



TITLE: Utility of Coronary Artery Calcium Measurement
In Cardiovascular disease

AUTHOR: Jeffrey A. Tice, M.D.
Assistant Adjunct Professor of Medicine
Division of General Internal Medicine
University of California, San Francisco

PUBLISHER NAME: California Technology Assessment Forum

DATE OF PUBLICATION: February 16, 2005

PLACE OF PUBLICATION: San Francisco, California



UTILITY OF CORONARY ARTERY CALCIUM MEASUREMENT IN CARDIOVASCULAR DISEASE

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of coronary artery calcium measurements to predict cardiovascular events. This update to the June 2000 review was prompted by reports regarding pending changes to the American College of Cardiology / American Heart Association consensus document (O'Rourke, Brundage, et. al. 2000), which turned out to be premature (Loscalzo, Bonow, *et al.*, 2004).

BACKGROUND

Coronary artery disease (CAD) causes approximately 500,000 deaths every year and is the leading cause of death in both men and women in the U.S. The cause of CAD is atherosclerotic plaques that develop in the coronary arteries. Given the availability of therapies that decrease mortality from CAD, early detection and treatment could save many lives. Unfortunately the gold standard for the diagnosis of CAD is coronary angiography, an invasive test with rare, but serious complications.

Electron Beam Computed Tomography

Electron Beam Computed Tomography (EBCT) is a recently developed technique used primarily for the detection and quantification of coronary artery calcification (CAC). Many studies have demonstrated that CAC develops almost exclusively in atherosclerotic plaques. The CAC score correlates with the volume of atherosclerotic plaque in pathology studies (Simons, Schwartz *et al.*, 1992; Mautner, Mautner *et al.*, 1994). However, it is not always present in early plaques and it may be present in plaques that do not affect blood flow through the artery (Eggen, Strong *et al.*, 1965; Kajinami, Seki *et al.*, 1997). Furthermore the degree of calcification does not correlate well with the location and severity of stenoses (Chernoff, Ritchie *et al.*, 1997; Reddy, Chernoff *et al.*, 1998; Kajinami, Seki *et al.*, 1997).

EBCT (also known as cine CT or ultrafast CT) is capable of obtaining an image in 50 milliseconds. In contrast to conventional CT, EBCT scanners do not use a rotating x-ray tube. Instead, an electron gun creates an electron beam that is deflected to sweep over semicircular tungsten targets arranged around the patient where the x-rays are created. The x-rays then penetrate the patients body and are registered by an array of detectors. By avoiding mechanical movement, the image acquisition time is shortened. Combining rapid image acquisition with timing triggered by the electrocardiogram (EKG) minimizes motion artifacts. Thus, EBCT can image the heart. Scanning is performed with the patient in a supine position holding his or her breath (Achenbach, Moshage *et al.*, 1998).

Coronary artery calcium scores are most often calculated using the Agatston method (Agatston, Janowitz *et al.*, 1990). The areas of the scan that correspond to coronary arteries with CT tissue density score > 130 Hounsfield units are summed. However, there are differences in the ways the Agatston scoring method has been implemented in different studies. The minimum area of density considered significant enough to be included in the total score, the thickness of the CT slice (3 mm or 6 mm) and the number of slices acquired (usually 20-40) vary from study to study. Implications of these variations will be discussed in greater detail under the TA Criterion 3 section of this review.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Three electron beam CT scanners Imatron C-100, Imatron C-150 and the e-Speed EBT Scanner System (Imatron, South San Francisco, CA) have received FDA 510(k) clearance.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words electron beam computed tomography or ultrafast computed tomography or coronary artery calcium. These were cross-referenced with the keyword cardiovascular disease. The search was performed for the period of 1966 through December 2004. The bibliographies of systematic reviews and key articles were manually searched for additional references (. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

There are three indications for EBCT which will be covered in this review: (1) the use of EBCT as a screening test to identify asymptomatic patients at high risk for future coronary heart disease events; (2) the use of EBCT as a diagnostic test in patients with symptoms suggestive of CAD; and (3) the use of EBCT to assess response to therapy for coronary heart disease.

Prediction of Cardiovascular Events in Asymptomatic Patients

The literature search found at least 27 publications describing five cohorts (Table 1) of patients followed prospectively after measurement of CAC. These cohorts include a total of 9,605 individuals followed for 3 to 7 years in their most recent publications. They consistently report that CAC scores predict future cardiovascular outcomes and most have shown that it is still predictive of future events after adjusting for standard cardiovascular risk factors. The key

question is whether the additional information significantly improves predictive accuracy. There are over 40 measurements (C-reactive protein, lipoprotein-a, ankle-brachial index, carotid intimal-medial thickness, homocysteine, etc.), which have been shown to be independent risk factors for future cardiovascular events, but few have become part of routine cardiovascular risk assessment (Hackam and Anand, 2003). A statistically significant independent risk factor does not necessarily improve risk assessment (Pepe, Janes *et al.*, 2004), so comparisons to standard risk assessment models are required in order to demonstrate clinical utility.

The current standard for cardiovascular event prediction is the Framingham risk score (FRS) (Wilson, D'Agostino *et al.*, 1998), a complex calculation using age, sex, office blood pressure level, cholesterol levels, diabetes, tobacco use and left ventricular hypertrophy to predict an individual's 10-year risk for future events. There is no equivalent equation that incorporates CAC measurements or that compare predictions from CAC to the Framingham predictions. In order to be of clinical value, studies need to demonstrate that CAC scores significantly improve the discriminatory accuracy of the FRS as assessed by the concordance index (c-index). Only two of the published studies of EBCT have addressed this question and they come to different conclusions using data from the same South Bay Heart Watch cohort study (Detrano, Wong *et al.*, 1999; Greenland, LaBree *et al.*, 2004). The remaining cohorts measured risk factors for CAD by self-report alone and thus have no data on cholesterol levels, blood pressure or EKG findings (Arad, Spadaro *et al.*, 2000; Wong, Hsu *et al.*, 2000; Raggi, Cooil *et al.*, 2001; Kondos, Hoff *et al.*, 2003). This limits the ability of these studies to adjust for known CAD risk factors when assessing the independent association of CAC with CAD.

There is no randomized controlled trial evidence demonstrating improved clinical outcomes for patients in whom EBCT results were used to guide patient management. While this is often the case for diagnostic tests, some novel cardiovascular tests have met this standard (Mueller, Scholer *et al.*, 2004). One randomized trial assessed the affect of knowledge of CAC scores on modifiable risk factors and predicted CHD risk in the year following EBCT scanning (O'Malley, Feuerstein *et al.*, 2003).

TA Criterion 2 is met. Level of Evidence: 2, 3, 4, 5

Diagnosis of Coronary Artery Disease in Symptomatic Patients

The literature search identified at least 54 cross-sectional studies evaluating the sensitivity and specificity of CAC scores for the diagnosis of CAD. Many of the studies had overlapping patient populations, included patients with known CAD or used non-standard definitions for the diagnosis of CAD. We limited the analysis to studies of patients with symptoms of chest pain who did not have a prior diagnosis of CAD. All patients were required to have coronary angiography with significant CAD defined by at least a 50% stenosis in at least one coronary artery. This left 14 studies including 4,062 patients (Table 2). Commonly cited articles that did not meet our inclusion criteria are described in Table 3. These articles were excluded because the data was presented in prior publications, the patients

had known CAD or belonged to specific subgroups (post-cardiac transplant, heart failure, end stage renal disease), the definition of CAD was non-standard or angiography was not performed on all patients. The available evidence focuses on the test characteristics (sensitivity and specificity) of EBCT, but not its effect on health outcomes. The literature is noticeably deficient in offering direct comparisons to other commonly available non-invasive methods to diagnose CAD such as exercise treadmill testing (ETT), single photon emission computed tomography (SPECT) and exercise echocardiography.

TA Criterion 2 is met. Level of Evidence: 3, 4, 5

Assessment of Response to Therapy

Four studies were identified which assess the effect of statin treatment on CAC scores over time. None of the studies assessed whether treatment decisions based on change in CAC scores affect health outcomes or improved future risk prediction compared to the FRS, the change in LDL or other non-invasive measures such as carotid intima-media thickness (CIMT).

TA Criterion 2 is not met. Level of Evidence: 5

TA Criterion 3: The technology must improve the net health outcomes.

