Clinical and Population Studies

Inflammation, Statin Therapy, and Risk of Stroke After an Acute Coronary Syndrome in the MIRACL Study

Scott Kinlay, Gregory G. Schwartz, Anders G. Olsson, Nader Rifai, Michael Szarek, David D. Waters, Peter Libby, Peter Ganz, for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators

Objective—Patients with acute coronary syndromes have an increased risk of stroke. We measured markers of inflammation in the MIRACL study, a randomized trial of atorvastatin versus placebo in acute coronary syndromes, to assess the relationship of inflammation to stroke.

Methods and Results—Baseline C-reactive protein (CRP), serum amyloid A (SAA), and interleukin-6 (IL-6) were collected in 2926 (95%) subjects. Baseline markers were related to stroke risk over the 16 weeks of the study. Subjects who subsequently experienced a stroke had higher CRP (27.5 versus 10.2 mg/L, \( P = 0.0032 \)), SAA (30.5 versus 16.0 mg/L, \( P = 0.031 \)), IL-6 (11 231 versus 6841 pg/L, \( P = 0.004 \)), and troponin (6.03 versus 3.19 ng/mL \( P = 0.0032 \)). The risk of stroke was related to greater CRP, SAA, and IL-6 in the placebo group only. Similarly, there was a graded increase in risk of stroke across quartiles of inflammatory markers in the placebo patients only.

Conclusions—In acute coronary syndromes, the early risk of stroke relates to both heightened inflammation and size of myocardial necrosis. Treatment with atorvastatin abrogated the risk associated with elevated markers of inflammation in this study, a finding that provides a novel rationale for the use of statins in acute coronary syndromes. (Arterioscler Thromb Vasc Biol. 2008;28:142-147.)

Key Words: stroke ■ acute coronary syndromes ■ inflammation ■ CRP ■ statin

An acute coronary syndrome tends to draw attention to the heart, whereas the high risk of stroke in this setting often goes unappreciated. For example, the risk of stroke in the month after an acute coronary syndrome is up to 10 times higher (2% to 3%) than the 1 month risk of stroke among patients with stable angina or remote myocardial infarction.1 Although, cardiac emboli may cause strokes, 1 population study indicated that strokes within 1 month of myocardial infarction were seldom related to left ventricular thrombus.2 Furthermore, temporal analyses suggest no difference in the rate of strokes with the introduction of thrombolytic therapy or primary percutaneous coronary intervention (PCI) for myocardial infarction, therapies that preserve cardiac wall motion and prevent the formation of mural thrombi.1,2

Intracranial arterial occlusion and emboli from atherosclerotic plaques in the carotid arteries and aortic arch can also cause stroke.3,4 Patients with acute coronary syndromes have more prevalent complex plaques in the carotid arteries,5 lesions more likely to lead to stroke and transient ischemic attack (TIA) than less complex plaques.6,7 Like their coronary counterparts, complex carotid plaques exhibit more commonly plaque disruption and inflammation, with abundant accumulations of activated leukocytes and the expression of cellular adhesion molecules.5,8,9 Serum concentrations of C-reactive protein (CRP) reflect in part vascular inflammation, and are higher in patients with complex compared with simple carotid plaques.10 CRP concentrations relate to incident stroke in healthy populations,10–14 but the relationship of CRP and of other soluble markers of inflammation to stroke early after an acute coronary syndrome is unknown.

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, atorvastatin reduced significantly the risk of stroke over 16 weeks compared with placebo in patients presenting with an acute coronary syndrome.15 As likely the last placebo-controlled statin trial in this setting, the MIRACL study offers the opportunity to assess the role of inflammation on the early risk of stroke after an acute coronary syndrome, and the effect of statin therapy.

Methods

Prior reports describe the design and main results of the MIRACL study.15,16 MIRACL was a multi-center study conducted in 122 centers in 19 countries in 3086 patients admitted to hospital with unstable...
angina or non—Q wave acute myocardial infarction. These diagnoses required chest discomfort lasting at least 15 minutes within the 24 hours preceding hospitalization and objective evidence of myocardial ischemia. The diagnosis of unstable angina required new or dynamic ST-segment or T-wave changes on the ECG, or a new wall motion or myocardial perfusion abnormality. The diagnosis of non-Q wave myocardial infarction required elevation of serum creatine kinase or its MB fraction, or troponin to a level exceeding 2 times the upper limit of normal. Patients were excluded if the serum cholesterol exceeded 270 mg/dL or if coronary revascularization was anticipated or occurred within 3 months (coronary bypass surgery) or 6 months (percutaneous coronary intervention). Other exclusions included severe congestive heart failure, dialysis-dependent renal failure, and insulin-requiring diabetes mellitus. All patients provided informed consent and the local institutional review boards approved the protocol.

