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ACC/AHA 2002 Guideline Update 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 to Update the 1999 Guidelines for the Management of Patients With Chronic Stable Angina)

The Clinical Efficacy Assessment Subcommittee of the ACP-ASIM acknowledges the scientific validity of this product as a background paper and as a review that captures the levels of evidence in the management of patients with chronic stable angina as of November 17, 2002.

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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 as changes occur. (See Appendix 1 for conflict of interest information for writing committee members.)

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. There are circumstances where deviations from these guidelines are appropriate.

The Summary Article is published in the January 1, 2003 issue of the *Journal of the American College of Cardiology* and the January 7/14, 2003 issue of *Circulation*. The full-text guideline is posted on the ACC and AHA World Wide Web sites. Copies of the full text and summary article are available from both organizations.

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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 United States. 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 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. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful and effective.

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, 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. Methodologic support was provided by the University of California, San Francisco-Stanford (UCSF-Stanford) Evidence Based Practice Center (EPC). This document was reviewed by two outside reviewers nominated by the ACC, two outside reviewers nominated by the AHA, and two outside reviewers nominated by the ACP-ASIM. This document was approved for publication by the governing bodies of the ACC, AHA, and the Clinical Efficacy Assessment Subcommittee of the ACP-ASIM. The task force will review these guidelines 1

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, including those with previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The diagnosis, risk stratification, and treatment sections of these guidelines are intended to apply to symptomatic patients. Where appropriate, separate subsections consider the approach to the special group of asymptomatic patients with known or suspected coronary artery disease (CAD) on the basis of a history and/or electrocardiographic (ECG) evidence of previous myocardial infarction (MI), coronary angiography, or an abnormal noninvasive test. The inclusion of asymptomatic patients with abnormal noninvasive tests does not constitute an endorsement of such tests for the purposes of screening but simply acknowledges the clinical reality that such patients often present for evaluation after such tests have been performed. Multiple ACC/AHA guidelines and scientific statements have discouraged the use of ambulatory monitoring, treadmill testing, stress echocardiography, stress myocardial perfusion imaging, and electron-beam computed tomography (EBCT), previously called ultrafast CT, as routine screening tests in asymptomatic individuals. The reader is referred to these documents (Table 1) for a detailed discussion of screening, which is 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 after 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 MI, the reader is referred to the "ACC/AHA Guidelines for the Management of Patients With

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

Guideline (Reference Number)	Sponsor	Year of Publication
Guidelines		
Radionuclide imaging (12)	ACC/AHA	1995
Echocardiography (13)	ACC/AHA	1997
Exercise testing: 2002 Update (894)	ACC/AHA	2002
Valvular heart disease (15)	ACC/AHA	1998
Ambulatory electrocardiography (896)	ACC/AHA	1999
Coronary angiography (17)	ACC/AHA	1999
Coronary artery bypass surgery (19)	ACC/AHA	1999
Unstable angina and non–ST-elevation MI: 2002 Update (893)	ACC/AHA	2002
Percutaneous coronary intervention (1032)	ACC/AHA	2001
Statements		
Secondary prevention guidelines: 2001 update	AHA/ACC	2001
National Cholesterol Education Program (987)	NHLBI	2001
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
Bethesda Conference on insurability and employability of the patient with ischemic heart disease (27)	ACC	1989

ACC indicates American College of Cardiology; AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; ACP-ASIM, American College of Physicians–American Society of Internal Medicine; and AHCPR, Agency for Health Care Policy and Research.
The ACC/AHA guidelines are available at www.acc.org and www.americanheart.org.

Acute Myocardial Infarction: 1999 Update" (892). For patients with unstable angina, the reader is referred to the "ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction" (893). 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 more than 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 CABG. 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).

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 for such deviation. 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 United States who fall within these guidelines, but clearly it is measured in the millions. The reported annual incidence of angina is 213 per 100 000 population greater than 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 Americans 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 United States (892). 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 United States (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 × 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 United States (Table 2) and is responsible for 1 of every 4.8 deaths (9). The morbidity associated with this disease is also considerable: each year, more than 1 000 000 patients have an MI. Many more are hospitalized 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 after coronary revascularization, and 15% to 20% of patients rated their own health fair or poor despite revascularization. These data

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

	Death Rate per 100,000 Population	
Group	**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.

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).

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 more than $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 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 relative value unit is used, the direct cost to Medicare of these 61.2 million relative value units 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 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,

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.

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, which suggests that the clinical management of such patients is highly variable. The reasons for such variation in management are unknown.

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.

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

Recommendation

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, or high). ***(Level of Evidence: B)***

1. 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 at least one 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 noncardiac 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.

2. 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

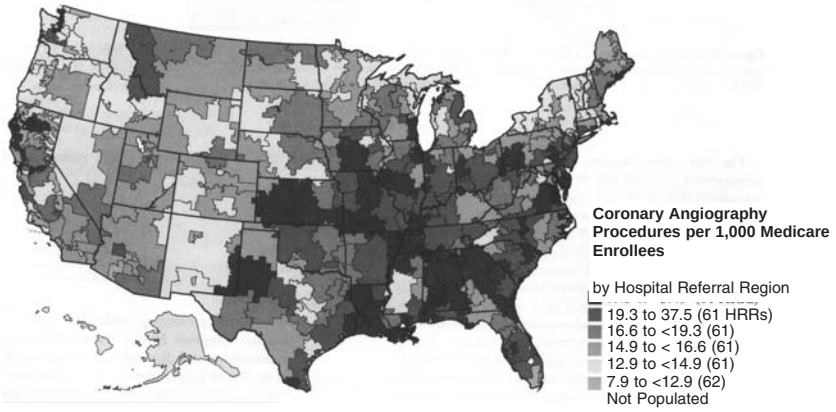

Figure 1. Map depicting coronary angiography rates in the U.S. HRR = hospital referral region. From Wennberg et al. (11) with permission.

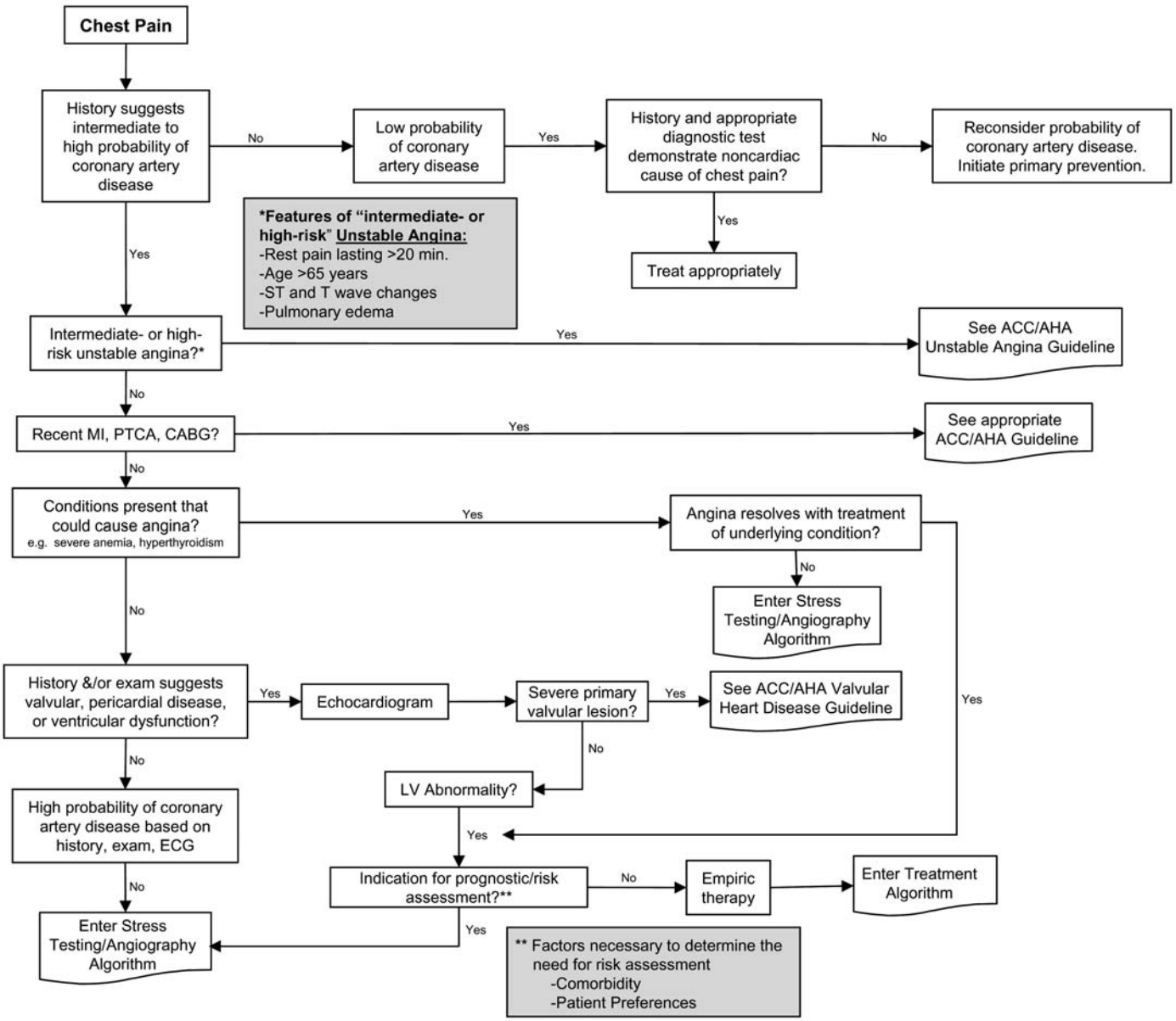

Figure 2. Clinical assessment. MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; ACC, American College of Cardiology; AHA, American Heart Association; LV, left ventricular; and ECG, electrocardiogram.

with a high degree of accuracy (29). Significant CAD is defined angiographically as CAD with greater than or equal to 70% diameter stenosis of at least one major epicardial artery segment or greater than or equal to 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, 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.

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).

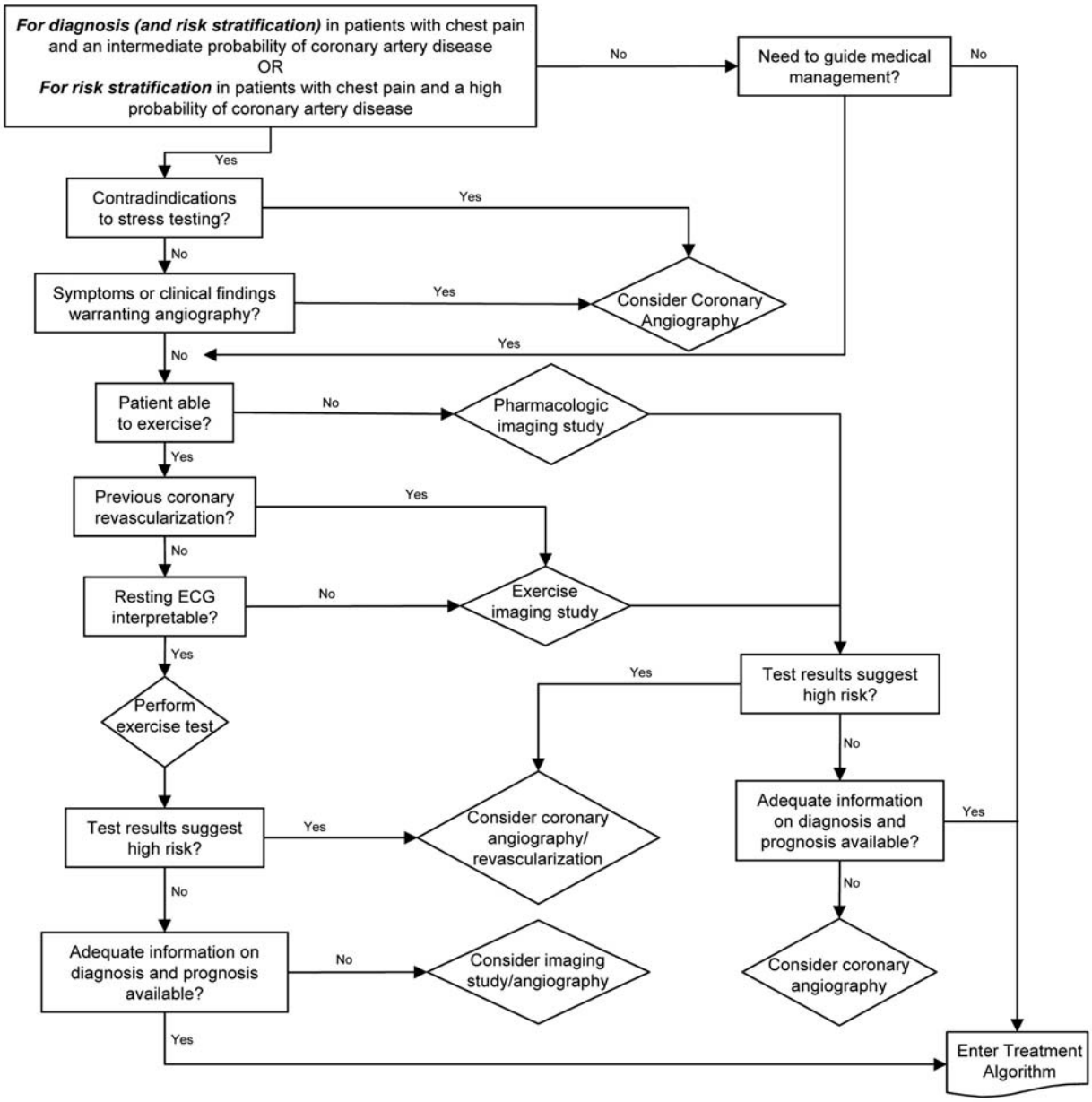

Figure 3. Stress testing/angiography. ECG indicates electrocardiogram.

Angina is further classified as stable or unstable (893). 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 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.

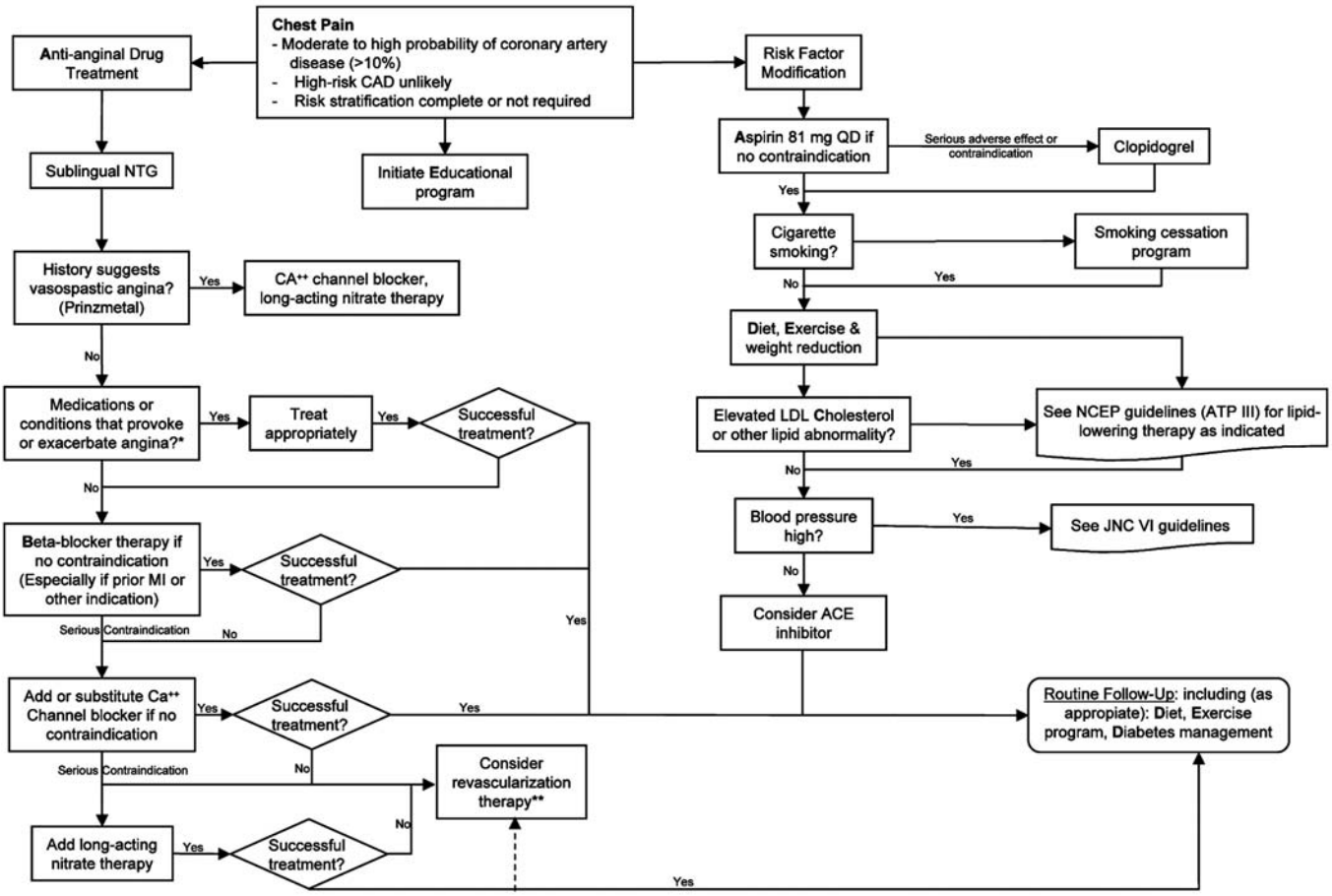

Figure 4. Treatment. CAD indicates coronary artery disease; NTG, nitroglycerin; MI, myocardial infarction; NCEP, National Cholesterol Education Program; JNC, Joint National Committee. *Conditions that exacerbate or provoke angina are medications (vasodilators, excessive thyroid replacement, and vasoconstrictors), other cardiac problems (tachyarrhythmias, bradyarrhythmias, valvular heart disease, especially aortic stenosis), and other medical problems (hypertrophic, cardiomyopathy, profound anemia, uncontrolled hypertension, hyperthyroidism, hypoxemia). **At any point in this process, based on coronary anatomy, severity of anginal symptoms, and patient preferences, it is reasonable to consider evaluation for coronary revascularization. Unless a patient is documented to have left main, three-vessel, or two-vessel coronary artery disease 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 coronary intervention or coronary artery bypass grafting.

Physical

The physical examination is often normal in patients with stable angina (33). However, an examination made during an episode of pain can be beneficial. An S_4 or S_3 sound or gallop, mitral regurgitant murmur, paradoxically split S_2, or bibasilar rales or chest wall heave that disappears when the pain subsides are all predictive of CAD (34). Even though the physical examination is generally not helpful for confirming CAD, a careful cardiovascular examination 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 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.

3. 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

Table 5. Clinical Classification of Chest Pain

Typical 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.
Atypical angina (probable)
Meets 2 of the above characteristics.
Noncardiac chest pain
Meets one or none of the typical anginal characteristics.

Modified from Diamond, JACC, 1983 (45).

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 greater than or equal to 1-mm ST-segment depression is observed. The test sensitivity is 50% and specificity 90% (894).

In patients with a low probability of CAD (5%), the positive predictive value of an abnormal test result is only 21%. If 1000 low-probability patients are tested, 120 will test positive. Of these, 95 will not have significant CAD. Before testing such a group, the clinician must weigh the value of correctly diagnosing CAD in 25 patients against the cost of a stress test for all 1000 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 (894).

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 examination characteristics most helpful in predicting CAD were determined. With these characteristics, predictive models (logistic regression equations) were devel-

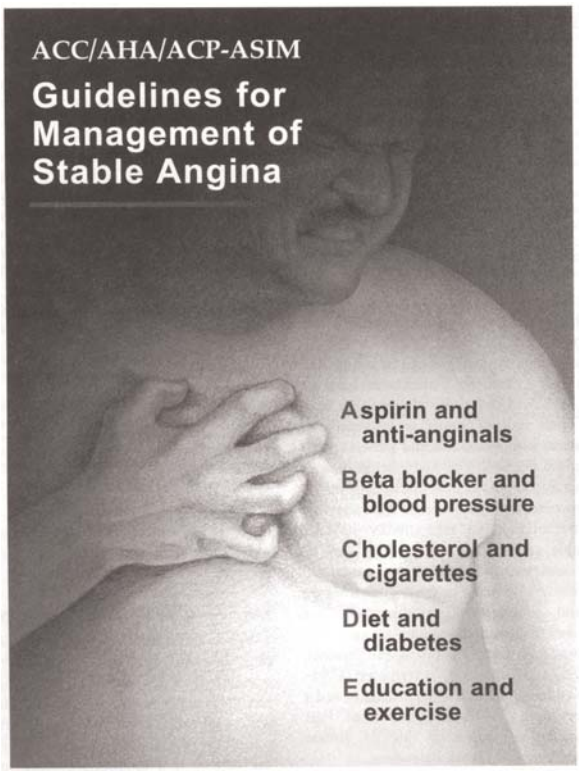

Figure 5. Treatment mnemonic: the 10 most important elements of stable angina management.

Table 6. Three Principal Presentations of Unstable Angina (893)

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).

CCSC indicates Canadian Cardiovascular Society Classification.

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.

oped. 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 greater than 250 mg per dl), and diabetes (glucose greater than 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.

4. 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 more than 20 000 patients. In both studies, 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 less than 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 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 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 less than 55 years old with atypical angina and no risk factors is less than 10%, but if diabetes, smoking, and hyperlipidemia are present, the likelihood jumps to 40%.

5. 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

Table 8. Short-Term Risk of Death or Nonfatal Myocardial Infarction in Patients With Unstable Angina (893)

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:
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 indicates 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.

often be referred only after therapeutic trials, time, or noncardiac diagnostic studies fail to eliminate CAD as a possibility. Correction 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, although 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.

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.

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.

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)***

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 y	3-35	1-19	8-59	2-39	30-88	10-78
45 y	9-47	2-22	21-70	5-43	51-92	20-79
55 y	23-59	4-25	45-79	10-47	80-95	38-82
65 y	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 ECGs. If ST-T-wave changes or Q waves had been present, the likelihood of CAD would be higher in each entry of the table.

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

Nonischemic 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
		Choledocholithiasis		Thought disorders
		Cholangitis		(e.g., fixed delusions)
		Peptic ulcer		
		Pancreatitis		

3. **Fasting lipid panel, including total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and calculated low-density lipoprotein (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, perhaps because of increased platelet aggregation, and 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 because of an outflow tract gradient, and end-diastolic pressure may be even higher owing to severe LV hypertrophy (LVH).

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 less than 9 g per dl of hemoglobin, and ST-T wave changes (depression or inversion) may be seen when hemoglobin drops below 7 g per dl.

Table 12. Conditions Provoking or Exacerbating Ischemia

Increased Oxygen Demand	Decreased Oxygen Supply
Noncardiac	*Noncardiac*
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
	Obstructive sleep apnea
Cardiac	Sickle cell disease
Hypertrophic cardiomyopathy	Sympathomimetic toxicity (e.g., cocaine use)
Aortic stenosis	Hyperviscosity
Dilated cardiomyopathy	Polycythemia
Tachycardia	Leukemia
Ventricular	Thrombocytosis
Supraventricular	Hypergammaglobulinemia
	Cardiac
	Aortic stenosis
	Hypertrophic cardiomyopathy

Hypoxemia resulting from pulmonary disease (e.g., pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial fibrosis, or 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 noncardiac 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 (CHF), 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.** ***(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 greater than or equal to 50% of patients with chronic stable angina (49). A normal rest ECG does not exclude severe CAD. ECG evidence of LVH 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 atrioventricular (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 approximately 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 for 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, AV 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 LV 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 severe 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%.

Electron-Beam Computed Tomography

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%; and the positive predictive value varied considerably from 55% to 84% and the 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 is the subject of the ACC/AHA Expert Consensus Document on Electron-Beam Computed Tomography for the Diagnosis and Prognosis of Coronary Artery Disease (895).

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 less than 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 less than 1 mm of baseline ST-segment depression. *(Level of Evidence: B)***
4. **Patients with ECG criteria for LVH and less than 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 owing 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 2002 Guideline Update for Exercise Testing" (894).

Although exercise testing is generally a safe procedure, both MI and death occur at a rate of less than or equal to 1 per 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 (59,894). Additional factors are relative contraindications: left main coronary stenosis, moderate aortic stenosis, electrolyte abnormalities, systolic hypertension greater than 200 mm Hg, diastolic blood pressure greater than 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 AV block (59,894). 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 CHF.

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 United States.

There are clear advantages in customizing the protocol to the individual patient to allow exercise lasting 6 to 12 minutes (69). Exercise capacity should be reported in estimated metabolic equivalents (METs) of exercise. (One MET is the standard basal oxygen uptake of 3.5 ml per 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 Centers for Medicare and Medicaid Services [CMS]) 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 more than 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 greater than or equal to 1 mm in leads without diagnostic Q waves (other than V_1 or aVR).

Relative indications for stopping include a drop in systolic blood pressure of more than 10 mm Hg from baseline blood pressure despite an increase in workload in the absence of other evidence of ischemia; more than 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 intraventricular conduction delay that cannot be distinguished from ventricular tachycardia; increasing chest pain; systolic blood pressure greater than 250 mm Hg; or diastolic blood pressure greater than 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 greater than or equal to 1 mm of horizontal or downsloping ST-segment depression or elevation for greater than or equal to 60 to 80 ms after the end of the QRS complex, either during or after exercise (894).

Cost and Availability

The exercise ECG is the least costly diagnostic test, with the cost of stress echocardiography being at least two-fold higher, stress single-photon mission computed tomography (SPECT) myocardial imaging at least five-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, because 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 72% of the treadmill exercise tests charged to Medicare in 1998 were performed as office procedures, and 27% of these charges were submitted by noncardiologists (894).

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.

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

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.

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

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, knowledge of the sensitivity and specificity of the exercise test and the patient's pretest probability of obstructive CAD is especially important when the results of exercise testing are interpreted.

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 (894). 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 in 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, LVH, and rest ST depression and those taking digoxin (894).

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 approximately 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 2002 Guideline Update for Exercise Testing" (894). 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 resting ECG is normal.

LEFT VENTRICULAR HYPERTROPHY WITH REPOLARIZATION ABNORMALITY. Left ventricular hypertrophy with repolarization abnormality on the rest ECG is associated with more false-positive test results because of decreased specificity.

REST ST-SEGMENT DEPRESSION. 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 less than or equal to 1 mm of 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 lead 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 less than 1 mV per second 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 greater than or equal to 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, an absence of exercise-induced chest pain, and markedly downsloping PR segments in the inferior leads. This issue of atrial repolarization waves is addressed in the "ACC/AHA 2002 Guideline Update for Exercise Testing" (894).

ST ELEVATION. When the rest ECG is normal, ST elevation (other than in lead 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).

ST-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. 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 neg-

ative 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 greater than or equal to 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 greater than 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 LVH 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.

ASYMPTOMATIC PATIENTS

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

Class IIb

Asymptomatic patients with possible myocardial ischemia on ambulatory ECG monitoring or with severe coronary calcification on EBCT (exceptions based on the rest ECG are the same as those listed above under Class III for symptomatic patients). ***(Level of Evidence: C)***

Class III (These recommendations are identical to those for symptomatic patients.)

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 owing to prior MI or coronary angiography; however, testing can assess functional capacity and prognosis, as discussed in Section III.** ***(Level of Evidence: B)***

The use of exercise ECG testing in asymptomatic patients as a means of screening for CAD is discussed in detail in the "ACC/AHA 2002 Guideline Update for Exercise Testing" (894) and is beyond the scope of this document. Interested readers are referred to that guideline for additional recommendations for the use of exercise ECG testing as an initial screening test.

In the absence of symptoms, ambulatory ECG monitoring can reveal transient ST-segment depression suggestive of CAD. However, as indicated in the "ACC/AHA Guidelines for Ambulatory Electrocardiography" (896), there is presently no evidence that ambulatory ECG monitoring provides reliable information concerning ischemia in asymptomatic subjects without known CAD.

In the absence of symptoms, EBCT is sometimes used as a means of screening for CAD. However, as indicated in the "ACC/AHA Expert Consensus Document on Electron-Beam Computed Tomography for the Diagnosis and Prognosis of Coronary Artery Disease" (895), available data are insufficient to support recommending EBCT for this purpose to asymptomatic members of the general public.

Physicians are often confronted with concerned asymptomatic patients with abnormal findings on ambulatory ECG and EBCT. Although the published data on this situation are scant, in the absence of symptoms, such patients have a low pretest probability of significant CAD. A negative exercise 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. The presence of severe coronary calcification on EBCT is common in older individuals. Because the evidence supporting the value of additional testing after EBCT is scant, the Committee suggests that further testing be reserved for individuals with severe calcification, defined as a calcium score greater than the 75th percentile for age- and gender-matched populations.

Asymptomatic patients with an established diagnosis of CAD because of prior MI or coronary angiography do not require exercise ECG testing for diagnosis. As discussed below in Section III, exercise ECG testing may be used for risk stratification in such patients, although its utility in asymptomatic patients is not well established.

3. Echocardiography

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, or akinesis) or by using a scoring system that describes the summated wall-motion score that reflects 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 approximately 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 dysfunc-

tion (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 PCI 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 or 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 less than 1 mm ST depression on the baseline ECG. *(Level of Evidence: B)***
   b. **LVH with less than 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 PCI 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) (894): 1) complete left bundle-branch block, electronically paced ventricular rhythm, pre-excitation (Wolff-Parkinson-White) syndrome, and other similar ECG conduction abnormalities; 2) patients who have more than 1 mm of ST-segment depression at rest, including those with LVH 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 and degradation 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 fewer than 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 these patients. Dipyridamole and adenosine side effects are antagonized by aminophylline, although this drug is ordinarily not needed after adenosine because of the latter's ultrashort half-life (less than 10 s).

Dobutamine in high doses (20 to 40 mcg $\cdot$ kg^{-1} $\cdot$ 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 probability 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, whereas 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 ^{201}Tl, 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, ^{201}Tl, ^{99m}Tc sestamibi, or ^{99m}Tc tetrofosmin can be used interchangeably with similar diagnostic accuracy in CAD.

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
Quin˜ones (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.

Myocardial perfusion imaging may use either planar or 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 ^{201}Tl 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 ^{201}Tl 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 ^{201}Tl 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 be explained in part 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 ^{201}Tl myocardial perfusion imaging (207-209), pharmacologic interventions have

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
Sylven (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.

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) 0.94 (f)	0.83 (m) 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.

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 ^{201}Tl 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 perfusion 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 (RNA) 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 at least one LV segment with stress, 2) a decrease in wall thickening in at least one 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 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 3210 patients, the range of reported overall sensitivities, uncorrected for posttest referral bias,

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) 0.90 (f)	0.96 (m) 0.79 (f)
Elhendy (316)	1997	306	0.73 (m) 0.76 (f)	0.77 (m) 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.

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

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 United States 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 greater than 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 (894). 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 in 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 ^{99m}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 CAD or a low pretest likelihood of CAD, both ^{201}Tl SPECT and ^{99m}Tc sestamibi had a similar sensitivity for detection of CAD in women (84.3% and 80.4% for greater than or equal to 70% stenosis) (248). However, ^{99m}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 echocar-

diography 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 lesser 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, ^{99m}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 (894). 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.

Asymptomatic Patients

Recommendations for Cardiac Stress Imaging as the Initial Test for Diagnosis in Asymptomatic Patients

Class IIb

1. **Exercise perfusion imaging or exercise echocardiography in asymptomatic patients with severe coronary calcification on EBCT who are able to exercise and have one of the following baseline ECG abnormalities:**
   a. **Pre-excitation (Wolff-Parkinson-White) syndrome. *(Level of Evidence: C)***
   b. **More than 1 mm of ST depression at rest. *(Level of Evidence: C)***
2. **Adenosine or dipyridamole myocardial perfusion imaging in asymptomatic patients with severe coronary calcification on EBCT but with one of the following baseline ECG abnormalities:**
   a. **Electronically paced ventricular rhythm. *(Level of Evidence: C)***
   b. **Left bundle-branch block. *(Level of Evidence: C)***
3. **Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with possible myocardial ischemia on ambulatory ECG monitoring or with severe coronary calcification on EBCT who are unable to exercise. *(Level of Evidence: C)***

Class III

1. **Exercise or dobutamine echocardiography in asymptomatic patients with left bundle-branch block. *(Level of Evidence: C)***
2. **Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging, or dobutamine echocardiography as the initial stress test in an asymptomatic patient with a normal rest ECG who is not taking digoxin. *(Level of Evidence: C)***
3. **Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in asymptomatic patients who are able to exercise and do not have left bundle-branch block or electronically paced ventricular rhythm. *(Level of Evidence: C)***

Recommendations for Cardiac Stress Imaging After Exercise ECG Testing for Diagnosis in Asymptomatic Patients

Class IIb

1. **Exercise myocardial perfusion imaging or exercise echocardiography in asymptomatic patients with an intermediate-risk or high-risk Duke treadmill score on exercise ECG testing. *(Level of Evidence: C)***
2. **Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in asymptomatic patients with a previously inadequate exercise ECG. *(Level of Evidence: C)***

Class III

Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging, or dobutamine echocardiography in asymptomatic patients with a low-risk Duke treadmill score on exercise ECG testing. *(Level of Evidence: C)*

As previously discussed in Section II.C.2, asymptomatic patients with abnormal findings on ambulatory ECG or EBCT who are able to exercise can be evaluated with exercise ECG testing, although the efficacy of exercise ECG testing in asymptomatic patients is not well established. Stress imaging procedures (i.e., either stress myocardial perfusion imaging or stress echocardiography) are generally not indi-

cated as the initial stress test in most such patients. In patients with resting ECG abnormalities that preclude adequate interpretation of the exercise ECG, the interpretation of the ST segment on ambulatory monitoring is also unreliable and is not an indication for either exercise testing or stress imaging. However, in patients with resting ECG abnormalities that preclude adequate interpretation of the exercise ECG, stress imaging procedures are preferable to the exercise ECG for the evaluation of severe coronary calcification on EBCT. If the baseline ECG shows pre-excitation or greater than 1 mm of ST depression, exercise stress imaging procedures are preferred. If the resting ECG shows a ventricularly paced rhythm or left bundle-branch block, vasodilator perfusion imaging is preferred. In patients who are unable to exercise, pharmacologic stress imaging is preferable to exercise ECG testing. The preference for stress imaging under these circumstances is based on the available literature in symptomatic patients. There are scant published data on the use of stress imaging procedures in asymptomatic patients in general, and in particular on asymptomatic patients with resting ECG abnormalities or asymptomatic patients who are unable to exercise. Thus, the efficacy of these procedures in asymptomatic patients is not well established. In asymptomatic patients with an intermediate-risk or high-risk Duke treadmill score on exercise ECG testing, stress imaging procedures are potentially useful as a second diagnostic test. Given the low pretest probability of asymptomatic patients, an abnormal exercise ECG in such a patient is likely a false-positive that will be confirmed by a negative stress image. However, the published data demonstrating the efficacy of stress imaging procedures in these specific circumstances are scant. In the presence of a low-risk Duke treadmill score on exercise ECG testing, stress imaging procedures in asymptomatic patients are usually not justified.

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 = NS). On the other hand, overall specificity (uncorrected for referral bias) tended to favor stress echocardiography (86% vs. 77%; p = 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 (1328 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 sensitivity; p = 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 less than 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. This cost per 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 per 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, the cost per QALY ratios would have decreased for both tests. Marwick also argued that the cost per 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 per-

fusion 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 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.

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 database—especially in evaluation of prognosis

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 because of 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 classic 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 approximately equal to 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 (12,13,894) (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 re-emphasize the value of a history of typical effort angina in middle-aged or elderly men, of whom approximately 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 pectoris have significant obstructive coronary disease (see following section).

E. 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 because of 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 may 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 owing 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.

1. 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).

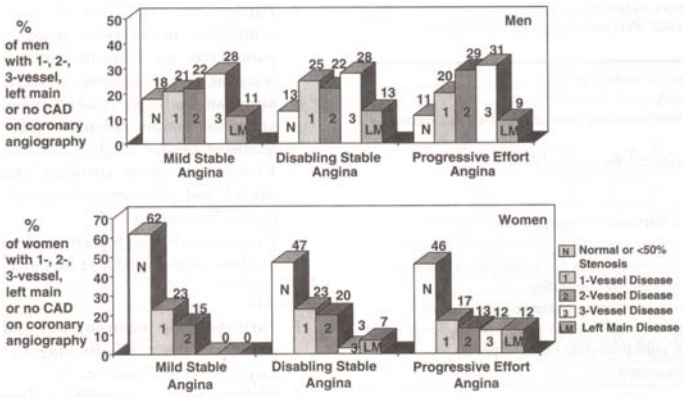

Figure 6. Coronary angiography findings in patients with chronic effort-induced angina pectoris. Top: Percentage of men with one-vessel, two-vessel, three-vessel, left main or no coronary artery disease on coronary angioraphy. Bottom: Percentage of women with one-vessel, two-vessel, three-vessel, left main, or no coronary artery disease on coronary angiography. N indicates 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).

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, two 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).

2. 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 greater than or equal to 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 more than 65 years old (345).

3. 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 3447 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 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).

4. 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, CT, 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.

5. 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 and to establish revascularization options (see Section IV).

Asymptomatic Patients

Coronary angiography is generally not indicated for diagnosis in asymptomatic patients. In specific rare circumstances (see Section III), it may be indicated for risk stratification in asymptomatic patients.

III. RISK STRATIFICATION

A. Clinical Assessment

1. 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 characteristics. 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, which indicates 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 (less than 75% diameter stenosis). In contrast, most of the "significant" plaques (greater than 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, which may explain the occasional acute coronary event that occurs shortly after a negative treadmill test result.

2. 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 surpris-

ingly 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 that suggest 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 (greater than 1 chance in 2) of severe disease on the basis of clinical parameters alone. Such patients should be considered for direct referral to angiography, because 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.

Descriptive information about the chest pain is very important in assessment of patient prognosis and 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 CHF, which reflect LV function, convey an adverse prognosis.

All the studies evaluating clinical characteristics as predictors of severe CAD used 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

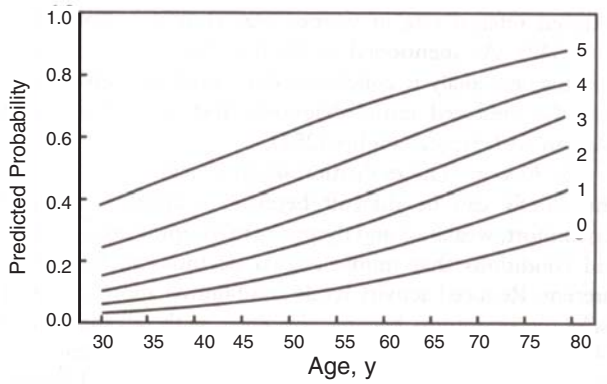

Figure 7. Nomogram showing the probability of severe (three-vessel or left main) coronary disease based on a five-point score. One point is awarded for each of the following variables: male gender, typical angina, history and electrocardiographic evidence of myocardial infarction, diabetes and use of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

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 3 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. Electrocardiogram/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 at least 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 AV block, atrial fibrillation, or ventricular tachyarrhythmias (362). The presence of LVH 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, which indicates 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 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 that suggests 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, cardiac imaging may be helpful in establishing pathophysiologic mechanisms and guiding therapy in patients who have clinical signs or symptoms of heart failure in addition to chronic stable angina. 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 if the status of LV systolic and diastolic function (by echocardiography or radionuclide imaging), valvular function, and pulmonary artery pressure (by echocardiographic transthoracic echo-Doppler techniques) is known.

