

## **Q: Which patients may benefit from coronary artery calcification scoring?**

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**A:** ALTHOUGH WE STILL HAVE NO evidence from randomized trials that patients have better outcomes if we measure the calcification in their coronary arteries, a growing body of evidence shows that we can estimate risk more accurately than with a risk model score alone if we also score coronary artery calcification in asymptomatic patients, especially those at intermediate risk.

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Current guidelines<sup>1</sup> recommend using the Framingham Risk Score or a similar tool to estimate coronary risk in asymptomatic patients, but these tools have only modest accuracy. Calcification scoring is accurate, inexpensive, quick, widely available, low-risk, and does not appear to increase medical costs afterward. In addition to improving risk stratification, it may also encourage patients to adhere better to drug therapy and lifestyle modification.

### **■ HOW IS CORONARY ARTERY CALCIFICATION MEASURED?**

Calcification of the coronary arteries is synonymous with atherosclerosis. It can easily be detected with computed tomography without contrast (**FIGURE 1**), and the amount can be quantified with a scoring system such as the volu-

metric score or the Agatston score. The latter, which is more commonly used, is based on the product of the area of the calcium deposits and the x-ray attenuation in Hounsfield units.

Scores can be roughly categorized (with some overlap owing to data from different studies) as:

- Low risk: 0 Agatston units (AU)
- Average risk: 1–112 AU
- Moderate risk: 100–400 AU
- High risk: 400–999 AU
- Very high risk: 1,000 AU.<sup>2</sup>

The actual test takes only a few seconds, and the patient can usually be out the door in 15 minutes or less. It does not require iodinated contrast and the radiation dose is minimal, usually less than 1 mSv, equivalent to fewer than 10 chest radiographs.<sup>3</sup>

The cost is typically between \$200 and \$500. The test is usually not covered by health insurance, but this differs by insurer and by state; for example, coverage is mandated in Texas, and the test is covered by United Healthcare.

### **■ WHAT IS THE EVIDENCE IN FAVOR OF CALCIFICATION SCORING?**

Cohort studies with long-term follow-up show that calcification scoring has robust prognostic ability. A pooled analysis of several of these studies<sup>2</sup> showed that a higher score strongly correlated with a higher risk of cardiac events over 3 to 5 years. Compared with the risk in people with a score of 0, the risk was twice as high in those with a score of 1 to 112, four times as high with a score of 100 to 400, seven times as high with a score of 400 to 499, and 10 times as high with a score greater than 1,000.<sup>2</sup>

**When added to a risk model score, calcification scoring can improve estimation of coronary risk in asymptomatic patients at intermediate risk**

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A cohort study of more than 25,000 patients had similar conclusions about the magnitude of risk associated with coronary calcification.<sup>4</sup> It also found that the 10-year risk of death was 0.6% in patients with a score of 0, 3.4% with a score of 101 to 399, 5.3% with a score of 400 to 699, 6.1% with a score of 700 to 999, and 12.2% with a score greater than 1,000.

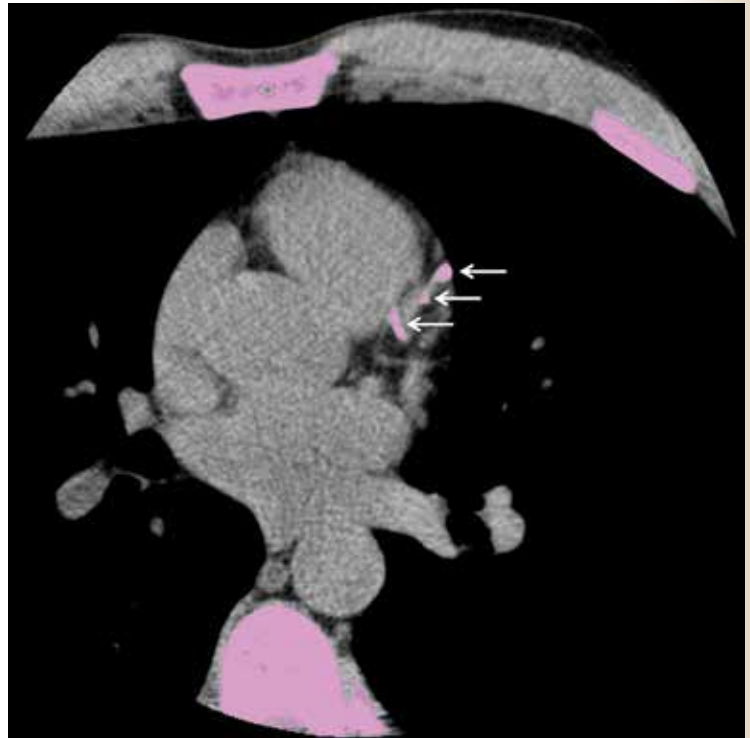
Although progression of coronary artery calcification may predict the risk of death from any cause,<sup>5</sup> the clinical utility of serial measurements is not yet apparent, especially since statin therapy—our front-line treatment for coronary disease—has not been shown to slow the progression of calcification.

