CME CREDIT

MICHAEL S. LAUER, MD

Director, Exercise Stress Laboratory, Departments of Cardiovascular Medicine and Quantitative Health Sciences, Cleveland Clinic; Professor of Medicine, Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine; contributing editor, *JAMA*

What is the best test for a patient with classic angina?

ABSTRACT

Symptoms that suggest myocardial ischemia raise two questions: does the patient have severe, hemodynamically obstructive coronary artery disease, and is he or she at risk for premature death or an early, major nonfatal cardiac event? Noninvasive cardiac testing may help with the first question in patients with an intermediate risk of coronary artery disease, and with the second question in patients with either an intermediate or a high risk of disease. Although the diagnostic value of noninvasive tests may be overestimated owing to referral bias, these tests are powerful when used for prognostic purposes. In patients with a normal resting electrocardiogram and no prior revascularization, a regular exercise stress test without imaging should suffice. However, no randomized trials have been done to determine if this strategy leads to better outcomes than with empiric therapy.

A 58-YEAR-OLD MAN presents with substernal exertional chest discomfort. This occurs only with moderate to vigorous physical activity and is quickly relieved with rest. He has medically controlled hypertension (his systolic blood pressure is 132 mm Hg); he does not smoke. His total cholesterol concentration is 225 mg/dL and his high-density lipoprotein (HDL) cholesterol concentration is 37 mg/dL. A resting electrocardiogram is within normal limits.

To best evaluate his chest discomfort, which test should he undergo:

- A regular exercise test?
- An exercise test with imaging?
- Cardiac catheterization?
- Calcium scanning (electron beam computed tomography [CT])?
- CT coronary angiography?
- None of the above?

ANSWERING TWO QUESTIONS

Evaluation of patients like this one with symptoms that suggest myocardial ischemia involves trying to answer one or two questions[1]:

- *Does he have severe, hemodynamically obstructive coronary artery disease?*
- *Is he at risk for premature death or an early, major nonfatal cardiac event, such as a large myocardial infarction?*

Testing can help with both diagnosis and prognosis

These two questions reflect two entirely different clinical perspectives. The first question addresses diagnosis, the second, prognosis. The first diagnostic question can be thought of as a miniature cross-sectional study: given that one finding is present on a diagnostic test, how likely is it that another finding would be noted on a "gold standard" test? The second prognostic question mirrors a cohort study. Given that this patient has a certain finding on a test now, what is the likelihood that a bad outcome will occur later?

Current guidelines from the American Heart Association and American College of Cardiology suggest that noninvasive cardiac testing may be of use for both diagnostic and prognostic purposes.[2,3] Specifically, the guide-

The author has received funding under National Institutes of Health grants R01 HL-66004-2, R01 HL072771-01, P50 HL-77107-1, and K12 HD049091-01.

TABLE 1

Probability of significant obstructive coronary disease

SYMPTOMS	PROBABILITY (%)	
	WOMEN	MEN
Definite angina	68	95
Possible angina	30	71
Nonspecific chest pain	6	18

REDBERG RF, SHAW LJ. DIAGNOSIS OF CORONARY ARTERY DISEASE IN WOMEN. PROG CARDIOVASC DIS 2003; 46:239–258.

lines recommend that testing be performed for diagnostic purposes in patients with chest discomfort and with an intermediate risk of coronary artery disease.[2,3] This is in line with classic Bayesian thinking, by which a diagnostic test is most likely to be useful if the pretest likelihood of disease is 50%; that is, if there is true uncertainty.

The guidelines also recommend using tests for risk stratification, or prognosis, in patients with chest discomfort and with either an intermediate or high risk of having coronary artery disease.[2,3]

A diagnostic test is most useful if the pretest probability of disease is 50%

WHAT IS THIS PATIENT'S PRETEST PROBABILITY OF DISEASE?

Let us now consider the patient in question. We could assess his pretest probability of having disease by considering his age, sex, and symptoms[3] or by considering his age, sex, and risk factors.[4] If we consider his age, sex, and symptoms, we can use previously published data[5] to conclude that he has a high pretest probability (90%) of having coronary artery disease (TABLE 1).

Symptoms can be classified according to how he would answer three questions:

- *Is your discomfort substernal?*
- *Is your discomfort brought on by physical or mental exertion?*
- *Is your discomfort quickly relieved by rest or sublingual nitroglycerin?*

If the answer to all three questions is yes, he has "typical angina." If he answers yes to two questions, he has "atypical angina," whereas an affirmative response to fewer than two questions means he has "nonanginal chest pain." In the case of our patient, there really is no diagnostic mystery: he has typical angina pectoris related to coronary atherosclerosis.

