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Complete List of Authors:	Sizhe, Wan; First Affiliated Hospital of Nanchang University, Gastroenterology Chenkai, Huan; First Affiliated Hospital of Nanchang University, Gastroenterology xuan, Zhu; First Affiliated Hospital of Nanchang University, Gastroenterology
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Systematic review with a meta-analysis: Clinical effects of statins on the reduction of portal hypertension and variceal haemorrhage in cirrhotic patients

Si-Zhe Wan,[1] Chen-Kai Huang,[1] Xuan Zhu[1]

[1]Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

Correspondence to：Prof. Xuan Zhu, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University, 17 Yongwai Main St, Nanchang 330006, Jiangxi, China; jyyfyzx@163.com

Abstract

Background: Statins may improve outcomes in patients with cirrhosis. We performed a systematic review and meta-analysis to evaluate the effect of statins on patients with cirrhosis and related complications, especially portal hypertension and variceal haemorrhage.

Methods: Studies were searched in the Pubmed, EMBASE and Cochrane library databases up to February 2019. The outcomes of interest were associations between statin use and improvement in portal hypertension (reduction ≥20% of baseline or to ≤12 mmHg) and the risk of variceal haemorrhage. The relative risk (RR) with a 95% confidence interval (Cl) was pooled and calculated using a random effects model. Subgroup analyses were performed based on the characteristics of the studies.

RESULTS: Eight studies (7 randomized controlled trials (RCTs) and 1 observational study) with 3,195 patients were included. The pooled RR for reduction in portal hypertension was 1.91(95% CI, 1.04-3.52; I2=63%) in 6 RCTs. On subgroup analysis of studies that used statin for one month, the RR was 2.01 (95% Cl, 1.31-3.10; I2=0%); the pooled RR for studies that used statins for three months was 3.76 (95% Cl, 0.36-39.77; I2=75%); the pooled RR for studies that used NSBB in the control group was 1.42 (95% CI, 0.82-2.45; I2=64%); the pooled RR for studies that used a drug that was not reported in the control group was 4.21 (95%

CI, 1.52-11.70; I2=0%); the pooled RR for studies that used simvastatin was 2.20 (95% Cl, 0.92-5.29; I2=69%); RR for study using atorvastatin was 1.82 (95% Cl, 1.00-3.30). For the risk of a variceal haemorrhage, the RR based on an observational study was 0.47 (95% CI, 0.23-0.94); in two randomized controlled trials, the pooled RR was 0.88 (95% CI, 0.52-1.50; I2=0%). Overall, the summed RR was 0.64 (95% CI, 0.42-0.99; I2=6%).
Conclusion: Statins may improve hypertension and decrease the risk of variceal haemorrhage according to our assessment. However, further and larger RCTs are needed to confirm this conclusion.

Article summary

1) Cirrhosis is an increasing global health problem.

2) A growing interest in the potential benefits of statins in patients with liver diseases has recently emerged. Some studies have confirmed the roles of statin use in patients with cirrhosis against the development of portal hypertension and the occurrence of variceal haemorrhage.

3) Statins may improve portal hypertension and the risk of variceal haemorrhage through reducing HVPG in cirrhotic patients.

4) Large RCTs are needed to confirm statins beneficial effects in patients with liver diseases.

5) The mechanism of therapeutic effect of statin in liver disease should be be investigated in the future.

INTRODUCTION

Cirrhosis is increasingly prevalent worldwide, as a result of a variety of chronic liver diseases. Cirrhosis, including compensate and decompensate, was in the top 8 causes of death in the United States in 2010 and led to more than 49,500 deaths.[1] The median survival of patients with compensated cirrhosis is >12 years, and patients with decompensated cirrhosis exhibit a median survival of <2 years.[2] Portal hypertension and

oesophageal varices are common complications of cirrhosis, and these conditions develop into variceal haemorrhage, which produces a mortality of 10–15% per episode.[3] The hepatic venous pressure gradient (HVPG) is a significant indicator of portal hypertension and varices bleeding. Reduction in HVPG indicates an improvement in portal hypertension and a decline in bleeding risk.[4]

Statins are widely used in clinical practice because of their exact and effective lipid-lowering effects.[5 6] The use of statins in patients with liver disease has long been limited by concerns of their potential hepatotoxicity, which have been raised by anecdotal evidence of increased liver enzymes following statin use or the possible trapping of lipids in the liver.[7] Some residual concern remains among primary care physicians in prescribing statins to patients with underlying liver disease because some of doctors still believe that these patients are at increased risk for hepatotoxicity.[8] However, a growing interest in the potential benefits of statins in patients with liver diseases has recently emerged.[7 9-12] Recent *in vivo* and *in vitro* experiments have gradually demonstrated that statins also exhibit anti-inflammatory[13], immune-modulating,[14] anti-proliferative,[15] and anti-oxidant[16] effects as well as improved endothelial function[17] and inhibit platelet aggregation[18] and certain Gram-negative bacteria.[19 20] These findings led to the development of statins in basic research of liver disease and laid a solid foundation for clinical practice.

We performed a systematic review and meta-analysis based on the most recent studies (randomized controlled trials (RCTs) and a cohort study) to evaluate the effects of statins in patients with cirrhosis and related complications, especially portal hypertension and variceal haemorrhage.

METHOD

Search Strategy

Pubmed, Embase, Cochrane Controlled Trial Registry and The Cochrane Library were searched up to February 2019 to identify all relevant articles on the effect of statins in liver cirrhosis and retrieve pertinent studies. No language restrictions were imposed. An experienced medical librarian designed and implemented the search strategy. Electronic databases were searched using the following search terms: liver cirrhosis, ascites, portal hypertension, statin, Hydroxymethylglutaryl-CoA reductase inhibitors. Two reviewers (SZW and CKH) independently assessed the titles and abstracts of the studies that met the eligibility, criteria for inclusion.

Data Abstraction

Two reviewers (SZW and CKH) independently extracted the data.

The following data were collected from each study: year of publication, study design, inclusion criteria, exclusion criteria, aetiology of cirrhosis, total number of patients in each group, primary outcome reported, and CTP (Child–Turcotte–Pugh) class, and ascites. Any divergence between the reviewers was discussed with a third reviewer (XZ), and agreement was reached by consensus.

We used the Newcastle–Ottawa scale to determine the quality of the cohort studies, and the Cochrane tool was used to determine the risk of bias for RCTs.

Outcomes Assessed

Our primary outcome of interest was the association between statin use and the reduction in portal hypertension. The secondary outcomes of interest were the association between statin use and variceal bleeding. Several subgroup analyses were performed based on the quality of the studies, medication time, types of drugs in the control group, and types of statins.

Quality of Evidence

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework to evaluate the quality of the evidence.[21] The GRADE approach for systematic reviews defines the quality of a body of evidence as the extent to which one can be confident that an estimate of an effect or association is close to the quantity of specific interest. The following factors were considered in determining the quality of evidence: risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

Statistical Analysis

The trials and patient characteristics are reported as the ,number of observations and proportions. The relative risk (RR) and 95% confidence interval (CI) that achieved a target hemodynamic response in each group was pooled using the DerSimonian and Laird random effects model.[22] Inter-trial heterogeneity was statistically assessed using the chi-square test and is expressed as the I^2 value, and I^2 values >50% were reflective of substantial heterogeneity.[23] A formal assessment of publication bias using the egger test was performed (Supplementary figure 1).

Patient and Public Involvement

This meta-analysis did not involve patients or the public

RESULTS

Search Results

A total of 2,676 potentially eligible references were retrieved in the literature search, and 2,624 were excluded based on the titles and abstracts. A further 44 articles, referred to as full articles, were deemed ineligible. Twelve studies were excluded for lack of interesting results. Eight studies with a total of 3,195 patients met our inclusion criteria and were included in our meta-analysis (7 RCTs and 1 observational study).[10 24-30] Six studies included patients who exhibited the target reduction in HVPG > 20% from baseline or < 12 mm-Hg in the statins group. Three studies included events of variceal bleeding in patients with cirrhosis. Figure 1 summarizes the search strategy.

Description of included studies

Table 1 shows the characteristics of these studies. These studies included 3,195 liver cirrhosis patients, of whom 902 patients were exposed to statins. One study was performed exclusively in patients with HCV mono-infection, and seven studies included cirrhosis with multiple underlying aetiologies. The medication time of statins was one month in three studies. However, statins were used for three months in three studies. Six studies provided the desired data as regarded decrease in HVPG (reduction > 20% or <12 mm-Hg).

The only observational study was of high quality, as exhibited by the high Newcastle-Ottawa quality score. Table 2 summarizes the methodological qualities of the observational study and RCTs. Figure 2 shows the methodological qualities of the RCTs

Table 3 summarizes the characteristics of the 3,195 patients included in the eight studies. Statins users and nonusers were generally male because the cirrhosis incidence in females was lower than that in males. Patients were mostly categorized as CTP A and B classes, 221 of 255 (87%) in two studies. No appreciable differences in the complications of cirrhosis, such as ascites or previous variceal bleeding, were observed between the two study groups across the eight studies.

Outcome evaluation

Improvement in Portal Hypertension

Six studies including 301 patients evaluated the improvement in portal hypertension in cirrhosis. Overall, a decrease in HVPG (**>** 20% from baseline or **<** 12 mm-Hg) was achieved with statins in 57 of 135 evaluable patients compared to 36 of 141 patients in the control group (RR, 1.91; 95%

Cl, 1.04-3.52; I^2=63%). Three subgroup analyses were performed, based on the medication time, types of drug used in the control group, and types of statins. Subgroup analysis of the medication time of statins included three studies that used statins for one month (RR, 2.01; 95% Cl, 1.31-3.10; I^2=0%) and three studies that used statins for three months (RR, 3.76; 95% Cl, 0.36-39.77; I^2=75%) (Figure 3). The second subgroup analysis was based on the types of drugs used in the control group, including NSBB and not explicitly reported drugs. The pooled RR for NSBB users was 1.42 (95% CI, 0.82-2.45; I^2=64%), and the pooled RR for the not explicitly reported drugs was 4.21 (95% CI, 1.52-11.70; I^2=0%) (Figure 4). The third subgroup analysis was based on the types of statins. Five studies used simvastatin (RR, 2.20; 95% Cl, 0.92-5.29; I^2=69%), and one study used atorvastatin (RR, 1.82; 95% Cl, 1.00-3.30) (Figure 5).

There was moderate persuasion supporting the use of statins associated with an improvement in portal hypertension based on the RCTs. However, the result was limited by the study size (109 events in 301 patients).

Risk of variceal haemorrhage

Three studies including 3,025 patients evaluated the association between statin use and the occurrence of variceal bleeding. Overall, 27 events occurred in 765 statin users, and 81 events were reported in 2152 nonusers. A subgroup analysis was performed based on the type of trial. Overall, the pooled RR for the risk of variceal haemorrhage was 0.64 (95% CI, 0.42-0.99; I^2=6%). The RR for the only one observational study was 0.47 (95% CI, 0.23-0.94). The pooled RR for the two RCTs studies was 0.88 (95% CI, 0.52-1.50; I^2=0%) (Figure 6).

