Statin Use and Risk of Cirrhosis and Related Complications in Patients with Chronic Liver Diseases: a Systematic Review and Meta-analysis

Rebecca G. Kim, MD, MS[1], **Rohit Loomba, MD, MHSc**[2,3,4], **Larry J. Prokop, MLS**[5], and **Siddharth Singh, MD, MS**[2,6]

[1]Division of Internal Medicine, Department of Medicine, University of California at San Diego, La Jolla, California

[2]Division of Gastroenterology, Department of Medicine, University of California at San Diego, La Jolla, CA

[3]NAFLD Research Center, Department of Medicine, University of California at San Diego, La Jolla, CA

[4]Division of Epidemiology, Department of Family Medicine and Public Health, University of California at San Diego, La Jolla, CA

[5]Department of Library Services, Mayo Clinic, Rochester, MN

[6]Division of Biomedical Informatics, Department of Medicine, University of California at San Diego, La Jolla, CA

Abstract

Background & Aims—Statins have been variably shown to decrease risk and complications of chronic liver diseases (CLDs). We performed a systematic review and meta-analysis to evaluate the association between statins and risk of cirrhosis and related complications in patients with CLDs.

Methods—Through a systematic literature search up to March 2017, we identified 13 studies (3 randomized trials, 10 cohort studies) in adults with CLDs, reporting the association between statin

Please address correspondence to: Siddharth Singh, M.D., M.S., Assistant Professor of Medicine, Division of Gastroenterology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, sis040@ucsd.edu, Phone: 858-657-5271, Fax: 858-657-7259.

use and risk of development of cirrhosis, decompensated cirrhosis, improvements in portal hypertension, or mortality. Pooled relative risk (RR) estimates with 95% CIs were calculated using random effects model. GRADE criteria were used to assess quality of evidence.

Results—Among 121,058 patients with CLDs (84.5% with hepatitis C), 46% were exposed to statins. In patients with cirrhosis, statin use was associated with 46% lower risk of hepatic decompensation (4 studies; RR, 0.54; 95% CI, 0.46–0.62; I_2=0%; moderate quality evidence), and 46% lower mortality (5 studies; RR, 0.54; 95% CI, 0.47–0.61; I_2=10%; moderate quality evidence). In patients with CLD without cirrhosis, statin use was associated with a non-significant (58% lower) risk of development of cirrhosis or fibrosis progression (5 studies; RR, 0.42; 95% CI, 0.16–1.11; I_2=99%; very low quality evidence). In 3 randomized controlled trials, statin use was associated with 27% lower risk of variceal bleeding or progression of portal hypertension (hazard ratio, 0.73; 95% CI, 0.59–0.91; I_2=0%; moderate quality evidence).

Conclusion—Based on a systematic review and meta-analysis, statin use is probably associated with lower risk of hepatic decompensation and mortality, and might reduce portal hypertension, in patients with CLDs. Prospective observational studies and randomized controlled trials are needed to confirm this observation.

INTRODUCTION

Chronic liver diseases (CLDs) are a significant cause of morbidity and mortality worldwide. According to the Centers for Disease Control, in 2013, CLDs and cirrhosis were among the top 15 causes of death in the United States, and the mortality rate continues to increase each year leading to over 35,000 deaths in 2013[1]. Currently, there are no medications to prevent or reverse hepatic decompensation, though treatment of underlying etiology may slow progression of fibrosis.

Statins are one class of medications being studied to determine their effect on progression and decompensation of CLDs. Statins are lipid-lowering agents, which act by inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, leading to inhibition of cholesterogenesis and decreased serum cholesterol levels[2–10]. Besides their lipid-lowering effects, statins also decrease oxidative stress and inflammation by decreasing activation of inflammatory cells[11–14], and improve endothelial function by increasing synthesis of nitric oxide, restoring the function of endothelial cells, and increasing the number of endothelial progenitor cells[15–23]. *In vitro* and preclinical studies have also suggested a favorable impact of statins on hepatic inflammation, fibrosis, and hepatic vascular tone[24–29]. Epidemiological studies have observed a protective association between statin use and hepatocellular cancer[30–32]. Recent studies have also suggested an association between statin use and risk of fibrosis progression and hepatic decompensation in patients with CLDs, although the effects have been variable[33–43].

