

Influence of Lipid-Lowering Therapy on the Progression of Coronary Artery Calcification

A Prospective Evaluation

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Background—Coronary calcification measured by fast computed tomography techniques is a surrogate marker of coronary atherosclerotic plaque burden. In a cohort study, we prospectively investigated whether lipid-lowering therapy with a cholesterol synthesis enzyme inhibitor reduces the progression of coronary calcification.

Methods and Results—In 66 patients with coronary calcifications in electron beam tomography (EBT), LDL cholesterol >130 mg/dL, and no lipid-lowering treatment, the EBT scan was repeated after a mean interval of 14 months and treatment with cerivastatin was initiated (0.3 mg/d). After 12 months of treatment, a third EBT scan was performed. Coronary calcifications were quantified using a volumetric score. Cerivastatin therapy lowered the mean LDL cholesterol level from 164 ± 30 to 107 ± 21 mg/dL. The median calcified volume was 155 mm^3 (range, 15 to 1849) at baseline, 201 mm^3 (19 to 2486) after 14 months without treatment, and 203 mm^3 (15 to 2569) after 12 months of cerivastatin treatment. The median annualized absolute increase in coronary calcium was 25 mm^3 during the untreated versus 11 mm^3 during the treatment period ($P=0.01$). The median annual relative increase in coronary calcium was 25% during the untreated versus 8.8% during the treatment period ($P<0.0001$). In 32 patients with an LDL cholesterol level <100 mg/dL under treatment, the median relative change was 27% during the untreated versus -3.4% during the treatment period ($P=0.0001$).

Conclusions—Treatment with the cholesterol synthesis enzyme inhibitor cerivastatin significantly reduces coronary calcium progression in patients with LDL cholesterol >130 mg/dL. (*Circulation*. 2002;106:1077-1082.)

Key Words: coronary disease ■ calcium ■ arteriosclerosis ■ lipids

Coronary calcifications are associated with atherosclerotic coronary artery plaque,¹⁻³ and the amount of coronary calcifications has been shown to correlate with the overall coronary plaque burden.⁴⁻⁶ The presence and extent of coronary calcifications can be assessed noninvasively using fast CT techniques, such as electron beam tomography (EBT)^{7,8} or multislice CT.^{9,10} Several investigations have shown that the quantity of coronary calcium measured by CT progresses over time.^{9,11-15} Consistently, an increase in coronary calcium progression with increasing baseline calcium scores has been observed.^{9,14,15} In the only investigation that included asymptomatic, randomly selected individuals, Maher et al¹¹ observed a 24% mean annual increase in the amount of coronary calcification when quantified using the Agatston score.

In their recent analysis, Schmermund et al¹⁴ observed a moderate relationship between LDL cholesterol levels and

the degree of progression of coronary calcification, whereas two other groups have observed an association of lipid-lowering treatment and the rate of calcium progression in retrospective analyses.^{12,13} So far, however, no prospective investigation has been published that could prove an effect of lipid-lowering drug treatment on the progression of coronary calcifications. We therefore conducted a cohort study that prospectively compared the rate of change in the amount of coronary calcification before and during lipid-lowering therapy with the cholesterol synthesis enzyme inhibitor cerivastatin.

Methods

Patients

From a database of patients who had received an EBT scan for assessment of coronary calcifications in one of the two study centers, all patients were identified who met the following criteria: time

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interval of at least 12 months since the EBT scan with a documented Agatston score of at least 20, no known coronary artery disease or symptoms suggestive of disease, LDL cholesterol of at least 130 mg/dL at the time of the EBT scan, presence of sinus rhythm, and normal renal function. All of these patients who lived within a reasonable distance from the participating centers were contacted by telephone, and if they denied having received any lipid-lowering therapy during the time interval since the original EBT scan and continued to meet the inclusion criteria, they were invited to schedule a follow-up EBT examination and take part in the investigation.

The study was terminated in August 2001 because of the withdrawal of cerivastatin from the German market. By then, 86 patients had been included in the protocol, but only 66 patients (59 men, 7 women; mean age, 61 years; range, 36 to 79 years) had completed the study (see Results).

The study protocol was approved by the institutional review boards, and all patients gave informed consent to participation in the investigation.

Electron Beam Tomography

All EBT scans were performed using C-150XP electron beam tomography scanners (GE/Imatron Inc) according to a standard protocol.⁷ Using the scanner's high-resolution single-slice mode with 3-mm slice thickness and an acquisition time of 100 ms per image, 40 consecutive axial cross-sections of the heart were acquired in inspiratory breath-hold, triggered to the ECG at 80% of the R-R interval.

