

## ACC/AHA PRACTICE GUIDELINES

## ACC/AHA Guidelines for Exercise Testing

A Report of the American College of Cardiology/American Heart Association  
Task Force on Practice Guidelines (Committee on Exercise Testing)

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## Preamble

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the management or prevention of disease states. Rigorous and expert analysis of the available data documenting relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and impact the overall cost of care favorably by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, whose charge is to develop and revise practice guidelines for important cardiovascular diseases and procedures. Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing groups are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes when data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered as well as frequency of follow-up and cost-effectiveness.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated yearly and as changes occur.

These practice guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the physician and patient in light of all of the circumstances presented by that patient.

The executive summary and recommendations are published in the July 1 issue of *Circulation*. The full text is published in *Journal of the American College of Cardiology*. Reprints of the full text and the executive summary are available from both organizations.

These guidelines have been officially endorsed by the American College of Sports Medicine, the American Society of Echocardiography and the American Society of Nuclear Cardiology.

*James L. Ritchie, MD, FACC*

*Chair, ACC/AHA Task Force on Practice Guidelines*

## I. Introduction

The American College of Cardiology/American Heart Association Task Force on Practice Guidelines was formed to make recommendations regarding the appropriate use of testing in the diagnosis and treatment of patients with known or suspected cardiovascular disease. Exercise testing is widely available and relatively low cost. For the purposes of this document, exercise testing is a cardiovascular stress test using treadmill or bicycle exercise and electrocardiographic and blood pressure monitoring. Pharmacological stress and the use of imaging modalities (radionuclide imaging, echocardiography) are beyond the scope of these guidelines.

The current committee was given the task of reviewing and revising the guidelines for exercise testing published in September 1986. Since that report, many new studies have been published regarding the usefulness of exercise testing for prediction of outcome in both symptomatic and asymptomatic patients. The usefulness of oxygen consumption measurements in association with exercise testing to identify patients who are candidates for cardiac transplantation has been recognized. The usefulness and cost-effectiveness of exercise testing has been compared with more expensive imaging procedures in selected patient subsets. All of these developments are considered in these guidelines.

In considering the use of exercise testing in individual patients, the following factors are important:

1. The quality, expertise, and experience of the professional and technical staff performing and interpreting the study
2. The sensitivity, specificity, and accuracy of the technique
3. The cost and accuracy of the technique as compared with more expensive imaging procedures
4. The effect of positive or negative results on clinical decision making
5. The potential psychological benefits of patient reassurance

The format of these guidelines includes a brief description of exercise testing followed by a discussion of its usefulness in specific clinical situations. Usefulness is considered for (1) diagnosis; (2) severity of disease/risk assessment/prognosis in patients with known or suspected chronic coronary artery disease (CAD); (3) risk assessment of patients early after myocardial infarction; (4) specific clinical populations identified by gender, age, other cardiac disease, or prior coronary revascularization; and (5) pediatric populations. The recommendations for particular situations are summarized in each section.

The committee reviewed and compiled all pertinent pub-

lished reports (excluding abstracts) through a computerized search of the English-language literature since 1975 and a manual search of final articles. Specific attention was devoted to identification and compilation of appropriate meta-analyses. Detailed evidence tables were developed whenever necessary using specific criteria detailed in the guidelines. The meta-analyses and evidence tables were extensively reviewed by an expert in methodologies. Inaccuracies and inconsistencies in the original publications were identified and corrected whenever possible. The recommendations made are based primarily on these published data. Because there are essentially no randomized trials assessing health outcomes for diagnostic tests, the committee has not ranked the available scientific evidence in an A, B, or C fashion (as was done in other ACC/AHA documents). When few or no data exist, this is noted in the text, and the recommendations are based on the expert consensus of the committee.

The ACC/AHA classifications I, II, and III are used to summarize indications as follows:

*Class I:* Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

*Class II:* Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

*Ila:* Weight of evidence/opinion is in favor of usefulness/efficacy.

*Ilb:* Usefulness/efficacy is less well established by evidence/opinion.

*Class III:* Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

A complete list of the hundreds of publications covering many decades of exercise testing is beyond the scope of these guidelines, and only selected references are included. The committee consisted of acknowledged experts in exercise testing, as well as general cardiologists, a general internist, a family medicine physician, and cardiologists with expertise in the use of stress imaging modalities. The committee included representatives of the American Academy of Family Physicians, the American College of Sports Medicine, and the American College of Physicians. Both the academic and private practice sectors, as well as both adult and pediatric expertise, were represented. This document was reviewed by three outside reviewers nominated by the ACC and by three outside reviewers nominated by the AHA, as well as by outside reviewers nominated by the American Academy of Family Physicians, the American College of Physicians, the American College of Sports Medicine, the American Society of Echocardiography, and the American Society of Nuclear Cardiology. This document will be reviewed 2 years after publication and yearly thereafter by the task force to determine whether a revision is needed. These guidelines will be considered current unless the task force revises or withdraws them from distribution.

This report overlaps with several previously published ACC/AHA guidelines for patient treatment that potentially involve exercise testing, including guidelines for perioperative cardiovascular evaluation for noncardiac surgery,<sup>1</sup> guidelines for management of patients with acute myocardial infarction,<sup>2</sup> guidelines for percutaneous transluminal coronary angioplasty,<sup>3</sup> and guidelines and indications for coronary artery bypass graft surgery.<sup>4</sup> These guidelines are not intended to include information previously covered in guidelines for the use of noninvasive imaging modalities. This report does not include a discussion of radionuclide angiography, myocardial perfusion imaging, or positron emission tomography, which are covered in the recently published guidelines for clinical use of cardiac radionuclide imaging.<sup>5</sup> This report also does not include any discussion of stress echocardiography, which is covered in the recently published guidelines for clinical application of echocardiography.<sup>6</sup> For clarity, there are occasional references to the use of both radionuclide and echocardiographic imaging techniques. However, these brief references are not intended to provide a comprehensive understanding of the use of these imaging modalities. For such an understanding, the reader is referred to the other published guidelines. These guidelines do apply to both adults and children.

### *Exercise Testing Procedure*

**General Overview** Exercise testing is a well-established procedure that has been in widespread clinical use for many decades. It is beyond the scope of this document to provide a detailed "how-to" description of this procedure. Such a description is available in previous publications from the AHA, including the statement on exercise standards,<sup>7</sup> guidelines for clinical exercise testing laboratories,<sup>8</sup> and guidelines for exercise testing in the pediatric age group,<sup>9</sup> to which interested readers are referred. This section is intended to provide a brief overview of the exercise testing procedure.

**Indications and Safety** Although exercise testing is generally a safe procedure, both myocardial infarction and death have been reported and can be expected to occur at a rate of up to 1 per 2500 tests.<sup>10</sup> Good clinical judgment should therefore be used in deciding which patients should undergo exercise testing. Absolute and relative contraindications to exercise testing are summarized in Table 1.

Exercise testing should be supervised by an appropriately trained physician. As indicated in the ACP/ACC/AHA task force statement on clinical competence in exercise testing,<sup>11</sup> exercise testing in selected patients can be safely performed by properly trained nurses, exercise physiologists, physical therapists, or medical technicians working directly under the supervision of a physician, who should be in the immediate vicinity and available for emergencies. The electrocardiogram, heart rate, and blood pressure should be carefully monitored and recorded during each stage of exercise as well as during ST-segment abnormalities and chest pain. The patient should be continuously monitored for transient rhythm disturbances, ST-segment changes, and other electrocardiographic manifes-

**Table 1.** Contraindications to Exercise Testing

Absolute
<ul style="list-style-type: none"> <li>• Acute myocardial infarction (within 2 d)</li> <li>• Unstable angina not previously stabilized by medical therapy*</li> <li>• Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise</li> <li>• Symptomatic severe aortic stenosis</li> <li>• Uncontrolled symptomatic heart failure</li> <li>• Acute pulmonary embolus or pulmonary infarction</li> <li>• Acute myocarditis or pericarditis</li> <li>• Acute aortic dissection</li> </ul>
Relative†
<ul style="list-style-type: none"> <li>• Left main coronary stenosis</li> <li>• Moderate stenotic valvular heart disease</li> <li>• Electrolyte abnormalities</li> <li>• Severe arterial hypertension‡</li> <li>• Tachyarrhythmias or bradyarrhythmias</li> <li>• Hypertrophic cardiomyopathy and other forms of outflow tract obstruction</li> <li>• Mental or physical impairment leading to inability to exercise adequately</li> <li>• High-degree atrioventricular block</li> </ul>

\*Appropriate timing of testing depends on level of risk of unstable angina, as defined by AHCPR Unstable Angina Guidelines.<sup>14</sup> †Relative contraindications can be superseded if the benefits of exercise outweigh the risks. ‡In the absence of definitive evidence, the committee suggests systolic blood pressure of >200 mm Hg and/or diastolic blood pressure of >110 mm Hg. Modified from Fletcher et al.<sup>7</sup>

tations of myocardial ischemia. Further details are provided in the AHA guidelines for clinical exercise testing laboratories.<sup>8</sup>

**Equipment and Protocols** Both treadmill and cycle ergometer devices are available for exercise testing. Although cycle ergometers are generally less expensive, smaller, and less noisy than treadmills and produce less motion of the upper body, the fatigue of the quadriceps muscles in patients who are not experienced cyclists is a major limitation, because subjects usually stop before reaching their maximum oxygen uptake. As a result, treadmills are much more commonly used in the United States for exercise testing.

Commonly used treadmill protocols are summarized in a variety of published documents. Although much of the published data are based on the Bruce protocol, there are clear advantages to customizing the protocol to the individual patient to allow 6 to 12 minutes of exercise.<sup>12</sup> Exercise capacity should be reported in estimated metabolic equivalents (METs) of exercise. If exercise capacity is also reported in minutes, the nature of the protocol should be clearly specified.

**Exercise End Points** Although exercise testing is commonly terminated when subjects reach an arbitrary percentage of predicted maximum heart rate, it should be recognized that other end points (summarized in Table 2) are strongly preferred. There is a wide spectrum of individual subject values around the regression line for maximum heart rate, which may therefore be beyond the limit of some patients and submaximal for others. The target heart rate approach has obvious additional limitations in patients receiving  $\beta$ -blockers, those with heart rate impairment, or those with excessive heart rate response. The use of rating of perceived exertion scales, such as the Borg scale (see Appendix 1),<sup>13</sup> is often helpful in

**Table 2.** Indications for Terminating Exercise Testing

Absolute indications
<ul style="list-style-type: none"> <li>• Drop in systolic blood pressure of &gt;10 mm Hg from baseline blood pressure despite an increase in work load, when accompanied by other evidence of ischemia</li> <li>• Moderate to severe angina</li> <li>• Increasing nervous system symptoms (eg, ataxia, dizziness, or near-syncope)</li> <li>• Signs of poor perfusion (cyanosis or pallor)</li> <li>• Technical difficulties in monitoring ECG or systolic blood pressure</li> <li>• Subject's desire to stop</li> <li>• Sustained ventricular tachycardia</li> <li>• ST elevation (<math>\geq 1.0</math> mm) in leads without diagnostic Q-waves (other than V<sub>1</sub> or aVR)</li> </ul>
Relative indications
<ul style="list-style-type: none"> <li>• Drop in systolic blood pressure of <math>\geq 10</math> mm Hg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischemia</li> <li>• ST or QRS changes such as excessive ST depression (&gt;2 mm of horizontal or downsloping ST-segment depression) or marked axis shift</li> <li>• Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias</li> <li>• Fatigue, shortness of breath, wheezing, leg cramps, or claudication</li> <li>• Development of bundle branch block or IVCD that cannot be distinguished from ventricular tachycardia</li> <li>• Increasing chest pain</li> <li>• Hypertensive response*</li> </ul>

\*In the absence of definitive evidence, the committee suggests systolic blood pressure of >250 mm Hg and/or a diastolic blood pressure of >115 mm Hg. ECG indicates electrocardiogram; PVCs, premature ventricular contractions; ICD, implantable cardioverter-defibrillator discharge; and IVCD, intraventricular conduction delay. Modified from Fletcher et al.<sup>7</sup>

assessment of patient fatigue. Symptom-limited testing using the Borg scale as an aid is very important when the test is used to assess functional capacity. Rating of perceived exertion is less helpful in pediatric populations.

**Interpretation of the Exercise Test** Interpretation of the exercise test should include exercise capacity and clinical, hemodynamic, and electrocardiographic response. The occurrence of ischemic chest pain consistent with angina is important, particularly if it forces termination of the test. Abnormalities in exercise capacity, systolic blood pressure response to exercise, and heart rate response to exercise are important findings. The most important electrocardiographic findings are ST depression and elevation. The most commonly used definition for a positive exercise test result from an electrocardiographic standpoint is greater than or equal to 1 mm of horizontal or downsloping ST-segment depression or elevation for at least 60 to 80 milliseconds after the end of the QRS complex.<sup>4</sup> The details of interpretation are covered elsewhere in these guidelines.

**Cost and Availability** There are relatively few published studies comparing the cost-effectiveness of treadmill exercise testing with more expensive imaging procedures. Compared with imaging procedures such as stress echocardiography, stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging, and coronary angiography, treadmill exercise testing can be performed at a much lower

**Table 3.** Medicare Fees and Volumes of Commonly Used Diagnostic Procedures

Procedure	1996 CPT Code(s)	1996 Total (Professional and Technical) Medicare RVUs	1994 Medicare Data		
			Number Performed	Percent Charged by Cardiologists	Percent Office-Based
Treadmill exercise test	93015 or 93016-93018	3.30	875,780*	67*	66*
Stress echocardiography	93350, 93015	7.95 (plus any Doppler charge)	213,404	78	67
Stress SPECT myocardial perfusion imaging	78465, 93015	17.45 (plus isotope charge)	889,319	†	34
Left heart catheterization with left ventriculogram and coronary angiography	93510, 93543, 93545, 93555, 93556	66.83	728,763	88	<1

\*These numbers are estimates, after excluding treadmill exercise tests performed with perfusion imaging. †There are no reliable data regarding this percentage. CPT indicates current procedural terminology; RVUs, relative value units; and SPECT, single-photon emission computed tomography.

cost. Table 3 is a comparison of 1996 Medicare RVUs (relative value units, professional and technical) for treadmill exercise testing and selected imaging procedures. These RVUs provide an estimate of relative costs. Compared with the treadmill exercise test, the cost of stress echocardiography is at least 2.4 times higher, stress SPECT myocardial imaging 5.3 times higher, and coronary angiography 20 times higher. Lower cost of the treadmill exercise test alone does not necessarily result in a lower overall cost of patient care, as the cost of additional testing and interventions may be higher when the initial treadmill exercise test is less accurate than these more sophisticated procedures.

Treadmill exercise testing is performed frequently. As shown in Table 3, treadmill exercise tests are performed about as often as the most frequent imaging procedure (stress SPECT myocardial perfusion imaging). An estimated two thirds of the treadmill exercise tests charged to Medicare in 1994 were performed as office procedures, and 33% of the charges were submitted by noncardiologists. Thus, treadmill exercise tests are more widely performed, do not always require a cardiologist, and are convenient for the patient because they are often an office-based procedure.

**Clinical Context** The vast majority of treadmill exercise testing is performed in adults with symptoms of known or suspected ischemic heart disease. Special groups who represent exceptions to this norm are discussed in detail in sections VI and VII. Sections II through IV reflect the variety of patients and clinical decisions (so-called "nodal points") for which exercise testing is used. Although this document is not intended to be a guideline for the management of stable chest pain, the committee thought that it was important to provide an overall context for the use of exercise testing to facilitate the use of these guidelines (Fig 1).

Patients who are candidates for exercise testing may have stable symptoms of chest pain, may be stabilized by medical therapy following symptoms of unstable chest pain, or may be post-myocardial infarction or postrevascularization patients. The clinician should first address whether the diagnosis of CAD is certain, based on the patient's history, electrocardiogram, and symptoms of chest pain. The important factors involved in addressing this question are covered in section II of

this document, which focuses on the use of treadmill exercise testing for diagnosis.

Even in patients for whom the diagnosis of CAD is certain, based on age, gender, description of chest pain, and history of prior myocardial infarction, there usually is a clinical need for risk or prognostic assessment to determine the need for possible coronary angiography or revascularization. The potential role of treadmill exercise testing in such patients is detailed in section III.

Post-myocardial infarction patients represent a common first presentation of ischemic heart disease. They are a subset of patients who may need risk or prognostic assessment. This subgroup is considered in detail in section IV, which includes a discussion of the implications of acute reperfusion therapy for interpretation of exercise testing in this population.

## II. Exercise Testing in Diagnosis of Obstructive Coronary Artery Disease

### Class I

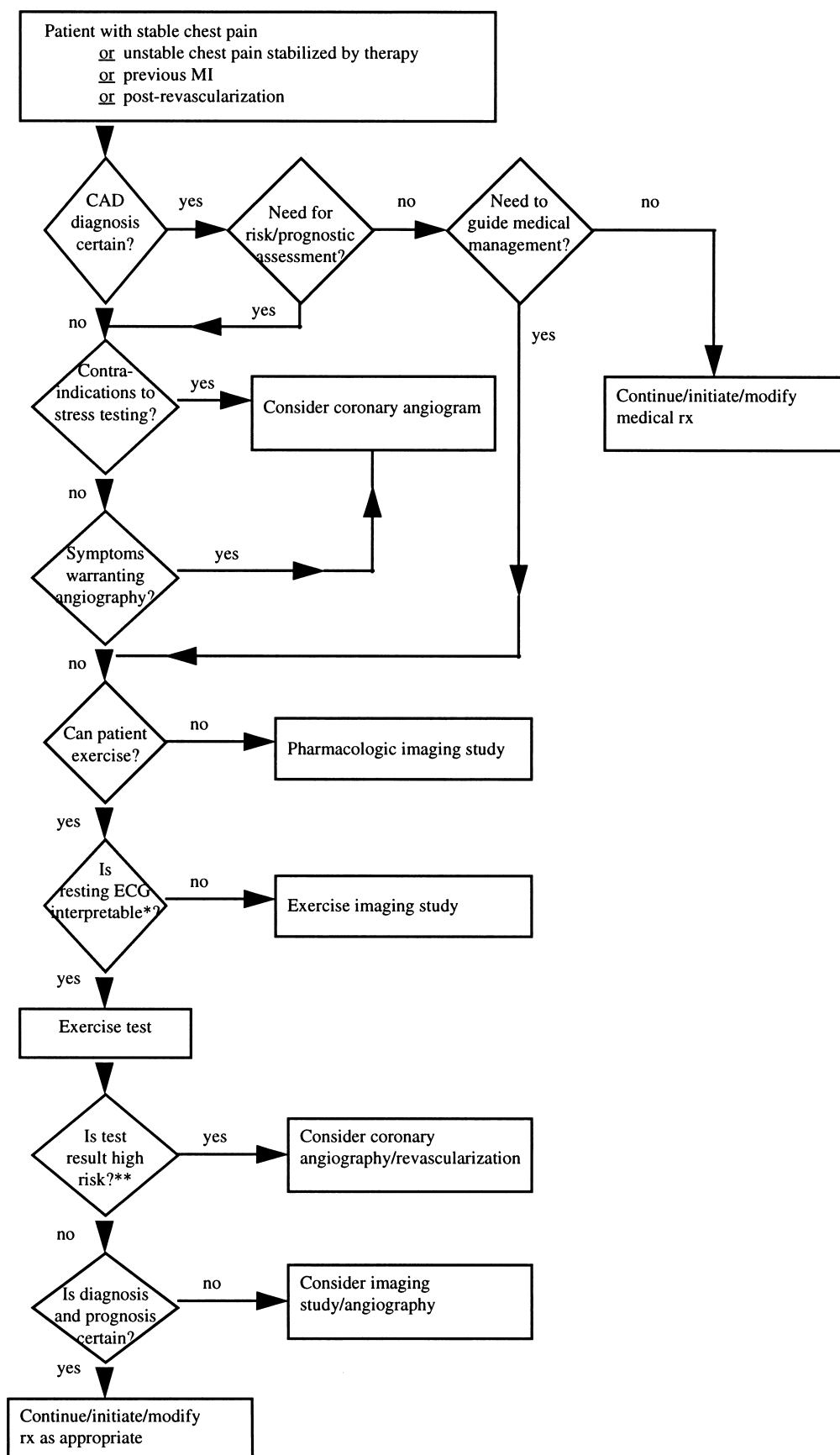
1. Adult patients (including those with complete right bundle branch block or less than 1 mm of resting ST depression) with an intermediate pretest probability of CAD (Table 4), based on gender, age, and symptoms (specific exceptions are noted under Classes II and III below).

### Class IIa

1. Patients with vasospastic angina.

### Class IIb

1. Patients with a high pretest probability of CAD by age, symptoms, and gender.
2. Patients with a low pretest probability of CAD by age, symptoms, and gender.
3. Patients with less than 1 mm of baseline ST depression and taking digoxin.
4. Patients with electrocardiographic criteria for left ventricular hypertrophy (LVH) and less than 1 mm of baseline ST depression.



**Figure 1.** Clinical context for exercise testing for patients with suspected ischemic heart disease. \*Electrocardiogram interpretable unless preexcitation, electronically paced rhythm, left bundle branch block, or resting ST-segment depression >1 mm. See text for discussion of digoxin use, left ventricular hypertrophy, and ST depression <1 mm. \*\*For example, high-risk if Duke treadmill score predicts average annual cardiovascular mortality >3% (see Fig 2 for nomogram). CAD indicates coronary artery disease, ECG, electrocardiogram; MI, myocardial infarction; and rx, treatment.



**Table 4.** Pretest Probability of Coronary Artery Disease by Age, Gender, and Symptoms\*

Age (y)	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

\*No data exist for patients <30 or >69 years, but it can be assumed that prevalence of CAD increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range. High indicates >90%; intermediate, 10%–90%; low, <10%; and very low, <5%.

### Class III

1. Patients with the following baseline ECG abnormalities:
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - Greater than 1 mm of resting ST depression
  - Complete left bundle branch block
2. Patients with a documented myocardial infarction or prior coronary angiography demonstrating significant disease have an established diagnosis of CAD; however, ischemia and risk can be determined by testing (see sections III and IV).

### Rationale

The exercise test may be used if the diagnosis of CAD is uncertain. Although other clinical findings, such as dyspnea on exertion, resting ECG abnormalities, or multiple risk factors for atherosclerosis may suggest the possibility of CAD, the most predictive clinical finding is a history of chest pain or discomfort. Myocardial ischemia is the most important cause of chest pain and is most commonly a consequence of underlying coronary disease. CAD that has not resulted in sufficient luminal occlusion to cause ischemia during stress<sup>15</sup> can still lead to ischemic events through spasm, plaque rupture, and thrombosis, but most catastrophic events are associated with extensive atherosclerosis. These nonobstructive lesions explain some of the events that occur after a normal exercise test (see section III). Although the coronary angiogram has obvious limitations,<sup>16</sup> angiographic lesions remain the clinical gold standard. Results of correlative studies have been divided over the use of 50% or 70% luminal occlusion. Meta-analysis of the studies has not demonstrated that the criteria affect the test characteristics.

### Pretest Probability

The clinician's estimation of pretest probability of obstructive CAD is based on the patient's history (including age, gender, chest pain characteristics), physical examination and initial testing, and the clinician's experience with this type of

problem. Table 4 is a modification of the literature review of Diamond and Forrester.<sup>17</sup> Typical or definite angina makes the pretest probability of disease so high that the test result does not dramatically change probability. However, the test can be performed in these patients for other reasons. Atypical or probable angina in a 50-year-old man or a 60-year-old woman is associated with about a 50% probability for CAD. Diagnostic testing is most valuable in this intermediate pretest probability category, because the test result has the largest potential effect on diagnostic outcome. Typical or definite angina can be defined as (1) substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and nitroglycerin. Atypical or probable angina can be defined as chest pain or discomfort that lacks one of the three characteristics of definite or typical angina.<sup>18</sup>

Detailed nomograms are available incorporating the effects of a history of prior infarction, electrocardiographic Q waves, electrocardiographic ST and T-wave changes, diabetes, smoking, and hypercholesterolemia.<sup>19</sup> History and electrocardiographic evidence of prior infarction dramatically affects pretest probability. Diabetes has only a modest impact. Smoking and hypercholesterolemia have a minimal impact.

