Efficacy of Statins in Cerebral Vasospasm, Mortality, and Delayed Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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■ BACKGROUND: **Aneurysmal subarachnoid hemorrhage (aSAH) is an acute cerebrovascular disease with frequent cerebral vasospasm and delayed cerebral ischemia (DCI). The use of statins for patients with aSAH is controversial. The present study evaluated the efficacy of statins in aSAH-induced vasospasm, DCI, delayed ischemic neurological deficit (DIND), mortality, and other outcomes.**

■ METHODS: **A literature search was performed in PubMed, EMBASE, and the Cochrane Library. English reports of patients with aSAH who had been treated with statins without combination were included. The outcomes, including cerebral vasospasm, DIND, DCI, mortality, disability, and creatine kinase/alanine aminotransferase/aspartic transaminase elevation, were extracted for meta-analysis.**

■ RESULTS: **A total of 13 studies, with 776 versus 821 patients treated with statins versus placebo, were retained for the statistical meta-analysis. The results showed that statin administration significantly reduced the frequency of vasospasm (relative risk [RR], 0.76; 95% confidence interval [CI], 0.63–0.91; *P* = 0.003), DIND (RR, 0.76; 95% CI, 0.63–0.91; *P* = 0.003), vasospasm-DCI (RR, 0.49; 95% CI, 0.32–0.74; *P* = 0.0008), and mortality (RR, 0.73; 95% CI, 0.54–0.98; *P* = 0.03). Statins showed insignificant efficacy in the prevention of disability (RR, 0.92; 95% CI, 0.71–1.20), a neurological poor prognosis (RR, 0.75; 95% CI, 0.45–1.27), and creatine kinase/alanine aminotransferase/aspartic transaminase elevation (RR, 1.90; 95% CI, 0.55–6.50).**

■ CONCLUSIONS: **Statins significantly reduced the incidence of vasospasm, DIND, DCI, and mortality in individuals with aSAH, suggesting its efficacy in aSAH.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) is an acute cerebrovascular and devastating hemorrhagic stroke, accounting for ~5% of strokes.[1,2] Aneurysmal SAH (aSAH) is a type of nontraumatic SAH, and both have destructive effects on the central nervous system. aSAH mainly threatens the population aged ≥50 years, which is younger than the population threatened by stroke. aSAH also has a greater incidence in women than in men.[1,3,4] Vasospasm and delayed cerebral ischemia (DCI) have been the major causes of SAH-induced mortality and a poor prognosis.[5,6] Vasospasm is the primary cause of mortality in the intensive care unit.[5] It has been reported that ~50% patients who survive SAH will have long-term cognitive impairment.[7,8]

The prevention of vasospasm after aSAH has been effective in reducing aSAH-related mortality.[9] Both intrathecal nicardipine and statins have been effective in treating aSAH-induced vasospasm.[9,10] However, the treatment and guidelines for the management of aSAH have been under constant revision and improvement during the past years owing to the development and

Key words
- Aneurysmal subarachnoid hemorrhage
- Delayed cerebral ischemia
- Mortality
- Statins
- Vasospasm

Abbreviations and Acronyms
aSAH: Aneurysmal subarachnoid hemorrhage
ALT: Alanine aminotransferase
AST: Aspartate transaminase
CI: Confidence interval
CK: Creatine kinase
DCI: Delayed cerebral ischemia
DIND: Delayed ischemic neurological deficit
GOS: Glasgow outcome scale
IL: Interleukin
MRS: Modified Rankin scale
RR: Relative risk
SAH: Subarachnoid hemorrhage

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the side effects of new drugs. Statins have been reported to be effective in preventing cerebral vasospasm.[10,11] However, its efficacies in the prevention of mortality and DCI and the prognosis of disability in the central nervous system have not been outstanding.[3,12,13] However, a great controversy has ensued because of statin-related myotoxicity and its side effects on organs, such as active liver disease and kidney dysfunction.

We performed the present systematic review to evaluate the efficacy of statins in aSAH-induced cerebral vasospasm, DCI, neurological prognosis, mortality, disability, and other adverse events. We hope the present study will provide evidence to help ascertain the usefulness of statins for the clinical management of aSAH.

METHODS

Neither human nor animal samples were used in our study; therefore, ethics committee approval was not required.

