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ACC/AHA 2002 Guideline Update 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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This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org) and the American Heart Association (www.americanheart.org). Copies of this document (the complete guidelines) are available for $5 each by calling 800-253-4636 (US only) or writing the American College of Cardiology Resource Center, 9111 Old Georgetown Road, Bethesda, MD 20814-1699 (ask for No. 71-0231). To obtain a reprint of the shorter version (executive summary describing the changes to the guidelines) planned for subsequent publication in the *Journal of the American College of Cardiology* and *Circulation*, ask for reprint No. 71-0232. To purchase additional reprints (specify version and reprint number): up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1789, fax 214-691-6342, or email pubauth@heart.org.

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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 summary article highlighting changes from the 1997 guideline to the 2002 guideline is published in the October 1 issue of *Circulation* and the October 16 issue of the *Journal of the American College of Cardiology*. The full-text guideline is posted on the ACC and AHA Web sites. Copies of the full-text and summary article are available from both organizations.

The 1997 guidelines were officially endorsed by the American College of Sports Medicine, the American Society of Echocardiography, and the American Society of Nuclear Cardiology.

Raymond J. Gibbons, MD, FACC
Chair, ACC/AHA Task Force on Practice Guidelines

I. INTRODUCTION

The ACC/AHA 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 that uses treadmill or bicycle exercise and electrocardiographic and blood pressure monitoring. Pharmacological stress and the use of imaging modalities (e.g., radionuclide imaging and 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 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 published 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 with specific criteria detailed in the guidelines. The meta-analyses and evidence tables were reviewed extensively 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. In the original guidelines, the committee did not rank the available scientific evidence in an A, B, or C fashion. The level of evidence is provided for new recommendations appearing in this update. The weight of evidence was ranked highest (1) if the data were derived from multiple randomized clinical trials that involved large numbers of patients and intermediate (B) if the data were derived from a limited number of randomized trials that involved small numbers of patients or from careful analyses of nonrandomized studies or observational registries. A lower rank (C) was given when expert consensus was the primary basis for the recommendation. 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.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: 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 and cardiologists with expertise in the use of stress imaging modalities. Both the academic and private practice sectors, as well as both adult and pediatric expertise, were represented. This document was reviewed by two outside reviewers nominated by the ACC and two outside reviewers nominated by the AHA, as well as by the ACC/AHA Task Force on Practice Guidelines. This document will be reviewed annually 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 (344), guidelines for management of patients with acute myocardial infarction (345), guidelines for percutaneous coronary intervention (346), guidelines and indications for coronary artery bypass graft surgery (347), and guidelines for management of patients with chronic stable angina (348). The reader is referred to these other guidelines for a more complete description of the role of exercise testing in clinical decision making and a comparison of exercise electrocardiography with noninvasive imaging modalities. The general context for the use of exercise testing is outlined in Fig. 1. 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 discus-

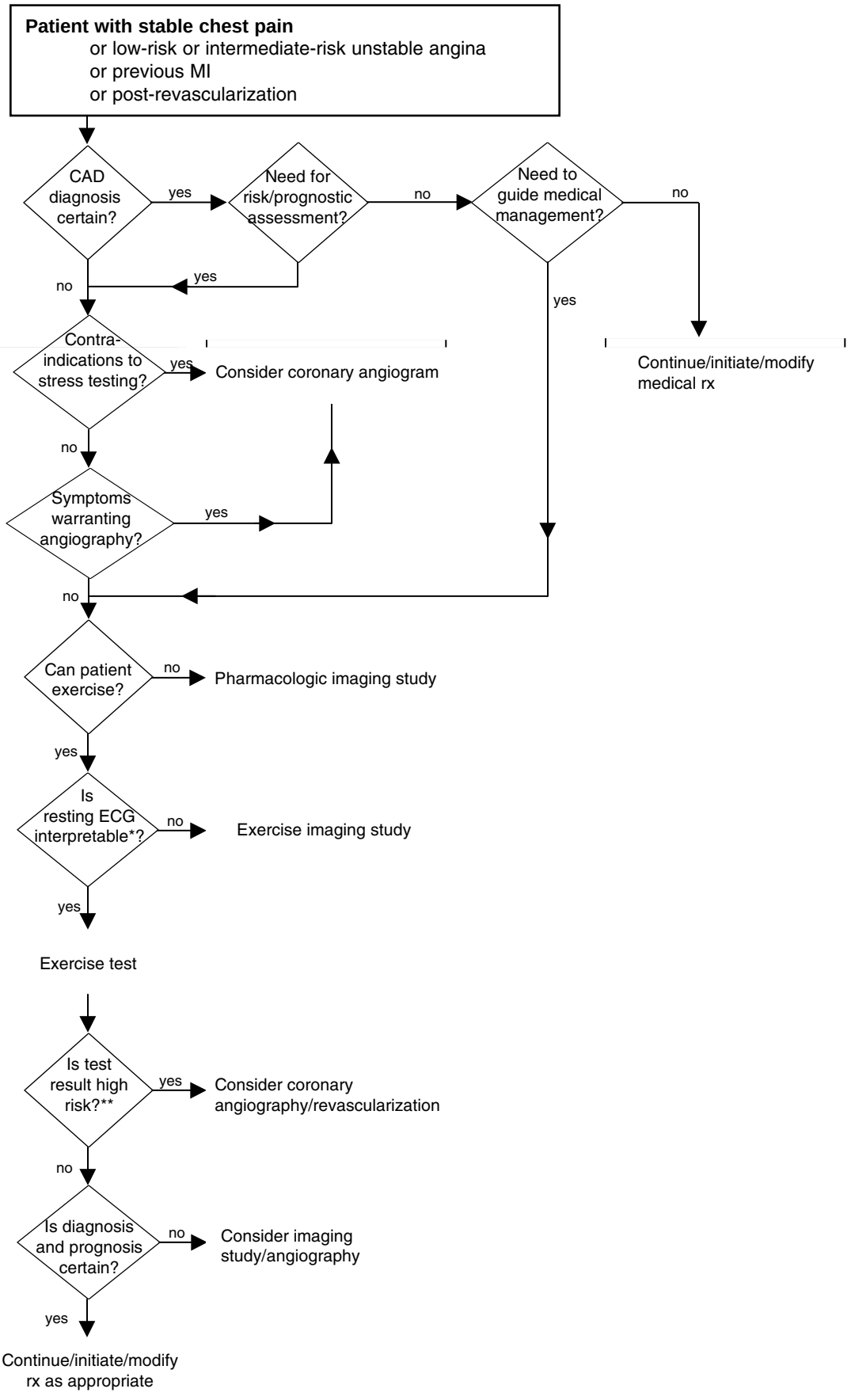

Figure 1. Clinical context for exercise testing for patients with suspected ischemic heart disease. *Electrocardiogram interpretable unless pre-excitation, electronically paced rhythm, left bundle branch block, or resting ST-segment depression greater than 1 mm. See text for discussion of digoxin use,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

sion of radionuclide angiography, myocardial perfusion imaging, or positron emission tomography, which are covered in the published guidelines for clinical use of cardiac radionuclide imaging (5). This report also does not include any discussion of stress echocardiography, which is covered in the published guidelines for clinical application of echocardiography (349). 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 (7), guidelines for clinical exercise testing laboratories (8), and guidelines for exercise testing in the pediatric age group (9), 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 (10). 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 American College of Physicians/ACC/AHA task force statement on clinical competence in exercise testing (11), exercise testing in selected patients can be performed safely by properly trained nurses, exercise physiologists, physician assistants, 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 (ECG), heart rate, and blood pressure should be monitored carefully and recorded during each stage of exercise and during ST-segment abnormalities and chest pain. The patient should be monitored continuously for transient rhythm disturbances, ST-segment changes, and other electrocardiographic manifestations of myocardial ischemia. Further details are provided in the AHA guidelines for clinical exercise testing laboratories (8).

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 (12). 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 specified clearly.

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, and those with excessive heart rate response. The use of rating of perceived exertion scales, such as the Borg scale (Appendix 1) (13), is often helpful in

Table 1. Contraindications to Exercise Testing

Absolute
- Acute myocardial infarction (within 2 d)
- High-risk unstable angina*
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Acute aortic dissection

Relative†
- Left main coronary stenosis
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities
- Severe arterial hypertension‡
- Tachyarrhythmias or bradyarrhythmias
- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
- Mental or physical impairment leading to inability to exercise adequately
- High-degree atrioventricular block

*ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction (350) (see Table 17).
†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.[7]

Table 2. Indications for Terminating Exercise Testing

Absolute indications
- Drop in systolic blood pressure of >10 mm Hg from baselineblood pressure despite an increase in workload, when accompanied by other evidence of ischemia
- Moderate to severe angina
- Increasing nervous system symptoms (eg, ataxia, dizziness, or near-syncope)
- Signs of poor perfusion (cyanosis or pallor)
- Technical difficulties in monitoring ECG or systolic blood pressure
- Subject's desire to stop
- Sustained ventricular tachycardia
- ST elevation (≥1.0 mm) in leads without diagnostic Q-waves (other than V_1 or aVR)

Relative indications
- Drop in systolic blood pressure of (≥10 mm Hg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischemia
- ST or QRS changes such as excessive ST depression (>2 mm of horizontal or downsloping ST-segment depression) or marked axis shift
- Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias
- Fatigue, shortness of breath, wheezing, leg cramps, or claudication
- Development of bundle-branch block or IVCD that cannot be distinguished from ventricular tachycardia
- Increasing chest pain
- Hypertensive response*

*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.[7]

assessment of patient fatigue. Symptom-limited testing with 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 visual interpretation of 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 (ms) after the end of the QRS complex (347). 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 cost. Table 3 is a comparison of year 2000 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 2.1 times higher, stress SPECT myocardial imaging 5.7 times higher, and coronary angiography 21.7 times higher. Lower cost of the treadmill exercise test alone does not necessarily result in a lower overall cost of patient care, because the sum of 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 (Table 3). An estimated 72% of the treadmill exercise tests charged to Medicare in 1998 were performed as office procedures, and 27% of the charges were submitted by noncardiologists.

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

Procedure	1998 CPT Code(s)	2000 Total (Professional and Technical) Medicare RVUs	1998 Medicare Data		
			Number Performed	Percent Charged by Cardiologists	Percent Office-Based
Treadmill exercise test	93015 or 93016–93018	3.12	533,000*	73*	72*
Stress echocardiography	93350, 93015	6.16 (plus any Doppler charge)	353,942	80	64
Stress SPECT myocardial perfusion imaging	78465, 93015	17.79 (plus isotope charge)	1,362,210	†	43
Left heart catheterization with left ventriculogram and coronary angiography	93510, 93543, 93545, 93555, 93556	67.58	901,625	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.

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 after symptoms of unstable chest pain, or may be post-myocardial infarction or postrevascularization patients. Patients who are unable to exercise or who have uninterpretable ECGs because of pre-excitation, electronically paced rhythm, left bundle-branch block, or ST depression greater than 1 mm require imaging studies and are beyond the scope of these guidelines. Imaging studies are considered in other ACC/AHA guidelines (5,348-350). The clinician should first address whether the diagnosis of CAD is certain, given the patient's history, ECG, 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 on the basis of 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 TO DIAGNOSE OBSTRUCTIVE CAD

Class I

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) on the basis of gender, age, and symptoms (specific exceptions are noted under Classes II and III below).

Class IIa

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.**

Class III

1. **Patients with the following baseline ECG abnormalities:**
   - **Pre-excitation (Wolff-Parkinson-White) syndrome**
   - **Electronically paced ventricular rhythm**
   - **Greater than 1 mm of resting ST depression**
   - **Complete left bundle-branch block**

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%.

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 (15) 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 (16), angiographic lesions remain the clinical gold standard. Results of correlative studies have been divided concerning 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, and 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 (17). Typical or definite angina makes the pretest probability of disease so high that the test result does not dramatically change the 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 approximately a 50% probability of 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/or 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 (18). Other clinical scores have been developed that could better predict pretest probability (351).

