

## Lipid-lowering agents in the management of nonalcoholic fatty liver disease

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**Core tip:** Accumulating data suggest that statins are safe in patients with nonalcoholic fatty liver disease (NAFLD) and that they reduce the increased cardiovascular morbidity of this population. However, it is still unclear whether statins are also useful as a treatment for NAFLD *per se*, since there are very limited and conflicting data on their effects on liver histology. There is also very scarce evidence regarding the safety and efficacy of other lipid-lowering agents in patients with NAFLD.

### Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries and is associated not only with increased risk for liver disease-related complications but also with higher cardiovascular morbidity. Accordingly, lipid-lowering agents are frequently considered in these patients to reduce cardiovascular risk. However, there have been concerns regarding the safety of these agents in patients with chronic liver diseases. In the present review, we discuss the safety of lipid-lowering agents in patients with NAFLD as well as their effects on both cardiovascular and liver disease in this population. Accumulating data suggest that statins are safe in patients with NAFLD and that they reduce the increased cardiovascular morbidity of this population. However, it is still unclear whether statins are also useful as a treatment for NAFLD *per se*, since there are very limited and conflicting data on their effects on liver histology. There is also very scarce evidence regarding the safety and efficacy of other lipid-lowering agents in patients with NAFLD. Randomized controlled studies are needed to evaluate the role of lipid-lowering agents and particularly statins for the prevention of both cardiovascular and liver disease-related complications in this high-risk population.

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### INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by increased amount of fat in the liver in the absence of increased alcohol consumption<sup>[1]</sup>. NAFLD covers a wide range of histological disorders, ranging from isolated hepatic steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by the coexistence of steatosis with varying degrees of inflammation and fibrosis, whereas some patients progress further to develop cirrhosis<sup>[2,3]</sup>. NAFLD is the most common chronic liver disease in developed countries<sup>[4-6]</sup>. Indeed, 34%-46% of the general population has liver steatosis and 12% has NASH<sup>[4,5]</sup>. Moreover, almost 75% of patients with persistently elevated transaminase levels have NAFLD<sup>[6]</sup>.

Several cross-sectional studies showed that patients with NAFLD have a greater atherosclerotic burden and a higher prevalence of cardiovascular disease (CVD)<sup>[7-9]</sup>. Moreover, observational studies suggest that patients with NAFLD have increased cardiovascular risk and that CVD is the leading cause of death in this population<sup>[10-13]</sup>. Since NAFLD and CVD have many common risk factors (*e.g.*, abdominal obesity, type 2 diabetes mellitus (T2DM), insulin resistance, inflammation and oxidative stress), the increased CVD risk in patients with NAFLD might be partly explained by their shared pathogenesis<sup>[14-17]</sup>. However, there is increased CVD risk in patients with NAFLD even in the absence of T2DM, suggesting that NAFLD is directly causative of CVD<sup>[18]</sup>.

Given the increased cardiovascular risk of patients with NAFLD, aggressive management of CVD risk factors is an essential part of the treatment of these patients. Lipid-lowering treatment is one of the pillars of CVD prevention strategies and primarily consists of administration of statins aiming at reducing low-density lipoprotein cholesterol (LDL-C) levels. The rationale behind this approach is that elevated LDL-C levels are a major independent cardiovascular risk factor<sup>[19]</sup> and that LDL-C lowering with statins reduces CVD morbidity and mortality<sup>[20]</sup>. However, an increase in transaminase levels is the most common adverse effect of statins<sup>[21]</sup>. Moreover, physicians are reluctant to administer statins in patients with elevated transaminase levels<sup>[21]</sup>. Similar considerations apply for other lipid-lowering treatments, which can be considered in patients who do not achieve LDL-C levels despite treatment with statins or in patients with elevated non-high density lipoprotein cholesterol (non-HDL-C) levels<sup>[22]</sup>. On the other hand, preliminary data suggest that statins and other lipid-lowering agents might reduce transaminase levels in patients with NAFLD and might also have beneficial effects on CVD morbidity<sup>[23,24]</sup>.

In the present review, we discuss the safety of lipid-lowering agents in patients with NAFLD as well as their effects on both CVD and liver disease in this population.

## STATINS IN PATIENTS WITH NAFLD

### Safety

Accumulating data suggest that statins are safe in patients with NAFLD. In an observational study in hyperlipidemic patients with elevated transaminases, the incidence of further increase in transaminase levels during treatment with statins was similar compared with patients who had elevated transaminase levels but were not prescribed a statin<sup>[25]</sup>. Moreover, the incidence of severe elevations in transaminases did not differ during statin treatment between patients who had elevated transaminase levels at baseline and those who had normal transaminases<sup>[25]</sup>.

