

ACC/AHA/ACP-ASIM PRACTICE GUIDELINES

ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina

A Report of the American College of Cardiology/
American Heart Association Task Force on Practice Guidelines
(Committee on Management of Patients With Chronic Stable Angina)

COMMITTEE MEMBERS

RAYMOND J. GIBBONS, MD, FACC, *Chair*

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JENNIFER DALEY, MD, FACP
JOHN S. DOUGLAS, MD, FACC
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BRUCE W. LYTLE, MD, FACC
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WILLIAM P. SCHAFER, MD, FACC
SANKEY V. WILLIAMS, MD, FACP

TASK FORCE MEMBERS

JAMES L. RITCHIE, MD, FACC, *Chair*
RAYMOND J. GIBBONS, MD, FACC, *Vice Chair*

MELVIN D. CHEITLIN, MD, FACC
KIM A. EAGLE, MD, FACC
TIMOTHY J. GARDNER, MD, FACC
ARTHUR GARSON, JR, MD, MPH, FACC

RICHARD O. RUSSELL, MD, FACC
THOMAS J. RYAN, MD, FACC
SIDNEY C. SMITH, JR, MD, FACC

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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 have a favorable impact on the overall cost of care 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 where 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, and prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the physician and patient in light of all of the circumstances presented by that patient.

The executive summary and recommendations are published in the June 1, 1999 issue of *Circulation*. The full text is published in the June 1999 issue of the *Journal of the American College of Cardiology*. Reprints of the full text and the executive summary are available from both organizations.

James L. Ritchie, MD, FACC
Chair, ACC/AHA Task Force on Practice Guidelines

I. INTRODUCTION AND OVERVIEW

A. Organization of Committee and Evidence Review

The ACC/AHA Task Force on Practice Guidelines was formed to make recommendations regarding the diagnosis and treatment of patients with known or suspected cardiovascular disease. Ischemic heart disease is the single leading cause of death in the U.S. The most common manifestation of this disease is chronic stable angina. Recognizing the importance of the management of this common entity and the absence of national clinical practice guidelines in this area, the task force formed the current committee to develop guidelines for the management of patients with stable angina. Because this problem is frequently encountered in the practice of internal medicine, the task force invited the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) to serve as a partner in this effort by naming four general internists to serve on the committee.

The committee reviewed and compiled published reports (excluding abstracts) through a series of computerized literature searches of the English language research literature since 1975 and a manual search of selected final articles. Details of the specific searches conducted for particular sections are provided as appropriate. Detailed evidence tables were developed whenever necessary on the basis of specific criteria outlined in the individual sections. The recommendations were based primarily on these published data. The weight of the evidence was ranked high (A) if the data were derived from multiple randomized clinical trials with large numbers of patients and intermediate (B) if the data were derived from a limited number of randomized

trials with small numbers of patients, careful analyses of nonrandomized studies or observational registries. A low rank (C) was given when expert consensus was the primary basis for the recommendation.

The customary ACC/AHA classifications I, II and III are used in tables that summarize both the evidence and expert opinion and provide final recommendations for both patient evaluation and therapy:

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

Class II Conditions for which there is conflicting evidence 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 many publications on various aspects of this subject is beyond the scope of these guidelines; only selected references are included. The committee consisted of acknowledged experts in general internal medicine from the ACP-ASIM, family medicine from the American Academy of Family Physicians (AAFP), and general cardiology as well as persons with recognized expertise in more specialized areas, including noninvasive testing, preventive cardiology, coronary intervention, and cardiovascular surgery. Both the academic and private practice sectors were represented. This document was reviewed by three outside reviewers nominated by the ACC, three outside reviewers nominated by the AHA, three outside reviewers nominated by the ACP-ASIM, and two outside reviewers nominated by the AAFP. This document was approved for publication by the governing bodies of the ACC, AHA, and ACP-ASIM. The task force will review these guidelines one year after publication and yearly thereafter to determine whether revisions are needed. These guidelines will be considered current unless the task force revises or withdraws them from distribution.

B. Scope of the Guidelines

These guidelines are intended to apply to adult patients with stable chest pain syndromes and known or suspected ischemic heart disease. Patients who have "ischemic equivalents," such as dyspnea or arm pain with exertion, are included in these guidelines. Some patients with ischemic heart disease may become asymptomatic with appropriate therapy. As a result, the follow-up sections of the guidelines may apply to patients who were previously symptomatic. However, the diagnosis, risk stratification and treatment

sections of the guidelines are intended to apply to symptomatic patients. Asymptomatic patients with "silent ischemia" or known coronary artery disease (CAD) that has been detected in the absence of symptoms are beyond the scope of these guidelines. Pediatric patients are also beyond the scope of these guidelines because ischemic heart disease is very unusual in such patients and is primarily related to the presence of coronary artery anomalies. Patients with chest pain syndromes following cardiac transplantation are also not included in these guidelines.

Patients with nonanginal chest pain are generally at lower risk for ischemic heart disease. Often their chest pain syndromes have identifiable noncardiac causes. Such patients are included in these guidelines if there is sufficient suspicion of heart disease to warrant cardiac evaluation. If the evaluation demonstrates that ischemic heart disease is unlikely and noncardiac causes are the primary focus of evaluation, such patients are beyond the scope of these guidelines. If the initial cardiac evaluation demonstrates that ischemic heart disease is possible, subsequent management of such patients does fall within these guidelines.

Acute ischemic syndromes are not included in these guidelines. For patients with acute myocardial infarction (MI), the reader is referred to the "ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction" (1). For patients with unstable angina, the reader is referred to the Agency for Health Care Policy and Research (AHCPR) clinical practice guideline on unstable angina (2), which was endorsed by the ACC and the AHA. This guideline for unstable angina did describe some low-risk patients who should not be hospitalized but instead evaluated as outpatients. Such patients are indistinguishable from many patients with stable chest pain syndromes and are therefore within the scope of the present guidelines. Patients whose recent unstable angina was satisfactorily treated by medical therapy and who then present with a recurrence of symptoms with a stable pattern fall within the scope of the present guidelines. Similarly, patients with MI who subsequently present with stable chest pain symptoms >30 days after the initial event are within the scope of the present guidelines.

The present guidelines do not apply to patients with chest pain symptoms early after revascularization by either percutaneous techniques or coronary artery bypass grafting. Although the division between "early" and "late" symptoms is arbitrary, the committee believed that these guidelines should not be applied to patients who develop recurrent symptoms within six months of revascularization.

C. Overlap With Other Guidelines

These guidelines will overlap with a large number of recently published (or soon to be published) clinical practice guidelines developed by the ACC/AHA Task Force on Practice Guidelines; the National Heart, Lung, and Blood Institute (NHLBI); and the ACP-ASIM (Table 1).

Table 1. Recent Clinical Practice Guidelines and Policy Statements Which Overlap With This Guideline

Guideline	Sponsor	Year of Publication
Radionuclide imaging (12)	ACC/AHA	1995
Echocardiography (13)	ACC/AHA	1997
Exercise testing (14)	ACC/AHA	1997
Valvular heart disease (15)	ACC/AHA	1998
Ambulatory monitoring (16)	ACC/AHA	1999
Coronary angiography (17)	ACC/AHA	1999
Percutaneous transluminal coronary angioplasty (18)	ACC/AHA	1999 or 2000
Coronary artery bypass surgery (19)	ACC/AHA	1999
National cholesterol education project (20)	NHLBI	1996
National hypertension education (21)	NHLBI	1997
Management of hypercholesterolemia (22)	ACP-ASIM	1996
Bethesda Conference on risk factor reduction (23)	ACC	1996
Clinical practice guideline: cardiac rehabilitation (24)	AHCPR	1995
Coronary artery calcification: pathophysiology, imaging methods, and clinical implications (25)	AHA	1996
Counseling postmenopausal women about preventive hormone therapy (26)	ACP-ASIM	1992
Bethesda Conference on insurability and employability of the patient with ischemic heart disease (27)	ACC	1989

This report includes text and recommendations from many of these guidelines, which are clearly indicated. Additions and revisions have been made where appropriate to reflect more recently available evidence. This report specifically indicates rare situations in which it deviates from previous guidelines and presents the rationale. In some cases, this report attempts to combine previous sets of similar and dissimilar recommendations into one set of final recommendations. Although this report includes a significant amount of material from the previous guidelines, by necessity the material was often condensed into a succinct summary. These guidelines are not intended to provide a comprehensive understanding of the imaging modalities, therapeutic modalities, and clinical problems detailed in other guidelines. For such an understanding, the reader is referred to the original guidelines listed in the references.

D. Magnitude of the Problem

There is no question that ischemic heart disease remains a major public health problem. Chronic stable angina is the initial manifestation of ischemic heart disease in approximately one half of patients (3,4). It is difficult to estimate the number of patients with chronic chest pain syndromes in the U.S. who fall within these guidelines, but clearly it is measured in the millions. The reported annual incidence of angina is 213/100,000 population >30 years old (3). When the Framingham Heart Study (4) is considered, an additional 350,000 Americans each year are covered by these guidelines. The AHA has estimated that 6,200,000 Amer-

icans have chest pain (5); however, this may be a conservative estimate.

The prevalence of angina can also be estimated by extrapolating from the number of MIs in the U.S. (1). About one half of patients presenting at the hospital with MI have preceding angina (6). The best current estimate is that there are 1,100,000 patients with MI each year in the U.S. (5); about one half of these (550,000) survive until hospitalization. Two population-based studies (from Olmsted County, Minnesota, and Framingham, Massachusetts) examined the annual rates of MI in patients with symptoms of angina and reported similar rates of 3% to 3.5% per year (4,7). On this basis, it can be estimated that there are 30 patients with stable angina for every patient with infarction who is hospitalized. As a result, the number of patients with stable angina can be estimated as $30 \times 550,000$, or 16,500,000. This estimate does not include patients who do not seek medical attention for their chest pain or whose chest pain has a noncardiac cause. Thus, it is likely that the present guidelines cover at least six million Americans and conceivably more than twice that number.

Ischemic heart disease is important not only because of its prevalence but also because of its associated morbidity and mortality. Despite the well-documented recent decline in cardiovascular mortality (8), ischemic heart disease remains the leading single cause of death in the U.S. (Table 2) and is responsible for 1 of every 4.8 deaths (9). The morbidity associated with this disease is also considerable: each year >1,000,000 patients have an MI. Many more are hospital-

Table 2. Death Rates Due to Diseases of the Heart and Cancer, United States—1995

Group	Death Rate per 100,000 Population	
	Diseases of the Heart	Cancer
White males	297.9	228.1
Black males	244.2	209.1
White females	297.4	202.4
Black females	231.1	159.1

From Report of Final Mortality Statistics, 1995, Centers for Disease Control and Prevention (8). These rates are not adjusted for age.

ized for unstable angina and evaluation and treatment of stable chest pain syndromes. Beyond the need for hospitalization, many patients with chronic chest pain syndromes are temporarily unable to perform normal activities for hours or days, thereby experiencing a reduced quality of life. According to the recently published data from the Bypass Angioplasty Revascularization Investigation (10), about 30% of patients never return to work following coronary revascularization, and 15% to 20% of patients rated their own health fair or poor despite revascularization. These data confirm the widespread clinical impression that ischemic heart disease continues to be associated with considerable patient morbidity despite the decline in cardiovascular mortality.

The economic costs of chronic ischemic heart disease are enormous. Some insight into the potential cost can be obtained by examining Medicare data for inpatient diagnosis-related groups (DRGs) and diagnostic tests. Table 3 shows the number of patients hospitalized under various DRGs during 1995 and associated direct payments by Medicare. These DRGs represent only hospitalization of patients covered by Medicare. The table includes estimates for the proportion of inpatient admissions for unstable angina, MI, and revascularization for patients with a history of stable angina. Direct costs associated

with non-Medicare patients hospitalized for the same diagnoses are probably about the same as the covered charges under Medicare. Thus, the direct costs of hospitalization are >\$15 billion.

Table 4 shows the Medicare fees and volumes of commonly used diagnostic procedures in ischemic heart disease. Although some of these procedures may have been performed for other diagnoses and some of the cost of the technical procedure relative value units (RVUs) may have been for inpatients listed in Table 3, the magnitude of the direct costs is considerable. When the 1998 Medicare reimbursement of \$36.6873 per RVU is used, the direct cost to Medicare of these 61.2 million RVUs can be estimated at \$2.25 billion. Again, assuming that the non-Medicare patient costs are at least as great, the estimated cost of these diagnostic procedures alone would be about \$4.5 billion.

These estimates of the direct costs associated with chronic stable angina obviously do not take into account the indirect costs of workdays lost, reduced productivity, long-term medication, and associated other effects. The indirect costs have been estimated to be almost as great as direct costs (4). The magnitude of the problem can be succinctly summarized: chronic stable angina affects many millions of Americans, with associated annual costs that are measured in tens of billions of dollars.

Given the magnitude of this problem, the need for practice guidelines is self-evident. This need is further reinforced by the available information, which suggests considerable regional differences in the management of ischemic heart disease. Figure 1 shows published information from the Medicare database for rates of coronary angiography in different counties of the country (11). Three- and four-fold differences in adjusted rates for this procedure in different counties within the same state are not uncommon, suggesting that the clinical management of such patients is highly variable. The reasons for such variation in management are unknown.

Table 3. Medicare Experience With Commonly Used DRGs Involving Patients With Stable Angina

DRG #	Description	1995 Discharges	Covered Charges (million)	Medicare Payments (million)	% of Pts with History of Stable Angina	Medicare Payments for Pts with Stable Angina
125	Coronary disease/cath	62,251	\$ 519.8	\$ 215.9	95*	205.1
143	Chest pain	139,145	641.8	268.1	100	268.1
124	Unstable angina	145,560	1,734.8	770.6	85†	655.0
121	MI with cath	167,202	2,333.5	1,020.8	55‡	561.4
122	MI without cath	91,569	892.0	350.8	55‡	192.9
112	PTCA	201,066	3,897.7	1,801.9	83§	1,495.6
106	CABG with cath	101,057	5,144.0	3,626.9	83§	3,010.3
107	CABG without cath	64,212	2,473.2	1,280.9	83§	1,063.1
						7,451.5

*Some patients may have heart failure. †Based on TIMI III trial (28). ‡Based on Canadian Assessment of Myocardial Infarction Study (6). §Based on BARI study (10), assuming that 85% of patients with unstable angina had preceding stable angina (see † above).

Table 4. Medicare Fees and Volumes of Commonly Used Diagnostic Procedures for Chronic Stable Angina

Procedure	1998 CPT Code(s)	1998 Total (Professional and Technical) Medicare RVUs	Number Performed (1996)	Estimated % for Stable Angina	Estimated Total RVUs
Echocardiogram	93307	5.96	3,935,344	20%	4,690,930
Doppler echo	93320	2.61	3,423,899	20%	1,787,233
Treadmill exercise test	93015 or 93016-93018	3.25	689,851*	80%	1,793,612
Stress echocardiography	93350, 93015	6.81	303,047	80%	1,651,000
Stress SPECT myocardial perfusion imaging	78465, 93015	17.41	1,158,389	80%	16,134,041
Left heart catheterization with left ventriculogram and coronary angiography	93510, 93543, 93545, 93555, 93556	66.18	664,936†	80%	35,204,371
					61,261,187

*Estimated by subtracting (93350 + 78465) from (93015 + 93018), since the total number of charges under 93015 and 93018 includes stress echo and stress SPECT. †Estimated from Medicare data. One source (David Wennberg, personal communication) has suggested this number could be as high as 771,925.

This table does not include information on positron emission tomography (PET), or electronic beam computed tomography (EBCT) for coronary calcification. There were no CPT codes for PET in 1996, and there are no current CPT codes for coronary calcification by EBCT.

E. Organization of the Guidelines

These guidelines are arbitrarily divided into four sections: diagnosis, risk stratification, treatment and patient follow-up. Experienced clinicians will quickly recognize

that the distinctions between these sections may be arbitrary and unrealistic in individual patients. However, for most clinical decision making, these divisions are helpful and facilitate presentation and analysis of the available evidence.

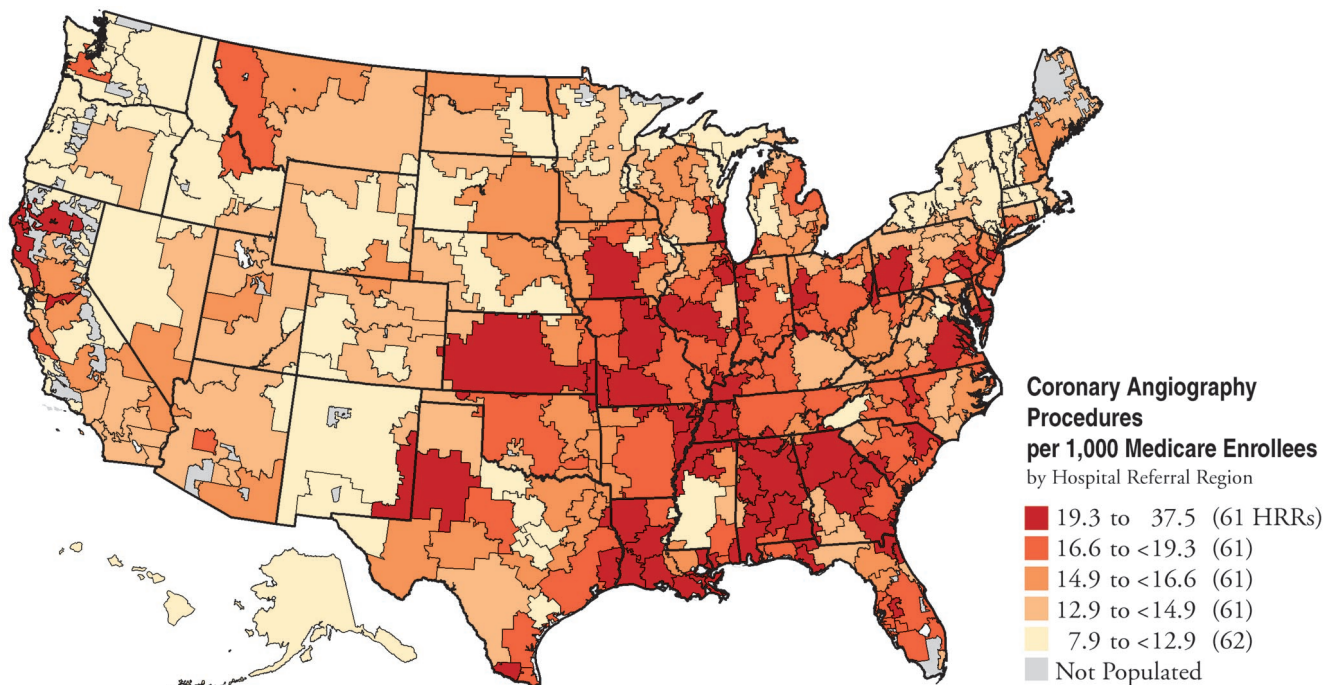


Figure 1. Map depicting coronary angiography rates in the U.S. HRR = hospital referral region. From Wennberg et al. (11) with permission.

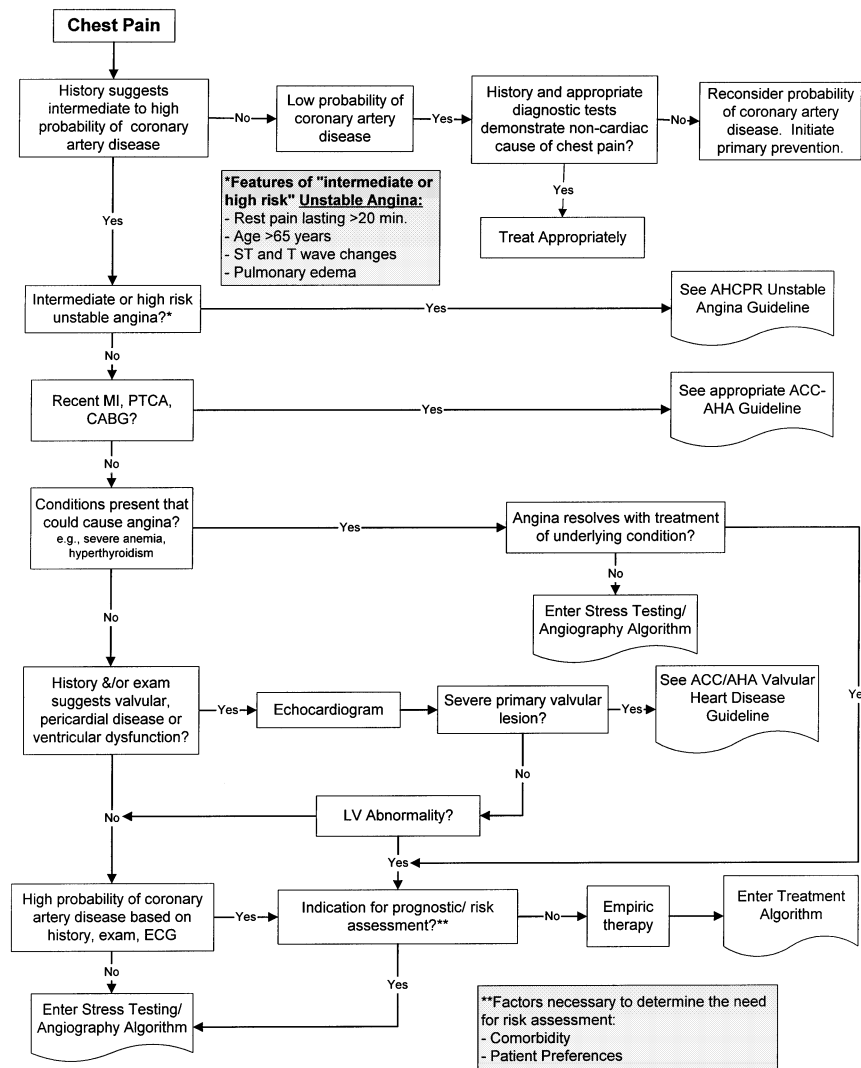


Figure 2. Clinical assessment. AHCPR = Agency for Health Care Policy and Research; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; ACC = American College of Cardiology; AHA = American Heart Association; LV = left ventricular; and ECG = electrocardiogram.

The three flow diagrams that follow summarize the management of stable angina in three algorithms: clinical assessment (Fig. 2), stress testing/angiography (Fig. 3), and treatment (Fig. 4). The treatment mnemonic (Fig. 5) is intended to highlight the 10 treatment elements that the committee considered most important.

Although the evaluation of many patients will require all three algorithms, this is not always true. Some patients may require only clinical assessment to determine that they do not belong within these guidelines. Others may require only clinical assessment and treatment if the probability of CAD is high and patient preferences and comorbidities preclude revascularization (and therefore the need for risk stratification). The stress testing/angiography algorithm may be required either for diagnosis (and risk stratification) in patients with a moderate probability of CAD or for risk

stratification only in patients with a high probability of CAD.

II. DIAGNOSIS

A. History and Physical

Recommendations

Class I: In patients presenting with chest pain, a detailed symptom history, focused physical examination, and directed risk-factor assessment should be performed. With this information, the clinician should estimate the probability of significant CAD (i.e., low, intermediate, high). (Level of Evidence: B)

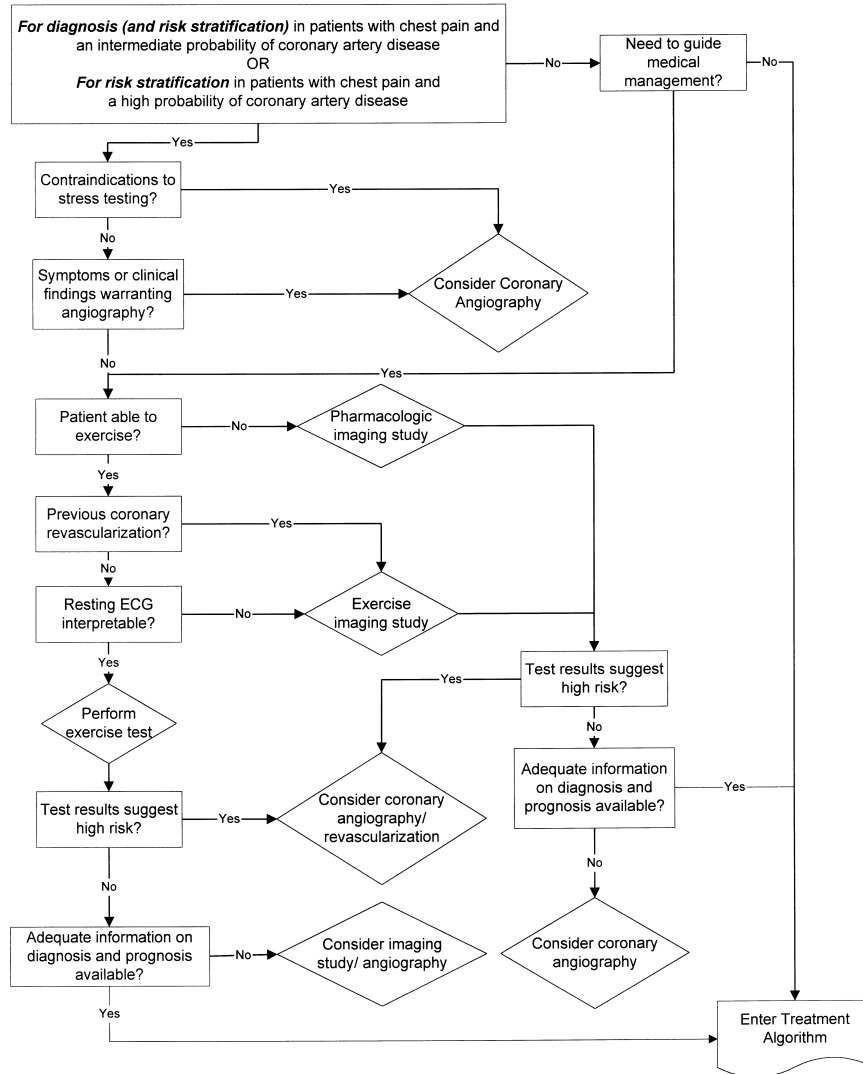


Figure 3. Stress testing/angiography. ECG = electrocardiogram.

Definition of Angina

Angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back or arm. It is typically aggravated by exertion or emotional stress and relieved by nitroglycerin. Angina usually occurs in patients with CAD involving ≥ 1 large epicardial artery. However, angina can also occur in persons with valvular heart disease, hypertrophic cardiomyopathy and uncontrolled hypertension. It can be present in patients with normal coronary arteries and myocardial ischemia related to spasm or endothelial dysfunction. Angina is also a symptom in patients with non-cardiac conditions of the esophagus, chest wall or lungs. Once cardiac causes have been excluded, the management of patients with these noncardiac conditions is outside the scope of these guidelines.

Clinical Evaluation of Patients With Chest Pain

History

The clinical examination is the most important step in the evaluation of the patient with chest pain, allowing the clinician to estimate the likelihood of clinically significant CAD with a high degree of accuracy (29). Significant CAD is defined angiographically as CAD with $\geq 70\%$ diameter stenosis of ≥ 1 major epicardial artery segment or $\geq 50\%$ diameter stenosis of the left main coronary artery. Although lesions of less stenosis can cause angina, they have much less prognostic significance (30).

The first step, a detailed description of the symptom complex, enables the clinician to characterize the chest pain (31). Five components are typically considered: quality,

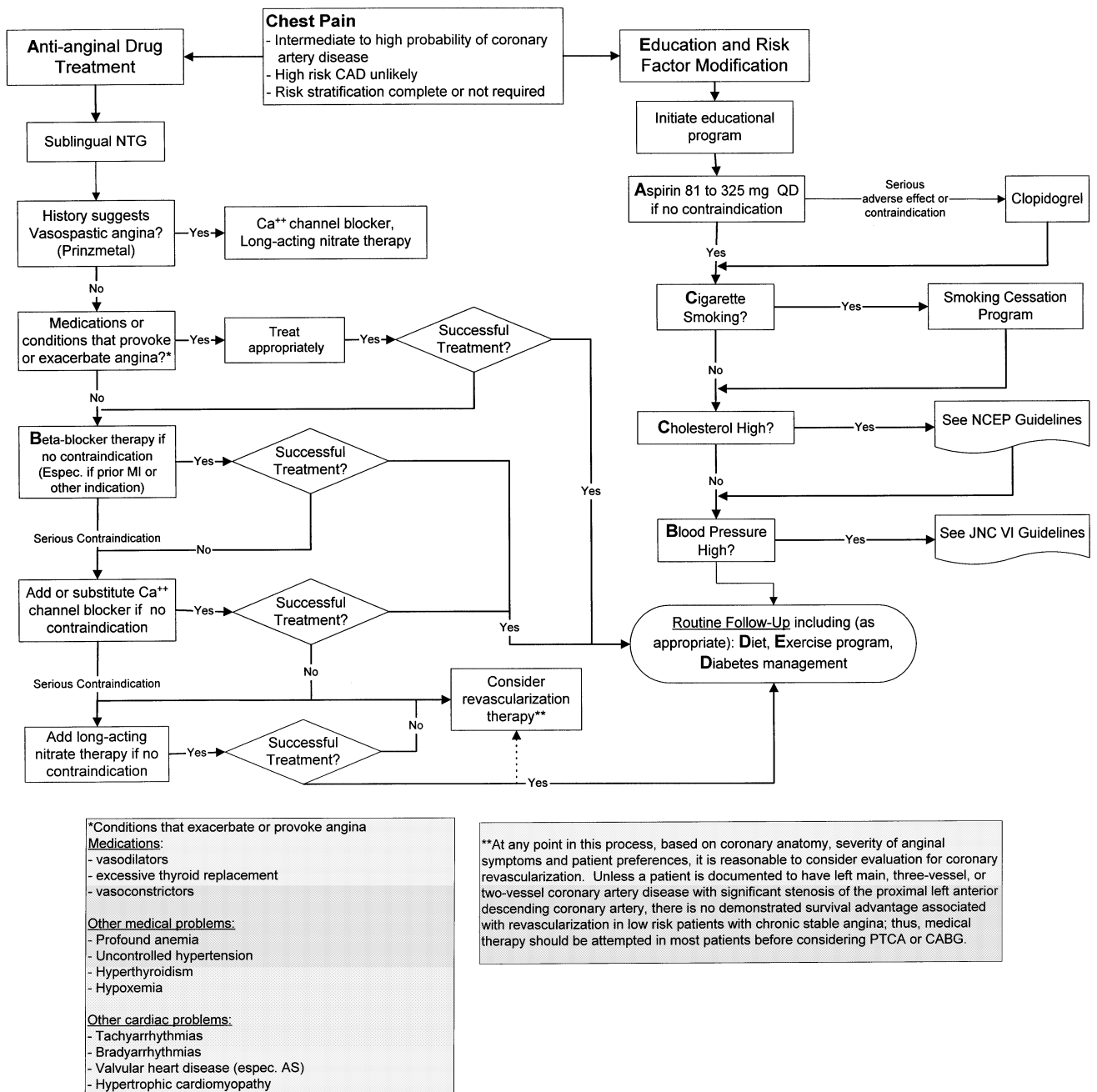


Figure 4. Treatment. CAD = coronary artery disease; NTG = nitroglycerin; MI = myocardial infarction; NCEP = National Cholesterol Education Program; JNC = Joint National Committee. *Vasodilators, excessive thyroid replacement, vasoconstrictors, profound anemia, uncontrolled hypertension, hyperthyroidism, hypoxemia, tachyarrhythmias, bradyarrhythmias, valvular heart disease (especially aortic stenosis) and hypertrophic cardiomyopathy. **On the basis of coronary anatomy, severity of anginal symptoms, and patient preferences, it is reasonable to consider evaluation for coronary revascularization. Unless a patient has documented left main, three-vessel, or two-vessel CAD with significant stenosis of the proximal left anterior descending coronary artery, there is no demonstrated survival advantage associated with revascularization in low-risk patients with chronic stable angina. Thus, medical therapy should be attempted in most patients before considering percutaneous transluminal coronary angioplasty or coronary artery bypass graft.

location, duration of pain, factors that provoke the pain and factors that relieve the pain. Various adjectives have been used by patients to describe the quality of the anginal pain: “squeezing,” “griplike,” “pressurelike,” “suffocating” and

“heavy” are common. Not infrequently, patients insist that their symptom is a “discomfort” but not “pain.” Angina is almost never sharp or stabbing, and it usually does not change with position or respiration.

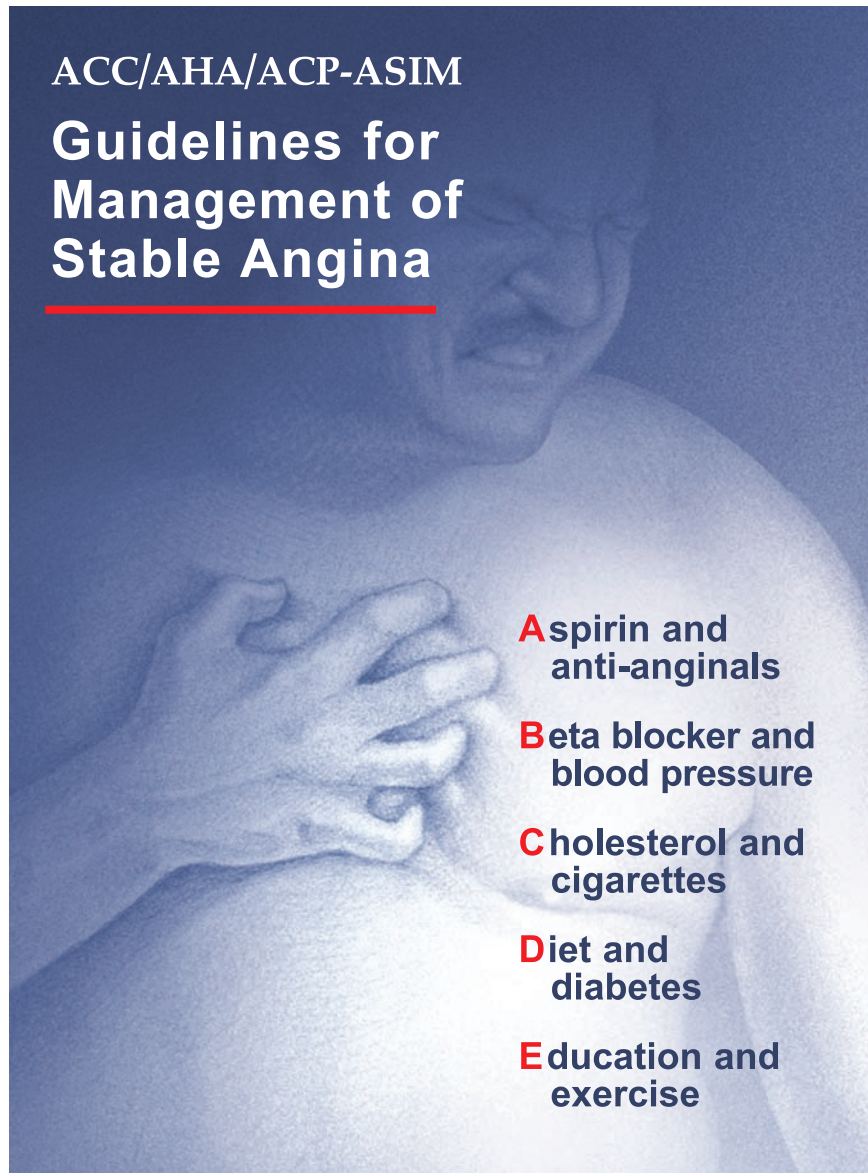


Figure 5. Treatment mnemonic: the 10 most important treatment elements of stable angina management.

The anginal episode is typically minutes in duration. Fleeting discomfort or a dull ache lasting for hours is rarely angina. The location of angina is usually substernal, but radiation to the neck, jaw, epigastrium, or arms is not uncommon. Pain above the mandible, below the epigastrium, or localized to a small area over the left lateral chest wall is rarely anginal. Angina is generally precipitated by exertion or emotional stress and commonly relieved by rest. Sublingual nitroglycerin also relieves angina, usually within 30 s to several minutes.

After the history of the pain is obtained, the physician makes a global assessment of the symptom complex. One classification scheme for chest pain in many studies uses three groups: typical angina, atypical angina or noncardiac chest pain (32) (Table 5).

Angina is further classified as stable or unstable (2). Unstable angina is important in that its presence predicts a much higher short-term risk of an acute coronary event. Unstable angina is operationally defined as angina that

Table 5. Clinical Classification of Chest Pain

<i>Typical</i> angina (definite)
1) Substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or NTG.
<i>Atypical</i> angina (probable)
- Meets 2 of the above characteristics.
<i>Noncardiac</i> chest pain
- Meets one or none of the typical anginal characteristics.

Modified from Diamond, JACC, 1983 (45).

Table 6. Three Principal Presentations of Unstable Angina (2)

Rest angina	Angina occurring at rest and usually prolonged >20 minutes occurring within a week of presentation.
New onset angina	Angina of at least CCSC III severity with onset within 2 months of initial presentation.
Increasing angina	Previously diagnosed angina that is distinctly more frequent, longer in duration or lower in threshold (i.e., increased by at least one CCSC class within 2 months of initial presentation to at least CCSC III severity).

Note: CCSC = Canadian Cardiovascular Society Classification.

presents in one of three principal ways: rest angina, severe new-onset angina, or increasing angina (Tables 6 and 7). Most important, unstable angina patients can be subdivided by their short-term risk (Table 8). Patients at high or moderate risk often have coronary artery plaques that have recently ruptured. Their risk of death is intermediate, between that of patients with acute MI and patients with stable angina. The initial evaluation of high- or moderate-risk patients with unstable angina is best carried out in the inpatient setting. However, low-risk patients with unstable angina have a short-term risk not substantially different from those with stable angina. Their evaluation can be accomplished safely and expeditiously in an outpatient setting. The recommendations made in these guidelines do not apply to high- and moderate-risk unstable angina but are applicable to the low-risk unstable angina group.

After a detailed chest pain history is taken, the presence of risk factors for CAD (23) should be determined. Cigarette smoking, hyperlipidemia, diabetes, hypertension and a family history of premature CAD are all important. Past history of cerebrovascular or peripheral vascular disease increases the likelihood that CAD will be present.

Physical

The physical examination is often normal in patients with stable angina (33). However, an exam made during an episode of pain can be beneficial. An S₄ or S₃ sound or gallop, mitral regurgitant murmur, a paradoxically split S₂ or bibasilar rales or chest wall heave that disappears when the pain subsides are all predictive of CAD (34). Even though the physical is generally not helpful for confirming CAD, a careful cardiovascular exam may reveal other conditions associated with angina, such as valvular heart disease or hypertrophic cardiomyopathy. Evidence of noncoronary atherosclerotic disease—a carotid bruit, diminished pedal pulse or abdominal aneurysm—increases the likelihood of CAD. Elevated blood pressure, xanthomas and retinal exudates point to the presence of CAD risk factors. Palpation of the chest wall often reveals tender areas in patients whose chest pain is caused by musculoskeletal chest wall syndromes (35). However, pain produced by pressure on the

Table 7. Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System (46)

Class I	Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina (occurs) with strenuous, rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.

Source: Campeau L. Grading of angina pectoris [letter]. *Circulation*, 54:522-523, 1976. Copyright © 1976, American Heart Association, Inc. Reprinted with permission.

chest wall may be present even if the patient has angina due to ischemic heart disease. The presence of a rub will point to pericardial or pleural disease.

Developing the Probability Estimate

When the initial history and physical are complete, the physician and patient find themselves asking the same question: "Is it the heart?" In certain instances, the physician can confidently assure the patient that it is not. Patients with noncardiac chest pain are generally at lower risk for ischemic heart disease. As indicated on the flow diagram, the history and appropriate diagnostic tests will usually focus on noncardiac causes of chest pain. Appropriate treatment and follow-up for the noncardiac condition can be prescribed, and the patient can be educated about CAD and risk factors, especially if he or she rarely sees a physician.

When there is sufficient suspicion of heart disease to warrant cardiac evaluation, the clinician should make a probability estimate of the likelihood of CAD. The importance of doing so is obvious when considering how this estimate affects the utility of a commonly used diagnostic test: the standard exercise test. Consider how interpretation of the standard exercise test would be affected by varying the pretest probability of disease from 5% to 50% to 90% (36). In this example, the exercise test is considered positive if ≥ 1 -mm ST-segment depression is observed. The test sensitivity is 50% and specificity 90% (14).

In patients with a low probability of CAD (5%), the positive predictive value of an abnormal test result is only 21%. If 1,000 low-probability patients are tested, 120 will test positive. Of these, 95 will not have significant CAD. Before testing such a

Table 8. Short-Term Risk of Death or Nonfatal Myocardial Infarction in Patients With Unstable Angina (2)

High Risk	Intermediate Risk	Low Risk
At least one of the following features must be present:	No high-risk features but must have any of the following:	No high- or intermediate-risk feature but may have any of the following features:
Prolonged ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD	Increased angina frequency, severity, or duration
Pulmonary edema, most likely related to ischemia	Rest angina (>20 min or relieved with sublingual nitroglycerin)	Angina provoked at a lower threshold
Angina at rest with dynamic ST changes ≥ 1 mm	Nocturnal angina	New onset angina with onset 2 weeks to 2 months prior to presentation
Angina with new or worsening MR murmur	Angina with dynamic T-wave changes	Normal or unchanged ECG
Angina with S ₃ or new/worsening rales	New onset CCSC III or IV angina in the past 2 weeks with moderate or high likelihood of CAD	
Angina with hypotension	Pathologic Q waves or resting ST depression ≤ 1 mm in multiple lead groups (anterior, inferior, lateral) Age > 65 years	

CCSC = Canadian Cardiovascular Society Classification.

