Does Pretreatment With Statins Improve Clinical Outcome After Stroke? A Pilot Case-Referent Study

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Background and Purpose—In primary and secondary prevention trials, statins have been shown to reduce the risk of stroke. In addition to lipid lowering, statins have a number of antiatherothrombotic and neuroprotective properties. In a preliminary observational study, we explored whether clinical outcome is improved in patients who are on treatment with statins when stroke occurs.

Methods—We conducted a population-based case-referent study of 25- to 74-year-old stroke patients with, for each case of a patient who was on statin treatment at the onset of stroke (n = 125), 2 referent patients who were not treated with statins but were matched for age, gender, year of onset, and stroke subtype (n = 250).

Results—The unadjusted odds ratio for early discharge to home (versus late discharge or death) was 1.41 (95% CI 0.91 to 2.17) when patients on statin treatment were compared with referent stroke patients not on statins. Prognostic factors were, in general, more unfavorable among patients on statins. When this was adjusted for in a logistic regression model, the use of statins was a moderately strong but statistically nonsignificant predictor of discharge to home (multiple-adjusted odds ratio 1.42, 95% CI 0.90 to 2.22).

Conclusions—The statistical power of this case-referent study was such that only large beneficial effects of statins in acute stroke could be confirmed. However, the observed trend, together with experimental observations, is interesting enough to warrant a more detailed analysis of the relationship between statins and stroke outcome. (Stroke. 2001;32:1112-1115.)

Key Words: case-control studies ■ neuroprotection ■ statins ■ stroke outcome

L ipid-lowering statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. In doing so, they block the rate-limiting step of the mevalonate pathway and inhibit cholesterol synthesis. The depletion of intracellular cholesterol in hepatocytes leads to an upregulation of the hepatic LDL receptors, which promotes a lowering of LDL levels. In clinical trials aimed at primary or secondary prevention of coronary heart disease, statins have been associated with a marked reduction in the risk of stroke.1–4

There are a number of observations that indicate statins have beneficial effects on atherothrombotic processes beyond those mediated by their lipid-lowering properties. Perhaps most relevant to stroke is the discrepancy between interventional studies with statins and observational studies. The reduction in stroke events in clinical trials of statins is much greater (20% to 30% relative risk reduction)3,4 than what is expected from the very weak relations between serum cholesterol levels and risk of stroke reported in observational studies.5 Also, the same degree of lipid reduction by other means, such as ileal bypass surgery, has not been associated with as substantial a reduction in cardiovascular risk as has treatment with statins.6 The magnitude of atherosclerotic plaque regression during statin treatment has been relatively small, and it is unlikely that this accounts for all beneficial effects.7 Also, it was recently shown that, in patients with acute ischemic stroke, high cholesterol levels predict better clinical outcome.8

A number of properties other than lipid lowering may help to explain the apparent beneficial effects of statins, including normalization of endothelial dysfunction, anti-inflammatory effects, plaque stabilization, and antithrombogenic effects7 (see also Discussion). Statins may also have direct neuroprotective effects against ischemic brain damage.9

Taken together, these observations suggest that treatment with statins may not only reduce the risk of stroke but also improve clinical outcome once a stroke has occurred. To make a preliminary assessment of whether this concept is worth evaluating in greater detail in the clinical setting, we performed a pilot population-based case-referent study in which the clinical outcome in patients who were on statin therapy when stroke occurred was compared with that in acute stroke patients who were not on statins.

Subjects and Methods

This study included 25- to 74-year-old male and female stroke patients in the 2 northern-most counties in Sweden, a sparsely populated area with 9 emergency care hospitals. It is based on data...
obtained from the Northern Sweden WHO MONICA Stroke Study.\textsuperscript{10} The MONICA study is population based, but the present study included only hospitalized patients, and it excluded patients with subarachnoid hemorrhage. Data collection included medical history, symptoms, and CT findings. Methods for classification and diagnosis of stroke have been described elsewhere.\textsuperscript{10,11}

The medical records of 1499 consecutive patients in the MONICA stroke register covering the period of January 1, 1997, to May 31, 2000, were reviewed retrospectively. One hundred twenty-five patients on medication with statins at the time of acute stroke were identified as cases (8.3% of all hospitalized cases of stroke). Of these, 17 were on atorvastatin, 1 on cerivastatin, 1 on fluvastatin, 5 on pravastatin, and 101 on simvastatin. Each case was matched to 2 referents from the same register.\textsuperscript{11} The 250 referents were not medicated with statins at the time of stroke. In the absence of uniform measurement of outcome among the 9 hospitals, “poor” outcome was operationally defined as hospitalization for >1 week or death. Patients discharged to home within 1 week were considered to have “good” outcome. In sensitivity analyses, discharge to home within 2 weeks was used as an alternative indicator of good outcome. Patients who died or were discharged early to a rehabilitation unit or nursing home were included in the poor outcome group.

