Guidelines for the Management of Patients with Chronic Stable Angina: Diagnosis and Risk Stratification

Sankey V. Williams, MD; Stephan D. Fihn, MD, MPH; and Raymond J. Gibbons, MD*

Patients with suspected chronic stable angina can be evaluated in three stages. In stage one, the clinician uses information from the history, physical examination, laboratory tests for diabetes and hyperlipidemia, and resting electrocardiography to estimate the patient's probability of coronary artery disease (CAD). In stage two, additional testing for patients with a low probability of CAD focuses on diagnosing noncoronary causes of chest pain. Patients with a high probability of CAD have stress tests to assess their risk from CAD, and patients with an intermediate probability of CAD have stress tests to estimate the probability of CAD and assess their risk from CAD. Most patients with new-onset angina can start stress testing with exercise electrocardiography. The initial stress test should be a stress imaging procedure for patients with rest ST-segment depression greater than 1 mm, complete left bundle-branch block, ventricular paced rhythm, preexcitation syndrome, or previous revascularization with percutaneous coronary angioplasty or coronary artery bypass grafting. Patients who cannot exercise can have an imaging procedure with stress induced by pharmacologic agents. In stage three, patients with a predicted average annual cardiac mortality rate between 1% and 3% should have a stress imaging study or coronary angiography with left ventriculography. Those with a known left ventricular dysfunction should have cardiac catheterization. Patients with CAD who have an estimated annual mortality rate greater than 3% should have cardiac catheterization to determine whether their anatomy is suitable for revascularization. Patients with an estimated annual mortality rate less than 1% can begin to receive medical therapy.

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For author affiliations and current addresses, see end of text.
See editorial comment on pp 527-529.

This article is the first of two papers about the care of patients with chronic stable angina. The second paper, which deals with the treatment of patients with chronic stable angina, will be published in a future issue. Both articles have been adapted from materials created by the Committee on Guidelines for Chronic Stable Angina sponsored by the American College of Cardiology (ACC), the American Heart Association (AHA), and the American College of Physicians–American Society of Internal Medicine (ACP–ASIM) (1–3). The adaptations in these articles are intended to make the information more useful for clinicians who do not specialize in the care of patients with heart disease.

The committee created the original materials after reviewing published reports identified in part through MEDLINE searches of the English literature from 1975 through 1998. The weight of the evidence was ranked high and given a grade of A if the data were derived from multiple randomized clinical trials involving many patients. The weight of the evidence was ranked intermediate and given a grade of B if the data were derived from a few randomized trials involving small numbers of patients, nonrandomized studies, or observational registries. A lower rank and a grade of C were given when an expert consensus was the primary basis for the recommendation.

We used the following classification system for final recommendations. Class I referred to conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective; class II referred to conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment; class IIa referred to conditions for which the weight of evidence or opinion is in favor of usefulness or efficacy of a procedure or treatment; class IIb referred to conditions for which usefulness or efficacy of a procedure or treatment is less well established by evidence or opinion; and class III referred to conditions for which there is evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

For the sake of brevity, we have combined some original recommendations and omitted others, especially

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those that affect fewer patients, are based on weaker evidence, or recommend that interventions not be done.

Scope of the Guidelines

These recommendations are intended for adult patients with stable chest pain syndromes and known or suspected ischemic heart disease and patients who have "ischemic equivalents," such as dyspnea or arm pain with exertion. Also, some recommendations about follow-up apply to patients who become asymptomatic during therapy. These guidelines are not intended for patients with acute ischemic syndromes, patients with chest pain after cardiac transplantation, patients with chest pain within 6 months of revascularization by percutaneous techniques or coronary artery bypass grafting (CABG), patients with coronary artery disease (CAD) detected without symptoms, patients with nonanginal chest pain, or pediatric patients.

The Initial Evaluation

The initial evaluation of patients presenting with chest pain includes a detailed history, a focused physical examination, and performance of a few tests and procedures that are useful for estimating the probability of significant CAD (**Figure 1**). *Significant CAD* is defined as an obstruction of at least one major epicardial artery that occupies at least 70% of the artery's cross-sectional diameter or an obstruction of the left main coronary artery that occupies at least 50% of its diameter.

The history should elicit specific information about chest pain because accurate characterization helps determine whether CAD is the cause of angina. Angina usually occurs in patients with CAD, but it can occur in patients with unobstructed coronary arteries who have myocardial ischemia related to an arterial spasm or endothelial dysfunction. It also can occur in patients with other cardiovascular problems, such as aortic stenosis, hypertrophic cardiomyopathy, or uncontrolled hypertension. Symptoms that mimic angina can also occur in patients with noncardiac conditions involving the chest wall, esophagus, or lung.

The following characteristics of chest pain should be determined: quality, location, duration, and the presence of factors that provoke and relieve the pain. Angina is characterized by a substernal pain or discomfort, although it may radiate to the neck, jaw, epigastrium, or arms. Patients often describe the quality of angina with characteristic terms, such as *squeezing*, *grip-like*, *pressure-like*, *suffocating*, or *heavy*. Angina usually lasts for minutes. Exertion or emotional stress provokes it, and rest or nitroglycerin relieves it, typically within 30 seconds to several minutes.