Hence, to better understand the association between statin use and outcomes in patients with CLDs, we performed a systematic review with meta-analysis of randomized controlled trials (RCTs) and cohort studies to evaluate the association between statin exposure and (a) risk of fibrosis progression and development of cirrhosis (in patients with non-cirrhotic CLDs), (b) risk of hepatic decompensation and mortality (in all patients with cirrhotic or non-cirrhotic CLDs), and (c) risk of progression of portal hypertension (in patients with cirrhosis). We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria to appraise quality of evidence.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[44], using an *a priori* established protocol.

Selection Criteria

We included RCTs or cohort studies that met the following inclusion criteria: (1) conducted in adults with CLDs due to any cause, and reported baseline degree of CLDs – fibrosis without cirrhosis, compensated cirrhosis, or decompensated cirrhosis, (2) evaluated and clearly defined exposure to statins, (3) reported association between statin exposure and cirrhosis-related outcomes in patients, (4) with an acceptable measure of association such as hazard ratios (HRs), relative risk (RR) or odds ratios (ORs), or provided data for their calculations. Inclusion was not restricted by study size, language, or publication type. We excluded: (a) case-control studies (high risk of recall bias) and cross-sectional studies (confounding by disease severity, and unable to infer exposure-outcome association), (b) studies focusing only on association between statin use and risk of HCC and (c) studies which provided insufficient information to calculate measure of association. When the same population was used in multiple publications, only data from the most recent all-inclusive report were included.

Search Strategy

To identify all relevant articles on the effect of statins in CLD, we first conducted a systematic literature search of MEDLINE (1946 through August 8, 2016), Embase (1988 through August 8, 2016), Cochrane Central Register of Controlled Trials (1991 through July, 2016), Cochrane Database and Systematic Reviews (2005 through August 3, 2016), Scopus (1823 through August 8, 2016), and Web of Science (1975 through August 8, 2016) databases, with no language restrictions; after peer review, an updated literature search of PubMed was performed on March 25, 2017 to identify any additional studies. The search strategy was designed and implemented by an experienced medical librarian with input from the study's investigators, using controlled vocabulary supplemented with keywords, for studies on statin use in CLDs. The details of the search strategy are reported in the Supplementary Appendix. Two reviewers (RGK, SS) independently assessed the title and abstract of studies identified in the primary search for inclusion, and the full text of remaining articles were examined to determine whether they met inclusion criteria. In addition, conference abstracts from major gastroenterology and hepatology conferences (American Association for the Study of Liver Diseases, European Association for the Study

of the Liver, and Digestive Disease Week) from 2012–2016, as well as bibliography of the selected articles and review articles on the topic were manually searched for additional studies.

Data Abstraction

Two reviewers (RGK, SS) independently abstracted data onto a standardized form. Data collected from each study included the following: time period of study/year of publication, country of the population studied, study design, inclusion and exclusion criteria, type of medication, dose and duration of statin use (if reported), primary outcome reported, secondary outcomes, information source for exposure measurement, total number of participants in each group (statin exposure vs no exposure), HRs, RRs or ORs, and 95% confidence intervals (CI) with and without adjustment for confounding factors. We extracted data on the following confounding risk factors for progression of fibrosis and/or decompensation of cirrhosis: age, sex, etiology of chronic liver disease, Child-Pugh score, diabetes mellitus, coronary artery disease, alcoholic liver disease/alcohol use, LDL, use of ACE-Is and aspirin, and use of nonstatin lipid-lowering medications.

Risk of bias was assessed using the Cochrane risk of bias tool for RCTs[45], and using the Newcastle Ottawa Scale for cohort studies[46].

Outcomes Assessed

Our primary outcomes of interest were the association between statin use and (a) risk of fibrosis progression and/or development of cirrhosis (in patients with baseline non-cirrhotic CLDs), (b) risk of developing decompensated cirrhosis (in patients with baseline compensated cirrhosis), (c) all-cause mortality (in all patients with CLDs) and (d) progression of portal hypertension (variceal bleeding) (in patients with cirrhosis with established portal hypertension). RCTs and observational studies were analyzed separately. Subgroup analyses based on underlying etiology of CLDs were performed for outcomes if there were   2 studies for each subgroup.

Statistical Analysis

We used the random-effects model described by DerSimonian and Laird to calculate pooled RR and 95% CI[47]. Adjusted RR reported in studies was used for analysis to account for confounding variables. We assessed heterogeneity using the I^2 statistic; values of <30%, 30%–59%, 60%–75%, and >75% were classified as low, moderate, substantial, and considerable heterogeneity, respectively[48]. Due to paucity of number of studies, a formal assessment of publication bias using funnel plots was not performed. All p-values were two-tailed, and a probability level <0.05 was considered statistically significant.

