Do Statins Improve Outcomes and Reduce the Incidence of Vasospasm After Aneurysmal Subarachnoid Hemorrhage
A Meta-Analysis

Victoria A.H. Sillberg, BSc; George A. Wells, MSc, PhD; Jeffrey J. Perry, MD, MSc

Background and Purpose—Subarachnoid hemorrhage (SAH) is a relatively rare cause of stroke with a high rate of morbidity and mortality, primarily due to the occurrence of delayed vasospasm. To date, many therapies have been proposed to help prevent vasospasm, but very few have been proven effective. The initiation of statin therapy after SAH may be effective in reducing the incidence of vasospasm; however, the only studies that have examined this effect have been small. This meta-analysis attempted to determine whether statins reduce morbidity and mortality after aneurysmal SAH.

Methods—MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for randomized, controlled trials relating to the use of statins in SAH. Foreign language and abstract articles were included. Two independent reviewers assessed studies for eligibility, data extraction, and quality. Primary outcome was the incidence of radiographically confirmed clinical vasospasm; secondary outcomes were incidence of delayed ischemic deficits and mortality.

Results—The incidence of vasospasm (relative risk [RR] 0.73; 95% CI, 0.54 to 0.99), delayed ischemic deficits (RR 0.38; 95% CI, 0.17 to 0.83), and mortality (RR 0.22; 95% CI, 0.06 to 0.82) were significantly reduced in the statin group. For these outcomes, we calculated a number needed to treat of 6.25, 5, and 6.7, respectively.

Conclusions—Initiation of statin therapy after aneurysmal SAH significantly reduces the incidence of vasospasm, delayed ischemic deficits, and mortality. This is consistent with animal research and retrospective studies and supports the routine use of statins in the care of patients with aneurysmal SAH. (Stroke. 2008;39:2622-2626.)

Key Words: subarachnoid hemorrhage ■ vasospasm ■ statins ■ meta-analysis

Aneurysmal subarachnoid hemorrhage (SAH) is the cause of ≈5% of strokes.1 Despite the relatively low incidence, the disability and loss of productive life years associated with SAH approaches that of the most common cause of stroke, cerebral ischemia, because it occurs in younger individuals and is associated with a high rate of morbidity and mortality. The leading cause of morbidity and mortality in SAH patients is cerebral vasospasm, in which there is narrowing of the cerebral arterial vessels, leading to increased vascular resistance and ischemia.2 The pathogenesis of cerebral vasospasm is poorly understood, and thus, treatments to prevent the onset of vasospasm, including calcium channel antagonists, corticosteroids, and antifibrinolytic and antiplatelet agents, have demonstrated variable effectiveness. Recent research has begun to focus on hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, as a way to prevent vasospasm.

Statins were initially developed as cholesterol-lowering agents but have effects that are independent of their cholesterol-lowering mechanisms, known as “pleiotropic” effects. Statins reduce inflammation and cell proliferation, increase the synthesis of nitric oxide in the body through upregulation of endothelial nitric oxide synthase, and prevent thrombogenesis, all of which could be beneficial in preventing delayed vasospasm.3,4 Research in animals has shown that administration of statins increases levels of endothelial nitric oxide synthase proteins in the body, increases cerebral arterial diameter, and reduces neurologic deficit associated with induced SAH.5,6 There have been very few human studies on the effects of statins in SAH, and those that have been done have been small; however, they suggest that statins, when administered after aneurysmal SAH, may help improve outcomes, including reducing the incidence and severity of cerebral vasospasm.7-10

All randomized, controlled trials that evaluated the effect of statins in aneurysmal SAH have been in small populations of patients. There has been no previous systematic review to investigate the effects of these statins in the treatment of SAH. The goal of this meta-analysis was to determine whether statins are effective in preventing cerebral vasospasm in patients who have had aneurysmal SAH.

