

# Management of dyslipidaemia in patients with comorbidities—facing the challenge

## *Value and limitations of lipid-lowering drugs in liver disease Effects/Interactions of lipid-lowering agents on/with the liver*

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This review aims to examine the evidence on the benefits and risks of lipid-lowering drugs in patients with liver disease. Elevated liver enzyme levels often lead to cautious discontinuation of these drugs, potentially withholding from patients their benefit in reducing cardiovascular disease morbidity and mortality. Using a literature search of PubMed, we examine the efficacy and safety profiles of various lipid-lowering agents, including statins, ezetimibe, bempedoic acid, PCSK9 inhibitors, fibrates, and icosapent ethyl, focusing particularly on their potential side effects related to liver health. A major challenge in the assessment of drug-induced hepatotoxicity is the fact that it relies heavily on case reports rather than real-world evidence. There is currently a lack of robust evidence on lipid-lowering therapy in people with pre-existing liver disease. Nevertheless, we have attempted to summarize the available data for all the drugs mentioned in order to provide guidance for the treatment of patients with liver dysfunction. This review highlights the need for further research to optimize treatment strategies for patients with coexisting liver and cardiovascular disease.

## Aims of this review article

The consideration of liver disease in clinical medicine often leads to a reflexive decision to withhold lipid-lowering drugs from affected patients. However, this reflex may harm patients by depriving them of well-established benefits of lipid lowering therapy on morbidity and mortality related to cardiovascular disease (CVD). The aim of this article is to examine the evidence for both the benefits and risks of lipid-lowering drugs on the liver. Given that this risk-benefit balance varies according to the pharmacological properties of different classes of lipid-lowering drugs, each class will be discussed separately. It is

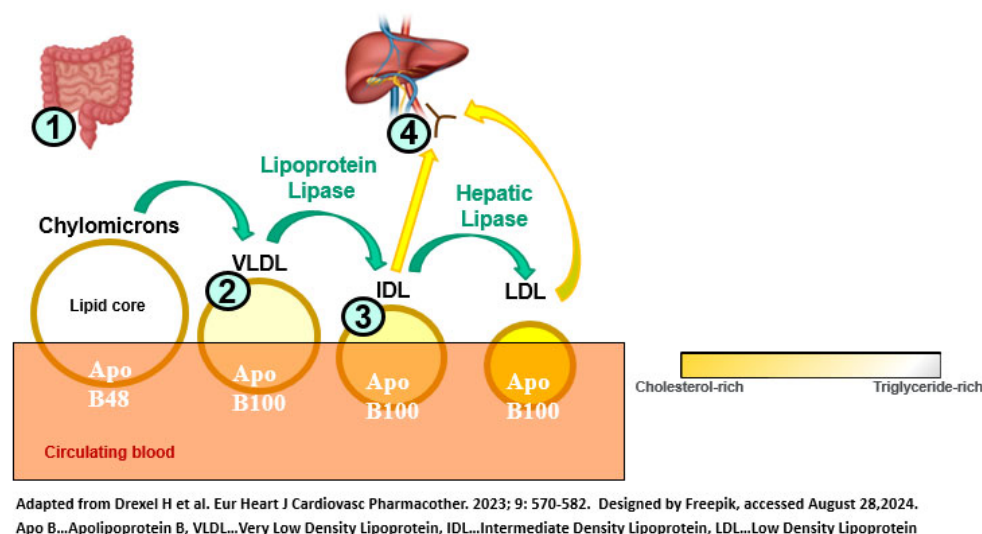
important to note the current lack of robust, validated evidence regarding lipid-lowering therapy in individuals with pre-existing liver disease. The ultimate goal of the article is to provide guidance on therapy for patient with hepatic impairments, specifically to identify who will or will not benefit from lipid-lowering treatment in relation to CVD outcomes.

## Physiological preface

To begin this topic, it is worthwhile to first consider the central role of the liver in lipoprotein metabolism. The liver exclusively synthesizes

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**Figure 1** Role of the liver in lipoprotein metabolism. The figure describes the central role of the liver for lipoprotein synthesis and metabolism. Apo B100 is uniquely synthesized in the hepatocyte, the gut synthesizes the truncated Apo B48. Together with other amphiphilic molecules (free cholesterol and phospholipids), the Apo B proteins enable the transport of the apolar core lipids in the aqueous blood plasma. The classes of lipid-lowering drugs described in this article act at the following sites: (1) ezetimibe; (2) and (3) fibrates and omega-3-fatty-acids; and (4) statins, bempedoic acid, and PCSK9 antibodies as well as inclisiran.

