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EDITORIAL COMMENT

Total Coronary Artery Calcium Score Remains Preferred Metric to Refine Risk Prediction in Nearly All Patients*

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Cardiovascular risk prediction remains an imperfect science. Current risk prediction models rely on demographic information, medical history, and laboratory tests. Scoring tools such as the Framingham Risk Score (1) help clinicians to stratify patients into low-, intermediate-, and high-risk categories of developing coronary heart disease (CHD). Its limitations include its generalizability to underrepresented minorities and its relatively short 10-year perspective in defining risk (2). Moreover, relatively few women qualify for aspirin or statin therapy before age 65 years (3,4).

Although the Framingham Risk Score is the standard tool for guiding the aggressiveness with which pharmacological and lifestyle interventions are recommended, most clinicians would like to know which "low-risk" patients actually have advanced subclinical atherosclerosis for their age and gender and which "low-risk" subjects actually have no or minimal plaque burden. There is great interest in quantifying atherosclerosis to determine whether to initiate aspirin and statin therapy rather than waiting until the patient has an event or qualifies for these treatments by reaching the currently designated threshold of a 10% risk of a hard event (heart attack or CHD death) over the next decade.

See page 61

Total coronary artery calcium scores (CACS) are strongly associated with total atherosclerotic plaque burden, with correlation coefficients of about 0.90 (5,6). Clear evidence regarding the prognostic strength of CACS in predicting CHD events has now emerged in multiple prospective studies that have been summarized in recent American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) statements (6,7). As compared with those without any coronary calcification, a recent meta-analysis found relative risk ratios for a CACS of 100 to 400, 401 to 1,000, and >1,000 of 4.3 (95% confidence interval [CI] 3.5 to 5.2, $p < 0.0001$), 7.2 (95% CI 5.2 to 9.9, $p < 0.0001$), and 10.8 (95% CI 4.2 to 27.7, $p < 0.0001$), respectively (8). Moreover, subjects with no CAC had a very low rate (approximately 0.4%) of a hard event over 3 to 5 years of observation.

The latest AHA and ACCF statements indicate that a CAC scan can be a useful tool in refining risk prediction in intermediate-risk adults (6,7). Intermediate risk is currently defined by national guidelines as a 10-year risk of 10% to 20% of a hard event (6–8), but it was previously classified by the 2003 ACCF Bethesda Conference on Atherosclerosis Imaging as a 6% to 20% risk of a hard event (9). In our view, this expanded 6% to 20% category is more useful when trying to more accurately risk stratify persons with a family history of premature CHD or in people with several components of the metabolic syndrome, because the Framingham Risk Score does not take into account family history, triglyceride levels, or waist circumference (3).

Previous studies have primarily used total CACS to predict coronary risk (10,11). The total calcium score correlates with the amount of coronary atherosclerosis and provides an estimate of an individual's total plaque burden. However, further refinement of coronary risk might theoretically be obtained by more closely examining the number and extent of calcified lesions within the coronary tree.

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In this issue of *JACC: Cardiovascular Imaging*, Williams et al. (12) report the findings of their study addressing this question. They sought to determine whether additional information on the number and location of calcified plaques adds to the strong prognostic value of total CACS. They analyzed nearly 15,000 asymptomatic individuals free of coronary artery disease, but with ≥1 cardiac risk factor, who were referred for CACS.

The total number of calcified lesions was strongly associated with mortality. However, this risk seemed to be explained by the total burden of CAC because when analyses were stratified by categories of total CACS, the number of lesions no longer seemed to provide significant prognostic information. One exception was in the small subgroup of subjects with elevated CACS (>400) that was concentrated in 1 or 2 lesions, in which the relative risk of mortality was particularly high. The investigators also report associations between lesion count in the left main artery and mortality and that a high CACS in the left main and left anterior descending arteries is associated with increased risk of mortality, whereas a high CACS in the circumflex and right coronary arteries is not.

Their conclusions should be interpreted with several caveats. The multivariable models adjust for the traditional risk factors of age, gender, smoking, diabetes, hypertension, and hyperlipidemia, but not for a family history of premature CHD. They also used the dichotomized categories of hypertension and hyperlipidemia rather than the individual components of systolic and diastolic blood pressure and total and high-density lipoprotein cholesterol, all of which may be somewhat stronger determinants of CAC.

Second, the investigators do not present the results of some of their subgroup analyses with CIs. One positive finding in the study was that the number of lesions predicted mortality independent of total CACS when the CACS was high and focally located on 1 or 2 lesions. The investigators do not provide the number of subjects who fall into this unusual category, which we might expect to be very small. Similarly, a large number of lesions in the left main artery were associated with increased mortality. However, <1% of subjects had even 3 left main artery lesions, making any extrapolation to ≥6 lesions less stable risk estimates. Mohlenkamp et al. (13) previously reported that calcium scores >1,000 in left main artery disease were the only independent predictor of hard events (hazard ratio 4.5, 95% CI 1.1 to 17.8).

The current study may have had additional power to detect the incremental prognostic value of the number, location, and extent of coronary lesions if data regarding cause of death were available or if nonfatal cardiovascular outcomes had been included. The failure of the location and number of calcifications in predicting cardiovascular outcomes after accounting for total CACS is not entirely unexpected. Although total CACS tracks well with total plaque burden, there is little correlation between individual calcifications and luminal stenoses seen on angiography (14).

Our goal should be to target our therapies to those who would most benefit from them. As we improve the accuracy with which we categorize patients into risk strata, we will be better equipped to decide when to promote aggressive lifestyle changes and when to institute antiplatelet therapy or more stringent cholesterol (and perhaps blood pressure) goals. Future studies may yet improve on the current metric of total CACS in risk stratification, but until then the aggregate value seems to be the most useful parameter.

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