In univariate analyses, statistical significance in differences of proportions was evaluated by the \( \chi^2 \) test. Despite the matching procedure, the groups treated and not treated with statins were found not to be matched in comorbidity. Therefore, conditional multiple logistic regression was used to identify statistically significant predictors of outcome. In the regression models, cases and referents were analyzed together, and the matching variables (age, gender, and stroke subtype) were included together with other clinical items as possible independent predictors of outcome.

The study was approved by the Research Ethical Committee at Umeå University.

### Results

In Table 1, cases and referents are compared in prognostic variables and outcome. The 2 groups were identical in the matching variables (age, gender, and stroke subtype). In general, patients who were on statins when stroke occurred had more concomitant disorders. The differences in the proportions with a history of myocardial infarction and stroke were highly significant.

Overall outcome tended to be better among patients on treatment with statins when stroke occurred compared with patients not on treatment (Table 1). The unadjusted odds ratio for good outcome was 1.41 (95% CI 0.91 to 2.17) in favor of patients on statins. Recalculated, the odds reduction for poor outcome was 29\%, and the absolute risk reduction was 8\%.

To adjust for the uneven distribution of comorbidity between the 2 groups, a conditional logistic regression model was used with discharge of >1 week after admission or death (as opposed to discharge to home within 1 week) as the dependent variable. Independent variables in the model were gender, age, comorbidity (see Table 1), and present use of statins. After the rejection of independent variables with \( P > 0.5 \) (gender and history of myocardial infarction), the results of the final regression model are shown in Table 2. Only ischemic stroke (versus intracerebral hemorrhage) and the absence of diabetes reached statistical significance as independent predictors of early discharge to home. Although the model indicated a trend toward better outcome in patients on statin therapy, independent of other predictors, this was not statistically significant (95% CI 0.90 to 2.22; \( P = 0.13 \)). If this were to be a real beneficial effect, it is modest in size as indicated by an odds ratio of 1.42.

In a sensitivity analysis, discharge to home within 2 weeks (rather than 1 week) was used as the dependent variable. The conditional logistic model showed essentially the same results with an odds ratio of 1.39 for use of statins as predictor.

| TABLE 1. Prognostic Factors and Outcome in Patients on Treatment With Statins at Onset of Acute Stroke and in Referent Patients Not on Treatment With Statins |
|-----------------|-----------------|-----------------|
| Patient Characteristic | Treatment With Statins (n=125) | Treatment Without Statins (n=250) | \( P^* \) |
| | Yes | No | |
| **M/F, n** | 92/33 | 184/66 | 0.23 |
| **Age, y (mean±SD)** | 66.7±6.7 | 66.4±6.7 | 0.15 |
| **Stroke subtype, n (%)** | | | |
| Ischemic with cardiac source of embolism\(\dagger\) | 14 (11) | 28 (11) | 0.67 |
| Ischemic without cardiac source of embolism\(\dagger\) | 93 (74) | 186 (74) | 0.0001 |
| Intracerebral hemorrhage | 18 (14) | 36 (14) | 0.46 |
| **Medical history, n (%)** | | | |
| Previous stroke | 39 (31) | 27 (11) | <0.0001 |
| Previous myocardial infarction | 42 (34) | 17 (7) | <0.0001 |
| Diabetes | 22 (18) | 31 (12) | 0.23 |
| **Outcome, n (%)\(\dagger\)** | | | |
| Good | 65 (52) | 109 (44) | 0.15 |
| Poor | 60 (48) | 141 (56) | 0.0001 |

*\( \chi^2 \) test. \( \dagger \)Atrial fibrillation or other severe arrhythmia, myocardial infarction within past 4 weeks, or clinically relevant valvular disease. \( \ddagger \)As defined in the text.
TABLE 2. Conditional Logistic Regression Analysis of
Independent Predictors of Discharge to Home Within 1 Week
(Versus Discharge Later or to Institutional Care or Death)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Odds Ratio† (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke (vs intracerebral hemorrhage)</td>
<td>3.91 (1.97–7.76)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.40 (0.23–0.70)</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of statins</td>
<td>1.42 (0.90–2.22)</td>
<td>0.13</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>0.69 (0.42–1.13)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.99 (0.96–1.02)</td>
<td>0.40</td>
</tr>
<tr>
<td>Cardiac source of embolism†</td>
<td>1.28 (0.65–2.53)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

†Final model after exclusion of variables with P > 0.5 in an initial model (gender and history of myocardial infarction).

