

ORIGINAL ARTICLE

# Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators\*

## ABSTRACT

### BACKGROUND

Lipid-lowering therapy with statins reduces the risk of cardiovascular events, but the optimal level of low-density lipoprotein (LDL) cholesterol is unclear.

### METHODS

We enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Follow-up lasted 18 to 36 months (mean, 24).

### RESULTS

The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group ( $P < 0.001$ ). Kaplan–Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin ( $P = 0.005$ ; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.

### CONCLUSIONS

Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (C.P.C., E.B., C.H.M., M.A.P.); the University of Pennsylvania, Philadelphia (D.J.R.); the University of Montreal, Montreal (J.L.R.); Bristol-Myers Squibb, Princeton, N.J. (R.B., S.V.J.); and the Nottingham Clinical Research Group, Nottingham, United Kingdom (K.A.H., A.M.S.). Address reprint requests to Dr. Cannon at the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at [cpcannon@partners.org](mailto:cpcannon@partners.org).

\*The investigators and research coordinators who participated in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) study are listed in the Appendix.

N Engl J Med 2004;350.

Copyright © 2004 Massachusetts Medical Society.

SEVERAL LARGE, RANDOMIZED, CONTROLLED trials have documented that cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of death or cardiovascular events across a wide range of cholesterol levels whether or not patients have a history of coronary artery disease.<sup>1-7</sup> The doses of statins used in these trials reduced low-density lipoprotein (LDL) cholesterol levels by 25 to 35 percent, and current guidelines recommend a target LDL cholesterol level of less than 100 mg per deciliter (2.59 mmol per liter) for patients with established coronary artery disease or diabetes.<sup>8,9</sup> It is not clear whether lowering lipid levels further would increase the clinical benefit. Accordingly, the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) trial was designed to compare the standard degree of LDL cholesterol lowering to approximately 100 mg per deciliter with the use of 40 mg of pravastatin daily<sup>2,3</sup> with more intensive LDL cholesterol lowering to approximately 70 mg per deciliter (1.81 mmol per liter) with the use of 80 mg of atorvastatin daily<sup>10</sup> as a mean of preventing death or major cardiovascular events in patients with an acute coronary syndrome.

## METHODS

### PATIENT POPULATION

Between November 15, 2000, and December 22, 2001, 4162 patients were enrolled at 349 sites in eight countries (see the Appendix). The protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients. As described previously,<sup>11</sup> men and women who were at least 18 years old were eligible for inclusion if they had been hospitalized for an acute coronary syndrome — either acute myocardial infarction (with or without electrocardiographic evidence of ST-segment elevation) or high-risk unstable angina — in the preceding 10 days. Patients had to be in stable condition and were to be enrolled after a percutaneous revascularization procedure if one was planned. Finally, patients had to have a total cholesterol level of 240 mg per deciliter (6.21 mmol per liter) or less, measured at the local hospital within the first 24 hours after the onset of the acute coronary syndrome or up to six months earlier if no sample had been obtained during the first 24 hours. Patients who were receiving long-term lipid-lowering therapy at the time of their in-

dex acute coronary syndrome had to have a total cholesterol level of 200 mg per deciliter (5.18 mmol per liter) or less at the time of screening in the local hospital.

Patients were ineligible for the study if they had a coexisting condition that shortened expected survival to less than two years, were receiving therapy with any statin at a dose of 80 mg per day at the time of their index event or lipid-lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomization or were likely to require such treatment during the study period (because atorvastatin is metabolized by this pathway), had undergone percutaneous coronary intervention within the previous six months (other than for the qualifying event) or coronary-artery bypass surgery within the previous two months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, had an unexplained elevation in the creatine kinase level that was more than three times the upper limit of normal and that was not related to myocardial infarction, or had a creatinine level of more than 2.0 mg per deciliter (176.8  $\mu$ mol per liter).

### STUDY PROTOCOL

The protocol specified that patients were to receive standard medical and interventional treatment for acute coronary syndromes, including aspirin at a dose of 75 to 325 mg daily, with or without clopidogrel or warfarin. Patients were not permitted to be treated with any lipid-modifying therapy other than the study drug. Eligible patients were randomly assigned in a 1:1 ratio to receive 40 mg of pravastatin or 80 mg of atorvastatin daily in a double-blind, double-dummy fashion. In addition, patients were also randomly assigned to receive with the use of a two-by-two factorial design a 10-day course of gatifloxacin or placebo every month during the trial. The results of the antibiotic component of the trial are not reported here.

Patients were seen for follow-up visits and received dietary counseling<sup>8</sup> at 30 days, at 4 months, and every 4 months thereafter until their final visit in August or September 2003. Patients who discontinued the study drug during the trial were followed by means of telephone calls. Blood samples were obtained at randomization, at 30 days, at 4, 8, 12, and

16 months, and at the final visit for the measurement of lipids and other components that were part of the safety assessment. Measurements were made at the core laboratories listed in the Appendix. LDL cholesterol levels were monitored, and the protocol specified that the dose of pravastatin was to increase to 80 mg in a blinded fashion if the LDL cholesterol level exceeded 125 mg per deciliter (3.23 mmol per liter) on two consecutive visits and the patient had been taking study medication and had returned for the required study visits. The dose of either study drug could be halved in the event of abnormal liver-function results, elevations in creatine kinase levels, or myalgias.

