Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes: The MIRACL Study: A Randomized Controlled Trial

Gregory G. Schwartz; Anders G. Olsson; Michael D. Ezekowitz; et al.


http://jama.ama-assn.org/cgi/content/full/285/13/1711

Correction
Correction is appended to this PDF and also available at http://jama.ama-assn.org/cgi/content/full/jama:286/5/536
Contact me if this article is corrected.

Citations
This article has been cited 1012 times.
Contact me when this article is cited.

Topic collections
Nutritional and Metabolic Disorders; Lipids and Lipid Disorders; Cardiovascular System; Randomized Controlled Trial; Cardiovascular Disease/ Myocardial Infarction
Contact me when new articles are published in these topic areas.

Related Articles published in the same issue
Lipid-Lowering Therapy in Acute Coronary Syndromes

April 4, 2001

Related Letters
Atorvastatin for Acute Coronary Syndromes

Aggressive Lipid-Lowering Therapy and Regression of Coronary Atheroma
Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes
The MIRACL Study: A Randomized Controlled Trial

Gregory G. Schwartz, MD, PhD
Anders G. Olsson, MD, PhD
Michael D. Ezekowitz, MD, PhD
Peter Ganz, MD
Michael F. Oliver, MD
David Waters, MD
Andreas Zeiher, MD
Bernard R. Chaitman, MD
Sally Leslie, PhD
Theresa Stern, PhD
for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators

**Background**
Blood cholesterol lowering with statins has been regarded as a long-term strategy to reduce death and ischemic cardiovascular events in patients with stable coronary heart disease, with significant effects evident after approximately 2 years of treatment. Previous trials excluded patients who had experienced recent unstable angina or acute myocardial infarction (MI). However, it is within the early period after an acute coronary syndrome (ACS) that patients experience the highest rate of death and recurrent ischemic events. To date, it has not been determined whether initiation of treatment with a statin soon after an ACS can reduce the occurrence of these early events.

**Context**
Patients experience the highest rate of death and recurrent ischemic events during the early period after an acute coronary syndrome, but it is not known whether early initiation of treatment with a statin can reduce the occurrence of these early events.

**Objective**
To determine whether treatment with atorvastatin, 80 mg/d, initiated 24 to 96 hours after an acute coronary syndrome, reduces death and nonfatal ischemic events.

**Design and Setting**
A randomized, double-blind trial conducted from May 1997 to September 1999, with follow-up through 16 weeks at 122 clinical centers in Europe, North America, South Africa, and Australasia.

**Patients**
A total of 3086 adults aged 18 years or older with unstable angina or non-Q-wave acute myocardial infarction.

**Interventions**
Patients were stratified by center and randomly assigned to receive treatment with atorvastatin (80 mg/d) or matching placebo between 24 and 96 hours after hospital admission.

**Main Outcome Measures**
Primary end point event defined as death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization.

**Results**
A primary end point event occurred in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group (relative risk [RR], 0.84; 95% confidence interval [CI], 0.70-1.00; P = .048). There were no significant differences in risk of death, nonfatal myocardial infarction, or cardiac arrest between the atorvastatin group and the placebo group, although the atorvastatin group had a lower risk of symptomatic ischemia with objective evidence and requiring emergency rehospitalization (6.2% vs 8.4%; RR, 0.74; 95% CI, 0.57-0.95; P = .02). Likewise, there were no significant differences between the atorvastatin group and the placebo group in the incidence of secondary outcomes of coronary revascularization procedures, worsening heart failure, or worsening angina, although there were fewer strokes in the atorvastatin group than in the placebo group (12 vs 24 events; P = .045). In the atorvastatin group, mean low-density lipoprotein cholesterol level declined from 124 mg/dL (3.2 mmol/L) to 72 mg/dL (1.9 mmol/L). Abnormal liver transaminases (>3 times upper limit of normal) were more common in the atorvastatin group than in the placebo group (2.5% vs 0.6%; P < .001).

**Conclusion**
For patients with acute coronary syndrome, lipid-lowering therapy with atorvastatin, 80 mg/d, reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization.

JAMA. 2001;285:1711-1718

For editorial comment see p 1758.

©2001 American Medical Association. All rights reserved.
atherial function,

decrease platelet aggregability and thrombus deposition,

and reduce vascular inflammation.

Each of these mechanisms might be expected to have a favorable impact in the early period following an ACS.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study tested the hypothesis that treatment with atorvastatin (80 mg/d), initiated soon after presentation with unstable angina or non-Q-wave acute MI, reduces the occurrence of early, recurrent ischemic events and death.

