**TITLE**

# Update on cardiovascular risk in non-alcoholic fatty liver disease


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## ABSTRACT

### PURPOSE OF REVIEW

To summarise recent evidence demonstrating increased cardiovascular disease (CVD) risk, and how CVD risk may be reduced, in patients with non-alcoholic fatty liver disease (NAFLD).

### RECENT FINDINGS

NAFLD is a multi-system disease, defined by a spectrum of liver fat-associated conditions extending from simple steatosis, to inflammation, fibrosis and cirrhosis. NAFLD not only increases risk of liver morbidity and mortality but also increases risk of CVD morbidity and mortality and is associated with recognised CVD risk factors such as hypertension, atherogenic dyslipidaemia, type 2 diabetes and chronic kidney disease. Evidence suggests that liver fibrosis stage may be a strong CVD risk factor. Lifestyle measures (e.g. weight loss and increased physical activity) are effective in improving CVD risk factors. Hypoglycaemic agents, such as the peroxisome proliferator-activated receptor gamma agonist pioglitazone and the glucagon-like peptide-1 receptor agonist liraglutide, reduce cardiovascular risk and may improve liver histology. Statin and antihypertensive treatments are safe and currently it is unclear whether novel anti-fibrotic drugs will reduce CVD risk.

### SUMMARY

Assessment and treatment of increased cardiovascular risk is important in patients with NAFLD. If not contra-indicated, pioglitazone or a GLP-1 agonist should be considered and may benefit both CVD risk and early liver disease.



### KEYWORDS

“cardiovascular disease”, “non-alcoholic fatty liver disease”, “non-alcoholic steatohepatitis”, “cardiovascular risk”, “cardiovascular”.

**MAIN TEXT**

## 1.0 INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease ranging from simple steatosis of the liver to the more severe form non-alcoholic steatohepatitis (NASH). Patients with NAFLD may develop liver-related complications such as worsening liver fibrosis, liver cirrhosis and hepatocellular carcinoma (HCC).[1] The presence of NASH is particularly strongly associated with rate of progression of liver fibrosis.[2] However, the most common cause of death in people with NAFLD is not liver-related death but cardiovascular disease (CVD) related death.[3] NAFLD is associated with several CVD risk factors including central obesity[4],[5], hypertension[5],[6], chronic kidney disease (CKD)[7], hyperlipidaemia[5] and the metabolic syndrome (MetS).[5] Worryingly, NAFLD is extremely common, affecting approximately 25% of the global adult population.[5], with a particularly high prevalence in patients with type 2 diabetes mellitus (T2DM).[8] The global prevalence of NAFLD and NASH amongst people with T2DM is reported to be as high as 55% and 37% respectively.[8] Amongst patients admitted for coronary angiography it is reported that up to 58% of patients have NAFLD.[9]

Historically there may have been a perception amongst non-gastroenterologists that NAFLD is not common in their own patient group.[10] Clinicians may also be falsely reassured by relatively normal liver enzyme levels which will inevitably result in patients being inappropriately reassured that they do not have serious liver disease. For example in a biopsy series of 305 individuals with NAFLD, 24% of the patients with normal alanine transaminase (ALT) levels (women, ALT≤30 iU/L; men, ALT≤45 iU/L) had advanced fibrosis (Kleiner stage 3-4).[11]

In this brief review, we discuss the atherogenic lipid profile in patients with NAFLD and the association between NAFLD and CVD outcomes. We discuss the CVD effects of pharmacological agents used in the treatment of T2DM that are thought to also have beneficial liver effects, and we discuss the CVD effects of pharmacological agents that are specifically being tested for the treatment of liver disease in NAFLD.

## 2.0 ATHEROGENIC LIPOPROTEIN PHENOTYPE, LIPID METABOLISM AND GENOTYPES AFFECTING CVD RISK IN NAFLD

The typical lipid profile in NAFLD is referred to as the atherogenic lipoprotein phenotype consisting of high fasting concentration of triglyceride (TG), low concentration of high density lipoprotein cholesterol (HDL) and

increased small dense low density lipoprotein (sdLDL).[12-14] NAFLD also appears to be associated with increased concentration of atherogenic remnant lipoprotein cholesterol which, when fasting, is the cholesterol in intermediate density and very low density lipoprotein cholesterol (IDL and VLDL)[15], and increased remnant lipoprotein cholesterol is associated with development of coronary artery disease.[16] NAFLD is strongly associated with insulin resistance and obesity[17] and in NAFLD the combination of dietary overload, expansion of adipose tissue and lipolysis of adipose tissue secondary to insulin resistance, leads to increased flux of free fatty acids to the liver.[18] NAFLD is associated decreased hepatic insulin clearance, insulin resistance and hyperinsulinaemia which stimulates hepatic fatty acid synthesis [19].

