Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Progression of Coronary Artery Calcium and Risk of First Myocardial Infarction in Patients Receiving Cholesterol-Lowering Therapy

Paolo Raggi, Tracy Q. Callister and Leslee J. Shaw

Arterioscler Thromb Vasc Biol. 2004;24:1272-1277; originally published online April 1, 2004;
doi: 10.1161/01.ATV.0000127024.40516.ef
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636

Progression of Coronary Artery Calcium and Risk of First Myocardial Infarction in Patients Receiving Cholesterol-Lowering Therapy

Paolo Raggi, Tracy Q. Callister, Leslee J. Shaw,

Objective—Statins reduce cardiovascular risk and slow progression of coronary artery calcium (CAC). We investigated whether CAC progression and low-density lipoprotein (LDL) reduction have a complementary prognostic impact.

Methods and Results—We measured the change in CAC in 495 asymptomatic subjects submitted to sequential electron-beam tomography (EBT) scanning. Statins were started after the initial EBT scan. Myocardial infarction (MI) was recorded in 41 subjects during a follow-up of 3.2±0.7 years. Mean LDL level did not differ between groups (118±25 mg/dL versus 122±30 mg/dL, MI versus no MI). On average, MI subjects demonstrated a CAC change of 42%±23% yearly; event-free subjects showed a 17%±25% yearly change ($P=0.0001$). Relative risk of having an MI in the presence of CAC progression was 17.2-fold (95% CI: 4.1 to 71.2) higher than without CAC progression ($P<0.0001$). In a Cox proportional hazard model, the follow-up score ($P=0.034$) as well as a score change >15% per year ($P<0.001$) were independent predictors of time to MI.

Conclusions—Progression of CAC was significantly greater in patients receiving statins who had an MI compared with event-free subjects despite similar LDL control. Continued expansion of CAC may indicate failure of some patients to benefit from statin therapy and an increased risk of having cardiovascular events. **(*Arterioscler Thromb Vasc Biol.* 2004;24:1272-1277.)**

Key Words: atherosclerotic imaging ■ computed tomograph ■ prognosis ■ low-density lipoprotein cholesterol

Therapy with HMG-CoA reductase inhibitors (statins) has proven extremely useful in reducing cardiovascular morbidity and mortality in primary and secondary prevention.[1–6] Despite the proven effectiveness of statins in reducing total and low-density lipoprotein (LDL) cholesterol, several patients will still have an event while receiving these drugs. Hence, important questions remain as to identification of subjects at risk despite statin treatment and to the mechanisms underlying this apparent treatment failure. It has previously been shown that serial electron beam tomography (EBT) scanning can be used to follow-up the progression of coronary artery calcium (CAC), and that progression of CAC is slowed with aggressive lipid-lowering therapy.[7–9] Nonetheless, it remains to be proven that slowing of the coronary artery calcification process will translate into a reduced risk of events as previously demonstrated with regression of luminal stenosis in angiographic trials.[10–14] The ability of EBT to indirectly demonstrate changes in atherosclerotic plaque burden over time could provide some insight in the mechanisms by which statins prevent an event or fail to do so in treated individuals. Furthermore, the noninvasive nature of this and other similar tools could prove extremely helpful in the development and evaluation of effectiveness of novel treatment strategies for atherosclerosis. In this observational study, we assessed the temporal CAC change in individuals receiving treatment with statins who underwent sequential EBT scanning. The temporal CAC change of 41 patients who had either a fatal or a nonfatal myocardial infarction (MI) while on treatment was compared with that of a similar group of individuals who remained asymptomatic over time.

