Coronary Artery Calcium Scoring Using Electron-Beam Computed Tomography: Where Does This Test Fit into a Clinical Practice?

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Studies have indicated that the very early detection of a coronary artery burden is possible with electron-beam computed tomography (EBCT). However, both the Prevention Conference V and the ACC/AHA Expert Consensus Document on EBCT have recommended against the routine use of EBCT for screening for coronary artery disease in asymptomatic individuals. Moreover, there is no evidence so far to support using the results of EBCT in an asymptomatic patient to select a therapy or to guide referral to invasive investigations. The clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment. EBCT is highly sensitive, but its specificity is low. In fact, when referral to angiography is based on the results of EBCT, referrals will be made for very few patients with normal results while many referrals will be made for those with abnormal results. The outcome will be that, in clinical practice, the observed sensitivity of EBCT will be increased, and the observed specificity will be reduced. To date, there are no well-conducted studies that clearly demonstrate the incremental value of calcium scoring over traditional assessments of risk factors, and the clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment.

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Interest in coronary artery calcium (CAC) scoring continues to grow despite the initial mix of uncertainty and enthusiasm that came from the American College of Cardiology/American Heart Association (AHA/ACC) regarding the use of this relatively new, noninvasive imaging technique. There is a growing body of supportive literature demonstrating a role for CAC scoring in a variety of settings, including the diagnosis of coronary artery disease (CAD), as a prognostic indicator in known disease, and as a screening tool in selected populations.

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Calcium deposition accompanies the development of atherosclerotic CAD, and calcium can be detected in 96% of patients presenting with plaque rupture as a first CAD event.[1] The calcium burden increases with age and can be quantified by electron-beam computed tomography (EBCT) scoring using the Agatston method.[2] (The discussion below describes the method of calculating the score and the sources of error.)

Where Does Noninvasive Calcium Scoring Fit into Clinical Practice?

A. Screening

Scenario 1: An asymptomatic man, aged 45, presents for a routine screening and asks about having an EBCT. His father died from a myocardial infarction at age 46, and he has a low-density lipoprotein (LDL) cholesterol level of 170 mg/dL. He is normotensive, a nonsmoker, and moderately overweight. What can you tell this patient?

Very early detection of a coronary artery calcium burden is possible with EBCT. The calcium burden increases with age and correlates with the risk of subsequent myocardial events. However, the routine use of EBCT for screening for CAD in asymptomatic individuals was recommended against by both the Prevention Conference V[3] and the ACC/AHA Expert Consensus Document on electron-beam computed tomography[4] on the basis that it did not provide clear additional information above traditional risk-factor assessments.

There are relatively few studies that address the role of EBCT as a screening test in asymptomatic populations, and the ideal study is unlikely ever to be undertaken, given the challenge of noninvasive testing assessment in this population. The low event rates in such populations mean that any study would require either very large numbers of participants or an extended follow-up period to establish a clear pattern of cardiac event rates relative to a baseline calcium score. Furthermore, in this type of cohort, endpoints such as unstable angina, revascularization, or hospitalization should be used as softer markers for the development of symptomatic CAD.

There is also a need to compare the calcium score to other proven methods of risk stratification that mimic a physician's clinical risk assessment, such as the Framingham risk index (FRI). Today's understanding of the importance of cardiac risk-factor modification makes it unethical to leave patients with untreated risk factors for the purpose of conducting a longitudinal study. Additionally, it is very difficult to avoid having a bias toward making referrals to invasive investigations on the basis of the calcium score.

A number of studies have evaluated the relationship between conventional risk factors and CAC. Systolic blood pressure, lipid values, and/or obesity have all been identified as correlates of CAC in young adults,[5] men with cardiac risk factors,[6,7] women,[8] and asymptomatic men.[9] Taylor and colleagues[9] compared EBCT to clinical and serological risk-profiling using scoring from the FRI in 630 asymptomatic U.S. army personnel, aged 39–45 years, at low risk (5-year risk, based on the FRI, of 1.6 ± 1.2%). CAC was present in 20.6% of the men and 4.3% of the women. The authors found that conventional risk factors explained very little of the variation in CAC and proposed that EBCT is justified as a means of ascertaining this information in patients.

