Statin Use and Microbleeds in Patients With Spontaneous Intracerebral Hemorrhage

Diogo C. Haussen, MD; Nils Henninger, MD; Sandeep Kumar, MD; Magdy Selim, MD, PhD

Background and Purpose—Statins have been associated with increased risk of intracerebral hemorrhage (ICH), particularly in elderly patients with previous ICH. Recurrent ICH in the elderly is often related to cerebral amyloid angiopathy. Therefore, we investigated whether statin use is associated with increased prevalence and severity of microbleeds (MB), particularly cortico-subcortical microbleeds (csMB), which are frequently observed in cerebral amyloid angiopathy.

Methods—We studied 163 consecutive patients with spontaneous ICH who underwent magnetic resonance imaging within 30 days of presentation. We retrieved clinical information and analyzed magnetic resonance imaging for the presence, location, and number of MB, which were divided into csMB or other (other MB). We performed group comparisons stratified by statin use and by the presence vs absence of any MB (csMB and/or other MB) or csMB alone.

Results—Sixty-four percent had lobar ICH. Overall, 53% had microbleeds and 39% had csMB. Statin users were older, had significantly lower cholesterol and low-density lipoprotein levels, and higher prevalence of hypertension, diabetes, dyslipidemia, and antiplatelet use. The prevalence and number of other MB were similar in statin-treated and statin-untreated individuals. However, more statin-treated patients had csMB (57% vs 33%; P=0.007), with almost twice as many lesions (4.6 vs 2.4; P=0.007) compared with untreated patients. Age and statin use were independently associated with both the presence and increased number of MB (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.00–1.06; P=0.01 and OR, 1.03; 95% CI, 1.00–1.06; P=0.01 and OR, 4.15; 95% CI, 1.54–11.20; P<0.01) in multivariate analyses.

Conclusions—Statin use in patients with ICH is independently associated with MB, especially csMB. Future studies are needed to confirm our findings and to investigate whether csMB can serve as a surrogate marker for ICH risk in statin-treated patients. (Stroke. 2012;43:2677-2681.)

Key Words: • amyloid angiopathy • brain imaging • hemosiderin • intracerebral hemorrhage • intracranial hemorrhage • microbleed • statins

Recent studies have suggested that therapy with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) may increase the risk of intracerebral hemorrhage (ICH).1,2 The risk of ICH was reported to increase with advancing age and in those with history of ICH, and it did not seem to correlate with low-density lipoprotein (LDL) levels.2,3 This has led some to consider avoiding statins in lobar ICH survivors.4 Statins have many beneficial effects,5 and their discontinuation might deprive subpopulations from the benefits of therapy. Consequently, further studies are needed to identify patients at higher risk.

Recurrent lobar ICH in older patients is often related to cerebral amyloid angiopathy (CAA). Microbleeds (MB) are not uncommonly seen in patients with ICH, and those in the cortico-subcortical regions are frequently present in patients with CAA.6,7 The presence of MB is a surrogate marker of vessel fragility and, likely, greater risk of ICH recurrence.6,7

Considering that ICH and MB might share pathophysiological mechanisms, we aimed to examine the relationship between statin use and the presence of MB in patients with spontaneous ICH.2,8 We hypothesized that statin treatment is associated with an increased prevalence and severity of MB, particularly cortico-subcortical MB (csMB), which are frequently observed in CAA.

Materials and Methods
We performed a retrospective review of our prospectively collected ICH database from 2008 to 2011, and we identified consecutive patients with spontaneous ICH who had magnetic resonance imaging (MRI) within 30 days of their ICH presentation. We retrieved baseline clinical and demographic information including age, sex, comorbid conditions, medication use on admission (antiplatelet agents, anticoagulants, and statins), systolic and diastolic blood pressures on initial evaluation, and admission laboratory results (including lipid profile, serum glucose, and international normalized ratio). History of hypertension was defined as self-report of previous

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diagnosis of hypertension by the patients or their families or documentation in medical records of the presence of a premorbid clinical diagnosis of hypertension, whether treated or untreated. Patients with current sympathomimetic drug use, coagulopathy (defined as international normalized ratio $>1.7$), or warfarin use at any time before ICH onset were excluded to avoid the confounding effects of these variables on MB. Similarly, patients with secondary causes of ICH such as cerebral vascular malformations, aneurysmal bleed, head trauma, or malignancy were not included in this study.

