ACC/AHA Expert Consensus Document

American College of Cardiology/American Heart Association Expert Consensus Document on Electron-Beam Computed Tomography for the Diagnosis and Prognosis of Coronary Artery Disease

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Executive Summary

Coronary artery calcification is part of the development of atherosclerosis; it occurs exclusively in atherosclerotic arteries and is absent in the normal vessel wall. Electron-beam computed tomography (EBCT), the focus of this document, is a highly sensitive technique for detecting coronary artery calcium and is being used with increasing frequency for the screening of asymptomatic people to assess those at high risk for developing coronary heart disease (CHD) and cardiac events, as well as for the diagnosis of obstructive coronary artery disease (CAD) in symptomatic patients. The use of EBCT has the greatest potential for further determination of risk, particularly in elderly asymptomatic patients and others at intermediate risk. The calcium score has been advocated by some as a potential surrogate for age in risk-assessment models. EBCT has also been proposed as a useful technique for assessing the progression or regression of coronary artery stenosis in response to treatment of risk factors such as hypercholesterolemia.

EBCT uses an electron beam in stationary tungsten targets, which permits very rapid scanning times. Serial transaxial images are obtained in 100 ms with a thickness of 3 to 6 mm for purposes of detecting coronary artery calcium. Thirty to 40 adjacent axial scans are obtained during 1 to 2 breath-holding sequences. Current EBCT software permits quantification of calcium area and density. Histological studies support the association of tissue densities of 130 Hounsfield units (HU) with calcified plaque. However, a plaque vulnerable to fissure or erosion can be present in the absence of calcium. Also, sex differences play a role in the development of coronary calcium, the prevalence of calcium in women being half that of men until age 60 years. EBCT calcium scores have correlated with pathological examination of the atherosclerotic plaque.

This American College of Cardiology (ACC)/American Heart Association (AHA) Writing Group reviewed the literature on EBCT published between 1988 and 1999 and also used information obtained when possible from articles in press and data sets from EBCT research centers. We also reviewed the Blue Cross/Blue Shield (BC/BS) Technology Evaluation Center (TEC) assessment of EBCT for screening asymptomatic patients for CAD and for diagnosing CHD in symptomatic patients. Three members of this Writing Group attended the recent AHA Prevention V Conference on "Identification of the High-Risk Patient for Primary Prevention," and one of our members is also a participant in the design of the National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) forthcoming Multiethnic Study

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of Atherosclerosis (MESA), which will include a prospective assessment of EBCT in asymptomatic people.

We performed meta-analysis on the relationship between CHD and calcium prevalence in patients undergoing EBCT and cardiac catheterization to determine the diagnostic accuracy of EBCT in catheterized patients. We also performed a meta-analysis of published data in order to compare the diagnostic characteristics of the available alternative tests for detecting angiographic obstructive CAD. The studies demonstrate a high sensitivity of EBCT for CAD, a much lower specificity, and an overall predictive accuracy of ≈70% in typical CAD patient populations. The test has proven to have a predictive accuracy approximately equivalent to alternative methods for diagnosing CAD but has not been found to be superior to alternative noninvasive methods (eg, SPECT [single photon emission computed tomography] imaging). The majority of the members of the Writing Group would not recommend EBCT for diagnosing obstructive CAD because of its low specificity (high percentage of false-positive results), which can result in additional expensive and unnecessary testing to rule out a diagnosis of CAD. The 1999 ACC/AHA Coronary Angiography Guideline Committee reached a similar conclusion.[1]

Because the severity of coronary atherosclerosis is known to be associated with risk of coronary events, coronary calcium scores should likewise correlate with risk for coronary events. However, for a test to be most valuable when asymptomatic patients are screened, it should increase the likelihood of CHD above the probability determined by standard and readily available assessments, such as the Framingham risk model based on levels of blood pressure, cholesterol, high-density lipoprotein (HDL) cholesterol, cigarette smoking, plasma glucose, and age. The published literature does not completely answer the question of whether the EBCT calcium score is additive to the Framingham score for defining CHD risk in asymptomatic patients. In one recent large study,[2] the addition of EBCT data provided no incremental value to the risk determined by the Framingham and National Cholesterol Education Program risk factors in a direct comparison. There have been other studies that examine this point,[2–4] but those reports did not adequately test whether EBCT scores were incremental to the other risk factor data. This is an area of important current investigation, including the NIH/NHLBI's MESA study. It is possible that a positive calcium score might be valuable in determining whether a patient who appears to be at intermediate CHD risk is actually at high risk. Conversely, a low or absent EBCT calcium score may also prove useful in determining a low likelihood of developing CHD. This may be particularly beneficial in elderly asymptomatic patients in whom the management of other risk factors may be modified according to the calcium score. Selected use of coronary calcium scores when a physician is faced with the patient with intermediate coronary disease risk may be appropriate. However, the published literature does not clearly define which asymptomatic people require or will benefit from EBCT. Additional appropriately designed studies of EBCT for this purpose are strongly encouraged. In the setting of this degree of uncertainty, EBCT screening should not be made available to the general public without a physician's request.

The usefulness of EBCT in determination of changing calcium scores that correlate with regression or progression of CHD is currently being studied intensively. However, the test-to-test variability and the interrater reliability of the calcium score measurement in the same individual studied at close intervals in time have been deterrents to the recommendation of serial EBCT scans for determining the response of coronary artery stenosis lesions to medical interventions designed to cause regression of disease. The Writing Group concluded that this is a promising use of EBCT, but the small number of published studies require corroboration before EBCT can be widely recommended for this purpose.

Our conclusions are consistent with the recommendation of the Agency for Health Care Policy and Research–funded BC/BS TEC, the Prevention V Conference report of the AHA (Dr Philip Greenland), and the MESA project currently being planned by the NIH/NHLBI. The latter study will evaluate EBCT and other techniques in the long-term assessment of CHD risk in 6500 apparently healthy people. As additional data are obtained, our conclusion might require revision.

This Writing Group encourages further properly designed outcomes research using EBCT and additional studies of the role of EBCT and patient follow-up for assessing progression or regression of CHD.

I. Preamble

The present document is an Expert Consensus Document that includes evidence about the use of EBCT for the detection of calcium as a marker of coronary atherosclerosis. This type of document is intended to inform practitioners, payers, and other interested parties of the opinion of the ACC, often in collaboration with the AHA, concerning evolving areas of clinical practice and/or technologies that are widely available or new to the practice community. Topics chosen for coverage by Expert Consensus Documents are so designed because the evidence base and experience with technology or clinical practice are not considered sufficiently well developed to be evaluated by the formal ACC/AHA Practice Guidelines process. Often, as in this case, the topic is the subject of considerable ongoing investigation. Thus, the reader should view the Expert Consensus Document as the best attempt of the ACC and AHA to inform and guide clinical practice in areas where rigorous evidence may not yet be available or the evidence to date is not widely accepted. Where feasible, Expert Consensus Documents will include indications or contraindications. Some topics covered by Expert Consensus Documents will be addressed subsequently by the ACC/AHA Practice Guidelines Committee.

II. Consensus Statement Method

The ACC has not previously provided a scientific statement or a consensus document relative to the use of EBCT. At its first meeting, each member of this ACC/AHA Writing Group indicated in writing any relationship to advisory committees, speakers' bureaus, or stock holdings that could be perceived as a conflict of interest; no relevant conflicts of interest were reported. The first step in the development of this document

was to obtain a complete literature review from the Griffith Resource Library at the ACC concerning EBCT from 1995 to 1998 (National Library of Medicine's Elhill System). Additional relevant prior or subsequently published references have also been identified, as well as manuscripts currently in press. At the first meeting, various members of the Writing Group were asked to provide a description and analysis of EBCT for identifying coronary risk in the asymptomatic patient, for determining the likelihood of obstructive CAD in symptomatic patients, and for detecting the progression or regression of coronary atherosclerotic lesions in patients with known CHD. Each individual contributor to these parts of the document had his or her initial written presentation critiqued by 1 or 2 additional members of this Writing Group. Additional members of the Writing Group provided text concerning the accuracy of the test, alternative approaches to the detection of obstructive CAD, and the economic impact of developing new technology in this era of constrained resources.

