Understanding the Utility of Zero Coronary Calcium as a Prognostic Test
A Bayesian Approach

Michael J. Blaha, MD, MPH; Roger S. Blumenthal, MD; Matthew J. Budoff, MD; Khurram Nasir, MD, MPH

Coronary artery calcium (CAC) is nearly pathognomonic for the presence of coronary atherosclerosis, although not all coronary plaque is calcified. As such, cardiac CT scans for CAC are highly specific but less sensitive for the presence of some coronary atherosclerosis. In contrast, these tests are highly sensitive but less specific for detecting obstructive atherosclerotic coronary artery disease (CAD).

A Bayesian approach is critical for discerning the value of new tests. When used in the intended population, a test with high sensitivity is excellent for ruling out disease (ie, highly sensitive tests produce a high negative predictive value [NPV] when negative). For this reason, there is interest in using “zero” CAC scores to predict excellent prognosis—and potentially conserve medical resources—in the large population of patients at intermediate midterm risk of developing clinical cardiovascular disease.

Bayes Theorem

The efficiency of any test relies on the frequency of disease in the population tested (the prior probability distribution). For example, take the D-dimer test for deep venous thrombosis and pulmonary embolism. If a D-dimer is checked in all outpatients, not all coronary plaque is calcified. As such, cardiac CT frequency of thrombosis in this scenario. If a D-dimer is tested in patients with acute dyspnea and a swollen lower extremity, there will be a low NPV given the high incidence of pulmonary embolism in such patients. Stated in mathematical terms, the likelihood of thrombosis (A) given a positive D-dimer (B) depends not only on the conditional probability of B given the presence or absence of A (the test characteristics), but also on the marginal probability of A independent of B (the prior probability distribution).

This principle is summarized in probability theory by Bayes theorem (Figure 1). Knowingly or unknowingly, Bayes theorem underlies essentially all clinical decision making. When applied to the individual patient, the prior probability distribution is understood to be the clinician’s coherent pretest belief of a particular clinical result, for example, the reasoned suspicion of a pulmonary embolism or obstructive CAD. Bayes theorem thus will describe how the perfectly rational clinician’s suspicion will change in response to empirical evidence, such as results of a test.

CAC=0 in Asymptomatic Patients

In clinical practice, CAC is used most commonly per American Heart Association and American College of Cardiology guidelines for improving global risk stratification in asymptomatic patients at moderately elevated risk. Results are interpreted in terms of prognosis and are used to guide intensity of lifestyle recommendations and choice of pharmacotherapy and for patient motivation. Ideally, the prior probability distribution of the target population places patients at intermediate (5% to 20%) 10-year risk for developing clinical cardiovascular disease. The lower boundary of 5% 10-year risk was suggested in a recent study by Taylor et al.

A recent illustrative study followed 44,000 asymptomatic patients receiving CAC scans over a mean of 6 years for the occurrence of all-cause mortality. Patients were referred because their physicians had an intermediate suspicion of substantial atherosclerosis. In this study, CAC=0 portended an excellent prognosis, with an estimated 10-year mortality of 1%. Patients with a CAC >10 had a 4- to 8-fold increased risk of dying compared to those with a CAC=0.

A recent pooled analysis of prior studies again demonstrated very low cardiac event rates in asymptomatic individuals with CAC=0. Among 29,312 individuals with CAC=0, just 0.47% experienced a cardiac event over the 3- to 5-year follow-up. Importantly, the excellent prognosis of CAC=0 holds across diverse ethnic groups and among women, the elderly, and patients with diabetes.

Although many risk factors, traditional risk scores, and novel serum biomarkers are available for quantifying increased risk in asymptomatic patients, none of these have sufficient sensitivity to exclude clinically important CAD.
the primary prevention population, CAC=0 stands alone as perhaps the most powerful negative risk factor for near-term development of a coronary event.

**CAC=0 in Clearly Symptomatic Patients**

Clearly symptomatic patients represent the extreme opposite end of the prior probability spectrum. For example, Haberl et al. studied the utility of CAC among 133 high-risk symptomatic patients with positive stress tests and a resultant decision to refer for cardiac catheterization. Just 18% of the sample had CAC=0, and 32% of these patients had significant stenoses on invasive angiography. Another recent study examined 40 high-risk patients with suspected acute coronary syndrome (ACS), 70% of whom were ultimately shown to have obstructive CAD. In this study, CAC=0 was associated with markedly reduced likelihood of obstructive CAD, yet 39% of patients with CAC=0 still had obstructive disease.