Search Strategy

The present review was designed, conducted, and prepared in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.[14] English reports in PubMed (1946 to December 2018) and EMBASE (1974 to December 2018) databases and the Cochrane library (updated to December 2018) were screened using the literature search terms: "statin[MeSH Terms]" OR "simvastatin[MeSH Terms]" OR "pravastatin[MeSH Terms]" OR "lovastatin[MeSH Terms]" OR "atorvastatin[MeSH Terms]" OR "fluvastatin[MeSH Terms]" AND "aneurysmal subarachnoid haemorrhage" OR "subarachnoid haemorrhage" AND "randomized controlled trial [MeSH]" OR "random allocation [MeSH]" OR "[singl* OR doubl* OR trebl* OR tripl*]" AND "[blind* OR mask*]." Other additional eligible studies were manually obtained from reference lists and review studies.

Criteria for Article Inclusion and Exclusion

Inclusion Criteria. Reports were included if they met the following criteria: 1) randomized controlled trials; 2) no sexual, age, or racial restrictions; 3) aSAH diagnosed using computed tomography or lumbar punctures; 4) patients treated with statins; and 5) outcomes data for vasospasm, vasospasm-DCI, and repeat hemorrhage.

Exclusion Criteria. Reports were excluded if they had met the following criteria: 1) animal experiment; 2) SAH due to other etiologies, not intracranial aneurysm; 3) no unambiguous definition provided for delayed ischemic neurological deficits (DIND), nervous system dysfunction, and adverse events; 4) treatment with nonstatins; and 5) clinical observations, reviews, and trials without statistical analysis.

Article Quality Evaluation

The quality of the reports was performed independently by 2 of us (J.S., K.C.Z.). The quality was assessed using the 5-point Jadad scoring tool.[15] A Jadad score of $\geq$3 was considered the threshold of high quality, and reports with a score of $\leq$2 were required to be reviewed. Evidence strength was evaluated using the Cochrane Collaboration tool GradePro (available at: http://ims.cochrane.org/revman/otherresources/gradepro/download).

OUTCOMES AND DETECTION METHOD

The primary outcomes were 1) vasospasm frequency; 2) vasospasm-associated DIND frequency; 3) vasospasm-delayed DCI; and 4) mortality of aSAH. Vasospasm was diagnosed from the clinical findings combined with transcranial Doppler or angiography. DIND was diagnosed by ischemic symptoms of the central nervous system and the Glasgow coma scale score. Both the Glasgow outcome scale (GOS) score and modified Rankin scale (MRS) score were used for the evaluation of prognosis. A poor prognosis was identified as a GOS score of 1–4 and MRS scores of 4–6.

The secondary outcomes were the frequency of adverse events and the 3 times greater than the normal range of alanine aminotransferase (ALT), aspartic transaminase (AST), and creatine kinase (CK).

Pooled Analysis

Revman, version 5.0, software (available at: https://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download/installation) was used for the meta-analysis. The 95% confidence intervals (CIs) and relative risk (RR) were calculated. Heterogeneity (I^2) was assessed using the χ^2 test. Reports with heterogeneity ($I^2 \geq 50\%$) were assessed for sensitivity and were gathered into subgroups according to the clinical traits, after the heterogeneity assessment until homogeneity was reached ($I^2 < 50\%$). Meta-analyses for the data from the reports with homogeneity ($I^2 < 50\%$) and heterogeneity ($I^2 \geq 50\%$) were performed using fixed effects and random effects models, respectively.[16,17]

RESULTS

Study Selection

The primary search of the databases yielded 302 studies reported in English, including 128 from PubMed, 89 from Embase and 85 from the Cochrane Library. The PRISMA diagram for article selection is shown in **Figure 1**. A total of 99 duplications, 39 reviews, 64 observations, 63 case reports, 8 nonrandomized controlled trials, 15 studies without aSAH, and 2 without the necessary outcome variables were excluded, and only 1 study was retrieved from the reference lists (**Figure 1**). Finally, 13 studies with data available for meta-analysis[1-3,11-13,18-24] were included in the present study. No publication bias was found for the 13 included reports (**Figure 2**).

Baseline Characteristics of Included Articles

All 13 included studies had been reported from 2005 to 2017. A total of 776 patients with aSAH had been treated with statins (40 or 80 mg/day of simvastatin for 14–21 days[1-3,11,18-24] or 40 mg/day of pravastatin for 14 days[12,13]; **Table 1**). The other 821 patients had received a placebo. Most patients were women (66.88%), and the mean age of all the patients was 54.33 years (**Table 1**).

