likely to have undiagnosed CAD and have worse outcomes when hospitalized for other CVDs, such as heart failure. Undiagnosed diabetes may be recognized at the time of an acute event, such as MI.

Aggressive treatment of cardiovascular risk factors, such as elevated cholesterol levels, is associated with reduced cardiovascular risk in patients with diabetes. Early recognition and treatment are important in reducing the burden of CVD and the morbidity and mortality associated with diabetes.

Systemic Inflammatory Conditions

The prevalence of atherosclerosis is increased and the risk for CVD is higher in patients with systemic inflammatory conditions, such as systemic lupus erythematosus and rheumatoid arthritis. The risk for CAD is nearly 60% higher in patients with rheumatoid arthritis and is doubled in patients with systemic lupus erythematosus. Patients with systemic lupus erythematosus and antiphospholipid antibodies have a higher prevalence of CAD and MI; the relative risk for MI is higher in younger patients with systemic lupus erythematosus than in age-matched controls. The risk for CVD in patients with rheumatoid arthritis increases from twofold at baseline to threefold over 10 years when compared with the general population. The increased risk is likely a result of the inflammatory process, including a prothrombic state, in addition to traditional cardiovascular risk factors.

Chronic Kidney Disease

Chronic kidney disease, defined as reduced estimated glomerular filtration rate, is associated with higher incidence of CVD and worse cardiovascular outcomes. Beyond the risk attributable to traditional risk factors, the risk for cardiovascular events is higher in patients with kidney dysfunction. CVD is the leading cause of death in patients with end-stage kidney disease, and the risk for CVD-related death is 5 to 30 times higher in patients undergoing dialysis than in those with similar risk factors and preserved kidney function. The presence of moderately increased albuminuria (microalbuminuria) independently increases the risk for cardiovascular events.

Despite excessive cardiovascular risk, there is evidence that patients with chronic kidney disease do not receive appropriate preventive therapies, such as statins. Data indicate that patients undergoing hemodialysis do not benefit from secondary prevention with statins.

HIV

Increased survival of patients infected with HIV due to effective antiretroviral therapy has resulted in the increased development of non-AIDS-related complications, including CVD. Patients with HIV have a 1.5 times increased risk for CVD, and cardiovascular mortality is increasing in the HIV-infected population. The increased risk is likely multifactorial, related to antiretroviral therapy–associated dyslipidemia, insulin resistance, medications associated with CVD events (such as protease inhibitors), viral load, and disease-related increases in risk factors (dyslipidemia, diabetes).

KEY POINTS

- Hyperlipidemia, type 2 diabetes mellitus, obesity, and tobacco use confer greater risk for coronary artery disease in women than in men.
- Delayed diagnosis of coronary artery disease in women is often due to the presentation of atypical chest pain.
- Cardiovascular disease risk is increased in patients with diabetes mellitus, systemic inflammatory conditions, HIV, and chronic kidney disease.
- Statin therapy should not be used for secondary prevention of cardiovascular disease in patients on hemodialysis. HVC

Diagnostic Testing in Cardiology

Clinical History and Physical Examination

The clinical history and physical examination are cornerstones in the diagnosis of cardiovascular disease. A careful history that includes symptom characteristics, timing, and duration; factors that exacerbate or relieve symptoms; and functional capacity is critical to ensure a focused and appropriate diagnostic evaluation. Abnormal findings on the cardiovascular examination may also raise suspicion for specific cardiac conditions and guide the selection of tests.

Cardiovascular testing provides both diagnostic and prognostic information, and its use should be guided by symptoms, the pretest likelihood of heart disease, and whether testing results will alter patient management.

Diagnostic Testing for Atherosclerotic Coronary Artery Disease

Diagnostic testing for coronary artery disease (CAD) can be categorized as providing functional and/or anatomic information regarding atherosclerotic disease burden. Functional studies reveal the presence of ischemia (exercise electrocardiography [ECG], single-photon emission CT [SPECT], PET), the extent and severity of ischemia (SPECT, PET), information on coronary blood flow (PET, fractional flow reserve (FFR)–CT), and development of wall motion abnormalities (echocardiography, cardiac magnetic resonance [CMR] imaging). Anatomic information is obtained from invasive angiography, coronary CT angiography (CTA), and coronary artery calcium (CAC) scoring. Cardiac diagnostic testing modalities are summarized in **Table 1**.

