Vascular Medicine

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 We included published and unpublished data from 23 randomized trials and 19 observational studies.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;124:2233-2242.)

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

Statins prevent cardiovasular events in both primary and secondary prevention settings. An updated overview of randomized data from the Cholesterol Treatment Trialsists’ 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 2242**

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 systematic 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 randomized 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 through 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 Database, Database of Abstracts of Reviews of Effects, European Medicines Agency Web site, Excerpta Medica, Healthstar, International 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 Conference 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 intracerebral 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 association 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=1,1005). We deemed P<0.05 as statistically significant. We used Comprehensive Meta Analysis 2.0 (Englewood, NJ) for all analyses.

Results

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>4D11</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>ACAPS23</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/TexCAPS19</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>ALERT12</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>ALLHAT14</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>ASCOT13</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>ASPEN24</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>AURORA7</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 al16</td>
<td>626</td>
<td>1</td>
<td>1.0</td>
<td>Postmenopausal women with mild hypercholesterolemia</td>
<td>5</td>
</tr>
<tr>
<td>CARE20</td>
<td>4159</td>
<td>8</td>
<td>5.0</td>
<td>Patients with myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>CLAPT27</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>CORONA9</td>
<td>5011</td>
<td>24</td>
<td>2.7</td>
<td>Chronic ischemic heart failure</td>
<td>5</td>
</tr>
<tr>
<td>GISSI-HF8</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-P28</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>GREACE25</td>
<td>1600</td>
<td>2</td>
<td>3.0</td>
<td>Patients with established CAD</td>
<td>3</td>
</tr>
<tr>
<td>HPS16</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>JUPITER3</td>
<td>17 802</td>
<td>15</td>
<td>1.9</td>
<td>Asymptomatic patients with elevated C-reactive protein</td>
<td>4</td>
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<tr>
<td>LIPID18</td>
<td>9014</td>
<td>26</td>
<td>6.1</td>
<td>Patients with coronary artery disease</td>
<td>4</td>
</tr>
<tr>
<td>MEGA10</td>
<td>7832</td>
<td>35</td>
<td>5.3</td>
<td>Asymptomatic patients with hypercholesterolemia</td>
<td>3</td>
</tr>
<tr>
<td>MIRACL17</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>PROSPER21</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>SPARCL2</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>SSSS12</td>
<td>4444</td>
<td>11</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, DeutscheDiabetes-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 for 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: An Assessment of Survival and Cardiovascular Events; 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-P, 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.

*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.\(^2\) 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.\(^2\) 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 \((I^2=66\%)\). This may be due to healthy user bias because
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 (RR 1.12, 95% CI 0.93–1.35).1 Given the rarity of intracerebral hemorrhage relative to other cardiovascular events in most settings, a 10% to 12% increase in this outcome would be more than offset by reductions in a range of ischemic events. Even taking the upper limit of the 95% CI for the randomized trials summarized here, the absolute risk increase would be very small at 0.096% from nearly 4 years of treatment (equivalent to a number needed to treat to cause 1 additional bleed of 1044).

The intensity of cholesterol lowering did not correlate with risk for intracerebral hemorrhage in the randomized trials; an 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).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).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.49 A second major limitation is that poor adherence in observational settings may bias risk toward

<table>
<thead>
<tr>
<th>Table 2. Descriptive Characteristics of the Observational Studies</th>
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<tbody>
<tr>
<td>Study</td>
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<tr>
<td>-------</td>
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<tr>
<td>Arima et al30</td>
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<tr>
<td>Bhatt et al29</td>
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<tr>
<td>Bushnell et al, 200431</td>
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<tr>
<td>Bushnell et al, 200632</td>
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<tr>
<td>Capampangan et al33</td>
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<tr>
<td>Chang et al34</td>
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<tr>
<td>Chen et al35</td>
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<tr>
<td>Douketis et al36</td>
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<tr>
<td>FitzMaurice et al38</td>
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<tr>
<td>Gregoire et al39</td>
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<tr>
<td>Hackam et al46</td>
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<tr>
<td>Kennedy et al40</td>
</tr>
<tr>
<td>Sasaki et al41†</td>
</tr>
<tr>
<td>Simon et al42</td>
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<tr>
<td>Tirschwell et al42</td>
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<tr>
<td>Uchiyama et al47</td>
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<tr>
<td>Verdel et al43</td>
</tr>
<tr>
<td>Verzini et al44</td>
</tr>
<tr>
<td>Woo et al45</td>
</tr>
</tbody>
</table>