There are also genetic factors that affect lipid metabolism in NAFLD and that also potentially modify NAFLD-associated CVD risk.[20] It is difficult to predict which patients with NAFLD will develop predominantly hepatic complications (e.g cirrhosis and HCC) and which patients will develop predominantly non-hepatic complications (e.g. T2DM, CVD and CKD).[17] Five genes have emerged as reproducibly and robustly predisposing individuals to development of liver disease in NAFLD: patatin-like phospholipase domain-containing protein 3 (PNPLA3); trans-membrane 6 super family 2 (TM6SF2); glucokinase regulator (GCKR); membrane bound O-acyltransferase domain containing 7 (MBOAT7); and 17-beta hydroxysteroid dehydrogenase-13 (HSD17B13).[20] The complex contributory roles of these genes are beyond the scope of this review. However, it remains of considerable interest whether genetic variations individually or collectively can differentially influence the risk of hepatic disease, versus CVD risk. The first genetic variant which was found to be associated with NASH, is a non-synonymous single-nucleotide polymorphism in PNPLA3 known as rs738409 c.444 C>G p.I148M.[21] PNPLA3 is a storage protein but cleaves fatty acids from membrane lipids by its lipase activity.[22] PNPLA3 encodes a lipid droplet protein and is involved at this lipolytic step. This genetic variant PNPLA3 I148M is associated with higher serum ALT levels[23], increased liver steatosis and fibrosis[23] and increased prevalence of HCC.[24],[25] Conversely, although advanced forms of NAFLD are associated with increased risk of CVD, there is little evidence proving conclusively that accumulation of liver fat specifically, causes atherosclerosis.[26] Compared to ancestral PNPLA3 148I (as the reference allele) there may even be a slightly reduced risk of incident CVD in those with PNPLA3 148M, odds ratio (OR) 0.98 (95% confidence interval (CI) 0.96–1.00).[27] Similar results were obtained by screening DNA sequence variants on an exome-focused genotyping array in >300,000 participants with replication in >280,000 participants. In this analysis, *PNPLA3* 148M and also TM6SF2 E167K, were associated with higher

liver fat levels, higher risk for T2DM, but lower levels of serum triglyceride (which is a good proxy for VLDL concentrations in the fasted state) and lower risk of CVD.[28] The decreased risk of CVD with *PNPLA3* 148M was small but more significant [OR 0.96 (95%CI 0.94–0.97), *P* = 0.00000004 and for TM6SF2 E167K OR 0.95 (95%CI 0.93–0.98), *P* = 0.0003]. Thus, in NAFLD, the presence of these two genotypes creates a disconnect between the severity of liver disease and the risk of CVD. Specifically, despite both genotypes being associated with more severe liver disease and increased risk of T2DM, the presence of either genotype is associated with lower levels of serum TG and lower risk of CVD. That both genotypes are known to influence VLDL[29] and are associated with lower levels of fasting TG levels[30],[31], suggests a plausible mechanism by which NAFLD increases CVD risk; namely via NAFLD-associated increased production of VLDL. With the frequently observed NAFLD-associated increase in TG rich-VLDL, there is increased cholesterol ester transfer protein activity, that regulates the reciprocal exchange of TG from TG rich lipoproteins with cholesterol esters from cholesterol ester-rich lipoproteins such as HDL and low density lipoprotein (LDL). The net effect of these exchanges is a consequent decrease in HDL cholesterol concentration, an increase in sdLDL levels which together with increased fasting TG concentrations is referred to as the atherogenic lipoprotein phenotype (described above).

## 3.0 CARDIOVASCULAR RISK IN NAFLD

The commonest cause of death in patients with NAFLD is CVD.[3] Historically there has been debate as to whether NAFLD is independently associated with CVD risk, or whether its association with other CVD risk factors is responsible for the relationship between NAFLD and CVD.[32] Indeed, a recent study of >17 million patients in a primary care database added to the debate, when its findings suggested there was no independent association between NAFLD and acute myocardial infarction (AMI).[33] In the dataset there were >120,000 patients with NAFLD. The hazard ratio for acute myocardial infarction after adjusting for blood pressure, T2DM, total cholesterol level, statin use, and hypertension was 1.01 (95% CI, 0.91, 1.12). However, only <2% of the primary care population studied had a diagnosis of NAFLD, which appears to be a profound underestimate based on numerous observations in recent years.[5] This would suggest misclassification of some subjects in the control group with the potential for subsequent misclassification bias attenuating the strength of any association towards the null.

