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# Stress testing and noninvasive coronary imaging: What's the best test for my patient?

## ABSTRACT

Coronary artery disease (CAD) causes significant morbidity and mortality. Accurate noninvasive evaluation is important to facilitate appropriate diagnosis and treatment. The ubiquitous nature of CAD requires all practitioners, regardless of their specialty, to be familiar with noninvasive diagnostic modalities. This article reviews currently available tests, including specific features, diagnostic and prognostic value, strengths, and limitations.

## KEY POINTS

Noninvasive cardiac imaging (stress testing or anatomic evaluation) is warranted in patients who present with symptoms suspected to be cardiac, and in asymptomatic patients in clinical scenarios in which possible CAD needs to be assessed or excluded.

Patients with symptoms and low to intermediate pretest probability for CAD are ideal candidates for electrocardiography exercise stress testing, stress echocardiography, or coronary computed tomography angiography.

Myocardial perfusion imaging is particularly useful in patients with known underlying CAD to determine if ischemia is present, and positron emission tomography stress imaging provides greater accuracy in those who are obese.

CORONARY ARTERY DISEASE (CAD) is the leading cause of death in both men and women in the United States.<sup>1</sup> Its diagnosis and risk stratification are an important aspect of medical care for all practitioners, regardless of specialty.

Coronary catheterization has been the technical standard for the diagnosis of CAD and is the recommended pathway for patients who are at high risk or who present with acute coronary syndrome.<sup>2,3</sup> However, given that chest pain and anginal-equivalent symptoms are frequent in patients presenting to community clinics and emergency rooms and on inpatient wards, many practitioners need the skills and knowledge to conduct cardiac risk evaluation.

Noninvasive testing is often used to categorize patients as being at lower risk or having noncardiac chest pain vs those who are likely to have ischemia or obstructive CAD, which may require invasive coronary catheterization for further evaluation or intervention.

Testing for CAD may be functional or anatomic (Table 1). In this article, we review what each test measures, its specific features, diagnostic and prognostic value, clinical utility, and limitations. These considerations help practitioners select the best test for a patient in a given setting or provide answers to a specific clinical question.

## CORONARY ARTERY DISEASE

CAD is an inflammatory pathologic process that starts as fatty streaks in the intimal layers of coronary arteries, then progresses to nonobstructive and then obstructive atherosclerotic

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plaques. The process is driven by genetic and environmental cardiovascular risk factors.<sup>4</sup> Ischemia occurs when coronary atherosclerotic plaque becomes severely stenotic or obstructive (generally if stenosis is  $\geq 50\%$  in the left main coronary artery and  $\geq 70\%$  in the other epicardial coronary arteries), and it may be associated with symptoms of angina or dyspnea.<sup>4</sup>

Moderate stenosis (50%–70%) may also cause ischemia and anginal-equivalent symptoms due to lesion characteristics such as location and length of plaque, presence of endothelial dysfunction, and presence of microvascular disease.<sup>5</sup> Both obstructive and nonobstructive coronary stenosis may be complicated by acute plaque rupture and thrombosis, leading to acute loss of blood flow to the myocardium and myocardial infarction.<sup>4</sup>

Clinical scores incorporate variables such as age, sex, cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, history of smoking, family history of CAD), changes on electrocardiography (ECG), cardiac enzyme levels, and symptoms. These scores help determine if patients have a low, intermediate, or high pretest probability of CAD.<sup>2,3,6</sup>

Chest pain may be classified as noncardiac, atypical angina, and typical angina. Women and patients with diabetes may present without chest pain but with anginal-equivalent symptoms such as shortness of breath on exertion or arm pain, or they may also have silent ischemia.

Patients presenting with the acute coronary syndrome, high pretest probability of CAD, or concerning clinical features proceed straight to invasive coronary angiography. Noninvasive imaging (stress testing or anatomical evaluation) is warranted in those who present with symptoms that are suspected to be cardiac, particularly if the patient has an increased pretest probability of CAD.

