No Relationship of Lipid-Lowering Agents to Hematoma Growth
Pooled Analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials Studies

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Background and Purpose—Controversy persists over statins and risk of intracerebral hemorrhage. We determined associations of premorbid lipid-lowering therapy and outcomes among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT).

Methods—The pooled data of INTERACT 1 and 2 (international, multicenter, prospective, open, blinded end point, randomized controlled trials of patients with intracerebral hemorrhage [<6 hours] and elevated systolic blood pressure) were analyzed with regard to associations of baseline lipid-lowering treatment and clinical outcomes of 3184 participants in a multivariate model. Associations of lipid-lowering therapy and hematoma growth (baseline to 24 hours) were estimated in ANCOVA.

Results—Among 204 patients (6.5%) with baseline lipid-lowering treatment, 90-day clinical outcomes were not significantly different after adjustment for confounding variables including region and age. In the computed tomographic substudy, 24-hour hematoma growth was greater in 124 patients (9%) with, compared with those without, prior lipid-lowering therapy. However, this association was not significant between groups (9.2 versus 6.8 mL; \( P < 0.13 \)), after adjustment for prior antithrombotic therapy.

Conclusions—No independent associations were found between lipid-lowering medication and adverse outcomes in patients with intracerebral hemorrhage.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00226096 and NCT00716079.

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Key Words: cerebral hemorrhage, statins, HMG-CoA

Lipid-lowering therapy with 3-hydroxy-3-methyl-glutaryl-CoA enzyme (HMG-CoA) reductase inhibitors (statins) is a proven effective treatment for prevention of ischemic vascular events. Controversy persists over whether statins increase the risk of intracerebral hemorrhage (ICH). A recent systematic overview of randomized trials found no association of statins and the risk of ICH,1 but no study has examined their association with hematoma growth which may be promoted by ancillary mechanisms, such as inhibition of platelet aggregation and thrombogenesis.7,8 We examined associations of lipid-lowering therapy, mainly with statins, and hematoma growth and clinical outcomes in participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT).

Methods
Details of the INTERACT 1 and 2 studies are outlined elsewhere.9 In summary, these were international, multicenter, open, blinded end point, randomized controlled trials with a common protocol that collectively compromised 3243 patients with spontaneous ICH (<6 hours of onset) and elevated systolic blood pressure (150–220 mm Hg) randomly allocated to receive intensive or guideline-based blood pressure management. In predefined computed tomographic substudies, 1310 consecutive patients underwent 24 hour repeat computed tomography. Demographics, clinical characteristics, and medical history including current medications including use of any lipid-lowering therapy including statins, were recorded at the time of enrolment. ICH severity was measured using the Glasgow Coma Scale and National Institutes of Health Stroke Scale at baseline, 24 hours, and day 7 (or earlier on hospital discharge).

The primary clinical outcome was death or major disability (or dependency), defined as a score of 3 to 6 on the modified Rankin Score
at 90 days. Secondary outcome included absolute growth of hematoma volume at 24 hours.

Associations of prior use of lipid-lowering therapy and absolute increase in hematoma volume for 24 hours were assessed by an ANCOVA. Effects on functional outcome stratified analysis with c-statistics (area under receiver operating curve) were applied to assess for multicollinearity across variables. All data were analyzed using SAS version 9.3 (SAS Institute).

Results
There were 3184 participants included in the analyses, with 204 (6.5%) on lipid-lowering therapy at the time of ICH. Crude analysis showed that the lipid-lowering group had a higher case fatality (20.6% versus 11.3%; \( P < 0.0001 \)), dependency (47.5% versus 40.7%; \( P = 0.06 \)), and combined mortality or dependency (68.1% versus 52.1%; \( P < 0.0001 \)). However, Table 1 shows these associations were no longer significant, mortality (\( P = 0.67 \)), dependency (\( P = 0.72 \)), and mortality and dependency (\( P = 0.79 \)), after adjustment for the covariates, in particular region and age. Stratified analysis showed no significant differences in the effects of lipid-lowering therapy on death or dependency (\( P = 0.281 \) for homogeneity). In a multivariate model that included age, region, and anticoagulants, antiplatelet therapy, time from onset to computed tomography, hematoma volume, and location of hematoma at baseline, achieved systolic blood pressure (1–24 hours) and trial.

