Hypercholesterolemia, HMG-CoA Reductase Inhibitors, and Risk of Intracerebral Hemorrhage

A Case–Control Study

Daniel Woo, MD; Brett M. Kissela, MD; Jane C. Khoury, MS; Laura R. Sauerbeck, RN, MS; Mary A. Haverbusch, RN, BSN; Jerzy P. Szafarski, MD, PhD; James M. Gebel, MD; Arthur M. Pancioli, MD; Edward C. Jauch, MD; Alexander Schneider, MD; Dawn Kleindorfer, MD; Joseph P. Broderick, MD

Background and Purpose—Several studies have demonstrated an association between hypocholesterolemia and intracerebral hemorrhage (ICH). We tested the hypothesis that hypercholesterolemia or use of HMG-CoA reductase inhibitors (statin) agents, or both, are associated with ICH.

Methods—This study was part of the preplanned midway analysis of an ongoing, population-based, case-control study of the genetic and environmental risk factors of hemorrhagic stroke. Conditional stepwise logistic regression modeling was used to determine if self-reported hypercholesterolemia or statin use, or both, were independent risk factors for ICH.

Results—Between December 1, 1997, and June 30, 2000, 188 cases of ICH and 366 age-, race-, and gender-matched controls were enrolled. Hypercholesterolemia and statin use were less common among cases than controls: 25% versus 38% (P = 0.003) and 9% versus 17% (P = 0.03), respectively. Hypercholesterolemia with statin use was associated with less risk of ICH (OR = 0.30; P = 0.0008) in multivariable analysis after controlling for alcohol use, hypertension, previous stroke, first-degree relative with ICH, education level, and apolipoprotein E alleles.

Conclusion—Hypercholesterolemia was associated with a lower risk of ICH. We have not found an increased risk of ICH with the widespread use of statins in our population. Given the lack of cholesterol levels in the current study, further studies are needed to determine if lower cholesterol levels secondary to statin use bear the same risk as low cholesterol levels for ICH.

Key Words: stroke ■ hemorrhage ■ hypercholesterolemia ■ HMG-CoA reductase inhibitors ■ apolipoproteins ■ risk factors

Spontaneous intracerebral hemorrhage (ICH) occurs with an annual incidence rate of 15 to 19 per 100 000,1 and the 30-day case fatality rate is 40% to 50%.2 Several studies have demonstrated that low cholesterol or hypocholesterolemia is a risk factor for ICH,3–7 and others have reported that high cholesterol is protective against ICH.8–10 Theoretically, lipid-lowering medications may increase the risk of cerebral hemorrhage given that high cholesterol has been found to be protective against ICH.3 We tested the hypothesis that hypercholesterolemia or use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (also known as statins), or both, would be associated with ICH using a population-based, case-control study of the genetic and environmental risk factors of hemorrhagic stroke.

Materials and Methods
The methods of the Genetic and Environmental Risk Factors of Hemorrhagic Stroke Study have been previously published.11,12 Current medications are recorded and then classified according to the American Hospital Formulary System. We found that of 87 subjects using an antilipid medication, 78 (90%) subjects were using statin agents. Therefore, we analyzed both antilipid medication and statin use separately. The results were not significantly different, and because statins were the predominant antilipid medication used, we report the analysis using only statins.

Apolipoprotein E Genotyping
Four buccal brush samples are obtained from each case and control at the time of interview and stored at 20°C. After DNA is isolated, 2 μL are used to perform polymerase chain reaction (PCR) of apolipoprotein E (apoE) genotype. ApoE analysis is performed by PCR using established protocols.13 Our cases and controls were found to be in Hardy–Weinberg equilibrium.11

Statistical Analysis
The data were managed and analyzed using SAS (SAS Institute). Bivariate and multivariable analysis for the association of independent variables with stroke was achieved using a conditional logistic
modeling approach (Procedure Proportional Hazards Regression). Results are reported as odds ratios with their associated 95% confidence intervals. Methodology used for the multivariable analysis used a backward elimination procedure for risk factors with significance levels of $P < 0.10$. Analyses were performed for all cases of ICH, as well as for the 2 subgroups of lobar and nonlobar ICH.

As expected, all of our subjects using statins or other antilipid medications also had a history of hypercholesterolemia. Odds ratios and associated 95% confidence intervals are provided for the model including hypercholesterolemia and for the model with the interaction of hypercholesterolemia and statin use. In secondary analysis, we examined potential interactions between apoE genotype and statin use. This analysis included the statistically significant risk factors identified in the multivariate-reduced model for all hemorrhages, lobar hemorrhages, and nonlobar hemorrhages. Odds ratios and associated 95% confidence intervals are provided for this model.

### Results

Of 188 cases of ICH, 67 (36%) were lobar ICH and 121 (64%) were nonlobar ICH. Of the ICH cases, 50% were male, 21% were black, and the average age was 65 years. Of the lobar ICH cases, 48% were male, 19% were black, and for the nonlobar ICH cases, 52% were male and 21% were black, and the average age for both subgroups was 65 years.