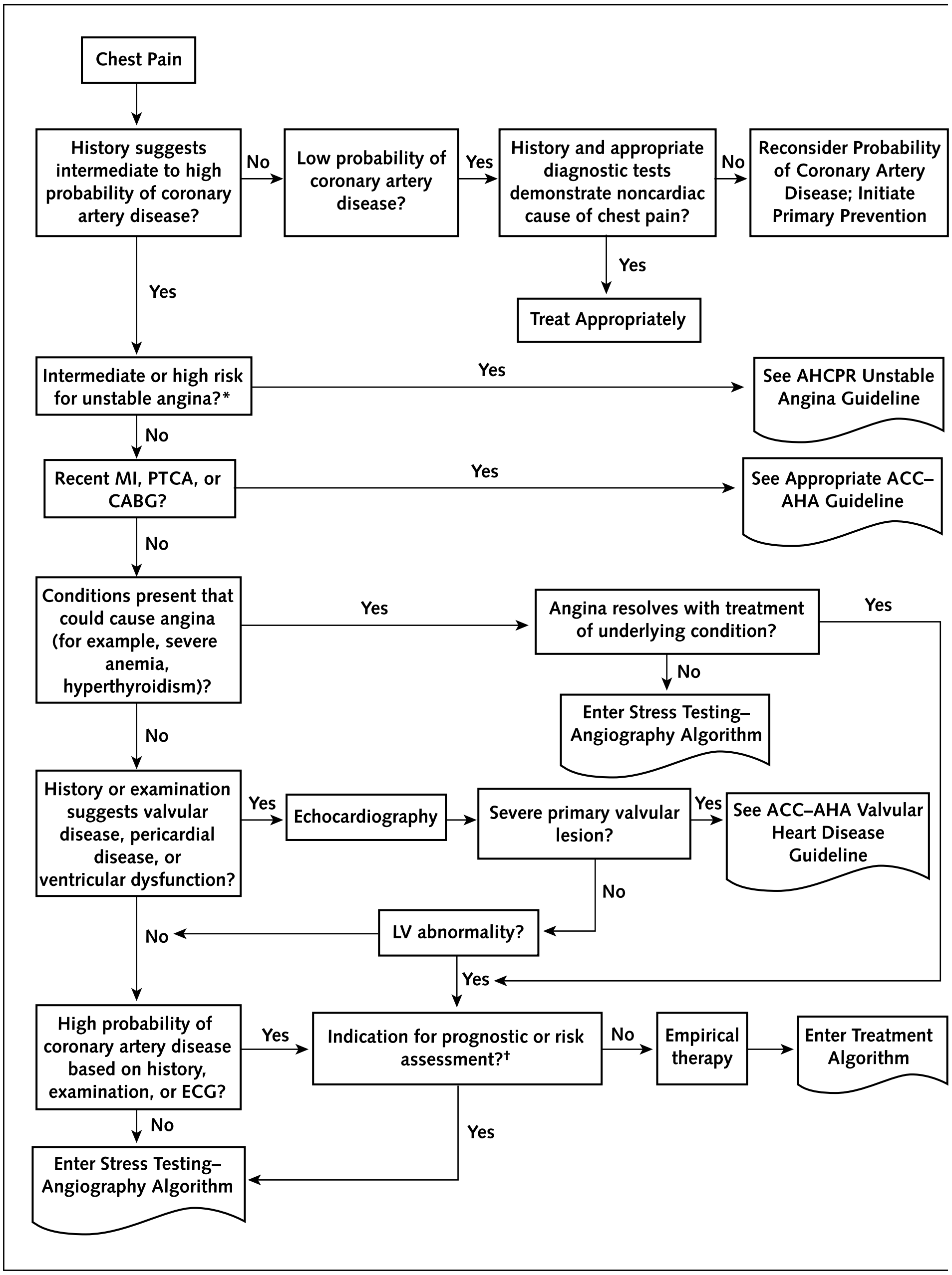
After the history is obtained, the clinician should classify the chest pain. Typical angina has the following characteristics: 1) substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or nitroglycerin. Atypical angina has two of the three characteristics of typical angina, while noncardiac chest pain has one or none of the characteristics of typical angina. The term *noncardiac chest pain* means that the probability of CAD is low. The term *nonspecific chest pain* more accurately describes this situation, but tradition prevents its use.

In patients with angina, the severity of pain should be graded according to the Canadian Cardiovascular Society (CCS) classification system (**Table 1**) (6). Although grading chest pain is less useful for establishing a diagnosis or estimating risk, it is essential for evaluating the effects of therapy.

In patients with angina, the stability of pain should be assessed. Patients have unstable angina if the pain started recently; is more easily provoked; or occurs with increased frequency, severity, or duration (7). Some patients with unstable angina have a measurable risk for short-term death (8). Those characterized as high risk have a 1.7% probability of dying within 30 days, and those characterized as moderate risk have a 1.2% probability. These patients have pain at rest, nocturnal pain, signs or symptoms of heart failure, or new or ischemic changes on resting electrocardiography (ECG). They should be evaluated in the inpatient setting. However, patients with unstable angina whose pain has been present for at least 2 weeks and who lack any of angina's more worrisome clinical features, including ECG changes, can be evaluated in an outpatient setting because their probability of death or myocardial infarction within 30 days is indistinguishable from zero. The initial history should also include information about the risk factors for CAD, such as smoking, hyperlipidemia, diabetes, hypertension, and a family history of premature CAD.

Findings on physical examination are often normal

Figure 1. **Diagnosis of chest pain.**



ACC = American College of Cardiology; AHA = American Heart Association; AHCPR = Agency for Health Care Policy and Research; CABG = coronary artery bypass grafting; ECG = electrocardiography; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty. See references 4 and 5 for the AHCPR Unstable Angina Guideline and the ACC–AHA Valvular Heart Disease Guideline, respectively. * Rest pain lasting more than 20 minutes, age older than 65 years, ST and T-wave changes, and pulmonary edema. † Comorbid conditions and patient preferences.

in patients with stable angina (9). During an episode of pain, however, there uncommonly may be an S_4 or S_3 gallop, a mitral regurgitant murmur, a paradoxically split S_2, bibasilar rales, or a chest wall heave. Each of these findings makes CAD more likely, especially if the finding disappears when the pain goes away (10). Evidence of noncoronary atherosclerotic disease, such as a carotid bruit, diminished pedal pulses, or an abdominal aneurysm, increases the likelihood of CAD. Elevated blood pressure, xanthomas, and retinal exudates identify CAD risk factors.

Table 2 lists recommendations for the tests and procedures that we believe should be used in the initial evaluation of patients with suspected chronic stable angina. Resting, 12-lead ECG should be performed, although the results will be normal in 50% of patients with chronic stable angina (11). Therefore, results on normal resting ECG do not exclude CAD. Evidence on ECG of left ventricular hypertrophy or ST T-wave changes consistent with myocardial ischemia favor the diagnosis of angina (12). The presence of arrhythmias, such as atrial fibrillation or ventricular tachyarrhythmias, also increases the probability of CAD, but other types of cardiac disease frequently cause these arrhythmias. Q waves suggesting a previous myocardial infarction make CAD very likely, although an isolated Q wave in lead III or a QS pattern in lead V_1 and V_2 is often nonspecific. Atrioventricular block may suggest multivessel CAD but is also nonspecific.

