

AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY IN STABLE CORONARY ARTERY DISEASE

BERTRAM PITT, M.D., DAVID WATERS, M.D., WILLIAM VIRGIL BROWN, M.D., AD J. VAN BOVEN, M.D., PH.D.,
LEONARD SCHWARTZ, M.D., LAWRENCE M. TITLE, M.D., DANIEL EISENBERG, M.D., LINDA SHURZINSKE, M.S.,
AND LISA S. MCCORMICK, PHARM.D., FOR THE ATORVASTATIN VERSUS REVASCULARIZATION TREATMENT INVESTIGATORS*

ABSTRACT

Background Percutaneous coronary revascularization is widely used in improving symptoms and exercise performance in patients with ischemic heart disease and stable angina pectoris. In this study, we compared percutaneous coronary revascularization with lipid-lowering treatment for reducing the incidence of ischemic events.

Methods We studied 341 patients with stable coronary artery disease, relatively normal left ventricular function, asymptomatic or mild-to-moderate angina, and a serum level of low-density lipoprotein (LDL) cholesterol of at least 115 mg per deciliter (3.0 mmol per liter) who were referred for percutaneous revascularization. We randomly assigned the patients either to receive medical treatment with atorvastatin, at 80 mg per day (164 patients), or to undergo the recommended percutaneous revascularization procedure (angioplasty) followed by usual care, which could include lipid-lowering treatment (177 patients). The follow-up period was 18 months.

Results Twenty-two (13 percent) of the patients who received aggressive lipid-lowering treatment with atorvastatin (resulting in a 46 percent reduction in the mean serum LDL cholesterol level, to 77 mg per deciliter [2.0 mmol per liter]) had ischemic events, as compared with 37 (21 percent) of the patients who underwent angioplasty (who had an 18 percent reduction in the mean serum LDL cholesterol level, to 119 mg per deciliter [3.0 mmol per liter]). The incidence of ischemic events was thus 36 percent lower in the atorvastatin group over an 18-month period ($P=0.048$, which was not statistically significant after adjustment for interim analyses). This reduction in events was due to a smaller number of angioplasty procedures, coronary-artery bypass operations, and hospitalizations for worsening angina. As compared with the patients who were treated with angioplasty and usual care, the patients who received atorvastatin had a significantly longer time to the first ischemic event ($P=0.03$).

Conclusions In low-risk patients with stable coronary artery disease, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events. (N Engl J Med 1999;341:70-6.)

©1999, Massachusetts Medical Society.

CORONARY revascularization by percutaneous techniques is widely used in the treatment of patients with stable angina pectoris, inducible myocardial ischemia, or both. Studies comparing medical treatment and percutaneous revascularization suggested that patients who underwent revascularization had an improvement in their quality of life, exercise performance, or both.¹⁻³ However, the effect of medical treatment, as compared with percutaneous revascularization, on the incidence of ischemic events and the need for subsequent revascularization was less certain. Lipid-lowering treatment has been shown to reduce significantly the incidence of cardiovascular events, overall mortality, and the need for revascularization.^{4,5} We postulated that in patients with one- or two-vessel coronary artery disease, relatively normal left ventricular function, and no severe symptoms of angina pectoris, treatment with atorvastatin could delay or prevent the need for revascularization without increasing the risk of ischemic events. In a randomized, controlled study, we compared the outcomes in patients who received atorvastatin with the outcomes in similar patients who underwent percutaneous revascularization, with or without stenting, and then received usual medical treatment, which could include lipid-lowering medication.

METHODS

Study Design

The design of the Atorvastatin versus Revascularization Treatment study has been reported previously.⁶ The study was an 18-month, open-label, randomized, multicenter study of patients with stable coronary artery disease, a serum level of low-density lipoprotein (LDL) cholesterol of at least 115 mg per deciliter (3.0 mmol per liter), and a serum level of triglycerides of no more than 500 mg per deciliter (5.6 mmol per liter). The patients had stenosis of 50 percent or more in at least one coronary artery and

From the Department of Medicine, University of Michigan School of Medicine, Ann Arbor (B.P.); the Division of Cardiology, Hartford Hospital, Hartford, Conn. (D.W.); the Department of Medicine, Emory University School of Medicine, Atlanta (W.V.B.); Thoraxcentre, University Hospital, Groningen, the Netherlands (A.J.B.); the Department of Medicine, Toronto Hospital, Toronto (L. Schwartz); the Division of Cardiology, Queen Elizabeth II Health Sciences Centre, Halifax, N.S. (L.M.T.); Providence Saint Joseph Medical Center, Los Angeles (D.E.); and Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Mich. (L. Shurzinske, L.S.M.). Address reprint requests to Dr. Pitt at the Division of Cardiology, University of Michigan Medical Center, 3910 Taubman, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0366, or at bpitt@umich.edu.

