

Guidelines for the Management of Patients with Chronic Stable Angina: Treatment

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

The dual aims of treating patients with chronic stable angina are 1) to reduce morbidity and mortality and 2) to eliminate angina with minimal adverse effects and allow the patient to return to normal activities. In the absence of contraindications, β -blockers are recommended as initial therapy. All β -blockers seem to be equally effective. If the patient has serious contraindications to β -blockers, unacceptable side effects, or persistent angina, calcium antagonists should be administered. Long-acting dihydropyridine and nondihydropyridine agents are generally as effective as β -blockers in relieving angina. Long-acting nitrates are considered third-line therapy because a nitrate-free interval is required to avoid developing tolerance. All long-acting nitrates seem to be equally effective.

Patients with angina should take 75 to 325 mg of aspirin daily unless they have contraindications. Such risk factors as smoking, elevated low-density lipoprotein cholesterol level, diabetes, and hypertension should be treated appropriately.

Coronary revascularization has not been shown to improve survival for most patients with chronic angina but may be required to control symptoms. However, coronary artery bypass grafting

(CABG) is often indicated for symptomatic patients with left-main disease, three-vessel disease, or two-vessel disease including proximal stenosis of the left anterior descending coronary artery; it improves their survival. Percutaneous transluminal coronary angioplasty is an alternative to CABG for patients with normal left ventricular function and favorable angiographic features. Coronary artery bypass grafting is initially more effective in relieving angina than medical therapy, but the two procedures yield similar results after 5 to 10 years. Eighty percent of patients who undergo CABG remain angina-free 5 years after surgery. In low-risk patients, percutaneous transluminal coronary angioplasty seems to control angina better than medical therapy, but recurrent angina and repeated procedures are more likely than with CABG.

Patient education is an important component of management. Long-term follow-up should be individualized to ascertain clinical stability at regular intervals and to reassess prognosis when warranted.

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For author affiliations and current addresses, see end of text.

This paper is the second of two articles about management of chronic stable angina. The first article (1) discussed the diagnosis and risk stratification of patients; this article discusses treatment. Both articles were adapted from materials created by the Committee on Guidelines for Chronic Stable Angina, which was 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) (2, 3). The adaptations in these articles integrate an unusually large amount of recent information and are intended to make the information more useful for clinicians who do not specialize in the care of patients with heart disease.

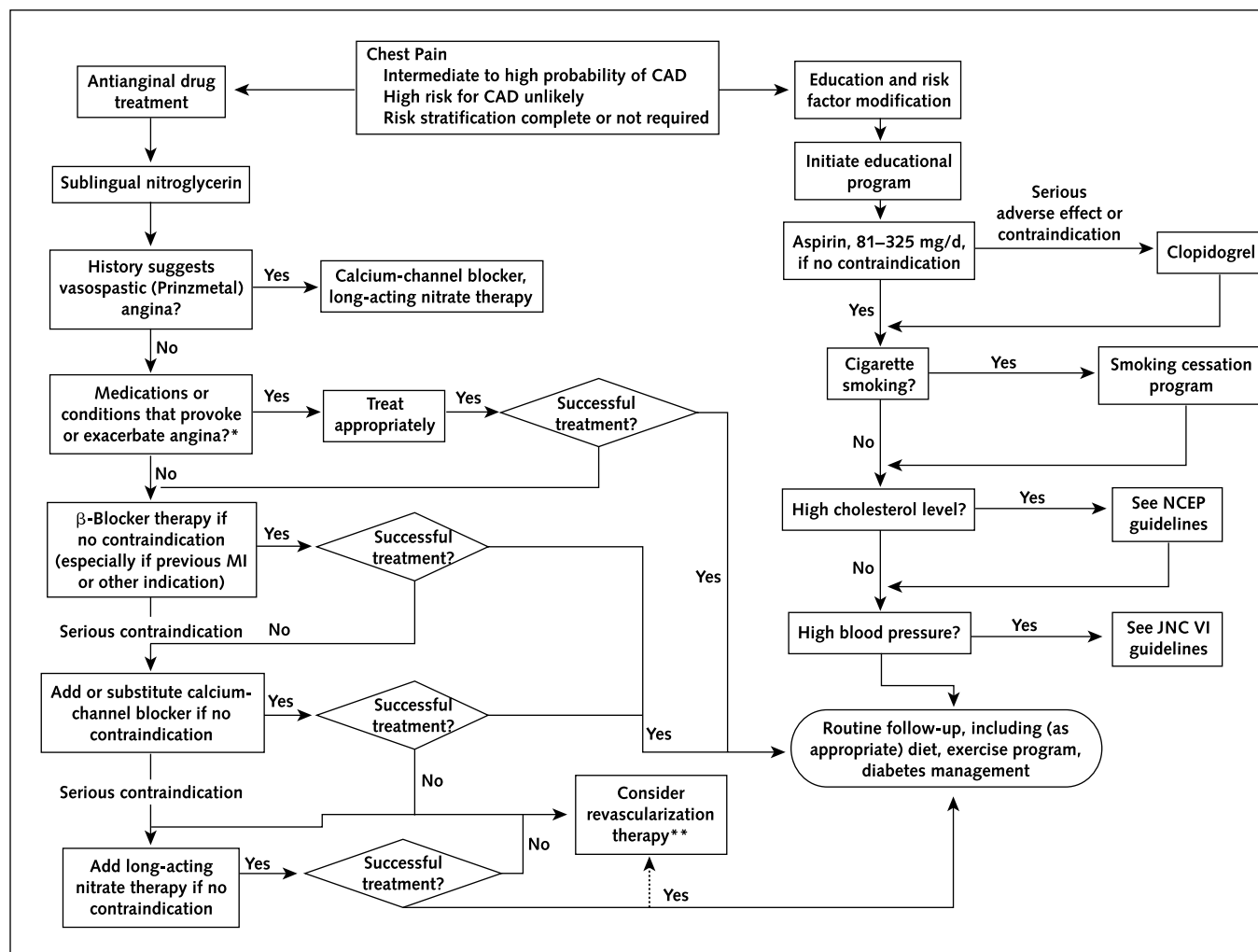
The committee created the original materials after reviewing published reports identified through comprehensive computerized MEDLINE searches of the English literature between 1975 and 1998. Targeted searches

on specific topics were conducted up to October 2000. 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 and efficacy of a procedure or treatment; class IIa referred to conditions for which the weight of evidence and opinion is in

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Figure. Guideline for treatment of chronic stable angina.