DISCUSSION

This meta-analysis demonstrated the possible roles of statin use in patients with cirrhosis against the development of portal hypertension and the occurrence of variceal haemorrhage in 8 studies (7 RCTs and 1 cohort study). The availability of statins was proven to lead to the decrease in portal hypertension and variceal bleeding across all trials. The summary RR between the numbers of HVPG reductions achieved in statin users and nonusers was 1.91 (95% Cl, 1.04-3.52; I^2=63%) in favour of statins. We performed three subgroup analyses because of the substantial heterogeneity. The subgroup analysis based on the medication time of statin use supported the improvement in portal pressure at the one-month assessment (RR, 2.01; 95% Cl, 1.31-3.10; I^2=0%). However, this effect was not statistically significant at the three-month assessment (RR, 3.76; 95% Cl, 0.36-39.77; I^2=75%). These results suggest that the

effects of statins are not dose-dependent and lead to strong curative effects in patients who used statins for one month compared to patients with a longer duration of use. Several possible mechanisms may explain the biological plausibility of our findings. The hepatotoxicity of statins occurs via regulation of the P450 cytochrome in immune-mediated liver damage, which activates apoptosis and T cell-induced liver injury.[31 32] Previous clinical research[33-36] confirmed these observations, which offset the benefits of statins over a longer treatment period. No considerable differences were observed in subgroup analyses for the use of NSBB in the control group (RR, 1.42; 95% CI, 0.82-2.45; I^2=64%). We presume that improvements of portal hypertension by NSBB is the underlying mechanism. NSBB is clinically used to treat portal hypertension because of its efficacy in decreasing HVPG and variceal haemorrhage.[37-40] Therefore, the use of NSBB in the control group may lead to no significant difference between the statin user and nonuser groups. Different types of statins exhibit inconsistent pharmacological actions. Therefore, patients were stratified by the statin varieties. The pooled RR in a subset of patients who received simvastatin was 2.20(95% Cl, 0.92-5.29; I^2=69%), which indicates no improvement. Atorvastatin users exhibited a decrease in portal pressure (RR, 1.82; 95% Cl, 1.00-3.30). High quality evidence was included, but discrepancies, such as the medication time may have led to imprecision.

Events of variceal haemorrhage were satisfactorily reported in three studies. The effect of statins on variceal bleeding as a common cause of death in patients with portal hypertension was also investigated. The pooled RR was 0.64 (95% CI, 0.42-0.99; I^2=6%). However, the reduction in the pooled RR of the risk of variceal haemorrhage failed to reach statistical significance with statin use in two RCTs (RR, 0.88; 95% CI, 0.52-1.50; I^2=0%). Notably, the only observational study confirmed the superiority of statins in lowering the risk of variceal bleeding (RR, 0.47; 95% CI, 0.23-0.94). The characteristics of different types of experiments may be responsible for the inconsistency.

Statins have received increasing attention in clinical research in the field of various liver diseases including liver cirrhosis, hepatocellular carcinoma, fatty liver disease, viral hepatitis and other related liver diseases, in recent years.[6] Studies have confirmed that statins are safe and effective for some patients with these liver diseases.[41] A population-based study[9] evaluated the effects of statins on reducing decompensation, mortality, and HCC in HBV, HCV, and alcohol-related cirrhosis. This study demonstrated that statins reduced decompensation (P<0.0001), mortality (P<0.0001), and the risk of HCC (P=0.009) in patients with cirrhosis, and this correlation was dose-dependent. The risk of decompensation in patients with cirrhosis caused by chronic HBV (RR,

0.39; 95% Cl, 0.25-0.62) or HCV infection (RR, 0.51; 95% Cl, 0.29-0.93) was lower in patients taking statins. The effect of statins on reducing the risk of cirrhosis decompensation was statistically significant in alcohol cirrhotic patients (RR, 0.69; 95% Cl, 0.45-1.07). In general, the use of statins reduced the decompensation rate of HBV, HCV and alcohol-related cirrhosis. Two recent studies[42 43] demonstrated that statins were safe in patients with NAFLD and exhibited beneficial effects decreasing steatosis and fibrosis and preventing disease progression. Multiple previous studies demonstrated the benefit of statins on liver systems. A randomized trial of patients with cirrhosis and significant portal hypertension observed that the nitric oxide levels in hepatic venous blood, as a key vasodilator mediating the hepatic vascular resistance,[44-46] were increased in the statins group compare to those in the control group. A decrease in portal hypertension was also observed in patients who received statins.[47]

More research groups have begun to support the use of statin in some patients with chronic liver disease or cirrhosis based on these studies.[48 49] Some researchers believe that statins may also be able to be used as an adjuvant therapy in any chronic liver disease patients with indications for statins use to prevent decompensation or delay the progression of patients with decompensated cirrhosis.[50] However, this information was derived from retrospective cohort studies, and prospective studies are needed to confirm these beneficial effects.

This meta-analysis evaluated the role of statins in patients with cirrhosis as a decline in portal pressure and risk of variceal haemorrhage. We performed a comprehensive literature search that met the well-defined inclusion criteria. Eight studies were included, primarily consisting of RCTs. These studies were high quality studies as graded by the Cochrane tool for assessing risk of bias or the Newcastle–Ottawa scale. Several subgroup analyses were completed based on the characteristics of the studies to further ascertain the precision of results.

However, several limitations exist in our meta-analysis. The inclusion and exclusion criteria were inconsistent in all of the studies. Seven RCTs were included, but the number of patients enrolled was relatively fewer in the RCTs (471 patients). Patients with various etiologies of cirrhosis were not researched separately because of insufficient information, which may explain the substantial heterogeneity. We adjusted the individual studies for various confounders (e.g., age, sex, CTP score, and MELD score). However, residual confounders that could not be completely adjusted remained. These situations may have affected the precision and credibility of our estimates. Non-alcoholic fatty liver disease, as a metabolic disease, may exhibit closer relevance with lipid-lowering drug statins. Unfortunately, no eligible NAFLD research was included.

In conclusion, our analyses based on RCTs and an observational

study indicated a beneficial effect of statins on reducing portal hypertension and variceal haemorrhage. However, the assessment can not serve as clinical guideline for the wide use of statins in cirrhosis with portal hypertension because of the limited quantity and quality of the included studies. Previous research reported the potential protective effects of statins against cirrhosis and HCC progression, and the potential benefits of statins may outweigh the theoretical risks. Notably, adverse events related to statins were rarely reported in studies. Large RCTs are required before statins are clinically used to treat patients with cirrhosis and complications.

Contributors SZW planned the study. SZW and CKH screened the literature and collected data. SZW, CKH and XZ conducted the meta-analysis and wrote the manuscript.

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Competing interests None declared

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

Figure 2. Risk of bias assessed using the Cochrane risk of bias tool for RCTs

Figure 3. Forest plot to evaluate the role of statins in the reduction of portal hypertension using a subgroup analysis based on medication time of statins.

Figure 4. Forest plot to evaluate the role of statins in the reduction of portal hypertension using subgroup analysis based on the types of drugs in the control group.

Figure 5. Forest plot to evaluate the role of statins in the reduction of portal hypertension using subgroup analysis based on types of statins.

Figure 6. Forest plot to evaluate the role of statins in the reduction of the risk of variceal haemorrhage using subgroup analysis based on types of statins.

Supplementary Figure 1. egger's test to identify publication bias. SND, standard normal deviation; PTH, portal hypertension; VH, variceal haemorrhage.

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Table 1. Characteristics of the included studies

Study, year	Design	Inclusion criteria	Exclusion criteria	Aetiology of cirrhosis	Groups	N	Outcomes of interest	Outcomes	
								Statins users(n)	Non-users (n)
Mohanty, 2016	Retrospective	HCV positive patients defined by ICD-9 codes Compensated cirrhosis	HIV or HBV coinfection Decompensation or HCC before or within 180 days after index date No laboratory results No follow-up Died within 180 days after index date Statin users with only one prescription fill or more than 365 days between first and second fill	HCV	Statins Nonusers	685 2062	Variceal hemorrhage	Variceal Hemorrhage:9	58
Abraldes, 2009	RCT	Age between 18 and 75 years, positive diagnosis of cirrhosis, and severe portal hypertension defined as HVPG of 12 mm Hg or greater	Pregnancy Cholestatic liver disease Severe liver failure, evaluated by the presence of a serum bilirubin level greater than 5 mg/dL, prothrombin rate less than 40% Hepatic encephalopathy grades II–IV Child–Pugh score of 12 or greater Serum creatinine level greater than 1.5 mg/dl Hepatocellular Carcinoma Portal vein thrombosis	Mixed	Statins Nonusers	28 27	Reduction in portal hypertension	Reduction in portal hypertension:9	3
Abraldes, 2016	RCT	Age between 18 and 80 years Previous diagnosis of liver cirrhosis Index variceal bleeding within the previous 5-10 days Plan to start standard treatment for the prevention of variceal rebleeding In woman documented absence of pregnancy and commitment to use adequate contraception if applicable	Pregnancy or lactation multifocal hepatocellular carcinoma or a single nodule > 5 cm in diameter. Creatinine > 2 mg/dl Child-Pugh score > 13 points Contraindication for statins Patients with HIV infection on protease inhibitors Pre-treatment with portosystemic shunt (surgical or percutaneous) Index bleeding due to gastric varices Complete portal vein thrombosis or portal vein cavernomatosis. Patients previously treated with the combination of endoscopic banding ligation and NSBB (before the index episode)	Mixed	Statins Nonusers	69 78	Variceal haemorrhage	variceal haemorrhage:14	18

			Patients previously treated with statins within one month of randomization.						
Alvarado, 2016	RCT	Cirrhosis, CSPH and high-risk oesophageal varices without previous bleeding	NR	Mixed	Statins Nonusers	43 44	Reduction in portal hypertension	Reduction in portal hypertension:16	8
Bishnu, 2018	RCT	Age: 18–60 years. Cirrhosis (diagnosed clinically, radiologically, or histopathologically). Portal hypertension (history of variceal bleed, ascites, splenomegaly, oesophageal varices on upper GI endoscopy, or history of having undergone EVL).	Child-Pugh-Turcott (CPT) class C. Hepatic encephalopathy grades II–IV. Hepatocellular carcinoma Portal vein thrombosis or cavernomatosis. Hepatic venous outflow tract obstruction Previous portosystemic shunt surgery Obstructive airway diseases Cardiac conduction abnormalities Peripheral vascular disease Congestive cardiac failure NYHA class II–IV Renal insufficiency (serum creatinine > 2 mg/dl) Previous episodes of rhabdomyolysis Hypersensitivity to HMG-CoA reductase inhibitors Previous treatment with HMG-CoA reductase inhibitor Participation in a concurring clinical trial Pregnancy or plan to conceive during study period	Mixed	Statins Nonusers	11 12	Reduction in portal hypertension Variceal haemorrhage	Reduction in portal hypertension:10 Variceal haemorrhage:4	6 5
Flores, 2014	RCT	Cirrhosis and portal hypertension detected using abdominal ultrasound with colour Doppler flowmetry or upper digestive endoscopy	NR	Mixed	Statins Nonusers	11 11	Reduction in portal hypertension	Reduction in portal hypertension:4	0
Pollo-	RCT	Age 18–75 years Diagnosis of cirrhosis with	Aminotransferases levels >3 times above the upper	Mixed	Statins	11	Reduction in	Reduction in	0

