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## BENEFICIAL EFFECTS OF CHOLESTEROL-LOWERING THERAPY ON THE CORONARY ENDOTHELIUM IN PATIENTS WITH CORONARY ARTERY DISEASE

CHARLES B. TREASURE, M.D., J. LARRY KLEIN, M.D., WILLIAM S. WEINTRAUB, M.D., J. DAVID TALLEY, M.D.,  
MICHAEL E. STILLABOWER, M.D., ANDRZEJ S. KOSINSKI, PH.D., JIAN ZHANG, M.S.,  
STEPHEN J. BOCCUZZI, PH.D., JOHN C. CEDARHOLM, M.D., AND R. WAYNE ALEXANDER, M.D., PH.D.

**Abstract Background.** Impaired endothelium-mediated relaxation contributes to vasospasm and myocardial ischemia in patients with coronary artery disease. We hypothesized that cholesterol-lowering therapy with the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor lovastatin could improve endothelium-mediated responses in patients with coronary atherosclerosis.

**Methods.** In a randomized, double-blind, placebo-controlled trial, we studied coronary endothelial responses in 23 patients randomly assigned to either lovastatin (40 mg twice daily; 11 patients) or placebo (12 patients) plus a lipid-lowering diet (American Heart Association Step 1 diet). Patients were studied 12 days after randomization and again at 5½ months. These patients had total cholesterol levels ranging from 160 to 300 mg per deciliter (4.1 to 7.8 mmol per liter) and were undergoing coronary angioplasty. At the initial and follow-up studies, patients received serial intracoronary infusions (in a coronary artery not undergoing angioplasty) of acetylcholine to assess endothelium-mediated vasodilatation. The responses of the coronary vessels were analyzed with quantitative angiography.

CHOLESTEROL-LOWERING therapy has been associated with a decreased risk of ischemic coronary events and with angiographically detectable regression of atherosclerosis.<sup>1-5</sup> However, regression of atherosclerosis as assessed by angiography has been slight as compared with clinical outcomes, which have been substantially improved.<sup>3,4</sup> This important effect on clinical outcomes may be related to improved function of the coronary endothelium.

The endothelium is intimately involved in the pathogenesis of atherosclerosis.<sup>6</sup> Oxidative modification of low-density lipoprotein (LDL) cholesterol by the endothelium is thought to be an important step in the in-

**Results.** The patients in the placebo and lovastatin groups had similar responses to acetylcholine at a mean of 12 days of therapy (expressed as the percentage of change in diameter in response to acetylcholine doses of  $10^{-9}$  M,  $10^{-8}$  M,  $10^{-7}$  M, and  $10^{-6}$  M). In the placebo group, the respective mean ( $\pm$ SE) changes were  $1\pm 2$ ,  $0\pm 2$ ,  $-2\pm 4$ , and  $-19\pm 4$  percent; in the lovastatin group, they were  $-2\pm 2$ ,  $-4\pm 4$ ,  $-12\pm 5$ , and  $-16\pm 7$  percent ( $P=0.32$ ). (Coronary-artery constriction is reflected by negative numbers.) The responses to acetylcholine in the placebo group after a mean of 5.5 months of therapy were  $-3\pm 3$ ,  $-1\pm 2$ ,  $-8\pm 4$ , and  $-18\pm 5$  percent, respectively; there was significant improvement in the lovastatin group, which had responses of  $3\pm 3$ ,  $3\pm 3$ ,  $0\pm 2$ , and  $0\pm 3$  percent ( $P=0.004$ ).

**Conclusions.** Cholesterol lowering with lovastatin significantly improved endothelium-mediated responses in the coronary arteries of patients with atherosclerosis. Such improvement in the local regulation of coronary arterial tone could potentially relieve ischemic symptoms and signal the stabilization of the atherosclerotic plaque. (N Engl J Med 1995;332:481-7.)

itiation of atherosclerosis.<sup>7</sup> Oxidized LDL cholesterol impairs endothelium-mediated relaxation in isolated arterial segments.<sup>8</sup> Hypercholesterolemia and atherosclerosis impair endothelium-mediated vasodilator responses in animal models<sup>9</sup> and humans.<sup>10</sup> This loss of endothelium-mediated vasodilatation is thought to be involved in the pathogenesis of myocardial ischemia.<sup>11</sup> In hypercholesterolemic animal models, the return to a normal diet only partially restores the morphologic features of the vessel, but it reestablishes normal endothelium-mediated relaxation.<sup>9</sup>

