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Introduction

Noel Bairey Merz, MD

The practice of cardiology has been evolving steadily over many decades. Advancements in technology and techniques for diagnosing and managing heart disease have helped us to reduce cardiovascular mortality rates. Awareness of heart disease among women and the practitioners who treat them has also grown in recent years, although the management of female cardiac patients still lags behind that of their male counterparts.

Important goals in the practice of cardiology include heart disease prevention, early diagnosis, noninvasive diagnostic and management modalities, and more accurate risk assessment and treatment guidance. Many tools exist to help address these objectives, including risk-assessment scores and surveys, routine stress testing, nuclear and ultrasound imaging with exercise or pharmacologic stress, and electron-beam computed tomography (EBCT) to measure coronary calcium levels.

Risk assessment of cardiac patients is increasingly important because the more accurate the prognosis and risk stratification, the more appropriate the treatment. The management of low- and high-risk patients is relatively straightforward—the former requiring moderate preventive attention at the most, and the latter generally requiring revascularization procedures.

Intermediate-risk patients, however—who comprise a large proportion of the cardiac patient population—pose more of a dilemma in management decision making. Sometimes these patients are undertreated, and their disease is inadvertently allowed to progress. Other times, these patients undergo invasive revascularization when medical and lifestyle management may have been effective. Further evaluation of intermediate-risk patients to more accurately define their risk can lead to more appropriate care, improved outcomes, and more efficient utilization of healthcare resources.

To shed more light on current techniques for cardiovascular assessment, a roundtable meeting was held in Laguna Beach, California, on January 21, 2005. The roundtable convened 4 thought leaders in preventive cardiology and cardiovascular risk assessment. The articles published in this supplement to The American Journal of Cardiology reflect the discussions held at that meeting.

In the first article, I discuss methods of defining risk in patients. Two in-depth case studies are presented that illustrate the use of the various available tools for risk stratification and management guidance for both symptomatic and asymptomatic patients.

Next, Drs. Martha Gulati and Patrick E. McBride present the uses and limitations of submaximal exercise testing in cardiac patients, indicating when such testing is appropriate and when patients should be referred for alternative assessment. They also discuss “hidden” candidates for pharmacologic stress testing (ie, those patients in whom the inability to exercise adequately for nuclear imaging may not be obvious). (Note: Although Dr. Gulati was unable to attend the meeting because of inclement weather, her presentation was discussed and she coauthored the article published herein.)

Dr. Paolo Raggi then discusses the use of EBCT to assess the presence and extent of coronary artery calcification. While research continues to explore this growing area of interest in cardiology, early studies to date suggest a role for coronary calcium assessment in the risk stratification of patients.

Finally, Drs. Leslee J. Shaw and Daniel S. Berman describe sequential myocardial perfusion imaging. Although the use of nuclear imaging to assess myocardial perfusion has increased significantly in recent years, most clinicians use such tests as a onetime assessment. However, as Dr. Shaw points out, repeated testing can have great value in monitoring disease progression and assessing the effectiveness of therapies and risk management strategies.
Assessment of Patients at Intermediate Cardiac Risk

Noel Bairey Merz, MD

Optimal management of patients who are considered to be at intermediate risk for coronary artery disease (CAD) and cardiac events is not straightforward. Some risk assessment findings in these patients often prompt physicians to pursue revascularization procedures that may not be necessary, whereas other findings may result in undertreatment.

A number of risk assessment tools are available to further define such patients’ risks and prognoses. Having a better understanding of the risk scores and imaging modalities can help physicians to optimize patient management decisions and will ultimately result in improved patient outcomes.

Defining Risk Groups

Patients at intermediate risk fall into 2 general groups: asymptomatic and symptomatic. In asymptomatic patients, the goal of assessment is generally prognosis; in symptomatic patients, the goal is diagnosis—to guide symptomatic therapy—as well as prognosis. Asymptomatic patients are initially assessed with tools such as the Framingham scoring system, which is the first step in risk assessment for all patients. After evaluation with a scoring system, symptomatic patients are typically referred for noninvasive cardiac testing, usually an exercise stress test, to determine the cause of their symptoms.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) uses the Framingham Global Coronary Heart Disease Risk Assessment in the expert consensus algorithm for cardiac risk stratification; this has become the clinical standard for initial patient CAD risk categorization. The NCEP ATP III categorizes patients into 3 initial risk groups based on major risk factors and the presence of other cardiovascular disease (Table 1).

On the basis of these risk factors, patients are stratified into low-, intermediate-, or high-risk categories (Figure 1). Each category reflects the patient’s risk for a major coronary event (ie, nonfatal myocardial infarction [MI] or cardiac death) occurring within 10 years.1

Patients at Intermediate Risk

Initial risk stratification is used to guide the course of patient management. Patients who are categorized as at low risk are generally reassured, given appropriate lifestyle recommendations, and asked to return for periodic retesting. Patients at high risk are managed more aggressively, with preventive strategies that include daily use of low-dose aspirin and lipid-lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). For asymptomatic patients at high risk, screening for obstructive CAD may be appropriate. Further steps for management and additional testing of patients at intermediate risk, however, are not clear-cut.

A number of tools for further risk stratification exist and can be used in patients initially categorized as at intermediate risk:

- The office-based Framingham Coronary Heart Disease Risk Factor Prediction Chart estimates prognostic CAD risk and is recommended for annual assessment in all adults.2
- The combined Diamond/Coronary Artery Surgery Study (CASS) Angina Symptom Index is used to estimate the pretest likelihood of CAD in symptomatic patients.3,4
- The Duke Noninvasive Prognostic Index (DNPI) determines prognosis primarily on the basis of exercise stress test results, including exercise test duration, presence of electrocardiographic ST-segment depression, and symptom response to stress.5,6
- The Duke Coronary Angiographic Prognostic Index (DCAPI)—used to calculate patients’ prognostic risk,
including risk for cardiovascular events and death—is based on coronary angiography results, left ventricular ejection fraction (LVEF), and medical comorbidity.

- The Yusuf Score determines prognostic risk for patients with established CAD according to medical and surgical (ie, revascularization) management.

Table 2 outlines suggested next steps in assessment of patients at intermediate risk that are derived from the expert consensus of the American Heart Association's (AHA) Prevention Conference V.

The following case studies demonstrate the use of the various risk assessment tools in asymptomatic and symptomatic patients who are at intermediate risk.

### Case Studies

**Case 1. Asymptomatic intermediate risk:** The patient was a 46-year-old man who was asymptomatic for CAD. He had a positive family history of premature CAD (his father had an MI at 50 years of age). He also had a 10-year history of hyperlipidemia, for which his primary care physician had prescribed simvastatin. For unknown reasons, the patient discontinued the simvastatin therapy. The patient’s age and plasma level of low-density lipoprotein (LDL) cholesterol gave him ≥2 risk factors, so he fell into the NCEP ATP III intermediate-risk category.

**Framingham score:** The patient was first evaluated with the office-based Framingham Global Coronary Heart Disease Risk Assessment, which takes into account the following factors: age, sex, cigarette smoking, blood lipid levels, blood pressure, presence or absence of diabetes mellitus, and electrocardiographic findings (eg, left ventricular hypertrophy). The risk factors are weighted and summarized using a score sheet to produce a 10-year cardiac event risk assessment. Table 3 shows the results of the patient’s Framingham risk assessment.

The patient’s plasma levels of LDL and high-density lipoprotein (HDL) cholesterol were problematic, but his other factors were not indicative of risk. Notably, the patient had a high level of physical activity, engaging in aerobic exercise daily. Based on the Framingham Global Coronary Heart Disease Risk Assessment, his 10-year risk for nonfatal MI or CAD death was 13%, which is considered intermediate (10% to 20%). Based on this risk level, appropriate
management is low-dose aspirin daily and consideration of additional testing to determine the need for lipid-lowering statin therapy.

**Electron-beam computed tomography (EBCT):** This patient’s referring physician decided to perform further risk assessment and ordered a coronary calcium scan, which was accomplished by means of EBCT. The patient’s total coronary calcium score (CCS) was 450, with the calcium distribution predominantly in the left anterior descending coronary artery and the right coronary artery. When applied to a CCS risk model,10 this corresponds to a 13% 10-year risk, which is the same level of intermediate risk for this patient determined by the Framingham Global Coronary Heart Disease Risk Assessment.

Confirmation of this patient’s intermediate Framingham risk by means of a method that is also strongly determined by CAD risk factors was somewhat reassuring. However, a CCS >400 is correlated with an approximate 30% likelihood of obstructive CAD. The question of whether lipid-lowering statin therapy was indicated remained unanswered, and a new question arose regarding the need for additional testing to rule out obstructive CAD.

**Single-photon emission computed tomography (SPECT) and the DNPI:** On the basis of the EBCT findings, the patient’s physician ordered exercise SPECT for detection of obstructive CAD. Table 411 shows the patient’s SPECT results.

The DNPI was then used to reassess the patient’s risk, taking into account the following factors5: age, pretest clinical index, LVEF, and workload achieved (functional capacity or duration of stress protocol). The DNPI determined that this patient’s risk of nonfatal MI or CAD death was 4% over 10 years. This was substantially lower than the 13% risk calculated by means of the Framingham score and CCS. The difference was due, in large part, to the patient’s high exercise capacity, which portended an overall good prognosis regarding potential for nonfatal MI and cardiac death.

Although the patient’s DNPI score indicated relatively low risk, it is important to remember that he has a family history and risk factors that should not be ignored when deciding on further assessment and treatment strategy.

**Coronary angiography and assessment tools:** Despite this patient’s overall relatively good prognosis based on multiple measurements—specifically, his high exercise capacity, normal LVEF during exercise, and
distal nature of myocardial ischemia on SPECT, all of which dictated a medical management course for CAD—the referring physician ordered coronary angiography to determine the extent and severity of obstructive CAD. The results are shown in Table 5.

Two assessment tools can be used to determine prognosis on the basis of coronary angiographic findings:

- The DCAPI model provides prognostic outcomes by means of coronary angiography and associated comorbidities.5
- The Yusuf Score provides prognostic outcomes information for both medical management and management with surgical revascularization in patients with obstructive CAD.7,8

These tools use the following similar set of parameters to determine prognostic risk: angina, hypertension, diabetes, resting ST-segment depression, history of MI, age, sex, LVEF, disease of the left anterior descending coronary artery, disease of the right coronary artery, functional capacity, peripheral vascular disease, other comorbidity, and urgent/emergent surgery. The patient’s DCAPI score of 150 translated to an 8% 5-year mortality risk (or approximately a 16% 10-year risk by extrapolation) with medical management. His Yusuf Score (0.89) fell into the lowest tertile, which translated to a 10% 5-year mortality risk (approximately a 20% 10-year risk by extrapolation) if he underwent coronary artery bypass graft (CABG) surgery.

**Discussion and follow-up**: The calculated risks using the additional information obtained after extensive testing of this patient were similar to the risk (intermediate) determined initially with the Framingham score and CCS. Rather than undergo coronary angiography, this patient could have been managed medically, with intensified global risk-factor management. To reassure physicians and patients about this management strategy, a patient can again undergo exercise SPECT after 6 to 12 months to assess the efficacy of the strategy. If the exercise capacity or magnitude of ischemia is worsening, additional testing can be conducted as appropriate. The additional knowledge of this patient’s coronary artery anatomy, obtained during angiographic testing at this time, added little real prognostic value in this case.

Despite the stenosis noted on angiography, this patient remained at intermediate risk. The fact that he was able to exercise to 100% capacity and perform 14 minutes on the treadmill using the Bruce protocol11 without experiencing angina or diagnostic ST-segment changes indicates that revascularization procedures would not likely help this patient. The Yusuf Score indicated that CABG would not lower his mortality risk compared with medical management. Importantly, surgical revascularization in this patient actually adds risk (ie, prognosis is worse), as shown in the Yusuf Score compared with the DCAPI score. This is likely due to the risks of surgery not being offset in subjects at low to intermediate risk, possibly due to the disruption of collateral coronary blood flow that can occur with bypass surgery.

Nonetheless, the patient’s referring cardiologist chose to recommend CABG. The patient had an uncomplicated postoperative course. Repeat SPECT after revascularization (performed for cardiac rehabilitation) demonstrated abnormalities

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**Table 4**

Results of single-photon emission computed tomography (SPECT) in an asymptomatic 46-year-old male patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration</td>
<td>14 min (Bruce protocol)11</td>
</tr>
<tr>
<td>Age-predicted maximum heart rate achieved</td>
<td>100%</td>
</tr>
<tr>
<td>Angina on exercise</td>
<td>No</td>
</tr>
<tr>
<td>ST-segment change</td>
<td>Nondiagnostic ST-segment elevation at peak exercise</td>
</tr>
<tr>
<td>Defects</td>
<td>Reversible distal anterior and apical defect, 10% hypoperfused myocardium</td>
</tr>
<tr>
<td>Peak LVEF</td>
<td>0.61</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction.