METHODS

Study Population

The design of the MIRACL study has been described in detail previously. It was conducted at 122 centers in Europe, North America, South Africa, and Australasia. Eligible patients were adults aged 18 years or older with chest pain or discomfort of at least 15 minutes’ duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and represented a change from their usual anginal pattern. In addition, diagnosis of unstable angina required evidence of myocardial ischemia by at least 1 of the following: new or dynamic ST-wave or T-wave changes or ST-T-wave changes in at least 2 contiguous standard electrocardiographic leads, a new wall motion abnormality by echocardiography, a new and reversible myocardial perfusion defect by radionuclide scintigraphy, or elevation of cardiac troponin to a level exceeding 2 times the upper limit of normal (ULN). Diagnosis of non-Q-wave acute MI required elevation of serum creatine kinase or its MB fraction, or troponin to a level exceeding 2 times the ULN.

Patients were excluded if the serum total cholesterol level at screening exceeded 270 mg/dL (7 mmol/L) (sites in Poland and South Africa used levels of 310 mg/dL [8 mmol/L]). There was no lower limit on cholesterol level at entry. Patients were excluded if coronary revascularization was planned or anticipated at the time of screening. Other exclusion criteria were: evidence of Q-wave acute MI within the preceding 4 weeks; coronary artery bypass surgery within the preceding 3 months; percutaneous coronary intervention within the preceding 6 months; left bundle-branch block or paced ventricular rhythm; severe congestive heart failure (New York Heart Association class IIIb or IV); concurrent treatment with other lipid-regulating agents (except niacin at doses of 500 mg/d), vitamin E (except at doses ≤400 IU/d), or drugs associated with rhabdomyolysis in combination with statins; severe anemia; renal failure requiring dialysis; hepatic dysfunction (alanine aminotransferase greater than 2 times ULN); insulin-dependent diabetes; pregnancy or lactation.

Study Design

The study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by local ethics committees or institutional review boards. Written informed consent was obtained from all patients. Between 24 and 96 hours after hospital admission, eligible patients were randomly assigned with stratification by center to double-blind treatment with atorvastatin (80 mg/d) or matching placebo for 16 weeks. Treating physicians were requested not to perform any determinations of serum lipid levels in the local hospital laboratory during the study period. The protocol did not restrict or specify any other diagnostic or therapeutic measures, except as noted in the exclusion criteria. All patients received instruction and counseling to promote compliance with a National Cholesterol Education Program Step I diet. Patients were seen in follow-up 2, 6, and 16 weeks after the initiation of therapy. Laboratory testing was performed centrally at baseline and at 6 and 16 weeks. An independent data and safety monitoring board reviewed the results of 3 planned interim analyses using P<.001 for the primary end point analysis as a statistical stopping guideline. On each occasion, continuation of the study was recommended.

End Points

Patients were monitored for ischemic events for 16 weeks after randomization. All end points were adjudicated by a committee of 6 cardiologists, who were blinded to treatment assignment. The primary combined end point was death, nonfatal acute MI, cardiac arrest with re-suscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization. A blinded core laboratory confirmed electrocardiographic entry criteria and diagnosis of acute MI from electrocardiographic and cardiac enzyme data, using previously published criteria. Cardiac arrest with resuscitation and recurrent symptomatic myocardial ischemia with objective evidence and emergency rehospitalization were diagnosed according to previously published criteria. The latter diagnosis required both exacerbation of the patient’s usual symptoms and new objective evidence of ischemia (electrocardiographic, echocardiographic, or scintigraphic) with a definite change from a comparison study performed after the index (inclusion) ischemic event.

Secondary end points were the occurrence of each primary end point component as well as nonfatal stroke, new or worsening congestive heart failure requiring hospitalization, worsening angina requiring rehospitalization but without new objective evidence of ischemia, coronary revascularization by surgical or percutaneous means, time to first occurrence of any primary or secondary end point, and percentage changes in blood lipid levels from baseline to end of study. When recurrent symptomatic ischemia with objective evidence or worsening congestive heart failure occurred during the index hospitalization or a subsequent hospitalization for another reason, the event was classified as an end point if the end point committee judged that the event would have required rehospitalization had it occurred outside of hospital.
**Statistical Analysis**

The initial sample size requirement was 2100 patients, based on the assumption of 20% occurrence of a primary end point event among placebo-treated patients and 14% occurrence among atorvastatin-treated patients (ie, an average occurrence of 17% in both treatment groups), 2-sided significance level of .05, and 95% power.\(^\text{13}\) Pooled data (blinded to treatment assignment) from the first 1260 patients indicated that the occurrence of primary end points was 13% (ie, 4% less than predicted). Consequently, the steering committee recommended an increase in sample size to 3000 patients to maintain 95% power to detect a 30% relative treatment effect and 80% power to detect a 25% relative treatment effect.

