Prognostic Value of Coronary Artery Calcification
Matthew J. Budoff, MD

Objective: The quantitation of coronary artery calcium using electron beam tomography (EBT) has been proposed as an early detection method. The objective of this paper is to summarize the known data about coronary artery calcium and event prediction with EBT and spiral computed tomography (CT).

Design: Comprehensive review of the literature, including MEDLINE and abstracts from recent radiology and cardiology meetings.

Data sources: 9 manuscripts involving EBT were identified, encompassing 6320 persons. There were no published prognostic studies of spiral CT.

Outcome measure: Cardiac endpoints were described as hard (fatal or nonfatal myocardial infarction) and soft clinical events (revascularization).

Results: The predictive ability of EBT for coronary artery disease events was studied in 3 manuscripts in symptomatic persons and in 6 manuscripts in asymptomatic persons. Summary risk for 3 studies of symptomatic populations (total, 1000 patients followed for an average of 3.5 years) demonstrated that EBT-derived calcium scores confer a 9.3-fold increased risk for cardiac events. Similarly, a composite of 6 studies of asymptomatic persons (5320 persons followed for 3.6 years) demonstrated a 10.9-fold increase risk of suffering a cardiac event.

Conclusion: This ability to predict future cardiac events, in both symptomatic and asymptomatic persons, will potentially add to the ability of the medical community to identify high-risk individuals prior to the cardiovascular event. Larger and longer population studies in asymptomatic populations are underway.

Given the burden of coronary artery disease (CAD), accounting for over 500,000 deaths annually, there is a need for new strategies for identifying high-risk individuals prior to the first event [1]. The initial manifestation of CAD in up to 50% of patients is a serious or life-ending event, such as sudden death or extensive myocardial infarction (MI) [2,3]. While lifestyle changes and certain pharmacological interventions have been shown to increase the life expectancy of high-risk persons [4], establishing an inexpensive and safe screening test that can accurately identify persons who have unrecognized CAD would be of enormous benefit.

Unfortunately, many previous attempts at screening were directed at finding advanced luminal obstruction (eg, exercise treadmill testing, stress nuclear testing, stress echocardiography). Multiple trials have now demonstrated that a vast majority of heart attacks occur at the site of a nonobstructive plaque [5]. Coronary occlusion and MI most frequently evolve from mild to moderate stenoses [5–7]. This minimal stenosis can rupture, causing death or MI, in the absence of an advanced (highly stenotic) lesion in the coronary tree. Furthermore, research over the past decade has demonstrated that luminal obstruction is not the greatest predictor of cardiac events. Studies of patients dying from either acute MI or sudden cardiac death have also demonstrated that the extent of coronary atherosclerosis, rather than the severity of stenosis, is the most important predictor [8,9]. Thus, the need to measure coronary plaque burden, rather than stenosis severity (as seen on cardiac catheterization), has become paramount to risk stratification.

Coronary Artery Calcification and Atherosclerosis
Calcific deposits in coronary arteries are pathognomonic of atherosclerosis [10,11]. Histopathological [11,12,13] and intravascular ultrasound [14,15,16] studies confirm the close correlation between atherosclerotic plaque burden and extent of coronary artery calcification (CAC). Investigators measured plaque volume and demonstrated consistent and direct relations between CAC and plaque volume by autopsy and intravascular ultrasound. Electron beam tomography (EBT) can accurately and noninvasively quantitate the amount of CAC ($r > 0.90$) [17,18]. Other noninvasive modalities to diagnose CAD focus on physiological consequences of coronary obstruction, while EBT coronary calcium represents an anatomic measure of plaque burden [19].

Calcification and Plaque Rupture
Although calcification is ubiquitous in complex coronary atherosclerotic plaques, calcium appears to be more than just...
an innocent bystander for the disease. It is associated with an increased risk of plaque rupture and thrombosis [20,21]. The presence of a soft plaque with a point of weakness adjacent to an area of calcification predisposes the plaque to rupture [22]. However, as the calcific and fibrotic plaque lesions are much stiffer than the softer cellular lesions, calcification may actually be an attempt by the arterial walls to stabilize themselves and thereby minimize the risk of plaque rupture. Thus, it may be that early or moderate arcs of calcification render a plaque more prone to rupture, whereas extensive concentric calcification (seen particularly in the very elderly), may render a plaque less likely to rupture [23]. Regardless of the ongoing debate as to the exact composition of the “vulnerable plaque,” CAC is almost always ubiquitous in patients who suffer cardiac events.