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Grundy[10] has taken this concept further and proposed that the CAC score might be used to replace age in the FRI scoring, as it may be a more powerful risk predictor than age, particularly in the elderly population. He acknowledges that a new Framingham risk study would be needed to prove the role of EBCT in risk assessment, but that this is not likely to occur.

A more important question to address is whether CAC is predictive of outcomes, which is a more rigorous approach to validating the

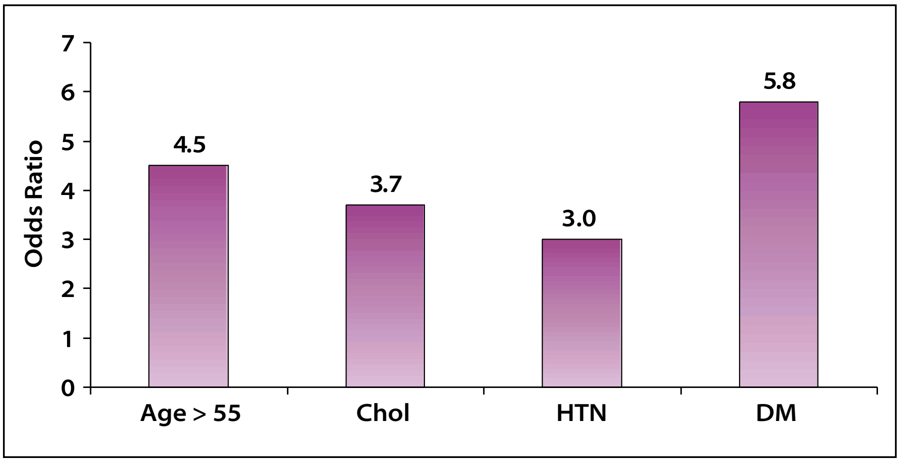

Figure 1. *Odds ratios from risk-adjusted analysis utilizing a logistic regression model for prediction of adverse events on follow-up. Chol, hypercholesterolemia; HTN, hypertension; DM, diabetes mellitus. Based on data from Arad et al.*[11]

application of noninvasive testing. There are a limited number of studies assessing the role of EBCT in asymptomatic cohorts leading toward a prognostic endpoint. Arad and associates[11] reported event rates for 1172 asymptomatic subjects followed up at 43 months (range, 38–47 months) after EBCT. Among the participants, 70% had 2 or more cardiac risk factors and 71% were male. There were 39 events (a 3.3% coronary-event rate) during the follow-up interval (3 deaths, 15 nonfatal myocardial infarctions, 11 coronary artery bypass grafting operations, and 10 coronary angioplasties). Individuals sustaining events had a higher mean calcium score, but it should be noted that 3 events occurred in patients in whom the calcium score was in the lower 2 quartiles. For a threshold Agatston score of ≥80, EBCT had an overall sensitivity of 85%, a specificity of 75%, a positive predictive value of 10%, and a negative predictive value of 99%. This threshold was associated with an odds ratio of 16.1 (95% confidence interval [CI], 6.7-38.9) for prediction of all cardiac events.

Unfortunately, this study also had numerous methodological issues. Of the 1172 patients in the study, only 787 were included in the analysis because of missing data, and the proportion of the 39 events that were also excluded was not stated. Thus, this study was even more underpowered than appeared at first glance. If the results of the multivariable modelling can be accepted as written, the authors found that after adjusting for CAC, various clinical factors remained predictive of adverse outcomes. These results suggest that factors such as hypertension, diabetes, hypercholesterolemia, and age modulate the risk of adverse outcomes associated with any value of CAC.

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Based on their models, a patient with an EBCT CAC score of less than 160 may not necessarily be at low risk if other cardiac risk factors are present (see Figure 1). For example, the presence of age > 55 years, elevated cholesterol, hypertension, and diabetes increased the patient risk by 4.5, 3.7, 3.0, and 5.8-fold, respectively. Hence, the presence of a low CAC score alone may not necessarily be associated with low risk if more than one of these cardiac risk factors are present. The risk associated with a normal or low CAC score in the presence of multiple cardiac risk factors is unclear.

