Effect of statin treatment on vasospasm-related morbidity and functional outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

*Jian Shen, MD, Kai-Yuan Huang, MD, Yu Zhu, MD, Jian-Wei Pan, MD, PhD, Hao Jiang, MD, Yu-Xiang Weng, MD, and Ren-Ya Zhan, MD, PhD

Department of Neurosurgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou City, Zhejiang Province, People's Republic of China

OBJECTIVE The efficacy of statin therapy in treating aneurysmal subarachnoid hemorrhage (SAH) remains controversial. In this meta-analysis, the authors investigated whether statin treatment significantly reduced the incidence of cerebral vasospasm and delayed neurological deficits, promoting a better outcome after aneurysmal SAH.

METHODS A literature search of the PubMed, Ovid, and Cochrane Library databases was performed for randomized controlled trials (RCTs) and prospective cohort studies investigating the effect of statin treatment. The end points of cerebral vasospasm, delayed ischemic neurological deficit (DIND), delayed cerebral infarction, mortality, and favorable outcome were statistically analyzed.

RESULTS Six RCTs and 2 prospective cohort studies met the eligibility criteria, and a total of 1461 patients were included. The meta-analysis demonstrated a significant decrease in the incidence of cerebral vasospasm (relative risk [RR] 0.76, 95% confidence interval [CI] 0.61–0.96) in patients treated with statins after aneurysmal SAH. However, no significant benefit was observed for DIND (RR 0.88, 95% CI 0.70–1.12), delayed cerebral infarction (RR 0.66, 95% CI 0.33–1.31), mortality (RR 0.69, 95% CI 0.39–1.24) or favorable outcome, according to assessment by the modified Rankin Scale or Glasgow Outcome Scale (RR 0.99, 95% CI 0.92–1.17).

CONCLUSIONS Treatment with statins significantly decreased the occurrence of vasospasm after aneurysmal SAH. The incidence of DIND, delayed cerebral infarction, and mortality were not affected by statin treatment. Future research should focus on DIND and how statins influence DIND.

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KEY WORDS subarachnoid hemorrhage; vasospasm; delayed ischemic neurological deficit; statin; meta-analysis; aneurysm; vascular disorders

ANEURYSMAL subarachnoid hemorrhage (SAH) accounts for 3%–5% of all strokes and affects 600,000 patients worldwide per year.^{35,39} It typically affects a younger population than other types of stroke, and its combined morbidity and mortality reaches as high as 50%.^{1,39} Cerebral vasospasm is a common complication occurring 4–14 days after surgery in patients with aneurysmal SAH, and this can lead to severe delayed ischemic neurological deficit (DIND) and delayed cerebral infarction, which are indicative of a poor prognosis.^{12,14,18,22} Therefore, pharmacological treatments have targeted the

prevention of cerebral vasospasm, with disappointing results.⁴⁰ Nimodipine is the only drug that has moderately reduced vasospasm and DIND after SAH.^{25,47}

Recent studies have identified statin drugs as a potential treatment for vasospasm; multiple vascular functions for statin have been revealed using animal models that might help to reduce vasospasm in patients after aneurysmal SAH.^{4,8,13,24,28,32} However, the results from published clinical trials have been controversial. Some Phase II trials found that statin was effective in decreasing the incidence of vasospasm, while others have failed to confirm these

ABBREVIATIONS CI = confidence interval; DIND = delayed ischemic neurological deficit; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HDS-SAH = High-Dose Simvastatin for Aneurysmal Subarachnoid Hemorrhage; HHH = hypertension, hypervolemia, and hemodilution; M-H = Mantel-Haenszel; mRS = modified Rankin Scale; RCT = randomized controlled trial; RR = relative risk; SAH = subarachnoid hemorrhage; STASH = Simvastatin in Aneurysmal Subarachnoid Hemorrhage; TCD = transcranial Doppler; WFNS = World Federation of Neurosurgical Societies.

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* Drs. Shen, Huang, and Zhu contributed equally to this work.

findings.^{5,10,18,37,42,44} Meta-analyses have also produced inconsistent results. Four studies demonstrated a beneficial effect of statin treatment in at least 1 aspect,^{33,34,36,48} while no benefits were reported by the authors of 3 additional studies.^{16,17,41} Recently, 2 large-scale multicenter Phase III trials—Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) and High-Dose Simvastatin for Aneurysmal Subarachnoid Hemorrhage (HDS-SAH)—yielded disappointing findings; no benefits of simvastatin treatment were observed in patients with aneurysmal SAH during the STASH study, while authors of the HDS-SAH study reported that treatment with high doses of simvastatin (80 mg) was no more effective than treatment with low doses (40 mg).^{13,44,47} Both studies had limitations; no details of vasospasm were described in the STASH study, and no control group was used in the HDS-SAH study, making it difficult to draw firm conclusions.¹⁷ Therefore, the effect of statins on vasospasm remains unclear; positive effects may have been neutralized through an adverse pathway. Alternatively, statins may not be effective in humans. These questions currently remain unanswered.

