ABSTRACT

- **Objective:** To summarize the known data about coronary artery calcium (CAC) scoring and event prediction with electron beam tomography and spiral computed tomography.
- **Methods:** Review of the literature, including MEDLINE and abstracts from recent radiology and cardiology meetings.
- **Results:** The predictive ability of CAC for future coronary events was clearly demonstrated in several studies. Furthermore, benefit was seen with regards to patient compliance.
- **Conclusion:** CAC scoring is a well validated risk assessment tool and represents a major advance in screening for coronary artery disease. Cardiologists and primary care physicians should be educated on the ways to incorporate this screening tool into clinical practice. Additionally, more research must be done in the future regarding CAC progression and the impact of our various treatments for coronary artery disease.

Although the burden of cardiovascular disease has been decreasing over the last few years in the Western world, over 650,000 asymptomatic patients with no known coronary artery disease present with acute coronary events annually [1]. These patients demonstrate a shortcoming in our current approach to prevention. As is shown time and time again, the first presentation of these patients is often a life-ending event. Although great strides have been made in primary prevention, enormous benefit would be seen from earlier detection of asymptomatic cardiovascular disease.

Previous attempts at screening were primarily directed at finding advanced luminal obstruction (e.g., exercise treadmill testing, stress nuclear testing, stress echocardiography). It has since been demonstrated that a vast majority of myocardial infarctions occur at sites of nonobstructive plaque [2]. Coronary occlusion and myocardial infarction most frequently evolve from mild to moderate stenoses. These minimal stenoses can rupture, causing death or myocardial infarction in the absence of an advanced (highly stenotic) lesion in the coronary tree. Furthermore, research over the past decade has demonstrated that luminal obstruction is not the greatest predictor of cardiac events. Studies of patients dying from either acute myocardial infarction or sudden cardiac death have also demonstrated that the extent of coronary atherosclerosis, rather than the severity of stenosis, is the most important predictor [3,4]. Thus, the need to measure coronary plaque burden, rather than stenosis severity (as seen on cardiac catheterization), has become paramount in risk stratification.

**CORONARY ARTERY CALCIFICATION AND PATHOPHYSIOLOGY**

Coronary artery calcification (CAC) is pathognomonic for coronary artery atherosclerosis, as this is the only vascular disease that causes calcification of coronary arteries [5,6]. Histopathological and intravascular ultrasound studies have demonstrated the close correlation between plaque burden and CAC [6-11]. It was shown by Rumberger et al that the total area of CAC correlates in a linear fashion with total area of coronary artery plaque on a segmental, individual, and whole coronary artery system basis. This group also demonstrated that coronary calcium generally comprises about 20% of total plaque size [12].

Atherogenesis begins with lipid accumulation, cell proliferation, and extracellular matrix synthesis. These atherosclerotic plaques are associated with circulating proteins normally associated with bone remodeling, and these proteins are believed to regulate the accumulation of the hydroxyapatite form of calcium phosphate in these lesions.
Whether CAC is a result of the ongoing inflammation associated with plaque formation or an attempt to repair damage to the vascular wall is not clearly understood. It is also unknown whether CAC is a dynamic phenomenon, like the ongoing formation and degradation of bone tissue.

Although calcification is ubiquitous in complex coronary atherosclerotic plaques, it is unknown if calcium is more than just an innocent bystander. It has been shown that it portends an increased risk of plaque rupture and thrombosis [13]. Furthermore, it has been demonstrated that soft plaque with points of weakness adjacent to an area of calcification predispose the plaque to rupture [14,15]. However, as the calcific and fibrotic plaque lesions are much stiffer than the softer cellular lesions, calcification may actually be an attempt by the arterial walls to stabilize themselves and thereby minimize the risk of plaque rupture. Thus, it may be that early or moderate arcs of calcification render a plaque more prone to rupture, whereas extensive concentric calcification (seen particularly in the very elderly) may render a plaque less likely to rupture. Regardless of the ongoing debate as to the exact composition of the “vulnerable plaque,” CAC is almost always ubiquitous in patients who suffer cardiac events.