*Other investigators are listed in the Appendix.

had been recommended for treatment with percutaneous revascularization. The patients were asymptomatic or had Canadian Cardiovascular Society (CCS) class I or II angina (four patients had more severe angina) and were able to complete at least four minutes of a treadmill test conducted according to the Bruce protocol or a bicycle exercise test at 20 W per minute without marked electrocardiographic changes indicative of ischemia.⁷⁻⁹ Major criteria for exclusion from the study were left main coronary artery disease, triple-vessel disease, unstable angina or myocardial infarction within the previous two weeks, and an ejection fraction of less than 40 percent. Informed consent was obtained from the study patients, and the research protocol was approved by the appropriate institutional review boards.

Treatment

The patients were stratified according to whether they had single- or double-vessel disease (defined as stenosis of 50 percent or more in one or two coronary arteries, respectively) and were then randomly assigned either to receive medical treatment with 80 mg of atorvastatin (Lipitor, Parke-Davis, Ann Arbor, Mich.) per day or to undergo the recommended percutaneous revascularization procedure (angioplasty), followed by usual care, which could include lipid-lowering treatment. There was no washout period for patients already receiving lipid-lowering medication. Patients assigned to receive atorvastatin discontinued any other lipid-lowering medication they might have been taking and began taking atorvastatin (80 mg per day), whereas patients assigned to angioplasty and usual care were allowed to continue their current drug regimen.

Statistical Analysis

An independent end-points committee, the members of which were unaware of the treatment assignments, reviewed all ischemic events, and all analyses were based on the committee's classification of ischemic events.

The Cochran-Mantel-Haenszel test, with stratification according to the participating center and the extent of disease, was used in an intention-to-treat analysis to compare the two treatment groups in regard to the proportion of patients with ischemic events. We defined an ischemic event as at least one of the following: death from cardiac causes, resuscitation after cardiac arrest, nonfatal myocardial infarction, cerebrovascular accident, coronary-artery bypass grafting, angioplasty, and worsening angina with objective evidence resulting in hospitalization. We used a Cox proportional-hazards analysis and Kaplan-Meier curves to examine the time to a first ischemic event.

The sample size was planned to provide the study with 85 percent power, with a two-sided level of significance of 5 percent for the detection of a difference between treatment groups in the proportion of patients with ischemic events. Assumptions included event rates of 20 percent and 35 percent over a period of 18 months in the atorvastatin and angioplasty groups, respectively.

Because of concern about the safety of patients not undergoing percutaneous revascularization as the initial treatment, we performed two interim analyses, using the O'Brien-Fleming stopping rule. Consequently, the significance level for the final analysis of the incidence of ischemic events was adjusted from 5 percent to 4.5 percent.¹⁰ All remaining variables were tested with a 5 percent level of significance.

RESULTS

Patients

A total of 341 patients at 37 centers in North America and Europe were randomly assigned to treatment groups between July 1995 and December 1996. The characteristics of the patients in the two treatment groups were similar at base line (Table 1). There were small but significant differences between the groups in terms of sex, concurrent use of aspirin