Results on ECG performed during chest pain are abnormal in approximately 50% of patients with angina who have normal results on resting ECG. Sinus tachycardia occurs commonly; bradyarrhythmias are less common. ST T-wave depression or inversion on resting ECG or "pseudo-normalization" of these abnormalities during pain is another indicator of CAD (13). Tachyarrhythmias, atrioventricular blocks, left anterior fascicular block, or bundle-branch block occurring with chest pain also increases the probability of coronary heart disease. ST-segment elevation or depression also increases the probability of CAD, and it increases the risk for myocardial infarction or death because there is ischemia at a low workload. Results of chest radiography are often normal in patients with stable angina, and its usefulness as a routine test is not well established.

Ultra-fast electron-beam computed tomography is now frequently used to detect coronary artery calcification, which is a sensitive indicator of coronary stenosis (14). However, the specificity of electron-beam computed tomography is in the range of 41% to 76%, which means that many results are false positive. Moreover, the reliability of serial electron-beam computed tomography examinations varies markedly (15–17). Therefore, the role of electron-beam computed tomography in the diagnosis and monitoring of CAD remains controversial.

Table 1. **Grading of Angina by the Canadian Cardiovascular Society Classification System**

Class	Description
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.
II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
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.
IV	Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.

Rest Echocardiography and Radionuclide Angiography

Neither echocardiography nor radionuclide angiography at rest is necessary in most patients undergoing an evaluation for angina. Transthoracic echocardiographic imaging and Doppler recording are useful when a murmur or other finding suggests aortic stenosis, hypertrophic cardiomyopathy, or other structural cardiac problems that may cause angina without coexisting CAD.

Table 2. **Recommendations for Initial Laboratory Tests, Electrocardiography, and Chest Radiography for the Diagnosis of Chronic Stable Angina***

Class	Recommendations†
I	Hemoglobin (C)
	Fasting glucose (C)
	Fasting lipid panel, including total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol (C)
	Resting ECG in patients without an obvious noncardiac cause of chest pain (B)
	Resting ECG during an episode of chest pain (B)
	Chest radiography in patients with signs or symptoms of congestive heart failure, valvular heart disease, pericardial disease, aortic dissection–aneurysm (B)
IIa	Chest radiography in patients with signs or symptoms of pulmonary disease (B)
IIb	Electron-beam computed tomography (B)
	Resting ECG in patients with an obvious noncardiac cause of chest pain (C)

* ECG = electrocardiography; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† Letters in parentheses represent levels of evidence. See text for details.

Table 3. **Recommendations for Rest Echocardiography or Radionuclide Angiography in Patients with Suspected Chronic Stable Angina**

Class	Recommendations*
I	Echocardiography in patients with a systolic murmur suggestive of aortic stenosis, hypertrophic cardiomyopathy, or mitral regurgitation (C)
	Echocardiography or radionuclide angiography in patients with a history of previous myocardial infarction, pathologic Q waves, or symptoms or signs suggestive of heart failure, to assess left ventricular function (B)
	Echocardiography or radionuclide angiography in patients with complex ventricular arrhythmias, to assess left ventricular function (B)
IIb	Echocardiography in patients with a click or a murmur, to diagnose mitral valve prolapse (C)

* Letters in parentheses represent levels of evidence. See text for details.

Echocardiography is of arguable utility in establishing the presence of a mitral valve prolapse in patients who have an audible click or murmur or who are suspected of having this diagnosis (5).

In patients who do not have signs or symptoms of heart failure, a history of myocardial infarction, or Q waves on ECG, assessing left ventricular function with rest echocardiography or radionuclide angiography is not necessary because results are typically normal without ischemia. For example, more than 90% of patients with normal results on rest ECG have normal left ventricular function (18–20). In patients with heart failure, a history of myocardial infarction, or Q waves, however, measuring the ejection fraction at rest helps with risk stratification (21). For example, a rest ejection fraction less than 0.35 is associated with an annual mortality rate exceeding 3% (22). These procedures also may identify the cause of heart failure. **Table 3** lists recommendations for performing rest echocardiography and radionuclide angiography in patients with chronic stable angina.

COMORBID CONDITIONS

In all patients, and particularly those with typical angina, comorbid conditions that may exacerbate ischemic heart disease or precipitate myocardial ischemia without significant coronary artery obstruction should be identified. These comorbid conditions include such cardiac conditions as tachyarrhythmias, aortic stenosis, and hypertrophic cardiomyopathy. They also include noncardiac conditions, such as anemia, hyperthyroidism, hypoxemia, sickle-cell disease, severe hypertension, and cocaine abuse. Less common conditions are hyperthermia, particularly if accompanied by volume contraction, and conditions associated with hyperviscosity, such as polycythemia, leukemia, thrombocytosis, and hypergammaglobulinemia (23).

ESTIMATING THE PROBABILITY OF CORONARY ARTERY DISEASE

In patients without an obvious, noncardiac cause of chest pain, the probability of significant CAD should be estimated because that estimate is used to guide decisions about performing additional tests and procedures. Estimates of the probability of significant CAD are based primarily on the type of pain and the patient's age and sex (**Table 4**) (24–27). However, other factors increase the probability of CAD, including smoking at least half a pack of cigarettes per day within the past 5 years or smoking for at least 25 pack-years, characteristic changes on resting ECG, a total cholesterol level greater than 6.48 mmol/L (>250 mg/dL), and a fasting glucose level greater than 7.77 mmol/L (>140 mg/dL). Other risk factors, such as family history and hypertension, are not strongly predictive.

Data from different studies yield percentages of CAD that differ slightly from those in **Table 4**, and thus all such estimates are imprecise to some degree. Also, nearly all studies have been based on patients referred to university centers. The only study that compared the probabilities in patients from university centers with the probabilities in patients from primary care practices found good agreement for patients with moderate to high probabilities of CAD. For patients with lower probabilities of CAD, however, the data from university centers overestimated the probability of CAD in patients from primary care practices (25). Therefore, additional caution is necessary when estimating the probability of CAD in patients from primary care practices with lower probabilities of CAD.

