Over 600,000 myocardial infarctions (MIs) occur yearly in the United States, and more than half of patients whose MI presents as sudden cardiac death have no antecedent symptoms. Furthermore, men >40 years of age have an almost 50% lifetime risk of developing coronary heart disease (CHD) and women of the same age have a risk of approximately 1 in 3. The Framingham Risk Score (FRS) is the most commonly used CHD risk prediction model and is an integral component of cardiovascular screening and lipid-lowering guidelines. Although the FRS provides a reasonable estimation of risk in certain subgroups, it was derived from a relatively homogenous population in an era when pharmacological treatment options and use were limited. Furthermore, chronologic age is the dominant risk factor in the FRS equation, although it is a poor surrogate for atherosclerotic burden and limits the personalization of risk estimates. As a result, the majority of MI occurs in individuals classified as low or moderate risk who therefore do not meet the Adult Treatment Panel (ATP) III criteria for statin therapy.

To improve risk estimation, recent research has focused on identifying novel risk predictors. However, when they are added to existing risk prediction models, there is little improvement in CHD risk stratification. As a result, there is an increasing interest in selectively using atherosclerosis imaging to increase the accuracy of traditional risk prediction models in persons broadly classified as intermediate risk. Coronary artery calcium (CAC), measured using noncontrast cardiac CT, is a relatively low-cost and noninvasive imaging technique. CAC testing provides an individualized measure of atherosclerotic burden that integrates an individual’s cumulative lifetime risk factor exposure that cannot be obtained from serum markers.

The use of CAC screening in select patients is included in the American College of Cardiology Foundation/American Heart Association guidelines and adoption of CAC as part of a primary prevention strategy has garnered considerable interest. As such, this is an ideal time to reflect on the current state of literature supporting CAC. Although the risk prediction data categorically demonstrate strong associations, most studies investigating CAC are of an observational cohort design and cannot definitively prove an independent impact of CAC screening on management decisions, patient behavior, and cardiovascular outcomes.

In this article, we briefly summarize the existing evidence for the use of CAC scanning in primary prevention and then shift to our primary aim of investigating the randomized evidence of the impact of CAC on lifestyle modification, risk factors, and downstream testing. We provide an updated meta-analysis and highlight the paucity of randomized data. Finally, we discuss the complex reasons for this literature gap and delineate questions that must be answered by future trials.

The Power of CAC
CAC provides a quantitative and reproducible measurement of the calcified portion of coronary plaque that is nearly pathognomonic for coronary atherosclerosis and strongly predictive of CHD. The Rotterdam Heart Study followed 1795 asymptomatic individuals with a mean age of 71 years. Compared with individuals with little to no coronary calcium, individuals with extensive calcification, CAC >1000 Agatston units, were >8 times as likely to develop incident MI or CHD mortality. Taylor et al demonstrated analogous results in a younger patient population with a mean age of 43 years in which there was an almost 12-fold increased risk for sudden cardiac death, MI, or unstable angina in those subjects with any coronary calcium compared with none. The ability of CAC score to predict CHD risk has also been observed between sexes, ethnic groups, and among those with only a small amount of calcification. The Multi-Ethnic Study of Atherosclerosis (MESA) cohort measured CAC in a diverse sample of approximately 6800 asymptomatic men and women with no history of a CHD event. Individuals with even mild...
calcification, CAC 1 to 100, had a significantly increased risk of CHD compared with those with no calcification (hazard ratio, 3.61; 95% confidence interval [CI], 1.9–6.7). Among individuals with normal low-density lipoprotein cholesterol in MESA, the presence of any CAC was still strongly associated with an increased risk of CHD (hazard ratio, 6.65; 95% CI, 2.99–14.78). Conversely, an elevated high sensitivity C-reactive protein, the common competitor of CAC for added risk prediction, did not predict CHD events in MESA (hazard ratio, 0.98; 95% CI, 0.62–1.57).

The Power of Zero
A CAC scan with zero coronary calcification stands alone as the most powerful negative risk factor for CHD and restratifies a significant proportion of individuals from an intermediate- to a low-risk group in which conservative treatment strategies can be used. A recent meta-analysis incorporated results from 13 studies of 71,595 asymptomatic subjects with a mean follow-up of 4 years. Those with a CAC of 0 had a relative risk of 0.15 (95% CI, 0.11–0.21) for developing a cardiovascular event compared with individuals with any CAC.

In a different cohort, Blaha et al reported on 44,052 asymptomatic patients in which a CAC of 0 was associated with <1% 10-year risk of all-cause mortality, indicating an excellent long-term prognosis. Even among patients with multiple conventional risk factors, a CAC of 0 is associated with a low absolute number of events. The strong negative risk predictive value of a CAC of 0 has also been demonstrated across a diverse range of patient populations, including women, diabetics, and the elderly.