TABLE 1. Diagnostic Testing for Coronary Artery Disease

Diagnostic Test	Utility	Advantages	Limitations
Exercise Stress Testing			
Exercise ECG	Initial diagnostic test in most patients suspected of having CAD	Data acquired on exercise capacity, blood pressure and heart rate response, and provoked symptoms	Not useful when baseline ECG is abnormal (LVH, LBBB, paced rhythm, preexcitation, >1-mm ST-segment depression)
Stress echocardiography	Recommended when baseline ECG findings are abnormal or when information on a particular area of myocardium at risk is needed	Exercise data acquired along with imaging for wall motion abnormalities to indicate ischemia Allows evaluation of valve function and pulmonary pressures Relatively portable and less costly than nuclear protocols Entire study is completed in <1 h	Image quality is suboptimal in some patients but can be improved with microbubble transpulmonary contrast Image interpretation is difficult when baseline wall motion abnormalities are present Diagnostic accuracy decreases with single-vessel disease or delayed stress image acquisition
Nuclear SPECT perfusion	Recommended when baseline ECG findings are abnormal or when information on a particular area of myocardium at risk is needed With LBBB, conduction delay in the septum may cause false-positive abnormalities; vasodilator stress can improve the accuracy of perfusion imaging	Gating (image acquisition coordinated with the cardiac cycle); use of higher-energy agents, such as technetium; and techniques used to correct for attenuation provide improved specificity Late reperfusion imaging allows evaluation of myocardial viability if thallium is used	Attenuation artifacts can be caused by breast tissue or diaphragm interference; attenuation correction and software programs can improve image interpretation Radiation exposure
Pharmacologic Stress Testing			
Dobutamine echocardiography	Recommended in patients who cannot exercise or when information on an area of myocardium at risk is needed	Because the patient is supine, images are acquired continuously, allowing the test to be stopped as soon as ischemia is evident	Contraindications are severe baseline hypertension, unstable angina, severe tachyarrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, and large aortic aneurysm
Vasodilator nuclear perfusion (adenosine, dipyridamole, regadenoson)	Recommended in patients who cannot exercise Minimizes septal abnormalities frequently seen with nuclear perfusion scanning in patients with LBBB	Vasodilator stress testing may minimize effect of β-blockade on perfusion defect size Imaging can be performed sooner after myocardial infarction with vasodilator stress	Contraindications are active bronchospastic airway disease, theophylline use, sick sinus syndrome, hypotension, and high-degree AV block Caffeine must be withheld 12-24 h before the test Adenosine or dipyridamole may cause chest pain, dyspnea, or flushing Radiation exposure
Dobutamine nuclear perfusion	Recommended in patients who cannot exercise and have contraindications to vasodilator stress Recommended when information on an area of myocardium at risk is needed	Has sensitivity and specificity similar to those of exercise or vasodilator perfusion imaging for diagnosis of myocardial ischemia	Contraindications are severe baseline hypertension, unstable angina, severe tachyarrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, and large aortic aneurysm Radiation exposure
PET/CT	Provides best perfusion images in larger patients Provides data on myocardial perfusion, function, and viability	Study duration is shorter and radiation dose is lower than with conventional nuclear perfusion imaging Absolute myocardial blood flow can be measured Can be combined with CAC scoring	Not widely available More expensive than other imaging modalities Used with pharmacologic stress only (no exercise protocol) Radiation exposure

(Continued on the next page)

TABLE 1. Diagnostic Testing for Coronary Artery Disease *(Continued)*

Diagnostic Test	Utility	Advantages	Limitations
Dobutamine or adenosine CMR imaging	Provides excellent spatial resolution for wall motion abnormalities during dobutamine infusion Identifies perfusion abnormalities during adenosine infusion with gadolinium as contrast agent Provides data on infarction and viability using gadolinium contrast Identifies anomalous coronary artery origin	Accurate test for myocardial ischemia or viability	Some patients experience claustrophobia May be contraindicated in patients with pacemaker, ICD, or other implanted device Gadolinium is contraindicated in patients with kidney failure Sinus rhythm and a slower heart rate are needed for improved image quality Limited availability and expertise
Other Tests			
Coronary angiography	Provides anatomic diagnosis of the presence and severity of CAD	Percutaneous revascularization can be performed after diagnostic study	Invasive Risks of vascular access and radiocontrast exposure (kidney dysfunction, allergy, bleeding) Radiation exposure
CAC scoring	May inform treatment decisions for patients with intermediate 10-year risk for cardiovascular events	CAC scores are predictive of cardiovascular risk in selected patients	Does not provide data on coronary luminal narrowing Radiation exposure
Coronary CT angiography	Identifies anomalous coronary arteries Useful for selected patients with intermediate risk for CAD	Coronary artery vessel lumen and atherosclerotic lesions can be visualized in detail	Requires high-resolution (64-slice) CT instruments Does not provide detailed images of distal vessel anatomy Catheterization will be needed if intervention is planned Ability to quantify lesion severity can be limited by significant calcification Radiation and radiocontrast exposure

AV = atrioventricular; CAC = coronary artery calcium; CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; SPECT = single-photon emission CT.

Cardiac Stress Testing

Cardiac stress testing is commonly performed to diagnose CAD. Appropriate, cost-effective stress testing is based on the history, physical examination, and pretest probability of CAD, which takes into account age, sex, symptoms, and prevalence of disease. Cardiac stress testing is most effectively used in patients with an intermediate pretest probability of CAD, in whom a positive test result significantly increases disease likelihood and a negative test result significantly decreases likelihood (see Coronary Artery Disease). Performing stress testing in persons with a low likelihood of disease (such as young patients with atypical symptoms) yields a high incidence of false-positive test results, potentially resulting in unnecessary testing, inaccurate diagnoses, and harms. In patients with a high pretest probability of disease, invasive angiography rather than stress testing is appropriate.

Assessment of the patient's functional capacity and ability to exercise is important in determining the most appropriate stress testing. Exercise ECG is recommended as the initial test of choice in patients with normal findings on baseline ECG. If there are baseline ECG abnormalities (such as ST-segment depression >1 mm, left bundle branch block, left ventricular hypertrophy, paced rhythm, or preexcitation), ST-segment changes with exercise cannot be used to evaluate for the presence of obstructive CAD; these abnormalities will result in a nondiagnostic ECG stress test. Functional testing with imaging (with exercise or pharmacologic stress) or anatomic assessment with coronary CTA is indicated in these instances.

Stress testing may also be used for risk assessment in patients known or suspected to have CAD. The ability to exercise and, more important, exercise capacity are strong predictors of cardiovascular events. ECG changes, hemodynamic

CONT.

response to exercise (blood pressure and heart rate recovery), and other measures (such as the Duke Treadmill Score) also provide prognostic information. Stress imaging studies provide information on the extent and severity of disease, which is helpful for risk assessment.

The decision of whether to withhold cardiac medications, such as nitrates and β-blockers, before stress testing should be individualized. In patients who are undergoing exercise stress testing to diagnose CAD, cardiac medications that impair heart rate response (β-blockers) should be withheld for at least 24 hours before testing because these agents may lead to an inadequate peak heart rate. If the stress test is being performed to evaluate symptoms or determine prognosis in a patient with known CAD, patients should continue their cardioactive medication regimen.

