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Coronary artery calcium scoring: A valuable tool in primary care

IN 1984, JIM FIXX, who wrote *The Complete Book of Running*,¹ went out for his daily run and died of a massive heart attack. He was 48. Unbeknownst to him, he had 3-vessel coronary artery disease.

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His case illustrates the difficulty of diagnosing coronary artery disease in patients who have no symptoms of it. For many, the initial presentation is myocardial infarction or death. Until recently, there was no reliable way to diagnose subclinical coronary artery disease other than angiography, and there is still no way to rule it out. As a result, physicians have concentrated less on diagnosing subclinical disease and more on assessing the risk of myocardial infarction.

■ ASSESSING RISK

The risk factors for coronary artery disease (age, male sex, smoking, hypertension, and cholesterol) have been well known for half a century. By combining risk factors with the appropriate weighting, it is possible to predict an individual's risk of a myocardial infarction.

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines applied this risk-based approach to prescribing statins for primary prevention.² Instead of focusing on low-density lipoprotein cholesterol concentration, which by itself is a poor predictor of myocardial infarction, they recommended using the Pooled Cohort Equation³ to determine the risk of a cardiovascular event within 10 years. For patients at high risk (> 7.5%), the benefits of a

doi:10.3949/ccjm.85a.18077

statin generally outweigh the harms. For those at low risk (< 5%), the opposite is true. For patients in between, there is room for shared decision-making.

Debate has focused on the predictive accuracy of the equation, the threshold for treatment, and the fact that almost all men over 60 qualify for treatment.⁴ These objections stem from the focus on risk rather than on diagnosis of the underlying disease.

Because one-third of “high-risk” patients never develop cardiovascular disease,⁵ the risk-based approach necessitates overtreatment. Those without disease cannot benefit from treatment but nonetheless suffer its side effects, cost, and inconvenience. Raising treatment thresholds (eg, treating only patients whose 10-year risk exceeds 10%) improves the ratio of patients with disease to those without but also misses diseased patients who have few risk factors. “Low risk” is not “no risk.”

■ TESTING FOR DISEASE IN THOSE AT INTERMEDIATE RISK

Diagnostic testing is preferred if such testing is safe and inexpensive.

In this issue of *Cleveland Clinic Journal of Medicine*, Parikh and colleagues⁶ review coronary artery calcium scoring, a diagnostic test for coronary artery disease. They conclude that calcium scoring is strongly predictive but should be reserved for patients at intermediate risk to help them decide about treatment. This is clearly the right approach, but the authors leave the term “intermediate” undefined, and their clinical examples offer little guidance as to where the borders lie.

The ACC/AHA guidelines specify a narrow intermediate range (5.0%–7.4%). For

Coronary calcium scoring is safe and accurate, but who should be tested?

these patients, calcium scoring could reclassify most as being at high or low risk, helping to clarify whether statins are indicated.

However, only 12% of patients fall into this category.⁷ What about patients at higher risk? Could they be reclassified as being at low risk if their calcium score was 0?⁸ Conversely, could some low-risk patients discover that they are at high risk and perhaps take action?

The ACC/AHA guidelines recommend against calcium scoring in these circumstances. One concern was that calcium scoring had not been tested with the Pooled Cohort Equation. Another concern related to cost and radiation exposure, but as Parikh et al point out, the cost has now fallen to less than \$100, and radiation exposure is similar to that with mammography.

■ SHOULD WE TEST PATIENTS AT HIGH OR LOW RISK?

Who, then, should we test? For patients at high or low risk according to the Pooled Cohort Equation, 2 questions determine whether calcium scoring is warranted: how much would an extremely high or low score (ie, 0 or > 400) change the risk of an event, and how likely is an extreme score?

The first question relates to the usefulness of the test, the second to its cost-effectiveness. If even an extreme score cannot move a patient's risk into or out of the treatment range, then testing is unwarranted. At the same time, if few patients have an extreme score, then cost per test that changes practice will be high.

Because calcium scoring is a direct test for disease, it is extremely predictive. When added to risk-factor models, it substantially improves discrimination⁹ and exhibits excellent calibration.¹⁰ This is true whether the outcome is a major cardiovascular event or death from any cause.

But the calcium score is not strong enough to override all other risk factors. A patient with a predicted 10-year risk of 18% according to the Pooled Cohort Equation and a calcium score of 0 could be reclassified as being at low risk, but a patient with a 10-year predicted risk of 35% could not. The same is true for patients at low risk. A patient with a 4% risk and a cal-

cium score higher than 400 would be reclassified as being at high risk, but not a patient with a 1% risk.

Extreme calcium scores are common, especially in patients at high risk. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, 45% of patients with a 10-year predicted risk of 7.5% to 20% had a calcium score of 0, reclassifying them into the low-risk category.¹¹ Even if the predicted risk was greater than 20%, 1 in 4 patients had a score of 0. In contrast, if the 10-year predicted risk was below 5%, one-fifth of patients had a calcium score greater than 0, but only 4% had a score greater than 100.