On the other hand, a previous 2016 meta-analysis of 16 observational studies that included ~34,000 middle-aged individuals with a median 6.9-year follow-up demonstrated an independent association between NAFLD and CVD outcomes.[34] That meta-analysis showed that after adjustment for potential confounders individuals with NAFLD had a 64% higher risk of developing fatal and/or non-fatal CVD events compared to those without NAFLD.

There is also evidence that in a general population undergoing comprehensive health check-up, those individuals with NAFLD have a higher coronary artery calcification score (CACS) on coronary CT scan compared to individuals without NAFLD, median baseline CACS 4.0 vs 1.0 ($p<0.001$) respectively.[35] Furthermore, over an average duration of follow-up of 3.9 years, the annual rate of CACS progression in individuals with NAFLD was 22% vs 17% in those without NAFLD ($p<0.001$).[35]

More recently, a prospective cohort study of 325 patients admitted with AMI evaluated risk of adverse cardiovascular outcome, defined as electrocardiogram instability (ventricular tachycardia, ventricular fibrillation or atrioventricular block), hemodynamic instability (systolic blood pressure <90 mmHg caused by heart failure or shock), and death during hospitalization.[36] Multivariate logistic regression analysis demonstrated that NAFLD was an independent predictor for AMI patients' adverse cardiovascular events, odds ratio 1.11 (95%CI 1.04–1.32)[36]

Furthermore, there is the suggestion that the risk of CVD events parallels the underlying severity of NAFLD, and that the stage of liver fibrosis is the strongest histologic predictor of adverse liver-related outcomes as well as potentially predict CVD outcomes in NAFLD.[37],[38]

## 4.0 POTENTIAL DRUG THERAPY IN NAFLD

To date, the cornerstone of management in people with NAFLD has been lifestyle modification leading to weight loss.[39] After 52 weeks, weight loss of ≥7% was associated with resolution of NASH and regression of fibrosis.[40] Furthermore, weight loss has additional cardiometabolic effects which include reduction in HbA1c, reduction in triglyceride concentration and reduction in need for antihypertensive therapy.[41] The three European Associations for the Study of the Liver, Obesity and Diabetes (EASL, EASO, EASD), as well as American Association for the Study of Liver Disease (AASLD), clinical practice guidelines for

management of NAFLD emphasize that in overweight or obese individuals with NAFLD, 5-10% weight loss is the primary aim of lifestyle interventions.[42],[43]

Nonetheless, pharmacotherapy remains a potentially complementary option for those who do lose weight or is a potential alternative in those who do not manage to lose weight. Current recommendations are that pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis. Patients with less severe disease but at high risk of disease progression (i.e. with T2DM, MetS, persistently increased ALT, high necroinflammation) could also be candidates for treatment to prevent disease progression.[43]

Below we discuss important drugs that are currently licensed for conditions associated with NAFLD, and which may also benefit liver disease in NAFLD. We also discuss the potential of newer antifibrotic agents to have deleterious secondary effects on CVD risk. The paradigm for the drug of choice in NAFLD would be a drug which not only improves liver-related risk, but also reduces CVD risk and improves glycaemic control (as illustrated in **Figure 1**).

### 4.1 PIOGLITAZONE AND PPAR AGONISTS

Peroxisome proliferator-activated receptors (PPAR) are a family of nuclear receptors that play a role in the regulation of many metabolic processes affecting risk of liver disease, T2DM and CVD. One such example is the PPAR-γ agonist pioglitazone (a thiazolidinedione class of drug). Although there are recognized side effects of pioglitazone, such as weight gain[44], worsened heart failure and/or oedema[45] and increased risk of bone fracture.[46] (There has been a previously observed association between pioglitazone use and bladder cancer[47] but there is no evidence of a causative relationship between pioglitazone and bladder cancer.) It is clear that pioglitazone benefits liver disease in NASH in patients both with, and without T2DM.[44],[48]

