Original Article
Effect of statins treatment for patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis of observational studies and randomized controlled trials

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Abstract: Vasospasm is one of the most common complications after aneurysmal subarachnoid hemorrhage. Statins have been proven to be effective to reduce the incidence of vasospasm both in experimental subarachnoid hemorrhage and several clinical trials before. This meta-analysis aimed to investigate the efficacy of statins for patients with aneurysmal subarachnoid hemorrhage. We made strict search strategies to select the randomized controlled trial and observational studies published up to December 20th 2014. Outcomes of interest were cerebral vasospasm, delayed cerebral ischemia and poor outcome. Data analyses of RCTs and observational studies were made separately. Finally six randomized clinical trial and eight observational studies were included in this meta-analysis. There were in total 1031 patients in six RCTs with 504 patients received statins and 527 patients in placebo group. 561 patients with statins compared with 1579 patients in no statin-use group were finally included in 8 observational studies. Outcomes included in this meta-analysis(cerebral vasospasm, DIC and poor outcome) all indicated no statistical significance between two groups both in RCTs and observational studies. No benefits of statins-use for patients with aneurysmal subarachnoid hemorrhage were observed in both RCTs and observational studies, which was quite different from the results of several previous meta-analysis.

Keywords: Statin, subarachnoid hemorrhage, vasospasm, delayed cerebral ischemia, poor outcome, meta-analysis

Introduction

Subarachnoid hemorrhage (SAH) is a relatively common cerebrovascular disease with an estimated annual incidence of 9/10,000 [1] and about 85% patients with SAH were caused by ruptured intracranial aneurysm [2]. Cerebral vasospasm, which may caused by various factors (inflammatory cascade, nitric oxide fluxes and alterations of intracellular calcium dynamics, et al.) [3], is one of the most common complications after aSAH. Vasospasm occurs with high incidence mainly in 7-10 days after aSAH and then gradually disappeared in 21 days [4]. There are 20-40% patients with subarachnoid hemorrhage developed with a complication of symptomatic vasospasm and about 30% of patients with cerebral ischemia or infraction after aSAH were caused by vasospasm [5, 6]. Patients experienced DCI in their duration of hospital stay had increased risk of neuropsychological deficits compared with patients with

no DCI after aSAH [7]. Delayed cerebral ischemia (DCI) with an incidence of 30% in patients with initial hemorrhage remains a desperate obstacle in achieving good outcome despite positive anti-vasospasm therapy after aSAH [8].

Medical treatment for vasospasm or DCI was disappointed. Nimodipine as the noly drug recommended by American Stroke Association was investigated to achieve good neurological outcomes rather than cerebral vasospasm, while on the other hand efficacy of other drugs including nicardipine, magnesium sulfate, fasudil etc. remained unknown [4]. Recently, increasingly clinical trials explored the efficacy of statins were conducted. Roles of statins such as increase eNOS protein, middle cerebral artery diameter, down-regulated the formation of microclots and decrease the number of microthrombi of statins were proven to be effective in experimental subarachnoid haemorrhage [9-11]. But it remains controversial

because the results of randomized clinical trials investigated the benefit of statins-use in patients with aSAH were contrary.Three meta-analysis on RCT [12-14] and two articles [15, 16] contained both observational studies and RCTs were performed in last few years.A large-scale Phase III study [20] together with two additional observational studies [27, 28] were included in this review compared with the latest meta-analysis [14, 15]. So it is necessary to conducted a meta-analysis to obtain the evidence of statins for patients with aneurysmal subarachnoid hemorrhage.

Methods

Study selection

This review was searched by two reviewers(Liu Junhui and Liu baohui) independently in the PubMed, Cochrane Library and Springer with restriction on the language of only published in English. The search was performed on 9 December 2014. The key words we used were "statin", "simvastatin", "pravastatin", "vasospasm" "subarachnoid hemorrhage" with a limitation of studies in human. Study selection was performed by two reviewers (Liu JH, Liu BH) independently and the third reviewer would step in if there were any disagreement. Discussions between reviewers were made to get a final consensus.