The primary combined end point was analyzed by time of first event, using a Cox proportional hazards model\(^\text{16}\) stratified by country and inclusion event (unstable angina or non–Q-wave acute MI). The occurrence of each end point was analyzed using the Cochran Mantel-Haenszel method,\(^\text{17}\) stratified by country and inclusion event. All end point analyses were performed on an intention-to-treat basis, with all randomized patients included in the analyses. Censoring occurred for patients who did not experience an end point prior to completing the study as planned or prior to early withdrawal from the study. In the case of censoring, the survival time corresponded to the day of final study contact. Interaction of treatment assignment with baseline demographic and clinical characteristics and baseline lipid levels was examined. Percent changes from baseline in blood lipid levels were adjusted using an analysis of covariance model with treatment assignment, country, inclusion event, and baseline value as covariates. Lipid analyses were performed on a modified intention-to-treat basis, with all randomized patients who had both a baseline measurement and at least 1 double-blind measurement included in the analyses. The last double-blind measurement collected after randomization was carried forward for patients who did not have a lipid measurement at 16 weeks.

The study protocol specified 3 interim analyses of safety and efficacy by the data safety and monitoring board. A significance level of \(P = .001\) was used for each interim analysis, with a significance level for the final analysis adjusted to \(P = .049\) to preserve to the overall type I error rate at \(P = .05\). The testing of all secondary objectives was done at the 2-sided \(P = .05\) level of significance.

**RESULTS**

**Patients**

Between May 1997 and September 1999, 3086 patients were enrolled; 1538 were randomly assigned to receive atorvastatin and 1548 to receive placebo (FIGURE 1). Demographic and clinical characteristics of the patients assigned to the 2 treatment groups were similar at baseline (TABLE 1). The mean time between hospitalization for the inclusion event and randomization into the study was 63 hours in both groups. Information was collected as planned for all study patients except 8 (0.5%) in the atorvastatin group and 3 (0.2%) in the placebo group who were lost to follow-up. Intended follow-up was 112 days (16 weeks). A patient was considered lost to follow up if he/she withdrew early and there was no final follow-up data for the patient or if he/she was followed up for less than 100 days without experiencing a primary end point.

**Compliance**

Compliance with prescribed study treatment, defined as the number of days that patients took study medication (determined by last day of study medication) divided by the number of days of intended treatment (112 days), was 86% in the atorvastatin group and 88% in the placebo group. Treatment was discontinued prematurely in 173 (11.2%) atorvastatin-treated patients and 160 (10.3%) placebo-treated patients, a nonsignificant difference. Twenty-three patients in the atorvastatin group and 26 patients in the placebo group were treated with an open-label lipid-lowering medication after premature discontinuation of study medication. Reasons for premature discontinuation of treatment are indicated in Figure 1.

---

**Figure 1. Trial Profile**

![Diagram of trial profile](https://www.jama.com)

Number of patients screened was not determined. Follow-up information was sought for all patients who were withdrawn early from the study (prior to the a priori cutoff of 100 days).

---

©2001 American Medical Association. All rights reserved.
Concurrent Medications

Similar medications were administered to patients in the placebo and atorvastatin groups, both prior to and after admission to hospital for the inclusion ischemic event (Table 2). Aspirin, heparin, nitrates, and β-blockers were administered to a majority of patients; however, platelet glycoprotein IIb/IIIa receptor antagonists were used in only 1% of patients.

Serum Lipid Levels

At the time of randomization, serum lipid levels were nearly identical in both groups (Figure 2) with mean LDL cholesterol level of 124 mg/dL (3.2 mmol/L), mean triglycerides level of 184 mg/dL (2.0 mmol/L), and mean HDL cholesterol level of 46 mg/dL (1.2 mmol/L). At 6 weeks, reductions in total and LDL cholesterol and triglycerides with atorvastatin were essentially complete. At the end of the study, LDL cholesterol had increased by an adjusted mean of 12% to 135 mg/dL (3.5 mmol/L) in the placebo group and decreased by an adjusted mean of 40% to 72 mg/dL (1.9 mmol/L) in the atorvastatin group. Triglycerides increased by an adjusted mean of 9% to 187 mg/dL (2.1 mmol/L) in the placebo group and decreased by an adjusted mean of 16% to 139 mg/dL (1.6 mmol/L) in the atorvastatin group. Changes in HDL cholesterol during the study were minor in both groups.

End Point Events

During the 16-week study period, a primary end point event occurred in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group, an absolute difference of 2.6% (Figure 3 and Table 3). Atorvastatin treatment significantly reduced the risk of the primary combined end point (relative risk [RR], 0.84; 95% confidence interval [CI], 0.70-1.00; P = .048). There were no significant differences in risk of death, nonfatal acute MI, or cardiac arrest with resuscitation between the atorvastatin group and the placebo group, al-

Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 1548)</th>
<th>Atorvastatin (n = 1538)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (12)</td>
<td>65 (12)</td>
</tr>
<tr>
<td>Women</td>
<td>528 (34.1)</td>
<td>546 (35.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1324 (85.5)</td>
<td>1317 (85.6)</td>
</tr>
<tr>
<td>Black</td>
<td>44 (2.8)</td>
<td>51 (3.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>58 (3.7)</td>
<td>40 (2.6)</td>
</tr>
<tr>
<td>Other*</td>
<td>122 (7.9)</td>
<td>130 (8.5)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>85 (5.5)</td>
<td>87 (5.7)</td>
</tr>
<tr>
<td>Europe</td>
<td>775 (50.1)</td>
<td>771 (50.1)</td>
</tr>
<tr>
<td>North America</td>
<td>519 (33.5)</td>
<td>510 (33.2)</td>
</tr>
<tr>
<td>South Africa</td>
<td>169 (10.9)</td>
<td>170 (11.0)</td>
</tr>
<tr>
<td>Inclusion event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>705 (45.5)</td>
<td>726 (47.2)</td>
</tr>
<tr>
<td>Non-Q-wave acute myocardial infarction</td>
<td>843 (54.5)</td>
<td>812 (52.8)</td>
</tr>
<tr>
<td>Time from hospital admission to randomization, mean (SD), h</td>
<td>63 (25)</td>
<td>63 (24)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>122 (7.9)</td>
<td>131 (8.5)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>136 (8.8)</td>
<td>130 (8.5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>139 (9.0)</td>
<td>148 (9.6)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>392 (25.3)</td>
<td>382 (24.8)</td>
</tr>
<tr>
<td>Prior myocardial revascularization</td>
<td>121 (7.8)</td>
<td>112 (7.3)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>52 (3.4)</td>
<td>41 (2.7)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>430 (27.8)</td>
<td>429 (27.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>846 (54.7)</td>
<td>843 (54.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>373 (24.1)</td>
<td>342 (22.2)</td>
</tr>
</tbody>
</table>
| *Predominantly people of mixed race in countries such as South Africa.

Table 2. Concurrent Medications According to Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prior to Hospitalization for Index Event</th>
<th>During or Following Hospitalization for Index Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 1548)</td>
<td>Atorvastatin (n = 1538)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>275 (17.8)</td>
<td>279 (18.1)</td>
</tr>
<tr>
<td></td>
<td>1412 (91.2)</td>
<td>1400 (91.0)</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa receptor antagonists</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>19 (1.2)</td>
<td>14 (0.9)</td>
</tr>
<tr>
<td>Other antplatelet agents</td>
<td>11 (0.7)</td>
<td>8 (0.5)</td>
</tr>
<tr>
<td></td>
<td>176 (11.4)</td>
<td>174 (11.3)</td>
</tr>
<tr>
<td>Heparin</td>
<td>6 (0.4)</td>
<td>8 (0.5)</td>
</tr>
<tr>
<td></td>
<td>1154 (74.6)</td>
<td>1147 (74.6)</td>
</tr>
<tr>
<td>Oral anticoagulants (coumarines)</td>
<td>24 (1.6)</td>
<td>27 (1.8)</td>
</tr>
<tr>
<td></td>
<td>129 (8.3)</td>
<td>119 (7.7)</td>
</tr>
<tr>
<td>Fibriolytic agents</td>
<td>0</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td></td>
<td>137 (8.9)</td>
<td>109 (7.1)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>215 (13.9)</td>
<td>230 (15.0)</td>
</tr>
<tr>
<td></td>
<td>1396 (90.2)</td>
<td>1389 (90.3)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>170 (11.0)</td>
<td>162 (10.5)</td>
</tr>
<tr>
<td></td>
<td>1200 (77.5)</td>
<td>1192 (77.5)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>139 (9.0)</td>
<td>125 (8.1)</td>
</tr>
<tr>
<td></td>
<td>745 (48.1)</td>
<td>735 (47.8)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers</td>
<td>183 (11.8)</td>
<td>187 (12.2)</td>
</tr>
<tr>
<td></td>
<td>769 (49.7)</td>
<td>746 (48.5)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>55 (3.6)</td>
<td>59 (3.8)</td>
</tr>
<tr>
<td></td>
<td>171 (11.1)</td>
<td>182 (11.8)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>21 (1.4)</td>
<td>7 (0.5)</td>
</tr>
<tr>
<td></td>
<td>47 (3.0)*</td>
<td>30 (2.0)*</td>
</tr>
</tbody>
</table>
| *After randomization, not including study medication.
though the atorvastatin group had a lower risk of recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization (RR, 0.74; 95% CI, 0.57-0.95; P = .02) (Table 3 and Figure 4).

There were no significant interactions between treatment assignment and any of the baseline characteristics listed in Table 1 or the baseline values of any of the measured serum lipid levels. In particular, the reduction of primary ischemic events by atorvastatin did not appear to depend on the baseline level of LDL cholesterol. Among patients who had baseline LDL cholesterol levels of less than or equal to the median value of 121 mg/dL (3.1 mmol/L), primary endpoint events occurred in 231 patients (15.0%) in the atorvastatin group and 288 patients (18.6%) in the placebo group (RR, 0.77; 95% CI, 0.59-0.98). Among patients who had baseline LDL cholesterol levels greater than the median value, primary endpoint events occurred in 231 patients (15.0%) in the atorvastatin group and 257 patients (16.6%) in the placebo group (RR, 0.92; 95% CI, 0.71-1.19). Moreover, among atorvastatin-treated patients, there was no significant association between the percentage change in LDL cholesterol from baseline to end of study (dichotomized by the median percentage change) and the occurrence of a primary endpoint event.