Note: Estimation of the short-term risks of death and nonfatal MI 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.

group, the clinician must weigh the value of correctly diagnosing CAD in 25 patients against the cost of a stress test for all 1,000 patients plus the cost of misdiagnosis—undue anxiety, further invasive testing, unnecessary medications or higher insurance premiums—for the 95 patients with a false-positive test result. In patients with a high probability of CAD (90%), a positive test result raises the probability of disease to 98% and a negative test result lowers probability to 83%. Although exercise testing has prognostic value in these patients (see Section III, C-2) (37), a negative test result obviously does not allow the clinician to discard the diagnosis of CAD. In patients with a 50% probability of CAD, a positive test result increases the likelihood of disease to 83% and a negative test result decreases the likelihood to 36%. The test separates this group of patients into two distinct subgroups: one in whom CAD almost certainly exists and the other for whom the diagnosis, although far from being excluded, is doubtful. An accurate estimate of the likelihood of CAD is necessary for interpretation of further test results and good clinical decision making about therapy.

Although it may seem premature to predict the probability of CAD after the history and physical, the clinicopathological study performed by Diamond and Forrester (38) demonstrated that it is possible. By combining data from a series of angiography studies performed in the 1960s and the 1970s, they showed that the simple clinical observations of pain type, age, and gender were powerful predictors of the likelihood of CAD. For instance, a 64-year-old man with typical angina has a 94% likelihood of having significant CAD. A 32-year-old woman with nonanginal chest pain has a 1% chance of CAD (14).

The value of the Diamond and Forrester approach was subsequently confirmed in prospective studies at Duke and Stanford. In these studies, both men and women were referred to cardiology specialty clinics for cardiac catheterization (39,40) or cardiac stress testing (41), and the initial clinical exam characteristics most helpful in predicting CAD were determined. With these characteristics, predictive models (logistic regression equations) were developed. When prospectively applied to another group of patients referred to the same specialty clinic, the models worked well. As in Diamond and Forrester's original work, age, gender and pain type were the most powerful predictors. Other characteristics that strengthened the predictive abilities of the models were smoking (defined as a history of smoking half a pack or more of cigarettes per day within five years of the study or at least 25 pack-years), Q wave or ST-T-wave changes, hyperlipidemia (defined as a cholesterol level >250 mg/dL) and diabetes (glucose >140). Of these risk factors, diabetes had the greatest influence on increasing risk. Other significant risk factors, such as family history and hypertension, were not as strongly predictive and did not improve the power of equations.

Generalizability of the Predictive Models

Although these models worked well prospectively in the settings in which they were developed, clinicians must assess how reliable they will be when used in their own practices. The Diamond and Forrester probabilities were compared with those published in the Coronary Artery Surgery Study (CASS) (42), a large 15-center study that compared clinical and angiographic findings in >20,000 patients. In both studies,

Table 9. Pretest Likelihood of CAD in Symptomatic Patients According to Age and Sex* (Combined Diamond/Forrester and CASS Data) (38,42)

Age Years	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

*Each value represents the percent with significant CAD on catheterization.

probability tables were presented in which patients were categorized by age, gender, and pain type. Tables with 24 patient groupings were published. With the exception of adults <50 years old with atypical angina for whom the CASS data estimated a probability of disease 17% higher than the Diamond-Forrester data, the agreement between studies was very close: the difference averaged 5%. Because the results were so similar, the committee combined the probabilities from both studies in one evidence table (Table 9).

It is more difficult to compare the Duke data directly with the CASS and Diamond-Forrester tables because within each age, gender, and pain type grouping, the patient's predicted probability of disease varies, depending on the presence or absence of electrocardiogram (ECG) findings (Q waves or ST-T changes) or risk factors (smoking, diabetes, hyperlipidemia). Table 10 presents the Duke data for mid-decade patients (35, 45, 55, and 65 years old). Two probabilities are given. The first is for a low-risk patient with no risk factors and a normal ECG. The second is for a high-risk patient who smokes and has diabetes and hyperlipidemia but has a normal ECG. The presence of ECG changes would increase the probability of coronary disease even more. When Tables 9 and 10 are compared, the correlation between studies is quite strong. Apparent in the Duke data is the importance of risk factors in modifying the

Table 10. Comparing Pretest Likelihoods of CAD in Low-Risk Symptomatic Patients With High-Risk Symptomatic Patients—Duke Database (41)

Age Years	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
	Men	Women	Men	Women	Men	Women
35 yr	3-35	1-19	8-59	2-39	30-88	10-78
45 yr	9-47	2-22	21-70	5-43	51-92	20-79
55 yr	23-59	4-25	45-79	10-47	80-95	38-82
65 yr	49-69	9-29	71-86	20-51	93-97	56-84

Each value represents the percent with significant CAD. The first is the percentage for a low-risk, mid-decade patient without diabetes, smoking, or hyperlipidemia. The second is that of the same age patient with diabetes, smoking, and hyperlipidemia. Both high- and low-risk patients have normal resting ECG's. If ST-T-wave changes or Q waves had been present, the likelihood of CAD would be higher in each entry of the table.

likelihood of disease. This becomes more important the younger the patient and the more atypical the pain. For example, the likelihood of disease for women <55 years old with atypical angina and no risk factors is <10%, but if diabetes, smoking and hyperlipidemia are present, the likelihood jumps to 40%.

Applicability of Models to Primary-Care Practices

All the studies mentioned above were university-based. The patients used to develop the models were largely referred. The only study that directly looked at applicability of the university-derived model to primary-care practices was the Stanford study (40). The university-derived equation was used and the likelihood of CAD was predicted for patients presenting to two urban primary-care clinics. The equation worked well for typical angina patients but substantially overpredicted CAD for patients at less risk.

Referral (or ascertainment) bias in these studies likely explains these differences (43,44) because the clinical decision-making process before the patient was referred is unknown. Primary-care providers do not unselectively refer all chest pain patients for cardiac evaluation. The disease probabilities for high-risk patients will vary little from the study because few primary-care physicians will fail to recommend cardiac evaluation for typical angina patients. However, younger patients with less classic pain stories will often be referred only after therapeutic trials, time or noncardiac diagnostic studies fail to eliminate CAD as a possibility. Correcting for referral bias is required before these models can be applied to primary-care practices. The Stanford study showed that it was possible to correct the model predictions by using the overall prevalence of CAD in the primary care population (40). Unfortunately, while Bayesian analysis might help a primary care provider improve the models, there are no studies examining how accurately providers calculate the prevalence of CAD among their chest pain patients, or how the prevalence of CAD varies among primary care settings. Primary-care physicians must therefore exercise caution when using these predictive equations, tables, or nomograms with patients presenting for the first time with chest pain. Whether the difference between the model estimates and actual likelihood of CAD is great enough to lead to a different diagnostic and therapeutic strategy is not known.

Ideally, the strategy a clinician uses to evaluate a patient with chest pain will also take into account the patient's preferences. Two patients with the same pretest probability of CAD may prefer different approaches because of variations in personal beliefs, economic situation or stage of life. Patient preference studies that inform physicians about what is an acceptable balance between the underdiagnosis and overdiagnosis of CAD have not been done.

Table 11. Alternative Diagnoses to Angina for Patients With Chest Pain

Non-Ischemic Cardiovascular	Pulmonary	Gastrointestinal	Chest Wall	Psychiatric
Aortic dissection	Pulmonary embolus	Esophageal	Costochondritis	Anxiety disorders
Pericarditis	Pneumothorax	Esophagitis	Fibrositis	Hyperventilation
	Pneumonia	Spasm	Rib fracture	Panic disorder
	Pleuritis	Reflux	Sternoclavicular arthritis	Primary anxiety
		Biliary	Herpes zoster	Affective disorders
		Colic	(before the rash)	(e.g., depression)
		Cholecystitis		Somatiform disorders
		Cholelithiasis		Thought disorders
		Cholangitis		(e.g., fixed delusions)
		Peptic ulcer		
		Pancreatitis		

B. Associated Conditions

Recommendations for Initial Laboratory Tests for Diagnosis

Class I

- 1. Hemoglobin.** (*Level of Evidence: C*)
- 2. Fasting glucose.** (*Level of Evidence: C*)
- 3. Fasting lipid panel, including total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol.** (*Level of Evidence: C*)

Using information gathered from the history and physical examination, the clinician should consider possibilities other than CAD in the differential diagnosis, because a number of other conditions can both cause and contribute to angina. In those patients with risk factors for CAD but an otherwise low probability history for angina, alternative diagnoses should be considered (Table 11).

In all patients, particularly those with typical angina, comorbid conditions that may precipitate “functional” angina (i.e., myocardial ischemia in the absence of significant anatomic coronary obstruction) should be considered. Generally, these are pathological entities that cause myocardial ischemia either by placing increased myocardial oxygen demands on the heart or by decreasing the myocardial oxygen supply (Table 12).

Increased oxygen demand can be produced by such entities as hyperthermia, hyperthyroidism, and cocaine abuse. Hyperthermia, particularly if accompanied by volume contraction due to diaphoresis or other fluid losses, can precipitate angina in the absence of significant CAD (47).

Hyperthyroidism, with its associated tachycardia and increased metabolic rate, increases oxygen demand and, perhaps because of increased platelet aggregation, may also decrease supply. These effects can readily lead to angina. In addition, elderly patients may not present with a typical clinical picture of thyrotoxicosis. Therefore, this possibility should be considered in the setting of minimal risk factors accompanied by a history of typical angina, particularly in older patients.

Sympathomimetic toxicity, of which cocaine is the prototype, not only increases myocardial oxygen demand but, through coronary vasospasm, simultaneously decreases supply, sometimes leading to infarction in young patients. Long-term cocaine use may also lead to development of angina by causing premature development of CAD (48).

Angina may occur in patients with severe uncontrolled hypertension due to increased wall tension, which increases myocardial oxygen demand, and increased left ventricular (LV) end-diastolic pressure, which decreases subendocardial perfusion. These same mechanisms contribute to angina in hypertrophic cardiomyopathy and aortic stenosis; however, in these conditions, wall tension may be even greater due to an outflow tract gradient, and end-diastolic pressure may be even higher due to severe LV hypertrophy.

Table 12. Conditions Provoking or Exacerbating Ischemia

Increased Oxygen Demand	Decreased Oxygen Supply
<i>Non-Cardiac</i>	<i>Non-Cardiac</i>
Hyperthermia	Anemia
Hyperthyroidism	Hypoxemia
Sympathomimetic toxicity (e.g., cocaine use)	Pneumonia
Hypertension	Asthma
Anxiety	Chronic obstructive pulmonary disease
Arteriovenous fistulae	Pulmonary hypertension
	Interstitial pulmonary fibrosis
<i>Cardiac</i>	Obstructive sleep apnea
Hypertrophic cardiomyopathy	Sickle cell disease
Aortic stenosis	Sympathomimetic toxicity (e.g., cocaine use)
Dilated cardiomyopathy	Hyperviscosity
Tachycardia	Polycythemia
Ventricular	Leukemia
Supraventricular	Thrombocytosis
	Hypergammaglobulinemia
	<i>Cardiac</i>
	Aortic stenosis
	Hypertrophic cardiomyopathy

Sustained tachycardia, either ventricular or supraventricular, may also increase myocardial oxygen demand. Paroxysmal tachycardias are more frequent conditions that contribute to angina. Unfortunately, they are often more difficult to diagnose.

Conditions that reduce myocardial oxygen supply must also be considered in the differential diagnosis of patients with angina.

Anemia reduces the oxygen-carrying capacity of the blood and also increases the cardiac workload. An increased cardiac output is associated with <9 g/dL of hemoglobin, and ST-T wave changes (depression or inversion) may be seen when hemoglobin drops below 7 g/dL.

Hypoxemia resulting from pulmonary disease (e.g., pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial fibrosis, obstructive sleep apnea) may also precipitate angina. Obstructive sleep apnea should be seriously considered in patients with only nocturnal symptoms.

Conditions that are associated with increased blood viscosity can increase coronary resistance and thereby decrease coronary artery blood flow, precipitating angina in patients without severe coronary stenoses. Increased viscosity is seen with polycythemia, leukemia, thrombocytosis and hypergammaglobulinemia.

C. Noninvasive Testing

1. ECG/Chest X-Ray

Recommendations for Electrocardiography, Chest X-Ray, or Electron Beam Computed Tomography in the Diagnosis of Chronic Stable Angina

Class I

1. Rest ECG in patients without an obvious non-cardiac cause of chest pain. (*Level of Evidence: B*)
2. Rest ECG during an episode of chest pain. (*Level of Evidence: B*)
3. Chest X-ray in patients with signs or symptoms of congestive heart failure, valvular heart disease, pericardial disease, or aortic dissection/aneurysm. (*Level of Evidence: B*)

Class IIa

Chest X-ray in patients with signs or symptoms of pulmonary disease. (*Level of Evidence: B*)

Class IIb

1. Chest X-ray in other patients. (*Level of Evidence: C*)
2. Electron beam computed tomography (EBCT). (*Level of Evidence: B*)

A rest 12-lead ECG should be recorded in all patients with symptoms suggestive of angina pectoris; however, it will be normal in $\geq 50\%$ of patients with chronic stable angina (49). A normal rest ECG does not exclude severe CAD. ECG evidence of LV hypertrophy or ST-T wave changes consistent with myocardial ischemia favor the

diagnosis of angina pectoris (50). Evidence of prior Q-wave MI on the ECG makes CAD very likely. However, certain Q-wave patterns are equivocal, such as an isolated Q in lead III or a QS pattern in leads V_1 and V_2 .

The presence of arrhythmias such as atrial fibrillation or ventricular tachyarrhythmia on the ECG in patients with chest pain also increases the probability of underlying CAD; however, these arrhythmias are frequently caused by other types of cardiac disease. Various degrees of AV block can be present in patients with chronic CAD but have many other causes and a very low specificity for the diagnosis. Left anterior fascicular block, right bundle-branch block and left bundle-branch block often occur in patients with CAD and frequently indicate the presence of multivessel CAD. However, these findings also lack specificity in the diagnosis of chronic stable angina.

An ECG obtained during chest pain is abnormal in $\approx 50\%$ of patients with angina who have a normal rest ECG. Sinus tachycardia occurs commonly; bradyarrhythmia is less common. The ST-segment elevation or depression establishes a high likelihood of angina and indicates ischemia at a low workload, portending an unfavorable prognosis. Many high-risk patients need no further noninvasive testing. Coronary arteriography usually defines the severity of coronary artery stenoses and the necessity and feasibility of myocardial revascularization. In patients with ST-T wave depression or inversion on the rest ECG, "pseudonormalization" of these abnormalities during pain is another indicator that CAD is likely (51). The occurrence of tachyarrhythmias, atrioventricular block, left anterior fascicular block or bundle-branch block with chest pain also increases the probability of coronary heart disease (CHD) and often leads to coronary arteriography.

The chest roentgenogram is often normal in patients with stable angina pectoris. Its usefulness as a routine test is not well established. It is more likely to be abnormal in patients with previous or acute MI, those with a noncoronary artery cause of chest pain and those with noncardiac chest discomfort. Cardiac enlargement may be attributable to previous MI, acute LV failure, pericardial effusion or chronic volume overload of the left ventricle such as occurs with aortic or mitral regurgitation. Abnormal physical findings, associated chest X-ray findings (e.g., pulmonary venous congestion), and abnormalities detected by noninvasive testing (echocardiography) may indicate the correct etiology.

Enlargement of the upper mediastinum often results from an ascending aortic aneurysm with or without dissection. Pruning or cutoffs of the pulmonary arteries or areas of segmental oligemia may indicate pulmonary infarction/embolism or other causes of pulmonary hypertension.

Coronary artery calcification increases the likelihood of symptomatic CAD. Fluoroscopically detectable coronary calcification is correlated with major-vessel occlusion in 94% of patients with chest pain (52); however, the sensitivity of the test is only 40%.

Ultrafast Computed Tomography

Ultrafast (electron beam) computed tomography is being used with increased frequency for the detection and quantification of coronary artery calcification (25). In seven studies including 50 to 710 patients, calcium of the coronary arteries detected by EBCT was an important indicator of angiographic coronary stenoses. In these studies of selected patients, the sensitivity of a positive EBCT detection of calcium for the presence of CAD varied from 85% to 100%; specificity ranged from only 41% to 76%; the positive predictive value varied considerably from 55% to 84% and negative predictive value from 84% to 100% (25). The presence and amount of calcium detected in coronary arteries by EBCT in two studies appeared to correlate with the presence and associated amount of atherosclerotic plaque (53,54). However, several studies (55-57) have shown a marked variability in repeated measures of coronary calcium by EBCT. Therefore, the use of serial EBCT scans in individual patients for identification and serial assessment of the progression or regression of calcium remains problematic. The proper role of EBCT is controversial and will be the subject of future ACC/AHA statements.

2. Exercise ECG for Diagnosis

Recommendations for Diagnosis of Obstructive CAD With Exercise ECG Testing Without an Imaging Modality

Class I

Patients with an intermediate pretest probability of CAD based on age, gender and symptoms, including those with complete right bundle-branch block or <1 mm of ST depression at rest (exceptions are listed below in classes II and III). (Level of Evidence: B)

Class IIa

Patients with suspected vasospastic angina. (Level of Evidence: C)

Class IIb

- 1. Patients with a high pretest probability of CAD by age, gender and symptoms. (Level of Evidence: B)**
- 2. Patients with a low pretest probability of CAD by age, gender and symptoms. (Level of Evidence: B)**
- 3. Patients taking digoxin whose ECG has <1 mm of baseline ST-segment depression. (Level of Evidence: B)**
- 4. Patients with ECG criteria for LV hypertrophy and <1 mm of baseline ST-segment depression. (Level of Evidence: B)**

Class III

- 1. Patients with the following baseline ECG abnormalities.**
 - a. Pre-excitation (Wolff-Parkinson-White) syndrome. (Level of Evidence: B)**

- b. Electronically paced ventricular rhythm. (Level of Evidence: B)**
 - c. More than 1 mm of ST depression at rest. (Level of Evidence: B)**
 - d. Complete left bundle-branch block. (Level of Evidence: B)**
- 2. Patients with an established diagnosis of CAD due to prior MI or coronary angiography; however, testing can assess functional capacity and prognosis, as discussed in section III. (Level of Evidence: B)**

Description of the Exercise Testing Procedure

Exercise testing is a well-established procedure that has been in widespread clinical use for many decades. Detailed descriptions of exercise testing are available in other publications (58-60). This section provides a brief overview based on the "ACC/AHA Guidelines for Exercise Testing" (14).

Although exercise testing is generally a safe procedure, both MI and death occur at a rate of $\leq 1/2500$ tests (61). The absolute contraindications to exercise testing include acute MI within two days, cardiac arrhythmias causing symptoms or hemodynamic compromise, symptomatic and severe aortic stenosis, symptomatic heart failure, acute pulmonary embolus or pulmonary infarction, acute myocarditis or pericarditis and acute aortic dissection (14,59). Additional factors are relative contraindications: left main coronary stenosis, moderate aortic stenosis, electrolyte abnormalities, systolic hypertension >200 mm Hg, diastolic blood pressure >110 mm Hg, tachyarrhythmias or bradyarrhythmias, hypertrophic cardiomyopathy and other forms of outflow tract obstruction, mental or physical impairment leading to an inability to exercise adequately and high-degree atrioventricular block (14,59). In the past, unstable angina was a contraindication to exercise testing. However, new information suggests that exercise treadmill (62-64) and pharmacologic (65-68) testing are safe in low-risk outpatients with unstable angina and in low- or intermediate-risk patients hospitalized with unstable angina in whom an MI has been ruled out and who are free of angina and congestive heart failure.

Both treadmill and cycle ergometer devices are used for exercise testing. Although cycle ergometers have important advantages, fatigue in the quadriceps muscles in patients who are not experienced cyclists usually makes them stop before reaching their maximum oxygen uptake. As a result, treadmills are more commonly used in the U.S.

There are clear advantages in customizing the protocol to the individual patient to allow exercise lasting 6 to 12 min (69). Exercise capacity should be reported in estimated METs of exercise. (One MET is the standard basal oxygen uptake of 3.5 mL/kg per min.) If exercise capacity is also reported in minutes, the protocol should be described clearly.

Exercise testing should be supervised by an appropriately trained physician (70), although personal supervision (as

defined by the Health Care Financing Administration [HCFA]) is not always required. The ECG, heart rate and blood pressure should be carefully monitored and recorded during each stage of exercise as well as during ST-segment abnormalities and chest pain. The patient should be monitored continuously for transient rhythm disturbances, ST-segment changes and other ECG manifestations of myocardial ischemia. Although exercise testing is commonly terminated when subjects reach a standard percentage (often 85%) of age-predicted maximum heart rate, there is great variability in maximum heart rates among individuals, so predicted values may be supramaximal for some patients and submaximal for others. Therefore, it is important to monitor the patient closely for other indications for stopping the test. Absolute indications for stopping include a drop in systolic blood pressure of >10 mm Hg from baseline blood pressure despite an increase in workload when accompanied by other evidence of ischemia; moderate to severe angina; increasing ataxia, dizziness or near syncope; signs of poor perfusion such as cyanosis or pallor; technical difficulties monitoring the ECG or systolic blood pressure; the subject's desire to stop; sustained ventricular tachycardia; or ST elevation ≥ 1 mm in leads without diagnostic Q waves (other than V₁ or aVR). Relative indications for stopping include a 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; >2 mm of horizontal or downsloping ST-segment depression; marked axis deviation; arrhythmias such as multifocal premature ventricular complexes (PVCs), triplets of PVCs, supraventricular tachycardia, heart block or bradyarrhythmias; symptoms such as fatigue, shortness of breath, wheezing, leg cramps or claudication; bundle-branch block or IVCD that cannot be distinguished from ventricular tachycardia; increasing chest pain; systolic blood pressure >250 mm Hg; or diastolic blood pressure >115 mm Hg (59). Rating the level of perceived exertion with the Borg scale (71) helps measure patient fatigue, and fatigue-limited testing is especially important when assessing functional capacity.

Interpretation of the Exercise Test

Interpretation of the exercise test should include symptomatic response, exercise capacity, hemodynamic response, and ECG 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 ECG findings are ST depression and ST elevation. The most commonly used definition for a positive exercise test is ≥ 1 mm of horizontal or downsloping ST-segment depression or elevation for ≥ 60 to 80 ms after the end of the QRS complex, either during or after exercise (14).

Cost and Availability

The exercise ECG is the least costly diagnostic test, with the cost of stress echocardiography ≥ 2 -fold higher, stress SPECT myocardial imaging at least 5-fold higher, and coronary angiography 20-fold higher. A lower cost of the treadmill exercise test alone does not necessarily result in a lower overall cost of patient care, however, as the cost of additional testing and intervention may be higher because the exercise test is less accurate.

Treadmill exercise tests are performed frequently but somewhat less often than the most frequent imaging procedure, which is stress SPECT myocardial perfusion imaging. An estimated two thirds of the treadmill exercise tests charged to Medicare in 1994 were performed as office procedures, and 33% of these charges were submitted by noncardiologists (14).

Rationale

Diagnostic Characteristics of Exercise Tests

The sensitivity of the exercise test measures the probability that a patient with obstructive CAD will have a positive test result, whereas the specificity measures the probability that a patient without obstructive CAD will have a negative test result. Sensitivity and specificity are used to summarize the characteristics of diagnostic tests because they provide standard measures that can be used to compare different tests. Sensitivity and specificity alone, however, do not provide the information needed to interpret the results of exercise testing. That information can be calculated and expressed as predictive values. These calculations require the sensitivity and specificity of the exercise test along with the pretest probability that the patient has obstructive CAD.

Positive Predictive Value =

$$\frac{(\text{Pretest Probability})(\text{Sensitivity})}{(\text{Pretest Probability})(\text{Sensitivity}) + (1 - \text{Pretest Probability})(1 - \text{Specificity})}$$

The numerator refers to positive test results that are true-positive, and the denominator refers to all positive test results, true-positive and false-positive. The positive predictive value is the probability that the patient has obstructive CAD when the exercise test result is positive.

Negative Predictive Value

$$= \frac{(1 - \text{Pretest Probability})(\text{Specificity})}{(1 - \text{Pretest Probability})(\text{Specificity}) + (\text{Pretest Probability})(1 - \text{Sensitivity})}$$

The numerator refers to negative test results that are true-negative, and the denominator refers to all negative test results, both true-negative and false-negative. The negative predictive value is the probability that the patient does not have obstructive CAD when the exercise test result is

negative. Therefore, knowing the sensitivity and specificity of the exercise test and the patient's pretest probability of obstructive CAD is especially important when interpreting the results of exercise testing.

When interpreting estimates of the sensitivity and specificity of exercise testing, it is important to recognize a type of bias called workup verification, or posttest referral bias. This type of bias occurs when the results of exercise testing are used to decide which patients have the diagnosis of CAD verified or ruled out with a gold-standard procedure. This bias also occurs when patients with positive results on exercise testing are referred for coronary angiography and patients with negative results are not. Such a selection process curtails the number of true-negative results. The result of this type of bias is to raise the measured sensitivity and lower the measured specificity in relation to their true values.

Sensitivity and Specificity of the Exercise Test

A meta-analysis of 147 published reports describing 24,074 patients who underwent both coronary angiography and exercise testing found wide variation in sensitivity and specificity (14). Mean sensitivity was 68% with a standard deviation of 16%; mean specificity was 77% with a standard deviation of 17%. When the analysis considered only results from the 58 studies that focused on diagnostic tests by excluding patients with a prior MI, mean sensitivity was 67% and mean specificity 72%. When the analysis was restricted to the few studies that avoided workup bias by including only patients who agreed before any testing to have both exercise testing and coronary angiography, sensitivity was 50% and specificity 90% (73,74). In a more recent study of 814 men that was carefully designed to minimize workup bias, sensitivity was 45% and specificity 85% (75). Therefore, the true diagnostic value of the exercise ECG lies in its relatively high specificity. The modest sensitivity of the exercise ECG is generally lower than the sensitivity of imaging procedures (12,13).

Although the sensitivity and specificity of a diagnostic test are usually thought to be characteristics of the tests themselves and not affected by patient differences, this is not always the case. 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. The test has a lower specificity in those with valvular heart disease, LV hypertrophy and rest ST depression and those taking digoxin (14).

Physicians are often urged to consider more than just the ST segment when interpreting the exercise test, and some studies that use complex formulas to incorporate additional test information have found diagnoses made with this approach to be more accurate than those based only on the ST response (76,77). However, the diagnostic interpretation of the exercise test still centers around the ST response because different studies produce different formulas, and the

formulas provide similar results when compared with the judgment of experienced clinical cardiologists (75,78,79).

Pretest Probability

Diagnostic testing is most valuable when the pretest probability of obstructive CAD is intermediate: for example, when a 50-year-old man has atypical angina and the probability of CAD is $\approx 50\%$ (see Table 9). In these conditions, the test result has the largest effect on the posttest probability of disease and thus on clinical decisions.

The exact definition of the upper and lower boundaries of intermediate probability (e.g., 10% and 90%, 20% and 80%, 30% and 70%) is a matter of physician judgment in an individual situation. Among the factors relevant to the choice of these boundaries are the degree of uncertainty that is acceptable to physician and patient; the likelihood of an alternative diagnosis; the reliability, cost, and potential risks of further testing; and the benefits and risks of treatment in the absence of additional testing. Pauker and Kassirer (80) have described the application of decision analysis to this important issue. As indicated earlier, it should be recognized that the initial evaluation of patients with noncardiac pain will focus on noncardiac conditions. Clinical judgment in such patients may indicate that they are at low probability and do not require cardiac evaluation.

For the diagnosis of CAD, one possible arbitrary definition of intermediate probability that appears in published research is between 10% and 90%. This definition was first advocated 20 years ago (81), and has been used in several studies (82,83) and the "ACC/AHA Guidelines for Exercise Testing" (14). Although this range may seem very broad, many sizable patient groups (e.g., older men with typical angina and younger women with nonanginal pain) fall outside the intermediate probability range. When the probability of obstructive CAD is high, a positive test result only confirms the high probability of disease, and a negative test result may not decrease the probability of disease enough to make a clinical difference. Although the exercise test is less useful for the diagnosis of CAD when pretest probability is high, it can provide information about the patient's risk status and prognosis (see Section III). When the probability of obstructive CAD is very low, a negative test result only confirms the low probability of disease, and a positive test result may not increase the probability of disease enough to make a clinical difference.

Influence of Other Factors on Test Performance

Digoxin. Digoxin produces abnormal exercise-induced ST depression in 25% to 40% of apparently healthy normal subjects (84,85). The prevalence of abnormal responses is directly related to age.

Beta-Adrenergic Blocking Agent Therapy. Whenever possible, it is recommended that beta-blockers (and other anti-ischemic drugs) be withheld for four to five half-lives (usually about 48 h) before exercise stress testing for the diagnosis and initial risk stratification of patients with

suspected CAD. Ideally, these drugs should be withdrawn gradually to avoid a withdrawal phenomenon that may precipitate events (86,87). When beta-blockers cannot be stopped, stress testing may detect myocardial ischemia less reliably, but it usually will still be positive in patients at the highest risk.

Other Drugs. Antihypertensive agents and vasodilators can affect test performance by altering the hemodynamic response of blood pressure. Short-term administration of nitrates can attenuate the angina and ST depression associated with myocardial ischemia. Flecainide has been associated with exercise-induced ventricular tachycardia (88,89).

Left Bundle-Branch Block. Exercise-induced ST depression usually occurs with left bundle-branch block and is not associated with ischemia (90).

Right Bundle-Branch Block. Exercise-induced ST depression usually occurs with right bundle-branch block in the anterior chest leads (V_{1-3}) and has no association with ischemia (91). However, when it occurs in the left chest leads ($V_{5,6}$) or inferior leads (II, aVF), it has the same significance as it does when the rest ECG is normal.

LV Hypertrophy With Repolarization Abnormality on the rest ECG is associated with more false-positive test results due to decreased specificity.

Rest ST-Segment Depression is a marker for adverse cardiac events in patients with and without known CAD (92-99). Additional exercise-induced ST-segment depression in the patient with ≤ 1 mm rest ST-segment depression is a reasonably sensitive indicator of CAD.

ST-Segment Interpretation Issues

Lead Selection. Twelve-lead ECGs provide the greatest sensitivity. The V_5 alone consistently outperforms the inferior leads and the combination of V_5 with lead II. In patients without prior MI and with a normal rest ECG, the precordial leads alone are a reliable marker for CAD. In patients with a normal rest ECG, exercise-induced ST-segment depression confined to the inferior leads is of little value (100).

Upsloping ST Depression. Patients with ST-segment depression that slopes upward at < 1 mV/s probably have an increased probability of coronary disease (101,102). However, the ACC/AHA/ACP-ASIM Committee to Develop Guidelines for the Management of Chronic Stable Angina favors the use of the more common definition for a positive test, which is 1 mm of horizontal or downsloping ST depression or elevation for ≥ 60 to 80 milliseconds after the end of the QRS complex (72), because most of the published literature is based on this definition.

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 (103,104). Patients with false-positive exercise tests have a high peak exercise heart rate,

absence of exercise-induced chest pain, and markedly downsloping PR segments in the inferior leads. This issue of atrial repolarization waves was not addressed in the "ACC/AHA Guidelines for Exercise Testing" (14).

ST Elevation. When the rest ECG is normal, ST elevation (other than in aVR or V_1) is very rare, represents transmural ischemia caused by spasm or a critical lesion, greatly increases the likelihood of arrhythmias, and localizes the ischemia. When the rest ECG shows Q waves from an old MI, the significance of ST elevation is controversial. Some studies have suggested that it is due to wall motion abnormalities (105,106); other studies (107-109) have found it to be a marker of residual viability in the infarcted area.

R-Wave Changes. A multitude of factors affect the R-wave response to exercise (110), and the response does not have diagnostic significance (111,112).

Heart Rate Adjustment. Several methods of heart rate adjustment have been proposed to increase the diagnostic accuracy of the exercise ECG (113-116), but there is no convincing evidence of benefit (115-119). It is more important to consider exercise capacity than heart rate.

Computer Processing. Although computer processing of the exercise ECG can be helpful, it can also result in false-positive ST depression (120). To avoid this problem, the interpreting physician should always compare the unprocessed ECG with any computer-generated averages.

Special Groups

Women. The use of exercise testing in women presents difficulties that are not experienced in men. These difficulties reflect the differences between men and women regarding the prevalence of CAD and the sensitivity and specificity of exercise testing.

Although obstructive CAD is one of the principal causes of death in women, the prevalence (and thus the pretest probability) of this disease is lower in women than it is in men of comparable age, especially in premenopausal women. When compared with men, the lower pretest probability of disease in women means that more test results are false-positive. For example, almost half the women with anginal symptoms in the CASS study, many of whom had positive exercise test results, had normal coronary arteriograms (121).

Exercise testing is less sensitive in women than it is in men, and some studies have found it also to be less specific (14,73,83,122-131). Among the proposed reasons for these differences are the use of different criteria for defining coronary disease, differences in the prevalence of multivessel disease and prior MI, differences in the criteria for ST-segment positivity (132,133), differences in type of exercise, the inability of many women to exercise to maximum aerobic capacity (134,135), 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. To compensate for the limitations of the test in women, some investigators have developed predictive models that incorporate more information from the test than simply the amount and type of ST-segment change (130,131). Although this approach is attractive, its clinical application remains limited.

The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing (129). Although the optimal strategy for diagnosing obstructive CAD in women remains to be defined, the ACC/AHA/ACP-ASIM Committee to Develop Guidelines for the Management of Chronic Stable Angina believes there are currently insufficient data to justify replacing standard exercise testing with stress imaging when evaluating women for CAD. In many women with a low pretest likelihood of disease, a negative exercise test result will be sufficient, and imaging procedures will not be required (83).

The Elderly. Few data have been published about the use of exercise testing in people ≥ 70 years old. The 1989 National Health Interview Survey (136) found that the diagnosis of CAD was reported by 1.8% in men and 1.5% in women >75 years old. Silent ischemia is estimated to be present in 15% of 80-year-olds (137).

The performance of exercise testing poses additional problems in the elderly. Functional capacity often is compromised from muscle weakness and deconditioning, making the decision about an exercise test versus a pharmacologic stress test more important. More attention must be given to the mechanical hazards of exercise, and less challenging protocols should be used (138). Elderly patients are more likely to hold the hand rails tightly, thus reducing the validity of treadmill time for estimating METs. Arrhythmias occur more frequently with increasing age, especially at higher workloads (138). In some patients with problems of gait and coordination, a bicycle exercise test may be more attractive (139), but bicycle exercise is unfamiliar to most elderly patients.

The interpretation of exercise test results in the elderly differs from that in the young. The greater severity of coronary disease in this group increases the sensitivity of exercise testing (84%), but it also decreases the specificity (70%). The high prevalence of disease means that more test results are false-negative (140). False-positive test results may reflect the coexistence of LV hypertrophy from valvular disease and hypertension, as well as conduction disturbances. Other rest ECG abnormalities that complicate interpretation, including prior MI, also are more frequent.

Exercise testing in the elderly is more difficult both to do and to interpret, and the follow-up risks of coronary angiography and revascularization are greater. Despite these differences, exercise testing remains important in the elderly because the alternative to revascularization is medical therapy, which also has greater risks in this group.

3. Echocardiography (Resting)

Recommendations for Echocardiography for Diagnosis of Cause of Chest Pain in Patients With Suspected Chronic Stable Angina Pectoris

Class I

1. Patients with systolic murmur suggestive of aortic stenosis or hypertrophic cardiomyopathy. (*Level of Evidence: C*)
2. Evaluation of extent (severity) of ischemia (e.g., LV segmental wall motion abnormality) when the echocardiogram can be obtained during pain or within 30 min after its abatement. (*Level of Evidence: C*)

Class IIb

Patients with a click or murmur to diagnose mitral valve prolapse (15). (*Level of Evidence: C*)

Class III

Patients with a normal ECG, no history of MI and no signs or symptoms suggestive of heart failure, valvular heart disease, or hypertrophic cardiomyopathy. (*Level of Evidence: C*)

Echocardiography can be a useful tool for assisting in establishing a diagnosis of CAD. Echocardiography can also assist in defining the consequences of coronary disease in selected patients with chronic chest pain presumed to be chronic stable angina. However, most patients undergoing a diagnostic evaluation for angina do not need an echocardiogram.

Cause of Chest Pain Unclear: Confounding or Concurrent Cardiac Diagnoses

Transthoracic echocardiographic imaging and Doppler recording are useful when there is a murmur or other evidence for conditions such as aortic stenosis or hypertrophic cardiomyopathy coexisting with CAD. Echo-Doppler techniques usually provide accurate quantitative information regarding the presence and severity of a coexisting lesion, such as 1) whether there is concentric hypertrophy or asymmetric hypertrophy of the ventricular septum, LV apex, or free wall; 2) the severity of any aortic valvular or subvalvular gradient; and 3) the status of LV function (13).

Echocardiography is useful for establishing or excluding the diagnosis of mitral valve prolapse and establishing the need for infective endocarditis prophylaxis (15).

Global LV Systolic Function

Chronic ischemic heart disease, whether associated with angina pectoris or not, can result in impaired systolic LV function. The extent and severity of regional and global abnormalities are important considerations in choosing appropriate medical or surgical therapy. Routine estimation of parameters of global LV function, such as LV ejection fraction, is unnecessary for the diagnosis of chronic angina pectoris. For example, in patients with suspected angina and

a normal ECG, no history of MI, and no signs or symptoms of heart failure, echocardiography and radionuclide imaging are not indicated (141,142).

Segmental LV Wall Motion Abnormalities

Echocardiographic findings that may help establish the diagnosis of chronic ischemic heart disease include regional systolic wall motion abnormalities, e.g., hypokinesis (reduced wall motion), akinesis (absence of wall motion), dyskinesis (paradoxical wall motion) and failure of a wall segment to thicken normally during systole (13). Care must be taken to distinguish chronic CAD as a cause of ventricular septal wall motion abnormalities from other conditions, such as left bundle-branch block, presence of an intraventricular pacemaker, right ventricular volume overload, or prior cardiac surgery (13).

The extent of regional (segmental) LV dysfunction can be described by scoring LV wall segments individually as to degree of wall motion abnormality (e.g., hypokinesis, dyskinesis, akinesis) or by using a scoring system that describes the summated wall motion score reflecting the normality or abnormality of each segment (143-146). Segmental wall motion abnormalities are often detected in patients with a prior history of MI or significant Q waves on their ECGs. Their locations correlate well with the distribution of CAD and pathologic evidence of infarction (143,144,147-154). Regional wall motion abnormalities can also be seen in patients with transient myocardial ischemia, chronic ischemia (hibernating myocardium) and myocardial scar and in some patients with myocarditis or other conditions not associated with coronary occlusion (13). In patients in whom the LV endocardium is suboptimally imaged by standard transthoracic echocardiography, tissue harmonic imaging (155,156) with newer transducers and contrast echocardiography with intravenous injections of encapsulated gaseous microbubbles represent promising new solutions (157-159).

In patients with chronic stable angina pectoris without previous MI, LV wall motion is typically normal on the rest echocardiogram in the absence of ischemia. However, in the uncommon situation in which an echocardiogram can be recorded during ischemia or, in some cases (e.g., with stunned myocardium), up to 30 min after ischemia, the presence of regional systolic wall motion abnormalities (in a patient without known CAD) is a moderately accurate indicator of an increased likelihood of clinically significant CAD. According to pooled data, the positive predictive accuracy of this finding for acute ischemia or infarction has been reported to be $\approx 50\%$ (13). Conversely, the absence of regional wall motion abnormalities identifies a subset of patients at low risk for an acute infarction (147,160), with a pooled negative predictive accuracy of about 95%.

Ischemic Mitral Regurgitation

Other structural and functional alterations can complicate chronic ischemic heart disease associated with stable angina

pectoris. Mitral regurgitation may result from global LV systolic dysfunction (161), regional papillary muscle dysfunction (162), scarring and shortening of the submitral chords (163), papillary muscle rupture (164), or other causes. The presence, severity and mechanism of mitral regurgitation can be reliably detected with transthoracic imaging and Doppler echocardiographic techniques. Potential surgical approaches to mitral valve repair or replacement can also be defined echocardiographically (15).