**Electron Beam Tomography**

Electron beam tomography cardiac imaging involves obtaining thin slices (each 3 mm) of the heart and coronary arteries to evaluate for CAC. 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. Rapid image acquisition (100 msec) prevents image blurring and allows accurate visualization of very small calcium deposits in the coronary arteries. The calcific deposits in the arterial walls demonstrate a high attenuation compared to the surrounding soft tissue, and this permits the easy identification of CAC without injection of contrast medium [24]. This speed of acquisition (temporal resolution) greatly differentiates EBT from the results of the slower images from spiral (or multislice helical) computed tomography (CT) [25,26]. The only studies demonstrating similar results between EBT and spiral CT included elderly symptomatic men with very high plaque burdens [27,28]. The differences at lower scores may very well prove a major difference in prognostic ability. Since there is no improvement of temporal resolution with newer multislice CT scanners (each slice is still obtained in 250 to 330 msec), it is unlikely that closer correlations with EBT will be obtained. Furthermore, with thinner slices being obtained, more radiation is given to the patient, potentially increasing radiation doses to the patient with multislice CT by 6 to 38 times over EBT [29]. Only the long-term studies now underway (such as the ongoing Multiethnic Study of Atherosclerosis) will be able to demonstrate whether spiral CT has a role in prognostication.

**Calcification and Cardiac Risk in the Symptomatic Cohort**

Numerous studies demonstrate that the calcium detected by EBT is a marker of the total atherosclerotic burden, and the extent of coronary atheromatous disease remains the most powerful predictor of subsequent or recurrent cardiac events [30,31]. While useful for use in the symptomatic population to determine the presence and severity of obstructive disease [24,32], the most important data for this modality relates to its ability to predict future coronary events in both symptomatic and asymptomatic persons. The need for a screening test for early atherosclerosis is in part due to the failure of risk factors to predict cardiac events. Risk factors have been demonstrated to be poor predictors of future events, failing to predict one-third of future deaths due to coronary heart disease [33]. In a study of symptomatic patients by Kennedy et al [34], EBT-detected coronary calcium was a stronger independent predictor of disease and future events than a sum of all of the traditional risk factors combined.

This paper evaluated the published data to identify the prognostic ability of EBT. A comprehensive review of the literature, including MEDLINE and abstracts from recent radiology and cardiology meetings, was performed. Nine manuscripts involving EBT were identified, encompassing 6320 persons. Three studies involved symptomatic persons [35–37] and 6 studies involved asymptomatic persons [38–43].

CAC appears to be a far more powerful risk factor for coronary events than any other known risk factor [38]. Margolis and colleagues in 1980 found that patients referred for cardiac catheterization with coronary calcium on conventional fluoroscopy had a 5-year survival rate of 58% versus 87% in patients without detectable calcium [20]. This was independent of age, gender, and angiographically diseased vessels. Detrano et al’s multicenter study [35] 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. This study found an event rate increase 10 times higher in patients with calcium scores over the 75th percentile as compared to those below the 25th percentile (odds ratio [OR], 10.8 [95% confidence interval [CI], 1.4 to 85.6]). Logistic regression including gender, age, calcium score, and angiographically diseased vessels showed that only EBT calcium score predicted events. This study demonstrated that 86% of the events occurred in patients whose scores were 100 or greater, with significantly greater event-free survival in patients with lower scores ($P = 0.009$). 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 [6].

Keelan et al [36] followed 288 symptomatic persons who underwent angiography and EBT calcium scanning for a mean of 6.9 years. Event-free survival was significantly higher for patients with CAC scores less than 100 than it was for those with scores greater than 100 (relative risk [RR] 3.2 [95% CI, 1.2 to 8.7]) and above the median score (RR, 3.4 [CI, 1.3 to 8.7]). In the final stepwise Cox proportional hazards model that included risk factors, CAD event history; CAC measures; and angiographic measures of disease, age, and log-transformed
CAC score were the only independent predictors of future hard coronary events. Importantly, no conventional coronary risk factors other than age predicted events. While the study demonstrated that plaque burden by EBT was associated with increased cardiovascular risk over 7 years, the study was limited by its patient population. However, this study confirmed the previous findings of Detrano et al [35], which showed that CAC extent determined by EBT provides more prognostic information than angiography in symptomatic patients. This phenomenon is most likely due to the remodeling phenomenon, in which vessel wall enlargement compensates for increasing plaque volume [44]. However, CAC extent is unaffected by remodeling, and as the overall disease burden and the likelihood of vulnerable plaque increase, so does CAC extent [45].

