

**EFFECT OF PRAVASTATIN ON OUTCOMES AFTER CARDIAC TRANSPLANTATION**

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**Abstract** *Background.* Hypercholesterolemia is common after cardiac transplantation and may contribute to the development of coronary vasculopathy. Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, has been shown to be effective and safe in lowering cholesterol levels after cardiac transplantation. Cell-culture studies using inhibitors of HMG-CoA reductase have suggested an immunosuppressive effect.

*Methods.* Early after transplantation, we randomly assigned consecutive patients to receive either pravastatin (47 patients) or no HMG-CoA reductase inhibitor (50 patients).

*Results.* Twelve months after transplantation, the pravastatin group had lower mean ( $\pm$  SD) cholesterol levels than the control group ( $193 \pm 36$  vs.  $248 \pm 49$  mg per deciliter,  $P < 0.001$ ), less frequent cardiac rejection accompanied by hemodynamic compromise (3 vs. 14 patients,  $P = 0.005$ ), better survival (94 percent vs. 78 percent,  $P = 0.025$ ), and a lower incidence of coronary

vasculopathy in the transplant as determined by angiography and at autopsy (3 vs. 10 patients,  $P = 0.049$ ). There was no difference between the two groups in the incidence of mild or moderate episodes of cardiac rejection. In a subgroup of study patients, intracoronary ultrasound measurements at base line and one year after transplantation showed less progression in the pravastatin group in maximal intimal thickness ( $0.11 \pm 0.09$  mm, vs.  $0.23 \pm 0.16$  mm in the control group;  $P = 0.002$ ) and in the intimal index ( $0.05 \pm 0.03$  vs.  $0.10 \pm 0.10$ ,  $P = 0.031$ ). In a subgroup of patients, the cytotoxicity of natural killer cells was lower in the pravastatin group than in the control group (9.8 percent vs. 22.2 percent specific lysis,  $P = 0.014$ ).

*Conclusions.* After cardiac transplantation, pravastatin had beneficial effects on cholesterol levels, the incidence of rejection causing hemodynamic compromise, one-year survival, and the incidence of coronary vasculopathy. (*N Engl J Med* 1995;333:621-7.)

**H**YPERCHOLESTEROLEMIA is common after cardiac transplantation, affecting 60 to 80 percent of transplant recipients.<sup>1</sup> In addition, hypercholesterolemia has been associated with the development of coronary vasculopathy in transplants,<sup>2-4</sup> which is the major factor limiting long-term survival. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase lower blood cholesterol levels<sup>5</sup> and have been associated with the regression of atherosclerotic lesions in patients with atherosclerosis who are not transplant recipients.<sup>6-8</sup> In addition, studies in animals suggest that these drugs may affect coronary vasculopathy by a mechanism independent of cholesterol lowering.<sup>9</sup> In vitro studies with HMG-CoA reductase inhibitors have demonstrated the suppression of natural killer cells,<sup>10,11</sup> which could influence the development of acute rejection and subsequent coronary vasculopathy.

HMG-CoA reductase inhibitors have been used cautiously to treat hypercholesterolemia in patients with cardiac transplants because of concern about the development of myositis and rhabdomyolysis.<sup>12,13</sup> Unlike lipophilic HMG-CoA reductase inhibitors, pravastatin (Pravachol, Bristol-Myers Squibb, Princeton, N.J.) is hydrophilic. Therefore, it may have fewer toxic effects on skeletal muscle and has been reported to be safe and effective in patients with transplants.<sup>14</sup> Therefore, we performed a prospective, randomized, open-label trial in patients with cardiac transplants to assess

the effect of pravastatin on cholesterol lowering, rejection, survival, and the development of coronary vasculopathy.

**METHODS****Selection of Patients**

From July 1, 1992, through February 1, 1994, 107 adult patients underwent cardiac transplantation in our program. Eight patients died during the initial hospitalization after transplantation and were therefore not enrolled in the study, and two patients declined to participate in the study. The remaining 97 patients were randomly assigned to pravastatin (47 patients) or no pravastatin (50 patients) in addition to their immunosuppressive treatment with cyclosporine, prednisone, and azathioprine. The study design was approved by the institutional review board.

