Statins in Stroke Prevention and Carotid Atherosclerosis
Systematic Review and Up-to-Date Meta-Analysis

Pierre Amarenco, MD; Julien Labreuche, Bst; Philippa Lavallée, MD; Pierre-Jean Touboul, MD

Background and Purpose—Previously published meta-analyses exploring the effect of statins on stroke incidence included 20 000 patients and found a 2% to 30% risk reduction. It is not clear whether this is attributable to low-density lipoprotein–cholesterol (LDL-C) reduction. Statin trials have now included >90 000 patients. We have determined the effect of statins and LDL-C reduction on stroke prevention.

Summary of Review—We performed a systematic review and meta-analysis of all randomized trials testing statin drugs published before August 2003. The trials were identified using a computerized PubMed search. We analyzed separately statin effect on incident strokes and on carotid intima-media thickness (IMT) according to LDL-C reduction. The relative risk reduction for stroke was 21% (odds ratio [OR], 0.79 [0.73 to 0.85]), with no heterogeneity between trials. Fatal strokes were reduced but not significantly: by 9% (OR, 0.91 [0.76 to 1.10]). There was no increase in hemorrhagic strokes (OR, 0.90 [0.65 to 1.22]). Statin size effect was closely associated with LDL-C reduction. Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% (95% CI, 6.7 to 23.6) and carotid IMT by 0.73% per year (95% CI, 0.27 to 1.19).

Conclusions—Statins may reduce the incidence of all strokes without any increase in hemorrhagic strokes, and this effect is mainly driven by the extent of between-group LDL-C reduction. Carotid IMT progression also strongly correlated with LDL-C reduction. (Stroke. 2004;35:2902-2909.)

Key Words: cardiovascular disease ■ carotid arteries ■ intima-media thickness ■ risk ■ stroke ■ stroke prevention

In the past decade, cholesterol lowering with 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins) has proved to reduce vascular events significantly in primary and secondary prevention of coronary heart disease (CHD).1,2,6–14 The unexpected finding of a reduced incidence of stroke in the 2 first major statin trials conducted in patients with known CHD1,2 has aroused considerable interest and expectations for stroke prevention in the general population and in patients with previous stroke. Three meta-analyses pooled the data of these 2 trials and other smaller previously published trials involving a total of 20 000 patients.3–5 The consistent result among these meta-analyses was a stroke risk reduction of 2% to 30%. It is not clear whether this is attributable to a reduction in low-density lipoprotein–cholesterol (LDL-C) or to other pleiotropic effects of statins.

Since then, 9 major statin trials have been published.6–14 We have thus performed an up-to-date meta-analysis involving >90 000 patients, examining the effects of statins on stroke prevention and LDL-C reduction in this population.

Methods

Objectives
Our primary aim was to investigate the effect of statins on stroke incidence and stroke mortality. The second objective was to study the specific effect of statins on the incidence of hemorrhagic stroke. We also investigated the relationship between the magnitude of LDL-C reduction and the effect of statin treatment on stroke incidence. As an ancillary analysis, we also studied the relationship between LDL-C reduction and carotid artery intima-media thickness (IMT) change expressed as percentage increase or decrease per year in IMT studies.

Literature Search
We performed a systematic review of all randomized trials testing statin drugs and previous meta-analyses published before August 2003. The trials were identified using a computerized PubMed search. The keywords used for the search were pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, cerivastatin, rosvastatin, pitavastatin, HMG-CoA reductase inhibitor, statin, and cholesterol-lowering drugs. In addition, a manual search was performed using the reference lists from the trials identified.

Trial Selection
We included trials in which the patients were randomly assigned to statin or a control group (placebo or usual care treatment) and in which stroke events (brain infarction and hemorrhage) were recorded and the data were reported in intention-to-treat. Trials relating to primary or secondary prevention of CHD and trials using unifactorial or multifactorial interventions were considered eligible studies. Because it is a rather “soft” end point, we did not consider transient ischemic attacks (TIAs) as an end point in the meta-analysis. If the...
occurrence of stroke, hemorrhagic stroke, or LDL-C reduction was incompletely reported or not reported in the original publication, the author was contacted by mail to provide this information. Trials with no data available on the stroke end point or in which no stroke event occurred, and trials evaluating the dose-response ratio were excluded. We also excluded the KLIS trial* from the main analysis because the randomization was unsuccessful. Abbreviations of the trials are given in Table 1.

