Annals of Internal Medicine®

In the Clinic®

Chronic Coronary Artery Disease

Diagnosis

Treatment

Chronic coronary artery disease (CCAD) is a leading cause of death in the United States and many other countries. The defining pathobiology is an imbalance between the metabolic demands of the myocardium and oxygen supply, which most often results from coronary artery atherosclerosis. The classic presenting symptom of CCAD is angina, but clinical presentation varies greatly among patients. Since the last In the Clinic on CCAD (previously termed "stable ischemic heart disease") in 2019, several new medications have been approved to reduce ischemic complications.

CME/MOC activity available at Annals.org.

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Chronic coronary artery disease (CCAD) is a leading cause of death in many countries and is responsible for a substantial proportion of health care costs in the United States (1). The imbalance in oxygen demand and blood supply that results in CCAD is usually caused by atherosclerotic obstruction. Angina is the classic presentation of CCAD, and symptoms include chest pressure, jaw discomfort, arm discomfort, shortness of breath, epigastric discomfort, and variants of these symptoms. Of note, the shift in terminology from "stable ischemic heart disease" to "chronic coronary artery disease" reflects the continuum of care in patients with CAD from acute to chronic and mirrors the change made by the American Heart Association and the American College of Cardiology (2).

Diagnosis

Why is it important to differentiate patients with CCAD from those with unstable angina?

Stable angina is typically elicited by exertion or emotion and is relieved by rest or nitroglycerin. In contrast, the symptoms of unstable angina can occur at rest without an apparent trigger (see the **Box**: Principal Presentations of Unstable Angina). Acute coronary syndrome (ACS) includes 3 related clinical conditions that exist along a continuum of severity: 1) unstable angina, 2) non–ST-segment elevation myocardial infarction (MI), and 3) ST-segment elevation MI. The initial diagnosis and classification of ACS should be based on the clinical history, electrocardiographic findings, and cardiac troponin (cTn) testing. Unstable angina is defined by transient myocardial ischemia in the absence of significant myonecrosis detected by cTn. In contrast, patients with more prolonged or severe myocardial ischemia are diagnosed with MI and have elevated cTn. Management of ACS is time-sensitive and is described in guidelines from the American College of Cardiology and the American Heart Association (3).

Principal Presentations of Unstable Angina*

- Rest angina: Occurs at rest and usually lasts >20 minutes
- New-onset severe angina: Severe onset within 2 months of initial presentation
- Increasing angina: Previously diagnosed angina with a crescendo pattern of occurrence (increasing in intensity, duration, and/or frequency)

* *From reference 2.*

High-sensitivity cTn is useful for the diagnostic assessment of patients with chest pain (4). This is the preferred biomarker for detection or exclusion of myocardial injury given its superior sensitivity, negative predictive values, and shorter interval from the onset of chest pain to detectable levels compared with previous assays. High-sensitivity cTn is organ-specific but not disease-specific. Noncoronary cardiac and noncardiac causes of cardiomyocyte injury can result in elevated cTn concentrations; therefore, interpretation requires integration with all other clinical information.

What other diseases might be confused with CCAD?

Chest pain has traditionally been stratified into "typical" and "atypical" types. Chest pain that is more likely associated with ischemia consists of substernal chest discomfort that is provoked by exertion or emotional stress and relieved by rest or nitroglycerin. The more classic the chest discomfort is with regard to quality, location, radiation, and provoking and relieving factors, the more likely it is to be of cardiac ischemic origin (**Table**) (4).

"Atypical chest pain" is an ambiguous term whose use is discouraged (4). Instead, use of "cardiac," "possible

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Table. **Characteristics Associated With Cardiac, Possibly Cardiac, and Noncardiac Chest Pain Classifications**

Characteristic	*Cardiac*	*Possibly Cardiac*	*Noncardiac*
Quality	Pressure Heaviness Tightness	Stabbing Dull ache Burning	Sharp Ripping Pleuritic
Location	Retrosternal Left chest	Left and/or right arm Throat or jaw Upper abdomen	Localized Inframammary Lower abdomen or extremities
Radiation	Left arm Jaw	Right and/or left arm	Back Lower extremities
Duration	Gradual onset Offset within minutes of rest	Variable >30 min	Fleeting (seconds) Constant
Provocative features	Physical or emotional stress	Palpation Deep inspiration	No consistent associations Nonexertional
Palliative features	Rest Nitroglycerin	Delayed (>5 min) response to nitroglycerin	Walking Position change
Associated features	Dyspnea Nausea Diaphoresis	Fatigue Palpitations	–

cardiac," or "noncardiac" to describe the suspected cause of chest pain is encouraged. Women, patients with diabetes, and older adults may present with symptoms other than chest pain, such as exertional dyspnea, nausea, diaphoresis, and exaggerated fatigue. Some patients with symptoms suggesting CCAD have a different diagnosis (see the **Box**: Alternative Diagnoses to Angina for Patients With Chest Pain) (4).

Why is it important to estimate the probability of disease separately from the risk for death when evaluating patients with suspected CCAD?

The principal value of estimating the probability of CAD is to identify patients with a low probability (usually <5%) of CCAD who will benefit more from a work-up that focuses on non-CAD causes of chest pain (**Figure 1**) (5). Smoking history, hyperlipidemia, hypertension, diabetes, and family history of premature CAD (before age 55 years in men and age 65 years in women) all increase the likelihood of CAD (2). Coronary artery calcium (CAC) scoring quantified by the Agatston score with age- and gender-based percentiles can refine this likelihood. A CAC score of 100 or higher indicates a likelihood of obstructive CAD of at least 15%, and a score of 1000 or higher indicates a likelihood of at least 50% (6).

What should the physical examination entail?

Physical examination findings are often normal or nonspecific in patients with CCAD. Nevertheless, the clinician should look for evidence of decompensated heart failure, peripheral artery disease, and dyslipidemia because these can accompany CAD. Signs of decompensated heart failure include elevated jugular venous pulsation, S3 gallop, mitral regurgitation murmur, displaced apical impulse, pulmonary crackles, diminished breath sounds, dullness to chest percussion, hepatomegaly, and lower-extremity edema. Signs of noncoronary atherosclerotic vascular disease that increase the probability of CAD include carotid bruit and diminished or absent pedal pulses. Yellow patches or plaques on the skin caused by lipid deposits (xanthelasma and xanthomas) are often signs of inherited dyslipidemias.

What other preliminary tests should be used?