Exercise Electrocardiography

Stress testing should always be performed with exercise, unless exercise is contraindicated or the patient is unable to exercise. Exercise stress testing protocols use treadmill or stationary bicycle ergometry, and each protocol should increase workload in a stepwise manner over a period of 6 to 12 minutes to allow adequate time for development of maximal metabolic demand. A standard Bruce protocol increases the speed and grade of the treadmill every 3 minutes. Achieving 85% of the age-predicted maximal heart rate adequately rules out obstructive CAD; however, patients should exercise until limited by symptoms. Because heart rate and blood pressure are the major determinants of myocardial oxygen demand, achieving a rate pressure product (heart rate × systolic blood pressure) of at least 25,000 is considered an adequate workload and reflects overall left ventricular myocardial performance. Stress testing should be terminated when the patient has exerted maximal effort, requests to stop, or experiences significant angina or other physical symptoms. The test should also be stopped for exertional hypotension, significant hypertension (>200/110 mm Hg), ST-segment elevation or significant ST-segment depression, or ventricular or supraventricular arrhythmias.

Ischemia is defined by the development of horizontal or downsloping ST-segment depression of at least 1 mm occurring 80 milliseconds after the J point on exercise ECG, although ST-segment depression cannot localize ischemia (**Figure 1**). The development of hypotension or lack of blood pressure augmentation during exercise can indicate the presence of significant obstructive disease. Heart rate recovery after cessation of exercise provides incremental prognostic information. A heart rate drop of less than 12/min in the first minute after exercise termination is associated with higher mortality. Functional capacity is also a powerful predictor of outcomes; individuals unable to achieve 5 metabolic equivalents, or the first stage of a Bruce protocol, have higher all-cause mortality. Information obtained from exercise stress testing can be combined with clinical information in risk prediction models. The Duke Treadmill Score incorporates duration of exercise, development of symptoms, and degree of ST-segment depression to calculate 5-year all-cause mortality in patients without CAD.

Stress Testing with Adjunctive Imaging

In patients with obstructive CAD, reduced blood flow and myocardial ischemia lead to a progression of myocardial abnormalities, termed the ischemic cascade. Initially, ischemia induces changes in perfusion, followed by diastolic and (at a later stage) systolic dysfunction, ECG changes, and eventually angina. The addition of imaging studies to ECG stress testing

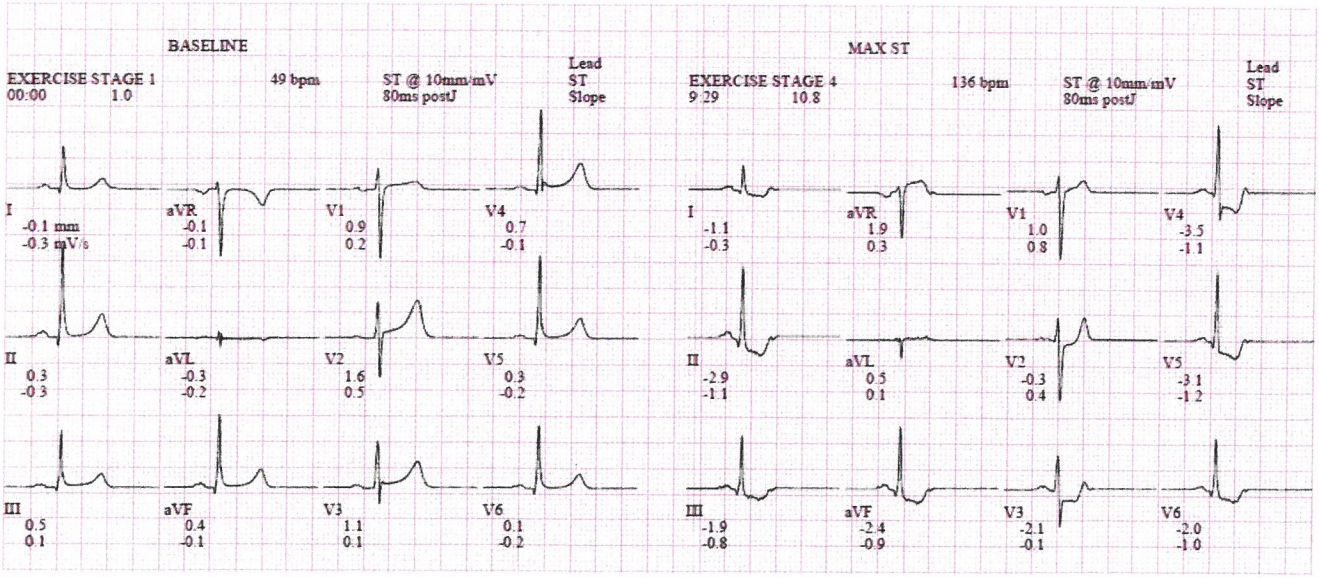

FIGURE 1. Electrocardiogram recorded before (*left*) and during (*right*) exercise stress testing. The presence of 2-mm downsloping ST-segment depressions in leads I, II, III, and aVF, and leads V_3 through V_6, during exercise indicates ischemia.

CONT.

increases diagnostic sensitivity by detecting earlier signs of ischemia.

Stress testing with imaging is indicated in patients with an inability to exercise, contraindications to exercise, baseline ECG abnormalities that would preclude interpretation of the exercise ECG, or indeterminate findings on the exercise ECG. Imaging with SPECT, PET, or CMR can be used to detect reduced myocardial perfusion as early evidence of ischemia. Systolic dysfunction, indicated by wall motion abnormalities during stress, can be detected by echocardiography or CMR imaging. Overall, imaging choice should consider characteristics of the patient and modality as well as local availability and expertise (see Table 1).