Quality of Evidence

We utilized the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to evaluate the quality of the evidence (or confidence in effect estimates)[49]. In determining quality of evidence, the following factors were considered: risk of bias in the body of the evidence, imprecision, indirectness (addressing a different population, intervention, or outcome, from the one under consideration), inconsistency of

findings, publication bias, magnitude of effect, dose-response relationship and other biases. The GRADE approach accounts for the inherent limitations in observational studies (selection bias, unmeasured confounding, etc.) by starting at low quality, and then potentially upgrading or downgrading based on the aforementioned factors.

RESULTS

Search Results

Of the 1706 unique studies identified using our search criteria, 13 studies met our inclusion criteria and were included in our meta-analysis (3 RCTs and 10 observational studies)[33–43, 50, 51] Six studies included participants with non-cirrhotic CLDs[35, 39–43], six studies included participants with compensated cirrhosis[36, 37, 42, 43, 50, 51], and three studies included individuals with decompensated cirrhosis[33, 34, 38]. One study was excluded as it represented a population already included in another, more recent study;[52] one small RCT of statins in NASH was excluded due to insufficient information[53]. Figure 1 shows the flow diagram summarizing study identification and selection.

Characteristics of Included Studies

The characteristics of these studies are shown in Table 1. Overall, these studies included 121,058 patients with CLDs, of whom 46% were exposed to statins. Four cohort studies were conducted in patients with HCV mono-infection, and one was conducted in patients with HIV-HCV co-infection; two studies were conducted exclusively in patients with HBV. One study was conducted exclusively in patients with alcoholic liver disease, and one study reported outcomes stratified in patients with HBV, HCV and alcoholic liver disease. Four observational studies were conducted in Asia, and five were conducted in the United States; among the five conducted in the US, three were conducted in the veteran population. The three included RCTs were conducted primarily to evaluate the efficacy of statins in patients with portal hypertension.

Patient-level characteristics are summarized in eTable 1. Patients exposed to statins were generally more likely to have associated diabetes, metabolic syndrome, and be exposed to metformin, aspirin and angiotensin-converting enzyme inhibitors, as compared to patients non-exposed to statins. Propensity-score matching was performed in 6 cohorts, and matched cohorts were comparable with regard to metabolic syndrome and exposure to concomitant therapies.

The median Newcastle-Ottawa quality score for the observational studies was 8 (range, 8–9); 8 of 8 studies were considered high quality. eTable 2 shows the methodological quality of observational studies, and eFigure 1 shows the methodological quality of RCTs.

Risk of Development of Cirrhosis or Progression of Fibrosis

Five studies reported risk of development of cirrhosis (or progression of fibrosis) in patients with baseline non-cirrhotic CLDs[35, 39–41, 43]. In three studies, diagnosis of cirrhosis (or fibrosis progression) was ascertained based on a combination of administrative claims codes and calculated serum fibrosis markers (FIB-4 or APRI); one study was a post-hoc analysis of

the HALT-C trial included patients with paired liver biopsies, with fibrosis progression defined based on increase in Ishak fibrosis stage by ≥2. One Taiwanese study in patients with HBV relied exclusively on administrative claims codes. Overall, on random-effects meta-analysis, risk of development of cirrhosis (or progression of fibrosis) was 58% lower in patients exposed to statins, as compared to non-exposed patients (RR, 0.42; 95% CI, 0.16–1.11), with considerable heterogeneity (I^2=99%) (Figure 2). On exclusion of one study, which relied exclusively on administrative claims codes with very large protective effect size, a 35% lower risk of development of cirrhosis (or progression of fibrosis) in statin-exposed patients was a more conservative estimate (RR, 0.65; 95% CI, 0.48–0.87), with considerable heterogeneity (I^2=89%). Three studies specifically reported the outcome of fibrosis progression (based on either paired liver biopsies or serum fibrosis markers)[39, 40, 43]. On meta-analysis of these studies, statin exposure was associated with a 27% lower risk of fibrosis progression (RR, 0.73; 95% CI, 0.54–1.00, p=0.049).

Overall confidence in these estimates was very low, primarily because of the observational nature of these studies with inherent biases due to absence of randomization, and imprecision due to wide CIs.

