Background and Purpose—A recent meta-analysis investigating the efficacy of statin treatment in patients with aneurysmal subarachnoid hemorrhage reported a reduced incidence of vasospasm, delayed cerebral ischemia, and mortality in statin-treated patients. However, the meta-analysis was criticized for its methodology, and several retrospective studies found no beneficial effect. We present the results of a new systematic review, which differs from the previous systematic review in its methodology, and by inclusion of the results of a fourth randomized, placebo-controlled trial.

Summary of Review—All randomized, placebo-controlled trials investigating the effect of statins on vasospasm, delayed cerebral ischemia, and functional outcome in patients with aneurysmal subarachnoid hemorrhage were included. Outcomes were the number of patients with transcranial Doppler vasospasm, delayed cerebral ischemia, poor outcome, and mortality during follow-up. Effect sizes were expressed in (pooled) risk ratio estimates. Data were pooled using random-effects models.

Results—In 4 studies, a total of 190 patients were included. No statistically significant effect was observed on transcranial Doppler vasospasm (pooled risk ratio, 0.99 [95% CI, 0.66 to 1.48]), delayed cerebral ischemia (pooled risk ratio, 0.57 [95% CI, 0.29 to 1.13]), poor outcome (pooled risk ratio, 0.92 [95% CI, 0.68 to 1.24]), or mortality (pooled risk ratio, 0.37 [95% CI, 0.13 to 1.10]).

Conclusion—The results of the present systematic review do not lend statistically significant support to the finding of a beneficial effect of statins in patients with aneurysmal subarachnoid hemorrhage as reported in a previous meta-analysis. (Stroke. 2010;41:e47-e52.)

Key Words: delayed cerebral ischemia ▪ outcome ▪ statins ▪ subarachnoid hemorrhage ▪ systematic review ▪ vasospasm

A common and serious complication after aneurysmal subarachnoid hemorrhage (SAH) is delayed cerebral ischemia (DCI), which occurs in approximately 30% of patients surviving the ictus of the hemorrhage.1,2 DCI is sometimes reversible, but may also progress to cerebral infarction, which is associated with an increased risk of severe disability and death.1,3

Currently, the only drug that decreases the incidence of DCI and poor outcome after SAH is nimodipine.4 Because the effect of nimodipine is relatively modest, much research efforts have been undertaken to develop and investigate new drugs to prevent and treat this complication. One of the suggested therapeutic options is treatment with statins. Recently, in 2 randomized, controlled Phase II studies, acute initiation of statin treatment directly after aneurysmal SAH decreased the incidence of radiological vasospasm and clinical signs of DCI. Moreover, mortality was reduced in patients who were treated with statins on top of nimodipine.5–7 However, a third Phase II trial8 and 3 studies with historical controls9–11 could not confirm the beneficial effects of statins. Nevertheless, because of the observed clinical effects in the first 2 randomized, controlled Phase II studies, the relatively low costs, and in the absence of the results from a large Phase III study, many hospitals introduced treatment with statins in everyday practice. This treatment policy was supported by a recent meta-analysis, which concluded that in patients with aneurysmal SAH, statins reduced the incidence of vasospasm, DCI, and mortality.12 However, this meta-anal-
ysis was criticized for its methodology and interpretation of results, especially with regard to the way data relating to vasospasm and DCI were combined.13,14 A large-scale Phase III study is presently being conducted to investigate the effect of statins in aneurysmal SAH (www.stashtrial.com), but the results are not expected soon. We present the results of a new systematic review, which differs from the previous systematic review in its methodology and by inclusion of the results of a fourth small randomized, placebo-controlled trial.15

