Statin Treatment and the Occurrence of Hemorrhagic Stroke in Patients With a History of Cerebrovascular Disease

Mervyn D.I. Vergouwen, MD; Rob J. de Haan, PhD; Marinus Vermeulen, MD, PhD; Yvo B.W.E.M. Roos, MD, PhD

Background and Purpose—The recently published Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that statins exert a marginally beneficial effect on stroke prevention in patients with a history of cerebrovascular disease. Interestingly, the magnitude of the beneficial effect shown in this study is smaller than in similar studies, which included patients without a history of cerebrovascular disease. In SPARCL, an increased occurrence of hemorrhagic strokes in patients on statin treatment was observed, an effect that was also earlier described in the Heart Protection Study in a subgroup of patients with a history of cerebrovascular disease. The purpose of this systematic review was therefore to investigate the effect of statin treatment on the occurrence of ischemic and hemorrhagic strokes in patients with a history of cerebrovascular disease.

Methods—We systematically searched the PUBMED database for the combination of the variables “statin” AND “stroke.” Furthermore, we searched for relevant studies in the Cochrane Library and Cochrane Central Register of Controlled Trials and handsearched citations. Pooled effect sizes were expressed in relative risk estimates with corresponding 95% CIs.

Results—Four studies were included investigating the effect of statins in 8832 patients with a history of cerebrovascular disease. The pooled relative risk for statin users of overall stroke during follow-up was 0.88 (95% CI: 0.78 to 0.99). The pooled relative risk of ischemic stroke was 0.80 (95% CI: 0.70 to 0.92) and of hemorrhagic stroke 1.73 (95% CI: 1.19 to 2.50).

Conclusion—In patients with a history of cerebrovascular disease, statins clearly decrease the risk of ischemic stroke. However, this beneficial effect is partly lost by an increased risk of hemorrhagic stroke.

Key Words: hemorrhagic stroke ■ ischemic stroke ■ review ■ statins

In the last decade, several randomized trials have shown that in patients with a history of vascular disease, statin treatment is beneficial in the prevention of new vascular events.1–4 However, in patients with cerebrovascular disease, it was unknown whether future strokes can be prevented by statin treatment. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was designed to study this question prospectively.5 This recently published study shows that statins exert a marginally beneficial effect on stroke prevention in patients with a history of cerebrovascular disease. The magnitude of the observed beneficial effect in this group of patients was smaller than in patients without a history of cerebrovascular disease.6,7 The reason why statin treatment is more effective in the prevention of strokes in patients without a history of cerebrovascular disease is unknown.

The results of the SPARCL study also show that statins appear to increase the occurrence of hemorrhagic stroke. Similar results were observed in a subgroup of patients with a history of cerebrovascular disease in the Heart Protection Study (HPS) in which statins increased the occurrence of hemorrhagic stroke without an effect on overall stroke incidence.7 Although low serum cholesterol levels have been associated with an increased incidence of hemorrhagic stroke, a large prospective meta-analysis including more than 90 000 patients, who mostly had no history of stroke or transient ischemic attacks (TIA), showed no increase in hemorrhagic stroke occurrence.8–10 The question remains whether the increased occurrence of hemorrhagic stroke in the HPS and SPARCL studies is a “play of chance” or that the observed effect is robust.

To answer this question, we decided to perform a systematic review concerning the effect of statin treatment on the
occurrence of ischemic and hemorrhagic strokes in patients with a history of cerebrovascular disease.

**Methods**

For this systematic review, the Cochrane Collaboration format was used.11

**Definitions**

A history of cerebrovascular disease was defined as a history of stroke, TIA, or carotid endarterectomy/angioplasty. Stroke was defined as the rapid onset of focal or global neurological deficit persisting ≥24 hours or leading to death, thought to be due to intracranial ischemia or hemorrhage. TIA was diagnosed when neurological symptoms lasted less than 24 hours. Overall stroke was defined as ischemic, hemorrhagic, or unclassified stroke. Stroke was considered unclassified in case information on CT or MRI scanning was lacking and no autopsy findings were available.

