News and Views From the Literature

Cardiac Risk

Coronary Calcium Scoring for All?

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Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Detrano R, Guerci AD, Carr JJ, et al.

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Coronary artery calcium scoring has been shown to add incremental predictive value to traditional cardiac risk factors in the prediction of subclinical atherosclerosis and future cardiac events.[1-3] However, previous studies have gathered data from patient populations that were predominantly white. Detrano and colleagues[4] sought to determine whether a coronary calcium score could predict future coronary events among 6722 asymptomatic subjects from 4 major US ethnic groups in 6 urban communities. The subject population was categorized as 38.6% white, 27.6% black, 21.9% Hispanic, and 11.9% Chinese.

Study participants were members of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort,[5] had no prior clinical cardiovascular disease, and ranged in age from 45 to 84 years. All subjects underwent either electron-beam computed tomography (CT) or multidetector CT for coronary calcium assessment and were followed for a median of 3.8 years (maximum, 5.3 years). Calcium scores (Agatston scores) were treated both as a continuous variable and stratified into 4 categories based on the following cut-off points: 0, 1 to 100, 101 to 300, and greater than 300. Endpoints were major coronary events (myocardial infarction and death from coronary heart disease) and any coronary event (defined as myocardial infarction, death from coronary heart disease, definite angina followed by coronary revascularization, definite angina not followed by coronary revascularization, and probable angina followed by coronary revascularization).

The prevalence of any coronary calcification (calcium score > 0) was highest in white subjects (men: 70.4%, women: 44.7%) and men. The prevalence of calcification in the other ethnic groups ranged from 52.0% to 59.2% for men and from 34.8% to 41.9% for women. A total of 162 patients had a coronary event during the follow-up period, with 89 major events (72 nonfatal myocardial infarctions, 17 cardiovascular deaths). These patients had a less favorable cardiovascular risk profile, but there was no difference between patients with and without coronary events when stratified by the 4 ethnic groups ($P = .26$).

Detrano and colleagues[4] first wanted to determine whether coronary calcium could be used to estimate coronary heart disease in the MESA cohort. Using the 4 stratified calcium score categories, they calculated unadjusted Kaplan-Meier cumulative-event curves and found a stepwise gradient increase in event rates among the 4 calcium score groups ($P < .001$). Subjects in the highest

Table 1
AUC for Risk Factors Alone Versus Risk Factors Plus CAC

	Major Coronary Events			Any Coronary Events		
Ethnic Group	AUC for Traditional Risk Factors	AUC for Risk Factors Plus Calcium Score	*P* Value	AUC for Traditional Risk Factors	AUC for Risk Factors Plus Calcium Score	*P* Value
White (n = 2598)	0.76	0.79	.10	0.75	0.79	.02
Chinese (n = 1852)	0.83	0.88	.05	0.74	0.85	< .001
Black (n = 1474)	0.79	0.87	.04	0.81	0.87	.005
Hispanic (n = 798)	0.84	0.86	.11	0.80	0.84	.10
Total (N = 6722)	0.79	0.83	.006	0.77	0.82	< .001

AUC, area under the operating curve; CAC, coronary artery calcium.
Adapted with permission from Detrano R et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358: 1336-1345.[4] Copyright © 2008 Massachusetts Medical Society. All rights reserved.

calcium score group (> 300) had the highest estimated rates for both major coronary events and any coronary events. The authors then used a Cox proportional hazard model to determine the risk of coronary events after adjustment for traditional cardiovascular risk factors, including age, sex, ethnic group, cigarette smoking, diabetes, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, and lipid-lowering and antihypertensive medications. They also found a gradient increase in hazard for both major coronary events and any coronary events when comparing patients with any calcium to patients with a calcium score of zero, after adjusting for risk factors. For both major coronary events and any coronary events, when compared with patients with no calcium, there was a greater than 3-fold increase in hazard for those with a calcium score of 1 to 100, a 7-fold increase for those with a calcium score of 101 to 300, and a greater than 6- to 9-fold increase for patients with a calcium score exceeding 300 (all $P < .001$). There was also a 20% increase in hazard for major coronary events and a 26% increase in any coronary events when the calcium score was doubled (both $P < .001$).