### Improving the accuracy of risk prediction

If a patient's 10-year coronary risk is intermediate (10% to 20%), calcification scoring can reclassify the risk as low or high in about 50% of cases and can improve the accuracy of risk prediction.<sup>6-8</sup>

For example, Elias-Smale et al<sup>6</sup> evaluated the effect of calcification scoring in 2,028 asymptomatic patients, with median follow-up of 9.2 years and 135 coronary events observed. Adding the calcification score to the Framingham model significantly improved risk classification, with a net reclassification improvement (NRI) of 0.14 ( $P < .01$ ). (NRI is a measure of discriminatory performance for a diagnostic test; higher is better.<sup>9</sup>) Reclassification was most robust in those at intermediate risk, 52% of whom were reclassified, with 30% reclassified to low risk and 22% reclassified to high risk.

Erbel et al<sup>7</sup> reported data from the Heinz Nixdorf Recall study, which used calcification scoring to estimate the NRI in 4,129 patients followed for 5 years. During this time there were 93 coronary deaths and non-fatal myocardial infarctions. The addition of the calcification score to the Framingham risk model resulted in an NRI of 0.21 ( $P = .0002$ ) for patients with a risk of 6% to 20% and 0.31 ( $P < .0001$ ) for those with a risk of 10% to 20%. Erbel et al also estimated the C statistic (area under the receiver operating characteristic curve; the maximum value is 1.0 and the higher the value the better) for the addition of the calcification score to the Framingham risk model and to the Adult



**FIGURE 1.** A sample frame from a coronary artery calcification score study. All structures above the threshold density that defines calcification are pink. Arrows indicate calcification within the left anterior descending coronary artery. The interpreting physician uses software to define the areas of calcification in each coronary vessel and sums them to yield a coronary artery calcification score.

Treatment Panel (ATP) III algorithm. They reported a significant increase of 0.681 to 0.749 with the Framingham model and 0.653 to 0.755 with the ATP III algorithm.

Polonsky et al<sup>8</sup> studied a cohort of 5,878 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) and estimated the event risk using a model based on Framingham risk characteristics. When the calcification score was added to the prediction model, 26% of the sample was reclassified to a new risk category. In intermediate-risk patients, 292 (16%) were reclassified as high risk, and 712 (39%) were reclassified as low risk, achieving an NRI of 0.55 (95% confidence interval 0.41 to 0.69;  $P < .001$ ). In addition, the C statistic for the prediction of cardiovascular events was 0.76 for the model based on Framingham risk characteristics and increased to 0.81 ( $P < .001$ ) with the addition of calcification scoring.

