

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030038
Article Type:	Research
Date Submitted by the Author:	27-Feb-2019
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
Keywords:	statin, portal hypertension, variceal haemorrhage, cirrhotic

SCHOLARONE™  
Manuscripts

# 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,<sup>1</sup> Chen-Kai Huang,<sup>1</sup> Xuan Zhu<sup>1</sup>

<sup>1</sup>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](mailto: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  $\geq 20\%$  of baseline or to  $\leq 12$  mmHg) and the risk of variceal haemorrhage. The relative risk (RR) with a 95% confidence interval (CI) 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;  $I^2=63\%$ ) in 6 RCTs. On subgroup analysis of studies that used statin for one month, the RR was 2.01 (95% CI, 1.31-3.10;  $I^2=0\%$ ); the pooled RR for studies that used statins for three months was 3.76 (95% CI, 0.36-39.77;  $I^2=75\%$ ); the pooled RR for studies that used NSBB in the control group was 1.42 (95% CI, 0.82-2.45;  $I^2=64\%$ ); the pooled RR for studies that used a drug that was not reported in the control group was 4.21 (95%

1  
2  
3 CI, 1.52-11.70; I2=0%); the pooled RR for studies that used simvastatin  
4 was 2.20 (95% CI, 0.92-5.29; I2=69%); RR for study using atorvastatin  
5 was 1.82 (95% CI, 1.00-3.30). For the risk of a variceal haemorrhage, the  
6 RR based on an observational study was 0.47 (95% CI, 0.23-0.94); in two  
7 randomized controlled trials, the pooled RR was 0.88 (95% CI, 0.52-  
8 1.50; I2=0%). Overall, the summed RR was 0.64 (95% CI, 0.42-0.99;  
9 I2=6%).

10  
11  
12 Conclusion: Statins may improve hypertension and decrease the risk of  
13 variceal haemorrhage according to our assessment. However, further and  
14 larger RCTs are needed to confirm this conclusion.  
15  
16

### 17 18 **Article summary**

19  
20 1) Cirrhosis is an increasing global health problem.

21  
22  
23 2) A growing interest in the potential benefits of statins in patients with  
24 liver diseases has recently emerged. Some studies have confirmed the roles  
25 of statin use in patients with cirrhosis against the development of portal  
26 hypertension and the occurrence of variceal haemorrhage.  
27

28  
29 3) Statins may improve portal hypertension and the risk of variceal  
30 haemorrhage through reducing HVPG in cirrhotic patients.  
31

32  
33 4) Large RCTs are needed to confirm statins beneficial effects in patients  
34 with liver diseases.  
35

36  
37 5) The mechanism of therapeutic effect of statin in liver disease should be  
38 be investigated in the future.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

## 50 **INTRODUCTION**

51  
52 Cirrhosis is increasingly prevalent worldwide, as a result of a variety  
53 of chronic liver diseases. Cirrhosis, including compensate and  
54 decompensate, was in the top 8 causes of death in the United States in 2010  
55 and led to more than 49,500 deaths.<sup>1</sup> The median survival of patients with  
56 compensated cirrhosis is >12 years, and patients with decompensated  
57 cirrhosis exhibit a median survival of <2 years.<sup>2</sup> Portal hypertension and  
58  
59  
60

oesophageal varices are common complications of cirrhosis, and these conditions develop into variceal haemorrhage, which produces a mortality of 10–15% per episode.<sup>3</sup> 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.<sup>4</sup>

Statins are widely used in clinical practice because of their exact and effective lipid-lowering effects.<sup>5 6</sup> 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.<sup>7</sup> 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.<sup>8</sup> However, a growing interest in the potential benefits of statins in patients with liver diseases has recently emerged.<sup>7 9-12</sup> Recent *in vivo* and *in vitro* experiments have gradually demonstrated that statins also exhibit anti-inflammatory<sup>13</sup>, immune-modulating,<sup>14</sup> anti-proliferative,<sup>15</sup> and anti-oxidant<sup>16</sup> effects as well as improved endothelial function<sup>17</sup> and inhibit platelet aggregation<sup>18</sup> and certain Gram-negative bacteria.<sup>19 20</sup> 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.

1  
2  
3 The following data were collected from each study: year of publication,  
4 study design, inclusion criteria, exclusion criteria, aetiology of cirrhosis,  
5 total number of patients in each group, primary outcome reported, and CTP  
6 (Child–Turcotte–Pugh) class, and ascites. Any divergence between the  
7 reviewers was discussed with a third reviewer (XZ), and agreement was  
8 reached by consensus.  
9

10  
11 We used the Newcastle–Ottawa scale to determine the quality of the  
12 cohort studies, and the Cochrane tool was used to determine the risk of bias  
13 for RCTs.  
14  
15

### 16 **Outcomes Assessed**

17  
18 Our primary outcome of interest was the association between statin  
19 use and the reduction in portal hypertension. The secondary outcomes of  
20 interest were the association between statin use and variceal bleeding.  
21 Several subgroup analyses were performed based on the quality of the  
22 studies, medication time, types of drugs in the control group, and types of  
23 statins.  
24  
25

### 26 **Quality of Evidence**

27  
28 We used the GRADE (Grading of Recommendations Assessment,  
29 Development, and Evaluation) framework to evaluate the quality of the  
30 evidence.<sup>21</sup> The GRADE approach for systematic reviews defines the  
31 quality of a body of evidence as the extent to which one can be confident  
32 that an estimate of an effect or association is close to the quantity of specific  
33 interest. The following factors were considered in determining the quality  
34 of evidence: risk of bias, directness of evidence, heterogeneity, precision  
35 of effect estimates, and risk of publication bias.  
36  
37  
38  
39

### 40 **Statistical Analysis**

41  
42 The trials and patient characteristics are reported as the number of  
43 observations and proportions. The relative risk (RR) and 95% confidence  
44 interval (CI) that achieved a target hemodynamic response in each group  
45 was pooled using the DerSimonian and Laird random effects model.<sup>22</sup>  
46 Inter-trial heterogeneity was statistically assessed using the chi-square test  
47 and is expressed as the  $I^2$  value, and  $I^2$  values  $>50\%$  were reflective of  
48 substantial heterogeneity.<sup>23</sup> A formal assessment of publication bias using  
49 the egger test was performed (Supplementary figure 1).  
50  
51  
52  
53

### 54 **Patient and Public Involvement**

55 This meta-analysis did not involve patients or the public  
56  
57

## 58 **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).<sup>10 24-30</sup> 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%



1  
2  
3 CI, 1.04-3.52;  $I^2=63\%$ ). Three subgroup analyses were performed, based  
4 on the medication time, types of drug used in the control group, and types  
5 of statins. Subgroup analysis of the medication time of statins included  
6 three studies that used statins for one month (RR, 2.01; 95% CI, 1.31-3.10;  
7  $I^2=0\%$ ) and three studies that used statins for three months (RR, 3.76; 95%  
8 CI, 0.36-39.77;  $I^2=75\%$ ) (Figure 3). The second subgroup analysis was  
9 based on the types of drugs used in the control group, including NSBB and  
10 not explicitly reported drugs. The pooled RR for NSBB users was 1.42 (95%  
11 CI, 0.82-2.45;  $I^2=64\%$ ), and the pooled RR for the not explicitly reported  
12 drugs was 4.21 (95% CI, 1.52-11.70;  $I^2=0\%$ ) (Figure 4). The third  
13 subgroup analysis was based on the types of statins. Five studies used  
14 simvastatin (RR, 2.20; 95% CI, 0.92-5.29;  $I^2=69\%$ ), and one study used  
15 atorvastatin (RR, 1.82; 95% CI, 1.00-3.30) (Figure 5).

16  
17  
18  
19  
20  
21 There was moderate persuasion supporting the use of statins associated  
22 with an improvement in portal hypertension based on the RCTs. However,  
23 the result was limited by the study size (109 events in 301 patients).

## 24 25 26 Risk of variceal haemorrhage

27  
28  
29 Three studies including 3,025 patients evaluated the association  
30 between statin use and the occurrence of variceal bleeding. Overall, 27  
31 events occurred in 765 statin users, and 81 events were reported in 2152  
32 nonusers. A subgroup analysis was performed based on the type of trial.  
33 Overall, the pooled RR for the risk of variceal haemorrhage was 0.64 (95%  
34 CI, 0.42-0.99;  $I^2=6\%$ ). The RR for the only one observational study was  
35 0.47 (95% CI, 0.23-0.94). The pooled RR for the two RCTs studies was  
36 0.88 (95% CI, 0.52-1.50;  $I^2=0\%$ ) (Figure 6).

## 40 41 DISCUSSION

42  
43  
44 This meta-analysis demonstrated the possible roles of statin use in  
45 patients with cirrhosis against the development of portal hypertension  
46 and the occurrence of variceal haemorrhage in 8 studies (7 RCTs and 1  
47 cohort study). The availability of statins was proven to lead to the  
48 decrease in portal hypertension and variceal bleeding across all trials.  
49 The summary RR between the numbers of HVPG reductions achieved in  
50 statin users and nonusers was 1.91 (95% CI, 1.04-3.52;  $I^2=63\%$ ) in  
51 favour of statins. We performed three subgroup analyses because of the  
52 substantial heterogeneity. The subgroup analysis based on the medication  
53 time of statin use supported the improvement in portal pressure at the  
54 one-month assessment (RR, 2.01; 95% CI, 1.31-3.10;  $I^2=0\%$ ). However,  
55 this effect was not statistically significant at the three-month assessment  
56 (RR, 3.76; 95% CI, 0.36-39.77;  $I^2=75\%$ ). These results suggest that the  
57  
58  
59  
60



1  
2  
3 effects of statins are not dose-dependent and lead to strong curative  
4 effects in patients who used statins for one month compared to patients  
5 with a longer duration of use. Several possible mechanisms may explain  
6 the biological plausibility of our findings. The hepatotoxicity of statins  
7 occurs via regulation of the P450 cytochrome in immune-mediated liver  
8 damage, which activates apoptosis and T cell-induced liver injury.<sup>31 32</sup>  
9 Previous clinical research<sup>33-36</sup> confirmed these observations, which offset  
10 the benefits of statins over a longer treatment period. No considerable  
11 differences were observed in subgroup analyses for the use of NSBB in  
12 the control group (RR, 1.42; 95% CI, 0.82-2.45; I<sup>2</sup>=64%). We presume  
13 that improvements of portal hypertension by NSBB is the underlying  
14 mechanism. NSBB is clinically used to treat portal hypertension because  
15 of its efficacy in decreasing HVPG and variceal haemorrhage.<sup>37-40</sup>  
16 Therefore, the use of NSBB in the control group may lead to no  
17 significant difference between the statin user and nonuser groups.  
18 Different types of statins exhibit inconsistent pharmacological actions.  
19 Therefore, patients were stratified by the statin varieties. The pooled RR  
20 in a subset of patients who received simvastatin was 2.20(95% CI, 0.92-  
21 5.29; I<sup>2</sup>=69%), which indicates no improvement. Atorvastatin users  
22 exhibited a decrease in portal pressure (RR, 1.82; 95% CI, 1.00-3.30).  
23 High quality evidence was included, but discrepancies, such as the  
24 medication time may have led to imprecision.

25  
26 Events of variceal haemorrhage were satisfactorily reported in three  
27 studies. The effect of statins on variceal bleeding as a common cause of  
28 death in patients with portal hypertension was also investigated. The  
29 pooled RR was 0.64 (95% CI, 0.42-0.99; I<sup>2</sup>=6%). However, the reduction  
30 in the pooled RR of the risk of variceal haemorrhage failed to reach  
31 statistical significance with statin use in two RCTs (RR, 0.88; 95% CI,  
32 0.52-1.50; I<sup>2</sup>=0%). Notably, the only observational study confirmed the  
33 superiority of statins in lowering the risk of variceal bleeding (RR, 0.47;  
34 95% CI, 0.23-0.94). The characteristics of different types of experiments  
35 may be responsible for the inconsistency.