Recently, a prospective cohort trial was published that investigated cognitive outcome after acute simvastatin treatment.⁴⁵ The observation period was not longer than 3 months; therefore, this type of study, with matched baseline characteristics and no loss to follow-up, may prove more useful than some small-scale randomized controlled trials (RCTs). A large-scale meta-analysis including RCTs and prospective cohort studies might reveal better evidence of the medical efficacy of statins in treating patients with aneurysmal SAH.

Methods

Search Strategy

We performed a literature search of the PubMed, Ovid, and Cochrane Library databases in November 2015. Additionally, we screened the US NIH clinicaltrials.gov database to identify ongoing clinical trials. The following search terms were used: 1) “statin” and “statin*” and “\$statin”; 2) “aneurysmal subarachnoid hemorrhage” and “subarachnoid h*emorrhage” and “subarachnoid hemorrhage.” We restricted the search to human studies, without any language limitations. All search results, including review articles, were evaluated by 2 investigators (J.W.P. and H.J.). Finally, the authors of the studies included in this meta-analysis were contacted to obtain any unpublished data related to the subject of our analysis.

Two investigators (J.W.P. and H.J.) independently selected potentially appropriate trials from the retrieved literature according to our inclusion criteria. The initial selection was based on a review of the title and abstract, and in a second selection the investigators reviewed the text in full. A consensus on which studies to include was established after a discussion between the investigators.

Eligibility Criteria

The following inclusion criteria were applied: 1) RCTs or prospective cohort studies investigated the effects of acute statin therapy in treating SAH; 2) patients were all diagnosed with aneurysmal SAH; 3) studies included at

least 1 of the following end points: cerebral vasospasm, DIND, delayed cerebral ischemia, outcomes measurements, and mortality.

The following exclusion criteria were applied: 1) the efficacy of statin treatment not investigated in human participants (such as experimental investigation and animal studies); 2) unmatched patient baseline characteristics between groups; 3) statin treatment of SAH not caused by ruptured aneurysm (such as trauma and arteriovenous malformation rupture); 4) statin treatment investigated prior to SAH or investigation into long-term use of statins; and 5) comparison of statin treatment with other drugs (such as magnesium sulfate and nimodipine).

Data Extraction

Data were extracted independently by 2 investigators (J.W.P. and H.J.), and a consensus was established. The following information was extracted from each publication: journal name, year of publication, first author, demographic information, baseline demographic and clinical characteristics, inclusion and exclusion criteria, interventions, and number of end points per subgroup. No unpublished data were received from the authors of the included studies.

Study End Points

The primary end point was cerebral vasospasm, and the secondary end points included DIND, delayed cerebral infarction, favorable outcomes, and mortality. The end points were defined according to the original studies (Table 1).

Statistical Analysis

Relative risks (RRs) and 95% confidence intervals (CIs) were calculated from the number of outcome events per subgroup to estimate the association of statin administration with various end point events. The heterogeneity of the study results was assessed by Cochran χ^2 Q statistics and the I^2 test, which determined whether the fixed-effects Mantel-Haenszel (M-H) or random-effects DerSimonian and Laird model was used. A p value ≤ 0.1 or I^2 value $\geq 50\%$ was considered indicative of heterogeneity. Sensitivity analyses were conducted to assess the influence of specific studies on the combined effect. All tests were 2-sided, and a p value ≤ 0.05 was considered significant. Statistical analyses were performed with Review Manager 5.3 and the Stata statistical software package (release 14.0; Stata Corp.).

Methodological Quality Assessment

Two investigators (J.W.P. and Y.X.W.) independently evaluated the methodological quality of the included trials with the Cochrane Collaboration's tool for assessing risk of bias, and a consensus was established.

Results

Search Results

One hundred sixteen studies were retrieved from PubMed, 57 from Ovid, 72 from the Cochrane Library, and 8 clinical trials were retrieved from the clinicaltrials.gov database. Duplicate studies and studies that did not

TABLE 1. Characteristics of patients with aneurysmal SAH in the 6 RCTs and 2 prospective cohort studies

