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

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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 a low positive predictive value (PPV) will result given the low terms, the likelihood of thrombosis (A) given a positive D-dimer extremity, there will be a low NPV given the high incidence of patients at intermediate midterm risk of developing clinical cardiovascular disease.

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Bayes Theorem

\[
P(A|B) = \frac{P(B|A)P(A)}{P(B)}
\]

Prior probability distribution

Figure 1. Mathematical representation of Bayes theorem. The probability of a disease being present (A) given the results of a test (B) dependent not only on the characteristics of the test \( P(B|A) \), but also on the prior probability distribution of the disease in the tested population \( P(A) \). The term \( P(B) \) is called the normalizing constant, interpreted as the marginal probability of B, and is required to make the Bayes equation fit a probability density function.

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 al11 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.12 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.13 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 definitely 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 al14 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,15 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.16,17 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.18 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,19 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.20–22 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
(ED) had an ACS in the absence of calcified plaque. These results are similar to the pooled analysis by Sarwar et al, who reported that a positive CAC score had a 99% sensitivity, 57% specificity, 24% PPV, and 99% NPV for the identification of ACS. Zero CAC was associated with a relative 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 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. Among 133 patients with CAC=0, only 1 (0.8%) 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 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. 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). 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

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