Review Article

JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

Statins in Cirrhosis: Hope or Hype?

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In recent years, studies have demonstrated the benefits of statins in a range of chronic diseases separate from cardiovascular outcomes. Early studies in the context of chronic liver disease have suggested favorable effects of statins leading to slowed fibrosis progression, reduced portal pressures, decreased rates of hepatic decompensation, and improved survival. This has increased interest in the potential role that statins may have in the management of chronic liver disease and cirrhosis, though many questions remain unanswered, including concerns regarding the safety of higher dose statins in patients with advanced decompensated cirrhosis. In this review, we provide an update on the current literature addressing the use of statins in patients with cirrhosis and highlight areas in which additional studies are needed. (J Clin Exp Hepatol xxxx;xxx:xxx)

Statin medications are well-recognized as lipid-lowering agents that act via inhibition of 3-hydroxy-3-methylglutaryl–coenzyme A reductase leading to downstream effects of decreased serum cholesterol levels.[1] They are most commonly prescribed in patients with known cardiovascular disease or risk factors for developing cardiovascular disease as studies have demonstrated significant reductions in risk of adverse cardiovascular events in these populations.[2] However, statins have also been shown to have pleiotropic effects including anti-inflammatory, anti-fibrotic, vasoprotective, and antioxidant effects, which has sparked interest in potential mitigation of complications of chronic liver disease (CLD).[3] Several cohort studies and randomized controlled trials (RCTs) investigating the role of statins in liver disease have emerged out of this curiosity and have shown promising results.

However, widespread concern over statin-associated hepatotoxicity and the long-standing hesitancy of prescribing this class of medications in patients with CLD, especially those with cirrhosis, continue to persist for many providers.[1,4,5] In recent years, several studies have emerged addressing safety concerns of statin use in patients with CLD and cirrhosis, which have helped to shape current prescribing practices. In this brief review, we will discuss the pleiotropic effects of statins, their potential benefits in patients with cirrhosis, and address their safety profile in this patient population.

PLEIOTROPIC EFFECTS OF STATINS AS RELEVANT TO CLD

The progression of CLD is characterized by chronic hepatic inflammation leading to progressive fibrosis and ultimately cirrhosis. These changes promote increased hepatic sinusoidal resistance and portal hypertension (pHTN), leading to an imbalance of vasoconstrictors and vasodilators that preserves flow across the liver at the expense of further increasing pHTN and reducing systemic vascular resistance.[6] Increased cell turnover related to chronic liver inflammation, regenerative efforts, and cirrhosis also independently increases the risk of oncogenesis and development of hepatocellular carcinoma (HCC). With these pathogenic considerations in mind, there is a strong theoretical basis for the pleiotropic effects of statins to mitigate progression of liver disease, cirrhosis decompensation, and development of HCC (Figure 1).

The molecular basis for the pleiotropic effects of statins are complex and multifold. Scientists postulate that these are largely mediated through the reduction of isoprenoid molecules that typically activate small GTPases such as Rho and Ras proteins.[7] Inhibition of Rho and Ras protein activation leads to downstream modulation of the nitric oxide (NO) pathway.[8] This leads to improved stability of endothelial nitric oxide synthase (eNOS) mRNA and ultimately increased availability of eNOS and NO molecules

Keywords: statin, cirrhosis, portal hypertension, decompensation, hepatocellular carcinoma

Received: 4.2.2023; *Accepted:* 1.5.2023; *Available online:* xxx

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Abbreviations: ACLF: acute-on-chronic liver failure; CLD: chronic liver disease; CTP: Child–Turcotte–Pugh; EV: esophageal varices; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HR: hazard ratio; HVPG: hepatic venous pressure gradient; iNOS: inducible nitric oxide synthase; KLF2: Kruppel-like factor 2; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NO: nitric oxide; OR: odds ratio; pHTN: portal hypertension; RCT: randomized controlled trial

https://doi.org/10.1016/j.jceh.2023.05.002

Please cite this article as: Shaffer and Mahmud, Statins in Cirrhosis: Hope or Hype?, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.05.002

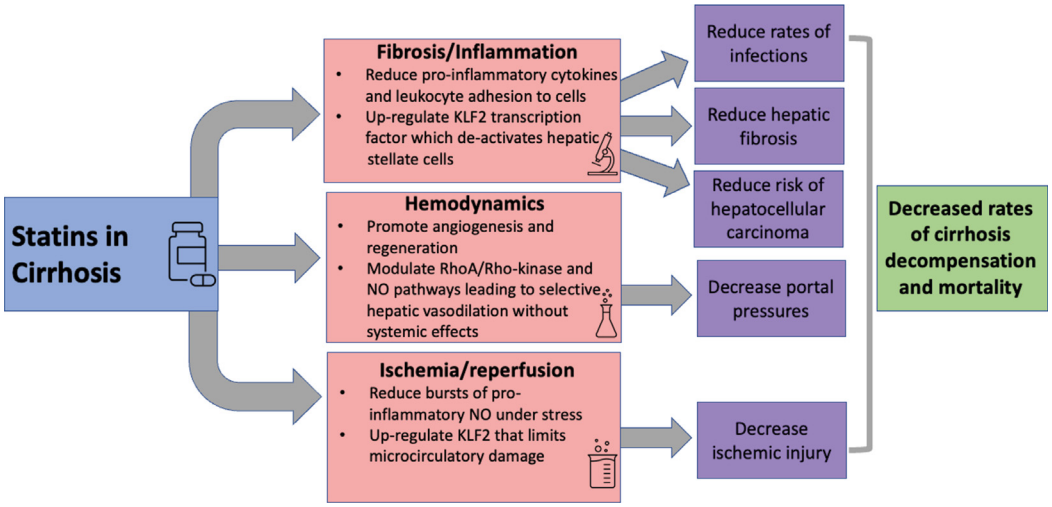

Figure 1 Hypothesized basis for impact of statins on cirrhosis-related outcomes.

