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Statin-treated patients with aneurysmal subarachnoid haemorrhage: a meta-analysis

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Abstract. – OBJECTIVE: The cerebral vasospasm, delayed ischemic neurological deficit (DIND), mortality and poor neurological outcome induced by aneurysmal subarachnoid haemorrhage (SAH) remain the major causes of morbidity and mortality in aneurysmal SAH patients. The effects of statin-treated for aneurysmal SAH patients were not comprehensively assessed.

PATIENTS AND METHODS: A systematically literature search was conducted in PubMed, EMBASE, ScienceDirect and Web of Science to identify relevant studies update to March 2015. Data were extracted and appraised independently by two authors. Moreover, fixed or random effects models were applied to calculate pooled results based on the degree of heterogeneity.

RESULT: Nine RCTs and three observational studies with a total of 1957 patients met the inclusion criteria. The results showed that statin treatment was not associated with a decrease in the occurrence of DIND (RR: 0.81, 95% CI: 0.66-1.00, p = 0.05), mortality (RR: 0.90, 95% CI: 0.69-1.18, p = 0.46) and poor neurological outcome (RR: 1.02, 95% CI: 0.86-1.20, p = 0.84), nonetheless, had a potential effect on reducing the incidence of vasospasm (RR: 0.77, 95% CI: 0.66-0.89, p = 0.0006).

CONCLUSIONS: This meta-analysis indicated that the use of statins decreases the occurrence of cerebral vasospasm, whereas did not support a beneficial effect of statins on the occurrence of DIND, death or poor neurological outcomes in patients with aneurysmal SAH.

Key Words:
Aneurysmal subarachnoid haemorrhage, Vasospasm, Mortality, Delayed ischemic neurological deficits, Statins, Meta-analysis.

Introduction

Subarachnoid haemorrhage (SAH) has a worldwide, age-adjusted annual incidence of approximately 4-7 cases per 100,000 people, including approximately 3-7% of individuals with strokes[1]. The most common reason for SAH may be aneurysms. Moreover, cerebral vasospasm, delayed ischemic neurological deficit (DIND) and arterial vasospasm induced by aneurysmal SAH, remain the major causes of morbidity and mortality in aneurysmal SAH patients[2]. Despite improvements in pharmacological attempts for aneurysmal SAH over the last decade□their efficacy has been largely disappointing[3-7], and the only effective pharmacological intervention in the acute treatment of SAH patients is nimodipine, a selective calcium-channel blocker[8]. However, the benefit of nimodipine for SAH is modest, and its mechanism is unclear[9-11]. Recently, accumulated studies have demonstrated that statins, which are 3-hydroxy-3 methylglutaryl (HMG) coenzyme A reductase inhibitors, offer several potential beneficial effects for patients with SAH or other diseases[12], such as improving endothelial function, raising cerebral blood flow,

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increasing cerebral endothelial nitric oxide synthase expression and ameliorating cerebral ischemia[13,14]. In some clinical studies, treatment with statins could reduce DIND, vasospasm, and mortality[15-18], whereas several other studies were unable to replicate these beneficial effects[19-22].

In 2014, Su et al[23] performed a meta-analysis to investigate the effects of statin-use on patients with aneurysmal SAH. They included 6 randomized controlled trials (RCTs) with a total of 249 patients and indicated that statin-use might play a positive role in reducing DIND and mortality. However, a more recent multicenter randomized phase 3 trial (simvastatin in aneurysmal subarachnoid haemorrhage, STASH) did not detect any benefit from the use of simvastatin in long-term or short-term outcomes in patients with aneurysmal SAH, which recruited 803 aneurysmal SAH patients[24]. Hence, the controversy regarding the effects of statin-use in patients with aneurysmal SAH remains. Here, we performed a comprehensive meta-analysis that included RCTs and observational studies to evaluate the effects of statin-use in patients with aneurysmal SAH.

Patients and Methods

Search Strategy

The PubMed, EMBASE, ScienceDirect and Web of Science databases were systematically searched for relevant articles using the search terms "statin", "simvastatin", "pravastatin", "atorvastatin", "aneurysmal subarachnoid haemorrhage" and "subarachnoid haemorrhage" up to March 2015. We also searched for studies limited to research in humans. Furthermore, additional relevant studies were identified by reading the references in the relevant articles.

Inclusion and Exclusion Criteria

All studies included in this meta-analysis were required to meet the following criteria: (1) it compared the effects of statins and placebo agent treatments in patients with aneurysmal SAH; (2) it assessed outcomes that included the incidence of vasospasm, mortality and DIND, as well as neurological recovery. The exclusion criteria were the following: (1) review articles, editorial comments, meta-analyses and duplicated studies; (2) lack of availability of the numbers of patients who survived or information regarding other outcomes; (3) no placebo agent comparison group.