Detailed nomograms are available that incorporate the effects of a history of prior infarction, electrocardiographic Q waves, electrocardiographic ST- and T-wave changes, diabetes, smoking, and hypercholesterolemia (19). History and electrocardiographic evidence of prior infarction dramatically affect pretest probability.

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 the application of any testing procedure for the separation of subjects without disease 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 those with heart disease. A certain value (discriminant value) is used to separate these two groups (i.e., 1 mm of ST-segment depression). If the value is set high (i.e., 2 mm of ST-segment depression) to ensure that nearly all subjects without the disease 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's 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 popu-

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

$$\text{Sensitivity} = [TP/(TP + FN)] \times 100 \qquad \text{Specificity} = [TN/(FP + TN)] \times 100$$

$$\text{Predictive value of an abnormal test (PV+)} = \frac{\text{Sensitivity} \times P(CAD)}{[\text{Sensitivity} \times P(CAD)] + [(1 - \text{Specificity})[1 - P(CAD)]]}$$

$$\text{Predictive accuracy} = [\text{Sensitivity} \times P(CAD)] + [\text{Specificity} \times [1 - P(CAD)]]$$

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); PV1, the percentage of those with an abnormal (1) test result who have disease; predictive accuracy, the percentage of correct classifications, both 1 and 2; and P(CAD), pretest probability.

lation 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 estimated accurately 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 (i.e., 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, for instance, 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).

Scores

Mathematical equations or scores developed from multivariable analysis of clinical and exercise test variables provide superior discrimination compared with use of only the ST-segment response to diagnose CAD. Such scores can provide probabilities of CAD that are more accurate than ST measurements alone (20,21). 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 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 workup bias, e.g., 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. In addition, the Duke treadmill prognostic score has been shown to be better than ST depression alone for diagnosing angiographic coronary disease (352). When these computational techniques have been compared with the judgment of experienced clinical cardiologists, the predictions have been comparable (22,23). 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 validating diagnostic tests should include consecutive or randomly selected patients for whom the diagnosis is in doubt (24). 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

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)
	9500 without CAD	90% specific	950 (FP)	8550 (TN)	= 21%
50	5000 with CAD	50% sensitive	2500 (TP)	2500 (FN)	2500/(2500 + 500)
	5000 without CAD	90% specific	500 (FP)	4500 (TN)	= 83%

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[25,26]

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.

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 (e.g., 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 ECG has been studied by meta-analysis (25,26). Criteria to judge the credibility and applicability of the results of studies evaluating diagnostic tests (27) were applied. Most of the studies failed to fulfill these criteria, particularly removal of workup bias. Workup bias refers to the fact that most reported studies were affected by clinical practice wherein test results were used to determine who should be included. However, this analysis provides the best description of the diagnostic accuracy of the 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, thus 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 in which workup bias was avoided by having patients agree to undergo both procedures, thereby fulfilling the other major criterion, the approximate sensitivity and specificity of 1 mm of horizontal or downward ST depression were 50% and 90%, respectively (28,29,353). These latter studies provide a true estimate of how standard electrocardiographic 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 sensitivity (about 50%) of the exercise ECG is generally less than the sensitivity of imaging procedures (349); however, the multivariable scores discussed previously appear to make the tests comparable.

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:

Table 8. Studies Including Resting ST Depression

Author	Year	Total Patients	Sensitivity	Specificity
Roitman[46]	1970	100	0.73	0.82
Erikssen[74]	1977	113	0.84	0.17
Silber[75]	1979	108	0.71	0.70
Dunn[76]	1979	125	0.70	0.65
Weiner[77]	1979	2045	0.79	0.69
Marcomichelakis[78]	1980	100	0.92	0.62
Morales-Ballejo[79]	1981	100	0.62	0.74
Machecourt[80]	1981	112	0.48	0.82
Guiteras[81]	1982	112	0.79	0.61
Santinga[82]	1982	113	0.56	0.86
Currie[83]	1983	105	0.77	0.82
Hlatky[84]	1984	3094	0.69	0.79
O'Hara[85]	1985	103	0.69	0.65
Machecourt[86]	1985	105	0.45	0.80
Huerta[87]	1985	114	0.90	0.60
Melin[88]	1985	135	0.61	0.79
Hung[89]	1985	171	0.85	0.63
Detry[90]	1985	284	0.64	0.72
Weiner[91]	1985	617	0.61	0.76
Ananich[92]	1986	111	0.55	0.92
Vincent[93]	1986	122	0.68	0.48
Detrano[94]	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[95]	1980	107	0.64	0.81
Nair[96]	1983	280	0.66	0.93
Furuse[97]	1987	135	0.77	0.83
Others*	1971–1984	318	0.59	0.78
Averages w/o ST depression		840	0.67	0.84

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

- 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 pre-exercise hyperventilation was associated with a decreased specificity, although there is no explanation 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 (26).

Table 10. Studies Including Digitalis

Author	Year	Total Patients	Sensitivity	Specificity
Roitman[46]	1970	100	0.73	0.82
Silber[75]	1979	108	0.71	0.70
Dunn[76]	1979	125	0.63	0.65
Marcomichelakis[78]	1980	100	0.92	0.62
Machecourt[80]	1981	112	0.48	0.82
Currie[83]	1983	105	0.77	0.82
Nair[96]	1983	280	0.66	0.93
Hlatky[84]	1984	3094	0.70	0.85
O'Hara[85]	1985	103	0.69	0.65
Machecourt[86]	1985	105	0.45	0.80
Huerta[87]	1985	114	0.90	0.60
Weiner[91]	1985	617	0.61	0.76
Ananich[92]	1986	111	0.55	0.92
Vincent[93]	1986	122	0.68	0.48
Detrano[94]	1986	303	0.69	0.73
Others*	1971 through 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[74]	1977	113	0.84	0.17
Weiner[77]	1979	2045	0.79	0.69
Morales-Ballejo[79]	1981	100	0.62	0.74
Guiteras[81]	1982	112	0.79	0.66
Santinga[82]	1982	113	0.56	0.86
Melin[88]	1985	135	0.61	0.79
Hung[89]	1985	171	0.85	0.63
Detry[90]	1985	284	0.64	0.72
Furuse[97]	1987	135	0.77	0.83
Others*	1978 through 1986	340	0.71	0.85
Averages w/o digitalis		3548	0.72	0.69

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

Confounders of Stress ECG Interpretation

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. Although specificity is lowered in the presence of resting ST depression less than 1 mm, the standard exercise test is still a reasonable first test option because sensitivity is increased. There is a divergence of opinion regarding two specific patient groups: those who are taking digoxin and have less than 1 mm of ST depression and those with LVH with less than 1 mm of resting ST depression. If the test result is negative, the likelihood of CAD is substantially reduced, but an abnormal response, has low specificity, and therefore further testing is indicated. In the

Table 12. Studies Including Left Ventricular Hypertrophy

Author	Year	Total Patients	Sensitivity	Specificity
Roitman[46]	1970	100	0.73	0.82
Erikssen[74]	1977	113	0.84	0.17
Silber[75]	1979	108	0.71	0.70
Dunn[76]	1979	125	0.70	0.65
Weiner[77]	1979	2045	0.79	0.69
Sketch[95]	1980	107	0.64	0.81
Machecourt[80]	1981	112	0.48	0.82
Hlatky[84]	1984	3094	0.69	0.79
O'Hara[85]	1985	103	0.69	0.65
Machecourt[86]	1985	105	0.45	0.80
Huerta[87]	1985	114	0.90	0.60
Weiner[91]	1985	617	0.61	0.76
Ananich[92]	1986	111	0.55	0.92
Vincent[93]	1986	122	0.68	0.48
Detrano[94]	1986	303	0.69	0.73
Others*	1974 through 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[78]	1980	100	0.92	0.62
Morales-Ballejo[79]	1981	100	0.62	0.74
Guiteras[81]	1982	112	0.79	0.66
Santinga[82]	1982	113	0.56	0.86
Currie[83]	1983	105	0.77	0.82
Nair[96]	1983	280	0.66	0.93
Melin[88]	1985	135	0.61	0.79
Hung[89]	1985	171	0.85	0.63
Detry[90]	1985	284	0.64	0.72
Furuse[97]	1987	135	0.77	0.83
Others*	1971 through 1983	442	0.69	0.84
Averages w/o LVH		1977	0.72	0.77

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

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.

Tables 8 through 13 were developed to resolve the issues of LVH, resting ST depression, and digoxin use. 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. These studies can be summarized as follows:

- 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 taking digoxin had a mean sensitivity of 68% and a mean specificity of 74%; studies that excluded patients taking digoxin had a mean sensitivity of 72% and a mean specificity of 69%.

When these results are compared 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 use 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 can be explained by differing degrees of workup bias (354), but it also demonstrates that some of the variability is explained by improper methods for testing and analysis. Upsloping ST depression should be considered borderline or negative.

Digoxin

Digoxin produces an abnormal ST-segment response to exercise. This abnormal ST depression occurs in 25% to 40% of healthy subjects studied (30,31) and is directly related to age. Two weeks are required to alleviate the effect on the repolarization pattern (32).

Left Ventricular Hypertrophy With Repolarization Abnormalities

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 additional 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 (38-42). Miranda et al. (43) 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 taking digoxin or with valvular or congenital heart disease were excluded. Ten percent of these selected male patients had persistent resting ST-segment depression that correlated with nearly twice the prevalence of severe coronary disease (30%) compared with those without resting ST-segment depression (16%). Diagnostic end points of two mm 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. (44) and Harris et al. (45), as well as a large study by Fearon et al. (355), had similar results.

Left Bundle-Branch Block

Exercise-induced ST depression usually occurs with left bundle-branch block and has no association with ischemia (36). Even up to 1 cm of ST depression can occur in healthy normal subjects. There is no level of ST-segment depression that confers diagnostic significance in left bundle-branch block.

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 (37). 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. The presence of right bundle-branch block does not appear to reduce the sensitivity, specificity, or predictive value of the stress ECG for the diagnosis of ischemia.

Beta-Blocker Therapy

Despite the marked effect of beta-blockers on maximal exercise heart rate, when patients were 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 (33). 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 or has hypertension. However, exercise testing in patients taking beta-blockers may have reduced diagnostic or prognostic value because of inadequate heart rate response. The decision to remove a patient from beta-blocker therapy for exercise testing should be made on an individual basis and should be done carefully to avoid a potential hemodynamic "rebound" effect, which can lead to accelerated angina or hypertension.

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) (34,35).

Atrial Repolarization

Atrial repolarization waves are opposite in direction to P waves and may extend into the ST segment and T wave. Exaggerated atrial repolarization waves during exercise can cause downsloping ST depression in the absence of ischemia. Patients with false-positive exercise tests based on this finding have a high peak exercise heart rate, absence of exercise-induced chest pain, and markedly downsloping PR segments in the inferior leads (356,357).

ST-Segment Interpretation Issues

Lead Selection

Lead V_5 alone consistently outperforms the inferior leads and the combination of lead V_5 with II, because lead II has a high false-positive rate. In patients without prior myocardial infarction and with 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 (48).

Right-Sided Chest Leads

In a new approach, Michaelides et al. (358) examined 245 patients who underwent exercise testing with standard 12 leads, right ventricular leads, and thallium-201 scintigraphy. They found sensitivities of 66%, 92%, and 93% and specificities of 88%, 88%, and 82%, respectively, for the detection of CAD by angiography, i.e., comparable results to perfusion scanning when right-sided leads were added. However, their study was performed in a population with an abnormally high prevalence of coronary disease, and the committee would not recommend clinical use of right-sided chest leads until these results are confirmed by others.

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 (49,50). If a slowly ascending slope is used as a criterion for abnormal findings, 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 (51-57). ST elevation on a normal ECG (other than in aVR or V_1) represents transmural ischemia (caused by spasm or a critical lesion), is very rare (0.1% in a clinical laboratory), and, in contrast to ST depression, is very arrhythmogenic and localizes the ischemia. When it occurs in leads V_2 through V_4, 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 caused by wall-motion abnormalities (58,59); other studies have found it to be a marker of residual viability in the infarcted area (60-62). Accompanying ST depression in such patients can be caused by a second area of ischemia or reciprocal changes.