Electrocardiography

All patients with suspected CCAD should have resting electrocardiography (4). Most patients with CCAD have a normal resting electrocardiogram (ECG), but pathologic Q waves indicate a prior MI. In addition, the presence of left bundle branch block, left ventricular hypertrophy,

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Alternative Diagnoses to Angina for Patients With Chest Pain*

- Nonischemic cardiovascular
  - Aortic dissection
  - Pericarditis
- Pulmonary
  - Embolus
  - Pneumothorax
  - Pneumonia
  - Pleuritis
- Gastrointestinal
  - Esophageal
    - Esophagitis
    - Spasm
    - Reflux
  - Biliary
    - Colic
    - Cholecystitis
    - Choledocholithiasis
    - Cholangitis
  - Peptic ulcer
  - Pancreatitis
- Chest wall
  - Costochondrosis
  - Fibrositis
  - Rib fracture
  - Sternoclavicular arthritis
  - Herpes zoster (before rash)
- Psychiatric
  - Anxiety disorders
    - Hyperventilation
    - Panic disorder
    - Primary anxiety
  - Affective disorders (e.g., depression)
  - Somatoform disorders
  - Thought disorders (e.g., fixed delusions)

* *From reference 4.*

or higher resting heart rate may indicate higher future risk in patients with established CCAD (2).

Chest radiography

Patients without an obvious noncardiac cause of angina should have chest radiography. Chest radiographs are frequently normal in patients with stable angina, but they may show evidence of decompensated heart failure, which worsens prognosis, or noncardiac causes of chest pain, including pneumonia, pneumothorax, or rib fractures (4).

Echocardiography

Echocardiography should be performed in patients who have signs or symptoms suggesting heart failure or cardiac valvular lesions; known prior infarction or a pathologic Q wave on an ECG suggesting prior infarction; or complex ventricular arrhythmias on an ECG, which could suggest underlying cardiomyopathy (4).

Which diagnostic test should follow the preliminary assessment?

Because the goal of noninvasive testing is to identify patients with CAD, the clinician must first consider the likelihood that the patient has CAD (pretest probability) (**Figure 1**) (4). The value of testing is greater when the diagnosis is more uncertain (for example, when the pretest probability of CAD is between 20% and 80%). Among patients with a low probability of CAD, additional testing may produce a false-positive result (**Figure 2**) (4).

For patients with stable chest pain who are at intermediate or high risk, the clinician may choose between diagnostic testing for ischemia (stress testing) or anatomical testing for CAD (coronary computed tomography angiography [CCTA] or invasive coronary angiography). With stress testing, the clinician must select the type of stress (exercise or pharmacologic) and the method to identify and measure ischemia (electrocardiography, echocardiography, single-photon emission computed tomography [SPECT], positron emission tomography [PET], or magnetic resonance imaging [MRI]).

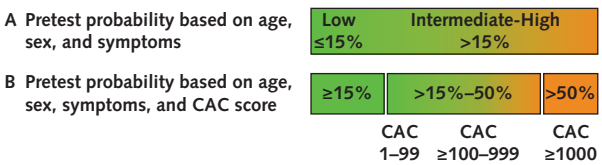
Exercise ECG stress testing

ECG stress testing for detection of CAD has a sensitivity of 68% and a specificity of 77% (7). False-negative results occur more often in patients with less severe disease and may be more frequent in women. The 2021 chest pain guidelines recommend stress imaging ("preferred," Class 1 recommendation) over exercise electrocardiography ("reasonable," Class 2a recommendation) for evaluation of patients with intermediate or high risk and no known CAD (4).

Figure 1. **Pretest probability of CAD in symptomatic patients, by age and sex.**

Pretest Probabilities of Obstructive CAD in Symptomatic Patients
(A) according to age, sex, and symptoms;
(B) according to age, sex, symptoms, and CAC

Age, y	Chest Pain		Dyspnea	
	Men	Women	Men	Women
30–39	≤4	≤5	0	3
40–49	≤22	≤10	12	3
50–59	≤32	≤13	20	9
60–69	≤44	≤16	27	14
70+	≤52	≤27	32	12



The pretest probability shown is for patients with anginal symptoms. Patients with lower-risk symptoms would be expected to have lower pretest probability. The darker green- and orange-shaded regions denote the groups in which noninvasive testing is most beneficial (pretest probability >15%). The light green–shaded regions denote the groups with pretest probability of CAD ≤15% in which the testing for diagnosis may be considered based on clinical judgment. If CAC is available, it can also be used to estimate the pretest probability based on CAC score. CAC = coronary artery calcium; CAD = coronary artery disease. Reproduced from Gulati M, Levy PD, Mukherjee D, et al, 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, *Circulation*, 2021, vol. 144, issue 22, e368-e454 (http://dx.doi.org/10.1161/CIR.0000000000001029), with permission.

In addition to providing information about the probability of obstructive CAD, exercise electrocardiography provides prognostic information if CAD is present. A longer duration of symptom-free exercise correlates with favorable cardiovascular mortality, whereas delayed heart rate recovery (8) and the extent of ST-segment depression or the presence of ST-segment elevation portends a poorer prognosis (9) (see the **Box**: Duke Treadmill Score).

An imaging stress test should be used if any of the following abnormalities is found on an ECG: complete left bundle branch block or paced ventricular rhythm, preexcitation syndrome, or resting ST-segment depression greater than 1 mm (4).

Pharmacologic stress

For patients who cannot exercise strenuously enough to generate a valid result, pharmacologic stress plus imaging can be used. Dobutamine is often used for stress when echocardiography is used for imaging, and the vasodilators regadenoson and dipyridamole are used for stress when nuclear myocardial perfusion is used for imaging.

Stress imaging modalities

Sensitivity is similar enough between echocardiography and SPECT that it is reasonable to select one based on local availability of skill and experience (4). Echocardiography avoids radiation exposure and provides information about valvular function and filling pressures. SPECT provides better-quality images in patients with overweight or obesity. Compared with SPECT, nuclear PET perfusion offers prognostic significance using calculation of coronary flow reserve, lower radiation burden, and shorter scan time (10). The main limitations of PET are higher cost and limited availability. Stress cardiac MRI has limited availability, and other limitations include cost, long duration of scanning, and potential contraindication