Reproducibility of Coronary Artery Calcification Scores

Almost all studies report that their coronary artery calcium scores were calculated using the Agatston method (Agatston, Janowitz *et al.*, 1990). However, the reproducibility of this CAC scoring is variable. The interobserver variability has been reported to be 2.5% (Agatston, Janowitz *et al.*, 1990) and 1.3% (Hernigou, Challande *et al.*, 1996), which is quite good. However, the inter-examination error (reproducibility when two scans are performed on the same patient and read independently) is much higher, ranging from 7.2% to 51% (Kajinami, Seki *et al.*, 1993; Bielak, Kaufmann *et al.*, 1994; Devries, Wolfkiel *et al.*, 1995; Shields, Mielke *et al.*, 1995; Hernigou, Challande *et al.*, 1996; Callister, Cooil *et al.*, 1998; Adamzik, Schmermund *et al.*, 1999). There have been several suggestions to improve the reproducibility of the test. A study by Callister, Cooil *et al.* (1998) found that volumetric methods to measure CAC by EBCT were better than the standard Agatston. Others have reported that using 6 mm slices rather than the more common 3 mm slice thickness improves the reproducibility (Wang, Detrano *et al.*, 1996), though this has been disputed (Mao, Child *et al.*, 2003). Non-standard timing of the image acquisition has also been reported to improve the quality of the data (Mao, Bakhsheshi *et al.*, 2001; Mao, Budoff *et al.*, 2001; Lu, Zhuang *et al.*, 2002). Finally, as other CT-based technologies have been promoted to measure CAC, a consortium developed standards, including a new scoring method to replace that of Agatston, that use a phantom facilitate calibration (Mitka, 2004). None of these methods have been used in the current literature on EBCT for risk assessment or diagnosis of CAD.

There also is controversy about the minimum area that should be used to diagnose the presence of coronary calcium. The original Agatston paper used $>1.02 \text{ mm}^2$, considering any smaller area of high CT number ($>130 \text{ HU}$) an artifact. Some published studies that report using the Agatston scoring method used 0.26 mm^2 as the minimum area for the presence of calcium (Devries, Wolfkiel *et al.*, 1995), while others use as high as 2.06 mm^2 as the minimum area (Bielak, Kaufmann *et al.*, 1994; Kaufmann, Sheedy *et al.*, 1995). The use of even larger areas for the detection of calcium should increase specificity by detecting only areas of true calcification but at the cost of sensitivity. Only one study assessed the effect of changing the size of the minimum area on EBCT test characteristics (Bielak, Kaufmann *et al.*, 1994). The study used Imatron C-100 scanner and 40- 3 mm cuts with "Agatston" scoring. A 30 cm^2 field of view (differs from study to study, hence pixel size varies) was used for repeatability studies in 256 patients with 512×512 reconstruction matrix. Thus, one pixel = $.343 \text{ mm}^2$. The study varied the minimum area $>130 \text{ HU}$ to be counted from 2-9 pixels ($0.69\text{-}3.09 \text{ mm}^2$). Comparing scans taken five minutes apart found that the same spot was found on both scans in 25% of cases at a 2-pixel threshold, up to 74% at 9 pixels. The same study also looked at how the sensitivity and specificity for detection of significant CAD changed as the minimum area definition changed. Significant CAD was present in 69/160 (43%) of the patients studied. These scans were done with a 26 cm^2 field of view and a 512×512 reconstruction matrix so one pixel = 0.258 mm^2 . They assessed the effect of limiting CAC scoring to foci of size 2, 4, 6, 8, 10 and 12 pixels ($0.52\text{-}3.10 \text{ mm}^2$). Prevalence of calcium in this study (i.e. $\text{CAC} > 0$) varied from 81% (129/160) at 0.52 mm^2 to 57% at the 3.10 mm^2 area definition. Sensitivity for significant CAD declines from 100% to 87% while specificity increased from 34% to 66% over the same range (minimal area 0.52 to 3.10). The authors concluded that the 2 mm^2 area gave the best results, though this approach has not been widely adopted. Bielak *et al.* (1994) argue that $0.52\text{-}1.04 \text{ mm}^2$ is too low an area to be used because less than 50% of those foci are found again on second scans.

Thus, the sensitivity for CAC varies significantly by the size of the minimum area used to define "calcification areas" that are then summed using the Agatston scoring system. The group that varies the most is the group labeled as $\text{CAC}=0$. Lack of standardization in this definition could have large effects on the estimates for risk associated with calcium scores. Ideally, all scans would be read using the same protocol, including minimum area.

Additional problems arise because the software used to perform the scoring also affects the results. One study reported that the CAC scores calculated by two different software programs used to score the same EBCT scans differed by an average of 14% (Adamzik, Schmermund *et al.*, 1999).

Prediction of Cardiovascular Events in Asymptomatic Patients

The prognostic significance of finding CAC remains uncertain. This is partly due to the fact that the probability of myocardial infarction is not solely determined by the amount of atherosclerosis, but also by the propensity of individual plaque segments to rupture and initiate clot formation. Thus, some authors have argued that even if CAC

correlated perfectly with the degree of atherosclerosis, it might not be a good predictor of coronary events (Detrano and Doherty, 1998).

At least 27 publications describe five cohorts (Table 1) of patients without symptoms of CAD who are followed for incident cardiovascular events after undergoing EBCT for assessment of CAC. CAC scores were consistently associated with CHD events, independent of traditional cardiovascular risk factors. However, only one of the studies directly measured blood pressure and lipid levels. The remainder relied on self-report of the presence or absence of hyperlipidemia, hypertension and diabetes.

There is also no consistency in how CAC scores are modeled in these analyses, making it very difficult to compare the strength of the association across studies. CAC scores have a very unusual distribution, with a large proportion of patients having no detectable calcium and the remainder of the patients having a distribution that tends to be highly skewed. Some authors have attempted to normalize the skewness by log-transforming the data, but this does not account for the large number of patients with a score of 0. There is no simple way to model the CAC score as a normally distributed, continuous variable. It is far easier to use categories to represent CAC score. To date, there is no standard way to categorize CAC scores.

Initial reports were criticized because they included revascularization (coronary angioplasty, stent placement, coronary artery bypass grafting) as outcomes in the analysis. Patients and their doctors were aware of the CAC scores. The fact that patients with higher CAC scores were more likely to receive revascularization may reflect bias due to knowledge of the CAC scores. Studies that reported the relationship with both soft and hard endpoints found much stronger associations with revascularization than with MI or CHD death. This is most dramatically illustrated in the largest cohort of EBCT in asymptomatic patients (Kondos, Hoff *et al.*, 2003). Among men, the presence of CAC had a relative risk of 49.4 (95% CI 6.9-353) for soft endpoints, but only 5.8 (95% CI 1.8-19) for hard endpoints. The RR was reduced further to 3.9, after adjusting for self reported risk factors. Later papers focused more on the incidence of so-called "hard" outcomes (myocardial infarction and CHD death).

The most recent publications from the five cohort studies (Table 1) report follow-up that ranges from 32 to 84 months. Most report hard outcomes separate from revascularization procedures. However all of the studies had less than 85 hard outcomes, which limits the ability to perform subgroup analyses in the studies. Only the Greenland study directly measured blood pressure, LDL and HDL cholesterol and EKG findings (to rule out prior MI and diagnose LVH for use in the Framingham risk calculation). The Greenland study also had the longest follow-up by almost 4 years and the largest number of hard outcomes. The Greenland study is unique in using 6 mm (less sensitive, more reproducible), rather than 3 mm thickness cuts, to measure CAC and in excluding diabetics, because prior analyses in the cohort indicated that CAC was less predictive of future events in patients with diabetes. The strength of the association of CAC with hard events was lower in the Greenland paper (3.9, 95% CI, 2.1-7.3 for CAC score >300 compared with 0)

than in the reports of Wong (8.8, 95% CI 2.2-35, for CAC score ≥ 271 compared with 0) or Kondos (7.2, 95% CI 2.0-26, for CAC score ≥ 170 compared with 0, in men only). It is interesting to note that the 95% CI for the Greenland results falls almost completely within the 95% CI for the other two studies, suggesting that the results may be more compatible than it seems at first glance. In sum, it appears that CAC scores do offer some information on risk of future events independent of traditional risk factors. Whether that independent information is clinically important remains unclear.

While not directly relevant here, the search identified one large cohort ($n=10,377$) of asymptomatic patients (Shaw *et al*, 2003) that assessed the value of coronary calcium scores for the prediction of all-cause mortality. The authors used Cox proportional hazards models to adjust for self-reported CAD risk factors. During a mean follow-up of 5.0 years, mortality was 2.4%. Compared with a CAC score of 10 or less, adjusted relative risk values for coronary calcium were 1.64, 1.74, 2.54, and 4.03 for scores of 11-100, 101-400, 401-1,000, and greater than 1,000 ($P < .001$ for all values). Five-year risk-adjusted survival was 99.0% for a calcium score of 10 or less and 95.0% for a score of greater than 1,000 ($P < .001$). The c-index increased from 0.72 for cardiac risk factors alone to 0.78 ($P < .001$) when the calcium score was added. The major weakness in this study, as in most described above, is the lack of measured risk factor data.

Several authors have attempted to synthesize the data from these cohorts using a variety of meta-analytic techniques (O'Malley *et al*, 2000; Pletcher *et al*, 2004). For example, Pletcher *et al* (2004) estimated adjusted relative risks associated with 3 categories of coronary artery calcium scores (1-100, 101-400, and >400), compared with a score of 0 the 4 studies with published results at the time of the analysis (all but Kondos, 2003). They reported a summary adjusted relative risk of 2.1 (95% confidence interval, 1.6-2.9) for a coronary artery calcium score of 1 to 100. Relative risk estimates for higher calcium scores were higher, but varied significantly among studies. Subgroup analyses suggested that differences among studies in outcome adjudication (blinded or not), measurement of other risk factors (direct or by patient history), tomographic slice thickness (3 or 6 mm), and/or proportion of female study subjects may account for this heterogeneity.

