Changes in Coronary Plaque Color and Morphology by Lipid-Lowering Therapy With Atorvastatin: Serial Evaluation by Coronary Angioscopy

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OBJECTIVES	Changes in coronary plaque color and morphology by statin therapy were evaluated using coronary angioscopy.
BACKGROUND	Coronary plaque stabilization by statin therapy has not been clarified in humans.
METHODS	Thirty-one patients with coronary artery disease were divided into either the comparison group (n = 16) or the atorvastatin group (n = 15). Before treatment and 12 months after, the color and complexity of 145 coronary plaques were determined according to angioscopic findings. The yellow score of the plaque was defined as 0 (white), 1 (light yellow), 2 (yellow), or 3 (dark yellow), and its disrupted score was defined as 0 (smooth surface) or 1 (irregular surface) and as 0 (without thrombus) or 1 (with thrombus). In each patient, the mean yellow score and mean disrupted score were calculated.
RESULTS	Mean low-density lipoprotein cholesterol (LDL-C) decreased by 45% in the atorvastatin group, whereas an increase of 9% was seen in the comparison group. The mean yellow score decreased from 2.03 to 1.13 in the atorvastatin group, whereas it increased from 1.67 to 1.99 in the comparison group. There was a good correlation between the change in the mean yellow score and the change in LDL-C levels ($r = 0.81$, $p < 0.0001$). The change in the mean yellow score and mean disrupted score differed significantly between the two groups ($p = 0.002$ and $p = 0.03$, respectively).
CONCLUSIONS	This is the first report clarifying detailed changes in coronary plaque by statin in humans. This study indicated that lipid-lowering therapy changes plaque color and morphology and should then lead to coronary plaque stabilization. (J Am Coll Cardiol 2003;42:680−6) © 2003 by the American College of Cardiology Foundation

Coronary plaque disruption or erosion with subsequent thrombus formation is the pathogenesis of acute coronary syndrome (ACS) (1–6). Primary and secondary prevention studies with statins have demonstrated the effect of lipid-lowering therapy on the reduction of ischemic cardiac

events. However, the effects of statins on the regression of atherosclerosis by coronary angiogram were not always dramatic (7–11). These phenomena have been explained by the fact that treatment with statins may change the composition of coronary plaque and thus lead to plaque stabilization.

Coronary angioscopy provides full color, high-resolution, three-dimensional images, and this modality enables us to obtain detailed information on coronary lumens, including plaque and thrombus. Previous angioscopic studies have shown that disrupted yellow plaques accompanied with thrombus formation are frequently noted as culprit lesions in patients with ACS, whereas smooth white plaques without thrombus formation are often noted in patients with stable angina or old myocardial infarction (MI) (1,2,12). Therefore, the color and morphology of coronary plaque are regarded as determining factors for plaque stability or instability.

This angioscopic study was designed to document the serial changes in plaque color and morphology by lipid-lowering therapy.

METHODS

Study design. This study was a prospective, open-label, single-center study of patients with coronary artery disease. A comparison group was designed in this study for comparison with the atorvastatin group. Nevertheless, this study was non-randomized. Patients were divided into the two groups according to their serum total cholesterol (T-CHO) levels at baseline. In those cases where T-CHO at baseline was under 220 mg/dl, no lipid-lowering medication was administered, whereas those cases with more than 220 mg/dl received atorvastatin based on the guidelines of the Japan Atherosclerosis Society. In the atorvastatin group, the target low-density lipoprotein cholesterol (LDL-C) level was <100 mg/dl. All patients received dietary counseling.

Fifteen patients were treated with atorvastatin, and 16 patients did not receive any lipid-lowering medication (comparison subjects). Before treatment and at the 12-month follow-up, coronary angiography and angioscopy were performed. Informed consent was obtained from all the study patients, and the research protocol was approved by our institutional review boards. Clinical follow-up visits occurred every month for up to 12 months. A blood sample was taken after 1, 2, 3, 6, and 12 months, and data were collected on compliance and clinical events.

Patients. The subjects in this study were regular patients who had successfully undergone percutaneous coronary intervention (PCI) for ischemic heart disease from December 2000 to May 2001.