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ATORVASTATIN GROUP (N=164)	ANGIOPLASTY GROUP (N=177)
Male sex — no. of patients (%)†	130 (79)	157 (89)
Race — no. of patients (%)		
White	157 (96)	168 (95)
Nonwhite	7 (4)	9 (5)
Age — yr	59±0.8	58±0.6
Mean ejection fraction (%)	61	61
Mean no. of risk factors	2.5	2.5
Current smoker — no. of patients (%)	39 (24)	37 (21)
Clinical history — no. of patients (%)		
Hyperlipidemia	129 (79)	143 (81)
Hypertension	76 (46)	79 (45)
Angina pectoris	126 (77)	139 (79)
Diabetes mellitus	28 (17)	26 (15)
Peripheral vascular disease	20 (12)	16 (9)
Myocardial infarction‡	73 (45)	70 (40)
Concurrent medication — no. of patients (%)		
Angiotensin-converting-enzyme inhibitor	14 (9)	14 (8)
Lipid-lowering agent	42 (26)	33 (19)
Aspirin or other anticoagulant†	27 (16)	46 (26)
Canadian Cardiovascular Society classification of angina — no. of patients (%)		
Asymptomatic	29 (18)	27 (15)
Class I	74 (45)	70 (40)
Class II	60 (37)	77 (44)
Class III	1 (1)	2 (1)
Class IV	0	1 (1)
Nature of coronary artery disease — no. of patients (%)		
Single-vessel	94 (57)	99 (56)
Double-vessel	70 (43)	78 (44)
Location of target lesions — no. of patients (%)§		
Left anterior descending coronary artery†	70 (43)	53 (30)
Left circumflex coronary artery	59 (36)	63 (36)
Right coronary artery	59 (36)	64 (36)

*This table reflects the final, verified data base. Some numbers may differ slightly from those in our earlier report,⁶ which used a working data base. Plus-minus values are means ±SE. Percentages may not sum to 100, because of rounding.

†P<0.05 for the comparison between the treatment groups.

‡Eleven percent of the patients in each treatment group had a myocardial infarction within two months before the screening visit.

§Some patients had more than one target lesion. Twenty-three of the patients in the atorvastatin group (14 percent) and 28 of the patients in the angioplasty group (16 percent) had lesions of the proximal left anterior descending coronary artery.

or other anticoagulants, and the presence of left anterior descending coronary artery disease. Separate analyses for each sex and for patients with and without left anterior descending coronary artery disease showed the trends within these subgroups to be similar to the overall results. In no subgroup was there a result favoring angioplasty.

One patient in the atorvastatin group never received atorvastatin, and 11 of the patients in the angioplasty group (6 percent) did not undergo revascularization as assigned because of refusal by the patient (8 patients), disease progression (1, who un-

derwent coronary-artery bypass grafting), regression of the lesion (1), and a procedure that was unsuccessful because of technical difficulty (1); these patients remained in the study. Four of the patients in the atorvastatin group (2 percent) and two of the patients in the angioplasty group (1 percent) withdrew from the study because of an adverse event (mild impotence in one patient in the atorvastatin group) or a decision by the patient (three patients in the atorvastatin group and two in the angioplasty group). In addition, eight of the patients in the atorvastatin group discontinued the study treatment (two because of elevations in the level of liver enzymes, five because of adverse events, and one because of a decision by the patient); these patients remained in the study. Overall, at least 95 percent of the patients were considered to be compliant with the atorvastatin regimen at each visit to the clinic. Follow-up information was collected on all patients at least 18 months after randomization; no patients were lost to follow-up.

Overall, 166 patients in the angioplasty group underwent the assigned procedure (with a total of 213 treated lesions). Concomitant stenting was used in 64 of the lesions, and atherectomy in 4. The mean percentages of stenosis in the target lesions before and after revascularization were 81 percent and 20 percent, respectively. The mean percentage of stenosis at base line in the atorvastatin group was 80 percent.

The patients' smoking status did not change throughout the study, whereas patients in both treatment groups made similar improvements in their eating and exercise habits.

Concurrent Medication

At screening, 75 patients (22 percent) were taking medication that modifies lipid levels. In the angioplasty group, 130 patients (73 percent) received lipid-lowering medication at some time during the study, of whom 125 (71 percent of the total group) received a statin (median dose, 20 mg per day), and 123 (69 percent) were receiving lipid-lowering medication at the end of the study. Atorvastatin received approval from U.S. and European regulatory authorities while the study was under way; as a result, 17 of the patients in the angioplasty group (10 percent) received prescriptions for atorvastatin (median dose, 20 mg per day). In the atorvastatin group, 153 patients (93 percent) continued to receive atorvastatin until the end of the study. During the study, aspirin was taken by 135 patients in the atorvastatin group (82 percent) and 158 in the angioplasty group (89 percent), although significantly more patients in the angioplasty group had been taking aspirin at base line.