**Study Design**

The patients randomly assigned to receive pravastatin began receiving a dose of 20 mg per day one to two weeks after transplantation. If they tolerated this dose after receiving it for one month, the dose was increased to 40 mg per day. Before discharge from the hospital, all the patients received dietary counseling from a staff nutritionist about following a low-fat, low-cholesterol diet. After six months, patients in the control group who had cholesterol levels of 300 mg per deciliter (7.76 mmol per liter) or higher were treated with cholestyramine (taken four hours after the dose of cyclosporine). During the first year after transplantation, endomyocardial biopsies, right heart catheterization, and echocardiography were performed, and blood was obtained for the determination of cholesterol, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, and creatine kinase concentrations, a complete blood count, and trough cyclosporine levels (whole-blood fluorescence polarization immunoassay, Abbott, Abbott Park, Ill.). These tests were performed weekly for the first month after transplantation, then every two weeks for one month, every three weeks for two months, every month for two months, and every two months for six months. All endomyocardial-biopsy specimens were examined by pathologists unaware of the treatment assignments.

All patients with cardiac transplants who presented with signs and symptoms of heart failure underwent endomyocardial biopsy. These

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patients were presumed to have cardiac rejection regardless of the results of the biopsy. Hemodynamic compromise was considered to be present when any of the following criteria were met: a cardiac index  $\leq 2.0$  liters per minute per square meter of body-surface area; a pulmonary-artery wedge pressure  $\geq 20$  mm Hg; a short-term decrease in the left ventricular ejection fraction (detected echocardiographically) by an absolute value of 0.20 as compared with the value on the previous echocardiogram; or sudden death due to cardiac rejection confirmed at autopsy.

The primary end points for the study included the effects of pravastatin on cholesterol levels, cardiac rejection, survival, and the development of coronary vasculopathy in the transplant. Survival was defined as remaining alive without requiring a second transplantation.

### Angiography and Intracoronary Ultrasonography

Coronary angiography and intracoronary ultrasonography were performed at base line (four to six weeks after transplantation) and one year after transplantation to determine whether coronary vasculopathy was present in each patient. A diagnosis of coronary vasculopathy was made if there was stenosis (luminal narrowing) of 50 percent or more or substantial distal pruning of the coronary arteries on the one-year angiogram as compared with the base-line angiogram. The base-line and one-year angiograms were reviewed side by side by two independent reviewers who were unaware of the patient's name, the date of the angiogram, and the treatment assignment. Intracoronary ultrasonography was performed immediately after coronary angiography in the left anterior descending coronary artery with a 30-MHz, 4.3-French intracoronary ultrasound catheter (CVIS, Sunnyvale, Calif.). The recordings included a 30-second slow pulling back of the catheter from its most distal position (in the mid-distal left anterior descending artery) to the left main portion of the left coronary artery. The ultrasound recordings were analyzed by quantitative morphometry, which included 10 randomly selected sites taken from the left anterior descending artery during the slow pulling back of the catheter. The measurements were recorded during diastole on super VHS and analyzed off-line by computerized planimetry. These measurements included the maximal intimal thickness, the plaque area, the total vessel area, and the intimal index, defined as the ratio of the plaque area to the overall vessel area. The intracoronary ultrasound images were analyzed by one reviewer (to minimize variability) who was unaware of the treatment assignments.

### Immunosuppression

All patients received the immunosuppressant agents cyclosporine, prednisone, and azathioprine. Episodes of focal moderate or moderate cardiac rejection (grades 2 and 3, respectively, of the classification system of the International Society for Heart and Lung Transplantation) were diagnosed on the basis of an analysis of the endomyocardial-biopsy specimens by pathologists who were unaware of the treatment assignments.

### Assay of Natural-Killer-Cell Cytotoxicity

Before the completion of the study, a reduction in the rate of cardiac rejection accompanied by hemodynamic compromise was apparent in the pravastatin group. An assay of peripheral-blood natural killer cells (based on previous *in vitro* studies) was performed in the final 20 patients randomized, to determine whether pravastatin was causing further immunosuppression in the study group as compared with the control group. Blood samples were collected for the analysis of cytotoxicity of natural killer cells for six months during the follow-up period, at the time of the routine endomyocardial biopsies. The assay of natural-killer-cell cytotoxicity was performed as described by Wang et al.<sup>15</sup>

### Statistical Analysis

Appropriate two-tailed t-tests and chi-square tests were used to assess the differences between study groups. The Wilcoxon log-rank statistic was used to compare Kaplan-Meier survival curves. Pearson correlation coefficients were used to measure the strength of the linear relation between two variables. An analysis of variance (assuming compound symmetry in an unbalanced repeated measure) was

used to assess differences between groups in the weighted average (weighted for multiple samples over time) of natural-killer-cell cytotoxicity. The mean percentage of specific lysis for each group was estimated as a measure of natural-killer-cell cytotoxicity with the BMDP statistical software package. In all tests, P values of 0.05 or less were considered to indicate statistical significance.