Studies included

Inclusion criteria: ① RCTs, observational studies investigated the effects of statins in subarachnoid hemorrhage. ② Patients included were all diagnosed as aneurysmal subarachnoid hemorrhage prior to the studies. ③ Outcomes reported in studies included cerebral vasospasm, delayed cerebral ischemia (DCI) or poor outcome. ④ Outcomes were compared between patients treated with statins and patients using no stains.

Exclusion criteria: ① studies investigated efficacy of statins in animals; ② trials investigated statins on subarachnoid hemorrhage caused by other diseases(head injury, arteriovenous malformation rupture and so on) ; ③ trials represented no clear definition on vasospasm, DCI or poor outcome. ④ RCTs compared statins with other drugs (magnesium sulfate, Nimodipine, etc).

Outcome measures: Definitions of cerebral vasospasm varied among studies with little difference and it was necessary to use individual definition of vasospasm to perform this meta-analysis. Delayed cerebral ischemia was identified as delayed clinical neurological deterioration with infraction on CT or MRI regardless of other causes (hydrocephalus or re-bleeding). Poor outcome was observed in most studies by using Glasgow outcome scale or modified Rankin scale. Number of patients died during the treatment period had already been included in poor outcome, so we did not pool data on mortality separately.

Quality assessment of included studies

RCTs included were made strict quality assessment by two reviewers (Liu Junhui and Liu baohui) according to the Cochrane Collaboration format [17] independently. Five items including sequence generation, allocation concealment, incomplete outcome data,selective outcome reporting and other bias were taken into account to quality assessment. "YES" indicates a low risk of bias, "NO" indicates a high risk of bias and "UNCLEAR" indicates unclear or unknown risk of bias. Studies was defined as low quality if one or more items is "NO" (Grade C), while high quality meant YES for every item (Grade A). Grade B implied one or more items is "UNCLEAR". We did not use the Cochrane Collaboration format to assess the risk bias of observational studies included and only qualitative description was made for each observational studies.

Data extraction and analysis

Two reviewers (Liu Junhui and Liu baohui) independently made the data extraction after reading the full text of all the included studies. Publication data, author, number of patients, interventions, study design, cerebral vasospasm, DCI or poor outcome were recorded in this systematic review. A third reviewer (Ding hao) was consulted if there was a disagreement and discussions were made to get a final consensus. Data analyses of RCTs and observational studies were made separately. RevMan 5.1 was used to make data analysis vasospasm, DCI and poor outcome were all dichotomous and odd rates was used for all outcomes with a 95% confidence interval (CI). Fixed effect model and Random effects model were select-