36  
37 Statins have received increasing attention in clinical research in the  
38 field of various liver diseases including liver cirrhosis, hepatocellular  
39 carcinoma, fatty liver disease, viral hepatitis and other related liver  
40 diseases, in recent years.<sup>6</sup> Studies have confirmed that statins are safe and  
41 effective for some patients with these liver diseases.<sup>41</sup> A population-based  
42 study<sup>9</sup> evaluated the effects of statins on reducing decompensation,  
43 mortality, and HCC in HBV, HCV, and alcohol-related cirrhosis. This  
44 study demonstrated that statins reduced decompensation (P<0.0001),  
45 mortality (P<0.0001), and the risk of HCC (P=0.009) in patients with  
46 cirrhosis, and this correlation was dose-dependent. The risk of  
47 decompensation in patients with cirrhosis caused by chronic HBV (RR,  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

0.39; 95% CI, 0.25-0.62) or HCV infection (RR, 0.51; 95% CI, 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% CI, 0.45-1.07). In general, the use of statins reduced the decompensation rate of HBV, HCV and alcohol-related cirrhosis. Two recent studies<sup>42 43</sup> 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,<sup>44-46</sup> 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.<sup>47</sup>

More research groups have begun to support the use of statin in some patients with chronic liver disease or cirrhosis based on these studies.<sup>48 49</sup> 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.<sup>50</sup> 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

1  
2  
3 study indicated a beneficial effect of statins on reducing portal  
4 hypertension and variceal haemorrhage. However, the assessment can not  
5 serve as clinical guideline for the wide use of statins in cirrhosis with portal  
6 hypertension because of the limited quantity and quality of the included  
7 studies. Previous research reported the potential protective effects of  
8 statins against cirrhosis and HCC progression, and the potential benefits of  
9 statins may outweigh the theoretical risks. Notably, adverse events related  
10 to statins were rarely reported in studies. Large RCTs are required before  
11 statins are clinically used to treat patients with cirrhosis and complications.  
12  
13  
14  
15  
16  
17  
18  
19

### 20 **licence statement**

21  
22 The Submitting Author accepts and understands that any supply made  
23 under these terms is made by BMJ to the Submitting Author unless you are  
24 acting as an employee on behalf of your employer or a postgraduate  
25 student of an affiliated institution which is paying any applicable article  
26 publishing charge (“APC”) for Open Access articles. Where the  
27 Submitting Author wishes to make the Work available on an Open Access  
28 basis (and intends to pay the relevant APC), the terms of reuse of such  
29 Open Access shall be governed by a Creative Commons licence – details  
30 of these licences and which Creative Commons licence will apply to this  
31 Work are set out in our licence referred to above.  
32  
33  
34  
35  
36  
37

38 **Contributors** SZW planned the study. SZW and CKH screened the  
39 literature and collected data. SZW, CKH and XZ conducted the meta-  
40 analysis and wrote the manuscript.  
41  
42

43 **Funding** This research was supported by the National Natural Science  
44 Foundation of China (grant number 81660110).  
45  
46

47 **Competing interests** None declared  
48  
49

50 **Acknowledgement** Thanks for the economic support from the National  
51 Natural Science Foundation of China  
52  
53  
54  
55  
56  
57

58 **Figure 1. PRISMA (Preferred Reporting Items for Systematic**  
59 **Reviews and Meta-Analyses) flowchart.**  
60

1  
2  
3  
4  
5 **Figure 2. Risk of bias assessed using the Cochrane risk of bias tool for**  
6 **RCTs**  
7

8 **Figure 3. Forest plot to evaluate the role of statins in the reduction of**  
9 **portal hypertension using a subgroup analysis based on medication**  
10 **time of statins.**  
11  
12

13  
14 **Figure 4. Forest plot to evaluate the role of statins in the reduction of**  
15 **portal hypertension using subgroup analysis based on the types of**  
16 **drugs in the control group.**  
17  
18

19 **Figure 5. Forest plot to evaluate the role of statins in the reduction of**  
20 **portal hypertension using subgroup analysis based on types of statins.**  
21  
22

23 **Figure 6. Forest plot to evaluate the role of statins in the reduction of**  
24 **the risk of variceal haemorrhage using subgroup analysis based on**  
25 **types of statins.**  
26  
27

28  
29 **Supplementary Figure 1. egger's test to identify publication bias. SND,**  
30 **standard normal deviation; PTH, portal hypertension; VH, variceal**  
31 **haemorrhage.**  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *Jama* 2013;310(6):591-608. doi: 10.1001/jama.2013.13805 [published Online First: 2013/07/12]
2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;44(1):217-31. doi: 10.1016/j.jhep.2005.10.013
3. D'Amico G, Luca A. Natural history. Clinical-haemodynamic correlations. Prediction of the risk of bleeding. *Bailliere's clinical gastroenterology* 1997;11(2):243-56. [published Online First: 1997/06/01]
4. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007;133(2):481-8. doi: 10.1053/j.gastro.2007.05.024 [published Online First: 2007/08/08]
5. Sirtori CR. The pharmacology of statins. *Pharmacol Res* 2014;88:3-11. doi: 10.1016/j.phrs.2014.03.002 [published Online First: 2014/03/25]
6. Pose E, Trebicka J, Mookerjee RP, et al. Statins: old drugs as new therapy for liver diseases? *J Hepatol* 2018 doi: 10.1016/j.jhep.2018.07.019 [published Online First: 2018/08/04]
7. Tsochatzis EA, Bosch J. Statins in cirrhosis-Ready for prime time. *Hepatology (Baltimore, Md)* 2017;66(3):697-99. doi: 10.1002/hep.29277 [published Online First: 2017/05/26]
8. Moctezuma-Velazquez C, Abraldes JG, Montano-Loza AJ. The Use of Statins in Patients With Chronic Liver Disease and Cirrhosis. *Curr Treat Options Gastroenterol* 2018;16(2):226-40. doi: 10.1007/s11938-018-0180-4 [published Online First: 2018/03/25]
9. Chang FM, Wang YP, Lang HC, et al. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: A population-based study. *Hepatology (Baltimore, Md)* 2017;66(3):896-907. doi: 10.1002/hep.29172 [published Online First: 2017/03/21]
10. Abraldes JG, Villanueva C, Aracil C, et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis. *Gastroenterology* 2016;150(5):1160-70.e3. doi: 10.1053/j.gastro.2016.01.004 [published Online First: 2016/01/18]
11. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018;39(27):2526-39. doi: 10.1093/eurheartj/ehy182 [published Online First: 2018/05/03]
12. Shin JY, Azoulay L, Filion KB. Statin Use in Patients With Hepatitis C-related Cirrhosis: True Benefit or Immortal Time Bias? *Gastroenterology* 2016;151(2):373. doi: 10.1053/j.gastro.2015.11.055 [published Online First: 2016/07/05]
13. Chang CH, Hsu YM, Chen YC, et al. Anti-inflammatory effects of hydrophilic and lipophilic statins with hyaluronic acid against LPS-induced inflammation in porcine articular chondrocytes. *J Orthop Res* 2014;32(4):557-65. doi: 10.1002/jor.22536 [published Online First: 2013/12/05]
14. Kolawole EM, McLeod JJ, Ndaw V, et al. Fluvastatin Suppresses Mast Cell and Basophil IgE Responses: Genotype-Dependent Effects. *J Immunol* 2016;196(4):1461-70. doi: 10.4049/jimmunol.1501932 [published Online First: 2016/01/17]
15. Feldt M, Bjarnadottir O, Kimbung S, et al. Statin-induced anti-proliferative effects via cyclin D1 and p27 in a window-of-opportunity breast cancer trial. *J Transl Med* 2015;13:133. doi: 10.1186/s12967-015-0486-0 [published Online First: 2015/05/01]
16. Ramma W, Ahmed A. Therapeutic potential of statins and the induction of heme oxygenase-1 in preeclampsia. *J Reprod Immunol* 2014;101-102:153-60. doi: 10.1016/j.jri.2013.12.120 [published Online First: 2014/02/08]
17. Oikonomou E, Siasos G, Zaromitidou M, et al. Atorvastatin treatment improves endothelial function through endothelial progenitor cells mobilization in ischemic heart failure patients. *Atherosclerosis* 2015;238(2):159-64. doi: 10.1016/j.atherosclerosis.2014.12.014 [published Online First: 2014/12/20]
18. Camargo LM, Franca CN, Izar MC, et al. Effects of simvastatin/ezetimibe on microparticles, endothelial progenitor cells and platelet aggregation in subjects with coronary heart



- disease under antiplatelet therapy. *Braz J Med Biol Res* 2014;47(5):432-7. [published Online First: 2014/04/25]
19. Mehl A, Harthug S, Lydersen S, et al. Prior statin use and 90-day mortality in Gram-negative and Gram-positive bloodstream infection: a prospective observational study. *Eur J Clin Microbiol Infect Dis* 2015;34(3):609-17. doi: 10.1007/s10096-014-2269-6 [published Online First: 2014/11/07]
20. de Paula TP, Santos PC, Arifa R, et al. Treatment with Atorvastatin Provides Additional Benefits to Imipenem in a Model of Gram-Negative Pneumonia Induced by *Klebsiella pneumoniae* in Mice. *Antimicrob Agents Chemother* 2018;62(5) doi: 10.1128/aac.00764-17 [published Online First: 2018/02/22]
21. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of clinical epidemiology* 2013;66(2):151-7. doi: 10.1016/j.jclinepi.2012.01.006 [published Online First: 2012/05/01]
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88. [published Online First: 1986/09/01]
23. Higgins JP, Thompson SG, Deeks JJ. Measuring inconsistency in metaanalyses *BMJ* 2003;327:557-60.
24. Mohanty A, Tate JP, Garcia-Tsao G. Statins Are Associated With a Decreased Risk of Decompensation and Death in Veterans With Hepatitis C-Related Compensated Cirrhosis. *Gastroenterology* 2016;150(2):430-40.e1. doi: 10.1053/j.gastro.2015.10.007 [published Online First: 2015/10/21]
25. Abraldes JG, Albillos A, Banares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009;136(5):1651-8. doi: 10.1053/j.gastro.2009.01.043 [published Online First: 2009/02/12]
26. Alvarado-Tapias E, Ardèvol A, Pavel O, et al. Hemodynamic effects of carvedilol plus simvastatin in cirrhosis with portal hypertension and no-response to  $\beta$ -blockers: A double-blind randomized trial. *Hepatology (Baltimore, Md)* 2016;64(1):74A.
27. Bishnu S, Ahammed SKM, Sarkar A, et al. Effects of atorvastatin on portal hemodynamics and clinical outcomes in patients with cirrhosis with portal hypertension: A proof-of-concept study. *European Journal of Gastroenterology and Hepatology* 2018;30(1):54-59. doi: 10.1097/MEG.0000000000001006
28. Flores PP, Rezende GF, Cassano U, et al. Effect of simvastatin in portal hypertension. *Hepatology (Baltimore, Md)* 2014;60:1191A. doi: 10.1002/hep.27536
29. Pollo-Flores P, Soldan M, Santos UC, et al. Three months of simvastatin therapy vs. placebo for severe portal hypertension in cirrhosis: A randomized controlled trial. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015;47(11):957-63. doi: 10.1016/j.dld.2015.07.156 [published Online First: 2015/09/01]
30. Rajan V, Choudhary A, Jindal A, et al. Addition of simvastatin to carvedilol does not improve hemodynamic response in cirrhotics with varices without prior bleed: Preliminary results of an open label RCT. *Hepatology (Baltimore, Md)* 2016;64(6):1134A-35A.
31. Bhardwaj SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. *Clinics in liver disease* 2007;11(3):597-613, vii. doi: 10.1016/j.cld.2007.06.010 [published Online First: 2007/08/29]
32. Kubota T, Fujisaki K, Itoh Y, et al. Apoptotic injury in cultured human hepatocytes induced by HMG-CoA reductase inhibitors. *Biochemical pharmacology* 2004;67(12):2175-86. doi: 10.1016/j.bcp.2004.02.037 [published Online First: 2004/05/28]
33. Ballare M, Campanini M, Airoidi G, et al. Hepatotoxicity of hydroxy-methyl-glutaryl-coenzyme A reductase inhibitors. *Minerva gastroenterologica e dietologica* 1992;38(1):41-4. [published Online First: 1992/01/01]
34. Heuer T, Gerards H, Pauw M, et al. [Toxic liver damage caused by HMG-CoA reductase inhibitor]. *Medizinische Klinik (Munich, Germany : 1983)* 2000;95(11):642-4. [published Online First: 2001/01/06]
35. Koornstra JJ, Ottervanger JP, Fehmers MC, et al. [Clinically manifest liver lesions during use of simvastatin]. *Nederlands tijdschrift voor geneeskunde* 1996;140(15):846-8. [published Online First: 1996/04/13]
36. Black DM, Bakker-Arkema RG, Nawrocki JW. An overview of the clinical safety profile of