Another recent study [37] reported a 50-month mean follow-up of a chest pain population. Cox proportional hazards regression showed CAC to be associated with a greater risk for having a new cardiovascular event independent of age, gender, race, and other risk factors. Those with any CAC had an increased risk of new cardiovascular events (OR, 27.8 [95% CI, 1.88, 815]; P = 0.02). Multivariate logistic regression analysis demonstrated CAC score and age- and gender-matched calcium percentiles to be the strongest predictors of future events.

The summary risk ratio for a combined coronary event (eg, death, MI, or revascularization) was 9.3 in these studies of symptomatic persons (Table 1). This represents 3 studies including 1000 persons, followed for an average of 42 months. EBT outperformed angiography and all risk factors in event prediction in all studies in which both were tested.

**Table 1. Characteristics and Risk Ratios for Follow-up Studies in Symptomatic Populations**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>% Male</th>
<th>Mean Age, Yr</th>
<th>Follow-up Duration, Mo</th>
<th>Cutoff for Risk Assessment</th>
<th>Risk Ratio</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrano [35]</td>
<td>491</td>
<td>—</td>
<td>—</td>
<td>30</td>
<td>Top quartile</td>
<td>10.8</td>
<td>49</td>
</tr>
<tr>
<td>Keelan [36]</td>
<td>288</td>
<td>77</td>
<td>56</td>
<td>83</td>
<td>Median (&gt; 480 CAC)</td>
<td>3.4</td>
<td>29</td>
</tr>
<tr>
<td>Georgiou [37]</td>
<td>221</td>
<td>54</td>
<td>53</td>
<td>50</td>
<td>Median*</td>
<td>13.1</td>
<td>22</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1000</td>
<td>—</td>
<td>55</td>
<td>42</td>
<td>—</td>
<td>9.3</td>
<td>100</td>
</tr>
</tbody>
</table>

CAC = coronary artery calcification score.

*Using age- and gender-matched cohorts representing scores above the median.

Risk Prediction in the Asymptomatic Population

The potential utility of any screening tool is greatest in the asymptomatic (primary prevention) population. Determining where to apply more aggressive therapies, including cholesterol reduction, antiplatelet therapy, diet, and exercise, is of greatest interest to the preventive health community. With the recent withdrawal from the marketplace of 1 of the statin medications due to safety concerns (cerivastatin), the need to identify persons who would benefit from these medications is even greater. While the short- and long-term risks of the statins have been shown to be minimal overall [46], targeting therapy to those who will benefit will clearly improve any risk or cost profile for this therapy. Similarly, if a high-risk population can be identified by a screening test, further evaluation to find and treat modifiable risk factors could be implemented, potentially including further lipoprotein analysis, C-reactive protein, homocysteine, and many other potentially modifiable factors.

Several studies of CAC have been performed in the asymptomatic population. The first reported a 19-month follow-up of 1289 asymptomatic patients and found a 6.9-fold increase of hard events (MI and cardiac death) in patients with calcium scores over 50 compared to those with negative or lower scores [47]. Arad et al [48] initially reported a 19-month follow-up of 1173 patients over 19 months, finding CAC to be the strongest predictor of future cardiac events. 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 [38]. During this 3.6-year follow-up period, 39 patients suffered coronary events. The mean CAC score was 764 among subjects with events as compared to 135 among those without events (P < 0.001). Patients with EBT scores above 80 were 22 times more likely to suffer an MI or death over the follow-up period (OR, 22.3 [CI, 5.1 to 97.4]). The odds ratio of suffering a coronary event remained high (14.3 to 20.2) after adjustment for cardiovascular risk factors.

The longest follow-up data available are from Agatston et al, in which 367 patients were followed up to 6 years. Agatston noted a significant difference in the mean coronary calcium scores for patients with cardiac events (399 ± 424), versus those without cardiac events (76 ± 207) [39]. This difference was computed to an odds ratio of 21.2 for coronary events in patients with CAC scores greater than 26, and 16.9 for scores above 50 (hard events).

It should be noted that caution should be used in screening an older population. Our group published an analysis in an older population (1196 patients, 89% male, mean age 66 years) [40]. This study demonstrated that while coronary
calcium was a significant predictor of future cardiac events, it did not have great power over traditional risk factors to discriminate who would develop CAD events. The composite endpoint of coronary death or infarction was significantly higher in the upper tertiles of the calcium score ($P < 0.01$).