Outcome Measures

The primary outcome was the incidence of vasospasms, which was defined by either transcranial Doppler (TCD) confirmation or angiographic confirmation as previously described[18,22]. The secondary outcomes were neurological recovery, DIND, and mortality during follow-up. A subgroup analysis was performed by the types of statin used and the study design. In addition, DIND was defined as the clinical symptoms and signs of new ischemic neurologic deficits that were not attributable to other causes such as infection or rebleeding, regardless of the presence of TCD or angiographic confirmation. Poor neurological recovery was defined on a modified Rankin Scale (mRS) of 3-6 points or a Glasgow Outcome Scale (GOS) of 1-4 points as previously described[16].

Quality Assessment

To evaluate the risk of bias in the included RCTs, two authors independently assessed the quality of each trial using the Cochrane Collaboration's tool[25]. There were seven items in this scale, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Moreover, each item could be divided as low risk, high risk or unclear risk. Any disagreements were discussed among the authors until they reached a consensus.

Statistical Analysis

Cochrane RevMan (version 5.1) software was used to perform the meta-analysis. All outcome variables were dichotomous, and relative risk (RR) was calculated with a 95% confidence interval (CI) using either a fixed-effects model or a random-effects model in light of the observed heterogeneity. Statistical heterogeneity for each pooled summary was estimated using Cochran's Q statistic and the I^2 statistic[26,27]. Heterogeneity was considered to be significant when $I^2 \geq 50\%$ or when a X-square test resulted in $p < 0.1$; in these case, a random-effects model was used, otherwise, a fixed-effects model was selected[28]. When heterogeneity was observed, a sensitivity analysis was conducted to explore the possible explanations for the heterogeneity. Publication bias was assessed using an examination of funnel plots and Egger's regression asymmetry tests[29].

Results

Selection of Studies and Study Characteristics

Eighty papers were identified through the comprehensive search strategy. After screening the titles and abstracts, 16 studies met our predefined inclusion criteria and 74 articles were excluded because they were case reports, review articles, letters to the editor or duplicate studies. The full texts of the remaining 16 studies were reviewed, and 4 of these were removed because they evaluated the effects of statin-use on pre-admission or pre-haemorrhage in patients with aneurysmal SAH[17,30-32]. Finally, 9 RCTs and 3 observational studies were included in the present meta-analysis. The selection process is shown in Figure 1.

In the present meta-analysis, 9 RCTs[16,18-20,22,24,33-35] and 3 observational studies[21,36,37] were included, involving a total of 1957 patients. Of these, 6 studies used a WFNS grade distribution[16,19,20,24,36,37], 7 studies used the Fisher grade distribution[16,18,19,21,24,36,37], and 3 studies used the Hunt and Hess grade distribution[18,21,22]. In addition, the location of the aneurysm and treatment of the aneurysms by clipping or coiling were reported in 7[16,19-22,24,37] and 6 articles, respectively[16,18,21,22,24,37]. Finally, the detailed characteristics of the included studies are presented in Table I.

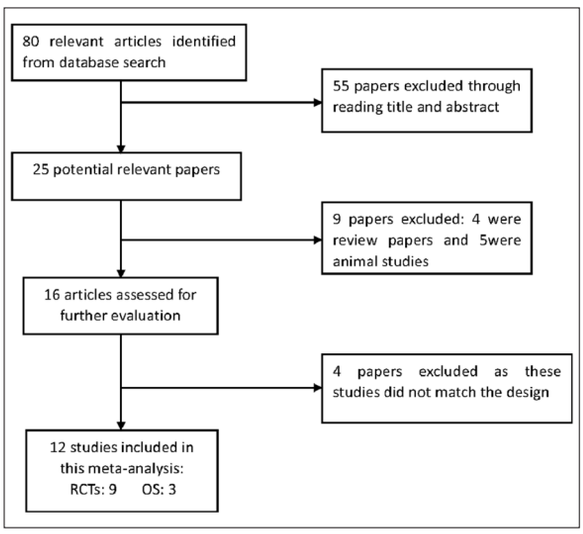

Figure 1. Selection process for the inclusion of studies in the meta-analysis.

A Cochrane risk of bias assessment was used to assess the quality of the included RCTs. We determined that a publication presented unclear risk if no specific illustration regarding the study design was found in the paper (Figure 2).

Table I. Characteristics of included studies (RCT: 574/645).

