

## Subspecialty Clinics: Cardiology

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# Electron Beam Computed Tomographic Coronary Calcium Scanning: A Review and Guidelines for Use in Asymptomatic Persons

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## Abstract

Coronary artery disease is the No. 1 cause of death in the developed world. Effective means of treatment such as drug therapy to lower cholesterol levels are available, but clinical application to patients at highest risk remains imprecise. Electron beam computed tomography (EBCT) has been suggested as a means to diagnose subclinical coronary disease and facilitate risk stratification, but no current interpretive consensus exists in clinical practice. We critically reviewed current, pertinent literature regarding EBCT coronary calcium scanning from a clinical perspective and, in particular, studies that evaluated it as a measure of atherosclerotic coronary disease. Additionally, we reviewed studies that quantified the EBCT "calcium score" in relationship to coronary heart disease events. The available data suggest that the EBCT calcium score can help identify persons at higher than anticipated risk of future coronary events: the greater the EBCT coronary calcium score, the greater the extent of atherosclerotic plaque disease. Based on the literature review, we offer EBCT interpretation guidelines as they relate to drug therapy and risk reduction in asymptomatic persons with borderline cholesterol levels. Considerable evidence shows that coronary calcium is specific for atherosclerotic plaque and that it can be sensitively detected and accurately quantified by using EBCT. The coronary calcium score can help guide initiation of clinical prevention programs as part of a risk stratification and management scheme aimed at improving outcomes in patients determined to be at highest risk of coronary disease for their respective age and gender.

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CI=confidence interval; EBCT=electron beam computed tomography

Ischemic heart disease is the No. 1 cause of death in the developed world and will likely remain No. 1 well into the next millennium.<sup>1</sup> Approximately 50% of myocardial infarctions occur in patients with no prior history of heart disease, and 68% of these infarctions are due to lesions representing a diameter stenosis of less than 50%.<sup>2</sup> An increased serum cholesterol level has been established as a risk factor for coronary disease, but approximately 35% of patients with established disease have a total cholesterol level lower than 200 mg/dL. In fact, conventional "risk factors" fail to predict up to one-third of future deaths due to coronary heart disease.<sup>3,4</sup> Because effective means are available for treating manifest heart disease and for preventing the progression of coronary disease and acute coronary events, accurate identification of persons at risk is essential for efficient and accurate implementation of preventive strategies as part of a case management scenario.

Coronary artery calcium is intimately associated with mural atheromatous plaque.<sup>5-8</sup> The American Heart Association recently reviewed the data validating electron beam computed tomography (EBCT) and its ability to detect and quantify coronary calcification noninvasively.<sup>9</sup> A direct relationship has been established between coronary artery calcium as measured by EBCT and both histologic<sup>10,11</sup> and in vivo intravascular ultrasound<sup>12,13</sup> measures of atherosclerotic plaque on a heart-by-heart, vessel-by-vessel, and segment-by-segment basis.

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Additionally, evidence is increasing that the common clinical measure of coronary calcium by EBCT, the "calcium score,"<sup>14</sup> has a significant predictive value for subsequent cardiac events in both symptomatic and asymptomatic patients.<sup>15-18</sup> The National Heart, Lung, and Blood Institute (NHLBI) recently put forward an RFP (request for proposals) using EBCT, among other noninvasive methods, to study subclinical cardiovascular disease (RFP-NIH-NHLBI-HC-98).

The presence and amount of coronary artery calcification determined by EBCT have been suggested as a means to assess patients at risk of premature coronary disease or those with nondiagnostic chest pain syndromes.<sup>9,19</sup> Guidelines, however, regarding measurements or estimates of coronary mural plaque burden by determination of the "calcium score," especially in "at risk" but asymptomatic persons, have not previously been established for potential application to clinical practice.

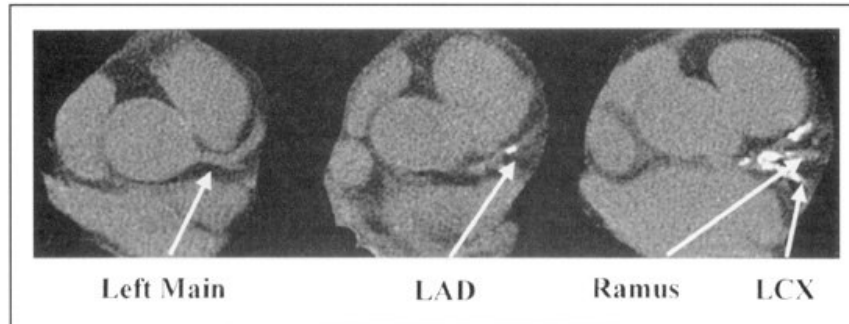


Fig. 1. Single-level noncontrast electron beam computed tomographic scans at base of heart of three patients. Each scan shows ascending aorta (circular structure in middle of each image), pulmonary artery (right and anterior to aorta), superior vena cava (immediately left of aorta), left atrium (posterior to aorta), and proximal portions of left main, left anterior descending (LAD), ramus intermedius (Ramus), and left circumflex (LCX) coronary arteries. Scan on left showed no coronary calcium, whereas scans in middle and on right showed moderate and extensive amounts of coronary artery calcification, respectively.

