Risk Assessment of Patients with Known or Suspected CAD Using Stress Myocardial Perfusion SPECT

Part II: Determining Cost-Effective Test Strategies

Rory Hachamovitch, MD

St Francis Hospital, Roslyn, NY

In this era of cost containment, each step of a testing protocol must be evaluated carefully for appropriateness and prognostic value. Exercise stress single-photon emission CT (SPECT) is finding a niche in the examination of patients with known or suspected coronary artery disease. When preceded by careful patient screening, stress SPECT, alone or combined with other testing, may prove to be a tool that is both cost-effective and clinically effective. [Rev Cardiovasc Med. *2001;2(1):41-47*]

Key words: Coronary artery disease • Exercise test • Radionuclide imaging • Risk factors • Risk stratification

As discussed in Part I of this article (see Main Points, Part I, page 43),[1] to validate a test as part of a testing strategy, it is not sufficient to demonstrate that it yields added value; one must also show that its incorporation into the strategy will result in equal, if not superior, outcomes—at a lower cost. This is known as the incremental economic value of the test, as compared with the incremental statistical or clinical value of the test. For example, does the use of myocardial perfusion imaging (MPI) result in greater cost benefit when used as part of an overall patient strategy? By measuring the cost implications of a test only when it is incorporated into a testing strategy, this analytic approach takes into account both referral to and referral from the test of interest. This leads to the development of patient strategies that minimize expense by referring to testing only those patients not at low or very high risk based on previous information.

Cost Implications of the Use of SPECT

Berman and colleagues[2] from Cedars-Sinai Medical Center examined 1702 patients referred for exercise stress dual-isotope single-photon emission CT (SPECT) who were followed for a mean of 20 ± 5 months for occurrence of hard events (cardiac death or nonfatal myocardial infarction [MI]). Risk stratification and cost-effectiveness were examined at 3 separate instances in a clinical algorithm (Figure 1):

- Patients at low risk for coronary artery disease (CAD) defined by clinical and historical information alone (pre–exercise treadmill test [ETT]).
- Patients at low risk for CAD after ETT.
- Patients at intermediate to high risk for CAD after ETT.