Methods

Patient Selection and Follow-Up Techniques

Patients enrolled in this cohort study included a nonconsecutive series of asymptomatic individuals seen in a clinical practice and were not part of a randomized and controlled clinical trail. All subjects were given treatment with HMG-CoA reductase inhibitors (statins) by their treating physicians *only after* the performance of the initial EBT scan. Hence, these data do not reflect the effect of a specific statin such as that noted in a previous small prospective clinical trial.[9] Repeat EBT imaging was performed after a median interval of 3 years (25th, 75th percentile: 2.8 to 3.6 years) to verify the progression of coronary calcification while using treatment. The inclusion criteria were presence of baseline coronary calcification with a score ≥ 30 and consent to undergo sequential EBT scanning. Exclusion criteria were intolerance to statins, previous history of coronary artery disease, coronary stent implantation, and coronary artery bypass surgery.

Received February 13, 2004; revision accepted March 18, 2004.

From Tulane University School of Medicine (P.R.), New Orleans, La; EBT Research Foundation (T.Q.C.), Nashville, Tenn; and Atlanta Cardiovascular Research Institute (L.J.S.), Atlanta, Ga.

Correspondence to Dr Paolo Raggi, 1430 Tulane Avenue, SL-48. New Orleans, LA 70112. E-mail praggi@tulane.edu

Arterioscler Thromb Vasc Biol. **is available at http://www.atvbaha.org** **DOI: 10.1161/01.ATV.0000127024.40516.ef**

As recommended in a previous publication,[15] a baseline calcium volume score ≥ 30 (see later for imaging method details) was required for inclusion in the study for 2 main reasons: (1) above this threshold, the variability of the quantitative scoring method is minimized; and (2) there is a smaller risk to overestimate a percentage change that might occur on the basis of a small initial score. In fact, a 10-unit increase over a baseline score of 10 would represent a 100% increase, whereas the same absolute increase above a baseline score of 35, for example, would only constitute ≈30% increase.

All subjects gave informed consent to undergo sequential EBT imaging and we obtained approval from our internal review board to review the medical records of these individuals by virtue of maintaining patient records confidentiality.

Data Collection for Historical Risk Factors

For the majority of patients, EBT screening was performed because of the presence of established risk factors for CAD. Information on risk factors was obtained by means of patient questionnaires and only categorical information was collected at the time of scanning. Hypertension was defined as known but untreated hypertension or current treatment with antihypertensive medications; current treatment with insulin or hypoglycemic agents or diet control were considered evidence of diabetic status; current smoking or smoking within 3 months before the first EBT scan were considered evidence of an active smoking status. Hypercholesterolemia was defined as known although untreated or treated hypercholesterolemia.

Intercurrent Statin Treatment

Because of the presence of CAC, all 495 patients were treated with a statin after the initial EBT screening test and were kept on this treatment in the interval between a minimum of 2 consecutive EBT scans. The mean on-treatment LDL cholesterol level was obtained from reviewing the medical record of each patient enlisted in the study and a mean value was calculated from averaging all test results obtained during the treatment period.

Follow-Up Methods

We reviewed the medical records of 495 individuals free of coronary artery disease referred by primary care physicians for EBT screening. Information regarding the occurrence of events was collected by means of phone interview with the study subjects or members of their families and was confirmed by review of pertinent medical records or by direct confirmation provided by the treating physician. All events considered in this analysis occurred after the performance of at least 2 sequential EBT scans.

Imaging Methods

EBT imaging was performed on a C-150 scanner (GE/Imatron) at 1 imaging site (Nashville, Tenn) and with the same hardware and software over time. All images were analyzed on a NetraMD workstation (ScImage). Thirty-six to 40 thin (3-mm), contiguous slices were obtained starting at the level of the carina and proceeding caudal to the level of the diaphragm. We used a prospective imaging technique with electrocardiographic triggering of the EBT gun at 60% to 80% of the R-to-R interval. A field of view of 30 cm^2 was used (pixel size: 0.586 mm) and a minimum of 3 pixels was necessary to identify a focus of calcification. All calcified areas with a density >130 Hounsfield units within the border of the coronary arteries were used for scoring. Calcium scoring was performed with a volumetric method (calcium volume score [CVS]) based on isotropic interpolation.[15] This method has previously been shown to have a greater interscan reproducibility and has been used in previous follow-up studies.[7,9] The EBT imaging parameters used for the initial study were carefully duplicated during the follow-up studies in each individual patient to ensure that the estimated CVS changes were not caused by a technical error rather than a true change. Images were reviewed independently by 2 experienced investigators (P.R. and T.Q.C.) and were carefully scrutinized for the presence of motion and scatter artifacts. Because the images were reviewed once and only by 1 investigator each time, no interobserver or intraobserver variability was calculated. However, given the previous experience of the 2 interpreting physicians, long-term cooperation, and the use of the same workstation and software, it is very likely that an interreader variability not >10% may have occurred.