During the time when this document was being developed, a discussion of EBCT and CHD risk prediction in the asymptomatic individual (atherosclerotic burden) was held at the Prevention V Conference of the AHA in San Francisco, Calif, on October 28, 1998. It was cochaired by 2 members of this Writing Group (Drs Philip Greenland and Scott Grundy). A third member of this Writing Group (Dr Victor Froelicher) participated in Writing Group III at the AHA Prevention Conference.

The BC/BS TEC, with a large research staff and one of the AHCPR evidence-based practice centers, provides technology assessment services to BC/BS member plans, managed care plans, and others. They do not directly recommend reimbursement or nonreimbursement. They recently assessed the EBCT detection of coronary artery calcium, including its cost-effectiveness, and presented their results to the BC/BS Medical Advisory Board on December 10, 1998, at a meeting attended by the Chair of this Writing Group (Dr O'Rourke). In discussions with ACC leadership, the BC/BS Advisory Panel TEC indicated their willingness to make the results of their assessment on EBCT available to this Writing Group. The BC/BS "TEC Assessment of Diagnosis and Screening for Coronary Artery Disease With Electron Beam Computed Tomography" has recently been completed.*

Also relevant to this report is the initiation of the MESA project by the NHLBI. The MESA protocol, which is in its design phase, will assess the relationship between baseline risk factors and other possible indicators of subclinical disease and future clinical outcomes. There will be a 10-year follow-up, and coronary artery calcium will be evaluated by either EBCT or helical computed tomography (CT) to determine its utility in risk stratification.

III. Principles of Technology Assessment

The development of new medical technology has been a major factor contributing not only to the improved health of the American public, but also to the rising cost of health care.[5] On the basis of current estimates, as much as one third to one half of the higher real expenditures for health care are due to an increase in the volume and intensity of services that include the use of new technology.[5–7] Of course, this technology has been invaluable for many patients.

During the past 2 decades, a number of innovative techniques have been introduced within diagnostic cardiology that have resulted in improved test performance (ie, sensitivity) for the detection of obstructive CAD. Improvements in test accuracy in the area of diagnostic cardiology have been uniformly associated with higher test costs. Historically, as new technology was developed, it was expected that users would pay for newer, more high-tech imaging tests without any justification of the incremental cost of the new technology. The resulting economic pressures placed on physicians in the current era of healthcare reform are forcing a rethinking of the medical applications of a number of testing modalities. The evaluation of CHD can utilize many testing modalities. The Writing Group accepted the principle that the future of any new technology must now undergo a rigorous evaluation before routine use and application in daily clinical decision making. The limited diffusion of new technologies (eg, EBCT and contrast-enhanced echocardiography) in today's healthcare market indicates that clinicians and healthcare administrators are making more cautious choices about new technology by awaiting a greater compendium of results applied throughout a wide variety of patient subsets. Although a new test may be less expensive than others previously available, in some cases, tests with low specificity may result in add-on tests that lead to additional costs without improving patient outcomes.

Although not every decision in clinical medicine will be supported by randomized trials, broader evidence for the use of EBCT is needed. Promising tests or therapies that seem intuitively attractive have often not proved to be effective when evidence was required (eg, systolic time intervals, digital subtraction left cineangiography, and aortic valvuloplasty).

In estimating the accuracy of a noninvasive test for obstructive CAD, there are methodological limitations that hinder our understanding of true predictive accuracy. In general, positive results are more likely to be published, reflecting publication bias, with an overestimation of test accuracy.

Another common problem that often occurs early in the evaluation of a new imaging modality is that of limited challenge. Limited challenge is present in studies that compare test results from diseased and normal populations (extreme ends of the disease-prevalence continuum). In general, it is the goal of this type of analysis for the abnormal test results to occur in diseased patients and for normal test results to occur in patients without obstructive disease. Because the patient populations are extremely skewed, the results overestimate test accuracy.

The most notable limitation to assessing diagnostic accuracy is the calculation of test sensitivity and specificity. The patients who proceed to diagnostic cardiac catheterization define this calculation. In general, a predominant number of

*Blue Cross/Blue Shield Association (1999). Diagnosis and screening for coronary artery disease with electron beam computed tomography. TEC Assessment Program, 13 No. 27. March 1999.

patients who proceed to cardiac catheterization are those with abnormal test results, reflecting the routine workup for suspected obstructive CAD (workup or verification bias). As a result of a greater number of patients with abnormal test results being referred to the "gold standard" of coronary angiography, test sensitivity is enhanced. Conversely, those patients with normal test results who are referred to arteriography include patients with high-risk clinical history of symptoms and those with other myocardial or valvular heart disease. Thus, test specificity is lowered and poorly reflects the exclusion of disease in patients with normal or low-risk test results.

The failure to eliminate workup bias has been a problem with most of the studies evaluating the diagnostic characteristics of a noninvasive test for the detection of obstructive CAD. Normal clinical practice results in certain patients being selected or referred for a test (referral bias), with only certain patients being selected for further evaluation (posttest bias). For instance, after an exercise test, cardiac catheterization would be chosen particularly for those with a low exercise capacity and/or abnormal ST response. Most of the studies that have evaluated the characteristics of tests for CAD, using the appropriate gold standard of cardiac catheterization, have some degree of workup bias.

An important third consideration is the importance of the end points chosen when data other than the coronary arteriogram are used. Hard end points are myocardial infarction and death, whereas soft end points include chest pain and coronary interventions. Screening studies provide the best example of the problem with using soft end points instead of hard end points. When angina is included as an end point, nonspecific symptoms in a subject with an abnormal test result are more likely to be called CAD during the follow-up period. Hard end points, like death or myocardial infarction, eliminate this misclassification and are more appropriate.

There is a definite problem with the use of interventions as cardiac end points. With modern treatment, there often are inadequate numbers of cardiovascular deaths and infarctions in most populations studied to obtain statistically significant results. Therefore, to have enough end points, follow-up studies have often included bypass surgery or percutaneous coronary artery interventions as end points. In fact, very often the majority of the end points are interventions. This is problematic, because the test result often determines who undergoes these procedures, and it is invalid to include them as events predicted by the test.

In screening studies, the populations should truly be asymptomatic and should represent a random or systematically selected sample of the target population. Volunteers are not appropriate, because they usually represent the extremes of the population: the most healthy and those who are concerned for personal reasons regarding their health (eg, family history or symptoms they chose to deny). Volunteers represent a subtle form of limited challenge by introducing the extremes into the data set.

A problematic surrogate is the use of other test results such as nuclear imaging instead of angiography as a gold standard. It is well known that nuclear imaging has limitations in predicting obstructive CAD and cannot be used to replace the best standard available. Surrogates for standards should be considered carefully and justified only when they perform equal to or better than the standard itself.

Screening can be defined as the presumptive identification of unrecognized disease by the use of procedures that can be applied rapidly. The relative value of techniques for identifying individuals who have asymptomatic or latent obstructive CAD should be assessed to optimally and cost-effectively direct secondary preventive efforts toward those with disease.

