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Optimize your use of stress tests: A Q&A guide

How reliable are cardiac stress tests? Is preop stress testing worthwhile? Would a stress echo be a better option in some cases? Read on.

PRACTICE RECOMMENDATIONS

□ *Order exercise stress testing without imaging for patients with a low to intermediate probability of coronary artery disease (CAD), unless preexisting electrocardiographic (EKG) changes would render such a test nondiagnostic.* **C**

□ *Order stress testing with imaging for patients with preexisting EKG changes and/or a high probability of CAD.* **C**

□ *Do not use stress testing to screen asymptomatic patients for CAD.* **C**

□ *Consider pharmacologic testing for patients who are unable to exercise to an appropriate cardiac workload; it has the same predictive value as a nuclear exercise stress test.* **B**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

Exercise has been used for cardiac stress testing for decades. But testing and imaging techniques and knowledge of the efficacy of this common diagnostic tool continue to evolve. Optimizing your use of stress testing requires that you familiarize yourself with the latest evidence. The evidence-based answers to these 6 questions will help you do just that.

1 How reliable are exercise stress tests?

That depends, of course, on any number of variables, including the protocol utilized, the number of stenotic vessels, the degree of stenosis, and even the sex of the patient.

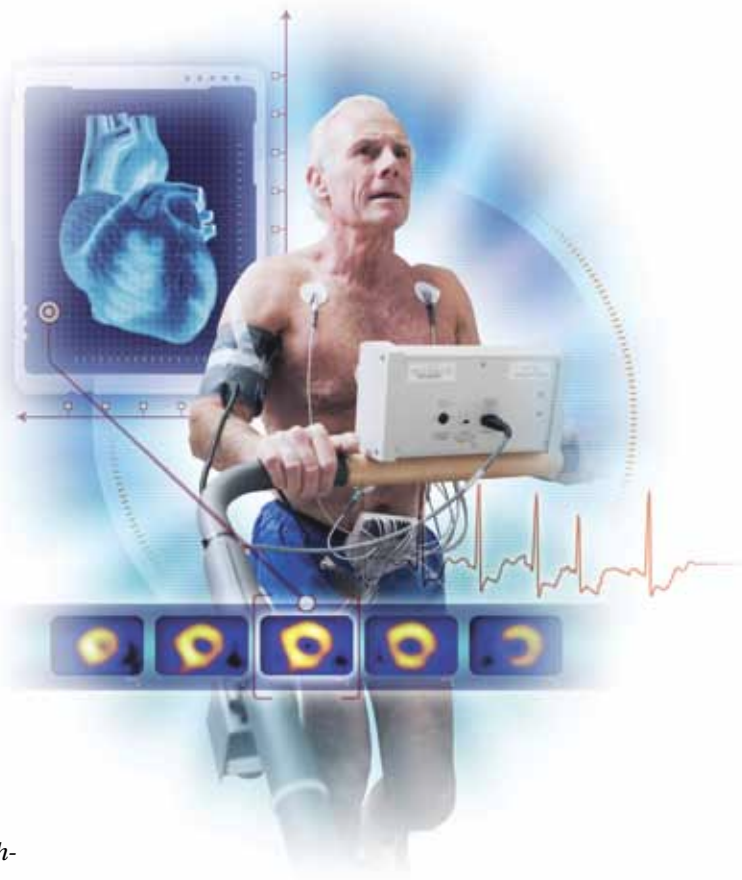
False-negative and false-positive results are frequent in treadmill testing without imaging. (For more on the different protocols, see “Standard and nuclear exercise stress tests: A look at protocols” on page 264.) Sensitivity is related to the number of stenotic vessels and the degree of stenosis. For a man with single-vessel disease and $\geq 70\%$ stenosis, the likelihood of an abnormal test is only 50% to 60%. Even in a man with left main artery disease, the sensitivity is only about 85%.¹

In some cases, failure to reach a cardiac workload sufficient to produce ischemia can lead to a false-negative test, and it is up to the physician performing the test to label it as nondiagnostic. Other reasons for false-positive or false-negative results include preexisting ST segment abnormalities, which can cause false-positive elevation of the ST segment during exercise; the use of digitalis, which affects the ST segment; and the presence of ventricular hypertrophy or cardiomyopathy.¹ Patients with any of these conditions should undergo stress testing with imaging instead.