CAD = coronary artery disease; JNC = Joint National Committee; MI = myocardial infarction; NCEP = National Cholesterol Education Program. The NCEP and JNC VI guidelines are references 4 and 5, respectively. *Medications: vasodilators, excessive thyroid replacement, and vasoconstrictors; other medical problems: profound anemia, uncontrolled hypertension, hyperthyroidism, and hypoxemia; other cardiac problems: tachyarrhythmias, bradyarrhythmias, valvular heart disease (especially aortic stenosis), and hypertrophic cardiomyopathy. **At any point in this process, on the basis of coronary anatomy, severity of anginal symptoms, and patient preferences, it is reasonable to consider evaluation for coronary revascularization. Unless a patient 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, no demonstrated survival advantage is associated with revascularization in low-risk patients with chronic stable angina; thus, medical therapy should be attempted in most patients before percutaneous transluminal coronary angioplasty or coronary artery bypass surgery is considered.

favor of usefulness of efficacy; class IIb referred to conditions for which usefulness or efficacy was less well established by evidence and 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

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

SCOPE OF 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

Table 1. Properties of β -Blockers in Clinical Use

| Drug | Selectivity | Partial Agonist Activity | Usual Dosage 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/d |
| Nadolol | None | No | 40–80 mg/d |
| Timolol | None | No | 10 mg twice daily |
| Acebutolol | β_1 | Yes | 200–600 mg twice daily |
| Betaxolol | β_1 | No | 10–20 mg/d |
| Bisoprolol | β_1 | No | 10 mg/d |
| Esmolol (intravenous) | β_1 | No | 50–300 μ g/kg of body weight per minute |
| Labetalol* | None | Yes | 200–600 mg twice daily |
| Pindolol | None | Yes | 2.5–7.5 mg 3 times daily |

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

pain with exertion. Also, some recommendations about follow-up apply to patients who become asymptomatic while receiving 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 either 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.

We anticipate that these guidelines will be of greatest use to primary care physicians who regularly manage patients with ischemic heart disease. Cardiac specialists may find the guidelines helpful in summarizing information on controversial topics.

The treatment of patients with stable angina has the dual aims of reducing morbidity and mortality and of alleviating symptoms by reducing ischemia through antianginal treatment and risk factor modification (Figure). For most patients, the goal of treatment should be complete, or nearly complete (that is, Canadian Cardiovascular Society [CCS] class I [6]), elimination of anginal pain with minimal adverse effects and return to normal activities. Other considerations guiding treatment are cost-effectiveness and patient preference.

ANTIANGINAL TREATMENT

The mainstays of antianginal drug therapy are β -adrenoreceptor–blocking agents (β -blockers), calcium antagonists, and nitrates. All patients with angina should receive a prescription for sublingual nitroglycerin and instructions on its use. They should understand that as a

short-acting drug, it may be used frequently without long-term consequences. For patients with vasospastic angina who may have mainly rest and nocturnal angina, long-acting nitrates or calcium antagonists are indicated. Medications or medical conditions that might precipitate angina must be addressed appropriately.

β -Blockers

Absent contraindications, β -blockers should be regarded as initial therapy for stable angina for all patients, including the elderly and those with a history of infarction or revascularization (7). β -Blockers reduce the incidence of cardiac events and improve survival after myocardial infarction (MI) and in hypertensive patients (8). Limited data suggest that this is also true for patients with stable angina who have not had an MI (9–14).

All β -blockers, including those with α - or β -adrenergic antagonist properties, are equally effective in preventing angina and ischemia during exercise (Table 1) (15–20). The β -blocker dose should be adjusted to reduce the resting heart rate to 55 to 60 beats/min, although a lower heart rate is acceptable if tolerated by the patient. Ideally, the dose given should limit the increase in heart rate during exercise to 75% of the rate that provokes ischemia.

The absolute cardiac contraindications to β -blockers are severe bradycardia, high-degree atrioventricular block, the sick sinus syndrome, and severe, unstable left ventricular failure. Asthma, depression, and peripheral vascular disease are relative contraindications and apply only when severe. No convincing evidence shows that diabetic patients tolerate β -blockers less well than other patients. β -Blockers can worsen vasospastic angina (21).

The most common adverse effects are fatigue, a reduction in maximal exercise capacity of up to 15%, lethargy, insomnia, nightmares, and worsening claudication (22). Impotence occurs in 1% of men who take β -blockers, and erectile dysfunction is reported in up to 26% (23). It is unclear, however, how often these common side effects are truly a result of β -blocker therapy.

