

Coronary Calcium on Electron Beam Tomography Imaging as a Surrogate Marker of Coronary Artery Disease

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Although currently recognized risk factors for coronary artery disease are helpful to predict the development of atherosclerosis, their ability to identify individual patients at risk of events is limited. Therefore, surrogate markers are being investigated to identify disease in its early phases in an attempt to decrease cardiovascular morbidity and mortality. Coronary artery calcification is a useful surrogate marker of coronary artery disease, and it can be visualized and measured noninvasively by means of electron beam tomography (EBT) imaging. Atherosclerosis starts to infiltrate the arterial intima layer much before luminal stenosis develops. Calcium is present in the large majority of mature atherosclerotic

plaques, although, in rare cases, it may be absent. Recent research indicates that in selected patient subsets, coronary calcium may add incremental prognostic value to conventional risk factors for coronary artery disease and should therefore be used in association with such factors. EBT imaging for detection of arterial calcification is best employed in asymptomatic individuals at intermediate risk of coronary artery disease, symptomatic patients at low risk of coronary artery disease, and to track disease progression. ©2001 by Excerpta Medica, Inc.

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The first manifestation of coronary artery disease is often a drastic event, either myocardial infarction or death.¹ Research has demonstrated that our long preoccupation with the severity of coronary luminal stenosis may be wrong. In fact, the majority of acute events are caused by noncritical arterial stenoses.^{2,3}

The introduction of the notion of vascular remodeling, whereby vessels affected by incipient atherosclerotic processes undergo progressive enlargement of the lumen, renders the concept of angiographic normality and critical stenosis obsolete. Furthermore, although widely accepted by the medical and lay community as good indicators of risk, current epidemiology concepts indicate that conventional risk factors are suboptimal predictors of cardiovascular events. In fact, it is fairly often seen that patients assessed to be at low-to-intermediate risk of disease according to such criteria as the Framingham risk index have unexpected events. Therefore, surrogate markers of disease are needed for a better risk stratification of asymptomatic individuals.

CORONARY CALCIFICATION

One such marker is coronary calcification, which often accompanies atherosclerosis (Figure 1). Although coronary calcification can be detected by means of spiral computed tomography, the scanners employing such technology are often too slow to obtain clear and motionless pictures of the heart. On the contrary, image acquisition proceeds very rapidly with the electron beam computed tomography (EBT) scanners.

EBT is currently the gold standard for calcium detection in the coronary arteries (see Appendix). This fourth generation, computed tomography scanner utilizes a different imaging algorithm compared with mechanical computed tomography. In this design, there is no rotation of an x-ray source-detector pair around the patient. Instead, a fan of electrons is swept at high speed along a 210° ring of tungsten placed under the patient's radiologic cradle and an x-ray fan is generated. As the fan cycles, the detectors placed in the dome of the gantry collect attenuation profiles utilized in the final image reconstruction. Imaging is timed to the point in diastole when the motion of the heart is least (approximately 40–60% of the R-to-R cycle on the electrocardiogram) and each image requires approximately 50–100 msec for completion. This is in comparison with the fastest currently available spiral computed tomography scans that require approximately 250–300 msec per image.

Coronary atherosclerosis develops at a young age, and calcium accumulates from the very early stages of plaque development, indeed, as early as the fatty streak stage.⁴ However, the amount of calcium present in the plaque at this point is not sufficient to be detected by an imaging technology such as EBT. As the atheroma grows and develops into a larger and more mature stage, with collection of more cholesterol debris, inflammatory cells, and fibrotic tissue, calcium accumulates as larger and more visible plates located at the base of the intima. At this stage, it becomes easily detectable by means of EBT surface imaging.

Janowitz et al⁵ compared the extent of coronary calcium found in 1,396 men and 502 women on EBT imaging with historical coronary pathologic data. In all age groups and both sexes, there was a high correlation ($r = 0.95-0.97$) between coronary calcium seen on EBT images and atherosclerosis found by

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microscopic examination. These findings indicate that the sensitivity of EBT for detection of coronary artery disease is very high.