Exclusion criteria were left main disease, severe three-vessel disease, MI within the previous four weeks, an ejection fraction < 40%, past administration of any lipid-lowering medication, secondary causes of hypercholesterolemia, severe hypertriglyceridemia (>400 mg/dl), and chronic inflammatory disease. Patients who had no angioscopic yellow or disrupted plaques, except those at the PCI sites, were excluded. Those plaques located within 10 mm proximal and distal to the percutaneous intervention sites were also excluded.

Blood and physical examinations. At baseline, systolic and diastolic blood pressure, fasting plasma glucose, hemoglobin A1c, serum uric acid, and body mass index were measured. At baseline and follow-up, fasting serum T-CHO, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) were measured; LDL-C was calculated according to Friedwald's formula.

Medical therapies. The patients in the comparison group continued with therapies for coronary risk factor reduction exclusive of hyperlipidemia. The patients in the atorvastatin group had the administration of atorvastatin added to these therapies. The initial daily dose of atorvastatin was 10 mg, and this dose was increased up to 30 mg to reach the target LDL-C levels (<100 mg/dl).

Coronary angiography and target lesion revascularization. A coronary angiogram was obtained at baseline, six months, and 12 months follow-up. In the case of angiographic restenosis at six months, target lesion revascularization was performed. The vessel contour, such as irregularity and haziness, in the segments evaluated using coronary angioscopy was identified by consensus of two independent angiographers.

Coronary angioscopic imaging. Coronary angioscopic examinations were performed at baseline and 12 months follow-up. An imaging catheter (Vecmova, Clinical Supply Co., Gifu, Japan) was used, and the angioscopic procedure had been previously reported (1,2,12). Before observation, the white balance was adjusted for color correction. During angioscopic observation, an exclusive assistant adjusted the light power to keep a regular degree of brightness on the target plaque. Light power was adjusted to avoid reflection and to obtain images with adequate brightness for determining plaque color. Angioscopic images and fluoroscopy during angioscopic observation were recorded on DVD videotape for analysis later. The exact position of the angioscopic catheter at the site of target plaque was recorded by angiogram to ensure a reliable comparison.

Definition and analysis of angioscopic findings. Coronary arteries were observed by coronary angioscopy, and the existence and number of the yellow or disrupted plaques were evaluated. For each plaque, the score of the color and complexity of the coronary plaques were determined as follows: the yellow score was defined as 0 (white), 1 (light yellow), 2 (yellow), or 3 (dark yellow), and the disrupted score was defined as 0 (smooth surface) or 1 (irregular surface) and as 0 (without thrombus) or 1 (with thrombus) (Fig. 1). In each patient, the mean yellow score and mean disrupted score were calculated as the total of the yellow score and disrupted score of all the plaques divided by the number of plaques, respectively.

Angioscopic images were analyzed independently by two observers blinded to treatment assignment, patients' clinical background, and the order of the angioscopic examination. The intra-observers agreement was measured by having an observer repeat the assessment of 20 images (presented in random order) one week later. The inter-observer agreement was measured by having the two observers compare the assessment of the 20 images. Intra- and inter-observer agreements were both 95%. If there was no consensus concerning the angioscopic scores, the data in question were excluded from the study.

