Noninvasive Screening for Coronary Artery Disease With Computed Tomography Is Useful

Melvin E. Clouse, Jersey Chen, Harlan M. Krumholz, Melvin E. Clouse, Jersey Chen and Harlan M. Krumholz

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How useful is computed tomography for screening for coronary artery disease?

Noninvasive Screening for Coronary Artery Disease With Computed Tomography Is Useful

Melvin E. Clouse, MD

The introduction of new ideas and concepts that lead to change in practice has always caused some degree of controversy, especially in medicine. At first glance, the concept of noninvasive imaging for calcium as a screen to identify patients at high risk for future coronary events would seem the most intense; however, one must only reflect on past controversies to gain an appropriate perspective. The controversy over radical mastectomy versus segmental resection or lumpectomy with radiation therapy has raged for the past 50 years, and only recently have data from the 20-year follow-up of a randomized trial comparing these forms of treatment been put forward.[1,2] The process of establishing the chest roentgenogram as a standard diagnostic method in the diagnosis of respiratory disease spanned 30 years and was opposed by many of the leading physicians of the day, including Osler,[3] who believed a good clinical examination was superior. In 1915, Crane[4] stated that the chest roentgenogram that "claims a delicacy, rapidity and precision outranking the stethoscope and the percussion finger must expect to run a gauntlet of merciless criticism." The chest roentgenogram largely came into general use in the 1930s, when it was recognized that ≈15% of the deaths in the United States were due to tuberculosis, and a massive screening process was instituted after World War II.[5] Establishment of the chest roentgenogram as a diagnostic tool was based largely on the belief in technology and innovation; to date, however, no prospective randomized studies have been conducted to determine whether the chest roentgenogram has indeed affected the outcome of patients with cardiopulmonary diseases. Thankfully, the coronary artery calcium (CAC) examination has been placed under intense scrutiny, and although the construct and ethics of a prospective randomized study have yet to be decided, it is appropriate to review and discuss how it may help in treating patients with subclinical atherosclerosis and to determine its absolute predictive value and its relationship to the Framingham Risks score and National Cholesterol Education Panel Adult Treatment Panel III (NCEP ATP III) guidelines because it is the only noninvasive test available to evaluate insults to the arterial wall from all risk factors causing atherosclerosis.

The concept of imaging coronary arteries for calcification in vivo arose shortly after the discovery of x-rays by scientists who demonstrated calcification within the coronary arteries but were limited by current technology.[6–8] After publications by Habbe and Wright[9] and Van der Straeten,[10] Blankenhorn and Stern, in a landmark article, scientifically established the fact that calcification in the coronary arteries is directly related to atherosclerosis.[9–13] Recent studies have confirmed

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From the Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass (M.E.C.); Section of Cardiology, Department of Medicine, Beth Israel-Deaconess Medical Center, Boston, Mass (J.C.); and the Sections of Cardiovascular Medicine, Department of Medicine; Health Policy and Administration, Department of Epidemiology and Public Health; and Robert Wood Johnson Clinical Scholars Program, Department of Medicine, Yale University School of Medicine, and Center for Outcomes Research and Evaluation, Yale-New Haven Health, New Haven, Conn (H.M.K.).

Correspondence to Melvin E. Clouse, MD, Vice Chairman, Director of Research, Beth Israel Deaconess Medical Center, Deaconess Professor of Radiology, Harvard Medical School, 1 Deaconess Rd, Room 302, Boston, MA 02215 (e-mail mclouse@bidmc.harvard.edu); or Dr Harlan M. Krumholz, Yale University School of Medicine, 333 Cedar St, PO Box 208088, New Haven, CT 06520-8088 (e-mail harlan.krumholz@yale.edu).

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that the development of arterial calcification is intimately associated with vascular remodeling and atherosclerotic plaque and is controlled largely by cellular and subcellular mechanisms.[14–17] Histopathological studies have also shown that calcification is found more frequently in advanced atherosclerotic plaque and is associated with plaque in larger arteries than in peripheral coronary arteries.[18–20] In 1903, Monckeberg described calcification that occurs in the media, usually in the peripheral and visceral arteries and only occasionally in the coronary arteries, and is not associated with atherosclerosis.[21]

Historically, cardiac fluoroscopy was frequently used to detect calcium in the coronary arteries because it was much more sensitive for detecting calcium than the standard chest roentgenogram. In 1987, Detrano and Froelicher[22] summarized studies involving 2670 patients undergoing coronary arteriography and equated the findings of calcification for detecting significant stenosis (>50% diameter) with a sensitivity of 40% to 79% and specificity of 52% to 95%. That same year, Reinmueller and Lipton[23] studied a small group of patients and demonstrated that CT was much more sensitive for detecting calcification than fluoroscopy (62% versus 35%). However, image quality was degraded by cardiac motion.

The new era for imaging CAC began with the introduction of the high-speed cine-CT scanner. The cine-CT/ultrafast CT scanner, later designated the electron-beam CT (EBCT), performed 3-mm-thick cross-sectional slices in 50 to 100 ms with exposure gated to 80% of the R-R interval. Thus, the heart could be examined in a single breathhold with the x-ray beam passing from the source through the body to a detector array; the recorded data were transformed through a filtered back-projection reconstruction technique into 2D images.

Agatston et al,[24] guided by a method originally conceived by David King (Imatron), used the EBCT to quantify CAC, working on the premise of using the calcium score as an independent predictor for future myocardial events, as indicated by Margolis et al[25] in 1980. They established the scientific basis for the scoring system based on an x-ray attenuation coefficient or CT numbers measured in Hounsfield units by selecting the maximum calcium density within the area. The area of calcium was calculated from the field of view and the image matrix that, on the standardized protocol, relate to 3 pixels or 1 mm^2 with a density of 130 Hounsfield units. Statistical analysis was performed on the log-transformed total score and on the square root of the number of lesions to normalize the data. After completing a scan with the same parameters using a high-resolution volume mode with 3-mm-thick slices, they repeated the same scan in a single-slice mode with 20 and then 40 contiguous slices throughout the heart with no interslice gaps. Callister et al[26] improved the reproducibility of the calcium score, especially in the lower ranges, by introducing the volume score (isotropic interpolation) method.

The ability to identify individuals at high risk and thus to direct appropriate therapies to prevent further myocardial events would be a great benefit to society because cardiovascular disease is the most important health problem in America and the Western world, accounting for 38.5% of all deaths. The death rate from cardiovascular disease is greater than the second through the seventh leading causes of adult death, including cancer, AIDS, accidents, homicides, infections, and diabetes mellitus. The total cost for treating far-advanced, ie, end-stage, cardiovascular disease is enormous. The estimation has increased from $286.5 billion in 1999 to $368.4 billion in 2004, accounting for a third of the cost of our $1 trillion healthcare economy. The cost for physician care and testing is only 10% ($31 billion), with the remainder being for patient care.[27,28] The current methods of diagnosis and treatment have had little effect on the outcome of a disease that is largely preventable with institution of strict risk factor modification and statin therapy if discovered early.[29–34] Up to 50% of patients with atherosclerotic disease present with either ischemic heart disease or sudden death, and for 150 thousand individuals, a fatal heart attack is the first symptom of heart disease.[27,28] Fifty percent of these myocardial infarctions (MIs) occur in patients with no prior history of disease, and 68% of these are due to lesions representing a stenosis diameter <50%. Cholesterol is perceived as one of the most important risk factors for coronary artery disease, but ≈35% with established heart disease have total cholesterol levels <250 mg/dL; thus, cholesterol has failed to predict up to one third of future deaths resulting from coronary artery disease. In a recent study, 204 men <55 years of age and women <65 years of age presenting with acute MI had cholesterol tests performed within 12 hours of admission. Sixty-eight percent had LDL cholesterol levels <131 mg/dL, 41% had LDL cholesterol levels <100 mg/dL, and 38% had LDL cholesterol levels >130 mg/dL. Only 25% of these patients, all of whom subsequently suffered MI, would have qualified for lipid-lowering therapy under the current NCEP ATP III guidelines.[35]

Comparison of EBCT CAC Score With Other Noninvasive Tests

Patients with typical angina/symptoms of coronary heart disease normally undergo routine noninvasive tests such as exercise ECG, echocardiography, myocardial scintigraphy, or pharmacological stress tests. These tests are used when patients are symptomatic with far-advanced disease, are based on indirect signs of atherosclerosis that result from inadequate myocardial perfusion, and have a high pretest probability of being positive.

The consensus statement reports on a large meta-analysis with high sensitivities, specificities, and accuracy for the exercise treadmill test (ETT) in the range of 68%, 77%, and 73%, respectively, for ECG; 89%, 80%, and 89% for myocardial perfusion; and 85%, 84%, and 87% for pharmacological scintigraphy/echocardiography compared with 91%, 49%, and 70% for EBCT.[36] Others give lower and more variable sensitivity and specificities of 85% to 77% for echocardiography, 87% to 63% for myocardial scintigraphy,

and 84% to 44% for pharmacological treadmill testing, depending on the number of vessels involved.[37–39] Such results are influenced by gender, age, cardiac rhythm, and inability to exercise.

Haberl et al,[40] like most investigators, reported a higher sensitivity and specificity and less variability for EBCT. With cut points for calcium scores of >20th, >100th, and >75th percentile of age groups, the sensitivity for detecting stenoses decreased to 97%, 93%, and 81%, respectively, for men and 98%, 82%, and 76% for women. Specificity increased up to 77% for both. Sensitivity and specificity are related to the cut points for the calcium score for which there currently is no agreement. The negative predictive value for a zero calcium score was 99%.[40] Kajinami et al[41] also reported an overall accuracy of 85% for EBCT compared with 71% for myocardial scintigraphy.

Regardless of the variability of the reported data, the ETT/myocardial perfusion tests provide a high accuracy for predicting future myocardial events.[42] Therefore, they are an essential part of the diagnostic armamentarium. They are performed to detect the possibility of flow-limiting lesions (far-advanced disease) but when negative give no information as to the presence of significant plaque burden and do not identify patients with subclinical atherosclerosis who may be at risk for future myocardial events, thereby alerting the patient/and physician to vigorously pursue preventive measures. Therefore, the calcium examination should be used in low-yield situations such as atypical chest pain to screen and possibly reduce the number of patients subjected to invasive procedures when the above noninvasive tests are not conclusive. Intravascular ultrasound is a more accurate method for plaque evaluation, but its usefulness in routine clinical decision making is limited because of its invasive nature.