More recently, an analysis from the CORE 64 (Coronary Artery Evaluation using 64-slice Multidetector CT) study tested the utility of CAC for excluding obstructive CAD among patients referred for cardiac catheterization because of their concerning clinical presentation. In these patients with a high suspicion of obstructive CAD, a CAC=0 score markedly reduced the likelihood of >70% stenosis (15% versus 58% for CAC >10) but not sufficiently to use CAC to definitively exclude important CAD.

Should clinicians be surprised by these results? A Bayesian analysis would suggest that there will likely never be a noninvasive test that conclusively excludes obstructive CAD in clearly symptomatic patients with a high pretest likelihood of obstructive CAD. This clinical picture warrants ischemic testing and invasive angiography. Other testing is likely inappropriate.

In fact, even cardiac CT coronary angiography (CCTA) lacks a role in symptomatic patients with a high pretest probability of obstructive CAD. In a landmark study, Meijboom et al. demonstrated that among patients with high pretest probability of CAD, the estimated posttest likelihood of significant CAD after a negative CCTA scan remained 17%. Shown again in another recent study, the prior probability in this scenario is too persuasive: Probability theory suggests that the clinician can never comfortably exclude obstructive CAD in this scenario without the gold standard test (invasive angiography).

**Prior Probability and Proper Applications for CAC Testing**

Unemphasized differences in the medical literature regarding prior probability distributions (ie, asymptomatic versus clearly symptomatic patients) and goals of testing (prognosis versus diagnosis) likely have hampered the unbiased assessment of the utility of CAC. We are concerned that the true value of subclinical atherosclerosis detection will be lost in an era where tests are increasingly ordered in the wrong patients. Understanding Bayes theorem is paramount.

CAC testing, particularly the finding of CAC=0, could be cost saving when used appropriately. Among asymptomatic patients, a finding of CAC=0 confers such a low risk that clinicians might find themselves comfortable prescribing less costly medications to achieve less stringent lipid targets and focusing on lifestyle therapy. Fewer stress and imaging studies would be needed, and prior studies of the “warranty period” of CAC=0 suggest that scans should not be repeated for at least 4 to 5 years. The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study, which showed a very low frequency of testing and invasive procedures among the large CAC=0 group, has provided early proof of principle of this concept. A clinical trial testing this theory is needed.

It is important to note that the presence of increased CAC does not present a mandate for further testing (ie, stress testing) in an asymptomatic patient. The specificity, and therefore PPV, of CAC for the diagnosis of obstructive CAD is low. Rather, CAC should be considered a prognostic test, and these patients should be treated more aggressively with high-dose lifestyle therapy and risk-reducing medications. Indeed, contrary to a recent editorial, a Bayesian approach would never support the use of CAC to determine who needs angiography in patients otherwise not considered for such a test.

The Bayesian clinician will not be surprised that CAC is unhelpful in the clearly symptomatic patient. However, what about patients in the middle of the risk continuum? Does a Bayesian approach support use of CAC in lower-risk symptomatic patients presenting with chest pain?

**Does CAC=0 Have a Role in the Low-Risk Symptomatic Patient Presenting to the Emergency Department?**

Consensus statements currently support the use of CAC=0 as a filter before invasive angiography in the appropriate low-risk symptomatic population. They argue that a finding of CAC=0 may be associated with such a favorable near-term prognosis that low-risk patients presenting with ECG-equival, cardiac enzyme-negative chest pain (up to 55% to 60% of chest pain presentations) could be safely discharged without further testing.