To predict coronary events in each of the 4 ethnic groups, the authors first used a Cox regression model with adjustment for risk factors and interactions of the ethnic groups with both calcium score and diabetes. They found a significant 15% to 39% increase in the hazard for major and any coronary events that was associated with a doubling of the coronary calcium score. (The 1 exception to this finding was the risk of a major coronary event in the Chinese subjects [hazard ratio, 1.25; 95% confidence interval, 0.95-1.63; $P = .11$].) The authors then determined the incremental predictive value of adding the coronary calcium score to traditional risk factors by using the area under the curve (AUC) for predicting major and any coronary events, according to ethnic groups and the total cohort (Table 1). An AUC value can range from 0.5 to 1.0, with 0.50 being similar to a random coin toss and 1.0 being perfect discrimination. For major coronary events, the baseline AUCs for risk factors alone was quite good and ranged from 0.76 to 0.84 for the 4 ethnic groups and 0.79 for the total cohort. The addition of coronary calcium to risk factors had incremental benefit over standard risk factors alone in the Chinese subjects (AUC increased from 0.83 to 0.88; $P = .05$), the black subjects (AUC increased from 0.79 to 0.87; $P = .04$), and the total cohort (AUC increased from 0.79 to 0.83; $P = .006$). However, the addition of coronary calcium to risk factors did not significantly change the AUC among white subjects (AUC changed from 0.76 to 0.79; $P = .10$) or Hispanic subjects (AUC changed from 0.84 to 0.86; $P = .11$). Similarly, for any coronary events, the AUC predicted from baseline risk factors alone ranged from 0.74 to 0.81 for the 4 ethnic groups and was 0.77 for the total cohort. There was an incremental predictive value for adding the calcium score to risk factors in most groups; AUC increased from 0.75 to 0.79 in the white subjects ($P = .02$), from 0.74 to 0.85 ($P < .001$) in the Chinese subjects, from 0.81 to 0.87 ($P = .005$) in the black subjects, and from 0.77 to 0.82 ($P < .001$) in the total cohort. Interestingly, as with the major coronary events, addition of the calcium score did not significantly increase the incremental value in predicting any coronary events in Hispanic subjects (AUC increased from 0.80 to 0.84; $P = .10$).

The authors concluded that the coronary calcium score has utility and is a "strong predictor of incident coronary heart disease" in the MESA population, with a benefit that is not limited to white patients. They also found that the calcium score provides incremental value beyond that of traditional risk factors for predicting coronary events in the total MESA cohort. These conclusions provide a compelling argument for the integration of the calcium score into standard clinical practice in primary preventive cardiology for asymptomatic patients. However, such a broad, population-based strategy for all asymptomatic patients may not be feasible.

Potential Limitations

Radiation

One potential limitation in the use of calcium scoring is that the test requires a small dose of ionizing radiation. However, the dose is quite small; reportedly, 1.0 to 1.3 mSv with electron-beam CT[6] and 3 mSv with the newer, multidetector CT (1 mSv using prospectively triggered scans and 3 mSv using retrospectively gated scans).[7] To put these numbers into perspective, the annual background radiation in the United States is 3.0 mSv.[8] The radiation issue has been more closely scrutinized in coronary CT angiography,[9-12] but dose-saving algorithms to reduce radiation are also applicable to calcium scoring. Clinicians are encouraged to implement them and to follow the ALARA (As Low As Reasonably Achievable) principle.[7,9,12] Furthermore, the estimated risks of fatal malignancy or death from radiation exposure or the lifetime odds of dying among 1000 individuals are 0.05 from a 1 mSv calcium score test and 0.5 from a 10 mSv coronary CT angiography. In comparison, the lifetime odds of dying from a motor vehicle accident are 11.9, from a pedestrian accident are 1.6, and from being struck by lightning are 0.013.[7,13] Thus, the associated radiation exposure from a single calcium score scan is less of a public health concern.

