Prior Statin Use May Be Associated With Improved Stroke Outcome After Tissue Plasminogen Activator

José Álvarez-Sabín, MD, PhD; Rafael Huertas, MD; Manolo Quintana; Marta Rubiera, MD; Pilar Delgado, MD; Marc Ribó, MD, PhD; Carlos A. Molina, MD, PhD; Joan Montaner, MD, PhD

Background and Purpose—Statins may exert some neuroprotection, because use before stroke onset has been related to better outcome and reduced mortality. The purpose of this study was to evaluate whether patients who receive tissue plasminogen activator have better outcome when statins were taken before stroke.

Methods—We evaluated 145 patients with a stroke involving the middle cerebral artery (who received tissue plasminogen activator treatment (<3 hours)).

Results—Fifty-eight patients (40%) became functionally independent at 3 months. Factors associated with good outcome were age (68 versus 74.4 years, \( P<0.001 \)), baseline National Institutes of Health Stroke Scale score (13 versus 18, \( P<0.001 \)), and proximal middle cerebral artery occlusion (56.1% versus 84.3%, \( P<0.001 \)). Statins were the only drug taken before stroke that conditioned neurologic outcome. In fact, among patients who were functionally independent, 27.3% were under statins at the time of the index stroke as compared with 13.6% among the group of patients who were dependent or dead by the end of the study period (\( P=0.046 \)). A logistic regression model identified baseline National Institutes of Health Stroke Scale score <15 (OR: 5.8, 95% CI: 2.05 to 16.36, \( P=0.001 \)), age <70 years (OR: 2.93, 95% CI: 1.13 to 7.59, \( P=0.027 \)), and previous treatment with statins (OR: 5.26, 95% CI: 1.48 to 18.72, \( P=0.027 \)) as independent predictors of good functional outcome.

Conclusions—Patients under statins at the moment of stroke who received thrombolytics had an improved neurologic outcome. (Stroke. 2007;38:1076-1078.)

Key Words: neuroprotection ■ statin ■ stroke ■ thrombolysis ■ t-PA

In addition to reducing ischemic stroke,\(^1\) there is evidence supporting that statins are also neuroprotective.\(^2\) In fact, statins have been successfully tested in animal models of acute cerebral ischemia.\(^3\) Moreover, observational studies indicate that patients who are treated with a statin before or early after an ischemic stroke have a more favorable outcome than those who are not.\(^5\)–\(^9\)

In the present work, we aimed to test whether these observations might also be extended to thrombolysis field, searching whether patients with stroke who were treated with tissue plasminogen activator (t-PA) in the 3-hour time window have a different outcome related to statin intake.

Materials and Methods

Study Population

We conducted a retrospective analysis of all 155 consecutive patients with a stroke involving the middle cerebral artery who received t-PA treatment according to National Institute of Neurological Disorders and Stroke criteria in a teaching hospital over a 3-year period (2002–2005). The definitive analysis was performed using only those 145 patients for whom the main outcome measure, modified Rankin Scale (mRS) at 3 months, was available. Among those 10 patients in whom mRS scores were not available, only one patient was receiving statins.

Statistical Analyses

All analyses were done using the SPSS 12.0 statistical package. Statistical significance for differences between patients with good (mRS score ≤2) and poor (mRS >2) outcome was assessed by Pearson \( \chi^2 \) or Fisher exact test for categorical variables and the Mann-Whitney \( U \) or Student \( t \) test for continuous variables. Age and National Institutes of Health Stroke Scale score were categorized using a receiver operator characteristic curve, which is a graphic plot of the sensitivity versus (1-specificity) to obtain the best discrimination between good and poor outcome. A logistic regression model was performed to identify independent predictors of good outcome. A level of \( P<0.05 \) was accepted as statistically significant.

Results

Demographic, risk factor profile, and baseline clinical findings of the 145 t-PA-treated patients included in the definitive analysis are shown in Table 1.

Regarding outcome, 58 patients (40%) became functionally independent at 3 months. Factors associated with good outcome were age (68 versus 74.4, \( P<0.001 \)), baseline National Institutes of Health Stroke Scale score (13 versus 18,