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 less than 35% is associated with an annual mortality rate greater than 3% per year.

Current echocardiographic techniques permit a comprehensive assessment of LV size and function (366,377). 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 with 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).

Left Ventricular 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 ^{201}Tl 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 the choice of 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).

Asymptomatic Patients

In asymptomatic patients with a history of documented MI or Q waves on ECG, measurement of global LV systolic function is important. The recommendations listed earlier in this section for symptomatic patients are applicable. Echocardiography or RNA may help to confirm the history or ECG evidence of prior infarction by the demonstration of global or regional dysfunction. A decreased ejection fraction is prognostically important even in the absence of symptoms. Therapy with an angiotensin converting enzyme (ACE) inhibitor and a beta-blocker may then be appropriate. This issue is addressed in detail in the "ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult" (897).

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. **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 who have undergone cardiac catheterization to identify ischemia in the distribution of 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 2002 Guideline Update for Exercise Testing" (894).

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 that 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, LVH, 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 (greater than 1 mm), complete left bundle-branch block, ventricular paced rhythm, or pre-excitation. Although exercise capacity can be assessed in such patients, exercise-induced ischemia cannot. Patients unable to exercise because of 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 the inclusion of 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.

A second group of prognostic markers is related to exercise-induced ischemia. ST-segment depression and elevation

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	Clinical Variables Imaging Modality	N	End Point (Follow-up)	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 Tl-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 Tl-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 Tl-201	1,451	D/MI/Rev (12 months)	Yes	p = 0.28	Stepwise testing reduced cost by 64%
Christian	(397)	SPECT Tl-201	267	D/MI/Rev (34 months)	Yes	p = ns	Overall 4-year infarctfree survival was excellent at 95%
Mattera	(399)	SPECT Tl-201 or sestamibi	313	D/MI (12 months)	No	p = ns	Only 1 hard event
Mattera	(399)	SPECT Tl-201 or sestamibi	313	D/MI/Rev/UA (12 months)	No*	p = ns (Nl ECG vs. Nl MPI) p = 0.04 (Abn ECG vs. Abn MPI)	Stepwise testing (using clinical variables) reduced cost by 38%

Abn indicates abnormal; D, death; LM, left main; MI, myocardial infarction; MPI, myocardial perfusion imaging; Nl, normal; Rev, revascularization (after 3 months, except for Mattera); ROC, receiver operator characteristic curve analysis; UA, unstable angina; V, vessel. 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.

(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 times the ST-segment deviation, during or after exercise, in millimeters) minus (4 times 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).

Several studies have highlighted the prognostic performance of other parameters from the exercise test: chronotropic incompetence (898,899), abnormal heart rate recovery (900-905), and delayed systolic blood pressure response (906). As indicated in the 2002 update of the ACC/AHA Guidelines for Exercise Testing (907), further work is needed to define their role in the risk stratification of symptomatic patients relative to other well-validated treadmill test parameters.

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 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

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

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 (less than 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 less than or equal to 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 greater than or equal to 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 or More 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 6 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 PCI

Similar considerations apply to angioplasty patients. Restenosis is more frequent, however. Although most restenosis occurs less than 6 months after angioplasty, a period 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%, 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 PCI with either exercise ECGs or stress imaging, because restenosis commonly induces silent ischemia. The rationale for this approach is that ischemia, whether painful or silent, worsens prognosis (413,414). This approach appears 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, or suboptimal PCI 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.

Recommendations for Exercise Testing for Risk Assessment and Prognosis in Asymptomatic Patients

Class IIb

Asymptomatic patients with possible myocardial ischemia on ambulatory ECG monitoring or with severe coronary calcification on EBCT (exceptions are listed below in III). *(Level of Evidence: C)*

Class III

1. **Asymptomatic patients with possible myocardial ischemia on ambulatory ECG monitoring or with severe coronary calcification on EBCT, but 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)***

In asymptomatic patients with known or suspected CAD on the basis of possible myocardial ischemia on ambulatory ECG monitoring, severe coronary calcification on EBCT, or an established diagnosis of CAD because of prior MI or coronary angiography, risk stratification and prognosis are more important considerations than diagnosis. Because the treatment of asymptomatic patients cannot improve their symptoms, the principal goal of evaluation and treatment is the improvement of patient outcome by reducing the rate of death and nonfatal MI. In one large study dominated by asymptomatic patients, the Duke treadmill score predicted subsequent cardiac events . However, the absolute event rate was low, even in patients with high-risk scores, which suggests that the ability to improve outcome with revascularization in such patients is limited. Asymptomatic patients with intermediate-risk or high-risk Duke treadmill scores may be candidates for more intensive risk factor reduction. Patients with low-risk Duke treadmill scores can clearly be reassured regarding their low risk for subsequent cardiac events.

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 who either have 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 PCI.** ***(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, or 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, or 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 PCI.** ***(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 with 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 (894). 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 ^{99m}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 to assess 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 3594 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 5183 consecutive patients who underwent myocardial perfusion studies during stress and later at rest, patients with normal scans were at low risk (less than 0.5% per year) for cardiac death and MI during 642 (plus or minus 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 nonfatal 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 ^{99m}Tc-based agents followed by perfusion imaging or perfusion imaging with 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 greater than 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

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) ETT	Tl-201 (planar)	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	99.2 (per year)	6.5 (per year)	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) Dyp.	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

Abn indicates abnormal; CAD, 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.

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 (894). 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 in 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, ^{99m}Tc sestamibi may be preferable to ^{201}Tl scintigraphy for determining prognosis and 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 (12). Obese patients often have suboptimal perfusion images, especially with ^{201}Tl because of the marked photon attenuation by soft tissue. In these patients, ^{99m}Tc sestamibi is probably the most appropriate and should provide images of better quality than ^{201}Tl.

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 ^{201}Tl (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) were classified as high-risk patients (n = 20). 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) that included more than 300 patients followed up 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 PCI 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 (894).

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 fewer follow-up data than with radionuclide imaging. Recently, McCully et al. (476) assessed the outcomes of 1325 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 more than 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

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 indicates follow-up; Abn, abnormal; 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.

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 (894). 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 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 (aged 55 plus or minus 10 years) between 1989 and 1993 (129), with a follow-up of 41 (plus or minus 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% plus or minus 3% vs. 64% plus or minus 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 should still be 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 PCI, 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 six months or more 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 the 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).

ASYMPTOMATIC PATIENTS

Recommendations for Cardiac Stress Imaging as the Initial Test for Risk Stratification in Asymptomatic Patients

Class IIb

1. **Exercise perfusion imaging or exercise echocardiography in asymptomatic patients with severe coronary calcification on EBCT who are able to exercise and have one of the following baseline ECG abnormalities:**
   a. **Pre-excitation (Wolff-Parkinson-White) syndrome. *(Level of Evidence: C)***
   b. **More than 1 mm of ST depression at rest. *(Level of Evidence: C)***
2. **Adenosine or dipyridamole myocardial perfusion imaging in patients with severe coronary calcification on EBCT, but with one of the following baseline ECG abnormalities:**
   a. **Electronically paced ventricular rhythm. *(Level of Evidence: C)***
   b. **Left bundle-branch block. *(Level of Evidence: C)***
3. **Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with possible myocardial ischemia on ambulatory ECG monitoring or with severe coronary calcification on EBCT who are unable to exercise. *(Level of Evidence: C)***

Class III

1. **Exercise or dobutamine echocardiography in asymptomatic patients with left bundle-branch block. *(Level of Evidence: C)***
2. **Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging, or dobutamine echocardiography as the initial stress test in an asymptomatic patient with a normal rest ECG who is not taking digoxin. *(Level of Evidence: C)***
3. **Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in asymptomatic patients who are able to exercise. *(Level of Evidence: C)***

Recommendations for Cardiac Stress Imaging After Exercise ECG Testing for Risk Stratification in Asymptomatic Patients

Class IIb

1. **Exercise myocardial perfusion imaging or exercise echocardiography in asymptomatic patients with an intermediate-risk or high-risk Duke treadmill score on exercise ECG testing. *(Level of Evidence: C)***
2. **Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in asymptomatic patients with a previously inadequate exercise ECG. *(Level of Evidence: C)***

Class III

Exercise myocardial perfusion imaging, exercise echocardiography, adenosine or dipyridamole myocardial perfusion imaging, or dobutamine echocardiography in asymptomatic patients with a low-risk Duke treadmill score on exercise ECG testing. *(Level of Evidence: C)*

As already discussed in Section III.C.2, asymptomatic patients who are able to exercise can usually be evaluated with exercise ECG testing. Stress imaging procedures should be reserved for patients with resting ECG abnormalities and severe coronary calcification on EBCT, patients who are unable to exercise, and as a second test for patients with an intermediate-risk or high-risk Duke treadmill score on initial exercise ECG testing. Published data demonstrating the efficacy of stress imaging procedures in these specific circum-

stances are scant. Some of the published series listed in Tables 21 and 22 did include asymptomatic patients. However, this subset of patients was generally not analyzed separately. Blumenthal et al. reported a small study using exercise thallium testing in siblings of patients with premature coronary atherosclerosis (814). They demonstrated that the combination of an abnormal exercise ECG and a positive thallium image was prognostically important. However, many of the events included in their analysis were subsequent revascularizations, the performance of which was clearly influenced by the results of the exercise thallium test. Given the generally low event rate in asymptomatic patients, the ability of stress imaging procedures to identify a subset with a substantial absolute risk of subsequent events is problematic, with the possible exception of patients with previous MI.

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%), which shows the limited predictive value of symptom severity alone (485). Patients with mild anginal symptoms may have severe coronary disease (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 (94,488). 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 (12,13,37,894) (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 with 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 less than or equal to 1%. In contrast, patients with a survival advantage with CABG, such as those with three-vessel disease, have an annual mortality rate greater than or equal to 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 regardless of their symptomatic status. When appropriately used, noninvasive tests are less costly than coronary angiography and have an acceptable predictive value for adverse events (12,13,37,485,894). 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), because the total number of tests is reduced (335).

1. 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**

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 < 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%).

fraction less than 45%), CCS class I or II angina, and demonstrable ischemia but less than high-risk criteria on noninvasive testing. *(Level of Evidence: C)*

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 greater than 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)***

2. 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 less than 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 CAD (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 less than 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 less than 35% were 73%, 54%, and 21%, respectively (p less than 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 prognostic index, 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 greater than 95% proximal LAD stenosis was reported to be 59% compared with a rate of 79% for three-vessel disease without LAD stenosis (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 with 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, and presence of thrombus) and the number of lesions posing jeopardy to regions of contracting myocardium, the possible role of collaterals, and the 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.

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, ≥95%	32	91
2-vessel disease	37	88
2-vessel disease, both ≥95%	42	86
1-vessel disease, ≥95% proximal LAD	48	83
2-vessel disease, ≥95% LAD	48	83
2-vessel disease, ≥95% proximal LAD	56	79
3-vessel disease	56	79
3-vessel disease, ≥95% in at least 1	63	73
3-vessel disease, 75% proximal LAD	67	67
3-vessel disease, ≥95% proximal LAD	74	59

*Assuming medical treatment only. CAD indicates 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.

3. 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 accounts for late recurrence of chronic stable angina. Saphenous vein graft lesions represent a particularly unstable form of atherosclerosis that 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 more than 5 years after surgery, especially when ischemia is noninvasive-

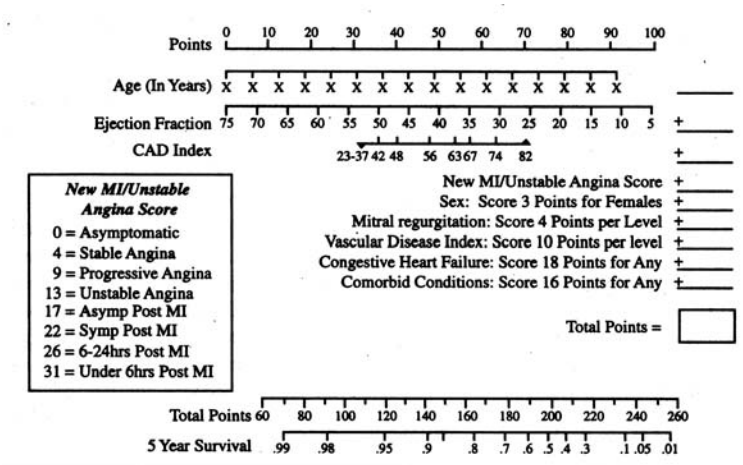

Figure 8. Nomogram for prediction of five-year survival from clinical, physical examination and cardiac catheterization findings. Asymp indicates asymptomatic; CAD, coronary artery disease; MI, myocardial infarction; and Symp, symptomatic. From Califf RM, Armstrong PW, Carver JR, et al: Task Force 5.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

ly 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).

4. Asymptomatic Patients

Coronary Angiography for Risk Stratification in Asymptomatic Patients

Recommendations

Class IIa

Patients with high-risk criteria suggesting ischemia on noninvasive testing (Table 23, items 2-9). *(Level of Evidence: C)*

Class IIb

1. **Patients with inadequate prognostic information after noninvasive testing. *(Level of Evidence: C)***
2. **Patients with clinical characteristics that indicate a high likelihood of severe CAD. *(Level of Evidence: C)***

Class III

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

The noninvasive test findings that identify high-risk patients (Table 23) are based on studies in symptomatic patients. These findings are probably also applicable to asymptomatic patients but are associated with a lower level of absolute risk in the absence of symptoms. As indicated earlier, the committee does not endorse such tests for the purposes of screening; their inclusion here acknowledges the reality that such patients often present after such tests have been performed. The presence of LV dysfunction in an asymptomatic patient probably does not by itself justify coronary angiography. However, the other high-risk noninvasive test findings that are detailed in Table 23, which reflect myocardial ischemia, are probably appropriate indications for coronary angiography, although there are only limited data to support this approach.

As discussed earlier, clinical characteristics are important in estimating the likelihood of severe CAD in symptomatic patients. These same characteristics are presumably helpful in the assessment of asymptomatic patients, although there are limited data to this effect. When clinical characteristics suggest a high risk of severe CAD, coronary angiography may be indicated, but this is not well established.

IV. TREATMENT

A. Pharmacologic Therapy

Recommendations for Pharmacotherapy to Prevent MI and Death and to 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)* or without prior MI. *(Level of Evidence: B)***
3. **Angiotensin converting enzyme inhibitor in all patients with CAD* who also have diabetes and/or LV systolic dysfunction. *(Level of Evidence: A)***
4. **Low-density lipoprotein–lowering therapy in patients with documented or suspected CAD and LDL cholesterol greater than 130 mg per dl, with a target LDL of less than 100 mg per dl. *(Level of Evidence: A)***
5. **Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina. *(Level of Evidence: B)***
6. **Calcium antagonists† or long-acting nitrates as initial therapy for reduction of symptoms when beta-blockers are contraindicated. *(Level of Evidence: B)***
7. **Calcium antagonists† or long-acting nitrates in combination with beta-blockers when initial treatment with beta-blockers is not successful. *(Level of Evidence: B)***
8. **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)***

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. **In patients with documented or suspected CAD and LDL cholesterol 100 to 129 mg per dl, several therapeutic options are available: *(Level of Evidence: B)***
   a. **Lifestyle and/or drug therapies to lower LDL to less than 100 mg per dl.**
   b. **Weight reduction and increased physical activity in persons with the metabolic syndrome (see page 74).**
   c. **Institution of treatment of other lipid or nonlipid risk factors; consider use of nicotinic acid or fibric acid for elevated triglycerides or low HDL cholesterol.**
4. **Angiotensin converting enzyme inhibitor in patients with CAD or other vascular disease. *(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)***

*Significant CAD by angiography or previous MI.
†Short-acting, dihydropyridine calcium antagonists should be avoided.

1. 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 antiischemic 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.

2. Measurement of Health Status and Quality of Life in Patients With Stable Angina

The traditional method to rate the severity of angina is the CCS classification (described earlier) or related schemas. These systems, however, are relatively general, may be insensitive to modest changes in symptoms or physical function, and may not permit accurate comparisons among patients. For example, two patients who experience symptoms with "usual activity" may in fact maintain very different levels of usual activity. Moreover, the CCS classification is intended to be applied by physicians and may not accurately reflect patients' own perceptions. For these reasons, questionnaires have been created to measure health status and physical function, both in general and specifically in relation to the symptoms and limitations associated with ischemic heart disease. Because both types of instruments are often used in clinical trials of new therapies such as revascularization and medications, practicing clinicians should possess a basic understanding of them to interpret the results.

Measures of health-related quality of life are often criticized as being overly subjective and unreliable in comparison with "hard" clinical end points such as death and MI. Such criticisms, however, overlook the fact that many of these measures have scales with internal consistencies (reflected by the Cronbach alpha statistic) that typically exceed 0.7 or 0.8 (908-912) and test-retest reliabilities that typically range from 0.7 to 0.9 or higher (910,913). This level of reliability approximates or exceeds that for total exercise time on treadmill testing (914) or interrater reliability of measurements of significant stenosis on coronary angiograms (915). Moreover, scores on health status questionnaires are predictive of future clinical events and utilization of health resources (916-919).

A thorough discussion of health-related quality of life is beyond the scope of these guidelines, and for more detail, the interested reader should consult general texts on this topic (920,921). A basic understanding includes knowledge of the attributes of a valid, reliable, and sensitive measure, as well as the differences between generic and condition-specific measures. A valid questionnaire is one that actually measures the characteristics of interest. By way of analogy, sphygmomanometry is valid because it produces measurements that are highly correlated with direct measurements of true intra-arterial pressure. Unfortunately, when attempting to quantify subjective characteristics, such as the severity of pain or dyspnea, there is no gold or reference standard by which to prove validity. Thus, measures of health status must often be compared with other indirect measures. For example, questionnaires measuring physical function in patients with CAD have been validated against treadmill performance (909,922), and measures of anginal severity have been compared with use of antianginal medications or degree of improvement after revascularization (911,923,924). Additionally, questionnaires should be shown to be clinically responsive, i.e., capable of differentiating clinically important improvement or deterioration from random or nonspecific changes in condition.

Generic measures of health status are designed to measure the global health of an individual, including physical and mental function and symptoms. Of the dozens of generic health-related quality of life questionnaires, three reliable and valid ones have been used most commonly in patients with heart disease—the Medical Outcomes Study Short-Form 36 (SF-36) (925,926), the Sickness Impact Profile (927,928), and the Nottingham Health Survey (929). Because generic questionnaires are designed for use with a wide variety of persons, including those who are healthy and those with chronic illnesses, they are often long and may be insensitive to subtle but clinically important changes in the status of a specific condition such as angina. For this reason, several reliable and valid questionnaires have been developed specifically to evaluate patients with ischemic heart disease and are usually preferred to generic instruments (Table 24a). Testing to determine responsiveness to clinical change has been less uniform. At present, there is no general consensus

Table 24a. Disease-Specific Measures for Patients With Chronic Stable Angina

Questionnaire/ Reference	Self-Administered	Number of Items	Scales	Reliable	Valid
CCS Classification (1034)	No	Variable	Physical limitations and symptoms	Yes	Yes
Seattle Angina Questionnaire (909,923)	Yes	19	1. Physical limitation 2. Anginal stability 3. Anginal frequency 4. Treatment satisfaction 5. Disease perception/ quality of life	Yes	Yes
Angina Pectoris Quality of Life Questionnaire (908,1035,1036)	Yes	22	1. Physical activities 2. Somatic symptoms 3. Emotional distress 4. Life satisfaction	Yes	Yes
Specific Activity Questionnaire (911,1037,1038)	Yes	13	Functional capacity	Unknown	Yes
Quality of Life After MI (1039,1040)	Yes	27	1. Physical 2. Emotional 3. Social	Yes	Yes
Cardiac Health Profile (910)	Yes	19	1. CCS scale 2. Quality of life 3. Mental health	Yes	Yes

CCS indicates Canadian Cardiovascular Society; MI, myocardial infarction.

that the performance of any one instrument is clearly superior, although the Seattle Angina Questionnaire is probably used most widely at the present time (930-934). On the basis of demonstration of reliability, validity, and responsiveness, the Seattle Angina Questionnaire was certified by the Medical Outcomes Trust, which has assumed its international distribution, and it has been translated into more than a dozen languages (935). The Seattle Angina Questionnaire has been or is currently being used in more than two dozen randomized trials of therapy and cohort studies of patients with ischemic heart disease and has been demonstrated to accurately predict mortality for a period of two years (936-948). Unfortunately, scores from one questionnaire cannot readily be compared with those from a different questionnaire. Furthermore, there is presently no conclusive evidence that use of either general or condition-specific health status measures in clinical practice improves outcomes.

3. Pharmacotherapy to Prevent MI and Death

Antiplatelet Agents

Aspirin exerts an antithrombotic effect by inhibiting cyclooxygenase and synthesis of platelet thromboxane A_2. The use of aspirin in more than 3000 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 (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 A_2, and platelet activating factor (518,519). It also reduces blood viscosity because of a 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 to its platelet receptors and thereby blocking adenosine diphosphate–dependent activation of the glycoprotein IIb/IIIa complex. In a randomized trial that compared clopidogrel with aspirin in patients with previous MI, stroke, or symptomatic 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 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. A meta-analysis of 287 randomized trials showed that the reduction in vascular events was comparable for doses of 75 to 150 mg daily and 160 to 325 mg daily; however, daily doses of less than 75 mg had less benefit (949).

Antithrombotic Therapy

Disturbed fibrinolytic function, such as elevated tissue plasminogen activator antigen, high plasminogen activator inhibitor, and low tissue plasminogen activator antigen 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 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 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 a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor in patients with documented CAD (including stable angina) with a baseline total cholesterol between 212 and 308 mg per dl was associated with 30% to 35% reductions in both mortality rate and major coronary events. In the Cholesterol And Recurrent Events (CARE) study (534), in both men and women with previous MI and total plasma cholesterol levels less than 240 mg per dl (mean 209) and LDL cholesterol levels of 115 to 174 mg per 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.

Angiotensin Converting Enzyme Inhibitors

The potential cardiovascular protective effects of ACE inhibitors have been suspected for some time. As early as 1990, results from the Survival And Ventricular Enlargement (SAVE) and Studies Of Left Ventricular Dysfunction (SOLVD) trials showed that ACE inhibitors reduced the incidence of recurrent MI and that this effect could not be attributed to the effect on blood pressure alone (950). At the same time, Alderman demonstrated that a high plasma renin was associated with a significantly higher incidence of death from MI in patients with moderate hypertension and that this effect was independent of blood pressure level (951).

The results of the Heart Outcomes Prevention Evaluation (HOPE) trial now confirm that use of the ACE inhibitor ramipril (10 mg per day) reduced cardiovascular death, MI, and stroke in patients who were at high risk for, or had, vascular disease in the absence of heart failure (952). The primary outcome in HOPE was a composite of cardiovascular death, MI, and stroke. However, the results of HOPE were so definitive that each of the components of the primary outcome by itself also showed statistical significance. Furthermore, only a small part of the benefit could be attributed to a reduction in blood pressure (–2 to –3 mm Hg). These vasculoprotective effects of the ACE inhibitor ramipril should not be surprising when one considers the location and function of ACE within the vasculature.

Greater than 90% of ACE is tissue bound, whereas only 10% of ACE is present in soluble form in the plasma. In nonatherosclerotic arteries, the majority of tissue ACE is bound to the cell membranes of endothelial cells on the

luminal surface of the vessel walls, and there is a large concentration of ACE within the adventitial vasa vasorum endothelium (953). It is now well appreciated that atherosclerosis represents different stages of a process that is in large part mediated by the endothelial cell. Thus, in the early stage, ACE, with its predominant location for the endothelial cells, would be an important mediator of local angiotensin II and bradykinin levels that could have an important impact on endothelial function. Indeed, treatment with the ACE inhibitor quinapril (40 mg per day) resulted in amelioration of endothelial dysfunction of coronary arteries in patients who did not have severe hyperlipidemia or evidence of heart failure (954). In more advanced lesions, ACE was also localized to the endothelium of the microvasculature throughout the plaque in association with increased angiotensin II.

Angiotensin converting enzyme generates angiotensin II from angiotensin I and catalyzes the degradation of bradykinin to inactive metabolites (955). Thus, ACE provides an important physiologic function in the balance between angiotensin II and bradykinin within the plasma, but more importantly in the vessel wall (956). Indeed, Vaughn and coworkers have shown that ramipril treatment resulted in a 44% reduction in plasma plasminogen activator inhibitor-1 antigen levels ($p = 0.004$) and a 22% reduction in plasminogen activator inhibitor-1 activity ($p = 0.02$) in post-MI patients compared with placebo (957). Thus, ramipril shifted the fibrinolytic balance toward lysis after a MI, a biochemical action that may account for the reduced risk of MI in clinical trials (950,952). Taken together, ACE inhibition shifts the balance of ongoing vascular mechanisms in favor of those promoting vasodilatory, antiaggregatory, antiproliferative, and antithrombotic effects.

The results of HOPE were extremely impressive when one considers the magnitude of the difference between ramipril and placebo in the primary outcomes of cardiovascular death, MI, and stroke. The HOPE study was unique in that of the 9541 patients in this study, 3577 (37.5%) had diabetes. There was a very significant reduction in diabetic complications, a composite for the development of diabetic nephropathy, need for renal dialysis, and laser therapy for diabetic retinopathy, in those patients receiving ramipril. Even more fascinating was the finding that among the patients who were not designated as diabetic at the beginning of the trial, fewer were diagnosed with diabetes during the four-year observation period if they were treated with ramipril. Prior to the HOPE trial, numerous clinical trials suggested that ACE inhibitor treatment may delay or prevent cardiovascular outcomes in patients with diabetes after an MI, in the presence of hypertension, and in the presence of a low ejection fraction or heart failure (Table 24b). Furthermore, ACE inhibitors may also prevent overt nephropathy and other microvascular outcomes in patients with type 1 or type 2 diabetes (Table 24b).

The Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO)-HOPE (957a), a substudy of the HOPE study, has provided new clinical data on the cardiorenal therapeutic benefits of ACE inhibitor intervention in a broad range of middle-aged patients with diabetes mellitus who are at high risk for cardiovascular events. The risk of MI was reduced by 22% ($p = 0.01$), stroke by 33% ($p = 0.0074$), cardiovascular death by 37% ($p = 0.0001$), and the combined primary outcome of these events by 25% ($p = 0.0004$). Ramipril also lowered the risk of overt nephropathy by 24% ($p = 0.027$).

Angiotensin converting enzyme inhibitors should be used as routine secondary prevention for patients with known CAD, particularly in diabetics without severe renal disease. There are two ongoing clinical trials evaluating the effect of two different ACE inhibitors (trandolapril and perindopril) in patient populations that are similar but in many respects distinctly different from the HOPE patient population. The Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) study is randomizing patients who have had a percutaneous transluminal angioplasty or CABG, an MI, or angiographic evidence of single-vessel disease to trandolapril or placebo. The European trial on reduction of cardiac events with perindopril in stable CAD (EUROPA) will enroll a similar group of patients and will also include those with positive stress tests. Both studies will exclude patients with heart failure. Furthermore, these studies do not include patients with diabetes mellitus. Accordingly, these studies should answer the question whether a vasculoprotective effect can be accomplished in a lower-risk group of patients than those enrolled in the HOPE study.

Table 24b. Beneficial Effects of ACE Inhibition in Patients With Diabetes Mellitus

Clinical Condition	Outcome	Treatment	Reference
DM	Progression of proteinuria	Enalapril vs. placebo	(1041)
DM	Death, dialysis, and renal insufficiency	Captopril vs. placebo	(1042)
DM	Progression of nephropathy	Enalapril vs. placebo	(1043)
DM	Progression of retinopathy	Lisinopril vs. placebo	(1044)
DM + HBP	Incidence of fatal and nonfatal MI	Enalapril vs. nisoldipine	(1045)
DM + HBP	Incidence of MI, stroke, or unstable angina	Fosinopril vs. amlodipine	(1046)
DM + acute MI	Six-week survival	Lisinopril vs. placebo	(1047)
DM + chronic CHF	Mortality	Enalapril vs. placebo	(1048)
DM + HBP	Cardiovascular events	Captopril vs. placebo	(1049)
DM + HBP	Cardiovascular events	Captopril vs. atenolol	(1050)

DM indicates diabetes mellitus; HBP, high blood pressure; MI, myocardial infarction; CHF, congestive heart failure.

Another important question is whether the vasculoprotective effect would be obtained with any one of the many ACE inhibitors available to the clinician. This is the subject of continuing controversy. Quantitative differences do exist among the ACE inhibitors, and optimal doses for therapeutic benefit must be established in large-scale clinical trials such as those outlined above. It is of interest that the HOPE, PEACE, and EUROPA trials use "tissue ACE inhibitors" that have high lipophilicity and enzyme-binding capabilities. It has been postulated but not proved that ACE inhibitors with these properties provide greater penetrance into the atherosclerotic plaque and more effective inhibition of tissue ACE inhibitors. Others believe that this is a "class effect," because enalapril improved outcomes in CONSENSUS II (Cooperative North Scandinavian Enalapril Survival Study) (959) and SOLVD (960), and captopril improved five-year survival in the SAVE trial (961). Regardless of the outcome of these studies, there appears to be a particular mandate for the use of ACE inhibitors in secondary prevention in patients with diabetes and CAD. In the ongoing Bypass and COURAGE trials, ACE inhibitors are prescribed for all diabetics with documented ischemic heart disease unless contraindicated. The ACE inhibitor used in the BARI-2-D trial is quinapril (an agent with high lipophilicity and enzyme-binding capabilities—a tissue ACE).

Antianginal and Anti-ischemic Therapy

Antianginal and anti-ischemic drug therapy are administered in conjunction with pharmacotherapy to prevent MI and death, although some interventions, such as beta-blockers and CABG in certain high-risk groups, simultaneously improve angina and ischemia while preventing MI and sudden cardiac death. The main goal of antianginal therapy, however, is to reduce symptoms of cardiac ischemia and thus improve physical function and quality of life. The most effective agents for relieving ischemia and angina are beta-blockers, calcium antagonists, and nitrates.

BETA-BLOCKERS. *Mechanism of action.* Activation of beta-receptors is associated with an increase in heart rate, acceleration of conduction through the 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 adenosine monophosphate, 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-blockers 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 per min. In patients with more severe angina, heart rate can be reduced to less than 50 beats per 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 to be effective in stable angina (537-539). Agents with combined alpha- and beta-adrenergic antagonist properties have also proved effective in the management of chronic stable angina (540,541). Beta-block-

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 mcg/kg/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.

ers 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); therefore, they should 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, controlled 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 (APSIS) (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 treat-

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
APSIS/Rehnqvist	Eur Heart J1996	809	Metoprolol* 406	Verapamil 403	3.4 y	Death	22	25	1.01 (0.63, 1.6)
						Cardiac death	19	19	
						Nonfatal MI	17	14	
TIBET/Dargie	Eur Heart J 1996	458	Atenolol 226	Nifedipine* 232	2 y	Cardiac death	3	6	1.22 (0.63, 2.4)
						Nonfatal MI	14	15	
IMAGE/Savonitto	JACC 1996	127	Metoprolol* 65	Nifedipine* 62	6 wk	Death	1	0	0.5 (0.05, 5.8)
						Nonfatal MI	1	1	
de Vries	Int J Card 1996	128	Atenolol 66	Nifedipine* 62	4 wk	Nonfatal MI	0	1	1.07 (0.2, 55)
TIBBS/Von Arnim	JACC 1995	330	Bisoprolol 161	Nifedipine* 169	4 wk	Nonfatal MI	0	1	1.91 (0.06, 57)
Ahuja	Int J Card 1993	134	Metoprolol 68	Diltiazem 66	4 wk	Death or MI	0	0	1.03 (0.02, 53)
							Death or MI		Summary OR
Total		1986	992	994			58	62	1.06 (0.73, 1.54)

*Long-acting preparations.

ed with 100 mg of 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, 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 at least two episodes of transient myocardial ischemia during 48 h of ambulatory ECG monitoring were randomized to either 10 mg of bisoprolol once daily or 20 mg of 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 was assessed in patients with stable angina pectoris. In this study, 280 patients less than or equal to 75 years old with stable angina for at least six months and a positive exercise test were randomized to receive 200 mg of metoprolol daily or 20 mg of nifedipine twice daily for six weeks after a two-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, pre-existing high degree of AV block, sick sinus syndrome, and severe, unstable LV failure (mild CHF may actually be an indication for 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 the most common 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 the sense of fatigue may be increased (564). The average incidence of impotence is about 1%; however, lack of or inadequate erection has been observed in less than or equal to 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 channels: L type, T type, and 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 variable 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 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

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			
Bepridil	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	

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 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 vasoselective 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 Fosinopril versus Amlodipine Cardiovascular Events randomized Trial (FACET) (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 the major contraindication for the use of calcium

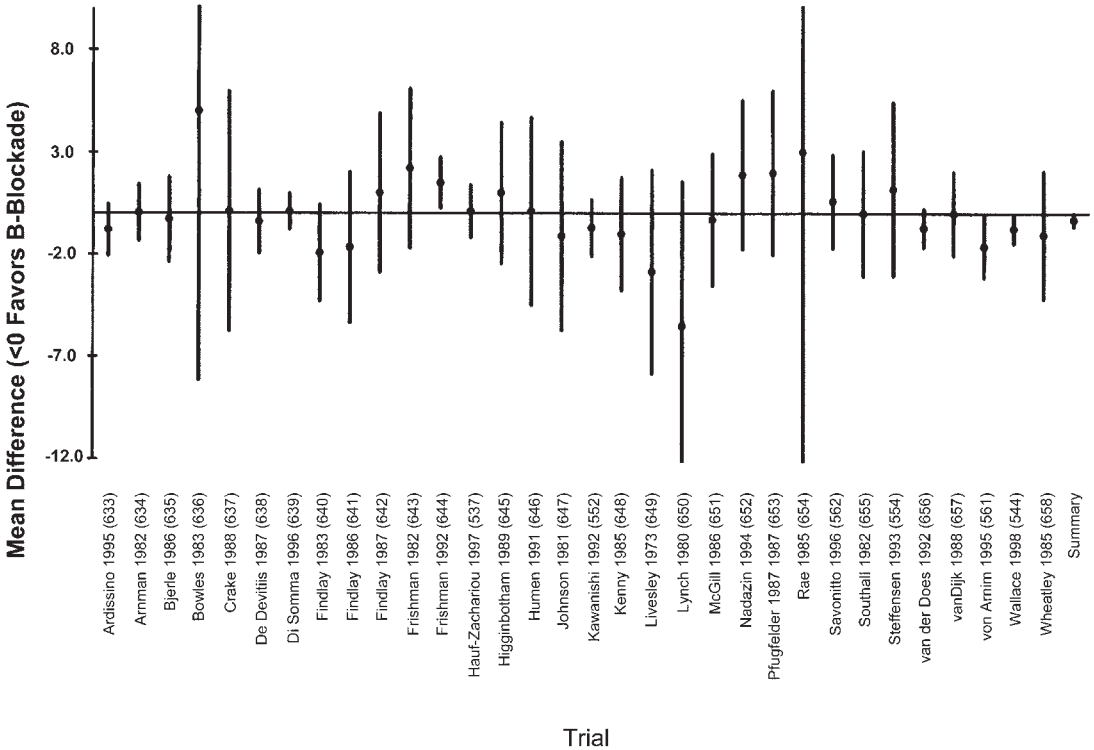

Figure 9. Beta-blockers versus calcium antagonists: angina relief. Source: Heidenreich PA, for the UCSF-Stanford Evidence-based Practice Center (AHCPR).

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 bepridil.

Side effects. Hypotension, depression of cardiac function, and worsening heart failure may occur during long-term treatment with any calcium antagonist (589-591) (Table 27). 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

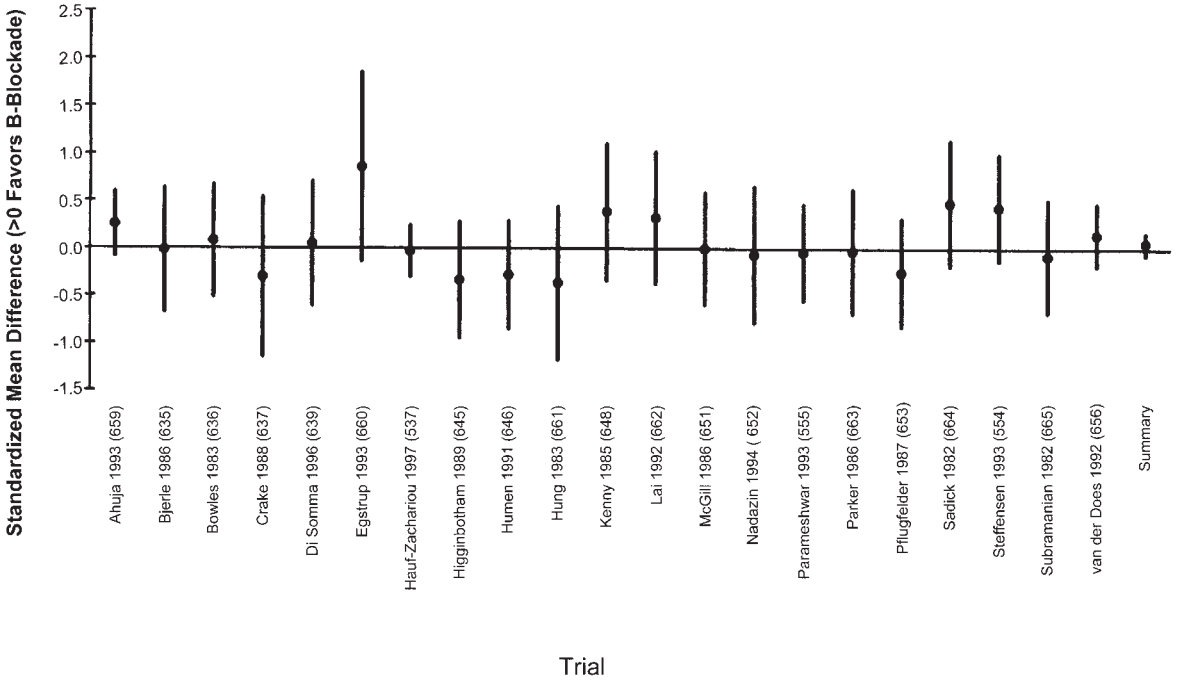

Figure 10. Beta-blockers versus calcium antagonists: exercise time to 1-mm ST depression. The Subramanian article reported similar information to the Bowles article. Source: Heidenreich PA, for the UCSF-Stanford Evidence-based Practice Center (AHCPR).

sinus node dysfunction may occur with heart rate–modulating calcium antagonists. Bepridil can induce polymorphic 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 and 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 angina pectoris was assessed. In this randomized, double-blind, placebo-controlled, multicenter trial, 315 men, aged 35 to 80 years, with stable angina, at least three attacks of angina per week, and at least four ischemic episodes during 48 h of ambulatory ECG monitoring were randomized to receive either 5 or 10 mg of 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. Nitroglycerin 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. Because 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 antiischemic 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 sprays 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 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 presyn-

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	1½–7 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	2.5–13 mg	4–8 h
	Buccal	1–3 mg 3 times daily	3–5 h
	Intravenous	5–200 mcg/min	Tolerance in 7–8 h
Isosorbide Dinitrate	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	2–2½ 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 60–240 mg once daily	12–24 h
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

cope or syncope (554,555). Rarely, sublingual nitroglycerin administration can produce bradycardia and hypotension, probably due to activation of the Bezold-Jarisch reflex.