Calcium Antagonists

If a patient has serious contraindications to β -blockers, if β -blockers cause unacceptable adverse effects, or if they fail to adequately control anginal symptoms, calcium antagonists should be administered as second-line agents. These drugs have a variable, although uniformly

Table 2. Properties of Calcium Antagonists in Clinical Use

| Agent | Usual Dosage | Duration of Action | Adverse Effects |
|-------------------------|--|--------------------|---|
| Dihydropyridines | | | |
| Nifedipine | Immediate release, 30–90 mg/d orally Slow release, 30–180 mg/d orally | Short | Hypotension, dizziness, flushing, nausea, constipation, edema |
| Amlodipine | 5–10 mg/d | Long | Headache, edema |
| Felodipine | 5–10 mg/d | Long | Headache, edema |
| Isradipine | 2.5–10 mg twice daily | Medium | Headache, fatigue |
| Nicardipine | 20–40 mg three times daily | Short | Headache, dizziness, flushing, edema |
| Nisoldipine | 20–40 mg/d | Short | Similar to nifedipine |
| Nitrendipine | 20 mg daily or twice daily | Medium | Similar to nifedipine |
| Miscellaneous | | | |
| Bepidil | 200–400 mg/d | Long | Arrhythmias, dizziness, nausea |
| Diltiazem | Immediate release, 30–80 four times daily Slow release, 120–320 mg/d | Short Long | Hypotension, dizziness, flushing, bradycardia, edema |
| Verapamil | Immediate release, 80–160 mg twice daily Slow release, 120–480 mg/d | Short Long | Hypotension, myocardial depression, heart failure, edema, bradycardia |

negative, inotropic effect and produce peripheral vasodilatation. Among dihydropyridines, nifedipine exerts far more pronounced negative inotropic effects than such newer, relatively vasoselective agents as amlodipine and felodipine (Table 2). Diltiazem and verapamil reduce heart rate by sinus node slowing or by the decreasing ventricular response in atrial flutter or fibrillation.

In six randomized trials involving a combined total of nearly 2000 patients, various calcium antagonists were as effective as β -blockers in relieving angina and improving exercise time (9, 11–14, 24). Nisoldipine, however, seems to be no more effective than placebo (25). Short-acting nifedipine, diltiazem, verapamil, and amlodipine prevented angina completely in 70% of patients with vasospastic angina and substantially reduced its frequency in another 20% (26–28).

Adverse effects of all calcium antagonists include hypotension, peripheral edema, depression of cardiac function, and constipation (29–31) (Table 2). Headache, flushing, and dizziness also occur. Verapamil and diltiazem can cause bradycardia, atrioventricular dissociation, atrioventricular block, and sinus node dysfunction and should not be used in patients with these rhythms. Bepidil can induce polymorphous ventricular tachycardia associated with increased QT interval (32). Decompensated heart failure is a contraindication to calcium antagonists, although some patients with reduced left ventricular function may tolerate vasoselective dihydropyridines.

Substantial data indicate that short- and intermediate-acting dihydropyridine calcium antagonists (nifedipine, diltiazem, verapamil, and nisoldipine) may heighten

the risk for MI by up to 60% (33, 34). Even though some data fail to show this effect, these agents should generally be avoided (35, 36). Compared with β -blockers, the slow-release or long-acting vasoselective calcium antagonists have not been reported to predispose patients to adverse cardiac events, although few patients have been studied to date.

Nitroglycerin and Nitrates

Long-acting nitrates should be considered for patients who cannot tolerate or fail to respond adequately to β -blockers and calcium antagonists. Nitrates reduce preload, dilate coronary arteries (37, 38), and also possess antithrombotic and antiplatelet effects (39). In patients with exertional angina, nitrates improve exercise tolerance and extend the time to onset of angina and ischemia with exertion.

Sublingual tablets or spray are suitable for immediate relief of effort or rest angina and can be used prophylactically before exercise (Table 3). All long-acting nitrates seem equally effective in preventing angina when a sufficient nitrate-free interval is provided (40, 41).

Nitrates are relatively contraindicated in patients with hypertrophic obstructive cardiomyopathy because they can precipitate syncope by aggravating left ventricular outflow tract obstruction and mitral regurgitation. Nitroglycerin can also cause syncope in patients with severe valvular aortic stenosis and should be avoided. Coadministration of nitrates and sildenafil (Viagra [Pfizer Inc., New York, New York]) can cause life-threatening hypotension (42).

The major drawback of long-term nitrate therapy is

the development of tolerance. This can be avoided by ensuring that the patient has no nitrates in his or her system for 8 to 12 hours daily (43). The most common adverse effect is headache, which sometimes abates without discontinuation of therapy. Other adverse effects include hypotension, presyncope, syncope, and, rarely, bradycardia.

Selecting a Therapeutic Regimen

Often, coexisting medical conditions influence the choice of medication (Table 4). Moreover, it is frequently preferable to prescribe a combination of agents. β -Blockers and nitrates are often more effective when used together than when used separately (44–46). β -Blockers attenuate the reflex tachycardia induced by nitrates, while nitrates help to counteract the bradycardia caused by β -blockers. Nitrates are also more effective when combined with calcium antagonists (22, 47–52).

β -Blockers can also be combined with calcium antagonists, especially the slow-release dihydropyridines or newer, long-acting dihydropyridines (53–55). In combination, these drugs generally produce greater relief of angina, reduction in ischemic episodes, and improvement in maximal exercise time (12, 14, 56–61). The tachycardia caused by some calcium antagonists is counteracted by β -blockers. Combining β -blockers with verapamil or diltiazem, however, can induce severe bradycardia, fatigue, or atrioventricular block.

Evaluating the Effectiveness of Medical Therapy

Although the cardinal symptom of stable CAD is anginal chest pain or “anginal equivalent” symptoms, such as exertional dyspnea, some patients may be bothered more by palpitations or syncope caused by arrhythmias or fatigue, edema, or orthopnea due to heart failure. The primary criterion for successful therapy is complete relief of angina, but patients’ unique symptoms, expectations, and preferences must be considered. For example, the treatment goal for an otherwise healthy, active patient should be complete elimination of chest pain and return to vigorous activity. Conversely, a chronically ill, elderly patient with severe angina may be satisfied with a reduction in symptoms that permits performance of limited activities of daily living.