Risk of Decompensation of Cirrhosis

Four studies reported on risk of progression to decompensated cirrhosis, in patients baseline compensated cirrhosis[36, 37, 50] or non-cirrhotic CLDs[35]. Three studies relied on validated administrative claims codes for development of decompensated cirrhosis, and one used individual medical record review. On meta-analysis, statin use was associated with a 46% lower risk of progression to decompensated cirrhosis (RR 0.54; 95% CI, 0.46–0.62), with minimal heterogeneity (I^2=0%) (Figure 3). On restricting analysis only to patients with baseline compensated cirrhosis (excluding patients with non-cirrhotic CLDs), a similar protective association of between statin use and risk of hepatic decompensation was observed (RR, 0.54; 95% CI, 0.44–0.66). On subgroup analyses by etiology of underlying CLD, no considerable differences were observed in patients with CLD due to HBV, HCV, alcoholic liver disease or mixed etiology (Table 2).

Overall confidence in these estimates was moderate, primarily because of the observational nature of these studies with inherent biases due to absence of randomization; due to large effect size, evidence was rated up.

Risk of Mortality

Six studies reported on risk of mortality in patients with CLDs (five studies in patients with cirrhosis, one study in patients with non-cirrhotic CLDs)[34, 36, 37, 42, 50, 51]. Five studies were observational studies, and one was an RCT primarily focusing on addition of simvastatin or placebo to standard of care in patients with decompensated cirrhosis with prior variceal bleeding. On meta-analysis, statin use was associated with a 39% lower risk of mortality (RR 0.61; 95% CI, 0.48–0.78), with considerable heterogeneity (I^2=77%) (Figure 4). On restricting analysis only to patients with baseline cirrhosis (excluding patients with non-cirrhotic CLDs),[42] a similar protective association was observed (RR, 0.54; 95% CI, 0.47–0.61), with minimal heterogeneity (I^2=10%). On subgroup analyses by etiology of

underlying CLD, no considerable differences were observed in patients with CLD due to HBV, HCV, alcoholic liver disease or mixed etiology (Table 2).

When focusing on use of statins only in patients with baseline cirrhosis, overall confidence in estimates was moderate, primarily because of the observational nature of these studies with inherent biases due to absence of randomization, and large effect size; in evaluating all patients with CLDs, evidence was rated as low quality due to serious inconsistency.

Improvement in Portal Hypertension

Four studies reported on risk of re-bleeding or clinically significant improvement in portal hypertension in patients with baseline cirrhosis.[33, 34, 37, 38] On meta-analysis of 3 RCTs, statin use was associated with a 27% lower risk of re-bleeding (or failure to improve portal hypertension) (RR 0.73; 95% CI, 0.59–0.91), with minimal heterogeneity (I^2=0%) (Figure 5). In the single observational study in patients with compensated HCV-related cirrhosis, statin use was associated with a 61% lower risk of portal hypertension-related bleeding (RR, 0.39; 95% CI, 0.19–0.79).

Based on RCTs, there was moderate confidence in estimates supporting the use of statins for decreasing risk of variceal bleeding in patients with established portal hypertension. Evidence was rated down for imprecision due to small number of events (110 events in 236 patients), and short duration trials.

DISCUSSION

In this systematic review and meta-analysis of 13 studies on the association between statins and risk of clinically relevant outcomes in 121,058 patients with CLDs, we made several key observations. First, moderate quality evidence supports the use of statins for decreasing the risk of hepatic decompensation by 46% especially in patients with baseline compensated cirrhosis, though there is very low confidence in estimates supporting the use of statins to decrease risk of fibrosis progression or development of cirrhosis in patients with non-cirrhotic CLDs. Second, low quality evidence suggests that statins may lower mortality risk by 39% in all patients with CLDs; in a subset of patients with baseline cirrhosis, moderate quality evidence suggests a 46% lower risk of mortality with statin use. Third, moderate quality evidence also suggests a moderate benefit of statins in decreasing the risk of variceal bleeding or progression of portal hypertension by 27%, especially in patients with known portal hypertension. This study, along with previous evidence on the potential protective association between statin use and risk of HCC in patients with CLDs, provides further impetus to perform larger RCTs to evaluate the role of statins in high-risk patients, such as those with compensated cirrhosis.