Nevertheless, patients in the low-risk category whose baseline risk is close to 5% may wish to undergo calcium scoring, because a positive test opens the door to a potentially lifesaving treatment. In general, the closer patients are to the treatment threshold, the more likely they are to be reclassified by calcium scoring.

The Society for Cardiovascular Computed Tomography currently recommends coronary artery calcium scoring for patients whose 10-year risk is between 5% and 20%.¹² These numbers are easy to remember and a reasonable approximation of the number of patients likely to benefit from testing.

■ COMBINING CALCIUM SCORING WITH TRADITIONAL RISK FACTORS

Primary care physicians interested in more exact personalized medicine can use a risk calculator derived from the MESA cohort.¹³ Based on 10-year outcomes for 6,814 participants, Blaha et al⁸ derived and validated this risk-prediction tool incorporating all the elements of the Pooled Cohort Equation in addition to family history, race, and calcium score.

The tool offered good discrimination and calibration when validated against 2 external cohorts (the Heinz Nixdorf Recall Study and the Dallas Heart Study).¹⁰ The C statistics were 0.78 and 0.82, with 10-year risk predicted by the tool within half a percent of the observed event rate in each cohort.

The online calculator displays the 10-year risk based on risk factors alone or including a calcium score, allowing the clinician to gauge

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the value of testing. For example, a 70-year-old nonsmoking white man with a total cholesterol level of 240 mg/dL, high-density lipoprotein cholesterol 40 mg/dL, and systolic blood pressure 130 mm Hg on amlodipine has a 15.2% 10-year risk (well above the 7.5% threshold for statin therapy). However, if his calcium score is 0, his risk falls to 4.3% (well below the threshold). Sharing such information with patients could help them to decide

whether to undergo coronary artery calcium scoring.

Ultimately, the decision to take a statin for primary prevention of coronary artery disease is a personal one. It involves weighing risks, benefits, and preferences. Physicians can facilitate the process by providing information and guidance. Patients are best served by having the most accurate information. In many cases, that information should include calcium scoring. ■

REFERENCES

1. **Fixx JF.** *The Complete Book of Running.* New York: Random House, 1977.
2. **Goff DC, Jr, Lloyd-Jones DM, Bennett G, et al.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129(25 suppl 2):S49–S73. doi:10.1161/01.cir.0000437741.48606.98
3. **American Heart Association, American College of Cardiology.** 2013 Prevention guidelines tools. CV risk calculator. ASCVD risk calculator. https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp. Accessed August 17, 2018.
4. **Pencina MJ, Navar-Boggan AM, D'Agostino RB, Sr, et al.** Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014; 370(15):1422–1431. doi:10.1056/NEJMoa1315665
5. **Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM.** Lifetime risk and years lived free of total cardiovascular disease. *JAMA* 2012; 308(17):1795–1801. doi:10.1001/jama.2012.14312
6. **Parikh P, Shah N, Ahmed H, Schoenhagen P, Fares M.** Coronary artery calcium scoring: its practicality and clinical utility in primary care. *Cleve Clin J Med* 2018; 85(9):707–716. doi:10.3949/ccjm.85a.17097
7. **Blaha MJ, Dardari ZA, Blumenthal RS, Martin SS, Nasir K, Al-Mallah MH.** The new "intermediate risk" group: a comparative analysis of the new 2013 ACC/AHA risk assessment guidelines versus prior guidelines in men. *Atherosclerosis* 2014; 237(1):1–4. doi:10.1016/j.atherosclerosis.2014.08.024
8. **Blaha MJ, Cainzos-Achirica M, Greenland P, et al.** Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2016; 133(9):849–858. doi:10.1161/CIRCULATIONAHA.115.018524
9. **Peters SAE, den Ruijter HM, Bots ML, Moons KGM.** Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart* 2012; 98(3):177–184. doi:10.1136/heartjnl-2011-300747
10. **McClelland RL, Jorgensen NW, Budoff M, et al.** Ten-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the Multi-Ethnic Study of Atherosclerosis with validation in the Heinz Nixdorf Recall Study and the Dallas Heart Study. *J Am Coll Cardiol* 2015; 66(15):1643–1653. doi:10.1016/j.jacc.2015.08.035
11. **Nasir K, Bittencourt MS, Blaha MJ, et al.** Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2015; 66(15):1657–1668. doi:10.1016/j.jacc.2015.07.066
12. **Hecht H, Blaha MJ, Berman DS, et al.** Clinical indications for coronary artery calcium scoring in asymptomatic patients: expert consensus statement from the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr* 2017; 11(2):157–168. doi:10.1016/j.jcct.2017.02.010
13. **MESA.** The Multi-Ethnic Study of Atherosclerosis. MESA 10-year CHD risk with coronary artery calcification. www.mesa-nhlbi.org/MESA-CHDRisk/MesaRiskScore/RiskScore.aspx. Accessed August 17, 2018.

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