Apolipoprotein B100 (Apo B100), the key protein component of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, and low-density lipoprotein (LDL-C) (Figure 1). The liver thus assembles and secretes these lipoproteins. In contrast, the gut-derived chylomicrons and their remnants are constituted by the truncated Apo B 48 protein.

In the context of decompensated liver disease, where protein synthesis is reduced, the liver's ability to assemble and secrete lipoproteins is diminished, leading to altered lipid patterns.

As shown in Figure 1, the Apo B100 carrying lipoproteins differ in their content of apolar lipids, namely cholesteryl esters and triglycerides (TGs). In terms of clinical chemistry, such particles cause hypercholesterolemia, hypertriglyceridemia, or a combination of both.

Severe liver diseases impairing the synthetic capacity of the liver such as cirrhosis are lipid lowering *per se* because synthesis and assembly of TGs and cholesteryl esters as well as secretion of lipoproteins are major actions of the liver. Therefore, decompensated liver disease is not considered in this article.

## Pharmacological preface

Statins competitively inhibit HMG-CoA (hydroxymethylglutaryl-coenzyme A) reductase, which lowers intracellular cholesterol. Due to the relative lack of cholesterol in the cells, LDL receptors on the hepatocytes are upregulated and LDL clearance from the blood is increased.<sup>1</sup>

A specific aspect of statins is their tendency to increase aminotransferase levels. In the field of fatty liver disease, a change of paradigm has been observed. Initially, there was concern that this increase may be a limitation of statin therapy in all hepatic disease, leading to the exclusion of patients with advanced liver disease from major clinical trials.

However, accumulating data have not shown that elevated aminotransferase levels negatively impact clinical outcome. Mild elevation

in alanine aminotransferase (ALT) occurs in 0.5%–2.0% of patients on statin treatment—more commonly with potent statins or high doses—but these elevations have not been associated with true hepatotoxicity or significant changes in liver function. Consistently, current guidelines do not recommend routine monitoring of ALT levels during statin treatment.<sup>2</sup>

Recent data in non-alcoholic fatty liver disease (NAFLD) now even point to a beneficial effect of statin treatment, which will be discussed in the following chapters as well as the specific effects of non-statin drugs.

Ezetimibe is a lipid-lowering agent acting as a cholesterol absorption inhibitor. It blocks the absorption of endo- and exogenous cholesterol in the small intestine by binding to and inactivating the transport protein NPC1L1 (Niemann-Pick C1-Like 1).<sup>3</sup>

Bempedoic acid is a lipid-lowering agent inhibiting ATP citrate lyase (ACL). The effects are based on the inhibition of cholesterol synthesis by inhibiting the ACL enzyme. This enzyme is upstream of HMG-CoA reductase, the drug target of statins. Bempedoic acid is a prodrug that must be enzymatically activated.<sup>4</sup>

Monoclonal PCSK9 antibodies act by binding to the circulating proprotein convertase subtilisin/kexin type 9 (PCSK9), which can therefore no longer bind to LDL receptors and promote their degradation.<sup>5</sup>

Inclisiran is a small interfering RNA (siRNA) molecule designed to inhibit the intracellular translation of PCSK9. By targeting the mRNA that encodes PCSK9 within hepatocytes, inclisiran reduces the synthesis of the PCSK9 protein.<sup>6</sup>

Fibrates increase fatty acid degradation in peroxisomes by binding to the intracellular peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ). This binding leads to increased degradation of LDL-C and inhibition and degradation of VLDL synthesis. Furthermore, fibrates inhibit HMG-CoA reductase and triglyceride synthesis by inhibiting acetyl-CoA carboxylase. They activate extrahepatic lipoprotein lipase and thus promote the breakdown of triglyceride-rich lipoproteins.<sup>7–9</sup>

