

EDITORIAL COMMENT

The Prognostic Accuracy of Coronary Calcification*

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In this issue of the *Journal*, Budoff et al. (1) report the relationship of calcified coronary plaque to all-cause mortality in 25,253 asymptomatic middle-age men and women followed up for an average of 6.8 years. Their findings fall into 3 categories:

1. The coronary calcium score predicted all-cause mortality.
2. The coronary calcium score predicted all-cause mortality more accurately than standard coronary artery disease (CAD) risk factors.
3. Calcium score-specific mortality was similar in this cohort (from California) and a cohort of 10,377 asymptomatic middle-age men and women from Tennessee (2); hence, the results of this study are generalizable.

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That the coronary calcium score predicted all-cause mortality in this study is important and indisputable. It is important because it circumvents arguments about the validity of CAD end points used in prior studies of electron beam computed tomography (CT) scanning. It is indisputable because of the overwhelming strength of association between coronary calcification and death. The chi-square value linking the calcium score and mortality was 82 after adjustment for age and standard CAD risk factors. In keeping with natural history studies based on coronary angiography (3), mortality rates increased as a function of the number of diseased (i.e., calcified) vessels. This relationship was so strong that it applied to mildly as well as heavily calcified vessels (calcium scores of 10 to 100 and >100, respectively). Finally, in univariate analysis and in terms more familiar to the clinician, the calcium score predicted all-cause mortality with an area under the receiver-operator characteristic (ROC) curve of 0.81. Given that standard CAD risk factors predict nonfatal myocardial infarction and coronary death with an area under the ROC curve of around

0.75 (4,5), more accurate prediction of all-cause mortality with electron beam CT scanning is astonishing. Is it real?

The answer to this question is yes, especially in an intermediate- to high-risk population. The reason for this qualification is that, in very round numbers, atherosclerotic cardiovascular disease (ASCVD) currently accounts for about 33% of deaths in the U.S. (6). If the coronary calcium score predicted all of these deaths correctly and was completely unrelated to all other deaths (area under the ROC curve of 0.50 for non-ASCVD deaths), then the area under the ROC curve for all-cause mortality would be 0.667 ($0.333 + [0.5 \times 0.667]$). A higher area under the curve must be the result of a substantially higher incidence of ASCVD deaths, some relationship between coronary calcification and non-ASCVD deaths, or both. There is a link between coronary calcification and a host of non-ASCVD deaths (cancer, degenerative neurologic diseases, etc.), namely, age, so “both” is probably the explanation for the high ROC curve area.

The second major finding is that the coronary calcium score predicted all-cause mortality more accurately than standard CAD risk factors. The basis for this conclusion is that the area under the ROC curve was 0.76 ± 0.02 after adjustment for risk factors, whereas the area under the ROC curve was only 0.61 ± 0.03 for risk factors ($p < 0.0001$). Again, a discerning reader must ask whether it is real.

This question has several components, the first of which is whether CAD risk factors predict all-cause mortality. This would be quite an accomplishment, given that two-thirds of Americans currently die of causes other than ASCVD. Nevertheless, several studies have found a relationship between risk factors and all-cause mortality (7). In a brief literature search on this subject, I was unable to find any studies that reported this relationship in terms of ROC curve areas. This failure is probably just as well, because, for the reasons cited in paragraph 3, the ROC curve area would vary as a function of the CAD risk profile of the population studied. Thus, it is impossible to say that CAD risk factors predict all-cause mortality with an ROC curve area of X , let alone to use X as a basis for comparison with values obtained in this study.

What remains is the observation that the calcium score predicted all-cause mortality independently of self-reported risk factors. The use of self-reported risk factors is controversial because errors degrade standard test performance more than the performance of an alternative test based on direct measurement, in this case, the calcium score. However, studies of self-reported risk factors indicate a high degree of accuracy in educated populations (8,9). Reduction of the risk factor ROC curve area because of reporting errors is therefore probably modest. A more serious confounder is the treatment of hypertension and hypercholesterolemia. At the same time, the administration of aspirin and more vigorous treatment of elevated lipid levels because of high coronary calcium scores also likely diminishes the prognostic accuracy of the calcified plaque (10). Thus, the adjusted

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calcium score ROC curve area (0.76 ± 0.02) and the risk factor ROC curve area (0.61 ± 0.03) probably both understate their association with mortality. The gap between the two curve areas is so wide as to make its elimination by direct measurement of risk factors unlikely. This assertion is supported by another important observation: the calcium score predicted all-cause mortality more accurately than age ($p < 0.001$). The investigators could reinforce the conclusion that the calcium score predicted mortality more accurately than risk factors by separate analyses of the relationship between self-reported and measured cholesterol (the latter being available in 11,275 of the 25,253 subjects) and mortality. If measured and self-reported cholesterol levels are similarly associated with all-cause mortality, the argument against self-reported risk factors is profoundly weakened.

Finally, the investigators assert that the results of their study are generalizable. This is the weakest conclusion of their study. It is based on allegedly similar mortality at 5 years in the present cohort and a previously reported cohort of 10,377 asymptomatic middle-age adults from Tennessee (2). Although this may be the case, it is not apparent to the naked eye. The survival curves suggest mortality rates about 40% lower in California at 4 years, and, for persons with calcium scores of 400 to 1,000, survival in California was better at 12 years than survival in Tennessee at 5 years (see Fig. 2, table at bottom). Perhaps, as Pittsburgh Pirate shortstop Dale Berra said of his father, Yankee legend Yogi Berra, "Our similarities are different" (11). The Tennessee cohort had an even higher prevalence of CAD risk factors than the present study, but was on average 3 years younger. Maybe, and despite their size, the study populations are not large enough to detect the net effect of these differences, whatever it is. More importantly, the risk factor prevalences indicate that the referring doctors understood that screening tests are best applied to persons at intermediate risk and/or, in the case of a family history of premature CAD (a euphemism for currently unknown genetic factors), persons with an otherwise unmeasurable determinant of CAD events.

A large and consistent body of evidence indicates that the coronary calcium score is more closely associated with CAD and CAD events than standard risk factors. This includes 4 studies of the severity and extent of CAD, defined angiographically (12–15), 2 cross-sectional studies (acute myocardial infarction and sudden death [16,17]), 5 retrospective studies with clinical outcomes (18–22), and 6 prospective studies with clinical outcomes (23–28). Although the retrospective studies suffer from self-reported risk factors and, in some cases, low rates of follow-up, the prospective studies are not so limited. The present study is the second to show that the calcium score predicts all-cause mortality independently of and/or more accurately than standard risk factors (2). There are no exceptions to this consistent record of incremental prognostic value of the coronary calcium score, which now comprises more than 300,000 patient years of observation. It is time to move on to the remaining

important questions about calcified coronary plaque: prognostic accuracy in minorities, the effect of screening on outcomes, and cost-effectiveness.

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