Atherosclerosis Imaging and Calcified Plaque: Coronary Artery Disease Risk Assessment

Matthew J. Budoff

Over the last decade, there has been increased recognition that atherosclerosis imaging adds greatly to the ability to identify patients at high risk for cardiac events. Technologies such as electron beam computed tomography and carotid intimal media thickness have contributed significantly to our understanding of the prevalence of preclinical atherosclerosis and its consequences. Guidelines and policy toward these modalities have shifted, with increased recognition of the importance among experts in cardiology, lipidology, and preventive medicine. Because most adverse events related to atherosclerosis occur in individuals at an intermediate risk, data suggest that it will be most cost-effective to concentrate screening efforts on this group of patients. This article reviews the current understanding of the value of coronary artery calcium screening in asymptomatic and symptomatic patients. The validity of measuring coronary artery calcium with new multislice computed tomography scanners is also reviewed. Accurate measurement of subclinical coronary atherosclerosis should significantly improve the accuracy of global cardiovascular risk prediction and allow for tracking of atherosclerosis burden as well as better prediction of future cardiovascular events.
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Atherosclerosis is the primary cause of morbidity and mortality in every industrialized nation.[1] Identification of persons at high risk for cardiovascular events is the major focus of primary prevention efforts because lifestyle changes and pharmacological interventions have been shown to increase the life expectancy of high-risk persons.[2] The initial manifestation of coronary artery disease (CAD) is a myocardial infarction (MI) or death in up to 50% of patients.[3] Most cardiac events occur in the intermediate risk population, where aggressive risk-factor modification is often not applied.

Unfortunately, traditional risk factor assessment helps predict only 60% to 65% of cardiac risk, while many individuals continue to suffer events in the absence of established risk factors for atherosclerosis.[4] The Framingham equations, using cigarette smoking, systemic hypertension, elevated low-density lipoprotein cholesterol (LDL-C), family history of premature CAD, age, and diabetes, provide an estimate of risk based on the median risk of developing CAD in a population but are not ideal to estimate risk in individual patients.[5] Although the Framingham Study[6] and the Multiple Risk Factor Intervention Trial[7] showed an association between serum cholesterol and coronary heart disease mortality, almost half the excess deaths occurred in those with cholesterol levels of 182-244 mg/dL.[8] With the mean blood cholesterol levels for men and women being 211 and 215 mg/dL,[9] respectively, the majority of the adult population is at risk and thus, by itself, cholesterol levels (including LDL and high-density lipoprotein cholesterol) are not discriminating enough to be a screening test for heart disease. Recent data from the Framingham Heart Study suggest that, after adjustment for other factors, only 27% of coronary heart disease events among men and 34% among women were attributable to elevated cholesterol.[10]

From the Division of Cardiology, Saint John's Cardiovascular Research Center, Harbor-UCLA Medical Center Research and Education Institute, Torrance, CA.

Address reprint requests to Matthew J. Budoff, MD, Harbor-UCLA Research and Education Institute, 1124 W. Carson Street, RB2 Torrance, CA 90502.

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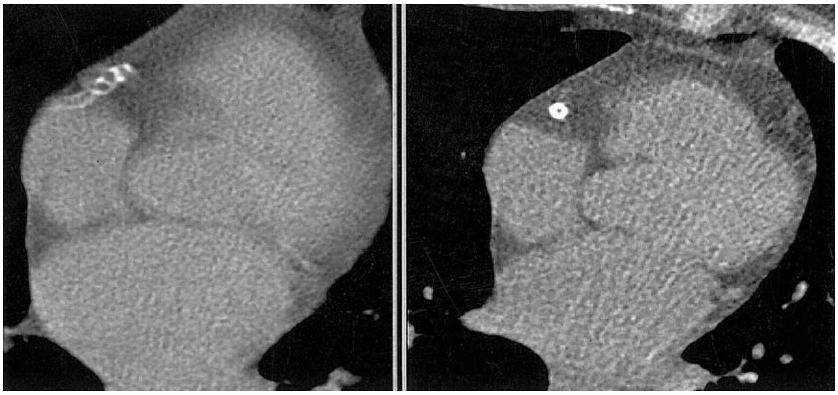

Fig 1. Patient underwent scanning with MSCT (left, 250-millisecond image acquisition) showing significant streak artifacts of the right coronary artery (white arrow). The patient then underwent EBT (right, 100-millisecond acquisition) showing no motion artifact in the right coronary artery. This is because of improved temporal resolution with electron beam tomography.

Reinforcement for the need for a new risk algorithm comes from the understanding that the obstructive coronary plaque (stenosis in the artery of >50% severity) is often not the site of the cardiac event. Multiple trials have now shown that the vast majority of heart attacks occur at the site of a nonobstructive plaque.[11] Coronary occlusion and MI most frequently evolve from mild to moderate stenoses.[12,13] Thus, exercise testing or pharmacologic cardiac imaging (nuclear or echo), which diagnose high-grade coronary stenosis, will fail to identify a vast number of asymptomatic patients at risk. Studies of patients dying from either acute MI or sudden cardiac death have shown that the extent of coronary atherosclerosis, rather than the severity of stenosis, is the most important predictor.[14] Thus, the need to measure atherosclerosis burden has become paramount to risk stratification.