Randomized controlled studies also support the safety of statins in patients with NAFLD. The West of Scotland Coronary Prevention Study trial compared the effects on CVD events of pravastatin 40 mg/d and placebo in men without established CVD but with LDL-C levels > 155 mg/dL whereas the Cholesterol and Recurrent Events

and Long-term Intervention with Pravastatin in Ischemic Disease trials compared pravastatin 40 mg/d and placebo in patients with established coronary heart disease (CHD). In a post-hoc analysis of these 3 trials, the risk of further increase in transaminase levels among patients who had elevated transaminase levels at baseline was similar in those treated with pravastatin and those administered placebo<sup>[26]</sup>. In the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) trial, patients with myocardial infarction (MI) were randomly assigned to receive atorvastatin aiming at LDL-C levels < 100 mg/dL or conventional treatment; only 14% of the latter group received a statin. In a post-hoc analysis of this trial, patients with elevated transaminase levels < 3 times the upper limit of normal (ULN) who were given atorvastatin (mean dose 24 mg/d) experienced a normalization of transaminase levels<sup>[22]</sup>. In contrast, patients with elevated transaminase levels who did not receive statins did not show any change in transaminase levels<sup>[23]</sup>. Similar results were observed in the Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes trial, where treatment of patients with metabolic syndrome with atorvastatin at a mean dose of 24-34 mg/d resulted in normalization of transaminase levels in the subgroup of patients with elevated transaminase levels at baseline<sup>[27]</sup>.

Very recently, a post-hoc analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial also showed that treatment of patients with MI with atorvastatin 40-80 mg/d or simvastatin 20-40 mg/d reduces transaminase levels in patients with elevated levels at baseline<sup>[24]</sup>. It should be emphasized that the diagnosis of NAFLD in all these studies was not based on liver biopsy but on the presence of fatty liver in ultrasound and on the exclusion of other common causes of chronic liver disease (*i.e.*, chronic hepatitis B or C, increased alcohol consumption)<sup>[22,23,26]</sup>. Moreover, patients with transaminase levels > 3 times the ULN were excluded from all studies<sup>[23,24,27]</sup>.

Based on these reassuring data regarding the safety of statin treatment in patients with elevated transaminase levels, current guidelines state that mild elevations of transaminase levels (< 3 times the ULN) are not a contraindication for the administration of statins, provided that patients are followed-up regularly<sup>[1,28]</sup>. Importantly, statins do not interact with agents that are used in the treatment of NAFLD (*e.g.*, vitamin E, pioglitazone, metformin, ursodeoxycholic acid, angiotensin receptor blockers) and therefore, can be safely coadministered with the latter agents<sup>[1,29]</sup>.

### Effects on cardiovascular events

Emerging data suggest that statins are not only safe in patients with NAFLD but also decrease the elevated CVD risk of this population<sup>[30]</sup>. In the GREACE trial, treatment with atorvastatin reduced CVD events by 39% compared with no statin treatment in patients with MI and normal transaminase levels at baseline<sup>[23]</sup>. In contrast, CVD morbidity was reduced by 68% with atorvastatin

treatment in patients with elevated transaminase levels, a reduction significantly greater than in patients with normal transaminase levels<sup>[23]</sup>. The IDEAL trial recently confirmed these findings. In IDEAL, atorvastatin 40-80 mg/d reduced major CVD events more than simvastatin 20-40 mg/d in patients with MI and elevated transaminase levels<sup>[24]</sup>. In contrast, the incidence of major CVD events did not differ between atorvastatin- and simvastatin-treated patients with normal transaminase levels<sup>[24]</sup>. Despite these promising data on the effects of statins on CVD morbidity in patients with NAFLD and the increased CVD risk of this population, it should be emphasized that current guidelines do not differentiate LDL-C targets between patients with NAFLD and the general population<sup>[22]</sup>. Accordingly, LDL-C targets are < 70 mg/dL in patients with NAFLD who have established CVD, T2DM or chronic kidney disease. In the absence of the latter comorbidities, LDL-C targets are < 70, < 100 and < 115 mg/dL in patients with NAFLD and SCORE risk  $\geq 10$ , 5-9 and 1%-4%, respectively<sup>[22]</sup>.