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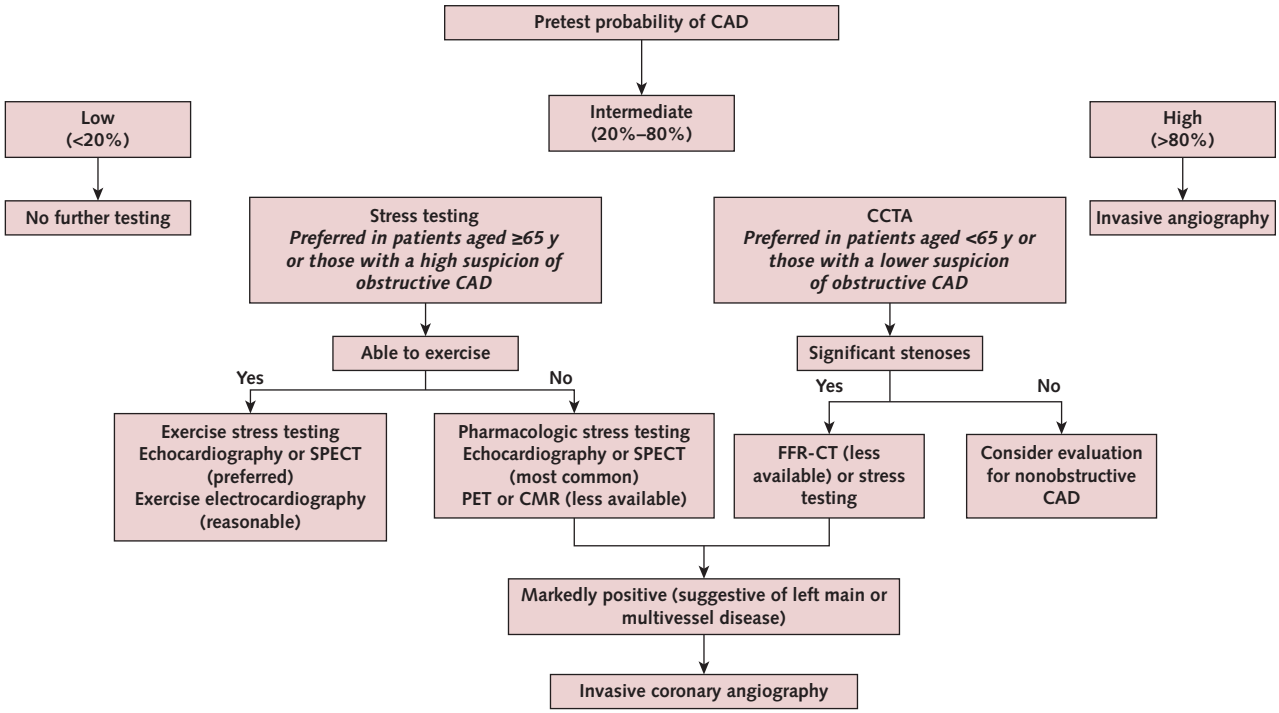
Figure 2. **Diagnosis of CAD in patients with stable chest pain.**



CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CMR = cardiovascular magnetic resonance imaging; FFR-CT = fractional flow reserve with computed tomography; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

in patients with metal devices or severe kidney dysfunction.

CCTA

CCTA is a noninvasive alternative to stress testing that provides anatomical instead of functional information. Whereas stress testing assesses left ventricular wall motion abnormalities or perfusion defects to determine whether obstructive CAD is present, CCTA directly visualizes the coronary arteries to quantify the degree of stenosis and assess plaque characteristics.

CCTA is preferable in people younger than 65 years who are not receiving optimal preventive therapies, while stress testing may be advantageous in those aged 65 years or older because coronary calcification and existing stents interfere with the ability to evaluate for stenoses (4). Randomized trials have shown that CCTA and stress testing have similar effectiveness in patients with symptomatic CCAD (11, 12).

When should invasive coronary angiography be used as the initial test?

Noninvasive testing is less helpful in patients with a high likelihood of disease (>90%) based on symptoms and risk factors, and moving directly to invasive coronary angiography is appropriate

Duke Treadmill Score*

Calculated as minutes of exercise − (5 × maximal ST-segment deviation in millimeters) − (0 for no chest pain, 4 for angina with exertion, or 8 if angina is the reason for stopping the test)

A score >5 indicates low risk (predicted 1-year mortality of about 0.25%), a score of 4 to −10 indicates intermediate risk (about 1.25%), and a score below −11 indicates high risk (about 5.25%)

* *From reference 9.*

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(2, 4). Using coronary angiography as the initial diagnostic test for CAD is also indicated for patients presenting with life-threatening ventricular arrhythmias or a new and unexplained reduction in ejection fraction.

How should the diagnostic approach change when the patient has known CAD?

In patients with known CAD, testing should be performed if there is new-onset or persistent stable chest pain to identify areas of ischemia and thus targets for revascularization. In patients with frequent angina or severe stress-induced ischemia on functional testing, referral to invasive coronary angiography is preferred (Class 1 recommendation) over CCTA (Class 2a recommendation) (4).

Can patients have angina without obstructive CAD?

Up to 30% of patients presenting with angina have ischemia and no obstructive coronary artery disease (INOCA); this is more common among women. Coronary or microvascular flow abnormalities on PET or cardiac MRI (4, 13) can aid in diagnosis of INOCA and initiation of antianginal therapies (14, 15). Of note, epicardial coronary spasm (Prinzmetal or variant angina) is present in only about 5% of clinically stable women with angina and INOCA (13).

When should clinicians refer patients with suspected CCAD to specialists?

Clinicians should consider consulting a cardiologist for patients who have an uncertain diagnosis after noninvasive testing, a contraindication to noninvasive testing, or a high likelihood of CAD warranting coronary angiography (2, 4). Patients with suspected INOCA should also be referred to a cardiologist (13).

Diagnosis... The most useful early predictors of clinically important CAD are age, sex, type of chest pain, smoking history, and presence of comorbid conditions, including hyperlipidemia and diabetes. The physical examination can identify cardiac disease other than CAD and conditions that exacerbate angina, such as hypertension, valve disease, and anemia. All patients should have resting electrocardiography and chest radiography, and almost all should have noninvasive evaluation of coronary function using an exercise or pharmacologic stress test with electrocardiography alone or in combination with imaging by echocardiography or SPECT. Noninvasive evaluation of coronary anatomy with CCTA is an alternative for patients younger than 65 years without known CAD.

CLINICAL BOTTOM LINE

Treatment

What are the goals of treatment?

All patients with CCAD should receive therapy for risk factor modification, prevention of thrombosis, mitigation of atherosclerotic progression, and improvement in functional capacity. There are 2 categories of treatment goals: prevention of ischemic events, and reduction of the burden of angina. This distinction is useful because not all therapies reduce symptoms and prevent ischemic events. For example, randomized trials show that percutaneous coronary revascularization of stable lesions reduces symptoms but does not reduce MI or mortality (16–18).