We hypothesized that aggressive lipid-lowering therapy could improve the function of coronary-artery endothelium in patients with coronary atherosclerosis. We investigated this hypothesis in a multicenter, double-blind, placebo-controlled substudy of the Lovastatin Restenosis Trial.<sup>12</sup>

## METHODS

### Population of Patients

This prospective, randomized, double-blind, placebo-controlled study evaluated the short-term (12-day) and longer-term (5½-month) effects on coronary endothelial vasodilator function of a lip-

From the Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta (C.B.T., J.L.K., W.S.W., J.Z., R.W.A.); the Division of Cardiology, Department of Medicine, University of Louisville School of Medicine, Louisville, Ky. (J.D.T.); the Division of Cardiology, Medical Center of Delaware, Newark (M.E.S.); the Division of Biostatistics, School of Public Health, Emory University, Atlanta (A.S.K.); Merck Research Laboratories, Rahway, N.J. (S.J.B.); and the Division of Cardiology, Sanger Clinic, Charlotte, N.C. (J.C.C.). Address reprint requests to Dr. Treasure at P.O. Drawer LL, Emory University, Atlanta, GA 30322.

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id-lowering diet and treatment with lovastatin (Mevacor, Merck, Rahway, N.J.; 40 mg twice daily) or placebo. The responses to acetylcholine, an endothelium-dependent vasodilator, and to nitroglycerin, an endothelium-independent vasodilator, were assessed in 23 of 404 patients who gave informed consent and were randomized in the Lovastatin Restenosis Trial.<sup>12</sup> Briefly, patients included in the Lovastatin Restenosis Trial were 30 to 81 years old, had a clinical requirement for coronary angioplasty at a nonoccluded site and a total serum cholesterol concentration ranging from 160 to 300 mg per deciliter (4.1 to 7.8 mmol per liter), and had not previously been treated with lipid-lowering medications. Patients with secondary hypercholesterolemia, hypertriglyceridemia, insulin-dependent diabetes mellitus, liver or renal disease, previous coronary angioplasty, coronary bypass surgery (within the past six months), or myocardial infarction (within the past month) were excluded from the study.

Diagnostic coronary cineangiograms of patients in the Lovastatin Restenosis Trial were reviewed to determine the patients' suitability for this substudy. Patients with unstable angina, stenosis of the left main coronary artery, stenosis of  $\geq 50$  percent in at least two of the three major coronary arteries, proximal diameter of the study vessel of less than 2 mm, a left ventricular ejection fraction below 30 percent, or a combination of these features were excluded from the study. In every case, the vessel studied was the branch of the left coronary artery not undergoing angioplasty. No patient had prior angioplasty, previous therapy with cholesterol-lowering medications, a recent myocardial infarction, or bypass surgery. No patient had insulin-dependent diabetes mellitus, hypertriglyceridemia, or valvular heart disease.

After the patients were determined to fulfill the above criteria, they gave informed consent for this study in accordance with the guidelines established by the institutional review boards of the participating centers. The patients were then randomly assigned to receive dietary counseling (with the American Heart Association Step 1 diet) and either lovastatin (40 mg orally twice daily) or placebo. The following information was collected for all patients: age, sex, any history of cigarette smoking within the previous three months, any history of hypertension (previous diagnosis of hypertension), and any family history of premature coronary atherosclerosis (myocardial infarction in a first-degree relative before the age of 55 years). Serum lipid concentrations were evaluated with the patient fasting at randomization, at the time of angioplasty, and six months after angioplasty.

### Study Design

Treatment with vasoactive medications was discontinued 12 to 24 hours before angioplasty. In the cardiac catheterization laboratory, immediately before coronary angioplasty, patients underwent the following procedure (previously described in detail<sup>13</sup>). After administration of heparin, a 3-French coronary infusion catheter (Cook, Bloomington, Ind.) was advanced through a guiding catheter into a proximal segment of the coronary artery. Infusions of acetylcholine chloride (Miochol, Iolab Pharmaceuticals, Claremont, Calif.) and nitroglycerin were administered through the infusion catheter as previously described.<sup>13</sup> Just before the end of each infusion, coronary arteriography was performed with non-ionic contrast medium (Omnipaque, Sanofi-Winthrop, New York) and a power injector (Medrad, Pittsburgh). At the completion of the infusion, coronary angioplasty was performed, with subsequent clinical follow-up as outlined in the Lovastatin Restenosis Trial.<sup>12</sup> An identical infusion was performed at the time of the 5½-month follow-up catheterization, with the initial angiographic views and the position of the infusion catheter reproduced exactly.