Although risk stratification was achieved in the 3 situations, it was cost-

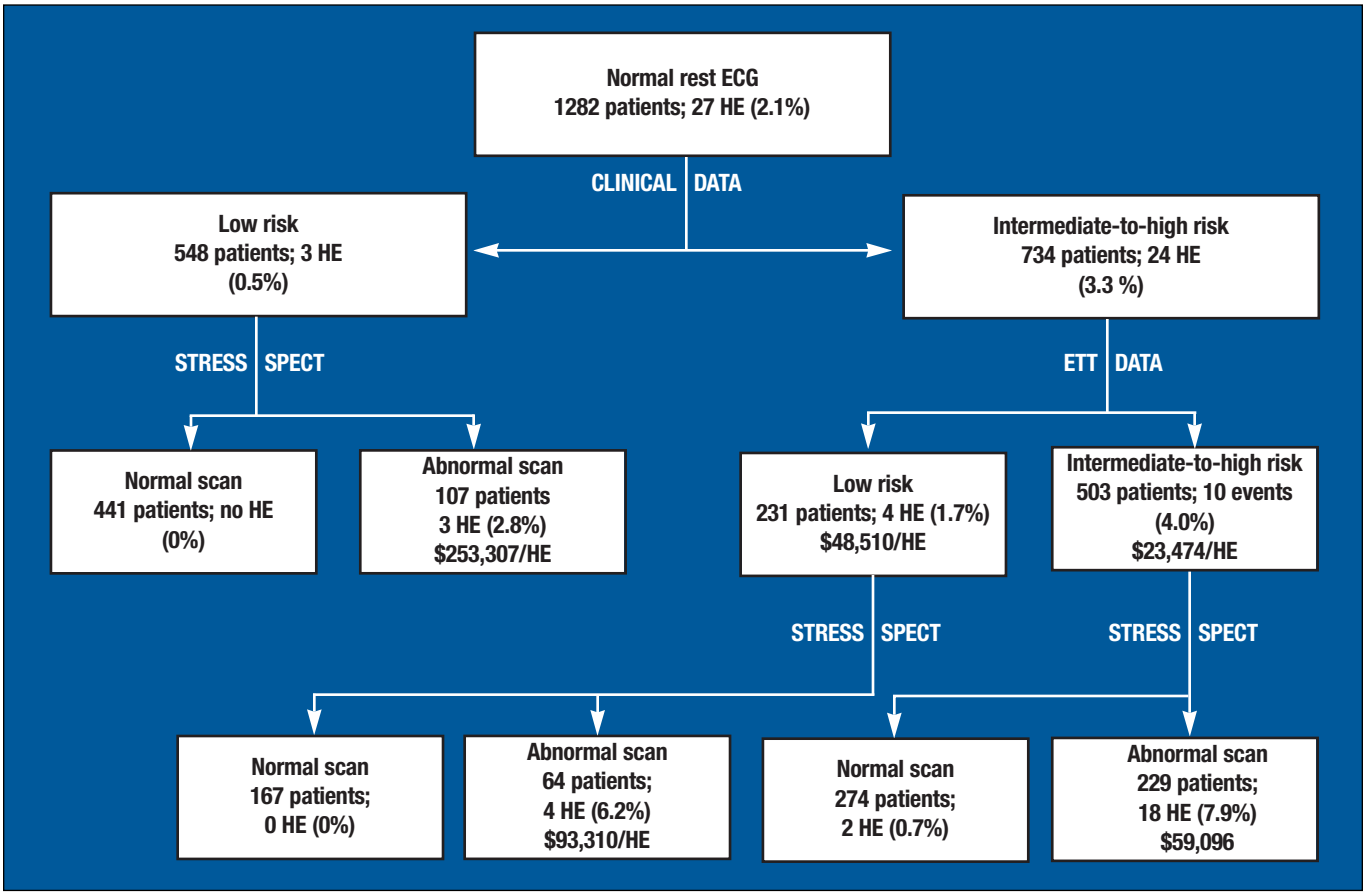

Figure 1. An example of outcomes and cost of care in a strategy of sequential testing. The uppermost box begins with 1282 patients with resting ECG interpretable for an exercise treadmill test (ETT). The first risk stratification is based on clinical data alone, separating the overall cohort into a low–clinical risk group and an intermediate– to high–clinical risk group. Usually, patients at low clinical risk are not thought to warrant further evaluation. Those at intermediate to high clinical risk require further workup and are referred to ETT. A second risk stratification by ETT data is shown on the right side of the figure. Patients at intermediate to high clinical risk are further stratified into low-risk and intermediate- to high-risk subsets. Risk stratification by the results of nuclear testing is shown in 3 clinical risk groups: patients at low risk (hard event [HE] rate of 0.5%), patients at low risk after ETT (HE rate of 1.7%), and patients at intermediate to high risk after ETT (HE rate of 4.0%). In all 3 of these subgroups, the stratification shown is statistically significant. The cost-effectiveness ratio (cost per HE identified) is shown within the same box as are the abnormal scans. (SPECT, single-photon emission CT.)

effective (cost per hard event identified) only in those patients with an intermediate risk of CAD. Cost-effectiveness of a test only in the patient cohort in which it is considered clinically appropriate suggests the possibility that cost-effectiveness and clinical effectiveness may be related.

These results were extended by Shaw and colleagues[3] in a study examining a cohort of 3620 stable, symptomatic patients with an intermediate Duke treadmill score. These patients underwent stress MPI and were followed for a mean of 3 years. The study found that exercise stress SPECT stratified this cohort with respect to risk of cardiac death; it also was cost-saving when compared with a strategy not using SPECT.

Both the Berman and Shaw studies support the concept of a hierarchical testing strategy in which testing is performed initially using simpler, lower-cost examinations (clinical evaluation, ETT); only those patients judged not to be at low risk are then sent to technologically more complex, higher-cost tests. By limiting more expensive testing to a smaller number of higher-risk patients, successful risk stratification is achieved while resource use is minimized. The information derived from each test, in turn, is used optimally.