Eight criteria have been proposed for the selection of a screening procedure:

1. The procedure is acceptable and appropriate.
2. The quantity and/or quality of life can be favorably altered.
3. The results of intervention outweigh any adverse effects.
4. The target disease has an asymptomatic period during which its outcome can be altered.
5. Acceptable treatments are available.
6. The prevalence and seriousness of the disease justify the costs of intervention.
7. The procedure is relatively easy and inexpensive.
8. Sufficient resources are available.

In addition, 7 guidelines have been recommended for deciding whether a community screening program does more harm than good:

1. Has the program's effectiveness been demonstrated in a randomized trial, and if so,
2. Are efficacious treatments available?
3. Does the current burden of suffering warrant screening?
4. Is there a good screening test?
5. Does the program reach those who could benefit from it?
6. Can the healthcare system cope with the screening program?
7. Will those who had a positive screening comply with subsequent advice and interventions?

The demonstration of the effectiveness of a screening technique requires the randomization of the target population, with half receiving the screening technique; standardized action taken in response to the screening test results; and then outcomes assessment. For the screening technique to be effective, the screening group must have lower mortality and/or morbidity. Such a study has been completed for mammography but not for any cardiac testing modalities. The next best validation of efficacy is to demonstrate that the technique improves the determination of those asymptomatic individuals with higher risk for events over that possible with the available risk factors. Mathematical modeling makes it possible to determine how well a population will be classified if the characteristics of the testing methods are known.

IV. Introduction to EBCT Consensus Report

Coronary arterial calcification is part of the development of atherosclerosis, occurs exclusively in atherosclerotic arteries, and is absent in the normal vessel wall.[8–10] Coronary artery calcification occurs in small amounts in the early lesions of atherosclerosis that appear in the second and third decades of

life; it is found more frequently in advanced lesions and in older age. Although there is a positive correlation between the site and the amount of coronary artery calcium and the percent of coronary luminal narrowing at the same anatomic site, the relation is nonlinear and has large confidence limits.[11] The relation of arterial calcification, like that of angiographic coronary artery stenosis, to the probability of plaque rupture is unknown.[12,13] Vulnerable plaque is frequently present in the absence of calcification.[14] Although EBCT and helical CT have been very sensitive in defining coronary artery calcium and may provide a measure of total coronary plaque burden, calcium does not concentrate exclusively at sites with severe coronary artery stenosis.[15]

EBCT, the subject of this document, uses an electron gun and a stationary tungsten "target" rather than a standard x-ray tube to generate x-rays, thus permitting very rapid scanning times. EBCT serial transaxial images are obtained in 100 ms with a scan slice thickness of 3 to 6 mm for the purpose of detecting coronary calcium. Thirty to 40 adjacent axial scans usually are obtained. The scans usually are obtained during 1 or 2 breath-holding sequences and are triggered by the ECG signal at 80% of the R-R interval, near end diastole before atrial contraction, thus minimizing the effect of cardiac motion. The rapid image-acquisition time virtually eliminates motion artifact related to cardiac contraction. Thus, specific epicardial coronary arteries are easily visualized by EBCT because the lower CT density of periarterial fat markedly contrasts to blood in the coronary arteries, whereas the mural calcium is identified because of its high CT density relative to soft tissue and blood.[16] Also, the scanner software allows quantification of calcium area and density. A calcium scoring system has been devised based on the x-ray attenuation coefficient, or CT number measured in Hounsfield units, and the area of calcium deposits.[17] A study for coronary calcium is completed within 10 to 15 minutes, requiring only a few seconds of scanning time.

EBCT has been used with increasing frequency in the United States and other countries during the past 10 years in screening asymptomatic individuals for the purpose of identifying those at high risk for developing clinical signs and symptoms due to obstructive CHD. More recently, EBCT has been used to identify the likelihood of CHD in patients who present with nondiagnostic chest pain. Currently, EBCT is being studied for the assessment of progression or regression of coronary artery lesions after interventions in patients with modifiable risk factors for CHD.[18] There have been considerable data published in various medical journals supporting the usefulness of EBCT for detecting the presence and density of calcium in atherosclerotic coronary arteries.

A writing group of the AHA developed a scientific statement for health professionals in 1996[15] that concluded that there was no role at that time for the use of EBCT for screening populations of young, healthy individuals with no risk factors and that the importance of calcification in such individuals was inconclusive.

This Writing Group agrees with the following points indicated in that scientific statement:

1. A negative EBCT test makes the presence of atherosclerotic plaque, including unstable plaque, very unlikely.
2. A negative test is highly unlikely in the presence of significant luminal obstructive disease.
3. Negative tests occur in the majority of patients who have angiographically normal coronary arteries.
4. A negative test may be consistent with a low risk of a cardiovascular event in the next 2 to 5 years.
5. A positive EBCT confirms the presence of a coronary atherosclerotic plaque.
6. The greater the amount of calcium, the greater the likelihood of occlusive CAD, but there is not a 1-to-1 relationship, and findings may not be site specific.
7. The total amount of calcium correlates best with the total amount of atherosclerotic plaque, although the true "plaque burden" is underestimated.
8. A high calcium score may be consistent with moderate to high risk of a cardiovascular event within the next 2 to 5 years.

V. Risk Assessment for CHD in Asymptomatic Populations

Possibly as many as half of first coronary events (including sudden cardiac death) occur in asymptomatic people. Therefore, screening for both clinically silent CHD and the risk of developing clinical CHD represents 2 major health challenges. Lipid-lowering drug trials in asymptomatic people,[19] including those with hypercholesterolemia and with relatively unremarkable lipid levels,[20] have revealed the potential for risk reduction of CHD events in primary prevention. Thus, the potential exists for many asymptomatic people to benefit from identification and risk reduction in the asymptomatic phase of CHD. A screening modality that properly classifies at-risk asymptomatic individuals could be extremely valuable in prevention of CHD. The AHA Prevention V Conference was designed to consider the opportunities that might currently exist to improve risk stratification among asymptomatic people. EBCT was considered at the Prevention V Conference along with several other tests, such as carotid ultrasound, ankle-brachial index, and MRI. The full Prevention V Conference report is available elsewhere.[21]

Major risk factors including cigarette smoking, hypertension, elevated low-density lipoprotein (LDL) cholesterol, low HDL cholesterol, diabetes mellitus, and advancing age are clearly related to extent of coronary atherosclerosis and to the risk of clinical CHD events. All except advancing age are believed to be direct causes of coronary atherosclerosis.[22] Variations in plaque burden and risk are most likely due to genetic susceptibility and other factors, such as risk factor combinations, duration of risk factor exposures, and biological and laboratory variability. As mentioned, EBCT is one of several measures of subclinical coronary atherosclerosis that are under consideration for improving the process of risk assessment in asymptomatic people. It has been advanced by some that the calcium score may become a surrogate for age in the determination of individuals who are at high risk for coronary events.[22]

EBCT is a sensitive means of detecting coronary calcium.[11] Histological studies support the association of tissue densities

TABLE 1. Risk Stratification With Measures Derived From EBCT

Study	n	Entry Criteria	Event Definition	% Follow-Up	Mean Follow-Up, y	Annualized Event Rate, %	Calcium Definition	CAC Prevalence, %
Arad et al, 1996[3]	1173	Asymptomatic, prior CAD or angina	Cardiac death, MI, thromboembolic stroke, revascularization	99.8	1.6	1.5	Score ≥100	11.8
Secci et al, 1997[4]*	326	Asymptomatic ≥1 risk factor, no prior MI or angina	Death, MI	90	2.7	1.5	Score >156	50.0
Detrano et al, 1999[2]	1196	Asymptomatic with multiple risk factors, no prior MI or angina	Death, MI	99	3.4	1.6	Score >0 (median=44)	68

n indicates number of individuals studied; CAC, coronary artery calcium; and MI, myocardial infarction.
*A subgroup of a larger report by Detrano et al.