Discussion

These results provide some support for the hypothesis that patients who are on treatment with statins have a better clinical outcome than do patients who are not on statins. The strength of the study is that it used a well-defined and well-validated patient cohort. The original cohort from which cases and referents were drawn included all those hospitalized for acute stroke in a geographically defined 25- to 74-year-old population and during a specified period of time. Validation studies have shown that (with the exclusion of subarachnoid hemorrhage) ~91% of the total stroke population in this age is hospitalized, whereas 4% die outside the hospital and 5% are not admitted but survive.13,14

There are, nevertheless, methodological problems that warrant caution in interpretation of the findings. First, this was an observational study. Although the 2 groups were matched in some prognostic variables, there was an uneven distribution in comorbidities, and in a history of myocardial infarction in particular. This was adjusted for in the logistic regression model, but it may well be that an imbalance in prognostic factors not recorded in the study influenced the results.

Second, the patients in this case-control study were obtained from several hospitals, and no common neurological or functional outcome scale was used in these hospitals. Therefore, the operational definitions of “good” and “poor” outcome are crude and may have reduced the possibility to detect any differences. In sensitivity analyses, the odds ratios for the use of statins were similar whether discharge to home within 1 or 2 weeks was used to define good outcome. Nevertheless, more precise assessments of outcome would increase the possibilities to detect an effect of use of statins in stroke patients.

Third, the statistical power was weak. Only 125 of the 1499 patients screened were on statins when stroke occurred. This could perhaps be interpreted as an effect of successful stroke prevention by statins. However, during the years covered by the study, prescriptions for statins were low in Sweden (albeit rapidly increasing). The number of cases was obviously too low to permit moderate beneficial effects of statins on stroke outcome to be detected. With 125 cases, the odds ratio in favor of statins would have had to be as high as 2.08 to reach statistical significance between cases and referents; the observed unadjusted as well as adjusted odds ratios were 1.41. If statins improve outcome in patients with acute stroke, the effect size is probably modest. The effect size would, however, be of the same magnitude as that in tissue plasminogen activator trials (odds ratio of 1.27 for good outcome in a recent meta-analysis15).

Fourth, all stroke subtypes were analyzed together in the main analyses (although logistic models in which intracerebral hemorrhages were excluded produced the same results). Larger studies may reveal specific effects in some selected phenotypes of ischemic stroke.

A fifth limitation of the study is that all statins were considered together. Although the lipid-lowering effect is class specific, the statins may not share other effects on the thromboembolic processes.16 Divergent effects of different statins on fibrinogen levels, whole blood viscosity, plasminogen activator inhibitor-1 levels, lipoprotein(a) levels, and smooth muscle cell proliferation have been reported.7 Our study was too small to permit subanalyses based on individual statins. However, the results mainly reflect the effects of simvastatin, which was used by the majority of patients on statins (81%).

Despite these methodological limitations, the present results together with previous observations are interesting enough to warrant a more detailed analysis of the relationship between statins and stroke outcome. Experimental research with animal stroke models have demonstrated that statins may have a number of important neuroprotective properties that are likely to attenuate the effects of ischemia on the brain vasculature and parenchyma.9 Such putative beneficial effects of statins should be added to their effects on atherothrombotic processes, including inhibition of a number of factors that enhance smooth muscle proliferation and plaque neovascularization and inhibition of platelet aggregation.7 Lipophilic statins (fluvastatin, simvastatin) affect components of the coagulation system in an anticoagulant direction.7 Statins may also act as antioxidants.7

It may be argued that the fact that our patients were afflicted by stroke while on treatment with a statin testifies that the drug has proved itself to be ineffective in this particular subset of patients. This supposition can be confirmed or refuted only in an interventional trial. As we discussed, the actions of statins in the acute phase of stroke may be quite different from those in the preventive setting.

With the surge in the use of statins in subjects at risk for cardiovascular events, larger observational studies of the effects of statins in acute stroke are becoming increasingly
feasible. Further studies on the pretreatment and posttreatment effects of statins in animal models of stroke may also contribute to our understanding of if and how statins may improve outcome. Our results indicate that the design of any clinical trial of statins in the acute phase of stroke must be based on an estimated modest 20% to 40% reduction in the risk for poor outcome.

Acknowledgments
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