Effect of Statins on Intracerebral Hemorrhage Outcome and Recurrence

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Background and Purpose—3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have been associated with improved outcome after ischemic stroke and subarachnoid hemorrhage but an increased risk of incident intracerebral hemorrhage (ICH). We investigated (1) whether statin use before ICH was associated with functional independence at 90 days, and (2) whether survivors exposed to statins after ICH had an increased risk of recurrence.

Methods—We analyzed 629 consecutive ICH patients with 90-day outcome data enrolled in a prospective cohort study between 1998 to 2005. Statin use was determined by patient interview at the time of ICH and supplemented by medical record review. Independent status was defined as Glasgow Outcome Scale 4 or 5. ICH survivors were followed by telephone interview every 6 months.

Results—Statins were used by 149/629 (24%) before ICH. There was no effect of pre-ICH statin use on the rates of functional independence (28% versus 29%, \( \text{P} = 0.84 \)) or mortality (46% versus 45%, \( \text{P} = 0.93 \)). Medical comorbidities and warfarin use were more common in statin users. Hematoma volumes were similar (median 28 cm\(^3\) in pre-ICH statin users compared to 22 cm\(^3\) in nonusers, \( \text{P} = 0.18 \)). The multivariable-adjusted odds ratio for independent status in pre-ICH statin users was 1.16 (95% CI 0.65 to 2.10, \( \text{P} = 0.62 \)). ICH survivors treated with statins after discharge did not have a higher risk of recurrence (adjusted HR 0.82, 95% CI 0.34 to 1.99, \( \text{P} = 0.66 \)).

Conclusions—Pre-ICH statin use is not associated with improved ICH functional outcome or mortality. Post-ICH statin use is not associated with an increased risk of ICH recurrence. (Stroke. 2008;39:000-000.)

Key Words: intracerebral hemorrhage ▪ outcome ▪ statins

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have effects in addition to decreasing cholesterol synthesis. Statin-treated animals have better outcomes in experimental models of ischemic stroke and intracerebral hemorrhage (ICH). Human studies suggest that statins are associated with better outcomes after ischemic stroke and subarachnoid hemorrhage.

By contrast, it is not known whether pre-ICH statin use confers better outcomes in patients with ICH. Some of the pleiotropic effects of statins, such as decreased platelet aggregation and decreased thrombogenesis, could promote hematoma expansion or increase the risk of recurrent hemorrhage. Patients randomized to atorvastatin in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial had an increased incidence of ICH, a finding contrary to accumulated evidence from other randomized trials that suggested no increased incidence.

Therefore we investigated two hypotheses: (1) that statin before the onset of ICH is associated with improved outcome at 90 days, and (2) that ICH survivors taking statins are more likely to have ICH recurrence.

Methods

Statins and ICH Outcome

We retrospectively analyzed data from an ongoing single center prospective longitudinal cohort study of primary ICH. All patients with a baseline admission CT scan, stored in digital DICOM format, and determination of functional status at 90 days were eligible. For patients in whom consent could not be obtained, medical record information was stored in a database registry without patient identifiers. Clinical information, including medication use and dosage, was abstracted from the medical record and supplemented by interview. ICH volume was determined by computer-assisted segmentation.

There were 795 consecutive admissions with symptom onset between January 1, 1998 and August 31, 2005. Baseline CT scan was...
not performed or was missing in 467/95 (6%), and other data were missing in 19/795 subjects (3%), leaving 730 subjects with complete baseline information.

Death within 30 days occurred in 251/730, leaving 479/730 30-day survivors. Consenting survivors or a proxy informant (together representing 273/479 of the 30-day survivors, 57%), were interviewed by telephone at 90 days to determine the Glasgow Outcome Scale (GOS) score. To reduce bias we also retrospectively determined GOS at ≥90 days from the medical records of 105/206 nonparticipating ICH survivors. The 101/206 registry subjects without follow-up information had similar baseline characteristics as subjects with follow-up information, except fewer had lobar ICH location ($P=0.02$). Therefore, in sum, 90-day GOS was determined in a total of 629/730 potential subjects (86%).