To examine the topographic relation of atherosclerotic plaques and calcified foci in the coronary arteries, Simons et al⁶ performed sequential proximal-caudal histologic sections in 525 coronary artery specimens. In all of the sections, they demonstrated a good correlation between the total atherosclerotic plaque area and the area of calcification. Although the calcified area was only a portion of the total atherosclerotic area, calcium appeared to be an excellent marker of disease. It is important to remember that the identification of areas of calcification within the coronary artery tree does not equate to identifying the potential point of plaque rupture, but rather it indicates the presence of more disseminated atherosclerosis.

COMPARISON OF EBT WITH OTHER INVESTIGATIVE METHODS

The sensitivity of EBT compares well with other tools used to investigate the presence of atherosclerotic disease. One study comparing EBT and intravascular ultrasound (IVUS) in 56 patients found that EBT was positive in 97% of patients showing plaque with IVUS imaging.⁷ When IVUS showed soft plaque only, EBT demonstrated the presence of coronary calcium 47% of the time. Interestingly, 25% of the patients with no plaque on IVUS showed calcium on EBT imaging. This apparent paradox might be explained by the probable absence of amounts of calcium sufficient to cause acoustic shadowing.

The ability of EBT to predict the presence of coronary atherosclerosis has also been compared with that of carotid ultrasound. Seese et al⁸ conducted a comparative study in 80 patients. The study found both an increased thickening of the intima-media layer and coronary calcification in approximately 60% of patients. Calcium was present in the absence of intima-media thickening in approximately 20% of the patients, whereas carotid wall thickening but no coronary calcium was found in approximately 13% of the cases. The Pearson correlation coefficient for the presence of significant luminal stenosis found on coronary angiography was significantly greater for EBT than for carotid ultrasound.⁸

CORONARY CALCIFICATION SCORING METHODS

Coronary calcification is quantitated via a score calculated according to the Agatston's method.⁹ The area of a calcified plaque is multiplied by a coefficient estimated on the basis of the peak density of the calcified lesion. For a density of 130–200 Hounsfield Units (HU), the density coefficient is 1, for 201–300 HU it is 2, for 301–400 HU it is 3, and for ≥ 401 HU the density coefficient used is 4. The main limitation of this score is its limited reproducibility that renders it inadequate for sequential scanning. For this reason, another scoring method was recently introduced—the

calcium volume score—which demonstrates very low interscan variability.¹⁰ However, the Agatston score has been used extensively both for clinical applications and in research.¹¹

Nomograms of calcium scores obtained by submitting asymptomatic individuals to EBT screening indicate the expected distribution of coronary calcification in the general population. In a recent study, Raggi et al¹² published tables of calcium score percentiles derived from scoring 9,728 individuals asymptomatic for coronary artery disease (Table 1). Men demonstrate a rapid increase in prevalence and extent of coronary calcification after age 40. In women, on the contrary, calcium scores increase very slowly and a significant growth is not seen until 10 to 15 years later than among men. Further, the calcium score values in women are on the average smaller than in men.

CORONARY CALCIFICATION SCORES AND THE PREDICTION OF CARDIOVASCULAR EVENTS

Coronary artery calcium appears to be a good predictor of cardiovascular events. Arad et al¹³ followed 1,172 patients for an average of 3.6 years. A total of 39 mixed coronary events (death, myocardial infarction, and revascularizations) were recorded during the follow-up period. Patients with events had a significantly greater calcium score at screening than patients without events (764 ± 935 vs 135 ± 432 , $p < 0.0001$). Furthermore, a calcium score >160 was associated with an odds ratio of having any coronary event of 15.8 and with an odds ratio of 22.2 for having a hard coronary event. The area under the receiver operating characteristics curve (ROC) was large, both for all coronary events considered together and for hard coronary events alone (0.84 and 0.86, respectively). Detrano et al¹⁴ studied a group of 491 symptomatic patients who were submitted to sequential cardiac catheterization and EBT imaging. During an average follow-up time of 30 ± 13 months, 13 deaths and 8 nonfatal myocardial infarctions were recorded. Patients with a score above the median (score median = 75.3) had a 6-fold greater number of events than those below the median. In logistic regression analyses that included age, gender, the number of angiographically diseased vessels, and log-calcium score, the latter was the only independent predictor of events. Surprisingly, in a second study performed by Detrano et al¹⁵ in a group of 1,196 asymptomatic, high-risk, older individuals, the predictive ability of coronary calcium scores was no greater than that of conventional risk factors and both were defined as suboptimal estimates of risk. However, the conclusions of this study were weakened by the use of a nonstandard imaging protocol that likely caused the loss of significant imaging information in a group of patients already at very high risk of events because of the presence of multiple risk factors.¹⁶ It is likely that the loss of imaging information coupled with a high prevalence of risk factors



FIGURE 1. Moderate size calcium deposit in the middle portion of the left anterior descending coronary artery (within white circle).