Table 2 lists the common indications for stress testing and coronary computed tomography (CT) angiography.<sup>3,7–10</sup>

## **ELECTROCARDIOGRAPHY EXERCISE STRESS TESTING**

### **Test features**

ECG exercise stress testing is the workhorse in community and hospital practices as an initial functional test to evaluate chest pain and sus-

**TABLE 1**

### **Testing for coronary artery disease**

<b>Functional</b>	Electrocardiography exercise stress test
	Stress echocardiography
	Nuclear medicine myocardial perfusion imaging techniques
	Single-photon emission computed tomography
	Positron emission tomography
<b>Anatomic</b>	Cardiac magnetic resonance imaging with stress perfusion
	Coronary computed tomography angiography
	Invasive coronary catheterization

pected CAD. Patients with low or intermediate pretest probability for CAD are ideal candidates for ECG exercise stress testing.<sup>11</sup>

The Bruce protocol is the most commonly used format. It starts the patient on a treadmill at a speed of 1.7 miles per hour and a 10% incline. Every 3 minutes, the speed and angle of incline are increased.

Standard 12-lead ECG is used. If motion artifact occurs, moving the extremity electrodes to the torso and ensuring good electrode contact with the skin (eg, shaving if required) may help.

Baseline ECG is taken before starting. The stress test continues until the patient is fatigued and asks to stop or develops cardiac symptoms, significant ECG changes, or other high-risk features.

An ECG stress test is considered diagnostic if the patient achieves at least 85% of the maximum age-predicted heart rate. If a test is terminated before achieving this threshold because of positive findings but the results meet the ECG criteria for ischemia, then the results are still considered positive for ischemia. However, if a test is terminated before achieving 85% of the predicted heart rate and there are no ECG changes, it is considered nondiagnostic as it is not known whether ischemic changes would have occurred if the patient had continued to the required workload.

### **Diagnostic and prognostic features**

An ECG stress test is considered positive for ischemia if there is at least a 1-mm horizontal or down-sloping ST-segment depression. Up-sloping ST-segment depression is not considered a positive finding. An ST-segment elevation greater than 1 mm is highly suggestive of significant ischemia.

**An ECG stress test is positive for ischemia if there is at least a 1-mm horizontal or down-sloping ST-segment depression**

TABLE 2

### Common indications for stress testing and coronary computed tomography angiography

#### Assessment for coronary artery disease

- Angina or anginal equivalent symptoms and negative cardiac enzymes
- Atypical symptoms in patients with diabetes or with high probability of diabetes
- New diagnosis of cardiomyopathy (to define whether the cause is ischemic or nonischemic)
- New or increasing heart failure symptoms despite adherence to medical therapy
- Re-evaluation of known heart failure (systolic or diastolic) in patients with a change in clinical status without a clear precipitating change in medication or diet
- Arrhythmias such as ventricular tachycardia or atrial fibrillation (to exclude ischemia as the cause) or new left bundle-branch block
- To exclude severe ischemia prior to noncardiac surgery in those with increased coronary artery disease risks, angina symptoms, or poor exercise capacity (< 4 metabolic equivalents)
- To define presence or absence of ischemia in those with moderate coronary stenosis (stress test or fractional flow reserve-computed tomography)
- Evaluation of anomalous coronary arteries

#### Stress testing for indications other than coronary artery disease assessment

- Valve assessment
  - Mitral valve stenosis or regurgitation severity (exercise stress echocardiography)
  - Low-flow low gradient aortic stenosis (dobutamine stress echocardiography)
- Exercise-induced pulmonary hypertension or diastolic dysfunction (exercise stress echocardiography)
- Hypertrophic cardiomyopathy to demonstrate provokable left ventricular outflow tract obstruction (exercise stress echocardiography)
- Exercise-induced arrhythmia or chronotropic incompetence (exercise stress echocardiography)
- To define cardiopulmonary disease and aerobic exercise capacity (metabolic stress test)

Data from references 3 and 7–10.