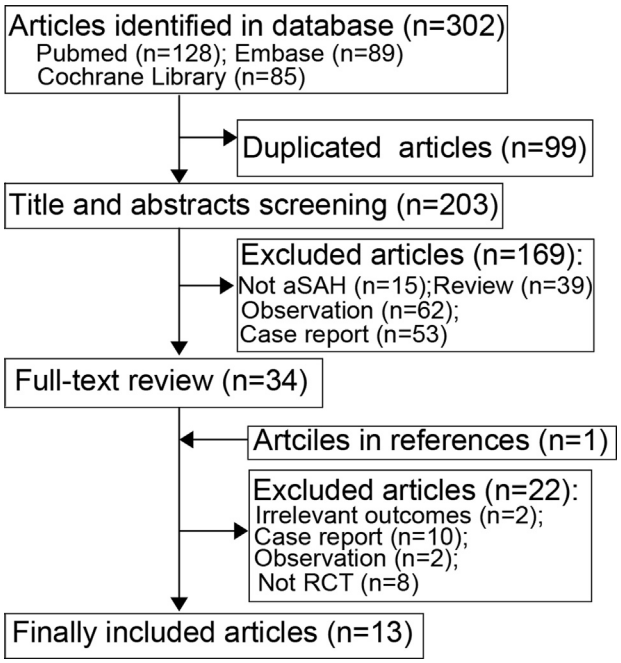

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram for study selection and inclusion. aSAH, Aneurysmal subarachnoid hemorrhage; RCT, randomized controlled trial.

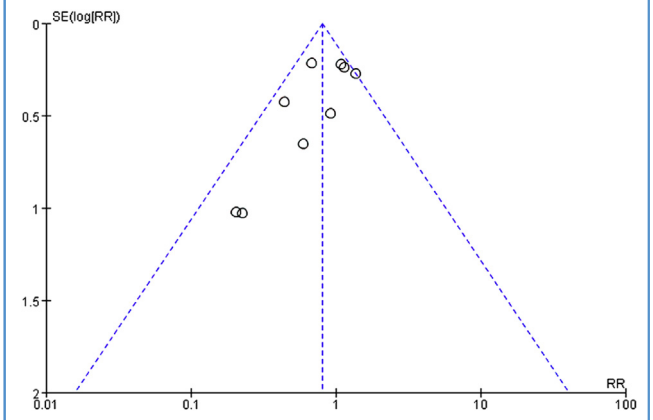

Figure 2. Funnel plot for the bias assessment. RR, relative risk; SE, standard error.

Statins Reduced the Frequency of Vasospasm

Ten studies, with 221 statin-treated patients and 220 placebo-treated patients with aSAH, had data available for vasospasm frequency.[2,11,12,18,19,21-24] The meta-analysis showed that statin treatment significantly reduced the frequency of vasospasm compared with placebo (RR, 0.77; 95% CI, 0.64–0.93; $P = 0.008$; $I^2 = 40\%$; fixed effects model; Figure 3), suggesting that statin administration was effective in reducing vasospasm frequency in individuals with aSAH.

Statins Reduced aSAH-Induced DIND

All 13 studies and 1597 patients with aSAH ($n = 776$, statins; $n = 821$, placebo) were available for the evaluation of the efficacy of statins in DIND prevention. The meta-analysis showed that the frequency of DIND in individuals with aSAH was significantly reduced by statins compared with placebo (RR, 0.76; 95% CI, 0.63–0.91; $P = 0.003$; $I^2 = 45\%$; fixed effects model; Figure 4). This pooled analysis showed that statins were effective in preventing the development of aSAH-induced DIND.

Statins Reduced Vasospasm-DCI

Five studies (215 patients) were available for the evaluation of the efficacy of statins in preventing vasospasm-DCI. The use of statins significantly reduced the morbidity of vasospasm-induced DCI in patients with aSAH compared with placebo (RR, 0.49; 95% CI, 0.32–0.74; $P = 0.0008$; $I^2 = 47\%$; fixed effects model; Figure 5). Thus, statin administration was effective in reducing the incidence of vasospasm-DCI in individuals with aSAH.

Statin Treatment Reduced aSAH-Induced Mortality

Twelve studies[2,3,11,12,18-24] reported nonsignificant or unchanged mortality for patients with aSAH at discharge, 3 or 6 months after surgery, or in intensive care units when comparing statins and placebo. However, the meta-analysis showed an obvious difference in the mortality between individuals with aSAH in the statins and placebo groups (RR, 0.73; 95% CI, 0.54–0.98; $P = 0.03$; $I^2 = 27\%$; fixed effects model; Figure 6). Therefore, statins were effective in reducing the aSAH-induced mortality of patients with aSAH.