Noninvasive Testing Versus Direct Catheterization in Stable Patients with Angina

The Economics of Noninvasive Diagnosis (END) group[4] performed the most important cost-effectiveness study to date in this field. The group

Main Points, Part I

- To successfully use a risk-based approach as a guide to therapy, it is necessary to have clearly defined risk levels, data on the benefit ratio of various therapies within risk categories, and a means to identify risk for a patient with a particular set of characteristics.
- Stress single-photon emission CT (SPECT) adds more prognostic information than clinical and historic data for women than for men.
- During a 5-year period, stress nuclear studies stratified risk of cardiac death in patients with known coronary artery disease (CAD), while exercise ECG failed to do so.
- A normal stress SPECT is associated with a lower cardiac event rate than is a normal stress echocardiogram.
- Stress SPECT enhanced risk stratification in patients with low, intermediate, and high pretest likelihood of CAD.
- Limiting more expensive testing, such as SPECT, to a smaller number of intermediate- and high-risk patients, rather than to low-risk patients, achieves successful risk stratification and efficient resource utilization.

examined a cohort of 11,372 consecutive patients with stable angina who were referred for evaluation to either a conservative strategy (stress MPI as initial testing plus selective catheterization in patients with ischemia, 5826 patients) or an aggressive strategy (cardiac catheterization, 5423 patients). After adjusting for the underlying clinical risk of the 2 groups, the frequency of cardiac death and/or nonfatal MI on follow-up did not differ between the 2 strategies (Figure 2). Within all clinical risk subsets, the costs of care for these patients, both short-term (diagnostic) and long-term (follow-up), were significantly lower in the cohort first evaluated by noninvasive testing (Figure 3). Again, the ability of a normal stress SPECT study to identify patients at low risk for adverse outcomes who will not benefit from subsequent testing or catheterization and the addition of stress SPECT to a testing strategy in patients with anginal symptoms results in cost savings and preserved outcomes. Unpublished data from this study also indicated that the rate of normal angiograms at the time of catheterization was significantly lowered by the use of SPECT.

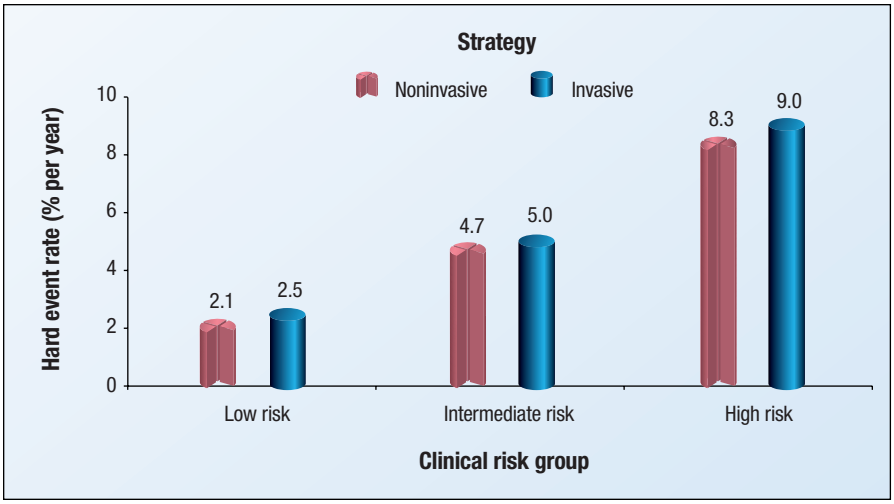

Figure 2. Rates of cardiac death and/or nonfatal myocardial infarction (MI) for patients referred for noninvasive (red bars) and invasive (blue bars) evaluation strategies are shown as a function of the clinical risk group. No statistically significant difference between hard event rates of strategies (within clinical risk categories) was present. A statistically significant increase in hard event rate as a function of increasing clinical risk category was present in both strategies examined. (Adapted from Shaw LJ et al. *J Am Coll Cardiol*. 1999.[4])

Perfusion-Function Protocols

The development of technetium 99m–labeled perfusion agents, such as sestamibi, and advances in SPECT software have resulted in gated SPECT studies becoming routine in almost all laboratories. Thus, left ventricular (LV) volumes, ejection fraction (EF), and LV and right ventricular (RV) wall motion can be evaluated as a routine part of testing. Given the additional costs/reimbursements for this information, the added utility of these measures will be closely examined.

