



Clinical evidence of efficacy of simvastatin for aneurysmal subarachnoid hemorrhage

Jinghui Lin¹, Houxian Liu¹, Jianjun Jiang²,
Conglin Jia¹, Bin Zhang¹ and Xiang Gao²

Abstract

Objective: The present study was performed to explore the therapeutic potential of simvastatin in subarachnoid hemorrhage (SAH) in the context of the Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) trial.

Methods: MEDLINE, EMBASE, and the Cochrane Library were searched for all randomized controlled trials (RCTs) investigating the therapeutic effect of simvastatin on aneurysmal SAH. We applied a random-effects model to calculate the data.

Results: Five RCTs involving 951 patients met the eligibility criteria. We found no statistically significant effects on vasospasm detected by transcranial cerebral Doppler (relative risk [RR], 0.91; 95% confidence interval [CI], 0.55–1.49), delayed cerebral ischemia (DCI) (RR, 0.85; 95% CI, 0.63–1.14), or all-cause mortality (RR, 1.02; 95% CI, 0.67–1.54). Subgroup analysis showed that these consolidated results were stable at different doses, different times to start of treatment, and different courses of treatment in all included RCTs. Sensitivity analysis showed that the STASH trial, which had a large population, did not influence the consolidated results of all three outcomes.

Conclusions: Simvastatin showed no benefits in decreasing the incidence of vasospasm, DCI, or all-cause mortality after aneurysmal SAH. We conclude that patients with SAH should not be treated routinely with simvastatin during the acute stage.

Keywords

Delayed cerebral ischemia, meta-analysis, simvastatin, subarachnoid hemorrhage, vasospasm

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Introduction

Aneurysmal subarachnoid hemorrhage (SAH) remains a common subtype of cerebral hemorrhagic stroke and is associated with a high mortality rate, primarily because of the occurrence of delayed vasospasm and

¹Department of Neurosurgery, Fenghua People's Hospital, Ningbo, Zhejiang, China

²Department of Neurosurgery, Ningbo First Hospital, Ningbo, Zhejiang, China

Corresponding author:

Xiang Gao, Department of Neurosurgery, Ningbo First Hospital, 59 Liuting Road, Ningbo, Zhejiang 315000, China.
Email: gaolianghuashan@126.com



early brain injury.^{1,2} Only nimodipine is recommended to manage delayed vasospasm according to current guidelines, but this agent has limited efficacy.³ Therefore, new drugs are required to improve the outcome of patients with SAH.

Statins represent potential agents with which to prevent delayed vasospasm.³ Animal studies have shown that statins can reduce inflammation and decrease platelet activation; however, they also increase the expression of endothelial nitric oxide synthase.⁴ All of these effects can prevent delayed vasospasm.⁴ Simvastatin is considered to be more lipophilic and have a higher blood–brain barrier permeability than other statins.⁵ At the same dose, simvastatin has twice the cholesterol-lowering effect of pravastatin.⁵ Therefore, simvastatin has become the main research target in detecting the efficacy of statins on vasospasm and delayed cerebral ischemia (DCI) after aneurysmal SAH. To date, five randomized controlled trials (RCTs)^{6–10} have been performed to detect the benefit of simvastatin over placebo based on the use of nimodipine. Unfortunately, the results of these clinical trials were inconsistent. Two phase II RCTs have shown a potential benefit of simvastatin therapy with respect to lower rates of radiologic vasospasm, DCI, and even mortality.^{6,7} However, two other phase II RCTs revealed opposite results: simvastatin showed no significant effects on the rates of vasospasm, DCI, and mortality.^{8,9} All of these studies were single-center, phase II studies with small samples of fewer than 100 patients. Therefore, it is difficult to draw a credible conclusion. *Lancet Neurology* recently published a large multicenter phase III RCT (Simvastatin in Aneurysmal Subarachnoid Hemorrhage [STASH] trial) investigating the benefit of simvastatin in patients with aneurysmal SAH.¹⁰ The results showed that simvastatin treatment (40 mg/day, on 96 h of the ictus for up to 21 days) had no beneficial effect on

the modified Rankin scale score or DCI of patients with SAH at discharge or 6 months later, which was questioned for using low-dose simvastatin at 40 mg/day. Another RCT verified the hypothesis that high-dose simvastatin might improve the clinical outcomes after aneurysmal SAH.¹¹ We performed a meta-analysis to determine whether simvastatin plays a beneficial role in reducing delayed vasospasm, DCI, and mortality after aneurysmal SAH.

