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

Part I: The Ongoing Evolution of Clinical Evidence

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In this era of cost containment and evidence-based medicine, validation of a test's diagnostic ability may be only the beginning step to its acceptance and use. In the imaging world, a test gains cost-effectiveness points if it not only is an independent predictor of outcomes but also adds prognostic information to pretest data. If the test can be used to risk-stratify patients, its value is further enhanced. This review discusses how one of the newer imaging techniques, single-photon emission CT, ranks with regard to the risk assessment of patients with coronary artery disease.
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Key words: Coronary artery disease • Exercise test • Radionuclide imaging • Risk factors • Risk stratification

As we face the new millennium, coronary artery disease (CAD) remains the greatest cause of death not only in the United States but also in other industrialized nations.[1] Cardiovascular mortality rates have been at epidemic levels for several decades. In 1996, CAD resulted in 476,124 deaths in the United States, a number that increases to more than 725,000 (of more than 2 million deaths in the United States) if related syndromes are included.[1] The mortality rates associated with this disease have decreased markedly over the years, predominantly in white men. The age-adjusted mortality rate for myocardial infarction (MI) has decreased from 226.4 per 100,000 in 1950 to 124.1 per 100,000 in 1987, and the adjusted rate for cerebrovascular events has decreased from 88.8 per 100,000 to 30.7 per 100,000 during the same period.[1]

The decline in cardiovascular morbidity and mortality that has occurred during the past 10 to 20 years can be attributed, in large part, to improvements in diagnostic and therapeutic options available to physicians and to the decrease in lag time between the development and validation of technology and its incorporation into clinical practice.[1,2] New technologies are in widespread use today, including therapeutic, such as newer percutaneous revascularization techniques, and diagnostic, such as stress echocardiography or gated myocardial perfusion single-photon emission CT (SPECT) using technetium-99m agents. Also, these technologies are being used in ever-increasing numbers; cardiac catheterizations have increased from about

Main Points

- 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 over 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.

300,000 in 1979 to more than 1.2 million in 1996, with similar increases in coronary artery bypass surgery procedures (about 100,000 to 600,000 over the same interval) and percutaneous transluminal coronary angioplasty (PTCA) procedures (about 40,000 to 150,000).[1]

Although the increased use of new technology has impacted cardiovascular survival, the cost implications have been enormous. National health expenditures have increased from $26.9 billion in 1960 (5.9% of the gross national product [GNP]) to $247.3 billion in 1980 (8.9% of the GNP) to $1035.1 billion in 1996 (13.6% of the GNP).[1,2] Estimates are that increases in the use of new technology account for as much as one third to one half of the increases in health care costs.[3] If one considers the increasing demand for this lifesaving (albeit expensive) technology, the accelerating development and cost, and the continued aging of the US population (resulting in an increased proportion of the population with CAD), serious concerns arise regarding the future financing of health care.

The Era of Cost-Containment in Medicine

Because of the economic burdens of new technology on health care, a revolution in how medicine is practiced has occurred since the 1980s.[4] Pressure has been brought to limit health care costs, and rethinking of clinical strategies is common. Newer ways of analyzing and applying medical information, such as evidence-based approaches to medical care and the use of cost-effectiveness analysis (to determine the greatest health gain per dollar spent ["bang for the buck"]), have won widespread acceptance.[5]

For patients with CAD in particular, risk-based approaches have become important because of the considerable evidence that the risk of adverse outcomes can be reduced by appropriate preventive and therapeutic strategies.[5] Further, the cost-effectiveness of interventions varies with the level of risk in the cohort in question. The concept that calculating the level of risk for a particular patient can aid in the selection of a therapeutic strategy has grown increasingly popular.[5] To successfully harness this approach, it is necessary to have agreed-on definitions for levels of risk, data regarding the benefit ratio of various therapies within risk categories, and a means to identify risk for a patient who has a particular set of characteristics.

It has become imperative to validate newer, expensive technologies before their routine application (and reimbursement) as well as to reassess more established technology. This new form of technology assessment emphasizes the measurement of the incremental or added value of a test (ie, what information a test yields beyond what was already known about the patient) and the cost implications of its use.[4,6,7] It is this change in approach that has fueled a surge in the literature of stress SPECT with regard to its prognostic value and application in risk stratification as well as its cost-effectiveness.

Measurement of Incremental Prognostic Value: Methodologic Considerations

The measurement of incremental value has become central to the evaluation of all noninvasive testing. The focus on incremental value demonstrates a shift from showing that a test is a superior *independent* predictor of adverse outcomes, compared with clinical or historic data, to demonstrating that the test can *add* information regarding patient status to the clinical or historic data.[4,6,7]

Briefly, the incremental value of a test such as SPECT may be assessed by several statistical tests but is most commonly evaluated by multivariable models that control (risk-adjust) for available clinical data (eg, historic or pretest

information) and then determine the increase in predictive power from the results of noninvasive testing. The added value is often quantified by a change in model chi-square (χ^2). This test statistic can be thought of as a means to quantitate the amount of information that is known from a set of data variables.