Study Design
Between 24 and 96 hours after hospital admission, patients were randomized to double blind treatment with atorvastatin 80 mg/d or matching placebo for 16 weeks. The primary efficacy measure was the time to first occurrence of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or worsening angina with new objective evidence of ischemia and requiring emergency hospitalization. The stroke end points from this trial were excluded because of their subjective nature. Transient ischemic attacks were defined as the time to first occurrence of death, nonfatal acute myocardial infarction, and current smoking. Finally, the receiver operator characteristics of the inflammatory markers were graphed from the incidence of stroke among quartiles of the markers. Statistic significance was defined as a *P*<0.05.

Results
As reported previously, over the 16 weeks of follow-up there were 31 nonfatal strokes, and 36 fatal or nonfatal strokes (Placebo: 24 (1.6%), Atorvastatin: 12 (0.8%), *P*=0.04). This analysis concerns the 2926 (95%) subjects with baseline CRP measured, including all 36 subjects who had fatal and nonfatal strokes and 2889 subjects who were stroke free.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Subjects With CRP Measured and by Stroke Outcome</th>
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<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
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<tr>
<td><strong>Inclusion event, n (%)</strong></td>
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<tr>
<td>Unstable angina</td>
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<tr>
<td>Non—Q—wave myocardial infarction</td>
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<tr>
<td><strong>Medical history before randomization, n (%)</strong></td>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Coronary revascularization</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Current smoking</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td><strong>Baseline LDL cholesterol, mg/dL, mean (SD)</strong></td>
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<td><strong>Baseline HDL cholesterol, mg/dL, mean (SD)</strong></td>
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<tr>
<td><strong>Baseline inflammatory markers, median (25%—75%)</strong></td>
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<tr>
<td>CRP, mg/L</td>
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<tr>
<td>SAA, mg/L</td>
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<tr>
<td>IL-6, pg/L</td>
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<tr>
<td>Troponin, pg/mL, mean (SD)</td>
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</table>

Measurement of Inflammatory Markers
For this study, blood was collected into serum and EDTA tubes at baseline. The tubes were centrifuged on site and the serum or plasma separated and shipped to a core laboratory for storage at −70°C. Serum CRP and SAA were measured using high sensitivity immunonephelometry (Dade Behring). Plasma IL-6 was measured by ELISA (R&D Systems). The reproducibility of the assays over the study period was excellent (coefficients of variation for CRP: 4.5% at 12.6 mg/L; SAA: 6.2% at 14.8 mg/L; IL-6: 7.0% at 4.7 pg/mL). Troponin I was measured at baseline using the ACS:180 Chemiluminescence cTnl Immunoassay (Bayer Diagnostics).

Data Analysis
As described previously, the distributions of the CRP, SAA, and IL-6 were skewed, and the markers were log-transformed for the statistical models and anti—log-transformed for descriptive purposes, yielding geometric means and 95% confidence intervals (95%CI). The relationships between baseline inflammatory markers and stroke (fatal or nonfatal) over 16 weeks were assessed with Cox proportional hazards models in all subjects and by treatment group using log-transformed markers as a continuous distribution, and then in quartiles based on all subjects with the lowest quartile treated with atorvastatin as the reference group. The models were stratified by index event, age, and sex. Multivariate models included adjustment for baseline troponin levels and the previously reported risk factors for stroke in the MIRACL study of prior cerebrovascular disease, myocardial infarction, and current smoking. Finally, the receiver operator characteristics of the inflammatory markers were graphed from the incidence of stroke among quartiles of the markers.
to be smokers. The average baseline inflammatory markers and troponin were higher in subjects who developed stroke. Figure 1A shows univariate hazard ratios for stroke for the 3 inflammatory markers. Stroke was significantly related to greater concentrations of baseline CRP, SAA, and IL-6. Adjustments for baseline troponin did not substantially change these hazard ratios (All subjects per standard deviation in log marker: CRP: 1.38 (95%CI=1.05, 1.83), SAA: 1.26 (95%CI=1.02, 1.55), IL-6: 1.47 (95%CI=1.06, 2.05). Hazard ratios adjusted for troponin and other significant covariates from Table 1 were very similar (Figure 1B). In separate models, treatment group-by-baseline marker interaction terms were not statistically significant (probability values: CRP=0.41, SAA=0.15, IL-6=0.40). However, the main effects analyses showed strong and statistically significant relationships to stroke in the placebo group and failed to show such relationships in the atorvastatin group (Figure 1A and 1B).