One of the arguments for the use of EBCT is that knowledge about the presence of CAC will increase patient motivation to change modifiable risk factors (smoking, cholesterol, blood pressure) in ways that reduce the patient's risk for CAD events. One randomized clinical trial assessed the effects of incorporating EBCT as a motivational factor into a cardiovascular screening program in the context of either intensive case management (ICM) or usual care, by assessing its impact over one year on a composite measure of projected risk. The study used a 2 x 2 factorial design with one year of follow-up. A consecutive sample of 450 asymptomatic active-duty U.S. Army personnel, aged 39 to 45 years, were enrolled between January 1999 and March 2001 (mean age, 42 years; 79% male; 66 [15%] had coronary calcification; mean [SD] predicted 10-year coronary risk, 5.85% [3.85%]). Patients were randomly assigned

to one of four intervention arms: EBT results provided in the setting of either ICM (n = 111), usual care (n = 119) or EBT results withheld in the setting of either ICM (n = 124) or usual care (n = 96). The primary outcome measure was change in a composite measure of risk, the 10-year FRS. Comparing the groups who received EBCT results with those who did not, the mean absolute risk change in 10-year FRS was +0.30 vs. +0.36 (P = .81). Comparing the groups who received ICM with those who received usual care, the mean absolute risk change in 10-year FRS was -0.06 vs. +0.74 (P = .003). Improvement or stabilization of cardiovascular risk was noted in 157 patients (40.2%). In multivariable analyses predicting change in FRS, after controlling for knowledge of coronary calcification, motivation for change and multiple psychological variables, only the number of risk factors (odds ratio, 1.42; 95% confidence interval (CI), 1.16-1.75 for each additional risk factor) and receipt of ICM (odds ratio, 1.62; 95% CI, 1.04-2.52) were associated with improved or stabilized projected risk. The investigators concluded that using coronary calcification screening to motivate patients to make evidence-based changes in risk factors was not associated with improvement in modifiable cardiovascular risk at one year. However, case management did improve cardiovascular risk compared with usual care. The study was performed in a population of relatively low risk individuals and the prevalence of CAC was low. This may have limited the ability of the study to see any effect of CAC scores on risk behaviors. On the other hand, case management in this same population was able to significantly impact risk. The study offers no evidence to support the use of CAC to motivate change in modifiable risk factors for CHD.

TA Criterion 3 is not met.

Diagnosis of Coronary Artery Disease in Symptomatic Patients

Table 2 summarizes 14 studies (4,062 patients) evaluating the sensitivity and specificity of EBCT for the diagnosis of CAD. All patients had coronary angiography. CAD was defined as at least 50% stenosis in at least one coronary artery. EBCT was considered positive if the CAC score was greater than 0, although some authors report their results using other cutpoints as well. As is true for any diagnostic test that is a continuous measurement, using a lower cutpoint increases sensitivity, but decreases specificity. No optimal cutpoint has been defined for the CAC score, but 0 is used by almost every research group.

Even though studies including patients with known CAD were excluded, there is likely some residual spectrum bias because all of the patients had some indication for coronary angiography. The prevalence of significant CAD ranged from 43% to 78% in the studies (pooled average 53%) which is higher than would be expected in a population of patients presenting with chest pain. Including a higher risk population in the group of patients studied will tend to overestimate the sensitivity of the test, though it should not significantly affect the specificity.

The sensitivity ranged from 77% to 100% and specificity ranged from 21% to 73%. Combining the data from all studies gives pooled sensitivity of 96% and a pooled specificity of 37%. As noted above, the sensitivity of EBCT for CAC in part depends on the minimal area >130 HU allowed to contribute to the CAC score. This ranges from 0.26

mm² to 2.06 mm². Studies defining CAC with minimal areas less than 1 mm² had a higher pooled sensitivity than those using ≥ 1 mm² (98% vs. 92%), but the pooled specificity was lower (35% vs. 40%).

The largest published study (Haberl, Becker *et al.*, 2001) enrolled 1,764 patients (1,225 men and 539 women) with suspected CAD from a single center in Germany. All patients underwent calcium screening with EBCT and conventional coronary angiography. They acquired 40- 3 mm slices during the scan. A calcified plaque was defined as a lesion of at least two adjacent pixels (0.51 mm²) with a signal density of at least 130 HU. 56% of men and 47% of women had significant CAD. Using a CAC score greater than 0 to define a positive test, the sensitivity was 99% and the specificity was 23% for men. Similarly, the sensitivity was 100% and the specificity was 40% for women. The authors also explored using other cut points for a positive test. If CAC scores ≥ 20 , ≥ 100 or \geq age and sex specific 75th percentile were used to define a positive test, the sensitivity to detect CAD decreased to 97%, 93% and 81%, respectively, in men; to 98%, 82% and 76%, respectively, in women. At the same time, the specificity increased to 62%, 75% and 72% in men and to 69%, 76% and 77% in women. CAC scores were significantly higher in men than women in all age groups. However, receiver-operating characteristic curves indicated that the test can be performed with equal accuracy in all of these subgroups. The authors concluded that EBCT is a highly sensitive and moderately specific test to predict CAD. However, neither this study nor the others demonstrated improved health outcomes due to the high sensitivity of CAC.

TA Criterion 3 is not met.

Assessment of Response to Therapy

A non-invasive method to measure changes in plaque volume would be a boon to research on new therapies for atherosclerosis. Because CAC scores correlate with total plaque burden (Simons, Schwartz *et al.*, 1992; Mautner, Mautner *et al.*, 1994; Rumberger, Simons *et al.*, 1995; Sangiorgi, Rumberger *et al.*, 1998). EBCT may be an effective method to assess response to therapy. Unfortunately, the poor inter-scan variability discussed above limits the sensitivity of EBCT to detect change in individuals over time. It may be more useful in populations, but that needs to be demonstrated in intervention trials. Four published studies compared changes in CAC over time with LDL cholesterol levels.

The earliest study (Callister, Raggi *et al.*, 1998) described changes in total calcium volume (not the Agatston score) in 149 patients without a history of CAD. All patients had a baseline EBCT and repeat scan 12-15 months later. Treatment with statins was done at the discretion of the patient's physician. Change in the calcium volume score correlated with average LDL cholesterol levels over the study period. The authors describe three groups of patients: those treated with statins with an LDL level <120 mg/dl (n=65); treated patients with LDL > 120 mg/dl (n=40) and untreated patients (n=44, mean LDL 147 mg/dl). The average changes in calcium volume score were -7%, +25% and +52%, respectively.

Slowing in the rate of progression was also demonstrated in a clinical trial (Achenbach, Ropers *et al.*, 2002) of 66 patients started on cerivastatin. The progression of coronary calcium volume over one year of treatment was lower than that observed during one year prior to treatment (+11 mm³ vs. 25 mm³, p=0.01).

In contrast to recent trials demonstrating less plaque progression and improved clinical outcomes with aggressive lipid lowering (Kent, Coyle *et al.*, 2004; Nissen, Tuzcu *et al.*, 2004), intensive lipid-lowering therapy did not affect CAC progression (Hecht and Harman, 2003). In this study, the effect of aggressive LDL cholesterol lowering (to \leq 80 vs. $>$ 80 mg/dl) on calcified coronary plaque progression was evaluated in 182 consecutive asymptomatic patients after 1.2 years of treatment with statins alone or in combination with niacin. Despite the greater improvement in lipids in the \leq 80 vs. $>$ 80 mg/dl groups, there were no differences in calcified plaque progression (9.3%/year vs. 9.1%/year, p NS).

A more recent trial also failed to find a correlation (Wong, Kawakubo *et al.*, 2004) between lipid lowering and calcium scores. 761 subjects (mean age 64.5 years; 91% men; 69% positive for CAC) in an ongoing cohort study underwent baseline and follow-up (after 7 years) EBCT for CAC. Subjects were stratified into low-risk ($<$ 2 risk factors), intermediate-risk \geq 2 risk factors but $<$ 20% risk of coronary heart disease over 10 years), or high-risk \geq 2 risk factors and $>$ 20% risk of coronary heart disease in 10 years or diabetes) groups. After adjustment for other risk factors and baseline CAC volume, CAC progression was similar between those with adequate and those with inadequate control of LDL cholesterol (p = 0.68) and across categories of optimal, intermediate and higher risk LDL cholesterol (p = 0.40). However, higher levels of HDL cholesterol (\geq 60 mg/dl) were associated with less progression of CAC volume (151 vs. 203 mm³ in those with HDL cholesterol $<$ 40 mg/dl, p = 0.03). Thus, in this study CAC progression was not associated with LDL cholesterol level.