Table 1. Details of 6 randomized clinical trials

Author	year	study	Nub. of patients		Intervention	Definition (Nub. Of Patients)		
			statin	placebo		Vasospasm	DCI	Poor outcome
John R. Lynch	2005	RCT	19	20	Patients were randomized within 48 hours of symptom onset to receive either simvastatin (80 mg daily; n=19) or placebo (n=20) for 14 days	clinical impression (delayed ischemic deficit not associated with rebleed, infection, or hydrocephalus) in the presence of 1 confirmatory radiographic test (angiography or transcranial Doppler demonstrating mean VMCA >160 m/sec (5/12).	N/A	N/A
Chou, S.H	2008	RCT	19	20	Thirty-nine statin-naïve Fisher grade 3 SAH subjects were double-blind randomized to receive simvastatin 80 mg/d (n=19) or placebo (n=20),	TCD vasospasm was defined as any peak systolic middle cerebral artery velocity (PSVMCA) >200 cm/s and a Lindegaard ratio of ≥3 (13/10).	Any 2 or more point fall in modified Glasgow Coma Scale or unaccountable new focal neurological deficit lasting 2 h (7/10)	mRS 3-6 (9/10)
Vergouwen, MD	2009	RCT	16	16	Patients were randomized to simvastatin 80 mg or placebo once daily.	no vasospasm (Vmean in any measured cerebral artery < 120 cm/sec), mild vasospasm (Vmean >120 and < 160 cm/sec), moderate vasospasm (Vmean >160 and < 200 cm/sec), severe vasospasm (Vmean >200 cm/sec) (12/11).	Development of focal neurological impairment and/or a drop in the Glasgow Coma Scale by 2 points (6/5).	GOS 1-4 (9/11)
K. Garg	2012	RCT	19	19	All patients with aSAH admitted within 96 h of ictus were randomized to receive either Simvastatin or placebo 80 mg/day for 14 days.	new ischemic neurologic deficits in first two weeks after the ictus and presence of either angiographic confirmation of vasospasm or TCD velocities> 160 cm/sec (4/3).	N/A	Median GOS and mRS were 5/4 , 1/0.5,respectively. (N/A)
Kirkpatrick, PJ.	2014	RCT	391	412	Patients were randomly allocated (1:1) to receive either simvastatin 40 mg or placebo once a day for up to 21 days.	N/A	Delayed ischaemic was defined as deficit as a deterioration of ≥2 points on the GOSe that could not be attributed to any other cause including sepsis (61/67).	mRS 4-6 (157/157)
Tseng, M.Y.	2005	RCT	40	40	Patients within 72 hours from the ictus were randomized equally to receive either oral pravastatin (40 mg) or placebo daily for up to 14 days	TCD vasospasm defined as mean blood flow velocity >120 cm/s with Lindegaard ratio ≥3 (17/25).	DCI was defined as vasospasm-related if it was associated with severe vasospasm on TCD, defined as blood flow velocity 200 cm/s with Lindegaard ratio 3 (2/12).	mRS 3-6 (17/21)

RCT, randomized clinical trial; VSP, vasospasm; DCI, delayed cerebral ischemia; TCD, transcranial Doppler; aSAH, Aneurysmal subarachnoid hemorrhage; mRS, modified Rankin scale; GOS, Glasgow outcome scale; N/A, not access.

Table 2. Details of all the observational studies included

| Author | year | study | NO. of patients | | Interventions | Definition (Nub. Of Patients) | | |
			statins	no statin		Vasospasm	DCI	Poor outcome
Singhal, A.B.	2005	Rsp. study	36	478	Statins vs no statin	Symptomatic and symptomatic vasospasm were all included and the latter was identified by angiography, TCDs, or parenchymal hypodensity on head CT scan (28/291).	N/A	N/A
Parra, A.	2005	Rsp. study	20	40	Statins vs no statin	N/A	Symptomatic or silent delayed infarction not attributed to any other cause in our definition of DCI and a modified DCI variable (1/14).	N/A
McGirt, M.J.	2006	Rsp. study	15	100	Statins vs no statin	Patients with DINDs improved with3-H therapy and TCD flow velocities ≥200 cm/s or vasospasm demonstrated on angiography in spite of partial or no response to 3-H therapy (1/48).	N/A	N/A
S.I. Moskowitz	2007	Rsp. study	26	282	Statins vs no statin	Angiography or transcranial ultrasonography demonstrating flow velocities ≥120 cm/s in any primary cerebral vessel combined with clinical criteria (6/86).	N/A	N/A
Kramer, A.H.	2008	Rsp. study	71	79	Statins vs no statin	Radiographic vasospasm is defined as at least moderate vasospasm (30% narrowing) (29/33).	Hypodensities on CT scans and diffusion abnormalities on MRI (16/22).	GOS 1-3 (28/28)
McGirt, M.J.	2009	Psp. study	170	170	Simvastatin vs no statin	Delayed neurological decline either responding to 3-H therapy or related with angiographic vasospasm (43/52).	N/A	GOS(1-2) (37/31)
Sanchez PenaP.	2012	Rsp. study	142	136	Statins vs no statin	In awake unsedated patients: TCD velocities 120 cm/s or a 50 cm/s change in mean TCD velocity, while in sedated patients mean velocity 200 cm/s or an increase 50 cm/sec (32/47).	N/A	GOS 1-3 (30/30)
Lizza, B.D.	2014	Psp. study	41	254	Statins vs no statin	Mean TCD flow velocity at two thresholds of ≥120 cm/s, development of clinical signs or symptoms, or arterial stenosis on angiography (20/140).	A new hypodensity on CT or on MRI of the brain as a new area of increased intensity on B1000 with decreased intensity on apparent diffusion coefficient maps (1/16).	mRS4-6 (14/60)