Authors & Year	Study Type	Statin/ Placebo (no. of patients)	Mean Age (yrs ± SD)	Female (%)	WFNS Grade ≥ IV (statin/ placebo, total)	Fisher Grade ≥ IV (%)	Clipping (%)	Intervention
Lynch et al., 2015	RCT	19/20	56 ± 15	33 (85)		2 (5)	17 (44)	Patients randomized w/in 48 hrs of symptom onset to receive either 80 mg simvastatin daily or placebo for 14 days
Tseng et al., 2005	RCT	40/40	53 ± 12	44 (55)	13/13, 26 (33%)		52 (65)	Patients w/in 72 hrs from ictus were randomized equally to receive either 40 mg oral pravastatin or placebo daily for up to 14 days
Chou et al., 2008	RCT	19/20	53 ± 13	29 (74)	5/4, 9 (23%)	0 (0)	33 (85)	Thirty-nine statin-naïve Fisher Grade 3 SAH patients were double-blind randomized to receive simvastatin 80 mg/day or placebo
Macedo et al., 2010	RCT, no blind	11/9				8 (38)		Prospective, randomized, nonblind studies, 80 mg simvastatin daily w/in 72 hrs of ictus & a control group not used for 21 days
Garg et al., 2013	RCT	19/19	49 ± 9	17 (45)	1/0, 1 (3%)	0 (0)	38 (100)	All patients w/ aneurysmal SAH admitted w/in 96 hrs of ictus randomized to receive either simvastatin or placebo 80 mg/day for 14 days
Kirkpatrick et al., 2014	RCT	391/412	50 ± 10	551 (69)	95/89, 184 (23%)	406 (51)	256 (32)	Patients randomly assigned (1:1) to receive either simvastatin 40 mg or placebo daily for 21 days
McGirt et al., 2009	Psp	170/170	53 ± 13	256 (73)	45/34, 79 (23%)	125 (37)	275 (81)	80 mg simvastatin per day from admission until at least 14 days compared w/ control group w/o simvastatin treatment
Wong et al., 2015	Psp	51/51	57 ± 10	74 (73)	6/6, 12 (12%)		42 (41)	HDS-SAH patients randomly assigned to receive either 80 mg or 40 mg of simvastatin daily for 3 wks, w/ matched patients w/o simvastatin treatment in CD-SAH study

CD-SAH = Cognitive Dysfunction after Aneurysmal Subarachnoid Hemorrhage; Psp = prospective cohort studies.

meet the inclusion criteria were excluded. Two RCTs were excluded based on unmatched baseline patient characteristics: 1) Vergouwen et al. 2009, in which there were 44% of patients (7/16) in the simvastatin group and 6% of patients (1/16) in the placebo group, with a World Federation of Neurosurgical Societies (WFNS) score ≥ 4 ($p = 0.00$, Fisher's exact test); and 2) Diringer et al. 2014, in which there were 13% of patients in the simvastatin group and 42% of patients in the placebo group, with a WFNS score of 3–5.^{7,42} Six RCTs and 2 prospective studies qualified for the meta-analysis.^{5,10,13,18,21,23,37,45} A flowchart of the literature search for eligible articles is shown in Fig. 1.

Characteristics of Eligible Studies

The characteristics of the included studies are listed in Table 1. The eligibility criteria for patients recruited were similar between the trials. A total of 1461 patients were included: 1019 patients from 6 RCTs and 442 patients from 2 prospective studies.^{5,10,13,18,21,37,42,45} Four hundred ninety-nine patients received statin treatment and 520 patients received placebo treatment in 6 RCTs. Two hundred twenty-one patients received statin treatment and 221 patients received placebo treatment in 2 prospective studies. Baseline characteristics were described in detail, except in 1 study.²¹ Seventy percent of the patients were female (1004/1441). WFNS or Hunt and Hess grades were described in all studies except 2.^{18,21} Twenty-two percent of patients (311/1402) were in an initial comatose

state (WFNS Grade ≥ 4). The Fisher grade was provided in 6 studies, and 43% of patients (541/1252) were Fisher Grade IV.^{5,10,13,18,21,23} Management of ruptured aneurysms was described in all except 1 study, and 49% of patients (713/1441) underwent microsurgical clipping.²¹ Patient characteristics with a potential effect on the outcomes were similar between the simvastatin and placebo groups. Details of administered treatments, including nimodipine and fluid therapy, were described in all studies.

Definitions of Study End Points

Definitions and results of the study end points are presented in Table 2. Vasospasm was defined in multiple ways in some studies; we analyzed the transcranial Doppler (TCD) cerebral artery velocity in this meta-analysis. Four studies used TCD cerebral artery velocity to detect vasospasm, and these velocities varied.^{5,10,18,37} In the studies by McGirt et al. and Macedo et al., vasospasm was defined as responding to the combination of induced hypertension, hypervolemia, and hemodilution (HHH) therapy, or angiographic change.^{21,23}

Definitions of the secondary end points also varied; new ischemic neurological deficits or a decrease in 2 or more points on the modified Glasgow Coma Scale (GCS) were the criteria of DIND in 5 studies.^{5,10,13,37,45} Delayed cerebral infarction was mainly confirmed by CT, MRI, or other radiological strategies in 4 studies.^{5,13,37,44} Mortality rates were provided in 6 studies, and the Glasgow

FIG. 1. Flowchart of the literature search procedure. Psps = prospective studies.