In summary, the results concerning the association between LDL-cholesterol levels (observationally or in response to therapy) and progression of coronary artery calcium (usually measured by volume rather than the Agatston score) are conflicting. Most likely, the differences are due to heterogeneity in the patient populations, different measurements of CAC and different statistical approaches to the analysis. To date, there are no data concerning the impact of therapeutic decisions based on changing CAC volume on clinical outcomes.

TA Criterion 3 is not met.

Harms

There are several potential harms from the use of EBCT. There has been more attention paid recently to the potential risks from radiation exposure, particularly if EBCT for CAC is performed as part of repeated total body scans (Brenner and Elliston, 2004). The use of EBCT for CAC measurement uses substantially less radiation, but if there is little clinical value to CAC scores, the radiation will result in net harm.

Of greater concern is the effect of incidental findings on the CT scan unrelated to CAC. One study reported the prevalence of so-called “incidentalomas” during EBCT scans (Elgin, O’Malley, *et al.*, 2002). The population scanned was relatively young (mean 42 years, range 39-46), male (82%) and rated their health as excellent (88%). They found 91 incidental findings in 79 patients (8% prevalence). The most common organs involved were the lungs (29%), bones (24%), and liver (18%). Less than half (40%) were rated as minor (requiring telephone call reassurance only). It is unclear whether the balance of these incidental findings were beneficial (early detection of disease that benefits from early treatment) or harmful (further office visits, invasive tests, anxiety for benign disease). In this study, none of the lung nodules or breast masses turned out to be cancer. An earlier study (Humold, Schmermund, *et al.*, 2001) in an older population reported their prevalence of incidental EBCT findings to be 53%.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Prediction of Cardiovascular Events in Asymptomatic Patients

As noted earlier, the alternative to EBCT is risk stratification combining standard cardiovascular risk factors using the FRS (Wilson, D’Agostino *et al.*, 1998). Although it has acknowledged limitations, the standard approach to assessing the incremental information gained in a predictive model is to compare the c-index of each model, which is equivalent to the area under the ROC curve (Pepe, Janes *et al.*, 2004). Two papers directly assessed the additive value of EBCT to risk scores derived using the Framingham equation. The first (Detrano, Wong *et al.*, 1999) included participants in the South Bay Heart Watch study who were greater than 45 years old with at least one coronary risk factor. They underwent computed tomography (CT) examination between 1990-1992 and were contacted yearly to assess CHD events. The 1,196 asymptomatic participants with complete risk-factor assessment and EBCT scanning were followed up for 41 months. The mean age of the cohort was 66 years and the mean three-year Framingham risk was 3.3+/-3.6%. 68% had detectable coronary calcium. There were 17 coronary deaths (1.4%) and 29 nonfatal infarctions (2.4%). The receiver operating characteristic (ROC) curve areas calculated from the Framingham model and the calcium score were 0.68+/-0.05 and 0.64+/-0.05, respectively (P=NS). When calcium score was included as a variable in the Framingham model, the ROC area did not change significantly (0.68+/-0.05 to 0.71+/-0.04; P=NS). The authors concluded that EBCT calcium score did not add significant incremental information to risk factors and its use in clinical screening is not justified at this time.

The second study (Greenland, LaBree *et al.*, 2004) analyzed the same cohort, but excluded patients with diabetes because an earlier analysis of the South Bay Heart Watch cohort found that EBCT had less utility at predicting CAD events in diabetics (Qu, Le *et al.*, 2003). At the time of this analysis, the cohort had much longer follow-up and more hard events had occurred, giving the authors greater power to detect a difference. The study also set out to determine whether CAC assessment combined with FRS in asymptomatic adults provides prognostic information superior to either method alone and whether the combined approach can more accurately guide primary preventive

strategies in patients with CHD risk factors. This analysis included 1,312 participants with CAC results, but then excluded 269 participants with diabetes and 14 participants with either missing data or with a coronary event before EBCT was performed. The calcium scores were grouped into the following four categories: 0, 1-100, 101-300 and greater than 300. The primary outcome for this analysis was nonfatal myocardial infarction or CHD death. During a median of 7.0 years of follow-up, 84 patients experienced MI or CHD death. There were 291 (28%) participants with a 10-year FRS of more than 20% and 221 (21%) with a CACS of more than 300. Compared with an FRS of less than 10%, an FRS of more than 20% predicted the risk of MI or CHD death (RR, 14.3; 95% CI; 2.0-104; P =.009). Compared with a CACS of zero, a CACS of more than 300 was predictive (RR, 3.9; 95% CI, 2.1-7.3; P<.001). Across categories of FRS, CACS was predictive of risk among patients with an FRS higher than 10% (P<.001), but not in those with a FRS less than 10%, although this may reflect low power in this small subgroup.

In this analysis, the c-index for the FRS was 0.63 and the c-index for the combination of FRS plus CAC scores was 0.68 (p<0.001). It is worthwhile remembering that the c-index only has value from 0.50 to 1.0, so that the change represents a 38% increase in the predictive accuracy of the model. On the other hand, a c-index of 0.68 is still quite modest, though equivalent to the c-index calculated for the FRS alone in Detrano's original analysis. The c-index for the FRS calculated in this analysis (0.63) is much lower than that reported in other studies validating the FRS (Liao, McGee *et al.*, 1999; D'Agostino, Grundy *et al.*, 2001; Thomsen, McGee *et al.*, 2002). However, the authors conclude that high CACS can modify predicted risk obtained from FRS alone, especially among patients in the intermediate-risk category in whom clinical decision-making is most uncertain.

Using an alternate approach, Pletcher *et al* (2004) sought to combine information from the CAC score with information from conventional cardiac risk factors to produce post-test risk estimates, and to determine whether the score may add clinically useful information. They measured the independent cross-sectional associations between conventional cardiac risk factors and the CAC score among asymptomatic persons referred for non-contrast electron beam computed tomography (n=9341, age 35-88 years, 40% female). Using the resulting multivariable models and published CAC score-specific relative risk estimates, they modeled the effect of CAC scores on risk calculated using Framingham risk scores. They concluded that combining information from the CAC score with information from conventional risk factors can change risk assessment enough to change recommendations for preventive treatment, especially in the intermediate risk group (10-20% 10-year risk by Framingham risk score). Thus, their findings match those of Greenland *et al* (2004).

Given the many markers of pre-clinical CAD that are competing to improve risk assessment, the NIH/NHLBI initiated the Multiethnic Study of Atherosclerosis (MESA). MESA is a 10-year cohort study in 6,500 asymptomatic individuals. Many of the novel risk factors that are independent of traditional CAD risk factors have been measured in the cohort, including coronary artery calcium. One of the primary goals of the study is to evaluate the independent contribution of indicators of subclinical disease to risk prediction models. The results of this study should be able to refute or confirm

that ability of CAC to change the risk assessment for patient's at intermediate FRS risk in ways that could affect clinical care and thus, patient outcomes.

TA Criterion 4 is not met.

Diagnosis of Coronary Artery Disease in Symptomatic Patients

Among symptomatic patients, coronary angiography remains the standard for proving the presence and severity of CAD. However, it is an invasive procedure with potential procedure related risk (Ha, Cho *et al.*, 1999). Non-invasive alternatives to angiography include ETT, nuclear perfusion studies (most commonly SPECT or thallium-201 myocardial perfusion scintigraphy) and exercise echocardiography (Kates, Vedala *et al.*, 1999; He, Hedrick *et al.*, 2000). Systematic reviews estimate the sensitivity of SPECT to be 88% and the specificity 77% (Garber and Solomon, 1999). Similar estimates for exercise echocardiography are 76% and 88%, respectively (Garber and Solomon, 1999).

The summary estimates from pooled meta-analyses (Fleischmann, Hunink *et al.*, 1998; Garber and Solomon, 1999) of the sensitivity and specificity of the non-invasive diagnostic tests commonly used in patients with symptoms of CAD are given in Table 4 along with the results from the pooled analysis in this review.

Table 4: Test Characteristics of Non-Invasive Tests for CAD

Test	Sensitivity	Specificity	LR+	LR-
ETT	68%	77%	2.7	.42
ETT-Thallium	79%	73%	2.9	.29
Stress-echo	76%	88%	6.3	.30
Stress-SPECT	88%	77%	3.8	.16
EBCT	96%	37%	1.5	.09

As summarized under TA Criterion 3, EBCT has higher sensitivity but lower specificity than established alternatives. Using a CAC score greater than 0 as the threshold for a positive EBCT test would decrease the sensitivity, but increase the specificity. Several authors have suggested using age and sex specific percentile cut points, but there is not yet consensus in the field. The ideal way to compare the accuracy of these non-invasive tests would be to compare the area under the ROC curves for tests performed in the same patient population. Unfortunately, those data are not available. As a crude alternative, the sum of sensitivity and specificity for standard alternatives ranges from 145% for ETT alone, up to 165% for SPECT. Because of the low specificity, the sum for EBCT is much lower at 133%. However, in one of the analyses presented in the study of Haberl *et al.* (2001), using a cut point of 100 for the CAC score gave a summed sensitivity and specificity of 168% in men and 158% in women. This analysis suggests that a cut point might be found that gives EBCT test characteristics similar to those of other non-invasive tests.