It has become highly desirable to detect atherosclerosis in its early stages to implement effective preventive measures rather than apply delayed treatment. Furthermore, the high sensitivity of coronary artery calcium (CAC) makes this test potentially useful as a filter before hospital admission or angiography in patients with chest pain. The data supporting the use of electron beam tomography (EBT) in asymptomatic and symptomatic patients will be reviewed.

Coronary Artery Calcification and Atherosclerosis

Calcific deposits in coronary arteries are pathognomonic of atherosclerosis.[15,16] Histopathological[17] and intravascular ultrasound[18-20] studies confirm the close correlation between atherosclerotic plaque burden and extent of CAC. EBT can accurately and noninvasively quantitate the amount of CAC ($r > 0.90$).[21,22] Other noninvasive modalities to diagnose CAD focus on physiologic consequences of coronary obstruction, whereas EBT coronary calcium represents an anatomic measure of plaque burden. Accurate and noninvasive measures of atherosclerosis in the person at high risk should allow better assessment of processes associated with disease progression as well as of therapies to prevent the progression or even induce regression of atherosclerosis and clinical CAD.[23]

EBT

EBT is a fourth-generation computed tomography imaging process able to obtain thin slices of the heart and coronary arteries to evaluate for CAC. Rapid image acquisition because of the absence of a moving x-ray source allows approximately 5 times greater imaging speed than multislice spiral computed tomography (MSCT), thereby limiting the respiratory and cardiac motion artifacts (Fig 1). Usually 30 to 40 axial images are obtained to include the full length of the myocardium. The entire coronary artery tree is imaged during a single 20- to 30-second breath hold. Nomogram tables of the calcium score distribution in large numbers of asymptomatic persons have been published.[24] These nomogram tables can be used to classify patients on the basis of the extent of their atherosclerotic disease compared with the expected norm. In men, there is a rapid increase in the prevalence and extent of coronary calcifica-

Table 1. Nomogram of Over 21,000 Asymptomatic Patients Scanned at Harbor-UCLA Medical Center

Asymptomatic Women (N = 6027)

	</=40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	>75
10%	0	0	0	0	0	0	0	0	0
20%	0	0	0	0	0	0	0	0	6
25%	0	0	0	0	0	0	0	4	25
30%	0	0	0	0	0	0	0	10	40
40%	0	0	0	0	0	0	3	29	86
50%	0	0	0	0	0	2	17	67	157
60%	0	0	0	0	2	17	48	120	314
70%	0	0	0	3	12	55	114	217	403
75%	0	0	2	7	29	81	163	310	577
80%	0	0	3	16	56	114	215	398	775
90%	2	5	35	79	166	273	481	738	1,193

Asymptomatic Men (N = 15,238)

	</=35	35-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	>75
10%	0	0	0	0	0	0	0	1	8	17
20%	0	0	0	0	0	0	5	23	51	91
25%	0	0	0	0	0	1	12	41	81	148
30%	0	0	0	0	0	4	25	66	121	233
40%	0	0	0	0	4	15	59	128	216	358
50%	0	0	0	2	14	42	114	211	328	562
60%	0	0	1	8	36	89	206	351	493	816
70%	0	1	4	26	80	166	335	554	749	1,223
75%	0	3	8	41	116	227	421	709	918	1,409
80%	2	5	14	67	161	314	543	888	1,119	1,658
90%	12	23	56	174	379	654	996	1,484	1,667	2,396

tion after age 45; in women, this increase is delayed for 10 to 15 years (Table 1).

EBT as a Diagnostic Tool in Symptomatic Persons

As opposed to other noninvasive modalities to diagnose CAD focusing on physiologic consequences of coronary obstruction, EBT coronary calcium represents an anatomic measure of plaque burden.[20,21,25] Studies comparing pathologic and EBT findings have shown that the degree of luminal narrowing is weakly correlated with the amount of calcification on a site-by-site basis,[26-28] whereas total calcium score is more closely associated with the presence and severity of maximum angiographic stenosis.[29-31] Although a positive EBT study (presence of CAC) is nearly 100% specific for atheromatous coronary plaque,[32] the ability of EBT to predict significant stenosis in a highly specific manner has been challenged. Because both obstructive and nonobstructive lesions have calcification present in the intima, CAC is not specific to obstructive disease.[33] It needs to be underscored that, although increasing calcium scores are more predictive of obstructive CAD, there is not a 1 to 1 relationship between calcification and stenosis. The overall specificity of any CAC for obstructive CAD is approximately 66%.[34] Rumberger et al[35] showed that higher calcium scores are associated with a greater specificity for obstructive disease at the expense of sensitivity; for example, a threshold score of 368 on EBT was 95% specific for the presence of obstructive CAD. EBT has been shown to be comparable to nuclear exercise testing in the detection of obstructive CAD.[33,36] The accuracy of EBT is not limited by concurrent medication, the patient's ability to exercise, or baseline electrocardiogram abnormalities.