There were no significant differences between groups in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina without objective evidence of ischemia occurrence of at least 1 secondary end point, or occurrence of at least 1 primary or secondary end point. There were significant differences between groups for incidence of nonfatal stroke, which occurred in 9 patients in the atorvastatin group, compared with 22 patients in the placebo group (RR, 0.41; 95% CI, 0.20-0.87; P = .02) and either fatal or nonfatal stroke, which occurred in 12 patients in the atorvastatin group, compared with 24 patients in the placebo group (RR, 0.50; 95% CI, 0.26-0.99; P = .045).

Safety

No serious adverse event occurred with a frequency of more than 1% in either group. Abnormal liver transaminase levels (>3 times ULN) occurred in 38 patients (2.5%) in the atorvastatin group and in 9 patients (0.6%) in the placebo group (P < .001). Three of these 38 patients in the atorvastatin group were hospitalized with a diagnosis of hepatitis (elevated liver transaminases associated in 2 cases with jaundice and/or fever). In each case these abnormalities resolved following discontinuation of the drug. There were no documented cases of myositis.

The number needed to treat to prevent 1 primary endpoint event (death, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency hospitalization) was 38. The number needed to treat to prevent 1 primary endpoint event or nonfatal stroke was 33. The number needed to treat to cause 1 case of elevated liver transaminases (>3 times ULN on 2 determinations) was 53.

COMMENT

In this trial, early treatment with atorvastatin 80 mg/d reduced recurrent ischemic events over a 16-week treatment period among patients with unstable angina or non–Q-wave acute MI. There was a 2.6% absolute reduction and a 16% relative reduction in the primary combined end point of death, nonfatal acute MI, cardiac arrest with resuscitation, or worsening symptomatic myocardial ischemia with objective evidence and emergency rehospitalization.

Our finding that treatment with 80 mg/d of atorvastatin, initiated 24 to 96 hours after an ACS, reduces the risk of elevation of cholesterol and triglycerides.

Values are mean (95% confidence interval). To convert values for cholesterol to mmol/L, multiply by 0.0259; to convert values for triglycerides to mmol/L, multiply by 0.0113. The differences between treatment groups (atorvastatin minus placebo) in adjusted mean percentage change from baseline at 6 weeks and at 16 weeks, respectively, were −37.5 and −34.0 (both P < .001) for total cholesterol; −55.9 and −52.0 (both P < .001) for low-density lipoprotein cholesterol; −0.6 (not significant) and 1.6 (P = .04) for high-density lipoprotein cholesterol; and −27.5 and −25.0 (both P < .001) for triglycerides.
Based on Cox proportional hazards analysis.† The RRs (95% CIs) are based on Cox Mantel-Haenszel analysis.

The occurrence of stroke was significantly reduced in the atorvastatin group compared with the placebo group, suggesting that atorvastatin treatment also may produce beneficial effects on cerebrovascular events within 16 weeks, although the number of stroke events in each group was small.

Patients with Q-wave acute MI were excluded from this study because factors that are unlikely to be affected by cholesterol lowering, such as left ventricular dysfunction, ventricular arrhythmias, and mechanical complications represent the major determinants of short-term outcome. Patients for whom a coronary revascularization procedure was planned or anticipated at the time of screening were excluded so that adverse events related to the procedures or to restenosis after angioplasty would not complicate assessment of the effect of atorvastatin treatment. The effects of atorvastatin for these groups of patients are unknown.

Despite a low rate of revascularization, patients in our trial experienced a similar incidence of death and nonfatal acute MI as patients in another large, contemporary trial of ACSs.5 In comparing event rates among trials, it is noteworthy that our trial did not include as end points events that occurred during the median 63-hour period between hospital admission and randomization.

This study was not powered to detect differences between treatment groups in the individual components of the primary composite end point. Although death, nonfatal MI, and cardiac arrest occurred slightly less frequently in the atorvastatin group than in the placebo group, the differences in these end points were not statistically significant. Most of the intergroup difference in the combined primary end point resulted from a reduction in recurrent symptomatic myocardial ischemia with objective evidence and emergency rehospitalization (absolute risk reduction 2.2%; 26% reduction in RR in the atorvastatin group; P = .02).