Methods
MEDLINE (1950 to April week 4 2007), EMBASE (1980 to 2007 week 18), and the Cochrane Central Register of Controlled Trials

Received October 24, 2007; final revision received January 30, 2008; accepted January 31, 2008.
From the Ottawa Health Research Institute (V.A.H.S.), the Department of Epidemiology and Community Medicine (G.A.W.), and the Department of Emergency Medicine (J.J.P.), University of Ottawa, Ottawa, Canada.
Correspondence to Dr Jeffrey J. Perry, Clinical Epidemiology Program, F6, Ottawa Hospital, Civic Campus, 1053 Carling Ave, Ottawa, Ontario K1Y 4E9 Canada. E-mail jperry@ohri.ca
© 2008 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.107.508341

2622
(second quarter 2007) were searched to identify all studies related to the use of statins in SAH. The search strategy included key words such as “subarachnoid hemorrhage,” “statins,” and “vasospasm,” as well as all known generic and trade names for the statin class of medications (Appendix). Previously validated randomized, control trial filters were applied to the MEDLINE and EMBASE searches. The search strategy was reviewed by library personnel to ensure completeness. All foreign language journals were included, as were articles published as abstracts only. The references of identified articles were searched for citations that might have been missed by the electronic search, and authors were contacted for unpublished or in press data.

Two independent assessors (V.A.H.S., J.J.P.) reviewed titles, selected studies for inclusion according to specific criteria (including only randomized controlled trials, administration of a statin to patients after aneurysmal SAH, and measurement of ≥1 of our outcome variables). Interrater agreement was calculated by κ statistics. All disagreements were resolved by consensus. Data were extracted by 2 independent reviewers (V.A.H.S., J.J.P.) who used standardized data collection forms.

We included all randomized, controlled trials and controlled clinical trials that met the following criteria: (1) The study reported outcomes for incidence of clinical vasospasm, incidence of vasospasm-related delayed ischemic deficits, or mortality; (2) Some patients in 1 study arm received a statin medication; and (3) The study examined patients with confirmed aneurysmal SAH.

Methodologic quality was assessed independently by 2 reviewers (V.A.H.S., J.J.P.). Both reviewers rated all studies on the Jadad scale. This is a validated scale of 5 levels ranging from 0 for low-quality studies to 5 for high-quality studies that were well-blinded, well-randomized, and accounted for all patients intended for the study. Studies were deemed to be of high quality if they received a Jadad score of ≥3. Interrater agreement was measured for both study quality assessments by the κ statistic (V.A.H.S., J.J.P.). The primary outcome was the incidence of clinical cerebral vasospasm, which is defined as the clinical manifestation of vasospasm (ie, a neurologic deficit not associated with a rebleed, hydrocephalus, or infection) that has been radiographically determined with an imaging modality such as transcranial Doppler or cerebral angiography as reported by the study’s authors. Secondary outcomes included mortality and incidence of vasospasm-related delayed ischemic deficits.

Studies were combined with the use of Review Manager 4.2.10.13 All outcome variables were dichotomous, so relative risk (RR) was calculated with a fixed-effects model and 95% CIs. Statistical heterogeneity was assessed by a χ2 test with a probability value of 0.05 predetermined to indicate significant heterogeneity, as well as visual inspection of the graphic representation of the studies with their 95% CIs. In addition, the I2 test was used to assess heterogeneity. Publication bias was assessed through visual examination of funnel plots.

Results

Our search strategy (see Appendix) identified 160 titles. Of these, the abstracts of 26 articles were examined. Twenty-one articles were excluded because they were duplicates, reviews, or letters or because they were not randomized, controlled trials. Five randomized, controlled trials were identified in which patients in 1 trial arm received statin therapy after SAH and another in which they received placebo. Two of these studies were excluded because they were duplicate articles from the same study but with different outcomes. The κ statistic for selection by title was 0.64 (95% CI, 0.46 to 0.82) and for abstract it was 0.57 (95% CI, 0.08 to 1.0), whereas the κ statistic for included studies was 1.0. The κ for high-quality studies (ie, Jadad score ≥3) was 1.0. The characteristics of the 3 included studies are reported in Table 1. All 3 studies were double-blinded, randomized, controlled trials in which 1 treatment arm received statin therapy and another received placebo. Overall, 78 patients received statin therapy and 80 received placebo.