Statistical Analysis

Annualized changes in calcium volume score are presented as absolute and percentage changes. Values are presented as median or mean±SD, unless otherwise specified. $P<0.05$ was considered statistically significant. Continuous variables were compared by means of unpaired and paired t testing or analysis of variance techniques. Categorical variables were compared by χ^2 statistic.

A minimum yearly CVS change of ≥ 15% or <15% was chosen to represent a true score change. This limit was chosen because it was shown to have a high specificity in a previous publication.[15] The average CVS progression of a historical group of 44 individuals not treated with statins was used to gauge the natural history of calcified coronary artery disease. As previously published,[7] the baseline characteristics and CVS scores of the controls were very similar to those of the patients in the current study. The CVS change demonstrated by the historical controls was then compared with the change occurred in the subjects comprised in the current study using meta-analytic techniques to compare the means between the 2 samples (Fastpro). No outcome data, however, were available for the historical controls.

Event rates and extent of CVS change were analyzed in the entire cohort and in subgroups of individuals identified according to the LDL level reached with statin treatment. Patients who reached an LDL level ≤ 100 mg/dL were considered to have been treated to goal according to recommendations on secondary prevention of cardiovascular disease.[16]

Multivariable models were used to identify the best predictors of CVS progression. Univariable and multivariable Cox proportional hazard models were used to assess time to first MI among several candidate variables, including CVS change as well as traditional cardiac risk factors including age. Relative risk ratio and 95% confidence intervals (95% CI) for the development of first MI were calculated from the Cox model in the subjects with CVS regression or stabilization and those with definite score progression. A first-order test for interaction of baseline LDL by CVS change was also calculated.

Results

Baseline Clinical Characteristics

The average patient age was 57±8 years (Table 1). Almost two-thirds of the subjects were men and had hypertension, whereas hyperlipidemia was reported by 76% of study subjects. The average baseline CVS was 327±363, which represents a moderate value. At baseline, 33% of the patients had a CVS ranging from 30 to 100, 39% had a score from 101 to 400, 20% had a score of 401 to 1000, and 8% had a score exceeding 1000. Although patients who had an MI tended to have a higher baseline CVS than event-free subjects, the difference was not statistically significant ($P=0.18$). All other clinical characteristics were similar between the 2 patient groups.

Change in Calcium Volume Score and Events

The mean interval between sequential EBT scans was 1.9±1 years for the entire cohort with a range of 1 to 6 years. The average interval from the time of the first EBT scan to the time of the follow-up contact with the individual patient or his/her assignee was 3.2±0.7 years. During follow-up, net regression of CVS was noted in 20% of the event-free individuals and in none of the patients having an MI.