Detection of coronary calcium by EBT has been shown to be highly sensitive for the presence of significant CAD. A recent report of 1,764 persons undergoing angiography and EBT similarly showed a very high sensitivity and negative predictive value in men and women (>99%).[37] Thus, a score of 0 (no coronary calcium) can virtually exclude those patients with obstructive CAD, making this test an effective filter before invasive angiography.

In a study of 1,851 patients undergoing angiography and CAC measure,[34] EBT calcium scanning in conjunction with pretest probability of disease derived by a combination of age, gender, and risk factors can assist the clinician in predicting the severity and extent of angiographically significant CAD in symptomatic patients. Recent guidelines support the use of EBT in symptomatic persons, stating that EBT is "sufficiently accurate for predicting the presence of angiographic stenosis."[38]

Another common use of CAC is to determine the etiology of cardiomyopathy. The clinical manifestations of patients with ischemic cardiomyopathy are often indistinguishable from those patients with primary dilated cardiomyopathy. Budoff et al[39] showed in 120 patients with heart failure of unknown etiology that the presence of CAC was associated with a 99% sensitivity for ischemic cardiomyopathy.

Another application of EBT relates to the triage of chest pain patients. Three studies have documented that EBT is a rapid and efficient screening tool for patients admitted to the emergency department with chest pain and nonspecific electrocardiograms.[40-42] These studies show sensitivities of 98% to 100% for identifying patients with acute MI and very low subsequent event rates for persons with negative tests. The high sensitivity and negative predictive value may allow early discharge of those patients with nondiagnostic ECG and negative EBT scans (scores = 0). Thus, exclusion of coronary calcium may therefore be used as an effective filter before invasive diagnostic procedures or hospital admission.

EBT and Prognostication

The most powerful and important data for this modality relate to its ability to predict future coronary events in both symptomatic and asymptomatic persons. Risk factors have been shown to be suboptimal predictors of future events, failing to predict one third of future deaths caused by CAD.[43] It has been known for some time that CAC may have a negative prognostic significance in symptomatic individuals. In 1980, Margolis et al[44] assessed the significance of CAC found on fluoroscopy in 800 patients undergoing coronary angiography. The patients with CAC had a 5-year survival rate of 58% compared with a rate of 87% for the patients without CAC. In a symptomatic patients study by Kennedy,[45] EBT detected CAC was a stronger independent predictor of disease and future events than a sum of all of the traditional risk factors combined.

Three prognostic studies have been reported in the symptomatic population. A multicenter study[46] of 491 patients undergoing coronary angiography and EBT scanning found that higher calcium scores were associated with an increased risk of coronary events over the next 30 months as compared with patients in the lowest quartile of score (odds ratio 10.8, 95% confidence interval [CI] 1.4-85.6). In multivariate analysis, the only predictor of a hard cardiac event was log calcium score. The ability to predict future events was greater with EBT calcium scores than with measures of angiographic severity, reinforcing the idea that plaque burden, and not stenosis severity, is a more important marker of disease.[12]

Keelan et al[47] followed 288 symptomatic persons who underwent angiography and EBT calcium scanning for a mean of 6.9 years and found that age and CAC score were the only independent predictors of future hard coronary events (relative risk 3.20, 95% CI 1.17-8.71). Only 1 in 87 patients with CAC <20 experienced a subsequent hard event during follow-up. Importantly, after stepwise multivariable analysis, neither angiographic stenosis nor conventional coronary risk factors (other than age) predicted events. This study confirmed the previous findings of Detrano et al[46] that CAC extent determined by EBT provides more prognostic information than angiography or risk factors in symptomatic patients. Another recent study[41] observed 192 patients for an average of 50 ± 10 months after undergoing an EBT study while in the emergency department for chest discomfort.[31] The investigators found that the presence of CAC (calcium score >0) and increasing absolute calcium score values were strongly related to the occurrence of hard events ($P < .001$) and all cardiovascular events ($P < .001$). The patients with absolute calcium scores in the top 2 quartiles had a relative risk of 13.1 (95% CI, 5.6-36; $P < .001$) for new cardiovascular events as compared with the patients in the bottom 2 quartiles. The annualized cardiovascular event rate was 0.6% for subjects with a CAC score of 0 compared with an annual rate of 13.9% for patients with a coronary artery calcium score >400 ($P < .001$).