≥130 HU with calcified arterial plaque.[23] However, noncalcified plaque and lipid-laden "vulnerable" plaque can be present in the absence of EBCT calcium.[15] High calcium scores increase the probability of vulnerable plaques but do not identify specific vulnerable lesions.[15]

Calcium accumulates in coronary arteries in an age-related manner, and the accumulation appears to be exponential, because calcium continually deposits in preexisting lesions; thus, all scores must be adjusted for age, as well as for sex. As an example, a calcium score of 100, which is sometimes used as a standard for high risk, is at the 50th percentile for individuals 60 years of age and at the 25th percentile for those who are 50 years old.

The presence and extent of coronary calcium appear closely related to overall atherosclerotic coronary plaque "burden"; however, there are few reports of long-term follow-up in asymptomatic populations linking coronary calcium scores with risk of subsequent coronary events (Table 1). The individuals studied by Secci et al[4] represent a subgroup of the larger study by Detrano et al.[2] For the purpose of this document, we focused our attention on the estimation of hard coronary events, including cardiac death or nonfatal myocardial infarction, as well as other combined event estimation. The use of combined-event analysis, including coronary revascularization procedures, remains controversial, because test results per se may influence the treatment decision. However, revascularization that occurs remote from the test result is reflective of failed medical therapy and unrelated to EBCT test results. We present both hard coronary event and combined-event models in this review. In addition, we attempted to collect follow-up data that were analyzed by risk-adjusted methods and/or stratified analysis that included important cardiac risk factors. There are a total of 4 published articles on the subject of risk estimation with coronary calcium scores.[2–4,24]

Unadjusted Estimation of Outcome

In the published series by Arad et al,[3] 1173 asymptomatic subjects underwent EBCT in the years 1993 to 1994, with an average follow-up of 19 months; in that period, 1 death and 7 nonfatal myocardial infarctions were documented. From that preliminary report, unadjusted comparisons of events revealed a significant association between coronary calcium and major coronary events (unadjusted odds ratios [OR] 20.0 to 35.4). Additional follow-up of 3.6 years and 18 cardiac events revealed a similar association of coronary calcium with cardiac death or myocardial infarction.[25] In a subset analysis of women and men, the positive predictive values were 11.0% and 18.0% and the negative predictive values were 99.3% and 99.1%, respectively. In a smaller series by Secci and colleagues,[4] 326 patients with ≥1 risk factor were followed up for 32 months with a 50% prevalence of coronary calcium scores >156. Half of all hard cardiac events occurred for patients with the highest-quartile 3-mm-scan coronary calcium score. In a pooled analysis, there appears to be an association with coronary calcium scores and cardiac events (Figure 1). With coronary calcium scores of <15, 100, 156 to 160, and 507 to 680, the positive predictive value increased from 1.5% to 4.8%, 6.4%, and 14%, respectively (Figure 1). The negative predictive values for the same coronary calcium scores were 98.5%, 97.9%, 95.9%, and 92.2%, respectively. Pooled and weighted-average (weighted by the sample size) predictive accuracies were 0.71 and 0.47. When coronary calcium score thresholds ranging from 75 to 150 were used, the summary relative risk was increased 23.7-fold with a 95% confidence interval (CI) from 0.711 to 101.2 ($P>0.20$). Similarly, when a combined end point of mortality plus all associated cardiovascular complications was used, Arad et al[3] reported a 61-fold higher OR in asymptomatic patients when

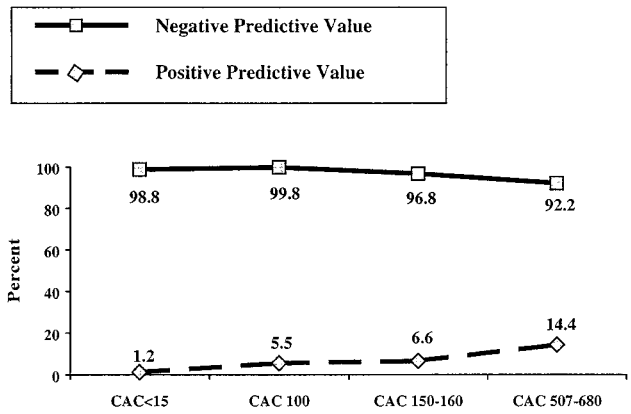

Figure 1. Positive and negative predictive value of EBCT coronary calcium scores from the Arad[3] and Secci[4] series (unadjusted for other risk factors).

a calcium score ≥100 was observed. By comparison, the OR was not elevated for their risk of death or myocardial infarction (OR 2.0, 95% CI 0.5 to 8.2, $P>0.20$).

Risk-Adjusted Estimation of Outcome

When outcome is evaluated, it is critical to consider the added value of test information after all of the information available to the clinician before EBCT referral has been weighed. This may be documented by examining risk-adjusted outcomes that control for established cardiac risk factors (eg, age and cholesterol levels). There have been several reports that have attempted to evaluate the incremental predictive value of the EBCT coronary calcium score in consideration with other cardiac risk factors. In general, because these data are still early in development, the small sample sizes and limited follow-up impair the statistical power in this outcome assessment. The most common method of evaluating outcomes in small samples of patients undergoing noninvasive testing is to use combined end points. In addition to the hard end points of death or myocardial infarction, other outcomes, including revascularization, are frequently used. Because revascularization is often precipitated by information derived from the test, the analysis is biased toward finding a significant association. Despite this limitation, we culled the preliminary data to estimate differences in outcome using hard and combined end points, because a proportion of the coronary revascularizations would be expected to occur remotely from the test and as a result of failed medical therapy.

A risk-adjusted logistic regression model estimating coronary events was performed in the Secci series.[4] When controlling for sex, age, diabetes mellitus, ECG left ventricular hypertrophy, smoking, hypertension, family history of disease, and cholesterol levels, the log of the coronary calcium score was not a significant estimator of cardiac death or myocardial infarction (risk-adjusted OR 1.24, 95% CI 0.49 to 3.11). When risk of death, myocardial infarction, or revascularization was estimated, the calcium score was an independent estimator of patient outcome (including referral to coronary surgical procedures), with a risk-adjusted OR of 2.87 (95% CI 1.04 to 7.94). Conversely, Detrano et al[24] reported application of stepwise logistic regression analysis in 491 symptomatic patients who were referred to coronary angiography (86% follow-up of patients). In that referral population, when controlling for established cardiac risk factors, the log of the calcium score was an independent estimator of combined cardiac events (including death or myocardial infarction). In a second report from the South Bay Heart Watch program,[2] the prognostic value of EBCT was evaluated in 1196 asymptomatic, high-coronary-risk subjects (mean follow-up of 41 months). The overall rate of cardiac death or myocardial infarction was 3.8% with a median coronary calcium score of 44. Multivariable models estimating coronary risk without and with the calcium scores revealed a similar ability to classify infarction or death (receiver operator characteristic [ROC] curve area without coronary calcium=0.68, ROC curve area with coronary calcium=0.71, $P=0.09$). The authors concluded that neither cardiac risk factor assessment nor EBCT was able to provide an adequate prediction of events in these generally high-risk subjects.

In the Secci study[4] of a subgroup of the patients included in the 1999 report by Detrano et al,[2] 6-mm-scan and 3-mm-scan protocols were compared in 326 patients; the 2 protocols were found to be equal in their predictive accuracy for cardiac events. Using pooled analysis of coronary calcium scores alone from the Arad[3] and Secci series[4] of <15, 100, 156 to 160, and 507 to 680, the positive predictive value increased from 1.2% to 5.5%, 6.6%, and 14%, respectively (Figure 1). The coronary events that went undetected by the higher threshold included many soft events, as did the entire group. One additional report appearing in abstract form is also worthy of mention.[26] Of a total of 367 self-referred middle-aged women and men followed up for 3 to 6 years, the OR for nonfatal myocardial infarction or cardiac death was 22 times greater for patients with the highest tertile of calcium scores than for those with scores in the lowest tertile. The increasing predictive values in these studies were associated with the calcium scores alone and were not compared with other methods of assessing risk.