**Table 5**

Results of coronary angiography in an asymptomatic 46-year-old male patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery</td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>No lesion</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>Severe (80%) proximal disease involving the first and second diagonals</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>No lesion</td>
</tr>
<tr>
<td>Right</td>
<td>75% Stenosis in the posterior descending artery</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>Normal</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>None</td>
</tr>
</tbody>
</table>

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Bairey Merz/Assessment of Patients at Intermediate Cardiac Risk
identical to those shown in the pre-CABG SPECT study—10% hypoperfused myocardium at the left ventricular apex at a similarly high workload. Subsequent coronary angiography showed that the grafts remained open. The patient was started on daily low-dose aspirin therapy postoperatively but remained untreated for dyslipidemia.

**Global risk medical management:** This patient was subsequently evaluated by another cardiologist, who prescribed atorvastatin 40 mg/day in addition to aspirin 81 mg/day. At follow-up, his lipid profile had improved significantly (Table 6). Long-acting niacin was also subsequently prescribed along with the atorvastatin, as a treatment for his mixed dyslipidemia, to raise his plasma levels of HDL cholesterol.

**Conclusions:** A variety of methods for determining global CAD, including noninvasive, angiographic, and surgical risk scores, are available but are underutilized in clinical practice. Physicians can be better educated on the use of risk assessment scoring tools and encouraged to use such methods in their daily practices. Accurate assessment of risk, prognosis, and impact of medical therapy compared with revascularization can help to optimize risk reduction. Revascularization based on angiographic visualization alone in patients whose condition is stable may not lower a patient’s mortality risk, and better use of risk-scoring tools can help spare patients who are at intermediate risk from unnecessary revascularization procedures and lead them toward effective medical management.

Statin therapy alone can reduce the 10-year risk of nonfatal and fatal CAD by approximately 35%,12,13 and with lipid-lowering medical management including a statin, this patient’s risk was further lowered, from 13% to 8%. Recent aggressive lipid-lowering studies further indicate that lowering LDL cholesterol to <1.81 to 1.94 mmol/L (<70 to 75 mg/dL) may provide further benefit for patients at risk.14,15 Aspirin therapy can be expected to further lower risk by approximately 20%.16 Simultaneously raising the HDL cholesterol plasma level with combination niacin and statin therapy appears to improve the risk reduction to 80%.17,18 Therefore, patients at low to intermediate risk can often be managed safely and effectively with evaluation for risk assessment scores, aggressive noninvasive medical treatment, and careful monitoring.

**Case 2. Symptomatic intermediate risk:** The patient was a symptomatic, 56-year-old woman. She had a several-year history of borderline hypertension (on the basis of her primary care physician’s report). She had discontinued her hormone replacement therapy because of recent negative study reports and was experiencing severe hot flashes, was unable to sleep, and was extremely irritable. She restarted hormone replacement therapy and visited the physician for consultation regarding the safety of such therapy.

During the review of symptoms, the patient disclosed that she experienced episodic chest tightness that was sometimes related to exertion or stress. She had recently visited her gynecologist for treatment of a vaginal yeast infection and underwent blood testing, which had revealed dyslipidemia and an elevated blood sugar level on random sampling (Table 7).

The patient was also sedentary and had abdominal obesity, with a waist girth of 36 in (91.44 cm) and a body mass index of 29. In addition, the patient had recently seen her primary care physician for an influenza vaccination. Neither that physician nor the gynecologist had discussed cardiovascular risk with her.

**Framingham Score and Diamond/CASS Angina Symptom Index:** The patient’s Framingham Global Coronary Heart Disease Risk Assessment score indicated a 14% (intermediate) 10-year risk for nonfatal or fatal CAD. She also had the metabolic syndrome, with centripetal obesity, low plasma levels of HDL cholesterol, prehypertension, and elevated plasma values for triglycerides, a complex of conditions that may be considered to constitute intermediate risk for most patients. Her elevated fasting blood glucose measurement did not quite meet the criterion for diabetes (>6.99 mmol/L [>126 mg/dL]), which is a CAD risk equivalent in the NCEP ATP III risk categories.19 According to the Diamond/CASS Angina Symptom Index, the patient had atypical angina (Table 8).3,4

**Adenosine stress SPECT and the DNPI:** The findings suggested that this symptomatic patient had an intermediate risk of angiographic CAD and future CAD events. For a

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### Table 6

Plasma lipid profiles before and after medical management in an asymptomatic 46-year-old male patient

<table>
<thead>
<tr>
<th>Lipid Component</th>
<th>No Medication (February 1999)</th>
<th>Atorvastatin (July 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L (mg/dL)</td>
<td>6.48 (250)</td>
<td>4.22 (163)</td>
</tr>
<tr>
<td>HDL-C, mmol/L (mg/dL)</td>
<td>0.91 (35)</td>
<td>1.01 (39)</td>
</tr>
<tr>
<td>LDL-C, mmol/L (mg/dL)</td>
<td>4.82 (186)</td>
<td>2.59 (100)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (mg/dL)</td>
<td>1.51 (134)</td>
<td>1.07 (95)</td>
</tr>
<tr>
<td>Total/HDL-C ratio</td>
<td>7.1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
symptomatic woman of this age who was at intermediate risk, exercise stress SPECT is an appropriate test for the purposes of diagnosis and symptomatic treatment, as well as to further define her prognostic risk and potential need for further evaluation and treatment. However, given the patient’s obesity and sedentary lifestyle, the cardiologist believed it was highly unlikely that the patient would exercise adequately to obtain diagnostic stress test results. Therefore, a pharmacologic adenosine stress SPECT test was ordered.

During the pharmacologic stress test, the patient developed chest symptoms but no ST-segment changes. SPECT revealed reversible mid-anterior hypoperfused myocardium (Figure 2) and an LVEF of 0.52. Based on these SPECT results, the DNPI determined a 20% 10-year risk of nonfatal MI or CAD death—the same risk indicated by the patient’s Framingham score.

**Discussion and treatment:** The fact that this patient had a normal angiogram and a low-risk DCAPI score represents a potential management problem. Many such patients do not receive medical treatment because their angiograms show that their coronary arteries are not obstructed. However, this woman likely required medical intervention in the form of risk factor management. Given her metabolic syndrome, hyperlipidemia, myocardial ischemia, and Framingham and DNPI calculated risk scores—which placed her at intermediate to high risk—she remained at an elevated risk for adverse CAD events despite her angiographic findings. Recent findings from the Women’s Ischemia Syndrome Evaluation (WISE) have demonstrated that evidence of myocardial ischemia is a predictor of adverse outcomes in women, even without the presence of obstructive CAD (Figure 4).

A new baseline lipid panel and some specialty laboratory assessments were obtained after treatment of the patient’s vaginal yeast infection (Table 9). Medical therapy was initiated with simvastatin 40 mg/day, amlodipine besylate 10 mg/day, benazepril hydrochloride 20 mg/day, and aspirin 81 mg/day. At follow-up evaluation, the patient’s lipid profile and metabolic parameters were substantially improved (Table 9).

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**Table 7**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>138/89</td>
</tr>
<tr>
<td>Blood sugar, mmol/L (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>23.43 (422)</td>
</tr>
<tr>
<td>Fasting</td>
<td>6.83 (123)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (mg/dL)</td>
<td>8.52 (329)</td>
</tr>
<tr>
<td>HDL-C, mmol/L (mg/dL)</td>
<td>1.06 (41)</td>
</tr>
<tr>
<td>LDL-C, mmol/L (mg/dL)</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (mg/dL)</td>
<td>5.65 (500)</td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

**Table 8**

<table>
<thead>
<tr>
<th>Questions asked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there substernal pain?</td>
</tr>
<tr>
<td>Is it triggered by exercise or emotional stress?</td>
</tr>
<tr>
<td>Is it relieved within 10 minutes by rest or sublingual nitroglycerin?</td>
</tr>
</tbody>
</table>

**Symptom category determination**

<table>
<thead>
<tr>
<th>No. of “yes” responses</th>
<th>Symptom category</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Typical angina</td>
</tr>
<tr>
<td>2</td>
<td>Atypical angina</td>
</tr>
<tr>
<td>1</td>
<td>Nonanginal</td>
</tr>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

Adapted with permission from *N Engl J Med* and *J Am Coll Cardiol*.
Conclusions: Symptomatic patients at intermediate risk for CAD can benefit from additional risk stratification. Global, prognostic, and ischemic risk scores should be factored in with coronary angiography results to optimize patient management.

Myocardial ischemia, even in patients with normal angiographic results, indicates a poor prognosis and should be managed with attention to risk factors and aggressive medical management. Integration of risk scores and imaging modalities can assist the clinician in optimizing the use of aggressive medical therapies as well as revascularization procedures when appropriate.

Another issue raised by this case is that physicians must become more adept at recognizing the metabolic syndrome and effectively managing risk factors and CAD risk in patients with the metabolic syndrome. The metabolic syndrome is a clustering of risk factors, including abdominal obesity, dyslipidemia, hypertension, glucose
intolerance or insulin resistance, and a prothrombotic or proinflammatory state. The patient in this case presented with a classic metabolic syndrome profile, yet several physicians did not recognize her condition or initiate risk factor management.

Summary

A number of available risk-assessment tools for CAD are underutilized in clinical practice. When patients who are initially classified as being at intermediate risk are evaluated, further assessment by means of scoring and imaging tools can add incremental diagnostic and prognostic values. These tools can also help guide the management of patients at intermediate risk.

Aggressive medical therapy and lifestyle modification can often result in substantial improvement in risk factors for CAD and obviate the need for revascularization procedures. Although revascularization is available, it does not necessarily lower risk for mortality or serious cardiac events in a patient at intermediate risk. A careful approach to weighing risks and benefits of the various medical and revascularization management strategies is a challenging task for physicians and patients. Use of the risk assessment tools discussed herein can help with this difficult decision-making process.

Enhanced use of risk assessment tools can be especially valuable in evaluating women who are at intermediate risk for CAD and CAD-related events. Cardiovascular risk in women often tends to be underestimated, and an overreliance on angiographic results can lead to undertreatment, even in symptomatic women. Improved physician education in terms of both risk assessment tools and identification of patients at risk for cardiovascular events can assist in improving patient management and outcomes.


Functional Capacity and Cardiovascular Assessment: Submaximal Exercise Testing and Hidden Candidates for Pharmacologic Stress

Martha Gulati, MD, MS,a,* and Patrick E. McBride, MD, MPHb

Submaximal exercise testing is often used to estimate functional capacity in non-athletes, to assess cardiovascular disease in elderly or frail patients, to demonstrate exercise equipment, or to risk-stratify patients after myocardial infarction. However, submaximal exercise testing is not sufficiently sensitive, specific, or predictive to have widespread clinical utility, except in post-myocardial infarction protocols. Many patients for whom submaximal exercise testing is not useful are unable to exercise sufficiently for maximal testing and are referred for imaging with pharmacologic stress. Although some patients who are unable to exercise adequately are easily recognized, many are not. The identification of such patients before they fail a maximal exercise test attempt is beneficial to both the patient and the imaging laboratory. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:11J–19J)

Exercise testing has many clinical applications, including measuring functional capacity, developing an exercise prescription, screening for coronary ischemia, monitoring effects of medication, and determining prognosis in patients with cardiovascular disease, as well as other clinical uses in cardiopulmonary patients.

Submaximal Exercise Testing

Although studies to determine the prognosis of patients with coronary artery disease (CAD) require maximal exercise, submaximal exercise testing is often used for other evaluations, including functional capacity estimation in nonathletes, assessment of elderly or frail patients, demonstration of exercise equipment, or risk stratification after myocardial infarction (MI). However, submaximal exercise testing has significant limitations, including reduced sensitivity and specificity for assessing myocardial ischemia and limited predictive value for estimating functional capacity.

Exercise Electrocardiography

Exercise electrocardiography (ECG) is useful for many clinical and other healthcare situations, including indirectly detecting myocardial ischemia, estimating functional capacity, developing an exercise prescription, evaluating exercise hemodynamics and heart rhythm during exercise, and determining prognosis after diagnosis of CAD.