Once the probability of CAD has been estimated numerically, that estimate should be characterized as low, intermediate, or high. This characterization is necessary because it is used to decide which additional tests and procedures are needed for diagnosis and risk assessment (**Figure 2**). Some experts believe that patients with probabilities less than 10% should be characterized as having a low probability of CAD, those with probabilities between 10% and 90% should be characterized as having an intermediate probability, and those with probabilities greater than 90% should be characterized as having a high probability. Other experts believe that the cutoff points should result in fewer patients having an intermediate probability of CAD and have suggested a range of 20% to 80%, as well as other ranges. There is disagreement about cutoff values because there is disagreement about the usefulness of additional testing in patients with probabilities near the cutoff values.

Additional Testing

In patients with a low probability of CAD, additional testing should focus on diagnosing noncoronary causes of chest pain. Other patients should enter the testing plan outlined in **Figure 2**, which focuses initially on stress testing. Patients with a high probability of CAD enter this plan to assess their risk from CAD. Patients with an intermediate probability of CAD enter this plan for the combined purposes of diagnosing CAD and assessing their risk from CAD. Whatever the probability of CAD, patients with severe comorbid conditions that are likely to limit life expectancy or prevent revascularization should not undergo further testing for CAD.

The initial stress test can be either exercise ECG or a stress imaging test. With stress imaging, exercise or pharmacologic stress can be used, and imaging can be done with echocardiography or with a myocardial perfusion study using a radionuclide. The choice of an initial stress test should be based, in part, on the patient's results on rest ECG, the patient's use of digoxin, and the patient's ability to exercise; digoxin and some abnormalities on rest ECG complicate interpretation of exercise ECG, and patients who cannot exercise can undergo imaging during pharmacologic stress. Most patients can start with exercise ECG, however, because most patients who present with angina for the first time are not taking digoxin, can exercise, and have normal results on rest ECG (28).

The choice of an initial stress test for patients who can have exercise ECG or cardiac stress imaging is important because the tests have different diagnostic accuracies, predictive powers, and costs. Several studies have examined this issue. One type of study measured outcomes in patients who received both exercise ECG and myocardial perfusion imaging (29–34). Another type of study used models to simulate outcomes with a broader range of tests (35, 36). In both types of studies, imaging resulted in benefit. However, the benefit was modest in all studies and costly in many studies, and the ratio of benefit to cost varied greatly from study to study.

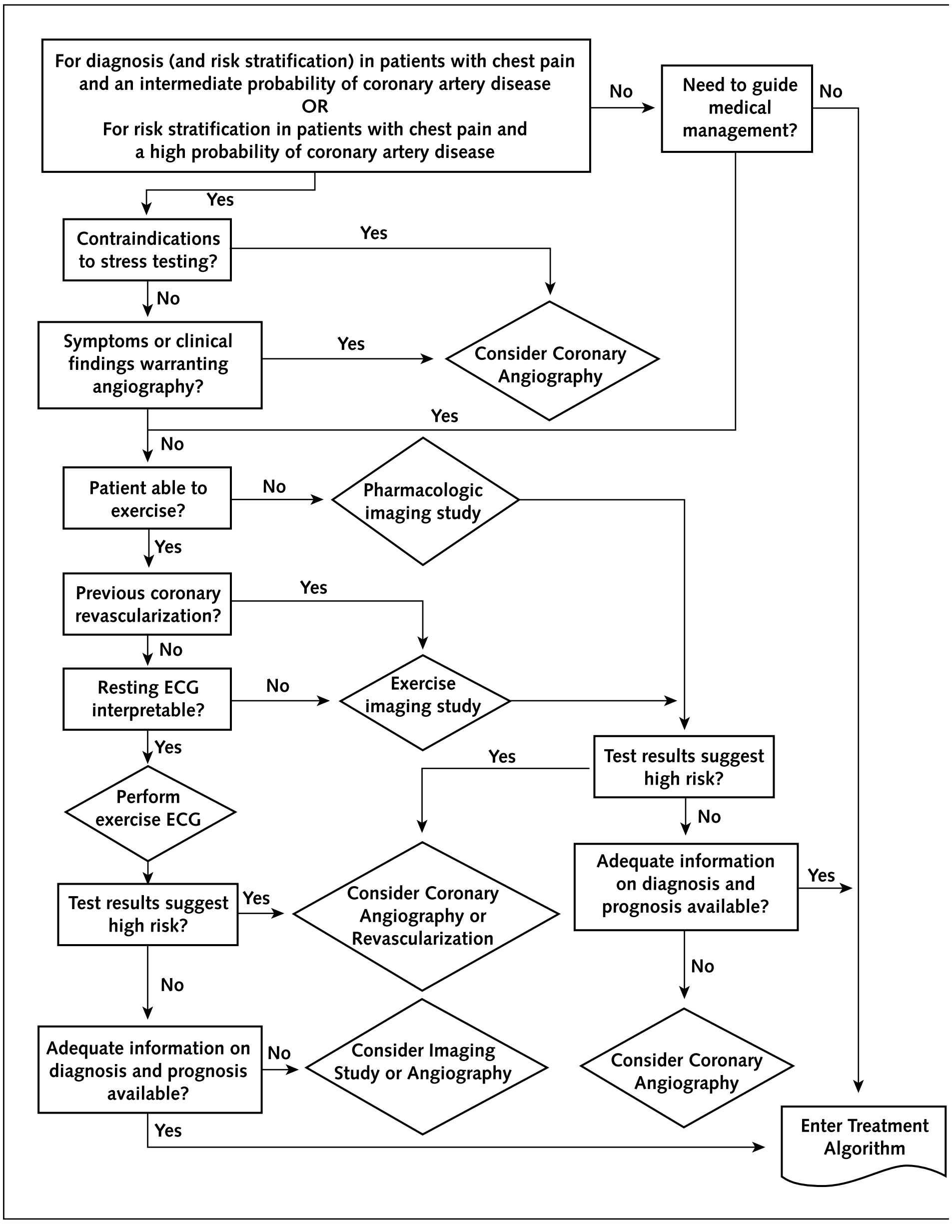
For these reasons, we prefer a stepwise strategy in which exercise ECG is done as the initial test in patients who have normal results on rest ECG, are not taking digoxin, and can exercise. In contrast, the initial test should be a stress imaging procedure for patients with rest ST-segment depression greater than 1 mm, complete left bundle-branch block, ventricular paced rhythm, preexcitation syndrome, or previous revascularization with percutaneous transluminal coronary angioplasty or CABG. Patients who are unable to exercise should undergo pharmacologic stress testing with imag-

