

# The Safety and Benefit of Statins in Liver Cirrhosis: a Review

## Authors

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## Abstract

Dyslipidemia is a primary, major risk factor for coronary artery disease CAD. The prevalence of dyslipidemia had decreased over the past 30 years, which may in part be explained by the steady increase in the use of lipid-lowering drug therapy, especially statins. Cardiovascular risk has been shown to be greater in liver disease (20% in the liver cirrhosis vs. 12% in the general population), where statins can play an important role as a primary and secondary prevention for CAD. Given patients with chronic liver disease,

especially liver cirrhosis are at risk of decreased hepatic clearance, there is concern that this patient population may be at higher risk for complications from statin therapy. Several retrospective studies showed that statin use in chronic liver disease and cirrhosis is safe, and even it was associated with lower mortality and lower rate of hepatic decompensation. This review discusses the safety and the different mechanisms where statins can decrease the rate of complications in liver cirrhosis, including portal hypertension, sepsis and the incidence of hepatocellular carcinoma.

## Introduction

Each year, an estimated 785 000 Americans will have a new coronary artery disease (CAD) event, and approximately 470 000 will have a recurrent attack. CAD caused approximately 1 of every 6 deaths in the United States in 2007 [1]. Dyslipidemia is a primary, major risk factor for CAD and may even be a prerequisite for CAD, occurring before other major risk factors come into play. An estimated 33 600 000 adults 20 years or older have total serum cholesterol levels of 240 mg/dL or greater, for a prevalence of 15% of the American population [2]. Analysis of 30 years national trends in serum lipid levels shows improvement in total cholesterol and LDL-C levels, which may in part be explained by the steady increase in the use of lipid-lowering drug therapy. However, 69% of US adults have LDL-C concentrations above 100 mg/dL [3]. Cirrhosis and other chronic liver diseases are also common disease-related causes of death. The exact prevalence of cirrhosis worldwide is unknown. In the United States approximately 32 000 people die each year from cirrhosis as was estimated in the year 2011 [4]. Liver cirrhosis was also found to be responsible for

around 170 000 deaths in Europe annually with very wide variations between different countries, ranging from around one per 100 000 for Greek women to 103 per 100 000 Hungarian men [5]. Cardiovascular risk has been shown to be greater in liver disease, specifically non-alcoholic fatty liver disease, hepatitis C infection and primary biliary cirrhosis [6]. A recent study also determined the prevalence of coronary artery disease in patients with cirrhosis to be 20%, compared to 12% in the general population [7]. To reduce cardiovascular risk, lipid-lowering agents such as statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are standard therapy for the general population. Statins undergo first-pass hepatic metabolism, generally through the cytochrome P450 system, and have been associated with elevations in liver enzymes [8]. Given patients with chronic liver disease, especially liver cirrhosis are at risk of decreased hepatic clearance, there is concern that this patient population may be at higher risk for complications from statin therapy [9].

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## Statins Induced Hepatotoxicity

Statins have a major role in reducing LDL cholesterol, mainly via its potent inhibition of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase. Because of their powerful effects on this liver enzyme, multiple medical trials have been performed to assess their safety [10]. Statin treatment has been associated with a broad spectrum of hepatic adverse effects. The most common is an asymptomatic and a transient elevation of serum aminotransferase levels that often occurs within the first 12 weeks of therapy. Most of the time, this disturbance is not correlated with histopathological changes and therefore does not meet the criteria of a true liver injury [11, 12]. Although the underlying mechanism remains unclear, it may result from changes in the lipid components of the hepatocyte membrane, leading to an increase in its permeability with a subsequent "leakage" of liver enzymes [13, 14]. In very rare cases in which true statin related hepatotoxicity has been demonstrated, no specific biochemical or histologic pattern of liver injury has been established. It can involve hepatocellular, cholestatic, or even mixed histologic patterns, and the proposed mechanism is either an idiosyncratic or an immunoallergic reaction [12, 13]. So in most of the cases, statins are associated with a transient increase in liver enzymes, and not a true liver injury.

## Safety of Statins in Cirrhosis

Statins undergo first-pass hepatic metabolism, generally through the cytochrome P450 system, and have been associated with elevations in liver enzymes. Given patients with chronic liver disease are at risk of decreased hepatic clearance, there is concern that this patient population may be at higher risk for complications from statin therapy [15]. In particular, there has been concern that statins may trigger hepatic decompensation in patients with a known diagnosis of cirrhosis resulting in significant morbidity and mortality. Several studies have shown that statins are generally well tolerated in patients with chronic liver disease such as non-alcoholic fatty liver disease NAFLD, primary biliary cirrhosis and hepatitis C [16, 17]. Multiple retrospective and prospective studies have shown that statin use is particularly beneficial in NAFLD and steatohepatitis, where it acts as an immunomodulatory and antioxidative agent. Actually it does not only decrease transaminases, but also ameliorate steatosis, and even reverse early phases of fibrosis [18].