Patients were followed for 18 to 36 months, with an average follow-up of 24 months. The trial continued until 925 events had been reported to the coordinating center, after which time all patients were requested to return for a final study visit. Eight patients (0.2 percent) were lost to follow-up.

#### END POINTS

The primary efficacy outcome measure was the time from randomization until the first occurrence of a component of the primary end point: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting (if these procedures were performed at least 30 days after randomization), and stroke. Myocardial infarction was defined by the presence of symptoms suggestive of ischemia or infarction, with either electrocardiographic evidence (new Q waves in two or more leads) or cardiac-marker evidence of infarction, according to the standard TIMI and American College of Cardiology definition.<sup>12,13</sup> Unstable angina was defined as ischemic discomfort at rest for at least 10 minutes prompting rehospitalization, combined with one of the following: ST-segment or T-wave changes, cardiac-marker elevations that were above the upper limit of normal but did not meet the criteria for myocardial infarction, or a second episode of ischemic chest discomfort lasting more than 10 minutes and that was distinct from the episode that had prompted hospitalization. Secondary end points were the risk of death from coronary heart disease, nonfatal myocardial infarction, or revascularization (if it was performed at least 30 days after randomization), the risk of death from coronary heart disease or nonfatal myocardial infarction, and the risk of the individual components of the primary end point.

#### STATISTICAL ANALYSIS

Although the trial was designed as a time-to-event study, the definition of noninferiority was arrived at through a consideration of two-year event rates. For the comparison of pravastatin with atorvastatin, we defined the prespecified boundary for noninferiority as an upper limit of the one-sided 95 percent confidence interval of the relative risk at two years of less than 1.17 (corresponding to a hazard ratio throughout follow-up of 1.198). Assuming a two-year event rate of 22 percent in the atorvastatin group and that the two treatments had equivalent efficacy, we determined that enrollment of 2000 patients per group would give the study a statistical power of 87 percent and that this power would be preserved if follow-up continued until 925 end-point events had occurred.<sup>14</sup> A central randomization system was used that involved a permuted-block design in which assignment was stratified according to center. Three interim assessments of efficacy and safety were carried out by the data and safety monitoring board. Rules for stopping the study early in the event that the superiority of either treatment was established were not prespecified.

All efficacy analyses are based on the intention-to-treat principle. Estimates of the hazard ratios and associated 95 percent confidence intervals comparing pravastatin with atorvastatin were obtained with the use of the Cox proportional-hazards model, with randomized treatment as the covariate and stratification according to the receipt of gatifloxacin or placebo. (Using the two-by-two factorial design, we conducted a preliminary test for interaction and found none. For the primary end point, the interaction P value was 0.90 and the hazard ratios comparing pravastatin with atorvastatin were almost identical for the gatifloxacin and placebo groups.) When it was determined that noninferiority was not demonstrated, the subsequent assessment of superiority was carried out with the use of two-sided confidence intervals. The investigators designed the trial and had free and complete access to the data. Data coordination was performed by the Nottingham Clinical Research Group (see the Appendix). Investigators at TIMI, the sponsor, and members of the Nottingham Clinical Research Group performed data analysis jointly.

---

#### RESULTS

---

The two groups of patients were well matched with regard to base-line characteristics, with the exception of a history of peripheral arterial disease, which

was more common in the pravastatin group than the atorvastatin group (P=0.03) (Table 1). Their average age was 58 years, and 22 percent were women. Before their index event, 18 percent of patients had had a myocardial infarction, 11 percent had previously undergone coronary-artery bypass surgery, and 18 percent had diabetes mellitus. The index event was high-risk unstable angina in approximately one third of the patients, myocardial infar-

tion without electrocardiographic evidence of ST-segment elevation in approximately one third, and myocardial infarction with ST-segment elevation in one third. Sixty-nine percent of patients underwent percutaneous coronary intervention for the treatment of their index acute coronary syndrome before randomization. One quarter of the patients were taking statin drugs at the time of the index event. Concomitant medications were administered