4. Stress Imaging Studies: Echocardiographic and Nuclear

Recommendations for Cardiac Stress Imaging as the Initial Test for Diagnosis in Patients With Chronic Stable Angina Who Are Able to Exercise **Class I**

- 1. Exercise myocardial perfusion imaging or exercise echocardiography in patients with an intermediate pretest probability of CAD who have one of the following baseline ECG abnormalities:**
 - a. Pre-excitation (Wolff-Parkinson-White) syndrome. (Level of Evidence: B)**
 - b. More than 1 mm of ST depression at rest. (Level of Evidence: B)**
- 2. Exercise myocardial perfusion imaging or exercise echocardiography in patients with prior revascularization (either PTCA or CABG). (Level of Evidence: B)**
- 3. Adenosine or dipyridamole myocardial perfusion imaging in patients with an intermediate pretest probability of CAD and one of the following baseline ECG abnormalities:**
 - a. Electronically paced ventricular rhythm. (Level of Evidence: C)**
 - b. Left bundle-branch block. (Level of Evidence: B)**

Class IIb

- 1. Exercise myocardial perfusion imaging and exercise echocardiography in patients with a low or high probability of CAD who have one of the following baseline ECG abnormalities:**
 - a. Pre-excitation (Wolff-Parkinson-White) syndrome. (Level of Evidence: B)**
 - b. More than 1 mm of ST depression. (Level of Evidence: B)**
- 2. Adenosine or dipyridamole myocardial perfusion imaging in patients with a low or high probability of CAD and one of the following baseline ECG abnormalities:**
 - a. Electronically paced ventricular rhythm. (Level of Evidence: C)**
 - b. Left bundle-branch block. (Level of Evidence: B)**

3. Exercise myocardial perfusion imaging or exercise echocardiography in patients with an intermediate probability of CAD who have one of the following:
 - a. Digoxin use with <1 mm ST depression on the baseline ECG. (*Level of Evidence: B*)
 - b. LVH with <1 mm ST depression on the baseline ECG. (*Level of Evidence: B*)
4. Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography as the initial stress test in a patient with a normal rest ECG who is not taking digoxin. (*Level of Evidence: B*)
5. Exercise or dobutamine echocardiography in patients with left bundle-branch block. (*Level of Evidence: C*)

Recommendations for Cardiac Stress Imaging as the Initial Test for Diagnosis in Patients With Chronic Stable Angina Who Are Unable to Exercise

Class I

1. Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with an intermediate pretest probability of CAD. (*Level of Evidence: B*)
2. Adenosine or dipyridamole stress myocardial perfusion imaging or dobutamine echocardiography in patients with prior revascularization (either PTCA or CABG). (*Level of Evidence: B*)

Class IIb

1. Adenosine or dipyridamole stress myocardial perfusion imaging or dobutamine echocardiography in patients with a low or high probability of CAD in the absence of electronically paced ventricular rhythm or left bundle-branch block. (*Level of Evidence: B*)
2. Adenosine or dipyridamole myocardial perfusion imaging in patients with a low or a high probability of CAD and one of the following baseline ECG abnormalities
 - a. Electronically paced ventricular rhythm. (*Level of Evidence: C*)
 - b. Left bundle-branch block. (*Level of Evidence: B*)
3. Dobutamine echocardiography in patients with left bundle-branch block. (*Level of Evidence: C*)

When to Do Stress Imaging

Patients who are good candidates for cardiac stress testing with imaging, as opposed to exercise ECG, include those in the following categories (see also Section II.C.3) (14): 1) complete left bundle-branch block, electronically paced ventricular rhythm, preexcitation (Wolff-Parkinson-White) syndrome and other similar ECG conduction abnormalities; 2) patients who have >1 mm of ST-segment depression at

rest, including those with LV hypertrophy or taking drugs such as digitalis; 3) patients who are unable to exercise to a level high enough to give meaningful results on routine stress ECG who should be considered for pharmacologic stress imaging tests; and 4) patients with angina who have undergone prior revascularization, in whom localization of ischemia, establishing the functional significance of lesions and demonstrating myocardial viability are important considerations.

Exercise and Pharmacologic Modalities Used in Stress Imaging

A variety of methods can be used to induce stress: 1) exercise (treadmill or upright or supine bicycle [see Section II.C.3]), and 2) pharmacologic techniques (either dobutamine or vasodilators). When the patient can exercise to develop an appropriate level of cardiovascular stress (e.g., 6 to 12 min), exercise stress testing (generally with a treadmill) is preferable to pharmacologic stress testing (see Section II.C.3). However, when the patient cannot exercise to the necessary level or in other specified circumstances (e.g., when stress echocardiography is being used in the assessment of myocardial viability), pharmacologic stress testing may be preferable. Three drugs are commonly used as substitutes for exercise stress testing: dipyridamole, adenosine and dobutamine. Dipyridamole and adenosine are vasodilators that are commonly used in conjunction with myocardial perfusion scintigraphy, whereas dobutamine is a positive inotropic (and chronotropic) agent commonly used with echocardiography.

Dipyridamole indirectly causes coronary vasodilation by inhibiting cellular uptake of adenosine, thereby increasing the blood and tissue levels of adenosine, which is a potent, direct coronary vasodilator and markedly increases coronary blood flow. The flow increase with adenosine or dipyridamole is of a lesser magnitude through stenotic arteries, creating heterogeneous myocardial perfusion, which can be observed with a perfusion tracer. Although this mechanism can exist independent of myocardial ischemia, in some patients, true myocardial ischemia can occur with either dipyridamole or adenosine because of a coronary steal phenomenon.

Both dipyridamole and adenosine are safe and well tolerated despite frequent mild side effects, which occur in 50% (165) and 80% (166,167) of patients, respectively. With dipyridamole infusion, the most common side effect was angina (18% to 42%), with arrhythmia occurring in <2%. Noncardiac side effects have included headache (5% to 23%), dizziness (5% to 21%), nausea (8% to 12%), and flushing (3%) (165). With adenosine infusion, chest pain has been reported in 57%, headache in 35%, flushing in 25%, shortness of breath in 15%, and first-degree AV block in 18%. Severe side effects are rare, but both dipyridamole and adenosine may cause severe bronchospasm in patients with asthma or chronic obstructive lung disease; therefore, they should be used with extreme caution—if at all—in

Table 13. Exercise SPECT Scintigraphy—Without Correction for Referral Bias

Author	Year	Total Patients	Sensitivity	Specificity
Tamaki (259)	1984	104	0.98	0.91
DePasquale (260)	1988	210	0.95	0.74
Iskandrian (226)	1989	461	0.82	0.60
Maddahi (261)	1989	138	0.95	0.56
Fintel (204)	1989	135	0.92	0.92
Van Train (262)	1990	318	0.94	0.43
Mahmarian (263)	1990	360	0.87	0.87
Gupta (214)	1992	144	0.82	0.80
Quiñones (264)	1992	112	0.76	0.81
Christian (265)	1992	688	0.92	0.74
Chae (128)	1993	243	0.71	0.65
Solot (266)	1993	128	0.89	0.90
Van Train (267)	1994	161	0.87	0.36
Rubello (268)	1995	120	0.92	0.61
Taillefer (248)	1997	115	0.87	0.92
Iskandrian (269)	1997	993	0.87	0.70
Others* (270-283)	1990-1998	842	0.87	0.75

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

these patients. Dipyridamole and adenosine side effects are antagonized by theophylline, although this drug is ordinarily not needed after adenosine because of the latter's ultrashort half-life (<10 s).

Dobutamine in high doses (20 to 40·μg kg⁻¹·min⁻¹) increases the three main determinants of myocardial oxygen demand, namely, heart rate, systolic blood pressure and myocardial contractility, thereby eliciting a secondary increase in myocardial blood flow and provoking ischemia. The flow increase (2-fold to 3-fold baseline values) is less than that elicited by adenosine or dipyridamole but is sufficient to demonstrate heterogeneous perfusion by radionuclide imaging. Although side effects are frequent during dobutamine infusion, the test appears to be relatively safe, even in the elderly (168-173). The most frequently reported noncardiac side effects (total 26%) in a study of 1118 patients included nausea (8%), anxiety (6%), headache (4%) and tremor (4%) (172). Common arrhythmias included premature ventricular beats (15%), premature atrial beats (8%), and supraventricular tachycardia and nonsustained ventricular tachycardia (3% to 4%). Atypical chest pain was reported in 8% and angina pectoris in approximately 20%.

Factors Affecting Accuracy of Noninvasive Testing

As already described for exercise ECG, apparent test performance can be altered by the pretest probability of CAD (38,174,175). The positive predictive value of a test declines as the disease prevalence decreases in the population under study, whereas the negative predictive accuracy increases (176). Stress imaging should generally not be used for routine diagnostic purposes in patients with a low or high pretest probability of disease. However, although stress imaging is less useful for diagnosis when the pretest prob-

ability of CAD is high, it can provide information about the patient's risk status and prognosis (see Section III.C.3).

As it is for exercise electrocardiography, the phenomenon of workup, verification, or posttest referral bias is an important factor influencing the sensitivity, specificity and predictive value of myocardial perfusion imaging and stress echocardiography (see Section II.C.3). The effects of posttest referral bias have been similar for myocardial perfusion/imaging (177,178) and exercise echocardiography (179). Correction for posttest referral bias results in strikingly lower sensitivity and higher specificity for both techniques (Tables 13 through 17). As a result of these changes in sensitivity and specificity, in a patient with an intermediate pretest probability of disease, correction for verification bias actually improves the diagnostic value of a positive test result while the value of a negative test result decreases (175).

Diagnostic Accuracy of Stress Imaging Techniques

Radionuclide Imaging. An excellent review of the use of radionuclide imaging in the diagnosis and localization of CAD was included in the "ACC/AHA Guidelines for Clinical Use of Cardiac Radionuclide Imaging," which was published in 1995 (12). This discussion, which focuses on myocardial perfusion imaging, borrows from this previous document but has been updated to reflect more recent publications. In patients with suspected or known chronic stable angina, the largest accumulated experience in myocardial perfusion imaging has been with the tracer ²⁰¹Tl, but the available evidence suggests that the newer tracers ^{99m}Tc sestamibi and ^{99m}Tc tetrofosmin yield similar diagnostic accuracy (180-190). Thus, for the most part, ²⁰¹Tl, ^{99m}Tc sestamibi or ^{99m}Tc tetrofosmin can be used interchangeably with similar diagnostic accuracy in CAD.

Table 14. Exercise Echocardiography—Without Correction for Referral Bias

Author	Year	Total Patients	Sensitivity	Specificity
Armstrong (284)	1987	123	0.88	0.86
Crouse (285)	1991	228	0.97	0.64
Marwick (286)	1992	150	0.84	0.86
Quiñones (264)	1992	112	0.74	0.88
Ryan (287)	1993	309	0.91	0.78
Hecht (288)	1993	136	0.94	0.88
Roger (289)	1994	150	0.91	—
Beleslin (224)	1994	136	0.88	0.82
Sylvén (277)	1994	160	0.72	0.50
Roger (145)	1995	127	0.88	0.72
Marwick (290)	1995	147	0.71	0.91
Marwick (129)	1995	161	0.80	0.81
Luotolahti (291)	1996	108	0.94	0.70
Others* (130,225,278-280,292-299)	1988-1996	741	0.83	0.91

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

Myocardial perfusion imaging may use either planar or single-photon emission computed tomographic (SPECT) techniques and visual analyses (191-194) or quantitative techniques (195-202). Quantification (e.g., using horizontal [195] or circumferential [196-198] profiles) may improve the sensitivity of the test, especially in patients with one-vessel disease (194,198-202). For ²⁰¹Tl planar scintigraphy, average reported values of sensitivity and specificity (not corrected for posttest referral bias) have been in the range of 83% and 88%, respectively, by visual analysis (191-194), and 90% and 80%, respectively, for quantitative analyses (194-203). The ²⁰¹Tl SPECT is generally more sensitive than planar imaging for diagnosing CAD, localizing hypoperfused vascular territories, identifying left anterior descending and left circumflex coronary artery stenoses (204), and correctly predicting the presence of multivessel CAD (205). The average (uncorrected for referral bias) sensitivity and specificity of exercise ²⁰¹Tl SPECT imaging are in the range

of 89% and 76%, respectively, for qualitative analyses (201,202,206) and 90% and 70%, respectively, for quantitative analyses (206).

The less-than-perfect sensitivity and specificity may in part be explained by the fact that visually estimated angiographic severity of coronary stenoses does not closely correlate with functional severity as assessed by coronary flow reserve after maximal pharmacologic coronary vasodilation (203). Furthermore, the lower-than-expected specificity in the more recent series, which has generally involved SPECT rather than planar imaging, may well be related to posttest referral bias (see above). Although patient selection undoubtedly plays a role in decreasing the specificity observed with SPECT compared with planar imaging, other factors, such as photon attenuation and artifacts created by the tomographic reconstruction process, are also likely important.

Since the introduction of dipyridamole-induced coronary vasodilation as an adjunct to ²⁰¹Tl myocardial perfusion

Table 15. Adenosine SPECT Scintigraphy—Without Correction for Referral Bias

Author	Year	Total Patients	Sensitivity	Specificity
Nishimura (210)	1991	101	0.87	0.90
Coyne (213)	1991	100	0.83	0.75
O'Keefe (300)	1992	121	0.92	0.64
Gupta (214)	1992	144	0.83	0.87
Iskandrian (301)	1993	339	0.90	0.90
Mohiuddin (302)	1996	202	0.87 (m)	0.83 (m)
			0.94 (f)	0.89 (f)
Amanullah (303)	1997	222	0.93	0.73
Amanullah (304)	1997	130	0.91	0.70
Iskandrian (269)	1997	550	0.90	0.86
Other* (170,212,305,306)	1990-1995	228	0.91	0.74

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

Table 16. Dobutamine Echocardiography—Without Correction for Referral Bias

Author	Year	Total Patients	Sensitivity		Specificity	
Sawada (307)	1991	103	0.89		0.85	
Marcovitz (308)	1992	141	0.96		0.66	
Marwick (170)	1993	217	0.72		0.83	
Takeuchi (309)	1993	120	0.85		0.93	
Baudhuin (310)	1993	136	0.79		0.83	
Ostojic (311)	1994	150	0.75		0.79	
Beleslin (224)	1994	136	0.82		0.76	
Pingitore (312)	1996	110	0.84		0.89	
Wu (313)	1996	104	0.94		0.38	
Hennessy (314)	1997	116	0.82		0.63	
Dionisopoulos (315)	1997	288	0.85 (m)		0.96 (m)	
			0.90 (f)		0.79 (f)	
Elhendy (316)	1997	306	0.73 (m)		0.77 (m)	
			0.76 (f)		0.94 (f)	
Hennessy (317)	1997	219	0.82		0.65	
Others* (225,280-283,318,319)	1993-1998	436	0.75		0.83	

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

imaging (207-209), pharmacologic interventions have become an important tool in noninvasive diagnosis of CAD (165,166,168-171,208-217). Dipyridamole planar scintigraphy has a high sensitivity (90% average, uncorrected) and acceptable specificity (70% average, uncorrected) for detection of CAD (165). Dipyridamole SPECT imaging with ²⁰¹Tl or ^{99m}Tc sestamibi appears to be at least as accurate as planar imaging (218-220). Results of myocardial perfusion imaging during adenosine infusion are similar to those obtained with dipyridamole and exercise imaging (212-214,216). Dobutamine perfusion imaging has significant limitations compared with vasodilator (dipyridamole or adenosine) perfusion imaging because it does not provoke as great an increase in coronary flow (221,222). Its use should therefore be restricted to patients with contraindications to dipyridamole and adenosine, although dobutamine perfu-

sion imaging has reasonable diagnostic accuracy (223). Because it should be used far less commonly than dipyridamole and adenosine, dobutamine perfusion imaging is not included in the recommendations.

Exercise and dobutamine radionuclide angiography are now performed very infrequently and are therefore also not included in the recommendations.

Stress Echocardiography. Stress echocardiography relies on imaging LV segmental wall motion and thickening during stress compared with baseline. Echocardiographic findings suggestive of myocardial ischemia include 1) a decrease in wall motion in ≥1 LV segment with stress, 2) a decrease in wall thickening in ≥1 LV segment with stress, and 3) compensatory hyperkinesis in complementary (nonischemic) wall segments. The advent of digital acquisition and storage, as well as side-by-side (or quad screen) display of

Table 17. Noninvasive Tests Before and After Adjustment for Referral Bias

Modality	Author	Year	Total Patients	Sensitivity		Specificity	
				Biased	Adjusted	Biased	Adjusted
Exercise ECG	Morise and Diamond (73)	1995	Men: 508	0.56	0.40	0.81	0.96
			Women: 284	0.47	0.33	0.73	0.89
Exercise planar thallium	Schwartz et al. (178)	1993	Men: 845	0.67	0.45	0.59	0.78
Exercise planar thallium	Diamond (177)	1986	Overall: 2269	0.91	0.68	0.34	0.71
Exercise SPECT thallium	Cecil et al. (320)	1996	Overall: 2688	0.98	0.82	0.14	0.59
Exercise/dipyridamole and SPECT sestamibi	Santana-Boado et al. (321)	1998	Men: 100	0.93	0.88	0.89	0.96
			Women: 63	0.85	0.87	0.91	0.91
Exercise echo	Roger et al. (179)	1997	Men: 244	0.78	0.42	0.37	0.83
			Women: 96	0.79	0.32	0.34	0.86

cineloops of LV images acquired at different levels of rest or stress, has facilitated efficiency and accuracy in interpretation of stress echocardiograms (13).

Stress echocardiography has been reported to have sensitivity and specificity for detecting CAD approximately in the range reported for stress myocardial imaging. In 36 studies reviewed that included 3,210 patients, the range of reported overall sensitivities, uncorrected for posttest referral bias, ranged from 70% to 97%; an average figure was approximately 85% for overall sensitivity for exercise echocardiography and 82% for dobutamine stress echocardiography (13). As expected, the reported sensitivity of exercise echocardiography for multivessel disease was higher (73% to 100%, average approximately 90%) than the sensitivity for one-vessel disease (63% to 93%, average approximately 79%) (13). In this series of studies, specificity ranged from 72% to 100%, with an average of approximately 86% for exercise echocardiography and 85% for dobutamine echocardiography.

Pharmacologic stress echocardiography is best accomplished with the use of dobutamine because it enhances myocardial contractile performance and wall motion, which can be evaluated directly by echocardiography. Dobutamine stress echocardiography has substantially higher sensitivity than vasodilator (dipyridamole or adenosine) stress echocardiography for detecting coronary stenoses (170,224,225). In a recent review of 36 studies, average sensitivity and specificity (uncorrected for referral bias) of dobutamine stress echocardiography in the detection of CAD were in the range of 82% (86% for multivessel disease) and 85%, respectively (13). Although dipyridamole echocardiography is performed abroad, it is used far less commonly in the U.S. and is not included in the recommendations.

Special Issues Related to Stress Cardiac Imaging

Concomitant Use of Drugs. The sensitivity of the exercise imaging study for diagnosis of CAD appears to be lower in patients taking beta-blockers (226-230). As recommended earlier for the exercise ECG (Section II.C.2), whenever possible, it is recommended that beta-blockers (and other anti-ischemic drugs) be withheld for four to five half-lives (usually about 48 h) before exercise imaging studies for the diagnosis and initial risk stratification of patients with suspected CAD. Nonetheless, in patients who exercise to a submaximal level because of the effect of drugs, perfusion or echocardiographic imaging still affords higher sensitivity than the exercise ECG alone (231).

Bundle-Branch Blocks. Several studies have observed an increased prevalence of myocardial perfusion defects during exercise imaging, in the absence of angiographic coronary disease, in patients with left bundle-branch block (232-234). These defects often involve the interventricular septum, may be reversible or fixed and are often absent during pharmacologic stress. Their exact mechanism is uncertain. Multiple studies (involving >200 patients) have found that perfusion imaging with pharmacologic vasodilation is more

accurate for identifying CAD in patients with left bundle-branch block (235-243). In contrast, only one small study of 24 patients has reported on the diagnostic usefulness of stress echocardiography in the presence of left bundle-branch block (244). The committee therefore believed that adenosine or dipyridamole myocardial perfusion imaging is preferred in these patients. Right bundle-branch block and left anterior hemiblock are not ordinarily associated with such perfusion defects.

Cardiac Stress Imaging in Selected Patient Subsets (Female, Elderly or Obese Patients, and Patients With Special Occupations). The treadmill ECG test is less accurate for diagnosis in women, who have a generally lower pretest likelihood of CAD than men (14). Myocardial perfusion imaging or echocardiography could be a logical addition to treadmill testing in this circumstance. However, the sensitivity of thallium perfusion scans may be lower in women than men (203,245). Artifacts due to breast attenuation, usually manifest in the anterior wall, can be an important caveat in the interpretation of women's perfusion scans, especially when ^{201}Tl is used as a tracer. More recently, the use of gated $^{99\text{m}}\text{Tc}$ sestamibi SPECT imaging has been associated with an apparent reduction in breast artifacts (246,247). In a recent prospective study of 115 women with either suspected or a low pretest likelihood of CAD, both ^{201}Tl SPECT and $^{99\text{m}}\text{Tc}$ sestamibi had a similar sensitivity for detection of CAD in women (84.3% and 80.4% for $\geq 70\%$ stenosis) (248). However, $^{99\text{m}}\text{Tc}$ sestamibi SPECT imaging had a better specificity (84.4% vs. 67.2%) and was further enhanced to 92.2% with ECG gating. Similarly, exercise or pharmacologic stress echocardiography may help avoid artifacts specifically due to breast attenuation. However, echocardiographic imaging in obese persons tends both to be technically more difficult and to produce images of less quality. As indicated earlier (Section II.C.2), the committee believes that there currently are insufficient data to justify replacing standard exercise testing with stress imaging in the initial evaluation of women.

Although some elderly patients can perform an adequate exercise test, many are unable to do so because of physical impairment. Pharmacologic stress imaging is an appropriate option in such patients. Very obese patients constitute a special problem because most imaging tables used for SPECT have weight-bearing limits (often 300 lb [135 kg]) that preclude imaging very heavy subjects. These subjects can still be imaged by planar scintigraphy. Obese patients often have suboptimal perfusion images, especially with ^{201}Tl , owing to the marked photon attenuation by soft tissue. In these patients, $^{99\text{m}}\text{Tc}$ sestamibi is probably most appropriate and should yield images of better quality than ^{201}Tl . Positron emission tomographic imaging is also likely to be superior to conventional myocardial perfusion imaging in these subjects. As noted above, exercise or pharmacologic stress echocardiography may yield suboptimal images in significantly obese subjects. Suboptimal images are also not

uncommon in patients with chest deformities and significant lung disease.

Persons whose occupation may affect public safety (e.g., airline pilots, truckers, bus drivers, railroad engineers, firefighters and law enforcement officers) or who are professional or high-profile athletes not uncommonly undergo periodic exercise testing for assessment of exercise capacity and prognostic evaluation of possible CAD (14). Although there are insufficient data to justify this approach, these evaluations are done for statutory reasons in some cases (27). For patients in these groups with chronic chest pain who are in the intermediate-to-high likelihood range for CAD, the threshold for adding imaging to standard exercise electrocardiography may properly be lower than in the average patient. Specifically, one might recommend that for persons in this risk category, in whom stress testing is being contemplated, stress imaging (with echocardiography or radionuclide perfusion imaging) should be the initial stress test.

Comparison of Myocardial Perfusion Imaging and Echocardiography

Sensitivity and Specificity. In an analysis of 11 studies involving 808 patients who had contemporaneous treadmill (or pharmacologic) stress echocardiography and perfusion scintigraphy, the overall (uncorrected for referral bias) sensitivity was 83% for stress perfusion imaging versus 78% for stress echocardiography ($p = \text{NS}$). On the other hand, overall specificity (uncorrected for referral bias) tended to favor stress echocardiography (86% vs. 77%; $p = \text{NS}$) (249).

More recently, Fleischmann et al. (250) performed a meta-analysis on 44 articles (published between 1990 and 1997), which examined the diagnostic accuracy of exercise tomographic myocardial perfusion imaging or exercise echocardiography. The overall sensitivity and specificity, respectively, were 85% and 77% for exercise echocardiography, 87% and 64% for exercise myocardial perfusion imaging, and 52% and 71% for exercise ECG. These estimates were not adjusted for referral bias. On the basis of receiver operator characteristic curves, which were also not adjusted for referral bias, exercise echocardiography had significantly better discriminatory power than exercise myocardial perfusion imaging.

Localization of Disease to Individual Coronary Arteries. Use of SPECT has provided diagnostic improvement over planar imaging for more precise localization of the vascular territories involved, particularly the identification of left circumflex coronary artery stenoses and prediction of multivessel CAD (201,202,206). O'Keefe et al. (141) reviewed data on 770 patients (1,328 diseased coronary arteries) in multiple studies who had exercise perfusion imaging versus 200 (704 diseased coronary arteries) who had undergone exercise echocardiography. In these data derived from 10 published studies, there was a nonsignificant trend toward improvement in localization of coronary disease by the radionuclide technique (79% vs. 65% uncorrected sensitiv-

ity; $p = \text{NS}$). For localization of disease to the circumflex coronary artery, however, the radionuclide method conferred a significant advantage in sensitivity (72% vs. 33%, uncorrected $p < 0.001$).

Importance of Local Expertise and Facilities. Echocardiographic and radionuclide stress imaging have complementary roles, and both add value to routine stress electrocardiography under the circumstances outlined above. The choice of which test to perform depends on issues of local expertise, available facilities and considerations of cost-effectiveness (see following text). Because of its lower cost and generally greater portability, stress echocardiography is more likely to be performed in the physician's office than stress radionuclide imaging; the availability of stress imaging in the office setting has both advantages and disadvantages for the patient (176).

Cost-Effectiveness Considerations. In this era of managed care, cost-effectiveness considerations have come into sharper focus in medical decision making. Commonly used measures of cost-effectiveness include the change in quality-adjusted life-years (QALY) per dollar of cost. The cost/ Δ QALY ratio is importantly affected by the pretest likelihood of CAD, test accuracy, and the cost and complication rates of the test (176,251,252). Patterson and Eisner (251) used an assumption for detection of significant CAD of 75% sensitivity and 90% specificity for stress echocardiography and 84% sensitivity and 87% specificity for SPECT perfusion imaging. They found that the cost/ Δ QALY ratio was 8% to 12% higher for stress echocardiography than for SPECT thallium imaging (251). However, Marwick (252) has argued that if Medicare reimbursement rates had been substituted for costs quoted by the authors and sensitivity/specificity data adjusted to 80% and 85%, respectively, for stress echocardiography, and 70% and 90%, respectively, for SPECT thallium imaging, that the cost/ Δ QALY ratios would have decreased for both tests. Marwick also argued that the cost/ Δ QALY ratio would have been slightly lower for stress echocardiography (compared with stress perfusion imaging) at coronary disease probability rates of 20% to 30% and slightly higher for stress echocardiography at probability rates of 40% to 80%.

A subsequent decision and cost-effectiveness analysis (253) used published data (uncorrected for referral bias) to compare exercise electrocardiography, exercise thallium perfusion imaging, exercise echocardiography and coronary angiography for the diagnosis of suspected CAD in a 55-year-old woman. Coronary angiography was most cost-effective in a woman of this age with definite angina, whereas exercise echocardiography was most cost-effective in the presence of atypical angina or nonanginal chest pain.

A summary of comparative advantages of stress myocardial perfusion imaging and stress echocardiography is provided in Table 18.

Recent Technical Developments. The published comparisons between stress echocardiography and stress myocardial

Table 18. Comparative Advantages of Stress Echocardiography and Stress Radionuclide Perfusion Imaging in Diagnosis of CAD

Advantages of Stress Echocardiography

1. Higher specificity
2. Versatility—more extensive evaluation of cardiac anatomy and function
3. Greater convenience/efficacy/availability
4. Lower cost

Advantages of Stress Perfusion Imaging

1. Higher technical success rate
2. Higher sensitivity—especially for single vessel coronary disease involving the left circumflex
3. Better accuracy in evaluating possible ischemia when multiple resting LV wall motion abnormalities are present
4. More extensive published data base—especially in evaluation of prognosis

perfusion imaging do not fully reflect the ongoing developments in both techniques.

For stress echocardiography, recent developments include tissue harmonic imaging and intravenous contrast agents, which can improve detection of endocardial borders (254,255).

For stress myocardial perfusion imaging, newer-generation gamma cameras and scatter correction improve resolution (256), and gating permits assessment of global and regional function (257) as well as more accurate characterization of equivocal findings (247). Attenuation correction is under development (258).

These recent advances in both stress echocardiography and stress myocardial perfusion imaging should improve diagnostic accuracy.

D. Invasive Testing: Value of Coronary Angiography

Recommendations for Coronary Angiography to Establish a Diagnosis in Patients With Suspected Angina, Including Those With Known CAD Who Have a Significant Change in Anginal Symptoms

Class I

Patients with known or possible angina pectoris who have survived sudden cardiac death. (Level of Evidence: B)

Class IIa

1. **Patients with an uncertain diagnosis after noninvasive testing in whom the benefit of a more certain diagnosis outweighs the risk and cost of coronary angiography. (Level of Evidence: C)**
2. **Patients who cannot undergo noninvasive testing due to disability, illness or morbid obesity. (Level of Evidence: C)**
3. **Patients with an occupational requirement for a definitive diagnosis. (Level of Evidence: C)**

4. **Patients who by virtue of young age at onset of symptoms, noninvasive imaging, or other clinical parameters are suspected of having a nonatherosclerotic cause for myocardial ischemia (coronary artery anomaly, Kawasaki disease, primary coronary artery dissection, radiation-induced vasculopathy). (Level of Evidence: C)**
5. **Patients in whom coronary artery spasm is suspected and provocative testing may be necessary. (Level of Evidence: C)**
6. **Patients with a high pretest probability of left main or three-vessel CAD. (Level of Evidence: C)**

Class IIb

1. **Patients with recurrent hospitalization for chest pain in whom a definite diagnosis is judged necessary. (Level of Evidence: C)**
2. **Patients with an overriding desire for a definitive diagnosis and a greater-than-low probability of CAD. (Level of Evidence: C)**

Class III

1. **Patients with significant comorbidity in whom the risk of coronary arteriography outweighs the benefit of the procedure. (Level of Evidence: C)**
2. **Patients with an overriding personal desire for a definitive diagnosis and a low probability of CAD. (Level of Evidence: C)**

This invasive technique for imaging the coronary artery lumen remains the most accurate for the diagnosis of clinically important obstructive coronary atherosclerosis and less common nonatherosclerotic causes of possible chronic stable angina pectoris such as coronary artery spasm, coronary anomaly, Kawasaki disease, primary coronary artery dissection and radiation-induced coronary vasculopathy (322-331). Early case studies correlating symptoms with the findings at coronary angiography reported that between 26% and 65% of patients with chest discomfort that was suggestive of but was not classical angina (i.e., atypical symptoms) had significant coronary stenoses due to atherosclerosis (38,332-334). In many patients with symptoms suggestive but not typical of chronic stable angina pectoris (i.e., pretest probability \approx 50%), the incremental value of noninvasive testing, when considered with other clinical data, may permit a sufficiently accurate diagnosis on which to base clinical management strategies (12-14) (see Section II.C). Incumbent on the physician is the responsibility for estimating the probability that the patient's symptoms are due to myocardial ischemia and matching the intensity of the evaluation to this estimation. All decisions regarding testing for possible CAD must be modulated by patient preference and comorbidity. It is important to reemphasize the value of a history of typical effort angina in middle-aged or elderly men in whom \approx 90% have significant coronary disease (38,332-334) and many have multivessel disease (see Fig. 6). In women, only about one half with classic angina

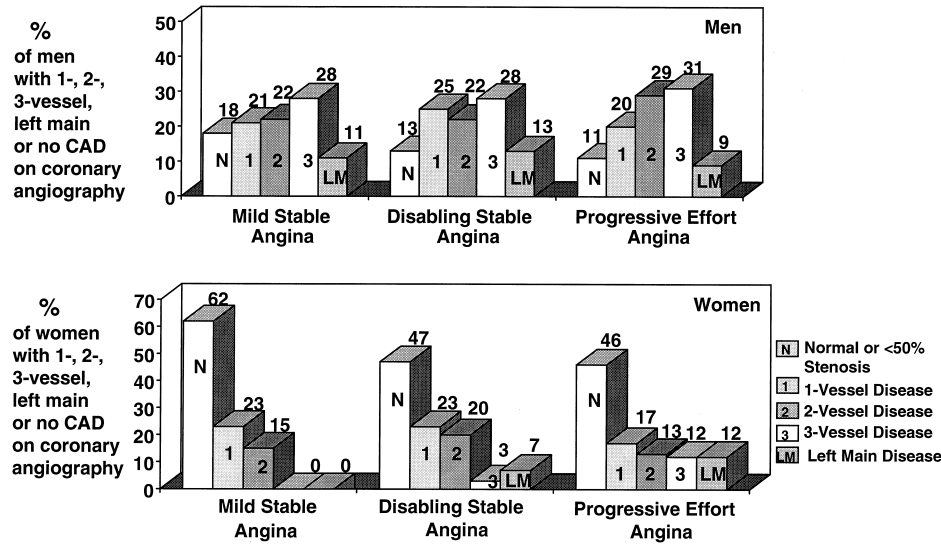


Figure 6. Coronary angiography findings in patients with chronic effort-induced angina pectoris. **Top:** Percentage of men with one-vessel, two-vessel, three-vessel, left main or no coronary artery disease on coronary angiography. **Bottom:** Percentage of women with one-vessel, two-vessel, three-vessel, left main, or no coronary artery disease on coronary angiography. N = normal or <50% stenosis; 1 = one-vessel disease; two = 2-vessel disease; three = 3-vessel disease; LM = left main disease. Data from Douglas and Hurst (333).

pectoris have significant obstructive coronary disease (see following section).

Indications for Coronary Angiography

Direct referral for diagnostic coronary angiography may be indicated in patients with chest pain possibly attributable to myocardial ischemia when noninvasive testing is contraindicated or unlikely to be adequate due to illness, disability or physical characteristics. For example, a patient with chest pain suggestive of chronic stable angina and coexisting chronic obstructive pulmonary disease who is not a candidate for exercise testing because of dyspnea, perfusion imaging with dipyridamole or adenosine because of bronchospasm and theophylline therapy or stress-echocardiography because of poor images may undergo coronary angiography with minimal risk.

Patients in whom noninvasive testing is abnormal but not clearly diagnostic may warrant clarification of an uncertain diagnosis by coronary angiography or in some cases by a second noninvasive test (imaging modality), which may be recommended for a low-likelihood patient with an intermediate-risk treadmill result (335). Coronary angiography may be most appropriate for a patient with a high-risk treadmill outcome.

In patients with symptoms suggestive but not characteristic of stable angina, direct referral to coronary angiography may be indicated when the patient's occupation or activity could constitute a risk to themselves or others (pilots, firefighters, police, professional athletes or serious runners) (27). In certain patients with typical or atypical symptoms suggestive of stable angina and a high clinical probability of severe CAD, direct referral to coronary angiography may be indicated and prove cost-effective (335). The diagnosis of

chronic stable angina in diabetic persons can be particularly difficult because of the paucity of symptomatic expressions of myocardial ischemia due to autonomic and sensory neuropathy, and a lowered threshold for coronary angiography is appropriate (336). The use of coronary angiography in patients with a high pretest probability of disease is in some patients as important in risk assessment (see Section III.A) as in diagnosis.

Women. The evaluation of chest pain in women has been scrutinized recently, and available data suggest that gender differences in presentation and disease manifestations should be considered (337). Atypical chest pain is more common in women, perhaps in relation to an increased prevalence of vasospasm as well as mitral valve prolapse and noncoronary chest pain syndromes. ECG treadmill exercise testing has a higher false-positive rate in women (38% to 67%) than men (7% to 44%) (338), largely because of the lower pretest likelihood of disease (339), but a low false-negative rate, which indicates that routine testing reliably excludes the presence of coronary disease when the results of noninvasive tests are negative. Despite the limitations of routine exercise ECG testing in women, it has been shown to reduce procedures without loss of diagnostic accuracy. Only 30% of women (in whom a reasonably certain diagnosis of CAD could not be reached or excluded) need be referred for further testing (83). Recent studies examining the outcome of patients undergoing diagnostic testing indicate that women with positive stress ECGs or stress thallium examinations were less frequently referred for additional noninvasive testing (4% vs. 20% for men) or coronary angiography (34% vs. 45%) (340). Although these findings suggest that a gender-based difference in clinical practice exists in this country, 2 reports indicate that the

reduced referral rate of women was clinically appropriate (341,342). As mentioned in Section II.C, a recent cost-effectiveness analysis concluded that coronary angiography was the preferred initial diagnostic test in a 55-year-old woman with typical angina (253).

The Elderly. The evaluation of chest pain syndromes in the elderly can be difficult because complaints of chest discomfort, weakness and dyspnea are common, and comorbid conditions that mimic angina pectoris are frequently present. Reduced activity levels and blunted appreciation of ischemic symptoms become the norm with advancing age (343). In large community studies of men and women ≥ 65 years old, those with atypical symptoms and typical angina were shown to have similar three-year cardiac mortality rates (344). An increased frequency of abnormal ECGs at rest and inability to exercise complicate noninvasive diagnostic testing, as does the increased prevalence of disease, which reduces the value of a negative noninvasive test. Diagnostic coronary angiography has very little increased risk (compared with younger patients) in older patients undergoing elective evaluation and is commonly used; in many centers, most patients who undergo this study are >65 -years-old (345).

Coronary Spasm. Coronary artery spasm is a well-recognized cause of chest pain at rest (346) and may also lead to variable threshold effort angina (323,324), but in a 10-year study of 3,447 patients who underwent provocative testing with ergonovine maleate, coronary spasm was most often associated with an atypical chest pain syndrome (322) and cigarette smoking. The lack of a classic presentation and requirement for provocative testing during coronary angiography may hinder making this diagnosis. Although some investigators have advocated noninvasive, provocative testing for coronary spasm (347), there is some risk of irreversible coronary spasm (348); for this reason, most recommend that provocative testing for coronary spasm be done in the cardiac catheterization environment, where administration of intracoronary nitroglycerin and other vasodilators is feasible and other support systems are available (349).

Coronary Anomaly. The anomalous origin and course of coronary arteries is an uncommon cause of chronic stable angina usually recognized unexpectedly at coronary angiography, but this diagnosis may be suspected in younger patients with signs or symptoms of myocardial ischemia (325-327) and recognized by noninvasive imaging modalities such as transesophageal echocardiography, computerized tomography, or magnetic resonance imaging. The presence of a continuous murmur can point to a diagnosis of anomalous origin of the left anterior descending or circumflex artery from the pulmonary artery or coronary arteriovenous fistula that should be confirmed by coronary angiography.

Resuscitation From Ventricular Fibrillation or Sustained Ventricular Tachycardia. Most patients experiencing sudden cardiac arrest or malignant arrhythmia have severe CAD (350). Therefore, coronary arteriography is warranted to

establish as precise a diagnosis as possible as well as to establish revascularization options (see Section IV).

III. RISK STRATIFICATION

A. Clinical Assessment

Prognosis of CAD for Death or Nonfatal MI: General Considerations

Coronary artery disease is a chronic disorder with a natural history that spans multiple decades. In each affected person, the disease typically cycles in and out of clinically defined phases: asymptomatic, stable angina, progressive angina and unstable angina or acute MI. 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 spectrum of disease.

The patient's risk is usually a function of four types of patient characteristic. The strongest predictor of long-term survival with CAD is the functioning of the LV. Ejection fraction is the most commonly used measure of the extent of LV dysfunction. A second patient characteristic is the anatomic extent and severity of atherosclerotic involvement of the coronary tree. The number of diseased vessels is the most common measure of this characteristic. A third characteristic provides evidence of a recent coronary plaque rupture, indicating a substantially increased short-term risk for cardiac death or nonfatal MI. Worsening clinical symptoms with unstable features is the major clinical marker of a plaque event. The fourth patient characteristic is 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. Patients with major cardiac risk factors, including smoking, hypercholesterolemia, diabetes mellitus and hypertension, are most likely to have progressive atherosclerosis with repeated coronary plaque events. Patients presenting at a younger age also may have more aggressive disease.

A growing body of pathologic, angiographic, angioscopic and intravascular ultrasonographic data support a pathophysiologic model in which most major cardiac events are initiated by microscopic ulcerations of vulnerable atherosclerotic plaques. Several lines of evidence have shown that the majority of vulnerable plaques appear "angiographically insignificant" before their rupture ($<75\%$ diameter stenosis). In contrast, most of the "significant" plaques ($>75\%$ 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 occurs shortly after a negative treadmill test result.

Risk Stratification With Clinical Parameters

Rigorous evidence for predictors of severe CAD (three-vessel and left main disease) derived solely from the history and physical examination in patients with chest pain is surprisingly limited. Presumably, this is because physicians routinely incorporate additional information (e.g., an ECG) into risk stratification.

Nevertheless, very useful information relevant to prognosis can be obtained from the history. This includes demographics such as age and gender as well as a medical history focusing on hypertension, diabetes, hypercholesterolemia, smoking, peripheral vascular or arterial disease and previous MI. As previously discussed, the description of the patient's chest discomfort can usually be easily assigned to one of three categories: typical angina, atypical angina and nonanginal chest pain (38).

The physical examination may also aid in risk stratification by determining the presence or absence of signs and symptoms that might alter the probability of severe CAD. Useful findings include those suggesting vascular disease (abnormal fundi, decreased peripheral pulses, bruits), long-standing hypertension (blood pressure, abnormal fundi), aortic valve stenosis or idiopathic hypertrophic subaortic stenosis (systolic murmur, abnormal carotid pulse, abnormal apical pulse), left-heart failure (third heart sound, displaced apical impulse, bibasilar rales), and right-heart failure (jugular venous distension, hepatomegaly, ascites, pedal edema).

Several studies have examined the value of clinical parameters for identifying the presence of severe (three-vessel or left main) CAD. Pryor et al. (134) identified 11 clinical characteristics that are important in estimating the likelihood of severe CAD: typical angina, previous MI, age, gender, duration of chest pain symptoms, risk factors (hypertension, diabetes, hyperlipidemia, smoking), carotid bruit and chest pain frequency. In a subsequent study, Pryor et al. (41) provided detailed equations for the prediction of both severe CAD and survival based on clinical parameters.