The American College of Sports Medicine (ACSM) and the American Heart Association (AHA) recommend maximal stress testing before participating in vigorous exercise for men aged ≥45 years and for women aged ≥55 years who have ≥2 CAD risk factors as well as for any patient with signs or symptoms of cardiopulmonary disease. Although neither ACSM nor AHA recommend submaximal testing as preparticipation screening before starting exercise programs, both organizations endorse guideline-supported submaximal protocols for risk stratification in post-MI patients.1,2

The reported sensitivity and specificity of submaximal testing for detecting myocardial ischemia have been based on studies correlating the ECG response to exercise with coronary angiographic data. Patient sex, age, coronary risk factors, and characteristics of chest pain also are important predictors of the pretest and posttest likelihood of CAD and the diagnostic accuracy of exercise ECG testing, with age and chest pain characteristics being the strongest indicators. Exercise test characteristics that increase sensitivity include maximal exercise testing, increased number of ECG leads used, use of imaging modalities in addition to ECG, older patient age, and CAD risk factors.

A major limitation of exercise ECG for the diagnosis of CAD is its limited sensitivity and specificity compared with coronary angiography, which is considered the “gold standard” for identifying coronary artery obstruction >70% (ie, the definition of CAD for stress testing). In a maximal exercise test, the patient achieves 85% to 90% of his or her predicted maximal heart rate or reports a score ≥18 on the Borg Perceived Exertion Scale. A test is considered adequate to demonstrate increased probability of ischemic heart disease if the patient reports chest discomfort or if abnormal
ECG findings are noted during the test, despite the patient’s workload, heart rate, or other hemodynamic principles. Studies that base CAD prognosis on stress testing require maximal exercise testing. The variables that predict future CAD risk are ECG changes at maximum workload, hemodynamic changes, and poor functional capacity.

The enhanced sensitivity of the maximal compared with the submaximal exercise test is critical for using exercise ECG for CAD screening. The American College of Cardiology (ACC)/AHA guideline for CAD screening with exercise ECG and/or imaging is as follows:

In patients who are classified as low risk on the basis of clinical and exercise testing information, there is no compelling evidence that an imaging modality adds significant new prognostic information to a standard exercise test. In this regard, a distinction should be made between studies that show a statistical advantage of imaging studies over exercise ECG alone and studies that demonstrate that the imaging data would change practice (eg, by shifting patients from moderate- to low- or high-risk categories). Because of its simplicity, lower cost, and widespread familiarity in its performance and interpretation, the standard treadmill ECG is the most reasonable exercise test to select in men with a normal resting ECG who are able to exercise. In patients with an intermediate-risk treadmill score, myocardial perfusion imaging appears to be of value for further risk stratification.

For patients with an intermediate pretest risk of CAD (ie, 25% to 75%), the overall sensitivity and specificity of exercise ECG testing were 68% and 77%, respectively, according to a meta-analysis of 147 published reports that compared exercise ECG testing with coronary angiography in >24,000 patients. The sensitivity and specificity of 1 mm of horizontal or downward ST depression have been shown to be 45% and 85%, respectively. Higher sensitivities are obtained with thallium imaging, single-photon emission computed tomography (SPECT) perfusion imaging, stress echocardiography, and positron emission tomography. High false-positive rates may be expected in patients with pretest probabilities of CAD <25% (eg, men aged <40 years or women aged <50 years with atypical chest pain) in whom the likelihood of a positive test indicating a significant coronary artery obstruction is low.

In a population of elderly men, exercise-induced ST depression and low peak functional capacity were recently demonstrated to be highly prognostic for cardiovascular death. A study of >13,000 men and women evaluated with maximal treadmill tests showed that patients in the lowest quintile of fitness had a >8- to 9-fold increased risk of cardiovascular death over the following 8 years. The high predictive value of exercise testing in this population is most likely the result of maximal testing and would be unlikely to be achieved with submaximal testing. Exercise testing used appropriately in high-risk sedentary individuals to further stratify their cardiovascular risk may be important to motivate them to exercise or provide important prognostic information.

**Exercise Test Protocols**

Most exercise testing protocols require progression from low workloads to higher workloads until either a predetermined end point is reached (ie, target heart rate, perceived exertion level, or workload) or signs or symptoms develop that limit further exertion. The most efficient exercise protocols are those that match the capabilities and physical working capacity of the patient, so that a maximal effort is reached in 6 to 12 minutes. Protocols that are too difficult, too short, or too long may not accurately measure the patient’s functional capacity. The appropriate protocol is usually determined from the patient’s clinical and exercise history.

Functional capacity is usually measured on a treadmill or stationary bicycle ergometer. A treadmill is preferred in the United States because cycling is not the generally preferred form of exercise in this country. The selection of an appropriate protocol for assessing functional capacity is important. If functional capacity is to be estimated from the exercise test time or peak work, especially if the test is submaximal or if the patient is not a regular exerciser, protocols that require significant increases in work between stages often are not accurate in predicting maximal functional capacity. Patients frequently stop prematurely because of a sudden, large increase in work that they perceive they cannot perform.

Protocols that include only modest increases in work from stage to stage, and that achieve fatigue-limited exercise in approximately 10 minutes, are preferable for estimating exercise functional capacity. Shorter durations may produce a nonlinear relation between O2 and work rate, whereas durations >12 minutes may cause subjects to terminate exercise because of muscle fatigue or orthopedic factors.

**Submaximal exercise testing:** Submaximal exercise testing has a much lower sensitivity and specificity than maximal exercise testing. However, submaximal testing may be useful in some clinical situations, including estimation of functional capacity for exercise prescription in nonathletes, assessment of elderly subjects not accustomed to vigorous exercise, and risk stratification after MI.

Assessing post-MI patients is generally the only useful function of submaximal exercise testing in a cardiology setting. Submaximal testing typically relies on estimating the maximal aerobic capacity from the work level achieved at the submaximal heart rate. This estimate leaves a potential for error because of the standard deviation in maximal heart rate, especially in patients with cardiopulmonary disease. Compared with measuring respiratory gases, estimating functional capacity at maximal work is limited, creating a greater potential for error in estimating maximal aerobic capacity from a submaximal test.
Submaximal testing involves several assumptions, according to the ACSM guidelines: (1) a steady-state heart rate is obtained for each exercise work rate, (2) a linear relation exists between heart rate and work rate, (3) the maximal heart rate for a given age is uniform, and (4) mechanical efficiency (i.e., $O_2$ at a given work rate) is the same for everyone.

Steady-state heart rates at each work rate and a linear relation between heart rate and work rate are usually the case, but maximal heart rate for age and mechanical efficiency are often quite variable. However, submaximal testing offers the following advantages: (1) reasonably good approximation of a healthy person’s functional capacity, (2) lower cost, (3) reduced risk, (4) less time and effort needed, and (5) can usually be performed without physician supervision.

Standardized protocols for submaximal stress testing are described by the ACSM. Testing is usually terminated when the patient has reached 85% of age-predicted maximal heart rate or 70% of heart rate reserve, or if clinical situations warrant stopping the test.

Submaximal exercise tests have the advantage of being safer than maximal exercise tests (although maximal tests are quite safe when properly conducted) and can be administered to a large number of people by exercise specialists in nonmedical settings, without physician supervision. (Physician supervision is recommended for any exercise test conducted on a high-risk patient—i.e., someone with signs or symptoms of cardiopulmonary disease or known cardiac, pulmonary, or metabolic disease.) However, the poor predictive value of functional capacity based on arbitrary submaximal heart rates (70% to 85% of predicted maximum for age) and the wide standard deviation in people’s heart rates limit the utility of submaximal exercise testing.

Another submaximal protocol, the 6- or 12-minute walk test, is conducted on a level surface, not on exercise equipment. These tests are used to measure outcomes in patients with heart failure and peripheral vascular disease who have undergone medical treatment and rehabilitation. The distance covered in such a test is a strong prognostic indicator. However, these tests are designed for use in specific populations and are beyond the scope of this article.

**Post-MI: Special indication for submaximal testing:** Submaximal exercise testing is recommended for patients before hospital discharge after acute MI. The protocol used for risk stratification after MI or unstable angina is limited to a predetermined workload (usually 5 metabolic equivalents [METs]) or a predetermined heart rate (usually 110 to 125 beats per minute for patients taking beta blockers). This protocol has been carefully developed to provide risk stratification information to determine the prognosis for these patients. The functional capacity or exercise duration achieved is a predictor of future adverse cardiac events. The failure to achieve 5 METs during treadmill exercise is a commonly used marker for increased risk.

Post-MI exercise testing can be performed as early as 4 to 5 days after the infarct. The test provides information on prognosis, the need for further assessment, activity, and exercise prescription, and information for medical management. The test can also provide information for patients who may be at risk for arrhythmias. The information can provide clearance or limitations regarding home or occupational activities. This test is also very useful for guiding the initial stages of a cardiac rehabilitation program. Indications for adverse prognosis from the test include ST depression, functional capacity of <5 METs, or hypotensive response to activity.

In these post-MI studies, the highest mortality rate occurs in the subset of patients who are unable to undergo exercise testing. Patients with chest pain, ST depression, or hemodynamic abnormalities during this low-level exercise testing have a poorer prognosis and are candidates for angiography or, possibly, revascularization.

Protocols used for post-MI patients are best when they are individualized or produced with a ramp-type protocol. The advantages of this approach include avoiding significant increments in workload, providing more accurate estimates of functional capacity, and individualizing the test.

**Case Studies**

**Case 1:** An active 60-year-old woman with no history of cardiovascular disease or other significant illness was evaluated before joining a fitness center. She had no major cardiovascular risk factors, besides her age and postmenopausal status, and no cardiopulmonary symptoms. The patient took her dog on a daily 2-mile walk and experienced no symptoms. She was interested in learning how to improve her fitness level and how to use some of the equipment in the fitness center.

Fitness center staff performed ECG during both treadmill and stationary bicycle exercise, using submaximal protocols, with the patient exercising to predetermined levels of 60% to 70% of her predicted maximum heart rate. Submaximal ECG results revealed no arrhythmias or ST/T wave changes, and the patient remained asymptomatic. The patient tolerated the exercise well, and the staff provided an aerobic exercise prescription using appropriate equipment in the fitness center.

**Case 2:** A 68-year-old man, who lives 110 miles from the nearest major medical center, had an inferior-wall MI. At presentation to his local hospital, he was given intravenous thrombolytic medication as well as other appropriate cardiac medications, and he was transferred to the major medical center on the following day. The patient remained stable throughout the hospital course, with stable hemodynamics and no recurrent chest pain or arrhythmias. Resting echocardiography demonstrated a preserved ejection fraction and an inferior wall MI.
On the fourth hospital day, the patient underwent submaximal exercise ECG, exercising to a predetermined level of 5 METs (heart rate, 123 beats per minute). The ECG results revealed no ST/T wave changes or arrhythmias, and the patient experienced no chest pain. His blood pressure demonstrated appropriate levels throughout the test, increasing to 138/82 mm Hg. He tolerated the exercise well. The patient was referred to outpatient cardiac rehabilitation for a graduated, supervised exercise program and case management for secondary prevention. He also was scheduled for a maximal radionuclear exercise stress test in 6 weeks.

Summary: Submaximal Exercise Testing

Exercise testing and the measurement of functional capacity provide a valuable tool for the diagnosis, treatment, and prognostic assessment in a wide variety of patients. The specific aspects of testing, such as the mode of exercise, protocol, end point, and analysis of respiratory gases, are highly dependent on the population being tested and the parameters being addressed. Despite the many recent advances in cardiac imaging, functional capacity assessment remains an important prognostic variable in the patient with cardiovascular disease. Submaximal testing is not sensitive, specific, or predictive enough to have widespread clinical utility, except in the protocols used for post-MI patients.

Many patients for whom submaximal exercise testing is not a useful option are unable to exercise adequately to perform a maximal test. Therefore, many patients referred for cardiac imaging will require pharmacologic stress to obtain adequate and meaningful test results. The clinical identification of such patients before they fail an attempt at maximal exercise will benefit both patients and imaging laboratories.

Maximal Heart Rate for Myocardial Perfusion Imaging

Maximal exercise performance is necessary to obtain adequate results with myocardial perfusion imaging (MPI). The inability of patients to reach their target heart rates (ie, ≥85% of the predicted maximal heart rate) can decrease the sensitivity of MPI and lead to false-negative results. Injecting a tracer for MPI at a submaximal exercise level can cause problems for both the patient and the medical staff, including need for another dose of tracer and reimaging, usually on a separate day, double radiation exposure for the patient, scheduling disruptions, delay in obtaining diagnostic information, and lost revenue (only 1 of the 2 procedures may be covered by insurance).

