Effects of Atorvastatin on Stroke in Patients With Unstable Angina or Non–Q-Wave Myocardial Infarction

A Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Substudy

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Background—This report describes the effect of intensive cholesterol lowering with atorvastatin on the incidence of nonfatal stroke, a secondary end point, in a randomized, placebo-controlled trial of patients with unstable angina or non–Q-wave myocardial infarction. The primary end point, a composite of death, nonfatal myocardial infarction, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization, was reduced from 17.4% in the placebo group to 14.8% in the atorvastatin group over the 16 weeks of the trial (P=0.048).

Methods and Results—Strokes were adjudicated by a blinded end-point committee using standard clinical and imaging criteria. The outcomes of nonfatal stroke and fatal plus nonfatal stroke were analyzed by time to first occurrence during the 16-week trial. Of 38 events (in 36 patients) adjudicated as fatal or nonfatal strokes, 3 were classified as hemorrhagic, one as embolic, and 29 as thrombotic or embolic; 5 could not be categorized. Nonfatal stroke occurred in 9 patients in the atorvastatin group and 22 in the placebo group (relative risk, 0.40; 95% confidence intervals, 0.19 to 0.88; P=0.02). Fatal or nonfatal stroke occurred in 12 atorvastatin patients and 24 placebo patients (relative risk, 0.49; 95% confidence intervals, 0.24 to 0.98; P=0.04). All 3 hemorrhagic strokes occurred in the placebo group.

Conclusion—Intensive cholesterol lowering with atorvastatin over 16 weeks in patients with acute coronary syndromes reduced the overall stroke rate by half and did not cause hemorrhagic stroke. These findings need to be confirmed in future trials. (Circulation. 2002;106:1690-1695.)

Key Words: cholesterol stroke angina myocardial infarction statins

Stroke is a relatively uncommon but potentially catastrophic complication of acute coronary syndromes.1 In these circumstances, stroke may be hemorrhagic (usually as a consequence of antithrombotic, antiplatelet, or fibrinolytic therapy), embolic (from the left atrium in association with atrial fibrillation or from a left ventricular thrombus), or atherosclerotic (caused by coexisting cerebrovascular disease). The age of patients presenting with acute coronary syndromes is gradually increasing, and the risk of stroke is higher in the elderly. The incidence of stroke may be underestimated from clinical trials of acute coronary syndromes because sicker and older patients are less likely to be enrolled.

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In the 3 major long-term statin trials involving patients with established coronary disease, stroke, or the combined end point of both, stroke and transient ischemic attack were significantly reduced after several years of active treat-

References

This finding is not surprising because the same mechanisms by which long-term statin treatment prevents plaque rupture in the coronary circulation are likely to apply in the cerebrovascular circulation, leading to a reduction in atherosclerotic events in both vascular beds. However, the risk of hemorrhagic stroke is significantly increased in subjects with spontaneously occurring low cholesterol levels; for example, the risk of death from hemorrhagic stroke was 3-fold higher in men with serum cholesterol levels <160 mg/dL in the Multiple Risk Factor Intervention Trial. Whether reducing cholesterol to very low levels with drugs increases the risk of hemorrhagic stroke is unknown.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study tested the hypothesis that an early, rapid, and profound reduction of serum cholesterol produced by high-dose atorvastatin treatment will reduce early recurrent events after an acute coronary syndrome. The trial randomized 3086 patients with unstable angina or non-Q-wave infarction to placebo or 80 mg/d atorvastatin, which was begun 24 to 96 hours after hospital admission. At the end of treatment, the mean LDL cholesterol level was 135 mg/dL in the placebo group and 72 mg/dL in the atorvastatin group. The primary, predefined end point was the time to first occurrence of death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization. This composite end point was reduced from 17.4% to 14.8%, a relative reduction of 16% \(P=0.048\). A secondary objective of the MIRACL trial was to determine the effect of this treatment on the incidence of stroke after acute coronary syndromes. The purpose of the present report is to describe the MIRACL results for stroke in detail.

Methods

Study Population
The design and main results of the MIRACL study have been described previously. The study was conducted at 122 centers in 19 countries. Patients with chest pain or discomfort lasting at least 15 minutes within the 24 hours preceding admission were eligible if objective evidence of myocardial ischemia was present. This usually consisted of new or dynamic ST or T-wave changes or elevated levels of cardiac troponin, creatine kinase, or its MB fraction, although patients could also qualify with a new echocardiographic wall motion abnormality or a new, reversible myocardial perfusion defect by radionuclide scintigraphy.