Hubbard et al. (351) identified five clinical parameters that were independently predictive of severe (three-vessel or left main) CAD: age, typical angina, diabetes, gender and prior MI (history or ECG). Hubbard then developed a five-point cardiac risk score. A composite graph (Fig. 7) estimates the probability of severe CAD. Each curve shows the probability of severe CAD as a function of age for a given cardiac risk score. As shown on this graph, some patients have a high likelihood (>1 chance in 2) of severe disease on the basis of clinical parameters alone. Such patients should be considered for direct referral to angiography, as noninvasive testing is highly unlikely to be normal and, if it is, may conceivably be false-negative. An example would be a 50-year-old male patient with diabetes, taking insulin, with typical angina and history and ECG evidence of previous MI. His estimated likelihood of severe disease is 60%; such a patient should be considered for angiography without further testing.

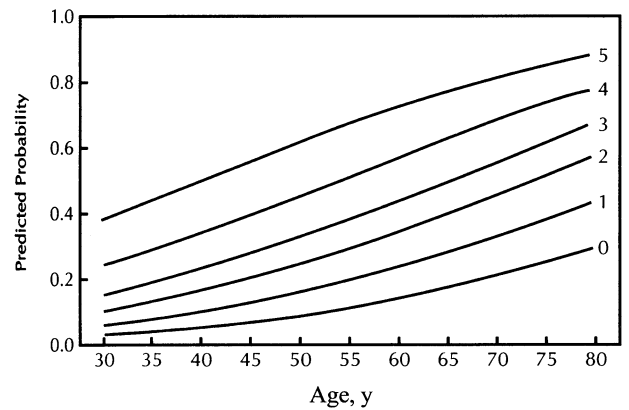


Figure 7. Nomogram showing the probability of severe (three-vessel or left main) coronary disease based on a five-point score. One point is awarded for each of the following variables: male gender, typical angina, history and electrocardiographic evidence of myocardial infarction, diabetes and use of insulin. Each curve shows the probability of severe coronary disease as a function of age. From Hubbard et al. (135), with permission.

Descriptive information about the chest pain is very important in assessment of patient prognosis as well as risk of severe CAD. However, because the extent and location of angiographically demonstrated occlusion, together with the degree of LV dysfunction, appear to have substantially greater prognostic power than symptom severity (96,352), many clinicians have come to rely almost exclusively on these "objective" measurements of disease and very little on the patient's history in choosing among the alternative management strategies for their patients. However, clinical parameters should not be ignored for risk stratification (41,353,354).

Califf et al. (95) have provided evidence that the aggregation of certain historical and ECG variables in an "angina score" offers prognostic information that is independent of and incremental to that detected by catheterization. The angina score was composed of three differentially weighted variables: the "anginal course," anginal frequency, and rest ECG ST-T wave abnormalities. Two features of the prognostic power of the angina score seem intuitively correct: 1) it had a greater impact on short-term prognosis than long-term prognosis, presumably reflecting the importance of a plaque rupture; and 2) it had greater prognostic value when the LV was normal than when it was abnormal, presumably because so much of the overall prognosis was determined by LV function when it was abnormal.

Peripheral vascular disease is another clinical parameter that is useful in stratifying risk. The presence of a carotid bruit, like male gender and previous MI, nearly doubles the risk for severe CAD (134). In addition to peripheral vascular disease, signs and symptoms related to congestive heart failure (CHF), which reflect LV function, convey an adverse prognosis.

All the studies evaluating clinical characteristics as predictors of severe CAD use only patients referred for further

evaluation of chest pain and cardiac catheterization. Although it does not undercut internal validity, this bias in the assembly of a cohort severely limits the generalizability (external validity) of study findings to all patients with CAD. However, it is likely that the overall "risk" of an unselected population is lower, so that patients described as "low risk" by these findings are still likely to be low risk.

Risk stratification of patients with stable angina using clinical parameters may facilitate the development of clearer indications of referral for exercise testing and cardiac catheterization. Long-term follow-up data from the CASS Registry (352) showed that 72% of the deaths occurred in the 38% of the population that had either LV dysfunction or severe coronary disease. The prognosis of patients with a normal ECG (which implies normal LV function at rest) and a low clinical risk for severe CAD is therefore excellent. Pryor et al. (41) showed that 37% of outpatients referred for noninvasive testing met the criteria for low risk. Fewer than 1% of these patients had left main artery disease or died within three years. The value of additional testing for risk stratification in such patients is modest. Lower-cost options such as treadmill testing should therefore be used whenever possible, and only the most abnormal results (described in Section III.2) should be referred to angiography.

B. ECG/Chest X-Ray

Patients with chronic stable angina who have rest ECG abnormalities are at greater risk than those with normal ECGs (355). Evidence of ≥ 1 prior MI on ECG indicates an increased risk for cardiac events. In fact, the presence of Q waves in multiple ECG leads, often accompanied by an R wave in lead V_1 (posterior infarction), is frequently associated with a markedly reduced LV ejection fraction, an important determinant of the natural history of patients with suspected atherosclerotic CHD (356). A "QRS score" has been used to indicate the extent of old or new MI (357), with the higher scores being associated with lower LV ejection fractions and a poorer long-term prognosis. The presence of persistent ST-T wave inversions, particularly in leads V_1 to V_3 of the rest ECG, is associated with an increased likelihood of future acute coronary events and a poor prognosis (358-361). A decreased prognosis for patients with angina pectoris is also likely when the ECG shows left bundle-branch block, bifascicular block (often left anterior fascicular block plus right bundle-branch block), second- or third-degree atrioventricular block, atrial fibrillation or ventricular tachyarrhythmias (362). The presence of LV hypertrophy by ECG criteria in a patient with angina pectoris is also associated with increased morbidity and mortality (361,363).

On the chest roentgenogram, the presence of cardiomegaly, an LV aneurysm or pulmonary venous congestion is associated with a poorer long-term prognosis than that which occurs in patients with a normal chest X-ray result. The presence of left atrial enlargement, indicating a higher

likelihood of pulmonary venous congestion or mitral regurgitation, is also a negative prognostic factor.

As indicated previously, the presence of calcium in the coronary arteries on chest X-ray or fluoroscopy in patients with symptomatic CAD suggests an increased risk of cardiac events (364). The presence and amount of coronary artery calcification by EBCT also correlates to some extent with the severity of CAD, but there is considerable patient variation.

C. Noninvasive Testing

1. Resting LV Function (Echocardiographic/Radionuclide Imaging)

Recommendations for Measurement of Rest LV Function by Echocardiography or Radionuclide Angiography in Patients With Chronic Stable Angina

Class I

- 1. Echocardiography or radionuclide angiography (RNA) in patients with a history of prior MI, pathologic Q waves or symptoms or signs suggestive of heart failure to assess LV function. (Level of Evidence: B)**
- 2. Echocardiography in patients with a systolic murmur suggesting mitral regurgitation to assess its severity and etiology. (Level of Evidence: C)**
- 3. Echocardiography or RNA in patients with complex ventricular arrhythmias to assess LV function. (Level of Evidence: B)**

Class III

- 1. Routine periodic reassessment of stable patients for whom no new change in therapy is contemplated. (Level of Evidence: C)**
- 2. Patients with a normal ECG, no history of MI and no symptoms or signs suggestive of CHF. (Level of Evidence: B)**

Importance of Assessing LV Function

Most patients undergoing a diagnostic evaluation for angina do not need an echocardiogram. However, in the chronic stable angina patient who has a history of documented MI or Q waves on ECG, measurement of global LV systolic function (e.g., ejection fraction) may be important in choosing appropriate medical or surgical therapy and making recommendations about activity level, rehabilitation and work status (13,365). Similarly, in patients who, in addition to chronic stable angina, have clinical signs or symptoms of heart failure, cardiac imaging may be helpful in establishing pathophysiologic mechanisms and guiding therapy. For example, a patient with heart failure might have predominantly systolic LV dysfunction, predominantly diastolic dysfunction, mitral or aortic valve disease, some combination of these abnormalities or a noncardiac cause for symptoms. The best treatment of the patient can be planned more rationally knowing the status of LV systolic

and diastolic function (by echocardiography or radionuclide imaging), valvular function, and pulmonary artery pressure (by transthoracic echo-Doppler techniques).

Assessment of Global LV Function

Left ventricular global systolic function and volumes have been well documented to be important predictors of prognosis in patients with cardiac disease. In patients with chronic ischemic heart disease, LV ejection fraction measured at rest by either echocardiography (352) or RNA (96,352,365) is predictive of long-term prognosis; as LV ejection fraction declines, mortality increases (352). A rest ejection fraction of <35% is associated with an annual mortality rate >3% per year.

Current echocardiographic techniques permit a comprehensive assessment of LV size and function (366,367). Two-dimensional echocardiographic LV ejection fraction may be measured quantitatively or reported qualitatively (by visual estimation) as increased; normal; or mildly, moderately, or severely reduced. When performed by skilled observers, visual estimation has been reported to yield ejection fractions that correspond closely to those obtained by angiography (368) or gated blood pool scanning (369). In addition to measures of LV systolic function, echo-Doppler characteristics of the pulsed Doppler transmitral velocity pattern can help assess diastolic function (370), although its independent prognostic value has not been established.

Left ventricular mass and wall thickness-to-chamber radius ratio, as measured from echocardiographic images, have both been shown to be independent of cardiovascular morbidity and mortality (371-373). The LV mass can be measured from two-dimensional or two-dimensionally directed M-mode echocardiographic images.

Radionuclide ejection fraction may be measured at rest using a gamma camera, a ^{99m}Tc tracer, and first-pass or gated equilibrium blood pool angiography (13) or gated SPECT perfusion imaging (257). Diastolic function can also be assessed by radionuclide ventriculography (374,375). It should be noted that LV ejection fraction and other indexes of myocardial contractile performance are limited by their dependence on loading conditions and heart rate (146,376).

Although magnetic resonance imaging is less widely disseminated, it may also be used to assess LV performance, including ejection fraction (377).

LV Segmental Wall Motion Abnormalities

In patients with chronic stable angina and a history of previous MI, segmental wall motion abnormalities can be seen not only in the zone(s) of prior infarction but also in areas with ischemic "stunning" or "hibernation" of myocardium that is nonfunctional but still viable (143,148,151,378-380). The sum of these segmental abnormalities reflects total ventricular functional impairment, which may overestimate true anatomic infarct size or radionuclide perfusion defect (380). Thus, echocardiographically derived infarct size (143)

correlates only modestly with ²⁰¹Tl perfusion defects (151), peak creatine kinase levels (148,381), hemodynamic changes (143) and pathologic findings (379). However, it does predict the development of early (382) and late (383) complications and mortality (143,384).

As mentioned previously (Sections II.C.3 and II.C.4), recent developments in both echocardiography (tissue harmonic imaging and intravenous contrast agents to assess the endocardium) and myocardial perfusion imaging (gated SPECT imaging to assess global and regional function) should improve the ability of both techniques to assess LV function.

Ischemic Mitral Regurgitation, LV Aneurysm, and LV Thrombosis

In patients with chronic ischemic heart disease, mitral regurgitation may result from global LV systolic dysfunction (161), regional papillary muscle dysfunction (162), scarring and shortening of the submitral chords (163), papillary muscle rupture (164), or other causes. The presence, severity and mechanism of mitral regurgitation can be reliably detected by transthoracic imaging and Doppler echocardiographic techniques (13). Potential surgical approaches also can be defined. In addition, chronic stable angina patients who have ischemic mitral regurgitation have a worse prognosis than those without regurgitation.

In patients with chronic angina and concomitant heart failure or significant ventricular arrhythmias, the presence or absence of ventricular aneurysm can generally be established by transthoracic echocardiography (385,386). When an aneurysm is demonstrated, the function of the nonaneurysmal portion of the left ventricle is an important consideration in choosing medical or surgical therapy (387).

Echocardiography is the definitive test for detecting intracardiac thrombi (388-394). The LV thrombi are most common in stable angina pectoris patients who have significant LV wall motion abnormalities.

In patients with anterior and apical infarctions (388,392-394), the presence of LV thrombi denotes an increased risk of both embolism (389) and death (391). In addition, the structural appearance of a thrombus, which can be defined by transthoracic (or transesophageal) echocardiography, has some prognostic significance. Sessile, laminar thrombi represent less of a potential embolic risk than do pedunculated and mobile thrombi (13).

2. Exercise Testing for Risk Stratification and Prognosis

Recommendations for Risk Assessment and Prognosis in Patients With an Intermediate or High Probability of CAD

Class I

- 1. Patients undergoing initial evaluation. (Exceptions are listed below in classes IIb and III.) (Level of Evidence: B)**

2. Patients after a significant change in cardiac symptoms. (Level of Evidence: C)

Class IIb

- 1. Patients with the following ECG abnormalities:**
 - a. Preexcitation (Wolff-Parkinson-White) syndrome. (Level of Evidence: B)**
 - b. Electronically paced ventricular rhythm. (Level of Evidence: B)**
 - c. More than 1 mm of ST depression at rest. (Level of Evidence: B)**
 - d. Complete left bundle-branch block. (Level of Evidence: B)**
- 2. Patients who have undergone cardiac catheterization to identify ischemia in the distribution of a coronary lesion of borderline severity. (Level of Evidence: C)**
- 3. Postrevascularization patients who have a significant change in anginal pattern suggestive of ischemia. (Level of Evidence: C)**

Class III

Patients with severe comorbidity likely to limit life expectancy or prevent revascularization. (Level of Evidence: C)

Risk Stratification for Death or MI: General Considerations

Risk stratification with the exercise test does not take place in isolation but as part of a process that includes other 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 what is already known about the patient's risk status. Most research on exercise testing has concentrated on its relationship with future survival and, to a lesser extent, freedom from MI. The summary presented here is based on the "ACC/AHA Guidelines for Exercise Testing" (14).

Risk Stratification With the Exercise Test

The risk of exercise testing in appropriately selected candidates is extremely low, and thus the main argument for not performing an exercise test is that the extra information provided would not be worth the extra cost of obtaining that information or the test might provide misinformation that could lead to inappropriate testing or therapy.

Unless cardiac catheterization is indicated, symptomatic patients with suspected or known CAD should usually undergo exercise testing to assess the risk of future cardiac events unless they have confounding features on the rest ECG. Furthermore, documentation of exercise-induced ischemia is desirable for most patients who are being evaluated for revascularization (72,395).

The choice of initial stress test should be based on the patient's rest ECG, physical ability to perform exercise, local expertise and available technologies. Patients with a normal rest ECG constitute a large and important subgroup. Most

patients who present with angina for the first time have a normal rest ECG (49). Such patients are very likely (92% to 96%) to have normal LV function (141,142,396) and therefore an excellent prognosis (49). The exercise ECG has a higher specificity in the absence of rest ST-T changes, LV hypertrophy and digoxin.

Several studies have examined the incremental value of exercise imaging procedures compared with the exercise ECG in patients with a normal rest ECG who are not taking digoxin (Table 19). In analyses (397,398) that included clinical and exercise ECG parameters for the prediction of left main or three-vessel disease, the modest benefit of imaging does not appear to justify its cost, which has been estimated at \$20,550 per additional patient correctly classified (397). For the prediction of subsequent cardiac events, four separate analyses have failed to demonstrate incremental value. Mattera et al. (399) did find some incremental value, but only for the prediction of hard and soft events (including unstable angina) and only if the exercise ECG was abnormal. They still favored a stepwise strategy that used the exercise ECG as the initial test, like that proposed by others (83,400).

For these reasons, the committee favored a stepwise strategy in which the exercise ECG, and not stress imaging procedures, is performed as the initial test in patients who are not taking digoxin, have a normal rest ECG, and are able to exercise. In contrast, a stress-imaging technique should be used for patients with widespread rest ST depression (>1 mm), complete left bundle-branch block, ventricular paced rhythm or preexcitation. Although exercise capacity can be assessed in such patients, exercise-induced ischemia cannot. Patients unable to exercise due to physical limitations such as reduced exercise capacity, arthritis, amputations, severe peripheral vascular disease or severe chronic obstructive pulmonary disease should undergo pharmacologic stress testing in combination with imaging.

The primary evidence that exercise testing can be used to estimate prognosis and assist in management decisions consists of seven observational studies (354,355,401-405). One of the strongest and most consistent prognostic markers is maximum exercise capacity. This measure is at least partly influenced by the extent of rest LV dysfunction and the amount of further LV dysfunction induced by exercise. However, the relationship between exercise capacity and LV function is complex, because exercise capacity is also affected by age, general physical conditioning, comorbidities and psychological state, especially depression (406). Exercise capacity is measured by maximum exercise duration, maximum MET level achieved, maximum workload achieved, maximum heart rate and double product. The specific variable used to measure exercise capacity is less important than including exercise capacity in the assessment. The translation of exercise duration or workload into METs provides a standard measure of performance regardless of the type of exercise test or protocol used.

Table 19. Studies Examining the Incremental Value of Exercise Imaging Studies for the Prediction of Severe CAD and Subsequent Cardiac Events in Patients With a Normal Resting ECG*

First Author	Ref	Imaging Modality	N	End point (Follow-up)	Clinical Variables Forced into Models	Statistical Significance	Clinical Impact
Gibbons	(398)	RNA	391	3V/LM	Yes	p < 0.01	Correct classifications increased slightly from 60 to 63%.
Christian	(397)	SPECT TI-201	411	3V/LM	Yes	p = ns (ROC) p = 0.02 (relaxed)	Net correct classifications increased slightly from 43% to 46%; cost per additional correct classification = \$20,550
Nallamothu	(407)	SPECT TI-201	321	3V/LM	No	p = 0.0001	Correct classification not analyzed
Simari	(408)	RNA	265	D/MI/Rev (51 months)	Yes	p = 0.18	Excellent event-free survival in patients with negative ECG or RNA
Ladenheim	(400)	Planar TI-201	1,451	D/MI/Rev (12 months)	Yes	p = 0.28	Stepwise testing reduced cost by 64%
Christian	(397)	SPECT TI-201	267	D/MI/Rev (34 months)	Yes	p = ns	Overall 4-year infarct-free survival was excellent at 95%
Mattera	(399)	SPECT TI-201 or sestamibi	313	D/MI (12 months)	No	p = ns	Only 1 hard event
Mattera	(399)	SPECT TI-201 or sestamibi	313	D/MI/Rev/UA (12 months)	No*	p = ns (NI ECG vs. NI MPI) p = 0.04 (Abn ECG vs. Abn MPI)	Stepwise testing (using clinical variables) reduced cost by 38%

ROC indicates receiver operator characteristic curve analysis; D = death; MI = myocardial infarction; Rev = revascularization (after 3 months, except for Mattera); UA = unstable angina; MPI = myocardial perfusion imaging. Patients taking digoxin were excluded from all studies except Ladenheim, where they were included if the ECG was interpreted as normal.

*Not included in statistical model, but considered in stepwise strategy.

A second group of prognostic markers is related to exercise-induced ischemia. The ST-segment depression and elevation (in leads without pathological Q waves and not in aVR) best summarize the prognostic information related to ischemia (401). Other variables are less powerful, including angina, the number of leads with ST-segment depression, the configuration of the ST depression (downsloping, horizontal or upsloping), and the duration of ST deviation into the recovery phase.

The Duke treadmill score combines this information and provides a way to calculate risk (37,401). The Duke treadmill score equals the exercise time in minutes minus (5 × the ST-segment deviation, during or after exercise, in millimeters) minus (4 × the angina index, which has a value of “0” if there is no angina, “1” if angina occurs, and “2” if angina is the reason for stopping the test). Among outpatients with suspected CAD, the two thirds of patients with scores indicating low risk had a four-year survival rate of 99% (average annual mortality rate 0.25%), and the 4% who had scores indicating high risk had a four-year survival rate of

79% (average annual mortality rate 5%) (see Table 20). The score works well for both inpatients and outpatients, and preliminary data suggest that the score works equally well for men and women (37,409,410). Only a small number of elderly patients have been studied, however. Comparable scores have been developed by others (402).

Because of its simplicity, lower cost and widespread familiarity with its performance and interpretation, the standard exercise test is the most reasonable one to select for men with a normal rest ECG who are able to exercise. The

Table 20. Survival According to Risk Groups Based on Duke Treadmill Scores

Risk Group (Score)	Percentage of Total	Four-Year Survival	Annual Mortality (Percent)
Low (≥ +5)	62	0.99	0.25
Moderate (-10 to +4)	34	0.95	1.25
High (< -10)	4	0.79	5.0

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.

Use of Exercise Test Results in Patient Management

The results of exercise testing may be used to titrate medical therapy to the desired level of effectiveness. For example, a normal heart rate response to exercise suggests that the dose of beta-blocker should be increased. Testing for this purpose should generally be performed with the patient on medication. The other major management step addressed by the exercise test is whether to proceed with additional testing, which might lead to revascularization.

Proceeding with additional testing usually involves imaging. Although both stress echocardiography and stress SPECT perfusion imaging have been used after exercise testing, only SPECT perfusion imaging has been studied in patients divided into risk groups based on the Duke treadmill score (410). In patients with an intermediate-risk treadmill score, imaging appears to be useful for further risk stratification. In patients with a high-risk treadmill score, imaging may identify enough low-risk patients who can avoid cardiac catheterization to justify the cost of routine imaging, but further study is required. Few patients (<5%) who have a low-risk treadmill score will be identified as high risk after imaging, and thus the cost of identifying these patients argues against routine imaging (410).

Patients with a predicted average annual cardiac mortality rate of $\leq 1\%$ per year (low-risk score) can be managed medically without the need for cardiac catheterization. Patients with a predicted average annual cardiac mortality rate $\geq 3\%$ per year (high-risk score) should be referred for cardiac catheterization. Patients with a predicted average annual cardiac mortality rate of 1% to 3% per year (intermediate-risk score) should have either cardiac catheterization or an exercise imaging study. Those with known LV dysfunction should have cardiac catheterization.

Recommendation for Exercise Testing in Patients With Chest Pain ≥ 6 Months After Revascularization

Class IIb

Patients with a significant change in anginal pattern suggestive of ischemia. (Level of Evidence: B)

Rationale

There are two postrevascularization phases. In the early phase, the goal of exercise testing is to determine the immediate result of revascularization. In the late phase, which begins six months after revascularization and is the focus of this discussion, the goal is to assist in the evaluation and management of patients with chronic established CAD. Exercise testing also may be helpful in guiding a cardiac rehabilitation program and return-to-work decisions.

Exercise Testing After CABG

Exercise testing distinguishes cardiac from noncardiac causes of chest pain, which is often atypical after surgery. After CABG, the exercise ECG has a number of limitations. Rest ECG abnormalities are frequent, and if an imaging test is not incorporated into the study, more attention must be paid to symptom status, hemodynamic response, and exercise capacity. Because of these considerations and the need to document the site of ischemia, stress imaging tests are preferred for evaluating patients in this group.

Exercise Testing After PTCA

Similar considerations apply to angioplasty patients. Restenosis is more frequent, however. Although most restenosis occurs <6 months after angioplasty, when these recommendations do not apply, restenosis does occur later. The exercise ECG is an insensitive predictor of restenosis, with sensitivities ranging from 40% to 55%, which are significantly less than those with SPECT (12,411) or exercise echocardiography (13,412). Because of these considerations and the need to document the site of ischemia, stress imaging tests are preferred for evaluating symptomatic patients in this group.

Some authorities advocate routine testing for all patients in the late phase after PTCA with either exercise ECGs or stress imaging, as restenosis commonly induces silent ischemia. The rationale for this approach is that ischemia, whether painful or silent, worsens prognosis (413,414). This approach seems particularly attractive for high-risk patients, for example, those with decreased LV function, multivessel CAD, proximal left anterior descending artery disease, previous sudden death, diabetes mellitus, hazardous occupations and suboptimal PTCA results. If routine testing is done, there are insufficient data to justify a particular frequency of testing after angioplasty. The alternative approach, which the committee labeled class IIb because the prognostic benefit of controlling silent ischemia needs to be proved, is to selectively evaluate only patients with a significant change in anginal pattern.

3. Stress Imaging Studies (Radionuclide and Echocardiography)

Recommendations for Cardiac Stress Imaging as the Initial Test for Risk Stratification of Patients With Chronic Stable Angina Who Are Able to Exercise

Class I

- 1. Exercise myocardial perfusion imaging or exercise echocardiography to identify the extent, severity and location of ischemia in patients who do not have left bundle-branch block or an electronically paced ventricular rhythm and have either an abnormal rest ECG or are using digoxin. (Level of Evidence: B)**

2. Dipyridamole or adenosine myocardial perfusion imaging in patients with left bundle-branch block or electronically paced ventricular rhythm. (*Level of Evidence: B*)
3. Exercise myocardial perfusion imaging or exercise echocardiography to assess the functional significance of coronary lesions (if not already known) in planning PTCA. (*Level of Evidence: B*)

Class IIb

1. Exercise or dobutamine echocardiography in patients with left bundle-branch block. (*Level of Evidence: C*)
2. Exercise, dipyridamole, adenosine myocardial perfusion imaging or exercise or dobutamine echocardiography as the initial test in patients who have a normal rest ECG and who are not taking digoxin. (*Level of Evidence: B*)

Class III

1. Exercise myocardial perfusion imaging in patients with left bundle-branch block. (*Level of Evidence: C*)
2. Exercise, dipyridamole, adenosine myocardial perfusion imaging or exercise or dobutamine echocardiography in patients with severe comorbidity likely to limit life expectation or prevent revascularization. (*Level of Evidence: C*)

Recommendations for Cardiac Stress Imaging as the Initial Test for Risk Stratification of Patients With Chronic Stable Angina Who Are Unable to Exercise

Class I

1. Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography to identify the extent, severity and location of ischemia in patients who do not have left bundle-branch block or electronically paced ventricular rhythm. (*Level of Evidence: B*)
2. Dipyridamole or adenosine myocardial perfusion imaging in patients with left bundle-branch block or electronically paced ventricular rhythm. (*Level of Evidence: B*)
3. Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography to assess the functional significance of coronary lesions (if not already known) in planning PTCA. (*Level of Evidence: B*)

Class IIb

Dobutamine echocardiography in patients with left bundle-branch block. (*Level of Evidence: C*)

Class III

Dipyridamole or adenosine myocardial perfusion imaging or dobutamine echocardiography in patients with severe comorbidity likely to limit life

expectation or prevent revascularization. (*Level of Evidence: C*)

Available Stress Imaging Approaches

Stress imaging studies in which radionuclide myocardial perfusion imaging techniques or two-dimensional echocardiography at rest and during stress are useful for risk stratification and determination of the most beneficial management strategy for patients with chronic stable angina (415-417). Whenever possible, treadmill or bicycle exercise should be used as the most appropriate form of stress because it provides the most information concerning patient symptoms, cardiovascular function and hemodynamic response during usual forms of activity (14). In fact, the inability to perform a bicycle or exercise treadmill test is in itself a negative prognostic factor for patients with chronic CAD.

In patients who cannot perform an adequate amount of bicycle or treadmill exercise, various types of pharmacologic stress are useful for risk stratification (12,13,217,418). The selection of the type of pharmacologic stress will depend on specific patient factors such as the patient's heart rate and blood pressure, the presence or absence of bronchospastic disease, the presence of left bundle-branch block or a pacemaker and the likelihood of ventricular arrhythmias.

Pharmacologic agents are often used to increase cardiac workload as a substitute for treadmill or bicycle exercise or to cause an increase in overall coronary blood flow (224,225). For the former effect, adrenergic-stimulating drugs (such as dobutamine or arbutamine) are usually used, and for the latter effect, vasodilating agents (such as dipyridamole or adenosine) are generally used (12,13,217,224,225,418) (see Section II.C.4).

Radionuclide imaging has played a major role in risk stratification of patients with CAD. Either planar (three conventional views) or SPECT (multiple tomographic slices in three planes) imaging with ^{201}Tl or $^{99\text{m}}\text{Tc}$ perfusion tracers with images obtained at stress and during rest provide important information about the severity of functionally significant CAD (180-188,191,192,199,204,205,419).

More recently, stress echocardiography has been used for assessing patients with chronic stable angina; thus, the amount of prognostic data obtained with this approach is somewhat limited. Nevertheless, the presence or absence of inducible myocardial wall motion abnormalities has useful predictive value in patients undergoing exercise or pharmacologic stress echocardiography. A negative stress echocardiography study denotes a low cardiovascular event rate during follow-up (420-428).

Important Findings on Stress Perfusion Studies for Risk Stratification

Normal poststress thallium scan results are highly predictive of a benign prognosis even in patients with known coronary disease (12). A collation of 16 studies involving 3,594 patients followed up for a mean of 29 months

indicated a rate of cardiac death and MI of 0.9% per year (429), nearly as low as that of the general population (430). In a recent prospective study of 5,183 consecutive patients who underwent myocardial perfusion studies during stress and later at rest, patients with normal scans were at low risk (<0.5% per year) for cardiac death and MI during 642 ± 226 days of mean follow-up, and rates of both outcomes increased significantly with worsening scan abnormalities (431). The presence of a normal stress myocardial perfusion scan indicates such a low likelihood of significant CAD that coronary arteriography is usually not indicated as a subsequent test. Although the published data are limited, the single exception would appear to be patients with high-risk treadmill scores and normal images (431).

The number, extent, and site of abnormalities on stress myocardial perfusion scintigrams reflect the location and severity of functionally significant coronary artery stenoses. Lung uptake of ^{201}Tl on postexercise or pharmacologic stress images is an indicator of stress-induced global LV dysfunction and is associated with pulmonary venous hypertension in the presence of multivessel CAD (432-435). Transient poststress ischemic LV dilation also correlates with severe two- or three-vessel CAD (436-439). Several studies have suggested that SPECT may be more accurate than planar imaging for determining the size of defects, detecting coronary and particularly left circumflex CAD and localizing abnormalities in the distribution of individual coronary arteries (180,204,419). However, more false-positive results are likely to result from photon attenuation during SPECT imaging (12).

The number, size, and location of perfusion abnormalities, the amount of lung uptake of ^{201}Tl on poststress images, and the presence or absence of poststress ischemic LV dilation can be combined to maximize the recognition of high-risk patients, including those with multivessel disease, left main CAD and disease of the proximal portion of the left anterior descending coronary artery (LAD). Incremental prognostic information from the results of stress myocardial perfusion imaging can determine the likelihood of subsequent important cardiac events. The number of transient perfusion defects, whether provoked by exercise or pharmacologic stress, is a reliable predictor of subsequent cardiac death or non-fatal MI (180,419,440-447). The number of stenotic coronary arteries may be less predictive than the number of reversible perfusion defects (440-450). The magnitude of the perfusion abnormality was the single most prognostic indicator in a study that demonstrated independent and incremental prognostic information from SPECT ^{201}Tl scintigraphy compared with that obtained from clinical, exercise treadmill and catheterization data (451). As indicated previously, increased lung uptake of thallium induced by exercise or pharmacologic stress is associated with a high risk for cardiac events (12,452).

Information concerning both myocardial perfusion and ventricular function at rest may be helpful in determining

the extent and severity of coronary disease (181,183,453). This combined information can be obtained by performing two separate exercise tests (e.g., stress perfusion scintigraphy and stress RNA) or combining the studies after one exercise test (e.g., first-pass RNA with $^{99\text{m}}\text{Tc}$ -based agents followed by perfusion imaging or perfusion imaging using gating). However, an additional benefit of the greater information provided by combined myocardial perfusion and ventricular function exercise testing has not been shown in clinical outcome or prognostic studies (12). Thus, one determination of LV function at rest and one measure of exercise/pharmacologic stress-induced myocardial perfusion or exercise ventricular function, but not both, are appropriate (12). The prognostic value of stress myocardial perfusion imaging in chronic stable angina is summarized in Table 21 (studies with >100 patients, who did not have recent MI, and that included both positive and negative perfusion images).

Application of Myocardial Perfusion Imaging to Specific Patient Subsets

Patients With a Normal Rest ECG. Myocardial perfusion imaging has little advantage over the less expensive treadmill exercise test in this subset of patients. Three separate studies (402,404,405) have demonstrated little (if any) incremental value of myocardial perfusion imaging in the initial evaluation of such patients. As mentioned previously (Section III.2), many such patients will have low-risk treadmill scores and will not require further evaluation.

Concomitant Use of Drugs. As mentioned previously (Sections II.2 and II.4), beta-blockers (and other anti-ischemic drugs) should be withheld for four to five half-lives before testing. However, even if these drugs are continued, most high-risk patients will usually still be identified (14). Nitrates may also decrease the extent of perfusion defects or even convert abnormal exercise scan results to normal results (462).

Women, the Elderly, or Obese Patients. The treadmill ECG test is less accurate for the diagnosis of CHD in women who have a lower pretest likelihood than men (194). However, the sensitivity of thallium perfusion scans may be lower in women than men (194,245). Artifacts due to breast attenuation, usually manifest in the anterior wall, can be an important consideration in the interpretation of women's scans, especially when ^{201}Tl is used as a tracer (12). As mentioned previously, $^{99\text{m}}\text{Tc}$ sestamibi may be preferable to ^{201}Tl scintigraphy for determining prognosis as well as diagnosing CAD in women with large breasts or breast implants (248).

Although many elderly patients can perform an exercise test, some are unable to do so because of physical impairment. Pharmacologic stress imaging is an appropriate option for risk stratification in such patients. Very obese patients constitute a specific problem because most imaging tables used for SPECT have weight-bearing limits (usually 300 to 450 lb) that preclude imaging very heavy subjects. These subjects can still be imaged by planar scintigraphy

Table 21. Prognostic Value of Stress Myocardial Imaging in Definite or Suspected Chronic Stable Angina

Author	Test	No.	Patient Population	Avg f/u (mo.)	% Abn Test	Event %	Pos. Pred. Value %	Neg. Pred. Value %	Relative Risk	Events
Ladenheim 1986 (441)	Tl-201 (planar) ETT	1689	CAD symptoms	12	50	4.4	7.5	98.7	10.6	Death, MI, CABG
Pollock 1992 (454)	Tl-201 (planar) ETT	501	Suspected CAD	52.8	N/A	18.5	N/A	N/A	2.2	Death or MI
Machecourt 1994 (455)	Tl-201 (SPECT) ETT or Dyp.	1929	Angina, prior MI, CABG, PTCA	33	63	5.2	3.8	99.4	9.1	Death or MI
Marie 1995 (456)	Tl-201 (SPECT) ETT	217	Suspected CAD	70	N/A	13.47	N/A	N/A	1.04	Death or MI
Kaul 1988 (444)	Tl-201 (planar) ETT	299	Suspected CAD	55.2	50	30	41.0	81.22	2.20	Death, MI or CABG
Hachamovitch 1998 (431)	Tl-201 + (SPECT) sestamibi, ETT, or adenosine	5183	Suspected CAD	21.4	43	5.3	5.3 (per yr)	99.2 (per yr)	6.5	Death or MI
Geleijnse 1996 (457)	Sestamibi (SPECT) dobutamine	392	CAD, Suspected CAD	22	67	11	16	98.5	14.5	Death or MI
Kamal 1994 (458)	Tl-201 (SPECT) adenosine	177	CAD	22	83	8	9.5	100	∞	Death or MI
Stratmann 1994 (459)	Sestamibi (SPECT) dipyridamole	534	Suspected CAD	13	66.5	11	15.4	98.3	8.4	Death or MI
Stratmann 1994 (460)	Sestamibi (SPECT) exercise	521	Stable angina	13	60.5	4.6	7.3	99.5	13.8	Death or MI
Iskandrian 1988 (443)	Tl-201 (planar) exercise	404	Suspected CAD, age >60	25	54.7	4	7.7	99.5	14.1	Death or MI
Iskandrian 1985 (461)	Tl-201 (planar) exercise	743	Suspected CAD	13	46	2.7	4.4	98.8	3.5	Death or MI

CAD indicates coronary artery disease; MI = myocardial infarction; ETT = exercise treadmill test; CABG = coronary artery bypass graft surgery; SPECT = single photon emission computed tomography; Dyp = dipyridamole; PTCA = percutaneous transluminal coronary angioplasty.

(12). Obese patients often have suboptimal perfusion images, especially with thallium-201 because of the marked photon attenuation by soft tissue. In these patients, technetium sestamibi is probably the most appropriate and should provide images of better quality than ²⁰¹Tl.

Left Bundle-Branch Block. As mentioned previously (Section II.4), pharmacologic stress perfusion imaging is preferable to exercise perfusion imaging in patients with left bundle-branch block. Recently, 245 patients with left bundle-branch block underwent SPECT imaging with

²⁰¹Tl (n = 173) or ^{99m}Tc sestamibi (n = 72) during dipyridamole (n = 153) or adenosine (n = 92) stress testing (463). Patients with a large, severe fixed defect, a large reversible defect or cardiac enlargement and either increased pulmonary uptake (thallium) or decreased ejection fraction (sestamibi) (n = 20) were classified as high-risk patients. The rest were classified as low risk. The three-year overall survival rate was 57% in the high-risk group compared with 87% in the low-risk group (p = 0.001). Patients with a low-risk scan had an overall survival rate that was not

significantly different from that of the U.S.-matched population ($p = 0.86$). The value of pharmacologic perfusion imaging for prognostication was confirmed in three other studies (464–466), which included >300 patients followed for a mean of nearly three years. Normal dipyridamole or adenosine scans were associated with a low cardiac event rate; large defects and increased pulmonary uptake were associated with a high cardiac event rate.

After Coronary Angiography. Myocardial perfusion imaging is useful in planning revascularization procedures because it demonstrates whether a specific coronary stenosis is associated with the stress-induced perfusion abnormality (12). Myocardial perfusion imaging is particularly helpful in determining the functional importance of single or multiple stenoses when PTCA is targeted to the “culprit lesion,” that is, the ischemia-provoking stenosis (12,463,467–469).

After Myocardial Revascularization. Myocardial perfusion imaging can be useful in several situations after coronary bypass surgery. In patients with ST-T wave abnormalities at rest, recurrent myocardial ischemia during stress can be better evaluated by exercise scintigraphy than ECG treadmill testing. In addition, approximately 30% have an abnormal ECG response on treadmill exercise testing early after bypass surgery (470); these patients can be assessed for potential and incomplete revascularization and the extent of myocardium affected. Patients with initial negative postoperative treadmill test results that later become positive usually have progressive ischemia due to either graft closure or progression of disease in the native circulation (471). Myocardial perfusion scintigraphy can be useful in determining the location, extent and severity of such ischemia (12). Its prognostic value has been demonstrated both early (472) and late (473–475) after CABG.

After Exercise Testing. In patients who perform a treadmill exercise test that is not associated with an adequate exercise effort necessary to risk-stratify the patient appropriately, a repeat exercise test with thallium scintigraphy or a myocardial perfusion imaging test with pharmacologic stress may give a better indication of the presence or absence of high-risk coronary disease (14).

Important Findings on Stress Echocardiography for Risk Stratification

Stress echocardiography is both sensitive and specific for detecting inducible myocardial ischemia in patients with chronic stable angina (13) (see Section II.C.4). Compared with standard exercise treadmill testing, stress echocardiography provides an additional clinical value for detecting and localizing myocardial ischemia. The results of stress echocardiography may provide important prognostic value. Several studies indicate that patients at low, intermediate and high risk for cardiac events can be stratified on the presence or absence of inducible wall motion abnormalities on stress echocardiography testing. A positive stress echocardiographic study can be useful in determining the location and severity of inducible ischemia, even in a patient with a high

pretest likelihood that disease is present. A negative stress echocardiographic evaluation predicts a low risk for future cardiovascular events (420–428).

However, the value of a negative study compared with a negative thallium study must be further documented because there are less follow-up data compared with radionuclide imaging. Recently, McCully et al. (476) assessed the outcomes of 1,325 patients who had normal exercise echocardiograms with overall and cardiac event-free survival as end points. Cardiac events included cardiac death, nonfatal MI, and coronary revascularization. The event-free survival rates were 99.2% at one year, 97.8% at two years, and 97.4% at three years. Table 22 summarizes the prognostic value of stress echocardiography from the literature (studies with >100 patients who did not have recent MI and that included both positive and negative echocardiograms). The presence of ischemia on the exercise echocardiogram is independent and incremental to clinical and exercise data in predicting cardiac events in both men and women (477,478).

The prognosis is not benign in patients with a positive stress echocardiographic study. In this subset, morbid or fatal cardiovascular events are more likely, but the overall event rates are rather variable. Hence, the cost-effectiveness of using routine stress echocardiographic testing to establish prognosis is uncertain.

In general, patients with a positive ECG response to treadmill stress testing but no inducible wall motion abnormality on stress echocardiography have a very low rate of adverse cardiovascular events during follow-up (13,420,421), albeit higher than in patients with negative ECG results as well. However, the number of patients followed up after both stress ECG and stress echocardiography is relatively small, and there has been no breakdown into groups with various METs achieved during ECG treadmill testing and with different risks according to the treadmill score (see Section II.C.2).

In patients with a significant clinical suspicion of CAD, stress echocardiography is appropriate for risk stratification when standard exercise testing is likely to be suboptimal (14). A variety of methods can be used to induce stress. Treadmill stress echocardiography may have lowered sensitivity if there is a significant delay from the end of exercise to the acquisition of postexercise images. Dobutamine stress echocardiography has substantially higher sensitivity than vasodilator stress echocardiography for detecting coronary stenoses (13,224,225,479). Sensitivity can also be diminished if all myocardial segments are not adequately visualized.