TABLE 1 Normal Distribution of Calcium Scores in 9,728 Asymptomatic Patients

| | Age in Years | | | | | | |
|----------------------|--------------------|--------------------|----------------------|----------------------|--------------------|--------------------|--------------------|
| | 35-39 (n = 479) | 40-44 (n = 859) | 45-49 (n = 1,066) | 50-54 (n = 1,085) | 55-59 (n = 853) | 60-64 (n = 613) | 65-70 (n = 478) |
| Men (n = 5,433) | | | | | | | |
| 25th percentile | 0 | 0 | 0 | 0 | 3 | 14 | 28 |
| 50th percentile | 0 | 0 | 3 | 16 | 41 | 118 | 151 |
| 75th percentile | 2 | 11 | 44 | 101 | 187 | 434 | 569 |
| 90th percentile | 21 | 64 | 176 | 320 | 502 | 804 | 1,178 |
| | Age in Years | | | | | | |
| | 35-39 (n = 288) | 40-44 (n = 589) | 45-49 (n = 822) | 50-54 (n = 903) | 55-59 (n = 693) | 60-64 (n = 515) | 65-70 (n = 485) |
| Women (n = 4,297) | | | | | | | |
| 25th percentile | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 50th percentile | 0 | 0 | 0 | 0 | 0 | 4 | 24 |
| 75th percentile | 0 | 0 | 0 | 10 | 33 | 87 | 123 |
| 90th percentile | 4 | 9 | 23 | 66 | 140 | 310 | 362 |

reduced the efficacy of coronary calcium as a predictor.

In contrast with the above findings, Raggi et al¹² published very encouraging results from a follow-up of 632 asymptomatic patients screened with EBT. At the end of an average follow-up period of 32 ± 7 months, 19 myocardial infarctions and 8 deaths were recorded. Events were clustered in patients demonstrating a calcium score in the upper quartile for age and gender (19 of 27 events: 70%). Furthermore, the event rate in the upper quartile of calcium score percentile was 20 times higher than in the lowest quartile, whereas the event rate in the upper quartile of risk factors was 6 times higher than in the lowest-risk group. Therefore, the hazard ratio for having an event was significantly greater for patients with a high calcium score percentile than for patients with a high-risk

profile. Conversely, the event rate in the lowest quartile of calcium score percentile was extremely low (absolute event rate: 0.2% per year). Using ROC curve analysis, Raggi et al further demonstrated that the area under the curve for coronary calcium score percentiles was significantly greater than that of traditional risk factors for prediction of hard coronary events (0.8 vs 0.7, $p = 0.028$).¹⁷ This indicates that the presence of high calcium score percentiles carries a severe prognostic implication that appears to be incremental to that provided by the presence of risk factors for disease. Accordingly, Grundy¹⁸ recently suggested a modification of the Framingham Global Risk Score with the introduction of a weighted factor based on the individual's calcium score percentile (Table 2). With this approach the patient's Framingham risk score should be adjusted upward in the presence of a high

