

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Treatment of Dyslipidemia in Common Liver Diseases



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Dyslipidemia is common in the general population and increases the risk of cardiovascular disease. Treatment of dyslipidemia is effective in decreasing morbidity from cardiovascular disease. Because the liver is the primary source of cholesterol and other lipids in the body, medications for dyslipidemia, such as statins, target genes in the liver. Furthermore, the liver plays a role in the metabolism of many drugs, including those that are used to treat dyslipidemia. It is not surprising, therefore, that many practitioners are hesitant to prescribe medicines to treat dyslipidemia in the setting of liver disease. This update is aimed at summarizing current understanding of the safety of treating patients who have various liver diseases and dyslipidemia with lipid-lowering drugs (Table 1).

The 2013 American College of Cardiology/American Heart Association guidelines, published in 2014, should be used to guide treatment of dyslipidemia in patients with the liver diseases discussed in this update.¹ The guidelines recommend that adults with cardiovascular disease or a low-density lipoprotein (LDL) level ≥ 190 mg/dL be treated with high-intensity statins, with the goal of reducing LDL levels by 50%. Individuals 45–70 years of age with diabetes mellitus and a serum LDL level < 189 mg/dL or persons with a $> 7.5\%$ global 10-year risk of cardiovascular disease can be treated with moderate-intensity statins, with the goal of reducing LDL levels by 30%–50% (Table 2).

Drug-Induced Liver Injury

From 8% to 9% of persons in the general population have an elevated aminotransferase level, a common clinical problem.² In these persons, an evaluation to determine the cause of the aminotransferase elevation is warranted, particularly before a new drug is started, because they may have a common underdiagnosed condition, such as nonalcoholic fatty liver disease (NAFLD), excessive alcohol use, or viral hepatitis. Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) are by far the most common medication used to treat dyslipidemia and are known to cause elevations of serum alanine aminotransferase (ALT) levels in

persons with previously normal levels. Overall, persons on low-to-moderate statin doses have, on average, a 1% chance of having an elevated ALT level.³ At most, 3% of patients on statins develop elevations in serum ALT levels.³ The effect is generally dose dependent, with higher doses of statins increasing the chances of an elevated ALT level. These mild elevations do not generally indicate serious toxicity.

Elevations in aminotransferase level indicative of serious liver injury caused by a drug are rare but can be life threatening. Zimmermann^{4,5} observed that jaundiced patients with elevated aminotransferase levels had a poorer prognosis than patients with elevated aminotransferase levels without jaundice. That observation was further developed into Hy's Law to identify patients with potentially fatal drug-induced liver injury (DILI).⁶ To meet criteria for DILI, patients must have elevations of ALT or aspartate aminotransferase levels ≥ 3 times the upper limit of normal (ULN) and have elevations of the total serum bilirubin level > 2 times the ULN with no other identified cause of the increased liver biochemical tests (eg, biliary obstruction, another liver disease, other drug toxicity) except for the offending drug.⁶ DILI from statins occurs in 1 in 100,000 persons and can have a variety of histologic presentations.^{7,8} There can be an asymptomatic rise in the ALT level (< 3 times ULN) that can improve with continued stain use, so-called adaptation; hepatitis with an ALT level > 3 times ULN and clinical liver disease; cholestatic hepatitis with development of jaundice; and autoantibody-associated DILI with the development of positive antinuclear antibodies and antimitochondrial or smooth muscle antibodies with or without plasma cells in liver biopsy specimens. In general, however, statins can be used in individuals with

Abbreviations used in this paper: ALT, alanine aminotransferase; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PBC, primary biliary cholangitis; RCT, randomized controlled trial; ULN, upper limit of normal.

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Table 1. Best Practice Advice: Treatment of Dyslipidemia in Liver Disease**DILI**

BPA #1 Statins often (3%) cause benign elevations in serum ALT or AST levels and should not be considered contraindicated in patients with liver disease.

BPA #2 Liver biochemical tests are recommended before starting a statin but do not need to be checked routinely while statins are taken unless clinically significant side effects develop.

BPA #3 Increases in serum ALT or AST levels to >3 times ULN with evidence of cholestasis (bilirubin >2 times ULN) (in the absence of biliary obstruction) after statins are started generally require that the statin be stopped. A work-up for DILI should include testing for the presence of other underlying causes of liver disease or other medications that may have precipitated the reaction besides or in addition to the statin.

BPA #4 If DILI or ALF occurs in a patient taking a statin, other statins should be avoided in that patient.