TABLE 1. Clinical Characteristics of 495 Patients Submitted to Sequential EBT Scanning

	All Patients	Events	No Events
Age	57±8	57±7	58±8
Men (%)	311 (63)	29 (71)	282 (62)
Systemic hypertension (%)	281 (57)	22 (54)	259 (57)
Diabetes mellitus (%)	76 (15)	9 (22)	67 (15)
Smoking (%)	196 (40)	17 (41)	179 (39)
Hyperlipidemia (%)	375 (76)	31 (76)	344 (76)
Mean baseline CVS	327±363 (196)	440±478 (235)	317±349 (195)
Baseline CVS 30–100 (%)	155 (31)	10 (24)	145 (32)
Baseline CVS 101–400 (%)	206 (42)	15 (37)	191 (42)
Baseline CVS 401–1000 (%)	102 (21)	10 (24)	92 (20)
Baseline CVS >1000 (%)	32 (7)	6 (15)	26 (6)
On-treatment LDL-c	122±30 (120)	118±25 (117)	122±30 (120)

CVS indicates calcium volume score; SD, standard deviation; LDL-c, low-density lipoprotein cholesterol.

All comparisons between patients with events and event-free subjects were nonsignificant.

Values are expressed as mean±SD; median and percentages are in parentheses.

However, 2 (5%) MI patients had a minimal increase in CVS (<15%/year), as opposed to 244 (54%) of the event-free survivors ($P=0.0001$). In a multivariable model, the best predictors of a yearly CVS increase ≥15% were smoking ($P=0.032$), male gender ($P=0.014$), and baseline CVS ($P=0.002$).

Overall, 41 MIs were recorded in 29 men and 12 women (Table 1). The mean absolute CVS change was 131±130 in patients who had an MI and 44±77 in subjects free of events ($P<0.0001$). Similarly, the mean percentage CVS change in the 41 patients who had an MI was significantly greater than that of the 454 subjects free of events (42%±23% versus 17%±25%, $P<0.0001$). For comparison, the mean relative yearly increase in CVS in historical controls, not treated with a statin, was 52%±36% (meta-analytic comparison of means $P=0.61$).

Change in Calcium Volume Score According to Change in LDL

The mean LDL level on treatment (Table 1) did not differ in the 2 groups (118±25 mg/dL versus 122±30 mg/dL, for MI and no MI group, respectively, P=NS). Of the 495 subjects followed-up, 134 patients (27% of total) reached a level of LDL <100 mg/dL. Overall, these subjects showed a mean yearly increase in CVS of 12%±21% (absolute change: 41±72), whereas the 361 subjects with an LDL ≥100 mg/dL showed a 22%±27% (absolute change: 55±90) mean yearly CVS increase ($P=0.0002$).

Table 2 shows the mean percent yearly CVS change in all study patients, subjects with events, event-free survivors, and historical controls according to the level of LDL reached. None of the untreated historical controls reached LDL <100 mg/dL; therefore, these data cannot be provided. There was a statistically significant difference in mean yearly CVS progression between the 11 patients who had an MI with a LDL <100 mg/dL and event-free survivors with the same LDL level (36%±14% [median 34%] versus 10%±20% [median 9.5%]; $P<0.0001$). Similarly, there was a statistically different progression in mean yearly CVS among individuals in the 2 groups who attained an LDL ≥100 mg/dL (43%±26% [median 38%] versus 20%±27% [median 14%]; $P<0.0001$).

TABLE 2. Mean and Median Percentage Yearly Calcium Volume Score Change in All Study Subjects, Patients With Myocardial Infarction During Follow-Up, Subjects Free of Events, Diabetic Patients, and Historical Controls According to Level of LDL Attained

	LDL <100 mg/dL (%)	LDL ≥100 mg/dL (%)	*P* Value for Comparison Between LDL Groups
All study subjects (N=495)	12±21 (11.0)	22±27 (17.0)	0.0002
Patients having an MI (N=41)	36±14 (34)*	43±26 (38)†§	NS
Event-free survivors (N=454)	10±20 (9.5)*‡¶	20±27 (14)†	<0.0001
Diabetic patients having an MI (N=9)	45±16 (42)‡	46±19 (35)§	NS
Event-free diabetic patients (N=67)	16±20 (14)¶	20±32 (13)	NS
Untreated historical controls (N=44)	N/A	52±36% (42)§	N/A

*†‡$P<0.0001$.

§¶NS (not significant).