At any point in a patient’s management, it is reasonable to consider percutaneous transluminal coronary angioplasty (PTCA) or CABG on the basis of known or suspected coronary anatomy, severity of symptoms, and the patient’s preferences. Although revascularization prolongs survival for specific small subgroups of patients, most cannot expect improved survival. In patients who cannot expect a survival benefit, medical therapy should usually be attempted before revascularization is considered. Most low-risk patients should be treated with two, and preferably all three, of the available classes of drugs before medical therapy is judged to have failed.

Table 3. Nitroglycerin and Nitrates in Angina

| Compound | Route | Dose/Dosage | Duration of Effect |
|-------------------------|------------------------------|--|------------------------------------|
| Nitroglycerin | Sublingual tablets | 0.3–0.6 mg, up to 1.5 mg | 1.5–7 min |
| | Spray | 0.4 mg as needed | Similar to sublingual tablets |
| | Ointment | 2% 6 × 6 inches, 15 × 15 cm 7.5–40 mg | 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 |
| Isosorbide dinitrate | Intravenous | 5–200 μ g/min | Tolerance in 7–8 h |
| | Sublingual | 2.5–15 mg | Up to 60 min |
| | Oral | 5–80 mg twice daily or three times daily | Up to 8 h |
| | Spray | 1.25 mg/d | 2–3 min |
| | Chewable | 5 mg | 2–2.5 h |
| | Oral slow release | 40 mg daily or twice daily | Up to 8 h |
| | Intravenous | 1.25–5.0 mg/h | Tolerance in 7–8 h |
| Isosorbide mononitrate | Ointment | 100 mg/24 h | Not effective |
| | Oral | 20 mg twice daily 60–240 mg/d | 12–24 h |
| | Pentaerythritol tetranitrate | Sublingual | 10 mg, as needed |
| Erythritol tetranitrate | Sublingual | 5–10 mg, as needed | Not known |
| | Oral | 10–30 mg three times daily | Not known |

Table 4. Recommended Drug Therapy (Calcium Antagonist Compared with β -Blocker) in Patients with Angina and Associated Conditions*

| Variable | Recommended Treatment (and Alternative) | Avoid |
|--|--|---|
| Medical conditions | | |
| Systemic hypertension | β -Blockers (calcium antagonists) | |
| Migraine or vascular headaches | β -Blockers (verapamil or diltiazem) | |
| Hyperthyroidism | β -Blockers | |
| Raynaud syndrome | Long-acting slow-release calcium antagonists | β -Blockers |
| Diabetes mellitus | β -Blockers, particularly in patients with previous MI or long-acting slow-release calcium antagonists | |
| Depression | Long-acting slow-release calcium antagonists | β -Blockers |
| Severe peripheral vascular disease | Calcium antagonists | β -Blockers |
| Cardiac arrhythmias and conduction abnormalities | | |
| Sinus bradycardia | Long-acting calcium antagonists that do not decrease heart rate | β -Blockers, diltiazem, verapamil |
| Sinus tachycardia | β -Blockers | |
| Supraventricular tachycardia | Verapamil, diltiazem, or β -blockers | |
| Atrioventricular block | Long-acting slow-release calcium antagonists that do not slow atrioventricular conduction | β -Blockers, verapamil, diltiazem |
| Rapid atrial fibrillation | Verapamil, diltiazem, or β -blockers | |
| Ventricular arrhythmias | β -Blockers | |
| Left ventricular dysfunction | | |
| Congestive heart failure | | |
| Mild (LVEF \geq 0.4) | β -Blockers | |
| Moderate to severe (LVEF $<$ 0.4) | Amlodipine, felodipine (nitrates), β -blockers | Verapamil, diltiazem |
| Left-sided valvular heart disease | | |
| Mild aortic stenosis | β -Blockers | |
| Aortic insufficiency | Long-acting slow-release dihydropyridines | |
| Mitral regurgitation | Long-acting slow-release dihydropyridines | |
| Mitral stenosis | β -Blockers | |
| Hypertrophic cardiomyopathy | β -Blockers, nondihydropyridine calcium antagonists | Nitrates, dihydropyridine calcium antagonists |

* LVEF = left ventricular ejection fraction; MI = myocardial infarction.

PHARMACOTHERAPY TO PREVENT MYOCARDIAL INFARCTION AND DEATH

Absent contraindications, all patients with ischemic heart disease should take 75 to 325 mg of aspirin daily regardless of cardiac symptoms (62, 63). Aspirin inhibits cyclooxygenase and synthesis of thromboxane A₂ and, in patients with stable angina, reduces the risk for adverse cardiovascular events by approximately 33% (64, 65). In patients with unstable angina, aspirin decreases the short- and long-term risks for fatal and nonfatal MI (66, 67). The beneficial effects of aspirin in preventing MI and sudden death are in addition to the effects of β -blockers (63).

For patients who cannot take aspirin, the thienopyridine derivatives, ticlopidine and clopidogrel, are alternative antiplatelet agents (68–70). Ticlopidine decreases platelet dysfunction in patients with stable angina but, unlike aspirin, does not seem to prevent adverse cardiovascular events (71, 72). It may, however, induce neutropenia and, infrequently, thrombotic thrombocytopenic purpura. Clopidogrel seems to have a greater

antithrombotic effect than ticlopidine and is at least as effective as aspirin in preventing MI and stroke among high-risk patients (73). However, no studies have examined clopidogrel in patients with stable angina.

