High-Dose Atorvastatin Enhances the Decline in Inflammatory Markers in Patients With Acute Coronary Syndromes in the MIRACL Study

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Conclusions—High-dose atorvastatin potentiated the decline in inflammation in patients with acute coronary syndromes.

Background—Inflammation promotes acute coronary syndromes and ensuing clinical complications. Although statins reduce inflammatory markers in asymptomatic adults or in patients with stable angina, the effect of statins on the markedly heightened inflammation in patients with acute coronary syndromes is unknown.

Methods and Results—We measured C-reactive protein (CRP), serum amyloid A (SAA), and interleukin 6 (IL-6) in 2402 subjects enrolled the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study. Subjects with unstable angina or non–Q-wave myocardial infarction were randomized to atorvastatin 80 mg/d or placebo within 24 to 96 hours of hospital admission and treated for 16 weeks. The effect of treatment on inflammatory markers was assessed by ANCOVA after adjustment for presenting syndrome, country, and initial level of marker. All 3 markers were markedly elevated at randomization and declined over the 16 weeks in both treatment groups. Compared with placebo, atorvastatin significantly reduced CRP, −83% (95% CI, −84%, −81%) versus −74% (95% CI, −75%, −71%) (P<0.0001) and SAA, −80% (95% CI, −82%, −78%) versus −77% (−79%, −75%) (P=0.0006) but not IL-6, −55% (95% CI, −57%, −53%) versus −53% (95% CI, −55%, −51%) (P=0.3). Reductions in CRP and SAA were observed in patients with unstable angina and non–Q-wave myocardial infarction, with initial LDL cholesterol <3.2 or ≥3.2 mmol/L (125 mg/dL), age ≥65 or <65 years, and in men and women. By 16 weeks, CRP was 34% lower with atorvastatin than with placebo.

Conclusions—High-dose atorvastatin potentiated the decline in inflammation in patients with acute coronary syndromes.

This supports the value of early statin therapy in these patients. (Circulation. 2003;108:1560-1566.)

Key Words: inflammation ▪ myocardial infarction ▪ angina

Cardiovascular events typically arise from the disruption of atherosclerotic plaques that contain numerous inflammatory cells. Inflammatory cells release cytokines that inhibit the production of collagen and enzymes that degrade extracellular matrix in the fibrous cap of atherosclerotic plaques. Activated inflammatory cells produce tissue factor that promotes thrombus formation by disrupted atheroma.

Although histopathologic assessment of inflammation within atheromas is impractical in the clinical setting, circulating markers of inflammation can provide readily measured insights. Proteins secreted by activated leukocytes and activated vascular cells, including interleukin 6 (IL-6), circulate in small but detectable quantities. IL-6 is probably the principal “messenger” cytokine that stimulate hepatocytes to produce large amounts of C-reactive protein (CRP) and serum amyloid A (SAA), components of the acute-phase response. During inflammatory disorders, serum concentrations of acute-phase proteins can rise dramatically and in acute...
coronary syndromes relate to the risk of subsequent cardiovascular events. In unstable angina, marked elevations in markers are presumably derived from vascular inflammation. Infarcted myocardium, when present, provides a second source of inflammation.

Although HMG-CoA reductase inhibitors (statins) can reduce the concentration of CRP in subjects free of overt cardiovascular disease or in patients with stable coronary disease, it is uncertain whether statins moderate the pronounced inflammation associated with acute coronary syndromes. Furthermore, it is uncertain whether statins reduce CRP selectively or whether they can modulate other markers of inflammation.

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, high-dose atorvastatin (80 mg/d) started within 24 to 96 hours of admission for unstable angina or non–Q-wave myocardial infarction reduced recurrent ischemic events over a 16-week treatment period compared with placebo. We investigated whether atorvastatin, compared with placebo, affected the circulating concentrations of CRP, SAA, and IL-6 in the MIRACL study population.