## RESULTS

### Characteristics of the Patients

There were no differences between the pravastatin group and the control group at base line, except for a higher number of second transplantations in the control group (in seven patients, as compared with three patients receiving pravastatin) (Table 1). Because patients with second transplants have higher rates of morbidity and mortality, we conducted additional analyses for the primary end points from which these patients were excluded. After transplantation, there were no significant differences between the two study groups in maintenance doses of immunosuppressant agents or trough cyclosporine blood levels, although slightly more patients in the pravastatin group were able to be weaned from prednisone (Table 2).

There were no significant differences between groups in the number of infectious complications requiring antibiotic therapy (5 in the pravastatin group vs. 8 in the control group), the number of episodes of clinical cytomegalovirus infection (4 vs. 5), the degree of renal impairment at one year (mean [ $\pm$ SD] serum creatinine level,  $1.6 \pm 0.4$  vs.  $1.8 \pm 0.4$  mg per deciliter [ $140 \pm 40$  vs.  $160 \pm 40$   $\mu$ mol per liter]), or the use of calcium-channel blockers (14 vs. 13 patients) or angiotensin-converting-enzyme inhibitors (9 vs. 14 patients) to treat hypertension. There was no difference between the groups in blood pressure (mean of measurements 3, 6, 9, and 12 months after transplantation,  $125 \pm 13/77 \pm 10$  mm Hg in the pravastatin group and  $122 \pm 14/79 \pm 10$  mm Hg in the control group).

### Cholesterol Levels

Base-line cholesterol levels were similar in the two study groups ( $174 \pm 51$  mg per deciliter [ $4.50 \pm 1.32$  mmol per liter] in the pravastatin group vs.  $184 \pm 51$

Table 1. Base-Line Characteristics of the Patients According to Study Group.\*

CHARACTERISTIC	PRAVASTATIN (N = 47)	CONTROL (N = 50)	INTRACORONARY ULTRASONOGRAPHY	
			PRAVASTATIN (N = 27)	CONTROL (N = 21)
Age (yr)				
Recipient	51 $\pm$ 10	53 $\pm$ 11	53 $\pm$ 10	55 $\pm$ 10
Donor	32 $\pm$ 15	30 $\pm$ 15	33 $\pm$ 15	32 $\pm$ 13
Female recipient (%)	19	26	18	24
CAD before surgery (%)	43	54	52	62
No. of HLA matches/patient	0.8 $\pm$ 1.0	0.7 $\pm$ 0.8	0.8 $\pm$ 0.9	0.8 $\pm$ 0.8
Duration of ischemia (min)	185 $\pm$ 62	168 $\pm$ 52	188 $\pm$ 62	173 $\pm$ 46
CMV-positive donor, CMV-negative recipient (%)	17	22	15	19
Second transplant (%)	6	14	7	14

\*Plus-minus values are means  $\pm$  SD. CAD denotes coronary artery disease, and CMV cytomegalovirus. The 48 patients who underwent ultrasonography were a subgroup of the 97 randomized study patients.

