Coronary artery calcium (CAC) scoring by computed tomography (CT) has been the subject of intense interest and critical scrutiny since it was first reported as a clinical tool in 1990.1 With improvements in study design, greater availability of coronary CT scanners, and increased attention to the posttest prognosis of patient samples and asymptomatic individuals who have undergone coronary CT, CAC measurement is now considered a potentially useful test for improving coronary risk assessment in selected intermediate-risk asymptomatic patients in whom high CAC scores signify increased cardiovascular risk beyond that predicted by conventional cardiovascular risk factors alone.2

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At the other end of the spectrum, does a very low CAC score signify very low risk? An American Heart Association writing group3 stated that a CAC score of zero (CAC=0; ie, no calcified plaque detected) indicated 1) that the presence of atherosclerotic plaque, including unstable or vulnerable plaque, was highly unlikely; 2) that the presence of significant luminal obstructive disease was highly unlikely (negative predictive value on the order of 95% to 99%); and 3) that the risk of a cardiovascular event in the next 2 to 5 years was quite low (0.1 per 100 person-years). In addition, at least 1 early study suggested that CAC=0 might be useful in the emergency room setting as a tool to rule out myocardial ischemia in symptomatic patients.4 A recent review article5 suggested the same conclusions. However, as pointed out by a different writing group of the American Heart Association and the American College of Cardiology,2 prognostic studies of CAC scoring in symptomatic patients have been limited by biased samples (eg, patients referred for invasive coronary angiography who also underwent CAC testing), incomplete follow-up for posttest events, and small numbers of hard outcome events. Thus, in 2007, CT experts had reached no consensus on the role of CAC testing in symptomatic patients.3,4,5

The study by Schenker et al in the current issue of Circulation6 reports important new information on the role of coronary CT in symptomatic patients. The study included patients who were referred for evaluation of myocardial ischemia. All had rest-stress Rubidium-82 positron emission tomography perfusion imaging and CAC scoring performed on a hybrid positron emission tomography–CT scanner, and complete data including follow-up for clinical events were available in 606 patients. On the basis of clinical information,7 the authors estimated that patients described in this report had a mean likelihood of significant anatomic coronary artery disease of nearly 60%. Considering the mean age of 61 years and the high prevalence of both cardiopulmonary symptoms and cardiovascular risk factors, it is not surprising that the mean CAC score in the overall sample was high at 429±869 Agatston units. Of the 165 patients found to have myocardial ischemia by positron emission tomography scan, 34 had CAC=0, and of these, 4 had a cardiac event in the subsequent 1.4 years of follow-up (mean event rate 8.2 per 100 person-years). In 441 patients who were nonischemic by positron emission tomography scan, 179 had CAC=0, and of these, 7 had a subsequent cardiac event in the 1.4 years of follow-up (estimated event rate 2.6 per 100 person-years). Finally, in 213 patients in this study with CAC=0, inducible ischemia occurred in 16%.

Rates of inducible ischemia and subsequent cardiac events in the patients with CAC=0 in the study of Schenker et al6 far exceed those reported in all previous studies (see Table). The authors indicate why they believe that inducible ischemia in patients with CAC=0 in their experience is so much higher than in previous studies. For example, Schenker et al6 note that the study of Rozanski et al8 which considered a patient group that was largely asymptomatic in a screening setting, reported an overall event rate of myocardial infarction or cardiac death among 1153 patients of 0.9 per 100 person-years; notably, the “events” included late revascularization. Schenker et al6 conclude that this marked difference in event rates in their study versus that of Rozanski et al8 is likely due to patient differences between the samples.

We agree with Schenker et al6 that the interpretation of a CAC test, as is the case with all other diagnostic tests in cardiology, must take into account the patient population, presence or absence of symptoms, and the clinical setting. In other words, the pretest probability of disease as well as the test result must be considered when interpreting the test result. The data of Schenker et al6 illustrate this point exquisitely in terms of the clinical meaning of a CAC=0 test result. As shown in the Table, in largely asymptomatic samples, event rates in patients with CAC=0 are generally low, ranging from 0.04 per 100 person-years in the lowest-

How Low-Risk Is a Coronary Calcium Score of Zero? The Importance of Conditional Probability

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.108.767665
Table 1. Compendium of Studies Involving Coronary Artery Calcium Scoring by Computed Tomography in Various Patient Samples, With Follow-Up for Clinical Events