Methods

Study Population

MIRACL was a multicenter 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 representing a change in the usual pattern of angina. The diagnosis of unstable angina required new or dynamic ST-wave or T-wave changes in at least 2 contiguous ECG leads 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 of troponin I to a level exceeding 2 times the upper limit of normal. All patients provided informed consent. The protocol was approved by local institutional review boards.

Study Design

Between 24 and 96 hours after hospital admission, patients were randomly assigned 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.

Measurement of Inflammatory Markers

For this study, blood was collected into a serum tube and into a tube with EDTA anticoagulant at baseline and at 16 weeks. The tubes were centrifuged on site, and the serum or plasma was separated and shipped to a core laboratory for storage at −70°C. The paired baseline and 16-week samples were shipped to the laboratory and measured in batches.

CRP and SAA were measured by high-sensitivity immunonephelometry (Dade Behring). 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 with the ACS:180 Chemiluminescence cTnI Immunounassay (Bayer Diagnostics).

Data Analysis

This report focuses on the 2402 (78%) of the 3086 subjects in the MIRACL study with baseline and 16-week samples available for measurement of inflammatory markers. As expected, the distributions of the inflammatory markers were skewed. To meet the distributional assumptions of the statistical models, the markers were log-transformed for the statistical models and antilog-transformed for descriptive purposes, yielding geometric means and 95% CIs for baseline, week-16 levels, and the change in levels over the study period. The prespecified primary end point was the difference between treatment groups in change in CRP over the 16-week study period. The primary end point was assessed by ANCOVA adjusted for presenting syndrome (unstable angina and non–Q-wave MI), country, and initial level of marker. Secondary end points included the difference between the treatment groups in change in SAA and IL-6 over 16 weeks, comparisons of the markers at 16 weeks, and the changes in each inflammatory marker over 16 weeks according to presenting syndrome, baseline LDL cholesterol (above and below the median value of 3.2 mmol/L [125 mg/dL]), sex, and age (≥65 or <65 years old). We also examined the change in inflammatory markers according to the following categories defined by the initial troponin level: no detectable myocardial necrosis (troponin I, <0.1 ng/mL), below the diagnostic threshold of myocardial infarction (troponin I, 0.1 to 1.0 ng/mL), and myocardial infarction (troponin I, >1.0 ng/mL). Statistical significance was defined as a value of \( P<0.05 \).

Results

The baseline characteristics of the 2402 subjects did not differ significantly between the 2 treatment groups or compared with the entire study population in the MIRACL Study (Table 1). The average LDL cholesterol was 3.2 mmol/L (125 mg/dL), and there was a significantly greater reduction in LDL with atorvastatin [from 3.2 mmol/L (124 mg/dL) to 1.9 mmol/L (72 mg/dL)] compared with placebo [from 3.2 mmol/L (125 mg/dL) to 3.5 mmol/L (136 mg/dL)], \( P<0.0001 \) versus atorvastatin over the 16 week study.

Markers of Inflammation

As expected, the circulating levels of CRP, SAA, and IL-6 were markedly elevated within 24 to 96 hours of hospitalization of the acute coronary event (Figure 1). There was a substantial decrease over 16 weeks in the placebo group in all 3 markers, consistent with at least partial resolution of the inflammatory process after the acute coronary event. Compared with placebo, use of atorvastatin was associated with a greater reduction in CRP (\( P<0.0001 \)) and SAA (\( P=0.0006 \)) (Table 2). Moreover, after 16 weeks of treatment, CRP was 34% lower and SAA 13% lower in patients treated with atorvastatin compared with placebo (Figure 2).

Compared with placebo, atorvastatin did not significantly enhance the reduction in circulating IL-6 over 16 weeks (\( P=0.3 \)).

