Statins and Intracerebral Hemorrhage
Collaborative Systematic Review and Meta-Analysis

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Background—A recent large, randomized trial suggested that statins may increase the risk of intracerebral hemorrhage. Accordingly, we systematically reviewed the association of statins with intracerebral hemorrhage in randomized and observational data.

Methods and Results—We screened 17 electronic bibliographic databases to identify eligible studies and consulted with experts in the field. We used DerSimonian-Laird random-effects models to compute summary risk ratios with 95% confidence intervals. Randomized trials, cohort studies, and case-control studies were analyzed separately. Only adjusted risk estimates were used for pooling observational data. We included published and unpublished data from 23 randomized trials and 19 observational studies. The complete data set comprised 248,391 patients and 14,784 intracerebral hemorrhages. Statins were not associated with an increased risk of intracerebral hemorrhage in randomized trials (risk ratio, 1.10; 95% confidence interval, 0.86–1.41), cohort studies (risk ratio, 0.94; 95% confidence interval, 0.81–1.10), or case-control studies (risk ratio, 0.60; 95% confidence interval, 0.41–0.88). Substantial statistical heterogeneity was evident for the case-control studies (I² = 66%, P = 0.01), but not for the cohort studies (I² = 0%, P = 0.48) or randomized trials (I² = 30%, P = 0.09). Sensitivity analyses by study design features, patient characteristics, or magnitude of cholesterol lowering did not materially alter the results.

Conclusions—We found no evidence that statins were associated with intracerebral hemorrhage; if such a risk is present, its absolute magnitude is likely to be small and outweighed by the other cardiovascular benefits of these drugs. (Circulation. 2011;124:00-00.)

Key Words: cerebrovascular disorders ■ hemorrhage ■ meta-analysis ■ statins

Statins prevent cardiovascular events in both primary and secondary prevention settings. An updated overview of randomized data from the Cholesterol Treatment Trials’ Collaboration found that statins reduced the risk of major vascular events by 22% (95% confidence interval [CI], 0.76–0.80).1 Conversely, a large, randomized trial in patients with cerebrovascular disease suggested increased risk for a study-defined end point of hemorrhagic stroke in patients

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receiving atorvastatin versus placebo (hazard ratio, 1.66; 95%
CI, 1.08–2.55). This finding, the result of a post hoc
analysis, has led to some uncertainty regarding the balance of
benefits and risks of statins, particularly in patients with a
history of cerebrovascular disease.

Clinical Perspective on p ●●●

Several mechanisms might explain an association between
statins and intracerebral hemorrhage. Statins are at least
mildly antithrombotic agents that inhibit platelet aggregation,
enhance fibrinolysis, and reduce thrombosis. In a recent large
primary prevention trial, rosuvastatin reduced the risk of
venous thromboembolism by 43% (hazard ratio, 0.57; 95%
CI, 0.37–0.86), with reductions in both provoked and unprovoked thrombosis. In addition, cholesterol may be
essential for blood vessel integrity in the brain. Intracerebral
hemorrhage is thought to arise from small breaks in
the walls of perforator arteries that branch orthogonally
from major cerebral vessels; intraparenchymal bleeding
may occur when the clotting system is unable to compensate
for these disruptions.

Given these issues, we performed a comprehensive sys-
tematic review and meta-analysis of all available data, both
published and unpublished, of the association of statins with
intracerebral hemorrhage. Because of the widespread use of
statins in the general community, we analyzed both random-
ized and observational data to accumulate a broad range of
typical settings and statin regimens.

Methods

Study Selection and Literature Search

We selected randomized trials and observational studies (regardless
of language, publication status, and sample size) that included data
on the frequency of intracerebral hemorrhage and statin exposure.
Most studies defined intracerebral hemorrhage as intraparenchymal
brain hemorrhage confirmed by neuroimaging or autopsy; however,
we also included studies that defined intracerebral hemorrhage using
International Classification of Disease diagnosis codes (which have
been shown to be accurate for this end point). We excluded articles
that aggregated statins with other lipid-lowering classes (although we
contacted authors to inquire whether a separate analysis of statins
was available). We excluded studies focused solely on intracranial
hemorrhage after intravenous or intra-arterial thrombolysis for acute
ischemic stroke. All studies were adjudicated by 2 independent
reviewers (D.G.H. and M. Mrkobrada), with disagreements resolved
during discussion and consensus.