Limited data exist regarding the added value of function data over perfusion data. The long-term prognostic value of SPECT during a mean follow-up period of 70 months was examined by Marie and colleagues.[5] These investigators followed 217 patients with known or suspected CAD who underwent exercise stress thallium-201 (Tl-201) SPECT, coronary angiography, and rest radionuclide angiography. These authors found that the total defect extent on the stress Tl-201 SPECT study was the best independent predictor of hard events and

Main Points, Part II

- When a test is cost-effective only in the patient group for which it is clinically effective, this suggests that cost-effectiveness and clinical effectiveness may be related.
- Limiting more expensive testing to a small number of higher-risk patients results in successful risk stratification and maximal resource utilization.
- A normal stress single-photon emission CT (SPECT) study can identify patients at low risk for adverse outcomes who will not benefit from further testing; adding stress SPECT to a testing strategy for patients with angina can produce cost savings.
- Gated SPECT studies provide additional information on left ventricular volume, ejection fraction, and left and right ventricular wall motion.
- Combined perfusion-function protocols yield greater incremental prognostic value than do stress perfusion SPECT studies alone.

provided incremental prognostic information, compared with clinical, exercise testing, and catheterization variables. The extent of reversible Tl-201 SPECT perfusion defects, however, was the sole SPECT variable providing incremental information to the LVEF data. This study extends previous reports in demonstrating the added value of SPECT not only with respect to pre-SPECT data but also over combined pre-SPECT, resting function, and anatomic information.

Initial reports evaluating this technology are promising. A report of 1695 patients who underwent exercise or adenosine stress dual-isotope rest Tl-201/stress technetium 99m sestamibi gated SPECT revealed that this combined perfusion-function protocol yielded greater incremental prognostic value than did stress perfusion SPECT alone.[6] Even in the setting of an abnormal scan, gated SPECT EF data further stratified patients into subgroups with relatively lower (1.6% per year) and higher (4.4% per year) risk ($P < .05$). As predictors of individual events, it appeared that perfusion markers were better predictors of "softer events" (MI, late revascularization), while function markers were better predictors of cardiac death (Figure 4).

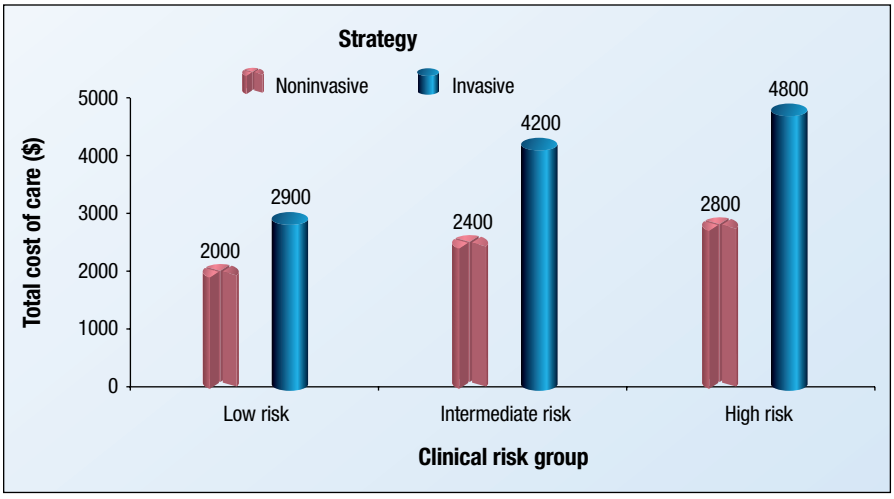

Figure 3. Costs of care per patient for the noninvasive (red bars) and invasive (blue bars) strategies are shown as a function of clinical risk group. The costs of care were significantly lower in the noninvasive strategy, compared with the invasive strategy, in all clinical risk subsets. (Adapted from Shaw LJ et al. *J Am Coll Cardiol.* 1999.[4])

Perfusion and function measures may be predictive of different end points. Lee and colleagues[7] from Duke University studied 571 stable patients with symptomatic CAD. These patients had upright rest/exercise first-pass radionuclide angiography within 3 months of catheterization, were treated medically, and had a median follow-up of 5.4 years (Figure 5). In comparing the ability of rest and exercise radionuclide wall motion data for predicting cardiovascular death, the authors found that exercise wall motion variables were equal to angiographic data. Prediction of all cardiovascular events (death or nonfatal MI) was significantly weaker than was prediction of the sole end point of cardiac death. These findings are contrary to those found with exercise SPECT, where the addition of MI as an end point to cardiac death results in an increase in the measured predictive power of the test. These findings suggest that perfusion markers may be a better predictor of softer outcomes than are function measures.