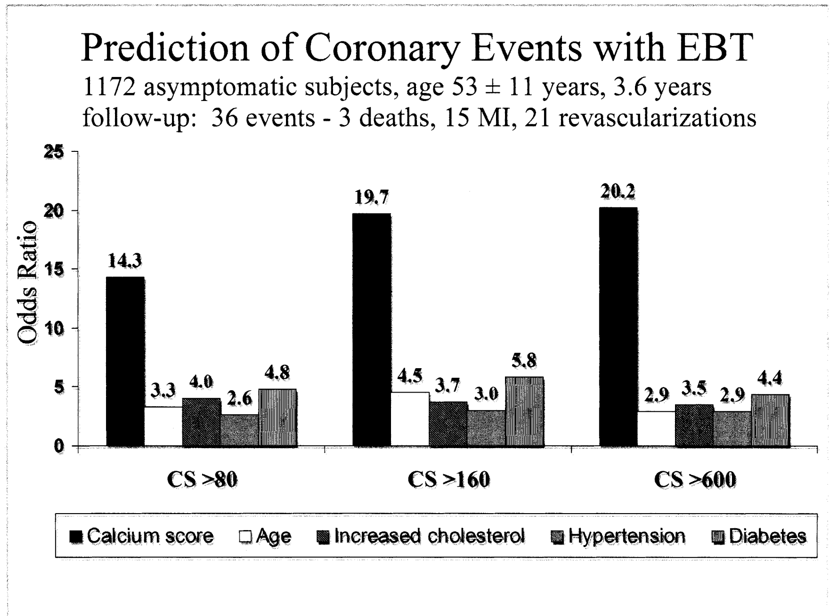

Fig 2. Prediction of cardiac events in asymptomatic patients by EBT coronary calcium scores and comparison with NCEP risk factors. See text for details.

Prediction of Events in Asymptomatic Individuals

At least half of all first coronary events occur in asymptomatic individuals who are unaware that they have developed silent CAD. Several lipid-lowering trials have shown that substantial risk reduction can be attained with both secondary and primary prevention measures.[2,48] However, these studies have required many thousands of subjects to show benefits and documented that risk reduction is only on the order of 25% to 37%, suggesting that better screening modalities are needed to identify asymptomatic individuals at risk of hard events. The data showing CAC as a marker of increased cardiac risk has grown considerably over the last several years. Several large prospective trials have been published showing the prognostic ability of EBT to identify patients at high risk of cardiac events.

Arad et al[49] initially reported a 19-month follow-up of 1,173 patients. Asymptomatic individuals were scanned using EBT as well as measures of traditional risk factors and followed prospectively for cardiac events. This study showed CAC to be the strongest predictor of future cardiac events, with patients in the highest score category over 20 times more likely to suffer a cardiac event (odds ratio 22.3, CI 5.1-97.4). This prospective study now has been carried out for a total of 3.6 years of follow-up, maintaining the strong power of this technology to predict future cardiac events (Fig 2). [50] The subjects who had an event had significantly larger calcium scores than did the subjects with no events (764 ± 935 *v* 135 ± 432, $P < .0001$). A calcium score >160 was associated with a high likelihood of having a soft event (odds ratio, 15.8) or a hard event (odds ratio, 20.2). The predictive ability of the absolute calcium score was excellent for all coronary events and for hard events alone (receiver operating characteristic, 0.84 and 0.86, respectively).

Agatston et al[51] reported the longest follow-up data. There was a significant difference in the mean CAC scores for patients with cardiac events (399 ± 424) versus those without (76 ± 207) showing an odds ratio of 21.2 for coronary events in patients with CAC scores of >26 and 16.9 for scores above 50 (hard events). A 10-year follow-up of 1,783 patients revealed that patients who had scores >600 had an increased all-cause mortality (27%) significantly greater than those with low or zero scores (score 0-79, 3% all-cause 10-year mortality).[52]

Detrano et al[53] published an analysis in an older population (1,196 patients, 89% men, mean age 66 years). This study showed that although CAC

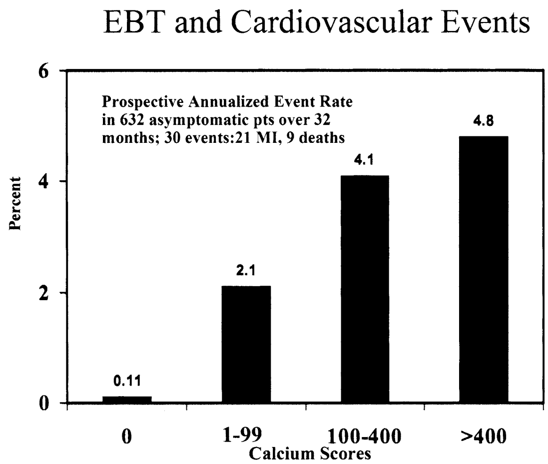

Fig 3. Prediction of cardiac events in asymptomatic patients by EBT coronary calcium scores. See text for details.

was a significant predictor of future cardiac events, it did not have great power over traditional risk factors to discriminate who will develop CAD events. Unfortunately, this study used limited scanning protocols (6-mm thick slices) that have since proven not as sensitive as the standard protocol (3 mm) and a definition of a calcific focus that was up to 16 times greater than other studies (>8 mm^2).[54] Subsequent data in this same cohort[55] showed that EBT-derived coronary calcium scores were incremental in predicting cardiac risk, consistent with prior data. In this study, the predictive power of CAC constituted most of the risk prediction, as the relative risk of hard cardiac events increased from 1 to 4.9 with increasing calcium tertiles ($P = .005$), whereas C-reactive protein failed to add independent prognostic value for hard cardiac events. The authors showed that the use of EBT-derived calcium scores strongly predicted future cardiac events in a high-risk cohort.