### Diagnostic Characteristics and Test Performance

**Sensitivity and Specificity** Sensitivity is the percentage of patients with a disease who will have an abnormal test. Specificity is the percentage of patients free of disease who will have a normal test. The method of calculating these terms is shown in Table 5.

**Cut Point or Discriminant Value.** A basic step in applying any testing procedure for the separation of normal subjects from patients with disease is to determine a value measured by the test that best separates the two groups. The problem with any diagnostic test is that there is a large overlap of measurement values of a test in the groups with and without disease. All tests used for diagnosis of CAD have considerable overlap in the range of measurements for the normal population and for those with heart disease. A certain value (discriminant value) is used to separate these two groups (ie, 1 mm of

**Table 5.** Definitions and Calculation of the Terms Used to Quantify the Diagnostic Accuracy of a Test

Sensitivity = [TP/(TP + FN)] × 100		Specificity = [TN/(FP + TN)] × 100
Predictive value of an abnormal test (PV+) = $\frac{\text{Sensitivity} \times \text{P(CAD)}}{[\text{Sensitivity} \times \text{P(CAD)}] + [(1 - \text{Specificity})[1 - \text{P(CAD)}]]}$		
Predictive accuracy = [Sensitivity × P(CAD)] + [Specificity × [1 - P(CAD)]]		

TP indicates those with an abnormal test result and disease (true-positives); TN, those with a normal test result and no disease (true-negatives); FP, those with an abnormal test result but no disease (false-positives); FN, those with a normal test result but disease (false-negatives); PV+, the percentage of those with an abnormal (+) test result who have disease; predictive accuracy, the percentage of correct classifications, both + and –; and P(CAD), pretest probability.

ST-segment depression). If the value is set high (ie, 2 mm of ST-segment depression) to ensure that nearly all normal subjects have a normal test, giving the test a high specificity, then a substantial number of those with the disease appear to be normal, reducing the test sensitivity. There may be reasons for wanting to adjust a test to have a relatively higher sensitivity, but sensitivity and specificity are inversely related.

**Population Effect.** Sensitivity and specificity are inversely related, affected by the population tested, and determined by the choice of a cut point or discriminant value. Once a discriminant value that determines the specificity and sensitivity of a test is chosen, then the population tested must be considered. If the population is skewed toward persons with a greater severity of disease, then the test will have a higher sensitivity for any cut point chosen. For instance, the exercise test has a higher sensitivity in the elderly and persons with three-vessel disease than in younger persons and those with one-vessel disease. A test can have a lower specificity if it is used in persons in whom false-positive results are more likely, such as those with valvular heart disease, LVH, resting ST depression, and patients taking digoxin.

**Predictive Value.** The predictive value of a positive test is another term that defines the diagnostic performance of a test and is determined by sensitivity and specificity. Table 5 shows how predictive value is calculated. Note that it is dependent on

the prevalence of disease in the population tested. Table 6 demonstrates how disease prevalence affects the calculation.

The positive predictive value of an abnormal test result is the percentage of persons with an abnormal test result who have a disease. Predictive value cannot be estimated directly from the demonstrated specificity or sensitivity of a test, but it is dependent on disease prevalence (pretest probability of disease).

**Probability Analysis** The information most important to a clinician attempting to make a diagnosis is the probability of the patient having or not having the disease once the test result is known. Such a probability cannot be accurately estimated from the test result and the diagnostic characteristics of the test alone. Knowledge of the probability of the patient having the disease before the test is administered (ie, pretest probability) is also required. Bayes' theorem states that the probability of a patient having the disease after a test is performed will be the product of the disease probability before the test and the probability that the test provided a true result. The clinician often makes this calculation intuitively when he or she suspects a false result when a 30-year-old woman with atypical angina has an abnormal exercise test result (low pretest probability). The same abnormal response would be intuitively considered a true-positive result in a 60-year-old man with typical angina pectoris (high pretest probability).

**Table 6.** Effect of Disease Prevalence on Predictive Value of a Positive Test

Prevalence of CAD (%)	Subjects	Test Characteristics	Number With Abnormal Test Result	Number With Normal Test Result	Predictive Value of a Positive Result
5	500 with CAD	50% sensitive	250 (TP)	250 (FN)	$250/(250 + 950)$ = 21%
	9500 without CAD	90% specific	950 (FP)	8550 (TN)	
50	5000 with CAD	50% sensitive	2500 (TP)	2500 (FN)	$2500/(2500 + 500)$ = 83%
	5000 without CAD	90% specific	500 (FP)	4500 (TN)	

Calculation of the predictive value of an abnormal test (positive predictive value) using a test with a sensitivity of 50% and a specificity of 90% in two populations of 10,000 patients, one with a CAD prevalence of 5% and the other with a prevalence of 50%. In a test with characteristics like the exercise ECG, the predictive value of 1 mm of ST depression increases from 21% when there is a 5% prevalence of disease to 83% when there is a 50% prevalence of disease. Thus, four times as many of those with an abnormal test result will be found to have coronary disease when the patient population increases from a 5% prevalence of CAD to a 50% prevalence. These calculations demonstrate the important influence that prevalence has on the positive predictive value. PV+ is the test performance characteristic most apparent to the clinician using the test. This explains the greater percentage of false-positive results found when the test is used as a screening procedure in an asymptomatic group (with a low prevalence of CAD) as opposed to when it is used as a diagnostic procedure in patients with symptoms most likely due to CAD (higher prevalence of CAD). For 5% prevalence:  $PV+ = 250/(250 + 950) = 21\%$ . For 50% prevalence:  $PV+ = 2500/(2500 + 500) = 83\%$ . CAD indicates coronary artery disease; TP, true-positive; FN, false-negative; FP, false-positive; and TN, true-negative.

**Table 7.** Meta-Analyses of Exercise Testing<sup>25,26</sup>

Grouping	Number of Studies	Total Number of Patients	Sens (%)	Spec (%)	Predictive Accuracy (%)
Meta-analysis of standard exercise test	147	24,047	68	77	73
Meta-analysis without MI	58	11,691	67	72	69
Meta-analysis without workup bias	3	> 1000	50	90	69
Meta-analysis with ST depression	22	9153	69	70	69
Meta-analysis without ST depression	3	840	67	84	75
Meta-analysis with digoxin	15	6338	68	74	71
Meta-analysis without digoxin	9	3548	72	69	70
Meta-analysis with LVH	15	8016	68	69	68
Meta-analysis without LVH	10	1977	72	77	74

Sens indicates sensitivity; Spec, specificity; MI, myocardial infarction; and LVH, left ventricular hypertrophy.

Scores developed from multivariable analysis of clinical and exercise test variables provide superior discrimination compared with using only the ST-segment response to diagnose CAD. Such scores can provide probabilities of CAD that are more accurate than ST measurements alone.<sup>20,21</sup> However, diagnostic interpretation of the exercise test still centers around the ST response, because the clinician remains uncertain about which other variables to apply and how to include them in prediction. Although the statistical models proposed have proved to be superior, the available equations have differed as to variables and coefficients chosen. In addition, the equations were usually derived in study populations with a higher prevalence of disease than seen in clinical settings because of work-up bias, ie, the results of the exercise test were used to decide who would undergo cardiac catheterization. For these reasons, use of these equations remains controversial and limited. Several such equations are shown in Appendix 2. However, when these computational techniques have been compared with the judgment of experienced clinical cardiologists, the predictions have been comparable.<sup>22,23</sup> Physicians are often urged to “use” more than just the ST segment in interpreting the exercise test; these equations provide the only scientific means to do so.

### *Believability Criteria for Diagnostic Tests*

Studies should include consecutive or randomly selected patients for whom the diagnosis is in doubt.<sup>24</sup> Any diagnostic test appears to function well if obviously normal subjects are compared with those who obviously have the disease in question (a “limited challenge”). The more relevant issue is to evaluate patients who are suspected but not known to have the disease of interest and to differentiate those who do from those who do not. If the patients enrolled in the study do not represent this diagnostic dilemma group, the test may perform well in the study but not in clinical practice. Problems arise when patients who most certainly have the disease (ie, post-myocardial infarction patients) are included in this diagnostic sample. Post-myocardial infarction patients may be included in studies to predict disease severity but should not be included

in studies attempting to distinguish those with disease from those without disease.

### *Diagnostic Accuracy of the Standard Exercise Test*

The variability of the reported diagnostic accuracy of the exercise electrocardiogram (ECG) has been studied by meta-analysis.<sup>25,26</sup> The criteria to judge the credibility and applicability of the results of studies evaluating diagnostic tests<sup>27</sup> were applied. Most of the studies failed to fulfill these criteria, particularly removal of work-up bias. However, this analysis provides the best description of the diagnostic accuracy of the

**Table 8.** Studies Including Resting ST Depression

Author	Year	Total Patients	Sensitivity	Specificity
Roitman <sup>46</sup>	1970	100	0.73	0.82
Erikssen <sup>74</sup>	1977	113	0.84	0.17
Silber <sup>75</sup>	1979	108	0.71	0.70
Dunn <sup>76</sup>	1979	125	0.70	0.65
Weiner <sup>77</sup>	1979	2045	0.79	0.69
Marcomichelakis <sup>78</sup>	1980	100	0.92	0.62
Morales-Ballejo <sup>79</sup>	1981	100	0.62	0.74
Machecourt <sup>80</sup>	1981	112	0.48	0.82
Guiteras <sup>81</sup>	1982	112	0.79	0.61
Santinga <sup>82</sup>	1982	113	0.56	0.86
Currie <sup>83</sup>	1983	105	0.77	0.82
Hlatky <sup>84</sup>	1984	3094	0.69	0.79
O'Hara <sup>85</sup>	1985	103	0.69	0.65
Machecourt <sup>86</sup>	1985	105	0.45	0.80
Huerta <sup>87</sup>	1985	114	0.90	0.60
Melin <sup>88</sup>	1985	135	0.61	0.79
Hung <sup>89</sup>	1985	171	0.85	0.63
Detry <sup>90</sup>	1985	284	0.64	0.72
Weiner <sup>91</sup>	1985	617	0.61	0.76
Ananich <sup>92</sup>	1986	111	0.55	0.92
Vincent <sup>93</sup>	1986	122	0.68	0.48
Detrano <sup>94</sup>	1986	303	0.69	0.73
Others (11)*	1974–1986	861	0.71	0.73
Averages with ST depression		9153	0.69	0.70

\*Eleven other studies, each with <100 subjects, combined.

**Table 9.** Studies Excluding Resting ST Depression

Author	Year	Total Patients	Sensitivity	Specificity
Sketch <sup>95</sup>	1980	107	0.64	0.81
Nair <sup>96</sup>	1983	280	0.66	0.93
Furuse <sup>97</sup>	1987	135	0.77	0.83
Others*	1971–1984	318	0.59	0.78
Averages without ST depression		840	0.67	0.84

\*Four other studies, each with <100 subjects, combined.

exercise test. Meta-analysis of 147 consecutively published reports (Tables 7 through 13) involving 24 074 patients who underwent both coronary angiography and exercise testing revealed a wide variability in sensitivity and specificity (mean sensitivity was 68%, with a range of 23% to 100% and a standard deviation of 16%; mean specificity was 77%, with a range of 17% to 100% and a standard deviation of 17%). However, only the results in the 58 studies (which included 11 691 patients from this meta-analysis) that removed patients with a prior myocardial infarction, fulfilling one of the criteria for evaluating a diagnostic test, accurately portray the performance of the test. These studies demonstrated a mean sensitivity of 67% and a mean specificity of 72%. In the few studies where work-up bias was avoided by having patients agree to undergo both procedures, fulfilling the other major criterion, the approximate sensitivity and specificity of 1 mm of horizontal or downward ST depression were 50% and 90%, respectively.<sup>28,29</sup> These latter studies provide a true estimate of how standard ECG criteria perform in patients with chest pain typically seen by the internist or family practitioner. As mentioned previously, sensitivity will be higher in patients with three-vessel disease and lower in patients with one-vessel disease. It is apparent that the true diagnostic value of the exercise ECG lies in its relatively high specificity. The modest

**Table 10.** Studies Including Digitalis

Author	Year	Total Patients	Sensitivity	Specificity
Roitman <sup>46</sup>	1970	100	0.73	0.82
Silber <sup>75</sup>	1979	108	0.71	0.70
Dunn <sup>76</sup>	1979	125	0.63	0.65
Marcomichelakis <sup>78</sup>	1980	100	0.92	0.62
Machecourt <sup>80</sup>	1981	112	0.48	0.82
Currie <sup>83</sup>	1983	105	0.77	0.82
Nair <sup>96</sup>	1983	280	0.66	0.93
Hlatky <sup>84</sup>	1984	3094	0.70	0.85
O'Hara <sup>85</sup>	1985	103	0.69	0.65
Machecourt <sup>86</sup>	1985	105	0.45	0.80
Huerta <sup>87</sup>	1985	114	0.90	0.60
Weiner <sup>91</sup>	1985	617	0.61	0.76
Ananich <sup>92</sup>	1986	111	0.55	0.92
Vincent <sup>93</sup>	1986	122	0.68	0.48
Detrano <sup>94</sup>	1986	303	0.69	0.73
Others*	1971–1986	839	0.64	0.69
Averages with digitalis		6338	0.68	0.74

\*Ten other studies, each with <100 subjects, combined.

**Table 11.** Studies Excluding Digitalis

Author	Year	Total Patients	Sensitivity	Specificity
Erikssen <sup>74</sup>	1977	113	0.84	0.17
Weiner <sup>77</sup>	1979	2045	0.79	0.69
Morales-Ballejo <sup>79</sup>	1981	100	0.62	0.74
Guiteras <sup>81</sup>	1982	112	0.79	0.66
Santiga <sup>82</sup>	1982	113	0.56	0.86
Melin <sup>88</sup>	1985	135	0.61	0.79
Hung <sup>89</sup>	1985	171	0.85	0.63
Detry <sup>90</sup>	1985	284	0.64	0.72
Furuse <sup>97</sup>	1987	135	0.77	0.83
Others*	1978–1986	340	0.71	0.85
Averages without digitalis		3548	0.72	0.69

\*Five other studies, each with <100 subjects, combined.

sensitivity of the exercise ECG is generally less than the sensitivity of imaging procedures.<sup>5,6</sup>

**Sensitivity From Meta-Analysis** *Sensitivity* (percentage of those with coronary disease who had an abnormal ST response) was found to be significantly and independently related to two study characteristics:

- Sensitivity decreased when equivocal tests were considered normal.
- Comparison with a new, “better” test lowered the sensitivity of the exercise ECG (publication bias).

**Specificity From Meta-Analysis** *Specificity* (percentage of those without coronary disease who had a normal ST response) was found to be significantly and independently related to two variables:

- When upsloping ST depression was classified as abnormal, specificity was lowered and sensitivity increased.
- The use of preexercise hyperventilation was associated with a decreased specificity, although there is no expla-

**Table 12.** Studies Including Left Ventricular Hypertrophy

Author	Year	Total Patients	Sensitivity	Specificity
Roitman <sup>46</sup>	1970	100	0.73	0.82
Erikssen <sup>74</sup>	1977	113	0.84	0.17
Silber <sup>75</sup>	1979	108	0.71	0.70
Dunn <sup>76</sup>	1979	125	0.70	0.65
Weiner <sup>77</sup>	1979	2045	0.79	0.69
Sketch <sup>95</sup>	1980	107	0.64	0.81
Machecourt <sup>80</sup>	1981	112	0.48	0.82
Hlatky <sup>84</sup>	1984	3094	0.69	0.79
O'Hara <sup>85</sup>	1985	103	0.69	0.65
Machecourt <sup>86</sup>	1985	105	0.45	0.80
Huerta <sup>87</sup>	1985	114	0.90	0.60
Weiner <sup>91</sup>	1985	617	0.61	0.76
Ananich <sup>92</sup>	1986	111	0.55	0.92
Vincent <sup>93</sup>	1986	122	0.68	0.48
Detrano <sup>94</sup>	1986	303	0.69	0.73
Others*	1974–1986	737	0.67	0.68
Averages with LVH		8016	0.68	0.69

\*Nine other studies, each with <100 subjects, combined. LVH indicates left ventricular hypertrophy.

**Table 13.** Studies Excluding Left Ventricular Hypertrophy

Author	Year	Total Patients	Sensitivity	Specificity
Marcomichelakis <sup>78</sup>	1980	100	0.92	0.62
Morales-Ballejo <sup>79</sup>	1981	100	0.62	0.74
Guiteras <sup>81</sup>	1982	112	0.79	0.66
Santinga <sup>82</sup>	1982	113	0.56	0.86
Currie <sup>83</sup>	1983	105	0.77	0.82
Nair <sup>96</sup>	1983	280	0.66	0.93
Melin <sup>88</sup>	1985	135	0.61	0.79
Hung <sup>89</sup>	1985	171	0.85	0.63
Detry <sup>90</sup>	1985	284	0.64	0.72
Furuse <sup>97</sup>	1987	135	0.77	0.83
Others*	1971-1983	442	0.69	0.84
Averages without LVH	1977		0.72	0.77

\*Six other studies, each with <100 subjects, combined. LVH indicates left ventricular hypertrophy.

nation for this association. Hyperventilation was once thought to reveal false-positive ST responders by bringing out ST depression with a stimulus other than ischemia; however, this has not been validated, and it is no longer recommended as a routine to be performed before standard testing.<sup>26</sup>

The Tables 8 to 13 in the appendix were developed for resolving the issues of LVH, resting ST depression, and digoxin. Of the 58 studies, only those that provided sensitivity, specificity, and total patient numbers were considered, and only those with more than 100 patients were considered separately. Regarding the effect of resting ECG abnormalities, the studies that included patients with LVH had a mean sensitivity of 68% and a mean specificity of 69%; the studies that excluded them had a mean sensitivity of 72% and a mean specificity of 77%. Studies that included patients with resting ST depression had a mean sensitivity of 69% and a mean specificity of 70%; studies that excluded them had a mean sensitivity of 67% and a mean specificity of 84%. Studies that included patients receiving digoxin had a mean sensitivity of 68% and a mean specificity of 74%; studies that excluded patients on digoxin had a mean sensitivity of 72% and a mean specificity of 69%. Comparing these results with the average sensitivity of 67% and specificity of 72% as well as to themselves, only LVH and resting ST depression appear to lower specificity. However, other studies in apparently healthy persons (see below) have suggested that digoxin also lowers specificity.

These meta-analyses provide only indirect evidence regarding these potentially important factors, because they assume that the study populations were otherwise equal with respect to characteristics that might influence test performance. This critical assumption has not been confirmed and may not be true.

The wide variability in test performance apparent from this meta-analysis makes it important that clinicians use proper methods for testing and analysis. Upsloping ST depression should be considered borderline or negative. Hyperventilation is no longer routinely recommended before testing.

## *Influence of Other Factors on Test Performance*

**Drugs Digoxin.** Digoxin produces abnormal exercise-induced ST depression in 25% to 40% of apparently healthy normal subjects.<sup>30,31</sup> The prevalence of abnormal responses is directly related to age. Although patients must be off the medication for at least 2 weeks for its effect to be gone, it is not necessary to do so before diagnostic testing.<sup>32</sup>

**$\beta$ -Blocker Therapy.** Despite the marked effect of  $\beta$ -blockers on maximal exercise heart rate, with patients subgrouped according to  $\beta$ -blocker administration initiated by their referring physician, no differences in test performance were found in a consecutive group of men being evaluated for possible CAD.<sup>33</sup> For routine exercise testing, it appears unnecessary for physicians to accept the risk of stopping  $\beta$ -blockers before testing when a patient exhibits possible symptoms of ischemia. However, exercise testing in patients on  $\beta$ -blockers may have reduced diagnostic value due to inadequate heart rate response.

**Other Drugs.** Various medications, including antihypertensive agents and vasodilators, can affect test performance by altering the hemodynamic response of blood pressure. Acute administration of nitrates can attenuate the angina and ST depression associated with myocardial ischemia. Flecainide has been associated with exercise-induced ventricular tachycardia (VT).<sup>34,35</sup>

## *Electrocardiographic Abnormalities*

**Left Bundle Branch Block** Exercise-induced ST depression usually occurs with left bundle branch block and has no association with ischemia.<sup>36</sup> Even up to 1 cm of ST depression can occur in healthy normal subjects.

**Right Bundle Branch Block** Exercise-induced ST depression usually occurs with right bundle branch block in the anterior chest leads ( $V_1$  through  $V_3$ ) and is not associated with ischemia.<sup>37</sup> However, in the left chest leads ( $V_5$  and  $V_6$ ) or inferior leads (II and aVF), its test characteristics are similar to those of a normal resting ECG.

**Left Ventricular Hypertrophy With Repolarization Abnormalities** As discussed previously, this ECG abnormality is associated with a decreased specificity of exercise testing, but sensitivity is unaffected. Therefore, a standard exercise test may still be the first test, with referrals for further tests only indicated in patients with an abnormal test result.

**Resting ST Depression** Resting ST-segment depression has been identified as a marker for adverse cardiac events in patients with and without known CAD.<sup>38-42</sup> Miranda et al<sup>43</sup> performed a retrospective study of 223 patients without clinical or electrocardiographic evidence of prior myocardial infarction. Women, patients with resting ECGs showing left bundle branch block or LVH, and those on digoxin or with valvular or congenital heart disease were excluded. Ten percent had persistent resting ST-segment depression and nearly twice the prevalence of severe coronary disease (30%) than those without resting ST-segment depression (16%). Two millimeters of additional exercise-induced ST-segment depression or

downsloping depression of 1 mm or more in recovery were particularly useful markers in these patients for diagnosis of any coronary disease (likelihood ratio 3.4, sensitivity 67%, specificity 80%). Smaller studies by Kansal et al<sup>44</sup> and Harris et al<sup>45</sup> had similar results.

Other studies have found decreased specificity in patients with resting ST-segment depression.<sup>46,47</sup> However, these studies included bundle branch blocks, previous infarction, “non-specific” ST-T changes such as T-wave inversions and/or flattening; additionally, those with LVH and resting ST-segment depression were not considered separately. The three studies that considered isolated resting ST depression and the meta-analysis support the conclusion that additional exercise-induced ST-segment depression in patients with resting ST-segment depression represents a reasonably sensitive indicator of CAD.

### *Overview of Confounders: Digoxin, Resting ST Depression, and Left Ventricular Hypertrophy*

The meta-analysis was reprocessed, considering the status of digoxin, resting ST depression, and LVH as exclusion criteria in the 58 studies that excluded patients with a myocardial infarction. Only those that included at least 100 patients and provided patient numbers as well as both sensitivity and specificity were considered in the average. Those studies with less than 100 patients were averaged together as “other” studies. The results are summarized in Tables 7 to 13. Although specificity is lowered in the presence of resting ST depression of less than 1 mm, the standard exercise test is still the first test option. There is a divergence of opinion regarding patients taking digoxin with less than 1 mm of ST depression and those with LVH with less than 1 mm of resting ST depression, but the standard exercise test is still a reasonable first test opinion in such patients. If the test result is negative, the likelihood of CAD is substantially reduced, but if an abnormal response is obtained, further testing is indicated. Resting ST-segment depression is a marker for a higher prevalence of severe CAD and is associated with a poor prognosis; standard exercise testing continues to be diagnostically useful in these patients. In the published data there are few patients with resting ST depression greater than 1 mm. It was the consensus of the committee that exercise testing is unlikely to provide important diagnostic information in such patients and that exercise imaging modalities are preferred in this subset of patients.