Statistical analysis. Data are presented as the mean ± SD. Whether data were normally distributed or not was examined by the Kolmogrov-Smirnov test. If data were normally distributed, an unpaired Student t test was used to compare the two groups. Otherwise, a Mann Whitney U test was used. The changes in lipoprotein levels, CRP levels, and angioscopic scores in each group from baseline to follow-up were tested with a paired Student t test. Differences in the changes in angioscopic scores from baseline to follow-up between the two groups were analyzed with analysis of covariance, in which changes in angioscopic scores are the dependent variables and in which treatment with atorvastatin and angioscopic scores at baseline are the independent variables. The categorical variable was analyzed using the
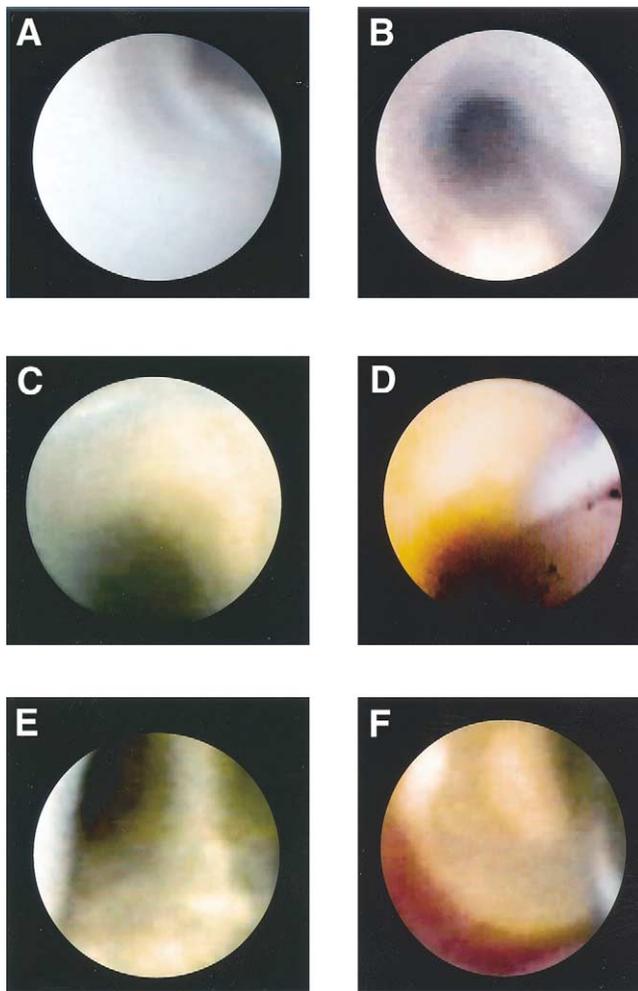
Figure 1. (A) White plaque (yellow score: 0). **(B) Light yellow plaque** (yellow score: 1). **(C) Yellow plaque** (yellow score: 2). **(D) Dark yellow plaque** (yellow score: 3). **(E) Yellow and irregular plaque** (disrupted score: 1). **(F) Yellow plaque with a red thrombus** (disrupted score: 1).

Fisher exact probability test. The correlation between the two parameters was evaluated by linear regression analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients. Thirty-three patients were screened to find yellow or disrupted plaques using coronary angioscopy. Two patients were excluded because they had no yellow or disrupted plaques except those at the PCI sites. Finally, 31 patients were examined in this study.

Clinical characteristics at baseline except for lipoprotein levels were comparable in the comparison group (n = 16) and the atorvastatin group (n = 15) (Table 1).

Changes in lipoprotein levels and CRP levels. Changes in lipoprotein levels and CRP levels in the two groups are shown (Table 2). At baseline, T-CHO and LDL-C levels were significantly higher in the atorvastatin group than in the comparison group. In the comparison group, T-CHO and LDL-C increased during follow-up, whereas, in the

Table 1. Baseline Characteristics of Patients in the Comparison and Atorvastatin Groups

