

## Coronary Artery Calcium and Cardiac Events Is Electron-Beam Tomography Ready for Prime Time?

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Cardiovascular diseases in general and coronary artery disease in particular remain the number one cause of death and disability in all industrialized and many emerging countries all over the world. There has been considerable interest in developing better methods to predict future events so that preventive therapy can be targeted toward those at increased risk. Although in excess of 300 risk factors have been identified, most are highly collinear with each other, such that they are not independent. The number of independent risk factors is relatively small. Perhaps the best prediction algorithm for people who are at risk but who have not had a previous event is the Framingham risk score.<sup>1</sup> The Framingham score, which measures age, sex, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking, and systolic blood pressure, has been incorporated into the National Cholesterol Education Program Adult Treatment Panel III guidelines, and thus has been recommended to help guide therapy.<sup>2</sup> There is recognition that the Framingham risk score is limited. It has been evaluated with a *c* index. The *c* index is equivalent to the area under a receiver-operator characteristic curve, and measures for any pair of patients, one who has an event and one who has not, the fraction of pairs correctly identified. A *c* index of 0.5 is equivalent to chance and a *c* index of 1.0 is perfect discrimination. The Framingham score has a *c* index of 0.68 to 0.77, depending on the exact specifications of the model.<sup>2</sup> Clearly, there has been interest in improving the ability to predict future events. Recently, C-reactive protein (CRP), a measure of inflammation, has been shown to predict future events, to be independent of other risk factors in the Framingham score, and to be a more powerful predictor of events than low-density lipoprotein cholesterol.<sup>3</sup> There is also interest in determining whether measures of oxidative stress, such as myeloperoxidase or nitrotyrosine, can also predict events, although the data for measures of oxidative stress remain less certain than measures of inflammation.<sup>4,5</sup>

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The next major risk factor to be considered is imaging of coronary calcium. This has a theoretical advantage in that

coronary calcium is frequently seen in atherosclerotic lesions in the vasculature but is rarely seen otherwise. Thus, imaging of coronary calcium may be viewed as direct imaging of the presence of atherosclerosis. Although this idea is quite attractive, it does need to be proven that finding coronary calcium will predict events, and that as a risk factor it adds to other risk factors that are already being collected. The study by Kondos et al<sup>6</sup> adds substantially to our information about the role of coronary calcium in predicting future events.

Kondos et al<sup>6</sup> used electron beam tomography (EBT) to image the coronary arteries of 8855 self-referred men and women who had not had a prior cardiovascular event. Follow-up was available at  $37 \pm 13$  months on 5635 subjects, 4151 of whom were men and 1484 of whom were women. Multivariate correlates of events were determined by Cox model analysis, permitting the assessment of the independent contribution of risk factors to predicting outcome. Hard events included cardiovascular death and myocardial infarction. Hospital records and death certificates were used to determine the number of cardiovascular deaths. Published criteria were used to establish the number of myocardial infarctions, but the methods to do so are not entirely clear from the article. Soft events include coronary revascularization, either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). During follow-up, there were 257 events, 244 of which were confirmed. Twenty non-cardiac deaths were excluded, leaving 224 events, 58 hard events (21 deaths, 37 myocardial infarctions), and 92 CABGs and 74 PCIs. The risk factors smoking, hypercholesterolemia, diabetes, and hypertension were assessed by survey. The diagnoses of hypercholesterolemia, diabetes, and hypertension were validated in a previously published study, with good validation for hypercholesterolemia ( $\kappa$  statistic 0.796) and diabetes ( $\kappa$  statistic 0.783), but not hypertension ( $\kappa$  statistic 0.36). The low  $\kappa$  statistic for hypertension was ascribed to good blood pressure control. Coronary calcium was assessed by EBT using a GE Imatron C-100 scanner. The calcium score was calculated using the Agatston method<sup>7</sup> and expressed as an age/gender percentile.<sup>8</sup> The calcium score was predictive of hard and soft events in men (relative risks [RR] 3.86, 95% confidence interval [CI] 1.17 to 12.70, and RR 26.8, 95% CI 3.72 to 193, respectively) and of soft events in women (RR 3.08, 95% CI 1.11 to 8.58). These relative risks are corrected for age, tobacco abuse, hypercholesterolemia, diabetes, and hypertension. Risks for hard and soft event in men and soft events in women increased with increasing quartile of coronary calcium score. For hard events in men, the relative risk was

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significantly  $>1$  for the third and fourth quartile of coronary calcium score, and for soft events it was  $>1$  for the second, third, and fourth quartile of coronary calcium score. For soft events in women, the relative risk of the coronary calcium score was only predictive for events in the fourth quartile.