In vitro and preclinical studies have shown various effects of statins on hepatic cells and vasculature. In cirrhosis, one of the leading causes of decompensation is increasing hepatic vascular resistance which causes increased portal pressure, potentially mediated by insufficient vasodilator nitric oxide[54–56]. In a randomized trial of 30 patients with cirrhosis with clinically significant portal hypertension (HVPG   12mmHg), Zafra et al found a significant increase in nitric oxide levels in hepatic venous blood in patients who received

simvastatin, as compared to patients who received placebo[24]. Abraldes et al made a similar observation in CCl4 cirrhotic rats treated with simvastatin, with a selective increase in hepatic nitric oxide production, which was associated with improvement in liver sinusoidal endothelial dysfunction and decreased vasoconstriction[25]. Other studies have shown statins may also have anti-inflammatory effects and anti-fibrotic properties on hepatic cells[26]. Trebicka and colleagues observed early treatment with atorvastatin in bile duct ligated rats results in inhibition of hepatic stellate cells leading to significantly reduced fibrosis as measured by hepatic hydroxyproline content[27].

We were unable to perform a meta-analysis of dose and duration effects of statins due to insufficient information. However, four included observational studies suggested that the effects of statins were dose-dependent, with strong effect estimates in patients with >1 year of statin use as compared to patients with shorter duration of use. Similarly, several different types of statins were studied, and observed effects were assumed to be class-specific effects. However, it is possible that lipophilic and lipophobic statins may have differential efficacy in decreasing fibrosis progression.

The strengths of this systematic review include: (a) comprehensive and systematic literature search with well-defined inclusion criteria; (b) quantitative and qualitative assessment of several clinically relevant outcomes in pre-defined subgroups of patients with CLDs; and (c) GRADE-based quality assessment to allow effective translation of findings into clinical guidelines.

Our study has several limitations. First, evidence was based on observational studies for several outcomes. Observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Despite adjusting for numerous covariates, it is not possible to eliminate the potential of residual confounding, in particular, confounding by indication, and for potential immortal time bias. Immortal time bias refers to failure to account for time between disease diagnosis (for example, chronic liver diseases) and exposure ascertainment (for example to statins) in survival analyses which may overestimate the beneficial effects of exposure.[57] We rated down the quality of evidence accordingly to low quality for all estimates derived from observational studies. Second, considerable heterogeneity was observed for some outcomes, including risk of progression of fibrosis or cirrhosis, and mortality. Subgroup analyses based on etiology of underlying CLD could not explain observed heterogeneity; however, heterogeneity in effect estimates for mortality were explained by excluding one study which included patients with non-cirrhotic CLD, whereas the effects were homogenous in patients with cirrhosis. Other potential sources of heterogeneity, which could not be adequately assessed, include methodological differences in identifying patients with CLDs, exposure ascertainment (definition of statin exposure), and outcome assessment (definition of fibrosis progression/cirrhosis, decompensated cirrhosis, etc.). It is important to note, however, that heterogeneity was primarily due to differences in effect size and not in effect direction, and summary estimates in all included studies suggested a favorable effect of statins on outcomes of interest. Third, studies did not consistently adjust for the same confounding variables; only 6 studies performed propensity score matching. Moreover, depending on outcome, specific confounding factors may be more relevant. For example, for the outcome "development of

cirrhosis or progression of fibrosis", previous etiological treatment for liver disease, whether definitive cure of the etiological factor was achieved, baseline platelet count and albumin concentration, fibrosis scores and histology whenever available, are relevant. However, it is important to note that statin use is more likely to be observed in patients with metabolic syndrome, which is an independent factor associated with fibrosis progression and adverse outcomes in patients with CLDs; hence, any potential bias due to failure to adjust for confounders, may possibly accentuate the observed protective effects of statins. Fourth, some studies relied on administrative codes, and their performance for CLDs, cirrhosis- and related complications may be unreliable. Finally, due to the small number of studies, statistical tests for small study effects were not performed; given the nascency of the field, reporting bias is a valid concern. We did not contact investigators of original studies for unpublished data.