The purposes of our investigation were (1) to put the currently available literature regarding coronary artery calcification into clinical perspective and (2) to offer a consensus for guidelines on clinical performance of EBCT coronary artery calcium scanning and interpretation of findings with specific reference to its use in asymptomatic persons.

#### ELECTRON BEAM COMPUTED TOMOGRAPHY

EBCT uses a stationary source-detector combination and a rotating electron beam to produce serial and contiguous thin-section 100-ms scans at end-diastole in synchrony with the heart cycle. Scanning of the entire heart can be completed in one or two short breath holds. Standardized methods for scanning, identification, and quantification of coronary artery calcium with use of EBCT have been established.<sup>9</sup>

In the mural vascular surfaces, calcium demonstrates relatively high x-ray densities that are approximately 2- to 10-fold higher than the surrounding soft tissue. Thus, the appearance of high-density intramural calcium deposits adjacent to low-density soft tissue and surrounding fat makes visual identification of calcium in the coronary arteries by EBCT readily apparent, even to untrained observers. Examples of no, moderate, and extensive proximal coronary calcification are shown in Figure 1. Anatomic details in each illustration show the aorta, pulmonary artery, left atrium, and proximal portions of the left main, left anterior descending, and circumflex coronary arteries. The high-density material surrounding the coronary sections in the middle and right images of Figure 1 represents coronary artery calcification. Agatston and colleagues<sup>14</sup> developed a calcium scoring algorithm for EBCT images that is now widely used in research and clinical practice. The "calcium score" is a product of the area of calcification per coronary tomographic segment and a factor rated 1 through 4 dictated by the maximal calcium x-ray density within that segment. A calcium score can be calculated for a given coronary segment, a specific coronary artery, or for the entire coronary system; however, most studies have reported on the use of a composite "score" for the entire epicardial coronary system (left main, left anterior descending, left circumflex, and right coronary arteries). An example of the calcium scoring method is shown in Figure 2. The composite score for those two tomograms (Fig. 2) is  $60+16=76$ ; in reality, when the entire study was analyzed in addition to these two levels, the total calcium score for that 43-year-old woman was in excess of 400.

#### CALCIUM, ATHEROSCLEROTIC PLAQUE, AND EXTENT OF DISEASE

Calcification of the coronary arteries is actually calcium phosphate in the form of hydroxyapatite (the major inorganic component of bone). The pathophysiologic mechanisms of coronary artery calcification were recently reviewed.<sup>9</sup> In contrast to the commonly held theory that coronary calcium is a degenerative process, its participation in atherosclerotic plaque development is active and regulated in a fashion similar to bone mineralization.<sup>9,20-23</sup> Although its role in coronary disease remains unclear, intramural calcium can be variably

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observed in many degrees of atherosclerotic involvement. A study by Rumberger and coworkers<sup>11</sup> emphasized that the total area of coronary artery calcification quantified by EBCT is linearly correlated ( $r=0.90$ ) with the total area of histologic coronary artery plaque. Although the total atherosclerotic plaque burden was tracked by the total calcium burden, not all plaque was found to be calcified, and the total calcium area was about 20% of the total atherosclerotic plaque area. A recent article by Baumgart and associates<sup>12</sup> compared direct intracoronary ultrasound measures during angiography with EBCT scanning and confirmed a direct association of coronary calcium score with localization and extent of atherosclerotic plaques in vivo. Schmermund and colleagues,<sup>13</sup> in a subset of the same patients studied by Baumgart and coworkers, also demonstrated that, in patients with acute coronary syndromes but nonobstructive coronary disease, the number of plaques identified as calcified by EBCT were roughly proportional to the number of noncalcified plaques identified by intravascular ultrasonography. Although the mean ratio of calcified to noncalcified coronary segments in this patient group was close to 1:1, it was highly variable among individual patients.