CAC Scoring

To be used effectively, EBCT CAC must be validated. How accurate is it for identifying calcium? How reproducible is the score? What variation is there between 2 scans taken several minutes apart in the same patient? The reproducibility and variability of the EBCT calcium score have been studied extensively. Earlier reports have shown significant variability, between 14% and 38%; however, these imaging algorithms are no longer up to date. Previously, the limitations on slice number, suboptimal gating, and table motion led to higher interscan variability. Hardware for EBCT has improved significantly, and there has been marked improvement in the reproducibility of the calcium score. A recent study of 1311 asymptomatic individuals undergoing 2 scans 3 minutes apart resulted in an average interscan variability of 15% to 17%.[43] Another study using a newer protocol demonstrated a mean interscan variability of 16% to 19% and a median variability of 4% to 8.9% for the Agatston and volumetric scores.[44] There was also significant improvement in the quantification of calcium score with the introduction of the volumetric method. The inherent issue of cardiac motion will continue to be a problem, especially for the right coronary and left circumflex arteries.[45,46] Several investigators have suggested triggering exposure to 40% of the R-R interval and have reported an interscan variability of 11.5%. However, others have not found this necessary.[44]

Multirow detector computed tomography (MDCT) has recently been introduced for CAC scoring. Investigators have found significant interscan variability and reproducibility with single-slice scanners at rotational speeds of 800 ms. The variability has been most marked using densities of 90 rather than 130 Hounsfield units.[47] MDCT technology for CAC scoring is improving rapidly. Initial reports were from dual and 4-slice scanners with variabilities of 25.2% for overlapping images with volume scoring and 45.5% for Agatston scoring.[48] MDCT scanners can image a section of the heart simultaneously with ECG gating in either the prospective (ECG triggering) or retrospective mode for segmented reconstruction. This allows a gapless helical scan of the entire heart. Prospective gating usually produces 3-mm-thick slices with a temporal resolution of 200 or 250 ms. Temporal resolution of 100 to 125 ms can be achieved with the retrospective mode with overlapping slices but with a marked increase in radiation dose. Now, 4-MDCT and 8-MDCT scanners are being replaced with 16-MDCT scanners. Reconstruction algorithms have improved with retrospective gating. Furthermore, we can expect 32- and 64-MDCT scanners to have rotational speeds of 330 ms, which will allow temporal resolutions of 175 or 87 ms to improve resolution and to reduce cardiac motion.

A recent study of 32 patients demonstrated a variability of 20.4% for Agatston scoring and 13.9% for volumetric scoring for MDCT.[49] Another recent publication comparing MDCT with EBCT shows high correlation of scores at every calcium level and similar areas under receiver-operating characteristic (ROC) curve.[50] A more recent report of 100 patients undergoing both MDCT and EBCT shows similar sensitivity and specificity of 98.7% and 100%, respectively. The variability of the volume score was 20%; the mass score was 20.3%.[51]

There is significant discussion as to the most appropriate scoring method, ie, Agatston, volume, and mass scores. However, regardless of imaging technology and methods of obtaining and measuring calcium score, the Agatston method is the standard now and for the foreseeable future. This is predicated on the significant available database for these scores and outcomes data currently in use because clinicians know the significance of a certain score using the Agatston method. Volume scores are similar, although slightly lower, and mass scores are significantly lower. Almost all scoring software now gives all 3 scores simultaneously for each subject; therefore, all are readily available.

Radiation Dose

Radiation dose for CT scanning is significant, and every effort is being made to reduce the dose. MDCT scanning is usually performed with prospective gating with 3-mm slice thickness. The effective radiation dose for MDCT scoring

was 1 to 1.5 mSv for men and 1 to 1.8 mSv for women using 100 to 140 mA and 140 kV. The equivalent dose for EBCT is 0.7 to 1.0 mSv for men and 1.3 mSv for women. These dose rates are based on prospective triggering rather than retrospective triggering using thinner overlapping slice segments that improve spatial resolution.[52] To reduce radiation exposure using these retrospective gating algorithms with 4-MDCT, Mahnken et al[53] report an effective radiation dose of 3.01 mSv (range, 2.5 to 4.18 mSv) for men and 4.44 mSv (range, 3.28 to 5.88 mSv) for women. Trabold et al[54] and Flohr et al[55] report dose rates for 16-MDCT that are similar to the previous MDCT scanners. Hirota et al,[56] however, report effective dose rates with gated studies of 2.6 and 4.1 mSv using 100 and 150 mA and 120 kV, respectively. The dose rates for CT coronary arteriography are much higher, 9.3 and 11.3 mSv using 300 mA. Most investigators did not use β-blockers to reduce heart rate and cardiac motion. Although both EBCT and MDCT have inherent limitations using 100- and 200-ms exposures, EBCT (e-speed) does image at 50 ms, if needed, for high resolution. Reducing the heart rate from 75 to 65 bpm increases the diastolic phase from 530 to 620 ms, whereas the systolic phase is increased only from 270 to 300 ms. Scanning at a lower heart rate would significantly reduce the in-plane motion of the coronary arteries; however, a significant number of patients will have heart rates >75 bpm, which may predicate the use of retrospective gating.

Significance of CAC

Recent reports have confirmed that atherosclerosis is the only disease associated with coronary calcification and that calcification is intimately associated with plaque.[14,18,36,56,57] CAC is an active process seen in all stages of plaque development. It is strongly correlated with age and increases significantly after 50 years of age. It parallels the prevalence of atherosclerotic plaque development as demonstrated by intracoronary ultrasound, which shows significant noncalcified plaque of 17% in 20-year-old individuals, increasing to 85% in individuals >50 years of age.[58] The EBCT calcium score follows the same pattern of calcification in all age groups and progresses rapidly after 50 years of age.[59] There is a slight gender variation in women, with lower scores in the early decade, but this is eliminated in the 65 to 70 years of age group.[60]

The correlation of plaque calcification within noncalcified plaque as demonstrated by EBCT was established by Simons et al[57] and Rumberger et al[61–63] with excellent histological studies on randomly selected hearts quantifying CAC and total plaque by measuring direct histological plaque area and percent luminal stenosis. These studies demonstrated that the calcium score correlated linearly with total plaque area and that calcified plaque accounted for only 20% of the total plaque burden. In addition, a calcium area 1 mm in diameter predicted mild stenosis, whereas a calcified area of 3 mm was more likely to be associated with significant luminal narrowing. These studies also noted that calcium is a reflection of total plaque burden but that the calcium score does not translate in a one-to-one fashion to direct luminal narrowing. A study by Sangiorgi et al[64] suggests that this is related to the remodeling phenomenon reported by Glagov et al.[65] Baumgart et al[63] confirmed the direct association of CAC score with hard and soft plaque using intracoronary ultrasound and arteriography. For plaques with and without calcification, the sensitivity was 97% and 47% and specificity was 80% and 75%, with an overall accuracy of 82% and 69% respectively, thus confirming the high sensitivity for detecting calcium and the high negative predictive value of a negative EBCT score.[63]

In addition, EBCT has demonstrated its ability to quantify atherosclerotic plaque and, by virtue of the score, measure the severity, ie, stage of disease, in the coronary artery in direct comparison to pathological studies, regardless of age and gender.[61,62] The scores are reproducible and interscan variability is sufficient for use in research and clinical studies. The 4-, 8-, and 16-MDCT scanners have been shown to be comparable with respect to quantifying the calcium score.

The most important application of the EBCT CAC examination is the high negative predictive value of a zero CAC score. It indicates that no calcium is present. It also indicates that there is little likelihood of significant arterial stenosis (negative predictive value, ≈95% to 99%). A negative score is consistent with a low risk for hard coronary event (0.1% per year) or any event in the next 2 to 5 years.[36,57]

Although there may be controversy over the use of the calcium score to diagnose obstructive disease, there is little controversy in its ability to detect calcified plaque. The ability of the CAC to estimate total plaque burden, ie, stage of disease, is the most significant predictor for future myocardial events.[66] Therefore, the importance of the CAC score lies in its ability to identify individuals at risk and to integrate this information with other risk factors for risk stratification and goal-directed prevention.

CAC as a Predictor for Future Myocardial Events

It has long been known that CAC is related to atherosclerosis, and individuals dying of coronary artery disease have significantly more calcification than that seen in age-matched control subjects.[67] In addition, calcification is the best indicator for severity, ie, stage of the disease. It would seem intuitive that calcification represents the sum total of insults to the arterial wall from all risk factors. It therefore should be an important predictor for future myocardial events and should be compared with the standard risk factors and NCEP guidelines. It is also known that a major portion of acute ischemic cardiac events occur from rupture of vulnerable plaques that are hemodynamically insignificant in asymptomatic individuals. Thus, it is important to evaluate the significance of CAC as a predictor for future myocardial events.

Five recent studies have evaluated the significance of CAC as a predictor for future myocardial events since the initial article by Arad et al[68] in 1996. These articles have been selected for this review and include data from a total of

17 976 subjects who were self-/physician referred and 6897 prospectively enrolled for EBCT CAC studies. The mean age varied from 52 to 59 years; 51% to 79.45% were men, and 20.6% to 49% were women. The participants were asymptomatic with no prior history of coronary artery disease. In the self-/physician-referred group, most were 40 to 70 years of age, with equal numbers <40 and >70 years of age. In the St Francis Heart Study (SFHS), the mean age was 53±11 years; in the South Bay Heart Watch Study (SBHW), the mean age was >45 years, and most had at least 1 abnormal risk factor that would place them in the intermediate- to high-risk category for Framingham Risk Score (FRS)/NCEP ATP II guidelines (>10% estimated 8- to 10-year risk for developing coronary heart disease [CHD]). On evaluation, the conventional risk factors were reported to be in the range of 45% for hypertension, 10% for diabetes, 60% for hypercholesterolemia, and 40% for smoking. The mean follow-up was 32±7 to 51±9 months in the self-/physician-referred group and 4.3 and 8.5 years for the SFHS and the SBHW groups, respectively.