Although abnormal fibrinolytic function has been observed in patients with chronic stable angina (74), no controlled trials have definitively established the effectiveness of long-term antithrombotic therapy, such as low-molecular-weight heparin, warfarin, or newer antiplatelet and antithrombotic agents such as glycoprotein IIb/IIIa inhibitors and recombinant hirudin (75–77).

MODIFICATION OF RISK FACTORS

Recommendations about treatment of risk factors in patients with chronic stable angina are based largely on inference from observational studies and clinical trials of primary and secondary interventions conducted in the larger population of patients with ischemic heart disease. The clinician should focus on common risk factors for

Table 5. Recommendations for Treatment of Risk Factors*

| |
|--|
| <p>Class I Treatment of hypertension according to Joint National Conference VI guidelines (A) Smoking cessation therapy (B) Management of diabetes (C) Exercise training program (B) Lipid-lowering therapy in patients with documented or suspected CAD and LDL cholesterol level ≥ 3.37 mmol/L (≥ 130 mg/dL), with a target LDL cholesterol level < 2.59 mmol/L (< 100 mg/dL) (A) Weight reduction in obese patients in the presence of hypertension, hyperlipidemia, or diabetes mellitus (C)</p> <p>Class IIa Lipid-lowering therapy in patients with documented or suspected CAD and an LDL cholesterol level of 2.59–3.34 mmol/L (100–129 mg/dL), with a target LDL cholesterol level < 2.59 mmol/L (< 100 mg/dL) (B)</p> <p>Class IIb Hormonal replacement therapy in postmenopausal women in the absence of contraindications (B)</p> |
|--|

* CAD = coronary artery disease; LDL = low-density lipoprotein. Letters in parentheses represent levels of evidence. See text for details.

which interventions have been shown to reduce the incidence of coronary disease events (Table 5).

Cigarette Smoking

Smoking increases cardiovascular death in a dose-dependent fashion; relative risks among heavy smokers approach 5.5 (78–81). Smoking also augments effects of other risk factors (82). Risk for MI decreases rapidly after smoking cessation, whereas patients who continue to smoke have a 22% to 47% increase in risk for reinfarction and death (83). Continued smoking after bypass grafting increases the risk for death, MI, and angina.

Although randomized clinical trials of smoking cessation have not been done in patients with stable angina, studies done in primary prevention settings have shown reductions of 7% to 47% in cardiac event rates (84–86). Patients with symptomatic coronary disease are highly receptive to smoking cessation. Up to 32% of patients stop smoking at the time of a cardiac event, and this rate can be significantly enhanced by use of new behavioral and pharmacologic approaches and involvement of experienced allied health care professionals (87).

Low-Density Lipoprotein Cholesterol Level and Diet

Each 2% to 3% increase in total cholesterol level is associated with a 1% increase in risk for coronary events, beginning at less than 4.65 $\mu\text{mol/L}$ (< 180 mg/dL) (88, 89). Most of the risk is related to low-density lipopro-

tein (LDL) cholesterol. Early trials of bile acid sequestrants (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate), or niacin, in addition to diet, showed reductions of 6% to 15% in total cholesterol level. This finding was associated with a reduction of 2% to 3% in fatal and nonfatal coronary events for every 1% reduction in total cholesterol level (90). More recently, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been shown to reduce mortality rates and clinical events in both primary prevention and secondary prevention settings and to be safe for long-term use (91). In the Scandinavian Simvastatin Survival Study, treatment of patients with documented CAD (including stable angina) resulted in significant changes in total cholesterol level (–25%), LDL cholesterol level (–35%), and high-density lipoprotein (HDL) cholesterol level (8%) that were associated with 30% to 35% reductions in both mortality rates and major coronary events (92). These benefits extended to women, patients older than 60 years of age, and patients with low pretreatment LDL cholesterol values. In the Cholesterol and Recurrent Events (CARE) study, treatment with pravastatin resulted in a 24% reduction in the risk for nonfatal MI or fatal coronary events in patients with previous MI who had low total cholesterol levels (mean, 5.40 $\mu\text{mol/L}$ [209 mg/dL]) and LDL cholesterol levels (mean, 3.59 $\mu\text{mol/L}$ [139 mg/dL]) (93).

Most patients with stable angina should benefit from decreased LDL cholesterol levels, even if they have values considered acceptable for primary prevention. A low-fat, high-fiber diet should be initiated when the LDL cholesterol level exceeds 2.59 $\mu\text{mol/L}$ (100 mg/dL). In three trials, diets that were rich in fiber and antioxidants (88), monounsaturated fat (94), or fish (95) were associated with 32% to 66% reductions in cardiac mortality rates. More research is needed, however, before these diets or diets enriched with other foods should be recommended. Drug treatment is warranted when LDL cholesterol levels are greater than 3.36 $\mu\text{mol/L}$ (130 mg/dL). The goal of treatment is an LDL cholesterol level of 2.59 $\mu\text{mol/L}$ (100 mg/dL) or less.

Although earlier data demonstrated that lipid-lowering therapy induced angiographic stabilization or regression of coronary lesions, it is now evident that despite aggressive reduction of LDL cholesterol levels, progression continues in 25% to 60% of patients.

Hypertension

The incidence of coronary events is strongly related to blood pressure (96–98) and is reduced by antihypertensive treatment (99), particularly in elderly persons (100) as well as patients with chronic stable angina (5, 101–103). Blood pressure should be decreased to below 130/85 mm Hg in patients with coronary disease and diabetes, heart failure, or renal failure, or below 140/90 mm Hg in patients who have coronary disease without these coexisting conditions (101). Changes in lifestyle and diet should be used initially, but if blood pressure remains elevated, medication should be prescribed. β -Blockers or calcium-channel antagonists are especially useful for patients with angina. Short-acting calcium antagonists should be avoided (33, 34, 102).