Therefore, earlier identification of patients who may not be able to exercise adequately and reach their target heart rates would likely benefit patients and testing laboratories alike, allowing the appropriate use of pharmacologic stress testing.

Hidden Candidates for Pharmacologic Stress Testing

In some cases, it may be obvious that a patient will likely be unable to perform maximal exercise. Patients who are extremely obese, who are elderly, who have failed to exercise adequately during a past test, or who have an exercise-limiting physical condition are obvious candidates for pharmacologic stress. However, many other patients who may be harder to identify are also unlikely to achieve maximal exercise levels or may have other specific reasons why a pharmacologic stress test would be the best choice for assessment of myocardial perfusion.

Early post-MI assessment: Although patients are not referred for exercise stress testing during the early post-MI period, this population warrants discussion here as candidates for pharmacologic stress. MPI with SPECT has been shown to be useful in guiding post-MI treatment. In the ongoing Adenosine Sestamibi SPECT Post-Infarction Evaluation (INSPIRE) trial, patients who were stable after acute MI underwent SPECT MPI with adenosine stress. Those found to be at high risk were randomized to receive either intensive medical therapy or revascularization plus intensive medical therapy. They were then reassessed with SPECT 6 to 12 weeks later, and the majority (79%) had a >9% reduction in total perfusion defect size (p <0.0001). These results show that pharmacologic stress SPECT is an accurate method of early post-MI risk assessment and that intensive medical therapy alone is comparable to medical therapy plus revascularization in reducing ischemia on MPI.

Left bundle-branch block (LBBB): LBBB refers to a condition in which the electrical impulses traveling through the left bundle branch become slowed or blocked. The right ventricle receives the electrical impulse first, causing the left ventricle to contract slightly after the right ventricle. LBBB is a marker for CAD, cardiomyopathy, long-standing hypertension, and severe aortic valve disease.

Patients with LBBB but no CAD often have false-positive results on exercise MPI, demonstrating defects similar to those seen in patients with CAD. The appearance of a reversible septal perfusion defect is commonly seen in patients with LBBB during exercise stress, mimicking septal ischemia. Studies have shown that pharmacologic stress MPI is associated with fewer false-positive results in patients with LBBB and provides important prognostic information in this population.

Serial evaluation in patients with known or suspected CAD: The use of stress MPI to evaluate patients with known or suspected CAD is increasing. A number of studies have shown repeat MPI to be useful for assessing changes in stress-induced ischemia in patients undergoing medical cardiovascular treatment.

Compared with exercise stress, pharmacologic stress MPI may provide a more accurate picture of changes in a
patient’s condition over time. Because the stress level achieved with pharmacologic stressors is relatively consistent at each test, variables in exercise workload and stress effects are reduced or eliminated. Therefore, test conditions are easier to reproduce and provide a more accurate assessment of myocardial perfusion changes. (For more on serial MPI, see the article “Sequential Single-Photon Emission Computed Tomography in Myocardial Perfusion Imaging” by Shaw and Berman in this supplement.)

Women and stress testing: Exercise ECG has been shown to have a lower diagnostic accuracy for CAD in women than in men. The accuracy of exercise ECG in women is highly variable and can be affected by a number of factors, including exercise capacity and hormonal status. Women also generally have smaller coronary vessels than men, and small blood vessels may cause lower sensitivity and specificity of exercise testing.

For women, the occurrence of ST-segment depression (≥1 mm) on ECG does not provide the diagnostic accuracy that it does on ECG for men. In premenopausal women, endogenous estrogen can precipitate ST-segment depression and cause a false-positive test result. A recent study was conducted to determine whether the significance of ST-segment depression during adenosine stress MPI is different between men and women. In a cohort of 959 patients (43% women), ST depression that occurred with adenosine was shown to be an important marker of angiographically significant CAD in both men and women. The presence of ST-segment depression was associated with left main disease and 3-vessel CAD.

Because an exaggerated heart rate response to exertion can occur in deconditioned women, exercise testing should be continued until maximal symptom-limited exercise capacity is reached, rather than stopping when the patient reaches 85% of maximal predicted heart rate. Women unable to perform a minimum of 5 METs of exercise are candidates for pharmacologic stress MPI.

Women also present with CAD approximately 10 years later in life than men, which may contribute to a lower exercise capacity. However, it has been shown that, compared with men, even women of the same age are less likely to be able to achieve an adequate exercise heart rate. Regardless of the reasons, 40% of women who are referred for exercise stress SPECT MPI are candidates for pharmacologic stress.

African American and Hispanic women: Although the recognition and management of heart disease in women need to be improved in general, African American and Hispanic women merit special attention. African American women are at greater risk for heart disease than any other population group in the United States, having a higher prevalence of CAD, angina pectoris, and obesity. CAD is the leading cause of death among African American women, who are twice as likely as their white counterparts to have a cardiac event.

Mexican American women in the United States have the highest prevalence of diabetes mellitus of any other population group. Heart disease and stroke are the leading causes of death among Hispanic women, and >25% of Hispanics in general are in the highest category of elevated cholesterol levels (i.e., ≥240 mg/dL).

African American women have the highest rates of overweight and obesity of any population group in the United States. Among African American women aged ≥40 years, >80% are overweight, and >50% are obese. Hispanic women have been shown to have a higher rate of physical inactivity. Therefore, many women within these populations may be unable to exercise adequately for stress testing and should be considered candidates for pharmacologic stress testing.

Diabetes: Adults with diabetes have a 2- to 4-times higher heart disease death rate than adults with no diabetes, and diabetes is considered a coronary risk equivalent. Combined with the increasing prevalence of diabetes in the United States, this increased rate underscores the importance of cardiovascular assessment and management in this population.

Exercise ECG appears to be less reliable for detecting significant CAD in patients with diabetes compared with their nondiabetic counterparts and is of limited value in this population because of lower exercise capacity, inability to reach target heart rate, and absence of chest pain during exercise. Blood pressure and heart rate responses to exercise are often blunted in patients with diabetes because of an elevated resting heart rate.

The AHA supports the use of exercise or pharmacologic stress MPI as an alternative to treadmill testing in patients with diabetes, and the American Diabetes Association (ADA) has recognized the usefulness of stress MPI in patients with diabetes for the following: (1) evaluation of patients who have inadequate exercise stress test results; (2) risk stratification of asymptomatic patients who have mildly or moderately positive exercise stress test results; (3) evaluation of symptomatic patients who have mild angina and normal or near-normal ECG results; (4) evaluation of symptomatic patients who have atypical angina and baseline ECG abnormalities; and (5) evaluation of symptomatic patients who have atypical chest pain, normal ECGs, and ≥2 cardiac risk factors.

Stress SPECT can provide significant prognostic value in the assessment of patients with diabetes. Because of the exercise and heart rate issues associated with diabetes, significantly more patients with than without diabetes who have CAD symptoms undergo pharmacologic rather than exercise stress testing (Figure 1).

For patients with diabetes, SPECT with adenosine stress has been shown to provide important risk stratification information as well as significant incremental prognostic value over historical and clinical data.
The metabolic syndrome: The metabolic syndrome is an underrecognized condition marked by a cluster of risk factors, including abdominal obesity, atherogenic dyslipidemia, high blood pressure, insulin resistance or glucose intolerance, prothrombotic state (eg, high fibrinogen or plasminogen activator inhibitor–1 blood level), and proinflammatory state (eg, elevated high-sensitivity C-reactive protein blood level).

The presence of 3 of the 5 risk factors in Table 1 are necessary for a diagnosis of metabolic syndrome. Patients with metabolic syndrome are at increased risk for CAD. In the Framingham study, the presence of metabolic syndrome alone predicted approximately 25% of all new-onset cardiovascular disease cases. Of metabolic syndrome patients, 84% are obese, and women with metabolic syndrome have been shown to be less active and to have lower cardiovascular fitness levels than women without metabolic syndrome. Obesity and low fitness levels can hinder an individual’s ability to exercise adequately. Therefore, when patients with metabolic syndrome are referred for stress testing, pharmacologic stress should be considered for those who are unable to perform maximal exercise testing or to achieve maximal exercise heart rates.

Growing elderly population: The elderly population in the United States is increasing rapidly. The number of people aged ≥65 years is projected to at least double over the period from 2000 to 2030, from approximately 35 million to ≥71 million. That number is expected to exceed 86.5 million by 2050.

Given the normal physical limitations that come with aging, as well as activity-limiting conditions such as arthritis and osteoporosis, functional capacity is generally reduced in the elderly. Therefore, many elderly patients are candidates for pharmacologic stress testing, and the use of pharmacologic stress in this population will undoubtedly increase as the elderly population increases.

Exercise Capacity

Exercise capacity has been shown to be an independent predictor of death in both men and in women. In a large cohort of asymptomatic women from the St. James Women Take Heart Project, the risk of death was reduced by 17% with every 1-MET increase in exercise capacity (p < 0.001). Compared with women in the highest exercise capacity category (>8 METs), the risk of death doubled for those in the 5- to 8-MET category and tripled for those in the <5-MET category. The relation between exercise capacity and death had been previously shown in men, but the St. James study showed that exercise capacity is even more predictive in women. Although exercise capacity provides this important prognostic information, it does not necessarily provide diagnostic information, particularly if a patient has limited physical function resulting in a submaximal stress test (as described earlier).

An individual’s functional capacity can be accurately estimated, without the patient having to attempt physical
activity, by using the Duke Activity Status Index (DASI), a self-administered questionnaire (Table 2).54,55

The scores for each “yes” answer are added, and the sum is the patient’s DASI score. The maximum possible score for the full DASI questionnaire is 58.2 (although some researchers have modified the questionnaire for their purposes6,57). Functional capacity is assessed based on the estimated peak oxygen uptake, as determined by the following equation54:

\[
\text{Estimated Peak Oxygen Uptake in mL/min} = (0.43 \times \text{DASI score}) + 9.6
\]

Given its accuracy in the assessment of functional capacity, the DASI may be a reliable method of identifying patients who will likely be unable to exercise adequately for stress testing. Implementing the DASI questionnaire before referring patients for stress tests may reduce the number of inadequate or aborted tests, which can place undesirable burdens on both patients and testing facilities.

Summary: Hidden candidates for pharmacologic stress testing: Although the need for pharmacologic rather than exercise stress testing is relatively obvious for some patients, the ability of many patients to exercise adequately for stress testing is unclear. Results of submaximal exercise tests are often nondiagnostic and ambiguous, and aborted stress-imaging tests can be a burden for testing facilities and patients. Facilities lose schedule time, and patients are often forced to return on another day or receive another dose of a radiotracer.

Pre-referral identification of patients who may not be, or who definitely are not, able to exercise adequately for stress testing would benefit both patients and testing facilities and would provide more timely diagnostic and prognostic information. Physician education on various patient types who may require pharmacologic stress testing and more widespread use of the DASI questionnaire would greatly improve the early recognition of such patients and increase the efficiency and benefit of cardiac testing.

Case Studies

Case 1: A 54-year-old overweight African American woman was referred for cardiac risk assessment after describing dyspnea when climbing the stairs in her building. She had a history of type 2 diabetes and hypertension, as well as a 30-pack-year smoking history. She was sedentary, and based on her DASI score, her exercise capacity was 4.5 METs.

The patient underwent adenosine stress SPECT imaging. She tolerated the adenosine but demonstrated ST-segment depression during the infusion. Her myocardial perfusion scan was remarkable for transient ischemic dilatation with stress, showing a large, reversible defect involving the anterior wall, septum, and apex. Angiography was performed, revealing a 70% distal left main lesion as well as 70% proximal left anterior descending artery, 50% mid-circumflex, and 70% proximal right coronary artery lesions.

A 3-vessel coronary artery bypass graft was performed. The patient recovered uneventfully and was discharged with a regimen of appropriate cardiovascular medications. She completed a phase-2 cardiac rehabilitation program. Since her procedure, she has lost 10 lb (4.5 kg), has quit smoking, and has begun a regular exercise program. She remains asymptomatic.

Case 2: A 52-year-old African American man was referred for exercise stress SPECT imaging after a new LBBB was noted when ECG results were compared with ECG results from 15 years earlier. The patient had hypertension as well as a family history of hypertension. He had no other cardiac risk factors and was quite physically active.

For his SPECT test, the patient exercised for 10 minutes and 18 seconds, but stopped because of leg pain. He had no ST-segment changes on his ECG, but his myocardial perfusion images revealed a reversible septal defect. The reading cardiologist noted the LBBB on the ECG and recommended that the patient undergo adenosine stress SPECT.