Table 4. **Percentage of Patients with Coronary Artery Disease in University Centers***

Age	Nonanginal Chest Pain				Atypical Angina				Typical Angina			
	Men with CAD without Diabetes, Smoking, or Hyperlipidemia	Men with CAD with Diabetes, Smoking, and Hyperlipidemia	Women with CAD without Diabetes, Smoking, or Hyperlipidemia	Women with CAD with Diabetes, Smoking, and Hyperlipidemia	Men with CAD without Diabetes, Smoking, or Hyperlipidemia	Men with CAD with Diabetes, Smoking, and Hyperlipidemia	Women with CAD without Diabetes, Smoking, or Hyperlipidemia	Women with CAD with Diabetes, Smoking, and Hyperlipidemia	Men with CAD without Diabetes, Smoking, or Hyperlipidemia	Men with CAD with Diabetes, Smoking, and Hyperlipidemia	Women with CAD without Diabetes, Smoking, or Hyperlipidemia	Women with CAD with Diabetes, Smoking, and Hyperlipidemia
y	←					%						→
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

* All values refer to patients with normal results on resting electrocardiography. If ST T-wave changes or Q waves are present on resting electrocardiography, each value should be increased. CAD = coronary artery disease.

Figure 2. **Stress testing and angiography.**



ECG = electrocardiography.

ing. For women, the optimal testing strategy is less well defined; however, until adequate data are available to resolve this issue, it is reasonable to use the same strategy in women.

Exercise Electrocardiography Testing

Exercise ECG testing plays a central role in the evaluation of chest pain. Although it is generally safe, both myocardial infarction and death occur during or immediately after testing at a rate of up to 1 per 2500 tests (37). The absolute contraindications to exercise testing include acute myocardial infarction within 2 days, cardiac arrhythmias causing symptoms or hemodynamic compromise, symptomatic or severe aortic stenosis, and symptomatic heart failure (38, 39). Relative contraindications include left main coronary stenosis, electrolyte abnormalities, systolic blood pressure exceeding 200 mm Hg, diastolic blood pressure exceeding 110 mm Hg, arrhythmias, hypertrophic cardiomyopathy and other forms of outflow tract obstruction, and high-degree atrioventricular blocks. Exercise testing (40–42) and pharmacologic testing (43–45) are safe in outpatients with unstable angina if they are low risk. They are safe in patients hospitalized with unstable angina if the patients are low or intermediate risk, if myocardial infarction has been ruled out, and they do not have congestive heart failure.

Although bicycle devices are available, treadmills are more commonly used in the United States. A customized protocol that enables the patient to exercise for 6 to 12 minutes is desirable (46).

The person interpreting the test results should report the patient's symptomatic response, exercise capacity in metabolic equivalents (METs), systolic blood pressure, heart rate, and electrocardiographic response. The occurrence of ischemic chest pain consistent with angina is important, particularly if it forces termination of the test. The most important electrocardiographic findings are ST-segment depression and ST-segment elevation. The most commonly used definition for a positive result on exercise testing is greater than or equal to 1 mm of horizontal or downsloping ST-segment depression or elevation for at least 60 to 80 milliseconds after the end of the QRS complex (47).

The results of exercise ECG testing are less accurate than many clinicians believe. In a meta-analysis of 147 published reports describing 24 074 patients, the mean sensitivity of exercise ECG was 68% and the mean specificity was 77%, although there was wide variation (38). Sensitivity and specificity are lower when the test is done only in patients without a previous myocardial infarction. These measures of test performance are biased, however, because patients who had a positive test result were more likely to have angiography than patients with a negative test result. When studies that avoid this type of bias are considered, the sensitivity is even lower (45% to 50%) but the specificity is higher (85% to 90%) (48–50). Therefore, the true diagnostic value of exercise ECG lies in its high specificity: It yields few false-positive results.

Besides its role in diagnosing CAD, exercise ECG also provides information about the patient's prognosis (51–57). This information is summarized in the Duke treadmill score, which predicts the patient's risk for death (53, 58). The Duke treadmill score equals the exercise time in minutes minus five times the ST-segment deviation (during or after exercise, in mm) minus four times the angina index (0 if there is no angina, 4 if angina occurs, and 8 if angina is the reason for stopping the test).

Table 5. **Annual Mortality Rate according to Risk Groups, Based on Duke Treadmill Scores***

Risk Group (Duke Treadmill Score)	Proportion of Total	Annual Mortality Rate
	%	
Low (≥5 or >4)	62	0.25
Moderate (−10 to 4)	34	1.25
High (<−10)	4	5.0

* The Duke treadmill score equals the exercise time in minutes minus (five times the ST-segment deviation, during or after exercise, in millimeters) minus (four times the angina index [0 if there is no angina, 4 if angina occurs, and 8 if angina is the reason for stopping the test]).

Among outpatients with suspected CAD, patients with scores indicating low risk had an average annual mortality rate of 0.25% and those with scores indicating high risk had an annual mortality rate of 5% (**Table 5**). The score works well for both inpatients and outpatients, and preliminary data suggest that the score works equally well for men and women (58–60). Only a few elderly patients have been studied, however.

In patients who are found to have an intermediate risk for myocardial infarction or death after exercise ECG, cardiac stress imaging seems useful for further risk stratification, although only myocardial perfusion imaging has been studied in patients divided into risk groups (59, 61). Routine cardiac stress imaging of patients with a high-risk exercise ECG score may identify enough low-risk patients who can avoid cardiac catheterization to justify the cost of routine imaging, but further study is required. Fewer than 5% of patients who have a low-risk exercise ECG score will be identified as high risk after cardiac stress imaging. Thus, the cost of identifying these patients argues against routine imaging.