that modulate vascular and endothelial function.[7] Similar effects on the NO pathway are further mediated by increased expression of transcription factor Kruppel-like factor 2 (KLF2), which is responsible for regulating about 40% of the endothelial genome.[7,9]

Statins modulate these pathways with specific impacts on hepatic cells. Statin inhibition of RhoA/Rho-kinase signaling and downstream NO pathway regulation leads to vasoconstrictor-promoted smooth muscle contraction within hepatic stellate cells (HSC).[10,11] Much of the effects of statins in preventing ischemic injury and modulating portal pressures are thought to be related to this pathway.

The abovementioned transcription factor KLF2 is expressed in all key liver cell types.[10] It is responsible for the expression of genes related to apoptosis, inflammation, oxidative stress, thrombosis, and vasodilation.[10] Upregulation of KLF2 by statins via the Rac1-MEK5-ERK5-MEF2 axis induces deactivation of HSCs involved in fibrosis and improves liver sinusoidal endothelial cell function.[10,12–14] This mechanism is likely responsible for much of the anti-fibrotic and anti-inflammatory effects of statins.

PRECLINICAL STUDIES IN LIVER DISEASE

Like most scientific developments that begin in in vitro or animal studies, the investigation of statin use in CLD is no different. These studies have laid the groundwork for past and future human studies of statins in cirrhosis.

Fibrosis and Inflammation

Statins have favorable anti-fibrotic outcomes in experimental models of liver disease. Through complex mechanisms outlined above, statins reduce liver fibrosis via a reduction in HSC activity. Furthermore, they dampen inflammation by reducing leukocyte adhesion to cells, decreasing pro-inflammatory cytokines, and inhibiting immune cell activation and growth.[15] Chong *et al.* found that fluvastatin attenuates fibrinogenesis in rat-based nonalcoholic steatohepatitis models via disruption of paracrine signaling on HSCs.[16] Other studies using bile duct ligated animal models representative of obstructive hepatic injury demonstrated similar hepatoprotective effects of statins at least in part mediated by disruption of inflammatory cytokines and leukocyte activation.[17,18] Of note, these anti-fibrotic effects have only been observed in early stages of fibrosis compared to late liver fibrosis models.[18]

Portal Hypertension

Statins mobilize endothelial progenitor cells to promote angiogenesis and regeneration.[15] Furthermore, they have been shown to modulate the imbalance in vascular tone regulatory pathways (i.e., RhoA/Rho-kinase and NO) that leads to pHTN in cirrhosis. In these processes, extrahepatic endothelial cells are overactivated and increase NO production, leading to vasodilation, while intrahepatic cells are hypoactive, leading to decreased NO production and ultimately vasoconstriction.[11,13–15,19,20] Recent studies have shown that statins selectively upregulate NO production in hepatic microvasculature, leading to selective vasodilation at the liver and improvement in portal pressure.[11,21,22] Trebicka *et al.* used bile duct ligated rat models of cirrhosis to demonstrate that atorvastatin leads to a reduction in portal pressure without significantly affecting systemic mean arterial pressure via the mechanisms described above.[11] Similar results were demonstrated in several other studies using rat models of liver cirrhosis.[14,22,23] These outcomes in early animal models suggested the potential vasoprotective effects of statins that have been a focus in many recent human studies.

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Ischemia and Reperfusion

Hepatic cells are highly prone to ischemic and reperfusion injury, which is largely driven by the inducible nitric oxide synthase-nitric oxide and the KLF2 pathway. Statins prevent or limit ischemia and reperfusion injury by reducing the production of nitric oxide synthase, which limits bursts of pro-inflammatory NO under stress.[10,12,24] Additionally, they upregulate transcription factor KLF2, which limits microcirculatory damage in these situations.[10] The molecular basis for antioxidant effects of statins has translated to preclinical studies. Hide *et al.* found that warm ischemia and reperfusion injury in rat hepatocytes was blunted by simvastatin administration, which was also observed in rats with biliary cirrhosis in the study by Meireles *et al.*[25,26] Furthermore, one study found that liver grafts with steatosis in rats that received a prior dose of simvastatin before liver procurement had markedly less liver injury and endothelial cell dysfunction.[27]

HUMAN STUDIES OF STATINS IN CIRRHOSIS

With evolving data (largely from animal studies) over the last 2 decades regarding the pleiotropic effects of statins, there has been a surge of interest in conducting human studies assessing the impact of statins on cirrhosis-related outcomes. To identify relevant studies to discuss in this review, we performed a MEDLINE search using the following keyword combinations: [statin OR HMG-CoA reductase inhibitor] AND [liver disease OR cirrhosis OR decompensation OR hepatocellular carcinoma OR liver cancer]. All manuscript titles and abstracts were screened by LRS for relevance, and the references for each included study were also reviewed to identify additional relevant studies. The characteristics of the final included studies are summarized in tables, which include retrospective cohort studies (Table 1), RCTs (Table 2), and clinical trials in process (Table 3). Several observations can be gleaned from a literature review on this topic, including statin impact on hepatic venous pressure gradient (HVPG), prognosis of cirrhosis as it relates to mortality and decompensation, impact on infection and HCC, the dose-dependent impact of statins, and statin safety profile.