	Comparison (n = 16)	Atorvastatin (n = 15)	p Value
Age (yrs)	62 ± 9	59 ± 10	0.39
Gender (male)	14 (88)	11 (73)	0.29
Risk factors for coronary artery disease			
Hypertension	12 (75)	7 (47)	0.11
Diabetes mellitus	5 (31)	3 (20)	0.38
Current smoker	8 (50)	10 (67)	0.28
Obesity	4 (25)	6 (40)	0.30
Family history	4 (25)	4 (27)	0.62
Hyperuricemia	2 (13)	2 (13)	0.68
Diagnosis for coronary artery disease			
Myocardial infarction (convalescent stage)	13 (81)	9 (60)	0.18
Stable angina	2 (13)	4 (27)	0.29
Unstable angina	1 (6)	2 (13)	0.47
Number of diseased vessels			
One-vessel disease	10 (63)	9 (60)	0.59
Two-vessel disease	6 (38)	6 (40)	
Medication use:			
Aspirin	15 (94)	14 (93)	0.74
Ticlopidine	13 (81)	13 (87)	0.53
Warfarin	1 (6)	0 (0)	0.52
Beta-blockers	5 (31)	5 (33)	0.60
Calcium channel blockers	6 (38)	4 (27)	0.40
Angiotensin-converting enzyme inhibitors	6 (38)	8 (53)	0.30
Angiotensin II receptor antagonists	6 (38)	2 (13)	0.13
Diuretics	1 (6)	1 (7)	0.75
Oral hypoglycemic agents	2 (13)	3 (20)	0.47
Insulin	1 (6)	0 (0)	0.52
Systolic blood pressure (mm Hg)	123 ± 12	119 ± 11	0.34
Diastolic blood pressure (mm Hg)	74 ± 12	69 ± 7	0.17
Fasting plasma glucose (mg/dl)	105 ± 16	105 ± 24	1.00
Hemoglobin A1c (%)	5.5 ± 1.1	5.5 ± 1.1	1.00
Uric acid (mg/dl)	6.0 ± 1.4	5.4 ± 1.4	0.24
Body mass index (kg/m²)	23.8 ± 1.9	24.4 ± 3.1	0.52

Except for age, systolic and diastolic blood pressure, fasting plasma glucose, hemoglobin A1c, uric acid, and body mass index, which are the mean ± SD, values represent n (%).

atorvastatin group, T-CHO, TG, and LDL-C decreased significantly by 35%, 31%, and 45%, respectively. Target LDL-C levels were obtained by one patient in the comparison group and by 10 patients in the atorvastatin group. The final daily dose of atorvastatin was 10 mg in eight, 20 mg in six, and 30 mg in one patient, respectively.

C-reactive protein levels did not change in the two groups. There was a tendency for CRP levels in the atorvastatin group to decrease.

Coronary angiography. At baseline, three segments in the comparison group and three segments in the atorvastatin group were identified as angiographic irregularities. The segment accompanied with haziness was not recognized. At the 12-month follow-up, irregularity remained in three segments in the comparison group while it disappeared in two segments in the atorvastatin group. There was no new

Table 2. Lipoprotein and CRP Levels of Patients in the Comparison and Atorvastatin Groups at Baseline and During Follow-Up

	Baseline					Follow-up				
	T-CHO	**TG**	**HDL-C**	**LDL-C**	**CRP**	**T-CHO**	**TG**	**HDL-C**	**LDL-C**	**CRP**
Comparison group (n = 16)	204 ± 17	173 ± 58	41 ± 8	128 ± 18	0.18 ± 0.20	215 ± 23 (+6%)	167 ± 67 (−1%)	42 ± 10 (+5%)	139 ± 24 (+9%)	0.17 ± 0.14
Atorvastatin group (n = 15)	263 ± 37	203 ± 91	42 ± 13	180 ± 41	0.24 ± 0.30	169 ± 25 (−35%)	123 ± 43 (−31%)	46 ± 12 (+23%)	99 ± 27 (−45%)	0.07 ± 0.03
p Value (comparison vs. atorvastatin)	<0.0001	0.28	0.80	<0.001	0.51	<0.0001	0.04	0.32	<0.001	0.01
Comparison group, p value (baseline vs. follow-up)						0.04	0.66	0.50	0.02	0.83
Atorvastatin group, p value (baseline vs. follow-up)						<0.0001	0.002	0.11	<0.001	0.05

Values represent mg/dL and the mean ± SD.
CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; T-CHO = total cholesterol; TG = triglycerides.