Several factors can affect the results of exercise ECG testing. Digoxin produces exercise-induced ST-segment depression in 25% to 40% of apparently healthy persons, with a higher prevalence in the elderly (62). β-Blockers (and other anti-ischemic drugs) may lead to false-negative test results, particularly in low-risk patients, and should be withheld whenever possible for

Table 6. **Recommendations for Exercise Electrocardiography without Imaging***

Class	Recommendations†
I	For the diagnosis of CAD in patients with an intermediate probability of CAD based on age, sex, and symptoms, including those with complete right bundle-branch block or with <1 mm of resting ST-segment depression (exceptions are listed below in classes IIb and III) (B)
	For risk assessment and prognosis in the initial evaluation of patients with an intermediate or high probability of CAD based on age, sex, and symptoms (exceptions are listed below in classes IIb and III) (B)
IIa	For diagnosis in patients with suspected vasospastic angina (C)
IIb	For diagnosis in patients with a high probability of CAD according to age, sex, and symptoms (B)
	For diagnosis in patients with a low probability of CAD according to age, sex, and symptoms (B)
	For diagnosis in patients taking digoxin whose ECGs show <1 mm of baseline ST-segment depression (B)
	For diagnosis in patients with ECG criteria for left ventricular hypertrophy and <1 mm of baseline ST-segment depression (B)
III	For diagnosis in patients with the following baseline ECG abnormalities
	Preexcitation (Wolff–Parkinson–White) syndrome (B)
	Electronically paced ventricular rhythm (B)
	>1 mm of resting ST-segment depression (B)
	Complete left bundle-branch block (B)‡
	For risk assessment and prognosis in patients with severe comorbid conditions that are likely to limit life expectancy or prevent revascularization (C)

* CAD = coronary artery disease; ECG = electrocardiography.
† Letters in parentheses represent levels of evidence. See text for details.
‡ Although exercise ECG testing cannot diagnose CAD in these patients, the patient's exercise capacity during testing can be used for risk assessment and prognosis.

four to five half-lives (usually about 48 hours) before exercise stress testing. Antihypertensives and vasodilators can alter hemodynamic responses, and nitrates can attenuate angina and ST-segment depression. Exercise-induced ST-segment depression usually occurs with a left bundle-branch block and has no association with ischemia (63). Exercise-induced ST-segment depression in the anterior chest leads (V_{1-3}) usually occurs with a right bundle-branch block and has no association with ischemia (64), but depression in the left chest leads ($V_{5,\ 6}$) or inferior leads (II, aVF) does suggest ischemia. Left ventricular hypertrophy with repolarization abnormality on resting ECG makes the exercise test less specific. In patients with ST-segment depression on resting ECG that is less than or equal to 1 mm, additional exercise-induced ST-segment depression is a reasonably sensitive indicator of CAD.

Special considerations apply to specific groups of patients undergoing exercise ECG. Exercise testing is less sensitive and possibly less specific in women than in men (38, 49, 65–75). Moreover, because CAD is generally less prevalent in women, the false-positive rate of exercise ECG is much higher, approaching 50%, especially among premenopausal women (76).

Exercise testing in elderly patients poses several problems (77–80). Muscle weakness and deconditioning reduce functional capacity and induce patients to hold the handrails tightly, which may invalidate the calculations for METs performed. Impaired gait and coordination require less challenging protocols. Frequent abnormalities on resting ECG complicate the interpretation of results, and arrhythmias during testing are more frequent in elderly patients, especially at higher workloads. The false-positive rate is higher and the specificity is lower in elderly patients than in younger patients, although the sensitivity is higher.

Recommendations for exercise ECG in the diagnosis and risk stratification of patients with chronic stable angina are listed in **Table 6**.

Cardiac Stress Imaging

Cardiac stress imaging involves echocardiography or myocardial perfusion imaging (81–83). In both procedures, the images are obtained during rest and during stress. Also, both procedures can measure the extent of coronary artery involvement, but stress echocardiography does this by measuring regional wall motion and stress myocardial perfusion imaging does this by measuring regional blood flow.

Patients who cannot exercise can be stressed with pharmacologic agents. Such pharmacologic agents as dobutamine increase cardiac contractility and heart rate, which provokes regional wall abnormalities in regions supplied by obstructed arteries. Other agents, such as dipyridamole and adenosine, dilate normal coronary arteries more than partially obstructed ones to accentuate any differences in blood flow (21, 84–88). Whenever possible, exercise should be used because it provides more information than pharmacologic stress (38). In fact, the inability to do an exercise test is itself a negative prognostic factor.

The most commonly used tracers for myocardial perfusion imaging are ^{201}thallium and ^{99m}technetium, including the technetium-labeled agent sestamibi. The views are either three conventional planar views or mul-

Table 7. **Recommendations for Cardiac Stress Imaging in Patients with Chronic Stable Angina***

Variable	Recommendation†
Patients who are able to exercise	
Class I	Exercise myocardial perfusion imaging or exercise echocardiography to identify the extent, severity, and location of ischemia in patients who do not have left bundle-branch block or an electronically paced ventricular rhythm and have abnormal results on rest ECG or are using digoxin (B)
	Dipyridamole or adenosine myocardial perfusion imaging in patients with left bundle-branch block or electronically paced ventricular rhythm (B)
	Exercise myocardial perfusion imaging or exercise echocardiography in patients with an intermediate pretest probability of CAD who have preexcitation (Wolff–Parkinson–White) syndrome or >1 mm of rest ST-segment depression (B)
	Exercise myocardial perfusion imaging or exercise echocardiography in patients with previous PTCA or CABG (B)
Class IIb	Exercise or dobutamine echocardiography in patients with left bundle-branch block (C)
	Exercise, dipyridamole, or adenosine myocardial perfusion imaging or exercise or dobutamine echocardiography as the initial stress test in patients who have normal results on rest ECG and are not taking digoxin (B)
Class III	Exercise myocardial perfusion imaging in patients with left bundle-branch block (C)
	Exercise, dipyridamole, or adenosine myocardial imaging or dobutamine echocardiography for risk stratification in patients with severe comorbid conditions that are likely to limit life expectancy or prevent revascularization (C)
Patients who are unable to exercise	
Class I	Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with an intermediate pretest probability of CAD (B)
	Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with previous revascularization (PTCA or CABG) (B)
	Adenosine or dipyridamole 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 (B)
	Adenosine or dipyridamole myocardial perfusion imaging in patients with left bundle-branch block or electronically paced ventricular rhythm (B)
Class IIb	Dobutamine echocardiography in patients with left bundle-branch block (C)
Class III	Adenosine or dipyridamole myocardial perfusion imaging or dobutamine echocardiography in patients with severe comorbid conditions that are likely to limit life expectation or prevent revascularization (C)

* CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiography; PTCA = percutaneous transluminal coronary angioplasty.
† Letters in parentheses represent levels of evidence. See text for details.

tiple tomographic slices in three planes (single-photon emission computed tomography [SPECT]).