**Radiological Data**

Two stroke-trained neurologists, blinded to clinical data, independently reviewed the MRI scans to determine the presence of MB and their locations and numbers. The MRI was typically performed early after ICH, with an average time from symptom onset to scan of 2.3 ($\pm 4.0$) days, and average time from presentation to our referring hospital to MRI of 1.7 ($\pm 3.8$) days. MB were defined as small focal areas of very low signal intensity on T2* gradient-echo MRI scans measuring 2 to 10 mm in diameter. Inter-rater agreement was obtained for the first 20 patients (kappa=0.81; $P<0.01$), followed by a consensus read of the remaining scans. Lesions were excluded if they were suspicious for vessels, calcifications, choroid plexus, and low-signal averaging from adjacent bone. In addition, we excluded MB located within 10 mm of the primary ICH, as well as lesions classified as uncertain (Figure). MB were classified according to their location in csMB vs other MB (oMB; basal ganglia, thalamus, internal capsule, brainstem, and/or cerebellum). The ICH location was also recorded and classified as lobar vs nonlobar (basal ganglia, thalamus, internal capsule, brainstem, and cerebellum).

**Statistical Analysis**

We performed group comparisons stratified by statin treatment (on vs off), and by the presence vs absence of any MB (csMB and/or oMB) or csMB alone. Categorical variables were compared by $\chi^2$ test or Fisher exact test as appropriate, and continuous variables were compared by Mann-Whitney U test. Statistical significance was set at $P \leq 0.05$. Multivariate binary logistic regression analyses were performed using the presence of any MB and csMB as the dependent variable, including variables with $P>0.1$ on univariate analyses and other variables associated with statin use (hyperlipidemia, diabetes, coronary artery disease, hypertension, and antiplatelet use), as appropriate, using a variable selection method.

**Results**

We identified 337 patients with primary spontaneous ICH. A total of 176 patients underwent MRI within 30 days of their ICH. Of these, 13 were excluded because of suboptimal MRI image quality. The baseline characteristics of the included (n=163) and excluded (n=174) patients were similar, with the exceptions that included patients were younger ($68.4 \pm 15.2$ years vs $72.1 \pm 13.8$; $P=0.032$), had lower prevalence of hypertension (66% vs 76%; $P=0.03$) and more frequently had lobar ICH (64% vs 40%; $P<0.01$). Likewise, the baseline characteristics of patients who underwent MRI within 30 days vs those who did not were similar, with the exceptions that patients who underwent MRI were younger ($P<0.001$) and had a lower prevalence of history of hypertension ($P=0.03$). Also, 59% of patients with lobar bleed had MRI vs 36% of those with nonlobar ICH ($P=0.01$).

The baseline characteristics of the 163 patients included in this analysis were as follows: mean age $68.4 \pm (15.2)$ years; 59% males; 104 patients (64%) had a lobar ICH; and 59 (36%) had a nonlobar ICH (basal ganglia, thalamus, and internal capsule: n=46; brainstem: n=7; cerebellum: n=6). No co-occurrence of nonlobar and lobar ICH was observed. Overall, 24% of the patients had only csMB (mean number of lesions, $6.4 \pm 11.2$), 13% had only oMB (1.1 $\pm 0.4$), and 15% had both csMB and oMB (14.8 $\pm 20.3$). Patients with lobar ICH were older than individuals with nonlobar ICH (70.6 $\pm 15.4$ years vs 64.0 $\pm 14.7$; $P=0.006$). The prevalence and count of any MB and of csMB were similar in patients with lobar and nonlobar ICH. However, oMB were more prevalent in patients with nonlobar ICH compared with patients with lobar ICH (50% vs 18%; $P<0.001$) and in higher counts (2.1 $\pm 5.6$ vs 0.2 $\pm 0.6$; $P<0.001$).