### Effects on liver histology

There are very limited data on the effects of statins on liver steatosis, inflammation and fibrosis in patients with NAFLD. In small uncontrolled studies ( $n = 4-22$ ), treatment with statins reduced steatosis and ballooning but had no effect on fibrosis; the effect on inflammation was inconsistent between studies<sup>[31-35]</sup>. In the only randomized placebo-controlled study, the administration of simvastatin for 12 mo in 16 patients with NASH had no effect on liver histology compared with placebo<sup>[36]</sup>. The interpretation of the findings of these studies is obviously hampered by the small number of patients and the lack of a control group in most of them. Moreover, the follow-up time might have been too short to evaluate the effects of statins on liver fibrosis. Considerably longer follow-up will also be required to assess any benefit of statins on the long-term sequelae of NAFLD, *i.e.*, cirrhosis and hepatocellular cancer (HCC). Notably, observational studies reported a decreased risk of HCC in patients treated with statins regardless of the cause (NAFLD, hepatitis B or C)<sup>[37-39]</sup>. Indeed, in a recent meta-analysis of 10 studies ( $n = 1459417$ ), statins reduced the risk for HCC by 37%<sup>[37]</sup>. Given the limited data on the effects of statins on liver histology in patients with NAFLD, recent guidelines mention that statins should not be used as a treatment for NAFLD<sup>[1]</sup>.

## OTHER LIPID-LOWERING AGENTS IN PATIENTS WITH NAFLD

### Ezetimibe

In patients who cannot achieve LDL-C targets despite treatment with the maximal tolerated dose of a potent statin, ezetimibe can be added to statin treatment<sup>[22]</sup>. Ezetimibe does not appear to be associated with increased risk for transaminase elevations when administered to patients with transaminase levels within the normal range<sup>[40]</sup>.

In an uncontrolled study in 8 patients with NAFLD, treatment with ezetimibe for 1 year reduced transaminase levels but had no effect on liver steatosis assessed with ultrasonography<sup>[41]</sup>. In another uncontrolled study in 10 patients with NASH, treatment with ezetimibe for 6 mo reduced transaminase levels and ameliorated steatosis in liver biopsy but had no effect on ballooning, inflammation or fibrosis<sup>[42]</sup>. In another uncontrolled study in 45 patients with NAFLD, ezetimibe reduced transaminase levels and ameliorated steatosis, inflammation and ballooning in liver biopsy but had no effect on fibrosis after 2 years<sup>[43]</sup>. In a recent randomized controlled study in 32 patients with NAFLD, ezetimibe combined with diet for 6 mo had similar effects on transaminase levels and on liver histology as diet alone<sup>[44]</sup>. There are no randomized controlled studies that evaluated whether combination of ezetimibe with statins reduces CVD events more than monotherapy with statins.

### Bile-acid binding resins

Another option to achieve LDL-C targets in patients who do not reach them despite treatment with the maximal tolerated dose of a potent statin is to add a bile-acid binding resin (BAS)<sup>[22]</sup>. These agents lack systemic side effects since they are not absorbed by the gastrointestinal tract and are not associated with increases in transaminase levels<sup>[45]</sup>. Colesevelam is a newer member of this class and is associated with lower rates of gastrointestinal side effects than other BAS<sup>[45]</sup>. However, in a recent randomized, placebo-controlled study in 50 patients with NASH, treatment with colesevelam for 24 wk increased liver steatosis assessed with magnetic resonance imaging<sup>[46]</sup>. Nevertheless, in the subgroup of patients who underwent a second liver biopsy at the end of follow-up ( $n = 31$ ), the effects of colesevelam on liver steatosis, inflammation and fibrosis were similar to those of placebo<sup>[46]</sup>. An early uncontrolled study in 10 patients with NASH reported a decrease in transaminase levels, steatosis and inflammation but no change in fibrosis after treatment with another BAS, probucol, for 1 year<sup>[47]</sup>. In contrast, in a more recent uncontrolled study in 26 patients with NASH, treatment with probucol for 6 mo decreased transaminase levels but had no effect on steatosis, ballooning, inflammation or fibrosis<sup>[48]</sup>. The Lipid Research Clinics Coronary Primary Prevention Trial is the only study that evaluated the effects of BAS on CVD events and showed that treatment of hypercholesterolemic men without CHD with cholestyramine for 7.4 years reduced CHD events compared with placebo<sup>[49]</sup>. However, no separate analyses of the effects of cholestyramine on CVD events were performed in patients with elevated transaminase levels.