The primary outcome, incidence of vasospasm, was calculated for all 3 studies. The incidence of vasospasm was significantly less in patients who received statin therapy (RR = 0.73; 95% CI, 0.54 to 0.99; the Figure, a). The number needed to treat (NNT) for this outcome is 6.1. The χ2 test was not significant for this group. The incidence of vasospasm-related delayed ischemic deficits was significantly lower in patients who received statin therapy (RR = 0.38; 95% CI, 0.17 to 0.83; Figure, b). The NNT for this outcome is 5.0. The χ2 test for heterogeneity was not significant for this group. The incidence of mortality was also significantly decreased in patients who received statin therapy (RR = 0.22; 95% CI, 0.06 to 0.82; Figure, c). The NNT for this outcome is 6.7. The χ2 test for heterogeneity was not significant for this group of studies.

Discussion

The results of this meta-analysis demonstrate that statin therapy is superior to placebo for decreasing the incidence of cerebral vasospasm, overall mortality, and the incidence of delayed ischemic deficits after SAH. Based on these results, administration of a statin to all patients (for whom the drug is not contraindicated) after SAH should be encouraged.

The finding that statins decrease the incidence of radiographically confirmed clinical vasospasm after SAH is supported by findings in animal research, as well as the trials conducted by Lynch and colleagues and Tseng and colleagues, all of whom found a decreased incidence of vasospasm with statin therapy. It is also consistent with the finding of 2 retrospective studies, 1 of which found that discontinuation of prior statin use in patients after SAH led to an increased incidence of vasospasm, and another study that found a significant decrease in vasospasm among statin users whose therapy was continued during hospitalization. This suggests that statin use imparts cerebrovascular protection that is lost once the medication is discontinued. It is, however,
inconsistent with the preliminary results reported by Ogilvy and colleagues.17

We found that the incidence of vasospasm-related delayed ischemic deficits was significantly lower in the statin group. This is supported by animal as well as human research, which has reported improved neurologic outcomes and functional status in patients who received statins either before or after SAH.5,18 In randomized, controlled trials, Tseng et al8 also reported a significant decrease in delayed ischemic deficits for those who received statins; however, preliminary results from the study of Ogilvy et al17 did not support this finding, although visual examination of their results revealed a trend toward a decreased incidence of vasospasm-related delayed ischemic deficits that did not reach statistical significance. The NNT for this outcome was 5, indicating that statin therapy is required for 5 people to prevent 1 delayed ischemic deficit. This low NNT strongly supports statin use in eligible patients.

Finally, this analysis demonstrated a significant decrease in mortality in patients who received statin therapy. This concept is supported by the study conducted by Lynch et al.7 The results reported by Ogilvy et al17 do not support this finding; however, once again, their results did show a trend toward decreased mortality in patients who received statin therapy. This finding does contradict the results of a retrospective cohort study conducted by Parra and colleagues,18 who found no significant difference in mortality at 14 days between patients who received statins and those who did not. The NNT calculated from our study for this outcome is 6.7, which is very low and strongly supportive of statin use after aneurysmal SAH.

There was no significant preictal statin use in any of the 3 studies. Ogilvy et al17 and Tseng et al8 both excluded patients with prior statin exposure from their study, and in the study conducted by Lynch and colleagues,7 only 2 patients in the statin group and 1 patient in the control group were on statin therapy at the time of the SAH. There was no indication in the study by Lynch et al7 that patients received concurrent therapy with any of the other drugs that have been proposed for treatment of SAH (ie, calcium antagonists, corticosteroids, fibrinolytic agents, or antiplatelet therapy). In the study conducted by Ogilvy et al,19 patients with angiographically confirmed vasospasm received intra-arterial nicardipine, a calcium channel blocker with higher selectivity to cerebral blood vessels. In the study by Tseng et al,5 all patients received concurrent nimodipine treatment. There is no indication how many patients received this therapy; therefore, any potential influence on their results cannot be assessed.