Methods

Study protocol

The present study protocol was drafted following the Cochrane Collaboration format prior to study initiation. This protocol contained the patients' background information, a flow diagram, the search strategy, inclusion and exclusion criteria, outcome definitions, the statistical design, the methods of determining the risk of bias, and the discussion. We also conducted a clear division of labor and reached a consensus about the solution of controversy during performing this meta-analysis. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.¹² Ethical approval was not required because the meta-analysis was conducted using published data.

Information sources and search

MEDLINE, EMBASE, and the Cochrane Library were searched by two independent authors (J.H.L. and H.X.L.). The main search strategy involved the combination of the variables “simvastatin” AND “subarachnoid hemorrhage.” Searches were restricted to the English language and matched the titles and abstracts of studies. To insure that all relevant studies were included in this systematic review, the reference lists of the RCTs and systematic reviews were manually

screened in addition to performing the electronic database search. Appendix 1 provides the full details of the search strategy.

Eligibility criteria, study selection, and data collection

Double-blind RCTs were included if they met the following criteria: i) patients had aneurysmal SAH diagnosed by computed tomography angiography or digital subtraction angiography, ii) simvastatin was regularly administered during the initial 2 to 3 weeks following SAH, and iii) outcomes of interest were compared between the simvastatin and placebo groups. Studies assessing outcomes based on simvastatin use prior to aneurysm rupture were excluded. Outcomes of interest based on intention-to-treat datasets included vasospasm detected by transcranial cerebral Doppler (TCD), the incidence of DCI, and all-cause mortality. DCI was assessed by clinical scales or cerebral angiography.

The following data were extracted: study characteristics (such as lead author, publication year, and study setting), participant characteristics (such as diagnostic criteria, sex, age, and type of operation), intervention details (such as dose ranges, time to treatment from SAH, and follow-up time), and outcome measures.

Risk of bias and quality assessment

Biases in the included trials were assessed by two independent investigators (J.L. and H.L.) using a seven-point quality control scale recommended by the Cochrane Handbook.¹³ The items included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. Each item was categorized as high, low, or unclear risk. The GRADE approach, which contains five items (risk of bias, inconsistency, indirectness, imprecision, and publication bias), was used to assess the quality of the evidence.

Data analysis

Data were processed using Review Manager 5.2 from the Cochrane Collaboration. Dichotomous outcomes were analyzed as the risk ratio (relative risk [RR] and 95% confidence interval [CI]) using the Mantel–Haenszel technique and a random-effects model. Statistical heterogeneity was estimated by the I^2 statistic. Tests were two-tailed, and $P < 0.05$ was considered statistically significant in all analyses. All analyses were performed on an intention-to-treat basis.

Results

According to the initially established search strategy, 738 records were retrieved from MEDLINE, EMBASE, and the Cochrane Library. After removing duplicates, irrelevant records, and non-RCTs, 17 full-text articles were assessed for eligibility. Among them, 12 records were excluded for the following reasons: secondary analysis of previously published RCTs, meta-analysis review, and RCT without a placebo-control group. Ultimately, 5 RCTs involving 951 patients were included in the qualitative analysis (Figure 1). The main characteristics of the included studies are listed in Table 1.