Study	Design	Follow-up time	Age (S/C) (mean)	Female (S/C)	Treatment	Duration	S/C (n)	Total
Chou 2008	RCT	ND	50/56	13/16	Simvastatin 80 mg	up to 21 days or until discharge	19/20	39
Vergouwen 2009	RCT	3 months and 6 months	53/54	8/12	Simvastatin 80 mg	up to 15 days	16/16	32
Garg 2013	RCT	1, 3 and 6 months	49.4/48.8	8/9	Simvastatin 80 mg	up to 14 days	19/19	38
Tseng 2005	RCT	ND	53.8/52	25/19	Pravastatin 40 mg	up to 14 days	40/40	80
Kirkpatrick 2014	RCT	6 months	51/49	260/291	Simvastatin 40 mg	up to 21 days	391/412	803
Lynch 2005	RCT	ND	65/47 (median)	6/17	Simvastatin 80 mg	up to 14 days	19/20	39
Oglivy 2006	RCT	ND	ND	ND	Simvastatin 80 mg	ND	19/20	39
Macedo 2009	RCT	ND	ND	ND	Simvastatin 80 mg	up to 21 days	11/10	21
Jaschinski 2008	RCT	ND	ND	ND	Pravastatin 40 mg	ND	40/58	98
Sanchez-Pena 2012	Case and historical controls study	1 year	ND	ND	Aatorvastatin 40 mg	up to 21 days	142/136	278
McGirt 2009	Prospective observational cohort study	ND	53/53	120/136	Simvastatin 80 mg	up to 14 days	170/170	340
Kramer 2008	Retrospectively cohort study	ND	56/55	54/50	Simvastatin 80 mg	ND	71/79	150

Abbreviations: RCT, random controlled trial; ND, no detailed data; S/C, statin-treated/control.

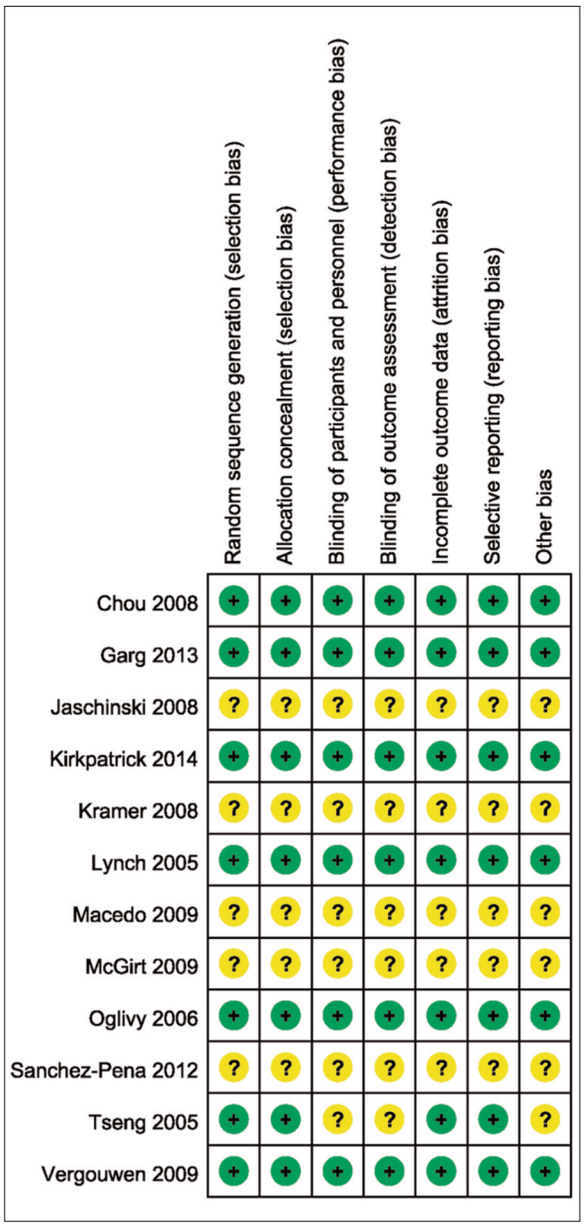

Figure 2. Quality assessment of the included RCTs using the Cochrane risk of bias assessment.

Meta-Analysis

Vasospasm

A total of 10 studies including 7 RCTs and 3 cohort studies investigated the effects of stain treatment on the incidence of vasospasm. The incidence of vasospasm was 169/526 and 224/530 in statin-treated patients and placebo-treated patients, respectively. A moderately significant reduction in the occurrence of vasospasm was observed (RR = 0.77, 95% CI = 0.66-0.89, p = 0.0006) when a fixed-effects model was used (I^2 = 29% and p = 0.18 for heterogeneity) (Figure 3A and Table II).