**Table 1. Base-Line Characteristics of the Patients.\***

Characteristic	40 mg of Pravastatin (N=2063)	80 mg of Atorvastatin (N=2099)
Age — yr	58.3±11.3	58.1±11.2
Male sex — no. (%)	1617 (78.4)	1634 (77.8)
White race — no. (%)	1865 (90.4)	1911 (91.0)
Diabetes mellitus — no. (%)	361 (17.5)	373 (17.8)
Hypertension — no. (%)	1014 (49.2)	1077 (51.3)
Current smoker — no. (%)	766 (37.1)	763 (36.4)
Prior myocardial infarction — no. (%)	395 (19.1)	374 (17.8)
Percutaneous coronary intervention — no. (%)		
Before index event	320 (15.5)	322 (15.3)
For treatment of index event	1426 (69.1)	1442 (68.7)
Coronary bypass surgery before index event — no. (%)	221 (10.7)	233 (11.1)
Peripheral arterial disease — no. (%)	136 (6.6)	105 (5.0)
Prior statin therapy — no. (%)	514 (24.9)	535 (25.5)
Index event — no. (%)		
Unstable angina	614 (29.8)	604 (28.8)
MI without ST-segment elevation	757 (36.7)	747 (35.6)
MI with ST-segment elevation	690 (33.4)	748 (35.6)
Lipid values		
Total cholesterol		
No. of patients	1981	2014
Median — mg/dl	180	181
Interquartile range — mg/dl	158–202	160–205
LDL cholesterol		
No. of patients	1973	2003
Median — mg/dl	106	106
Interquartile range — mg/dl	87–127	89–128
HDL cholesterol		
No. of patients	1981	2014
Median — mg/dl	39	38
Interquartile range — mg/dl	33–46	32–46
Triglycerides		
No. of patients	1984	2016
Median — mg/dl	154	158
Interquartile range — mg/dl	115–207	119–214

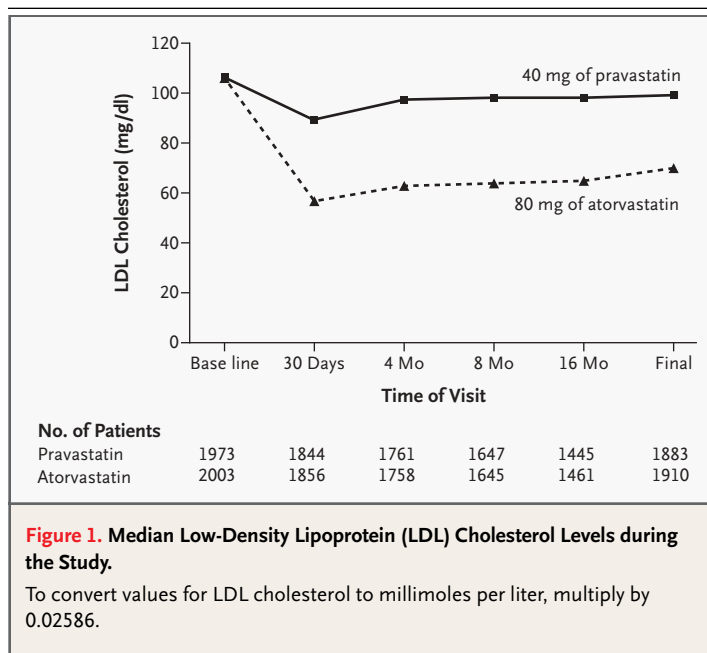
\* Plus–minus values are means ±SD. None of the differences between groups were significant with the exception of a history of peripheral arterial disease (P=0.03). Two patients did not have information regarding the electrocardiographic type of acute coronary syndrome, and one patient had missing information regarding prior statin use. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

to patients during the treatment period as follows: aspirin to 93 percent, warfarin to 8 percent, clopidogrel or ticlodipine to 72 percent initially and 20 percent at one year, beta-blockers to 85 percent, angiotensin-converting-enzyme inhibitors to 69 percent, and angiotensin-receptor blockers to 14 percent.

At the time of randomization, a median of seven days after the onset of the index event, the median LDL cholesterol levels were 106 mg per deciliter (2.74 mmol per liter) before treatment in each group (Fig. 1). The LDL cholesterol levels achieved during follow-up were 95 mg per deciliter (2.46 mmol per liter; interquartile range, 79 to 113 mg per deciliter [2.04 to 2.92 mmol per liter]) in the pravastatin group and 62 mg per deciliter (1.60 mmol per liter; interquartile range, 50 to 79 mg per deciliter [1.29 to 2.04 mmol per liter]) in the atorvastatin group ( $P<0.001$ ). Among 2985 patients (75 percent) who had not previously received statin therapy, the median LDL cholesterol levels had fallen by 22 percent at 30 days in the pravastatin group and by 51 percent in the atorvastatin group ( $P<0.001$ ). As anticipated, among the 990 patients who had previously received statin therapy (25 percent), LDL cholesterol levels were essentially unchanged from base line (during statin therapy) in the pravastatin group, whereas they fell by an additional 32 percent in the atorvastatin group ( $P<0.001$ ). Median high-density lipoprotein cholesterol levels rose during follow-up by 8.1 percent in the pravastatin group and 6.5 percent in the atorvastatin group ( $P<0.001$ ). Median C-reactive protein levels fell from 12.3 mg per liter at base line in each group to 2.1 mg per liter in the pravastatin group and 1.3 mg per liter in the atorvastatin group ( $P<0.001$ ).