The Power of Addition
CAC is an established independent risk factor for CHD, but ultimately the clinical use of any new CHD risk marker lies in its ability to improve on the current risk prediction models. The incremental value of CAC was investigated in MESA using a model adding CAC to the Framingham risk factors demonstrating an increase in the C-statistic from 0.77 to 0.82 (P<0.001). This change represents an improvement from a C-statistic with an acceptable discriminative value (0.7–0.8) to an excellent discriminative value (0.8–0.9).

In the same study, this combined model was examined within different ethnic groups and the addition of CAC to the Framingham risk factors increased the C-statistic by as much as 0.11. By comparison, other individual novel risk factors have shown little incremental value when integrated into the FRS. For example, Melander et al incorporated several novel serum biomarkers into a conventional risk model and found no improvement with a C-statistic of 0.009 (P=0.08).

To further investigate CAC’s additional discriminative power, Polonsky et al investigated the Net Reclassification Index of CAC in MESA. Net Reclassification Index determines the frequency of appropriate versus inappropriate reclassification (defined as whether or not an event occurs) from one risk group to another. When CAC was added to the MESA-recalibrated FRS, there was a Net Reclassification Index of 0.25 (95% CI, 0.16–0.34) for the entire study group and a Net Reclassification Index of 0.55 (95% CI, 0.41–0.69) for the intermediate-risk group. Therefore, among intermediate-risk participants, 55% were reclassified as either high risk (16%) or low risk (39%). Incorporating CAC into the FRS resulted in an additional 23% of patients who went on to develop CHD being reclassified from intermediate to high risk and an additional 13% who did not develop CHD during follow-up to be reclassified as low risk. These findings demonstrate the significant additional discriminative value of CAC and underscore the clinically use of this information.

The Impact of CAC Screening on Lifestyle Modification, Risk Factors, and Downstream Testing: A Meta-Analysis
Although requiring proof that a test improves outcomes is nearly unprecedented in cardiovascular medicine, this level of evidence may be required for routine use of CAC given the tremendous public health implications of worldwide CHD screening. At this time, there are few studies that have investigated the results from a CAC scan may impact clinical outcomes and they are predominantly observational.

For example, Wong et al reported on a group of 703 asymptomatic individuals who were primarily self-referred for CAC scanning. Those with any CAC were more likely to start aspirin (relative risk, 1.86; P<0.01) or a cholesterol-lowering medication (relative risk, 3.54; P=0.01) compared with those without CAC. A similar relationship was observed in a group of 1640 men with a mean age of 43 years. Those men with any CAC were >3 times as likely to use either aspirin (P<0.001) or a statin (P<0.001) and almost 7 times as likely to use both aspirin and a statin (P<0.001) in comparison to men without CAC. Orakzai et al followed 980 individuals for a mean of 3 years and found that those with a CAC score ≥400 were more likely to increase their amount of exercise (OR, 2.03; 95% CI, 1.26–3.27) and modify their diet (OR, 2.66; 95% CI, 1.63–4.32) compared with individuals without CAC.

Although these results are suggestive of true clinical reclassification, there are important limitations. These studies did not have a control group without CAC testing; therefore, no comparison can be made with individuals who received risk assessment in the usual fashion. There was no long-term follow-up for clinical events. Additionally, the subjects in these groups were either self-selected or referred by their primary care physician to undergo CAC scanning and may be more highly motivated than the general population.

Hackam et al investigated the downstream effect of imaging on behavior, but this meta-analysis included trials with a variety of cardiac imaging techniques. Since then, results from EISNER, the largest randomized controlled trial yet to investigate the impact of CAC screening on CHD, were published. We performed an update to the meta-analysis reported by Hackam et al by conducting a thorough up-to-date literature review, incorporating the EISNER trial results, and only including trials using CAC.

We identified 4 trials with a total of 2490 participants, >75% of whom came from the EISNER trial (Table). The trials were published between 2003 and 2011 with follow-up time ranging from 1 to 4 years. Three of the trials reported a change in cardiovascular risk factors or FRS as their primary outcome. Obuchowski et al performed total-body CT in addition to CAC and the results were not stratified between...
the 2 imaging modalities. The number of participants in each trial varied from 50 to 1934. The trial conducted by Lederman et al36 was conducted exclusively among women and the other 3 trials consisted of at least 50% male participants.

All 4 trials collected data on smoking habits, with 3 of the trials reporting a nonsignificant increase in smoking cessation in the scan versus no-scan group; the pooled mean was 1.15 (95% CI, 0.77 to 1.71). Three trials reported results for body mass index and 2 for glycohemoglobin with nonsignificant pooled estimates of −0.05 kg/m² (95% CI, −0.16 to 0.06) and 0.04% (95% CI, −0.06 to 0.15), respectively, for the scan versus no-scan groups.