DIND

The proportion of patients with DIND was reported in 7 articles, wherein it was found to occur 115/596 in statin-treated patients compared with 158/645 in placebo-treated patients (RR=0.81, 95% CI= 0.66-1.00, p=0.05) (Figure 3B and Table II). Moreover, heterogeneity was not observed in the pooled analysis (I^2 = 30%, p = 0.20 for heterogeneity).

Mortality

Data regarding mortality was acquired from 9 studies. We observed that the incidence of mortality was 84/725 and 99/765 in statin-treated patients and placebo-treated patients, respectively. There was no significant heterogeneity (I^2 = 30%, p = 0.18 for heterogeneity) between these studies. Therefore, a fixed-effects model was applied. The result indicated that statin-treatment was not associated with a significant decrease in the occurrence of mortality (RR = 0.90, 95% CI = 0.69-1.18, p = 0.46) (Figure 3C and Table II).

Neurological Outcomes

A total of 7 articles reported detailed data regarding neurological outcomes. However, in line with the definition of a poor neurological outcome used in previous studies, 4 of these studies were eligible for the pooled analysis. The results of the meta-analysis showed that there was no significant difference between two groups (181/556 in statin-treated group and 183/575 in placebo-treated group, RR: 1.02, 95% CI: 0.86-1.20, p = 0.84) with no substantial heterogeneity (I^2 = 0%, p = 0.75).

Subgroup Meta-Analysis

Given that the evidence acquired from these RCTs showed high reliability and simvastatin was used in most of studies, we performed a subgroup meta-analysis that was stratified by RCT and simvastatin. Outcomes are shown in Table II. According to the meta-analysis from the RCTs and simvastatin, the outcomes for the occurrence of DIND, mortality or poor neurological outcomes were not materially changed between the two groups. However, the incidence of vasospasm was still significantly decreased in the statin-treated patients, compared to the placebo-treated patients.

