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CLINICAL TRIAL

Dose-related effect of statins in patients with endovascular coiling or microsurgical clipping for aneurysmal subarachnoid hemorrhage: updated study-level meta-analysis

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Abstract
Purpose We aimed to quantitatively assess the effects of short-term statin use on delayed ischemic neurologic deficits (DINDs) and clinical outcomes in patients with aneurysmal subarachnoid hemorrhage (SAH) through a meta-analysis of the available evidence.
Methods We searched the electronic databases up to April 8, 2016 to retrieve relevant studies comparing the outcomes between immediate statin-treated in statin-naïve patients and untreated patients following aneurysmal SAH. Meta-analysis was performed using Review Manager 5.3.
Results Eight randomized controlled clinical trials (RCTs) and 5 observational studies involving 2148 patients met the eligibility criteria. In the RCTs, statins were found to significantly reduce the occurrence of DINDs (relative risk (RR), 0.76; 95% confidence interval (CI), 0.61–0.94; $P = 0.01$), but did not significantly reduce poor functional outcomes (RR, 1.01; 95% CI, 0.87–1.16; $P = 0.93$) or mortality (RR, 0.80; 95% CI, 0.58–1.11; $P = 0.18$). In observational studies, statin use was not associated with any reduction in DINDs, poor outcome, or mortality. Meta-analysis of RCTs indicated a significant reduction in DINDs and mortality in patients with high-dose statin use (RR, 0.63; 95% CI, 0.42–0.95; $P = 0.03$; $I^2 = 0\%$; and RR, 0.36; 95% CI, 0.15–0.86; $P = 0.02$; $I^2 = 0\%$, respectively).
Conclusion The present meta-analysis suggests that statin use may prevent DINDs in patients with aneurysmal SAH. Based on our findings, the role of statins in improving neurological outcome was limited. However, the risk of DINDs and mortality decreased with higher statin doses in a dose-dependent manner. Hence, further well-designed RCTs with modified protocols in specific patients are required.

Keywords Subarachnoid hemorrhage · Vasospasm · Delayed ischemic neurological deficit · Statins · Meta-analysis

Introduction

Cerebral vasospasm that follows subarachnoid hemorrhage (SAH) usually occurs between 7 and 10 days after ictus and spontaneously resolves after 21 days [1]. The onset of cerebral ischemia and infarction is speculated to be multifactorial, and involves distal microcirculatory failure, reduced collateral circulation, and genetic or physiological variations in cellular tolerance to ischemia [2, 3]. Delayed ischemic neurological deficits (DINDs), related to cerebral vasospasm, occur in 20–30% of patients with aneurysmal SAH and is a major cause of morbidity and mortality due to SAH [4, 5].

Several ongoing studies seek to prevent cerebral vasospasm and ischemic complications, on the basis of previous basic studies that have highlighted the decisive role of endothelial dysfunction at the microcirculatory level [6]. Some

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clinical trials have investigated the efficacy of statin, endothelin-1 antagonist, and magnesium sulfate on cerebral vasospasm [7]. Although extensive research on this pathophysiologic mechanism has been conducted, no effective prophylactic therapy has been elucidated thus far.

Several recent studies have evaluated the efficacy of statins for DINDs. The pleiotropic effects of statins, including endothelial nitric oxide synthase expression, decreased oxidative stress, and decreased microclot formation, are reportedly effective for experimental SAH [8, 9]. Three randomized controlled trials (RCTs; 2 involving 80 mg simvastatin and 1 involving 40 mg pravastatin) have confirmed the efficacy of statin; however, recently conducted RCTs do no support its clinical efficacy [10–14]. Furthermore, recent meta-analysis showed that statins decrease DINDs and mortality, without any effects on the functional outcome [15]. Thus, the effects of early statin treatment in patients with aneurysmal SAH remain controversial. Moreover, most of the studies used statins with varying potency, and hence, the dose-related effect of statins for DINDs and the clinical outcomes after aneurysmal SAH remain unclear. Here, we conducted a meta-analysis of RCTs and observational studies to quantitatively assess the effects of short-term statin use on DINDs, functional outcome, and survival in patients with aneurysmal SAH.

Methods

We conducted an extensive search of databases to identify studies that evaluated the effects of statins in patients with aneurysmal SAH according to the Cochrane Review Method [16].

Search strategy

A literature search for systematic reviews was conducted using three English databases—Ovid-Medline, Ovid-EMBASE, and Cochrane Library—up to April 8, 2016. To ensure a highly sensitive search, we designed search strategies that included pertinent MeSH keywords, common keywords, and their comprehensive combination. Search strategies were modified for each database by using free text terms and controlled vocabularies. The details of the search strategies are described in Online Resource 1. There was no language restriction, and no filters of any kind were applied for the strategy. The bibliographies of the published relevant articles were also reviewed to identify additional publications. After removing duplications, 2002 references were imported for an initial screening based on the title and abstract.

