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EDITORIAL COMMENT

Coronary Artery Calcium

Need for More Clarity in Guidelines*

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The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Prevention Guidelines made several important contributions. For example, preeminence was assigned to statin therapy for optimal atherosclerotic cardiovascular disease (ASCVD) risk reduction, with proper emphasis placed on statin intensity. In a welcome change, the new prevention guidelines recommended a strict absolute risk-based treatment algorithm for most primary prevention patients based on the principle of maximizing net benefit. The Clinician-Patient Risk Discussion succeeded in bringing the importance of shared decision making in primary prevention into sharp focus (1).

However, the 2013 ACC/AHA whiffed when it came to coronary artery calcium (CAC) testing. Despite mounting data supporting its usefulness for personalizing risk estimates, the guideline assigned a lukewarm IIB recommendation to the use of CAC "when a risk-based treatment decision is uncertain" (2). Although many hoped for a more detailed recommendation that might provide more specific direction for physicians in the selective use of CAC, little guidance was offered on the ideal target population. Prior ACC/AHA guidelines on risk stratification of asymptomatic adults were actually more favorable and concrete, offering a IIA recommendation for intermediate-risk patients (specifically defined as 10% to 20% 10-year coronary heart disease (CHD) risk using the Framingham Risk Score) (3). Perhaps most surprising, in the ACC/AHA guidelines CAC was assigned equal footing with other nontraditional predictors such as high-sensitivity C-reactive protein and the ankle-brachial index. This stands in contrast to unequivocal evidence of CAC superiority from comparative effectiveness studies published both before and after dissemination of the guidelines (4,5).

Unfortunately, to many in the imaging community, it seems as though the otherwise laudable guidelines lacked complete literature review and nuance with regard to CAC. For example, in the 2013 ACC/AHA guidelines, only high CAC scores were discussed and considered clinically actionable. The guidelines state that among individuals whose risk is uncertain, CAC >300 or CAC >75th percentile for age, sex, and ethnicity can be used as a rationale to prescribe lipid-lowering therapy. Those most familiar with CAC scoring know that these 2 criteria are somewhat arbitrarily chosen and identify *very* different patient populations. Frequent users of CAC scoring also know that the value of CAC extends beyond identifying high-risk cases. A CAC score of 0 —a common finding— is the strongest "negative risk marker" in cardiovascular medicine, with implications for identifying individuals at much lower risk than would have otherwise been suspected (6). Understanding the potential value of low CAC scores is particularly important when seeking to balance the reduced treatment threshold and resultant more pervasive treatment recommendations in the new ACC/AHA guidelines.

Three pivotal studies have now been published examining the implications of the CAC testing within the framework of the new ACC/AHA guidelines. The first, focusing specifically on the value of a CAC score of 0, was published by Nasir et al. (7) from the MESA (Multi-Ethnic Study of Atherosclerosis) study. This study showed that 57% of MESA study participants who would be considered for statin therapy (5.0% to 7.5% 10-year ASCVD risk) and 41% of individuals recommended for statin therapy (7.5% to 20.0%

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10-year ASCVD risk) have a CAC score of 0. These individuals were found to be at much lower risk than would have been predicted by the Pooled Cohort Equations (~1.6% and ~4.6% 10-year risk, respectively).

Pursnani et al. (8) studied 2,435 statin-naive individuals drawn from the Offspring and Third Generation cohorts from the Framingham Heart Study (8). Although the ACC/AHA guidelines improved the sensitivity for detecting cases of high CAC compared with prior ATPIII guidelines, approximately 33% of participants who would be recommended statin therapy had a CAC score of 0, with a corresponding 10-year ASCVD risk of just 1.6%.