We used a multistep approach to find studies. First, we searched
17 electronic bibliographic databases from inception until June 1,
2011: Cardiosource Clinical Trials, Cochrane Central Register of
Controlled Trials, Cochrane Health Technology Assessment Data-
base, Database of Abstracts of Reviews of Effects, European
Medicines Agency Web site, Excerpta Medica, Healthstar, Interna-
tional Standard Randomized Controlled Trial Number Register,
Medline, NIH www.ClinicalTrials.gov, OVID Full Text Journals,
PreMedline, Stroke Trials Registry, UpToDate Online, US Food
and Drug Administration Web site, Web of Science With Con-
fERENCE Proceedings, and What’s What Online. We adapted search
terms to each database and updated the search during the analysis
phase using automated e-mail alerts (Table I in the online-only
Data Supplement).

Second, we used the “find similar” and “find citing articles”
functions in bibliographic databases to locate related articles. Third,
we manually screened bibliographies of statin product monographs,
review articles, eligible primary studies, treatment guidelines, and
previous meta-analyses. Fourth, we reviewed abstract proceedings of
cardiology, neurology, and endocrinology meetings that had not yet
been indexed in bibliographic databases. Finally, we contacted
authors of studies that reported rates of statin exposure and intrace-
rebral hemorrhage in their publications but did not report an
exposure-outcome association; we successfully obtained these data
in >90% of cases.

Data Abstraction

We used a pilot-tested data abstraction form to extract information
from each study, compiling data in an electronic spreadsheet with
double data entry. We extracted details on sample setting, statin
regimen (agents and dosing), duration of follow-up, events, and
methodological quality. For randomized trials, we recorded the
number of events and patients at risk in each arm using an
intention-to-treat framework and computed risk ratios (RRs) for each
study, which were subsequently pooled. For observational studies,
we recorded adjusted effect estimates and 95% CIs for the associa-
tion of statins with intracerebral hemorrhage; CIs were converted to
SEs with standard formulas.

We used the Jadad scale to measure methodological quality for
randomized trials with points recorded for randomized sequence
generation, blinding, and description of withdrawals and dropouts;
we also recorded loss to follow-up and requested such data from
authors when it was not available. We used the Downs and Black
scale to measure methodological quality for observational studies,
again requesting clarification from authors for missing details. The
scale includes items on quality of reporting, external validity,
internal validity, and statistical power. We also reviewed design
articles and secondary reports to supplement our measurement of
methodological quality. We converted the Downs-Black and Jadad
scales to a common unweighted fraction ranging from 0 to 1.0 for
use in meta-regression.

Statistical Analyses

We performed a DerSimonian-Laird random-effects meta-analysis to
pool effect estimates across studies. We reported summary effects as
RRs with 95% CIs. We assessed heterogeneity using the I² statistic.
Descriptive statistics were expressed as medians with interquartile
ranges (IQRs).

In the primary analysis, we reported separate pooled estimates for
randomized trials, cohort studies, and case-control studies. We
analyzed the single available case-crossover study together with the
cohort studies, given the reduced vulnerability of case-crossover
studies to confounding by patient characteristics. We tested for
publication bias by inspecting funnel plots and performing Begg and
Mazumdar rank correlation tests for each of the 3 major study
designs.

Sensitivity Analyses

We prespecified several additional analyses to assess the robustness
of our results and to explore potential sources of heterogeneity. First,
we tested the effect of removing 1 study at a time on the pooled RR
for each of the 3 main study designs. The purpose of this analysis
was to check whether individual studies (such as Stroke Prevention
by Aggressive Reduction in Cholesterol Levels [SPARCL]) unduly
influenced overall results. Second, we repeated the primary analysis
using a fixed-effects model. The purpose of this analysis was to
assess the influence of statistical heterogeneity on the overall
findings by comparing the result with the more conservative random-
effects model.

Third, we examined whether effect estimates varied according to
several predefined study characteristics, namely length of follow-up,
methodological quality (modeled as a fraction as noted above), trial
epoch (the midpoint of accrual), disease incidence (the control group
event rate), statin efficacy (the absolute difference in low-density
lipoprotein [LDL] cholesterol between treated and untreated patients and the achieved on-treatment LDL level), statin type (the 6 different types of statins), sample origin (Western, Asian, or mixed), and prevention status (modeled as primary or secondary prevention, ie, patients with or without a history of cardiovascular disease at study entry, and separately modeled according to history of cerebrovascular disease). We tested follow-up duration and disease incidence in randomized trials and cohort studies only because these metrics were not applicable to case-control or crossover studies. Reduction in LDL cholesterol achieved and statin type were modeled only for randomized trials because these variables were not available from any observational study. We performed these analyses using univariate random-effects meta-regression with the logarithm of the RR as the outcome variable. Finally, as a test of consistency, we assessed the impact of statins on total and ischemic stroke for the randomized trials (n=110055). We deemed P<0.05 as statistically significant. We used Comprehensive Meta Analysis 2.0 (Englewood, NJ) for all analyses.