**Table 2. Characteristics of Immunosuppression after Transplantation, According to Study Group.\***

VARIABLE	PRAVASTATIN (N = 47)	CONTROL (N = 50)	INTRACORONARY ULTRASONOGRAPHY	
			PRAVASTATIN (N = 27)	CONTROL (N = 21)
Cyclosporine dose (mg/kg/day)				
At 3 mo	4.1±1.9	4.2±1.5	3.9±1.9	4.0±1.5
At 6 mo	4.2±2.0	3.9±1.2	4.2±1.9	3.6±0.9
At 9 mo	4.2±2.2	3.8±1.0	4.1±1.7	3.6±0.9
At 12 mo	4.2±1.8	3.7±1.3	4.1±1.7	3.5±1.2
Prednisone dose (mg/kg/day)				
At 3 mo	0.2±0.1	0.2±0.1	0.2±0.1	0.2±0.1
At 6 mo	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
At 9 mo	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
At 12 mo	0.1±0.1	0.1±0.1	0.1±0.1	0.1±0.1
Azathioprine dose (mg/kg/day)				
At 3 mo	1.6±0.6	1.8±0.5	1.6±0.6	1.8±0.6
At 6 mo	1.7±0.5	1.7±0.5	1.6±0.5	1.6±0.6
At 9 mo	1.6±0.7	1.6±0.6	1.6±0.7	1.4±0.7
At 12 mo	1.5±0.7	1.5±0.6	1.4±0.8	1.4±0.7
Whole-blood cyclosporine level (ng/ml)				
At 3 mo	562±204	544±155	568±163	563±215
At 6 mo	495±194	518±205	528±224	479±181
At 9 mo	495±151	481±139	484±150	485±156
At 12 mo	483±167	493±213	427±117	447±140
No. of patients weaned from prednisone	10	7	6	5

\*Plus–minus values are means ±SD. There were no significant differences between groups.

mg per deciliter [ $4.76 \pm 1.32$  mmol per liter] in the control group). During the first year after transplantation, the mean cholesterol level (as averaged from the levels measured at 3, 6, 9, and 12 months) was significantly lower in the pravastatin group than in the control group ( $193 \pm 36$  vs.  $248 \pm 49$  mg per deciliter [ $4.99 \pm 0.93$  vs.  $6.41 \pm 1.27$  mmol per liter],  $P < 0.001$ ) (Fig. 1). All the patients in the pravastatin group were receiving 40 mg of pravastatin per day by two months after transplantation. The pravastatin group, as compared with the control group, had significantly lower mean low-density lipoprotein cholesterol levels ( $116 \pm 32$  vs.  $158 \pm 27$  mg per deciliter [ $3.00 \pm 0.82$  vs.  $4.08 \pm 0.70$  mmol per liter],  $P < 0.001$ ), lower mean triglyceride levels ( $148 \pm 67$  vs.  $219 \pm 144$  mg per deciliter [ $1.67 \pm 0.76$  vs.  $2.47 \pm 1.62$  mmol per liter],  $P = 0.006$ ), and higher mean high-density lipoprotein cholesterol levels ( $52 \pm 19$  vs.  $43 \pm 13$  mg per deciliter [ $1.34 \pm 0.49$  vs.  $1.11 \pm 0.34$  mmol per liter],  $P = 0.039$ ). The results of the lipid analysis did not change significantly when the 10 patients with second transplants were excluded. Only two patients in the control group were given cholestyramine, which further reduced their cholesterol levels by 5 percent over a three-month period. No elevated levels of creatine kinase or aminotransferases (i.e., to more than three times the normal value), myositis, or rhabdomyolysis was documented in any patient. A minority of patients were weaned from corticosteroids (Table 2). Because the actual corticosteroid-free period was short (one to two months), it is not known whether it had any significant effect on cholesterol levels.

### Cardiac Rejection

The average number of episodes of mild (grade 1A or 1B) or moderate (grade 2, 3A, or 3B) cardiac rejection

per patient did not differ significantly between the two groups (in which the frequency of biopsy was similar) (Table 3). These results did not change significantly when the patients with second transplants were excluded from the analysis. Although it was not a primary end point in the trial, the development of cardiac rejection accompanied by hemodynamic compromise was markedly less frequent in the patients treated with pravastatin than in the control patients (3 vs. 14,  $P = 0.005$ ) (Table 4). According to the grading of endomyocardial-biopsy specimens, 65 percent of these 17 patients had moderate rejection, whereas 35 percent did not, suggesting either that there was an error in the sampling of endomyocardial-biopsy specimens or that humoral rejection was involved.<sup>16</sup>