### Fibrates

In patients at high or very high CVD risk who have triglyceride levels > 200 mg/dL after achieving LDL-C targets with a statin, fibrates can be added to achieve non-HDL-C targets<sup>[22]</sup>. The combination of fenofibrate with statins does not appear to increase transaminase or



creatinine kinase levels more than statin monotherapy<sup>[50]</sup>. In contrast, the combination of gemfibrozil with a statin is associated with increased risk for rhabdomyolysis and is contraindicated<sup>[22]</sup>. Regarding the effects of fibrates on NAFLD, in a placebo-controlled study in 27 patients with NAFLD, fenofibrate had no effect on hepatic triglyceride content<sup>[51]</sup>. In a larger study in 186 patients with MetS and NAFLD, the combination of fenofibrate and atorvastatin was not more effective than atorvastatin monotherapy in reducing transaminase levels and liver echogenicity<sup>[52]</sup>. In the only study that evaluated the effects of fenofibrate on liver histology, the administration of fenofibrate for 48 wk in 16 patients with NAFLD decreased transaminase levels and improved ballooning but had no effect on steatosis, inflammation or fibrosis<sup>[53]</sup>. The only study that evaluated the effects of fibrate and statin combination on CVD events is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial<sup>[50]</sup>. In ACCORD, patients with T2DM who were being treated with simvastatin 20-40 mg/d were randomized to receive fenofibrate or placebo<sup>[50]</sup>. After a mean follow-up of 4.7 years, CVD event rates did not differ between the 2 groups<sup>[50]</sup>. Again, there have not been performed separate analyses of the effects of fenofibrate on CVD events in patients with elevated transaminase levels who were enrolled in the ACCORD trial.

### Omega-3 fatty acids

Another option to reach non-HDL-C targets is to add omega-3 fatty acids to statin treatment<sup>[22]</sup>. This combination is not associated with increased risk for transaminase elevations<sup>[54]</sup>. Small uncontrolled studies in patients with NAFLD reported a reduction in transaminase levels during treatment with omega-3 fatty acids<sup>[55,56]</sup>. In 2 controlled studies ( $n = 40$  and  $144$ , respectively), omega-3 fatty acids combined with diet reduced transaminase levels and hepatic fatty infiltration in ultrasound more than diet alone in patients with NAFLD<sup>[57,58]</sup>. In the only study that assessed the effects of omega-3 fatty acids on liver histology, treatment with the omega-3 fatty acid eicosapentaenoic acid (EPA) for 12 mo reduced transaminase levels in 23 patients with NASH<sup>[59]</sup>. An improvement in liver steatosis, ballooning, inflammation and fibrosis was observed in 6 out of 7 patients who underwent liver biopsy at the end of follow-up<sup>[59]</sup>. The only study that evaluated the effects of high doses of omega-3 fatty acids on CVD events is the Japan EPA Lipid Intervention Study (JELIS), in which Japanese patients with hypercholesterolemia were randomly assigned to receive statin alone or statin combined with EPA 1800 mg/d<sup>[54]</sup>. The addition of EPA reduced CVD events by 19% compared with statin monotherapy<sup>[54]</sup>. However, this study was performed in a population with increased background fish consumption and it is unclear whether these findings are applicable to other populations<sup>[54]</sup>. Again, the effects of omega-3 fatty acid and statin combination on CVD events were not analyzed separately in patients with elevated transaminase levels in the JELIS trial.

### Nicotinic acid

A final option to achieve non-HDL-C targets is to combine statins with nicotinic acid<sup>[22]</sup>. However, this combination is associated with increased risk for elevations in transaminase levels compared with statin monotherapy<sup>[60,61]</sup>. Moreover, there are very limited data on the effects of nicotinic acid in NAFLD. In a placebo-controlled study in 27 patients with NAFLD, nicotinic acid had no effect on hepatic triglyceride content<sup>[51]</sup>. More importantly, 2 recent studies showed that the combination of nicotinic acid with a statin does not decrease CVD events more than statin monotherapy<sup>[60,61]</sup>. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study, patients with CVD who were on simvastatin 20-40 mg/d, were randomized to receive nicotinic acid or placebo<sup>[60]</sup>. After a mean follow-up of 3 years, the incidence of the primary end-point (death from CHD, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization) did not differ between the 2 groups and an increase in the risk of ischemic stroke was observed in patients who received nicotinic acid<sup>[60]</sup>. In the Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study, patients with established CVD who were on simvastatin 40 mg/d were randomized to receive nicotinic acid or placebo<sup>[62]</sup>. After a median follow-up of 4 years, the incidence of CVD events did not differ between the two groups<sup>[62]</sup>. Neither of these studies evaluated separately patients with elevated transaminase levels.

## CONCLUSION

Accumulating data suggest that statins are safe in patients with NAFLD and that they reduce the increased cardiovascular morbidity of this population. However, it is still unclear whether statins are also useful as a treatment for NAFLD *per se*, since there are very limited and conflicting data on their effects on liver histology. There is also very scarce evidence regarding the safety and efficacy of other lipid-lowering agents in patients with NAFLD. Randomized controlled studies are needed to evaluate the role of lipid-lowering agents and particularly statins for the prevention of both CVD and liver disease-related complications in this high-risk population.

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