Table 3. Number and Distribution of Coronary Plaques

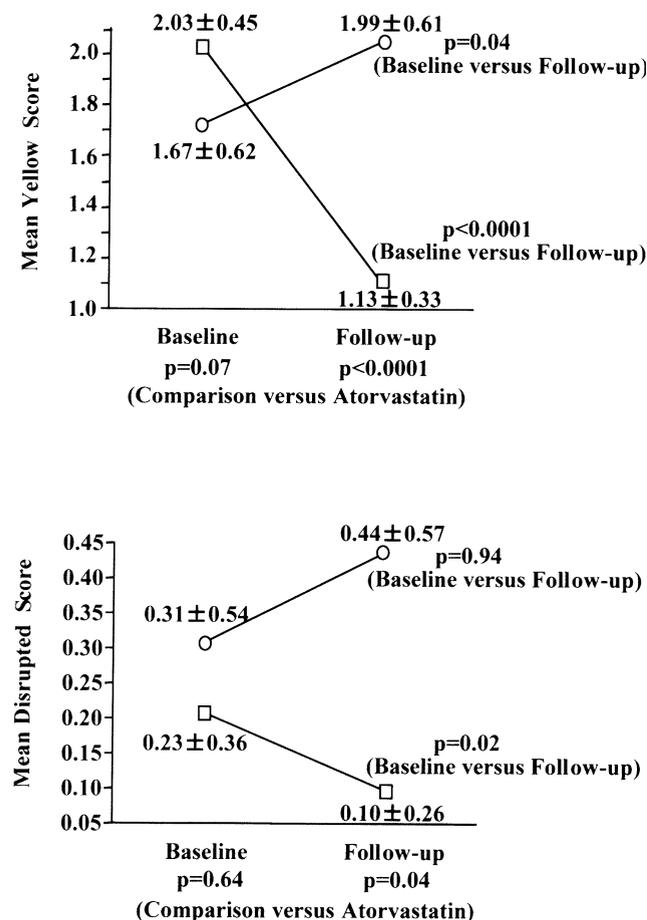|	Comparison Group	Atorvastatin Group	p Value
Number of coronary plaques	68	77	
Number of observed coronary arteries by coronary angioscopy			
Right coronary artery	10	7	0.37
Left anterior descending artery	7	10	0.21
Left circumflex artery	16	13	0.44
Distribution of coronary plaques			
Right coronary artery	26	22	0.15
Left anterior descending artery	24	26	0.49
Left circumflex artery	18	29	0.10

appearance of angiographic irregularity or haziness in either group.

Clinical outcome. There were no withdrawals due to drug-related side effects in either group. Three patients in the comparison group and two patients in the atorvastatin group underwent target lesion revascularization based on angiographic restenosis at six months. There was no occurrence of ACS in either group.

Analysis of angioscopic findings. A total of 152 yellow or disrupted plaques in 63 coronary arteries were identified at baseline. Seven plaques, whose angioscopic scores at baseline or follow-up could not be agreed on by the observers, were excluded. Therefore, 145 coronary plaques were used for this study (Table 3). The changes in the mean yellow score and mean disrupted score of the two groups are shown in Figure 2. At baseline, there were no significant differences in these scores between the two groups. In the atorvastatin group, these two angioscopic scores decreased significantly from baseline to follow-up. In the comparison group, the mean yellow score increased significantly. The changes in the mean yellow score and mean disrupted score between the two groups differed significantly (p = 0.002 and p = 0.03, respectively). In the atorvastatin group, three thrombi disappeared, and five irregular plaques changed into smooth plaques. In the comparison group, two thrombi appeared, one thrombus disappeared, and five smooth plaques changed into irregular plaques. Two typical cases are shown in Figure 3. There was a good correlation between the change in the mean yellow score and the change in LDL-C levels (Fig. 4). There was no correlation between the change in the mean disrupted score and the change in LDL-C levels (r = 0.42, p = 0.10).

DISCUSSION

Histological studies have revealed that atherosclerotic plaques prone to disruption, so-called "vulnerable plaques," are commonly composed of a thin fibrous cap, lipid-rich cores, and many inflammatory cells, such as macrophages, foam cells, and T-lymphocytes (3,4). Previous angioscopic studies have established that irregular yellow plaques with thrombus are commonly observed at the sites of culprit lesions in patients with ACS (1,2). Furthermore, a prospec-

Figure 2. Changes in mean yellow score and mean disrupted score from baseline to follow-up. The **open circles** represent the comparison group (n = 16); the **open squares** represent the atorvastatin group (n = 15). In the atorvastatin group, the mean yellow score and mean disrupted score decreased significantly from baseline to follow-up. In the comparison group, the mean yellow score increased significantly.