How Do We Use This Information Clinically?

In applying the information gained from EBCT to a clinical setting, it should be asked how the test results would change the management of the individual patient. There is no evidence thus far to support the use of EBCT results for selecting therapy or for guiding referral to invasive investigations in an asymptomatic patient. In the case scenario described above, the advice to modify risk factors is unaltered by knowledge of a calcium score. The presence of treatable cardiac risk factors necessitate their modification, irrespective of the test results.

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With respect to altering a referral to subsequent noninvasive testing, there is also a paucity of data. Inducible ischemia was correlated

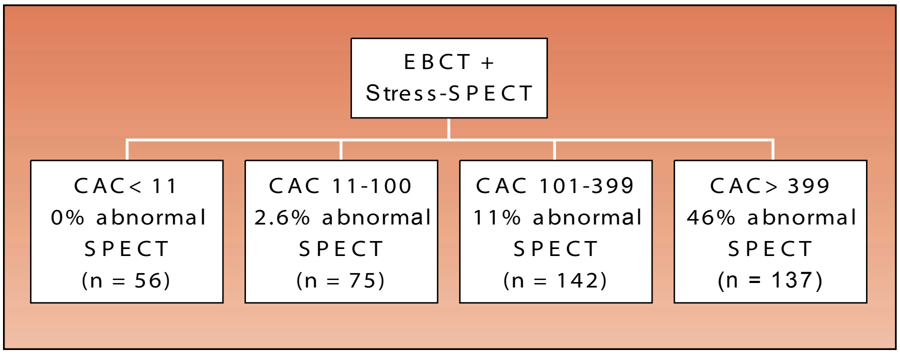


Figure 2. *Frequency of abnormal stress single-photon emission computed tomography (SPECT) results as a function of electron beam computed tomography (EBCT) scores (coronary artery calcium [CAC] scores < 11, 11-100, 101-399, and > 399). The number of patients in the subgroup is shown by (n). Based on data from He at al.*[12]

with the calcium score, in a recent paper from Baylor University.[12] Of 3895 relatively asymptomatic patients having EBCT, 411 were also investigated with stress single-proton emission computed tomography (SPECT). The subgroup of patients undergoing stress-SPECT was older and had greater numbers of CAD risk factors. Within this group, the mean CAC score was significantly higher in subjects who had inducible ischemia. When a threshold calcium score was used, no one with a CAC score ≤ 10 had an abnormal SPECT, compared to 81 of 355 (23%) individuals with CAC scores > 10. Abnormal SPECT studies were predominantly observed in subjects with CAC scores ≥ 400 (this level of coronary calcium was seen in only 10% of the overall cohort of 3895 patients) (see Figure 2). This suggests that significant levels of EBCT abnormalities need to be present before stress-induced ischemia is detectable. These results suggest that there is a potential role for EBCT as a screening test to identify which otherwise low-risk patients might be candidates for more expensive stress-imaging modalities.