Stress testing with adjunctive imaging compares wall motion, perfusion, and/or metabolism at baseline and after stress, depending on the modality used (**Table 2**). Exercise is the stress modality of choice. Patients should undergo pharmacologic stress if they are unable to exercise or have contraindications to exercise. Dobutamine, like exercise, increases myocardial oxygen demand and elicits ischemia because of insufficient perfusion to the affected myocardium. Vasodilators, such as dipyridamole, regadenoson, and adenosine, produce hyperemia and a flow disparity between myocardium supplied by unobstructed vessels and myocardium supplied by the stenotic vessel because of the inability of the distal vasculature to dilate. In patients with left bundle branch block undergoing nuclear stress testing, vasodilator-induced stress is preferred to exercise or dobutamine because of the potential for false-positive septal perfusion abnormalities.

TABLE 2. Interpretation of Stress Testing with Imaging Results

Stress SPECT		
At Rest	**After Stressor**	**Interpretation**
Normal	Normal	Normal
Normal	Perfusion defect	Stress-induced myocardial ischemia
Perfusion defect	Perfusion defect	Infarct
Normal	LV dilation	Small or no distinct zone of ischemia, possible balanced ischemia or multivessel CAD
Stress Echocardiography		
At Rest	**After Stressor**	**Interpretation**
Normal	Normal	Normal
Normal	Wall motion abnormality	Stress-induced myocardial ischemia
Regional wall motion abnormalities	Regional wall motion abnormalities	Infarct
Normal	LV dilation	Small or no distinct zone of ischemia, possible balanced ischemia or multivessel CAD

CAD = coronary artery disease; LV = left ventricular; SPECT = single-photon emission CT.

Stress Echocardiography

Exercise stress echocardiography provides information on ischemia, hemodynamic significance of valvular abnormalities, and pulmonary pressures during exercise. Exercise is performed with supine or upright bicycle ergometry, which allows for continuous imaging, or with a treadmill protocol, which requires acquisition of post-stress images within 90 seconds. The development of new wall motion abnormalities indicates ischemia in the visualized territory. Resting wall motion abnormalities that do not change at peak exercise may indicate infarcted or hibernating myocardium (chronic but potentially reversible ischemic dysfunction).

With pharmacologic stress echocardiography, dobutamine is progressively infused (up to 40 μg/kg/min) to achieve 85% of age-predicted maximal heart rate. Atropine is administered if the target heart rate is not achieved. The development of new wall motion abnormalities indicates myocardial ischemia. Dobutamine infusion may also be used in patients with low-gradient aortic stenosis to help differentiate between severe aortic stenosis and pseudostenosis. Patients with reduced systolic function who are able to augment their stroke volume in the setting of severe aortic stenosis may benefit from aortic valve replacement.

Interpretation of stress echocardiography findings is more subjective than with other tests, and the sensitivity of stress echocardiography may be reduced in the setting of baseline wall motion abnormalities, systolic dysfunction, or single-vessel disease.

Nuclear Stress Testing

Nuclear stress testing compares blood flow in the myocardium to diagnose ischemia. In SPECT myocardial perfusion imaging, a radiotracer is injected at rest and at peak exercise/vasodilation, and the radiotracer is taken up by the myocardium relative to blood flow. Rest images are compared with those obtained after exercise or pharmacologic stress. Perfusion defects observed on images obtained after stress indicate flow-limiting CAD (**Figure 2**). Regions with fixed defects can indicate infarcted or hibernating myocardium, and viability assessment can help distinguish between the two. Gated images can provide an assessment of left ventricular systolic function.

SPECT imaging can also quantify the extent and severity of disease, providing additional prognostic information. High-risk features, such as several regions of hypoperfusion, a lack of augmentation or a reduction in post-stress ejection fraction, transient cavity dilatation, and wall motion abnormalities, are associated with a worse prognosis.

Technetium-based myocardial perfusion imaging has higher sensitivity and specificity than thallium-based studies and also provides better image quality. Technetium-based

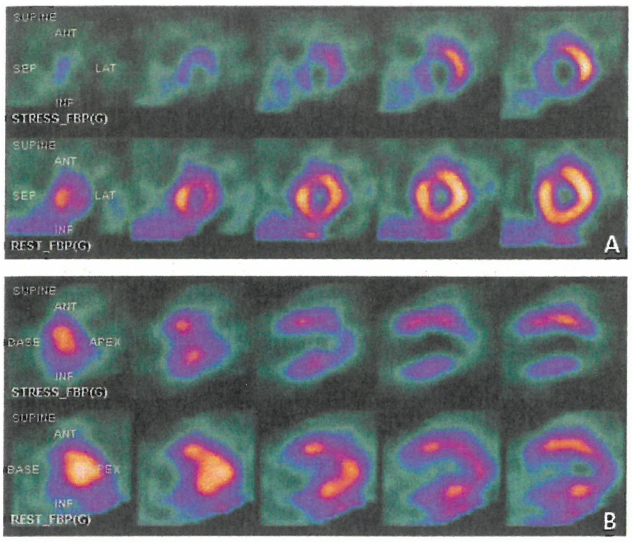

FIGURE 2. Selected images from a nuclear perfusion single-photon emission CT (SPECT) stress study. Short-axis views (*panel A*) of the heart with stress (*top row*) and at rest (*bottom row*) show a radiotracer defect in the septum and inferior wall that is filled on the rest images. Long-axis views (*panel B*) demonstrate an apical filling defect with stress (*top row*) that is perfused on rest images (*bottom row*).

CONT.

agents are taken up with blood flow and are bound to the mitochondria, allowing for delayed imaging. In contrast, uptake of thallium requires active metabolism, which can be useful to assess myocardial viability (**Table 3**).