### *ST-Segment Interpretation Issues*

**Lead Selection** Lead V<sub>5</sub> alone consistently outperforms the inferior leads and the combination of lead V<sub>5</sub> with II, because lead II has a high false-positive rate. In patients without prior myocardial infarction and normal resting ECGs, the precordial leads alone are a reliable marker for CAD, and monitoring of inferior limb leads adds little additional diagnostic information. In patients with a normal resting ECG,

exercise-induced ST-segment depression confined to the inferior leads is of little value for identification of coronary disease.<sup>48</sup>

**Upsloping ST Depression** Downsloping ST-segment depression is a stronger predictor of CAD than horizontal depression, and both are more predictive than upsloping depression. However, patients with slowly upsloping ST-segment depression, for example, when the slope is less than 1 mV/s, probably have an increased probability of coronary disease.<sup>49,50</sup> If a slowly ascending slope is used as a criterion for abnormal, the specificity of exercise testing will be decreased (more false-positive results), although the test becomes more sensitive. The committee favored the use of the more commonly used definition for a positive test: 1 mm of horizontal or downsloping ST depression (zero or negative slope visually).

**ST Elevation** Early repolarization is a common resting pattern of ST elevation in normal persons. Exercise-induced ST-segment elevation is always considered from the baseline ST level. ST elevation is relatively common after a Q-wave infarction, but ST elevation in leads without Q waves occurs in only 1 of 1000 patients seen in a typical exercise laboratory.<sup>51–57</sup> ST elevation on a normal ECG (other than in aVR or V<sub>1</sub>) represents transmural ischemia (caused by spasm or a critical lesion), is very rare (0.1% in a clinical lab), and in contrast to ST depression is very arrhythmogenic and localizes the ischemia. When it occurs in leads V<sub>2</sub> through V<sub>4</sub>, the left anterior descending artery is involved, in the lateral leads the left circumflex and diagonals are involved; and in leads II, III, and aVF the right coronary artery is involved. When the resting ECG shows Q waves of an old myocardial infarction, the significance of ST elevation is controversial. Some studies have suggested that ST elevation is due to wall motion abnormalities<sup>58,59</sup>; other studies have found it to be a marker of residual viability in the infarcted area.<sup>60–62</sup> Accompanying ST depression in such patients can be due to a second area of ischemia or reciprocal changes.

**R-Wave Changes** Many factors affect the R-wave amplitude response to exercise,<sup>63</sup> and the response does not have diagnostic significance.<sup>64,65</sup> R-wave amplitude typically increases from rest to submaximal exercise, perhaps to a heart rate of 130 beats per minute (bpm), then decreases to a minimum at maximal exercise.<sup>66</sup> If a patient were limited by objective signs or subjective symptoms, R-wave amplitude would increase from rest to such an end point. Such patients may be demonstrating a normal R-wave response but are classified as abnormal because of a submaximal effort. Exercise-induced changes in R-wave amplitude have no independent predictive power but are associated with CAD because such patients are often submaximally tested, and an R-wave decrease normally occurs at maximal exercise. Adjusting the amount of ST-segment depression by the R-wave height has not been shown to consistently improve the diagnostic value of exercise-induced ST depression.

**Heart Rate Adjustment** Several methods of heart rate adjustment have been proposed to increase the diagnostic accuracy of the exercise ECG. The maximal slope is computed

either manually<sup>67</sup> or by computer.<sup>68</sup> A second technique divides the difference between ST depression at peak exercise by the exercise-induced increase in heart rate.<sup>69,70</sup> Although the initial reports were promising, neither meta-analysis<sup>25</sup> nor a subsequent study<sup>71</sup> found convincing evidence of benefit. The potential explanations for these discordant findings are detailed elsewhere.<sup>71,72</sup> As described in sections III and IV, it is more important to consider exercise capacity rather than exercise heart rate in interpretation of exercise tests.

**Computer Processing** Although computer processing of the exercise ECG can be helpful, it can result in a false-positive indication of ST depression.<sup>73</sup> To avoid this problem, the physician should always be provided with ECG recordings of the raw unprocessed ECG data for comparison with any averages the exercise test monitor generates. It is preferable that averages always be contiguously preceded by the raw ECG data. The degree of filtering and preprocessing should always be presented along with the ECG recordings and should be compared with the AHA recommendations (0 to 100 Hz using notched power line frequency filters). It is preferable that the AHA standards be the default setting. All averages should be carefully labeled and explained, particularly those that simulate raw data. Simulation of raw data with averaged data should be avoided. Obvious breaks should be inserted between averaged ECG complexes. Averages should be check marked to indicate the PR isoelectric line as well as the ST measurement points. None of the computerized scores or measurements have been sufficiently validated to recommend their widespread use.

### III. Risk Assessment and Prognosis in Patients With Symptoms or a Prior History of Coronary Artery Disease

#### Class I

1. Patients undergoing initial evaluation with suspected or known CAD. Specific exceptions are noted below in Class IIb.
2. Patients with suspected or known CAD previously evaluated with significant change in clinical status.

#### Class IIb

1. Patients with the following ECG abnormalities:
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - Greater than 1 mm of resting ST depression
  - Complete left bundle branch block
2. Patients with a stable clinical course who undergo periodic monitoring to guide treatment.

#### Class III

1. Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization.

### *Risk Stratification: General Considerations*

Risk or prognostic stratification is one of the pivotal activities in medical practice. Virtually all patient management decisions are driven by the clinician's assessment of the patient's prognosis. During the initial encounter, the physician collects a standard data set of history, physical exam, and laboratory test data items. Using these data, the physician formulates a working diagnosis and risk assessment and selects an initial management strategy.<sup>98</sup> This strategy may consist of additional noninvasive testing, referral for prompt cardiac catheterization, or performance of a therapeutic trial. The additional data resulting from these management steps may affirm the initial risk assessment, cause it to be modified, or result in a completely revised risk assessment. The updated risk assessment in turn may indicate the need for further testing and/or therapy. Each additional patient-physician encounter provides an opportunity to update the risk assessment and modify the therapeutic plan appropriately.

The most important implication of the foregoing for these guidelines is that risk stratification with the exercise test does not take place in isolation but as part of a process that includes more readily accessible (and sometimes less expensive) data from the clinical exam and other laboratory tests. Thus, the value of exercise testing for risk stratification must be considered in light of what is added to that which is already known about the patient's risk status.

Whereas prognosis typically refers to probability of survival, other outcomes such as freedom from myocardial infarction, symptom status, functional capacity, and other aspects of quality of life are equally important to many patients. Most research on exercise testing, however, has concentrated on the relation between test parameters and future survival (and, to a lesser extent, freedom from myocardial infarction). These outcomes will be primarily considered in this section of the guidelines.

### *Prognosis of Coronary Artery Disease: General Considerations*

CAD is a chronic disorder with a natural history that spans multiple decades. In each affected individual the disease typically cycles in and out of a number of clinically defined phases: asymptomatic or presymptomatic, stable angina, progressive angina, unstable angina, or acute myocardial infarction. Although the specific approach to risk stratification of the coronary disease patient can vary according to the phase of the disease in which the patient presents, some general concepts apply across the coronary disease spectrum.

Conceptually the probability of cardiac death in a patient with CAD can be viewed as the sum of the risks at the time of evaluation (the current risk state) and the risk that the disease will progress over time to a higher or lower risk state. The patient's current risk state is a function of five major types of prognostic measures (Table 14). The strongest predictor of long-term survival with CAD is function of the left ventricle. In particular, the extent of damage or dysfunction and the success

**Table 14.** Prognostic Factors for Patients With Coronary Disease

Prognostic factors for current risk state
Left ventricular function/damage
History of prior MI
Pathologic Q waves on the resting ECG
Congestive heart failure symptoms
Cardiomegaly on the chest x-ray
Ejection fraction
End-systolic volume
Regional LV wall motion abnormalities
Conduction disturbances on the ECG
Mitral regurgitation
Exercise duration/tolerance
Severity of CAD
Anatomic extent and severity of CAD
Collateral vessels present
Transient ischemia on ambulatory monitor
Exercise- or stress-induced ST deviation
Coronary plaque event
Progressive or unstable ischemic symptoms
Transient ischemia on resting ECG
Electrical stability
Ventricular arrhythmias
General health
Age
Noncoronary comorbidity
Prognostic factors for change in risk state
Factors predisposing to disease progression
Smoking
Hyperlipidemia
Diabetes mellitus
Hypertension
Other genetic/metabolic factors

MI indicates myocardial infarction; ECG, electrocardiogram; LV, left ventricular; and CAD, coronary artery disease.

of mechanisms used by the cardiovascular system to compensate for that damage are of paramount importance. Many different clinical and laboratory parameters provide information about the extent of left ventricular dysfunction (Table 14). Ejection fraction is the most commonly used measure, but it alone does not completely describe the prognostic information in left ventricular function. Another group of prognostic factors describes the anatomic extent and severity of atherosclerotic involvement of the coronary tree. The number of diseased vessels is the most common measure of this domain. More details about the coronary anatomy add important prognostic information to this simple measure. A third group of prognostic factors provides evidence of a recent coronary plaque rupture, indicating a substantially increased short-term risk for cardiac death or nonfatal myocardial infarction. Worsening clinical symptoms with unstable features is the major clinical marker of a plaque event. The fourth group of prognostic factors is related to the presence of electrical instability of the myocardium and the propensity for malignant ventricular arrhythmia. The final group of prognostic factors describes general health and noncoronary comorbidity.

The probability that a given patient will progress to a

higher- or lower-risk disease state depends primarily on factors related to the aggressiveness of the underlying atherosclerotic process (Table 14). Patients with the major cardiac risk factors, including smoking, hypercholesterolemia, diabetes mellitus, and hypertension, are most likely to evidence progressive atherosclerosis with repeated coronary plaque events. Patients with symptomatic coronary disease at a younger age also may have a more aggressive disease process.

A growing body of pathological, angiographic, angioscopic, and intravascular ultrasonographic data support a pathophysiological model in which most major cardiac events (sudden death, acute myocardial infarction, unstable angina) are initiated by microscopic ruptures of high-risk or vulnerable atherosclerotic plaques. Characteristically, vulnerable plaques have a cholesterol gruel core and a thin fibrous cap. Various nonspecific factors may act as triggers and cause a vulnerable plaque to rupture at thinned sites around the shoulders of the cap. This exposes inner plaque material to the flowing intra-arterial blood and initiates formation of a platelet-fibrin thrombus over the area of rupture. Clinically the rupture may seal without detectable sequelae, or the patient may experience worsening angina, acute myocardial infarction, or sudden cardiac death. Several lines of evidence have shown that the majority of vulnerable plaques appear “angiographically insignificant” before rupture (ie, less than 75% diameter stenosis). In contrast, most “significant” plaques (greater than or equal to 75% stenosis) visualized at angiography are at low risk for plaque rupture. Thus, the ability of stress testing of any type to detect vulnerable atherosclerotic lesions may be limited by the smaller size and lesser effect on coronary blood flow of these plaques and may explain the occasional acute coronary event that may occur not long after a negative treadmill test.

### *Risk Stratification With the Exercise Test*

The major exercise ECG testing measures that have been proposed as prognostic markers are listed in Table 15. Because the exercise test is a diagnostic tool rather than a therapy, its effect on patient outcomes is necessarily indirect. To the extent that the test guides clinicians to select more appropriate or effective therapies, the exercise test will improve outcomes. However, no randomized trials of exercise testing versus no exercise testing have been performed. The entire evidence base for exercise testing therefore consists of observational studies. No direct evidence links different exercise testing strategies with differing outcomes.

As described previously, the risks of exercise testing in appropriately selected candidates are extremely low. Thus, the main arguments for not performing an exercise test in many clinical situations are that the information provided would not justify the extra costs of obtaining that information (ie, the test would not be cost-effective in that given situation) and/or the test might provide misleading information that could lead to inappropriate or unnecessary additional testing or therapy (both of which may have higher risks than exercise testing).

In reviewing the published evidence in this area, the



**Table 15.** Measurements Available From the Exercise Treadmill Test

Electrocardiographic
Maximum ST depression
Maximum ST elevation
ST-depression slope (downsloping, horizontal, upsloping)
Number of leads showing ST changes
Duration of ST deviation into recovery
ST/HR indexes
Exercise-induced ventricular arrhythmias
Time to onset of ST deviation
Hemodynamic
Maximum exercise heart rate
Maximum exercise systolic blood pressure
Maximum exercise double product (HR × BP)
Total exercise duration
Exertional hypotension (drop below preexercise value)
Chronotropic incompetence
Symptomatic
Exercise-induced angina
Exercise-limiting symptoms
Time to onset of angina

HR indicates heart rate; and BP, blood pressure.

subcommittee focused on studies that examined hard cardiac outcome events (death alone or death plus myocardial infarction) and had at least five (and preferably 10) outcome events for every candidate variable evaluated. Use of appropriate multivariable statistical techniques was also a requirement for selection. Special emphasis was given to studies that evaluated the incremental effects of the exercise test beyond the prognostic information available from the clinical evaluation (history, physical examination, and resting 12-lead ECG).

**Symptomatic Patients With Nonacute Coronary Artery Disease** Unless cardiac catheterization is indicated, patients with suspected or known CAD and new or changing symptoms suggesting ischemia should generally undergo exercise testing to assess the risk of future cardiac events. As described in the ACC/AHA guidelines for percutaneous transluminal coronary angioplasty and for coronary artery bypass grafting, documentation of exercise- or stress-induced ischemia is desirable for most patients who are being evaluated for revascularization.<sup>3,4</sup>

Choice of initial stress testing modality should be based on evaluation of the patient's resting ECG, physical ability to perform exercise, and local expertise and technology. For risk assessment, the exercise test should be the standard initial mode of stress testing used in patients with a normal ECG who are not taking digoxin.<sup>99-101</sup> Patients with widespread resting ST depression (greater than or equal to 1 mm), complete left bundle branch block, ventricular paced rhythm, or preexcitation should usually be tested with an imaging modality. Exercise testing may still provide useful prognostic information in patients with these ECG changes but cannot be used to identify ischemia. Patients unable to exercise because of physical limitations affecting exercise capacity (eg, arthritis, amputations, severe peripheral vascular disease, severe chronic obstructive pulmonary

disease, general debility), should undergo pharmacological stress testing in combination with imaging.

In patients with suspected or known symptomatic coronary disease, exercise testing can be used to estimate prognosis and assist in management decisions. The primary evidence in this area consists of seven observational studies of the prognostic value of the exercise ECG (Table 16). An overview of the available literature has shown some inconsistency among studies in the exercise variables identified as independent prognostic factors. These differences are at least partially attributable to differences in the spectrum of patients referred for testing, the amount of crossover to coronary revascularization, and the sample size/statistical power of the analysis.<sup>109</sup>

One of the strongest and most consistent prognostic markers identified in exercise testing is maximum exercise capacity, which is at least partly influenced by the extent of resting left ventricular dysfunction and the amount of further LV dysfunction induced by exercise. However, the relation between exercise capacity and LV function is complex, because exercise capacity is also affected by age, general physical conditioning, comorbidities, and psychological state (especially the presence of depression).<sup>110</sup> Several exercise parameters can be used as markers of exercise capacity (Table 15), including maximal exercise duration, maximum MET level achieved, maximum workload achieved, maximum heart rate, and double product. When interpreting the exercise test, it is very important to take exercise capacity into account; the specific variable used to summarize this aspect of test performance is less important. The translation of exercise duration or workload into METs (oxygen uptake expressed in multiples of basal oxygen uptake, 3.5 O<sub>2</sub> mL/kg per minute) has the advantage of providing a common measure of performance regardless of the type of exercise test or protocol used. Although such translations are based on approximations and are not as accurate for individual patients as measured maximal oxygen uptake (VO<sub>2max</sub>), VO<sub>2max</sub> has not been studied for prognostic purposes in large series of patients with chest pain.

A second group of prognostic exercise testing markers relates to exercise-induced ischemia. These markers include exercise-induced ST-segment depression, exercise-induced ST-segment elevation (in leads without pathological Q waves and not in aVR), and exercise-induced angina. In a large exercise testing cohort, exercise ST deviation (elevation or depression) best summarized the prognostic information from this area.<sup>103</sup> Other less powerful prognostic ST variables included the number of leads showing significant ST-segment depression, configuration of the exercise-induced ST depression (downsloping, horizontal, or upsloping), and duration of ST deviation into the recovery phase of the test.

Two early influential studies of exercise treadmill testing and prognosis were reported from the Duke Cardiovascular Disease Databank and the Coronary Artery Surgery Study Registry. Using the Duke database, McNeer and coworkers<sup>111</sup> demonstrated that an "early positive" exercise test result (ST depression greater than or equal to 1 mm in the first two stages of the Bruce protocol) identified a high-risk population,

**Table 16.** Prognostic Studies of Exercise Testing

Study	Years of Enrollment	N	Length of Follow-up (y)	Independent Prognostic Factors
CASS <sup>102</sup>	1974–1979	4083	5	1. CHF 2. TM stage 3. Exercise-induced ST depression
Duke <sup>103</sup>	1969–1981	2842	5	1. Exercise-induced ST deviation 2. Exercise-induced angina 3. Exercise duration
Long Beach VA <sup>104</sup>	1984–1990	2546	5	1. CHF/digoxin use 2. METs 3. Max SBP 4. Exercise-induced ST depression
Italian CNR <sup>105</sup>	1976–1979	1083	5.5	1. Q wave 2. Prior MI 3. Effort ischemia 4. Exercise capacity
Belgian <sup>106</sup>	1978–1985	470	5	1. Age 2. Score of maximum HR, ST depression, angina, watts, ST slope
German <sup>107</sup>	1975–1978	1238	4.5	1. Exercise tolerance (watts) 2. Maximum HR
Seattle Heart Watch <sup>108</sup>	1971–1974	733	3.3	1. CHF 2. Maximum double product 3. Max SBP 4. Angina 5. Resting ST depression

CASS indicates Coronary Artery Surgery Study; CHF, congestive heart failure; TM, treadmill; VA, Veterans Administration; METs, metabolic equivalents; Max, maximum; SBP, systolic blood pressure; CNR, Consiglio Nazionale Ricerche; MI, myocardial infarction; and HR, heart rate.

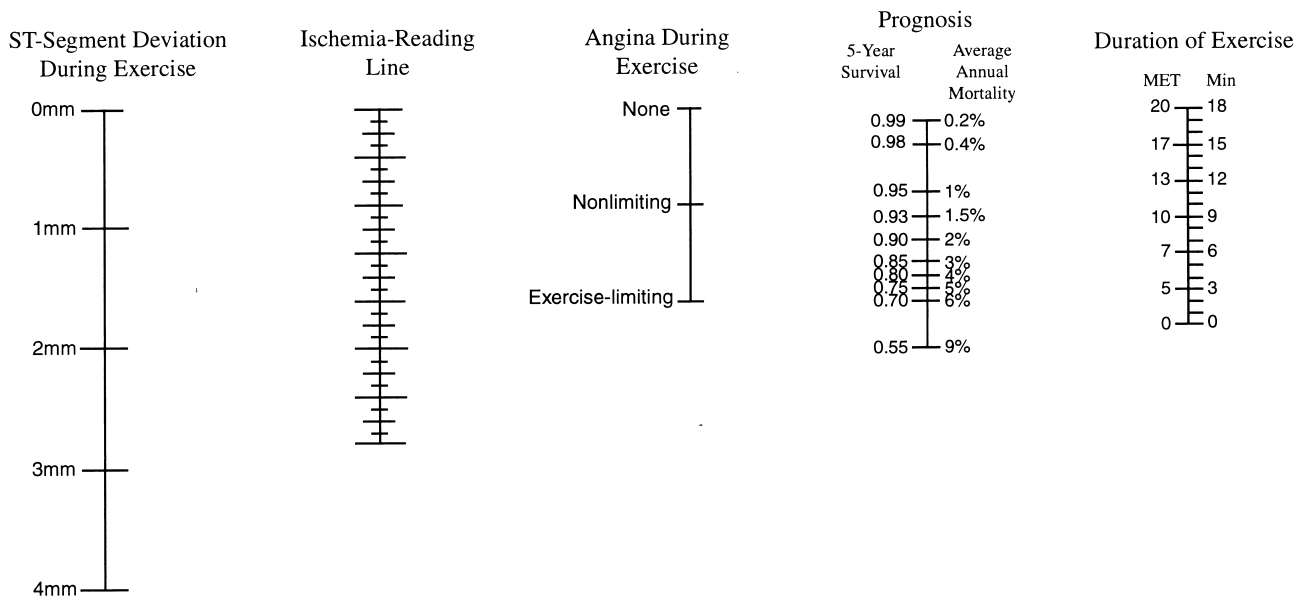
whereas patients who could exercise into stage IV were at low risk regardless of the ST response. Weiner and colleagues,<sup>102</sup> using the Coronary Artery Surgery Study Registry, analyzed 4083 medically treated patients and identified 12% as high risk on the basis of greater than or equal to 0.1 mV exercise-induced ST-segment depression and inability to complete stage I of the Bruce protocol. These patients had an average annual mortality rate of 5% per year. Patients who could exercise to at least stage III of the Bruce protocol without ST-segment changes (34%) constituted the low-risk group (estimated annual mortality, less than 1%).

Several recent studies have attempted to incorporate multiple exercise variables into a prognostic score. Using Cox regression analysis, Mark and colleagues<sup>103</sup> created the Duke treadmill score using data from 2842 inpatients with known or suspected CAD who underwent exercise tests before diagnostic angiography. None of the patients had prior revascularization or recent myocardial infarction. The resulting treadmill score was calculated:

treadmill score = exercise time – 5 × (amount of ST-segment deviation in millimeters) – 4 × exercise angina index (which had a value of 0 if there was no exercise angina, 1 if exercise angina occurred, and 2 if angina was the reason the patient stopped exercising).

The high-risk group defined by this score (score less than or equal to –11, 13% of patients) had an average annual cardiovascular mortality greater than or equal to 5%. Low-risk patients had a score greater than or equal to +5 (34% of patients) and an average annual cardiovascular mortality rate of 0.5%. In multivariable Cox regression analysis, the Duke treadmill score added significant prognostic information to the standard clinical data plus the major catheterization variables (number of diseased vessels, ejection fraction). To improve ease of use, the Duke treadmill score was converted into a nomogram (Fig 2). The score has subsequently been validated in 613 outpatients at Duke who did not all go on to coronary angiography and in exercise-testing populations at several other centers.<sup>112–114</sup> The treadmill score was even more useful for outpatients: approximately two thirds had treadmill scores indicating low risk. Preliminary data suggest that the score works equally well with men and women.<sup>115</sup> A limitation is the small number of elderly patients represented in studies evaluating this score.

Froelicher and colleagues<sup>104</sup> have developed a prognostic score using 2546 patients from Long Beach Veterans Administration Hospital. This score includes two variables in common with the Duke treadmill score (exercise duration or the MET equivalent and millimeters of ST changes) and two different variables (drop in exercise systolic blood pressure



**Figure 2.** Nomogram of the prognostic relations embodied in the treadmill score. Prognosis is determined in five steps: (1) The observed amount of exercise-induced ST-segment deviation (the largest elevation or depression after resting changes have been subtracted) is marked on the line for ST-segment deviation during exercise. (2) The observed degree of angina during exercise is marked on the line for angina. (3) The marks for ST-segment deviation and degree of angina are connected with a straight edge. The point where this line intersects the ischemia-reading line is noted. (4) The total number of minutes of exercise in treadmill testing according to the Bruce protocol (or the equivalent in multiples of resting oxygen consumption [METs] from an alternative protocol) is marked on the exercise-duration line. (5) The mark for ischemia is connected with that for exercise duration. The point at which this line intersects the line for prognosis indicates the 5-year cardiovascular survival rate and average annual cardiovascular mortality for patients with these characteristics. Patients with <1 mm of exercise-induced ST-segment depression should be counted as having 0 mm. Angina during exercise refers to typical effort angina or an equivalent exercise-induced symptom that represents the patient's presenting complaint. This nomogram applies to patients with known or suspected coronary artery disease, without prior revascularization or recent myocardial infarction, who undergo exercise testing before coronary angiography. Modified from Mark et al.<sup>112</sup>

below resting value and history of congestive heart failure or use of digoxin). The score is calculated as:

$5 \times (\text{CHF/Dig [yes=1; no=0]}) + \text{exercise-induced ST depression in millimeters} + \text{change in systolic blood pressure score} - \text{METs}$ , where systolic blood pressure = 0 for increase greater than 40 mm Hg, 1 for increase of 31 to 40 mm Hg, 2 for increase of 21 to 30 mm Hg, 4 for increase of 0 to 11 mm Hg, and 5 for a reduction below standing systolic preexercise blood pressure.