One retrospective cohort study was done on 93,106 patients with laboratory or clinical evidence of liver disease, where they studied the safety of lovastatin. The primary outcome was a pattern of liver-test abnormalities, secondary outcomes included liver injury (defined as moderate or severe, depending on the degree of ALT level elevations) or the development of either clinical cirrhosis or liver failure. Lovastatin exposure was associated with a lower incidence of all endpoints, including the primary outcome (IRR=0.28, 95% CI 0.12, 0.55), moderate liver injury (IRR=0.56, 95% CI 0.47, 0.65), severe liver injury (IRR=0.50, 95% CI 0.29, 0.81) and the occurrence of either cirrhosis or liver failure (IRR=0.29, 95% CI 0.21, 0.38). In conclusion, in this retrospective analysis, exposure to lovastatin was not associated with an increased risk of adverse hepatic outcomes [19]. Another retrospective cohort study evaluated 81 patients with liver cirrhosis proven on biopsy from 1988 to 2011, who were on statins more than 3 months, and they were compared to a matched

group (162) with no statin use. They included all the stages of liver cirrhosis. The primary end point was mortality, and secondary outcome was decompensation in baseline-compensated patients. Decompensation was defined as ascites, jaundice/bilirubin >2.5 mg/dL, and/or hepatic encephalopathy or variceal hemorrhage. Median follow-up: 36 months in statin users and 30 months in controls. Simvastatin was the most commonly used statin (49.4%) followed by atorvastatin (29.6%). A total of 70.4% of patients were Child-Pugh A. The multivariate analysis showed that statin users had lower mortality rate (HR: 0.53,  $p=0.01$ ). Subgroup analysis showed that Child-Pugh A patients with cirrhosis at baseline who had received statins had longer survival compared to the control group,  $p=0.005$  (7 vs. 14.4 years). The same result was seen regarding the rate of decompensation (30% in statin users vs. 45% in non users, HR: 0.58,  $p=0.04$ ). But when looking into each specific event, they found that statin use was only protective against the occurrence of ascites [statin 16% vs. no statin 31%,  $p=0.017$ ]. Variceal hemorrhage was significantly less likely to occur in patients not on statins [statin 11% vs. no statin 2%,  $p=0.02$ ]. And there was no statistically significant difference in the development of jaundice [statin 3% vs. no statin 9%] or hepatic encephalopathy [statin 19% vs. no statin 20%] between the statin group and the control group. The contradictory finding between the mortality and the outcomes maybe due to the heterogeneity of the sample, and the non assessment of other predictors of decompensation like NSAIDs, alcohol, tobacco and obesity [20].

These retrospective studies suggest that the use of statins is safe in compensated liver cirrhosis, but we need more prospective studies to prove its benefit in reducing mortality and morbidity.

## a. Benefit of Statins in Liver Cirrhosis: Portal Hypertension

Portal hypertension is an almost unavoidable consequence of advanced liver disease and is directly or indirectly responsible for major clinical complications such as bleeding from ruptured esophageal varices, a leading cause of death in patients with cirrhosis. Increased hepatic resistance is the first pathophysiological phenomenon that causes portal hypertension in cirrhosis. Although traditionally considered a mechanical consequence of the disruption of the liver vascular architecture caused by the cirrhotic process, an increased hepatic vascular tone significantly contributes to increased hepatic resistance and portal pressure in cirrhosis [21]. Studies in experimental models of cirrhosis suggest that endothelial nitric oxide release is impaired in liver microvasculature [22] and that this may be a major factor that contributes to increased hepatic resistance in cirrhosis. And this phenomenon is aggravated postprandial where insufficient NO leads to more vasculature resistance and more increase in the portal hypertension. Statins have pleiotropic effects: they decrease oxidative stress and inflammation at the vessel wall, have antithrombotic properties, and improve endothelial function, increasing NO production in endothelial cells [23, 24]. This last effect seems to be mediated through the phosphatidylinositol 3-kinase-dependent activation of protein kinase Akt, leading to NOS phosphorylation at Ser 1177, with subsequent increased activity [25]. This hypothesis was shown in an experimental study done on 17 patients with compensated liver cirrhosis and portal hypertension, who were randomized to receive simvastatin 40 mg vs. placebo, and they found that those who received

simvastatin had higher levels of hepatic vein NO and lesser hepatic resistance [26]. And the same result was seen in a randomized control trial done by Abraldes et al., where 59 patients with cirrhosis and portal hypertension (HVPG > 12 mm Hg) were randomized to groups that were given simvastatin 20 mg/day for 1 month (increased to 40 mg/day at day 15) or placebo in a double-blind clinical trial. Simvastatin significantly decreased HVPG (8.3%) without deleterious effects in systemic hemodynamics, and had a beneficial effect on improving liver perfusion and function. These effects were additive with those of  $\beta$ -adrenergic blockers [27].