TABLE 3. Interpretation of Myocardial Viability Study Results

SPECT Viability Testing		
Initial Study (at Rest)	**Rest Study Repeated After 4-24 h (with Thallium)**	**Interpretation**
Perfusion defect	Perfusion defect	Fixed defect: infarct, no viability
Perfusion defect	Reperfusion of area	Viable myocardium
PET Viability Testing		
Baseline	**Metabolism**	**Interpretation**
Perfusion defect	Metabolically active	Viable myocardium
Echocardiographic Viability Testing		
Baseline	**Response to Dobutamine**	**Interpretation**
Wall motion abnormality	Low dose: improvement of function	Biphasic response indicates viable myocardium
	Higher dose: worsening of function	

SPECT = single-photon emission CT.

Cardiac PET provides excellent diagnostic and prognostic information for patients known or suspected to have CAD. PET provides better temporal and spatial resolution than does SPECT imaging, which is helpful in patients who are obese or who have nondiagnostic SPECT results. CT may be used with PET to provide information on the presence of coronary artery calcification. PET radiotracers have a short half-life, resulting in lower radiation exposure and necessitating the use of vasodilators. Vasodilator stress allows for assessment of peak stress ejection fraction, quantification of absolute myocardial blood flow, and evaluation of myocardial metabolism. The utility of PET imaging in cardiac patients is limited by availability of the technology.

Cardiovascular Magnetic Resonance Imaging

CMR imaging is used with dobutamine to assess development of wall motion abnormalities or with vasodilators to assess perfusion. Right and left systolic function can be assessed with gated imaging. CMR imaging is commonly used to evaluate inflammatory or infiltrative diseases, pericardial diseases, and the extent and severity of infarction. Viability can be determined by evaluating the extent of myocardial fibrosis (nonviable myocardium) within the left ventricular region. CMR imaging is limited by operator expertise, length of time for image acquisition, and availability.

KEY POINTS

- Cardiac stress testing is best used in patients with an intermediate pretest probability of coronary artery disease.
- In patients undergoing cardiac stress testing, exercise is the preferred stressor because it provides additional prognostic information, including functional capacity and hemodynamic response.
- Stress testing with imaging is indicated in patients with an inability to exercise, contraindications to exercise, baseline electrocardiographic (ECG) abnormalities that would preclude interpretation of exercise ECG results, or indeterminate findings on exercise ECG.

Visualization of the Coronary Anatomy

Anatomic assessment of the coronary arteries can be performed with noninvasive coronary CTA or invasive angiography. Both tests require administration of contrast agents and expose the patient to radiation. CTA interpretation can be limited in cases of extensive calcification and with assessment of distal arteries.

In symptomatic patients with an intermediate risk for CAD, CTA may be helpful in ruling out CAD. In the PROMISE trial, 10,000 symptomatic patients suspected of having CAD were evaluated with an initial strategy of anatomic testing with CTA or functional testing. In patients with an intermediate pretest probability of CAD, the composite cardiovascular event rate was low (<1% per year) in both groups, and outcomes (death, myocardial infarction, hospitalization for

unstable angina, or major procedural complication) at 2 years did not differ between groups.

H Coronary CTA may also play a role in the evaluation of acute chest pain in the emergency department. CTA is appropriate in patients suspected of having an acute aortic syndrome or a coronary embolism. Coronary CTA may be helpful in patients with low or intermediate likelihood of non-ST-elevation acute coronary syndrome who have a low TIMI risk score, negative troponin level, or nonischemic ECG. It may also be useful in patients with an equivocal diagnosis of non-ST-elevation acute coronary syndrome who have an equivocal initial troponin level or single troponin elevation without further symptoms of acute coronary syndrome, or in patients who have ischemic symptoms that resolved hours before undergoing testing. Careful consideration of patient factors and selection of appropriate testing are essential to avoid additional unnecessary testing and the associated costs and potential harms.

Coronary angiography during a cardiac catheterization procedure is an invasive test in which nonionic contrast material is injected into the coronary arteries (or bypass grafts) by using long, thin (<2-mm) catheters. Arterial access is obtained by using the femoral or radial artery, and radiation exposure is required. This test should be considered in patients who have a high pretest probability of obstructive CAD, including symptomatic patients with abnormal findings on noninvasive functional or anatomic testing or with an acute coronary syndrome.

The addition of FFR to invasive angiography and CTA can provide additional functional information, including the hemodynamic significance of a lesion and need for intervention. FFR is the ratio of blood flow distal to the stenosis to blood flow proximal to the stenosis at maximal flow. It is typically measured during cardiac catheterization by placing a pressure wire across the stenosis and inducing conditions of maximal hyperemia, usually with adenosine. FFR-CT is an FDA-approved diagnostic test that provides both anatomic and functional data; it has higher specificity for the diagnosis of obstructive CAD than does CTA alone. Performance of FFR-CT is similar to performance of invasive FFR during angiography. The availability of this test and its delayed interpretation may limit its use in patients with acute symptoms. H

KEY POINT

- Coronary angiography and CT angiography (CTA) provide anatomic information regarding the extent and severity of coronary artery disease; however, the diagnostic value of CTA may be limited in cases of extensive calcification.

Coronary Artery Calcium Scoring

Coronary artery calcification indicates atherosclerosis and may be quantified with electron-beam or multidetector CT. Although CAC scoring provides information regarding the burden of disease, it cannot determine the degree of obstruction. CAC measurement has been used for diagnosis and risk assessment in both symptomatic and asymptomatic patients; however, assessment of CAC in asymptomatic patients should be limited to those at intermediate risk (according to the Framingham score) in whom risk reclassification will influence primary prevention therapy.

