Favorable Outcome of Ischemic Stroke in Patients Pretreated with Statins

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Background and Purpose—Statins may be beneficial for patients with acute ischemic stroke. We tested the hypothesis that patients pretreated with statins at the onset of stroke have less severe neurological effects and a better outcome.

Methods—We prospectively included consecutive patients with ischemic stroke of <24-hour duration. We recorded demographic data, vascular risk factors, Oxfordshire Classification, National Institutes of Health Stroke Scale (NIHSS) score, admission blood glucose and body temperature, cause (Trial of Org 10172 in Acute Treatment [TOAST] criteria), neurological progression at day 3, previous statin treatment, and outcome at 3 months. We analyzed the data using univariate methods and a logistic regression with the dependent variable of good outcome (modified Rankin Scale [mRS] 0 to 1, Barthel Index [BI] 95 to 100).

Results—We included 167 patients (mean age 70.7±12 years, 94 men). Thirty patients (18%) were using statins when admitted. In the statin group, the median NIHSS score was not significantly lower and the risk of progression was not significantly reduced. Favorable outcomes at 3 months were more frequent in the statin group (80% versus 61.3%, P=0.059 with the mRS; 76.7% versus 51.8%, P=0.015 with the BI). Predictors of favorable outcome with the BI were: NIHSS score at admission (OR: 0.72; CI: 0.65 to 0.80; P=0.0001), age (OR: 0.96; CI: 0.92 to 0.99; P=0.017), and statin group (OR: 5.55; CI: 1.42 to 17.8; P=0.012).

Conclusions—Statins may provide benefits for the long-term functional outcome when administered before the onset of cerebral ischemia. However, randomized controlled trials will be required to evaluate the validity of our results. (Stroke. 2004;35:1117-1123.)

Key Words: outcome ■ ischemia ■ statins

Statins belong to a group of drugs that lowers the level of lipids. They have broad effects, some of which are potentially beneficial for patients with ischemic stroke. There is evidence that statins have neuroprotective properties for the acute ischemic brain. Also, statins promote stabilization of atherosclerotic plaques. Furthermore, statins reduce the risk of stroke in patients with coronary artery disease. But there are potential drawbacks of statin therapy, because high cholesterol levels have been associated with lower mortality in acute ischemic stroke. To confuse the issue further, lower cholesterol levels have been associated with a high risk of hemorrhagic stroke. Although there are beneficial and negative effects, there is a need to evaluate the early and long-term clinical benefits of statin therapy for patients with acute cerebral ischemia. In a retrospective study, Jonsson et al showed that the overall outcome tended to be better in patients pretreated with statins than in matched controls. We tested the hypothesis that pretreatment with statins lessens the severity of stroke and improves the functional outcome. We did a prospective study of consecutive patients with acute ischemic stroke. We analyzed whether patients who were already being treated with statins at the time of stroke were affected less neurologically and had a better long-term functional outcome than patients who were not receiving statins.

Materials and Methods

We studied consecutive patients with acute ischemic stroke who were admitted to the neurology departments of 3 different tertiary hospitals located in Barcelona, Spain. The inclusion criteria were: (1) clinical symptoms and signs attributable to cerebral ischemia of <24-hour duration (onset of symptoms was defined as the last time the patient was free of any symptoms); (2) acute or subacute cerebral computed tomography (CT) or magnetic resonance (MR) with changes typical of acute cerebral infarction; (3) previous modified Rankin scale (mRS) score of 0; and (4) no previous symptomatic...
cerebral infarction or intracerebral hemorrhage. Patients were excluded if recombinant tissue plasminogen activator (rt-PA) was administered, or if the patient was included in any therapeutic trial.