Lipoprotein Levels

The patients who were randomly assigned to receive atorvastatin had significantly lower levels of LDL cholesterol, total cholesterol, and triglycerides than

the patients in the angioplasty group ($P < 0.05$) (Fig. 1). Because 22 percent of all patients were already receiving lipid-lowering medication at base line and there was no washout period, the changes in lipid levels reflect incremental changes from base-line values.

Ischemic Events

Twenty-two of the patients in the atorvastatin group (13 percent) and 37 in the angioplasty group (21 percent) had ischemic events, a difference of 36 percent ($P = 0.048$) (Table 2). Although this difference did not reach the level of significance as adjusted for interim analyses ($P = 0.045$), it did reach the conventional 5 percent level of significance. Twenty of the patients in the atorvastatin group (12 percent) underwent a revascularization procedure, either coronary-artery bypass grafting or percutaneous angioplasty, during the follow-up period, as compared with 29 of the patients in the angioplasty group (16 percent) who had a subsequent revascularization. Fourteen of the follow-up procedures in the angioplasty group (48 percent) involved the placement of at least one stent, whereas nine of the follow-up procedures in the atorvastatin group (41 percent) included stenting.

When the data on ischemic events were analyzed according to time, there was a greater difference between treatment groups after the first six months of treatment. Twelve of the patients in the atorvastatin group (7 percent) and 17 of the patients in the angioplasty group (10 percent) had a first event within six months after treatment was begun ($P = 0.45$). After the first six months, 10 patients in the atorvastatin group (6 percent) and 20 patients in the angioplasty group (11 percent) had a first event ($P = 0.09$).

Of the 23 patients in the atorvastatin group and the 28 patients in the angioplasty group who had a target lesion of the proximal left anterior descending coronary artery at base line (14 percent and 16 percent, respectively), 2 of the patients in the atorvastatin group (9 percent) had ischemic events, as compared with 7 of the patients in the angioplasty group (25 percent).

Treatment with atorvastatin, as compared with angioplasty, was associated with a significantly longer time to a first ischemic event ($P = 0.03$) and with a reduction in risk of 36 percent (Fig. 2).

Angina

At the end of the study, 67 patients in the atorvastatin group (41 percent) had an improvement in the CCS classification of angina symptoms, 78 (48 percent) had no change, and 19 (12 percent) had a deterioration. Of the patients in the angioplasty group, 95 (54 percent) had an improvement in the CCS classification, 70 (40 percent) had no change, and 12 (7 percent) had a deterioration. This difference between treatment groups significantly favored angioplasty ($P = 0.009$ by the Cochran–Mantel–Haenszel