Table 1 shows baseline demographics and MB distribution stratified by statin treatment. Patients using statins at ICH onset were older ($P=0.016$) and had higher prevalence of hypertension ($P=0.004$), diabetes ($P<0.001$), dyslipidemia ($P<0.001$), and coronary artery disease ($P=0.018$). Expectably, statin-treated patients were more frequently using antiplatelet therapy ($P<0.001$), and their mean total cholesterol ($P=0.007$) and LDL ($P<0.001$) levels were lower. Although the prevalence and number of MB were similar in statin-treated patients and patients not treated with statins, the overall presence and number of any MB (csMB and/or oMB) were higher in statin-treated patients. Consequently, patients using statins were more frequently found to have csMB (57% vs 33%; $P=0.007$), and almost twice as many were found to have csMB compared with patients not treated with statins (4.6 $\pm 11.3$ vs 2.4 $\pm 8$; $P=0.006$).

Table 2 depicts a comparison between patients with any MB (csMB and/or oMB) or no MB. Only age and statin use were significantly different between patients with and without any MB on univariate analysis. Age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01–1.05; $P=0.01$) and statin use (OR, 2.72; 95% CI, 1.02–7.22; $P=0.04$) remained as independent predictors of any MB on multivariate logistic regression analysis including variables associated with statin use, such as hypertension, hyperlipidemia, diabetes, coronary artery disease, and antiplatelet-use.
Table 1. Baseline Characteristics of Patients by Statin Treatment Group

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Statin, n=40</th>
<th>No Statin, n=123</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>74.5 (8.1)</td>
<td>66.4 (±16.4)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Male</td>
<td>22 (55%)</td>
<td>75 (61%)</td>
<td>0.504</td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (85%)</td>
<td>74 (60%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (50%)</td>
<td>14 (11%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (67%)</td>
<td>20 (16%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11 (27%)</td>
<td>13 (10%)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (10%)</td>
<td>5 (4%)</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Admission medications and BP

| Presence of any MB (mean) | 27 (67%) | 60 (48%) | 0.039* |
| Presence of csMB (mean)   | 5.9 (±14.8) | 3.2 (±9.0) | 0.021 |
| Presence of oMB           | 23 (57%)  | 41 (33%)  | 0.007* |
| Presence of any MB (mean) | 4.6 (±11.3) | 2.4 (±8.0) | 0.066* |
| Presence of any MB (mean) | 10 (25%)  | 37 (30%)  | 0.688 |
| Presence of oMB           | 1.1 (±4.6) | 0.8 (±2.7) | 0.625 |

BP indicates blood pressure; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; MB, microbleed; oMB, other microbleed.

Table 2. Baseline Characteristics of Patients With and Without Any Microbleed

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Any MB, n=87</th>
<th>No MB, n=76</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>71.4 (±13.4)</td>
<td>65.0 (±16.5)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Male</td>
<td>49 (56%)</td>
<td>48 (63%)</td>
<td>0.375</td>
</tr>
</tbody>
</table>

Admission medications and BP

| Presence of any MB (mean) | 27 (67%) | 60 (48%) | 0.039* |
| Presence of csMB (mean)   | 5.9 (±14.8) | 3.2 (±9.0) | 0.021 |
| Presence of oMB           | 23 (57%)  | 41 (33%)  | 0.007* |
| Presence of any MB (mean) | 4.6 (±11.3) | 2.4 (±8.0) | 0.066* |
| Presence of any MB (mean) | 10 (25%)  | 37 (30%)  | 0.688 |
| Presence of oMB           | 1.1 (±4.6) | 0.8 (±2.7) | 0.625 |

BP indicates blood pressure; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; MB, microbleed.