Outcome Scale (GOS) and modified Rankin Scale (mRS) scores were assessed in 7 studies.^{5,10,13,21,22,37,45} The time of assessment ranged from hospital discharge to 3–6 months after the ictus. In 2 RCTs, only the median GOS and mRS scores were provided, without the exact patient values for each score.^{10,21} A favorable outcome was defined as an mRS score ≤ 2 in 4 studies and a GOS score ≥ 3 in 1 study.^{5,13,23,37,45}

Risk of Bias Assessment

The quality of the included studies was measured by Cochrane risk of bias assessment. If bias was not addressed in the trials, we assumed an unclear risk. The 2 prospective studies showed a high risk for randomization and blinding, while 2 of the small-sample RCTs showed

unclear bias risk by failing to describe the WFNS grade. However, these conclusions are subjective (Fig. 2).

Outcomes of Meta-Analysis

The pooled results are shown in Fig. 3. The incidence of cerebral vasospasm was 29% (82/278) and 39% (108/278) in statin-treated and placebo-treated patients, respectively. The statin-treated group had a lower incidence of cerebral vasospasm (M-H pooled RR 0.76, 95% CI 0.61–0.96; $p = 0.02$). Analysis of heterogeneity revealed mild heterogeneity among the studies (heterogeneity $\chi^2 = 8.55$, $I^2 = 42\%$, $p = 0.13$). Sensitivity analysis revealed that 1 RCT was mainly responsible for the heterogeneity (omitted heterogeneity $\chi^2 = 3.26$, $I^2 = 0\%$, $p = 0.46$), which may be explained by the alternative definition of a vasospasm

TABLE 2. Definitions and results of the study end points of included trials

Authors & Year	Cerebral Vasospasm	DIND	Delayed Cerebral Infarction	Favorable Outcome	Mortality
Lynch et al., 2005	$V_{MCA} \geq 160$ cm/sec by TCD or angiography; 5/19 statins, 12/20 controls (p = 0.03)				
Tseng et al., 2005	$V_{MCA} \geq 120$ cm/sec, w/ a LR 3; 17/40 statins, 25/40 controls (p = 0.01)	Development of focal neurological deficits, a drop in GCS score by 2 points; 2/40 statins, 12/40 controls (p = 0.00)	New cerebral infarcts on CT scans; 2/40 statins, 12/40 controls (p = 0.00)	mRS scores assessed at discharge, mRS ≤ 2 ; 23/40 statins, 19/40 controls (p = 0.71)	At discharge; 2/40 statins, 8/40 controls (p = 0.04)
Chou et al., 2008	Peak systolic middle cerebral artery velocity (PSV _{MCA}) ≥ 200 cm/sec, w/ a LR 3; 13/19 statins, 10/20 controls (p = 0.24)	2 or more point decrease in modified GCS score, unaccountable new focal neurological deficit lasting 2 hrs; 7/19 statins, 10/20 controls (p = 0.41)	Lesion consistent w/ infarction on CT or MRI in the territory of angiographic or TCD vasospasm; 2/19 statins, 5/20 controls (p = 0.41)	mRS scores at discharge, mRS ≤ 2 ; 7/19 statins, 10/20 controls (p = 0.41)	At discharge; 0/19 statins, 3/20 controls (p = 0.23)
Macedo et al., 2010	Cerebral arteriography examination; 1/11 statins, 4/9 controls				At discharge; 2/11 statins, 6/9 controls
Garg et al., 2013	TCD velocities >160 cm/sec; 3/19 statins, 5/19 controls (p = 0.70)	New ischemic neurological deficits in 1st 2 wks after the ictus not attributable to other causes; 5/19 statins, 8/19 controls (p = 0.31)			At 6 mos following ictus; 1/19 statins, 3/19 controls (p ≥ 0.05)
Kirkpatrick et al., 2014		A deterioration of 2 or more points on the GCS score that could not be attributed to any other cause; 64/391 statins, 67/412 controls (p = 0.97)	Proven radiological infarct; 61/391 statins, 71/412 controls (p = 0.53)	mRS scores assessed at discharge, mRS ≤ 2 ; 233/391 statins, 251/412 controls (p = 0.61)	At 6 mos following ictus; 37/391 statins, 35/412 controls (p = 0.59)
McGirt et al., 2009	Responding to therapy, a delayed infarct on CT or angiographic vasospasm; 43/170 statins, 52/170 controls (p = 0.28)			GOS scores assessed at discharge, GOS ≥ 3 ; 133/170 statins, 139/170 controls (p = 0.42)	At discharge; 31/170 statins, 26/170 controls (p = 0.47)
Wong et al., 2015		A fall of 2 or more points on the modified GCS, new focal neurological deficit lasting more than 2 hrs, CT evidence; 20/51 statins, 18/51 controls (p = 0.67)	Confirmed by interval CT of brain; 8/51 statins, 7/51 controls (p = 0.78)	mRS scores assessed at 3 mos, mRS score ≤ 2 ; 43/51 statins, 36/51 controls (p = 0.10)	
Total	82/278 statins, 108/278 controls	98/520 statins, 115/542 controls	73/501 statins, 95/523 controls	439/671 statins, 455/693 controls	73/650 statins, 81/670 controls

LR = Lindegaard ratio; V_{MCA} = velocity of the middle cerebral artery.