Rsp., retrospective; Psp., prospective; DCI, delayed cerebral ischemia; DIND, delayed ischemic neurological deficit; TCD, transcranial Doppler; CT, computerized tomography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; GOS, Glasgow outcome scale; N/A, not access.
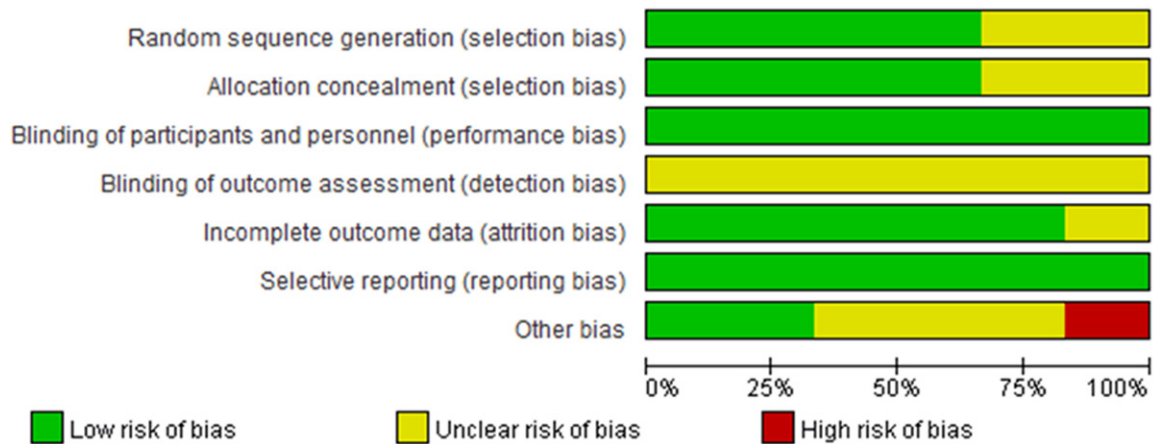
Figure 1. Risk of bias graph: judgements about each risk of bias item presented as percentages across all included studies.

ed according to different heterogeneities with significance set at P=0.05. Funnel plots was used to screen the potential publication bias.

Results

Search results

224 articles were originally screened in our literature after making the search in PubMed, Cochrane Library and Springer link. And then 107 articles were excluded because they were reviews or not published in English or studies focused on animals. There were in all 14 articles left after reading the full text of articles according to our inclusion and exclusion criterion.Finally,articles included in our systematic review were six RCTs [18-23] (5 on simvastatin [15-19] and 1 on pravastatin [20]) and 8 observational studies [24-31].

Details of included articles

Strict criterion were made to select the potential articles before data analysis. 6 RCTs [15-20] and 8 observational studies [21-28] were finally included in our review. One RCT [32] investigated simvastatin for patients with aSAH was excluded because patients in this studies were randomized to received either 40 mg or 80mg of simvastatin.There were in total 1031 patients in six RCTs [15-20] with 504 patients received statins and 527 patients in placebo group. 561 patients with statins compared with 1579 patients in no statin-use group were finally included in 8 observational studies [21-28]. Transcranial Doppler (TCD) was the most com-

mon method used to evaluate vasospasm in the majority of studies. Details of definition for vasospasm in articles were showed below. Delayed cerebral ischemia (DCI) was investigated in seven trials [16-18, 20, 22, 25, 28] and DCI were mainly detected by CT or MRI scan combined with clinical symptoms,although there were needs of TCD or angiographic evidence of vasospasm in one studies [20]. Poor outcome was explored by using GOS or mRS and the timing of in studies is various.Poor outcome was assessed at time of hospital discharge in five studies [17, 20, 25-27] and was obtained at 6 month in two RCTs [17, 19]. While quite from these studies in the timing of outcome assessment,functional outcomes were explored at 2 weeks, 4 weeks and 3 month in one study [28] and assessed at 1, 3, 6 month in another study [18]. Characteristics of studies and definitions for outcome of interest were showed in **Tables 1** and **2** respectively.