R-Wave Changes

Many factors affect the R-wave amplitude response to exercise (63), and the response does not have diagnostic significance (64,65). 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 (66). 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. Adjustment of 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.

ST-Heart Rate Adjustment

Several methods of heart rate adjustment have been proposed to increase the diagnostic accuracy of the exercise ECG. The maximal slope of the ST segment relative to heart rate is derived either manually (67) or by computer (68). A second technique, termed the ST/HR index, divides the difference between ST depression at peak exercise by the exercise-induced increase in heart rate (69,70). ST/HR adjustment has been the subject of several reviews since the last publication of these guidelines (359,360). The major articles that used this approach for diagnostic testing include Morise's report (361) of 1358 individuals undergoing exercise testing (only 152 with catheterization data) and the report by Okin et al. (362) considering heart rate reserve (238 controls and 337 patients with coronary disease). Viik et al. considered the maximum value of the ST/HR hysteresis over a different number of leads for the detection of CAD (363). The study population consisted of 127 patients with coronary disease and 220 patients with a low likelihood of the disease referred for an exercise test. Neither the study by Okin et al. or that by Viik et al. considered consecutive patients with chest pain, and both had limited challenge. Limited challenge favors the ST/HR index, because healthy patients have relatively high heart rates and sick patients have low heart rates, thus leading to a lower ST/HR index in those without disease and a higher index in sicker patients, the enrollment of relatively healthy patients in these studies presents a limited challenge to the ST/HR index. Likewise, the Morise study had a small number of patients who underwent angiography. The only study with neither of these limitations was QUEXTA (353). This large, multicenter study followed a protocol to reduce workup bias and was analyzed by independent statisticians. The ST/HR slope or index was not found to be more accurate than simple measurement of the ST segment. Although some studies in asymptomatic (and therefore very low likelihood) individuals have demonstrated additional prognostic value with the ST/HR adjustment, these data are not directly applicable to the issue of diagnosis in symptomatic patients (364,365). Nevertheless, one could take the perspective that the ST/HR approach in symptomatic patients has at least equivalent accuracy to the standard approach. Although not yet validated, there are situations in which the ST/HR approach could prove useful, such as in rendering a judgment concerning certain borderline or equivocal ST responses, e.g., ST-segment depression associated with a very high exercise heart rate.

Computer Processing

Although computer processing of the exercise ECG can be helpful, it can result in a false-positive indication of ST depression (73). 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 with 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 checkmarked to indicate the PR isoelectric line and the ST measurement points. None of the computerized scores or measurements have been validated sufficiently to recommend their widespread use. At least one study in which these shortcomings have been addressed has shown that computerized measurements are comparable to visual measurements, and, when combined with scores, they can provide excellent test characteristics (366).

III. RISK ASSESSMENT AND PROGNOSIS IN PATIENTS WITH SYMPTOMS OR A PRIOR HISTORY OF CAD

Class I

1. **Patients undergoing initial evaluation with suspected or known CAD, including those with complete right bundle-branch block or less than 1 mm of resting ST depression. Specific exceptions are noted below in Class IIb.**
2. **Patients with suspected or known CAD, previously evaluated, now presenting with significant change in clinical status.**
3. **Low-risk unstable angina patients (see Table 17) 8 to 12 hours after presentation who have been free of active ischemic or heart failure symptoms. *(Level of Evidence: B)***
4. **Intermediate-risk unstable angina patients (see Table 17) 2 to 3 days after presentation who have been free of active ischemic or heart failure symptoms. *(Level of Evidence: B)***

Class IIa

Intermediate-risk unstable angina patients (see Table 17) who have initial cardiac markers that are normal, a repeat ECG without significant change, and cardiac

markers 6 to 12 hours after the onset of symptoms that are normal and no other evidence of ischemia during observation. ***(Level of Evidence: B)***

Class IIb

1. **Patients with the following resting ECG abnormalities:**
   - **Pre-excitation (Wolff-Parkinson-White) syndrome**
   - **Electronically paced ventricular rhythm**
   - **1 mm or more of resting ST depression**
   - **Complete left bundle-branch block or any interventricular conduction defect with a QRS duration greater than 120 ms.**
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.**
2. **High-risk unstable angina patients (see Table 17).** ***(Level of Evidence: C)***

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 examination, and laboratory test data items. Using these data, the physician formulates a working diagnosis and risk assessment and selects an initial management strategy (98). This strategy may consist of additional noninvasive testing, referral for prompt cardiac catheterization, or performance of a therapeutic trial. The additional data that result 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 examination 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, 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 CAD: General Considerations

Coronary artery disease 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 of mechanisms used by the cardiovascular system to compensate for that damage are of paramount

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.

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 describe 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 provide evidence of a recent coronary plaque rupture, which indicates 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 are related to the presence of electrical instability of the myocardium and the propensity for malignant ventricular arrhythmia. The final group of prognostic factors describe 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 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 supports a pathophysiological model in which most major cardiac events (sudden death, acute myocardial infarction, and 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 (i.e., 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 (i.e., 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 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).

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.

Symptomatic Patients With Nonacute CAD

Unless cardiac catheterization is indicated, patients with suspected or known CAD and new or changing symptoms that suggest 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 (346,347).

Choice of initial stress testing modality should be based on evaluation of the patient's resting ECG, the patient's 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 (99-101). Patients with widespread resting ST depression (greater than or equal to 1 mm) or patients with, complete left bundle-branch block, an intraventricular conduction defect with a QRS duration greater than 120 ms, ventricular paced rhythm, or pre-excitation 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. The preserved prognostic value of exercise ECG testing in patients with nonspecific resting ST-T abnormalities, defined as ST depression of any magnitude, T-wave abnormalities, or both, not due to one of the secondary causes above, has been demonstrated (367). However, because fewer than 20 patients with ST depression greater than or equal to 1 mm were included in the study, there are not enough data to recommend an exercise ECG alone in this subgroup. Patients unable to exercise because of physical limitations that affect exercise capacity (e.g., arthritis, amputations, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, or 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 nine 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 (109).

One of the strongest and most consistent prognostic markers identified in exercise testing is maximum exercise capacity, which is influenced at least in part by the extent of resting left ventricular dysfunction and the amount of further left

Table 16. Prognostic Studies of Exercise Testing

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

ventricular dysfunction induced by exercise. However, the relation between exercise capacity and left ventricular function is complex, because exercise capacity is also affected by age, general physical conditioning, comorbidities, and psychological state (especially the presence of depression) (110). Several exercise parameters can be used as markers of exercise capacity (Table 15), including maximum exercise duration, maximum MET level achieved, maximum workload achieved, maximum heart rate, chronotropic incompetence, and double product. When the exercise test is being interpreted, it is very important that exercise capacity be taken 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_2 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 maximum oxygen uptake ($V_{O_{2max}}$), $V_{O_{2max}}$ 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 (103). Other less powerful prognostic ST variables included the number of leads that showed 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 (CASS) Registry. Using the Duke database, McNeer and coworkers (111) demonstrated that an "early positive" exercise test result (ST depression greater than or equal to 1 mm in the first 2 stages of the Bruce protocol) identified a high-risk population, whereas patients who could exercise into stage IV were at low risk regardless of the ST response. Weiner and colleagues (102), using the CASS Registry, analyzed 4083 medically treated patients and identified 12% as high risk on the basis of greater than or equal to 0.1 mV of 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 studies have attempted to incorporate multiple exercise variables into a prognostic score. Using Cox regression analysis, Mark and colleagues (103) created the Duke treadmill score with 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).

*Note that ST-segment deviation can be measured at 60 to 80 ms after the J point. If the amount of exercise-induced ST-segment deviation is less than 1 mm, the value entered into the score for ST deviation is 0. Exercise time is based on a standard Bruce protocol.

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 and ejection fraction). To improve ease of use, the Duke treadmill score was converted into a nomogram (Fig. 2). This nomogram uses both time on the Bruce protocol and corresponding METs, which can be calculated for other treadmill protocols. The score has subsequently been validated in 613 outpatients at Duke who did not all proceed to coronary angiography and in exercise-testing populations at several other centers (112-114). The treadmill score was even more useful for outpatients: approximately two thirds had treadmill scores that indicated low risk. The score works equally well with men and women, although women have a lower overall risk for any score value than men (368). The score has also been validated in patients with resting nonspecific ST-T-wave changes (367). A limitation is the small number of elderly patients represented in studies that evaluated this score.

The value of exercise treadmill testing for prognostic assessment in elderly subjects has been described in the Olmstead County cohort followed by the Mayo Clinic (369). As expected, the elderly patients (greater than or equal to 65 years) had more comorbidity and achieved a lower workload than their younger counterparts. They also had a significantly worse unadjusted survival. Workload expressed as METs was the only treadmill variable associated with all-cause mortality in both groups (adjusting for clinical prognostic variables), whereas both workload and exercise angina were associated with cardiac events (death plus myocardial infarction) in both groups. A positive ST response was not prognostic in the older patients when tested as a binary variable. Quantitative ST-segment deviation with exercise was apparently not available in this cohort, and the Duke Treadmill Score was not computed in this study.

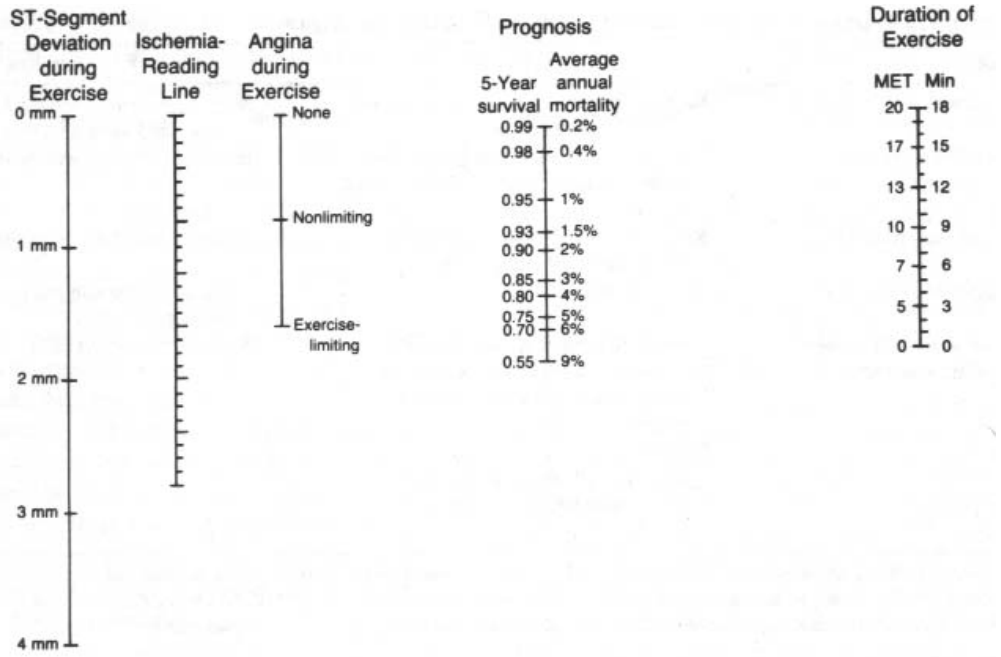

Figure 2. Nomogram of the prognostic relations embodied in the treadmill score. Prognosis is determined in five steps: (1) The observed amount of exercise-induced ST-segment deviation (the largest elevation or depression after resting changes have been subtracted) is marked on the line for ST-segment 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.[112]

Morrow and colleagues (104) 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 below resting value and history of congestive heart failure or use of digoxin). The score is calculated as follows: 5 × (CHF/digoxin [yes = 1; no = 0]) + exercise-induced ST depression in millimeters + change in systolic blood pressure score – 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 pre-exercise blood pressure. With this score, 77% of the Long Beach Veterans Administration Hospital 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%).