IMAGING

Until recently, electron beam tomography (EBT) was the principle method for acquiring the images used for calcium scoring. In fact, most of the data substantiating the importance of calcium scoring was acquired through EBT. Multidetector computed tomography (MDCT) is a newer, widely used imaging technology that will likely completely replace EBT for calcium scoring in the near future.

Electron Beam Tomography

EBT cardiac imaging involves obtaining thin slices (each 3 mm) of the heart and coronary arteries to evaluate for CAC. Usually 30 to 40 axial images are obtained to include the full length of the myocardium. The entire coronary artery tree is imaged during a single 20- to 30-second breathhold. Rapid image acquisition (100 msec) prevents image blurring and allows accurate visualization of very small calcium deposits in the coronary arteries. The calcific deposits in the arterial walls demonstrate a high attenuation compared to the surrounding soft tissue, and this permits the easy identification of CAC without injection of contrast medium.

Multidetector Computed Tomography

MDCT uses a rotating gantry with a special x-ray tube and a variable number of detectors to acquire images while a patient advances through on a moving table. MDCT is able to acquire 165–375-ms images in 0.5–3.0-mm intervals using prospective triggering if the heart rate is steady and < 60 bpm. To avoid coronary motion artifacts, image acquisition below 50 ms is needed, as the right coronary artery (RCA) exhibits translational motion of up to 60 mm/sec. The left anterior descending artery (LAD) and left circumflex artery (LCx) exhibit 20 to 40 mm/sec of translational motion. MDCT, therefore, is plagued by more motion artifacts than is EBCT.

The comparability of MDCT- and EBCT-derived CAC scores has been well validated by a number of studies involving more than 400 patients [16–19]. The most recent study between EBCT and 64-slice MDCT demonstrated that the inter-scan agreement for the presence of CAC was 99% [18]. There was a significant linear relationship between the scores from the 2 scanners and the inter-scanner variability was not significantly different. Multiple studies have further confirmed that 64-slice MDCT and EBCT were comparable for both Agatston and volumetric CAC scanning [19].

CLASSIFICATION

CAC scores show an uneven distribution in the general population. Previous and recent outcome studies led to the classification scheme proposed in the clinical expert consensus document of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) in 2007 [20]:

- 0 = no calcification
- > 0–100 = mild calcification
- > 100–400 = moderate calcification
- > 400–1000 = severe calcification
- > 1000 = extensive calcification

Modifications were used in other studies. In the first report from the Multi-Ethnic Study of Atherosclerosis (MESA) [21], a cut-point of 300 CAC was used to define high risk. For noncalcified plaques detected
by CT angiography, a highly reproducible method for quantification is not yet available and currently more qualitative instead of quantitative analyses are provided [22].

**PROGNOSTIC VALUE OF CAC SCORING**

The prognostic value of CAC scoring has been shown to be excellent in multiple large studies [23,24]. In 2000, Raggi et al [25] elegantly demonstrated a graded annualized event rate in a cohort of 632 asymptomatic patients followed for 32 months. Patients with 0 scores had an annualized event rate of 0.1%. Patients with scores of 1 to 99 had an event rate of 2.1%; scores of 100 to 400, an event rate of 4.1%; and scores > 400, an event rate of 4.8%. All positive CAC scores are associated with an annualized event rate of > 2.0%, which signifies a high-risk state (20% 10-year risk by Framingham) [20].

Shaw et al [26] showed that all-cause mortality increases proportionally with CAC score, even after adjustment for Framingham risk factors. In this retrospective study of 10,377 patients, Shaw and colleagues found that CAC scoring had superior outcome classification ability compared with Framingham risk assessment (area under the ROC curve 0.73 vs. 0.67; \( P < 0.001 \)). Even more impressive, after patients were stratified according to their Framingham risk, CAC scores were able to further stratify these patients. This additional risk stratification was particularly strong in the group of patients with intermediate Framingham risk scores. Finally, Shaw et al also showed that the relative risk of death for a CAC score of 10 is comparable to the relative mortality risk of diabetes, smoking, and hypertension [26].