**Functional capacity is the strongest prognostic marker of an ECG stress test**

A meta-analysis of 24,074 patients in 147 studies found that ECG stress testing for detecting CAD has a sensitivity of 68% and specificity of 77%.<sup>12</sup> The Coronary Artery Surgery Study database suggested that the development of ST depression and functional capacity (duration of exercise) are the 2 most prognostic markers.<sup>13</sup>

Functional capacity is the strongest prognostic marker of an ECG stress test.<sup>7,14</sup> It is estimated by metabolic equivalents (METs), which approximate oxygen uptake during exercise, with 1 MET representing 3.5 mL/kg/min. Laboratories estimate functional capacity from exercise duration in a specific exer-

cise protocol based on published nomograms. Prognostic markers from an ECG stress test are shown in **Table 3**.<sup>7,13–19</sup>

The Duke treadmill score<sup>20</sup> is reported by many laboratories and predicts 5-year mortality risk in patients without known CAD. It incorporates variables that include degree of ST change and symptoms, with lower scores associated with higher mortality and increased likelihood of significant CAD.<sup>20</sup>

#### Limitations

An ECG stress test result positive for ischemia usually has ST-segment depressions mostly in the inferior and precordial leads, and it may

TABLE 3

**Prognostic indicators on electrocardiography stress testing**

Indicator	Comments
Functional capacity	Strongest prognostic indicator, reported as metabolic equivalents. <sup>7,14</sup>
ST-segment depression or elevation	> 1-mm ST deviation is suggestive of ischemia. <sup>13</sup>
Exercise-induced hypotension	Defined as systolic blood pressure that is lower during exercise than while standing at rest before exercise, reflecting failure of cardiac output to increase during exercise.  Associated with severe coronary artery disease or left ventricular systolic dysfunction. <sup>15</sup>
Chronotropic incompetence	Failure of heart rate to increase as expected during exercise, defined as achieving < 80% of predicted heart rate (or < 62% for patients taking beta-blockers). <sup>16</sup>  Associated with increased all-cause and cardiovascular mortality. <sup>17</sup>
Impaired heart rate recovery	Heart rate fails to decrease normally after cessation of exercise.  Predicts all-cause mortality and cardiovascular events, including sudden death. <sup>18</sup>
Ventricular arrhythmia	Sustained ventricular tachycardia or ventricular fibrillation.  Associated with significant coronary artery disease or left ventricular dysfunction. <sup>19</sup>

not necessarily correspond to specific coronary artery territories.

An ECG stress test should not be used if any of the following abnormalities are found on ECG: complete left bundle-branch block or paced ventricular rhythm (limits interpretation of the test), pre-excitation syndrome, or greater than 1 mm of resting ST-segment depression.<sup>21</sup> Pronounced left ventricular (LV) hypertrophy or use of digoxin therapy can affect stress-related results. Patients with impaired mobility such as amputees or those with severe arthritis may not be able to safely exercise on the treadmill or go long enough to complete a diagnostic test. False-positive results may be more frequent in women.

Many of these limitations can be overcome by adding an imaging component to the stress test or performing a pharmacologic stress test in those who cannot exercise.

## ■ STRESS ECHOCARDIOGRAPHY

### Test features

Stress echocardiography uses imaging with echocardiography after exercise or pharma-

cologically induced stress to show coronary abnormalities. Ischemia is identified if there is a new or worsening regional wall-motion abnormality, which generally correlates with stenosis in the corresponding coronary territory. Stress echocardiography is most often used to diagnose CAD in patients in whom an ECG stress test would be contraindicated, uninterpretable, or nondiagnostic, or if their CAD risk is sufficient to warrant an imaging component to enhance the sensitivity and specificity of the test.