What is the role of patient education?

Patients should receive education on the underlying disease process and treatment goals and options, with an emphasis on lifestyle modifications and treatments to reduce those risk factors. Patients need to know that the angina of CCAD is not unstable angina, which requires prompt medical attention. However, they also need to know what to do if symptoms of an ACS do occur

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Points for Patient Education

Describe the difference between CCAD and ACS

Emphasize that the usual warning sign for ACS is typical chest pain occurring at rest or with minimal exertion

Explain what the patient should do in these circumstances:

- Chew and dissolve a 325-mg aspirin tablet (or four 81-mg tablets)
- Take sublingual nitroglycerin every 5 minutes for up to 3 doses (unless phosphodiesterase type 5 inhibitors have been used in the previous 24 hours)
- Immediately present to the nearest hospital with 24-hour service for cardiovascular emergencies

Suggest training on cardiopulmonary resuscitation for the patient's family

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(see the **Box**: Points for Patient Education). A patient's ability to adhere to recommended medical therapies and lifestyle changes may be impaired by low literacy, mental health concerns, social isolation, cultural beliefs, environmental factors, poverty, advanced age, or complex comorbid conditions.

Information on patient lifestyle modifications is provided in the **Appendix** (available at Annals.org).

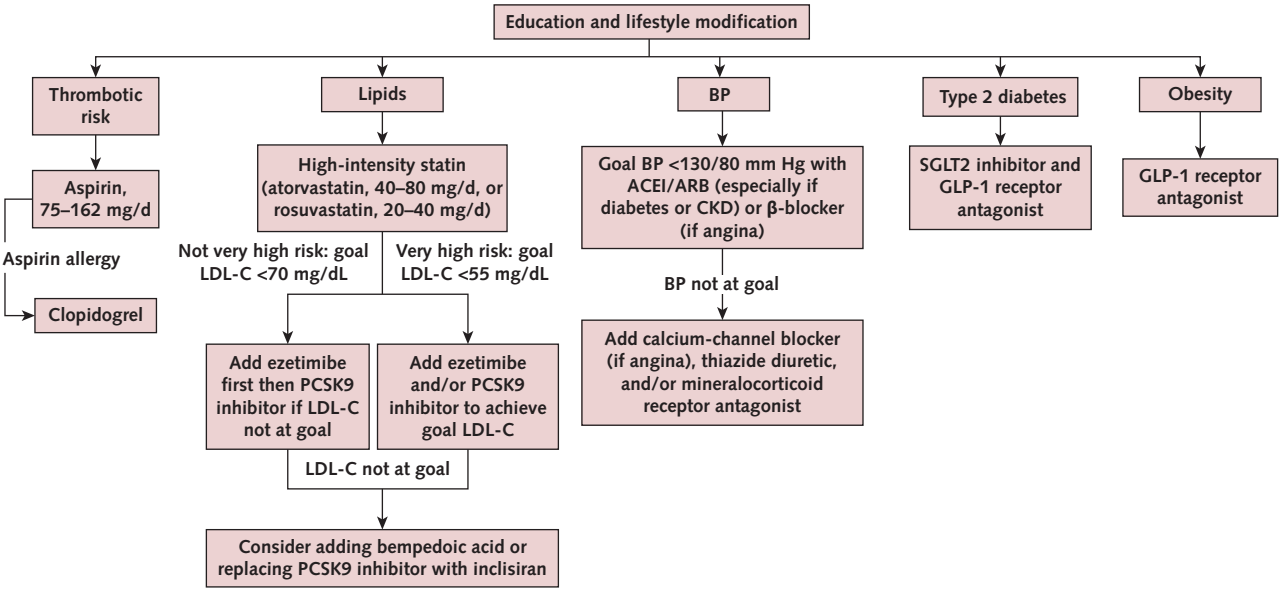
What is guideline-directed medical therapy?

Optimizing risk factors often requires more than lifestyle modification. An additional option is a combination of treatments that is appropriate for most patients, known as guideline-directed medical therapy (GDMT) (**Figure 3**).

Lipid management

Patients with atherosclerotic cardiovascular disease (ASCVD) are categorized into 1 of 2 groups (see the **Box**: Criteria for Defining Patients at Very High Risk for Future ASCVD Events). These categories are important in determining the low-density lipoprotein cholesterol (LDL-C) goal and recommended intensification for patients not meeting the goal. All patients with CCAD require a high-intensity statin (atorvastatin, 40 to 80 mg/d, or rosuvastatin, 20 to 40 mg/d),

Figure 3. **Guideline-directed medical therapy for patients with CCAD.**



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BP = blood pressure; CCAD = chronic coronary artery disease; CKD = chronic kidney disease; GLP-1 = glucagon-like peptide-1; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SGLT2 = sodium–glucose cotransporter-2.

Criteria for Defining Patients at Very High Risk* for Future ASCVD Events

Major ASCVD events
- Recent ACS (within the past 12 months)
- History of MI (other than recent ACS event)
- History of ischemic stroke
- Symptomatic peripheral artery disease (history of claudication with ankle–brachial index <0.85 or previous revascularization or amputation)

High-risk conditions
- Age ≥65 years
- Heterozygous familial hypercholesterolemia
- History of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
- Diabetes
- Hypertension
- Chronic kidney disease (estimated glomerular filtration rate of 15 to 59 mL/min/1.73 m^2)
- Current smoking
- Persistently elevated LDL-C level (≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
- History of congestive heart failure

* *Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.*

with a goal of a 50% reduction in LDL-C level (2). However, baseline LDL-C levels in patients before statin initiation are not always available in clinical practice, and goals of less than 70 mg/dL for those who are not at very high risk and less than 55 mg/dL for those at very high risk should be targeted (19).

For those not at very high risk, if an LDL-C level below 70 mg/dL is not achieved with high-intensity statin therapy or high-intensity statin therapy is not tolerated, ezetimibe can be prescribed first (20), followed by a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (evolocumab or alirocumab) (19). For patients at very high risk with an LDL-C level of 55 mg/dL or higher despite maximally tolerated statin therapy, a PCSK9 inhibitor may be used preferentially over ezetimibe (19), although randomized controlled trials have not evaluated whether an ezetimibe-first strategy is preferred before addition of a PCSK9 inhibitor.

The FOURIER trial evaluated evolocumab among patients with established ASCVD with an LDL-C level of 70 mg/dL or higher or a non–high-density lipoprotein cholesterol level of 100 mg/dL or higher on maximally tolerated statin therapy with or without ezetimibe. Cardiovascular events were significantly reduced by 15% with evolocumab, with greater benefit observed among those with additional high-risk clinical factors. No increased risk for neurocognitive adverse effects was observed, even among those achieving very low LDL-C levels (21).