Most studies reporting the sensitivity and specificity of stress imaging do not account for the bias created when patients with positive test results are referred for coronary angiography more frequently than patients with negative test results (89–91). For example, myocardial perfusion imaging with exercise, a thallium tracer, and planar views has higher uncorrected sensitivity and specificity (92–104) than corrected sensitivity and specificity, which are 45% to 68% and 71% to 78%, respectively (105). Myocardial perfusion imaging with exercise, a thallium tracer, and SPECT views has higher sensitivity and lower specificity (95–104), with corrected values of 82% for sensitivity and 59% for specificity (106).

Corrected values are not available for myocardial perfusion imaging with pharmacologic stress. According to uncorrected values, the results of myocardial perfusion imaging are almost as accurate with dipyridamole, a thallium tracer, and planar views as with exercise (107). In addition, myocardial perfusion imaging with dipyridamole, a thallium or sestamibi tracer, and SPECT views seems to be at least as accurate as planar imaging (108–110), although the specificity may be higher (111). The results of myocardial perfusion imaging with adenosine are similar to those obtained with dipyridamole and exercise imaging (112–116).

Corrected values for stress echocardiography are 32% to 42% for sensitivity and 83% to 86% for specificity (117), and the uncorrected values for exercise and dobutamine echocardiography are similar (118).

The prognostic value of stress myocardial perfusion imaging in patients with chronic stable angina has been measured in studies involving 3594 patients followed for a mean of 29 months (38, 119–129). These studies found that patients with normal results after exercise thallium imaging had a rate of cardiac death and myocardial infarction of 0.9% per year, which is nearly as low as that of the general population (130). A more recent prospective study of 5183 consecutive patients followed for a mean of 21 months found that patients

Table 8. **Noninvasive Test Results That Predict the Risk for Death***

High risk (>3% annual mortality rate)
Severe resting left ventricular dysfunction (left ventricular ejection fraction < 0.35)
High-risk exercise ECG score (Duke Score ≤ −10)
Severe left ventricular dysfunction during cardiac exercise imaging (left ventricular ejection fraction < 0.35)
Large perfusion defect during stress myocardial perfusion imaging (particularly if anterior)
Multiple perfusion defects of moderate size during stress myocardial perfusion imaging
Large, fixed defect with left ventricular dilation or increased lung uptake using rest radionuclide angiography with thallium
Moderate defect with left ventricular dilation or increased lung uptake during stress myocardial perfusion imaging with thallium
Defects in >2 segments with a low heart rate (<120 beats/min) or with a low dose of dobutamine (≤10 mg/kg of body weight per minute) during stress echocardiography
Evidence of extensive ischemia during stress echocardiography
Intermediate risk (1% to 3% annual mortality rate)
Mild or moderate resting left ventricular dysfunction (left ventricular ejection fraction, 0.35 to 0.49)
Intermediate risk exercise ECG score (Duke treadmill score, −10 to 4)
Moderate defects without left ventricular dilation or increased lung uptake during stress myocardial perfusion imaging
Limited defects involving ≤2 segments only at doses of dobutamine > 10 mg/kg per minute during stress echocardiography
Low risk (<1% annual mortality rate)
Low-risk exercise ECG score (Duke treadmill score ≥ 5 or > 4)
Normal or small defect at rest or during stress with myocardial perfusion imaging
Normal wall motion or no change in limited wall-motion abnormalities during stress echocardiography

* Each test result is an independent predictor of the risk for death. There is little understanding about how to predict risk by combining test results, except that when more than one test result is present, the result predicting a higher risk should be used to guide decisions.

with normal results after exercise myocardial perfusion tests had an annual rate of less than 0.5% for cardiac death and myocardial infarction (131). Therefore, a normal result after stress myocardial perfusion imaging indicates such a low risk that follow-up cardiac catheterization will not help with risk stratification, except perhaps for patients with a high-risk Duke score after exercise ECG testing.

Although stress myocardial perfusion imaging has been studied more than stress echocardiography, both methods are in widespread use, and a negative result after stress echocardiography also predicts a low risk for cardiovascular events (132–140). A recent study of 1325 patients followed for a median of 23 months found that patients with normal results after exercise echocardiography had an annual rate of 0.9% for myocardial infarction, revascularization, or cardiac death (141), which is similar to rates in people with normal results after exercise myocardial perfusion imaging.

Although echocardiographic and radionuclide stress imaging have complementary roles in estimating the patient's risk and prognosis, there is no reason to do both tests in the same patient. The choice of test depends on the local availability of the tests and the quality of the local expertise in conducting and interpreting them.

Some patients require special consideration. In patients with a left bundle-branch block, pharmacologic myocardial perfusion imaging is preferable to exercise myocardial perfusion imaging, dobutamine echocardiography, or exercise echocardiography (142–145). Although myocardial perfusion imaging is preferred to echocardiography for patients who are obese or who have chest wall deformities or significant lung disease, sestamibi provides better images than thallium in these patients. The sensitivity of perfusion scans may be lower in women than in men (103, 146) because artifacts caused by breast attenuation can complicate interpretation, especially when thallium is used.

Table 7 lists recommendations for stress echocardiography and myocardial perfusion imaging in patients with chronic stable angina.

Coronary Angiography and Left Ventriculography

Some patients require coronary angiography for diagnostic reasons because coronary angiography remains the most accurate procedure for the diagnosis of clinically important obstructive coronary atherosclerosis and also for uncommon, nonatherosclerotic causes of angina, such as coronary artery spasm, coronary anomaly, Kawasaki disease, and primary coronary artery dissection. Its role in the initial diagnosis of CAD, however, has largely been supplanted by noninvasive testing.