The data are considered in a series of sets. First, a χ^2 is determined for clinical and historic data. Then, a χ^2 is determined for this information with the addition of exercise treadmill test (ETT) data. Finally, the results of SPECT are added to generate a final χ^2. This approach yields information regarding the added value of ETT to historic and clinical data, as well as the addition of SPECT to all prenuclear information.[6,7] This stepwise approach mimics the order in which clinical information is accumulated by physicians and is equally legitimate for diagnostic, prognostic, economic, and functional outcomes.

Do stress SPECT studies yield added prognostic value? Ladenheim and colleagues[8] first introduced the concept of incremental prognostic value in a study of 1659 patients who had no history of previous MI or revascularization and who had undergone ETT with a stress-redistribution thallium protocol imaged with a planar technique. This study demonstrated that in certain patient subsets, prognostic information was increased by the addition of stress perfusion results even after clinical, historic, and ETT data were considered. In particular, the perfusion study added prognostic information for the subset of patients with abnormal resting ECGs.[8]

To date, numerous studies have extended these results to define the incremental prognostic value of stress SPECT in diverse patient subsets.[9-19] Of note is the fact that these subsets include men and women; patients with and without prior CAD, pharmacologic, and exercise stress; young and old patients. Also of interest is that exercise stress SPECT yields greater independent *and* incremental prognostic information for women than it does for men, despite numerous past issues regarding the value of this test in women.

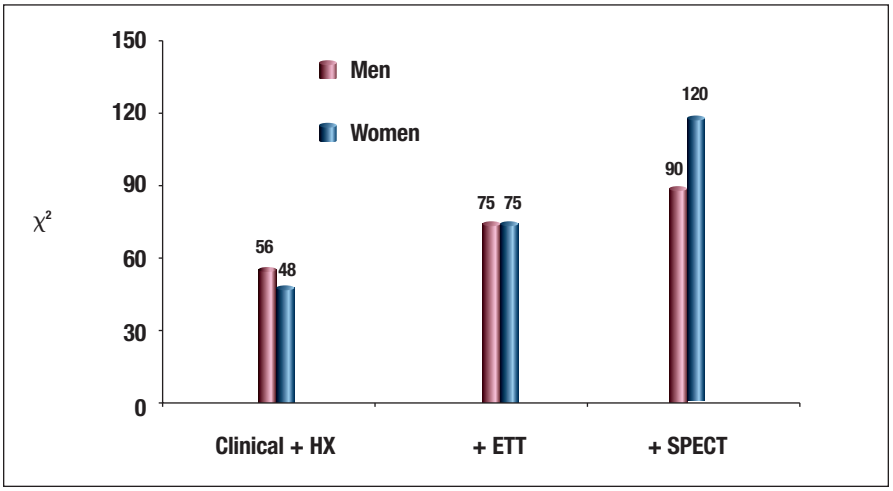

Figure 1. Values of global χ^2 in men and women for 3 models: clinical and historic data (HX) as the initial model; the addition of exercise treadmill test (ETT) data; and the addition of single-photon emission CT (SPECT) data after ETT data. The increase in χ^2 is statistically significant for both men and women for the addition of both ETT and SPECT data.

A recent study compared the prognostic value of stress SPECT in 2742 men and 1394 women[11] who underwent dual-isotope SPECT. The patient population was followed for 20 ± 5 months for cardiac death or nonfatal MI. The incremental value of nuclear testing was determined using both stepwise and Cox proportional hazards models (Figure 1). For men, clinical and historic information was predictive of adverse outcomes (global $\chi^2 = 56$), as it was for women (global $\chi^2 = 48$). In the Cox model, using clinical, historic, and ETT variables, the global χ^2 for men and women was identical (75). In this study, the Cox model for nuclear variables revealed that the global χ^2 for men (61) was less than that for women (114). Further, after adjusting for prescan information, the gain in total χ^2 was 15 for men (final global $\chi^2 = 90$) and 45 for women (final global $\chi^2 = 120$). Thus, this study revealed that stress SPECT adds more prognostic information for women than for men.