Search Results
We identified 3340 article citations for screening of titles, abstracts, and keywords (Figure 1). From these, we retrieved 237 articles in full for further consideration. After applying our selection criteria, we included 42 studies: 23 randomized trials2,3,7–28 and 19 observational studies.29–47 The authors of 14 reports provided outcome data not available in published form (specifically intracerebral hemorrhage in relation to statin exposure); in addition, 42 design articles, secondary reports, and other documents provided supplementary information on study methodology or variables related to treatment, follow-up, events, or sample characteristics (see the References section in the online-only Data Supplement). The complete data set included 248 391 patients and 14 784 intracerebral hemorrhages. Concordance for methodological quality between reviewers (DGH and MM) was excellent (Cohen’s κ=0.88).

Randomized Trials
The 23 randomized trials provided a cumulative total of 526 518 patient-years of follow-up with a median follow-up per trial of 3.9 years (IQR, 2.8–5.0 years; Table 1). Most trials (n=21, 91%) had Jadad scores of ≥3; only 2 had a lower Jadad rating.27,28 Few patients were lost to follow-up (median, 0.09%; IQR, 0.01%–0.46%). The median LDL cholesterol reduction achieved was 1.03 mmol/L (IQR, 0.93–1.36 mmol/L). Trials were evenly split into primary prevention settings (48%) and secondary prevention settings (52%). The summary random-effects RR was 1.10 (95% CI, 0.86–1.41; I²=30%; Figure 2). The equivalent absolute risk increase was 0.027% (95% CI, −0.042 to 0.096). We found no evidence of publication bias (Figure I in the online-only Data Supplement; P=0.67 for Begg and Mazumdar rank correlation test). We found reductions in total stroke (RR, 0.85; 95% CI, 0.78–0.93; I²=40%) and ischemic stroke (RR, 0.83; 95% CI, 0.75–0.92; I²=37%).