Pioglitazone is one of the currently available drugs which not only improves glycaemic control, but also improves liver histology and reduces CVD risk.[49] Previous meta-analysis has demonstrated that pioglitazone resolves NASH in 47% of cases.[44] Pioglitazone has also been shown to confer additional benefits to treat T2DM and decrease the risk of myocardial infarction and stroke.[50],[51] Indeed pioglitazone is the only drug which is recommended by the AASLD and EASL as potential pharmacotherapy in patients

with histologically proven NASH.[42],[43] **Figure 1** illustrates the multi-organ benefits[49] that pioglitazone confers as a potential agent for use in NAFLD. **Table 1** summarises the evidence of liver, diabetes and CVD benefits conferred by pioglitazone, as well as recognised side-effects that may preclude its use in certain individual cases.

There has also been considerable interest in other PPAR agonists in the treatment of NASH. A phase II trial, that tested the PPAR-α/δ agonist Elafibranor versus placebo, suggested in post-hoc analysis that Elafibranor significantly increased NASH resolution.[52] Furthermore, there appeared to be secondary benefits of Elafibranor which included significant reduction in LDL cholesterol, TG and HbA1c.[52] However, interim results from the phase III trial (RESOLVE-IT) of Elafibranor failed to show efficacy versus placebo.[53] Peer-reviewed publication of the findings of RESOLVE-IT and its extension phase are awaited. More recently, in patients with non-cirrhotic NASH, the results of a phase IIb trial of Lanifibranor (a combined PPAR-α/δ/γ agonist) versus placebo, were presented in abstract form.[54] This trial demonstrated that Lanifibranor reached its primary endpoint (histological improvement defined as ≥2 point reduction in steatosis, activity, fibrosis (SAF) Activity score) and also significantly increased serum HDL, decreased serum TG. A Phase 3 trial[55] of Lanifibranor has been announced and is being planned. In **Figure 1** we have suggested that Lanifibranor may be a potential trial drug for use in patients with biopsy proven NASH, but which also has potential secondary CVD benefits for the trial participants in terms of improving HDL and TG levels, decreasing glucose concentrations and decreasing CVD risk.

It is also of interest to consider the potential benefit of PPAR-α agonism with the agent fenofibrate.[56] Fenofibrate has been investigate in a 12 week multicentre double-blind placebo controlled randomised controlled trial (RCT).[56] Eligible candidates who were overweight and had a MRI-PDFF (magnetic resonance imaging proton density fat fraction) >5.5% were treated with fenofibrate 200mg, or omega-3 carboxylic acids, or placebo. Exclusion criteria included T2DM. However, in this study which used the non-histological primary endpoint of reduction in liver PDFF, fenofibrate did not change liver PDFF significantly versus placebo.

### 4.2 GLUCAGON-LIKE PEPTIDE-1 AGONISTS

The GLP-1 agonist liraglutide is a glucose-lowering agent used either in combination with drugs for diabetes, or as monotherapy (if metformin is contraindicated) (**Figure 1**). Liraglutide appears to decrease risk of major

cardiovascular events, acute myocardial infarction, cardiovascular-related mortality and all-cause mortality.[57],[58] However, in addition to these cardiovascular benefits, liraglutide appears to be significantly associated with resolution of NASH.[59] The double blinded randomised placebo-controlled LEAN trial demonstrated resolution of NASH at 48 weeks in 9/23 (39%) of patients who received liraglutide versus 2//22 (9%) of patients who received placebo.[59] However, it remains unclear whether there is a plausible biological mechanism for this observed effect other than weight loss, because in the LEAN trial there was a non-significant effect of liraglutide on NASH resolution after adjusting for weight loss.[59] The clinical CVD benefits and histological liver benefits of liraglutide are summarised in **Table 1**.

The class benefit of GLP-1 agonists on NASH resolution was also demonstrated in a recent randomized, double-blind, placebo-controlled, parallel-group trial of the GLP-1 agonist semaglutide in patients with NASH.[60] However, this study did not demonstrate any improvement in fibrosis stage. Furthermore, the authors did not adjust for the effect of weight loss on resolution of NASH. A recent open label randomised controlled trial of GLP-1 agonist dulaglutide versus usual care in patients with T2DM demonstrated a significant reduction in liver fat content defined by MRI-PDFF. There was also no adjustment for weight loss.[61]

Per-protocol analysis of randomised controlled trial of dulaglutide (n=27) vs standard care as control (n=25), demonstrated a significant relative reduction in liver fat content in those who received dulaglutide vs standard of care, -32.1% vs -5.7% respectively (p-0.004). However, similar to LEAN study, it is important to note that body weight and body mass index (BMI) declined more in the dulaglutide group vs standard of care.[61]

Therefore, the apparent secondary benefits of GLP-1 agonists on NASH resolution are relevant to clinicians managing CVD risk. However, at the current time it would still appear premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH.