Association with Decompensation and Mortality

Given the dramatic reduction in prognosis from median 12 years to median 2 years survival at the time of cirrhosis decompensation,[28] this is a primary outcome of interest in cirrhosis-related studies as decompensation invariably precedes liver-related death.[10] We identified eight cohort studies and seven published RCTs that investigated the effect of statin use on cirrhosis decompensation and/or mortality, as well as pHTN parameters.

Observational Studies

Retrospective cohort studies included large numbers of patients (of up to 84,963 in one study),[29] mainly derived from large patient databases, such as the Veterans Affairs Administration or Taiwan National Health Insurance database. The main etiologies of cirrhosis studied were hepatitis C virus (HCV), hepatitis B virus (HBV), and alcohol-associated cirrhosis,[29–35] with three studies including a wider range of cirrhosis etiologies, such as nonalcoholic fatty liver disease (NAFLD) and other less common etiologies (e.g., autoimmune hepatitis and cardiogenic cirrhosis).[29,30,33] One study looked at the association between statins and the development of acute on chronic liver failure (ACLF) in patients with cirrhosis, which is characterized by an acute decompensation, severe inflammation, and evidence of end-organ failure.[29] A follow-up study by this group also investigated the association of statin exposure with short-term mortality in patients with ACLF. For the other seven studies, the key endpoints were hepatic decompensation and/or mortality in cirrhosis with a few studies conducting subsequent analyses to assess duration/dose-dependent effects of statins. A majority of the studies used an unmatched sample together with propensity score matched analysis to evaluate these endpoints. A variety of specific statin medications were used in each study as the exposure arm was generally defined broadly as binary statin usage. In general, statin use was associated with an overall reduced risk of decompensation and mortality. After adjusting for key confounding variables, hazard ratios (HRs) for cirrhosis decompensation ranged from 0.29 to 0.55 and for mortality HRs ranged from 0.56 to 0.91. One of the largest retrospective cohort studies showed that there was a positive association between duration of statin use and reduced risk of mortality whereby each cumulative year of statin use independently reduced the rate of mortality by 8.0–8.7% in their study population.[30] This dose-dependent response was also seen in a Taiwanese study by Huang *et al.*, whereby the adjusted HR for risk of cirrhosis decompensation went from 0.61 to 0.23 with higher cumulative daily dose of statins.[35] The largest retrospective study by Mahmud *et al.* identified a HR of 0.62 for development of ACLF in patients with cirrhosis and statin usage, which was noted to be both dose and duration dependent.[29] The follow-up study showed that with at least 90 days of preceding statin exposure from hospitalization for ACLF, there was 18% lower odds of ACLF-related 28-day mortality and 24% lower odds of 90-day mortality.[36] Increasing statin dose exposure led to further decline in 90-day mortality. However, there are conflicting results in the study by Bang *et al.* who identified a clear association between statin use and reduction in mortality but did not observe a significant dose-dependent effect.[34] Of note, this study was

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Table 1 Observational Studies Addressing Use of Statins in Patients with Cirrhosis.

Study (authors, journal, year)	Source of data	Patient population	Number of patients	Follow-up duration	Endpoints of interest	Results	Comments
Mahmud *et al.*, *Journal of Hepatology*, 2022	Veterans Health Administration database	HCV, HBV, ALD, NAFLD, and other	46,515 no statin exposure, 22,876 on baseline statin, 15,572 new statin initiator	Time-updated at 30-day intervals through 5 years of follow-up	Risk of developing ACLF	Significant reduction in hazard of ACLF (HR 0.62; 95% CI 0.59–0.65)	Dose and duration-dependent response
Huang *et al.*, *American Journal of Gastroenterology*, 2016	Taiwanese National Health Insurance Research Database	HBV	6543 statin cohort, 6543 matched non-statin cohort	Up to 13 years of follow-up	Incidence of developing cirrhosis and decompensated cirrhosis	Significant reduction in incidence of cirrhosis (RR 0.433; 95% CI 0.344–0.515) and incidence of decompensated cirrhosis (RR 0.468; 95% CI 0.344–0.637)	Dose-dependent response Excluded patients with evidence of cirrhosis at the start
Mohanty *et al.*, *Gastroenterology*, 2016	Veterans Health Administration database	HCV	1323 statin cohort, 12,522 non-statin cohort	Median follow-up time of 1.5 years (non-statin cohort) and 2.5 years (statin cohort)	Risk of decompensation and mortality	Significantly lower risk of decompensation (HR 0.55; 95% CI 0.39–0.77) and mortality (HR 0.56; 95% CI 0.46–0.69)	Statin use specifically led to lower rates of ascites and esophageal variceal bleed; also led to significantly lower risk of HCC. Findings persisted after adjusting for liver-related lab values and scores.
Chang *et al.*, *Hepatology*, 2017	Taiwanese National Health Insurance Research Database	HCV, HBV, and ALD	1174 statin cohort, 6453 non-statin cohort	Mean follow-up period of 5.2–5.6 years	Risk of decompensation, mortality, and HCC	Significantly lower risk of decompensation (HR 0.39; 95% CI 0.30–0.50), mortality (HR 0.46; 95% CI 0.34–0.63), and HCC (HR 0.52; 95% CI 0.35–0.76)	Dose-dependent response In subgroup analysis, decreased risk of decompensation was borderline significant in alcohol-related cirrhosis. Additionally, lower rates of specifically ascites, EV bleed, and HE.