Application of Stress Echocardiography to Specific Patient Subsets

Women, the Elderly, and Obese Patients. There are some recent data concerning the usefulness of stress echocardiography in women compared with men. Two studies by Marwick and associates (129,479) define the predictive

Table 22. Prognostic Value of Stress Echocardiography in Definite or Suspected Coronary Heart Disease (Studies With n > 100, Not Recent MI, Both Positive/Negative Echocardiograms)

Author	Test	No.	Patient Population	Avg f/u (mo.)	% Abn Test	Event %	Pos. Pred. Value %	Neg. Pred. Value %	Relative Risk	Events
Krivokapich 1993 (421)	TME	360	Suspected CAD	12	18	14	34	92	4.3	MI, death, CABG or PTCA
Severi 1994 (423)	DIP	429	Suspected CAD	38	63	35	N/A	N/A	2.9	Death, MI, revascularization
Coletta 1995 (424)	DIP	268	CAD	16	17	5	61	98	25.4	Death or MI
Kamaran 1995 (427)	DSE	210	Suspected CAD, CAD	8	30	16	48	97	16	Death or MI
Williams 1996 (425)	DSE	108	CAD, LVEF, <40%	16	43	26	66	90	3.51	Death, MI, late revascularization
Marcovitz 1996 (428)	DSE	291	Suspected CAD, CAD	15	70	11	15	98	7.5	Death or MI
Heupler 1997 (479)	TME	508	Women with suspected CAD	41	19	17	47	92	9.8	Death, MI or revascularization
Marwick 1997 (480)	TME	463	Suspected CAD, CAD	44	40	17	60	81	6.47* 3.05†	Death, MI, UA
Chuah 1998 (481)	DSE	860	Suspected CAD, CAD	24	31	10	14	96	3.5	Death or MI

f/u = follow-up; nl = no chest pain; TME = treadmill echocardiogram; MI = myocardial infarction; DIP = dipyridamole echocardiogram; SBE = supine bicycle ergometry; CAD = known or suspected coronary artery disease; DSE = dobutamine stress echocardiogram; ECG = electrocardiogram; CP = chest pain (suspected coronary artery disease); CHF = congestive heart failure; EF = ejection fraction. Events include cardiac death, myocardial infarction, revascularization (in some series), and unstable angina requiring hospitalization (in some series).

*Echo ischemia. †Echo scar. Modified from reference (13) with permission.

value of exercise echocardiography as an independent predictor of cardiac events in women with known or suspected CAD. Symptom-limited exercise echocardiography was performed in 508 consecutive women (55 ± 10 years) between 1989 and 1993 (129), with a follow-up of 41 ± 10 months. Cardiac events occurred in 7% of women, and exercise echocardiography provided key prognostic information incremental to clinical and exercise testing data with a Cox proportional hazard model. In another group of women, the specificity of exercise echocardiography for indicating CAD and potential risk exceeded that of exercise electrocardiography (80 ± 3% vs. 64 ± 3%, p = 0.05) and was a more cost-effective approach (129). Although these data are promising, the committee thought that in most women, ECG treadmill testing is still the first choice for detecting high-risk inducible myocardial ischemia.

The echocardiographic window and the number of myocardial segments detected during exercise or dobutamine echocardiography are often suboptimal in very obese patients and many elderly patients who have chronic obstructive lung disease and a suboptimal echocardiographic window. As mentioned previously (Section II.C.3), tissue harmonic imaging and contrast echocardiography should improve detection of the endocardium.

Left Bundle-Branch Block. Like exercise myocardial perfusion imaging studies, the significance of stress-induced echocardiography wall motion abnormalities in patients with left bundle-branch block is unreliable (13). During either exercise or dobutamine stimulation, abnormal contraction of the intraventricular septum has been a frequent occurrence in patients with left bundle-branch block who do not have underlying disease of the LAD.

After Coronary Angiography. Echocardiographic studies may help in planning revascularization procedures by demonstrating the functional significance of a given coronary stenosis. This may be of particular value in determining the need for PTCA, especially when the degree of angiographic stenosis is of uncertain physiologic significance or when multiple lesions are present (13).

After Revascularization. When symptoms persist or recur ≥6 months after CABG, echocardiographic testing can be useful. Abnormal baseline ECG findings after cardiac surgery are common, and postbypass patients frequently have abnormal ECG responses on standard treadmill testing. When symptoms of ischemia suggest incomplete revascularization, stress echocardiography studies may demonstrate the location and severity of residual ischemia. When symptoms recur after initial relief and stress echocardiogram

demonstrates inducible ischemia, either graft closure or the development of new coronary artery obstructive lesions is likely (482).

After Treadmill Exercise Testing. As with stress myocardial perfusion imaging, stress echocardiography may provide additional information in patients unable to perform appropriate exercise on the treadmill and in those who have an intermediate risk determined by ECG criteria during exercise testing (13).

D. Coronary Angiography and Left Ventriculography

The availability of potent but expensive strategies to reduce the long-term risk of CAD mandates that the patients most likely to benefit, namely those at increased risk, be identified. This effort poses a significant challenge to both the cardiovascular specialist and primary-care physician (41,134,333,483-486). It is important to recognize that the science of risk prediction is only now evolving, and in the case of coronary atherosclerosis methods of identifying vulnerable plaques, the precursors of coronary events, are lacking (41,134,333,485-487).

Assessment of cardiac risk and decisions regarding further testing usually begin with simple, repeatable, and inexpensive assessments of history and physical examination and extend to noninvasive or invasive testing, depending on outcome. Clinical risk factors are in general additive, and a crude estimate of one-year mortality can be obtained from these variables. An index has been developed that is the sum of the age plus a score based on symptoms plus comorbidity (diabetes, peripheral vascular disease, cerebrovascular disease, prior MI) (485). It is important to note that one-year mortality rates of patients without severe comorbidity who have stable, progressive and unstable angina are similar (range 1.3% to 1.7%), showing the limited predictive value of symptom severity alone (485). Patients with mild anginal symptoms may have severe coronary disease (Fig. 6) (41,333,485), which is detectable only with noninvasive or invasive testing. LV dysfunction is a powerful determinant of long-term survival in patients with chronic stable angina pectoris (96,488). It may be inferred from extensive Q-wave formation on ECG or history of CHF or measured noninvasively by echocardiography, radionuclide techniques or contrast angiography at the time of coronary angiography. The coexistence of significant LV dysfunction and chronic stable angina constitutes increased risk and warrants careful further evaluation.

Risk stratification of patients with chronic stable angina by stress testing with exercise or pharmacologic agents has been shown to permit identification of groups of patients with low, intermediate, or high risk of subsequent cardiac events (12-14,37) (see Sections III.B and III.C). Although one recent study (431) suggested that myocardial perfusion imaging can identify patients who are at low risk of death but increased risk of nonfatal MI, the major current focus of noninvasive risk stratification is on subsequent patient mortality. The rationale is to identify patients in whom

coronary angiography and subsequent revascularization might improve survival. Such a strategy can be effective only if the patient's prognosis on medical therapy is sufficiently poor that it can be improved.

Previous experience in the randomized trials of CABG demonstrated that patients randomized to initial CABG had a lower mortality rate than those treated with medical therapy only if they were at substantial risk (489). Low-risk patients who did not have a lower mortality rate with CABG had a five-year survival rate of about 95% with medical therapy. This is equivalent to an annual mortality rate of 1%. As a result, coronary angiography to identify patients whose prognosis can be improved is inappropriate when the estimated annual mortality rate is $\leq 1\%$. In contrast, patients with a survival advantage with CABG, such as those with three-vessel disease, have an annual mortality rate $\geq 3\%$. Coronary angiography is appropriate for patients whose mortality risk is in this range.

Noninvasive test findings that identify high-risk patients are listed in Table 23. Patients identified as high risk are generally referred for coronary arteriography independent of their symptomatic status. When appropriately used, noninvasive tests are less costly than coronary angiography and have an acceptable predictive value for adverse events (12-14,37,485). This is most true when the pretest probability of severe CAD is low. When the pretest probability of severe CAD is high, direct referral for coronary angiography without noninvasive testing has been shown to be most cost-effective (see Section III.A) as the total number of tests is reduced (335).

Coronary Angiography for Risk Stratification in Patients With Chronic Stable Angina

Recommendations

Class I

1. **Patients with disabling (Canadian Cardiovascular Society [CCS] classes III and IV) chronic stable angina despite medical therapy. (Level of Evidence: B)**
2. **Patients with high-risk criteria on noninvasive testing (Table 23) regardless of anginal severity. (Level of Evidence: B)**
3. **Patients with angina who have survived sudden cardiac death or serious ventricular arrhythmia. (Level of Evidence: B)**
4. **Patients with angina and symptoms and signs of CHF. (Level of Evidence: C)**
5. **Patients with clinical characteristics that indicate a high likelihood of severe CAD. (Level of Evidence: C)**

Class IIa

1. **Patients with significant LV dysfunction (ejection fraction $< 45\%$), CCS class I or II angina, and demonstrable ischemia but less than high-risk criteria on noninvasive testing. (Level of Evidence: C)**

Table 23. Noninvasive Risk Stratification

High-Risk (greater than 3% annual mortality rate)

1. Severe resting left ventricular dysfunction (LVEF < 35%)
2. High-risk treadmill score (score ≤ -11)
3. Severe exercise left ventricular dysfunction (exercise LVEF < 35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. Stress echocardiographic evidence of extensive ischemia

Intermediate Risk (1%–3% annual mortality rate)

1. Mild/moderate resting left ventricular dysfunction (LVEF = 35% to 49%)
2. Intermediate-risk treadmill score ($-11 < \text{score} < 5$)
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving less than or equal to two segments

Low-Risk (less than 1% annual mortality rate)

1. Low-risk treadmill score (score ≥ 5)
2. Normal or small myocardial perfusion defect at rest or with stress*
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress*

*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting left ventricular dysfunction (LVEF < 35%).

2. Patients with inadequate prognostic information after noninvasive testing. (Level of Evidence: C)

Class IIb

1. **Patients with CCS class I or II angina, preserved LV function (ejection fraction >45%), and less than high-risk criteria on noninvasive testing. (Level of Evidence: C)**
2. **Patients with CCS class III or IV angina, which with medical therapy improves to class I or II. (Level of Evidence: C)**
3. **Patients with CCS class I or II angina but intolerance (unacceptable side effects) to adequate medical therapy. (Level of Evidence: C)**

Class III

1. **Patients with CCS class I or II angina who respond to medical therapy and who have no evidence of ischemia on noninvasive testing. (Level of Evidence: C)**

2. Patients who prefer to avoid revascularization. (Level of Evidence: C)

Risk Stratification With Coronary Angiography

Coronary angiography, the traditional gold standard for clinical assessment of coronary atherosclerosis, has limitations. Coronary angiography is not a reliable indicator of the functional significance of a coronary stenosis and is insensitive in detection of a thrombus (an indicator of disease activity) (203,490). More important, coronary angiography is ineffective in determining which plaques have characteristics likely to lead to acute coronary events, that is, the vulnerable plaque with a large lipid core, thin fibrous cap and increased macrophages (491–494). Serial angiographic studies performed before and after acute events and early after MI suggest that plaques resulting in unstable angina and MI commonly produced <50% stenosis before the acute event and were therefore angiographically “silent” (495,496).

Despite these limitations of coronary angiography, the extent and severity of coronary disease and LV dysfunction identified on angiography are the most powerful clinical predictors of long-term outcome (41,134,485,497,498). Several prognostic indexes have been used to relate disease severity to the risk of subsequent cardiac events; the simplest and most widely used is the classification of disease into one-vessel, two-vessel, three-vessel, or left main coronary artery disease (96,499–501). In the CASS registry of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 91% compared with 74% for those with one-vessel disease, 59% for those with two-vessel disease, and 40% for those with three-vessel disease ($p < 0.001$) (488). The effect of LV dysfunction on survival was quite dramatic. In the CASS registry, the 12-year survival rate of patients with ejection fractions in the range of 50% to 100%, 35% to 49%, and <35% were 73%, 54%, and 21%, respectively ($p < 0.0001$) (488). The importance of proximal coronary stenoses over distal lesions was recognized, and a “jeopardy score” was developed in which the prognostic significance of lesions was weighed as a function of lesion location (502). Recent angiographic studies indicate that a direct correlation also exists between the angiographic severity of coronary disease and the amount of angiographically insignificant plaque buildup elsewhere in the coronary tree. These studies suggest that the higher mortality rate of patients with multivessel disease may occur because they have more mildly stenotic or nonstenotic plaques that are potential sites for acute coronary events than those with one-vessel disease (503). Whether new technology such as magnetic resonance imaging and EBCT scanning will provide incremental prognostic value by identifying and quantifying plaque and its components remains to be determined (504).

For many years, it has been known that patients with severe stenosis of the left main coronary artery have a poor prognosis when treated medically. In a hierarchical prog-

Table 24. CAD Prognostic Index

Extent of CAD	Prognostic Weight (0-100)	5-Year Survival Rate (%)*
1-vessel disease, 75%	23	93
>1-vessel disease, 50% to 74%	23	93
1-vessel disease, $\geq 95\%$	32	91
2-vessel disease	37	88
2-vessel disease, both $\geq 95\%$	42	86
1-vessel disease, $\geq 95\%$ proximal LAD	48	83
2-vessel disease, $\geq 95\%$ LAD	48	83
2-vessel disease, $\geq 95\%$ proximal LAD	56	79
3-vessel disease	56	79
3-vessel disease, $\geq 95\%$ in at least 1	63	73
3-vessel disease, 75% proximal LAD	67	67
3-vessel disease, $\geq 95\%$ proximal LAD	74	59

*Assuming medical treatment only. CAD = coronary artery disease; LAD = left anterior descending coronary artery. From Califf RM, Armstrong PW, Carver JR, et al: Task Force 5. Stratification of patients into high-, medium- and low-risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996;27:964-1047.

nostic index developed recently, patients with severe left main coronary artery stenosis were given a prognostic weight of 100 and patients with no angiographic disease a weight of 0 (501). A gradient of risk existed between these extremes, with three-, two-, and one-vessel disease having decreasing risk. The presence of severe proximal LAD disease significantly reduces the survival rate. The five-year survival rate with three-vessel disease plus $>95\%$ proximal LAD stenosis was reported to be 59% compared with three-vessel disease without LAD stenosis of 79% (Table 24). A nomogram for predicting the five-year survival rate has been developed that incorporates clinical history, physical examination, coronary angiography and LV ejection fraction (see Fig. 8). The importance of considering clinical factors and especially LV function in estimating the risk of a given coronary angiographic finding is illustrated by comparing the predicted five-year survival rate of 65-year-old men with stable angina, three-vessel disease, and normal ventricular function with that of 65-year-old men with stable angina, three-vessel disease, heart failure, and an ejection fraction of 30%. The five-year survival rate for the former is 93%, whereas patients with the same characteristics but heart failure and reduced ejection fraction had a predicted survival rate of only 58% (501).

An additional but less quantifiable benefit of coronary angiography and left ventriculography derives from the ability of experienced angiographers to integrate the two studies. Coronary artery lesion characteristics (e.g., stenosis severity, length, complexity, presence of thrombus) as well as the number of lesions posing jeopardy to regions of contracting myocardium, possible role of collaterals and mass of jeopardized viable myocardium may afford some insight into the consequences of subsequent vessel occlusion. For example, a patient with a noncontracting inferior

or lateral wall and severe proximal stenosis of a very large LAD would be at substantial risk of developing cardiogenic shock if the LAD occluded. This integration of coronary angiography and left ventriculography permits the best estimate of the potential benefit of revascularization strategies discussed below.

Patients With Previous CABG

Patients who have previously undergone CABG are a particularly heterogeneous group with respect to the anatomic basis of ischemia and its implications for subsequent morbidity and mortality. Progression of native CAD is not uncommon, but more frequently saphenous vein graft attrition or the development of obstructive atherosclerotic vein graft lesions account for late recurrence of chronic stable angina. Saphenous vein graft lesions represent a particularly unstable form of atherosclerosis, which is prone to rapid progression and thrombotic occlusion (505-508). Consequently, a low threshold for angiographic evaluation is recommended for patients who develop chronic stable angina >5 years after surgery, especially when ischemia is noninvasively documented in the distribution of a vein graft, the LAD is supplied by a vein graft, or multiple vein grafts are present. The outcome of patients with vein graft disease can be improved by reoperation (509,510), and in some patients, symptoms can be relieved by percutaneous catheter-based strategies (511).

IV. TREATMENT

A. Pharmacologic Therapy

Recommendations for Pharmacotherapy to Prevent MI and Death and Reduce Symptoms

Class I

1. Aspirin in the absence of contraindications. (*Level of Evidence: A*)
2. Beta-blockers as initial therapy in the absence of contraindications in patients with prior MI. (*Level of Evidence: A*)
3. Beta-blockers as initial therapy in the absence of contraindications in patients without prior MI. (*Level of Evidence: B*)
4. Calcium antagonists* or long-acting nitrates as initial therapy when beta-blockers are contraindicated. (*Level of Evidence: B*)
5. Calcium antagonists* or long-acting nitrates in combination with beta-blockers when initial treatment with beta-blockers is not successful. (*Level of Evidence: B*)
6. Calcium antagonists* and long-acting nitrates as a substitute for beta-blockers if initial treatment with beta-blockers leads to unacceptable side effects. (*Level of Evidence: C*)

*Short-acting dihydropyridine calcium antagonists should be avoided.

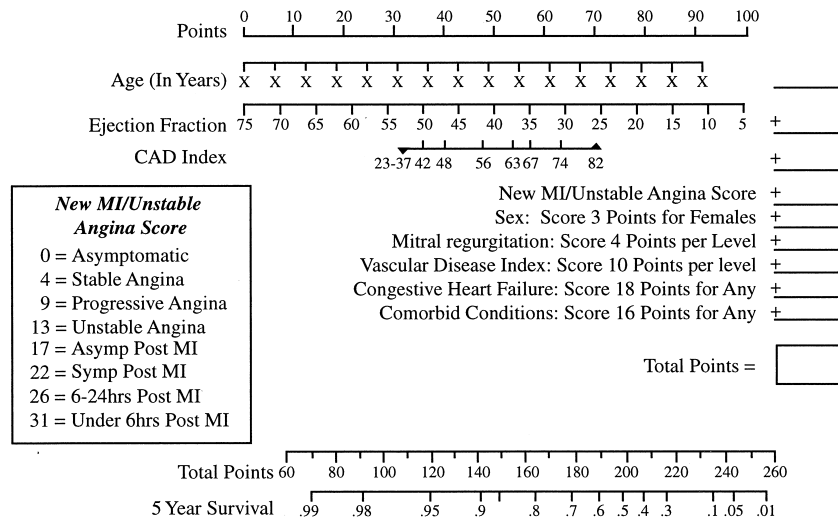


Figure 8. Nomogram for prediction of five-year survival from clinical, physical examination and cardiac catheterization findings. Asymp = asymptomatic; CAD = coronary artery disease; MI = myocardial infarction; and Symp = symptomatic. From Califf RM, Armstrong PW, Carver JR, et al: Task Force 5. Stratification of patients into high-, medium- and low-risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996;27:964-1047.

7. Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina. (Level of Evidence: C)
8. Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol >130 mg/dL, with a target LDL of <100 mg/dL. (Level of Evidence: A)

Class IIa

1. Clopidogrel when aspirin is absolutely contraindicated. (Level of Evidence: B)
2. Long-acting nondihydropyridine calcium antagonists* instead of beta-blockers as initial therapy. (Level of Evidence: B)
3. Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol 100 to 129 mg/dL, with a target LDL of 100 mg/dL. (Level of Evidence: B)

Class IIb

Low-intensity anticoagulation with warfarin in addition to aspirin. (Level of Evidence: B)

Class III

1. Dipyridamole. (Level of Evidence: B)
2. Chelation therapy. (Level of Evidence: B)

*Short-acting dihydropyridine calcium antagonists should be avoided.

Overview of Treatment

The treatment of stable angina has two major purposes. The first is to prevent MI and death and thereby increase the “quantity” of life. The second is to reduce symptoms of angina and occurrence of ischemia, which should improve the quality of life.

Therapy directed toward preventing death has the highest priority. When two different therapeutic strategies are equally effective in alleviating symptoms of angina, the therapy with a definite or very likely advantage in preventing death should be recommended. For example, coronary artery bypass surgery is the preferred therapy for patients with significant left main CAD because it prolongs life. However, in many patients with mild angina, one-vessel CAD, and normal LV function, medical therapy, coronary angioplasty and coronary artery bypass surgery are all reasonable options. The choice of therapy often depends on the clinical response to initial medical therapy, although some patients may prefer coronary revascularization. Patient education, cost-effectiveness and patient preference are important components in this decision-making process.

The section on pharmacologic therapy considers treatments to prevent MI and death first; antianginal and anti-ischemic therapy to alleviate symptoms, reduce ischemia, and improve quality of life are considered in a second section. Pharmacologic therapy directed toward prevention of MI and death has expanded greatly in recent years with the emergence of evidence that demonstrates the efficacy of lipid-lowering agents for this purpose. For that reason, the committee has chosen to discuss lipid-lowering drugs in two sections of these guidelines: briefly in the following section on pharmacological therapy and in more detail in the later section on risk factor reduction. The committee believes that the emergence of such medical therapy for prevention of MI and death represents a new treatment paradigm that should be recognized by all healthcare professionals involved in the care of patients with stable angina.

Pharmacotherapy to Prevent MI and Death

Antiplatelet Agents

Aspirin exerts an antithrombotic effect by inhibiting cyclo-oxygenase and synthesis of platelet thromboxane A₂. The use of aspirin in >3,000 patients with stable angina was associated with a 33% (on average) reduction in the risk of adverse cardiovascular events (512,513). In patients with unstable angina, aspirin decreases the short and long-term risk of fatal and nonfatal MI (514,515). In the Physicians' Health Study (516), aspirin (325 mg), given on alternate days to asymptomatic persons, was associated with a decreased incidence of MI.

In the Swedish Angina Pectoris Aspirin Trial (SAPAT) (517) in patients with stable angina, the addition of 75 mg of aspirin to sotalol resulted in a 34% reduction in primary outcome events of MI and sudden death and a 32% decrease in secondary vascular events.

Ticlopidine is a thienopyridine derivative that inhibits platelet aggregation induced by adenosine diphosphate and low concentrations of thrombin, collagen, thromboxane A₂, and platelet activating factor (518,519). It also reduces blood viscosity due to reduction in plasma fibrinogen and an increase in red cell deformability (520). Ticlopidine decreases platelet function in patients with stable angina but, unlike aspirin, has not been shown to decrease adverse cardiovascular events (521,522). It may, however, induce neutropenia and, albeit infrequently, thrombotic thrombocytopenic purpura (TTP).

Clopidogrel, also a thienopyridine derivative, is chemically related to ticlopidine but appears to possess a greater antithrombotic effect than ticlopidine (523). Clopidogrel prevents adenosine diphosphate-mediated activation of platelets by selectively and irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptors and thereby affecting ADP-dependent activation of the GP IIb-IIIa complex. In a randomized trial that compared clopidogrel with aspirin in patients with previous MI, stroke and peripheral vascular disease (i.e., at risk of ischemic events), clopidogrel appeared to be slightly more effective than aspirin in decreasing the combined risk of MI, vascular death or ischemic stroke (524). However, no further studies have been performed to confirm the efficacy of clopidogrel in patients with stable angina.

Dipyridamole is a pyrimido-pyrimidine derivative that exerts vasodilatory effects on coronary resistance vessels and also has antithrombotic effects. Dipyridamole increases intracellular platelet cyclic adenosine monophosphate (cyclic AMP) by inhibiting the enzyme phosphodiesterase, activating the enzyme adenylate cyclase, and inhibiting uptake of adenosine from vascular endothelium and erythrocytes (525). Increased plasma adenosine is associated with vasodilation. Because even the usual oral doses of dipyridamole can enhance exercise-induced myocardial ischemia in patients with stable angina (526), it should not be used as an antiplatelet agent.

Aspirin 75 to 325 mg daily should be used routinely in all patients with acute and chronic ischemic heart disease with or without manifest symptoms in the absence of contraindications.

Antithrombotic Therapy

Disturbed fibrinolytic function such as elevated tissue plasminogen activator antigen (tPA-ag), high plasminogen activator inhibitor (PAI-1), and low tPA-ag responses after exercise has been found to be associated with an increased risk of subsequent cardiovascular deaths in patients with chronic stable angina (527), providing the rationale for long-term antithrombotic therapy. In small placebo-controlled studies among patients with chronic stable angina, daily subcutaneous administration of low-molecular-weight heparin decreased the fibrinogen level, which was associated with improved clinical class and exercise time to 1-mm ST depression and peak ST depression (528). However, the clinical experience of such therapy is extremely limited. The efficacy of newer antiplatelet and antithrombotic agents such as glycoprotein IIb/IIIa inhibitors and recombinant hirudin in the management of patients with chronic stable angina has not been established (529). Low-intensity oral anticoagulation with warfarin (international normalized ratio [INR] 1.47) has been shown to decrease the risk of ischemic events (coronary death and fatal and nonfatal MI) in a randomized trial of patients with risk factors for atherosclerosis but without symptoms of angina (530). This benefit was incremental to that provided by aspirin.

Lipid-Lowering Agents

Earlier lipid-lowering trials with the use of bile acid sequestrant (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate), or niacin reported reductions in total cholesterol of 6% to 15%. The pooled data from these studies also suggested that every 1% reduction in total cholesterol could reduce coronary events by 2% (531). Angiographic trials have addressed the effects of lipid-lowering therapy on anatomic changes of the coronary atherosclerotic plaques. Active treatment was associated with less progression, more stabilization, and more regression of these plaque lesions and decreased incidence of clinical events. A meta-analysis (532) of 37 trials demonstrated that treatment-mediated reductions in cholesterol are significantly associated with the observed reductions in CHD mortality and total mortality rates.

Recent clinical trials have documented that LDL-lowering agents can decrease the risk of adverse ischemic events in patients with established CAD. In the Scandinavian Simvastatin Survival Study (4S) (533), treatment with an HMG-CoA reductase inhibitor in patients with documented CAD (including stable angina) with a baseline total cholesterol between 212 and 308 mg/dL was associated with 30% to 35% reductions in both mortality rate and major coronary events. In the Cholesterol And Recurrent Events

Table 25. Properties of Beta-Blockers in Clinical Use

Drugs	Selectivity	Partial Agonist Activity	Usual Dose for Angina
Propranolol	None	No	20–80 mg twice daily
Metoprolol	β_1	No	50–200 mg twice daily
Atenolol	β_1	No	50–200 mg/day
Nadolol	None	No	40–80 mg/day
Timolol	None	No	10 mg twice daily
Acebutolol	β_1	Yes	200–600 mg twice daily
Betaxolol	β_1	No	10–20 mg/day
Bisoprolol	β_1	No	10 mg/day
Esmolol (intravenous)	β_1	No	50–300 $\mu\text{g}/\text{kg}/\text{min}$
Labetalol*	None	Yes	200–600 mg twice daily
Pindolol	None	Yes	2.5–7.5 mg 3 times daily

*Labetalol is a combined alpha- and β -blocker.

(CARE) study (534), in both men and women with previous MI and total plasma cholesterol levels <240 mg/dL (mean 209) and LDL-cholesterol levels of 115 to 174 mg/dL (mean 139), treatment with an HMG-CoA reductase inhibitor (statin) was associated with a 24% reduction in risk for fatal or nonfatal MI. These clinical trials indicate that in patients with established CAD, including chronic stable angina, lipid-lowering therapy should be recommended even in the presence of mild to moderate elevations of LDL cholesterol.

Antianginal and Anti-ischemic Therapy

Antianginal and anti-ischemic drug therapy consists of beta-adrenoreceptor blocking agents (beta-blockers), calcium antagonists, and nitrates. Other classes of drugs, such as ACE inhibitors, amiodarone, “metabolic agents,” and nonconventional therapy, also have been used in certain subsets of patients with stable angina, but their clinical effectiveness has not been confirmed.

BETA-BLOCKERS. *Mechanism of Action.* Activation of beta-receptors is associated with an increase in heart rate, acceleration of conduction through the atrioventricular (AV) node, and increased contractility. Inhibition of beta-receptors is associated with a reduction in inotropic state and sinus rate and slowing of AV conduction. Some beta-blockers have partial agonist activity, also called intrinsic sympathomimetic activity, and may not decrease heart rate and blood pressure at rest.

The decrease in heart rate, contractility and arterial pressure with beta-blockers is associated with decreased myocardial oxygen demand. A reduction in heart rate also increases diastolic perfusion time, which may enhance LV perfusion. Although beta-blockers have the potential to increase coronary vascular resistance by the formation of cyclic AMP, the clinical relevance of this pharmacodynamic effect remains uncertain. A marked slowing of heart rate may increase LV diastolic wall tension, which may increase

myocardial oxygen demand; the concomitant use of nitrates can offset these potentially deleterious effects of beta-blockers.

Clinical Effectiveness. Various types of beta-blocker are available for treatment of hypertension and angina. The pharmacokinetic and pharmacodynamic effects of these agents are summarized in Table 25. All beta-blockers appear to be equally effective in angina pectoris. In patients with chronic stable exertional angina, these agents decrease the heart rate–blood pressure product during exercise, and the onset of angina or the ischemic threshold during exercise is delayed or avoided (535,536). In the treatment of stable angina, it is conventional to adjust the dose of beta-blockers to reduce heart rate at rest to 55 to 60 beats/min. In patients with more severe angina, heart rate can be reduced to <50 beats/min, provided that there are no symptoms associated with bradycardia and heart block does not develop. In patients with stable exertional angina, beta-blockers limit the increase in heart rate during exercise, which ideally should not exceed 75% of the heart rate response associated with onset of ischemia. Beta-blockers with additional vasodilating properties have also been found effective in stable angina (537–539). Agents with combined alpha- and beta-adrenergic antagonist properties have also been found effective in the management of chronic stable angina (540,541). Beta-blockers are clearly effective in controlling exercise-induced angina (542,543). Controlled studies comparing beta-blockers with calcium antagonists have reported equal efficacy in controlling stable angina (544–547). In patients with postinfarction stable angina and those who require antianginal therapy after revascularization, treatment with beta-blockers appears to be effective in controlling symptomatic and asymptomatic ischemic episodes (548). In elderly patients with hypertension without manifest CAD, beta-blockers as first-line therapy were reported to be ineffective in preventing cardiovascular mortality and all-cause mortality compared with diuretics.

However, beta-blockers are still the anti-ischemic drug of choice in elderly patients with stable angina (549).

Beta-blockers are frequently combined with nitrates for treatment of chronic stable angina. Nitrates tend to increase sympathetic tone and may cause reflex tachycardia, which is attenuated with the concomitant use of beta-blockers. The potential increase in LV volume and end-diastolic pressure and wall tension associated with decreased heart rate with beta-blockers is counteracted by the concomitant use of nitroglycerin. Thus, combination therapy with nitrates and beta-blockers appears to be more effective than nitrates or beta-blockers alone (550,551). Beta-blockers may also be combined with calcium antagonists. For combination therapy, slow-release dihydropyridines or new-generation, long-acting dihydropyridines are the calcium antagonists of choice (552-556). The tendency to develop tachycardia with these calcium antagonists is counteracted by the concomitant use of beta-blockers. Beta-blockers should be combined with verapamil and diltiazem with caution, because extreme bradycardia or AV block may occur. When beta-blockers are added to high-dose diltiazem or verapamil, marked fatigue may also result.

In patients with pure vasospastic angina (Prinzmetal angina) without fixed obstructive lesions, beta-blockers are ineffective and may increase the tendency to induce coronary vasospasm from unopposed alpha-receptor activity (557); they should therefore not be used.

Patient Outcomes. Beta-blockers have been shown in many randomized trials to improve the survival rate of patients with recent MI. These agents have also been shown in several large randomized trials to improve the survival rate and prevent stroke and CHF in patients with hypertension (558). The effects of beta-blockers in patients with stable angina without prior MI or hypertension have been investigated in a few small randomized control trials (Table 26).

In the Total Ischemic Burden European Trial (TIBET) (559), the combination of atenolol and nifedipine produced a nonsignificant trend toward a lower rate of cardiac death, nonfatal MI and unstable angina. There was no difference between atenolol and nifedipine. The Angina Prognosis Study in Stockholm (APSYS) (560) reported no difference between metoprolol and verapamil treatment in patients with chronic stable angina in relation to mortality, cardiovascular end points and measures of quality of life. In the Atenolol Silent Ischemia Trial (ASIST) (413), patients with documented CAD and mild angina (CCS class I or II) were treated with 100 mg atenolol daily; the number and mean duration of ischemic episodes detected by 48 h of ambulatory ECG monitoring were decreased after four weeks of therapy compared with placebo. After one year, fewer patients in the atenolol group experienced the combined end point of death, ventricular tachycardia and fibrillation, MI, hospitalization, aggravation of angina or revascularization (413). The atenolol-treated patients had a longer time until their first adverse event. In patients with stable angina,

Table 26. Randomized Trials in Stable Angina Comparing Beta-Blockers and Calcium Antagonists

Trial Author	Journal Year	N	Beta Blocker ARM 1 n =	Ca-Blocker ARM 2 n =	Follow up	Outcome	Results ARM 1 n =	Result ARM 2 n =	Odds Ratio ARM 2/ARM 1 For Death or MI
APSYS/Rehnqvist	Eur Heart J 1996	809	Metoprolol* 406	Verapamil 403	3.4 years	Death	22	25	1.01 (0.63, 1.6)
						Cardiac death	19	19	
						Non fatal MI	17	14	
TIBET/Dargie	Eur Heart J 1996	458	Atenolol 226	Nifedipine* 232	2 years	Cardiac death	3	6	1.22 (0.63, 2.4)
						Non fatal MI	14	15	
IMAGE/Savonitto	JACC 1996	127	Metoprolol* 65	Nifedipine* 62	6 wks	Death	1	0	0.5 (0.05, 5.8)
						Non fatal MI	1	1	
de Vries	Int J Card 1996	128	Atenolol 66	Nifedipine* 62	4 wks	Non fatal MI	0	1	1.07 (0.2, 55)
TIBBS/Von Arnim	JACC 1995	330	Bisoprolol 161	Nifedipine* 169	4 wks	Non fatal MI	0	1	1.91 (0.06, 57)
Ahuja	Int J Card 1993	134	Metoprolol 68	Diltiazem 66	4 wks	Death or MI	0	0	1.03 (0.02, 53)
Total		1986	992	994		Death or MI	58	62	Summary OR 1.06 (0.73, 1.54)

*Long-acting preparations.

the effects of bisoprolol (a vasodilator beta-blocker) and nifedipine on transient myocardial ischemia were studied in a prospective randomized controlled trial Total Ischemic Burden Bisoprolol Study (TIBBS) (561). In this study, 330 patients with stable angina pectoris and a positive exercise test with ST-segment depression and ≥ 2 episodes of transient myocardial ischemia during 48 h of ambulatory ECG monitoring were randomized to either 10 mg bisoprolol once daily or 20 mg slow-release nifedipine twice daily for four weeks. The doses were then doubled for an additional four weeks. Both bisoprolol and nifedipine reduced the number and duration of ischemic episodes in patients with stable angina. However, bisoprolol was more effective than nifedipine. In the International Multicenter Angina Exercise Study (IMAGE) (562), the efficacy of metoprolol alone, nifedipine alone, and the combination of metoprolol and nifedipine were assessed in patients with stable angina pectoris. In this study, 280 patients ≤ 75 years old with stable angina for ≥ 6 months and a positive exercise test were randomized to receive 200 mg metoprolol daily or 20 mg nifedipine twice daily for 6 weeks after a 2-week placebo period. The patients were then randomized to the addition of the second drug or placebo for four more weeks. Both metoprolol and nifedipine were effective as monotherapy in increasing exercise time, although metoprolol was more effective than nifedipine (562). The combination therapy also increased the exercise time compared with either drug alone.

Contraindications. The absolute cardiac contraindications for the use of beta-blockers are severe bradycardia, preexisting high degree of AV block, sick sinus syndrome and severe, unstable LV failure (mild CHF may actually be an indication from beta-blockers) (563). Asthma and bronchospastic disease, severe depression, and peripheral vascular disease are relative contraindications. Most diabetic patients will tolerate beta-blockers, although these drugs should be used cautiously in patients who require insulin.

Side Effects. Fatigue, inability to perform exercise, lethargy, insomnia, nightmares, worsening claudication and impotence are frequently experienced side effects. The mechanism of fatigue is not clear. During exercise, the total maximal work achievable is reduced by approximately 15% with long-term therapy and may increase the sense of fatigue (564). The average incidence of impotence is about 1%; however, lack of or inadequate erection has been observed in $\leq 26\%$ of patients (565). Changes in quality of life have not been systematically studied in patients with chronic stable angina treated with beta-blockers.

CALCIUM ANTAGONISTS. Mechanisms of Action. These agents reduce the transmembrane flux of calcium via the calcium channels. There are three types of voltage-dependent calcium channel: L type, T type, or N type. They are categorized according to whether they are characteristically large in conductance, transient in duration of opening, or neuronal in distribution (566). The pharmacodynamics of calcium antagonists are summarized in Table 27.

All calcium antagonists exert a negative inotropic effect. In smooth muscle, calcium ions also regulate the contractile mechanism, and calcium antagonists reduce smooth muscle tension in the peripheral vascular bed, which is associated with vasodilation.

Calcium antagonists, including the newer, second-generation vasoselective dihydropyridine agents and nondihydropyridine drugs such as verapamil and diltiazem, decrease coronary vascular resistance and increase coronary blood flow. All of these agents cause dilation of the epicardial conduit vessels and the arteriolar resistance vessels. Dilation of the epicardial coronary arteries is the principal mechanism of the beneficial effect of calcium antagonists for relieving vasospastic angina. Calcium antagonists also decrease myocardial oxygen demand primarily by reduction of systemic vascular resistance and arterial pressure. The negative inotropic effect of calcium antagonists also decreases the myocardial oxygen requirement. However, the negative inotropic effect varies considerably with different types of calcium antagonist. Among dihydropyridines, nifedipine probably exerts the most pronounced negative inotropic effect, and newer-generation, relatively vasoselective dihydropyridines such as amlodipine and felodipine exert much less of a negative inotropic effect. The new T-channel blocker mibefradil also appears to exert a less negative inotropic effect (567,568). However, mibefradil has been withdrawn from clinical use because of adverse drug interactions and is not discussed further in this document. Diltiazem and verapamil can reduce heart rate by slowing the sinus node or decreasing ventricular response in patients with atrial flutter and fibrillation due to reduction in AV conduction. Calcium antagonists are therefore useful for treatment of both demand and supply ischemia (569-575).

Calcium Antagonists in Chronic Stable Angina. Randomized clinical trials comparing calcium antagonists and beta-blockers have demonstrated that calcium antagonists are generally equally as effective as beta-blockers in relieving angina (Fig. 9) and improving exercise time to onset of angina or ischemia (Fig. 10). The clinical effectiveness of calcium antagonists was evident with both dihydropyridine and nondihydropyridine agents and various dosing regimens.

Calcium Antagonists in Vasospastic Angina. In patients with vasospastic (Prinzmetal) angina, calcium antagonists have been shown to be effective in reducing the incidence of angina. Short-acting nifedipine, diltiazem, and verapamil all appeared to completely abolish the recurrence of angina in approximately 70% of patients; in another 20% of patients, the frequency of angina was reduced substantially (576-579). A randomized placebo-controlled trial has also been performed with the use of newer, vasoselective, long-acting dihydropyridine amlodipine in the management of patients with vasospastic angina (580). In this study, 52 patients with well documented vasospastic angina were randomized to receive either amlodipine or placebo. The rate of anginal

Table 27. Properties of Calcium Antagonists in Clinical Use

Drugs	Usual Dose	Duration of Action	Side Effects
Dihydropyridines			
Nifedipine	Immediate release: 30-90 mg daily orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
	Slow release: 30-180 mg orally		
Amlodipine	5-10 mg qd	Long	Headache, edema
Felodipine	5-10 mg qd	Long	Headache, edema
Isradipine	2.5-10 mg bid	Medium	Headache, fatigue
Nicardipine	20-40 mg tid	Short	Headache, dizziness, flushing, edema
Nisoldipine	20-40 mg qd	Short	Similar to nifedipine
Nitrendipine	20 mg qd or bid	Medium	Similar to nifedipine
Miscellaneous			
Bepidil	200-400 mg qd	Long	Arrhythmias, dizziness, nausea
Diltiazem	Immediate release: 30-80 mg 4 times daily	Short	Hypotension, dizziness, flushing, bradycardia, edema
	Slow release: 120-320 mg qd	Long	
Verapamil	Immediate release: 80-160 mg tid	Short	Hypotension, myocardial depression, heart failure, edema, bradycardia
	Slow release: 120-480 mg qd	Long	

episodes decreased significantly with amlodipine treatment compared with placebo, and the intake of nitroglycerin tablets showed a substantial reduction.

Patient Outcomes. Retrospective case control studies report that in patients with hypertension, treatment with immediate-acting nifedipine, diltiazem and verapamil was associated with increased risk of MI by 31%, 63% and 61%, respectively (581). A meta-analysis of 16 trials that used immediate-release and short-acting nifedipine in patients with MI and unstable angina reported a dose-related influence on excess mortality (582). However, further analysis of the published reports has failed to confirm an increased risk of adverse cardiac events with calcium antagonists (583,584). Furthermore, slow-release or long-acting vaso-selective calcium antagonists have been reported to be effective in improving symptoms and decreasing the risk of adverse cardiac events (585). However, in the Appropriate Blood Pressure Control in Diabetes (ABCD) study (586), the use of nisoldipine, a relatively short-acting dihydropyridine calcium antagonist, was associated with a higher incidence of fatal and nonfatal MI compared with enalapril, an ACE inhibitor. In an earlier trial of patients with stable angina, nisoldipine was not effective in relieving angina compared with placebo. Furthermore, larger doses tended to increase the incidence of adverse events (587). These data

indicate that relatively short-acting dihydropyridine calcium antagonists have the potential to enhance the risk of adverse cardiac events and should be avoided. In contrast, long-acting calcium antagonists, including slow-release and long-acting dihydropyridines and nondihydropyridines, are effective in relieving symptoms in patients with chronic stable angina. They should be used in combination with beta-blockers when initial treatment with beta-blockers is not successful or as a substitute for beta-blockers when initial treatment leads to unacceptable side effects. However, their use is not without potential hazard, as demonstrated by the FACET trial (588), in which amlodipine was associated with a higher incidence of cardiovascular events than fosinopril, an ACE inhibitor.