Regrettably, there are no studies directly comparing EBCT to non-invasive alternatives in patients who subsequently have coronary angiography to definitively diagnose the presence or absence of significant CAD. Furthermore, the available evidence does not report any data on the effect of the technology on health outcomes.

TA Criterion 4 is not met.

Assessment of Response to Therapy

The gold standard to assess the response to therapy is to compare clinical outcomes in patients randomized to receive the therapy or placebo. However, studies requiring clinical outcomes take years to accrue enough events and are enormously expensive. Other alternatives to EBCT under investigation include quantitative coronary angiography, CIMT by ultrasound and intravascular ultrasound. At least 11 studies have investigated the utility of CIMT, the other non-invasive approach and response to therapies designed to lower risk for CAD (Grobbee and Bots, 2004). None of the studies directly compare EBCT to CIMT. The studies of change in CAC suggest that changes in CAC progression may reflect response to statin therapy, but average changes in most of the studies still demonstrated increased CAC over time. None of the studies investigated whether the change in CAC was a better predictor of risk reduction or future events than simpler measures like change in LDL or HDL cholesterol, change in the FRS, or the current media favorite, change in C-reactive protein (Nissen, Tuzcu *et al.*, 2005; Ridker, Cannon *et al.*, 2005).

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Whether the use of EBCT improves health outcomes when used to identify asymptomatic individuals at risk for CAD, diagnose symptomatic patients with CAD, or evaluate the response to therapies for CAD has not been demonstrated in the investigational setting.

TA Criterion 5 is not met.

Table 1: Prospective Cohort Studies of CAC for the Prediction of CVD Events in Patients without Known CHD

Study	N	Follow-up (Months) % Completing	Sample	Age ± SD (years) % Female	CAC Measurement (Minimum size) Cut thickness	Outcome ? Blinded	# Outcomes Annual Rate	Variables Included in MV Adjustment	RR (95% CI)	C-index
Arad 2000	1,172	43 100%		53 ± 11 29%	130 HU (2 pixels, 0.93 mm ²) 3 mm	CHD death + non-fatal MI + revascularization No	39 0.5%	Age (cat) Sex Diabetes (hx, cat) Hypertension (hx, cat) Smoking (hx, cat) High cholesterol (hx, cat) Family history (hx, cat)	14.3 (4.9-42.3) for CAC >80 vs. ≤ 80.	NR
Wong 2000	926	40 61%		54 ± 10 21%	130 HU (1 pixel, 0.51mm ²) 3 mm	CHD death + non-fatal MI + stroke + revascularization Yes	28 0.2%	Age (NR) Sex Diabetes (hx, cat) Hypertension (hx, cat) Smoking (hx, cat) High cholesterol (hx, cat)	0 Referent 1-15 0.7 (0.1-6.6) 16-80 3.3 (0.8-12.8) 81-270 4.5 (1.2-16.8) ≥271 8.8 (2.2-35.1)	NR
Raggi 2001	676	32 NR		52 ± 10 49%	130 HU (3 pixels, 1.03 mm ²) 3 mm	CHD death + non-fatal MI No	30 1.7%	Age (continuous) Sex Diabetes (hx, cat) Hypertension (hx, cat) Smoking (hx, cat) High cholesterol (hx, cat)	1.03 (1.02-1.05) per age- and sex- specific percentile increase in CAC	NR
Kondos 2003	5,635	37 64%	Asymptomatic ages 30-76. Self referred for EBCT.	51±9 26%	130 HU (4 pixels, 1 mm ²) 3 mm	CHD death + non-fatal MI + revascularization Yes	224 1.2% all 0.3% hard CHD death 21 MI 37 CABG 92 PTCA 74	Age (NR) Sex Diabetes (hx, Y/N) Hypertension (hx, Y/N) Smoking (hx, Y/N) High cholesterol (hx, Y/N)	<u>Men – hard events</u> 0 Referent 1-3.8 1.8 (0.4-7.9) 4.0-30.5 2.8 (0.7-11) 31-169 5.6 (1.6-20) ≥170 7.2 (2.0-26) <u>Women – hard events</u> NR – adding CAC to model with standard risk factors did not significantly improve the model. Quartiles of CAC with 0 as reference group	NR
Greenland 2004	1,029 of 1,312 in full cohort	84 50%	Asymptomatic with risk factors for CHD but no diabetes.	66 ± 8 10%	130 HU (4 pixels, 1.36 mm ²) 6 mm	CHD death + non-fatal MI Yes	84 1.3%	Age (cat) Sex Diabetes (excluded) Hypertension (direct, cat) Smoking (direct, cat) LDL (direct, continuous) HDL (direct, continuous) Family history (hx, cat)	1.3 (1.2-1.5) per 1 SD increase in CAC (399) Unadjusted for other risk factors 0 Referent 1-100 1.5 (0.7-2.9) 101-300 2.1 (1.0-4.3) >300 3.9 (2.1-7.3)	0.63 for FRS 0.68 for FRS + CAC

Table 2: Cross-sectional Studies of CAC for the Diagnosis of CAD in Patients with Symptoms

Study	N	Sample	Age % Female	CAC Measurement ? Blinded	CAD Definition ? Blinded	% CAD	Sensitivity	Specificity	TP	FP	FN	TN	LR+	LR-
Breen 1992	100	Elective coronary angiography.	47±8 9	130 HU (2 pixels) Yes	≥50% stenosis NR	47	100	47	47	28	0	25	1.9	0.00
Bielak 1994	160	Mayo clinic. Indications for coronary angiography.	48 17	130 HU (8 pixels, 2.06 mm ²) NR	≥50% stenosis NR	43	90	62	62	35	7	56	2.3	0.16
Fallovollita 1994	106	Age < 50 with coronary angiography.	44±5 26	130 HU (4 pixels, ~1 mm ²) NR	≥50% stenosis Yes	56	85	45	50	26	9	21	1.5	0.34
Devries 1995	140	Indications for coronary angiography, excluded if prior CABG.	56±12 50	130 HU (1 pixel, 0.26 mm ²) NR	>70% stenosis NR	43	97	41	58	47	2	33	1.6	0.08
Rumberger 1995	139	Diagnostic coronary angiography, no prior CAD diagnosis.	50 36	130 HU (2 pixels, 0.50-0.68 mm ²) NR	≥ 50% stenosis NR	47	98	39	64	45	1	29	1.6	0.04
Yaghoubi 1995	67	UCLA. Symptomatic patients referred for coronary angiography.	55±10 52	130 HU (1 pixel, 0.34 mm ²) NR	> 50% stenosis NR	49	97	56	32	15	1	19	2.2	0.05
Braun 1996	102	Coronary angiography for suspected CAD.	56±8 28	130 HU (0.51 mm ²) NR	> 50% stenosis NR	78	93	73	74	6	6	16	3.4	0.10
Budoff 1996	710	6 sites, coronary angiography for suspected CAD in "most" cases.	56±12 36	130 HU (0.68 mm ² 3 sites, 1.02 mm ² 3 sites) NR	> 50% stenosis NR	60	95	44	404	159	23	124	1.7	0.12
Detrano 1996	491	5 centers. Patients referred for angiogram.	55±12 43	130 HU (1 mm ²) Yes	>50% stenosis Yes	43	95	31	200	193	11	87	1.4	0.17
Baumgart 1997	57	Patients referred for angiography.	54±9 21	130 HU (4 pixels, 1 mm ²) Yes	≥ 50% stenosis Yes	51	97	21	28	22	1	6	1.2	0.16
Haberl 2001	1,764	Suspected CAD referred for coronary angiography.	57±15 31	130 HU (2 pixels, 0.51 mm ²) NR	≥ 50% stenosis Yes	53	99	30	935	580	5	244	1.4	0.02
Lamont 2002	153	+ treadmill referred for coronary angiography.	58±10 24	NR Yes	>49% stenosis Yes	73	98	66	110	14	2	27	2.9	0.03
Yao 2004	73	Suspected CAD referred for angiography, no prior MI.	53±11	130 HU (4 pixels, >1 mm ²) NR	≥ 50% stenosis NR	48	77	55	27	17	8	21	1.7	0.41

Table 3: Commonly Cited Cross-sectional Studies of CAC for the Diagnosis of CAD Not Included in the Primary Analysis Because of Non-standard Patient Population, Different Definition of Significant CAD, or a Different CAC Cutoff