**Selection Criteria**

**Types of Studies, Participants, and Intervention**

All randomized, placebo-controlled trials investigating the effect of statins on stroke prevention in patients with a history of cerebrovascular disease were included either in a main analysis or in a subgroup analysis and regardless of dosage and type of statin. Trials were eligible for inclusion if the treatment duration was at least 1 year.

**Types of Outcome Measures**

Outcome was the number of patients with overall stroke during follow-up and the number of patients with hemorrhagic stroke and ischemic stroke. Additionally, a sensitivity analysis was performed for patients with unclassified stroke in the HPS and SPARCL studies, because these studies investigated stroke subtypes during follow-up. For this sensitivity analysis, the assumption was made that all patients only had one stroke during follow-up to avoid double calculations. First, we considered that all patients in the HPS and SPARCL studies with unclassified stroke had hemorrhagic stroke. Second, all patients with unclassified stroke in these 2 studies were designated to have an ischemic stroke. In another sensitivity analysis, all patients with hemorrhagic stroke as an entry event in the SPARCL study were excluded because this was the most significant predictor of having hemorrhagic stroke during follow-up in this study.

To place the results also in a wider clinical perspective, we performed a secondary analysis in which the number of patients with a first major vascular event during follow-up was investigated.

**Search Strategy for Identification of Studies**

We systematically searched the PUBMED database up to 2007 (week 9) for the combination of the variables “statin” AND “stroke.” The search was limited to studies in humans. Furthermore, we searched for relevant studies in the Cochrane Library and the Cochrane Central Register of Controlled Trials. Citations used in manuscripts that were included in the present review were handsearched.

**Statistics**

Data were processed in Review Manager 4.2 as supplied by the Cochrane Collaboration. Effect sizes were expressed in (pooled) relative risk (RR) estimates. Statistical uncertainty was expressed in 95% CIs. In case the $\chi^2$ analysis showed our data to be heterogeneous (probability value set at ≤0.30), we used a random effects model. If no heterogeneity could be demonstrated, we used a fixed effects model. If a study did not report on the number of patients on placebo and statin treatment, these numbers were calculated from percentages presented in figures.

**Results**

Besides the HPS and SPARCL studies, our systematic search revealed 2 additional randomized, controlled trials in which the effect of statins on stroke prevention was investigated in subgroups of patients. These studies were the Cholesterol and Recurrent Events (CARE) study and the Long-Term Intervention with Pravastatin in Ischemic Diseases (LIPID) study.12,13 A Cochrane review on interventions in the management on serum lipids for preventing stroke recurrence provided additional data on stroke incidence in the LIPID study.14 The characteristics of the included studies are listed in Table 1. Stroke incidence and number of patients with a first major vascular event during follow-up are listed in Table 2. All analyses in the included studies were performed on an intention-to-treat basis.

**Description of Included Studies**

In the CARE study, the effect of 40 mg pravastatin a day was studied in 4159 patients with myocardial infarction.1 Later, the CARE Endpoints Committee reviewed all reported cerebrovascular events to investigate the relation between pravastatin treatment and stroke outcome.12 Baseline characteristics of 211 patients with a history of cerebrovascular disease were not described. For all patients in the CARE study who had a stroke during follow-up, stroke subtypes were described. However, in the subgroup of patients with a history of cerebrovascular disease, stroke subtypes and the number of patients with a first major vascular event during follow-up were not recorded.
In the LIPID study, the effect of 40 mg pravastatin daily was studied in 9014 patients with myocardial infarction and unstable angina pectoris. The effect of pravastatin on stroke was a secondary outcome and described separately. In total, 325 patients in the pravastatin group and 285 patients in the placebo group had a history of stroke or TIA. Baseline characteristics of patients with a history of cerebrovascular disease were not described. Although for the total group of patients with stroke in the LIPID study, distinction was made for stroke subtypes, in the subgroup of patients with a history of cerebrovascular disease, stroke subtypes during follow-up were not described. The number of patients with a first major vascular event in this group of patients was not described.

