

EFFECT OF HMG-CoA REDUCTASE INHIBITORS ON CORONARY ARTERY DISEASE AS ASSESSED BY ELECTRON-BEAM COMPUTED TOMOGRAPHY

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ABSTRACT

Background Angiographic studies of the regression of coronary artery disease are invasive and costly, and they permit only limited assessment of changes in the extent of atherosclerotic disease. Electron-beam computed tomography (CT) is noninvasive and inexpensive. The entire coronary-artery tree can be studied during a single imaging session, and the volume of coronary calcification as quantified with this technique correlates closely with the total burden of atherosclerotic plaque.

Methods We conducted a retrospective study of 149 patients (61 percent men and 39 percent women; age range, 32 to 75 years) with no history of coronary artery disease who were referred by their primary care physicians for screening electron-beam CT. All patients underwent base-line scanning and follow-up assessment after a minimum of 12 months (range, 12 to 15), and a volumetric calcium score was calculated as an estimate of the total burden of plaque. Treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors was begun at the discretion of the referring physician. Serial measurements of low-density lipoprotein (LDL) cholesterol were obtained, and the change in the calcium-volume score was correlated with average LDL cholesterol levels.

Results One hundred five patients (70 percent) received treatment with HMG-CoA reductase inhibitors, and 44 patients (30 percent) did not. At follow-up, a net reduction in the calcium-volume score was observed only in the 65 treated patients whose final LDL cholesterol levels were less than 120 mg per deciliter (3.10 mmol per liter) (mean \pm SD) change in the score, -7 ± 23 percent; $P=0.01$). Untreated patients had an average LDL cholesterol level of at least 120 mg per deciliter and at the time of follow-up had a significant net increase in mean calcium-volume score (mean change, $+52 \pm 36$ percent; $P<0.001$). The 40 treated patients who had average LDL cholesterol levels of at least 120 mg per deciliter had a measurable increase in mean calcium-volume score (mean change, $+25 \pm 22$ percent, $P<0.001$), although it was smaller than the increase in the untreated patients.

Conclusions The extent to which the volume of atherosclerotic plaque decreased, stabilized, or increased was directly related to treatment with HMG-CoA reductase inhibitors and the resulting serum LDL cholesterol levels. These changes can be determined noninvasively by electron-beam CT and quantified with use of a calcium-volume score. (N Engl J Med 1998;339:1972-8.)

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BOTH primary prevention and secondary prevention of coronary artery disease are being widely investigated.^{1,2} Preventive cardiology would benefit from the introduction of noninvasive techniques that accurately quantify the extent of coronary atherosclerosis. The studies conducted to date on the regression of coronary artery disease have used arteriographic techniques.³⁻¹⁰ These methods are invasive and costly, and they require lengthy and elaborate analysis by expert investigators. Furthermore, long follow-up times are necessary to detect small changes in the minimal luminal diameter at the level of focal stenoses. However, small gains in luminal diameter have been shown to correspond to substantial clinical benefits.¹¹ Electron-beam computed tomography (CT) can rapidly and noninvasively quantify the extent of coronary-artery calcification within the entire coronary-artery tree, closely approximating the total plaque burden as measured at autopsy.¹²⁻¹⁹

One of the most appealing features of electron-beam CT is the potential to detect the progression or regression of coronary atherosclerotic disease noninvasively. However, the reportedly limited reproducibility of the traditional calcium score has hampered the application of electron-beam CT to this field.²⁰⁻²⁴ To circumvent this problem, we developed a novel calcium-volume score with a high degree of reproducibility between scans.²⁵ This score represents the volume of plaque and is based on the assumption that aging plaques may become smaller in volume while becoming denser.^{21,26,27} The score has a wide range of values and varies according to age, sex, and other factors. In this retrospective study, we sought to test the hypothesis that there is a relation between treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and the change in coronary-plaque volume, as assessed by electron-beam CT, over the course of one year.