BPA #5 DILI and ALF caused by statins are rare (1 in 100,000 and 1 in 1,000,000, respectively), so fear of developing these effects should not be used to justify avoidance of statins when an individual may benefit from them.

BPA #6 Statins are contraindicated in patients with ALF because of the patients' poor prognosis.

BPA #7 Other lipid-lowering medications, such as niacin, ezetimibe, or fibrates, may cause DILI, but such instances are exceedingly rare and should not prevent starting these medications in a patient who may benefit from them.

NAFLD

BPA #8 Although NAFLD and NASH are not considered traditional risk factors for cardiovascular disease, they are associated with dyslipidemia. The 2013 ACC/AHA guidelines should be used to assess cardiovascular risk in patients with NAFLD and to guide the need for lipid-lowering pharmacotherapy.

BPA #9 Statins, ezetimibe, omega-3 fatty acids, and fibrates are safe and well tolerated in the setting of NAFLD and NASH.

BPA #10 A statin is first-line treatment of elevated serum LDL levels in patients with NAFLD who are deemed to be at increased risk for adverse cardiovascular disease outcomes. Statin therapy is associated with reductions in serum LDL levels and cardiovascular disease prevention in patients with NAFLD.

BPA #11 Ezetimibe may also be used for treatment of elevated LDL levels, either as primary therapy in patients who are statin intolerant or in addition to a statin when the statin is insufficient to reduce LDL levels. Ezetimibe is associated with reductions in LDL levels, but its efficacy for cardiovascular disease prevention is unknown.

BPA #12 Omega-3 fatty acids and fibrates are indicated for the treatment of isolated hypertriglyceridemia.

BPA #13 There is no conclusive evidence that treatment of dyslipidemia with any agent (statin, fibrate, fish oil) improves the histology of NASH or liver-related outcomes.

Viral Hepatitis

BPA #14 Despite causing a reduction in serum lipid levels, chronic HCV infection is associated with an increased risk of acute myocardial infarction. Serum LDL and total cholesterol levels rebound after spontaneous and treatment-induced viral clearance. Therefore, lipid levels should be monitored after HCV clearance to determine if a patient has a new indication for treatment of dyslipidemia.

BPA #15 The impact of chronic HBV infection on serum lipid levels is not well described, but HBV infection may decrease serum triglyceride and HDL levels.

Table 1. Continued

BPA #16 Management of patients with HBV or HCV infection and dyslipidemia should be guided by standard recommendations for the treatment of dyslipidemia.

BPA #17 Statins are safe to use in patients with either chronic HCV or HBV infection, but attention should be paid to potential interactions between statins and antiviral agents.

PBC

BPA #18 Dyslipidemia in the form of elevated serum cholesterol and triglyceride levels is common in PBC, does not increase the risk of cardiovascular disease, and does not need to be treated with lipid-lowering agents unless other concomitant cardiovascular risk factors are present.

BPA #19 Lipid-lowering agents, such as statins, are not contraindicated in patients with PBC with compensated liver disease but should not be used in patients with decompensated disease. BPA #20 Second-line treatments for PBC, such as fibrates and OCA, can affect lipid levels. Until more is known about the effect of OCA on cardiovascular disease, OCA in particular should be avoided in patients with PBC who have cardiovascular disease or risk factors for disease. OCA should be dosed weekly rather than daily in PBC patients with Child-Pugh class B or C cirrhosis.

BPA #21 There is no compelling evidence that statins can improve outcomes in patients with PBC; they should not be used as primary agents for treatment of this disease.

Cirrhosis

BPA #22 Statins can be safely used in patients with Child-Pugh class A cirrhosis for cardiovascular risk reduction if indicated.

BPA #23 Statins should be avoided in patients with Child-Pugh class B or C cirrhosis because of the patients' poor prognosis, not because of increased hepatotoxicity.

Post-Transplant Dyslipidemia

BPA #24 Dyslipidemia is common following liver transplantation, affecting up to 62% of transplant recipients. Pretransplant obesity and diabetes mellitus increase the risk of post-transplant dyslipidemia. Post-transplant weight gain and immunosuppressant medications, including calcineurin inhibitors and the mTOR inhibitor sirolimus, also increase the risk of post-transplant dyslipidemia.

BPA #25 Lipid-lowering agents, specifically statins, are not associated with an increased risk of hepatotoxicity in the post-transplant population and may be used as needed to treat dyslipidemia.