(peak systolic middle cerebral artery velocity ≥ 200 cm/sec; omitted M-H pooled RR 0.70, 95% CI 0.55–0.90, p = 0.01).⁵

DIND was observed in 19% (98/520) of statin-treated patients and 21% (115/542) of placebo-treated patients, with no statistically significant difference between the 2 groups (M-H pooled RR 0.88, 95% CI 0.70–1.12, p = 0.31). The heterogeneity of DIND was mild (heterogeneity $\chi^2 = 7.45$, $I^2 = 46\%$, p = 0.11). Sensitivity analysis revealed that heterogeneity of DIND was significantly reduced by eliminating the pravastatin study (omitted heterogeneity $\chi^2 = 1.75$, $I^2 = 0\%$, p = 0.63), while the RR was not significantly affected (omitted M-H pooled RR 0.97, 95% CI 0.76–1.24, p = 0.80).³⁷

Delayed cerebral infarction did not differ significantly between statin-treated and placebo-treated patients (statin-treated 15% [73/501], placebo-treated 18% [95/523], M-H pooled RR 0.66, 95% CI 0.33–1.31, p = 0.24). There was moderate heterogeneity in the occurrence of delayed cerebral infarction among the studies (heterogeneity $\chi^2 = 6.44$, $I^2 = 53\%$, p = 0.09), and sensitivity analysis showed that the pravastatin study significantly enhanced heterogeneity (omitted heterogeneity $\chi^2 = 1.22$, $I^2 = 0\%$, p = 0.54), while the RR was not affected (omitted M-H pooled RR 0.90, 95% CI 0.67–1.20, p = 0.46).³⁷

Favorable outcome was measured by mRS score in 4 studies and by GOS score in 1 study.^{5,13,23,37,45} There was no significant difference in the number of patients with

FIG. 2. Quality of the included RCTs and prospective cohort studies assessed by Cochrane risk of bias assessment. Figure is available in color online only.

a favorable outcome between statin-treated and placebo-treated groups (statin-treated 65% [439/671], placebo-treated 66% [455/693], M-H pooled RR 0.99, 95% CI 0.92–1.07, $p = 0.87$). There was no heterogeneity in the number of patients having a favorable outcome among the studies (heterogeneity $\chi^2 = 4.91$, $I^2 = 19\%$, $p = 0.30$), and sensitivity analysis revealed that the exclusion of any study did not significantly influence the RR estimate. There was also no significant difference in the overall mortality rate between the statin-treated and placebo-treated groups (statin-treated 11% [73/650], placebo-treated 12% [81/670], M-H pooled RR 0.69, 95% CI 0.39–1.24, $p = 0.22$), and no heterogeneity in the mortality rate was observed between the studies (heterogeneity $\chi^2 = 10.36$, $I^2 = 52\%$, $p = 0.07$). Sensitivity analysis revealed that the RR estimate and heterogeneity were not affected by the exclusion of any study (Table 3).

Meta-Analysis of Subgroups

We included 2 prospective cohort studies and 6 RCTs, which may have enhanced the potential clinical heterogeneity.^{23,45} One RCT used pravastatin (a hydrophilic statin) while the others used simvastatin (a lipophilic statin). Additionally, to measure patient outcome, some studies used mRS score while others used GOS score. To address this heterogeneity, we conducted subgroup meta-analyses (Table 4).

There was moderate heterogeneity in vasospasm analysis among the RCTs (heterogeneity $\chi^2 = 8.72$, $I^2 = 54\%$, $p = 0.07$), which was not significant according to the random method (random M-H pooled RR 0.70, 95% CI 0.42–1.18; $p = 0.18$) on a small-scale analysis of 216 patients.^{5,10,18,21,37} The occurrence of DIND, delayed cerebral infarction, favorable outcome, and death were not significantly different between RCTs and prospective cohort studies. The incidence of cerebral vasospasm was not significantly altered by simvastatin treatment (random M-H pooled RR 0.77, 95% CI 0.48–1.23, $p = 0.27$), and the level of heterogeneity was moderate (heterogeneity $\chi^2 = 7.97$, $I^2 = 50\%$, $p = 0.09$).^{5,10,13,18,21,23} No significant difference was observed in the incidence of other outcomes in the simvastatin-treated

subgroup analysis. Pravastatin treatment appears to reduce the incidence of DIND and delayed cerebral infarction according to the study by Tseng et al.³⁷ Omission of this study reduced the heterogeneity of the DIND and delayed cerebral infarction analysis. A similar effect was observed on the favorable outcomes measured by the mRS and GOS.