In conclusion, through a systematic review and meta-analysis, moderate quality evidence suggests beneficial effect of statins on risk of hepatic decompensation and mortality, and variceal bleeding, especially in patients with known compensated cirrhosis, and low quality evidence suggests a mortality benefit in patients with CLDs. Together with previous evidence on the potential protective association between statin exposure and risk of HCC, and their safety in this patient population, this suggests that statins may potentially improve patient-relevant outcomes in patients with CLDs and improve survival without significant additional costs. Large, pragmatic RCTs in patients with compensated cirrhosis, are required to confirm these observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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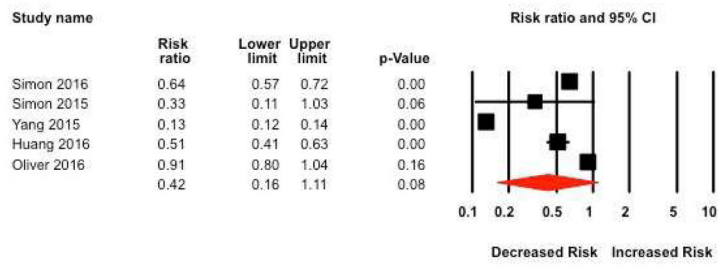
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Identification

Electronic database search – 1749 articles

1 additional record identified through other sources (manual abstract search)

1706 records after duplicates removed

Screening

1706 Abstracts Reviewed

Excluded based on title and abstract review – 1686
- Basic science articles, review articles, editorials
- Conference abstracts without additional data
- Alternative outcomes measured

Updated search during peer review – 2 studies

Eligibility

22 Full Texts Reviewed

Excluded – 9
- Patient population used in more recent study – 1
- Studies of NASH and changes in steatosis – 1
- Did not report outcomes of interest - 7

Included

Effect of Statins on CLDs:
10 cohort studies and 3 RCTs included in meta-analysis

Figure 1.
Study selection flowsheet

Statins and Risk of Development of Cirrhosis or Fibrosis Progression

Study name	Risk ratio	Lower limit	Upper limit	p-Value
Simon 2016	0.64	0.57	0.72	0.00
Simon 2015	0.33	0.11	1.03	0.06
Yang 2015	0.13	0.12	0.14	0.00
Huang 2016	0.51	0.41	0.63	0.00
Oliver 2016	0.91	0.80	1.04	0.16
	0.42	0.16	1.11	0.08

Figure 2.

Forest plot showing the association between statin exposure and risk of progression of fibrosis or development of cirrhosis

Statin Exposure and Risk of Decompensation of Cirrhosis

Study name	Risk ratio	Lower limit	Upper limit	p-Value
Mohanty 2015 - HCV	0.55	0.39	0.78	0.00
Kumar 2014 - Mixed	0.58	0.34	0.98	0.04
Huang 2016 - HBV	0.53	0.43	0.66	0.00
Chang 2017 - HBV	0.39	0.25	0.61	0.00
Chang 2017 - HCV	0.51	0.28	0.91	0.02
Chang 2017 - EtOH	0.69	0.45	1.06	0.09
	0.54	0.46	0.62	0.00
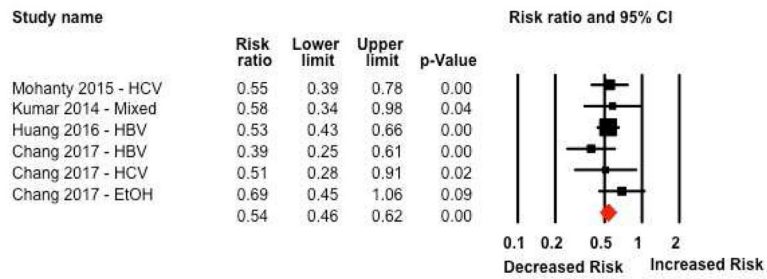
Figure 3.

Forest plot showing the association between statin exposure and risk of decompensation of cirrhosis. Of note, on restricting analysis only to patients with baseline compensated cirrhosis (excluding patients with non-cirrhotic CLDs in Huang et al), a similar protective association of between statin use and risk of hepatic decompensation was observed (RR, 0.54; 95% CI, 0.44–0.66)

Statin Exposure and Risk of All-Cause Mortality

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Risk ratio and 95% CI
Abraldes 2016 - Mixed	0.39	0.15	0.99	0.05	
Mohanty 2015 - HCV	0.55	0.45	0.68	0.00	
Kumar 2014 - Mixed	0.53	0.33	0.86	0.01	
Hsiang 2015 - HBV	0.92	0.76	1.11	0.39	
Bang 2016 - EtOH	0.51	0.44	0.59	0.00	
Chang 2017 - HBV	0.39	0.21	0.72	0.00	
Chang 2017 - HCV	0.96	0.51	1.80	0.90	
Chang 2017 - EtOH	0.76	0.43	1.35	0.35	
	0.61	0.48	0.78	0.00	