Raggi et al[56] followed 632 asymptomatic individuals with risk factors for CAD for an average of 32 ± 7 months and reported the occurrence of 19 MIs and 8 deaths. Of these events, 70% occurred in patients with a calcium score in the upper quartile for age and sex. A zero score was associated with a 0.11%/year event rate compared with 4.8 %/year with a score >400 (Fig 3). The event rate in patients with calcium scores in the highest quartile was 22 times the event rate in patients with calcium scores in the lowest quartile. It was 3 times greater than the relative risk of the upper quartile versus lower quartile of all the National Cholesterol Education Program (NCEP) risk factors combined, significantly outperforming risk factors in cardiac event prediction (Fig 4). They showed the incremental benefit of adding calcium scores to conventional risk factors. Multiple logistic regression analyses showed that calcium score percentile was the only significant predictor of

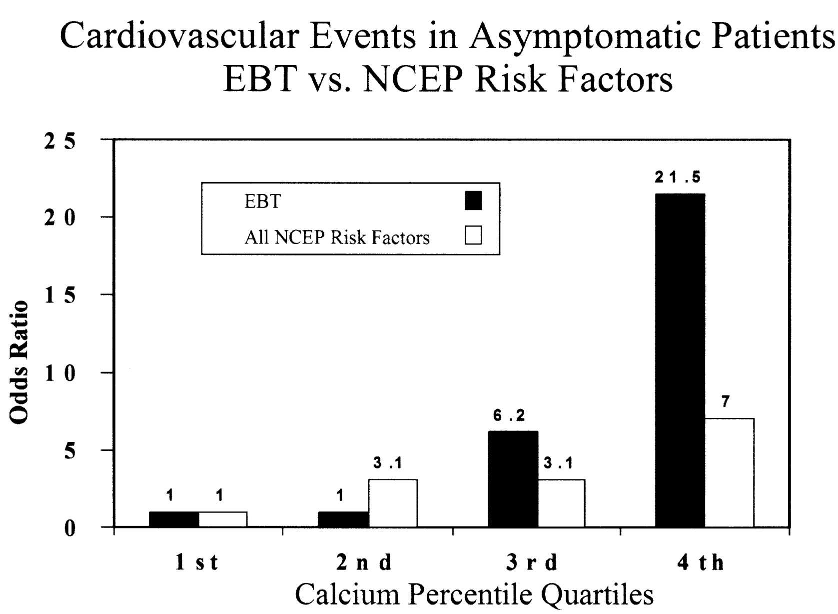

Fig 4. Prediction of cardiac events in asymptomatic patients by EBT coronary calcium percentiles ad comparison with NCEP risk factors. See text for details.

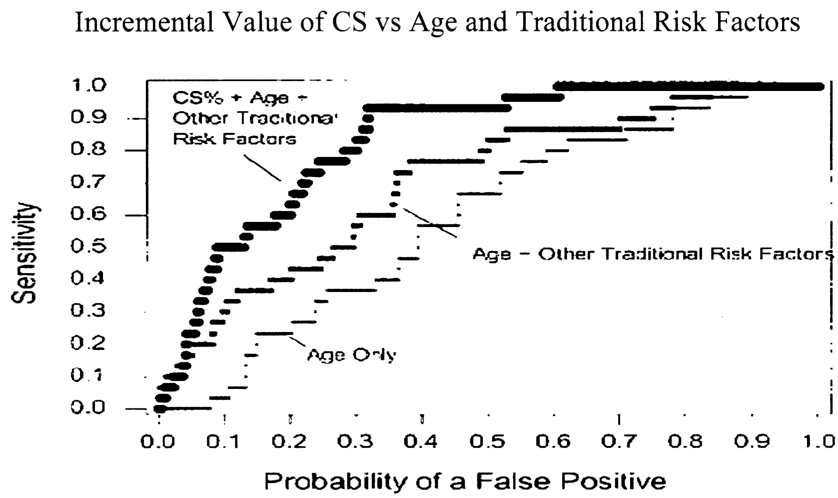

Fig 5. Incremental value of EBT coronary calcium scanning. See text for details. (Reprinted with permission of the American Heart Journal.)

events and provided incremental prognostic value when added to traditional risk factors for CAD (χ^2, $P < .001$). In a comparison of receiver-operator characteristic curves for prediction of hard events, the area under the curve for CAC score plus conventional risk factors and age was significantly larger than that obtained by use of traditional risk factors and age separately as predictors (0.84 *v* 0.71, respectively, $P < .001$). Furthermore, the area under the curve of CAC score alone was significantly larger than that of traditional risk factors and age combined (0.82 *v* 0.71, $P = .028$) (Fig 5).