Study selection

According to certain pre-determined study selection criteria, two reviewers (K.-S.C. and S.-H.L.) independently screened the titles and abstracts of the references to exclude irrelevant studies, and a full-text review was subsequently performed for potentially relevant articles. RCTs and observational studies published in English were included if they met the following inclusion criteria: (1) studies that focused on patients with aneurysmal SAH only, (2) comparative studies between statin-treated and non-statin-treated group in statin-naïve patients, and (3) studies that reported at least one of the following outcome measures with DINDs: cerebral vasospasm, functional outcome, or mortality. Studies were excluded if they (1) were not original articles or (2) were pre-clinical studies; conference abstracts were considered if only they had been confirmed as peer-reviewed RCTs.

Data extraction

The study characteristics and results of selected studies were extracted by two independent reviewers (K.-S.C. and S.-H.L.), using a standardized data collection form. Any disagreement unresolved by discussion was reviewed by the other co-authors (T.L. and Y.-S.C.). The following variables were extracted from the studies: first author, year of publication, country, study design, characteristics of the study population, protocol of statin treatment (type of statin, dosage used, and duration of statin use), definitions of vasospasm, DINDs, poor functional outcome, mortality, and potential side effects. The initial clinical assessment, as reflected by the World Federation of Neurosurgeons Societies (WFNS) grade or Hunt-Hess (H-H) grade was also recorded.

The outcomes of interest included the incidence of vasospasm (as detected via transcranial Doppler (TCD) or conventional angiography), DINDs, poor functional outcome, and mortality during follow-up. DIND was defined as the clinical manifestation of ischemia, regardless of the presence of radiographically confirmed vasospasm, not attributable to other causes such as rebleeding, hydrocephalus, or metabolic derangement. DINDs were described as “clinical/symptomatic vasospasm” or “delayed ischemic deficits” in some studies. We assessed the occurrence of DINDs as defined in individual studies. Poor functional outcome was evaluated by using the modified Rankin Scale (mRS) score or Glasgow Outcome Scale (GOS) score, based on the definitions of each study. If the above variables were not mentioned in the studies, we requested for the data via an email to each corresponding author.

Quality assessment

Quality assessment was also independently performed by the reviewers using the risk of bias tool of the Cochrane group, including selection bias, performance bias, detection bias, attrition bias, and reporting bias [16]. The methodological quality of the identified studies was assessed independently by K.-S.C. and S.-H.L. Reviewers selected the terms "low risk of bias," "high risk of bias," or "unclear" to define each study. Any unresolved disagreements between the reviewers were resolved through discussion or via review from the third author. Publication bias was not assessable in these trials. Tests for funnel plot asymmetry are generally only performed when at least 10 studies are included in the meta-analysis. As our analyses for each study design only included eight and five studies (for RCTs and observational studies, respectively), tests for asymmetry would be ineffective, as they would be unable to differentiate chance from asymmetry. We did not use the Cochrane Collaboration format to assess the risk bias of the observational studies included, and hence, only a qualitative description was made for each observational study.

Statistical analysis

In the main analysis, we investigated the association between statin use and DINDs/unfavorable functional outcome/mortality after aneurysmal SAH. The results of RCTs and observational studies were pooled separately and then together. For dichotomous variables, a pooled relative risk (RR) with 95% confidence interval (CI) was calculated by using a fixed effects model in the absence of significant heterogeneity [17].

To assess heterogeneity, we estimated the proportion of between-study inconsistency via I^2 statistics, wherein values of 25, 50, and 75% were considered low, moderate, and high, respectively [18]. In addition, the chi square test with significance set at $P < 0.10$ was used to assess heterogeneity. When substantial heterogeneity was found, the random effects model was employed to pool the studies. A sensitivity analysis was performed by the sequential removal of individual studies, on at a time, and by the estimation of the overall pooled estimate for the remaining studies.

We conducted planned subgroup analyses based on the study design (RCTs versus observational studies), stain dose (higher versus lower statin dose), statin type (simvastatin versus other statins); type of predominant procedure (clipping versus coiling), proportion of high-grade patients (WFNS or H-H grade, ≥25 versus <25%), and methodological quality of the study (high versus low). Because well-designed RCTs or updated meta-analyses have a major impact on the primary study design, including study population, planned pattern of statin treatment, and clinical practice patterns, we evaluated the impact of publication date on the overall effect of pooled RRs for statin use via subgroup meta-analysis. We performed all meta-analyses using Review Manager, version 5.3 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014), and $P < 0.05$ was considered statistically significant.

Results

Study selection and characteristics

The process of identifying eligible studies is shown in Fig. 1. Searches of the databases led to the collection of 2338 articles. A total of 2002 studies remained after excluding the duplicate articles. Of these, 1899 irrelevant publications were excluded, based on the screening of titles and abstracts. A total of 103 potentially relevant studies were fully reviewed with the full text. Among them, 90 articles were excluded because of the following reasons: review articles (n = 15), abstracts from congresses (n = 27), animal studies (n = 15), letters (n = 16), gray literature (n = 2), study design does not fulfill the inclusion criteria (n = 10), shared identical population (n = 2), and study protocol (n = 2). Finally, 2148 patients from 13 studies met the inclusion criteria and were included in the meta-analysis [10–13, 19–27].