In summary, review of the small number of reports in the literature reveals that EBCT calcium score can predict CAD risk. Current data, however, include relatively small samples (fewer than 3000 asymptomatic subjects) with rare occurrences of hard coronary events (death or myocardial infarction). Prediction of all types of hard CAD events has not been demonstrated in patient samples. Importantly, the incremental value of EBCT over "traditional" multivariate risk-assessment models has not yet been established.[2]

Although preliminary data are intriguing with respect to risk prediction in the asymptomatic patient, available data are insufficient to support recommending EBCT to asymptomatic members of the general public or for routine clinical use. Further studies are enthusiastically recommended for determining the additive predictive effect of the calcium score in patients with intermediate risk, particularly in the elderly. The use of EBCT in selected asymptomatic patients can be justified when performed in the context of a medical assessment only after the more standard cardiac risk assessment is considered insufficient by the physician to direct further therapy plans.

Comparative Modalities for Risk Assessment

The diagnostic accuracy of other comparative modalities has been explored in a number of prior reports.[27–31] Although the predictive value of testing has been limited in asymptomatic patient groups, high-risk subsets have been identified when information from risk factors and tests is combined. For example, when testing was performed in patients with multiple risk factors, a markedly abnormal ECG exercise test was associated with a significant increase in cardiac event risk.[31] When risk in asymptomatic patients was evaluated with combined test information, the presence of abnormalities on both the exercise ECG and myocardial perfusion study increased the OR from 3.6- to 14.5-fold for the development of future clinical coronary disease (48% had cardiac events over a 4-year period).[31] Similarly, the positive predictive value of exercise myocardial perfusion imaging in asymp-

TABLE 2. Coronary Disease and Calcium Prevalence in Patients Undergoing EBCT and Cardiac Catheterization

Study	Study Patients, n	Entry Criteria	CAD Definition	CAD Prevalence, %	Calcium Definition	CAC Prevalence, %
Tanenbaum et al, 1989[11]	54		≥70%	79.6	Detectable calcium	70.4
Agatston et al, 1990[17]	584		≥50% or prior MI	18.7	Score >0	77.1
Breen et al, 1992[33]	100		≥50%	47.0	Score >0	75.0
Bielak et al, 1994[34]	160		≥50%	48.8	Hyperattenuating foci >2 mm^2	50.0
Kaufmann et al, 1995[35]	160	Age <60 y, no prior CAD or transplant history	≥50%	69.4	Detectable calcium	60.6
Devries et al, 1995[36]	140		≥70%	70.0	Score >1	75.0
Kajinami et al, 1993[37]	251		≥75%	53.0	Score >0	55.0
Rumberger et al, 1995[38]	139	Age <60 y, no prior CAD or transplant history	≥50%	46.8	Detectable calcium	78.4
Braun et al, 1996[39]	102		>50%	78.4	Detectable calcium	78.4
Budoff et al, 1996[40]	710		>50%	60.1	Detectable calcium	79.3
Detrano et al, 1996[24]	491		≥50%	43.0	Score >100	43.0
Fallavollita et al, 1994[41]	98	<50% Stenosis	Luminal irregularities	60.2	Score ≥5	40.8
Baumgart et al, 1997[42]	57		≥50%	51.0	Score >0	42.1
Schmermund et al, 1997[43]	118	Acute ischemic syndromes	>50%	93.2	Score >0	89.8
Kennedy et al, 1998[44]	368		>50%	42.9	Detectable calcium	81.0
Schmermund et al, 1998[32]	49	<20% Stenosis	Vessel wall irregularities/ increased lumen caliber	53.1	Spotty coronary calcium	57.1
Pooled estimates	3683			48.8		74.9
Median	140			56.6		75.0
Average	224			60.0		68.3

CAC indicates coronary artery calcium.

tomatic patients with an abnormal exercise ECG for obstructive CAD is 74%.[27,28] Targeting treatment to high-risk patients with noninvasive tests should lead to important alterations in outcome. The long-term benefit of treatment of patients with abnormal ECGs was recently reported from MRFIT (Multiple Risk Factor Intervention Trial; 11 880 subjects).[29] After adjustment for baseline clinical risk, the aggressive risk factor–reduction program in the special-intervention group resulted in a 61% reduction in the relative risk of death due to CHD in men with a positive test (defined by use of the exercise ECG ST/HR index) compared with those in the usual-care group.[29] Whether or not EBCT will detect more patients at high risk remains to be proven.

The AHA Prevention V Conference considered several other alternative tests for assessment of coronary risk in asymptomatic people. The ankle-brachial blood pressure index and B-mode carotid Doppler ultrasound assessment of intimal-medial thickness, for example, have both been demonstrated to add substantial incremental value in risk prediction over and above traditional Framingham-type risk score, particularly in persons aged 55 years and older. None of these tests have been compared directly to EBCT in any study for coronary event prediction. The NHLBI MESA study is intended to determine which comparative measures are additive to traditional coronary risk factor models.

VI. Diagnosis of Patients With Possible CHD by EBCT

EBCT can be used as a noninvasive diagnostic technique for detecting obstructive CAD. To define its test characteristics and to compare it with other noninvasive tests, a meta-analysis was performed by our Writing Group.

Methods

MEDLINE searching strategies with the keyword “electron beam computed tomography” were used. Each abstract was reviewed online for study content including the diagnostic or prognostic accuracy of coronary calcium scores determined by EBCT. Entry criteria were limited to reports on the use of EBCT to assess the diagnostic or prognostic accuracy of coronary artery calcium. Workup bias (verification bias) could not be excluded in all cases. Investigators were queried as to patient overlap, and 2 reports were excluded. Data collection included documentation of a 2×2 frequency table of significant coronary disease by coronary artery calcium score thresholds with the best threshold as identified in each report. Individual study determination of significant coronary disease and calcium score cut points varied by study and are detailed in Table 2. For diagnostic accuracy, the sensitivity (true-positives/[true-positives plus false-negatives]) and specificity (true-negatives/[true-negatives plus false-positives]) of

TABLE 3. Diagnostic Accuracy of EBCT in Catheterized Patients

Study	True −	True +	False −	False +	Sensitivity, %	Specificity, %	Predictive Accuracy, %	OR	LCI	UCI
Tanenbaum et al, 1989[11]	11	38	5	0	88.4	100.0	90.7	148.7	9.6	2314.0
Agatston et al, 1990[17]	134	105	0	345	100.0	28.0	40.9	72.6	5.8	910.9
Breen et al, 1992[33]	25	47	0	28	100.0	47.2	72.0	32.9	2.4	453.8
Bielak et al, 1994[34]	68	66	14	12	82.5	85.0	83.8	26.7	11.5	62.0
Kaufmann et al, 1995[35]	42	90	7	21	92.8	66.7	82.5	25.7	10.1	65.1
Devries et al, 1995[36]	33	58	2	47	96.7	41.3	65.0	20.2	4.6	87.3
Kajinami et al, 1993[37]	106	121	12	12	91.0	90.0	90.4	101.6	43.9	235.1
Rumberger et al, 1995[38]	29	176	1	45	99.4	25.7	81.7	39.8	5.6	284.3
Braun et al, 1996[39]	16	74	6	6	92.5	72.7	88.2	32.8	9.4	114.9
Budoff et al, 1996[40]	124	404	23	159	94.6	43.8	74.4	13.7	8.5	22.2
Detrano et al, 1996[24]	200	148	80	63	70.0	71.0	70.9	5.9	4.0	8.7
Fallavollita et al, 1994[41]	34	35	5	24	87.5	58.6	70.4	9.9	3.4	28.9
Baumgart et al, 1997[42]	6	18	1	22	94.7	21.4	51.1	63.6	7.4	545.2
Schmermund et al, 1997[43]	7	105	1	5	99.1	58.3	94.9	141.6	15.3	1308.0
Kennedy et al, 1998[44]	64	151	7	146	95.6	30.5	58.4	9.5	4.19	21.3
Schmermund et al, 1998[32]	14	19	9	7	67.9	66.7	67.3	4.2	1.27	14.1
Pooled statistics	913	1655	173	942	90.5	49.2	69.6	212.3	4.3	105.8
Median					93.7	58.5	78.1	72.8	8.5	114.9
Average					91.8	55.0	77.0	52.9	11.8	367.0
Weighted average					80.4	39.9	59.1	21.3	4.3	105.7

