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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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) in computed tomographic substudies participants (n=1310) 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.

Keywords: cerebral hemorrhage • statins, HMG-CoA

Received October 2, 2014; final revision received December 3, 2014; accepted January 6, 2015.

* A list of all INTERACT Investigators is given in the online-only Data Supplement.

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.007664
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 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 antithrombotics for ICH volume growth. Lipid-lowering agents are often used concurrently with antithrombotics 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[9] 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 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.

**Table 2. Lipid-Lowering Treatment and Hematoma Growth**

<table>
<thead>
<tr>
<th>Hematoma Growth</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
All authors contributed to the study rationale and interpretation of the results. Dr Arima contributed to data analysis. All authors participated in the drafting and approval of the final manuscript and take responsibility for the content and interpretation of this article.

Sources of Funding
The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial studies were funded by the National Health and Medical Research Council of Australia.

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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Stroke. published online February 5, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/02/05/STROKEAHA.114.007664

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/02/05/STROKEAHA.114.007664.DC1

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