Patients were excluded if serum cholesterol exceeded 270 mg/dL, but there was no lower limit on cholesterol level at entry. Patients were excluded if coronary revascularization was anticipated, if an acute Q-wave MI had occurred within 1 month, coronary bypass surgery had occurred within the preceding 3 months, or a percutaneous coronary intervention had occurred within 6 months. Left bundle-branch block or paced ventricular rhythm, severe congestive heart failure, concurrent treatment with other lipid-lowering drugs (except low-dose niacin), severe anemia, renal failure requiring dialysis, hepatic dysfunction, insulin-dependent diabetes, pregnancy or lactation, and the use of drugs associated with rhabdomyolysis when combined with statins were other exclusion factors. All patients provided written, informed consent, and each local institutional review board approved the protocol.

Study Design
Between 24 and 96 hours (mean, 63 hours) after hospital admission, patients were randomly assigned to double-blind treatment with atorvastatin 80 mg/d or matching placebo for 16 weeks. All patients received instruction to promote compliance with the National Cholesterol Education Program Step I diet. Patients were seen in follow-up 2, 6, and 16 weeks after initiation of therapy, and laboratory testing was performed centrally at baseline and at 6 and 16 weeks.

Patients were monitored for end point events for 16 weeks after randomization. A committee of 6 cardiologists blinded to treatment assignment adjudicated all end points. The primary end point was a composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization. Predetermined secondary end points were nonfatal stroke, new or worsening congestive heart failure, worsening angina requiring hospitalization but without new objective evidence of ischemia, and coronary revascularization. Examination of fatal plus nonfatal stroke was a post hoc analysis.

The End Point Committee established clinical and imaging criteria to determine whether stroke had occurred and to classify strokes as hemorrhagic, embolic, thrombotic, or “unable to determine.” Transient ischemic attacks were not included as an end point and were not adjudicated by the committee because of their subjective nature.

Statistical Analysis
Time to first occurrence of nonfatal stroke and time to first occurrence of fatal plus nonfatal stroke were analyzed using stratified Cox proportional hazards models and were displayed using Kaplan-Meier curves. The Cox proportional hazards analyses were stratified by country and index event (unstable angina or non–Q-wave MI). Stepwise regression analyses were performed to determine predictors of nonfatal stroke and of fatal plus nonfatal stroke. The stratified Cox proportional hazards model that was used for the original stroke analyses was used as the starting point for the stepwise analyses. Baseline variables (Table 1) were added one by one to the original Cox model in the stepwise analysis, beginning with the variable with the smallest probability value. The stepwise process ended when none of the variables outside the model had a probability value <0.05 and every variable in the model had a \(P<0.10\).

Results
The clinical features at baseline of the 1538 patients randomized to atorvastatin and the 1548 randomized to placebo were similar, as shown for those with and without stroke in Table 1. Before hospitalization for the index event, 18% of the patients were taking aspirin, 2% an oral anticoagulant, 14% a nitrate, 11% a \(\beta\)-blocker, 9% a calcium channel blocker, and 12% an ACE inhibitor or angiotensin-II receptor blocker.

Serum Lipid Levels
At the time of randomization, serum lipid levels were similar in both groups; mean levels were 206 mg/dL for total cholesterol, 124 mg/dL for LDL cholesterol, 46 mg/dL for HDL cholesterol, and 182 mg/dL for triglycerides. Lipids were measured at 6 and 16 weeks after randomization; by 6 weeks, the reductions in total and LDL cholesterol and triglycerides with atorvastatin were essentially complete. Total and LDL cholesterol increased slightly during the study in the placebo group. LDL cholesterol increased by an adjusted mean of 12% from baseline to the end of treatment in the placebo group, to 135 mg/dL, and decreased by an adjusted mean of 40% in the atorvastatin group, to 72 mg/dL.

Stroke
As listed in Table 2, nonfatal stroke occurred in 22 placebo-treated and 9 atorvastatin-treated patients (relative risk, 0.40;
95% confidence intervals, 0.19 to 0.88; \( P \leq 0.02 \)). Fatal plus nonfatal stroke occurred in 24 placebo and 12 atorvastatin patients (relative risk, 0.49; 95% confidence intervals, 0.24 to 0.98; \( P \leq 0.04 \). The Kaplan-Meier curve for time to first nonfatal stroke in the 2 treatment groups is illustrated in the Figure. Stroke was associated with other adverse outcomes: 9 of the 36 stroke patients died, 5 from a fatal stroke, and 7 others experienced a nonfatal MI during the follow-up period. Each of the nonfatal MIs occurred before the stroke; the interval between the MI and the stroke ranged from 2 to 86 days, with 4 occurring within 14 days.

Only 3 strokes were classified with certainty as hemorrhagic, and all 3 were in the placebo group. Of the 8 strokes classified as either hemorrhagic or indeterminate, 5 were in the placebo group. Most of the strokes could be classified as either thrombotic or embolic, but a distinction could not be made between these 2 possibilities. Six strokes, all nonfatal, occurred within 14 days of a coronary intervention: 5 strokes of indeterminate origin followed coronary bypass surgery, 1 stroke occurred 10 days after an elective angioplasty.