Other Antianginal Agents and Therapies. Molsidomine, a sydnonimine that has pharmacologic 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). A reduction of exercise-induced myocardial ischemia has been reported with the addition of an ACE inhibitor in patients with stable angina with optimal beta-blockade and normal LV function (962). The serotonin antagonist ketanserin appears not to be an effective antianginal agent (626). Labetalol, a beta- and alpha-adrenoceptor 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).

Controversies exist regarding antianginal efficacy of the sex hormones. Both an increase in the treadmill exercise time to myocardial ischemia and lack of such benefit has been observed with 17-beta-estradiol in postmenopausal women with stable angina (963,964). In a randomized, double-blind, placebo-controlled study that included a relatively small number of men with chronic stable angina, low-dose transdermal testosterone therapy has been reported to improve angina threshold (965). 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. The use of antibiotics to treat CAD is not recommended.

4. Choice of Pharmacologic Therapy in Chronic Stable Angina

The primary consideration in the choice of pharmacologic 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 believes 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

1. 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 to 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 is 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.

2. Initial Treatment

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

A = **A**spirin and Antianginal therapy
B = **B**eta-blocker and Blood pressure
C = **C**igarette smoking and Cholesterol
D = **D**iet and Diabetes
E = **E**ducation and Exercise

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.

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 MI) 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, verapamil, diltiazem
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 ≥ 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

MI indicates myocardial infarction; LVEF, left ventricular ejection fraction.

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.

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 commit-

tee 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.

3. Asymptomatic Patients

Recommendations for Pharmacotherapy to Prevent MI and Death in Asymptomatic Patients

Class I

1. **Aspirin in the absence of contraindication in patients with prior MI. *(Level of Evidence: A)***
2. **Beta-blockers as initial therapy in the absence of contraindications in patients with prior MI. *(Level of Evidence: B)***
3. **Lipid-lowering therapy in patients with documented CAD and LDL cholesterol greater than 130 mg per dl, with a target LDL of less than 100 mg per dl. *(Level of Evidence: A)***
4. **ACE inhibitor in patients with CAD who also have diabetes and/or systolic dysfunction. *(Level of Evidence: A)***

Class IIa

1. **Aspirin in the absence of contraindications in patients without prior MI. (*Level of Evidence: B)***
2. **Beta-blockers as initial therapy in the absence of contraindications in patients without prior MI. *(Level of Evidence: C)***
3. **Lipid-lowering therapy in patients with documented CAD and LDL cholesterol of 100 to 129 mg per dl, with a target LDL of 100 mg per dl. *(Level of Evidence: C)***
4. **Angiotensin converting enzyme inhibitor in all patients with diabetes who do not have contraindications due to severe renal disease. *(Level of Evidence: B)***

Even in asymptomatic patients, aspirin and beta-blockers are recommended in patients with prior MI. The data in support of these recommendations are detailed in the ACC/AHA Guideline for the Management of Patients With Acute Myocardial Infarction: 1999 Update (892).

In the absence of prior MI, patients with documented CAD on the basis of noninvasive testing or coronary angiography probably also benefit from aspirin, although the data on this specific subset of patients are limited.

Several studies have investigated the potential role of beta-blockers in patients with asymptomatic ischemia demonstrated on exercise testing and/or ambulatory monitoring (966-968). The data generally demonstrate a benefit from beta-blocker therapy, but not all trials have been positive (966-969).

Lipid-lowering therapy in asymptomatic patients with documented CAD was demonstrated to decrease the rate of adverse ischemic events in the 4S trial (533), as well as in the CARE study (534) and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial (970), as previously mentioned.

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).

A particularly important facet of education is helping patients to understand their medication regimens. That many patients with cardiac disease fail to properly use prescribed medications is well documented (971). Moreover, poor adherence with cardiac medications is associated with increased mortality, increased morbidity, and excess hospitalization (972-975). Problems with medication adherence are related to the number of medications prescribed and the complexity and expense of the regimen. Improving patients' adherence to medications require a multifaceted approach that can involve nurses, pharmacists, health educators, educational materials, and automated systems, as well as physicians (976).

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).

1. 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, they have 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 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 cardiopulmonary resuscitation (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.

2. 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 due to 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 (i.e., immediately when pain begins or before stressful activity) and how often (i.e., three times spaced five minutes apart if pain persists) to take sublingual nitrates 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 hours 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. **Comprehensive cardiac rehabilitation program (including exercise). *(Level of Evidence: B)***
5. **Low-density lipoprotein-lowering therapy in patients with documented or suspected CAD and LDL cholesterol greater than or equal to 130 mg per dl, with a target LDL of less than 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
1. **In patients with documented or suspected CAD and LDL cholesterol 100 to 129 mg/dl, several therapeutic options are available:**
   a. **Lifestyle and/or drug therapies to lower LDL to less than 100 mg per dl. *(Level of Evidence: B)***
   b. **Weight reduction and increased physical activity in persons with the metabolic syndrome. *(Level of Evidence: B)***
   c. **Institution of treatment of other lipid or nonlipid risk factors; consider use of nicotinic acid or fibric acid for elevated triglycerides or low HDL cholesterol. *(Level of Evidence: B)***
2. **Therapy to lower non-HDL cholesterol in patients with documented or suspected CAD and triglycerides of greater than 200 mg per dl, with a target non-HDL cholesterol of less than 130 mg per dl. *(Level of Evidence: B)***
3. **Weight reduction in obese patients in the absence of hypertension, hyperlipidemia, or diabetes mellitus. *(Level of Evidence: C)***

Class IIa
1. **Folate therapy in patients with elevated homocysteine levels. *(Level of Evidence: C)***
2. **Identification and appropriate treatment of clinical depression to improve CAD outcomes. *(Level of Evidence: C)***
3. **Intervention directed at psychosocial stress reduction. *(Level of Evidence: C)***

Class III
1. **Initiation of hormone replacement therapy in postmenopausal women for the purpose of reducing cardiovascular risk. *(Level of Evidence: A)***
2. **Vitamin C and E supplementation. *(Level of Evidence: A)***
3. **Chelation therapy. *(Level of Evidence: C)***
4. **Garlic. *(Level of Evidence: C)***
5. **Acupuncture. *(Level of Evidence: C)***
6. **Coenzyme Q. *(Level of Evidence: C)***

1. 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). The benefit of this system is that it allows for changes in the categorization as new evidence becomes available. 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 that cannot be modified or the modification of which would be unlikely to change the incidence of coronary disease events.

2. 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

Goals	Interventions and Recommendations		
Smoking: Goal complete cessation	Assess tobacco use. Strongly encourage patient and family to stop smoking and to avoid second-hand smoke. Provide counseling, pharmacological therapy (including nicotine replacement and buproprion), and formal cessation programs as appropriate.		
BP control: Goal <140/90 mm Hg or <130/85 mm Hg if heart failure or renal insufficiency <130/80 mm Hg if diabetes	Initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients with blood pressure ≥130 mm Hg systolic or 80 mm Hg diastolic Add blood pressure medication, individualized to other patient requirements and characteristics (i.e., age, race, need for drugs with specific benefits) **if** blood pressure is not <140 mm Hg systolic or 90 mm Hg diastolic, **or** if blood pressure is not <130 mm Hg systolic or 85 mm Hg diastolic for individuals with heart failure or renal insufficiency (<80 mm Hg diastolic for individuals with diabetes)..		
Lipid Management: Primary goal LDL<100 mg/dl	Start dietary therapy in all patients (<7% saturated fat and <200 mg/dl cholesterol) and promote physical activity and weight management. Encourage increased consumption of omega-3 fatty acids. Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute event. If patients are hospitalized, consider adding drug therapy on discharge. Add drug therapy according to the following guide:		
	LDL <100 mg/dl (baseline or on-treatment) Further LDL-lowering therapy not required Consider fibrate or niacin (if low HDL or high TG)	LDL 100-129 mg/dl (baseline or on-treatment) Therapeutic options: Intensify LDL-lowering therapy (statin or resin*) Fibrate or niacin (if low HDL or high TG) Consider combined drug therapy (statin + fibrate or niacin) (if low HDL or high TG)	LDL ≥130 mg/dl (baseline or on-treatment) Intensify LDL-lowering therapy (statin or resin*) Add or increase drug therapy with lifestyle therapies
Lipid Management: Secondary goal If TG ≥200 mg/dl then non-HDL† should be <130 mg/dl	If TG ≥150 mg/dl or HDL<40 mg/dl: Emphasize weight management and physical activity. Advise smoking cessation. If TG 200-499 mg/dl: Consider fibrate or niacin *after* LDL-lowering therapy* If TG ≥500 mg/dl: Consider fibrate or niacin *before* LDL-lowering therapy* Consider omega-3 fatty acids as adjunct for high TG		
Physical activity: Minimum goal 30 minutes 3 to 4 days per week Optimal daily	Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30 to 60 minutes of activity, preferably daily, or at least 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work). Advise medically supervised programs for moderate- to high-risk patients.		
Weight management: Goal BMI 18.5–24.9 kg/m^2	Calculate BMI and measure waist circumferences as part of evaluation. Monitor response of BMI and waist circumference to therapy. Start weight management and physical activity as appropriate. Desirable BMI range is 18.5-24.9 kg/m^2. When BMI ≥25 kg/m^2, goal for waist circumference is ≤40 inches in men and ≤35 in women.		
Diabetes management: Goal HbA1$_c$ <7%	Appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose, as indicated by HbA1$_c$. Treatment of other risks (eg, physical activity, weight management, BP, and cholesterol management).		
Antiplatelet agents/ anticoagulants:	Start and continue indefinitely aspirin 75 to 325 mg/d if not contraindicated. Consider clopidogrel as an alternative if aspirin contraindicated. Manage warfarin to international normalized ratio=2.0 to 3.0 in post-MI patients when clinically indicated or for those not able to take aspirin or clopidogrel.		
ACE inhibitors	Treat all patients indefinitely post-MI; start early in stable high-risk patients (anterior MI, previous MI, Killip class II [S_3 gallop, rales, radiographic CHF]). Consider chronic therapy for all other patients with coronary or other vascular disease unless contraindicated Use as needed to manage blood pressure or symptoms in all other patients.		
β-blockers:	Start in all post-MI and acute 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.		

ACE indicates angiotensin-converting enzyme; BP, blood pressure; TG, triglycerides; BMI, body mass index; HbA1$_c$, major fraction of adult hemoglobin; MI, myocardial infarction; and CHF, congestive heart failure.
*The use of resin is relatively contraindicated when TG >200 mg/dl.
†Non-HDL cholesterol = total cholesterol minus HDL cholesterol.

Figure 11. 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. Reprinted with permission from Smith et al. (1052).

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 that strongly suggested 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).

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.

Patients with symptomatic coronary disease form the group most receptive to treatment directed to smoking cessation. Taylor and coworkers (703) have shown that no more than 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 pharmacological approaches (including nicotine replacement therapy and buproprion) 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 less than 180 mg per dl (719,720). 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 (721). 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 at least five years.

Angiographic trials, for which a much smaller number of participants are required, provide firm evidence linking 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-analysis (707) of more than 2000 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 (statins). 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), CARE (534), and LIPID (970). 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 greater than 60 years old. The study also demonstrated that long-term (five-year) administration of a statin was safe, and there was no increase in non-CHD death. In the CARE study, 4159 patients (3583 men and 576 women) with prior MI who had plasma total cholesterol levels less than 240 mg per dl (mean 209) and LDL cholesterol levels of 115 to 174 mg per dl (mean 139) were randomized to receive pravastatin or placebo. Active treatment was associated with a 24% reduction in risk (95% confidence interval, 9% to 36%; $p = 0.003$) for nonfatal MI or a fatal coronary event. LIPID was similar to CARE, although with a larger sample size (9014 patients); the 24% reduction in death from CHD (8.3% in the placebo group, 6.4% in the treatment group) was highly significant (p less than 0.001).

The results of the largest cholesterol-lowering trial yet performed, the Heart Protection Study (HPS), were published as this update was in the final stages of preparation (958). This trial included more than 20 000 men and women aged 40 to 80 years with coronary disease, other vascular disease, diabetes, and/or hypertension. Patients were randomized to simvastatin 40 mg or matching placebo and were followed up for a mean of five years. The primary end point, total mortality, was reduced by statin treatment by approximately 25% overall and similarly in all important prespecified subgroups, including women, patients more than 75 years old, diabetics, and individuals with baseline LDL cholesterol of less than 100 mg per dl. Analysis of these data by all appropriate authorities, including the National Cholesterol Education Project, will be necessary to clarify their implications for these guidelines.

Thus, 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 and drug treatment are warranted in the vast majority of patients. The goal of treatment is an LDL cholesterol level less than 100 mg per dl. When LDL cholesterol is 101 to 129 mg per dl, either at baseline or with LDL-lowering therapy, several therapeutic options are available:

- Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.
- Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome (see page 74).
- Delay use or intensification of LDL-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (eg, nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol levels.

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 treatments. 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 more than 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 because of 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 more than 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 lowering blood pressure in the elderly. A recent meta-analysis found that the absolute reduction of coronary events in older subjects (2.7 per 1000 person-years) was more than twice as great as that in younger subjects (1.0 per 1000 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 lowering blood pressure 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 greater than or equal to 140 mm Hg systolic or greater than or equal to 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, LVH, heart failure, retinopathy, and nephropathy are indicators of increased cardiovascular disease risk. The target of therapy is a reduction in blood pressure to less than 130 mm Hg systolic and less than 85 mm Hg diastolic in patients with coronary disease and coexisting diabetes, heart failure, or renal failure and less than 140 per 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 less than 140 over 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., because of 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 (718,719,892).

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).

Left Ventricular Hypertrophy

Left ventricular hypertrophy 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 more than six 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 associated with increased fibrinogen levels. Exercise and smoking cessation appear to favorably alter fibrinogen levels, as do fibric 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, tissue plasminogen activator, 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.

3. 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 greater than 126 mg per 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, and type II, non–insulin-dependent diabetes mellitus. 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 greater in men and four-fold greater in women. The National Cholesterol Education Program estimates that 25% of all heart attacks in the United States 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.

NON-HDL CHOLESTEROL. The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded very low density lipoproteins (VLDL), commonly called "remnant lipoproteins." In clinical practice, non-HDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, non-HDL cholesterol can be a target of cholesterol-lowering therapy. Moreover, non-HDL cholesterol is highly correlated with total apolipoprotein B (apoB) (977,978); apoB is the major apolipoprotein of all atherogenic lipoproteins. Serum total apoB also has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events (979-986). Because of the high correlation between non-HDL cholesterol and apoB levels (977,978), non-HDL cholesterol represents an acceptable surrogate marker for total apoB; the latter is not widely available for routine measurement in clinical practice. Therefore, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) (987) identifies the sum of LDL and VLDL cholesterol (termed "non-HDL cholesterol" [total cholesterol – HDL cholesterol]) as a secondary target of therapy in persons with high triglycerides (greater than 200 mg per dl). The goal for non-HDL cholesterol (for persons with serum triglycerides greater than or equal to 200 mg per dl) is 130 mg per dl; this is 30 mg per dl higher than the goal for LDL cholesterol, because the normal VLDL cholesterol level is 30 mg per dl.

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 per 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, metabolic syndrome [see page 74], impaired glucose tolerance, 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. Analysis is complicated because

completed trials have used drugs that raise HDL and also lower LDL cholesterol or triglyceride levels. The recent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) trial (988), however, revealed that modification of other lipid risk factors can reduce risk for CHD when LDL cholesterol is in the range of 100 to 129 mg per dl. In this trial, patients with low LDL (mean 112 mg per dl) were treated with gemfibrozil for five years. Gemfibrozil therapy, which raised HDL and lowered triglyceride, reduced the primary end point of fatal and nonfatal MI by 22% without significantly lowering LDL cholesterol levels. There was no suggestion of an increased risk of non-CHD mortality. As mentioned previously, when LDL cholesterol is 101 to 129 mg per dl, the use of other lipid-modifying drugs (e.g., nicotinic acid or fibric acid) should be considered if the patient has a low HDL cholesterol.

The National Cholesterol Education Program ATP III has defined a low HDL cholesterol level as less than 40 mg per dl (987). 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, and/or physical exercise). ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise HDL cholesterol. A low HDL level should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL cholesterol; ATP III guidelines for diet, exercise, and drug therapy should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to other issues. When a low HDL cholesterol level is associated with high triglycerides (200 to 499 mg per dl), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined earlier. Also, if triglycerides are less than 200 mg per dl (isolated low HDL cholesterol), drugs to raise HDL (fibrates or nicotinic acid) can be considered. Nicotinic acid and fibrates usually raise HDL levels appreciably, as do HMG-CoA reductase inhibitors.

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). Recently, however, a borderline (150 to 199 mg per dl) or high triglyceride level (greater than 200 mg per dl) has been established by meta-analyses of prospective studies as an independent risk factor for CHD (987,989,990).

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 increased physical activity. Drugs that can lower triglycerides include nicotinic acid, fibrate derivatives, and, to a lesser degree, statins. It is not clear whether treatment directed at high triglyceride levels will reduce risk for initial or recurrent CHD events. Also, triglyceride measurements vary considerable for individual patients. Accordingly, the ATP III (987) provides guidance for the management of elevated triglyceride levels by focusing on a combination of therapeutic lifestyle changes and by a secondary lipid target for non-HDL cholesterol.

Obesity

Obesity is a common condition associated with increased risk for coronary disease and mortality (755,756). Obesity is defined as a body mass index (weight in kilograms divided by the square of height in meters) of 30 kg per m^2, and overweight begins at 25 kg per m^2 (991). 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. Risk is particularly raised in the presence of abdominal obesity, which can be identified by a waist circumference greater than 102 cm (40 inches) in men or 88 cm (35 inches) in women (991). Because weight reduction in overweight and obese people is a method to reduce multiple other risk factors, it is an important component of secondary prevention of CHD. 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 Agency for Health Care Policy and Research (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 have been 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 post–coronary revascularization patients. Although it is attractive to apply this evidence to patients with stable angina, such an extrapolation is not appropriate, because most patients with stable angina have not had 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, because 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 not only will 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, patient's 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.

4. 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 fewer than 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 ^{201}T1. Three of the four studies (759,763,770) demonstrated a reduction in objective measures of ischemia

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 y	↑ ex. tolerance ↑ O_2 consumption
May	(764)	121	N/A	OR	E	10–12 mo	↑ O_2 consumption ↑ max HR-BP
Sebrechts	(759)	56	100	OR	E	1 y	↑ ex. duration
Oldridge	(760)	22	100	OR/H	E	3 mo	↑ O_2 consumption
Schuler	(705)	113	100	OR	M	1 y	↑ work capacity ↑ max HR-BP
Hambrecht	(761)	88	100	Hosp/H	M	1 y	↑ O_2 consumption ↑ ex. duration
Fletcher	(762)	88 Disabled	100	H	E	6 mo	NS (ex. duration or O_2 consumption)
Haskell	(765)	300	86	H	M	4 y	↑ ex. tolerance

Res indicates 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.

in those patients randomized to the exercise group compared with the control group. The last 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, because 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 post-MI patients. Given the underlying biological 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 1827 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 four years, respectively. Most studies have found a statistically 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 that it 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 demonstrated 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

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 y	↓	↓ thallium ischemia score
Sebrechts	(759)	56	100	E	1 y	—	↑ thallium uptake
Ornish	(763)	48	N/A	M	1 y	NS	—
Todd	(770)	40	100	E	1 y	↓	↓ ST depression (ambulatory monitor)
Schuler	(705)	113	100	M	1 y	—	↓ ST depression (exercise) NS (exercise thallium defect or redistribution)

NS indicates 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 mo	*	—	—	—	—
Oberman	(772)	651	100	E	1 y	NS	—	—	↓	—
Ornish	(763)	46	89	M	24 d	↓	↓	—	↓	—
Ornish	(769)	48	88	M	1 y	↓	NS	↓	NS	↓
Nikolaus	(773)	45	100	E	1 y	NS	—	—	↓	—
Schuler	(705)	92	100	E	1 y	↓	NS	↓	↓	↓
Watts	(774)	74	100	M	39 mo	↓	NS	↓	—	—
Hambrecht	(761)	88	100	E	1 y	↓	NS	↓	NS	↓
Haskell	(765)	300	86	M	4 y	↓	↑	↓	↓	↓
		1827 (52 female)								

*No statistics reported.
↓ indicates 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.

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 per 32 593 patient-hours of exercise and a nonfatal MI rate of 1 per 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 per 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 after MI. As indicated earlier, the committee believes 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 have experienced an MI. Fifteen randomized control trials, 10 of which involved exercise as the major intervention and five 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 three cardiac deaths in the usual-care group and two in the intervention group, as well as ten nonfatal MIs in the usual-care group and four in the intervention group. When cardiac events initiating hospitalization, including death, MI, PCI, and CABG, were tabulated, there were 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.

THE METABOLIC SYNDROME. Evidence is accumulating that risk for future CHD events can be reduced beyond LDL-lowering therapy by modification of a specific secondary target of therapy—the metabolic syndrome—represented by a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called insulin resistance, in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance. In a field that has been confused by nomenclature, ATP III has introduced a standard definition for the diagnosis of the metabolic syndrome, as shown in Table 33a. The metabolic syndrome is considered to be present when three or more of the characteristics are present.

Management of the metabolic syndrome has a two-fold objective: (1) to reduce underlying causes (i.e., obesity and physical inactivity) and (2) to treat associated nonlipid and lipid risk factors. First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity, after appropriate control of LDL cholesterol. In patients with triglycerides greater than 200 mg per dl, a non-HDL cholesterol goal of less than 130 mg per dl is a secondary target (see Table 33a).

Table 33a. Characteristics Used to Define the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	greater than 102 cm (40 in)
Women	greater than 88 cm (35 in)
Triglycerides	Greater than or equal to 150 mg per dl
HDL cholesterol	
Men	Less than 40 mg per dl
Women	Less than 50 mg per dl
Blood pressure	Greater than or equal to 130/85 mm Hg
Fasting serum glucose	Greater than or equal to 110 mg per dl

HDL indicates high-density lipoprotein.

5. 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 plus or minus 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, but there is no evidence that it will reduce cardiac events. The safety of pharmacologic therapy for depression in patients with ischemic heart disease is under investigation.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a lipoprotein particle that has been linked to CHD risk in observational studies (822,823). Lipoprotein(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.

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 with risk for MI was not significant. Clinical trials are lacking on the effect of alcohol intake on CHD risk.

6. 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 (987).

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.

7. Other Proposed Therapies That Have Not Been Shown to Reduce Risk for Coronary Disease Events

Fish Oils and Garlic

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 that ranged 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.

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).

Evidence from clinical trials is negative regarding the effects of supplementation with antioxidant vitamins. Although several small trials and *in vitro* data from basic research in vascular biology have suggested that vitamin C and/or E might interfere with formation of atherosclerotic lesions, two large randomized clinical trials have shown no benefit when vitamin E was given to patients after myocardial infarction (GISSI-P) or in those with vascular disease or diabetics with a high-risk CAD profile (992-994). Furthermore, a small coronary regression trial, the HDL Atherosclerosis Treatment Study (HATS), suggested an

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	½–1 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.

adverse effect of antioxidant vitamins on coronary atherosclerosis, clinical events, and HDL and apoA-1 metabolism (992,994). The use of vitamin E (administered with vitamin C and beta-carotene) was the subject of a large (20 000 participants) trial of patients at risk for CAD and with CAD (995). Antioxidant therapy had no effect on the end points of cardiovascular death, cardiovascular events, stroke, or revascularization, considered alone or in combination. Although previous observational and epidemiologic studies have suggested a benefit from dietary supplementation with antioxidants or a diet rich in antioxidants, especially vitamin E, there is currently no basis for recommending that patients take vitamin C or E supplements or other antioxidants for the express purpose of preventing or treating CAD.

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.

Anti-Inflammatory Agents

It is now recognized that inflammation is a common and critical component of atherothrombosis. High sensitive C-reactive protein has been the most extensively studied marker. However, routine measurement of any of the emerging risk factors, such as hs-CRP, is not recommended. It would appear to have the most potential usefulness for risk assessment in middle-aged or older persons in whom standard risk factors decline in predictive power (987). Although statins have been advocated as they modify the CRP measurement, there is as yet no evidence that they modify inflammation.

Postmenopausal Hormonal Replacement Therapy

Both estrogenic and androgenic hormones produced by the ovary have appeared to be 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 years, 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). Numerous epidemiologic studies have suggested a favorable influence of estrogen replacement therapy on the primary prevention of CAD in postmenopausal women (792-794). Furthermore, prospective studies of the effects of estrogen administration on cardiac risk factors demonstrate an increase in HDL cholesterol, a decrease in LDL cholesterol (788-791), and positive physiologic effects on the vascular smooth muscle and the endothelium.

Based on the above, postmenopausal estrogen replacement has previously been advocated for both primary and secondary prevention of CAD in women. 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 cardiovascular events during the first two years, more thromboembolic events, and more gallbladder disease (996). A subsequent angiographic study also revealed no benefit from hormonal replacement therapy (997). Another prospective randomized controlled trial using hormone replacement therapy in women with a history of stroke found no benefit in reducing mortality or stroke after 2.8 years (998). The Women's Health Initiative, a randomized controlled primary prevention trial of estrogen plus progestin, found that the overall health risks of this therapy exceeded its benefits (999). Thus, current information suggests that hormone replacement therapy in postmenopausal women does not reduce risk for major vascular events or coronary deaths in secondary prevention. Women who are taking hormone replacement therapy and who have vascular disease can continue this therapy if it is being prescribed for other well-established indications and

no better alternative therapies are appropriate. There is, however, at the present time no basis for adding or continuing estrogens in postmenopausal women with clinically evident CAD or cerebrovascular disease in an effort to prevent or retard progression of their underlying disease (1000).

If a woman develops an acute CAD event while undergoing hormone replacement therapy, it is prudent to consider discontinuance of the therapy (1000). In women who are immobilized, hormone replacement therapy should be discontinued or venous thromboembolism prophylaxis should be used .

Other randomized trials of hormone replacement therapy in primary and secondary prevention of CAD in postmenopausal women are being conducted. As their results become available over the next several years, this recommendation may require modification.

Chelation Therapy

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.

8. Asymptomatic Patients

In asymptomatic patients with documented CAD on the basis of noninvasive testing or coronary angiography, the treatment of risk factors outlined above is clearly appropriate. The same recommendations should apply to these patients.

In the absence of documented CAD, asymptomatic patients should also undergo treatment of risk factors according to primary prevention standards. Therapy should be directed toward hypertension, smoking cessation, diabetes, exercise training, and weight reduction in the presence of other risk factors. In the absence of documented CAD, lipid-lowering therapy should be administered according to the primary prevention standards outlined in the ATP III guidelines (987).

E. Revascularization for Chronic Stable Angina

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

Class I

1. **Coronary artery bypass grafting for patients with significant left main coronary disease. *(Level of Evidence: A)***
2. **Coronary artery bypass grafting for patients with three-vessel disease. The survival benefit is greater in patients with abnormal LV function (ejection fraction less than 50%). *(Level of Evidence: A)***
3. **Coronary artery bypass grafting for patients with two-vessel disease with significant proximal LAD CAD and either abnormal LV function (ejection fraction less than 50%) or demonstrable ischemia on noninvasive testing. *(Level of Evidence: A)***
4. **Percutaneous coronary intervention for patients with two- or three-vessel disease with significant proximal LAD CAD, who have anatomy suitable for catheter-based therapy and normal LV function and who do not have treated diabetes. *(Level of Evidence: B)***
5. **Percutaneous coronary intervention or CABG for patients with one- or two-vessel CAD without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)***
6. **Coronary artery bypass grafting for patients with one- or two-vessel CAD without significant proximal LAD CAD who have survived sudden cardiac death or sustained ventricular tachycardia. *(Level of Evidence: C)***
7. **In patients with prior PCI, CABG or PCI for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing. *(Level of Evidence: C)***
8. **Percutaneous coronary intervention 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 PCI for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery. *(Level of Evidence: C)***
2. **Use of PCI 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 PCI or CABG for patients with one-vessel disease with significant proximal LAD disease. *(Level of Evidence: B)***

Class IIb

1. **Compared with CABG, PCI for patients with two- or three-vessel disease with significant proximal LAD 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 PCI for patients with significant left main coronary disease who are not candidates for CABG. *(Level of Evidence: C)***
3. **PCI for patients with one- or two-vessel CAD without significant proximal LAD CAD who have survived sudden cardiac death or sustained ventricular tachycardia. *(Level of Evidence: C)***

Class III

1. **Use of PCI or CABG for patients with one- or two-**

vessel CAD without significant proximal LAD 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 PCI 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 PCI or CABG for patients with insignificant coronary stenosis (less than 50% diameter). *(Level of Evidence: C)*

4. Use of PCI 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 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 PCI, 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 PCI (as percutaneous transluminal coronary angioplasty [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 transthoracic (laser) myocardial revascularization. However, this technique, which is still in its infancy, is primarily used as an alternative when neither CABG nor PCI is feasible.

1. 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 involved 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 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 one week to one year after operation and 20% to 25% by five years after surgery. Beyond five postoperative years, the development of vein graft atherosclerosis further compromised grafts so that by 10 postoperative years, approximately 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 one 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), more than 90% of grafts are still functioning more than 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.

2. Coronary Artery Bypass Grafting 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 Administration 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 greater than 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 and 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 performed 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 with either 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.

In elderly patients, revascularization appears to improve quality of life and morbidity compared with medical therapy (1001).

3. Percutaneous Coronary Intervention

Percutaneous coronary intervention began in 1977 as PTCA, a strategy in which 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 PCI 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 PCI 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 PCI. The risk of acute coronary occlusion during PCI 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 PCI. The other disadvantages of PCI are that many patients do not have an anatomy suitable for per-

cutaneous treatment and that restenosis occurs in 30% to 40% of treated lesions within six months (875-877).

Despite some disadvantages, the efficacy of PCI in producing symptom relief for some patient subsets has become rapidly apparent, and the number of PCI procedures performed has grown so rapidly that today PCI 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.

Recommendations for Alternative Therapies for Chronic Stable Angina in Patients Refractory to Medical Therapy Who Are Not Candidates for Percutaneous Intervention or Surgical Revascularization

Class IIa

Surgical laser transmyocardial revascularization. ***(Level of Evidence: A)***

Class IIb

1. **Enhanced external counterpulsation.** ***(Level of Evidence: B)***
2. **Spinal cord stimulation.** ***(Level of Evidence: B)***

Other Therapies in Patients With Refractory Angina

Since the previous draft of these guidelines (1002), evidence has emerged regarding the relative efficacy, or lack thereof, of a number of techniques for the management of refractory chronic angina pectoris. These techniques should only be used in patients who cannot be managed adequately by medical therapy and who are not candidates for revascularization (interventional and/or surgical). In this section, data are reviewed regarding three techniques: spinal cord stimulation, enhanced external counterpulsation, and laser transmyocardial revascularization (see Recommendations).

SPINAL CORD STIMULATION. Since approximately 1987, spinal cord stimulation (SCS) has been proposed as a method for providing analgesia for patients with chronic angina pectoris refractory to medical, catheter interventional, or surgical therapy. The efficacy of SCS depends on the accurate placement of the stimulating electrode in the dorsal epidural space, usually at the C7-T1 level. A review of the literature has revealed two small randomized clinical trials involving implanted spinal cord stimulators, one of which directly tested its efficacy (see Table 34a beginning on page 82). One report studied the efficacy of SCS in 13 treated patients versus 12 control subjects; both groups with chronic intractable angina pectoris were studied for six weeks (1003). In the SCS group, compared with the control group, exercise duration, time to angina, and perceived quality of life all increased. Furthermore, the number of anginal attacks, sublingual nitrate consumption, prevalence of ischemic episodes on 48-h ECG, and degree of ST-segment depression on the exercise ECG all decreased. The authors concluded that SCS was effective in the treatment of chronic intractable angina pectoris and that its effect was exerted through an anti-ischemic action (1003).

Another small randomized trial involved 24 patients with refractory angina who had implanted spinal cord stimulators (1004). After randomization to the study, the withdrawal-of-SCS group (n = 12) had their SCS set active during the first four weeks, followed by four weeks of withholding stimulation. In the control group (n = 12), SCS was switched off during the four weeks before the end of the study. The authors found no increase in anginal complaints or ischemia after withholding stimulation. Neurohormonal levels and aerobic capacity were also not altered. The authors concluded that there was no adverse clinical rebound phenomenon after withholding neurostimulation in patients with refractory angina pectoris.

In a more recent randomized, prospective, open comparison of CABG surgery (n = 51 patients) and SCS (n = 53 patients) in patients with no a priori prognostic benefit from CABG and with an increased risk for surgical complications, anginal symptoms decreased in the SCS group despite discontinued stimulation. Also noted was a lack of effect of SCS on ischemic ST changes (1005). These authors suggested that their results could indicate a long-term primary analgesic effect of SCS.

Nine other studies, either retrospective (1006-1008) or prospective (1003,1009-1013) cohort studies, were identified in the literature. These studies have purported to show that SCS is effective in decreasing the number of anginal episodes and in preventing hospital admissions, apparently without masking serious ischemic symptoms or leading to silent ischemia (1008,1013). A significant increase in the average exercise time on the treadmill has also been reported during SCS (1003). However, analgesic effects of SCS may be observed despite discontinuation of CPS and in the absence of changes in myocardial ischemia. In summary, although most published reports appear promising, there is still a paucity of data on the intermediate- and long-term benefit of these devices.

ENHANCED EXTERNAL COUNTERPULSATION. Another nonpharmacologic technique that has been described for treatment of patients with chronic stable angina is known as enhanced external counterpulsation (EECP). This technique uses a series of cuffs that are wrapped around both of the patient's legs. Using compressed air, pressure is applied via the cuffs to the patient's lower extremities in a sequence synchronized with the cardiac cycle. Specifically, in early diastole, pressure is applied sequentially from the lower legs to the lower and upper thighs, to propel blood back to the heart. The procedure results in an increase in arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation).

EECP was evaluated in a randomized, placebo-controlled multicenter trial to determine its safety and efficacy (1014). As shown in Table 34a, 139 patients with chronic stable angina, documented CAD, and a positive exercise treadmill test were randomly assigned to receive EECP (35 hours of active counterpulsation) or inactive EECP over a four- to seven-

week period. The authors concluded that EECP decreased angina frequency (p less than 0.05) and improved time to exercise-induced ischemia (p = 0.01). In addition, treatment was relatively well tolerated and free of limiting side effects in most patients. However, the sample size in this study was relatively small.

Two multicenter registry studies that included 978 patients from 43 centers (1015) and 2289 patients from more than 100 centers (1016) evaluated the safety and effectiveness of EECP in treating chronic stable angina. These studies found the treatment to be generally well tolerated and efficacious; anginal symptoms were improved in approximately 75% to 80% of patients. However, additional clinical trial data are necessary before this technology can be recommended definitively.

LASER TRANSMYOCARDIAL REVASCULARIZATION. Another emerging technique that has been studied for the treatment of more severe chronic stable angina refractory to medical or other therapies is laser transmyocardial revascularization (TMR). This technique has either been performed in the operating room (using a carbon dioxide or holmium:YAG laser) or by a percutaneous approach with a specialized (holmium:YAG laser) catheter. Eight prospective randomized clinical trials have been performed, two using the percutaneous technique and the other six using an epicardial surgical technique (942,945,1017-1021). The goal in both approaches is to create a series of transmural endomyocardial channels to improve myocardial revascularization.

PERCUTANEOUS TMR. The two randomized percutaneous TMR trials, enrolling about 550 patients, reported symptomatic improvement among 45% and 66% of patients compared with 13% for best medical therapy (942); one of these has not yet been published (http://www.eclipsesurg.com/professionals/professionals.cfm). The studies have generally assessed parameters such as angina class, freedom from angina, exercise tolerance, and quality of life score. In general, these studies have shown improvement in severity of angina class, exercise tolerance, and quality of life, as well as increased freedom from angina. However, percutaneous TMR technology has not been approved by the Food and Drug Administration; therefore, percutaneous TMR should still be considered an experimental therapy.

SURGICAL TMR. The surgical TMR technique has also generally been associated with improvement in symptoms in patients with chronic stable angina. The mechanism for improvement in angina symptoms is still controversial. Possible mechanisms for this improvement include increased myocardial perfusion, denervation of the myocardium, stimulation of angiogenesis, or perhaps some other unknown mechanism (1022-1024). On the other hand, there are conflicting data regarding improvement in exercise capacity; two studies demonstrated no improvement (1017,1021), whereas a third study demonstrated improvement (945). Three studies also assessed myocardial perfusion using thallium scans (945,1018,1019). Only one of these studies demonstrated an improvement in myocardial perfusion in patients who underwent TMR versus those continuing to receive only medical therapy (1019). Despite the apparent benefit in decreasing angina symptoms, no definite benefit has been demonstrated in terms of increasing myocardial perfusion.

In the Society of Thoracic Surgeons database for surgical TMR (1025), 80% of surgical TMR cases had been performed in conjunction with CABG. In a recent multicenter, randomized controlled trial comparing TMR plus CABG to CABG alone in patients not amenable to complete revascularization by CABG alone, one-year survival was better in the combination therapy group (95% vs. 89%, p = 0.05) (1020). In general, angina relief and exercise treadmill improvement were no different at 12-month follow-up. Furthermore, there are currently no published studies to document the long-term efficacy of surgical TMR. Nonetheless, this technique appears to provide symptomatic relief for end-stage chronic angina in the short term. Additional follow-up studies are necessary to evaluate procedural efficacy in patients who have undergone surgical laser TMR alone, as well as coronary bypass surgery plus TMR.