### Quantitative Coronary Angiography

All films were analyzed at a central angiographic laboratory (Emory University) by investigators unaware of the study medication and film sequence. Up to five segments of the study vessel were selected for quantitative analysis on the basis of the availability of clearly definable segments. The study-vessel segments were chosen without the investigator's knowledge of the study medication, the film sequence, or the arterial responses to drug infusions. Available angiographic landmarks were used to ensure the measurement of

identical segments at the initial and follow-up studies and with all infusions. The guiding catheter was measured before the initial control angiogram and before the final nitroglycerin angiogram to ensure that there was no notable change in tube height, table height, or angiographic view during the study and to allow calibration of the vessel dimensions.

Four end-diastolic cine frames from each infusion were chosen and marked for analysis by an experienced angiographer who was unaware of the study medication and film sequence. Each frame was optically magnified two to three times and digitized at eight bits per pixel (with a 256-level gray scale). The vessel dimensions were analyzed with a previously validated automated edge-detection system (CAAS II software, PIE Medical, Maastricht, the Netherlands).<sup>14</sup> Measurements from four frames were averaged to calculate a mean value for the diameter of each segment in the study vessel.

For each patient, the arterial segment with the most constriction in response to acetylcholine in the initial study was studied at follow-up, and the two values were compared; in addition, the responses in all study-vessel segments were compared.

### Statistical Analysis

The chi-square test or Fisher's exact test was used to determine the level of significance of differences between treatment groups with respect to categorical variables.<sup>15</sup> Data are presented as means  $\pm$  SE. A t-test or Wilcoxon two-sample test was used to determine the significance of differences between treatment groups with respect to continuous variables.<sup>15</sup>

Dose responses to acetylcholine were compared between treatment groups with the uniform-correlation model<sup>16</sup> (intraclass correlation matrix<sup>17</sup>), which accounts for the correlations in responses to serial doses (in the analyses of the most constricting segments) and for both doses and segments (in the analyses of all segments) in individual patients. The effect of lovastatin was derived by comparing a model containing the dose only with a model containing the dose, the treatment, and the interaction of dose and treatment. The analysis was performed with the Proc Mixed program of SAS software.<sup>18</sup>

Probability values less than or equal to 0.05 were considered to indicate statistical significance (by the two-tailed alternative hypothesis).

### RESULTS

The patients in the lovastatin and placebo groups underwent coronary angioplasty  $12 \pm 2$  days after randomization, and 23 patients (11 assigned to lovastatin and 12 assigned to placebo) were studied successfully. Follow-up catheterization was performed  $5.5 \pm 0.3$  months after randomization in 19 of these patients. The four patients who were not studied at follow-up included one patient assigned to placebo who had vessel closure within 24 hours of angioplasty, one patient assigned to placebo who had unstable angina requiring vasodilator therapy during follow-up catheterization, one patient assigned to lovastatin who received vasodilator therapy immediately before the follow-up study, and one patient assigned to lovastatin whose infusion catheter was mistakenly placed in a side branch at follow-up.

### Clinical Data

The base-line clinical, hemodynamic, and angiographic characteristics of the patients in the lovastatin and placebo groups were similar (Table 1). Lipid levels were similar in the patients in the two groups at the time of randomization. At 12 days, serum levels of total and LDL cholesterol had decreased significantly in the patients receiving lovastatin and remained significantly diminished at 5½ months. In the patients receiving placebo, lipid levels did not change significantly

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Study Patients.\*

CHARACTERISTIC	LOVASTATIN GROUP	PLACEBO GROUP	P VALUE
Age (yr)	59±2	59±3	0.83
Sex (M/F)	7/4	6/6	0.68
History of smoking	6	9	0.40
Family history of CAD	8	8	1.00
History of hypertension	5	7	0.54
Total no. of risk factors	3.4±0.3	3.7±0.3	0.60
Heart rate (beats/min)	71±4	74±3	0.46
Arterial pressure (mm Hg)	141±7/83±3	157±10/86±3	0.20/0.48
Ejection fraction (%)	58±4	60±2	0.97
No. of diseased vessels			
1	7	7	1.00
2	4	5	
Serum cholesterol (mg/dl)†			
At randomization			
Total	230±10	222±10	0.81
HDL	35±2	40±3	0.21
LDL	148±7	143±9	0.93
	<i>mean ±SE (% change from base line)</i>		
At initial study (12 days)			
Total	145±9 (-37)	190±12 (-14)	0.01
HDL	33±3 (-6)	34±3 (-15)	0.62
LDL	99±7 (-33)	134±9 (-6)	0.009
At follow-up study (5½ mo)			
Total	158±13 (-31)	210±12 (-5)	0.02
HDL	39±7 (+11)	34±4 (-15)	0.83
LDL	110±8 (-26)	144±10 (+1)	0.02

\*Plus-minus values are means ±SE. CAD denotes coronary artery disease, HDL high-density lipoprotein, and LDL low-density lipoprotein.