Six strokes occurred within 14 days of coronary revascularization procedures (5 after surgical bypass and 1 after percutaneous intervention). Analyses excluding patients who subsequently had coronary artery bypass surgery or angioplasty and also patients with an elevated troponin continued to show similar relationships (Hazard ratios for all subjects per standard deviation in log marker: CRP: 1.58 [95%CI=1.07, 2.34], SAA: 1.47 [95%CI=1.03, 1.85], IL-6: 1.54 [95%CI=1.08, 2.76]).

The incidence of stroke across the quartiles of baseline inflammatory markers is shown in Table 2. Figure 2, shows the risk of stroke by quartiles of baseline inflammatory markers and by treatment group. Unadjusted and adjusted hazard ratios, revealed a graded, robust increase in the risk of stroke across higher quartiles of baseline inflammatory markers for the placebo group. In contrast, greater levels of inflammatory markers were not associated with the risk of stroke in the atorvastatin group, denoting that atorvastatin ameliorated the risk of stroke associated with high concentrations of inflammatory markers at the presenting acute coronary syndrome.

Receiver operator characteristics (ROC) for values of inflammatory markers exceeding the upper values in each quartile are shown in Figure 3, along with the ROCs of the clinical risk factors for stroke of past cerebrovascular disease, past myocardial infarction, and past congestive heart failure. The placebo group is shown separately as their risk relationships are not confounded by statin therapy.

The ROC curves for the inflammatory markers in all subjects and the placebo group show modest improvements beyond chance (ie, the 95%CI for area under the ROC curve exceeding 0.50). For all subjects, the areas under the ROC curves were: CRP: 0.63 (95%CI=0.54, 0.71), SAA: 0.58 (95%=0.50, 0.67), and IL-6: 0.62 (95%CI=0.54, 0.70). For the placebo group, the areas under the ROC curves were: CRP: 0.67

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Table 2. Incidence of Stroke (No. of Strokes/No. in Quartile) Over 16 Weeks Across Quartiles of Inflammatory Markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>≤4.3</td>
<td>4.4 to ≤10.2</td>
<td>10.3 to ≤35.3</td>
<td>&gt;35.3 to 58.0</td>
</tr>
<tr>
<td>Placebo, strokesotal (%)</td>
<td>2/370 (0.54)</td>
<td>3/369 (0.81)</td>
<td>8/376 (2.13)</td>
<td>11/352 (3.13)</td>
</tr>
<tr>
<td>Atorvastatin, strokesotal (%)</td>
<td>2/364 (0.55)</td>
<td>4/356 (1.12)</td>
<td>2/358 (0.56)</td>
<td>4/380 (1.05)</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>≤5.0</td>
<td>6.0 to ≤16.0</td>
<td>17.0 to ≤83.0</td>
<td>&gt;83.0</td>
</tr>
<tr>
<td>Placebo, strokesotal (%)</td>
<td>3/359 (0.84)</td>
<td>3/388 (0.77)</td>
<td>8/363 (2.20)</td>
<td>10/356 (2.81)</td>
</tr>
<tr>
<td>Atorvastatin, strokesotal (%)</td>
<td>2/350 (0.57)</td>
<td>5/375 (1.33)</td>
<td>3/359 (0.84)</td>
<td>2/373 (0.54)</td>
</tr>
<tr>
<td>IL6, pg/L</td>
<td>≤3756</td>
<td>&gt;3756 to ≤6902</td>
<td>&gt;6902 to ≤14876</td>
<td>&gt;14876</td>
</tr>
<tr>
<td>Placebo, strokesotal (%)</td>
<td>3/370 (0.81)</td>
<td>3/359 (0.84)</td>
<td>8/358 (2.23)</td>
<td>9/346 (2.60)</td>
</tr>
<tr>
<td>Atorvastatin, strokesotal (%)</td>
<td>0/343 (0.00)</td>
<td>3/354 (0.85)</td>
<td>7/355 (1.97)</td>
<td>2/367 (0.54)</td>
</tr>
</tbody>
</table>
(95% CI = 0.58, 0.77), SAA = 0.64 (95% CI = 0.54, 0.75), and IL-6 = 0.63 (95% CI = 0.53, 0.74). The ROCs of the clinical variables of past myocardial infarction, past cerebrovascular disease, and congestive heart failure fell on the curves for the CRP, SAA, and IL-6, and thus had similar prediction characteristics as to the inflammatory markers (Figure 3).