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Table 1 (*Continued*)

Study (authors, journal, year)	Source of data	Patient population	Number of patients	Follow-up duration	Endpoints of interest	Results	Comments
Bang *et al.*, *Alimentary Pharmacology and Therapeutics*, 2017	Danish National Patient Registry	ALD	794 statin cohort, 4623 non-statin cohort	Estimated median follow-up time of 4 years	Risk of mortality (primary outcome) and decompensation (secondary outcome)	Significantly lower risk of mortality (HR 0.57; 95% CI 0.45–0.71) and risk of decompensation (HR 0.37; 95% CI 0.27–0.50)	Found no dose-dependent response
Kumar *et al.*, *Digestive Diseases and Sciences*, 2014	Partners Research Patient Data Registry	HCV, ALD, HBV, NASH, and other	81 statin cohort, 162 non-statin cohort	Median follow-up 36 months in statin users and 30 months in statin non-users	Risk of mortality (primary outcome) and decompensation (secondary outcome)	Significantly lower rate of mortality (HR 0.66; 95% CI 0.33–0.86) and lower rate of decompensation (HR 0.62; 95% CI 0.34–0.98)	Small sample size, but patients had biopsy-proven cirrhosis to be included in study
Motzkus *et al.*, *Alimentary Pharmacology and Therapeutics*, 2013	Veterans Health Administration database	HCV, alcohol-associated, and NASH	2468 statin cohort, 16,408 non-statin cohort, 503 other cholesterol-lowering medications cohort	Median follow-up 1194 days	Infection rates	Lower rate of hospitalizations with infection in statin cohort compared to non-statin cohort (HR 0.67; 95% CI 0.47–0.95)	Comparing association between statin users and other cholesterol-lowering medications cohort, there was no longer a statistically significant difference but trend toward significance
Kaplan *et al.*, *Gastroenterology*, 2019	Veterans Health Administration database	HCV, ALD, NASH, and other	21,921 existing statin users, 53,063 statin naõve (8794 subsequently initiated statin therapy)	Median follow-up 900 days for existing statin users, 1905 days for statin naõve	Risk of decompensation, mortality, and HCC	Lower rate of mortality: existing user (HR 0.92; 95% CI 0.90–0.94) and in new initiators (HR 0.91; 95% CI 0.89–0.93); trend toward decreased rates of decompensation and HCC	Separated exposure between existing statin user and new initiator. Small sample of patients with CTP C did not demonstrate a survival benefit with statin

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Table 1 (*Continued*)

Study (authors, journal, year)	Source of data	Patient population	Number of patients	Follow-up duration	Endpoints of interest	Results	Comments
Simon *et al.*, *Hepatology*, 2016	Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES)	HCV (if received at least 14 days of treatment)	4165 statin cohort, 4970 non-statin cohort	Median follow-up 97.9 months for statin users, 81.6 months for non-statin users	Progression of liver fibrosis, development of cirrhosis, and incident HCC	Statistically significant lower rate of fibrosis progression (HR 0.74, 95% CI 0.59–0.93), reduction in development of cirrhosis (HR 0.6, 95% CI 0.53–0.68), and lower incidence of HCC (HR 0.51; 95% CI 0.36–0.72)	Dose-dependent response in outcomes
Chapin *et al.*, JHEP Reports, 2023	Veterans Health Administration database	HCV, HBV, ALD, NAFLD, and other	3017 statin exposure cohort, 8714 non-statin cohort	90 days post-hospitalization	28-day mortality, 90-day mortality	18% reduction in ACLF-related 28-day mortality (95% CI 0.73–0.93, $P = 0.001$) and 24% lower odds of 90-day mortality (95% CI 0.68–0.86, $P < 0.001$)	Dose-dependent response in outcomes for 90-day mortality

ACLF, acute on chronic liver failure; ALD, alcohol-associated liver disease; CI, confidence interval; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; pHTN, portal hypertension; PLsec, prognostic liver secretome signature; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis.

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Table 2 Randomized Controlled Trials Addressing Use of Statins in Patients with Cirrhosis.