†To convert values for total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.02586.

over the 5½ months of the study. The data on lipid levels are shown in Table 1.

### Epicardial Coronary-Artery Responses to Acetylcholine

Responses to acetylcholine were studied in the left anterior descending coronary artery in 5 patients (2 in the lovastatin group and 3 in the placebo group) and in the circumflex coronary artery in 18 patients (9 in each group). No study vessel had a stenosis obstructing more than 50 percent of the lumen.

Short-term lipid-lowering therapy did not significantly alter the coronary-artery endothelial responses to acetylcholine (Table 2). In the analysis of mean changes in all segments in the placebo group at 12 days (an analysis in which negative numbers indicate constriction), the diameter of the epicardial coronary artery changed by 2±1 percent, 1±1 percent, 0±2 percent, and -7±2 percent in response to serial infusions of acetylcholine (at concentrations of 10<sup>-9</sup> M, 10<sup>-8</sup> M, 10<sup>-7</sup> M, and 10<sup>-6</sup> M, respectively). In the lovastatin group, the response of the epicardial coronary artery was similar at 12 days (changes, 0±1 percent, -2±1 percent, -5±2 percent, and -6±3 percent in response to the respective concentrations of acetylcholine; P=0.53). In the analysis of the most constricting segment in the placebo group, the most responsive epicardial coronary-artery segment changed by 1±2 percent, 0±2 percent, -2±4 percent, and -19±4 percent in response to serial infusions of acetylcholine at the respective concentrations. In the lovastatin group,

the most responsive epicardial coronary-artery segment responded similarly to the respective concentrations of acetylcholine (-2±2 percent, -4±4 percent, -12±5 percent, and -16±7 percent; P=0.32). Since the predicted and observed means were similar, the uniform-correlation model provided a good fit for the observed data.

Longer-term lipid-lowering therapy significantly improved epicardial coronary-artery responses to acetylcholine (Table 2 and Fig. 1, 2, 3, and 4). In the analysis of all segments in the placebo group at 5½ months, the epicardial coronary artery continued to constrict in response to serial infusions of acetylcholine at concentrations of 10<sup>-9</sup> M, 10<sup>-8</sup> M, 10<sup>-7</sup> M, and 10<sup>-6</sup> M (changes in diameter, -1±1 percent, 1±1 percent, -2±2 percent, and -9±3 percent, respectively). In the lovastatin group, the response to acetylcholine at 5½ months was significantly improved (3±1 percent, 2±2 percent, 0±2 percent, and 2±3 percent) in response to the respective concentrations of acetylcholine (P=0.013) (Fig. 1). In the analysis of the most constricting segment in the placebo group, the most responsive epicardial coronary-artery segment (as determined in the initial study) continued to constrict (by -3±3 percent, -1±2 percent, -8±4 percent, and -18±5 percent) in response to serial infusions of acetylcholine at the respective concentrations. In the lovastatin group at 5½ months, the response to the respective concentrations of acetylcholine was significantly improved (changes in diameter, 3±3 percent, 3±3 percent, 0±2 percent, and 0±3 percent; P=0.004) (Fig. 2). Again, because the predicted and observed means were similar, the uniform-correlation model provided a good fit for the observed data.

Table 2. Epicardial Coronary-Artery Responses to Acetylcholine, Expressed as the Percentage of Change in Luminal Diameter.