- atorvastatin (lipitor), a new HMG-CoA reductase inhibitor. *Archives of internal medicine* 1998;158(6):577-84. [published Online First: 1998/04/01]
37. Lebrech D, Poynard T, Bernuau J, et al. A randomised controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. *Drugs* 1989;37 Suppl 2:30-4; discussion 47. [published Online First: 1989/01/01]
38. Hillon P, Lebrech D, Munoz C, et al. Comparison of the effects of a cardioselective and a nonselective beta-blocker on portal hypertension in patients with cirrhosis. *Hepatology (Baltimore, Md)* 1982;2(5):528-31. [published Online First: 1982/09/01]
39. Aramaki T, Sekiyama T, Katsuta Y, et al. Long-term haemodynamic effects of a 4-week regimen of nipradilol, a new beta-blocker with nitrovasodilating properties, in patients with portal hypertension due to cirrhosis. A comparative study with propranolol. *J Hepatol* 1992;15(1-2):48-53. [published Online First: 1992/05/01]
40. Gatta A, Sacerdoti D, Merkel C, et al. Use of a nonselective beta-blocker, nadolol, in the treatment of portal hypertension in cirrhotics. *International journal of clinical pharmacology research* 1985;5(6):413-8. [published Online First: 1985/01/01]
41. Pastori D, Polimeni L, Baratta F, et al. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015;47(1):4-11. doi: 10.1016/j.dld.2014.07.170 [published Online First: 2014/09/17]
42. Dongiovanni P, Petta S, Mannisto V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol* 2015;63(3):705-12. doi: 10.1016/j.jhep.2015.05.006 [published Online First: 2015/05/20]
43. Nascimbeni F, Aron-Wisnewsky J, Pais R, et al. Statins, antidiabetic medications and liver histology in patients with diabetes with non-alcoholic fatty liver disease. *BMJ open gastroenterology* 2016;3(1):e000075. doi: 10.1136/bmjgast-2015-000075 [published Online First: 2016/04/26]
44. Gupta TK, Toruner M, Chung MK, et al. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology (Baltimore, Md)* 1998;28(4):926-31. doi: 10.1002/hep.510280405 [published Online First: 1998/10/02]
45. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. *Gastroenterology* 1998;114(2):344-51. [published Online First: 1998/02/07]
46. Shah V, Toruner M, Haddad F, et al. Impaired endothelial nitric oxide synthase activity associated with enhanced caveolin binding in experimental cirrhosis in the rat. *Gastroenterology* 1999;117(5):1222-8. [published Online First: 1999/10/27]
47. Zafra C, Abraldes JG, Turnes J, et al. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. *Gastroenterology* 2004;126(3):749-55. [published Online First: 2004/02/28]
48. Lin CY. Statins and risk of decompensation in hepatitis B virus-related and hepatitis C virus-related cirrhosis: Methodological issues. *Hepatology (Baltimore, Md)* 2018;67(3):1174. doi: 10.1002/hep.29687 [published Online First: 2017/11/25]
49. Kim G, Jang SY, Nam CM, et al. Statin use and the risk of hepatocellular carcinoma in patients at high risk: A nationwide nested case-control study. *J Hepatol* 2018;68(3):476-84. doi: 10.1016/j.jhep.2017.10.018 [published Online First: 2017/11/07]
50. Magan-Fernandez A, Rizzo M, Montalto G, et al. Statins in liver disease: not only prevention of cardiovascular events. *Expert review of gastroenterology & hepatology* 2018;12(8):743-44. doi: 10.1080/17474124.2018.1477588 [published Online First: 2018/05/18]

Study, year	Design	Inclusion criteria	Exclusion criteria	Aetiology of cirrhotics	Groups	N	Outcomes of interest	Outcomes	
								Statin users(n)	Non-users (n)
1 2 3 4 5 6 7 8 9 10 11	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
12 13 14 15 16 17 18 19 20	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
21 22 23 24 25 26 27 28 29 30 31	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

32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

1  
2  
3  
4

5			Patients previously treated with statins within one month of randomization.							
6										
7	Alvarado ,	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
8	2016									
9										
10	Bishnu,	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-Turcotte (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
11	2018									
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										
25										
26	Flores,	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
27	2014									
28										
29										
30										
31										
32										
33										
34										
35										
36										
37										
38	Bollo-	RCT	Age 18–75 years Diagnosis of cirrhosis with	Aminotransferases levels >3 times above the upper	Mixed	Statins	11	Reduction in	Reduction in	0

39  
40  
41  
42  
43  
44  
45  
46

1  
2  
3  
4

<p>5Flores 62015</p>		<p>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</p>	<p>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 &gt;1.5 mg/dL) Bleeding disorder (prothrombin activity test &lt;30% or platelets count &lt;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</p>		<p>Nonusers</p>	<p>13</p>	<p>portal hypertension</p>	<p>portal hypertension:6</p>	
<p>16Rajan, 172016</p>	<p>RCT</p>	<p>Cirrhotics with varices who had never bled</p>	<p>NR</p>	<p>Mixed</p>	<p>Statins Nonusers</p>	<p>44 46</p>	<p>Reduction in portal hypertension</p>	<p>Reduction in portal hypertension:2 2</p>	<p>25</p>

18  
19  
20 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.

21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

**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**

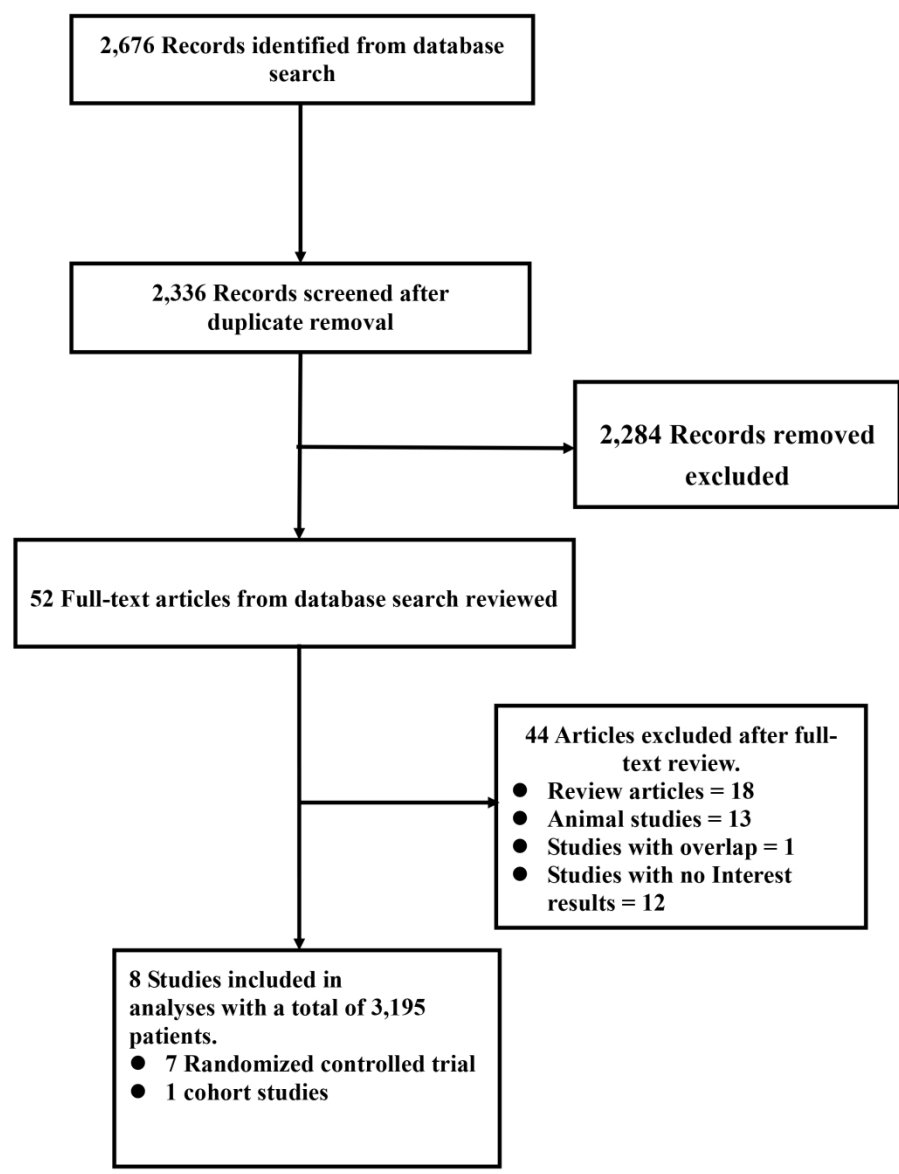
	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Quality		
Abraldes 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality		
Abraldes, 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality		
Alvarado 2016	Low risk	Low risk	Low 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
<b>Mohanty,2016</b>	Statins Nonusers	685 2062	56 56	671 2021	685/0 2062/0	NR NR	NR NR	NR NR
<b>Abraldes,2009</b>	Statins Nonusers	28 27	58 56	17 21	NR NR	18/10/0 16/8/3	14 16	6 9
<b>Abraldes,2016</b>	Statins Nonusers	69 78	57 57	45 53	20/49 19/55	15/68/17 24/62/14	15 16	NR NR
<b>Alvarado,2016</b>	Statins Nonusers	43 44	56 54	31 35	NR NR	NR NR	NR NR	NR NR
<b>Bishnu,2018</b>	Statins Nonusers	11 12	44 47	9 12	0/4 1/6	NR NR	5 6	6 5
<b>Flores,2014</b>	Statins Nonusers	11 11	46 43	23 30	NR NR	NR NR	NR NR	NR NR
<b>Pollo-Flores,2015</b>	Statins Nonusers	11 13	57 59	6 7	NR NR	NR NR	2 3	5 3
<b>Rajan,2016</b>	Statins Nonusers	44 46	51 53	30 35	NR NR	NR NR	NR NR	NR NR