Table 1. Lipid-Lowering Treatment on Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Lipid Lowering (n=204)</th>
<th>No Lipid Lowering (n=2980)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or dependency</td>
<td>139 (68.1)</td>
<td>1552 (52.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>42 (20.6)</td>
<td>338 (11.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dependency</td>
<td>97 (47.5)</td>
<td>1214 (40.7)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Data are numbers (%).

*Adjusted for age, region, and oral anticoagulants, antiplatelet therapy, time from onset to computed tomography, hematoma volume, and location of hematoma at baseline, achieved systolic blood pressure (1–24 hours) and trial.

Discussion
This study found no difference in clinical outcomes, initial ICH volume, or 24-hour hematoma volume growth between patients with and without lipid-lowering therapy at the time of acute ICH.

The main confounder variables were age and region for clinical outcomes and antithrombosis for ICH volume growth. Lipid-lowering agents are often used concurrently with antithrombosis in patients with cardiovascular disease; few patients take lipid-lowering therapy in isolation.

Despite being the largest ICH study to date, it might still be underpowered to demonstrate a small independent effect of statins on hematoma growth or other major outcomes. Although the use of lipid-lowering agents was low in INTERACT, with two thirds of patients included from China and selected according to the clinical trial criteria, the large and heterogeneous population with prospectively collected and standardized outcome measures allowed a robust examination of associations in a broad range of patients. A weakness of the analysis is the absence of information on the specific type of lipid-lowering medication used. The common hypothesis that lipid-lowering agents might promote hematoma growth and adverse functional outcomes was not confirmed in our study. Most recently, Flint et al\(^{10}\) concluded that statins may improve 30-day outcomes in ICH based on a retrospective study. Our study provided a broader assessment of outcomes including hematoma growth and takes account of a number of confounders, most importantly of antithrombotic medication, but we are not able to assess any potential interacting effects of neuroprotection and promotion of ICH growth. Further studies are required to determine these and other specific effects. The main focus of our analysis was

Table 2. Lipid-Lowering Treatment and Hematoma Growth

<table>
<thead>
<tr>
<th></th>
<th>Lipid Lowering (n=124)</th>
<th>No Lipid Lowering (n=1185)</th>
<th>Difference (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>7.2 (1.3 to 4.6)</td>
<td>3.0 (0.4 to 2.1)</td>
<td>4.2 (7.0 to 1.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>9.2 (1.7 to 5.9)</td>
<td>6.8 (1.4 to 4.1)</td>
<td>2.4 (5.4 to −0.7)</td>
<td>0.130</td>
</tr>
</tbody>
</table>

Data are mL and 95% CI. CI indicates confidence interval.

*Adjusted for age, region, and oral anticoagulants, antiplatelet therapy, time from onset to computed tomography, hematoma volume, and location of hematoma at baseline, achieved systolic blood pressure (1–24 hours) and trial.
on the overall safety of lipid-lowering agents in the event of ICH and confirmation of a net benefit of these agents which have been established in prevention of ischemic strokes.

In conclusion, lipid-lowering therapy was not associated with adverse clinical outcomes including increased cerebral bleeding in patients with acute ICH.

Acknowledgments
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Disclosures
Dr Arima holds an Australian Research Council Future Fellowship. Dr Anderson holds a Senior Principal Research Fellowship of the National Health and Medical Research Council of Australia, has speaking engagements with Covidien and Takeda China, and is a member of Advisory Boards for Pfizer and The Medicines Company. M. Krause was a member of the Advisory Board for Boehringer-Ingelheim. The other authors report no conflicts.

References
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