Nuclear stress testing is indicated for patients who have baseline EKG abnormalities, suspected false-positive or



After a negative radionuclide stress test, the rate of cardiac events is less than 1% per year—and the event rate is lower in women than in men.



false-negative results from a stress test *without* imaging, known CAD or previous revascularization, a pacemaker, or a moderate to high likelihood of a CAD diagnosis. The addition of a tracer isotope and imaging boosts the test's predictive value.¹

The positive predictive value of nuclear stress testing is difficult to calculate because an abnormal test should lead to initiation of therapy designed to reduce the risk of cardiac death or myocardial infarction (MI). Numerous studies have found the rate of cardiac events after a *negative* radionuclide stress test to be less than 1% per year.² The event rate after a negative test is lower in women than in men; after a positive test, however, the event rate in women is 2 to 3 times *higher*.^{2,3} Overall, stress testing is less sensitive in women than in men, at least in part because of their lower likelihood of CAD associated with any given symptom set.⁴

2 When should you rule out stress testing?

Stress testing is unnecessary in asymptomatic patients. Numerous studies have documented the lack of benefit from screening asymptomatic people for CAD using exercise stress testing.^{5,6} The US Preventive Services Task Force gives this a Grade D recommenda-

tion—recommending against routine stress testing.⁷

There are also numerous contraindications, both absolute and relative (TABLE).⁸ Relative contraindications, which include severe hypertension, left main coronary stenosis, moderate stenotic valvular disease, electrolyte abnormalities, cardiomyopathy, serious mental or physical impairment, and atrioventricular block are conditions that are likely to interfere with test performance or reliability.

Absolute contraindications, generally related to unstable cardiopulmonary disease, pose a far more serious threat. Indeed, administering a treadmill stress test to a patient with 1 or more absolute contraindications greatly increases the risk of death associated with the test.⁸

Even if a patient does not have any relative or absolute contraindications, there is still some risk of moving forward with the test. There is about a 1 in 2500 risk of MI or death during, or related to, exercise stress testing.⁸ The greater the likelihood that a patient has CAD, the higher the risk.

There is also a risk of hospitalization after the test, usually related to persistent chest pain or arrhythmias. (I generally admit patients whose chest pain is unresponsive to

Standard and nuclear exercise stress tests: A look at protocols

Exercise stress testing can be done with a number of treadmill protocols. The most widely used are:^{18,19}

- the Bruce Protocol (the most common),¹ which increases the slope of the treadmill and the speed of the belt in 3-minute intervals;
- the Modified Bruce Protocol, a less aggressive format in which slope and speed are alternatively increased; and
- the Naughton Protocol (typically reserved for patients whose ability to walk is limited), which starts with a very slow belt speed and a nearly flat slope and increases both elements slowly.

During the test, heart rate and BP are measured, along with continuous EKG monitoring, but the frequency of BP measurement and 12-lead EKG printouts varies among testing facilities.

Patients must attain a heart rate of 85% of their age-predicted maximum for the test to be considered diagnostic; they typically exercise until they're unable to continue or they develop symptoms that prompt the clinician performing the test to stop it. Monitoring continues for some time after the patient stops exercising—usually 4 to 5 minutes in an asymptomatic patient, or until any symptoms and EKG changes that developed during the test resolve. If chest pain or EKG changes persist, the patient may need to be admitted to the hospital.

The procedure for nuclear stress testing is similar, except that the patient must estimate when he or she can only walk for 1 more minute. A tracer isotope is injected at that time.

For years, thallium was used for this purpose. However, thallium is taken up by the perfused myocardium and has the drawback of rapid redistribution with resolution of ischemia, which can lead to false-negative tests.²⁰

Technetium (^{99m}Tc-labeled sestamibi), which is commonly used for other nuclide scans, is now the preferred isotope for nuclear stress tests.²¹ It is taken up by mitochondria in the perfused myocardium and does not redistribute, which results in fewer false-negative scans. Additionally, the energy emitted by ^{99m}Tc-labeled sestamibi is higher and produces cleaner pictures.²¹

Single photon emission computed tomography (SPECT) scans are taken in 3 planes as part of the nuclear stress test. A set of resting scans is taken before the exercise test. The isotope is then allowed to wash out and another dose is injected at peak cardiac workload so a second set of scans can be taken and compared with the resting images.

Perfusion defects that are present both at rest and with stress indicate an area of infarction, whereas defects that appear with stress but not at rest indicate ischemia. The probable location of the coronary artery lesions responsible for the ischemia can be inferred from the area in which the defects appear.

