Coronary Calcification and Coronary Artery Disease

Gottlieb et al. (1) report computed tomography (CT) calcium scores in 291 patients (73% male) being referred for coronary angiography. The majority (95%) had either intermediate or high pre-test probability of coronary disease, and 42 (19.6%) had presented as emergencies with unstable angina. The authors report a surprisingly low sensitivity of only 45% for a calcium score of 0 to predict the absence of ≥50% lesions, that led your editorialist (2) to question the incremental value of calcium scoring for diagnosing coronary artery disease (CAD). Yet, as stated in the editorial, the value of any diagnostic test is critically dependent on the population in which it is applied. Calcium scoring has been recommended as a useful rule-out in patients with a low probability of CAD, based on meta-analysis that yields sensitivity estimates in excess of 90%, higher than most other methods of noninvasive testing (3). The patient population in the Gottlieb et al. (1) study is quite inappropriate for challenging this recommendation based on their high pre-test probability, their preselection for cardiac catheterization, their male predominance, and their high rates of unstable presentation. It is unclear what added value a calcium score could possibly make to the diagnosis of CAD in this group. Nevertheless, among the Gottlieb et al. (1) population, we find clues to the real value of calcium scanning for CAD rule-out in the 8 patients with a low pre-test probability of disease and a zero calcium score, none of whom had angiographic CAD. At present, we are often prepared to base diagnostic decisions in such patients on treadmill stress testing despite its low sensitivity (4) and negligible incremental value for risk assessment (5). It is in this low-risk population of patients with stable chest pain and a low pre-test probability of CAD that calcium scoring is likely to find its place as a simple and safe means for disease rule-out in clinical practice.

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Coronary Calcium Remains an Effective Filter for Invasive Angiography

Gottlieb et al. (1) question the current guidelines in regard to coronary calcium scoring (CCS) in symptomatic persons and suggest their small study trumps 25 years of published literature. Coronary artery calcium (CAC) guidelines are written based on >1,000 studies, including several that were 5 to 10 times larger than the cohort reported. Furthermore, the authors excluded 89 patients who were enrolled in CORE64 (Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors) who had CAC >600. Imagine a paper stating hypertension does not correlate with left ventricular hypertrophy, but the study inconspicuously eliminated patients who had significant hypertension.

The real issue is that CORE64 is divergent from almost all CAC literature. Almost every published study of CAC, including 2,000+ participant multicenter trials undergoing CAC and invasive angiography, demonstrate high sensitivity (>90%) and lower specificity (<50%) (2). Sarwar et al. (3) demonstrated a sensitivity of 98% for CAC to detect obstructive disease among 10,355 symptomatic patients with a 56% prevalence (identical prevalence to Gottlieb et al. [1]). Results from the first multicenter 64-slice computed tomography angiography (CTA) trial demonstrated CAC sensitivity of 94% and specificity 42% for >50% stenosis by quantitative coronary angiography (4). Gottlieb et al. (1) present the opposite results (sensitivity 45% and specificity 91%), calling into question study design, equipment, or CAC methodology, not validity of CAC testing. Hypotheses why the Gottlieb et al. (1) study diverges from the CAC literature include: threshold for CAC (attenuation >130 Hounsfield units [HU], developed for electron beam tomography [2], not validated for Aquilion 64 [Toshiba Medical Systems, Otawara, Japan]), pixel size (requiring larger minimum area for CAC results in lower sensitivity, methodology not reported in Gottlieb et al. [1]), patient selection (including acute coronary syndrome [ACS], known coronary artery disease [CAD], and prior revascularization), or other technical scanner issues (filters, reconstruction kernels). It has been demonstrated that different scanners have different operating characteristics and different CAC reproducibility (5). A CAC threshold of 110 HU was suggested for multidetector computed tomography (MDCT) scanners, and this simple methodological correction may yield more typical results (2).

Surprisingly, the authors went beyond the scope of their study to discuss prognostic implications. CAC prognostic studies have reported on follow-up of over 100,000 patients, clearly demonstrating a zero score carries excellent long-term prognosis (2,3). We followed patients for 8 years after emergency room admission, and patients with zero scores experienced coronary events (3), and 7 studies followed 3,924 symptomatic persons over 42 months, demonstrating CAC safety and efficacy. A recent CAC study followed 1,031 patients after hospitalization for chest pain (6).