CAC scores are categorized as follows: 0, no disease; 1 to 99, mild disease; 100 to 399, moderate disease; and above 400, severe disease. These scores should be interpreted in the setting of age, ethnicity, and sex. Specific nomograms and risk calculators, such as the MESA risk calculator (www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx), can be used for risk prediction. The absence of CAC is associated with a low risk for cardiovascular events.

KEY POINT

- Assessment of coronary artery calcification in asymptomatic patients should be limited to those at intermediate risk in whom reclassification of risk will influence primary prevention therapy. HVC

Risks of Diagnostic Testing for Coronary Artery Disease

Cardiac diagnostic testing carries risks related to exercise; exposure to pharmacologic stress testing agents, radiation, or contrast agents; and vascular access for invasive procedures. Additionally, inappropriate initial testing may lead to unnecessary downstream testing with added physical and financial costs.

There is a very small risk for myocardial infarction or death (1/2500 patients) in patients undergoing exercise stress testing. Absolute contraindications to exercise include unstable angina or acute myocardial infarction, uncontrolled arrhythmias, decompensated heart failure, acute pulmonary embolism or deep venous thrombosis, acute pericarditis or myocarditis, acute aortic dissection, and severe symptomatic aortic stenosis. Relative contraindications are left main coronary artery stenosis, hypertrophic cardiomyopathy with severe obstruction, electrolyte abnormalities, high-degree atrioventricular block, and significant arrhythmias.

Vasodilator stress agents (most commonly adenosine) are associated with the side effects of chest pain, headache, and flushing. Atrioventricular block and bronchospasm may also occur. Theophylline may be given after the test to reverse these effects. Vasodilator stress testing is contraindicated in patients with reactive airways disease with active wheezing, systolic blood pressure of less than 90 mm Hg, sick sinus syndrome, or high-degree atrioventricular block.

Nuclear stress testing with SPECT and PET, CAC scoring, coronary CTA, and coronary angiography all expose the patient to radiation; however, advances in techniques have resulted in reduction of overall radiation exposure. The level of radiation exposure depends on the procedure, equipment, radiopharmaceutical agent, operator technique, and patient characteristics (such as body size).

Contrast agents used in invasive angiography, coronary CTA, CMR imaging, and echocardiography also pose a risk to the patient. CMR imaging that requires gadolinium contrast may rarely cause nephrogenic systemic fibrosis, particularly in patients with underlying kidney disease. Iodinated contrast material used in CT may result in acute kidney injury. Microbubble contrast agents are used to enhance the endocardial borders in echocardiography and can cause hypersensitivity reactions in rare instances.

Coronary angiography can be complicated by vascular access problems; bleeding complications; coronary artery dissection; aortic dissection; and plaque disruption or thrombus leading to peripheral emboli, stroke, or myocardial infarction. Femoral artery access can be complicated by retroperitoneal hemorrhage, which should be suspected in patients with hypotension, back or flank pain, and/or a drop in hemoglobin level. Pseudoaneurysms at the arterial puncture sites occur more commonly with femoral artery access and may manifest as a large hematoma or new bruit at the access site.

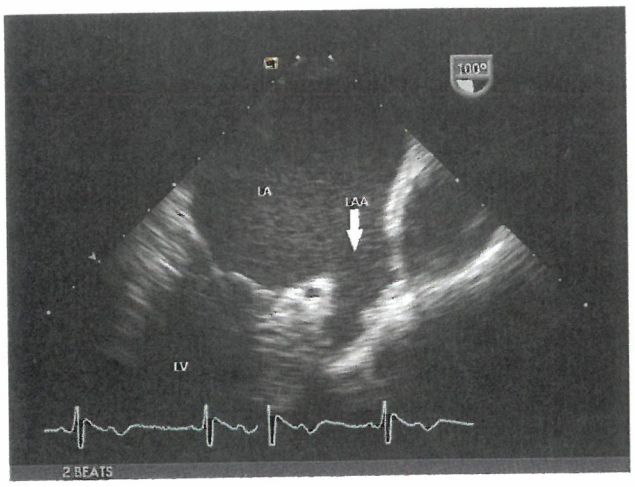

FIGURE 3. Transesophageal echocardiogram. The transducer is posterior to the heart, and the left atrium (LA) and left atrial appendage (LAA, *arrow*) are more easily seen than with transthoracic echocardiography, showing an absence of thrombus in the appendage. LV = left ventricle.

Diagnostic Testing for Structural Heart Disease

Diagnostic testing for structural heart disease should be considered in patients with a suggestive history and physical examination, such as those with a systolic murmur that is grade 3/6 or higher, a late or holosystolic murmur, a diastolic or continuous murmur, or a murmur with accompanying symptoms. Routine imaging of known structural disease is unnecessary unless there is a change in the clinical presentation or examination. A change in functional status in patients with known underlying structural disease warrants evaluation. Imaging modalities to evaluate for structural heart disease are listed in **Table 4**.

The mainstay of noninvasive cardiovascular imaging for structural abnormalities is transthoracic echocardiography (TTE). TTE evaluates right and left ventricular size, thickness, and function, including wall motion abnormalities. It can also be used to obtain information on valvular function (including regurgitation or stenosis), diastolic function, filling pressures, and the pericardium. The presence of an intracardiac shunt can be evaluated with the use of agitated saline contrast. Initial assessment for endocarditis can also be performed with TTE.

Transesophageal echocardiography (TEE) is commonly used to evaluate for the diagnosis of infective endocarditis in patients with a high pretest probability and to assess for complications of endocarditis (such as abscess). TEE may also be used to better visualize valvular pathology, particularly when surgical repair or percutaneous intervention is planned; to evaluate specific structures that cannot be well visualized on TTE (such as prosthetic heart valves) or patients with poor transthoracic imaging; to evaluate acute aortic abnormalities; and to rule out left atrial thrombus before cardioversion (**Figure 3**). TEE requires moderate sedation and placement of the TEE probe in the distal esophagus and stomach. Contraindications include esophageal strictures or active esophageal varices. Esophageal injury, including perforation and bleeding, are potential complications of TEE.