PERCUTANEOUS CORONARY INTERVENTION 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 less than 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 (879). In the Atorvastatin Versus Revascularization Treatment trial (AVERT), 341 patients with mild stable angina and normal LV function were randomized to medical therapy including atorvastatin 80 mg or to PTCA. Angina relief was superior in the PTCA groups, but at 18 months, this group had more ischemic events, primarily hospitalizations and repeat revascularization (21% vs 13%, p = 0.048) (1026). These results parallel a meta-analysis of the 953 patients with mild or no symptoms entered into randomized comparison of PTCA and medical therapy (see Figure 12) (1027). It is important to note, however, that lipid-lowering therapy in AVERT was different in the two groups of patients. There was a markedly lower LDL

Table 34a. Other Therapies and Refractory Angina—Evidence Table

Study/ Reference	Design	Study Population	Intervention	Clinical End Points	Results	Comment
Spinal Cord Stimulation						
Hautvast et al. 1998 (1003)	Randomized controlled clinical trial to assess the efficacy of spinal cord stimulation (SCS) as a treatment for chronic intractable angina pectoris	13 treated patients and 12 control patients with chronic angina	Efficacy of SCS as a treatment for chronic intractable angina pectoris was studied for 6 weeks	Exercise capacity and ischemia, daily frequency of anginal attacks, nitrate tablet consumption, and perceived quality of life	Compared with control, exercise duration (p = 0.03), time to angina (p = 0.01) and perceived quality of life (p = 0.03) increased; anginal attacks and sublingual nitrate consumption (p = 0.01) and ischemic episodes on 48-h ECG (p = 0.04) decreased. Also, ST-segment depression on exercise ECG decreased at comparable workload (p = 0.01).	The authors concluded that SCS is effective in chronic intractable angina pectoris, and its effect is exerted through anti-ischemic action, rather than as a placebo effect from surgery.
Jessurun et al. 1999 (1004)	Randomized controlled clinical trial to assess the recurrence of myocardial ischemia after withholding electrical neuro-stimulation	24 patients with refractory angina and an implanted spinal cord stimulator	After randomization to the study (i.e., withdrawal group, n = 12), SCS was set active during the first 4 weeks, followed by 4 weeks of withholding stimulation. In the control group, SCS was switched off during the 4 weeks before end of study	Angina pectoris episodes, nitroglycerin intake, ischemia, heart rate variability, neurohormonal status, and symptom-limited aerobic capacity were evaluated	There was no increase in anginal complaints or ischemia after withholding stimulation. Neuro-hormonal levels and aerobic capacity were not altered.	The authors concluded that there is no adverse clinical rebound phenomenon after withholding neurostimulation in patients with refractory angina pectoris.
Norrsell et al. 2000 (1005)	Randomized, pros-pective open com-parison of CABG and SCS in patients with no projected prognostic benefit from CABG and an increased risk of surgical complications	104 patients—51 randomized to CABG and 53 to SCS	CABG or SCS	ST-segment depression on ECG, frequency of anginal attacks, number of ischemic episodes, and total ischemic burden (time – voltage area under 1-mm cutoff value), heart rate variability	Number and duration of ischemic episodes decreased in CABG group but remained unchanged in the SCS group (both p less than 0.05). Number of anginal attacks decreased significantly at follow-up for both treatment groups (p less than 0.0001).	Both CABG and SCS decreased anginal attacks; only CABG decreased number of ischemic episodes. The fact that anginal symptoms decreased in SCS group in spite of discontinued stimulation and lack of effects on ischemic ST changes could indicate a long-term primary analgesic effect of SCS.
Enhanced External Counterpulsation						
MUST-EECP The Multicenter Study of Enhanced External Counter-pulsation Arora et al. 1999 (1014)	Randomized, placebo-controlled multicenter trial to determine the safety and efficacy of EECP	139 patients with chronic stable angina. Patients with Class I-III Canadian Cardiovascular Society Classification (CCSC) angina were eligible with documented CAD and positive exercise tolerance test	Patients were randomly assigned to receive EECP (35 hours) or inactive EECP over 4-7 weeks.	Primary end point was exer-cise duration and time to development of greater than 1-mm ST-segment depres-sion, average daily anginal attack count, and nitroglyc-erin usage	In the active counterpulsation group, exercise duration increased from 426 ± 20 s at baseline to 470 ± 20 s after treatment. Exercise duration increased in both groups, but the between-group difference was not significant (p greater than 0.3). Time to greater than or equal to 1-mm ST-segment depression increased significantly from baseline in active EECP compared with inactive EECP (p = 0.01). More active-EECP patients saw a decrease and fewer experienced an increase in angina episodes than with inactive-EECP patients (p less than 0.05). Nitro-glycerin usage decreased in active EECP but did not change in the inactive-EECP group. The between-group difference was not significant (p greater than 0.7)	The authors concluded that EECP decreased angina frequency and improved time to exercise-induced ischemia. Additionally, treatment was relatively well tolerated and free of limiting side effects in most patients. However, the trial included a very small sample size.

Table 34a (continued). Other Therapies and Refractory Angina—Evidence Table

Study/ Reference	Design	Study Population	Intervention	Clinical End Points	Results	Comment
Enhanced External Counterpulsation (continued)						
IEPR International EECP Patient Registry Barsness et al. 2001 (1015)	Multicenter registry	978 patients from 43 clinical centers with chronic angina participating in the MUST-EECP trial for whom data at baseline and completion of EECP were available. 70% had CCSC class III or IV angina, 62% used nitroglycerin, 81% had undergone previous revascularization, and 69% were considered unsuitable for either PCI or CABG at baseline.	Patients all received EECP therapy for a minimum of at least 1 h	End points included mean diastolic augmentation area ratio, CCSC angina class, number of anginal episodes per week, nitroglycerin use, and quality-of-life assessment	Treatment course (usually 35 hours) was completed in 86%, of whom 81% reported improvement of at least one angina class immediately after last treatment. Adverse events during EECP treatment include unstable angina in 2.4%, episodes of congestive heart failure in 2.1%, musculoskeletal complaints in 2.1%, and skin breakdown in 1.1%.	The authors concluded that in a broad patient population, EECP was a safe and effective treatment.
EECP Consortium Lawson et al. 2000 (1016)	Multicenter registry	2289 patients, predominantly Caucasian (92%), with angina, enrolled from over 100 centers. Purpose was to evaluate safety and effectiveness of EECP in a nonuniversity general clinical practice setting.	Daily 1- to 2-h treatment sessions were typically administered for a total treatment course of 35 hours. The average treatment time was 33.43 ± 12.3 h. Most patients (60%) received 35 h of EECP treatment.	Angina class (CCS functional class)	Angina class improved in 74% of patients with limiting angina (CCS functional class II-IV), with patients most impaired at baseline demonstrating the greatest improvement (39.5% of patients in CCS III and IV improved 2 or more classes). There were rare reports of deterioration in anginal class during therapy, with 0.2% of patients worsening by 1 CCS class. A total of 91 adverse patient experiences were noted. The largest defined category was musculoskeletal and skin trauma, with 23 adverse experiences including joint and muscle pain, leg swelling, bruising, or abrasion. Cardiac events included MI, angina, chest pain, silent ischemia, ECG changes, arrhythmia, and pulmonary edema. Younger patients showed a significantly greater likelihood of benefit with EECP.	The authors concluded that in a nonuniversity clinical practice setting, EECP was a safe and practical treat ment for angina.
Surgical Transmyocardial Revascularization						
Norwegian Trial Aaberge et al. 2000 (1017)	Randomized controlled clinical trial	100 patients with refractory angina not eligible for conventional revascularization were block-randomized in a 1:1 ratio to receive continued optimal MT or TMR in addition to MT	Optimal MT or TMR in addition to MT	Clinical end points included symptoms, exercise performance, and effect on maximal oxygen consumption (MVO_2)	TMR resulted in significant relief in angina symptoms after 3 and 12 months compared with baseline. Time to chest pain during exercise increased from baseline by 78 s after 3 months (p = NS) and 66 s (p less than 0.01) after 12 months in the TMR group, whereas total exercise time and MVO2 were unchanged. No significant changes were observed in the MT group. Perioperative mortality was 4%. One-year mortality was 12% in the TMR group and 8% in the MT group (p = NS).	The authors concluded that TMR was performed with low perioperative mortality and caused significant symptomatic improvement but no improvement in exercise capacity.

Table 34a (continued). Other Therapies and Refractory Angina—Evidence Table

Study/ Reference	Design	Study Population	Intervention	Clinical End Points	Results	Comment
Surgical Transmyocardial Revascularization (continued)						
Allen et al. 2000 (1051)	Multicenter, blinded, prospective randomized controlled clinical trial	A total of 263 patients whose standard of care was CABG and who had 1 or more ischemic areas not amenable to bypass grafting	Patients were prospectively randomized to receive CABG of suitable vessels plus TMR to areas not graftable (n = 132) or CABG alone with nongraftable areas left unrevascularized (n = 131)	Operative and 1-year all-cause mortality rates; requirement for postoperative left ventricular support; 30-day and 1-year major adverse cardiac events, defined as MI or death; angina class assessment; exercise treadmill scores; and repeat PTCA or CABG	The operative mortality rate after CABG/TMR was 1.5% (2/132) versus 7.6% (10/131) after CABG alone (p = 0.02). At 30 days, freedom from death and MI was was enhanced after CABG/TMR compared with CABG alone (97% vs 91%, p = 0.04). One-year Kaplan-Meier survival (95% vs 89%, p = 0.05) and freedom from major adverse cardiac events, defined as death or MI (92% vs 86%, p = 0.09), favored the combination of CABG and TMR. Baseline to 12-month improvement in angina and exercise treadmill scores was similar between groups.	The authors concluded that TMR combined with CABG in patients not amenable to complete revascularization by CABG was safe; however, angina relief and exercise treadmill improvement were indistinguishable between groups at 12 months of follow-up.
Allen et al. 1999 (1018)	Prospective randomized controlled clinical trial conducted between March 1996 and July 1998 at 18 centers	275 patients with medically refractory class IV angina and coronary disease that could not be treated with percutaneous or surgical revascularization	Patients were randomly assigned to receive TMR followed by continued MT (132 patients) or MT alone (143 patients)	Survival free of cardiac events, freedom from treatment failure, rate of freedom from cardiac-related rehospitalization, exercise tolerance, quality of life, and myocardial perfusion assessed by thallium scans	After 1 year of follow-up, 76% of patients who had undergone TMR had improvement in angina (a reduction of 2 or more classes) compared with 32% of patients who received MT alone (p less than 0.001). Kaplan-Meier survival estimates at 1 year (based on an intention-to-treat analysis) were similar for patients assigned to undergo TMR and those assigned to receive MT alone (84% and 89%, respectively; p = 0.23). At 1 year, patients in the TMR group had a higher rate of survival free of cardiac events (54%, vs. 31% in the MT group; p less than 0.001), a higher rate of freedom from treatment failure (73% vs. 47%, p less than 0.001), and a higher rate of freedom from cardiac-related rehospitalization (61% vs. 33%, p less than 0.001). Exercise tolerance and quality-of-life scores were also higher in the TMR group than in the MT group (exercise tolerance, 5.0 vs. 3.9 METs; p = 0.05; quality-of-life score, 21 vs. 12; p = 0.003). However, there were no differences in myocardial perfusion between the 2 groups.	The authors concluded that patients with refractory angina who underwent TMR and received continued MT, compared with similar patients who received MT alone, had a significantly better outcome with respect to improvement in angina, survival free of cardiac events, freedom from treatment failure, and freedom from cardiac-related rehospitalization. However, there was no difference in myocardial perfusion between the TMR and MT groups.

Table 34a (continued). Other Therapies and Refractory Angina—Evidence Table

Study/ Reference	Design	Study Population	Intervention	Clinical End Points	Results	Comment
Surgical Transmyocardial Revascularization (continued)						
Schofield et al. 1999 (1021)	Randomized controlled clinical trial	188 patients with refractory angina	Patients were randomly assigned to TMR plus normal MT or MT alone	Exercise capacity assessed with the treadmill test and 12-min walk at baseline and 3, 6, and 12 months after surgery	Mean treadmill exercise time, adjusted for baseline values, was 40 s (95% CI, –15 to 94 s) longer in the TMR group than in the MT group at 12 months (p = 0.152). Mean 12-min walk distance was 33 m (–7 to 74) farther in TMR patients than MT patients (p = 0.108) at 12 months. However, these differences were not significant or clinically important. Perioperative mortality was 5%. Survival at 12 months was 89% (83%-96%) in the TMR group and 96% (92%-100%) in the MT group (p = 0.14). CCS angina score had decreased by at least 2 classes in 25% of TMR and 4% of MT patients at 12 months (p less than 0.001).	Although TMR did result in a significant decrease in angina score compared with MT, the authors concluded that the adoption of TMR cannot be advocated at this time.
Frazier et al. 1999 (1019)	Prospective randomized controlled multicenter trial	192 patients who had CCS class III or IV angina that was refractory to MT, reversible ischemia of the left ventricular free wall, and coronary disease that was not amenable to CABG or PTCA	91 patients were randomly assigned to undergo TMR and 101 patients to receive continued MT. Note: 60 of the 101 patients crossed over from MT to TMR	Severity of angina (according to CCS angina classification), quality of life, and cardiac perfusion (as assessed by thallium-201 scanning) were measured at baseline and 3, 6, and 12 months after randomization	At 12 months, angina had improved by at least 2 CCS angina classes in 72% of patients assigned to TMR compared with 13% of patients assigned to MT who continued MT (p less than 0.001). Patients in the TMR group also had a significantly improved quality of life compared with the MT group. Myocardial perfusion improved by 20% in the TMR group and worsened by 27% in the MT group (p = 0.002). In the first year of follow-up, 2% of patients assigned to undergo TMR were hospitalized because of unstable angina compared with 69% of patients assigned to MT (p less than 0.001). The perioperative mortality rate associated with TMR was 3%. The rate of survival at 12 months was 85% in the TMR group and 79% in the MT group (p = 0.50).	The authors concluded that TMR improved cardiac perfusion and clinical status over a 12-month period for those patients in whom CABG and PTCA were precluded.

Table 34a (continued). Other Therapies and Refractory Angina—Evidence Table

Study/ Reference	Design	Study Population	Intervention	Clinical End Points	Results	Comment
Surgical Transmyocardial Revascularization (continued)						
ATLANTIC Trial Burkhoff et al. 1999 (945)	Prospective randomized controlled clinical trial	182 patients from 16 US centers with CCS angina class III or IV, reversible ischemia, and incomplete response to other therapies	Patients were randomly assigned to TMR and continued MT (n = 92) or continued MT alone (n = 90)	Angina class, exercise tolerance, Seattle Angina Questionnaire for quality of life, dipyridamole thallium stress test. Assessments were conducted at baseline and 3, 6, and independent masked angina assessment at 12 months	At 12 months, total exercise tolerance increased by a median of 65 s in the TMR group compared with a 46 s decrease in the MT-only group (p less than 0.0001, median difference 111 s). Independent CCS angina score was II or lower in 47.8% of the TMR group compared with 14.3% in the MT-only group (p less than 0.001). Each Seattle Angina Questionnaire index score increased in the TMR group significantly more than in the MT-only group (p less than 0.001). The change in percentage of myocardium with fixed and reversible defects from baseline to the 3-, 6-, and 12-month visit did not differ significantly between the 2 groups.	The authors concluded that TMR lowered angina scores, increased exercise tolerance, and improved patients' perception of quality of life. Thallium scans done under a fixed degree of chemically induced vasodilatory stress showed no improvements in blood flow after TMR.

SCS indicates spinal cord stimulation; ECG, electrocardiogram; CABG, coronary artery bypass grafting; EECP, enhanced external counterpulsation; CCSC, Canadian Cardiovascular Society classification; PCI, percutaneous coronary intervention; MT, medical treatment; TMR, transmyocardial revascularization; MI, myocardial infarction; METs, metabolic equivalents.

cholesterol in the medical therapy group. These studies suggest that an initial medical approach with aggressive lipid lowering is appropriate in minimally symptomatic patients with stable angina.

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 PCI to treat patients with chronic stable angina and characteristics that define a high risk of mortality is currently being tested in the COURAGE trial.

Medical Management Versus PCI 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 at least one 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 less than 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 at least 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 PCI 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%) compared with medical treatment (32%) (p less than 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 less than 0.006).

Use of PCI 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 who 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 Revascularization Investigation (BARI) trial (883) and the single-center Emory Angioplasty Surgery Trial (EAST) (884).

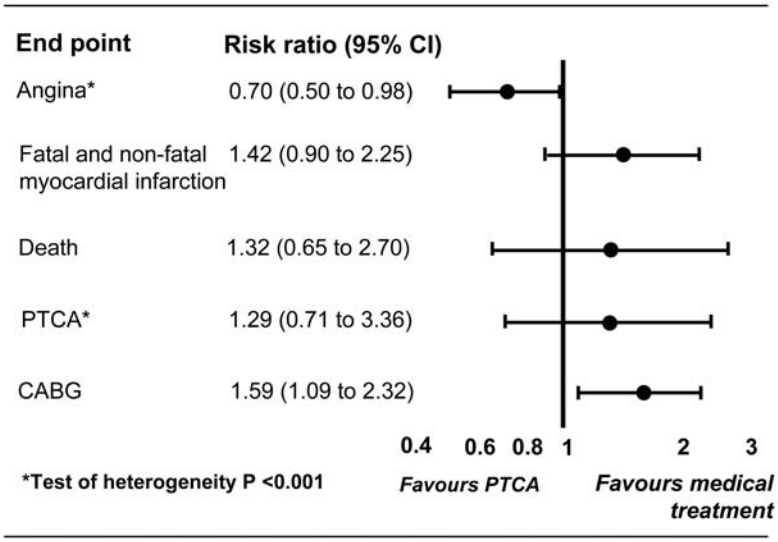

Figure 12. Pooled risk ratios for various end points from six randomized controlled trials comparing percutaneous transluminal coronary angioplasty (PTCA) with medical treatment in patients with nonacute coronary heart disease. CABG indicates coronary artery bypass grafting. n = 953 for PTCA and 951 for medical treatment. Reprinted with permission from Bucher C, et al., Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. BMJ 2000;321:73-77 (1027).

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 who 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 greater than 50%); a history of CHF was rare (fewer than 10%). In the BARI trial, 37% of patients had a proximal LAD lesion. In the EAST trial, more than 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 were at high risk for death without revascularization.

The results of both these trials at an approximately seven- to eight-year follow-up interval have shown that early and late survival rates have been equivalent for the PTCA and CABG groups (1028,1029). 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 five years, after which the curves began to diverge but failed to reach a statistically significant difference at eight years (surgical survival 75.5%, PTCA 60.1%; $p = 0.23$).

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 groups needed to take antianginal medications.

The latest randomized trial comparing percutaneous and surgical coronary revascularization was the European Arterial Revascularization Therapies Study (ARTS) (1030). A total of 1205 patients with multivessel disease suitable for either therapy were randomly assigned to coronary stenting or bypass surgery. At one year, there was no significant difference between the two groups with respect to mortality, stroke, or MI. Event-free survival was higher in the surgery group (87.8% vs 73.8%, p less than 0.001), but surgery was more expensive by $2973 per patient in spite of more repeat revascularizations in the stent group (16.8% vs 3.5%) (1030). At 12 months, surgery patients had an improved perception of mobility, usual activity, and freedom from anxiety or depression than patients in the stent group, although overall quality-of-life evaluation was similar.

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, except in ARTS, received intracoronary stents, a change in percutaneous technique that has decreased the rate of emergency bypass surgery and may decrease the incidence of restenosis (1030). Fourth, the follow-up period of the PTCA-CABG studies extends only eight years at this writing, a point at which the adverse effect of vein graft atherosclerosis has not yet been fully realized. Fifth, none of these trials used aggressive lipid-lowering therapy or IIb/IIIa platelet receptor inhibitors. Sixth, although most of the patients in the surgical groups received LITA-LAD grafts, few patients underwent extensive arterial revascularization or off-pump bypass surgery. All these changes in technique may conceivably change the relative benefit ratios of CABG and PCI for some patient subgroups.

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 included patients with previous bypass surgery. The trials of initial medical versus initial surgical management excluded patients greater than 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 greater than 70 years old and none greater than 80 years old were included. The committee believes that patients with significant CAD who have survived sudden cardiac death or sustained ventricular tachycardia are best treated with CABG rather than PCI. 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 PCI. The risk of sudden death or ventricular arrhythmias recurring is likely to be greater with PCI than CABG because of the known risk of restenosis after PCI.

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 patients with left main stenoses greater than or equal to 70% and those with multivessel CAD with a proximal LAD stenosis greater than or equal to 70% and abnormal LV function have a better late survival rate if they have coronary bypass surgery. Because the randomized trials of PCI versus bypass surgery included an inadequate number of patients in these high-risk subsets, it cannot be assumed that the alternative strategy of PCI 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 PCI does not compromise survival for patients with normal LV function who are good angiographic candidates for PCI. 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, PCI may be considered an alternative to CABG if the patient is a favorable angiographic candidate for PCI.

Caution should be used in the treatment of diabetic patients with PCI, 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 with 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, PCI 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 PCI, 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 PCI involved less initial morbidity cost and a shorter hospital stay. On the other hand, recurrent angina and repeat procedures (either CABG or PCI) were much more common after PCI. By five postoperative years, the total costs of both procedures appeared to be equivalent.

Most patients with symptoms and ischemia based on one-vessel disease can be treated effectively with PCI. For symptomatic patients with lesions unfavorable for PCI 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 PCI.

4. 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 not only by progression of native-vessel CAD but also by 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 (greater than 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 (less than 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 PCI 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 (less than 5 years after operation) stenoses in saphenous vein grafts can be treated successfully 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 more than five 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.

5. Asymptomatic Patients

Recommendations for Revascularization with PCI and CABG in Asymptomatic Patients

Class I (These recommendations are identical to those for symptomatic patients.)

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

Class IIa (This recommendation is identical to the Class IIa recommendation for symptomatic patients.)

Percutaneous coronary intervention or CABG for patients with one-vessel disease with significant proximal LAD CAD. *(Level of Evidence: C)*

Class IIb (Recommendations 1, 2, and 3 are identical to the recommendations for symptomatic patients. Recommendations 4 and 5 are identical to Class IIa recommendations for symptomatic patients.)

1. **Compared with CABG, PCI for patients with 2- or 3-vessel disease with significant proximal LAD 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 PCI for patients with significant left main coronary disease who are not candidates for CABG. *(Level of Evidence: C)***
3. **Percutaneous coronary intervention for patients with one- or two-vessel CAD without significant proximal LAD CAD who have survived sudden cardiac death or sustained ventricular tachycardia. *(Level of Evidence: C)***
4. **Repeat CABG for patients with multiple saphenous vein graft stenoses, with high-risk criteria on noninvasive testing, especially when there is significant stenosis of a graft supplying the LAD. Percutaneous coronary intervention may be appropriate for focal saphenous vein graft lesions or multiple stenoses in poor candidates for reoperative surgery. *(Level of Evidence: C)***
5. **Percutaneous coronary intervention or CABG for patients with one- or two-vessel CAD without significant proximal LAD CAD but with a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing. *(Level of Evidence: C)***

Class III (These recommendations are identical to the Class III recommendations for symptomatic patients.)

1. **Use of PCI or CABG for patients with one- or two-vessel CAD without significant proximal LAD CAD and**
   a. **only a small area of viable myocardium or**
   b. **no demonstrable ischemia on noninvasive testing. *(Level of Evidence: C)***
2. **Use of PCI 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 PCI or CABG for patients with insignificant coronary stenosis (less than 50% diameter). *(Level of Evidence: C)***

4. **Use of PCI in patients with significant left main CAD who are candidates for CABG. *(Level of Evidence: B)***

In asymptomatic patients, revascularization cannot improve symptoms. The only appropriate indication for revascularization with either PCI or CABG is therefore to improve prognosis. Most of the recommendations for revascularization that appear earlier in this section for patients with stable angina also apply to asymptomatic patients, because their underlying rationale is to improve prognosis. The single recommendation for revascularization in patients who have not been successfully treated by medical therapy is the exception and obviously does not apply to asymptomatic patients. However, the level of evidence in support of these recommendations in asymptomatic patients is clearly weaker than in symptomatic patients. Most of the available randomized trial data have focused on symptomatic patients. Their extrapolation to asymptomatic patients appears reasonable but is based on far more limited evidence.

In the CASS registry, asymptomatic patients with left main CAD who underwent CABG had a better outcome than those patients treated with medical therapy, but this was not a randomized trial (1031). The most compelling randomized trial data on asymptomatic patients comes from the previously mentioned ACIP study (880,881). In patients with CAD who were either free of angina or had well-controlled symptoms, patients randomized to revascularization had a lower cardiac event rate than patients who were randomized to medical management guided by angina or medical management guided by noninvasive ischemia. The patients entered in this study, who were required to have ischemia during ambulatory monitoring and exercise testing, as well as significant CAD, were more likely to have extensive CAD and prior MI. In the overall study group, 39% of the patients had three-vessel disease, 40% had prior MI, and 22% had prior revascularization, and 59% had angina within the previous 6 weeks. Many of the patients enrolled in this trial presumably came to medical attention because of symptoms or prior MI. The degree to which the results of ACIP can be applied to patients who have never been symptomatic and have less severe asymptomatic CAD is uncertain.

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

Recommendations for Echocardiography, Treadmill Exercise Testing, Stress Radionuclide Imaging, Stress Echocardiography 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 by echocardiography or radionuclide imaging 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 radionuclide imaging or stress echocardiography 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 radionuclide imaging or stress echocardiography 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 radionuclide imaging or stress echocardiography 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 greater than 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 less than three years in patients who have no change in clinical status and an estimated annual mortality rate less than 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 or echocardiography 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 or echocardiographic 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

A. Patients Not Addressed in This Section of the Guidelines

1. 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 (892).
- 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 (892).
- Patients who have had an MI who develop stable angina more than 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 (1032,1033).
- Patients who have had angioplasty or CABG and develop angina within six months of revascularization should be monitored according to the PCI and CABG guidelines (1032,1033).

2. 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 as 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 (893) 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 communication 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 examination should identify any change in peripheral pulses and new bruits. The abdominal examination 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 ATP III guidelines, which recommend follow-up fasting blood work six to eight weeks after initiation of lipid-lowering drug therapy, including liver function testing and assessment of the cholesterol profile, and then periodically 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 less than 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 more than six months after coronary angioplasty who have undergone complete revascularization and who 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 greater than 3%. Examples of such patients include those with an ejection fraction less than 50% and significant CAD in more than one 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 (greater than 1% and less than 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 LV 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.

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REFERENCES

1. Reference deleted during update.

APPENDIX 1. Committee to Update the 1999 Guidelines for the Management of Patients With Chronic Stable Angina—Disclosure of Relationships With Industry

Committee Member Name	Research Grant	Speakers Bureau/ Honoraria	Stock Ownership	Consultant
Dr. Raymond Gibbons	Wyeth Ayerst Radiant Medical Medco Research (King Pharmaceuticals)	None	None	Medco Research (King Pharmaceuticals) Collateral Therapeutics Medicure, Inc. DOV Pharmaceutical
Dr. Jonathan Abrams	None	None	None	None
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Dr. Prakash Deedwania	None	None	None	None
Dr. John S. Douglas	Guidant, investigator Johnson & Johnson Novoste AVE SciMed Otsuka	None Johnson & Johnson Medicure, Inc.	Pfizer	None
Dr. T. Bruce Ferguson, Jr.	Pfizer	None	None	None
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Dr. Theodore D. Fraker, Jr.,	None	None	None	None
Dr. Julius M. Gardin	None	None	None	None
Dr. Robert A. O'Rourke	Merck Pfizer Astra Zenica DuPont All companies related to the COURAGE Trial			
Dr. Richard C. Pasternak	Merck/Pfizer	None	None	None
Dr. Sankey V. Williams	Pharmacia and Upjohn Searle	None	None	None

This table represents the actual or potential committee-member relationships with industry that were reported orally at the initial writing committee meeting on March 17, 2001 and updated in conjunction with all meetings and conference calls of the writing committee. It does not reflect any actual or potential relationships at the time of publication.

2. Reference deleted during update.
3. Elveback LR, Connolly DC, Melton LJ III. Coronary heart disease in residents of Rochester, Minnesota 7. Incidence, 1950 through 1982. Mayo Clin Proc 1986;61:896-900.
4. Kannel WB, Feinleib M. Natural history of angina pectoris in the Framingham study. Prognosis and survival. Am J Cardiol 1972;29:154-63.
5. The American Heart Association. 1999 Heart and Stroke Statistical Update. Dallas: American Heart Association, 1999.
6. Rouleau JL, Talajic M, Sussex B, et al. Myocardial infarction patients in the 1990s—their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. J Am Coll Cardiol 1996;27:1119-27.
7. Elveback LR, Connolly DC. Coronary heart disease in residents of Rochester, Minnesota, V. Prognosis of patients with coronary heart disease based on initial manifestation. Mayo Clin Proc 1985;60:305-11.
8. National Center for Health Statistics. Report of final mortality statistics, 1995. Hyattsville, Md: Public Health Service; 1997. Monthly vital statistics report. Vol 45, No. 11.
9. The American Heart Association. Biostatistical Fact Sheets. Dallas, TX: American Heart Association, 1997:1-29.
10. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease: a multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. JAMA 1997;277:715-21.
11. Wennberg JE, Bubolz TA, Fisher ES, et al. The Dartmouth Atlas of Health Care in the United States. In: Cooper MM, ed. Chicago: American Hospital Publishing, 1996:123.
12. Ritchie JL, Bateman TM, Bonow RO, et al. Guidelines for clinical use of cardiac radionuclide imaging. Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. J Am Coll Cardiol 1995;25:521-47.
13. Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. Circulation 1997;95:1686-744.
14. Reference deleted during update.
15. Bonow RO, Carabello B, de Leon AC Jr, et al. ACC/AHA Guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;32:1486-588.
16. Reference deleted during update.
17. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography). J Am Coll Cardiol 1999;33:1756-824.
18. Reference deleted during update.
19. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999;34:1262-347.
20. Reference deleted during update.
21. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413-46.
22. American College of Physicians. Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults. Part 1. Ann Intern Med 1996;124:515-7.
23. 27th Bethesda Conference. Matching the intensity of risk factor management with the hazard for coronary disease events. September 14-15, 1995. J Am Coll Cardiol 1996;27:957-1047.
24. Wenger NK, Froelicher ES, Smith LK, et al. Cardiac Rehabilitation. Clinical Practice Guideline No. 17. Rockville, Md: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute; 1995. AHCPR publication No. 96-0672.
25. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association Writing Group. Circulation 1996;94:1175-92.
26. Reference deleted during update.
27. 20th Bethesda Conference. Insurability and employability of the patient with ischemic heart disease. October 3-4, 1988. J Am Coll Cardiol 1989;14:1004-44.
28. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994;89: 1545-56.
29. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology, A Basic Science for Clinical Medicine. Boston: Little Brown, 1991:20.
30. Harris PJ, Behar VS, Conley MJ, et al. The prognostic significance of 50% coronary stenosis in medically treated patients with coronary artery disease. Circulation 1980;62:240-8.
31. Rutherford JD, Braunwald E. Chronic ischemic heart disease. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicines. 4th ed. Philadelphia: WB Saunders, 1992:1293-5.
32. Diamond GA. A clinically relevant classification of chest discomfort [letter]. J Am Coll Cardiol 1983;1:574-5.
33. Chatterjee K. Recognition and management of patients with stable angina pectoris. In: Goldman L, Braunwald E, eds. Primary Cardiology. Philadelphia: WB Saunders, 1998:234-56.
34. Levine HJ. Difficult problems in the diagnosis of chest pain. Am Heart J 1980;100:108-18.
35 Wise CM, Semble EL, Dalton CB. Musculoskeletal chest wall syndromes in patients with noncardiac chest pain: a study of 100 patients. Arch Phys Med Rehabil 1992;73:147-9.
36. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology, A Basic Science for Clinical Medicine Boston: Little Brown, 1991:93-8.
37. Mark DB, Shaw L, Harrell FE, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849-53.
38. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-8.

39. Pryor DB, Harrell FE, Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. Am J Med 1983;75:771-80.
40. Sox HC, Hickam DH, Marton KI, et al. Using the patient's history to estimate the probability of coronary artery disease: a comparison of primary care and referral practices [published erratum appears in Am J Med 1990;89:550]. Am J Med 1990;89:7-14.
41. Pryor DB, Shaw L, McCants CB, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Ann Intern Med 1993;118:81-90.
42. Chaitman BR, Bourassa MG, Davis K, et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981;64:360-7.
43. Evans AT. Sensitivity and specificity of the history and physical examination for coronary artery disease [letter; comment]. Ann Intern Med 1994;120:344-5.
44. Laskey WK. Assessment of cardiovascular risk: a return to basics [editorial]. Ann Intern Med 1993;118:149-50.
45. Diamond GA, Staniloff HM, Forrester JS, Pollock BH, Swan HJ. Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary disease. J Am Coll Cardiol 1983;1:444-55.
46. Campeau L. Grading of angina pectoris [letter]. Circulation 1976;54:522-3.
47. Knochel JP, Beisel WR, Herndon EG, Gerard ES, Barry KG. The renal, cardiovascular, hematologic and serum electrolyte abnormalities of heatstroke. Am J Med 1961;30:299-309.
48. Hollander JE. The management of cocaine-associated myocardial ischemia. N Engl J Med 1995;333:1267-72.
49 Connolly DC, Elveback LR, Oxman HA. Coronary heart disease in residents of Rochester, Minnesota, IV. Prognostic value of the resting electrocardiogram at the time of initial diagnosis of angina pectoris. Mayo Clin Proc 1984;59:247-50.
50. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation 1994;90:1786-93.
51. Fisch C. Electrocardiography and vectorcardiography. In: Braunwald E, ed. Heart Disease. A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia: WB Saunders, 1992:145.
52. Margolis JR, Chen JT, Kong Y, Peter RH, Behar VS, Kisslo JA. The diagnostic and prognostic significance of coronary artery calcification: a report of 800 cases. Radiology 1980;137:609-16.
53. Mautner SL, Mautner GC, Froehlich J, et al. Coronary artery disease: prediction with in vitro electron beam CT. Radiology 1994;192:625-30.
54. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. Circulation 1995;92:2157-62.
55. Janowitz WR, Agatston AS, Viamonte M Jr. Comparison of serial quantitative evaluation of calcified coronary artery plaque by ultrafast computed tomography in persons with and without obstructive coronary artery disease. Am J Cardiol 1991;68:1-6.
56. Devries S, Wolfkiel C, Shah V, Chomka E, Rich S. Reproducibility of the measurement of coronary calcium with ultrafast computed tomography. Am J Cardiol 1995;75:973-5.
57. Detrano R, Wang S, Tang W, Brundage B, Wong N. Thick slice electron beam tomographic scanning allows reproducible and accurate assessments of coronary calcific deposits. Circulation 1995;92(suppl I):I-650.
58. Washington RL, Bricker JT, Alpert BS, et al. Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation 1994;90:2166-79.
59. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for healthcare professionals from the American Heart Association. Circulation 1995;91:580-615.
60. Pina IL, Balady GJ, Hanson P, Labovitz AJ, Madonna DW, Myers J. Guidelines for clinical exercise testing laboratories. A statement for healthcare professionals from the Committee on Exercise and Cardiac Rehabilitation, American Heart Association. Circulation 1995;91:912-21.
61. Stuart RJ, Ellestad MH. National survey of exercise stress testing facilities. Chest 1980;77:94-7.
62. Lewis WR, Amsterdam EA. Utility and safety of immediate exercise testing of low-risk patients admitted to the hospital for suspected acute myocardial infarction. Am J Cardiol 1994;74:987-90.
63. Gomez MA, Anderson JL, Karagounis LA, Muhlestein JB, Mooers FB. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). J Am Coll Cardiol 1996;28:25-33.
64. Polanczyk CA, Johnson PA, Hartley LH, Walls RM, Shaykevich S, Lee TH. Clinical correlates and prognostic significance of early negative exercise tolerance test in patients with acute chest pain seen in the hospital emergency department. Am J Cardiol 1998;81:288-92.
65. Brown KA, O'Meara J, Chambers CE, Plante DA. Ability of dipyridamole-thallium-201 imaging one to four days after acute myocardial infarction to predict in-hospital and late recurrent myocardial ischemic events. Am J Cardiol 1990;65:160-7.
66. Mahmarian JJ, Mahmarian AC, Marks GF, Pratt CM, Verani MS. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol 1995;25:1333-40.
67. Dakik HA, Mahmarian JJ, Kimball KT, Koutelou MG, Medrano R, Verani MS. Prognostic value of exercise 201Tl tomography in patients treated with thrombolytic therapy during acute myocardial infarction. Circulation 1996;94:2735-42.
68. Heller GV, Brown KA, Landin RJ, Haber SB. Safety of early intravenous dipyridamole technetium 99m sestamibi SPECT myocardial perfusion imaging after uncomplicated first myocardial infarction: Early Post MI IV Dipyridamole Study (EPIDS). Am Heart J 1997;134:105-11.
69. Myers J, Froelicher VF. Optimizing the exercise test for pharmacological investigations. Circulation 1990;82:1839-46.
70. Schlant RC, Friesinger GC, Leonard JJ. Clinical competence in exercise testing. A statement for physicians from the ACP/ACC/AHA Task Force on Clinical Privileges in Cardiology. J Am Coll Cardiol 1990;16:1061-5.
71. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-81.
72. Guidelines and indications for coronary artery bypass graft surgery. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol 1991;17:543-89.
73. Morise AP, Diamond GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased

populations of men and women. Am Heart J 1995;130:741-7.
74. DelCampo J, Do D, Umann T, McGowan V, Froning J, Froelicher VF. Comparison of computerized and standard visual criteria of exercise ECG for diagnosis of coronary artery disease. Ann Non-Invasive Electrocardiography [RTF annotation: Please verify journal title in reference 74.]1996;1:430-42.
75. Froelicher VF, Lehmann KG, Thomas R, et al. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography. Ann Intern Med 1998;128:965-74.
76. Ellestad MH, Savitz S, Bergdall D, Teske J. The false positive stress test. Multivariate analysis of 215 subjects with hemodynamic, angiographic and clinical data. Am J Cardiol 1977;40:681-5.
77. Yamada H, Do D, Morise A, Atwood JE, Froelicher VF. Review of studies using multivariable analysis of clinical and exercise test data to predict angiographic coronary artery disease. Prog Cardiovasc Dis 1997;39:457-81.
78. Lee KL, Pryor DB, Harrell FE, et al. Predicting outcome in coronary disease: statistical models versus expert clinicians. Am J Med 1986;80:553-60.
79. Detrano R, Bobbio M, Olson H, et al. Computer probability estimates of angiographic coronary artery disease: transportability and comparison with cardiologists' estimates. Comput Biomed Res 1992;25:468-85.
80. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980;302:1109-17.
81. Diamond GA, Forrester JS, Hirsch M, et al. Application of conditional probability analysis to the clinical diagnosis of coronary artery disease. J Clin Invest 1980;65:1210-21.
82. Goldman L, Cook EF, Mitchell N, et al. Incremental value of the exercise test for diagnosing the presence or absence of coronary artery disease. Circulation 1982;66:945-53.
83. Melin JA, Wijns W, Vanbutsele RJ, et al. Alternative diagnostic strategies for coronary artery disease in women: demonstration of the usefulness and efficiency of probability analysis. Circulation 1985;71:535-42.
84. Sketch MH, Mooss AN, Butler ML, Nair CK, Mohiuddin SM. Digoxin-induced positive exercise tests: their clinical and prognostic significance. Am J Cardiol 1981;48:655-9.
85. Le Winter MM, Crawford MH, O'Rourke RA, Karliner JS. The effects of oral propranolol, digoxin and combination therapy on the resting and exercise electrocardiogram. Am Heart J 1977;93:202-9.
86. Egstrup K. Transient myocardial ischemia after abrupt withdrawal of antianginal therapy in chronic stable angina. Am J Cardiol 1988;61:1219-22.
87. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990;263:1653-7.
88. Cantwell JD, Murray PM, Thomas RJ. Current management of severe exercise-related cardiac events. Chest 1988;93:1264-9.
89. Anastasiou-Nana MI, Anderson JL, Stewart JR, et al. Occurrence of exercise-induced and spontaneous wide complex tachycardia during therapy with flecainide for complex ventricular arrhythmias: a probable proarrhythmic effect. Am Heart J 1987;113:1071-7.
90. Whinnery JE, Froelicher VF, Stuart AJ. The electrocardiographic response to maximal treadmill exercise in asymptomatic men with left bundle branch block. Am Heart J 1977;94:316-24.
91. Whinnery JE, Froelicher VF, Longo MR, Triebwasser JH. The electrocardiographic response to maximal treadmill exercise of asymptomatic men with right bundle branch block. Chest 1977;71:335-40.
92. Blackburn H. Canadian Colloquium on Computer-Assisted Interpretation of Electrocardiograms, VI. Importance of the electrocardiogram in populations outside the hospital. Can Med Assoc J 1973;108:1262-5.
93. Cullen K, Stenhouse NS, Wearne KL, Cumpston GN. Electrocardiograms and 13 year cardiovascular mortality in Busselton study. Br Heart J 1982;47:209-12.
94. Aronow WS. Correlation of ischemic ST-segment depression on the resting electrocardiogram with new cardiac events in 1,106 patients over 62 years of age. Am J Cardiol 1989;64:232-3.
95. Califf RM, Mark DB, Harrell FE, et al. Importance of clinical measures of ischemia in the prognosis of patients with documented coronary artery disease. J Am Coll Cardiol 1988;11:20-6.
96. Harris PJ, Harrell FE, Lee KL, Behar VS, Rosati RA. Survival in medically treated coronary artery disease. Circulation 1979;60:1259-69.
97. Miranda CP, Lehmann KG, Froelicher VF. Correlation between resting ST segment depression, exercise testing, coronary angiography, and long-term prognosis. Am Heart J 1991;122:1617-28.
98. Kansal S, Roitman D, Sheffield LT. Stress testing with ST-segment depression at rest. An angiographic correlation. Circulation 1976;54:636-9.
99. Harris FJ, DeMaria AN, Lee G, Miller RR, Amsterdam EA, Mason DT. Value and limitations of exercise testing in detecting coronary disease with normal and abnormal resting electrocardiograms. Adv Cardiol 1978:11-5.
100. Miranda CP, Liu J, Kadar A, et al. Usefulness of exercise-induced ST-segment depression in the inferior leads during exercise testing as a marker for coronary artery disease. Am J Cardiol 1992;69:303-7.
101. Rijneke RD, Ascoop CA, Talmon JL. Clinical significance of upsloping ST segments in exercise electrocardiography. Circulation 1980;61:671-8.
102. Stuart RJ, Ellestad MH. Upsloping S-T segments in exercise stress testing. Six year follow-up study of 438 patients and correlation with 248 angiograms. Am J Cardiol 1976;37:19-22.
103. Sapin PM, Koch G, Blauwet MB, McCarthy JJ, Hinds SW, Gettes LS. Identification of false positive exercise tests with use of electrocardiographic criteria: a possible role for atrial repolarization waves. J Am Coll Cardiol 1991;18:127-35.
104. Sapin PM, Blauwet MB, Koch GG, Gettes LS. Exaggerated atrial repolarization waves as a predictor of false positive exercise tests in an unselected population. J Electrocardiol 1995;28:313-21.
105. Manvi KN, Ellestad MH. Elevated ST segments with exercise in ventricular aneurysm. J Electrocardiol 1972;5:317-23.
106. Haines DE, Beller GA, Watson DD, Kaiser DL, Sayre SL, Gibson RS. Exercise-induced ST segment elevation 2 weeks after uncomplicated myocardial infarction: contributing factors and prognostic significance. J Am Coll Cardiol 1987;9:996-1003.
107. Margonato A, Ballarotto C, Bonetti F, et al. Assessment of residual tissue viability by exercise testing in recent myocardial infarction: comparison of the electrocardiogram and myocardial perfusion scintigraphy. J Am Coll Cardiol 1992;19:948-52.
108. Margonato A, Chierchia SL, Xuereb RG, et al. Specificity and sensitivity of exercise-induced ST segment elevation for detection of residual viability: comparison with fluorodeoxyglucose and positron emission tomography. J Am Coll Cardiol 1995;25:1032-