To assess the amount and quantity of coronary calcifications, EBT images were transferred to an offline workstation (NetraMD, ScImage). One single investigator evaluated all EBT scans in a blinded fashion. While the EBT data sets were grouped by patient, the sequence of the three scans was randomized and the operator was unaware of the study identification numbers and dates. Semiautomated software was used that automatically identified all pixels with a CT density of 130 HU or more and determined the quantity of coronary calcification after the preidentified lesions were manually assigned to the different coronary arteries. Three measures of coronary calcium were used in the study. Primary measure was a volume score, which was determined after isotropic interpolation to minimize partial volume effects^{16,17} and yields the calcified volume within the coronary arteries in mm³; secondary measures were the Agatston score, the calculation of which is based on the area and peak density of the calcified lesions,⁷ and a mass score, which was obtained by multiplying the calcified volume by the volumetrically averaged CT density of the calcified lesions.

Study Protocol

The mean interval from the first to the second EBT scan was 421 ± 72 days (504 to 348 days). At the time of the second EBT scan, fasting lipid values as well as liver enzymes, serum creatinine, and creatine kinase were measured and lipid-lowering therapy with cerivastatin (Lipobay, Bayer Vital AG) at a fixed dose of 0.3 mg/d was initiated. Patients were instructed to keep any other medical therapy un-

changed. Follow-up visits after 6 weeks, 3 months, and 6 months were arranged, during which patients were questioned regarding cardiovascular events and medication side effects, blood tests were repeated, and new medication was handed out. After 1 year of treatment (mean interval, 370 ± 9 days), a third EBT scan was performed and blood tests were repeated. At every EBT visit, the patient's blood pressure and body weight were taken and smoking status, physical activity, and dietary habits were recorded using a standardized questionnaire.

Data Analysis

The changes in the amount of coronary calcification during the first, untreated period were assessed by subtracting the values measured in the first EBT scan from those measured in the second EBT scan, dividing the difference by the actual number of days that passed between scan 1 and scan 2 and multiplying this fraction by 365 (annualized change). The percent change was obtained by dividing the annualized absolute change by the amount of the first scan (annualized percent change). Changes in the second (treatment) year were determined in an analogous fashion.

To statistically analyze the differences between the first (untreated) and the second (treatment) time period, the Wilcoxon matched-pairs signed-ranks test was used. $P < 0.05$ was considered to represent a significant difference.

Results

Clinical Follow-Up

Of the 86 patients who were initially included in the study, 20 patients did not complete follow-up through the third EBT scan. In 14 patients, treatment was interrupted after a mean interval of 7 months (3 to 10 months) because of the withdrawal of cerivastatin from the German market and consequent premature termination of the study. Six other patients did not complete the study for other reasons. In 3 patients, cerivastatin treatment was terminated because they did not tolerate the medication due to muscular pain, and one patient chose to stop taking the medication when the CK level rose to 205 U/L after 6 months of treatment. Two other patients refused to return for the third EBT scan without indicating specific reasons or medication side effects. Thus, a total of 66 patients completed the protocol and could be evaluated.

Overall, a CK level above the upper normal value (80 U/L) was observed in 17 patients. However, in these patients, the mean CK level was only 117 U/L, and the highest measured level was 307 U/L. Elevated liver enzymes were not observed in any patient.

There were 5 active smokers among the 66 patients who completed the study, and no patient changed his or her

TABLE 1. Fasting Serum Lipid Levels Before Initiation of Cerivastatin Treatment* and During Treatment With Cerivastatin† at a Fixed Dose of 0.3 mg/d in 66 Patients

	Before Treatment, mg/dL	During Treatment, mg/dL	Reduction, %	P
Total cholesterol	244 ± 32	188 ± 28	-23	<0.0001
LDL cholesterol	164 ± 30	107 ± 21	-35	<0.0001
HDL cholesterol	51 ± 12	52 ± 12	+1.7	0.3
Triglycerides	184 ± 106	152 ± 68	-17	0.004

*Mean values measured at first and second EBT.

†Mean values measured during the 4 follow-up visits at 6 weeks, 3 months, 6 months, and 12 months.