BPA #26 Calcineurin inhibitors, like several statins, are metabolized by CYP3A4 and may increase the risk of statin-associated myopathy. Pravastatin and fluvastatin are not metabolized by CYP3A4 and do not increase the risk of statin-associated myopathy when used with a calcineurin inhibitor.

ALT, alanine aminotransferase; ACC, American College of Cardiology; AHA, American Heart Association; ALF, acute liver failure; AST, alanine aminotransferase; BPA, best practice advice; CYP, cytochrome P-450; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mTOR, mechanistic target of rapamycin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PBC, primary biliary cholangitis; ULN, upper limit of normal.

autoimmune disorders including autoimmune hepatitis. General care should be taken to ensure that medications taken for autoimmune hepatitis or other disorders do not affect the catabolism or excretion of statins, thereby

Table 2. Indications for Pharmacologic Reduction of Serum LDL Levels in the General Population

Presence of clinical atherosclerotic cardiovascular disease (coronary heart disease, symptomatic carotid artery disease, stroke/transient ischemic attack, peripheral artery disease, abdominal aortic aneurysm)
Adults 40–77 years of age with diabetes mellitus and LDL levels of 70–189 mg/dL
Adults 40–75 years of age with a global 10-year risk of cardiovascular disease $\geq 7.5\%$ and an LDL level of 70–189 mg/dL
Adults with an LDL level ≥ 190 mg/dL

Adapted from 2013 American Heart Association/American College of Cardiology guidelines.¹

LDL, low-density lipoproteins.

altering their effective dose. Statins can also cause acute liver failure in 1 in 1,000,000 persons.

The liver safety of statins has recently been reviewed and guidelines published for their use.⁹ It is recommended that liver biochemical tests be checked before a statin is started. However, routine periodic monitoring of serum ALT levels does not seem to detect or prevent serious liver injury in association with statin use and is not recommended. Only if and when a patient shows clinical signs, such as fever or jaundice, of adverse effects from a statin should liver biochemical tests be rechecked. If DILI from a statin is suspected, then a full work-up should be initiated to ensure that the cause is the statin and not a secondary liver disease or another drug (reviewed in Ref.⁹).

Niacin, ezetimibe, and fibrates, which are also used to treat serum lipid disorders, have all been reported to cause DILI. If a patient had DILI or acute liver failure from a statin, this class of medications should not be used in that patient again, and an alternative class of lipid-lowering drugs can be tried.⁷ Statins are contraindicated in patients with decompensated liver disease or acute liver failure (see later) but are otherwise safe, even at high doses, and efficacious in lowering lipid levels in patients with compensated liver disease.¹⁰

Nonalcoholic Fatty Liver Disease

Dyslipidemia is common among persons with NAFLD and plays a critical role in the development of cardiovascular disease, the leading cause of mortality among these persons. Dyslipidemia associated with NAFLD is typically characterized by a pattern of hypertriglyceridemia, increased LDL levels, and reduced high-density lipoprotein (HDL) levels. Although patients with NAFLD have a higher risk of cardiovascular complications compared with the general population, NAFLD and nonalcoholic steatohepatitis (NASH) are not considered traditional risk factors for cardiovascular disease. Therefore, cardiovascular risk should be assessed according to the 2013 American College of Cardiology/

American Heart Association guidelines, which use presence of known coronary artery disease, cardiovascular risk factors, and 10-year cardiovascular event risk assessment to determine the need for treatment with lipid-lowering agents and to establish LDL targets for primary and secondary cardiovascular risk prevention (Table 2; discussed later).

Diet and exercise are the first-line approaches to reduce LDL levels. When diet and exercise are insufficient, statins are the first-line pharmacologic agents for LDL reduction and have proven benefit for primary and secondary prevention of cardiovascular disease. Several studies have demonstrated that statins are effective in reducing LDL levels and cardiovascular events and are safe in patients with NAFLD. Intensive statin therapy (eg, pravastatin, 80 mg daily) was associated with a significant reduction in LDL levels compared with placebo among patients with chronic liver disease primarily caused by NAFLD (mean percentage LDL reduction, 30.6%; standard deviation, 16.5%).¹⁰ In a post hoc analysis of the ATTEMPT study, a greater benefit in primary cardiovascular disease prevention was observed among patients with NAFLD and metabolic syndrome in whom LDL reduction was aggressive with intensive statin therapy (atorvastatin titrated from 10 to 80 mg daily) aimed to reduce LDL levels to <100 mg/dL compared with those in whom the LDL reduction was aimed to reduce the level to <130 mg/dL.¹¹ Post hoc analyses of 2 large randomized controlled trials (RCTs) (GREACE and IDEAL studies) also found superior secondary cardiovascular disease prevention benefit in association with intensive statin therapy among patients with increased aminotransferase levels attributed to NAFLD. In the IDEAL study, compared with moderate statin therapy, intensive statin therapy (atorvastatin, 80 mg daily) was associated with a 44% relative risk reduction in secondary cardiovascular events (hazard ratio, 0.556; 95% confidence interval, 0.367–0.842).¹² In the GREACE study, compared with usual care, intensive statin therapy (atorvastatin titrated from 10 to 80 mg daily for an LDL goal of <100 mg/dL) was associated with a 68% relative risk reduction ($P < .0001$).¹¹ Both studies found greater cardiovascular benefit among patients with increased aminotransferase levels than in those with normal levels.