Table 3 shows a comparison between patients with and without csMB. Patients with csMB were older (72.7±11.3 vs 65.6±16.7 years; P=0.012) and were on statin treatment more than as commonly compared with those without csMB (36% vs 17%; P=0.007). In addition, there was a trend for a higher prevalence of males (P=0.097) and lower LDL levels among csMB patients (P=0.083). In multivariate logistic regression analysis, age (OR, 1.03; 95% CI, 1.00–1.06; P=0.01) and statin use (OR, 4.15; 95% CI, 1.54–11.20; P=0.001) emerged as independent factors associated with the presence of csMB (Table 4). The variables “statin therapy” and “LDL levels” were significantly intercorrelated (ρ=0.35; P<0.001); therefore, only statin therapy was included as a covariate in the multivariate model.

Considering that strictly csMB are suggestive of CAA and that mixed csMB and oMB are less likely to be CAA-related, we executed a multivariate logistic regression after excluding the 25 patients with concomitant presence of csMB and oMB. The association between statin use and the presence of csMB remained strong (OR, 8.01; 95% CI, 2.25–28.43; P=0.001).

Discussion

We demonstrate an association between statin therapy and increased presence and number of MB, particularly csMB in our cohort of ICH patients. In contrast, we found no correlation between statin therapy and the presence or number of oMB.

A previous study reported a negative association between statin use and the overall presence of MB in patients with ischemic stroke and transient ischemic attacks. However, the effect of statins on the specific subtypes of MB (csMB and oMB) was not analyzed in this study. Moreover, ischemic stroke and transient ischemic attacks may not share the same underlying pathophysiological changes as ICH.

Statin use has been suggested to increase the risk of hemorrhage recurrence in ICH patients. Interestingly, the use of antiplatelets or anticoagulants had no overall effect on the risk of ICH in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, whereas male sex, statin therapy, previous ICH, and advancing age were the main factors that accounted for increased risk of ICH. Although these latter clinical characteristics are suggestive of amyloid-related ICH, the association between
Previous studies have indicated that the risk of ICH in statin-treated patients seems independent of the LDL cholesterol levels; likewise, the relationship between MB and LDL levels does not seem to be significant.²,₄,₁₇,₁₈ Our findings of an association between statin use and the presence and severity of MB, especially csMB, suggest that increased risk of ICH with statin use might be explained by increased prevalence of underlying statin-sensitive CAA microvascular burden, and they raise the intriguing possibility that using T₂ gradient-echo gradient echo MRI might potentially help to stratify statin-treated patients who are at highest risk for ICH.

It is important to emphasize that our findings should be considered hypothesis-generating in the absence of other data linking statin use to CAA and should not be used to withhold statin therapy in patients with MB. The decision of whether to continue or discontinue statin therapy after ICH should be made on a case-by-case basis after taking into considerations the patient’s overall risk factors for vascular disease and recurrent ICH.³

The present study has other limitations attributed to its retrospective nature and to the small number of statin-treated patients in our cohort. Because of its design, we are unable to determine a temporal relationship between statin use and MB that would be important to support causality.

We did not control for statin dosing, duration of treatment, or compliance because these data were not collected. Despite statistical adjustments, “confounding by indication” related to statin use may still exist. Moreover, we cannot rule out selection bias because only half of our ICH patients underwent MRI within the prespecified period for inclusion. This is likely attributed to patients with higher prevalence of ICH cases of hypertensive etiology in the excluded group, in whom further diagnostic investigations with MRI were not deemed necessary. Therefore, our results may not necessarily be generalizable to all ICH patients.

## Conclusions

In conclusion, our finding of an increased presence and number of MB, particularly csMB, in ICH patients receiving statins adds to the accumulating body of evidence relating to the risks of ICH with this class of medications. Future prospective studies to further probe the causal relationship between statin use, csMBs, and ICH, and to examine the prognostic value of the presence and severity of csMB in statin-treated patients are warranted.

## Disclosures

None.

## References


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