Assessment of risk of bias of RCTs

The Cochrane Collaboration format [2] was used to assess the risk of bias of all the RCTs. Details of methodological quality assessment were showed in **Figure 1**. All trials included were randomized, double-blind and placebo-controlled clinical trials. Sequence generation and Allocation concealment in four [17-20] of six trials were adequately generated.Outcomes of interest in this systematic review were reported adequately in five trials [16-20]. As a result, five trials were defined as Grade B and one trials were regarded as Grade C.
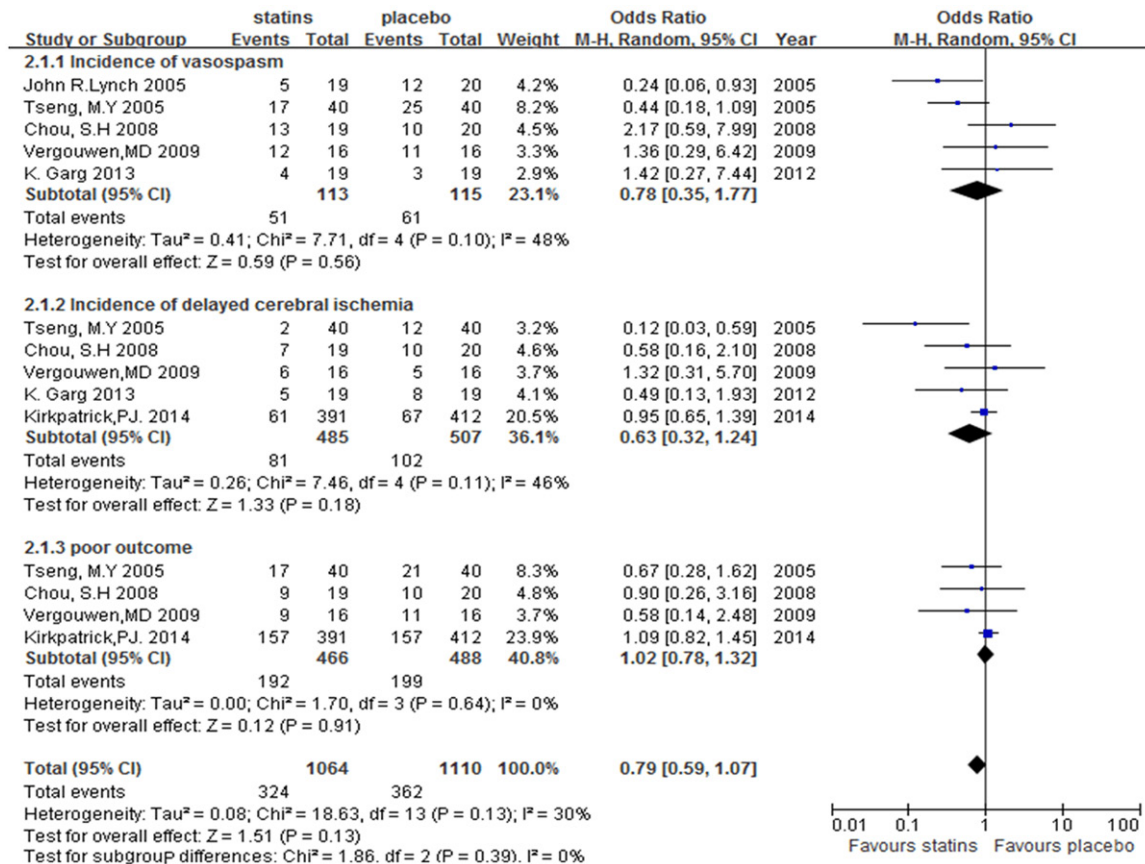
Figure 2. Odd ratios of vasospasm, DCI and poor outcome of RCTs.