We could also assess his pretest risk of a major coronary event by using a version of the Framingham score (TABLE 2),[4] which enables one to calculate a predicted risk of a major cardiac event, given his demographics and risk factors. The version of the Framingham score shown in TABLE 2 is designed for patients without diabetes; other gender-specific versions do include diabetes.[6] Another risk scheme, derived in Europe, accounts for regional factors as well as diabetes.[7,8]

As shown in TABLE 2, our patient's pretest risk is 15%. That is, during the next 10 years, his chances of having a major cardiac event are approximately 1.5% per year. This would put him into an intermediate risk category.

We are left with the conclusion that he has an intermediate to high risk of significant coronary disease.

SHOULD WE THINK DIAGNOSTICALLY OR PROGNOSTICALLY?

As we decide which test to use, we also have to decide which mode of thinking is most appropriate, diagnostic or prognostic.

Diagnostic value of noninvasive tests is overestimated

The diagnostic value of nearly all noninvasive tests is overestimated in the literature because of failure to take into account referral bias.[9–12] This occurs when the performance of a gold standard test is at least in part affected by the result of the diagnostic test being studied.

As physicians believe that the noninvasive test is likely to be correct, patients with an abnormal test result are more likely to be referred for the gold standard, coronary angiography. This bias, by which patients undergoing coronary angiography are much more likely to have an abnormal diagnostic test result than the population at large, is also known as workup bias and results in substantial inflation in sensitivity and deflation in specificity.[11] Indeed, the true sensitivity of stress testing, stress echocardiography, and stress nuclear imaging is actually quite poor, at levels of 67% or less.[9–12]

Another problem is that the gold standard test itself is problematic, as coronary angiography is only a picture of the whole of the artery but tells us nothing about the disease in the arterial wall, which is where the real problem is.[13]

Noninvasive tests are good for risk stratification

On the other hand, noninvasive tests are powerful when used for prognostic purposes.

Extensive data show that stress testing or stress testing with imaging is a powerful risk stratifier in patients with symptoms that make one suspect coronary disease.[14–19]

There are few data on the value of calcium scanning for predicting risk in patients with symptoms, although some literature suggests that it has some value in patients without symptoms.[20] CT coronary angiography is an exciting and relatively new technology,[21] but no long-term prognostic data are available. Cardiac catheterization provides information about coronary anatomy, but it has been shown to actually be inferior to functional testing for predicting outcomes.[13,22]

TABLE 2

The patient's Framingham risk score

Age	58
Sex	Male
Total cholesterol	225 mg/dL
High-density lipoprotein cholesterol	37 mg/dL
Smoker	No
Systolic blood pressure	132 mm Hg
On medication for high blood pressure	Yes
Risk score*	**15%**

*The risk score shown was derived on the basis of an equation. Other National Cholesterol Education Program materials, such as Adult Treatment Panel III (ATP III) print products, use a point-based system to calculate a risk score that approximates the equation-based one. See **http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof**.

To interpret the risk score and for specific information about coronary heart disease risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see ATP III Executive Summary[4] and ATP III At-a-Glance.

EXERCISE TESTING VS EMPIRIC THERAPY

This then leaves us with three choices: a regular exercise test, an exercise test with imaging, or empiric medical therapy.

The guidelines are quite clear that among patients with normal resting electrocardiograms and no prior revascularization, a regular exercise test should suffice; this is true for both men and women.[2,3] Indeed, data from Cleveland Clinic and elsewhere have shown that in such patients, additional imaging is unlikely to provide additional prognostically valuable information.[19] Thus, if this patient had a stress test indicating low risk as assessed by functional capacity,[14,23] heart rate dynamics,[17,18,24,25] and ventricular ectopy,[15] he is likely to still be at low risk even if his imaging study is abnormal.[19]

This leaves us with two options, namely, obtaining a regular exercise test without imaging or just proceeding with empiric medical therapy. While current guidelines clearly suggest that risk stratification is appropriate as opposed to empiric medical therapy,[2,3] it is important to note that there has been no randomized trial showing that such a strategy improves outcome. The currently accepted paradigm is that risk stratification identifies the patients who are most likely to benefit from aggressive therapy[26] and, conversely identifies patients who are most likely to be best managed conservatively.