Several studies have highlighted the prognostic importance of other parameters from the exercise test. Chronotropic incompetence, defined as either failure to achieve 80% to 85% of the age-predicted maximum exercise heart rate or a low chronotropic index (heart rate adjusted to MET level), was associated with an 84% increase in the risk of all-cause mortality over a 2-year follow-up in 1877 men and 1076 women who were referred to the Cleveland Clinic for symptom-limited thallium treadmill testing (370,371). The Cleveland Clinic investigators have also demonstrated the prognostic importance of an abnormal heart rate recovery pattern after exercise testing. Defined as a change of less than or equal to 12 bpm from peak exercise heart rate to heart rate measured 2 minutes later, an abnormal heart rate recovery was strongly predictive of all-cause mortality at 6 years in 2428 patients referred for thallium exercise testing (372). The importance of this parameter has been confirmed in four subsequent studies from the same investigators (373-376) and independently in a comparatively high-risk male population from two Veterans Affairs Medical Centers (377). Similar trends have been suggested for a delayed systolic blood pressure response after exercise, defined as a value greater than 1 for systolic blood pressure at 3 minutes of recovery divided by systolic blood pressure at 1 minute of recovery. This finding was associated with severe CAD in a study of 493 patients at the Cleveland Clinic who had both symptom-limited exercise testing and coronary angiography (within 90 days) (378). In a study of 9454 consecutive patients, most of whom were asymptomatic, the Cleveland Clinic investigators reported that abnormal heart rate recovery and the Duke treadmill score were independent predic-

tors of mortality (376). Further work is needed to define the role of chronotropic incompetence, abnormal heart rate recovery, and delayed blood pressure response in the risk stratification of symptomatic patients relative to other well-validated treadmill test parameters.

In patients who are classified as low risk on the basis of clinical and exercise testing information, there is no compelling evidence that an imaging modality adds significant new prognostic information to a standard exercise test. In this regard, a distinction should be made between studies that show a statistical advantage of imaging studies over exercise ECG alone and studies that demonstrate that the imaging data would change practice (e.g., 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 (114). Patients with an intermediate-risk treadmill score and normal or near-normal exercise myocardial perfusion images and normal cardiac size are at low risk for future cardiac death and can be managed medically (379).

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 with exercise test parameters. For example, in one large cohort of chronic CAD patients, the predictive power of exercise ST depression for cardiovascular death alone and cardiovascular death plus nonfatal myocardial infarction was almost identical, despite the fact that addition of the nonfatal events should have substantially boosted the predictive power (i.e., more outcome events should yield better power in prognostic models) (103). 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 (116). 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 that a nonfatal myocardial infarction will occur. 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 epidemiologic 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.

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 (e.g., those with a predicted average annual cardiac mortality rate 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 (e.g., patients with a strongly positive test result in Fig. 2 or predicted average annual cardiac mortality rate greater than or equal to 4% per year) should usually be referred for cardiac catheterization. Patients with an intermediate-risk exercise test result (e.g., predicted average annual cardiac mortality rate 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.

Patients With Acute Coronary Syndrome

Acute coronary syndrome (ACS; unstable angina or acute myocardial infarction) 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 ACS 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 ACS relates to this acute and convalescent period.

The ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction has been published (350). A clinical risk stratification algorithm useful for

selecting the initial management strategy is seen in Table 17. Patients are separated into low-, intermediate-, or high-risk groups based on history, physical examination, and initial 12-lead ECG, and cardiac markers. (Note that this table is meant to be illustrative rather than comprehensive or definitive.) Low-risk patients, who include patients with new-onset or progressive angina with symptoms provoked by walking one block or one flight of stairs, in this scheme can typically be treated on an outpatient basis. Most intermediate-risk patients can be cared for in a monitored hospital bed, whereas 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 intermediate-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. In low-risk patients, testing can be performed when patients have been free of active ischemic or heart failure symptoms for a minimum of 8 to 12 hours (14). Intermediate-risk patients can be tested after 2 to 3 days, but selected patients can be evaluated earlier as part of a carefully constructed chest pain management protocol (see section on chest pain centers below). 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. Little evidence exists with which to define the safety of early exercise testing in unstable angina (117,380). One review of this area found 3 studies covering 632 patients with stabilized unstable angina who had a 0.5% death or myocardial infarction rate within 24 hours of their exercise test (380).

The limited evidence available supports the use of exercise testing in ACS patients with appropriate indications as soon as the patient has stabilized clinically. Larsson and colleagues (118) 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 that occurred during the first year.

The Research on Instability in Coronary Artery Disease (RISC) study group (119) 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.

In 766 unstable angina patients enrolled in the Fragmin During Instability in Coronary Artery Disease (FRISC) study between 1992 and 1994 who had both a troponin T level and a predischarge exercise test, the combination of a positive troponin T and exercise-induced ST depression stratified patients into groups with a risk of death or myocardial infarction that ranged from 1% to 20% (381). In 395 women enrolled in FRISC I with stabilized unstable angina who underwent a symptom-limited stress test at days 5 to 8, risk for cardiac events in the next 6 months could be stratified from 1% to 19%. Important exercise variables included not only ischemic parameters such as ST depression and chest pain but also parameters that reflected cardiac workload.

Chest Pain Centers

Over the last decade, increasing experience has been gained with the use of exercise testing in emergency department chest pain centers (see Table 17a) (380). The goal of a chest pain center is to provide rapid and efficient risk stratification and management for chest pain patients believed to possibly have acute coronary disease. A variety of physical and administrative setups have been used for chest pain centers in medical centers across the country; review of these details is beyond the scope of these guidelines. In most of the published series, exercise testing has been reserved for the investigation of patients who are low-risk on the basis of history and physical examination, 12-lead ECG, and serum markers. In the study by Gibler et al. (382), 1010 patients were evaluated by clinical examination, 9 hours of continuous ST monitoring, serial 12-lead ECGs, serial measurement of creatine kinase-MB levels, and resting echocardiograms. Patients without high-risk markers on the basis of this evaluation (78%) underwent a symptom-limited Bruce exercise ECG test. There were no adverse events from the testing, and the authors estimated a 5% prevalence of CAD in the tested population. These results are generally representative of the results in the approximately 2100 chest pain patients who have undergone exercise testing as part of a chest pain center protocol report (Table 17a) (380). The prevalence of CAD is extremely low in such chest pain patients, and the risk of adverse events with testing is correspondingly low.

Farkouh and colleagues from the Mayo Clinic examined the use of exercise testing in 424 intermediate-risk unstable angina patients (as defined by the ACC/AHA Committee to Develop Guidelines for the Management of Patients With Unstable Angina) as part of a randomized trial of admission to a chest pain unit versus standard hospital admission (383). There was no significant difference in event rates (death, myocardial infarction, or congestive heart failure) between the 212 patients in the hospital admission group and the 212 patients in the chest pain unit group. Of the total chest pain unit group, 60 met the criteria for hospitalization before stress testing, 55 had an indeterminate or high-risk test result, and 97 had a negative stress test. There were no complica-

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

Feature	High Risk At least one of the following features must be present	Intermediate Risk No high-risk feature but must have one of the following features	Low Risk No high- or intermediate-risk feature but may have any of the following features:
History		Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of Pain	Prolonged, ongoing (>20 min) pain at rest	Prolonged (>20 min) resting angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20 min) or relieved with rest or sublingual NTG)	New-onset or progressive-CCSC III or IV angina in the past 2 weeks with moderate or high likelihood of CAD.
Clinical Findings	Pulmonary edema, most likely related to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age older than 75 years	Age older than 70 years	
ECG Findings	Angina at rest with transient ST changes ≥0.05 mV BBB, new or presumed new/sustained ventricular tachycardia	T-wave inversions greater than 0.2 mV Pathologic Q waves	Normal or unchanged ECG during an episode of chest discomfort
Biochemical Cardiac Markers	Elevated (e.g., troponin T or I greater than 0.1 mg per ml)	Slightly elevated (e.g., troponin T >0.01 but <0.1 mg per ml	Normal

CCSC indicates Canadian Cardiovascular Society Classification; CAD, coronary artery disease; MR, mitral regurgitation; ECG, electrocardiography; BBB, bundle-branch block; MI, myocardial infarction; CABG, coronary artery bypass graft. Note: Estimation of the short-term risks of death and nonfatal cardiac ischemic events in unstable angina is a complex multivariable problem that cannot be fully specified in a table such as this. Therefore, the table is meant to offer general guidance and illustration rather than rigid algorithms. Adapted from AHCPR Clinical Practice Guideline No. 10, Unstable Angina: Diagnosis and Management, May 1994.

American College of Cardiology Foundation - www.acc.org
American Heart Association - www.americanheart.org

Table 17a. Summary of Studies Using Exercise ECG Testing in Chest Pain Centers

Investigator, y	Reference	No. of Subjects	Follow-up Period	ExECG	Adverse Events*	% Disease Prevalence	Clinical Outcome
Tsakonis (1991)	(423)	28	6.1 months	Modified Bruce (SLM)	0	0	Exercise testing was safe
Kerns (1993)	(424)	32	6 months	Bruce (APMHR)	0	0	Exercise testing was safe; reduced cost vs. admission
Gibler (1995)	(382)	1010	30 days	Bruce (SLM)	0	5	Sensitivity = 29%, Specificity = 99.4%, Positive Predictive Value = 44%†, Negative Predictive Value = 98.7%†
Gomez (1996)	(425)	50 50 controls	None	Cornell (SLM)	0	6	No difference in clinical outcome; reduced cost vs. admitted control
Zalenski (1998)	(426)	317	None – pts admitted for reference diagnosis	Modified Bruce	0	9.5	Sensitivity = 90%, Specificity = 50%‡, Negative Predictive Value = 98%‡
Polanczyk (1998)	(427)	276§	6 months	Modified Bruce	0	25	Sensitivity = 73%, Specificity 74%, Negative Predictive Value = 98%
Farkouh (1998)	(383)	424	6 months	Not specified	0		Intermediate risk patients were studied; no difference in clinical outcomes¶; reduced cost vs. admitted control

APMHR = age-predicted maximum heart rate end point, SLM = symptom-limited maximum end point.
* Death or myocardial infarction.
† With respect to diagnosis if admitted, and 30-day follow-up on all patients.
‡ With respect to reference diagnosis from admission of all patients.
§ Included 70 patients (25%) with a history of CHD.
¶ Comparison of those admitted to hospital vs. chest pain center.

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tions directly attributable to the performance of a stress test in these patients.

These results demonstrate that exercise testing is safe in low-risk chest pain patients presenting to the emergency department. In addition, testing appears safe in carefully selected intermediate-risk patients. Use of early exercise testing in emergency department chest pain centers improves the efficiency of management of these patients (and may lower costs) without compromising safety. However, exercise testing in this setting should only be done as part of a carefully constructed management protocol and only after the patients have been screened for high-risk features or other indicators for hospital admission.