The first publication to assess the potential predictive value of CAC for future myocardial events was an analysis of 1173 in a 19-month follow-up that reported sensitivities of 89%, 89%, and 50% (inadequate number of subjects) and specificities of 77%, 82%, and 95% for calcium scores of 100, 160, and 680, respectively. Odds ratios (ORs) ranged from 20.0 to 35.4 ($P<0.00001$ for hard and soft events). The ROC curve analyses comparing the NCEP II guidelines to EBCT scores were 0.74 and 0.91, respectively, indicating the possible significance of the EBCT CAC score as a significant predictor.[68] A recent article from the same investigators reported on a 3.6-year follow-up of 1172 patients with a 99% response rate. CAC scores remained independently associated with outcomes of hard and soft cardiac events after adjustment for self-reported standard risk factors. The areas under the ROC curve were 0.84 and 0.86 for the prediction of all coronary events and nonfatal MIs and death, respectively, and CAC scores >160 and <160 were associated with an OR of 15.8 and 22.2, respectively. Hard coronary events progressed with increasing CAC scores ($P<0.0001$).[69] Raggi et al[70] compared a group of 172 patients who had EBCT imaging within 60 days of an unheralded MI with 632 self-/physician-referred asymptomatic patients with a 32±7-month follow-up. The groups' demographics, including age and calcium scores, were similar. The annualized event ranged from 0.09 to 1.05 (12-fold difference) between the lowest and highest quartiles in patients identified by conventional risk factors and 0.045 to 2.7 (59-fold difference) when grouping was done according to CAC quartiles, indicating that although standard risk factors are important, CAC percentiles are substantially more important for identifying patients at risk.[70] In a previous study, these same authors, analyzing 676 patients and using 10 122 asymptomatic patients as control subjects, demonstrated that CAC score percentiles were a significant predictor for coronary events and incrementally added to the prognostic value of traditional risk factors for CAD ($P<0.001$). Area under the ROC curves for hard events, when added to conventional risk factors, was significantly larger than conventional risk factors alone as predictors (0.84 versus 0.71; $P<0.001$). The area under the curve using CAC score percentiles alone was significantly greater than conventional risk factors (0.82 versus 0.71; $P=0.028$). The authors conclude that age- and sex-specific CAC score percentiles provide the best predictive model and add incremental predictive information to conventional risk factors.[71]

Kondos et al[72] reported on a group of 5635 asymptomatic patients (64% response). The mean age was 59±9 years, with a follow-up of 37±13 months. The prevalence of CAD risk factors was less than reported in the National Health and Nutrition Survey (NHANES) and Atherosclerosis Risk in Communities (ARIC) except for hypercholesterolemia, which was higher. Using univariate and multivariate analysis comparing those with and without events demonstrated that increasing age, smoking, diabetes, and hypertension were all significant ($P<0.001$). The probability value was not significant for individuals with or without hypercholesterolemia. Patients with CAC scores in the first quartile (1.0–3.8) had a relative risk (RR) of 1.76 (95% CI, 0.39 to 7.88) compared with those in the top quartile with scores >170 (RR, 7.24; 95% CI, 2.01 to 26.15) of developing a hard coronary event compared with those without CAC. In another large study of 10 377 self-/physician-referred patients, the authors demonstrated that the 5-year risk-adjusted survival was 99.0% for a CAC score <10 and 95.0% for those with CAC scores >1000 ($P<0.001$).[73] The area under the ROC curve of 0.72 for conventional risk factors increased to 0.78 when CAC scores were added to the model ($P<0.001$). Wong et al[74] has also reported on 926 asymptomatic individuals with mean age of 54 years who were followed up for 3.3 years. After adjustment for age, gender, and other risk factors the RR (CAC score of 81 to 270 and >270 compared with 0) for hard coronary events was 4.5 ($P<0.05$) and 8.8 for soft events ($P<0.001$).

To date, there have been 3 prospective study reports: 2 from the SBHW that focused on different analyses and 1 from the SFHS. Guerci et al[75] reports a prospective study of 5585 subjects of approximately the same age (59±5 years) that followed baseline CAC scores and FRS with a 4.3-year follow-up at SFHS. A score of >100 predicted all cardiovascular events, all coronary events, nonfatal MI, and coronary deaths with an RR of 9.5 to 10.7 at 4.3 years compared with a score of <100. The area under the ROC curve for was 0.71 and 0.81 for CAC scores.[75]

The SBHW study began in 1990 as a prospective study to determine the prognostic accuracy of cardiac fluoroscopy in 1461 asymptomatic patients >45 years of age with at least 1 abnormal risk factor (>10% estimated risk for developing CHD by early Framingham risk equation) selected from a community mailing campaign. Beginning in 1992, the investigators began using EBCT. An early report by Secci et al,[76] who selected 326 of 462 original study participants, noted

after a follow-up of only 2.7 years that the prediction of nonfatal MI and death based on the calcium score did not reach statistical significance (OR, 3.1; $P=0.07$).[76] Detrano et al[77] later reported on the same SBHW group of 1196 asymptomatic high-coronary-risk subjects with a mean age of 66 years. The ROC curves from the Framingham model, their own data-derived risk model, and the CAC score were 0.69 ± 0.05, 0.68 ± 0.05, and 0.64 ± 0.05, respectively (P=NS), demonstrating that the EBCT, although no better a predictor than FRS, nevertheless was equal to the sum of all risk factors in predicting cardiac events. This report was a major factor for the final report from the ACC/AHA consensus document largely because of the incomplete representation of the data.[36] The ACC/AHA panel neglected to mention that the Detrano group also did not find the Framingham risk model to be a significant predictor. A more recent study by Park et al,[78] also from SBHW, selected 967 subjects from the 1461 participants and conducted a Cox regression analysis with C-reactive protein ≤10 mg/L to estimate the risk-factor–adjusted RRs of CAC and C-reactive protein for occurrence of hard and soft coronary events. CAC was a predictor for MI/coronary death ($P<0.005$) and any cardiovascular event ($P<0.0001$); C-reactive protein was a predictor of any cardiovascular event ($P<0.003$).[78] Risk group analyses showed that the risk increased with increasing CAC and C-reactive protein combined ($P<0.003$ for MI/coronary death and $P<0.001$ for any cardiovascular event). Greenland et al,[79] also from the SBHW group, reported on 1312 subjects in a long-term follow-up with a median of 7 years. Excluded from the original 1461 participants were 269 with diabetes and 14 with missing data or coronary events before the CAC was performed. Compared with a CAC score of 0, a CAC score of >300 was predictive (hazard ratio, 3.9; $P<0.001$). Across all FRS categories, CAC was predictive of risk among patients with an FRS >10% ($P<0.001$) but not <10%. The ROC curves for FRS alone were 0.63 and 0.68 for FRS plus CAC score, demonstrating the importance of incorporating the CAC with conventional risk factors. Except for the early studies of the SBHW, all prognostic studies using EBCT have demonstrated independent and incremental value compared with FRS analysis for predicting future cardiac events.

CAC in Clinical Studies

The scientific basis for CAC examination has been validated, and the scanning technology has undergone intense evaluation. The reproducibility and interscan variability have improved sufficiently to be used in clinical studies for further evaluation of its usefulness. To this end, there are several specific clinical uses of importance with associated publications that should be reviewed.

First, the CAC score can be followed to document the change over time to compare the rate of progression/stabilization/regression to correlate the score with hard and soft coronary events as it relates to strict risk factor modification similar to the studies of Nissen[80] with intracoronary ultrasound. Janowitz et al[81] first reported a pilot study of a small group of patients by angiography with obstructive disease who showed a 48% increase in CAC scores compared with a 22% increase in score for those without obstructive disease. Budoff and Raggi[82] reported on 1178 patients from 9 investigations in a meta-analysis. The studies show rates of progression with variation between 18% and 44%.[82]

Other investigators have extended this concept of tracking the calcium score after statin therapy. Callister et al[83] found the calcium score to increase in those individuals not treated with statin therapy and observed a significant reduction in the calcium score in those treated with statin therapy and whose final LDL cholesterol levels decreased to <120 mg/dL.[83] Even individuals treated less aggressively demonstrated an increase in volume score significantly lower than those who were untreated. Budoff et al,[84] in a similar observational study, showed that hypercholesterolemic patients on statin therapy had an annual rate of progression in their calcium score of 15% compared with a 39% increase in the nontreated group. This represents a 61% reduction in progression with statin therapy ($P<0.001$).

So does the progression of the calcium score, ie, atherosclerosis, translate into hard coronary events? Studies of patient outcomes observed over time for evidence of coronary calcium progression have been reported. In a retrospective study of 817 asymptomatic patients who were followed up for 2.2 ± 1.3 years, the mean absolute and percentage CAC volume scores from those with MI were $147\pm152\%$ and $47\pm50\%$, respectively, compared with $63\pm128\%$ and $26\pm32\%$ ($P<0.001$, $P<0.01$) for those without coronary events.[85] In another study, 225 moderate- to high-risk asymptomatic subjects with calcium scores >20 were followed up for 1 to 7 years. The annual event rate for patients who demonstrated coronary calcium score progression >35% per year showed a relative risk of a coronary event of >17.7 compared with those whose calcium scores progressed <20% per year. The only other independent predictor was age. Hypertension, diabetes, cholesterol, tobacco use, family history, coronary artery disease, and gender failed to predict events.[86] Thus, progression of coronary artery atherosclerosis can be observed noninvasively by monitoring the progression of the calcium score. It also gives the clinician a method to measure the effectiveness of therapy and to allow better assessment of the process associated with progressive disease.