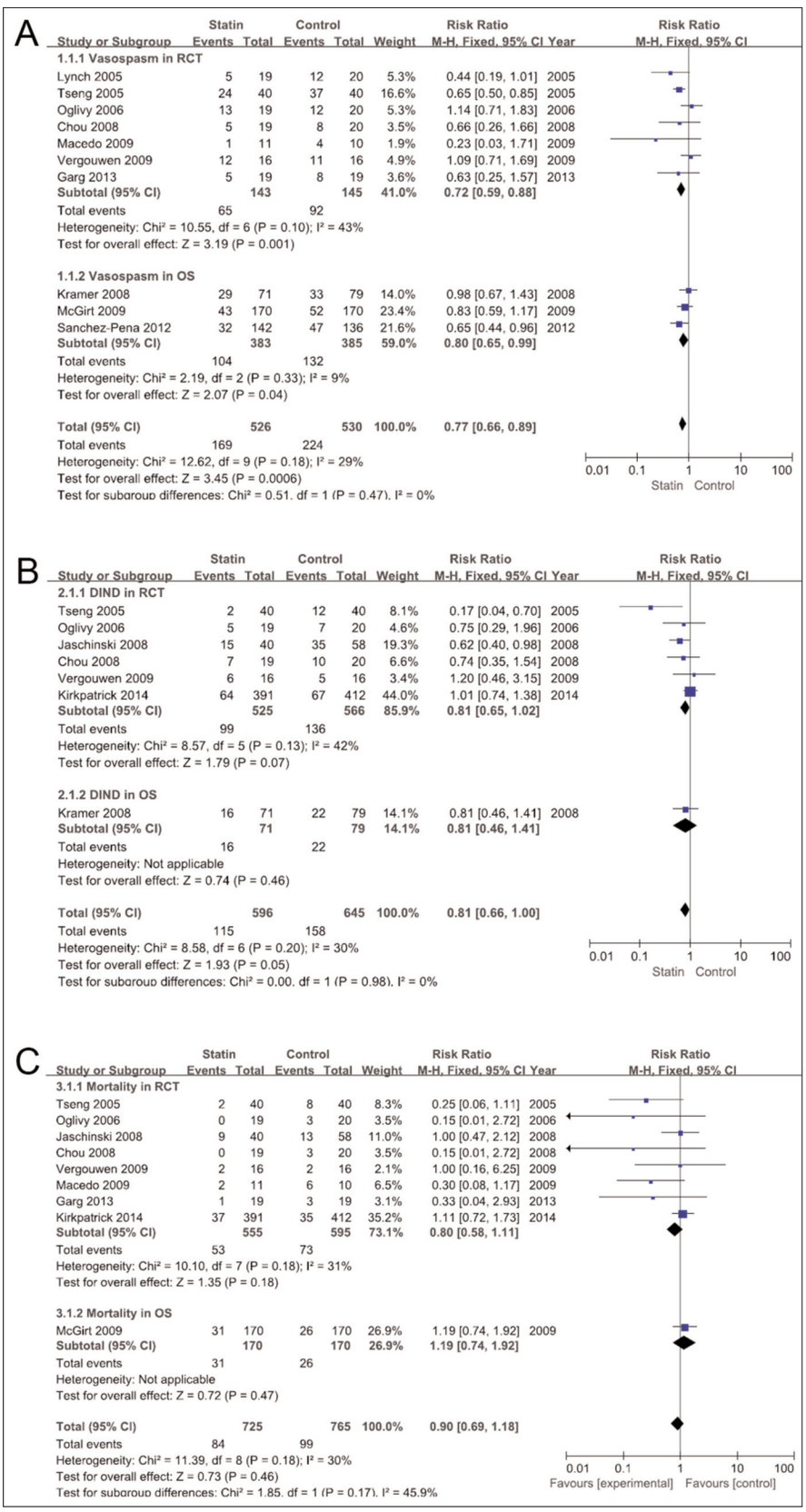

Figure 3. Efficacy of statin treatment for the prevention of the following outcomes: vasospasm ***(A)***, DIND ***(B)***, and mortality ***(C)***.

Table II. Outcome of meta-analysis.

Outcomes		Number of patients	Statin	Control	Model	RR (95% CI)	I^2 (%)	P_h
Vasospasm	All	1056	169/526	224/530	F	0.77 [0.66, 0.89]	29	0.18
	RCT	288	65/143	92/145	F	0.72 [0.59, 0.88]	43	0.10
	Simvastatin	548	84/273	107/275	F	0.79 [0.64, 0.99]	27	0.22
DIND	All	1241	115/596	158/645	F	0.81 [0.66, 1.00]	30	0.20
	RCT	1091	99/525	136/566	F	0.81 [0.65, 1.02]	42	0.13
	Simvastatin	913	82/445	89/468	F	0.97 [0.74, 1.26]	0	0.79
Mortality	All	1490	84/725	99/765	F	0.90 [0.69, 1.18]	30	0.18
	RCT	1150	53/555	73/595	F	0.80 [0.58, 1.11]	31	0.18
	Simvastatin	1312	73/645	78/667	F	0.96 [0.71, 1.29]	26	0.23
Poor neurological outcome	All	1211	198/596	204/615	F	1.00 [0.85, 1.17]	0	0.73
	RCT	933	146/454	156/479	F	0.98 [0.82, 1.18]	0	0.59
	Simvastatin	853	129/414	135/439	F	1.01 [0.83, 1.23]	0	0.55
	Discharge	922	186/450	188/472	F	1.04 [0.89, 1.21]	0	0.45
	3 months	32	42293	14/16	–	0.71 [0.47, 1.09]	–	–
	6 months	814	117/395	125/419	F	0.99 [0.80, 1.22]	0	0.48
	1 year	278	52/142	48/136	–	1.04 [0.76, 1.42]	–	–

Abbreviations: DIND, delayed ischemic neurological deficit; All, all eligible studies; RCT, random controlled trial; F, fixed-effects model; CI, confidence interval; P*h*: *p* value for heterogeneity.

With regard to poor neurological outcomes, we performed a meta-analysis based on the follow-up period. Whether the time at which poor neurological outcome was evaluated at discharge, 3 months, 6 months or 1 year later, the statin-treated group did not show an advantage in reducing the occurrence of poor neurological outcome compared to the control group.

Publication Bias

Publication bias was assessed using funnel plots and Egger's tests. As shown in Figure 4, the shapes of the funnel plots did not show evidence of obvious asymmetry. Moreover, the results of the Egger's tests also supported this finding and did not show any evidence of publication bias ($p_{\text{for Egger's test}} = 0.495$).

Discussion

Statins were shown to have neuroprotective effects in patients with aneurysmal SAH in two small RCTs published in 2005 that showed results including a reduced incidence of cerebral vasospasm and DIND. Nevertheless, these results were not observed in subsequent RCTs. These inconsistencies may be due to the limited sample sizes in the studies and their inadequate statistical power. Thus, we performed a meta-analysis of all eligible RCTs and observational studies to address these ambiguities. The results of the present meta-analysis included 12 studies with 1957 patients (9 RCTs and 3 observational studies) and showed that statins therapy in patients with aneurysmal SAH significantly reduced the prevalence of cerebral vasospasm, whereas, it did not provide a significant benefit in terms of reducing DIND, poor neurological outcomes and mortality.