STUDY AND CONCENTRATION OF ACETYLCHOLINE	PLACEBO GROUP	LOVASTATIN GROUP	P VALUE*
	<i>% change in diameter (95% CI)†</i>		
<b>Analysis of all segments</b>			
Initial (12 days)			0.53
10 <sup>-9</sup> M	2 (-3.4 to 6.4)	0 (-5.0 to 5.3)	
10 <sup>-8</sup> M	1 (-4.4 to 5.3)	-2 (-6.9 to 3.5)	
10 <sup>-7</sup> M	0 (-4.9 to 4.9)	-5 (-10.7 to -0.4)	
10 <sup>-6</sup> M	-7 (-12.4 to -2.7)	-6 (-13.9 to -2.8)	
Follow-up (5½ mo)			0.013
10 <sup>-9</sup> M	-1 (-6.3 to 3.5)	3 (-2.1 to 8.3)	
10 <sup>-8</sup> M	1 (-4.3 to 5.5)	2 (-3.2 to 7.2)	
10 <sup>-7</sup> M	-2 (-7.7 to 2.0)	0 (-4.3 to 6.1)	
10 <sup>-6</sup> M	-9 (-14.8 to -5.0)	2 (-3.6 to 7.5)	
<b>Analysis of most constricting segment</b>			
Initial (12 days)			0.32
10 <sup>-9</sup> M	1 (-6.3 to 8.5)	-2 (-9.5 to 5.9)	
10 <sup>-8</sup> M	0 (-6.7 to 8.0)	-4 (-11.9 to 3.5)	
10 <sup>-7</sup> M	-2 (-9.1 to 5.7)	-12 (-20.1 to -4.7)	
10 <sup>-6</sup> M	-19 (-26.9 to -12.2)	-16 (-28.0 to -10.6)	
Follow-up (5½ mo)			0.004
10 <sup>-9</sup> M	-3 (-8.9 to 3.4)	3 (-3.6 to 9.4)	
10 <sup>-8</sup> M	-1 (-6.9 to 5.4)	3 (-3.1 to 9.9)	
10 <sup>-7</sup> M	-8 (-14.5 to -2.2)	0 (-6.6 to 6.4)	
10 <sup>-6</sup> M	-18 (-24.7 to -12.4)	0 (-6.6 to 7.8)	

\*P values are for the comparison between the study groups.

†CI denotes confidence interval.

Representative coronary angiograms showing endothelial responses in patients in the two groups are shown in Figure 3. The patient in the placebo group had similar and substantial vasoconstriction in response to acetylcholine in both studies (Fig. 3, left-hand panels), whereas the patient in the lovastatin group had substantial vasoconstriction in the initial study, with dramatic improvement at follow-up in the response to acetylcholine (a mild vasodilator response) (Fig. 3, right-hand panels). In the patients assigned to placebo, the mean change in response to the peak

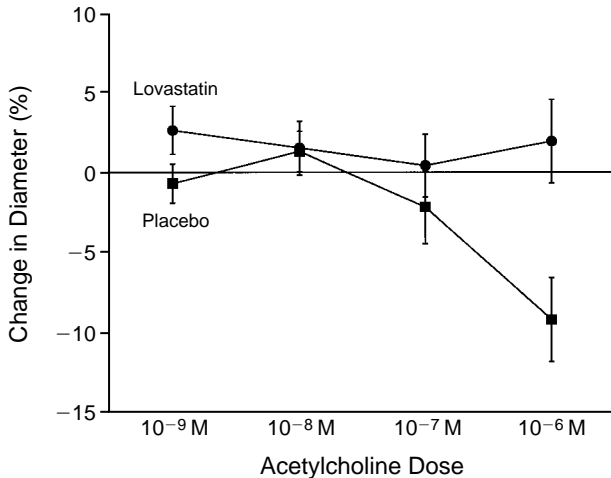


Figure 1. Mean ( $\pm$ SE) Responses in All Segments of the Epicardial Coronary Artery to Serial Infusions of Acetylcholine in the Two Groups at the Follow-up (5½ Months) Study.

Responses are expressed as the percentage of change in diameter from the base-line value in all segments. The response to acetylcholine was significantly better in the lovastatin group than in the placebo group ( $P=0.013$ ). Negative numbers indicate vasoconstriction.

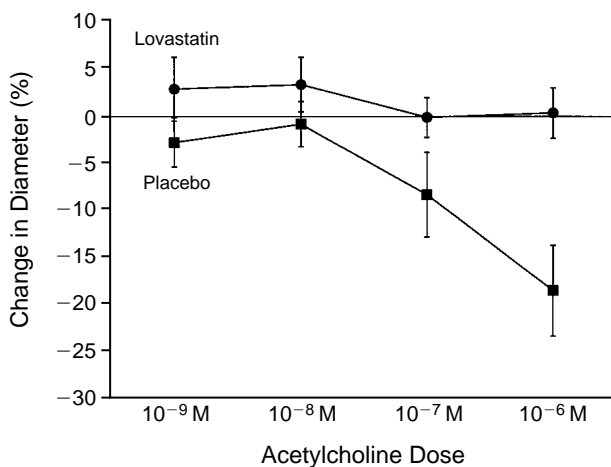


Figure 2. Mean ( $\pm$ SE) Responses in the Most Constricting Segment of the Epicardial Coronary Artery to Serial Infusions of Acetylcholine in the Two Groups at the Follow-up (5½ Months) Study. Responses are expressed as the percentage of change in diameter from the base-line value in the most constricting segment. The response to acetylcholine was significantly better in the lovastatin group than in the placebo group ( $P=0.004$ ). Negative numbers indicate vasoconstriction.