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-Progesterone 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.
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

<table>
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<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
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<td>0.97 (0.45 to 2.09)</td>
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</tr>
<tr>
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<td>6.6</td>
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<td>17.2</td>
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<tr>
<td>Verzini et al</td>
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<td>0.3</td>
</tr>
<tr>
<td>Overall</td>
<td>1.03 (0.82 to 1.30)</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 3. Meta-analysis of observational studies of statins and intracerebral hemorrhage. Random-effects meta-analysis with DerSimonian-Laird effect estimates. Data are plotted on a logarithmic scale. Individual study point estimates are shown as squares sized according to study precision; 95% confidence intervals (CIs) are shown as horizontal whiskers. Overall effects (with 95% CIs) are shown as diamonds for the case-control and cohort studies. RR indicates risk ratio.
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

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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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</tr>
</tbody>
</table>
| Cochrane Databases (Central, DARE, Health Technology Assessments, Systematic Reviews) | #1. MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees  
#2. (atorvastatin OR lipitor OR CI-981 OR CI981 OR lipotonorm OR cerivastatin OR baycol OR lipobay OR rivastatin OR Certa OR compactin OR mevastatin OR ML236B OR ML 236B OR fluvastatin OR lescol OR XU 62320 OR XU62320 OR fluindostatin OR lovastatin 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 nisvastatin OR itavastatin OR P 872441 OR P872441 OR NK 104 OR NK104 OR livalo OR pravastatin OR epistatin OR iliip OR RMS-431 OR RMS431 OR SQ 31000 OR SQ31000 OR vasten OR bristacol OR CS 514 OR CS514 OR lipemol OR mevalotin OR pravachol OR elisor OR selekline OR pravacol OR pravasin OR lipoapat OR red yeast rice OR cholestin OR rosuvastatin OR ZD4522 OR ZD 4522 OR crestor OR simvastatin OR zocor OR MK733 OR MK 733 OR L 654969 OR L654969)  
#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 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 haemorrhage" OR "CNS hemorrhage" OR "CNS bleed" OR "intraparenchymal haemorrhage" 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 |
coenzyme a reductase inhibitor/
3. 1 and 2
4. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
5. intracranial hemorrhages/ or exp intracerebral hemorrhage/ or exp basal ganglia hemorrhage/ or exp putaminal hemorrhage/ or exp intracranial hemorrhage, hypertensive/
6. 4 and 5
7. statins
8. statins OR atorvastatin OR simvastatin OR rosuvastatin OR cerivastatin OR pitavastatin OR lovastatin OR pravastatin OR statin
9. ((h?emorr$ or bleed$) adj2 (stroke or strokes or cerebral or intracerebral or cerebrovascular or cerebro$ or intracranial or cranial or CNS or "central nervous system" or neurologic$ or neuraxial or neuroaxial or brain or intraparenchymal or parenchymal)).mp.
10. (7 or 8) and 9
11. (statins or atorvastatin or simvastatin or rosuvastatin or cerivastatin or pitavastatin or lovastatin or pravastatin or statin or "HMG CoA reductase" or "hydroxymethylglutaryl").mp.
12. (11 or 7 or 8) and 10
13. 3 or 6 or 12