8.
109. Lombardo A, Loperfido F, Pennestri F, et al. Significance of transient ST-T segment changes during dobutamine testing in Q wave myocardial infarction. J Am Coll Cardiol 1996;27:599-605.
110. Kentala E, Luurila O. Response of R wave amplitude to postural changes and to exercise. A study of healthy subjects and patients surviving acute myocardial infarction. Ann Clin Res 1975;7:258-63.
111. Bonoris PE, Greenberg PS, Christison GW, Castellanet MJ, Ellestad MH. Evaluation of R wave amplitude changes versus ST-segment depression in stress testing. Circulation 1978;57:904-10.
112. De Feyter PJ, Jong de JP, Roos JP, van Eenige MJ, de Jong JP. Diagnostic incapacity of exercise-induced QRS wave amplitude changes to detect coronary artery disease and left ventricular dysfunction. Eur Heart J 1982;3:9-16.
113. Elamin MS, Boyle R, Kardash MM, et al. Accurate detection of coronary heart disease by new exercise test. Br Heart J 1982;48:311-20.
114. Okin PM, Kligfield P. Computer-based implementation of the ST-segment/heart rate slope. Am J Cardiol 1989;64:926-30.
115. Detrano R, Salcedo E, Passalacqua M, Friis R. Exercise electrocardiographic variables: a critical appraisal. J Am Coll Cardiol 1986;8:836-47.
116. Kligfield P, Ameisen O, Okin PM. Heart rate adjustment of ST segment depression for improved detection of coronary artery disease. Circulation 1989;79:245-55.
117. Lachterman B, Lehmann KG, Detrano R, Neutel J, Froelicher VF. Comparison of ST segment/heart rate index to standard ST criteria for analysis of exercise electrocardiogram. Circulation 1990;82:44-50.
118. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation 1989;80:87-98.
119. Pryor DB. The academic life cycle of a noninvasive test [editorial]. Circulation 1990;82:302-4.
120. Milliken JA, Abdollah H, Burggraf GW. False-positive treadmill exercise tests due to computer signal averaging. Am J Cardiol 1990;65:946-8.
121. Kennedy JW, Killip T, Fisher LD, Alderman EL, Gillespie MJ, Mock MD. The clinical spectrum of coronary artery disease and its surgical and medical management, 1974-1979. The Coronary Artery Surgery Study. Circulation 1982;66:III-16-23.
122. Hlatky MA, Pryor DB, Harrell FE, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. Am J Med 1984;77:64-71.
123. Linhart JW, Laws JG, Satinsky JD. Maximum treadmill exercise electrocardiography in female patients. Circulation 1974;50:1173-8.
124. Sketch MH, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. Am J Cardiol 1975;36:169-73.
125. Barolsky SM, Gilbert CA, Faruqui A, Nutter DO, Schlant RC. Differences in electrocardiographic response to exercise of women and men: a non-Bayesian factor. Circulation 1979;60:1021-7.
126. Ilsley C, Canepa-Anson R, Westgate C, Webb S, Rickards A, Poole-Wilson P. Influence of R wave analysis upon diagnostic accuracy of exercise testing in women. Br Heart J 1982;48:161-8.
127. Hung J, Chaitman BR, Lam J, et al. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. J Am Coll Cardiol 1984;4:8-16.
128. Chae SC, Heo J, Iskandrian AS, Wasserleben V, Cave V. Identification of extensive coronary artery disease in women by exercise single-photon emission computed tomographic (SPECT) thallium imaging. J Am Coll Cardiol 1993;21:1305-11.
129. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. J Am Coll Cardiol 1995;26:335-41.
130. Williams MJ, Marwick TH, O'Gorman D, Foale RA. Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in women. Am J Cardiol 1994;74:435-8.
131. Robert AR, Melin JA, Detry JM. Logistic discriminant analysis improves diagnostic accuracy of exercise testing for coronary artery disease in women. Circulation 1991;83:1202-9.
132. Okin PM, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. Circulation 1995;92:1209-16.
133. Pratt CM, Francis MJ, Divine GW, Young JB. Exercise testing in women with chest pain. Are there additional exercise characteristics that predict true positive test results? Chest 1989;95:139-44.
134. Pryor DB, Shaw L, Harrell FE, et al. Estimating the likelihood of severe coronary artery disease. Am J Med 1991;90:553-62.
135. Hubbard BL, Gibbons RJ, Lapeyre AC, Zinsmeister AR, Clements IP. Identification of severe coronary artery disease using simple clinical parameters. Arch Intern Med 1992;152:309-12.
136. DeStefano F, Merritt RK, Anda RF, Casper ML, Eaker ED. Trends in nonfatal coronary heart disease in the United States, 1980 through 1989. Arch Intern Med 1993;153:2489-94.
137. Fleg JL, Gerstenblith G, Zonderman AB, et al. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers. Circulation 1990;81:428-36.
138. Vasilomanolakis EC. Geriatric cardiology: when exercise stress testing is justified. Geriatrics 1985;40:47-50.
139. Martinez-Caro D, Alegria E, Lorente D, Azpilicueta J, Calabuig J, Ancin R. Diagnostic value of stress testing in the elderly. Eur Heart J 1984;5(Suppl E):63-7.
140. Kasser IS, Bruce RA. Comparative effects of aging and coronary heart disease on submaximal and maximal exercise. Circulation 1969;39:759-74.
141. O'Keefe JH Jr, Zinsmeister AR, Gibbons RJ. Value of normal electrocardiographic findings in predicting resting left ventricular function in patients with chest pain and suspected coronary artery disease. Am J Med 1989;86:658-62.
142. Christian TF, Miller TD, Chareonthaitawee P, Hodge DO, O'Connor MK, Gibbons RJ. Prevalence of normal resting left ventricular function with normal rest electrocardiograms. Am J Cardiol 1997;79:1295-8.
143. Heger JJ, Weyman AE, Wann LS, Rogers EW, Dillon JC, Feigenbaum H. Cross-sectional echocardiographic analysis of the extent of left ventricular asynergy in acute myocardial infarction. Circulation 1980;61:1113-8.
144. Jaarsma W, Visser CA, van Eenige MJ, Verheugt FW, Kupper AJ, Roos JP. Predictive value of two-dimensional echocardiographic and hemodynamic measurements on admission with acute myocardial infarction. J Am Soc Echocardiogr 1988;1:187-93.
145. Roger VL, Pellikka PA, Oh JK, Miller FA, Seward JB, Tajik AJ. Stress echocardiography. Part I. Exercise echocardiography: techniques, implementation, clinical applications, and correlations. Mayo Clin Proc 1995;70:5-15.

146. Aurigemma GP, Gaasch WH, Villegas B, Meyer TE. Noninvasive assessment of left ventricular mass, chamber volume, and contractile function. Curr Probl Cardiol 1995;20:361-440.
147. Horowitz RS, Morganroth J, Parrotto C, Chen CC, Soffer J, Pauletto FJ. Immediate diagnosis of acute myocardial infarction by two-dimensional echocardiography. Circulation 1982;65:323-9.
148. Gibson RS, Bishop HL, Stamm RB, Crampton RS, Beller GA, Martin RP. Value of early two dimensional echocardiography in patients with acute myocardial infarction. Am J Cardiol 1982; 49:1110-9.
149. Kerber RE, Abboud FM. Echocardiographic detection of regional myocardial infarction: an experimental study. Circulation 1973;47:997-1005.
150. Weiss JL, Bulkley BH, Hutchins GM, Mason SJ. Two-dimensional echocardiographic recognition of myocardial injury in man: comparison with postmortem studies. Circulation 1981;63:401-8.
151. Nixon JV, Narahara KA, Smitherman TC. Estimation of myocardial involvement in patients with acute myocardial infarction by two-dimensional echocardiography. Circulation 1980;62:1248-55.
152. Distante A, Picano E, Moscarelli E, Palombo C, Benassi A, L'Abbate A. Echocardiographic versus hemodynamic monitoring during attacks of variant angina pectoris. Am J Cardiol 1985;55:1319-22.
153. Shibata J, Takahashi H, Itaya M, et al. Cross-sectional echocardiographic visualization of the infarcted site in myocardial infarction: correlation with electrocardiographic and coronary angiographic findings. J Cardiogr 1982;12:885-94.
154. Tennant R, Wiggers CJ. The effect of coronary artery occlusion on myocardial contraction. Am J Physiol 1935;112:351-61.
155. Burns PN. Harmonic imaging with ultrasound contrast agents. Clin Radiol 1996;51(Suppl 1):50-5.
156. Christopher T. Finite amplitude distortion-based inhomogeneous pulse echo ultrasonic imaging. IEEE Trans Ultrasonics Ferroelectrics Frequency Control 1997;44:125-39.
157. Kaul S, Glasheen WP, Oliner JD, Kelly P, Gascho JA. Relation between anterograde blood flow through a coronary artery and the size of the perfusion bed it supplies: experimental and clinical implications. J Am Coll Cardiol 1991;17:1403-13.
158. Ito H, Okamura A, Iwakura K, et al. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. Circulation 1996;93:1993-9.
159. Porter T, Li S, Kilzer K, Deligonul U. Correlation between quantitative angiographic lesion severity and myocardial contrast intensity during a continuous infusion of perfluorocarbon-containing microbubbles. J Am Soc Echocardiogr 1998;11:702-10.
160. Peels CH, Visser CA, Kupper AJ, Visser FC, Roos JP. Usefulness of two-dimensional echocardiography for immediate detection of myocardial ischemia in the emergency room. Am J Cardiol 1990;65:687-91.
161. Kaul S, Spotnitz WD, Glasheen WP, Touchstone DA. Mechanism of ischemic mitral regurgitation. An experimental evaluation. Circulation 1991;84:2167-80.
162. Kono T, Sabbah HN, Rosman H, et al. Mechanism of functional mitral regurgitation during acute myocardial ischemia. J Am Coll Cardiol 1992;19:1101-5.
163. Godley RW, Wann LS, Rogers EW, Feigenbaum H, Weyman AE. Incomplete mitral leaflet closure in patients with papillary muscle dysfunction. Circulation 1981;63:565-71.
164. Nishimura RA, Schaff HV, Shub C, Gersh BJ, Edwards WD, Tajik AJ. Papillary muscle rupture complicating acute myocardial infarction: analysis of 17 patients. Am J Cardiol 1983;51:373-7.
165. Leppo JA. Dipyridamole-thallium imaging: the lazy man's stress test. J Nucl Med 1989;30:281-7.
166. Abreu A, Mahmarian JJ, Nishimura S, Boyce TM, Verani MS. Tolerance and safety of pharmacologic coronary vasodilation with adenosine in association with thallium-201 scintigraphy in patients with suspected coronary artery disease. J Am Coll Cardiol 1991;18:730-5.
167. Verani MS. Adenosine thallium 201 myocardial perfusion scintigraphy. Am Heart J 1991;122:269-78.
168. Mason JR, Palac RT, Freeman ML, et al. Thallium scintigraphy during dobutamine infusion: nonexercise-dependent screening test for coronary disease. Am Heart J 1984;107:481-5.
169. Pennell DJ, Underwood SR, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. J Am Coll Cardiol 1991;18:1471-9.
170. Marwick T, Willemart B, D'Hondt AM, et al. Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and 99mTc-MIBI single photon emission computed tomography. Circulation 1993;87:345-54.
171. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. J Am Coll Cardiol 1993;21:1583-90.
172 Mertes H, Sawada SG, Ryan T, et al. Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography: experience in 1,118 patients. Circulation 1993;88:15-9.
173. Hiro J, Hiro T, Reid CL, Ebrahimi R, Matsuzaki M, Gardin JM. Safety and results of dobutamine stress echocardiography in women versus men and in patients older and younger than 75 years of age. Am J Cardiol 1997;80:1014-20.
174. Rozanski A, Diamond GA, Berman D, Forrester JS, Morris D, Swan HJC. The declining specificity of exercise radionuclide ventriculography. N Engl J Med 1983;309:518-22.
175. Douglas PS. Is noninvasive testing for coronary artery disease accurate? Circulation 1997;95:299-302.
176. Kaul S. Technical, economic, interpretative, and outcomes issues regarding utilization of cardiac imaging techniques in patients with known or suspected coronary artery disease. Am J Cardiol 1995;75:18D-24D.
177. Diamond GA. Reverend Bayes' silent majority: an alternative factor affecting sensitivity and specificity of exercise electrocardiography. Am J Cardiol 1986;57:1175-80.
178. Schwartz RS, Jackson WG, Cello PV, Richardson LA, Hickman JR. Accuracy of exercise 201-Tl myocardial scintigraphy in asymptomatic young men. Circulation 1993;87:165-72.
179. Roger VL, Pelikka PA, Bell MR, Chow CWH, Bailey KR, Seward JB. Sex and test verification bias: impact on the diagnostic value of exercise echocardiography. Circulation 1997;95:405-10.
180. Kiat H, Berman DS, Maddahi J. Comparison of planar and tomographic exercise thallium-201 imaging methods for the evaluation of coronary artery disease. J Am Coll Cardiol 1989;13:613-6.
181. Iskandrian AS, Heo J, Kong B, Lyons E, Marsch S. Use of technetium-99m isonitrile (RP-30A) in assessing left ventricular perfusion and function at rest and during exercise in coronary artery disease, and comparison with coronary arteriography and exercise thallium-201 SPECT imaging. Am J Cardiol 1989;64:270-5.
182. Taillefer R, Laflamme L, Dupras G, Picard M, Phaneuf DC,

Leveille J. Myocardial perfusion imaging with 99mTc-methoxy-isobutyl-isonitrile (MIBI): comparison of short and long time intervals between rest and stress injections. Preliminary results. Eur J Nucl Med 1988;13:515-22.
183. Maddahi J, Kiat H, Van Train KF, et al. Myocardial perfusion imaging with technetium-99m sestamibi SPECT in the evaluation of coronary artery disease. Am J Cardiol 1990;66:55E-62E.
184. Kahn JK, McGhie I, Akers MS, et al. Quantitative rotational tomography with 201Tl and 99mTc 2-methoxy-isobutyl-isonitrile. A direct comparison in normal individuals and patients with coronary artery disease. Circulation 1989;79:1282-93.
185. Wackers FJ, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 1989;30:301-11.
186. Maisey MN, Mistry R, Sowton E. Planar imaging techniques used with technetium-99m sestamibi to evaluate chronic myocardial ischemia. Am J Cardiol 1990;66:47E-54E.
187. Maddahi J, Kiat H, Friedman JD, Berman DS, Van Train KK, Garcia EV. Technetium-99m-sestamibi myocardial perfusion imaging for evaluation of coronary artery disease. In: Zaret BL, Beller GA, eds. Nuclear Cardiology: State of the Art and Future Directions. St. Louis: Mosby, 1993:191-200.
188. Verani MS. Thallium-201 and technetium-99m perfusion agents: where we are in 1992. In: Zaret BL, Beller GA, eds. Nuclear Cardiology: State of the Art and Future Directions. St. Louis: Mosby, 1993:216-24.
189. Sridhara BS, Braat S, Rigo P, Itti R, Cload P, Lahiri A. Comparison of myocardial perfusion imaging with technetium-99m tetrofosmin versus thallium-201 in coronary artery disease. Am J Cardiol 1993;72:1015-9.
190. Zaret BL, Rigo P, Wackers FJ, et al. Myocardial perfusion imaging with 99mTc tetrofosmin. Comparison to 201Tl imaging and coronary angiography in a phase III multicenter trial. Circulation 1995;91:313-9.
191. Verani MS, Marcus ML, Razzak MA, Ehrhardt JC. Sensitivity and specificity of thallium-201 perfusion scintigrams under exercise in the diagnosis of coronary artery disease. J Nucl Med 1978;19:773-82.
192. Okada RD, Boucher CA, Strauss HW, Pohost GM. Exercise radionuclide imaging approaches to coronary artery disease. Am J Cardiol 1980;46:1188-204.
193. Gibson RS, Beller GA. Should exercise electrocardiographic testing be replaced by radioscope methods? In: Rahimtoola SH, Brest AN, eds. Controversies in Coronary Artery Disease. Philadelphia: FA Davis, 1983:1-31.
194. Detrano R, Janosi A, Lyons KP, Marcondes G, Abbassi N, Froelicher VF. Factors affecting sensitivity and specificity of a diagnostic test: the exercise thallium scintigram. Am J Med 1988;84:699-710.
195. Watson DD, Campbell NP, Read EK, Gibson RS, Teates CD, Beller GA. Spatial and temporal quantitation of plane thallium myocardial images. J Nucl Med 1981;22:577-84.
196. Burow RD, Pond M, Schafer AW, Becker L. Circumferential profiles: a new method for computer analysis of thallium-201 myocardial perfusion images. J Nucl Med 1979;20:771-7.
197. Garcia E, Maddahi J, Berman D, Waxman A. Space/time quantitation of thallium-201 myocardial scintigraphy. J Nucl Med 1981;22:309-17.
198. Wackers FJ, Fetterman RC, Mattera JA, Clements JP. Quantitative planar thallium-201 stress scintigraphy: a critical evaluation of the method. Semin Nucl Med 1985;15:46-66.
199. Kaul S, Boucher CA, Newell JB, et al. Determination of the quantitative thallium imaging variables that optimize detection of coronary artery disease. J Am Coll Cardiol 1986;7:527-37.
200. Zaret BL, Wackers FJT, Soufer R. Nuclear cardiology. In: Braunwald E, ed. Heart Disease. Philadelphia: Saunders, 1992:276-311.
201. Maddahi J, Garcia EV, Berman DS, Waxman A, Swan HJ, Forrester J. Improved noninvasive assessment of coronary artery disease by quantitative analysis of regional stress myocardial distribution and washout of thallium-201. Circulation 1981;64:924-35.
202. Gerson MC, Thomas SR, Van Heertum RL. Tomographic myocardial perfusion imaging. In: Gerson MC, ed. Cardiac Nuclear Medicine. New York: McGraw-Hill, 1991:25-52.
203. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819-24.
204. Fintel DJ, Links JM, Brinker JA, Frank TL, Parker M, Becker LC. Improved diagnostic performance of exercise thallium-201 single photon emission computed tomography over planar imaging in the diagnosis of coronary artery disease: a receiver operating characteristic analysis. J Am Coll Cardiol 1989;13:600-12.
205. Nohara R, Kambara H, Suzuki Y, et al. Stress scintigraphy using single-photon emission computed tomography in the evaluation of coronary artery disease. Am J Cardiol 1984;53:1250-4.
206. Mahmarian JJ, Verani MS. Exercise thallium-201 perfusion scintigraphy in the assessment of coronary artery disease. Am J Cardiol 1991;67:2D-11D.
207. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation, I. Physiologic basis and experimental validation. Am J Cardiol 1978;41:267-78.
208. Gould KL, Westcott RJ, Albro PC, Hamilton GW. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilatation, II. Clinical methodology and feasibility. Am J Cardiol 1978;41:279-87.
209. Albro PC, Gould KL, Westcott RJ, Hamilton GW, Ritchie JL, Williams DL. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilatation, III. Clinical trial. Am J Cardiol 1978;42:751-60.
210. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacologic coronary vasodilation with adenosine for assessing coronary artery disease. J Am Coll Cardiol 1991;18:736-45.
211. Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. Circulation 1990;82:80-7.
212. Nguyen T, Heo J, Ogilby JD, Iskandrian AS. Single photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia: correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. J Am Coll Cardiol 1990;16:1375-83.
213. Coyne EP, Belvedere DA, Vande Streek PR, Weiland FL, Evans RB, Spaccavento LJ. Thallium-201 scintigraphy after intravenous infusion of adenosine compared with exercise thallium testing in the diagnosis of coronary artery disease. J Am Coll Cardiol 1991; 17:1289-94.
214. Gupta NC, Esterbrooks DJ, Hilleman DE, Mohiuddin SM. Comparison of adenosine and exercise thallium-201 single-photon emission computed tomography (SPECT) myocardial perfu-

sion imaging. The GE SPECT Multicenter Adenosine Study Group. J Am Coll Cardiol 1992;19:248-57.
215. Ogilby JD, Iskandrian AS, Untereker WJ, Heo J, Nguyen TN, Mercuro J. Effect of intravenous adenosine infusion on myocardial perfusion and function: hemodynamic/angiographic and scintigraphic study. Circulation 1992;86:887-95.
216. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Equivalence between adenosine and exercise thallium-201 myocardial tomography: a multicenter, prospective, crossover trial. J Am Coll Cardiol 1992;20:265-75.
217. Verani MS. Pharmacologic stress myocardial perfusion imaging. Curr Probl Cardiol 1993;18:481-525.
218. Borges-Neto S, Mahmarian JJ, Jain A, Roberts R, Verani MS. Quantitative thallium-201 single photon emission computed tomography after oral dipyridamole for assessing the presence, anatomic location and severity of coronary artery disease. J Am Coll Cardiol 1988;11:962-9.
219. Kettunen R, Huikuri HV, Heikkila J, Takkunen JT. Usefulness of technetium-99m-MIBI and thallium-201 in tomographic imaging combined with high-dose dipyridamole and handgrip exercise for detecting coronary artery disease. Am J Cardiol 1991;68:575-9.
220. Parodi O, Marcassa C, Casucci R, et al. Accuracy and safety of technetium-99m hexakis 2-methoxy-2-isobutyl isonitrile (Sestamibi) myocardial scintigraphy with high dose dipyridamole test in patients with effort angina pectoris: a multicenter study. Italian Group of Nuclear Cardiology. J Am Coll Cardiol 1991;18:1439-44.
221. Wu JC, Yun JJ, Heller EN, et al. Limitations of dobutamine for enhancing flow heterogeneity in the presence of single coronary stenosis: implications for technetium-99m-sestamibi imaging. J Nucl Med 1998;39:417-25.
222. Calnon DA, Glover DK, Beller GA, et al. Effects of dobutamine stress on myocardial blood flow, 99mTc sestamibi uptake, and systolic wall thickening in the presence of coronary artery stenoses: implications for dobutamine stress testing. Circulation 1997;96:2353-60.
223. Iftikhar I, Koutelou M, Mahmarian JJ, Verani MS. Simultaneous perfusion tomography and radionuclide angiography during dobutamine stress. J Nucl Med 1996;37:1306-10.
224. Beleslin BD, Ostojic M, Stepanovic J, et al. Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. Circulation 1994;90:1168-76.
225. Dagianti A, Penco M, Agati L, Sciomer S, Rosanio S, Fedele F. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease [published erratum appears in J Am Coll Cardiol 1995;26:1114]. J Am Coll Cardiol 1995;26:18-25.
226. Iskandrian AS, Heo J, Kong B, Lyons E. Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients. J Am Coll Cardiol 1989;14:1477-86.
227. Steele P, Sklar J, Kirch D, Vogel R, Rhodes CA. Thallium-201 myocardial imaging during maximal and submaximal exercise: comparison of submaximal exercise with propranolol. Am Heart J 1983;106:1353-7.
228. Hockings B, Saltissi S, Croft DN, Webb-Peploe MM. Effect of beta adrenergic blockade on thallium-201 myocardial perfusion imaging. Br Heart J 1983;49:83-9.
229. Martin GJ, Henkin RE, Scanlon PJ. Beta blockers and the sensitivity of the thallium treadmill test. Chest 1987;92:486-7.
230. Zacca NM, Verani MS, Chahine RA, Miller RR. Effect of nifedipine on exercise-induced left ventricular dysfunction and myocardial hypoperfusion in stable angina. Am J Cardiol 1982;50:689-95.
231. Esquivel L, Pollock SG, Beller GA, Gibson RS, Watson DD, Kaul S. Effect of the degree of effort on the sensitivity of the exercise thallium-201 stress test in symptomatic coronary artery disease. Am J Cardiol 1989;63:160-5.
232. Braat SH, Brugada P, Bar FW, Gorgels AP, Wellens HJ. Thallium-201 exercise scintigraphy and left bundle branch block. Am J Cardiol 1985;55:224-6.
233. Hirzel HO, Senn M, Nuesch K, et al. Thallium-201 scintigraphy in complete left bundle branch block. Am J Cardiol 1984;53:764-9.
234. DePuey EG, Guertler-Krawczynska E, Robbins WL. Thallium-201 SPECT in coronary artery disease patients with left bundle branch block. J Nucl Med 1988;29:1479-85.
235. Burns RJ, Galligan L, Wright LM, Lawand S, Burke RJ, Gladstone PJ. Improved specificity of myocardial thallium-201 single-photon emission computed tomography in patients with left bundle branch block by dipyridamole. Am J Cardiol 1991; 68:504-8.
236. Rockett JF, Wood WC, Moinuddin M, Loveless V, Parrish B. Intravenous dipyridamole thallium-201 SPECT imaging in patients with left bundle branch block. Clin Nucl Med 1990;15:401-7.
237. O'Keefe JH Jr, Bateman TM, Barnhart CS. Adenosine thallium-201 is superior to exercise thallium-201 for detecting coronary artery disease in patients with left bundle branch block. J Am Coll Cardiol 1993;21:1332-8.
238. Vaduganathan P, He ZX, Raghavan C, Mahmarian JJ, Verani MS. Detection of left anterior descending coronary artery stenosis in patients with left bundle branch block: exercise, adenosine or dobutamine imaging? J Am Coll Cardiol 1996;28:543-50.
239. Morais J, Soucy JP, Sestier F, Lamoureux F, Lamoureux J, Danais S. Dipyridamole testing compared to exercise stress for thallium-201 imaging in patients with left bundle branch block. Can J Cardiol 1990;6:5-8.
240. Jukema JW, van der Wall EE, van der Vis-Melsen MJ, Kruyswijk HH, Bruschke AV. Dipyridamole thallium-201 scintigraphy for improved detection of left anterior descending coronary artery stenosis in patients with left bundle branch block. Eur Heart J 1993;14:53-6.
241. Larcos G, Brown ML, Gibbons RJ. Role of dipyridamole thallium-201 imaging in left bundle branch block. Am J Cardiol 1991;68:1097-8.
242. Patel R, Bushnell DL, Wagner R, Stumbris R. Frequency of false-positive septal defects on adenosine/201Tl images in patients with left bundle branch block. Nucl Med Commun 1995;16:137-9.
243. Lebtahi NE, Stauffer JC, Delaloye AB. Left bundle branch block and coronary artery disease: accuracy of dipyridamole thallium-201 single-photon emission computed tomography in patients with exercise anteroseptal perfusion defects. J Nucl Cardiol 1997;4:266-73.
244. Mairesse GH, Marwick TH, Arnese M, et al. Improved identification of coronary artery disease in patients with left bundle branch block by use of dobutamine stress echocardiography and comparison with myocardial perfusion tomography. Am J Cardiol 1995;76:321-5.
245. Osbakken MD, Okada RD, Boucher CA, Strauss HW, Pohost GM. Comparison of exercise perfusion and ventricular function imaging: an analysis of factors affecting the diagnostic accuracy of each technique. J Am Coll Cardiol 1984;3:272-83.

246. DePuey EG, Rozanski A. Using gated technetium-99m-sestamibi SPECT to characterize fixed myocardial defects as infarct or artifact. J Nucl Med 1995;36:952-5.
247. Smanio PE, Watson DD, Segalla DL, Vinson EL, Smith WH, Beller GA. Value of gating of technetium-99m sestamibi single-photon emission computed tomographic imaging. J Am Coll Cardiol 1997;30:1687-92.
248. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. J Am Coll Cardiol 1997;29:69-77.
249. O'Keefe JH, Barnhart CS, Bateman TM. Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity. Am J Cardiol 1995;75:25D-34D.
250. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging: a meta-analysis of diagnostic test performance. JAMA 1998;280:913-20.
251. Patterson RE, Eisner RL. Cost analysis of noninvasive testing. In: Marwick TH, ed. Cardiac Stress Testing and Imaging: A Clinician's Guide. New York: Churchill Livingstone, 1996;5:113-24.
252. Leung DY, Dawson IG, Thomas JD, Marwick TH. Accuracy and cost-effectiveness of exercise echocardiography for detection of coronary artery disease in patients with mitral valve prolapse. Am Heart J 1997;134:1052-7.
253. Kim C, Kwok YS, Saha S, Redberg RF. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. Am Heart J 1999;137:1019-27.
254. Porter TR, Li S, Kilzer K, Deligonul U. Effect of significant two-vessel versus one-vessel coronary artery stenosis on myocardial contrast defects observed with intermittent harmonic imaging after intravenous contrast injection during dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:1399-406.
255. Porter TR, Kricsfeld A, Deligonul U, Xie F. Detection of regional perfusion abnormalities during adenosine stress echocardiography with intravenous perfluorocarbon-exposed sonicated dextrose albumin. Am Heart J 1996;132:41-7.
256. O'Connor MK, Caiati C, Christian TF, Gibbons RJ. Effects of scatter correction on the measurement of infarct size from SPECT cardiac phantom studies. J Nucl Med 1995;36:2080-6.
257. Germano G, Erel J, Lewin H, Kavanagh PB, Berman DS. Automatic quantitation of regional myocardial wall motion and thickening from gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 1997;30:1360-7.
258. Ficaro EP, Fessler JA, Shreve PD, Kritzman JN, Rose PA, Corbett JR. Simultaneous transmission/emission myocardial perfusion tomography. Diagnostic accuracy of attenuation-corrected 99mTc-sestamibi single-photon emission computed tomography. Circulation 1996;93:463-73.
259. Tamaki N, Yonekura Y, Mukai T, et al. Stress thallium-201 transaxial emission computed tomography: quantitative versus qualitative analysis for evaluation of coronary artery disease. J Am Coll Cardiol 1984;4:1213-21.
260. DePasquale EE, Nody AC, DePuey EG, et al. Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease. Circulation 1988;77:316-27.
261. Maddahi J, Van Train K, Prigent F, et al. Quantitative single photon emission computed thallium-201 tomography for detection and localization of coronary artery disease: optimization and prospective validation of a new technique. J Am Coll Cardiol 1989;14:1689-99.
262. Van Train KF, Maddahi J, Berman DS, et al. Quantitative analysis of tomographic stress thallium-201 myocardial scintigrams: a multicenter trial. J Nucl Med 1990;31:1168-79.
263. Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS. Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. J Am Coll Cardiol 1990;15:318-29.
264. Quiñones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus 201Tl single-photon emission computed tomography in evaluation of coronary artery disease: analysis of 292 patients. Circulation 1992;85:1026-31.
265. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Noninvasive identification of severe coronary artery disease using exercise tomographic thallium-201 imaging. Am J Cardiol 1992;70:14-20.
266. Solot G, Hermans J, Merlo P, et al. Correlation of 99mTc-sestamibi SPECT with coronary angiography in general hospital practice. Nucl Med Commun 1993;14:23-9.
267. Van Train KF, Garcia EV, Maddahi J, et al. Multicenter trial validation for quantitative analysis of same-day rest-stress technetium-99m-sestamibi myocardial tomograms. J Nucl Med 1994;35:609-18.
268. Rubello D, Zanco P, Candelpergher G, et al. Usefulness of 99mTc-MIBI stress myocardial SPECT bull's-eye quantification in coronary artery disease. Q J Nucl Med 1995;39:111-5.
269. Iskandrian AE, Heo J, Nallamothu N. Detection of coronary artery disease in women with use of stress single-photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 1997;4:329-35.
270. Palmas W, Friedman JD, Diamond GA, Silber H, Kiat H, Berman DS. Incremental value of simultaneous assessment of myocardial function and perfusion with technetium-99m sestamibi for prediction of extent of coronary artery disease. J Am Coll Cardiol 1995;25:1024-31.
271. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. J Am Coll Cardiol 1993;22:1455-64.
272. Kiat H, Van Train KF, Maddahi J, et al. Development and prospective application of quantitative 2-day stress-rest Tc-99m methoxy isobutyl isonitrile SPECT for the diagnosis of coronary artery disease. Am Heart J 1990;120:1255-66.
273. Van Train KF, Areeda J, Garcia EV, et al. Quantitative same-day rest-stress technetium-99m-sestamibi SPECT: definition and validation of stress normal limits and criteria for abnormality. J Nucl Med 1993;34:1494-502.
274. Fleming RM, Kirkeeide RL, Taegtmeyer H, Adyanthaya A, Cassidy DB, Goldstein RA. Comparison of technetium-99m teboroxime tomography with automated quantitative coronary arteriography and thallium-201 tomographic imaging. J Am Coll Cardiol 1991;17:1297-302.
275. Minoves M, Garcia A, Magrina J, Pavia J, Herranz R, Setoain J. Evaluation of myocardial perfusion defects by means of bull's eye images. Clin Cardiol 1993;16:16-22.
276. Heiba SI, Hayat NJ, Salman HS, et al. Technetium-99m-MIBI myocardial SPECT: supine versus right lateral imaging and comparison with coronary arteriography. J Nucl Med 1997;38:1510-14.
277. Sylven C, Hagerman I, Ylen M, Nyquist O, Nowak J. Variance

ECG detection of coronary artery disease—a comparison with exercise stress test and myocardial scintigraphy. Clin Cardiol 1994;17:132-40.
278. Hecht HS, DeBord L, Shaw R, et al. Supine bicycle stress echocardiography versus tomographic thallium-201 exercise imaging for the detection of coronary artery disease. J Am Soc Echocardiogr 1993;6:177-85.
279. Pozzoli MM, Fioretti PM, Salustri A, Reijs AE, Roelandt JR. Exercise echocardiography and technetium-99m MIBI single-photon emission computed tomography in the detection of coronary artery disease. Am J Cardiol 1991;67:350-5.
280. Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. Am J Cardiol 1993;72:555-9.
281. Oguzhan A, Kisacik HL, Ozdemir K, et al. Comparison of exercise stress testing with dobutamine stress echocardiography and exercise technetium-99m isonitrile single photon emission computerized tomography for diagnosis of coronary artery disease. Jpn Heart J 1997;38:333-44.
282. Ho YL, Wu CC, Huang PJ, et al. Assessment of coronary artery disease in women by dobutamine stress echocardiography: comparison with stress thallium-201 single-photon emission computed tomography and exercise electrocardiography. Am Heart J 1998;135:655-62.
283. Ho YL, Wu CC, Huang PJ, et al. Dobutamine stress echocardiography compared with exercise thallium-201 single-photon emission computed tomography in detecting coronary artery disease-effect of exercise level on accuracy. Cardiology 1997;88:379-85.
284. Armstrong WF, O'Donnell J, Ryan T, Feigenbaum H. Effect of prior myocardial infarction and extent and location of coronary disease on accuracy of exercise echocardiography. J Am Coll Cardiol 1987;10:531-8.
285. Crouse LJ, Harbrecht JJ, Vacek JL, Rosamond TL, Kramer PH. Exercise echocardiography as a screening test for coronary artery disease and correlation with coronary arteriography. Am J Cardiol 1991;67:1213-8.
286. Marwick TH, Nemec JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting. J Am Coll Cardiol 1992;19:74-81.
287. Ryan T, Segar DS, Sawada SG, et al. Detection of coronary artery disease with upright bicycle exercise echocardiography. J Am Soc Echocardiogr 1993;6:186-97.
288. Hecht HS, DeBord L, Shaw R, et al. Digital supine bicycle stress echocardiography: a new technique for evaluating coronary artery disease. J Am Coll Cardiol 1993;21:950-6.
289. Roger VL, Pellikka PA, Oh JK, Bailey KR, Tajik AJ. Identification of multivessel coronary artery disease by exercise echocardiography. J Am Coll Cardiol 1994;24:109-14.
290. Marwick TH, Torelli J, Harjai K, et al. Influence of left ventricular hypertrophy on detection of coronary artery disease using exercise echocardiography. J Am Coll Cardiol 1995;26:1180-6.
291. Luotolahti M, Saraste M, Hartiala J. Exercise echocardiography in the diagnosis of coronary artery disease. Ann Med 1996;28:73-7.
292. Tawa CB, Baker WB, Kleiman NS, Trakhtenbroit A, Desir R, Zoghbi WA. Comparison of adenosine echocardiography, with and without isometric handgrip, to exercise echocardiography in the detection of ischemia in patients with coronary artery disease. J Am Soc Echocardiogr 1996;9:33-43.
293. Bjornstad K, Aakhus S, Hatle L. Comparison of digital dipyridamole stress echocardiography and upright bicycle stress echocardiography for identification of coronary artery stenosis. Cardiology 1995;86:514-20.
294. Marangelli V, Iliceto S, Piccinni G, De Martino G, Sorgente L, Rizzon P. Detection of coronary artery disease by digital stress echocardiography: comparison of exercise, transesophageal atrial pacing and dipyridamole echocardiography. J Am Coll Cardiol 1994;24:117-24.
295. Salustri A, Pozzoli MM, Hermans W, et al. Relationship between exercise echocardiography and perfusion single-photon emission computed tomography in patients with single-vessel coronary artery disease. Am Heart J 1992;124:75-83.
296. Galanti G, Sciagra R, Comeglio M, et al. Diagnostic accuracy of peak exercise echocardiography in coronary artery disease: comparison with thallium-201 myocardial scintigraphy. Am Heart J 1991;122:1609-16.
297. Ryan T, Vasey CG, Presti CF, O'Donnell JA, Feigenbaum H, Armstrong WF. Exercise echocardiography: detection of coronary artery disease in patients with normal left ventricular wall motion at rest. J Am Coll Cardiol 1988;11:993-9.
298. Alam M, Hoglund C, Thorstrand C, Carlens P. Effects of exercise on the displacement of the atrioventricular plane in patients with coronary artery disease: a new echocardiographic method of detecting reversible myocardial ischaemia. Eur Heart J 1991;12:760-5.
299. Tian J, Zhang G, Wang X, Cui J, Xiao J. Exercise echocardiography: feasibility and value for detection of coronary artery disease. Chin Med J (Engl) 1996;105:381-4.
300. O'Keefe JH Jr, Bateman TM, Silvestri R, Barnhart C. Safety and diagnostic accuracy of adenosine thallium-201 scintigraphy in patients unable to exercise and those with left bundle branch block. Am Heart J 1992;124:614-21.
301. Iskandrian AS, Heo J, Lemlek J, et al. Identification of high-risk patients with left main and three-vessel coronary artery disease by adenosine-single photon emission computed tomographic thallium imaging. Am Heart J 1993;125:1130-5.
302. Mohiuddin SM, Ravage CK, Esterbrooks DJ, Lucas BD Jr, Hilleman DE. The comparative safety and diagnostic accuracy of adenosine myocardial perfusion imaging in women versus men. Pharmacotherapy 1996;16:646-51.
303. Amanullah AM, Berman DS, Hachamovitch R, Kiat H, Kang X, Friedman JD. Identification of severe or extensive coronary artery disease in women by adenosine technetium-99m sestamibi SPECT. Am J Cardiol 1997;80:132-7.
304. Amanullah AM, Berman DS, Kiat H, Friedman JD. Usefulness of hemodynamic changes during adenosine infusion in predicting the diagnostic accuracy of adenosine technetium-99m sestamibi single-photon emission computed tomography (SPECT). Am J Cardiol 1997;79:1319-22.
305. Wang FP, Amanullah AM, Kiat H, Friedman JD, Berman DS. Diagnostic efficacy of stress technetium 99m-labeled sestamibi myocardial perfusion single-photon emission computed tomography in detection of coronary artery disease among patients over age 80. J Nucl Cardiol 1995;2:380-8.
306. Samuels B, Kiat H, Friedman JD, Berman DS. Adenosine pharmacologic stress myocardial perfusion tomographic imaging in patients with significant aortic stenosis: diagnostic efficacy and comparison of clinical, hemodynamic and electrocardiographic variables with 100 age-matched control subjects. J Am Coll Cardiol 1995;25:99-106.
307. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83:1605-14.