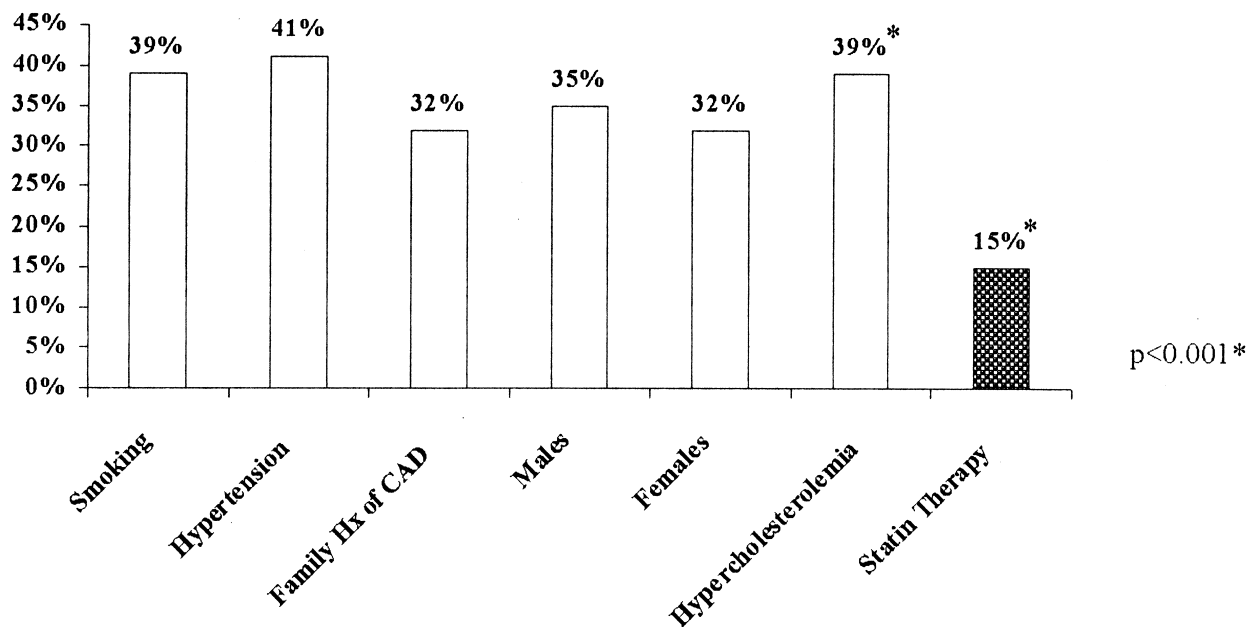


FIGURE 2. The average annualized progression of calcium score does not differ among patients with various risk factors for coronary artery disease. The only statistical difference is noted between hypercholesterolemic patients treated or untreated with statins. CAD = coronary artery disease; Hx = history. (Modified with permission from *Am J Cardiol*.²⁰)

calcium score percentile, or downward in the presence of a small calcium score percentile level.

EBT, DISEASE PROGRESSION, AND ASSESSMENT OF RESPONSE TO TREATMENT

One of the most appealing applications of EBT imaging is the noninvasive follow-up of the progression of coronary artery disease. As mentioned earlier, initial studies on the interscan variability of the Agatston's calcium score showed that this measurement had limited reproducibility and it was therefore considered unreliable for sequential studies.

In response to the need for a more reliable score, Callister et al¹⁰ recently introduced a new volumetric calcium score based on the principle of isotropic interpolation. The score does not require the use of the scalar density coefficient needed for the calculation of the Agatston's score, and due to the interpolation methodology, it is slightly less affected by partial

volume averaging effects. The volumetric score demonstrated high reproducibility compared with the traditional score in an experimental study,¹⁰ and it was therefore considered reliable to perform sequential EBT studies. Indeed, it was employed in an initial experience with 149 asymptomatic individuals with coronary calcification referred by primary care physicians for a screening EBT.¹⁹ Patients who received treatment with statins showed stabilization and even regression of the calcium volume score after a year from screening (average volume score change: $5 \pm 28\%$). On the contrary, all untreated patients showed a significant score progression (average volume score change: $52 \pm 36\%$, $p < 0.001$ for comparison with treated patients). Of interest, the majority of aggressively treated patients (63%) showed net score regression when they achieved a level of LDL cholesterol < 120 mg/dL (average volume score change: $-7 \pm 23\%$). Budoff et al²⁰ followed 299 asymptomatic individuals who underwent EBT screening for coronary atherosclerosis for a period of 1–6.5 years. On sequential scanning, they observed that the average yearly score increase was similar for all untreated patients irrespective of baseline characteristics and risk factors (Figure 2). However, calcium score progression was statistically smaller in patients treated with statins than in untreated patients ($15 \pm 8\%$ per year vs $39 \pm 12\%$ per year, $p < 0.001$). Although these were observational and nonrandomized studies, they clearly indicated that EBT calcium scores can be gainfully employed to assess response to medical therapy for atherosclerosis (Figure 3).