METHODS

Patients

We reviewed the medical records of 195 consecutive asymptomatic patients, with no history of coronary artery disease, who were referred by their primary care physicians for sequential elec-

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tron-beam scanning procedures at intervals of 12 to 15 months. All information on risk factors for coronary artery disease was obtained by review of the patients' medical records. The patients in this observational study either were not receiving any lipid-lowering therapy or were receiving HMG-CoA reductase inhibitors as their only lipid-lowering medications. In every case, the choice whether to begin lipid-lowering therapy was made by the referring physician. Serial measurements of low-density lipoprotein (LDL) cholesterol were obtained throughout the study, and the values were averaged. Forty-six patients were excluded from the study: 30 (15 percent) because of inadequate image quality and 16 (8 percent) because they had an initial calcium-volume score below 30. The study group was composed of the remaining 149 patients. The study protocol was approved by the institutional review board of the Electron Beam Tomography Research Foundation.

Imaging Procedures

All patients underwent imaging with an Imatron C-100 scanner (Imatron, South San Francisco, Calif.). Imaging was performed with a 100-msec scanning time and a single-slice thickness of 3 mm. A total of 40 slices were obtained during two breath-holding periods. Tomographic imaging was electrocardiographically triggered at 80 percent of the RR interval. All areas of calcification within the borders of a coronary artery with a minimal optical density of 130 Hounsfield units were computed. A calcified coronary plaque was considered present if at least four consecutive pixels with signal density of at least 130 Hounsfield units were measured (an area equivalent to 2.24 mm²). The acquired images were reviewed at a NetraMD workstation (ScImage, Los Altos, Calif.). Patients were included in this study only if complete data were available from their scans, without misregistration of slices due to artifacts of motion, respiration, or asynchronous electrocardiographic triggering. To ensure the continuity and consistency of the interpretation of scores, a single expert investigator, unaware of the patients' clinical status and the temporal sequence of the studies, reviewed all the scans.

Calculation of Calcium-Volume Scores

The traditional calcium score is calculated by multiplying the area of a calcified plaque by a signal-density cofactor. When lipid-lowering agents reduce the soft lipid core of a calcified plaque, the density of the plaque and its calcium score increase, whereas its volume may decrease. Therefore, in this study we used a novel scoring system to calculate the volume of a plaque according to the principle of isotropic interpolation.^{25,28-30} Our software allowed us to slice the volume lying between two imaging planes into several sections. The density of each section was then determined relative to that of the original imaging planes by a process of mathematical interpolation. The process was repeated at high speed in all three spatial orthogonal directions, and the volume of a calcified plaque was calculated.²⁵ The final score is presented as a whole number to facilitate comparison with the traditional calcium score, although it is actually a volume measured in fractions of cubic millimeters (values in cubic millimeters were multiplied by 1000 to generate whole numbers). In an earlier study, we assessed the variability of the calcium-volume score between scans and compared it with the variability of the traditional score.²⁵ The reproducibility of the interpolated volume score was consistently superior to that of the traditional score, and the accuracy of the newer scoring system was significantly greater than that of the latter ($P < 0.001$), with an overall 39.5 percent reduction in error. The median interscan variability of the calcium-volume score was 8.9 percent for all scoring levels (5.8 percent when the score was 30 or more). To ensure maximal accuracy in our analysis of changes in calcium-volume scores over time, we included in this study only patients with an initial calcium-volume score of at least 30. Since the variability of the traditional calcium score is too great,²⁰⁻²⁵ we decided not to use this traditional score.

