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

Philip Greenland, MD; Robert O. Bonow, MD

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. 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.

At the other end of the spectrum, does a very low CAC score signify very low risk? An American Heart Association writing group 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. A recent review article suggested the same conclusions. However, as pointed out by a different writing group of the American Heart Association, atherosclerotic plaque may be present in up to 30% of patients with 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 al 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 al note that the study of Rozanski et al, 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. In the 252 patient subset with CAC=0, only 3 events occurred in the follow-up period, with annualized event rates of 0.47 per 100 person-years; notably, the “events” included late revascularization. Schenker et al conclude that this marked difference in event rates in their study versus that of Rozanski et al is likely due to patient differences between the samples.

We agree with Schenker et al 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 al 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-
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. 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 al were all physician-referred for provocative testing based on cardiac symptoms or other evidence of intermediate-to-high risk of anatomic coronary disease. 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/H11005 patients 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. And in patients such as those reported by Schenker et al, 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 Bayes 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 al 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

<table>
<thead>
<tr>
<th>Study†</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>
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<tbody>
<tr>
<td>Georgiou et al</td>
<td>Emergency room patients with chest pain</td>
<td>192</td>
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<td>606</td>
<td>61</td>
<td>1.4</td>
<td>11</td>
<td>7.7</td>
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<td>3.6</td>
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<td>1,153</td>
<td>58.4</td>
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<td>1.1</td>
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*12 patients with CAC=0 had coronary revascularization. Number includes only the patients with CAC=0 who had no interventions at all.


Key Words: Editorials □ coronary disease □ imaging □ prognosis
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