### 4.3 OBETICHOLIC ACID FARNESOID X RECEPTOR AGONISTS

Obeticholic acid (OCA) is bile acid analogue that is a potent ligand for the farnesoid X receptor (FXR), which is a nuclear receptor/transcription factor involved in regulation of bile acids, lipid and glucose metabolism, and hepatic inflammation and fibrosis.[62]. In a phase 2 trial of OCA in patients with biopsy-proven NASH, OCA was significantly associated with an improvement in NAFLD activity score without worsening in fibrosis.[63] However, in the phase 2 trial of OCA in NASH[63] and the subsequent phase 3 trial of OCA

treatment in patients with NASH[64], there was a significant decrease in HDL cholesterol and increase in LDL cholesterol in patients treated with OCA. Concurrent prescription of atorvastatin 10mg may mitigate OCA-induced increases in LDL concentration[65]. However, it is well accepted that in patients treated with statins there is still on-treatment residual CVD risk and the true effects of OCA on CVD risk may not become clear until longer follow-up is available.

### 4.4 LIPID LOWERING THERAPIES

#### 4.4.1 STATINS

There is a longstanding association between statin therapy and mild elevations in liver transaminases.[66] This may help explain the previous observation that NAFLD is associated with a decreased rate of prescription of statins despite being indicated based on CVD risk.[67] However, both the AASLD and EASL clinical practice guidelines recommend that statins are safe in patients with NAFLD/NASH and that statins are not associated with serious liver injury in patients with NAFLD/NASH.[42],[43] A previous cross-sectional analysis of a 167,729 people in the Netherlands [which defined the presence of NAFLD based on the non-invasive Fatty Liver Index[68] (FLI)] demonstrated that the presence of NAFLD was associated with an increased estimated 10-year cardiovascular risk and indication for statin treatment.[69]

There is growing interest in the prognostic benefit of statin on overall mortality in patients with chronic liver disease[70], and given the association between NAFLD and CVD risk discussed in **Section 3.0**, it would appear rationale to consider the potential clinical benefit of statin therapy in patients with NAFLD.[71] However, studies to date have not demonstrated robust evidence of benefit of statin therapy on liver-related outcomes in patients with NAFLD/NASH. Nelson A et al. previously published findings of a randomised controlled trial of simvastatin versus placebo in patients with histologically defined NASH.[72] This study showed no benefit of statins on histological severity, but the study was very small with only 10 patients having a follow-up biopsy at 1 year.[72] A previous Cochrane review[73] of randomised clinical trials using statins for the primary treatment for NAFLD/NASH was only able to consider two studies that were eligible for inclusion. One of the included studies was the study discussed above[72], and the other study[74] was an open label randomised study of atorvastatin vs fenofibrate vs both drugs, with no placebo-controlled arm, that did not test treatment effects on histological endpoints.

Therefore, in view of the lack of large-scale randomised placebo-controlled trials to test the effects of statins on liver histological endpoints; neither AASLD nor EASL, currently recommend statin use specifically to treat liver disease in NAFLD.[42],[43].

### 4.4.2 EZETIMIBE

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) was a large international, multicenter randomized controlled trial, designed to assess the impact of ezetimibe on CV morbidity and mortality, in patients admitted to the hospital with recent acute coronary syndrome (ACS).[75] In an additional prospective analysis[76] of the IMPROVE IT Simon TG et al. applied the NAFLD Fibrosis Score (NFS)[77] to 14,819 patients randomised to ezetimibe/simvastatin or placebo/simvastatin. The results of this study demonstrated that the high-risk NFS group had a higher risk of CV events, compared to lower risk NFS group. However, there was no adjustment made for T2DM or BMI, both of which are variables in the NFS. Furthermore, in the sensitivity analysis, when diabetes was excluded there was no significant difference in CVD risk between high- and low-risk NFS groups. The authors also concluded that the high-risk NFS group was significantly more likely to benefit from early ezetimibe treatment. However, the interventions in this trial were not randomised based on NFS-group, and given the study design, the NFS-groups were not well matched, with significant differences between the groups in age, sex, BMI, smoking status, hypertension, T2DM, stroke, history of AMI, and history of coronary artery bypass grafting.