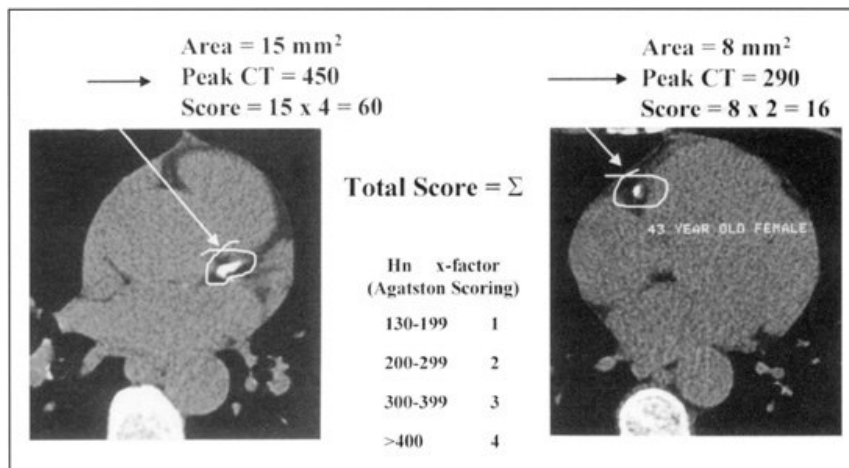


Fig. 2. Representative method of coronary calcium scoring by electron beam computed tomography with use of Agatston method.<sup>9</sup> Area surrounding calcification is identified by standardized computer program that determines total area of calcification by using threshold greater than 130 Hounsfield units. Peak x-ray density (Hounsfield unit) is then determined, and a multiplier of the calcium area is determined according to the table. For image on left (left anterior descending coronary artery), calcium score is 60. For image on right (right coronary artery), calcium score is 16. For these two slices, score would be 76. Total calcium score (see text for details) is the sum of all individual tomographic calcium scores for the entire epicardial coronary artery system. CT=computed tomography; Hn=Hounsfield.

Despite the fact that rupture of vulnerable lipid-laden plaque has been proposed as the predominant mechanism of sudden cardiac death and myocardial infarction,<sup>2,24</sup> Farb and associates<sup>25</sup> found that plaque erosion may account for up to 30% of acute coronary thromboses. They noted mural calcification in 69% of cases of coronary plaque rupture (of a lipid core) but in only 23% of cases of plaque erosion. Thus, coronary calcification is a common, but variable, feature of "unstable" and stable plaque. Berliner and colleagues<sup>26</sup> suggested that inconstant mechanical factors may contribute to the potential for plaque instability at demarcation lines between plaques demonstrating different morphologic characteristics (that is, "hard" versus "soft").

#### CORONARY CALCIUM AND LUMINAL DISEASE SEVERITY

Researchers at the Mayo Clinic<sup>27,28</sup> and the National Institutes of Health<sup>10</sup> performed EBCT scanning on dissected coronary vessels from autopsied hearts and showed a nonlinear correlation of EBCT-quantified coronary calcium with the severity of coronary luminal narrowing but with large confidence limits; they confirmed that the coronary artery calcium area, although related to measures of luminal narrowing, cannot be used for direct quantification of stenosis severity on a segment-by-segment basis. More recently, Sangiorgi and associates<sup>29</sup> examined quantitative histologic calcification, plaque, and lumen narrowing and suggested that these differences may be largely dependent on atherosclerotic coronary remodeling. The absence of calcification, however, did correlate with the absence of advanced luminal disease on a site-by-site basis. A previous study by Simons and coworkers<sup>27</sup> determined that coronary calcification demonstrated on EBCT was present in 97.5% of all coronary segments with "significant" histologic coronary disease (that is, 75% or greater area or approximately a 50% or greater diameter stenosis).

In 100 patients younger than 60 years who underwent both diagnostic coronary angiography and EBCT, Breen and colleagues<sup>30</sup> showed that the absence of identifiable coronary calcium (that is, an EBCT calcium score of 0) had a predictive value of 100% for ruling out the presence of any epicardial coronary lesions with 50% or greater diameter stenosis. An expanded report from that same laboratory has shown that the sensitivity of EBCT-