B. Diagnosis and Prognosis

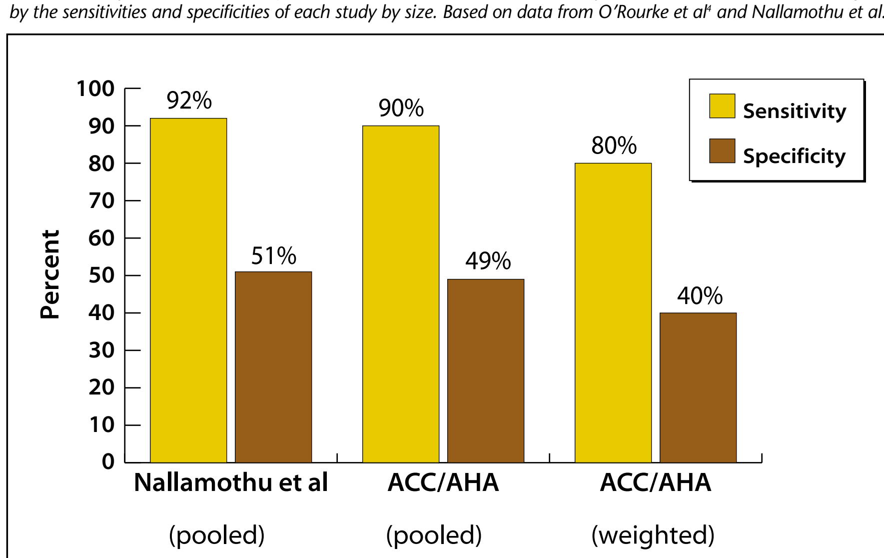
Scenario 2: A 49-year-old overweight male with hypertension and an increased LDL-cholesterol presents for an assessment of atypical symptoms. The resting electrocardiogram (ECG) is normal and you suggest an exercise stress test. The patient asks about EBCT as an alternative or as an additional investigation.

In this scenario, the potential role of EBCT is in defining the presence of CAD or perhaps in risk-stratifying for future events in a patient with an intermediate likelihood of disease.

There are several meta-analyses that address the question of diagnosis of CAD by EBCT, using an anatomic endpoint (ie, the presence or absence of important epicardial CAD). Nallamothu and colleagues[13] sought to estimate the accuracy of EBCT in diagnosing obstructive CAD (>50% stenoses). Nine studies with 1662 patients were included in the analysis after a search of the literature through February 2000. The pooled sensitivity for EBCT was 92.3% (95% CI, 90.7%-94.0%), and the pooled specificity was 51.2% (95% CI, 47.5%-54.9%). This heterogeneous group included patients with known CAD, left ventricular dysfunction, and valvular heart disease. The ACC/AHA consensus document meta-analysis[4] included a total of 3683 patients enrolled in 16 studies. The pooled sensitivity for EBCT in this meta-analysis was 90.5%, and specificity was 49.2%. These two meta-analyses demonstrate the pattern common to all literature describing the diagnostic role of EBCT in occlusive CAD; that is, that EBCT is highly sensitive but its specificity is low (see Figure 3).

There have been several approaches to enhancing the specificity of EBCT. Haberl and colleagues[14] published a large, single-center study of 1764

Figure 3. *Reported sensitivities and specificities of electron beam computed tomography using anatomic endpoints based on two published meta-analyses. Results shown were based on either pooled estimates or estimates weighted by the sensitivities and specificities of each study by size. Based on data from O'Rourke et al*[4] *and Nallamothu et al.*[13]



patients, all of whom were symptomatic and had a diagnostic coronary angiography and EBCT. The EBCT calcium score was assessed in terms of the ability to detect 50% or 75% coronary artery stenoses with differing threshold levels of observed calcium: none, ≥ the 20th, ≥ the 100th, or ≥ the 75th percentile of age groups. The absence of calcium was associated with a <1% risk of significant CAD. If this had been applied as a screening test prior to angiography, the catheter study could have been avoided in 11% of men and 22% of women. The sensitivity for detection of >50% stenoses was 99% in men and 100% in women for the test criteria of "any calcium," but specificity was consequently low at 23% of men and 40% of women. When a cut of score of >20 was used (ie, increasing the threshold for an abnormal study) sensitivities were maintained at 97% in men and 98% in women, but specificity increased to 62% and 69% for men and women, respectively.

Another proposed approach to enhancing the specificity of EBCT is to combine it with another test, for example, with treadmill exercise. It has been suggested by Shavelle and colleagues[15] that EBCT is more sensitive than either treadmill-ECG or technetium-stress testing and, in combination with a treadmill-ECG, offers specificity equal to stress-SPECT for the identification of individuals with obstructive angiographic CAD. In a selected study group, EBCT alone had a sensitivity of 96% and a specificity of 47% for detection of CAD. Combining the treadmill-ECG with EBCT, however, increased the specificity to 83%, but reduced the sensitivity to 72%. These results were compared to the figures for exercise stress-SPECT with technetium Tc 99m agents alone, which had a specificity of 69% and a sensitivity of 78%.