### Methods

For this systematic review, the Cochrane Collaboration format was used.16

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Type of Statin Treatment</th>
<th>Age Eligibility, Years</th>
<th>Major Exclusion Criteria</th>
<th>Definition of Vasospasm</th>
<th>Definition of Delayed Cerebral Ischemia</th>
<th>Time of Latest Blinded Functional Outcome Measurement</th>
<th>Type of Functional Outcome Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tseng et al (2005, 2007)6,7</td>
<td>80</td>
<td>Pravastatin 40 mg once daily, during 14 days or until discharge</td>
<td>18 – 84</td>
<td>(1) nonaneurysmal SAH; (2) contraindication to statin use; (3) history of liver or renal dysfunction or alanine aminotransferase &gt; 50 U/L; (4) pregnancy; (5) &gt; 72 hours after SAH</td>
<td>TCD vasospasm defined as mean blood flow velocity &gt; 120 cm/s with Lindegaard ratio &gt; 3</td>
<td>DCI was defined as vasospasm-related if it was associated with severe vasospasm on TCD, defined as blood flow velocity &gt; 200 cm/s with Lindegaard ratio &gt; 3</td>
<td>At discharge</td>
<td>mRS</td>
</tr>
<tr>
<td>Lynch et al (2005)5</td>
<td>39</td>
<td>Simvastatin 80 mg once daily, during 14 days</td>
<td>Unknown</td>
<td>&gt; 48 hours after SAH</td>
<td>Vasospasm not categorized, only highest mean velocity in middle cerebral artery per group presented</td>
<td>Clinical impression (delayed ischemic deficit not associated with rebleed, infection, or hydrocephalus) in the presence of ≥ 1 confirmatory radiographic test (angiography or TCD demonstrating mean blood flow velocity in MCA &gt; 160 m/s)</td>
<td>Not an end point</td>
<td>-</td>
</tr>
<tr>
<td>Chou et al (2008)6</td>
<td>39</td>
<td>Simvastatin 80 mg daily, until discharge from neurointensive care unit or a maximum of 21 days</td>
<td>&gt; 18</td>
<td>(1) prismatic use of statins; (2) contraindication to statin use; (3) abnormal baseline serum creatine phosphokinase, alanine aminotransferase, or aspartate aminotransferase; (4) Fisher grade higher or lower than 3; (5) aneurism not secured; (6) &gt; 96 hours after SAH; (7) high risk for early mortality (Hunt and Hess Grade V or intracranial pressure &gt; 30 cm H₂O for &gt; 30 minutes)</td>
<td>TCD vasospasm defined as any peak systolic middle cerebral artery blood flow velocity &gt; 200 cm/s and a Lindegaard ratio of &gt; 3; angiographic vasospasm was defined as focal or generalized reduction of cerebral arterial caliber on conventional cerebral angiogram confirmed by a neuroradiologist and a neurocritical care physician</td>
<td>Unaccountable new focal neurological deficit lasting ≥ 2 hours or any ≥ 2-point fall in modified GOS</td>
<td>At discharge</td>
<td>mRS</td>
</tr>
<tr>
<td>Vergouwen et al (2009)15</td>
<td>32</td>
<td>Simvastatin 80 mg once daily, until day 14 after SAH</td>
<td>≥ 18</td>
<td>(1) nonaneurysmal SAH; (2) contraindication to simvastatin (active liver disease, liver alanine aminotransferase or aspartate aminotransferase &gt; 3 times the normal upper limit, myopathy); (4) kidney insufficiency; (5) pregnancy or lactation; (6) &gt; 72 hours after SAH; (7) if death appeared imminent</td>
<td>TCD vasospasm, distinguished in mild, moderate, and severe (mean blood flow velocity in middle cerebral artery or anterior cerebral artery ≥ 120 cm/s and &lt; 160 cm/s, ≥ 160 cm/s and &lt; 200 cm/s, and ≥ 200 cm/s, respectively)</td>
<td>Development of focal neurological impairment and/or a drop in the Glasgow Coma Scale by ≥ 2 points</td>
<td>6 months after SAH</td>
<td>GOS</td>
</tr>
</tbody>
</table>
Table 2. Outcome Events*

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Statin</th>
<th>Placebo</th>
<th>Statin</th>
<th>Placebo</th>
<th>Statin</th>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>19</td>
<td>20</td>
<td>19</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>TCD vasospasm (%)</td>
<td>25 (63)</td>
<td>17 (43)</td>
<td>20 (50)</td>
<td>13 (68)</td>
<td>11 (69)</td>
<td>12 (75)</td>
<td>10 (50)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>DCI (%)</td>
<td>12 (30)</td>
<td>2 (5)</td>
<td>12 (60)</td>
<td>5 (26)</td>
<td>10 (50)</td>
<td>7 (37)</td>
<td>5 (31)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Poor outcome (%)</td>
<td>21 (53)</td>
<td>17 (43)</td>
<td>10 (50)</td>
<td>12 (63)</td>
<td>11 (69)</td>
<td>9 (56)</td>
<td>2 (13)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Death (%)</td>
<td>8 (20)</td>
<td>2 (5)</td>
<td>...</td>
<td>...</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>2 (13)</td>
<td>2 (13)</td>
</tr>
</tbody>
</table>

*TCD vasospasm was defined as increased blood flow velocities, as measured by TCD examination, with mean blood flow velocities of at least 120 cm/s or peak blood flow velocities of at least 200 cm/s either with or without a Lindegaard ratio >3. DCI was defined as the clinical symptoms and signs of ischemia regardless of the presence of vasospasm as measured on angiography or with TCD, not accountable to other causes such as rebleeding or hydrocephalus. Poor outcome was defined as a mRS of 3 to 6. A GOS of 1 to 4 was considered equivalent to a mRS of 3 to 6. Functional outcome and death were measured at the last blinded follow-up visit, which was either at discharge or 6 months after SAH.