#### PRIMARY END POINT

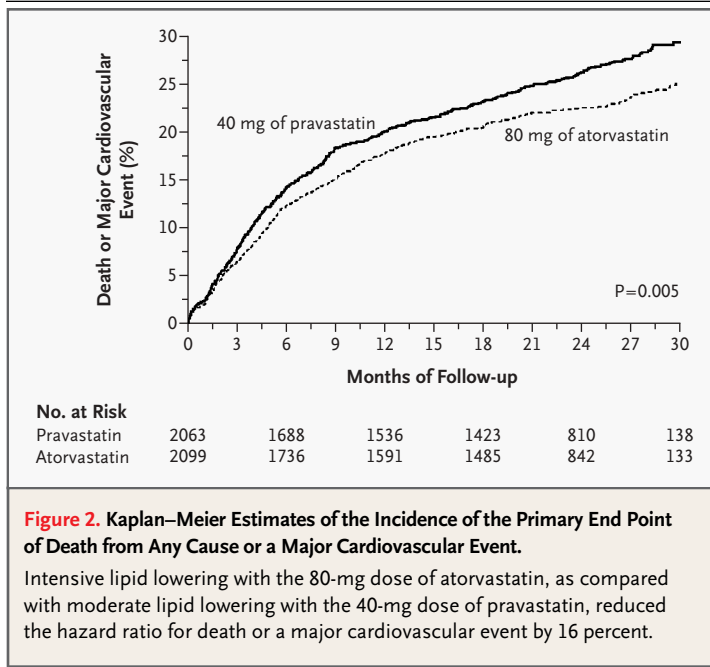
For all randomized patients, the Kaplan–Meier event rates of the primary end point at two years were 26.3 percent in the standard-dose pravastatin group and 22.4 percent in the high-dose atorvastatin group, representing a 16 percent reduction in the hazard ratio favoring atorvastatin ( $P=0.005$ ; 95 percent confidence interval, 5 to 26 percent) (Fig. 2); this difference did not meet the criteria for equivalence. The benefit of high-dose atorvastatin as compared with standard-dose pravastatin emerged as early as 30 days and was consistent over time (Fig. 3). The risk of the secondary end point of death due to coronary heart disease, myocardial infarction, or revascularization was similarly reduced by 14 per-



cent in the atorvastatin group ( $P=0.029$ ), with a two-year event rate of 19.7 percent, as compared with 22.3 percent in the pravastatin group. The risk of death, myocardial infarction, or urgent revascularization was reduced by 25 percent in the atorvastatin group ( $P<0.001$ ).

Among the individual components of the primary end point, there was a consistent pattern of benefit favoring high-dose atorvastatin over standard-dose pravastatin, which included a significant 14 percent reduction in the need for revascularization ( $P=0.04$ ), a 29 percent reduction in the risk of recurrent unstable angina ( $P=0.02$ ), and nonsignificant reductions in the rates of death from any cause (28 percent,  $P=0.07$ ) and of death or myocardial infarction (18 percent,  $P=0.06$ ) (Fig. 4). Stroke was infrequent, but the rates did not differ significantly between the groups.

The benefit of high-dose atorvastatin was consistent across the prespecified subgroups, including men and women, patients with unstable angina and those with myocardial infarction, and those with and those without diabetes mellitus (Fig. 5). The benefit appeared to be greater among patients with a base-line LDL cholesterol level of at least 125 mg per deciliter, a prespecified subgroup, with a 34 percent reduction in the hazard ratio, as compared with a 7 percent reduction among patients with a base-line LDL cholesterol below 125 mg per deciliter ( $P$  for interaction=0.02).



#### TOLERABILITY AND SAFETY

The rates of discontinuation of treatment because of an adverse event or the patient's preference or for other reasons were 21.4 percent in the pravastatin group and 22.8 percent in the atorvastatin group at one year ( $P=0.30$ ) and 33.0 percent and 30.4 percent, respectively, at two years ( $P=0.11$ ). During treatment, the dose of pravastatin was increased to 80 mg in 8 percent of patients, and the dose was halved among 1.4 percent of the patients in the pravastatin group and 1.9 percent of those in the atorvastatin group ( $P=0.20$ ), owing to side effects or liver-function abnormalities. The percentages of patients who had elevations in alanine aminotransferase levels that were more than three times the upper limit of normal were 1.1 percent in the pravastatin group and 3.3 percent in the atorvastatin group ( $P<0.001$ ). The study medication was discontinued by the investigators because of a report of myalgias or muscle aches or elevations in creatine kinase levels in 2.7 percent of pravastatin-treated patients, as compared with 3.3 percent of atorvastatin-treated patients ( $P=0.23$ ). There were no cases of rhabdomyolysis in either group.

#### DISCUSSION

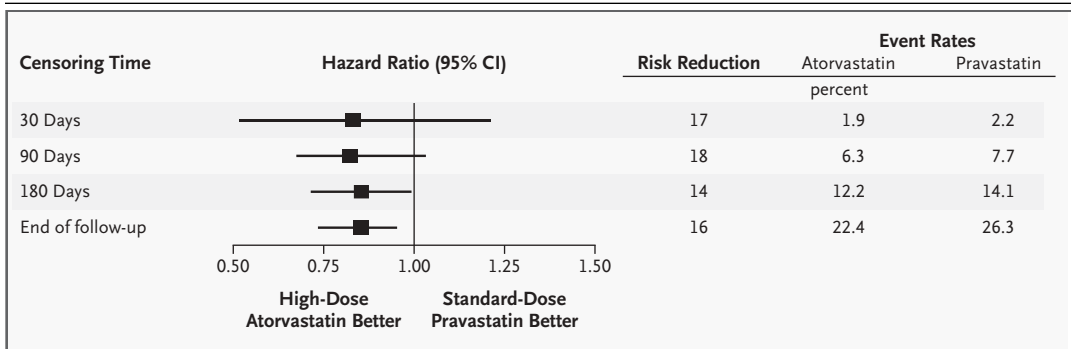
In this comparison of two statin regimens of different lipid-lowering intensities for the prevention of