Study	N	Sample	Age % Female	CAC Measurement ? Blinded	CAD Definition ? Blinded	% CAD	Sensitivity	Specificity	TP	FP	FN	TN
Tanenbaum 1989	54	Illinois consecutive patients with indications for coronary angiography.	54±16 33	130 HU (? Pixels) Yes	>70% stenosis NR	80	88	100	38	0	5	11
Agatson 1990	584	Mixed sample, only 123 had coronary angiography.	48±10 30	130 HU (2 pixels, 1 mm ²) Yes	≥50% stenosis or prior MI Yes	19	96	57	105	202	4	273
Bormann 1992	50	Only imaged 1 st 2 cm each vessel.							15	25	1	9
Barbir 1994	102	Heart transplant patients' annual coronary angiography.	53 14	130 HU (2 pixels, 0.5 mm ²) Yes	≥50% stenosis Yes	18	83	63	15	31	3	53
Kajinami 1995	251	Elective angiography, no prior PTCA, CABG, or MI.	56±14 31	130 HU (2 pixels, 0.51 mm ²) Yes	> 75% on densitometry or ≥50% stenosis Yes	53	91	50	121	59	12	59
Kaufmann 1995	160	Age<60 y, no prior CAD.		130 HU (8 pixels, 2 mm ²) NR	≥50% stenosis NR	40	94	61	60	37	4	59
Rumberger 1997	213	Patients referred for angiogram, no prior CAD.	50±9 25	130 HU (CAC score≥80)	≥ 50% stenosis NR	53	84	83	94	17	18	84
Schmermund 1997	118	Acute coronary syndromes: 101 prior MI, 17 unstable angina.	57±11 17	130 HU (4 pixels, ≥1.03 mm ²) NR	>50% stenosis NR	93	95	88	105	1	5	7
Budoff 1998	125	EF<40% referred for angiography.	55 35	130 HU (2 pixels)	≥ 50% stenosis Yes	58	99	83	71	9	1	44
Becker 1999	42	Suspected CAD.	61±8 0	130 HU (2 pixels, 0.5 mm ²) NR	>50% stenosis NR	88	NR	NR	NR	NR	NR	NR
Chen 2001	116	Chinese referred for coronary angiogram.	66±10 15	130 HU (NR) NR	≥ 50% stenosis Yes	55	98	44	63	29	1	23
Sharples 2004	18	Consecutive patients with ESRD referred for angiogram.	54±3 50	13 HU (NR) Yes	>50% stenosis Yes	72	100	20	13	4	0	1

CONCLUSION

Five prospective studies reported on the use of EBCT to identify asymptomatic individuals at high risk for CAD. All five found that the CAC score is a predictor of future CAD events, independent of traditional risk factors for CAD. However, four of the five studies measured the risk factors by patient self-report only, which limits the ability of models to fully control for the other risk factors. More importantly, only one of the studies assessed the improvements in risk assessment that occur when adding EBCT and CAC scores to the standard risk assessment tool, the FRS. In their initial analysis, the authors concluded that EBCT did not improve the predictive accuracy of the Framingham model. In a subsequent paper, the authors excluded diabetics and focused on patients at intermediate risk (10%-20%, 10-year risk) for CHD. In this reanalysis, the authors found that the calcium score did change the risk estimate for patients in ways that could affect recommendations for primary prevention with aspirin or statin therapy. Given that this conclusion results from a re-analysis of a subgroup of the study, it is prudent to await confirmation of the finding in a second study, before basing clinical practice on it. MESA, an NIH sponsored prospective cohort study of 6,500 asymptomatic men and women that measured EBCT and many other risk factors for CAD, should clarify the role of EBCT for risk assessment in patients without known CAD. One randomized clinical trial examined whether knowledge of CAC scores changed patient behavior in ways that reduced subsequent risk. One year later, the study found no difference in risk scores between patients informed of their CAC scores and those who were blinded to their CAC scores. Considered together, current literature is not sufficient to determine whether EBCT improves net health outcomes compared to conventional risk factor stratification.

EBCT provides a sensitive means of detecting coronary calcification, which is a sign of coronary arteriosclerosis. Using a cut point of 0, EBCT has a high negative predictive value for coronary disease, but a limited specificity. Because the CAC score is a continuous measure, various studies have varied the threshold or cut-off for defining an abnormal test result, but there is no consensus regarding the ideal cut point to use. Current data suggest that EBCT is more sensitive, but less specific than other non-invasive tests used to diagnose CAD in patients with symptoms suggestive of CAD. Unfortunately, there are no studies that directly compare EBCT to other non-invasive studies in which patients also had the gold standard, coronary angiography. Comparing summary data from meta-analyses suggests that the overall accuracy of EBCT is not as high as SPECT or exercise echocardiography.

The between scan reproducibility of coronary calcium scoring using the Agatston scoring method is often greater than 20%. This greatly limits the utility of EBCT for monitoring progression of CAD in individuals. Recent international efforts at standardization have developed a new scoring method and phantoms for calibration that should improve the reproducibility of CAC scores. However, these methods are not yet widely used and there are limited published data using the new scoring system. Current data on the utility of EBCT to assess response to therapy are limited and inconsistent. There are no comparisons with a gold standard or with competing alternative technologies.

RECOMMENDATION

It is recommended that the use of EBCT to measure CAC

- (1) As a screening test to identify asymptomatic patients at high risk for future coronary heart disease events does not meet technology assessment criteria 3, 4, or 5 for safety, effectiveness, and improvement in health outcomes.
- (2) As a diagnostic test in patients with symptoms suggestive of CAD does not meet technology assessment criteria 3, 4, or 5 for safety, effectiveness, and improvement in health outcomes.
- (3) To assess response to therapy for coronary heart disease does not meet technology assessment criteria 2, 3, 4, or 5 for safety, effectiveness, and improvement in health outcomes.

February 16, 2005

It is the opinion of the reviewer that criteria were not met as stated in the draft recommendation. However, after listening to the testimony of invited experts and further clarification of the data as the experts understand it, the CTAF panel voted to accept the following recommendation:

That the use of EBCT to measure Coronary Artery Calcium:

- (1) As a screening test for asymptomatic patients who are at intermediate risk for coronary heart disease, EBCT calcium scoring meets CTAF Technology Assessment Criteria 1 through 5.
- (2) As a diagnostic test in patients with symptoms suggestive of CAD (patients with chest pain), EBCT calcium scoring is a useful technology to predict those patients who will have underlying coronary heart disease, and meets CTAF Technology Assessment Criteria 1 through 5.
- (3) To assess response to therapy for coronary heart disease does not meet CTAF Technology Assessment Criteria.

OPINIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center conducted a review of this technology in 1998 and found that it did not meet criteria. TEC has recently conducted a review of contrast-enhanced cardiac computed tomography angiography.

Centers for Medicare and Medicaid Services (CMS)

The CMS does not have a national policy specific to the use of this technology. One CMS provider, Wisconsin Physicians Insurance Service does have a policy which indicates that EBCT is considered investigational.

American College of Cardiology, California Chapter (ACCCA)

The California Chapter of the ACC has provided a statement supporting the use of coronary calcium scanning. A representative attended the meeting.

American Heart Association (AHA)

The AHA has been invited to provide an opinion regarding the use of coronary calcium scanning. A representative was not able to attend the meeting.

ABBREVIATIONS USED IN THIS REVIEW

CAD:	Coronary Artery Disease	EBCT:	Electron Beam Computed Tomography
CAC:	Coronary Artery Calcification	EKG:	Electrocardiogram
DARE:	Database of Abstracts of Reviews of Effects	C-Index:	Concordance Index
ETT:	Exercise Treadmill Testing	CIMT:	Carotid Intima-Media Thickness
SPECT:	Single Photon Emission Computed Tomography	LDL:	Low Density Lipoprotein
CHD:	Coronary Heart Disease	MI:	Myocardial Infarction
RR:	Relative Risk	CI:	Confidence Interval
HDL:	High Density Lipoprotein	LVH:	Left Ventricular Hypertrophy
HU:	Hounsfield Units	HR:	Hazard Ratio
CT:	Computed Tomography	ROC:	Receiver Operating Characteristic
ICM:	Intensive Case Management	FRS:	Framingham Risk Score
MESA:	Multiethnic Study of Atherosclerosis		