dose of acetylcholine was +1 percent (from -19 percent constriction in the initial study to -18 percent at follow-up). In the patients assigned to lovastatin, the mean change in response to the peak dose of acetylcholine was +16 percent (from -16 percent constriction in the initial study to 0 percent at follow-up) (Fig. 4).

#### Epicardial Coronary-Artery Responses to Nitroglycerin

The patients in the two study groups had similar epicardial coronary-artery responses to nitroglycerin (increase in diameter in the initial study,  $13\pm 3$  percent in the placebo group vs.  $13\pm 2$  percent in the lovastatin group; at follow-up,  $16\pm 4$  percent in the placebo group vs.  $16\pm 2$  percent in the lovastatin group;  $P$  not significant for any comparison).

#### Correlation between Lipid Levels and Endothelial Response

There was a significant inverse relation between the LDL cholesterol level and the arterial response to acetylcholine at follow-up in the most constricting segment ( $r=-0.46$ ,  $P<0.05$ ). Decreased levels of LDL cholesterol at follow-up were associated with improved responses to acetylcholine. No other significant relations between changes in lipid levels and arterial responses to acetylcholine were found.

#### DISCUSSION

We have demonstrated that six months of lipid-lowering therapy with lovastatin can improve coronary endothelium-mediated vasodilator responses in patients with coronary atherosclerosis. Although LDL cholesterol levels are reduced in a matter of days to weeks, improvement in the endothelial response lags behind, suggesting that the reversal of coronary endothelial dysfunction requires prolonged therapy. In this study, lipid-lowering therapy improved but did not completely normalize the endothelial response to acetylcholine, suggesting that the restoration of normal endothelium-mediated vasodilatation may require even more extended therapy, as has been noted in studies in animals.<sup>9</sup> We have shown that lipid-lowering therapy has an important beneficial effect on the regulation of coronary arterial tone in patients with symptomatic coronary atherosclerosis.

The degradation of endothelial nitric oxide appears to be increased in experimental models of atherosclerosis, leading to decreased vasodilator activity.<sup>19,20</sup> In animal models of atherosclerosis, scavenging of superoxide anions can restore endothelium-mediated relaxation to nearly normal.<sup>21</sup> This observation is consistent with the theory that byproducts of the oxidative environment (oxygen-derived free radicals) destroy nitric oxide, accounting for the diminished endothelium-dependent vasodilatation and increased vasoconstriction in atherosclerosis.

This theory is attractive in the context of the current understanding of atherogenesis. In atherosclerosis, the reduction-oxidation state within the vessel wall is altered in a way that favors oxidation. This oxidative state is essential for the propagation of the atherosclerosis.