308. Marcovitz PA, Armstrong WF. Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. Am J Cardiol 1992;69:1269-73.
309. Takeuchi M, Araki M, Nakashima Y, Kuroiwa A. Comparison of dobutamine stress echocardiography and stress thallium-201 single-photon emission computed tomography for detecting coronary artery disease. J Am Soc Echocardiogr 1993;6:593-602.
310. Baudhuin T, Marwick T, Melin J, Wijns W, D'Hondt AM, Detry JM. Diagnosis of coronary artery disease in elderly patients: safety and efficacy of dobutamine echocardiography. Eur Heart J 1993;14:799-803.
311. Ostojic M, Picano E, Beleslin B, et al. Dipyridamole-dobutamine echocardiography: a novel test for the detection of milder forms of coronary artery disease. J Am Coll Cardiol 1994;23:1115-22.
312. Pingitore A, Picano E, Colosso MQ, et al. The atropine factor in pharmacologic stress echocardiography. Echo Persantine (EPIC) and Echo Dobutamine International Cooperative (EDIC) Study Groups. J Am Coll Cardiol 1996;27:1164-70.
313. Wu CC, Ho YL, Kao SL, et al. Dobutamine stress echocardiography for detecting coronary artery disease. Cardiology 1996;87:244-9.
314. Hennessy TG, Codd MB, Hennessy MS, et al. Comparison of dobutamine stress echocardiography and treadmill exercise electrocardiography for detection of coronary artery disease. Coron Artery Dis 1997;8:689-95.
315. Dionisopoulos PN, Collins JD, Smart SC, Knickelbine TA, Sagar KB. The value of dobutamine stress echocardiography for the detection of coronary artery disease in women. J Am Soc Echocardiogr 1997;10:811-7.
316. Elhendy A, Geleijnse ML, van Domburg RT, et al. Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease. Am J Cardiol 1997;80:1414-8.
317. Hennessy TG, Codd MB, McCarthy C, Kane G, McCann HA, Sugrue DD. Dobutamine stress echocardiography in the detection of coronary artery disease in a clinical practice setting. Int J Cardiol 1997;62:55-62.
318. Cohen JL, Ottenweller JE, George AK, Duvvuri S. Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. Am J Cardiol 1993;72:1226-31.
319. Marwick TH, D'Hondt AM, Mairesse GH, et al. Comparative ability of dobutamine and exercise stress in inducing myocardial ischaemia in active patients [published erratum appears in Br Heart J 1994;72:590]. Br Heart J 1994;72:31-8.
320. Cecil MP, Kosinski AS, Jones MT, et al. The importance of work-up (verification) bias correction in assessing the accuracy of SPECT thallium-201 testing for the diagnosis of coronary artery disease. J Clin Epidemiol 1996;49:735-42.
321. Santana-Boado C, Candell-Riera J, Castell-Conesa J, et al. Diagnostic accuracy of technetium-99m-MIBI myocardial SPECT in women and men. J Nucl Med 1998;39:751-5.
322. Harding MB, Leithe ME, Mark DB, et al. Ergonovine maleate testing during cardiac catheterization: a 10-year perspective in 3,447 patients without significant coronary artery disease or Prinzmetal's variant angina [published erratum appears in J Am Coll Cardiol 1993;21:848]. J Am Coll Cardiol 1992;20:107-11.
323. Mark DB, Califf RM, Morris KG, et al. Clinical characteristics and long-term survival of patients with variant angina. Circulation 1984;69:880-8.
324. Hillis LD, Braunwald E. Coronary-artery spasm. N Engl J Med 1978;299:695-702.
325. Roberts WC. Major anomalies of coronary arterial origin seen in adulthood. Am Heart J 1986;111:941-63.
326. Serota H, Barth CW, Seuc CA, Vandormael M, Aguirre F, Kern MJ. Rapid identification of the course of anomalous coronary arteries in adults: the "dot and eye" method. Am J Cardiol 1990;65:891-8.
327. Burks JM, Rothrock DR. Anomalous right coronary artery from the left sinus of Valsalva: demonstration of extensive collateral circulation. Cathet Cardiovasc Diagn 1996;39:67-70.
328. Hamada S, Yoshimura N, Takamiya M. Images in cardiovascular medicine: noninvasive imaging of anomalous origin of the left coronary artery from the pulmonary artery. Circulation 1998;97:219.
329. Burns JC, Shike H, Gordon JB, Malhotra A, Schoenwetter M, Kawasaki T. Sequelae of Kawasaki disease in adolescents and young adults. J Am Coll Cardiol 1996;28:253-7.
330. DeMaio SJ, Kinsella SH, Silverman ME. Clinical course and long-term prognosis of spontaneous coronary artery dissection. Am J Cardiol 1989;64:471-4.
331. Om A, Ellahham S, Vetrovec GW. Radiation-induced coronary artery disease. Am Heart J 1992;124:1598-602.
332. Proudfit WL, Shirey EK, Sones FM Jr. Selective cine coronary arteriography. Correlation with clinical findings in 1,000 patients. Circulation 1966;33:901-10.
333. Douglas JS Jr, Hurst JW. Limitations of symptoms in the recognition of coronary atherosclerotic heart disease. In: Hurst JW, ed. Hurst's the Heart. New York: McGraw Hill, 1979:3-12.
334. Welch CC, Proudfit WL, Sheldon WC. Coronary arteriographic findings in 1,000 women under age 50. Am J Cardiol 1975; 35:211-5.
335. Patterson RE, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. Circulation 1995;91:54-65.
336. Ambepityia G, Kopelman PG, Ingram D, Swash M, Mills PG, Timmis AD. Exertional myocardial ischemia in diabetes: a quantitative analysis of anginal perceptual threshold and the influence of autonomic function. J Am Coll Cardiol 1990;15:72-7.
337. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996;334:1311-5.
338. Gibbons RJ. Exercise ECG testing with and without radionuclide studies. In: Wenger NK, Speroff L, Packard B, eds. Cardiovascular Health and Disease in Women. Greenwich, CT: Le Jacq Communications, 1993:73-80.
339. DeSanctis RW. Clinical manifestations of coronary artery disease: chest pain in women. In: Wenger NK, Speroff L, Packard B, eds. Cardiovascular Health and Disease in Women. Greenwich, CT: Le Jacq Communications, 1993:67-72.
340. Shaw LJ, Miller DD, Romeis JC, Kargl D, Younis LT, Chaitman BR. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120:559-66.
341. Mark DB, Shaw LK, DeLong ER, Califf RM, Pryor DB. Absence of sex bias in the referral of patients for cardiac catheterization. N Engl J Med 1994;330:1101-6.
342. Hachamovitch R, Berman DS, Kiat H, et al. Gender-related differences in clinical management after exercise nuclear testing. J Am Coll Cardiol 1995;26:1457-64.
342. Kurita A, Takase B, Uehata A, et al. Painless myocardial ischemia in elderly patients compared with middle-aged patients and its relation to treadmill testing and coronary hemodynamics. Clin Cardiol 1991;14:886-90.

343. LaCroix AZ, Guralnik JM, Curb JD, Wallace RB, Ostfeld AM, Hennekens CH. Chest pain and coronary heart disease mortality among older men and women in three communities. Circulation 1990;81:437-46.
345. Johnson LW, Lozner EC, Johnson S, et al. Coronary arteriography 1984-1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. I. Results and complications. Cathet Cardiovasc Diagn 1989;17:5-10.
346. Bertrand ME, Lablanche JM, Tilmant PY, et al. Frequency of provoked coronary arterial spasm in 1,089 consecutive patients undergoing coronary arteriography. Circulation 1982;65:1299-306.
347. Song JK, Lee SJ, Kang DH, et al. Ergonovine echocardiography as a screening test for diagnosis of vasospastic angina before coronary angiography. J Am Coll Cardiol 1996;27:1156-61.
348. Wolf NM, Meister SG. Irreversible coronary occlusion and ergonovine [letter]. Circulation 1982;66:252.
349. Pepine CJ. Ergonovine echocardiography for coronary spasm: facts and wishful thinking. J Am Coll Cardiol 1996;27:1162-3.
350. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997;336:1629-33.
351. Hubbard BL, et al. Prospective evaluation of a clinical and exercise-test model for the prediction of left main coronary artery disease. Ann Intern Med 1993;118:81-90.
352. Mock MB, Ringqvist I, Fisher LD, et al. Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. Circulation 1982;66:562-8.
353. Weiner DA, McCabe CH, Ryan TJ. Identification of patients with left main and three vessel coronary disease with clinical and exercise test variables. Am J Cardiol 1980;46:21-7.
354. Weiner DA, Ryan TJ, McCabe CH, et al. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. J Am Coll Cardiol 1984;3:772-9.
355. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. Circulation 1979;59:421-30.
356. Block WJ Jr, Crumpacker EL, Dry TJ, Gage RP. Prognosis of angina pectoris: observations in 6,882 cases. JAMA 1952;150: 259-64.
357. Ideker RE, Wagner GS, Ruth WK, et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. II. Correlation with quantitative anatomic findings for anterior infarcts. Am J Cardiol 1982;49:1604-14.
358. European Coronary Surgery Study Group. Prospective randomised study of coronary artery bypass surgery in stable angina pectoris. Second interim report by the European Coronary Surgery Study Group. Lancet 1980;2:491-5.
359. Murphy ML, Hultgren HN, Detre K, Thomsen J, Takaro T. Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration cooperative study. N Engl J Med 1977;297:621-7.
360. Proudfit WJ, Bruschke AV, MacMillan JP, Williams GW, Sones FM Jr. Fifteen year survival study of patients with obstructive coronary artery disease. Circulation 1983;68:986-97.
361. Frank CW, Weinblatt E, Shapiro S. Angina pectoris in men. Prognostic significance of selected medical factors. Circulation 1973;47:509-17.
362. Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S, Chaudhary BS. Ventricular premature complexes in prognosis of angina. Circulation 1980;61:1172-82.
363. Detre K, Peduzzi P, Murphy M, et al. Effect of bypass surgery on survival in patients in low- and high-risk subgroups delineated by the use of simple clinical variables. Circulation 1981;63:1329-38.
364. Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996;27:285-90.
365. Henry WL, Ware J, Gardin JM, Hepner SI, McKay J, Weiner M. Echocardiographic measurements in normal subjects. Growth-related changes that occur between infancy and early adulthood. Circulation 1978;57:278-85.
366. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
367. Vuille C, Weyman AE. Left ventricle, I: general considerations, assessment of chamber size and function. In: Weyman AE, ed. Principles and Practice of Echocardiography. 2nd ed. Philadelphia: Lea & Febiger, 1994:575-624.
368. Stamm RB, Carabello BA, Mayers DL, Martin RP. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. Am Heart J 1982;104:136-44.
369. Amico AF, Lichtenberg GS, Reisner SA, Stone CK, Schwartz RG, Meltzer RS. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. Am Heart J 1989;118:1259-65.
370. Oh JK, Ding ZP, Gersh BJ, Bailey KR, Tajik AJ. Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. J Am Soc Echocardiogr 1992;5:497-503.
371. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. Ann Intern Med 1989;110:101-7.
372. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561-6.
373. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345-52.
374. Smith VE, Schulman P, Karimeddini MK, White WB, Meeran MK, Katz AM. Rapid ventricular filling in left ventricular hypertrophy, II. Pathologic hypertrophy. J Am Coll Cardiol 1985;5:869-74.
375. Bonow RO, Vitale DF, Bacharach SL, Maron BJ, Green MV. Effects of aging on asynchronous left ventricular regional function and global ventricular filling in normal human subjects. J Am Coll Cardiol 1988;11:50-8.
376. Borow KM, Neumann A, Wynne J. Sensitivity of end-systolic pressure-dimension and pressure-volume relations to the inotropic state in humans. Circulation 1982;65:988-97.
377. Martin ET, Fuisz AR, Pohost GM. Imaging cardiac structure and pump function. Cardiol Clin 1998;16:135-60.
378. Parisi AF, Moynihan PF, Folland ED, Strauss WE, Sharma GV, Sasahara AA. Echocardiography in acute and remote myocardial infarction. Am J Cardiol 1980;46:1205-14.
379. Shen W, Khandheria BK, Edwards WD, et al. Value and limitations of two-dimensional echocardiography in predicting myocar-

dial infarct size. Am J Cardiol 1991;68:1143-9.
380. Oh JK, Gibbons RJ, Christian TF, et al. Correlation of regional wall motion abnormalities detected by two-dimensional echocardiography with perfusion defect determined by technetium 99m sestamibi imaging in patients treated with reperfusion therapy during acute myocardial infarction. Am Heart J 1996;131:32-7.
381. Visser CA, Lie KI, Kan G, Meltzer R, Durrer D. Detection and quantification of acute, isolated myocardial infarction by two dimensional echocardiography. Am J Cardiol 1981;47:1020-5.
382. Horowitz RS, Morganroth J. Immediate detection of early high-risk patients with acute myocardial infarction using two-dimensional echocardiographic evaluation of left ventricular regional wall motion abnormalities. Am Heart J 1982;103:814-22.
383. Bhatnagar SK, Moussa MA, Al-Yusuf AR. The role of prehospital discharge two-dimensional echocardiography in determining the prognosis of survivors of first myocardial infarction. Am Heart J 1985;109:472-7.
384. Nelson GR, Cohn PF, Gorlin R. Prognosis in medically-treated coronary artery disease: influence of ejection fraction compared to other parameters. Circulation 1975;52:408-12.
385. Weyman AE, Peskoe SM, Williams ES, Dillon JC, Feigenbaum H. Detection of left ventricular aneurysms by cross-sectional echocardiography. Circulation 1976;54:936-44.
386. Visser CA, Kan G, David GK, Lie KI, Durrer D. Echocardiographic-cineangiographic correlation in detecting left ventricular aneurysm: a prospective study of 422 patients. Am J Cardiol 1982;50:337-41.
387. Barrett MJ, Charuzi Y, Corday E. Ventricular aneurysm: cross-sectional echocardiographic approach. Am J Cardiol 1980;46: 1133-7.
388. Keren A, Goldberg S, Gottlieb S, et al. Natural history of left ventricular thrombi: their appearance and resolution in the posthospitalization period of acute myocardial infarction. J Am Coll Cardiol 1990;15:790-800.
389. Visser CA, Kan G, Meltzer RS, Dunning AJ, Roelandt J. Embolic potential of left ventricular thrombus after myocardial infarction: a two-dimensional echocardiographic study of 119 patients. J Am Coll Cardiol 1985;5:1276-80.
390. DeMaria AN, Bommer W, Neumann A, et al. Left ventricular thrombi identified by cross-sectional echocardiography. Ann Intern Med 1979;90:14-8.
391. Spirito P, Bellotti P, Chiarella F, Domenicucci S, Sementa A, Vecchio C. Prognostic significance and natural history of left ventricular thrombi in patients with acute anterior myocardial infarction: a two-dimensional echocardiographic study. Circulation 1985;72:774-80.
392. Gueret P, Dubourg O, Ferrier A, Farcot JC, Rigaud M, Bourdarias JP. Effects of full-dose heparin anticoagulation on the development of left ventricular thrombosis in acute transmural myocardial infarction. J Am Coll Cardiol 1986;8:419-26.
393. Keating EC, Gross SA, Schlamowitz RA, et al. Mural thrombi in myocardial infarctions. Prospective evaluation by two-dimensional echocardiography. Am J Med 1983;74:989-95.
394. Stratton JR, Lighty GW, Pearlman AS, Ritchie JL. Detection of left ventricular thrombus by two-dimensional echocardiography: sensitivity, specificity, and causes of uncertainty. Circulation 1982;66:156-66.
395. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1993;22:2033-54.
396. Rihal CS, Davis KB, Kennedy JW, Gersh BJ. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. Am J Cardiol 1995;75:220-3.
397. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Exercise tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiograms. Ann Intern Med 1994;121:825-32.
398. Gibbons RJ, Zinsmeister AR, Miller TD, Clements IP. Supine exercise electrocardiography compared with exercise radionuclide angiography in noninvasive identification of severe coronary artery disease. Ann Intern Med 1990;112:743-9.
399. Mattera JA, Arain SA, Sinusas AJ, Finta L, Wackers FJ III. Exercise testing with myocardial perfusion imaging in patients with normal baseline electrocardiograms: cost savings with a stepwise diagnostic strategy. J Nucl Cardiol 1998;5:498-506.
400. Ladenheim ML, Kotler TS, Pollock BH, Berman DS, Diamond GA. Incremental prognostic power of clinical history, exercise electrocardiography and myocardial perfusion scintigraphy in suspected coronary artery disease. Am J Cardiol 1987;59:270-7.
401. Mark DB, Hlatky MA, Harrell FE, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987;106:793-800.
402. Morrow K, Morris CK, Froelicher VF, et al. Prediction of cardiovascular death in men undergoing noninvasive evaluation for coronary artery disease. Ann Intern Med 1993;118:689-95.
403. Brunelli C, Cristofani R, L'Abbate A. Long-term survival in medically treated patients with ischaemic heart disease and prognostic importance of clinical and electrocardiographic data (the Italian CNR Multicentre Prospective Study OD1). Eur Heart J 1989;10:292-303.
404. Luwaert RJ, Melin JA, Brohet CR, et al. Non-invasive data provide independent prognostic information in patients with chest pain without previous myocardial infarction: findings in male patients who have had cardiac catheterization. Eur Heart J 1988;9:418-26.
405. Gohlke H, Samek L, Betz P, Roskamm H. Exercise testing provides additional prognostic information in angiographically defined subgroups of patients with coronary artery disease. Circulation 1983;68:979-85.
406. Smith RF, Johnson G, Ziesche S, Bhat G, Blankenship K, Cohn JN. Functional capacity in heart failure. Comparison of methods for assessment and their relation to other indexes of heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87:VI88-93.
407. Nallamothu N, Ghods M, Heo J, Iskandrian AS. Comparison of thallium-201 single-photon emission computed tomography and electrocardiographic response during exercise in patients with normal rest electrocardiographic results. J Am Coll Cardiol 1995;25:830-6.
408. Simari RD, Miller TD, Zinsmeister AR, Gibbons RJ. Capabilities of supine exercise electrocardiography versus exercise radionuclide angiography in predicting coronary events. Am J Cardiol 1991;67:573-7.
409. Bruce RA, DeRouen TA, Hossack KF. Pilot study examining the motivational effects of maximal exercise testing to modify risk factors and health habits. Cardiology 1980;66:111-9.
410. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation 1996;93:905-14.

411. Hecht HS, Shaw RE, Chin HL, Ryan C, Stertzer SH, Myler RK. Silent ischemia after coronary angioplasty: evaluation of restenosis and extent of ischemia in asymptomatic patients by tomographic thallium-201 exercise imaging and comparison with symptomatic patients. J Am Coll Cardiol 1991;17:670-7.
412. Hecht HS, DeBord L, Shaw R, et al. Usefulness of supine bicycle stress echocardiography for detection of restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1993;71:293-6.
413. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). Circulation 1994;90:762-8.
414. Knatterud GL, Bourassa MG, Pepine CJ, et al. Effects of treatment strategies to suppress ischemia in patients with coronary artery disease: 12-week results of the Asymptomatic Cardiac Ischemia Pilot (ACIP) study. J Am Coll Cardiol 1994;24:11-20.
415. Bonow RO. Diagnosis and risk stratification in coronary artery disease: nuclear cardiology versus stress echocardiography. J Nucl Cardiol 1997;4:S172-8.
416. Marcovitz PA. Prognostic issues in stress echocardiography. Prog Cardiovasc Dis 1997;39:533-42.
417. Boyne TS, Koplan BA, Parsons WJ, Smith WH, Watson DD, Beller GA. Predicting adverse outcome with exercise SPECT technetium-99m sestamibi imaging in patients with suspected or known coronary artery disease. Am J Cardiol 1997;79:270-4.
418. Leppo JA. Comparison of pharmacologic stress agents. J Nucl Cardiol 1996;3:S22-6.
419. Kiat H, Maddahi J, Roy LT, et al. Comparison of technetium 99m methoxy isobutyl isonitrile and thallium 201 for evaluation of coronary artery disease by planar and tomographic methods. Am Heart J 1989;117:1-11.
420. Sawada SG, Ryan T, Conley MJ, Corya BC, Feigenbaum H, Armstrong WF. Prognostic value of a normal exercise echocardiogram. Am Heart J 1990;120:49-55.
421. Krivokapich J, Child JS, Gerber RS, Lem V, Moser D. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing twelve months. Am J Cardiol 1993;71:646-51.
422. Mazeika PK, Nadazdin A, Oakley CM. Prognostic value of dobutamine echocardiography in patients with high pretest likelihood of coronary artery disease. Am J Cardiol 1993;71:33-9.
423. Severi S, Picano E, Michelassi C, et al. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease. Comparison with exercise electrocardiography. Circulation 1994;89:1160-73.
424. Coletta C, Galati A, Greco G, et al. Prognostic value of high dose dipyridamole echocardiography in patients with chronic coronary artery disease and preserved left ventricular function. J Am Coll Cardiol 1995;26:887-94.
425. Williams MJ, Odabashian J, Lauer MS, Thomas JD, Marwick TH. Prognostic value of dobutamine echocardiography in patients with left ventricular dysfunction. J Am Coll Cardiol 1996;27:132-9.
426. Afridi I, Quinones MA, Zoghbi WA, Cheirif J. Dobutamine stress echocardiography: sensitivity, specificity, and predictive value for future cardiac events. Am Heart J 1994;127:1510-5.
427. Kamaran M, Teague SM, Finkelhor RS, Dawson N, Bahler RC. Prognostic value of dobutamine stress echocardiography in patients referred because of suspected coronary artery disease. Am J Cardiol 1995;76:887-91.
428. Marcovitz PA, Shayna V, Horn RA, Hepner A, Armstrong WF. Value of dobutamine stress echocardiography in determining the prognosis of patients with known or suspected coronary artery disease. Am J Cardiol 1996;78:404-8.
429. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. Circulation 1991;83:363-81.
430. National Center for Health Statistics. Vital Statistics of the United States, 1979, Vol II: Mortality, Part A. Washington, DC: US Government Printing Office; 1984. US Department of Health and Human Services publication (PHS) 84-1101.
431. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion SPECT for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction [published erratum appears in Circulation 1998;98:120]. Circulation 1998;97:533-43.
432. Boucher CA, Zir LM, Beller GA, et al. Increased lung uptake of thallium-201 during exercise myocardial imaging: clinical, hemodynamic and angiographic implications in patients with coronary artery disease. Am J Cardiol 1980;46:189-96.
433. Nishimura S, Mahmarian JJ, Verani MS. Significance of increased lung thallium uptake during adenosine thallium-201 scintigraphy. J Nucl Med 1992;33:1600-7.
434. Beller GA. Radionuclide perfusion imaging techniques for evaluation of patients with known or suspected coronary artery disease. Adv Intern Med 1997;42:139-201.
435. Cox JL, Wright LM, Burns RJ. Prognostic significance of increased thallium-201 lung uptake during dipyridamole myocardial scintigraphy: comparison with exercise scintigraphy. Can J Cardiol 1995;11:689-94.
436. Weiss AT, Berman DS, Lew AS, et al. Transient ischemic dilation of the left ventricle on stress thallium-201 scintigraphy: a marker of severe and extensive coronary artery disease. J Am Coll Cardiol 1987;9:752-9.
437. Krawczynska EG, Weintraub WS, Garcia EV, Folks RD, Jones ME, Alazraki NP. Left ventricular dilatation and multivessel coronary artery disease on thallium-201 SPECT are important prognostic indicators in patients with large defects in the left anterior descending distribution. Am J Cardiol 1994;74:1233-9.
438. Veilleux M, Lette J, Mansur A, et al. Prognostic implications of transient left ventricular cavitary dilation during exercise and dipyridamole-thallium imaging. Can J Cardiol 1994;10:259-62.
439. McClellan JR, Travin MI, Herman SD, et al. Prognostic importance of scintigraphic left ventricular cavity dilation during intravenous dipyridamole technetium-99m sestamibi myocardial tomographic imaging in predicting coronary events. Am J Cardiol 1997;79:600-5.
440. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. J Am Coll Cardiol 1983;1:994-1001.
441. Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986;7:464-71.
442. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole thallium scintigraphy for evaluation of ischemic heart disease. J Am Coll Cardiol 1990;15:109-16.
443. Iskandrian AS, Heo J, Decoskey D, Askenase A, Segal BL. Use of exercise thallium-201 imaging for risk stratification of elderly patients with coronary artery disease. Am J Cardiol 1988;61:269-72.
444. Kaul S, Lilly DR, Gascho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain:

comparison with cardiac catheterization. Circulation 1988; 77:745-58.
445. Staniloff HM, Forrester JS, Berman DS, Swan HJ. Prediction of death, myocardial infarction, and worsening chest pain using thallium scintigraphy and exercise electrocardiography. J Nucl Med 1986;27:1842-8.
446. Stratmann HG, Mark AL, Walter KE, Williams GA. Prognostic value of atrial pacing and thallium-201 scintigraphy in patients with stable chest pain. Am J Cardiol 1989;64:985-90.
447. Younis LT, Byers S, Shaw L, Barth G, Goodgold H, Chaitman BR. Prognostic importance of silent myocardial ischemia detected by intravenous dipyridamole thallium myocardial imaging in asymptomatic patients with coronary artery disease. J Am Coll Cardiol 1989;14:1635-41.
448. Berman DS, Hachamovitch R. Risk assessment in patients with stable coronary artery disease: incremental value of nuclear imaging. J Nucl Cardiol 1996;3:S41-9.
449. Gioia G, Milan E, Giubbini R, DePace N, Heo J, Iskandrian AS. Prognostic value of tomographic rest-redistribution thallium 201 imaging in medically treated patients with coronary artery disease and left ventricular dysfunction. J Nucl Cardiol 1996;3:150-6.
450. Kaul S, Finkelstein DM, Homma S, Leavitt M, Okada RD, Boucher CA. Superiority of quantitative exercise thallium-201 variables in determining long-term prognosis in ambulatory patients with chest pain: a comparison with cardiac catheterization. J Am Coll Cardiol 1988;12:25-34.
451. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993;22:665-70.
452. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. N Engl J Med 1987;317:1486-9.
453. Borges-Neto S, Coleman RE, Potts JM, Jones RH. Combined exercise radionuclide angiocardiography and single photon emission computed tomography perfusion studies for assessment of coronary artery disease. Semin Nucl Med 1991;21:223-9.
454. Pollock SG, Abbott RD, Boucher CA, Beller GA, Kaul S. Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease: validation of models based on these tests. Circulation 1992;85:237-40.
455. Machecourt J, Longere P, Fagret D, et al. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect. J Am Coll Cardiol 1994;23:1096-106.
456. Marie YP, Danchin N, Durand JF, et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography. J Am Coll Cardiol 1995;26:879-86.
457. Geleijnse ML, Elhendy A, van Domburg RT, et al. Prognostic value of dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain. J Am Coll Cardiol 1996;28:447-54.
458. Kamal AM, Fattah AA, Pancholy S, et al. Prognostic value of adenosine single-photon emission computed tomographic thallium imaging in medically treated patients with angiographic evidence of coronary artery disease. J Nucl Cardiol 1994;1:254-61.
459. Stratmann HG, Tamesis BR, Younis LT, Wittry MD, Miller DD. Prognostic value of dipyridamole technetium-99m sestamibi myocardial tomography in patients with stable chest pain who are unable to exercise. Am J Cardiol 1994;73:647-52.
460. Stratmann HG, Williams GA, Wittry MD, Chaitman BR, Miller DD. Exercise technetium-99m sestamibi tomography for cardiac risk stratification of patients with stable chest pain. Circulation 1994;89:615-22.
461. Iskandrian AS, Hakki AH, Kane-Marsch S. Prognostic implications of exercise thallium-201 scintigraphy in patients with suspected or known coronary artery disease. Am Heart J 1985;110:135-43.
462. Aoki M, Sakai K, Koyanagi S, Takeshita A, Nakamura M. Effect of nitroglycerin on coronary collateral function during exercise evaluated by quantitative analysis of thallium-201 single photon emission computed tomography. Am Heart J 1991;121:1361-6.
463. Wagdy HM, Hodge D, Christian TF, Miller TD, Gibbons RJ. Prognostic value of vasodilator myocardial perfusion imaging in patients with left bundle branch block. Circulation 1998;97:1563-70.
464. Nallamothu N, Bagheri B, Acio ER, Heo J, Iskandrian AE. Prognostic value of stress myocardial perfusion single photon emission computed tomography imaging in patients with left ventricular bundle branch block. J Nucl Cardiol 1997;4:487-93.
465. Nigam A, Humen DP. Prognostic value of myocardial perfusion imaging with exercise and/or dipyridamole hyperemia in patients with preexisting left bundle branch block. J Nucl Med 1998;39:579-81.
466. Gil VM, Almeida M, Ventosa A, et al. Prognosis in patients with left bundle branch block and normal dipyridamole thallium-201 scintigraphy. J Nucl Cardiol 1998;5:414-7.
467. Kostkiewicz M, Jarosz W, Tracz W, et al. Thallium-201 myocardial perfusion imaging in patients before and after successful percutaneous transluminal coronary angioplasty. Int J Cardiol 1996;53:299-304.
468. Zhao XQ, Brown BG, Stewart DK, et al. Effectiveness of revascularization in the Emory Angioplasty versus Surgery Trial. A randomized comparison of coronary angioplasty with bypass surgery. Circulation 1996;93:1954-62.
469. Lewis BS, Hardoff R, Merdler A, et al. Importance of immediate and very early postprocedural angiographic and thallium-201 single photon emission computed tomographic perfusion measurements in predicting late results after coronary intervention. Am Heart J 1995;130:425-32.
470. Ritchie JL, Narahara KA, Trobaugh GB, Williams DL, Hamilton GW. Thallium-201 myocardial imaging before and after coronary revascularization: assessment of regional myocardial blood flow and graft patency. Circulation 1977;56:830-6.
471. Verani MS, Marcus ML, Spoto G, Rossi NP, Ehrhardt JC, Razzak MA. Thallium-201 myocardial perfusion scintigrams in the evaluation of aorto-coronary saphenous surgery. J Nucl Med 1978;19:765-72.
472. Miller TD, Christian TF, Hodge DO, Mullan BP, Gibbons RJ. Prognostic value of exercise thallium-201 imaging performed within 2 years of coronary artery bypass graft surgery. J Am Coll Cardiol 1998;31:848-54.
473. Palmas W, Bingham S, Diamond GA, et al. Incremental prognostic value of exercise thallium-201 myocardial single-photon emission computed tomography late after coronary artery bypass surgery. J Am Coll Cardiol 1995;25:403-9.
474. Lauer MS, Lytle B, Pashkow F, Snader CE, Marwick TH. Prediction of death and myocardial infarction by screening with exercise-thallium testing after coronary-artery-bypass grafting. Lancet 1998;351:615-22.