Images are typically obtained from standard views including the parasternal long-axis and short-axis views, and apical long-axis and apical 2- and 4-chamber views to show the wall motion in each of the LV walls before and after stress (**Figure 1**). Results are analyzed and scored using a 17-segment model of the LV (divided into apical, mid, and basal segments), with each segment graded on a 4-degree scale of regional wall-motion analysis (normokinesis, hypokinesis, dyskinesis, and akinesis).<sup>22</sup>

**On stress echocardiography, ischemia is identified if there is a new or worsening regional wall-motion abnormality**

Intravenous (IV) echo contrast agents can be used to improve visualization of the endocardium if the image quality is suboptimal, particularly in patients with large body habitus or lung disease, or if more than 2 contiguous myocardial segments have poor endocardial definition. Echo contrast agents do not contain iodine and have been shown to improve the accuracy of the assessment of ventricular volume and ejection fraction, enhance recognition of wall-motion abnormalities, and improve reproducibility.<sup>23</sup>

Stress echocardiography can be exercise-based on a treadmill or bicycle, or pharmacologically based with dobutamine infusion. Treadmill stress tests most often use the Bruce protocol.

It is important to obtain postexercise imaging as soon as possible after exercise stops, as regional wall-motion abnormalities that persist into recovery become less pronounced and resolve as the heart rate comes down.<sup>22</sup> As such, the patient is moved immediately from the treadmill to the imaging bed in a left lateral decubitus position for poststress imaging.

Stress echocardiography using a bicycle (supine or upright), although less frequent, is quieter, which permits sensitive precordial measurements with less motion artifact and allows imaging while the patient is exercising at different stages during the stress test. When used, it is often for valvular or hemodynamic assessment.

Exercise stress echocardiography may allow for hemodynamic evaluation in addition to that for ischemia. Doppler assessment may be helpful in patients with dyspnea and suspected exercise-induced diastolic dysfunction or pulmonary hypertension<sup>24</sup> or in those with mitral valve stenosis or regurgitation that is clinically suspected to be more severe than a resting echocardiogram suggests. Stress echocardiography can also assess for dynamic LV outflow-tract obstruction in hypertrophic cardiomyopathy.

Pharmacologic stress echocardiography can assess for ischemia in patients who cannot exercise or can help define the severity of aortic stenosis, particularly when low-flow, low-gradient severe aortic stenosis is suspected. This is performed predominantly with dobutamine infusion, although it is possible to use di-

pyridamole or adenosine for ischemia testing. Dobutamine is a synthetic catecholamine that stimulates beta-1 adrenergic receptors causing a chronotropic effect (increase in heart rate) and an inotropic effect (increase in myocardial contractility), resulting in increased oxygen demand. The typical dobutamine stress protocol consists of continuous IV infusion of dobutamine in 3-minute increments, starting with 5 mg/kg/min and increasing to a maximum of 40 mg/kg/min.<sup>25</sup> Dobutamine may have an arrhythmogenic or hypertensive effect, and requires monitoring throughout. Patients with severe conduction disorders or advanced asthma or airway disease are not affected by dobutamine.

### Diagnostic and prognostic features

Stress echocardiography results are reported by description of wall motion as normal, ischemic, viable, or scarred myocardium. Normal myocardium has normal motion of segments at rest, and after stress, all segments demonstrate either normal motion or hyperkinesia, with overall increase in ejection fraction. When the myocardium is ischemic, contractile function goes from normal to hypokinetic, akinetic, or dyskinetic after stress, in at least 2 adjacent segments for the test to be positive.<sup>26</sup> When myocardium is scarred (due to previous MI), resting dysfunction (hypokinesis or akinesis) remains fixed after stress.

The myocardium is considered viable when segments with resting hypokinesis show either a maintained improvement with stress (indicating the presence of “stunning”) or improvement during an early stress phase with subsequent deterioration in contractility at peak (ie, biphasic response), which portends potential improvement with revascularization.<sup>27</sup>

Other features that may suggest significant ischemia are a decrease in LV ejection fraction after exercise (instead of an increase) or an increase in the LV cavity size after stress (expected to decrease as a result of increased contractility).