Statistical Analysis

In this retrospective analysis, patients were classified into three groups. Group 1 consisted of patients who were not treated with HMG-CoA reductase inhibitors. Groups 2 and 3 consisted of treated patients. In group 2 the average levels of LDL cholesterol were at least 120 mg per deciliter (3.10 mmol per liter), and in group 3 they were less than 120 mg per deciliter. Within each group, the change in the calcium-volume score from base line to follow-up was expressed in both absolute and relative terms. Standard summary statistics, including mean and median of changes in the score, were used to document the results in each group, and the paired t-test was used to determine the significance of the difference in the average changes within each group. The sign test was used to construct confidence intervals. Comparisons of mean relative changes in the calcium-volume score between groups were made with the two-sample t-test. A two-sample z test was used to document the significance of the difference between groups in the proportion of patients for whom a change in calcium-volume score was found. Regression analysis was used to summarize the relation between the relative change in the calcium-volume score and the average LDL cholesterol level in treated patients. Confidence intervals around the fitted regression line were calculated.

Residual plots and the runs test³¹ were used to confirm that there were no violations of the basic assumptions of regression analysis. Patients were matched in order to compare the relative change in the calcium-volume score among groups of patients after correction for differences in the base-line calcium-volume score and the average LDL cholesterol level. Finally, an analysis of covariance was conducted in two cohorts of patients selected from the subgroups of treated and untreated patients defined according to LDL cholesterol level. These analyses were performed to adjust for the possible influence of differences in base-line calcium-volume scores on final scores. P values of less than 0.05 (two-tailed) were considered to indicate significance. All values are expressed as means \pm SD.

RESULTS

The base-line clinical characteristics of the study patients are presented in Table 1. Among the 149 pa-

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	GROUP 1: UNTREATED PATIENTS (N=44)	GROUP 2: TREATED PATIENTS WITH LDL CHOLESTEROL ≥120 mg/dl (N=40)	GROUP 3: TREATED PATIENTS WITH LDL CHOLESTEROL <120 mg/dl (N=65)
Age (yr)	56±11	57±8	56±7
Male sex (%)	66	57	62
Current smoker (%)	23	20	18
Hyperlipidemia (%)	83	90	80
Systemic hypertension (%)	50	43	44
Diabetes mellitus (%)	12	20	25
Calcium-volume score			
Initial			
Mean	479±629	1017±2062	980±1611
Median	219	305	361
At follow-up			
Mean	646±762	1254±2483	956±1700
Median	353	399	340

*Plus-minus values are means \pm SD. To convert cholesterol values to millimoles per liter, multiply by 0.02586.

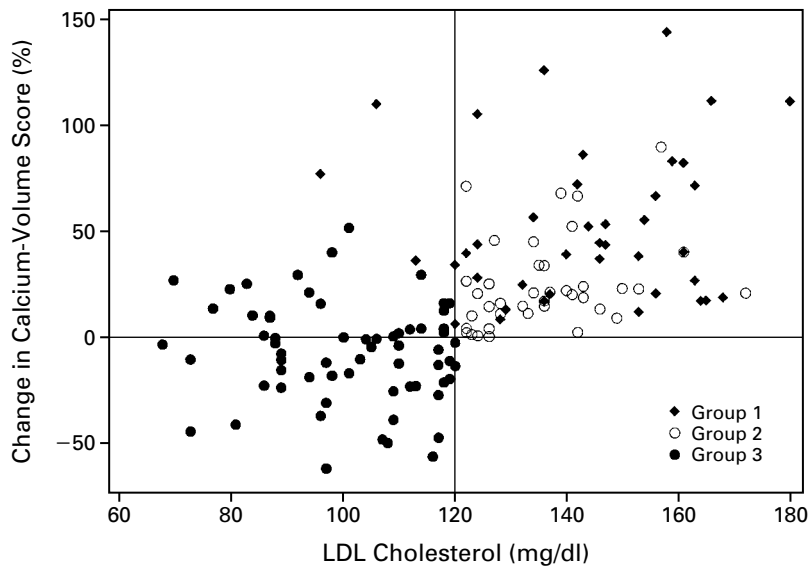


Figure 1. Scatter Plot of the Percent Change in the Calcium-Volume Score at One Year in Relation to the Average LDL Cholesterol Level for All Patients.