Cerebral vasospasm is an important cause of cerebral ischemia and death following aneurysmal SAH, and the prevention of this condition

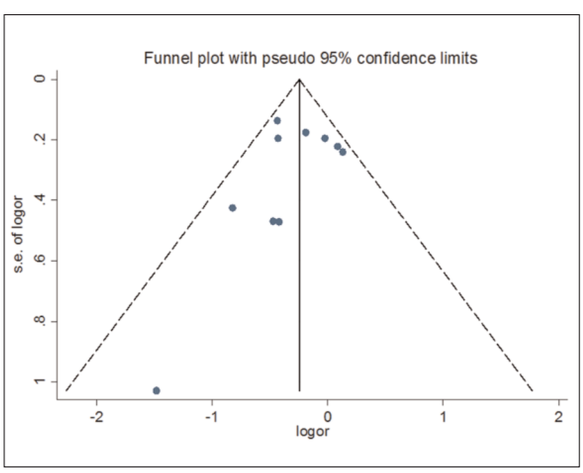

Figure 4. Funnel plot of publication bias.

remains a key target of pharmacological treatments for aneurysmal SAH. Ecker et al[38] first reported the presence of intracranial artery vasospasm with reference to a ruptured aneurysm. Multiple signalling pathways have been shown[39-41] to be responsible for cerebral vasospasm after aneurysmal SAH, including pathways involved in the induction of inflammation by blood degradation products and the endothelin-1 and nitric oxide (NO) synthetic pathways. Recently, both *in vitro* and *in vivo* studies have suggested that statins could biochemically remodel the endothelium, inhibit a number of inflammatory processes during cerebral ischemia and reperfusion, reduce lipoprotein oxidation and ameliorate free radical injury. However, the results of previous clinical trials were inconclusive. Three studies[16,18,36] showed that statin therapy after aneurysmal SAH significantly reduced the incidence of vasospasm, which was not observed in the other studies. In this meta-analysis, the results showed a significant decrease in the rate of cerebral vasospasm in stain-treated patients with aneurysmal SAH, which was also observed in the RCTs subgroups. Whereas a recent multicenter RCT (STASH) was not included due to the lack of available data regarding the incidence of cerebral vasospasm. Hence, these results should be interpreted with caution[24].

To date, DIND remains a major source of disability in patients with SAH and it is often associated with cerebral vasospasm. Given the beneficial effect of simvastatin on reducing DIND in patients after aneurysmal SAH, the results of our pooled-analysis showed a non-significant difference in the occurrence of DIND between statin-treated and control groups and also in the subgroup analysis by study type. In all eligible RCTs, the occurrence of DIND varied from 5.00% to 37.50% and 16.26% to 60.34% in the stain-treated and placebo-treated groups, respectively. The similarity between vasospasm-related DIND resulting from an impairment in cerebral blood flow and DIND resulting from delayed clinical manifestations might, at least in part, lead to the inconclusive results seen in previous studies.

The results of previous studies were also inconsistent regarding mortality after aneurysmal SAH. A recent meta-analysis showed that statin-treatment prevented the occurrence of death; nonetheless, interpretation of the results of that meta-analysis might be viewed with caution due to its small sample size, which only included only 6 RCTs with 249 patients. The current meta-analysis (involving 1150 patients) did not find any evidence to support a beneficial effect on lowering the occurrence of death in statin-treated in patients with SAH. For the analysis of functional outcomes, we did not observe a significant difference between any two groups at discharge or a 3-months, 6-months, or 1-year follow-up. Because the definition of a poor neurological outcome was sometimes a mRS of 3-6 points or GOS of 1-4 points, we were only able to acquire available information from 4 studies[20,22,24,36]. However, two articles defined a poor neurological outcome as a GOS of 1-2 or 1-3 points[21,37], and some studies did not report the effects of statin-treatment on functional outcomes in SAH patients[18,34,35], and this might have influenced the interpretation of the results of our meta-analysis.

Despite significantly increasing the statistical power of this study by pooling data from different studies, some limitations should be considered in this meta-analysis. Firstly, two RCT papers that have been published only as abstracts presented a high risk in the blinding of participants and outcome assessments[34,35]. Secondly, there were differences in the dosages of statin-used (80 mg or 40 mg once daily), and a higher dosage of statins might have a more positive effect. Moreover, the criteria for outcome assessments were also varied among the included studies, for example, the criteria for cerebral vasospasm assessment was a mean blood flow velocity (V_{mean}) > 120 cm/s by transcranial Doppler (TCD) in some studies whereas Lynch et al and Garg et al defined vasospasm as V_{mean} > 160 cm/s, which might have influenced the results.