TABLE 2 Adjustment of the Weight Assigned to Age in the Framingham Index Score by Using the Calcium Score Percentiles

| Percentile | Point Adjustment |
|------------|------------------|
| 0–24th | –2 |
| 25–49th | –1 |
| 50–74th | +1 |
| 75–90th | +2 |
| >90th | +3 |

Adapted from *Am J Cardiol*.¹⁸

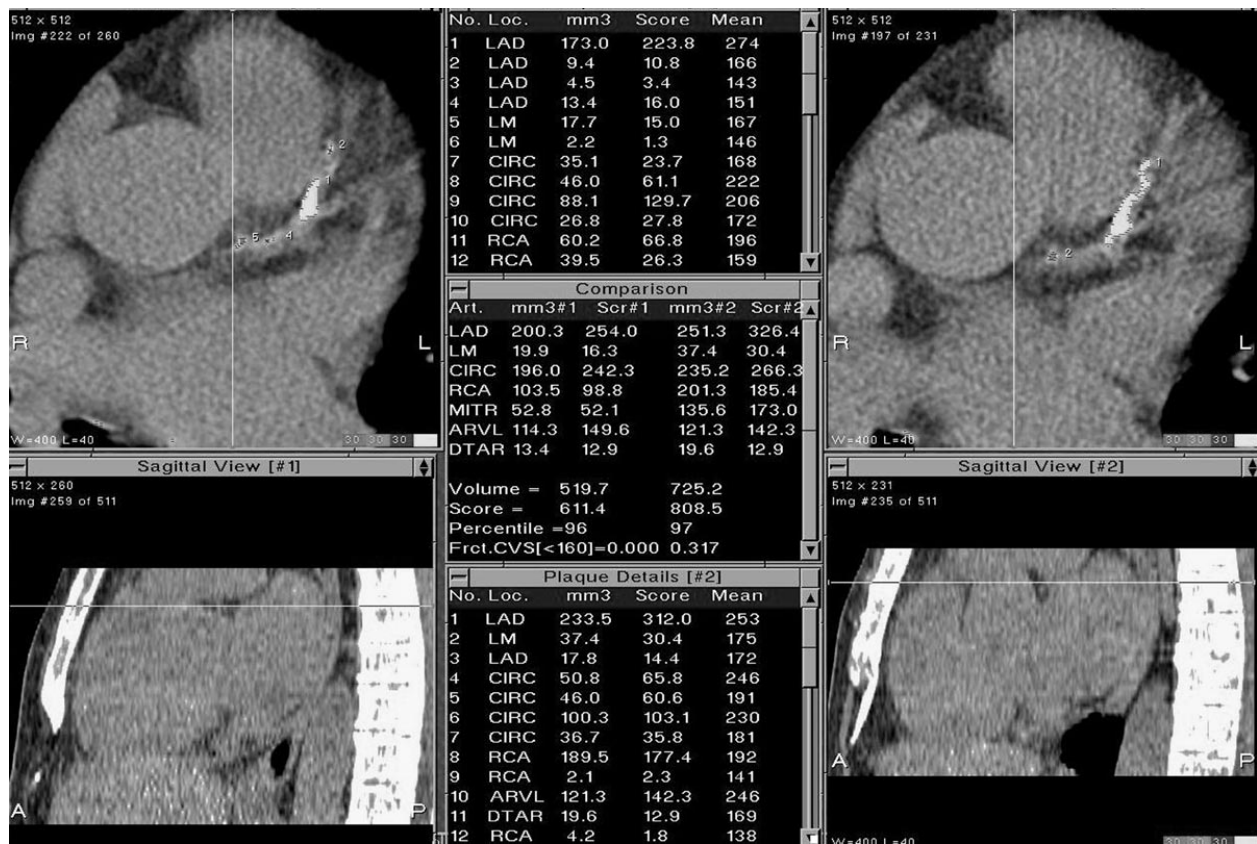


FIGURE 3. Comparison of baseline (upper left inset) and follow-up (upper right inset) electron beam tomography (EBT) scans in a patient not treated with statins. The initial calcium volume score of 519 has increased to a score of 725 (ie, 40% increase in 1 year). A calcium deposit in the middle portion of the left anterior descending coronary artery has visibly expanded.