IV. AFTER MYOCARDIAL INFARCTION

Class I

1. **Before discharge for prognostic assessment, activity prescription, evaluation of medical therapy (submaximal at about 4 to 6 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

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

Class IIb

1. **Patients with the following ECG abnormalities:**
   - **Complete left bundle-branch block**
   - **Pre-excitation syndrome**
   - **LVH**
   - **Digoxin therapy**
   - **Greater than 1 mm of resting ST-segment depression**
   - **Electronically paced ventricular rhythm**
2. **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.**
2. **At any time to evaluate patients with acute myocardial infarction who have uncompensated congestive heart failure, cardiac arrhythmia, or noncardiac conditions that severely limit their ability to exercise.** ***(Level of Evidence: C)***
3. **Before discharge to evaluate patients who have already been selected for, or have undergone, cardiac catheterization. Although a stress test may be useful before or after catheterization to evaluate or identify ischemia in the distribution of a coronary lesion of borderline severity, stress imaging tests are recommended.** ***(Level of Evidence: C)***

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 (345). Although some of the evidence is presented in more detail here and a few references are added, the committee did not believe 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. Because 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 of thrombolytic agents, greater use of revascularization strategies, and increased use of beta-adrenergic blocking agents and angiotensin converting enzyme inhibitors continue to change the clinical presentation of the postinfarction patient (120-125). 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 (121) 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. (122) 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 because of either clinical instability or disabling comorbidities, e.g., unstable angina, uncontrolled heart failure, uncontrolled arrhythmias, and neurological, orthopedic, or vascular impairment of the lower extremities. In the largest series to date, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) investigators (123) reported that nearly 40% of the 10,219-patient cohort did not undergo exercise testing within 28 days of myocardial infarction. This report and several other studies in patients who have received thrombolytic therapy (126) and those who have not (127-129) reported that patients who are unable to perform an exercise test have a much higher adverse event rate than those who are able. With

***Exceptions are noted under Classes IIb and III.**

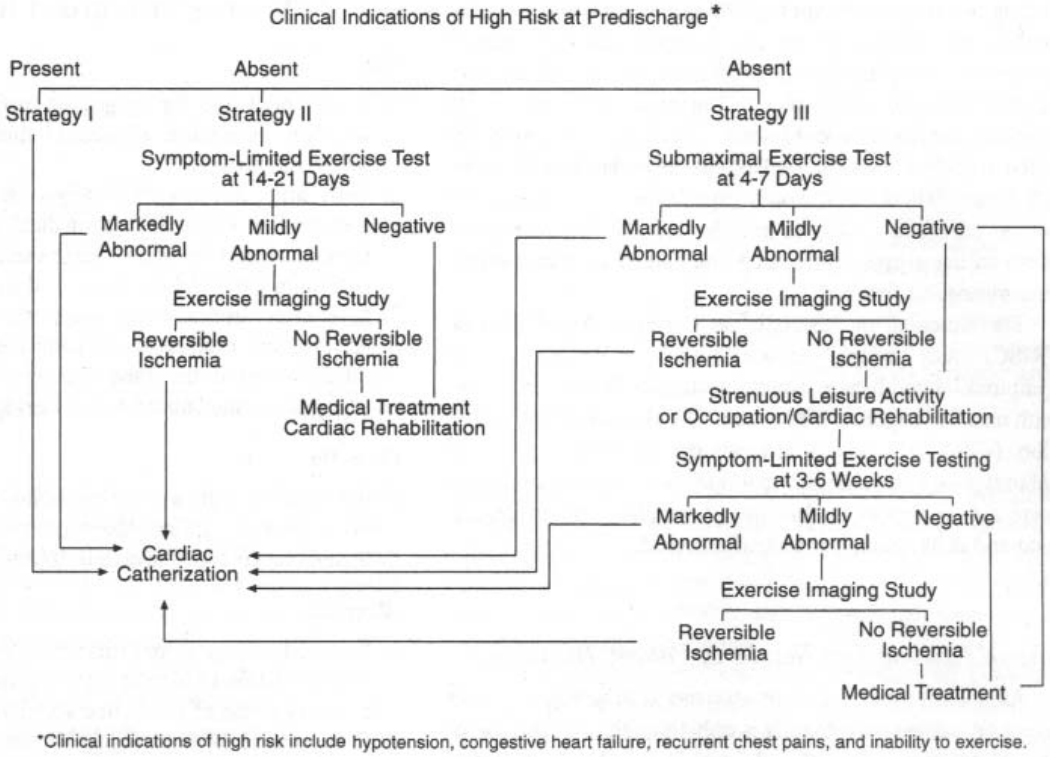

Figure 3. Strategies for exercise test evaluation soon after myocardial infarction. If patients are at high risk for ischemic events, based on clinical criteria, they should undergo invasive evaluation to determine if they are candidates for coronary revascularization procedures (strategy I). For patients 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.[345]

this background, the role of exercise testing after myocardial infarction will be presented. The use of exercise or pharmacological imaging studies (nuclear and echocardiography) is not discussed here, because their use is presented in detail in the ACC/AHA Guidelines for Clinical Use of Cardiac Radionuclide Imaging (5), Guidelines for the Clinical Application of Echocardiography (349), and Guidelines for the Management of Patients With Acute Myocardial Infarction (345).

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 use 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 because of left bundle-branch block, pre-excitation syndrome, LVH, or digoxin therapy, or those who demonstrate major (greater than 1 mm) ST-segment depression or elevation, an exercise or pharmacological imaging study should be considered, because 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. Timing of predischarge exercise tests in the literature ranges from 5 to 26 days after infarction (126,129-132). In 2 separate observational studies, exercise tests have been performed within 3 days after myocardial infarction (124,384) without occurrence of exercise-related deaths, myocardial infarction, or sustained VT; however, more data are needed to establish the safety and utility of this very early protocol. Postdischarge tests have been performed early (14 to 21 days), at 6 weeks (133), or at 6 months after infarction (134). The exercise pro-

tocols 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% of the predicted maximum heart rate, or a peak MET level of 5 (131). Symptom-limited tests are designed to continue until the patient demonstrates signs or symptoms that necessitate termination of exercise (i.e., 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) (135). The most commonly used treadmill protocols are the modified Bruce, the modified Naughton, and the standard Bruce (131). The ramp treadmill or cycle ergometer protocols offer the advantage of steady gradual increases in work rate and better estimation of functional capacity (136) but have not been widely studied in patients early after myocardial infarction.

Some 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 represents a better estimate of peak functional capacity (130,135,137,385). Thus, early symptom-limited tests have the potential to be more useful in activity prescription 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 that is 1.9 times that of submaximal tests, although the overall fatal event rate is quite low (130,131,135). 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 (121) 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 (138) demonstrated 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 was 1% at 1 month and 3.6% at 1 year. Recurrent ischemia occurred in 7% of this group. Data from the GISSI-2 study (386) demonstrated that elderly patients (aged 70 years or more) treated with thrombolytic therapy, aspirin (90%), and intravenous beta-blockers (48%) who were able to perform an exercise test within the first month after myocardial infarction had a favorable prognosis irrespective of the test results. The 6-month mortality rate in these patients was remarkably low at 2.3% but still higher than that in younger patients (1.1%).

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 after discharge is therefore not surprising and substantially reduces the predictive accuracy of early exercise testing.

There is limited evidence of 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.

Inability to Exercise

Data from GUSTO (138) and other large thrombolytic trials (123,126,386) demonstrate that those patients unable to perform an exercise test have the highest adverse cardiac event rate, whereas uncomplicated stable patients have a low cardiac event rate even before they undergo further risk assessment by exercise testing. Earlier studies in patients not receiving thrombolytic agents demonstrated a similarly high event rate in those patients unable to exercise (127,129). 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 (139-141). However, more recent studies are limited in that coronary revascularization inter-

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[141] (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 inferiorposterior MI.
Shaw[150] (1996)	15,613 Meta-analysis (2 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: • Exercise ST depression (or 1.7) • Impaired systolic blood pressure (or 4.0) • Limited exercise capacity (or 4.0) 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.

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[123] (1995) GISSI-2 study	6296	6296	Symptom-limited	28 d	6 mo	• 7.1% mortality in those unable to exercise • 1.7% mortality in those with a positive test result • 0.9% mortality in those with negative test results • Predictors of mortality: — Angina + ≥1 mm ST? — ST ↓ ≥1 mm at <100 W or <6 min exercise — <6 min exercise or peak work rate <100 W — SBP rise <28 mm Hg from rest
Chaitman[126] (1993) TIMI-2 Study	2502	2502	Submaximal	2 wk	1 y	• 1261 who underwent ETT were randomly assigned to conservative strategy • 9.3% mortality in those unable to exercise vs 2.3% in those who underwent ETT • 2.4% mortality with exercise ST ↓ vs. 0.6% without (P = 0 .13) • 9.3% underwent revascularization before discharge
Stevenson[148] (1993)	256	256	Symptom-limited	7–21 d	10 mo (6–12 mo)	• Predictors of recurrent ischemia: — ST segment ↓ ≥1 mm — Exercise tolerance <7 METs
Arnold[153] (1993)	981	490	Symptom-limited	Predischarge	1 y	• 260 of 981 subjects were randomly assigned to receive immediate PTCA • 3.6 relative risk of mortality in those unable to exercise • Exercise test predictors of mortality: — SBP rise <30 mm Hg from rest
Mickley[157] (1993)	123	35	Symptom-limited	1.4 wk	1 y	• ST depression >1 mm predicted future angina but not reinfarction or death
Piccalò[169] (1992)	157	157	Symptom-limited	15 d	6 mo	• 30% of patients with positive exercise test underwent coronary revascularization • 90% of patients without angina or ST ↓ ≥1 mm had no cardiac events in follow-up

*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.[2]

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ventions are often performed in persons who demonstrate an ischemic response (126,129,135,142,143), 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 than in those without ischemia (144-146). The GISSI-2 trial (123) 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 (147), ST depression at a low exercise level (148,149), or ST depression among patients with controlled heart failure (127) to be independent predictors of death or nonfatal myocardial infarction.

A meta-analysis (Table 18) that evaluated exercise testing within 6 weeks of myocardial infarction demonstrated 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 thrombolytic agents (150).

Exercise Capacity

MET level or exercise duration achieved on exercise testing is an important predictor of adverse cardiac events after myocardial infarction (123,125,129,132,134,143,148, 149,151). This observation appears to hold true for tests performed on the treadmill and the cycle ergometer. Failure to achieve 5 METs during treadmill exercise is associated with a worse prognosis (129,134,147,148).

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 (123,132,134,152,153). Inability to attain a systolic blood pressure greater than 110 mm Hg predicted poor outcome in patients with Q-wave infarcts (129) but not among those with non–Q-wave infarcts (127). The GISSI-2 investigators reported that a peak heart rate (in bpm)–blood pressure (in mm Hg) product less than 21,700 during exercise testing was an independent predictor of 6-month mortality after myocardial infarction (relative risk, 1.71) in patients treated with thrombolytic therapy, although the overall mortality rate in this study population was low (387).

Other Variables

Several studies demonstrated that the occurrence of exercise-induced ischemia was similar in patients with Q-wave and non–Q-wave infarctions (130,135,144,154-157). 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 (158). 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 (345). Thus, the number of patients taking these agents at the time of the postinfarction exercise test continues to grow (122). Beta-adrenergic blockers reduce the occurrence of angina and ischemic ST changes and lengthen the time to ischemia on exercise testing (128,159-161). Although beta-adrenergic blockade attenuates the ischemic response, two long-term follow-up studies demonstrated that these agents do not interfere with poor functional capacity as a marker of adverse prognosis (128,161). 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 medical 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 (see Table 19a) (7,388) but should be used only as a guide, with the understanding that the intensity at which activities are performed will directly influence the amount of energy required. Most domestic chores and activities require fewer 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 fewer than 5 METs. In the 15% of persons in the labor force whose work involves heavy manual labor (162), 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, or exercise-induced ischemia and in those who are otherwise

Table 19a. Estimated Energy Requirements for Various Activities*

1 MET	Can you take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk a block or two on level ground at 2 to 3 mph or 3.2 to 4.8 km per h?	4 METs	Climb a flight of stairs or walk up a hill? Walk on level ground at 4 mph or 6.4 km per h? Run a short distance? Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture? Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
4 METs	Do light work around the house like dusting or washing dishes?	Greater than 10 METs	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

MET indicates metabolic equivalent.
*Adapted from the AHA Exercise Standards (7) and Duke Activity Status Index (428).

apprehensive about returning to a physically demanding occupation (163-165,389).

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 (166). Randomized trials of cardiac rehabilitation after myocardial infarction show consistent trends toward survival benefit among patients enrolled in cardiac rehabilitation programs (162,166). Meta-analyses of these trials have calculated a significant 20% to 25% reduction in cardiovascular death in patients enrolled in such programs (167). Moreover, higher levels of physical fitness according to an exercise tolerance test are associated with reduced subsequent mortality (123,129,132,134,143,148,149,151). 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 (166).