Second, the NCEP II guidelines have been used to identify patients with subclinical atherosclerosis at high or low risk for future myocardial events. One of the most important benefits of the CAC score is identifying early asymptomatic disease with or without calcium because the negative predictive value is ≈99%. A recent study to determine the relationship between NCEP ATP II guidelines and EBCT for treatment of asymptomatic atherosclerosis involved 304 asymptomatic women who had EBCT evaluation and were classified as NCEP high and low risk according to LDL levels and EBCT positive or negative according to the presence or absence of calcified plaque. Forty-two percent (n=227) were

EBCT positive and 58% were EBCT negative (0 score). Women who were EBCT positive had higher cholesterol and triglyceride levels than EBCT-negative women. However, NCEP-higher-risk women made up 53.5% of the EBCT-positive group and 37.7% of the EBCT-negative group; 46.5% of the NCEP-lower-risk group were EBCT positive and 62.3% were EBCT negative. Using NCEP guidelines, 46.5% (n=59) of the EBCT-positive patients would not have received therapy, and 37.7% (n =66) in the EBCT-negative group would have had unnecessary statin therapy. Thus, only 58.9% of the study population would have been appropriately identified by NCEP guidelines. There was no difference between groups when age was eliminated from the Framingham risk calculation. Further studies of this type are needed to determine whether CAC scoring can truly help in triaging those patients at risk for future events and to decide whether individuals should have calcium scoring before being placed on statin therapy.[87] This study also indicates the possible benefit of incorporating the CAC score with the FRS, as demonstrated by Greenland et al.[79]

There is a possible cost-saving benefit for using EBCT in the workup of patients with new-onset chest pain in the category of low or intermediate pretest probability. Physicians are frequently faced with the task of evaluating patients with new-onset chest pain of questionable significance with low or intermediate pretest probability. The standard workup is the ETT. The ETT is known for its low sensitivity, specificity, and accuracy.[37,38,88] Patients may also undergo myocardial perfusion imaging, which adds significantly to the diagnostic and prognostic accuracy of ETT but adds significantly to the cost of the diagnostic workup because myocardial perfusion imaging costs more than ETT and CAC imaging combined. To approach this problem, Rumberger et al[89] studied an assimilated prototype ambulatory patient population model with a cut point for the EBCT calcium score of 168 to achieve a sensitivity and specificity of 71% and 90%, respectively, for >50% obstructive coronary artery disease. Their total direct testing costs increased in proportion to disease prevalence. The cost based directly on patients correctly diagnosed decreased as a function of disease prevalence. The cut point for a calcium score of 80 was also cost effective with a disease prevalence of 70%.[89] A more recent study published in 2000 used a cut point for the EBCT CAC score of 150 for a sensitivity of 79% and specificity of 89% for the prevalence of obstructive disease using a Bayesian cost model in a prospective group of low- to moderate-risk patients. The authors, using actual patient data and cost reimbursement rates for EBCT and ETT as initial testing, demonstrated a cost savings of 44% and 15% when disease prevalence was 0% and 100%, respectively. The authors agree that although the EBCT CAC does not give the prognostic information for a positive MPI test, this is balanced by the number of EBCT-positive patients below a score of 150 who could then implement strict risk factor modification to prevent progression to myocardial events.[90]

Conclusions

Atherosclerosis is an indolent long-term, mostly preventable disease with significant plaque formation in the early years. The prevalence of the disease with significant plaque formation is 17%, 37%, 60%, 71%, and 85% in the second through sixth decades of life. These data are in parallel with the development of calcification in the coronary arteries from large databases and the incidence of hard (nonfatal MI, death) and soft cardiovascular events. Atherosclerotic cardiovascular disease accounts for 38.5% of all deaths in the United States. This is in contrast to 15% of all deaths from tuberculosis in 1930, when a large screening effort was instituted whereby individuals could stop at a screening van on the street for a chest x-ray.[5] For those who die from CHD, 84.7% are >65 years of age. Eighty percent of CHD mortality in individuals <65 years of age occurs during the first attack, and 57% of men and 64% of women who die suddenly of CHD have had no previous symptoms.[27,28] In addition, the cost is $368.4 billion (more than one third of the total US healthcare costs) for treating this end-stage disease when premature death can be prevented with risk factor modification. The current method of predicting these events comes from the excellent studies that have evolved from the Framingham Heart Study's identification of risk factors and include age, hypertension, hypercholesterolemia, smoking, diabetes, obesity, and family history. The FRS is the reference standard for comparing any test that may be helpful for increasing risk prediction that may lead to treatments to prevent progression, ie, to reduce cardiovascular events and premature death.

The current controversy questions whether CAC should be used as an additional predictor for future coronary events. The answer is yes for the following reasons. The scientific basis for the examination has been validated. The technology has reached the point where the CAC score is accurate and reproducible, the interscan variability is acceptable by either EBCT or MDCT, and the examination can be performed throughout the country. The examination is not operator dependent and has a very high negative predictive value. It is the only noninvasive method to estimate total plaque burden, which is the most important predictor for future cardiac events. The real nexus of the controversy is how important are the data derived from patient/physician referral and prospective enrollment such as the SBHW/SFHS in contrast to the methods used to derive the FRS, ie, prospective randomized studies. After analyzing the data from 5 reports involving self-/physician-referred, SBHW, and SFHS subjects, one must conclude that there is very little difference in the data. The area under the ROC curves in all publications varies from 0.6 to 0.74 for FRS (NCEP II) and from 0.84 to 0.91 for CAC score cut points in the highest tertile or quartile scores. The incidence of hard and soft coronary events increases with increasing CAC score. In the most recent publication from SBHW, the areas under the ROC curve were 0.63 for FRS and 0.68 for FRS plus CAC. Both FRS and CAC in a graded fashion were independent predictors in all FRS categories >10% but not <10%. In addition, these

findings demonstrate that the CAC score adds to coronary event prediction over and above that predicted by FRS. This report is also the longest reported (8.5 years) follow-up; however, the significance of the 5 (self-/physician-referred) reports cannot be discounted. The SBHW, although a prospective study, selected intermediate- to high-risk subjects.[77] Therefore, the selection bias is such that there would be very little difference in risk from the beginning and the difference in any risk factor, ie, CAC scores and FRS, may be small. In addition, any difference would become obvious only with long-term follow-up as demonstrated. This is probably the reason why the first report showed no difference in predictability of either the FRS and the CAC score and longer follow-up uncovered this significance. In addition, the authors used 6-mm slices, which resulted in undersampling the volume, lowering all scores, especially in the lower percentile, and possibly reducing the low scores to zero.

The patient selection for the self-/physician referrals may include individuals with a variable number of risks, thereby accentuating the differences at an earlier stage. However, one cannot discount the incidence of disease in the population regardless of selection. Any population study selecting patients >45 years of age would have an incidence of significant atherosclerosis of 71% to 85% and a majority in the high-risk group from the outset, as evidenced by the demographics of disease prevalence and cardiovascular events reported in these age groups.

With respect to selection in a prospective random versus prospective selection, it would be interesting to analyze the Framingham study data from the original group. That selection was from community volunteers who were not randomized versus those who were later randomly recruited. One would expect that a larger number of low-risk individuals would be included in the nonrandom group, that initially the incidence of cardiovascular events would be less in this group, but that later both the incidence of disease and the event rate would be the same. It is not the purpose of this communication to discuss how a prospective random study should be done and if it is ethical to perform one. However, it is mentioned to highlight the problem of constructing a prospective randomized study when the disease prevalence is the same relative to the age group and to ask whether the expected outcome would be different from the data collected from the self/physician/prospective studies reviewed.

Regardless, the introduction of the CAC test is no different from the lifecycle of any new test such as the chest x-ray that had been viewed as a disruptive technology from any industry.[91] Almost all leading physicians and established professionals other than those performing the new test will initially oppose it, viewing it as useless; however, the emergent disruptive technology eventually emerges above the performance trajectory line when significant benefit is demonstrated. The disruptive technology nearly always wins, as in the case of the chest x-ray, when superior results are validated. The reason the self-/physician-referred centers flourish is that the highly educated and motivated patients see the benefit of knowing whether they have significant disease and what they (not their doctor) should do about it. They do not want to wait until they have angina (far-advanced heart disease) to know. It is imperative that we take a proactive integrated approach to earlier coronary risk assessment.

The conclusion from this review is that the CAC score should be (1) added to/integrated with the FRS in the intermediate- and high-risk groups as suggested by Greenland et al[79] and should be used as a guide for therapy in addition to correction of other risk factors such as changes in lifestyle, diet, weight reduction, and exercise; (2) incorporated into treatment evaluation (statin therapy) by following the CAC score over time to evaluate its significance as a predictor for future cardiac events as it relates to progression, regression, or stabilization; (3) included in the decision tree for ETT to screen those patients with a low test probability and to reduce invasive testing and thereby reduce costs; and (4) used to evaluate the significance of the CAC versus the FRS. Are all subjects with high-risk FRS truly at risk, and how does this relate to the CAC score? It is well known that the FRS does not predict all future myocardial events and the NCEP ATP II guidelines were, by today's standard, deficient by evidence of the change in cut points for total and LDL cholesterol levels in the ATP III guidelines. What cut points should be used for total cholesterol, LDL, and triglycerides? Likewise, are patients with any calcium score at high risk, and if not, what score level (cut points for CAC score) should be considered high risk? Rumberger et al[92] demonstrated that calcium score cut points can be associated with severity of disease and reported ranges in sensitivity and specificity for luminal stenosis varying from >20% to 100% associated with specific calcium scores. The next question is also 2-fold: Are the current guidelines from the databases sufficient to recommend statin therapy when the CAC score is above the 75th percentile, or should they be recommended above the 50th percentile?

I recognize that these are thorny issues but am hopeful that the medical establishment can unite to reconcile differences and promote an inclusive approach to heart disease that recognizes the preventable nature of the most important health problem facing the nation.

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Screening for Coronary Artery Disease With Electron-Beam Computed Tomography Is Not Useful

Jersey Chen, MD, MPH; Harlan M. Krumholz, MD, SM

Electron-beam CT (EBCT) is an emerging technology for the detection of coronary artery calcifications and the assessment of cardiovascular risk. Although the utility of EBCT remains controversial, its use has increased markedly, with an estimated 300 000 scans performed annually in the United States.[1] The rationale for EBCT is that traditional risk factor analysis fails to detect many patients who will suffer a cardiovascular event, necessitating better methods of risk stratification.[2] Although technological innovation in EBCT imaging is progressing, the state of the evidence supporting its use in screening is lagging.

Before commencing on routine EBCT screening of asymptomatic patients, there are several questions to be carefully considered. Does EBCT accurately and reproducibly measure coronary calcium? Second, does EBCT improve on existing methods of predicting coronary artery disease (CAD) events? Most importantly, does EBCT screening reduce mortality, improve quality of life, or lower costs without subjecting patients to unnecessary risks? On the basis of the current medical literature, the technology falls short in these areas.

EBCT for the Detection and Quantification of Coronary Artery Calcium

Until recently, the ability to assess accurately the amount of coronary artery calcification was limited by cardiac motion. EBCT is a novel technology in which the generation of an electron beam against stationary tungsten targets, combined with ECG gating, yields very rapid tomographic images of the heart. Computer software then quantifies the amount of calcium within the coronary arteries and calculates a coronary artery calcium score.[3] Although modern multidetector CT scanners can now calculate calcium scores,[4,5] most published clinical assessments of coronary calcium scores were conducted with EBCT.