## Challenges in describing drug-induced hepatotoxicity

A significant issue in the characterization of drug-induced hepatotoxicity is the reliance on case reports rather than real-world data. An American research group utilized health data from U.S. veterans (about 7.9 million individuals; 92.5% men) and showed that lipid-lowering agents such as atorvastatin, rosuvastatin, ezetimibe, and fenofibrate result in fewer than 1.0 cases of acute liver failure requiring hospitalization per 10 000 person-years (=Group 5; medications were organized into groups 1–5 with frequency of occurrence of acute liver injury). This cohort study included only individuals without pre-existing liver or gallbladder disease. A total of 194 potentially hepatotoxic drugs were examined, each of which had at least four published case reports of hepatotoxicity. In contrast, Groups 1 and 2 include 17 drugs associated with >5.0 events per 10 000 person-years, indicating a higher potential for hepatotoxicity (including stavudine, lenalidomide, metronidazole, clarithromycin, ketoconazole, amoxicillin-clavulanate, among others). Surprisingly, 11 of these 17 medications were not considered highly hepatotoxic in case reports published in LiverTox by the National Institutes of Health, revealing a discrepancy with real-world data. Conversely, statins, often flagged in case reports as particularly hepatotoxic, were found to be low-risk in these real-world assessments.<sup>10</sup>

## Effects of lipid-lowering agents on the liver

### Statins

HMG-CoA reductase inhibitors have been a breakthrough in the primary and secondary prevention of CVD since 1987. Large randomized controlled trials (RCTs) have confirmed their effectiveness, though these studies often excluded individuals with liver disease.<sup>11,12</sup>

The most common side effects of statins are muscle pain and elevation of transaminases. Case reports indicate that liver enzyme increases typically occur within weeks or months after initiating statin therapy, regardless of the specific statin used.<sup>13</sup> Routine laboratory monitoring of liver enzymes and creatine kinase (CK) is generally recommended in clinical practice. The issue of drug-induced liver injury (DILI) from statins has been repeatedly debated.<sup>14</sup> While statin therapy is frequently associated with increased levels of ALT and aspartate aminotransferase (AST) in RCTs, there is minimal evidence linking these increases to clinical or histological liver damage.<sup>15,16</sup> Hepatotoxicity is unlikely if ALT elevations are asymptomatic and bilirubin levels remain normal.<sup>17</sup> However, the European Medicines Agency (EMA) considers active liver disease or unexplained persistent elevation of transaminases to more than three times the upper limit of normal (ULN) as contraindication for statin therapy.<sup>18</sup>

In 2012, the U.S. Food and Drug Administration (FDA) updated its labelling for statins to recommend routine liver tests prior to initiating statin therapy and only during therapy if symptoms such as pain, nausea, vomiting, jaundice, ascites, or other signs of acute liver failure occur.<sup>19</sup> Large meta-analyses of randomized trials in both primary and secondary cardiovascular prevention have shown no increased discontinuation rates of statins due to ALT levels or muscle symptoms.<sup>20,21</sup>

A comprehensive review on gender differences in statin therapy reports mixed results, with women generally underrepresented in large RCT analyses.<sup>22</sup> Some studies indicate increased muscle toxicity and a higher incidence of type 2 diabetes mellitus in women, but no significant sex differences regarding liver effects have been observed so far.<sup>22,23</sup>

In the often overlooked geriatric patient population, a prospective study in China assessed the safety of statins concerning liver disease

in 515 individuals aged 80–98. Among the study participants, 24 experienced an increase in transaminase levels: 62.5% mild, 29.2% moderate, and 8.3% severe, with no significant differences between the different types of statins and no instances of hepatic failure. In this study, transaminase levels increased between two weeks and six months.<sup>24</sup>

Potential drug interactions in the context of polypharmacy should not be overlooked, especially in the elderly population. Particular caution is warranted with statins that are metabolized by CYP3A4 and CYP2C9, and a thorough interaction check should be conducted before initiating therapy. Some medications used by patients with increased cardiovascular risk due to rheumatologic conditions require special attention: For instance, methotrexate can impair liver function, particularly when used in combination with statin therapy.<sup>25</sup> Tocilizumab, an IL-6 inhibitor, can alter statin levels by reversing CYP3A4 inhibition.<sup>26</sup> Grapefruit juice can increase statin concentrations by up to 260% and should be avoided.<sup>27</sup> Additionally, red yeast rice should not be co-administered with statins due to its pharmacological similarity to lovastatin. In patients receiving antiviral therapy for hepatitis, certain statins may be contraindicated based on the specific antiviral agents used. Regular alcohol consumption also necessitates a careful benefit-risk assessment. For more detailed information on drug interactions, refer to 'A Clinician's Guide to Statin Drug-Drug Interactions'.<sup>28</sup>