β -Blockers without intrinsic sympathomimetic activity are recommended for patients with stable angina who have had previous MI; they reduce the risk for subsequent MI and sudden cardiac death. Angiotensin-converting enzyme (ACE) inhibitors are also recommended in hypertensive patients with left ventricular systolic dysfunction or diabetes (101, 104). If β -blockers are contraindicated or do not control blood pressure or anginal symptoms, verapamil or diltiazem may be considered because they modestly reduce cardiac events and mortality rates after non-Q-wave MI or MI with preserved left ventricular function (105–107).

Diabetes Mellitus

Defined as a fasting blood glucose level exceeding 6.99 mmol/L (>126 mg/dL) (108), diabetes increases the risk for coronary death threefold to tenfold in patients with type 1 diabetes and twofold to fourfold in those with type 2 diabetes (109–111). Approximately 25% of all MIs in the United States occur in diabetic patients, and outcomes are worse than in patients without diabetes (112–114). Although there is currently no direct evidence of benefit, it is reasonable to pursue strict glycemic control in diabetic patients with stable angina in the hope that the known lower risk for microvascular complications in patients with type 1 diabetes might be present for cardiovascular complications (110, 115–117). Of course, hypertension, obesity, and elevated LDL cholesterol levels should be managed aggressively.

High-Density Lipoprotein Cholesterol

It is estimated that a 1-mg/dL decrease in HDL cholesterol level translates into a 2% to 3% increase in risk for coronary events (118). Levels of HDL cholesterol below 0.91 μ mol/L (<35 mg/dL) are common in patients with obesity, diabetes, smoking, high LDL cholesterol levels, and physical inactivity (119). Therefore, diet, weight loss, and exercise should be recommended to patients with coronary disease and low HDL cholesterol levels. In one randomized trial (120), patients with known coronary heart disease, HDL cholesterol levels below 1.03 μ mol/L (<40 mg/dL), and LDL cholesterol levels below 3.62 μ mol/L (140 mg/dL) were given gemfibrozil. Over 5 years, the relative risk for MI or cardiovascular death decreased by 22%, even though LDL cholesterol values did not change significantly (120). When clinically indicated, drug therapy should be directed at the entire lipid profile. Nicotinic acid and fibrates can appreciably increase HDL cholesterol levels, while HMG-CoA reductase inhibitors and estrogen replacement therapy do so to a lesser degree.

Exercise and Weight Reduction

Exercise training has usually been studied as part of a multifactorial risk factor reduction effort, making its independent contribution difficult to quantify. Training significantly enhances exercise tolerance (89, 121–127) and modestly improves symptoms and ischemia in men with stable angina (89, 123, 126, 128). Women may benefit equally as much (129–131). Patients with previous MI derive a 20% to 30% reduction in cardiac deaths from exercise training (132, 133), but no reduction in nonfatal MI. Although it is uncertain whether these results can be extrapolated to patients with stable angina and no history of MI, such patients should still be counseled to undertake an exercise program. The risk for serious cardiac events during cardiac rehabilitation is very low (133, 134).

Obesity is associated with increased risk for coronary disease and death (135). Absent data from clinical trials, it is nonetheless reasonable to recommend weight reduction to obese patients with coronary disease, if only to favorably affect other risk factors (for example, hypertension, glucose intolerance, and low levels of HDL cholesterol). Counseling from a dietitian may be helpful to many patients.

Other Putative Risk Factors

Several other potentially modifiable risk factors have been studied in patients with CAD, but not specifically in patients with stable angina. Women who become menopausal, either naturally or surgically, are at risk for accelerated CAD (136). Despite the favorable effects of hormone replacement on LDL and HDL cholesterol (137–139) and extensive observational data indicating a lower risk for MI (140–142), the first randomized trial performed showed no reduction in cardiovascular events in women with known CAD during 4 years of follow-up (143). Data from this trial and a longitudinal cohort study suggest an increase in recurrent coronary events shortly after the initiation of hormone replacement therapy (144). However, more definitive assessment of the effects of hormone replacement on CAD must await the results of ongoing trials. In the interim, the decision to initiate hormone replacement therapy must be based on other factors and discussed thoroughly with each patient.

No evidence shows that stress reduction programs improve prognosis in patients with stable angina, but anxiety disorders and depression should be appropriately treated (145, 146).

Although triglyceride levels predict CHD risk (147), it is not clear whether this is a direct relationship or whether treatment directed at high triglyceride levels will reduce risk for initial or recurrent CHD events. Hypertriglyceridemia should be treated in accordance with national recommendations (4). Lipoprotein(a) has been linked to CHD risk (148–150), but no prospective intervention trial has specifically studied the effects of lipoprotein(a) lowering. Elevated levels of homocysteine are associated with increased risk for atherosclerosis and CAD (151–153). Although supplementation with vitamins B₆, B₁₂, and folic acid usually decreases homocysteine levels, clinical trials are needed to test whether such treatment is beneficial. Similarly, although treatment with antioxidants, such as vitamin C, β -carotene, and probucol, is promising, substantiation of benefit is required before it can be adopted into clinical practice. Treatment with vitamin E does not seem to be beneficial (154, 155).

REVASCULARIZATION

Coronary artery bypass grafting is performed by using saphenous vein or arterial grafts, usually in the internal thoracic (mammary) artery. Even with use of

platelet inhibitors, the incidence of vein graft thrombosis is 6% to 11% in the first postoperative year (156–158). Subsequent atherosclerotic occlusion may occur despite aggressive lipid-lowering therapy (159). Arterial grafts occlude much more slowly; approximately 10% are occluded at 10 years after surgery (160, 161).