Furthermore, the continued accumulation of coronary artery calcium appears to portend a negative outcome. In a limited follow-up of 2.5-year duration of 269 asymptomatic individuals submitted to sequential EBT scanning, Raggi et al²¹ recorded 25 cardiovascular events (16 revascularizations and 9 hard events). Of these, 23 events occurred in patients who showed progression of coronary calcification and only 2 in patients who showed regression or stabilization of disease. The average progression in patients who underwent a revascularization procedure and those who had a hard event was similar (40% and 39%, respectively, $p = \text{NS}$) and significantly greater than that of the overall group ($24 \pm 7\%$, $p < 0.05$) and that of patients who did not have an event ($22 \pm 17\%$, $p < 0.001$).

Similarly, Shah et al²² followed 225 patients with serial EBT scans for an average period of 3 years (range, 1 to 7 years). Eight myocardial infarctions and 18 revascularizations were recorded during the follow-up period. The average score change in patients having events was significantly larger than in patients who did not have an event (78% vs 37%, $p < 0.001$), and no events were recorded in patients with stabilization or regression of disease. On multivariate analyses, the odds ratio for having an event for patients

with calcium score progression $>20\%$ per year was 14.6, whereas older age was associated with odds of 6.7 and diabetes mellitus with odds of 2.8. These 2 preliminary studies showed quite clearly that the continued growth of coronary calcium is associated with a real prognostic danger of cardiovascular events.

CONCLUSION

In summary, coronary calcium is an excellent marker of underlying atherosclerotic disease that has accumulated in the context of the vascular wall. Calcium screening is best employed in asymptomatic subjects at intermediate risk of coronary artery disease to address the presence of atherosclerotic disease and to assess the risk of the individual patient. Because the majority of cardiovascular events happen in patients at intermediate risk, an effective risk stratification tool—such as EBT—can be most helpful in adjusting the individual's risk level. However, to maximize the specificity of the technology, screening should be performed in predefined age cohorts.²³ Specifically, men should undergo screening between ages 35 and 55 or 60, whereas women should be subjected to screening between ages 40 and 70 to 75 (Figure 4). In all other