N/A indicates not available.

Median changes are shown between parentheses.

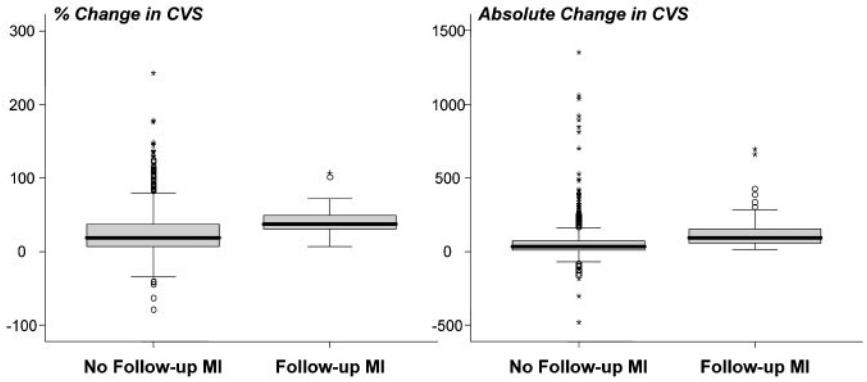

Figure 1. Box plot of the median, quartiles, and extreme values of CVS change for patients with and without a follow-up MI.

Interestingly, the mean yearly CVS progression was not different among MI patients classified according to an LDL goal of >100 mg/dL or <100 mg/dL (43%±16% versus 36%±14%, *P*=NS). On the contrary, CVS progression was significantly different for event-free subjects stratified according to the same LDL strata (21%±27% versus 12%±21%, *P*<0.0001). To formally test this relationship of CVS change and baseline LDL of <100 mg/dL or ≥100 mg/dL, the first-order test for interaction was highly significant (*P*<0.0001).

Gender and Diabetes Specific Changes in Calcium Volume Scores

The average LDL levels for the men and women in our cohort were not significantly different (122±30 mg/dL versus 121±30 mg/dL, respectively, *P*=NS). An equal proportion of individuals of either gender reached a level of LDL <100 mg/dL (27% of men and 28% of women) with equal effect on CVS progression (*P*=NS). The mean yearly CVS change in men and women who had an MI was not statistically different (44%±24% versus 36%±21%, respectively; *P*=NS).

However, there was a significant difference in CVS progression between diabetic patients who sustained an MI and those who remained event-free (46%±17% versus 19%±29%; *P*=0.007). Nonetheless, it should be noted that the number of diabetic patients in the MI group was small (n=9).

Although the average and median temporal changes in CVS differed significantly between MI patients and event-free survivors, there was a substantial overlap between patient groups (Figure 1).

Univariable and Multivariable Cox Proportional Hazards Model

In a multivariable model, the best predictors of MI were CVS change ≥15% per year (*P*<0.0001, RR: 17.9; 95% CI: 4.3 to 74.2) and final CVS (*P*=0.034, RR: 1.5; 95% CI: 1.1 to 2.1), whereas diabetes mellitus (*P*=0.18, RR: 1.7; 95% CI: 0.8 to 3.6) and LDL level (*P*=0.18, RR: 0.99; 95% CI: 0.99 to 1.0) were of borderline significance.

Overall, event-free survival was 97% versus 66% for patients without and with a yearly CVS change ≥15% (Figure 2, *P*<0.0001). The relative risk of suffering a MI in the presence of CVS progression was 17.2-fold (95% CI=4.1 to 71.2) higher than that of subjects without progression (*P*<0.0001). There was an interaction between baseline CVS and extent of CVS change over time in identifying high-risk cohorts (*P*<0.0001). In fact, for patients with <15% per year CVS progression, event-free survival was ≥ 97% at 6 years regardless of the baseline calcium score (Figure 3). However, for patients with intercurrent CVS progression ≥15% per year, the time to MI and the frequency of MI were greatest for patients with baseline CVS ≥400. In the patients with CVS change ≥15%, the relative risk of first MI was 3.8-fold (95% CI: 1.8 to 8.0), 6.4-fold (95% CI: 2.7 to 14.8), and 12.0-fold (95% CI: 4.5 to 32.0) higher when the baseline CVS was 101 to 400, 401 to 1000, and ≥1,000, respectively (*P*<0.0001). Specifically, the time to MI was, on average, 1.5 to 3.5 years shorter for patients who had a baseline calcium score of 401 to 1000 and ≥1000 (*P*<0.0001), respectively.