The Importance of Examining Post-SPECT Resource Utilization

Assessment of resource utilization after SPECT can help determine whether inappropriate bias exists with respect to the use of post-test interventions. For example, an ongoing issue is whether

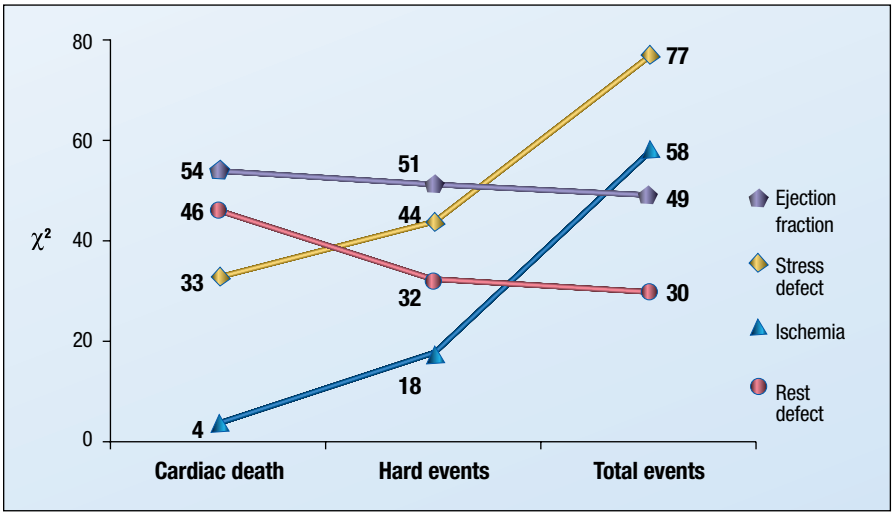

Figure 4. Results of Cox proportional hazards model analysis for single variable predictors. Outcome used is shown on the x axis (cardiac death, hard events [cardiac death or nonfatal myocardial infarction], and total events [hard event or late revascularization, a surrogate for clinical progression or worsening of disease]). The variables examined include poststress ejection fraction (EF), the extent and severity of the stress perfusion abnormalities (stress defect), the extent and severity of the ischemia present (ischemia), and the extent and severity of rest defects present (rest defect). The EF variable was a better predictor of cardiac death but decreased in power with the "softer" end points (late revascularization). The prognostic value of the stress defects and ischemia improved with the softer end points and were less predictive of the harder end point (cardiac death).

men and women are treated similarly with respect to cardiovascular testing and interventions. Many studies have suggested that sex-related differences exist in the clinical management of CAD after noninvasive testing.

A recent study examined 3211 consecutive patients (1074 women and 2137 men) who underwent exercise dual-isotope SPECT and had follow-up for referral to cardiac catheterization within 60 days following nuclear testing.[8] These investigators found that after stress SPECT, men were referred to catheterization more frequently than women (10.6% vs 7.1%; $P < .001$). In the cohort examined, however, men had more severe and more extensive abnormalities found on SPECT testing, compared with women. To overcome these baseline differences, a multiple logistic regression analysis was performed to adjust for the extent and severity of scan abnormalities and for other differences between men and women, such as age at time of testing. After adjusting for these differences, no sex-related differences were present with respect to referral to catheterization (Figure 6). Hence, analysis of resource utilization allows insight into the appropriateness of referral patterns, particularly when inappropriate bias appears to be present.