Definitions

Angiographic vasospasm was defined as focal or generalized reduction of cerebral arterial caliber on conventional cerebral angiogram confirmed by a neuroradiologist and a neurocritical care physician. Transcranial Doppler (TCD) vasospasm was defined as increased blood flow velocities with mean blood flow velocities of at least 120 cm/s or peak blood flow velocities of at least 200 cm/s. For the present systematic review, we decided to pool data on TCD vasospasm, and not angiographic vasospasm, because only one study performed angiography to investigate the presence of vasospasm and only when TCD blood flow velocities were abnormal or in case of clinical suspicion. 

Delayed cerebral ischemia was defined as the clinical symptoms and signs of ischemia regardless of the presence of vasospasm as measured on angiography or with TCD not accountable to other causes such as rebleeding or hydrocephalus.

Poor outcome was defined as a modified Rankin Scale (mRS) of 3 to 6, including death, determined at the latest blinded follow-up visit in the study. In studies that reported outcome at a Glasgow Outcome Scale (GOS), a GOS of 1 to 4 was considered to be equivalent to a mRS of 3 to 6.

Selection Criteria

Types of Studies, Participants, and Intervention

All randomized, placebo-controlled trials investigating the effect of statins on vasospasm, DCI, and functional outcome in patients with aneurysmal SAH were included regardless of type of statin, dosage used, and follow-up duration.

Types of Outcome Measures

Outcomes were the number of patients with TCD vasospasm, DCI, poor outcome, and mortality during follow-up. A subgroup analysis was performed for the type of statin used, in which studies that randomized patients to the same type of statin were separately pooled.

Search Strategy for Identification of Studies

Two of the authors (M.D.I.V. and Y.B.W.E.M.R.) systematically searched the PubMed database up to 2009 (Week 15) for the combination of the variables “statin” AND “subarachnoid hemorrhage.” The search was limited to studies in humans. Furthermore, we searched for relevant studies in the Cochrane Library and the Cochrane Central Register of Controlled Trials. Citations used in manuscripts that were included in the present review were hand searched.

Assessment of Risk of Bias in Included Studies

To assess risk of bias in each included study, 2 review authors (M.D.I.V., Y.B.W.E.M.R.) independently assessed methodological quality both for the items allocation concealment and blinding.

Statistics

Data were processed in Review Manager 5.0.18 as supplied by the Cochrane Collaboration. Effect sizes were expressed in (pooled) risk ratio (RR) estimates. Statistical uncertainty was expressed in 95% CIs. Pooled data were interpreted to be heterogeneous in case the probability value of the χ² test was ≤0.20. However, because only few studies were included with low numbers of patients, we decided to use a random-effects model in all analyses.

Results

Four randomized, placebo-controlled trials investigating the effect of statins on vasospasm, DCI, and outcome in patients with aneurysmal SAH were included describing 190 patients in total.5–8,15 The characteristics of the included studies are listed in Table 1. Outcome events of the studies are listed in Table 2. Three of the 4 studies explicitly stated that all analyses were performed on an intention-to-treat basis.6,8,15

Analyses

For the analysis of the occurrence of DCI, data from all 4 studies including all 190 patients were available (94 patients randomized to statin treatment and 96 patients to placebo).5,6,8,15 For the analyses of the occurrence of TCD vasospasm, poor outcome, and mortality, data of 3 studies including 151 patients were available (75 patients randomized to statin treatment and 76 patients to placebo).6,8,15

In all 3 studies, a different definition of TCD vasospasm was used with various cutoff points of blood flow velocities with either mean or peak blood flow velocities and, in some studies, in combination with a Lindegaard ratio of >3 (Table 1).6,8,15 The overall number of patients who had TCD vasospasm was 42 in the statin group and 46 in the placebo group (pooled RR, 0.99 [95% CI, 0.66 to 1.48]; Figure 1). Data in the TCD vasospasm meta-analysis demonstrated heterogeneity (P=0.10).