True −, no disease in a negative test; True +, disease in a positive test; False −, disease in a negative test; False +, no disease in a positive test; LCI, lower 95% CI; and UCI, upper 95% CI.

coronary calcium scores were calculated. Average, median, and weighted-average (proportional to the sample size) scores were calculated. ORs and 95% CIs were calculated with FASTPRO software. Meta-analysis included calculation of a summary OR (95% CI) by use of a random-effects model (ie, empirical Bayes method). A χ^2 test for homogeneity was used to examine the combinability of the studies. For a test for homogeneity, a value of $P>0.05$ indicates that the studies may be combined in the form of a summary measure (df=number of studies−1).

Results

A total of 3683 patients were enrolled in 16 studies evaluating the diagnostic accuracy of EBCT (Table 2). Inclusion criteria were diagnostic catheterization for patients without prior history of coronary disease or prior cardiac transplantation. Two reports[24,32] included only patients with nonobstructive coronary disease as defined by a stenosis <50% or <20%. On average, significant coronary disease was reported in 57.2% of the patients. Significant luminal stenosis was defined as luminal irregularities in 2 reports, >50% or ≥50% stenosis in 11 reports, and ≥70% or ≥75% stenosis in 3 reports. Definitions of the optimal coronary artery calcium score for each report included detectable calcium (n=8), scores >0 to 5 (n=7), and scores >100 (n=1). Significant coronary artery calcium was reported on average in 65.8% of patients (Table 2).

Additional Summary ORs

Varying stenotic lesion cut points: minimal stenosis=6.78 (2.95 to 15.58); >50% stenosis=16.42 (5.08 to 53.07); >70% stenosis=49.83 (24.11 to 103.0).

Varying stenotic lesion cut points: detectable calcium or score ≥5 =25.61 (9.6 to 68.37); score ≥100=5.87 (3.97 to 8.7) including only the Detrano series.[2]

χ^2 Test for homogeneity for all studies=63.31, df=15, $P<0.0001$.

Test for homogeneity for diagnostic catheterization patients=56.26, df=12, $P<0.0001$.

χ^2 Test for homogeneity for diagnostic catheterization patients with detectable calcium or score cut point of 0, 1, or 5=16.25, df=9, $P=0.62$.

χ^2 Test for homogeneity for diagnostic catheterization patients with nonobstructive disease=1.08, df=1, $P=0.30$.

Table 3 depicts the frequency of published EBCT data and pooled accuracy estimates from 16 reports (n=3683). The weighted-average (by sample size) sensitivity and specificity were 80.4% and 39.9%, respectively. This may be compared with the pooled sensitivity and specificity values of 90.5%

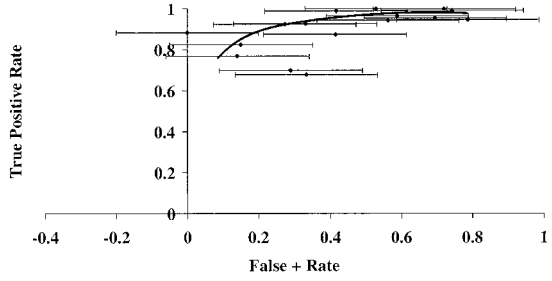

Figure 2. Summary ROC curve (95% CI) of diagnostic accuracy data in EBCT revealing a high test sensitivity (ie, true-positive rate) achieved at a high false-positive rate.

and 49.2%, respectively. Individual study sensitivity values ranged from 68% to 100%, whereas specificity values ranged from 21% to 100%. Calculation of a summary ROC curve (Figure 2) revealed that high-sensitivity values were consistently associated with exceedingly high false-positive rates. Predictive accuracy (ie, percent correct classification) ranged from 41% to 95% (weighted average=59%, pooled value=70%).

The weighted-average or summary odds were elevated 20-fold with an abnormal coronary calcium score (95% CI 4.6 to 87.8). Additional summary ORs were also calculated with various anatomic and calcium score cut points. For detection of minimal, >50%, and >70% stenosis at cardiac catheterization, the summary odds increased from 6.8-fold (95% CI 3 to 15.6) to 16.4-fold (95% CI 5.1 to 53.1) to 50-fold (95% CI 24.1 to 103.0); that is, the odds of significant coronary disease increased when greater angiographic lesion thresholds were used for significant disease (although the confidence bounds widened). Significant coronary calcium scores had a higher accuracy in detecting disease with stenosis >50%. Higher coronary calcium scores increased the likelihood of detecting significant coronary disease. A threshold of detectable calcium or a score ≥5 was associated with an odds of significant disease of 25.6-fold (95% CI 9.6 to 68.4). From the Detrano series,[2] the odds of significant disease for a score ≥100 was 5.9-fold higher (95% CI 4 to 8.7). Of note is the significant heterogeneity statistic for the 16 studies ($P<0.0001$), indicating populations too diverse to provide meaningful summary estimates. The diversity is due to the use of various coronary calcium score thresholds, patient entry criteria, and angiographic disease thresholds. A nonsignificant homogeneity statistic was noted when studies used minimal calcium score thresholds (detectable calcium or score of 0, 1, or 5 [$P=0.62$]). Similarly, the 2 reports[2,3] were similar for patients with nonobstructive disease estimating minimal coronary stenosis ($P=0.30$). These results indicate extreme heterogeneity across the study results, and the summary statistics should then be viewed as representing divergent patient samples.

Using a different approach, Schmermund and associates[45] recently examined 291 patients with suspected CHD who underwent risk factor determination as defined by the National Cholesterol Education Program, EBCT, and clinically indicated coronary angiography. On the basis of a simple algorithm ("noninvasive index"), the authors were able to separate patients with and without 3-vessel and/or left main CAD using EBCT. Also, Guerci et al[46] recently studied 290 men and women undergoing coronary arteriography for clinical indications and concluded that EBCT scanning improved discrimination over conventional risk factors in the identification of persons with angiographic coronary disease. Because this study was conducted in a symptomatic population with an angiographic end point, its application is limited to such patients.

Comparison With Other Tests for Diagnosis

It is appropriate to compare EBCT with the older diagnostic modalities, particularly the standard ECG exercise test, which is a mature, established technology. The equipment and personnel for performing stress electrocardiography, myocardial perfusion imaging, and echocardiography are readily available. Also, for the exercise test, the equipment is relatively inexpensive, so that replacing or updating it is not a major cost factor. The ECG exercise test, like the echocardiogram, can be performed in the doctor's office and does not require injections or exposure to radiation. Furthermore, it can determine the degree of disability and impairment to quality of life, as well as be the first step in rehabilitation and alteration of an important risk factor (physical inactivity).