Statins Effects on aSAH-Induced Disability and Neurological Poor Prognosis

We also reviewed the influence of statins on the prognosis of neurological function in subjects with aSAH. Disability was evaluated using the GOS or MRS scores, and a poor outcome or disability was defined by a GOS score of 1–4 and MRS score of 3–6. The meta-analysis showed that no significant difference in disability (RR, 0.92; 95% CI, 0.71–1.20; $P = 0.54$; $I^2 = 0\%$; fixed effects model; Figure 7A) and neurological poor prognosis (RR, 0.75; 95% CI, 0.45–1.27; $P = 0.28$; $I^2 = 0\%$; fixed effects model; Figure 7B) between the statins and placebo groups. These results suggest that statins insignificantly improved the neurological prognosis of patients with aSAH despite its efficacy in the prevention of vasospasm, DIND, DCI, and mortality.

Statins Did Not Influence CK/AST/ALT Levels

Finally, we analyzed the effect of statins on CK/AST/ALT elevation. Three studies[2,11,18] (<60 patients with aSAH) were available for the meta-analysis. We found that statins insignificantly upregulated the CK/AST/ALT level (RR, 1.90; 95% CI, 0.55–6.50; $P = 0.31$; $I^2 = 0\%$; fixed effects model; Figure 7C).

DISCUSSION

The results from the present study have confirmed that the administration of statins (simvastatin and pravastatin)

Table 1. Baseline Characteristics From 13 Included Reports

Investigator	Study Size (*n*; Statin; Control)	Age (years)	Female Sex (*n*; %)	Vasospasm	DIND	Mortality	Drug (Dosage; mg/day)	Treatment Duration (days)
Lynch et al.,[11] 2006	39 (19; 20)	56 ± 15	33 (85)	Angiographic or TCD (VMCA >160 cm/second)	Clinical impression of DIND (unrelated to repeat bleeding, hydrocephalus, or infection) with confirmatory radiographic findings	Not defined	Simvastatin (80)	14
Tseng et al.,[12] 2005	80 (40; 40)	53 ± 12	44 (55)	TCD (VMCA >120 cm/second; LR >3)	Development of focal neurological deficits or decrease in GCS score of ≥2 points	At discharge	Pravastatin (40)	≤14
Chou et al.,[18] 2008	39 (19; 20)	53 ± 13	29 (75)	TCD (systolic MCA flow velocity >200 cm/second; LR >3)	Decrease in modified GCS score of ≥2 points or unaccountable new focal neurological deficit lasting ≥2 hours	At discharge	Simvastatin (80)	≤21 or at discharge
Jaschinski et al.,[20] 2008	98 (40; 58)	ND	ND	ND	Not defined	ICU	Pravastatin (40)	ND
Vergouwen et al.,[24] 2009	32 (16; 16)	53 ± 11	20 (63)	TCD (VMCA or VACA ≥120 cm/second)	Gradual deterioration with focal neurologic impairment and/or a decrease in GCS score of ≥2 points	GCS score at 3 months	Simvastatin (80)	15
Macedo et al.,[21] 2009	20 (11; 9)	ND	ND	Cerebral arteriography	Altered neurological signals in presence of changes suggestive of vasospasm or clinical and CT correlation	Not defined	Simvastatin (80)	21
Garg et al.,[2] 2013	38 (19; 19)	49 ± 9	17 (45)	TCD (maximal MCA velocity ≥160 cm/second)	New ischemic neurological deficits in first 2 weeks after ictus not attributable to other causes	Not defined	Simvastatin (80)	14
Kirkpatrick et al.,[3] 2014	803 (391; 412)	50 ± 10	551 (69)	ND	Deterioration in GCS score of ≥2 points not attributable to any other cause, including sepsis	Mortality at 6 months	Simvastatin (40)	21 or until discharge
Wong et al.,[1] 2013	255 (124; 131)	57 ± 10	165 (65)	ND	Decrease in GCS score of ≥2 points or new focal neurological deficit lasting >2 hours	MRS score at 3 months	Simvastatin (80)	21
Diringer et al.,[19] 2016	25 (13; 12)	60 ± 11	16 (64)	Angiography	New focal deficit or global decline in consciousness after exclusion of other causes of neurological deterioration	mRS score at 6 months	Simvastatin (80)	14
Naraoka et al.,[13] 2018	108 (54; 54)	58 ± 11	74 (69)	Angiography	New focal, neurological deficits. or decrease in GCS score of ≥2 points	ND	Pravastatin (4)	14
Macedo et al.,[22] 2009	21 (11; 10)	ND	ND	Angiography	Change in neurological status with angiographic vasospasm	ND	Simvastatin (80)	21
Ogilvy et al.,[23] 2006	39 (19; 20)	ND	ND	ND	ND	ND	Simvastatin (80)	ND

DIND, delayed ischemic neurological deficit; TCD, transcranial Doppler; VMCA, blood flow velocity in ipsilateral middle cerebral artery; LR, Lindegaard ratio (mean blood flow velocity of middle cerebral artery to extracranial internal carotid artery); GCS, Glasgow coma scale; MCA, middle cerebral artery; ND, no detailed data; ICU, intensive care unit; VACA, mean blood velocity of anterior cerebral artery; CT, computed tomography; mRS, modified Rankin scale.