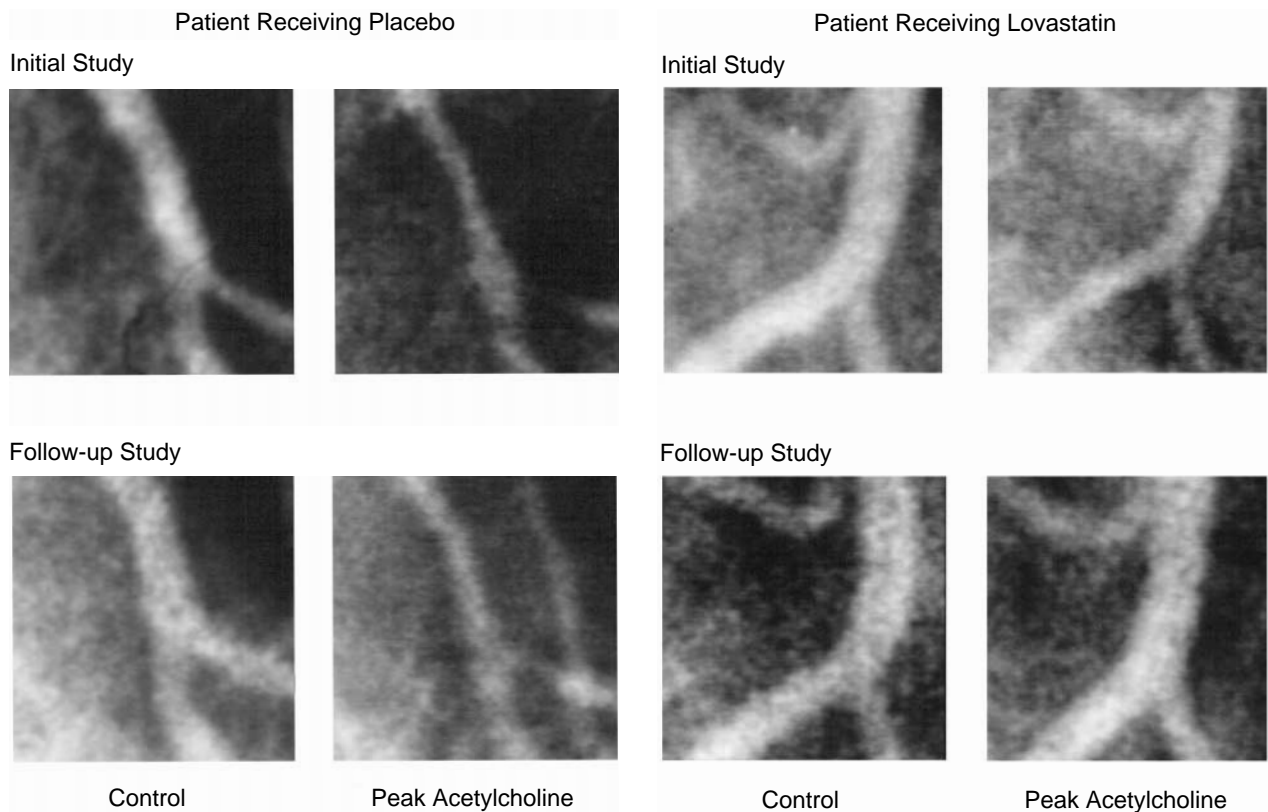


Figure 3. Representative Coronary Angiograms of Patients in the Placebo and Lovastatin Groups.

The left-hand panels show a segment of the circumflex marginal coronary artery at the initial (12 days) and follow-up (5½ months) studies in a patient assigned to placebo. There is substantial and similar vasoconstriction in response to acetylcholine in both studies. The right-hand panels show a segment of the circumflex coronary artery at the initial (12 days) and follow-up (5½ months) studies in a patient assigned to lovastatin. There is substantial vasoconstriction in response to the peak infusion of acetylcholine in the initial study, with marked improvement (a mild vasodilator response) in the follow-up study.

rotic process. Therefore, any byproducts of oxidative metabolism may well be important contributors to the molecular pathobiology of atherosclerosis. A reduction in serum cholesterol is associated with the normalization of oxygen-derived free radical production<sup>22</sup> and endothelium-mediated vasodilatation without normalization of the morphologic characteristics of the vessel.<sup>9</sup> A similar mechanism could explain the observed improvement in endothelium-mediated responses in our patients.

Previous trials of cholesterol-lowering therapy have demonstrated moderate regression or lack of progression of coronary atherosclerosis<sup>2-5</sup> and in some cases substantial improvement in clinical outcome,<sup>3,4</sup> suggesting a beneficial effect of lipid lowering on vessel function. Leung et al.<sup>23</sup> and Egashira et al.<sup>24</sup> have demonstrated improvement in both epicardial<sup>23,24</sup> and microvascular<sup>24</sup> coronary endothelial responses with lipid-lowering therapy. However, neither study was randomized or placebo-controlled. The present trial shows that lipid lowering has no effect in the short term but improves coronary endothelial function in the longer term in patients with symptomatic atherosclerotic coronary artery disease.

There is no consensus as yet that lowering lipid

levels in patients with coronary atherosclerosis reduces the rates of cardiac events.<sup>2-5</sup> It is clear, however, from previous trials of cholesterol lowering that the effects on angiographically defined coronary disease are slight. If large clinical trials now under way<sup>25</sup> confirm that the treatment of elevated cholesterol levels in coronary artery disease decreases the rates of events, the implication will be that in determining clinical outcome, changes in the functional status of the arterial wall may be more important than improvement in the degree of stenosis.