475. Nallamothu N, Johnson JH, Bagheri B, Heo J, Iskandrian AE. Utility of stress single-photon emission computed tomography (SPECT) perfusion imaging in predicting outcome after coronary artery bypass grafting. Am J Cardiol 1997;80:1517-21.
476. McCully RB, Roger VL, Mahoney DW, et al. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: follow-up of 1,325 patients. J Am Coll Cardiol 1998;31:144-9.
477. Marwick T, D'Hondt AM, Baudhuin T, et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both? J Am Coll Cardiol 1993;22:159-67.
478. Marwick TH. Use of stress echocardiography for the prognostic assessment of patients with stable chronic coronary artery disease. Eur Heart J 1997;18(Suppl D):D97-101.
479. Heupler S, Mehta R, Lobo A, Leung D, Marwick TH. Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. J Am Coll Cardiol 1997;30:414-20.
480. Marwick TH, Mehta R, Arheart K, Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. J Am Coll Cardiol 1997;30:83-90.
481. Chuah SC, Pellikka PA, Roger VL, McCully RB, Seward JB. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. Circulation 1998;97:1474-80.
482. AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. Lancet 1990;335:427-31.
483. Truett J, Cornfield J, Kannel W. A multivariate analysis of the risk of coronary heart disease in Framingham. J Chronic Dis 1967;20:511-24.
484. Hlatky MA, Califf RM, Harrell FE, et al. Clinical judgment and therapeutic decision making. J Am Coll Cardiol 1990;15:1-14.
485. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. J Am Coll Cardiol 1996;27:1007-19.
486. Ambrose JA, Fuster V. Can we predict future acute coronary events in patients with stable coronary artery disease? JAMA 1997;277:343-4.
487. Daley J, Shwartz M. Developing risk-adjustment methods. In: Iezzone LI, ed. Risk Adjustment for Measuring Health Care Outcomes. Ann Arbor, MI: Health Administration Press, 1994:199-238.
488. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1994;90:2645-57.
489. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration [published erratum appears in Lancet 1994;344:1446]. Lancet 1994;344:563-70.
490. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995;92:2333-42.
491. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657-71.
492. Mann JM, Davies MJ. Vulnerable plaque. Relation of characteristics to degree of stenosis in human coronary arteries. Circulation 1996;94:928-31.
493. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91:2844-50.
494. Fuster V, Fallon JT, Nemerson Y. Coronary thrombosis. Lancet 1996;348(Suppl 1):S7-10.
495. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56-62.
496. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157-66.
497. Ringqvist I, Fisher LD, Mock M, Davis KB, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). J Clin Invest 1983;71:1854-66.
498. The Veterans Administration Coronary Artery Bypass Cooperative Study Group. Eleven year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. N Engl J Med 1984;311:1333-9.
499. Alderman EL, Bourassa MG, Cohen LS, et al. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation 1990;82:1629-46.
500. Gersh BJ, Califf RM, Loop FD, Akins CW, Pryor DB, Takaro TC. Coronary bypass surgery in chronic stable angina. Circulation 1989;79:I46-59.
501. Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. Circulation 1994;89:2015-25.
502. Califf RM, Phillips HRI, Hindman MC, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985;5:1055-63.
503. Nakagomi A, Celermajer DS, Lumley T, Freedman SB. Angiographic severity of coronary narrowing is a surrogate marker for the extent of coronary atherosclerosis. Am J Cardiol 1996;78:516-9.
504. Toussaint JF, LaMuraglia GM, Southern JF, Fuster V, Kantor HL. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. Circulation 1996;94:932-8.
505. Waller BF, Rothbaum DA, Gorfinkel HJ, Ulbright TM, Linnemeier TJ, Berger SM. Morphologic observations after percutaneous transluminal balloon angioplasty of early and late aortocoronary saphenous vein bypass grafts. J Am Coll Cardiol 1984;4:784-92.
506. Neitzel GF, Barboriak JJ, Pintar K, Qureshi I. Atherosclerosis in aortocoronary bypass grafts: morphologic study and risk factor analysis 6 to 12 years after surgery. Arteriosclerosis 1986;6:594-600.
507. Walts AE, Fishbein MC, Sustaita H, Matloff JM. Ruptured atheromatous plaques in saphenous vein coronary artery bypass grafts: a mechanism of acute, thrombotic, late graft occlusion. Circulation 1982;65:197-201.
508. Tilli FV, Kaplan BM, Safian RD, et al. Angioscopic plaque friability: a new risk factor for procedural complications following saphenous vein graft interventions (abstract). J Am Coll Cardiol 1996;27(Suppl A):364A.
509. Lytle BW, Loop FD, Taylor PC, et al. The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein bypass grafts to coronary arteries. J Thorac Cardiovasc Surg 1993;105:605-12.
510. Lytle BW, Loop FD, Taylor PC, et al. Vein graft disease: the clin-

ical impact of stenoses in saphenous vein bypass grafts to coronary arteries. J Thorac Cardiovasc Surg 1992;103:831-40.
511. Savage MP, Douglas JS Jr, Fischman DL, et al. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. N Engl J Med 1997;337:740-7.
512. Ridker PM, Manson JE, Gaziano JM, Buring JE, Hennekens CH. Low-dose aspirin therapy for chronic stable angina. A randomized, placebo-controlled clinical trial. Ann Intern Med 1991;114:835-9.
513. Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1995;308:81-106.
514. Lewis HD, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.
515. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985;313:1369-75.
516. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.
517. Juul-Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Lancet 1992;340:1421-5.
518. McTavish D, Faulds D, Goa KL. Ticlopidine. An updated review of its pharmacology and therapeutic use in platelet-dependent disorders. Drugs 1990;40:238-59.
519. Ticlopidine [editorial]. Lancet 1991;337:459-60.
520. de Maat MP, Arnold AE, van Buuren S, Wilson JH, Kluft C. Modulation of plasma fibrinogen levels by ticlopidine in healthy volunteers and patients with stable angina pectoris. Thromb Haemost 1996;76:166-70.
521. Hirsh J, Dalen JE, Fuster V, Harker LB, Patrono C, Roth G. Aspirin and other platelet-active drugs. The relationship among dose, effectiveness, and side effects. Chest 1995;108:247S-57S.
522. Cimminiello D, Agugua F, et al. Antiplatelet treatment with ticlopidine in unstable angina: a controlled multicenter clinical trial. Circulation 1990;82:17-26.
523. Savi P, Laplace MC, Maffrand JP, Herbert JM. Binding of [3H]-2-methylthio ADP to rat platelets—effect of clopidogrel and ticlopidine J Pharmacol Exp Ther 1994;269:772-7.
524. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.
525. Gresele P, Arnout J, Deckmyn H, Vermylen J. Mechanism of the antiplatelet action of dipyridamole in whole blood: modulation of adenosine concentration and activity. Thromb Haemost 1986;55:12-8.
526. Tsuya T, Okada M, Horie H, Ishikawa K. Effect of dipyridamole at the usual oral dose on exercise-induced myocardial ischemia in stable angina pectoris. Am J Cardiol 1990;66:275-8.
527. Held C, Hjemdahl P, Rehnqvist N, et al. Fibrinolytic variables and cardiovascular prognosis in patients with stable angina pectoris treated with verapamil or metoprolol. Results from the Angina Prognosis study in Stockholm. Circulation 1997;95:2380-6.
528. Melandri G, Semprini F, Cervi V, et al. Benefit of adding low molecular weight heparin to the conventional treatment of stable angina pectoris. A double-blind, randomized, placebo-controlled trial. Circulation 1993;88:2517-23.
529. van den Bos AA, Deckers JW, Heyndrickx GR, et al. Safety and efficacy of recombinant hirudin (CGP 39 393) versus heparin in patients with stable angina undergoing coronary angioplasty. Circulation 1993;88:2058-66.
530. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. Lancet 1998;351:233-41.
531. Larosa JC, Hunninghake D, Bush D, et al. The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. The Task Force on Cholesterol Issues, American Heart Association. Circulation 1990;81:1721-33.
532. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation 1998;97:946-52.
533. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
534. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001-9.
535. Frishman WH, Heiman M, Soberman J, Greenberg S, Eff J. Comparison of celiprolol and propranolol in stable angina pectoris. Celiprolol International Angina Study Group. Am J Cardiol 1991;67:665-70.
536. Narahara KA. Double-blind comparison of once daily betaxolol versus propranolol four times daily in stable angina pectoris. Betaxolol Investigators Group. Am J Cardiol 1990;65:577-82.
537. Hauf-Zachariou U, Blackwood RA, Gunawardena KA, O'Donnell JG, Garnham S, Pfarr E. Carvedilol versus verapamil in chronic stable angina: a multicentre trial. Eur J Clin Pharmacol 1997;52:95-100.
538. Raftery EB. The preventative effects of vasodilating beta-blockers in cardiovascular disease. Eur Heart J 1996;17(Suppl B):30-8.
539. McLenachan JM, Findlay IN, Wilson JT, Dargie HJ. Twenty-four-hour beta-blockade in stable angina pectoris: a study of atenolol and betaxolol. J Cardiovasc Pharmacol 1992;20:311-5.
540. Prida XE, Hill JA, Feldman RL. Systemic and coronary hemodynamic effects of combined alpha- and beta-adrenergic blockade (labetalol) in normotensive patients with stable angina pectoris and positive exercise stress test responses. Am J Cardiol 1987;59:1084-8.
541. Capone P, Mayol R. Celiprolol in the treatment of exercise induced angina pectoris. J Cardiovasc Pharmacol 1986;8(Suppl 4):S135-7.
542. Ryden L. Efficacy of epanolol versus metoprolol in angina pectoris: report from a Swedish multicentre study of exercise tolerance. J Intern Med 1992;231:7-11.
543. Boberg J, Larsen FF, Pehrsson SK. The effects of beta blockade with (epanolol) and without (atenolol) intrinsic sympathomimetic activity in stable angina pectoris. The Visacor Study Group. Clin Cardiol 1992;15:591-5.
544. Wallace WA, Wellington KL, Chess MA, Liang CS. Comparison of nifedipine gastrointestinal therapeutic system and atenolol on antianginal efficacies and exercise hemodynamic responses in stable angina pectoris. Am J Cardiol 1994;73:23-8.

545. de Vries RJ, van den Heuvel AF, Lok DJ, et al. Nifedipine gastrointestinal therapeutic system versus atenolol in stable angina pectoris. The Netherlands Working Group on Cardiovascular Research (WCN). Int J Cardiol 1996;57:143-50.
546. Fox KM, Mulcahy D, Findlay I, Ford I, Dargie HJ. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. Eur Heart J 1996;17:96-103.
547. van de Ven LL, Vermeulen A, Tans JG, et al. Which drug to choose for stable angina pectoris: a comparative study between bisoprolol and nitrates. Int J Cardiol 1995;47:217-23.
548. Gruppo Italiano per lo Studio della Sopravvivenza nell-infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994;343:1115-22.
549. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279:1903-7.
550. Waysbort J, Meshulam N, Brunner D. Isosorbide-5-mononitrate and atenolol in the treatment of stable exertional angina. Cardiology 1991;79(Suppl 2):19-26:19-26.
551. Krepp HP. Evaluation of the antianginal and anti-ischemic efficacy of slow-release isosorbide-5-mononitrate capsules, bupranolol and their combination, in patients with chronic stable angina pectoris. Cardiology 1991;79(Suppl 2):14-8.
552. Kawanishi DT, Reid CL, Morrison EC, Rahimtoola SH. Response of angina and ischemia to long-term treatment in patients with chronic stable angina: a double-blind randomized individualized dosing trial of nifedipine, propranolol and their combination. J Am Coll Cardiol 1992;19:409-17.
553. Meyer TE, Adnams C, Commerford P. Comparison of the efficacy of atenolol and its combination with slow-release nifedipine in chronic stable angina. Cardiovasc Drugs Ther 1993;7:909-13.
554. Steffensen R, Grande P, Pedersen F, Haunso S. Effects of atenolol and diltiazem on exercise tolerance and ambulatory ischaemia. Int J Cardiol 1993;40:143-53.
555. Parameshwar J, Keegan J, Mulcahy D, et al. Atenolol or nicardipine alone is as efficacious in stable angina as their combination: a double blind randomised trial. Int J Cardiol 1993;40:135-41.
556. Foale RA. Atenolol versus the fixed combination of atenolol and nifedipine in stable angina pectoris. Eur Heart J 1993;14:1369-74.
557. Tilmant PY, Lablanche JM, Thieuleux FA, Dupuis BA, Bertrand ME. Detrimental effect of propranolol in patients with coronary arterial spasm countered by combination with diltiazem. Am J Cardiol 1983;52:230-3.
558. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. JAMA 1997;277:739-45.
559. Dargie HJ, Ford I, Fox KM. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group. Eur Heart J 1996;17:104-12.
560. Rehnqvist N, Hjemdahl P, Billing E, et al. Treatment of stable angina pectoris with calcium antagonists and beta-blockers. The APSIS study. Angina Prognosis Study in Stockholm. Cardiologia 1995;40(Suppl 1):301.
561. von Arnim T. Medical treatment to reduce total ischemic burden: Total Ischemic Burden Bisoprolol Study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. The TIBBS Investigators. J Am Coll Cardiol 1995;25:231-8.
562. Savonitto S, Ardissiono D, Egstrup K, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multicenter Angina Exercise (IMAGE) Study. J Am Coll Cardiol 1996;27:311-6.
563. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation 1998;98:1184-91.
564. Bassan MM, Weiler-Ravell D, Shalev O. Comparison of the antianginal effectiveness of nifedipine, verapamil, and isosorbide dinitrate in patients receiving propranolol: a double-blind study. Circulation 1983;68:568-75.
565. Wassertheil-Smoller S, Oberman A, Blaufox MD, Davis B, Langford H. The Trial of Antihypertensive Interventions and Management (TAIM) Study: final results with regard to blood pressure, cardiovascular risk, and quality of life. Am J Hypertens 1992;5:37-44.
566. Bassan MM, Weiler-Ravell D. The additive antianginal action of oral isosorbide dinitrate in patients receiving propranolol. Magnitude and duration of effect. Chest 1983;83:233-40.
567. Braun S, van der Wall EE, Emanuelsson H, Kobrin I. Effects of a new calcium antagonist, mibefradil (Ro 40-5967), on silent ischemia in patients with stable chronic angina pectoris: a multicenter placebo-controlled study. The Mibefradil International Study Group. J Am Coll Cardiol 1996;27:317-22.
568. Bakx AL, van der Wall EE, Braun S, Emanuelsson H, Bruschke AV, Kobrin I. Effects of the new calcium antagonist mibefradil (Ro 40-5967) on exercise duration in patients with chronic stable angina pectoris: a multicenter, placebo-controlled study. Ro 40-5967 International Study Group. Am Heart J 1995;130:748-57.
569. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. Drugs 1996;51:792-819.
570. Glasser SP, Ripa S, Garland WT, et al. Antianginal and antiischemic efficacy of monotherapy extended-release nisoldipine (Coat Core) in chronic stable angina. J Clin Pharmacol 1995;35:780-4.
571. Boman K, Saetre H, Karlsson LG, et al. Antianginal effect of conventional and controlled release diltiazem in stable angina pectoris. Eur J Clin Pharmacol 1995;49:27-30.
572. Walker JM, Curry PV, Bailey AE, Steare SE. A comparison of nifedipine once daily (Adalat LA), isosorbide mononitrate once daily, and isosorbide dinitrate twice daily in patients with chronic stable angina. Int J Cardiol 1996;53:117-26.
573. Ezekowitz MD, Hossack K, Mehta JL, et al. Amlodipine in chronic stable angina: results of a multicenter double-blind crossover trial. Am Heart J 1995;129:527-35.
574. Thadani U, Chrysant S, Gorwit J, et al. Duration of effects of isradipine during twice daily therapy in angina pectoris. Cardiovasc Drugs Ther 1994;8:199-210.
575. Ekelund LG, Ulvenstam G, Walldius G, Aberg A. Effects of felodipine versus nifedipine on exercise tolerance in stable angina pectoris. Am J Cardiol 1994;73:658-60.
576. Pepine CJ, Feldman RL, Whittle J, Curry RC, Conti CR. Effect of diltiazem in patients with variant angina: a randomized double-blind trial. Am Heart J 1981;101:719-25.
577. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. N Engl J Med 1980;302:1269-73.
578. Hill JA, Feldman RL, Pepine CJ, Conti CR. Randomized double-

blind comparison of nifedipine and isosorbide dinitrate in patients with coronary arterial spasm. Am J Cardiol 1982;49:431-8.
579. Johnson SM, Mauritson DR, Willerson JT, Cary JR, Hillis LD. Verapamil administration in variant angina pectoris. Efficacy shown by ECG monitoring. JAMA 1981;245:1849-51.
580. Chahine RA, Feldman RL, Giles TD, et al. Randomized placebo-controlled trial of amlodipine in vasospastic angina. Amlodipine Study 160 Group. J Am Coll Cardiol 1993;21:1365-70.
581. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995;274:620-5.
582. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. Circulation 1995;92:1326-31.
583. Opie LH, Messerli FH. Nifedipine and mortality. Grave defects in the dossier. Circulation 1995;92:1068-73.
584. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organization and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. J Hypertens 1997;15:105-15.
585. Parmley WW, Nesto RW, Singh BN, Deanfield J, Gottlieb SO. Attenuation of the circadian patterns of myocardial ischemia with nifedipine GITS in patients with chronic stable angina. N-CAP Study Group. J Am Coll Cardiol 1992;19:1380-9.
586. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52.
587. Thadani U, Zellner SR, Glasser S, et al. Double-blind, dose-response, placebo-controlled multicenter study of nisoldipine: a new second-generation calcium channel blocker in angina pectoris. Circulation 1991;84:2398-408.
588. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and non-insulin dependent diabetes mellitus. Diabetes Care 1998;21:597-603.
589. Singh BN. Comparative efficacy and safety of bepridil and diltiazem in chronic stable angina pectoris refractory to diltiazem. The Bepridil Collaborative Study Group. Am J Cardiol 1991;68:306-12.
590. Bremner AD, Fell PJ, Hosie J, James IG, Saul PA, Taylor SH. Early side-effects of antihypertensive therapy: comparison of amlodipine and nifedipine retard. J Hum Hypertens 1993;7:79-81.
591. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990;82:1954-61.
592. Singh BN. Safety profile of bepridil determined from clinical trials in chronic stable angina in the United States. Am J Cardiol 1992;69:68D-74D.
593. Deanfield JE, Detry JM, Lichtlen PR, Magnani B, Sellier P, Thaulow E. Amlodipine reduces transient myocardial ischemia in patients with coronary artery disease: double-blind Circadian Anti-Ischemia Program in Europe (CAPE Trial). J Am Coll Cardiol 1994;24:1460-7.
594. Lehmann G, Reiniger G, Beyerle A, Rudolph W. Pharmacokinetics and additional anti-ischaemic effectiveness of amlodipine, a once-daily calcium antagonist, during acute and long-term therapy of stable angina pectoris in patients pre-treated with a beta-blocker. Eur Heart J 1993;14:1531-5.
595. Glasser SP. Nisoldipine coat core as concomitant therapy in chronic stable angina pectoris. Am J Cardiol 1995;75:68E-70E.
596. Ronnevik PK, Silke B, Ostergaard O. Felodipine in addition to beta-adrenergic blockade for angina pectoris. a multicentre, randomized, placebo-controlled trial. Eur Heart J 1995;16:1535-41.
597. Abrams J. Nitroglycerin and long-acting nitrates in clinical practice. Am J Med 1983;74:85-94.
598. Kaski JC, Plaza LR, Meran DO, Araujo L, Chierchia S, Maseri A. Improved coronary supply: prevailing mechanism of action of nitrates in chronic stable angina. Am Heart J 1985;110:238-45.
599. Lacoste LL, Theroux P, Lidon RM, Colucci R, Lam JY. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. Ad Hoc Subcommittee of the Liaison Antithrombotic properties of transdermal nitroglycerin in stable angina pectoris. Am J Cardiol 1994;73:1058-62.
600. Tirlapur VG, Mir MA. Cardiorespiratory effects of isosorbide dinitrate and nifedipine in combination with nadolol: a double-blind comparative study of beneficial and adverse antianginal drug interactions. Am J Cardiol 1984;53:487-92.
601. Schneider W, Maul FD, Bussmann WD, Lang E, Hor G, Kaltenbach M. Comparison of the antianginal efficacy of isosorbide dinitrate (ISDN) 40 mg and verapamil 120 mg three times daily in the acute trial and following two-week treatment. Eur Heart J 1988;9:149-58.
602. Ankier SI, Fay L, Warrington SJ, Woodings DF. A multicentre open comparison of isosorbide-5-mononitrate and nifedipine given prophylactically to general practice patients with chronic stable angina pectoris. J Int Med Res 1989;17:172-8.
603. Emanuelsson H, Ake H, Kristi M, Arina R. Effects of diltiazem and isosorbide-5-mononitrate, alone and in combination, on patients with stable angina pectoris. Eur J Clin Pharmacol 1989; 36:561-5.
604. Akhras F, Chambers J, Jefferies S, Jackson G. A randomised double-blind crossover study of isosorbide mononitrate and nifedipine retard in chronic stable angina. Int J Cardiol 1989;24:191-6.
605. Akhras F, Jackson G. Efficacy of nifedipine and isosorbide mononitrate in combination with atenolol in stable angina. Lancet 1991;338:1036-9.
606. Abrams J. Glyceryl trinitrate (nitroglycerin) and the organic nitrates. Choosing the method of administration. Drugs 1987; 34:391-403.
607. Silber S. Nitrates: why and how should they be used today? Current status of the clinical usefulness of nitroglycerin, isosorbide dinitrate and isosorbide-5-mononitrate. Eur J Clin Pharmacol 1990;38(Suppl 1):S35-51.
608. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. J Am Coll Cardiol 1999;33:273-82.
609. Fung HL, Bauer JA. Mechanisms of nitrate tolerance. Cardiovasc Drugs Ther 1994;8:489-99.
610. Chirkov YY, Chirkova LP, Horowitz JD. Nitroglycerin tolerance at the platelet level in patients with angina pectoris. Am J Cardiol 1997;80:128-31.
611. Boesgaard S, Aldershvile J, Pedersen F, Pietersen A, Madsen JK, Grande P. Continuous oral N-acetylcysteine treatment and development of nitrate tolerance in patients with stable angina pectoris. J Cardiovasc Pharmacol 1991;17:889-93.
612. Balestrini AE, Menzio AC, Cabral R, et al. Penbutolol and molsidomine synergism in angina pectoris. A double blind ergometric trial. Eur J Clin Pharmacol 1984;27:1-5.
613. Meeter K, Kelder JC, Tijssen JG, et al. Efficacy of nicorandil versus propranolol in mild stable angina pectoris of effort: a long-

term, double-blind, randomized study. J Cardiovasc Pharmacol 1992;20(Suppl 3):S59-66.
614. Guermonprez JL, Blin P, Peterlongo F. A double-blind comparison of the long-term efficacy of a potassium channel opener and a calcium antagonist in stable angina pectoris. Eur Heart J 1993;14(Suppl B):30-4.
615. Hughes LO, Rose EL, Lahiri A, Raftery EB. Comparison of nicorandil and atenolol in stable angina pectoris. Am J Cardiol 1990;66:679-82.
616. Detry JM, Sellier P, Pennaforte S, Cokkinos D, Dargie H, Mathes P. Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Trimetazidine European Multicenter Study Group. Br J Clin Pharmacol 1994;37:279-88.
617. Detry JM, Leclercq PJ. Trimetazidine European Multicenter Study versus propranolol in stable angina pectoris: contribution of Holter electrocardiographic ambulatory monitoring. Am J Cardiol 1995;76:8B-11B.
618. Cacciatore L, Cerio R, Ciarimboli M, et al. The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study. Drugs Exp Clin Res 1991;17:225-35.
619. Cocco G, Rousseau MF, Bouvy T, et al. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with beta-blocker or diltiazem. J Cardiovasc Pharmacol 1992;20:131-8.
620. Upward JW, Akhras F, Jackson G. Oral labetalol in the management of stable angina pectoris in normotensive patients. Br Heart J 1985;53:53-7.
621. Crea F, Pupita G, Galassi AR, et al. Effects of theophylline, atenolol and their combination on myocardial ischemia in stable angina pectoris. Am J Cardiol 1990;66:1157-62.
622. Balakumaran K, Jovanovic A, Fels PW, et al. ST 567 (alinidine) in stable angina: a comparison with metoprolol. Eur Heart J 1987;8(Suppl L):153-7.
623. Frishman WH, Pepine CJ, Weiss RJ, Baiker WM. Addition of zatebradine, a direct sinus node inhibitor, provides no greater exercise tolerance benefit in patients with angina taking extended-release nifedipine: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The Zatebradine Study Group. J Am Coll Cardiol 1995;26:305-12.
624. Ikram H, Low CJ, Shirlaw TM, et al. Angiotensin converting enzyme inhibition in chronic stable angina: effects on myocardial ischaemia and comparison with nifedipine. Br Heart J 1994; 71:30-3.
625. Klein WW, Khurmi NS, Eber B, Dusleag J. Effects of benazepril and metoprolol OROS alone and in combination on myocardial ischemia in patients with chronic stable angina. J Am Coll Cardiol 1990;16:948-56.
626. Cameron HA, Cameron CM, Ramsay LE. Comparison of single doses of ketanserin and placebo in chronic stable angina. Br J Clin Pharmacol 1986;22:114-6.
627. Feldman RL, Prida XE, Hill JA. Systemic and coronary hemodynamic effects of combined oral alpha- and beta-adrenergic blockade (labetalol) in normotensive patients with stable angina pectoris and positive exercise stress tests. Clin Cardiol 1988;11:383-8.
628. Raubach KH, Vlahov V, Wolter K, Bussmann WD. Double-blind randomized multicenter study on the efficacy of trapidil versus isosorbide dinitrate in stable angina pectoris. Clin Cardiol 1997;20:483-8.
629. Glasser SP, Singh SN, Humen DP. Safety and efficacy of monotherapy with fantofarone, a novel calcium channel antagonist, in patients with chronic stable angina pectoris. Fantofarone Study Group. J Clin Pharmacol 1997;37:53-7.
630. Lawson WE, Hui JC, Zheng ZS, et al. Can angiographic findings predict which coronary patients will benefit from enhanced external counterpulsation? Am J Cardiol 1996;77:1107-9.
631. Lawson WE, Hui JC, Zheng ZS, et al. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. Am J Cardiol 1995;75:840-1.
632. Wang TJ, Stafford RS. National patterns and predictors of beta-blocker use in patients with coronary artery disease. Arch Intern Med 1998;158:1901-6.
633. Ardissino D, Savonitto S, Egstrup K, et al. Selection of medical treatment in stable angina pectoris: results of the International Multicenter Angina Exercise (IMAGE) Study. J Am Coll Cardiol 1995;25:1516-21.
634. Arnman K, Ryden L. Comparison of metoprolol and verapamil in the treatment of angina pectoris. Am J Cardiol 1982;49:821-7.
635. Bjerle P, Olofsson, Glimvik O. Nicardipine and propranolol in angina pectoris: a comparative study with special reference to ergometer working capacity tests. Br J Clin Pharmacol 1986; 22:339S-43S.
636. Bowles MJ, Bala Subramanian V, Davies AB, Raftery EB. Double-blind randomized crossover trial of verapamil and propranolol in chronic stable angina. Am Heart J 1983;106:1297-306.
637. Crake T, Mulcahy D, Wright C, Fox K. Labetalol in the treatment of stable exertional angina pectoris: a comparison with nifedipine. Eur Heart J 1988;9:1200-5.
638. de Divitiis O, Liguori V, Di Somma S, et al. Bisoprolol in the treatment of angina pectoris: a double blind comparison with verapamil. Eur Heart J 1987;8(Suppl M):43-54.
639. Di Somma S, de Divitiis M, Bertocchi F, et al. Treatment of hypertension associated with stable angina pectoris: favourable interaction between new metoprolol formulation (OROS) and nifedipine. Cardiologia 1996;41:635-43.
640. Findlay IN, Dargie HJ. The effects of nifedipine, atenolol and that combination on left ventricular function. Postgrad Med J 1983;59(Suppl 2):70-3.
641. Findlay IN, MacLeod K, Ford M, Gillen G, Elliott AT, Dargie HJ. Treatment of angina pectoris with nifedipine and atenolol: efficacy and effect on cardiac function. Br Heart J 1986;55:240-5.
642. Findlay IN, MacLeod K, Gillen G, Elliott AT, Aitchison T, Dargie HJ. A double blind placebo controlled comparison of verapamil, atenolol, and their combination in patients with chronic stable angina pectoris. Br Heart J 1987;57:336-43.
643. Frishman WH, Klein NA, Klein P, et al. Comparison of oral propranolol and verapamil for combined systemic hypertension and angina pectoris: a placebo-controlled double-blind randomized crossover trial. Am J Cardiol 1982;50:1164-72.
644. Frishman WH. Comparative efficacy and concomitant use of bepridil and beta blockers in the management of angina pectoris. Am J Cardiol 1992;69:50D-55D.
645. Higginbotham MB, Morris KG, Coleman RE, Cobb FR. Chronic stable angina monotherapy. Nifedipine versus propranolol. Am J Med 1989;86:1-5.
646. Humen DP, Kostuk WJ. Clinical response and effects on left ventricular function of isosorbide dinitrate added to propranolol or diltiazem monotherapy in patients with chronic stable angina. Can J Cardiol 1991;7:74-80.
647. Johnson SM, Mauritson DR, Corbett JR, Woodward W, Willerson JT, Hillis LD. Double-blind, randomized, placebo-controlled comparison of propranolol and verapamil in the treatment of patients with stable angina pectoris. Am J Med 1981;71:443-51.

648. Kenny J, Kiff P, Holmes J, Jewitt DE. Beneficial effects of diltiazem and propranolol, alone and in combination, in patients with stable angina pectoris. Br Heart J 1985;53:43-6.
649. Livesley B, Catley PF, Campbell RC, Oram S. Double-blind evaluation of verapamil, propranolol, and isosorbide dinitrate against a placebo in the treatment of angina pectoris. Br Med J 1973; 1:375-8.
650. Lynch P, Dargie H, Krikler S, Krikler D. Objective assessment of antianginal treatment: a double-blind comparison of propranolol, nifedipine, and their combination. Br Med J 1980;281:184-7.
651. McGill D, McKenzie W, McCredie M. Comparison of nicardipine and propranolol for chronic stable angina pectoris. Am J Cardiol 1986;57:39-43.
652. Nadazdin A, Davies GJ. Investigation of therapeutic mechanisms of atenolol and diltiazem in patients with variable-threshold angina. Am Heart J 1994;127:312-7.
653. Pflugfelder PW, Humen DP, O'Brien PA, Purves PD, Jablonsky G, Kostuk WJ. Comparison of bepridil with nadolol for angina pectoris. Am J Cardiol 1987;59:1283-8.
654. Rae AP, Beattie JM, Lawrie TD, Hutton I. Comparative clinical efficacy of bepridil, propranolol and placebo in patients with chronic stable angina. Br J Clin Pharmacol 1985;19:343-52.
655. Southall E, Nutt NR, Thomas RD. Chronic stable angina: comparison of verapamil and propranolol. J Int Med Res 1982;10:361-6.
656. van der Does R, Eberhardt R, Derr I, Ehmer B. Efficacy and safety of carvedilol in comparison with nifedipine sustained-release in chronic stable angina. J Cardiovasc Pharmacol 1992;19(Suppl 1):S122-7.
657. van Dijk RB, Lie KI, Crijns HJ. Diltiazem in comparison with metoprolol in stable angina pectoris. Eur Heart J 1988;9:1194-9.
658. Wheatley D. A comparison of diltiazem and atenolol in angina. Postgrad Med J 1985;61:785-9.
659. Ahuja RC, Sinha N, Kumar RR, Saran RK. Effect of metoprolol and diltiazem on the total ischaemic burden in patients with chronic stable angina: a randomized controlled trial. Int J Cardiol 1993;41:191-9.
660. Egstrup K, Andersen PE Jr. Transient myocardial ischemia during nifedipine therapy in stable angina pectoris, and its relation to coronary collateral flow and comparison with metoprolol. Am J Cardiol 1993;71:177-83.
661. Hung J, Lamb IH, Connolly SJ, Jutzy KR, Goris ML, Schroeder JS. The effect of diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: a double-blind, randomized, and placebo-controlled study. Circulation 1983;68:560-7.
662. Lai C, Onnis E, Orani E, et al. Felodipine improves the antiischaemic effect of metoprolol in stable effort-induced angina. Drug Invest 1992;4:30-3.
663. Parker JO, Farrell B. Comparative antianginal effects of bepridil and propranolol in angina pectoris. Am J Cardiol 1986;58:449-52.
664. Sadick NN, Tan AT, Fletcher PJ, Morris J, Kelly DT. A double-blind randomized trial of propranolol and verapamil in the treatment of effort angina. Circulation 1982;66:574-9.
665. Subramanian VB, Bowles MJ, Davies AB, Raftery EB. Calcium channel blockade as primary therapy for stable angina pectoris. A double-blind placebo-controlled comparison of verapamil and propranolol. Am J Cardiol 1982;50:1158-63.
666. Missed opportunities in preventive counseling for cardiovascular disease—United States, 1995. MMWR Morb Mortal Wkly Rep 1998;47:91-5.
667. Plach S, Wierenga ME, Heidrich SM. Effect of a postdischarge education class on coronary artery disease knowledge and self-reported health-promoting behaviors. Heart Lung 1996;25:367-72.
668. O'Neill C, Normand C, Cupples M, McKnight A. Cost effectiveness of personal health education in primary care for people with angina in the greater Belfast area of Northern Ireland. J Epidemiol Community Health 1996;50:538-40.
669. Larson CO, Nelson EC, Gustafson D, Batalden PB. The relationship between meeting patients' information needs and their satisfaction with hospital care and general health status outcomes. Int J Qual Health Care 1996;8:447-56.
670. Lewis BS, Lynch WD. The effect of physician advice on exercise behavior. Prev Med 1993;22:110-21.
671. Ockene JK, Kristeller J, Pbert L, et al. The physician-delivered smoking intervention project: can short-term interventions produce long-term effects for a general outpatient population? Health Psychol 1994;13:278-81.
672. Liao L, Jollis JG, DeLong ER, Peterson ED, Morris KG, Mark DB. Impact of an interactive video on decision making of patients with ischemic heart disease. J Gen Intern Med 1996;11:373-6.
673. Hill J. A practical guide to patient education and information giving. Baillieres Clin Rheumatol 1997;11:109-27.
674. Kingsbury K. Taking AIM: how to teach primary and secondary prevention effectively. Can J Cardiol 1998;14(Suppl A):22A-26A.
675. Winslow E, Bohannon N, Brunton SA, Mayhew HE. Lifestyle modification: weight control, exercise, and smoking cessation. Am J Med 1996;101:25S-31S.
676. The multiple risk factor intervention trial (MRFIT). A national study of primary prevention of coronary heart disease. JAMA 1976;235:825-7.
677. Moore SM. Effects of interventions to promote recovery in coronary artery bypass surgical patients. J Cardiovasc Nurs 1997; 12:59-70.
678. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. JAMA 1988;260:945-50.
679. Duryee R. The efficacy of inpatient education after myocardial infarction. Heart Lung 1992;21:217-25.
680. Wang WW. The educational needs of myocardial infarction patients. Prog Cardiovasc Nurs 1994;9:28-36.
681. Chan V. Content areas for cardiac teaching: patients' perceptions of the importance of teaching content after myocardial infarction. J Adv Nurs 1990;15:1139-45.
682. Rhodes KS, Bookstein LC, Aaronson LS, Mercer NM, Orringer CE. Intensive nutrition counseling enhances outcomes of National Cholesterol Education Program dietary therapy. J Am Diet Assoc 1996;96:1003-10.
683. Czar ML, Engler MM. Perceived learning needs of patients with coronary artery disease using a questionnaire assessment tool. Heart Lung 1997;26:109-17.
684. Albarran JW, Bridger S. Problems with providing education on resuming sexual activity after myocardial infarction: developing written information for patients. Intensive Crit Care Nurs 1997; 13:2-11.
685. Dracup K, Alonzo AA, Atkins JM, et al. The physician's role in minimizing prehospital delay in patients at high risk for acute myocardial infarction: recommendations from the National Heart Attack Alert Program. Working Group on Educational Strategies to Prevent Prehospital Delay in Patients at High Risk for Acute Myocardial Infarction. Ann Intern Med 1997;126:645-51.
686. Gaspoz JM, Unger PF, Urban P, et al. Impact of a public campaign on pre-hospital delay in patients reporting chest pain. Heart

1996;76:150-5.
687. AHA Home Page. Available at: http://www.americanheart.org/Heart_and_ Stroke_A_Z_Guide/cvds.html.
688. Dracup K, Moser DK, Guzy PM, Taylor SE, Marsden C. Is cardiopulmonary resuscitation training deleterious for family members of cardiac patients? Am J Public Health 1994;84:116-8.
689. Pasternak RC, Grundy SM, Levy D, Thompson SD. Task Force III: spectrum of risk factors for coronary heart disease. J Am Coll Cardiol 1996;27:978-90.
690. McBride PE. The health consequences of smoking. Cardiovascular diseases. Med Clin North Am 1992;76:333-53.
691. Government Printing Office. Reducing the Health Consequences of Smoking: 25 Years of Progress. Washington DC: Government Printing Office, 1989.
692. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976;2:1525-36.
693. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1990;322:213-7.
694. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Atherosclerosis 1994;110:121-61.
695. The health benefits of smoking cessation. A report of the Surgeon General. Washington, DC: US Department of Health and Human Services, 1990.
696. Rose GA, Hamilton PJS, Colwell L, Shipley MJ. A randomised controlled trial of antismoking advice: 10 year results. J Epidemiol Community Health 1982;36:102-8.
697. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. JAMA 1982;248:1465-77.
698. Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. Lancet 1981;2:1303-10.
699. Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study. Am Heart J 1986;113:1006-10.
700. Davis JW, Hartman CR, Lewis HD Jr, et al. Cigarette smoking-induced enhancement of platelet function: lack of prevention by aspirin in men with coronary artery disease. J Lab Clin Med 1985;105:479-83.
701. Taylor AE, Johnson DC, Kazemi H. Environmental tobacco smoke and cardiovascular disease. A position paper from the Council on Cardiopulmonary and Critical Care, American Heart Association. Circulation 1992;86:699-702.
702. Winniford MD, Jansen DE, Reynolds GA, et al. Cigarette smoking-induced coronary vasoconstriction in atherosclerotic coronary artery disease and prevention by calcium antagonists and nitroglycerin. Am J Cardiol 1987;59:203-7.
703. Taylor CB, Houston-Miller N, Killen JD, et al. Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. Ann Intern Med 1990;113:118-23.
704. Singh RB, Rastogi SS, Verma R, et al. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. BMJ 1992;304:1015-9.
705. Schuler G, Hambrecht R, Schlierf G, et al. Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease. Circulation 1992;86:1-11.
706. Superko HR, Krauss RM. Coronary artery disease regression: convincing evidence for the benefit of aggressive lipoprotein management. Circulation 1994;90:1056-69.
707. Rossouw JE. Lipid-lowering interventions in angiographic trials. Am J Cardiol 1995;76:86C-92C.
708. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154-83.
709. Stamler J, Neaton J, Wentworth D. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. Hypertension 1993;13:2-12.
710. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765-74.
711. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 1967;202:1028-34.
712. Effects of treatment on morbidity in hypertension, II: results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143-52.
713. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-38.
714. Cutler JA, Psaty BM, McMahon S, Furberg CD. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BM, eds. Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York: Raven Press, 1995:253-70.
715. Hennekens CH, Albert CM, Godfried SL, Gaziano JM, Buring JE. Adjunctive drug therapy of acute myocardial infarction—evidence from clinical trials. N Engl J Med 1996;335:1660-7.
716. Smith SC Jr, Blair SN, Criqui MH, et al. AHA consensus panel statement: preventing heart attack and death in patients with coronary disease. The Secondary Prevention Panel. J Am Coll Cardiol 1995;26:292-4.
717. Alderman MH, Cohen H, Roque R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. Lancet 1997;349:594-8.
718. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. J Am Coll Cardiol 1996;27:1214-8.
719. Gibson RS, Boden WE. Calcium channel antagonists: friend or foe in postinfarction patients? Am J Hypertens 1996;9:172S-6S.
720. Kannel WB. Coronary risk factors: an overview. In: Willerson JT, Cohn JN, eds. Cardiovascular Medicine. New York: Churchill Livingstone, 1995:1809-92.
721. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. Ann Intern Med 1988;108:7-13.
722. Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study. Ann Intern Med 1970; 72:813-22.
723. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med 1969;71:89-105.
724. Casale PN, Devereux RB, Milner M, et al. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med

1986;105:173-8.
725. Liao Y, Cooper RS, McGee DL, Mensah GA, Ghali JK. The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. JAMA 1995;273:1592-7.
726. Bikkina M, Levy D, Evans JC, et al. Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. JAMA 1994;272:33-6.
727. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992; 117:831-6.
728. Dahlof B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. Am J Hypertens 1992;5:95-110.
729. Neaton JD, Grimm RH, Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA 1993;270:713-24.
730. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994;308:81-106.
731. Ridker PM. An epidemiologic assessment of thrombotic risk factors for cardiovascular disease. Curr Opin Lipidol 1992;3:285-90.
732. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.
733. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Intern Med 1993; 118:956-63.
734. Kannel WB, D'Agostino RB, Belanger AJ. Update on fibrinogen as a cardiovascular risk factor. Ann Epidemiol 1992;2:457-66.
735. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Engl J Med 1995;332:635-41.
736. Heinrich J, Balleisen L, Schulte H, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. Arterioscler Thromb 1994;14:54-9.
737. Trip MD, Manger Cats V, Van Capelle FJL, Vreeken J. Platelet hyperreactivity and prognosis in survivors of myocardial infarction. N Engl J Med 1990;322:1549-54.
738. Elwood PC, Renaud S, Sharp DS, Beswick AD, O'Brien JR, Yarnell JWG. Ischemic heart disease and platelet aggregation: The Caerphilly Collaborative Heart Disease Study. Circulation 1991;83:38-44.
739. Jansson JH, Nilsson TK, Johnson O. von Willebrand factor in plasma: a novel risk factor for recurrent myocardial infarction and death. Br Heart J 1991;66:351-5.
740. American Diabetes Association. Clinical practice recommendations 1998: screening for type 2 diabetes. Diabetes Care 1998;21(Suppl 1):1-98.
741. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
742. Getz GS. Report on the workshop on diabetes and mechanisms of atherogenesis. September 17th and 18th, 1992, Bethesda, Maryland. Arterioscler Thromb 1993;13:459-64.
743. Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Cayatte AJ, Rozek MM. Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. Circulation 1992;15:1156-67.
744. Stamler J. Epidemiology, established major risk factors, and the primary prevention of coronary heart disease. In: Parmley WW, Chatterjee K, eds. Cardiology. Philadelphia: JB Lippincott; 1987:1-41.
745. Butler WJ, Ostrander LD, Carman WJ, Lamphiear DE. Mortality from coronary heart disease in the Tecumseh study: long-term effect of diabetes mellitus, glucose tolerance and other risk factors. Am J Epidemiol 1985;121:541-7.
746. Alderman EL, Corley SD, Fisher LD, et al. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. J Am Coll Cardiol 1993;22:1141-54.
747. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329:304-9.
748. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
749. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65.
750. Connaughton M, Weber J. Diabetes in coronary artery disease: time to stop taking the tablets. Heart 1998;80:108-9.
751. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
752. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-20.
753. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8-15.
754. Reference deleted during update.
755. Manson JE, Gaziano JM, Jonas MA, Hennekens CH. Antioxidants and cardiovascular disease: a review. J Am Coll Nutr 1993;12:426-32.
756. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983;67:968-77.
757. Fletcher GF, Balady G, Blair SN, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation 1996;94:857-62.
758. Froelicher V, Jensen D, Genter F, et al. A randomized trial of exercise training in patients with coronary heart disease. JAMA 1984;252:1291-7.
759. Sebrechts CP, Klein JL, Ahnve S, Froelicher VF, Ashburn WL. Myocardial perfusion changes following 1 year of exercise training assessed by thallium-201 circumferential count profiles. Am Heart J 1986;112:1217-26.
760. Oldridge NB, McCartney N, Hicks A, Jones NL. Maximal isokinetic cycle ergometry in patients with coronary artery disease.