This study did not attempt, however, to identify what the added value of EBCT was over clinical factors or exercise-ECG in the diagnosis of coronary disease. More importantly, this study failed to consider the multiple other types of information derived from the exercise treadmill test (ETT), such as exercise time, hemodynamic response, and stress-induced symptoms. Further, this study failed to demonstrate the incremental value of EBCT over the aggregate of information physicians ordinarily have at this decision node—a combination of clinical, historical, and ETT information.

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Additionally, it must be recognized that if EBCT were incorporated into routine clinical practice, the already low specificity of EBCT would be expected to be lowered even further. As has been shown multiple times since the first description of post-test referral bias, the incorporation of a new noninvasive test into clinical practice results in a shift of referral patterns, such that the referral to a "gold-standard" test (eg, angiography) will be based on this new test, hence evaluation of this new test using the "gold standard" introduces a marked bias. When a referral to angiography is to be based on the results of EBCT, very few patients with normal results will be referred, but many patients with abnormal EBCT results will be referred. The outcome of this will be that a greater number of false positives and true positives than true negatives or false negatives will be selected, thus increasing the observed sensitivity and reducing the observed specificity of the test in clinical practice (see Figure 4).

Risk Stratification

As suggested by numerous recent guidelines, there is a need to base the approach to patients with both suspected and known CAD on their risk of adverse outcomes rather than on their likelihood of anatomic disease. With regard to the risk stratification of the patient described in the scenario above, there is evidence that the degree of calcium burden is related to the risk of future cardiac events. Studies have shown that relatively more cardiac events occur in patients with higher than lower quartiles of calcium scores.[1,11,16] The absence of detectable calcium by EBCT is associated with a 0.11% per year event-rate in asymptomatic populations. In a cohort of patients post-myocardial infarction, however, 4% had no detectable calcium.[16] Further, as pointed out above, the risk associated with a low CAC in patients with multiple risk factors is also undefined.

Raggi[17] has suggested that the value of a high calcium score in risk stratification is superior to that of traditional CAD risk factors, based on the observed relative risk of events in the high quartiles of calcium scores compared to the highest quartile of CAD risk factors. Like all other noninvasive modalities, EBCT must be shown to have incremental value over currently available methods before it can be applied in clinical practice for predicting prognosis or risk. However, to date, there are no well-conducted studies that clearly demonstrate the incremental value

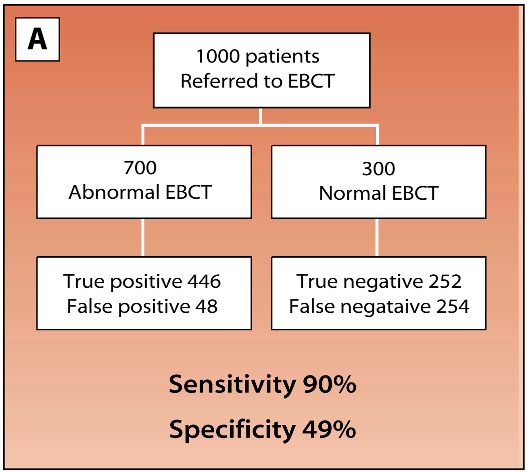

Figure 4. A: *Based on data regarding the accuracy and prevalence of electron beam computed tomography (EBCT) results extracted from O'Rourke et al[4] (positive predictive value, 84%; negative predictive value, 64%; prevalence of abnormal EBCT, 70%), of 1000 patients presenting to EBCT, 70% (n = 700) will have abnormal EBCT results and 300 will have normal EBCT results. Based on the positive and negative predictive values for EBCT, the anticipated sensitivity and specificity of EBCT are shown. This result is similar to that found in O'Rourke at al.[4]*