In the HPS, the effect of 40 mg simvastatin a day was studied in 20,536 patients with heterogeneous vascular disease. In a secondary analysis, the effect of simvastatin on the prevention of major vascular events such as stroke was studied in a subgroup of 3280 patients with a known history of cerebrovascular disease, which was defined as nondisabling ischemic stroke, TIA, carotid endarterectomy, or angioplasty. We calculated from the figures that 1643 patients were randomized to simvastatin and 1637 patients to placebo. During follow-up, subarachnoid hemorrhage was classified as stroke, whereas TIAs and subdural hematomas were not. In the HPS, a major vascular event was defined as nonfatal myocardial infarction or coronary death, stroke of any type, and coronary and noncoronary revascularization.

The SPARCL study enrolled 4731 patients who had a stroke or TIA within 1 to 6 months before study entry. Stroke or TIA had to be diagnosed by a neurologist within 30 days after the event. In contrast to the HPS, the SPARCL study also included patients with a hemorrhagic stroke at study entry; however, the number of patients who had a hemorrhagic stroke at study entry was small (1.9% in the

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No. of Patients</th>
<th>No. of Patients With a History of Cerebrovascular Disease</th>
<th>Age, years</th>
<th>Major Inclusion Criteria</th>
<th>Major Exclusion Criteria</th>
<th>Cholesterol Levels</th>
<th>Follow-Up of Main Study, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE</td>
<td>4159</td>
<td>211</td>
<td>21–75</td>
<td>Myocardial infarction</td>
<td>Prior sensitivity to statins, nonresponsiveness (≤10% decrease in total cholesterol)</td>
<td>Total cholesterol &lt;240 mg/dL, LDL cholesterol 115–174 mg/dL</td>
<td>5 (median)</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>610</td>
<td>31–75</td>
<td>Myocardial infarction or unstable angina pectoris in previous 3–36 months</td>
<td>Treatment with other lipid-lowering drugs</td>
<td>Total cholesterol 155–271 mg/dL</td>
<td>6.1 (mean)</td>
</tr>
<tr>
<td>HPS</td>
<td>20,536</td>
<td>3280</td>
<td>40–80</td>
<td>Nondisabling ischemic stroke</td>
<td>Stroke within previous 6 months, TIA, carotid endarterectomy and angioplasty</td>
<td>Nonfasting total cholesterol ≥135 mg/dL</td>
<td>4.8 (mean)</td>
</tr>
<tr>
<td>SPARCL</td>
<td>4731</td>
<td>4731</td>
<td>&gt;18</td>
<td>Ischemic stroke, TIA, hemorrhagic stroke</td>
<td>Patients functionally dependent, atrial fibrillation, other cardiac sources of embolism, known coronary heart disease, subarachnoid hemorrhage</td>
<td>LDL cholesterol 100–190 mg/dL</td>
<td>4.9 (median)</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein.

In the LIPID study, the effect of 40 mg pravastatin daily was studied in 9014 patients with myocardial infarction and unstable angina pectoris. The effect of pravastatin on stroke was a secondary outcome and described separately. In total, 325 patients in the pravastatin group and 285 patients in the placebo group had a history of stroke or TIA. Baseline characteristics of patients with a history of cerebrovascular disease were not described. Although for the total group of patients with stroke in the LIPID study, distinction was made for stroke subtypes, in the subgroup of patients with a history of cerebrovascular disease, stroke subtypes during follow-up were not described. The number of patients with a first major vascular event in this group of patients was not described.