Wong et al[57] followed 926 asymptomatic men and women (mean age 54 years) for an average of 3.3 years. Sixty percent of men and 40% of women had a positive scan at baseline. Calcium scores were significantly higher in patients with events than in patients without events. The presence of CAC and increasing score quartiles were related to the occurrence of new MI ($P < .05$), revascularization ($P < .001$) and total cardiovascular events ($P < .001$). The risk ratio for events in patients whose absolute calcium score was in the upper quartile (score >271) compared with individuals whose absolute calcium score was in the lowest quartile (score <15) was 12 (relative risk 8.8 and 0.72, respectively; $P < .001$), with risk factors adding no incremental prognostic information to the calcium score information.

A meta-analysis[58] of 5 studies involving 4,348 subjects found that a calcium score above a median score was associated with an increased risk of a combined outcome of nonfatal infarction, death, or revascularization (risk ratio 8.7, 95% CI 2.7-28.1) and of a hard event, ie, death or infarction (risk ratio 4.2, 95% CI 1.6-11.3). Another summary article included 9 manuscripts involving EBT, encompassing 6,320 persons.[59] Summary risk for 3 studies of symptomatic populations (total 1,000 patients followed for an average of 3.5 years) showed that EBT-derived calcium scores confer a 9.3-fold increased risk for cardiac events. Similarly, a composite of 6 studies of asymptomatic persons (5,320 persons followed for 3.6 years) showed a 10.9-fold increase risk of suffering a cardiac event.

More recently, larger trials have been reported showing approximately 10-fold increased risk with the presence of CAC. In a prospective study of 5,585 subjects aged 59.5 ± 5 years, a calcium score >100 predicted all atherosclerotic cardiovascular disease events, all coronary events, and the sum of nonfatal myocardial infarction and coronary death events with relative risks of 9.5 to 10.7 at 4.3 years.[60] The calcium score also predicted events independently of and more accurately than measured risk factors. The area under the receiver operating characteristic curve for event prediction with risk factors alone in this study was 0.71, increasing to 0.81 with EBCT testing ($P < .01$). This prospective study strongly showed the ability to use this test to identify patients who do not need therapy. In this study, only 19% of patients had scores above the diagnostic threshold (calcium score ≥100); yet relying on this threshold had a negative predictive power of 99.2%. Thus, clinicians can focus on a smaller, yet higher-risk population (10.7-fold increased risk in this group) for risk-reduction therapy.

In another study, Kondos et al[61] reported 37-month follow-up on 5,635 initially asymptomatic low- to intermediate-risk adults. In men, events (n = 192) were associated with the presence of CAC (relative risk = 10.5, $P < .001$), diabetes (relative risk = 1.98, $P = .008$), and smoking (relative risk = 1.4, $P = .025$), whereas in women events (n = 32) were linked to the presence of CAC (relative risk = 2.6, $P = .037$) and not risk factors. Although follow-up was only obtained in 64% of patients, patients with scores >170 had a relative risk for developing hard cardiac events of 7.24 (95% CI, 2.01-26.15) after multivariate analysis was performed with adjustment for age and other CAD risk factors. The presence of CAC provided incremental prognostic information over age and other risk factors.

Retrospective data also support the prognostic value of EBT-detected CAC for both heart attack and stroke. In the Rotterdam Coronary Calcification Study, 2,013 participants (mean age 71 ± 5.7 years) were evaluated. Compared with subjects in the lowest calcium score category (0-100), the age-adjusted odds ratio for myocardial infarction in the highest score category was 7.7 (95% CI 4.1-14.5) for men and 6.7 (95% CI 2.4-19.1) for women.[62] Subjects were 3 times more likely to have experienced a stroke with calcium scores >500 (odds ratio 3.3, 95% CI 1.5-7.2) as compared with subjects in the lowest calcium score category (<100) and adjusting for carotid intimal thickness and cardiovascular risk factors did not alter the risk estimates.[63]

Until recently, there was still controversy as to the prognostic significance of very high calcium scores; some investigators suggested that the presence of CAC may stabilize the atherosclerotic plaque. The previously mentioned studies would all dispute that higher calcium scores were associated with a higher rate of cardiac events. To address this question more directly, a cohort of 98 patients with extreme calcifications (score >1,000) were followed for 17 months.[64] During the follow-up period, 35 patients (36%) suffered a hard cardiac event (myocardial infarction or cardiac death). The annualized event rate was 25%, showing that a very high calcium score in an asymptomatic person portends a very high risk of a hard cardiac event in the short term.

Based on results of studies presented earlier, Grundy[65] recently suggested modifying the Framingham Global Risk Score by using a weighted factor based on the patient's individual calcium score percentile. According to the proposed modification, the Framingham Risk Score assigned to a subject undergoing EBT screening for asymptomatic CAD should be increased if the person's calcium score is in a high percentile.[65] Recommendations for use of EBT have now been published.[66] The NCEP has made new recommendations as of February 2001, and these recommendations specifically recommend use of EBT to assist in risk stratification in elderly and intermediate risk patients. The new NCEP guidelines[67] support the conclusions of the Prevention Conference V and the ACC/AHA report that high CACs signify and confirm increased risk for future cardiac events.[38] "Therefore, measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons. In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and sex) denotes advanced coronary atherosclerosis and provides a rationale for intensified LDL-lowering therapy."[67]

Spiral CT

EBT is able to acquire high-resolution images of the heart in 100 milliseconds and gate to the cardiac cycle, taking advantage of the diastolic imaging phase when cardiac motion is the least. Previously, helical (spiral or mechanical) computed tomography (CT) scanners were unable to gate the electrocardiogram and had acquisition times greater than 1 second, far too slow to "freeze" cardiac motion. However, helical scanners have undergone great evolution during the last 3 to 5 years. The newest scanners can obtain images with a scan rotation of 420 milliseconds, and with partial scanning, image acquisition takes between 210 and 320 milliseconds.