cardiovascular events, intensive therapy with high-dose atorvastatin resulted in a median LDL cholesterol level of 62 mg per deciliter, as compared with a level of 95 mg per deciliter for standard-dose pravastatin. Among patients who had recently been hospitalized for an acute coronary syndrome, the more intensive regimen resulted in a lower risk of death from any cause or major cardiac events than did a more moderate degree of lipid lowering with the use of a standard dose of a statin. Although prior placebo-controlled studies have shown that a standard-dose statin is beneficial,<sup>1-7</sup> we demonstrated that more intensive lipid lowering significantly increased this clinical benefit.

Although the exact mechanism of the benefit cannot be established solely on the basis of our results, the extent of the benefit afforded by the 80-mg dose of atorvastatin is in keeping with what would be expected on the basis of the greater degree of lipid lowering produced by this regimen. In the Heart Protection study, statin treatment resulted in an LDL cholesterol level that was 40 mg per deciliter (1.03 mmol per liter) lower than the value in the placebo group and that was accompanied by a 25 percent reduction in cardiovascular events. In our study, the LDL cholesterol level was 33 mg per deciliter (0.85 mmol per liter) lower in the atorvastatin group than in the pravastatin group. This difference should translate into a 20 percent reduction in clinical events, which is very similar to the 16 percent reduction we observed and suggests that much of the benefit is attributable to the difference in the degree of LDL cholesterol lowering. However, we cannot exclude the possibility that the difference in clinical outcomes may be due in part to non-lipid-related pleiotropic effects, which may differ between the two the statins we used.<sup>15</sup> Future trials involving different doses of a single statin should help address this possibility.

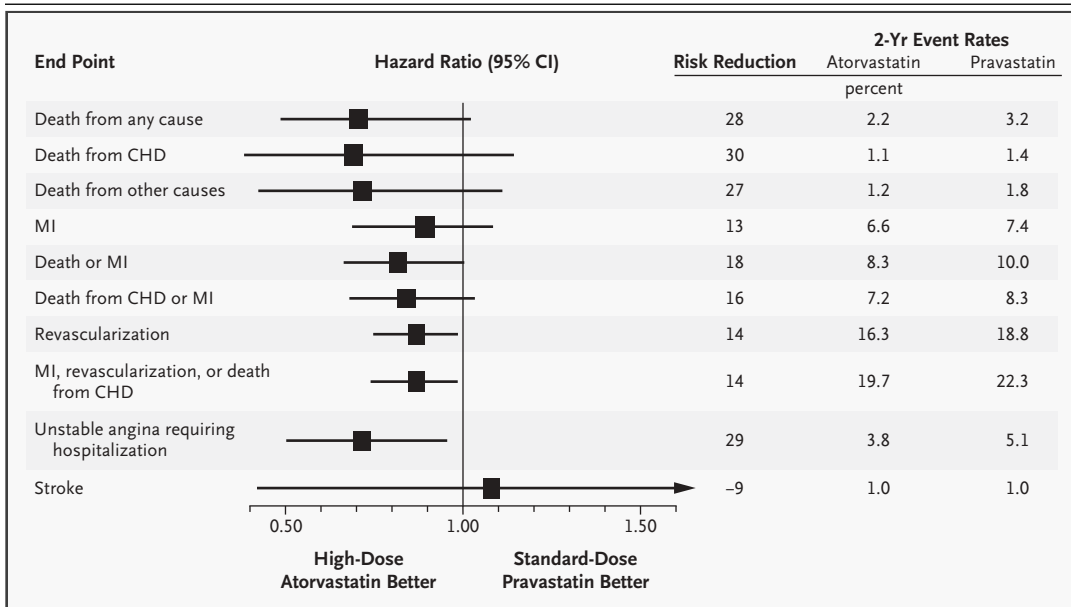
Intensive therapy with high-dose atorvastatin had a consistent beneficial effect on cardiac events, including a significant 29 percent reduction in the risk of recurrent unstable angina and a 14 percent reduction in the need for revascularization. The reduction in the rate of death from any cause was of borderline significance (28 percent,  $P=0.07$ ), suggesting that more aggressive lipid lowering is important not only to reduce the risk of recurrent ischemia, but possibly also to decrease the risk of fatal events.

The reduction in clinical events with the more intensive lipid-lowering therapy was apparent as



**Figure 3.** Hazard Ratio for the the Primary End Point of Death from Any Cause or a Major Cardiovascular Event at 30, 90, and 180 Days and at the End of Follow-up in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group.

Event rates are Kaplan–Meier estimates censored at the time points indicated with the use of the average duration of follow-up (two years). CI denotes confidence interval.