In the HPS, the effect of 40 mg simvastatin a day was studied in 20,536 patients with heterogeneous vascular disease. In a secondary analysis, the effect of simvastatin on the prevention of major vascular events such as stroke was studied in a subgroup of 3280 patients with a known history of cerebrovascular disease, which was defined as nondisabling ischemic stroke, TIA, carotid endarterectomy, or angioplasty. We calculated from the figures that 1643 patients were randomized to simvastatin and 1637 patients to placebo. During follow-up, subarachnoid hemorrhage was classified as stroke, whereas TIAs and subdural hematomas were not. In the HPS, a major vascular event was defined as nonfatal myocardial infarction or coronary death, stroke of any type, and coronary and noncoronary revascularization.

The SPARCL study enrolled 4731 patients who had a stroke or TIA within 1 to 6 months before study entry. Stroke or TIA had to be diagnosed by a neurologist within 30 days after the event. In total, 2365 patients were randomized to receive 80 mg atorvastatin per day and 2366 patients were randomized to placebo. In contrast to the HPS, the SPARCL study also included patients with a hemorrhagic stroke at study entry; however, the number of patients who had a hemorrhagic stroke at study entry was small (1.9% in the

| Table 2. No. of Patients With a History of Cerebrovascular Disease With Overall Stroke, Stroke Subtypes, and First Major Vascular Event* |
|-------------------------------------------------|----------------|----------------|----------------|-----------------|-----------------|----------------|
| Study   | CARE            | LIPID         | HPS            | SPARCL          |                 |                 |
| No. of Patients | Statin N (%) | Placebo N (%) | Statin N (%) | Placebo N (%) | Statin N (%) | Placebo N (%) |
| Overall stroke | 15 (13.5) | 20 (20) | 169 (10.3) | 170 (10.4) | 265 (11.2) | 311 (13.1) |
| Ischemic stroke | ... | ... | 100 (6.1) | 122 (7.5) | 218 (9.2) | 274 (11.6) |
| Hemorrhagic stroke | ... | ... | 21 (1.3) | 11 (0.7) | 55 (2.3) | 33 (1.4) |
| Unclassified stroke | 15 (13.5) | 20 (20) | 48 (2.9) | 42 (2.6) | 7 (0.3) | 12 (0.5) |
| First major vascular event | ... | ... | 406 (24.7) | 488 (29.8) | 334 (14.1) | 407 (17.2) |

*Total number of patients with stroke subtypes may exceed number of patients with overall stroke, because patients may have different types of stroke.
placebo group and 2.0% in the placebo group). In a secondary analysis, presented at the recent International Stroke Conference 2007 in San Francisco, it was shown that hemorrhagic strokes in the SPARCL study were most prevalent in patients who were enrolled in the study with a hemorrhagic stroke as an entry event. Forty-five patients in the atorvastatin group had a hemorrhagic stroke as an entry event. In this group of patients, 3 had ischemic stroke and 7 patients had hemorrhagic stroke during follow-up. In the 48 patients with hemorrhagic stroke as an entry event randomized to placebo, 2 patients had ischemic stroke and 2 patients had hemorrhagic stroke during follow-up. In the SPARCL study, a major cardiovascular event was defined as stroke plus any major coronary event.

Analyses

Because no statistical heterogeneity could be demonstrated, all pooled analyses were based on a fixed effects model. For the analysis of the occurrence of overall stroke, data of 8832 patients were available. In total, 4444 patients were randomized to statin treatment and 4388 patients to placebo. The overall number of patients who had a stroke was 480 in the statin group and 539 in the placebo group (pooled RR 0.88 [95% CI: 0.78 to 0.99]; Figure 1).

For the analyses of the occurrence of ischemic and hemorrhagic stroke, only data from the HPS and SPARCL studies were available. Therefore, the analysis of the risk of ischemic and hemorrhagic stroke was based on 8011 patients. In total, 4008 patients were randomized to statin treatment and 4003 patients to placebo. In patients randomized to statin treatment, 318 patients had ischemic stroke and 76 had hemorrhagic stroke. In the placebo group, 396 patients had ischemic stroke and 44 had hemorrhagic stroke. In patients treated with statins, the pooled RR of ischemic stroke was 0.80 (95% CI: 0.70 to 0.92; Figure 2) and of hemorrhagic stroke 1.73 (95% CI: 1.19 to 2.50; Figure 3).