Contraindications. In general, overt decompensated heart failure is a contraindication for the use of calcium antagonists, although new-generation vasoselective dihydropyridines (i.e., amlodipine, felodipine) are tolerated by patients with reduced LV ejection fraction. Bradycardia, sinus node dysfunction, and AV nodal block are contraindications for the use of heart rate-modulating calcium antagonists. A long QT interval is a contraindication for the use of mibefradil and bepridil.

Side Effects. (589-591) (Table 27). Hypotension, depression of cardiac function and worsening heart failure may

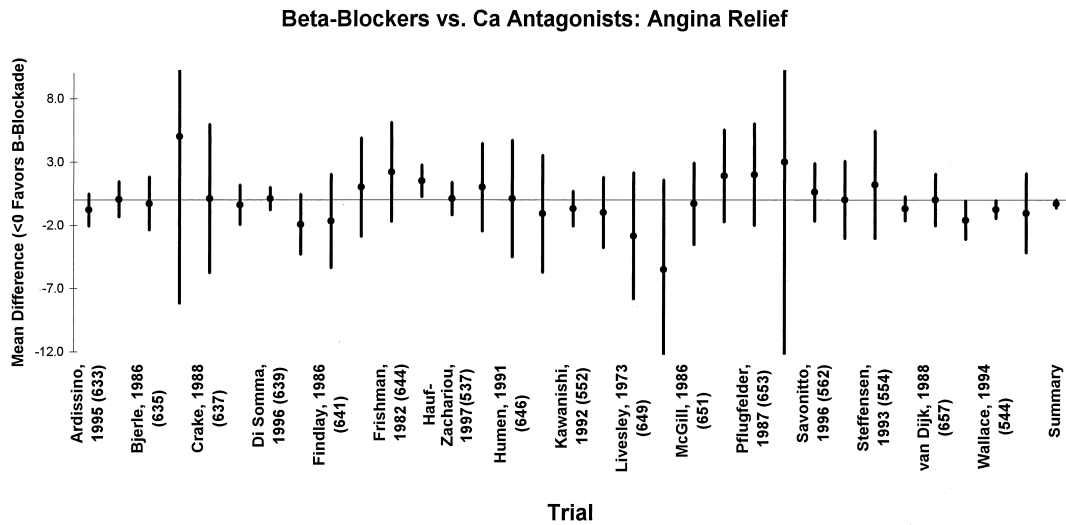


Figure 9. Beta-blockers versus calcium antagonists: angina relief.

occur during long-term treatment with any calcium antagonist. Peripheral edema and constipation are recognized side effects of all calcium antagonists. Headache, flushing, dizziness and nonspecific central nervous system symptoms may also occur. Bradycardia, AV dissociation, AV block, and sinus node dysfunction may occur with heart rate-modulating calcium antagonists. Bepridil can induce polymorphous ventricular tachycardia associated with an increased QT interval (592).

Combination Therapy With Calcium Antagonists. In general, in combination with beta-blockers, calcium antagonists

produce greater antianginal efficacy in patients with stable angina (552-556). In the IMAGE trial (562), the combination of metoprolol and nifedipine was effective in reducing the incidence of ischemia as well as improving exercise tolerance compared with either drug alone. In the TIBBS trial (561), the combination of bisoprolol and nifedipine was effective in reducing the number and duration of ischemic episodes in patients with stable angina. In the Circadian Anti-ischemic Program in Europe (CAPE) trial (593), the effect of one daily dose of amlodipine on the circadian pattern of myocardial ischemia in patients with stable

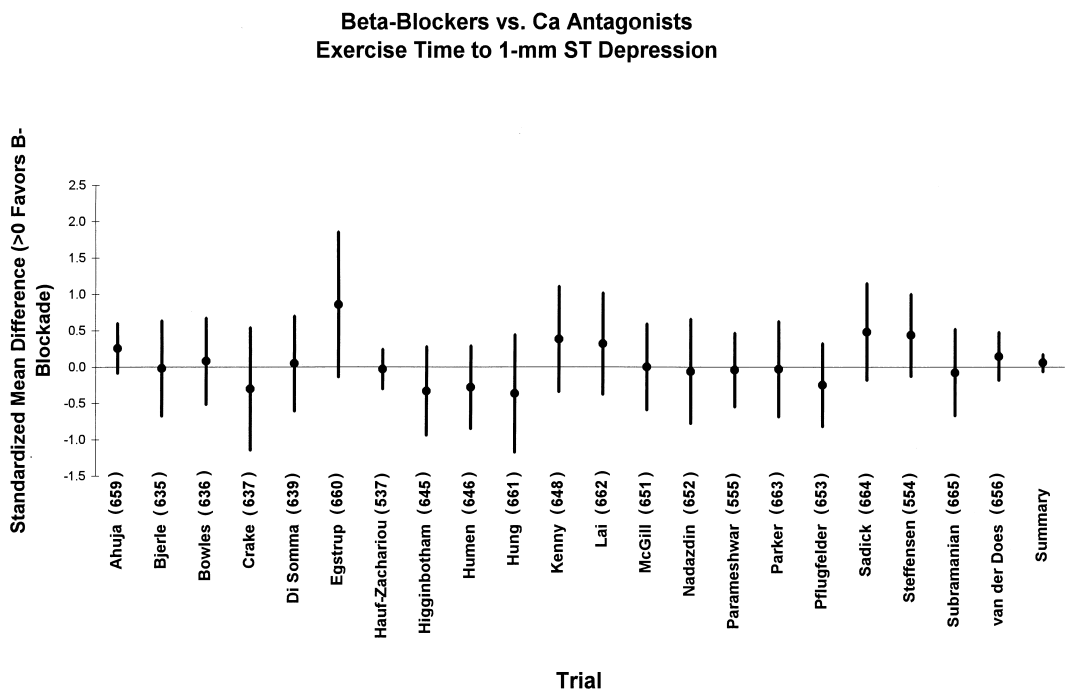


Figure 10. Beta-blockers versus calcium antagonists: exercise time to 1-mm ST depression.

Table 28. Nitroglycerin and Nitrates in Angina

Compound	Route	Dose	Duration of Effect
Nitroglycerin	Sublingual tablets	0.3-0.6 mg up to 1.5 mg	1 ¹ / ₂ -7 min
	Spray	0.4 mg as needed	Similar to sublingual tablets
	Ointment	2% 6 × 6 in., 15 × 15 cm 7.5-40 mg	Effect up to 7 h
	Transdermal	0.2-0.8 mg/h every 12 h	8-12 h during intermittent therapy
	Oral sustained release	2.5 mg-13 mg	4-8 h
	Buccal	1-3 mg 3 times daily	3-5 h
Isosorbide Dinitrate	Intravenous	5-200 mg/min	Tolerance in 7-8 h
	Sublingual	2.5-15 mg	Up to 60 min
	Oral	5-80 mg, 2-3 times daily	Up to 8 h
	Spray	1.25 mg daily	2-3 min
	Chewable	5 mg	2-2 ¹ / ₂ h
	Oral slow release	40 mg 1-2 daily	Up to 8 h
	Intravenous	1.25-5.0 mg/h	Tolerance in 7-8 h
Ointment	100 mg/24 h	Not effective	
Isosorbide Mononitrate	Oral	20 mg twice daily	12-24 h
		60-240 mg once daily	
Pentaerythritol Tetranitrate	Sublingual	10 mg as needed	Not known
Erythritol Tetranitrate	Sublingual	5-10 mg as needed	Not known
	Oral	10-30 3 times daily	Not known

angina pectoris was assessed (593). In this randomized, double-blind, placebo-controlled, multicenter trial, 315 men, aged 35 to 80 years, with stable angina, ≥ 3 attacks of angina per week, and ≥ 4 ischemic episodes during 48 h of ambulatory ECG monitoring were randomized to receive either 5 or 10 mg amlodipine per day or placebo for 8 weeks. Amlodipine was used in addition to regular antianginal therapy. There was a substantial reduction in the frequency of both symptomatic and asymptomatic ischemic episodes with the use of amlodipine. The long-acting, relatively vasoselective dihydropyridine calcium antagonists enhance antianginal efficacy in patients with stable angina when combined with beta-blockers (594-596). Maximal exercise time and work time to angina onset are increased and subjective indexes, including anginal frequency and nitroglycerin tablet consumption, decrease.

NITROGLYCERIN AND NITRATES. Mechanisms of Action. Nitrates are endothelium-independent vasodilators that produce beneficial effects by both reducing the myocardial oxygen requirement and improving myocardial perfusion (597,598). The reduction in myocardial oxygen demand and consumption results from the reduction of LV volume and arterial pressure primarily due to reduced preload. A reduction in central aortic pressure can also result from improved nitroglycerin-induced central arterial compliance. Nitro-

glycerin also exerts antithrombotic and antiplatelet effects in patients with stable angina (599). A reflex increase in sympathetic activity, which may increase heart rate and contractile state, occurs in some patients. In general, however, the net effect of nitroglycerin and nitrates is a reduction in myocardial oxygen demand.

Nitrates dilate large epicardial coronary arteries and collateral vessels. The vasodilating effect on epicardial coronary arteries with or without atherosclerotic CAD is beneficial in relieving coronary vasospasm in patients with vasospastic angina. As nitroglycerin decreases myocardial oxygen requirements and improves myocardial perfusion, these agents are effective in relieving both demand and supply ischemia.

Clinical Effectiveness. In patients with exertional stable angina, nitrates improve exercise tolerance, time to onset of angina, and ST-segment depression during the treadmill exercise test. In combination with beta-blockers or calcium antagonists, nitrates produce greater antianginal and anti-ischemic effects in patients with stable angina (564,566,600-605).

The properties of commonly used preparations available for clinical use are summarized in Table 28. Sublingual nitroglycerin tablets or nitroglycerin spray are suitable for immediate relief of effort or rest angina and can also be used

for prophylaxis to avoid ischemic episodes when used several minutes before planned exercise. As treatment to prevent the recurrence of angina, long-acting nitrate preparations such as isosorbide dinitrate, mononitrates, transdermal nitroglycerin patches and nitroglycerin ointment are used. All long-acting nitrates, including isosorbide dinitrates and mononitrates, appear to be equally effective when a sufficient nitrate-free interval is provided (606,607).

Contraindications. Nitroglycerin and nitrates are relatively contraindicated in hypertrophic obstructive cardiomyopathy, because in these patients, nitrates can increase LV outflow tract obstruction and severity of mitral regurgitation and can precipitate presyncope or syncope. In patients with severe aortic valve stenosis, nitroglycerin should be avoided because of the risk of inducing syncope. However, nitroglycerin can be used for relief of angina.

The interaction between nitrates and sildenafil is discussed in detail elsewhere (608). The coadministration of nitrates and sildenafil significantly increases the risk of potentially life-threatening hypotension. Patients who take nitrates should be warned of the potentially serious consequences of taking sildenafil within the 24-h interval after taking a nitrate preparation, including sublingual nitroglycerin.

Side Effects. The major problem with long-term use of nitroglycerin and long-acting nitrates is development of nitrate tolerance (609). Tolerance develops not only to antianginal and hemodynamic effects but also to platelet antiaggregatory effects (610). The mechanism for development of nitrate tolerance still remains unclear. The decreased availability of sulfhydryl (SH) radicals, activation of the renin-angiotensin-aldosterone system, an increase in intravascular volume due to an altered transvascular Starling gradient, and generation of free radicals with enhanced degradation of nitric oxide have been proposed. The concurrent administration of an SH donor such as SH containing ACE inhibitors, acetyl or methyl cysteine (611) and diuretics has been suggested to reduce the development of nitrate tolerance. Concomitant administration of hydralazine has also been reported to reduce nitrate tolerance. However, for practical purposes, less frequent administration of nitroglycerin with an adequate nitrate-free interval (8 to 12 h) appears to be the most effective method of preventing nitrate tolerance (553). The most common side effect during nitrate therapy is headache. Sometimes the headaches abate during long-term nitrate therapy even when antianginal efficacy is maintained. Patients may develop hypotension and presyncope or syncope (554,555). Rarely, sublingual nitroglycerin administration can produce bradycardia and hypotension, probably due to activation of the Bezold Jarish reflex.

OTHER ANTIANGINAL AGENTS AND THERAPIES. Molsidomine, a sydnonimine which has pharmacological properties similar to those of nitrates, has been shown to be beneficial in the management of symptomatic patients with chronic stable angina (612). Nicorandil, a potassium channel activator, also has pharmacologic properties similar to

those of nitrates and may be effective in treatment of stable angina (613-615). Metabolic agents such as trimetazidine, ranolazine, and L-carnitine have been observed to produce antianginal effects in some patients (616-619). Bradycardic agents such as alindine and zatebradin have been used for treatment of stable angina (620,621), but their efficacy has not been well documented (622,623). Angiotensin converting enzyme inhibitors have been investigated for treatment of stable angina, but their efficacy has not been established (624,625). The serotonin antagonist ketanserin appears not to be an effective antianginal agent (626). Labetalol, a beta- and alpha-adrenoreceptor blocking agent, has been shown to produce beneficial antianginal effects (620,627). Nonselective phosphodiesterase inhibitors such as theophylline and trapidil have been reported to produce beneficial antianginal effects (621,628). Fantofarone, a calcium antagonist, exerts an inhibitory effect on the sinus node and decreases heart rate. Like other calcium antagonists, it is a potent peripheral and coronary vasodilator. In controlled studies, its beneficial antianginal effects in patients with chronic stable angina have been observed (629). Further studies, however, will be required to determine the efficacy of these newer antianginal drugs.

Chelation therapy and acupuncture have not been found to be effective to relieve symptoms and are not recommended for treatment of chronic stable angina. Although several small observational studies have suggested benefit from enhanced external counterpulsation (630,631), the available evidence does not support a recommendation for its use. The standard use of antibiotics is also not recommended.

Choice of Pharmacologic Therapy in Chronic Stable Angina

The primary consideration in the choice of pharmacological agents for treatment of angina should be to improve prognosis. Aspirin and lipid-lowering therapy have been shown to reduce the risk of death and nonfatal MI in both primary and secondary prevention trials. These data strongly suggest that cardiac events will also be reduced among patients with chronic stable angina, an expectation corroborated by direct evidence in small, randomized trials with aspirin.

Beta-blockers also reduce cardiac events when used as secondary prevention in postinfarction patients and reduce mortality and morbidity among patients with hypertension. On the basis of their potentially beneficial effects on morbidity and mortality, beta-blockers should be strongly considered as initial therapy for chronic stable angina. They appear to be underused (632). Diabetes mellitus is not a contraindication to their use. Nitrates have not been shown to reduce mortality with acute MI or in patients with CAD. Immediate-release or short-acting dihydropyridine calcium antagonists have been reported to increase adverse cardiac events. However, long-acting or slow-release dihydropyridines, or nondihydropyridines, have the potential to relieve symptoms in

patients with chronic stable angina without enhancing the risk of adverse cardiac events. No conclusive evidence exists to indicate that either long-acting nitrates or calcium antagonists are superior for long-term treatment for symptomatic relief of angina. The committee believed that long-acting calcium antagonists are often preferable to long-acting nitrates for maintenance therapy because of their sustained 24-h effects. However, the patient's and treating physician's preferences should always be considered.

Special Clinical Situations

Newer-generation, vasoselective, long-acting dihydropyridine calcium antagonists such as amlodipine or felodipine can be used in patients with depressed LV systolic function. In patients who have sinus node dysfunction, rest bradycardia, or AV block, beta-blockers or heart rate-modulating calcium antagonists should be avoided. In patients with insulin-dependent diabetes, beta-blockers should be used with caution because they can mask hypoglycemic symptoms. In patients with mild peripheral vascular disease, there is no contraindication for use of beta-blockers or calcium antagonists. However, in patients with severe peripheral vascular disease with ischemic symptoms at rest, it is desirable to avoid beta-blockers, and calcium antagonists are preferred. In patients with hypertrophic obstructive cardiomyopathy, the use of nitrates and dihydropyridine calcium antagonists should be avoided. In these patients, beta-blockers or heart rate-modulating calcium antagonists may be useful. In patients with severe aortic stenosis, all vasodilators, including nitrates, should be used cautiously because of the risk of inducing hypotension and syncope. Associated conditions that influence the choice of therapy are summarized in Table 29.

Patients with angina may have other cardiac conditions, e.g., CHF, that will require other special treatment, such as diuretics and ACE inhibitors. These issues are covered in other ACC/AHA guidelines.

B. Definition of Successful Treatment and Initiation of Treatment

Successful Treatment

Definition of Successful Treatment of Chronic Stable Angina

The treatment of chronic stable angina has two complementary objectives: to reduce the risk of mortality and morbid events and reduce symptoms. From the patient's perspective, it is often the latter that is of greater concern. The cardinal symptom of stable CAD is anginal chest pain or equivalent symptoms such as exertional dyspnea. Often the patient suffers not only from the discomfort of the symptom itself but also from accompanying limitations on activities and the associated anxiety that the symptoms may produce. Uncertainty about prognosis may be an additional source of anxiety. For some patients, the predominant

symptoms may be palpitations or syncope that are caused by arrhythmias or fatigue, edema or orthopnea caused by heart failure.

Because of the variation in symptom complexes among patients and patients' unique perceptions, expectations and preferences, it is impossible to create a definition of treatment success that is universally accepted. For example, given an otherwise healthy, active patient, the treatment goal may be complete elimination of chest pain and a return to vigorous physical activity. Conversely, an elderly patient with more severe angina and several coexisting medical problems may be satisfied with a reduction in symptoms that enables performance of only limited activities of daily living.

The committee agreed that for most patients, the goal of treatment should be complete, or nearly complete, elimination of anginal chest pain and return to normal activities and a functional capacity of CCS class I angina. This goal should be accomplished with minimal side effects of therapy. This definition of successful therapy must be modified in light of the clinical characteristics and preferences of each patient.

Initial Treatment

The initial treatment of the patient should include all the elements in the following mnemonic:

- | |
|--|
| <p>A = Aspirin and Antianginal therapy
B = Beta-blocker and Blood pressure
C = Cigarette smoking and Cholesterol
D = Diet and Diabetes
E = Education and Exercise</p> |
|--|

In constructing a flow diagram to reflect the treatment process, the committee thought that it was clinically helpful to divide the entire treatment process into two parts: 1) antianginal treatment and 2) education and risk factor modification. The assignment of each treatment element to one of these two subdivisions is self-evident, with the possible exception of aspirin. Given the fact that aspirin clearly reduces the risk of subsequent heart attack and death but has no known benefit in preventing angina, the committee thought that it was best assigned to the education and risk factor component, as reflected in the flow diagram.

All patients with angina should receive a prescription for sublingual nitroglycerin and education about its proper use. It is particularly important for patients to recognize that this is a short-acting drug with no known long-term consequences so that they will not be reluctant to use it.

If the patient's history has a prominent feature of rest and nocturnal angina suggesting vasospasm, initiation of therapy with long-acting nitrates or calcium antagonists is appropriate.

Table 29. Recommended Drug Therapy (Calcium Antagonist vs. Beta-Blocker) in Patients With Angina and Associated Conditions

Condition	Recommended Treatment (and Alternative)	Avoid
Medical Conditions		
Systemic hypertension	Beta-blockers (calcium antagonists)	
Migraine or vascular headaches	Beta-blockers (verapamil or diltiazem)	
Asthma or chronic obstructive pulmonary disease with bronchospasm	Verapamil or diltiazem	Beta-blockers
Hyperthyroidism	Beta-blockers	
Raynaud's syndrome	Long-acting slow-release calcium antagonists	Beta-blockers
Insulin-dependent diabetes mellitus	Beta-blockers (particularly if prior myocardial infarction) or long-acting slow-release calcium antagonists	
Non-insulin-dependent diabetes mellitus	Beta blockers or long-acting slow-release calcium antagonists	
Depression	Long-acting slow-release calcium antagonists	Beta-blockers
Mild peripheral vascular disease	Beta-blockers or calcium antagonists	
Severe peripheral vascular disease with rest ischemia	Calcium antagonists	Beta-blockers
Cardiac Arrhythmias and Conduction Abnormalities		
Sinus bradycardia	Long-acting slow-release calcium antagonists that do not decrease heart rate	Beta-blockers, diltiazem, verapamil
Sinus tachycardia (not due to heart failure)	Beta-blockers	
Supraventricular tachycardia	Verapamil, diltiazem, or beta-blockers	
Atrioventricular block	Long-acting slow-release calcium antagonists that do not slow A-V conduction	Beta-blockers, verapamil, diltiazem
Rapid atrial fibrillation (with digitalis)	Verapamil, diltiazem, or beta-blockers	
Ventricular arrhythmias	Beta blockers	
Left Ventricular Dysfunction		
Congestive heart failure		
Mild (LVEF \geq 40%)	Beta-blockers	
Moderate to severe (LVEF < 40%)	Amlodipine or felodipine (nitrates)	Verapamil, diltiazem
Left-sided valvular heart disease		
Mild aortic stenosis	Beta-blockers	
Aortic insufficiency	Long-acting slow-release dihydropyridines	
Mitral regurgitation	Long-acting slow-release dihydropyridines	
Mitral stenosis	Beta-blockers	
Hypertrophic cardiomyopathy	Beta-blockers, non-dihydropyridine calcium antagonist	Nitrates, dihydropyridine calcium antagonists

As mentioned previously, medications or conditions that are known to provoke or exacerbate angina must be recognized and treated appropriately. On occasion, angina may resolve with appropriate treatment of these conditions. If so, no further antianginal therapy is required. Usually, anginal symptoms improve but are not relieved by the treatment of such conditions, and further therapy should then be initiated.

The committee favored the use of a beta-blocker as initial therapy in the absence of contraindications. The evidence for this approach is strongest in the presence of prior MI, for which this class of drugs has been shown to reduce mortality. Because these drugs have also been shown to reduce mortality in the treatment of isolated hypertension, the committee favored their use as initial therapy even in the absence of prior MI.

If serious contraindications with beta-blockers exist, unacceptable side effects occur with their use, or angina persists despite their use, calcium antagonists should then be administered.

If serious contraindications to calcium antagonists exist, unacceptable side effects occur with their use, or angina persists despite their use, long-acting nitrate therapy should then be prescribed.

At any point, on the basis of coronary anatomy, severity of anginal symptoms and patient preferences, it is reasonable to consider evaluation for coronary revascularization. As discussed in the revascularization section, certain categories of patients, a minority of the total group, have a demonstrated survival advantage with revascularization. However, for most patients, for whom no demonstrated

survival advantage is associated with revascularization, medical therapy should be attempted before angioplasty or surgery is considered. The extent of the effort that should be undertaken with medical therapy obviously depends on the individual patient. In general, the committee thought that low-risk patients should be treated with at least two, and preferably all three, available classes of drugs before medical therapy is considered a failure.

C. Education of Patients With Chronic Stable Angina

Because the presentation of ischemic heart disease is often dramatic and because of impressive recent technological advances, healthcare providers tend to focus on diagnostic and therapeutic interventions, often overlooking critically important aspects of high-quality care. Chief among these neglected areas is the education of patients. In the 1995 National Ambulatory Medical Care Survey (666), counseling about physical activity and diet occurred during only 19% and 23%, respectively, of general medical visits. This shortcoming was observed across specialties, including cardiology, internal medicine and family practice.

Effective education is critical to enlisting patients' full and meaningful participation in therapeutic and preventive efforts and in allaying their natural concerns and anxieties. This in turn is likely to lead to a patient who not only is better informed and more satisfied with his or her care but who is also able to achieve a better quality of life and improved survival (667-669).

Patient education should be viewed as a continuous process that ought to be part of every patient encounter. It is a process that must be individualized so that information is presented at appropriate times and in a manner that is readily understandable. It is frequently advisable to address patients' overriding concerns initially, for example, their short-term prognosis. In directly addressing worrisome issues, it is possible to put patients more at ease and make them more receptive to addressing other issues, such as modification of risk factors. This is true even when the short-term prognosis cannot be fully addressed until additional testing has been conducted.

It is also essential to recognize that adequate education is likely to lead to better adherence to medication regimens and programs for risk factor reduction. Even brief suggestions from a physician about exercise or smoking cessation can have a meaningful effect (670,671). Moreover, an informed patient will be better able to understand treatment decisions and express preferences that are an important component of the decision-making process (672).

Principles of Patient Education

A thorough discussion of the philosophies of and approaches to patient education is beyond the scope of this section. There are several useful reviews on this topic, including several that focus on ischemic heart disease (673-675). It has been demonstrated that well-designed educational programs can improve patients' knowledge and

in some instances has been shown to improve outcomes (676). These approaches form the basis for commonly used educational programs, such as those conducted before CABG (677) and after MI (678,679). A variety of principles should be followed to help ensure that educational efforts are successful.

1. Assess the patient's baseline understanding. This serves not only to help establish a starting point for education but also helps to engage the patient. Healthcare providers are often surprised at the idiosyncratic notions that patients have about their own medical conditions and therapeutic approaches (680,681).
2. Elicit the patient's desire for information. Adults prefer to set their own agendas, and they learn better when they can control the flow of information.
3. Use epidemiologic and clinical evidence. As clinical decision making becomes increasingly based on scientific evidence, it is reasonable to share that evidence with patients. Epidemiologic data can assist in formulating an approach to patient education. In many patients, for example, smoking reduction/cessation is likely to confer a greater reduction in risk than treatment of modestly elevated lipid levels; thus, smoking should be addressed first. Scientific evidence can help persuade patients about the effectiveness of various interventions.
4. Use ancillary personnel and professional patient educators when appropriate. One reason that physicians often fail to perform adequate patient education is that the time available for a patient encounter is constrained, and education must be performed along with a long list of other tasks. Reimbursement for educational activities is poor. Furthermore, physicians are not trained to be effective health educators, and many feel uncomfortable in this role. Fortunately, in many settings, trained health educators, such as those specializing in diabetes or cardiac disease, are available. Personnel from related disciplines such as physical therapy, nutrition, pharmacology, and so forth also have much to offer patients with ischemic heart disease (682).
5. Use professionally prepared resources when available. A vast array of informational materials and classes are available to assist with patient education. These materials include books, pamphlets and other printed materials, audiotapes and videotapes, computer software, and most recently, sites on the World Wide Web. The latter source is convenient for medical personnel and patients with access to personal computers. The AHA, for example, maintains a Web site (<http://www.americanheart.org>) that presents detailed and practical dietary recommendations, information about physical activity, and a thorough discussion of heart attacks and CPR. There also are links to other

Web sites, such as the National Cholesterol Education Program. For patients who do not have access to a computer, work stations can be set up in the clinic or physician's office, relevant pages can be printed or patients can be referred to hospital or public libraries.

6. Develop a plan with the patient. It is necessary to convey a great deal of information to patients about their condition. It is advisable to hold discussions over time, taking into consideration many factors, which include the patient's level of sophistication and prior educational attainment, language barriers, relevant clinical factors and social support. For example, it might be counterproductive to attempt to coax a patient into simultaneously changing several behaviors, such as smoking, diet, exercise and taking (and purchasing) multiple new medications. Achieving optimal adherence often requires problem solving with the patient. To improve compliance with medications, the healthcare provider may need to spend time understanding the patient's schedule and suggesting strategies such as placing pill containers by the toothbrush or purchasing a watch with multiple alarms to serve as reminders.
7. Involve family members in educational efforts. It is advisable and often necessary to include family members in educational efforts. Many topics such as dietary changes require the involvement of the person who actually prepares the meals. Efforts to encourage smoking cessation or weight loss or increase physical activity may be enhanced by enlisting the support of family members who can reinforce messages and may themselves benefit from participation.
8. Remind, repeat, and reinforce. Almost all learning deteriorates without reinforcement. At regular intervals, the patients' understanding should be reassessed, and key information should be repeated as warranted. Patients should be congratulated for progress even when their ultimate goals are not fully achieved. Even though the patient who has reduced his or her use of cigarettes from two packs to one pack per day has not quit smoking, that 50% reduction in exposure is important and may simply represent a milestone on the path to complete cessation.

Information for Patients

There is a great deal of information that patients with ischemic heart disease want to and should learn. This information falls into the categories listed in the following section.

General Aspects of Ischemic Heart Disease

PATHOLOGY AND PATHOPHYSIOLOGY. Patients vary in the level of detail they want to know about ischemic heart disease. Because therapy for angina is closely tied to the underlying pathophysiology, an understanding of these

derangements and the effects of medications or interventions often helps patients to comply with therapy. Patients are often interested in learning about their own coronary anatomy and its relationship to cardiac events (683).

RISK FACTORS. It is useful to review the important known risk factors.

COMPLICATIONS. Some patients may want to know about the potential complications of ischemic heart disease, such as unstable angina, MI, heart failure, arrhythmia and sudden cardiac death.

Patient-Specific Information

PROGNOSIS. Most patients are keenly interested in understanding their own risk of complications, especially in the short term. To the extent possible, it is useful to provide numerical estimates for risk of infarction or death from cardiovascular events because many patients assume that their short-term prognosis is worse than it actually is.

TREATMENT. Patients should be informed about their medications, including mechanisms of action, method of administration, and potentially adverse effects. It is helpful to be as specific as possible and to tie this information in with discussions of pathophysiology. For example, it can be explained that aspirin reduces platelet aggregation and prevents clot formation or that beta-blockers reduce myocardial oxygen demand. Patients should be carefully instructed about how and when to take their medications. For example, they should be told exactly when to take sublingual nitrates (i.e., immediately when pain begins or before stressful activity), how often (i.e., three times spaced five minutes apart if pain persists) and to sit down before taking the medication. Complete explanations of other tests and interventions should also be provided.

PHYSICAL ACTIVITY. The healthcare provider should have an explicit discussion with all patients about any limitations on physical activity. For most patients, this will consist of reassurance about their ability to continue normal activities, including sexual relations (684). Patients in special circumstances, for example, those who engage in extremely strenuous activity or have a high-risk occupation, may require special counseling. As mentioned previously, men with impotence who are considering the use of sildenafil should be warned of the potentially serious consequences of using both sildenafil and nitrates within 24 h of one another (608).

RISK FACTOR REDUCTION. It is essential that individual risk factors be reviewed with every patient. To engage patients in an effective program of behavioral change that will lessen the probability of subsequent cardiovascular events, a clear understanding of their relevant risk factors is required. The greatest emphasis should be placed on modifiable factors, beginning with those that have the greatest potential for reducing risk or are most likely to be favorably influenced.

For example, for an obese smoker, a greater initial reduction in risk would likely be realized through attention to smoking cessation than by pursuit of significant weight reduction.

CONTACTING THE MEDICAL SYSTEM. It is critically important that all patients and their families be clearly instructed about how and when to seek medical attention. In many communities, a major obstacle to effective therapy for acute coronary events is the failure of patients to promptly activate the emergency medical system (685,686). Patients should be given an action plan that covers 1) prompt use of aspirin and nitroglycerin if available, 2) how to access emergency medical services, and 3) location of the nearest hospital that offers 24-h emergency cardiovascular care. Reviewing the description of possible symptoms of myocardial infarction and the action plan in simple, understandable terms at each visit is extremely important. Discussions with patients and family members should emphasize the importance of acting promptly.

OTHER INFORMATION. In individual circumstances, special counseling is warranted. One quarter million people with ischemic heart disease die suddenly each year (687). For this reason, in many patients, CPR training for family members is advisable. Although some may find this anxiety-provoking, others appreciate having the potential to intervene constructively and not feel helpless if cardiac arrest occurs (688). Patients and their families should also be counseled when a potentially heritable condition such as familial hypercholesterolemia is responsible for premature coronary disease.

In summary, patient education requires a substantial investment in time by primary-care providers and specialists using an organized and thoughtful approach. The potential rewards for patients are also substantial in terms of improved quality of life, satisfaction, and adherence to medical therapy. As a result, many should also have improved physical function and survival.

D. Coronary Disease Risk Factors and Evidence That Treatment Can Reduce the Risk for Coronary Disease Events

Recommendations for Treatment of Risk Factors

Class I

1. Treatment of hypertension according to Joint National Conference VI guidelines. (*Level of Evidence: A*)
2. Smoking cessation therapy. (*Level of Evidence: B*)
3. Management of diabetes. (*Level of Evidence: C*)
4. Exercise training program. (*Level of Evidence: B*)
5. Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol ≥ 130 mg/dL, with a target LDL of < 100 mg/dL. (*Level of Evidence: A*)

6. Weight reduction in obese patients in the presence of hypertension, hyperlipidemia, or diabetes mellitus. (*Level of Evidence: C*)

Class IIa

Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol 100 to 129 mg/dL, with a target LDL < 100 mg/dL. (*Level of Evidence: B*)

Class IIb

1. Hormone replacement therapy in postmenopausal women in the absence of contraindications. (*Level of Evidence: B*)
2. Weight reduction in obese patients in the absence of hypertension, hyperlipidemia or diabetes mellitus. (*Level of Evidence: C*)
3. Folate therapy in patients with elevated homocysteine levels. (*Level of Evidence: C*)
4. Vitamin C and E supplementation. (*Level of Evidence: B*)
5. Identification and appropriate treatment of clinical depression. (*Level of Evidence: C*)
6. Intervention directed at psychosocial stress reduction. (*Level of Evidence: C*)

Class III

1. Chelation therapy. (*Level of Evidence: C*)
2. Garlic. (*Level of Evidence: C*)
3. Acupuncture. (*Level of Evidence: C*)

Categorization of Coronary Disease Risk Factors

The 27th Bethesda Conference proposed the following categorization of CAD risk factors based both on the strength of evidence for causation and the evidence that risk factor modification can reduce risk for clinical CAD events (688). Of note, evidence of benefit from treating these risk factors comes from observational studies and clinical trials. Secondary prevention trials providing evidence of benefit from risk factor modification are identified, but rarely have such trials been limited to patients with chronic stable angina. Consequently, recommendations about risk factor treatment in patients with chronic stable angina are based largely on inference from primary and secondary intervention studies.

Category

- I. Risk factors clearly associated with an increase in coronary disease risk for which interventions have been shown to reduce the incidence of coronary disease events.
- II. Risk factors clearly associated with an increase in coronary disease risk for which interventions are likely to reduce the incidence of coronary disease events.
- III. Risk factors clearly associated with an increase in coronary disease risk for which interventions

might reduce the incidence of coronary disease events.

IV. Risk factors associated with an increase in coronary disease risk but which cannot be modified or the modification of which would be unlikely to change the incidence of coronary disease events.

Risk Factors for Which Interventions Have Been Shown to Reduce the Incidence of Coronary Disease Events

Category I risk factors must be identified and, when present, treated as part of an optimal secondary prevention strategy in patients with chronic stable angina (see Fig. 11). They are common in this patient population and readily amenable to modification, and their treatment can have a favorable effect on clinical outcome. For these reasons, they are discussed in greater detail than other risk factors.

Cigarette Smoking

The evidence that cigarette smoking increases the risk for cardiovascular disease events is based primarily on observational studies, which have provided overwhelming support for such an association (690). The 1989 Surgeon General's report concluded, on the basis of case-control and cohort studies, that smoking increased cardiovascular disease mortality by 50% (691). A dose-response relationship has been reported between cigarettes smoked and cardiovascular disease risk in men (692) and women (693), with relative risks approaching 5.5 for fatal cardiovascular disease events among heavy smokers compared with nonsmokers (693). Smoking also amplifies the effect of other risk factors, thereby promoting acute cardiovascular events (694). Events related to thrombus formation, plaque instability and arrhythmias are all influenced by cigarette smoking. A smoking history should be obtained in all patients with coronary disease as part of a stepwise strategy aimed at smoking cessation (Table 30).

The 1990 Surgeon General's report (695) summarized clinical data which strongly suggest that smoking cessation reduces the risk of cardiovascular events. Prospective cohort studies show that the risk of MI declines rapidly in the first several months after smoking cessation. Patients who continue to smoke after acute MI have an increase in the risk of reinfarction and death; the increase in risk of death has ranged from 22% to 47%. Smoking also has been implicated in coronary bypass graft atherosclerosis and thrombosis. Continued smoking after bypass grafting is associated with a two-fold increase in the relative risk of death and an increase in nonfatal MI and angina.

Randomized clinical trials of smoking cessation have not been performed in patients with chronic stable angina. Three randomized smoking cessation trials have been performed in a primary prevention setting (696-698). Smoking cessation was associated with a reduction of 7% to 47%

in cardiac event rates in these trials. The rapidity of risk reduction after smoking cessation is consistent with the known adverse effects of smoking on fibrinogen levels (699) and platelet adhesion (700). Other rapidly reversible effects of smoking include increased blood carboxyhemoglobin levels, reduced HDL cholesterol (701), and coronary artery vasoconstriction (702).

Patients with symptomatic coronary disease form the group most receptive to treatment directed to smoking cessation. Taylor and coworkers (703) have shown that $\leq 32\%$ of patients will stop smoking at the time of a cardiac event and that this rate can be significantly enhanced to 61% by a nurse-managed smoking cessation program. New behavioral and pharmacologic approaches to smoking cessation are available for use by trained healthcare professionals (703). Few physicians are adequately trained in smoking-cessation techniques. Identification of experienced allied healthcare professionals who can implement smoking cessation programs for patients with coronary disease is a priority. The importance of a structured approach cannot be overemphasized. The rapidity and magnitude of risk reduction, as well as the other health-enhancing benefits of smoking cessation, argue for the incorporation of smoking cessation in all programs of secondary prevention of coronary disease.

LDL Cholesterol

Total cholesterol level has been linked to the development of CAD events with a continuous and graded relation, beginning at levels of <180 mg/dL (704,705). Most of this risk is due to LDL cholesterol. Evidence linking LDL cholesterol and CAD is derived from extensive epidemiologic, laboratory and clinical trial data. Epidemiologic studies indicate a 2% to 3% increase in risk for coronary events per 1% increase in LDL-cholesterol level (706). Measurement of LDL cholesterol is warranted in all patients with coronary disease.

Evidence that LDL cholesterol plays a causal role in the pathogenesis of atherosclerotic coronary disease comes from randomized, controlled clinical trials of lipid-lowering therapy. Several primary and secondary prevention trials have shown that LDL-cholesterol lowering is associated with a reduced risk of coronary disease events. Earlier lipid-lowering trials used bile-acid sequestrants (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate) or niacin in addition to diet. The reduction in total cholesterol in these early trials was 6% to 15% and was accompanied by a consistent trend toward a reduction in fatal and nonfatal coronary events. In seven of the early trials, the reduction in coronary events was statistically significant. Although the pooled data from these studies suggested that every 1% reduction in total cholesterol could reduce coronary events by 2%, the reduction in clinical events was 3% for every 1% reduction in total cholesterol in studies lasting ≥ 5 years.