Increasing numbers of studies indicate that statin use is generally safe in patients with well-controlled liver diseases, including hepatitis C and NAFLD. Contrary to common practice, the Liver Expert Panel, in 2006, concluded—based on a level of evidence ranging from 2B to 3D—that neither chronic liver disease nor compensated liver cirrhosis constitutes a contraindication to statin therapy.<sup>29</sup> Furthermore, the Statin Liver Safety Task Force updated its guidelines in 2014, affirming the safety of statin use in patients with NAFLD. However, distinguishing between NAFLD and the more serious non-alcoholic steatohepatitis remains challenging without histological findings.<sup>30</sup>

Randomized controlled trials investigating the use of statins in patients with liver cirrhosis and statins are limited. The available trials suggest that statins may reduce liver vascular resistance and portal pressure, providing an additive effect to baseline therapy with non-selective beta-blockers.<sup>31–33</sup>

Animal studies have proposed that statins inhibit hepatic myofibroblasts and decrease the production of profibrotic cytokines. These actions result in a reduction of hepatic stellate cells, the main cell type involved in liver fibrosis, and consequently, a decrease in fibrogenesis.<sup>34</sup> Another positive statin effect could be an improvement in liver microcirculation due to increased expression of Kruppel-like factor 2.<sup>35</sup>

The choice of statin and its dosage can impact the body differently. Hydrophilic statins, such as rosuvastatin and pravastatin, are associated with a higher risk of ALT elevation compared to lipophilic statins such as atorvastatin, simvastatin, and fluvastatin. In contrast, lipophilic statins are more likely to cause CK elevation, especially at higher doses.<sup>36</sup>

When transaminase levels are elevated threefold above the ULN due to statin treatment, it is advisable to suspend the medication for 4–6 weeks and recheck liver function. If symptoms are absent, a dose reduction may be sufficient. After pausing and observing decreased transaminase levels, it may be appropriate to restart with a low dose of another high-potency statin.<sup>2</sup> The above mentioned RCT conducted in an older patient population revealed that recovery of liver function following statin discontinuation typically required a timeframe of 2 weeks–3 months.<sup>24</sup> Elevated liver enzyme levels are generally dose dependent, with the highest statin doses being associated with more frequent occurrences of transaminase elevations.<sup>17</sup> A widely used motto in lipid management is 'start low, go slow,' to minimize adverse effects such as myopathy or elevations in liver enzymes. In less critical situations, this strategy allows for careful

dose titration, improving tolerability while achieving therapeutic goals. This approach ensures a balance between reducing cardiovascular risk and avoiding complications, especially for patients with comorbidities, older adults, or those at increased risk for drug interactions. However, in more urgent scenarios, such as acute coronary syndromes, a more aggressive initiation of high-intensity statins may be necessary despite the potential for increased side effects. But overall the risk of statin-induced serious hepatotoxicity is very low with 0.001%. For individuals intolerant to higher doses of statins (after rechallenge or switching to different statins), combining lower doses with adjunct therapies such as ezetimibe offers effective lipid control with fewer adverse effects.<sup>2,37–40</sup> This underlines the importance of personalized approaches to statin therapy, balancing therapeutic efficacy and safety according to individual patient profiles.

Looking ahead, genetic analyses within the context of precision medicine, although not yet state-of-the-art, could offer valuable insights. Studies have shown that genetic variations in liver transport proteins may lead to higher concentrations of statins and their metabolites, resulting in an increased incidence of myalgia and myopathy. Gene risk scores are currently under investigation to identify high-risk patients more efficiently and cost-effectively.<sup>41</sup>

With the rising prevalence of NAFLD in Western countries, the question arises whether these patients would benefit from statin therapy. A systematic review showed that statin initiation resulted in 35% ALT, 32% AST, and 26% GGT reduction in people with NAFLD. In contrast, no change of liver enzymes could be identified in observational studies.<sup>42</sup> To gain approval for the treatment of liver cirrhosis, more evidence is needed, particularly a proven reduction in decompensation such as variceal bleeding. In the largest RCT to date, the addition of simvastatin to standard therapy in secondary prevention after variceal bleeding improved survival but did not reduce complications rates.<sup>43</sup>

### Ezetimibe

Approved by the FDA in 2002, ezetimibe is often used as an add-on therapy to statins or in cases of statin intolerance. It inhibits cholesterol uptake in the intestine, leading to a reduction in LDL-C of up to 18%, along with a moderate increase in HDL-C as well as a reduction in TG.<sup>44,45</sup> Ezetimibe is recycled through the enterohepatic circle and is primarily excreted in the feces. Its cardiovascular benefits were demonstrated in the IMPROVE-IT trial, where it was used in combination with simvastatin vs. simvastatin alone.<sup>46</sup> Accordingly, the addition of ezetimibe as a second line treatment after maximally tolerated statin therapy is recommended by the ESC/EAS Guidelines since 2016.<sup>2,47–49</sup>