For each patient, we recorded the following data: (1) demographics (age, sex); (2) vascular risk factors (ie, presence or absence of high blood pressure, diabetes mellitus, ischemic heart disease, atrial fibrillation, peripheral artery disease, smoking habit, alcohol abuse, previous transient ischemic attack, hypercholesterolemia, and hypertriglyceridemia); (3) clinical presentation that was classified according to the Oxfordshire Community Stroke Project; (4) severity of the neurological deficit at admission as measured by the National Institutes of Health Stroke Scale (NIHSS) score at admission; (5) blood pressure, body temperature, and blood glucose at admission; (6) neurologic progression at day 3, defined by an increase in >3 points in the NIHSS score in comparison with the baseline NIHSS score; and (7) whether the patient was currently receiving statins. The type and dose was recorded. Additionally, the compliance was evaluated by asking the patient and relatives about the date and time that the patient took the statin for the last time, and; (8) cholesterol and triglyceride levels during the acute phase (within 1 week after admission, normal values at our center <6.2 mmol/L for cholesterol and <2.23 mmol/L for triglyceride); (9) cause of the cerebral infarction was considered after the completion of the appropriate complementary tests and was classified according to the Trial of Org 10172 in Acute Treatment (TOAST) investigators; (10) functional outcome as measured with the mRS and the Barthel Index (BI) at 3 months. Patients who died scored 6 in the mRS and 0 in the BI. A mRS of 0 to 1, or a BI score of 95 to 100 was considered as a favorable outcome.

Although there were no predefined guidelines for therapy during the acute, subacute, and chronic stages, all hospital centers had standard protocols.

### Statistical Analyses

To evaluate the severity of the stroke, we compared the median of NIHSS in both groups (statin and nonstatin) with the Mann–Whitney U test. The proportions of patients with and without neurological deterioration and the functional status at 3 months in each group were compared with contingency tables and the χ² test. We performed a forward logistic regression analysis with favorable outcome at 3 months as the dependent variable (separately for mRS and BI). The type and dose was recorded. Additionally, the compliance was evaluated by asking the patient and relatives about the date and time that the patient took the statin for the last time, and; (8) cholesterol and triglyceride levels during the acute phase (within 1 week after admission, normal values at our center <6.2 mmol/L for cholesterol and <2.23 mmol/L for triglyceride); (9) cause of the cerebral infarction was considered after the completion of the appropriate complementary tests and was classified according to the Trial of Org 10172 in Acute Treatment (TOAST) investigators; (10) functional outcome as measured with the mRS and the Barthel Index (BI) at 3 months. Patients who died scored 6 in the mRS and 0 in the BI. A mRS of 0 to 1, or a BI score of 95 to 100 was considered as a favorable outcome.

Although there were no predefined guidelines for therapy during the acute, subacute, and chronic stages, all hospital centers had standard protocols.

### Results

A total of 167 consecutive patients were prospectively evaluated. As shown in Table 1, they were divided into a statin group (n = 30) and a nonstatin group (n = 137). The mean age was ~70 in both groups and the sex distribution was 53% men in the statin group and 56% in the nonstatin group. None of these differences was statistically significant. Thirty patients (18%) were undergoing statin therapy when admitted to the emergency room. Four of them were using atorvastatin (10 to 20 mg/d), 14 simvastatin (20 to 40 mg/d), 7 pravastatin (20 to 40 mg/d), 4 lovastatin (20 mg/d), and 1 fluvastatin (dose unknown). All of the patients in the statin group, except 2, took the last dose of statin <24 hours before the onset of symptoms. The remaining 2 patients took the last dose of statin 48 to 72 hours before the onset of stroke. All patients who were receiving statins at admission, except 8 of them, were discharged while still using statin therapy. Nineteen of the 137 patients who were not receiving statins at admission were put on statin therapy after admission and at discharge (usually because of high lipid levels). Therefore, 27 patients (16%) were removed from 1 treatment group (statin or nonstatin) to the other, either during admission or at discharge. Patients in the statin group were included later than patients not taking statins, although the difference was not statistically significant (13.1±13.1 versus 8.4±6.7 hours, P = 0.06).

As shown in Table 1, most of the vascular risk factors were not significantly different in both groups, except for a significantly higher frequency of diabetes mellitus, transient ischemic attacks, hypercholesterolemia, and hypertriglyceridemia in the statin group.