All untreated patients (group 1) and treated patients with average LDL cholesterol levels of at least 120 mg per deciliter (group 2) had increased scores, whereas 63 percent of treated patients with average LDL cholesterol levels below 120 mg per deciliter (group 3) had decreased scores. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

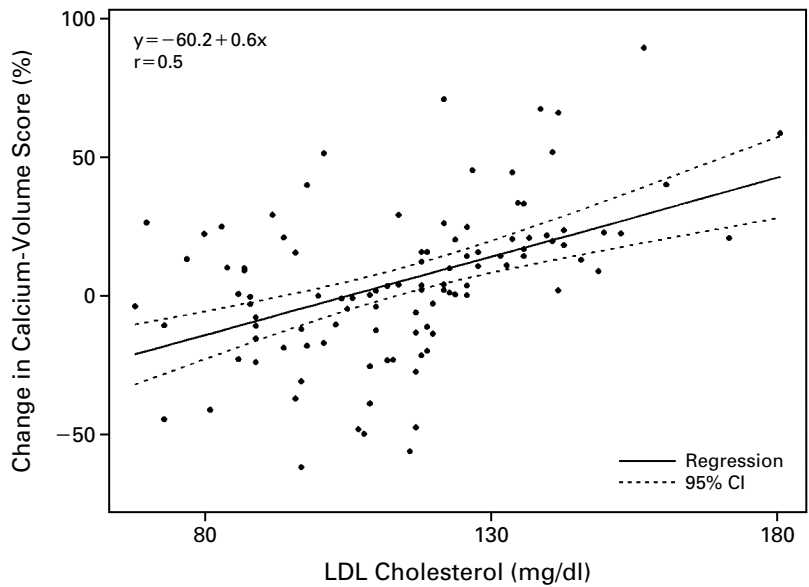


Figure 2. Regression Analysis of the Percent Change in the Calcium-Volume Score in Relation to the Average LDL Cholesterol Level in Treated Patients at One Year.

CI denotes confidence interval. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

tients, 61 percent of whom were men (age range, 32 to 75 years), 105 (70 percent) received treatment with HMG-CoA reductase inhibitors and 44 (30 percent) did not. The average interval between the initial and follow-up scans was 13.7 ± 0.6 months (range, 12 to 15 months).

Changes in Calcium-Volume Scores in Relation to LDL Cholesterol Levels

Figure 1 shows a scatter plot of the percent change in the calcium-volume score at one year in relation to the average LDL cholesterol level for each patient. The mean LDL cholesterol level was 114 ± 23 mg per deciliter (2.95 ± 0.59 mmol per liter) for treated patients and 147 ± 22 mg per deciliter (3.80 ± 0.57 mmol per liter) for untreated patients ($P < 0.001$). The average change in the calcium-volume score for the treated group was an increase of 5 ± 28 percent, as compared with 52 ± 36 percent for untreated patients ($P < 0.001$). All untreated patients had an increase in score. We found no differences in the degree of change in the calcium-volume score over time between men and women, although the numbers may have been too small to demonstrate a sex difference.

All patients with a net decrease in the score were treated patients with average LDL cholesterol levels of less than 120 mg per deciliter. Starting from this observation, we proceeded to analyze our data for changes in the mean calcium-volume scores in the three groups of patients. Figure 2 shows a plot of the percent change in the calcium-volume score at one year in relation to the average LDL cholesterol level for patients treated with HMG-CoA reductase inhibitors (groups 2 and 3). In this analysis the regression was significant (both the constant and the slope coefficient were significantly different from zero, $P < 0.001$) and showed a good linear relation ($r = 0.5$). In a similar regression analysis conducted for the untreated patients, the relation was not linear. Residual analysis supported the basic assumptions of this regression model.