Figure 1. Axial cross-sections (3-mm slice thickness) obtained by electron beam tomography in a 63-year-old patient at baseline (A), after 12 months without lipid-lowering treatment (B), and after 12 months of treatment with cerivastatin. The images show calcifications in the bifurcation of the left main coronary artery (arrow) and proximal left anterior descending coronary artery (arrowhead). Although an obvious increase can be seen from the first to the second EBT scan, there is only a slight increase from the second to the third EBT scan. Total volume score in EBT scan 1, 1143 mm³; in scan 2, 1488 mm³; and in scan 3, 1511 mm³.

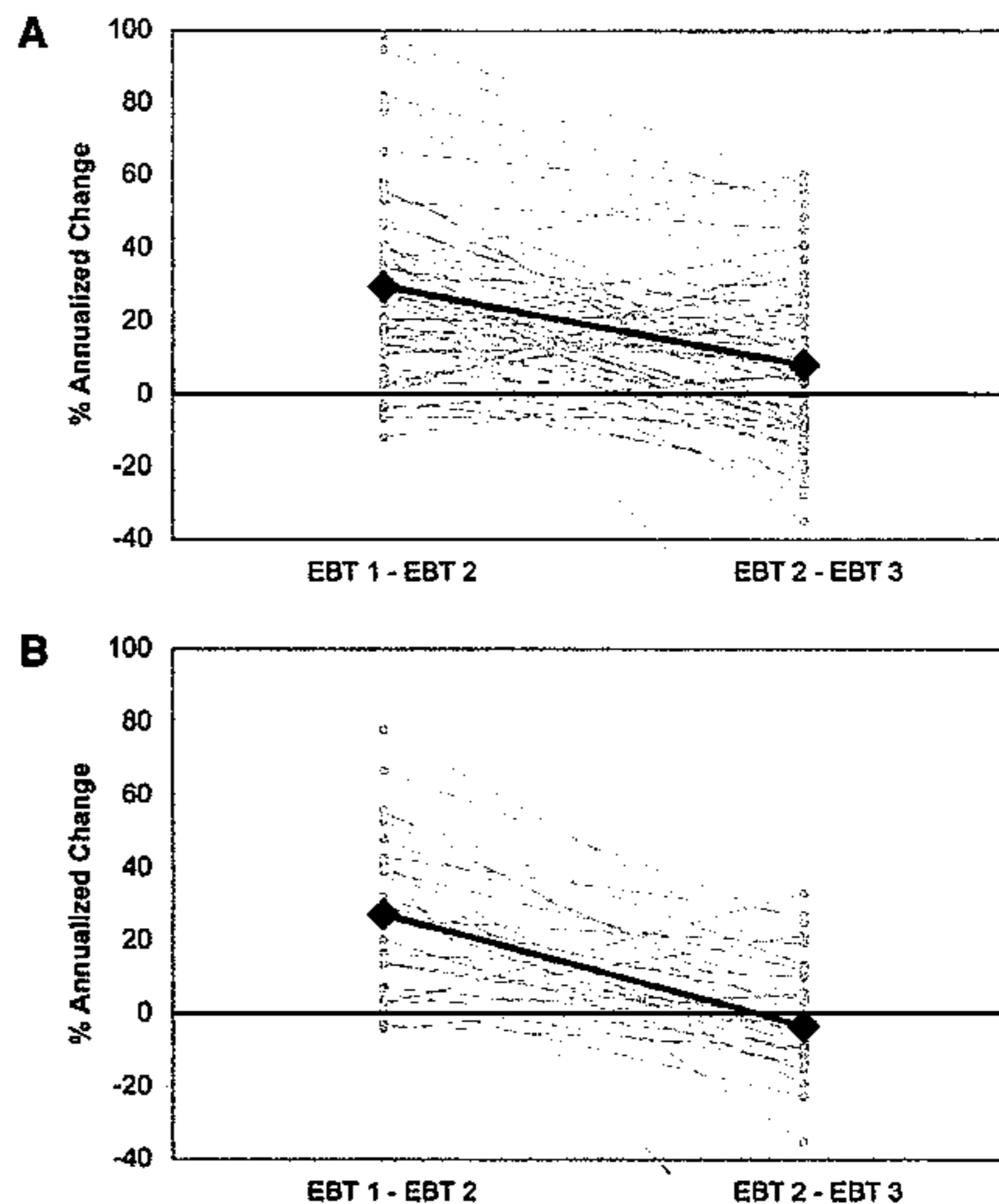


Figure 2. A, Annualized relative change of the volume score during the untreated period (EBT 1 to EBT 2) and during the treatment period (EBT 2 to EBT 3) for all 66 patients. Despite considerable interindividual variation, the median annualized relative change (diamonds, bold line) was significantly higher in the untreated interval compared with the treatment interval (25% vs 8.8%, $P < 0.0001$). B, Annualized relative change of the volume score in 32 patients who achieved an LDL cholesterol level of < 100 mg/dL under treatment with cerivastatin. The median annualized change (diamonds, bold line) decreased from 27% to -3.4% ($P = 0.0001$).