Clinical Incremental Prognostic Value—Demonstrating Enhanced Risk Stratification

Although the statistical approach described above is mathematically sound and quantifies the added value, clinically, the results of the analysis are less intuitive, difficult to apply , and of unclear relevance and applicability. Many clinicians are also of the opinion that regression methods do not mirror clinical reasoning. Thus, a modification of this incremental approach is to demonstrate enhanced risk stratification—that is, to show that after patients are risk-stratified using all data known before a nuclear test, statistically significant further risk stratification can be achieved by the results of the SPECT study.[6,7,10]

A vital consideration, however, is what constitutes an appropriate and

meaningful risk stratification. This is usually defined by 2 characteristics. First, a normal ("negative") study should be associated with a very low risk of adverse outcomes. The threshold for low risk is usually considered to be a frequency of hard events (cardiac death or nonfatal MI) of 1% or less per year of follow-up.[6,7] The low risk (fewer than 1% hard events per year) associated with normal stress SPECT studies is an important component of its ability to risk-stratify a variety of patient populations. To date, almost all studies examining the risk of patients following normal stress SPECT studies have reported rates of hard events of 1% or less per year of follow-up.[9-12,15-26] This low risk has been present with both SPECT and planar imaging; with exercise and pharmacologic stress; with thallium and sestamibi as imaging agents; and in all patient subsets based on sex, age, pretest likelihood of CAD, or history of CAD. Since normal studies can identify patients who are at sufficiently low risk for subsequent events that these occurrences can be safely managed medically, additional costly testing and interventions in such patients can be avoided.[10,27,28] Hence, both successful risk stratification and cost-effectiveness begin with the identification of low risk after noninvasive testing.

Normal Stress SPECT Studies in Patients With Documented CAD

To justify its use for risk stratification in patients with known CAD, a normal stress SPECT study must also demonstrate low risk in this cohort. Two small, single-site studies have shown that patients with documented CAD and normal stress perfusion studies have a low risk of adverse outcomes.[20,22]

More recently, investigators from the Angioplasty Compared to Medicine (ACME) trial[25] sought to evaluate the prognostic ability of cardiac exercise stress tests to predict cardiac mortality and morbidity in patients with documented CAD. A total of 328 patients with documented single- or double-vessel disease were assigned randomly to PTCA or medical therapy. Six months after randomization, maximal symptom-limited exercise tests were performed using electrocardiography in 300 of these patients and thallium scintigraphy in 270. The investigators followed the patients for a minimum of 5 years.

The authors found that the stress nuclear study, despite having been performed using the outdated planar technique, significantly stratified patients with respect to their risk of cardiac death 5 years later, and that exercise ECG failed to achieve this stratification (Figure 2). As important is the fact that within the cohort of patients assigned to nuclear testing, stratification was achieved within the subset of patients treated with PTCA but not within the subset assigned to medical therapy. The latter underwent stress testing while still taking their anti-ischemic medications, whereas the post-PTCA subgroup underwent stress testing while not taking such medications. In this study, patients with documented CAD and normal stress planar thallium studies were still at relative low risk at 5 years (cardiovascular mortality rates: PTCA arm, 1.4% per year; medical therapy arm, 1.8% per year); however, at 5 years after nuclear testing, an abnormal stress perfusion study showed a significantly greater event rate than did a normal study in the PTCA arm but not in the medical therapy arm. Perhaps the use of anti-ischemic medications masked or blunted the amount of inducible ischemia, thus compromising the performance of the nuclear study. To date, these are the only data that compare outcomes in patients tested while on or off medications.

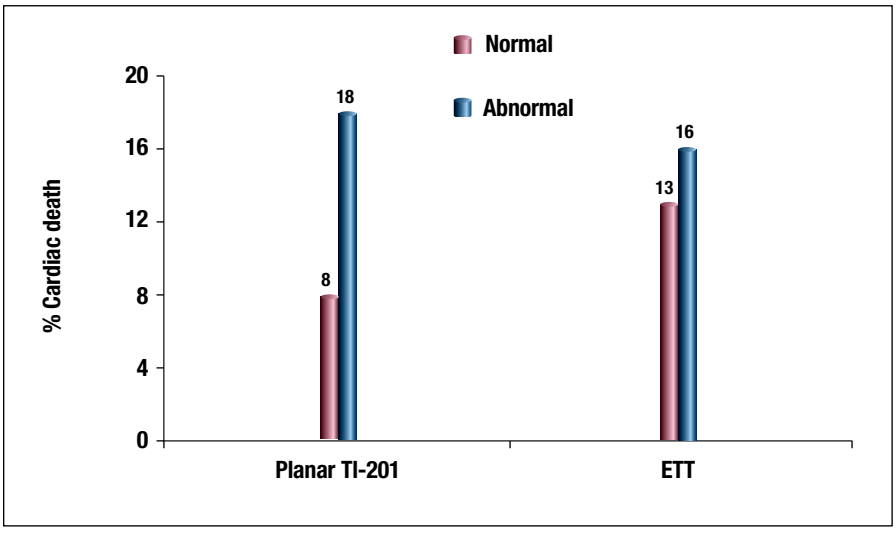

Figure 2. Cardiac mortality rates in patients with normal and abnormal stress planar thallium-201 (Tl-201) images and exercise treadmill test (ETT) results. Significant stratification was achieved by the planar Tl-201 test results, while the ETT failed to achieve significant stratification, based on a 5-year follow-up in the Angioplasty Compared to Medicine trial.[25]

