Simvastatin Reduces Vasospasm After Aneurysmal Subarachnoid Hemorrhage
Results of a Pilot Randomized Clinical Trial

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Background and Purpose—Cerebral vasospasm remains a major source of morbidity after aneurysmal subarachnoid hemorrhage (SAH). We demonstrate that simvastatin reduces serum markers of brain injury and attenuates vasospasm after SAH.

Methods—Patients with angiographically documented aneurysmal SAH were randomized within 48 hours of symptom onset to receive either simvastatin (80 mg daily; n=19) or placebo (n=20) for 14 days. Plasma alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase were recorded weekly to evaluate laboratory evidence of hepatitis or myositis. Serum markers of brain injury were recorded daily. The primary end point of vasospasm was defined as clinical impression (delayed ischemic deficit not associated with rebleed, infection, or hydrocephalus) in the presence of ≥1 confirmatory radiographic test (angiography or transcranial Doppler demonstrating mean V_MCA >160 m/sec).

Results—There were no significant differences in laboratory-defined transaminitis or myositis between groups. No patients developed clinical symptoms of myopathy or hepatitis. Plasma von Willebrand factor and S100 protein were decreased 3 to 10 days after SAH (P<0.05) in patients receiving simvastatin versus placebo. Highest mean middle cerebral artery transcranial Doppler velocities were significantly lower in the simvastatin-treated group (103±41 versus 149±47; P<0.01). In addition, vasospasm was significantly reduced (P<0.05) in the simvastatin-treated group (5 of 19) compared with those who received placebo (12 of 20).

Conclusion—The use of simvastatin as prophylaxis against delayed cerebral ischemia after aneurysmal SAH is a safe and well-tolerated intervention. Its use attenuates serum markers associated with brain injury and decreases the incidence of radiographic vasospasm and delayed ischemic deficit. (Stroke. 2005;36:2024-2026.)

Key Words: HMG-CoA reductase inhibitors ■ inflammation ■ subarachnoid hemorrhage ■ vasospasm, intracranial

Vasospasm remains a major cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage (SAH). Although treatment with nimodipine confers a modest benefit in patient outcomes after SAH, there are no definitive medical treatments for cerebral vasospasm. Studies have detected alterations in the profiles of inflammatory cytokines, markers of central nervous system and vascular injury in the setting of SAH and vasospasm. For example, plasma levels of von Willebrand factor (vWF), a marker of endothelial injury, and protein S100β, a marker of astrocyte activation, have been correlated with prognosis and occurrence of vasospasm after SAH. Independent of their cholesterol-lowering effect, statins have multiple biological properties, including down-regulating inflammation and upregulating endothelial NO synthase.1,2 In the present study, we hypothesized that early treatment with simvastatin after aneurysmal SAH is safe, will decrease vasospasm, and will reduce biochemical surrogates of endothelial injury and inflammation.

Methods

This study was approved by the Duke University Medical Center institutional review board. Thirty-nine patients presenting within 48 hours of aneurysmal SAH were randomized to receive 80 mg per day simvastatin (n=19) or placebo (n=20) for 14 days. All clinicians and investigators were blinded to treatment group. All patients underwent clipping or coiling within 48 hours of SAH. Liver transaminases and creatine phosphokinase (CPK) were recorded weekly to evaluate for early signs of hepatitis or myositis. Transaminitis was defined as alanine aminotransferase or aspartate aminotransferase >3-fold normal (>180 U/L) and myositis as CPK >1000

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U/L. Given the high predictive value mean transcranial Doppler (TCD) velocities ≥160 cm/s for cerebral vasospasm, all patients underwent thrice weekly serial TCD evaluation by a blinded neurosonologist. Our primary end point of vasospasm was defined as the clinical impression of a delayed ischemic neurological deficit (unrelated to rebleed, hydrocephalus, or infection) in the presence of a confirmatory radiographic test (VMCA ≥160 m/sec by TCD or angiography). Blood samples were collected daily for 14 days. Measurements of serum markers of injury were performed by Biosite Diagnostics.4

Statistical Analysis
Student t test was used for normally distributed data, and Wilcoxon rank-sum test for continuous and ordinal nonparametric variables. The presence of vasospasm in the 2 groups was compared with the χ2 statistic. Generalized estimating equations were used to evaluate the effect of statins on biomarkers. All analysis was performed using Graphpad and SAS Enterprise Guide Version 8.2.

Results
There were no baseline differences between groups (Table 1). Two patients in the treatment arm and 1 in the placebo arm were discontinued from the study for transaminase elevations in excess of 180 U/L (Table 2). All patients were included in the analysis on an intention-to-treat basis, and elevations of CPK and liver function test (LFTs) normalized within 24 hours.