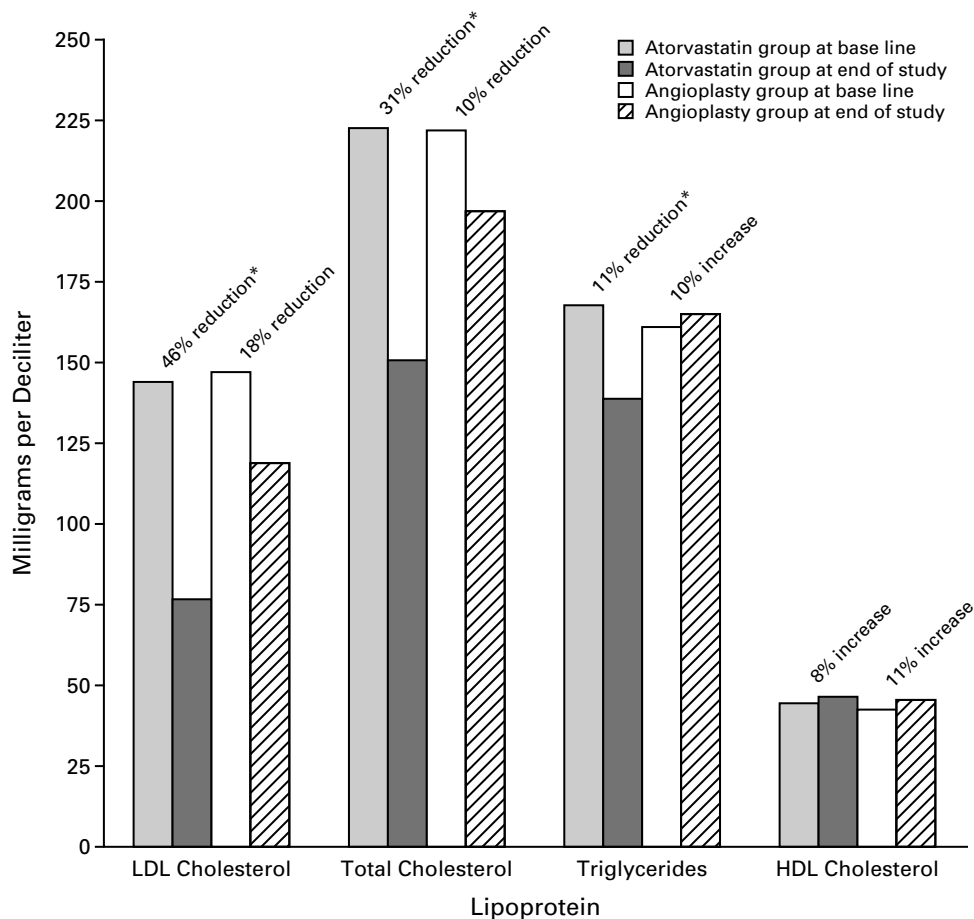


Figure 1. Changes in Lipoprotein Levels in the Atorvastatin Group and the Angioplasty Group. An asterisk denotes that the reduction was significantly different from that in the angioplasty group ($P < 0.05$). To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

TABLE 2. OCCURRENCE OF ISCHEMIC EVENTS ACCORDING TO TREATMENT GROUP.

ISCHEMIC EVENT	ATORVASTATIN GROUP (N=164)		ANGIOPLASTY GROUP (N=177)	
	NO. OF PATIENTS FOR WHOM THE EVENT WAS THE FIRST	NO. OF PATIENTS (%) WITH THE EVENT	NO. OF PATIENTS FOR WHOM THE EVENT WAS THE FIRST	NO. OF PATIENTS (%) WITH THE EVENT*
Death from cardiac causes	1	1 (0.6)	1	1 (0.6)
Resuscitation after cardiac arrest	0	0	0	0
Nonfatal myocardial infarction	2	4 (2.4)	4	5 (2.8)
Cerebrovascular accident	0	0	0	0
Coronary-artery bypass grafting	0	2 (1.2)	3	9 (5.1)
Angioplasty as an event	9	18 (11.0)	5	21 (11.9)
Worsening angina with objective evidence of myocardial ischemia resulting in hospitalization	10	11 (6.7)	24	25 (14.1)
Any ischemic event		22 (13.4)		37 (20.9)

*Twenty-nine of the patients in the angioplasty group underwent a revascularization procedure after the assigned angioplasty. One of the patients in the angioplasty group underwent both coronary-artery bypass grafting and angioplasty.

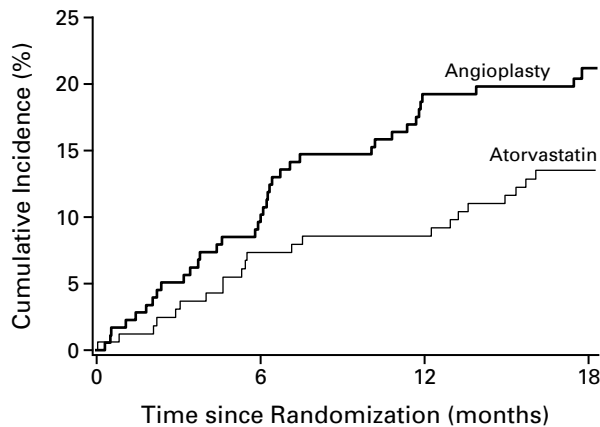


Figure 2. Cumulative Incidence of First Ischemic Events. The time to an ischemic event was significantly longer in the atorvastatin group ($P=0.03$), and the risk reduction was 36 percent (95 percent confidence interval, 5 to 67 percent).