In the sensitivity analysis that assumed that all patients of the HPS and SPARCL studies with unclassified stroke had ischemic stroke, the total number of patients with ischemic stroke was 373 in the statin group and 450 in the placebo group (pooled RR 0.83 [95% CI: 0.73 to 0.94]). When assuming that all patients with unclassified stroke in these 2 studies had hemorrhagic stroke, 131 patients randomized to statin treatment and 98 patients randomized to placebo had hemorrhagic stroke (pooled RR 1.33 [95% CI: 1.03 to 1.73]).

For the sensitivity analysis that excludes all patients with hemorrhagic stroke as an entry event in the SPARCL study, data of 7918 patients were available. In total, 3963 patients were randomized to statin treatment and 3955 patients to placebo. In patients randomized to statin treatment, 315 had ischemic stroke and 69 patients had hemorrhagic stroke. In the placebo group, 394 patients had ischemic stroke and 42 had hemorrhagic stroke. In patients treated with statins, the pooled RR of ischemic stroke was 0.80 (95% CI: 0.69 to 0.92) and of hemorrhagic stroke 1.64 (95% CI: 1.12 to 2.40).

For the analysis of first major vascular events, data of 8011 patients were available. In total, 4008 patients were randomized to statin treatment and 4003 patients to placebo. The total number of patients with a first major vascular event was 740 in the group randomized to statin treatment and 895 in the placebo group (pooled RR 0.83 [95% CI 0.76 to 0.90]).
Discussion

The present review including 8832 patients shows that treatment with statins in patients with a history of cerebrovascular disease reduces the recurrence of overall stroke. The analyses on occurrence of stroke subtypes demonstrate that statins decrease the occurrence of ischemic stroke but that this effect is partially counterbalanced by an increase in the occurrence of hemorrhagic stroke. Our results also show that in patients with a history of cerebrovascular disease, statins significantly decrease the incidence of major vascular events.

Both the HPS and SPARCL studies investigated the effect of statins on the occurrence of stroke subtypes. Most strokes were classified as either ischemic or hemorrhagic. However, some strokes could not be categorized. Probably, in this group of patients with unclassified stroke, the incidence of ischemic and hemorrhagic stroke had a similar distribution compared with patients with a classified stroke. To avoid preliminary conclusions, we performed sensitivity analyses in which the assumption was made that all patients with unclassified stroke had either ischemic or hemorrhagic stroke. The sensitivity analysis confirmed our results that statins decrease ischemic stroke risk and increase the risk of hemorrhagic stroke significantly.

Our results seem to be in contrast with 2 other reviews. A systematic review in patients of whom the majority did not have a history of cerebrovascular disease showed a pronounced decrease in stroke recurrence (OR 0.79 [95% CI 0.73 to 0.85]) without adverse effect on hemorrhagic stroke occurrence. A recent meta-analysis, including more than 90 000 patients randomized to statin treatment or placebo, did not show a difference in the occurrence of hemorrhagic stroke during follow-up. Again, most included trials were primary prevention trials or secondary prevention trials in which most patients did not have a history of stroke or TIA. Apparently, statins are only associated with an increased occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease.

A straightforward explanation for the increased occurrence of hemorrhagic stroke could be that the SPARCL study not only included patients with ischemic stroke as an entry event, but also patients with hemorrhagic stroke and that the increase in hemorrhagic stroke might be caused by the recurrence of hemorrhagic stroke in these patients. However, in the HPS in a subgroup of patients with a history of cerebrovascular disease, a similar increased risk of hemorrhagic stroke during follow-up was demonstrated, whereas this study did not include patients with hemorrhagic stroke. Moreover, a sensitivity analysis excluding all patients with a hemorrhagic stroke as an entry event in the SPARCL study showed that statin treatment was still associated with an increased risk of hemorrhagic stroke.

