The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

Intensive versus 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.

*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.

This article was published at www.nejm.org on March 8, 2004.

N Engl J Med 2004;350:1495-504.

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.[1-7] 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.[8,9] 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[2,3] 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[10] 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,[11] 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 index 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 μmol 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[8] 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.[12,13] 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.[14] 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 infarction 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

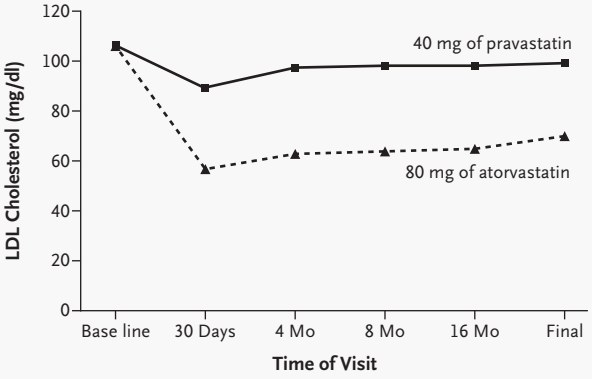
Table 1. Base-Line Characteristics of the Patients.*

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 MI — 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. MI denotes myocardial infarction, LDL low-density lipoprotein, and HDL high-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).



No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Figure 1. Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study.

To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

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 percent 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 baseline LDL cholesterol below 125 mg per deciliter (P for interaction=0.02).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.