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

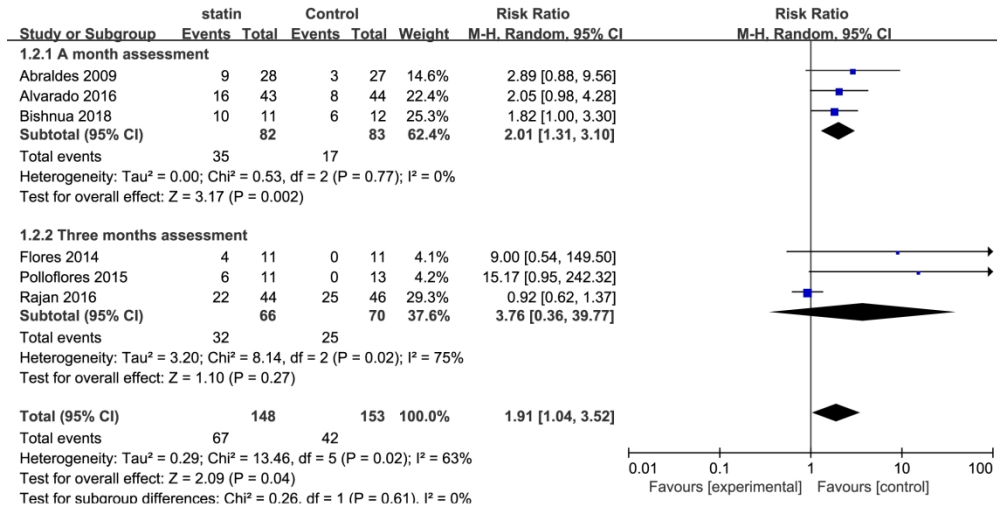


1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

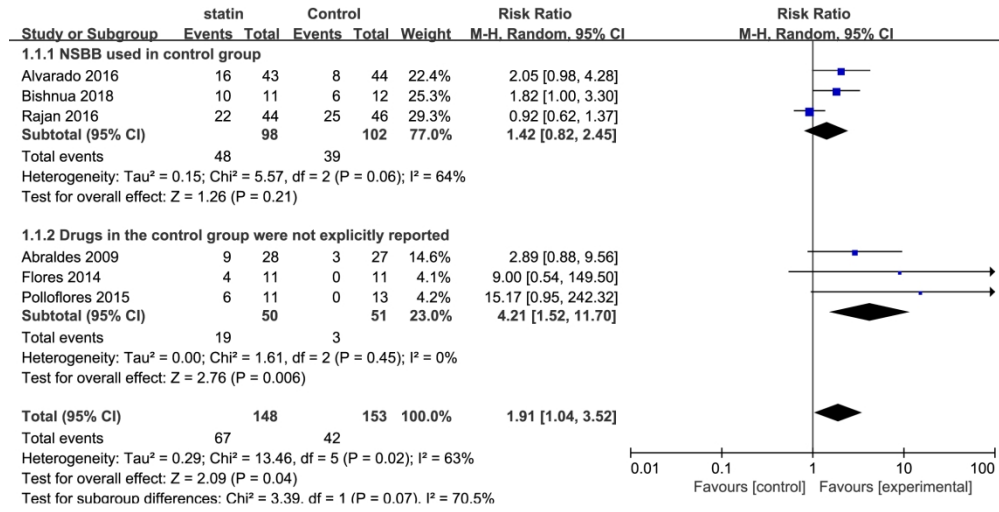
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abraldes 2009	+	+	+	+	+	+	+
Abraldes 2016	+	?	+	+	+	+	+
Alvarado 2016	+	+	+	+	?	+	+
Bishnua 2018	+	?	?	+	+	+	+
Flores 2014	+	+	+	+	+	?	?
Polloflores 2015	+	?	+	+	+	+	+
Rajan 2016	+	+	?	+	+	+	+

156x265mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

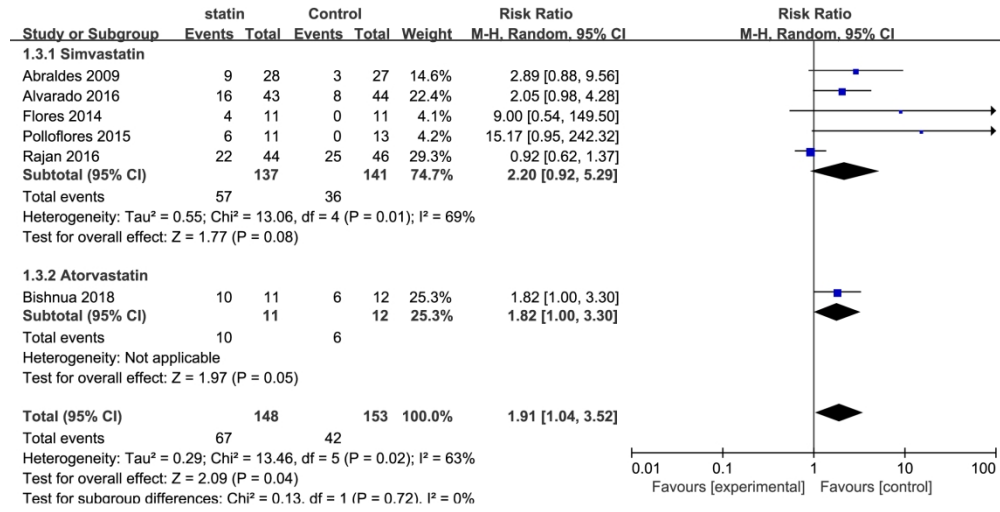


195x99mm (300 x 300 DPI)



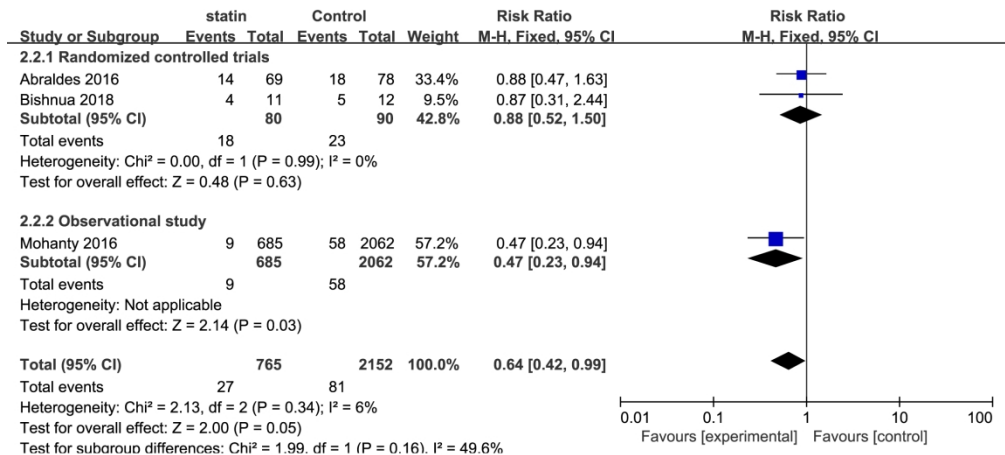
195x99mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



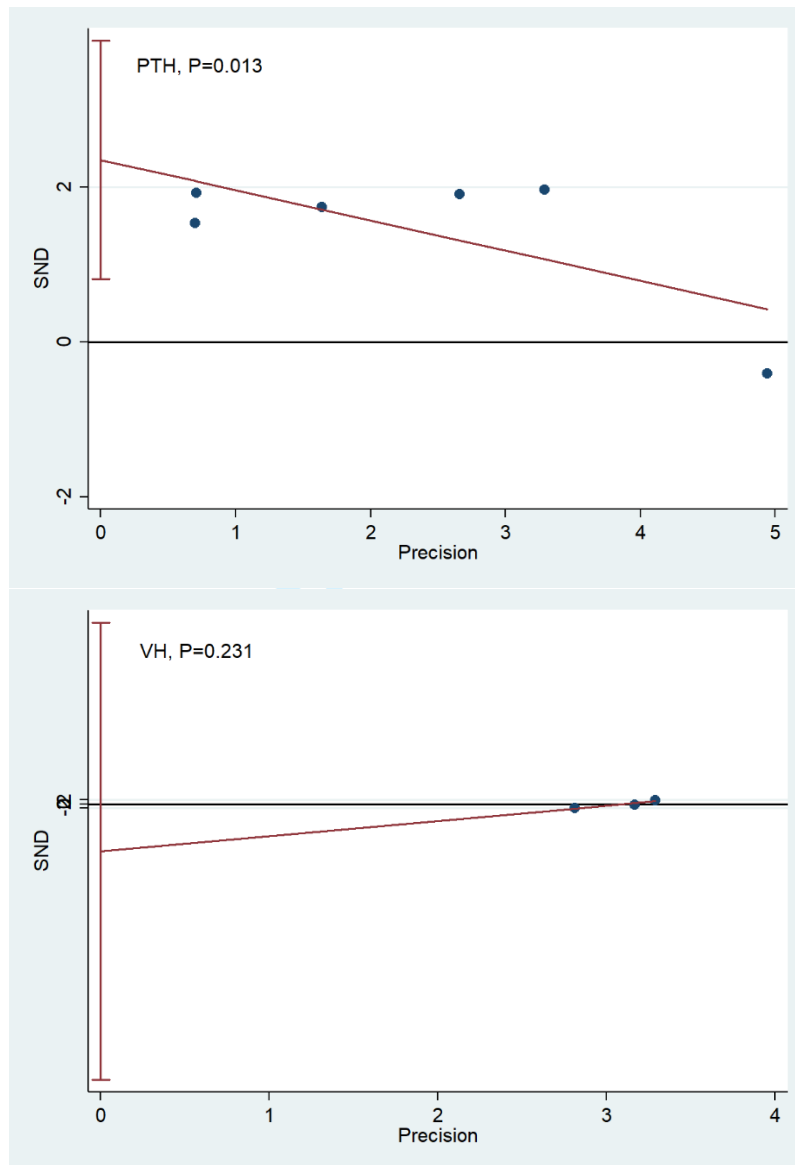
195x99mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



195x89mm (300 x 300 DPI)





**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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030038.R1
Article Type:	Research
Date Submitted by the Author:	23-May-2019
Complete List of Authors:	Wan, Sizhe; First Affiliated Hospital of Nanchang University, Gastroenterology Huang, Chenkai; First Affiliated Hospital of Nanchang University, Gastroenterology Zhu, Xuan; First Affiliated Hospital of Nanchang University, Gastroenterology
<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	portal hypertension, variceal haemorrhage, cirrhotic, statins, meta-analysis

SCHOLARONE™  
Manuscripts

# 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,<sup>1†</sup> Chen-Kai Huang,<sup>1†</sup> Xuan Zhu<sup>1</sup>

<sup>1</sup> 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](mailto: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  $\geq 20\%$  of baseline or to  $\leq 12$  mmHg) and the risk of variceal haemorrhage. The relative risk (RR) with a 95% confidence interval (CI) 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; I<sup>2</sup>=63%) in 6 RCTs. On subgroup analysis of studies that used statin for one month, the RR was 2.01 (95% CI, 1.31-3.10; I<sup>2</sup>=0%); the pooled RR for studies that used statins for three months was 3.76 (95% CI, 0.36-39.77; I<sup>2</sup>=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; I<sup>2</sup>=64%); the pooled RR for studies that used a drug that was not

1  
2  
3 reported in the control group was 4.21 (95% CI, 1.52-11.70; I<sup>2</sup>=0%); the  
4 pooled RR for studies that used simvastatin was 2.20 (95% CI, 0.92-5.29;  
5 I<sup>2</sup>=69%); RR for study using atorvastatin was 1.82 (95% CI, 1.00-3.30).  
6 For the risk of a variceal haemorrhage, the RR based on an observational  
7 study was 0.47 (95% CI, 0.23-0.94); in two randomized controlled trials,  
8 the pooled RR was 0.88 (95% CI, 0.52-1.50; I<sup>2</sup>=0%). Overall, the  
9 summed RR was 0.64 (95% CI, 0.42-0.99; I<sup>2</sup>=6%).