Outcomes of RCTs

TCD vasospasm was observed in five RCTs [15-20] included.There were 51 patients received statins suffered from vasospasm after aSAH compared with 61 patients in placebo group. We made a combination of all the events of TCD vasospasm together regardless of different definitions among studies and the result showed that there weren't any statistical difference between patients in statins-use group and placebo group (OR 0.78, 95% CI [0.35-1.77], P=0.56). The analysis of heterogenicity showed that there was moderate heterogenicity among trials included (Chi^2=7.71, df=4, P=0.10, I^2=48%) (**Figure 2**). Incidence of delayed cerebral ischemia were investigated in five studies and heterogenicity was high for this result (Chi^2=7.46 df=4 P=0.11 I^2=46%). 81 of 466 patients in statins-use group developed DCI after aSAH compared with 102 of 488 patients in placebo group(estimated pooled OR 0.63 95% CI [0.32-1.24] P=0.18), which indicated no statistical significance between two

groups. One study [18] offered result of poor outcome with a median mRS and GOS at 6 month, while in other two articles [16, 20] poor outcome was defined as a mRS (3 to 6) and was measured in another study [19] with a definition of a mRS 4 to 6 at 6 month. The overall number of patients with poor outcome was 192 in statin-use group and 199 in placebo group (pooled OR 1.02 95% CI [0.78-1.32] P=0.91).

Outcomes of observational studies

There were in total 2060 patients included in these 8 observational studies [21-28] with 521 patients in statins group and 1539 patients in no statins group (**Figure 3**). Four observational studies [23, 25-27] investigated the efficacy of statin-use for subarachnoid hemorrhage after aneurysm rupture and however another four studies [21, 22, 24, 28] explored the preadmission statin-use on efficacy for patients with aneurysmal subarachnoid hemorrhage. Cerebral vasospasm which was defined in different points of cerebral blood flow velocity were
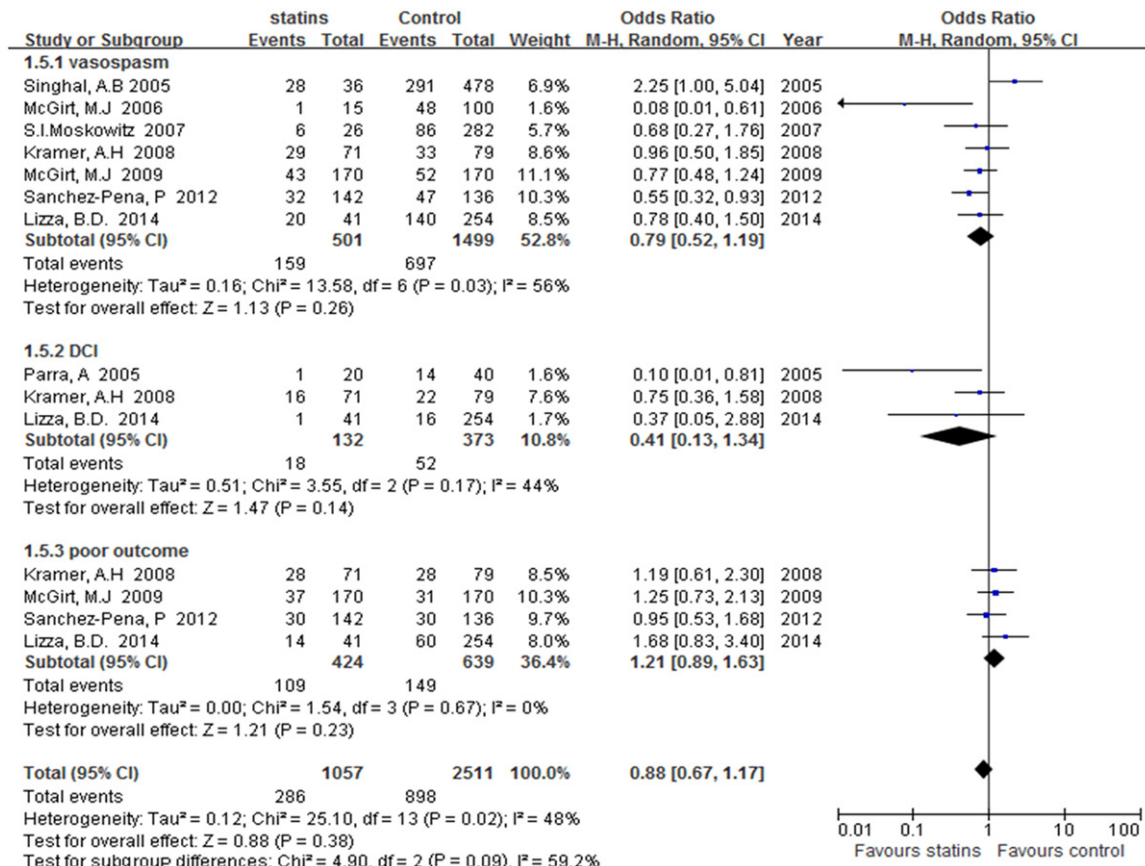
**Figure 3.** Odd ratios of vasospasm, DCI and poor outcome of observational studies.