Initial Presentation According to Unstable Angina or Non–Q-Wave Myocardial Infarction

Subjects presenting with non–Q-wave myocardial infarction had higher baseline levels of the inflammatory markers than those with unstable angina (Table 3). Compared with placebo, atorvastatin reduced CRP significantly in patients with unstable angina and with non–Q-wave myocardial infarction. Compared with placebo, atorvastatin reduced SAA in patients...
with non–Q-wave myocardial infarction, and there was a strong trend for a similar reduction in patients with unstable angina (Table 3).

Results According to Troponin Concentrations
There were 1275 subjects with troponin <1.0 ng/mL, a common diagnostic threshold for myocardial infarction for this assay. These subjects were divided further into those with troponin <0.1 ng/mL (no evidence of myocardial necrosis) and those with troponin between 0.1 and 1.0 ng/mL (no definite evidence of myocardial necrosis). The remaining 1016 subjects with troponin >1.0 ng/mL had definite evidence of myocardial necrosis on enrollment, which would be an additional source of inflammation. The decline in CRP and SAA was significantly greater with atorvastatin than with placebo in subjects without evidence of definite myocardial infarction (troponin I, 0.1 to 1.0 ng/mL) or even in subjects without any evidence of myocardial necrosis by this assay (troponin I, <0.1 ng/mL) (Table 4). These changes were consistent with treatment effects in the 1016 subjects with definite myocardial infarction (troponin >1.0 ng/mL) (Table 4).

Effect of Initial LDL Cholesterol
The initial levels of all 3 inflammatory markers were higher in subjects with LDL cholesterol below the median value of 3.2 mmol/L (125 mg/dL) than those with LDL above the median (Table 5). The subjects with LDL below the median had greater myocardial injury, with troponin levels that were higher than in subjects with LDL above the median (geometric mean, 0.95 versus 0.68 ng/mL, P<0.001).

The reduction in CRP was significantly greater with atorvastatin in both the high- and the low-LDL cholesterol subgroups (Table 5). The reduction in SAA was significantly greater with atorvastatin in the low-LDL cholesterol subgroup and showed a similar trend in the high-LDL cholesterol subgroup (Table 5).

Other Subgroups
Men and women and older (≥65 years) and younger (<65 years) subjects showed directional changes in the inflammatory markers with atorvastatin treatment compared with placebo that were similar to those of the entire cohort of MIRACL patients (Figure 2).

Discussion
The results of this study demonstrate that intensive use of atorvastatin enhances the resolution of the marked inflammatory response associated with acute coronary syndromes. At 16 weeks, CRP was 34% lower with atorvastatin than with placebo. Because the circulating concentrations of inflammatory markers are closely linked to cardiovascular outcomes, our results reinforce the clinical benefit observed in the
MIRACL study and support the value of intensive lipid lowering in this setting.

**Effect of Statins on Inflammation in Acute Coronary Syndromes**

Coronary inflammation can stimulate an acute-phase response in the absence of associated myocardial necrosis, because increases in CRP, SAA, and IL-6 are commonly observed in patients with unstable angina without detectable serum troponin. Nonetheless, inflammation is also abundant within the necrotic regions of myocardial infarcts. Atorvastatin reduced CRP and SAA in subjects without myocardial necrosis (undetectable troponin) and in those with myocardial necrosis. These data suggest that atorvastatin can ameliorate the vascular component of inflammation associated with this condition and support histological analyses from atherosclerotic animals and humans treated with statins. By reducing macrophage accumulation, statins may promote "plaque stabilization," a vascular mechanism consistent with a reduction in clinical events in the statin trials, including MIRACL.

Recent smaller studies in patients with stable coronary disease find a greater reduction in CRP with higher- than with lower-dose statins, and in another study of patients with type II diabetes, 80 mg/d atorvastatin reduced CRP more than 10 mg/d of atorvastatin. Our study could not assess the effect of low-dose statins, because we compared only 80 mg atorvastatin with placebo. However, these studies suggest that smaller doses of statins might have a lesser anti-inflammatory effect in acute coronary syndromes.