Angiographic trials, for which a much smaller number of participants are required, provide firm evidence linking

Risk Intervention	Recommendations																												
Smoking: <u>Goal</u> complete cessation	Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, and formal cessation programs as appropriate.																												
Lipid Management: <u>Primary goal</u> LDL<100 mg/dL <u>Secondary goals</u> HDL>35 mg/dL; TG<200 mg/dL	Start AHA Step II Diet in all patients: ≤30% fat, <7% saturated fat, <200 mg/dL cholesterol. Assess fasting lipid profile. In post-MI patients, lipid profile may take 4 to 6 weeks to stabilize. Add drug therapy according to the following guide: <table border="1" data-bbox="440 506 1361 898"> <tr> <td data-bbox="440 506 613 590">LDL<100 mg/dL No drug therapy</td> <td data-bbox="613 506 793 590">LDL 100 to 130 mg/dL Consider adding drug therapy to diet, as follows:</td> <td data-bbox="793 506 1154 590">LDL>130 mg/dL Add drug therapy to diet, as follows:</td> <td colspan="2" data-bbox="1154 506 1361 590">HDL<35 mg/dL Emphasize weight management and physical activity.</td> </tr> <tr> <td colspan="4" data-bbox="440 590 1154 684" style="text-align: center;"> Suggested drug therapy </td> <td data-bbox="1154 590 1361 684" rowspan="4"> Advise smoking cessation. If needed to achieve LDL goals, consider niacin, statin, fibrate. </td> </tr> <tr> <td data-bbox="440 684 613 758">TG <200 mg/dL</td> <td data-bbox="613 684 793 758">TG 200 to 400 mg/dL</td> <td data-bbox="793 684 1154 758">TG >400 mg/dL</td> <td colspan="2" data-bbox="1154 684 1361 758"></td> </tr> <tr> <td data-bbox="440 758 613 842">Statin Resin Niacin</td> <td data-bbox="613 758 793 842">Statin Niacin</td> <td data-bbox="793 758 1154 842">Consider combined drug therapy (niacin, fibrate, statin)</td> <td colspan="2" data-bbox="1154 758 1361 842"></td> </tr> <tr> <td colspan="4" data-bbox="440 842 1154 898" style="text-align: center;"> If LDL goal not achieved, consider combination therapy. </td> <td data-bbox="1154 842 1361 898"></td> </tr> </table>				LDL<100 mg/dL No drug therapy	LDL 100 to 130 mg/dL Consider adding drug therapy to diet, as follows:	LDL>130 mg/dL Add drug therapy to diet, as follows:	HDL<35 mg/dL Emphasize weight management and physical activity.		Suggested drug therapy				Advise smoking cessation. If needed to achieve LDL goals, consider niacin, statin, fibrate.	TG <200 mg/dL	TG 200 to 400 mg/dL	TG >400 mg/dL			Statin Resin Niacin	Statin Niacin	Consider combined drug therapy (niacin, fibrate, statin)			If LDL goal not achieved, consider combination therapy.				
LDL<100 mg/dL No drug therapy	LDL 100 to 130 mg/dL Consider adding drug therapy to diet, as follows:	LDL>130 mg/dL Add drug therapy to diet, as follows:	HDL<35 mg/dL Emphasize weight management and physical activity.																										
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TG <200 mg/dL	TG 200 to 400 mg/dL	TG >400 mg/dL																											
Statin Resin Niacin	Statin Niacin	Consider combined drug therapy (niacin, fibrate, statin)																											
If LDL goal not achieved, consider combination therapy.																													
Physical activity: <u>Minimum goal</u> 30 minutes 3 to 4 times per week	Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30 to 60 minutes of moderate-intensity activity 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, using stairs, gardening, household work). Maximum benefit 5 to 6 hours a week. Advise medically supervised programs for moderate- to high-risk patients.																												
Weight management:	Start intensive diet and appropriate physical activity intervention, as outlined above, in patients >120% of ideal weight for height. Particularly emphasize need for weight loss in patients with hypertension, elevated triglycerides, or elevated glucose levels.																												
Antiplatelet agents/ anticoagulants:	Start aspirin 80 to 325 mg/d if not contraindicated. Consider clopidogrel as an alternative if aspirin contraindicated. Manage warfarin to international normalized ratio=2 to 3.5 for post-MI patients not able to take aspirin or clopidogrel.																												
ACE inhibitors post-MI:	Start early post-MI in stable high-risk patients (anterior MI, previous MI, Killip class II [S ₃ gallop, rales, radiographic CHF]). Continue indefinitely for all with LV dysfunction (ejection fraction ≤40) or symptoms of failure. Use as needed to manage blood pressure or symptoms in all other patients.																												
Beta-blockers:	Start in most post-MI patients (arrhythmia, LV dysfunction, inducible ischemia) at 5 to 28 days. Continue 6 months minimum. Observe usual contraindications. Use as needed to manage angina, rhythm, or blood pressure in all other patients.																												
Estrogens:	Consider estrogen replacement in all postmenopausal women. Individualize recommendation consistent with other health risks.																												
Blood pressure control:* <u>Goal</u> ≤130/85 mm Hg	Initiate lifestyle modification—weight control, physical activity, alcohol moderation, and moderate sodium restriction—in all patients with blood pressure >130 mm Hg systolic or 85 mm Hg diastolic (drug therapy of diabetes, renal failure or heart failure). Add blood pressure medication, individualized to other patient requirements and characteristics (ie, age, race, need for drugs with specific benefits) if blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic.																												

Figure 11. Guide to comprehensive risk reduction for patients with coronary and other vascular disease. ACE = angiotensin-converting enzyme; AHA = American Heart Association; CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; MI = myocardial infarction; and TG = triglycerides. *National High Blood Pressure Education Program and National Cholesterol Education Program recommend new blood pressure levels that should trigger treatment: <130/85, life changes (plus medications when diabetes, CHF or renal failure are present); ≤140/90, life changes and medications. This figure has been updated to reflect this new information and the use of clopidogrel as an alternative to aspirin when the latter is contraindicated. Adapted from Smith et al. (716).

cholesterol reduction to favorable trends in coronary anatomy. In virtually all studies, the active treatment groups experienced less progression, more stabilization of lesions,

and more regression than the control groups. More importantly, these trends toward more favorable coronary anatomy were linked to reductions in clinical events. A meta-

Table 30. Smoking Cessation for the Primary Care Clinician

Strategy 1. Ask—systematically identify all tobacco users at every visit

- Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.

Strategy 2. Advise—strongly urge all smokers to quit

- In a clear, strong, and personalized manner, urge every smoker to quit.

Strategy 3. Identify smokers willing to make a quit attempt

- Ask every smoker if he or she is willing to make a quit attempt at this time.

Strategy 4. Assist—aid the patient in quitting

- Help the patient with a quit plan.
- Encourage nicotine replacement therapy or bupropion except in special circumstances.
- Give key advice on successful quitting.
- Provide supplementary materials.

Strategy 5. Arrange—schedule follow-up contact

- Schedule follow-up contact, either in person or via telephone.

Modified from Fiore MC, Bailey WC, Cohen JJ, et al. Smoking Cessation. Clinical Practice Guideline Number 18. AHCPR Publication No. 96-0692. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, 1996.

analysis (707) of >2,000 participants in 14 trials suggests that both LDL and HDL were important contributors to the beneficial effects.

The most recent studies of lipid-lowering therapy involve the HMG-CoA reductase inhibitors. A reduction in clinical events has been demonstrated in both primary and secondary prevention settings. Among the most conclusive secondary prevention trials to evaluate the effects of cholesterol lowering on clinical events were 4S (533) and CARE (534). In the 4S trial, mean changes with simvastatin in total cholesterol (−25%), LDL cholesterol (−35%), and HDL cholesterol (+8%) were statistically significant. These changes in blood lipids were associated with reductions of 30% to 35% in both mortality rate and major coronary events. Reductions in clinical events were noted in patients with LDL-cholesterol levels in the lower quartiles at baseline, women, and patients >60 years old. The study also demonstrated that long-term (five-year) administration of an HMG-CoA reductase-inhibiting drug was safe and there was no increase in non-CHD death. In the CARE study, 4,159 patients (3,583 men and 576 women) with prior MI who had plasma total cholesterol levels <240 mg/dL (mean 209) and LDL-cholesterol levels of 115 to 174 mg/dL (mean 139) were randomized to receive pravastatin or placebo. Active treatment was associated with a 24% reduction in risk (95% CI interval, 9% to 36%; $p = 0.003$) for nonfatal MI or a fatal coronary event.

The clinical trial data indicate that in patients with established coronary disease, including chronic stable angina pectoris, dietary intervention and treatment with lipid-lowering medications should not be limited to those with extreme values. The benefits of lipid-lowering therapy were evident in patients in the lowest baseline quartile of LDL cholesterol (modest elevations) in 4S and in those with minimal elevation of LDL-cholesterol level in the CARE study. These trials establish the benefits of aggressive lipid-lowering treatment for the most coronary disease patients, even when LDL cholesterol is within a range considered acceptable for patients in a primary prevention setting. For patients with established coronary disease, nonpharmaceutical treatment should be initiated when LDL cholesterol is >100 mg/dL, and drug treatment is warranted when LDL cholesterol is >130 mg/dL. The goal of treatment is an LDL-cholesterol level ≤ 100 mg/dL.

Finally, despite LDL-cholesterol reduction, arteriographic progression continues in many patients with coronary disease. Arteriographic trials demonstrate continued coronary lesion progression in 25% to 60% of subjects even with the most aggressive LDL-cholesterol lowering. Maximum benefit may require management of other lipid abnormalities (elevated triglycerides, low HDL cholesterol) and treatment of other atherogenic risk factors.

Hypertension

Data from numerous observational studies indicate a continuous and graded relation between blood pressure and cardiovascular disease risk (708,709). A meta-analysis by MacMahon and colleagues (710) of nine prospective, observational studies involving >400,000 subjects showed a strongly positive relationship between both systolic and diastolic blood pressure and CHD; the relationship was linear without a threshold effect and showed a relative risk that approached 3.0 at the highest pressures.

Hypertension probably predisposes patients to coronary events both as a result of the direct vascular injury caused by increases in blood pressure and its effects on the myocardium, including increased wall stress and myocardial oxygen demand.

The first and second Veterans Affairs Cooperative studies (711,712) were the first to definitively demonstrate the benefits of hypertension treatment. A meta-analysis of 17 randomized trials of therapy in >47,000 patients confirmed the beneficial effects of hypertension treatment on cardiovascular disease risk (713). More recent trials in older patients with systolic hypertension have underscored the benefits to be derived from blood pressure lowering in the elderly. A recent meta-analysis found that the absolute reduction of coronary events in older subjects (2.7/1,000 person-years) was more than twice as great as that in younger subjects (1.0/1,000 person-years) (714). This finding contrasts with clinical practice, in which hypertension often is less aggressively treated in older persons.

Clinical trial data on the effects of blood pressure lowering in hypertensive patients with established coronary disease are lacking. Nevertheless, blood pressure should be measured in all patients with coronary disease.

Hypertension Treatment

The National High Blood Pressure Education Program Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (21) recently recommended a system for categorizing levels of blood pressure and risk classes. Hypertension is present when the average blood pressure is ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic. High normal blood pressure is present when the systolic blood pressure is 130 to 139 mm Hg or diastolic pressure is 85 to 89 mm Hg. The level of blood pressure and the concomitant presence of risk factors, coexisting cardiovascular disease, or evidence of target-organ damage are used in the classification of blood pressure severity and to guide treatment. Coronary disease, diabetes, LV hypertrophy, heart failure, retinopathy and nephropathy are indicators of increased cardiovascular disease risk. The target of therapy is a reduction in blood pressure to < 130 mm Hg systolic and < 85 mm Hg diastolic in patients with coronary disease and coexisting diabetes, heart failure or renal failure and $< 140/90$ mm Hg in the absence of these coexisting conditions.

Hypertensive patients with chronic stable angina are at high risk for cardiovascular disease morbidity and mortality. The benefits and safety of hypertension treatment in such patients have been established (715,716). Treatment begins with nonpharmacologic means. When lifestyle modifications and dietary alterations adequately reduce blood pressure, pharmacologic intervention may be unnecessary. The modest benefit of antihypertensive therapy for coronary event reduction in clinical trials may underestimate the efficacy of this therapy in hypertensive patients with established coronary disease because in general, the higher the absolute risk of the population, the greater the magnitude of response to therapy.

Lowering the blood pressure too rapidly, especially when it precipitates reflex tachycardia and sympathetic activation, should be avoided. Blood pressure should be lowered to $< 140/90$ mm Hg, and even lower blood pressure is desirable if angina persists. When pharmacologic treatment is necessary, beta-blockers or calcium channel antagonists may be especially useful in patients with hypertension and angina pectoris; however, short-acting calcium antagonists should not be used (581,582,717). In patients with chronic stable angina who have had a prior MI, beta-blockers without intrinsic sympathomimetic activity should be used because they reduce the risk for subsequent MI or sudden cardiac death. Use of ACE inhibitors is also recommended in hypertensive patients with angina in whom LV systolic dysfunction is present to prevent subsequent heart failure and mortality (715). If beta-blockers are contraindicated (e.g., the presence of asthma) or ineffective in controlling

blood pressure or angina symptoms, verapamil or diltiazem should be considered because they have been shown to modestly reduce cardiac events and mortality after non-Q-wave MI and after MI with preserved LV function (1,718,719).

Finally, the risk of hypertension cannot be taken in isolation. This risk is unevenly distributed and closely related to the magnitude and number of coexisting risk factors, including hyperlipidemia, diabetes and smoking (720).

LV Hypertrophy

Left ventricular hypertrophy (LVH) is the response of the heart to chronic pressure or volume overload. Its prevalence and incidence are higher with increasing levels of blood pressure (721). Epidemiologic studies have implicated LVH as a risk factor for development of MI, CHF and sudden death (722,723). Its association with increased risk has been described in hospital and clinic-based studies (373,724,725) and population studies (371,372,726). Left ventricular hypertrophy has also been shown to predict outcome in patients with established CAD (727).

There is a growing body of evidence in hypertensive patients that LVH regression can occur in response to pharmacologic and nonpharmacologic (728,729) antihypertensive treatment. Recent data suggest that regression of LVH can reduce the cardiovascular disease burden associated with this condition. A report from the Framingham Heart Study found that subjects who demonstrated ECG evidence of LVH regression were at a substantially reduced risk for a cardiovascular event (50) compared with subjects who did not. Studies are needed to definitively establish the direct benefits of LVH regression. There are no clinical trials of LVH regression in patients with chronic stable angina.

Thrombogenic Factors

Coronary artery thrombosis is a trigger of acute MI. Aspirin has been documented to reduce risk for CHD events in both primary and secondary prevention settings (730). A number of prothrombotic factors have been identified and can be quantified (731). In the Physicians' Health Study, men in the top quartile of C-reactive protein values had three times the risk of MI and two times the risk of ischemic stroke compared with men with the lowest quartile values (732). The reduction in risk of MI associated with the use of aspirin was directly related to the level of C-reactive protein.

Elevated plasma fibrinogen levels predict CAD risk in prospective observational studies (733). The increase in risk related to fibrinogen is continuous and graded (734). In the presence of hypercholesterolemia, a high fibrinogen level increases CHD risk > 6 times (735), whereas a low fibrinogen level is associated with reduced risk, even in the presence of high total cholesterol levels (736). Elevated triglycerides, smoking and physical inactivity are all associ-

ated with increased fibrinogen levels. Exercise and smoking cessation appear to favorably alter fibrinogen levels, as do fibrinolytic acid-derivative drugs. Reducing fibrinogen levels could lower coronary disease risk by improving plasma viscosity and myocardial oxygen delivery and diminishing the risk of thrombosis (731). Anticoagulant or antiplatelet therapy may reduce the hazards associated with an elevated fibrinogen level even though these agents do not lower the fibrinogen level itself.

Several studies support an association between platelet function and vascular disease, a finding consistent with the known role of platelets in thrombosis, which is a precipitant of acute CAD events (731). Measures of platelet hyperaggregability, including the presence of spontaneous platelet aggregation (737) and increased platelet aggregability induced by conventional stimuli (738), provide evidence of an association between platelet aggregability and an increased risk for CAD events in both cohort and cross-sectional studies. This may explain the proved benefits of aspirin therapy in both primary and secondary prevention settings.

Other potential thrombogenic/hemostatic risk factors include factor VII, plasminogen activator inhibitor-1 (PAI-1), tPA, von Willebrand factor, protein C and antithrombin III (731,739). It is probable that anticoagulants can affect several of these factors, partially explaining their influence on decreasing CAD risk in certain secondary prevention settings.

Risk Factors for Which Interventions Are Likely to Reduce the Incidence of Coronary Disease Events

Diabetes Mellitus

Diabetes, which is defined as a fasting blood sugar >126 mg/dL (740), is present in a significant minority of adult Americans. Data supporting an important role of diabetes mellitus as a risk factor for cardiovascular disease come from a number of observational settings. This is true for both type I, insulin-dependent diabetes mellitus (IDDM), and type II, noninsulin-dependent diabetes mellitus (NIDDM). Atherosclerosis accounts for 80% of all diabetic mortality (741-743), with coronary disease alone responsible for 75% of total atherosclerotic deaths. In persons with type I diabetes, coronary mortality is increased three- to ten-fold; in patients with type II diabetes, risk for coronary mortality is two-fold in men and four-fold in women. The National Cholesterol Education Program estimates that 25% of all heart attacks in the U.S. occur in patients with diabetes (744,745). Diabetes is associated with a poor outcome in patients with established coronary disease, even after angiographic and other clinical characteristics are considered. For example, diabetic persons in the CASS registry experienced a 57% increase in the hazard of death after controlling for other known risk factors (746).

Although better metabolic control in persons with type I diabetes has been shown to lower the risk for microvascular complications (741,747-749), there is a paucity of data on the benefits of tighter metabolic control in type I or type II

diabetes with regard to reducing risk for coronary disease in either primary or secondary prevention settings. At present, it is worthwhile to pursue strict glycemic control in diabetic persons with chronic stable angina with the belief that this will provide benefits with regard to microvascular complications and also may reduce risk for other cardiovascular disease complications. However, convincing data from clinical trials are lacking. The long-standing controversy regarding the potentially adverse effects of oral hypoglycemic agents persists (750).

The common coexistence of other modifiable factors in the diabetic patient contributes to increased coronary disease risk, and they must be managed aggressively (751,752). These risk factors include hypertension, obesity and increased LDL-cholesterol levels. In addition, elevated triglyceride levels and low HDL-cholesterol levels are common in persons with diabetes.

HDL Cholesterol

Observational studies and clinical trials have documented a strong inverse association between HDL cholesterol and CAD risk. It has been estimated that a 1-mg/dL decline in HDL cholesterol is associated with a 2% to 3% increase in risk for coronary disease events (753). This inverse relation is observed in men and women and among asymptomatic persons as well as patients with established coronary disease.

Low levels of HDL cholesterol are often observed in persons with adverse risk profiles (obesity, diabetes, smoking, high levels of LDL cholesterol and triglycerides and physical inactivity). Although low levels of HDL are clearly associated with increased risk for CHD and there is good reason to conclude that such a relation is causal (e.g., biological plausibility), it has been difficult to demonstrate that raising HDL lowers CHD risk. No completed trial has been able to address the efficacy of raising HDL cholesterol alone; drugs that raise HDL also lower LDL cholesterol or triglyceride levels. The National Cholesterol Education Program Adult Treatment Panel II has defined a low HDL-cholesterol level as <35 mg/dL (754). Patients with established coronary disease and low HDL cholesterol are at high risk for recurrent events and should be targeted for aggressive nonpharmacologic treatment (dietary modification, weight loss, physical exercise) and, when appropriate, drug treatment directed at the entire lipid profile. Nicotinic acid and fibrates can raise HDL levels appreciably, as do HMG-CoA reductase inhibitors and estrogen replacement therapy to a lesser degree. The benefits of lowering LDL levels in coronary disease patients who have low HDL cholesterol and LDL levels <130 mg/dL have not been established, nor have the benefits of raising HDL levels in such persons.

Obesity

Obesity is a common condition associated with increased risk for coronary disease and mortality (755,756). Obesity is associated with and contributes to other coronary disease

risk factors, including high blood pressure, glucose intolerance, low HDL cholesterol, and elevated triglyceride levels. Hence, much of the increased CAD risk associated with obesity is mediated by these risk factors. It is likely that for obese patients with coronary disease, weight reduction can reduce risk for future coronary events because weight reduction will bring about improvements in these other modifiable risk factors. Because of the increased myocardial oxygen demand imposed by obesity and the demonstrated effects of weight loss on other coronary disease risk factors, weight reduction is indicated in all obese patients with chronic stable angina. Referral to a dietitian is often necessary to maximize the likelihood of success of a dietary weight loss program. No clinical trials have specifically examined the effect of weight loss on risk for coronary disease events.

Physical Inactivity

The evidence and recommendations presented here are based heavily on previously published documents, particularly the 27th Bethesda Conference on risk factor management (23), the AHCPR/NHLBI clinical practice guideline on cardiac rehabilitation (24), and the AHA scientific statement on exercise (757). Interested readers are referred to those documents for more detailed discussions of the evidence and organizational issues regarding performance of exercise training. Although this section focuses on the effects of exercise training, it is important to recognize that such training is usually incorporated into a multifactorial risk factor reduction effort, which includes smoking cessation, lipid management, and hypertension treatment, all of which were covered in previous sections. Many of the studies performed in the literature have tested multifactorial intervention rather than exercise training alone. The evidence presented here therefore assumes that exercise training is incorporated into such a multifactorial program whenever possible.

A large portion of the published evidence regarding exercise training focuses on post-MI or postcoronary revascularization patients. Although it is attractive to apply this evidence to patients with stable angina, such an extrapolation is not appropriate, as most patients with stable angina have not suffered an MI or undergone coronary revascularization, and patients with MI are more likely to have three-vessel or left main coronary artery disease and a more adverse short-term prognosis. This section therefore focuses on published data from patients with stable angina and, for the most part, will exclude data derived from patients with previous MI or coronary revascularization. The single exception is the subsection on safety issues, as the committee thought that the risk of exercise training in patients with stable angina should be no greater than that in patients with recent MI who have been studied extensively.

Any discussion of exercise training must acknowledge that it will not only usually be incorporated into a multifactorial intervention program but will have multiple effects.

It is biologically difficult to separate the effects of exercise training from the multiple secondary effects that it may have on confounding variables. For example, exercise training may lead to changes in patient weight, sense of well-being and antianginal medication. These effects will be clear confounders in interpreting the impact of exercise training on exercise tolerance, patient symptoms, and subsequent cardiac events. This presentation will assume that the primary and secondary effects of exercise training are closely intertwined and will make no effort to distinguish them.

Effects of Exercise Training on Exercise Tolerance, Symptoms, and Psychological Well-Being

Multiple randomized, controlled trials comparing exercise training with a "no-exercise" control group have demonstrated a statistically significant improvement in exercise tolerance for the exercise group versus the control group. These data, which are summarized in Table 31, are remarkable for several features. First, they are remarkably consistent (eight of nine studies with positive results; the single exception studied disabled patients) despite small sample sizes, multiple different outcome variables, and variable length of follow-up (24 days to 4 years). Four of the nine studies incorporated exercise training into a multifactorial intervention; five tested exercise training alone. A variety of different settings were used, including outpatient rehabilitation centers, home rehabilitation monitoring, and a residential unit. The major limitation of the published evidence is that it is based almost exclusively on male patients. Six of the nine studies (705,758-762) enrolled male patients exclusively. Two studies did not provide data about the gender of the patients enrolled (763,764). The largest study of 300 patients (765) enrolled only 41 women. Thus, there is relatively little evidence from randomized trials to confirm the efficacy of exercise training in female patients. Observational studies (766-768) have suggested that women benefit at least as much as men.

Given the consistently positive effect of exercise training on exercise capacity, it is not surprising that it also results in an improvement in symptomatology. However, the number of randomized trials demonstrating this point in patients with stable CHD is far fewer. As shown in Table 32, the three published randomized trials (758,769,770) have enrolled <250 patients. Two of the three studies (758,770) demonstrated a statistically significant decrease in patient symptoms, but one did not (769). The overall magnitude of these effects was modest.

Four randomized trials have examined the potential benefit of exercise training on objective measures of ischemia (Table 32). One study used ST-segment depression on ambulatory monitoring, and three used exercise myocardial perfusion imaging with ²⁰¹Tl. Three of the four studies (759,763,770) demonstrated a reduction in objective measures of ischemia in those patients randomized to the exercise group compared with the control group. The last

Table 31. Randomized Controlled Trials Examining the Effects of Exercise Training on Exercise Capacity in Patients With Stable Angina

First Author	Reference	N	Men (%)	Setting	Intervention	F/U	Outcome
Ornish	(763)	46	N/A	Res	M	24 d	↑ ex. tolerance
Froelicher	(758)	146	100	OR	E	1 yr	↑ ex. tolerance ↑ O ₂ consumption
May	(764)	121	N/A	OR	E	10-12 mos.	↑ O ₂ consumption ↑ max HR-BP
Sebrechts	(759)	56	100	OR	E	1 year	↑ ex. duration
Oldridge	(760)	22	100	OR/H	E	3 mos.	↑ O ₂ consumption
Schuler	(705)	113	100	OR	M	1 year	↑ work capacity ↑ max HR-BP
Hambrecht	(761)	88	100	Hosp/H	M	1 year	↑ O ₂ consumption ↑ ex. duration
Fletcher	(762)	88 Disabled	100	H	E	6 mos.	NS (ex. duration or O ₂ consumption)
Haskell	(765)	300	86	H	M	4 yrs.	↑ ex. tolerance

Res = Residential facility; OR = Outpatient rehab; H = home; Hosp = Hospital; M = Multifactorial; E = Exercise training only; ↑ = Statistically significant increase favoring intervention; NS = No significant difference between groups; N/A = Not available.

study (705) reported a significant decrease in ST depression during exercise but not in the exercise thallium defect or thallium redistribution. Although it is not specifically demonstrated in these studies, the threshold for ischemia is likely to increase with exercise training, as training reduces the heart rate-blood product at a given submaximal exercise workload.

There is a widespread belief among cardiac rehabilitation professionals that exercise training improves patients' sense of well-being. Although multiple randomized trials have used a variety of instruments to measure significant differences in various psychological outcomes between the exercise group and the control group, these trials have been conducted in patients following MI. Given the underlying biologic differences outlined above and the well-documented effects of MI on patients' sense of well-being, these results are not easily extrapolated to patients with stable angina. A single nonrandomized trial compared multifactorial intervention (including exercise and psychological intervention) in 60 treated patients with 60 control

patients (771). Follow-up was performed three months later. There was a significant reduction in disability scores, an improvement in well-being scores, and an improvement in positive affect scores in the intervention group. Thus, the evidence supporting an improvement in psychological parameters with exercise training in patients with stable angina is very limited.

Lipid Management and Disease Progression

Multiple randomized trials have examined the potential benefit of exercise training in the management of lipids (Table 33). Some of these trials have examined exercise training alone; others have studied exercise training as part of a multifactorial intervention. Again, the majority of subjects studied have been male. Of the 1,827 patients studied, only 52 were women. Most studies had a follow-up of one year. One study used a 24-day follow-up. Two other studies used much longer follow-ups of 39 months and 4 years, respectively. Most studies have found a statistically

Table 32. Randomized Controlled Trials Examining the Effects of Exercise Training on Symptoms and Objective Measures of Ischemia

First Author	Reference	N	Men (%)	Inter	F/U	Symptoms	Objective Ischemia
Froelicher	(758)	146	100	E	1 year	↓	↓ thallium ischemia score
Sebrechts	(759)	56	100	E	1 year	—	↑ thallium uptake
Ornish	(763)	48	N/A	M	1 year	NS	—
Todd	(770)	40	100	E	1 year	↓	↓ ST depression (ambulatory monitor)
Schuler	(705)	113	100	M	1 year	—	↓ ST depression (exercise) NS (exercise thallium defect or redistribution)

NS = No significant difference; ↑ = Statistically significant increase favoring intervention group; ↓ = Statistically significant decrease favoring intervention group; N/A = Not available; Inter = Intervention; M = Multifactorial; E = Exercise training only.

Table 33. Randomized Controlled Trials Examining the Effects of Exercise Training on Lipids and Angiographic Progression

First Author	Ref	N	Men (%)	Inter	F/U	Chol	HDL	LDL	Tri	Angio Progression/Regression
Plavsic	(786)	483	100	E	6/12 mos.	*	—	—	—	—
Oberman	(772)	651	100	E	1 yr.	NS	—	—	↓	—
Ornish	(763)	46	89	M	24 days	↓	↓	—	↓	—
Ornish	(769)	48	88	M	1 yr.	↓	NS	↓	NS	↓
Nikolaus	(773)	45	100	E	1 yr.	NS	—	—	↓	—
Schuler	(705)	92	100	E	1 yr.	↓	NS	↓	↓	↓
Watts	(774)	74	100	M	39 mos.	↓	NS	↓	—	—
Hambrecht	(761)	88	100	E	1 yr.	↓	NS	↓	NS	↓
Haskell	(765)	300	86	M	4 yr.	↓	↑	↓	↓	↓
		1827								
		(52 female)								

*No statistics reported.

↓ = Statistically significant decrease favoring intervention; ↑ = Statistically significant increase favoring intervention; Angio = Angiographic; E = Exercise training only; Inter = Intervention; m = Multifactorial; NS = No significant difference between groups; Tri = Triglycerides.

significant reduction in total cholesterol and LDL cholesterol (where reported) favoring the intervention group, but this finding has not been totally uniform. One larger, older study (772) did not show a significant reduction in cholesterol in the treatment group along with one more recent small study (773). Five of the seven studies that reported the results of intervention on triglycerides found a significant reduction favoring the treatment group. Two studies of 88 and 48 patients, respectively, did not (761,762). The results of intervention on HDL cholesterol have been far less impressive. Only one study (765) reported a statistically significant increase in HDL cholesterol favoring the treatment group. Four others (705,761,762,774) have not found any difference between the control and treatment groups. One study found a decrease in HDL cholesterol in the treatment group. The preponderance of evidence clearly suggests that exercise training is beneficial and associated with a reduction in total cholesterol, LDL cholesterol, and triglycerides compared with controlled therapy but has little effect on HDL cholesterol. However, it must be recognized that exercise training alone is unlikely to be sufficient in patients with a true lipid disorder.

Not surprisingly, this reduction in lipids has been associated with less disease progression according to angiographic follow-up. Four of the randomized trials of lipid management, all involving multifactorial intervention, performed follow-up angiography to assess disease progression. Three of the studies performed follow-up angiography at one year; the remaining study performed angiographic follow-up at four years. All the studies demonstrate significantly less disease progression and more disease regression in the intervention group.

Although exercise training has a beneficial effect on disease progression, it has not been associated with any consistent changes in cardiac hemodynamic measurements (775-777), LV systolic function (778-780), or coronary collateral circulation (763). In patients with heart failure and decreased LV

function, exercise training does produce favorable changes in the skeletal musculature (781), but there has not been a consistent effect on LV dysfunction (782,783).

Safety and Mortality

Physicians and patients are sometimes concerned about the safety of exercise training in patients with underlying coronary disease. Two major surveys of rehabilitation programs have been conducted to determine the rates of cardiovascular events based on questionnaire responses. One study of 30 programs in North America covering the period of 1960 to 1977 (780) found a nonfatal cardiac arrest rate of 1/32,593 patient-hours of exercise and a nonfatal MI rate of 1/34,600 patient-hours of exercise. A more recent study of 142 U.S. cardiac programs from 1980 to 1984 (784) reported an even lower nonfatal MI rate of 1/294,000 patient-hours. Thus, there is clearly a very low rate of serious cardiac events during cardiac rehabilitation.

These survey data are supported by the results of randomized trials following MI. As indicated earlier, the committee believed that these data can be appropriately extrapolated to patients with stable angina, because it is unlikely that patients with stable angina are at greater risk than those who are post-MI. Fifteen randomized control trials, 10 of which involved exercise as the major intervention and 5 of which used exercise as part of a multifactorial intervention, reported no statistically significant differences in the rates of reinfarction comparing patients in the intervention group with those in the control group (24). These randomized data clearly support the safety of exercise training. It is important to recognize that recent clinical practice, including acute reperfusion therapy for MI, the use of beta-blockers and ACE inhibitors after MI, and the aggressive use of revascularization, has probably further reduced the risk of exercise training compared with the previously reported literature.

Given its effects on lipid management and disease progression, it is attractive to hypothesize that exercise training

will reduce the subsequent risk of cardiac events. However, only one clinical trial has examined the influence of exercise training on subsequent cardiac events in patients with stable angina. Haskell *et al.* (765) enrolled 300 patients with stable angina, including some who were postrevascularization, in a four-year follow-up study comparing multifactorial intervention with usual care. The cardiac event rate in the study was low. There were 3 cardiac deaths in the usual-care group and 2 in the intervention group as well as 10 nonfatal MIs in the usual-care group and 4 in the intervention group. When cardiac events initiating hospitalization, including death, MI, PTCA and CABG, were tabulated, there was a total of 25 events in the intervention group and 44 in the usual-care group (risk ratio 0.61; $p = 0.05$). However, the cardiac event rate was not a primary a priori end point of the study. Although these data suggest a favorable effect of exercise training on patient outcome, they are clearly not definitive. In contrast, several meta-analyses of randomized trials in patients with previous MI have shown a 20% to 30% reduction in cardiac deaths with exercise training (678,785) but no reduction in nonfatal MI.

Postmenopausal Status

Both estrogenic and androgenic hormones produced by the ovary are protective against the development of atherosclerotic cardiovascular disease. When hormonal production decreases in the perimenopausal period over several years, the risk of CAD rises in postmenopausal women. By age 75, the risk of atherosclerotic cardiovascular disease among men and women is equal. Women have an accelerated risk of developing CAD if they experience an early menopause or abrupt onset of menopause through surgical removal or chemotherapeutic ablation of the ovaries. Loss of estrogen and onset of menopause result in an increase in LDL cholesterol, a small decrease in HDL cholesterol, and therefore an increased ratio of total to HDL cholesterol (787).

Postmenopausal estrogen replacement has been proposed for both primary and secondary prevention of CAD in women. Prospective studies of the effects of estrogen administration on cardiac risk factors demonstrate an increase in HDL cholesterol and a decrease in LDL cholesterol (788-791). Other effects of estrogen replacement include a decrease in the likelihood of thrombosis (788,791) and several positive physiologic effects on the vascular smooth muscle and the endothelium.

Numerous epidemiologic studies have been conducted to assess the influence of estrogen replacement therapy on the primary prevention of CAD in postmenopausal women (792-794). The Nurses' Health Study reported a relative risk of 0.56 for MI or death in current users of estrogen and a 0.83 relative risk for those women who had ever used estrogen replacement therapy. Other beneficial health effects of estrogen replacement therapy include prevention of osteoporosis and subsequent wrist and hip fractures and amelioration of menopausal symptoms (e.g., vasomotor

instability, vaginal dryness, mood swings). Studies of the efficacy of estrogen replacement therapy in women with established CAD are limited (795-798).

However, the first published randomized trial of estrogen plus progestin therapy in postmenopausal women with known CAD did not show any reduction in cardiovascular events over four years of follow-up (799), despite an 11% lower LDL cholesterol level and a 10% higher HDL-cholesterol level in those women receiving hormone replacement therapy. In addition, women receiving hormone replacement therapy had higher rates of thromboembolic events and gallbladder disease. Among women who received hormone replacement therapy, there was a trend toward lower late cardiovascular event rates, suggesting that additional studies now in progress may reveal a longer-term effect of hormone replacement therapy. Other randomized trials of hormone replacement therapy in primary and secondary prevention of CAD in postmenopausal women are being conducted, and their results will become available over the next several years.

Risk Factors for Which Interventions Might Reduce the Incidence of Coronary Disease Events

Psychosocial Factors

The evidence and recommendations presented here are based heavily on previously published documents, including the 27th Bethesda Conference on Risk Factor Management (23) and the AHCPR/NHLBI clinical practice guideline on cardiac rehabilitation (24). More detailed discussions of the complex issues involved are available in those documents. Education, counseling, and behavioral interventions are important elements of a multifactorial risk factor reduction effort directed at smoking cessation, lipid management and hypertension treatment, as previously mentioned. The evidence presented here therefore assumes that appropriate multifactorial intervention has been initiated in those areas and considers the specific application of similar broad-based efforts to reduce stress and address other psychological problems.

Most of the published evidence on stress management focuses on patients who are post-MI or postrevascularization. The extrapolation of the findings from such patient populations to patients with stable angina is questionable. Patients with MI are further along in the natural history of CAD, and the occurrence of MI may have itself altered their psyche, creating psychological problems or a difference in their overall response to general life stresses. Unfortunately, the published data regarding stress management in patients with stable angina are quite limited.

EVIDENCE LINKING STRESS AND PSYCHOLOGICAL FACTORS TO CAD. A variety of psychological factors, particularly type A personality, have been associated with the development of clinically apparent CAD (800,801). Epidemiologic evidence linking such psychological factors to CAD has not always

been consistent (802–805). Psychological stress, depression, anger and hostility (806,807) may be even more closely associated with coronary risk. More recently, studies have focused more specifically on measures of hostility, which appears to have a more powerful influence on coronary disease outcome than other psychosocial factors (808,809).

TREATMENT DIRECTED AT STRESS REDUCTION AND PSYCHOLOGICAL WELL-BEING. A number of randomized trials involving post-MI patients have shown that interventions designed to reduce stress can reduce recurrent cardiac events by 35% to 75% (810–812). The trials were generally small and used a wide variety of different approaches, including relaxation training, behavior modification and psychosocial support. Other psychological outcomes were also improved by intervention (24). However, for the reasons indicated above, it is not evident whether such results apply to patients with stable angina.

Two studies on stress management are potentially applicable to patients with stable angina. One was a small, nonrandomized trial of three weeks of relaxation training in association with a cardiac exercise program (813). Anxiety, somatization and depression scores were all lower in the treatment than the control group. More recently, Blumenthal et al. (814) examined the effects of a four-month program of exercise or stress management training in 107 patients with CAD and documented ischemia. Forty patients were assigned to a nonrandom, usual-care comparison group. The remaining patients were randomized to either exercise or stress management. The stress-management program included patient education, instruction in specific skills to reduce the components of stress, and biofeedback training. During follow-up of 38 ± 17 months, there was a significant reduction in overall cardiac events in the stress-management group compared with the nonrandom usual-care group. However, virtually all the events consisted of CABG or angioplasty. The exercise group had an event rate that was not statistically significantly different from either of the other groups. The predominance of revascularization events could potentially reflect a change in patient preference for revascularization as a result of education.

DEPRESSION AND ANXIETY. Many patients with CAD have depression or anxiety related to their disease that may be severe enough to benefit from short-term psychological treatment (815,816). Identification and treatment of depression should therefore be incorporated into the clinical management of patients with stable angina. The safety of pharmacologic therapy for depression in patients with ischemic heart disease is under investigation.

Triglycerides

Triglyceride levels are predictive of CHD risk in a variety of observational studies and clinical settings (817). Much of the association of triglycerides with CHD risk is related to other factors, including diabetes, obesity, hypertension, high LDL cholesterol and low HDL cholesterol (818). In addition,

hypertriglyceridemia is often found in association with abnormalities in hemostatic factors (819).

Nonpharmacologic management of high triglycerides consists of weight loss, reduction in alcohol consumption for those in whom this mechanism may be causal, smoking cessation and physical activity. Drugs that can lower triglycerides include nicotinic acid, fibrate derivatives, and to a lesser degree HmG CoA reductase inhibitors. It is not clear whether treatment directed at high triglyceride levels will reduce risk for initial or recurrent CHD events. Data from the Helsinki Study (820) indicated that among patients with elevated non-HDL cholesterol, treatment with gemfibrozil reduced risk for CHD events. This reduction in risk may be linked to the effects of treatment on lipid components other than triglyceride level.

A 1992 consensus development conference defined triglycerides of 200 to 400 mg/dL as “borderline high,” 400 to 1000 mg/dL as “high,” and >1000 mg/dL as “very high” (821). The National Cholesterol Education Program Adult Treatment Panel II provides guidance for the management of elevated triglyceride levels (754).

Lipoprotein(a)

Lipoprotein(a) (Lp[a]) is a lipoprotein particle that has been linked to CHD risk in observational studies (822,823). Lp(a) levels are largely genetically determined (822). Elevated Lp(a) levels are found in 15% to 20% of patients with premature CHD (824). Among conventional lipid agents, only niacin taken in high doses lowers Lp(a) levels (822). No prospective intervention trial has specifically studied the effect of Lp(a) lowering on risk of recurrent coronary disease events.

Homocysteine

Increased homocysteine levels are associated with increased risk of CAD, peripheral arterial disease and carotid disease (825–828). Although elevated homocysteine levels can occur as a result of inborn errors of metabolism such as homocystinuria, homocysteine levels can also be increased by deficiencies of vitamin B₆, vitamin B₁₂, and folate, which commonly occur in older persons (829,830). More than 20% of the older subjects evaluated by the Framingham Heart Study population had elevated homocysteine levels (829). In patients with coronary disease and elevated homocysteine levels, supplementation with vitamins B₆, B₁₂, and folic acid is relatively inexpensive and will usually lower homocysteine levels. Clinical trials are needed to determine whether such treatment is beneficial.

Oxidative Stress

Extensive laboratory data indicate that oxidation of LDL cholesterol promotes and accelerates the atherosclerosis process (831,832). Observational studies have documented an association between dietary intake of antioxidant vitamins (vitamin C, vitamin E, and beta carotene) and reduced risk for CHD (833).

Clinical trial evidence is incomplete regarding the potential benefits of supplementation with antioxidant vitamins.

A Finnish study (834) failed to show a reduction in CHD risk among middle-aged male smokers who received either beta carotene or vitamin E. In the Cambridge Heart Antioxidant Study (CHAOS) (835), dietary supplementation with vitamin E in patients with established ischemic heart disease reduced risk for nonfatal MI by 77% (CI 89% to 53%). In contrast, secondary analysis revealed a slight excess of cardiovascular deaths in the actively treated group (+18%, $p = 0.61$). Clinical trial data are not available to support vitamin C supplementation in patients with CHD.

Probucol is a lipid-lowering drug with antioxidant properties. In a recent clinical trial, patients with coronary disease undergoing angioplasty were treated with placebo, probucol, or multivitamins (beta carotene, vitamin E, and vitamin C). A reduction in restenosis was observed only with probucol (836). In the PQRST trial, however, treatment with probucol had no effect on femoral artery atherosclerosis (837).

Although dietary supplementation with antioxidants or a diet rich in foods with antioxidant potential, especially vitamin E, may be of benefit to patients with chronic stable angina, the benefits are still unresolved.

Consumption of Alcohol

Observational studies have repeatedly shown an inverse relation of moderate alcohol intake (approximately 1 to 3 drinks daily) to risk of CHD events (838-840). Excessive alcohol intake can promote many other medical problems that can outweigh its beneficial effects on CHD risk. Although some studies have suggested an association of wine consumption with a reduction in CHD risk that is greater than that observed for beer or spirits, this issue is unresolved.

The benefits of moderate alcohol consumption may be mediated through the effects of alcohol on HDL cholesterol. An alternative mechanism is the potentially beneficial effects of flavonoids. In the Zutphen Study (841), flavonoid consumption was inversely related to mortality from CHD, with risk in the lowest tertile of intake less than half that of the highest tertile. In contrast, in the Physicians' Health Study (842), the association of flavonoid intake to risk for MI was not significant. Clinical trials are lacking on the effect of alcohol intake on CHD risk.