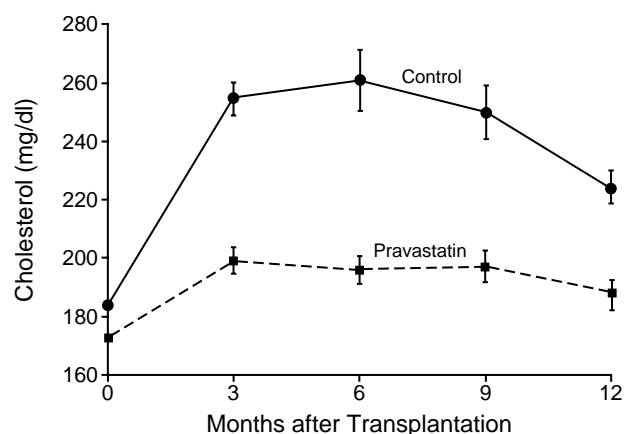
### Survival

One-year survival was significantly greater in the pravastatin group than in the control group (94 percent vs. 78 percent,  $P = 0.025$ ) (Fig. 2). The differences in survival between the two groups did not change significantly when the 10 patients with second transplants (including 1 patient in the pravastatin group and 3 patients in the control group who died) were excluded; after these exclusions, survival was 95 percent in the pravastatin group and 81 percent in the control group ( $P = 0.037$ ). During the first year after transplantation, three patients in the pravastatin group died, all because of cardiac rejection. In the control group, there were 10 deaths and 1 second transplantation (due to severe cardiac dysfunction as a result of coronary vasculopathy) in the first year after transplantation. Of the 10 deaths, 8 were due to cardiac rejection, 1 to cancer, and 1 to infection (following antirejection therapy).

### Coronary Vasculopathy

#### Results of Angiography

Coronary vasculopathy was detected angiographically in three patients in the pravastatin group and seven patients in the control group at the end of the first year after transplantation. Seven patients did not undergo



**Figure 1. Mean ( $\pm$ SE) Cholesterol Levels during the First Year after Cardiac Transplantation in the Study Patients.**

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

coronary angiography during that year because they died suddenly. All seven were examined at autopsy, and three of them, all in the control group, were found to have severe coronary vasculopathy in the transplant. The other four patients died suddenly from cardiac rejection. Therefore, the total number of patients found to have coronary vasculopathy in their transplants by angiography or at autopsy was higher in the control group (10 patients) than in the pravastatin group (3 patients) ( $P=0.049$ ). When patients with second transplants were excluded from the analysis, there were eight patients in the control group with coronary vasculopathy, as compared with two patients in the pravastatin group ( $P=0.057$ ).

#### Results of Intracoronary Ultrasonography

Of the 97 patients randomized, 48 patients had both base-line and one-year intracoronary ultrasonography. This procedure was not performed in the remaining 49 patients because of the unavailability of intracoronary ultrasonography (21 patients), safety considerations with regard to intracoronary ultrasonography at the time of angiography (5), the terms of the agreement with the health maintenance organization (16), or death in the first year, before the follow-up intracoronary ultrasonography (7). The demographic variables (Table 1) and characteristics of immunosuppression (Table 2) of the 27 patients in the pravastatin group and the 21 patients in the control group who underwent intracoronary ultrasonography did not differ significantly. After transplantation, more of the control patients who underwent intracoronary ultrasonography had cardiac rejection accompanied by hemodynamic compromise (four patients, as compared with one patient in the pravastatin group). The pravastatin group had significantly less progression than the control group with regard to maximal intimal thickness ( $0.11 \pm 0.09$  vs.  $0.23 \pm 0.16$  mm,  $P=0.002$ ) and the intimal index ( $0.05 \pm 0.03$  vs.  $0.10 \pm 0.10$ ,  $P=0.031$ ) (Fig. 3). The results of intracoronary ultrasonography did not change significantly when the five patients with second transplants who underwent this procedure (two in the pravastatin group and three in the control group) were excluded. Of the patients with coronary vasculopathy in their transplants as confirmed by angiography or at autopsy, six in the control group and

Table 3. Observed Incidence of Cardiac Rejection during the First Year in the Study Patients.\*

VARIABLE	PRAVASTATIN (N = 47)	CONTROL (N = 50)	P VALUE
Rejection (mean no. of episodes/ patient)†			
Mild	$1.9 \pm 1.3$	$2.0 \pm 1.2$	0.80
Focal moderate	$0.6 \pm 0.8$	$0.3 \pm 0.7$	0.12
Moderate	$0.7 \pm 0.9$	$0.5 \pm 0.7$	0.39
No. of rejections with hemody- namic compromise	3	14	0.005

\*Plus-minus values are means  $\pm$ SD.

