

EDITORIAL COMMENT

What Is the Prognostic Value of a Zero Calcium Score?*

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Despite remarkable advances in knowledge and technology, heart disease remains the leading cause of death in the U.S. Thus, the search continues for more effective ways to diagnose heart disease early, and hopefully prevent more cardiac deaths. More than 30 years ago, Diamond and Forrester (1) presented a method for predicting angiographic disease based on age, sex, and type of chest pain symptoms. To this day, American College of Cardiology/American Heart Association guidelines essentially use this clinical assessment to determine the probability of coronary artery disease (CAD). For patients whose assessment suggests an intermediate probability for CAD, clinicians typically recommend some type of stress test. Patients with abnormal stress tests then are often referred for invasive coronary angiography (ICA).

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As stress tests may not be scheduled easily in a triage setting, other tests have been proposed as faster and more convenient ways to decide who should be referred for ICA. For example, coronary artery calcium scoring (CS) has been suggested as a noninvasive test that can risk-stratify patients with chest pain and reliably identify candidates who may benefit from ICA. In support of this approach, a recent systematic review of CS studies of both symptomatic and asymptomatic populations led investigators to conclude that the absence of coronary calcification was a reliable predictor of the absence of angiographic CAD (2,3). Sarwar et al. (2) argued, therefore, that patients without coronary calcification are highly unlikely to have CAD and do not need further testing. Their review of 18 studies of the accuracy of CS for predicting CAD in symptomatic patients found a

negative predictive value of 93% and a positive predictive value of 68% (2).

A paper in this issue of the *Journal*, however, presents a starkly contrasting picture. In a substudy of their multicenter CORE64 (Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors) trial, Gottlieb et al. (4) analyzed 291 patients (73% men, average age 59 years) who, as part of a chest pain workup, underwent a coronary artery calcium scan followed by coronary angiography. Moreover, of the patients who had a CS of 0 (24% of the total population), 19% were found to have significant CAD (at least 1 >50% stenosis by angiography)—that is, nearly 1 in 5 patients had CAD that the CS failed to predict. Statistically, Gottlieb et al. (4) calculated a lower negative predictive value of CS of 68%, and a positive predictive value of 81%, leading them to conclude that a CS = 0 does not reliably rule out significant coronary disease, and to caution against use of the CS for this purpose.

So why the apparent discrepancies between the earlier systematic reviews and the current clinical trial by Gottlieb et al. (4)? Possibly, there were different characteristics in the 2 populations studied—age, sex, and cardiac risk factors. Pre-test probability of disease, for example, can substantially affect analysis of the clinical utility of a diagnostic test. The CORE64 study CS subgroup had more men than reported in the systematic review (73% vs. 60% men). However, both Gottlieb et al. (4) and Sarwar et al. (2) reported the exact same prevalence of obstructive coronary artery disease by angiography: 56% in their populations.

Although CS and ICA are both anatomic tests, they measure different stages of the atherosclerotic process. Coronary calcification is thought to occur late in the atherosclerotic pathway (and may be a marker for plaque stability), whereas obstructive atherosclerotic disease seen by ICA may not be directly associated with calcification. Thus, it is not surprising that significant CAD can occur in the absence of calcification.

For the clinician, any new diagnostic test poses the critical issue of “what information will I learn from this test that I didn’t already know, and how will this additional information lead to improved care of this patient?” Gottlieb et al. (4) suggest that the benefit of a CS for risk stratification is not yet proven. Neither Gottlieb nor Sarwar give us any information on how the CS adds incremental information to the traditional predictors for CAD, such as clinical assessment and stress testing.

This apparent lack of predictive value of a CS should be enough to give a clinician pause. When combined with the significant radiation risks of coronary artery calcium scans, however, clinicians must use extreme caution when ordering such scans. Indeed, recent data show that the cancer risk from a single coronary artery calcium test at age 40 years may be as many as 9 cancers per 100,000 men and 28 cancers per 100,000 women (5). Gibbons and Gerber (6)

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argue that we must consider the cancer risk when ordering coronary artery calcium scans (or any other nuclear test), and that providers must discuss both risks and benefits with the patient. Radiation risks are even higher when the CS is used in addition to other testing for ischemia such as myocardial perfusion imaging.

In any event, the findings by Gottlieb et al. (4) squarely raise a key question: what is the added value of a CS? In particular, does a CS add, even incrementally, to the predictive value for CAD established 30 years ago based simply on demographics and type of chest pain? This question cannot be answered precisely, because the studies of the CS as a predictor of CAD or cardiac events have not analyzed the incremental risk prediction over clinical assessment. However, the conflicting results from Gottlieb et al. (4) and Sarwar et al. (2) suggest that more data, from populations of varying pre-test probability of CAD with angiographic and meaningful clinical end points such as nonfatal myocardial infarction and cardiac death, are needed to answer this question. Until then, a CS of 0 cannot be interpreted as a reassurance of the absence of CAD. The findings by Gottlieb et al. (4) reinforce the importance of comparing new diagnostic tests to more traditional clinical predictors, especially when the tests expose patients to known risks but uncertain benefits. The CS, in particular, may yet have its place in the clinician's arsenal for evaluation

of patients with chest pain, but until its benefits are clearly established, we must take great care when subjecting patients to it.

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