Post-SPECT resource utilization has also been examined, measuring the rate of referral to catheterization after SPECT in patients without known CAD.[9] It appears that within subgroups of low, intermediate, and high clinical risk, referral to catheterization increased as a function of the scan results. Within any scan result category, increasing clinical risk was also associated with an increase in the rate of referral to catheterization. It appears that referring physicians appropriately combined patient information from the results of the nuclear study and clinical information to formulate their post-SPECT referral plans. It must be noted that the referral rate to catheterization for patients with a high likelihood of CAD and moderate to severely abnormal scan results was only 56%, a lower number than would be anticipated. Although it is difficult to understand the appropriateness of this rate, other centers not using the dual-isotope approach have reported similar rates of referral to catheterization.[10]

Optimization of Post-SPECT Therapy

There is limited information to date comparing the use of medical therapy with revascularization after stress MPI; which of these therapeutic options is "appropriate" is undefined. This is an important issue, given the relatively low rates of referral to catheterization after stress MPI (40% to 60% catheterization rate in patients with no previous CAD and moderate to severely abnormal scans). An unadjusted analysis from a large study cited above[11] suggested a survival advantage for revascularization over medical therapy as the initial treatment in patients with severely abnormal stress MPI results (Figure 7).

By performing risk-adjusted multivariate analyses in large observational studies, it is possible to estimate the relative benefit of medical versus revascularization strategies. Figure 8 shows the results of such an analysis in 1727 patients from the Cedars-Sinai Medical Center nuclear cardiology database with severely abnormal scans (among whom 134 cardiac deaths occurred over a 20-month follow-up period). Based on a Cox proportional hazards model (in which adjustment was made for all predictors of adverse outcome as well as the likelihood of the

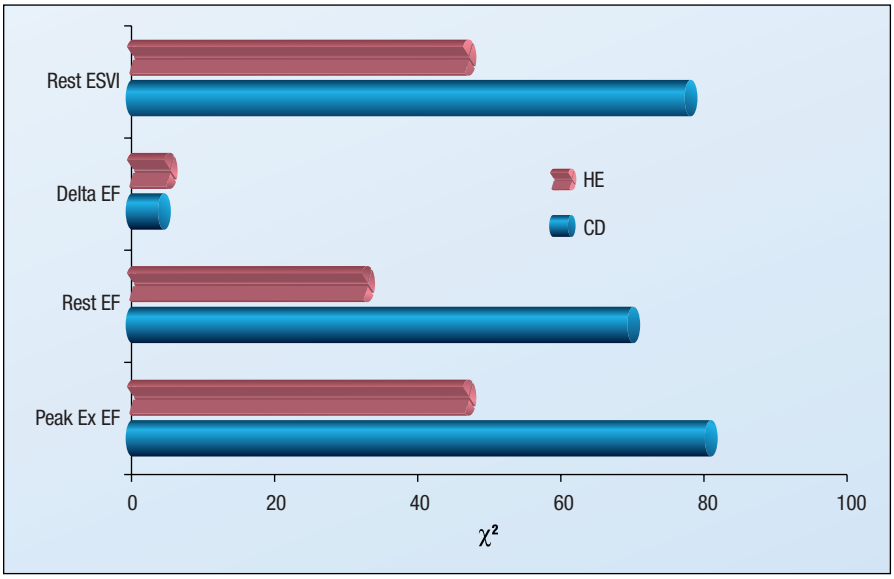

Figure 5. Single variable χ^2 for the prediction of cardiac death (CD, blue bars) and hard events (HE, red bars) for a series of variables derived from exercise wall motion studies: ESVI, end systolic volume index; EF, ejection fraction; Ex, exercise. Note that the values of χ^2 for all variables decreased when the end point was changed from CD to HE, despite the fact that the total number of end points in the analysis increased.

patient's being referred for revascularization), a clear survival benefit in favor of early revascularization over early medical therapy is present ($P < .01$).

Living with Cost Containment

A number of "rules of thumb" regarding the use of noninvasive testing can be suggested to apply to daily practice. Although no data from randomized clinical trials are available to guide our application of stress SPECT, the large, well-analyzed observational data sets examined to date may yield a number of lessons.

Before use of any noninvasive test, physicians should ask whether there has been appropriate patient screening. Patient clinical risk should be carefully determined by evaluating the results of physical examination, a carefully taken history, a resting ECG, and any other relevant clinical information.

If noninvasive testing is to be performed, a sequential, stepwise approach should be taken, initially using less expensive tests, followed by technologically more advanced (and more expensive) tests in patients found to be at intermediate to high risk at the previous step. At each step of testing, those patients found to be at low risk (less than 1% risk for adverse outcomes per year) require no further testing; however, aggressive risk factor modification should not be forgotten for those patients. Thus, at each step of an optimal testing algorithm, the majority of patients will require no further testing, while a minority will be sent on for additional tests. The limited data we have suggest that test use that is cost-effective usually is also clinically effective.