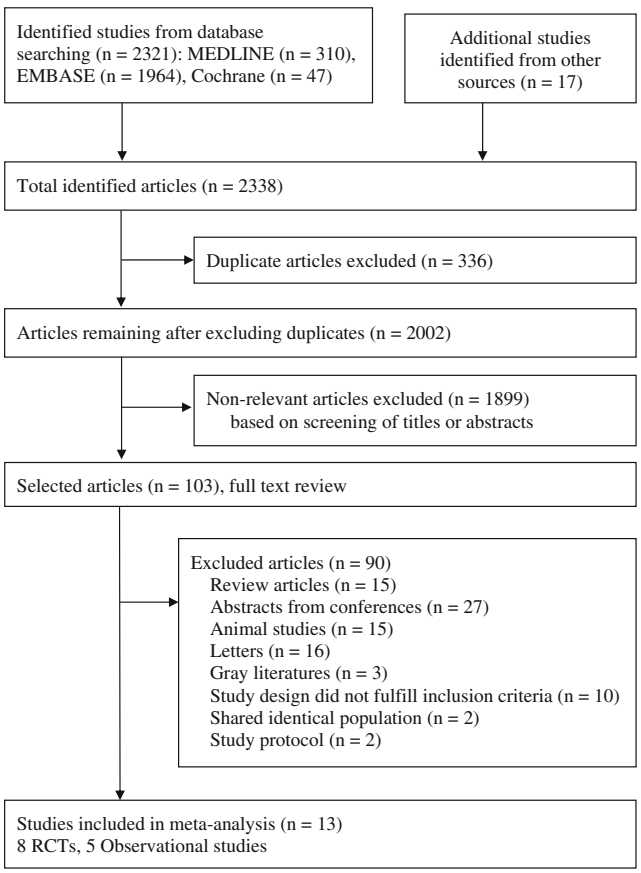

Fig. 1 Flow diagram for identification of relevant studies

The main characteristics of the 13 eligible publications are shown in Table 1. The selected studies included eight RCTs and five observational (four prospective) studies. A total of 1150 patients (53.5%) were assessed from 8 RCTs (555 received statins) [10–13, 19–22], whereas a total of 998 patients (46.5%) were assessed from 5 observational studies (504 received statins) [23–27]. Thus, the 13 eligible studies involved 1059 participants in the statin-treated group and 1089 in the non-statin-treated group. Two RCTs were published as abstracts, but had been peer-reviewed [20, 21]. Six of the eight RCTs explicitly stated that all analyses were performed on an intention-to-treat basis [10–13, 19, 20]. Statins were initially administered within 96 h of ictus in all of the included studies. Eight studies utilized "higher dose" statin (80 mg simvastatin or 40 mg atorvastatin), at an equivalent dose of 80 mg simvastatin per day for 14–21 days [11, 12, 19, 21–23, 26, 27]. In contrast, "lower dose" statin (40 mg pravastatin or 20–40 mg simvastatin), at an equivalent dose of ≤40 mg simvastatin, was used in 5 studies [10, 13, 20, 24, 25]. The SAH clinical grade was reported in 12 studies, and the initial status was comatose in 564 (27%) of 2109 patients (WFNS or H-H grades IV–V) [10, 12, 13, 19–27]. Deeply comatose patients (WFNS or H-H grade V) were excluded from two RCTs [12, 22]. The Fisher grade was described in 9 studies; 834 (44%) of 1899 patients were classified as Fisher grade IV [11, 13, 21–27]. The management of ruptured aneurysms markedly varied; microsurgical clipping was predominantly performed in seven studies [10, 12, 20, 22–24, 26], whereas the remaining were treated with endovascular coil embolization [11, 13, 19, 21, 25, 27].

Quality of the included studies

Details of our assessment of the quality of the included studies are presented in Online Resource 2. Six studies [10–13, 19, 22] included randomized, double-blinded, placebo-controlled trials, whereas two studies [20, 21] were randomized only in terms of the choice of statin or non-statin treatment, without any blinding method. Five studies [10–13, 19] included an intention-to-treat analysis. All the observational studies included consecutive patients. The three more recent studies were prospectively performed in terms of outcome assessment [25–27]. All the five studies had a "before and after" design, and more recent patients were treated with statins. The investigators determining the outcomes were not blinded to patient information.

Effects of interventions

Effect of statin use on DINDs

All 13 studies involving 2148 patients reported the occurrence of DINDs. The authors' definitions for DINDs markedly varied in terms of the duration of focal neurologic deficits or neurologic deterioration, and the need for TCD or angiographic evidence of vasospasm. Four studies used a purely clinical definition of DINDs [12, 13, 19, 25], whereas other studies verified DINDs by clinical symptoms in combination with TCD or angiographically confirmed vasospasm [10, 11, 20–24, 26, 27].