Performed with an inflatable balloon, PTCA has the advantages of relative safety, short hospital stays, early return to activity, and the capacity to perform multiple procedures. The main disadvantages of PTCA are 1) it carries a small risk for acute coronary occlusion, 2) many patients are not anatomically suitable, and 3) restenosis occurs in 30% to 40% of treated lesions within 6 months (162–164). Accumulating evidence shows that intracoronary stenting significantly reduces the incidence of restenosis in patients with acute MI (165, 166) and with stable angina (163, 167, 168) and yields better clinical outcomes (169, 170). Additional technological advances may further improve outcomes. Other mechanical devices, including rotating blades or burrs or lasers, are occasionally used in special circumstances.

Compared with medical therapy, CABG improves survival in patients with stenosis of the left main coronary artery, three-vessel disease, or two-vessel disease including the proximal left anterior descending artery (171–173). Limited evidence shows that survival might be improved by initial surgery for patients with isolated stenosis of the proximal left anterior descending artery, regardless of ventricular function (174). Initially, CABG is more effective in relieving angina than medical therapy; 80% of patients are free of symptoms for 5 years (175). However, after 5 to 10 years, medical treatment and surgery provide equivalent results.

Percutaneous transluminal coronary angioplasty seems to relieve angina more effectively than medical therapy in low-risk patients but does not improve survival; additional procedures are often necessary (176, 177). Several trials, including two in the United States, have examined whether PTCA and CABG yield similar outcomes in higher-risk patients who are favorable surgical candidates. Survival was equivalent after PTCA and CABG in the Emory Angioplasty versus Surgery Trial (EAST) (178). In the Bypass Angioplasty Revascularization Investigation (BARI) (179), survival was equivalent at 5 years but better with CABG after 7 years (180). Diabetic patients with several severe lesions had better survival after CABG in BARI (181) but not in

EAST. The difference in diabetic patients explained the 7-year survival difference seen in BARI. In both trials, patients assigned to CABG were more likely to be free of angina. In both trials, 54% of patients who had PTCA required additional revascularization procedures during 5 years of follow-up, compared with 8% and 14% of the CABG groups in BARI and EAST, respectively.

Studies such as these must be interpreted cautiously because most enrolled patients had multivessel disease, were at relatively low risk for cardiac events, and were followed for 5 years or less before evident vein graft atherosclerosis. Elderly patients, women, and persons with previous bypass surgery were infrequently studied. Moreover, advances such as aggressive lipid lowering, intracoronary stents, and more frequent use of arterial grafts in CABG were often not assessed.

RECOMMENDATIONS FOR REVASCULARIZATION

Invasive treatment has not been shown to improve survival for most patients with chronic angina but may be required to control symptoms. However, because it prolongs survival, CABG is recommended for symptomatic patients with left main disease, three-vessel disease, or two-vessel disease including stenosis of the proximal left anterior descending artery (Table 6). Percutaneous transluminal coronary angioplasty is an alternative to CABG for patients with normal left ventricular function and favorable angiographic features. Diabetic patients may be an exception because they often have extensive disease; the results of BARI suggest better survival after CABG than after PTCA.

Both PTCA and CABG have low initial mortality rates (1% to 1.5%). The former involves less initial morbidity and cost, but recurrent angina and repeated procedures (either CABG or PTCA) are required more often. By the fifth postoperative year, the total cost of both procedures seems to be equivalent.

Most patients with single-vessel disease symptoms can be effectively treated with PTCA. For symptomatic patients who have lesions unfavorable for PTCA or who wish to decrease the risk for subsequent procedures, CABG produces excellent long-term outcomes. Patients with significant CAD who have survived sudden cardiac death or sustained ventricular tachycardia are probably best treated with CABG rather than PTCA.

Although scant data are available from patients who develop recurrent angina after CABG, it seems that

Table 6. Recommendations for Revascularization Using Percutaneous Transluminal Coronary Angioplasty (or Other Catheter-Based Techniques) and Coronary Artery Bypass Grafting in Patients with Stable Angina*

Class I

- CABG for patients with significant left main coronary disease (A)
- CABG for patients with three-vessel disease. The survival benefit is greater in patients with abnormal left ventricular function (<0.5) (A)
- CABG for patients with two-vessel disease with significant proximal left anterior descending CAD *and* either abnormal left ventricular function (<0.5) or demonstrable ischemia on noninvasive testing (A)
- PTCA for patients with three-vessel disease or two-vessel disease with significant proximal left anterior descending CAD who have anatomy suitable for catheter-based therapy, have normal left ventricular function, and *do not have* treated diabetes (B)
- PTCA or CABG for patients with one-vessel or two-vessel CAD *without* significant proximal left anterior descending CAD, but with a *large* area of viable myocardium *and* high-risk criteria on noninvasive testing (B)
- CABG for patients with one-vessel or two-vessel CAD *without* significant proximal left anterior descending CAD who have survived sudden cardiac death or sustained ventricular tachycardia (C)
- In patients with previous PTCA, CABG, or PTCA for recurrent stenosis associated with a large area of viable myocardium or high-risk criteria on noninvasive testing (C)
- PTCA or CABG for patients who have not been successfully treated (see text) by medical therapy and can be revascularized with acceptable risk (B)

Class IIa

- Repeated CABG for patients with multiple SVG stenoses, especially when there is significant stenosis of a graft supplying the left anterior descending coronary artery. PTCA may be appropriate for focal SVG lesions or multiple stenoses in poor candidates for reoperative surgery (C)
- PTCA or CABG for patients with one-vessel or two-vessel CAD *without* significant proximal left anterior descending CAD but with a *moderate-size* area of viable myocardium and demonstrable ischemia on noninvasive testing (B)
- PTCA or CABG for patients with single-vessel disease with significant proximal left anterior descending CAD (B)

Class IIb

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

* CABG = coronary artery bypass grafting; CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty; SVG = saphenous vein graft. Letters in parentheses represent levels of evidence. See text for details. In these recommendations, PTCA is used to indicate PTCA, other catheter-based techniques (such as stents, atherectomy, and laser therapy), or both.

medical therapy, PTCA, and surgery are all associated with a higher risk than is seen in patients with disease in native arteries. No definitive recommendation is possible; however, patients with severe recurrent angina and multiple vein grafts with late stenoses should consider reoperation in the absence of major contraindications,

particularly if a stenotic vein graft supplies the left anterior descending artery (182). Certain symptomatic patients whose angina is caused by stenoses of native vessels or by early (<5 years after operation) focal stenoses in vein grafts can be successfully treated with PTCA.