†According to the system established by the International Society for Heart and Lung Transplantation, mild cardiac rejection is classified as grade 1A or 1B, focal moderate rejection as grade 2, and moderate rejection as grade 3A or 3B.

Table 4. Clinical Characteristics and Outcomes of Patients Presenting with Cardiac Rejection Accompanied by Hemodynamic Compromise.

PATIENT NO.	REJECTION WITH COMPROMISE		OUTCOME	
	CRITERIA*	TIME OF OCCURRENCE (MO AFTER TRANSPLANTATION)		GRADE†
<b>Control group</b>				
1	I, W, E	1.1	3A	Died
2	I, W, E	1.2	3A	Died
3	E	1.2	3A	Alive
4	I, W, E	1.4	1A	Died
5	E	2.0	1A	Alive
6	I, W, E	4.1	3B	Died
7	I, W, E	4.4	3A	Died
8	I, W, E	4.3	3A	Died
9	W, E	4.0	1B	Alive
10	I, E	4.1	1A	Alive
11	S	4.3	3B	Died
12	E	8.0	3A	Alive
13	S	8.4	3A	Died
14	I, W, E	10.1	1A	Underwent 2nd transplantation
<b>Pravastatin group</b>				
15	I, W, E	4.0	1A	Died
16	I, E	6.7	2	Died
17	I, E	7.0	3A	Died

\*The criteria used in the diagnosis of cardiac rejection accompanied by hemodynamic compromise were as follows: I, cardiac index  $\leq 2.0$  liters per minute per square meter; W, pulmonary-artery wedge pressure  $\geq 20$  mm Hg; E, short-term decrease in the echocardiographically measured left ventricular ejection fraction by an absolute reduction of 0.20; and S, sudden death due to rejection (confirmed at autopsy).

†According to the classification system of the International Society for Heart and Lung Transplantation.

two in the pravastatin group did not have intracoronary ultrasonography.

#### Relation to Cholesterol Levels within Study Groups

There was no correlation between higher cholesterol levels and the development of either cardiac rejection accompanied by hemodynamic compromise or coronary vasculopathy in the transplant (as detected by angiography or at autopsy). Among the patients who underwent intracoronary ultrasonography in both study groups, there was no correlation between cholesterol levels and the progression of intimal thickness (measured as either maximal intimal thickness or the intimal index).

#### Natural-Killer-Cell Activity

A subgroup of 20 consecutive patients, 9 in the pravastatin group and 11 in the control group, were assessed for natural-killer-cell cytotoxicity. The base-line characteristics and postoperative characteristics of immunosuppression (including cyclosporine trough levels) of these patients were similar to those of the corresponding study groups as a whole. Among the patients in the subgroup, there was only one infectious episode requiring antibiotic therapy (in a patient assigned to receive pravastatin).

Peripheral-blood samples were obtained for the assessment of natural-killer-cell cytotoxicity during a six-month period. An average of 4.8 samples per patient were collected in the pravastatin group, and 4.7 samples per patient were collected in the control group. Blood samples taken during episodes of cardiac

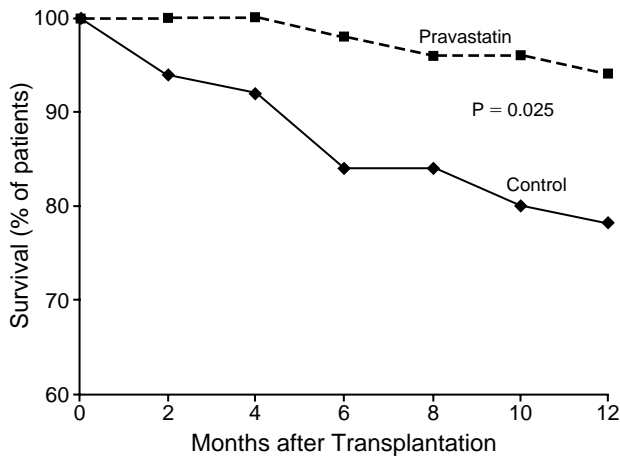


Figure 2. Survival during the First Year after Cardiac Transplantation in the Study Patients.

rejection (as confirmed by endomyocardial biopsy) or infection were excluded, and all data on one control patient with severe rejection were excluded. There was significantly lower natural-killer-cell cytotoxicity in the weighted average of multiple samples collected over time in the pravastatin group than in the control group (9.8 percent vs. 22.2 percent specific lysis,  $P=0.014$ ).