The ODYSSEY OUTCOMES trial evaluated alirocumab use in patients with an ACS event 1 to 12 months earlier on maximally tolerated statin therapy with or without ezetimibe. Cardiovascular events were significantly reduced by 15% with alirocumab, especially in those with additional high-risk clinical factors (22).

Additional options for lipid-lowering therapy in patients with CCAD who have not achieved an LDL-C goal despite maximally tolerated statin therapy include bempedoic acid and inclisiran. Bempedoic acid has been shown to reduce risk for cardiac events in statin-intolerant patients with CAD (23). Inclisiran, a small interfering RNA therapeutic agent, reduces hepatic synthesis of PCSK9; although a 50% decrease in LDL-C level has been observed, no outcome studies are available to date (24). Inclisiran may be considered in patients who warrant PCSK9 inhibitors but have poor adherence, experience adverse effects, or are unable to self-inject.

In patients with CCAD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids has no benefit in reducing cardiovascular risk (2).

The REDUCE-IT trial showed that a high dose of a purified and stable fish oil (icosapent ethyl) compared with a mineral oil placebo reduced relative risk for cardiovascular events by 25% in patients with CCAD who already were taking aspirin and high-dose statins, had LDL-C levels of 41 to 100 mg/dL, and had

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fasting triglyceride levels of 135 to 499 mg/dL (25).

Despite the positive results of REDUCE-IT, there has been minimal enthusiasm for incorporating icosapent ethyl into clinical practice. Incident atrial fibrillation is more common with icosapent ethyl and other omega-3 fatty acid formulations. In addition, the mineral oil placebo used in REDUCE-IT has adverse effects on lipid and inflammatory biomarkers (26), suggesting that mineral oil may not be an inert placebo. In fact, other trials of fish oil formulations using non–mineral oil placebo did not show the same benefit in cardiovascular outcomes. Secondary causes of elevated triglyceride levels (such as medications, diabetes, or lifestyle) should be addressed before icosapent ethyl is considered.

Hypertension

Hypertension is an important independent risk factor for CAD events. There is a doubling of cardiovascular risk for each increase of 20 mm Hg in systolic blood pressure (BP) or 10 mm Hg in diastolic BP (27).

The SPRINT trial showed that when antihypertensive medications were used to reduce systolic BP from 135 to 121 mm Hg in patients with CCAD who were older than 50 years, the number of major adverse cardiovascular events decreased by 31% (28).

Current guidelines recommend a BP goal below 130/80 mm Hg in patients with CCAD (2). The choice of BP medication often depends on other indications. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers are considered first-line agents for management of hypertension in patients with CCAD (29, 30), especially those with diabetes (29) or chronic kidney disease (31, 32). β-Blockers may be prescribed for angina and can also control hypertension but are not considered first-line therapy. Additional agents for optimization may include dihydropyridine calcium-channel blockers, long-acting thiazide diuretics, and mineralocorticoid receptor antagonists (2).

Diabetes

Diabetes increases risk for CCAD; the risk for death due to coronary events in patients with diabetes is equivalent to that in patients with a previous MI (33). Early diagnosis of diabetes and intensive focus on optimal blood glucose control are essential.

Historically, hemoglobin A_{1c}–lowering therapies have successfully reduced microvascular (retinopathy, neuropathy, and nephropathy) but not macrovascular (stroke and MI) complications. However, 2 classes of medications for glycemic control have now demonstrated cardiovascular benefit in patients with CCAD and type 2 diabetes: sodium–glucose cotransporter-2 (SGLT2) inhibitors (34–38), and glucagon-like peptide-1 (GLP-1) receptor agonists (39–42).

In patients with diabetes and CCAD, an SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin) or a GLP-1 receptor agonist (dulaglutide, liraglutide, or semaglutide) with proven cardiovascular benefit is recommended to reduce the risk for cardiovascular outcomes (2). Combined therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist with demonstrated cardiovascular benefit offers additive reduction in adverse cardiovascular and kidney events (2, 43). Although metformin remains the preferred initial agent for management of diabetes, SGLT2 inhibitors and/or GLP-1 receptor agonists should be used in patients with CCAD even if glucose control is already acceptable with metformin (43).

Obesity

Although improved diet and exercise are key elements of behavior change, they do not always translate to weight loss. Furthermore, intensive lifestyle intervention may not improve cardiovascular outcomes in patients with obesity, even those with type 2 diabetes (44). The introduction of incretin-based

therapies (the general term comprising the GLP-1 receptor agonists liraglutide and semaglutide and the dual GLP-1 receptor agonist/glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide) has changed the landscape of obesity management pharmacotherapy. Liraglutide, semaglutide, and tirzepatide were initially approved by the U.S. Food and Drug Administration (FDA) to treat diabetes and are now approved for obesity, with body weight reductions of 8.0%, 14.9%, and 20.9%, respectively (45–47).

Incretin-based therapies reduce the risk for a composite primary outcome of cardiovascular death, MI, or stroke in patients with diabetes (39, 40, 42, 48). The benefit of semaglutide has been extended to patients without diabetes (49).

In the SELECT trial, patients without diabetes but with cardiovascular disease and body mass index over 27 kg/m^2 were randomly assigned to semaglutide or placebo for 52 weeks. Semaglutide resulted in significant weight loss as well as a reduction in a composite of cardiovascular death, MI, and stroke (49).

Weight loss surgery may also be considered, especially for patients with diabetes, for whom Roux-en-Y gastric bypass reduces the frequency of cardiovascular events (50).

Which medical therapies can prevent MI or death in CCAD, independent of risk factors?

Antiplatelet therapy

Low-dose aspirin (75 to 162 mg/d) is recommended to reduce risk for MI and cardiovascular disease in patients with CCAD (51). Importantly, low-dose aspirin is as effective as high-dose aspirin (325 mg/d) and carries lower bleeding risk. In aspirin-intolerant patients, clopidogrel is an acceptable alternative. Neither prasugrel nor ticagrelor has been studied in CCAD (2).

Immunizations

Patients with CCAD should receive annual vaccinations against influenza (2, 52), COVID-19 per public health guidelines, and pneumococcal pneumonia (2).

