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# Predicting Cardiovascular Events with Coronary Calcium Scoring

William S. Weintraub, M.D., and George A. Diamond, M.D.

The thoughtful clinician takes it to be self-evident that intensity of therapy should be proportional to risk of disease.[1,2] Ever since Bigger coined the term "risk stratification" to characterize this intuitive process,[3] more than 3000 articles (according to a recent PubMed literature search) have been published on the subject — at a rate that is doubling every 5 years.[4] Nearly 40% of these articles focus on cardiovascular medicine, where "risk stratification" has become something of a mantra for rational, evidence-based clinical management.

Predicting who will have a cardiovascular event is indeed an important clinical and societal goal. Currently, the United States spends more than $400 billion annually on cardiovascular diseases.[5] However, that disease is common or expensive is not in itself sufficient reason to try to predict it. What is necessary is that reasonable steps can be taken to prevent events. In the case of coronary disease, multiple steps can be taken: patients can stop smoking; they can begin to exercise, control their diet, and lose weight; and when blood lipid levels are abnormal and hypertension or diabetes is present, then pharmacologic therapy can be instituted to reduce risk if nonpharmacologic means fail. The importance of these risk factors has been recognized for more than 45 years, since researchers involved with the Framingham Study published a seminal paper on the subject.[6]

The ability of a risk factor to predict these events as they occur over time may be assessed by the relative risk, or hazard ratio, which is the incidence of events in patients with the risk factor divided by the incidence of events in patients without the risk factor. Models based on the values of risk factors can be created to calculate the probability of an event. How well a model predicts the observed probability of an event across levels of risk is called calibration, while the ability to predict who will and who will not have an event is called discrimination. Thus, calibration and discrimination are not the same, and there is an upper limit to how well a perfectly calibrated model can discriminate.[7] A model's discrimination is often assessed with the c-index (equivalent to the area under the receiver-operating-characteristic curve), which is the fraction of pairs of subjects (one who has an event and one who does not) for which the probability of an event is higher in the subject who has the event. A c-index can vary from 0.5 (no ability to discriminate with half the pairs predicted correctly) to 1.0 (perfect discrimination with all pairs predicted correctly).

The Framingham score remains the most common way to predict cardiovascular risk.[8] By assessment of a few readily available clinical and laboratory variables (age, sex, total cholesterol level, high-density lipoprotein cholesterol level, smoking status, and systolic blood pressure), the 10-year risk of a cardiovascular event can be rapidly and conveniently calculated with a discriminant accuracy of approximately 75%.[8,9] Although this model may be viewed as offering only limited ability to predict individual events, it is inexpensive to assess and provides an opportunity to intervene in cases of cigarette smoking and abnormalities in blood pressure and lipid level.

New risk factors are continually being proposed that could improve discrimination. Popular ones are high-sensitivity tests for C-reactive protein, a biomarker of inflammation, and the

coronary-artery calcium score.[10,11] The problem of adding any one new risk factor to the well-established Framingham score is that a new risk factor will have a limited effect on discrimination unless its relative risk is quite high — in the range of 10 or so.[12] For a new risk factor to be useful, it must offer both a large relative risk and a therapeutic target.

The coronary calcium score would seem to be an ideal new risk factor, since it essentially visualizes coronary atherosclerosis.[11] However, coronary calcium correlates strongly with key risk factors such as age and sex. Furthermore, coronary calcium does not point out sites of present or future unstable atherosclerotic plaques. Coronary calcium does predict risk, presumably because the more calcium, the greater the atherosclerotic burden and thus risk.

In this issue of the *Journal*, Detrano et al.[13] offer new data on coronary calcium scoring as an adjunct to the Framingham risk score in four ethnic groups. This study derives from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort of 6722 men and women of whom 39% were white, 28% were black, 22% were Hispanic, and 12% were Chinese. The subjects were followed for a median of 3.8 years. There were 162 coronary heart disease events, including 89 nonfatal myocardial infarctions or deaths from coronary heart disease. As compared with subjects with a coronary calcium score of 0, subjects with a score between 1 and 100 had a hazard ratio of 3.61 (95% confidence interval [CI], 1.96 to 6.65), subjects with a score from 101 to 300 had a hazard ratio of 7.73 (95% CI, 4.13 to 14.47), and subjects with a score over 300 had a hazard ratio of 9.67 (95% CI, 5.20 to 17.98). The model predicted similarly in the four ethnic groups considered. Discriminant accuracy (measured with the c-index) increased from 0.79 for risk factors alone to 0.83 for risk factors plus calcium score ($P=0.006$), with respect to myocardial infarction and death, and from 0.77 to 0.82 ($P<0.001$) for all coronary heart disease events.

The MESA results confirm previous studies that showed that calcium scoring does predict events, as do other risk factors.[14-16] But is this relatively small improvement in accuracy worth it? Does calcium scoring provide value? Here the issue is uncertain. There can be value only if patient outcomes improve (i.e., if calcium scoring can be shown to change care in such a way that there are fewer events in the future). This could happen if, for instance, control of blood pressure or lipid levels was made more aggressive in the presence of coronary calcium. Even if outcomes are improved, this does not establish value without additional consideration of the direct and indirect costs of care. In principle, if improved outcomes could be shown as a result of coronary calcium scoring, if those improved outcomes could be translated into improved survival or health status, and if the cost of calcium scoring and downstream costs related to additional testing, therapies, and events could be predicted, then the cost-effectiveness of calcium scoring could be determined. However, the cost-effectiveness of calcium scoring will depend on choosing cost-effective preventive strategies, which are not necessarily related to the test. The cost-effectiveness analyses of calcium scoring have been reviewed by Shaw et al.,[17] who found studies to date to be relatively preliminary. They also found that the investigators had not fully considered all clinically relevant preventive strategies.[18]

Consequently, there are not sufficient data available to offer a robust assessment of cost-effectiveness. It is a high standard for diagnostic testing to convincingly show cost-effectiveness. However, that eventually will be the standard, especially for screening tests that may be costly and for which the events may occur years in the future and the ability to guide therapy during that time is uncertain.

Thus, coronary calcium scoring remains an interesting technique for predicting events, in addition to the simple Framingham score. Nonetheless, the role of coronary calcium screening — and of risk stratification in general, beyond the Framingham score — remains unknown.

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From the Christiana Care Health System, Newark, DE (W.S.W.); and Cedars–Sinai Medical Center, Los Angeles (G.A.D.).

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