioli F, Petroni ML, et al. Effects of antidiabetic agents on steatosis and fibrosis biomarkers in type 2 diabetes: a real-world data analysis. *Liver Int*. 2021;41(4):731-742. doi:10.1111/liv.14799
19. Möser CZO, Rothe M, Hwang JH, et al. Incident myocardial infarction is associated with insulin resistance and liver fibrosis scores. *Diabetes*. 2020;69(suppl 1):22-LB.
20. Elimam H, Abdulla AM, Taha IM. Inflammatory markers and control of type 2 diabetes mellitus. *Diabetes Metab Syndr*. 2019;13(1):800-804. doi:10.1016/j.dsx.2018.11.061
21. Jesri A, Okonofua EC, Egan BM. Platelet and white blood cell counts are elevated in patients with the metabolic syndrome. *J Clin Hypertens (Greenwich)*. 2005;7(12):705-711; quiz 712-3. doi:10.1111/j.1524-6175.2005.04809.x
22. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. *J Clin Epidemiol*. 1997;50(6):693-703. doi:10.1016/s0895-4356(97)00015-2
23. Treeprasertsuk S, Björnsson E, Enders F, Suwanwalaikorn S, Lindor KD. NAFLD fibrosis score: a prognostic predictor for mortality and liver complications among NAFLD patients. *World J Gastroenterol*. 2013;19(8):1219-1229. doi:10.3748/wjg.v19.i8.1219
24. Golabi P, Stepanova M, Pham HT, et al. Non-alcoholic steatofibrosis (NASF) can independently predict mortality in patients with non-alcoholic fatty liver disease (NAFLD). *BMJ Open Gastroenterol*. 2018; 5(1):e000198. doi:10.1136/bmjgast-2018-000198
25. Leite NC, Cardoso CRL, Salles GF. Importance of non-invasive liver fibrosis scores for mortality and complications development in individuals with type 2 diabetes. *J Diabetes Complications*. 2021;35(5): 107879. doi:10.1016/j.jdiacomp.2021.107879
26. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. *Hepatology*. 2013;57(4):1357-1365. doi:10.1002/hep.26156
27. Ciardullo S, Muraca E, Perra S, et al. Screening for non-alcoholic fatty liver disease in type 2 diabetes using non-invasive scores and association with diabetic complications. *BMJ Open Diabetes Res Care*. 2020;8(1):e000904. doi:10.1136/bmjdrc-2019-000904
28. Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of nephropathy in type 2 diabetic patients. *Kidney Int*. 2004;66(4):1596-1605. doi:10.1111/j.1523-1755.2004.00925.x
29. Lok AS, Everhart JE, Chung RT, et al. Evolution of hepatic steatosis in patients with advanced hepatitis C: results from the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial. *Hepatology*. 2009;49(6):1828-1837. doi:10.1002/hep.22865
30. Doehner W, Gerstein HC, Ried J, et al. Obesity and weight loss are inversely related to mortality and cardiovascular outcome in prediabetes and type 2 diabetes: data from the ORIGIN trial. *Eur Heart J*. 2020;41(28):2668-2677. doi:10.1093/eurheartj/ehaa293
31. Cardoso CRL, Villela-Nogueira CA, Leite NC, Salles GF. Prognostic impact of liver fibrosis and steatosis by transient elastography for cardiovascular and mortality outcomes in individuals with nonalcoholic fatty liver disease and type 2 diabetes: the Rio de Janeiro Cohort Study. *Cardiovasc Diabetol*. 2021;20(1):193. doi:10.1186/s12933-021-01388-2
32. Monteiro P, Bergenstal RM, Toural E, et al. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial. *Age Ageing*. 2019;48(6):859-866. doi:10.1093/ageing/afz096
33. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation*. 2019; 139(11):1384-1395. doi:10.1161/circulationaha.118.037778
34. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. *JHEP Rep*. 2020;2(2):100067. doi:10.1016/j.jhepr.2020.100067
35. Vilar-Gomez E, Calzadilla-Bertot L, Friedman SL, et al. Serum biomarkers can predict a change in liver fibrosis 1 year after lifestyle intervention for biopsy-proven NASH. *Liver Int*. 2017;37(12):1887-1896. doi:10.1111/liv.13480
36. McHenry S, Park Y, Davidson NO. Validation of the Dallas steatosis index to predict nonalcoholic fatty liver disease in the UK Biobank population. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21):00573-5. [online ahead of print] doi:10.1016/j.cgh.2021.05.035.
37. Bertot LC, Jeffrey GP, de Boer B, et al. Diabetes impacts prediction of cirrhosis and prognosis by non-invasive fibrosis models in non-alcoholic fatty liver disease. *Liver Int*. 2018;38(10):1793-1802. doi:10.1111/liv.13739
38. Bril F, McPhaul MJ, Caulfield MP, et al. Performance of plasma biomarkers and diagnostic panels for nonalcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes. *Diabetes Care*. 2020;43(2):290-297. doi:10.2337/dc19-1071
39. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357. doi:10.1002/hep.29367
40. American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(suppl 1):S37-s47. doi:10.2337/dc20-S004

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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