EDITORIAL COMMENT

Coronary Artery Calcium: The Cup Is 96% Full*

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The MESA (Multiethnic Study of Atherosclerosis) study was designed to investigate the prevalence and progression of subclinical atherosclerosis, including that defined by coronary artery calcium (CAC) scanning, in an asymptomatic, primary prevention population (1,2). Along with several other large prospective studies, it has established CAC as a strong prognosticator of cardiac events, significantly superior and additive to all risk-factor–based assessments (Framingham, Prospective Cardiovascular Münster, European Society of Cardiology) (1–4). Remarkably, it has not yet been recommended by the American College of Cardiology/American Heart Association guidelines for screening the intermediate-risk population, for which the strongest endorsement has been “it may be reasonable” (5). The persistent criticism has been the absence of randomized studies demonstrating a positive effect of CAC on outcomes (6), notwithstanding a similar absence of outcome data for risk-factor–based assessments that are routinely recommended and for all of the cardiology diagnostic modalities.

The relationship of CAC to significant stenoses has been extensively investigated in symptomatic patients, and the direct relationship of increasing CAC with obstructive disease is well-documented, with a 99% sensitivity for ≥50% stenosis in symptomatic patients referred for angiography (7,8). However, the relatively low specificity of CAC—ranging from 23% for CAC >0 to 79% for CAC >100 (7,8)—has been cited as a major shortcom-

ing, even though CAC scanning was never intended to detect obstructive disease and get patients into the catheterization laboratory; the purpose has always been to detect the early subclinical stages of the disease for which the specificity is virtually 100% and keep patients out of the catheterization laboratory by practicing aggressive prevention.

The remarkably benign prognosis (0.17%/year event rate, including revascularization) (Table 1) of a 0 CAC in the major prospective studies of asymptomatic patients (2–4) is superior to that of nuclear stress testing (9) and stress echocardiography (10). Nonetheless, the occurrence of events subsequent to a 0 CAC has been well documented. Retrospective studies in both older (114 patients, mean age 57 ± 11 years) (11) and younger (102 patients, mean age 41 ± 7 years) (12) populations have yielded a 5% incidence of 0 CAC in those who presented with acute events in both age ranges. More recently, the association of 0 calcium scores with significant obstructive disease has been described in chest pain patients undergoing both computed tomographic angiography (CTA) and catheter-based angiography (13,14). In 688 patients with chest pain syndromes, 125 patients had 0 CAC, 7% of which had ≥50% stenosis (13). In 40 patients admitted with suspected acute coronary syndrome, 13 patients had 0 CAC, and 5 of these (39%) had >50% stenosis (14).

The study by Rosen et al. (15) in this issue of iJACC is the first to prospectively evaluate a very large asymptomatic cohort of individuals with known 0 CAC for obstructive disease. Of 6,814 patients enrolled in the MESA study, 3,563 had 0 CAC. In the first 6 years, 175 underwent coronary angiography after a median interval of 18 months from the CAC scan, 80% for clinical indications (angina, myocardial infarction, or congestive heart failure), 5% as a direct result of the CT study, and

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6% due to a positive stress test. In 7 patients (4%) with ≥75% stenosis, the CAC was 0; 10% to 20% of the vessels with ≥75% stenosis had 0 CAC. Of the 3,563 with a 0 CAC, only 11 (0.3%) had ≥50% stenosis on clinically indicated catheter angiography. The authors concluded: “...the degrees of coronary artery calcified plaque scores predict the severity of coronary stenosis of individual coronary arteries in patients who subsequently require coronary catheterization for clinical indications. Among those individuals who underwent coronary angiography during this time frame due to clinical indication and were found to have significant coronary artery disease, there is a considerable number of patients (10–20%) who had a zero calcium score in the corresponding coronary beds at baseline. Yet, only a minority of them (4%) had a total zero calcium score” (15). This MESA study, by virtue of its prospective design in a large cohort, very likely offers the truest estimate of the incidence of 0 CAC obstructive disease, even though only those 0 CAC patients who underwent clinically indicated coronary angiography were evaluated. The incidence of obstructive disease would very likely have been higher if all patients had undergone angiography. It must be clearly stated that the 10% to 20% prevalence of 0 CAC in arteries with ≥75% stenosis (15) is much less clinically relevant and is misleading, because it was concentrated in only 4% of the patients.

All the same, the 96% negative predictive value in patients presenting with chest pain implies that a 0 CAC does not provide sufficient reassurance. Therefore, CAC scanning is not an appropriate tool for chest pain evaluation. A prior or recent 0 CAC in a symptomatic patient must be followed by additional testing to rule out coronary artery disease with significant stenoses.

It is critical that the results not be misinterpreted as a shortcoming of CAC by extrapolating them to the entire cohort of asymptomatic patients, as the title “Relationship Between Baseline Coronary Calcium Score and Demonstration of Coronary Artery Stenoses During Follow-Up: MESA (Multi-Ethnic Study of Atherosclerosis)” (15) would suggest. The very low incidence (0.3%) of clinically indicated catheter angiography in 3,563 0 CAC asymptomatic patients in the MESA study and the low (4%) occurrence of significant obstruction in the selected symptomatic 0 CAC group (15), almost identical to the 5% previously reported in patients presenting with an acute event (13,14), must be emphasized to hasten rather than further delay the acceptance of CAC scanning.

A strong argument can be made for requiring CAC before stress testing in asymptomatic patients, for whom the Class IIb indication for evaluation of patients with multiple risk factors (16) is commonly applied. A 0 CAC would obviate the need for stress testing, which is associated with a poor positive predictive accuracy in a low-prevalence asymptomatic population, as well as the avoidable normal coronary angiography and attendant costs, morbidity, and mortality. In addition, less aggressive drug therapy would be appropriate for 0 CAC patients. In the current cost-conscious, evidence-based environment, the burden of proof should be on those who choose to use lipid-lowering medications in this remarkably low-risk group; demonstration that drug therapy in the 0 CAC group significantly reduces events below 0.17%/year in a randomized trial should be required. At the other end of the spectrum, CAC identifies the higher risk pool of patients out of which 95% to 96% of the events will emerge; it is this group that will benefit from highly targeted aggressive treatment. As Rosen et al. (15) have demonstrated, “the CAC cup is 96% full.”

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### Table 1. Prospective Prognostic Studies That Have Assessed the Prognostic Value of a 0 Coronary Calcium Score

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Total Patients, n</th>
<th>0 CAC Patients, n</th>
<th>Follow-Up, yrs</th>
<th>MI + Death, %/yr (n)</th>
<th>All Events, %/yr (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrano et al. (2)</td>
<td>6,722</td>
<td>3,409</td>
<td>3.9 median</td>
<td>0.06% (8)</td>
<td>0.11% (15)</td>
</tr>
<tr>
<td>Arad et al. (3)</td>
<td>5,585</td>
<td>1,504</td>
<td>4.3 mean</td>
<td>Not available</td>
<td>0.13% (8)</td>
</tr>
<tr>
<td>Becker et al. (4)</td>
<td>1,726</td>
<td>379</td>
<td>3.4 mean</td>
<td>0% (0)</td>
<td>0.9% (12)</td>
</tr>
<tr>
<td>Pooled data</td>
<td>14,303</td>
<td>5,282</td>
<td>3.9</td>
<td>Not available</td>
<td>0.17% (35)</td>
</tr>
</tbody>
</table>

CAC = coronary artery calcium; MI = myocardial infarction.
REFERENCES


Key Words: coronary artery calcium • obstructive coronary artery disease.