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 (7,164,390). For these reasons, symptom-limited exercise testing before program initiation is needed for all patients in whom cardiac rehabilitation is recommended (ie, those with recent myocardial infarction, recent coronary artery bypass surgery, recent coronary angioplasty, chronic stable angina, or controlled heart failure) (7,166).

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 (166).

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 of the ability of exercise testing to stratify patients who have not received reperfusion therapy according to risk in the current era. Their mortality rates are higher than for those who either have received thrombolytic therapy or 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 6 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 (3).

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; and 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 WITH 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

Evaluation of exercise capacity when indicated for medical reasons in patients in whom the estimates of exercise capacity from exercise test time or work rate are 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

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 (V_{O_2}), carbon dioxide output (V_{CO_2}), minute ventilation, and ventilatory/anaerobic threshold. V_{O_2} at maximal exercise is considered the best index of aerobic capacity and cardiorespiratory function. Maximal V_{O_2} is defined as the point at which no further increase in measured V_{O_2} occurs despite an increase in work rate (a plateau is reached) during graded exercise testing. Peak V_{O_2} is the highest V_{O_2} attained during graded exercise testing, but the term does not imply that a plateau in measured V_{O_2} is reached. Most clinical studies report peak V_{O_2} rather than maximal V_{O_2} because the latter is often difficult to determine precisely. Estimation of aerobic capacity with published formulas based on exercise time or work rate without direct measurement is limited by physiological and methodological inaccuracies. This is illustrated in Fig. 4, which demonstrates the wide scatter of measured V_{O_2} per given treadmill time on a progressive treadmill protocol. Exercise protocols with large increments in work rate per stage (136) (Fig. 5), the use of handrail support during

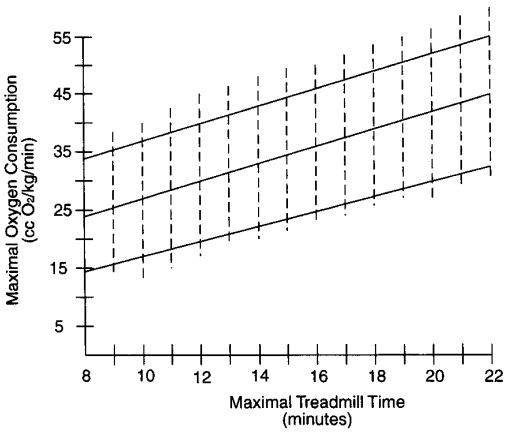

Figure 4. Relation of treadmill time (independent of specific protocol) to measured oxygen uptake using a progressive treadmill protocol. From Froelicher et al[174] with permission.

treadmill exercise (170), and the application of a single regression formula to a wide variety of heterogeneous populations (171), which range from the extremely fit to those impaired by heart or lung disease, all limit the reliability of V_{O_2} estimates. However, direct measures of V_{O_2} are reliable and reproducible and provide the most accurate assessment of functional capacity (172). 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 online analysis systems. In addition to peak or maximal V_{O_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 represents the amount of carbon dioxide produced divided by the

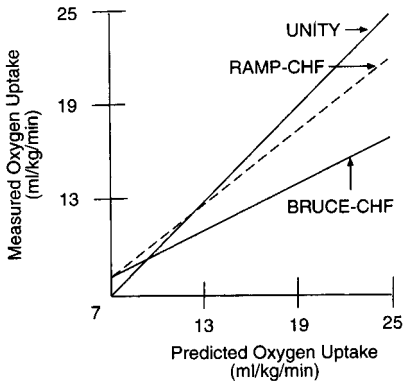

Figure 5. Relation between measured versus predicted oxygen uptake for the Bruce protocol and progressive ramp protocol in patients with heart failure. Unity is achieved when predicted oxygen uptake is equal to measured oxygen uptake. CHF indicates congestive heart failure. From Froelicher et al[174]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

amount of oxygen consumed. The respiratory exchange ratio generally ranges from 0.7 to 0.85 at rest and is dependent in part on the predominant fuel used for cellular metabolism. At high levels of exercise, CO_2 production exceeds V_{O_2}, and thus a respiratory exchange ratio greater than 1.0 often indicates that the subject is giving a near-maximal level of effort.

Another index of relative work effort is the ventilatory/anaerobic threshold (VAT). This is a point during exercise at which ventilation abruptly increases despite linear increases in work rate and V_{O_2}. At exercise intensities beyond the VAT, endurance time is greatly diminished. In most patients, the VAT is highly reproducible; however, in patients with heart failure, this may not be the case. The VAT cannot be measured in some patients, particularly those with very poor exercise capacity (391). 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 (173). 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 (V_E) and V_{CO_2} with increasing work rates and an abrupt increase in the respiratory exchange ratio and fraction of O_2 in expired air (F_{EO_2}); 2) an increase in V_E/V_{O_2} without an increase in V_E/V_{CO_2}, and an increase in V_{EO_2} without a decrease in the fraction of C_{O_2} in expired air; 3) the lowest V_E/V_{O_2} value measured during exercise; and 4) a curvilinear increase in V_E and V_{CO_2} with a linear increase in V_{O_2} (Fig. 6) (173,174). Further details on the methodology and interpretation of data obtained during ventilatory gas analysis are available (8,174,175).

Measurement of expiratory gases during exercise testing can provide the best estimate of functional capacity, grade the severity of functional impairment, objectively evaluate the response to interventions that may affect exercise capacity, objectively track the progression of disease that may limit exercise capacity, and assist in differentiating cardiac from pulmonary limitations in exercise capacity (176).

Normal values for maximal oxygen uptake among healthy adults at different ages are available (7) 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 V_{O_2}, heart rate, or total fitness in children. Normal values for VAT in children are provided elsewhere (9). 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 (177). This may be most useful when the heart rate response to exercise is not a reliable indicator of exercise intensity (e.g., 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 (178-181,392-394). The exercise capacity of patients with heart failure based on their peak V_{O_2} and VAT can be divided into four classes, as shown in Table 21 (182). 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 by this technique has improved ability to identify those with the poorest prognosis, who should be considered for heart transplantation (183,184) (Table 22). Abnormal ventilatory and chronotropic responses to exercise are also predictors of outcome in patients with heart failure (394,395). Also, evaluation of the rate of V_{O_2} decline during exercise recovery (V_{O_2} kinetics) may provide additional information regarding the

Table 20. Classification of Exercise Intensity Based on Oxygen Uptake[177]

Intensity	% VO_{2max}
Very light	<25
Light	25–44
Moderate	45–59
Hard	60–84
Very hard	≥85
Maximal	100

VO_{2max} indicates maximal oxygen uptake.

Table 21. Classification of Exercise Capacity in Patients With Heart Failure, Based on Peak Oxygen Uptake and Ventilatory Anaerobic Threshold[182]

Class	Impairment	Peak V_{O_2} (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

V_{O_2} indicates oxygen uptake; and VAT, ventilatory anaerobic threshold.

Table 22. Guidelines for Peak Exercise Oxygen Uptake as a Criterion for Cardiac Transplantation[184]

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

V_{O_2} indicates oxygen uptake.

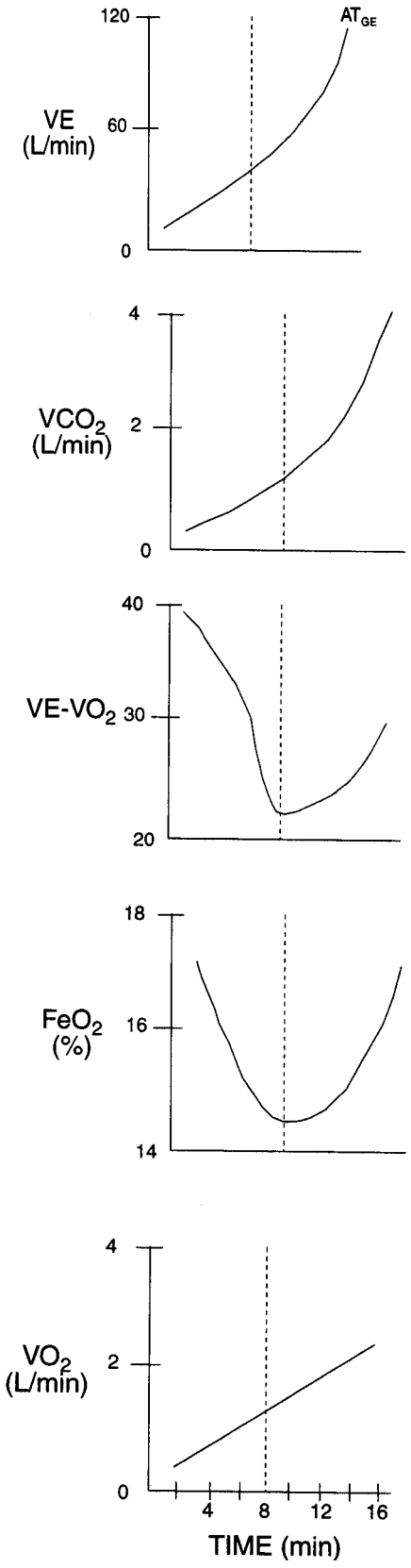

Figure 6. Measurements used to determine the gas exchange anaerobic threshold (Atge) using a progressive treadmill protocol. V_E indicates minute ventilation; V_{CO_2}, carbon dioxide production; V_{O_2}, oxygen uptake; and FeO_2, fraction of expired air that is oxygen. From Froelicher et al[174] with permission.

functional state in heart failure patients. Prolonged recovery time of V_{O_2} has been correlated with poorer exercise tolerance, lower peak V_{O_2} (396-398), and a lower cardiac index (399) than in those with normal oxygen kinetics. Most investigators conclude that measurement of peak V_{O_2} yields the best prognostic information in heart failure patients. Evaluation of submaximal and recovery ventilatory responses may be particularly useful when exercise to near-maximal levels (respiratory exchange ratio greater than 1) is not achieved (394-399).

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 (170). 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 (8).

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 (185). The probability of coronary disease in women, based on age, gender, and the nature of symptoms (17), is most commonly in the low- to intermediate-probability range, especially in premenopausal women. Although typical angina is as meaningful in women older than 60 years as it is in men (186), the clinical diagnosis of coronary disease in women may be difficult to make: almost half the women with symptoms in CASS (187), who were younger than 65 years of age, had normal coronary arteriograms. Compared with men, women less than 60 years old had less extensive coronary disease. From a Bayesian standpoint, the lower 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 ECG 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 (188). Studies examining the accuracy of ST-segment interpretation for the diagnosis of coronary disease according to gender are summarized in Table 23 (84,88,186,189-192,194-199). Kwok et al. reported a weighted mean sensitivity of 0.61 (95% confidence interval, 0.54–0.68) and specificity of 0.70 (95% confidence interval, 0.64–0.75) in a meta-analysis of 19 ECG studies in women, each of which included at least 50 subjects (400). Variations in results in women may be caused by the use of different criteria for defining coronary disease, differences in population selection (including prevalence of prior myocardial infarc-

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[189] (1972)	112	49	>70% dia	12	38	79%, n = 42	66%, n = 70
Linhart[190] (1974)	98	46	>50% dia	na	34	71%, n = 24	78%, n = 74
Sketch[191] (1975)	56	50	>75% dia	na	27	50%, n = 10	78%, n = 46
Barolsky[192] (1979)	92	50	>50% dia	16	41	60%, n = 30	68%, n = 62
Weiner[193] (1979)	580	na	>70% dia	16	48	76%, n = 169	64%, n = 411
Ilsley[194] (1982)	62	51	>50% dia	27	44	67%, n = 27	74%, n = 35
Hung[195] (1984)	92	51	>70% dia	16	51	75%, n = 28	59%, n = 64
Hlatky[84] (1984)	613	na	>75% dia	na	na	57%, n = 194	86%, n = 419
Melin[88] (1985)	93	51	>50% dia	20	30	58%, n = 24	80%, n = 69
Robert[196] (1991)	135	53	>50% dia	29	37	68%, n = 56	48%, n = 79
Chae[197] (1993)	114	na	>50% dia	na	54	66%, n = 71	60%, n = 43
Williams[198] (1994)	70	60	>50% dia	19	57	67%, n = 33	51%, n = 37
Marwick[199] (1995)	118	60	>50% dia	17	58	77%, n = 48	56%, n = 70
Morise[200] (1995)†	264	56	>50% dia	27	33	46%, n = 81	74%, n = 151
Morise[200] (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.

tion and multivessel disease), and differences in performance of the test, including criteria for ST-segment positivity and type of exercise. In a series of 976 symptomatic women referred for exercise testing and coronary angiography, Alexander et al. reported that a low-, moderate-, and high-risk Duke treadmill score predicted CAD greater than or equal to 75% in 19.1%, 34.9%, and 89.2% of subjects, respectively (368). The frequency of 3-vessel disease greater than or equal to 75% or left main coronary disease was 3.5%, 12.4%, and 46%, respectively (368).