Observational Studies
The 19 observational studies (n=117 948 patients) included 12 cohort studies, 6 case-control studies, and 1 case-crossover study (Table 2). The cohort studies provided a total of 219 459 patient-years of follow-up (median, 3.0 years; IQR, 1.4–4.1 years). The median Downs and Black score was 21 points (IQR, 18–22), with studies typically losing points for “comprehensive description of adverse events,” “masking of study subjects,” and “statistical power.” The pooled cohort and case-control RRs were 0.94 (95% CI, 0.81–1.10; I²=0%) and 0.60 (95% CI, 0.41–0.88; I²=66%; Figure 3), respectively. The latter suggests substantial heterogeneity for the case-control data. We found no compelling evidence of publication bias (P=0.67 for cohort studies and P=0.06 for case-control studies; Figures II and III in the online-only Data Supplement). We found no association between statins and...
Table 1. Descriptive Characteristics of the Randomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>ICH, n</th>
<th>Follow-Up, y</th>
<th>Population or Setting</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>1255</td>
<td>13</td>
<td>4.0</td>
<td>Subjects with type 2 diabetes mellitus receiving maintenance hemodialysis</td>
<td>5</td>
</tr>
<tr>
<td>ACAPS</td>
<td>919</td>
<td>3</td>
<td>2.8</td>
<td>Asymptomatic patients with subclinical atherosclerosis and dyslipidemia</td>
<td>4</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>6605</td>
<td>1</td>
<td>5.2</td>
<td>Patients with normal or mildly elevated total and LDL cholesterol, low HDL cholesterol, and no clinically evident atherosclerotic disease</td>
<td>4</td>
</tr>
<tr>
<td>ALERT</td>
<td>2102</td>
<td>27</td>
<td>6.7</td>
<td>Patients with renal transplants, stable graft function, receiving cyclosporine</td>
<td>4</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>10 355</td>
<td>22</td>
<td>4.8</td>
<td>Patients with hypertension and at least 1 other risk factor for coronary heart disease</td>
<td>3</td>
</tr>
<tr>
<td>ASCOT</td>
<td>10 305</td>
<td>31</td>
<td>3.3</td>
<td>Hypertensive patients with at least 3 other cardiovascular risk factors</td>
<td>5</td>
</tr>
<tr>
<td>ASPEN</td>
<td>2410</td>
<td>6</td>
<td>4.0</td>
<td>Mainly primary prevention patients with type 2 diabetes mellitus</td>
<td>4</td>
</tr>
<tr>
<td>AURORA</td>
<td>2776</td>
<td>43</td>
<td>3.8</td>
<td>Patients receiving maintenance hemodialysis</td>
<td>4</td>
</tr>
<tr>
<td>Bone et al</td>
<td>626</td>
<td>1</td>
<td>1.0</td>
<td>Postmenopausal women with mild hypercholesterolemia</td>
<td>5</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>8</td>
<td>5.0</td>
<td>Patients with myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>CLAPT</td>
<td>226</td>
<td>1</td>
<td>2.0</td>
<td>Men scheduled to undergo elective coronary angioplasty</td>
<td>2</td>
</tr>
<tr>
<td>CORONA</td>
<td>5011</td>
<td>24</td>
<td>2.7</td>
<td>Chronic ischemic heart failure</td>
<td>5</td>
</tr>
<tr>
<td>GISSI-HF</td>
<td>4574</td>
<td>14</td>
<td>3.9</td>
<td>Chronic heart failure (regardless of cause)</td>
<td>5</td>
</tr>
<tr>
<td>GISSI-PD</td>
<td>4271</td>
<td>1</td>
<td>2.0</td>
<td>Patients with recent acute myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>GREACE</td>
<td>1600</td>
<td>2</td>
<td>3.0</td>
<td>Patients with established CAD</td>
<td>3</td>
</tr>
<tr>
<td>HPS</td>
<td>20 536</td>
<td>104</td>
<td>5.0</td>
<td>Patients with coronary disease, other occlusive vascular disease, or diabetes mellitus</td>
<td>5</td>
</tr>
<tr>
<td>JUPITER</td>
<td>17 802</td>
<td>15</td>
<td>1.9</td>
<td>Asymptomatic patients with elevated C-reactive protein</td>
<td>4</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>26</td>
<td>6.1</td>
<td>Patients with coronary artery disease</td>
<td>4</td>
</tr>
<tr>
<td>MEGA</td>
<td>7832</td>
<td>35</td>
<td>5.3</td>
<td>Asymptomatic patients with hypercholesterolemia</td>
<td>3</td>
</tr>
<tr>
<td>MIRACL</td>
<td>3086</td>
<td>3</td>
<td>0.3</td>
<td>Patients with recent acute coronary syndrome</td>
<td>4</td>
</tr>
<tr>
<td>PROSPER</td>
<td>5804</td>
<td>18</td>
<td>3.2</td>
<td>Elderly patients with vascular disease or risk factors for vascular disease</td>
<td>5</td>
</tr>
<tr>
<td>SPARCL</td>
<td>4731</td>
<td>88</td>
<td>4.9</td>
<td>Patients with a history of stroke or TIA</td>
<td>4</td>
</tr>
<tr>
<td>SSSS</td>
<td>4444</td>
<td>41</td>
<td>5.4</td>
<td>Patients with coronary artery disease</td>
<td>5</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CAD, coronary artery disease; TIA, transient ischemic attack; 4D, Deutsche Diabetes-Dialyse-Studie; ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of Lescol in Renal Transplantation; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ASPEN, Atorvastatin Study in Prevention of Coronary Heart Disease Endpoints in Non-insulin-Dependent Diabetes Mellitus; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis; CARE, Cholesterol and Recurrent Events; CLAPT, Cholesterol Lowering Atherosclerosis PTCA trial; CORONA, Controlled Rosuvastatin in Multinational Trial in Heart Failure; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico–Heart Failure; GISSI-PD, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico–Prevention; GREACE, Greek Atorvastatin and Coronary-Heart-Disease Evaluation; HPS, Heart Protection Study; JUPITER, Justification for the Use of Statins in Prevention of Cardiovascular Disease With Pravastatin in Japan; MIRACL, Myocardial Ischemia Reduction with Acute Cholesterol Lowering; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; and SSSS, Scandinavian Simvastatin Survival Study.

*Extended follow-up.