Flores 2015		portal hypertension detected using an abdominal ultrasound with colour Doppler and an upper digestive endoscopy showing gastroesophageal varices Both procedures were r performed within the previous six months	limit of normal (ULN) Recent (within the last 6 months) or current use of simvastatin Portal vein thrombosis, contrast medium allergy Hepatocellular carcinoma or any other malignancy reducing life expectancy Renal failure (creatinine level >1.5 mg/dL) Bleeding disorder (prothrombin activity test <30% or platelets count <35,000/mcL) or decompensated cirrhosis characterized by severe ascites or grade II or overt encephalopathy Patients with alcoholic cirrhosis were abstinent from alcohol consumption for at least one year		Nonusers	13	portal hypertension	portal hypertension:6	
Rajan, 2016	RCT	Cirrhotics with varices who had never bled	NR	Mixed	Statins Nonusers	44 46	Reduction in portal hypertension	Reduction in portal hypertension:22	25

ALT, Alanine aminotransferase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human Immunodeficiency virus; ICD-9, International Classification of Disease – 9; NR, Not reported.

Table 2. Quality assessment of the observational studies using the Newcastle–Ottawa Scale

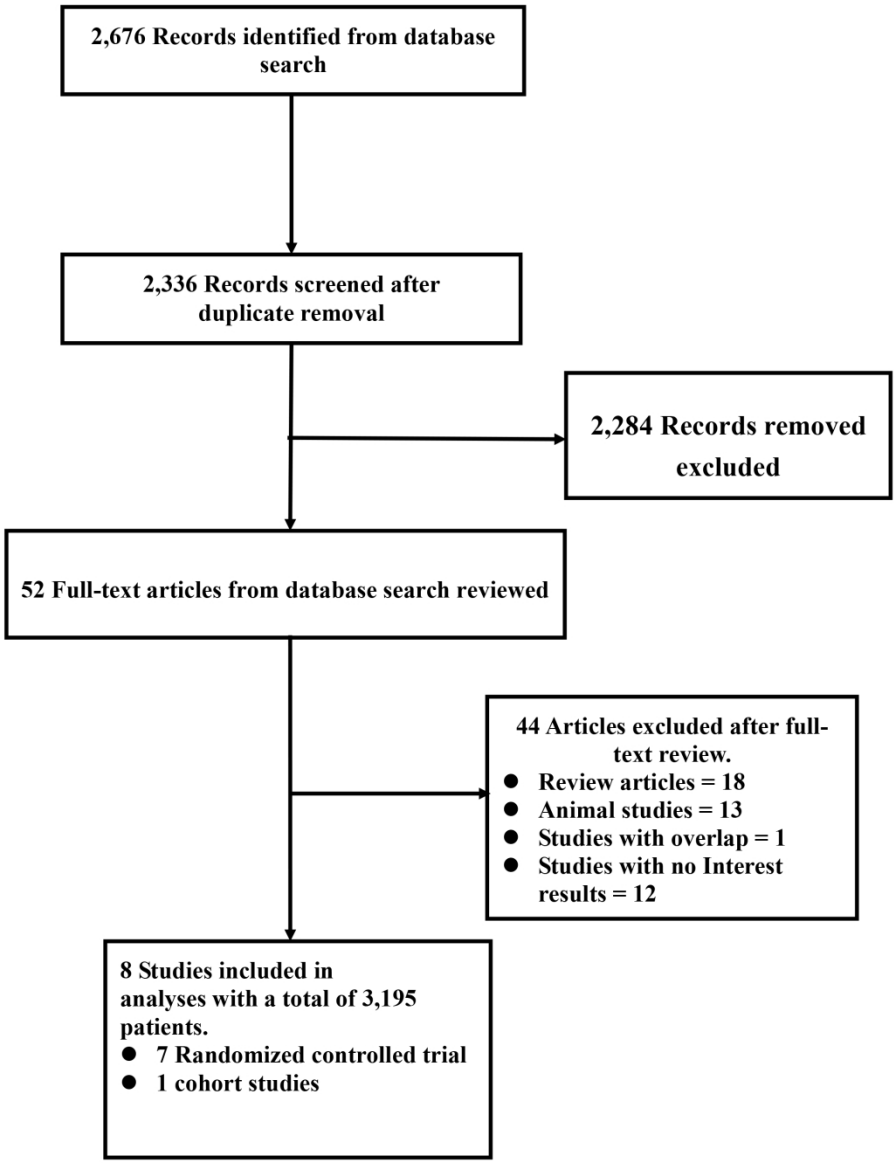
Studies	Selection				Comparability	Outcome			Quality
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at start	Adjustment for primary and secondary factors	Assessment by record linkage	Long enough follow-up for outcome to occur	Adequacy of follow-up	
Mohanty 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality

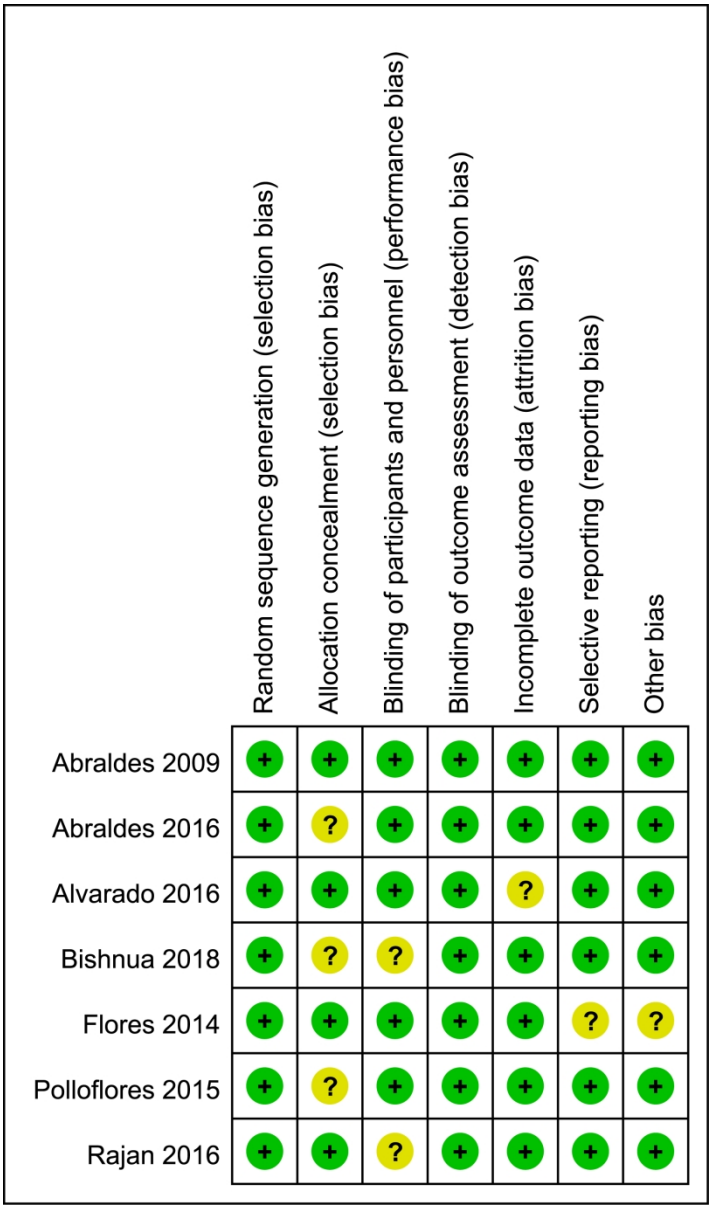
Quality assessment of the randomized controlled trials using the Cochrane tool for assessing the risk of bias

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Quality		
Abraldes 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality		
Abraldes, 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality		
Alvarado 2016	Low risk	Low risk	Low risk	unclear risk	Low risk	Low risk	High quality		
Bishnua , 2018	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High quality		
Flores 2014	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	High quality		
Polloflores 2015	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High quality		
Rajan 2016	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	High quality		

Table 3. Characteristics of participants in the included studies

	Treatment group	Patients N	Age Y	Males N	Viral/ Alcoholic Aetiology,N	Child-Pugh class A/B/ C, N	Ascites N	Previous variceal bleeding, N
Mohanty,2016	Statins Nonusers	685 2062	56 56	671 2021	685/0 2062/0	NR NR	NR NR	NR NR
Abraldes,2009	Statins Nonusers	28 27	58 56	17 21	NR NR	18/10/0 16/8/3	14 16	6 9
Abraldes,2016	Statins Nonusers	69 78	57 57	45 53	20/49 19/55	15/68/17 24/62/14	15 16	NR NR
Alvarado,2016	Statins Nonusers	43 44	56 54	31 35	NR NR	NR NR	NR NR	NR NR
Bishnu,2018	Statins Nonusers	11 12	44 47	9 12	0/4 1/6	NR NR	5 6	6 5
Flores,2014	Statins Nonusers	11 11	46 43	23 30	NR NR	NR NR	NR NR	NR NR
Pollo-Flores,2015	Statins Nonusers	11 13	57 59	6 7	NR NR	NR NR	2 3	5 3
Rajan,2016	Statins Nonusers	44 46	51 53	30 35	NR NR	NR NR	NR NR	NR NR


2,676 Records identified from database search
2,336 Records screened after duplicate removal
2,284 Records removed excluded
52 Full-text articles from database search reviewed
44 Articles excluded after full-text review.
Review articles = 18
Animal studies = 13
Studies with overlap = 1
Studies with no Interest results = 12
8 Studies included in analyses with a total of 3,195 patients.
7 Randomized controlled trial
1 cohort studies