10  
11 Conclusion: Statins may improve hypertension and decrease the risk of  
12 variceal haemorrhage according to our assessment. However, further and  
13 larger RCTs are needed to confirm this conclusion.  
14  
15  
16

17  
18 **Key words: Statins; Portal hypertension; Variceal haemorrhage;**  
19 **cirrhotic; Meta-analysis**  
20  
21

## 22 23 24 Strengths and limitations

- 25  
26  
27 1) This will be the most comprehensive review of published and  
28 unpublished data of clinical effects of statins on the reduction of portal  
29 hypertension and variceal haemorrhage.  
30  
31  
32 2) This systematic review provides strong evidence for clinicians using  
33 statins to treat portal hypertension and variceal haemorrhage.  
34  
35  
36 3) Eligible studies screening, data extraction, and quality assessment  
37 were performed by two independent reviewers to reduce the potential for  
38 reviewer bias.  
39  
40  
41 4) Large RCTs are needed to confirm statins beneficial effects in patients  
42 with liver diseases. 5) Only studies in the English language have been  
43 included in the analysis.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

## 55 56 INTRODUCTION

57  
58 Cirrhosis is increasingly prevalent worldwide, as a result of a variety  
59 of chronic liver diseases. Cirrhosis, including compensate and  
60

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

13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Statins are widely used in clinical practice because of their exact and  
effective lipid-lowering effects.<sup>5 6</sup> 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.<sup>7</sup> 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.<sup>8</sup>  
However, a growing interest in the potential benefits of statins in patients  
with liver diseases has recently emerged.<sup>7 9-12</sup> Recent *in vivo* and *in vitro*  
experiments have gradually demonstrated that statins also exhibit anti-  
inflammatory<sup>13</sup>, immune-modulating,<sup>14</sup> anti-proliferative,<sup>15</sup> and anti-  
oxidant<sup>16</sup> effects as well as improved endothelial function<sup>17</sup> and inhibit  
platelet aggregation<sup>18</sup> and certain Gram-negative bacteria.<sup>19 20</sup> 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

1  
2  
3 and CKH) independently assessed the titles and abstracts of the studies that  
4 met the eligibility, criteria for inclusion.  
5  
6

### 7 **Data Abstraction**

8 Two reviewers (SZW and CKH) independently extracted the data.  
9 The following data were collected from each study: year of publication,  
10 study design, inclusion criteria, exclusion criteria, aetiology of cirrhosis,  
11 total number of patients in each group, primary outcome reported, and CTP  
12 (Child–Turcotte–Pugh) class, and ascites. Any divergence between the  
13 reviewers was discussed with a third reviewer (XZ), and agreement was  
14 reached by consensus.  
15  
16

17 We used the Newcastle–Ottawa scale to determine the quality of the  
18 cohort studies, and the Cochrane tool was used to determine the risk of bias  
19 for RCTs.  
20  
21  
22

### 23 **Outcomes Assessed**

24 Our primary outcome of interest was the association between statin  
25 use and the reduction in portal hypertension. The secondary outcomes of  
26 interest were the association between statin use and variceal bleeding.  
27 Several subgroup analyses were performed based on the quality of the  
28 studies, medication time, types of drugs in the control group, and types of  
29 statins. The adverse effects of statins were not included in the study due to  
30 insufficient information.  
31  
32  
33  
34

### 35 **Quality of Evidence**

36 We used the GRADE (Grading of Recommendations Assessment,  
37 Development, and Evaluation) framework to evaluate the quality of the  
38 evidence.<sup>21</sup> The GRADE approach for systematic reviews defines the  
39 quality of a body of evidence as the extent to which one can be confident  
40 that an estimate of an effect or association is close to the quantity of specific  
41 interest. The following factors were considered in determining the quality  
42 of evidence: risk of bias, directness of evidence, heterogeneity, precision  
43 of effect estimates, and risk of publication bias.  
44  
45  
46  
47  
48

### 49 **Statistical Analysis**

50 The trials and patient characteristics are reported as the ,number of  
51 observations and proportions. The relative risk (RR) and 95% confidence  
52 interval (CI) that achieved a target hemodynamic response in each group  
53 was pooled using the DerSimonian and Laird random effects model.<sup>22</sup>  
54 Inter-trial heterogeneity was statistically assessed using the chi-square test  
55 and is expressed as the  $I^2$  value, and  $I^2$  values >50% were reflective of  
56 substantial heterogeneity.<sup>23</sup> A formal assessment of publication bias using  
57 the egger test was performed (Supplementary figure 1).  
58  
59  
60



## 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).<sup>10 24-30</sup> 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

1  
2  
3  
4  
5  
6 Six studies including 301 patients evaluated the improvement in  
7 portal hypertension in cirrhosis. Overall, a decrease in HVPG ( $> 20\%$  from  
8 baseline or  $< 12$  mm-Hg) was achieved with statins in 57 of 135 evaluable  
9 patients compared to 36 of 141 patients in the control group (RR, 1.91; 95%  
10 CI, 1.04-3.52;  $I^2=63\%$ ). Three subgroup analyses were performed, based  
11 on the medication time, types of drug used in the control group, and types  
12 of statins. Subgroup analysis of the medication time of statins included  
13 three studies that used statins for one month (RR, 2.01; 95% CI, 1.31-3.10;  
14  $I^2=0\%$ ) and three studies that used statins for three months (RR, 3.76; 95%  
15 CI, 0.36-39.77;  $I^2=75\%$ ) (Figure 3). The second subgroup analysis was  
16 based on the types of drugs used in the control group, including non-  
17 selective beta blockers (NSBB) and not explicitly reported drugs. The  
18 pooled RR for NSBB users was 1.42 (95% CI, 0.82-2.45;  $I^2=64\%$ ), and the  
19 pooled RR for the not explicitly reported drugs was 4.21 (95% CI, 1.52-  
20 11.70;  $I^2=0\%$ ) (Figure 4). The third subgroup analysis was based on the  
21 types of statins. Five studies used simvastatin (RR, 2.20; 95% CI, 0.92-  
22 5.29;  $I^2=69\%$ ), and one study used atorvastatin (RR, 1.82; 95% CI, 1.00-  
23 3.30) (Figure 5).

24  
25  
26  
27  
28  
29  
30  
31  
32 There was moderate persuasion supporting the use of statins associated  
33 with an improvement in portal hypertension based on the RCTs. However,  
34 the result was limited by the study size (109 events in 301 patients).  
35

### 36 Risk of variceal haemorrhage

37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

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).

## 51 DISCUSSION

52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

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.

1  
2  
3 The summary RR between the numbers of HVPG reductions achieved in  
4 statin users and nonusers was 1.91 (95% CI, 1.04-3.52;  $I^2=63\%$ ) in  
5 favour of statins. We performed three subgroup analyses because of the  
6 substantial heterogeneity. The subgroup analysis based on the medication  
7 time of statin use supported the improvement in portal pressure at the  
8 one-month assessment (RR, 2.01; 95% CI, 1.31-3.10;  $I^2=0\%$ ). However,  
9 this effect was not statistically significant at the three-month assessment  
10 (RR, 3.76; 95% CI, 0.36-39.77;  $I^2=75\%$ ). These results suggest that the  
11 effects of statins are not dose-dependent and lead to strong curative  
12 effects in patients who used statins for one month compared to patients  
13 with a longer duration of use. Several possible mechanisms may explain  
14 the biological plausibility of our findings. The hepatotoxicity of statins  
15 occurs via regulation of the P450 cytochrome in immune-mediated liver  
16 damage, which activates apoptosis and T cell-induced liver injury.<sup>31 32</sup>  
17 Previous clinical research<sup>33-36</sup> confirmed these observations, which offset  
18 the benefits of statins over a longer treatment period. No considerable  
19 differences were observed in subgroup analyses for the use of NSBB in  
20 the control group (RR, 1.42; 95% CI, 0.82-2.45;  $I^2=64\%$ ). We presume  
21 that improvements of portal hypertension by NSBB is the underlying  
22 mechanism. NSBB is clinically used to treat portal hypertension because  
23 of its efficacy in decreasing HVPG and variceal haemorrhage.<sup>37-40</sup>  
24 Therefore, the use of NSBB in the control group may lead to no  
25 significant difference between the statin user and nonuser groups.  
26 Different types of statins exhibit inconsistent pharmacological actions.  
27 Therefore, patients were stratified by the statin varieties. The pooled RR  
28 in a subset of patients who received simvastatin was 2.20(95% CI, 0.92-  
29 5.29;  $I^2=69\%$ ), which indicates no improvement. Atorvastatin users  
30 exhibited a decrease in portal pressure (RR, 1.82; 95% CI, 1.00-3.30).  
31 High quality evidence was included, but discrepancies, such as the  
32 medication time may have led to imprecision.

33  
34 Events of variceal haemorrhage were satisfactorily reported in three  
35 studies. The effect of statins on variceal bleeding as a common cause of  
36 death in patients with portal hypertension was also investigated. The  
37 pooled RR was 0.64 (95% CI, 0.42-0.99;  $I^2=6\%$ ). However, the reduction  
38 in the pooled RR of the risk of variceal haemorrhage failed to reach  
39 statistical significance with statin use in two RCTs (RR, 0.88; 95% CI,  
40 0.52-1.50;  $I^2=0\%$ ). Notably, the only observational study confirmed the  
41 superiority of statins in lowering the risk of variceal bleeding (RR, 0.47;  
42 95% CI, 0.23-0.94). The characteristics of different types of experiments  
43 may be responsible for the inconsistency.

44  
45 Statins have received increasing attention in clinical research in the  
46 field of various liver diseases including liver cirrhosis, hepatocellular  
47 carcinoma, fatty liver disease, viral hepatitis and other related liver  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 diseases, in recent years.<sup>6</sup> Studies have confirmed that statins are safe and  
4 effective for some patients with these liver diseases.<sup>41</sup> A population-based  
5 study<sup>9</sup> evaluated the effects of statins on reducing decompensation,  
6 mortality, and HCC in HBV, HCV, and alcohol-related cirrhosis. This  
7 study demonstrated that statins reduced decompensation ( $P < 0.0001$ ),  
8 mortality ( $P < 0.0001$ ), and the risk of HCC ( $P = 0.009$ ) in patients with  
9 cirrhosis, and this correlation was dose-dependent. The risk of  
10 decompensation in patients with cirrhosis caused by chronic HBV (RR,  
11 0.39; 95% CI, 0.25-0.62) or HCV infection (RR, 0.51; 95% CI, 0.29-0.93)  
12 was lower in patients taking statins. The effect of statins on reducing the  
13 risk of cirrhosis decompensation was statistically significant in alcohol  
14 cirrhotic patients (RR, 0.69; 95% CI, 0.45-1.07). In general, the use of  
15 statins reduced the decompensation rate of HBV, HCV and alcohol-related  
16 cirrhosis. Two recent studies<sup>42 43</sup> demonstrated that statins were safe in  
17 patients with NAFLD and exhibited beneficial effects decreasing steatosis  
18 and fibrosis and preventing disease progression. Multiple previous studies  
19 demonstrated the benefit of statins on liver systems. A randomized trial of  
20 patients with cirrhosis and significant portal hypertension observed that the  
21 nitric oxide levels in hepatic venous blood, as a key vasodilator mediating  
22 the hepatic vascular resistance,<sup>44-46</sup> were increased in the statins group  
23 compare to those in the control group. A decrease in portal hypertension  
24 was also observed in patients who received statins.<sup>47</sup> Marrone<sup>48</sup> studies  
25 have also confirmed that the use of statins in cirrhotic animals can reduce  
26 liver fibrosis and prevent further deterioration of cirrhosis by inhibiting the  
27 activation of hepatic stellate cell;. This may also be a potential mechanism  
28 for the efficacy of statins.