In the 4 studies, 3 different definitions of DCI were used (Table 1).5,6,8,15 Two studies had a pure clinical definition of DCI, which was similar in both studies.8,15 Two other studies used a clinical definition of DCI in combination with the detection of vasospasm by a radiographic test (vasospasm-associated DCI).5,6 In the latter 2 studies, the definition of radiographic vasospasm differed (Table 1). The overall number of patients who developed DCI was 20 in the statin group.
and 39 in the placebo group (pooled RR, 0.57 [95% CI, 0.29 to 1.13]; Figure 2), but this difference was not statistically significant and mainly contributed by 2 of the 4 studies.5,6 Data in the DCI meta-analysis also demonstrated heterogeneity (P=0.10).

Poor outcome was defined as a mRS of 3 to 6 in 2 studies6,8 and was measured with the GOS in another study.15 One study had the final blinded follow-up visit at discharge8 and 2 studies 6 months after SAH.6,7,15 However, although in one study functional outcome was measured 6 months after SAH, we had to use functional outcome data measured at discharge, because at 6 months, no numbers on poor outcome and mortality were presented, only odds ratios.7 The overall number of patients with poor outcome was 38 in the statin group and 42 in the placebo group (pooled RR, 0.92 [95% CI, 0.68 to 1.24]; Figure 3). Data on poor outcome did not indicate heterogeneity (P=0.42).

In total, 4 patients died in the statin group and 13 patients in the placebo group (pooled RR, 0.37 [95% CI, 0.13 to 1.10]; Figure 4), but this difference was not statistically significant and mainly contributed to by one study.6 Data on mortality did not indicate heterogeneity (P=0.40).

Subgroup Analysis
A subgroup analysis was performed for type of statin. Three studies, with a total of 110 patients, randomized patients to either simvastatin or placebo.5,8,15 Separate pooling of these studies showed a clear reduction of the statistical heterogeneity with regard to TCD vasospasm (χ² test, P=0.51) and DCI (P=0.30). In patients randomized to simvastatin, no effect was observed on TCD vasospasm (RR, 1.19 [95% CI, 0.85 to 1.67]), DCI (RR, 0.70 [95% CI, 0.41 to 1.20]), poor outcome (RR, 1.01 [95% CI, 0.66 to 1.51]), or mortality (RR, 0.54 [95% CI, 0.09 to 3.26]; see also Figures 1, 2, 3, and 4, respectively). One other study, including 80 patients, randomized patients to either pravastatin or placebo.6 Patients randomized to pravastatin had a significantly lower risk of DCI (RR, 0.17 [95% CI, 0.04 to 0.70]), but not of TCD vasospasm, poor outcome, or mortality.

Assessment of Risk of Bias in Included Studies
For allocation concealment, risk of bias was low in 2 studies6,15 and unclear in 2 studies.5,8 For blinding, risk of bias was low in 2 studies6,15 and unclear in 2 studies.5,8 For both items, no high risk of bias was observed in any of the studies. The authors of this systematic review acknowledge potential
risk of bias, because they are the authors of one of the studies included in this systematic review.15

Discussion
In contrast to the results of the previous meta-analysis,12 the results of the present systematic review did not detect a statistically significant reduction in TCD vasospasm, DCI, poor neurological outcome, or death. A subgroup analysis, pooling homogenous data of the 3 studies that randomized patients to simvastatin, also detected no statistically significant effect on any of the outcome parameters. Patients randomized to pravastatin had a significantly lower risk of DCI, but not of TCD vasospasm, poor outcome, or mortality. However, the effect of pravastatin was only investigated in one study.

The present systematic review differs in several ways from a previously published meta-analysis.12 First, we used random-effects models only, resulting in wider confidence intervals around the summarize measures. In the previous meta-analysis, only fixed-effects models were used, which was based on a quite tolerant statistical cutoff of heterogeneity (P=0.05). However, in our opinion, a more stringent approach is warranted in view of the limited number of studies and included patients. Had we used a fixed-effects approach in meta-analyses in which data did not indicate heterogeneity (probability value χ² test ≥0.20), this would have resulted in a significant beneficial effect of statins on mortality (pooled RR, 0.34 [95% CI, 0.12 to 0.94]) as observed in the previous meta-analysis. However, as pointed out by others, if there had been one less death in the placebo group or one more in the statin group, the difference would no longer have been statistically significant.14 Second, in the previous meta-analysis, some of the combining of data were erroneous, because the data on symptomatic vasospasm of one study were used in the meta-analysis on TCD vasospasm, whereas it should have been inserted in the DCI meta-analysis.12–14 Third, we added a fourth randomized, placebo-controlled study to the review so that more patients were available for the analyses.15