tive study has demonstrated that yellow plaque frequently causes ACS (13). In contrast, smooth white plaque, often observed in ischemia-related lesions of patients with stable angina or old MI, has a thick fibrous cap or is completely fibrous (12,14,15). These facts suggest that the color and complexity are the determinant factors of plaque stability or instability. In general, yellow plaque is believed to be more vulnerable than white plaque (12,16,17). However, the grade of the yellow plaque varies. In this study, the color and complexity of the coronary plaques were evaluated semi-quantitatively as angioscopic scores. We hypothesized that lipid-lowering therapy would change the quality of the plaque and that this change would be recognized as a reduction of the yellow score and disrupted score by coronary angioscopy.

Changes in plaque color. This study indicated that lipid-lowering therapy by atorvastatin dramatically decreased the yellow grade of coronary plaque. An experimental study revealed that lipid-lowering by diet reduced matrix metalloproteinase activity and increased collagen content in rabbit atheroma (18). A pathological study of human carotid

plaques obtained by carotid endoatherectomy demonstrated that a lipid-lowering therapy with pravastatin decreased lipid content and inflammatory activity and increased collagen content (19). Similar changes in coronary plaques might be caused by a lipid-lowering therapy in living humans. A recent in vivo study of the comparison between integrated backscatter intravascular ultrasound and coronary angiography revealed that plaque color in angioscopy depended not on the thickness of the lipid-core but on the thickness of the fibrous cap (15). Increased collagen content should make thin fibrous caps thicker. Therefore, increased collagen content and decreased lipid content of coronary plaques by lipid-lowering therapy appear to reduce angioscopic yellow grade.

In the comparison group, the mean yellow score increased at the 12-month follow-up in spite of baseline T-CHO levels <220 mg/dl. A previous prospective, randomized, double-blind trial showed that a conventional lipid-lowering therapy with simvastatin for two years was associated with increased intima-media thickness (IMT) of the carotid artery, whereas an aggressive lipid-lowering therapy with high doses of atorvastatin decreased the IMT in patients with familial hypercholesterolemia (20). A three-dimensional intravascular ultrasound study showed that one year of conventional therapy for hyperlipidemia, excluding atorvastatin, increased the volume of the coronary plaques (21). These facts suggest that atherosclerosis progresses during conventional therapies for hyperlipidemia. Therefore, the increase in the mean yellow score in the comparison group may be indicative of the natural progression of atherosclerosis.

Changes in plaque complexity. In the atorvastatin group, three thrombi had disappeared at the follow-up. Statins have not only a direct lipid-lowering action but also other indirect actions, so-called "pleiotropic effects." An antithrombic effect is one of these pleiotropic effects. Statins prevent the expression of endothelial tissue factor (22). Moreover, atorvastatin reduced TG levels by 31% in this study. It is well known that the reduction in TG levels decreases plasminogen activator inhibitor-1 activity, which is a major inhibitor of the fibrinolytic system. Atorvastatin also inhibits platelet deposition on eroded vessel walls (23). These effects of atorvastatin must indicate antithrombic and platelet inhibition. The disappearance of coronary thrombi may be explained by the fact that atorvastatin has antithrombic and platelet inhibition effects.

In five plaques, an irregular surface changed into a smooth surface after treatment with atorvastatin. The precise mechanism of this morphologic change in the plaques has been unknown. However, this change may be one of the processes involved in plaque stabilization.