29  
30  
31  
32  
33  
34  
35  
36  
37  
38 More research groups have begun to support the use of statin in some  
39 patients with chronic liver disease or cirrhosis based on these studies.<sup>49 50</sup>  
40 Some researchers believe that statins may also be able to be used as an  
41 adjuvant therapy in any chronic liver disease patients with indications for  
42 statins use to prevent decompensation or delay the progression of patients  
43 with decompensated cirrhosis.<sup>51</sup> However, this information was derived  
44 from retrospective cohort studies, and prospective studies are needed to  
45 confirm these beneficial effects.

46  
47  
48  
49 This meta-analysis evaluated the role of statins in patients with  
50 cirrhosis as a decline in portal pressure and risk of variceal haemorrhage.  
51 We performed a comprehensive literature search that met the well-defined  
52 inclusion criteria. Eight studies were included, primarily consisting of  
53 RCTs. These studies were high quality studies as graded by the Cochrane  
54 tool for assessing risk of bias or the Newcastle–Ottawa scale. Several  
55 subgroup analyses were completed based on the characteristics of the  
56 studies to further ascertain the precision of results.

57  
58  
59 However, several limitations exist in our meta-analysis. In some of  
60

1  
2  
3 the results, we have a large heterogeneity, which may be due to the  
4 inconsistency of the inclusion and exclusion criteria we included in the  
5 study. In addition, patients with various etiologies of cirrhosis were not  
6 researched separately because of insufficient information, which may  
7 explain the substantial heterogeneity. So we performed a subgroup  
8 analysis to try to eliminate this difference, significantly reducing  
9 heterogeneity in some subgroup analyses. Seven RCTs were included, but  
10 the number of patients enrolled was relatively fewer in the RCTs (471  
11 patients). Although individual studies adjusted for various confounders  
12 (e.g., age, sex, CTP score, and MELD score), there are residual  
13 confounders that could not be completely adjusted remained. These  
14 situations may have affected the precision and credibility of our estimates.  
15 In two studies, the 0 event counts in the control group may be due to the  
16 fact that the placebo used in the control group is not a drug such as NSBB  
17 that has been proven to have a reduced portal pressure, leading to a wide  
18 95% confidence intervals. The quality assessment of the RCT suggests that  
19 the quality of the two studies is acceptable, so we have no good reason to  
20 exclude these studies. The number of patients included in some studies is  
21 insufficient, so continuity corrections is not used, which may increase the  
22 risk of bias. Non-alcoholic fatty liver disease, as a metabolic disease, may  
23 exhibit closer relevance with lipid-lowering drug statins. Unfortunately, no  
24 eligible NAFLD research was included.

25  
26 In conclusion, our analyses based on RCTs and an observational  
27 study indicated a beneficial effect of statins on reducing portal  
28 hypertension and variceal haemorrhage. However, the assessment can not  
29 serve as clinical guideline for the wide use of statins in cirrhosis with portal  
30 hypertension because of the limited quantity and quality of the included  
31 studies. Previous research reported the potential protective effects of  
32 statins against cirrhosis and HCC progression, and the potential benefits of  
33 statins may outweigh the theoretical risks. Notably, adverse events related  
34 to statins were rarely reported in studies. Large RCTs are required before  
35 statins are clinically used to treat patients with cirrhosis and complications.

### 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 **licence statement**

51  
52  
53 The Submitting Author accepts and understands that any supply made  
54 under these terms is made by BMJ to the Submitting Author unless you are  
55 acting as an employee on behalf of your employer or a postgraduate  
56 student of an affiliated institution which is paying any applicable article  
57 publishing charge (“APC”) for Open Access articles. Where the  
58 Submitting Author wishes to make the Work available on an Open Access  
59  
60



1  
2  
3 basis (and intends to pay the relevant APC), the terms of reuse of such  
4 Open Access shall be governed by a Creative Commons licence – details  
5 of these licences and which Creative Commons licence will apply to this  
6 Work are set out in our licence referred to above.  
7  
8  
9

10  
11  
12 **Contributors:** SZW and CKH contributed equally to this study. SZW  
13 planned the study. SZW and CKH screened the literature and collected  
14 data. SZW, CKH and XZ conducted the meta-analysis and wrote the  
15 manuscript.  
16  
17  
18

19  
20 **Funding:** This study was supported by the National Natural Science  
21 Foundation of China (grant number: 81660110), the “Gan-Po Talent 555”  
22 Project of Jiangxi Province, and the Nanchang University Graduate  
23 Innovation Special Fund Project (grant number: CX2018205).  
24  
25

26 **Competing interests:** None declared.  
27

28  
29 **Data availability statement:** The data used to support the findings of this  
30 study are available from the author upon request.  
31  
32

33 **Acknowledgement:** Thanks for the economic support from the National  
34 Natural Science Foundation of China  
35  
36  
37  
38  
39  
40

41 **Figure 1. PRISMA (Preferred Reporting Items for Systematic**  
42 **Reviews and Meta-Analyses) flowchart.**  
43  
44

45 **Figure 2. Risk of bias assessed using the Cochrane risk of bias tool for**  
46 **RCTs**  
47  
48

49 **Figure 3. Forest plot to evaluate the role of statins in the reduction of**  
50 **portal hypertension using a subgroup analysis based on medication**  
51 **time of statins.**  
52  
53

54 **Figure 4. Forest plot to evaluate the role of statins in the reduction of**  
55 **portal hypertension using subgroup analysis based on the types of**  
56 **drugs in the control group.**  
57  
58

59 **Figure 5. Forest plot to evaluate the role of statins in the reduction of**  
60

1  
2  
3 **portal hypertension using subgroup analysis based on types of statins.**  
4  
5

6 **Figure 6. Forest plot to evaluate the role of statins in the reduction of**  
7 **the risk of variceal haemorrhage using subgroup analysis based on**  
8 **types of statins.**  
9

10  
11 **Supplementary Figure 1. egger's test to identify publication bias. SND,**  
12 **standard normal deviation; PTH, portal hypertension; VH, variceal**  
13 **haemorrhage.**  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *Jama* 2013;310(6):591-608. doi: 10.1001/jama.2013.13805 [published Online First: 2013/07/12]
2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;44(1):217-31. doi: 10.1016/j.jhep.2005.10.013
3. D'Amico G, Luca A. Natural history. Clinical-haemodynamic correlations. Prediction of the risk of bleeding. *Bailliere's clinical gastroenterology* 1997;11(2):243-56. [published Online First: 1997/06/01]
4. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007;133(2):481-8. doi: 10.1053/j.gastro.2007.05.024 [published Online First: 2007/08/08]
5. Sirtori CR. The pharmacology of statins. *Pharmacol Res* 2014;88:3-11. doi: 10.1016/j.phrs.2014.03.002 [published Online First: 2014/03/25]
6. Pose E, Trebicka J, Mookerjee RP, et al. Statins: old drugs as new therapy for liver diseases? *J Hepatol* 2018 doi: 10.1016/j.jhep.2018.07.019 [published Online First: 2018/08/04]
7. Tsochatzis EA, Bosch J. Statins in cirrhosis-Ready for prime time. *Hepatology (Baltimore, Md)* 2017;66(3):697-99. doi: 10.1002/hep.29277
8. Moctezuma-Velazquez C, Abraldes JG, Montano-Loza AJ. The Use of Statins in Patients With Chronic Liver Disease and Cirrhosis. *Curr Treat Options Gastroenterol* 2018;16(2):226-40. doi: 10.1007/s11938-018-0180-4 [published Online First: 2018/03/25]
9. Chang FM, Wang YP, Lang HC, et al. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: A population-based study. *Hepatology (Baltimore, Md)* 2017;66(3):896-907. doi: 10.1002/hep.29172 [published Online First: 2017/03/21]
10. Abraldes JG, Villanueva C, Aracil C, et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis. *Gastroenterology* 2016;150(5):1160-70.e3. doi: 10.1053/j.gastro.2016.01.004 [published Online First: 2016/01/18]
11. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018;39(27):2526-39. doi: 10.1093/eurheartj/ehy182 [published Online First: 2018/05/03]
12. Shin JY, Azoulay L, Filion KB. Statin Use in Patients With Hepatitis C-related Cirrhosis: True Benefit or Immortal Time Bias? *Gastroenterology* 2016;151(2):373. doi: 10.1053/j.gastro.2015.11.055 [published Online First: 2016/07/05]
13. Chang CH, Hsu YM, Chen YC, et al. Anti-inflammatory effects of hydrophilic and lipophilic statins with hyaluronic acid against LPS-induced inflammation in porcine articular chondrocytes. *J Orthop Res* 2014;32(4):557-65. doi: 10.1002/jor.22536 [published Online First: 2013/12/05]
14. Kolawole EM, McLeod JJ, Ndaw V, et al. Fluvastatin Suppresses Mast Cell and Basophil IgE Responses: Genotype-Dependent Effects. *J Immunol* 2016;196(4):1461-70. doi: 10.4049/jimmunol.1501932 [published Online First: 2016/01/17]
15. Feldt M, Bjarnadottir O, Kimbung S, et al. Statin-induced anti-proliferative effects via cyclin D1 and p27 in a window-of-opportunity breast cancer trial. *J Transl Med* 2015;13:133. doi: 10.1186/s12967-015-0486-0 [published Online First: 2015/05/01]
16. Ramma W, Ahmed A. Therapeutic potential of statins and the induction of heme oxygenase-1 in preeclampsia. *J Reprod Immunol* 2014;101-102:153-60. doi: 10.1016/j.jri.2013.12.120 [published Online First: 2014/02/08]
17. Oikonomou E, Siasos G, Zaromitidou M, et al. Atorvastatin treatment improves endothelial function through endothelial progenitor cells mobilization in ischemic heart failure patients. *Atherosclerosis* 2015;238(2):159-64. doi: 10.1016/j.atherosclerosis.2014.12.014 [published Online First: 2014/12/20]
18. Camargo LM, Franca CN, Izar MC, et al. Effects of simvastatin/ezetimibe on microparticles, endothelial progenitor cells and platelet aggregation in subjects with coronary heart



