Use of Coronary Artery Calcium Scanning to Screen for Coronary Atherosclerosis Among Early Middle-Age Adults*

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Coronary atherosclerosis is a highly prevalent and progressive disorder that is characterized by a long latent phase before the onset of clinical symptoms. Fatty streaks are commonly found in the vascular walls of children and progress with high frequency to significant fibrous plaques by early adulthood (1,2). Some of these evolve to become susceptible to hemorrhage, rupture, and thrombosis, with resultant acute coronary events. Because these events frequently occur without premonitory symptoms, the need to initiate management and prevention of coronary artery disease (CAD) well before the development of clinically manifest heart disease is now well accepted. Recent panels recommend the use of coronary artery calcium (CAC) scanning or carotid ultrasound for screening those asymptomatic individuals with an intermediate Framingham Risk Score (FRS) (3), but these recommendations are largely based on the study of populations older than 50 years of age. There is currently no consensus regarding whether and how to screen for CAD in early middle age.

This issue is addressed in an important new study by Okwuosa et al. (4) in this issue of *iJACC*. In their investigation, they assessed the prevalence and distribution of CAC according to FRS levels among 33- to 45-year-old individuals in the CARDIA (Coronary Artery Risk Development in Young Adults) study. As part of their analysis, they assessed a new metric proposed by Rembold (5): assessment of screening benefit according to the number needed to screen (NNS). In the present study, the NNS is based on the number of individuals needed to screen to detect CAC abnormality, with separate NNS values determined for detecting CAC scores >0 and ≥100. In their cohort of 2,831 individuals, the prevalence of a CAC score >0 was 9.9% and a CAC score ≥100 was 1.8%. Their principal conclusion is that application of CAC scanning in only 33- to 45-year-old individuals with a FRS >10% can be beneficial because in this subgroup CAC scores ≥100 occur with high frequency (17.2%), resulting in a low NNS (~6). We examine these findings from 4 perspectives: the optimal goal of testing, the utility of NNS, the use of the FRS, and the overall relevance of screening for CAC in young adults.

The Goal of Testing Young Middle-Age Adults

The assessment of a test’s effectiveness is critically dependent on the predominant goal of testing. A key question in analyzing the findings of the CARDIA study is whether the optimal goal should be the detection of the ~2% with a CAC score of ≥100 or the detection of the ~10% with a CAC score >0. We suggest that the better goal should be the detection of any CAC, based on 3 observations. First, the presence of any CAC provides definitive evidence of atherosclerosis and can thus be viewed as sufficient evidence to manage CAD risk factors aggressively. Second, because CAC is not commonplace among adults who are 33 to 45 years old, the detection of any CAC abnormality in such adults...
already identifies those at relatively high long-term risk of cardiac events. For instance, even when one just considers individuals at the upper limit of their cohort’s age range, men at 45 years, those with CAC scores of only 5 to 10 are already within the 80th to 85th percentiles and women are within the 95th percentile for CAC abnormality. The absolute CAC score is a better predictor of clinical outcomes than percentile score, but subjects with such high CAC percentile scores are nevertheless at decidedly high risk of the development of subsequent clinical events (6). Third, the importance of even mild CAC abnormalities was underscored by 2 recent large studies that found that CAC scores of only 1 to 10 increased subsequent clinical event rates by 2- to 3-fold compared with CAC scores of 0 (7,8). Combined, these observations provide a strong rationale for developing a screening strategy based on detecting CAC scores \( > 0 \) rather than \( \leq 100 \).

**Number Needed to Screen**

What might constitute an optimal NNS may be influenced by a complexity of factors, including the nature of the study population and the consequences of testing. Thus, this metric deserves further study to assess its practical clinical utility. Although Okwuosa et al. (4) derived that the NNS to detect a CAC score of \( \geq 100 \) is \( \sim 6 \) for a FRS \( > 10 \), reassessment of their data reveal that the NNS for the alternative goal of detecting a CAC score \( > 0 \) would be only 3.6 based on an FRS threshold of \( > 5 \% \) (Table 1). Of note, screening subjects with an FRS \( > 5 \% \) instead of \( > 10 \% \) would only increase the total percentage of subjects screened from 2\% to 6\% in the CARDIA study. The rationale for using an FRS \( > 5 \% \) as a triage point for young adults is supported by the findings of the Prospective Army Coronary Calcium Project, which followed a screened adult population with a mean age of 42 for 5.6 years after CAC scanning (9). During follow-up, \(<1\%\) of subjects with an FRS \(<5\%\) experienced a cardiac event compared with 28.6\% of the subjects with an FRS \( > 5 \% \).