Changes in CRP levels. A recent pathological study with coronary arteries demonstrated that there was a positive correlation between the staining intensity for CRP of macrophages, lipid-core, and serum CRP levels. Moreover, a strong correlation between serum CRP levels and in-
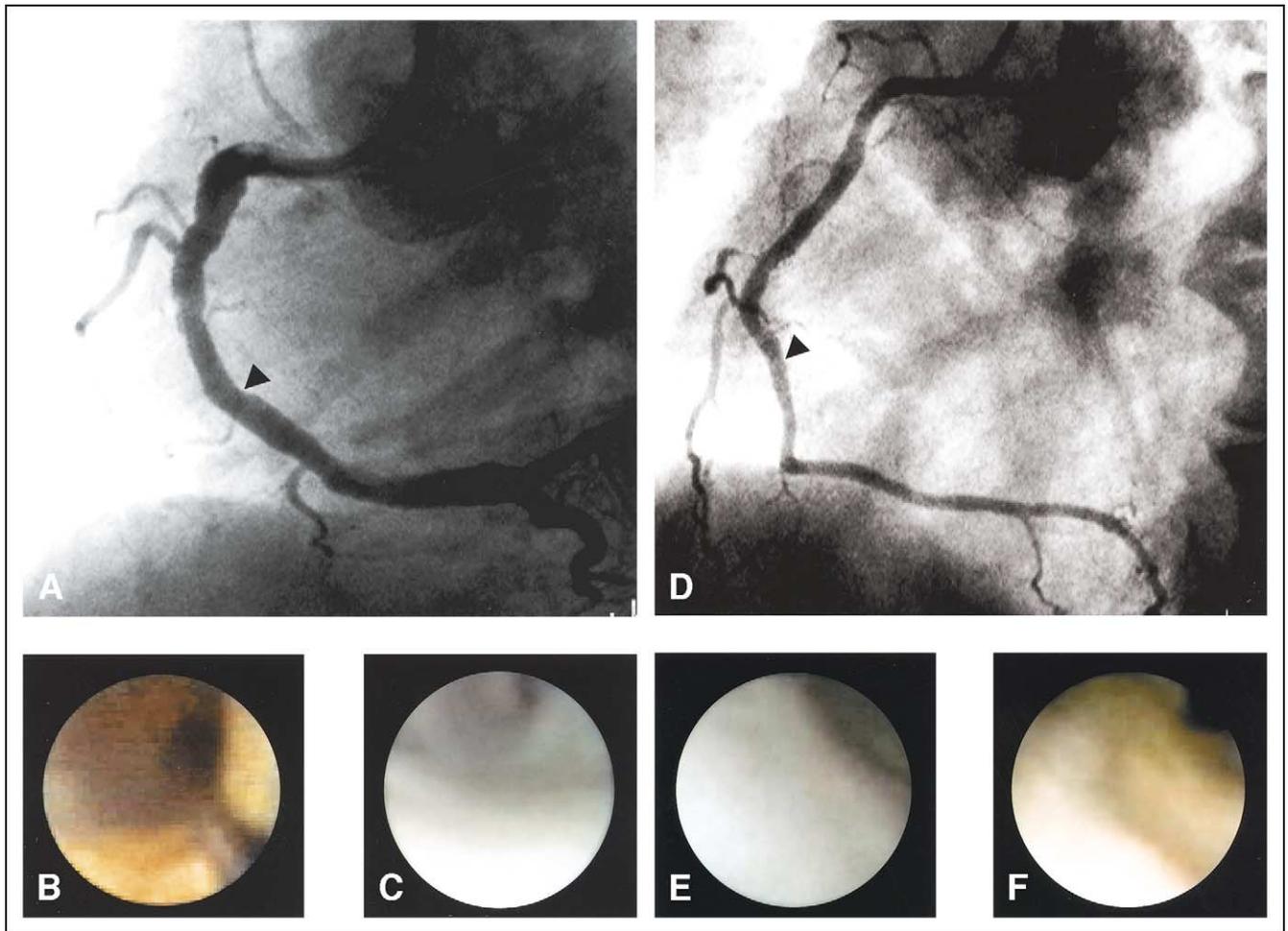
Figure 3. Changes in angioscopic findings from baseline to follow-up. **(A)** A right coronary angiogram of a patient in the atorvastatin group. **(B) Yellow plaque** in a patient in the atorvastatin group at baseline. **Yellow plaque** (yellow score: 3) was observed in the mid-portion of the right coronary artery at baseline **(arrow in A).** The surface of this plaque was smooth, and a thrombus was not noted (disrupted score: 0). **(C) White plaque** in a patient in the atorvastatin group at follow-up. After treatment with atorvastatin, the **yellow plaque** changed into a completely **white plaque**. Both the yellow score and disrupted score were 0. **(D)** A right coronary angiogram of a patient in the comparison group. **(E) Yellow plaque** in a patient in the comparison group at baseline. **Yellow plaque** (yellow score: 1) was observed in the mid-portion of the right coronary artery at baseline **(arrow in D).** The surface of this plaque was smooth, and a thrombus was not noted (disrupted score: 0). **(F) Yellow plaque** in a patient in the comparison group at follow-up. After 12 months of follow-up without lipid-lowering medication, the yellow score had increased to 2, and the surface of this plaque had become irregular (disrupted score: 1).