0.1 0.2 0.5 1 2
Decreased Risk Increased Risk
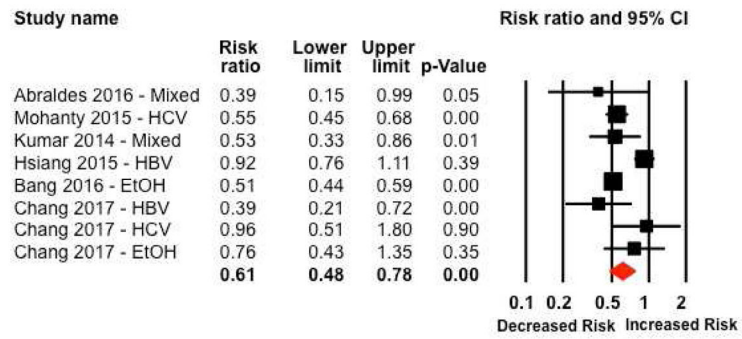
Figure 4.

Forest plot showing the association between statin exposure and risk of all-cause mortality. On restricting analysis only to patients with baseline cirrhosis (excluding patients with non-cirrhotic CLDs),[42] a similar protective association was observed (RR, 0.54; 95% CI, 0.47–0.61), with minimal heterogeneity (I^2=10%).

Statins and Risk of Progression of Portal Hypertension

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Events / Total	
					Statins	Placebo
Abraldes 2016	0.87	0.51	1.50	0.63	17 / 69	22 / 78
Pollo-Flores 2015	0.58	0.37	0.91	0.02	8 / 14	20 / 20
Abraldes 2009	0.76	0.57	1.02	0.07	19 / 28	24 / 27
	0.73	0.59	0.91	0.01	44 / 111	66 / 125

Risk ratio and 95% CI

0.2　0.5　1　2

Decreased Risk　Increased Risk
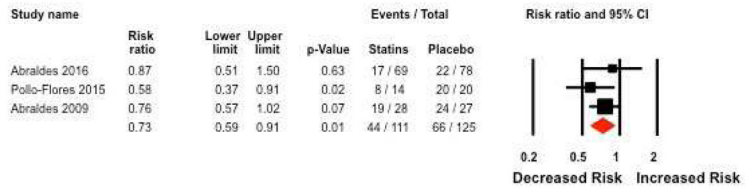
Figure 5.
Forest plot showing the association between statin exposure and risk of progression of portal hypertension

Table 1

Characteristics of Included Studies Assessing the Risk of Cirrhosis and Related Complications with Statin Use