The definitive study of stress testing may never be done

The final answer then is to refer this patient for a regular exercise test without imaging, although it must be acknowledged that the definitive randomized trial showing that pursuing this strategy improves outcomes has yet to be done and may never be done.

WHAT TO DO WITH THE RESULTS?

What to do with the results of the exercise test will be covered in greater detail in a future article, but I will address it briefly here.

The exercise test should primarily be interpreted on the basis of the findings that have clear prognostic value, ie, functional capacity,[14,23] heart rate responses during[25] and after[17,18] exercise, and ventricular ectopy.[15] The ST segment is a relatively minor predictor of risk.[27]

If this patient has a low-risk result on a stress test, then medical therapy with aspirin, a statin, and antihypertensive medications would be appropriate.[3]

If this patient has a high-risk stress test, it might be reasonable to proceed with coronary angiography.[3]

If the results indicate intermediate risk, then a subsequent stress test with imaging would make sense,[3] and if a large area of ischemia were found, then coronary angiography should follow.

REFERENCES

1. **Lauer MS.** Exercise electrocardiogram testing and prognosis. Novel markers and predictive instruments. Cardiol Clin 2001; 19:401–414.
2. **Gibbons RJ, Balady GJ, Bricker JT, et al.** ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002; 106:1883–1892.
3. **Gibbons RJ, Abrams J, Chatterjee K, et al.** ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation 2003; 107:149–158.
4. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285:2486–2497.
5. **Redberg RF, Shaw LJ.** Diagnosis of coronary artery disease in women. Prog Cardiovasc Dis 2003; 46:239–258.
6. **D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P.** Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001; 286:180–187.
7. **Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS.** Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. JAMA 2004; 292:1462–1468.
8. **Conroy RM, Pyorala K, Fitzgerald AP, et al.** Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24:987–1003.
9. **Blackstone EH, Lauer MS.** Caveat emptor: the treachery of work-up bias. J Thorac Cardiovasc Surg 2004; 128:341–344.
10. **Miller TD, Hodge DO, Christian TF, Milavetz JJ, Bailey KR, Gibbons RJ.** Effects of adjustment for referral bias on the sensitivity and specificity of single photon emission computed tomography for the diagnosis of coronary artery disease. Am J Med 2002; 112:290–297.
11. **Froelicher VF, Lehmann KG, Thomas R, et al.** The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography. Ann Intern Med 1998; 128:965–974.
12. **Roger VL, Pellikka PA, Bell MR, Chow CW, Bailey KR, Seward JB.** Sex and test verification bias. Impact on the diagnostic value of exercise echocardiography. Circulation 1997; 95:405–410.
13. **Topol EJ, Nissen SE.** Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995; 92:2333–2342.
14. **Gulati M, Black HR, Shaw LJ, et al.** The prognostic value of a nomogram for exercise capacity in women. N Engl J Med 2005; 353:468–475.
15. **Frolkis JP, Pothier CE, Blackstone EH, Lauer MS.** Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 2003; 348:781–790.
16. **Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS.** Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: the case of stress echocardiography. Circulation 2001; 104:1911–1916.
17. **Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS.** Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000; 284:1392–1398.
18. **Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS.** Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999; 341:1351–1357.
19. **Diaz LA, Brunken RC, Blackstone EH, Snader CE, Lauer MS.** Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. J Am Coll Cardiol 2001; 37:1558–1564.
20. **Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC.** Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004; 291:210–215.
21. **Hoffmann MH, Shi H, Schmitz BL, et al.** Noninvasive coronary angiography with multislice computed tomography. JAMA 2005; 293:2471–2478.
22. **Pollock SG, Abbott RD, Boucher CA, Beller GA, Kaul S.** Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease. Validation of models based on these tests. Circulation 1992; 85:237–248.
23. **Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE.** Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002; 346:793–801.
24. **Shetler K, Marcus R, Froelicher VF, et al.** Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 2001; 38:1980–1987.
25. **Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH.** Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999; 281:524–529.
26. **Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE.** 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. J Am Coll Cardiol 1996; 27:1007–1019.
27. **Goraya TY, Jacobsen SJ, Pellikka PA, et al.** Prognostic value of treadmill exercise testing in elderly persons. Ann Intern Med 2000; 132:862–870.

ADDRESS: *Michael S. Lauer, MD, Departments of Cardiovascular Medicine and Quantitative Health Sciences, JJ40, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail lauerm@ccf.org.*