TABLE 3. USE OF ANTIANGINAL MEDICATION AT BASE LINE AND AT THE END OF THE STUDY.

ANTIANGINAL MEDICATION	ATORVASTATIN GROUP (N=164)	ANGIOPLASTY GROUP (N=177)
	no. of patients (%)	
Base line		
Beta-blockers	101 (62)	122 (69)
Nitrates	93 (57)	101 (57)
Calcium-channel blockers	76 (46)	78 (44)
Any type	147 (90)	164 (93)
End of study		
Beta-blockers	98 (60)	108 (61)
Nitrates	98 (60)	88 (50)
Calcium-channel blockers	80 (49)	78 (44)
Any type	147 (90)	159 (90)

test). However, this outcome variable was the only one not reviewed by the end-points committee.

The percentage of patients receiving antianginal medication was similar in the treatment groups both at base line and at the end of the study, although in many cases the nitrates prescribed were only nitroglycerin to be taken as needed (Table 3). More patients started to use or increased their doses of antianginal medications in the angioplasty group (18 percent) than in the atorvastatin group (8 percent), and fewer patients stopped using antianginal medications or decreased their doses in the angioplasty group (16 percent) than in the atorvastatin group (21 percent).

At base line, 25 percent of the patients in the atorvastatin group and 24 percent of the patients in the angioplasty group were receiving two antianginal drugs, and 15 percent and 12 percent, respectively, were receiving three. At the end of the study, 24 per-

cent of each group were receiving two antianginal drugs, and 12 percent and 13 percent, respectively, were receiving three.

Quality of Life

The patients' quality of life was assessed at base line and at 6 and 18 months after randomization with use of the 36-item Medical Outcomes Study Short-Form General Health Survey.^{11,12} Both treatment groups had a mean increase in the summary scores for physical and mental health at both the 6-month and 18-month assessments, denoting an improvement in the quality of life from base line. Mean increases in scores ranged from 2.9 to 6.3; the increases were slightly larger in the angioplasty group. Given the variability and the small sample, we could not determine any differences between the two groups in terms of quality of life.

Safety

The adverse events reported were similar in the two treatment groups. Seventeen of the patients in the atorvastatin group (10 percent) reported serious adverse events, none of which were considered to be related to atorvastatin therapy. In 13 patients, the serious events led to, or resulted from, diagnostic or surgical procedures (colectomy [2 patients], cholecystectomy [2 patients], gastrectomy, appendectomy [2 patients], dilation and curettage, placement of hip screws, repair of a right femoral artery, magnetic resonance imaging and radiography of the femur, pacemaker implantation, and electrophysiologic study of an implanted pacemaker). The other four patients had bronchopneumonia; abdominal pain, constipation, and atypical chest pain; a urinary tract infection and prostate cancer; and rheumatoid arthritis.

Twenty-eight of the patients in the angioplasty group (16 percent) had serious adverse events. Six of these patients (21 percent) had events that were considered to be related to the angioplasty procedure (thrombosis at the access site, dissection, arteriovenous fistula, coronary occlusion, occlusion of iliac stenosis, and femoral hematoma). Four of the patients in the atorvastatin group (2 percent) had persistent, clinically important elevations in the level of aspartate or alanine aminotransferase (defined as a level that was more than three times the upper limit of normal). No patient in either treatment group had persistent, clinically important elevations in the creatine kinase level (defined as a level that was more than 10 times the upper limit of normal). Seven cancers were diagnosed during the study: three in patients in the atorvastatin group and four in patients in the angioplasty group.

DISCUSSION

Our study suggests that aggressive lowering of LDL cholesterol levels with atorvastatin (to a mean

level of 77 mg per deciliter in our study group) is at least as effective as angioplasty followed by usual care (which reduced the LDL cholesterol level to 119 mg per deciliter in our study) in reducing the incidence of ischemic events in low-risk patients who have been referred for revascularization.