**Use of the FRS as the Triage Criterion for CAC Screening in Younger Adults**

The FRS considers age, sex, serum cholesterol, blood pressure, diabetes, and smoking status. However, the FRS does not consider other important parameters of risk that can shape long-term outcomes among younger adults, including obesity, the presence of a family history of premature heart disease, physical inactivity and/or poor fitness, and the chronicity of risk factors. Notably, in this regard, because of the very high weighting given to age in the formulation of the FRS, many younger subjects with important CAD risk factors have only modest increases in FRS. This potential limitation of the FRS also extends to women older than 45 years of age. For instance, in the population-based MESA (Multi-Ethnic Study of Atherosclerosis), 90\% of women older than 45 years of age were classified as low risk by FRS (\(<10\%\) in 10 years). Thirty-two percent of these women had a CAC score \( > 0 \), and their hazard ratio for cardiac events was 6.5 compared with those with a CAC score of \( 0 \) (10). Given these limitations, we suggest that the use of the FRS is not an optimal means of triaging younger adults for screening tests. Indeed, previous work from the CARDIA study established that increased body mass index, a family history of premature CAD, and the chronicity of CAD risk factors are all predictors of CAC abnormality in individuals between the ages of 33 and 45 years (11–13). Thus, a triaging algorithm that includes all CAD risk factors might be preferable to use instead of the FRS in young adults. Future algorithm should further distinguish the practical minimal age range for applying CAC scanning in women versus men.

**Clinical Relevance**

Not only is cardiac risk assessment challenging among younger adults but so too is subsequent risk management. Individuals between the ages of 33 and 45 years are predominantly asymptomatic and

**Table 1. Number Needed to Screen to Detect CAC Abnormality (Score >0)**

<table>
<thead>
<tr>
<th>FRS Threshold, %</th>
<th>No. of Subjects Above Threshold</th>
<th>% of Total Subjects</th>
<th>No. With CAC Score &gt;0</th>
<th>Prevalence of CAC Score &gt;0, %</th>
<th>NNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &gt; 10 )</td>
<td>58</td>
<td>2.0</td>
<td>26</td>
<td>44.8</td>
<td>2.2</td>
</tr>
<tr>
<td>( &gt; 5 )</td>
<td>120</td>
<td>4.1</td>
<td>48</td>
<td>27.7</td>
<td>3.6</td>
</tr>
<tr>
<td>( &gt; 2.5 )</td>
<td>460</td>
<td>16.2</td>
<td>106</td>
<td>23.0</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Adapted from the data of Okwuosa et al. (4).

CAC = coronary artery calcium; FRS = Framingham Risk Score; NNS = number needed to screen.
are less likely to seek physician care or have CAD risk factors identified on an incidental basis. Moreover because health issues are a more future-oriented concern in younger than in older individuals, they are more prone to postpone acting on health advice (14). Such procrastination, although common, is unfortunate because behavioral and medical intervention in younger adults offers the greatest opportunity to ward off risk factors that will result from negative health habits, such as poor nutrition, overeating, sedentary lifestyles, and smoking. The presence of a favorable risk factor profile in young adults is highly predictive of longer longevity (15) and improved quality of life and lower medical costs in old age (16,17). In fact, seminal work from the Framingham study revealed that if one makes it to age 50 with a completely normal CAD risk profile, the subsequent lifetime risk of the development of clinical CAD is reduced by ~90% in women and by ~80% in men (18).

Potentially, the application of CAC scanning in early middle age may be beneficial by heightening physician concern and thus their subsequent medical management of patients with CAC abnormalities and/or by motivating subjects toward greater health self-care. Recent experience from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial, which compared the 4-year impact randomized to CAC scanning versus no scanning among older middle-age adults, might be instructive in this regard (19). The study demonstrated that CAC scanning results in less FRS progression without any increase in downstream medical resource use. However, caution must be applied in applying the results of the EISNER trial to young adults. In particular, it remains to be determined whether CAC scanning could indeed improve behavior by motivating young subjects with evidence of CAC abnormality to become more present oriented as to their health risk and thereby more serious with respect to initiating behavioral change.

In conclusion, the present study by Okwuosa et al. (4) provides important information regarding the selective use of CAC scanning to screen for CAD among asymptomatic individuals between 33 and 45 years of age. Further study should assess whether a risk score that accounts for the impact of risk factors over time is better than the FRS for selecting patients for CAC scanning. In the interim, given the increased risk associated with any CAC abnormality, we suggest that a FRS score >5% would be a more effective threshold for applying CAC scanning in young middle aged adults.

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Key Words: atherosclerosis • coronary artery calcium • coronary artery disease.