Previously, lipid-lowering therapy was not considered part of the pharmacologic armamentarium for the relief of angina. This study demonstrates that aggressive lipid lowering can have a marked effect on the regulation of coronary arterial tone, favoring diminished vasoconstriction, improved vasodilatation, or both. These effects do not occur immediately, but are observed several months after therapy is instituted. Using positron-emission tomography to assess myocardial perfusion, Gould et al.<sup>26</sup> have suggested that lipid lowering may have beneficial effects on vessel function as early as three months after the start of therapy. More extended periods of lipid-lowering therapy could result in further movement of the endotheli-

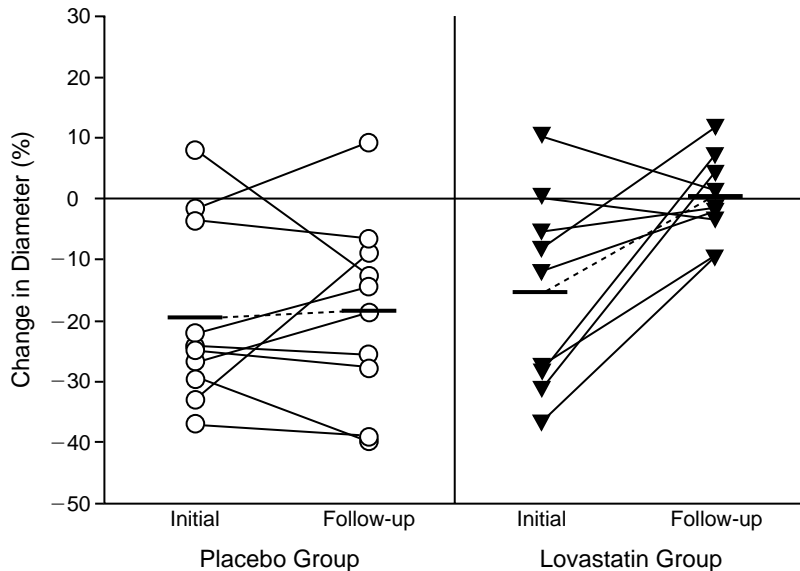


Figure 4. Individual Responses to the Peak Dose of Acetylcholine among Those in the Placebo Group (10 Patients) and the Lovastatin Group (9 Patients) Who Were Studied Both Initially and at Follow-up.

The most constricting segment in each patient was studied. Solid lines represent responses in individual patients, and dashed lines indicate the difference between the mean responses in the initial study (at 12 days) and the follow-up study (at 5½ months). Negative numbers indicate vasoconstriction.

um-dependent response toward normal levels. The time course of functional improvement and the usefulness of lipid lowering as antianginal therapy will need further definition.

The improvement in endothelium-mediated relaxation after 5½ months of lipid-lowering therapy may serve as a marker for a more generalized improvement in endothelial function. The ability of the endothelium to regulate vascular growth, thrombus formation, and the inflammatory activity of the vessel wall may also improve with lipid lowering. If this is true, strategies designed to alter the course of atherosclerotic vascular disease may focus on the ability of the endothelium to regulate vessel tone as a surrogate marker for vascular health.

This study evaluated endothelial function in minimally obstructed coronary arteries in patients with substantial atherosclerotic obstruction at other sites in the coronary arterial tree. Lipid lowering appears to improve endothelial function in these minimally obstructed vessels. This study did not address the ability of lipid lowering to improve endothelial function in severely stenotic coronary arteries.

Since the initial evaluation was conducted after 12 days of study medication, no true base-line study was performed. By comparing an approximation of a true base-line study (the initial study in the lovastatin group) with the 5½-month follow-up study in the lovastatin group, we demonstrated a significant improvement in endothelial function. Without a true base-line study, we cannot precisely assess the degree of improvement expected with lipid lowering. However, we have answered the principal question — whether

abnormal coronary endothelial responses improve with this therapy. We believe that the actual degree of improvement in endothelial responses would only have been more dramatic had a true base-line study been performed.

This study has demonstrated that aggressive lipid lowering with lovastatin can significantly improve endothelial regulation of coronary arterial tone in patients with coronary atherosclerosis. Aggressive lipid lowering may become part of our armamentarium for the treatment of ischemic coronary syndromes. In addition, clinical assessment of the regulation of endothelial tone may become a starting point for directing preventive approaches and an end point for the evaluation of therapeutic efficacy in coronary atherosclerosis. An ability to improve vascular function and stabilize atherosclerotic plaques, combined with a reliable, inexpensive means of detecting this effect, could potentially

avert the need for costly surgical or catheter-based therapies in many patients.

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