Risk Factors Associated With Increased Risk but That Cannot Be Modified or the Modification of Which Would Be Unlikely to Change the Incidence of Coronary Disease Events

Advancing age, male gender and a positive family history of premature CHD are nonmodifiable risk factors for CHD that exert their influence on CHD risk to a large extent through other modifiable risk factors noted above. The National Cholesterol Education Program defines a family history of premature CHD as definite MI or sudden death before the age of 55 years in a father or other male first-degree relative or before the age of 65 in a mother or other female first-degree relative (20).

Many other risk factors for CHD have been proposed (843), and many more will be in the future. At present, there is little evidence that modification of risk factors other than those covered in categories I through III above will reduce risk for initial or recurrent CHD events.

Other Proposed Therapies

Diet

Diet is an important contributor to multiple other risk factors discussed above, including LDL- and HDL-cholesterol levels, blood pressure, obesity, impaired glucose tolerance and antioxidant and vitamin intake. Consequently, dietary modification can promote a favorable CHD risk profile by affecting multiple risk pathways. Dietary therapy has been assessed in seven randomized clinical trials performed in CHD patients. Several early trials (844-846) failed to demonstrate beneficial effects of diet on CHD risk. Of the later trials (704,847-849), three demonstrated statistically significant reductions in cardiac mortality rate associated with dietary therapy ranging from 32% to 66% (704,847,849). These low-fat diets were high in fiber and antioxidant-rich foods (704), monounsaturated fat (849), or fish (847).

Some studies have found an inverse association between fish consumption and CHD risk (850). Meta-analyses of clinical trials have suggested that restenosis after coronary angioplasty may be reduced by fish oils (851,852); however, the results are inconclusive. Additional well-designed trials are needed.

There are no randomized trials of garlic therapy in patients with stable angina. However, garlic has been evaluated as a treatment for two risk factors of coronary artery disease (hypertension and hypercholesterolemia [Table 34]). Two meta-analyses of garlic therapy for treatment of hypercholesterolemia and hypertension were published in the early 1990s (853,854). These suggested a small benefit with garlic therapy. More recently, two rigorous studies of garlic as a treatment for hypercholesterolemia have found no measurable effect (855,856). The current evidence does not suggest that there is a clinically significant benefit in cholesterol reduction or blood-pressure lowering with garlic therapy.

Therapies That Have Not Been Shown to Reduce Risk for Coronary Disease Events

There is no evidence to support the use of chelation therapy to treat atherosclerotic cardiovascular disease. Four randomized clinical trials in patients with atherosclerotic cardiovascular disease (intermittent claudication) found no evidence of a beneficial effect of chelation therapy on progression of disease or clinical outcome (858). These results, combined with the potential for harm from chelation therapy, indicate that chelation therapy has no role in the treatment of chronic stable angina.

Table 34. Randomized Trials and Meta-Analyses of Garlic Therapy for Risk Treatment of Risk Factors

Author	Year	Study Type	Patients	Daily Dose & Preparation	Effect of Garlic
Hypercholesterolemia					
Berthold (855)	1998	RCT	25*	10 mg steam distilled oil	No difference in multiple measures
Isaacsohn (856)	1998	RCT	40	900 mg powder	No difference in multiple measures
Jain (857)	1993	RCT	42	900 mg powder	Reduction in LDL of 11% vs. 3% for placebo
Warshafsky (853)	1993	Meta-analysis	5 trials	1/2-1 clove per day	Reduction in total cholesterol of 95 mg/dL
Hypertension					
Silagy (854)	1994	Meta-analysis	8 trials	600-900 mg powder	Small reduction in systolic and diastolic BP

RCT indicates randomized controlled trial.
*Cross-over study.

E. Revascularization for Chronic Stable Angina

Recommendations for Revascularization With PTCA (or Other Catheter-Based Techniques) and CABG in Patients With Stable Angina*

Class I

1. CABG for patients with significant left main coronary disease. (*Level of Evidence: A*)
2. CABG for patients with three-vessel disease. The survival benefit is greater in patients with abnormal LV function (ejection fraction <50%). (*Level of Evidence: A*)
3. CABG for patients with two-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (ejection fraction <50%) or demonstrable ischemia on noninvasive testing. (*Level of Evidence: A*)
4. PTCA for patients with two- or three-vessel disease with significant proximal left anterior descending CAD, who have anatomy suitable for catheter-based therapy, normal LV function and who do not have treated diabetes. (*Level of Evidence: B*)
5. PTCA or CABG for patients with one- or two-vessel CAD without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*Level of Evidence: B*)
6. CABG for patients with one- or two-vessel CAD without significant proximal left anterior descending CAD who have survived sudden cardiac death or sustained ventricular tachycardia. (*Level of Evidence: C*)
7. In patients with prior PTCA, CABG or PTCA for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing. (*Level of Evidence: C*)

8. PTCA or CABG for patients who have not been successfully treated by medical therapy (see text) and can undergo revascularization with acceptable risk. (*Level of Evidence: B*)

Class IIa

1. Repeat CABG for patients with multiple saphenous vein graft stenoses, especially when there is significant stenosis of a graft supplying the LAD. It may be appropriate to use PTCA for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery. (*Level of Evidence: C*)
2. Use of PTCA or CABG for patients with one- or two-vessel CAD without significant proximal LAD disease but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing. (*Level of Evidence: B*)
3. Use of PTCA or CABG for patients with one-vessel disease with significant proximal LAD disease. (*Level of Evidence: B*)

Class IIb

1. Compared with CABG, PTCA for patients with two- or three-vessel disease with significant proximal left anterior descending CAD, who have anatomy suitable for catheter-based therapy, and who have treated diabetes or abnormal LV function. (*Level of Evidence: B*)
2. Use of PTCA for patients with significant left main coronary disease who are not candidates for CABG. (*Level of Evidence: C*)
3. PTCA for patients with one- or two-vessel CAD without significant proximal left anterior descending CAD who have survived sudden cardiac death or sustained ventricular tachycardia. (*Level of Evidence: C*)

Class III

1. Use of PTCA or CABG for patients with one- or two-vessel CAD without significant proximal left

*Note: PTCA is used in these recommendations to indicate PTCA or other catheter-based techniques, such as stents, atherectomy and laser therapy.

- anterior descending CAD, who have mild symptoms that are unlikely due to myocardial ischemia or who have not received an adequate trial of medical therapy and
- a. Have only a small area of viable myocardium or
 - b. Have no demonstrable ischemia on noninvasive testing. (*Level of Evidence: C*)
2. Use of PTCA or CABG for patients with borderline coronary stenoses (50% to 60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing. (*Level of Evidence: C*)
 3. Use of PTCA or CABG for patients with insignificant coronary stenosis (<50% diameter). (*Level of Evidence: C*)
 4. Use of PTCA in patients with significant left main coronary artery disease who are candidates for CABG. (*Level of Evidence: B*)

There are currently two well-established revascularization approaches to treatment of chronic stable angina caused by coronary atherosclerosis. One is coronary artery bypass grafting (CABG), in which segments of autologous arteries or veins are used to reroute blood around relatively long segments of the proximal coronary artery. The other is percutaneous transluminal coronary angioplasty (PTCA), a technique that uses catheter-borne mechanical or laser devices to open a (usually) short area of stenosis from within the coronary artery. Since the introduction of bypass surgery in 1967 and PTCA in 1977, it has become clear that both strategies can contribute to the effective treatment of patients with chronic stable angina, and both have weaknesses. A major problem in trying to assess the role of these invasive treatments is that demonstration of their effectiveness requires long-term follow-up. Although these long-term follow-up studies are being accomplished, treatments have changed, usually for the better.

Revascularization is also potentially feasible with trans-thoracic (laser) myocardial revascularization. However, this technique, which is still in its infancy, is primarily used as an alternative when neither CABG nor PTCA is feasible.

Coronary Artery Bypass Surgery

Coronary bypass surgery has a 30-year history. For most patients, the operation requires a median sternotomy incision and cardiopulmonary bypass. At present, there are alternative, less invasive forms of bypass surgery under investigation, and some limited "mini" operations may acquire the status of standard clinical treatment. However, at this point, only fairly simple bypass operations are consistently possible with less invasive techniques, and all the studies that have documented the long-term effectiveness of bypass surgery in terms of graft patency, symptom relief and lower death rate have been carried out involving

patients operated on with standard techniques. With these standard approaches to bypass surgery, extensive revascularization of complex CAD can be accomplished with relative safety.

Bypass grafts are constructed with saphenous vein (SVG) or arterial grafts, most commonly the internal thoracic (mammary) artery (ITA). One disadvantage of bypass grafting with the saphenous vein is that there is an attrition of vein grafts with time due to intrinsic changes that may occur in the grafts. Data from the 1970s showed occlusion rates of saphenous vein grafts of 10% to 15% within 1 week to 1 year after operation and 20% to 25% by 5 years after surgery. Beyond five postoperative years, the development of vein graft atherosclerosis further compromised grafts so that by 10 postoperative years, ≈40% of saphenous vein grafts were occluded, and approximately half of the patent grafts showed atherosclerotic changes (859-861). Fortunately, progress has been made in preventing vein graft attrition. Randomized prospective studies have shown that perioperative and long-term treatment with platelet inhibitors have significantly decreased the occlusion rate of saphenous vein grafts at 1 year after surgery to 6% to 11% (862-864), and long-term occurrence and progression of vein graft atherosclerosis appear to be significantly decreased by aggressive lipid-lowering strategies (865). However, despite these advances, vein graft atherosclerosis is still the greatest problem compromising long-term effectiveness of CABG.

Arterial grafts, most notably the ITA, have a much lower early and late occlusion rate than vein grafts, and in the case of the left ITA to the LAD bypass graft (LITA-LAD), >90% of grafts are still functioning >10 years after surgery (859,866,867). Furthermore, the occurrence of late atherosclerosis in patent ITA grafts is extremely rare, and even at 20 postoperative years, the occlusion rate of these grafts is very low. The use of the LITA-LAD graft has also been shown to improve long-term clinical outcome in terms of survival and freedom from reoperation, and this strategy is now a standard part of bypass surgery at most institutions (866,868). The right ITA has also been used for bypass grafts at some centers and excellent long-term results have been noted, but that strategy has not become widespread. Other arterial grafts, including the right gastroepiploic artery, the radial arteries and inferior epigastric arteries have all shown promise, and excellent early results in terms of graft patency have been documented. However, the strategy of extensive arterial revascularization has not become widespread, and long-term outcomes are as yet unknown.

CABG Versus Medical Management

The goals of coronary bypass surgery are to alleviate symptoms and prolong life expectancy. Early in the history of CABG, it became clear that successful bypass surgery relieved angina or lessened symptoms. To investigate the question of whether bypass surgery prolonged survival, three large multicenter randomized trials, the Veterans Adminis-

tration Cooperative Study (VA Study) (869), the European Coronary Surgery Study (ECSS) (870), and CASS (871), were undertaken. These trials compared the strategy of initial bypass surgery with initial medical management with regard to long-term survival and symptom status for patients with mild or moderate symptoms. Severely symptomatic patients were excluded from the randomized portions of these trials, and crossover from medical to surgical therapy was allowed. The lessons learned from these trials concerning survival rate were that the subsets of patients for whom bypass surgery improved the survival rate the most were patients who were at high risk of death without surgery. The characteristics that defined high-risk groups include the angiographic characteristics of left main coronary artery stenosis, three-vessel disease with abnormal LV function, two- or three-vessel disease with a >75% stenosis in the proximal LAD, and the clinical descriptors of an abnormal baseline ECG and a markedly positive exercise test.

Recently, a meta-analysis of these three major randomized trials of initial surgery versus medical management as well as other smaller trials has confirmed the survival benefit achieved by surgery at 10 postoperative years for patients with three-vessel disease, two-vessel disease, or even one-vessel disease that included a stenosis of the proximal LAD (489). The survival rate of these patients was improved by surgery whether they had normal or abnormal LV function (489). For patients without a proximal LAD stenosis, bypass surgery improved the mortality rate only for those with three-vessel disease or left main stenosis.

It is important to note that the largest and most pertinent of the trials (ECSS and CASS) contained only patients with mild or moderate symptoms; severely symptomatic patients were excluded from randomization. In CASS, these symptomatic patients excluded from randomization were monitored in the CASS registry. Analysis of this prospective but nonrandomized database showed that initial bypass surgery dramatically improved the survival rate of severely symptomatic patients with three-vessel disease regardless of ventricular function and regardless of the presence or absence of proximal stenoses (872).

Coronary bypass surgery consistently improves the symptoms of patients with angina. Observational studies have noted freedom from angina for approximately 80% of patients at five postoperative years (72). In the randomized trials of surgery versus medical therapy, patients receiving initial surgery experienced superior relief of angina at five postoperative years. The advantage for the group initially treated with surgery became less by 10 postoperative years, in part because during this time many patients initially assigned to medical therapy crossed over to receive bypass surgery (873). In the studies included in the meta-analysis (489), 41% of the patients assigned to the medical treatment group had crossed over and undergone bypass surgery by 10 postoperative years. This crossover effect is important to recognize in any study of long-term outcome in which invasive studies are compared with medical management.

Conversely, patients who underwent initial surgery also had a progressive increase in the incidence of reoperation with the passage of time, although less of an incidence than that of patients crossing over from medical to surgical therapy.

The crossover effect, however, does not totally explain the observations that the survival advantage and improved symptoms for patients treated with initial surgery decreased with time beyond five postoperative years. It is probable that much of this deterioration was related to late vein graft failure. It is also important to note that these trials were carried out in the relatively early years of bypass surgery and outcomes of the procedure have improved over time. Few patients received ITA grafts or were treated either with platelet inhibitors or lipid-lowering agents, strategies that have all been clearly shown to improve the long-term outcome of patients undergoing bypass surgery. The improvements in short- and long-term survival rates after bypass surgery that have occurred since the randomized studies were conducted have been documented by observational studies (866,868,874), but further CABG-medical treatment randomized trials have not been conducted. Another weakness of the randomized trials that must be kept in mind when interpreting their current implications is that tremendous advances in imaging techniques have allowed a more accurate definition of ischemia and thus allowed identification of patients at "high risk" of events with medical treatment alone that did not exist during the years of the randomized trials. The randomized trials were based on angiographic anatomy and baseline ventricular function. However, improved imaging techniques have allowed a more accurate definition of groups that can potentially benefit from revascularization.

PTCA

Percutaneous transluminal coronary angioplasty (PTCA) for CAD was introduced in 1977, in this strategy a catheter-borne balloon was inflated at the point of coronary stenosis. Alternative mechanical devices for percutaneous treatments have been developed and have included rotating blades or burrs designed to remove atheromatous material, lasers to achieve photoablation of lesions and metal intracoronary stents designed to structurally maintain lumen diameter. The advantages of PTCA for the treatment of CAD are many and include a low level of procedure-related morbidity, a low procedure-related mortality rate in properly selected patients, a short hospital stay, early return to activity and the feasibility of multiple procedures. The disadvantages of PTCA are that it is not feasible for many patients, there is a significant incidence of restenosis in lesions that are successfully treated, and there is a risk of acute coronary occlusion during PTCA. The risk of acute coronary occlusion during PTCA was a serious problem in the early years of percutaneous treatments, but the advent of intracoronary stents, improved selection of vessels for treatment and improved pharmacologic therapies have greatly

decreased the risk of acute occlusion and procedure-related cardiac morbidity as well as emergency coronary bypass surgery associated with PTCA. The other disadvantages of PTCA are that many patients do not have an anatomy suitable for percutaneous treatment and that restenosis occurs in 30% to 40% of treated lesions within six months (875-877).

Despite some disadvantages, the efficacy of PTCA in producing symptom relief for some patient subsets has become rapidly apparent, and the number of PTCA procedures performed has grown so rapidly that today PTCA is performed more commonly than bypass surgery. Initially used to treat only proximal one-vessel CAD, the concepts of percutaneous treatment have been extended to more complex situations.

PTCA Versus Medical Treatment

The initial randomized study that compared PTCA with medical management alone for the treatment of chronic stable angina was the Veterans Affairs Angioplasty Compared to Medicine (ACME) Trial, which involved patients with one-vessel disease and exercise-induced ischemia. In a six-month follow-up, the death rate was expectedly low for both the PTCA and medically treated groups, and 64% of the PTCA group were free of angina versus 46% of the medically treated group ($p < 0.01$) (878).

A second randomized trial comparing initial PTCA versus initial medical management (Randomized Intervention Treatment of Angina [RITA-2]) included a majority of patients with one-vessel disease (60%) and some angina (only 20% without angina) monitored over a 2.7-year median follow-up interval. There was a slightly greater risk of death or MI for the PTCA group ($p = 0.02$), although those risks were low for both groups. The greater risk of MI in the PTCA group was due to enzyme elevations during the procedure. The PTCA patients had less angina three months after randomization, although by two years the differences between the two groups were small (7.6% more medically treated patients had angina). Some of that narrowing of the difference in symptom status was due to the crossover of medically treated patients to PTCA or bypass surgery. By one year, 15% of the medically treated group had crossed over to PTCA or CABG and 14.9% of the initial PTCA group had undergone repeat PTCA or CABG. Thus, compared with medically treated patients, the PTCA group had improved symptoms, although re-intervention was often needed to maintain that symptomatic improvement (879).

Both of these randomized studies of PTCA versus medical management have involved patients who were at a low risk of mortality even with medical management. The use of PTCA to treat patients with chronic stable angina and characteristics that define a high risk of mortality has not been tested.

Medical Management Versus PTCA or CABG

The most current study of medical management versus revascularization is the Asymptomatic Cardiac Ischemia Pilot (ACIP) study. This study included patients with CAD who were either free of angina or had symptoms that were well controlled with medical management but ≥ 1 episode of asymptomatic ischemia documented during 48-h ambulatory ECG monitoring. The three arms of the study were medical management guided by angina, medical management conducted by ambulatory ECG monitoring and revascularization (either CABG or PTCA, depending on the judgment of the investigators). At a two-year follow-up, the 170 patients randomized to revascularization (PTCA in 92 patients, CABG in 78) had a significantly lower death rate ($p < 0.005$) than those in either of the medically managed groups. Furthermore, 29% of the patients randomized to medical management underwent nonprotocol (crossover) revascularization during the two-year follow-up. Patients with a $\geq 50\%$ LAD stenosis appeared to derive the most benefit from revascularization (880). Patients with ischemia on ambulatory ECG monitoring frequently had multivessel disease, severe proximal stenoses and complex plaque (881).

Use of PTCA Versus Medical Management Versus CABG

One randomized three-arm trial (the Medicine, Angioplasty or Surgery Study [MASS]) (882) compared PTCA, medical treatment and CABG (LITA-LAD) for the treatment of isolated, severe, proximal LAD stenosis in patients with lesions ideal for treatment with PTCA. With 214 patients randomized and monitored for three years, there was no difference in mortality or MI rate among the three groups. Both revascularization strategies resulted in more asymptomatic patients (CABG, 98%; PTCA, 82%) when compared with medical treatment (32%) ($p < 0.01$), but no patient in any treatment group had severe angina at follow-up. Patients assigned to PTCA and medicine had more revascularization procedures during the follow-up period than did the patients assigned to surgery. The primary end point of the study was the combined incidence of cardiac death, MI or refractory angina requiring revascularization. That combined end point occurred more often for patients assigned to PTCA (17 [24%]) and medical therapy (12 [17%]) than for those assigned to bypass surgery (2 [3%], $p < 0.006$).

Use of PTCA Versus Use of CABG

Multiple trials have compared the strategy of initial PTCA with initial CABG for treatment of multivessel CAD. In general, the goal of these trials has been to try to answer the question of whether or not there are subsets of patients that pay a penalty in terms of survival for initial treatment with PTCA. The two U.S. trials of PTCA versus CABG are the multicenter Bypass Angioplasty Revascular-

ization Investigation (BARI) Trial (883) and the one-center Emory Angioplasty Surgery Trial (EAST) (884).

Both trials included patients with both stable and unstable angina who were considered suitable candidates for either PTCA or CABG. There are no PTCA versus CABG trials of patients with only chronic stable angina, and the results of the trials that were conducted did not appear to vary according to whether the patients had stable or unstable angina. Therefore, in trying to understand the invasive treatment of patients with chronic stable angina, these trials represent the best data available. It is important to note that because of the requirement that the patients be good candidates for PTCA, the PTCA versus surgery trials included a minority of the total spectrum of patients with multivessel disease that are considered for revascularization. For example, in the EAST trial, 16% of the patients who were screened were considered eligible for inclusion, and in the BARI trial, 60% of the patients considered possible clinical and angiographic candidates were thought to be anatomically unsuitable for PTCA when subjected to careful angiographic review (885). In both trials, a majority of patients had two- rather than three-vessel disease and normal LV function (ejection fraction >50%); a history of CHF was rare (<10%). In the BARI trial, 37% of patients had a proximal LAD lesion. In the EAST trial, >70% of patients had proximal LAD lesions, but the definition of an LAD lesion allowed more distal stenoses to be considered. Therefore, these trials did not include large numbers of patients who are at high risk for death without revascularization.

The results of both these trials at an \approx 5-year follow-up interval have shown that early and late survival rates have been equivalent for the PTCA and CABG groups. In the BARI trial, the subgroup of patients with treated diabetes had a significantly better survival rate with CABG. That survival advantage for CABG was focused in the group of diabetic patients with multiple severe lesions (886). In the EAST trial, persons with diabetes had an equivalent survival rate with CABG or PTCA at three years. Longer-term follow-up data from the BARI and EAST trials have not yet been published.

In both trials, the biggest differences in late outcomes were the need for repeat revascularization procedures and symptom status. In both BARI and EAST, 54% of PTCA patients underwent subsequent revascularization procedures during the five-year follow-up versus 8% of the BARI CABG group and 13% of the EAST CABG group. In addition, the rate of freedom from angina was better in the CABG group in both EAST and BARI, and fewer patients in the CABG group needed to take antianginal medications.

These and other randomized trials have provided important insights into the choice of interventional therapy for some patient subgroups, but there are also some clear limitations of these trials in terms of current recommendations for treatment of a broad spectrum of patients with multivessel CAD. First, because the patients included in the trials were a select minority of acceptable-risk patients with

multivessel disease who were good angiographic candidates for PTCA, the long-term outcome benefit of PTCA in the treatment of subsets of high-risk patients, particularly those in whom CABG has been shown to prolong survival most, has not been definitely established. Second, the results of these trials should not be applied to patients who are not good angiographic candidates for PTCA. Third, few patients in the PTCA-CABG randomized trials received intracoronary stents, a change in percutaneous technique that has decreased the rate of emergency bypass surgery and may decrease the incidence of restenosis but has not yet been subjected to long-term scrutiny. Fourth, the follow-up period of the PTCA-CABG studies extends only five years at this writing, a point at which the adverse effect of vein graft atherosclerosis has not yet become apparent. Fifth, although most of the patients in the surgical groups received LITA-LAD grafts, few patients underwent extensive arterial revascularization. All these changes in technique may conceivably change the relative benefit ratios of CABG and PTCA for some patient subgroups. Sixth, none of these trials used aggressive lipid-lowering therapy.

Finally, it is critical to understand that important patient subgroups, elderly patients, women and patients with previous bypass surgery were either not represented or were underrepresented in the randomized trials discussed. None of these trials have included patients with previous bypass surgery. The trials of initial medical versus initial surgical management excluded patients >65 years old and contained very few women. In the trials of PTCA versus surgery, women were included and reasonably well represented, but few patients >70 years old and none >80 were included.

The committee thought that patients with significant CAD who have survived sudden cardiac death or sustained ventricular tachycardia are best treated with CABG rather than PTCA. This subject is discussed in detail elsewhere (887). Use of CABG reduces sudden cardiac death compared with medical therapy (888) and appears to be beneficial in uncontrolled series of patients with prior cardiac arrest (889). There are few available data on this issue for PTCA. The risk of sudden death or ventricular arrhythmias recurring is likely to be greater with PTCA than CABG because of the known risk of restenosis after PTCA.

Recommendations for Revascularization in Patients With Native-Vessel CAD

Advances have been made in medical therapy that reduce MI and death and decrease the rate of progression of coronary stenoses. However, there is still no evidence that medical treatment alone sufficiently improves the life expectancy of the high-risk subgroups that were defined by the trials of medical treatment versus bypass surgery.

The randomized trials of initial medical treatment versus initial surgery showed that the patients with left main stenoses \geq 70% and those with multivessel CAD with a proximal LAD stenosis \geq 70% and abnormal LV function

have a better late survival rate if they have coronary bypass surgery. Because the randomized trials of PTCA versus bypass surgery included an inadequate number of patients in these high-risk subsets, it cannot be assumed that the alternative strategy of PTCA produces equivalent late survival in such patients.

Meta-analysis (489) of the randomized trials of medical management versus CABG has further indicated that patients without severe symptoms but with a proximal LAD lesion have a better survival rate with surgery, even if they have normal LV function and only one-vessel disease. For these patients, data from the PTCA versus CABG trials appear to show that, at least for the first five years, the alternative revascularization strategy of PTCA does not compromise survival for patients with normal LV function who are good angiographic candidates for PTCA.

Severely symptomatic patients with three-vessel disease have a better survival rate with surgery than medical management even in the absence of a proximal LAD lesion and the presence of good LV function. Severely symptomatic patients with abnormal LV function should have surgery. For good angiographic candidates who have normal LV function, PTCA may be considered an alternative to CABG if the patient is a favorable angiographic candidate for PTCA.

Caution should be used in the treatment of diabetic patients with PTCA, particularly in the setting of multivessel, multilesion, severe CAD, because the BARI trial showed that patients with diabetes had a better survival rate with CABG than PTCA (886).

Most patients with chronic angina have not been shown to have an increased survival rate with invasive treatment but may require invasive treatment for control of their symptoms. For patients with two-vessel disease, PTCA and surgery are both acceptable, and patients and physicians can select therapies based on an analysis of the advantages and disadvantages of the two forms of treatment. For patients with multivessel disease who are candidates for both surgery and PTCA, the current advantages and disadvantages of both procedures have been defined by the randomized trials. Both procedures had a low initial mortality rate (1% to 1.5%), but PTCA involved less initial morbidity cost and a lower hospital stay. On the other hand, recurrent angina and repeat procedures (either CABG or PTCA) were much more common after PTCA. By five postoperative years, the total cost of both procedures appeared to be equivalent.

Most patients with symptoms and ischemia based on one-vessel disease can be effectively treated with PTCA. For symptomatic patients with lesions unfavorable for PTCA or who wish to decrease the risk of undergoing subsequent procedures, CABG is an acceptable alternative and produces excellent long-term outcomes.

An important observation of the EAST trial was that the patients in the EAST registry (those deemed appropriate for randomization but not randomized and whose therapy was determined by patient-physician choice) appeared to have slightly better outcomes than either of the randomized

groups (890). In particular, the PTCA registry patients had better long-term outcome than the randomized PTCA patients did. These observations appear to suggest that even within a group of patients with similar baseline clinical and angiographic characteristics, the judgments of experienced interventional cardiologists and surgeons as to the best therapy may produce better outcomes than therapy by protocol or random choice. Furthermore, those judgments often appear to be based on the angiographic characteristics that influence the likelihood of a successful outcome with PTCA.

Patients With Previous Bypass Surgery

The previous sections apply only to patients with native-vessel CAD. The randomized studies of invasive therapy for chronic angina have all excluded patients who developed recurrent angina after previous bypass surgery. Patients with previous bypass surgery differ in many ways from those who have never had the surgery. First, their pathology is different. For patients with previous surgery, myocardial ischemia and jeopardy may be produced by progression of native-vessel CAD but also stenoses in vein grafts produced by intimal fibroplasia or vein graft atherosclerosis, pathologies that are distinct from native-vessel CAD. Few existing data define outcomes for risk-stratified groups of patients who develop recurrent angina after bypass surgery. Those that do indicate that patients with ischemia produced by late atherosclerotic stenoses in vein grafts are at higher risk with medical treatment alone than those with ischemia produced by native-vessel disease (510). Second, the risks of coronary reoperation are increased relative to the risks of primary coronary bypass procedures. Third, the risks of percutaneous treatment of vein graft stenoses are also increased, and long-term outcome is not as good as that documented for treatment of native-vessel lesions. Only one observational study contains data comparing medical and surgical treatments of risk-stratified groups of patients with previous bypass surgery. That study shows that patients with late (>5 years after operation) stenoses in saphenous vein grafts had a better survival rate with reoperation than initial medical management, particularly if a stenotic vein graft supplied the LAD (509). Patients with early (<5 years after operation) stenoses in vein grafts did not appear to have a better survival rate with reoperation, although their symptom status improved.

The heterogeneity of patients with previous bypass surgery makes treatment protocols difficult to establish. Patients with multiple vein grafts with late stenoses or late stenoses in an LAD vein graft should have reoperation in the absence of major contraindications to surgery. Despite improvement in the procedure-related complications of PTCA for vein graft stenoses by the use of coronary stents, stenting has not significantly decreased the incidence of restenosis in vein grafts (511) and is not an equivalent form of revascularization for patients with late vein graft stenoses. However, many symptomatic patients whose angina is

caused by native-vessel stenoses or focal and early (<5 years after operation) stenoses in saphenous vein grafts can be successfully treated with percutaneous techniques.

These guidelines are only general principles for patients with previous bypass surgery, and there are many gray areas. As indicated in Section III.D, a low threshold for angiographic evaluation is indicated for patients who develop chronic stable angina >5 years after surgery, especially when ischemia is documented noninvasively (473-475). Decisions about further therapy should be made with experienced invasive cardiologists and cardiac surgeons.

V. PATIENT FOLLOW-UP: MONITORING OF SYMPTOMS AND ANTIANGINAL THERAPY

Recommendations for Echocardiography, Treadmill Exercise Testing, Stress Imaging Studies and Coronary Angiography During Patient Follow-up

Class I

1. Chest X-ray for patients with evidence of new or worsening CHF. (*Level of Evidence: C*)
2. Assessment of LV ejection fraction and segmental wall motion in patients with new or worsening CHF or evidence of intervening MI by history or ECG. (*Level of Evidence: C*)
3. Echocardiography for evidence of new or worsening valvular heart disease. (*Level of Evidence: C*)
4. Treadmill exercise test for patients without prior revascularization who have a significant change in clinical status, are able to exercise and do not have any of the ECG abnormalities listed below in number 5. (*Level of Evidence: C*)
5. Stress imaging procedures for patients without prior revascularization who have a significant change in clinical status and are unable to exercise or have one of the following ECG abnormalities:
 - a. Pre-excitation (Wolff-Parkinson-White) syndrome. (*Level of Evidence: C*)
 - b. Electronically paced ventricular rhythm. (*Level of Evidence: C*)
 - c. More than 1 mm of rest ST depression. (*Level of Evidence: C*)
 - d. Complete left bundle-branch block. (*Level of Evidence: C*)
6. Stress imaging procedures for patients who have a significant change in clinical status and required a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results. (*Level of Evidence: C*)
7. Stress imaging procedures for patients with prior revascularization who have a significant change in clinical status. (*Level of Evidence: C*)
8. Coronary angiography in patients with marked limitation of ordinary activity (CCS class III) despite maximal medical therapy. (*Level of Evidence: C*)

Class IIb

Annual treadmill exercise testing in patients who have no change in clinical status, can exercise, have none of the ECG abnormalities listed in number 5 and have an estimated annual mortality rate >1%. (*Level of Evidence: C*)

Class III

1. Echocardiography or radionuclide imaging for assessment of LV ejection fraction and segmental wall motion in patients with a normal ECG, no history of MI and no evidence of CHF. (*Level of Evidence: C*)
2. Repeat treadmill exercise testing in <3 years in patients who have no change in clinical status and an estimated annual mortality rate ≤1% on their initial evaluation, as demonstrated by one of the following:
 - a. Low-risk Duke treadmill score (without imaging). (*Level of Evidence: C*)
 - b. Low-risk Duke treadmill score with negative imaging. (*Level of Evidence: C*)
 - c. Normal LV function and a normal coronary angiogram. (*Level of Evidence: C*)
 - d. Normal LV function and insignificant CAD. (*Level of Evidence: C*)
3. Stress imaging procedures for patients who have no change in clinical status and a normal rest ECG, are not taking digoxin, are able to exercise and did not require a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results. (*Level of Evidence: C*)
4. Repeat coronary angiography in patients with no change in clinical status, no change on repeat exercise testing or stress imaging and insignificant CAD on initial evaluation. (*Level of Evidence: C*)

Patients Not Addressed by This Section of the Guidelines and Level of Evidence for Recommendations for Follow-up

Patients Not Addressed in This Section of the Guidelines

Follow-up of patients in the following categories is not addressed by this section of the guidelines:

- Patients who have had an MI without subsequent symptoms. These patients should be evaluated according to the acute MI guidelines (1).
- Patients who have had an acute MI and develop chest pain within 30 days of the acute MI should be evaluated according to the acute MI guidelines (1).
- Patients who have had an MI who develop stable angina >30 days after infarction. These patients should have the initial assessment and therapy recommended for all patients.
- Patients who have had revascularization with angioplasty

or CABG without subsequent symptoms. These patients should be monitored according to guidelines provided elsewhere (18,19).

- Patients who have had angioplasty or CABG and develop angina within six months of revascularization should be monitored according to the PTCA and CABG guidelines (18,19).

Level of Evidence for Recommendations on Follow-up of Patients With Chronic Stable Angina

Although evidence of the influence of antiplatelet therapy, anti-ischemic therapy, revascularization, and risk factor reduction on health status outcome in patients with chronic stable angina exists, published evidence of the efficacy of specific strategies for the follow-up of patients with chronic stable angina on patient outcome does not. The recommendations in this section of the guidelines are therefore based on the consensus of the committee rather than published evidence.

Questions to Be Addressed in Follow-up of Patients With Chronic Stable Angina

There are five questions that must be answered regularly during the follow-up of the patient who is receiving treatment for chronic stable angina:

1. Has the patient decreased his or her level of physical activity since the last visit?
2. Have the patient's anginal symptoms increased in frequency and become more severe since the last visit? If the symptoms have worsened or the patient has decreased his or her physical activity to avoid precipitating angina, then he or she should be evaluated and treated appropriately according to either the unstable angina (2) or chronic stable angina guideline.
3. How well is the patient tolerating therapy?
4. How successful has the patient been in modifying risk factors and improving knowledge about ischemic heart disease?
5. Has the patient developed any new comorbid illnesses or has the severity or treatment of known comorbid illnesses worsened the patient's angina?

Follow-up: Frequency and Methods

The committee believes that the patient with successfully treated chronic stable angina should have a follow-up evaluation every 4 to 12 months. A more precise interval cannot be recommended because many factors influence the length of the follow-up period. During the first year of therapy, evaluations every four to six months are recommended. After the first year of therapy, annual evaluations are recommended if the patient is stable and reliable enough to call or make an appointment when anginal symptoms become worse or other symptoms occur. Patients who are comanaged by their primary-care physician and cardiologists may alternate these visits, provided that communica-

tion among physicians is excellent and all appropriate issues are addressed at each visit. Annual office visits can be supplemented by telephone or other types of contact between the patient and the physicians caring for him or her. Patients who cannot reliably identify and report changes in their status or who need more support with their treatment or risk factor reduction should be seen more frequently.

Focused Follow-up Visit: History

General Status and New Concerns

The open-ended question "How are you doing?" is recommended because it reveals many important issues. A general assessment of the patient's functional status and health-related quality of life may reveal additional issues that affect angina. For example, loss of weight may indicate depression or hyperthyroidism. Angina may be exacerbated by a personal financial crisis that prevents the patient from refilling prescriptions for medications. Open-ended questions should be followed by specific questions about the frequency, severity and quality of angina. Symptoms that have worsened should prompt reevaluation as outlined in these guidelines. A detailed history of the patient's level of activity is critical, because anginal symptoms may remain stable only because stressful activities have been eliminated. If the patient's account is not reliable, the assessment of a spouse, other family members, or friends needs to be included.

Anginal Symptoms and Antianginal and Antiplatelet Therapy

A careful history of the characteristics of the patient's angina, including exacerbating and alleviating conditions (outlined in Section II.A), must be repeated at each visit. Detailed questions should be asked about common drug side effects. An assessment should be made of the patient's adherence to the treatment program. Special emphasis should be given to aspirin because of its effectiveness, low cost, and minimal side effects. Providing a written prescription may help patients follow the recommendation for aspirin therapy.

Modifiable Risk Factors

Each patient should be asked specific questions about his or her modifiable risk factors (Section IV.C).

Review of Existing Comorbid Illnesses That May Influence Chronic Stable Angina

Specific questions should be asked about exacerbating illnesses and conditions (Section II.B). The elderly deserve extra attention, especially with regard to a drug's side effects and the impact of polypharmacy.

Focused Follow-up Visit: Physical Examination

The physical examination should be determined by the patient's history. Every patient should have weight, blood

pressure and pulse noted. Jugular venous pressure and wave form, carotid pulse magnitude and upstroke and the presence or absence of carotid bruits should be noted. Pulmonary examination, with special attention to rales, rhonchi, wheezing and decreased breath sounds is required. The cardiac examination should note the presence of gallops, a new or changed murmur, the location of the apical impulse, and any change from previous examinations. The vascular exam should identify any change in peripheral pulses and new bruits. The abdominal exam should identify hepatomegaly, hepatojugular reflux and the presence of any pulsatile masses suggestive of abdominal aortic aneurysm. The presence of new or worsening peripheral edema should be noted.

Laboratory Examination on Follow-up Visits

Glucose

The committee supports the current American Diabetes Association recommendation to screen patients not known to have diabetes with a fasting blood glucose measurement every three years and annual measurement of glycosylated hemoglobin for persons with established diabetes (740).

Cholesterol

The committee supports the National Cholesterol Education Program Adult Treatment Panel II guidelines, which recommend follow-up fasting blood work six to eight weeks after initiating lipid-lowering drug therapy, including liver function testing and assessment of the cholesterol profile, and then every 8 to 12 weeks during the first year of therapy. Subsequent cholesterol measurements at four- to six-month intervals are recommended. Long-term studies (up to seven years) demonstrate sustained benefit from continued therapy.

Laboratory Assessment for Noncardiac Comorbid Conditions

Routine measurement of hemoglobin, thyroid function, serum electrolytes, renal function or oxygen saturation is not recommended. These tests should be obtained when required by the patient's history, physical examination or clinical course.

ECG and Follow-up Stress Testing

The ECG can be repeated when medications affecting cardiac conduction are initiated or changed. A repeat ECG is indicated for a change in the anginal pattern, symptoms or findings suggestive of a dysrhythmia or conduction abnormality and near or frank syncope. There is no clear evidence showing that routine, periodic ECGs are useful in the absence of a change in history or physical examination.

Despite widespread use of follow-up stress testing in patients with stable angina, there are very few published data establishing its utility. The natural history of various patient cohorts with stable angina is well documented, and using the rationale described above, the committee formulated the following guidelines by expert consensus. On the

basis of the clinical, noninvasive and invasive data acquired during the initial evaluation, the clinician should be able to formulate an estimate of the patient's cardiovascular risk over the next three years. In the absence of a change in clinical status, low-risk patients with an estimated annual mortality rate of <1% over each year of the interval do not require repeat stress testing for three years after the initial evaluation. Examples of such patients are those with low-risk Duke treadmill scores either without imaging or with negative imaging (four-year cardiovascular survival rate, 99%), those with normal LV function and normal coronary angiograms, and those with normal LV function and insignificant CAD. The first group includes patients with chest pain >6 months after coronary angioplasty who have undergone complete revascularization and do not have significant restenosis as demonstrated by angiography. Annual follow-up testing in the absence of a change in symptoms has not been adequately studied; it might be useful in high-risk patients with an estimated annual mortality rate >3%. Examples of such patients include those with an ejection fraction <50% and significant CAD in ≥ 1 major vessel and those with treated diabetes and multivessel CAD who have not undergone CABG. Follow-up testing should be performed in a stable high-risk patient only if the initial decision not to proceed with revascularization may change if the patient's estimated risk worsens. Patients with an intermediate-risk ($\geq 1\%$ and $\leq 3\%$) annual mortality rate are more problematic on the basis of the limited data available. They may merit testing at an interval of one to three years, depending on their individual circumstances.

The choice of stress test to be used in patient follow-up testing should be dictated by considerations similar to those outlined earlier for the initial evaluation of the patient. In patients with interpretable exercise ECGs who are capable of exercise, treadmill exercise testing remains the first choice. Whenever possible, follow-up testing should be done using the same stress and imaging techniques to permit the most valid comparison with the original study. When different modes of stress and imaging are used, it is much more difficult to judge whether an apparent change in results is due to differences in the modality or a change in the patient's underlying status. In a patient who was able to exercise on the initial evaluation, the inability to exercise for follow-up testing is in and of itself a worrisome feature that suggests a definite change in functional and clinical status. In interpreting the results of follow-up testing, the physician must recognize that there is inherent variability in the tests that does not necessarily reflect a change in the patient's prognosis. For example, in one placebo-controlled trial that used serial exercise thallium testing, the treadmill time on repeat testing in the placebo group had a standard deviation of 1.3 min and the measured thallium perfusion defect of the left ventricle a standard deviation of about 5% (891). Both estimates suggest that even one standard deviation (67% confidence limits) on repeat testing includes a considerable range of results.

STAFF

American College of Cardiology

Christine W. McEntee, Executive Vice President
Dawn R. Phoubandith, MSW, Manager, Practice Guidelines
Kristi R. Mitchell, MPH, Researcher, Scientific and Research Services
Gwen C. Pigman, MLS, Assistant Director, On-Line and Library Services

American Heart Association

Rodman D. Starke, MD, FACC, Senior Vice President
Kathryn A. Taubert, PhD, Senior Scientist

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