A meta-analysis has demonstrated that stress echocardiography with exercise, dobutamine, dipyridamole, and adenosine has a sensitivity of 83%, 81%, 72%, and 79%, respectively, and a specificity of 84%, 84%, 95%, and

**On stress echocardiography, a decrease in LV ejection fraction after exercise or an increase in LV cavity size after stress can suggest significant ischemia**



91%, respectively.<sup>28</sup> Stress echocardiography is generally considered more specific than nuclear perfusion imaging, although nuclear perfusion imaging is considered more sensitive.<sup>29</sup>

A strength of stress echocardiography is improved diagnostic accuracy compared with stress ECG alone without ionizing radiation exposure. As such, it is often the preferred test for middle-aged women who may have symptoms and intermediate cardiovascular risk. It may also be desirable in patients who have dyspnea, in whom other hemodynamic evaluation can be done in the same test.

Stress echocardiography has prognostic value. A normal test with no regional wall-motion abnormalities confers a less than 1% per year cardiac event rate. Increasing severity of regional wall-motion abnormalities after peak stress corresponds to higher clinical event rates.<sup>8</sup>

### Limitations

As with all imaging, interpretation of a stress echocardiogram may be affected by subjectivity. Thus, it is important to have good imaging protocols and quality acquisitions along with experienced practitioners to interpret the images. Stress echocardiography may miss mild ischemia that is due to small, distal, or branch-vessel disease, and it is considered slightly less sensitive than nuclear imaging.<sup>30</sup> Patients with obesity or emphysema may have poor acoustic windows, resulting in suboptimal images.

## ■ NUCLEAR MEDICINE MYOCARDIAL PERFUSION IMAGING

### Test features

Nuclear myocardial perfusion imaging (MPI) may be performed by either single-photon emission CT (SPECT) or positron emission tomography (PET). As with stress echocardiography, MPI stress testing may be exercise or pharmacologically induced. MPI involves IV administration of radioactive tracers. A gamma camera detects radio emissions from the tracer that perfuses the myocardium. Tracer uptake depends on flow dynamics as well as myocyte membrane integrity. Color-coded images of myocardial perfusion pre- and post-stress are generated in different axes to allow assessment for each coronary distribution.<sup>31</sup>

The radioisotopes and cameras used in

PET and SPECT differ. PET generally uses rubidium or ammonia radionuclides for perfusion imaging, and fluorodeoxyglucose (FDG) may be used to assess myocardial viability and inflammation. SPECT scanners predominantly use technetium 99 (sestamibi) for perfusion imaging. Thallium has been phased out because of associated high radiation.