Using this score, 77% of the Long Beach VA population were at low risk (with less than 2% average annual mortality),

18% were at moderate risk (average annual mortality, 7%), and 6% were at high risk (average annual mortality, 15%).

There is no compelling evidence in patients who are classified as low risk based on clinical and exercise testing information 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.<sup>114</sup>

The optimal testing strategy remains less well defined in women. Until adequate data are available to resolve this issue, it is reasonable to use exercise testing for risk stratification in women as readily as in men with proper consideration of the importance of the pretest risk state.

One important issue that has received inadequate study is the relative value of exercise testing for predicting future cardiac deaths versus future myocardial infarctions (fatal or nonfatal). Pathophysiological considerations based on the coronary plaque event model described earlier suggest that acute myocardial infarctions caused by rupture of a relatively small vulnerable plaque would be difficult to predict accurately using exercise test parameters. For example, in one large cohort the predictive power of exercise ST depression for cardiovascular death alone and cardiovascular death plus nonfatal myocardial infarction were almost identical, despite the fact that adding

**Table 17.** Short-Term Risk of Death or Nonfatal Infarction in Patients With Unstable Angina

High Risk	Intermediate Risk	Low Risk
At least one of the following features must be present	No high-risk feature but any of the following features must be present:	No high- or intermediate-risk feature but may have any of the following features:
Prolonged, ongoing (>20 min) pain at rest	Prolonged (>20 min) resting angina, now resolved, with moderate or high likelihood of CAD	Increased frequency, severity, or duration of angina
Pulmonary edema, most likely related to ischemia	Resting angina (>20 min or relieved with rest or sublingual nitroglycerin)	Angina provoked at a lower threshold
Angina at rest with dynamic ST changes $\geq 1$ mm	Nocturnal angina	New-onset angina with onset 2 weeks to 2 months before presentation
Angina with new or worsening MR murmur	Angina with dynamic T-wave changes	Normal or unchanged ECG
Angina with $S_3$ or new/worsening rales	New-onset CCSC III or IV angina in the past 2 weeks with moderate or high likelihood of CAD	
Angina with hypotension	Pathological Q waves or resting ST depression $\geq 1$ mm in multiple-lead groups (anterior, inferior, lateral)	
	Age >65 y	

This table offers general guidance and illustration rather than rigid algorithms. Estimation of the short-term risks of death and nonfatal myocardial infarction in unstable angina is a complex multivariable problem that cannot be fully specified in a table such as this. From AHCPR Clinical Practice Guideline, Number 10.<sup>14</sup> CAD indicates coronary artery disease; MR, mitral regurgitation; ECG, electrocardiogram; and CCSC, Canadian Cardiovascular Society class.

the nonfatal events should have substantially boosted the predictive power (ie, more outcome events should yield better power in prognostic models).<sup>103</sup> In another exercise cohort with long-term follow-up, no relation between exercise capacity and the probability of a follow-up nonfatal myocardial infarction was found.<sup>116</sup> Available data suggest that the exercise test results give a better guide to the likelihood that a patient will die (given that a plaque event occurs) than they do to the likelihood of a nonfatal myocardial infarction. This presumably occurs because patients with severe and/or extensive coronary disease are much less likely to withstand the challenge to their myocardial circulation caused by a major plaque event. However, it is difficult to relate the pathophysiology of coronary events directly to the results of observational epidemiological studies. There may, for example, be a correlation between the presence and number of nonobstructive vulnerable or high-risk plaques and the total coronary atherosclerotic burden (obstructive and nonobstructive). Exercise test results are, in turn, correlated with the presence and severity of obstructive coronary disease.

**Patients With Unstable Angina** Unstable angina represents an acute phase in the life cycle of the patient with chronic coronary disease. It may be a presenting feature or may interrupt a quiescent phase of clinically manifested disease. The natural history of unstable angina involves progression to either death or myocardial infarction on the one hand or return to the chronic stable phase of CAD on the other. These events typically play out over a period of 4 to 6 weeks. Thus, the role and timing of exercise testing in unstable angina relates to this acute and convalescent period.

The Agency for Health Care Policy and Research<sup>14</sup> recently published guidelines for the diagnosis and treatment of unstable angina, which have been endorsed by the ACC and the

AHA. A clinical risk stratification algorithm useful for selecting the initial management strategy is seen in Table 17. Patients are separated into low-, moderate-, or high-risk groups based on history, physical examination, and initial 12-lead ECG. Low-risk patients in this scheme can typically be treated on an outpatient basis. Most moderate-risk patients can be cared for in a monitored hospital bed, while high-risk patients are typically admitted to an intensive care unit.

Exercise or pharmacological stress testing should generally be an integral part of the evaluation of low-risk patients with unstable angina who are evaluated on an outpatient basis. In most cases testing should be performed within 72 hours of presentation. In low- or moderate-risk patients with unstable angina who have been hospitalized for evaluation, exercise or pharmacological stress testing should generally be performed unless cardiac catheterization is indicated. Testing can be performed when patients have been free of active ischemic or heart failure symptoms for a minimum of 48 hours.<sup>14</sup> In general, as with patients with stable angina, the exercise treadmill test should be the standard mode of stress testing in patients with a normal resting ECG who are not taking digoxin.

A majority of patients with unstable angina have an underlying ruptured plaque and significant CAD. Some have a ruptured plaque without angiographically significant lesions in any coronary segment. Still others have no evidence of a ruptured plaque or atherosclerotic coronary lesions. Very little evidence exists with which to define the safety of early exercise testing in unstable angina.<sup>117</sup> In addition, many available studies contain both unstable angina and post-myocardial infarction patients.

The limited evidence available supports the use of exercise

testing in patients with appropriate indications as soon as the patient has stabilized clinically. Larsson and colleagues<sup>118</sup> compared a symptom-limited predischARGE (3 to 7 days) exercise test with a test performed at 1 month in 189 patients with unstable angina or non-Q-wave infarction. The prognostic value of the two tests was similar, but the earlier test identified additional patients who would experience events during the period before the 1-month exercise test. In this population these earlier events represented one half of all events occurring during the first year.

The Research on Instability in Coronary Artery Disease (RISC) study group<sup>119</sup> examined the use of predischARGE symptom-limited bicycle exercise testing in 740 men admitted with unstable angina (51%) or non-Q-wave myocardial infarction (49%). The major independent predictors of 1-year infarction-free survival in multivariable regression analysis were the number of leads with ischemic ST-segment depression and peak exercise workload achieved.

### *Use of Exercise Test Results in Patient Treatment*

As a diagnostic technique, exercise testing has no direct effect on patient outcomes. It is only through judicious use of the information gained that the test is linked with improved outcomes. Thus, the post-exercise test prognosis or risk points to a particular management strategy that is viewed as most appropriate (based on expected outcomes).

There is little evidence linking different exercise-defined risk groups with alternative classes of medical therapy. However, the results of exercise testing may be used to titrate medical therapy up to a desired level. The other major management step addressed by exercise testing is whether to proceed with additional testing (which might ultimately lead to revascularization). An important caveat is that decisions about additional testing (especially cardiac catheterization) must take into account patient preferences and comorbidity. Patients with severe coexisting diseases that make them poor candidates for revascularization in general should be managed without invasive evaluation, regardless of the results of stress testing.

Patients with a low-risk exercise test result (eg, those with a predicted average annual cardiac mortality less than or equal to 1% per year) can be treated medically without need for referral to cardiac catheterization. Patients with a high-risk exercise test result (eg, patients with a strongly positive test result in Fig 2 or predicted average annual cardiac mortality greater than or equal to 4% per year) should usually be referred for cardiac catheterization. Patients with an intermediate-risk exercise test result (eg, predicted average annual cardiac mortality of 2% to 3% per year) should be referred for additional testing, either cardiac catheterization or an exercise imaging study. An intermediate-risk stress test result in a patient with evidence of left ventricular dysfunction should usually prompt referral for cardiac catheterization.

## **IV. After Myocardial Infarction**

### **Class I**

1. Before discharge for prognostic assessment, activity prescription, evaluation of medical therapy (submaximal at about 4 to 7 days).\*
2. Early after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the predischARGE exercise test was not done (symptom-limited/about 14 to 21 days).\*
3. Late after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the early exercise test was submaximal (symptom-limited/about 3 to 6 weeks).\*

### **Class IIa**

1. After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization.

### **Class IIb**

1. Before discharge in patients who have undergone cardiac catheterization to identify ischemia in the distribution of a coronary lesion of borderline severity.
2. Patients with the following ECG abnormalities:
  - Complete left bundle branch block
  - Preexcitation syndrome
  - Left ventricular hypertrophy
  - Digoxin therapy
  - Greater than 1 mm of resting ST-segment depression
  - Electronically paced ventricular rhythm
3. Periodic monitoring in patients who continue to participate in exercise training or cardiac rehabilitation.

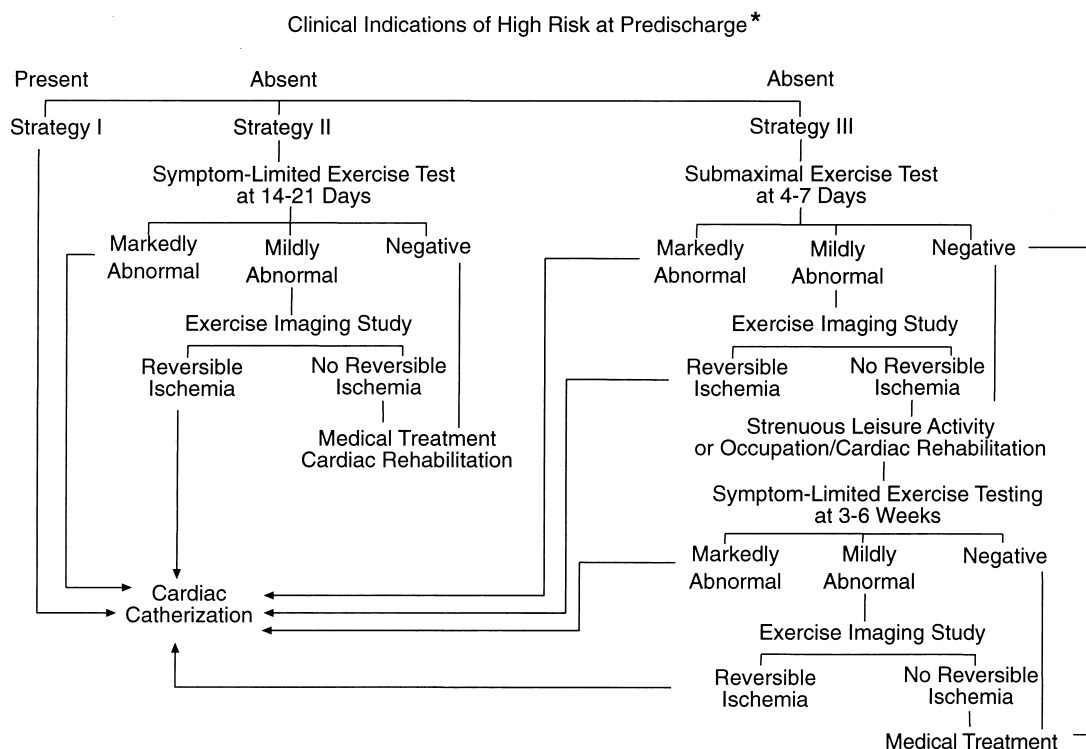
### **Class III**

1. Severe comorbidity likely to limit life expectancy and/or candidacy for revascularization.

The above recommendations, the text, and Fig 3 are largely based on the ACC/AHA guidelines for the management of patients with acute myocardial infarction.<sup>2</sup> Although some of the evidence is presented in more detail here and a few recent references are added, the committee did not feel that there was sufficient new evidence to justify a major revision of the previously published recommendations.

Exercise testing is useful in evaluation and treatment of patients after myocardial infarction. As therapies and treatment strategies for myocardial infarction have changed dramatically, particularly over the past decade, the current role of exercise testing must be viewed in the context of the patients who present for testing. Shorter hospital stays, widespread use

\*Exceptions are noted under Classes IIb and III.



\*Clinical indications of high risk include hypotension, congestive heart failure, recurrent chest pains, and inability to exercise.

of thrombolytic agents, greater use of revascularization strategies, and increased use of  $\beta$ -adrenergic blocking agents and angiotensin converting enzyme inhibitors continues to change the clinical presentation of the postinfarction patient.<sup>120–125</sup> Not all patients will have received each of these various therapies; hence, survivors of myocardial infarction are quite heterogeneous. The Canadian Assessment of Myocardial Infarction (CAMI) study<sup>121</sup> reported that among 3178 consecutive patients with acute myocardial infarction, 45% received thrombolytic agents, 20% underwent coronary angioplasty, and 8% had coronary artery bypass surgery. Medications at the time of hospital discharge included  $\beta$ -blockers in 61%, angiotensin converting enzyme inhibitors in 24%, and aspirin in 86%. Lavie et al<sup>122</sup> have documented increased use of these newer treatments, noting that a greater proportion of patients who undergo exercise testing after myocardial infarction tend to have inferior infarcts and Q-wave infarcts, are older, and have a greater functional capacity. It must also be realized that a large percentage of postinfarction patients will not undergo exercise testing due either to clinical instability or disabling comorbidities, eg, unstable angina, uncontrolled heart failure, uncontrolled arrhythmias, and neurological, orthopedic, or vascular impairment of the lower extremities. In the largest series to date, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) investigators<sup>123</sup> have reported that nearly 40% of the 10 219-patient cohort did not undergo exercise testing within 28 days of myocardial infarction. This and several other studies in patients who have received thrombolytic therapy<sup>126</sup> and those who have not<sup>127–129</sup>

**Figure 3.** Strategies for exercise test evaluation soon after myocardial infarction. If patients are at high risk for ischemic events, based on clinical criteria, they should undergo invasive evaluation to determine if they are candidates for coronary revascularization procedures (strategy I). For patients initially deemed to be at low risk at the time of discharge after myocardial infarction, two strategies for performing exercise testing can be used. One is a symptom-limited exercise test at 14 to 21 days (strategy II). If the patient is on digoxin or if the baseline electrocardiogram precludes accurate interpretation of ST-segment changes (eg, baseline left bundle branch block or left ventricular hypertrophy), then an initial exercise imaging study could be performed. The results of exercise testing should be stratified to determine the need for additional invasive or exercise perfusion studies. Another strategy (strategy III) is to perform a submaximal exercise test at 4 to 7 days after myocardial infarction or just before hospital discharge. The exercise test results could be stratified using the guidelines in strategy I. If the exercise test studies are negative, a second symptom-limited exercise test could be repeated at 3 to 6 weeks for patients undergoing vigorous activity during leisure time activities, at work, or exercise training as part of cardiac rehabilitation. The extent of reversible ischemia on the exercise imaging study should be considered before proceeding to cardiac catheterization. A small area contiguous to the infarct zone may not necessarily require catheterization. Modified from ACC/AHA guidelines.<sup>2</sup>

report that patients who are unable to perform an exercise test have a much higher adverse event rate than those who are able. With this background, the role of exercise testing after myocardial infarction will be presented. The use of exercise or pharmacological imaging studies (nuclear and echocardiography) are not discussed here, as they are presented in detail in the ACC/AHA guidelines for clinical use of cardiac radionu-

clide imaging,<sup>5</sup> guidelines for clinical application of echocardiography,<sup>6</sup> and guidelines for management of acute myocardial infarction.<sup>2</sup>

Exercise testing after myocardial infarction yields information in the following areas: (1) risk stratification and assessment of prognosis; (2) functional capacity for activity prescription after hospital discharge, including domestic and occupational work evaluation and exercise training as part of comprehensive cardiac risk reduction and rehabilitation; and (3) assessment of adequacy of medical therapy and the need to employ other diagnostic or treatment options.

### *Exercise Test Logistics*

**Exclusions From Testing** The absolute and relative contraindications to exercise testing are presented in Table 1. In patients with an abnormal resting ECG due to left bundle branch block, preexcitation syndrome, LVH, digoxin therapy, or those demonstrating major (greater than 1 mm) ST-segment depression or elevation, an exercise or pharmacological imaging study should be considered, as the accuracy of the exercise ECG in detecting provokeable ischemia is reduced.

**Timing and Protocol** Exercise tests can be characterized according to the time after myocardial infarction when the test is performed and the protocol used. The timing of the predischARGE exercise test continues to shorten, as does the hospital stay for patients with an uncomplicated myocardial infarction. PredischARGE exercise tests in the recent literature range from 5 to 26 days after infarction.<sup>126,129-132</sup> Exercise tests have been performed as early as 3 days after myocardial infarction<sup>124</sup>; however, the safety of this very early protocol has not been established. Postdischarge tests have been performed early (14 to 21 days), at 6 weeks,<sup>133</sup> or at 6 months after infarction.<sup>134</sup> The exercise protocols can be either submaximal or symptom-limited. Submaximal protocols have a predetermined end point often defined as a peak heart rate of 120 bpm, or 70% predicted maximum heart rate, or a peak MET level of 5.<sup>131</sup> Symptom-limited tests are designed to continue until the patient demonstrates signs and/or symptoms that necessitate termination of exercise (ie, angina, fatigue, greater than or equal to 2 mm of ST-segment depression, ventricular arrhythmias, or greater than or equal to a 10 mm Hg drop in systolic blood pressure from the resting blood pressure).<sup>135</sup> The most commonly used treadmill protocols are the modified Bruce, the modified Naughton, and the standard Bruce.<sup>131</sup> The ramp treadmill or cycle ergometer protocols offer the advantage of steady gradual increases in work rate and better estimation of functional capacity<sup>136</sup> but have not been widely studied in patients early after myocardial infarction.

Recent studies have evaluated symptom-limited protocols at 4 to 7 days after myocardial infarction and have included patients treated with thrombolytic agents. These studies demonstrate that such testing yields ischemic responses nearly twice as often as submaximal tests and are a better estimate of peak functional capacity.<sup>130,135,137</sup> Thus, early symptom-limited tests have the potential to be more useful in activity prescrip-

tion before discharge. However, the additive prognostic value from information obtained from the performance of symptom-limited protocols within days rather than weeks after myocardial infarction has not yet been established.

**Safety** Exercise testing after myocardial infarction appears to be safe. The incidence of fatal cardiac events, including fatal myocardial infarction and cardiac rupture, is 0.03%, nonfatal myocardial infarction and successfully resuscitated cardiac arrest is 0.09%, and complex arrhythmias, including VT, is 1.4%. Symptom-limited protocols have an event rate which is 1.9 times that of submaximal tests, although the overall fatal event rate is quite low.<sup>130,131,135</sup> The majority of the safety data are based on exercise testing performed more than 7 days after myocardial infarction. The number of patients reported at 4 to 7 days is more limited, and typically time is reported as a mean value or a range so that it is impossible to determine how many patients were studied at 4 days.

### *Risk Stratification and Prognosis*

The prognosis among survivors of myocardial infarction continues to improve, particularly in patients who have received thrombolytic therapy and revascularization during hospitalization. One-year postdischarge mortality in the CAMI study<sup>121</sup> was 8.4% and was distinctly lower in the 45% of patients who received thrombolytic therapy (3.7% mortality) and in the 28% who underwent coronary angioplasty (3% mortality) or coronary artery bypass surgery (3.7% mortality). Data from the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) trial<sup>138</sup> demonstrate that 57% of the 41 021 patients who received thrombolytic therapy had no complications (no recurrent ischemia, reinfarction, heart failure, stroke, or invasive procedures) at 4 days after myocardial infarction. The mortality rate at 1 month was 1% and at 1 year, 3.6%. Recurrent ischemia occurred in 7% of this group.

The improvement in 1-year mortality in patients who have received thrombolytic therapy is multifactorial. Such patients are (1) less likely to have severe three-vessel CAD; (2) have a smaller infarct size; and (3) frequently undergo coronary angiography in lieu of exercise testing. Consequently the patient population that presently undergoes predischARGE exercise testing in clinical trials of thrombolytic therapy is far different from less selected historical populations or concurrent patient populations not treated with thrombolytic therapy. Their low cardiac event rate following discharge is therefore not surprising and substantially reduces the predictive accuracy of early exercise testing.

There is limited evidence on the ability of exercise testing to risk stratify patients who have *not* received reperfusion in the current era. Although their subsequent mortality rates are lower than in patients treated in the prethrombolytic era because of therapeutic advances and revascularization, their absolute event rates are higher than in patients who have received thrombolytic therapy. Although the available evidence is limited, exercise testing presumably can still assist in the risk stratification of such patients.

**Table 18.** Meta-Analyses of Exercise Electrocardiographic Testing After Myocardial Infarction

Author (Year)	Number of Patients Who Underwent ETT	Number of Patients Treated With Thrombolysis	Type of Test	Timing After MI	Length of Follow-up	Outcome
Froelicher <sup>141</sup> (1987)	5331 Meta-analysis of 24 studies (1973–1986)	0	Treadmill or cycle	1.6–9.0 wk	0.25–5.70 y	Patients excluded from exercise testing had the highest mortality. Abnormal systolic blood pressure response and poor exercise capacity were predictive of poor prognosis. Submaximal or predischARGE testing has greater predictive power than postdischarge or maximal testing. Exercise-induced ST-segment depression is predictive of increased risk only in patients with inferior-posterior MI.
Shaw <sup>150</sup> (1996)	15,613 Meta-analysis (28 studies of exercise-ETT, 1980–1995)	10,067	Treadmill or cycle	1–6 wk	1 y	The odds ratio for cardiac death was significantly higher for patients with: <ul style="list-style-type: none"><li>• Exercise ST depression (or 1.7)</li><li>• Impaired systolic blood pressure (or 4.0)</li><li>• Limited exercise capacity (or 4.0)</li></ul> The rate of cardiac death or MI in persons with exercise-induced ST depression is lower in those receiving thrombolytic therapy compared with those without thrombolysis (8% vs 18%).

ETT indicates exercise treadmill testing, and MI, myocardial infarction.

**Inability to Exercise** Data from GUSTO<sup>138</sup> and other large thrombolytic trials<sup>123,126</sup> demonstrate that those patients unable to perform an exercise test have the highest adverse cardiac event rate, while uncomplicated stable patients have a low cardiac event rate even before undergoing further risk assessment by exercise testing. Earlier studies in patients not receiving thrombolytic agents demonstrate a similarly high event rate in those patients unable to exercise.<sup>127,129</sup> A comparison of selected studies is shown in Tables 18 and 19.

**Exercise-Induced Ischemia** Some, but not all, studies performed in the prethrombolytic era demonstrated that exercise-induced ischemic ST-segment depression after myocardial infarction was an important predictor of cardiac mortality.<sup>139–141</sup> However, more recent studies are limited in that coronary revascularization interventions are often performed in persons who demonstrate an ischemic response,<sup>126,129,135,142,143</sup> thus reducing the predictive value of exercise-induced ischemia for cardiac death or reinfarction.

Angiographic studies have demonstrated more multivessel CAD in those with exercise-induced ischemia after myocardial infarction compared with those without ischemia.<sup>144–146</sup> The GISSI-2 trial<sup>123</sup> demonstrated that symptomatic but not silent ischemic ST depression greater than or equal to 1 mm on exercise testing at 28 days after myocardial infarction in patients treated with thrombolytic therapy was an independent predictor of cardiac mortality, but the absolute mortality of such patients remains low (1.7%) by historical standards. Other studies have shown only ST-segment depression greater

than 2 mm,<sup>147</sup> ST depression at a low exercise level,<sup>148,149</sup> or ST depression among patients with controlled heart failure<sup>127</sup> to be independent predictors of death or nonfatal myocardial infarction.