This speed of acquisition (temporal resolution) greatly differentiates EBT from the results of the slower images from helical CT.[68,69] The only early studies showing similar results between EBT and spiral CT consisted of elderly symptomatic men with very high plaque burdens.[70,71] A recent comparison study in 70 asymptomatic patients undergoing both EBT and spiral CT concluded that "spiral CT has not yet proved to be a feasible alternative to electron-beam CT for coronary artery calcium quantification."[69]

Helical CT has improved greatly with the development of MSCT detector systems, which can acquire 4 to 16 simultaneous slices of 2.5 mm each. MSCT uses gantry rotation speeds of 420 to 500 milliseconds, partial reconstruction algorithms, prospective or retrospective gating, and image acquisition times of about 210 to 300 milliseconds during 1 heartbeat.

Retrospective gating involves acquiring approximately 400 images of the heart and discarding those that did not occur at the proper time in diastole. This retrospective approach is not practical for widespread application as it markedly increases the radiation dose, image analysis time, inter- and intrareader variability, and interscan variability.[69] A more practical approach is prospective gating, which is similar to the methods used by EBT. This acquires an image only at the chosen time (diastole) and reduces variability and radiation. For MSCT, the images are best when the resting heart rate is less than 60 beats per minute; at faster heart rates, motion artifacts may become more prominent.

Becker et al[72] studied 100 patients comparing MSCT with EBCT and reported a modest correlation between the 2 modalities. In this study, the percentage variability was 32% between the 2 modalities for CAC score. Moreover, the level of individual precision was limited and the scores <100 appeared to have the most deviation by MSCT as compared with EBT.

Horiguchi et al[73] showed that MSCT with a retrospective ECG-gating algorithm showed a high correlation with CAC scores determined using EBT in 20 normal volunteers. However, this retrospective approach led to a radiation dose that was 13 times higher than EBT.

Generally, the higher tube currents available with MSCT devices lead to images with somewhat better signal-to-noise ratio and higher spatial resolution when compared with EBCT. However, tube current is generally higher with MSCT, which adds to the radiation exposure. Radiation exposure from prospectively gated MSCT studies (in which all the data gathered are used to make an image) is much less than from retrospectively gated studies; however, the patient doses for MSCT are uniformly higher than EBT.[74] In a recent study of radiation doses, EBT yielded doses of 1.0 to 1.3 mSev, MSCT 1.8 to 6.1 mSev, and coronary angiography 2.1 to 2.3 mSev.[75]

Retrospective gating may offer some advantages at higher heart rates because it can better compensate for heart rate changes and it allows segmented reconstruction to reduce scan acquisition times. Because radiation is continuously applied while only a fraction of the acquired data is used, high radiation doses (6-13 Rad/study) significantly limit the clinical applicability of this modality. Furthermore, the radiation dose delivered by MSCT is anterior, closer to radio-sensitive organs including the breast, thyroid, and orbits, as compared with a posterior dose given by EBT. The manufacturers are attempting to develop a protocol that may reduce radiation doses with MSCT, by attempting to rapidly turn off the beam when it passes behind the subject. Results from a recent study showed that ECG-controlled tube current modulation allows significant dose reduction of 48% and 45% in men and women, respectively, while performing retrospectively ECG-gated MSCT of the heart.[76]

Reproducibility

A promise of CT scanning technologies is to accurately and noninvasively measure atherosclerosis burden, to be able to track changes over time, and to assess efficacy of therapy. This ability to assess progression is dependent on the reproducibility of the technologies. Reproducibility was initially a concern for repeated testing, but hardware and software improvements have lowered interscan variability to a median of 4% to 8%.[77] With excellent inter- and intraobserver variability (1%), this test can measure plaque burden and follow atherosclerosis over time. Using new gating algorithms, EBT interscan reproducibility has been shown to be approximately 11%, with interreader variability approximately 3% and intrareader variability less than 1%.[78] This has been significantly more problematic with MSCT. The interscan variability is between 32% and 40%, leading to the conclusion that "helical CT is not sufficiently reproducible to allow serial quantification of total calcium score over time."[79] Interreader variability with helical CT is also problematic, with a mean interreader variability of 4.5% for EBT compared with 41.5% for helical CT, and suggested double reading all studies to better assess coronary calcium.[69]

Helical CT currently has a higher radiation dose, is less reproducible, and less validated; however, it has a higher spatial resolution and lower temporal resolution than EBT. Because of these limitations, EBT currently remains the gold standard for cardiac CT imaging, including noninvasive angiography and calcium plaque assessment.