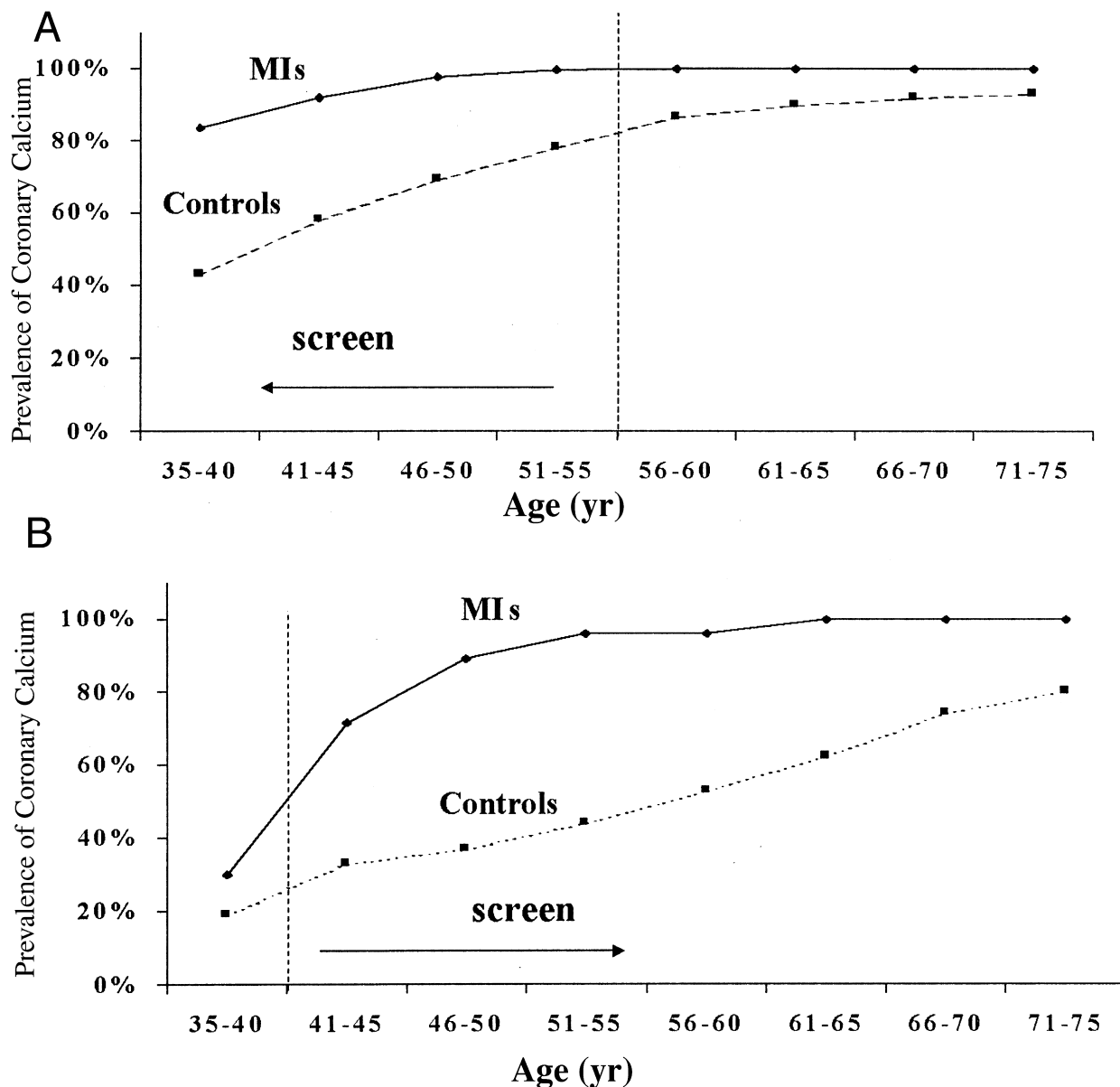


FIGURE 4. These paired curves indicate the age at which electron beam tomography (EBT) screening is most appropriate in men (A) and women (B) to identify patients at risk of having a hard coronary event. MI = myocardial infarction.

age groups, the sensitivity of coronary calcium for prediction of hard coronary events remains high, but the specificity is too low.

EBT can also be useful to follow-up the progression of disease and the response of atherosclerosis to targeted medical therapy. The ease and safety with which follow-up information can be obtained in a short period of time renders EBT one of the preferred tools to study the effects of new therapeutic agents designed to interfere with the natural history of atherosclerosis. Nonetheless, further investigation will be needed to confirm that slowing the progression and inducing the regression of coronary artery calcium

accumulation portends a reduction in cardiovascular events.

DISCUSSION

Jacques D. Barth, MD, PhD (Los Angeles, California): EBT calcium screening has been surrounded by strong emotional feelings. Why do you think that is? **Paolo Raggi, MD (New Orleans, Louisiana):** I think there are several reasons. First, the field has received very negative publicity from an abusive use of advertisement in the mass media. This has damaged the scientific validity of the “calcium message” in the eyes

of physicians not completely familiar with its meaning. Also, most physicians think of coronary calcium as a stabilizing element for the atherosclerotic plaque and find it hard to accept that it might be a harbinger of adverse prognosis. We need to educate clinicians that a calcified lesion is merely a marker for the presence of other atherosclerotic sites with unstable plaque and that this tool should not be used to identify patients with obstructive luminal disease. As it is clear that our worst enemy is arterial-wall disease and not luminal stenosis, it is imperative to define its extent and confine its effects before it strikes. It is a hindrance that the tool is estranged to physicians. On the other hand, it also receives a very high level of patient's acceptability because of its noninvasive nature. If the fact that calcium detection truly helps to identify patients at risk is confirmed in larger studies, more clinicians will eventually be convinced of its effectiveness and become supportive.

