

Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease: A Clinical Practice Guideline from the American College of Physicians

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In 1999, the American College of Physicians (ACP), then the American College of Physicians–American Society of Internal Medicine, and the American College of Cardiology/American Heart Association (ACC/AHA) developed joint guidelines on the management of patients with chronic stable angina. The ACC/AHA then published an updated guideline in 2002, which ACP recognized as a scientifically valid review of the evidence and background paper. This ACP guideline summarizes the recommendations of the 2002 ACC/AHA updated guideline and underscores the recommendations most likely to be important to physicians seeing patients in the primary care setting. This guideline is the second of 2 that provide guidance on the management of patients with chronic stable angina. This document covers treatment and follow-up of symptomatic patients who have not had an acute myocardial infarction or revascularization procedure in the previ-

ous 6 months. Sections addressing asymptomatic patients are also included. *Asymptomatic* refers to patients with known or suspected coronary disease based on a history or electrocardiographic evidence of previous myocardial infarction, coronary angiography, or abnormal results on noninvasive tests. A previous guideline covered diagnosis and risk stratification for symptomatic patients who have not had an acute myocardial infarction or revascularization procedure in the previous 6 months and asymptomatic patients with known or suspected coronary disease based on a history or electrocardiographic evidence of previous myocardial infarction, coronary angiography, or abnormal results on noninvasive tests.

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In 1999, the American College of Physicians (ACP), then the American College of Physicians–American Society of Internal Medicine, and the American College of Cardiology/American Heart Association (ACC/AHA) developed joint guidelines on the management of patients with chronic stable angina (1). The ACC/AHA published an updated guideline in 2002 (2), which ACP recognized as a scientifically valid, high-quality review of the evidence and background paper. This ACP guideline summarizes the recommendations of the 2002 ACC/AHA updated guideline and underscores the recommendations most likely to be important to physicians seeing patients in the primary care setting. For more in-depth analysis and details, readers should refer to the full-text guideline at www.acc.org/clinical/guidelines/stable/stable.pdf. This guideline is the second ACP guideline on the management of patients with chronic stable angina. The first ACP guideline covered diagnosis and risk stratification (3). For guidance on revascularization, readers should refer to the 2002 ACC/AHA guidelines on chronic stable angina (2) and unstable angina (4).

This document covers treatment and follow-up for symptomatic patients who have not had an acute myocar-

dial infarction (MI) or revascularization procedure in the previous 6 months. Sections also address asymptomatic patients with known or suspected coronary disease based on electrocardiographic evidence of previous MI, coronary angiography, or abnormal results on noninvasive tests. This in no way constitutes an endorsement of noninvasive testing in asymptomatic patients for the purposes of “screening” but rather acknowledges the clinical reality that patients often present after having undergone such an evaluation. Although this guideline covers pharmacologic therapy, physicians should always recommend lifestyle modifications, such as smoking cessation, appropriate diet, and exercise, to patients.

The target audience for this guideline is all clinicians who manage patients with chronic stable angina. The target patient population is patients without known coronary disease whose symptoms suggest chronic stable angina, patients who present with known chronic stable angina, and asymptomatic patients with evidence suggesting coronary disease on previous testing. This guideline does not apply to patients with unstable angina because they have a high to moderate short-term risk for an acute coronary event.

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METHODS

The ACP has traditionally developed evidence-based guidelines. The ACP bases guideline recommendations on the results of systematic reviews of high-quality evidence (several well-designed randomized, controlled trials) and meta-analyses where appropriate. Without good evidence from randomized trials, the ACP will not make recommendations but will underscore practices that are not supported by evidence. Since this document is based on the ACC/AHA guidelines, the College has maintained the levels of evidence as designated by the ACC/AHA in the recommendation statements: A level A recommendation is based on evidence from several randomized clinical trials with large numbers of patients; a level B recommendation is based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries; and a level C recommendation is based on expert consensus.

PHARMACOLOGIC THERAPY

Overview of Treatment

The treatment of stable angina has 2 major purposes. The first is to prevent MI and death and thereby increase the length of life. The second is to reduce symptoms of angina and occurrence of ischemia, which should improve quality of life. Therapy directed toward preventing death has the highest priority. When 2 different therapeutic strategies are equally effective in alleviating symptoms of angina, the therapy with an advantage in preventing death should be recommended. Patient education, cost-effectiveness, and patient preferences are important components in this decision-making process. This section on pharmacologic therapy considers treatments to prevent MI and death first, then antianginal and anti-ischemic therapy to alleviate symptoms, reduce ischemia, and improve quality of life.