Study (authors, journal, year)	Source of data	Patient population	Number of patients	Statin type/ Daily dose	Duration of statin use at follow-up	Endpoints of interest	Results	Comments
Abraldes *et al.*, *Gastroenterology*, 2016	Multi-center academic hospitals (14 centers)	ALD, HBV, HCV, PBC, NASH, and other cirrhosis; index EV bleed 5–10 days prior to start of study	69 patients received statin, 78 patients received placebo	Simvastatin 40 mg	Two years	Composite of rebleeding (EV) and mortality; rebleeding alone, mortality alone	Non-significant composite endpoint ($P = 0.423$); statin significantly reduced mortality (HR 0.39; 95% CI 0.15–0.99); non-significant outcome of rebleeding alone ($P = 0.583$)	Non-significant outcome for primary outcome. Higher proportion of rhabdomyolysis in patients with advanced liver disease.
Abraldes *et al.*, *Gastroenterology*, 2009	Multi-center academic hospitals (3 centers)	ALD, HBV, HCV, and other cirrhosis; HVPG >12 mmHg at start	29 patients received statin, 30 patients received placebo	Simvastatin 40 mg	One month	Change in HVPG	HVPG significantly decreased by −8.3% (by −11.0% in those receiving a beta blocker and −5.9% in those who were not); no decrease in placebo group	No significant difference in adverse events; excluded patients with advanced liver failure
Pollo-Flores *et al.*, *Digestive and Liver Disease*, 2015	Single center university hospital	Cirrhosis and pHTN (HVPG >5 mmHg)	14 patients received simvastatin, 20 patients received placebo	Simvastatin 40 mg	Three months	Decrease in HVPG of at least 20% from baseline or <12 mmHg	Clinically significant decrease in HVPG in 55% of patients with simvastatin (median −2 mmHg, $P = 0.02$), no difference in placebo group (median 0 mmHg)	No significant difference in adverse events. Previous EV bleed or medium/large EV were independently associated with a higher response rate to simvastatin
Elwan *et al.*, *F1000 Research*, 2018	Single center university hospital	Liver cirrhosis with clinical signs of pHTN	20 patients received simvastatin, 20 patients received placebo	Simvastatin 20 mg for 2 weeks; then 40 mg for remaining 2 weeks	One month	Changes in measures of pHTN evaluated by doppler ultrasound	Significant decrease in hepatic artery resistance index (0.785–0.717; $P < 0.001$), decrease in pHTN index (3.915–1.605; $P = 0.024$), and increase in modified liver vascular index (11.54–13.31; $P = 0.009$)	No significant difference in adverse events

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Table 2 (*Continued*)

Study (authors, journal, year)	Source of data	Patient population	Number of patients	Statin type/ Daily dose	Duration of statin use at follow-up	Endpoints of interest	Results	Comments
Bishnu *et al.*, *European Journal of Gastroenterology and Hepatology*, 2018	Single center university hospital	Liver cirrhosis with clinical signs of pHTN	12 patients received propranolol alone, 12 patients received atorvastatin and propranolol	Atorvastatin 20 mg	One year	Change in HVPG	Significant decrease in HVPG of 4.81 ± 2.82 in statin group vs. 2.58 ± 1.88 mmHg in non-statin group ($P = 0.041$)	No difference in clinical outcomes at 1 year (including: EV bleed, HE, ascites, SBP, and mortality)
Wani *et al.*, *World Journal of Hepatology*, 2017	Single center university hospital	Liver cirrhosis with evidence of EV and HVPG >12 mmHg at start	62 carvedilol responders, 35 carvedilol non-responders who had addition of simvastatin	Simvastatin 40 mg	Three months	Effect on HVPG of at least 20% from baseline or <12 mmHg	Mean reduction of HVPG from baseline was 5.5 ± 1.7 mmHg for carvedilol responders and 2.8 ± 1.6 mmHg for non-responders ($P < 0.001$); 42.1% of carvedilol had a significant response after additional of simvastatin	No significant difference in adverse events
Vijayaraghavan *et al.*, American Journal of Gastroenterology, 2020	Single center university hospital	Liver cirrhosis with EV and baseline HVPG >12 mmHg	110 carvedilol alone, 110 carvedilol plus simvastatin	Simvastatin 20 mg for 2 weeks; then 40 mg for remaining 2 weeks	Three months	Effect on HVPG of at least 20% from baseline or <12 mmHg; secondary bleeding episodes, death, and adverse events	Mean HVPG reduction (17.3% vs. 17.8%, $P = 0.98$) and hemodynamic response (95% CI 0.43–1.83; $P = 0.74$) was not different between the two groups	Non-significant outcome for primary outcome. Three patients on simvastatin (3.7%) developed transient transaminitis and elevated creatine kinase

ACLF, acute on chronic liver failure; ALD, alcohol-associated liver disease; CI, confidence interval; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; pHTN, portal hypertension; PLsec, prognostic liver secretome signature; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis.

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Table 3 Ongoing Randomized Controlled Trials Addressing Use of Statins in Patients with Cirrhosis.

Principal Investigator	Sponsor	Patient population	Number of patients	Follow-up duration	Arms	Endpoints of interest	Comments
Thit M Kronborg	Copenhagen University Hospital	Liver cirrhosis with pHTN (HVPG >10 mmHg)	-Part one: 48 patients -Part two: 162 patients	1.5 years	Atorvastatin vs. placebo (control)	Composite numbers of death of liver transplantation; number of hospitalizations for liver-related complications	Secondary outcomes include molecular endpoints and inflammation/ macrophage activation and protein activity
Marc Goodman	National Cancer Institute	Liver cirrhosis with MELD=<20	Estimated 80 patients	6 months	Simvastatin vs. placebo (control)	Change in serum AFP-L3%	AFP-L3% serves as an advanced tumor marker for HCC
David Kaplan	VA Office of Research and Development	Compensated liver cirrhosis due to HBV, HCV, ALD, or NAFLD; U.S. veteran population	Estimated 500 patients	Two years	Simvastatin vs. placebo (control)	Survival free from cirrhosis decompensation	Largest known RCT on this topic to date
Raymond Chung	University of Texas Southwestern Medical Center	Advanced liver fibrosis or cirrhosis who are at high risk of HCC by risk calculator	Estimated 60 patients	48 weeks	Atorvastatin vs. placebo (control)	Reduced amount of high-risk PLsec and reduced magnitude of high-risk PLsec	Measure of HCC response is PLsec
Dong Hyun Sinn (responsible party)	Samsung Medical Center	HBV cirrhosis	Estimated 36 patients	24 weeks	Atorvastatin vs. placebo (control)	Response rate with improvement in liver stiffness	A responder is defined as % change in spleen stiffness decreased by 10% or more from baseline
Guilherme Rezende (responsible party)	Universidade Federal do Rio de Janeiro	Liver cirrhosis with previous EV bleeding	Estimated 80 patients	16 weeks	Propranolol non-responders: rosuvastatin vs. placebo; Carvedilol non-responders: rosuvastatin vs. placebo	Change in HVPG with beta blocker plus statin or placebo (12 mmHg or lower)	Comparing both beta blockers (propranolol and carvedilol), as well as additional effects of statin therapy