Gated imaging—serial images that are coupled with EKG changes, then reassembled to produce a moving image of the heart—is now usually part of the process. The result can be examined for areas of wall motion abnormalities and used to calculate an ejection fraction.²²

3 doses of nitroglycerine or who develop EKG changes that persist after 20 minutes at rest.) The test also raises the possibility of injury from the equipment, such as sprains or fractures caused by falling from the treadmill.

Nuclear stress testing also has a small risk of an allergic reaction to the isotope used as a tracer. The radiation dose is 8 to 9 mSV, comparable to a computed tomography (CT) scan of the chest and generally less than that of a coronary angiogram.⁹

3 Does the evidence support the use of stress tests for asymptomatic patients with diabetes? Are prep stress tests advisable?

The jury is still out on both questions.

■ **The question of asymptomatic testing for patients with diabetes mellitus**, who are more likely than those without the disease to develop CAD, frequently arises. Although individuals with diabetes have higher rates of silent ischemia than the general population, however, estimates of this prevalence vary widely.¹⁰ There are no clear guidelines for evaluation of asymptomatic diabetic patients with exercise stress testing. (See “Test your skills with these 3 cases” on page 266.)

The addition of nuclide imaging adds diagnostic value to the test, but it is still not clear that this should be the preferred test for patients with diabetes who have normal resting EKGs.^{10,11} A recent randomized controlled trial investigating screening with pharmacologic stress testing in asymptomatic patients with type 2 diabetes did not show a reduction in cardiac event rates in patients who were screened compared with those who were not screened.¹²

■ **Similarly, preoperative stress testing** is subject to debate.¹³ Many studies have been done to evaluate the utility of preoperative stress testing, with revascularization procedures done before the planned surgery when significant CAD is found. (See “Before surgery: Have you done enough to mitigate risk?” *J Fam Pract.* 2010;59:202-211.) And, while many demonstrate the predictive power of various parameters that stress tests measure, literature reviews show that—with the exception of patients with unstable CAD—postop

event rates are about the same for patients who underwent stress testing and subsequent revascularization vs those who were treated medically instead.^{13,14}

4 If your patient requires a pharmacologic stress test, what are your options besides adenosine?

While adenosine is the agent of choice, dipyridamole and dobutamine are other options. When any of these agents are used, it's important to consider the side effects of each, and which drugs your patient will need to avoid prior to the stress test.

■ **Adenosine is a mediator of coronary vasodilation.** The drug dilates normal coronary arteries preferentially to stenotic vessels and causes redistribution of blood flow away from areas of the myocardium with compromised circulation.

■ **Dipyridamole, a mediator of adenosine release,** is sometimes used instead. Both drugs are given as a 4-minute infusion, with injection of the tracer late in the infusion.

■ **The adverse effects of adenosine** occur early in the infusion, and include dyspnea, bronchospasm, chest pain, nausea, and headache. Bradycardia can be marked, and brief periods of complete heart block and long sinus pauses may occur. Hypotension can likewise be profound. Many of these effects are extremely disturbing to the patient under-going the test, but they disappear within 30 seconds of stopping the infusion.

■ **Dipyridamole has similar adverse effects,** although heart block is not part of its adverse effect profile. In addition, the drug's adverse effects occur later in the infusion than those associated with adenosine and last well after it is finished. However, dipyridamole's side effects can be reversed with intravenous aminophylline without compromising the accuracy of the test.

■ **Drugs to avoid that day.** Methylxanthines antagonize adenosine and dipyridamole, and thus must be avoided on the day of the test. Caffeine and theophylline are among the substances to be avoided, although the

TABLE

Stress testing: Absolute and relative contraindications⁸

Absolute contraindications

Recent MI (<2 days)

Unstable angina

Uncontrolled ventricular arrhythmia

Uncontrolled atrial arrhythmia that compromises cardiac function

Symptomatic HF (uncontrolled)

Severe aortic stenosis (uncontrolled)

Dissecting aneurysm (suspected or confirmed)

Myocarditis (active)

Pulmonary or systemic embolus (recent)

Acute pericarditis

Relative contraindications*

Severe hypertension

Left main coronary stenosis

Moderate stenotic valvular disease

Electrolyte abnormalities

Cardiomyopathy, including hypertrophic cardiomyopathy

Mental or physical impairment that results in an inability to exercise adequately

High-degree atrioventricular block

HF, heart failure; MI, myocardial infarction.

*Relative contraindications are conditions that are likely to interfere with test performance or reliability.

degree to which they affect test results has been questioned recently.¹⁵

■ **Severe COPD and asthma**—especially in patients with uncontrolled wheezing—are relative contraindications to the use of adenosine and dipyridamole.