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TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Data</th>
<th>All Patients</th>
<th>No Statins</th>
<th>Statins</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>71.9 (10.8)</td>
<td>71.8</td>
<td>70.5</td>
<td>0.568</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>75 (51.7)</td>
<td>51.8%</td>
<td>53.8%</td>
<td>0.852</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (51.7)</td>
<td>48.6%</td>
<td>69.2%</td>
<td>0.059</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28 (19.4)</td>
<td>15.5%</td>
<td>34.6%</td>
<td>0.025</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>48 (33.8)</td>
<td>18.2%</td>
<td>96.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>26 (18.3)</td>
<td>8.2%</td>
<td>57.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>29 (23.2)</td>
<td>26%</td>
<td>10.5%</td>
<td>0.145</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>55 (38.2)</td>
<td>38.2%</td>
<td>34.6%</td>
<td>0.735</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>18 (13.0)</td>
<td>11.3%</td>
<td>19.2%</td>
<td>0.281</td>
</tr>
<tr>
<td>Proximal occlusion, n (%)</td>
<td>102 (72.9)</td>
<td>72.9%</td>
<td>80%</td>
<td>0.465</td>
</tr>
<tr>
<td>Baseline National Institutes of Stroke Scale score, median (quartiles 1–3)</td>
<td>17 (12–20)</td>
<td>17</td>
<td>18</td>
<td>0.901</td>
</tr>
</tbody>
</table>

Table 2 shows the univariate analysis results. The table includes the following risk factors: age, sex, hypertension, diabetes mellitus, hypercholesterolemia, coronary disease, smoking, atrial fibrillation, previous stroke, proximal occlusion, and baseline National Institutes of Health Stroke Scale score. The table also shows the number of patients with different outcomes and the corresponding p-values.

P<0.001, and proximal middle cerebral artery occlusion (56.1% versus 84.3%, P<0.001) (Table 2). No differences were found regarding etiology or any risk factor. The relationship between previous treatments and outcome are described in Table 3. Statins was the only drug taken before admission to human beings. The unadjusted OR for early discharge to home was 1.41 (95% CI: 0.91 to 2.17), and prior treatment with statins (OR: 5.26, 95% CI: 1.48 to 18.72, P=0.027) as independent predictors of good functional outcome at 3 months.

No differences were found for recanalization rates or hemorrhagic transformations regarding statin use (data not shown). Considering mortality rates, a total of 28 patients died by the end of the study, which accounted for 19.3% of the sample and 32.2% of patients in the dependent-death group. There were no differences in mortality rates regarding statin intake. In fact, among dead patients, 24% were on statins as compared with 17.6% receiving statins among those who were alive by the end of the study (P=0.453).

**Discussion**

The first observational study in humans investigating the effect of pretreatment with statins on stroke outcome reported a borderline trend toward better outcome at hospital discharge. The unadjusted OR for early discharge to home was 1.41 (95% CI: 0.91 to 2.17) when patients on statin treatment were compared with referent stroke patients not on statins. However, this study did not distinguish between hemorrhagic and ischemic stroke, and only 8.3% of patients were taking statins.

In an observational study of 436 patients admitted to the National Institutes of Health Suburban Hospital Stroke Program between July 2000 and December 2002, 22% of patients were taking a statin when they were admitted. In that study, 51% of patients taking statins had a good outcome compared with 38% of patients not taking statins (P=0.03). After adjustment for confounding factors, statin pretreatment was associated with a 2.9 odds (95% CI: 1.2 to 6.7, P=0.02) of a good outcome at the time of hospital discharge.

Another study included 167 patients with stroke of which 18% were using statins when admitted, a level similar to ours. In the statin group, the risk of neurologic deterioration at day 3 was not significantly reduced, although 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 Barthel Index). Therefore, this study indicates that prior use of statins provides benefits for long-term functional outcome rather than for a short-term improvement.
Our results point in the same direction and extend the benefit of pretreatment with statins to the stroke thrombolysis arena.

In view of these optimistic results, we wondered if initiating statins as soon as possible is the best treatment for every patient with stroke. In fact, animal studies have shown that treatment with simvastatin after middle cerebral artery occlusion prevented the increase in brain infarct volume occurring at 24 hours and induced a 46.6% reduction after 48 hours. Additionally, the preliminary results of a pilot clinical trial to study the safety and efficacy of statins in human stroke have been reported, suggesting for the first time that simvastatin therapy initiated in the acute phase of ischemic stroke might improve neurologic outcome.

Apart from other mechanisms of benefit proposed for statins, this class of drugs have been shown to upregulate t-PA and downregulate plasminogen activator inhibitor-1 expression through a similar mechanism involving the inhibition of Rho geranylgeranylation, which might be important in the setting of thrombolysis. Moreover, a very recent study in an embolic model of cerebral ischemia demonstrates that combination treatment with atorvastatin and t-PA exerts a neuroprotective effect when administered 4 hours after stroke. In fact, rats in the combination treatment group had a mean lesion volume reduction of 38% ($P<0.0001$), with these rats not showing any increase in the incidence of hemorrhage compared with the control group.

In conclusion, our study shows that patients receiving statins at the time of stroke who received thrombolytics had an improved neurologic outcome. A large clinical trial is needed to confirm whether similar results might be obtained by combining both t-PA and statins in the acute phase of ischemic stroke.

Disclosures

None.

References

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