Paul Hopkins, MD (Salt Lake City, Utah): We just obtained funding to study several hundred patients affected by familial hypercholesterolemia by means of multislice helical computed tomography. The study will require assessment of coronary calcification at the beginning and at the end of a 3-year follow-up and it will entail therapy with antioxidants. Therefore, it will not be a lipid intervention study. I am worried by the fact that patients with lipid-rich plaques not showing coronary calcium may have a myocardial infarction despite a negative EBT scan. I wonder if multislice computed tomography will be sensitive enough to detect calcium in patients with familial hypercholesterolemia.

Dr. Raggi: Patients with familial hypercholesterolemia develop a very aggressive and accelerated form of atherosclerosis, and it has been shown that young adults with heterozygous familial hypercholesterolemia have a high prevalence of coronary calcification.²⁴ Because calcium accumulates in the growing plaque from its inception, it is likely that you will be able to detect calcifications even in the young patients with familial hypercholesterolemia you intend to study. Currently there are no long-term follow-up data on outcome of patients with familial hypercholesterolemia studied by either EBT or multislice computed tomography. However, Jensen et al²⁵ found that the age-adjusted coronary calcium score was strongly associated with the risk of developing symptomatic coronary artery disease in these patients. In patients not affected by familial hypercholesterolemia, a calcium score of 0 portends an extremely good prognosis in the short term (3–4 year follow-up) as shown above. The same may not necessarily apply to patients affected by familial hypercholesterolemia who likely have a larger number of uncalcified plaques. To improve the sensitivity of computed tomography imaging, one might consider lowering the minimal density threshold for the identification of calcified plaque from the traditional 130 HU to a lower limit in an attempt to enhance plaque detection. However, this would obvi-

ously reduce the specificity of the information collected.

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APPENDIX: METHODOLOGY FOR PERFORMING RESEARCH-QUALITY SERIAL EBT SCANNING TO FOLLOW PROGRESSION OF CALCIFIED ATHEROSCLEROTIC PLAQUES

The following criteria apply exclusively to follow-up studies performed on EBT C-150 scanners (Imatron, South San Francisco, CA) as there are currently no data to support the use of multislice computed tomography scanners for the performance of serial imaging. Indeed, publications demonstrating the reproducibility of calcium scores obtained with mechanical computed tomography scanners are not available. Furthermore, the presence on the market of different computed tomography brands and models, utilizing radically different imaging algorithms, reduces greatly the comparability of results obtained with various types of equipment.

At the present time there is no evidence that repeating EBT scans before 12 months have elapsed from the time of screening may show any significant change in calcium score. Ongoing clinical studies will evaluate such question.

An Electron Beam Tomography Core Laboratory (EBT Core Lab) with experience in serial scanning procedures should be responsible for the qualitative and quantitative analysis of all EBT study scans. The reviewer(s) in the EBT Core Lab should be blinded to the patient's treatment.

Ad-hoc patient identification codes should be created to maintain patients' privacy.

Imaging time should be 100 msec per slice on single-slice mode. The slice

thickness should be kept at 3 mm with 0.5-mm overlap for superior reproducibility of the calcium volume score. A total of 36–40 slices should be obtained during 1 breath-holding period to encompass the entire length of the heart. Tomographic imaging should be electrocardiographically triggered at 40–60% of the RR interval. The percentage of the RR interval should remain constant for all scans performed on the same patient. A scanning field of view of 26 cm² is preferred. The size of the field of view should not be changed on follow-up scans to prevent changes in pixel size.

Each EBT scan sent to the EBT Core Lab should be screened for image quality and protocol compliance. All scans should be checked for presence of motion artifacts and acquisition of complete data sets without exclusion of any slices comprising the cranial–caudal length of the heart. Because of the importance of acquiring perfect and complete data sets, patients with atrial fibrillation, which may cause significant motion artifacts, should not be included in follow-up research studies. If the arrhythmia is considered transient and probably remitting, consideration should be given to scanning the patient at a later date.

The atherosclerotic plaque(s) found in each vessel must be analyzed using a workstation equipped with isotropic calcium volume scoring capabilities. At this time, a baseline calcium volume score ≥ 30 is preferable for a patient's inclusion in a follow-up study to guarantee maximum reproducibility of the calcium score.

When the plaque identification is completed, the partial calcium volume score for each vessel as well as the total calcium volume score should be automatically exported to an electronic database for storage. All acquired and elaborated data should also be stored on electronic media, such as magnetic optical disks, for future reference.