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Table 2
The Duke Activity Status Index (DASI) Questionnaire

<table>
<thead>
<tr>
<th>Item</th>
<th>Activity</th>
<th>Scoring</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Can you take care of yourself (eating, dressing, bathing, or using the toilet)?</td>
<td></td>
<td>2.75</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Can you walk indoors, such as around your house?</td>
<td></td>
<td>1.75</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Can you walk 1 or 2 blocks on level ground?</td>
<td></td>
<td>2.75</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Can you climb a flight of stairs or walk up a hill?</td>
<td></td>
<td>5.50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Can you run a short distance?</td>
<td></td>
<td>8.00</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Can you do light work around the house, like dusting or washing dishes?</td>
<td></td>
<td>2.70</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Can you do moderate work around the house, like vacuuming, sweeping floors, or carrying in groceries?</td>
<td></td>
<td>3.50</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Can you do heavy work around the house, like scrubbing floors or lifting and moving heavy furniture?</td>
<td></td>
<td>8.00</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Can you do yard work, like raking leaves, weeding, or pushing a power mower?</td>
<td></td>
<td>4.50</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Can you have sexual relations?</td>
<td></td>
<td>5.25</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Can you participate in moderate recreational activities, like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?</td>
<td></td>
<td>6.00</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Can you participate in strenuous sports, like swimming, singles tennis, football, basketball, or skiing?</td>
<td></td>
<td>7.50</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Am J Cardiol.45
The patient returned 1 week later for his pharmacologic stress test.

The myocardial perfusion images from the adenosine stress test showed no perfusion defect in the septal area. The patient’s blood pressure was controlled with medications, and no further cardiac testing was performed. This case reinforces the use of adenosine stress SPECT as the first-line choice in patients with known LBBB. Interpretation of the original myocardial perfusion scan could have resulted in needless (and risky) further studies, such as angiography.

Also, repeat testing after an inconclusive exercise test is time-consuming and is not cost-effective and it can result in a delay in diagnosis.

29. Cerqueira MD. Diagnostic testing strategies for CAD: special issues related to gender. Am J Cardiol 1995;75:52D–60D.
Role of Electron-Beam Computed Tomography and Nuclear Stress Testing in Cardiovascular Risk Assessment

Paolo Raggi, MD

Although it is well recognized that stenotic coronary artery lesions carry a significant risk for cardiac events, the importance of nonstenotic lesions is generally underappreciated. However, many acute myocardial infarctions are caused by lesions that cause <50% stenosis. Coronary artery calcification is being increasingly studied as a marker of risk for cardiac events. Measurement of coronary artery calcium using electron-beam computed tomography is emerging as a useful tool to further risk-stratify patients who are otherwise at intermediate risk for events. Coronary calcium scores have been shown to add independent predictive value to traditional risk assessment. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:20J–27J)

Although healthcare professionals recognize the importance of treating patients at high risk for cardiovascular events, they often do not appreciate the importance of further evaluating patients at intermediate risk. As would generally be expected, the intermediate-risk population accounts for the majority of patients seen in general and specialty practices and constitutes approximately 40% of all asymptomatic patients.1 Approximately 50% of men and 64% of women who experience sudden cardiac death or nonfatal myocardial infarction (MI) are asymptomatic before such events.2 Therefore, to have an effective impact on the cardiovascular disease epidemic, intermediate-risk patients—who experience the bulk of cardiovascular events—should become the focus of much more intensive preventive efforts than those used currently.

Importance of Nonstenotic Lesions

Physicians are well aware of the importance of treating patients with stenotic coronary artery lesions. However, a large number of coronary events in asymptomatic subjects occur with nonobstructive disease. Both pathologic and clinical studies have shown that the majority of acute MIs are triggered by lesions that cause <50% stenosis of the vessel lumen (Figure 1).3–5

The progression of coronary artery plaque is a slow and insidious process (Figure 2). Although advanced and obstructive disease obviously pose a high risk for cardiovascular events, nonstenotic lesions can also be dangerous because the eruption of the inflamed and lipid-rich pool could cause a sudden luminal thrombosis. Therefore, it is hoped that implementing lifestyle modifications and starting medical treatment during the early phases of plaque development might help to reduce plaque progression and risk.

Coronary Artery Calcium

One additional method available to the clinician to help determine the extent of a patient’s risk is the use of atherosclerotic imaging modalities, such as computed tomography (CT) imaging for coronary artery calcification. This marker, detectable both with electron-beam computed tomography (EBCT) and multidetector CT, has been shown to be a useful tool to help further stratify intermediate-risk patients. CT scanners can detect coronary artery calcium (CAC) early in the atherosclerotic process, when the atherosclerotic burden is not yet obstructive. Calcium continues to accumulate as the atherosclerotic plaque expands (see Figure 2). Therefore, the CAC can demonstrate that plaque development is underway and, combined with other risk factor information, help to determine the course of clinical management.

The correlation of EBCT-determined CAC and actual plaque area has been validated in several autopsy studies, one of which is summarized in Figure 3.6

What factors contribute to CAC? Many risk factors known to contribute to atherosclerosis development are associated with the presence of CAC. However, traditional risk factors justify only a portion of the variance in CAC, indicating that atherosclerosis develops from mechanisms beyond those currently known.

Genetic factors may indeed play a significant role in plaque development. Valdes and colleagues7 assessed the association of CAC and traditional risk factors, including diabetes mellitus, hyperlipidemia, cigarette smoking, and poorly controlled hypertension, in healthy, asymptomatic
subjects with proven family histories of premature coronary artery disease (CAD). In that study, age and triglyceride levels were the only traditional risk factors associated with CAC in men, and accounted for only 30% of the observed variation. In women, age, body mass index, and triglycerides were the only traditional risk factors significantly associated with CAC and accounted for only 22.2% of the observed variation. Contrary to what might be expected, lifestyle risk factors, such as obesity and cigarette smoking, were not associated with CAC in this study cohort. Therefore, genetic risk factors appear to account for a large portion of the variation in atherosclerosis development.

A recent study assessed the prevalence and extent of CAC in Portugal, Brazil, and the United States (R. D. Santos, personal communication, 2005). The United States was found to have the highest prevalence of CAC across all age groups, even after adjusting for risk factors such as dyslipidemia. Portugal had the lowest prevalence of CAC.
Additionally, the United States had the highest rate of CAD mortality, and coronary calcium scores (CCS) appeared to correlate with the respective CAD mortality rates in all 3 countries (R. D. Santos, personal communication, 2005) (Figure 4).

Interestingly, although the Portuguese study population had the lowest prevalence of CAC and CAD mortality, the prevalence of several risk factors was higher than in the other 2 countries (R. D. Santos, personal communication, 2005). These data appear to confirm that atherosclerosis has a major genetic component and that a higher CCS is associated with greater cardiovascular event rates.

**Prognostic utility of the CCS:** In a study of traditional risk factors and CCS, a prospective cohort (n = 632) was screened with EBCT and followed for a mean of 32 months. Patients were divided into quartiles based on the presence of risk factors and CCS percentiles (adjusted for age and sex). The annualized rates for hard events (ie, MI or CAD death) are shown in Table 1.

Stratification by both risk factors and CCS correlated with coronary events. However, the risk ratio in the highest risk factor quartile was 6.5-fold higher than that in the lowest quartile (13/2 = 6.5), while the risk ratio in the highest CCS quartile was 19-fold higher than that in the lowest quartile (19/1 = 19). Additionally, the odds ratios for events in the upper 2 CCS quartiles were substantially greater than those in the upper 2 risk factor quartiles (6.2 and 21.5 vs 3.1 and 7.0, respectively). This suggests that, although traditional risk factors are valuable predictors, use of CCS percentiles may be a better method of identifying patients at risk for coronary events.

A more recent study showed the incremental value of CCS percentiles over traditional risk factors for prediction of MI and CAD death in 671 asymptomatic subjects. CCS percentiles alone showed significantly better predictive value than traditional risk factors plus age (p = 0.028). When CCS percentile, traditional risk factors, and age were added together, the combination of all 3 was significantly more predictive than age plus traditional risk factors or age alone (receiver operating characteristic curve, 0.84 vs 0.71; p <0.001) (Figure 5).

A large observational study used risk-adjusted multivariable models for the prediction of all-cause mortality in 10,357 asymptomatic patients screened with EBCT. Risk factors and CCS were determined in this large cohort of patients, who were followed for an average of 5 years. CCS was determined to provide independent and incremental predictive value over traditional risk factors (Figure 6).

Comparing the life statistics for the US population and the death rate recorded in this study in relation to the presence of CAC, it was determined that having a CCS >400 adds 15 to 28 years, statistically, to a patient’s age. A CCS of ≤10 is associated with a lower patient age by 8 to 10 years. Therefore, a low CCS “adds” years of life, whereas a high CCS “shortens” life by a considerable number of years.

---

**Table 1**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>CCS Percentile</th>
<th>Event Rate</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>1 (0.2%)</td>
<td>6 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>6 (1.4%)</td>
<td>6 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>19 (4.5%)</td>
<td>13 (3.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from *Circulation.*

---

Figure 4. Coronary artery disease (CAD) mortality rates and coronary calcium score (CCS) in Portugal, Brazil, and the United States. (R. D. Santos, personal communication, 2005.)
The added value of using the CCS along with the Framingham risk score was shown in a study of 1,029 asymptomatic adults with \( \geq 1 \) coronary risk factor who were followed for a median of 7 years.\(^\text{12}\) A high CCS was found to modify the risk predicted by the Framingham score, especially in intermediate-risk patients (Figure 7).\(^\text{12}\)

CCS adds incremental value to risk assessment in both women and men.\(^\text{13}\) Figure 8 shows the 5-year predicted mortality for women and men in low-, intermediate-, and high-risk Framingham score groups as enhanced by CCS inclusion. CCS did not add much predictive value for patients in the low-risk category, but added significant predictive value for intermediate- and high-risk patients. Although CCS added prognostic value for both sexes, women appeared to derive an even greater benefit than men from an assessment of atherosclerosis burden, likely because of the weaker applicability of Framingham risk categories in women than in men.\(^\text{13}\)

CAC has also been used in combination with other markers of risk, such as C-reactive protein, and this has been shown to be a useful method for further risk stratification in intermediate-risk patients.\(^\text{14}\) In a study by Park and colleagues,\(^\text{14}\) the risk factor–adjusted relative risk for CAC and C-reactive protein for the occurrence of hard events (non-fatal MI or coronary death) or any cardiovascular event (MI,
coronary death, revascularization, or stroke) was assessed using data from 967 participants without diabetes who were followed for an average of 76.8 months. CAC was found to be a significant predictor of both hard events and any cardiovascular event ($p < 0.005$), and C-reactive protein was found to be a significant predictor of any cardiovascular event ($p = 0.03$) and a nonsignificant predictor of hard events ($p = 0.09$). The combination of high CCS and high C-reactive protein levels posed an approximate 6-fold increase in the risk of MI and coronary death and a 7-fold increase in the risk of stroke.
increase in the risk of any cardiovascular event between the lowest and highest risk groups.\textsuperscript{14}

**CCS in patients with diabetes:** CCS may have some utility in patients with high baseline risk, specifically patients with diabetes.\textsuperscript{15} A study of 10,377 patients followed for all-cause mortality for an average of 5 years found a significantly higher average CCS in patients with diabetes \((281 \pm 567)\) than in nondiabetic patients \((119 \pm 341)\) \((p <0.0001)\). A risk factor–adjusted model showed a significant interaction of CCS with diabetes \((p <0.00001)\), indicating a greater increase in mortality for patients with diabetes versus patients without diabetes for every increase in CCS.\textsuperscript{15} Survival by CCS is shown in Figure 9.\textsuperscript{15} Although the overall mortality rate was significantly higher among patients with \((3.5\%)\) than without \((2.0\%)\) diabetes, patients with diabetes who had very low levels of CAC or no visible CAC on EBCT had a very low risk of death \((0.8\%\) at 5 years). These findings reinforce the notion that the absence of CAC (ie, atherosclerosis) portends a good prognosis, even in high-risk populations.\textsuperscript{15}

Such additional prognostic data may be especially important in patients with diabetes. Patients with diabetes who have normal stress echocardiography and stress single-photon emission computed tomography (SPECT) have been shown to experience high event rates compared with their nondiabetic counterparts.\textsuperscript{16,17} Therefore, normal stress test results may not provide sufficient prognostic information in these patients and may give them false reassurance. Adding measures of atherosclerotic burden, such as the CCS, may help to more accurately risk-stratify these patients.