At the current time, an exercise ECG should be considered as the first step in testing for both men and women who have resting ECGs that are not interpretable for an ETT. If there is local expertise, a stress myocardial perfusion scan is probably the best "next test." If not, other stress imaging modalities should be considered.

Patients with normal SPECT studies are clearly at very low risk for adverse outcomes, independent of the type of stress performed, the isotope used, and the cohort examined. This has been shown in numerous studies using stress MPI, but this is usually not the case for other stress imaging procedures, such as stress echocardiography. Patients with mildly abnormal

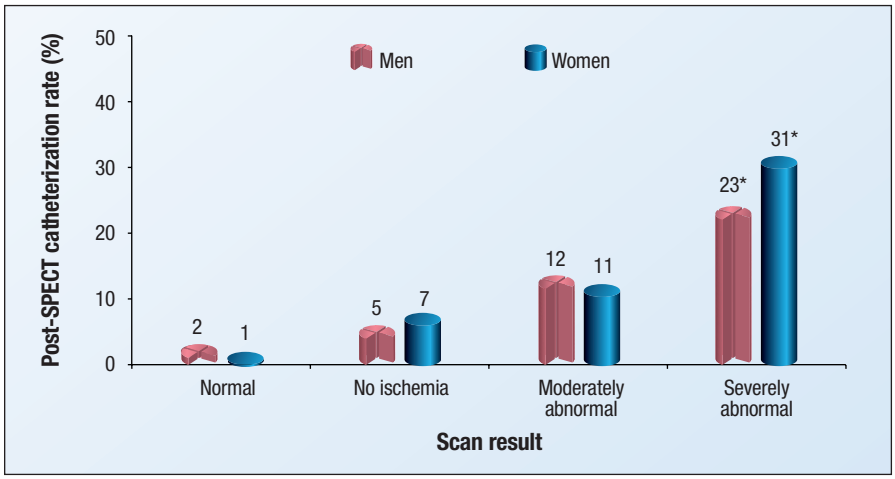

Figure 6. Frequency of referral to catheterization early (within 60 days) after stress single-photon emission CT (SPECT) in men (red bars) and women (blue bars). In the scan category with the most ischemia, a statistically significant greater rate of catheterization was present for women, compared with men ($P < .05$). (Adapted from Hachamovitch R et al. *J Am Coll Cardiol*. 1995.[8])

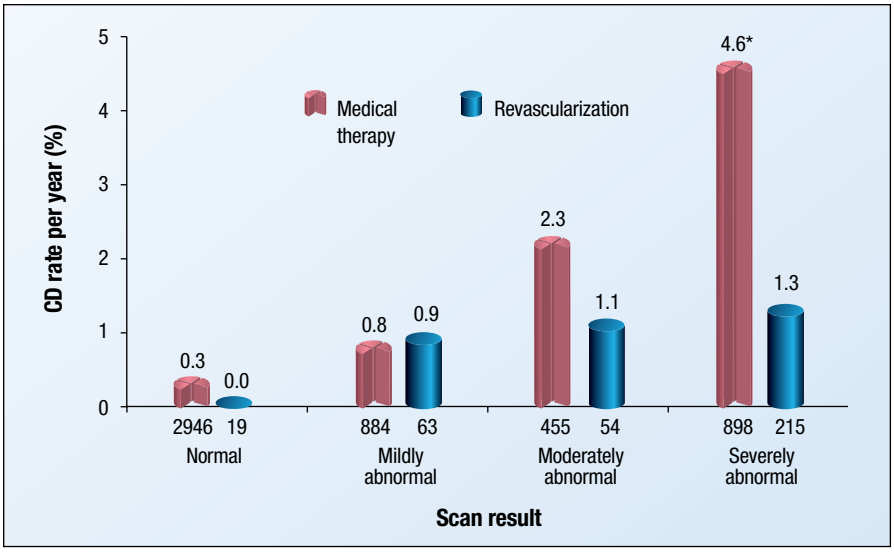

Figure 7. Frequencies per year of cardiac death (CD) in patients after stress single-photon emission CT (SPECT) treated with revascularization within 60 days of SPECT (blue bars) or medical therapy (red bars). A statistically significant greater rate of CD was present in patients with severely abnormal scans receiving medical therapy, compared with revascularization. Numbers of patients are shown beneath bars. (Data from Hachamovitch R et al. *Circulation*. 1998.[11])

results are at low risk for cardiac death, although they are at intermediate risk for MI. Such patients may benefit from aggressive medical management rather than from intervention.