Conclusions

The use of statins following aneurysmal SAH might have a potential effect on reducing the occurrence of cerebral vasospasm in patients, whereas their use may not be associated with a decrease in the occurrence of mortality, DIND or poor neurological outcomes. Moreover, in light of the variations in methodology in the included RCTs and observational studies, the results should also be interpreted carefully. Finally, additional large and multicenter RCTs are required to validate our results.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009; 8: 355-369.

2) Connolly ES Jr., Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P, American Heart Association Stroke C, Council on Cardiovascular R, Intervention, Council on Cardiovascular N, Council on Cardiovascular S, Anesthesia, Council on Clinical C. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke 2012; 43: 1711-1737.

3) Siasios I, Kapsalaki EZ, Fountas KN. Cerebral vasospasm pharmacological treatment: an update. Neurol Res Int 2013; 2013: 571328.

4) Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, Vajkoczy P, Wanke I, Bach D, Frey A, Marr A, Roux S, Kassell N. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol 2011; 10: 618-625.

5) van den Bergh WM, Algra A, van Kooten F, Dirven CM, van Gijn J, Vermeulen M, Rinkel GJ, Group MS. Magnesium sulfate in aneurysmal subarachnoid hemorrhage: a randomized controlled trial. Stroke 2005; 36: 1011-1015.

6) Shaw MD, Vermeulen M, Murray GD, Pickard JD, Bell BA, Teasdale GM. Efficacy and safety of the endothelin, receptor antagonist TAK-044 in treating subarachnoid hemorrhage: a report by the Steering Committee on behalf of the UK/Netherlands/Eire TAK-044 Subarachnoid Haemorrhage Study Group. J Neurosurg 2000; 93: 992-997.

7) Haley EC, Jr., Kassell NF, Apperson-Hansen C, Maile MH, Alves WM. A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. J Neurosurg 1997; 86: 467-474.

8) Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, Lang DA, Nelson R, Richards P. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. Br Med J 1989; 298: 636-642.

9) Bederson JB, Connolly ES, Jr., Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE, Jr., Harbaugh RE, Patel AB, Rosenwasser RH, American Heart A. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009; 40: 994-1025.

10) Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev 2007: CD000277.

11) Loch Macdonald R. Management of cerebral vasospasm. Neurosurg Rev 2006; 29: 179-193.

12) Cheng HH, Tang TT, He Q, Huang LJ, Lin XL, Chen M, Yang C, Geng DF, Jiang SP. Beneficial effects of statins on outcomes in pneumonia: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2014; 18: 2294-2305.

13) Sugawara T, Ayer R, Zhang JH. Role of statins in cerebral vasospasm. Acta Neurochir Suppl 2008; 104: 287-290.

14) McGirt MJ, Lynch JR, Parra A, Sheng H, Pearlstein RD, Laskowitz DT, Pelligrino DA, Warner DS. Simvastatin increases endothelial nitric oxide synthase and ameliorates cerebral vasospasm resulting from subarachnoid hemorrhage. Stroke 2002; 33: 2950-2956.

15) Tseng MY, Hutchinson PJ, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute pravastatin treatment on intensity of rescue therapy, length of inpatient stay, and 6-month outcome in patients after aneurysmal subarachnoid hemorrhage. Stroke 2007; 38: 1545-1550.

16) Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomized placebo-controlled trial. Stroke 2005; 36: 1627-1632.

17) Parra A, Kreiter KT, Williams S, Sciacca R, Mack WJ, Naidech AM, Commichau CS, Fitzsimmons BF, Janjua N, Mayer SA, Connolly ES, Jr. Effect of prior statin use on functional outcome and delayed vasospasm after acute aneurysmal subarachnoid hemorrhage: a matched controlled cohort study. Neurosurgery 2005; 56: 476-484; discussion 476-484.

18) Lynch JR, Wang H, McGirt MJ, Floyd J, Friedman AH, Coon AL, Blessing R, Alexander MJ, Graffagnino C, Warner DS, Laskowitz DT. Simvastatin reduces vasospasm after aneurysmal subarachnoid hemorrhage: results of a pilot randomized clinical trial. Stroke 2005; 36: 2024-2026.