Discussion

In the MIRACL study, high-dose atorvastatin significantly reduced the elevated risk of stroke in the 16 weeks after an acute coronary syndrome compared with placebo. The current analysis explored potential inflammatory mechanisms for the link between stroke and acute coronary syndromes and the benefit of atorvastatin. In the setting of high concentrations of inflammatory markers typical of the early period after acute coronary syndromes, there were consistent relationships between elevations for each of the 3 markers of inflammation (CRP, SAA, and IL-6) assessed 24 to 96 hours after hospital admission and the 4-month risk of nonfatal and fatal stroke. This relationship was statistically significant in the placebo group and not in the atorvastatin group.

Figure 2. Hazard ratios of stroke in the 16 weeks after an acute coronary syndrome by quartiles of inflammatory markers in the placebo and atorvastatin groups. Graphs show univariate hazard and hazard adjusted for baseline troponin, prior cardiovascular disease, myocardial infarction, and current smoking. *P < 0.025, †P < 0.05.

Figure 3. Receiver operator characteristics for values of inflammatory markers exceeding the upper limits of each quartile and for the clinical history of prior myocardial infarction (MI), prior cerebrovascular disease (CVD), and prior congestive heart failure (CHF). Graphs are for all subjects and the placebo group.
Potential Mechanisms of Stroke

In the MIRACL study, 38 strokes occurred in 36 subjects and the majority (30/38) were classified as thrombotic or embolic strokes.\textsuperscript{15} The sources of emboli to consider would include the carotid arteries, aortic arch, or the heart.\textsuperscript{3,4} Although in studies of selected patient groups, large or anterior myocardial infarction increases the risk of stroke,\textsuperscript{18–20} in the Northern Sweden MONICA study (a population study), only 20% of strokes within 1 month of a myocardial infarct were associated with left ventricular thrombus.\textsuperscript{2} In the MIRACL study, troponin elevation related to the risk of stroke, suggesting that larger myocardial infarcts more likely serve as a source of cerebral emboli.

Six strokes in the MIRACL study occurred within 14 days of coronary revascularization (5 after surgical bypass and 1 after percutaneous intervention) and could reflect procedure-induced embolization from the aorta or the heart. However, a subgroup analysis excluding subjects with coronary revascularization and also excluding subjects with elevated troponin values continued to show a significant relationship between inflammation and the risk of stroke suggesting thrombosis or embolism within the cervical-cerebral circulation as a likely culprit. Consistent with our findings, several studies using immunohistochemistry show that statins stabilize features associated with carotid plaque vulnerability.\textsuperscript{21–23}

Complex carotid plaques are more prevalent in patients with acute coronary syndromes compared with those with stable angina.\textsuperscript{5} These plaques exhibit similar “high-risk” features to coronary plaques responsible for acute coronary syndromes. Plaques removed during carotid endarterectomy or at postmortem examinations of fatal carotid occlusions consistently show inflammatory cell infiltration, plaque rupture, and intraplaque hemorrhage.\textsuperscript{3,4,9} Complex or ulcerated carotid plaques are more likely to demonstrate these inflammatory and hemorrhagic features than smooth carotid plaques.\textsuperscript{8} The coronary arteries of patients with acute coronary syndrome also show wide-spread inflammation, as suggested by Berk and Buffon.\textsuperscript{24,25} The similar pathological findings in carotid and coronary arteries suggest an even wider inflammatory state involving multiple vascular beds that mechanistically links acute coronary syndromes to the elevated risk of stroke.

