The past 2 decades have witnessed great progress in the treatment of advanced cardiovascular disease. Mortality of revascularization is close to or below 1% among cardiovascular centers of excellence, and a larger segment of the population has gained access to advanced cardiovascular care. Yet the burden of cardiovascular disease has risen over the same period. Every year, more than 500,000 U.S. residents die from a cardiac event. Altogether, cardiovascular and cerebrovascular diseases account for >25% of all deaths in developed countries (1).

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Over the past decade, cardiovascular diseases have moved among the top causes of death in the adult populations of India and China, the 2 fastest growing economies in the world. This paradox suggests that further efforts to improve treatment will be unlikely to have a great impact on reducing the socioeconomic burden of cardiovascular disease in our society. Rather, through effective prevention, we should aim to reduce the prevalence of atherosclerosis. One logical approach is to promote lifestyle modification. Some have even suggested the possibility of implementing primary prevention, including pharmacologic therapy, throughout the adult population. At the present, adopting such a radical concept would be limited by cost, drug side effects, and limited compliance. Alternatively, many have proposed screening as a way of identifying those subjects at greater risk who would most likely benefit from primary prevention. Risk stratification through clinical history, physical examination, and serum biomarkers has been extensively validated, and tools such as the Framingham or Reynolds risk scores have been adopted in clinical practice by most primary care practitioners. Nevertheless, although these tools identify subsets of the general population at low or high risk, they leave a significant number of subjects in an undetermined category. As an alternative or complementary tool, noninvasive atherosclerosis imaging has been promoted on the premise that early detection and quantification of atherosclerotic plaque burden may be a better predictor of risk and thus allow cost-efficient targeting of the population at risk. For such a screening method to be effective, it must be widely available, safe, highly reproducible, and inexpensive. Most experts would agree that the calcium score scan meets these characteristics (2), explaining its wide acceptance among the medical community and the public despite the limited insurance reimbursement. Moreover, several large-scale retrospective and a few prospective studies have unequivocally demonstrated the superior predictive accuracy of the calcium score for short- and long-term cardiovascular events.

In epidemiologic studies, coronary artery calcification has been associated with a higher risk of myocardial infarction (MI), even in asymptomatic patients. Growing evidence suggests that measurement of coronary calcium may be particularly valuable in therapy decisions for patients with an intermediate risk of coronary events. In these patients with intermediate risk based on clinical factors, a calcium score >300 is significantly associated with increased rates of MI and coronary death (3). The value of the calcium score has been recognized by the American Heart Association (4) and the National Cholesterol Education Program Adult
Treatment Panel III (5). In their opinion, asymptomatic patients at intermediate risk (10-year risk of 10% to 20% and 2 or more coronary risk factors according to the Framingham criteria) constitute the group that could benefit the most from changes in treatment and lifestyle; thus, in this group, the quantification of calcium score would be indicated most clearly.

In this issue of JACC, Sarwar et al. (6) report on a meta-analysis of 49 studies to investigate the value of the absence of coronary calcification (CAC = 0) for predicting events in symptomatic and asymptomatic patients, obstructive coronary artery disease in patients undergoing invasive or computed tomography coronary angiography, ischemia in patients undergoing stress myocardial perfusion imaging (MPI), and acute coronary syndromes in patients with acute chest pain.

In this meta-analysis, the authors show consistency in the relative risk ratios (Figs. 1 and 2 of Sarwar et al. [6]) for cardiac events in symptomatic and asymptomatic subjects with zero and nonzero CAC. Most studies have demonstrated a remarkably low event rate in asymptomatic patients with zero CAC. Recently, the MESA (Multi-Ethnic Study of Atherosclerosis) trial showed that only 8 of 3,409 subjects with zero CAC experienced a major cardiac event at a median follow-up of 3.8 years (7). Importantly, the prevalence of zero CAC in the studied population varied between 30% and 65% according to sex and ethnicity. Thus, a significant segment of the population could be categorized as having very low short-term risk. On the other hand, the same study demonstrated that the added predictive value for major coronary events of the calcium score was marginal, increasing the area under the curve from 0.79 to 0.83 compared with evaluation of risk factors alone. This finding suggests that the utility of calcium scoring is limited when applied to the general population. An earlier study by Greenland (3) demonstrated that the clinical value of this test was greatest in patients with intermediate Framingham risk.

One limitation of the meta-analysis performed by Sarwar et al. (6) is the absence of clinical data to further address the incremental prognostic value of a zero CAC over clinical risk factors.

The meta-analysis performed in symptomatic subjects also demonstrated that a zero CAC was associated with a very low event rate in this group. However, at least 1 of the studies included (8) found that the incidence of obstructive CAD in chest pain patients with zero CAC is not negligible (7.2%). In these patients, coronary obstruction was caused by noncalcified atheroma. Clearly, pre-test probability of disease is an important consideration when applying the results of a calcium score for clinical decision making in symptomatic patients.

Finally, many patients with zero CAC have a positive MPI but a good prognosis. It is possible that many of these cases represent false-positive MPI studies. An important application of calcium scoring thus may be to reduce the incidence of false-positive MPI and unnecessary coronary angiography.

In summary, the calcium score scan, as supported by this meta-analysis, is a very promising imaging biomarker of atherosclerosis. The absence of coronary calcification is associated with a very low incidence of cardiac events at 3 to 5 years. Although the strong prognostic utility of the calcium score is unquestionable, further studies are needed to elucidate the subject populations in which this test provides incremental prognostic utility over clinical risk assessment and serum biomarkers. Moreover, future studies are needed to address whether performing a calcium score leads to treatment modifications that will result in improved clinical outcomes and to prove that performing a calcium score to identify higher-risk populations is superior as a strategy to providing “an ounce of prevention” to the population as a whole.

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