Risk Ratio Plot

Table 3. Occurrence of Primary and Secondary Outcome Events*  

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%) of Patients</th>
<th>Placebo (n = 1548)</th>
<th>Atorvastatin (n = 1538)</th>
<th>RR (95% CI)†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death and/or nonfatal acute MI</td>
<td>169 (10.9)</td>
<td>155 (10.1)</td>
<td>0.92 (0.75-1.13)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>68 (4.4)</td>
<td>64 (4.2)</td>
<td>0.94 (0.67-1.31)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal acute MI</td>
<td>113 (7.3)</td>
<td>101 (6.6)</td>
<td>0.90 (0.69-1.16)</td>
<td></td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>10 (0.6)</td>
<td>8 (0.5)</td>
<td>0.82 (0.33-2.06)</td>
<td></td>
</tr>
<tr>
<td>Recurrent symptomatic myocardial ischemia</td>
<td>130 (8.4)</td>
<td>95 (6.2)</td>
<td>0.74 (0.57-0.95)</td>
<td></td>
</tr>
<tr>
<td>with objective evidence and emergency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rehospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any outcome</strong></td>
<td>269 (17.4)</td>
<td>228 (14.8)</td>
<td>0.84 (0.70-1.00)‡</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal and nonfatal</td>
<td>24 (1.6)</td>
<td>12 (0.8)</td>
<td>0.50 (0.26-0.99)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>22 (1.4)</td>
<td>9 (0.6)</td>
<td>0.41 (0.20-0.87)</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>250 (16.1)</td>
<td>254 (16.5)</td>
<td>1.02 (0.87-1.20)</td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>143 (9.2)</td>
<td>150 (9.8)</td>
<td>1.06 (0.85-1.32)</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>110 (7.1)</td>
<td>106 (6.9)</td>
<td>0.97 (0.75-1.25)</td>
<td></td>
</tr>
<tr>
<td>Worsening angina without new objective</td>
<td>106 (6.8)</td>
<td>91 (5.9)</td>
<td>0.86 (0.66-1.13)</td>
<td></td>
</tr>
<tr>
<td>evidence of ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New or worsening congestive heart failure</td>
<td>43 (2.8)</td>
<td>40 (2.6)</td>
<td>0.94 (0.62-1.43)</td>
<td></td>
</tr>
<tr>
<td>requiring rehospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any outcome</td>
<td>344 (22.2)</td>
<td>344 (22.4)</td>
<td>1.01 (0.88-1.15)</td>
<td></td>
</tr>
<tr>
<td>Any primary or secondary outcome</td>
<td>475 (30.7)</td>
<td>450 (29.3)</td>
<td>0.95 (0.86-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; and MI, myocardial infarction.
† The RRs (95% CIs) are based on Cox Mantel-Haenszel analysis.
‡Based on Cox proportional hazards analysis.

Figure 4. Risk Ratio Plot

Death, nonfatal acute myocardial infarction, and resuscitated cardiac arrest were not significantly reduced in the atorvastatin group compared with the placebo group. Recurrent symptomatic myocardial ischemia with objective evidence and requiring urgent rehospitalization was significantly reduced in the atorvastatin group compared with the placebo group (relative risk, 0.74; 95% confidence interval, 0.57-0.95).

Recurrent ischemic events extends the findings of previous studies that used conventional doses of other statins in patients with stable coronary heart disease. In these previous studies, small differences in event rates were noted in the early period after randomization, but 1 to 2 years of treatment were required before a significant reduction in cardiovascular events could be documented.1,3 While the relative benefit of treatment observed in the present trial over 16 weeks is less than that observed in the previous trials over periods of 5 to 7 years, the absolute reduction in events (2.6%) in the present trial is greater than that achieved during a comparable length of time in a stable population.
ous long-term trials of statins in patients with coronary heart disease (139-188 mg/dL [3.6-4.9 mmol/L]).\textsuperscript{1-3} Moreover, the benefit of atorvastatin in our study did not appear to depend on baseline LDL cholesterol levels or baseline levels of other lipid fractions. This is consistent with subgroup analysis of one\textsuperscript{18} but not another\textsuperscript{2} long-term study of a statin in patients with average LDL cholesterol levels. In our study, it is possible that the finding is related to more serious illness and therefore greater acute phase decreases of serum lipoprotein levels among patients with lower baseline lipid levels. Nonetheless, the observation suggests that the decision to initiate intensive lipid-lowering therapy after an ACS should not necessarily be influenced by serum lipid levels at the time of the event.

Despite relatively low baseline levels of LDL cholesterol in our study, 16 weeks of atorvastatin treatment produced a further reduction to a mean level of 72 mg/dL (1.9 mmol/L), a level lower than that achieved with active treatment in the Scandinavian Simvastatin Survival Study (4S),\textsuperscript{7} Cholesterol and Recurrent Events trial (CARE),\textsuperscript{2} or Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial.\textsuperscript{3} Some available evidence suggests that greater LDL cholesterol lowering (with higher doses of a statin) results in greater reduction of ischemic cardiovascular events than moderate LDL cholesterol lowering (with lower doses of a statin).\textsuperscript{19}

In the present trial, we were able to test the effects of 1 dose of atorvastatin. We chose the 80-mg dose to produce a large average reduction in serum cholesterol levels. Our data do not allow us to determine if a lower dose of atorvastatin, or gradual dose titration to a predetermined LDL cholesterol level, would achieve similar benefits.