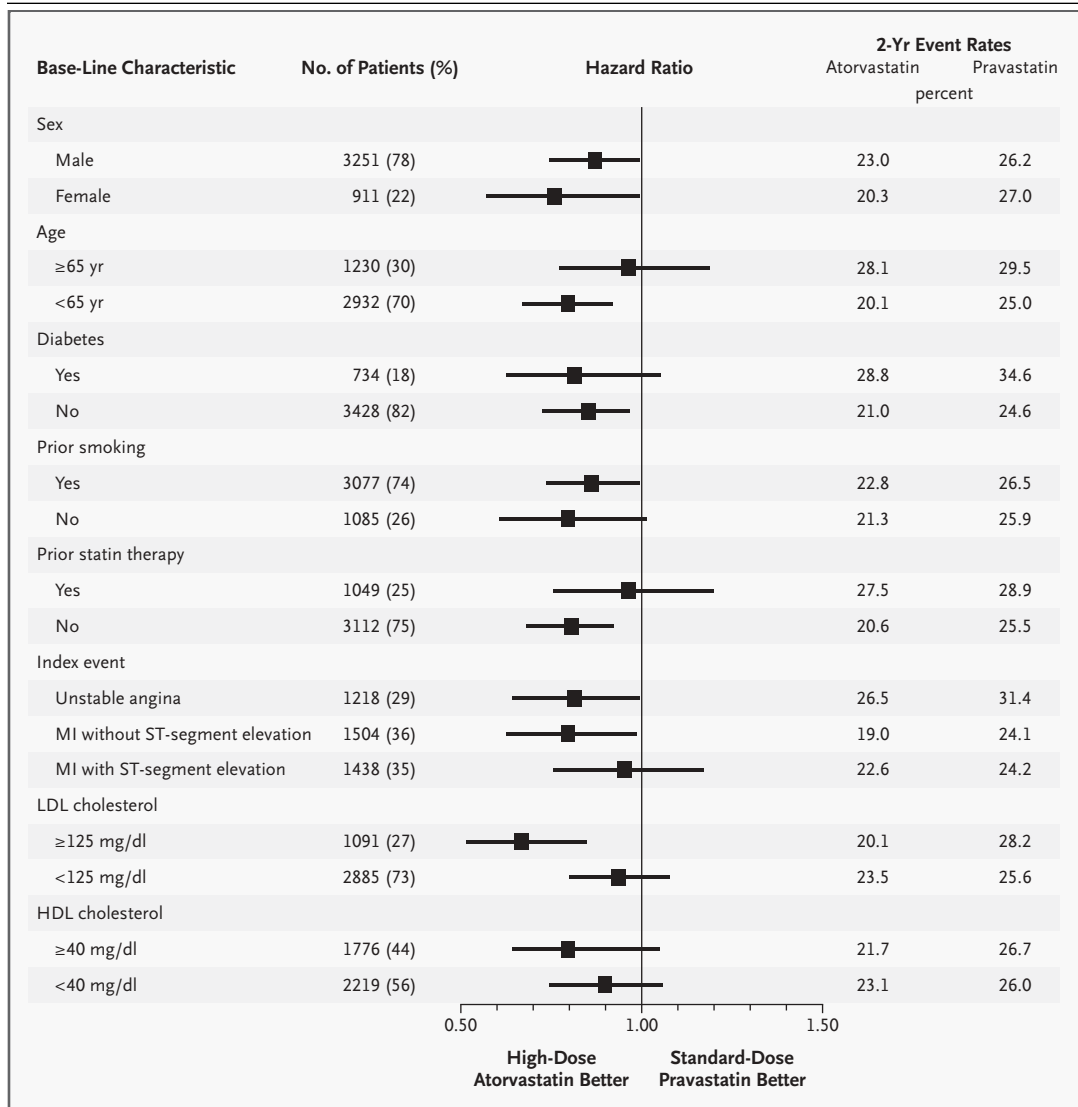


**Figure 4.** Estimates of the Hazard Ratio for the Secondary End Points and the Individual Components of the Primary End Point in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group.

CI denotes confidence interval, CHD coronary heart disease, and MI myocardial infarction. Revascularization was performed at least 30 days after randomization.

early as 30 days after the start of therapy. This rapid time frame is similar to that reported with statin treatment in the placebo-controlled Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial<sup>16</sup> and in prior observational studies.<sup>17,18</sup> We studied patients who had been hospitalized for an acute coronary syndrome and

enrolled them immediately after their condition had stabilized. Three quarters of the patients were treated with an early invasive strategy, and the majority were treated with multiple medications for secondary prevention, including antiplatelet therapy, beta-blockers, and angiotensin-converting–enzyme inhibitors (and a statin as part of the trial design).



**Figure 5. Two-Year Event Rates and Estimates of the Hazard Ratio for the Primary End Point in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group, According to Base-Line Characteristics.**

A test for interaction was significant only for a base-line low-density lipoprotein (LDL) value of at least 125 mg per deciliter, as compared with a value of less than 125 mg per deciliter (P=0.02). LDL cholesterol was measured at base line in a total of 3976 patients, and high-density lipoprotein (HDL) cholesterol was measured in 3995. Two patients did not have information regarding the electrocardiographic type of acute coronary syndrome, and one patient had missing information regarding prior statin use. MI denotes myocardial infarction.