**Effect of Treatment on Individual Inflammatory Markers**

The anti-inflammatory effect of statins was not limited to a reduction in CRP. Atorvastatin had a consistent effect on both inflammatory markers produced primarily in the liver, CRP and SAA. IL-6 is a cytokine that circulates in much lower concentrations than CRP and SAA. Absence of a significant reduction in IL-6 by atorvastatin could be related to its greater diurnal variability and shorter half-life (2 to 4 hours) compared with CRP (20 hours) and SAA (24 to 48 hours). Accordingly, it is likely that IL-6 was changing more rapidly than CRP or SAA when the initial blood samples were obtained in the present study (24 to 96 hours after hospital admission), increasing its variance compared with CRP and SAA. Although the reductions in IL-6 with atorvastatin were not statistically significant, the trend observed for this marker agreed with the changes seen with CRP and SAA.

### Table 2. Inflammatory Markers at Baseline and 16 Weeks and Change Over 16 Weeks

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo (n=1216), Mean (95% CI)</th>
<th>Atorvastatin (n=1186), Mean (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>11.0 (10.1, 11.9)</td>
<td>11.5 (10.6, 12.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline</td>
<td>16 weeks</td>
<td>Change (95% CI)</td>
<td>74% (71%, 75%)</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>22.4 (20.4, 24.7)</td>
<td>23.0 (20.9, 25.4)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Baseline</td>
<td>16 weeks</td>
<td>Change (95% CI)</td>
<td>77% (75%, 79%)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>7.5 (7.0, 7.9)</td>
<td>7.6 (7.2, 8.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline</td>
<td>16 weeks</td>
<td>Change (95% CI)</td>
<td>53% (51%, 55%)</td>
</tr>
</tbody>
</table>

*Mean indicates geometric mean, P value from ANCOVA after adjustment for baseline level, country, and presenting syndrome.

**Figure 2.** Percent difference (95% CIs) between atorvastatin and placebo in inflammatory markers at 16 weeks for all subjects and by sex and age subgroups. Negative value indicates atorvastatin lower than placebo. NQMI indicates non–Q-wave myocardial infarction; UAP, unstable angina pectoris.
Reduction in CRP by Atorvastatin May Be Anti-Inflammatory

In addition to its role as a marker of inflammation, CRP may be a direct participant in vascular inflammation and plaque destabilization. Immunohistochemical staining of atherosclerotic plaques has colocalized CRP with complement proteins and macrophages. Serum levels of CRP correlate with the amount of CRP in atheroma and with anatomic features of plaque destabilization.

In experimental studies, CRP has a number of potentially important proinflammatory actions. It attenuates the production of nitric oxide by endothelial cells and increases the endothelial expression of cellular adhesion molecules. CRP is chemotactic for monocytes. CRP may also increase the susceptibility of endothelial cells to destruction by cell lysis, a mechanism that could lead to plaque erosion or rupture, which precipitates acute coronary syndromes.

Thus, although the reduction in CRP by atorvastatin certainly serves as a marker of reduced inflammation, it may also attenuate a potential direct inflammatory trigger to cardiovascular events.

**Impact of Initial LDL Cholesterol**

Our finding that patients with below-average LDL cholesterol demonstrate the same reduction in the inflammatory markers CRP and SAA as patients with above-average LDL cholesterol supports the clinical benefit observed in this subgroup in the main trial.4