Event Rates in Normal Studies Using Other Noninvasive Modalities

A number of other modalities are cur-

rently capable of performing stress imaging studies. Stress echocardiography, in particular, has gained widespread acceptance. Although the ability of stress echocardiography and stress SPECT to identify CAD (as measured by sensitivity and specificity) are probably similar,[29] test referral bias virtually eliminates the possibility of validly comparing the technologies.[30,31]

On the other hand, these 2 imaging modalities clearly differ when analyzed toward a prognostic end point. To date, the most pressing question regarding the use of stress echocardiography is the ability of a normal study to identify patients who are truly at low risk (fewer than 1% hard events per year). A meta-analysis of risk after a normal study revealed that summary estimates of hard event rates per year in patients with normal studies were 1.3% (95% confidence interval [CI], 0.8% to 1.7%) for stress echocardiography and 0.7% (95% CI, 0.5% to 0.9%) for SPECT.[32] Meta-regression of all 26 published studies revealed that after adjusting for differences between the populations tested, the modality used significantly affected the hard event rate in normal studies, with normal stress SPECT studies stratifying patients as having significantly lower risk ($P = .004$).

Risk Stratification and Abnormal Scan Results

The second important characteristic of risk stratification is that the majority of events (more than 80% to 90%) should occur in those patients who had abnormal studies—that is, of the patients referred for testing, the test should identify the majority of those who were at risk. Finally, the event rate associated with an abnormal test result should not only be greater than that associated with a normal scan, but the relative risk of an abnormal scan compared with a normal scan should exceed 1, and the CI of the relative risk should not include 1. This relative risk defines the effectiveness of the stratification.

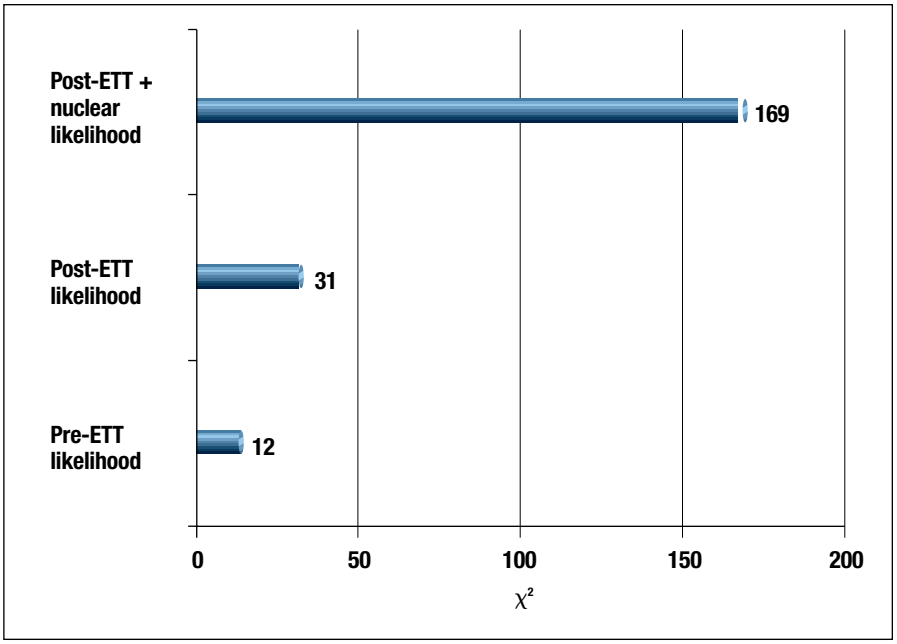

Figure 3. Values of global χ^2 in patients with no history of coronary artery disease who underwent stress single-photon emission CT (SPECT) and were followed. A statistically significant increase in χ^2 is present comparing clinical (pre-exercise treadmill test [ETT]) data with clinical plus ETT (post-ETT) data and the addition of SPECT (post-ETT + nuclear) data.