In the RCTs, DIND developed in 19% (105/555) patients in the statin-treated group, as compared to 26% (153/595) patients in the non-statin-treated group. Pooled RCT data showed that acute statin treatment was associated with a reduced risk of DINDs after aneurysmal SAH (RR, 0.76; 95% CI, 0.61–0.94; $P = 0.01$; 8 studies; 1150 patients; Fig. 2). In observational studies, DIND was observed in 27% (137/504) of statin-treated patients and 31% (152/494) of non-statin-treated patients. However, the difference between the 2 groups was not statistically significant (RR, 0.87; 95% CI, 0.72–1.06; $P = 0.16$; 5 studies; 998 patients; Fig. 2).

When all 13 studies were combined using a fixed effects model, acute statin treatment was found to be associated with a significant reduction in DINDs after aneurysmal SAH (RR, 0.82; 95% CI, 0.71–0.94; $P = 0.006$; 13 studies; 2148 patients; Fig. 2). However, there was no definite evidence of heterogeneity ($I^2 = 35\%$; $P = 0.10$).

Effect of statin use on unfavorable functional outcomes

Functional outcomes were assessed based on the mRS or GOS score in 10 of 13 studies (6 RCTs: 1073 patients; 4 observational studies: 898 patients) [10, 12, 13, 19–21, 23, 25–27]. Unfavorable functional outcome was defined as an mRS score of 3–6 in four studies [10, 12, 13, 25] or a GOS score of 1–3 in the other six studies [19–21, 23, 26, 27]. Functional outcome was assessed at variable time intervals from ictus (at discharge, 3 months, 6 months, or 1 year).

Among the RCTs, an unfavorable functional outcome was observed in 41% (211/517) of cases in the statin-treated group, in comparison with 41% (226/556) of cases in the non-statin-treated group. The difference between the 2 groups was not statistically significant (RR, 1.01; 95%, CI 0.87–1.16; $P = 0.93$; 6 studies; 1073 patients; Fig. 3). In the observational studies, poor neurological outcome was noted in 27% (141/455) of statin-treated patients and 31% (126/443) of non-statin-treated patients. Meta-analysis showed that stain use did not improve the probability of good neurologic outcomes (RR, 1.07; 95% CI, 0.88–1.31; $P = 0.48$; 4 studies, 898 patients; Fig. 3).

When we assessed all 10 studies based on the occurrence of unfavorable functional outcomes, as defined in individual studies, meta-analysis using a fixed effects model showed that acute statin treatment did not significantly reduce the functional disability after aneurysmal SAH (RR, 1.03; 95% CI, 0.92–1.16; $P = 0.60$; 10 studies; 1971 patients; Fig. 3). There was also no statistical difference in the unfavorable outcome when

Table 1 Characteristics of studies included in the review

Study	Design	No. of patients statin/control	Age, year (range)	Statin dose/potency	Started within duration	H-H or WFNS (%) ≥ IV	Fisher ≥IV (%)	Clip/Coil (%)	DINDs	Unfavorable outcome
Tseng 2005 [10]	RCT	80 (40/40)	53 ± 12	Pravastatin 40 mg/day, L	72 h max 14 days or until D/C	32.5	–	65/16	DID: focal neurologic deficits or GCS drop ≥2 with TCD vasospasm	mRS ≥3 at D/C
Lynch 2005 [11]	RCT	39 (19/20)	56 ± 15	Simvastatin 80 mg/day, H	48 h 14 days	–	5	44/56	Clinical impression of DID with TCD or angiographic vasospasm	–
Chou 2008 [12]	RCT	39 (19/20)	53 ± 13	Simvastatin 80 mg/day, H	96 h max 21 days or until D/C	23	–	85/15	DIND: GCS drop ≥2 or unaccountable new focal neurologic deficit ≥2 h	mRS ≥3 at D/C
Jaschinski 2008 [20]	RCT	98 (40/58)	–	Pravastatin 40 mg/day, L	24 h until D/C	34	–	43/24	DID: change in neurological status or new infarct on CT	GOS at ICU D/C
Vergouwen 2009 [19]	RCT	32 (16/16)	54 ± 11	Simvastatin 80 mg/day, H	72 h 15 days	25	–	23/77	DCI: gradual deterioration with focal neurologic impairment and/or decreased level of consciousness of GCS drop ≥2	GOS ≤ 3 at 6 months
Macedo 2009 [21]	RCT	21 (11/10)	–	Simvastatin 80 mg/day, H	72 h 21 days	10	38	0/100	Change in neurological status with angiographic vasospasm or new infarct on CT	GOS at D/C
Garg 2013 [22]	RCT	38 (19/19)	49 ± 9	Simvastatin 80 mg/day, H	96 h 14 days	3	0	100/0	Clinical cerebral vasospasm: new ischemic neurologic deficits in the first 2 weeks after the ictus with TCD or angiographic vasospasm	GOS/mRS at 6 months
Kirkpatrick 2014 [13]	RCT	803 (391/412)	50 (20–69)	Simvastatin 40 mg/day, L	96 h 21 days or until D/C	23	51	33/66	DID: GCS drop ≥2	mRS ≥3 at 6 months
Kramer 2008 [23]	OS	150 (71/79)	55 (53–59)	Simvastatin 80 mg/day, H	72 h 14 days	32	31	53/47	Clinical vasospasm: change in neurological status and ≥moderate vasospasm and physician's decision to treatment	GOS ≤3 at 6 weeks
Kerz 2008 [24]	OS	100 (49/51)	55 (47–64)	Simvastatin 20, 40 mg/day, L	24 h 14 days	33	62	45/32	GCS drop ≥2 or a new focal deficit with angiographic vasospasm	–
Kern 2009 [25]	OS	130 (72/58)	–	Pravastatin 40 mg/day, L	48 h 14 days	25	35	38/52	Clinical vasospasm: focal neurologic deficits	mRS at D/C
McGirt 2009 [26]	OS	340 (170/170)	53 ± 14	Simvastatin 80 mg/day, H	– 14 days	23	37	81/19	Symptomatic cerebral vasospasm: change in neurological status and either improvement with triple H therapy, delayed infarct on CT, or concomitant radiographic vasospasm	GOS ≤2 at D/C
Sanchez-Peña 2012 [27]	OS	278 (142/136)	53 ± 14	Atorvastatin 40 mg/day, H	96 h 21 days	32	50	17/83	The event of clinical deterioration or new symptoms with TCD vasospasm	GOS ≤3 at 1 year