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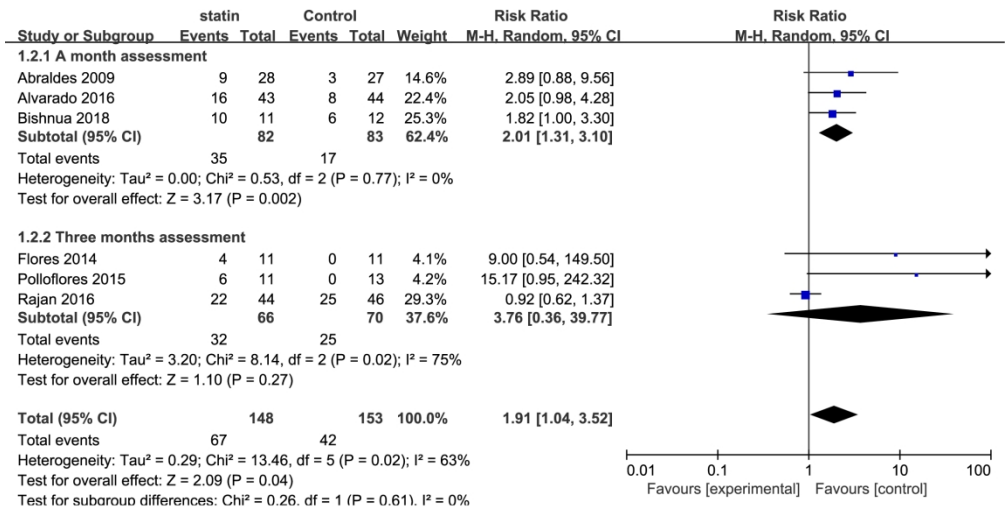

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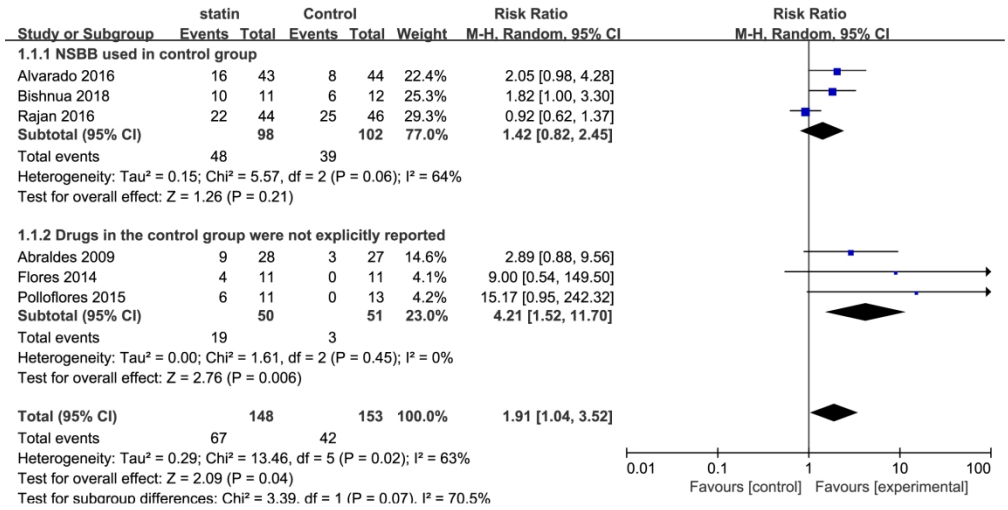

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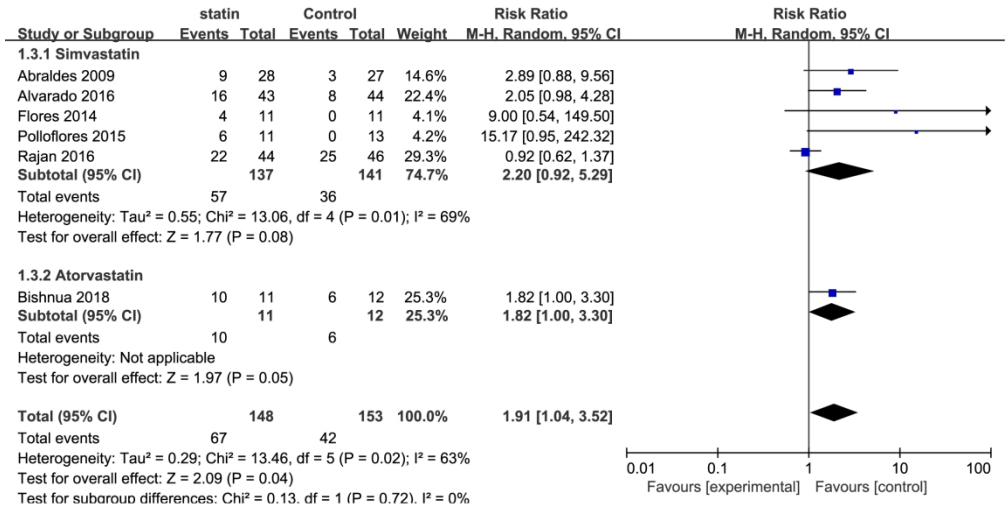

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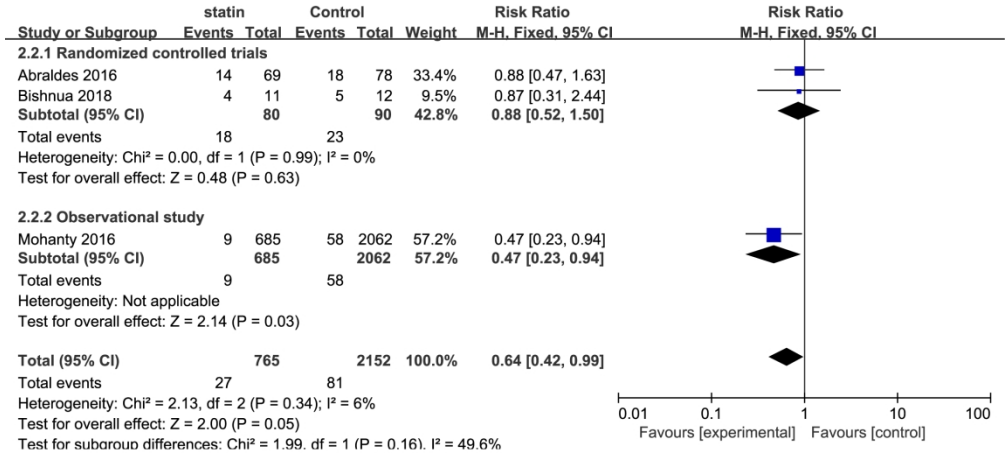

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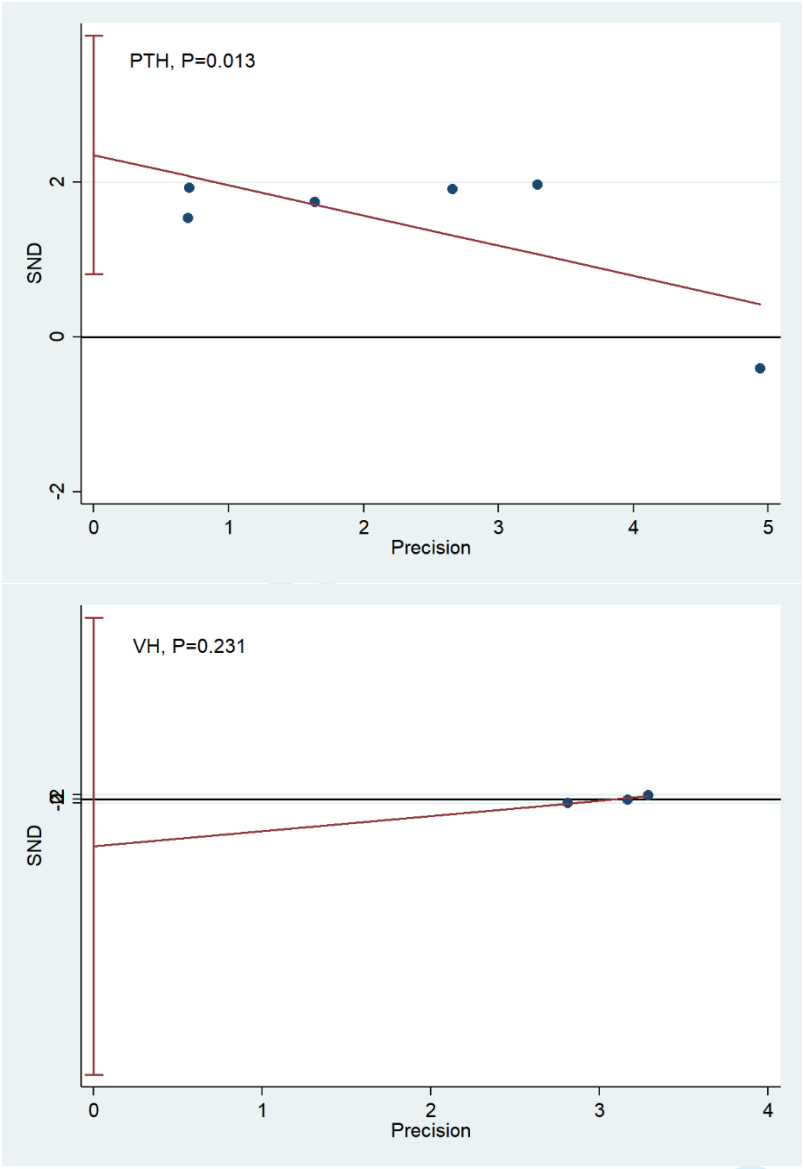

Supplementary Figure 1. egger's test to identify publication bias. SND, standard normal deviation; PTH, portal hypertension; VH, variceal haemorrhage.

BMJ Open

Systematic review with a meta-analysis: Clinical effects of statins on the reduction of portal hypertension and variceal haemorrhage in cirrhotic patients

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Systematic review with a meta-analysis: Clinical effects of statins on the reduction of portal hypertension and variceal haemorrhage in cirrhotic patients

Si-Zhe Wan,[1†] Chen-Kai Huang,[1†] Xuan Zhu[1]

[1] Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
† SZW and CKH contributed equally to this study.

Correspondence to：Prof. Xuan Zhu, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University, 17 Yongwai Main St, Nanchang 330006, Jiangxi, China; jyyfyzx@163.com

Abstract

Background: Statins may improve outcomes in patients with cirrhosis. We performed a systematic review and meta-analysis to evaluate the effect of statins on patients with cirrhosis and related complications, especially portal hypertension and variceal haemorrhage.
Methods: Studies were searched in the Pubmed, EMBASE and Cochrane library databases up to February 2019. The outcomes of interest were associations between statin use and improvement in portal hypertension (reduction ≥20% of baseline or to ≤12 mmHg) and the risk of variceal haemorrhage. The relative risk (RR) with a 95% confidence interval (Cl) was pooled and calculated using a random effects model. Subgroup analyses were performed based on the characteristics of the studies.
RESULTS: Eight studies (7 randomized controlled trials (RCTs) and 1 observational study) with 3,195 patients were included. The pooled RR for reduction in portal hypertension was 1.91(95% CI, 1.04-3.52; I2=63%) in 6 RCTs. On subgroup analysis of studies that used statin for one month, the RR was 2.01 (95% Cl, 1.31-3.10; I2=0%); the pooled RR for studies that used statins for three months was 3.76 (95% Cl, 0.36-39.77; I2=75%); the pooled RR for studies that used non-selective beta blockers (NSBB) in the control group was 1.42 (95% CI, 0.82-2.45; I2=64%); the pooled RR for studies that used a drug that was not

reported in the control group was 4.21 (95% CI, 1.52-11.70; I2=0%); the pooled RR for studies that used simvastatin was 2.20 (95% Cl, 0.92-5.29; I2=69%); RR for study using atorvastatin was 1.82 (95% Cl, 1.00-3.30). For the risk of a variceal haemorrhage, the RR based on an observational study was 0.47 (95% CI, 0.23-0.94); in two randomized controlled trials, the pooled RR was 0.88 (95% CI, 0.52-1.50; I2=0%). Overall, the summed RR was 0.64 (95% CI, 0.42-0.99; I2=6%).
Conclusion: Statins may improve hypertension and decrease the risk of variceal haemorrhage according to our assessment. However, further and larger RCTs are needed to confirm this conclusion.