ACLF, acute on chronic liver failure; ALD, alcohol-associated liver disease; CI, confidence interval; EV, esophageal varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; pHTN, portal hypertension; PLsec, prognostic liver secretome signature; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis.

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limited to patients with alcohol-related cirrhosis in a Danish patient registry, raising questions of external validity to broader cirrhosis cohorts. Nonetheless, such discrepancies in the literature indicate that additional studies are needed to identify variation in the association between statins and key liver-related outcomes across different demographics, etiologies of liver disease, and comorbidity profiles.

As noted, it is important to acknowledge the limitations of these studies, which may call into question the generalizability of these findings. First, it is well recognized that nonrandomized studies such as cohort studies are subject to bias from residual uncontrolled confounding. Second, there is a predominance of studies investigating HCV, HBV, and alcohol-associated cirrhosis, with little attention paid to NAFLD/nonalcoholic steatohepatitis-related cirrhosis populations who arguably may garner the most positive effects from statin use. Third, there are limited data on specific statin types so that conclusions may be perceived as generalizable to all statin types, when in reality this may not be the case. Fourth, as identified and addressed by Kaplan *et al.*, few prior studies have accounted for the time-updated presence of hyperlipidemia in their patient population, which could potentially serve as a complex confounder for the outcome of mortality and thus lead to overestimation of statin effect size.[30] Finally, all of the studies either excluded patients with Child–Turcotte–Pugh (CTP) class C or included only a small number of these patients; thus, it is difficult to make reasonable conclusions about statin efficacy in this population.

Randomized Controlled Trials

RCTs in this area have primarily focused on the direct effects of statins in potentially reducing pHTN in patients with cirrhosis with a few investigating the additive effect of statins and nonselective beta blockers (standard of care).[21,37–42] These studies are based on the concept that pHTN is a hallmark feature of liver cirrhosis characterized by an elevated HVPG above 5 mmHg. Once HVPG is elevated above 10 mmHg, clinical decompensations such as the accumulation of ascites may occur. Above an HVPG of 12 mmHg, patients have a high risk of esophageal variceal (EV) bleeding.[39] Thus, HVPG serves as a prognostic indicator in patients with cirrhosis,[39] and RCTs have generally established a clinical target of an HVPG less than 12 mmHg in patients with cirrhosis.[37] In these studies, methods of measuring HVPG or other surrogates of pHTN (i.e., pHTN index and modified liver vascular index) varied and included the gold standard of direct hepatic vein catheterization,[21,37,39] endoscopic doppler ultrasound,[39] and/or noninvasive abdominal doppler ultrasound.[40] Five of the six studies investigated simvastatin specifically,[21,37,39–41] with only one investigating atorvastatin.[38] Statins alone were shown to significantly reduce measures of pHTN. Furthermore, as best highlighted in the study by Abraldes *et al.*, the effect of statins on portal pressure reduction was independent of and additive to the effects of beta blockers in their study population.[37] These additive effects were similarly observed in other studies.[21,38,39] However, the RCT by Vijayaraghavan *et al.* did not observe an additive hemodynamic response with simvastatin and carvedilol compared to carvedilol alone.[41] While the results are mixed, one could speculate that there may be a role for dual therapy with statin and nonselective beta blocker or a benefit in statin monotherapy if a patient cannot tolerate beta blocker therapy for portal pressure reduction. Moving beyond portal pressure reduction as an endpoint, Abraldes *et al.* published another RCT 7 years later that investigated whether the addition of simvastatin to standard of care (i.e., beta blocker and EV band ligation) could prevent EV rebleeding (primary outcome) or improve survival (secondary outcome) in patients with cirrhosis who experienced an EV bleed.[42] They found no difference in their primary outcome of EV rebleeding events; however, they did observe a statistically significant improvement in survival for statin-exposed patients with CTP class A or B disease through 2 years of maximum follow-up.[42]

Similar to the cohort studies discussed above, there are important limitations to discuss with these RCTs. First, sample size in the RCTs ranged from 23 to 158 patients and most excluded patients with CTP class C disease. This may impact the generalizability of findings to patients with the most advanced stages of cirrhosis. Second, the time for assessment of change in hepatic vein hemodynamics after the introduction of a statin was relatively short, ranging from 1 month to 3 months, and it is thus unclear whether observed reductions in portal pressure attributable to statins are persistent over longer period of time. Third, the selection criteria varied across RCTs, as did the comparator groups. All studies included patients with liver cirrhosis and evidence of pHTN, but the degree of cirrhosis severity and markers of pHTN differed. For example, Bishnu *et al.* and Abraldes *et al.* (2009 and 2016) excluded patients in CTP class C and Child–Pugh score=>13, respectively,[37,38,42] whereas Wani *et al.* excluded patients with severe liver failure INR > 2.5 or bilirubin > 5.[21] Elwan *et al.* excluded patients with severe grade III-IV HE, while Pollo-Flores *et al.* excluded patients with severe ascites or grade II HE.[39,40] Furthermore, some studies had inclusion criteria for specific measures of HVPG, such as greater than 12 mmHg,[21,37] while others based pHTN parameters on clinical features, such as ascites, EV ± bleeding event, splenomegaly, or low-grade HE.[38,40] Lastly, the comparator groups differed among studies. Four studies compared a statin exposure group to placebo,[37,39,40,42] whereas two studies compared beta