The sample size for this trial was determined on the basis of an expected 25% to 30% reduction of primary end points in the atorvastatin group compared with the placebo group. Therefore, the trial had lower power to detect the actual reduction of 16%, resulting in a marginally significant P value for the primary efficacy analysis. These results suggest a need for further trials of statins in ACSs and may be helpful in determining the sample size of such trials.

Atovrastatin was generally well tolerated in this patient population. There were no documented cases of myositis, which is the most serious adverse effect of statins. Levels of serum transaminases exceeding 3 times the ULN were detected in 2.5% of atorvastatin-treated patients and 0.6% of placebo-treated patients.

In conclusion, the results of this trial indicate that treatment with 80 mg/d of atorvastatin, initiated during the acute phase of unstable angina or non-Q wave acute MI, reduces the risk of early, recurrent ischemic events, primarily recurrent symptomatic ischemia requiring hospitalization.

Author Affiliations: Cardiology Section, Veterans Af-
sfairs Medical Center and University of Colorado Health Sci-
cences Center, Denver (Dr Schwartz); Faculty of Health Sci-
tences, University of Linköping, Linköping, Sweden (Dr Olsson); Hahnemann University, Phila-
delphia, Pa (Dr Ezekowitz); Cardiovascular Division, Brigham and Women’s Hospital and Harvard Medi-
cal School, Boston, Mass (Dr Ganz); Cardiac Medi-
cine, National Heart and Lung Institute, Imperial Col-
lege, London, England (Dr Oliver); Division of Cardiology, San Francisco General Hospital and Uni-
versity of California, San Francisco (Dr Watts); Car-
diology Department, Johann Wolfgang Goethe Uni-
versity, Frankfurt, Germany (Dr Zeiher);Division of Cardiology, St Louis University School of Medicine, St Louis, Mo (Dr Chairman); Pfizer Pharmaceutical Research, New York, NY (Dr (Dre)); and Pfizer Phar-
maceutical Research, Ann Arbor, Mich (Dr Stern). Dr Oliver is now retired.

Author Contributions: Dr Schwartz, as principal in-
vestigator of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the ac-
curacy of the data analyses.

Study concept and design: Schwartz, Olsson, Ezekow-
itz, Ganz, Oliver, Waters, Zeiher.

Acquisition of data: Schwartz, Olsson, Ezekow-
itz, Ganz, Oliver, Waters, Zeiher, Chairman, Les-
lie, Stern.

Analysis and interpretation of data: Schwartz, Ol-
sson, Ezekowitz, Ganz, Oliver, Waters, Zeiher, Chairman, Lee.

Drafting of the manuscript: Schwartz, Olsson, Ezeko-
itz, Ganz, Oliver, Waters, Zeiher, Chairman, Leslie.

Critical revision of the manuscript for important in-
tellectual content: Schwartz, Olsson, Ezekowitz, Ganz, Oliver, Waters, Zeiher, Chairman, Leslie, Stern.

Statistical expertise: Stern.

Obtained funding: Schwartz, Olsson.

Administrative, technical, or material support: Ganz, Leslie.

Study supervision: Schwartz, Olsson, Ezekowitz, Ganz, Oliver, Waters, Zeiher.

Financial Disclosures: Dr Schwartz served as a con-
sultant to Parke Davis and Pfizer Pharmaceutical re-
search, but he received no personal remuneration, in-
stead a consultant’s fee was paid to a nonprofit research foundation to support his basic research work. Dr Olsson has been a consultant for AstraZeneca, NEOMA, Novartis, and Pfizer and has received re-
search grants from AstraZeneca, Bayer, Bristol-
Myers Squibb, Merck, NEOMA, Pfizer, and Pharma-
dia. Dr Ezekowitz is in Pfizer’s speaker’s program and also serves as a consultant for Pfizer for a different pro-
gram outside this study. Dr Oliver received funding from Parke Davis and Pfizer during the trial for ex-
spenses incurred in relation to the trial. Dr Waters has received honoraria for lectures and payment for con-
sulting from Pfizer. Dr Chairman served as the prin-
cipal investigator for the Core ECG Laboratory and re-
ceived a research contract for his work.

Funding/Support: Supported by a grant from Pfizer Inc. Pfizer provided the atorvastatin and matching place-
bo used in this study.

MIRACL Investigators, Participating Centers, and Commit-
tee Members:

Investigators: Australia (117 patients): Auchen-
flower: D. Coliquojouh; Bedford Park: R. Minson; C.
Aronay; Hindmarsh: A. A. Milne.

Canada (87 patients): B. Brown; Dartmouth: G. D. J.
Lambert; Guelph: C. P. Legg.