The results of our systematic review have to be interpreted with caution. Although 4 studies were included, the total number of patients was only 190. The largest study included 80 patients.6 The 3 smallest studied only 32, 39, and 39 patients, respectively.5,8,15 These small numbers of patients make studies more prone to a “failure of randomization” in terms of imbalance between important prognostic factors at baseline. In one study, there was an abnormally high rate of DCI (60%) in the placebo group,5 suggesting an imbalance of

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 pravastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tseng 2005</td>
<td>17</td>
<td>40</td>
<td>21</td>
<td>40</td>
<td>41.1%</td>
<td>0.81 [0.51, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>49</td>
<td>40</td>
<td></td>
<td>80</td>
<td>41.1%</td>
<td>0.81 [0.51, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>17</td>
<td>40</td>
<td></td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable Test for overall effect: Z = 0.86 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.3.2 simvastatin |                 |                |              |              |       |                               |                               |
| Chou 2008         | 12              | 19             | 20           | 20           | 28.8% | 1.26 [0.72, 2.20]             |                               |
| Vergouwen 2009    | 9               | 16             | 11           | 16           | 30.1% | 0.82 [0.47, 1.41]             |                               |
| Subtotal (95% CI) | 35              | 36             |              | 71           | 56.9% | 1.01 [0.66, 1.55]             |                               |
| Total events      | 21              | 21             |              | 42           |       |                               |                               |
| Heterogeneity: Tau² = 0.02, Chi² = 1.20, df = 1 (P = 0.27); I² = 17% Test for overall effect: Z = 0.06 (P = 0.96) |
| Total (95% CI)    | 75              | 76             | 100.0%       | 151          |       | 0.92 [0.66, 1.24]             |                               |
| Total events      | 38              | 42             |              | 80           |       |                               |                               |
| Heterogeneity: Tau² = 0.00, Chi² = 1.71, df = 2 (P = 0.42); I² = 0% Test for overall effect: Z = 0.53 (P = 0.60) |

Figure 3. (Pooled) RR estimates for patients on statin treatment to have poor outcome.

Figure 4. (Pooled) RR estimated of mortality for patients on statin treatment.
prognostic baseline characteristics, compared with 26% in the statin group, which is similar to epidemiological data. In 2 of 4 studies, risk of bias for both the items “allocation concealment” and “blinding” cannot be ruled out.

In this review, several assumptions had to be made in the combining of data, because in the included studies, various definitions were used to describe TCD vasospasm, DCI, and poor outcome. For the analysis of TCD vasospasm, 2 studies used a mean blood flow velocity cutoff of 120 cm/s, and one of the 2 studies used this cutoff value in combination with a Lindegaard ratio >3. The third study used a definition of a peak middle cerebral artery blood flow velocity of more than 200 cm/s in combination with a Lindegaard ratio >3. For the definition of DCI, 2 studies used a pure clinical definition of DCI. In 2 other studies, DCI was defined as clinical symptoms of DCI in combination with the presence of vasospasm measured with either angiography or TCD. In 2 studies, functional outcome was assessed with the mRS and in one study with the GOS. The GOS scores of the latter study were transformed to a Rankin grading. Furthermore, the timing of measuring functional outcome differed between groups either at discharge or at 6 months after SAH. One might argue that the definition of poor outcome, namely a mRS score of 3 to 6, was liberal. We selected this definition of poor outcome because it was the functional outcome measure in 2 of the included studies and because we agree that this dichotomy is reasonable. With a modified Rankin scale of 3, there is a moderate disability, and patients are not able to carry out all previous activities any longer.

The results of the present systematic review do not lend statistically significant support to the finding of a beneficial effect of statins in patients with aneurysmal SAH as reported in a previous meta-analysis. However, because our systematic review only included 190 patients, and the incidence of DCI, poor neurological outcome, and mortality in absolute numbers was lower in the statin group in more than half of the included studies, a possible benefit of statins cannot be excluded. Only the results of a large-scale Phase III study such as the Statins for Aneurysmal Subarachnoid Hemorrhage (STASH) trial will give the definitive answer whether statin treatment is beneficial in patients with aneurysmal SAH.

Disclosures
The authors of this systematic review are the authors of one of the studies included in this systematic review.

References
Effect of Statin Treatment on Vasospasm, Delayed Cerebral Ischemia, and Functional Outcome in Patients With Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis Update
Mervyn D.I. Vergouwen, Rob J. de Haan, Marinus Vermeulen and Yvo B.W.E.M. Roos

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