Anti-inflammatory therapy

Inflammation is a key component in the development of atherosclerosis. However, the anti-inflammatory agents canakinumab (53) and methotrexate (53) have shown mixed results, and neither is recommended in CCAD. Colchicine reduced the risk for recurrent cardiovascular events in patients with CCAD, though with a trend toward increased deaths from noncardiovascular causes (54). There may be benefit after MI (55), and colchicine is FDA-approved for this indication. However, given its narrow therapeutic window, dependence on adequate kidney function for clearance, and potential for drug–drug interactions, colchicine is typically limited to patients who remain at very high risk despite optimal GDMT (2).

Which medical therapies relieve symptoms?

β-Blockers decrease myocardial oxygen demand via decreases in contractility, heart rate, or both, while nitrates and dihydropyridine calcium-channel blockers improve hemodynamics via vasodilation. All are effective first-line antianginal medications in patients with stable chronic angina (2).

β-Blocker therapy

All β-blockers are effective in reducing angina; the dosage should be titrated to achieve a resting heart rate between 55 and 60 beats/min. In patients with reduced left ventricular function, metoprolol succinate, bisoprolol, and carvedilol reduce long-term mortality. β-Blockers should be used with caution in patients taking nondihydropyridine calcium-channel blockers (verapamil, diltiazem) because of additive negative inotropic and chronotropic effects. Caution should be used in the setting of significant conduction disease. Of note, long-term routine β-blocker therapy improves outcomes in patients with CCAD only if they have had an MI in the previous year, have a left ventricular ejection fraction of 50% or lower, or

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have another primary indication for β-blocker therapy, such as rate control of atrial fibrillation (56). Thus, given potential intolerance due to fatigue and exertional limitations, routine β-blocker use outside of these indications is not recommended.

Calcium-channel blockers

Dihydropyridine calcium-channel blockers, such as amlodipine, are effective for anginal relief. Short-acting formulations, such as short-acting nifedipine, should be avoided because they can paradoxically worsen angina by acutely lowering BP, resulting in reflex tachycardia and increased myocardial oxygen demand. Non-dihydropyridine calcium-channel blockers should not be used in patients with left ventricular dysfunction due to increased adverse events associated with their negative chronotropic and inotropic effects.

Nitrates

Short-acting nitrates (sublingual nitroglycerin or nitroglycerin spray) can be used for immediate relief of angina. Patients can administer 1 dose every 5 minutes for up to 3 doses. Long-acting nitrates (isosorbide mononitrate and nitroglycerin patch formulations) provide constant vasodilation. A nitrate-free interval of 8 to 12 hours, generally at night, is needed to avoid nitrate tolerance and reduced efficacy; this can be provided by isosorbide dinitrate. Patients must be warned about the interaction between nitrates and phosphodiesterase type 5 inhibitors (sildenafil and tadalafil) and advised to alert emergency medical services about recent use of these drugs.

Ranolazine

Ranolazine may be used in patients who have angina despite optimal or maximal therapy with β-blockers, calcium-channel blockers, and/or nitrates (2). It is prescribed solely for symptom relief, with no evidence of improvement in clinical outcomes, and it may be associated with symptomatic orthostasis. Ranolazine has a modest QT-prolonging effect but no proarrhythmic effects. Dose reduction is indicated in patients receiving moderate inhibitors of cytochrome P450 3A4 (CYP3A4), such as verapamil and diltiazem. Ranolazine should not be used in combination with strong CYP3A4 inhibitors (clarithromycin, itraconazole, ketoconazole, several HIV medications) because of resultant increases in serum ranolazine levels.

Which patients are candidates for revascularization with coronary artery bypass grafting or percutaneous coronary intervention?

Percutaneous coronary intervention (PCI) comprises catheter-based techniques, usually with insertion of drug-eluting stents to improve coronary blood flow by relieving coronary obstruction. Coronary artery bypass grafting (CABG) uses surgical grafts to deliver blood beyond the diseased proximal coronary segments. Although several randomized trials have shown that routine revascularization (typically percutaneous) does not reduce major adverse cardiac events (16–18), an integrated risk assessment can identify patients who may benefit from revascularization, as outlined in the next 2 sections.

Which patients should receive revascularization to improve symptoms?

There is greater initial reduction in angina and improved quality of life with GDMT plus revascularization versus GDMT alone (57). However, the differences narrow over time as patients who initially received GDMT alone begin to have revascularization for persistent symptoms.

In the ORBITA trial, patients with stable angina were randomly assigned to PCI versus a sham procedure (58). PCI did not increase exercise time by more than the effect of a placebo procedure. In addition, after the blinded 6-week follow-up, 85% of patients who had a sham procedure elected to undergo PCI.

Furthermore, there is no demonstrated benefit in trials of PCI versus GDMT in CCAD with stable angina (16, 17).

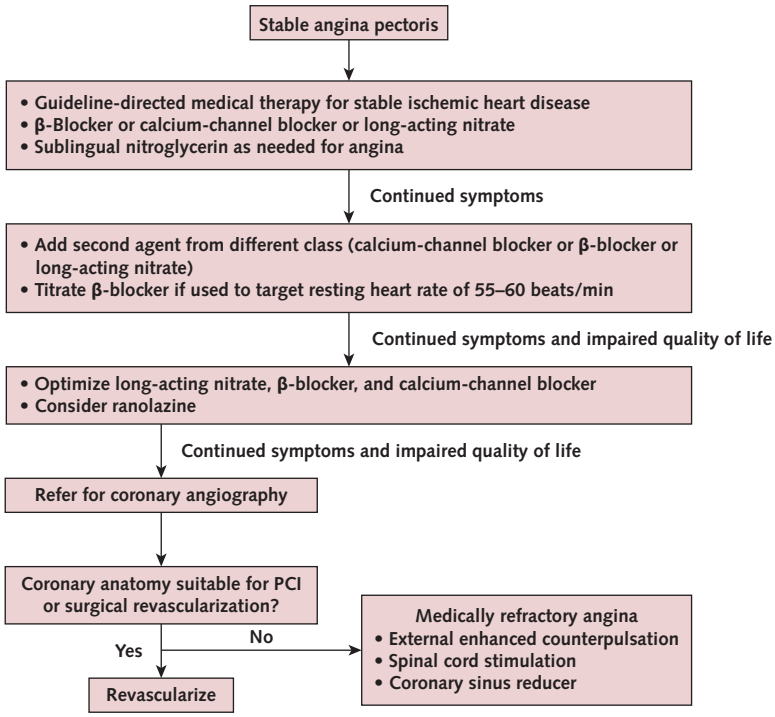
The ISCHEMIA trial randomly assigned patients with moderate or severe ischemia to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed. There was no difference in the risk for ischemic cardiovascular events or death from any cause over a median of 3.2 years (16).