- disease under antiplatelet therapy. *Braz J Med Biol Res* 2014;47(5):432-7. [published Online First: 2014/04/25]
19. Mehl A, Harthug S, Lydersen S, et al. Prior statin use and 90-day mortality in Gram-negative and Gram-positive bloodstream infection: a prospective observational study. *Eur J Clin Microbiol Infect Dis* 2015;34(3):609-17. doi: 10.1007/s10096-014-2269-6 [published Online First: 2014/11/07]
20. de Paula TP, Santos PC, Arifa R, et al. Treatment with Atorvastatin Provides Additional Benefits to Imipenem in a Model of Gram-Negative Pneumonia Induced by *Klebsiella pneumoniae* in Mice. *Antimicrob Agents Chemother* 2018;62(5) doi: 10.1128/aac.00764-17 [published Online First: 2018/02/22]
21. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of clinical epidemiology* 2013;66(2):151-7. doi: 10.1016/j.jclinepi.2012.01.006 [published Online First: 2012/05/01]
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88. [published Online First: 1986/09/01]
23. Higgins JP, Thompson SG, Deeks JJ. Measuring inconsistency in metaanalyses *BMJ* 2003;327:557-60.
24. Mohanty A, Tate JP, Garcia-Tsao G. Statins Are Associated With a Decreased Risk of Decompensation and Death in Veterans With Hepatitis C-Related Compensated Cirrhosis. *Gastroenterology* 2016;150(2):430-40.e1. doi: 10.1053/j.gastro.2015.10.007 [published Online First: 2015/10/21]
25. Abralde JG, Albillos A, Banares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009;136(5):1651-8. doi: 10.1053/j.gastro.2009.01.043 [published Online First: 2009/02/12]
26. Alvarado-Tapias E, Ardèvol A, Pavel O, et al. Hemodynamic effects of carvedilol plus simvastatin in cirrhosis with portal hypertension and no-response to  $\beta$ -blockers: A double-blind randomized trial. *Hepatology (Baltimore, Md)* 2016;64(1):74A.
27. Bishnu S, Ahammed SKM, Sarkar A, et al. Effects of atorvastatin on portal hemodynamics and clinical outcomes in patients with cirrhosis with portal hypertension: A proof-of-concept study. *European Journal of Gastroenterology and Hepatology* 2018;30(1):54-59. doi: 10.1097/MEG.0000000000001006
28. Flores PP, Rezende GF, Cassano U, et al. Effect of simvastatin in portal hypertension. *Hepatology (Baltimore, Md)* 2014;60:1191A. doi: 10.1002/hep.27536
29. Pollo-Flores P, Soldan M, Santos UC, et al. Three months of simvastatin therapy vs. placebo for severe portal hypertension in cirrhosis: A randomized controlled trial. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015;47(11):957-63. doi: 10.1016/j.dld.2015.07.156 [published Online First: 2015/09/01]
30. Rajan V, Choudhary A, Jindal A, et al. Addition of simvastatin to carvedilol does not improve hemodynamic response in cirrhotics with varices without prior bleed: Preliminary results of an open label RCT. *Hepatology (Baltimore, Md)* 2016;64(6):1134A-35A.
31. Bhardwaj SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. *Clinics in liver disease* 2007;11(3):597-613, vii. doi: 10.1016/j.cld.2007.06.010 [published Online First: 2007/08/29]
32. Kubota T, Fujisaki K, Itoh Y, et al. Apoptotic injury in cultured human hepatocytes induced by HMG-CoA reductase inhibitors. *Biochemical pharmacology* 2004;67(12):2175-86. doi: 10.1016/j.bcp.2004.02.037 [published Online First: 2004/05/28]
33. Ballare M, Campanini M, Airoidi G, et al. Hepatotoxicity of hydroxy-methyl-glutaryl-coenzyme A reductase inhibitors. *Minerva gastroenterologica e dietologica* 1992;38(1):41-4. [published Online First: 1992/01/01]
34. Heuer T, Gerards H, Pauw M, et al. [Toxic liver damage caused by HMG-CoA reductase inhibitor]. *Medizinische Klinik (Munich, Germany : 1983)* 2000;95(11):642-4. [published Online First: 2001/01/06]
35. Koornstra JJ, Ottervanger JP, Fehmers MC, et al. [Clinically manifest liver lesions during use of simvastatin]. *Nederlands tijdschrift voor geneeskunde* 1996;140(15):846-8. [published Online First: 1996/04/13]
36. Black DM, Bakker-Arkema RG, Nawrocki JW. An overview of the clinical safety profile of

- atorvastatin (lipitor), a new HMG-CoA reductase inhibitor. *Archives of internal medicine* 1998;158(6):577-84. [published Online First: 1998/04/01]
37. Lebrech D, Poynard T, Bernuau J, et al. A randomised controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. *Drugs* 1989;37 Suppl 2:30-4; discussion 47. [published Online First: 1989/01/01]
38. Hillon P, Lebrech D, Munoz C, et al. Comparison of the effects of a cardioselective and a nonselective beta-blocker on portal hypertension in patients with cirrhosis. *Hepatology (Baltimore, Md)* 1982;2(5):528-31. [published Online First: 1982/09/01]
39. Aramaki T, Sekiyama T, Katsuta Y, et al. Long-term haemodynamic effects of a 4-week regimen of nipradilol, a new beta-blocker with nitrovasodilating properties, in patients with portal hypertension due to cirrhosis. A comparative study with propranolol. *J Hepatol* 1992;15(1-2):48-53. [published Online First: 1992/05/01]
40. Gatta A, Sacerdoti D, Merkel C, et al. Use of a nonselective beta-blocker, nadolol, in the treatment of portal hypertension in cirrhotics. *International journal of clinical pharmacology research* 1985;5(6):413-8. [published Online First: 1985/01/01]
41. Pastori D, Polimeni L, Baratta F, et al. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015;47(1):4-11. doi: 10.1016/j.dld.2014.07.170 [published Online First: 2014/09/17]
42. Dongiovanni P, Petta S, Mannisto V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol* 2015;63(3):705-12. doi: 10.1016/j.jhep.2015.05.006 [published Online First: 2015/05/20]
43. Nascimbeni F, Aron-Wisnewsky J, Pais R, et al. Statins, antidiabetic medications and liver histology in patients with diabetes with non-alcoholic fatty liver disease. *BMJ open gastroenterology* 2016;3(1):e000075. doi: 10.1136/bmjgast-2015-000075 [published Online First: 2016/04/26]
44. Gupta TK, Toruner M, Chung MK, et al. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology (Baltimore, Md)* 1998;28(4):926-31. doi: 10.1002/hep.510280405 [published Online First: 1998/10/02]
45. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. *Gastroenterology* 1998;114(2):344-51. [published Online First: 1998/02/07]
46. Shah V, Toruner M, Haddad F, et al. Impaired endothelial nitric oxide synthase activity associated with enhanced caveolin binding in experimental cirrhosis in the rat. *Gastroenterology* 1999;117(5):1222-8. [published Online First: 1999/10/27]
47. Zafra C, Abraldes JG, Turnes J, et al. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. *Gastroenterology* 2004;126(3):749-55. [published Online First: 2004/02/28]
48. Marrone G, Maeso-Diaz R, Garcia-Cardena G, et al. KLF2 exerts antifibrotic and vasoprotective effects in cirrhotic rat livers: behind the molecular mechanisms of statins. *Gut* 2015;64(9):1434-43. doi: 10.1136/gutjnl-2014-308338
49. Lin CY. Statins and risk of decompensation in hepatitis B virus-related and hepatitis C virus-related cirrhosis: Methodological issues. *Hepatology (Baltimore, Md)* 2018;67(3):1174. doi: 10.1002/hep.29687 [published Online First: 2017/11/25]
50. Kim G, Jang SY, Nam CM, et al. Statin use and the risk of hepatocellular carcinoma in patients at high risk: A nationwide nested case-control study. *J Hepatol* 2018;68(3):476-84. doi: 10.1016/j.jhep.2017.10.018 [published Online First: 2017/11/07]
51. Magan-Fernandez A, Rizzo M, Montalto G, et al. Statins in liver disease: not only prevention of cardiovascular events. *Expert review of gastroenterology & hepatology* 2018;12(8):743-44. doi: 10.1080/17474124.2018.1477588 [published Online First: 2018/05/18]

Study, year	Design	Inclusion criteria	Exclusion criteria	Aetiology of cirrhotics	Groups	N	Outcomes of interest	Outcomes	
								Statin users(n)	Non-users (n)
1 2 3 4									
5 6 7 8 9 10 11	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
12 13 14 15 16 17 18 19 20	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
21 22 23 24 25 26 27 28 29 30 31	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

1  
2  
3  
4

5			Patients previously treated with statins within one month of randomization.							
6										
7	Alvarado ,	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
8	2016									
9										
10	Bishnu,	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-Turcotte (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
11	2018									
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										
25										
26	Flores,	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
27	2014									
28										
29										
30										
31										
32										
33										
34										
35										
36										
37										
38	Bollo-	RCT	Age 18–75 years Diagnosis of cirrhosis with	Aminotransferases levels >3 times above the upper	Mixed	Statins	11	Reduction in	Reduction in	0

39  
40  
41  
42  
43  
44  
45  
46

1  
2  
3  
4

5 6 7 8 9 10 11 12 13 14 15		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	
16 17 18 19	RCT	Cirrhotics with varices who had never bled	NR	Mixed	Statins Nonusers	44 46	Reduction in portal hypertension	Reduction in portal hypertension:2 2	25
20 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.									

21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

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

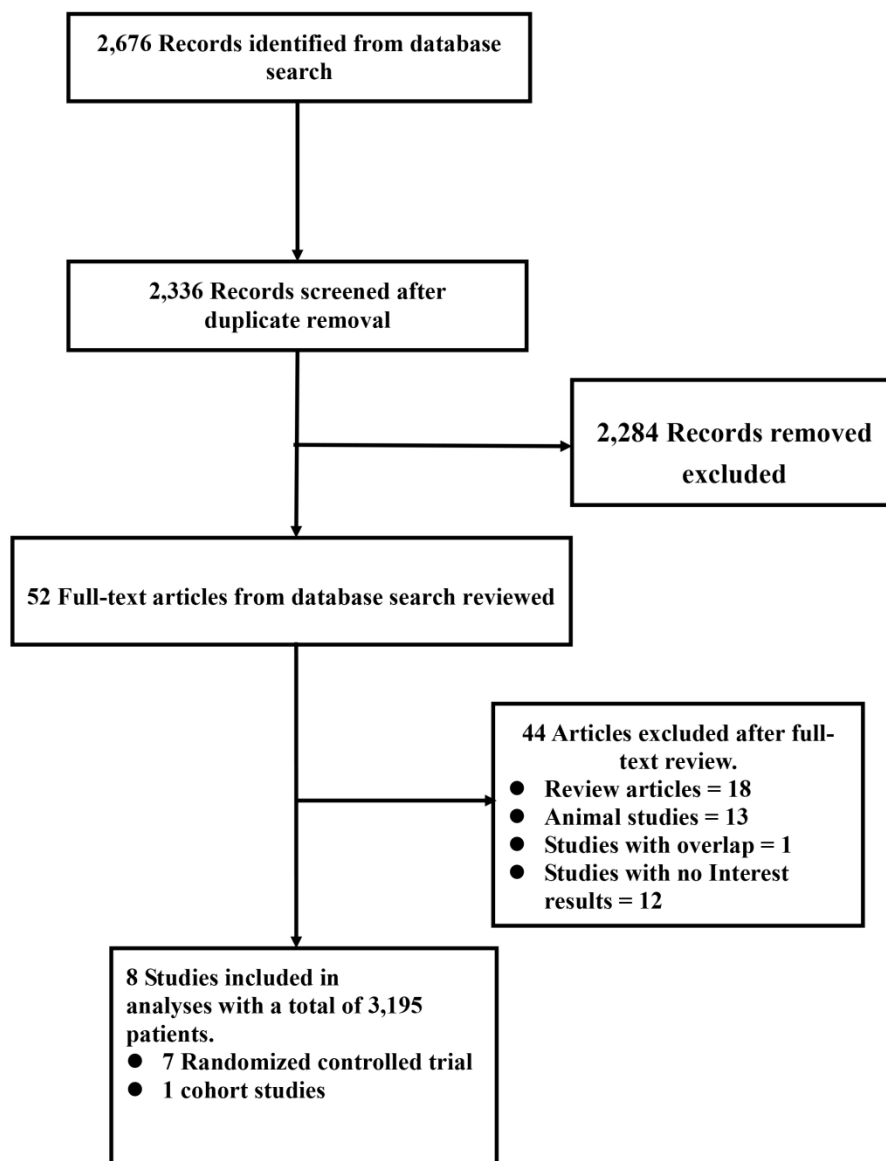
Studies	Selection				Comparability	Outcome			Quality
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at start	Adjustment for primary and secondary factors	Assessment by record linkage	Long enough follow-up for outcome to occur	Adequacy 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
<b>Mohanty,2016</b>	Statins Nonusers	685 2062	56 56	671 2021	685/0 2062/0	NR NR	NR NR	NR NR
<b>Abraldes,2009</b>	Statins Nonusers	28 27	58 56	17 21	NR NR	18/10/0 16/8/3	14 16	6 9
<b>Abraldes,2016</b>	Statins Nonusers	69 78	57 57	45 53	20/49 19/55	15/68/17 24/62/14	15 16	NR NR
<b>Alvarado,2016</b>	Statins Nonusers	43 44	56 54	31 35	NR NR	NR NR	NR NR	NR NR
<b>Bishnu,2018</b>	Statins Nonusers	11 12	44 47	9 12	0/4 1/6	NR NR	5 6	6 5
<b>Flores,2014</b>	Statins Nonusers	11 11	46 43	23 30	NR NR	NR NR	NR NR	NR NR
<b>Pollo-Flores,2015</b>	Statins Nonusers	11 13	57 59	6 7	NR NR	NR NR	2 3	5 3
<b>Rajan,2016</b>	Statins Nonusers	44 46	51 53	30 35	NR NR	NR NR	NR NR	NR NR