No. number, *H-H* Hunt-Hess grade, *WFNS* World Federation of Neurosurgeons Societies grade, *DINDs* delayed ischemic neurologic deficits, *RCT* randomized controlled trial, *OS* observational study, *H/L* high/low, *D/C* discharge, *DID* delayed ischemic deficit, *GCS* Glasgow Coma Scale, *TCD* transcranial Doppler, *DCI* delayed cerebral ischemia, *CT* computed tomography, *mRS* modified Rankin scale, *GOS* Glasgow Outcome Scale

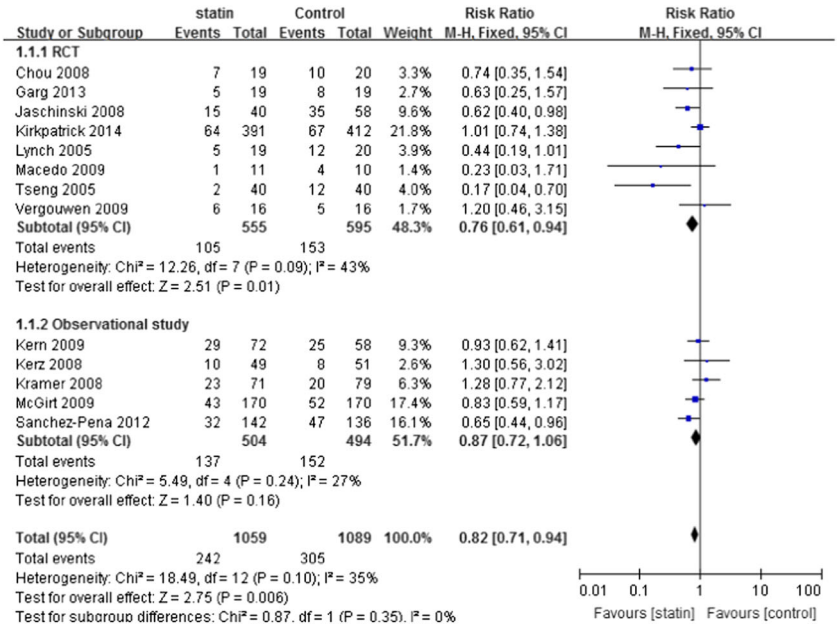

Fig. 2 Meta-analysis of relevant studies assessing DINDs according to statin treatment (fixed effects model)

analyzed according to the dose of statins. Moreover, there was no definite evidence of heterogeneity (I^2 = 0%; P = 0.92). These findings indicate that acute statin treatment may not affect functional outcome after aneurysmal SAH.

Effect of statin use on mortality

Twelve studies with 1870 patients were available for the analysis of mortality (8 RCTs: 1150 patients; 4 observational studies: 720 patients) [10–13, 19–26]. Among the RCTs, death occurred in 53 of 555 (10%) statin-treated patients as compared to 73 of 595 (12%) non-statin-treated patients. The pooled RR for mortality at the end of the scheduled follow-up period was 0.80, with a possible trend towards reduced mortality (95% CI, 0.58–1.11; P = 0.18; 8 studies: 1150 patients; Fig. 4). Although there was a trend towards reduced mortality for the statin-treated group, statistical significance was not achieved, possibly due to the overwhelming weight (48.1%) of the STASH trial in the pooled analysis, as a result of its large sample size (803 patients) and the high proportion of patients with events [13]. After excluding this article, the pooled RR for mortality was found to be 0.53 (95% CI, 0.29–0.96; P = 0.04; I^2 = 10%). Among the observational studies, death occurred in 64 of 362 (18%) statin-treated patients as compared to 56 of 358 (16%) non-statin-treated patients. Statin use in the acute post-ictal period of aneurysmal SAH was not associated with any reduction in mortality (RR, 1.12; 95% CI, 0.81–1.56; P = 0.49; 4 studies: 720 patients; Fig. 4).