detected coronary calcium was between 94 and 97% for the presence of any arteriographic narrowing, with an overall negative predictive value of greater than 95% for significant (50% or greater stenosis) disease.<sup>31</sup> A study by Fallavollita and associates,<sup>32</sup> however, suggested that this degree of accuracy in identifying coronary disease may not be possible in all patient groups. In their investigation of 106 patients younger than 50 years, the negative predictive value for significant angiographic disease overall was only 85%. Furthermore, the sensitivity of coronary calcium for detecting 50% or greater stenoses in 28 patients with single-vessel disease was only 75%. In that study, however, only twenty 3-mm sections were examined in comparison with 30 to 40 sections in most other studies, and thus the entire coronary system was not imaged. Schmermund and coworkers<sup>33</sup> found that EBCT detected coronary calcium in almost all subjects with acute coronary syndromes and in 96% of those with obstructive disease, but some patients had a calcium score of 0. Most notably, the absence of coronary calcium was found in younger patients who tended to be active cigarette smokers and who had minimal or no focal atherosclerosis detected on intravascular ultrasonography. In a separate multicenter study by Budoff and colleagues,<sup>34</sup> EBCT demonstrated coronary calcium in 404 of 427 patients subsequently found to have angiographically confirmed significant coronary disease (95% sensitivity). Thus, the predominant theory from the literature is that coronary calcium detected by EBCT has a very high sensitivity for significant histologic and angiographic luminal disease.

Alternatively, the specificity of EBCT has been reported to be low to moderate, ranging from 35 to 38% for any angiographic narrowing<sup>31</sup> and from 45<sup>33</sup> to 66%<sup>31</sup> for "significant" disease. Budoff and associates,<sup>34</sup> however, found specificity for significant disease to increase with the number of calcified vessels: 54% for one-vessel calcification and 78%, 89%, and 98% for two-, three-, and four-vessel calcification, respectively. To address the issues of calcification specificity in a more comprehensive manner, Kaufmann and coworkers<sup>35</sup> performed receiver operating characteristic analysis in 160 patients who underwent coronary angiography, followed by EBCT. They attempted to determine optimal quantities of calcium (that is, "cutpoints") to distinguish among no (normal), mild (maximal diameter stenosis, 10 to 40%), and significant (50% or greater stenosis) luminal disease. By using the total coronary calcium area defined by EBCT, the best cutpoint for discriminating between persons without versus those with any angiographic disease was the presence of any single calcium area 2 mm<sup>2</sup> or greater (sensitivity, 81%; specificity, 86%; accuracy, 83%). For persons without in comparison to those with significant luminal disease, the optimal cutpoint was a calcium area of 18 mm<sup>2</sup> (sensitivity, 86%; specificity, 81%; accuracy, 83%).

Rumberger performed receiver operating characteristic analysis on studies from 213 consecutive patients who underwent EBCT scanning in conjunction with clinically indicated coronary angiography and determined total calcium scores that provided 90%<sup>19,36</sup> and 95%<sup>19</sup> specificities for variable degrees of angiographic luminal disease. A portion of those results are listed in Table 1. For example, an EBCT calcium score exceeding 27 gives a 90% specificity for at least a 20% or greater coronary stenosis, whereas a calcium score exceeding 371 has a 90% specificity for at least one 70% or greater luminal stenosis. Finally, a recent report by Guerci and colleagues<sup>37</sup> demonstrated a high correlation (but with moderate scatter about the regression) between the square root of the total EBCT calcium score and maximal percent luminal stenoses within the epicardial coronary system in 18 asymptomatic patients undergoing diagnostic angiography. Thus, application of selected EBCT coronary calcium area or calcium score cutpoints and ranges has a potential for predicting the likely severity of luminal narrowing found at angiography. Nevertheless, we reemphasize that clinical interpretation of the calcium areas or calcium scores and ranges of scores and their relationships to angiographic disease should be considered only as guidelines at best because, as previously discussed, a direct one-to-one correlation between coronary calcium as detected by EBCT and luminal disease is not possible.

#### CORONARY CALCIUM AS A PROGNOSTIC INDICATOR

The data discussed thus far are consistent with the "area" or "score" for coronary calcification quantified by EBCT being viewed as a surrogate for the overall atherosclerotic plaque burden as well as providing for ranges of variable sensitivity and specificity of associated luminal narrowing. Although calcification may be a histologic feature of both "stable" and "unstable" plaques, a reasonable assumption is that a greater overall plaque burden increases the likelihood of greater proportions of both plaque subtypes. Indeed, the extent of coronary atheromatous disease remains the most powerful predictor of subsequent or recurrent cardiac events.<sup>38</sup> The implications for prognostication by using quantification of coronary calcium by EBCT should not be predicted solely on the site and severity of the calcified plaque per se or even the likely severity of luminal narrowing, but by the fact that the extent of atherosclerotic disease and the presence of plaques of variable morphologic characteristics increase in direct proportion to the amount of detectable calcified plaques.