### DISCUSSION

The results of this randomized study suggest that the early use of pravastatin after cardiac transplantation safely lowers cholesterol levels, decreases the incidence of major rejection, improves one-year survival, and reduces the development of coronary vasculopathy. These benefits may result from a direct reduction of cholesterol, an effect of lower cholesterol levels on immune function, a cholesterol-independent effect of pra-

vastatin on immune function, or another cause as yet unknown.

Pravastatin did not change the overall incidence of cardiac rejection, but it decreased the rate of rejection accompanied by hemodynamic compromise, resulting in better survival. Rejection accompanied by hemodynamic compromise has often been associated with humoral rejection<sup>16,17</sup> (i.e., that occurring without producing marked lymphocytic infiltration in endomyocardial-biopsy specimens), an observation that agrees with our findings. In the first year after transplantation, death due to cardiac rejection was relatively common in the control group, occurring in eight patients. Four of these patients had concomitant infection (due to antirejection therapy) but were not reported as having died of infection, which could explain the higher rates of rejection and lower infection-related mortality in this study.

In a multinational study of patients with hyperlipidemia,<sup>18</sup> pravastatin reduced total cholesterol levels and rates of all cardiovascular events beginning six months after the start of the study. In our study, the drug appeared to reduce the development of coronary vasculopathy as diagnosed by coronary angiography, at autopsy, or by intracoronary ultrasonography (the last of which is more sensitive in measuring the early presence of such vasculopathy). Maximal intimal thickness (the measurement of the most severely atherosclerotic area) and the intimal index (the ratio of the area of plaque to the total vessel area), which together provide a description of the plaque burden in relation to coronary-artery size, were the two measurements made by intracoronary ultrasonography. Pathological specimens from patients with cardiac transplants who have severe coronary vasculopathy have been reported to have a high cholesterol content.<sup>19</sup> Therefore, early cholesterol lowering with pravastatin may play a part in decreasing

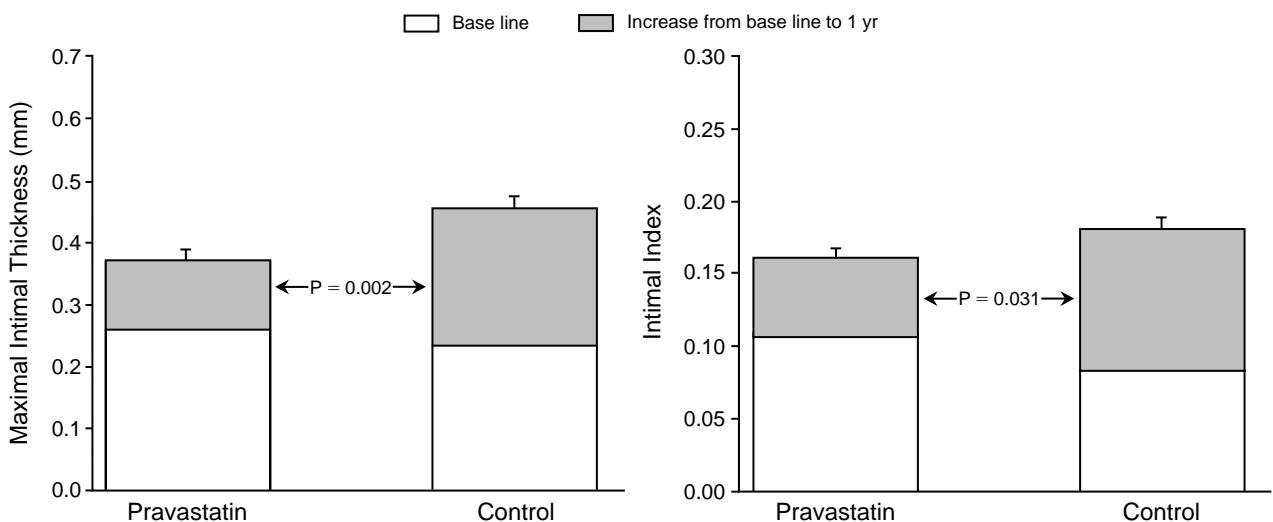


Figure 3. Results of Intracoronary Ultrasonography.