KEY POINTS

- Transthoracic echocardiography is used to evaluate patients with valvular abnormalities, congenital heart disease, pericardial disease, or left or right ventricular dysfunction.
- Transesophageal echocardiography is the most accurate test to evaluate endocarditis, prosthetic valves, and left atrial thrombus.

Diagnostic Testing for Cardiac Arrhythmias

The initial study in patients with a history of palpitations, presyncope, or syncope when an arrhythmia is suspected should be 12-lead resting ECG. The ECG may show evidence of preexcitation, ectopic rhythms, atrioventricular block, or intraventricular conduction delay, providing insight into the cause of the symptoms. Echocardiography should be performed in patients suspected of having structural heart disease.

The intermittent and fleeting nature of arrhythmias can make diagnosis difficult. Diagnostic studies are selected on the basis of the presence and frequency of symptoms and the duration and timing of the recording (**Table 5**). If symptoms occur daily, a 24- or 48-hour ambulatory ECG monitor (Holter monitor) may be used. Infrequent symptomatic events may be captured with an external patient-triggered event recorder if the event lasts long enough for the patient to trigger the device. A looping event recorder captures several seconds of the ECG

TABLE 4. Diagnostic Testing for Structural Heart Disease

Diagnostic Test	Major Indications	Advantages	Limitations
Transthoracic echocardiography	Heart failure Cardiomyopathy Valve disease Congenital heart disease Pulmonary hypertension Aortic disease Pericardial disease	Accurate diagnosis of presence and severity of structural heart disease Quantitation of LV size and function, pulmonary pressures, valve function, and intracardiac shunts Widely available, portable, fast	Operator-dependent data acquisition; interpretation requires expertise Variability in instrumentation Image quality limits diagnosis in some patients (COPD, large body habitus) May require microbubble contrast agents
Transesophageal echocardiography	Endocarditis Prosthetic valve dysfunction Aortic disease Left atrial thrombus	High-quality images, especially of posterior cardiac structures Most accurate test for evaluation of endocarditis, prosthetic valves, and left atrial thrombus	Requires esophageal intubation, typically with conscious sedation
Three-dimensional echocardiography	Mitral valve disease ASD (percutaneous ASD closure)	Improved tomographic imaging Used during cardiac procedures for device placement Improved assessment of LV global/regional systolic function	Adjunct to two-dimensional imaging Limited by availability and expertise
Radionuclide angiography (MUGA)	Evaluation of LV systolic function	Quantitative EF measurements Accurate for serial LVEF measurements (e.g., to evaluate for cardiotoxicity from chemotherapy)	Radiation exposure Provides no data on other cardiac structures
Cardiac catheterization (left and right)	Congenital heart disease Coronary artery disease Valve assessment Shunt assessment	Direct measurement of intracardiac pressures, gradients, and shunts Contrast angiography provides visualization of complex cardiac anatomy Allows percutaneous intervention for structural heart disease	Invasive Radiation and radiocontrast exposure Images not tomographic, limiting evaluation of complex three-dimensional anatomy
Coronary CT angiography	Coronary artery disease Congenital heart disease	Visualization of complex cardiac anatomy High-resolution tomographic images	Invasive Radiation and radiocontrast exposure Image acquisition improved with sinus rhythm and slower heart rate
CMR imaging	Congenital heart disease Aortic disease Myocardial disease (infiltrative disease, myocarditis, hypertrophic cardiomyopathy) RV cardiomyopathy (ARVC) Quantitation of LV mass and function	High-resolution tomographic imaging and blood-flow data Quantitative RV volumes and EF No ionizing radiation or contrast material Enables three-dimensional reconstruction of aortic and coronary anatomy	Limited by availability and expertise Patient claustrophobia May be contraindicated in patients with pacemaker, ICD, or other implanted devices Gadolinium is contraindicated in patients with kidney failure Sinus rhythm and slower heart rate are needed for improved image quality
Chest CT with contrast	Aortic disease Coronary artery disease Cardiac masses Pericardial disease	High-resolution tomographic images Enables three-dimensional reconstruction of vascular structures	Radiation and radiocontrast exposure

ARVC = arrhythmogenic right ventricular cardiomyopathy; ASD = atrial septal defect; CMR = cardiac magnetic resonance; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; RV = right ventricular.