Improvement in maximal isokinetic cycle ergometry with cardiac rehabilitation. Med Sci Sports Exerc 1989;21:308-12.
761. Hambrecht R, Niebauer J, Marburger C, et al. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. J Am Coll Cardiol 1993;22:468-77.
762. Fletcher BJ, Dunbar SB, Felner JM, et al. Exercise testing and training in physically disabled men with clinical evidence of coronary artery disease. Am J Cardiol 1994;73:170-4.
763. Ornish D, Scherwitz LW, Doody RS, et al. Effects of stress management training and dietary changes in treating ischemic heart disease. JAMA 1983;249:54-9.
764. May GA, Nagle FJ. Changes in rate-pressure product with physical training of individuals with coronary artery disease. Phys Ther 1984;64:1361-6.
765. Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: The Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1994;89:975-90.
766. Cannistra LB, Balady GJ, O'Malley CJ, Weiner DA, Ryan TJ. Comparison of the clinical profile and outcome of women and men in cardiac rehabilitation. Am J Cardiol 1992;69:1274-9.
767. O'Callaghan WG, Teo KK, O'Riordan J, Webb H, Dolphin T, Horgan JH. Comparative response of male and female patients with coronary artery disease to exercise rehabilitation. Eur Heart J 1984;5:649-51.
768. Oldridge NB, LaSalle D, Jones NL. Exercise rehabilitation of female patients with coronary heart disease. Am Heart J 1980; 100:755-7.
769. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 1990;336:129-33.
770. Todd IC, Ballantyne D. Effects of exercise training on the total ischaemic burden: an assessment by 24 hour ambulatory electrocardiographic monitoring. Br Heart J 1992;68:560-6.
771. Denollet J. Emotional distress and fatigue in coronary heart disease: the Global Mood Scale (GMS). Psychol Med 1993;23:111-21.
772. Oberman A, Cleary P, Larosa JC, Hellerstein HK, Naughton J. Changes in risk factors among participants in a long-term exercise rehabilitation program. Adv Cardiol 1982;31:168-75.
773. Nikolaus T, Schlierf G, Vogel G, Schuler G, Wagner I. Treatment of coronary heart disease with diet and exercise—problems of compliance. Ann Nutr Metab 1991;35:1-7.
774. Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). Lancet 1992;339:563-9.
775. Lee AP, Ice R, Blessey R, Sanmarco ME. Long-term effects of physical training on coronary patients with impaired ventricular function. Circulation 1979;60:1519-26.
776. Kennedy CC, Spiekerman RE, Lindsay MI, Mankin HT, Frye RL, McCallister BD. One-year graduated exercise program for men with angina pectoris: evaluation by physiologic studies and coronary arteriography. Mayo Clin Proc 1976;51:231-6.
777. Letac B, Cribier A, Desplanches JF. A study of left ventricular function in coronary patients before and after physical training. Circulation 1977;56:375-8.
778. Hung J, Gordon EP, Houston N, Haskell WL, Goris ML, DeBusk RF. Changes in rest and exercise myocardial perfusion and left ventricular function 3 to 26 weeks after clinically uncomplicated acute myocardial infarction: effects of exercise training. Am J Cardiol 1984;54:943-50.
779. Giannuzzi P, Tavazzi L, Temporelli PL, et al. Long-term physical training and left ventricular remodeling after anterior myocardial infarction: results of the Exercise in Anterior Myocardial Infarction (EAMI) trial. EAMI Study Group. J Am Coll Cardiol 1993;22:1821-9.
780. Grodzinski E, Jette M, Blumchen G, Borer JS. Effects of a four-week training program on left ventricular function as assessed by radionuclide ventriculography. J Cardiopulm Rehabil 1987;7:518-24.
781. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. Circulation 1988;78:506-15.
782. Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography. J Am Coll Cardiol 1988;12:362-72.
783. Hertzeanu HL, Shemesh J, Aron LA, et al. Ventricular arrhythmias in rehabilitated and nonrehabilitated post-myocardial infarction patients with left ventricular dysfunction. Am J Cardiol 1993;71:24-7.
784. Haskell WL, Van Camp SP, Peterson RA. Cardiovascular complications of outpatient cardiac rehabilitation programs. JAMA 1986;256:1160-3.
785. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation 1989;80:234-44.
786. Plavsic C, Turkulin K, Perman Z, et al. The results of exercise therapy in coronary prone individuals and coronary patients. G Ital Cardiol 1976;6:422-32.
787. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641-6.
788. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [published erratum appears in JAMA 1995 Dec 6;274:1676]. JAMA 1995;273:199-208.
789. Manolio TA, Furberg CD, Shemanski L, et al. Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. The CHS Collaborative Research Group. Circulation 1993;88:2163-71.
790. Hong MK, Romm PA, Reagan K, Green CE, Rackley CE. Effects of estrogen replacement therapy on serum lipid values and angiographically defined coronary artery disease in postmenopausal women. Am J Cardiol 1992;69:176-8.
791. Nabulsi AA, Folsom AR, White A, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. N Engl J Med 1993;328:1069-75.
792. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991;20:47-63.
793. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. N Engl J Med 1991;325:756-62.
794. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992;117:1016-37.

795. Sullivan JM, Vander Zwaag R, Lemp GF, et al. Postmenopausal estrogen use and coronary atherosclerosis. Ann Intern Med 1988; 108:358-63.
796. Gruchow HW, Anderson AJ, Barboriak JJ, Sobocinski KA. Postmenopausal use of estrogen and occlusion of coronary arteries. Am Heart J 1988;115:954-63.
797. Sullivan JM, Vander Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease. Effect on survival in postmenopausal women. Arch Intern Med 1990;150:2557-62.
798. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. Am J Cardiol 1997;79:847-50.
799. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-13.
800. Friedman M, Rosenman RH. Association of specific overt behavior patterns with blood and cardiovascular findings: blood cholesterol level, blood clotting time, incidence of arcus senilis and clinical coronary artery disease. JAMA 1959;169:1286-97.
801. Rosenman RH, Brand RJ, Sholtz RI, Friedman M. Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. Am J Cardiol 1976; 37:903-10.
802. Rosenman RH, Brand RJ, Jenkins D, Friedman M, Straus R, Wurm M. Coronary heart disease in Western Collaborative Group Study. Final follow-up experience of 8½ years. JAMA 1975; 233:872-7.
803. Case RB, Heller SS, Case NB, Moss AJ. Type A behavior and survival after acute myocardial infarction. N Engl J Med 1985; 312:737-41.
804. Shekelle RB, Gale M, Norusis M. Type A score (Jenkins Activity Survey) and risk of recurrent coronary heart disease in the Aspirin Myocardial Infarction Study. Am J Cardiol 1985;56:221-5.
805. Shekelle RB, Hulley SB, Neaton JD, et al. The MRFIT behavior pattern study, II. Type A behavior and incidence of coronary heart disease. Am J Epidemiol 1985;122:559-70.
806. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. JAMA 1993;270:1819-25.
807. Williams RB. Neurobiology, cellular and molecular biology, and psychosomatic medicine. Psychosom Med 1994;56:308-15.
808. Barefoot JC, Dahlstrom WG, Williams RB Jr. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. Psychosom Med 1983;45:59-63.
809. Shekelle RB, Gale M, Ostfeld AM, Paul O. Hostility, risk of coronary heart disease, and mortality. Psychosom Med 1983;45:109-14.
810. Frasure-Smith N, Prince R. The ischemic heart disease life stress. Monetary program: impact on mortality. Psychosom Med 1985; 47:431-45.
811. Friedman M, Thoresen CE, Gill JJ, et al. Alteration of type A behavior and reduction in cardiac recurrences in postmyocardial infarction patients. Am Heart J 1984;108:237-48.
812. Nunes EV, Frank KA, Kornfeld DS. Psychologic treatment for the type A behavior pattern and for coronary heart disease: a meta-analysis of the literature. Psychosom Med 1987;49:159-73.
813. Bohachick P. Progressive relaxation training in cardiac rehabilitation: effect on psychologic variables. Nurs Res 1984;33:283-7.
814. Blumenthal JA, Jiang W, Babyak MA, et al. Stress management and exercise training in cardiac patients with myocardial ischemia: effects on prognosis and evaluation of mechanisms. Arch Intern Med 1997;157:2213-23.
815. Carney RM, Rich MW, Tevelde A, Saini J, Clark K, Jaffe AS. Major depressive disorder in coronary artery disease. Am J Cardiol 1987;60:1273-5.
816. Schleifer SJ, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;149:1785-9.
817. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study [published erratum appears in Circulation 1998 May 19;97:1995]. Circulation 1998;97:1029-36.
818. Reaven GM. Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia, and coronary heart disease. Am Heart J 1991;121:1283-8.
819. Grundy SM, Vega GL. Two different views of the relationship of hypertriglyceridemia to coronary heart disease. Implications for treatment. Arch Intern Med 1992;152:28-34.
820. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45.
821. NIH Consensus Development Panel on Triglyceride H-DL and Coronary Heart Disease. Triglyceride, high-density lipoprotein, and coronary heart disease. JAMA 1993;269:505-10.
822. Scanu AM, Lawn RM, Berg K. Lipoprotein(a) and atherosclerosis. Ann Intern Med 1991;115:209-18.
823. Kostner GM, Krempler F. Lipoprotein(a). Curr Opin Lipidol 1992;3:279-84.
824. Genest JJ, Jenner JL, McNamara JR, et al. Prevalence of lipoprotein (a) [Lp(a)] excess in coronary artery disease. Am J Cardiol 1991;67:1039-145.
825. Genest J Jr, Malinow MR. Homocysteine and coronary artery disease. Curr Opin Lipidol 1992;3:295-9.
826. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 1991;324:1149-55.
827. Stampfer MJ, Malinow MR, Willett WC, et al. A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. JAMA 1992;268:877-81.
828. Selhub J, Jacques PF, Bostom AG, et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. N Engl J Med 1995;332:286-91.
829. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA 1993;270:2693-8.
830. Ubbink JB, Vermaak WJ, van der Merwe A, Becker PJ. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. Am J Clin Nutr 1993;57:47-53.
831. Berliner JA, Navab M, Fogelman AM, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. Circulation 1995;91:2488-96.
832. Jialal I, Scaccini C. Antioxidants and atherosclerosis. Curr Opin Lipidol 1992;3:324-8.
833. Nyyssonen K, Parviainen MT, Salonen R, Tuomilehto J, Salonen JT. Vitamin C deficiency and risk of myocardial infarction: prospective population study of men from eastern Finland. BMJ 1997;314:634-8.
834. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35.
835. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in

patients with coronary disease: Cambridge Heart Antioxident Study. Lancet 1996;347:781-6.
836. Rodes J, Cote G, Lesperance J, et al. Prevention of restenosis after angioplasty in small coronary arteries with probucol. Circulation 1998;97:429-36.
837. Regnstrom J, Walldius G, Nilsson S, et al. The effect of probucol on low density lipoprotein oxidation and femoral atherosclerosis. Atherosclerosis 1996;125:217-29.
838. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med 1993;329:1829-34.
839. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med 1988;319:267-73.
840. Yano K, Rhoads G, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. N Engl J Med 1977;297:405-9.
841. Hertog MG,Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993;342:1007-11.
842. Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med 1996;125:384-9.
843. Hopkins PN, Williams RR. A survey of 246 suggested coronary risk factors. Atherosclerosis 1981;40:1-52.
844. Ball KP, Hanington E, McAllen PM, et al. Low fat diet in myocardial infarction. Lancet 1965;2:501-4.
845. Rose GA, Thompson WB, Williams RT. Corn oil in treatment of ischemic heart disease. BMJ 1965;1:1531-3.
846. Woodhill JM, Palmer AJ, Leelerthaepin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. Adv Exp Med Biol 1978;109:317-30.
847. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet And Reinfarction Trial (DART). Lancet 1989;2:757-61.
848. Leren P. The Oslo diet-heart study. Eleven-year report. Circulation 1970;42:935-42.
849. Lorgeril M, Mamelle N, Salen P, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454-9.
850. Israel DH, Gorlin R. Fish oils in prevention of atherosclerosis. J Am Coll Cardiol 1992;19:174-85.
851. O'Connor GT, Malenka DJ, Olmstead ME, Johnson PS, Hennekens CH. A meta-analysis of randomized trials of fish oils in the prevention of restenosis following coronary angioplasty. Am J Prev Med 1992;8:186-92.
852. Gapinski JP, Van Ruiswyk JV, Heudebart GR, Schectman GS. Preventing restenosis with fish oils following coronary angioplasty: a meta-analysis. Arch Intern Med 1993;153:1595-601.
853. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol: a meta-analysis. Ann Intern Med 1993; 119:599-605.
854. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens 1994;12:463-8.
855. Berthold HK, Sudhop T, von Bergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. JAMA 1998;279:1900-2.
856. Isaacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch Intern Med 1998;158:1189-94.
857. Jain AK, Vargas R, Gotzkowsky S, McMahon FG. Can garlic reduce levels of serum lipids? A controlled clinical study. Am J Med 1993;94:632-5.
858. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. Circulation 1997;96:1031-3.
859. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. J Thorac Cardiovasc Surg 1985;89:248-58.
860. Bourassa MG, Campeau L, Lesperance J. Changes in grafts and in coronary arteries after coronary bypass surgery. Cardiovasc Clin 1991;21:83-100.
861. FitzGibbon GM, Leach AJ, Kafka HP, Keon WJ. Coronary bypass graft fate: long-term angiographic study. J Am Coll Cardiol 1991;17:1075-80.
862. Chesebro JH, Fuster V, Elveback LR, et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. N Engl J Med 1984;310:209-14.
863. Gavaghan TP, Gebski V, Baron DW. Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study. Circulation 1991;83:1526-33.
864. Goldman S, Copeland J, Moritz T, et al. Starting aspirin therapy after operation. Effects on early graft patency. Department of Veterans Affairs Cooperative Study Group. Circulation 1991; 84:520-6.
865. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997;336:153-62.
866. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1-6.
867. Lytle BW, Cosgrove DM III. Coronary artery bypass surgery. Curr Probl Surg 1992;29:733-807.
868. Cameron A, Davis KB, Green G, Schaff HV. Coronary bypass surgery with internal-thoracic-artery grafts—effects on survival over a 15-year period. N Engl J Med 1996;334:216-9.
869. The VA Coronary Artery Bypass Surgery Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for stable angina. Circulation 1992;86:121-30.
870. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 1988; 319:332-7.
871. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. N Engl J Med 1985;312:1665-71.
872. Myers WO, Schaff HV, Gersh BJ, et al. Improved survival of surgically treated patients with triple vessel coronary artery disease and severe angina pectoris. A report from the Coronary Artery Surgery Study (CASS) registry. J Thorac Cardiovasc Surg 1989; 97:487-95.
873. Rogers WJ, Coggin CJ, Gersh BJ, et al. Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery. The Coronary Artery Surgery Study (CASS). Circulation 1990;82:1647-58.
874. Califf RM, Harrell FE Jr, Lee KL, et al. The evolution of medical and surgical therapy for coronary artery disease: a 15-year perspective. JAMA 1989;261:2077-86.

875. Topol EJ, Leya F, Pinkerton CA, et al. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. N Engl J Med 1993;329:221-7.
876. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496-501.
877. Adelman AG, Cohen EA, Kimball BP, et al. A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. N Engl J Med 1993;329:228-33.
878. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med 1992;326:10-6.
879. RITA-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet 1997;350:461-8.
880. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037-43.
881. Sharaf BL, Williams DO, Miele NJ, et al. A detailed angiographic analysis of patients with ambulatory electrocardiographic ischemia: results from the Asymptomatic Cardiac Ischemia Pilot (ACIP) Study Angiographic Core Laboratory. J Am Coll Cardiol 1997;29:78-84.
882. Hueb WA, Bellotti G, de Oliveira SA, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol 1995;26:1600-5.
883. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease [published erratum appears in N Engl J Med 1997;336:147]. N Engl J Med 1996; 335:217-25.
884. King SBI, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med 1994;331:1044-50.
885. Moliterno DJ, Elliott JM. Randomized trials of myocardial revascularization. Curr Probl Cardiol 1995;20:125-90.
886. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1997;96:1761-9.
887. O'Rourke RA. Role of myocardial revascularization in sudden cardiac death. Circulation 1992;85:I-112-I-117.
888. Holmes DR Jr, Davis K, Gersh BJ, Mock M, Pettinger MB. Risk factor profiles of patients with sudden cardiac death and death from other cardiac causes. A report from the Coronary Artery Surgery Study (CASS). J Am Coll Cardiol 1989;13:524-31.
889. Tresch DD, Wetherbee JN, Siegel R, et al. Long-term follow-up of survivors of prehospital sudden cardiac death treated with coronary bypass surgery. Am Heart J 1985;110:1139-45.
890. King SBI, Barnhart HX, Kosinski AS, et al. Angioplasty or surgery for multivessel coronary artery disease: comparison of eligible registry and randomized patients in the EAST trial and influence of treatment selection on outcomes. Emory Angioplasty versus Surgery Trial Investigators. Am J Cardiol 1997;79:1453-9.
891. Mahmarian JJ, Moye LA, Verani MS, Bloom MF, Pratt CM. High reproducibility of myocardial perfusion defects in patients undergoing serial exercise thallium-201 tomography. Am J Cardiol 1995;75:1116-9.
892. Ryan TJ, Antman EM, Brooks NH, et al. 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction. 1999. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/nov96/1999/index.htm. Accessed October 17, 2002.
893. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of the Patients with Unstable Angina). 2002. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/unstable/incorporated/index.htm. Accessed October 17, 2002.
894. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). 2002. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/exercise/exercise_clean.pdf. Accessed October 17, 2002.
895. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol 2000;36:326-40.
896. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA guidelines for ambulatory electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol 1999;34:912-48.
897. Hunt SM, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001; American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm. Accessed October 17, 2002.
898. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93:1520-6.
899. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999;281:524-9.
900. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351-7.
901. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med 2000;132:552-5.

902. Diaz LA, Brunken RC, Blackstone EH, Snader CE, Lauer MS. Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. J Am Coll Cardiol 2001;37:1558-64.
903. Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: the case of stress echocardiography. Circulation 2001;104:1911-6.
904. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000; 284:1392-8.
905. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 2001; 38:1980-7.
906. McHam SA, Marwick TH, Pashkow FJ, Lauer MS. Delayed systolic blood pressure recovery after graded exercise: an independent correlate of angiographic coronary disease. J Am Coll Cardiol 1999;34:754-9.
907. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 Guideline Update for Exercise Testing. 2002. www.acc.org/clinical/guidelines/exercise/dirIndex.htm.
908. Marquis P, Fayol C, Joire JE, Leplege A. Psychometric properties of a specific quality of life questionnaire in angina pectoris patients. Qual Life Res 1995;4:540-6.
909. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-41.
910. Wahrborg P, Emanuelsson H. The cardiac health profile: content, reliability and validity of a new disease-specific quality of life questionnaire. Coron Artery Dis 1996;7:823-9.
911. Alonso J, Permanyer-Miralda G, Cascant P, Brotons C, Prieto L, Soler-Soler J. Measuring functional status of chronic coronary patients. Reliability, validity and responsiveness to clinical change of the reduced version of the Duke Activity Status Index (DASI). Eur Heart J 1997;18:414-9.
912. Failde I, Ramos I. Validity and reliability of the SF-36 Health Survey Questionnaire in patients with coronary artery disease. J Clin Epidemiol 2000;53:359-65.
913. Dougherty CM, Dewhurst T, Nichol WP, Spertus J. Comparison of three quality of life instruments in stable angina pectoris: Seattle Angina Questionnaire, Short Form Health Survey (SF-36), and Quality of Life Index-Cardiac Version III. J Clin Epidemiol 1998;51:569-75.
914. Sullivan M, Genter F, Savvides M, Roberts M, Myers J, Froelicher V. The reproducibility of hemodynamic, electrocardiographic, and gas exchange data during treadmill exercise in patients with stable angina pectoris. Chest 1984;86:375-82.
915. Sanz ML, Mancini J, LeFree MT, et al. Variability of quantitative digital subtraction coronary angiography before and after percutaneous transluminal coronary angioplasty. Am J Cardiol 1987;60:55-60.
916. Davis RB, Iezzoni LI, Phillips RS, Reiley P, Coffman GA, Safran C. Predicting in-hospital mortality. The importance of functional status information. Med Care 1995;33:906-21.
917. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998;279:1187-93.
918. Reuben DB, Rubenstein LV, Hirsch SH, Hays RD. Value of functional status as a predictor of mortality: results of a prospective study. Am J Med 1992;93:663-9.
919. Scott WK, Macera CA, Cornman CB, Sharpe PA. Functional health status as a predictor of mortality in men and women over 65. J Clin Epidemiol 1997;50:291-6.
920. Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1996.
921. Staquet MJ, Hays RDFPM, eds. Quality of Life Assessment in Clinical Trials: Methods and Practice. New York: Oxford University Press, 1998.
922. Sjoland H, Wiklund I, Caidahl K, Haglid M, Westberg S, Herlitz J. Improvement in quality of life and exercise capacity after coronary bypass surgery. Arch Intern Med 1996;156:265-71.
923. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Fihn SD. Monitoring the quality of life in patients with coronary artery disease. Am J Cardiol 1994;74:1240-4.
924. Bliley AV, Ferrans CE. Quality of life after coronary angioplasty. Heart Lung 1993;22:193-9.
925. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36), II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.
926. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36), III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40-66.
927. Pollard WE, Bobbitt RA, Bergner M, Martin DP, Gilson BS. The Sickness Impact Profile: reliability of a health status measure. Med Care 1976;14:146-55.
928. Bergner M, Bobbitt RA, Pollard WE, Martin DP, Gilson BS. The sickness impact profile: validation of a health status measure. Med Care 1976;14:57-67.
929. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Pract 1985;35:185-8.
930. Brown N, Melville M, Gray D, Young T, Skene AM, Hampton JR. Comparison of the SF-36 health survey questionnaire with the Nottingham Health Profile in long-term survivors of a myocardial infarction. J Public Health Med 2000;22:167-75.
931. Dempster M, Donnelly M. Measuring the health related quality of life of people with ischaemic heart disease. Heart 2000;83:641-4.
932. Visser MC, Fletcher AE, Parr G, Simpson A, Bulpitt CJ. A comparison of three quality of life instruments in subjects with angina pectoris: the Sickness Impact Profile, the Nottingham Health Profile, and the Quality of Well Being Scale. J Clin Epidemiol 1994;47:157-63.
933. Bliven BD, Green CP, Spertus JA. Review of available instruments and methods for assessing quality of life in anti-anginal trials. Drugs Aging 1998;13:311-320.
934. Gandjour A, Lauterbach KW. Review of quality-of-life evaluations in patients with angina pectoris. Pharmacoeconomics 1999;16:141-52.
935. Spertus J. Seattle Angina Questionnaire (SAQ). Available at: www.outcomes-trust.org/instruments.htm#saq. Accessed August 30, 2002.
936. Simons M, Annex BH, Laham RJ, et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double-blind, randomized, controlled clinical trial. Circulation 2002;105:788-93.
937. Laham RJ, Chronos NA, Pike M, et al. Intracoronary basic fibroblast growth factor (FGF-2) in patients with severe ischemic heart

disease: results of a phase I open-label dose escalation study. J Am Coll Cardiol 2000;36:2132-9.
938. Maxwell AJ, Zapien MP, Pearce GL, MacCallum G, Stone PH. Randomized trial of a medical food for the dietary management of chronic, stable angina. J Am Coll Cardiol 2002;39:37-45.
939. Rinfret S, Grines CL, Cosgrove RS, et al. Quality of life after balloon angioplasty or stenting for acute myocardial infarction. One-year results from the Stent-PAMI trial. J Am Coll Cardiol 2001;38:1614-21.
940. Spertus JA, Jones PG, Coen M, et al. Transmyocardial CO(2) laser revascularization improves symptoms, function, and quality of life: 12-month results from a randomized controlled trial. Am J Med 2001;111:341-8.
941. Horvath KA, Aranki SF, Cohn LH, et al. Sustained angina relief 5 years after transmyocardial laser revascularization with a CO(2) laser. Circulation 2001;104:I81-4
942. Oesterle SN, Sanborn TA, Ali N, et al. Percutaneous transmyocardial laser revascularisation for severe angina: the PACIFIC randomised trial. Potential Class Improvement From Intramyocardial Channels. Lancet 2000;356:1705-10.
943. Seto TB, Taira DA, Berezin R, et al. Percutaneous coronary revascularization in elderly patients: impact on functional status and quality of life. Ann Intern Med 2000;132:955-8.
944. Fruitman DS, MacDougall CE, Ross DB. Cardiac surgery in octogenarians: can elderly patients benefit? Quality of life after cardiac surgery. Ann Thorac Surg 1999;68:2129-35.
945. Burkhoff D, Schmidt S, Schulman SP, et al. Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. ATLANTIC Investigators. Angina Treatments-Lasers and Normal Therapies in Comparison. Lancet 1999; 354:885-90.
946. Weintraub WS, Culler SD, Kosinski A, et al. Economics, health-related quality of life, and cost-effectiveness methods for the TACTICS (Treat Angina With Aggrastat [tirofiban]] and Determine Cost of Therapy with Invasive or Conservative Strategy)-TIMI 18 trial. Am J Cardiol 1999;83:317-22.
947. MacDonald P, Stadnyk K, Cossett J, Klassen G, Johnstone D, Rockwood K. Outcomes of coronary artery bypass surgery in elderly people. Can J Cardiol 1998;14:1215-22.
948. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. Circulation 2002;106:43-9.
949. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
950. Lonn EM, Yusuf S, Jha P, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. Circulation 1994;90:2056-69.
951. Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med 1991;324:1098-104.
952. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53.
953. Diet F, Pratt RE, Berry GJ, Momose N, Gibbons GH, Dzau VJ. Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease. Circulation 1996;94:2756-67.
954. Mancini GB, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. Circulation 1996;94:258-65.
955. Dell'Italia LJ, Oparil S. Bradykinin in the heart: friend or foe? Circulation 1999;100:2305-7.
956. Gainer JV, Morrow JD, Loveland A, King DJ, Brown NJ. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med 1998;339:1285-92.
957. Vaughan DE, Rouleau JL, Ridker PM, Arnold JM, Menapace FJ, Pfeffer MA. Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction. HEART Study Investigators. Circulation 1997;96:442-7.
957a. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. [erratum appears in Lancet 2000;356:860] Lancet 2000;355:253-259.
958. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
959. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429-35.
960. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992; 327:685-91.
961. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival And Ventricular Enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669-77.
962. van den Heuvel AF, Dunselman PH, Kingma T, et al. Reduction of exercise-induced myocardial ischemia during add-on treatment with the angiotensin-converting enzyme inhibitor enalapril in patients with normal left ventricular function and optimal beta blockade. J Am Coll Cardiol 2001;37:470-4.
963. Rosano GM, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. Lancet 1993;342:133-6.
964. Manhem K, Ahlm H, Dellborg M, Milsom I. Acute effects of transdermal estrogen in postmenopausal women with coronary artery disease. Using a clinically relevant estrogen dose and concurrent antianginal therapy. Cardiology 2000;94:86-90.
965. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation 2000;102:1906-11.
966. Deedwania PC, Carbajal EV, Nelson JR, Hait H. Anti-ischemic effects of atenolol versus nifedipine in patients with coronary artery disease and ambulatory silent ischemia. J Am Coll Cardiol 1991;17:963-9.
967. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). Circulation 1994;90:762-8.
968. Chaitman BR, Stone PH, Knatterud GL, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study: impact of anti- ischemia

therapy on 12-week rest electrocardiogram and exercise test outcomes. The ACIP Investigators. J Am Coll Cardiol 1995;26:585-93.
969. Davies RF, Habibi H, Klinke WP, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. J Am Coll Cardiol 1995;25:619-25.
970. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
971. Bedell SE, Jabbour S, Goldberg R, et al. Discrepancies in the use of medications: their extent and predictors in an outpatient practice. Arch Intern Med 2000;160:2129-34.
972. McDermott MM, Schmitt B, Wallner E. Impact of medication nonadherence on coronary heart disease outcomes. A critical review. Arch Intern Med 1997;157:1921-9.
973. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990;263:1653-7.
974. Horwitz RI, Viscoli CM, Berkman L, et al. Treatment adherence and risk of death after a myocardial infarction. Lancet 1990;336:542-5.
975. Gallagher EJ, Viscoli CM, Horwitz RI. The relationship of treatment adherence to the risk of death after myocardial infarction in women. JAMA 1993;270:742-4.
976. Haynes RB, Montangue P, Olier T, McKibbon KA, Brouwers MC, Kanani R. Interventions for helping patients to follow prescriptions for medications. In: Cochran Database System. Oxford, UK: Update Software; 2000:CD000011.
977. Vega GL, Grundy SM. Primary hypertriglyceridemia with borderline high cholesterol and elevated apolipoprotein B concentrations. Comparison of gemfibrozil vs lovastatin therapy. JAMA 1990;264:2759-63.
978. Abate N, Vega GL, Grundy SM. Variability in cholesterol content and physical properties of lipoproteins containing apolipoprotein B-100. Atherosclerosis 1993;104:159-71.
979. Sniderman AD. Apolipoprotein B and apolipoprotein AI as predictors of coronary artery disease. Can J Cardiol 1988;4(Suppl A):24A-30A.
980. Reinhart RA, Gani K, Arndt MR, Broste SK. Apolipoproteins A-I and B as predictors of angiographically defined coronary artery disease. Arch Intern Med 1990;150:1629-33.
981. Sniderman A, Vu H, Cianflone K. Effect of moderate hypertriglyceridemia on the relation of plasma total and LDL apo B levels. Atherosclerosis 1991;89:109-16.
982. Tornvall P, Bavenholm P, Landou C, de Faire U, Hamsten A. Relation of plasma levels and composition of apolipoprotein B-containing lipoproteins to angiographically defined coronary artery disease in young patients with myocardial infarction. Circulation 1993;88:2180-9.
983. Westerveld HT, van Lennep JE, van Lennep HW, et al. Apolipoprotein B and coronary artery disease in women: a cross-sectional study in women undergoing their first coronary angiography. Arterioscler Thromb Vasc Biol 1998;18:1101-7.
984. Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. Circulation 1996;94:273-8.
985. Gotto AM Jr, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Circulation 2000; 101:477-84.
986. Lemieux I, Pascot A, Couillard C, et al. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? Circulation 2000;102:179-84.
987. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
988. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410-8.
989. Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J 1998;19(Suppl M):M8-14.
990. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998;81:7B-12B.
991. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. Obes Res 1998;6(Suppl 2):51S-209S.
992. Cheung MC, Zhao XQ, Chait A, Albers JJ, Brown BG. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. Arterioscler Thromb Vasc Biol 2001;21:1320-6.
993. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:154-60.
994. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583-92.
995. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:22-33.
996. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605-13.
997. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med 2000;343:522-9.
998. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001;345:1243-9.
999. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
1000. Mosca L, Collins P, Herrington DM, et al. Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 2001;104:499-503.
1001. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a ran-

domised trial. Lancet 2001;358:951-7.
1002. Gibbons RJ, Chatterjee K, Daley J, et al. 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). J Am Coll Cardiol 1999;33:2092-197.
1003. Hautvast RW, DeJongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. Am Heart J 1998; 136:1114-20.
1004. Jessurun GA, DeJongste MJ, Hautvast RW, et al. Clinical follow-up after cessation of chronic electrical neuromodulation in patients with severe coronary artery disease: a prospective randomized controlled study on putative involvement of sympathetic activity. Pacing Clin Electrophysiol 1999;22:1432-9.
1005. Norrsell H, Pilhall M, Eliasson T, Mannheimer C. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. Cardiology 2000;94:12-8.
1006. Jessurun GA, Ten Vaarwerk IA, DeJongste MJ, Tio RA, Staal MJ. Sequelae of spinal cord stimulation for refractory angina pectoris. Reliability and safety profile of long-term clinical application. Coron Artery Dis 1997;8:33-8.
1007. TenVaarwerk IA, Jessurun GA, DeJongste MJ, et al. Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. The Working Group on Neurocardiology. Heart 1999;82:82-8.
1008. Murray S, Carson KG, Ewings PD, Collins PD, James MA. Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. Heart 1999;82:89-92.
1009. De Landsheere C, Mannheimer C, Habets A, et al. Effect of spinal cord stimulation on regional myocardial perfusion assessed by positron emission tomography. Am J Cardiol 1992; 69:1143-9.
1010. Eliasson T, Albertsson P, Hardhammar P, Emanuelsson H, Augustinsson LE, Mannheimer C. Spinal cord stimulation in angina pectoris with normal coronary arteriograms. Coron Artery Dis 1993;4:819-27.
1011. de Jongste MJ, Nagelkerke D, Hooyschuur CM, et al. Stimulation characteristics, complications, and efficacy of spinal cord stimulation systems in patients with refractory angina: a prospective feasibility study. Pacing Clin Electrophysiol 1994;17:1751-60.
1012. Hautvast RW, Blanksma PK, DeJongste MJ, et al. Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. Am J Cardiol 1996;77:462-7.
1013. Greco S, Auriti A, Fiume D, et al. Spinal cord stimulation for the treatment of refractory angina pectoris: a two-year follow-up. Pacing Clin Electrophysiol 1999;22:26-32.
1014. Arora RR, Chou TM, Jain D, et al. The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999;33:1833-40.
1015. Barsness G, Feldman AM, Holmes DR Jr, Holubkov R, Kelsey SF, Kennard ED. The International EECP Patient Registry (IEPR): design, methods, baseline characteristics, and acute results. Clin Cardiol 2001;24:435-42.
1016. Lawson WE, Hui JC, Lang G. Treatment benefit in the enhanced external counterpulsation consortium. Cardiology 2000;94:31-5.
1017. Aaberge L, Nordstrand K, Dragsund M, et al. Transmyocardial revascularization with CO2 laser in patients with refractory angina pectoris. Clinical results from the Norwegian randomized trial. J Am Coll Cardiol 2000;35:1170-7.
1018. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med 1999;341:1029-36.
1019. Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. N Engl J Med 1999;341:1021-8.
1020. Held C, Hjemdahl P, Hakan WN, et al. Inflammatory and hemostatic markers in relation to cardiovascular prognosis in patients with stable angina pectoris. Results from the APSIS study. The Angina Prognosis Study in Stockholm. Atherosclerosis 2000;148:179-88.
1021. Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial. Lancet 1999;353:519-24.
1022. Horvath KA, Smith WJ, Laurence RG, Schoen FJ, Appleyard RF, Cohn LH. Recovery and viability of an acute myocardial infarct after transmyocardial laser revascularization. J Am Coll Cardiol 1995;25:258-63.
1023. Yamamoto N, Kohmoto T, Gu A, DeRosa C, Smith CR, Burkhoff D. Angiogenesis is enhanced in ischemic canine myocardium by transmyocardial laser revascularization. J Am Coll Cardiol 1998;31:1426-33.
1024. Kwong KF, Kanellopoulos GK, Nickols JC, et al. Transmyocardial laser treatment denervates canine myocardium. J Thorac Cardiovasc Surg 1997;114:883-9.
1025. STS National Database. The Society of Thoracic Surgeons Web site. Available at: http://www.sts.org.
1026. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med 1999;341:70-6.
1027. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. BMJ 2000;321:73-7.
1028. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol 2000;35:1122-9.
1029. King SB III, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS. Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). J Am Coll Cardiol 2000;35:1116-21.
1030. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-24.
1031. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. Circulation 1989;79:1171-9.
1032. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 2001;37:2215-38.
1033. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: a report of the

American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999;34:1262-347.

1034. Campeau L. Grading of angina pectoris [letter]. Circulation 1976;54:522-3.
1035. Wiklund I, Comerford MB, Dimenas E. The relationship between exercise tolerance and quality of life in angina pectoris. Clin Cardiol 1991;14:204-8.
1036. Marquis P, Fayol C, Joire JE. Clinical validation of a quality of life questionnaire in angina pectoris patients. Eur Heart J 1995;16:1554-60.
1037. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation 1981;64:1227-34.
1038. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:651-4.
1039. Hillers TK, Guyatt GH, Oldridge N, et al. Quality of life after myocardial infarction. J Clin Epidemiol 1994;47:1287-96.
1040. Valenti L, Lim L, Heller RF, Knapp J. An improved questionnaire for assessing quality of life after acute myocardial infarction. Qual Life Res 1996;5:151-61.
1041. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993;118:577-81.
1042. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456-62.
1043. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med 1996;156:286-9.
1044. Chaturvedi N, Sjolie AK, Stephenson JM, et al. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. Lancet 1998;351:28-31.
1045. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52.
1046. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.
1047. Zuanetti G, Latini R, Maggioni AP, Franzosi M, Santoro L, Tognoni G. Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study. Circulation 1997;96:4239-45.
1048. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol 1996;77:1017-20.
1049. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-6.
1050. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.
1051. Allen KB, Dowling RD, DelRossi AJ, et al. Transmyocardial laser revascularization combined with coronary artery bypass grafting: a multicenter, blinded, prospective, randomized, controlled trial. J Thorac Cardiovasc Surg 2000;119:540-9.
1052. Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001;104:1577-9.