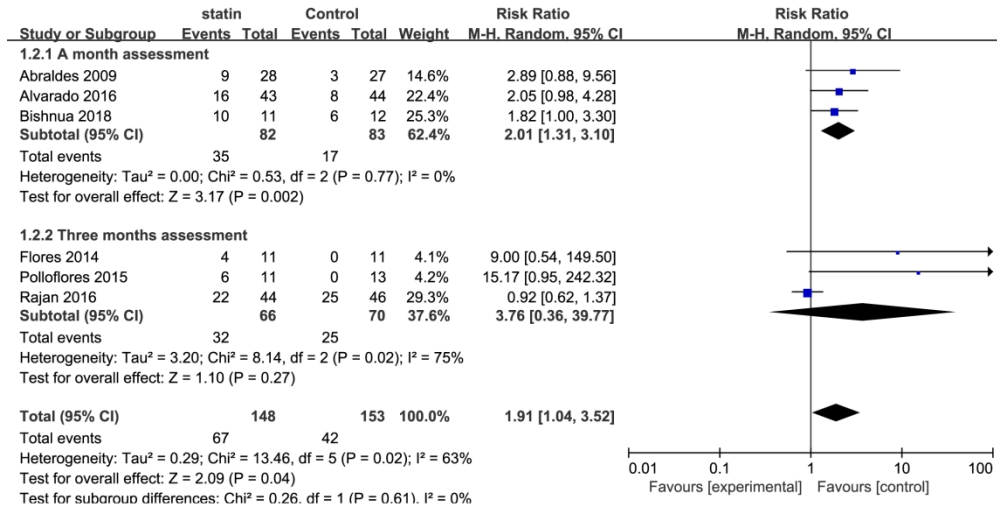


1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abraldes 2009	+	+	+	+	+	+	+
Abraldes 2016	+	?	+	+	+	+	+
Alvarado 2016	+	+	+	+	?	+	+
Bishnua 2018	+	?	?	+	+	+	+
Flores 2014	+	+	+	+	+	?	?
Polloflores 2015	+	?	+	+	+	+	+
Rajan 2016	+	+	?	+	+	+	+

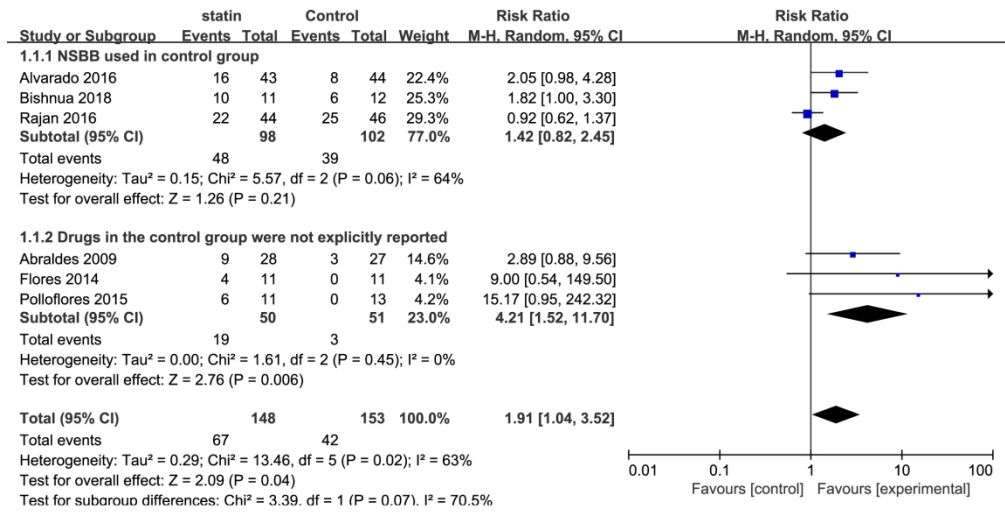
156x265mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

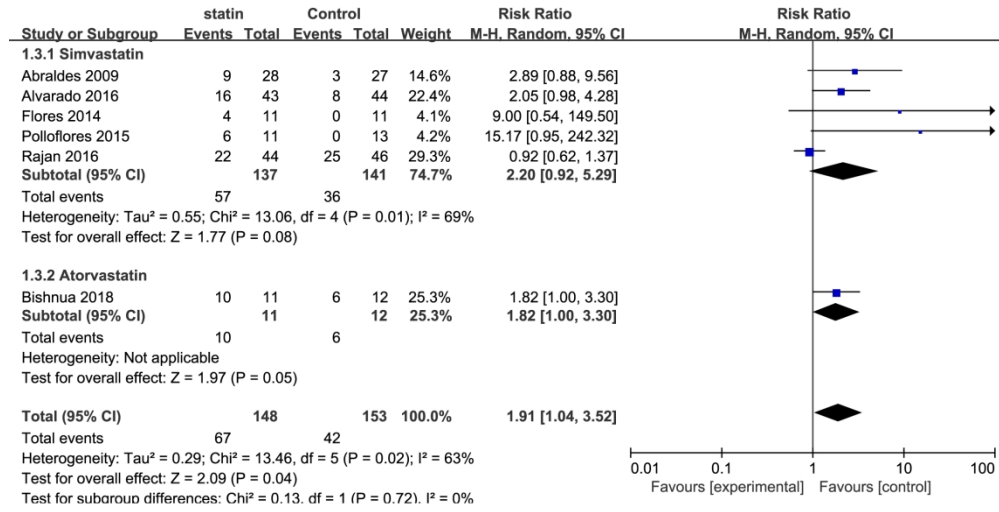


195x99mm (300 x 300 DPI)

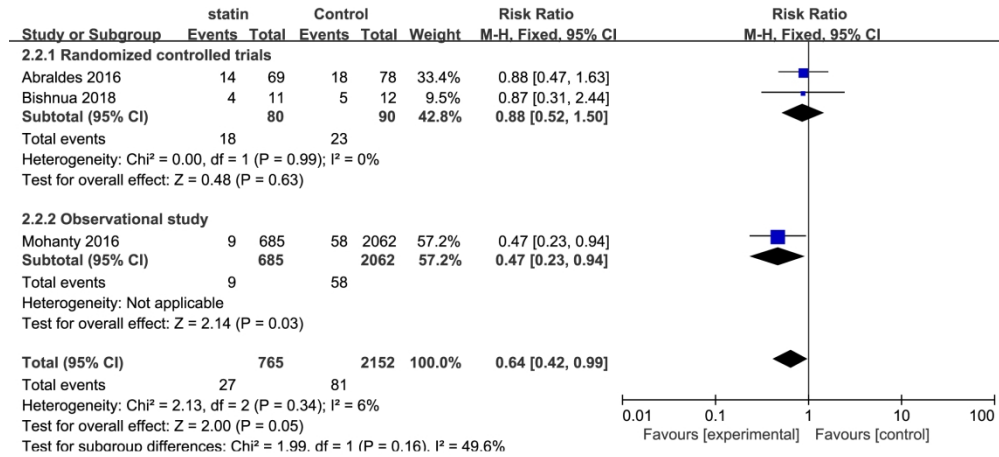
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



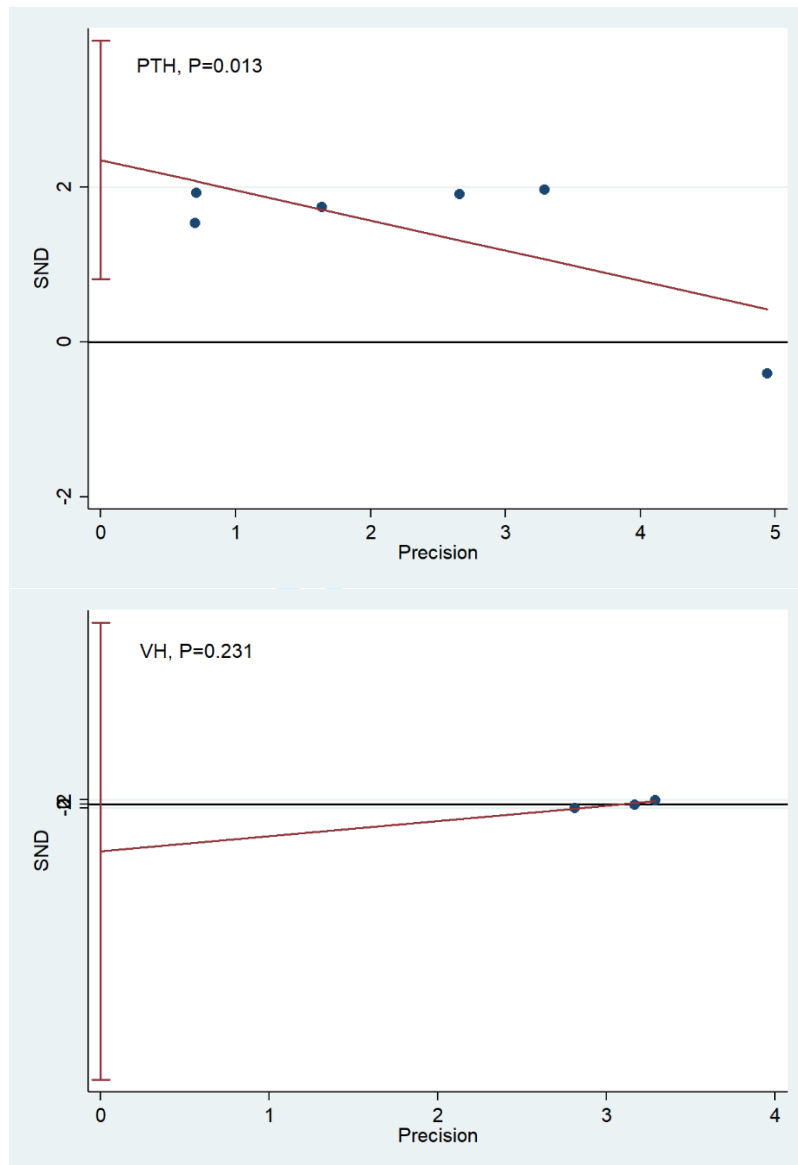
195x99mm (300 x 300 DPI)



195x99mm (300 x 300 DPI)



195x89mm (300 x 300 DPI)



**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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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.	Supplementary 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

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

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
<b>FUNDING</b>			
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

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2