Recent clinical practice guidelines for coronary artery calcium (CAC) testing in asymptomatic people vary in their advice about routine testing from moderately enthusiastic support to frank opposition. The 2010 Clinical Practice Guideline Panel of the American College of Cardiology and the American Heart Association (ACC/AHA) published an extensive published data review and assessment of the utility of a large number of tests and procedures for risk assessment of the asymptomatic adult (1). Recommendations for CAC scoring ranged from Class IIa (reasonable to perform the procedure) to Class III (should not be done).

The ACC/AHA recommendations for CAC testing, by different patient categories, are shown in Table 1. Level of evidence for all of the ACC/AHA CAC recommendations was regarded as B, primarily because there are no randomized trials that have tested the role of CAC scoring in asymptomatic patients for evidence of improved health outcomes (1). At the opposite end of the spectrum, a 2009 report from the U.S. Preventive Services Task Force concluded that “current evidence does not support the routine use” of CAC testing for risk stratification of intermediate-risk persons (2). The U.S. Preventive Services Task Force generally looks for randomized trial evidence and, in its absence, advises against testing as it did for CAC screening. The Institute of Medicine reflected uncertainty in this area, despite enthusiastic support from certain groups in the clinical community (3), and listed CAC testing for routine risk assessment as 1 of its Top 100 areas of priority for comparative effectiveness research (4). Furthermore, the Institute of Medicine placed an emphasis on assessing the utility of a large number of tests and procedures for risk assessment of the asymptomatic adult (1). Recommendations for CAC scoring ranged from Class IIa (reasonable to perform the procedure) to Class III (should not be done).

The report in this issue of the Journal by van Kempen et al. (9) addresses the role of CAC testing in asymptomatic individuals with cost-effectiveness analysis (CEA) and comparative effectiveness analysis. Its primary conclusion is that screening for CAC with CT in individuals at intermediate risk of CHD is probably cost-effective in men but is unlikely to be cost-effective in women. The CEA uses recent evidence on risk reclassification from the Rotterdam Study (7) to design competing risk assessment strategies, so this report is the most up-to-date CEA on this topic. How should this new report influence the thinking about routine CAC testing? And is this sufficient to avert a clinical trial to more fully address the topic?

The discussion by van Kempen et al. (9) recognizes a number of concerns that must be considered. First, the authors cite limitations of their work, including the focus only on intermediate-risk patients, so the recommendations should be limited only to this category of patients. This is
not a major drawback, however, because this is the patient category most frequently discussed as likely to benefit from risk reclassification. More importantly, the authors note that, as with all models of screening and diagnostic tests, the differences between the various strategies in terms of quality-adjusted life years were small. There was considerable uncertainty demonstrated in the sensitivity analyses, such that the optimal strategy could be routine CAC testing but might also be moderate dose “statin therapy” for everyone not already taking statins (nearly a “treat all” option). Additionally, although neither “current practice” nor “current guidelines” emerged as the dominant strategy in these models, if Adult Treatment Panel guidelines are updated to expand the indications for statins, it is possible that they will be more commonly used in routine practice. As a result, CAC testing could become less valuable in selecting patients for statin treatment and improving clinical outcomes. All of these scenarios lead to the conclusion that additional information beyond that available from the CEA by van Kempen et al. (9) might be needed, before a convincing and definitive change in clinical practice guidelines would be justified.

Several recent articles have advocated alternative approaches in preventive cardiology rather than more “personalized” assessment of cardiovascular risk with biomarkers such as CAC (10–12). Hingorani and Psaty (12), in an editorial published in 2009, posed the question: “Is it time to get more or less personal in primary prevention of cardiovascular disease?” Their main point—which is reflected in all risk prediction models, including those that incorporate CAC (6–8)—is that the models are neither highly sensitive nor highly specific. Although the treatment thresholds of the models can be adjusted to achieve higher sensitivity, when this is done, specificity is very poor and treatment would need to be widespread (13). Commonly used risk prediction models such as the Framingham Risk Score, when using a threshold for treatment above 20% in 10 years, miss large numbers of patients destined to develop an event. Slightly lower risk thresholds also miss large numbers of cases. For example, in the MESA study (5), with 209 CHD events occurring over 5 years, 57 (27%) occurred in patients predicted to be in the lowest-risk group (predicted risk <3% in 5 years). Even the addition of CAC to the Framingham risk factors still classified 51 of the 209 people (24%) who developed near-term events as “lowest risk.” The Reynolds Risk Score has similar problems in identifying the highest-risk people (14,15). In the Women’s Health Study, 44% of the patients who developed cardiovascular events were classified in the lowest-risk group on the basis of traditional risk factors alone. Forty-two percent of the participants with events still remained in the lowest-risk category, after adding high-sensitivity C-reactive protein and family history to the model. In the Physicians Health Study II, more than 500 CHD events occurred among men classified as intermediate risk on the basis of traditional risk factors. Only 13% of the intermediate-risk participants who experienced events were reclassified to high risk with the Reynolds Risk Score for Men.

Recognizing problems with so-called “personalized risk” approaches led Hingorani and Psaty (12) to consider treatment strategies that avoid individual testing and simply treat with statins everyone above a certain age, a method recommended earlier by Law and Wald (13). This “treat all” approach emerged as the dominant strategy in some of the sensitivity analyses by van Kempen et al. (9), yet with different assumptions in place CAC testing was the “winning” approach.

With the residual uncertainty in this important area of preventive medicine, we believe that the only way to determine the “best” strategy is to conduct a clinical trial with CAC testing to select patients for more or less intensive treatments. Others have also advocated for such a trial (16,17). Judging from the very similar results for the strategies compared in the van Kempen et al. (9) cost-effectiveness analysis, it is obvious that such a trial would need to enroll a large number of patients who were followed for at least 4 to 5 years. The study would be challenging logistically as well as costly. However, in the absence of such a trial, the options seem to be so close to one another on careful analysis that reasonable errors in the assumptions can lead to very different conclusions. We conclude that there is not enough evidence, even with the newer data on risk reclassification, to justify a change in current clinical practice recommendations. A screening trial with CAC measurement is long overdue.

Reprint requests and correspondence: Dr. Philip Greenland, Feinberg School of Medicine, Northwestern University, 750 North Lake Shore Drive, 11th Floor, Chicago, Illinois 60611. E-mail: p-greenland@northwestern.edu.

---

**Table 1** Recommendations for CAC Scoring From the American College of Cardiology and the American Heart Association, 2010

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendation</th>
<th>Level of Evidence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-yr risk)</td>
<td>B</td>
</tr>
<tr>
<td>IIb</td>
<td>Measurement of CAC might be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-yr risk)</td>
<td>B</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>Persons at low risk (&lt;3% 10-yr risk) should not undergo CAC measurement for cardiovascular risk assessment</td>
<td>B</td>
</tr>
</tbody>
</table>

Data from Greenland et al. (1).

CAC = coronary artery calcium.
REFERENCES


Key Words: coronary heart disease • cost-effectiveness analysis • CT coronary calcium • CT screening • primary prevention.