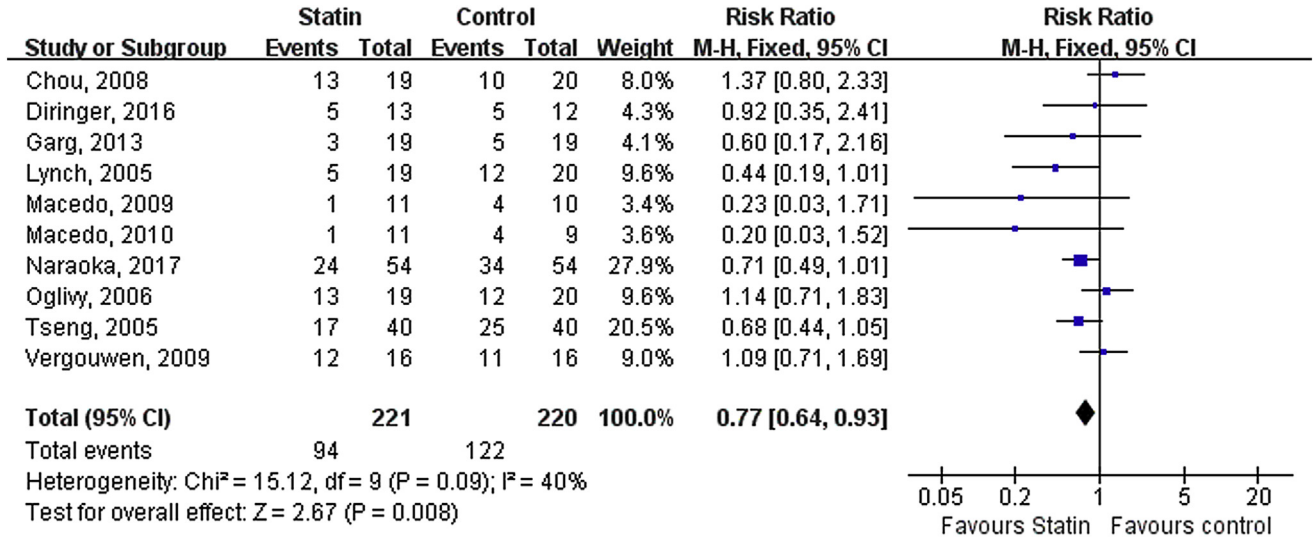

Figure 3. Forest plot for the effectiveness of statins in the prevention of Aneurysmal subarachnoid hemorrhage-induced vasospasm. CI, confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

significantly reduces the frequency of cerebral vasospasm, DCI, DIND, and mortality in patients with aSAH at discharge, 3 or 6 months after surgery, and in the intensive care unit. However, statins had no efficacy against aSAH-induced neurological dysfunction, a poor prognosis of neurological function, and disability. These results suggest that the statins are effective in aSAH management. Our results differ from those reported by Shen et al.,[10] who confirmed that statins were effective in preventing cerebral vasospasm but not in preventing vasospasm-induced DIND, DCI, or mortality. The results from our present