For the IMT analysis, we included all statin trials with common carotid artery wall thickness measurements as an end point. For 1 trial (Asymptomatic Carotid Artery Progression Study [ACAPS]), these data were lacking, and we used the combined end point, which included the mean maximum IMT thickness in the common carotid artery, internal carotid artery, and its bifurcation. For the purpose of this analysis, we used the data from the active and placebo or usual care control groups separately (the usual care control groups in the randomization was unsuccessful). The summary effect of statin treatment on the incidence of all strokes and fatal strokes was subsequently assessed with the fixed-effect meta-analysis. Statistical Analysis

The summary effect of statin treatment on the incidence of all strokes and fatal strokes was subsequently assessed with the fixed-effect meta-analysis.
multiple outcomes model. Because the stroke rate in all the selected trials was low, the Mantel–Haenszel method was used to calculate the pooled odds ratios (ORs). Individual ORs were estimated as the cross-product of cell counts in the corresponding 2 × 2 table, with the variance of log-ORs equal to the sum of the reciprocal cell counts. Eight trials with zero stroke deaths in both treatment groups were excluded for analyses of fatal stroke end point. For trials with no events in 1 group, a pseudocount of 0.25 was added to each cell for these calculations. The between-trials homogeneity of the ORs was tested with the Breslow–Day method. Sensitivity analyses were conducted, first by excluding the trials for which stroke was not a prespecified secondary end point, and second by including the KLIS trial.

The specific effect of statin treatment on the incidence of hemorrhagic stroke was also studied by the same methods. We included in this analysis all trials for which the occurrence of hemorrhagic stroke was available. To test the evidence of between-group LDL-C change on stroke incidence, we used an inverse-variance–weighted linear regression on the log-OR for stroke. The relationship between LDL-C change and carotid artery IMT change expressed as percentage increase or decrease per year was investigated with linear regression weighted by the size of each group.

We assessed the evidence of bias with a funnel plot. We measured the degree of funnel plot asymmetry by the intercept from an unweighted regression of standard normal deviate (log-OR for all stroke divided by its SE against precision [inverse of SE]). Statistical testing was conducted at the 2-tailed level of 0.05, with no evidence of heterogeneity between trials (P=0.35). The relative odds reduction was −21% (95% CI, −27% to −15%). Sensitivity analyses did not change this finding. After exclusion of trials for which stroke was not a prespecified end point,18–33 the pooled OR for stroke incidence was 0.80 (95% CI, 0.74 to 0.87), and after inclusion of the KLIS trial,9 the pooled OR was 0.79 (95% CI, 0.74 to 0.86).

### Results

We identified 26 statin trials that met all our criteria and 1 large statin trial8 with unsuccessful randomization.1,2,6–34 The characteristics of these trials are presented in Table 1.

#### All Strokes, Stroke Mortality, and Hemorrhagic Strokes

### All Strokes

When the 26 trials included in the main analysis (Figure 1) were combined, the summary effect of statins was significant (P<0.0001), with no evidence of heterogeneity between trials (P=0.35). The relative odds reduction was −21% (95% CI, −27% to −15%). Sensitivity analyses did not change this finding. After exclusion of trials for which stroke was not a prespecified end point,18–33 the pooled OR for stroke incidence was 0.80 (95% CI, 0.74 to 0.87), and after inclusion of the KLIS trial,9 the pooled OR was 0.79 (95% CI, 0.74 to 0.86).

### Stroke Death

Because separate information about fatal and nonfatal stroke was not available in the ASCOT-LLA,14 AFCAPS/TexCAPS,8 and Post-CABG reports,22 these trials could not be included in this part of the meta-analysis. Eight trials with zero stroke deaths were also not included in this analy-