International Standard Randomised Controlled Trial Number Register
intracerebral haemorrhage OR intraintracerebral hemorrhage OR intracerebral bleed OR cerebral haemorrhage OR intracerebral hemorrhage OR Cerebral bleed OR haemorrhagic stroke OR hemorrhagic stroke OR brain haemorrhage OR brain hemorrhage OR brain bleed OR central nervous system haemorrhage OR central nervous system hemorrhage OR central nervous system bleed OR neuraxial hemorrhage OR neuraxial haemorrhage OR neuraxial bleed OR CNS haemorrhage OR CNS hemorrhage OR CNS bleed OR intraparenchymal hemorrhage OR intraparenchymal bleeding OR parenchymal hemorrhage OR parenchymal haemorrhage OR parenchymal bleed

ClinicalTrials.gov
Search Terms: intracerebral haemorrhage OR intraintracerebral hemorrhage OR intracerebral bleed OR cerebral haemorrhage OR intracerebral hemorrhage OR Cerebral bleed OR haemorrhagic stroke OR hemorrhagic stroke OR brain haemorrhage OR brain hemorrhage OR brain bleed OR central nervous system haemorrhage OR central nervous system hemorrhage OR central nervous system bleed OR neuraxial hemorrhage OR neuraxial haemorrhage OR neuraxial bleed OR CNS haemorrhage OR CNS hemorrhage OR CNS bleed OR intraparenchymal hemorrhage OR intraparenchymal bleeding OR parenchymal hemorrhage OR parenchymal haemorrhage OR parenchymal bleed
Interventions: statin OR statins OR hydroxymethylglutaryl OR HMG OR reductase inhibitor OR atorvastatin OR lipitor OR CI-981 OR CI981 OR liptonorm OR cerivastatin OR baycol OR lipobay OR rivastatin OR Certa OR compactin OR mevastatin OR ML236B OR ML 236B OR fluvastatin OR ilescol OR XU 62320 OR XU62320 OR fluindostatin OR lovastatin OR 6-methylcompactin OR mevacor OR MK803 OR MK803 OR mevinolin OR monacolin K OR 6-methylcompactin OR meglutol OR pitavastatin OR nisvastatin OR itavastatin OR P 872441 OR P872441 OR NK 104 OR NK104 OR livalo OR pravastatin OR eptastatin OR liplat OR RMS-431 OR RMS431 OR SQ 31000 OR SQ31000 OR vasten OR bristacol OR CS 514 OR CS514 OR Lipemol OR mevalotin OR pravachol OR elisor OR selektine OR pravocol OR pravasin OR lipostat OR red yeast rice OR cholesterol OR rosuvastatin OR ZD4522 OR ZD 4522 OR crestor OR simvastatin OR zocor OR MK733 OR MK 733 OR L 654969 OR L654969

Stroke Trials Registry
Search for trials: statin OR statins OR hydroxymethylglutaryl OR HMG OR reductase inhibitor OR atorvastatin OR lipitor OR CI-981 OR CI981 OR liptonorm OR cerivastatin OR baycol OR lipobay OR rivastatin OR Certa OR compactin OR mevastatin OR ML236B OR ML 236B OR fluvastatin OR ilescol OR XU 62320 OR XU62320 OR fluindostatin OR lovastatin OR 6-methylcompactin OR mevacor OR MK803 OR MK803 OR mevinolin OR monacolin K OR 6-methylcompactin OR meglutol OR pitavastatin OR nisvastatin OR itavastatin OR P 872441 OR P872441 OR NK 104 OR NK104 OR livalo OR pravastatin OR eptastatin OR liplat OR RMS-431 OR RMS431
OR SQ 31000 OR SQ31000 OR vasten OR bristacol OR CS 514 OR CS514 OR lipemol OR mevalotin OR pravachol OR elisor OR selektine OR pravacol OR pravasin OR lipostat OR red yeast rice OR cholestin OR rosuvastatin OR ZD4522 OR ZD 4522 OR crestor OR simvastatin OR zocor OR MK733 OR MK 733 OR L 654969 OR L654969