Interestingly, the cardiovascular effects (and EKG changes) associated with these drugs are not necessarily indicative of CAD. Thus, the entire EKG portion of a pharmacologic stress test is not useful in interpreting the finding. One small study suggests that, unlike exercise stress testing, adenosine stress testing may be safe in patients with severe aortic stenosis.¹⁶

CONTINUED

Test your skills with these 3 cases

CASE 1 ▶ Daniel G, a 68-year-old whom you've been treating for hypertension for more than 10 years, is about 25 pounds overweight. He has decided to begin an exercise regimen, and the trainer he hired to work with him at the gym has asked for medical clearance.

CASE 2 ▶ Marge H, age 73, has peripheral neuropathy and spinal stenosis. She sees a neurologist regularly, but has come to see you today to report that for the last several nights, her heart has been racing and she's felt an uncomfortable sensation in her chest.

CASE 3 ▶ Ed W, a trim 56-year-old, has been swimming 5 days a week for years. Last week, he experienced a tightening in his chest in the middle of his swim. The pain subsided shortly after he stopped swimming, but it returned as soon as he got up to full speed again. He asks whether you think it's a pulled muscle or angina.

Should any—or all—of these patients undergo cardiac stress testing?

CASE 1 ▶ Daniel's case highlights the discrepancy between commonly held beliefs and medical evidence. For decades, people have been told to get a medical evaluation before starting an exercise program, and a stress test has commonly been part of that evaluation. However, numerous studies have failed to show a benefit of stress testing in asymptomatic people. The US Preventive Services Task Force recommends against routine stress testing in asymptomatic people.⁷ And, while the American Heart Association/American College of Cardiology guidelines suggest that stress testing in men over the age of 45 with 1 or more risk factors may occasionally yield useful information, the organizations acknowledge that this opinion is based on weak information.²³

You tell Daniel that moderate exercise is unlikely to provoke a serious cardiac event and that if symptoms arise during exercise, he should report them promptly so that appropriate testing can be ordered.

CASE 2 ▶ Marge's primary complaint sounds more like an arrhythmia than angina. However, coronary ischemia cannot be excluded; ischemia could be caused by decreased cardiac output from an arrhythmia, or it could be the cause of an arrhythmia. A Holter monitor would be a good initial test for this patient, followed by stress testing to determine if angina is the cause of her symptoms. Because of Marge's peripheral neuropathy and spinal stenosis, she may be a candidate for a pharmacologic stress test.

Given that stress testing is less sensitive in women than in men, there is a widespread belief that women should not be tested with exercise stress testing alone. However, the available literature suggests that this test has appropriate predictive value for women with an intermediate CAD risk.⁴

CASE 3 ▶ Ed presents with typical symptoms of angina pectoris. While some noncardiac diseases—esophageal spasm, for example—can cause nearly identical symptoms, the likelihood that this patient has symptomatic CAD is high. Thus, he should undergo stress testing with nuclide imaging. This patient is physically fit and therefore can take an exercise test, which will provide information—most notably, functional capacity and the level of exertion needed to cause symptoms—that a pharmacologic stress test would not.

■ **Dobutamine is another alternative** for pharmacologic stress testing, for patients who cannot take adenosine or are unable to stop theophylline or similar medications. An infusion of dobutamine with an escalating dose, sometimes including atropine, is used to accelerate the heart rate to 85% of the patient's age-predicted maximum. The stress is primarily due to the chronotropic effect of the drug, but dobutamine has some coronary vasodilatory activity and may also induce

some redistribution of coronary blood flow, similar to the effect of adenosine.

■ **The positive and negative predictive values** of pharmacologic stress testing are the same as for nuclear stress testing. Unlike exercise testing, however, functional capacity cannot be inferred from a pharmacologic stress test.

About 10% of patients undergoing pharmacologic stress testing will have a nondiagnostic test. The sensitivity of the test varies among studies, but it is approximately 84%,

95%, and 100% for single-, double-, and triple-vessel disease, respectively. Patients with negative tests have an event rate of less than 1% per year.¹⁷

5 Is stress echocardiography comparable to stress testing?

Yes. Stress echocardiography, which involves echocardiographic studies taken before and after stress, can substitute for either exercise or pharmacologic stress testing (the stress can be achieved either with exercise or an infusion of dobutamine), and it has certain advantages: Stress echocardiography is cheaper than nuclear stress testing, and there is no radiation involved. In addition, stress echocardiography yields positive and negative predictive values similar to those seen with nuclear stress testing.^{2,3} The presence of ischemia is inferred from localized wall motion abnormalities.