A recent meta-analysis (Table 18) that evaluated exercise testing within 6 weeks of myocardial infarction demonstrates the odds ratio for cardiac death among those with exercise-induced ischemic ST-segment depression (greater than or equal to 1 mm) to be 1.7 compared with those without such ischemia. However, the positive predictive value of exercise-induced ST depression for cardiac death or myocardial infarction at 1 year was found to be only 8% in patients treated with thrombolytic agents versus 18% in those not treated with thrombolytics.<sup>150</sup>

**Exercise Capacity** MET level or exercise duration achieved on exercise testing is an important predictors of adverse cardiac events after myocardial infarction.<sup>123,125,129,132,134,143,148,149,151</sup>

This observation appears to hold true for tests performed on the treadmill as well as the cycle ergometer. Failure to achieve 5 METs during treadmill exercise is associated with a worse prognosis.<sup>129,134,147,148</sup>

**Blood Pressure** Failure to increase systolic blood pressure by 10 to 30 mm Hg during exercise testing has been shown to be an independent predictor of adverse outcome in patients after myocardial infarction.<sup>123,132,134,152,153</sup> Inability to attain a systolic blood pressure greater than 110 mm Hg predicted poor outcome in patients with Q-wave infarcts<sup>129</sup> but not among those with non-Q-wave infarcts.<sup>127</sup>



**Table 19.** Selected Studies\* of Exercise Testing After Myocardial Infarction in the Thrombolytic Era

Author (Year)	Number of Patients Who Underwent ETT	Number of Patients Treated With Thrombolysis	Type of Test	Timing After MI	Length of Follow-up	Outcome
Villella <sup>123</sup> (1995) GISSI-2 study	6296	6296	Symptom-limited	28 d	6 mo	<ul style="list-style-type: none"><li>• 7.1% mortality in those unable to exercise</li><li>• 1.7% mortality in those with a positive test result</li><li>• 0.9% mortality in those with negative test results</li><li>• Predictors of mortality:<ul style="list-style-type: none"><li>— Angina + <math>\geq 1</math> mm ST?</li><li>— ST <math>\downarrow \geq 1</math> mm at <math>&lt;100</math> W or <math>&lt;6</math> min exercise</li><li>— <math>&lt;6</math> min exercise or peak work rate <math>&lt;100</math> W</li><li>— SBP rise <math>&lt;28</math> mm Hg from rest</li></ul></li></ul>
Chaitman <sup>126</sup> (1993) TIMI-2 Study	2502	2502	Submaximal	2 wk	1 y	<ul style="list-style-type: none"><li>• 1261 who underwent ETT were randomly assigned to conservative strategy</li><li>• 9.3% mortality in those unable to exercise vs 2.3% in those who underwent ETT</li><li>• 2.4% mortality with exercise ST <math>\downarrow</math> vs 0.6% without (<math>P = .13</math>)</li><li>• 9.3% underwent revascularization before discharge</li></ul>
Stevenson <sup>148</sup> (1993)	256	256	Symptom-limited	7–21 d	10 mo (6–12 mo)	<ul style="list-style-type: none"><li>• Predictors of recurrent ischemia:<ul style="list-style-type: none"><li>— ST segment <math>\downarrow \geq 1</math> mm</li><li>— Exercise tolerance <math>&lt;7</math> METs</li></ul></li></ul>
Arnold <sup>153</sup> (1993)	981	490	Symptom-limited	Predischarge	1 y	<ul style="list-style-type: none"><li>• 260 of 981 subjects were randomly assigned to receive immediate PTCA</li><li>• 3.6 relative risk of mortality in those unable to exercise</li><li>• Exercise test predictors of mortality:<ul style="list-style-type: none"><li>— SBP rise <math>&lt;30</math> mm Hg from rest</li></ul></li></ul>
Mickley <sup>157</sup> (1993)	123	35	Symptom-limited	1.4 wk	1 y	<ul style="list-style-type: none"><li>• ST depression <math>&gt;1</math> mm predicted future angina but not reinfarction or death</li></ul>
Piccalò <sup>169</sup> (1992)	157	157	Symptom-limited	15 d	6 mo	<ul style="list-style-type: none"><li>• 30% of patients with positive exercise test underwent coronary revascularization</li><li>• 90% of patients without angina or ST <math>\downarrow \geq 1</math> mm had no cardiac events in follow-up</li></ul>

\*Selected studies were derived from a MEDLINE search of reports from 1980 to 1995 of all studies that presented a separate analysis to evaluate predischarge exercise-electrocardiographic testing and included patients (some or all) who have received thrombolytic therapy. Studies in which exercise imaging variables were entered into multivariate analysis were excluded. ETT indicates exercise electrocardiographic testing; MI, myocardial infarction; GISSI-2, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 2 Trial; SBP, systolic blood pressure; TIMI-2, Thrombolysis in Myocardial Infarction II Trial; METs, metabolic equivalents; and PTCA, percutaneous transluminal coronary angiography. Modified from ACC/AHA guidelines.<sup>2</sup>

**Other Variables** Several studies demonstrate that the occurrence of exercise-induced ischemia is similar in patients with Q-wave and non-Q-wave infarctions.<sup>130,135,144,154–157</sup> One study found that exercise-induced ST segment depression in patients with non-Q-wave myocardial infarction was associated with greater risk of cardiac death than that of ST depression in patients with Q-wave infarction.<sup>158</sup> The use of  $\beta$ -adrenergic blocking agents after myocardial infarction has increased over the past decade. They are used in the treatment of acute ischemia and arrhythmia and for their effect in reducing early and late mortality after infarction.<sup>2</sup> Thus, the number of patients taking these agents at the time of the

postinfarction exercise test continues to grow.<sup>122</sup>  $\beta$ -Adrenergic blockers reduce the occurrence of angina and ischemic ST changes and lengthen the time to ischemia on exercise testing.<sup>128,159–161</sup> Although  $\beta$ -adrenergic blockade attenuates the ischemic response, two long-term follow-up studies have demonstrated that these agents do not interfere with poor functional capacity as a marker of adverse prognosis.<sup>128,161</sup> Patients taking  $\beta$ -blockers after myocardial infarction should continue to do so at the time of exercise testing. Because patients will be taking these medications for an indefinite period after infarction, the exercise test response while patients are taking  $\beta$ -blockers provides information about the adequacy of medi-

cal therapy in preventing ischemia and arrhythmias as well as controlling heart rate and blood pressure response during exercise.

### *Activity Counseling*

Exercise testing after myocardial infarction is useful for counseling patients and their families about domestic, recreational, and occupational activities that can be safely performed after discharge from the hospital. Functional capacity in METs derived from the exercise test can be used to estimate tolerance for specific activities. Published charts that provide an estimate of energy requirements for various activities are available<sup>7</sup> but should be used only as a guide, with the knowledge that the intensity at which activities are performed will directly influence the amount of energy required. Most domestic chores and activities require less than 5 METs; hence, a submaximal test at the time of hospital discharge can be useful in counseling regarding the first several weeks after myocardial infarction.

The follow-up symptom-limited testing performed 3 to 6 weeks after myocardial infarction can assist in further activity prescription and issues concerning return to work. Most occupational activities require less than 5 METs. In the 15% of persons in the labor force whose work involves heavy manual labor,<sup>162</sup> the exercise test data should not be used as the sole criterion for recommendations regarding return to work. Energy demands for lifting heavy objects, temperature, and environmental and psychological stresses are not assessed by routine exercise tests and must be taken into consideration. Simulated work tests can be performed in patients with low functional capacity, left ventricular dysfunction, exercise-induced ischemia, and those who are otherwise apprehensive about returning to a physically demanding occupation.<sup>163–165</sup>

### *Cardiac Rehabilitation*

Cardiac rehabilitation combines prescriptive exercise training with coronary risk factor modification in patients with heart disease. It is considered standard care that should be integrated into the treatment plan of patients with CAD.<sup>166</sup> Randomized trials of cardiac rehabilitation after myocardial infarction show consistent trends toward survival benefit among patients enrolled in cardiac rehabilitation programs.<sup>162,166</sup> Meta-analyses of these trials have calculated a significant 20% to 25% reduction in cardiovascular death in patients enrolled in such programs.<sup>167</sup> Moreover, higher levels of physical fitness when measured on an exercise tolerance test are associated with reduced subsequent mortality.<sup>123,129,132,134,143,148,149,151</sup> Exercise training improves exercise capacity among cardiac patients by 11% to 66% after 3 to 6 months of training, with the greatest benefits among those who are most unfit.<sup>166</sup>

Exercise testing in cardiac rehabilitation is essential in development of the exercise prescription to establish a safe and effective training intensity, in risk stratification of patients to determine the level of supervision and monitoring required

during exercise training sessions, and in evaluation of training program outcome.<sup>7,164,168</sup> For these reasons, symptom-limited exercise testing before program initiation is needed for all patients in whom cardiac rehabilitation is recommended (recent myocardial infarction, recent coronary artery bypass surgery, recent coronary angioplasty, chronic stable angina, controlled heart failure).<sup>7,166</sup>

Exercise testing in the stable cardiac patient who continues an exercise training program is often performed after the initial 8 to 12 weeks of exercise training and periodically thereafter, although there are no available studies to assess its value. Such testing may be useful to rewrite the exercise prescription, evaluate improvement in functional capacity, and provide feedback to the patient.<sup>166</sup>

### *Summary*

Contemporary treatment of the patient with acute myocardial infarction includes one or more of the following: medical therapy, thrombolytic agents, and coronary revascularization. These interventions have led to marked improvement in the prognosis of the postinfarction patient, particularly those who have been treated with reperfusion. The patient population eligible for predischARGE exercise testing in clinical trials of thrombolytic therapy is therefore far different from less selected historical populations. Their low cardiac event rate substantially reduces the predictive accuracy of early exercise testing. However, there is limited evidence on the ability of exercise testing to risk stratify patients who have *not* received reperfusion therapy in the current era. Their mortality rates are higher than those who received either thrombolytic therapy or who have undergone coronary revascularization. Thus, exercise testing presumably can still assist in risk stratification of such patients. Patients who have not undergone coronary revascularization and are unable to undergo exercise testing have the worst prognosis.

Exercise testing after myocardial infarction is safe. Submaximal testing can be performed at about 4 to 7 days; about 3 to 6 weeks later a symptom-limited exercise test can be performed. Alternatively, symptom-limited tests can be conducted early after discharge at about 14 to 21 days. Strategies for exercise test evaluation after myocardial infarction are outlined in Fig 3.<sup>3</sup>

Exercise test predictors of adverse outcome in the postinfarction patient include ischemic ST-segment depression greater than or equal to 1 mm, particularly if accompanied by symptoms, at a low level of exercise, or in the presence of controlled heart failure; functional capacity less than 5 METs; inadequate blood pressure response (peak systolic blood pressure less than 110 mm Hg or less than 30 mm increase from resting level).

Exercise testing is useful in activity counseling after discharge from the hospital. Exercise testing is also an important tool in exercise training as part of comprehensive cardiac rehabilitation. It is used to develop and modify the exercise prescription and assess the patient's response to and progress in the exercise training program.

## V. Exercise Testing Using Ventilatory Gas Analysis

### Class I

1. Evaluation of exercise capacity and response to therapy in patients with heart failure who are being considered for heart transplantation.
2. Assistance in the differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain.

### Class IIa

1. Evaluation of exercise capacity when indicated for medical reasons in patients in whom subjective assessment of maximal exercise is unreliable.

### Class IIb

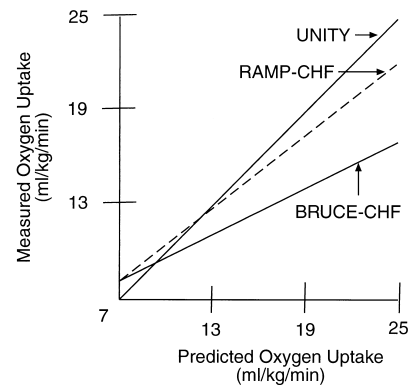
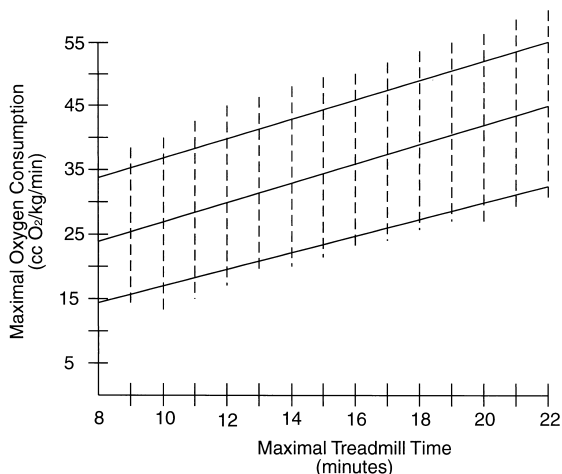
1. Evaluation of the patient's response to specific therapeutic interventions in which improvement of exercise tolerance is an important goal or end point.
2. Determination of the intensity for exercise training as part of comprehensive cardiac rehabilitation.

### Class III

1. Routine use to evaluate exercise capacity.

Ventilatory gas exchange analysis during exercise testing is a useful adjunctive tool in assessment of patients with cardiovascular and pulmonary disease. Measures of gas exchange primarily include oxygen uptake ( $\text{VO}_2$ ), carbon dioxide output ( $\text{VCO}_2$ ), minute ventilation, and ventilatory/anaerobic threshold.  $\text{VO}_2$  at maximal exercise is considered the best index of aerobic capacity and cardiorespiratory function. Maximal  $\text{VO}_2$  is defined as the point at which no further increase in measured  $\text{VO}_2$  occurs despite an increase in work rate (a plateau is reached) during graded exercise testing. Peak  $\text{VO}_2$  is the

**Figure 4.** Relation of treadmill time (independent of specific protocol) to measured oxygen uptake using a progressive treadmill protocol. From Froelicher et al<sup>174</sup> with permission.



**Figure 5.** Relation between measured versus predicted oxygen uptake for the Bruce protocol and progressive ramp protocol in patients with heart failure. Unity is achieved when predicted oxygen uptake is equal to measured oxygen uptake. CHF indicates congestive heart failure. From Froelicher et al<sup>174</sup> with permission.

highest  $\text{VO}_2$  attained during graded exercise testing, but the term does not imply that a plateau in measured  $\text{VO}_2$  is reached. Most clinical studies report peak  $\text{VO}_2$  rather than maximal  $\text{VO}_2$ , as the latter is often difficult to determine precisely. Estimation of peak aerobic capacity using published formulas without direct measurement is limited by physiological and methodological inaccuracies. This is illustrated in Fig 4, which demonstrates the wide scatter of measured  $\text{VO}_2$  per given treadmill time on a progressive treadmill protocol. Exercise protocols with large increments in work rate per stage<sup>136</sup> (Fig 5), the use of handrail support during treadmill exercise,<sup>170</sup> and the application of a single regression formula to a wide variety of heterogeneous populations,<sup>171</sup> which range from the extremely fit to those impaired by heart or lung disease, all limit the reliability of  $\text{VO}_2$  estimates. However, direct measures of  $\text{VO}_2$  are reliable and reproducible and provide the most accurate assessment of functional capacity.<sup>172</sup> Gas exchange data can provide important information to evaluate functional capacity and distinguish cardiovascular from pulmonary limitations during exercise.

The measurement of gas exchange variables has been simplified in recent years with the development of rapid gas analyzers for oxygen and carbon dioxide and computerized on-line analysis systems. In addition to peak or maximal  $\text{VO}_2$ , other valuable measures can be obtained. Minute ventilation and its relation to carbon dioxide production and oxygen consumption yield useful parameters of cardiac and pulmonary function. The respiratory exchange ratio (RER) represents the amount of carbon dioxide produced divided by the amount of oxygen consumed. The RER generally ranges from 0.7 to 0.85 at rest and is partly dependent on the predominant fuel used for cellular metabolism. At high levels of exercise,  $\text{CO}_2$  production exceeds  $\text{VO}_2$ , and thus an RER greater than 1.0 often indicates that the subject is giving a maximal level of effort.

Another index of relative work effort is the ventilatory/anaerobic threshold (VAT). This is a highly reproducible point during exercise at which ventilation abruptly increases despite

linear increases in work rate. Shortly beyond the anaerobic threshold, fatigue usually ensues. The term anaerobic threshold is based on the hypothesis that at a given work rate, the oxygen supplied to exercising muscles does not meet the oxygen requirements. This imbalance increases anaerobic glycolysis for energy generation, yielding lactate as a metabolic byproduct.<sup>173</sup> Although the anaerobic threshold is a defined end point that can be established by several different methods, the actual cause of the observed abrupt rise in minute ventilation remains controversial. This hypothesis is supported by the fact that measured lactate levels increase at the point at which minute ventilation begins its curvilinear relation to work rate. However, whether muscle hypoxia is a main stimulus for increased lactate production is not yet clear. Thus, the true anaerobic threshold at the muscle cell level, the onset of blood lactate accumulation, and the VAT are separate but related events that occur during exercise.

The VAT is determined by several easily recognized measurements that can be obtained during respiratory gas analysis. These include (1) a departure of linearity of minute ventilation ( $\dot{V}_E$ ) and  $\dot{V}_{CO_2}$  with increasing work rates and an abrupt increase in the RER and fraction of  $O_2$  in expired air ( $FE_{O_2}$ ); (2) an increase in  $\dot{V}_E/\dot{V}_{O_2}$  without an increase in  $\dot{V}_E/\dot{V}_{CO_2}$ , and an increase in  $FE_{O_2}$  without a decrease in the fraction of  $CO_2$  in expired air; (3) the lowest  $\dot{V}_E/\dot{V}_{O_2}$  value measured during exercise; and (4) a curvilinear increase in  $\dot{V}_E$  and  $\dot{V}_{CO_2}$  with a linear increase in  $\dot{V}_{O_2}$  (Fig 6).<sup>173,174</sup> Further details on the methodology and interpretation of data obtained during ventilatory gas analysis are available.<sup>8,174,175</sup>

Measurement of expiratory gases during exercise testing can (1) provide the best estimate of functional capacity; (2) grade the severity of functional impairment; (3) objectively evaluate the response to interventions that may affect exercise capacity; (4) objectively track the progression of disease that may limit exercise capacity; and (5) assist in differentiating cardiac from pulmonary limitations in exercise capacity.<sup>176</sup>

Normal values for maximal oxygen uptake among healthy adults at different ages are available<sup>7</sup> and may serve as a useful reference in the evaluation of exercise capacity. The VAT has been proposed as a more sensitive index of fitness than maximal  $\dot{V}_{O_2}$ , heart rate, or total fitness in children. Normal values for VAT in children are provided elsewhere.<sup>9</sup> Determination of exercise training intensity to maintain or improve health and fitness among persons with or without heart disease can be derived from direct measurements of peak oxygen consumption as shown in Table 20.<sup>177</sup> This may be most useful when the heart rate response to exercise is not a reliable indicator of exercise intensity (eg, patients with fixed-rate pacemakers). Rating of perceived exertion is also helpful in this setting.

Data derived from exercise testing with ventilatory gas analysis have proved to be reliable and important measures in the evaluation of patients with heart failure.<sup>178–181</sup> The exercise capacity of patients with heart failure based on their peak  $\dot{V}_{O_2}$  and VAT can be divided into four classes as shown in Table 21.<sup>182</sup> This classification system is limited in that age and gender are not taken into account. Moreover, peak exercise

capacity does not necessarily reflect the daily activities of heart failure patients. Stratification of ambulatory heart failure patients using this technique has improved ability to identify those with the poorest prognosis, who should be considered for heart transplantation.<sup>183,184</sup> (See Table 22.)

The technique of ventilatory gas measurement has a number of potential limitations that hinder its broad applicability. Gas exchange measurement systems are costly and require meticulous maintenance and calibration for optimal use.<sup>170</sup> Personnel who administer tests and interpret results must be trained and proficient in this technique. Finally, the test requires additional cost and time as well as patient cooperation.<sup>8</sup>

## VI. Special Groups: Women, Asymptomatic Individuals, and Postrevascularization Patients

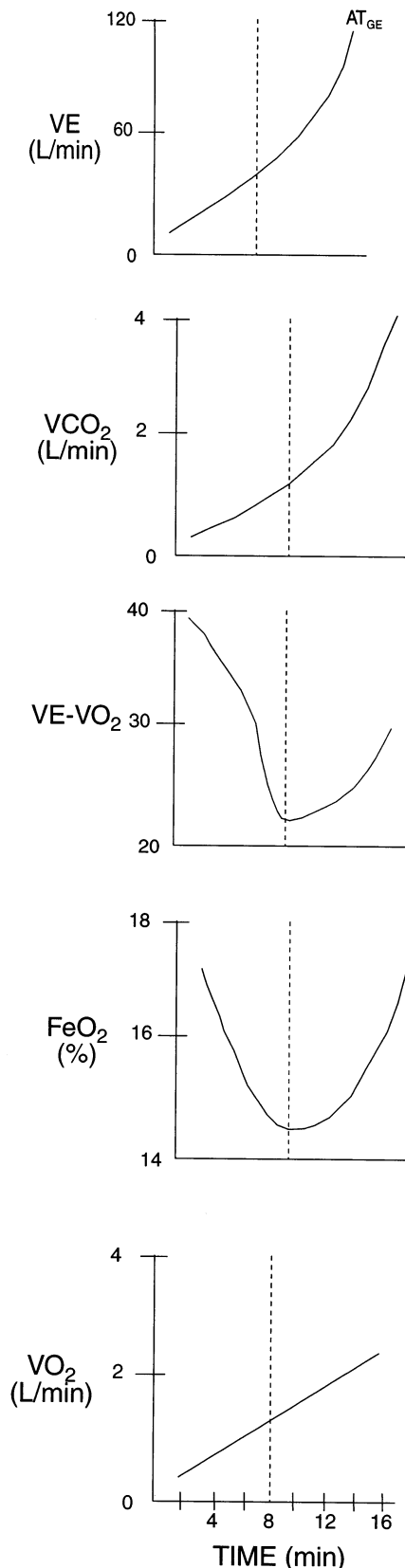
### *Women*

**Rationale** Cardiovascular disease is one of the principal causes of death in women, exceeding mortality due to breast cancer by a factor of 11.<sup>185</sup> The probability of coronary disease in women, based on age, gender, and the nature of symptoms,<sup>17</sup> is most commonly in the low to intermediate probability range, especially in premenopausal women. While typical angina is as meaningful in women older than 60 years as in men,<sup>186</sup> the clinical diagnosis of coronary disease in women may be difficult to make: almost half the women with anginal symptoms in the Coronary Artery Surgery Study (CASS)<sup>187</sup> (who were younger than 65) had normal coronary arteriograms. From a Bayesian standpoint, the low prevalence of CAD presents a particularly difficult situation for noninvasive testing. Moreover, the results of functional testing—exercise capacity, ST-segment changes, and imaging tests—may be influenced by gender.

**Accuracy of Electrocardiographic Analysis in Women.** The ST response to exercise appears to be gender-related from an early age, with ST-segment abnormalities more commonly reported in third-grade girls than boys.<sup>188</sup> Studies examining the accuracy of ST-segment interpretation for the diagnosis of coronary disease according to gender are summarized in Table 23.<sup>84,88,186,189–192,194–199</sup> Variations in results in women may be due to the use of different criteria for defining coronary disease, differences in population selection (including prevalence of prior myocardial infarction and multivessel disease), and differences in performance of the test, including criteria for ST-segment positivity, and type of exercise.