Outcomes analysis

Four trials^{6–9} involving 148 patients were available for analysis of vasospasm detected by TCD. No statistically significant effect on vasospasm detected by TCD was observed between the simvastatin and placebo groups (RR, 0.91; 95% CI, 0.55–1.49) (Figure 2(a)). Data heterogeneity was apparent due to various definitions of vasospasm detected by TCD ($I^2 = 53.0\%$, $P = 0.09$) (Figure 2(a)). The quality of the evidence was very low.

Five studies^{6–10} involving 951 patients were available for analysis of the incidence of DCI. Simvastatin showed no statistically

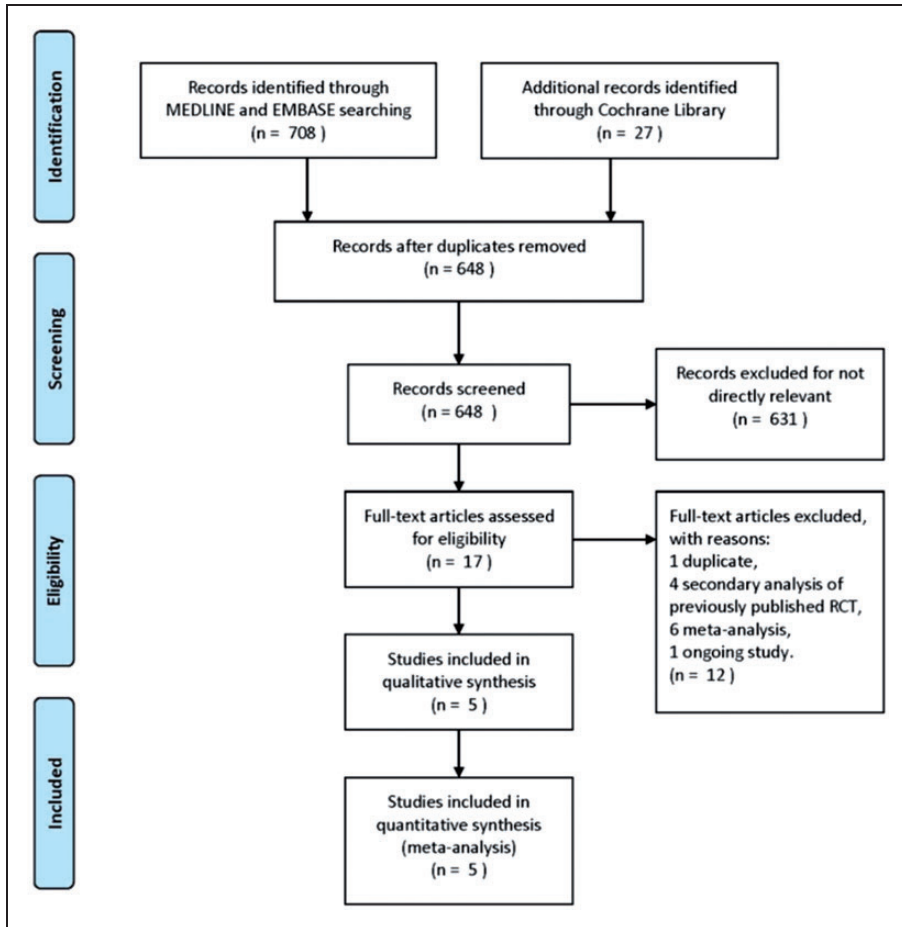


Figure 1. Study search, selection, and inclusion process.
RCT: randomized controlled trial.

significant effect on reducing DCI (RR, 0.85; 95% CI, 0.63–1.14) (Figure 2(b)). No data heterogeneity was observed ($I^2 = 12.0\%$) (Figure 2(b)). The quality of the evidence was moderate.

Four studies^{7–10} involving 912 patients were available for analysis of all-cause mortality. Simvastatin did not decrease all-cause mortality (RR, 1.02; 95% CI, 0.67–1.54) (Figure 2(c)). No evidence existed for data heterogeneity ($I^2 = 0\%$) (Figure 2(c)). The quality of the evidence was moderate.