In this study, neither traditional risk factors nor EBT coronary calcium accurately predicted future events. We identified several factors that limited our study. First, our study sample was very homogenous, mostly elderly men with hypertension and/or diabetes. Secondly, we utilized a minimum area for calcification that was much larger (16 times) than other studies, requiring a very large focus of calcification to qualify as a lesion. It is likely that smaller plaques can be destabilizing and large areas of calcification protective. Finally, we utilized a scanning protocol (6 mm–thick slices) that has proven to be not as sensitive as the standard protocol (3 mm) [49]. However, in this study, among of the population most likely to benefit from screening for heart disease (ages 45 to 62 years) the relative risk of developing a cardiac event was 6.3 ($P < 0.001$) [50]. Thus, performing the study properly and targeting of the correct population is of great importance when applying this test. Secci [51] reported a subset study of 326 patients, with 8 of 9 hard events and 20 of 21 total cardiac events (hard events and revascularization) occurring in those patients with EBT calcium scores over 15 ($P < 0.001$), demonstrating excellent prognostic ability.

A meta-analysis [52] of 5 studies (2 abstracts and 3 manuscripts) [53] involving 4348 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 to 28.1]) and of a hard event (eg, death or infarction [risk ratio 4.2 [95% CI, 1.6 to 11.3]). The authors concluded that there exists a “moderate to strong association between coronary calcification as detected by EBT and hard and soft coronary outcomes.”

In a recent study of 676 asymptomatic patients (mean age, 52 years; 51% men) prospectively followed for 32 ± 7 months by Raggi et al [41], calcium scores outperformed risk factors in cardiac event prediction and demonstrated the incremental benefit of adding calcium scores to conventional risk factors. Multiple logistic regression analyses demonstrated that calcium score (adjusted for age) was the only significant predictor of events and provided incremental prognostic value when added to traditional risk factors for CAD (chi-square, $P < 0.001$). In a comparison of receiver-operator characteristic curves for prediction of hard events, the area under the curve for calcium score percentile 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 versus 0.71, respectively; $P < 0.001$). Furthermore, the area under the curve of calcium scores alone was significantly larger than that of traditional risk factors and age combined (0.82 versus 0.71; $P = 0.028$). Increasing age- and gender-matched scores were even more predictive. Thus, patients with scores above the median had an odds ratio of 5.5 (3.0 to 10.1) for fatal and nonfatal MI. The risk increased with increasing scores, and for patients with scores above the 90th percentile (as compared to age- and gender-matched peers), the odds ratio increased to 21.6 (7.3 to 64.1). The authors concluded that “an age- and sex-specific calcium score provides the best predictive model for the occurrence of hard coronary events and adds incremental prognostic information to conventional risk factors for CAD.”

Similarly, in a recent publication by Wong et al [42], 928 asymptomatic men and women (mean age, 54 years) followed for an average of 3.3 years with an absolute CAC score in the upper 3rd and 4th quartiles showed a relative risk for cardiovascular events of 4.5 and 8.8 times that of patients in the lowest quartile, respectively. With use of Cox proportional-hazards, it was shown that patients with CAC had a greater risk of events than patients without CAC independent of age, sex, and risk factors.

The summary risk ratio for a combined coronary event (death, MI, or revascularization) was 10.7 in these studies of asymptomatic persons (Table 2). This represents 6 studies including 5320 persons, followed for an average of 43 months. EBT outperformed risk factors and other demographic variables for event prediction in all studies, except for the study of elderly persons by Detrano et al [40].

**Comparisons with Other Screening Tests and Implications for Risk Stratification**

To put these figures in perspective, screening stress tests predict future cardiac events with an odds ratio of 1 to 3 at 6 years [38]. Cholesterol values, hypertension, diabetes, and other Framingham risk factors have been reported to be associated with odds ratios of 1 to 3 for future cardiac events [54]. C-reactive protein, a marker of inflammation, demonstrated an odds ratio of 2 to 4.4 for predicting future cardiac events [55]. Thus, with an odds ratio of 4.2 to 22, EBT-detected CAC appears to be a more comprehensive measure of future cardiac risk. The importance of finding new predictors of risk is highlighted by the known suboptimal predictive value of conventional risk factors. Despite the use of a multifactorial approach to risk stratification, as advocated in the Framingham study and the National Cholesterol Education Program guidelines, more than 50% of the hard coronary events remain unpredictable and occur in patients at intermediate risk [56].