Some of the newer stress imaging modalities have the advantage of being able to localize ischemia as well as diagnose CHD when the baseline ECG negates ST analysis (eg, >1-mm ST depression, left bundle-branch block, or Wolff-Parkinson-White syndrome). The alternatives to the ECG exercise test also have the advantage of not requiring the patient to exercise and are particularly valuable for the clinical assessment of those who cannot walk. However, although the newer technologies appear to have better diagnostic characteristics, this is not always the case, particularly when factors other than ST-segment changes during the exercise test are used in scores.[47]

Test evaluation has been advanced by the writings of Feinstein and associates,[48,49] as well as others,[50] resulting in an improved ability to evaluate studies of test characteristics. Many researchers have applied these guidelines along with meta-analysis to obtain a consensus on the diagnostic characteristics of the available tests for angiographic CHD.[51,52] Table 4 presents some of the results using meta-analysis and data from multiple studies.

Because sensitivity and specificity are inversely related and are altered by the chosen cut point for normal versus abnormal results, the predictive accuracy (percentage of patients correctly classified as having normal and abnormal results) is a convenient way to compare tests. For instance, although the sensitivity and specificity for exercise testing and EBCT are nearly opposite, the predictive accuracy of the tests is similar. This means that altering their cut points (ie, lowering the amount of ST-segment depression or raising the coronary artery calcium score) would result in similar sensitivities and specificities. Because predictive accuracy refers to the number of individuals correctly classified of 100 tested, simple comparison of the predictive accuracy provides an estimate of the number of additional patients classified by substituting one test for another. However, this does assume a disease prevalence of 50% as the intermediate probability for appropriate use of diagnostic tests (ie, predictive accuracy is affected by disease prevalence).

Exercise ECG Test

Gianrossi et al[53] investigated the variability of the reported diagnostic accuracy of the exercise ECG for CAD by applying meta-analysis. One hundred forty-seven consecutively published reports involving 24 074 patients who underwent both coronary angiography and exercise testing were summarized and the results entered into a computer spreadsheet. Wide variability in sensitivity and specificity was found (mean sensitivity was 68%, with a range of 23% to 100% and a standard deviation of 16%; mean specificity was 77%, with

TABLE 4. Comparison of Exercise Testing and Add-Ons or Other Test Modalities

Grouping	No. of Studies	Total No. of Patients	Sensitivity, %	Specificity, %	Predictive Accuracy, %
Meta-analysis of standard exercise ECG	147	24 047	68	77	73
Excluding MI patients	41	11 691	67	74	69
Limiting workup bias	2	2350	50	90	69
Meta-analysis of exercise test scores	24	11 788			80
Perfusion scintigraphy	2	28 751	89	80	89
Exercise echocardiography	58	5000	85	79	83
Nonexercise stress tests					
Pharmacological stress scintigraphy	11	<1000	85	91	87
Dobutamine echocardiography	5	<1000	88	84	86
EBCT	16	3683	91	49	70

MI indicates myocardial infarction.

a range of 17% to 100% and a standard deviation of 17%). The median predictive accuracy (percentage of total true-positives and true-negatives) was ≈73%.

To more accurately portray the performance of the exercise test, only the results in 41 of the original 147 studies were reanalyzed. These 41 studies excluded patients with a prior myocardial infarction, fulfilling one of the criteria for evaluating a diagnostic test, and provided all of the numbers for calculating test performance. These 41 studies, including >10 000 patients, demonstrated a lower mean sensitivity of 68% and a lower mean specificity of 74%; this means that there also was a lower predictive accuracy (69% rather than 73%). In 2 studies[54,55] in which workup bias was reduced by design, fulfilling the other major criteria, the sensitivity was ≈50% and the specificity 90%, with the predictive accuracy remaining at 70%. Workup bias was not removed in any of the other studies of diagnostic tests.

Myocardial Perfusion Imaging and Echocardiography

Fleischmann and associates[56] reviewed the contemporary literature to compare the diagnostic performance of exercise echocardiography and exercise nuclear perfusion scanning in the diagnosis of CAD. Studies published between January 1990 and October 1997 identified from a MEDLINE search, bibliographies of reviews and original articles, and suggestions from experts in each area were considered if they discussed exercise echocardiography and/or exercise perfusion imaging with thallium or sestamibi (primarily SPECT) for detection or evaluation of CAD; if data on coronary angiography were presented as the reference test; and if the absolute numbers of true-positive, false-negative, true-negative, and false-positive observations were available or derivable from the data presented. Studies performed exclusively in patients after myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting or in those with recent unstable coronary syndromes were excluded. Two reviewers used a standardized spreadsheet to independently extract clinical variables, technical factors, and test performance. Discrepancies were resolved by consensus. Forty-four articles (not unique patient data sets) met inclusion criteria: 24 reported exercise echocardiography results in 2637 patients with a weighted mean age of 59 years, of whom 69% were men, 66% had angiographic coronary disease, and 20% had prior myocardial infarction; and 27 reported exercise SPECT in 3237 patients, of whom 70% were men, 78% had angiographic coronary disease, and 33% had prior myocardial infarction. In pooled data weighted by the sample size of each study, exercise echocardiography had a sensitivity of 85% (95% CI 83% to 87%) with a specificity of 77% (95% CI 74% to 80%). Exercise perfusion yielded a similar sensitivity of 87% (95% CI 86% to 88%) but a lower specificity of 64% (95% CI 60% to 68%). Data from 2 registries on SPECT imaging in >20 000 patients revealed sensitivity and specificity values of 89% and 80%, respectively.

In summary, it is difficult to determine with certainty from our meta-analysis whether the studies of EBCT suffer from limited challenge and workup bias, as is frequently found in studies of diagnostic procedures. However, the 16 studies averaged in Tables 2 and 3 demonstrated a high sensitivity but a low specificity, with a predictive accuracy of ≈70% or less. These data for EBCT can be compared with the results from meta-analyses of other diagnostic procedures. A positive test will clearly lead to increased patient anxiety, even if the clinician chooses to disregard it or to use it to focus on risk factor modification, and even if a subsequent test is negative. A positive test can also lead to coronary angiography and revascularization, as demonstrated in the follow-up series on asymptomatic patients. Most importantly, most clinicians who perform diagnostic testing are actually also using that test result to stratify the patient according to risk. Existing modalities such as exercise testing, perfusion scintigraphy, and exercise echocardiography are extraordinarily well validated with respect to prognostic implications, as demonstrated in the previous sections on asymptomatic CAD; EBCT is not as well studied. Moreover, given the tremendous prognostic information that is implicit in exercise capacity, even when it is combined with imaging, EBCT starts with a disadvantage compared with existing modalities in symptomatic patients who can exercise.

Although adjusting the cut point for calcium density (coronary artery calcium score) alters the sensitivity and specificity, the EBCT is not superior to other currently available diagnostic procedures for diagnosis of angiographic

CHD. Direct comparisons of EBCT studies with other commonly used tests for detecting CHD have revealed modest correlations of abnormal test results.[57] Although EBCT is a relatively inexpensive test, its reported low specificity for obstructive CAD may lead to unnecessary additional workups in a patient with a positive calcium score. However, the true specificity may be somewhat higher than our meta-analysis suggests, and there is no published evidence that additional testing necessarily results from the use of EBCT.