Subgroup analysis

A subgroup analysis was performed to detect the influence of different drug doses, different times to start of treatment, and different courses of treatment in the included RCTs. With respect to drug dose, four studies^{6–9} used simvastatin at 80 mg/day and one study¹⁰ used simvastatin at 40 mg/day (details in Table 1). No differences were observed in vasospasm detected by TCD, DCI, or all-cause mortality (details in Table 2) between the high- and low-dose groups. With respect

Table 1. Characteristics of the included studies.

Articles	Age	Male	White	Clipping	Included criteria	Drugs	Dose	Treatment	Follow-up	Definition of vasospasm	Definition of DCI
Lynch et al. 2005	65 (NC)	16%	32%	47%	Radiological confirmation of SAH; evidence of SAH; <48 h from ictus	Simvastatin	80 mg/d	14 days	NC	Either: angiographic confirmation or TCD velocity of >160 cm/s	Clinical impression
Chou et al. 2008	50 (14)	32%	NC	89%	Radiological confirmation of SAH; evidence of SAH; <96 h from ictus	Simvastatin	80 mg/d	21 days; nimodipine and an anticonvulsant for basic treatment	At discharge	Vasospasm detected by TCD (velocity of >200 cm/s and Lindegaard ratio of >3)	Clinical infarct (≥ 2 on GOS scale or unaccountable new focal neurological deficit lasting ≥ 2 hours)
Vergouwen et al. 2009	53 (11)	50%	NC	23%	CT confirmatory evidence of SAH or bleeding in the cerebrospinal fluid with CT showing aneurysm; <72 h from ictus	Simvastatin	80 mg/d	14 days; nimodipine as the basic treatment: 60 mg every 4 h	6 months	Vasospasm detected by TCD (velocity of >120 cm/s)	Clinical infarct (≥ 2 on GOS scale)
Garg et al. 2013	49.4 (1.8)	58%	NC	100%	Radiological confirmation of SAH; <96 h from ictus	Simvastatin	80 mg/d	14 days	6 months	Either: angiographic confirmation or TCD velocity of >160 cm/s	NC
Kirkpatrick et al. 2014	51 (9.5)	34%	92%	30%	Radiological confirmation of SAH; <96 h from ictus	Simvastatin	40 mg/d	21 days	6 months	NC	Clinical infarct (≥ 2 on GOS scale)
Wong et al. 2015	49 (9.8)	29%	88%	33%	Radiological confirmation of SAH; <96 h from ictus	Placebo	-	21 days	3 months	/	Radiological infarct (confirmed by CT)
	56 (11)	38%	NC	49%	Radiological confirmation of SAH; <96 h from ictus	Simvastatin	80 mg/d	21 days	3 months	/	Radiological infarct (confirmed by CT)
	57 (12)	32%	NC	56%	Radiological confirmation of SAH; <96 h from ictus	Simvastatin	40 mg/d				

CT: computed tomography; CTA: computed tomography angiography; DCI: delayed cerebral ischemia; DSA: digital subtraction angiography; GOS: Glasgow outcome scale; MRA: magnetic resonance imaging; NC: not clear; SAH: subarachnoid hemorrhage; TCD: transcranial cerebral Doppler.