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### Table 2. Characteristics of the Selected IMT Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arteries</th>
<th>Regimen Group</th>
<th>Randomized patients (N)</th>
<th>Mean* age, y</th>
<th>Male* Gender, %</th>
<th>Baseline* mean IMT (mm)</th>
<th>IMT change (%/yr) (N)</th>
<th>Baseline* mean LDL-C (mg/dL)</th>
<th>LDL-C reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER</td>
<td>CCA† (far wall)</td>
<td>Lovastatin (80 mg/day) Pravastatin (40 mg/day)</td>
<td>70/68</td>
<td>60</td>
<td>71</td>
<td>0.62</td>
<td>−5.4/4.1</td>
<td>151</td>
<td>−49/−30</td>
</tr>
<tr>
<td>ASAP</td>
<td>CCA† (near and far wall) Simvastatin (40 mg/day)</td>
<td>160/165</td>
<td>48</td>
<td>39</td>
<td>0.87</td>
<td>−2.4/−1.0</td>
<td>309</td>
<td>−52/−42</td>
<td></td>
</tr>
<tr>
<td>LIPID§</td>
<td>CCA† (far wall)</td>
<td>Pravastatin (40 mg/day) Placebo + Diet</td>
<td>273/249</td>
<td>61</td>
<td>88</td>
<td>0.8</td>
<td>−0.4/−1.5</td>
<td>155</td>
<td>−28/−5</td>
</tr>
<tr>
<td>CAIUS</td>
<td>CCA† (near and far wall) Placebo</td>
<td>151/154</td>
<td>55</td>
<td>53</td>
<td>0.74</td>
<td>−0.4/−1.0</td>
<td>181</td>
<td>−22/3</td>
<td></td>
</tr>
<tr>
<td>KAPS</td>
<td>CCA† (far wall)</td>
<td>Pravastatin (40 mg/day) Placebo</td>
<td>224/233</td>
<td>57</td>
<td>100</td>
<td>1.35</td>
<td>0.7/2.1</td>
<td>189</td>
<td>−27/−2</td>
</tr>
<tr>
<td>REGRESS</td>
<td>CCA† (far wall)</td>
<td>Pravastatin (40 mg/day) Placebo</td>
<td>131/124</td>
<td>56</td>
<td>100</td>
<td>0.79</td>
<td>−0.9/−2.2</td>
<td>168</td>
<td>−26/−1</td>
</tr>
<tr>
<td>PLAC II</td>
<td>CCA† (near and far wall) Pravastatin (20–40 mg/day) Placebo + Diet</td>
<td>75/76</td>
<td>63</td>
<td>85</td>
<td>1.01</td>
<td>1.6/3.4</td>
<td>166</td>
<td>−28/−1</td>
<td></td>
</tr>
<tr>
<td>ACAPS</td>
<td>CCA + CB + C4AT (near and far wall) Lovastatin (20–40 mg/day) Placebo + Diet</td>
<td>231/230</td>
<td>62</td>
<td>52</td>
<td>1.32</td>
<td>−0.7/0.5</td>
<td>156</td>
<td>−28/−0</td>
<td></td>
</tr>
<tr>
<td>MARS§</td>
<td>CCA (far wall)</td>
<td>Lovastatin (80 mg/day) Placebo + Diet</td>
<td>99/89</td>
<td>58</td>
<td>92</td>
<td>0.73</td>
<td>−5.0/2.7</td>
<td>157</td>
<td>−45/−3</td>
</tr>
</tbody>
</table>

*Means of age, IMT and LDL-C, and percentage of male gender on entry to study in all randomised patients; †mean IMT value is given; ‡average of maximum IMT value is given; §right side of the neck was examined only.

CCA indicates common carotid artery; CB, carotid bulb; ICA, internal carotid artery; CFA, superficial femoral artery; A, active treatment; C, control group; ARBITER, Arterial Biology for Investigation of the Treatment Effects of Reducing Cholesterol; ASAP, Aggressive vs conventional lipid lowering on Atherosclerosis Progression; CAIUS, Carotid Atherosclerosis Italian Ultrasound Study; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; KAPS, Kuopio Atherosclerosis Prevention Study; PLAC-II, Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries; ACAPS, Asymptomatic Carotid Artery Progression Study; REGRESS, Regression Growth Evaluation Statin Study.

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### Figure 1. ORs for all strokes in individual trials, small trials18–28,31–34 (data combined to simplify the presentation), and all trials. *Pooled OR for all strokes in small trials18–27,30–33 calculated with the Mantel–Haenszel method.
The pooled analysis for the remaining 15 trials showed no significant reduction in fatal strokes with statins ($P = 0.37$) and no heterogeneity between trials ($P = 0.71$; Figure 2). This result was not modified in the sensitivity analysis with a pooled OR of 0.94 (95% CI, 0.78 to 1.13; $P = 0.52$).

**Hemorrhagic Stroke**

Information on the incidence of hemorrhagic stroke was available in 12 trials, representing 49,843 randomized patients (KLIS included). Four trials with zero hemorrhagic strokes were not included in this analysis. Among the remaining 8 trials, a hemorrhagic stroke occurred in 78 patients in the statin group (0.32%) and 84 patients in the control group (0.36%). As shown in Figure 3, the specific effect of statins on the incidence of hemorrhagic stroke was not significant, with a pooled OR of 0.90 (95% CI, 0.65 to 1.22). We found the same results after excluding the KLIS trial (OR, 0.91; 95% CI, 0.65 to 1.26).