Table 2 shows that the 4 clinical classifications did not show significant differences between the 2 groups. However, as depicted in Table 3, the stroke causes were not equivalent in both groups: lacunar cause was significantly more frequent (40% versus 25%) and undetermined cause was less frequent (0% versus 17%) in the statin group (P = 0.04). Median NIHSS scores at admission were lower in the statin group, but this difference was not statistically significant (5 versus 6, P = 0.76). Other prognostic factors such as age, blood pressure, body temperature, blood glucose, and cholesterol levels also showed no significant difference between both groups.

### TABLE 1. Demographic Data and Distribution of Vascular Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Statin Group n (%)</th>
<th>Nonstatin Group n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>30 (18)</td>
<td>137 (82)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>70.6±11.1</td>
<td>70.8±12.3</td>
<td>0.93</td>
</tr>
<tr>
<td>Sex distribution (% men)</td>
<td>53.3</td>
<td>56.2</td>
<td>0.84</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>21 (72)</td>
<td>83 (60)</td>
<td>0.21</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (47)</td>
<td>30 (22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5 (17)</td>
<td>9 (6.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (24)</td>
<td>45 (33)</td>
<td>0.67</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>4 (14)</td>
<td>7 (5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>9 (31)</td>
<td>38 (27.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2 (7)</td>
<td>11 (8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>7 (24)</td>
<td>9 (6.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28 (93)</td>
<td>18 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>7 (24)</td>
<td>10 (7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### TABLE 2. Distribution of Clinical Stroke Syndromes

<table>
<thead>
<tr>
<th></th>
<th>Statin Group n (%)</th>
<th>Nonstatin Group n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>30 (18)</td>
<td>137 (82)</td>
</tr>
<tr>
<td>Total anterior cerebral syndrome</td>
<td>5 (17)</td>
<td>25 (18)</td>
</tr>
<tr>
<td>Partial anterior cerebral syndrome</td>
<td>9 (30)</td>
<td>49 (36)</td>
</tr>
<tr>
<td>Lacunar cerebral syndrome</td>
<td>14 (47)</td>
<td>39 (28.5)</td>
</tr>
<tr>
<td>Posterior cerebral syndrome</td>
<td>2 (6)</td>
<td>24 (17.5)</td>
</tr>
</tbody>
</table>

Global P = 0.21
Neurological progression was seen in only 1 (3.3%) patient in the statin group compared with 11 (8.1%) in the nonstatin group, but this difference was not statistically significant. Ten patients (6%) died, 1 (3.4%) in the statin group and 9 (6.6%) in the nonstatin group, but this difference was not statistically significant. Ten patients in the statin group compared with 11 (8.1%) in the nonstatin group, but this difference was not statistically significant. Ten patients in the statin group compared with 11 (8.1%) in the nonstatin group, but this difference was not statistically significant. Ten patients in the statin group compared with 11 (8.1%) in the nonstatin group, but this difference was not statistically significant.

The percentage of patients who were living without significant disability as measured by the BI was significantly higher in the group pretreated with statins (76.7% versus 51.8%, \( P=0.015 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)) and of borderline significance when measured with the mRS (80% versus 61.3%, \( P=0.057 \)).

The univariate analyses of variables associated with the functional outcome are shown in Table 4. The results of the logistic regression analyses were analyzed separately for mRS and the BI. As shown in Table 5, the independent predictive variables for a BI score of 95 to 100 were: NIHSS score at admission (OR: 0.72), age (OR: 0.96), and statin group (OR: 5.55). The only independent predictive variable for a mRS score of 0 to 1 was the NIHSS at admission (OR: 0.76; CI: 0.70 to 0.82; \( P<0.0001 \)). The functional outcome for patients who received statin at any time (pretreated, during hospital admission, or at discharge) showed borderline significance with the BI (\( P=0.057 \)) and a nonsignificant difference with the mRS scale (\( P=0.10 \)).