REFERENCES

1. Achenbach, S., W. Moshage, *et al.* (1998). "Value of electron-beam computed tomography for the noninvasive detection of high-grade coronary-artery stenoses and occlusions." N Engl J Med 339(27): 1964-71.
2. Achenbach, S., D. Ropers, *et al.* (2002). "Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation." Circulation 106(9): 1077-82.
3. Ackerman, J. A., J. D. Talley, *et al.* (1993). "Manifestations of coronary atherosclerosis in young trauma victims--an autopsy study." Journal of the American College of Cardiology 22(2): 459-467.
4. Adamzik, M., A. Schmermund, *et al.* (1999). "Comparison of two different software systems for electron-beam CT-derived quantification of coronary calcification." Invest Radiol 34(12): 767-73.
5. Adragao, T., A. Pires, *et al.* (2004). "A simple vascular calcification score predicts cardiovascular risk in haemodialysis patients." Nephrol Dial Transplant 19(6): 1480-8.
6. Agatston, A. S., W. R. Janowitz, *et al.* (1990). "Quantification of coronary artery calcium using ultrafast computed tomography." J Am Coll Cardiol 15(4): 827-32.
7. Agatston, A. S., W. R. Janowitz, *et al.* (1996). "Electron beam CT coronary calcium predicts future coronary events (Abstract 2097, Oct 1996)." Circulation 94(8, Supplement 1): I-360.
8. Arad, Y. (1998). "Electron beam computed tomography for the diagnosis of cardiac disease." S Afr Med J 88(5): 558-63.
9. Arad, Y. (2002). "Beyond traditional risk factor analysis for coronary artery disease: The case for coronary artery calcium assessment with electron beam computed tomography." Prev Cardiol 5(2): 62-67.
10. Arad, Y., L. A. Spadaro, *et al.* (1998). "3.6 years follow-up of 1136 asymptomatic adults undergoing electron beam CT (EBCT) of the coronary arteries (Abstract 855-6, Feb 1998)." Journal of the American College of Cardiology: 210A.
11. Arad, Y., L. A. Spadaro, *et al.* (1996). "Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects." Circulation 93(11): 1951-3.
12. Arad, Y., L. A. Spadaro, *et al.* (2000). "Prediction of coronary events with electron beam computed tomography." J Am Coll Cardiol 36(4): 1253-1260.
13. Barbir, M., T. Bowker, *et al.* (1994). "Ultrafast computed tomographic scanning for detection of coronary disease in cardiac transplant recipients." Am J Cardiol 74(9): 941-4.
14. Baumgart, D., A. Schmermund, *et al.* (1997). "Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis." J Am Coll Cardiol 30(1): 57-64.
15. Becker, A., A. Knez, *et al.* (2001). "Prognostic value of coronary calcifications for cardiovascular events in patients with diabetes mellitus (Abstract 2535, Oct 2001)." Circulation 104(17 (Supp II)): II-536.
16. Becker, C. R., A. Knez, *et al.* (1999). "Detection and quantification of coronary artery calcification with electron-beam and conventional CT." Eur Radiol 9(4): 620-4.
17. Bielak, L. F., R. B. Kaufmann, *et al.* (1994). "Small lesions in the heart identified at electron beam CT: calcification or noise?" Radiology 192(3): 631-6.

18. Bormann, J. L., W. Stanford, *et al.* (1992). "Ultrafast computed tomographic detection of coronary artery calcification as an indicator of stenosis." Am J Card Imaging 6: 191-196.
19. Braun, J., M. Oldendorf, *et al.* (1996). "Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients." Am J Kidney Dis 27(3): 394-401.
20. Breen, J. F., P. F. d. Sheedy, *et al.* (1992). "Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease." Radiology 185(2): 435-9.
21. Brenner, D. J. and C. D. Elliston (2004). "Estimated radiation risks potentially associated with full-body CT screening." Radiology 232(3): 735-8.
22. Budoff, M. J., D. Georgiou, *et al.* (1996). "Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study." Circulation 93(5): 898-904.
23. Budoff, M. J., D. M. Shavelle, *et al.* (1998). "Usefulness of electron beam computed tomography scanning for distinguishing ischemic from nonischemic cardiomyopathy." J Am Coll Cardiol 32(5): 1173-8.
24. Buenano, A. I., F. Lopez-Jimenez, *et al.* (2000). "Coronary calcium score and all cause mortality (Abstract 1936, Oct 2000)." Circulation 102(18 (Supp II)): II-398.
25. Callister, T. Q., B. Cooil, *et al.* (1998). "Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method." Radiology 208(3): 807-14.
26. Callister, T. Q., P. Raggi, *et al.* (1998). "Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography." N Engl J Med 339(27): 1972-8.
27. Chen, L. C., P. Y. Ding, *et al.* (2001). "Coronary artery calcium determined by electron beam computed tomography for predicting angiographic coronary artery disease in moderate- to high-risk Chinese patients." Cardiology 95(4): 183-9.
28. Chernoff, D. M., C. J. Ritchie, *et al.* (1997). "Evaluation of electron beam CT coronary angiography in healthy subjects." AJR Am J Roentgenol 169(1): 93-9.
29. D'Agostino, R. B., Sr., S. Grundy, *et al.* (2001). "Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic group's investigation." Jama 286(2): 180-7.
30. Detrano, R. and T. Doherty (1998). "Electron beam CT and coronary calcium score." Circulation 97(20): 2095-6.
31. Detrano, R., T. Hsiai, *et al.* (1996). "Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography [see comments]." J Am Coll Cardiol 27(2): 285-90.
32. Detrano, R. C., N. D. Wong, *et al.* (1999). "Coronary calcium does not accurately predict near-term future coronary events in high-risk adults." Circulation 99(20): 2633-8.
33. Devries, S., C. Wolfkiel, *et al.* (1995). "Influence of age and gender on the presence of coronary calcium detected by ultrafast computed tomography." J Am Coll Cardiol 25(1): 76-82.
34. Devries, S., C. Wolfkiel, *et al.* (1995). "Reproducibility of the measurement of coronary calcium with ultrafast computed tomography." Am J Cardiol 75(14): 973-5.
35. Eggen, D. A., J. P. Strong, *et al.* (1965). "Coronary calcification. Relationship to clinically significant coronary lesions and race, sex, and topographic distribution." Circulation 32(6): 948-55.

36. Elgin, E. E., P. G. O'Malley, *et al.* (2002). "Frequency and severity of "incidentalomas" encountered during electron beam computed tomography for coronary calcium in middle-aged army personnel." Am J Cardiol 90(5): 543-5.
37. Fallavollita, J. A., A. S. Brody, *et al.* (1994). "Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery disease. Comparison with angiography in patients < 50 years old." Circulation 89(1): 285-90.
38. Fleischmann, K. E., M. G. Hunink, *et al.* (1998). "Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance." Jama 280(10): 913-20.
39. Garber, A. M. and N. A. Solomon (1999). "Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease [see comments]." Ann Intern Med 130(9): 719-28.
40. Greenland, P., L. LaBree, *et al.* (2004). "Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals." JAMA 291(2): 210-5.
41. Greenland, P., S. C. Smith, Jr., *et al.* (2001). "Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests." Circulation 104(15): 1863-7.
42. Grobbee, D. E. and M. L. Bots (2004). "Atherosclerotic disease regression with statins: studies using vascular markers." Int J Cardiol 96(3): 447-59.
43. Ha, J. W., S. Y. Cho, *et al.* (1999). "Noninvasive evaluation of coronary artery bypass graft patency using three-dimensional angiography obtained with contrast-enhanced electron beam CT." AJR Am J Roentgenol 172(4): 1055-9.
44. Haberl, R., A. Becker, *et al.* (2001). "Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients." J Am Coll Cardiol 37(2): 451-7.
45. Hackam, D. G. and S. S. Anand (2003). "Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence." Jama 290(7): 932-40.
46. He, Z. X., T. D. Hedrick, *et al.* (2000). "Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia." Circulation 101(3): 244-51.
47. Hecht, H. S. and S. M. Harman (2003). "Relation of aggressiveness of lipid-lowering treatment to changes in calcified plaque burden by electron beam tomography." Am J Cardiol 92(3): 334-6.
48. Hernigou, A., P. Challande, *et al.* (1996). "Reproducibility of coronary calcification detection with electron-beam computed tomography." Eur Radiol 6(2): 210-6.
49. Hunold, P., A. Schmermund, *et al.* (2001). "Prevalence and clinical significance of accidental findings in electron-beam tomographic scans for coronary artery calcification." Eur Heart J 22(18): 1748-58.
50. Kajinami, K., H. Seki, *et al.* (1993). "Quantification of coronary artery calcification using ultrafast computed tomography: reproducibility of measurements." Coron Artery Dis 4(12): 1103-8.
51. Kajinami, K., H. Seki, *et al.* (1995). "Noninvasive prediction of coronary atherosclerosis by quantification of coronary artery calcification using electron beam computed tomography: comparison with electrocardiographic and thallium exercise stress test results." J Am Coll Cardiol 26(5): 1209-21.