**Between-Group Difference in LDL-C Reduction**

No heterogeneity of the effect of statin was detected between trials. However, the duration of treatment and the statin regimen (dosage, compound, and use of statin in the control group) differed between trials (Table 1). We then studied the relationship between the size effect of statin treatment on stroke incidence and LDL-C reduction in the 26 trials included in the main analysis. As shown in Figure 4, this relation was significant ($r = 0.58; P = 0.002$). Each 10% LDL-C reduction was estimated to reduce the risk of all strokes by 15.6% (95% CI, 6.7 to 23.6). Robustness analyses were performed first by excluding small trials and the PROSPER trial because of the absence of information on between-group LDL-C reduction either at the end of the trial or throughout the entire duration of the trial, and second by including the KLIS trial. The correlation between-group LDL-C reduction and effect size of statin treatment remained significant ($r = 0.89, P = 0.0001; r = 0.55, P = 0.003$, respectively), with the same estimated stroke reduction for each 10% reduction in LDL-C (15.0% [95% CI, 9.8 to 19.9]; 13.7% [95% CI, 5.3 to 21.2], respectively).

**Carotid IMT**

We identified 9 trials that met our criteria (Table 2). As shown in Figure 5, there was a strong correlation between LDL reduction and carotid IMT reduction ($r = 0.65; P = 0.004$). Each 10% reduction in LDL-C was estimated to reduce the carotid IMT by 0.73% per year (95% CI, 0.27 to 1.19).

**Assessment of Presence of Biases**

Funnel plotting of the log-ORs for all strokes versus precision showed an asymmetry (Figure 6) that was confirmed by the Egger’s analysis (intercept $= 0.48; 90\%$ CI, $-0.89$ to $0.070; P = 0.056$). This result suggested the presence of some biases in our meta-analysis.

**Discussion**

This meta-analysis of >90,000 randomized patients shows that statins significantly reduced all strokes without increasing brain hemorrhage. However, stroke death was not significantly reduced.

Statins have now been studied in 7 different populations: CHD, hypercholesterolemia, normocholesterolemia, the elderly, hypertensives, diabetics, and previous stroke. Stroke incidence was reduced in all of them except patients with previous stroke, for which we have very limited data, mostly from the HPS trial. In that trial, major vascular events (major coronary event, stroke, revascularization) were reduced by 19% in patients with
previous stroke before randomization. This reduction of the composite primary end point was entirely attributable to the reduction of major coronary events and of revascularizations because there was no reduction in stroke recurrence (10.4% in each group); this surprising finding is possibly a result of the late inclusion of patients at a mean of 4.3 years after their stroke or TIA at a moment when patients were less likely to have stroke events and more likely to have coronary events; thus, speculation about the lack of reduction of recurrent stroke with statins in patients treated within 4 years post-stroke or TIA would be premature.

We found no increase in hemorrhagic stroke despite the fact that stroke reduction was also observed in patients with low baseline LDL-C, as shown in the HPS, LIPID, and ASCOT trials. Increased hemorrhagic stroke in these patients was a concern after observational cohorts showed that low cholesterol levels were associated with a greater risk of hemorrhagic stroke. A study using T2*-weighted gradient-echo brain MRI scans showed that LDL-C concentrations were significantly lower in patients with a severe degree of microbleeding. Low cholesterol levels are frequent in patients in poor condition such as weight loss, severe handicap, and severe and chronic illness, which may have constituted confounding factors for the relationship between the occurrence of a hemorrhagic stroke and low total cholesterol in observational studies.

One striking finding of the meta-analysis was that the greater the between-group difference in LDL-C reduction, the greater the reduction in stroke risk. This means that LDL-C reduction was probably the main mechanism whereby statins reduced stroke events. Indeed, in our meta-analysis, LDL-C reduction could explain between one third and 80% of the variance of stroke risk reduction, which also leaves room for possible additional pleiotropic effects. This was already apparent in the HPS trial, in which LDL-C reduction was the main explanation for stroke risk and coronary event reduction in the group receiving statin. The only trial in which stroke reduction did not parallel LDL-C reduction was the PROSPER trial, in which the between-group LDL-C reduction was 40 mg after 3 months. However, information on the between-group LDL-C difference throughout the trial or at the end of the trial has not yet been published. In ALLHAT and KLIS, in which the between-group LDL-C difference was 24 and 11 mg, respectively, stroke risk was not significantly reduced. All positive trials had a between-group LDL-C difference of at least 35 mg. Although statins may reduce stroke incidence by reducing blood cholesterol levels, cholesterol levels have never been clearly associated with stroke in epidemiological studies. In the Framingham Study, there was a positive association between carotid stenosis, hypercholesterolemia, and CHD. In the same epidemiological study, over a period of 34 years, moderate carotid stenosis exceeding 25% in men was associated with an increase of 20 mm Hg in systolic blood pressure (2.11 [1.51 to 2.97]), 10 mg/dL in total cholesterol level (1.10 [1.03 to 1.16]), and 5 pack years of smoking (1.08 [1.03 to 1.13]); the result was similar in women. These results clearly suggested that the cumulative effects of these important risk factors, including cholesterol levels, interfere with the development of carotid stenosis and further argued for a global cardiovascular risk approach on the basis of the Framingham or PROCAM score to prevent...
the development of atherothrombotic disease, even for carotid atherothrombosis.