Univariate comparisons of the rate of a history of high cholesterol by direct interview as well as use of statin use are shown in Table 1. A history of high cholesterol was more common among controls than cases, which was significant for all cases of ICH and the nonlobar subset of ICH. There was a trend toward a history of high cholesterol for the controls compared with the cases of lobar ICH. The number of lobar ICH cases is approximately half the number of nonlobar ICH cases, which leads to less power to detect differences. Also, despite having similar age, race, and gender distributions, the control population for lobar ICH cases had a lower rate of reported high cholesterol than the control cases for nonlobar ICH.

Statin use was found to be more common among controls than among cases. The statistical significance of this difference was lost for the lobar ICH subgroup, although the trend continued in the same direction. Among those subjects with history of hypercholesterolemia, there was no difference in the rate of statin use between cases and controls (41% versus 45%, respectively). The number of subjects with either apoE2 or apoE4 allele was small and did not demonstrate any associations (data not shown). Thus, they were combined together as individuals having either apoE2 or apoE4 allele.

Table 2 shows the prevalence of the risk factors examined, and the odds ratios and associated 95% CI for the main effects. Because of significant overlap between hypercholesterolemia and statin use, we were unable to include them as separate variables in the same model. Thus, Table 2 shows

### TABLE 1. Rate of High Cholesterol and Statin Use by ICH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Case %</th>
<th>Control %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of high cholesterol</td>
<td>Case</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>All ICH (n=188)</td>
<td>25%</td>
<td>38%</td>
<td>0.003</td>
</tr>
<tr>
<td>Lobar ICH (n=67)</td>
<td>21%</td>
<td>33%</td>
<td>0.08</td>
</tr>
<tr>
<td>Nonlobar ICH (n=121)</td>
<td>28%</td>
<td>41%</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin use</td>
<td>Case</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>All ICH (n=188)</td>
<td>9%</td>
<td>17%</td>
<td>0.03</td>
</tr>
<tr>
<td>Lobar ICH (n=67)</td>
<td>9%</td>
<td>15%</td>
<td>0.21</td>
</tr>
<tr>
<td>Nonlobar ICH (n=121)</td>
<td>8%</td>
<td>18%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage. $P$ calculated using conditional logistic regression.

### TABLE 2. Risk Factors for ICH: Bivariate and Multivariable Odds Ratios and 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Case % N=188</th>
<th>Control % N=366</th>
<th>Bivariate OR (95% CI)</th>
<th>Multivariable OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE2 or E4</td>
<td>47</td>
<td>41</td>
<td>1.26 (0.89–1.79)</td>
<td>1.65 (1.00–2.71)</td>
</tr>
<tr>
<td>ApoE3/E3</td>
<td>53</td>
<td>59</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63</td>
<td>44</td>
<td>2.48 (1.67–3.70)</td>
<td>2.61 (1.63–4.18)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>15</td>
<td>3</td>
<td>8.33 (3.43–20.22)</td>
<td>6.85 (2.46–19.05)</td>
</tr>
<tr>
<td>Frequent alcohol</td>
<td>11</td>
<td>5.5</td>
<td>2.08 (1.04–4.14)</td>
<td>2.32 (1.06–5.07)</td>
</tr>
<tr>
<td>First-degree relative with ICH</td>
<td>6</td>
<td>1</td>
<td>5.16 (1.63–16.31)</td>
<td>6.63 (1.78–24.73)</td>
</tr>
<tr>
<td>Education &lt;12th grade</td>
<td>28</td>
<td>13</td>
<td>3.17 (1.91–5.27)</td>
<td>2.36 (1.32–4.24)</td>
</tr>
<tr>
<td>Education ≥12th grade</td>
<td>35</td>
<td>34</td>
<td>1.60 (1.03–2.47)</td>
<td>1.46 (0.90–2.37)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>12</td>
<td>4</td>
<td>3.13 (1.57–6.24)</td>
<td>1.67 (0.72–3.86)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>25</td>
<td>38</td>
<td>0.55 (0.37–0.82)</td>
<td>0.30 (0.12–0.74)</td>
</tr>
<tr>
<td>HC without statin</td>
<td>18</td>
<td>22</td>
<td>0.66 (0.41–1.05)</td>
<td>0.77 (0.41–1.44)</td>
</tr>
<tr>
<td>HC with statin</td>
<td>7</td>
<td>16</td>
<td>0.42 (0.23–0.76)</td>
<td>0.30 (0.12–0.74)</td>
</tr>
<tr>
<td>No HC</td>
<td>75</td>
<td>62</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Cholesterol by apo E</td>
<td>0.98</td>
<td>(0.39–2.45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariable model controlled for presence of hypertension, previous stroke, frequent alcohol use, first-degree relative with ICH, and education level.

ApoE2 or E4 indicates carrier or homozygote of apoE2 or E4; ICH, intracerebral hemorrhage; HC, hypercholesterolemia.
Given that high cholesterol is associated with decreased risk of ICH, although the interaction was not statistically significant (P=0.07 and 0.18, respectively).