The pathophysiology and clinical significance of coronary artery calcification have been the subject of extensive scientific study.[6,7] Calcification is a feature of several advanced types of atherosclerotic lesions that cause symptoms of ischemic heart disease or adverse cardiac events.[8,9] One histopathological study examined 13 autopsy hearts and found that coronary artery calcification on EBCT had a sensitivity and specificity of 59% and 90%, respectively, and a positive and negative predictive value of 87% and 65%, respectively for the presence of atheromatous lesions.[10] The low sensitivity and negative predictive value, however, indicate that CAD is often present without detectable coronary calcium. A histopathological study[11] also found a variable degree of calcification in atherosclerotic lesions, with some diffusely diseased coronary arterial segments with no coronary calcium present. Another study by Rumberger et al[12] examined 38 coronary arteries from 13 autopsy hearts that were dissected and scanned with EBCT. The sums of histological plaque areas and the whole-coronary-system calcium by EBCT were correlated, but the EBCT calcium area represented only about one fifth the total histological atherosclerotic plaque area. Hence, EBCT calcium score is an imperfect measure of total atherosclerotic burden.

However, the importance of coronary calcium with respect to cardiac events is now questioned. The underlying assumptions of EBCT are challenged by the new, emerging understanding of CAD risk that is based not on the presence of angiographic stenoses but instead on the presence of vulnerable plaques. The vulnerable plaque that leads to acute coronary syndromes consists primarily of a soft lipid core with a thin fibrous cap rather than calcium, and it is not necessarily obstructive.[13] Although calcium often is found in ruptured plaques, the presence or absence of calcium does not reliably discriminate between unstable and stable plaques.[9,14] As a result, the calcium score is an imperfect measure of total atherosclerotic burden, which itself is an imperfect measure of vulnerable plaque and clinical CAD events.

There are technical concerns with EBCT as an emerging technology. For example, reproducibility is an important crite-

TABLE 1. Sensitivity and Specificity of Stress Testing and EBCT for Angiographic CAD

Type of Stress Testing	Studies, n	Patients, n	Sensitivity, %	Specificity, %
Meta-analysis of standard stress ECG testing	147	24 047	68	77
Excluding MI patients	41	11 691	67	74
Perfusion scintigraphy	2	28 751	89	80
Exercise echocardiography	58	5000	85	79
Nonexercise stress tests				
Pharmacological stress scintigraphy	11	<1000	85	91
Dobutamine echocardiography	5	<1000	88	84
EBCT (from O'Rourke et al[23])	16	3683	91	49
EBCT (from Nallamothu et al[24])	9	1662	92	51

Adapted from O'Rourke et al.[23]

rion for a diagnostic test.[15] However, EBCT is subject to considerable interscan variability. For example, a study of 1000 patients found that the mean percentage difference in calcium scores between 2 consecutive EBCT scans was 28% for women and 43% for men with the Agatston method.[16] Another study of 298 patients found a mean interscan variability of 21.6% with an absolute difference in calcium score between 2 consecutive scans of 44.1 (SD, 95.6); patients with lower calcium scores had higher interscan variability.[17] Technical innovations to improve the reproducibility of calcium score include the use of volumetric scoring techniques[18,19] or modifying the ECG triggering method.[20,21] Although there may be progress towards reducing interexamination variability, EBCT image acquisition and reconstruction methods still need to be standardized to establish results that are fully comparable across scanners and patients.[22]

Do Calcium Scores Correlate With Angiographic Stenoses?

Two meta-analyses have examined the relationship between calcium scores and lesions on coronary angiography. The first review was conducted as part of the 2000 American College of Cardiology/American Heart Association (ACC/AHA) Expert Consensus Document on EBCT for the Diagnosis and Prognosis of CAD.[23] After 16 studies of 3683 patients without known CAD who underwent cardiac catheterization were analyzed, the pooled estimates of sensitivity and specificity for angiographic lesions were 90.5% and 49.2%, respectively. However, the definition of "clinically significant" CAD varied across studies, ranging from luminal irregularities in 2 studies to ≥50% stenosis in 11 studies to ≥70% or ≥75% stenosis in 3 studies. Similarly, the definition of an abnormal EBCT also varied, with 8 studies using a calcium score >0, 7 studies using a score from 0 to 5, and 1 study using a score >100. Another meta-analysis by Nallamothu et al[24] examined 9 studies of 1662 patients and found estimates of sensitivity and specificity of 92.3% and 51.2%, respectively. In this meta-analysis, the definition of a significant lesion was similar across studies (>50% stenosis in 8 studies and >75% using densitometry in 1 study); however, there was more variation in defining the area of calcification that represented an abnormal result, ranging from 0.5 to 2 mm^2 of increased density.

It is important to note that studies of EBCT using a gold standard of coronary angiography are limited. As discussed, vulnerable plaques that lead to CAD events are not necessarily obstructive.[13] In addition, not all patients with angiographic plaques are destined to suffer from cardiac events in their lifetime. The latter concept is known as "pseudodisease"—a preclinical lesion exists but does not progress during a patient's lifetime or a preclinical lesion progresses so slowly that the patient dies of other conditions before symptoms occur.[25] Detection of pseudodisease will not change patient outcomes.

Second, these studies are limited in generalizability to a screening population because they examined subjects who had a high enough degree of suspicion for CAD that cardiac catheterization was performed. Because these patients do not represent a population-based sample of screening candidates, the resulting sensitivity and specificity may be less generalizable to asymptomatic subjects. Selecting an appropriate study population is important when evaluating the accuracy of a diagnostic test to avoid spectrum bias, a phenomenon that occurs when a diagnostic test performs differently in different groups of patients.[26]

How does EBCT compare with other modalities that assess for the presence of clinically significant obstructive coronary stenoses? Table 1 lists estimates of sensitivity and specificity of the major forms of stress testing for angiographically apparent CAD from the ACC/AHA Expert Consensus Document.[23] In a meta-analysis of 147 studies of standard exercise ECG testing, Gianrossi et al[27] reported ECG testing to have a sensitivity of 68% and a specificity of 77% for angiographic CAD. When restricted to patients without prior myocardial infarction, an analysis of 41 studies demonstrated a sensitivity of 67% and specificity of 74% for ECG stress testing.[23] Adding imaging improves sensitivity for exercise echocardiography (sensitivity, 85%; specificity, 79%) and SPECT imaging (sensitivity, 89%; specificity, 80%) for angiographic CAD.[23] Overall the sensitivity of

TABLE 2. Studies of EBCT and CAD Events in Asymptomatic Patients

Study	Subjects, n	Mean±SD Age, y	Male, %	Nonwhite, %	Follow-Up, mo (%)*	Events	Annual Event Rate† (Nonfatal MI and CAD Death), %	Coronary Artery Calcium		Risk Factors
								Definition	Prevalence	
Arad et al[33] (follow-up of Arad et al[87])	1172	53±11	71	5	43 (99.6)	CAD death, 3; MI, 15; Revasc, 21	0.4	>0	≈50% from Arad et al[87]	Pt reported
Detrano et al[36]	1196	66±8	89	12	41 (99)	CAD death, 17; MI, 29; Revasc, 42	1.1	>0	≈67	Measured
Wong et al[34]	926	54±10	79	NR	(61)	Death, 0; MI, 6; CVA, 2; Revasc, 20	0.2	>0	57	Pt reported
Raggi et al[41] (follow-up of Raggi et al[35])	676	52±10	51	NR	32(NR)	CAD death, 9; MI, 21	1.7	>0	53	Pt reported
Kondros et al[38]	5635	50±9	74	5	37 (64)	CAD death, 21; MI, 37; Revasc, 66	0.3	>0	74 men, 51 women	Pt reported
Shaw et al[39]	10 377	53±0.10	60	NR	60 (100)	All-cause death, 249	0.5 (All-cause death)	≥11	43	Pt reported
Greenland et al[40] (subset of Detrano et al[36])	1029	66±8	90	15	76 (87.5)	CAD death, 16; MI, 68	0.7	>100	50	Measured
Vliegenhart et al[88]	1795	71±6	43	NR	40 (99)	CAD death or MI, 40; Revasc, 11; CVA, 38	0.2	>0	63	Pt report and measured
Arad et al[89]	4903	59±6	65	12%	52 (94)	CAD death or MI, 40; Revasc, 59; CVA, 7	0.2	>0	49	Pt reported
LaMonte et al[90]	10 746	54±10	64	<3%	42 (67)	CAD death, 19; MI, 62; Revasc, 206	0.7	>100	50	Measured

Adapted from Pletcher et al.[37]

*Average follow-up: duration (rate).

†Annual event rate: events/person-year.

NR indicates not reported; Revasc, revascularization; Pt, patient; and CVA, cerebral vascular accident.

EBCT for angiographic CAD appears comparable to or slightly higher than exercise echocardiography or SPECT, whereas the specificity of EBCT for angiographic CAD appears lower. However, it is important to note that exercise testing is a functional study that offers additional prognostic information beyond whether CAD is likely present; eg, exercise capacity[28] and heart rate recovery[29] have been shown to be significant predictors of mortality. In contrast, EBCT is strictly an anatomic test that is unable to provide prognostic physiological measures of fitness.

Does EBCT Improve Prediction of Clinical Outcomes?

The most important question for clinicians is whether calcium scores predict CAD outcomes beyond what is already known from information that is readily available for most patients. That is, does EBCT improve on our ability to predict clinical events beyond existing methods of CAD risk stratification such as the Framingham Risk Score (FRS)[30] in the United States or the Systemic Coronary Risk Evaluation System[31] in Europe? Because calcium scores and traditional risk factors are correlated,[32] the information from EBCT may be redundant.

Ten studies that examined calcium scores and clinical outcomes in asymptomatic patients are summarized in Table 2.

A meta-analysis by Pletcher et al[37] calculated pooled estimates from 4 studies of 3970 patients with 100 hard events of MI or CAD deaths. The authors extracted the results from the multivariate analysis in each individual study that controlled for traditional risk factors, standardized results into ORs for risk of MI or CAD death, and then calculated a summary estimate. Compared with patients with a calcium score of 0, patients with a calcium score from 1 to 100 had a higher risk for CAD events (OR, 2.1; 95% CI, 1.6 to 2.9). Calcium scores of 101 to 400 (OR, 5.4; 95% CI, 2.2 to 13) and >400 (OR, 10; 95% CI, 3.1 to 34) also had higher event rates, although CIs were wide.