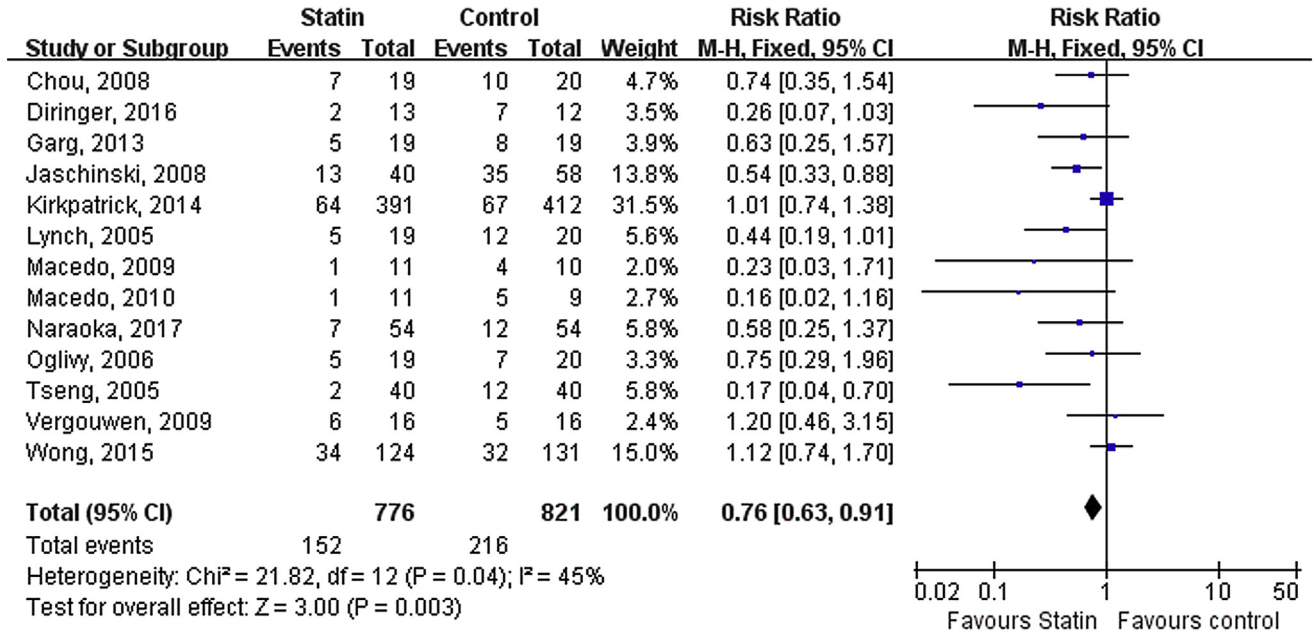

Figure 4. Forest plot for the efficacy of statins in Aneurysmal subarachnoid hemorrhage-induced delayed ischemic neurological deficit. CI, confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

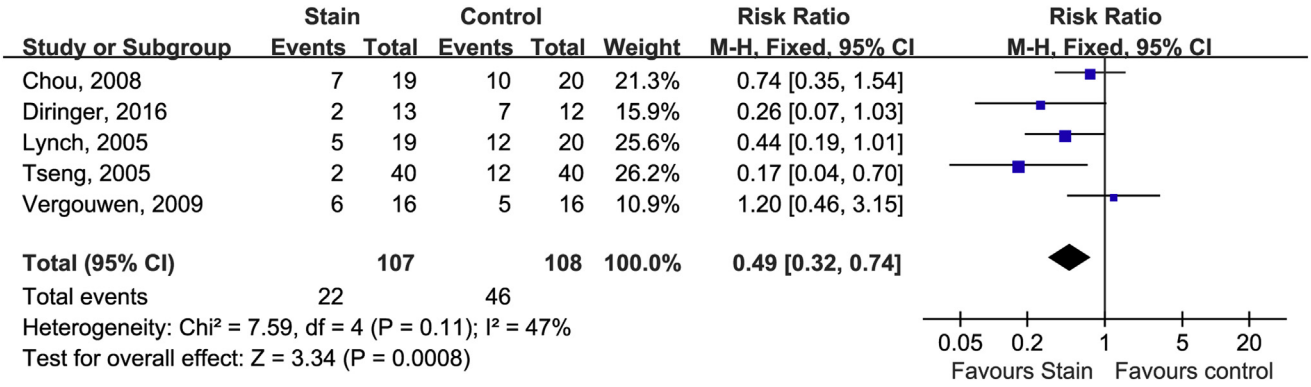

Figure 5. Meta-analysis of the efficacy of statins in preventing vasospasm-delayed cerebral ischemia. CI, confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

meta-analysis of the included studies, however, have confirmed the efficacy of statins in preventing vasospasm, DIND, DCI, and mortality.

Increasing evidence has shown that the inflammation, specifically neuroinflammation, is related to the secondary outcomes after aSAH, including DIND, DCI, and vasospasm.[25,26] Neuroinflammation has important roles in the pathogenesis of intracranial aneurysms[27] and in the expansion of brain injury after aSAH.[25,28] The presence of increased inflammation in patients with aSAH has been confirmed.[26,29] Increasing evidence has shown the positive correlation of interleukin (IL)-6 and white blood cell counts with the frequency of DCI and vasospasm after aSAH.[26,29,30] Neeraj et al.[28] and Atangana et al.[31] reported that inflammation can induce the catabolic state and increase the C-reactive protein/transthyretin ratio, which then increased the frequency and risk of hospital-acquired infections and poor outcomes after SAH. However, management of the inflammatory response prevented the occurrence of vasospasm after aSAH.[32] Galea et al.[4] performed a clinical trial using an IL-1 receptor antagonist for 6 months and found improved GOS scores in patients with aSAH.[4] The results from these studies suggest the crucial roles of inflammation in aSAH development and