Key words: Statins; Portal hypertension; Variceal haemorrhage; cirrhotic; Meta-analysis

Strengths and limitations

1) This will be the most comprehensive review of published and unpublished data of clinical effects of statins on the reduction of portal hypertension and variceal haemorrhage.

2) This systematic review provides strong evidence for clinicians using statins to treat portal hypertension and variceal haemorrhage.

3) Eligible studies screening, data extraction, and quality assessment were performed by two independent reviewers to reduce the potential for reviewer bias.

4) Large RCTs are needed to confirm statins beneficial effects in patients with liver diseases.5) Only studies in the English language have been included in the analysis.

INTRODUCTION

Cirrhosis is increasingly prevalent worldwide, as a result of a variety of chronic liver diseases. Cirrhosis, including compensate and

decompensate, was in the top 8 causes of death in the United States in 2010 and led to more than 49,500 deaths.[1] The median survival of patients with compensated cirrhosis is >12 years, and patients with decompensated cirrhosis exhibit a median survival of <2 years.[2] Portal hypertension and oesophageal varices are common complications of cirrhosis, and these conditions develop into variceal haemorrhage, which produces a mortality of 10–15% per episode.[3] The hepatic venous pressure gradient (HVPG) is a significant indicator of portal hypertension and varices bleeding. Reduction in HVPG indicates an improvement in portal hypertension and a decline in bleeding risk.[4]

Statins are widely used in clinical practice because of their exact and effective lipid-lowering effects.[5 6] The use of statins in patients with liver disease has long been limited by concerns of their potential hepatotoxicity, which have been raised by anecdotal evidence of increased liver enzymes following statin use or the possible trapping of lipids in the liver.[7] Some residual concern remains among primary care physicians in prescribing statins to patients with underlying liver disease because some of doctors still believe that these patients are at increased risk for hepatotoxicity.[8] However, a growing interest in the potential benefits of statins in patients with liver diseases has recently emerged.[7 9-12] Recent *in vivo* and *in vitro* experiments have gradually demonstrated that statins also exhibit anti-inflammatory[13], immune-modulating,[14] anti-proliferative,[15] and anti-oxidant[16] effects as well as improved endothelial function[17] and inhibit platelet aggregation[18] and certain Gram-negative bacteria.[19 20] These findings led to the development of statins in basic research of liver disease and laid a solid foundation for clinical practice.

We performed a systematic review and meta-analysis based on the most recent studies (randomized controlled trials (RCTs) and a cohort study) to evaluate the effects of statins in patients with cirrhosis and related complications, especially portal hypertension and variceal haemorrhage.

METHOD

Search Strategy

Pubmed, Embase, Cochrane Controlled Trial Registry and The Cochrane Library were searched up to February 2019 to identify all relevant articles on the effect of statins in liver cirrhosis and retrieve pertinent studies (Supplementary method). No language restrictions were imposed. An experienced medical librarian designed and implemented the search strategy. Electronic databases were searched using the following search terms: liver cirrhosis, ascites, portal hypertension, statin, Hydroxymethylglutaryl-CoA reductase inhibitors. The detailed search strategy is available in the "Supplementary method". Two reviewers (SZW

and CKH) independently assessed the titles and abstracts of the studies that met the eligibility, criteria for inclusion.

Data Abstraction

Two reviewers (SZW and CKH) independently extracted the data. The following data were collected from each study: year of publication, study design, inclusion criteria, exclusion criteria, aetiology of cirrhosis, total number of patients in each group, primary outcome reported, and CTP (Child–Turcotte–Pugh) class, and ascites. Any divergence between the reviewers was discussed with a third reviewer (XZ), and agreement was reached by consensus.

We used the Newcastle–Ottawa scale to determine the quality of the cohort studies, and the Cochrane tool was used to determine the risk of bias for RCTs.

Outcomes Assessed

Our primary outcome of interest was the association between statin use and the reduction in portal hypertension. The secondary outcomes of interest were the association between statin use and variceal bleeding. Several subgroup analyses were performed based on the quality of the studies, medication time, types of drugs in the control group, and types of statins. The adverse effects of statins were not included in the study due to insufficient information.

Quality of Evidence

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework to evaluate the quality of the evidence.[21] The GRADE approach for systematic reviews defines the quality of a body of evidence as the extent to which one can be confident that an estimate of an effect or association is close to the quantity of specific interest. The following factors were considered in determining the quality of evidence: risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

Statistical Analysis

The trials and patient characteristics are reported as the ,number of observations and proportions. The relative risk (RR) and 95% confidence interval (CI) that achieved a target hemodynamic response in each group was pooled using the DerSimonian and Laird random effects model.[22] Inter-trial heterogeneity was statistically assessed using the chi-square test and is expressed as the I^2 value, and I^2 values >50% were reflective of substantial heterogeneity.[23] A formal assessment of publication bias using the egger test was performed (Supplementary figure 1).

Patient and Public Involvement

This meta-analysis did not involve patients or the public

RESULTS

Search Results

A total of 2,676 potentially eligible references were retrieved in the literature search, and 2,624 were excluded based on the titles and abstracts. A further 44 articles, referred to as full articles, were deemed ineligible. Twelve studies were excluded because they did not clearly report the number of patients with improved in portal hypertension and variceal haemorrhage Eight studies with a total of 3,195 patients met our inclusion criteria and were included in our meta-analysis (7 RCTs and 1 observational study).[10 24-30] Six studies included patients who exhibited the target reduction in HVPG > 20% from baseline or < 12 mm-Hg in the statins group. Three studies included events of variceal bleeding in patients with cirrhosis. Figure 1 summarizes the search strategy.

Description of included studies

Table 1 shows the characteristics of these studies. These studies included 3,195 liver cirrhosis patients, of whom 902 patients were exposed to statins. One study was performed exclusively in patients with HCV mono-infection, and seven studies included cirrhosis with multiple underlying aetiologies. The medication time of statins was one month in three studies. However, statins were used for three months in three studies. Six studies provided the desired data as regarded decrease in HVPG (reduction > 20% or <12 mm-Hg).

The only observational study was of high quality, as exhibited by the high Newcastle-Ottawa quality score. Table 2 summarizes the methodological qualities of the observational study and RCTs. Figure 2 shows the methodological qualities of the RCTs

Table 3 summarizes the characteristics of the 3,195 patients included in the eight studies. Statins users and nonusers were generally male because the cirrhosis incidence in females was lower than that in males. Patients were mostly categorized as CTP A and B classes, 221 of 255 (87%) in two studies. No appreciable differences in the complications of cirrhosis, such as ascites or previous variceal bleeding, were observed between the two study groups across the eight studies.

Outcome evaluation

Improvement in Portal Hypertension

Six studies including 301 patients evaluated the improvement in portal hypertension in cirrhosis. Overall, a decrease in HVPG (> 20% from baseline or < 12 mm-Hg) was achieved with statins in 57 of 135 evaluable patients compared to 36 of 141 patients in the control group (RR, 1.91; 95% Cl, 1.04-3.52; I^2=63%). Three subgroup analyses were performed, based on the medication time, types of drug used in the control group, and types of statins. Subgroup analysis of the medication time of statins included three studies that used statins for one month (RR, 2.01; 95% Cl, 1.31-3.10; I^2=0%) and three studies that used statins for three months (RR, 3.76; 95% Cl, 0.36-39.77; I^2=75%) (Figure 3). The second subgroup analysis was based on the types of drugs used in the control group, including non-selective beta blockers (NSBB) and not explicitly reported drugs. The pooled RR for NSBB users was 1.42 (95% CI, 0.82-2.45; I^2=64%), and the pooled RR for the not explicitly reported drugs was 4.21 (95% CI, 1.52-11.70; I^2=0%) (Figure 4). The third subgroup analysis was based on the types of statins. Five studies used simvastatin (RR, 2.20; 95% Cl, 0.92-5.29; I^2=69%), and one study used atorvastatin (RR, 1.82; 95% Cl, 1.00-3.30) (Figure 5).

There was moderate persuasion supporting the use of statins associated with an improvement in portal hypertension based on the RCTs. However, the result was limited by the study size (109 events in 301 patients).

Risk of variceal haemorrhage

Three studies including 3,025 patients evaluated the association between statin use and the occurrence of variceal bleeding. Overall, 27 events occurred in 765 statin users, and 81 events were reported in 2152 nonusers. A subgroup analysis was performed based on the type of trial. Overall, the pooled RR for the risk of variceal haemorrhage was 0.64 (95% CI, 0.42-0.99; I^2=6%). The RR for the only one observational study was 0.47 (95% CI, 0.23-0.94). The pooled RR for the two RCTs studies was 0.88 (95% CI, 0.52-1.50; I^2=0%) (Figure 6).

DISCUSSION

This meta-analysis demonstrated the possible roles of statin use in patients with cirrhosis against the development of portal hypertension and the occurrence of variceal haemorrhage in 8 studies (7 RCTs and 1 cohort study). The availability of statins was proven to lead to the decrease in portal hypertension and variceal bleeding across all trials.

The summary RR between the numbers of HVPG reductions achieved in statin users and nonusers was 1.91 (95% Cl, 1.04-3.52; I^2=63%) in favour of statins. We performed three subgroup analyses because of the substantial heterogeneity. The subgroup analysis based on the medication time of statin use supported the improvement in portal pressure at the one-month assessment (RR, 2.01; 95% Cl, 1.31-3.10; I^2=0%). However, this effect was not statistically significant at the three-month assessment (RR, 3.76; 95% Cl, 0.36-39.77; I^2=75%). These results suggest that the effects of statins are not dose-dependent and lead to strong curative effects in patients who used statins for one month compared to patients with a longer duration of use. Several possible mechanisms may explain the biological plausibility of our findings. The hepatotoxicity of statins occurs via regulation of the P450 cytochrome in immune-mediated liver damage, which activates apoptosis and T cell-induced liver injury.[31 32] Previous clinical research[33-36] confirmed these observations, which offset the benefits of statins over a longer treatment period. No considerable differences were observed in subgroup analyses for the use of NSBB in the control group (RR, 1.42; 95% CI, 0.82-2.45; I^2=64%). We presume that improvements of portal hypertension by NSBB is the underlying mechanism. NSBB is clinically used to treat portal hypertension because of its efficacy in decreasing HVPG and variceal haemorrhage.[37-40] Therefore, the use of NSBB in the control group may lead to no significant difference between the statin user and nonuser groups. Different types of statins exhibit inconsistent pharmacological actions. Therefore, patients were stratified by the statin varieties. The pooled RR in a subset of patients who received simvastatin was 2.20(95% Cl, 0.92-5.29; I^2=69%), which indicates no improvement. Atorvastatin users exhibited a decrease in portal pressure (RR, 1.82; 95% Cl, 1.00-3.30). High quality evidence was included, but discrepancies, such as the medication time may have led to imprecision.