**Discussion**

Our study suggests that if a patient is being treated with statins and has a stroke, the long-term functional outcome is better than that of a patient who was not receiving statins at the onset of stroke. However, there was no significant benefit in the short-term of statin therapy before admission. There was an absolute difference of 25% (by the BI, \( P=0.015 \)) or

### TABLE 3. Distribution of Stroke Causes

<table>
<thead>
<tr>
<th>Stroke Cause</th>
<th>Statin Group n (%)</th>
<th>Nonstatin Group n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>30 (18)</td>
<td>137 (82)</td>
</tr>
<tr>
<td>Large-artery atheromatosis</td>
<td>8 (27)</td>
<td>33 (24)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>9 (30)</td>
<td>45 (33)</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>12 (40)</td>
<td>34 (25)</td>
</tr>
<tr>
<td>Unusual</td>
<td>1 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0 (0)</td>
<td>23 (17)</td>
</tr>
</tbody>
</table>

Global \( P=0.04 \)

### TABLE 4. Variables Related to Functional Outcome at 3 Months in Univariate Analyses

<table>
<thead>
<tr>
<th>Rankin Score 0 to 1 (n=108)</th>
<th>Rankin Score &gt;1 (n=59)</th>
<th>( P )</th>
<th>Barthel Index 95 to 100 (n=94)</th>
<th>Barthel Index 0 to 90 (n=73)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.7±11.6</td>
<td>72.6±12.6</td>
<td>0.15</td>
<td>68.7±12</td>
<td>73.3±11.7</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>63</td>
<td>42.4</td>
<td>0.01</td>
<td>66</td>
<td>42.5</td>
</tr>
<tr>
<td>Body temperature (admission)</td>
<td>36.1±0.4</td>
<td>36.3±0.6</td>
<td>0.05</td>
<td>36.1±0.4</td>
<td>36.3±0.6</td>
</tr>
<tr>
<td>Blood glucose (admission)</td>
<td>6.87±3.37</td>
<td>7.02±3.36</td>
<td>0.79</td>
<td>7.02±3.37</td>
<td>6.80±3.36</td>
</tr>
<tr>
<td>Systolic blood pressure (admission)</td>
<td>157±27.4</td>
<td>156.7±28.9</td>
<td>0.95</td>
<td>158.7±26.4</td>
<td>154.3±29.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (admission)</td>
<td>86.6±14.5</td>
<td>88±14.7</td>
<td>0.62</td>
<td>87.6±15</td>
<td>86.3±13.9</td>
</tr>
<tr>
<td>NIHSS (admission)</td>
<td>4.1±3.4</td>
<td>13.4±7.3</td>
<td>&lt;0.0001</td>
<td>3.6±2.7</td>
<td>12.2±7.3</td>
</tr>
<tr>
<td>Hypercholesterolemia (% after admission)</td>
<td>12</td>
<td>10.2</td>
<td>0.80</td>
<td>11</td>
<td>11.7</td>
</tr>
<tr>
<td>Hypertriglyceridemia (% after admission)</td>
<td>10.2</td>
<td>5.8</td>
<td>0.57</td>
<td>6.8</td>
<td>10.6</td>
</tr>
<tr>
<td>High blood pressure (%)</td>
<td>62</td>
<td>62.7</td>
<td>0.99</td>
<td>62.8</td>
<td>61.6</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>27.8</td>
<td>23.7</td>
<td>0.71</td>
<td>28.7</td>
<td>23.3</td>
</tr>
<tr>
<td>Acute myocardial infarction (%)</td>
<td>7.4</td>
<td>10.2</td>
<td>0.56</td>
<td>6.4</td>
<td>11</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>23.1</td>
<td>45.8</td>
<td>0.03</td>
<td>22.3</td>
<td>42.5</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>7.4</td>
<td>5.1</td>
<td>0.74</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>29.6</td>
<td>25.4</td>
<td>0.59</td>
<td>30.9</td>
<td>24.7</td>
</tr>
<tr>
<td>Alcohol abuse (%)</td>
<td>7.4</td>
<td>8.5</td>
<td>0.77</td>
<td>8.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Transient ischemic attack (%)</td>
<td>12</td>
<td>6.8</td>
<td>0.42</td>
<td>13.8</td>
<td>5.5</td>
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<tr>
<td>Previous hypercholesterolemia (%)</td>
<td>31.5</td>
<td>20.3</td>
<td>0.14</td>
<td>34</td>
<td>19.2</td>
</tr>
<tr>
<td>Previous hypertriglyceridemia (%)</td>
<td>13.9</td>
<td>3.4</td>
<td>0.03</td>
<td>14.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Oxfordshire classification*</td>
<td>49.2</td>
<td>0.9</td>
<td>&lt;0.0001</td>
<td>39.7</td>
<td>1.1</td>
</tr>
<tr>
<td>TOAST classification†</td>
<td>25</td>
<td>45.8</td>
<td>0.004</td>
<td>23.4</td>
<td>43.8</td>
</tr>
<tr>
<td>Progression at day 3</td>
<td>0</td>
<td>20.3</td>
<td>&lt;0.0001</td>
<td>0</td>
<td>16.4</td>
</tr>
<tr>
<td>Statin at admission</td>
<td>22.2</td>
<td>10.2</td>
<td>0.059</td>
<td>24.5</td>
<td>9.6</td>
</tr>
</tbody>
</table>