Risk stratification using stress myocardial perfusion imaging (MPI). A number of studies have evaluated the ability of stress SPECT to further risk-stratify patients after pre-SPECT information is considered. A recent study examined 2200 patients who underwent rest thallium-exercise stress sestamibi dual-isotope SPECT and who had no prior history of CAD at the time of their index study.[12] The authors, first examining statistical incremental value, showed that after adjusting for clinical history and ETT results, the addition of stress SPECT information resulted in a dramatic and statistically significant increase in global χ^2 for the prediction of hard events (χ^2 increase: 31 to 169, $P < .001$) (Figure 3). Clinically more relevant is that after stratifying the patients into low-, intermediate-, and high-risk groups based on their prescan likelihood of CAD, the results of nuclear testing further stratified all prescan risk groups. Normal scan results were at an exceedingly low event rate (fewer than 1% per year) within all clinical risk subgroups (low, intermediate, and high likelihood of CAD), and the rate of hard events increased significantly as a function of the scan result, a demonstration of clinical incremental value (Figure 4). This pattern of very low risk in the setting of normal scan results and significantly increasing risk as a function of worsening scan results was present in both men and women as well as in young and old patients. This enhanced risk stratification achieved by nuclear testing in both men and women was demonstrated previously, with the interesting finding that stress MPI showed greater discrimination for high-risk

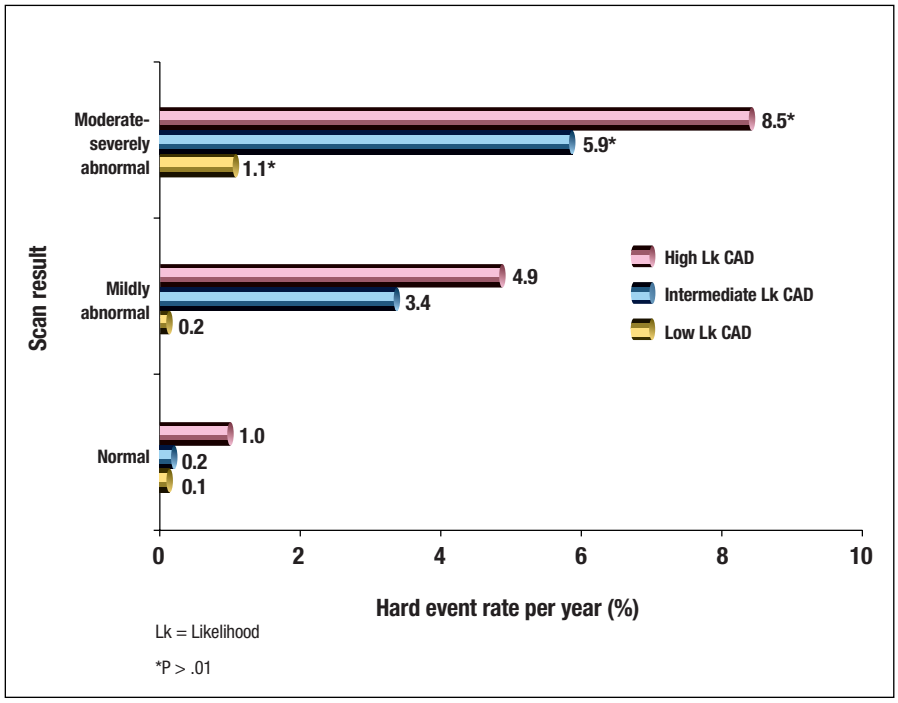

Figure 4. Rates of hard events (cardiac death or nonfatal myocardial infarction) per year of follow-up in patients with normal, mildly abnormal, and moderate to severely abnormal scans. A statistically significant increase in hard event rate is present between categories of prescan likelihood of coronary artery disease (CAD).

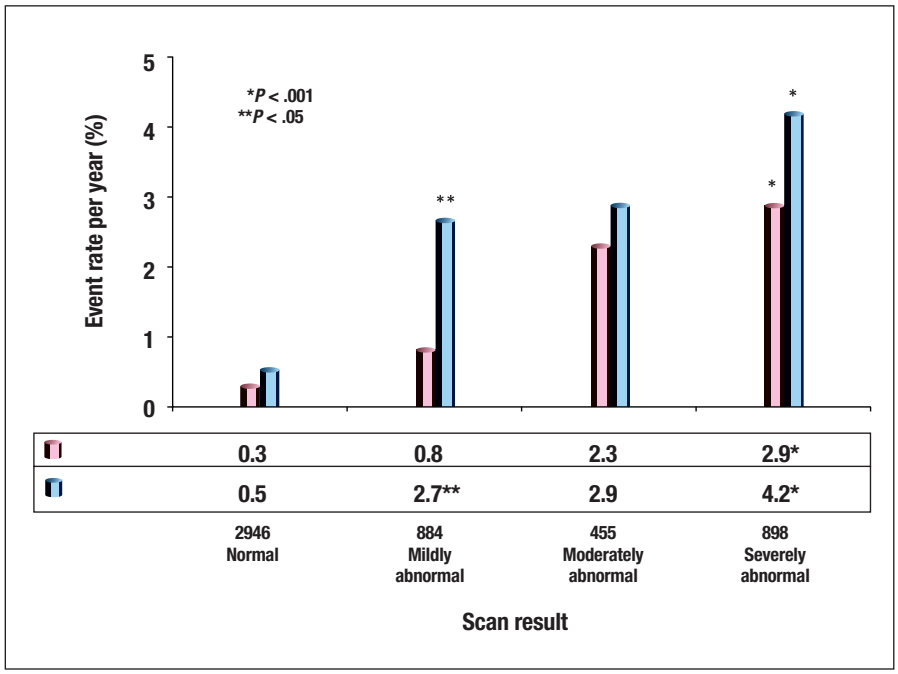

Figure 5. Rates of cardiac death and nonfatal myocardial infarction in patients undergoing dual-isotope stress single-photon emission CT and follow-up. Event rates are expressed per year and within categories of scan results (normal, mildly abnormal, moderately abnormal, and severely abnormal scans).

women than for high-risk men.