In a cohort of 5635 asymptomatic patients, Kondos et al [27] showed the relative risk for cardiac events with a positive CAC score is 10.5, compared with only 1.98 for diabetes and 1.4 for smoking.

The St. Francis Heart Study, a prospective study of 5585 predominantly moderate- to moderately high-risk asymptomatic patients, confirmed previous study results by showing an increasing event rate with increasing CAC scores [28]. Moreover, CAC scores > 100 were associated with relative risks from 12- to 32-fold, which represented an absolute event rate of > 2% per year. Sixty-seven percent of the patients in this study who were classified as intermediate risk by Framingham were reclassified using CAC tertiles, with outcomes confirmed by the monitoring of cardiac events in the study. Several newer population-based prognostic studies will be discussed below.

**CALCIFICATION AND CARDIAC RISK IN THE ASYMPTOMATIC COHORT**

The main purpose of obtaining a CAC score is to detect subclinical atherosclerosis. In the 2010 ACC/AHA guidelines for assessment of cardiovascular risk in asymptomatic patients, measurement of CAC score to assess cardiovascular risk in asymptomatic patients at intermediate risk (10% to 20% 10-year risk based on Framingham risk score) is a Class IIa recommendation. Measurement of CAC score in asymptomatic patients at low-intermediate risk (6% to 10% 10-year risk) is a Class IIb recommendation. CAC evaluation is not recommended for low-risk patients (< 6% 10-year risk). In the ACC/SCCT/ACR/AHA/ASE/ASNC/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography, CAC scoring was deemed appropriate in low-risk asymptomatic patients with no known CAD if they have a family history of premature CAD. CAC scoring in asymptomatic patients with no history of CAD who were at intermediate risk was also deemed appropriate.

It remains to be seen if in the future CAC scoring may be recommended in low-risk patients. In a cohort of 222 young patients presenting with myocardial infarction as the first sign of coronary artery disease, Akosah et al showed that 70% were in lower-risk categories [29]. Schmermund et al and Pohle et al indicated that 95% of acute myocardial infarction patients would have been identified with a positive CAC irrespective of age [30,31]. Of note, the 2006 SHAPE guidelines recommend CAC scoring (or measurement of carotid intima-media thickening) in all but the very lowest-risk asymptomatic men older than 45 years and women older than 55 years, with treatment based on CAC score [32].

Finally, the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults says CAC scoring is reasonable for asymptomatic diabetic persons aged 40 years and older (Class IIa recommendation). It also emphasizes that stress myocardial perfusion imaging may be considered in asymptomatic diabetic persons considered to be at high risk for CAD, including if CAC score is > 400 (Class IIb recommendation) [33].

Calcium scores of 0 to 100 are indicative of low plaque burden and low event rates. In the Heinz Nixdorf Recall study, 30% of men and 70% of women were
in this score range. Event rates were only 0.31% per year in men and 0.12% in women, representing a low risk cohort. As these patients were at low risk, lifestyle changes and nonpharmacologic interventions were recommended as treatment [34].

LOW-RISK ASYMPTOMATIC SUBJECTS AND PROGRESSION OF CAC

The CAC progression rate ranges from 15% to 25% per year. In a group with a mean age of 59 years, the mean annual relative progression of CAC was 51% and the median progression 32%. Other authors found a mean annual increase in the range of 24% to 33%. Based on the analysis of accuracy and reproducibility, a limit of ≥15% CAC or an increase in square root-transformed CAC volume ≥2.5 mm$^3$ can be used to differentiate a random from nonrandom change [35–37].