<table>
<thead>
<tr>
<th>Study Ref</th>
<th>Patient Type</th>
<th>No. of Patients in Full Study</th>
<th>Mean Age, y</th>
<th>Follow-Up Duration, y</th>
<th>Events in Persons With CAC=0 Scores, n</th>
<th>Events Per Year in CAC=0 Patients, Mean</th>
<th>Total No. of Persons With CAC=0</th>
<th>Annual Event Rate in CAC=0 Patients, Per 100 People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgiou et al</td>
<td>Emergency room patients with chest pain</td>
<td>192</td>
<td>53</td>
<td>4.2</td>
<td>0</td>
<td>0</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>Schenker et al</td>
<td>Referred for cardiac evaluation</td>
<td>606</td>
<td>61</td>
<td>1.4</td>
<td>11</td>
<td>7.7</td>
<td>213</td>
<td>3.6</td>
</tr>
<tr>
<td>Rozanski et al</td>
<td>Mixed sample of self-referred and MD-referred</td>
<td>1,153</td>
<td>58.4</td>
<td>2.7</td>
<td>3</td>
<td>1.1</td>
<td>252</td>
<td>0.47</td>
</tr>
<tr>
<td>Greenland et al</td>
<td>Asymptomatic with at least 1 risk factor</td>
<td>1,312</td>
<td>66</td>
<td>7.0</td>
<td>14</td>
<td>2.0</td>
<td>316</td>
<td>0.63</td>
</tr>
<tr>
<td>Keelan et al</td>
<td>Coronary angiography patients</td>
<td>288</td>
<td>56</td>
<td>6.9</td>
<td>0</td>
<td>0</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Arad et al</td>
<td>Asymptomatic</td>
<td>1,173</td>
<td>53</td>
<td>3.6</td>
<td>2</td>
<td>0.55</td>
<td>496</td>
<td>0.11</td>
</tr>
<tr>
<td>Raggi et al</td>
<td>Asymptomatic</td>
<td>632</td>
<td>52</td>
<td>2.7</td>
<td>1</td>
<td>0.37</td>
<td>292</td>
<td>0.13</td>
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<tr>
<td>Wong et al</td>
<td>Asymptomatic</td>
<td>926</td>
<td>54</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
<td>392</td>
<td>0</td>
</tr>
<tr>
<td>Arad et al</td>
<td>Asymptomatic</td>
<td>4,613</td>
<td>59</td>
<td>4.3</td>
<td>8</td>
<td>1.8</td>
<td>1504</td>
<td>0.12</td>
</tr>
<tr>
<td>Kondos et al</td>
<td>Self-referred—mostly asymptomatic</td>
<td>5,635</td>
<td>51</td>
<td>3.1</td>
<td>5</td>
<td>1.6</td>
<td>1816</td>
<td>0.09</td>
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<tr>
<td>Anand et al</td>
<td>Asymptomatic type 2 diabetic patients</td>
<td>510</td>
<td>53</td>
<td>3.0</td>
<td>1</td>
<td>0.33</td>
<td>274</td>
<td>0.12</td>
</tr>
<tr>
<td>Taylor et al</td>
<td>Asymptomatic</td>
<td>2000</td>
<td>43</td>
<td>3.0</td>
<td>2</td>
<td>0.67</td>
<td>1791</td>
<td>0.04</td>
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<tr>
<td>Church et al</td>
<td>Preventive evaluation patients</td>
<td>10,746</td>
<td>54</td>
<td>3.5</td>
<td>7</td>
<td>2.0</td>
<td>5472</td>
<td>0.04</td>
</tr>
<tr>
<td>Becker et al</td>
<td>Asymptomatic</td>
<td>1,726</td>
<td>58</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
<td>367*</td>
<td>0</td>
</tr>
</tbody>
</table>

*12 patients with CAC=0 had coronary revascularization. Number includes only the patients with CAC=0 who had no interventions at all.

risk populations to as high as 0.63 per 100 person-years in an older asymptomatic cohort that also required at least 1 risk factor for study inclusion.9 In striking contrast to all of the previous studies that included only asymptomatic patients, or a mix of symptomatic and asymptomatic patients, the patients reported by Schenker et al6 were all physician-referred for provocative testing based on cardiac symptoms or other evidence of intermediate-to-high risk of anatomic coronary disease.7 Symptomatic or otherwise, the clinical scenarios warranted diagnostic information on inducible ischemia and not merely CAC testing. In these higher-risk patients, event rates were markedly higher for CAC=0 patients6 than in all prior reports (see Table).

The message of these findings is clear and bears emphasis here. When the pretest probability of coronary artery disease is low (eg, asymptomatic screening setting), a CAC score of zero is associated with low risk of coronary artery disease and low risk of near-term coronary events (see Table). In older asymptomatic patients with risk factors, CAC=0 is associated with a moderate increased risk of events.9 And in patients such as those reported by Schenker et al,6 with clinical signs and symptoms associated with an intermediate-to-high risk of coronary disease, CAC=0 is often associated with myocardial ischemia on provocative testing (16% in their patients) and with a high risk of near-term coronary events (nearly 9 times higher than previously reported for any asymptomatic cohort). It is appropriate to question the added value of the CAC score in this moderately high-risk patient group. Was the extra cost and extra radiation burden balanced by extra clinical value? Reverend Bayes20 is proven correct again, and once again we learn that a high pretest probability should alert us to the concern that a “negative test” does not “rule-out” disease as it does when pretest probability is low. The data of Schenker et al6 remind us of the importance of the clinical setting and the need to carefully assess the patient before ordering a test.

Disclosures
Dr Greenland reports having served in the past 2 years as a consultant for GE/Toshiba and Pfizer. Dr Bonow reports no conflicts.

References


Key Words: Editorials | coronary disease | imaging | prognosis