Study; Location	Design	Time period; Follow-up (y)	Total no. of patients (statin users)	Etiology of CLD; baseline patient population	Outcomes of interest	Outcome Statins users	Outcome Non-users	Variables adjusted for*
Chang, 2017; Taiwan[50]	Propensity-score matched cohort	2000–2013; Statin users vs. non-users: 5.5 vs. 5.4	1350 (675, 50%)	HBV, HCV, EtOH; compensated cirrhosis	Decompensated cirrhosis; Mortality	Decompensated cirrhosis: 14% Mortality: 9%	28% 18%	1,2,3,5,14,16,18,19
Bang, 2016; Denmark[51]	Propensity-score matched cohort	1995–2010; NR	3530 (706, 20%)	EtOH; compensated and decompensated cirrhosis	Mortality	In patients with compensated cirrhosis: 88 per 1000p-y; In patients with decompensated cirrhosis: 142 per 1000p-y	200 per 1000p-y 240 per 1000p-y	1,2,19,21
Huang, 2016; Taiwan[35]	Propensity-score matched cohort	1997–2009; Statin users vs. non-users: 4.7 vs. 4.6	13086, (6543, 50%)	HBV; non-cirrhotic CLD	Cirrhosis; Decompensated cirrhosis	Cirrhosis: 2.6%; Decompensated cirrhosis: 0.9%	6.1%; 1.9%	1–5,8,11,12,16
Oliver, 2016; United States[43]	Retrospective cohort	1999–2010; 6.2	5985 (949, 16%)	HIV-HCV co-infection; non-cirrhotic CLD	Progression to cirrhosis	37.8% developed cirrhosis		1,3–5,12,15,16,17
Simon, 2016; United States[39]	Retrospective cohort	2001–2014; statin users vs. non-users: 6.8 vs. 8.2	9135 (4165, 46%)	HCV; non-cirrhotic CLD	Progression to cirrhosis	Cirrhosis: 14.0%	21.4%	NR
Hsiang, 2015; Hong Kong[42]	Propensity-score matched cohort	2000–2012; statin users vs. non-users: 1.6 vs. 2.6	53513 (2%)	HBV; non-cirrhotic CLD, compensated cirrhosis	Mortality	Mortality within 1y: 6.5%	14.3%	1,3,6,7,9,13,14,18,19
Mohanty, 2015; United States[37]	Propensity-score matched cohort	1996–2009; statin users vs. non-users: 2.3 vs. 1.7	2747 (685, 25%)	HCV; compensated cirrhosis	Decompensated cirrhosis, variceal hemorrhage, death	Decompensated cirrhosis: 2.1%; Variceal hemorrhage: 0.5%; Death: 6.3%	3.9%; 1.3%; 11.1%	1–7,10,12–15,20
Simon, 2015; United States[40]	Retrospective cohort	2000–2004; 3.5	543 (29, 5%)	HCV; non-cirrhotic CLD	Progression of fibrosis	Fibrosis progression: 10%	28%	4,6,8
Yang, 2015; Taiwan[41]	Propensity-score matched cohort	1999–2010; statin users vs. non-users: 378843 p-y vs. 687559 p-y	84213 (28071, 33%)	HCV; non-cirrhotic CLD	Cirrhosis	Cirrhosis: 6.0%	21.9%	1–3,21
Kumar, 2014; United States[36]	Retrospective cohort	1988–2011; statin users vs. non-users: 3 vs. 2.5	243 (81, 33%)	Mixed; compensated cirrhosis	Decompensated cirrhosis; mortality	Decompensated cirrhosis: 30.0%; Survival (median, in y): 10.8y	40.5%; 6.3y	7–11
Abraldes, 2016; Spain[34]	RCT	2010–2013; 1	147 (69, 47%)	Mixed; decompensated cirrhosis with recent variceal bleeding	Recurrent variceal hemorrhage; mortality	Recurrent variceal hemorrhage: 25%; Death: 9%	28%; 22%	NA
Pollo-Flores, 2015; Brazil[38]	RCT	2011–2013; 0.25	24 (13, 54%)	Mixed; decompensated cirrhosis	Reduction in portal hypertension	Reduction in portal hypertension: 55%	0%	NA

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Study; Location	Design	Time period; Follow-up (y)	Total no. of patients (statin users)	Etiology of CLD; baseline patient population	Outcomes of interest	Outcome		Variables adjusted for*
						Statins users	Non-users	
Abraldes, 2009; Spain[33]	RCT	2004–2007; 0.1	55 (28, 50%)	Mixed; decompensated cirrhosis	Reduction in portal hypertension	Reduction in portal hypertension: 32%	11%	NA

*
1, age; 2, gender; 3, diabetes mellitus; 4, body mass index/obesity; 5, hypertension; 6, platelet count; 7, albumin; 8 NAFLD/steatosis; 9, beta-blocker; 10, MELD; 11, HCC; 12, lipid panel; 13, total bilirubin; 14, cardiovascular disease; 15, race; 16, treatment of underlying CLD (HBV, HCV, HIV); 17, disease-specific prognostic factors (CD4 count for HIV; HCV genotype); 18, cirrhosis complications; 19, other medications (warfarin, antiplatelet/NSAID, fibrate, loop diuretic, other diuretic, ACE-I/ARB, nucleos()ide analogue, metformin, sulfonylurea, thiazolidinedione, insulin); 20, other comorbidities (CKD, PAD, etc.); 21, socioeconomic status

Table 2

Subgroup analysis based on etiology of chronic liver diseases

Etiology of CLD	No. of studies	Risk Ratio (95% CI)	p-interaction
Outcome: Mortality			
HBV	2	0.63 (0.27–1.45)	0.84
HCV	2	0.67 (0.40–1.13)	
Alcoholic liver disease	2	0.56 (0.40–0.79)	
Mixed	2	0.50 (0.32–0.76)	
Outcome: Decompensated Cirrhosis			
HBV	2	0.49 (0.37–0.64)	0.62
HCV	2	0.54 (0.40–0.73)	
Alcoholic liver disease	1	0.69 (0.45–1.06)	
Mixed	1	0.58 (0.34–0.98)	