TABLE 5. Diagnostic Testing for Suspected or Known Cardiac Arrhythmias

Diagnostic Test or Device	Indications	Advantages	Limitations
Resting ECG	Initial diagnostic test in all patients	12-lead ECG recorded during the arrhythmia often identifies the specific arrhythmia	Most arrhythmias are intermittent and not recorded on resting ECG
Ambulatory ECG (Holter monitor)	Frequent (at least daily) asymptomatic or symptomatic arrhythmias	Records every heart beat during a 24- or 48-h period for later analysis Patient log allows correlation with symptoms	Not helpful when arrhythmia occurs less frequently ECG leads limit patient activities
Long-term external ECG monitor	Infrequent asymptomatic or symptomatic arrhythmias	Provides continuous rhythm recording for up to 30 days	Adhesive attachment to chest Detection of rhythm abnormalities that are asymptomatic or not clinically significant
Exercise ECG	Arrhythmias provoked by exercise	Allows diagnosis of exercise-related arrhythmias Allows assessment of impact of arrhythmia on blood pressure	Physician supervision needed during testing Most arrhythmias are not exercise related
Patient-triggered event recorder	Infrequent symptomatic arrhythmias that last more than 1-2 min	Small, pocket-sized recorder is held to the chest when symptoms are present Recorded data are transmitted to central monitoring service	Symptomatic arrhythmias must last long enough for patient to activate the device Arrhythmia onset is not recorded Not useful for syncope or extremely brief arrhythmias
Looping event recorder (wearable)	Infrequent, symptomatic, brief arrhythmias Syncope	Continuous ECG signal is recorded (with the previous 30 s to 2 min saved) when the patient activates the recording mode Arrhythmia onset is recorded	ECG leads limit patient activities Device records only when activated by patient
Implantable loop recorder	Very infrequent asymptomatic or symptomatic arrhythmias	Long-term continuous ECG monitoring with patient-triggered or heart rate–triggered episode storage Specific heart rate or QRS parameters can be set to initiate recording of data	Invasive procedure with minor risks Device must be explanted later
Mobile cardiac outpatient telemetry	Continuous outpatient ECG recording for precise quantification or capture of rare arrhythmia	Auto-triggered and patient-triggered capture of arrhythmic events Up to 96 h of retrievable memory	ECG leads limit patient activities Resource intensive
Electrophysiology study	Used for inducing, identifying, and clarifying the mechanism of arrhythmia as well as potential treatment (catheter ablation)	Origin and mechanism of an arrhythmia can be precisely defined	Invasive procedure with some risk Some arrhythmias may not be inducible, particularly if the patient is sedated

ECG = electrocardiography.

signal before the device is triggered; it is useful for syncope or presyncope associated with arrhythmias. A longer-term external ECG monitor or an implanted loop recorder may be warranted in patients with very infrequent events.

Exercise stress testing is also frequently used in patients suspected of having or known to have arrhythmia. Treadmill stress testing is an important tool for evaluating chronotropic response, ischemia, and exercise-induced or adrenergically induced arrhythmia.

Most patients do not require diagnostic electrophysiology testing. Electrophysiology testing may be indicated in patients in whom the diagnosis remains indeterminate or in settings in which catheter-based interventions may be needed to treat refractory arrhythmias.

KEY POINT

- The initial study in patients with a history of palpitations, presyncope, or syncope when an arrhythmia is suspected should be 12-lead resting electrocardiography.

Coronary Artery Disease

Stable Angina Pectoris

Diagnosis and Evaluation

Stable angina pectoris is defined as reproducible angina symptoms (chest pain or pressure) of at least 2 months' duration that are precipitated by exertion or emotional stress and have not appreciably worsened. In contrast, unstable angina is defined by new-onset angina or angina occurring at a relatively low level of exertion, occurring at rest, or accelerating in frequency or severity. Unstable angina is associated with increased short-term risk for acute myocardial infarction (MI). As such, the evaluation of patients with angina should include a focused history, eliciting the duration of symptoms, aggravating and relieving factors, and whether symptoms have worsened. Although angina is classically described as tightness, heaviness, or gripping in the chest, it is important to recognize that classic symptoms may be absent, and some demographic groups (women and patients with diabetes mellitus) may have atypical symptoms, including exertional dyspnea.

The physical examination should include an evaluation of the cardiovascular system and a search for findings suggesting conditions that mimic angina, including heart failure, pulmonary hypertension, valvular heart disease (particularly aortic stenosis), and hypertrophic cardiomyopathy. The first step in diagnostic testing is to determine the pretest probability (or likelihood) of coronary artery disease (CAD) (**Table 6**). Baseline resting electrocardiography (ECG) is required to rule out ongoing ischemia and to guide the choice of stress test (**Figure 4**). The selection of tests for evaluating chest pain is discussed in Diagnostic Testing in Cardiology. Stress testing is most useful in patients with an intermediate probability of CAD; however, when the pretest probability of CAD is high, testing may provide prognostic information. Other diagnoses should be pursued in patients with normal findings on stress testing. If the stress test yields abnormal results, additional evaluation should be considered.

General Approach to Treatment of Stable Angina Pectoris

All patients with angina should receive guideline-directed medical therapy consisting of risk factor modification, cardioprotective medications, and antianginal medications (**Figure 5**). Lifestyle modifications, including regular physical activity, weight loss, tobacco cessation, and dietary changes, should be strongly encouraged, and blood pressure control (with a goal of <130/80 mm Hg) and diabetes management should be emphasized. Cardioprotective medications are indicated in patients with CAD to prevent thrombosis and halt further progression of atherosclerotic plaque. Antianginal medications reduce cardiac workload or increase myocardial oxygen delivery, resulting in decreased angina and improved functional capacity.

Cardioprotective Medications

Aspirin reduces the risk for MI and cardiovascular death in patients with stable angina. Guidelines recommend low-dose aspirin (75-162 mg/d) because it is as effective in preventing MI as high-dose aspirin (325 mg/d) and confers a lower bleeding risk. In aspirin-intolerant patients, clopidogrel, a platelet $P2Y_{12}$ receptor inhibitor, is an acceptable alternative. Neither prasugrel nor ticagrelor has been studied in the context of stable angina, and their role in managing this condition remains to be established.

Lipid-lowering therapy, targeting LDL cholesterol in particular, is indicated to reduce the risk for vascular events and

TABLE 6. Pretest Likelihood of Coronary Artery Disease in Symptomatic Patients According to Age and Sex[a]

	Pretest Likelihood					
	Nonanginal Chest Pain[b]		Atypical Angina[c]		Typical Angina[d]	
Age (y)	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

[a]Each value represents the percentage with significant coronary artery disease on catheterization.

[b]Nonanginal chest pain has one or none of the components for typical angina.

[c]Atypical angina has two of the three components for typical angina.

[d]Typical angina has three components: (1) substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin.

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