### TABLE 1. Baseline Patient Characteristics by Treatment Group and Stroke Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Stroke</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=1524)</td>
<td>Atorvastatin (n=1526)</td>
</tr>
<tr>
<td>Age, y</td>
<td>65±12</td>
<td>65±12</td>
</tr>
<tr>
<td>Women</td>
<td>516 (34)</td>
<td>543 (36)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>428 (28)</td>
<td>428 (28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>829 (54)</td>
<td>838 (55)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>368 (24)</td>
<td>339 (22)</td>
</tr>
<tr>
<td>Medical history before randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>119 (8)</td>
<td>127 (8)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>132 (9)</td>
<td>126 (8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>137 (9)</td>
<td>145 (10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>382 (25)</td>
<td>377 (25)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>173 (11)</td>
<td>151 (10)</td>
</tr>
<tr>
<td>Inclusion event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>697 (46)</td>
<td>722 (47)</td>
</tr>
<tr>
<td>Non–Q-wave myocardial infarction</td>
<td>827 (54)</td>
<td>804 (53)</td>
</tr>
<tr>
<td>Baseline lipid measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>207±38</td>
<td>205±39</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>125±34</td>
<td>123±34</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>46±12</td>
<td>47±13</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>185±93</td>
<td>181±94</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of patients (%).

### TABLE 2. Strokes by Treatment and Type

<table>
<thead>
<tr>
<th>Type of Stroke</th>
<th>Placebo (n=1548)</th>
<th>Atorvastatin (n=1538)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of strokes</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Type of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Embolic</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic/embolic</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Number of patients experiencing a stroke (( P=0.04 )) (%)</td>
<td>24 (1.6)</td>
<td>12 (0.8)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2 (0.1)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Nonfatal stroke (( P=0.02 ))</td>
<td>22 (1.4)</td>
<td>9 (0.6)</td>
</tr>
</tbody>
</table>

Kaplan-Meier estimates for nonfatal stroke. The relative risk of nonfatal stroke in the atorvastatin group compared with the placebo group was 0.40 (95% confidence intervals, 0.19 to 0.88; \( P=0.02 \)), as based on a Cox proportional hazards analysis.
and one hemorrhagic stroke was diagnosed on the day after coronary stent placement in a patient treated with aspirin and heparin during the procedure.

Predictors of Stroke
As shown in Table 1, patients with stroke were, on average, 5 years older than the rest of the study population and were more likely to be women and to have a history of heart failure, cerebrovascular disease, or MI. Baseline lipid levels did not differ in patients who subsequently developed stroke. The medications used by patients during the trial were similar for patients with and without stroke in the 2 treatment groups (Table 3). In the atorvastatin group, on-treatment lipid levels were similar for patients with and without stroke.

By stepwise Cox proportional hazards analysis, 4 variables emerged as predictors of nonfatal stroke (Table 4). The risk of experiencing a nonfatal stroke for patients with a history of cerebrovascular disease was 3.44 times the risk for those without a previous MI was 1.99 times the risk of those without a previous MI. Treatment with atorvastatin was associated with a relative risk of 0.28 the risk of current smokers, for current smokers, the risk of experiencing a nonfatal stroke was 0.28 the risk of current smokers.

Discussion
In this trial, treatment with 80 mg/d atorvastatin, initiated soon after an episode of unstable angina or non–Q-wave MI, reduced the rate of nonfatal stroke and fatal plus nonfatal stroke by ≈50% over the ensuing 16 weeks. The incidence of stroke in the placebo group (1.6% over 16 weeks) is comparable to the 0.7% and 0.8% incidences at 30 days in 2 trials of acute coronary syndromes with large numbers of patients without ST elevation. In a registry of >18,000 patients with non–ST-elevation acute coronary syndrome, the stroke rate over a 6-month follow-up was 1.3%.

Previous Studies of Cholesterol Lowering and Stroke
To date, MIRACL is the only large, randomized trial to assess the short-term effects of cholesterol lowering in acute coronary syndromes. Long-term therapy with simvastatin or pravastatin in patients with stable coronary disease has been shown to reduce the risk of stroke or the combined end point of stroke and transient ischemic attack. In those trials, the reduction in coronary events and in cerebrovascular events was not apparent until 1 to 2 years after the initiation of treatment. This contrasts to the pattern in MIRACL, where the reduction in stroke and recurrent coronary events was apparent within weeks. This difference between MIRACL and the previous long-term statin trials may be a consequence of the much higher annualized stroke rate in MIRACL, with a treatment effect emerging earlier only because a sufficient number of events have occurred. An alternative explanation is that some patients with acute coronary syndromes may also have unstable plaques in other arterial beds.