The effects of ezetimibe on the liver have not yet been adequately addressed in clinical trials. According to the product information, ezetimibe can be prescribed in cases of mild hepatic insufficiency. However, it is not recommended in cases of moderate to severe hepatic insufficiency due to increased bioavailability (i.e. higher area under the curve) according to literature. Long-term analysis comparing moderate intensity statins with ezetimibe vs. high-dose statins has shown no increase of transaminase or CK levels, suggesting comparable safety.<sup>44</sup> In a study involving 25 liver transplant recipients in Canada, the LDL-C lowering effect of ezetimibe at 6 months was found to be comparable to that observed in other populations, with no graft rejection or significant changes in laboratory values.<sup>50</sup>

### Bempedoic acid

Bempedoic acid was approved for use in CVD prevention by the EMA in 2020. This prodrug is transformed into its active form only in the liver, where it inhibits ATP-citrate lyase, an enzyme upstream of HMG-CoA reductase. As a result, it has no effect on the skeletal muscle,

making it a suitable option for patients experiencing muscle pain or weakness associated with elevated CK levels during statin treatment.

In the recently published CLEAR Outcome Study, bempedoic acid demonstrated a significant reduction of the composite primary endpoint (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) compared to placebo. Nearly 14 000 'statin intolerant' patients were enrolled in the study and followed for >3 years. Although liver enzymes elevations were more frequently reported in the bempedoic acid group (4.5% with the drug vs. 3.0% with placebo), these elevations did not lead to a higher drug discontinuation.<sup>51</sup>

A meta-analysis of 10 studies also found that bempedoic acid was significantly associated with increased rates of elevated liver enzymes compared to placebo. However, detailed information on the extent of the enzyme elevation, the presence of symptoms, and whether these led to therapy discontinuation is lacking.<sup>52</sup>

One approach to avoid the side effects of high-dose statin therapy while still achieving goal LDL-C levels is combination therapy with statins and bempedoic acid. A study by Jadhav et al.<sup>53</sup> evaluated this combination using various statin formulations in a model, with a primary focus on the potential reduction of muscle-related and glycaemic side effects, but with less emphasis on the elevation of transaminases. Moreover, the combination therapy with ezetimibe is now frequently used.<sup>54</sup>

A well-known potential side effect of bempedoic acid is an increase in uric acid levels, which can lead to more frequent gout attacks.<sup>55</sup> Additionally, the maximum statin dose is not recommended in combination therapies with bempedoic acid, as this could lead to increased statin-typical side effects.<sup>56</sup>

So far, there are only very small experimental studies on the effects of bempedoic acid in liver dysfunction. Similar to fibrates, bempedoic acid is considered an agonist at PPAR, which suggests a potential reduction in hepatic steatosis.<sup>57</sup> Recent reviews have also discussed possible anti-fibrotic and anti-inflammatory effects of bempedoic acid. Among other effects, bempedoic acid has been reported to reduce lipogenesis and increase fatty acid beta-oxidation in hepatocytes.<sup>58</sup>

### PCSK9 inhibitors (PCSK9i)

#### PCSK9 Antibodies

Evolocumab and alirocumab are humanized monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) and were approved by the FDA and EMA in 2015 for lowering LDL-C. PCSK9i are administered subcutaneously (s.c.), with doses given every two to 4 weeks, depending on the dosage. In addition to lowering LDL-C, they have been shown to reduce lipoprotein (a) [Lp(a)] levels up to 30%. Other potential effects on metabolic processes, inflammation, and the immune system are also under investigation.<sup>59,60</sup>

In a large review of eight RCTs, alirocumab and evolocumab demonstrated an 18% reduction in MACE in individuals with diabetes. The studies discussed within the review reported mild hyperglycaemia but did not observe the development of diabetes mellitus during therapy. Liver function and other side effects were not a primary focus of this investigation.<sup>61</sup>

The evidence for the use of PCSK9i in patients with liver failure is very limited. According to the product information, moderate hepatic impairment may reduce LDL-C lowering efficacy and should be monitored frequently. It is important to mention that patients with Child-Pugh class C liver cirrhosis were not included in the trials.<sup>60</sup>