A relationship between the presence of coronary arterial calcification and cardiovascular events has been shown by using fluoroscopy<sup>39,40</sup> and conventional CT.<sup>41</sup> Fluoroscopy and conventional x-ray CT, however, cannot be used for an accurate quantification of the amount of calcium present, as can be done with EBCT.<sup>9</sup>

Four large studies have been published regarding cardiac prognosis and EBCT calcium score. Detrano and colleagues<sup>15</sup> examined the relative prognostic value of coronary calcium for predicting coronary heart disease-related events in 491 patients (mean age, 55±12 years) referred for angiography who also underwent EBCT scanning. Thirteen documented coronary heart disease-related deaths (sudden cardiac death in 12 and a fatal infarction in 1) and 8 nonfatal myocardial infarctions occurred, with an 86% complete follow-up during a period of 30±13 months. Total EBCT coronary artery calcium scores were divided into quartiles. One patient with a calcium score in the first quartile (score, 0 to 2.1) had a cardiac event (fatal infarction), 2 patients with initial calcium scores in the second quartile (range, 2.1 to 75.3) had events, 8 in the third quartile (range, 75.3 to 397.1)

had events, and 10 in the fourth quartile (score, greater than 397.1) had events. With use of these data, the odds ratio for total cardiac events during follow-up of patients with calcium scores above the 75th percentile in comparison with those whose scores were below the 25th percentile would be 10.8 (95% confidence interval [CI], 1.4 to 85.6). These investigators also found that application of a bivariate logistic regression showed that the log calcium score significantly predicted the probability of a coronary heart disease-related event, and this was independent of the severity of disease determined by angiography. Furthermore, during follow-up, event-free survival was significantly greater ( $P=0.009$ ) for patients with a calcium score below the median (that is, 50th percentile) value of 100 than for those whose calcium score was 100 or higher.

**TABLE 1. —TOTAL EBCT CALCIUM SCORE “CUTPOINTS” FOR 90% SPECIFICITY OF AT LEAST ONE CORONARY LESION BEING WITHIN THE PRESCRIBED ANGIOGRAPHIC DISEASE SEVERITY\*†**

Angiographic disease severity (% diameter stenosis)	EBCT calcium score range (90% specificity)
≥20	27-88
≥30	89-127
≥40	128-166
≥50	167-370
≥70	≥371

\*EBCT=electron beam computed tomography.

†Based on results in 213 patients who underwent EBCT and angiography.

Data from Rumberger and associates.<sup>19,36</sup>

Arad and coworkers<sup>16</sup> monitored 1,173 initially asymptomatic patients (mean age, 53±11 years), who had no known coronary disease, for a mean of 19 months after they underwent a screening EBCT coronary calcium scan. Eighteen subjects had 26 cardiovascular events: 1 death, 7 nonfatal myocardial infarctions, 8 coronary bypass grafting procedures, 9 coronary angioplasties, and 1 nonhemorrhagic stroke. The magnitude of the coronary calcium score at the time of the index EBCT scan was highly predictive of subsequent development of symptomatic cardiovascular disease during follow-up. Odds ratios ranged from 20:1 for a calcium score of 100 to 35:1 for a calcium score of 160. This study has now been carried out for a total of 3.6 years of follow-up, with maintenance of an odds ratio for any cardiac event in this initially asymptomatic population of 23:1 for a baseline calcium score of 160 or greater.<sup>42</sup>

Secci and colleagues<sup>17</sup> described a 32-month follow-up of 326 elderly (mean age, 66±8 years) but initially asymptomatic subjects who underwent EBCT scanning. Dividing initial calcium scores into quartiles, they demonstrated a significant trend for more subsequent revascularizations and total cardiac events (including sudden cardiac death or myocardial infarction or both) for calcium scores above the median, especially when the baseline score was at or above the 75th percentile; however, examination of the trend for “hard events” alone (cardiac death, documented myocardial infarction) failed to reach statistical significance. For combined hard and soft events, the odds ratio for those with a calcium score in the highest quartile (18 events) in comparison with those in the lowest quartile (3 events) would calculate as 7.5 (CI, 2.1 to 27).

Finally, Agatston and associates<sup>18</sup> described (in abstract form) 367 originally asymptomatic men and women (mean age, 52 years) who underwent initial EBCT coronary calcium screening and were then followed up for 36 to 72 months. A total of 26 events occurred, including the development of angina, myocardial infarction, or need for revascularization (coronary angioplasty or bypass grafting). The mean baseline calcium score for patients with a cardiac event was 399±424, whereas it was 76±207 ( $P<0.01$ ) for those without events. Furthermore, the odds ratio for the development of symptomatic coronary disease was 6.9 (95% CI, 1.7 to 28.5) for those with an initial calcium score greater than 50 and 2.7 (95% CI, 0.6 to 11.7) for those with a calcium score between 1 and 49.