Sensitivity Analyses

Omission of 1 study at a time suggested that no single randomized trial had a major influence on the summary RR for the randomized data (Figure IV in the online-only Data Supplement); in addition, the fixed-effects model gave nearly identical results (pooled RR, 1.12; 95% CI, 0.93–1.34). Similar findings were noted for the cohort studies (Figure V in the online-only Data Supplement; pooled fixed-effect model: RR, 0.94; 95% CI, 0.81–1.10). No single study appeared to influence the aggregate case-control data (Figure VI in the online-only Data Supplement), and the fixed-effects model for case-control studies continued to suggest a protective (albeit attenuated) association (RR, 0.81; 95% CI, 0.71–0.91).

In meta-regression of all 42 studies, we found no association between effect size and study region (P = 0.23), patient prevention status (P = 0.36), history of cerebrovascular disease (P = 0.09), methodological quality (P = 0.27), or study epoch (P = 0.80). Among all longitudinal studies (cohorts and randomized trials), we found no influence of study duration (P = 0.17) or baseline event rate (P = 0.96). Finally, among the randomized trials, we found no association between intrace-
rebral hemorrhage and the degree of LDL lowering achieved (P=0.91), on-treatment LDL (P=0.90), or the type of statin used (P=0.53).

**Discussion**

Our extensive meta-analysis of published and unpublished evidence was unable to discern a significantly increased risk for intracerebral hemorrhage in relation to statins. The lack of harmful association was consistent in both randomized and nonrandomized studies, was independent of study quality, and was maintained across epoch, setting, and baseline risk. There was also no suggestion that greater degrees of cholesterol lowering were associated with greater risks of intracerebral hemorrhage. Aggregated data from the randomized trials demonstrated reductions in total and ischemic strokes.

Although concerns regarding the association of low cholesterol and brain hemorrhage were first recorded several decades ago, the recent SPARCL trial was the first major signal of risk linking statin therapy with this complication. As noted by the investigators of this trial, “hemorrhagic stroke” was a post hoc end point that was not specified during the trial design. Within hemorrhagic stroke, investigators did not differentiate between subarachnoid and intracerebral hemorrhage; furthermore, rates of fatal hemorrhagic stroke were not increased in SPARCL. It is possible that this association was due to chance alone; the main trial article presents 49 distinct statistical analyses. Among 11 studies (including SPARCL) exclusively enrolling patients with cerebrovascular disease, we found no evidence that statins selectively increased the risk of intracerebral hemorrhage (RR, 1.03; 95% CI, 0.82–1.30; Figure 4).