There is currently no evidence to indicate when statin therapy is best begun after SAH; however, cerebral vasospasm is generally believed to occur within 4 to 10 days after SAH.20 Statin treatment was started within 96 hours of SAH in all studies (Lynch et al,7 48 hours; Tseng et al,8 72 hours; Ogilvy et al,19 96 hours). The optimal length of statin therapy has also not yet been determined. In the study conducted by Lynch et al,7 therapy was continued for 14 days. Tseng et al8 continued therapy for a maximum of 14 days or until hospital discharge (47.5% completed 14 days of therapy), and in the study conducted by Ogilvy et al,19 therapy was continued for the duration of the patients’ stay in the intensive care unit. They reported a maximum duration of 21 days but did not report the average duration of treatment.

No meta-analyses have focused exclusively on the effects of statin therapy after aneurysmal SAH. There are currently 2 publications that we are aware of that have reviewed the current treatments available to prevent cerebral vasospasm in SAH and that mention the potential role for statin therapy. The first review by Naval and colleagues21 on the different proposed methods of cerebral protection after SAH summarized the current evidence from randomized, controlled trials and retrospective studies that have been conducted on the potential for statins in this role. The second review by Weyer and colleagues22 was a meta-analytic review of the different treatments that are currently considered for the management of vasospasm after aneurysmal SAH. This study addressed statin use very briefly and only included the studies by Lynch et al7 and Tseng et al.8

The body of research on the effect of statins after SAH is small. The trials conducted to date have been summarized in Table 2. In addition to human studies, there have been 3 animal studies5,6,14 that have reported the effects of statins on cerebral vasospasm after induction of SAH. All 3 studies used simvastatin either for pretreatment or posttreatment after SAH. All 3 studies found a significant increase in target arterial diameter, which indicates a decreased incidence of cerebral vasospasm. In human research, Tseng et al8,10 published 2 additional articles on results from the same study as the Tseng et al article that we included for meta-analysis but examined different outcomes. They showed generally more favorable outcomes for the group that received statin therapy. Three other retrospective studies examined outcomes in patients who received statin therapy before SAH. One study by McGirt et al16 (N=115 patients) reported an 11-fold decrease in the incidence of vasospasm among patients who had received statin therapy for at least 1 month before SAH and who continued to receive statin therapy throughout their hospital stay. A second study by Parra et al18 (N=60 patients)
found an improvement in the incidence of delayed ischemic deficits, although these authors reported no impact on mortality. The third study by Singhal and colleagues15 (N=514 patients) reported an increased risk of vasospasm in patients who had been on statin therapy before SAH. This effect is postulated to be due to the effect of acute discontinuation of statin therapy on hospital admission, which would further support the belief that statins are protective against vasospasm. Together, these studies support a beneficial role for statin therapy after SAH.

Limitations
The major limitation of this review is the small sample size, with a total of only 158 patients. There have not been any large randomized, controlled trials for examining the use of statins after SAH, and there have been very few small trials. We identified only 2 small studies and 1 abstract publication that met our inclusion criteria. The second limitation is that the heterogeneity test for the primary outcome was significant, indicating that it may not be appropriate to combine the included studies for this outcome.

Strengths
We believe that our study has several strengths. Our analysis is unique in that it is the only meta-analysis that we are aware of to examine the use of statin therapy after aneurysmal SAH. We also used a very open search strategy to include all non-English and abstract publications that related to our topic to be as inclusive as possible. Our use of 2 independent reviewers also helped to ensure that we included only appropriate and high-quality studies. We contacted the authors of all identified studies directly in an attempt to obtain unpublished or in press data. We also contacted the authors of 1 in-progress clinical trial in an attempt to gather more information.