Cost

Another issue yet to be resolved is the cost-effectiveness of calcium scoring as a screening tool. As of 2006, the United States spent more than $400 billion per year on cardiovascular diseases.[14] A report by Taylor and colleagues[3] estimates a marginal cost-effectiveness of calcium scoring, assuming a 30% improvement in survival related to primary prevention, of $37,633 per quality-adjusted life-year saved among at-risk men. However, Shaw and coworkers[15] reported in a meta-analysis of cost-effectiveness studies that the issue of cost-effectiveness remained largely unsettled. It is unclear what the costs and effects of further downstream testing would be if such a strategy is implemented. In the current era, in which certain statin therapies have become generic and much more affordable, it may be more cost-effective to treat all patients who have modifiable risk factors for coronary artery disease with aggressive medical therapy, particularly because results from this study show that the calcium score was not incrementally better than standard risk factors in predicting either major or any events in Hispanic subjects or in predicting major events in white subjects.

Patient Population

Which patients should undergo calcium scoring? The current guidelines from the American College of Cardiology Foundation/American Heart Association 2007 clinical expert consensus state that there is "limited clinical value" in obtaining a calcium score in low-risk patients, identified by Framingham Risk score, because their chance of having a coronary event is less than 1.0% per year.[16] Additionally, there is no role for a calcium score in patients at high risk because these patients should be treated aggressively with lifestyle modification and pharmacologic agents, regardless of any test results, according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report.[16-18] However, the asymptomatic patients to gain the most from a calcium score are those at intermediate risk (with 2 or more risk factors) for coronary heart disease because they have a 10% to 20% risk for 10-year events and can be reclassified to either a lower or higher risk group depending on their calcium score.[18] In these patients, a calcium score of zero would allow them to be reclassified as low risk (with a 10-year event rate $< 10\%$), and they would require less aggressive medical therapy; a high calcium score would reclassify them as high risk (with a 10-year event rate $\geq 20\%$), and, thus, aggressive medical therapy would be warranted.[16,18,19] The benefit of reclassification could also potentially apply to those with 1 risk factor. It is always important for physicians to emphasize lifestyle modification to patients, regardless of risk factors, because it is the least invasive and most inexpensive strategy. One other point worth considering is the measurement that defines a "high" calcium score. Is it greater than 300, as in the MESA study, or greater than 400, as in other studies?[16,20]

Although the current MESA analysis showed an overall incremental predictive value for the total cohort, not all subgroups showed benefit beyond that seen with traditional risk factors. In addition to the AUC comparison, an interesting analysis would have been to see if the addition of a calcium score to risk factors would have allowed for reclassification of the different ethnic groups to reduce misclassification and improve the specificity for predicting coronary events.[21] This analysis should also be performed with gender stratification; as this study and others have shown, women have later onset of subclinical atherosclerosis by 10 years and, hence, have a lower calcium score, than their age-matched male counterparts until the age of 60 years.[22,23] Thus, results of the MESA study do not change the current guideline recommendations on primary prevention of coronary heart disease in asymptomatic patients.

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Conclusion

Calcium scoring continues to hold great utility as a valuable, noninvasive imaging modality to risk stratify and reclassify asymptomatic patients at intermediate risk of cardiovascular disease.[16] This study shows that this approach can be expanded to ethnic groups other than white patients. However, it is uncertain whether use of calcium scoring as a screening tool in a population-based strategy would be a cost-effective strategy in preventive cardiovascular medicine. At this time, calcium scoring can help clinicians determine how aggressive management strategies should be in asymptomatic, intermediate-risk patients. ■

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