Statins are well tolerated and not associated with liver-related adverse events among patients with NAFLD and dyslipidemia.^{10,13,14} In RCTs, patients with NAFLD who were treated with intensive statin therapy experienced significant reductions in aminotransferase levels compared with control subjects.¹⁰ Observational studies have similarly reported significant reductions in aminotransferase levels and steatosis on liver biopsy specimens in statin-treated patients with NAFLD. However, histologic improvements in ballooning and fibrosis have not been observed in association with statins.

Experience with ezetimibe in patients with NAFLD is much less extensive than that with statins. Treatment with ezetimibe, 10 mg daily, was associated with

significant reductions in LDL and total cholesterol levels among patients with NAFLD in several observational studies¹⁵⁻¹⁸ and 1 small open-label RCT.¹⁹ However, there have been no studies looking at the effect of ezetimibe on cardiovascular disease prevention in patients with NAFLD. Ezetimibe may be associated with improvements in aminotransferase levels. Mixed results from studies evaluating the effect of ezetimibe on liver histology in patients with NASH suggest that ezetimibe may improve steatosis, NAFLD activity score, and hepatocyte ballooning but not fibrosis.^{15,17,19-23}

Omega-3 fatty acids and fenofibrates are safe and effective for the treatment of isolated hypertriglyceridemia. Neither medication is associated with improvement in liver histology in patients with NAFLD.

In summary, statin therapy is indicated for treatment of increased LDL levels among patients with NAFLD who are at increased risk for adverse outcomes of cardiovascular disease. Statin therapy is associated with reductions in LDL levels and prevention of cardiovascular disease. Ezetimibe may also be used for treatment of increased LDL levels and is associated with reductions in these levels, but its efficacy for cardiovascular disease prevention is unknown. Omega-3 fatty acids and fibrates are indicated for the treatment of hypertriglyceridemia. All of these agents are safe and well tolerated in patients with NAFLD. However, there is no conclusive evidence to date that treatment of dyslipidemia with any agent (statins, fibrates, omega-3 fatty acids) improves histology or liver-related outcomes in patients with NASH.

Viral Hepatitis

Hepatitis C

Hepatitis C virus (HCV) chronically infects up to 170 million individuals globally and can lead to the development of cirrhosis, hepatocellular carcinoma, and the need for liver transplantation.²⁴ HCV replication impacts host lipid metabolism via several mechanisms. HCV virions interact with circulating lipoproteins to infect hepatocytes via the LDL receptor and interact with the cell surface markers Niemann-Pick C1-like 1, a receptor for cholesterol resorption, and scavenger receptor class B member 1, which promotes uptake of cholesterol from lipoproteins.²⁵⁻²⁷ Once inside the hepatocyte, HCV interacts with host cytosolic lipid droplets and diacylglycerol O-acetyltransferase 1 to form the HCV core protein and uses an intermediate of the cholesterol synthesis pathway for replication.²⁷ HCV also uses host lipids for secretion by complexing with apoE-containing very-low-density lipoproteins and HDL.²⁸

These HCV-host interactions affect host circulating lipid levels. Both acute and chronic HCV infections lead to a decrease in serum LDL and total cholesterol levels.^{29,30} However, the lower lipid levels found in persons with HCV infection do not confer a decreased risk of cardiovascular disease; on the contrary, chronic

HCV infection is associated with an increased risk of acute myocardial infarction when compared with matched control subjects.^{31,32} Furthermore, LDL and total cholesterol levels rebound after spontaneous and treatment-induced viral clearance. Therefore, in patients with HCV infection, lipid levels should be monitored, with a special focus on lipid levels following HCV clearance, to determine if treatment of dyslipidemia is needed. Treatment with statins is safe in individuals with liver disease, including hepatitis C, and should be first-line therapy.³³