The primary disadvantage of stress echocardiography is that it can be administered only by a cardiologist who has been specially trained in this procedure. In contrast, any community hospital nuclear medicine department has the capacity to perform nuclear imaging, and most radiologists are able to interpret the nuclide scans. In my experience, decisions about whether to order nuclear cardiac stress testing or stress echocardiography are influenced not only by the availability of these modalities, but also by the skill of the physicians who will interpret the tests.

6 Which exercise-induced EKG changes are related to ischemia?

The only changes that correlate with myocardial ischemia are ST depression and ST elevation. J-point depression is almost universally seen with exercise. For this reason, the ST level is measured 80 milliseconds after the J point.

■ **ST depression—the most common abnormal finding**—indicates subendocardial ischemia. ST changes are most commonly seen in the inferior and lateral leads, but do not correlate with the location of ischemia. ST depression can be downsloping, horizontal, or upsloping.

A look at the stress test report

The report from the physician who performs or reads the stress test should contain the following elements:

Heart rate achieved, including both the rate itself and the percentage of the patient's age-predicted maximum that the heart rate represents. Failure to reach 85% of the maximum may be related to underlying cardiac or pulmonary disease, the use of beta-blockers, musculoskeletal disorders, or general deconditioning. However, it is obviously noteworthy if the patient develops chest pain or significant ST changes at a lower heart rate.

BP at peak exertion. There are no established levels for systolic BP at various ages. But failure of the systolic pressure to rise, or a drop in systolic pressure with exercise, indicates a lack of ventricular reserve and is a poor prognostic sign.

Functional capacity (METS). In addition to documenting the METS level itself, the report should compare it to the expected functional capacity based on the patient's age and sex.

Chest pain (or its absence). In addition to noting whether or not chest pain developed, the report should detail the character and intensity of any pain that the patient experienced, the time into the test and the heart rate at which it developed, and the response to rest or nitroglycerine.

ST changes. Unless something in the patient's condition changes, the workload required to produce symptoms or ST changes should be reproducible from test to test. The workload at which angina or ST changes occur is key to assessing disease severity.

Arrhythmias. Whether they're seen at rest or develop with exertion, arrhythmias should be noted, as well.

The final report should also indicate whether the test is negative, positive, or nondiagnostic for findings consistent with CAD. When ever possible, it should include a validated treadmill score, as well.

The first 2 are the most significant patterns, and 1 mm of ST depression is the minimum significant level. Upsloping ST depression is less significant, and 1.5 mm of depression is the minimum significant change.¹ The greater the degree of ST depression, the higher the likelihood that significant occlusion will be seen on coronary angiography. ST depression that develops in the recovery period is a rare occurrence but of equal significance to ST depression that occurs with exercise, and is probably due to ischemia caused by shunting of blood into skeletal muscle and away from the heart.¹

■ **ST elevation is less common, but more ominous** than ST depression, as it indicates transmural ischemia.¹ This finding most often



A decrease in systolic BP with exertion, or its failure to rise, is a poor prognostic sign.

indicates high-grade left anterior descending (LAD) or left main CAD. It is most often seen in the anterior leads, and the location of ST changes correlates with the area of ischemia. Bear in mind, however, that the correlation between ST elevation and transmural ischemia is true only if the patient has no history of MI. ST elevation in leads in which Q waves are present at rest usually indicates ventricular dyskinesia or aneurysm and not ischemia.¹

Pre-menopausal women and women who are taking estrogen supplements, in particular, are more likely than men to have false-positive ST changes, most likely because of a poorly understood effect of estrogen. The molecules of estrogen and of digitalis glycosides have some regions of structural similarity, and it is thought that both molecules can cause ST changes.¹⁰

And what about arrhythmias? Arrhythmias are often seen at rest and with exertion. Supraventricular arrhythmias, including

supraventricular tachycardia, are not associated with CAD. Premature ventricular contractions (PVCs) are common at peak exertion. PVCs are probably related to catecholamine release and do not indicate ischemia. (See “A look at the stress test report” on page 267.)

Ventricular tachycardia, however—defined as 3 or more consecutive PVCs—has a 90% correlation with significant coronary artery stenosis, as shown on angiography.¹

Rate-dependent conduction disturbances, including 2-to-1 atrioventricular block and bundle-branch blocks, may also be seen. These may be associated with ischemia, but are not highly predictive of coronary artery stenosis. Further testing may be indicated to determine whether stenosis is present. **JFP**

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