What can then be the cause of the increased occurrence of hemorrhagic stroke in this group of patients? First, although statins were originally introduced to lower serum cholesterol levels, recent studies provide increasing evidence for pleiotropic effects such as enhancing fibrinolysis and inhibiting blood coagulation. These pleiotropic effects are also a plausible explanation in a study investigating patients with acute ischemic stroke receiving recanalization therapy in which both prior statin use and low low-density lipoprotein cholesterol levels were associated with an increased risk of symptomatic hemorrhagic stroke transformation. A similar mechanism could also be involved in surgical patients, in which statins have been found to be associated with an increased incidence of postoperative bleeding complications.

Second, the observed increase in the occurrence of hemorrhagic stroke in this group of patients could also be caused by hemorrhages related to cerebral small vessel disease. In small vessel disease, ischemic stroke usually results from arteriolsclerosis and not from emboli. These patients with small vessel disease often have silent intracerebral microhemorrhages. Microhemorrhages have been shown to be more frequent in patients with ischemic stroke (26%) than in patients with myocardial infarction (4%) or peripheral artery disease (13%). This higher incidence of microhemorrhages in patients with strokes compared with patients with myocardial infarction or peripheral artery disease was considered to explain the observed higher incidence of hemorrhagic strokes in patients who were treated with anticoagulant treatment. Apparently, these silent microhemorrhages progress into clinical manifest macrohemorrhages by changes in the coagulation or fibrinolytic system. Because patients with ischemic stroke have a higher incidence of microhemorrhages, the effect of statins on the coagulation and fibrinolytic system may thus be responsible for the higher incidence of hemorrhagic stroke.

Third, it could also be hypothesized that an interaction between statins and antiplatelet or anticoagulant drugs leads to an increased bleeding risk. Unfortunately, the included studies did not provide data on hemorrhage risk caused by a possible interaction between statins and antiplatelet or anticoagulant therapy. However, to our knowledge, an interaction between statins and antiplatelet drugs has not been described in the literature previously. Some reports have shown that several types of statins enhance the anticoagulant effect of vitamin K antagonists as a result of anticoagulant drug metabolism inhibition or by a reduction of lipoprotein-dependent vitamin K absorption and hepatic storage. This effect has, for example, been observed in patients treated with simvastatin, but not in patients using atorvastatin. Nevertheless, the SPARCL study, which randomized patients to atorvastatin, showed an increased occurrence of hemorrhagic stroke. Thus, interactions between statins and anticoagulant drugs probably do not account for the increased occurrence of hemorrhagic stroke in this group of patients.

Because the current study shows that statins increase the risk of intracerebral hemorrhage in patients with a history of cerebrovascular disease, one could hypothesize that statin treatment also increases the risk of other major bleedings such as gastrointestinal hemorrhages. However, the studies included in the present review do not provide data on other major bleedings.

We realize that our study has some limitations. The 4 included trials had different inclusion and exclusion criteria. Furthermore, there were differences between studies in type of statin used and dosage and duration of treatment. In the CARE and LIPID studies, no data were given on time...
between baseline stroke or TIA and randomization. In the HPS, patients were randomized more than 6 months after baseline stroke (mean interval since most recent stroke or TIA 4.3 years), whereas in the SPARCL study, patients had a stroke or TIA within 1 to 6 months before study entry. Furthermore, in CARE, LIPID, and HPS, patients with a history of cerebrovascular disease were not randomized as a group. This may have resulted in imbalances in stroke risk factors for which no correction could be made. All these differences could have affected our results in some way; however, the observed consistency of the effect sizes between the reviewed studies indicates that these factors probably did not have an important impact. Moreover, the trials used different inclusion criteria for cholesterol levels. Nevertheless, in several studies, it has been shown that lipid levels at baseline are not a significant predictor of stroke occurrence. Finally, for the analysis investigating the effect of different inclusion criteria for cholesterol levels, Neverthe-

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Disclosures

None.

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Stroke. 2008;39:497-502; originally published online January 3, 2008;
doi: 10.1161/STROKEAHA.107.488791

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