### Statistical Analysis

Independent status was defined as GOS 4 or 5. Logistic regression models were constructed to determine whether pre-ICH statin use was associated with independent status or mortality. ICH volume was log-transformed, because of a nonnormal distribution, when analyzed as the dependent variable in multivariable linear regression. Age, ICH volume, and Glasgow coma scale (GCS) score were categorized according to cut-points established in univariate analysis, as follows: (1) age: ≤69, 70 to 79, ≥80, (2) ICH volume: 0 to 29 cm$^3$, 30 to 59 cm$^3$, ≥60 cm$^3$, (3) GCS: 3 to 10, 11 to 14, 15.

In ICH survivors univariate Cox regression models and Kaplan–Meier plots were used to determine subject characteristics associated with an increased hazard of recurrence. Post-ICH statin use was analyzed as a time-dependent variable because some subjects started or discontinued statins during the follow-up period. Post-ICH statin use and any variables associated with ICH recurrence ($P<0.20$) were entered into a multivariable Cox regression model, followed by backward elimination of nonsignificant variables ({$P>0.05$}). Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, North Carolina).

### Results

#### Pre-ICH Statin Use and ICH Outcome

Pre-ICH statin use was not associated with independent status or mortality (Table 1). Multivariable logistic regression models showed that pre-ICH statin use was not associated with independent status after adjustment for potential confounders (Table 2). Pre-ICH statin use was associated with a nonsignificant 19% increase in ICH volume on admission CT ($95\% \text{ CI } -7\% \text{ to } +51\%$, $P=0.16$) in a linear regression model controlling for other variables associated with ICH volume (male sex, hypertension, diabetes, previous ICH, and ICH location).

We considered whether the effect of statins use might vary according to outcome definition or patient subgroups. There was no difference in 30-day or 90-day survival in pre-ICH statin users (data not shown). Because statin withdrawal may worsen stroke outcome$^{13}$ we performed additional analyses subtracting subjects in whom statins were discontinued ($n=22$), or adding subjects in whom statins were started ($n=25$), and found similar results (data not shown). To test for a dose-response effect, those with dose information (105/149, 70%) were dichotomized according to whether the statin dose was ≤50% of the maximum dose recommended by the manufacturer’s labeling. Users of higher-dose statins ($n=25$), compared to nonusers ($n=480$), were not more likely to have independent status ($P=0.78$). Finally, we failed to confirm a hypothesis that statins would have a better effect in subjects with higher GCS (GCS >10) or smaller ICH volumes (<30 cm$^3$), tested using interaction terms in the regression models ($P>0.50$ for both).

#### Post-ICH Statin Use and Risk of Recurrence in ICH Survivors

Statins were used after ICH discharge in 79/229 (35%) of participating ICH survivors; 57 were discharged on statins and 22 started statins after discharge. Mean follow-up was 1.91±1.58 years, with a total of 437.5 person-years of follow-up and 140.8 person-years of post-ICH statin exposure. Post-ICH statin users were more likely to be older, male, to have been on warfarin before the index ICH, and to have CHD and diabetes ($P<0.05$ for all comparisons).

Recurrent ICH occurred in 26 subjects (11%). In univariate Cox regression analysis, lobar ICH location and history of additional ICH before the index event were the only predictors of recurrence ($P<0.05$). Post-ICH statin exposure was not associated with recurrence in univariate Cox regression.
Results occurred because of the play of chance, or differences had no effect on 30-day mortality. Whether the different bioidities. By contrast, treatment with statins improved sensorimotor recovery in 2 animal models of ICH.3,4 There may be biological differences, however, between animals and humans in the type of injury that occurs after ICH. In contrast to the animal studies, our subjects were taking various types and dosages than in the SPARCL trial,9 which could have led to systematic assessment of lipid levels. Because hemorrhagic stroke characteristics may themselves have been affected by pre-ICH statin use. Finally a third model was constructed with the same variables as the model B, but excluding subjects with negative prognostic features: deep coma (GCS 3 to 5), pre-ICH cognitive impairment, brainstem or cerebellar location, or ICH volume >60 cm³. The subject population of the Model C was therefore similar to that studied in recent clinical trials of ICH.

Discussion

We did not detect a difference in outcomes in patients taking statins before ICH, even after adjustment for medical comorbidities. By contrast, treatment with statins improved sensorimotor recovery in 2 animal models of ICH.3,4 There may be biological differences, however, between animals and humans in the type of injury that occurs after ICH. In contrast to the animal studies, our subjects were taking various types and doses of statins. A recent study suggested that statins are associated with decreased 30-day mortality but not improved functional outcome.14 In our larger study pre-ICH statin use had no effect on 30-day mortality. Whether the different results occurred because of the play of chance, or differences in the populations studied, is not clear.