These results were recently extended in a multicenter database registry of 5009 men and 3402 women, again finding that SPECT resulted in enhanced risk stratification.[17] Shaw and colleagues[18] investigated the role of SPECT in the elderly in great depth, confirming the presence of added value from SPECT in this cohort using either exercise or dipyridamole-induced stress.

Event-Specific Risk Stratification

Recently, an observational, single-site study of 5183 patients who underwent stress MPI and were followed for hard events examined the ability of stress SPECT to risk-stratify patients with regard to the risks of cardiac death and nonfatal MI as separate end points.[23] As expected, significant increases in the frequency of cardiac death and MI occurred as a function of worsening scan results (Figure 5). Of interest, however, is that patients with mildly abnormal stress radionuclide myocardial perfusion studies were at intermediate risk for MI (2.7% per year) but at low risk for cardiac death (0.8% per year). Perhaps a mildly abnormal perfusion study identifies patients with a high likelihood of CAD but the CAD present is mild or branch disease. Since revascularization has not been shown to lower the incidence of nonfatal MI but medical therapy has, these patients with mildly abnormal studies may be candidates for initial medical therapy if their functional status and quality of life are not compromised.

This pattern of outcomes—low risk of cardiac death in patients with mild CAD and intermediate risk of MI in the setting of CAD, the latter independent of the amount of disease present—that was described in this study is not an

original finding. In 1980, Harris and colleagues,[33] from the Duke University data bank, examined the relationship between the initial cardiac event that patients experienced during a mean follow-up of 5 years and the extent of anatomic coronary disease noted on an index catheterization (Figure 6). In patients with multivessel coronary disease or poor left ventricular function, cardiac death was the predominant initial cardiovascular event. On the other hand, nonfatal MI was the initial event in patients with single-vessel coronary disease. In these patients, the occurrences of nonfatal MI far outnumbered cardiac deaths. Thus, despite the presence of anatomic coronary disease, patients with mild CAD had excellent cardiovascular survival. This supports the possibility that risk stratification by means of noninvasive testing can identify the level of risk of varying outcomes that may best benefit from differing therapeutic approaches.

In the study of more than 5000 patients undergoing stress SPECT described above, a cost-analysis compared 2 strategies of referral to catheterization: one, after all abnormal studies; the other, only after a moderately or severely abnormal scan. The latter strategy yielded a 33.5% cost savings—without impact on outcomes—by decreasing the use of catheterization in patients with mildly abnormal scans.[23] ■

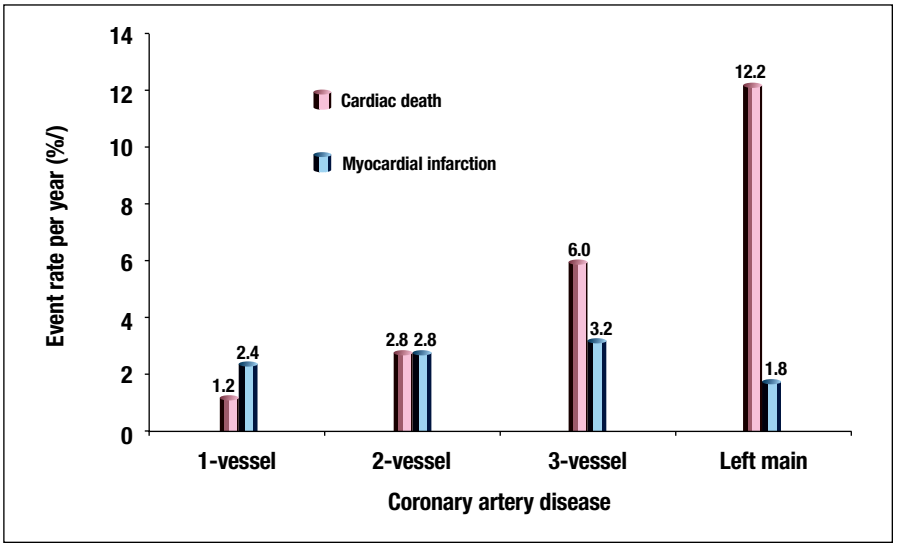

Figure 6. Rates of cardiac death and nonfatal myocardial infarction per year of follow-up in patients who were followed after index cardiac catheterization showing the extent of coronary artery disease.