Unfortunately, although a previous meta-analysis[78] of six studies of ezetimibe in NAFLD (two RCTs and four single arm trials) demonstrated a reduction in concentrations of liver enzymes, hepatic steatosis and hepatocellular ballooning; it did not demonstrate any evidence of histologically meaningful outcomes, i.e. fibrosis stage or inflammation. However, ezetimibe does appear to improve hepatic steatosis.[79] This meta-analysis included a 2015 RCT of 50 patients randomised to placebo or ezetimibe with histological diagnosis of NASH.[80] The primary outcome was a change in liver fat measured by MRI-PDFF. Ezetimibe was not significantly better than placebo at reducing liver fat. Therefore, given the lack of robust evidence to suggest a benefit of ezetimibe neither EASL nor AASLD clinical practice guidelines make any recommendations regarding use of ezetimibe in patients with NAFLD/NASH.[42],[43]

## 5.0 CONCLUSION

NAFLD is a common disease whose global prevalence is increasing with the epidemic of obesity. NAFLD is strongly associated with traditional cardiovascular risk factors such as hypertension, the atherogenic lipoprotein phenotype and T2DM, and CVD risk assessment is important in order to determine whether conventional treatment is warranted to attenuate CVD risk. Although genotyping remains a research tool, it is now becoming apparent that certain genotypes (e.g. PNPLA3 I148M and TM6SF2 E167K) have the capability of not only influencing the severity of liver disease, but also of modifying CVD risk.

Although weight loss is the most established management strategy, there are now available drugs that not only ameliorate the histological changes of NAFLD, but also reduce CVD risk, namely pioglitazone and GLP-1 agonists. To date there is no trial evidence showing the efficacy of both drugs used in combination in NAFLD. Since pioglitazone and GLP-1 agonists have different and complementary actions, we suggest that a factorial trial is needed, to test whether dual therapy is merited in the treatment of NASH. With regard to other agents in development for NAFLD, it is possible that some agents such as OCA will make CVD risk reduction more challenging. Therefore, knowledge of NAFLD and the relevant drugs used in patients with NAFLD will be important for any clinicians managing CVD risk in their clinic.

## KEY POINTS

- Non-alcoholic fatty liver disease is independently associated with cardiovascular risk
- The hypoglycaemic agents pioglitazone and liraglutide, which are indicated for use in type 2 diabetes, both improve cardiovascular related outcomes and improve liver histology.
- The only agent to demonstrate significant improvement in liver fibrosis in non-alcoholic fatty liver disease in a phase III trial is obeticholic acid.
- Obeticholic acid is associated with a significant decrease in high density lipoprotein cholesterol but also a marked increase in low density lipoprotein (LDL) cholesterol concentration.

## ABBREVIATIONS

AASLD, American Association for the Study of Liver Diseases

ALT, alanine aminotransferase

AMI, acute myocardial infarction

AST, aspartate aminotransferase

BMI, body mass index

CACS, coronary artery calcification score

CI, confidence interval

CKD, chronic kidney disease

CT, computed tomography

CVD, cardiovascular disease

EASD, European Association for the Study of Diabetes

EASL, European Association for the Study of the Liver

EASO, European Association for the Study of Obesity

FXR, farnesoid X receptor

GCKR, glucokinase regulator

GLP-1, glucagon-like peptide 1

HbA1c, glycated haemoglobin

HCC, hepatocellular carcinoma

HDL, high density lipoprotein (cholesterol)

HSD17B13, 17-beta hydroxysteroid dehydrogenase-13

IDL, intermediate density lipoprotein (cholesterol)

LDL, low density lipoprotein (cholesterol)

MBOAT7, membrane bound O-acyltransferase domain containing 7

MetS, metabolic syndrome

MRI-PDFF, magnetic resonance imaging proton density fat fraction

NAFLD, non-alcoholic fatty liver disease

NASH, non-alcoholic steatohepatitis

OCA, obeticholic acid

PNPLA3, patatin-like phospholipase domain-containing protein 3

PPAR, peroxisome proliferator-activated receptors

sdLDL, small dense low density lipoprotein (cholesterol)

T2DM, type 2 diabetes mellitus

TG, triglyceride

TM6SF2, trans-membrane 6 super family 2

VLDL, very low density lipoprotein

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**CONFLICTS OF INTEREST**

None.

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