mostly detected by TCD or cerebral angiography. Mean TCD/angiography cerebral velocity ≥120 cm/s was observed in the diagnosis of vasospasm in two articles [24, 27, 28] and MCV≥200 cm/s was detected in another two articles [23, 27]. No statistical significance was investigated in achieving cerebral vasospasm between statin group and no statin group in observational studies (159/501 vs 697/1499 OR 0.79 95% CI [0.52-1.19], P=0.26). DCI was observed in only three observational studies [22, 25, 28] and there were 18 of 132 patients suffered DCI in statins group compared with 52 of 373 patients in control group (OR 0.41 95% CI [0.13-1.34] P=0.14). GOS(1-3) and mRS (4-6) were both reported as poor outcome in Sanchez-Pena, P.et al.'s study [27], while data of GOS (1-3) was finally extracted to make the analysis in this review because only one observational study [28] presented poor outcome in mRS.As a result,poor outcome was finally defined as GOS (1-3) in two studies [25, 27], GOS (1-2) in one study [26] and mRS (4-6) [28] in another study.The pooled estimated OR

for poor outcome was 1.21 with P=0.23 (95% CI [0.89-1.63]), which was low in heterogenicity (I²=0%).

Discussion

Results of RCTs and observational studies were represented separately.We did not make a combination of different types of studies,which was quite different from the previous study conducted by Kramer, A.H. et al. [16], because they were all different from each other in study design, population, intervention and control.We used the random-effects models that would result in a wider confidence intervals to conducted the meta-analysis. There are lack of reliable handbook or scales for the quality assessment of observational study, so objective description was made in our systematic review for observational studies included. Outcomes (vasospasm, DCI, poor outcome) were all presented in funnel plots and the result showed the funnel plots was unsymmetric, which indicated reporting bias may exist in 6 RCTs [15-20] included (**Figure 4**).
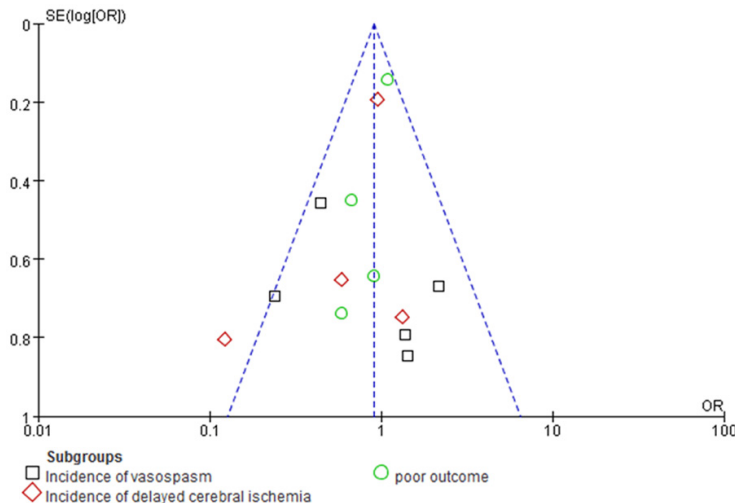
Figure 4. Funnel plot of outcomes of interest (vasospasm, DCI, poor outcome) in 6 RCTs.