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blocker and statin exposure group to a beta blocker alone group.[21,38] These differences in selection criteria and in comparator groups may impact study findings, and ultimately make it difficult to aggregate results of all RCTs.

With these limitations in mind, the current evidence from the above cohort studies and RCTs is promising. Observational data suggest that statins may be beneficial in patients with cirrhosis by reducing the risk of decompensation and ultimately mortality, and RCTs indicate that this may be mediated through statin-induced reductions in portal pressure in patients with previously established pHTN. Furthermore, these reductions appear to be additive to the effects of nonselective beta blockers. With numerous animal studies identifying other pleiotropic effects of statins, there may be additional mechanisms by which statins mitigate liver-related outcomes that are as-yet unexplored in RCTs.

Many unanswered questions remain prompting a call for future studies in this area. Most notably, key cirrhosis-related outcomes such as decompensation and mortality have not been the focus of prior RCTs. Based on a review of ClinicalTrials.gov, there are several forthcoming studies that will expand knowledge on the impact of statins and liver-related outcomes. One RCT trial will use direct measures of HVPG to determine the effects of combining a beta blocker with rosuvastatin in preventing variceal bleeding.[43] There are several other RCTs evaluating statin use in the context of cirrhosis progression, rate of hospitalization, rate of hepatic decompensation, and mortality.[44–46] Finally, one large national RCT (target sample size 500) will identify patients with cirrhosis at high risk of incident decompensation and will evaluate the impact of simvastatin on reducing hepatic decompensation and death.[45]

Statin Effects on Risk of Infection

While studies examining the association between statin use and risk of infections in patients with cirrhosis are limited, reported findings in other chronic diseases such as diabetes and vascular diseases are promising.[47] One of the few studies in cirrhosis is the retrospective cohort study by Motzkus-Feagans *et al.*; using a large cohort of veteran patients with cirrhosis (n = 19,379), the authors found that statin-exposed patients had a significant lower rate of hospitalizations for infection (rate of 0.67 less than statin nonusers).[48] There is some conflicting evidence in the cohort study by Mahmud *et al.* that similarly used a veteran population and found that patients using statins who developed ACLF were more likely to have an infection as an inciting event.[29] However, the primary results of that paper did demonstrate a reduction in developing ACLF with statin exposure, and those who did develop ACLF with statin exposure had lower rates of mortality compared to nonusers with ACLF.[29] Thus, one could argue that statins may modulate infection-related mortality, which has been previously supported in studies on sepsis,[47,49] albeit controversial.[50] Animal studies demonstrating the anti-inflammatory effects of statins in the liver are particularly interesting in this context, as mitigation of inflammation in the setting of infection may limit progression to multi-organ dysfunction and higher-grade ACLF.

Statin Effects on Hepatocellular Carcinoma

Prior studies have demonstrated myriad chemoprotective effects that may prevent development and growth of cancer, and thus, it is plausible that statin exposure could reduce the development of incident HCC in at-risk populations. While not completely understood, there are several proposed molecular mechanisms for the chemoprotective effects of statins against HCC that have emerged from in vitro and animal studies. Some are based on specific features of HCC cell lines, while others involve modulation of molecular pathways. For example, HCC cells have karyotype abnormalities in which statins selectively inhibit key cellular functions.[51] HCC cells are also dependent on cholesterol-rich membrane structures for cell stability and proliferation, which are disrupted by statins.[51] More generally, statins are thought to reduce tumor cell growth by promoting cell cycle arrest via disruption of the KRAS pathway and prevention of p21 and 27 signaling.[52] Statins also affect mitogen-active protein kinase pathways like Rho-kinase and integrins that are expressed on cell membranes, resulting in decreased tumor cell adhesion and ultimately inhibition of tumor growth and metastasis.[51,53–55] In translating results from in vitro studies to humans, there have been some promising results for statins.

In a meta-analysis by Singh *et al.*, statin users were less likely to develop HCC as compared to statin nonusers (adjusted odds ratio [OR] 0.63)[56] although included studies were not exclusively focused on patients with cirrhosis. One cohort study of veterans with treated HCV but without cirrhosis investigated three outcomes that included progression of liver fibrosis, development of cirrhosis, and incident HCC.[57] In adjusted models, the authors found that statins were associated with decreased fibrosis progression, reduced development of cirrhosis (OR 0.60), and a 49% reduction in the incidence of HCC.[57] Importantly, subsequent analysis suggested that the antineoplastic/chemoprotective effect of statins was independent of its anti-fibrotic effects.[57] Similar results demonstrating a chemoprotective effect of statins has been observed in several other cohort studies in patients in cirrhosis.[30,31] Nonetheless, given the limitations of observational studies, there are currently two forthcoming RCTs evaluating the effect of statin use on preventing HCC in high-risk cirrhosis populations.[58,59]