Cardiac catheterization is the final common diagnostic step for all patients. Care should be given, however, that the referral to catheterization is an appropriate one. Not all patients with abnormal scans require this step, and many may have equivalent or superior outcomes with lower cost of care by use of aggressive medical therapy without catheterization.

Finally, patients with moderately to severely abnormal scans, particularly when LV dysfunction is documented, are at higher risk for both cardiac death and MI and probably merit referral to catheterization to evaluate their candidacy for revascularization. ■

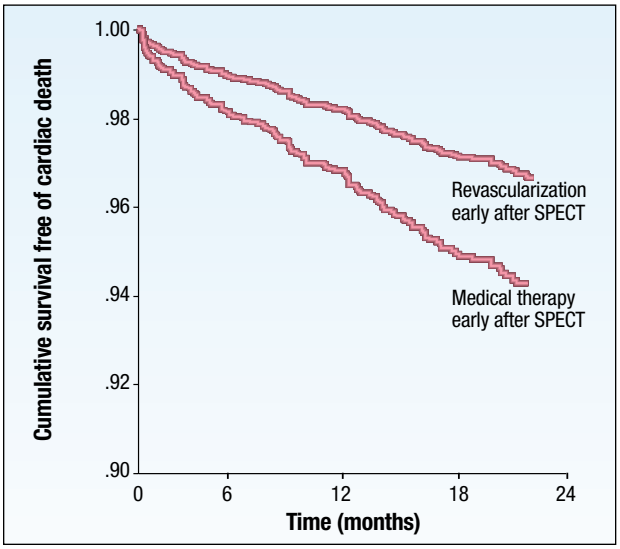

Figure 8. Survival benefits of early revascularization over early medical therapy. (SPECT, single-photon emission CT.)

References

1. Hachamovitch R. Risk assessment of patients with known or suspected CAD using stress myocardial perfusion SPECT, Part I: the ongoing evolution of clinical evidence. *Rev Cardiovasc Med*. 2000;1:91-102.
2. Berman DS, Hachamovitch R, Kiat H, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography [published erratum appears in *J Am Coll Cardiol*. 1996;27:756]. *J Am Coll Cardiol*. 1995;26:639-647.
3. Shaw LJ, Hachamovitch R, Peterson ED, et al. Using an outcomes-based approach to identify candidates for risk stratification after exercise treadmill testing. *J Gen Intern Med*. 1999;14:1-9.
4. Shaw LJ, Hachamovitch R, Berman DS, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. *J Am Coll Cardiol*. 1999;33:661-669.
5. Marie PY, Danchin N, Durand JF, et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography: incremental prognostic value compared with clinical, exercise testing, catheterization and radionuclide angiographic data. *J Am Coll Cardiol*. 1995;26:879-886.
6. Hachamovitch R, Lewin H, Cohen I, et al. Incremental prognostic value of gated SPECT ejection fraction in patients undergoing dual isotope exercise or adenosine stress. *J Nucl Med*. 1998;39:101P.
7. Lee KL, Pryor DB, Pieper KS, et al. Prognostic value of radionuclide angiography in medically treated patients with coronary artery disease: a comparison with clinical and catheterization variables. *Circulation*. 1990; 82:1705-1717.
8. Hachamovitch R, Berman DS, Kiat H, et al. Gender-related differences in clinical management after exercise nuclear testing. *J Am Coll Cardiol*. 1995;26:1457-1464.
9. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation*. 1996;93:905-914.
10. Bateman TM, O'Keefe JH Jr, Dong VM, et al. Coronary angiographic rates after stress single-photon emission computed tomographic scintigraphy. *J Nucl Cardiol*. 1995;2:217-223.
11. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation*. 1998;97:535-543.