In the ODYSSEY Outcome Trial, subjects with triple upper limit transaminases or CK, hepatitis B or C infection were excluded. Hepatic disorder was described equally infrequently in both the



alirocumab and placebo groups, at 5.3% and 5.7%, respectively. There was no significant increase in ALT, AST, or CK levels compared to placebo across the study population.<sup>62</sup> Similarly, the FOURIER study, which had comparable exclusion criteria, did not observe an increase in transaminases or CK levels.<sup>63</sup>

### Inclisiran (siRNA)

Inclisiran represents an siRNA therapy and inhibits the synthesis of PCSK9 by the liver. This drug is also administered s.c., but the dosing interval is much longer compared to PCSK9 inhibitors: It is given initially after three months, then every 6 months. Inclisiran binds extensively to liver-expressed asialoglycoprotein receptors, facilitating targeted uptake specifically into hepatocytes. Once internalized by hepatocytes, these molecules do not exhibit systemic side effects.

Inclisiran was approved by the EMA in 2020. According to product information, dose adjustments are not necessary for people with mild to moderate hepatic impairment. Although no data are available for patients with severe hepatic impairment (Child-Pugh class C), the drug is not contraindicated but should be used with caution.<sup>64</sup>

The ORION series demonstrated LDL-C reductions of up to 50% and LP(a) reductions of up to 26%. Recently, the ORION-3 program, a long-term follow-up of ORION-1 subjects over 4 years, was published. Increases in ALT and AST levels occurred in 5% and 8% of patients, respectively. There was also one case of hepatic fibrosis in a patient with baseline NAFLD.<sup>65</sup> Due to these findings, the ORION-6 trial was initiated to test inclisiran in a small population of 28 subjects with hepatic impairment. According to this study, inclisiran is expected to be safe up to moderate liver failure and well tolerated without the need for dose adjustment.<sup>66</sup> However, larger studies with longer observation period are needed to confirm these findings.

### Fibrates

Fibrates have been used since the 1960s to treat dyslipidaemia. Four different drugs (Bezafibrate, Ciprofibrate, Fenofibrate, and Gemfibrozil, a fibrate analogue) are still available in the EU. According to ESC guidelines, fibrates may be considered for treating high TG (>200 mg/dL) in combination with statins.<sup>67–71</sup> The cardiovascular benefits of fibrates have been widely debated due to inconsistent study results. Most recently, the PROMINENT trial, which tested a fifth promising fibrate, pemafibrate, published in 2022, showed no reduction in cardiovascular events despite a significant and marked reduction (–26.2%) in serum TG concentrations with pemafibrate vs. placebo. Whereas a higher incidence of venous thromboembolism and adverse renal effects were observed, NAFLD occurred less frequently in the pemafibrate cohort.<sup>72</sup>

Fibrates are associated with a reversible decline in renal function and an increase in transaminase levels. When combined with statins, caution is required due to the potential of myositis and hepatic side effects, which were mainly seen with the combination of cerivastatin and gemfibrozil. As a result, cerivastatin was withdrawn from the market.<sup>73,74</sup>

On the other hand, the SAFARI Trial, which combined fenofibrate and simvastatin, reported no increase in the frequency of side effects.<sup>75</sup> This combination was also examined in the ACCORD trial, which included a larger cohort of patients with type 2 diabetes mellitus and high CVD risk. Although the combination of fenofibrate and simvastatin did not reduce the risk of fatal cardiovascular events, non-fatal myocardial infarctions, or non-fatal strokes compared to simvastatin alone, there was no increased risk of myositis or rhabdomyolysis associated with this treatment combination.<sup>76</sup>

Regarding clofibrate, an increased biliary cholesterol secretion leading to a higher rate of cholecystectomies was found as a side effect. Yet, this does not appear to be a class effect, as biliary diseases

did not occur more frequently with either fenofibrate or gemfibrozil treatment.<sup>77–79</sup>

Fibrates could play a significant role in the future treatment of NAFLD. Beyond their lipid lowering effects, fibrates have anti-inflammatory and anti-oxidant pleiotropic qualities. Fenofibrate, in particular, acts as an agonist at PPAR $\alpha$ . This ligand-activated transcription factor is likely involved in hepatic lipid metabolism and the suppressing inflammatory responses.<sup>80,81</sup> However, a small double-blind RCT did not show a reduction in liver fat but rather an increase in total liver fat volume with fenofibrate in overweight or obese study participants with NAFLD, as quantified by magnetic resonance imaging.<sup>82</sup> In another RCT, NAFLD could not be detected biochemically or by sonography in 70% of patients after 54 weeks of combination therapy with atorvastatin and fenofibrate, indicating a reversal of NAFLD pathophysiology.<sup>83</sup>