VII. Assessment of Progression or Regression of CHD by EBCT

Significant benefit would be achieved if there were a clinically applicable, noninvasive method by which changes in plaque characteristics or volume could be monitored during pharmacological interventions. There have been several published studies[58–60] that have examined progression, stabilization, and regression of coronary artery lesions during aggressive risk factor modification, most notably lipid-lowering therapy. These data have suggested that there may be minimal to mild changes in angiographic lumen caliber associated with pharmacological therapy, but that these are significantly less than the subsequent clinical benefits found in the active-treatment group. It has been postulated that lipid-lowering therapy with the HMG-CoA (β-hydroxy-β-methylglutaryl–coenzyme A) reductase inhibitors likely results in "stabilization" of lipid-rich plaques and/or reduction in neointimal inflammation through a variety of mechanisms that remain incompletely defined.[61]

Quantification of coronary artery calcium has been shown to be reflective of the total atherosclerotic plaque burden.[23,62] This quantification can be determined in a straightforward fashion by use of EBCT. Therefore, the use of EBCT offers the potential to follow disease progression, stabilization, and possible regression through serial imaging. However, for this to become a clinical reality, the reproducibility of EBCT calcium scoring must be acceptable and the progression of disease in general should be greater than the error between successive EBCT scoring examinations. Furthermore, there must be evidence that EBCT is useful in serial evaluations of plaque disease with and without specific therapy.

There have been several studies that evaluated reproducibility of EBCT scanning and conventional scoring by the Agatston method.[17] Although calculation of the total calcium score from a single EBCT examination has been reported to have excellent interobserver and intraobserver reliability,[63] reproducibility from 2 scanning runs (interscan reliability) has varied from poor to only fair, depending on the laboratory and the method of calculation.[34,36,37,64] It has ranged from 14% to 51% variability (differences/mean).

Differences for total calcium scores between scan 1 and scan 2 taken only a few minutes apart are readily apparent, but they are generally small if scanning is performed in a skilled clinical laboratory. When studies in which there is a >10% to 15% discrepancy between the 2 calcium scores are carefully examined, clear reasons are apparent when the total calcium scores exceed 10. Greater percent changes are seen with lower scores. In one study,[4] the variability with a 6-mm-thickness scan protocol reduced the retest variability by 50%.

Callister and associates[65] evaluated an alternative method of determining EBCT calcium score by quantifying the actual volume of plaque analogous to that possible in prior histological investigations.[23,65] Callister et al examined 52 paired EBCT scans taken 5 minutes apart and calculated a total calcium volume score (CVS) versus the traditional Agatston calcium score. They concluded that use of CVS showed better reproducibility than the traditional Agatston calcium score, and its variability was considerably smaller than the measured calcium score increase found in untreated patients at the end of 1 year.

There are limited data available on the potential influence of pharmacological intervention on the assessment of plaque progression by EBCT. Callister and colleagues[66] retrospectively evaluated serial EBCT scans in 149 asymptomatic, hyperlipidemic patients (61% men, aged 32 to 75 years) for serial changes in plaque burden. Each patient had been referred for EBCT screening, none had documented CAD, and none were receiving HMG-CoA reductase inhibitors at baseline. Each was found to have documented coronary calcium on the initial scan and was referred back to his or her physician for follow-up. One hundred five patients (70%) were subsequently prescribed a statin medication, and 44 (30%) were left untreated. After 1 year, a repeat EBCT scan was done to assess possible changes from the baseline EBCT calcium study. For this investigation, the CVS method originally described by their laboratory[65] was used. Treated patients maintained a mean LDL cholesterol level of 114±23 mg/dL, whereas untreated patients had a mean value of 147±22 mg/dL. The average CVS change in the treated group over the follow-up period (13.7±0.6 months) was 5±28%, whereas for the untreated group, it was 52±36% ($P<0.001$). The treated group was further divided into 2 groups: those who achieved a target LDL of <120 mg/dL and those who achieved a target LDL of ≥120 mg/dL. In the treated group with the lower LDL level, there was a net change in CVS between baseline and follow-up of −7±23%, whereas in the treated group with the higher LDL level, there was a net change in CVS of 25±22% ($P<0.01$). These data suggest that plaque burden as assessed by EBCT can be influenced by the level of aggressiveness of antilipidemic therapy. Furthermore, these data are consistent with prior angiographic studies that suggest that there can be a net regression of coronary disease as a result of long-term statin therapy. However, the sample size was small, and follow-up was short. Additional data are required to determine whether these findings can be corroborated and especially whether these presumed changes in plaque burden are reflected in the alteration of cardiac events in more rigorous randomized, controlled clinical trials.

VIII. Cost-Effectiveness of EBCT

Increasingly, there is a demand to demonstrate that any new test or form of therapy improves patient outcome; this is often approached by performing a cost-effectiveness analysis. Cost-effectiveness analyses can be used to compare competing tests or forms of therapy and can offer the result as a

single number, the cost-effectiveness ratio, commonly expressed in cost per quality-adjusted life-year gained.[67] This ratio for a specific procedure or therapy may then be compared with other ratios for other medical interventions competing for scarce healthcare resources. To perform this analysis, it is necessary to be able to measure both the effect and cost of a test or form of therapy. To make these measurements in cost per quality-adjusted life-year gained, it is necessary to measure results over a lifetime or, more realistically, extrapolate short-term results to a lifetime. In the case of EBCT, there is uncertainty concerning even the short-term gain. To establish truly comparable groups that would provide comparable cost and outcome data, it would be necessary to conduct randomized trials comparing EBCT with a competing method. However, such trials would be difficult and expensive to conduct successfully. Furthermore, short-term trials might provide little information concerning long-term benefit.

When testing is considered, the recognition that randomized trials are not practical has led to the use of decision-analytic methods (that is, simulations) to try to estimate the cost for some benefit achieved.[68] The fundamental limitation with a simulation is that for a diagnostic modality, the downstream decision trees can become quite complicated depending on how test outcome affects subsequent decision making. EBCT in particular has not been used extensively and is a new technology with few data on the necessary resources and expected outcomes from test results. In such simulations, the cost-effectiveness analysis may bear little relation to reality. To avoid this problem, the benefit examined may be something less apparent than quality-adjusted life-years gained.

Given the difficulty of conducting randomized trials, the inherently limited nature of simulations, and the paucity of information of any kind at present, there is a limit as to what can be stated concerning the cost-effectiveness of EBCT. Rumberger et al[69] assessed the cost and effectiveness of EBCT as an approach to diagnosis of CAD "in theoretical analyses based on mathematical models." He used published sensitivity and specificity, and disease prevalence was tested by angiography alone, treadmill testing, stress echocardiography, stress thallium scans, or predetermined EBCT calcium score cut points followed by angiography if needed. The data developed support the use of EBCT as a minimal cost (short-term) and maximum effectiveness approach to the diagnosis of obstructive CAD in specific subsets of the general population. This test was a simulation and was limited by the use of cost per diagnosis achieved, rather than the marginal cost-effectiveness compared with a competing choice; however, it does provide preliminary information to help guide decision making. The problems of defining cost-effectiveness of EBCT are compounded by the several potential uses of EBCT. More assumptions must be made to define cost-effectiveness for diagnosis of early disease or atherosclerotic burden, and long-term outcome must be considered almost by necessity. Detailed decision-analytic models to examine the cost-effectiveness of EBCT both for diagnosis of coronary disease and for its ability to predict and modify the outcome of early disease are under development. Even these models will be limited both by the paucity of data and the difficulty in realistically defining downstream decisions. Future research should, at the very least, offer improved simulations to help define those patients and uses for which EBCT is cost-effective, perhaps using proxies for long-term outcome when possible, but using life-years gained or quality-adjusted life-years gained when appropriate.

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KEY WORDS: ACC/AHA Expert Consensus Document ■ tomography, electron-beam computed ■ coronary disease ■ diagnosis

American College of Cardiology/American Heart Association Expert Consensus Document on Electron-Beam Computed Tomography for the Diagnosis and Prognosis of Coronary Artery Disease: Committee Members

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