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Safety Profile of Statins in Cirrhosis

Potential statin hepatotoxicity is a frequent concern that has limited their use in patients with liver disease. Although asymptomatic, transient elevations in transaminases are commonly observed in new statin initiators, the rate of developing significant hepatotoxicity is rare, on the order of fewer than 2 cases per 1,000,000 patient-years.[15,60] Thus, patients with underlying liver disease (excluding those with decompensated cirrhosis) can safely be prescribed a statin with no concern for increased risk of hepatotoxicity compared to the general population.[5]

One statin-related side effect of particular concern is muscle toxicity, which can occur in its most severe form as rhabdomyolysis. Studies have suggested that patients with more advanced decompensated cirrhosis (CTP class B or C) are at increased risk of developing adverse events.[10] There are multiple theories thought to explain this association in advanced liver disease, including decreased activity of CYP3A4 which reduces statin metabolism, impaired expression of MRP2 that inhibits transport of statin to bile, and reduced expression of SLCO1B, which is an anion transporter responsible for hepatic uptake and metabolism of statins.[42,61] In the most recent Abraldes *et al.* RCT, 3% of included patients with more advanced decompensated cirrhosis (bilirubin >5; 2 of 69 patients) developed rhabdomyolysis while taking simvastatin 40 mg, whereas the rate of rhabdomyolysis in the general population is 0.1%.[15,42] None of the other six RCTs detailed above observed serious adverse events related to statins; however, these studies all excluded patients with bilirubin >5, had small sample sizes, and generally shorter duration of follow-up.[21,22,38–40] Another RCT conducted by Pose *et al.* showed a dose-dependent association between statin use plus rifaximin and muscle toxicity in patients with decompensated cirrhosis (CTP class B and C, excluding patients with bilirubin >5).[61] While no muscle toxicity occurred with simvastatin 20 mg plus rifaximin, 19% of patients (3 of 16 patients; 1 CTP B and 2 CTP C) taking simvastatin 40 mg plus rifaximin developed rhabdomyolysis.[61] While it is difficult to interpret this study in context given that rifaximin was added to the regimen, it does support dose-dependent adverse effects in statin use.

At present, there are no robust data to clearly recommend one statin formulation over another, nor specific dosing in the cirrhosis population. A majority of RCT studies involving patients with cirrhosis that have included secondary outcomes of adverse effects have used simvastatin 40 mg. Outside of the abovementioned Abraldes *et al.* study,[42] other studies did not see higher rates of adverse effects when excluding advanced cirrhosis. Until additional studies are conducted, we recommend the use of the lowest-effective dose of a statin to achieve targeted cardiovascular goals in patients with cirrhosis and the abrupt discontinuation of the statin with severe adverse effects.

Preliminary studies are investigating exciting ways of implementing statin targeted-drug therapy, which may optimize statin-related effects while limiting systemic adverse effects. The main principles behind novel statin formulations are centered on the fact that the oral bioavailability of statins in their current formulation are fairly low due to first-pass hepatic metabolism and reduced gut absorption. While there have been many investigative drug delivery systems ranging from periodontal gels and nanobeads to statin-loaded microspheres and parenteral formulations, nanoemulsifying and nanoparticle statin delivery systems have shown promising results for targeted delivery in experimental studies, mainly cardiovascular-focused.[62–66] While a better understanding of long-term adverse effects or therein mitigation of typical statin adverse effects with these novel technologies is needed, this is a promising step that may ultimately lead to better statin tolerance and more widespread use.

While additional studies are needed to assess the risk factors for adverse events and optimal dosing and statin type from a safety profile in patients with cirrhosis, the current data suggest that patients with CTP class B or C cirrhosis may be at increased risk of muscle toxicity and rhabdomyolysis, especially with higher dose statin exposure. Thus, statins should be used with a high-degree of caution in this vulnerable population as the risks may outweigh benefits.

In summary, the benefit of statins may extend beyond mitigation of cardiovascular disease in patients with CLD and cirrhosis. Observational studies have demonstrated associations between statins in reductions in cirrhosis decompensation, incident HCC, development of infections requiring hospitalization, and lower mortality. While these outcomes have infrequently been the focus of published RCTs, the clinical trials to date have consistently shown that statin exposure reduces portal pressures in patients with cirrhosis. Statins have been shown to be safe in patients with CLD and compensated cirrhosis. However, based on currently available evidence, they should be used with caution in patients with decompensated cirrhosis due to increased risk of rhabdomyolysis, especially with higher statin doses.

While we do not currently recommend prescribing statins to patient with cirrhosis outside of established cardiovascular indications, the potential role of statins in patients with CLD continues to evolve and may be clarified with forthcoming research. Future RCTs are needed to investigate patient-important outcomes of decompensation, incident HCC, and mortality, including delineation of liver-related and non-liver-related mortality. Studies should also seek to evaluate the impact of different statin formulations, doses, durations, and patient subsets that

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may experience variable tiers or benefit or harm. Finally, larger studies to better elucidate the safety profile of statins in the context of advanced liver disease will be important for prescribers and communication of risk to patients.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Both LRS and NM contributed to the intellectual genesis, drafting, and critical review of this manuscript.

CONFLICTS OF INTEREST

The authors have none to declare.

FUNDING

Nadim Mahmud is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (K08-DK124577) and has received support from Grifols unrelated to the topic of this manuscript.

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