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

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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 6,841 pg/L, \(P=0.004\)), and troponin (6.03 versus 3.19 ng/mL, \(P=0.0032\)). The risk of stroke was greater related to 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;28:000-000.)

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.8-10 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.15-18 MIRACL was a multi-center study conducted in 122 centers in 19 countries in 3086 patients admitted to hospital with unstable
were excluded because of their subjective nature. Nonfatal stroke was a predetermined secondary end point. Nonfatal and fatal stroke was not a predetermined end point. The Endpoint Committee used established clinical and imaging criteria to classify stroke as hemorrhagic, embolic, thrombotic, or “unable to determine.” Transient ischemic attacks were excluded because of their subjective nature.

**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).

## 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 1 shows the baseline characteristics of the subjects who had, and did not have, a fatal or nonfatal stroke during follow-up. Subjects who subsequently had a stroke were older, were more likely to have a past history of cerebrovascular disease, myocardial infarction and congestive heart failure, and were less likely to have a past history of cerebrovascular disease, myocardi...
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 $1.58 (95\%\text{CI} 1.07, 2.34)$, SAA $1.47 (95\%\text{CI} 1.03, 1.85)$, IL-6 $1.54 (95\%\text{CI} 1.08, 2.76)$). 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 $1.58 (95\%\text{CI} 1.07, 2.34)$, SAA $1.47 (95\%\text{CI} 1.03, 1.85)$, IL-6 $1.54 (95\%\text{CI} 1.08, 2.76)$).

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 (i.e., the 95% CI for area under the ROC curve exceeding 0.50). For all subjects, the areas under the ROC curves were: CRP $0.63 (95\%\text{CI} 0.54, 0.71)$, SAA $0.58 (95\%\text{CI} 0.50, 0.67)$, and IL-6 $0.62 (95\%\text{CI} 0.54, 0.70)$. For the placebo group, the areas under the ROC curves were: CRP $0.67$.
(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.\(^\text{15}\) 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) 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.
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. The sources of emboli to consider would include the carotid arteries, aortic arch, or the heart. Although studies of selected patient groups, large or anterior myocardial infarction increases the risk of stroke, 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.

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. 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), and a later analysis showed no difference between atorvastatin and pravastatin arms in the risk of stroke and TIA. 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 that could confound the relationships of inflammation to stroke risk and the effects of statin treatment. In the A to Z trial, 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. 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 peri-acute coronary syndromes and add to the rationale for intensive statin therapy in these patient groups.

Sources of Funding

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

Disclosures

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Arterioscler Thromb Vasc Biol. published online November 8, 2007;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2007/11/08/ATVBAHA.107.151787.citation

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