Although conducting larger prospective studies is necessary, especially in asymptomatic persons in different age-groups, these retrospective and prospective studies support the theory that the presence of coronary artery calcification is associated with a measurable risk of a definable ischemic cardiac event developing over a relatively brief period (19 to 72 months), and this risk increases in direct proportion to the EBCT calcium score. The magnitude of the risk for a person with moderate or greater coronary artery calcium, viewed as a surrogate to measures of total coronary atherosclerotic burden, is underscored when the relative risks for the development of symptomatic coronary disease are considered by using conventional risk factor analysis. Bostom and coworkers<sup>43</sup> reported a 15-year follow-up of 2,191 middle-aged initially asymptomatic men (20 to 54 years at enrollment in study) as part of the Framingham database. In this group, the relative risk of symptomatic coronary artery disease developing was 1.9:1 (95% CI, 1.2 to 2.9) for an increased Lp(a) lipoprotein level; 1.8:1 (95% CI, 1.2 to 2.6) for a total cholesterol level greater than 240 mg/dL; 1.8:1 (95% CI, 1.2 to 2.6) for a high-density

lipoprotein level less than 35 mg/dL; 3.6:1 (CI, 2.2 to 5.5) for cigarette smoking; and 1.2:1 (CI, 0.8 to 1.8) for systolic hypertension. Thus, on the basis of these comparisons, EBCT calcium score alone seems to be more predictive of cardiac events than traditional risk factors individually, and, as the only noninvasive method to localize and quantify the extent of the total coronary atherosclerotic plaque burden, it offers a measurable tool for improved risk stratification and prognosis.

**CALCIUM SCORES, AGE, AND GENDER**

The increasing incidence and magnitude of coronary calcification with advancing age<sup>44</sup> are reflections of the increased incidence of coronary atherosclerosis with advancing age.<sup>19</sup> Two reports, one a histopathologic study<sup>28</sup> and the other a clinical study,<sup>31</sup> have shown that, when matched for severity of luminal disease, EBCT coronary calcium area or score has similar predictive values in men and women. Thus, similar calcium scores are diagnostic of similar overall atherosclerotic plaque burdens, regardless of age and gender. The prognostic value, however, of a calcium score of 100 in a 40-year-old woman likely differs from a similar score in a 60-year-old man because the atherosclerotic process, regardless of conventional risk assessment, is more premature, accelerated, or aggressive in the woman than in the man. Therefore, clinical application of EBCT calcium scoring must consider the calcium score variability in the general population as a function of gender and age.

Abundant data exist regarding coronary calcification according to age and gender. Data for EBCT calcium scores at different ages of a population of 1,898 asymptomatic women and men studied by Janowitz and colleagues<sup>44</sup> are shown in Table 2. In women younger than 50 years, calcium scores exceeding 10 are extremely uncommon but are seen in about 25% (that is, the upper quartile) of men of similar age. Between ages 50 and 59 years, calcium scores exceeding 10 are found in the upper quartile in women, whereas calcium scores in men in this same quartile are closer to 100. Women between 60 and 69 years have calcium scores similar to men a decade younger. Men older than 60 years have calcium scores exceeding 100 as representative of the 50th percentile (that is, the median).

**IN WHICH PERSONS SHOULD EBCT SCANNING BE CONSIDERED?**

The Goldman criteria<sup>45</sup> for a diagnostic test in cardiology are as follows: it can be used “to plan or monitor therapy, to establish a diagnosis, to define the extent of a known disease, to estimate prognosis, or to reassure the physician or the patient.” These criteria are consistent with the use of EBCT in specific clinical situations.

In our opinion, a patient group in which EBCT scanning seems to have particular clinical application is asymptomatic persons in whom a decision regarding the need for medical risk intervention is uncertain. In such patients, scanning may establish the extent, if any, of calcified coronary plaque and assist the clinician in further risk stratification, factors that directly influence clinical decisions regarding aggressiveness of preventive therapies.<sup>46</sup> Currently, the best example of this strategy is in regard to the decision of whether to institute cholesterol-lowering drug therapy. Several large trials published during the past 4 years have confirmed the substantial benefit of cholesterol reduction in patients at high risk of future coronary events. The Scandinavian Simvastatin Survival Study (4S)<sup>47</sup> demonstrated that treatment with simvastatin in persons with known coronary disease and increased cholesterol levels resulted in a significant 30% reduction in total mortality. The Cholesterol and Recurrent Events (CARE) study<sup>48</sup> showed that, in patients with average serum cholesterol levels who had had an infarction, pravastatin treatment resulted in a significant 24% reduction in nonfatal reinfarction and death due to coronary heart disease. The West of Scotland Coronary Prevention trial<sup>49</sup> demonstrated that treatment with pravastatin in persons without known coronary disease but high cholesterol levels resulted in a significant 31% reduction in nonfatal infarction and coronary death. Finally, the recently published AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)<sup>50</sup> demonstrated that treatment with lovastatin in healthy persons without cardiovascular disease and average to mildly increased cholesterol levels reduced the risk of a first major coronary event by 36%. These studies have established that drug therapy for even mild hypercholesterolemia is a highly effective method of reducing cardiovascular events regardless of whether manifest coronary disease is present. Cholesterol-lowering medication and the need for medical follow-up are expensive and presumably lifelong; therefore, the clinical challenge is accurate identification of persons who are truly at high risk of the development of coronary disease or ischemic events and who would most likely benefit from drug therapy for hypercholesterolemia. When the decision of whether to institute cholesterol-lowering drug therapy is uncertain, the results of EBCT scanning may be useful in adjudicating issues of risk stratification that underlie this critical clinical decision. The higher the calcification score, the more compelling the rationale for drug therapy in patients with average or mild to moderate hypercholesterolemia in whom the need for drug therapy based on conventional risk assessment remains imprecise and is often uncertain.