However, by reducing LDL-C, statins first reduced the incidence of myocardial infarction (MI) and therefore reduced the incidence and thromboembolic complications of left ventricular (LV) mural thrombi. Statins may therefore simply reduce stroke incidence by reducing cardioembolic brain infarctions. In the MIRACL trial, statins were given immediately after an unstable angina or a non-Q-wave MI during a 4-month period. There was a significant reduction in MI and urgent rehospitalization for myocardial ischemia, as well as significant reduction in fatal and nonfatal strokes. Only 9 of the 36 strokes recorded were preceded by a nonfatal MI, with the stroke occurring between 2 and 86 days after the MI. This means that other mechanisms than the reduction in LV thrombus probably account for stroke prevention with statins.

It has also been suggested that statins can reduce blood pressure by 2 to 5 mm Hg and it is known that a 2 mm Hg reduction in systolic blood pressure may account for a 15% reduction in stroke incidence. However, a careful post hoc analysis in the LIPID trial somewhat contradicted this hypothesis because the systolic and diastolic blood pressures were equal at entry and at the end of trial. Unlike the patients in whom statins have been shown to reduce blood pressure, the patients in the LIPID trial were not hypertensives at baseline. We therefore need more data on hypertensive patients, as in the ASCOT and HPS trials, to see whether statins helped to reduce high blood pressure or not. Overall, in ASCOT, there was no obvious between-group difference in blood pressure goal (H11021). There was a significant reduction immediately after an unstable angina or a non-Q-wave MI. However, it is not yet known in ASCOT whether or not blood pressure decreased slightly more in patients on statins than in those on placebo.

Statins may also act on inflammation55,56 and on biological markers of plaque instability57 or the development of atherosclerosis, and IMT is known to be a strong predictor of the development of carotid plaque and stenosis and is clearly associated with stroke and cholesterol levels. In the HPS trial, there was a significant 50% decrease in carotid endarterectomy in patients receiving simvastatin compared with those receiving the placebo (42 versus 79 patients). IMT regression has not yet been associated with a reduction in clinical events. In our meta-analysis, we also found a strong relationship between the magnitude of IMT reduction and the reduction in LDL-C from baseline (Figure 5). This again supports the view that the greater the LDL-C reduction, the greater the IMT and stroke risk reductions, and even if statins also have “pleiotropic” effects, their main action in stroke prevention seems to be through LDL reduction.

The strength of this meta-analysis is that it was based on >90,000 randomized patients. However, biases were probably present because there was a significant asymmetry of the funnel plot (Figure 6). Biases attributable to small trials were the most likely explanation of this asymmetry because stroke in these trials was not a primary or even a secondary end point. Despite these potential biases, sensitivity analyses confirmed our main results. The limitations of this meta-analysis are that: (1) it was not based on individual data but on available data from the literature and additional information provided by the authors; (2) some authors did not send us additional information on the incidence of hemorrhagic stroke or recurrent strokes in patients with previous stroke before randomization or stroke incidence in some other important subgroups, such as age (young versus elderly subjects), gender, and low or average LDL-C at baseline; and (3) unfortunately, very limited data on ischemic stroke subtyping precluded any meta-analysis by ischemic stroke subtype, particularly among atherothrombotic, lacunar, cryptogenetic, and cardioembolic strokes.

The remaining burning question is whether statins with an aggressive LDL-C reduction actually reduce stroke recurrence in patients with a recent previous stroke and in the different ischemic stroke subtypes. This will be addressed in future trials.62

Acknowledgments

Public, academic, and institutional funding sources were used to perform this meta-analysis (PHRC AOA98004, SOS-ATTAQUE CEREBRALE Association) and the Formation de Recherche en Neurologie Vasculaire (Association Claude Bernard).

References


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Stroke. 2004;35:2902-2909; originally published online October 28, 2004;
doi: 10.1161/01.STR.0000147965.52712.fa
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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