**CCS and myocardial perfusion:** The CCS has shown utility in identifying asymptomatic subjects who may have silent myocardial ischemia. In an early study, 411 subjects underwent EBCT and stress SPECT imaging where indicated. Overall, >40% of the patients with a CCS >400 had identifiable myocardial ischemia on SPECT imaging.\textsuperscript{18}

Similarly, Berman et al\textsuperscript{19} recently published results supporting these findings, showing a correlation between increasing CCS and ischemic changes on SPECT myocardial perfusion imaging with increasing frequency as the score rose above 400. The frequency of abnormal SPECT results was <2% in patients with a CCS <100 and increased progressively with a CCS \(\geq 100\) \((p <0.0001)\). Notably, 56% of patients who had normal SPECT results had a CCS \(\geq 100\), suggesting that EBCT is an appropriate method to detect significant atherosclerosis in patients who have normal myocardial perfusion imaging results.\textsuperscript{19}

Figure 10 shows a suggested risk-assessment algorithm that demonstrates how EBCT and stress SPECT can be used effectively in combination to refine risk assessment in intermediate-risk patients.\textsuperscript{20}

**Statin Therapy and Coronary Artery Calcium**

Statin therapy may play an important role in slowing CAC progression.\textsuperscript{21} A total of 66 patients (mean age, 61 years) with a low-density lipoprotein (LDL) cholesterol >130 mg/dL underwent sequential EBCT to ascertain CAC progression over time. An EBCT was obtained at baseline and after a mean interval of 14 months without therapy. Ceriv-
Astatin therapy 0.3 mg/day was then initiated. After 12 months of treatment, a third EBCT was performed. Cerivastatin therapy lowered the mean LDL cholesterol level from 164 to 107 mg/dL and the mean total cholesterol level from 244 to 188 mg/dL. CAC progression was also slowed significantly during the treatment period (between the second and third EBCT) compared with the untreated period (between the first and second EBCT) (Figure 11).21 A yearly CCS increase of ≥15% was an independent predictor of time to MI (p < 0.001) (Figure 12).24 The results of this study suggest that continued progression of CAC indicates the failure of some patients to benefit from statin therapy as well as an increased risk for MI.

Case Studies

Case 1: The patient was a 55-year-old man with a total cholesterol level of 224 mg/dL and a systolic blood pressure of 130 mm Hg. He was a smoker and had a family history of premature CAD. Based on these factors, his 10-year Framingham risk of CAD mortality or a nonfatal coronary event was determined to be 16% (ie, intermediate risk). His cardiologist decided to perform an EBCT to assess for the presence of CAC. The EBCT showed a lack of CAC. With this new information added to his risk assessment, the patient’s new risk for obstructive CAD was reassessed to be approximately 5%. Therefore, CAC measurement was useful in refining this patient’s risk stratification and obtaining a more accurate prognosis.

Case 2: The patient was a 53-year-old man with diabetes, who was obese and had a total cholesterol level of 240 mg/dL. He reported atypical chest discomfort. His primary care physician ordered an EBCT, and the patient’s CCS was reported to be 458. The cardiologist decided to perform stress echocardiography for further assessment. Because the patient disclosed that he had “bad knees,” pharmacologic stress with dobutamine was used instead of exercise. The patient’s stress echocardiogram was normal, excluding with good probability the presence of obstructive CAD. The fact that his scan was normal does not, however, negate his substantial cardiovascular risk based on the high CCS. In fact, it has been shown that CCS can add prognostic information in patients with a normal or equivocal stress test result. In 1 study, 323 symptomatic patients referred for coronary angiography underwent exercise stress electrocardiography and EBCT on the day before angiography. EBCT added valuable risk-stratification information, and the use of the stress test and EBCT combined correctly classified 15% more patients than stress testing alone. Also, 90% of patients with 3-vessel or left main CAD were correctly identified with both tests combined, compared with only 64% with stress testing alone. The authors concluded that EBCT is a useful tool to further risk-stratify patients categorized as intermediate risk after exercise stress testing.
Conclusion

Further stratification of patients categorized as being at intermediate risk for coronary events is necessary to manage these patients appropriately. The importance of stenotic lesions is well recognized, but many intermediate-risk patients have nonstenotic lesions that also represent a serious coronary risk. Progression of atherosclerosis, even in patients whose LDL cholesterol has been successfully lowered with statin therapy, predicts a poor prognosis. Identification and early treatment of nonstenotic lesions may help prevent atherosclerosis progression and coronary events and improve patient outcomes.

Measurement of CAC appears to be an effective complementary strategy to quantify the atherosclerotic burden of patients with intermediate risk, which results in more accurate risk stratification and improved management of these patients. As research continues to show the utility of CAC and other atherosclerosis-imaging modalities, broader use of EBCT will likely be instituted in asymptomatic intermediate-risk patients.

Sequential Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

Leslee J. Shaw, PhD,* and Daniel S. Berman, MD

The utility of stress myocardial perfusion imaging (MPI) for the diagnosis and prognosis of coronary artery disease (CAD) has been firmly established in numerous clinical studies and has become an essential component of clinical practice. Stress MPI is now used regularly to guide initial risk stratification and management of patients with CAD. Because stress MPI provides an assessment of the physiologic significance of CAD, it is a particularly attractive procedure for assessing follow-up risk. Today, sequential stress MPI is being used increasingly to track disease progression, assess follow-up risk, detect restenosis following revascularization, and evaluate the efficacy of aggressive medical therapy and risk-factor modification. By providing serial snapshots of the disease and its impact on perfusion, sequential stress MPI may alter treatment decisions and ultimately improve long-term patient management and outcomes. Use of sequential stress MPI to detect changes in perfusion following surgical or medical therapies is being tested currently in the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) and Adenosine Sestamibi Single-Photon Emission Computed Tomography Postinfarction Evaluation (INSPIRE) trials. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:28J–39J)

Stress myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is increasingly used to evaluate the effectiveness of secondary prevention strategies by revealing a patient’s ischemic burden or progressive coronary artery disease (CAD) states while on any of an array of anti-ischemic therapeutic and risk factor–modification regimens.1–11 Over the last few decades, it has been established that stress MPI can provide important diagnostic and prognostic information and help guide both initial and follow-up risk-stratification assessments for patients with established CAD.12,13 The focus of this article is sequential monitoring using stress MPI in patients with established CAD. Those patients who have no prior diagnosis of CAD but who have notable stress-induced ischemia will generally proceed to coronary angiography for determination of the extent and severity of obstructive CAD, and a decision will be made whether they should undergo coronary revascularization.

At the heart of cardiovascular practice, coronary angiography forms the basis for interventional therapies, and the decision to undergo this procedure is increasingly made with consideration of the benefits and costs associated with its use. Coronary angiography is costly and invasive, which precludes its routine and frequent application, especially for patients with nonanginal or atypical postintervention chest pain symptoms. Furthermore, with the surging interest in aggressive anti-ischemic therapy and risk factor modification, the assessment of medical effectiveness has become a crucial part of secondary prevention strategies.

One benefit of using a noninvasive imaging approach such as stress MPI is that, combined with the angiographic data, noninvasive imaging provides an assessment of the physiologic significance of a coronary artery stenosis.14 Stress MPI is well suited to provide supplementary information in the assessment of patients after intervention because of its ability to define the extent and severity of reductions in regional blood flow and to provide correlative risk-stratification evidence.14 –17 It is this ability to define changes in perfusion that is appealing and provides the basis for sequential monitoring with stress MPI. Specifically, sequential stress MPI is increasingly being used to track disease progression, perform serial risk assessment, and evaluate the effectiveness of anti-ischemic or risk factor–modifying therapy—all of which can lead to improved long-term management strategies and the potential for improved patient outcomes.

Disease Management with Stress Myocardial Perfusion Imaging

A wealth of diagnostic accuracy and risk-stratification evidence forms the basis for reliance on stress MPI as an objective, validated clinical management tool.12,18–20 In a recent meta-analysis of findings in 69,655 patients, the an-
nal rate of cardiac death or nonfatal myocardial infarction (MI) was 0.85% (25th to 75th percentile, 0.6% to 1.2%) for low-risk (ie, normal or mildly abnormal) stress MPI scans and increased to 5.9% (25th to 75th percentile, 4.6% to 8.5%) for moderately to severely abnormal stress MPI scans.\(^{12}\) Event rates increase linearly within the range of MPI results from low to high risk such that we can readily identify the expected event rate by a given stress MPI result and decide the intensity of aggressive management on the basis of the stress MPI results. Furthermore, overall risk stratification has been developed and is highly generalizable to a variety of patient subsets, including women. From a recent meta-analysis, the relative risk for a moderately to severely abnormal stress MPI scan was elevated 9-fold in 13,039 women.\(^{21}\) Therefore, stress MPI is particularly useful in estimating a patient’s risk of hard cardiac events, including nonfatal MI or cardiovascular death.

Sequential assessment of the extent of ischemia with stress MPI can provide insight into the vasodilative effects of anti-ischemic therapies and is an effective method of tracking alterations in regional blood flow after revascularization.\(^{10}\) Additionally, more recent evidence extends the utility of sequential stress MPI to risk factor-modifying therapies that improve endothelial function. There is substantial evidence that restoration of endothelial function can be achieved with the lipid-lowering 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as well as with the insulin-sensitizing drug metformin. Furthermore, it is speculated that the marked reduction in clinical coronary events (ie, 35% risk reduction) is secondary to functional changes, as opposed to anatomic changes, within diseased arteries.\(^{22}\)

Both exercise and pharmacologic stress MPI have established high sensitivity and specificity for the diagnosis of CAD (Figure 1).\(^{18}\) When applying this diagnostic accuracy data, stress perfusion defect size (PDS) and extent strongly correlate with the presence and extent of a high-grade coronary stenosis and, importantly in the assessment of medical therapy, document large epicardial flow of the coronary bed.\(^{17,23}\) To the extent that coronary vasodilation is affected by the chronic inflammatory process of atherosclerosis, coronary disease progression and response to therapies can be monitored with stress MPI.\(^{14}\) A growing body of evidence supports the use of nuclear imaging to assess and document the effectiveness of medical management.\(^{3,8,24–26}\)

A continuing wealth of prognostic evidence, which is also highlighted in this article, extends this diagnostic evidence. Specifically, we use examples from the prognostic literature to illustrate the application of risk-stratification data as it relates to sequential stress MPI strategies.\(^{17,27}\) First, in a large observational series of patients with stable chest pain symptoms, the incremental risk of death or MI was reported to be a function of ischemic extent on MPI (Table 1).\(^{27}\) Table 1 shows the 3-year MI-free survival of patients with known CAD who would typically be referred for either medical management or percutaneous coronary intervention (PCI); it excludes patients with 3-vessel or left main CAD, since they would be referred for coronary bypass surgery. The extent of inducible ischemia, defined as the number of vascular territories with stress perfusion abnormalities, was proportionally related to MI-free survival. MI-free survival worsened from 98% to 95%, 92%, and 89% for patients with no ischemia to 1-, 2-, and 3-vessel ischemia, respectively (p <0.0001).

In a related observational study (N = 5,183), the extent and severity of stress MPI abnormalities were highly effective at stratifying patients’ risk for cardiac death or MI (Table 2).\(^{17}\) Scans were also able to identify patients at low risk for cardiac death but at intermediate risk for nonfatal MI. This study demonstrates that patients with mildly abnormal stress test scans may benefit from a noninvasive approach (ie, aggressive medical management) without the need for invasive procedures (Table 2).\(^{17}\)

For sequential monitoring, Table 2 shows the expected improvement in outcome with medical treatment within a range, from minimal (ie, approximately 5%) to as much as a 50% reduction in cardiac event rates. Table 2 also reports the expected change in event rates in patients who experience mild or more marked improvement between their first and second scans, ie, the change in expected outcome given the improvement on their posttreatment stress MPI scans. Patients with moderate to severe perfusion abnormalities may have more dramatic improvements in outcome. Approximately 3 of 7 patients with marked improvement can be expected to be event free because of intercurrent treatment that results in improved stress MPI results. In some cases, the scans of these patients normalize, as reported in the Angioplasty Compared to Medicine (ACME) study by Parisi and colleagues.\(^{7}\) Resolution of a patient’s MPI to a low-risk scan results in a dramatic improvement in event-free survival.\(^{7}\)

### Sequential Stress Myocardial Perfusion Imaging for Evaluation of Treatment Effectiveness

A number of studies have examined the utility of sequential stress MPI for assessing changes in stress-induced ischemia in patients receiving intercurrent nitrates, calcium antagonists, statins, or \(\beta\)-adrenergic receptor blocker (\(\beta\)-blocker) therapy, alone or in combination.\(^{1,2,4,6,8,9,11}\) In 25 patients with CAD and dyslipidemia, the anti-ischemic effect of 6 months of pravastatin therapy was assessed with sequential stress MPI.\(^{9}\) Improved stress myocardial perfusion was demonstrated in nearly 50% of the patients after 6 months of treatment. Importantly, from this series, improvements in serum lipid profiles were a predecessor for later improvements in the mean summed stress score. Specifically, serum lipid profiles exhibited improvement following 6 weeks of statin therapy, whereas no such improvement was reported.
in the mean summed stress score from baseline. However, at 6 months, significant improvement in the summed stress score was reported (p < 0.01) (Figure 2).9 Sequential stress MPI monitoring may distinguish additional prognostic benefits of statin therapy that are explained only in part by reductions in serum lipid levels.