52. Kajinami, K., H. Seki, *et al.* (1997). "Coronary calcification and coronary atherosclerosis: site by site comparative morphologic study of electron beam computed tomography and coronary angiography." J Am Coll Cardiol 29(7): 1549-56.
53. Kates, A. M., G. Vedala, *et al.* (1999). "Noninvasive coronary artery imaging in the diagnosis and management of patients with ischemic heart disease." Curr Opin Cardiol 14(4): 314-20.
54. Kaufmann, R. B., R. S. Schwartz, *et al.* (1994). "Three-year follow-up of 100 angiography/electron beam CT patients (Abstract 20, Oct 1994)." American Journal of Cardiac Imaging 8(4 Suppl 1): 9.
55. Kaufmann, R. B., P. F. Sheedy, 2nd, *et al.* (1995). "Quantity of coronary artery calcium detected by electron beam computed tomography in asymptomatic subjects and angiographically studied patients." Mayo Clin Proc 70(3): 223-32.
56. Kennedy (1995). "Coronary calcification by ultrafast CT is an independent predictor of obstructive coronary artery disease: A multivariate risk factor analysis." J Am Coll Card: 387A.
57. Kennedy, J., R. Shavelle, *et al.* (1998). "Coronary calcium and standard risk factors in symptomatic patients referred for coronary angiography." Am Heart J 135(4): 696-702.
58. Kent, S. M., L. C. Coyle, *et al.* (2004). "Marked low-density lipoprotein cholesterol reduction below current national cholesterol education program targets provides the greatest reduction in carotid atherosclerosis." Clin Cardiol 27(1): 17-21.
59. Kondos, G. T., J. A. Hoff, *et al.* (2003). "Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults." Circulation 107(20): 2571-6.
60. Lamont, D. H., M. J. Budoff, *et al.* (2002). "Coronary calcium scanning adds incremental value to patients with positive stress tests." Am Heart J 143(5): 861-7.
61. Laudon, D. A., L. F. Vukov, *et al.* (1999). "Use of electron-beam computed tomography in the evaluation of chest pain patients in the emergency department [see comments]." Ann Emerg Med 33(1): 15-21.
62. Liao, Y., D. L. McGee, *et al.* (1999). "How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts." Am Heart J 137(5): 837-45.
63. Lu, B., N. Zhuang, *et al.* (2002). "EKG-triggered CT data acquisition to reduce variability in coronary arterial calcium score." Radiology 224(3): 838-44.
64. Mao, S., H. Bakhsheshi, *et al.* (2001). "Effect of electrocardiogram triggering on reproducibility of coronary artery calcium scoring." Radiology 220(3): 707-11.
65. Mao, S., M. J. Budoff, *et al.* (2001). "Improved reproducibility of coronary artery calcium scoring by electron beam tomography with a new electrocardiographic trigger method." Invest Radiol 36(7): 363-7.
66. Mao, S., J. Child, *et al.* (2003). "Sensitivity to detect small coronary artery calcium lesions with varying slice thickness using electron beam tomography." Invest Radiol 38(3): 183-7.
67. Mautner, G. C., S. L. Mautner, *et al.* (1994). "Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation." Radiology 192(3): 619-23.
68. Mitka, M. (2004). "Standards set for CT calcium screening but its clinical value remains unclear." Jama 291(4): 408-11.

69. Mueller, C., A. Scholer, *et al.* (2004). "Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea." N Engl J Med 350(7): 647-54.
70. Nissen, S. E., E. M. Tuzcu, *et al.* (2004). "Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial." Jama 291(9): 1071-80.
71. Nissen, S. E., E. M. Tuzcu, *et al.* (2005). "Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease." N Engl J Med 352(1): 29-38.
72. O'Malley, P., A. J. Taylor, *et al.* (2000). "Prognostic value of coronary electron-beam computed tomography for coronary heart disease events in asymptomatic populations." Am J Cardiol 85(8): 945-8.
73. O'Malley, P. G., I. M. Feuerstein, *et al.* (2003). "Impact of electron beam tomography, with or without case management, on motivation, behavioral change, and cardiovascular risk profile: a randomized controlled trial." Jama 289(17): 2215-23.
74. Pepe, M. S., H. Janes, *et al.* (2004). "Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker." Am J Epidemiol 159(9): 882-90.
75. Pletcher, M. J., J. A. Tice, *et al.* (2004). "Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis." Arch Intern Med 164(12): 1285-92.
76. Pletcher, M. J., J. A. Tice, *et al.* (2004). "What does my patient's coronary artery calcium score mean? Combining information from the coronary artery calcium score with information from conventional risk factors to estimate coronary heart disease risk." BMC Med 2(1): 31.
77. Qu, W., T. T. Le, *et al.* (2003). "Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects." Diabetes Care 26(3): 905-10.
78. Raggi, P. (2001). "Coronary calcium on electron beam tomography imaging as a surrogate marker of coronary artery disease." Am J Cardiol(87(suppl)): 27A-34A.
79. Raggi, P., B. Cooil, *et al.* (2001). "Use of electron beam tomography data to develop models for prediction of hard coronary events." Am Heart J 141(3): 375-382.
80. Raggi, P., L. J. Shaw, *et al.* (2004). "Prognostic value of coronary artery calcium screening in subjects with and without diabetes." J Am Coll Cardiol 43(9): 1663-9.
81. Redberg, R. F. and L. J. Shaw (2002). "A review of electron beam computed tomography: Implications for coronary artery disease screening." Prev Cardiol 5(2): 71-78.
82. Reddy, G. P., D. M. Chernoff, *et al.* (1998). "Coronary artery stenoses: assessment with contrast-enhanced electron-beam CT and axial reconstructions." Radiology 208(1): 167-72.
83. Ridker, P. M., C. P. Cannon, *et al.* (2005). "C-reactive protein levels and outcomes after statin therapy." N Engl J Med 352(1): 20-8.
84. Rumberger, J. A., P. F. Sheedy, *et al.* (1997). "Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis." J Am Coll Cardiol 29(7): 1542-8.
85. Rumberger, J. A., P. F. I. Sheedy, *et al.* (1995). "Coronary calcium, as determined by electron beam computed tomography, and coronary disease on arteriogram. Effect of patient's sex on diagnosis." Circulation 91(5): 2995-2996.

86. Rumberger, J. A., D. B. Simons, *et al.* (1995). "Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study." Circulation 92(8): 2157-62.
87. Sangiorgi, G., J. A. Rumberger, *et al.* (1998). "Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology." J Am Coll Cardiol 31(1): 126-33.
88. Schmermund, A., D. Baumgart, *et al.* (1998). "Measuring the effect of risk factors on coronary atherosclerosis: coronary calcium score versus angiographic disease severity." J Am Coll Cardiol 31(6): 1267-73.
89. Schmermund, A., D. Baumgart, *et al.* (1997). "Coronary artery calcium in acute coronary syndromes: a comparative study of electron-beam computed tomography, coronary angiography, and intracoronary ultrasound in survivors of acute myocardial infarction and unstable angina." Circulation 96(5): 1461-9.
90. Schmermund, A., A. E. Denktas, *et al.* (1999). "Independent and incremental value of coronary artery calcium for predicting the extent of angiographic coronary artery disease: comparison with cardiac risk factors and radionuclide perfusion imaging." J Am Coll Cardiol 34(3): 777-86.
91. Schmermund, A., A. Stang, *et al.* (2004). "Prognostic value of electron-beam computed tomography-derived coronary calcium scores compared with clinical parameters in patients evaluated for coronary artery disease." Z Kardiol 93(9): 696-705.
92. Sharples, E. J., D. Pereira, *et al.* (2004). "Coronary artery calcification measured with electron-beam computerized tomography correlates poorly with coronary artery angiography in dialysis patients." Am J Kidney Dis 43(2): 313-9.
93. Shaw, L. J., P. Raggi, *et al.* (2003). "Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality." Radiology 228(3): 826-33.
94. Shields, J. P., C. H. Mielke, Jr., *et al.* (1995). "Reliability of electron beam computed tomography to detect coronary artery calcification." Am J Card Imaging 9(2): 62-6.
95. Simons, D. B., R. S. Schwartz, *et al.* (1992). "Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study." J Am Coll Cardiol 20(5): 1118-26.
96. Tanenbaum, S. R., G. T. Kondos, *et al.* (1989). "Detection of calcific deposits in coronary arteries by ultrafast computed tomography and correlation with angiography." Am J Cardiol 63(12): 870-2.
97. Thomsen, T. F., D. McGee, *et al.* (2002). "A cross-validation of risk-scores for coronary heart disease mortality based on data from the Glostrup Population Studies and Framingham Heart Study." Int J Epidemiol 31(4): 817-22.
98. Wang, S., R. C. Detrano, *et al.* (1996). "Detection of coronary calcification with electron-beam computed tomography: evaluation of interexamination reproducibility and comparison of three image-acquisition protocols." Am Heart J 132(3): 550-8.
99. Wilson, P. W., R. B. D'Agostino, *et al.* (1998). "Prediction of coronary heart disease using risk factor categories." Circulation 97(18): 1837-47.
100. Wong, N. D., J. C. Hsu, *et al.* (2000). "Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events." Am J Cardiol 86(5): 495-8.

101. Wong, N. D., M. Kawakubo, *et al.* (2004). "Relation of coronary calcium progression and control of lipids according to National Cholesterol Education Program guidelines." Am J Cardiol 94(4): 431-6.
102. Yaghoubi, S., W. Tang, *et al.* (1995). "Offline assessment of atherosclerotic coronary calcium from electron beam tomograms." Am J Card Imaging 9(4): 231-6.
103. Yang, T., T. M. Doherty, *et al.* (1999). "Alcohol consumption, coronary calcium, and coronary heart disease events." Am J Cardiol 84(7): 802-6.
104. Yao, Z., X. J. Liu, *et al.* (1997). "A comparison of 99mTc-MIBI myocardial SPET with electron beam computed tomography in the assessment of coronary artery disease." Eur J Nucl Med 24(9): 1115-20.
105. Yao, Z. M., W. Li, *et al.* (2004). "Comparison of (99mTc-methoxyisobutylisonitrile myocardial single-photon emission computed tomography and electron beam computed tomography for detecting coronary artery disease in patients with no myocardial infarction." Chin Med J (Engl) 117(5): 700-5.