Exercise-induced ST depression is less sensitive in women than men,<sup>84</sup> reflecting a lower prevalence of severe CAD and the inability of many women to exercise to maximum aerobic capacity.<sup>201,202</sup> The exercise ECG is commonly viewed as less specific in women than men, although Table 23 demonstrates that this finding has not been uniform. Even after patients with referral bias were excluded, the ST-segment response was found to be less accurate in women.<sup>28</sup> Significant gender differences were reported in unbiased estimates of sensitivity and specificity. However, these were modest (less than 10%),

**Figure 6.** Measurements used to determine the gas exchange anaerobic threshold (AT<sub>GE</sub>). V<sub>E</sub> indicates minute ventilation; VCO<sub>2</sub>, carbon dioxide production; VO<sub>2</sub>, oxygen uptake; and FeO<sub>2</sub>, fraction of expired air that is oxygen. From Froelicher et al<sup>174</sup> with permission.



**Table 20.** Classification of Exercise Intensity Based on Oxygen Uptake<sup>177</sup>

Intensity	% VO <sub>2max</sub>
Very light	< 25
Light	25-44
Moderate	45-59
Hard	60-84
Very hard	≥ 85
Maximal	100

VO<sub>2max</sub> indicates maximal oxygen uptake.

and did not appear to preclude the use of treadmill exercise testing in women.<sup>28</sup> A careful analysis of the incremental diagnostic value of treadmill testing found similar value in men and women.<sup>200</sup> Studies that have documented lower specificity in women have cited both lower disease prevalence and non-Bayesian factors,<sup>192</sup> which might include the greater prevalence of mitral valve prolapse and syndrome X in women, differences in microvascular function (leading perhaps to coronary spasm), and possibly hormonal differences.

The standard approach to exercise testing involves categorization of the ST-segment response as "positive" or "negative" results. The accuracy of exercise testing in women may be enhanced by attention to features other than the absolute level of ST depression. The ST/heart-rate relation has recently been shown to be of value<sup>203</sup> but awaits widespread application. Avoidance of identifying ST depression in the inferior leads and identification of test positivity based on persistent changes<sup>204</sup> enhance the predictive value of a positive test but may compromise the predictive value of a negative test. Finally, as the ST-segment response is a continuous variable, continuous analysis of the ST segment may recover the information lost from its analysis as a dichotomous variable. This analysis has been combined with non-ECG end points into multivariate models (see below).

**Non-ECG End Points.** The exercise test provides a wealth of other material, including exercise capacity, hemodynamic response to exercise, and the presence of cardiac symptoms, which are used in interpretation of the test result and are not apparent in ST analysis alone. The diagnostic contribution of these findings has been calculated in multivariate models, resulting in development of equations giving the likelihood of disease. The accuracy of exercise testing was significantly

**Table 21.** Classification of Exercise Capacity in Patients With Heart Failure, Based on Peak Oxygen Uptake and Ventilatory Anaerobic Threshold<sup>182</sup>

Class	Impairment	Peak VO <sub>2</sub> (mL/kg/min)	VAT (mL/kg/min)
A	None to mild	> 20	> 14
B	Mild to moderate	16-20	11-14
C	Moderate to severe	10-16	8-11
D	Severe	< 10	< 8

VO<sub>2</sub> indicates oxygen uptake; and VAT, ventilatory anaerobic threshold.

**Table 22.** Guidelines for Peak Exercise Oxygen Uptake as a Criterion for Cardiac Transplantation<sup>184</sup>

Category for Transplant	Peak $\dot{V}O_2$ (mL/kg/min)
Accepted indication	< 10
Probable indication	< 14
Inadequate indication	> 15

$\dot{V}O_2$  indicates oxygen uptake.

increased by the use of a multivariate model compared with ST-segment evaluation alone.<sup>196</sup> However, not all centers have reported these favorable findings,<sup>198</sup> and although the exercise score concept is attractive, its clinical application in women has remained limited.

**Conclusion.** The diagnosis of CAD in women presents difficulties that are not experienced in the investigation of men. These problems reflect differences in exercise physiology, body habitus, coronary physiology, and prevalence of CAD between men and women.

The accuracy of the exercise ECG for diagnosis of coronary disease in women may have important limitations. Physicians must be cognizant of the influence of submaximal exercise on sensitivity; patients likely to exercise submaximally should undergo pharmacological stress testing. Concern about false-positive ST-segment responses may be addressed by careful assessment of posttest probability and selective use of stress imaging tests before proceeding to angiography.<sup>88</sup> On the other hand, the difficulties posed by clinical evaluation of probability of CAD in women have led to speculation that stress imaging approaches may be an efficient initial alternative to the exercise ECG in women.<sup>199</sup> Although the optimal strategy for circumventing false-positive test results for diagnosis of CAD in women remains to be defined, there are

currently insufficient data to justify routine stress imaging tests as the initial test for CAD in women.

### *Diagnosis of Coronary Artery Disease in the Elderly*

**Rationale** Patients older than 65 years are usually defined as “elderly.” One possible subdivision of this group<sup>205</sup> is the “young old” (65 to 75 years) and the “old old” (older than 75); CAD is highly prevalent in symptomatic patients in both groups. With the aging of the population, the former now constitute a substantial proportion of patients; thus, this section focuses on patients older than 75 years. Unfortunately, few data have been published with respect to the use of exercise testing for diagnostic and prognostic assessment of CAD in this group. For example, tables used for the identification of pretest disease probability do not consider patients older than 70, and scores for assessing prognosis have not included elderly patients. Presumably the prevalence and risk of coronary disease increase with advancing age, but nonetheless, in 1989 the National Health Interview Survey<sup>206</sup> reported that the prevalence of diagnosed CAD was 1.8% in men over the age of 75 and 1.5% in women over 75. This disease is commonly occult, silent ischemia being estimated to be present in 15% of 80-year-olds.<sup>207</sup> On Bayesian grounds, the high prevalence and greater severity of coronary stenoses in this group increase the sensitivity of testing but make it harder to rule out significant disease.

The performance of exercise testing poses several problems in the elderly, but it is certainly not contraindicated in this group. Functional capacity is often compromised due to muscle weakness and deconditioning, and therefore the decision whether to send the patient for an exercise or pharmacological stress test is more important than in younger patients. In some patients with problems of gait and coordination, a bicycle exercise test may be more attractive than a treadmill exercise

**Table 23.** Sensitivity and Specificity of Exercise Electrocardiography in Women\*

Author (year)	n (Women)	Mean Age (y)	Definition of CAD	Multivessel CAD (%)	Positive Exercise Test Result (% of Women)	Sensitivity: Women (n = Patients With CAD)	Specificity: Women (n = Patients Without CAD)
Guiteras <sup>189</sup> (1972)	112	49	> 70% dia	12	38	79%, n = 42	66%, n = 70
Linhart <sup>190</sup> (1974)	98	46	> 50% dia	na	34	71%, n = 24	78%, n = 74
Sketch <sup>191</sup> (1975)	56	50	> 75% dia	na	27	50%, n = 10	78%, n = 46
Barolsky <sup>192</sup> (1979)	92	50	> 50% dia	16	41	60%, n = 30	68%, n = 62
Weiner <sup>193</sup> (1979)	580	na	> 70% dia	16	48	76%, n = 169	64%, n = 411
Ilsley <sup>194</sup> (1982)	62	51	> 50% dia	27	44	67%, n = 27	74%, n = 35
Hung <sup>195</sup> (1984)	92	51	> 70% dia	16	51	75%, n = 28	59%, n = 64
Hlatky <sup>84</sup> (1984)	613	na	> 75% dia	na	na	57%, n = 194	86%, n = 419
Melin <sup>88</sup> (1985)	93	51	> 50% dia	20	30	58%, n = 24	80%, n = 69
Robert <sup>196</sup> (1991)	135	53	> 50% dia	29	37	68%, n = 56	48%, n = 79
Chae <sup>197</sup> (1993)	114	na	> 50% dia	na	54	66%, n = 71	60%, n = 43
Williams <sup>198</sup> (1994)	70	60	> 50% dia	19	57	67%, n = 33	51%, n = 37
Marwick <sup>199</sup> (1995)	118	60	> 50% dia	17	58	77%, n = 48	56%, n = 70
Morise <sup>200</sup> (1995)†	264	56	> 50% dia	27	33	46%, n = 81	74%, n = 151
Morise <sup>200</sup> (1995)‡	288	57	> 50% dia	26	36	55%, n = 106	74%, n = 159

\*Studies of >50 women. †Derivation set. ‡Validation set. CAD indicates coronary artery disease; dia, diameter stenosis; and na, not available.

test,<sup>208</sup> but in older patients, bicycle exercise is often limited by unfamiliarity. Certainly, if treadmill exercise is used, more attention must be given to the mechanical hazards of exercise in elderly patients. More gradual protocols should be favored in selection of a treadmill exercise protocol in elderly patients.<sup>209</sup> Elderly patients are much more likely to hold on to the handrails tightly, reducing the validity of treadmill time for estimating METs.

Interpretation of exercise testing in the elderly differs slightly from that in the young. Resting ECG abnormalities, including prior myocardial infarction and intraventricular conduction delays, may compromise the availability of diagnostic data from the ECG. Nonetheless, the application of standard ST-segment response criteria to elderly subjects is not associated with significantly different accuracy from younger people.<sup>84</sup> Due to the greater prevalence of both CAD and severe CAD, it is not surprising that the exercise ECG in this group has a slightly higher sensitivity (84%) and lower specificity (70%) than in younger patients.<sup>210</sup> These false-positive results may also reflect the coexistence of LVH due to valvular disease and hypertension as well as conduction disturbances. Although the risk of coronary angiography may be greater in the elderly and the justification for coronary intervention may be less, the results of exercise testing in the elderly remain important, because medical therapy may itself carry risks in this group.

In addition to ST-segment criteria, attention should be paid to chronotropic and inotropic responses to exercise, exercise-induced arrhythmias, and exercise capacity. Arrhythmias occur more frequently with increasing age, especially at higher workloads but are not necessarily an adverse feature unless associated with evidence of ischemia.<sup>209</sup> Chronotropic incompetence (failure to achieve 85% of age-predicted maximum heart rate) and a hypotensive response to exercise are ominous features, as shown in other age groups. The presence of ST depression in asymptomatic elderly patients is not associated with high event rates,<sup>211</sup> and the positive predictive value of these features may be enhanced by consideration of other exercise parameters as well as a stepwise approach combined with stress imaging tests, discussed in the section on screening.

### *Exercise Testing in Asymptomatic Persons Without Known Coronary Artery Disease*

#### **Class I**

1. None.

#### **Class IIb**

1. Evaluation of persons with multiple risk factors.\*

\*Multiple risk factors are defined<sup>212</sup> as hypercholesterolemia (greater than 240 mg/dL), hypertension (systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg), smoking, diabetes, and family history of heart attack or sudden cardiac death in a first-degree relative younger than 60 years. An alternative approach might be to select patients with a Framingham risk score consistent with at least a moderate risk of serious cardiac events within 5 years.<sup>213</sup>

2. Evaluation of asymptomatic men older than 40 years and women older than 50 years:

- Who plan to start vigorous exercise (especially if sedentary)  
or
- Who are involved in occupations in which impairment might impact public safety  
or
- Who are at high risk for CAD due to other diseases (eg, chronic renal failure)

#### **Class III**

1. Routine screening of asymptomatic men or women.

**Rationale Background.** Studies of the natural history of CAD have shown early changes of atherosclerosis to be prominent in young, presumably asymptomatic military personnel and civilians dying from other causes.<sup>214</sup> CAD is responsible for over half a million deaths each year and 1.5 million hospitalizations for myocardial infarction, at a cost of more than \$100 billion a year in the United States.<sup>185</sup> In light of these human and economic costs, attention has turned to the early diagnosis of CAD in the hope that treatment may avoid complications and reduce the cost of acute treatment.

The purpose of screening is to either prolong life or improve its quality because of early detection of disease.<sup>215</sup> In asymptomatic patients with severe coronary disease, data from the CASS and the Asymptomatic Cardiac Ischemia Pilot (ACIP) study suggest that revascularization may prolong life.<sup>216,217</sup> However, the ACIP was a pilot study, and an NHLBI follow-up study has suggested that acute cardiac events in predominantly low-risk patients are unpredictable.<sup>218</sup> Diagnosis of ischemia may stratify patients for the intensity of risk factor modification.<sup>219</sup> Although this may seem inconsistent with the current position that simple risk reduction should be attempted in all patients,<sup>220</sup> the identification of functional impairment may motivate patients to be more compliant with risk factor modification.<sup>113</sup>

On the other hand, the use of exercise testing to screen for CAD poses problems from standpoints of both positive and negative predictive value. First, because these tests are used for the diagnosis of coronary disease in asymptomatic persons, mild coronary disease, which is prognostically benign, may be identified. Conversely, because many coronary events occur due to plaque rupture involving minor stenoses, the absence of flow-limiting stenoses (associated with a negative exercise test) does not preclude the occurrence of subsequent myocardial infarction.

**Diagnostic Considerations.** As discussed earlier, the posttest probability of coronary disease is dependent on the accuracy of the test and the pretest probability of disease. Unfortunately, the accuracy of exercise testing in asymptomatic persons has never been defined and probably never will be, because these persons could not undergo angiography. An alternative, observational approach involves analysis of the predictive value of a

positive test, which has ranged between 25%<sup>221</sup> and 72%.<sup>222</sup> These numbers are obviously influenced by work-up bias. Nonetheless, the predictive value of a positive test may be enhanced by consideration of not only the ST-segment response but also other exercise variables,<sup>223</sup> although attempts to enhance the predictive value of a positive test usually compromise the predictive value of a negative test. Nonetheless, additional risk stratification is possible by taking into account the severity of ST-segment depression and blood pressure response to exercise.<sup>224</sup>

**Prognostic Evaluation.** Despite these observations, the real issue is not to identify coronary disease but to predict outcome. Traditionally the prediction of myocardial infarction and death are considered the most important end points of screening, although these have been addressed in only the Seattle Heart Watch,<sup>212</sup> the Multiple Risk Factor Intervention Trial (MRFIT),<sup>225</sup> and Lipid Research Clinics (LRC)<sup>226</sup> studies. Angina is a less important end point, because intervention can be postponed until its onset without harming the patient. In addition, the use of angina as an end point has a methodological weakness, because the presence of a previous positive exercise test may make it more likely that chest pain symptoms are interpreted as anginal. Nonetheless, in the era of managed care, the likelihood of re-presentation with progressive symptoms may carry important cost implications, and for this reason other studies using a composite end point including angina have been included in Table 24.<sup>212,225–227,230,232,233</sup> In general, the relative risk of a subsequent event is increased in patients with a positive exercise test result, although the absolute risk of a cardiac event in an asymptomatic population remains in only the 1% range,<sup>225</sup> even if ST changes are associated with risk factors. A positive exercise test result is more predictive of later development of angina than occurrence of a major event. Even taking all end points (including subsequent angina) into account, a minority of patients with a positive test result experience cardiac events, but those with a positive test result may suffer from being labeled at risk, as they may undergo unnecessary, expensive, and potentially hazardous interventions.

Furthermore, most patients with subsequent cardiovascular death have a negative test result, because the sensitivity for detecting subsequent cardiovascular death is low. Because of the role of false-positive test results, several studies have recommended consideration of other data complementary to the presence of greater than 1 mm of ST-segment depression. Taking other factors into account in a multivariate analysis has shown exercise testing to be predictive of hard events,<sup>225,226,232</sup> with relative risks in the range of 4:1 or 5:1. These include other aspects of the ST-segment response, other exercise parameters, risk factors, and the results of stress-imaging tests.

**ST-SEGMENT RESPONSE.** More recent studies have replaced or supplemented use of greater than 0.1 mV of ST-segment depression with the ST integral<sup>225,226</sup> and the ST heart rate slope. The latter was predictive of outcome despite the fact that ST-segment analysis alone was not predictive of outcome in the Framingham study.<sup>232</sup>

**EXERCISE CAPACITY.** Interestingly there appears to be no relation between the performance of maximal or submaximal testing and the predictive value of the ST-segment response. However, the development of evidence of ischemia at low work load is associated with a relatively high risk of subsequent events. ST-segment depression occurring after fewer than 6 minutes of the Bruce protocol has been associated with a relative risk of 6.7 in men and 3.6 in women,<sup>212,226</sup> and ischemia at less than 5 minutes of exercise has been associated with a relative risk of 14.7 in men and 5.6 in women.<sup>230</sup>

**RISK FACTORS.** The Bayesian issues posed by testing patients with a low probability of CAD may be reduced a little by screening a slightly higher-risk group. This can be done by applying the test only to patients with risk factors for CAD (see next section).

**STRESS IMAGING TESTS.** Recently exercise testing was shown to be of value for screening patients with a family history of coronary disease. This study used a composite end point rather than hard events, and the addition of thallium imaging to the exercise test substantially increased the predictive value of the exercise data alone.<sup>234</sup>

**Who to Screen? POPULATION SCREENING.** General screening programs, for example, attempting to identify young patients with early disease, have the limitation that severe CAD (requiring intervention) in asymptomatic patients is exceedingly rare.<sup>17</sup> Although the physical risks of exercise testing are negligible,<sup>7</sup> false-positive test results may engender inappropriate anxiety and may have serious adverse consequences in relation to work and insurance. For these reasons, the use of exercise testing in healthy asymptomatic persons has not been recommended.<sup>235,236</sup>

**SCREENING IN PATIENTS WITH CORONARY ARTERY DISEASE RISK FACTORS.** The importance of accounting for the clinical situation of patients with a positive test result was best illustrated in the Seattle Heart Watch Study.<sup>212</sup> In this study the results of exercise testing were not predictive of outcome in the group as a whole, but in patients with one or more risk factors and two abnormal features on exercise testing (chest pain, exercise less than 6 minutes, attainment of less than 90% of predicted heart rate, or ST-segment depression), there was a 30-fold increment of cardiac risk, even though this group accounted for a small fraction (less than 10%) of the study population. Similarly, in the MRFIT study, although the intervention group showed only a trend to more favorable outcome compared with the usual care group, patients with a positive exercise test result significantly benefited by risk factor modification.<sup>237</sup>

Based on prognostic considerations, asymptomatic male patients older than 40 years with one or more risk factors (hypercholesterolemia, hypertension, smoking, diabetes, or family history of premature CAD) may obtain useful prognostic information from exercise testing. The greater the number of risk factors (ie, pretest probability), the more likely the patient will profit from screening. For these purposes, risk factors should be strictly defined: hypercholesterolemia as total cholesterol greater than 240 mg/dL, hypertension as systolic blood pressure greater than 140 mm Hg or diastolic blood



**Table 24.** Prediction of Cardiac Events by Exercise Testing in Studies of >500 Asymptomatic Individuals

Author or Study (year)	n	Women (%)	First ECG	Protocol	Exercise End Point	Criteria	Prevalence of ST Depression (%)		Events	Events per 1000 Patient/Y	Relative Risk for Events	Follow-up (y)
							Depression (%)	ST Depression (%)				
Froelicher <sup>227</sup> (1974)	1390	0	1965	Various	Maximal	ST depression	10.1	10.1	AP+MI+SCD	5.3	14.3	6.3
Bruce <sup>212</sup> (1980)	2365	0	Before 1975	Bruce	Maximal	Chest pain, ST depression, exercise duration, MHR < 90% predicted	11.1	11.1	AP+MI+SCD	3.5	29 for 2 of 4 exercise criteria, * 3.4 for ST depression	5.6
McHenry <sup>228</sup> (1984)	916	0	1968	Modified Bruce	Maximal	ST depression	2.5	2.5	AP+MI+SCD	5.6	4.9	12.7
Bruce <sup>229</sup> (1983)	4158	13	1971	Bruce	Maximal	Chest pain, ST depression, exercise duration, MHR < 90% predicted, RPP < 80% predicted	14.6	14.6	AP (23)+ MI (11)+ SCD (34)	MI = 3.4, AP = 7.1, composite 10.5	Exercise duration = 6.7 M, 3.6 W; chest pain = 3.5 M, 3.3 W; MHR = 2.4 M, 1.8 W; RPP = 2.4 M, 1.3 W; ST = 2.6 M, 6.7 W	6.1
Giagnoni <sup>226</sup> (1983)	514	27	1971	Various	Submaximal	ST depression	26.2	26.2	MI AP AP+MI+SCD	n/a	13.4 (univariate, MI) 3.4 (univariate AP) 5.6 (multivariate)	6.3
Allen <sup>230</sup> (1980)	888	35	1973	Ellestad	Maximal	ST depression, R-wave response, exercise duration	11.8	11.8	AP+MI+SCD	10.8	ST depression = 2.4 M, 1.9 W; R wave = 2.7 M, 1.9 W; exercise duration = 5.6 M, 14.7 W	8.4
LRC (Gordon, 1986) <sup>231</sup>	3178	0	1972	Modified Bruce	Maximal	ST response	5.7	5.7	CHD death	2.1	Strong positive = 5.0, all positive = 4.6	7
MRFIT (Rautaharju, 1986) <sup>225</sup>	6008	0	1972	Various	Submaximal	ST depression	12.2	12.2	CHD death AP MI	2.6 18.2 5.1	3.7 1.5 1.2	4.3
Framingham (Okin, 1991) <sup>232</sup>	3168	52	1971	Bruce	Maximal	ST depression, ST/HR index, recovery loop	14.6	14.6	AP+MI+SCD	4.8	ST depression = 1.2; ST/HR = 2.2; recovery loop = 2.1; combined = 3.6	4.3

\*Bruce protocol: The four exercise criteria were chest pain with exercise, short duration, heart rate impairment > 10%, ischemic ST depression. ECG indicates electrocardiogram; AP, angina pectoris; SCD, sudden cardiac death; MI, myocardial infarction; MHR, maximal heart rate; RPP, rate-pressure product; CHD, coronary heart disease; and HR, heart rate. Modified from Sada M, Detrano R. Screening for coronary artery disease. In: Marwick T, ed. *Cardiac Stress Testing and Imaging*. New York: Churchill Livingstone, 1996.

pressure greater than 90 mm Hg, smoking, diabetes, history of heart attack or sudden cardiac death in a first-degree relative less than 60 years old. An alternative approach would be to study patients with a certain level of cardiovascular risk expressed as a continuous variable and therefore accounting for not only the presence but also the severity of risk factors. Such data have been derived in asymptomatic persons from the Framingham study.<sup>213</sup> Attempts to extend screening to persons with lower degrees of risk are not recommended, as screening is unlikely to improve patient outcome.

**SCREENING IN OTHER PATIENT GROUPS AT HIGH RISK OF CORONARY ARTERY DISEASE.** Some patient subgroups are known to be at particularly high risk of coronary disease and are often asymptomatic in the presence of this disease. In addition to patients with diabetes and peripheral vascular disease,<sup>238</sup> they include persons with previous cardiac transplantation<sup>239</sup> and chronic renal failure.<sup>240</sup> These patients are more likely to have established coronary disease requiring intervention. Unfortunately, however, partly because of the prevalence of coexisting LVH, functional testing is often nondiagnostic, and standard noninvasive tests have proved particularly insensitive for detection of coronary artery vasculopathy after cardiac transplantation.<sup>241</sup> In these groups, stress imaging tests may be of more value for risk stratification.

**BEFORE FITNESS PROGRAM.** A distinction must be made between asymptomatic patients with and without a history of cardiac disease. Many asymptomatic patients presenting for advice about becoming fit are doing so because of the development of symptoms that they either deny or ascribe to noncardiac causes. Although small, the risk of sudden death during exercise in patients with cardiac disease (which has been estimated at 1 per 784 000 hours) is higher than that of the general population.<sup>242</sup> In those with a history of cardiac disease (including CAD), exercise testing is recommended as a means of stratifying risk.<sup>243</sup> Similarly, patients on antihypertensive therapy may benefit from exercise testing before training as a means of adjusting their exercise prescription.