Based on these trials, revascularization is indicated to improve symptoms in patients with lifestyle-limiting angina despite GDMT and significant stenoses amenable to revascularization (**Figure 4**) (7).

When revascularization is being considered, which patients should have CABG, and which ones should have PCI?

The decision for surgical versus percutaneous revascularization should be based on patient preferences, the complexity of the coronary anatomy (for example, SYNTAX score [59]), and surgical risk. There is survival benefit from CABG compared with PCI in patients with complex or diffuse coronary disease (60, 61), left main disease (62), and diabetes (18). CABG also improves 10-year survival compared with

Figure 4. **Management of stable angina pectoris.**



External enhanced counterpulsation, spinal cord stimulation, and coronary sinus reducer have limited evidence of benefit and availability. PCI = percutaneous coronary intervention.

medical therapy in multivessel disease and severe left ventricular dysfunction (63). Compared with saphenous vein grafts, arterial grafts offer superior long-term patency and lower rates of repeated revascularization (64), and thus internal mammary and radial artery grafts are the preferred conduits for CABG (65). Although myocardial viability is associated with improved survival and ventricular recovery after revascularization in patients with left ventricular dysfunction, the role of viability testing before revascularization has not been established.

Are there special considerations for women, older adults, or patients with chronic kidney disease?

Women

Women generally have lower incidence of CCAD than men until older age, but worse outcomes after MI. Microvascular disease, coronary spasm, and spontaneous CAD are more common in women (13). Angina-equivalent symptoms, such as dyspnea, are more common in women, although the patterns, duration, and frequency of symptoms are similar between men and women. Women receive aspirin and other antithrombotic medications less frequently than men and are less likely to have revascularization. Differences in presentation and testing may account for some of the observed differences in care between men and women with coronary disease, but more information about these discrepancies is needed.

Older adults

In adults aged 75 years or older, coronary stenoses tend to be more diffuse and severe, with higher prevalence of 3-vessel and left main disease (66). Common coexisting conditions of the pulmonary, gastrointestinal, and musculoskeletal systems can cause chest pain, making diagnosis challenging, even in patients with documented CCAD. By virtue of age and comorbid conditions, pretest probability in older adults is generally higher and stress testing with imaging is typically indicated. There is less frequent use of GDMT in older adults, possibly because pharmacotherapy is complicated by comorbid conditions. Shared decision making is particularly important when considering treatment options for older patients (2).

Patients with chronic kidney disease

Chronic kidney disease confers greater risk for CAD (67) and poor outcomes after interventions for acute MI (68). However, such patients also often require

Questions for Follow-up Visits

- Has the patient's physical activity decreased since the last visit?
- Has angina increased in frequency or become more severe since the last visit?
- How successful has the patient been in modifying risk factors and learning more about ischemic heart disease?
- Has the patient developed any new comorbid conditions, or has the severity or treatment of known comorbid conditions worsened angina?
- Is the patient taking prescribed medications, and are they causing adverse effects?

dye-based investigations. When possible, the risk for contrast nephropathy should be mitigated with adequate prehydration (69) and minimization of the volume of contrast media. There is no benefit of bicarbonate or *N*-acetyl-L-cysteine over normal saline for prevention of acute kidney injury (70). Otherwise, patients with chronic kidney disease and CCAD should receive similar GDMT to patients without chronic kidney disease (2).

How should patients with treated CCAD be followed?

Follow-up visits should be scheduled according to clinical stability and establishment of consistent communication with patients and other treating physicians. Appointments every 3 to 6 months during the first year of treatment and every 4 to 12 months thereafter are appropriate as long as angina remains stable and risk factor management is optimized.

During each visit, detailed information should be obtained (see the **Box**: Questions for Follow-up Visits).

Laboratory evaluation should be used to monitor modifiable risk factors. A fasting lipid panel can be performed as early as 4 weeks after initiation of lipid-lowering therapy to facilitate rapid titration and at least annually thereafter. Routine monitoring of creatine kinase and liver enzymes in patients receiving statins is not recommended. Hemoglobin A_{1c} should be measured twice annually. Routine periodic anatomical or ischemic testing without a change in clinical or functional status is not recommended for risk stratification or to guide therapeutic decision making in patients with CCAD.

Treatment... The primary goals of treating patients with CCAD are to minimize adverse cardiovascular outcomes and death while maximizing health and function. Education is essential to ensuring that patients understand the underlying disease process and recognize signs and symptoms of MI. Risk factor modification using a combination of behavioral change and medical therapy is critical to improving outcomes. All patients should receive GDMT to reduce risk for death and relieve symptoms. Revascularization should be considered for patients with persistent symptoms despite GDMT, especially those at higher risk for death.

CLINICAL BOTTOM LINE

In the Clinic
Tool Kit

Chronic Coronary Artery Disease

Patient Information

https://medlineplus.gov/coronaryarterydisease.html
https://medlineplus.gov/languages/coronaryarterydisease.html
Information on coronary artery disease in English and other languages from the National Institutes of Health's MedlinePlus.

https://www.nhlbi.nih.gov/health/coronary-heart-disease
https://www.nhlbi.nih.gov/es/salud/cardiopatia-coronaria
Information on coronary heart disease in English and Spanish from the National Heart, Lung, and Blood Institute.

https://www.heart.org/en/health-topics/heart-attack/about-heart-attacks/silent-ischemia-and-ischemic-heart-disease
Information on ischemic heart disease and silent ischemia from the American Heart Association.

Information for Health Professionals

https://www.ahajournals.org/doi/10.1161/CIR.0000000000001309
2025 guideline for the management of patients with acute coronary syndromes from the American College of Cardiology, American Heart Association, American College of Emergency Physicians, National Association of EMS Physicians, and Society for Cardiovascular Angiography and Interventions.

https://www.ahajournals.org/doi/10.1161/CIR.0000000000001168
2023 guideline for the management of patients with chronic coronary disease from the American Heart Association, American College of Cardiology, American College of Clinical Pharmacy, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association.

https://www.ahajournals.org/doi/10.1161/CIR.0000000000001029
2021 guideline for the evaluation and diagnosis of chest pain from the American Heart Association, American College of Cardiology, American Society of Echocardiography, American College of Chest Physicians, Society for Academic Emergency Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance.

WHAT YOU SHOULD KNOW ABOUT CHRONIC CORONARY ARTERY DISEASE

What Is Chronic Coronary Artery Disease?