Although individual studies[33,34,38–41,88–90] appear to suggest a correlation between calcium score and CAD events independent of traditional risk factors, we must be aware of several issues with these studies with respect to generalizability and methodological limitations in study design.

1. Study Cohorts Have Limited Generalizability

The cohorts of prior studies were limited in their generalizability to a screening population. Only 3 cohorts were based on population sampling methods.[42,88,89] The cohorts of other studies were convenience samples of patients who underwent EBCT, many of whom were self-referred and not necessarily representative of the general population. To avoid spectrum bias, the operating characteristics of a diagnostic test should be examined in an appropriately broad population of candidates for screening.[26]

One limitation of prior studies has been that they have enrolled predominantly male and white subjects. It is unclear whether EBCT has equivalent prognostic performance in women as in men. One study found that coronary calcium was significantly associated with death or MI for the 3065

men studied (RR, 3.86; 95% CI, 1.17 to 12.70) but not for the 751 women (RR, 1.53; 95% CI, 0.23 to 10.09),[38] although this study probably was underpowered to find a clinically important effect in women.[43] In LaMonte et al,[90] men in the top tertile of calcium score had an adjusted relative risk of 61.7 for CAD death, MI, or revascularization compared with men with a calcium score of zero; however, women in the top tertile of calcium score had a much smaller increase with an adjusted relative risk of 6.2 compared with women with a calcium score of zero. On the other hand, the meta-analysis by Pletcher et al[37] suggested a trend that studies with more female subjects had higher estimates of RR between calcium and CAD events, although an interaction was not specifically tested. Another study reanalyzing the data of Shaw et al[39] reported a significant interaction between coronary calcification and female gender on all-cause mortality (RR, 1.68; $P<0.0001$)[44]; the authors hypothesize that one reason why women may be at higher risk for death than men with the same calcium score is that women have smaller coronary arteries than men as determined by intravascular ultrasound, independently of body size.[45]

There is a paucity of data on nonwhite patients; the highest proportion of nonwhite patients reported was 15.1% (4.5% black).[40] Black patients with prior history of MI have less coronary calcium on EBCT[46] than white patients. In the South Bay Heart Watch cohort, coronary calcium seen on digital subtraction fluoroscopy was present in 59.9% of white subjects but only 35.5% of black subjects, yet more black subjects (23.7%) suffered cardiac events than white subjects (14.8%) after 70 months of follow-up.[47]

Another variation of spectrum bias occurs when pertinent subgroups are not analyzed separately.[15] For example, differences in test performance for diabetic and nondiabetic subjects may be important for EBCT screening. Suppose (as discussed in more detail below) that only nondiabetic patients were offered EBCT screening, because diabetic patients would receive primary prevention with aspirin and a statin as CAD equivalents regardless of additional testing. Although studies are conflicting as to whether calcium scores are more[48] or less[49] predictive of CAD events for diabetics compared with nondiabetics, the mere existence of a difference would nevertheless lead studies that included diabetic patients to inaccurately assess the true predictive ability of EBCT for nondiabetics. Yet, all studies of EBCT but one[40] analyzed diabetic and nondiabetic patients collectively, making their results less valid for a screening population consisting of only nondiabetic subjects.

2. There Were Multiple Methodological Limitations in Study Design

Prior studies of EBCT and outcome are also subject to a number of important methodological limitations. First, there is considerable heterogeneity in outcomes across studies because not all used hard end points of CAD death or MI. Two studies considered revascularization as a primary outcome along with CAD death and MI because of low rates of hard end points.[33,34] Use of revascularization as an outcome is problematic because a positive test itself often determines who undergoes these procedures, increasing the potential for work-up bias.[15,23] For example, knowledge of high calcium scores may have prompted patients to seek aggressive workup of stress testing and cardiac catheterization, which led to revascularization in the absence of symptoms. Another study did not examine the usual hard outcomes of CAD death or MI; instead it used all-cause mortality[39] Ascertainment of death also varied; medical records were commonly used, but in two studies[39,90] death was ascertained by a mortality database) with sensitivity for death ranging between 87.0% and 97.9% depending on search strategy.[50]

Second, not all studies had blinded adjudication of outcomes. As such, there is the possibility that knowledge of previous calcium score would bias determination of outcome. In subgroup analyses in the meta-analysis by Pletcher et al,[37] the 2 studies without blinded outcome adjudication[33,41] were more likely to report higher RRs for increasing calcium score, which is consistent with the expected direction of potential bias.

Third, relying on patients to self-report risk factors may result in biased estimates of the relationship between calcium scores and outcomes. For example, in 2 studies,[38,41] there was a surprising lack of correlation between several traditional risk factors and CAD events, which may be a consequence of misclassification by patient self-report. Dilution of these risk factors would overestimate the relationship between calcium scores and CAD events. Studies that obtained risk factors by patient history were more likely to report higher RRs for calcium score and outcomes, which is consistent with possible misclassification bias.[37]

Fourth, differences in EBCT protocols may also affect estimates of RR. For example, the most common EBCT slice thickness was 3 mm, whereas studies from the South Bay Heart Watch[36,40] used 6-mm slices. Although 6-mm slices have been reported to predict death and MI similarly to 3-mm slices,[51] 6-mm slices were less predictive of revascularization,[51] and thicker scan slices yielded less accurate assessments of calcium in EBCT studies using phantom targets.[52]

Lastly, lack of follow-up introduces potential bias. For example, it is possible that data on patients who suffered CAD events may have been more readily available than data on patients without events. Two studies reported particularly low rates: 61% in Wong et al[34] and 64% in Kondos et al.[38] A similar problem can occur when studies omit patients from their multivariate analysis. For example, Arad et al[33] excluded 33% of subjects from multivariate analysis because of incomplete data.

Overall, there still is a need for additional high-quality studies derived from representative populations with appropriate ethnic and gender diversity that are designed to minimize potential biases.

Will EBCT Change Clinical Management?

Even if calcium scores were accurate, reproducible, generalizable, and predictive of CAD risk, there still is the question of whether EBCT is clinically useful. Does the test offer sufficient information to alter patient management? Bayesian analysis implies that EBCT is much less informative in low-risk patients.[53,58] Bayes' theory states that the posttest probability of whether a patient has disease depends on the pretest level of risk and the characteristics of the test.[54] Assume that a typical low-risk patient has a pretest probability of 2% over 10 years for MI or death (the event rate for the low-FRS group of Greenland et al[40] was 1.4%). Assuming that a calcium score ≥80 has a sensitivity of 85% and a specificity of 75% for detecting coronary events (per Arad et al[33]), the resulting posttest probability of having a cardiac event within 10 years would be 6.5%,[58] which keeps the patient in the low-FRS category. The tendency for patients already at low risk to remain at low risk regardless of calcium score implies that EBCT is unlikely to be clinically useful in groups with low prevalence of disease.

Studies that stratified subjects by FRS[39,40,89] confirm the limited usefulness of EBCT for modifying prediction for MI or death in the low-FRS group. Greenland et al[40] demonstrated that a calcium score >300 did not significantly modify the predicted risk for CAD events in low-FRS patients. In the low-FRS group in Shaw et al,[39] calcium score categories (≤10, 11 to 100, 101 to 400, 401 to 1000, and >1000) only stratified predicted all-cause 5-year mortality from 0.9% to 3.9%. Although there was a 4-fold relative increase in the difference between the lowest and highest calcium scores in low-FRS patients, the resulting absolute risk level remained low regardless of calcium score.[53] In the study by Arad et al,[89] those subjects with low FRS and the highest tertile of calcium score had coronary event rates close to <1% per year, but included coronary revascularization as an event, so the FRS event rate of nonfatal MI or death remained low. While Vliegenthart et al[88] reported that calcium scores were significantly associated with CAD events in both subjects with 10-year FRS >20% and ≤20%, the study did not distinguish between low (<10%) and intermediate (10% to 20%) FRS, nor did it report absolute changes in risk, making it difficult to assess the utility of ECBT for low-FRS subjects in their study.

EBCT also appears unlikely to change management for high-risk patients. In theory, a negative EBCT test would reduce the posttest assessment of risk and could allow the possibility of discontinuing statin or aspirin therapy in an effort to reduce the potential for adverse side effects. However, the evidence from Greenland et al[40] suggests that EBCT will not substantially change predicted risk for patients with high FRS. In the subgroup of high-FRS subjects, a calcium score >300 was significantly associated with a higher 7-year event rate of 20% compared with calcium scores ≤300. However, high-FRS subjects with calcium scores ≤300 were still at substantial absolute risk for death or MI by 7 years, ranging from ≈11% to 13%.

Even a calcium score of zero does not guarantee the absence of events in high-risk patients. In the article by Greenland et al,[40] the 7-year event rate in high-FRS patients with a calcium score of zero was 9.3% (7 events in 75 patients).[40] In the study by Wong et al,[34] 4 of 23 patients (17.4%) who underwent revascularization had calcium scores of zero, demonstrating that the lack of calcium does not completely rule out CAD. Given that aspirin and statins are well-tolerated therapies, clinicians may be reluctant to discontinue these medications in high-risk patients even with a "negative EBCT." Because subjects with high FRS and low calcium scores are still at substantial absolute risk for CAD events, screening is unlikely to alter primary prevention strategies for this group.

There is no evidence to suggest that EBCT screening would change clinical management for another high-risk group: patients with diabetes mellitus. Because diabetic patients without heart disease may suffer CAD events at rates similar to those of nondiabetic patients with CAD,[55] diabetic patients are considered CAD equivalents for the purposes of cholesterol screening.[56] The American Diabetes Association position statement on primary prevention with aspirin is that therapy be considered in diabetics with high-risk features, including family history of CAD, smoking, hypertension, obesity, albuminuria, high lipids, or age >30 years.[57] Thus, there is little reason to screen diabetic patients with EBCT because most diabetics should be treated if indicated, regardless of calcium score. No study has shown that treating asymptomatic diabetic patients with antiischemic medications or revascularization confers benefit.[93]

Whether calcium scores change clinical management for diabetic patients by identifying low-risk subjects after EBCT is unclear. A reanalysis of the South Bay Heart Watch cohort found that calcium score categories did not predict MI or CAD death in 269 diabetic patients.[49] In contrast, Raggi et al[48] found that for every increase in calcium score, there was a greater increase in mortality for diabetic than for nondiabetic patients. Furthermore, they reported that among 267 diabetic and 4800 nondiabetic patients with no coronary calcium detected on EBCT, the 5-year all-cause survival was similar for diabetic and nondiabetic patients (98.8% versus 99.4, respectively; $P=0.49$). However, this analysis was underpowered (power for interaction, $\beta=0.47$ for $\alpha=0.05$),[48] was not specific for CAD death, and did not include nonfatal MI as an outcome. At this point, it is premature to consider low coronary calcium scores as sufficient for recommending against the National Cholesterol Education Program (NCEP) guidelines for treating cholesterol in diabetic patients as if they had existing CAD.