Cost-effectiveness

The use of EBT to better risk stratify patients could greatly reduce costs and better direct therapy. Recent European joint-society guidelines[80] recommend using aggressive risk-reduction therapy in asymptomatic patients if their absolute risk approximates that of patients with coronary heart disease. Drug therapy, although very effective, entails significant expense. The average cost of statin therapy in the United States is approximately $720 (US) per year,[81] not including physician visits or laboratory tests. With the recent withdrawal from the marketplace of one of the statin medications because of safety concerns (cerivastatin), the need to identify persons who would truly benefit from these medications is even greater. The absence of CAC in the asymptomatic patient identifies a group of patients at very low risk of events over the next 3 to 5 years.[32,38] Raggi[56] showed an annual event rate of only 0.11% for patients with scores of zero. Both the American College of Cardiology/American Heart Association writing group and the Prevention V Conference agreed that the negative predictive value of EBT is very high for short-term events.[38,82] In 1 model, CAC screening with EBT was shown to be a cost-effective screening test in asymptomatic individuals between 45 and 65 years of age.[83] Combining the power of this noninvasive tool with the effectiveness of statin drugs, aspirin, and other therapies will allow physicians to focus aggressive preventative treatment on those individuals with underlying atherosclerosis who are at highest risk of having future heart attacks and coronary death. Whether a score of zero will allow physicians to withhold therapy also remains to be prospectively tested. However, because most cardiac events occur in individuals at intermediate risk, it seems appropriate to concentrate screening efforts on this group of patients. Current guidelines suggest intermediate risk patients would benefit most from further risk stratification.[38,84] Recent work suggests that EBT can also improve risk prediction in intermediate-risk patients. Thus, with a prior probability of a coronary event in the intermediate range (>6% in 10 years but <20% in 10 years), a calcium score would yield a posttest probability in virtually all such patients greater than 2% per year, that is, a level similar to that in secondary prevention, or a coronary risk equivalent.[84]

Furthermore, Wong et al[85] showed that persons with CAC have been reported to be more likely to undertake preventive health measures, including beginning cholesterol- or blood pressure–lowering medications, starting aspirin, initiating an exercise program, following a low-fat diet, or quitting smoking.

Because a score of zero is associated with a very low (<1%) chance of obstructive CAD,[36] the use of EBT before angiography has been recommended.[86] In the symptomatic patient, evidence suggests that EBT may be more cost-effective at diagnosing CAD than traditional noninvasive testing, especially in women.[83]

Limitations of EBT and CT

The presence of CAC does not allow for reliable identification of the unstable or vulnerable plaque. However, CAC quantification appears to identify persons at increased risk. The available data suggest that although we cannot identify the vulnerable plaque, by measuring overall plaque burden, EBT can identify the vulnerable patient.[32] A positive EBT shows that advanced atherosclerosis exists in this person, and appropriate therapies should be applied.[38,82] Furthermore, because CAC is not specific for obstructive CAD, other testing may be necessary to confirm high grade stenosis before angiography.

Conclusions

The prognostic studies of EBT (Table 2), alone or in combination, provide consistent and supportive evidence that EBT-detected CAC carries significant prognostic weight. The presence of CAC in asymptomatic individuals predicts the occurrence of acute coronary events with greater accuracy than other screening tests, including risk fac-

Table 2. Characteristics and Risk Ratio for Follow-Up Studies Using Electron Beam Tomography

Author	Number	Symptoms	Mean Age (years)	Follow-up Duration (years)	Sex (% Male)	Calcium Score Cutoff	Risk Ratio
Georgiou[41]	192	Yes	53	4.2	54	Median†	13.1
Detrano[46]	491	Yes	57	2.5	64	Top Quartile	10.8
Keelan[47]	288	Yes	56	6.9	77	Median (>480)	3.2
Arad[49]	1,173	No	53	3.6	71	CAC >160	20.2
Agatston[51]	367	No	52	6.0	68	CAC >50	16.9
Detrano[53]	1,196	No	66	3.4	89	CAC >44	2.3
Park[55] (subset of 53)	967	No	67	6.4	91	CAC >142.1	4.9
Raggi[56]	632	No	52	2.7	51	Top Quintile*	15.4
Wong[57]	926	No	54	3.3	79	>270-Top Quartile	8.8
Arad[60]	5,585	No	59	4.3	70	CAC ≥ 100	10.7
Kondos[61]	5,635	No	51	3.1	74	CAC > 0	Men 10.5 Women 2.6

Abbreviations: CAC, coronary artery calcium score.
*Using age- and gender-matched cohorts, representing the top quintile.
†Using age- and gender-matched cohorts, representing top quartile.

tors.[45,50,57] Two ongoing trials (MESA trial in the United States and the Heinz Nixdorf Recall Study in Germany) will examine the value of EBT-derived CAC in the general population and provide more answers in relation to the role of CAC in primary prevention.

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