Discussion

The ongoing publication of new clinical trials and different eligibility criteria can make the results from previous meta-analyses controversial. Most previous meta-analyses have only included RCTs with a small number of patients (≤ 40), which were likely to have mismatched patient characteristics between the statin-treated and control groups. This represents a potential source of bias for previous meta-analyses. The patients' baseline characteristics should be carefully considered, especially when evaluating characteristics that have a great impact on the clinical end points. To our knowledge, patients with aneurysmal SAH and a high WFNS grade (4–5) have a higher incidence of DIND compared with patients with low WFNS grades.^{6,30} Hence, we only included studies with similar WFNS grades in the statin-treated and placebo-treated groups and excluded those studies with mismatched clinical characteristics between groups. Two recently published, large-scale multicenter randomized Phase III trials (STASH and HDS-SAH) have not investigated the relationship between statin treatment and vasospasm. The authors of the HDS-SAH study have recently published another prospective cohort trial that investigated the cognitive outcome following acute simvastatin treatment.⁴⁵ In our opinion, studies with matched baseline characteristics between the groups are preferable to RCTs if they had no loss to follow-up because of a short-term observation period (≤ 3 months). We excluded the retrospective cohort studies from our analysis because they had a larger bias than prospective studies and the study design, population, intervention, and control were variable.¹⁷

We included 6 RCTs and 2 prospective cohort studies that met our eligibility criteria, to generate a larger scale

FIG. 3. Forest plots of RRs to measure the efficacy of statin treatment on the prevention of cerebral vasospasm, DIND, delayed cerebral infarction, favorable neurological outcome, and mortality.

meta-analysis, and obtain a more accurate conclusion. Our meta-analysis was also the first to analyze cerebral infarction as an end point, which is difficult to distinguish from severe DIND, especially in comatose or sedated patients.^{26,43} DIND can either be reversible or progress to delayed cerebral infarction, which is often confirmed by an infarction lesion on CT or MRI scan within 6 weeks after

SAH. This is a common cause of unfavorable outcome and death.²⁶ After a series of analyses, we found that patients with aneurysmal SAH in the statin-treated groups have a significantly lower incidence of vasospasm. This finding is contradictory to 5 previous meta-studies and consistent with 2 meta-analyses previously published.^{16,17,33,34,36,41,48} The results regarding the secondary outcomes were

TABLE 3. Sensitivity analysis for mortality

Mortality	No. of Patients	No. of Studies	Statins	Placebo	RR (95% CI), p Value	I ² *	p Value (heterogeneity)*
All trials	1320	6	73/650	81/670	0.69 (0.39–1.24), 0.22	52%	0.07
RCTs	992	5	42/480	55/500	0.44 (0.17–1.12), 0.08	55%	0.06
Trials w/ simvastatin use	1240	5	71/610	73/630	0.99 (0.73–1.34), 0.94	43%	0.13
High-quality RCTs	959	4	40/469	49/491	0.50 (0.17–1.46), 0.21	51%	0.11
Trials informed baseline characteristics	1300	5	71/639	75/661	0.97 (0.72–1.32), 0.86	41%	0.15

* An I² value ≥ 50% or p value ≤ 0.1 was considered indicative of heterogeneity and a random-effects model was used.

disappointing. We found no evidence that statin treatment can improve DIND or delayed cerebral infarction. We also confirmed that there is no long-term benefit of statin treatment, evaluated by the mRS or GOS.

Previously published meta-analyses are summarized in Table 5. Compared with previous meta-analyses, our study has included the STASH study and imposed stricter eligibility criteria than other reviews, making our results more credible. Additionally, the present study has analyzed a larger number of patients in the meta-analysis (especially of vasospasm) and has a lower heterogeneity and higher power than those previously published. The clustering of

all end point results in our study is also a novel finding compared with previous meta-analyses of the same subject.

The reduction in vasospasm did not translate into a measurable clinical benefit according to our analysis. This finding is supported by a recent prospective study comparing the efficacy of different simvastatin doses on cerebral vasospasm.⁴⁶ This finding is very similar to that seen in the studies of clazosentan (the Clazosentan to Overcome Neurological Ischemia and Infarct Occurring After Subarachnoid Hemorrhage [CONSCIOUS] trials), in which vasospasm improvement occurs but functional outcome was