References

1. American Heart Association. *2000 Heart and Stroke Statistical Update*. Dallas: American Heart Association; 1999.
2. Health US. Hyattsville, Md: National Center for Health Statistics; 1999.
3. Ginzberg E, ed. *Health Services Research*. Cambridge, Mass: Harvard University Press; 1993.
4. Berman DS, Kiat H, Friedman JD, Diamond G. Clinical applications of exercise nuclear cardiology studies in the era of healthcare reform. *Am J Cardiol*. 1995;75:3D-13D.
5. Califf RM, Armstrong PW, Carver JR, et al. 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.
6. Hachamovitch R, Berman DS, Morise AP, Diamond GA. Statistical, epidemiological and fiscal issues in the evaluation of patients with coronary artery disease. *Q J Nucl Med*. 1996; 40:35-46.
7. Shaw LJ, Eisenstein EL, Hachamovitch R, et al. A primer of biostatistic and economic methods for diagnostic and prognostic modeling in nuclear cardiology: Part II. *J Nucl Cardiol*. 1997;4:52-60.
8. Ladenheim ML, Kotler TS, Pollock BH, et al. Incremental prognostic power of clinical history, exercise electrocardiography and myocardial perfusion scintigraphy in suspected coronary artery disease. *Am J Cardiol*. 1987; 59:270-277.
9. Alkeylani A, Miller DD, Shaw LJ, et al. Influence of race on the prediction of cardiac events with stress technetium-99m sestamibi tomographic imaging in patients with stable angina pectoris. *Am J Cardiol*. 1998;81:293-297.
10. 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.
11. Hachamovitch R, Berman DS, Kiat H, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. *J Am Coll Cardiol*. 1996;28:34-44.
12. 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.
13. Hachamovitch R, Berman DS, Kiat H, et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. *Am J Cardiol*. 1997;80:426-433.
14. Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol*. 1993;22:665-670.
15. Machecourt J, Longere P, Fagret D, et al. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect: study in 1,926 patients with follow-up at 33 months. *J Am Coll Cardiol*. 1994;23:1096-1106.
16. 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.
17. Marwick TH, Shaw LJ, Lauer MS, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Economics of Noninvasive Diagnosis (END) Study Group. *Am J Med*. 1999;106:172-178.
18. Shaw LJ, Miller DD, Romeis JC, et al. Prognostic value of noninvasive risk stratification in younger and older patients referred for evaluation of suspected coronary artery disease. *J Am Geriatr Soc*. 1996;44:1190-1197.
19. Shaw LJ, Hachamovitch R, Peterson ED, et al. Using an outcomes-based approach to identify candidates for risk stratification after exer-

cise treadmill testing. *J Gen Intern Med*. 1999; 14:1-9.
20. Abdel Fattah A, Kamal AM, Pancholy S, et al. Prognostic implications of normal exercise tomographic thallium images in patients with angiographic evidence of significant coronary artery disease. *Am J Cardiol*. 1994; 74:769-771.
21. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. *Circulation*. 1991;83:363-381.
22. Brown KA, Rowen M. Prognostic value of a normal exercise myocardial perfusion imaging study in patients with angiographically significant coronary artery disease. *Am J Cardiol*. 1993;71:865-867.
23. 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.
24. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol*. 1998;32:57-62.
25. Parisi AF, Hartigan PM, Folland ED. Evaluation of exercise thallium scintigraphy versus exercise electrocardiography in predicting survival outcomes and morbid cardiac events in patients with single- and double-vessel disease: findings from the Angioplasty Compared to Medicine (ACME) Study. *J Am Coll Cardiol*. 1997;30:1256-1263.
26. Schalet BD, Kegel JG, Heo J, et al. Prognostic implications of normal exercise SPECT thallium images in patients with strongly positive exercise electrocardiograms. *Am J Cardiol*. 1993;72:1201-1203.
27. Shaw LJ, Heller GV, Travin MI, et al. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. Economics of Noninvasive Diagnosis (END) Study Group. *J Nucl Cardiol*. 1999;6: 559-569.
28. 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.
29. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA*. 1998;280: 913-920.
30. Rozanski A, Diamond GA, Berman D, et al. The declining specificity of exercise radionuclide ventriculography. *N Engl J Med*. 1983; 309:518-522.
31. Roger VL, Pellikka PA, Bell MR, et al. Sex and test verification bias. Impact on the diagnostic value of exercise echocardiography. *Circulation*. 1997;95:405-410.
32. Hachamovitch R, Schnipper J, Young-Xu Y. Are patients with known or suspected coronary artery disease and normal stress imaging studies at low risk for adverse outcomes: meta-analysis of stress echocardiography and SPECT [abstract]. *J Am Coll Cardiol*. 2000;35: 547A. Abstract 1104-1116.
33. Harris PJ, Lee KL, Harrell FE Jr, et al. Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. *Circulation*. 1980;62:718-726.