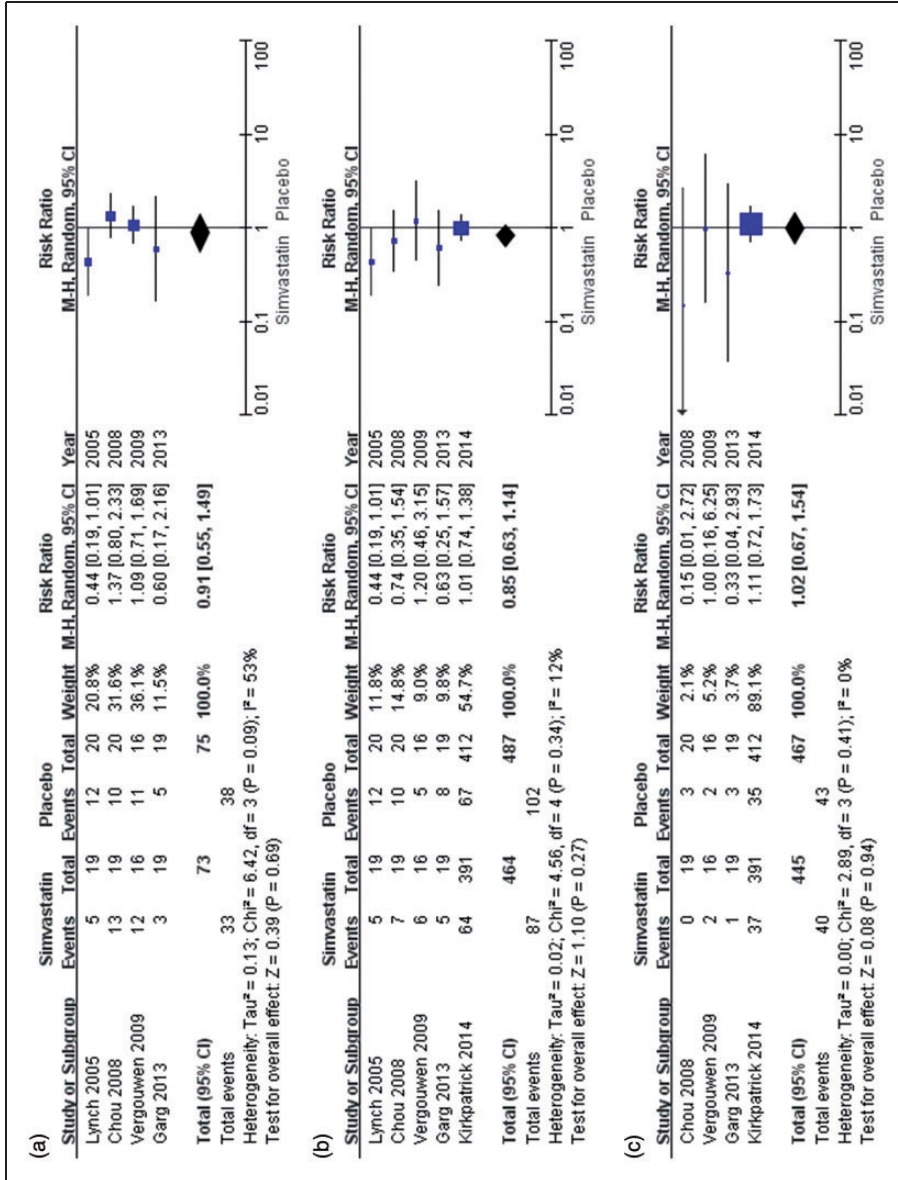


Figure 2. Efficacy and acceptability of simvastatin therapy for aneurysmal subarachnoid hemorrhage. (a) Pooled relative risk estimates for the incidence of vasospasm detected by transcranial cerebral Doppler (TCD). (b) Pooled relative risk estimates for the incidence of delayed cerebral ischemia. (c) Pooled relative risk estimates for all-cause mortality. The diamond indicates the estimated relative risk (95% confidence interval [CI]) for all patients together. M-H, Mantel-Haenszel.

Table 2. Sensitivity and subgroup analysis of efficacy and safety outcomes.