### Icosapent ethyl

Icosapent ethyl is a chemically modified form of eicosapentaenoic acid (EPA), distinct from other omega-3 fatty acid preparations, as it contains only EPA and no other omega-3 fatty acids such as docosahexaenoic acid. It is dosed at 2 g twice daily.<sup>84</sup> The potential benefits of icosapent ethyl are currently under clinical investigation, with data suggesting that, in addition to lowering TG, it may have anti-oxidant, anti-inflammatory, and plaque-stabilizing effects.

The REDUCE IT trial enrolled patients at high risk for CVD to evaluate the effects of icosapent-ethyl on top of statin therapy. After a median follow-up of almost 5 years, the TG levels in the drug group decreased by 18.3%, compared to a 2.2% increase in the placebo group. The primary CV endpoint was reduced by 4.8% in the icosapent ethyl group ( $P < 0.001$ ).<sup>85</sup> A post-hoc analysis revealed that icosapent ethyl was shown to reduce cardiovascular events in both active and former smokers to a similar extent as in non-smokers who received placebo therapy. Although icosapent-ethyl has not been tested on individuals with acute or severe liver disease, no significant liver-related adverse events were documented in the studied population.<sup>86</sup>

This led to a small coronary CT-based study in which 80 patients with established coronary artery disease and elevated TG received icosapent-ethyl or placebo in addition to statin therapy. While computed tomography showed no change in calcium density after 18 months, the icosapent-ethyl group exhibited reduced plaque volume and fewer fibrous plaques.<sup>87</sup>

### Combination therapy

The studies IMPROVE-IT, FOURIER, ODYSSEY Outcomes, CLEAR Outcomes, and REDUCE-IT have shown the significant benefits of add-on therapies such as ezetimibe, PCSK9 antibodies, bempedoic acid, and icosapent ethyl in combination with statins. According to international guidelines, statins should always be the first-line therapy unless contraindicated. Other agents should be added step by step if LDL goals are not met. This strategy can also be valuable in identifying which medication is associated with specific side effects. There are situations in high-risk populations and patients with recent cardiovascular events where an early initiation of combination therapy should be discussed. Here too, an individualized patient approach is essential.<sup>2,46,51,62,63,85,88–90</sup>

### Lp(a) lowering agents

Currently, no drugs are approved for directly lowering Lp(a).

However, the Apolipoprotein(a)-lowering RNA therapeutic [APO(a)-LRx], an antisense oligonucleotide designed to reduce Lp(a) levels, is under investigation. Antisense oligonucleotides can inhibit the production of apolipoprotein(a) in hepatocytes, which are responsible for producing Lp(a). One RCT demonstrated a reduction in Lp(a)

**Table 1** Current evidence regarding efficacy and safety of the discussed lipid-lowering drug classes in patients with liver disease (adapted Table 13 of 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Summary of recommendations for monitoring lipids and enzymes in patients, before and on lipid-lowering therapy<sup>1</sup>).