Antiplatelet Medications

Aspirin (75 to 325 mg daily) should be used routinely in all patients with acute and chronic ischemic heart disease with or without manifest symptoms and without contraindications. A meta-analysis of more than 200 trials showed that the reduction in vascular events was similar for dosages of 75 to 150 mg daily and 160 to 325 mg daily; however, daily doses less than 75 mg had less benefit (5–9). In a randomized trial that compared clopidogrel with aspirin in patients with previous MI, stroke, or symptomatic peripheral vascular disease (that is, those at risk for ischemic events), clopidogrel appeared to be slightly more effective than aspirin in decreasing the combined risk for MI, vascular death, or ischemic stroke (10). However, no further studies have confirmed the efficacy of clopidogrel in patients with stable angina; thus, clopidogrel is best reserved for patients who cannot take aspirin. Dipyridamole exerts vasodilatory effects on coronary resistance vessels and also has antithrombotic effects. However, the usual oral

doses of dipyridamole can enhance exercise-induced myocardial ischemia in patients with stable angina (11). Therefore it should not be used as an antiplatelet agent.

β -Blockers

β -Blockers also reduce cardiac events when used as secondary prevention in postinfarction patients and reduce mortality and morbidity among patients with hypertension. On the basis of their potentially beneficial effects on morbidity and mortality, β -blockers should be strongly considered as initial therapy for chronic stable angina. They seem to be underused (12). Diabetes mellitus is not a contraindication to their use, and diabetic patients seem to benefit as much as or more than patients without diabetes.

Lipid-Lowering Agents

Many recent clinical trials, notably the Heart Protection Study (HPS) (13) and the Cholesterol and Recurrent Events (CARE) study (14), have documented that low-density lipoprotein cholesterol-lowering agents can decrease the risk for adverse ischemic events in patients with established coronary artery disease (CAD) (13–16). These clinical trials indicate that in patients with established CAD, including chronic stable angina, lipid-lowering therapy with a statin should be recommended even in the presence of mild to moderate elevations of low-density lipoprotein cholesterol levels.

Angiotensin-Converting Enzyme Inhibitors

Recently, several trials have proven that angiotensin-converting enzyme (ACE) inhibitors reduce cardiovascular death, MI, and stroke in patients who were at risk for or who had vascular disease (without heart failure). In the Heart Outcomes Prevention Evaluation (HOPE) study (17), the ACE inhibitor ramipril (10 mg/d) reduced cardiovascular death, MI, and stroke in patients who were at high risk for or who had vascular disease without heart failure. Furthermore, only a small part of the benefit could be attributed to a reduction in blood pressure (decrease of 2 to 3 mm Hg). The European trial on reduction of cardiac events with perindopril in stable CAD (called the EUROPA study [18]) enrolled a group of patients similar to the HOPE participants but also included those with positive stress test results. Patients with heart failure and diabetes were excluded. This study showed that an ACE inhibitor can have a vasculoprotective effect in patients at lower risk than those enrolled in the HOPE study. Whether this is a class effect is a subject of continuing controversy but can be argued on the basis of additional positive studies with enalapril (19, 20) and captopril (21). Moreover, using ACE inhibitors for secondary prevention in patients with diabetes and CAD seems to be particularly beneficial. Currently, evidence for the use of angiotensin-receptor blockers in chronic stable angina is insufficient.

Nitrates and Calcium-Channel Blockers

Nitrates have not been shown to reduce mortality in patients with previous MI or in patients with CAD. Immediate-release or short-acting dihydropyridine calcium antagonists increase adverse cardiac events. However, long-acting or slow-release dihydropyridines, or nondihydropyridines, may relieve symptoms in patients with chronic stable angina without increasing the risk for adverse cardiac events. No conclusive evidence indicates that either long-acting nitrates or calcium antagonists are superior for long-term treatment to relieve the symptoms of angina. The ACC/AHA writing committee believes that long-acting calcium antagonists are often preferable to long-acting nitrates for maintenance therapy because of their sustained 24-hour effects. However, the presence of other conditions, such as hypertension, and the patient's and treating physician's preferences should always be considered. Calcium antagonists (long-acting) and long-acting nitrates may be substituted for β -blockers if β -blockers lead to unacceptable side effects. β -Blockers and long-acting calcium-channel blockers, unless contraindicated, are also options for use during nitrate-free intervals in patients' therapy.

