Accurate atherosclerotic cardiovascular (ASCVD) risk assessment is needed for both women and men to identify and intervene in individuals at risk for ASCVD. Previously developed global risk scores, such as the Framingham Risk Score, have had many limitations, particularly in women who are routinely categorized as lower risk than men. The newer ASCVD Risk Score that makes up the current guidelines for assessment of cardiovascular risk has been shown to overestimate risk in women. In addition, even in those with an optimal risk factor profile at the age of 55 years, there remains a substantial lifetime risk of ASCVD for both men and women (40% and 30%, respectively) who are unaccounted for by short-term (10 years) risk assessment.

In this issue of Circulation: Cardiovascular Imaging, Kelkar et al sought to determine the prognostic use of coronary artery calcium (CAC) scoring in a low-intermediate risk cohort of asymptomatic men and women. Despite the fact that CAC is currently not recommended as part of the risk stratification in low-intermediate risk individuals, this study demonstrated that the addition of CAC effectively identifies high-risk women, beyond what would be predicted based on risk factor assessment alone. This cohort was composed of women who were approximately a decade older than the men, and as such, closed the age gap that is usually used to justify the lower ASCVD risk score seen in women. Women in this cohort were significantly more likely to be hypertensive and more likely to smoke than men. Men were more likely to have dyslipidemia compared with women. At least two thirds of this cohort had a family history of premature coronary artery disease, with no significant differences between sexes. But it was women who surprisingly had a greater prevalence and extent of CAC; and it was women who had a significantly higher (>1.44x greater) 15-year mortality than men. The authors demonstrated that the Net Reclassification Improvement was 0.155 for women and 0.094 for men. This resulted in 6.2% of low-risk women correctly reclassified using CAC, compared with 3.9% of men. Similar findings were seen in the high-risk women reclassification but the numbers were small. In this cohort, a CAC >10 was associated with a greater hazards ratio of death for women compared with men. At any CAC level, the risk of mortality was greater for women compared with men, but a CAC ≥400 was associated with a greater risk of mortality in women than seen in men (hazard ratio, 6.53 versus 2.71; P<0.001), after controlling for traditional risk factors.

Most previous studies have often only assessed shorter-term prognostic abilities of CAC, but the advantage in this study is the 15-year outcomes that demonstrate the prognostic ability of CAC. One limitation of this study is that it is the authors who were only able to assess all-cause mortality, not nonfatal ASCVD events. As a result, it is more likely that this study underestimated the prognostic use of CAC in both women and men who were low-intermediate risk by global risk assessment. When compared with other cohorts such as the Multi-Ethnic Study of Atherosclerosis where CAC was also assessed, the women in this study had much higher rates of smoking and both sexes had a greater prevalence of a family history of premature coronary artery disease.

So how valuable is the picture that the CAC provides? As a result of this study, can we now move forward in using CAC in low-intermediate women whose actual risk may be under appreciated by tradition risk assessment tools? Unfortunately, this study is unable to make the case for this (Table). This study was of a referral cohort, and it is not clear what the impact of the CAC findings had on their ASCVD risk management and, ultimately, their outcomes. It is also unknown if there was any sex difference in the management of ASCVD risk factors based on the CAC results that might explain the higher mortality seen in women. This study was not designed to assess any intervention as a result of these findings. Nonetheless, as a result of this study’s findings, it makes the call by these authors and other investigators for a randomized control trial imperative. Given the incidence of ASCVD in women, it is unacceptable that we continue to use ASCVD risk scores that do not accurately identify risk in women. At the same time, we still do not have the answer if identifying subclinical atherosclerosis by CAC is an adequate reflection of risk and how to affect management to prevent ASCVD events. Whether CAC can more accurately assess risk in women needs to be examined before routine application of CAC can be justified in this population. Performance of CAC in low-intermediate risk women needs to demonstrate its ability to improve identification of those at risk beyond global risk scores, but also to determine if the results and the response to the CAC score...
will affect outcomes. Any screening tool for ASCVD will only be justified when it can trigger an intervention that results in improved outcomes and currently, these data are lacking. In addition, assessment of the cost effectiveness of doing such imaging as part of risk assessment will need to be evaluated.

Currently, global risk scores are the foundation of our preventive care and recommended by our current guidelines.\(^11\) But it is important for us to recognize the limitations of these risk scores, particularly in women where as many as 90% of the population cohort can be low risk.\(^12\) Further refinement of risk assessment is needed, specifically for women, if these tools continue to be the base of all guidelines that dictate preventive strategies for ASCVD. But at this time, assessment of CAC is a class IIb recommendation in this low-intermediate risk population and it should remain as such until we have adequate evidence to justify the use of CAC more broadly on the population at low-intermediate risk.\(^13\) Careful consideration about the use of CAC needs to be made because of the challenges associated with CAC imaging, including the psychological burden associated with the results, the risks related to radiation exposure, and the costs that would result in our already financially challenged healthcare system. The picture provided by CAC is still not clear and is still not yet worth a thousand words.

**Disclosures**

None.

### References


### Key Words

- Editorials
- atherosclerosis
- prognosis
- radiation exposure
- smoke

**Table. Principles for Evaluating Coronary Artery Calcium (CAC) Score as a Biomarker in Low-Intermediate Risk Patients**

<table>
<thead>
<tr>
<th>Evaluation of CAC as a Biomarker in Low-Intermediate Risk Patients</th>
<th>Cost effectiveness?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proof of concept: Does the CAC score differ between subjects with and without outcomes?</td>
<td>Yes</td>
</tr>
<tr>
<td>Prospective validation: Does the CAC score predict the development of outcomes in a prospective cohort or nested case–control study?</td>
<td>Yes</td>
</tr>
<tr>
<td>Incremental value: Does the CAC score add predictive value to established standard risk markers?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Clinical use: Does the CAC score change predicted risk sufficiently to change recommended therapy?</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical outcomes: Does the use of CAC improve clinical outcomes, especially when tested in a randomized clinical trial?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cost effectiveness: Does the use of CAC improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Global Risk Assessment and Coronary Artery Calcium Scoring in Low-Intermediate Risk Women: What Is a Picture Really Worth?
Martha Gulati

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