We found a 36 percent lower incidence of ischemic events over a period of 18 months in patients treated with atorvastatin as compared with angioplasty followed by usual medical care. This result narrowly missed the level of significance as adjusted for interim analyses. Nonetheless, our findings are important. This is particularly true given the significantly longer time to a first ischemic event in the patients treated with atorvastatin than in those who underwent angioplasty (Fig. 2). Most angioplasty-related events and restenoses occur within six months after revascularization. However, in this study, 20 of the patients in the angioplasty group (11 percent) had a first ischemic event after six months, as compared with 10 of the patients in the atorvastatin group (6 percent). The greater difference in the incidence of ischemic events after the first six months (Fig. 2) suggests that the chief explanation for the difference in the occurrence of ischemic events is the effect of the lowering of lipid levels with atorvastatin. In previous trials, lipid-lowering treatment has been shown to have a beneficial effect only after six or more months.^{4,5} This finding is supported by the Kaplan-Meier analysis (the time to the first ischemic event) in the present study, which showed a greater divergence between the two treatment groups after six months. Although it is possible that many ischemic events that occurred after six months among patients in the angioplasty group could have been related to complications of angioplasty, an analysis of individual angiograms indicated that restenosis could account for only a small percentage of the events. This finding suggests a delayed effect of lipid lowering, possibly due to an improvement in endothelial function (vasomotor tone).

Major coronary events were infrequent in both treatment groups; their incidence was only 2 percent per year. Fewer patients in the atorvastatin group than in the angioplasty group were hospitalized with worsening angina and objective evidence of myocardial ischemia (11 vs. 25), and fewer patients in the atorvastatin group underwent bypass surgery or angioplasty during follow-up (20 vs. 29). Of the patients randomly assigned to receive atorvastatin, 87 percent continued to receive medical therapy without having an ischemic event during 18 months of follow-up. As in previous trials comparing medical therapy with angioplasty, there was a small but significant improvement in the CCS angina class in patients randomly assigned to undergo angioplasty,¹⁻³ albeit with an increase in antianginal treatment. However, this improvement in the severity of angina among

patients in the angioplasty group was more than offset by the reduction in ischemic events and the longer time to a first event among patients in the atorvastatin group.

The 46 percent reduction in the LDL cholesterol level, to a mean level of 77 mg per deciliter, with the use of atorvastatin in this study was not associated with an increase in adverse events. The adverse events reported were similar in the two treatment groups, and only four of the patients in the atorvastatin group (2 percent) had persistently elevated aspartate or alanine aminotransferase levels.

It is unlikely that a longer follow-up period would have shown a benefit of angioplasty in comparison with medical treatment. Serial angiographic studies have shown that myocardial infarction occurs most often in lesions that originally appear to be hemodynamically unimportant and that would therefore not be subject to angioplasty.¹³ Thus, we postulate that the aggressive lowering of lipid levels is more likely than angioplasty of high-grade lesions to prevent further progression of these minimal coronary-artery lesions and thereby prevent plaque rupture.¹⁴ In cholesterol-lowering trials, there was little benefit of medical treatment over placebo in the first two years of treatment, and outcome curves began to diverge after this time.^{4,5} It could thus be argued that longer follow-up in our study might further favor medical treatment with atorvastatin.

Our results do not provide evidence in regard to the value of angioplasty in patients who have severe symptoms and whose quality of life has been severely affected or in high-risk patients with left ventricular dysfunction, left main coronary artery disease, or triple-vessel disease or in patients with angina pectoris who have less exercise tolerance. However, one might anticipate that aggressive lowering of lipid levels would complement angioplasty in such patients, particularly by stabilizing untreated lesions.

Until the results of additional long-term trials in a larger number of patients are available, aggressive lipid lowering with atorvastatin appears to be as safe and as effective as angioplasty and usual care in reducing the incidence of ischemic events. Moreover, it appears that in patients with relatively normal left ventricular function who do not have severe symptoms, an initial strategy of aggressive lipid lowering with atorvastatin may reduce the likelihood of ischemic events and thereby delay or prevent the need for revascularization. If at any time symptoms worsen or exercise performance deteriorates to the extent that it interferes with the quality of life, patients may elect to undergo revascularization without any apparent penalty for their initial decision.

Supported by a grant from Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company.

Drs. Pitt, Waters, and Brown are consultants to Parke-Davis. Ms. Shurzinske and Dr. McCormick are employees and stockholders of Parke-Davis.