*Percentage relates to total anterior cerebral syndrome, because this subtype was associated to worsen the outcome.
†Percentage relates to cardiac embolism, because this cause was associated with a worse outcome.
19% (by the mRS, P=0.059) favoring the statin group in the proportion of patients who ultimately achieved independence. Moreover, by logistic regression analyses, patients receiving statin before the onset of stroke were more likely to have a good functional outcome. This was true when the BI was measured, but not when the mRS was measured. Although both the BI and the mRS are valid measures of disability, they are not identical and the results obtained from both scales can differ slightly. However, we emphasize that the absolute benefit of statin therapy was impressive irrespective of the method of measurement. It is likely that a larger sample would provide more reliable results.

The mechanisms by which statins provide benefit to patients with acute ischemic stroke remain speculative and are likely multifactorial. Several studies indicate that statins have multiple effects beyond lowering the cholesterol level. Some of these effects could be neuroprotective. Statins interfere with platelet aggregation and have antiinflammatory, antioxidative, and antiapoptotic properties. Statins improve blood flow to the ischemic brain. In experimental animal models of stroke, statins showed a reduction in infarct size, improved neurological function, and increased cerebral blood flow. These results were seen when the statin was started either before or after the stroke.

The delay from symptom onset to the administration of a neuroprotective drug can mask the beneficial effects because of an irreversible neuronal injury by the time the drug reaches the injured tissue. Patients already receiving statins are at an advantage because of the immediate effect of the drug.

Our hypothesis was that pretreatment with statins lessens the severity of stroke and improves the functional outcome at 3 months. However, we found that the differences in NIHSS scores at admission and in the proportion of neurological progression between treated and nontreated patients were not statistically significant. The lower NIHSS scores at admission in the statin group could be attributed to a higher proportion of patients with lacunar infarction; however, in the multivariate analysis, the stroke cause was not prognostic. Although it is possible that statins do not provide appreciable neuroprotection or do not completely prevent neurological worsening in acute ischemic stroke, it may be that the effects of statins are too mild to be detected, or that our sample was not large enough to detect a beneficial effect or that the benefits of statins may be delayed to some extent. Finally, it is likely that not all of the pathophysiological mechanisms involved in neurological deterioration can be prevented by statins.

We observed that an increase in the proportion of patients who live functionally independent at 3 months is a long-term benefit. This is the most important finding of our study. In addition to the aforementioned effects, there are other effects of statin therapy that can be beneficial in the long-term. Statins reduce the risk of stroke in patients with coronary artery disease by 30%, regardless of the level of cholesterol. But there are no reports of a reduction in the frequency of stroke in patients treated with statins after a transient ischemic attack or after a cerebral infarction. Statins may reduce the incidence of cardioembolic stroke, retard the progression of extracranial carotid atherosclerosis, and also stabilize plaques, not only in extracranial arteries but also in intracranial arteries and in the aortic arch. In our study, the higher proportion of patients with a previous transient ischemic attack in the statin group could have triggered ischemic tolerance.