TABLE 4. Subgroup meta-analysis

Outcomes	No. of Patients	No. of Studies	Statins	Placebo	RR (95% CI), p Value	I ² (%)	p Value (heterogeneity)*
Cerebral vasospasm							
RCTs	216	5	39/108	56/108	0.70 (0.42–1.18), 0.18	54	0.07
Psps	340	1	43/170	52/170	0.83 (0.59–1.17), 0.28		
Simvastatin	476	5	65/238	83/238	0.77 (0.48–1.23), 0.27	50	0.09
Pravastatin	80	1	17/40	25/40	0.68 (0.44–1.05), 0.08		
DIND							
RCTs	960	4	78/469	97/491	0.68 (0.39–1.19), 0.18	55	0.08
Psps	102	1	20/51	18/51	1.11 (0.67–1.84), 0.68		
Simvastatin	982	4	96/480	103/502	0.97 (0.76–1.24), 0.80	0	0.63
Pravastatin	80	1	2/40	12/40	0.17 (0.04–0.70), 0.01		
Delayed cerebral infarction							
RCTs	922	3	65/450	88/472	0.48 (0.16–1.40), 0.18	67	0.05
Psps	102	1	8/51	7/51	1.14 (0.45–2.92), 0.78		
Simvastatin	944	3	71/461	83/483	0.90 (0.67–1.20), 0.46	0	0.54
Pravastatin	80	1	2/40	12/40	0.17 (0.04–0.70), 0.01		
Favorable outcomes							
RCTs	922	3	263/450	280/472	0.99 (0.89–1.10), 0.79	0	0.46
Psps	442	2	176/221	175/221	1.05 (0.85–1.30), 0.67	70	0.07
Simvastatin	1266	4	416/613	436/653	0.98 (0.91–1.06), 0.68	26	0.26
Pravastatin	80	1	23/40	19/40	1.21 (0.79–1.84), 0.37		
mRS	1024	4	306/501	316/523	1.01 (0.92–1.11), 0.84	27	0.25
GOS	340	1	133/170	139/170	0.96 (0.86–1.06), 0.42		
Mortality							
RCTs	980	5	42/480	55/500	0.44 (0.17–1.12), 0.08	55	0.06
Psps	340	1	31/170	26/170	1.19 (0.74–1.92), 0.47		
Simvastatin	1240	5	71/610	73/630	0.99 (0.73–1.34), 0.94	43	0.13
Pravastatin	80	1	2/40	8/40	0.25 (0.06–1.11), 0.07		

* An I² value ≥ 50% or p value ≤ 0.1 was considered indicative of heterogeneity and a random-effects model was used.

TABLE 5. Summary of previously published meta-analyses

Authors & Year	No. of Studies			Total no. Patients (statins/controls)	Vasospasm RR/OR, 95% CI, p Value; Heterogeneity, I^2 p Value	RR/OR, 95% CI, Heterogeneity, p Value			
	RCTs	Psp	Other*			No. of Patients (power)	DIND	Mortality	Outcomes
Sillberg et al., 2008	3	None	None	158 (78/80)	RR 0.73, 0.54–0.99, NS	RR 0.22, 0.06–0.82, NS	RR 0.38, 0.17–0.83, NS	RR 0.22, 0.06–0.82, NS	Outcomes
Kramer et al., 2010	6	None	None	309 (145/164)	OR 0.98, 0.35–2.78, $I^2 = 54\%$	OR 0.38, 0.23–0.65, $I^2 = 20\%$, $p = 0.29$	OR 0.51, 0.25–1.02, $I^2 = 26\%$, $p = 0.24$	No effect, $I^2 = 0\%$, $p = 0.77$	Strengths: RCTs only, no significant heterogeneity Weaknesses: Few studies & small sample size
Shen et al., 2013	6	1	5 All psp & other types	1851 (531/1320)		OR 0.80, 0.61–1.05, $I^2 = 37\%$, $p = 0.09$	OR 0.89, 0.56–1.40, $I^2 = 41\%$, $p = 0.08$	No effect, $I^2 = 0\%$, $p = 0.83$	Strengths: Large sample size, small heterogeneity Weaknesses: Low-quality studies included, low RCT weight
Vergouwen et al., 2010	4	None	None	190 (94/96)	RR 0.99, 0.66–1.48, $p = 0.95$; $I^2 = 56\%$, $p = 0.10$	RR 0.57, 0.29–1.13, $I^2 = 52\%$, $p = 0.10$	RR 0.92, 0.68–1.24, $I^2 = 0\%$, $p = 0.42$	RR 0.92, 0.68–1.24, $I^2 = 0\%$, $p = 0.42$	Strengths: RCTs only Weaknesses: Few studies & small sample size, significant heterogeneity
Tseng, 2011	6	None	None	309 (145/164)	RR 0.76, 0.59–1.00, low quality†	RR 0.60, 0.44–0.82, moderate quality‡	RR 0.62, 0.36–1.06, low quality‡	RR 0.97, 0.69–1.37, low quality‡	Strengths: RCTs only Weaknesses: No large sample RCTs included, small sample size
Su et al., 2014	6	None	None	249 (124/125)	RR 0.80, 0.54–1.17, $p = 0.25$; $I^2 = 49\%$, $p = 0.08$	RR 0.58, 0.37–0.92, $I^2 = 46\%$, $p = 0.14$	RR 0.30, 0.14–0.64, $I^2 = 0\%$, $p = 0.83$	RR 0.94, 0.77–1.16, $I^2 = 1\%$, $p = 0.39$	Strengths: RCTs only Weaknesses: No large sample RCTs included, small sample size
Liu & Chen, 2015	6	STASH	None	1031 (504/527)	OR 0.78, 0.35–1.77, $p = 0.26$; $I^2 = 48\%$, $p = 0.10$	OR 0.63, 0.32–1.24, $I^2 = 46\%$, $p = 0.11$	OR 1.02, 0.78–1.32, $I^2 = 0\%$, $p = 0.64$	OR 1.02, 0.78–1.32, $I^2 = 0\%$, $p = 0.64$	Strengths: RCTs only, 1 large sample RCT Weaknesses: Significant heterogeneity, only random effects applied
Zhang et al., 2015	7	None	None	347 (164/183)	RR 0.80, 0.53–1.21, $p = 0.29$; $I^2 = 52\%$, $p = 0.06$	RR 0.56, 0.41–0.75, $I^2 = 16\%$, $p = 0.31$	RR 0.54, 0.32–0.91, $I^2 = 13\%$, $p = 0.33$	RR 0.92, 0.71–1.20, $I^2 = 0\%$, $p = 0.81$	Strengths: RCTs only Weaknesses: No large sample RCTs included, small sample size
Present study	6	2	STASH & 1 psp	1461 (670/741)	RR 0.76, 0.61–0.96, $p = 0.02$; $I^2 = 42\%$, $p = 0.13$	RR 0.88, 0.70–1.12, $I^2 = 46\%$, $p = 0.11$	RR 0.69, 0.39–1.24, $I^2 = 52\%$, $p = 0.07$	RR 0.99, 0.92–1.17, $I^2 = 19\%$, $p = 0.30$	Strengths: 2 large scale studies Weaknesses: None