**TABLE 2. —PERCENTILE RANGE OF EBCT CORONARY ARTERY CALCIUM SCORE IN ASYMPTOMATIC WOMEN AND MEN, AS A FUNCTION OF AGE\***

Percentile rank	EBCT calcium scores					
	Women (N=502)			Men (N=1,396)		
	40-49 yr	50-59 yr	60-69 yr	40-49 yr	50-59 yr	60-69 yr
10	0	0	0	0	0	1
25	0	0	1	0	2	15

50	0	0	20	1	30	100
75	1	3	80	10	150	325
90	10	40	118	40	380	700
*EBCT=electron beam computed tomography.						
Data from Janowitz and associates. <sup>44</sup>						

**CLINICAL RECOMMENDATIONS**

Our proposed consensus guidelines for interpretation of EBCT calcium scoring based on the discussion heretofore are summarized in Table 3. Although a negative or extremely low calcium score (10 or lower) cannot totally exclude the presence of coronary atherosclerosis, it is consonant with the absence of a fixed (significant) coronary obstructive lesion (likelihood, 5 to 10% or lower), regardless of age and gender. In one study, 80% of men and women with a “negative” EBCT calcium scan were found to have angiographically “normal” coronary arteries, and an additional 15% had, at most, mild to moderate coronary luminal narrowing.<sup>31</sup> Fallavollita and colleagues<sup>51</sup> evaluated EBCT calcium scoring in 98 men and women who had no significant obstructive disease detected at coronary angiography and found that 87% with angiographically smooth coronary arteries had a calcium score of 5 or less. Thus, no specific further cardiac work-up would be recommended for this group, although a discussion of general public health guidelines for prevention of cardiovascular diseases is always appropriate.

Calcium scores of 11 to 100 are consistent with mild atherosclerotic plaque burden. Despite the fact that the likelihood of associated significant obstructive disease (50% stenosis or greater) is low (20% or less), atherosclerosis is clearly present. Although data<sup>18</sup> are limited to support a theory that calcium scores between 11 and 100 put a person at a measurably greater cardiac risk than does a score of 0, this range of scores definitely indicates a measurable coronary plaque. Fallavollita and colleagues<sup>51</sup> found that 59% of their patients with a calcium score of 5 or greater had at least luminal irregularities on angiography. In such patients, active risk modification is critical. Adherence to current National Cholesterol Education Program (NCEP) guidelines<sup>52</sup> for initiation of drug therapy for management of hypercholesterolemia (Table 4) are recommended, and daily use of aspirin may be indicated. Although the use of antioxidant medications remains moot, these drugs could be considered on an individual basis in this group with mild plaque disease as it relates to a risk to benefit scenario.

**TABLE 3. —RECOMMENDED EBCT CALCIUM SCORE GUIDELINES\*†**

EBCT calcium score	Plaque burden	Probability of significant CAD	Implications for CV risk	Recommendations
0	No identifiable plaque	Very low, generally <5%	Very low	Reassure patient while discussing general public health guidelines for primary prevention of CV diseases
1-10	Minimal identifiable plaque burden	Very unlikely, <10%	Low	Discuss general public health guidelines for primary prevention of CV diseases
11-100‡	Definite, at least mild atherosclerotic plaque burden	Mild or minimal coronary stenoses likely§	Moderate	Counsel about risk factor modification, strict adherence with NCEP ATP II primary prevention cholesterol guidelines, daily ASA/
101-400‡	Definite, at least moderate atherosclerotic plaque burden	Nonobstructive CAD highly likely, although obstructive disease possible§	Moderately high	Institute risk factor modification and secondary prevention NCEP ATP II guidelines. Consider exercise testing for further risk stratification
>400‡	Extensive atherosclerotic plaque burden	High likelihood (≥90%) of at least 1 “significant” coronary stenosis§.	High	Institute very aggressive risk factor modification. Consider exercise or pharmacologic stress imaging to evaluate for inducible ischemia

\*See text for more details.