Biological basis of neurological recovery after cerebral infarction is poorly understood. Besides reorganization of neuronal circuits and the effects of diaschisis, it must be emphasized that the mammalian adult brain has exhibited neurogenesis. A recent study demonstrated a statin-mediated amplification of neurogenesis, angiogenesis and synaptogenesis in a rat stroke model.

Jonsson et al compared the findings in 125 stroke patients pretreated with statins with those of 250 matched stroke controls. The overall outcome tended to be better in the statin group, although statin therapy was not an independent predictor of a good outcome. Their study was retrospective and the control group was not matched for severity of the neurological deficit. They also included patients with intracerebral hemorrhage. Taking into account these differences, it is noteworthy that their study and ours agreed that statins positively influence the functional outcome of patients with acute cerebral infarction.

The beneficial effects of statin therapy in acute ischemic stroke must be weighed against 2 potential risks. Low cholesterol may be associated with hemorrhagic stroke; however, in trials of patients with coronary artery disease, no increased risk of hemorrhagic stroke was noted among statin-treated patients. However, statin therapy may interfere with some neuroprotective effect of cholesterol.

We recognize that our study has several limitations. The assessment was not blind. The number of patients on statins was rather small; therefore, the statistical power of our results is limited. The low mortality and the low proportion of patients with neurological progression could be secondary to a selection bias because of the admission of younger patients and those with less severe symptoms, especially those who survived the first hours after their strokes. We cannot be sure of the doses and lengths of statin treatment, and it is possible that the beneficial effect depends on the length of treatment before stroke. These data are pertinent because some of the variable effects of statins appear early after the initiation of the therapy and such improvement can be observed over a period of weeks. It can also be argued that there are differences among statins in their potential benefits in acute ischemic stroke. The 16% of patients that were moved from 1 treatment group (statin or nonstatin) to the other makes the interpretation of our results difficult. Finally, to compare our studies to others, we used an arbitrary cut-off for mRS and BI, even though it is possible that different cut-off values may lead to different results.

In conclusion, we found that the use of statin before an acute ischemic stroke may improve the long-term outcome of patients. Definitive recommendations for the use of statins in stroke patients must await further experimental and clinical data. Our study suggests that for maximum benefit, statin therapy should be initiated within the first few hours of an ischemic stroke.
Acknowledgments

We are grateful to Professor William Stone for his helpful comments on the manuscript.

References


Statins, Stroke Outcome, and Stroke Prevention: When Should We Start Treatment?

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are a group of potent hypocholesterolemic agents that are widely used throughout the world. Many long-term clinical studies have demonstrated that statin therapy is associated with a reduced risk of vascular events—mainly coronary—even in so-called normocholesterolemic patients. Accordingly, guidelines for cholesterol treatment have been and are being modified, particularly for patients with ischemic heart disease (IHD). The magnitude of the effects is large. A recent meta-analysis1 has demonstrated that a decrease in low-density lipoprotein cholesterol levels by 1.8 mmol/L reduces the risk of IHD by 61% and the risk of stroke by 17%, preventing thromboembolic but not hemorrhagic strokes. The benefit of statins treatment has also been shown for patients with hypertension,2 diabetes mellitus,3 severe aortic arch plaques,4 and for high-risk patients in general.5 For secondary stroke prevention, however, the data are still somewhat circumstantial6 and a specific study is underway.7 In many of the studies, the beneficial effects of the statins were not directly related to their lipid-lowering properties, and data on many other effects of statins is accumulating.8,9 On the vascular wall, statins exert vasodilatation and plaque stabilizing effects by many ways, such as upregulation of endothelial nitric oxide synthase (eNOS),

Editorial Comment

Statins, Stroke Outcome, and Stroke Prevention: When Should We Start Treatment?
suppression of heightened macrophage activity with subsequent reduced production of several matrix metalloproteins and proinflammatory cytokines TNFα, IL-6, CRP, and reduction of vascular expression of adhesion molecules. Because all these factors enhance the thrombogenic potential of the atherosclerotic plaque, statins have a role in ameliorating this risk. Antiatherogenic properties of statins were demonstrated in retarding intimal medial thickening of the carotid wall, coronary plaque volume, and aortic atherosclerosis. A more rapid clinical effect was recently reported in patients with acute coronary syndrome: early statin administration was associated with reduced ischemic events within the first month of treatment. This effect was explained, at least in part, by a reduction in local inflammation.