**TABLE 3. Inflammatory Markers at Baseline and 16 Weeks and Change Over 16 Weeks According to Presenting Syndrome**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Placebo (n=544), Mean (95% CI)</th>
<th>Atorvastatin (n=555), Mean (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.6 (5.9, 7.3)</td>
<td>7.0 (6.2, 7.8)</td>
<td></td>
</tr>
<tr>
<td>16 weeks</td>
<td>3.1 (2.8, 3.4)</td>
<td>2.0 (1.8, 2.2)</td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>−55% (−52%, −58%)</td>
<td>−71% (−68%, −74%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.4 (11.0, 14.0)</td>
<td>13.8 (12.1, 15.7)</td>
<td></td>
</tr>
<tr>
<td>16 weeks</td>
<td>5.1 (4.6, 5.6)</td>
<td>4.7 (4.3, 5.1)</td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>−60% (−57%, −63%)</td>
<td>−64% (−61%, −67%)</td>
<td>0.07</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.8 (5.3, 6.2)</td>
<td>5.5 (5.0, 6.0)</td>
<td></td>
</tr>
<tr>
<td>16 weeks</td>
<td>3.6 (3.4, 4.0)</td>
<td>3.4 (3.2, 4.0)</td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>−36% (−33%, −38%)</td>
<td>−40% (−38%, −43%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Mean indicates geometric mean, P value from ANCOVA after adjustment for baseline level, country, and presenting syndrome.

**TABLE 4. Changes in Inflammatory Markers According to Categories of Initial Troponin Corresponding to No Detectable Myocardial Necrosis (<0.1 ng/mL), Below the Diagnostic Threshold for Myocardial Infarction (0.1–1.0 ng/mL), and Myocardial Infarction (>1.0 ng/mL)**

<table>
<thead>
<tr>
<th>Troponin Category, Marker</th>
<th>Placebo, Mean (95% CI)</th>
<th>Atorvastatin, Mean (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin &lt;0.1 ng/mL</td>
<td>n=376</td>
<td>n=386</td>
<td></td>
</tr>
<tr>
<td>Change in CRP</td>
<td>−54% (−46%, −60%)</td>
<td>−69% (−64%, −74%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in SAA</td>
<td>−57% (−50%, −63%)</td>
<td>−62% (−56%, −67%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Change in IL-6</td>
<td>−38% (−31%, −44%)</td>
<td>−42% (−35%, −48%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Troponin 0.1–1.0 ng/mL</td>
<td>n=262</td>
<td>n=251</td>
<td></td>
</tr>
<tr>
<td>Change in CRP</td>
<td>−56% (−47%, −63%)</td>
<td>−72% (−67%, −77%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in SAA</td>
<td>−53% (−46%, −60%)</td>
<td>−62% (−56%, −67%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Change in IL-6</td>
<td>−40% (−32%, −48%)</td>
<td>−43% (−36%, −50%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Troponin &gt;1.0 ng/mL</td>
<td>n=527</td>
<td>n=489</td>
<td></td>
</tr>
<tr>
<td>Change in CRP</td>
<td>−85% (−83%, −87%)</td>
<td>−91% (−89%, −92%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in SAA</td>
<td>−88% (−87%, −90%)</td>
<td>−90% (−89%, −92%)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Change in IL-6</td>
<td>−67% (−63%, −70%)</td>
<td>−67% (−63%, −71%)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
We found that patients with below-average LDL cholesterol have higher levels of inflammatory markers and higher serum troponin values than patients with above-average LDL cholesterol (Table 5). This inverse relationship between lipids and inflammatory markers may be explained by LDL cholesterol as an acute-phase reactant, but one that is reduced after an acute event. Thus, a low LDL cholesterol measured more than 24 hours after an acute coronary syndrome may define a population of sicker subjects.28 Our study suggests that in the acute coronary syndrome setting, future guidelines for lipid-lowering therapy might consider lower LDL cholesterol thresholds than those used for stable coronary syndromes.

In conclusion, intensive lipid lowering with high-dose atorvastatin potentiates the resolution of inflammation after acute coronary syndromes, as reflected by substantially lower levels of CRP and SAA at 16 weeks compared with placebo. These findings support an anti-inflammatory effect of high-dose statin therapy in patients with acute coronary syndromes; however, the minimum dose required for this effect and the relationship to reduction in risk require further study. Nevertheless, our results reinforce the concept of early lipid lowering soon after acute coronary syndromes.

Acknowledgments

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References


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