Chronic coronary artery disease (CCAD) occurs when the heart does not get enough oxygen because of poor blood flow. The heart gets its oxygen from blood flowing through small blood vessels and not from the large blood vessels used to pump blood through the body. When the heart does not get enough oxygen, you may feel pain or pressure in your chest, known as angina. Angina usually occurs during physical exercise or emotional stress when the heart has to work harder and needs more oxygen. It lasts for a few minutes and goes away with rest or medication. The most common cause of CCAD is obstruction of the small blood vessels. Early diagnosis and treatment are important to reduce risk for serious complications, such as a heart attack or stroke.

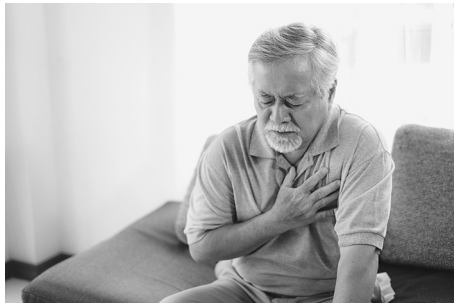
Am I at Risk?

CCAD is more common in men than in women, and it occurs more often in middle and older age. Risk factors include:

- Diabetes
- High blood pressure
- High cholesterol
- Cigarette smoking
- Being overweight
- Drinking alcohol
- A family history of heart disease at a young age

How Is It Diagnosed?

- Your health care provider will ask you questions about your symptoms and medical history.
- You will have a physical examination and may have blood tests.
- You may have additional tests to show how your heart is working. These tests are painless and include a chest x-ray; an electrocardiogram, which measures the electrical activity of the heart muscle; and an echocardiogram, which creates moving pictures of how your heart is functioning.
- You may have a stress test, which provides information on how exercise affects angina symptoms and heart functioning.
- Other tests may be needed, such as coronary angiography (also known as cardiac catheterization). This test looks directly at the heart blood vessels by filling them with dye and taking pictures to identify blockages.



How Is It Treated?

The goal of treatment is to prevent serious events, like a heart attack or stroke, and to reduce angina and other symptoms.

- A low dose of aspirin every day will help prevent a heart attack, unless you have risk factors that would make this unsafe for you.
- Several medications can reduce the frequency of angina symptoms, including nitrates and beta-blockers.
- If your arteries are clogged enough, your doctor may widen them with a nonsurgical procedure called percutaneous coronary intervention.
- Blockages that cannot be treated with percutaneous coronary intervention may need heart bypass surgery.

What Lifestyle Changes Should I Make?

The most important part of your treatment is to understand the disease and to make lifestyle changes that will improve your heart health, such as:

- Controlling other health conditions, such as high blood pressure, high cholesterol, and diabetes
- Quitting smoking
- Following a heart-healthy diet
- Increasing physical activity
- Limiting alcohol intake
- Reducing stress
- Getting an annual flu shot to help avoid heart complications from the virus

Questions for My Doctor

- What is my risk for chronic coronary artery disease?
- What are the warning signs of a heart attack?
- What exercise is safe for me to do?
- What medicines are best for me?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

American Heart Association
www.heart.org/en/health-topics/heart-attack/angina-chest-pain/angina-pectoris-stable-angina

Centers for Disease Control and Prevention
www.cdc.gov/heartdisease

Patient Information

Appendix: How Should Patients Modify Their Behavior?

About half the decrease in cardiovascular mortality during the past 40 years has been due to interventions directed at risk factors. According to one analysis, approximately 24% of the observed mortality reduction could be attributed to decreasing total cholesterol levels, 20% to decreasing systolic BP, 12% to reducing smoking, and 5% to increasing physical activity (71). Meaningful improvement in risk factors often requires a combination of pharmacologic and nonpharmacologic interventions. However, initial risk reduction should focus on promoting smoking cessation, moderating alcohol consumption, increasing physical activity, and following a heart-healthy diet (2).

Smoking Cessation

Smoking increases cardiovascular disease mortality by 50%, and smoking cessation is associated with a 36% reduction in death and a 32% reduction in MI (72). Among nondrug therapies, smoking cessation presents the greatest opportunity for risk reduction (73). Clinicians should systematically identify all tobacco users and recommend smoking cessation at each clinic visit because consistent, direct reminders increase the likelihood of quitting (74). Patients with symptomatic CAD are particularly receptive to this advice (75). Clinicians should help patients develop a plan that includes drugs (nicotine replacement, bupropion, varenicline) and smoking cessation programs that use counseling, peer support, and other social components (2, 76). Patients with CCAD who use e-cigarettes to support smoking cessation should be warned about the risks for developing long-term dependence and encouraged to quit use of e-cigarettes promptly to avoid potential long-term risks (77). Thus, although e-cigarettes increase the likelihood of successful smoking cessation compared with nicotine replacement therapy, because of the lack of long-term safety data and risks of sustained use, e-cigarettes are not recommended as first-line therapy for smoking cessation.

Physical Activity

Regular exercise reduces coronary heart disease mortality, improves functional capacity, and can decrease angina. Physicians should encourage patients with chronic stable angina to engage in moderate aerobic exercise. Guidelines recommend 150 minutes of at least moderate activity per week (2). Resistance training is also well tolerated and is associated with improvements in muscle strength, functional capacity, and control of cardiac risk factors (78). Patients with CCAD and angina and those who have had MI should first participate in a medically supervised cardiac rehabilitation program for 8 to 12 weeks to establish a prescribed exercise regimen (79).

Dietary Modification

An unhealthy diet contributes to dyslipidemia, hypertension, obesity, and diabetes. Current guidelines for CCAD suggest a diet that emphasizes vegetables, fruits, whole grains, legumes, healthy proteins (low-fat dairy products, poultry without the skin, fish and other seafood, and nuts), and nontropical vegetable oils. Intake of sweets, sugar-sweetened beverages, and red meat should be limited (2, 80). Avoiding high amounts of sodium is important for hypertension management (81).

Moderating Alcohol Consumption

Studies have consistently found a J-shaped relationship between alcohol consumption and coronary heart disease, with no benefit and probable harm beyond 2 drinks per day (82). In fact, more contemporary studies suggest that no safe level of alcohol use is acceptable and that previously observed cardioprotective effects of light-to-moderate alcohol use are likely confounded by other lifestyle and

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sociodemographic factors (83). Bouts of heavy drinking worsen hypertension and precipitate ischemia in CCAD and should be avoided (84, 85).

Psychological Well-being

Interventions to reduce psychological stress may improve clinical outcomes in patients with CCAD (86, 87). Clinicians should consider recommending that patients use counseling, meditation, or other interventions to manage stress to reduce risks and improve well-being.

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