Implications for Practice
The principal findings from this analysis, decreased incidence of vasospasm and decreased rates of delayed ischemic deficits and mortality, have important implications for the treatment of aneurysmal SAH. Currently, there are several therapies that have been proposed to improve outcomes after SAH, but only calcium channel antagonists have proven effective. Despite the limitations of this investigation, the results of this review support the use of statins in SAH, as they are a relatively safe medication and few patients need to be treated initiating statin therapy immediately after diagnosis of SAH. The optimal duration and dose of therapy cannot be determined from this study.

Implications for Future Research
In light of our findings and the small number of randomized, controlled trials that studied the impact of statin therapy after aneurysmal SAH, we believe that further investigation in this area is warranted. We are currently aware of 3 in-progress randomized, placebo-controlled, double-blind clinical trials examining the use of statin therapy after SAH. The first is a multicenter phase III trial (the STASH trial) with a planned enrollment of 800. The second smaller study has a planned

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Effect of Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulsara et al14</td>
<td>Double SAH canine model, N=13</td>
<td>Female mongrel dogs</td>
<td>1: no drug treatment; 2: simvastatin 20 mg/kg per day and cyclosporine 6 mg/kg per day; 3: simvastatin alone 20 mg/kg per day</td>
<td>Increased basilar artery diameter compared with control.</td>
</tr>
<tr>
<td>McGirt et al23</td>
<td>Mouse model of SAH, N=50</td>
<td>C57BL/6J male mice</td>
<td>For 14 days treated with 1: simvastatin; or 2: vehicle. Randomized to receive 1: SAH surgery; or 2: sham surgery</td>
<td>Increased middle cerebral artery diameter. Improved neurologic outcome.</td>
</tr>
<tr>
<td>McGirt et al8</td>
<td>Rabbit model of SAH, N=15</td>
<td>New Zealand White Rabbits</td>
<td>1: sham+vehicle; 2: SAH+vehicle; 3: SAH+simvastatin</td>
<td>Attenuated vasospasm compared with control.</td>
</tr>
<tr>
<td>McGirt et al16</td>
<td>Retrospective chart review, N=115</td>
<td>SAH</td>
<td>1: patients received at least 1 month of statin therapy before SAH; 2: patients did not receive statin therapy before SAH</td>
<td>Decreased incidence of vasospasm 11-fold.</td>
</tr>
<tr>
<td>Parra et al16</td>
<td>1:2 matched retrospective cohort study, N=60</td>
<td>SAH</td>
<td>1: patients received statin therapy before SAH; 2: patients who were not receiving statin therapy before SAH</td>
<td>Improved 14-day outcome. Lowered incidence of delayed cerebral ischemia and infarction. Prevented highest mean velocity elevation as measured with transcranial Doppler. No significant impact on mortality or global outcome.</td>
</tr>
<tr>
<td>Singhal et al15</td>
<td>Retrospective study, N=514</td>
<td>Aneurysmal SAH</td>
<td>1: patients received statin therapy before SAH; 2: patients who were not receiving statin therapy before SAH</td>
<td>Discontinuation after SAH increased risk of vasospasm. No increased risk for poor outcome or death.</td>
</tr>
<tr>
<td>Tseng et al9</td>
<td>Double-blind RCT, N=80</td>
<td>Aneurysmal SAH</td>
<td>1: 40 mg pravastatin daily for up to 14 days; 2: placebo daily for up to 14 days</td>
<td>Enhanced cerebral autoregulation.</td>
</tr>
<tr>
<td>Tseng et al10</td>
<td>Double-blind RCT, N=80</td>
<td>Aneurysmal SAH</td>
<td>1: 40 mg pravastatin daily for up to 14 days; 2: placebo daily for up to 14 days</td>
<td>Reduced traditional rescue therapy. Improved 6-month outcome. No effect on length of inpatient stay.</td>
</tr>
</tbody>
</table>

RCT indicates randomized, controlled trial.
enrollment of 150, and the third enrolled 104 patients. All 3 studies plan to use simvastatin. We hope that the results of these larger trials will further clarify the effects that we have reported. Further research into the optimal dose and duration of therapy should also be considered.