During follow-up, CAC did not change differently related to the coronary segments, but the changes were predicted by the typical predilection site of coronary atherosclerosis in the proximal part of the left coronary artery. Progression was evenly distributed in the right coronary artery, whereas it was mainly found in the proximal part of the LAD and LCx [35–37].

The mean CAC increase is dependent on the baseline CAC score. Thus, for a CAC score of 1–30, the mean increase is 3.1%; for CAC > 30–100, 26.1%; for CAC > 100–400, 28.9%; and for CAC > 400, 109.7%, resulting in annual percentage changes of 57%, 49%, 32%, and 15%. Related to the 75th percentile level, the percentage CAC progression is 62% for the LAD, 31% for the RCA, 31% for the left main stem, and 29% for the LCx, with lower rates for the distal RCA and LAD.

In the group with small amounts of CAC (1–10), the positive CAC score was indicative of progression in 80% of patients during a mean follow-up time of 1.9 ± 1.1 years. The risk of progression was predicted by male sex, hyperlipidemia, smoking, and baseline CAC scores. The P value was significant for hypertension, diabetes, older age, and low degree of calcium (below 100). The strongest predictors were found to be diabetes and smoking [35–37].

It has been demonstrated that over a period of 10 years, the CAC score increases according to the percentile distribution determined at baseline. Despite intense lifestyle changes and medical treatment with the effective lowering of low-density lipoprotein (LDL) cholesterol, CAC progression could not be attenuated. The natural history (increase of the CAC score) follows the population-based percentile distribution of CAC corrected for age and sex. This means on one hand that the established CAC percentile distribution is valid, and on the other hand that “vascular age” is predetermined and at the moment cannot be attenuated or even decreased.

INTERMEDIATE-RISK INDIVIDUALS AND CAC

CAC scanning is most effective in intermediate-risk asymptomatic patients, and imaging in these patients is a Class IIa recommendation in the ACCF/AHA guidelines for assessment of risk in asymptomatic adults. This recommendation is based on the MESA study, which demonstrated significant improvements in risk prediction when CAC scoring is added to traditional risk factors over a mean follow-up time of 5.8 years [38]. The study endpoints included myocardial infarction, death from CAD, definite or probable angina followed by coronary revascularization, and definite angina not followed by coronary revascularization. Five-year estimated incident risk was calculated for each participant and categorized as 0 to <3% (low), 3% to <10% (medium), and ≥10% (high).

Among 5878 participants, there were 209 coronary events, with 96 myocardial infarctions, 14 deaths, 12 resuscitated cardiac arrests, and 87 definite or probable or definite angina cases. When CAC was added to the model, 5.1% of patients were reclassified to high risk, and 16.4% of these experienced events. Conversely, 12.7% were reclassified to low risk, and 2.3% of these experienced events. In the intermediate-risk cohort, 16% were reclassified to high-risk and 39% to low-risk, with a net reclassification improvement of 55%. The improvement in risk classification was more balanced between events and no events for the intermediate-risk cohort than for the total cohort. Events occurred in 41% of intermediate-risk patients reclassified to high risk and in 13% of those reclassified to low risk.

The St. Francis Heart study, which used coronary revascularization, nonhemorrhagic stroke, vascular surgery, and myocardial infarction as the endpoint, showed in the intermediate-risk asymptomatic group that those with a low CAC had an extrapolated 10-year event rate of less than 10%, and for those with high CAC, an event rate of ≥20% [28].

In summary, independent prospective studies have demonstrated a high value of CAC in subjects with intermediate risk.
**HIGH-RISK INDIVIDUALS AND CAC**

As mentioned, in the MESA study, 5.1% of individuals were reclassified on the basis of their CAC score to high risk, and among those at high risk, 16.4% experienced events. In those reclassified to low risk from high risk, 6.3% experienced events [38].

In the Heinz Nixdorf Recall study, CAC in the high-risk category yielded a reclassification to low risk in 44% of men and 47% of women. The observed risk showed an event rate of 3.5% and 4.4% projected to a 10-year risk [34].