smoking habits during the study. The mean body weight was 85.3 kg at the first visit, 85.1 kg at the second visit, and 85.3 kg at the third visit. Twenty-six patients were taking antihypertensive medication at the first visit, 29 at the second, and 28 at the third. Mean systolic and diastolic blood pressures were 134/85 mm Hg, 132/85 mm Hg, and 135/85 mm Hg, respectively. Similarly, there were no changes in physical activity scores and dietary habits. One patient experienced an acute myocardial infarction during the treatment period (he was maintained in the study), and no other cardiac events were observed.

Table 1 lists the mean serum lipid values before and during treatment with cerivastatin (mean values of blood samples obtained before initiation of treatment and during the follow-up visits after treatment was initiated). The average total cholesterol and LDL cholesterol levels in the untreated period were 244 ± 32 mg/dL and 164 ± 30 mg/dL, respectively. A mean reduction of 23% (total cholesterol) and 35% (LDL cholesterol) was achieved by cerivastatin treatment. HDL levels increased slightly by 1.7%, and triglyceride levels fell by 17%.

Coronary Calcification

Progression of coronary calcification was significantly less pronounced during treatment with cerivastatin compared with

TABLE 2. Absolute and Relative Annualized Changes in the Quantity of Coronary Artery Calcification Expressed Through the Volume Score (in mm³), Agatston Score, and Mass Score (Without Units) During the Untreated and Treatment Period

	Annualized Change (Median Values)			
	Untreated Period		Treatment Period	
	Absolute	Relative, %	Absolute	Relative, %
All patients (n=66)				
Volume score	25 mm ³	25	11 mm ³	8.8
Agatston score	28	25	20	11
Mass score	6832	24	4658	11
Patients with LDL cholesterol <100 mg/dL during treatment (n=32)				
Volume score	26 mm ³	27	-2.1 mm ³	-3.4
Agatston score	42	28	0.9	0
Mass score	9647	25	2302	5.1

All values are medians.

the period before treatment was initiated (see Figure 1). The median volume of coronary calcification in the initial EBT scan was 155 mm³ (range, 14 to 1849 mm³). The median volume score in the second EBT scan, after an average interval of 421 days without lipid-lowering treatment, was 201 mm³ (range, 19 to 2486 mm³), and the median volume score in the third EBT scan, after an average interval of 370 days on treatment with cerivastatin, was 203 mm³, with a range from 15 to 2569 mm³. The median annualized absolute increase in calcified volume was 25 mm³ (range, -79 to 506) without treatment compared with 11 mm³ (range, -462 to 247) during treatment ($P=0.01$). The median relative annual increase was 25% without treatment and 8.8% during treatment ($P=0.0001$, see Figure 2 and Table 2).

A decrease in the amount of coronary calcium progression during the treatment period was also observed when other methods for quantification of coronary calcium were evaluated (see Figure 3). The median Agatston score increased from 165 (20.1 to 2239) to 199 (23.6 to 3118) in the untreated period and to 234 (21.6 to 3124) after 12 months of treatment, with a median annualized absolute increase of 28 score units without treatment compared with 20 score units during

treatment ($P=0.07$) and a median annualized relative increase of 25% before and 11% after initiation of cerivastatin treatment ($P=0.002$). The median calcium mass score was 32 785 (2839 to 417 874) at the first EBT scan, 43 812 (2925 to 571 780) at the second scan, and 46 800 (2978 to 606 284) at the third scan. A median annualized increase of 6832 in the untreated period and 4658 during the treatment period was found ($P=0.02$). The median annualized relative change decreased from 24% to 11% after treatment was initiated ($P=0.0009$).

In 32 patients, the mean LDL cholesterol measured at the follow-up visits during cerivastatin treatment was below 100 mg/dL (mean, 149±17 mg/dL before and 89±9 mg/dL during treatment). In these patients, the median annualized change of the calcified volume was 27% without treatment compared with -3.4% during treatment ($P=0.0001$). Similarly, the median relative changes were 28% versus 0% for the Agatston score ($P=0.0008$) and 25% versus 5.1% for the mass score ($P=0.0008$, see Table 2).