	Vasospasm detected by TCD		DCI		All-cause mortality	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
1. Sensitivity Analysis						
Excluded STASH trial	0.91 (0.55–1.49)	0.69	0.68 (0.45–1.04)	0.08	0.48 (0.14–1.70)	0.26
2. Subgroup Analysis: Drug Dosage						
Simvastatin 80 mg	0.91 (0.55–1.49)	0.69	0.68 (0.45–1.04)	0.08	0.48 (0.14–1.70)	0.26
Simvastatin 40 mg	–	–	1.01 (0.74–1.38)	0.97	1.11 (0.72–1.73)	0.63
3. Subgroup Analysis: Time to Start of Treatment						
Within 96 h of ictus	1.10 (0.52–2.32)	0.80	0.92 (0.70–1.22)	0.57	0.71 (0.25–2.05)	0.53
Within 72 or 48 h of ictus	0.73 (0.28–1.95)	0.53	0.70 (0.26–1.88)	0.48	1.00 (0.16–6.25)	1.00
4. Subgroup Analysis: Course of Treatment						
Period of up to 14 days	0.72 (0.35–1.47)	0.37	0.66 (0.37–1.18)	0.16	0.63 (0.16–2.57)	0.52
Period of up to 21 days	1.37 (0.80–2.33)	0.78	0.96 (0.72–1.28)	0.78	0.69 (0.13–3.73)	0.67

TCD: transcranial cerebral Doppler; DCI: delayed cerebral ischemia; RR: relative risk; CI: confidence interval.

to the times to start of treatment, three studies^{7,9,10} started simvastatin therapy within 96 h and the other two studies^{6,8} started simvastatin therapy within 72 or 48 h (details in Table 1). No differences in vasospasm detected by TCD, DCI, or all-cause mortality were observed between the two subgroups (details in Table 2). Finally, with respect to the course of treatment, two studies^{7,10} continued for 21 days and the other three studies^{6,8,9} continued for 14 days (details in Table 1). No differences in vasospasm detected by TCD, DCI, or all-cause mortality were observed between the two subgroups (details in Table 2). No evidence existed for data heterogeneity. The quality of the evidence was moderate.

Sensitivity analysis

A sensitivity analysis was necessary to detect the stability of the consolidated results among the included studies because of their various definitions of outcomes and different sample sizes. The sensitivity analysis showed that the STASH trial, which had a large population, did not influence the consolidated results of all three outcomes (Table 2). The quality of this evidence was moderate.

Risk of bias in included studies

The risk of bias with respect to allocation concealment was unclear in two studies.^{6,7} The risk of bias with respect to blinding of the outcome assessment was unclear in four studies.^{6–9} The risk of bias with respect to selective reporting was high in one study.⁶ No other items showed a high risk of bias (Figure 3).

Discussion

Simvastatin, as the most potentially effective statin in the treatment of SAH, has been investigated for several years.¹⁴ However, the efficacy of simvastatin in clinical practice remains controversial because of the lack of large multicenter prospective clinical trials. The recent STASH trial, which was expected to provide strong evidence for simvastatin in the treatment of SAH, revealed discouraging results in the *Lancet Neurology*.¹⁰ These results exacerbated the debate. The present meta-analysis has shown that simvastatin does not have significant effects on vasospasm detected by TCD, DCI, or all-cause mortality. Further subgroup analysis showed that these consolidated results were