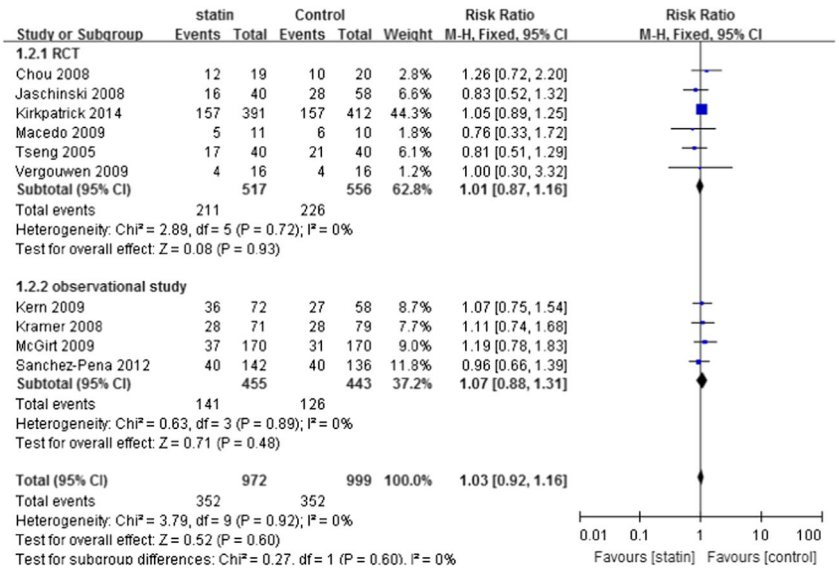

Fig. 3 Meta-analysis of relevant studies assessing functional outcome according to statin treatment (fixed effects model)

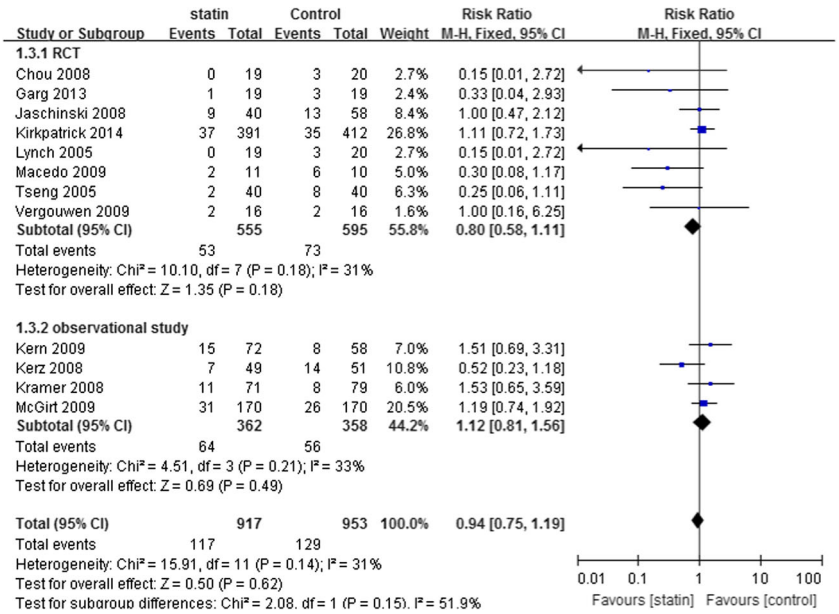

Fig. 4 Meta-analysis of relevant studies assessing mortality according to statin treatment (fixed effects model)

When all 12 studies were assessed using pooled analysis, no benefit of statin use after aneurysmal SAH on all-cause mortality was observed (RR, 0.94; 95% CI, 0.75–1.19; $P = 0.62$; 12 studies: 1870 patients; Fig. 4). Moreover, there was no definite evidence of heterogeneity ($I^2 = 31\%$; $P = 0.14$).