France (78 patients): Alger: B. Thivolet; Annecy: F.
Bert; Arras: V. Pluchart; Lyon: J. I. G. Lepers; Mar-
seille: A. J. L. Pannier; Nantes: F. J. B. P. Lafont; Paris:
J. P. DeYoung; Tours: Y. B. H. Auroy.

Germany (174 patients): Berlin: D. M. Frey; Bra-
mauer: J. R. Drozda; Chemnitz: K. F. Rolf; Darm-
stadt: D. Alesi; Frankfurt: A. A. Hoffmann; Grei-
zen: A. D. L. Ferro; Hamburg: E. Braaten; Han-
dorf: R. Berendes; Heidelberg: H. P. Stifter; Hel-
sinki: M. K. Launonen; Heidelberg: M. O. Krull; Kli-
bon: J. J. A. G. Sturzebecher; Munich: I. R. Kla-
pper; Munster: B. Neumann; Nuremberg: J. T. D.
Muller; Osnabruck: J. M. K.; Potsdam: M. R. A.
R. Seabra Gomes; Lisbon: L. Patricio; London, Eng-
land: B. R. J. P. Dart; Maidenhead: J. A. M. M.
Munster; Obuda: V. M. C.; Olten: F. Krekels; Pal-
ma: G. U. D. M.; Paris: C. Bouvier; Prague: J.
M. J. Y. F. A. M. M.; Rio de Janeiro: P. R. Seabra;
San Francisco (47 patients): Los Angeles: S. H. Chu;
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.
San Francisco: S. H. Chu; Seattle: J. A. L. P. D.


In our description of nature the purpose is not to dis- close the real essence of the phenomena, but only to track down, so far as it is possible, relations between the manifold aspects of our experience.

—Niels Bohr (1883-1962)
Laboratory Containment of Wild Poliovirus

To the Editor: A recent Medical News and Perspectives story reports that the global effort to eradicate poliovirus is 99% complete.1 However, attention recently has been drawn to potential problems with global eradication,2 including reintroduction of wild virus into a country free of circulating wild virus, reversion of the vaccine strain to a more neurotropic form of the virus and subsequent infection with this reverted strain, persistence of the virus in the environment, and failure to maintain adequate immunization levels.

Another theoretical possibility is the escape of wild virus from the laboratory. The last documented case of smallpox in the world was due to a laboratory infection3 and this could happen with poliovirus. Being aware of this possibility, the World Health Organization (WHO) has developed a framework for the laboratory containment of wild poliovirus and materials that may be potentially infectious for wild poliovirus.4 However, recent experience in Australia suggests that the process of laboratory containment will not be easy, at least for some countries, and may represent another impediment to global polio eradication.

Methods. We began implementation of the laboratory containment of wild poliovirus in February 2000, adapting the suggested approach of the WHO.3 We identified almost 2200 organizations in Australia that may have maintained a laboratory and storing biological materials. A further 288 did not respond to a series of questions to determine whether these materials included wild poliovirus or potentially infectious materials. Another 18 laboratories indicated that they stored wild poliovirus or potentially infectious materials, but only 4 (22%) provided a final inventory of them. Of all the organizations identified, 30% had not responded or had responded inadequately to the surveys by December 2000, despite numerous reminder and prompt telephone calls from staff of a call center that operated for 8 weeks from August to October 2000.

Comment. The containment process adopted in Australia depends on the goodwill of laboratory management and staff. There are no incentives or penalties associated with completion of the surveys and no responses were validated. It is likely that other countries will experience similar problems in establishing national inventories of wild poliovirus and potentially infectious materials. These difficulties will add to others recently highlighted and may affect the confidence with which the world can be certified free of wild poliovirus.

Heath Kelly, MBBS, MPH, FAFPHM
Nittita Prasopa-Plaizier, MPH
Susan Ballard, PhD
Victorian Infectious Diseases Reference Laboratory
Melbourne, Australia


CORRECTION

Incorrect Numbers: The Original Contribution entitled “Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes: The MIRACL Study: A Randomized Controlled Trial” published in the April 4, 2001, issue of The JOURNAL (2001;285:1711-1718) contained some incorrect numbers. On page 1715, in the first full paragraph in column 1, the third and fourth sentences should be replaced with: “Among patients who had baseline LDL cholesterol levels of less than or equal to the median value of 121 mg/dL (3.1 mmol/L), primary end point events occurred in 113 (15.0%) of 752 patients in the atorvastatin group and 136 (18.7%) of 729 patients in the placebo group (RR, 0.77; 95% CI, 0.59-0.98). Among patients who had baseline LDL cholesterol levels greater than the median value, primary end point events occurred in 109 (15.0%) of 726 patients in the atorvastatin group and 124 (16.6%) of 749 patients in the placebo group (RR, 0.92; 95% CI, 0.71-1.19). One hundred thirty patients did not have a complete set of baseline lipid measurements by the central laboratory and are not included in this analysis.”