19) Garg K, Sinha S, Kale SS, Chandra PS, Suri A, Singh MM, Kumar R, Sharma MS, Pandey RM, Sharma BS, Mahapatra AK. Role of simvastatin in prevention of vasospasm and improving functional outcome after aneurysmal sub-arachnoid hemorrhage: a prospective, randomized, double-blind, placebo-controlled pilot trial. Br J Neurosurg 2013; 27: 181-186.

20) Vergouwen MD, Meijers JC, Geskus RB, Coert BA, Horn J, Stroes ES, van der Poll T, Vermeulen M, Roos YB. Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomized trial. J Cereb Blood Flow Metab 2009; 29: 1444-1453.

21) McGirt MJ, Garces Ambrossi GL, Huang J, Tamargo RJ. Simvastatin for the prevention of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage: a single-institution prospective cohort study. J Neurosurg 2009; 110: 968-974.

22) Chou SH, Smith EE, Badjatia N, Nogueira RG, Sims JR, 2nd, Ogilvy CS, Rordorf GA, Ayata C. A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage. Stroke 2008; 39: 2891-2893.

23) Su SH, Xu W, Hai J, Wu YF, Yu F. Effects of statins-use for patients with aneurysmal subarachnoid hemorrhage: a meta-analysis of randomized controlled trials. Sci Rep 2014; 4: 4573.

24) Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD, Collaborators S. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol 2014; 13: 666-675.

25) JPT H. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration. http://handbookcochraneorg/2011; Accessed April 5, 2015.

26) Zintzaras E, Lau J. Synthesis of genetic association studies for pertinent gene-disease associations requires appropriate methodological and statistical approaches. J Clin Epidemiol 2008; 61: 634-645.

27) Trikalinos TA, Salanti G, Zintzaras E, Ioannidis JP. Meta-analysis methods. Adv Genet 2008; 60: 311-334.

28) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

29) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997; 315: 629-634.

30) Lizza BD, Kosteva A, Maas MB, Rosenberg NF, Liotta E, Guth J, Levasseur-Franklin KE, Naidech AM. Preadmission statin use does not improve functional outcomes or prevent delayed ischemic events in patients with spontaneous subarachnoid hemorrhage. Pharmacotherapy 2014; 34: 811-817.

31) Moskowitz SI, Ahrens C, Provencio JJ, Chow M, Rasmussen PA. Prehemorrhage statin use and the risk of vasospasm after aneurysmal subarachnoid hemorrhage. Surg Neurol 2009; 71: 311-317, discussion 317-318.

32) Kern M, Lam MM, Knuckey NW, Lind CR. Statins may not protect against vasospasm in subarachnoid haemorrhage. J Clin Neurosci 2009; 16: 527-530.

33) Oglivy C, Chou S, Ayata C, Smith E, Nogueira R, Rordorf G. Safety and feasibility of simvastatin in delayed vasospasm prevention following aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled study. Crit Care Med 2006; 34: A80.

34) Macedo S, Bello Y, Silva A, Siqueira C, Siqueira S, Brito L. Effects of simvastatin in prevention of vasospasm in nontraumatic subarachnoid hemorrhage: preliminary data. Crit Care 2009; 13: P103.

35) Jaschinski U, Scherer K, Lichtwarck M, Forst H. Impact of treatment with pravastatin on delayed ischemic disease and mortality after aneurysmal subarachnoid hemorrhage. Crit Care 2008; 12: P112.

36) Sanchez-Pena P, Nouet A, Clarencon F, Colonne C, Jean B, Le Jean L, Fonfrede M, Aout M, Vicaut E, Puybasset L. Atorvastatin decreases computed tomography and S100-assessed brain ischemia after subarachnoid aneurysmal hemorrhage: a comparative study. Crit Care Med 2012; 40: 594-602.

37) Kramer AH, Gurka MJ, Nathan B, Dumont AS, Kassell NF, Bleck TP. Statin use was not associated with less vasospasm or improved outcome after subarachnoid hemorrhage. Neurosurgery 2008; 62: 422-427; discussion 427-430.

38) Ecker A, Riemenschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. J Neurosurg 1951; 8: 660-667.

39) Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schutt S, Fritzinger M, Horn P, Vajkoczy P, Kreisel S, Brunner J, Schmiedek P, Hennerici M. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry 2001; 70: 534-537.

40) Jung CS, Oldfield EH, Harvey-White J, Espey MG, Zimmermann M, Seifert V, Pluta RM. Association of an endogenous inhibitor of nitric oxide synthase with cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 2007; 107: 945-950.

41) Macdonald RL, Weir BK. A review of hemoglobin and the pathogenesis of cerebral vasospasm. Stroke 1991; 22: 971-982.