Cardiac arrest is more likely to occur during exercise than at rest, and this association is much greater in sedentary than active persons.<sup>244</sup> Thus, when a sedentary person starts an exercise program, there is presumably a period of increased risk. For this reason, it has been recommended that middle-aged or older (ie, older than 40 to 50 years) men should undergo a screening exercise test if an exercise program more vigorous than walking is to be pursued. However, in asymptomatic patients without known cardiac disease, the absolute risk of a major cardiac event during activity is still small,<sup>245</sup> and there are no data to justify or criticize testing. In the LRC study of 3617 hypercholesterolemic men, the predictive value of a positive exercise test result for subsequent activity-related events was only 0.3% over 1 year and 4% over 7.4 years.<sup>246</sup>

**SPECIAL GROUPS.** Persons whose occupation may impact public safety (airline pilots, truck or bus drivers, railroad engineers, firefighters, and law enforcement officers) often undergo periodic exercise testing for assessment of exercise capacity and prognostic evaluation of possible coronary dis-

ease. There are insufficient data to justify this approach, although in some cases, evaluations are done for statutory reasons.

**Implications for Clinical Practice.** The use of exercise testing for identification of CAD in asymptomatic persons is a controversial topic for which the committee had difficulty defining guidelines concordant with widespread current practice. The existing data indicate that although disease may be identified, many more patients have false-positive test results. The consequences of such findings include unnecessary and expensive additional testing, adverse psychological implications, and misuse of data to influence employment and insurance decisions. Before performing an exercise test on an asymptomatic patient, these issues must be discussed and informed consent obtained. In view of these limitations, a minority of the committee favored a Class III recommendation for the use of exercise testing as a screening technique for CAD in patients with multiple risk factors or asymptomatic men older than 40 years or women older than 50 years who plan to start vigorous exercise.

The response to a positive exercise test should be modulated by the remainder of the exercise data, including exercise capacity, blood pressure response to exercise, and nonexercise considerations such as risk factor status. The response to the test might therefore vary from risk factor modification for a positive result in the absence of other risk variables to further investigation with an imaging protocol and treatment of CAD in patients with a markedly positive test result and multiple risk factors.

## *Valvular Heart Disease*

### **Class I**

1. None.

### **Class IIb**

1. Evaluation of exercise capacity of patients with valvular heart disease.\*

### **Class III**

1. Diagnosis of CAD in patients with valvular heart disease.

**Rationale** *Uses of Exercise Testing in Patients With Valvular Heart Disease.* In symptomatic patients with documented valvular stenosis or regurgitation, the course of treatment is usually clear and exercise testing is not required. However, the development of Doppler echocardiography has increased the number of asymptomatic patients with defined valvular abnormalities. The primary value of exercise testing in valvular heart disease is to objectively assess atypical symptoms, exercise capacity, and extent of disability, which may have implications for medical, surgical, and social decision making. This is

\*As noted earlier, the presence of symptomatic, severe aortic stenosis is a contraindication to exercise testing.

particularly of importance in the elderly, who are often asymptomatic because they are inactive. The use of the exercise ECG for diagnosis of CAD in these situations is limited by false-positive responses due to LVH and baseline ECG changes.

**Aortic Stenosis.** Severe aortic stenosis is classically considered a contraindication to exercise testing, and this is unquestionable in patients with severe symptomatic aortic stenosis, who should proceed to surgery. In truly asymptomatic patients, aortic valve replacement is probably not justified on prognostic grounds.<sup>247</sup> However, many elderly patients in this situation are asymptomatic because they are inactive, and planning treatment on clinical grounds in these patients may be difficult. The hemodynamic response to exercise may be of value in selecting a subpopulation of asymptomatic patients who are hemodynamically compromised by aortic stenosis, in whom more aggressive therapy might be considered.

Exercise testing is an accepted means of evaluating pediatric patients with aortic stenosis.<sup>248–250</sup> Three studies in adults with moderate to severe aortic stenosis (valve areas, 0.5 to 1.5 cm<sup>2</sup>; mean gradients, 18 to 64 mm Hg) have shown that with the appropriate precautions, principally involving careful observation of the patient with frequent blood pressure checks during exercise, exercise testing can be safely performed in patients with aortic stenosis.<sup>251–253</sup> In these circumstances the test should be directly supervised by a physician familiar with the patient's condition, and exercise should be terminated for inappropriate blood pressure augmentation, slowing of the heart rate with increasing exercise, or premature beats. If the blood pressure response to exercise is abnormal, a cool-down period on the treadmill is advisable to avoid left ventricular volume overload provoked by assuming a supine position.

Functional limitation is commonly found in "asymptomatic" patients with aortic stenosis.<sup>254</sup> Apart from exercise capacity, other important responses include a rapid augmentation of heart rate (which implies a fixed stroke volume) and either failure to augment systolic blood pressure with exercise or decreasing pressure with increasing workload.

**Mitral Stenosis.** Patients with severe mitral stenosis have a fixed stroke volume and are only able to augment cardiac output by increasing heart rate. Because the major indication for surgery in mitral stenosis is symptom status, exercise testing is of most value when a patient is thought to be asymptomatic due to inactivity or a discrepancy exists between the patient's symptom status and the valve area. When exercise testing is performed to clarify these issues, excessive heart rate responses to a relatively low level of exercise, reduction of cardiac output with exercise (evidenced by exercise-induced hypotension), and chest pain (due to ischemia secondary to low cardiac output, or pulmonary hypertension) are indicators in favor of earlier surgery.

**Aortic Regurgitation.** Because volume overload is less demanding on the heart than pressure overload, and because the reduction of diastolic duration with exercise favors forward cardiac output, exercise capacity is maintained until late in the course of aortic regurgitation. The decision to proceed to valve surgery is based on symptom status, left ventricular systolic

dysfunction, and left ventricular size.<sup>255</sup> Because ejection fraction is a reliable index of left ventricular function in aortic regurgitation, decisions regarding surgery are largely based on resting ejection fraction, and exercise testing is not commonly required, unless symptoms are ambiguous. The left ventricular response to exercise may be used to follow the response of asymptomatic patients to medical therapy.<sup>256</sup>

**Mitral Regurgitation.** Mild and moderate mitral regurgitation are generally well compensated, although exercise testing in these situations for assessment of CAD is often compromised by false-positive ST-segment changes, particularly in patients with mitral valve prolapse. Patients with severe mitral regurgitation may demonstrate reduction of exercise capacity and exercise-induced hypotension. As resting ejection fraction is a poor guide to ventricular function in patients with mitral regurgitation, combinations of exercise and assessment of left ventricular function may be of value in documenting occult dysfunction and provoking earlier surgery.<sup>257</sup> Recently the documentation of exercise-induced mitral regurgitation in patients with mitral valve prolapse but without regurgitation at rest has been associated with the subsequent development of progressive mitral regurgitation, congestive heart failure, and syncope.<sup>258</sup>

## *Exercise Testing Before and After Revascularization*

### **Class I**

1. Demonstration of ischemia before revascularization.
2. Evaluation of patients with recurrent symptoms suggesting ischemia after revascularization.

### **Class IIa**

1. After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization.

### **Class IIb**

1. Detection of restenosis in selected, high-risk asymptomatic patients within the first months after angioplasty.
2. Periodic monitoring of selected, high-risk asymptomatic patients for restenosis, graft occlusion, or disease progression.

### **Class III**

1. Localization of ischemia for determining the site of intervention.
2. Routine, periodic monitoring of asymptomatic patients after percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft without specific indications.

**Rationale Exercise Testing Before Revascularization.** Patients who undergo myocardial revascularization should have documented ischemic or viable myocardium, especially if they are asymptomatic.<sup>3,4,259</sup> Frequently, however, this requires a more sensitive test than the exercise ECG, particularly in the

**Table 25.** Predictive Value of Exercise Electrocardiographic Testing for Identification of Restenosis After Percutaneous Transluminal Coronary Angioplasty

Author (year)	n	Clinical	Post-PTCA (m)	Restenosis (%)	PV+ (%)	PV– (%)	Definition of Restenosis
Kadel <sup>268</sup> (1989)	398	Consecutive	Up to 6	33	66	75	> 70% luminal diameter stenosis
Honan <sup>269</sup> (1989)	144	Post MI	6	40	57	64	>75% luminal diameter stenosis
Schroeder <sup>270</sup> (1989)	111	Asymptomatic	6	12	53	63	> 70% luminal diameter stenosis
Laarman <sup>271</sup> (1990)	141	Asymptomatic	1 to 6	12	15	87	> 50% luminal diameter stenosis
el-Tamimi <sup>272</sup> (1990)	31	Consecutive	6	45	100	94	Loss of > 50% initial gain of lumen diameter
Bengtson <sup>265</sup> (1990)	200	Asymptomatic (n = 127)	6	44	46	63	> 75% luminal diameter stenosis
	200	Symptomatic (n = 66)	6	59	76	47	> 75% luminal diameter stenosis
Roth <sup>273</sup> (1994)	78	1-vessel CAD	6	28	37	77	> 50% luminal diameter stenosis
Desmet <sup>274</sup> (1995)	191	Asymptomatic	6	33	52	70	> 50% luminal diameter stenosis

PTCA indicates percutaneous transluminal coronary angioplasty; PV, predictive value; MI, myocardial infarction; and CAD, coronary artery disease.

setting of one-vessel disease, especially if the revascularized vessel supplies the posterior wall. Moreover, use of the exercise ECG is inappropriate in situations in which the culprit vessel must be defined. Documentation of baseline exercise capacity may be worthwhile in patients undergoing either myocardial revascularization or valvular interventions.

**Exercise Testing After Revascularization.** It is recognized that there are two phases after revascularization. In the early phase the goal of exercise testing is to determine the immediate result of revascularization. In the second or late phase the goal of exercise testing is to assist in evaluation and treatment of patients 6 months or more after revascularization, ie, with chronic established CAD (as outlined in section III).

Exercise testing may be helpful in guiding an appropriate cardiac rehabilitation program and return-to-work decisions. (See section IV.)

**Exercise Testing After Coronary Bypass Graft Surgery.** In symptomatic patients, exercise testing may be used to distinguish between cardiac and noncardiac causes of recurrent chest pain, which is often atypical after surgery. Incomplete revascularization or graft occlusion may be identified with the exercise ECG,<sup>260</sup> although not all results have been favorable.<sup>261</sup> Because of concerns about the accuracy of the exercise ECG in this group and because management decisions are based on not only the presence but the site and extent of ischemia, the exercise ECG is less desirable than stress-imaging tests.<sup>262</sup>

In asymptomatic patients, there is concern about development of silent graft disease, especially with venous conduits. The conversion of a markedly positive test result done preoperatively to a negative postoperative test result does correlate with successful revascularization.<sup>263</sup> However, in a follow-up study of events following exercise testing and evaluation of left ventricular function, the left ventricular ejection fraction, but not exercise variables, was predictive of outcome.<sup>264</sup> This may reflect lower sensitivity of the exercise ECG for ischemia and may be less true using stress imaging tests.

The exercise ECG has a number of limitations after coronary bypass surgery. Resting ECG abnormalities are frequent, and if an imaging test is not incorporated in the study, more

reliance must be placed on symptom status, hemodynamic response, and exercise capacity. Because of these considerations, together with the need to document the site of ischemia, stress imaging tests are more favored in this group, although there are insufficient data to justify recommending a particular frequency of testing.

**Exercise Testing After Percutaneous Transluminal Coronary Angioplasty.** Restenosis remains the single major limitation of percutaneous coronary interventions. This clinical end point reflects a complex underlying pathophysiology involving various combinations of residual coronary stenosis, recoil, and neointimal proliferation. Unfortunately, symptom status is an unreliable index to development of restenosis; many patients complain of noncardiac pain after angioplasty (false-positive symptoms), and many persons experience silent ischemia (false-negative symptoms). Silent restenosis is a common clinical manifestation, with 25% of asymptomatic patients documented as having ischemia on exercise testing.<sup>265</sup>

Because residual plaque is responsible for a significant proportion of restenosis, several centers have reported success in performing exercise testing early (1 to 3 days) after PTCA. The presence of ischemia in these tests is predictive of restenosis.<sup>266</sup> While ST-segment changes are a univariate predictor, the independent predictor at multivariate analysis proved to be ischemia on myocardial perfusion imaging. Moreover, in addition to the benefit of early exercise testing for the prediction of subsequent restenosis, the use of an exercise test within 1 to 3 days of angioplasty may facilitate earlier return to work and daily living activities,<sup>267</sup> although the safety of this approach has not been established, and exercise when unstable plaque exists may (at least theoretically) risk vessel occlusion.

If the aim of exercise testing is to identify restenosis rather than predict its probability of occurrence, patients may be tested later (for example, 3 to 6 months) after PTCA. Table 25 summarizes the variability in predictive value of the exercise test for restenosis,<sup>268–275</sup> partly reflecting varying populations studied, frequency, and criteria for restenosis. False-positive study results may be due to incomplete revascularization and angiographically unrecognized plaque fissures. False-negative

results may be caused by the failure of moderate (angiographically but not functionally significant) one-vessel stenoses to lead to significant ischemia. Some authorities have advocated routine testing, because restenosis is frequent and commonly induces silent ischemia. The rationale of this approach is that ischemia, whether painful or silent, worsens prognosis.<sup>276,277</sup> The alternative approach, which the committee favors, is to use a selective evaluation in patients considered to be at particularly high risk, because the prognostic benefit of controlling silent ischemia needs to be proved. Examples of patients who are likely to be at high risk include those with decreased left ventricular function, multivessel CAD, proximal left anterior descending disease, previous sudden death, diabetes mellitus, hazardous occupations, and suboptimal PTCA results. Whichever policy is followed, the exercise ECG is an insensitive predictor of restenosis, with sensitivities ranging from 40% to 55%, significantly less than those obtainable with SPECT<sup>5,278</sup> or exercise echocardiography.<sup>6,279</sup> The insensitivity of the exercise ECG probably reflects the high prevalence of one-vessel disease in this population.

In conclusion, the lower sensitivity of the exercise ECG (compared with imaging techniques) as well as its inability to localize disease limits its usefulness in patient management both before and after intervention. Despite the large numbers of procedures performed and widespread variation in use of exercise testing in this context, there are insufficient data to justify a particular testing regimen after intervention.

### *Investigation of Heart Rhythm Disorders*

#### **Class I**

1. Identification of appropriate settings in patients with rate-adaptive pacemakers.

#### **Class IIa**

1. Evaluation of patients with known or suspected exercise-induced arrhythmias.
2. Evaluation of medical, surgical, or ablative therapy in patients with exercise-induced arrhythmias (including atrial fibrillation).

#### **Class IIb**

1. Investigation of isolated ventricular ectopic beats in middle-aged patients without other evidence of CAD.

#### **Class III**

1. Investigation of isolated ectopic beats in young patients.

**Evaluation of Patients With Known or Suspected Exercise-Induced Arrhythmias** Use of exercise testing in patients with syncope may identify those with CAD, although this is not usually the cause of syncope. Syncope due to sinus node dysfunction, atrioventricular block, and tachycardias may also be identified.

**Ventricular Arrhythmias.** Exertional syncope due to tachycardias may reflect the presence of ischemia, other structural

abnormalities that induce an abnormal cardiac response to stress, and increased circulating catecholamines. The usefulness of exercise testing in patients with VT is variable, according to the cause of the tachycardia. In some syndromes, such as right ventricular outflow tract tachycardia in a normal heart, VT may be reproducibly induced during exercise testing. In adrenergic-dependent rhythm disturbances (including monomorphic VT as well as polymorphic VT related to long QT syndromes), ambulatory ECG monitoring may fail to supply the circumstances necessary for induction of VT, particularly if the patient is sedentary and the arrhythmia is infrequent. Use of exercise testing is therefore a useful prelude to electrophysiological study. Moreover, exercise testing may be of prognostic value in these patients: 12-month mortality is three times greater in persons exhibiting exercise-induced ectopy than those with ectopy at rest only,<sup>280</sup> and in patients with exercise-induced ectopy, mortality of those with complex ectopy exceeds that of those with simple ectopy.<sup>281</sup> In patients on antiarrhythmic therapy, sustained exercise-induced VT is associated with a high risk of sudden death,<sup>282</sup> and exercise testing has been used to unmask proarrhythmic responses.

While serious arrhythmias are uncommon in unselected populations undergoing exercise testing,<sup>283</sup> the use of maximal exercise testing in patients at risk of ventricular arrhythmia is associated with a 2.3% incidence of arrhythmias requiring cardioversion, intravenous drugs, or resuscitation.<sup>284</sup> Nonetheless, even in this population, testing can be performed with low mortality and few lasting morbid events. The main limitation of exercise testing in patients with malignant ventricular arrhythmias is related to its limited reproducibility. While it is sufficiently reproducible to serve as an adjunct in the evaluation and treatment of these patients,<sup>285</sup> other testing is also required.

**Supraventricular Arrhythmias.** Patients developing supraventricular arrhythmias during exercise often display marked tachycardia due to their heightened adrenergic state. In patients with Wolff-Parkinson-White syndrome, exercise testing may be used to help evaluate the risk of developing rapid ventricular response during atrial arrhythmias. Abrupt loss of preexcitation during exercise infers a longer antegrade refractory period in the accessory pathway than the atrioventricular node. It is unlikely that a rapid ventricular response will occur at heart rates above this rate. However, this response to exercise may be difficult to recognize because the adrenergic state speeds conduction in the atrioventricular node and therefore reduces the area of myocardium that is stimulated prematurely from the accessory pathway.

In patients with atrial fibrillation, the ventricular response is governed by the atrioventricular node, and the heart rate is therefore dependent on the rate of repolarization and the effective refractory period, both of which may be influenced by antiarrhythmic drugs used for rate control in patients with atrial fibrillation. Effective rate control at rest does not necessarily signify adequate rate control during exercise, and the titration of additional drugs for this purpose may be facilitated by exercise testing. The heart rate response to exercise in atrial

fibrillation comprises an initial reduction of heart rate, followed by delayed acceleration in very early exercise and an exaggerated heart rate response. Prolonged tachycardia often persists into the recovery period. In patients on medication, 95% demonstrate an abnormal chronotropic response early during exercise (74% being fast), and 84% demonstrate an abnormal chronotropic response during late exercise (53% being slow). Thus, the majority of patients with atrial fibrillation demonstrate an abnormal chronotropic response to exercise.<sup>286</sup>

**Sinus Node Dysfunction.** Exercise testing may distinguish resting bradycardia with a normal exercise heart rate response (which is seen in well-trained subjects with predominant parasympathetic tone) from sinus node dysfunction with resting bradycardia and in patients who fail to make an exercise response. Chronotropic incompetence has been variously defined, the most common definition being failure to achieve 85% of age-predicted maximum heart rate (ie, more than two standard deviations below age-predicted maximum).<sup>287</sup> The use of a heart rate response less than 100 bpm with maximal exercise<sup>288</sup> is specific but insensitive. A more complicated definition, recently shown to be prognostically significant,<sup>289</sup> is the ratio between heart rate and metabolic reserve used by stage II of the Bruce protocol.<sup>290</sup> Using various definitions, some authors have reported chronotropic incompetence in patients with sinus node dysfunction, whereas others have identified the sensitivity and specificity of this marker for sinus node dysfunction as being suboptimal. Moreover, exercise testing has limited reproducibility in this respect, and a normal test result does not negate the possibility of sinus node dysfunction. The use of exercise testing may, however, be particularly useful in showing the benefits of sensor-triggered rate-adaptive pacing, both in terms of absolute heart rate attained and the rate of increase of heart rate.

**Cardiac Pacemakers** The previous edition of the ACC/AHA guidelines for exercise testing<sup>291</sup> suggested that exercise testing was inappropriate in most patients with a permanent pacemaker. Indeed, this remains true from a diagnostic standpoint, and even the combination of exercise testing with imaging may be problematic for the diagnosis of coronary disease. However, the development of adaptive rate pacing using various physiological sensors has led to study of the exercise response being an important constituent in fine-tuning these devices.<sup>292,293</sup> Additionally, a number of studies have compared different pacing modes with respect to their influence on exercise capacity. In all of these situations, however, a formal exercise test may not be necessary, and the required data could be obtained during a 6-minute walk.<sup>294</sup>

Exercise testing in patients with implantable cardiac defibrillators (ICDs) may provoke arrhythmias or ICD discharge. Before testing, the programmed detection interval of the device should be known. If the device has been implanted for ventricular fibrillation (VF) or fast VT, this rate will normally exceed that attainable during sinus tachycardia, and the test can be terminated as the heart rate approaches 10 bpm below the detection interval of the device. Indeed, this approach is

informative if the test is being performed to assess the risk of sinus rate crossover.<sup>295</sup> In patients with slower programmed detection rates, the ICD may be reprogrammed to a faster rate for the test, or temporarily deactivated (usually by superimposition of a magnet). Care should be taken to avoid unnecessary shocks as they are both unpleasant and potentially hazardous.<sup>296</sup>

## VII. Pediatric Testing: Exercise Testing in Children and Adolescents

### Class I

1. Evaluation of exercise capacity in children or adolescents with congenital heart disease, those who have had surgery for congenital heart disease, and children who have acquired valvular or myocardial disease.
2. Evaluation of the rare child with a description of anginal chest pain.
3. Assessment of the response of an artificial pacing system to exertion.
4. Evaluation of exercise-related symptoms in young athletes.

### Class IIa

1. Evaluation of the adequacy of response to medical, surgical, or radiofrequency ablation treatment for children with a tachyarrhythmia that was found during exercise testing before therapy.
2. As an adjunct in assessment of the severity of congenital or acquired valvular lesions, especially aortic valve stenosis.
3. Evaluation of the rhythm during exercise in patients with known or suspected exercise-induced arrhythmia.

### Class IIb

1. As a component of the evaluation of children or adolescents who have a family history of unexplained sudden death related to exercise in young individuals.
2. Follow-up of cardiac abnormalities with possible late coronary involvement such as Kawasaki disease and systemic lupus erythematosus.
3. Assessment of ventricular rate response and development of ventricular arrhythmia in children and adolescents with congenital complete atrioventricular block.
4. Quantitation of the heart rate response to exercise in children and adolescents treated with  $\beta$ -blocker therapy to estimate the adequacy of  $\beta$ -blockade.
5. Measurement of response of shortening or prolongation of the corrected QT interval to exercise as an adjunct in the diagnosis of hereditary syndromes of prolongation of the QT interval.
6. Evaluation of blood pressure response and/or arm-to-leg gradient after repair of coarctation of the aorta.
7. Assessment of degree of desaturation with exercise in patients with relatively well-balanced or palliated cyanotic congenital cardiac defects.

### Class III

1. Screening before athletic participation by healthy children and adolescents.
2. Routine use of exercise testing for evaluating the usual nonanginal chest pain common in children and adolescents.
3. Evaluation of premature atrial and ventricular contractions in otherwise healthy children and adolescents.

### *Differences Between Pediatric and Adult Testing*

Ischemic heart disease is rare in a young population. This results in a much lower risk of routine testing as well as differences in indications, usefulness, and interpretation of exercise laboratory data in the pediatric population. Exercise testing of children and adolescents has a very low risk compared with testing of adults.<sup>297</sup> Complications of pediatric exercise testing are extremely infrequent, even when testing is done in populations of children with congenital cardiac defects and arrhythmias.<sup>9,297-300</sup> Applications of exercise testing in the young are most often related to measurement of exercise capacity, evaluation of known or possible abnormalities of cardiac rhythm, and evaluation of symptoms elicited by exertion. Exercise testing is rarely needed to look for occult coronary obstructions in the pediatric population. Exercise capacity is diminished in some children or adolescents with heart disease, and measurement is often useful in evaluating subjective limitations.