Patients with Average LDL Cholesterol Levels of at Least 120 mg per Deciliter

In the 44 untreated patients (group 1), the average LDL cholesterol level was 147 ± 22 mg per deciliter, and in the 40 treated patients whose LDL cholesterol levels remained at least 120 mg per deciliter (group 2), the average LDL cholesterol level was 139 ± 18 mg per deciliter (3.59 ± 0.47 mmol per liter). In both groups there was a significant increase in the calcium-volume score (Fig. 3). In group 1 the mean calcium-volume score was 479 ± 629 at base line and 646 ± 762 at follow-up; the mean increase per patient was 167 ± 179 ($P < 0.001$). In group 2 the mean calcium-volume score was 1017 ± 2062 at base line and 1254 ± 2483 at follow-up; the mean increase per pa-

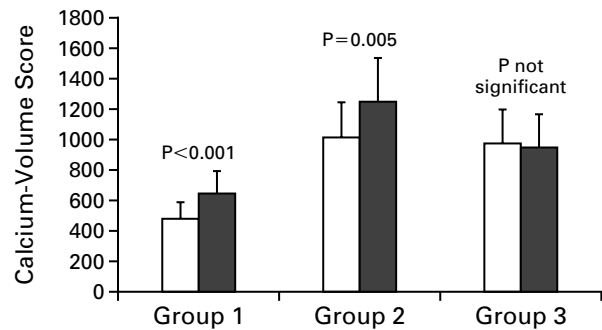


Figure 3. Initial Values (Open Bars) and Final Values (Solid Bars) for the Calcium-Volume Score in Relation to the Average LDL Cholesterol Level and Treatment Status.

Patients in group 1 were not treated with HMG-CoA reductase inhibitors; patients in group 2 were treated and had average LDL cholesterol levels of at least 120 mg per deciliter; patients in group 3 were treated and had average LDL cholesterol levels below 120 mg per deciliter. P values are for comparisons of initial and final values within groups.

tient was 237 ± 502 ($P = 0.005$). The mean percent changes in calcium-volume score were 52 ± 36 percent in group 1 and 25 ± 22 percent in group 2 ($P < 0.001$ for the difference in change between the groups). Thus, the percent increase in the calcium-volume score was significantly greater in untreated patients than in treated patients whose average LDL cholesterol levels were 120 mg per deciliter or more.

Patients with Average LDL Cholesterol Levels below 120 mg per Deciliter

Among the 65 treated patients in group 3, the average LDL cholesterol level was 100 ± 17 mg per deciliter (2.59 ± 0.44 mmol per liter). The average calcium-volume score in this group was 980 ± 1611 at base line and 956 ± 1700 at follow-up; the average change per patient was a decrease of 23 ± 261 (P not significant). The mean relative change in the calcium-volume score was a significant decrease of 7 ± 23 percent ($P = 0.01$). Sixty-three percent of the patients in this group had a net decrease in the calcium-volume score, but the remaining 37 percent had a net increase, despite medical treatment. On the other hand, no patient in either group 1 or 2 had regression of disease. Thus, patients whose LDL cholesterol levels had been reduced to below 120 mg per deciliter were much more likely to have a decreased calcium-volume score than patients who had received no treatment or whose LDL cholesterol levels had remained at or above 120 mg per deciliter despite treatment ($P < 0.001$ for the two-sample test for the proportion in group 3 vs. the proportions in groups 1 and 2). Among patients whose calcium-volume scores decreased, the mean percent change in score was -21 ± 17 percent and the median change was -17 percent.

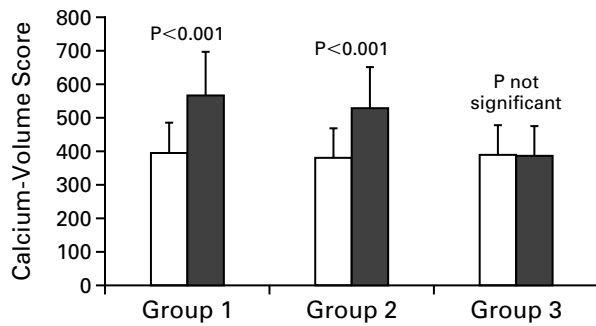


Figure 4. Initial Values (Open Bars) and Final Values (Solid Bars) for the Calcium-Volume Score in Patients Matched for Initial Score in Relation to the Average LDL Cholesterol Level and Treatment Status.

