Editorial Comment

Coronary Calcium Score and the New Guidelines
Back to Square One?*

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Previous guidelines for cardiovascular risk assessment recommended the use of a modified Framingham score to estimate the 10-year risk of hard coronary heart disease (CHD) events, defined as myocardial infarction and CHD death (1). Coronary artery calcium (CAC) scoring for refined stratification received Class IIa or IIb recommendations for those at intermediate (10% to 20%) or low to intermediate (6% to 10%) risk, respectively (2). In 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) released guidelines (3,4) endorsing new sex- and race-specific predictive equations derived from 5 large prospective cohorts, using conventional risk factors, and estimating 10- or 30-year risks of major atherosclerotic cardiovascular disease (ASCVD) events (also including stroke). The new guidelines advocate initiation or consideration of statin therapy based on absolute 10-year risk thresholds of ≥7.5% or 5% to 7.5%, respectively, as determined by these equations. CAC scoring is considered if uncertainty remains after conventional risk assessment (Class IIb recommendation).

Notably, whether CAC (or other markers) continue to provide meaningful prognostic information when these new equations are used needs revisiting (5). In this issue of the Journal, investigators from MESA (the Multi-Ethnic Study of Atherosclerosis) address this relevant question (6), primarily by evaluating the impact of absent CAC on reclassification from a statin-eligible to a statin-noneligible risk category. Nasir et al. (6) included 4,758 individuals comparable to those targeted in the new guidelines: 45 to 75 years of age, no previous cardiovascular disease or baseline lipid-lowering therapy, and low-density lipoprotein (LDL) cholesterol >70 mg/dl. Applying the updated equations, statins would have been “recommended” in 2,377 participants (50%) due to LDL ≥190 mg/dl (2%), diabetes and LDL 70 to 189 mg/dl (10%), or estimated 10-year risk ≥7.5% (38%) and “considered” in 12% of participants with 10-year risk of 5% to 7.5%.

During a median follow-up of 10.3 years, CAC scoring demonstrated discriminatory predictive ability across the 3 groups of statin “recommended,” “considered,” and “not recommended,” with respective ASCVD event rates of 5.2%, 1.5%, and 1.3% for those with a CAC score of 0, and 15%, 6%, and 9.6% if the Agatston CAC score was ≥100.

This important study confirms that, in the current era of updated and presumably improved predictive scores (7), CAC retains a strong ability to reclassify cardiovascular risk. In addition, it addresses a critical issue and represents a step in the right direction: in an environment with limited resources, efforts should be made to identify not only newer indications for therapy but also those who may not significantly benefit from it. In the case of statins for primary ASCVD prevention, the absence of CAC may represent such a tool, based on the data presented in this paper and also in Framingham cohorts (7). The study also raises, among others, several relevant questions.

Should we now use CAC scoring to screen for subclinical CHD? The authors contend that those with an
intermediate (5% to 20%) 10-year risk would be most likely to benefit from CAC scoring, and we agree. In the group “not recommended” for statins, the very low 10-year event rate (1.2%) argues against the need for further stratification. Even though those with a CAC score ≥100 had a 10-year risk of almost 10%, they represented only 4% of the group, and generalized scanning would likely be unjustified. In addition, these high rates should be taken with caution given that they derive from only 7 events. In the “statin-recommended” group as a whole, a CAC score of 0 was associated with a 5.2% event rate, not enough to reach the “no-statin” threshold under the new guidelines. The event rate of almost 12% in those with a very high (≥20%) risk despite the absence of calcification is well above the guideline-based threshold for therapy, so CAC scoring in this subgroup would not change management. Conversely, of those with 10-year risks of 7.5% to 20% (excluding individuals with LDL ≥190 mg/dl or diabetes), absent CAC may indicate a sufficiently reduced risk to consider withholding statins. Finally, measuring CAC could be reasonable in the “statin-considered” group (5% to 7.5% risk) given that this is relatively small (12%), a CAC score of 0 is common (57%), and it significantly downgrades 10-year risk (1.5% vs. 6.3% to 7.8%). However, if statins are not recommended below the 3% threshold and since the overall event rate was 4% in this group, CAC scoring would not be needed to begin with. Thus, based on this study, it could be argued that in the latter 2 groups, CAC scoring might deserve Class Ila and IIb recommendations, respectively: strikingly similar to the older guidelines.

Should we then measure CAC in all intermediate-risk individuals? The data presented by Nasir et al. (6) does not answer this question, but we would argue against it. First, CAC scoring is not without cost or (hypothetical) risks. Although, as pointed out by the authors, it may be cost-effective in the intermediate-risk U.S. population, cost-effectiveness models are based on multiple assumptions and extrapolations, are sensitive to numerous confounders, and cannot be generalized to other health environments. Second, if intermediate-risk individuals are willing to take statins (under the new guidelines), there seems to be little reason to recommend CAC scoring to prevent them from doing it. Third, the overestimation of risk with the new equations, reported in MESA and other populations (8) argues for the need of recalibration (5) and questions the comparison of CAC with a “sub-optimal” standard. Fourth, the potential benefit of CAC-driven statin therapy is based on assumptions of consistent and predictable statin efficacy. Although meta-analyses suggest an average risk reduction in the vicinity of 25% (9), there is substantial heterogeneity among primary prevention trials. Finally, and most importantly, a screening tool is generally considered justified when it can trigger an intervention of proven benefit in a specific context. Unfortunately, conclusive evidence that statins reduce events in those with elevated CAC scores does not exist. Class I evidence of conventional risk-driven statin therapy is similarly lacking, but this hardly justifies replacing an unproven method with another, particularly when one is almost universally available, and the other is not. However, in individual cases of borderline or uncertain risk, personal concerns, or statin side effects or disutility, CAC scoring probably remains the best tool that we have today to guide management.

Should we tailor statin therapy using CAC scoring? If one accepts the premise that statins are indicated based on absolute-risk thresholds, this seems reasonable. Although not in the high-risk group, the data from Nasir et al. (6) provide reassurance that withholding statins in those with a CAC score of 0 may likely be safe, at least in the midterm. In addition, the CAC score could be an important gatekeeper to avoid statin overtreatment if conventional scores overestimate risk. This editorialist also believes that individuals with a high CAC score (the definition of which remains debatable) would benefit from statins. The powerful prognostic implications of the CAC score as well as the substantial heterogeneity and ever-changing risk profiles of populations would thus support a more prominent role of CAC (as a marker of subclinical CHD) in routine stratification, which could be accomplished by integrating CAC results into risk scores, as recently proposed and validated (10). However, we have numerous recent examples of very reasonable hypotheses that are disproved when tested formally. Regarding CAC, numbers needed to treat (and cost-effectiveness) are estimated based on the assumption of similar relative risk reductions with statins in lower and higher risk groups; however, actual data suggest that relative benefit is in fact highest in the lowest risk categories (11). The same could be true across CAC strata.

For CAC scoring or other markers, including the new equations, to achieve Class I (or III) recommendations in clinical guidelines, all these questions will need to be addressed in a properly designed, prospective, randomized clinical trial. We therefore join our voice to that of the authors and others (12,13) encouraging the National Institutes of Health, perhaps in partnership with industry, to lead this effort. Although such an enterprise will undoubtedly
be daunting and costly, will not be perfect, and will not provide all answers, few prevention trials could have a broader impact on the population at large.

Alternatively, we can continue to speculate, assume, and extrapolate.

REFERENCES


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