Subgroup analysis

The results of subgroup analysis are presented in Online Resources 3 and 4. The overall treatment effect of statins on functional outcome was consistent, as no significant effect was noted in any subgroup (data not shown). We performed subgroup analysis according to the type of study (RCTs versus observational studies; Figs. 2, 3, and 4). Although acute statin treatment significantly reduced the DINDs after aneurysmal SAH among RCTs, the effect of statin use on DINDs in the RCTs was not significantly different from that in the observational studies ($P = 0.35$). Similarly, there were no differences according to the type of predominant procedure (clipping versus coiling), or to the proportion of high-grade patients (≥25 versus <25%). Unlike the type of study design, the type of characteristics of each study population should be carefully considered, as the findings of subgroup meta-analysis may be complicated by the intra-group difference. For example, a study with >25% high-grade patients also included several low-grade patients. Hence, we also performed study-level subgroup meta-analysis according to the stain dose (higher versus lower statin dose), statin type (simvastatin versus other statins), and the methodological quality of the study (high versus low). Eight studies compared the use of high-dose statin versus placebo or no treatment, whereas five studies compared the use of low-dose statins versus placebo or no treatment. High-dose statin use significantly reduced the risk of DINDs by 22% (RR, 0.78; 95% CI, 0.64–0.95; $P = 0.01$; $I^2 = 21\%$, 1217 patients; Online Resource 5), although the occurrence of death did not differ between the high-dose group and no treatment group (RR, 0.94; 95% CI, 0.65–1.35; $P = 0.73$; $I^2 = 32\%$, 757 patients; Online Resource 6). Meta-analysis of the RCTs showed a significant reduction in DINDs and mortality in the subgroup of patients with high-dose statin use (RR, 0.63; 95% CI, 0.42–0.95; $P = 0.03$; $I^2 = 0\%$, 232 patients; Fig. 5; and RR, 0.36; 95% CI, 0.15–0.86; $P = 0.02$; $I^2 = 0\%$, 232 patients; Fig. 6). There was no statistical difference in mortality and DINDs when analyzed according to the statin type or the methodological quality of the study.

Sensitivity analysis

Sensitivity analysis was performed via the sequential removal of individual studies, one at a time, and the estimation of the overall RR for the remaining studies. No individual study significantly influenced the overall pooled estimates, indicating that this meta-analysis outcome was statistically reliable.

Discussion

In this systematic review and meta-analysis, we found that statin therapy in the acute period of aneurysmal SAH does not improve the probability of favorable neurologic outcome or survival, although it was significantly associated with a reduced occurrence of DINDs in a dose-dependent manner. Among the RCTs, improved survival and reduced DINDs were observed in the pooled analysis when high-dose statins

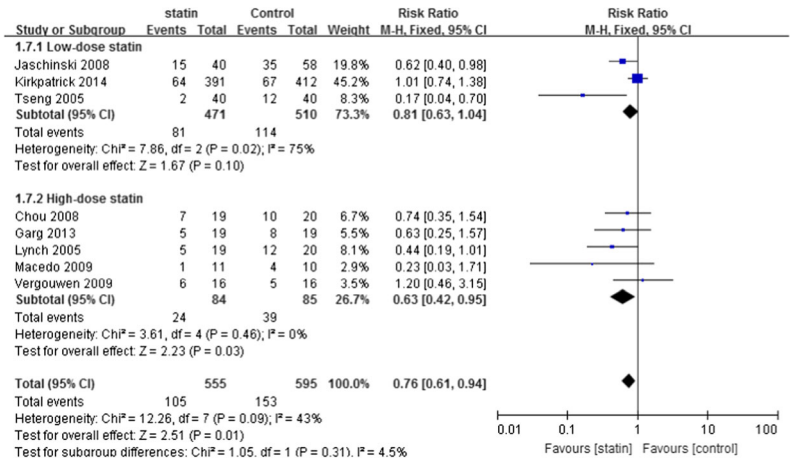

Fig. 5 Meta-analysis of RCTs assessing DINDs according to statin dose (fixed effects model)

at an equivalent dose of 80 mg simvastatin per day were used. The present data indicated that there was limited dissociation between DINDs and the neurological outcome parameters according to the stain dose (higher- versus lower-dose statins) or the type of study design (RCTs versus observational studies).

The dissociation between vasospasm-related morbidity (DINDs) and unfavorable neurological outcomes can be attributed to methodological problems, insensitivity of the clinical outcome, sample size, and multiple other factors (excluding vasospasm) contributing to poor outcomes (e.g., space-occupying hematoma, intraventricular hemorrhage, seizures, and other ischemic complications related to the procedure or critical care) [28, 29]. Moreover, the severity of the initial ictus may represent a non-ischemic mechanism underlying the effect of SAH itself on clinical outcomes, probably involving the development of early brain injury after aneurysmal SAH [6, 30]. Ischemic complications after aneurysmal SAH may arise from the SAH itself or from procedure-related events, or may even be of mixed origin. Since the nature of ischemic origin is mixed in real-world clinical practice, it is difficult to analyze the positive effects of statins on post-SAH ischemia and the clinical outcomes. Moreover, it is likely that statins cannot reduce procedure-related ischemia. In cases where cerebral ischemia and vasospasm are occasionally reversible, the data on symptomatic vasospasms or DINDs may not have any prognostic significance in clinical trials concerning aneurysmal SAH [31]. In fact, data from the most recently published studies on the prophylactic use of many drugs, such as statins, magnesium sulfate, or endothelin-receptor antagonists, for aneurysmal SAH suggest similar dissociations between vasospasm-related morbidity and clinical outcomes [15, 31–33]. In the absence of an association between DIND reduction and neurological outcome improvement, the effects of statins in clinical care should be carefully interpreted [34].