	Treatment may ↑ ALT	May lead to stop therapy	EMA approval for hepatopathy	Liver contraindication according to EMA	Potential positive effects on the liver in discussion	Measure ALT	ALT < 3x ULN	ALT > 3xULN
Statins	Yes; weeks to months after treatment start	Yes	No active liver disease, transaminases < 3x ULN	Active liver disease/unexplained persistent ↑ of transaminases > 3xULN	May ↓ liver vascular resistance and portal pressure; ↓ in fibrogenesis; improvement in liver microcirculation	Before treatment, once 8–12 weeks after starting the drug/dose increase	Continue therapy, check ALT again in 4–6 weeks	Stop therapy/reduce dose, check ALT again in 4–5 weeks, reintroduction possible after ALT is within range, ALT stays ↑ after treatment check for other reasons
Ezetimibe	Yes	Not known	Mild impairment: no dose adjustment; no data in moderate/severe hepatopathy	Active liver disease/unexplained persistent ↑ of transaminases > 3xULN	Tested in liver transplant recipients with no harm to graft or changes in lab values	Before treatment	–	–
Bempedoic acid	ALT ↑ uncommon; AST ↑ common, asymptomatic, > 3xULN possible, without bilirubin ↑ > 2xULN/cholestasis	No	mild—moderate impairment no dose adjustment; no data in severe hepatopathy (Child C)	–	Potential PPAR activator; may ↓ hepatic steatosis; antifibrotic and anti-inflammatory; may ↓ lipogenesis and ↑ fatty acid β-oxidation in hepatocytes	Before treatment	–	Stop therapy if ALT or AST stays persistent ↑ > 3xULN
PCSK9 Antibodies	No	No	Mild impairment no dose adjustment, moderate impairment may lead to ↓ effect on LDL-c ↓; no data in severe hepatopathy (Child C)	–	–	–	–	–
Inclisiran (siRNA)	Yes but < 3xULN, asymptomatic, no other signs of liver dysfunction	No	Mild—moderate impairment no dose adjustment in; moderate impairment may lead to ↓ effect on LDL-c ↓, no data in severe hepatopathy (Child C)	–	–	–	–	–
Fibrates	Yes common; mostly transient, minor, asymptomatic	Yes	–	Hepatopathy, unexplained persistent ↑ of transaminases	Potential anti-inflammatory and antioxidant pleiotropic qualities, PPARα activator	Before treatment, check every 3 months during first year of treatment + regular intervals thereafter	–	Stop therapy if ALT/AST > 3xULN
Icosapent ethyl	No	No	No data with acute or severe liver disease	–	–	When clinically indicated: before start + appropriate intervals during treatment	–	–

depending on the dose administered in a secondary prevention population. In this population, there was no increase in ALT or AST above three times the ULN observed.<sup>91</sup>

Another approach involves using siRNA molecules such as Olpasiran. In a dose finding RCT, Olpasiran therapy resulted in a strong Lp(a) reduction. The side effects were comparable to those in the placebo group and were not associated with increased liver enzyme levels.<sup>77</sup>

In a phase 1 trial with Muvalaplin, an oral small molecule inhibitor of Lp(a) formation, the maximum placebo-adjusted reduction in Lp(a) was over 60% with no signs of hepatic biochemical adverse events in subjects without liver disease.<sup>92</sup>

## Conclusion

To sum up, we analysed the hepatic safety profiles and potential benefits on the liver of several lipid lowering therapies used in clinical practice.

The most data on liver toxicity are available for statins and fibrates, which are generally associated with mild to moderate increases in liver enzymes, often transient and asymptomatic. A persistent increase in ALT above three times the ULN requires dose adjustment or discontinuation of therapy, though resuming treatment can be discussed after ALT normalization with statins. Severe hepatotoxicity with corresponding clinical symptoms is very rare overall. Elevations in liver enzymes have also been reported for bempedoic acid during therapy, but these usually do not lead to discontinuation. The same applies to ezetimibe, although detailed information regarding the extent of transaminase elevation and the need to stop therapy is lacking. For PCSK9 antibodies, inclisiran and icosapentethyl, the hepatic safety profile appears more favourable, with no significant increases in liver enzymes observed. However, it should be noted that the potent LDL-c lowering effect of these drugs may be reduced in cases of moderate liver disease. There is a lack of data regarding the tolerability of PCSK9 antibodies, inclisiran, icosapentethyl, bempedoic acid, and ezetimibe in patients with active or severe liver disease.

It is recommended to check liver enzymes, particularly ALT and AST, before starting therapy with statins, ezetimibe, bempedoic acid, and fibrates. For statins, fibrates, and ezetimibe, unexplained elevations (>3xULN) and active liver disease are contraindications for initiating therapy. After dose adjustments and initiation, a single follow-up check for statins and regular monitoring for fibrates are considered reasonable.

Regarding the potential positive effects of lipid lowering therapies on the liver, statins may reduce liver vascular resistance and improve microcirculation. Bempedoic acid shows anti-inflammatory and anti-fibrotic potential, while fibrates may have antioxidant and anti-inflammatory effects.

The current evidence is presented in [Table 1](#).

In conclusion, this analysis emphasizes the importance of individualized treatment decisions, ongoing monitoring, and further research to optimize therapy for patients with liver disease.

The present article adds to the respective considerations on kidney disease.<sup>93</sup>

More articles concerning the effects of co-morbidities on the use of LLD are in preparation by members of the ESC WG CVP.

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## Data availability

No new data were generated or analysed in support of this research.

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