A randomized trial in persons with stroke showed that 80 mg of atorvastatin per day increased the risk of ICH.9 We did not, however, find an increased risk of recurrence in ICH survivors treated with statins, but note that the current study has only modest power to detect a small increase in recurrence risk. In our study various statins were used, at lower dosages than in the SPARCL trial,9 which could have led to different results. The relationship between cholesterol levels and ICH recurrence could not be determined in our study because there was no systematic assessment of lipid levels. Our results are consistent with a population-based case-control study of ICH that concluded statin use in community practice was not associated with an increased risk of ICH.15

This main limitation of our study is that statin use was not randomly assigned, and therefore associations between statins and either ICH outcome or recurrent ICH may be confounded by other factors associated with statin use, even though we adjusted for recognized confounders using regression models. Our analysis of the dose-response effect of statins on ICH outcome uses the simplistic assumption that maximum dose strengths are equipotent across different drugs.

These data come from a relatively large series of consecutive ICH cases with functional outcome data and prospective follow-up and therefore provide a best estimate of the effect of statins on ICH outcome in the absence of large trials. We calculated that a trial of statins to improve 90-day outcome would need to include 1026 subjects (randomized 1:1 to statin or placebo) to have 90% power to detect an OR of 1.24, derived from Model C (Table 3), for independent status in the statin arm. Our study suggests that patients already taking statins for prevention of cardiovascular disease may safely continue them during and after ICH. For ICH survivors our data suggest that post-ICH statin exposure is not associated with a large increase in risk of recurrence, at least with the statin types and dosages used in community practice.

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Disclosures

None.

References


Table 2. Multivariable Models of the Effect of Statin Use Before ICH on 90-Day Independent Status (GOS 4 or 5)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for baseline</td>
<td>1.22</td>
<td>0.76 to 1.95</td>
<td>0.40</td>
</tr>
<tr>
<td>characteristics (see legend)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model B</td>
<td>1.16</td>
<td>0.65 to 2.10</td>
<td>0.62</td>
</tr>
<tr>
<td>Model A+adjusted for ICH</td>
<td>1.24</td>
<td>0.62 to 2.49</td>
<td>0.54</td>
</tr>
<tr>
<td>characteristics (see legend)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model C but restricted to</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>supratentorial ICH volume ≤60</td>
<td></td>
<td></td>
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<tr>
<td>cm³, without deep coma or pre-ICH cognitive impairment (n=314)</td>
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</table>

Three logistic regression models were constructed. In Model A variables in addition to pre-ICH statin use were the pre-ICH characteristics also associated with independent status in univariate analysis (P<0.20): age, coronary heart disease, ischemic stroke, pre-ICH cognitive impairment, atrial fibrillation, and pre-ICH warfarin use. Model B includes the same variables as Model A with the addition of characteristics of the hemorrhagic stroke associated with independent status in univariate analysis (P<0.20): GCS, ICH volume, and presence of intraventricular hemorrhage. The 2 models were constructed separately because hemorrhagic stroke characteristics may themselves have been affected by pre-ICH statin use. Finally a third model was constructed with the same variables as the model B, but excluding subjects with negative prognostic features: deep coma (GCS 3 to 5), pre-ICH cognitive impairment, brainstem or cerebellar location, or ICH volume >60 cm³. The subject population of the Model C was therefore similar to that studied in recent clinical trials of ICH.

GOS indicates Glasgow Outcome Scale; ICH, intracerebral hemorrhage.

Table 3. Multivariable Cox Regression Model of ICH Recurrence

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ICH statin use</td>
<td>0.82</td>
<td>0.34 to 1.99</td>
<td>0.66</td>
</tr>
<tr>
<td>Lobar ICH location</td>
<td>2.40</td>
<td>1.04 to 5.57</td>
<td>0.04</td>
</tr>
<tr>
<td>Additional history of ICH before index event</td>
<td>3.26</td>
<td>1.12 to 9.55</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Exposure to statin was entered as a time-dependent covariate to account for statin use during only part of the follow-up period in some subjects. ICH indicates intracerebral hemorrhage.


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