Mechanisms
The mechanisms through which statins might reduce the incidence of stroke have been the subject of considerable speculation. Most ischemic strokes are caused by thromboemboli from atheromatous disease outside the brain, most commonly the carotid arteries and aortic arch. Cholesterol lowering, specifically with statins, is associated with plaque stabilization in carotid artery specimens from patients undergoing endarterectomy and retardation of progression of carotid atherosclerosis. Statins also may interfere with the thrombotic component of atherosclerotic stroke by inhibiting the intrinsic coagulation cascade at multiple points and by correcting the increased thrombogenic potential of platelets that is associated with hyperlipidemia. Higher C-reactive protein levels, reflecting an active inflammatory process, are associated with more rapid development of early carotid atherosclerosis and with an increased risk of stroke in apparently healthy middle-aged men. Statins reduce C-reactive protein levels as soon as 6 weeks after the initiation of therapy.

Statins may also protect against stroke by improving blood flow to the ischemic brain and by making brain parenchyma more resistant to ischemia. This protection is mediated in part by the upregulation by statins of endothelial nitric oxide synthase. Nitric oxide produced by endothelial nitric oxide synthase exerts its protective effect by the inhibition of leukocyte and platelet adhesion, vasodilatation, and increased thromboresistance of the endothelium.

In contrast, the inducible form of nitric oxide synthase is elaborated by astrocytes and macrophages in response to
proinflammatory mediators during ischemia and reperfusion.\textsuperscript{9,20–22} A statin has been shown to inhibit the upregulation of inducible nitric oxide synthase, as mediated by cytokines in astrocytes and macrophages.\textsuperscript{23} As a result of these mechanisms, statins reduce cerebral infarct volume by approximately one third in mouse models.\textsuperscript{18,19}

**Low Cholesterol and Hemorrhagic Stroke**

An increased risk of hemorrhagic stroke has been documented in subjects with very low serum cholesterol levels from diverse geographic areas.\textsuperscript{5,24,25} However, no increase in hemorrhagic stroke has been seen in patients receiving cholesterol-lowering drugs in the major statin trials. In MIRACL, lowering LDL cholesterol to a mean of 72 mg/dL for 16 weeks in patients with acute coronary syndromes did not cause hemorrhagic stroke, and it reduced the overall incidence of stroke. Few patients have been treated with potent statins to reduce LDL cholesterol levels for periods of longer than a few months. In one report of 319 patients treated for up to 1 year with atorvastatin who had LDL cholesterol levels ≤80 mg/dL, including 21 patients with on-treatment LDL cholesterol levels ≤50 mg/dL, adverse effects were not increased compared with treated patients with higher LDL cholesterol levels.\textsuperscript{26} Longer follow-up of larger numbers of patients treated to these levels with statins is required to determine whether or not the risk of hemorrhagic stroke is increased.

**Smoking**

By stepwise Cox proportional hazards analysis, the risk of stroke in our study was much lower in smokers than in nonsmokers. The reason for this seemingly paradoxical finding was apparent when the clinical features of current smokers were compared with nonsmokers. Smokers were 10 years younger (58±11 versus 68±11 years) and were less likely to have diabetes (16% versus 26%), hypertension (42% versus 60%), a history of heart failure (5% versus 9%), or previous coronary revascularization (8% versus 12%). Current smoking thus seemed to be acting as a surrogate marker for variables associated with a low risk of stroke, particularly age. A similar pattern has been reported in patients with MI, with smokers having a better short-term prognosis, primarily because they are a decade younger than nonsmokers and have a better risk profile.\textsuperscript{27,28}

**Limitations of the Study**

A limitation of this study is that the reduction in stroke incidence observed with atorvastatin in MIRACL may be due to chance ($P=0.02$ to 0.04). Nonetheless, nonfatal stroke was a predefined secondary end point of the trial, and the reduction in stroke occurred over the same time period as the reduction in the primary end point, a composite of coronary events. The duration of follow-up was only 16 weeks, so the longer-term effect of atorvastatin on stroke incidence in patients with acute coronary syndromes is unknown.

Strokes were adjudicated by a blinded end point committee and were categorized as to type. However, a distinction between embolic and thrombotic causes could not be made in many cases. The investigations done to document stroke and to determine the cause varied widely across the countries participating in MIRACL. Transient ischemic attacks were not included as an end point because of their subjective nature and, thus, they were not adjudicated.

In conclusion, intensive cholesterol lowering with atorvastatin over 16 weeks in patients with acute coronary syndromes reduced the overall stroke rate by half (albeit with wide confidence intervals), without causing hemorrhagic stroke. Because of the very large numbers of patients who experience acute coronary syndromes, which is estimated to be 1 to 2 million per year in the United States alone, an absolute reduction in stroke in this order would correspond to a large number of preventable events. However, the findings of this analysis need to be confirmed in future randomized trials.

**Acknowledgment**

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**References**


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