Discussion

We investigated the effect of lipid-lowering therapy with the cholesterol synthesis inhibitor cerivastatin on the progression of coronary calcifications measured by EBT in patients with a baseline LDL cholesterol level of at least 130 mg/dL. Using a volumetric quantification algorithm, we found that lipid-lowering therapy significantly decreased the progression of the amount of coronary calcifications from 25% per year before treatment was initiated to a mean value of 8.8% per year during treatment with cerivastatin. Similar changes were observed when other algorithms for the quantification of coronary calcification were used, such as the traditionally used Agatston score (decrease from 25% to 11%) and a mass score, which takes into account both the volume and CT density of calcified lesions (decrease from 24% to 11%). In 32 patients who achieved a mean LDL cholesterol level <100 mg/dL during the treatment period (mean, 89 mg/dL), the progression of coronary calcification, on average, could be

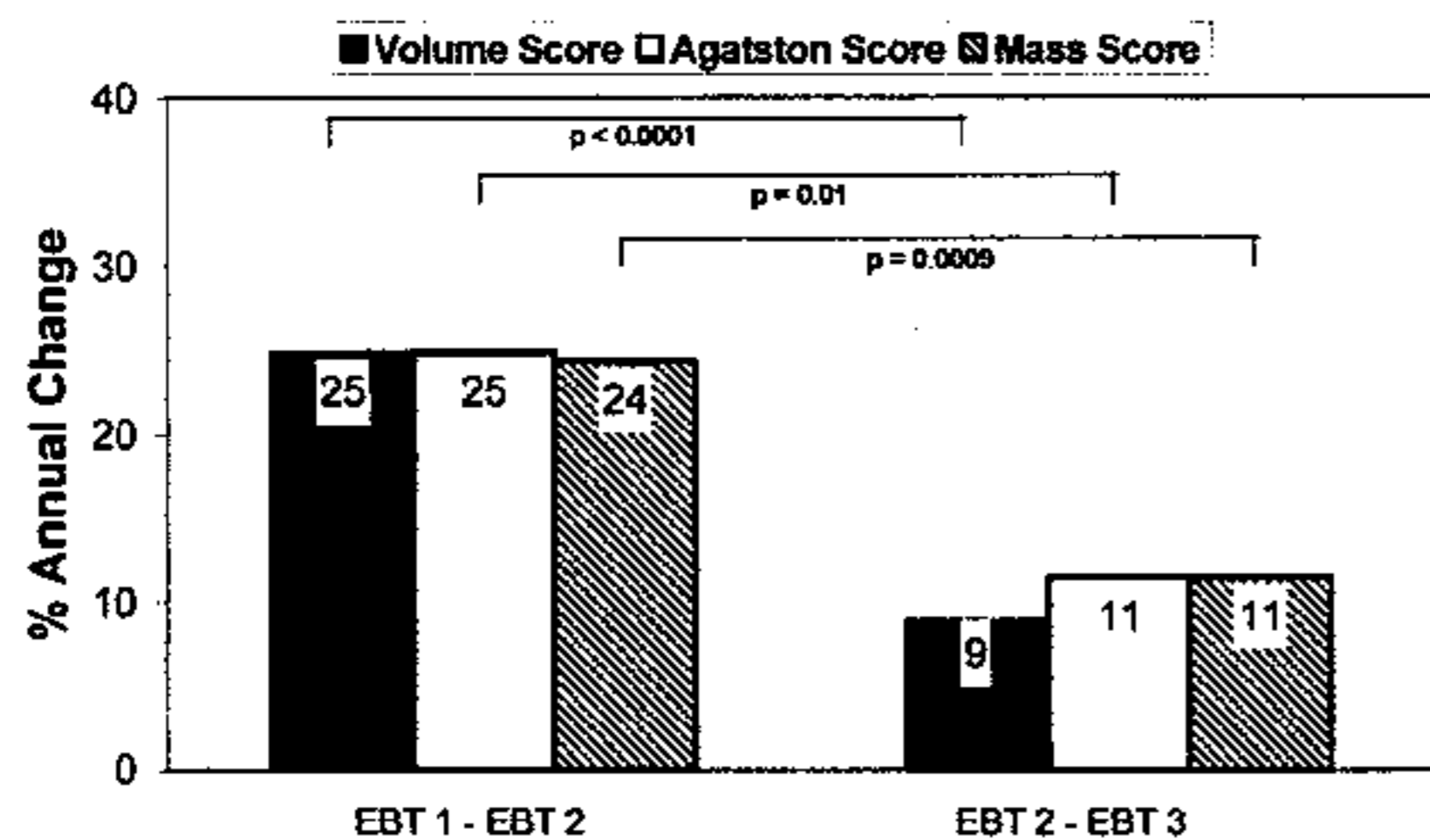


Figure 3. Median annualized relative increase in volume score, Agatston score, and mass score during the untreated period (EBT 1 to EBT 2) and the treatment period (EBT 2 to EBT 3). For all scores, a significant difference was observed.

stopped. The median annualized change of the calcified volume observed during the treatment period was -3.4% .

Although several previous reports investigated the progression of coronary calcifications^{8,9,11-15} and 2 of these studies retrospectively identified lipid-lowering treatment to be associated with reduced progression of coronary calcifications,^{12,13} our investigation is the first report that prospectively investigated the influence of lipid-lowering therapy on coronary calcium progression.

The mean changes in coronary calcium burden demonstrated a significant effect of lipid-lowering treatment after only 1 year of therapy. However, a large interindividual variation was observed. Most of this is probably explained by the variability of coronary calcification quantification by EBT.¹⁸ Other factors may have influenced the dynamics of the coronary atherosclerotic process and progression of coronary calcium, such as homocysteine levels¹⁹ or systemic inflammatory activity,^{20,21} but this was not measured in our study. Also, patients were asked not to change their concomitant medication, but effects mediated by calcium channel blockers,²² ACE inhibitors,^{23,24} or other drugs cannot be completely ruled out.

In 7 patients, regression of the volume score was observed during the untreated period, and in 24 patients, a decrease of the volume score was observed during treatment with cerivastatin. Based on dual EBT scans in 1376 individuals, Bielak et al¹⁸ published 95% limits of agreement for the calcified area, depending on the overall amount of calcification. None of the 7 patients who displayed a regression of the calcium score in the untreated period and only 3 of 24 patients with a decrease of the volume score during the treatment period showed