Having demonstrated that EBCT is unlikely to be clinically useful in low- and high-risk subjects, what is the evidence for patients at intermediate risk? In the work by Greenland et al,[40] intermediate-risk subjects with FRS 10% to 15% and calcium

scores >300 had event rates comparable to high-FRS subjects with calcium scores >300. Intermediate-risk subjects with FRS 16% to 20% and calcium scores >300 had predicted event rates comparable to high-FRS subjects with calcium scores ≤300. In Shaw et al,[39] calcium scores stratified 5-year all-cause mortality rates to a greater extent for intermediate-risk patients (1.1% to 9.0%) than low-risk patients (0.9% to 3.9%). Among intermediate-FRS subjects in Arad et al[89] with overall annual risk for death, MI, or revascularization of ≈1.1, those with the highest tertile of calcium scores had >2 events/year while those with the lowest two tertiles of calcium scores had event rates of ≈0.25 to 0.5 events/year.

Although EBCT screening in intermediate-risk patients may be promising, additional studies confirming prognostic utility are needed as prior studies were limited by a less commonly used scan slice thickness,[40] lack of CAD-specific outcomes,[39] and use of patient-reported risk factors[39,89]; however, even if EBCT refines risk estimates in intermediate-risk patients, there is no study that demonstrates that changes in clinical management in this subgroup will improve outcomes.

Does EBCT Improve Outcomes?

A worthwhile screening program does not merely detect disease; it must aim to improve clinical outcomes, reduce costs, or both. But for all the attention directed at EBCT as a screening tool, as yet no study has demonstrated that screening EBCT leads to improved patient outcomes.[58] Evidence that EBCT is effective in reducing mortality or morbidity is arguably the most important barrier that this technology must clear before its routine use can be justified.

Yet, screening with EBCT may not substantially improve outcomes for several reasons. First, a substantial number proportion of patients referred for EBCT have already met existing guideline criteria for primary prevention with a statin and should be treated regardless of their calcium score. In the above studies, a considerable proportion of patients reported hyperlipidemia (61.5%,[39] 59.5%,[41] 42%[33]) and likely already met NCEP Adult Treatment Panel (ATP) III guidelines for lipid-lowering therapy.[56] In fact, in the article by Shaw et al,[39] high cholesterol was paradoxically significantly associated with lower all-cause mortality, probably because these patients with high cholesterol were already prescribed statins.

A recently published clinical trial from St. Francis Heart Study was unable to definitively conclude that statin therapy was beneficial in reducing cardiovascular events for asymptomatic subjects with elevated calcium scores.[59] The study randomized 1005 patients with coronary calcium scores greater than the 80th percentile for age and gender to atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E 1000 units daily versus placebo. Treatment significantly lowered total cholesterol but did not significantly reduce the primary composite end point of coronary death, nonfatal MI, coronary or peripheral revascularization, or nonhemorrhagic stroke after after 4.3 years of follow-up (6.9% versus 9.9%, $P=0.08$). While post hoc analysis suggested that subjects with calcium score >400 had fewer events with treatment (8.7% versus 15.0%, $P=0.046$) this was not a prespecified end point. Neither the St. Francis Heart Study clinical trial[59] nor another randomized clinical trial of intensive versus moderate statin therapy[91] demonstrated that treatment affected the progression of coronary calcium.

Whether EBCT would lead to increased use of aspirin is also questionable. The AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke[60] suggest that aspirin be considered in patients with at least a 10% risk of CAD events over 10 years, ie, at least intermediate FRS. As such, the only patients in whom aspirin would be initiated are low-risk patients who become intermediate risk after EBCT. But, as demonstrated by the above Bayesian analysis, the likelihood of a low-risk patient becoming intermediate risk after EBCT is small.[53,58] There is currently no evidence that a high calcium score would affect other AHA recommendations such as smoking cessation, blood pressure control, and diabetes management.[60]

Although in theory EBCT could alter patient adherence to AHA recommendations for dietary intake, physical activity, and weight management, the evidence is mixed on whether EBCT convinces patients to make such lifestyle or behavioral changes. Patients with positive EBCT results were more likely to report losing weight, decreasing dietary fat intake, and consulting with a physician.[61] However, in a randomized clinical trial, patients who received data from EBCT did not modify their FRS after 1 year, and there was no effect on risk factors such as blood pressure, body mass index, cholesterol, physical activity, or smoking cessation.[62] Another study found that in a cohort of asymptomatic smokers, EBCT did not influence smoking cessation or smoking behavior.[63]

Finally, it is unclear whether EBCT would identify many patients who would benefit from revascularization. AHA/ACC guidelines for coronary artery bypass surgery suggest that asymptomatic patients with left main disease, 3-vessel disease, or depressed ejection fraction consider revascularization for survival benefit.[65] However, the prevalence of patients discovered with these findings by EBCT is unknown but likely small in an asymptomatic population. In patients with stable CAD without indications for bypass surgery, PCI has not been shown to reduce risk of death or MI.[92]

Thus, until there is evidence proving that EBCT is effective in lowering rates of cardiac death or MI, whether EBCT leads to substantial improvements in clinical outcomes remains unclear.

Does EBCT Screening Have Value for Money?

Healthcare spending in the United States rose by 7.7% in 2003 to $1.7 trillion.[66] Because medical resources are finite, it is important to assess whether EBCT screening reduces costs or at least offers value for money. Two detailed reviews of the costs associated with EBCT screening have recently been published.[1,67] Several studies have attempted to assess the costs

associated with EBCT.[67–71] However, 2 of these studies[69,70] examined EBCT in the workup of symptomatic patients who were, by definition not engaged in preventive screening.

Cost-effectiveness studies assess value in terms of the ratio of incremental cost per incremental quality-adjusted life years (QALYs) gained.[72] Ratios of <$50 000 to $100 000 per QALY are typically viewed as economically favorable. However, accurate cost assessment of EBCT is extremely difficult because of sensitivity to initial assumptions. To begin with, an intervention must be proved therapeutically effective by increasing survival or improving quality of life before it can be considered cost-effective. As mentioned above, whether EBCT will improve clinical outcomes is debatable.

EBCT may not be cost-effective due to the large number of subjects needed to be screened to avoid one event. From the entire screening population, EBCT would alter absolute risk levels primarily in intermediate FRS subjects with elevated calcium scores. We would then have to consider that primary prevention is only partially effective in reducing events (relative risk reduction of ≈27% for acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS] trial[64]). We must also take into account that therapy would be newly started in only a portion of patients with high calcium scores who did not already meet criteria from existing preventative guidelines. For example, the intermediate-risk patients in Greenland et al[40] with calcium score >300 had a mean LDL-cholesterol of 146 mg/dL; by NCEP ATP III guidelines more than half of these patients were already above the LDL-cholesterol goal of 130 mg/dL. As a result of all these factors, the number of patients needed to be screened to save a life or avoid MI would be considerable; this cost could be prohibitive per event avoided, even under the best-case scenario.

One study by O'Malley et al[68] examined the cost-effectiveness of EBCT over FRS alone in asymptomatic patients at intermediate risk (>1% events per year). They found that cost-effectiveness estimates were very sensitive to assumptions on the effectiveness of primary prevention, the incremental prognostic value of EBCT, and the decrease in utility from a positive EBCT. For example, the baseline case assumed that if primary prevention after EBCT reduced mortality by 30%, the cost was $86 752 per QALY, but reducing the efficacy slightly to 25% led to a large increase in cost to $1 700 000 per QALY. Because we are unsure of the incremental prognostic value of EBCT and the effectiveness of primary prevention therapies in patients with high calcium scores, accurate assessment of EBCT cost-effectiveness is a challenging proposition.

Cost-effectiveness analysis is also hampered by the lack of consensus about the workup of patients with high calcium scores. Although some clinicians would treat with medications alone, others may be more likely to use stress testing and subsequent cardiac catheterization and revascularization (on medico-legal grounds, perhaps). The intensity of diagnostic cardiac testing is a major determinant of the use of invasive cardiac procedures[73] and the downstream costs attributable to EBCT testing is likely substantial.

Finally, several other hidden costs should be considered. Incidental extra-cardiac findings on EBCT are not uncommon and require additional follow-up for 4% to 8% of patients scanned.[74–76] The follow-up associated with false positives from EBCT is important because it increases cost and decreases quality of life while providing little benefit, but few data are available to estimate the precise impact.

Cost-effectiveness varies substantially according to FRS. An analysis by Shaw et al[1,71] estimated that the costs to identify a death or MI were $73 000 for low-risk patients and $37 260 for intermediate-risk patients, with costs of identifying deaths alone of $402 000 for low-risk patients and $108 400 for intermediate-risk patients. These figures represent costs to detect an event, not costs to save a year of life, but already one can see that the economics are much more unfavorable for patients at low risk. The same authors also developed cost-effectiveness models that estimate the cost per year of life saved to be $506 719 for patients at low risk (0.6% annual event rate) and $30 742 and $42 339 for patients at intermediate risk (1.0% and 2.0% annual event rate, respectively).[67]

The unfavorably high cost per QALY in low-risk populations from EBCT screening is not surprising and is consistent with studies showing that diagnostic testing in asymptomatic patients with low risk for CAD using exercise ECG stress testing, SPECT, PET, and coronary angiography is not cost-effective.[77] Even statin therapy for the primary prevention of CAD in patients with high cholesterol is not cost-effective for very-low-risk patients; for all the cholesterol treatment recommendations of the NCEP to be considered cost-effective would require a threshold of $680 000 per QALY.[78]

Is EBCT a Risk-Free Test?