Nonetheless, early and continued separation of the event curves was observed in the more intensive lipid-lowering group. This early reduction in event rates in patients with acute coronary syndromes contrasts with the lag of approximately one to two years in prior studies of statins in patients with chronic atherosclerosis.<sup>1-6</sup> These data suggest that this population of patients with acute coronary syn-

dromes, who have a culprit lesion and frequently multiple additional vulnerable plaques as well,<sup>19,20</sup> can derive particular benefit from early and intensive lipid lowering with statins. The current guidelines of the American College of Cardiology and American Heart Association recommend instituting lipid-lowering therapy at the time of hospital discharge in patients with acute coronary syndromes, on the

theory that it will improve patients' compliance with the use of statins for long-term secondary prevention.<sup>21</sup> Our data are evidence that such therapy will also provide protection against early recurrent cardiovascular events.

After the early separation of the clinical-event curves, we also observed a continued benefit of atorvastatin therapy throughout the follow-up period of two and one-half years (Fig. 2). It cannot be determined from this study whether this longer-term benefit was due to ongoing intensive lipid-lowering therapy or was the result of an early benefit in stabilizing vulnerable plaques with the early and intensive treatment after the acute event. It also cannot be determined whether other differences between the two statins used explain the observed clinical benefit. Nonetheless, our findings suggest that patients with acute coronary syndromes who receive early and intensive lipid-lowering therapy continue to derive benefit in the chronic phase of atherosclerosis when high-dose statin therapy is maintained.

Our finding of a continued benefit of intensive lipid-lowering therapy during the follow-up phase is consistent with studies showing that such an approach results in a slower rate of progression of atherosclerosis in patients with stable coronary artery disease<sup>22</sup> or in those who undergo coronary-artery bypass grafting,<sup>23</sup> as well as in greater reductions in carotid intimal-medial thickening.<sup>24-26</sup> Although our study documented a benefit for up to an average of two years of follow-up, several large, ongoing trials involving patients with stable atherosclerosis will determine the five-year outcomes of intensive as compared with moderate lipid lowering.<sup>27</sup>

It is important to note that our safety and efficacy results were obtained in a carefully selected and monitored study population (for example, we excluded patients who were concomitantly receiving strong inhibitors of cytochrome P-450 3A4, because this is integral to the route of metabolism of atorvastatin). Although both drugs were generally well tolerated, there were significantly more liver-related side effects with high-dose atorvastatin than with standard-dose pravastatin. Patients in clinical practice generally have more coexisting conditions than did our patients, and they may not tolerate a high-dose statin regimen as well as our patients did. Thus, clinicians must take these factors into account when applying the results of our trial in clinical practice.

The National Cholesterol Education Program and European guidelines currently recommend that the goal of treatment in patients with established coronary artery disease should be an LDL cholesterol level of less than 100 mg per deciliter.<sup>8,9</sup> Although our data provide support for the use of this approach, given the substantially lower LDL cholesterol levels achieved in the group given 80 mg of atorvastatin daily (median, 62 mg per deciliter), our results suggest that after an acute coronary syndrome, the target LDL cholesterol level may be lower than that recommended in the current guidelines.

Supported by Bristol-Myers Squibb and Sankyo.

Drs. Rader and Pfeffer report having received consulting fees and lecture fees from Bristol-Myers Squibb. Drs. Joyal and Belder are employees of Bristol-Myers Squibb and have equity in the company. Dr. Rouleau reports having received consulting fees and lecture fees from Novartis.