We are indebted to D. McDougal, C. Justice, W. Foley Eggleston, and R. Overhiser for assistance in managing the study and to T. Stern, Ph.D., for statistical support.

APPENDIX

In addition to the authors, the principal investigators of the Atorvastatin versus Revascularization Treatment study were as follows: *United States* — D.M. Black and M. Pressler, Ann Arbor, Mich.; A.S. Brown, Lombard, Ill.; M.D. Ezekowitz, West Haven, Conn.; R.L. Feldman, Ocala, Fla.; C.M. Gibson, West Roxbury, Mass.; S.W. Halpern, Santa Rosa, Calif.; M.A. Kellett and L. Keilson, Portland, Me.; D. Lu, Washington, D.C.; B. MacCallister and R. VandenBelt, Ypsilanti, Mich.; M. Miller, Baltimore; W. O'Neill, Royal Oak, Mich.; C.J. Pepine, Gainesville, Fla.; A.L. Pucillo, Valhalla, N.Y.; and R. Wilensky, Philadelphia; *Canada* — T.J. Anderson, Calgary, Alta.; R.G. Carere, Vancouver, B.C.; G. Cote, Montreal; J. Ducas, Winnipeg, Man.; S. Lepage, Sherbrooke, Que.; L. Schwartz, Toronto; B. O'Neill and L. Tittle, Halifax, N.S.; *Europe* — France: J.L. Guermontprez, Paris; J. Puel, Toulouse; Germany: A. Frey, Bad Krozingen; F.X. Kleber, Berlin; H. Mudra, Munich; B. Wagner, Freiburg; A. Zeiher, Frankfurt; Italy: P. Zardini, Verona; Spain: E. Domingo, Barcelona; C. Macaya, Madrid; Switzerland: W. Kiowski, Zurich; the Netherlands: P. de Feyter, Rotterdam; A.J. van Boven, Groningen; United Kingdom: N.H. Brooks, Manchester; A.R. Rickards and A.D. Timmis, London; and D.H. Roberts, Blackpool.

The committees that participated in the study were as follows: Advisory-Data and Safety Monitoring Committee — B. Pitt, W.V. Brown, and D. Waters; End-Points Committee — R. DiBianco (chairperson), K. Eagle, A. Maseri, and C.M. O'Connor.

REFERENCES

1. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Engl J Med* 1992;326:10-6.
2. Hueb WA, Bellotti G, de Oliveira SA, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol* 1995;26:1600-5.
3. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* 1997;350:461-8.
4. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
5. Sacks FM, 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.
6. McCormick LS, Black DM, Waters D, Brown WV, Pitt B. Rationale, design, and baseline characteristics of a trial comparing aggressive lipid lowering with Atorvastatin Versus Revascularization Treatments (AVERT). *Am J Cardiol* 1997;80:1130-3.
7. Campeau L. Grading of angina pectoris. *Circulation* 1976;54:522-3.
8. Janicki JS, Weber KT. Equipment and protocols to evaluate the exercise response. In: Janicki JS, Weber KT, eds. *Cardiopulmonary exercise testing*. Section 9. Philadelphia: W.B. Saunders, 1986:147.
9. Brasseur LA, Mairaux PH, Kandouci AB, Detry JM. Respiratory and metabolic parameters during submaximal and maximal exercise in normal men. In: Rulli V, Messin R, Denolin H, eds. *Normal values in adult ergometry according to age, sex, and training*. Torino, Italy: Schiapparelli Farmaceutici, 1983:3-14 (pamphlet).
10. Geller NL, Pocock SJ. Design and analysis of clinical trials with group sequential stopping rules. In: Peace KE, ed. *Biopharmaceutical statistics for drug development*. New York: Marcel Dekker, 1988:489-508.
11. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). 1. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
12. Ware JE Jr, Snow KK, Kosinski M, Gandek B. *SF-36 health survey: manual and interpretation guide*. Boston: Health Institute, New England Medical Center, 1993.
13. Forrester JS, Shah PK. Lipid lowering versus revascularization: an idea whose time (for testing) has come. *Circulation* 1997;96:1360-2.
14. Waters D. Plaque stabilization: a mechanism for the beneficial effect of lipid-lowering therapies in angiographic studies. *Prog Cardiovasc Dis* 1994;37:107-20.