Exercise testing in children provides a number of technical challenges. Equipment must be modified for use by small children. Testing protocols may need to be normalized by size and weight. Norms for age and size on protocols being used are required for proper test interpretation.<sup>9,300</sup> Developmental factors as well as interpretation of data figure into the conduct of the test. Young children are less cooperative than older persons with maximum exercise testing. Experience at encouraging the reluctant youngster to maximal effort is needed for interpretable tests. It is usually difficult to differentiate limitations of exercise capacity from a lack of cooperation in pediatric testing. Because of this difficulty, ventilatory measurements are used in many pediatric exercise testing laboratories to measure respiratory exchange ratio and ventilatory anaerobic threshold.<sup>9,301</sup>

### *Exercise Testing for Specific Pediatric and Congenital Cardiac Problems (Table 26)*

**Exercise Testing of Children and Adolescents With Chest Pain** Chest pain is common in children and adolescents.<sup>302,303</sup> History and physical examination are generally adequate to confidently provide reassurance to patient and family. These episodes of benign chest pain are usually described as a brief stabbing or shooting pain that occurs with or without exercise. Pleuritic pain is common. Typical anginal symptoms are very uncommon. Routine use of exercise testing for evaluation of chest pain in children and adolescents is not required. Exercise testing is appropriate for evaluation of the uncommon child

with chest pain that is typical angina by description and consistently related to exercise. Exercise-induced bronchospasm is a cause of chest pain in children that is identified by pulmonary function measurement test protocols.<sup>304</sup>

**Exercise Testing of Patients With Unoperated Left-to-Right Shunts** Results of exercise testing in young persons with a left-to-right intracardiac shunt such as an atrial septal defect, a ventricular septal defect, or patent ductus arteriosus will generally be normal if the magnitude of the shunt is moderate or small. These persons are ordinarily asymptomatic, and exercise testing adds little to routine evaluation of these defects. Most of those with large shunts will be treated surgically before they reach an age at which exercise testing is practical. Older persons with a large left-to-right shunt often have a low exercise capacity. Exercise testing may help confirm or document subjective exercise impairment in these persons. Testing is not routinely required to make decisions about operative intervention in these older patients but can be of considerable value if the history of limitation is unclear.

Patients with substantial diastolic runoff from a large left-to-right shunt distal to the aortic valve (such as a large patent ductus arteriosus with low pulmonary vascular resistance) will occasionally have resting ST-segment depression due to a relative insufficiency of coronary perfusion during diastole. Left-to-right shunts beyond the tricuspid valve characteristically result in left ventricular volume overload, and large shunts result in LVH. ST-segment depression on the exercise ECG can be seen in these circumstances but provides little benefit in decisions about surgical intervention. False-positive exercise ECG changes are seen in some patients with left-to-right intracardiac shunts who are treated with digoxin.

Limited exercise capacity, arrhythmias, ST-segment changes on the exercise ECG, and/or decrease in oxygen saturation can be seen in exercise testing of patients with left-to-right shunt lesions who have developed severe elevations of pulmonary vascular resistance (Eisenmenger syndrome).<sup>305,306</sup> Exercise testing is potentially hazardous in this group of patients and generally should not be performed. Exercise testing has been used to evaluate response to specific therapies intended to diminish pulmonary resistance and improve pulmonary blood flow.

**Exercise Testing in Patients With Postoperative Left-to-Right Shunts** The great majority of patients in this group do very well, and long-term follow-up studies have shown good exercise performance in this group of patients many years later.<sup>307-309</sup> Routine exercise testing of these patients is not required. Indications for use of exercise testing in this population include symptoms related to exercise, known or suspected arrhythmias related to exercise, and subjective limitations of exertional capability. Atrial arrhythmias may develop years after repair of atrial defects in some patients and are often identified by exercise testing.<sup>310</sup> Exercise testing is of value as a part of evaluation of some patients with ventricular arrhythmias with a ventricular septal defect that was repaired in childhood.<sup>311</sup> Exercise testing is also of value in the group with an operated left-to-right shunt in whom pulmonary vas-

**Table 26.** Exercise Test Findings in Children With Cardiac Abnormalities

Lesion	Expected or Common Findings	Concerning Findings
Aortic stenosis	None	Ischemic ST changes Inadequate SBP response Exertional symptoms
Postoperative aortic stenosis	ST changes may be seen without predicting residual gradient	Arrhythmia Low $\text{VO}_2$ Inadequate SBP response
Aortic regurgitation	Same as postoperative aortic stenosis	Same as postoperative aortic stenosis
Pulmonary stenosis	None expected	ST change rarely found with very severe pulmonic stenosis
Treated pulmonary stenosis	None expected	None expected
Aortic coarctation, preoperative or postoperative	Hypertension Arm-to-leg systolic blood pressure gradient	Ischemic ST changes Diminished exercise capacity Severe hypertension
Atrial septal defect	Normal	None expected
Ventricular septal defect	None expected Poor exercise capacity if large shunt	Arrhythmia Desaturation
Mitral regurgitation	None expected	Low exercise capacity Ischemic ST changes
Mitral prolapse	False-positive ST changes common ST changes with hyperventilation	Arrhythmia
Hypertension	Normal rise in SBP with exertion, SBP levels above normal for work rate	Ischemic ST changes Arrhythmia Low exercise capacity
Cyanotic heart disease, palliated	Low chronotropic response Desaturation with exercise Low exercise capacity	Profound desaturation Ischemia Neurological changes
Postoperative Tetralogy of Fallot	Decreased chronotropic response Low physical capacity Right bundle branch block	Arrhythmias Drop in systolic blood pressure Desaturation
Postoperative arterial switch operation	Uncertain significance of suggestions of ischemia	Limited long-term data
Postoperative Mustard operation	Decreased chronotropic response Poor exercise capacity ST changes in right precordial leads	Arrhythmia Desaturation
Postoperative Fontan	Low physical working capacity Desaturation Drop in blood pressure during exercise	Profound cyanosis Arrhythmia
Kawasaki disease	None expected	Angina Abnormal wall motion Ischemic ST changes Perfusion abnormality (nuclear)
Cardiomyopathy	Low exercise capacity Low peak HR, low $\text{VO}_2$	Syncope, light-headedness Ischemic ST changes
Postoperative cardiac transplant	Slow rise in heart rate Normal working capacity Slightly low peak HR, normal $\text{VO}_2$ High postexercise HR	Ischemic ST changes Low working capacity
Cardiac pacemakers	Wenkebach at upper rate limit	Abnormal (over or under) sensing ventricular arrhythmias
Exertional syncope	None	Angina Mental status change Ischemic ST changes

\*Modified from Washington et al.<sup>9</sup> with permission. SBP indicates systolic blood pressure, and HR, heart rate.

cular resistance was elevated before surgery to evaluate both exercise capacity and propensity to arrhythmia. Exercise testing is often needed as part of the evaluation of the athlete after surgery for a left-to-right shunt lesion.<sup>243</sup>

**Exercise Testing With Unoperated or Palliated Cyanotic Congenital Cardiac Defects** Many of these patients will have an operation before an age at which exercise testing is practi-

cal. Some will present late or are not suitable for an operation other than a palliative procedure. Exercise capacity will usually be less than average, and oxygen saturation will decrease with exercise.<sup>312–314</sup> Chronotropic response to exercise is impaired with a low peak heart rate. Improvement in exercise capacity can be demonstrated after a shunt procedure. Although exercise testing answers specific questions in this group of patients,



there is not often a specific need for exercise testing in the planning of surgical intervention for these children.

#### **Exercise Testing for Patients With Coarctation of the Aorta**

Before school age, exercise capacity and cardiopulmonary function are usually normal after coarctation repair.<sup>315</sup> Systolic blood pressure during exercise and the postexercise arm-to-leg gradient potentially is of use to the clinician in the attempt to define whether a residual or recoarctation is present.<sup>316</sup> When patients with operated coarctation are tested, a greater arm-to-leg blood pressure gradient is found immediately after exercise than is found at rest. This has been thought to reflect residual obstruction<sup>317</sup> and has been used to compare results of different surgical approaches.<sup>318,319</sup> Some have used the post-exercise arm-to-leg gradient as an indication for repeat catheterization. Some observers have found that resting data are sufficient to select those who require further intervention. Factors other than residual obstruction may contribute to the postexercise arm-to-leg gradient.<sup>320,321</sup> Residual gradients during exercise may ultimately lead to hyperdynamic ventricular function and resting upper extremity hypertension.<sup>322</sup> Exercise-induced systolic blood pressure elevation has been thought to indicate residual obstruction,<sup>323,324</sup> but the wide range of variability in blood pressure response of normal children makes it difficult to use systolic blood pressure response alone in assessment of severity of residual coarctation.<sup>316</sup> Among pediatric cardiologists, there has been great variability in the use of exercise blood pressure data in planning further interventions in coarctation of the aorta.<sup>325</sup> Exercise testing may play an important role in evaluation of suitability for high-intensity sports participation after successful treatment of coarctation of the aorta.<sup>243</sup> Exercise testing is occasionally useful with coarctation of the aorta in assessing the hemodynamic significance of other associated cardiac defects (such as aortic valve disease).

**Exercise Testing for the Child or Adolescent With Pulmonary Stenosis** Although the transvalvular pressure gradient in pulmonary stenosis increases with exercise,<sup>326,327</sup> natural history data and strategies for intervention are based on resting measurements. Ventricular arrhythmia, cyanosis (from right-to-left shunting through a patent foramen ovale), or ischemic ST-segment changes develop with exercise in persons with severe pulmonary stenosis. Abnormalities in right ventricular function identified with exercise improve following relief of the obstruction.<sup>328</sup> Exercise testing is not required for management decisions in the majority of cases with pulmonary stenosis. Although exercise testing is not commonly needed for decisions about advisability for participation in high physical intensity sports after treatment of pulmonary stenosis,<sup>243</sup> athletes with severe pulmonary valve incompetence and a dilated right ventricle may require assessment before participation in sports.

**Exercise Testing for the Child or Adolescent With Aortic Stenosis or Regurgitation** Exercise testing has been used to help assess the severity of obstruction in children with aortic stenosis.<sup>248-250</sup> Before the development of reliable echocardiographic and Doppler methods, there was a greater need to rely

on exercise testing for children with aortic stenosis for assessment of the severity of aortic obstruction. Abnormalities found on exercise testing of children with aortic stenosis include ST-segment changes with exercise,<sup>250,329</sup> a drop in blood pressure or failure of appropriate increase in blood pressure with exercise,<sup>330</sup> and development of arrhythmias during exercise testing.<sup>331</sup> Although exercise-induced ST-segment changes have been correlated with the severity of obstruction, the resting gradient is not the sole determinant of these ST-segment changes. The major hemodynamic determinant of ST depression during exercise in patients with aortic stenosis seems to be the left ventricular oxygen demand supply ratio.<sup>329</sup> ST depression with exercise testing improves when the gradient has been relieved surgically,<sup>331</sup> although abnormalities after treatment seem to be of less predictive value than in unoperated patients.<sup>332</sup> Blood pressure response to exercise is extremely variable in children without heart disease, and lack of a rise in blood pressure with exercise is often seen in normal children. Although blood pressure rises less in children with severe aortic stenosis than it does in control subjects, blood pressure response is not diagnostic in individual patients.

Critical aortic stenosis can be identified by findings on examination and confirmed by echocardiography. Although the exercise test is likely to be abnormal in this setting, testing carries some risk, and the decision to recommend intervention is made without requiring exercise testing. Another group of patients who have very mild aortic stenosis can also be confidently identified by expert examination, confirmed, if necessary, by echocardiography. The exercise test adds little to assessment of severity in this group of patients, and an abnormal test result is likely to be a false-positive result. Exercise testing can provide useful information in combination with other data for management decisions about patients with aortic stenosis that is neither obviously quite severe or very mild. There are no criteria for operative intervention based on results of exercise testing alone.

Exercise testing is often used for issues of the advisability of sports participation by children with aortic stenosis and for children who have had treatment of aortic stenosis.<sup>243</sup>

Aortic regurgitation causes left ventricular dilation with static or dynamic exercise, and ST-segment changes during exercise are expected with hemodynamically significant aortic regurgitation. ST-segment changes in children with aortic stenosis and regurgitation are inaccurate in predicting gradient.<sup>333</sup> Exercise testing is often useful in evaluation of exercise capacity of children with aortic regurgitation and evaluation before participation in sports.<sup>243</sup>

#### **Exercise Testing After Surgery for Tetralogy of Fallot**

Exercise capacity improves after successful repair of tetralogy of Fallot. Low exercise capacity is found in many persons with significant residual hemodynamic abnormalities. Exercise testing has been used to identify children with arrhythmias. Complex ventricular arrhythmias observed during exercise testing are correlated with a risk of sudden cardiac death. Serial testing has been used to demonstrate the effectiveness of an antiarrhythmic therapeutic regimen. The possibility of late

development of arrhythmia after repair of tetralogy of Fallot led to a recommendation for periodic exercise testing (every 3 or 4 years) in postoperative tetralogy patients. This recommendation is most applicable to older patients who underwent surgery sometime ago. Diastolic restrictive physiology with exercise has recently been shown to predict a better long-term functional situation for patients with tetralogy of Fallot.<sup>334</sup> Exercise testing is often needed as part of the evaluation before intense athletic training and competition for these patients, primarily to assess their propensity to arrhythmias.

**Exercise Testing After the Fontan Operation (Total Systemic Venous to Pulmonary Connection)** Low exercise capacity, low cardiac output and low oxygen uptake, development of atrial or ventricular arrhythmias with exercise, limitation of peak exercise heart rate response, and development of cyanosis is usual with exercise testing in this group of patients. Improvement in exercise capacity compared with preoperative status can be demonstrated.<sup>314,335,336</sup> Exercise testing is helpful in evaluation of exercise capacity and screening for arrhythmia in the postoperative Fontan patient.

**Exercise Testing of Patients With Cardiomyopathy** Exercise testing of children with hypertrophic cardiomyopathy has not been a routine part of evaluation. Children with severe hypertrophy or obstruction are at risk for complications with exercise. Arrhythmias, ST-segment changes, drop in blood pressure, and low exercise cardiac output occur with testing.<sup>337,338</sup> Exercise testing is sometimes useful to help evaluate response to a specific therapy in patients with hypertrophic cardiomyopathy.

Children with dilated cardiomyopathy are likely to have a limited exercise capacity. ST-segment changes are often seen. The exercise test can be of value in identifying arrhythmias. Survival correlates with impaired exercise capacity. Information about exercise limitation influences decisions about the timing of cardiac transplantation.

Restrictive cardiomyopathy is less common than dilated or hypertrophic cardiomyopathy. These children tend to be identified later and seem less ill than those with dilated cardiomyopathy, although the time interval from diagnosis to death is shorter.<sup>339</sup> Near-normal exercise capacity is falsely reassuring in this setting.

**Exercise Testing of Children or Adolescents With Syncope** Features of syncope that suggest a potentially life-threatening cardiac event include an abrupt loss of consciousness (as opposed to a prodrome or aura), injury on impact (as opposed to a gradual “slump”), and syncope related to physical activity. Evaluation for possible arrhythmia, left ventricular outflow obstruction, and cardiomyopathy is appropriate. Exercise testing is an important component of evaluation of children or adolescents who have unexplained syncope related to physical exertion.

**Exercise Testing of Children or Adolescents With Atrial Arrhythmias** Premature atrial contractions are common and benign in young persons. Exercise test evaluation of premature atrial contractions in pediatric patients is not required.

The majority of children with supraventricular tachycardia

will not have exercise-induced tachycardia. Exercise testing helps in evaluation of selected cases in which the history suggests an exercise-related tachycardia. Serial exercise testing has been used to follow the response to therapy in cases of exercise-induced atrial tachycardias.

**Exercise Testing of Children or Adolescents With Ventricular Arrhythmias** Isolated premature ventricular depolarizations in asymptomatic children and adolescents usually disappear with the higher heart rates associated with exercise. It is not necessary to perform formal laboratory testing to demonstrate this.

Exercise testing is often of value in diagnosing VT and assessing the efficacy of treatment. VT with exercise is often observed in children with no structural heart abnormality as well as in children with myocarditis, cardiomyopathy, or a congenital cardiac malformation. Arrhythmogenic right ventricular dysplasia is particularly related to development of VT with exercise.

Measurement of the response of the shortening or prolongation of the corrected QT interval to exercise has been used as an adjunct in the diagnosis of hereditary syndromes of prolongation of the QT interval. Accuracy of measurement is suspect, and its usefulness for decision making in borderline cases has been questioned. T-wave alternans is a relatively specific but uncommon finding with exercise testing in patients with long QT-interval syndromes. Exercise testing occasionally identifies VT.

**Exercise Testing of Children or Adolescents With Conduction Abnormalities and in Pacemaker Follow-up** Ventricular rate response to exercise and development of ventricular arrhythmia with congenital complete atrioventricular block is useful in determining the need for artificial pacing. Assessment of sensing and capture of an artificial pacing system during exercise is useful in some cases. Exercise testing to evaluate the adequacy of rate responsiveness to exercise is useful in management.

**Exercise Testing of Children or Adolescents With Known or Suspected Coronary Artery Disease** Some cardiac abnormalities in childhood are predicted to be associated with development of coronary artery involvement later in life. Examples include persons who had surgery for anomalous left coronary artery from the pulmonary trunk (Bland-Garland-White syndrome). Some cases of tetralogy of Fallot include an anomalous right coronary artery arising from the left coronary artery or from the left sinus of Valsalva and crossing the right ventricular outflow tract in proximity to the infundibular resection. One concern has been possible coronary anastomotic obstruction late after neonatal arterial switch operation for transposition of the great arteries in which the coronary ostia must be translocated. Kawasaki disease with coronary aneurysms in early life is another possible source of development of coronary artery insufficiency. Exercise testing of asymptomatic youths in these categories before intense athletic competition and testing if symptoms of possible ischemic origin develop is indicated.

**Exercise Testing of Children or Adolescents With Cardiac Transplantation** Exercise for the patient with a transplanted heart is characterized by a relative inertia of the chronotropic response. Because of cardiac denervation, the heart rate rises in response to circulating catecholamines more slowly than in normal children. Exercise capacity is in the normal range in most patients. Some degree of reinnervation sometimes occurs years after transplantation, but anginal pain is often absent with transplant CAD. Bundle branch block is a common finding that limits the usefulness of exercise electrocardiography in this population. Exercise testing for ischemic changes has not supplanted periodic surveillance coronary angiography at pediatric transplant centers but is a useful adjunct in following children with heart transplants. The sensitivity and specificity of exercise testing for evaluation of posttransplant CAD in children is unknown.

**Exercise Testing After an Operation to Correct Transposition of the Great Arteries** The arterial switch operation is the current surgical treatment of transposition of the great arteries in most cases. Normal exercise tolerance and normal ST segments with exercise are seen in this group of children, although the length of follow-up available is less than for many other operations. Perfusion defects seen by radionuclide exercise testing are of uncertain significance.

Many older persons with transposition underwent repair with an atrial baffle. Exercise capacity and heart rate response to exercise are likely to be limited in this group of patients, although many are doing very well.<sup>340</sup> An inadequate chronotropic response is related to development of right ventricular dilation<sup>341</sup> and ultimately the need for a pacemaker.<sup>342</sup>

## Appendixes

### Appendix 1

**Borg Scale for Rating Perceived Exertion** Table A1 shows the original scale for rating perceived exertion (6 to 20) (left) and the newer 10-point category scale with ratio properties (right).

### Appendix 2

**Multivariable Analysis for the Diagnosis of Obstructive Coronary Artery Disease** The following examples of multivariable equations that can estimate the presence of angiographic CAD were chosen because they have been validated in large populations.

Morise et al<sup>343</sup> studied a total of 915 consecutive patients without a history of prior myocardial infarction or coronary artery bypass surgery who were referred to the exercise laboratory at West Virginia University Medical Center between June 1981 and December 1994 for evaluation of coronary disease. All patients had coronary angiography within 3 months of the exercise test. The patients were classified as having disease if there was at least a 50% lumen diameter narrowing in one or more vessels. When this criterion was

Table A1\*

15-Grade Scale		10-Grade Scale	
6		0	Nothing
7	Very, very light	0.5	Very, very weak (just noticeable)
8		1	Very weak
9	Very light	2	Weak (light)
10		3	Moderate
11	Fairly light	4	Somewhat strong
12		5	Strong (heavy)
13	Somewhat hard	6	
14		7	Very strong
15	Hard	8	
16		9	
17	Very hard	10	Very, very strong (almost maximum)
18			
19	Very, very hard		Maximum
20			

\*From Borg GA. *Med Sci Sports Exerc.* 1982;14:377–381. Reproduced with permission.

used, the prevalence of disease in this population was 41%. Morise generated the following logistic regression equation:

$$\text{Probability (0-1)} = 1 / (1 + e^{-(a + bx + cy)})$$

where a is the intercept, b and c are beta coefficients, and x and y are variable values as follows:

$$- .12 + (4.5 * [-3.61 + (0.076 * \text{age}) - (1.33 * \text{gender}) + (0.64 * \text{symptoms}) + (0.65 * \text{diabetes}) + (0.28 * \text{smoking}) - (1.46 * \text{body surface area}) + (0.50 * \text{estrogen}) + (0.33 * \text{number of risk factors}) - (.40 * \text{resting ECG})]) + (0.37 * \text{mm ST depression}) + (1.02 * \text{ST slope}) - (0.37 * \text{negative ST}) - (0.02 * \text{maximal heart rate})$$

Gender was coded as 1 for female and 0 for male. Symptoms were classified into four categories: typical, atypical, nonanginal pain, and no pain and coded with values of 4, 3, 2, and 1, respectively. Diabetes was coded as 1 if present and 0 if absent. Smoking was coded as 2 for current smoking, 1 for any prior smoking, and 0 for never smoked. Estrogen was coded as 0 for males, 1 for estrogen negative (postmenopausal and no estrogen), and -1 for estrogen positive (premenopausal or taking estrogen). Risk factors included history of hypertension, hypercholesterolemia, and obesity (BMI  $\geq 27$  kg/m<sup>2</sup>). Resting ECG was coded as 0 if normal and 1 if there were QRS or ST-T wave abnormalities. Millimeters ST depression was coded as 0 for women. ST slope was coded as 1 for downsloping and 0 for upsloping or horizontal. Negative ST was coded as 1 if ST depression was less than 1 mm depression horizontal or downsloping or ST depression was less than 1.5 mm upsloping.

Detrano et al<sup>23</sup> included 3549 patients from eight institutions in the United States and Europe who underwent exercise testing and angiography between 1978 and 1989. Disease was defined as greater than 50% diameter narrowing in at least one major coronary arterial branch, and the prevalence of disease according to this criterion was 64%. They considered a total of

**Table A2**

Variables	Significant	Predictor (%)
Gender	20/20	100
Chest pain symptoms	17/18	94
Age	19/27	70
Elevated cholesterol	8/13	62
Diabetes mellitus	6/14	43
Smoking history	4/12	33
Abnormal resting ECG	4/17	24
Hypertension	1/8	13
Family history of CAD	0/7	0
ST-segment slope	14/22	64
ST-segment depression	17/28	61
Maximal heart rate	16/28	57
Exercise capacity	11/24	46
Exercise-induced angina	11/26	42
Double product	2/13	15
Maximal systolic BP	1/12	8

BP indicates blood pressure; CAD, coronary artery disease; and ECG, electrocardiogram.

15 clinical and exercise variables that contributed significant and independent information to disease probability and had been judged clinically relevant by a panel of cardiologists as candidates for logistic regression. The selected Detrano equation intercept, variables, and coefficients are listed below:

$$1.9 + (0.025^* \text{ age}) - (0.6^* \text{ gender}) - (0.11^* \text{ symptoms}) - (0.05^* \text{ METs}) - (0.02^* \text{ maximal heart rate}) + (0.36^* \text{ exercise-induced angina}) + (0.59^* \text{ mm ST depression})$$

Gender was coded as 1 for female and -1 for male. Symptoms were classified into four categories: typical, atypical, nonanginal pain, and no pain, and coded with values of 1, 2, 3, and 4, respectively. Exercise angina was coded as 1 for presence and -1 for absence.

### Appendix 3

Table A2 shows the results of 24 studies that used multivariable techniques to predict disease presence (30 equations were created). The denominator is the number of equations that allowed the particular variable to be a candidate for the equation.

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