EDUCATION OF PATIENTS

Because CAD often presents dramatically, health care providers frequently focus on impressive recent technologic advances in diagnosis and therapy and neglect education. Effective education not only helps patients understand treatment decisions but also engages them in decision making (183). This approach increases their satisfaction with care and may enhance their quality of life and survival through better adherence to medication regimens and programs for risk factor reduction (184–186). At every encounter, a patient should receive individualized information presented in a timely and comprehensible manner. It is advisable to address patients' overriding concerns, such as short-term prognosis, early so that they will not distract attention from other issues, such as lifestyle changes. Even a brief suggestion from a physician about exercise or smoking cessation can be effective (187, 188). Well-designed educational programs about CABG (189) and MI (133, 190) can improve patients' knowledge and, in some instances, improve outcomes (191).

In addition to general information about pathophysiology, complications, and prognosis, patients should also be told about their treatments, diagnostic tests, limitations on physical activity, and individual risk factors. They should also receive instructions on how and when to seek medical attention. Cardiopulmonary resuscitation training is advisable for family members.

FOLLOW-UP

Despite the extensive evidence on the effectiveness of many therapeutic and diagnostic maneuvers, evidence supporting specific strategies for the follow-up of patients with chronic stable angina is lacking. Practice must therefore be based on clinical experience and expert consensus. Six key areas should be assessed regularly during follow-up: 1) changes in physical activity, 2) changes in frequency or severity of angina, 3) possible adverse effects of therapy, 4) adherence to prescribed medications and changes in lifestyle, 5) knowledge

about CAD, and 6) changes in other comorbid conditions and their treatment that might affect symptoms or treatment of CAD.

During the first year of therapy, follow-up evaluations every 4 to 6 months are recommended for the patient with successfully treated, chronic stable angina. If the patient remains stable and can be reliably expected to contact the provider in the event of any meaningful change in condition, then annual evaluations are recommended. Otherwise, more frequent visits are warranted. Patients who are comanaged by a primary care physician and a cardiologist may alternate these visits, provided that there is adequate communication between physicians. Annual office visits can be supplemented by telephone or by other types of contact between the patient and the health care system.

Laboratory testing, including monitoring of lipid abnormalities and glycemic control in diabetic patients, should be individualized. Electrocardiography is indicated when the anginal pattern changes, symptoms or findings suggest a dysrhythmia or conduction abnormality, or syncopal symptoms are present. No evidence shows that routine, periodic electrocardiography is useful without a change in history or physical examination.

Despite widespread use of stress testing for follow-up in patients with stable angina, few published data support this practice. Using clinical data and data from noninvasive and invasive tests acquired during the initial evaluation, the clinician should be able to estimate the patient's cardiovascular risk over the next 3 years. Low-risk patients with an estimated annual mortality rate less than 1% do not require repeated stress testing for 3 years after initial evaluation unless their clinical status changes. Examples include patients with low-risk Duke treadmill scores and those with normal left ventricular function and angiography showing normal coronaries or insignificant CAD. Annual follow-up testing in the absence of a change in symptoms should be considered in high-risk patients who have an estimated annual mortality rate of greater than 3%. Examples include patients with ejection fractions less than 0.50 and substantial CAD in at least one major vessel and patients with treated diabetes and multivessel CAD who have not had CABG. Follow-up testing should be done in a stable, high-risk patient only if a worsened estimated risk might change an initial decision not to proceed with revascularization. Patients with intermediate-risk annual mor-

tality rate (1% to 3%) warrant testing every 1 to 3 years, depending on their individual circumstances.

The choice of stress test for patient follow-up should be dictated by considerations similar to those used for an initial evaluation. In a patient with an interpretable exercise electrocardiogram who can still exercise, treadmill testing remains the first choice. If possible, follow-up testing should be performed with the same stress and imaging techniques as the original study to facilitate comparisons. If a patient becomes unable to exercise, this may in and of itself indicate clinical deterioration. It must be recognized that serial testing has inherent variability, and changes may not always necessarily reflect a genuine change in the patient's prognosis.

From VA Puget Sound Health Care System, Seattle, Washington; University of Pennsylvania, Philadelphia, Pennsylvania; Massachusetts General Hospital-Partners Health Care System, Boston, Massachusetts; and Mayo Medical Center, Rochester, Minnesota.

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Requests for Single Reprints: Stephan D. Fihn, MD, MPH, NW Health Services Research and Development Center of Excellence, VA Puget Sound Health Care System 152, 1660 South Columbian Way, Seattle, WA 98108.

Current Author Addresses: Dr. Fihn: NW Health Services Research and Development Center of Excellence, VA Puget Sound Health Care System 152, 1660 South Columbian Way, Seattle, WA 98108.

Dr. Williams: University of Pennsylvania, 423 Guardian Drive, 1220 Blockley Hall, Philadelphia, PA 19104-2676.

Dr. Daley: Massachusetts General Hospital, 50 Stamford Street, Boston, MA 02114.

Dr. Gibbons: Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

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