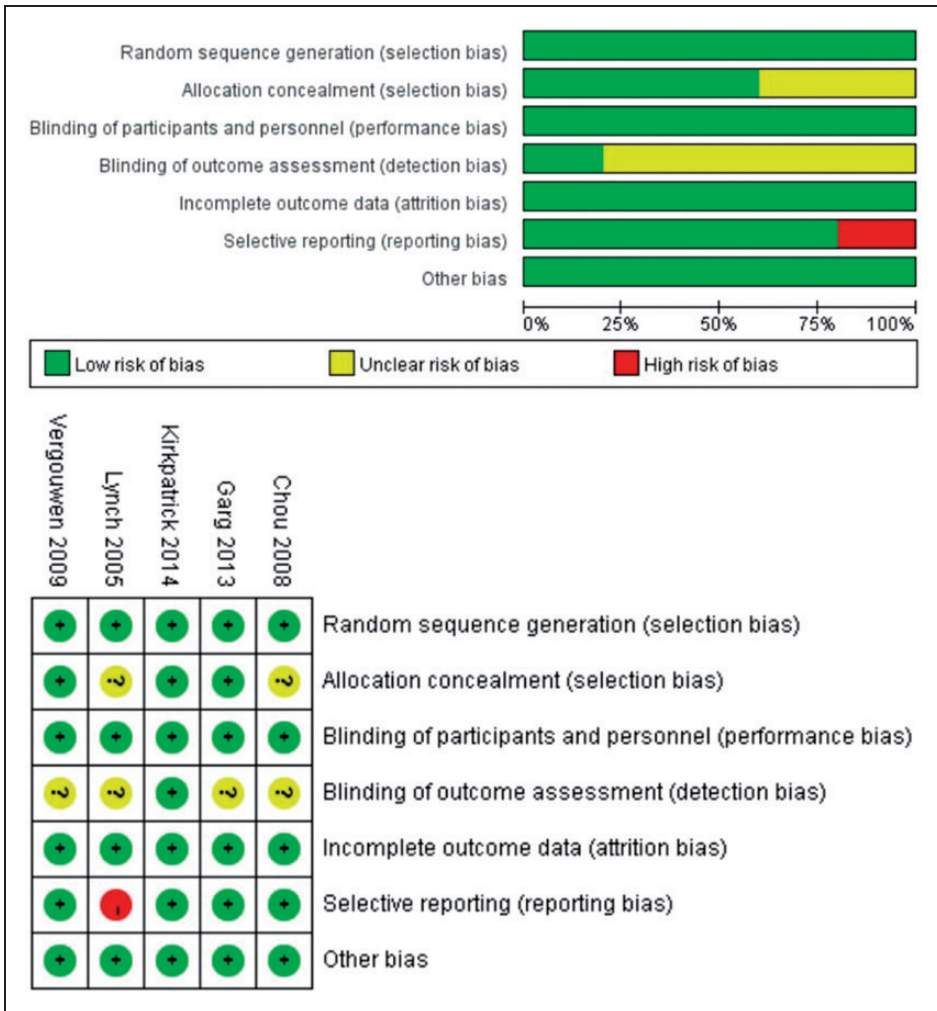


Figure 3. Summary of risk of bias in each study.

stable at different drug doses, different times to the start of treatment, and different courses of treatment in the included RCTs. Sensitivity analysis showed that the STASH trial, which had a large population, did not affect the consolidated results of all three outcomes. These results indicate that simvastatin has no benefit in decreasing the incidence of vasospasm, DCI, and all-cause mortality after aneurysmal SAH.

Cerebral vasospasm is responsible for the poor prognosis of aneurysmal SAH.¹⁵

Approximately 50% of patients with large arterial vasospasm eventually develop DCI, which is associated with a high mortality rate.^{16,17} Thus, the low incidence of cerebral vasospasm and DCI is considered to predict good functional recovery. In the present study, simvastatin had no significant effect on either vasospasm detected by TCD or DCI. Our findings are consistent with those of previous studies. To date, five retrospective studies,^{18–22} one prospective cohort study,²³ and five RCTs^{6–10} have evaluated

the efficacy of simvastatin on the incidence of vasospasm or DCI. Only one retrospective study¹⁸ and one RCT⁶ reported a decrease in vasospasm by simvastatin, but the study results were questionable due to several limitations. For example, Lynch et al.⁶ reported a high rate of vasospasm in their placebo group (60%), while the incidence of vasospasm in the simvastatin group was 26%, which is comparable with the incidence without treatment in a previous study.²⁴ This unrepresentative placebo group made the statistical analysis meaningless. Mortality is regarded as the most serious outcome of aneurysmal SAH, and it is usually analyzed to determine the acceptability and safety of treatment. Notably, however, the present study evaluated all-cause mortality, which cannot reflect the acceptability of simvastatin for SAH. Further studies are needed to classify the cause of mortality.