In the Rotterdam study, reclassification in the high-risk category occurred in 33% of men and 39% of women, with a similar percentage classified as high-risk in both sexes. For reclassified men, 5% moved to the low-risk group and 80% to the intermediate-risk group, whereas women 3% moved to the low-risk and 36% to the intermediate-risk group [39]. The overall reclassification percentage in the high-risk group was 34%, comparable to that reported in the MESA study.

In the St. Francis Heart study, the lower category of CAC was accompanied by a lower annual event rate which was, however, still > 20% 10-year risk. Additionally, CAC scores > 100 were associated with relative risks from 12 to 32 and were a secondary prevention equivalent with an event rate > 2% per year [28].

Currently, there is no overall agreement that patients in high-risk categories with low CAC scores who are reclassified to low risk can be treated differently compared with those at high risk. The MESA study demonstrated that individuals who were reclassified from high to low risk experienced an event rate that was higher than predicted. High-risk individuals should be treated regardless of the CAC value unless prospective randomized studies demonstrate that such a differentiation for risk stratification is safe. However, in those with excessive CAC (score > 1000), the reported event rates and the positive predictive accuracy seem to be so high that in these subjects, additional diagnostic workup may be needed in order to detect signs of myocardial ischemia.

**SYMPTOMATIC PATIENTS**

It is well established that symptomatic patients with CAC are also more likely to have events. The NICE guidelines, developed by the National Clinical Guideline Centre for Acute and Chronic Conditions in the United Kingdom, recommends CAC scoring as the first diagnostic intervention in patients with chest pain without known CAD who have a 10% to 29% likelihood of having CAD. NICE further recommends finding noncardiac causes of chest pain in those patients whose CAC score is 0. If the CAC score is 1 to 400, CT coronary angiography is recommended, and if the CAC score is > 400, invasive angiography is recommended. In a recent meta-analysis of 3924 symptomatic patients with 3.5 years of follow-up, patients with a positive CAC score had an event rate of 2.6% per year compared with only 0.5% per year in those with no CAC [40].

Interestingly, in a cohort of 1031 patients that presented to the emergency room with chest pain and had a nonischemic electrocardiogram, normal initial troponin, and no history of CAD, Nabi et al showed that a CAC score of 0 predicted a normal nuclear stress test and excellent short-term outcome [41]. In a cohort of 118 patients, Lamont et al showed that the absence of CAC in patients with false-positive treadmill stress tests had a negative predictive value of 90% [42]. This suggests that CAC scoring could potentially be used to rule out CAD in low probability patients with abnormal stress tests.

Despite these guidelines and studies, the practice of using calcium scoring in the workup of symptomatic patients is currently not part of the recommended algorithm in the United States.

**TREATMENT**

After CAC scoring, clinicians must make management decisions based on the results. Based on prognostic data from the St. Francis Heart Study, a CAC score > 100 is a CAD equivalent. In this same study, CAC scores > 400 or > 90th percentile are associated with a particularly high annual event risk (4.8% and 6.5%), and these patients may be good candidates for a more aggressive approach [28].

**Randomized Trials**

Two randomized trials have been performed showing benefit to undergoing CAC scanning and subsequent treatment. The St. Francis study was a double-blind, placebo-controlled, randomized clinical trial that evaluated treatment with atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha-tocopherol) 1000 U daily versus matching placebos in 1005 asymptomatic, apparently healthy men and women 50 to 70 years of age with coronary calcium scores at or above the 80th percentile for age and gender. Treatment re-
duced LDL cholesterol by 39.1% to 43.4% ($P < 0.001$) and triglycerides by 11.2% to 17.0% ($P < 0.02$), while reducing clinical endpoints by 30% (6.9% vs. 9.9%). Event rates were related to baseline calcium score, and even greater event reduction took place in a subgroup of participants with baseline calcium scores > 400 (8.7% vs. 15.0%; $P = 0.046$ [42% reduction]) [28].