Discussion

In this observational study of patients treated with statins, the temporal CVS increase was significantly greater in subjects who sustained a hard event compared with subjects who

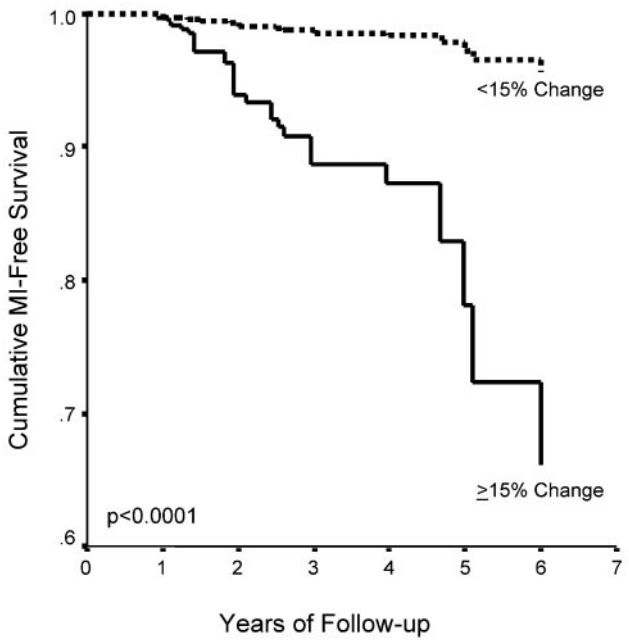

Figure 2. Cox proportional hazards survival curves demonstrating time to acute MI for patients with a yearly calcium volume score change ≥15% or <15%.

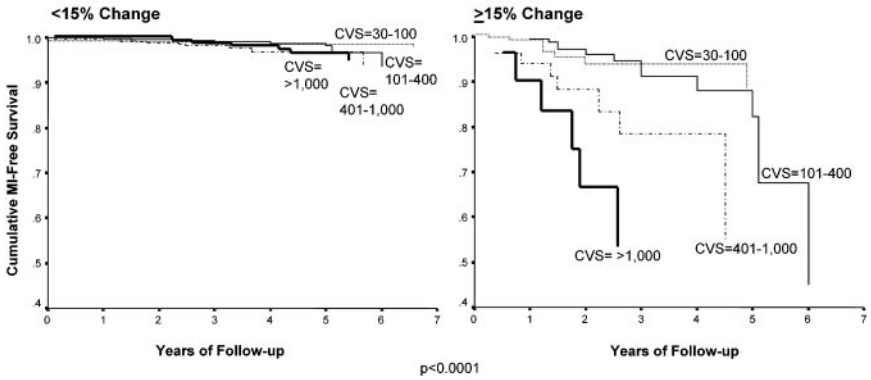

Figure 3. Cox proportional hazards survival curves demonstrating time to acute MI for patients with a yearly change in calcium volume score ≥15% or <15% according to baseline calcium score.

remained event-free. The risk of hard events was significantly higher in the presence of CVS progression despite low LDL serum levels, although the interaction of CVS change and LDL level on treatment was highly significant. The latter observation strongly suggests that a combination of serum markers and vascular markers may constitute a better way to gauge therapeutic effectiveness than isolated measurement of lipid levels. Several traditional risk factors along with the baseline calcium score values were independent predictors of CVS progression.