TABLE 1

## Effects of coronary artery calcification scoring on cost and patient adherence

| COHORT STUDIES                     | YEAR | NO. OF PATIENTS | COMPARISON                     | VARIABLE                              | ADJUSTED ODDS RATIO | PVALUE  |
|------------------------------------|------|-----------------|--------------------------------|---------------------------------------|---------------------|---------|
| <b>Kalia et al<sup>10</sup></b>    | 2006 | 505             | Highest vs lowest CAC quartile | Statin use                            | 9.26                | < .0001 |
| <b>Orakzai et al<sup>13</sup></b>  | 2008 | 980             | Highest vs lowest CAC quartile | Aspirin use                           | 2.98                | < .001  |
|                                    |      |                 |                                | Improved diet                         | 2.66                | < .001  |
|                                    |      |                 |                                | Increased exercise                    | 2.03                | < .001  |
| <b>Taylor et al<sup>12</sup></b>   | 2008 | 1,640           | Any CAC vs 0                   | Statin use                            | 1.37                | < .001  |
|                                    |      |                 |                                | Aspirin use                           | 1.25                | < .001  |
| <b>Nasir et al<sup>11</sup></b>    | 2010 | 6,814           | CAC > 400 AU vs 0              | Lipid-lowering drug use               | 1.53                | < .001  |
|                                    |      |                 |                                | BP-lowering drug use                  | 1.55                | < .001  |
|                                    |      |                 |                                | Aspirin use                           | 1.32                | < .001  |
| RANDOMIZED TRIAL                   | YEAR | NO. OF PATIENTS | COMPARISON                     | VARIABLE                              | OUTCOME             | PVALUE  |
| <b>Rozanski et al<sup>14</sup></b> | 2011 | 2,137           | CAC scoring vs control         | Medical costs                         | \$904 vs \$712      | .09     |
|                                    |      |                 |                                | Change in SBP, mm Hg                  | −7 vs −5            | .02     |
|                                    |      |                 |                                | Change in LDL, mg/dL                  | −17 vs −11          | .04     |
|                                    |      |                 |                                | Change in waist circumference, inches | 0 vs 1              | .01     |
|                                    |      |                 | CAC > 400 AU vs 0              | Exercise 3 or more times per week     | 47% vs 32%          | .03     |
|                                    |      |                 |                                | Change in weight, lb                  | −3 vs 1             | < .001  |
|                                    |      |                 |                                | Change in LDL-C, mg/dL                | −29 vs −12          | < .001  |
|                                    |      |                 |                                | Change in SBP, mm Hg                  | −9 vs −4            | < .001  |

AU = Agatston units; BP = blood pressure; CAC = coronary artery calcification; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure

### Improving adherence and care

Knowing that a patient has a higher calcification score, physicians are more likely to prescribe lipid-lowering and antihypertensive drugs (TABLE 1),<sup>10–12</sup> and patients with a higher score are also more often adherent to recommendations regarding diet and exercise.<sup>13</sup>

Rozanski et al,<sup>14</sup> in a randomized controlled trial, showed that measuring coronary artery calcification did not increase downstream medical spending. A modest improvement in systolic blood pressure ( $P = .02$ ), serum low-density lipoprotein level ( $P = .04$ ), and waist circumference ( $P = .01$ ) was observed in patients who had their calcification measured. Patients with the highest scores had the greatest improvement in coronary risk factors, including blood pressure, cholesterol, weight, and regular exercise.

On the other hand, other analyses have suggested that imaging tests are not effective

for motivating behavioral changes. This topic deserves more research.<sup>15</sup>

### Less utility in symptomatic disease

Coronary artery calcification scoring has less clinical utility in patients who already have coronary symptoms. Villines et al<sup>16</sup> described a cohort of 10,037 patients with coronary symptoms who underwent calcification scoring and computed tomographic coronary angiography and found that stenosis of greater than 50% was present in 3.5% of those who had a score of 0 and in 29% of those with a score higher than 0. Therefore, a score of 0 does not rule out obstructive coronary heart disease if the patient has symptoms. Conversely, these patients may still have coronary artery calcification even if perfusion stress imaging is normal,<sup>17,18</sup> and calcification scoring may have a role in the evaluation of equivocal stress tests.<sup>19</sup>

## CALCIFICATION SCORING GUIDELINES

In their most recent (2010) joint guidelines for assessing risk of coronary heart disease in asymptomatic patients,<sup>20</sup> the American College of Cardiology and the American Heart Association say coronary artery calcification scoring:

- Is recommended for asymptomatic patients at intermediate 10-year risk (10% to 20%) of coronary heart disease (class IIa recommendation, level of evidence B)
- May be acceptable for asymptomatic patients at low to intermediate risk (6% to 10%) (class IIb recommendation)
- Is discouraged for those at low risk (< 6%) (class III recommendation).

The most recent (2010) criteria for the appropriate use of cardiac computed tomography<sup>21</sup> provide similar recommendations. Specifically, coronary artery calcification scoring with noncontrast computed tomography was rated as appropriate for patients at intermediate risk (10% to 20%) of coronary heart disease

and for the specific subset of patients who are at low risk (6% to 10%) but who have a family history of premature coronary heart disease.

These recommendations are based on multiple lines of evidence that calcification scoring is a robust risk-predictor, can enhance risk estimates beyond traditional scoring strategies, and may—in theory—improve outcomes.

## CALCIFICATION SCORING'S LIMITATIONS

The images used for measuring coronary calcification do predict risk of cardiovascular events, but they are not adequate to assess the severity of coronary stenosis. Further, calcification scoring often leads to incidental findings, which can cause anxiety and possibly lead to more imaging, entailing more radiation exposure and expense. And as noted, there are no randomized trial data demonstrating a reduction in cardiovascular events with the use of calcification scoring.

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