Exercise-induced ST depression is less sensitive in women than in men (84), which reflects a lower prevalence of severe CAD and the inability of many women to exercise to maximum aerobic capacity (201,202). The exercise ECG is commonly viewed as less specific in women than in 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 (28). Significant gender differences were reported in unbiased estimates of sensitivity and specificity. However, these were modest (less than 10%) and did not appear to preclude the use of treadmill exercise testing in women (28). A careful analysis of the incremental diagnostic value of treadmill testing found similar values in men and women (200). Studies that have documented lower specificity in women have cited both lower disease prevalence and non-Bayesian factors (192), 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 been shown to be of value (203) but awaits widespread application. Avoidance of identifying ST depression in the inferior leads and identification of test positivity based on persistent changes (204) enhance the predictive value of a positive test but may compromise the predictive value of a negative test. Finally, because 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 (heart rate and blood pressure) response to exercise, and the presence of cardiac symptoms (e.g., chest discomfort or dyspnea), that are used in interpretation of the test result. The diagnostic contribution of these findings has been calculated in multivariate models, resulting in development of equations that give the likelihood of disease. The accuracy of exercise testing was significantly increased by the use of a multivariate model compared with ST-segment evaluation alone (196). However, not all centers have reported these favorable findings (198), and although the exercise score concept is attractive, its clinical application in women has remained limited. In a retrospective population-based cohort study of 1452 men and 741 women, exercise-induced angina, ischemic ECG changes, and workload were strongly associated with all-cause mortality in cardiac events in both sexes (401). Alexander et al. compared the Duke treadmill score in 976 women and 2249 men; 2-year mortality rates for women

were 1%, 2.2%, and 3.6% for low-, moderate-, and high-risk scores compared with 1.7%, 5.8%, and 16.6% in men, respectively. Women had a similar frequency of angina on the treadmill as men, but exertional angina in women was less often correlated with coronary disease presence (352,368).

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 be considered for 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 the patient proceeds to angiography (88). 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 (199). 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 CAD in the Elderly

Rationale

Patients older than 65 years are usually defined as "elderly." The elderly population is often classified in the following age groups: 65 to 75 years, 75 to 85 years, and 85 years or older (402). There are few published data on exercise testing in subjects 85 years or older. Therefore, this section primarily focuses on patients older than 75 years. Maximal aerobic capacity declines 8% to 10% per decade in sedentary men and women, with an approximate 50% reduction in exercise capacity between ages 30 and 80 years (403). Few data have been published with respect to the use of exercise testing for diagnostic and prognostic assessment of CAD in this group. Although angiographic tables show an increased gradient of risk for coronary disease and more extensive coronary disease in older patients (404), there are few data from patients older than 75 years, and scores for assessing prognosis have not included the very elderly patients. The prevalence and risk of coronary disease increase with advancing age, and in 1989, the National Health Interview Survey (206) reported that the prevalence of diagnosed CAD was 1.8% in men over the age of 75 and 1.5% in women over 75 years of age. This disease is commonly occult, with silent ischemia estimated to be present in 15% of 80-year-olds (207). On Bayesian grounds, the high prevalence and greater severity of coronary stenoses in this group increase the sensitivity of testing and 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 (405). Functional capacity is often compromised because of 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 test (208), 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 (209). 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 (84). Because of 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 (210). These false-positive results may also reflect the coexistence of LVH caused by 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 responses to exercise, exercise-induced arrhythmias, and exercise capacity (406). Arrhythmias occur more frequently with increasing age, especially at higher workloads, but are not necessarily an adverse feature unless associated with evidence of ischemia (209). Chronotropic incompetence (failure to achieve 85% of age-predicted maximum heart rate) is more common in elderly patients (407), and both it 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 (211), and the positive predictive value of these features may be enhanced by consideration of other exercise parameters and a stepwise approach combined with stress imaging tests, discussed in the section on screening.

Exercise Testing in Asymptomatic Persons Without Known CAD

Class I

None.

Class IIa

Evaluation of asymptomatic persons with diabetes mellitus who plan to start vigorous exercise (see page 39). ***(Level of Evidence: C)***

Class IIb

1. **Evaluation of persons with multiple risk factors as a guide to risk-reduction therapy.***
2. **Evaluation of asymptomatic men older than 45 years and women older than 55 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 (e.g., peripheral vascular disease and chronic renal failure)**

Class III

Routine screening of asymptomatic men or women.

*Multiple risk factors are defined (212) as hypercholesterolemia (greater than 240 mg per 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 (213).

Rationale

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 of other causes (214). CAD is responsible for more than half a million deaths each year and 1.5 million hospitalizations for myocardial infarction, at a cost of more than $100 billion per year in the United States (185). 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 (215). In CASS, asymptomatic subjects after infarction showed a trend toward improved survival after coronary bypass surgery when three-vessel disease and impaired left ventricular function were present. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study of patients with silent myocardial ischemia during testing (who had angina or were asymptomatic at other times), coronary revascularization was associated with a better long-term outcome than medical therapy (216,217). Both CASS and ACIP were studies of patients with angiographically documented coronary disease. ACIP was a pilot study, and a National Heart, Lung, and Blood Institute follow-up study has suggested that acute cardiac events in predominantly low-risk patients are unpredictable (218). The findings cannot be extrapolated to the use of exercise testing as a screening method to detect occult coronary disease. Diagnosis of ischemia may stratify patients for the intensity of risk factor modification (219). Although this may seem inconsistent with the current position that simple risk reduction should be attempted in all patients (220), the identification of functional impairment may motivate patients to be more compliant with risk factor modification (113).

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 because of 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% (221) and 72% (222). These numbers are obviously influenced by workup 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 (223), 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 (224).

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 is considered the most important end point of screening, although this has been addressed in only the Seattle Heart Watch (212), Multiple Risk Factor Intervention Trial (MRFIT) (225), and Lipid Research Clinics (226) 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 (212,225-227,230,232,233). 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% to 2% range per year (225), even if ST changes are associated with risk factors. A positive exercise test result is more predictive of later development of angina than of 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, because 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. When other factors have been taken into account in a multivariate analysis, exercise testing has been shown to be predictive of hard events (225,226,232), 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 (225,226), and the ST/HR slope. The latter was predictive of outcome despite the fact that ST-segment analysis alone was not predictive of outcome in the Framingham study (232).

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 workload is associated with a relatively high risk of subsequent events. ST-segment depression that occurs 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 (212,226), and ischemia at fewer than 5 minutes of exercise has been associated with a relative risk of 14.7 in men and 5.6 in women (230).

RISK FACTORS. The Bayesian issues posed by testing patients with a low probability of CAD may be reduced somewhat 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. Exercise testing has been shown to be of value for screening patients with a family history of coronary disease. The study by Blumenthal et al. 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 (234).

Who to Screen? POPULATION SCREENING. General screening programs (for example, those that attempt to identify young patients with early disease) have the limitation that severe CAD (requiring intervention) in asymptomatic patients is exceedingly rare (17). Although the physical risks of exercise testing are negligible (7), 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 routinely recommended (235,236,408).

SCREENING IN PATIENTS WITH CAD 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 (212). In this study, the results of exercise testing were not predictive of outcome in the group as a whole, but in patients with 1 or more risk factors and 2 abnormal features on exercise testing (chest pain, exercise for fewer 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. In MRFIT, significant concentration of cardiac risk was associated with an abnormal ST/HR index but not with abnormal standard exercise test criteria as judged by computer interpretation (237). Compared with patients in the usual-care group, cardiac events were reduced in the risk factor–modification group when the exercise test was positive according to the ST/HR index (409).

On the basis of prognostic considerations, asymptomatic male patients older than 45 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 (i.e., 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 pressure greater than 90 mm Hg, smoking, diabetes, and history of heart attack or sudden cardiac death in a first-degree relative less than 60 years old. The importance of more intensive risk factor management of persons with diabetes has been increasingly recognized, as reflected in the most recent national guidelines for cholesterol management (ATP III), hypertension (JNC VI) and diabetes control (see http://www.diabetes.org/main/info/link.jsp). In asymptomatic diabetic persons, the likelihood of cardiovascular disease is increased if at least 1 of the following is present: age older than 35 years, type 2 diabetes of greater than 10 years' duration, type 1 diabetes of greater than 15 years' duration, any additional atherosclerotic risk factor for CAD, presence of microvascular disease (proliferative retinopathy or nephropathy, including microalbuminuria), peripheral vascular disease, or autonomic neuropathy. Exercise testing is recommended if an individual meeting the criteria is about to embark on moderate- to high-intensity exercise (408,410).

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)
Froelicher[227] (1974)	1390	0	1965	Various	Maximal	ST depression	10.1	AP+MI+SCD	5.3	14.3	6.3
Bruce[212] (1980)	2365	0	Before 1975	Bruce	Maximal	Chest pain, ST depression, exercise duration, MHR , 90% predicted	11.1	AP+MI+SCD	3.	29 for 2 of 4 exercise criteria,* 3.4 for ST depression	5.6
McHenry[228] (1984)	916	0	1968 Balke	Modified	Maximal	ST depression	2.5	AP+MI+SCD	5.6	4.9	12.7
Bruce[229] (1983)	4158	13	1971	Bruce	Maximal	Chest pain, ST depression, exercise duration, MHR < 90% predicted, RPP <80% predicted	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; 1.8W; RPP = 2.4 M, 1.3 W; ST = 2.6 M, 6.7 W	6.1
Giagnoni[226] (1983)	514	27	1971	Various	Submaximal	ST depression	26.2	MI AP AP+MI+SCD	n/a	13.4 (univariate, MI) 3.4 (univariate AP) 5.6 (multivariate)	6.3
Allen[230] (1980)	888	35	1973	Ellestad	Maximal	ST depression, R-wave response, exercise duration	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 Strong positive = 5.0, all positive = 4.6	8.4
LRC (Gordon, 1986)[231]	3178	0	1972	Modified Bruce	Maximal	ST response	5.7	CHD death	2.1	3.7 1.5 1.2	7
MRFIT (Rautaharju, 1986)[225]	6008	0	1972	Various	Submaximal	ST depression	12.2	CHD death AP MI	2.6 18.2 5.1	ST depression = 1.2; ST/HR = 2.2; recovery loop = 2.1; combined = 3.6	
Framingham (Okin, 1991)[232]	3168	52	1971	Bruce	Maximal	ST depression, ST/HR index, recovery loop	14.6	AP+MI+SCD	4.8		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.[292]

An alternative approach would be to study patients with a certain level of cardiovascular risk expressed as a continuous variable, thereby 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 (213). Attempts to extend screening to persons with lower degrees of risk are not recommended because screening is unlikely to improve patient outcome.

SCREENING IN OTHER PATIENT GROUPS AT HIGH RISK OF CAD. 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 (238), these include persons with previous cardiac transplantation (239) or chronic renal failure (240). These patients are more likely to have established coronary disease that requires intervention. Unfortunately, however, in part 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 (241). In these groups, stress imaging tests may be of more value for risk stratification.