Change in blood pressure and cholesterol for the scan versus no-scan group was reported in 3 trials, with the exception of high-density lipoprotein, which was only available for 2 of the trials (Figure 1). The EISNER trial reported a significant reduction in systolic blood pressure, although the pooled estimate was −0.23 mmHg (95% CI, −2.25 to 2.71) for systolic blood pressure, −0.42 mmHg (95% CI, −1.18 to 0.35) for diastolic blood pressure, and −1.18 mg/dL (−5.50 to 3.14) for high-density lipoprotein. A significant reduction in low-density lipoprotein was noted in the EISNER trial, but the pooled estimate was 0.23 mg/dL (95% CI, −5.96 to 6.42).

Only the EISNER trial reported medication use according to CAC score.33 Rozanski et al reported that a higher CAC score was associated with a significant increase in the prescription of lipid-lowering medications (P < 0.001). In contrast, those with CAC = 0 were prescribed fewer lipid-lowering medications than the nonscan group (P = 0.02) and had a 25% reduction in their medication costs (P = 0.005).

Two studies investigated downstream testing with both reporting a nonsignificant increase in patients undergoing catheterization and angiography in the CAC scan group; pooled estimates were relative risk 1.17 (95% CI, 0.68 to 1.99) for angiography and relative risk 1.35 (95% CI, 0.69 to 2.63) for revascularization (Figure 2). In the EISNER trial, >60% of patients with CAC ≥ 400 had some form of downstream

Table. Characteristics of the 4 Included Trials Investigating the Impact of Coronary Artery Calcium Scanning on Cardiovascular Risk Factors and Downstream Testing

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Imaging Modality</th>
<th>Primary Outcome</th>
<th>No. of Participants</th>
<th>Age, Mean, y</th>
<th>Male, %</th>
<th>Follow-Up, y</th>
<th>Imaging Abnormality, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lederman et al, 200736</td>
<td>DHCT</td>
<td>CVD risk factors</td>
<td>56</td>
<td>65</td>
<td>0</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>O’Malley et al, 200334</td>
<td>EBT</td>
<td>10-y FRS event rate</td>
<td>450</td>
<td>42</td>
<td>79</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Obuchowski et al, 200735</td>
<td>Total body CT/MDCT</td>
<td>Incident clinical disease</td>
<td>50</td>
<td>55</td>
<td>50</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>Rozanski et al, 201133</td>
<td>EBT/MCT</td>
<td>CAD risk factors</td>
<td>1934</td>
<td>59</td>
<td>53</td>
<td>4</td>
<td>52</td>
</tr>
</tbody>
</table>

DHCT indicates double helical CT; EBT, electron beam tomography; MDCT, multidetector CT; MCT, multislice CT; CVD, cardiovascular disease; FRS, Framingham Risk Score; CAD, coronary artery disease; and N/A, not available.

*Defined as any abnormality.

Figure 1. Forest plot of the effect of coronary artery calcium screening on the mean change in blood pressure and cholesterol level.
stress testing versus approximately one fourth of those with CAC=0 ($P<0.001$). Those with CAC=0 had overall medical costs that were approximately 70% less than those incurred by individuals with a CAC $\geq 400$ ($P<0.001$).

Both the no-scan and scan group had a low absolute number of invasive cardiovascular procedures and there was no significant difference in medical costs between these groups with a median of $3649 spent for the no-scan group and $4053 for the scan group ($P=0.09$). Only the EISNER trial reported data on cardiovascular outcomes. Two participants in the no-scan group were diagnosed with MI versus 10 patients in the scan group ($P=0.36$). There were 3 cardiac deaths, 1 in the no-scan group and 2 in the scan group.

**Discussion**

Current primary prevention guidelines rely on the FRS to discriminate among low-, intermediate-, and high-risk individuals. Regrettably, a significant percentage of individuals classified as low risk still go on to develop CHD. An important reason for misclassification in conventional risk models is the use of age as a surrogate marker for atherosclerotic burden, which overlooks the considerable variation among individuals with similar levels of traditional risk factors. CAC is a unique risk predictor, because it provides an individualized measure of atherosclerotic burden, integrating risk exposure over a lifetime, which conventional risk models are unable to assess.

The most recent American College of Cardiology Foundation/American Heart Association guidelines give a Class IIa recommendation for the use of CAC as a reasonable procedure to aid in the risk assessment of patients with an intermediate 10-year cardiovascular risk. However, guidelines from other agencies vary considerably, mostly as a result of the limited evidence from randomized, controlled trials. This leaves the decision of whether or not to include CAC as part of a risk stratification protocol to the individual clinician’s judgment. CAC scanning does also have some small risks compared with serum markers. A CAC scan exposes an individual to approximately 1 mSv of radiation, which is comparable to a lumbar spine roentgenogram and much less than the 9- to 12-mSv dose from a typical nuclear myocardial perfusion scan. Incidental extracardiac findings may also be revealed by CAC scanning. The majority of these findings are pulmonary nodules of uncertain clinical significance, which are more likely to be found in older individuals and those with a history of smoking. However, only approximately 10% of these incidental findings necessitate further testing and observation.

