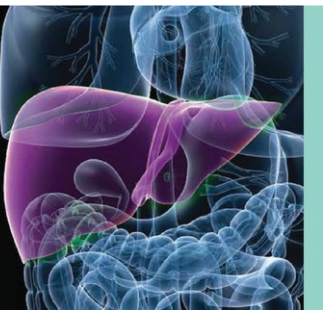

Patients With Chronic Liver Disease/Cirrhosis Should Not Take Statin Medications

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3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, a class of medications commonly known as statins, were originally developed to treat hypercholesterolemia by inhibiting the rate-limiting step in hepatic cholesterol biosynthesis, thus significantly lowering low-density lipoprotein, total cholesterol level, and to lesser extent, triglycerides and high-density lipoprotein.[1] Besides myositis, hepatotoxicity is one of the most well-known potential adverse reactions of statin use. The risk for hepatotoxicity is small, but looms large in the mind of providers because hepatotoxicity is a major source of underprescription in chronic liver disease.[2] Multiple studies have demonstrated the proven benefit of statin medications in decreasing cardiovascular morbidity and mortality.[3,4] This brief review will help to dispel the misconception that statins are unsafe in chronic liver disease and may, in fact, have benefit in this population.

Hepatotoxicity due to statin use is uncommon, associated with mild-to-moderate elevations in aminotransferases, and is usually self-limited often without need for discontinuation or dose adjustment.[5,6] During the registration trials, up to 2% of participants experienced mild-to-moderate elevations of aminotransferases without clinically apparent or significant liver injury.[3-5] In the Drug-Induced Liver Injury Network (DILIN), statin hepatotoxicity leading to clinically apparent liver injury was rare (1.8%), had variable patterns of injury and onset, and in three patients expressed phenotypic features of autoimmune liver injury (Table 1).[7] The Spanish Hepatotoxicity Registry (REH)

Abbreviations: chol/mixed, cholestatic or mixed type of drug-induced liver injury; CI, confidence interval; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; HC, hepatocellular; HCC, hepatocellular carcinoma; HR, hazard ratio; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PTH, portal hypertension; RCT, randomized control trial; REH, Spanish Hepatotoxicity Registry; RR, relative risk; SVR, sustained virologic response.

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TABLE 1. SUMMARY OF FOUR MAJOR STUDIES EVALUATING HEPATOTOXICITY OF STATINS

Study Characteristics	Sweden[10]	Iceland[9]	REH[8]	DILIN (USA)[7]
Type of study and data source	Population; Swedish Adverse Drug Reactions Advisory Committee	Prospective and population based	Prospective	Prospective
Total DILI cases, n	73	96	446	899
Statin cases, n	73	3	47	22
Median age, years (statin cases)	64	55	62	60
Male sex, %	55	44	49	32
Pattern of DILI	59% HC 30% cholestatic 11% mixed	42% HC 32% cholestatic 26% mixed	51% HC 49% chol/mixed	55% HC 45%
Jaundice, %	34	50	53	68
Latency, days	90	NA	57	155
Notable adverse clinical outcomes	Acute liver failure (2 simvastatin, 1 atorvastatin) resulting in 2 deaths and 1 orthotopic liver transplantation	NA	40% hospitalized 19% chronicity 2 deaths (but not due to statin DILI)	18% hospitalized 4 evidence of hepatic failure 1 death 4 chronicity

reported that 5.5% of cases (47/858) of drug-induced liver injury (DILI) were attributable to statins, with atorvastatin having the greatest number of cases and autoimmune phenotypes to be the predominant characteristic.[8] The prospective, population-based study in Iceland found only 3 cases of statin-induced hepatotoxicity among 7385 patients treated, and estimated the crude annual incidence rate as 19.1 cases/100,000 inhabitants.[9] Based on sales figures and spontaneous reporting in a population-based study from Sweden, Bjornsson et al.[10] found that statin-induced DILI occurred in 1.2/100,000 users. Several retrospective studies, cases series, and reports have implicated statins in hepatotoxicity, suggesting the rarity of this phenomenon.[10-13] Further, even in patients with chronic hepatitis C or nonalcoholic steatohepatitis (NASH) with abnormal aminotransferases, the addition of statins does not increase the risk for hepatotoxicity.[14,15] In 2004, Chalasani et al.[15] tested the hypothesis that patients with elevated liver enzymes have higher risk for statin hepatotoxicity. Their analysis found that patients with baseline abnormal liver enzymes who were prescribed a statin had no higher incidence of severe elevations in liver enzymes compared with a cohort of patients with normal liver enzymes prescribed a statin or a cohort of patients with abnormal liver enzymes not prescribed a statin.[15] A multicenter, randomized, placebo-controlled, parallel group trial comparing high-dose pravastatin with placebo found no increased risk for abnormal liver enzymes in patients with NASH and hepatitis C.[14] Despite this available evidence demonstrating the rarity, safety, and efficacy of statins, fears of hepatotoxicity remain among primary care providers and may contribute to statin underutilization.[2,16]