Events of variceal haemorrhage were satisfactorily reported in three studies. The effect of statins on variceal bleeding as a common cause of death in patients with portal hypertension was also investigated. The pooled RR was 0.64 (95% CI, 0.42-0.99; I^2=6%). However, the reduction in the pooled RR of the risk of variceal haemorrhage failed to reach statistical significance with statin use in two RCTs (RR, 0.88; 95% CI, 0.52-1.50; I^2=0%). Notably, the only observational study confirmed the superiority of statins in lowering the risk of variceal bleeding (RR, 0.47; 95% CI, 0.23-0.94). The characteristics of different types of experiments may be responsible for the inconsistency.

Statins have received increasing attention in clinical research in the field of various liver diseases including liver cirrhosis, hepatocellular carcinoma, fatty liver disease, viral hepatitis and other related liver

diseases, in recent years.[6] Studies have confirmed that statins are safe and effective for some patients with these liver diseases.[41] A population-based study[9] evaluated the effects of statins on reducing decompensation, mortality, and HCC in HBV, HCV, and alcohol-related cirrhosis. This study demonstrated that statins reduced decompensation (P<0.0001), mortality (P<0.0001), and the risk of HCC (P=0.009) in patients with cirrhosis, and this correlation was dose-dependent. The risk of decompensation in patients with cirrhosis caused by chronic HBV (RR, 0.39; 95% Cl, 0.25-0.62) or HCV infection (RR, 0.51; 95% Cl, 0.29-0.93) was lower in patients taking statins. The effect of statins on reducing the risk of cirrhosis decompensation was statistically significant in alcohol cirrhotic patients (RR, 0.69; 95% Cl, 0.45-1.07). In general, the use of statins reduced the decompensation rate of HBV, HCV and alcohol-related cirrhosis. Two recent studies[42 43] demonstrated that statins were safe in patients with NAFLD and exhibited beneficial effects decreasing steatosis and fibrosis and preventing disease progression. Multiple previous studies demonstrated the benefit of statins on liver systems. A randomized trial of patients with cirrhosis and significant portal hypertension observed that the nitric oxide levels in hepatic venous blood, as a key vasodilator mediating the hepatic vascular resistance,[44-46] were increased in the statins group compare to those in the control group. A decrease in portal hypertension was also observed in patients who received statins.[47] Marrone[48] studies have also confirmed that the use of statins in cirrhotic animals can reduce liver fibrosis and prevent further deterioration of cirrhosis by inhibiting the activation of hepatic stellate cell;. This may also be a potential mechanism for the efficacy of statins.

More research groups have begun to support the use of statin in some patients with chronic liver disease or cirrhosis based on these studies.[49 50] Some researchers believe that statins may also be able to be used as an adjuvant therapy in any chronic liver disease patients with indications for statins use to prevent decompensation or delay the progression of patients with decompensated cirrhosis.[51] However, this information was derived from retrospective cohort studies, and prospective studies are needed to confirm these beneficial effects.

This meta-analysis evaluated the role of statins in patients with cirrhosis as a decline in portal pressure and risk of variceal haemorrhage. We performed a comprehensive literature search that met the well-defined inclusion criteria. Eight studies were included, primarily consisting of RCTs. These studies were high quality studies as graded by the Cochrane tool for assessing risk of bias or the Newcastle–Ottawa scale. Several subgroup analyses were completed based on the characteristics of the studies to further ascertain the precision of results.

However, several limitations exist in our meta-analysis. In some of

the results, we have a large heterogeneity, which may be due to the inconsistency of the inclusion and exclusion criteria we included in the study. In addition, patients with various etiologies of cirrhosis were not researched separately because of insufficient information, which may explain the substantial heterogeneity. So we performed a subgroup analysis to try to eliminate this difference, significantly reducing heterogeneity in some subgroup analyses. Seven RCTs were included, but the number of patients enrolled was relatively fewer in the RCTs (471 patients). Although individual studies adjusted for various confounders (e.g., age, sex, CTP score, and MELD score), there are residual confounders that could not be completely adjusted remained. These situations may have affected the precision and credibility of our estimates. In two studies, the 0 event counts in the control group may be due to the fact that the placebo used in the control group is not a drug such as NSBB that has been proven to have a reduced portal pressure, leading to a wide 95% confidence intervals. The quality assessment of the RCT suggests that the quality of the two studies is acceptable, so we have no good reason to exclude these studies. The number of patients included in some studies is insufficient, so continuity corrections is not used, which may increase the risk of bias. Non-alcoholic fatty liver disease, as a metabolic disease, may exhibit closer relevance with lipid-lowering drug statins. Unfortunately, no eligible NAFLD research was included.

In conclusion, our analyses based on RCTs and an observational study indicated a beneficial effect of statins on reducing portal hypertension and variceal haemorrhage. However, the assessment can not serve as clinical guideline for the wide use of statins in cirrhosis with portal hypertension because of the limited quantity and quality of the included studies. Previous research reported the potential protective effects of statins against cirrhosis and HCC progression, and the potential benefits of statins may outweigh the theoretical risks. Notably, adverse events related to statins were rarely reported in studies. Large RCTs are required before statins are clinically used to treat patients with cirrhosis and complications.

licence statement

Contributors: SZW and CKH contributed equally to this study. SZW planned the study. SZW and CKH screened the literature and collected data. SZW, CKH and XZ conducted the meta-analysis and wrote the manuscript.

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Competing interests: None declared.

Data availability statement: The data used to support the findings of this study are available from the author upon request.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

Figure 2. Risk of bias assessed using the Cochrane risk of bias tool for RCTs

Figure 3. Forest plot to evaluate the role of statins in the reduction of portal hypertension using a subgroup analysis based on medication time of statins.

Figure 4. Forest plot to evaluate the role of statins in the reduction of portal hypertension using subgroup analysis based on the types of drugs in the control group.

Figure 5. Forest plot to evaluate the role of statins in the reduction of

portal hypertension using subgroup analysis based on types of statins.

Figure 6. Forest plot to evaluate the role of statins in the reduction of the risk of variceal haemorrhage using subgroup analysis based on types of statins.

Supplementary Figure 1. egger's test to identify publication bias. SND, standard normal deviation; PTH, portal hypertension; VH, variceal haemorrhage.

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Table 1. Characteristics of the included studies

Study, year	Design	Inclusion criteria	Exclusion criteria	Aetiology of cirrhosis	Groups	N	Outcomes of interest	Outcomes	
								Statins users(n)	Non-users (n)
Mohanty, 2016	Retrospective	HCV positive patients defined by ICD-9 codes Compensated cirrhosis	HIV or HBV coinfection Decompensation or HCC before or within 180 days after index date No laboratory results No follow-up Died within 180 days after index date Statin users with only one prescription fill or more than 365 days between first and second fill	HCV	Statins Nonusers	685 2062	Variceal hemorrhage	Variceal Hemorrhage:9	58
Abraldes, 2009	RCT	Age between 18 and 75 years, positive diagnosis of cirrhosis, and severe portal hypertension defined as HVPG of 12 mm Hg or greater	Pregnancy Cholestatic liver disease Severe liver failure, evaluated by the presence of a serum bilirubin level greater than 5 mg/dL, prothrombin rate less than 40% Hepatic encephalopathy grades II–IV Child–Pugh score of 12 or greater Serum creatinine level greater than 1.5 mg/dl Hepatocellular Carcinoma Portal vein thrombosis	Mixed	Statins Nonusers	28 27	Reduction in portal hypertension	Reduction in portal hypertension:9	3
Abraldes, 2016	RCT	Age between 18 and 80 years Previous diagnosis of liver cirrhosis Index variceal bleeding within the previous 5-10 days Plan to start standard treatment for the prevention of variceal rebleeding In woman documented absence of pregnancy and commitment to use adequate contraception if applicable	Pregnancy or lactation multifocal hepatocellular carcinoma or a single nodule > 5 cm in diameter. Creatinine > 2 mg/dl Child-Pugh score > 13 points Contraindication for statins Patients with HIV infection on protease inhibitors Pre-treatment with portosystemic shunt (surgical or percutaneous) Index bleeding due to gastric varices Complete portal vein thrombosis or portal vein cavernomatosis. Patients previously treated with the combination of endoscopic banding ligation and NSBB (before the index episode)	Mixed	Statins Nonusers	69 78	Variceal haemorrhage	variceal haemorrhage:14	18

			Patients previously treated with statins within one month of randomization.						
Alvarado , 2016	RCT	Cirrhosis, CSPH and high-risk oesophageal varices without previous bleeding	NR	Mixed	Statins Nonusers	43 44	Reduction in portal hypertension	Reduction in portal hypertension:16	8
Bishnu, 2018	RCT	Age: 18–60 years. Cirrhosis (diagnosed clinically, radiologically, or histopathologically). Portal hypertension (history of variceal bleed, ascites, splenomegaly, oesophageal varices on upper GI endoscopy, or history of having undergone EVL).	Child-Pugh-Turcott (CPT) class C. Hepatic encephalopathy grades II–IV. Hepatocellular carcinoma Portal vein thrombosis or cavernomatosis. Hepatic venous outflow tract obstruction Previous portosystemic shunt surgery Obstructive airway diseases Cardiac conduction abnormalities Peripheral vascular disease Congestive cardiac failure NYHA class II–IV Renal insufficiency (serum creatinine > 2 mg/dl) Previous episodes of rhabdomyolysis Hypersensitivity to HMG-CoA reductase inhibitors Previous treatment with HMG-CoA reductase inhibitor Participation in a concurring clinical trial Pregnancy or plan to conceive during study period	Mixed	Statins Nonusers	11 12	Reduction in portal hypertension Variceal haemorrhage	Reduction in portal hypertension:10 Variceal haemorrhage:4	6 5
Flores, 2014	RCT	Cirrhosis and portal hypertension detected using abdominal ultrasound with colour Doppler flowmetry or upper digestive endoscopy	NR	Mixed	Statins Nonusers	11 11	Reduction in portal hypertension	Reduction in portal hypertension:4	0
Pollo-	RCT	Age 18–75 years Diagnosis of cirrhosis with	Aminotransferases levels >3 times above the upper	Mixed	Statins	11	Reduction in	Reduction in	0

Flores 2015		portal hypertension detected using an abdominal ultrasound with colour Doppler and an upper digestive endoscopy showing gastroesophageal varices Both procedures were r performed within the previous six months	limit of normal (ULN) Recent (within the last 6 months) or current use of simvastatin Portal vein thrombosis, contrast medium allergy Hepatocellular carcinoma or any other malignancy reducing life expectancy Renal failure (creatinine level >1.5 mg/dL) Bleeding disorder (prothrombin activity test <30% or platelets count <35,000/mcL) or decompensated cirrhosis characterized by severe ascites or grade II or overt encephalopathy Patients with alcoholic cirrhosis were abstinent from alcohol consumption for at least one year		Nonusers	13	portal hypertension	portal hypertension:6	
Rajan, 2016	RCT	Cirrhotics with varices who had never bled	NR	Mixed	Statins Nonusers	44 46	Reduction in portal hypertension	Reduction in portal hypertension:22	25

ALT, Alanine aminotransferase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human Immunodeficiency virus; ICD-9, International Classification of Disease – 9; NR, Not reported.