Furthermore, compliance and patient behavior can be positively modified using this technology. Demonstrating to patients that they have atherosclerosis makes them more likely to become health conscious and increases their adherence to medical therapies. Wong et al [57] demonstrated 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, beginning an exercise program, following a low-fat diet, or quitting smoking.

The use of EBT to better risk stratify patients could greatly reduce costs and better direct therapy. In preventive medicine, a primary aim is to match intensity of therapy (eg, lipid lowering, antiplatelet) with absolute risk. Because drug therapy entails significant expense, choosing high-risk individuals for more aggressive therapy is the paradigm for every prevention cohort. The average cost of statin therapy in the United States is approximately $720 per year [58], not including physician visits or laboratory tests. The clinician must accurately identify those persons who would most likely benefit from this costly but potentially lifesaving therapy. In 1 model of cost-effectiveness, coronary artery screening with EBT was demonstrated to be a cost-effective screening test in asymptomatic individuals between 45 and 65 years of age, particularly if they are at increased risk of coronary events [59]. Combining the power of this noninvasive tool with the effectiveness of statin drugs and aspirin will allow physicians to focus aggressive preventative treatment on those individuals with underlying atherosclerosis who are at highest risk for having future heart attacks and coronary death. Prospective evaluation of this model is currently underway in a large population-based study. Since results are 7 years away, physicians should consider applying aspirin and cholesterol-reduction to those patients with detectable CAC in the interim. It is also obvious that the absence of CAC on coronary screening, even in the presence of risk factors, identifies a group of patients at very low risk of events over the next 3 to 5 years. 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 [60,61].

Caution in the widespread application of EBT has been voiced [61]. Direct patient advertising without physician interaction, inappropriate cardiac catheterization after detection of coronary calcification in asymptomatic persons, and limited data on cost-effectiveness have been deemed the largest shortcomings in this technology. Physicians must remember that detection of coronary calcium, especially in asymptomatic persons, generally should not lead to cardiac catheterization. The risk of obstruction on angiography with scores less than 400 are minimal [45]. Rather, a positive EBT should be considered indicative that there exists advanced atherosclerosis, and appropriate therapies should be applied [45,60,61].

Summary

Every study reported to date using EBT suggests a strong association between CAC and hard and soft coronary outcomes. The presence of CAC in asymptomatic individuals predicts the occurrence of acute coronary events with greater accuracy than other screening tests, including Framingham risk factors [34,38,41,42,50]. The use of this tool in further risk-stratifying intermediate- and high-risk asymptomatic persons is probably warranted based upon the available literature. Data using multislice spiral CT is not available, and this modality should not be used as a surrogate for EBT until more data is available.

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### Table 2. Characteristics and Risk Ratios for Follow-Up Studies in Asymptomatic Populations

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>% Male</th>
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<th>Follow-up Duration, Mo</th>
<th>Cutoff for Risk Assessment</th>
<th>Risk Ratio</th>
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<tr>
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<td>71</td>
<td>53</td>
<td>43</td>
<td>CAC &gt; 160</td>
<td>22.1</td>
<td>22</td>
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<tr>
<td>Detrano [40]</td>
<td>1196</td>
<td>89</td>
<td>66</td>
<td>41</td>
<td>CAC &gt; 44</td>
<td>2.3</td>
<td>22</td>
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<tr>
<td>Raggi [41]</td>
<td>676</td>
<td>51</td>
<td>52</td>
<td>32</td>
<td>Top quintile*</td>
<td>15.4</td>
<td>13</td>
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<td>52</td>
<td>72</td>
<td>CAC &gt; 50</td>
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<td>50</td>
<td>51</td>
<td>Top quartile†</td>
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<td>79</td>
<td>54</td>
<td>40</td>
<td>CAC &gt; 680 (top quartile)</td>
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<tr>
<td>TOTAL</td>
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<td>72</td>
<td>55</td>
<td>43</td>
<td>—</td>
<td>10.9</td>
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</tr>
</tbody>
</table>

CAC = coronary artery calcification score.

*Using age- and gender-matched cohorts representing the top quintile.

†Using age- and gender-matched cohorts representing the top quartile.
References

32. Shavellie DM, Budoff MJ, LaMont DH, et al. Exercise testing and electron beam computed tomography in the evaluation
CORONARY ARTERY CALCIFICATION