score changes that were larger than the reported 95% confidence margins. Even though the variability data published for the calcified area may not be directly transferred to the volume score we used in our investigation, it seems reasonable to assume that regression of calcium scores in our study was attributable to scan variability. Negative changes should probably not be considered evidence of an actual decrease of coronary calcium content. Animal studies have reported conflicting data as to whether calcium deposits in coronary atherosclerotic plaques may actually regress under long-term lipid-lowering therapy.²⁵⁻²⁸

Our study has several limitations. Even though recent studies have shown that ECG triggering at 80% of the R-R interval may result in higher interscan variability than triggering at an earlier cardiac phase,²⁹ we used 80% triggering throughout our study, because that was the standard when we performed our initial EBT scans and we could not change acquisition parameters during the course of the investigation. Also, on request, most patients were informed about their calcification scores, and it is conceivable that patients modified their lifestyle after being aware of an increase in coronary calcium during the untreated period. However, objective measures such as body weight showed no change during the study period. Furthermore, treatment was open-label and not placebo-controlled. The progression of coronary calcium was not compared in 2 simultaneous groups, but in 2 consecutive time periods. It therefore seems theoretically possible that the lower increase in the amount of coronary

calcification during the second (treatment) year represents a spontaneous decline and not a treatment effect. However, cerivastatin treatment not only resulted in a significant decrease in the relative change but also a significant decrease of the annualized absolute change in the amount of coronary calcium (25 mm^3 in the untreated versus 11 mm^3 in the treatment period). This is unexplained by the natural course, because 3 previous studies performed by EBT^{9,14,15} that investigated the progression of coronary calcification and its relationship to the baseline amount of calcium reported a significantly larger absolute increase in patients with higher coronary calcification scores at baseline.

It is unclear how changes in coronary calcification achieved by lipid-lowering therapy translate to changes in coronary atherosclerotic plaque volume and composition. Plaque calcification is known to be an actively regulated process,³⁰⁻³² and changes in coronary calcification therefore may be assumed to permit conclusions as to the activity of the atherosclerotic process. Quantification of coronary calcification by fast CT techniques therefore seems a promising tool for the assessment of coronary atherosclerosis progression, but the relationship between changes in the amount of coronary calcification and changes in overall plaque burden and plaque vulnerability deserves additional investigation.

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