Several confounding factors may lead to heterogeneity, such as vasospasm measurement technique, DCI diagnosis, and therapeutic regimen; however, these factors are unlikely to have influenced our results. TCD was regarded as the most common technique with which to detect vasospasm by measurement of the middle cerebral artery velocity. Four of the five studies in this meta-analysis used three definitions of vasospasm: any peak systolic middle cerebral artery velocity of >120 ,⁸ >160 ,^{6,9} or >200 ⁷ cm/s. However, the subgroup analysis showed that the consolidated results were stable (data not shown). The difficulty in diagnosing DCI is another confounding factor. Although emerging data showed that perfusion magnetic resonance imaging has high accuracy for identification of DCI,²⁵ its high costs have restricted its wide application. The five RCTs in this meta-analysis employed several neurological examinations to detect the incidence of DCI with a similar relevance ratio. We performed subgroup analyses according to the drug dose, time to the start of treatment, and course of treatment to detect the influence of the

various therapeutic regimens. The STASH trial was questionable because of its half-dose of simvastatin (40 mg/day) compared with the other four RCTs (80 mg/day), and this difference was regarded to influence the efficacy of simvastatin. The present subgroup analysis showed no efficacy of simvastatin at either 80 mg/day or 40 mg/day in reducing vasospasm, DCI, or all-cause mortality. Moreover, a recent trial also showed no superiority of high-dose (80 mg/day) compared with lower-dose (40 mg/day) simvastatin treatment for patients with aneurysmal SAH.¹¹ The different times to the start of treatment and various durations of simvastatin are also unlikely to influence the consolidated results. Cerebral vasospasm most frequently occurred 7 to 10 days after aneurysm rupture and resolved spontaneously after 21 days.³ Although three RCTs only provided simvastatin for 14 days,^{6,8,26} this is sufficient time to prevent the incidence of cerebral vasospasm. Similarly, the time to the start of treatment in the included RCTs ranged from 48 h to 96 h, which was prior to the onset of cerebral vasospasm. The results of the subgroup analysis also indicate that the time to the start of treatment and duration of simvastatin had no influence on the stability of the consolidated results.

There were several limitations in our analysis. First, the present systematic review included only 4 small RCTs involving 148 patients and the STASH trial involving 803 patients. The small sample is an important limitation in the present meta-analysis, although the sensitivity analysis showed that the STASH trial with its large population did not influence the consolidated results of all three outcomes. Second, the treatment mode for ruptured aneurysms may have played an important role in the final outcomes. Surgical treatments might cause the subarachnoid blood clots to fill both lateral ventricles, leading to worse outcomes after SAH.²⁷ Finally, the severity of the patients' conditions at the time of recruitment was

inconsistent among the RCTs. Thus, the efficacy of simvastatin in patients with severe SAH might have been neglected.

Conclusion

Simvastatin showed no benefits in decreasing the incidence of vasospasm, DCI, or all-cause mortality after aneurysmal SAH. Routine prescription of simvastatin for aneurysmal SAH might not be beneficial. Further studies are needed to explore the mechanism of simvastatin's neuroprotective effect. A multi-center prospective study of simvastatin for patients with SAH involving a large sample size and long-term follow-up is still needed.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Appendix I

(hydroxymethyl)glutaryl-CoA reductase inhibitor[Title/Abstract] OR hydroxymethylglutaryl coenzyme A reductase inhibitor[Title/Abstract] OR HMG-CoA reductase inhibitor[Title/Abstract] OR statin[Title/Abstract] OR anticholesteremic agents[Title/Abstract] OR simvastatin[Title/Abstract] AND (subarachnoid hemorrhage [Title/Abstract] OR subarachnoid haemorrhage[Title/Abstract] OR vasospasm[Title/Abstract] OR vasospastic[Title/Abstract] OR aneurysmal[Title/Abstract] OR aneurysm[Title/Abstract] OR delayed ischemic neurological deficit[Title/Abstract] OR delayed ischemic neurologic deficit[Title/Abstract] OR delayed neurologic deficit [Title/Abstract] OR delayed neurological deficit[Title/Abstract] OR delayed infarct [Title/Abstract] OR SAH[Title/Abstract] OR delayed cerebral ischemia[Title/Abstract]).