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tained-release dexfenfluramine, or placebo. Sustained-Release Dexfenfluramine Study Group. *N Engl J Med*. 1998;339:725-732.
13. Burger AJ, Sherman HB, Charlamb MJ, et al. Low prevalence of valvular heart disease in 226 phentermine-fenfluramine protocol subjects prospectively followed for up to 30 months. *J Am Coll Cardiol*. 1999;34:1153-1158.
14. Gardin JM, Schumacher D, Constantine G, et al. Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA*. 2000;283:1703-1709.
15. Teramae CY, Connolly HM, Grogan M, Miller FA Jr. Diet drug-related cardiac valve disease: the Mayo Clinic echocardiographic laboratory experience. *Mayo Clin Proc*. 2000;75:456-461.
16. Akasaka T, Yoshikawa J, Yoshida K, et al. Age-related valvular regurgitation: a study by pulsed Doppler echocardiography. *Circulation*. 1987;76: 262-265.
17. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study) [published correction appears in *Am J Cardiol*. 1999;84:1143]. *Am J Cardiol*. 1999;83:897-902.
18. Lepor NE, Gross SB, Daley WL, et al. Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. *Am J Cardiol*. 2000;86:107-110.
19. Jollis JG, Landolfo CK, Kisslo J, et al. Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation*. 2000;101: 2071-2077.
20. Li R, Serdula MK, Williamson DF, et al. Dose-effect of fenfluramine use on the severity of valvular heart disease among fen-phen patients with valvulopathy. *Int J Obes Relat Metab Disord*. 1999;23:926-928.
21. Weissman NJ, Tighe JF, Gottdiener JS, Gwynne JT. Prevalence of valvular-regurgitation associated with dexfenfluramine three to five months after discontinuation of treatment. *J Am Coll Cardiol*. 1999;24:2088-2095.
22. Davidoff R, McTiernan A, Constantine G, et al. Echocardiographic evaluation of women previously treated with fenfluramine: long-term follow-up of a randomized, double-blind, placebo-controlled trial. Presented at: 2nd Annual and Plenary Meeting of the Working Group on Echocardiography of the European Society of Cardiology; December 10, 1998; Trieste, Italy.
23. Shively BK, Roldan CA, Gill EA, et al. Prevalence and determinants of valvulopathy in patients treated with dexfenfluramine. *Circulation*. 1999; 100:2161-2167.
24. Hensrud DD, Connolly HM, Grogan M, et al. Echocardiographic improvement over time after cessation of use of fenfluramine and phentermine. *Mayo Clin Proc*. 1999;74:1191-1197.
25. Mast ST, Jollis JG, Ryan T, et al. The natural history of fenfluramine-associated valvulopathy assessed by echocardiography [abstract]. *J Am Coll Cardiol*. 2000;35(suppl A):523A-524A. Abstract 1001-170.
26. Douglas JG, Munro JF, Kitchin AH, et al. Pulmonary hypertension and fenfluramine. *Br Med J*. 1981;283(Clin Res):881-883.
27. Roche N, Labrune S, Braun JM, Huchon G. Pulmonary hypertension and dexfenfluramine. *Lancet*. 1992;339:436-437.
28. Brenot F, Herve P, Petitpretz P, et al. Primary pulmonary hypertension and fenfluramine use. *Br Heart J*. 1993;70:537-541.
29. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med*. 1996;335: 609-616.
30. Rich S, Rubin L, Walker AM, et al. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. *Chest*. 2000; 117:870-874.
31. Naeije R, Maggiorini M, Delcroix M, et al. Effects of chronic dexfenfluramine treatment on pulmonary hemodynamics in dogs. *Am J Respir Crit Care Med*. 1996;154:1347-1350.
32. Michelakis ED, Weir EK, Nelson DP, et al. Dexfenfluramine elevates systemic blood pressure by inhibiting potassium currents in vascular smooth muscle cells. *J Pharmacol Exp Ther*. 1999;291: 1143-1149.
33. Weir EK, Reeve HL, Johnson G, et al. A role for potassium channels in smooth muscle cells and platelets in the etiology of primary pulmonary hypertension. *Chest*. 1998;114(suppl 3):200S-204S.
34. Morse JH, Jones AC, Barst RJ, et al. Mapping of familial primary pulmonary hypertension locus (PPH1) to chromosome 2q31-q32. *Circulation*. 1997;95:2603-2606.
35. Bonow RO, Carabello B, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *Circulation*. 1998;98:1949-1984.
36. Klein AL, Burstow DJ, Tajik AJ, et al. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. *J Am Soc Echocardiogr*. 1990;3:54-63.