Patients in group 1 were not treated with HMG-CoA reductase inhibitors; patients in group 2 were treated and had average LDL cholesterol levels of at least 120 mg per deciliter; patients in group 3 were treated and had average LDL cholesterol levels below 120 mg per deciliter. P values are for comparisons of initial and final values within groups.

Matching of Patients

The average base-line calcium-volume score of the untreated patients was considerably lower than that of the patients in the two treated groups (Fig. 3). Because of concern that this difference might have affected the rates of change in the absolute score over time, we matched 24 patients from each group who had similar initial calcium-volume scores (within 15 percent) and assessed the percent change in the score between base line and follow-up (Fig. 4). The mean changes were $+57 \pm 37$ percent for group 1, $+26 \pm 23$ percent for group 2, and -2 ± 22 percent for group 3 ($P < 0.001$ by one-way analysis of variance for the overall comparison of the mean percent changes). These results were similar to the overall results of the comparison of the three groups. An analysis of covariance, in which the initial score was taken as the covariate, confirmed the results for matched pairs (mean changes, $+52 \pm 28$ percent for group 1, $+25 \pm 29$ percent for group 2, and -7 ± 30 percent for group 3; $P < 0.001$ for all comparisons). Thus, the initial calcium-volume score had no influence on the rate of growth of calcified plaques.

Further subgroup analysis addressed the interesting question of whether HMG-CoA reductase inhibitors have an effect on the evolution of atherosclerotic coronary artery disease beyond their ability to reduce absolute levels of LDL cholesterol. In this analysis, we matched 28 patients each from the treated and untreated groups with similar average levels (within 3 percent) of LDL cholesterol. The mean LDL cholesterol levels were 141 mg per deciliter (3.66 mmol per liter) for the treated group and 140 mg per deciliter (3.62 mmol per liter) for the untreated group; the median was 140 mg per deciliter

for both groups. The calcium-volume score increased by a mean of 50 ± 37 percent in the untreated group and 26 ± 22 percent in the treated group ($P < 0.001$). This difference represented a 48 percent lower rate of increase in the calcium-volume score for treated as compared with untreated patients, although both groups of patients had similar final LDL cholesterol levels. In an analysis of covariance conducted to ensure that the observed difference in the percent increase in calcium-volume score had not been influenced by the initial difference in calcium-volume score, the reduction in the rate of increase was 45 percent, which was still significant ($P < 0.05$).

DISCUSSION

In this retrospective study we demonstrated that treatment with HMG-CoA reductase inhibitors can reduce the volume of calcified plaque in the coronary arteries and that these changes can be quantified reliably and noninvasively by electron-beam CT.

To date, studies of the regression of coronary artery disease have used quantitative coronary angiography and have required a follow-up of several years to demonstrate small reductions in luminal stenosis.³⁻¹⁰ Angiographic studies are invasive, costly, and time consuming. Although these techniques permit the assessment of disease regression at the level of measurable focal stenoses, they do not provide information on the effects of therapy on the total burden of coronary-artery plaque. Furthermore, the arterial remodeling that is known to occur in vessels affected by an atherosclerotic process is very likely to affect the reliability of serial angiographic studies of luminal stenosis after medical interventions.³²⁻³⁴ In contrast, electron-beam CT is a rapid, noninvasive method that can be used to study the entire coronary-artery tree, and it is considerably less expensive than angiography.