As compared with the pravastatin group, the control group had significantly greater increases in maximal intimal thickness ( $P=0.002$ ) and the intimal index ( $P=0.031$ ) during the first year after cardiac transplantation. Maximal intimal thickness represents the thickness of the most severely atherosclerotic area, and the intimal index the ratio of the area of plaque to the total vessel area. Values obtained at one year are expressed as means  $\pm$  SE.

the incorporation of cholesterol into the coronary arteries of the donor heart.

In the present study, there did not appear to be a correlation between cholesterol levels and the development of coronary vasculopathy one year after transplantation. The absence of correlation may be due to the relatively small number of patients in each study group, the need for longer follow-up, or both. It also suggests that pravastatin may slow the progression of coronary vasculopathy by an effect independent of cholesterol reduction. Immunologic effects of HMG-CoA reductase inhibitors have been reported *in vitro* and may result from changes in circulating lipids or other effects. These reported immunologic effects include the regulation of DNA in cycling cells,<sup>20</sup> the inhibition of chemotaxis by monocytes,<sup>21</sup> the regulation of natural-killer-cell cytotoxicity,<sup>10,11,22</sup> and the inhibition of antibody-dependent cellular cytotoxicity.<sup>11</sup>

The decrease in natural-killer-cell cytotoxicity in the pravastatin group in this study suggests that pravastatin may cause an increased state of immunosuppression. HMG-CoA reductase inhibitors have been shown to decrease antibody-dependent cellular cytotoxicity and natural-killer-cell function, which have been implicated in the clinical rejection of renal allografts.<sup>23,24</sup> In an *in vitro* study, natural-killer-cell cytotoxicity was inhibited by as much as 95 percent by the HMG-CoA reductase inhibitor mevastatin and was restored by the addition of mevalonate, the product of the reductase enzyme, but not by cholesterol or dolichol. Cutts et al.<sup>10</sup> have postulated the existence of a metabolite of mevalonate that restores natural-killer-cell cytotoxicity, possibly through a modulation of the glycoprotein composition of a natural-killer-cell receptor or a requirement for a mevalonate-modified receptor component. The finding of decreased natural-killer-cell cytotoxicity in the pravastatin-treated patients we studied may itself be important or may be only a marker for other immunosuppressive effects possibly responsible both for the benefits seen in terms of survival and for the development of coronary vasculopathy.

Pravastatin may interact with cyclosporine, which blocks the synthesis of interleukin-2 in stimulated T lymphocytes. The addition of interleukin-2 restored the natural-killer-cell cytotoxicity and partly restored the antibody-dependent cytotoxicity that were inhibited in lovastatin-treated *in vitro* cell cultures, as reported by Cutts and Bankhurst.<sup>11</sup> A synergy between cyclosporine and pravastatin could explain increased immunosuppression in recipients of cardiac transplants, whereas patients without transplants who receive HMG-CoA reductase inhibitors for hypercholesterolemia do not have clinical immunosuppression.<sup>25</sup>

The number of patients in this study was relatively small, and the study was not blinded. However, survival was an objective end point and the findings on intracoronary ultrasonography were interpreted blindly. Intracoronary ultrasonography was not performed in all patients both at base line and after one year of follow-up; however, demographic data on the subgroup of pa-

tients in the pravastatin and control groups who underwent the procedure suggest they were comparable to the overall groups. Eight patients with coronary vasculopathy in their transplants diagnosed by angiography or at autopsy did not undergo intracoronary ultrasonography, and six of them were in the control group. Because the progression of intimal thickening seen on intracoronary ultrasonography in these patients would be expected to be considerable, the true means for the intimal changes may be even greater, leading to an underestimation of the differences in intimal thickening between the groups.

This study suggests that pravastatin lowers cholesterol levels; reduces the incidence of cardiac rejection accompanied by hemodynamic compromise, thereby increasing first-year survival; and reduces the development of coronary vasculopathy in the first year after cardiac transplantation. The inhibition of natural killer cells in pravastatin-treated patients suggests that pravastatin has an increased immunosuppressive effect in cyclosporine-treated patients with cardiac transplants. Long-term follow-up will be needed to determine whether pravastatin continues to have beneficial effects after one year.

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