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In this issue of *iJACC*, Mahabadi et al. (9) use data from the Heinz Nixdorf Recall study to examine the implications of CAC testing in the setting of both the European Society of Cardiology (ESC) and the ACC/AHA prevention algorithms (9). They demonstrate that among 3,745 statin-naive participants free of known ASCVD, 34% would be eligible for statins under the ESC guidelines (determined by some combinations of 10-year predicted risk, the presence of diabetes, and low-density lipoprotein cholesterol level), whereas a majority (56%) would be eligible under the ACC/AHA guidelines (>7.5% 10-year ASCVD risk). The main finding of this paper is that within both statin-eligible groups, CAC further stratified risk.

In participants eligible for statins under the ESC guidelines, 17% had a CAC score of 0 and 59% had a CAC score of <100. The CHD (2.6 and 2.7 per 1,000 person-years, respectively) and ASCVD (5.7 and 7.3 per 1,000 person-years, respectively) event rates in these statin-eligible groups were much lower than those observed in those with a CAC score of ≥100 (9.9 and 17.4 per 1,000 person-years, respectively).

Among individuals eligible for statins under the ACC/AHA guidelines, 19% had a CAC score of 0 and 62% had a CAC score of <100. Similar to the ESC guideline analysis, the CHD (2.7 and 3.3 per 1,000 person-years, respectively) and ASCVD (5.4 and 6.9 per 1,000 person-years, respectively) event rates in these groups were much lower than those observed for those with a CAC score of ≥100 (9.1 and 14.6 per 1,000 person-years, respectively).

The data from Mahabadi et al. (9) support the possibility of further risk stratification of both statin-ineligible and statin-eligible groups. Importantly, these results also enable comparison of the value of CAC in the ESC versus ACC/AHA guidelines and confirm one of the axioms of CAC testing—the role of the test shifts according to the patient population and treatment threshold. When the treatment threshold is higher (ESC), detection of unheralded high risk predominates, whereas when the treatment threshold is lower (ACC/AHA), the value of CAC shifts toward "de-risking" (10).

For example, under the ESC guidelines, 16% of individuals ineligible for statin therapy had a CAC score of ≥100 (number needed to scan [NNS] of just 6). In contrast, just 7% of those ineligible for statins under the ACC/AHA guidelines had a CAC score of ≥100 (NNS of 14). However, the Nasir et al. (7) analysis demonstrated that up to 50% of those with 10-year ASCVD risk of 5% to 10% have a CAC score of 0 (NNS of 2), clearly suggesting that the role of CAC in the ACC/AHA guidelines may be weighted toward identifying truly low-risk cases.

Strengths of the Mahabadi et al. (9) study include the large sample size, the well-known, well-phenotyped cohort, and the thoughtful analysis of CAC stratified by statin eligibility based on 2 distinct major guidelines. A weakness is the decision to treat CAC <100 as a low-risk group, even though data suggest a CAC score of 0 and perhaps 1 to 10 are more appropriate choices for truly distinct low-risk groups.

In light of recent data, what is the present role for CAC in clinical practice? It is clear that more guideline clarity is needed.

We believe that CAC should be assigned preeminence as an advanced risk stratification tool with potential utility in several clinical scenarios. Most importantly, CAC should be strongly considered in "intermediate-risk" patients who are statin reluctant or who desire shared decision making. CAC appears to consistently change clinical decision making in the 5% to 20% 10-year ASCVD risk group, and we believe this is the most appropriate modern definition of "intermediate risk" (7). In addition, CAC testing appears to be reasonable when the 10-year ASCVD risk is <5% in the setting of other major nontraditional risk factors, such as family history of premature disease or metabolic syndrome. We remain intrigued by the selective use of CAC in older individuals with ASCVD >20% whose risk is largely driven by age, especially when placed into a discussion about competing risks, potential drug-drug effects, and patient preferences toward longevity, quality of life, and preventive care. However, more data are needed to support this latter potential application of CAC testing.

In conclusion, we congratulate Mahabadi et al. (9) for providing additional data critical to the

understanding of most appropriate role of CAC. We predict that the next iteration of prevention guidelines will reflect the maturity of science in this field, leveraging the growing body of evidence to assign CAC a more meaningful role in everyday clinical risk stratification and shared decision making.

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