Your Coronary Calcium Scan Is Positive
Now What?*

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Coronary artery calcium (CAC) scanning by computed tomography is commonly performed as a screening test for coronary artery disease (CAD) risk assessment in clinical practice. For asymptomatic individuals without known CAD who are at intermediate to high risk, CAC scanning is assigned a “may be appropriate” rating according to American College of Cardiology appropriate use criteria (1) and a Class IIA indication according to American College of Cardiology practice guidelines (2). The results of CAC scanning can be applied to determine the aggressiveness of treating CAD risk factors. Additionally, the detection of a high CAC score can raise concern about prognostically significant obstructive CAD. Performing stress testing with single-photon emission computed tomography–myocardial perfusion imaging (SPECT-MPI) or echocardiography is considered appropriate in patients with an Agatston score $\geq 400$ (1).

Over the past 15 years several studies have examined the association between the results of CAC scanning and the frequency of myocardial ischemia. In this issue of JACC, Bavishi et al. (3) report the results of a meta-analysis of this topic. An initial literature search identified 281 potential studies. Twenty of these studies, which enrolled 7,155 patients, met their entry criteria. The authors applied 4 commonly used CAC cutoff categories: 0, 1 to 100, 101 to 399, and $\geq 400$. Twelve of the studies could be analyzed for CAC cutoff of 0 and 16 studies for CAC cutoff of 400. As expected there was an association between CAC and the prevalence of ischemia. In the studies that used a CAC cutoff of $>0$ versus 0, the pooled frequency of a positive CAC score was 86% for patients with ischemia versus 72% for patients without ischemia. Applying a CAC cutoff of $\geq 400$ versus <400, the corresponding percentages were 53% and 25%, respectively. Perhaps the most clinically useful data reported in this meta-analysis is the prevalence of ischemia according to CAC scores, derived from a subset of 6 studies involving 2,123 patients where patients were categorized by all 4 CAC scores. The prevalence increased modestly across the first 3 CAC categories and increased substantially for the fourth category: CAC = 0, 6.6%; CAC = 1 to 100, 8.5%; CAC = 100 to 399, 10.5%; CAC $\geq 400$, 23.6%.

Another important observation from this meta-analysis is the significant variability in results reported across studies. $I^2$ is a quantity that reflects the heterogeneity across studies that are included in a meta-analysis (4). $I^2$ was $>75\%$ for all of the analyses performed in this meta-analysis. $I^2$ values $>75\%$ are generally considered to indicate high heterogeneity. An example of the heterogeneity between studies is the prevalence of stress-induced ischemia, which ranged from 5.6% to 45.5%. In the subset of 6 studies that included all 4 categories of CAC scoring, the prevalence of ischemia for CAC = 0 ranged between 0.0% and 24.1% and for CAC $\geq 400$ the prevalence ranged between 12.4% and 57.1%. Bavishi et al. (3) suggest some potential reasons for the high heterogeneity in their analyses, including the small patient populations in many of the studies; differences in symptom status, CAD risk factors, and medication use between populations; and technical factors related to imaging.

There likely were additional factors related to patient selection and accuracy of imaging not addressed by the authors. During much of the 15-year time period covered by this meta-analysis, there was no general consensus concerning which patients were suitable candidates for CAD scanning. Furthermore, in some regions of the country this technology was heavily marketed and the cost of the test usually was not covered by insurance plans. All of these issues

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likely significantly impacted the selection of patients who underwent scanning. Studies examining the reproducibility of CAD and SPECT-MPI have reported disappointing results. In MESA (Multi-Ethnic Study of Atherosclerosis), 2 sequential CAC scans were obtained at baseline in 6,814 study participants (5). The measurement error between the 2 scans was large and approximately 100% for an Agatston score of 40. In the ADVANCE (Adenosine versus Regadenoson Comparative Evaluation for Myocardial Perfusion Imaging) phase 3 trial, the size of the ischemic defect was compared in 267 patients who underwent 2 adenosine SPECT-MPI studies performed 1 week apart (6). The rate of agreement between the 2 studies was only 64%. These issues of patient selection bias and variability in imaging results undoubtedly also contributed to the high heterogeneity.

The major role of a meta-analysis is its potential impact on clinical practice. The finding in this meta-analysis of a relatively low prevalence of ischemia in patients with a CAC of 0 is consistent with several prognostic studies demonstrating that this patient subset is at very low risk of experiencing a cardiac event (7). Unfortunately, the data from this meta-analysis are not robust enough to reliably identify a CAC threshold where stress imaging is clearly warranted, in part because of the high heterogeneity already acknowledged. Another factor to consider is that in this study ischemia was analyzed as a simple binary variable (present/absent). However, in clinical practice the most accepted way to determine the subsequent management of the patient is not the presence of any ischemia but rather the extent and severity of ischemia, most commonly measured by SPECT-MPI as the summed difference score.

An important clinical issue that is relevant to this meta-analysis but is not directly addressed by these data is the identification of patients suitable for CAC scanning. Currently CAC is appropriate only for asymptomatic patients and is rated “rarely appropriate” for symptomatic patients (1). Bavishi et al. (3) propose that CAC scanning potentially could serve as a cost-effective strategy for triaging symptomatic patients to stress imaging. The individual studies included in this meta-analysis enrolled both symptomatic and asymptomatic patients. However, because the results were not stratified by symptom status, this meta-analysis cannot address this issue. Although a CAC threshold above which additional testing is clearly warranted was not identified in this study, appropriate use criteria consider stress imaging appropriate for patients with CAC >100 (1). This recommendation relates to the current paradigm for managing CAD of identifying patients with severe ischemia who are candidates for coronary angiography and revascularization. This paradigm is based on a large body of observational literature demonstrating the prognostic value of SPECT-MPI (8) and improvement in outcome with revascularization (9). However, 3 recent large imaging substudies performed as part of the COURAGE (10), BARI-2D (11), and STICH (12) trials reported that ischemia not only failed to identify patients with better clinical outcome that is treated by revascularization but also that ischemia had no value as a stand-alone prognostic variable. The prognostic value of stress imaging in patients who are carefully treated with modern medical therapy and the role of revascularization in patients with extensive ischemia have come under question (13). The ongoing ISCHEMIA trial is designed to address this issue (14). The conclusion of Bavishi et al. (3) that more research with better designed studies is necessary to clarify the role of CAC and ischemia seems reasonable. However, a more fundamental issue that should first be clarified is the role of ischemia for outcome prediction and treatment selection to be certain that ischemia-based testing is the correct approach to further investigate patients with an elevated CAC score.

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