This misconception, and therefore reluctance to prescribe statins, may indirectly deny patients with chronic liver disease significant clinical benefit (Fig. 1). Unrelated to its lipid-lowering effects, statins have a wide array of pleiotropic effects, ranging from antioxidant, antifibrotic, anti-inflammatory, and improvement of endothelial dysfunction, making them a potentially attractive therapeutic option for patients with chronic liver disease (Table 2).[17] For example, the 2018 American Association for the Study of Liver Diseases guidelines recommend treatment of dyslipidemia with statins in patients with NASH to reduce cardiovascular morbidity and mortality.[18] Statin use appears safe and effective in small, noncontrolled studies for the treatment of dyslipidemia in patients with primary biliary cholangitis.[19] Further, large retrospective observational studies have demonstrated reduced risks of fibrosis progression, decompensation, hepatocellular (HC) carcinoma (HCC), and death in patients with viral hepatitis B or C who use statins.[20,21] In fact, in one study of patients with hepatitis B, statin use was not only associated with a decreased risk for HCC, but a decreased risk for all nonliver cancers.[22] In the posttransplant setting, dyslipidemia is common (62%) and can be treated effectively with statins (ideally fluvastatin or pravastatin), with careful monitoring of drug–drug interactions.[23,24] Finally, statins have a promising role in their impact on portal hypertension. In a randomized control trial (RCT) of simvastatin versus placebo in 55 patients, simvastatin was associated with an 8.3% reduction in hepatic venous pressure gradient, and this effect was additive to patients already taking beta blockers.[25] These findings and others led to an RCT comparing simvastatin with placebo added to standard therapy (esophageal variceal ligation

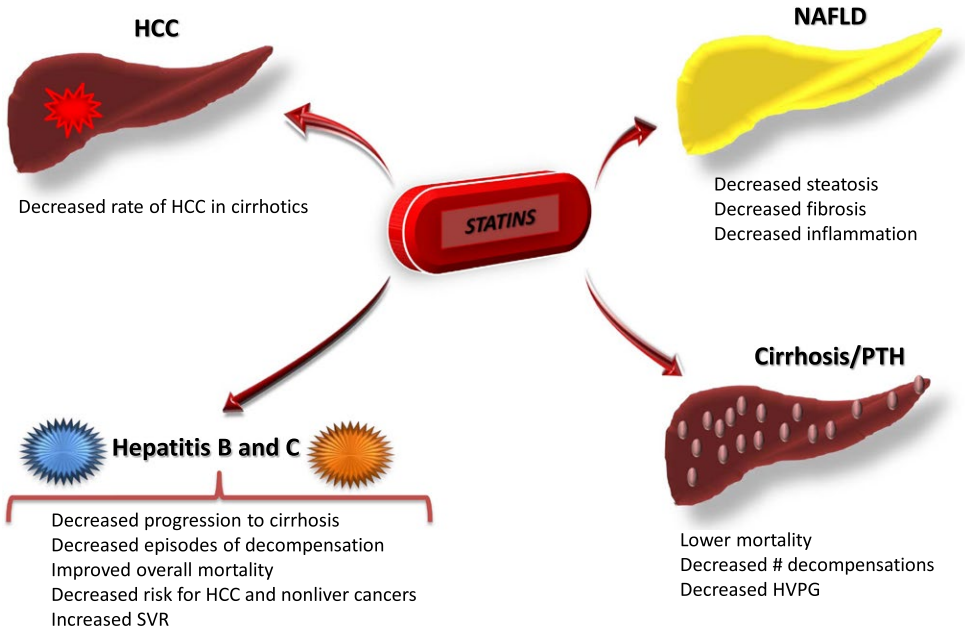

FIG 1 Clinical evidence of the benefit of statin use in chronic liver disease.

TABLE 2. KEY STUDIES SUPPORTING PLEIOTROPIC EFFECTS OF STATINS

Study Characteristics	Decompensation[20]	Fibrosis[21]	Malignancy[22]	Portal Hypertension[25]	Survival[26]
Study design	Retrospective cohort study Propensity-matching	Population-based cohort Propensity-matching	Population-based longitudinal cohort	Randomized, prospective, double-blind	Multicentered, randomized, placebo-controlled, double-blind, parallel
Study population	Hepatitis C Compensated cirrhosis Veterans	Chronic hepatitis B	Chronic hepatitis B	Cirrhosis	Cirrhosis
No. of study patients	685 statin users 2062 statin nonusers	6543	71,824	59	158
Statin	Simvastatin Lovastatin Pravastatin Fluvastatin Rosuvastatin	—	—	Simvastatin	Simvastatin
Statin dose	—	—	—	20 mg → 40 mg at day 15	20 mg → 40mg at day 15
Key findings	Statin use was associated with 40% decreased risk for decompensation and death compared with nonusers	Statin use was associated with lower incidence of cirrhosis (RR = 0.433; 95% CI, 0.344-0.515; *P* < 0.001) and decompensated cirrhosis (RR = 0.468; 95% CI, 0.344-0.637; *P* < 0.001) compared with non–statin users	Statin use was associated with reduced incidence of all cancers (HR 0.52; 95% CI, 0.48-0.57) and HCC (HR 0.28; 95% CI, 0.24-0.35) Dose-dependent effect of statins as chemoprevention for malignancy and liver cancer	Decreased HVPG by 8.3% with improvement in liver perfusion/function compared with placebo	Did not reduce rebleeding risk from esophageal varices; however, a 61% reduction in relative risk of death compared with placebo

and nonselective beta blockade) to assess risk for rebleeding and death. Although rebleeding did not occur less frequently in the statin group, overall survival was significantly improved in those who were randomized to simvastatin.[26]

In summary, the pleiotropic effects of statins make their use in diseases other than dyslipidemia and reduction of cardiovascular events attractive. Epidemiological, preclinical, and clinical studies have addressed the

misconception that statin use is harmful in patients with liver disease. However, indications for statin use in patients with chronic liver disease and cirrhosis continue to be the same as that of the general population. The American Gastroenterology Association recently published a clinical practice update based on expert review advocating the sensible use of statins to treat dyslipidemia in patients with liver disease.[27] In patients with chronic liver disease and compensated cirrhosis, statins are safe and effective and should not be avoided because of fears of hepatotoxicity. Statin use is not indicated and should be discontinued in acute hepatitis and decompensated cirrhosis. Further prospective and RCTs are needed to confirm the benefit of statins in patients with chronic liver disease.

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