Table 2. Quality assessment of the observational studies using the Newcastle–Ottawa Scale

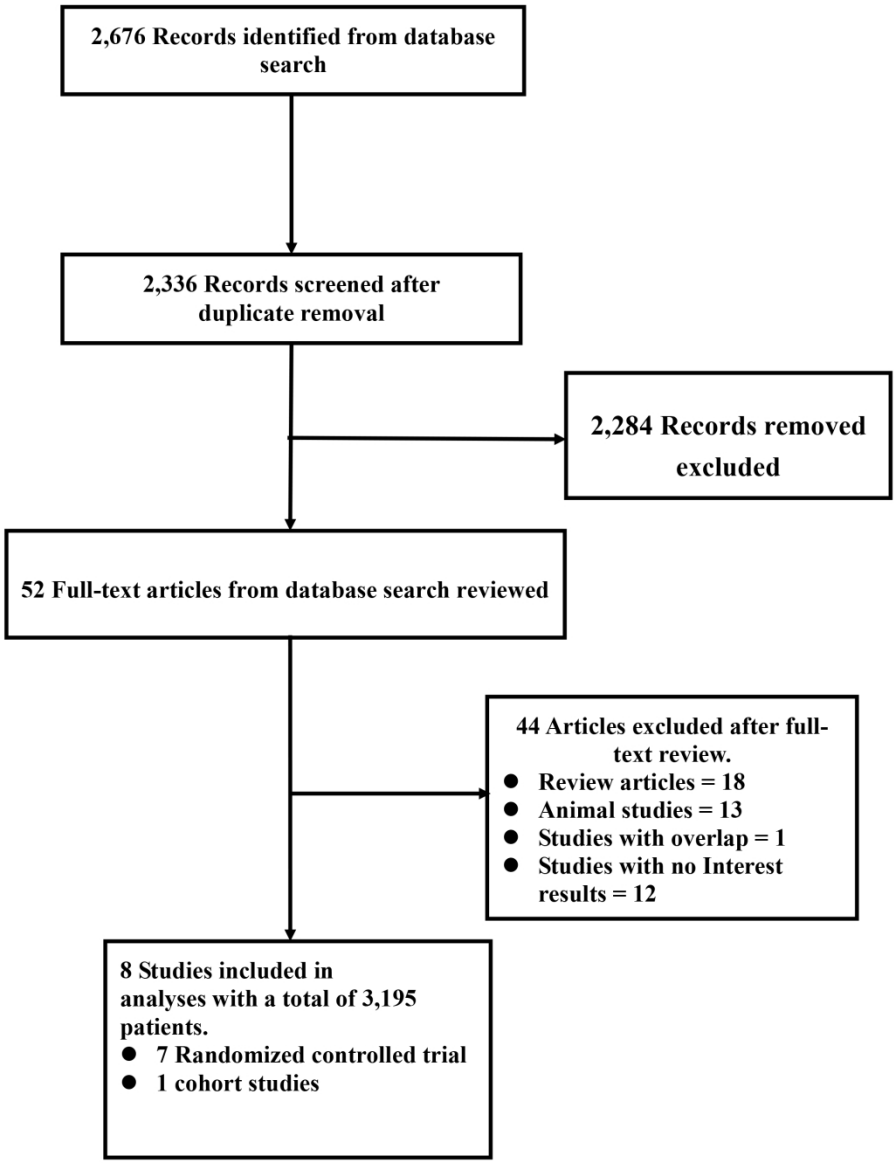
Studies	Selection				Comparability	Outcome			Quality
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at start	Adjustment for primary and secondary factors	Assessment by record linkage	Long enough follow-up for outcome to occur	Adequacy of follow-up	
Mohanty 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality

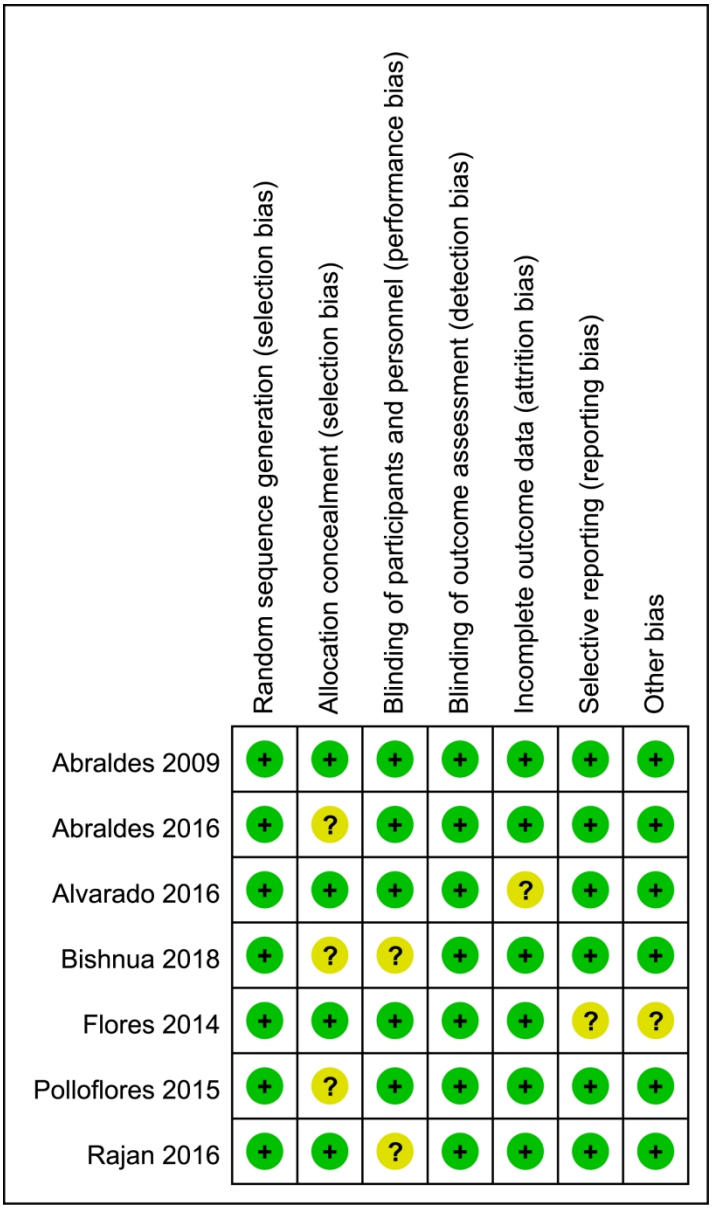
Quality assessment of the randomized controlled trials using the Cochrane tool for assessing the risk of bias

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Quality		
Abraldes 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality		
Abraldes, 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality		
Alvarado 2016	Low risk	Low risk	Low risk	unclear risk	Low risk	Low risk	High quality		
Bishnua , 2018	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High quality		
Flores 2014	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	High quality		
Polloflores 2015	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High quality		
Rajan 2016	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	High quality		

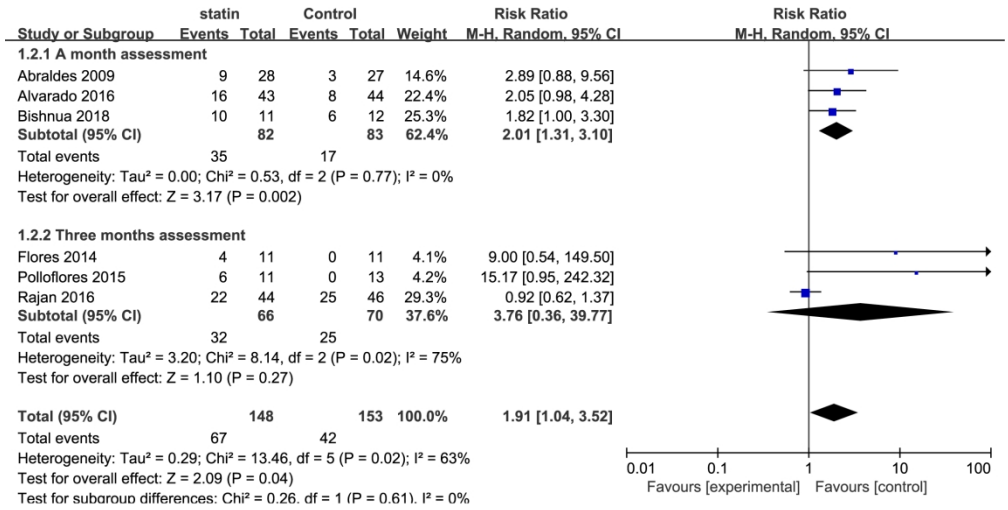
Table 3. Characteristics of participants in the included studies

	Treatment group	Patients N	Age Y	Males N	Viral/ Alcoholic Aetiology,N	Child-Pugh class A/B/ C, N	Ascites N	Previous variceal bleeding, N
Mohanty,2016	Statins Nonusers	685 2062	56 56	671 2021	685/0 2062/0	NR NR	NR NR	NR NR
Abraldes,2009	Statins Nonusers	28 27	58 56	17 21	NR NR	18/10/0 16/8/3	14 16	6 9
Abraldes,2016	Statins Nonusers	69 78	57 57	45 53	20/49 19/55	15/68/17 24/62/14	15 16	NR NR
Alvarado,2016	Statins Nonusers	43 44	56 54	31 35	NR NR	NR NR	NR NR	NR NR
Bishnu,2018	Statins Nonusers	11 12	44 47	9 12	0/4 1/6	NR NR	5 6	6 5
Flores,2014	Statins Nonusers	11 11	46 43	23 30	NR NR	NR NR	NR NR	NR NR
Pollo-Flores,2015	Statins Nonusers	11 13	57 59	6 7	NR NR	NR NR	2 3	5 3
Rajan,2016	Statins Nonusers	44 46	51 53	30 35	NR NR	NR NR	NR NR	NR NR


2,676 Records identified from database search
2,336 Records screened after duplicate removal
2,284 Records removed excluded
52 Full-text articles from database search reviewed
44 Articles excluded after full-text review.
Review articles = 18
Animal studies = 13
Studies with overlap = 1
Studies with no Interest results = 12
8 Studies included in analyses with a total of 3,195 patients.
7 Randomized controlled trial
1 cohort studies