The results of our updated meta-analysis indicate a dose-related effect of statins on DINDs and mortality after aneurysmal SAH. Although the high dose of statins did not improve the probability of favorable functional outcomes, the risk of DINDs and mortality decreased as the statin dose was increased in the acute period of aneurysmal SAH. After

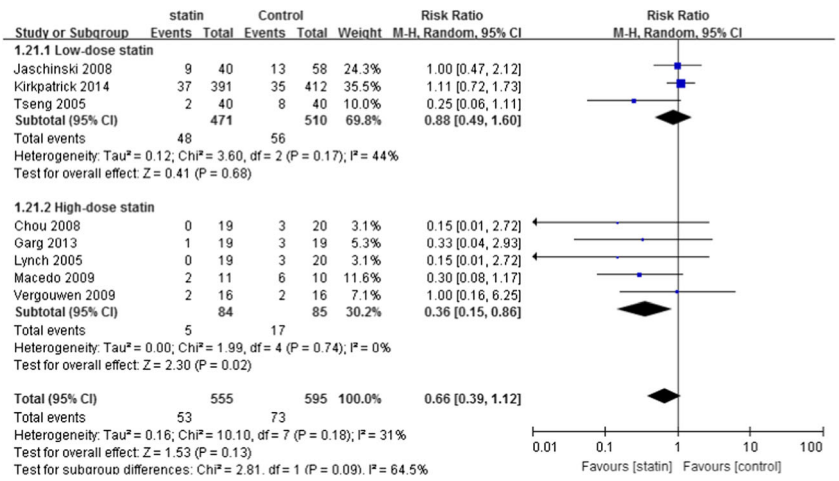

Fig. 6 Meta-analysis of RCTs assessing mortality according to statin dose (random effects model)

excluding the large STASH trial that used a low dose of statins (40 mg simvastatin) from among the RCTs, a significant association was still observed between statin use and survival. These findings might be attributed to the pleiotropic effects of statins, which have been reported to increase cerebral endothelial nitric oxide synthase expression, improve endothelial function, increase cerebral blood flow, and protect against ischemia [8, 35]. In the present study, statin doses that achieved LDL-cholesterol lowering >45% were considered as high doses (80 mg simvastatin or 40 mg atorvastatin); this threshold for high-potency statins was adopted from previous studies [36, 37]. Similar to the cholesterol-lowering properties of statins, most pleiotropic effects are mediated by HMG-CoA reductase inhibition and are dose-dependent [36, 38, 39]. However, the recently published High-Dose Simvastatin for Aneurysmal SAH (HDS-SAH; 80 mg simvastatin versus 40 mg simvastatin) trial did not support the superiority of high-dose compared with lower-dose simvastatin treatment for patients with aneurysmal SAH [14]. However, due to limitations related to the study population and protocol, the findings of the HDS-SAH trial may not be generalizable to real-world practice. First, several poor-grade patients were included in this trial, and hence, acute statin treatment may not have altered the clinical course. Second, this comparative study did not compare cases with high-dose statins and no simvastatin treatment. In the STASH trial, the administration of lower-dose statins (40 mg simvastatin) daily did not yield a reduction in DINDs or any improvements in the clinical outcomes [13]. Hence, future trials should evaluate the efficacy and safety of high-dose statins for aneurysmal SAH, in comparison with no statin treatment.

This meta-analysis has several limitations. First, a substantial amount of data included in this meta-analysis was obtained from nonrandomized observational studies. Although observational studies may be subject to hidden bias, these studies may also indicate the positive or negative effects of statins that may not be identified in RCTs, and may hence provide valuable evidence about the treatment effects in clinical practice [40, 41]. Second, our meta-analysis failed to identify cerebral infarctions that were closely associated with the clinical outcomes and link it with statin use, as the radiologic evaluation of the brain was not routinely repeated. Third, the publication of negative studies generally has less acceptance and impact in the literature; hence, it is possible that the lack of published negative studies concerning neurological outcomes may have affected the results of meta-analyses. Finally, our meta-analysis failed to obtain individual patient-level data from the assessed studies, which limited the further evaluation of the potential confounding factors in the assessment of functional outcomes after aneurysmal SAH.

Conclusions

In conclusion, the current systematic review and meta-analysis showed that statin use could potentially prevent DINDs in patients with aneurysmal SAH. Based on our current findings, although the role of statins in neurological outcome improvement was limited, the risk of DINDs and mortality decreased as the statin dose was increased, in a dose-dependent manner. Since the potential biases and confounders could not be fully excluded in this meta-analysis, well-designed RCTs that consider the potency of statins are required to confirm its association with clinical outcomes in the future.

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Author contributions All authors contributed to the design of the study. K.-S.C., T.L., W.K., and Y.C. undertook the searches and screened studies for eligibility. K.-S.C., J.M.K., and H.-J.Y. assessed the quality of papers and performed statistical analyses. K.-S.C. and S.H-.L. drafted the manuscript. T.L., W.K., and J.-H.C. moderated disagreements during data collection and analyzed the data. K.-S.C. and S.-H.L. critically revised the manuscript for important intellectual content. All authors revised the manuscript and approved the final version.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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