BEFORE FITNESS PROGRAM. Detailed recommendations regarding cardiovascular screening, including exercise testing, before an exercise training program is begun are provided elsewhere (388,411). A distinction must be made between asymptomatic patients with and without a history of cardiac disease. Some 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 supervised exercise in patients with cardiac disease (which has been estimated at 1 per 784,000 hours) is higher than that of the general population (242). In those with a history of cardiac disease (including CAD), exercise testing is recommended as a means of stratifying risk (243). Similarly, patients with diabetes and those undergoing 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 in active persons (244). Thus, when a sedentary person starts an exercise program, there is presumably a period of increased risk. For this reason, exercise testing of asymptomatic men older than 45 years and women older than 55 years can be considered 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 (245), and there are no data to justify or criticize testing. In the Lipid Research Clinics 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 (246).

SPECIAL GROUPS. Persons whose occupations may affect 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 disease. 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 an exercise test is performed on an asymptomatic patient, these issues must be discussed and informed consent obtained.

The response to a positive exercise test should be modulated by the remainder of the exercise data, including exercise capacity, heart rate and blood pressure response to exercise and in recovery, 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

In chronic aortic regurgitation, assessment of functional capacity and symptomatic responses in patients with a history of equivocal symptoms.

Class IIa

1. **In chronic aortic regurgitation, evaluation of symptoms and functional capacity before participation in athletic activities.**
2. **In chronic aortic regurgitation, prognostic assessment before aortic valve replacement in asymptomatic or minimally symptomatic patients with left ventricular dysfunction.**

Class IIb

Evaluation of exercise capacity in patients with valvular heart disease. Comprehensive discussion is found in the ACC/AHA valvular heart disease guidelines (412)**.**

Class III

Diagnosis of CAD in patients with moderate to severe valvular disease or with the following baseline ECG abnormalities:

- **Pre-excitation**
- **Electronically paced ventricular rhythm**
- **Greater than 1 mm ST depression**
- **Complete left bundle-branch block**

Rationale

Uses of Exercise Testing in Patients With Valvular Heart Disease as detailed in the ACC/AHA Guidelines on Management of Patients With Valvular Heart Disease (412)

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, evaluation of LV function during exercise with imaging modalities, and extent of disability, which may have implications for medical, surgical, and social decision making. This is 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 caused by 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 (247,412). However, many elderly patients in this situation are asymptomatic because they are inactive, and it may be difficult to plan treatment on clinical grounds in these patients. 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. Hypotension during exercise in asymptomatic patients with aortic stenosis is sufficient reason to consider aortic valve replacement. Exercise testing is also useful in evaluating aortic valve gradients in low-output flow states, and along with Doppler imaging, in counseling asymptomatic subjects with moderate to severe aortic valve gradients who are considering athletic programs.

Exercise testing is an accepted means of evaluating pediatric patients with aortic stenosis (248-250). Three studies in adults with moderate to severe aortic stenosis (valve areas of 0.5 to 1.5 cm^2; mean gradients of 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 (413-415). 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 assumption of a supine position.

Functional limitation is commonly found in asymptomatic patients with aortic stenosis (254). 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 the most value when a patient is thought to be asymptomatic because of inactivity or when 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, excessive exercise-induced pulmonary hypertension, reduction of cardiac output with exercise (evidenced by exercise-induced hypotension), and chest pain (caused by 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 (255). 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 monitor the response of asymptomatic patients to medical therapy (256). Additional recommendations are found in the ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease (412).

***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. Because resting ejection fraction is a poor guide to ventricular function in patients with mitral regurgitation, combinations of exercise testing and assessment of left ventricular function may be of value in documenting occult dysfunction and provoking earlier surgery (257). 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 (258). Exercise testing may help clarify objectively the functional capacity of the patient who is a poor historian. The test provides objective

evidence of functional capacity used to counsel patients before they embark on a physical activity program. Concomitant Doppler imaging may demonstrate severe mitral regurgitation in a patient with symptoms out of proportion to mild mitral regurgitation observed on the resting echocardiogram.

Exercise Testing Before and After Revascularization

Class I

1. **Demonstration of ischemia before revascularization.**
2. **Evaluation of patients with recurrent symptoms that suggest ischemia after revascularization.**

Class IIa

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 12 months after percutaneous coronary intervention (PCI).**
2. **Periodic monitoring of selected, high-risk asymptomatic patients for restenosis, graft occlusion, incomplete coronary revascularization, or disease progression.**

Class III

1. **Localization of ischemia for determining the site of intervention.**
2. **Routine, periodic monitoring of asymptomatic patients after percutaneous coronary intervention (PCI) or coronary artery bypass grafting 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 (259,346,347). Frequently, however, this requires a more sensitive test than the exercise ECG, particularly in the 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, i.e., 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 Artery Bypass Graft Surgery

In symptomatic patients, exercise testing may be used to distinguish between cardiac and noncardiac causes of recurrent chest pain after surgery. Incomplete revascularization or graft occlusion may be identified with the exercise ECG (260), although not all results have been favorable (261). 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 (262).

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 before surgery to a negative postoperative test result does correlate with successful revascularization (263). However, in a follow-up study of events after exercise testing and evaluation of left ventricular function, left ventricular ejection fraction but not exercise variables was predictive of outcome (264). This may reflect lower sensitivity of the exercise ECG for ischemia and may be less true with stress imaging tests. Exercise testing in an asymptomatic patient who has undergone successful coronary bypass grafting is not predictive of subsequent events when the test is performed within the first few years after the revascularization procedure (416). The test provides more useful information when the likelihood of coronary disease progression is enhanced (e.g., 5 to 10 years after coronary bypass grafting, in the presence of typical ischemia symptoms, diabetes mellitus, hemodialysis, or immunosuppressive therapy).

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 PCI

Restenosis remains the single major limitation of PCI. This clinical end point reflects a complex underlying pathophysiology that involves 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 non-

cardiac 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 (265). In patients destined to develop restenosis, stent placement generally delays the onset of restenosis by several months (417).

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 PCI. The presence of ischemia in these tests is predictive of restenosis (266). Whereas 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 PCI may facilitate earlier return to work and daily living activities (267), although the safety of this approach has not been established, and exercise when unstable plaque exists may (at least theoretically) provoke 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 PCI. Table 25 summarizes the variability in predictive value of the exercise test for restenosis (268-275), which reflects in part the different populations studied, the frequency, and the criteria for restenosis. False-positive study results may be the result of 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 (276,277). 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 PCI 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 (5,278) or exercise echocardiography (6,279). 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 and its inability to localize disease limits its usefulness in patient management both before and after PCI. 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 PCI.

Investigation of Heart Rhythm Disorders

Class I

1. **Identification of appropriate settings in patients with rate-adaptive pacemakers.**
2. **Evaluation of congenital complete heart block in patients considering increased physical activity or participation in competitive sports. *(Level of Evidence: C)***

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.**
2. **Investigation of prolonged first-degree atrioventricular block or type I second-degree Wenckebach, left bundle-branch block, right bundle-branch block, or isolated ectopic beats in young patients considering participation in competitive sports. *(Level of Evidence: C)***

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[268] (1989)	398	Consecutive	Up to 6	33	66	75	>70% luminal diameter stenosis
Honan[269] (1989)	144	Post MI	6	40	57	64	>75% luminal diameter stenosis
Schroeder[270] (1989)	111	Asymptomatic	6	12	53	63	>70% luminal diameter stenosis
Laarman[271] (1990)	141	Asymptomatic	1 to 6	12	15	87	>50% luminal diameter stenosis
el-Tamimi[272] (1990)	31	Consecutive	6	45	100	94	Loss of >50% initial gain of lumen diameter
Bengtson[265] (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[273] (1994)	78	1-vessel CAD	6	28	37	77	>50% luminal diameter stenosis
Desmet[274] (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.

Class III

Routine 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 and 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 3 times greater in persons exhibiting exercise-induced ectopy than in those with ectopy at rest only (280), and in patients with exercise-induced ectopy, the mortality rate for those with complex ectopy exceeds that for those with simple ectopy (281). In patients undergoing antiarrhythmic therapy, sustained exercise-induced VT is associated with a high risk of sudden death (282), and exercise testing has been used to unmask proarrhythmic responses.

Although serious arrhythmias are uncommon in unselected populations undergoing exercise testing (283), the use of maximal exercise testing in patients at risk of ventricular arrhythmia is associated with a 2.3% incidence of arrhythmias that require cardioversion, intravenous drugs, or resuscitation (284). 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. Although it is sufficiently reproducible to serve as an adjunct in the evaluation and treatment of these patients (285), other testing is also required.

Supraventricular Arrhythmias. Patients developing supraventricular arrhythmias during exercise often display marked tachycardia because of 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 pre-excitation during exercise infers a longer antegrade refractory period in the accessory pathway than in 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 taking medication, 95% demonstrate an abnormal chronotropic response early during exercise (74% being fast), and 84% demonstrate an abnormal chronotropic response late during exercise (53% being slow). Thus, the majority of patients with atrial fibrillation demonstrate an abnormal chronotropic response to exercise (286).

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 (i.e., more than two standard deviations below age-predicted maximum) (287). The use of a heart rate response less than 100 bpm with maximal exercise (288) is specific but insensitive. A more complicated definition shown to be prognostically significant (289) is the ratio between heart rate and metabolic reserve used by stage II of the Bruce protocol (290). 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 (291) 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 with various physiological sensors has led to study of

the exercise response being an important constituent in fine-tuning these devices (292,293). In a series of 21 patients with single-lead VDD systems, exercise testing was helpful in evaluating the quality of atrial sensing best expressed by the percentage of synchronized atrioventricular events and in evaluating the evolution of P-wave amplitude during exercise (418). 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 (294).

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 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 (295). 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, because they are both unpleasant and potentially hazardous (296).

Evaluation of Hypertension

Exercise testing has been used to identify patients with abnormal blood pressure response destined to develop hypertension. Identification of such patients may allow preventive measures that would delay or prevent the onset of this disease. In asymptomatic normotensive subjects, an exaggerated exercise systolic and diastolic blood pressure response during exercise, exaggerated peak systolic blood pressure greater than 214 mm Hg, or elevated systolic or diastolic blood pressure at 3 minutes into recovery is associated with significant increased long-term risk of hypertension (419,420). Exercise tolerance is decreased in patients with poor blood pressure control (421), and severe systemic hypertension may cause exercise-induced ST depression in the absence of atherosclerosis (422).

VII. PEDIATRIC TESTING: EXERCISE TESTING IN CHILDREN AND ADOLESCENTS

The pediatric section published as part of the original 1997 ACC/AHA Guidelines on Exercise Testing will be updated at a later date and is omitted from this document (including Table 26).

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 CAD

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. (343) 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 1 or more vessels. When this criterion was 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:

$$-0.12 + (4.5 \times [-3.61 + (0.076 \times \text{age}) - (1.33 \times \text{gender}) + (0.64 \times \text{symptoms}) + (0.65 \times \text{diabetes}) + (0.28 \times \text{smoking}) - (1.46 \times \text{body surface area}) + (0.50 \times \text{estrogen}) + (0.33 \times \text{number of risk factors}) - (0.40 \times \text{resting ECG})]) + (0.37 \times \text{mm ST depression}) + (1.02 \times \text{ST slope}) - (0.37 \times \text{negative ST}) - (0.02 \times \text{maximal heart rate})$$

Gender was coded as 1 for female and 0 for male. Symptoms were classified into 4 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 (post-

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.

menopausal and no estrogen), and –1 for estrogen positive (premenopausal or taking estrogen). Risk factors included history of hypertension, hypercholesterolemia, and obesity (body mass index greater than or equal to 27 kg/m^2). 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. (23) 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 1 major coronary arterial branch, and the prevalence of disease according to this criterion was 64%. They considered a total of 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:

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

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.

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.

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