The EISNER study assigned 2137 patients to groups that either did undergo CAC scanning or did not undergo CAC scanning before risk factor counseling. Compared with the no-scan group, the scan group showed a net favorable change in systolic blood pressure ($P = 0.02$), LDL cholesterol ($P = 0.04$), and waist circumference for those with increased abdominal girth ($P = 0.01$), and tendency to weight loss among overweight subjects ($P = 0.07$). While there was a mean rise in Framingham risk score in the no-scan group, the score remained static in the scan group ($0.7 \pm 5.1$ vs. $0.002 \pm 4.9$; $P = 0.003$). Within the scan group, increasing baseline CAC score was associated with a dose-response improvement in systolic and diastolic blood pressure ($P < 0.001$), total cholesterol ($P < 0.001$), LDL cholesterol ($P < 0.001$), triglycerides ($P < 0.001$), weight ($P < 0.001$), and Framingham risk score ($P < 0.003$). Downstream medical testing and costs in the scan group were comparable with those of the no-scan group, balanced by lower and higher resource utilization for subjects with normal CAC scans and CAC scores > 400, respectively [43].

**Guidelines**

Based on the American Heart Association's Prevention Conference V and the most recent National Cholesterol Education Program recommendations, Hecht recommends that patients with a CAC score of 0 should be treated as a low-risk Framingham equivalent, 1 to 10 (as long as < 75th percentile for age and gender) as moderate risk, 11 to 100 (as long as < 75th percentile) as moderately high risk, 101 to 400 or CAC > 75th percentile as high risk/CAD equivalent, and > 400 or > 90th percentile as highest risk [44].

Calcium scores > 100 are associated with a high rate of incident CHD events over the ensuing 3 to 5 years, so persons with calcium scores in this range are a suitable target group for stringent lifestyle recommendations, selection of evidence-based therapeutic agents to reduce cardiovascular risk, and a focus on adherence to medical recommendations.

**Effect on Adherence**

Interestingly, there have been numerous studies showing that CAC scoring improves patient compliance with therapeutic interventions. In a study of 505 asymptomatic patients, Kalia et al showed that over visualizing their CAC scan, 90% of patients with CAC > 400 complied with their statin therapy, compared with 75% for CAC 100 to 399, and only 44% for 0 CAC scores [45]. Similarly, in a study of 980 asymptomatic patients, Orakzai et al showed that ASA initiation, dietary changes, and exercise were much better in patients with CAC > 400 (61%, 67%, 56%) than in patients with 0 CAC (29%, 34%, 44%) [46]. In the Prospective Army Coronary Calcium study, among 1640 participants followed for 6 years, use of statin and aspirin was independently 3.5- and 3-fold greater in those with any coronary calcium measurement over 6 years, suggesting management changes following calcium screening in community-based cohorts [47]. Multiple logistic regression analysis, controlling for National Cholesterol Education Program (NCEP) risk variables, showed that CAC was independently associated with a significantly higher likelihood of use of statin, aspirin, or both (odds ratio [OR] 6.97; 95% confidence interval [CI] 4.81–10.10; $P < 0.001$). The OR for aspirin and statin use based on NCEP risk factors alone was dramatically lower (OR, 1.52; 95% CI, 1.27–1.82; $P < 0.001$).

Recent data from MESA suggest similar effects of CAC visualization on lipid-lowering and aspirin therapy [48].

**CONCLUSION**

CAC scoring is a well-validated risk assessment tool and represents a major advance in screening for coronary artery disease. CAC scoring has been shown to be superior for predicting outcomes compared with conventional risk factors. Cardiologists and primary care physicians must be educated on how to incorporate this screening tool into clinical practice. Additionally, more research must be done in the future regarding CAC progression and the impact of our various treatments for coronary artery disease.

Corresponding author: Matthew J. Budoff, MD, Div of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA, 1124 West Carson St, Torrance, CA, mbudoff@labiomed.org.

**REFERENCES**