creased number of coronary atheromas with thin fibrous caps was revealed (24). These facts suggest that CRP is a marker for coronary atherosclerosis, especially those lesions rich in lipid-core and macrophages. In this study, the serum concentration of CRP in the atorvastatin group tended to decrease. Atorvastatin inhibits inflammatory cell activity in atherosclerotic plaques. In a rabbit model of atherosclerosis, atorvastatin abolished macrophage infiltration and decreased monocyte chemoattractant protein levels in the neointima and in the media (25). The tendency of CRP reduction in the atorvastatin group may be reflected in coronary plaque stabilization by an anti-inflammatory effect.

Changes in LDL-C levels and the mean yellow score. This study revealed that there was a good correlation between the change in the mean yellow score and the change in LDL-C levels. Previous biochemical study demonstrated that treatment with atorvastatin decreased not only native LDL-C but also oxidized LDL-C in patients

with hyperlipidemia (26). Oxidized LDL-C plays a key role in the process of atherosclerosis. Oxidized LDL-C is taken in macrophages through the scavenger receptors. These macrophages transform into foam cells, and then they are deposited as lipid-core in the atherosclerotic lesions. Matrix metalloproteinase derived from macrophages breaks down various matrix proteins in the fibrous cap and weakens it. Therefore, LDL-C lowering decreases activity of inflammatory cells and lipid content and increases collagen content (18,19). A decrease of the angioscopic yellow score should indicate the plaque stabilization resulting from these changes in plaque composition. Our results support the theory that aggressive LDL-C lowering is beneficial to coronary plaque stabilization.

Study limitations. First, the number of patients in the study was small. However, a total of 145 coronary plaques were evaluated. Second, the evaluation of plaque color was rather subjective, although this kind of assessment is easy
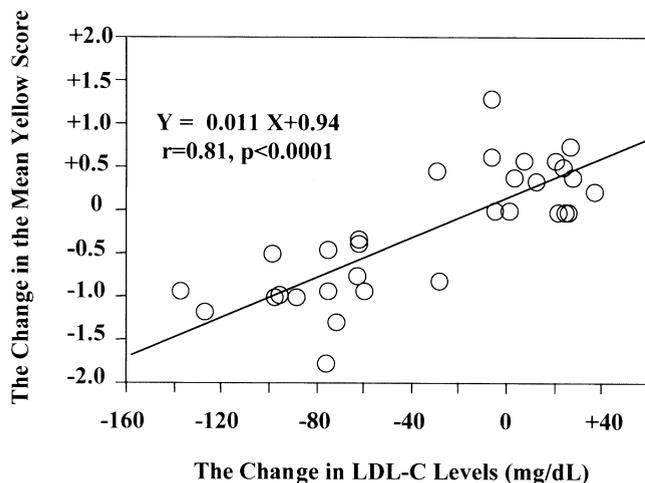
Figure 4. Relationship between the change in the mean yellow score and the change in LDL-C levels from baseline to follow-up. There was a good correlation between the change in the mean yellow score and the change in LDL-C levels from baseline to follow-up.

and practical. Therefore, those plaques without interobserver consensus with regard to angioscopic findings were excluded from this study. Third, whole angioscopic evaluation in three main coronary arteries was performed in some, but not all, study patients. Finally, this study was non-randomized. From an ethical point of view, based on several prevention studies with statins, those cases with serum T-CHO more than 220 mg/dl at baseline were treated for hyperlipidemia.

Conclusions. We have demonstrated that LDL-C lowering by atorvastatin resulted in the reduction of angioscopic yellow grade and complexity of coronary plaques. A lipid-lowering therapy changed the quality of coronary plaques and should lead to coronary plaque stability.

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