Of interest, the 6 case-control studies reported here suggest an inverse association between statins and intracerebral hemorrhage, although there was substantial statistical heterogeneity (I²=66%). This may be due to healthy user bias because...
Table 2. Descriptive Characteristics of the Observational Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>ICH, n</th>
<th>Follow-Up, y</th>
<th>Design</th>
<th>Population or Setting</th>
<th>Downs and Black Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arima et al\textsuperscript{30}</td>
<td>6103</td>
<td>111</td>
<td>3.9</td>
<td>Cohort</td>
<td>History of stroke or transient ischemic attack in the past 5 y</td>
<td>22</td>
</tr>
<tr>
<td>Bhatt et al\textsuperscript{29}</td>
<td>15 603</td>
<td>41</td>
<td>2.3</td>
<td>Cohort</td>
<td>Documented vascular disease or at high risk of having disease owing to multiple risk factors</td>
<td>21</td>
</tr>
<tr>
<td>Bushnell et al, 2004\textsuperscript{31}</td>
<td>2763</td>
<td>13</td>
<td>4.1</td>
<td>Cohort</td>
<td>Postmenopausal women with coronary artery disease</td>
<td>21</td>
</tr>
<tr>
<td>Bushnell et al, 2006\textsuperscript{32}</td>
<td>22 943</td>
<td>18</td>
<td>0.3</td>
<td>Cohort</td>
<td>Patients with coronary or extracoronary vascular disease</td>
<td>17</td>
</tr>
<tr>
<td>Capampangan et al\textsuperscript{33}</td>
<td>167</td>
<td>43</td>
<td>NA</td>
<td>Case-control</td>
<td>Acute ICH or ischemic stroke patients</td>
<td>14</td>
</tr>
<tr>
<td>Chang et al\textsuperscript{34}</td>
<td>9456</td>
<td>9456</td>
<td>NA</td>
<td>Case-crossover</td>
<td>Acute hemorrhagic or ischemic stroke patients</td>
<td>23</td>
</tr>
<tr>
<td>Chen et al\textsuperscript{35}</td>
<td>6504</td>
<td>118</td>
<td>3.0</td>
<td>Cohort</td>
<td>Adults without prior statin therapy admitted for first acute ischemic stroke or transient ischemic attack</td>
<td>24</td>
</tr>
<tr>
<td>Douketis et al\textsuperscript{36}</td>
<td>3509</td>
<td>319</td>
<td>NA</td>
<td>Case-control</td>
<td>Atrial fibrillation patients receiving warfarin</td>
<td>18</td>
</tr>
<tr>
<td>FitzMaurice et al\textsuperscript{37}</td>
<td>229</td>
<td>26</td>
<td>1.9</td>
<td>Cohort</td>
<td>ICH patients</td>
<td>21</td>
</tr>
<tr>
<td>Gregoire et al\textsuperscript{39}</td>
<td>76</td>
<td>49</td>
<td>NA</td>
<td>Case-control</td>
<td>ICH or age/sex-matched control subjects with ischemic stroke or transient ischemic attack</td>
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<tr>
<td>Hackam et al\textsuperscript{40}</td>
<td>17 872</td>
<td>213</td>
<td>4.2</td>
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<td>Acute ischemic stroke patients</td>
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<td>Kennedy et al\textsuperscript{41}</td>
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<td>Hospital LOS</td>
<td>Cohort</td>
<td>Post-carotid endarterectomy for carotid stenosis</td>
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<tr>
<td>Sasaki et al\textsuperscript{42†}</td>
<td>3853</td>
<td>19</td>
<td>5.1</td>
<td>Cohort</td>
<td>Adult men with hypercholesterolemia</td>
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<tr>
<td>Simon et al\textsuperscript{43}</td>
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<td>Tirschwell et al\textsuperscript{44}</td>
<td>8010</td>
<td>217</td>
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<td>Members of a health maintenance organization who either had drug-treated hypertension or were postmenopausal women</td>
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<td>Stroke patients (secondary analysis of JASAP randomized trial)</td>
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<td>554</td>
<td>188</td>
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<td>ICH patients</td>
<td>21</td>
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ICH indicates intracerebral hemorrhage; LOS, hospital length-of-stay; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; HERS, Heart Estrogen–Progestin Replacement Study; BRAVO, Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion; SYMPHONY, Sibrafiban vs Aspirin to Yield Maximum Protection From Ischemic Heart Events Post-acute Coronary Syndromes; JASAP, Japanese Aggrenox Stroke Prevention vs Aspirin Programme.

*Of a total of 32 points.
†This study was classified as an observational study because randomization to statin versus control was strongly subverted.

More rigorous study designs involving cohort, case-crossover, or randomized allocation did not suggest a protective effect. Alternatively, the possibility of publication bias for the case-control data cannot be ruled out. Our effect estimate for randomized trials (OR, 1.10; 95% CI, 0.86–1.42) is similar to a slightly smaller subset of placebo-controlled trials (n = 20) reported by the Cholesterol Treatment Trialists (RR 1.04; 95% CI, 0.61–1.78).\textsuperscript{48} The safety of additional analysis of 6 high-intensity versus moderate-intensity statin regimens reported by the Cholesterol Treatment Trialists also found no significant evidence for a dose-response gradient (RR, 1.21; 95% CI, 0.85–1.71).\textsuperscript{1} In keeping with this, the SPARCL investigators reported that patients who achieved a minimum 50% reduction in LDL cholesterol were at no greater risk than patients whose LDL cholesterol increased or did not change during the trial (hazard ratio, 1.04; 95% CI, 0.61–1.78).\textsuperscript{48} The safety of achieving extremely low cholesterol levels within trial data sets has been corroborated by others.

Our analysis has at least 3 important limitations. First, we had no access to individual patient data; hence, all analyses were performed at the study level. There may be patient characteristics that selectively interact with statin therapy to increase the risk of intracerebral hemorrhage. Conversely, published analyses of the SPARCL data set found no interaction between statin therapy and 16 baseline variables in terms of risk for this event.\textsuperscript{48} A second major limitation is that poor adherence in observational settings may bias risk toward...
the null, although many of the observational studies included here categorized statin exposure using a time-sensitive classification.31,33–36,38,39,41,44,45 This issue was not problematic for the randomized trials, most of which reported high rates of adherence. Third, intracerebral hemorrhage is a heterogeneous entity with differing origins and risks of recurrence; most classification systems differentiate between deep and lobar intracerebral bleeding, subsets with markedly different rates of recurrence. As with SPARCL, our study does not contain sufficient granularity to determine whether there is a subtype of cerebral bleeding that is selectively increased by statins. In addition, our focus was on statins and risk for
intracerebral hemorrhage, not on hemorrhagic transformation of acute ischemic stroke in the setting of thrombolysis. Whether statins improve outcome in the aftermath of intracerebral hemorrhage is a question not directly answered by our data.