It is now recognized that deposition of calcium in the coronary arteries is an active process that may be a response to damage caused by several types of noxious stimuli.³⁵ Furthermore, there is a direct correlation between the extent of coronary calcification and the total burden of atherosclerotic plaque.^{16,18,19} Schmermund et al. have recently shown that electron-beam CT is similar to coronary angiography in measuring the effects of several known risk factors on coronary atherosclerosis.³⁶ These findings suggest that it may be appropriate to use this new technique to assess the extent of disease and the benefits of therapy.

Our analysis showed that the rate of change in the volume of calcified coronary plaque, as determined by electron-beam CT, was significantly lower in treated than in untreated patients. Furthermore, this difference appeared to be related to the level of LDL cholesterol after treatment. Our study also demon-

strated that follow-up times can be much shorter with this technique than when angiography is used to assess the effects of medical therapy on atherosclerotic disease.

Stabilization of and decreases in plaque volume were found to begin at an LDL cholesterol level of less than 120 mg per deciliter. However, lipid-lowering therapy was effective in slowing increases in plaque volume at any level of LDL cholesterol. Treated patients in whom LDL cholesterol levels failed to drop below 120 mg per deciliter still had a slower progression of disease than untreated patients — even among patients matched with respect to the average LDL cholesterol level. This finding indicates that treatment at any level may produce a substantial slowing of the natural growth of coronary-artery plaque. In an analysis of data from the West of Scotland Coronary Prevention Study, outcomes were compared between patients in the treatment group and those in the placebo group who had the same final LDL cholesterol level.³⁷ Patients in the placebo group had a higher rate of coronary events than the pravastatin-treated patients. These intriguing observations appear to confirm that even when not used aggressively, therapy with HMG-CoA reductase inhibitors may beneficially influence the course of coronary artery disease.

Thirty-seven percent of treated patients who had average LDL cholesterol levels below 120 mg per deciliter had increases in plaque volume despite adequate therapy. This supports the hypothesis that other factors besides LDL cholesterol are involved in the progression of atherosclerotic disease. Some lipoproteins that are unaffected or only slightly affected by treatment with HMG-CoA reductase inhibitors, such as small, dense LDLs, Lp(a), and intermediate-density lipoproteins, or the presence of a low level of high-density lipoprotein cholesterol may contribute to the progression of the disease.³⁸⁻⁴⁰ Furthermore, factors other than lipoprotein, such as homocysteine, fibrinogen, C-reactive protein, and various infectious agents, may also play an important part in the initiation and continued progression of atherosclerosis.^{38,41-50} Future studies of the regression of coronary artery disease in patients treated with lipid-lowering agents will continue to investigate the contribution of all such factors.

Patients who did not receive treatment with HMG-CoA reductase inhibitors had lower initial calcium-volume scores than treated patients. This difference may have been due to physicians' bias toward treating patients with higher scores because of an assumption that a smaller amount of coronary calcification indicates less important atherosclerotic disease. However, since untreated patients uniformly had a more rapid, uninterrupted increase in plaque volume, such an assumption may not have been justified.

Limitations of the Study

Since various HMG-CoA reductase inhibitors were used at different doses, treatment could have had diverse effects on the progression of calcium-volume scores. An LDL cholesterol level of 120 mg per deciliter was arbitrarily selected as a cutoff point for analysis of change in calcium-volume scores, and it does not necessarily constitute a reference level for future studies. During the follow-up period, we did not assess the effect of the modification of any risk factor for coronary artery disease other than LDL cholesterol, although the base-line characteristics were similar in all groups of patients. Finally, this was a pilot study with the limitations inherent in a small sample.

Clinical Implications

Our study, like many others, has shown that HMG-CoA reductase inhibitors have beneficial effects on the natural course of coronary artery disease and that with adequate technique, electron-beam CT is an accurate method of documenting the evolution of calcified coronary plaque. The accuracy of this technique is such that even short-term follow-up may be sufficient to indicate the direction of the effect of treatment on the disease. The use of electron-beam CT as a diagnostic tool in preventive cardiology may make possible a new form of secondary prevention directed at asymptomatic patients with coronary calcifications.

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