Zero CCS occurred in 61%, predicting both normal nuclear and excellent short-term outcome, reiterating high sensitivity of CAC testing for events and obstruction.

CAC with an effective radiation dose that approximates mammography remains an effective filter for low-to-moderate pre-test probability symptomatic patients (2). The literature, with >1,000 CAC publications, is clear and, with 1 exception, consistent. CAC testing should remain a mainstay in both diagnosis and prognosis of the cardiac patient.

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Reply

We thank the authors for their letters and for the interest in our study and their thoughtful remarks. We would like to add some comments.

As Drs. Correia and Blaha noted, the predictive values found in our paper (1) have slightly different meanings than commonly utilized in other trials (2). This is so because we chose to take a different perspective. Our aim was to determine if a calcium score (CS) of 0 (positive scan for us) could predict the absence of obstructive coronary artery disease (CAD), whereas the other trials they refer to examined the question of whether the presence of calcium increases the likelihood of chest pain being related to significant stenosis (2). We thank both for the opportunity to further clarify this issue.

Using our approach of calling a zero CS a positive scan, the positive predictive value refers to the ability of zero calcium to rule out obstructive CAD. This is in fact the same message of a negative predictive value using the "conventional" approach. This predictive value was low in our study: 68%. Accordingly, the sensitivity of zero calcium to detect the absence of disease (i.e., to rule out obstructive CAD) was also low at 45%. As Dr. Blaha points out, when our results are interpreted from this perspective, they are clearly consistent with previously published studies (1,2).

We feel that our approach more accurately tests the utility of the CS when applied for this specific purpose, i.e., to rule out obstructive disease in symptomatic patients with suspected CAD to allow for discharge from the emergency department or to direct outpatient investigation to other causes of chest pain.

We agree with Drs. McEvoy, Timmis, and Blaha that high-quality research has been performed in determining the epidemiologic value of coronary calcium as a marker of atherosclerosis-related adverse events in asymptomatic individuals, and we thank them for stressing once again that our study did not investigate this patient population. Our study documents the limitations of coronary calcification in symptomatic individuals suspected of having obstructive CAD. In fact, it quantifies something that experienced clinical cardiologists already know and have incorporated in their clinical practice (i.e., noncalcified plaque can rupture and cause a myocardial infarction) and this phenomenon is not that uncommon, particularly among patients usually considered to be at low risk for coronary disease (e.g., women and younger individuals) (3). This was again confirmed in vivo in our study in which 20% of the totally occluded vessels were free from calcification (1).

Referring to the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial (4), Dr. Budoff states that it "demonstrated CAC sensitivity of 94% and specificity 42% for >50% stenosis by quantitative coronary angiography" and continues by stating that "Gottlieb et al. present the opposite results (sensitivity 45% and specificity 91%), calling into question study design, equipment, or CAC methodology, not validity of CAC testing." In fact, their results are very similar to ours, just expressed differently. As noted above, the ACCURACY CS sensitivity of 94% for the presence of stenosis matches our (CORE64 [Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors]) CS specificity of 91% for the absence of stenosis, whether their specificity of 42% for the presence of stenosis matches our sensitivity of 45% for the absence of stenosis.

Regarding our CS methodology, we followed standard imaging parameters and requirements recommended by the American College of Cardiology/American Heart Association guidelines (5). Although we recognize that multidetector computed tomography (MDCT) scanners have different performance parameters as compared with electron beam computed tomography (EBCT), in clinical practice, CS is more often measured with MDCT than EBCT due to the former's much better performance in coronary angiography.

One could be tempted to generalize our findings to all subgroups of patients, mixing symptomatic and asymptomatic patients as being the same. This is a grave mistake. Dr. Budoff states that our study trumps more than a 1,000 studies and that prognosis of zero CS has been assessed in over 100,000 patients, but he regrettably misses the fact that the vast majority of the published CS literature refers to *asymptomatic* patients.

Dr. Budoff questions exclusion of patients with CS >600 in our study. This group would, by definition, be irrelevant to our paper, the main point of which was to demonstrate the prevalence of significant disease in symptomatic patients having no coronary calcium.

While we take the opportunity to thank Dr. Rita Redberg for the time and effort in appraising our work and the comments on