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%, \( P = 0.84 \)) or mortality (46% versus 45%, \( P = 0.93 \)). 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, \( P = 0.18 \)). The multivariable-adjusted odds ratio for independent status in pre-ICH statin users was 1.16 (95% CI 0.65 to 2.10, \( P = 0.62 \)). 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, \( P = 0.66 \)).

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
not performed or was missing in 46/795 (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%).

### 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% CI −7% 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 and Atrial fibrillation 29 18 0.005

#### 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 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).

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

Statin use 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).

Recurrence 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.
mg of atorvastatin per day increased the risk of ICH.9 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.15 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 doses 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

### 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.

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### Disclosures

None.

### References


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