#### APPENDIX

The following investigators and research coordinators participated in the study (the complete list of investigators and coordinators is available at <http://www.timi.org>): *Operations Committee* — E. Braunwald (Study Chair), C. Cannon (Principal Investigator), T. Grayston, B. Muhlestein, D. Rader, J. Rouleau, and members of the Data Coordinating Center and Sponsor indicated with an asterisk; *Steering Committee* — Members of the Operations Committee and R. Byington, A. Castaigne, H. Darius, G. DeFerrari, B. Gersh, D. Gilbert, S. Grundy, G. Jackson, R. Knopp, I. Meredith, E. Ofili, M. Pfeffer, F. Sacks, P. Shah, S. Smith, A. Tonkin, J. Velasco; *TIMI Study Group* — C. McCabe (Project Director), \* S. McHale (Project Manager); *Sponsor* (Bristol-Myers Squibb, Princeton, N.J., and Wallingford, Conn.) — R. Belder, \* J. Breen, \* G. Cucinotta, S. Joyal, \* C.-S. Lin, K. Natarajan, \* S. Nichols; *Data Coordinating Center* (Nottingham Clinical Research Group, Nottingham, United Kingdom) — A. Skene, \* K. Hill; *Clinical Events Committee* — M. Pfeffer (Chairman), R. Guertin-Mercier; J. Potzka, R. Messing; *Physician Reviewers* — E. Ascher, P. Finn, R. Giugliano, J. Kirdar, D. Lee, A. Mirza, T. Rocco; *Biomarker Core Laboratory* (Brigham and Women's Hospital, Boston) — D. Morrow, P. Ridker, E. Danielson, G. Borkowski; *Chlamydia/Serology Core Laboratory* (John Hopkins University, Baltimore) — T. Quinn; C. Gaydos, B. Wood; *Electrocardiographic Core Laboratory* (eResearch Technology, Philadelphia) — J. Morganroth; *Special Lipid Core Laboratory* (University of Pennsylvania, Philadelphia) — D. Rader, M. Wolf; *Chemistry Core Laboratory* (LabCorp, Raritan, N.J.); *Data and Safety Monitoring Board* — A. Gotto (Chair), J. Bartlett, D. DeMets, J. Banas, T. Pearson; *Clinical Centers Enrolling the Most Patients (in order of enrollment)* — Huntsville Hospital, Huntsville, Ala.: W. Haught and K. Griffin; Fremantle Hospital, Fremantle, Wash.: R. Hendriks and D. Greenwell; Detar Hospital, Victoria, Tex.: H. Chandna and D. Holly; St. Francis Hospital, Tulsa, Okla.: J. Cassidy and N. Ritchie; Advanced Health Institute, Galax, Va.: J. Puma and E. Jones; Michigan Heart, Ypsilanti: J. Bengtson and C. Carulli; North Mississippi Medical Center, Tupelo: B. Bertolet and M. Jones; Wilford Hall Medical Center, Lackland Air Force Base, Lackland, Tex.: R. Krasuski and U. Ward; Queen Elizabeth Hospital, Woodville, Saskatchewan, Canada: J. Horowitz and R. Prideaux; Moses H. Cone Hospital, Greensboro, N.C.: T. Kelly and K. Cochran; Deaconess Medical Center, Spokane Wash.: D. Hollenbaugh and J. Mansfield; Louisiana Cardiology Associates, Baton Rouge: J. McLachlan and A. Yoches; New Mexico Heart Institute, Albuquerque: R. Orchard and S. Justice; River Cities Cardiology, Jeffersonville, Ind.: D. Denny and B. Vanvactor; Laval Hospital, Quebec, Canada: P. Bogaty and L. Boyer; Altru Health System Research Center, Grand Forks,

N.D.: A. Ahmed and D. Vold; Iowa Heart Center, Des Moines; W. Wickmeyer and N. Coffman; MetroHealth Medical Center, Cleveland; R. Finkelhor and M. Dettmer; Scarborough Cardiology Research, Scarborough, Ont., Canada; A. Ricci, and B. Bozek; Moses Cone Hospital, Greensboro, N.C.; T. Stuckey and S. Milks; Lake Forest Hospital, Bannockburn, Ill.; J. Alexander and K. Anderson; Centre Hospitalier Universitaire, Fleurimont, Que., Canada; S. LePage and L. Larrivee; Butterworth Hospital, Grand Rapids, Mich.; R. McNamara and B. Van Over; Centre Hospitalier Regional de Lanaudière, Quebec, Canada; S. Kouz and M. Roy; Craigavaon Area Hospital, Portadown, County Armagh, United Kingdom; A. Moriarty and D. McEneaney.

## REFERENCES

- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4 444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
- Sacks RM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Shepard J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.
- Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-30.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
- De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease and prevention in clinical practice. *Atherosclerosis* 2003;171:145-55.
- Davidson MH, Nawrocki JW, Weiss SR, et al. Effectiveness of atorvastatin for reducing low-density lipoprotein cholesterol to National Cholesterol Education Program treatment goals. *Am J Cardiol* 1997;80:347-8.
- Cannon CP, McCabe CH, Belder R, Breen J, Braunwald E. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial. *Am J Cardiol* 2002;89:860-1.
- Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000;102:149-56.
- Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes: a report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). *J Am Coll Cardiol* 2001;38:2114-30.
- Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. *Biometrics* 1986;42:507-19.
- Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering — are they clinically relevant? *Eur Heart J* 2003;24:225-48.
- Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711-8.
- Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001;285:430-6.
- Aronow HD, Topol EJ, Roe MT, et al. Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet* 2001;357:1063-8.
- Asakura M, Ueda Y, Yamaguchi O, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angioscopic study. *J Am Coll Cardiol* 2001;37:1284-8.
- Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000;343:915-22.
- Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction — 2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *Circulation* 2002;106:1893-900.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *JAMA* 2004;291:1071-80.
- Campeau L, Hunninghake DB, Knatterud GL, et al. Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors: NHLBI post coronary artery bypass graft clinical trial. *Circulation* 1999;99:3241-7.
- Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;106:2055-60.
- Kent SM, Coyle LC, Flaherty PJ, Markwood TT, Taylor AJ. Marked low-density lipoprotein cholesterol reduction below current National Cholesterol Education Program targets provides the greatest reduction in carotid atherosclerosis. *Clin Cardiol* 2004;27:17-21.
- Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001;357:577-81.
- LaRosa JC. New and emerging data from clinical trials of statins. *Curr Atheroscler Rep* 2004;6:12-9.

Copyright © 2004 Massachusetts Medical Society.