RECOMMENDATIONS FOR PHARMACOTHERAPY TO PREVENT MI AND DEATH AND TO REDUCE SYMPTOMS

Recommendation 1: The following agents should be used in patients with symptomatic chronic stable angina to prevent MI or death and to reduce symptoms:

Aspirin (level of evidence: A) or clopidogrel when aspirin is absolutely contraindicated (level of evidence: B)

β -Blockers in patients with previous MI (level of evidence: A) or without previous MI (level of evidence: B)

Low-density lipoprotein cholesterol-lowering therapy with a statin (level of evidence: A)

ACE inhibitor (level of evidence: A)

The following agents should be used in patients with symptomatic chronic stable angina to reduce symptoms only:

Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina (level of evidence: B)

Calcium antagonists (long-acting) or long-acting nitrates when β -blockers are clearly contraindicated (level of evidence: B)

Calcium antagonists (long-acting) or long-acting nitrates in combination with β -blockers when β -blockers alone are unsuccessful (level of evidence: B).

Recommendation 2: The following agents should not be used to prevent MI or death or to reduce symptoms in patients with symptomatic chronic stable angina:

Dipyridamole (level of evidence: B)

Chelation therapy (level of evidence: B).

PHARMACOTHERAPY FOR PREVENTING MI AND DEATH IN ASYMPTOMATIC PATIENTS WITH EVIDENCE SUGGESTING CAD ON PREVIOUS TESTING

Even if a patient is asymptomatic, aspirin and β -blockers are recommended in a patient with a previous MI. The data that support these recommendations are detailed in the ACC/AHA updated guideline for managing patients with acute MI (22). In the absence of previous MI, patients with documented CAD on the basis of noninvasive testing or coronary angiography probably also benefit from aspirin, although the data on such patients are limited. Several studies have investigated the potential role of β -blockers in patients with asymptomatic ischemia demonstrated on exercise testing or ambulatory monitoring (23–25). The data generally demonstrate a morbidity and mortality benefit from β -blocker therapy, but not all trials have been positive (26). There are no data from randomized, controlled trials on the use of β -blockers in asymptomatic patients without previous MI.

Lipid-lowering therapy in asymptomatic patients with documented CAD decreased the rate of adverse ischemic events in the Scandinavian Simvastatin Survival Study (4S) (15), the CARE study (14), the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial (27), and HPS (13).

RECOMMENDATIONS FOR PHARMACOTHERAPY TO PREVENT MI AND DEATH IN ASYMPTOMATIC PATIENTS WITH EVIDENCE SUGGESTING CAD ON PREVIOUS TESTING

Recommendation 3: In the absence of contraindications, the following agents should be used in asymptomatic patients to prevent MI and death:

Aspirin in patients with previous MI (level of evidence: A)

β -Blockers in patients with previous MI (level of evidence: B)

Lipid-lowering therapy with a statin in patients with documented CAD or type 2 diabetes mellitus (level of evidence: A)

ACE inhibitor in patients with CAD who also have diabetes, systolic dysfunction, or both (level of evidence: A).

Recommendation 4: The following agents also may be used in asymptomatic patients to prevent MI and death:

Aspirin in patients without previous MI (level of evidence: B)

ACE inhibitor in patients with diabetes and no contraindications (level of evidence: B).

ALTERNATIVE THERAPIES FOR PATIENTS WITH REFRACTORY ANGINA

Evidence is still lacking for the use of spinal cord stimulation, enhanced external counterpulsation, and laser

transmyocardial revascularization. The consensus of the ACC/AHA writing committee is that these techniques should be used only in patients who cannot be managed adequately by medical therapy and who are not candidates for revascularization (interventional or surgical). Of note, laser transmyocardial revascularization and enhanced external counterpulsation are approved for this indication by the U.S. Food and Drug Administration.