A number of reports have noted that cholesterol-lowering treatment in patients with hypercholesterolemia is associated with restoration of endothelial function and can result in improvements in myocardial perfusion reserve on positron emission tomography.28,29 In 17 hypercholesterolemic men who were treated with fluvastatin for 12 weeks, thallous chloride (thallium)–201 (201Tl) stress MPI demonstrated a 30% increase in myocardial perfusion in ischemic segments and significantly less improvement (5%) in normal segments (p < 0.005).30 Thus, it appears that impaired reactive hyperemia plays a central role in increasing a patient’s risk for major adverse cardiac outcomes and should figure prominently in targeting medical therapy.14 A recent meta-analysis by Bairey Merz and colleagues31 reported that evidence of peripheral or coronary endothelial dysfunction is associated with a nearly 10-fold (95% confidence interval [CI], 7.8 to 12.8) increased risk of major adverse cardiac events.

These results are particularly relevant for female populations that have a reduced frequency of obstructive CAD
but may exhibit impaired vascular function that is identifiable with nuclear imaging. This ability to demonstrate impaired vascular function may be the reason for the superior prognostic accuracy of SPECT imaging in women.12,21,32 As stated, changes in coronary flow reserve may be affected not only by fixed stenoses but also by intrinsic wall elasticity, endothelial integrity, and arterial wall responsiveness to vasodilators. Therefore, a worsening of PDS or severity may identify candidates for additional serum lipid–lowering therapy.14

Similarly, several reports note changes in MPI after nitrate treatment. Lewin and Berman3 demonstrated improvement in ischemia in patients taking once-daily extended-release isosorbide mononitrate 120 mg for 30 to 35 days. Repeated stress MPI with a resting thallium and exercise technetium-99m (99mTc) sulfur colloid hexakis 2-methoxyisobutyl isonitrile (sestamibi) MPI protocol demonstrated a 13% reduction from baseline in extent and a 14% decrease in severity of the total perfusion defect.3 Significant improvement in myocardial perfusion after transdermal nitroglycerin patch therapy has also been demonstrated, using quantitative thallium stress MPI.2 The average reduction in total PDS was 8.9%, with an average reduction of 11.4% in patients with the largest (≥20%) baseline defects.

Several studies have also demonstrated the effects of acute administration of anti-ischemic medications during active stress MPI.33–35 One study demonstrated a significant reduction in the likelihood of an abnormal scan in patients taking ≥1 anti-ischemic drug during pharmacologic stress MPI with dobutamine.33 In a related study by Shehata and colleagues,35 the acute effects of propranolol on perfusion defects with dobutamine stress MPI were assessed. In this report, stress MPI was performed on separate days, with and without pretest administration of intravenous propranolol. The results showed that both total and ischemic MPI defect sizes were reduced by 22% and 32%, respectively, after administration of propranolol.35 Sharir and associates34 performed dipyridamole stress MPI in 21 patients with CAD before and after the administration of combination therapy with calcium antagonists, nitrates, or β-blockers and demonstrated a 24% to 33% reduction in PDS after anti-ischemic treatment.

Important to this discussion is whether or not the normalization or improvement in myocardial perfusion is associated with improved cardiac survival. To assess this, Dakik and colleagues8 used adenosine stress MPI to compare the efficacy of medical therapy versus percutaneous transluminal coronary angioplasty for reducing postinfarc-

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**Table 1**

<table>
<thead>
<tr>
<th>Extent of Ischemia</th>
<th>MI-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>98</td>
</tr>
<tr>
<td>1 Vessel</td>
<td>95</td>
</tr>
<tr>
<td>2 Vessels</td>
<td>92</td>
</tr>
<tr>
<td>3 Vessels</td>
<td>89</td>
</tr>
</tbody>
</table>

MI = myocardial infarction.

* Analysis includes a Cox multivariable risk-adjusted model of catheterized patients with 1- or 2- vessel CAD.

Adapted from *Am J Cardiol.*27

**Table 2**

Expected change in rates of cardiac death or myocardial infarction (MI) associated with change in single-photon emission computed tomography (SPECT) scans

<table>
<thead>
<tr>
<th>Scan Results</th>
<th>Expected Rate of Cardiac Death or MI (%)17</th>
<th>Expected Improvement with Medical Treatment (%)</th>
<th>Expected Event Rate by Degree of Improvement27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.8</td>
<td>None–minimal</td>
<td>Mild Improvement (%)</td>
</tr>
<tr>
<td>Mildly abnormal</td>
<td>3.5</td>
<td>−25%–35% of patients will experience some improvement</td>
<td>Moderate to Marked Improvement (%)</td>
</tr>
<tr>
<td>Moderately abnormal</td>
<td>5.2</td>
<td>−50%–60% of patients will experience moderate improvement</td>
<td></td>
</tr>
<tr>
<td>Severely abnormal</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reprinted with permission from *Circulation*17; Expected rates of death or MI from *Am J Cardiol.*27 Rates are based on data from Cedars-Sinai Registry.
tion ischemia in 44 patients who had large total (≥20%) and ischemic (≥10%) left ventricular PDS at baseline. On repeated stress MPI, approximately 1 month after therapy was optimized, both medical therapy and angioplasty reduced total PDS similarly—by 12% and 15%, respectively. Ischemic PDS was reduced by 12% in both groups. Patients who experienced ≥9% reduction in PDS had significantly better event-free survival (96%) than those who did not (65%, p = 0.009). An earlier report of data from the ACME study, which used exercise thallium MPI, revealed that patients with 1- or 2-vessel disease who had a perfusion defect 6 months after either angioplasty or initiation of medical therapy had a significantly higher mortality rate (18%) than those who did not (8%; p = 0.02). It is important to note that in comparison, electrocardiography (ECG) was unable to differentiate low- and high-risk patient subsets.

Stress Myocardial Perfusion Imaging After Revascularization

A particular advantage to the use of stress MPI after revascularization is its capacity to locate and track changes in the extent and severity of perfusion abnormalities. For patients with atypical chest pain symptoms but a marked improvement in luminal flow or change in percentage of stenosis, routine coronary imaging after revascularization is not recommended. For patients with early postrevascularization angina, reangiography is generally supported by a concern over in-stent restenosis. However, in patients with recurrent symptoms (excluding unstable angina), coronary imaging has been shown to be useful in identifying the need for repeat coronary angiography. In patients who have had incomplete revascularization, routine imaging may be used to determine the extent to which remodeling or restenosis has occurred.

Stress MPI has been shown to be accurate in identifying the presence of restenosis, regardless of whether complete revascularization was achieved. One study reported the sensitivity, specificity, and accuracy for detecting restenosis by SPECT to be 96%, 75%, and 88%, respectively, in asymptomatic patients and 91%, 77%, and 85%, respectively, in symptomatic patients. The sensitivity and accuracy of exercise ECG were significantly lower: 40% and 44%, respectively, for silent ischemia; and 59% and 64%, respectively, for symptomatic ischemia (p <0.001). According to current reports in the medical literature, the overall mean sensitivity and specificity rates for SPECT detection of restenosis are 89% (range, 76% to 94%) and 75% (range, 46% to 84%), respectively.

Concerns over early imaging after PCI are based on a reportedly high rate of false positives (ie, ischemia but no underlying angiographic restenosis). False-positive results have been found to be more likely to occur when imaging is performed earlier rather than later after PCI. A meta-analysis showed a high positive and negative predictive value for restenosis when imaging was delayed 2 to 4 weeks after a procedure. This analysis demonstrated a steady decline in false-positive scans as follow-up time after the procedure increased, and the authors proposed that false-positive scans after...
PCI may be less common today because of improved resolution with technetium agents and improved restoration of blood flow with newer interventional techniques. Although recent experience suggests that false-positive rates after PCI are much lower than previously reported, it is still recommended that the use of nuclear imaging in such cases be symptom-driven and that early testing be discouraged.

A recent comprehensive review by Giedd and Bergmann indicated that, currently, PCI is more often performed in patients who are at higher risk with more complex lesions, making a reassessment of the degree of residual ischemia increasingly important. In this setting, stress MPI is applied as a gatekeeper for repeat coronary angiography and is used to correlate new or refractory symptoms with evidence of provocative ischemia in patients with stable symptoms (eg, Canadian Cardiovascular Society Class [CCSC] I–II). On the basis of the available evidence, post-PCI stress MPI can identify patients who are at high risk for a worsening prognosis. A number of reports have described application of the concept of sequential stress MPI to assess changes in the extent and severity of residual ischemia, both over time and after intercurrent surgical intervention.

Several available prognostic reports are noteworthy. In a recent report by Zhang and colleagues, the prognostic value of exercise 99mTc MPI was evaluated in 318 patients after PCI. Using a semiquantitative 20-segment scoring system, the annual rate of cardiac death or nonfatal MI was 4% for patients with ischemia compared with 0.2% for those with a low-risk stress MPI study (p <0.01). When evaluated in a multivariable Cox model, the summed stress score was the single greatest predictor of cardiac death or MI. Similarly, the differential prognostic significance of silent versus symptomatic ischemia was evaluated in a series of 356 patients who had undergone successful coronary stenting. This study revealed that the cardiac event rate was highest (69%) for patients with moderate to severe ischemia (ie, summed difference score >4). Cardiac event rates of 17% and 29% were observed for patients with normal or mildly ischemic MPI results (ie, summed difference score 1 to 4), respectively. Of note, more than half (52%) of patients with symptomatic ischemia experienced a cardiac event compared with only one third of patients who had asymptomatic ischemia after PCI.

**Ongoing Clinical Trials Using Sequential Stress Myocardial Perfusion Imaging**

A number of ongoing controlled clinical studies or randomized clinical trials are evaluating the role of sequential stress MPI to monitor the effectiveness of medical or surgical intervention in patients with CAD. These studies include:

- The Bypass Angioplasty Revascularization Investigation 2-D (in diabetics) (BARI 2-D), with principal investigator Ami Iskandrian, MD, at the University of Alabama at Birmingham.
- Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE), with principal investigators Daniel S. Berman, MD, and Leslee J. Shaw, PhD, at Cedars-Sinai Medical Center, Los Angeles, California.
- Adenosine Sestamibi SPECT [Single-Photon Emission Computed Tomography] Postinfarction Evaluation (INSPIRE), with principal investigator John J. Mahmarian, MD, at Baylor College of Medicine, Houston, Texas.

INSPIRE is evaluating the utility of SPECT for post-MI prognostic risk stratification as well as tracking subsequent risk based on stress-induced left ventricular PDS and extent of scintigraphic ischemia (Figure 3). The protocol design was recently published.

INSPIRE enrolled patients whose condition was stable following acute MI and who underwent initial SPECT MPI using adenosine stress approximately 2 to 5 days after MI. Patients were then aggressively treated with an array of anti-ischemic therapies and treatments aimed at risk factor modification. Those determined to be at high risk—ie, PDS ≥20%, ischemic PDS ≥10%, and left ventricular ejection fraction (LVEF) ≥0.35—were randomized to receive either intensive medical therapy or revascularization plus intensive medical therapy. Patients were then reassessed with stress MPI 6 to 12 weeks after the initial scan.

Preliminary findings from INSPIRE revealed that follow-up quantitative stress MPI studies demonstrated a significant reduction in total PDS. Nearly 8 of every 10 patients at high risk exhibited a marked improvement in their quantitative stress MPI scans. Marked improvement was defined as ≥9% change in PDS. A ≥9% reduction in PDS defines the 95% CI exceeding technique variability with sequential SPECT MPI. These results indicate that adenosine stress MPI can accurately assess risk very early after MI and that intensive medical therapy alone is comparable to medical therapy combined with revascularization in reducing ischemia on scintigraphy.