Direct referral for diagnostic coronary angiography may still be warranted in special cases (for example, when chest pain may be caused by ischemia and noninvasive testing is contraindicated or unlikely to be satisfactory because of illness, disability, or physical characteristics). Invasive testing may also be reasonable for some high-risk patients in whom results of noninvasive testing are abnormal but not clearly diagnostic or when the patient's occupation or activity could be a risk to themselves or others (for example, pilots, firefighters, and professional athletes).

Other groups also deserve special consideration. Recent studies have shown that women with positive results on exercise ECG or stress thallium examinations are less frequently referred for additional noninvasive testing (4% vs. 20% for men) or coronary angiography (34% vs. 45% for men) (147). It is uncertain what causes these differences and how they affect patient outcomes (148, 149).

In addition, the evaluation of chest pain in elderly persons can be difficult (149–151) because reports of chest discomfort, weakness, and dyspnea are common and comorbid conditions that mimic angina are frequently present. Blunted appreciation of ischemic symptoms is typical with advancing age. Increased frequency of abnormal results on resting ECG and inability to exercise complicate noninvasive diagnostic testing. The high prevalence of disease reduces the value of negative results on a noninvasive test. Also, diagnostic coronary angiography poses little increased risk in elderly patients compared with younger patients. In these circumstances, we believe it is reasonable to use diagnostic coronary angiography more frequently in elderly persons than in younger patients.

Other patients may require coronary angiography for prognosis because the extent and severity of coronary disease identified during coronary angiography and the amount of left ventricular dysfunction identified during left ventriculography are the most powerful clinical predictors of long-term outcomes (152–156). The simplest and most widely used way to describe the extent and severity of coronary disease separates patients into groups with one-vessel, two-vessel, three-vessel, or left main–left anterior descending CAD (157–160). The duration of survival decreases with involvement of additional vessels, and survival decreases even more with disease in the left main–left anterior descending coronary artery and with left ventricular dysfunction (153, 161).

Other patients require angiography because they are candidates for revascularization with either percutaneous techniques or CABG and angiography must be done first to determine whether their anatomy is suitable for revascularization. Such patients include those with angina and clinically evident congestive heart failure and those who have survived sudden death or serious ventricular arrhythmia.

Table 9. **Recommendations for Coronary Angiography with Left Ventriculography in Patients with Chronic Stable Angina***

Class	Recommendations†
I	Patients with disabling (CCS classes III and IV) chronic stable angina despite medical therapy (B)
	Patients with high-risk criteria on noninvasive testing regardless of anginal severity (B)
	Patients with angina who have survived sudden cardiac death or serious ventricular arrhythmia (B)
	Patients with angina and symptoms and signs of congestive heart failure (C)
IIa	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 (C)
	Patients who cannot undergo noninvasive testing because of disability, illness, or obesity (C)
	Patients with an occupational requirement for a definitive diagnosis (C)
	Patients with inadequate prognostic information after noninvasive testing (C)
IIb	Patients with recurrent hospitalizations for chest pain in whom a definite diagnosis is judged necessary (C)
III	Patients with significant comorbidity in whom the risk of coronary arteriography outweighs the benefit of the procedure (C)
	Patients with CCS class I or II angina who respond to medical therapy and have no evidence of ischemia on noninvasive testing (C)
	Patients who prefer to avoid revascularization (C)

* CCS = Canadian Cardiovascular Society.
† Letters in parentheses represent levels of evidence. See text for details.

Many patients who are being evaluated for chronic stable angina, however, are not included in any of these categories. For these patients, the question is whether they should have revascularization or start medical therapy and have revascularization only if medical therapy fails. It is important to refer patients to coronary angiography with left ventriculography when revascularization, if feasible, might improve survival. Such a strategy can be effective, however, only if the patient's prognosis on medical therapy is sufficiently poor that it can be improved with revascularization. Randomized trials of CABG have shown that only patients with a substantial risk for death had a better mortality rate when treated with CABG than when treated with medical therapy (162). Low-risk patients had an annual mortality rate of 1% with either CABG or medical therapy. Therefore, patients with a predicted average cardiac mortality rate of less than 1% per year can be managed medically without the need for cardiac catheterization, at least initially. Patients with a predicted average cardiac mortality rate greater than 3% per year should be referred for cardiac catheterization. Patients with a predicted average cardiac mortality rate of 1% to 3% per year should have either cardiac catheterization or a stress imaging study. Those with known left ventricular dysfunction should have cardiac catheterization.

Table 8 lists the noninvasive test results corresponding to risks for death that are less than 1%, between 1% and 3%, and greater than 3%. These data can be used to guide decisions about the need for cardiac catheterization to evaluate a patient for revascularization that may extend survival. **Table 9** lists our recommendations for performing coronary angiography with left ventriculography in patients with chronic stable angina.

From University of Pennsylvania, Philadelphia, Pennsylvania; VA Puget Sound Health Care System and University of Washington, Seattle, Washington; and Mayo Medical Center, Rochester, Minnesota.

Requests for Single Reprints: Sankey V. Williams, MD, 1220 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021; e-mail, sankey@wharton.upenn.edu.

Current Author Addresses: Dr. Williams: Division of General Internal Medicine, 1220 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021.
Dr. Fihn: VA Puget Sound Hospital, 1660 South Columbian Way (152), Seattle, WA 98108.
Dr. Gibbons: Department of Cardiology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905.

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On the table by the bed in my mother's apartment there were bottles of pills, tablets, capsules, liquid medicines, take this for that and that for this three times a day when it's not four but not when you're driving or operating heavy machinery, take before during and after meals avoiding alcohol and other stimulants and be sure you don't mix your medications, which Mam did, confusing the emphysema pills with pills for the pain of her new hip and the pills that put her to sleep or woke her up and the cortisone that bloated her and caused hair to grow on her chin so that she was terrified to leave the house without her little blue plastic razor in case she might be away awhile and in danger of sprouting all kinds of hair and she'd be ashamed of her life, so she would, ashamed of her life.

Frank McCourt
'Tis: A Memoir
New York: Scribner; 1999:357

Submitted by:
A.M. Clarfield, MD, FRCPC
Sarah Herzog Hospital
Jerusalem 91351, Israel

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