UpToDate v19.1
statins intracerebral hemorrhage
statins hemorrhagic stroke
statins intraparenchymal hemorrhage
HMG-CoA reductase inhibitors intracerebral hemorrhage
HMG-CoA reductase inhibitors hemorrhagic stroke
HMG-CoA reductase inhibitors intraparenchymal hemorrhage
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Food and Drug Administration
(intracerebral haemorrhage OR intracerebral hemorrhage OR intracerebral bleed OR cerebral haemorrhage OR intracerebral hemorrhage OR Cerebral bleed OR haemorrhagic stroke OR hemorrhagic stroke OR brain hemorrhage OR brain hemorrhage OR brain bleed OR central nervous system haemorrhage OR central nervous system hemorrhage OR central nervous system bleed OR neuraxial hemorrhage OR neuraxial bleed OR CNS haemorrhage OR CNS hemorrhage OR CNS bleed OR intraparenchymal hemorrhage OR intraparenchymal bleed OR parenchymal hemorrhage OR parenchymal hemorrhage OR parenchymal bleed) AND (statin OR statins OR hydroxymethylglutaryl OR HMG or reductase inhibitor OR atorvastatin OR lipitor OR CI-981 OR CI981 OR liptonorm OR cerivastatin OR baycol OR lipobay OR rivastatin OR Certa OR compactin OR mevastatin OR ML236B OR ML 236B OR fluvastatin OR lescol OR XU 62320 OR XU62320 OR fluindostatin OR lovastatin OR 6-methylcompactin OR mevacor OR MK803 OR MK 803 OR mevinolin OR monacolin K OR 6-methylcompactin OR meglutol OR pitavastatin OR nisvastatin OR itavastatin OR P 872441 OR P872441 OR NK 104 OR NK104 OR livalo OR pravastatin OR eptastatin OR liplat OR RMS-431 OR RMS431 OR SQ 31000 OR SQ31000 OR vasten OR bristacol OR CS 514 OR CS514 OR lipemol OR mevalotin OR pravachol OR elisor OR selektine OR pravacol OR pravasin OR lipostat OR red yeast rice OR cholestin OR rosuvastatin OR ZD4522 OR ZD 4522 OR crestor OR simvastatin OR zocor OR MK733 OR MK 733 OR L 654969 OR L654969)

Web of Science with Conference Proceedings
# 1 TS=((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))
Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

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Databases=SCI-EXPANDED, CPCI-S Timespan=All Years

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Databases=SCI-EXPANDED, CPCI-S Timespan=All Years
What’s What Online

Free text searches: statin, statins, hydroxymethylglutaryl, HMG, reductase inhibitor, atorvastatin, lipitor, CI-981, CI981, liptonorm, cerivastatin, baycol, lipobay, rivastatin, Certa, compactin, mevastatin, ML236B, ML 236B, fluvastatin, lescol, XU 62320, XU62320, fluindostatin, lovastatin, 6-methylcompactin, mevacor, MK803, MK 803, mevinolin, monacolin K, 6-methylcompactin, meglutol, pitavastatin, nisvastatin, itavastatin, P 872441, P872441, NK 104, NK104, livalo, pravastatin, eptastatin, liplat, RMS-431, RMS431, SQ 31000, SQ31000, vasten, bristacol, CS 514, CS514, lipemol, mevalotin, pravachol, elisor, selektine, pravacol, pravasin, lipostat, red yeast rice, cholestin, rosuvastatin, ZD4522, ZD 4522, crestor, simvastatin, zocor, MK733, MK 733, L 654969, L654969
Supplemental Figure 1. Funnel plot for randomized trials

Funnel Plot of Standard Error by Log Risk Ratio

Log risk ratio

Standard Error
Supplemental Figure 2. Funnel plot for cohort studies
Supplemental Figure 3. Funnel plot for case-control studies
Supplemental Figure 4. Study exclusion plot (randomized trials)

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<tr>
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<tr>
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</tr>
<tr>
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<td>ALLHAT</td>
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<td>1.17 (0.91 to 1.49)</td>
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<td>ASPEN</td>
<td>1.09 (0.84 to 1.41)</td>
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<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 5. Study exclusion plot (cohort studies)

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.
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

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