Effect of High-Dose Atorvastatin

We described previously an initial elevation and subsequent decline in inflammatory markers after an acute coronary syndrome among patients in the MIRACL trial.\textsuperscript{17} Furthermore, after 16 weeks of treatment with atorvastatin, compared with placebo, LDL cholesterol was 47% lower ($P<0.0001$), CRP was 34% lower ($P<0.0001$), and SAA was 13% lower ($P=0.0006$) but there was less impact on IL-6 (atorvastatin 3% lower than placebo, $P=0.3$).\textsuperscript{17} The present analysis shows that atorvastatin treatment markedly attenuated the risk of stroke associated with elevated levels of inflammatory markers (Figures 1 and 2). Together, these analyses suggest that statins reduce the high early risk of stroke in acute coronary syndromes by an antiinflammatory effect in carotid, intracerebral, and aortic atheromata—potentially mediated by lipid or nonlipid mechanisms. This hypothesis agrees with histopathologic observations of plaques removed at the time of elective carotid endarterectomy, where statin treatment reduces the abundance of inflammatory cells within 8 weeks, a time-frame entirely consistent with the findings in our study.\textsuperscript{23} More recently in the SPARCL study, high dose atorvastatin lowered the risk of recurrent stroke in patients with recent cerebrovascular events but who had no known coronary artery disease, also suggesting that this therapy targets vascular sources in the absence of any cardiac causes of stroke.\textsuperscript{26}

Additional mechanisms might contribute to the benefit of statins on strokes. In animals with ligation of the middle cerebral artery, statins increased nitric oxide bioavailability, augmented cerebral collateral blood flow, and reduced brain ischemia and infarct size.\textsuperscript{27} Accordingly, some cerebral ischemic events may not have reached a threshold of clinical detection as a result of atorvastatin treatment, resulting in a decreased number of adjudicated stroke end points. Unfortunately, scales of stroke severity were not applied in the MIRACL trial to allow further exploration of this hypothesis.

Other Studies of Statins in Stroke

Two other major randomized trials of statin therapy in acute coronary syndromes have compared high intensity versus moderate intensity statin therapy. Unlike this study, they did not have a placebo comparison group in which to study the natural history of inflammation and stroke after acute coronary syndromes. In the TIMI22-PROVE-IT study, the risk of stroke was relatively low (1% at 2 years),\textsuperscript{28} and a later analysis showed no difference between atorvastatin and pravastatin arms in the risk of stroke and TIA.\textsuperscript{29} However, 25% of subjects were on statins before enrollment compared with <1% in the MIRACL study. Prior statin therapy, even at modest doses, may reduce inflammation in carotid plaques\textsuperscript{23} that could confound the relationships of inflammation to stroke risk and the effects of statin treatment. In the A to Z trial,\textsuperscript{30} prior statin treatment was an exclusion criterion for enrollment. Rates of stroke were higher than in TIMI22-PROVE-IT and tended to be lower in the high-intensity treatment arm than in the moderate-intensity treatment arm (1.3% versus 1.8% over 2 years, $P=0.3$).

Clinical Implications

Patients with acute coronary syndromes are at high risk of stroke in the ensuing weeks and this study suggests that much of this risk relates to an inflammatory state marked by high plasma concentrations of CRP, SAA, and IL-6. Our study does not support widespread measurement of inflammatory markers in patients with acute coronary syndromes at this time. According to current guidelines, all patients with acute coronary syndrome should have consideration for intensive statin treatment to reduce the risk of coronary events.\textsuperscript{31} Our findings suggest that such treatment will have the added benefit of reducing the risk of stroke in this setting related to its antiinflammatory effects.

Conclusions

Acute coronary syndromes not only carry a high early risk of recurrent cardiac events but also have a high early risk of stroke. This elevated risk relates to a heightened inflamma-
tory state, but is attenuated by high dose atorvastatin. These findings provide new mechanistic insight into strokes periacute coronary syndromes and add to the rationale for intensive statin therapy in these patients.

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This study was supported by an unrestricted grant from Pfizer Pharmaceutica1. The Brigham and Women’s Hospital has a patent on the use of hsCRP in cardiovascular diagnosis.

Disclosures

References
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