The mean S100β concentration was nearly 4-fold lower in simvastatin-treated versus placebo-treated patients (69 versus 218 ng/mL; P<0.01) and vWF nearly 2-fold lower (14 versus 24 ng/mL; P<0.05; Figure). Using generalized estimating equations, concentrations of S100β (P<0.001) and vWF (P<0.001) were significantly lower in the simvastatin group versus the control group.

The overall rate of vasospasm was 43%. Five of 19 (26%) patients receiving simvastatin developed evidence of cerebral vasospasm during the study period versus 12 of 20 placebo patients (60%; P<0.05). Maximum mean middle cerebral artery (MCA) TCD velocity (cm/s) was also significantly decreased in the simvastatin group compared with the placebo group (103±41 and 149±47, respectively; P<0.01).

Discussion
Our primary finding was that patients treated with simvastatin had a lower incidence (P<0.05) of clinical vasospasm (confirmed by TCD criteria or angiographically) and a significant (P<0.01) reduction in MCA velocities as a function of simvastatin treatment.

We also examined biochemical surrogates defined previously to predict vasospasm and outcome. For example, we demonstrated that markers of endothelial injury such as vWF

### TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simvastatin (n=19)</th>
<th>Placebo (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range)</td>
<td>65 (48–73)</td>
<td>47 (41–53)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84% (16/19)</td>
<td>85% (17/20)</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>68% (13/19)</td>
<td>60% (12/20)</td>
<td></td>
</tr>
<tr>
<td>Fisher grade 3</td>
<td>84% (16/19)</td>
<td>90% (18/20)</td>
<td></td>
</tr>
<tr>
<td>Fisher grades 1 through 4</td>
<td>0, 2, 16, 1</td>
<td>0, 1, 18, 1</td>
<td></td>
</tr>
<tr>
<td>Hunt and Hess grade</td>
<td>3.0±1.1</td>
<td>3.1±0.8</td>
<td></td>
</tr>
<tr>
<td>Clipped/coiled</td>
<td>47%/53%</td>
<td>40%/60%</td>
<td></td>
</tr>
<tr>
<td>No. patients on statins at baseline</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Baseline demographic characteristics, clinical, and radiographical correlates of SAH severity were comparable between patients randomized to placebo and treatment arms.

### TABLE 2. Simvastatin Decreases Vasospasm

<table>
<thead>
<tr>
<th>Measure</th>
<th>Simvastatin (n=19)</th>
<th>Placebo (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminitis</td>
<td>11% (2/19)</td>
<td>5% (1/20)</td>
<td>NS</td>
</tr>
<tr>
<td>CPK elevation</td>
<td>5% (1/19)</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>Clinically significant myopathy or hepatic dysfunction</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>26% (5/19)</td>
<td>60% (12/20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Highest mean VMCA</td>
<td>103±41</td>
<td>149±47</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Two patients in the simvastatin group and 1 patient in the placebo group developed transaminitis (AST or ALT >180 U/L). One patient in the simvastatin group had CPK elevation (CPK >1000 U/L).
predicts occurrence of vasospasm.\textsuperscript{2} vWF is a multimeric glycoprotein involved in platelet–endothelial interactions under conditions of high shear stress.\textsuperscript{5} In the present study, treatment with simvastatin was associated with plasma concentrations of vWF on average nearly 30\% lower when compared with controls. Plasma and serum concentrations of S100\textsubscript{b}, a marker of astrocyte activation, have also been associated with vasospasm and functional outcome in this patient population.\textsuperscript{6} In the current study, we found that S100\textsubscript{b} was also significantly reduced in the simvastatin-treated group. This is consistent with the hypothesis that simvastatin exerts its therapeutic effect by endothelial-protective and anti-inflammatory properties.

Although we found that simvastatin treatment resulted in a decreased incidence of vasospasm, the question of whether this will translate into improved functional outcomes remains to be determined in a larger multicenter trial. The second limitation of this study is that the optimal dosage of simvastatin in the clinical setting has yet to be defined, and it is plausible that the short-term administration of higher doses may increase efficacy without compromising safety, although further dose escalation studies will be needed.

In conclusion, we demonstrate that simvastatin was well tolerated in this critically ill patient population. Moreover, statin therapy significantly reduced biochemical surrogates of inflammation and endothelial injury believed to play a mechanistic role in the development of vasospasm.\textsuperscript{2,6} Treatment with simvastatin reduced vasospasm incidence and was also associated with a reduction in TCD velocities and biochemical markers associated with vasospasm risk. The results of this pilot study suggest that the administration of simvastatin is as safe and well tolerated as any other intervention routinely used in the treatment of SAH, but that CPK and LFTs should be monitored.

\textbf{Acknowledgments}

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\textbf{References}

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