Conclusions
We found no association between statin exposure and intracerebral hemorrhage across a wide range of studies. This lack of association was remarkably consistent across settings, statin regimens, and study designs. Because risk factors for nonlobar intracerebral hemorrhage are similar to those for atherosclerotic events (including smoking, hypertension, obesity, and diabetes mellitus), clinicians should continue to use treatment algorithms that base the initiation of statins on each individual’s global risk for cardiovascular events.

Acknowledgments
We thank Boehringer Ingelheim for providing data from the Japanese Aggrenox Stroke Prevention Versus Aspirin Programme and Pfizer for confirming data on intracerebral hemorrhage in the Bone et al study.26 We are grateful to Donald Redelmeier, MD, MSHR, and Manav Vyas, MBBS, for providing helpful comments on a previous draft of this manuscript.

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Disclosures
Dr Bhatt has received research grants from Astra Zeneca, Bristol-Myers Squibb, Eisai, Sanofi-aventis, and The Medicines Company. Dr Psaty serves on a data and safety monitoring board for a clinical trial funded by Zoll LifeCor. Dr Newby reports no direct conflicts of interest with the content of this paper; a full disclosure of her support from Sanofi-Aventis and Bayer and honoraria from AstraZeneca, Roche, Glaxo Smith Kline, DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.


References


A large, randomized trial of statin therapy in patients with cerebrovascular disease suggested increased risk in a post hoc end point of hemorrhagic stroke. We conducted an extensive systematic review and meta-analysis of published and unpublished data sources to determine whether statin use is associated with an increased risk of intracerebral hemorrhage. The review comprised 42 studies (23 randomized trials and 19 observational studies). Analyzing the data by study design, we found no signal of risk for intracerebral hemorrhage in either subset of studies (randomized or observational). Meta-regression found no association between statin-related risk of intracerebral hemorrhage and study region, history of cerebrovascular disease, methodological quality, or study epoch. We also found no association between intracerebral hemorrhage and the degree of cholesterol lowering achieved or the type of statin used. We found no evidence that statins increase the risk of intracerebral hemorrhage; if such a risk is present, it is likely to be small in magnitude and outweighed by the proven cardiovascular benefits of these drugs.
Statins and Intracerebral Hemorrhage: Collaborative Systematic Review and Meta-Analysis


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### Supplemental Table 1. Search strategy for electronic databases

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#2. (atorvastatin OR lipitor OR CI-981 OR CI981 OR liptonorm OR cerivastatin OR baycol OR lipobay OR rivastatin OR Certa OR compactin OR mevasatin OR ML236B OR ML 236B OR fluvastatin OR 6-methylcompactin OR mevacor OR MK803 OR MK 803 OR mevinolin OR monacolin K )  
#3. (monacolin K OR 6-methylcompactin OR meglutol OR pitavastatin OR pravastatin OR simvastatin OR zocor OR MK733 OR MK 733 OR L 654969 OR L654969) AND (bleed*[stemmed] OR hemorrhagic*[stemmed] OR haemorrhage*[stemmed] OR haemorrhagic*[stemmed])  
#4. (HMG* OR hydroxymethylglutaryl* OR "reductase inhibitor*" OR statin*)  
#5. MeSH descriptor Intracranial Hemorrhages explode all trees  
#6. (hemorr* or haemorr* or bleed*) AND(stroke or strokes or cerebral or intracerebral or cerebrovascular or cerebro* or intracranial or cranial or CNS or "central nervous system" or neurologic* or neuraxial or neuroaxial or brain or intraparenchymal or parenchymal)  
#7. (#1 OR #2 OR #3 OR #4) AND (#5 OR #6) |
| **European Medicines Agency**                 | "intracerebral haemorrhage" OR "intracerebral hemorrhage" OR "intracerebral bleed" OR "cerebral haemorrhage" OR "cerebral hemorrhage" OR "Cerebral bleed" OR "hemorrhagic stroke" OR "hemorrhagic stroke" OR "brain haemorrhage" OR "brain hemorrhage" OR "brain bleed" OR "central nervous system hemorrhage" OR "central nervous system bleed" OR "neuraxial hemorrhage" OR "neuraxial haemorrhage" OR "neuraxial bleed" OR "CNS hemorrhage" OR "CNS hemorrhage" OR "CNS bleed" OR "intraparenchymal hemorrhage" OR "intraparenchymal hemorrhage" OR "intraparenchymal bleed" OR "parenchymal hemorrhage" OR "parenchymal haemorrhage" OR "parenchymal bleed" |
| **OVID Databases (Excerpta Medica, Healthstar, Medline, OVID Full Text, PreMedline)** | 1. exp brain hematoma/ or exp brain hemorrhage/ or exp brain ventricle hemorrhage/ or exp cerebellum hemorrhage/  
2. exp hydroxymethylglutaryl coenzyme a reductase/ or exp hydroxymethylglutaryl
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Supplemental Figure 1. Funnel plot for randomized trials