Summary
The use of statin therapy decreases the incidence of vasospasm, delayed ischemic deficits, and mortality after aneurysmal SAH. These results support the use of statins in aneurysmal SAH patients; however, larger randomized, controlled trials are needed to confirm their safety and efficacy.

Appendix

Medline (1950 to April week 4 2007)
Set Term Results: 1 Exp hydroxymethylglutaryl-CoA reductase inhibitors/ 13387; 2 Hydroxymethylglutaryl coenzyme a reductase inhibitors.tw 169; 3 Hydroxymethylglutaryl-CoA reductase inhibitors.tw 38; 4 HM-CoA reductase inhibitors.tw 2603; 5 Simvastatin/ 3128; 6 simvastatin.tw 3033; 7 zocor.tw 74; 8 atorvastatin.tw 2057; 9 lipitor.tw 68; 10 fluvastatin.tw 4; 11 fluvastatin.tw 920; 12 lescol.tw 55; 13 mevinolin.tw 334; 14 lovastatin.tw 2229; 15 lovastatin/ 3479 16 mevacor.tw 40; 17 rosuvastatin.tw 393; 18 crestor.tw 34; 19 cerivastatin/ 3789; 37 SAH.tw 3789; 39 ((vasospasm$ or spasm$ or aneurysm$ or hemorrhage$ or Hemorrhage$ or bleed$ or blood) adj3 (clinic$ adj trial$1).tw 106091; 31 cholesterol inhibitor$.tw 19; 32 cholesterol inhibitors/ 9943; 30 exp anticholesteremic agents/ 29124; 31 ((hypocholesterolic or hypocholesterolemic) adj (agent$ or drug$)).tw 12; 35 ((anticholesterol or antilipidemic or antihyperlipidemic) adj (agent$ or drug$)).tw 883; 33 simvastatin.tw 82304; 34 ((anticholesterol or antilipidemic or antihyperlipidemic) adj (agent$ or drug$)).tw 12; 35 or/1 to 34 34322; 36 simvastatin hemorrhage/ 11987.
37 (subarachnoid adj (hemorrhage or hemorrhage)).tw 1.
38 SAH.tw 3789; 39 ((vasospasm$ or spasm$ or aneurysm$ or hemorrhage$ or Hemorrhage$ or bleed$ or blood) adj3 (intracranial or Cerebral or Intracerebral or brain)).tw 65654; 40 vasospasm, intracranial/ 1005; 41 vasospasm$tw 6527; 42 intracranial aneurysm$/ 16163; 43 or/36 to 42 82304; 44 35 and 43 140; 45 randomized controlled trials/ 48327; 46 randomized controlled trial.pt. 234274; 47 random allocation/ 57750; 48 double blind method/ 91028; 49 single blind method/ 10880; 50 clinical trial.pt 453592; 51 exp clinical trials/ 190560; 52 or/45 to 51 610185; 53 (clinical adj trial$1).tw 100691; 54 ((singI$ or double$I$ or triple$I$ or triple$) adj (blind$ or mask$)).tw 87813; 55 placebo.tw 26128; 56 placebo$.tw 101854; 57 random$allocate$.tw 10260; 58 (allocate$.tw 12371; 59 or/53 to 58 246761; 60 52 or 59 678070; 61 case report.tw 123984; 62 letter.pt 588375; 63 historical article.pt 238491; 64 or/61 to 63 943869; 65 60 not 64 658546; 66 44 and 65 40.

Source of Funding
This study was supported in part by the Department of Emergency Medicine, University of Ottawa, Ottawa, Canada.

Disclosures
None.

References
Do Statins Improve Outcomes and Reduce the Incidence of Vasospasm After Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis
Victoria A.H. Sillberg, George A. Wells and Jeffrey J. Perry

*Stroke*. 2008;39:2622-2626; originally published online July 24, 2008;
doi: 10.1161/STROKEAHA.107.508341

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/9/2622

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/