For stroke, statin therapy is believed to be effective even earlier, leading to a better functional recovery; animal studies have recently shown the effects of statins on enhanced functional outcome and induction of brain plasticity when administered after stroke, probably by induction of angiogenesis, neurogenesis, and synaptogenesis. Lesion volumes have decreased regardless of cholesterol blood levels. Stroke protection is lost, however, within 2 to 4 days after withdrawal of statins treatment. These acute pleiotropic effects induce neuroprotection throughout several mechanisms including eNOS modulation (by augmenting regional cerebral blood flow), by inhibition of platelet aggregation, and by antiinflammatory effects.

Are these effects also applicable to human beings? A pilot case-referent study has shown a trend for a favorable outcome (earlier discharge to home) in patients pretreated with statins, and a pilot randomized study on the acute effects of simvastatin in ischemic stroke (MISTICS trial) has demonstrated beneficial effects.

In this issue, Marti-Fabregas et al present their experience with statin treatment and stroke outcome in 167 acute stroke patients, of which 18% were pretreated with statins. This was an open study in which patients were included prospectively and followed-up for 3 months.

Median National Institutes of Health Stroke Scale (NIHSS) scores at admission were lower in the statin group (5 versus 6) and neurological deterioration was less frequent in this group (3.3% versus 8.1% in the nonstatin group); yet, maybe because of the small sample size, these differences were not significant. At 3 months, statin treatment was found to be independently associated with a favorable outcome. The authors conclude that statins may provide long-term beneficial effects when given before the onset of acute stroke. They state that for maximum benefit, therapy should start within the first few hours of an acute stroke and declare that a randomized controlled study is needed to clarify the importance of statins on stroke outcome.

This article is important in strengthening previous observations; however, because of its nature (observational, unmatched), it still leaves some uncertainties. Apart from the limitations acknowledged by the authors in their discussion, there is also another concern, ie, the lack of information on concomitant treatment. It is possible that other medications confer neuroprotective properties, as has just recently been presented for angiotensin-converting enzyme (ACE) inhibitors. Also, the possibility that patients using statins are those that get, or can afford, better medical care was not ruled out.

Why were only 18% of the patients using statins? Given our current knowledge and the list of risk factors in the “control” group, this percent should have been higher. Alternatively, the fact that only 18% of the whole group were using statins suggests that a priori such patients are somewhat protected from stroke. Additionally, the higher rate of lacunar stroke in the treated group may imply that patients with large artery atherothrombosis are more protected because of the pleiotropic and plaque-stabilizing effects of statins.

This study provides information relating to the long-term beneficial effects of statins on stroke outcome, including, perhaps, an additional benefit at the subacute stage; however, this does not clarify the acute effects of statins and the importance of its administration in the hyperacute stage. Thus, the exact timing of statin administration in acute stroke remains open.

In the near future, however, with the completion of the SPARC study, it may be possible to answer 2 major questions: (1) are statins beneficial in the secondary prevention of stroke in all patients regardless of their premorbid conditions; and (2) are stroke outcomes in the statin-treated group milder and/or associated with a better outcome once they have occurred? We will also be able to learn which subtypes of strokes are mostly influenced by statins.

Within a few years, it seems that most high-risk patients will be treated with statins (the introduction of a “polypill” including a statin has been recently suggested for those patients), and thus only for a minority of the stroke patients will we be facing the dilemma of when to start treatment. Nonetheless, the importance of the pleiotropic effects of statins in acute stroke should be investigated in a prospective randomized study.

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References


Favorable Outcome of Ischemic Stroke in Patients Pretreated with Statins
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