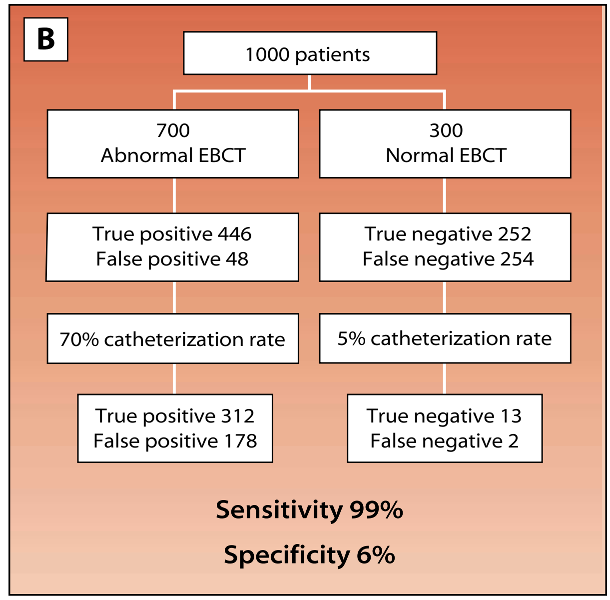

Figure 4. B: *Because the adaptation of a test into the community results in a significant post-test referral bias (if the test is used as the basis for referral to the "gold standard," ie, catheterization), we can attempt to estimate what the anticipated impact of a referral bias would be on sensitivity and specificity, based on the numbers shown in* **A.** *Assuming the same prevalence of abnormal EBCT as above (70%), we again have 700 abnormal and 300 normal EBCT results. If the EBCT results are used to formulate the decision to refer the patient to catheterization, we assume here that ~70% of abnormal and ~5% of normal EBCT results will be referred to catheterization (a referral pattern similar to that of stress-SPECT). Hence, the number of negative-result patients referred to catheterization is dramatically reduced, resulting in a slight increase (compared to that shown in* **A***) in predicted sensitivity to 99%, but a lowering of the predicted specificity to 6%. This pattern—increase in sensitivity and marked lowering of specificity—is that seen with a post-test referral bias.*

Of note, in practice, less than half of patients screened will have abnormal CAC scores. The higher proportion of abnormal CAC scores in the published papers reflects the result of using a population that was referred to catheterization. If a more realistic prevalence is assumed, the sensitivity and specificity of EBCT would be expected to be 80% and 69%, respectively, rather than 90% and 49%, based on the numbers used here. Further, if a post-test referral bias were imposed on these values, the resulting sensitivity and specificity would be 98% and 14%, respectively. Thus, a specificity of 50% for a new technology may not seem inadequate, but would not be satisfactory for use in clinical practice.

of calcium scoring over the traditional assessments of risk factors.

Monitoring of Disease

There is a potential role for EBCT in monitoring the progression or regression of disease in terms of the plaque burden. For this modality to be used in this context, the error or variability must be minimal in order to permit small changes in scores to have meaning. Early studies demonstrated a mean interscan calcium score reproducibility of only 14%–38%. Subsequent advances in hardware, acquisition protocols, and methods of calculating the calcium score have led to marked improvements in reproducibility, so that it is now realistic to see EBCT as a method for following plaque burden over time.

An increase in calcium scores of 18%–33% per year have been reported[18] with rates of progression greater in those with occlusive coronary disease compared to those without manifest disease. A recent small study of patients with end-stage renal disease demonstrated a mean calcium score increase of 59% per year, with a doubling of the score by the follow-up at 20 months.[19] Recent unpublished reports have also claimed that higher rates of progression of the plaque burden have been associated with a greater likelihood of coronary events.

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EBCT Can Also Be Used to Assess the Effect of Lipid-lowering Therapy

Callister and colleagues[20] observed a net 1-year reduction of 7% in the calcium volume scores for statin-treated patients in whom the final LDL-cholesterol levels were <120 mg/dL. They also found, however, a mean increase of 25% ± 22% in less aggressively treated individuals and 52% ± 36% increase in untreated patients.

What Are the Limitations of the Technology?

Paralleling the investigation of the application of the technique, there are continuing developments in the technology itself, with improved image quality, reproducibility, and the potential for CAC scoring using helical CT in addition to the standard EBCT.