In the COURAGE trial, the goals of the nuclear substudy included (1) to evaluate the prognostic significance of the extent and severity of inducible ischemia at baseline in patients with anatomically defined CAD, (2) to correlate the extent and severity of SPECT ischemia with recurrent symptoms after PCI or refractory symptoms in patients treated medically, and (3) to evaluate changes in MPI in a subset of 300 patients undergoing sequential SPECT 6 to 14 months after intercurrent medical or surgical intervention. A smaller substudy is specifically evaluating the utility of sequential stress MPI in the setting of aggressive risk factor modification, lifestyle intervention, and an array of anti-ischemic medical or surgical interventions. Lifestyle and risk factor modifi-
cations, along with symptom-driven anti-ischemic therapy, are expected to result in improvements in myocardial perfusion and global ventricular function. This type of research is part of a growing body of evidence on the use of imaging-guided intensive risk factor modification aimed at constraining progressive CAD states.28,29 This type of management strategy is consistent with other reports that use imaging to track disease progression.52 A recent review of imaging as a means to track atherosclerotic disease progression has been published by Taylor and colleagues.52 The clinical workup algorithm involved in the COURAGE trial and using stress MPI is detailed in Figure 4.

Better methods of evaluating functional or perfusion improvements over time may help to make aggressive medical therapy a more viable treatment option for patients with nonstenotic atherosclerotic disease. However, in appropriate patients, medical therapy and risk factor management with sequential stress MPI may be the best treatment strategy. Sequential imaging can assure the patient and physician that...
their therapeutic strategy is working and the ensuing management pathway should be continued. Likewise, it can reveal when noninvasive therapy is not providing a sufficient anti-ischemic benefit and revascularization may be appropriate. On the basis of the evidence to date, sequential MPI appears to have the potential to help physicians avoid, or at least delay the need for, invasive cardiovascular procedures.

Myocardial Perfusion Imaging–Driven Patient Management Strategies

For the COURAGE trial, published reports were synthesized using an evidence-based approach to medicine, which resulted in some general recommendations (Figure 5). In patients with known CAD who are receiving medical therapy or who have undergone PCI and have recurrent mild-to-moderate symptoms, stress MPI is recommended. On the basis of the stress MPI results, patients with poor left ventricular function (ie, LVEF ≤0.35) and those with >1 area of inducible ischemia should proceed to cardiac catheterization. Because risk reduction with therapy is greater for patients at high risk, patients with marked ischemia and systolic dysfunction will likely receive a greater benefit from aggressive intervention. Evidence further suggests that patients at low risk who have known CAD have excellent survival rates and generally do not require further testing with stress MPI. Thus, this evidence has been synthesized into a clinical workup algorithm for use in the COURAGE trial (Figure 5).

Clinical Considerations for Using Stress Myocardial Perfusion Imaging

There are several practical considerations when using a strategy of sequential monitoring. First, the goal of this type of imaging varies dramatically from previous research and from many practice standards for most imaging laboratories. Specifically, the goal of the second stress MPI scan is to evaluate the effectiveness of the therapeutic intervention and, as such, this repeat scan is done while the patient is taking medication. The first stress MPI scan is performed without medication to elucidate the patient’s ischemic burden. Following the initiation of an array of therapies, repeat testing is done to reveal the patient’s ischemic burden while on a given regimen and is thus performed with the medications taken as prescribed. Second, one has to be careful to compare an equivalent level of stress from pretherapeutic to
posttherapeutic intervention. One must take care when comparing ischemia on the repeat exercise MPI because the patient may be able to exercise longer before ischemia onset for the “on therapy” second scan. Importantly, the patient can have the same ischemic burden but at a substantially higher metabolic workload for each test. Thus, one must take care to compare the ischemic burden at an equivalent workload. For stress MPI laboratories, this entails injection of the radioisotope at an equivalent exercise stage. For this reason, many advocate an advantage of pharmacologic stress over exercise stress for sequential stress MPI because use of the same agent and protocol provides an equivalent, reproducible level of stress during each test.

A final consideration is to define “significant change” for sequential stress MPI. There are 2 approaches: (1) The INSPIRE approach examines change beyond the reproducibility of the scan or >9% change in the quantitative PDS. (2) The COURAGE approach requires a threshold change based on meaningful outcome differences. In the 20-segment myocardial model, this entails a change of ≧4 to denote clinical worsening or improvement.

**Summary**

The unfolding of evidence on the application of sequential stress MPI in large, multinational, randomized trials, such as COURAGE, defines a new era for nuclear cardiology. The application of stress MPI in trials such as COURAGE was made possible by the wealth of outcomes evidence from large observational cohorts. We hope that the evidence put forth in COURAGE, INSPIRE, and other trials will allow for patient management approaches that are more intrinsically intertwined with medical and surgical decision making. Furthermore, we hope that determination of the extent and severity of inducible ischemia by stress MPI may become an essential guide to the type and intensity of therapeutic intervention and that findings on stress MPI scans may become a surrogate outcome in sequential monitoring to determine whether therapies are sufficiently cardioprotective to reduce a patient’s future risk of major adverse cardiovascular events.

**Case Studies**

**Case 1:** The patient was a 50-year-old man with a 6-week history of exertional chest pain that radiated to his jaw and left arm. His ECG was normal. Cardiac catheterization revealed an 80% stenosis in the mid left anterior descending artery, a 50% stenosis in the right coronary artery, and a 90% stenosis in the posterior descending artery. His LVEF was moderately reduced (0.49).

This patient received aggressive medical therapy. After 1 year of treatment, he showed improvement across cardiovascular parameters (Table 3). At baseline, a large pharmacologic stress–induced anterior wall defect was visualized with dipyridamole stress MPI. After 1 year of medical therapy, repeated pharmacologic stress SPECT demonstrated complete resolution of the defect (Figure 6).

**Case 2:** The patient was enrolled in an aggressive anti-ischemic risk factor–modification program after the diagnosis of chronic angina (CCSC I–III) or stable postinfarction status. The patient underwent prospective stress SPECT at baseline and after 10 months of aggressive anti-ischemic therapy and risk–factor management. This case is illustrative of the promise of sequential monitoring and the dramatic effects of therapeutic intervention that may be illustrated using sequential SPECT imaging (D. S. Berman, unpublished data, 2005).

**Table 3**

Improvement in cardiovascular parameters from baseline to 1-year follow-up in a 50-year-old man with a 6-week history of exertional chest pain

<table>
<thead>
<tr>
<th>Anginal Status</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>BP</th>
<th>BMI</th>
<th>Exercise</th>
<th>Diet</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class* Episode Frequency</td>
<td>4.30 mmol/L (166 mg/dL)</td>
<td>0.98 mmol/L (38 mg/dL)</td>
<td>160/120</td>
<td>35.0</td>
<td>—</td>
<td>—</td>
<td>1.86 mmol/L (165 mg/dL)</td>
</tr>
<tr>
<td>1 Year 0 0</td>
<td>2.07 mmol/L (80 mg/dL)</td>
<td>1.11 mmol/L (43 mg/dL)</td>
<td>116/80</td>
<td>33.1</td>
<td>45 min, 5x per wk</td>
<td>Step 2</td>
<td>1.38 mmol/L (122 mg/dL)</td>
</tr>
</tbody>
</table>

AHA = American Heart Association; BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

* Canadian Cardiovascular Society Class.

Adapted from *Circulation* and L. J. Shaw, personal communication, 2005.
Conclusion

Stress MPI is frequently used as a means to discern a patient’s underlying obstructive CAD burden and to estimate a patient’s risk for major adverse cardiac events. However, sequential stress MPI can be used as a “snapshot” guide to patient care at a single point in time. Increasingly, new evidence is illuminating the role of sequential stress MPI as a means to track disease progression and to evaluate the effectiveness of intensive risk factor and lifestyle modifications, anti-ischemic therapies, and the completeness of revascularization over a given period of time. Real changes in myocardial perfusion and ventricular function demonstrated by sequential stress MPI may aid in reassessing risk and serve as a further guide to risk-based patient management. Improved risk assessment, more accurate prognostic information, and more detailed evaluation of the functional effects of treatment may lead to improved outcomes with less need for invasive procedures, resulting in equivalent outcomes but at lower societal healthcare costs. This type of strategy also focuses on a well-rounded approach to risk reduction, impacting changes in lifestyle, risk factors, and symptom-driven anti-ischemic therapies for the patient with CAD.


Cardiovascular disease (CVD) is the leading cause of death in the United States. In 2002, >927,000 people in the United States died of CVD. In 2005, CVD will result in an estimated $393.5 billion in costs (including both direct and indirect costs). Improved diagnosis, risk stratification, and management of patients with CVD may lead to improved outcomes and more efficient utilization of healthcare resources.

Of those who died of CVD in 2002, >50% (n = 493,600) were women, dispelling the long-held myth that CVD was primarily a man’s disease. In fact, while the CVD mortality rate among men dropped substantially between 1979 and 2002, the CVD mortality rate among women increased slightly (Figure 1).

Therefore, while improved diagnostic, risk assessment, and management techniques are needed for all patients, increased awareness about CVD is still necessary among women and their physicians. The documented gender gaps in CVD diagnosis and care that place women at risk for adverse outcomes are simply not acceptable.

Of the CVD deaths in 2002, 53% were caused by coronary heart disease (CHD). Sudden cardiac death accounts for >50% of all CHD mortality in the United States, with the majority resulting from underlying coronary artery disease. Of patients who experience sudden cardiac death, 20%–40% have no known history of heart disease, which underscores the need for continued improvement in coronary heart disease screening and management.

Intermediate-Risk Patients

During initial cardiac screening, a large proportion of patients are determined to have intermediate risk for heart disease. For example, by the Duke Treadmill Score, which is a currently accepted standard for risk stratification on treadmill testing, approximately 50% of symptomatic patients fall into the intermediate-risk category. Approximately 40% of all asymptomatic patients seen in general and specialty practices are considered to be at intermediate risk.

The management of intermediate-risk patients is not as clear-cut as that for low- or high-risk patients. The use of additional risk assessment approaches can further stratify these patients and help guide their management.

Nuclear Imaging

Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) has emerged as a valuable tool in the assessment of cardiac patients, for both diagnostic and prognostic purposes. Although MPI is generally performed at a single point in time to guide patient management, increasing evidence supports a role for sequential MPI with SPECT to track disease progression or regression or assess the effectiveness of risk-factor and lifestyle modifications, anti-ischemic therapies, or revascularization. Real changes in myocardial perfusion and ventricular function as demonstrated by repeated SPECT studies may help to reassess patients’ risk and provide further guidance in risk-based patient management.

Additionally, many patients are unable to exercise adequately for stress electrocardiography. Although submaximal exercise testing is appropriate for some uses, including estimating functional capacity in nonathletes and assessing patients after myocardial infarction, it does not have the sensitivity, specificity, or predictive value to be useful clinically in assessing patients for CHD. Patients who are unable to exercise adequately, then, should be referred for pharmacologic stress MPI or echocardiography.

Coronary Calcium Scores

The use of electron-beam computed tomography (EBCT) to determine the degree of coronary calcification (as expressed as a coronary calcium score) may also help to further risk-stratify patients. Mounting evidence suggests that EBCT may be an effective complementary strategy to assess a patient’s atherosclerotic burden and determine the amount of nonstenotic coronary lesions. The additional information offered by the patient’s coronary calcium score may help the physician make appropriate risk management and treatment decisions.

Conclusion

We have made significant strides in addressing heart disease in the last several decades. Improved diagnostic and management techniques have helped to reduce the overall CVD mortality rate. However, this improvement has been real-
ized for men far more than for women. Awareness of CVD among women and their healthcare providers is rising, but we need to continue to emphasize the importance of early detection and treatment of heart disease in the female population.

The knowledge and technology available to us continues to grow. Increased familiarity with risk assessment scores, nuclear MPI, EBCT coronary calcium measurements, and other CVD evaluation tools will lead to their more regular use by specialists and generalists alike. We anticipate that the increased use of these available tools will lead to improved risk assessment and management as well as more accurate diagnosis, prognosis, and guidance of patient management.

Also, the increasing rates of overweight, obesity, diabetes mellitus, and the metabolic syndrome among Americans must be aggressively managed. These conditions place patients at risk for CVD and should therefore be addressed as part of preventive cardiology initiatives. Behavior and lifestyle modifications, including an emphasis on heart-healthy diet and regular exercise, should be initiated early rather than waiting until after the recognition of risk factors or signs and symptoms of CVD.