This paper by Kondos et al<sup>6</sup> offers what are probably the most compelling data to date on coronary calcium to predict future events. However, there are a number of significant limitations. The most obvious limitation is that follow-up was available on only 64% of the patients. Although no bias in who was followed up was noted, this does remain a concern. The soft events in this study were coronary revascularization, either PCI or CABG. As pointed out by the authors, the presence of coronary calcium may have helped prompt physicians to refer their patients for coronary angiography and subsequent revascularization. Thus, PCI and CABG as endpoints are of uncertain importance. This leaves just 58 hard events. Only self-reported myocardial infarctions could be determined, so there may have been additional myocardial infarctions that were never accounted for. It is possible that there was greater surveillance of subjects with elevated calcium, such that systematic under-reporting of events with low scores is a least possible. Also, as pointed out by the authors, the study was probably underpowered to examine hard events in women. There is also concern about the measurement of the other risk factors, which were assessed by survey. Although the authors have validated the measures for hypercholesterolemia and diabetes, they could not validate the measure of hypertension. The other risk factors were not particularly strong correlates of events. Thus, only age was even a univariate risk factor for hard events in men, whereas only diabetes and hypertension were univariate risk factors for hard events in women. The limited ability of these risk factors to predict events does limit the models presented in this paper, and suggests that the confounding effects of these risk factors may not have been adequately accounted for. On the other hand, many risk factors are subject to therapeutic intervention, including tobacco abuse, hyperlipidemia, diabetes, and hypertension. Thus, the limited ability of these risk factors to predict events may reflect the fact that therapeutic efforts to control risk factors may have already been taking place in these patients who were sufficiently motivated to self refer for EBT. The authors could also have done more to justify their models, including the development of a c index as an additional measure of discrimination and development of measures of calibration and validation.

Although there are multiple limitations as noted above, this article<sup>6</sup> clearly does add to the literature on this subject. There have previously been several studies that have shown that coronary calcium predicts future cardiovascular events.<sup>9-12</sup> However, there has also been 1 study in which the additional information from EBT in older patients was more marginal.<sup>13</sup> The real question now is not whether EBT adds information, but rather whether it adds

sufficient information to justify its use, and if so, in which groups of patients.

EBT can only be justified if it can improve outcome. For EBT to successfully do this, it must be shown that the use of this test can help to successfully select appropriate therapy. Unfortunately, an unequivocal answer to this question is probably not possible, as this would require a massive clinical trial, which is extremely unlikely to ever be mounted. Thus, intermediate endpoints are necessary, in particular the prediction of events. Even a totally unequivocal answer to this question is quite a difficult undertaking. Finally, there is the question of whether EBT is cost-effective. EBT may add more information than either serum lipids or CRP measurement, but it is also considerably more expensive. As a clinical trial to evaluate EBT is unlikely to be attempted, there will be no opportunity for an economic evaluation as part of a clinical trial. Thus, the cost-effectiveness of EBT can only be evaluated using a decision-analytic simulation. Establishing the cost-effectiveness of testing with decision-analytic methods is notoriously difficult, as the downstream therapeutic choices and possible events can be quite complicated and difficult to predict. A satisfactory cost-effectiveness study of EBT has yet to be published.

Finally, then, is EBT ready for routine clinical use? This question has been considered without a definitive answer by the American College of Cardiology and the American Heart Association,<sup>14</sup> and this editorial cannot provide a final answer to this question either. However, there are a few points that can be made. Routine EBT for all adults probably cannot be justified. People at low risk should not need EBT, whereas people at high risk of events should have risk factors treated aggressively no matter what the EBT test shows. Thus, EBT would seem to be most useful in people in whom risk is uncertain and where EBT may help guide therapeutic or even further diagnostic options. Hopefully, as more information becomes available about this test, the place of EBT will be increasingly clear. The article by Kondos et al<sup>6</sup> is one more step in that direction.

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