Our observation may help understand why statins have a favorable, albeit partial, effect on reducing cardiovascular events. Indeed, primary and secondary prevention trials showed a 30% to 33% reduction in risk of death and myocardial infarction with statin therapy.[1–6] Hence, the protection afforded by this class of drug is far from being absolute and several mechanisms might subtend the residual observed risk despite therapy. Lack of compliance with treatment is an unlikely explanation for the results of our study given the good average LDL levels attained, whereas an escape from the protection afforded by this class of drugs could be suspected.

Enhanced intestinal absorption of cholesterol particles has been suggested as a potential explanation for the apparent failure of statin therapy. Indeed, recent evidence suggests that the beneficial effects of statin therapy on LDL metabolism could be markedly reduced—and in effect nullified—in patients prone to enhanced absorption of cholesterol from the gut.[17] In these patients, serum LDL levels are normal to low, thus masking the ineffectiveness of statin therapy.[17] Notably, patients enrolled in the 4S trial with increased intestinal absorption of cholesterol had a higher rate of events than subjects with lower absorption rates despite statin therapy.[18]

Furthermore, molecular mechanisms—as yet not fully understood—could help explain the incomplete effectiveness of statins therapy. The HMG-CoA reductase enzyme is a pivotal rate-limiting enzyme in the production of intracellular cholesterol and is selectively inhibited by statins. To inhibit excess synthesis of cholesterol, the HMG-CoA reductase enzyme is degraded in the presence of high levels of intracellular mevalonate and sterols. Statin resistance at the cellular level has been described to occur via 2 mechanisms: overexpression of the gene regulating secretion of the HMG-CoA reductase enzyme and loss of degrading ability of the enzyme in cell cultures exposed to high concentration of lipoproteins and lovastatin in the medium.[19]

Although the concept of statin resistance is a possible and attractive explanation for our observation, in this study we did not measure other potentially important variables besides LDL cholesterol that may modify outcome. Diabetic patients with events demonstrated a greater increase in CVS than event-free diabetic patients free of events. Because we did not measure hemoglobin-A1c, we were unable to verify whether the glycemic control had an effect on CVS progression and development of MI. Lipoproteins not affected—or incompletely affected by therapy with statins—such as Lp(a), small dense LDL, and other mediators of vascular damage (viruses, homocysteine, fibrinogen, *Chlamydia Pneumoniae*, and others) may also have played an important role that could not have been detected because of the design of our study. Nonetheless, LDL remains the main focus of treatment in primary and secondary prevention of cardiovascular disease,[16] and statins are currently the most potent antiatherosclerotic agents on the market. Hence, we feel that we focused our attention on a pertinent endpoint of therapy.

In preliminary studies, we and others have shown that EBT can be used to gauge the progression of coronary artery calcification and have suggested that this tool could become very useful to follow the effectiveness of medical therapy for atherosclerosis.[7–9,20] Those initial studies generated the need to demonstrate that slowing the arterial calcification process translates into effective event reduction. Although single calcified plaques may be less prone to rupture,[21–22] the change in global scoring seems to portend a negative prognosis. Two different mechanisms may be hypothesized to justify the occurrence of events predominantly in individuals with continuing expansion of CVS. The first is that accumulation of cholesterol within a plaque could not be effectively halted with statin therapy and that expansion of calcification was an indicator of continued plaque growth. Alternatively, more calcification in the follow-up period might be indicative of an actual repair process of the existing plaques induced by statin therapy. Nonetheless, the underlying inflammatory processes might have continued to progress inducing the formation of new and more vulnerable plaques prone to rupture. In either case, it appears that progression of coronary calcification in sequential EBT studies may translate into an increased risk of hard events.