PATIENT FOLLOW-UP: MONITORING SYMPTOMS AND ANTIANGINAL THERAPY

Little evidence has been published on the efficacy of specific strategies for the follow-up of patients with chronic stable angina on patient outcomes. All guidance in this section is based on level C evidence, in other words, expert opinion from the ACC/AHA guideline. As a matter of policy, the ACP seldom makes clinical policy recommendations on the basis of expert opinion. However, this clinical situation has become a particularly important problem for ACP membership. Therefore, in the absence of any high-grade evidence (level A or B), the ACP highlights the recommendations from the ACC/AHA document, which were developed by using expert opinion.

Questions To Be Addressed in Follow-up of Patients with Chronic Stable Angina

The ACC/AHA writing committee, on the basis of expert opinion, suggests that 5 questions should be answered regularly during the follow-up of a patient who is receiving treatment for chronic stable angina:

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

Follow-up: Frequency and Methods

By using expert opinion, the ACC/AHA writing committee suggests that patients should be evaluated every 4 to 6 months during the first year of therapy. After the first year of therapy, annual evaluations are recommended if the patient is stable and reliable enough to call or make an appointment when anginal symptoms become worse or other symptoms occur. Patients who are comanaged by their primary care physician and cardiologists may alter-

nate visits, provided that communication among physicians is excellent and all appropriate issues are addressed at each visit.

Use of Cardiac Testing during Follow-up

No clear evidence shows that routine, periodic cardiac testing of any sort is useful without a change in history or physical examination. The ACC/AHA writing committee consensus is that the following are indicated:

1. Repeated echocardiogram when therapy with medications affecting cardiac conduction are initiated or changed or when anginal pattern has changed, symptoms or findings suggest a dysrhythmia or conduction abnormality, or near or frank syncope occurs.
2. Chest radiography for patients with evidence of new or worsening congestive heart failure.
3. Assessment of left ventricular ejection fraction and segmental wall motion by echocardiography or radionuclide imaging in patients with new or worsening congestive heart failure or evidence of intervening MI by history or electrocardiography.
4. Echocardiography for patients with evidence of new or worsening valvular heart disease.
5. Treadmill exercise test for patients without previous revascularization who have a significant change in clinical status, can exercise, and have none of the electrocardiogram abnormalities listed in number 6.
6. Stress radionuclide imaging or stress echocardiography procedures for patients without previous revascularization who have a significant change in clinical status and cannot exercise or have 1 of the following electrocardiogram abnormalities: preexcitation (Wolff-Parkinson-White) syndrome, electronically paced ventricular rhythm, more than 1 mm of ST-segment depression at rest, or complete left bundle-branch block.
7. Stress radionuclide imaging or stress echocardiography procedures for patients who have a significant change in clinical status and require a stress imaging procedure on their initial evaluation because of equivocal or intermediate-risk results with exercise electrocardiography testing.
8. Stress radionuclide imaging or stress echocardiography procedures for patients with previous revascularization who have a significant change in clinical status.
9. Coronary angiography in patients with marked limitation of ordinary activity (Canadian Cardiovascular Society class III) despite maximal medical therapy.

The ACC/AHA writing committee *does not recommend* the following procedures in managing patients with chronic stable angina:

1. Echocardiography or radionuclide imaging for assessment of left ventricular ejection fraction and segmental wall motion in patients with a normal electrocardiogram, no history of MI, and no evidence of congestive heart failure.
2. Repeated treadmill exercise testing in less than 3 years in patients who have no change in clinical status and

an estimated annual mortality rate less than 1% on their initial evaluation, as demonstrated by one of the following: low-risk Duke treadmill score (without imaging), low-risk Duke treadmill score with negative imaging, normal left ventricular function and a normal coronary angiogram; or normal left ventricular function and clinically insignificant CAD.

3. Stress imaging or echocardiography procedures for patients who have no change in clinical status and a normal rest electrocardiogram, are not taking digoxin, can exercise, and did not require a stress imaging or echocardiographic procedure on their initial evaluation because of equivocal or intermediate-risk treadmill results.

4. Repeated coronary angiography in patients with no change in clinical status, no change on repeated exercise testing or stress imaging, and clinically insignificant CAD on initial evaluation.

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Note: Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians’ judgment. All ACP clinical practice guidelines are considered automatically withdrawn, or invalid, 5 years after publication or once an update has been issued.

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