EBCT appears to be a safe test because it is a noninvasive modality that does not require ischemia to be induced. However, several potential risks to screening may not be immediately apparent. This is particularly important because advertisements for self-referred imaging facilities often fail to provide balanced information on risks; some even omit mention of radiation.[79] The physician's doctrine of "*Primum non nocere*" (First, do no harm) mandates a high burden of proof for screening tests to demonstrate benefit without undue risks.

First, the long-term risk of radiation from EBCT is difficult to quantify. No study has examined the cancer risk specifically for EBCT. One study examining conventional full-body screening CT estimated an increase in lifetime attributable cancer mortality risk for a 45-year-old patient was 0.08% (≈1 of 1250 patients) from a single scan and ≈1.9% from 30 scans over a lifetime.[80] These risks are based on the higher total effective dose of full-body conventional CT (11.6 mSv for men and 13.5 mSv for women)[80] compared with a lower dose from EBCT (1.0

mSv for men and 1.3 mSv for women).[81] However, if multidetector row CT calcium scoring becomes more common for CAD screening, the radiation dosages would become higher (1.5 to 5.2 mSv for men and 1.8 to 6.2 mSv for women); the dosages from multidetector row CT coronary angiography are even higher (6.7 to 10.9 mSv for men and 8.1 to 13.0 mSv for women).[81] Furthermore, the risk for cancer rises with multiple examinations and with younger age at exposure. Having several screening EBCT scans over a lifetime or the proposed use of repeated EBCT scans to monitor changes in coronary artery plaque[82] would further increase radiation exposure. Because optimal number and onset of scanning have not been determined, how cancer risk alters the risk-benefit equation for EBCT requires further study.

False-positive test results also carry risk. Patients with false-positive results would undergo a diagnostic workup that includes stress testing or cardiac catheterization and their accompanying risks. The number of false positives resulting from EBCT is considerable. For example, in the study by Arad et al,[33] the positive predictive value for MI or CAD death over 3.6 years was 7% with a calcium score threshold of ≥160. In other words, 93% of patients with a "positive EBCT test" would not suffer a CAD event during this time. Even after the calcium score threshold was increased to ≥600, the positive predictive value increased only to 13%, implying that 87% of patients with a positive test would not suffer an event over 3.6 years. Even a proportion of individuals with true positive results will suffer needless harm by undergoing EBCT; subjects who have calcified coronary stenoses that will never manifest as events or symptoms (ie, pseudodisease)[25] may be prompted by high calcium scores to take on the risks of invasive procedures and revascularizations that will ultimately not benefit them.

False-negative results also have some risk if the false sense of security from a negative EBCT leads patients who actually have CAD to become complacent in lifestyle changes with respect to smoking, diet, or exercise or, worse yet, delay follow-up of symptoms of ischemia. Similarly, true-negative results can also lead to complacency regarding lifestyle modifications that impact morbidity and mortality outside of CAD. For example, a smoker who does not quit smoking after receiving a low calcium score is still at higher risk for lung cancer.

Lastly, the potential negative impact in quality of life from having a positive EBCT is a real but rarely considered risk. Patients may find themselves uninsurable for health or life insurance on the basis of a preexisting high calcium score. In addition, the quality of life of a patient at increased risk for CAD now becomes lower from worry and the inconveniences of being at risk, including more frequent medical follow-up and the need to take daily medications. A positive EBCT causes some disutility in patients with high calcium scores in that they are more likely to worry.[61] Although no data quantifying the disutility of living with a positive EBCT test currently exist, hypertension is similar to asymptomatic CAD in that patients must take daily medication and undergo routine follow-up for a condition without symptom; subjects with hypertension value a year of life at 94.4% relative to a year of a patient without hypertension.[83] Although it may seem theoretical, disutility arising from EBCT is an important factor in determining whether EBCT is cost-effective over the FRS.[68]

The Future of EBCT Research

Several on-going prospective studies are expected to provide important information about incremental risk stratification from EBCT. In the United States, the Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study will provide data on EBCT across age, race, and gender categories.[84] The Heinz Nixdorf Risk Factors, Evaluation of Coronary Calcium and Lifestyle (RECALL) is a population-based, prospective cohort study that will help to establish the incremental RR associated with the coronary calcium scores in a German population.[85]

Conclusions

The existing evidence for using EBCT as a screening tool for CAD in asymptomatic patients can be summarized as the following.

- No study has definitively demonstrated that screening with EBCT improves clinical outcomes by reducing mortality or morbidity from CAD.
- Widespread and routine EBCT screening is unlikely to benefit low-risk or high-risk patients. Few patients with low pre-test probability of CAD will change risk levels enough to lead to changes in medical management. Patients with high pretest probabilities or diabetes are essentially at CAD-equivalent risk regardless of calcium score, and treatment of risk factors rather than screening would be more appropriate. Although EBCT remains to be proven as an adjunctive risk-stratification tool in intermediate-risk patients, whether this would lead to a substantive improvement in patient outcomes through increased use of preventative therapies or lifestyle modifications is unknown.
- Prior studies have limited generalizability to a screening population (lack of gender and ethnic diversity) and are limited by several methodological concerns (use of soft end points such as revascularization, nonblinded adjudication of outcomes, potential misclassification of traditional risk factors, loss to follow-up).
- No study has demonstrated that EBCT reduces healthcare costs. Whether the additional costs caused by EBCT screening can be justified is unknown because of the uncertainty of the data that support baseline assumptions on effectiveness. The cost per year of life saved for EBCT screening appears to be at least an order of magnitude higher for low-risk patients compared with intermediate-risk patients and is not economically favorable. Additional downstream costs from EBCT screening (workup of false-positive results and incidental findings) may be substantial but are not fully characterized. Finally, the additional cancer risk resulting from EBCT remains to be assessed. If serial EBCT examina-

tions become routine for CAD screening, higher radiation dosages become more concerning.

EBCT is one of many contenders in a crowded field of emerging CAD risk assessment tools. For example, other noninvasive modalities (such as carotid intima-media thickness via ultrasound) and blood tests (such as C-reactive protein, homocysteine) are under investigation as improving our ability to risk-stratify patients.[86] Yet, with healthcare costs spiraling upwards, we as a society must be judicious in deciding which, if any, of these technologies provides a good (or any) return on investment; otherwise, we are committed to spending a considerable amount of money for an uncertain return and diverting resources from other areas.

Clinicians require high standards for assessing the value of new medical therapies and devices; evidence-based methods for evaluating screening strategies are just as important, as they ultimately dictate all downstream testing, treatments, and costs. We should seek clear evidence that a diagnostic test has benefit for particular patient populations in terms of therapeutic efficacy, acceptable safety, and affordability that take into account subsequent costs initiated by the screening test.

As technology improves, EBCT may someday provide meaningful increments in risk prediction for specific patients that lead to changes in clinical management that improve outcomes, all at reasonable cost and without excessive risk; however, at present, the linkage between EBCT and improved outcomes has not been demonstrated; thus, it is premature to recommend its routine use for screening asymptomatic patients for CAD.

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Response to Chen and Krumholz

Melvin E. Clouse, MD

The authors both for and against the CAC examination have presented an enormous amount of material in this debate, but it is up to the readers to decide whether the examination is worthwhile to them and their patients. In its simplest form, the value of the CAC is that it identifies individuals who have early or asymptomatic coronary artery disease and allows them to assume responsibility with their physician to institute preventive measures. It is unlikely that any

test will affect outcome in low-risk populations, and CAC should not be recommended in those groups. However, it may be beneficial in intermediate- and high-risk groups (candidates for statin therapy) and should be incorporated into both the FRS and subsequent treatment evaluation so that the CAC score may be followed over time. Readers should not be confused by distracting issues such as radiation dose (<2 mSv; background being 3 mSv) and annual allowable dose for radiation workers (50 mSv). Improving outcome, cost-effectiveness, and current study design and reducing healthcare costs are also problematic issues. The current cost for the CAC examination is $400; for single lipid profile, $218 to $378; and for statins, $1120 to $1700 per year. Yet, there is no noninvasive method other than CAC to evaluate treatment except survival and soft and hard coronary event data. For almost all other diseases, physicians expect to have a more definite end point to evaluate the results of their treatment. That said, the present status quo strategy has not reduced morbidity, mortality, or cost to either the individual or the healthcare system in general. The cost to the healthcare system to treat and care for end-stage cardiovascular disease is $368.4 billion. The cost of loss of productivity (3.7% of MIs occur in the 29- to 44-year-old group, 29% in the 45- to 64-year-old group, and 67% in those >65 years of age) is enormous. In addition, the average number or years of life lost from a heart attack is 11.5, and ≈42% die within 1 and 50% within 8 years after their first heart attack.[1] Readers must question whether the present strategy is satisfactory. I believe that an early warning system should be presented so that individuals may become proactive in reducing morbidity and mortality of their disease.

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Response to Clouse

Jersey Chen, MD, MPH; Harlan M. Krumholz, MD, SM

Dr Clouse's review in favor of CT screening for CAD relies on assumptions that require additional evidence. The belief that coronary calcium readily identifies atherosclerotic plaque at future risk of rupture may be overly speculative because the vulnerable plaque is typically composed of a lipid core with a thin fibrous cap and not necessarily calcified. Such vulnerable plaques may not be detectable by CT, and the clinical utility of a negative study is not clear. Even if coronary calcium were a marker for extensive vulnerable plaques, how much CT improves risk stratification beyond traditional risk factors and how this information translates into meaningful changes in clinical management remain to be quantified.

He proposes that the early detection of coronary calcification will prevent death and MI, but no study has demonstrated that CT screening improves patient outcomes. CT may ultimately share the same fate as chest radiography for screening smokers for lung cancer—a strategy abandoned because multiple clinical trials failed to demonstrate reductions in mortality. Before we commit to screening with CT, we require proof that this approach will either improve quality or quantity of life or lower overall health costs while maintaining comparable outcomes. If a benefit cannot be proved, then the value of CT screening is doubtful; it could place patients who ultimately would not become symptomatic on a needless testing and intervention cascade with potential for harm and substantial added costs.

Although Dr Clouse argues that the considerable medical and economic burden of CAD favors the rapid adoption this technology, it is precisely because the stakes are so high that we must demand high-quality evidence that CT, as well as other emerging predictors of risk, provides benefit before advocating its widespread use.