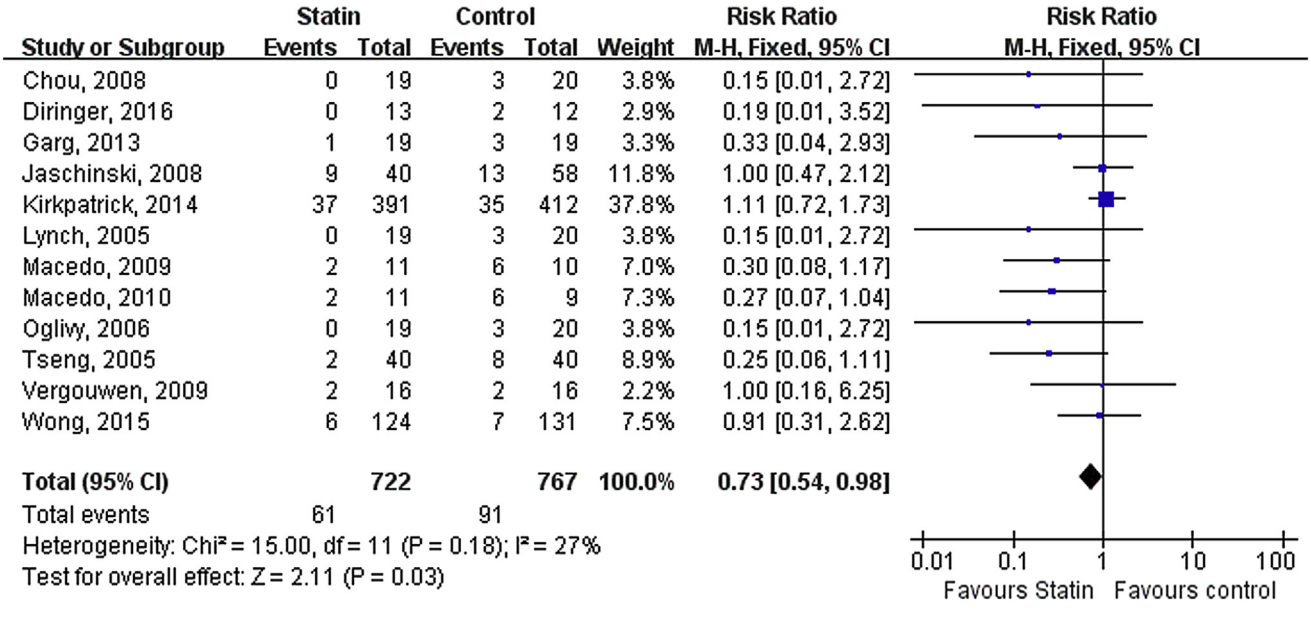

Figure 6. Efficacy of statins in Aneurysmal subarachnoid hemorrhage-induced mortality. CI, confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