Hepatitis B

Hepatitis B virus (HBV) chronically infects more than 240 million individuals worldwide and can lead to end-stage liver disease, hepatocellular carcinoma, and the need for liver transplantation.^{33,34} Like HCV, HBV interacts with lipid metabolism in the host. HBV uses the peptide Na⁺-taurocholate cotransporting polypeptide as a point of viral entry and an aid in the production of hepatitis B surface antigen. The binding of HBV to Na⁺-taurocholate cotransporting polypeptide impairs bile acid uptake, thereby leading to increased bile acid synthesis and bile acid conversion to cholesterol.³⁵ Hepatitis B surface antigen formation also relies, in part, on the host endoplasmic reticulum lipid bilayer and, once formed, is exported as a lipoprotein particle.³⁶

Expression of lipogenic genes may also be altered by HBV infection. Mouse models of HBV infection demonstrate increased expression of genes for SREBP2, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the LDL receptor, fatty acid synthase, ATP citrate lyase, peroxisome proliferator-activated receptor- γ , and apolipoprotein A1.^{37,38}

Data on host lipid levels during HBV infection in humans are limited. A case-control study found that HBV-infected individuals had lower serum triglyceride and HDL levels than age-matched control subjects. A second retrospective study found that serum HBV DNA levels were inversely correlated with serum triglyceride levels. No relationship between serum HDL and HBV DNA levels was seen.³⁹

As for HCV infection, there is a lack of data to guide lipid management in individuals with HBV infection. Clinicians should adhere to guidelines from the American College of Cardiology/American Heart Association on lipid management (Table 2).¹ Statin therapy is safe to use in patients with chronic hepatitis B and should not be withheld.

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune cholestatic liver disease associated with dyslipidemia. Individuals with PBC have a complex pattern of dyslipidemia (reviewed in Ref.⁴⁰). Patients with PBC have increased serum triglyceride

levels and variable HDL levels: patients with PBC and stage 1 or 2 fibrosis have increased HDL levels, those with stage 3 fibrosis have variable HDL levels, and those with stage 4 fibrosis have decreased HDL levels. These patients have increased total cholesterol levels largely because of elevations of lipoprotein X. Lipoprotein X is antiatherogenic; therefore, even though patients with PBC have dyslipidemia, the dyslipidemia may not lead to an increase in cardiovascular events. It is estimated, however, that about 10% of patients with PBC have a significant risk of cardiovascular disease and should be treated with medications to reduce that risk. Statins, ezetimibe, and fibrates have all been shown to be safe in patients with PBC.

Fibrates are second-line therapies for the treatment of cholestasis in patients with PBC and also affect serum lipids.⁴¹ Fibrates have anticholestatic effects through the activation of peroxisome proliferator-activated receptor and downregulation of bile acid synthesis pathways. Bezafibrate, 400 mg daily, alone or in combination with ursodeoxycholic acid, has been shown to lower serum alkaline phosphatase levels in small studies, but concern remains about ascertainment bias and the significance of biochemical rather than histologic or survival endpoints (reviewed in Ref.⁴¹). A large RCT is underway, and until the results are available, these medications may be used off-label in patients in whom the response to ursodeoxycholic acid is inadequate. Fibrates, however, do not significantly reduce the risk of cardiovascular events⁴² and should not be used for primary prevention of cardiovascular disease in patients with PBC and dyslipidemia.

Obeticholic acid (OCA) is a second-line therapy for the treatment of PBC and also affects serum lipids.⁴¹ OCA is a farnesoid-X receptor agonist that directly regulates genes involved in bile acid synthesis, secretion, transport, absorption, and detoxification. The phase 3 PBC OCA International Study of Efficacy (POISE)⁴³ showed a 33%–39% reduction in serum alkaline phosphatase levels in the group receiving 10 mg daily compared with 5% in the group receiving placebo ($P < .001$) at 12 months of treatment. However, patients taking OCA had an increase in LDL and total cholesterol levels and a decrease in HDL levels, the cardiovascular consequences of which remain to be determined. If cardiovascular risk is indeed increased in patients taking OCA, the medication may need to be coupled with a second medication to lower that risk. Thus, until more data are available, OCA should be avoided in patients with cardiovascular disease or risk factors for cardiovascular disease. Additionally, the recommended initial dose for patients with moderate to severe liver impairment (Child-Pugh B and C) is 5 mg once weekly, rather than the 5 mg daily used for other PBC patients (<https://www.fda.gov/downloads/Drugs/DrugSafety/UCM576880.pdf>). When daily dosing has been administered inadvertently in Child-Pugh B and C

patients, serious liver injury and death have been reported. Furthermore, up to 10% of patients discontinued treatment because of pruritus.