Our meta-analysis highlights the paucity of randomized evidence linking CAC scanning to improved intermediate and hard outcomes in primary prevention. We found only 4 randomized controlled trials that have investigated the relationship between CAC and CHD risk factors, downstream resource use, or hard outcomes. Of these, 2 trials had sample sizes of approximately 50 participants, whereas the EISNER trial accounts for >75% of the total participants studied to date. In contrast, observational CAC studies have enrolled up to 44,000 participants.

Our meta-analysis, of course, has a number of limitations, the most significant being the small number of available trials and modest total number of participants. As a result there is inadequate power to draw meaningful conclusions, even after pooling the results. In addition, due to the relatively short follow-up, it was unfeasible for the majority of trials to investigate fatal and nonfatal MI in a primary prevention population in which the absolute event rate is expected to be low. The trial conducted by O’Malley et al consisted of relatively young and healthy volunteers largely classified as low risk by the FRS who were not in the risk group most likely to benefit from CAC screening. However, these limitations underscore our primary message: there remains a remarkable paucity of randomized data.

Defining the optimal use of CAC was identified in 2009 as a top 100 priority by the Institute of Medicine and future trials are urgently needed to determine the impact of CAC screening on lifestyle modification, risk factor modification, and downstream testing. These trials will need to be randomized with...
a control group in which treatment is based on conventional risk stratification methods compared with an intervention group in which conventional risk assessment and treatment are augmented with CAC.

However, a number of challenges must be addressed before these trials can be implemented. Such trials will require long-term follow up of individuals who have a low to intermediate 10-year risk of developing CHD. Using this lower risk population will necessitate very large sample sizes and enormous expense (likely supported by the National Institutes of Health/National Heart, Lung and Blood Institute) to be powered for hard CHD outcomes. Additionally, CAC screening is an increasingly low-cost and low-risk strategy. Therefore, some may consider it improper to withhold CAC screening for patients who would qualify as per the American Heart Association’s IIa recommendation. Others will argue that generic statins and aspirin cannot be withheld from patients deemed low risk by FRS but with a heavy burden of CAC. It must also be considered that many physicians already aggressively prescribe statin therapy outside of existing guidelines to intermediate-risk patients even without the use of CAC, which may significantly diminish the potential risk reduction of CAC screening.

To receive a Class I recommendation, a screening examination must demonstrate significant benefit with minimal or no harm. At present, randomized controlled trial evidence of a reduction in cardiovascular risk factors or hard outcomes likely represents the evidence threshold necessary to determine if a Class I recommendation is justified for any CHD screening tool. It is expected that the upcoming ATP IV guidelines will lower the threshold for instituting statin therapy. In light of this expected change, CAC trials that focus on individuals with a 5% to 10% 10-year risk will likely provide the most clinically meaningful results. However, over the typical 5-year follow-up of a trial, only a small proportion of these individuals will experience a hard CHD outcome and therefore even larger sample sizes will be required to investigate these outcomes.

This is an interesting crossroad in the field of cardiology, because there appears to be a raising of the bar regarding the prerequisite level of benefit before accepting strategies for CHD risk screening. It is interesting that no such randomized evidence for improvement in CVD risk factors or outcomes currently exists for the FRS, Systematic Coronary Risk Evaluation (SCORE), QRISK, any individual test such as serum cholesterol or high-sensitivity C-reactive protein, or global risk assessment in general.

It will be many years before the results of CAC trials are available, which in the interim provides little guidance to determine which intermediate-risk patients should receive CAC scanning for further risk stratification and treatment decisions. Given the significant challenges that must be overcome to conduct such a trial, it is uncertain whether or not it would even be funded. In fact, a proposal submitted by Greenland et al to perform a prospective randomized CAC trial has to date not received funding. Therefore, the use of nonrandomized data may take on greater importance. One approach to bridge the literature gap is through the use of propensity matched analyses as have been used to assess downstream outcomes in coronary CT angiography. These studies provide a higher level of evidence than observational cohorts and are inexpensive compared with randomized, controlled trials. Furthermore, if performed at high-volume imaging centers, they could readily accrue large numbers of participants. Rigorous randomized assessment of CAC, FRS, or any other method of risk assessment such as use of high-sensitivity C-reactive protein is long overdue, and it is important to clarify the conclusive level of benefit that is required before CAC or any tool is used as part of a routine and universal risk prediction strategy.

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