156x265mm (300 x 300 DPI)



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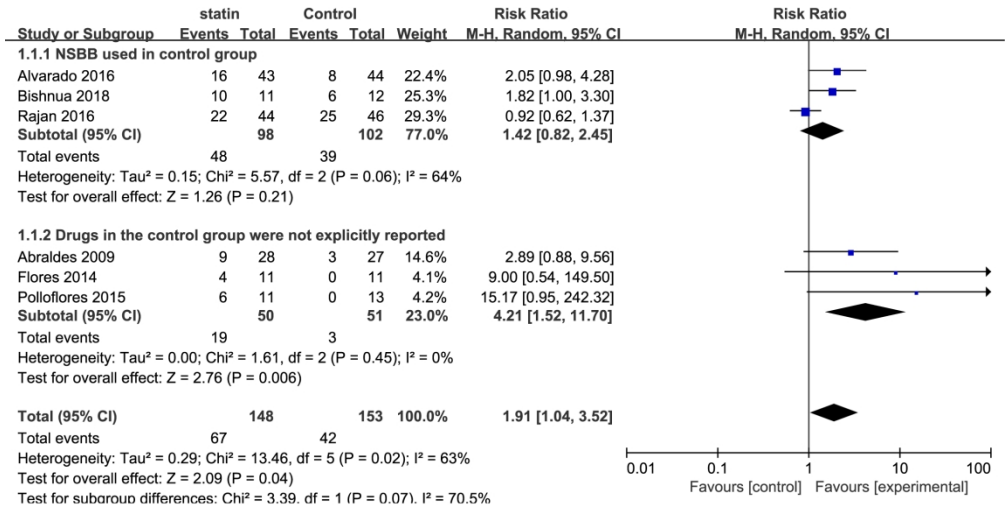

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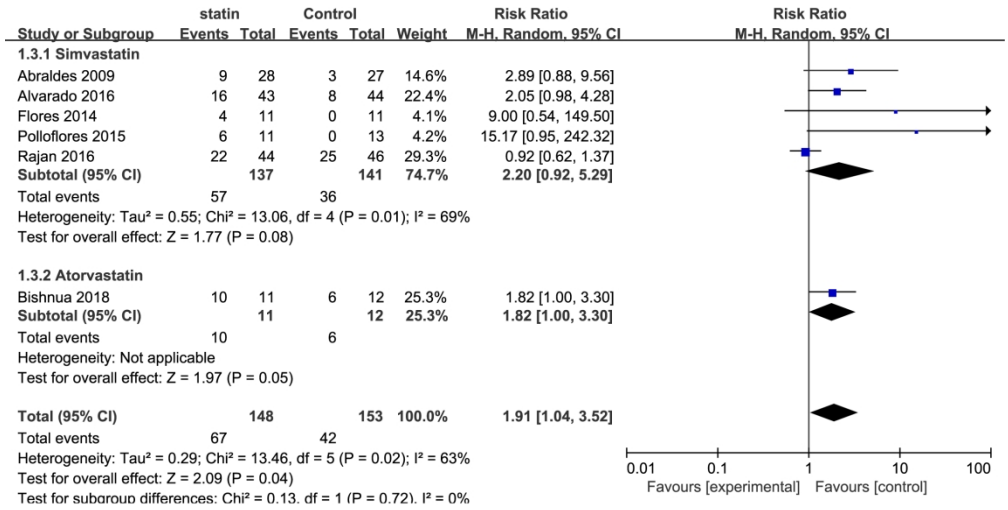

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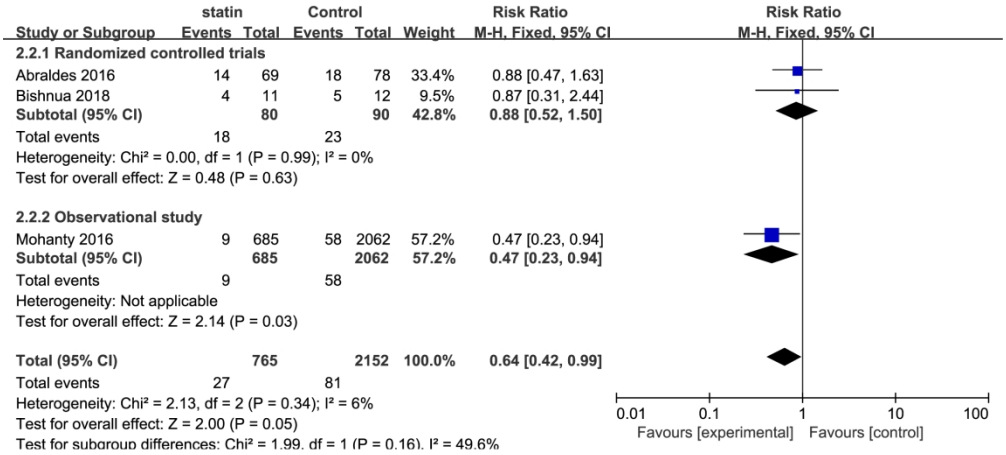

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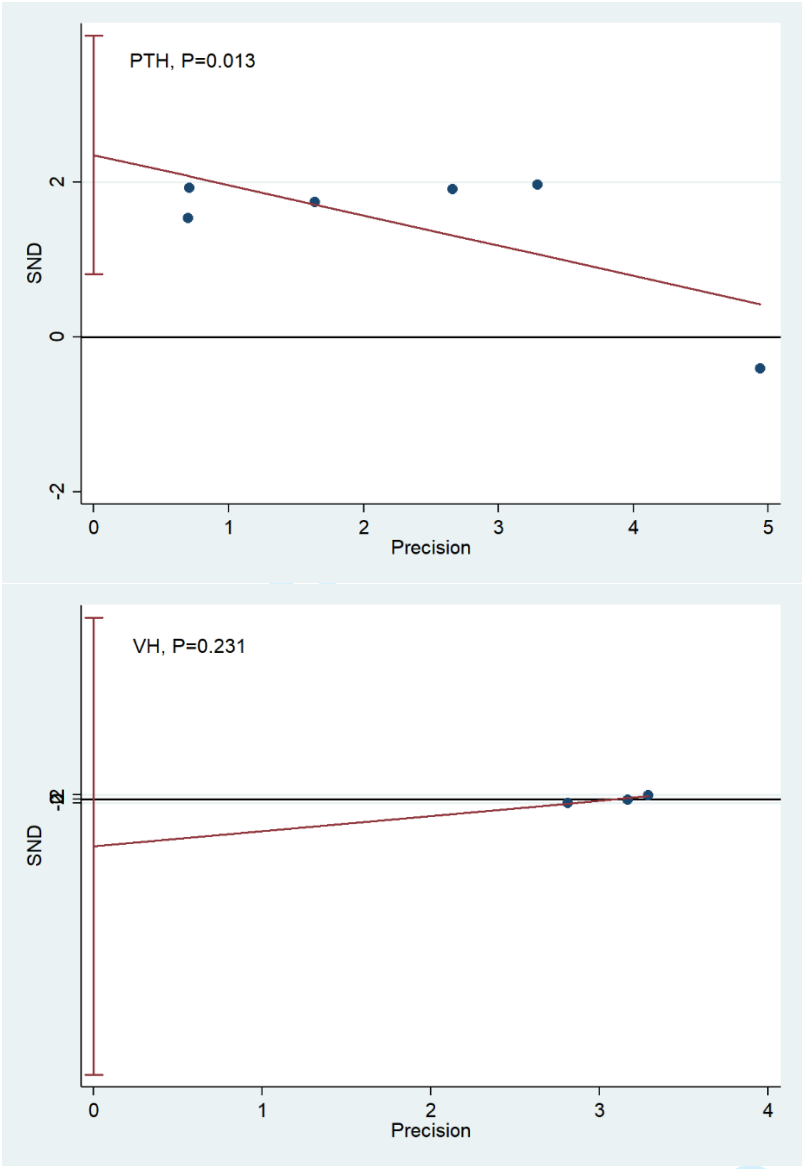

Supplementary Figure 1. egger's test to identify publication bias. SND, standard normal deviation; PTH, portal hypertension; VH, variceal haemorrhage.

Queries in pubmed

#4,"Search ((((Liver Cirrhosis[Mesh] OR liver cirrhosis OR Hypertension, Portal[Mesh] OR Ascites[Mesh] OR Liver Transplantation[Mesh] OR portal hypertension OR ascites OR liver transplant*)) OR (cirrhosis OR cirrhotic OR fibrosis OR fibrotic))) AND ((statin* OR monacolin OR Hydroxymethylglutaryl-CoA Reductase Inhibitors[Pharmacological Action] OR Hydroxymethylglutaryl-CoA Reductase Inhibitors[Mesh] OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Hydroxymethylglutaryl-CoA Reductase Inhibitor OR HMG coa reductase inhibitor OR HMG coa reductase inhibitors OR HMG-coa reductase inhibitor OR HMG-coa reductase inhibitors OR atorvastatin OR lipton OR lipitor OR CI 981 OR CI-981 OR simvastatin OR synvinolin OR zocor OR MK733 OR MK 733 OR MK-733 OR rosuvastatin OR ZD4522 OR crestor OR cerivastatin OR rivastatin OR Bay w 6228 OR bayol OR lipobay))) AND (((randomized controlled trial) OR (controlled clinical trial) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])))

#3,"Search ((randomized controlled trial) OR (controlled clinical trial) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]))

#2,"Search (statin* OR monacolin OR Hydroxymethylglutaryl-CoA Reductase Inhibitors[Pharmacological Action] OR Hydroxymethylglutaryl-CoA Reductase Inhibitors[Mesh] OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Hydroxymethylglutaryl-CoA Reductase Inhibitor OR HMG coa reductase inhibitor OR HMG coa reductase inhibitors OR HMG-coa reductase inhibitor OR HMG-coa reductase inhibitors OR atorvastatin OR lipton OR lipitor OR CI 981 OR CI-981 OR simvastatin OR synvinolin OR zocor OR MK733 OR MK 733 OR MK-733 OR rosuvastatin OR ZD4522 OR crestor OR cerivastatin OR rivastatin OR Bay w 6228 OR bayol OR lipobay)

#1,"Search ((Liver Cirrhosis[Mesh] OR liver cirrhosis OR Hypertension, Portal[Mesh] OR Ascites[Mesh] OR Liver Transplantation[Mesh] OR portal hypertension OR ascites OR liver transplant*)) OR (cirrhosis OR cirrhotic OR fibrosis OR fibrotic)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Search Strategy
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Description of included studies
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search Strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemtary Method
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Search Results
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data Abstraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Quality of Evidence
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Quality of Evidence
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Outcomes

PRISMA 2009 Checklist

			Assessed
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Statistical Analysis

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Data Abstraction
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Statistical Analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Search Results
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Description of included studies
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Description of included studies
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Outcome evaluation
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Outcome evaluation
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Data Abstraction
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Outcome evaluation
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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