Several studies have now shown that statins can lower LDL levels in patients with PBC who also have increased rates of cardiovascular disease. Atorvastatin, 10 mg daily for 1 year, in early stage PBC reduces total cholesterol, LDL cholesterol, LDL, and triglyceride levels without affecting progression of cholestasis.⁴⁴ Long-term atorvastatin use also led to reductions in total and LDL cholesterol levels.⁴⁵ Similar reductions in total cholesterol and LDL cholesterol levels were seen in patients treated with simvastatin, 20 mg daily.⁴⁶ Although initially considered promising treatments for PBC,⁴⁶ recent trials have not shown an effect of statins in reducing serum alkaline phosphatase levels.^{44,45} Studies also show that ezetimibe is safe in patients with PBC.⁴⁷ Therefore, statins and ezetimibe should be considered in patients with PBC with cardiovascular disease risk factors.

Cirrhosis

Although cirrhosis was previously thought to protect against atherosclerotic disease, work in recent years has demonstrated that the prevalence of coronary artery disease among patients with cirrhosis may be higher than that in the general population.^{48–50} Cardiovascular risk varies according to etiology of liver disease and is highest in cirrhosis caused by alcohol, HCV, and NASH^{51–53}; in NASH, the risk is mediated by concomitant risk factors for cardiovascular disease or by the presence of steatosis and insulin resistance. The risk of atherosclerosis is highest in NASH cirrhosis.⁵³ Cholestatic liver diseases, however, do not carry an overall increased risk of atherosclerotic disease.⁵¹

Statins are safe and can be used in patients with Child-Pugh class A cirrhosis.⁹ There are little to no available data regarding the safety and risks of statin use in patients with decompensated cirrhosis. The updated 2014 recommendations of the Liver Expert Panel assembled to address the safety of statins in liver disease⁹ provides some guidance and advises against statin use among patients with Child-Pugh class B or C cirrhosis. The underlying rationale is that the generally grave liver-related prognosis of patients with Child-Pugh class B or C cirrhosis makes it unlikely that they will benefit from the cardiovascular benefits associated with lipid-lowering therapy. In addition, moderate-to-severe hepatic impairment may result in reduced drug metabolism and consequently abnormally high serum drug levels (although an increased risk of hepatotoxicity has not been demonstrated).

In addition to lipid-lowering effects, statins are associated with reductions in portal pressure and may reduce the risk of decompensation among patients with HBV or HCV cirrhosis.^{54–56} However, the data are still

evolving, and use of statins to reduce portal pressure is not the standard of care. Therefore, statins should not be used for the treatment of portal hypertension.

Post-Transplant Dyslipidemia

Dyslipidemia is common following liver transplantation, occurring in up to 62% of transplant recipients.⁵⁷ Post-transplant dyslipidemia is seen most commonly in patients with obesity or diabetes mellitus pretransplantation but can develop in the absence of these comorbid conditions. Weight gain post-transplantation and use of immunosuppressant medications, including calcineurin inhibitors and the mechanistic target of rapamycin inhibitor sirolimus, also increase the risk of post-transplant dyslipidemia.⁵⁸

Lipid-lowering agents, specifically statins, are safe in the post-transplant population and should be used as needed to treat dyslipidemia.⁵⁹ Calcineurin inhibitors and several statins are metabolized by cytochrome P-450 3A4, and concurrent use may increase the risk of statin-associated myopathy. Pravastatin and fluvastatin are not metabolized by cytochrome P-450 3A4 and, when used with cyclosporine, may not increase the risk of statin-associated myopathy.^{59,60}

Conclusions

Lipid-lowering medications are safe and effective in lowering the risk of cardiovascular disease in individuals with compensated liver disease. Some lipid-lowering agents may help in the primary or secondary treatment of specific types of liver disease. Interactions with other drugs should be considered when choosing particular lipid-lowering medications. Only in patients with decompensated cirrhosis and in those with well-documented DILI from a lipid-lowering agent should these medications not be used.

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Conflicts of interest

The authors disclose no conflicts.

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