The models including hypercholesterolemia and separately shows the odds ratios using hypercholesterolemia and statin interaction. In addition, subsequent analysis demonstrated an interaction between statin use and apoE genotype, and the third and final model with this interaction was included.

Odds ratios for the interactions between statin use and apoE genotype are reported in Table 3. As compared with the nonhypercholesterolemia group with apoE3/E3 genotype (the referent group), the risks of all ICH and nonlobar ICH were significantly lower in the group of high cholesterol with statin use but not in those without statin use. However, the decreased risk in the group of high cholesterol and statin use was not found among those with an apoE2 or apoE4 allele regardless of statin use. This suggests a significant interaction of apoE genotype and statin use in determining the risk of all ICH (P=0.03 for interaction term of apoE and statin use). Similar relationships were also observed for nonlobar ICH and lobar ICH, although the interaction was not statistically significant (P=0.07 and 0.18, respectively).

### Discussion

Treatment with statins was found to be associated with an increased risk of ICH. A history of hypercholesterolemia was associated with decreased risk of ICH, as has been previously reported. Statin use was not more common among cases of ICH than among controls. There is some suggestion in the multivariable model that treatment with statins were associated with decreased risk of ICH as compared with a history of high cholesterol alone.

Although our study identified an association with decreased risk of ICH and a history of hypercholesterolemia, and although other studies have found an association with decreased risk of ICH with high levels of cholesterol, the mechanism by which this is mediated may be different from the risk of ICH associated with low levels of cholesterol. Our comparison is to a lack of history of high cholesterol, which may include those with very low levels of cholesterol or those with normal cholesterol levels or those with high cholesterol levels but were undiagnosed. The pathophysiologic mechanisms of hypercholesterolemia and their relationship with ICH risk may be very different than the pathophysiologic mechanism of low cholesterol and its increased risk of ICH. Given that high cholesterol is associated with decreased risk of ICH and that statin use has been found to decrease cholesterol levels, we sought to examine if this potential change may have increased or affected the risk of ICH.

However, a possible explanation for our results is that treatment with statins may be a strong indicator of hypercholesterolemia and that this factor alone is protective. A notable limitation of our analysis is the lack of serum cholesterol levels and, in particular, subgroups of cholesterol such as high-density lipoprotein and low-density lipoprotein levels. Treatment with lipid-lowering medications may not have been effective. Yet studies have demonstrated that after only 6 weeks of treatment with statin agents, low-density lipoprotein levels decrease an average of 33% to 37%. Nevertheless, we report only that the widespread use of statins in our population does not appear to have increased the risk of ICH. Further study is required to determine if lowering levels of cholesterol artificially using medications and statins bears the same risk of ICH as low cholesterol levels that occur naturally.

We lack sufficient power to examine the different types of lipid-lowering medications. Some studies have suggested that regardless of the initial level of cholesterol, treatment with statin agents may be beneficial to preventing cardiovascular disease. With increased sample size in the future, we may be able to examine the importance of different agents in the variability of response.

Cerebral amyloid angiopathy (CAA) is a pathophysiologic finding of both ICH and Alzheimer disease and has been found to occur almost exclusively in lobar regions of the brain. ApoE alleles have been associated with CAA, lobar ICH, and Alzheimer disease. It should be noted that statin use has been associated with a decreased risk of Alzheimer disease but unlike ICH, hypercholesterolemia is associated with an increased risk of Alzheimer disease. If the mechanism of the purported effect of statins on reducing Alzheimer disease is through cerebral amyloid angiopathy, one would expect that the statin effect would be greater for lobar rather than nonlobar ICH. We found that the use of statins and a history of hypercholesterolemia had similar rates for both lobar and nonlobar ICH, suggesting that statin use affects an overall risk of ICH rather than one mediated predominately through CAA.

Previous studies have demonstrated that the apoE genotype of a subject may determine their responsiveness to statin...
treatment. Orlov et al reported that patients with apoE2 were more likely to lower their cholesterol level if using a statin agent, and that those with an E4 allele were less likely to respond to a statin agent compared with those with an E3 allele, which was similar to findings by other investigators. 

In contrast, Sanlelly was unable to confirm that apoE affected cholesterol levels according to statin use. 

In further analysis of our data, we sought to determine if the presence of an E2 allele or an E4 allele altered the decreased association with ICH that we identified in multivariate analysis. However, our sample size of apoE2 or apoE4 allele was too small to identify significant relationships. The analysis did reveal that the decreased association with ICH was most strong among those with an apoE3/E3 genotype. The finding of a decreased association with statin use and apoE3/E3 genotype was true for both lobar ICH and nonlobar ICH. Because nonlobar ICH cases may have few cases of CAA, the mechanism of association with decreased risk is unlikely to be mediated through CAA alone.

In conclusion, hypercholesterolemia was associated with a lower risk of ICH. We have not found an increased risk of ICH with the widespread use of statins in our population. Yet given the lack of cholesterol levels with the current study, further studies are needed to determine if lower cholesterol levels secondary to statin use bear the same risk as low cholesterol levels for ICH.

Acknowledgments

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References

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