Funnel Plot of Standard Error by Log Risk Ratio
Supplemental Figure 2. Funnel plot for cohort studies

Funnel Plot of Standard Error by Log Risk Ratio

Standard Error

Log risk ratio

0
1
2
3
-2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0
Supplemental Figure 3. Funnel plot for case-control studies
Supplemental Figure 4. Study exclusion plot (randomized trials)

The effect of removing one study at a time on the pooled risk ratio for intracerebral hemorrhage is displayed as a square. Confidence intervals (95%) are displayed as horizontal whiskers. The overall estimate is displayed as a diamond at the bottom. Data are plotted on a logarithmic scale.

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR (95% CI) with trial removed</th>
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<td>4D</td>
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<td>1.12 (0.87 to 1.43)</td>
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<tr>
<td>AFCAPS/TexCAPS</td>
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<td>ALLHAT</td>
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</tr>
<tr>
<td>ASCOT</td>
<td>1.17 (0.91 to 1.49)</td>
</tr>
<tr>
<td>ASPEN</td>
<td>1.09 (0.84 to 1.41)</td>
</tr>
<tr>
<td>AURORA</td>
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<td>Bone et al</td>
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<td>CARE</td>
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<td>CLAPT</td>
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<tr>
<td>CORONA</td>
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<td>MEGA</td>
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<td>MIRACL</td>
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<td>PROSPER</td>
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<tr>
<td>SPARCL</td>
<td>1.04 (0.80 to 1.35)</td>
</tr>
<tr>
<td>SSSS</td>
<td>1.08 (0.84 to 1.41)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.10 (0.86 to 1.42)</td>
</tr>
</tbody>
</table>
The effect of removing one study at a time on the pooled risk ratio for intracerebral hemorrhage is displayed as a square. Confidence intervals (95%) are displayed as horizontal whiskers. The overall estimate is displayed as a diamond at the bottom. Data are plotted on a logarithmic scale.
Supplemental Figure 6. Study exclusion plot (case-control studies)

<table>
<thead>
<tr>
<th>Trial</th>
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</thead>
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<td>Capampangan</td>
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</tr>
<tr>
<td>Douketis</td>
<td>0.53 (0.31 to 0.92)</td>
</tr>
<tr>
<td>Gregoire</td>
<td>0.70 (0.51 to 0.96)</td>
</tr>
<tr>
<td>Tirschwell</td>
<td>0.62 (0.41 to 0.96)</td>
</tr>
<tr>
<td>Verdel</td>
<td>0.51 (0.31 to 0.83)</td>
</tr>
<tr>
<td>Woo</td>
<td>0.67 (0.46 to 0.97)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.60 (0.41 to 0.88)</td>
</tr>
</tbody>
</table>

The effect of removing one study at a time on the pooled risk ratio for intracerebral hemorrhage is displayed as a square. Confidence intervals (95%) are displayed as horizontal whiskers. The overall estimate is displayed as a diamond at the bottom. Data are plotted on a logarithmic scale.
SUPPLEMENTAL REFERENCES

1. Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction. *Am J Cardiol* 1993;71:393-400.


23 Kennedy J, Quan H, Feasby TE, Ghali WA. An audit tool for assessing the appropriateness of carotid endarterectomy. *BMC Health Serv Res* 2004;4:17.


28 PROGRESS Management Committee. PROGRESS - Perindopril Protection Against Recurrent Stroke Study +: characteristics of the study population at baseline. *Journal of Hypertension* 1999;17.