Statins decrease portal hypertension in liver cirrhosis, mainly through NO, but this effect should be studied in larger prospective trials.

### b. Benefit of Statins in Liver Cirrhosis: Sepsis

Over 27,000 deaths from cirrhosis and its complications occur annually [28]. In patients with cirrhosis, infections increase mortality and drive costs of care higher [29]. The mortality from infection in cirrhotic patients is not only due to its direct effect, but also due to the decompensation leading to more encephalopathy and kidney injuries. The use of statins, has recently emerged as a protective factor for infections. While the biological mechanism explaining these findings remains unknown, the anti-inflammatory and immunomodulatory properties of statins are thought to be involved, and in the immune system, statins may increase the ability of phagocytes to create extracellular traps [30]. And this benefit was seen in a retrospective cohort study done between 2001 and 2009, where they included 19,379 patients with compensated liver cirrhosis. They compared the rate of different type of infection between patients on statin (90.6% using simvastatin) vs. placebo. Compared with non-users, the rate of infection, mainly peritonitis/SBP and pneumonia, or death was significantly lower among statin users (HR: 0.67: 0.47–0.95) [31].

Statins decrease the risk of sepsis in liver cirrhosis, but more prospective studies are needed to prove this benefit.

### c. Benefit of Statins in Liver Cirrhosis: Hepatocellular Carcinoma

Hepatocellular cancer (HCC) is the fifth most common cancer worldwide in men and the second most frequent cause of cancer death, with an annual incidence of 0.5 million worldwide [32]. Cohort studies indicate that HCC is currently the major cause of liver-related death in patients with compensated cirrhosis. Hepatitis C virus (HCV) infection is associated with the highest HCC incidence in persons with cirrhosis, occurring twice as commonly in Japan than in the West (5-year cumulative incidence, 30% and 17%, respectively), followed by hereditary hemochromatosis (5-year cumulative incidence, 21%). In hepatitis B virus (HBV)-related cirrhosis, the 5-year cumulative HCC risk is 15% in high endemic areas and 10% in the West. In the absence of HCV and HBV infection, the HCC incidence is lower in alcoholic cirrhotics (5-year cumulative risk, 8%) and subjects with advanced biliary cirrhosis (5-year cumulative risk 4%) [33]. In vitro and animal studies have shown that in addition to cholesterol reduction, statins have antiproliferative, pro-apoptotic, anti-angiogenic, immunomodulatory, and anti-infective effects, which

prevent cancer growth [34]. Statins exert pro-apoptotic effects through regulation of the RAF/mitogen-activated protein kinase 1/extracellular signal-regulated kinase (MEK-ERK) pathway through an HMG-CoA reductase-dependent mechanism by activating caspases and decreasing Bcl-2 [35]. Statins inhibit the activation of the proteasome pathway, limiting the breakdown of cyclin dependent kinase inhibitors p21 and p27, thus allowing these molecules to exert their growth-inhibitory effects [35]. It is hypothesized that lipophilic statins (e.g., lovastatin, simvastatin) may have a greater chemoprotective effect than lipophobic statins (e.g., pravastatin) due to greater lipid solubility and membrane permeability [36].

Several observational studies suggest that statins may decrease the risk of HCC in patients with other underlying liver diseases. A recent meta-analysis published in 2013, evaluated 4298 cases of HCC in 1459417 patients [37]. The authors included both observational (n:7) and randomized trials (n:3), and found a 41% overall reduction in HCC risk with the use of statins. This was driven entirely by the observational studies (adjusted odds ratio [OR]: 0.6), with no benefit seen in the randomized trials (adjusted OR: 0.95) [37]. Interestingly, the reduction in risk was found to be higher in Asian populations in the observational trials compared to western populations, potentially attributable to interactions between statins and HBV. Observational studies of statin use in patients with underlying liver disease are subject to several types of biases. Most importantly is the study design and the heterogeneity within the groups. Most of the studies did not adjust for important variables including HCV, HBV, liver cirrhosis and diabetes mellitus, and the use of other potential medications that may also lower HCC risk, such as metformin [37]. These recent analyses of large cohorts suggest that statins may reduce the risk of hepatocellular carcinoma (HCC). But due to their observational nature, these studies may have been flawed by confounding by indication or immortal time bias.

### Conclusion

In conclusion, statin use is safe in patients with compensated liver cirrhosis [38]. It is beneficial in decreasing portal hypertension by increasing the nitric oxide level. Statins decrease the rate of infection and decompensation (mainly ascites). And patients with liver cirrhosis on statins may have lesser prevalence of hepatocellular carcinoma. But to note that most of these conclusions are based on small retrospective studies, and future randomized controlled trials are warranted to prove this benefit.

**Conflict of interest:** None.

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