OR = odds ratio; NS = not significant.

* Other = other types of studies, such as retrospective studies and case-control studies.

† A study that contained more than 80 patients was regarded as large scale.

‡ Overall quality of evidence, considering methodological/analysis flaws, strength of evidence, and information about potential according to Tseng et al.³

not improved and mortality rate was not reduced.^{20,31,38,47} Vasospasm is not the only cause of DIND. Regional hypoperfusion and oligemia frequently occurred in territory or patients without angiographic vasospasm, and other factors such as early brain injury, cortical spreading depression ischemia, cerebral autoregulatory failure, and microthrombosis have been reported to cause DIND.^{3,9,19,27,30} Taken together, these findings support a relationship between vasospasm and DIND and show that clinical deterioration due to DIND is more than simply angiographic vasospasm, and our findings support this.²⁹ Further research should focus on DIND and delayed cerebral infarction.²⁷ The failure of statin treatment may be attributed to an aggravation of other risk factors, despite its pharmacological efficacy in treating vasospasm. For example, some studies have shown that statins may increase the risk of intracerebral hemorrhage and hemorrhagic stroke by lowering the cholesterol level.^{2,11} It remains to be investigated whether the effectiveness of statin treatment can be improved in combination with other therapies, such as HHH therapy to reduce cerebral autoregulatory failure.¹⁵ The pathophysiological mechanism of these ischemic deficits and the possible relationship between statins and other etiologies of DIND remain to be elucidated.

There are several potential limitations to our meta-analysis. First, the included studies were not all RCTs, which may have enhanced the methodological heterogeneity. However, there are not enough published studies assessing DIND and delayed cerebral infarction to avoid heterogeneity altogether. Finally, substantial differences in the study design among RCTs, including differences in the treatment and outcome evaluation, were unavoidable, which may account for the heterogeneity between RCTs according to the subgroup analysis.

Conclusions

Statin treatment significantly reduced vasospasm but failed to reduce DIND, delayed cerebral infarction, or mortality rate. The outcome following aneurysmal SAH was also not improved by statin treatment. Further research should focus on DIND rather than simply on angiographic vasospasm and how statins influence DIND.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zhan. Acquisition of data: Pan, Jiang, Weng. Analysis and interpretation of data: Jiang, Weng. Drafting the article: Shen, Huang, Zhu. Critically revising the article: Pan, Shen, Huang, Zhu. Reviewed submitted version of manuscript: Pan, Shen, Huang, Zhu. Statistical analysis: Shen, Huang, Zhu. Study supervision: Pan.

Correspondence

Jian-Wei Pan, Department of Neurosurgery, First Affiliated Hospital, School of Medicine, Zhejiang University, No. 79 Qingchun Rd., Hangzhou City 310003, Zhejiang Province, People's Republic of China. email: sjzju@163.com.