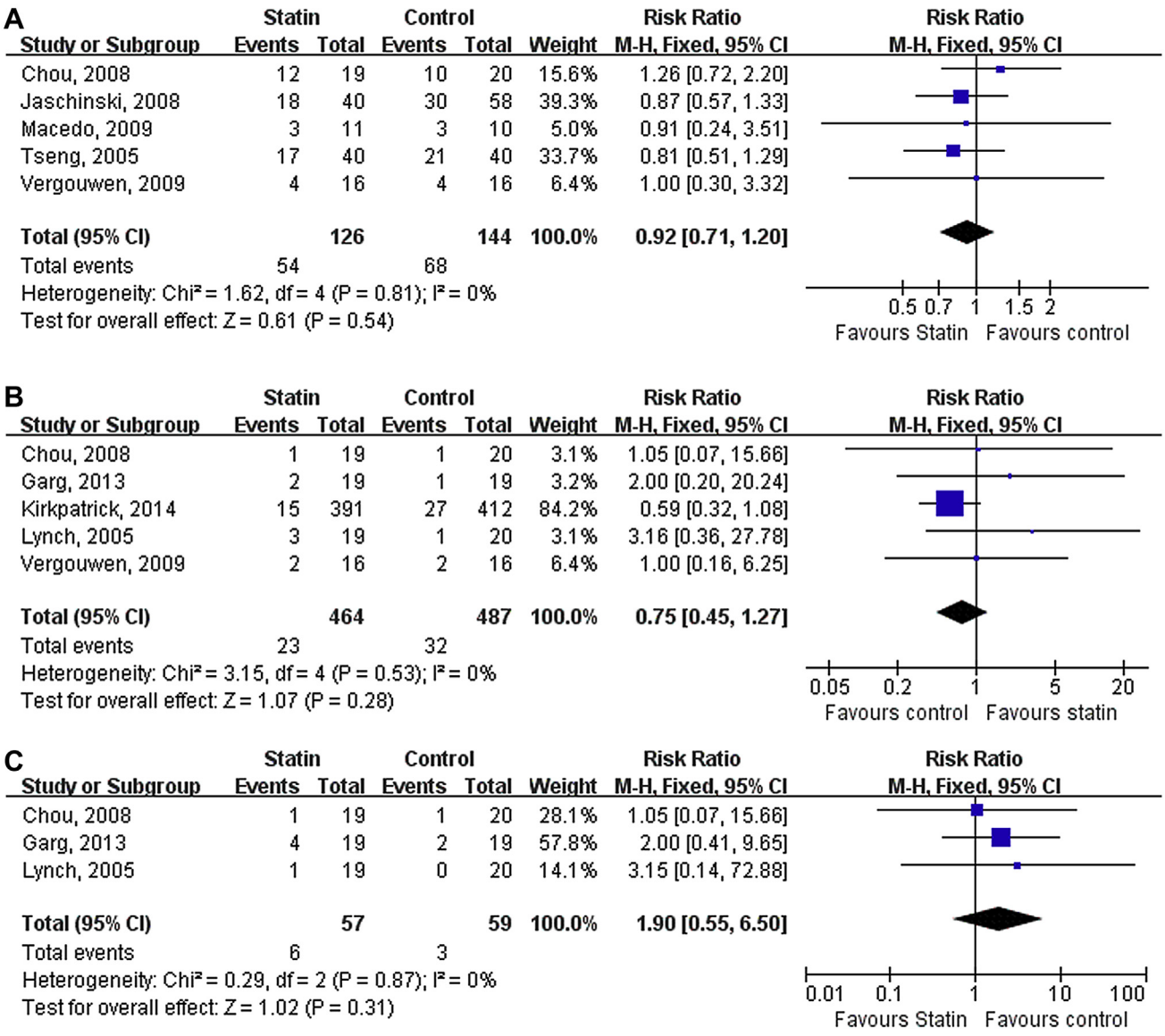

Figure 7. Efficacy of statin treatment in Aneurysmal subarachnoid hemorrhage-induced outcomes and adverse events. (**A**) Aneurysmal subarachnoid hemorrhage-induced disability, (**B**) neurological poor prognosis, and (**C**) creatine kinase/aspartate transaminase/alanine aminotransferase elevation were not different between the 2 groups.

prognosis and that an increased inflammation level might be an indicator of DCI development and frequent vasospasm after SAH.

The pleiotropic effects of statins, in addition to their anti-inflammatory effects, have been reported. Statins have been shown to improve cerebral vasomotor reactivity, cerebral blood flow, and fibrinolytic activity.[12] Statins used to treat aSAH. The decreased endothelial nitric oxide synthase and endothelial function after SAH could be increased by statin administration via activation of the phosphatidylinositol 3-kinase/Akt pathways and, therefore, decreased vasospasm and improved cerebral vasomotor reactivity and patient outcomes.[33-36] Statins enhanced angiogenesis, neurogenesis, and synaptogenesis in the brain of rats after stroke or traumatic injury.[37,38] It increased neurogenesis in the dentate gyrus and decreased delayed neuron death and the development of subdural hematoma.[38,39] Acute statin treatment improved recovery after intracerebral hemorrhage.[40] The use of statins for the prevention of vasospasm and DIND has shown promise in phase II clinical trials.[12] In accordance with their findings, the results from our present study have confirmed the efficacy of statins in preventing vasospasm, DIND, and DCI. These findings suggest the efficacy of statins in improving aSAH-induced brain injury.

CONCLUSIONS

The results from our present study have suggested that the administration of statins to patients with aSAH will reduced the mortality, cerebral vasospasm, DCI, and DIND. These effects might result from statins' anti-inflammatory, angiogenic, and neurogenic effects. However, the mechanism underlying statin-ameliorated cerebral vasospasm, DCI, and DIND has remained unclear. The ambiguous efficacy of statins in treating aSAH-induced disability and a neurological poor prognosis in patients with aSAH has shown that additional studies are needed.

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