Outcomes included in this meta-analysis (cerebral vasospasm, DIC and poor outcome) all indicated no statistical significance between two groups both in RCTs and observational studies. Cerebral vasospasm was the primary factor that led to death and severe disability after aSAH and there were about 20-30% of patients with cerebral infarction caused by vasospasm [33]. But result of incidence of cerebral vasospasm in this meta-analysis was disappointed, because no evidence was showed for patients with statins-use to obtain any benefits after aSAH both in RCTs and observational studies. Same result was observed in several meta-analysis [12-14] conducted before. Transcranial Doppler vasospasm in Vergouwen et al.'s study [13] demonstrated no statistically significant effect in patients treated with statins (pooled risk ratio, 0.99 [95% CI, 0.66 to 1.48]), While on the contrary the prevalence of vasospasm were significantly reduced in the statin group in Sillberg et al.'s article [12]. RCTs included are superior to observational study in methodology in conducting meta-analysis because patients in trials are randomized allocated and blinded to the treatment they received. So it is necessary to pay more attention to the results of meta-analysis of RCTs. DCI may caused by cerebral vasospams and may represented as neurologic deficit or as an drop GOS score [34] and DCI also developed in almost 30% patients survived from the initial hemorrhage [35]. Earlier study [12] investigated the efficacy of statin in aSAH demonstrated that delayed isch-

emic deficits were significantly reduced in patients with statins, but there were only three RCTs with small samples included in this meta-analysis of which the results should be treated cautiously. No statistical significance was observed in the results of DIC in RCTs in our meta-analysis and that was similar to relevant study [13], which suggested that patients in stain-use group did not achieve any reduction in DCI when compared with placebo group. Poor outcome with various definitions was mainly obtained by using mRS or GOS and after making a combination of all data on poor outcome, we found that patients treated with statins did not achieve a good outcome when compared with no-statins use both in RCTs and observational studies.

Difference of the results between RCTs and observational studies could be observed in Kramer A.H et al.'sstudy [16], in which statins were discovered to reduce the occurrence of DINDs significantly in RCTs, but was not associated with any reduction in observational studies.Outcomes of interest included in this articles were all negative and scarcely any difference was existed between the results of RCTs and observational studies in this systematic review. But results should be treated cautiously because the definitions for outcomes (vsasospasm, DCI and poor outcome) were not all the same among studies included. Although most RCTs were moderate risk of bias, there were still moderate or high heterogenicity in outcome of interest. Result of DCI achieved was mainly contributed by one study [20] which had 72.7% specific weight of the included studies and the result might be greatly influenced. What's more poor outcome was obtained at different time after aSAH in different studies,which was mainly determined at the latest follow-up visit in the study. Difference may existe in several observational studies because they were designed to investigate the efficacy of statins-use prior to aneurysm rupture, which was quite different from other studies included. Besides various statins inclduing simvastatin, pravastatin, atorvastatin and so on were used for patients with

aSAH in observational studies.Pravastatin was explored in one RCT [20] and simvastatin 80 mg was investigated in four RCTs [15-18], 40 mg in only one RCT [19]. Effects for preventing vasospasm, DCI or achieving good outcome after aSAH may differ among various statins, so without any distinctions there could be a great heterogenicity existed in our resluts. Details of method of statin-use for patients with aSAh were presented in observational studies, but dose of statins uesd remained unknown in the majority of studies.

Conclusion

Scarcely any difference was existed between the results of RCTs and observational studies in this systematic review. Summarizing the results of this systematic review, we did not find any evidence to identify the efficacy of statins for patients with aSAH both in RCTs and observational studies. However several limitations including limited number of RCTs and included patients, differences in study design among studies and no distinctions for different types of statins existed in this review, so more lager-scale RCTs should be conducted in the future to investigate the efficacy of statins in the management of patients with aSAH.

Disclosure of conflict of interest

None.

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