Standard EBCT protocols aim to visualize the entire coronary artery tree, usually by 3 mm slice intervals. The presence of a calcific lesion is usually defined as 2 adjacent pixels with a signal intensity > 130 Hounsfield units (H). The Agatston score is the sum of lesion scores from the four anatomic sites (left main, left anterior descending, circumflex, right coronary artery), where each lesion is weighted by multiplication with a density factor derived from the lesion's maximal H. This score has limitations in terms of reproducibility because of an inherent sensitivity to both partial volume effects and noise. There may also be variations in scores from one CT scanner to the next because of variations in the reconstruction algorithms used. Some authors have promoted the use of a volume score in order to improve the reproducibility of calcium scoring.[21]

Patient motion is the greatest source of error in calculating the calcium score from EBCT.

Patient motion is the greatest source of error in calculating the calcium score from EBCT.[22] Improvements in ECG-gating technology and image-acquisition times have led to improvements in score reproducibility.

Similar advances are also being made in helical CT technology. The availability of multi-slice CT detector systems and improvements in gantry-rotation speeds mean that image quality is approaching that of EBCT and may even be superior in terms of reproducibility.[23] Caution is required however, because existing databases developed with EBCT studies should not be applied to calcium scores obtained with helical CT technology or multi-slice CT detector systems. Additionally, there is concern regarding the potentially increased radiation exposure with multi-slice CT detector systems compared to that for EBCT.[18]

Conclusion

The clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment. There is a volume of evidence indicating that the calcium burden increases with age and that calcium detected by EBCT reflects the presence of calcified plaque in arterial disease. What is not clear is whether the detection and quantitation of this calcium provides clinically useful information incremental in value to a traditional assessment of risk factors. With respect to the clinical application and regular use of EBCT, a number of questions remain.

Questions with Respect to a "Normal" CAC Score

The likelihood of CAD is probably low. However, what is this likelihood or the risk of adverse outcomes in patients with multiple cardiac risk factors? Based on the published data, a patient with a low CAC score and with multiple risk factors may not have a low cardiac risk. Further, what are the implications, clinical and economic, of the exceedingly high false-positive rates associated with EBCT? (See Table 1.)

Questions with Respect to an "Abnormal" CAC Score

What is the appropriate management of the patient? Aggressive modification of risk factors is

Table 1
"Normal" CAC Score Considerations

With respect to a "normal" CAC score:

- The likelihood of coronary artery disease is probably low.
- However, what is the likelihood or risk of adverse outcomes in patients with multiple cardiac risk factors?
- Further, what are the implications, clinical and economic, of the exceedingly high false-positive rates associated with EBCT?

Table 2
"Abnormal" CAC Score Considerations

With respect to an "abnormal" CAC score:

- What is the appropriate management of the patient?
- Aggressive risk-factor modification is important, but should one proceed to catheterization or to tests of induced ischemia?
- Given the presence of treatable cardiac risk factors, was the EBCT result really needed to confirm the treatment required?

undoubtedly important, but should one proceed to catheterization or to tests of induced ischemia? Given the presence of treatable cardiac risk factors, was the EBCT result really needed to confirm the treatment required? (See Table 2.) ■

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Main Points

- The very early detection of a coronary artery burden is possible with electron beam computed tomography (EBCT). However, routine use of EBCT for screening for coronary artery disease in asymptomatic individuals was recommended against by both the Prevention Conference V and the ACC/AHA Expert Consensus Document on EBCT.
- There is no evidence thus far to support using EBCT results in an asymptomatic patient to select a therapy or to guide referral to invasive investigations. The clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment.
- Factors such as hypertension, diabetes, hypercholesterolemia, and age modulate the risk of adverse outcomes associated with any value of coronary artery calcium (CAC) scoring.
- EBCT is highly sensitive, but its specificity is low.
- When referral to angiography is based on the results of EBCT, very few patients with normal results will be referred, but many patients with abnormal results will be referred. The outcome will be that, in clinical practice, the observed sensitivity of EBCT will be increased and the observed specificity will be reduced.
- To date, there are no well-conducted studies that clearly demonstrate the incremental value of calcium scoring over traditional assessments of risk factors.