In the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) study, just 1 out of 368 low-risk patients presenting to the emergency department...
Table. Comparison of CAC=0 Versus Standard of Care Tests for Detection of Significant CAD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Radiation Dose, mSv</th>
<th>Estimated Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress ECG</td>
<td>68</td>
<td>77</td>
<td>0</td>
<td>110</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>87</td>
<td>68</td>
<td>0</td>
<td>415</td>
</tr>
<tr>
<td>Stress MPS</td>
<td>88</td>
<td>77</td>
<td>9.0–14.0</td>
<td>662</td>
</tr>
<tr>
<td>CAC=0</td>
<td>98</td>
<td>40</td>
<td>1.0–2.0</td>
<td>100–200†</td>
</tr>
</tbody>
</table>

When seeking a test to rule out disease, such as in the ED, a high sensitivity is desired. High specificity is desired when suspicion of disease is higher and confirmation is necessary. Data are from multiple meta-analyses, best summarized in Sarwar et al.6 and Halpern et al.28 MPS indicates myocardial perfusion scintigraphy (Tc99m sestamibi).

High sensitivity translates to high NPV.


When a CAC result was reported to have a positive score, there was a 99% probability of obstructive CAD.5 This high sensitivity is associated with a high NPV of 99%. However, specificity is lower, with only 57% specificity, 24% PPV, and 99% NPV for the identification of ACS. These results are similar to the pooled analysis by Sarwar et al.,6 who reported that a positive CAC score had a 99% sensitivity, 57% specificity, and 99% NPV for the identification of ACS. Zero CAC was associated with a risk ratio of 0.07 (95% CI, 0.03 to 0.19; P<0.00001) for ACS. In the most recent ED study, Fernandez-Friera et al.24 found that just 2 out of 133 low- to intermediate-risk patients with CAC=0 had obstructive CAD.

In another recent study, 263 low- to intermediate-risk patients presenting to the ED with chest pain underwent routine evaluation as well as CAC testing, with the CAC results remaining blinded.25 Among 133 patients with CAC=0, only 1 (<1%) had cardiac chest pain. Conversely, of the 31 patients shown to have cardiac chest pain, 30 (97%) had evidence of CAC on CT. All patients who subsequently met criteria for myocardial infarction had CAC. During long-term follow-up, patients without CAC experienced no cardiac events at 30 days, 1 year, and 5 years.

In the study of low- to intermediate-risk patients with the longest follow-up (up to 7 years), Georgiou et al.26 demonstrated an annual event rate of just 0.6% among low- to intermediate-risk patients presenting to the ED with CAC=0. The largest such study followed 1031 patients presenting to the ED with chest pain for subsequent clinical events.27 Cardiac events occurred in 32 (3.1%) patients during the index hospitalization (n=28) or after hospital discharge (n=4) (mean, 7.4 months). Only 2 (0.3%; 95% CI, 0.04% to 1.1%) events occurred in 625 patients with CAC=0.

Fast rule-out tests are commonly desired in the ED, similar to the use of D-dimer for pulmonary embolism. False-negatives are to be avoided. The prior probability distribution is critical for evaluating the utility of such tests.

For low-risk patients, CAC test characteristics compare favorably to the current less-sensitive standard of care modalities for increasing comfort when discharging patients from the ED (Table).28 CAC may have particular value in recurrent and chronic chest pain syndromes that lead to multiple ED presentations. Much more research is needed in the application of layered testing in these patients, where

CAC may serve as a gatekeeper for studies requiring contrast and pharmacological heart rate control (CCTA) or high-dose radiation and stress (stress nuclear perfusion), and these latter 2 studies may serve as a gatekeeper for invasive testing (cardiac catheterization). Prior studies of sequential testing suggest a negligible frequency of obstructive CAD29 and positive myocardial perfusion studies30 in low-risk patients with CAC=0, with the prevalence increasing sharply in higher-risk patients.31,32 These studies suggest that when the pretest probability places the symptomatic patient at intermediate likelihood of having obstructive CAD, CAC is less favorable, and tests with higher specificity (stress testing or CCTA) appear more to be appropriate initial tests.

Conclusion

A Bayesian approach is critical for new tests (Figure 2). Such an approach points to situations where CAC=0 is helpful (intermediate-risk asymptomatic patients, low-risk symptomatic patients) and where it is not helpful (very-low-risk asymptomatic patients, higher-risk symptomatic patients). Studies like that by Taylor et al4 have helped to define the lower boundary for CAC testing.

Disclosures

Dr Budoff is on the speaker’s bureau for GE Healthcare.

References


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