†ASA=acetaminophen; CAD=coronary artery disease; CV=cardiovascular; EBCT=electron beam computed tomography; NCEP ATP II=National Cholesterol Education Program (Adult Treatment Panel II).

‡If score >75th percentile for age/gender, advance to recommendations for next calcium score range (see text for details).

§See Table 1.

∕Oral administration of 80 to 325 mg.

Patients with at least moderate coronary artery calcium scores greater than 100 (or scores lower than 100 but exceeding the 75th percentile for age and gender) are at a moderately high risk and thus are candidates for aggressive risk factor modification, including strict control of diabetes and hypertension, dietary counseling, regular aerobic exercise, daily aspirin use, and drug treatment of even average to mild hypercholesterolemia (Table 5). Calcium scores of 101 to 400 are consistent with at least moderate coronary plaque and a high likelihood of associated moderate non-obstructive coronary disease (Table 1). An aggressive approach to drug therapy for lowering serum cholesterol levels should be considered in patients with these moderate coronary calcium scores because they seem to be at a significantly greater than anticipated moderate-term (19 to 72 months) risk for the development of symptomatic coronary disease. In such patients, clinical risk stratification may be further augmented through exercise testing, especially if borderline hypertension is a possibility, or by instruction and advisement about a formal exercise program.

**TABLE 4. —CURRENT NCEP GUIDELINES FOR DRUG TREATMENT OF HYPERCHOLESTEROLEMIA\***

Clinical situation	Level of LDL cholesterol (mg/dL)	
	Initiate therapy	Target
Without clinical CAD and average to low risk	≥190	<160
Without clinical CAD but high risk†	≥160	<130
With clinical CAD or other ASCVD	≥130	≤100

\*ASCVD=documented atherosclerotic cardiovascular disease; CAD=documented coronary artery disease; LDL=low-density lipoprotein; NCEP=National Cholesterol Education Program.

†High risk was defined by NCEP (Adult Treatment Panel II) as ≥2 cardiovascular risk factors.

Data from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.<sup>52</sup>

Patients with coronary calcium scores greater than 400 have advanced plaque disease, have a 90% specificity (Table 1) for at least one obstructive coronary lesion, and are at high risk for the development of symptomatic ischemic disease. They should undergo aggressive risk factor modification, as previously outlined, and should be strongly considered for further assessment such as stress testing with nuclear imaging or echocardiography to rule out inducible ischemia. In a group of asymptomatic patients undergoing EBCT screening, He and coworkers<sup>53</sup> reported (in abstract form) that about one-half with calcium scores exceeding 400 also had abnormal findings on single-photon emission computed tomographic thallium studies.

**TABLE 5. —RECOMMENDED GUIDELINES FOR USE OF EBCT CALCIUM SCANNING IN DRUG TREATMENT OF HYPERCHOLESTEROLEMIA\***

Clinical situation	Level of LDL cholesterol (mg/dL)	
	Initiate therapy	Target
Without clinical CAD and calcium score <10	≥190	<160
Without clinical CAD and calcium score 10-100	≥160	≤130
Without clinical CAD and calcium score >100†	≥130	≤100
With clinical CAD	≥130	≤100

\*CAD=coronary artery disease; EBCT=electron beam computed tomography; LDL=low-density lipoprotein.

†Or calcium scores exceeding >75th percentile for age and gender (see Table 2).

**SUMMARY**

Considerable evidence shows that coronary calcium is specific for atherosclerotic plaque and that it can be sensitively detected and accurately quantified by using EBCT. Furthermore, the greater the EBCT coronary calcium score, the greater the severity and extent of coronary disease. Finally, the EBCT calcium score seems to help identify persons at high risk of future coronary events. Based on this evidence, we have established guidelines for the clinical use of EBCT coronary scanning as it relates to asymptomatic "at risk" persons. These guidelines will undoubtedly undergo revision as more is learned in this rapidly progressing area. Although their development follows a judicious review of currently available data, their application in the management of patients with variable degrees of subclinical atherosclerosis remains unproved. Nevertheless, we believe that EBCT coronary scanning is appropriate in a selected subset of the population as a case management tool because of its potential to identify subclinical coronary plaque and therefore high-risk asymptomatic patients who are candidates for aggressive preventive therapies such as drug therapy even for average to mildly increased cholesterol levels.

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