This study presents important limitations. We reviewed only the records of patients with who received statins and had coronary calcification; therefore, these findings do not necessarily apply to all individuals treated with statins. We collected information on LDL alone and no other lipid subfractions. This was performed to adhere to the same model used in several published studies on the usefulness of EBT to follow progression of calcification,[7–9] and because LDL remains the main target of preventive therapies for cardiovascular disease.[16] Although there was a significant difference in mean CVS progression between patients having an event and those who remained asymptomatic during the follow-up period, there was a substantial overlap in score change between groups. Nonetheless, it should be remarked that in patients with events the CVS definitely progressed in 95% of the cases, whereas stabilization or minor regression was seen in approximately half of the event-free patients. Finally, the treating physicians used a variety of statins and there was no preset LDL goal.

In conclusion, in this observational study of subjects receiving statins, CVS progression was highly prevalent and significantly greater in patients who had a hard event compared with subjects who remained event-free during follow-up. These data suggest that a more direct measurement of the effect of medical therapy on the atherosclerotic plaque may be preferable to the single measurement of indirect markers of efficacy such as serum lipoprotein levels. Noninvasive imaging methodologies may potentially become very useful tools in assessing the effectiveness of therapy for atherosclerosis, although this concept deserves to be further analyzed in prospective and controlled clinical studies.

References

1. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333:1301–1307.
2. [No author] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.
3. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998;279:1615–1622.
4. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003; 361:1149–1158.
5. [No author]. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339: 1349–1357.
6. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002:360:7–22.
7. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron beam computed tomography. *N Engl J Med.* 1998;339: 1972–1977.
8. Budoff MJ, Lane KL, Bakhsheshi H, Mao S, Grassmann BO, Friedman BC, Brundage BH. Rates of progression of coronary calcium by electron beam tomography. *Am J Cardiol.* 2000;86:8–11.
9. Achenbach S, Ropers D, Pohle K, Leber A, Thilo C, Knez A, Menendez T, Maeffert R, Kusus M, Regenfus M, Bickel A, Haberl R, Steinbeck G, Moshage W, Daniel WG. Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. *Circulation.* 2002;106:1077–1082.
10. Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Cashin-Hemphill L, Hodis HN, DeBoer LW, Masteller MJ, Vailas LI, Alaupovic P, Kirsch LJ. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med.* 1993;119: 969–976.
11. MAAS investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study. *Lancet.* 1994;344:633–638.
12. Pitt B, Mancini BJ, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol.* 1995;26:1133–1139.
13. Levine GN, Keaney JF Jr., Vita JA. Cholesterol reduction in cardiovascular disease: clinical benefits and possible mechanisms. *N Engl J Med.* 1995;332:512–521.
14. Waters D, Pedersen TR. Review of cholesterol lowering therapy: coronary angiographs and event trials. *Am J Med.* 1996;101:4A34S–38S
15. Callister TQ, Cooil B, Raya S, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: Improved reproducibility of calcium scoring with an electron beam-CT volumetric method. *Radiology.* 1998;208:807–814.
16. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2489.
17. Gylling H, Miettinen TA. Baseline intestinal absorption and synthesis of cholesterol regulate its response to hypolipidaemic treatments in coronary patients. *Atherosclerosis.* 2002;160:477–481.
18. Miettinen TA, Gylling H, Strandberg T, Sarna S. Baseline serum cholestanol as predictor of coronary events in subgroup of Scandinavian simvastatin survival study. *BMJ.* 1998;316:1127–1130.
19. Ravid T, Avner R, Polak-Charcon S, Faust JR, Roitelmn J. Impaired regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase degradation in lovastatin-resistant cells. *J Biol Chem.* 1999;274:29341–29351.
20. Raggi P. Electron beam tomography as an endpoint for clinical trials of antiatherosclerotic therapy. *Curr Atherosc Rep.* 2000;2:284–289.
21. Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation.* 2001;103:1051–1056.
22. Beckman JA, Ganz J, Creager MA, Ganz P, Kinlay S. Relationship of clinical presentation and calcification of culprit coronary artery stenoses. *Arterioscler Thromb Vasc Biol.* 2001;10:1618–1622.