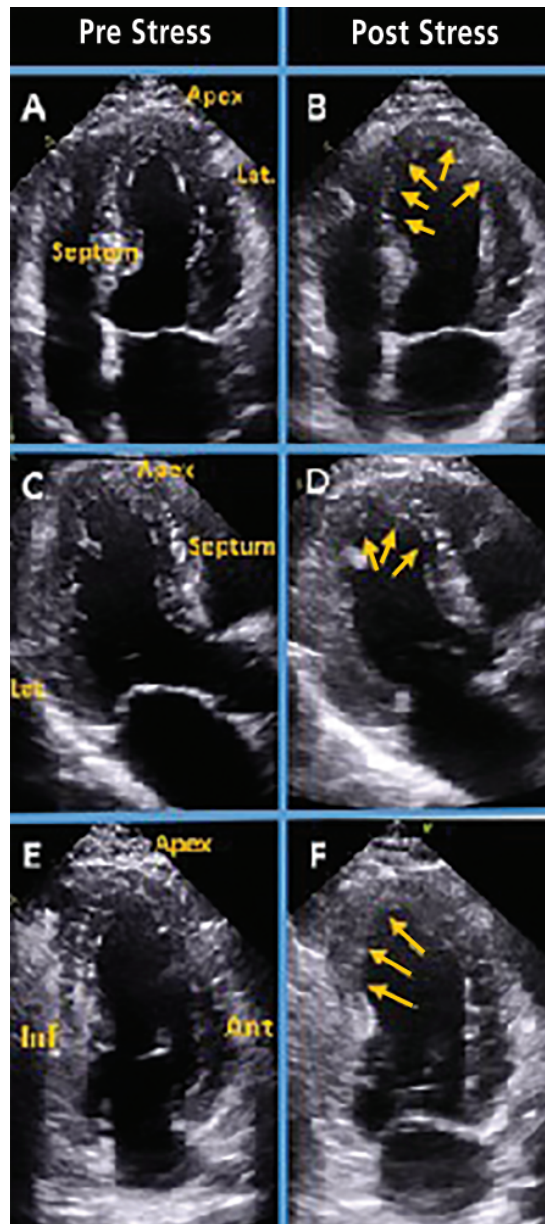
PET carries advantages over SPECT including superior image quality, due to more favorable tracer characteristics and count statistics. Positron-emitting radiotracers used in PET can produce higher-energy photons than those produced by SPECT radiotracers, resulting in less attenuation artifact. PET can also detect smaller and more subtle perfusion defects (typically 4–7 mm) owing to its higher spatial resolution than SPECT (typically 12–15 mm).<sup>32</sup> Other advantages of PET over SPECT include a lower radiation burden and shorter scan time.

Stress MPI can be exercise-induced (using the treadmill Bruce protocol, which has the added value of providing functional capacity data that is prognostic) or pharmacologic for those unable to exercise. Vasodilators are the most frequently used stress agents, primarily regadenoson (which has a more favorable profile) or dipyridamole and adenosine. Vasodilators increase coronary blood flow through their effect on the adenosine A<sub>2A</sub> receptor, which increases blood velocity and flow rate in normal vessels compared with a lesser response in stenotic vessels that are already maximally dilated, thus decreasing subendocardial flow to regions supplied by diseased vessels. Dobutamine infusion may also be used, although it is rare in MPI practice.

### Diagnostic and prognostic features

MPI enables clinicians to assess the physiologic significance of coronary stenosis by measuring heterogeneity in coronary flow. The ability to maintain the maximum flow (“coronary flow reserve”) is impaired when there is more than 50% coronary stenosis.<sup>33</sup> Normal myocardial perfusion is shown by homogeneous radiotracer distribution on both stress and rest images. In general, perfusion defects in a coronary territory that occur after stress with normal flow at rest suggest inducible ischemia, whereas a fixed defect in perfusion both at rest

**MPI enables clinicians to assess the physiologic significance of coronary stenosis by measuring heterogeneity in coronary flow**



**Figure 1.** Stress echocardiogram from a 54-year-old woman with chest pain shows ischemia in the left anterior descending artery and right coronary artery territories. Panels A and B show the 4-chamber view before and after the stress test. On the poststress image (B), the arrows point to hypokinesis at the apex and distal septum; enlargement of left ventricular cavity suggests significant ischemia. In the long-axis view (C, D), arrows point to hypokinesis at the apex and distal septum. In the 2-chamber view (E, F), arrows point to hypokinesis on the mid and apical inferior wall.

and after stress in a coronary distribution suggests either scarred myocardium (from prior myocardial infarction) or hibernating myocardium (which may improve in function if revascularized).<sup>34</sup>

MPI defects are generally reported with reference to the following:

- Defect size or extent: small (< 10% of LV myocardium affected), medium (10%–20% affected), or large (> 20% affected)
- Severity of perfusion defect (mild, moderate, severe)
- Extent of reversibility (reversible, irreversible)
- Location (based on 17-segment LV model and coronary artery territory).

Tomograms are also produced on MPI studies that estimate LV ejection fraction. The presence of transient ischemic dilation is a sign of severe ischemia. It refers to the enlargement of the LV poststress instead of decrease of cavity size as would be expected with increased contractility.

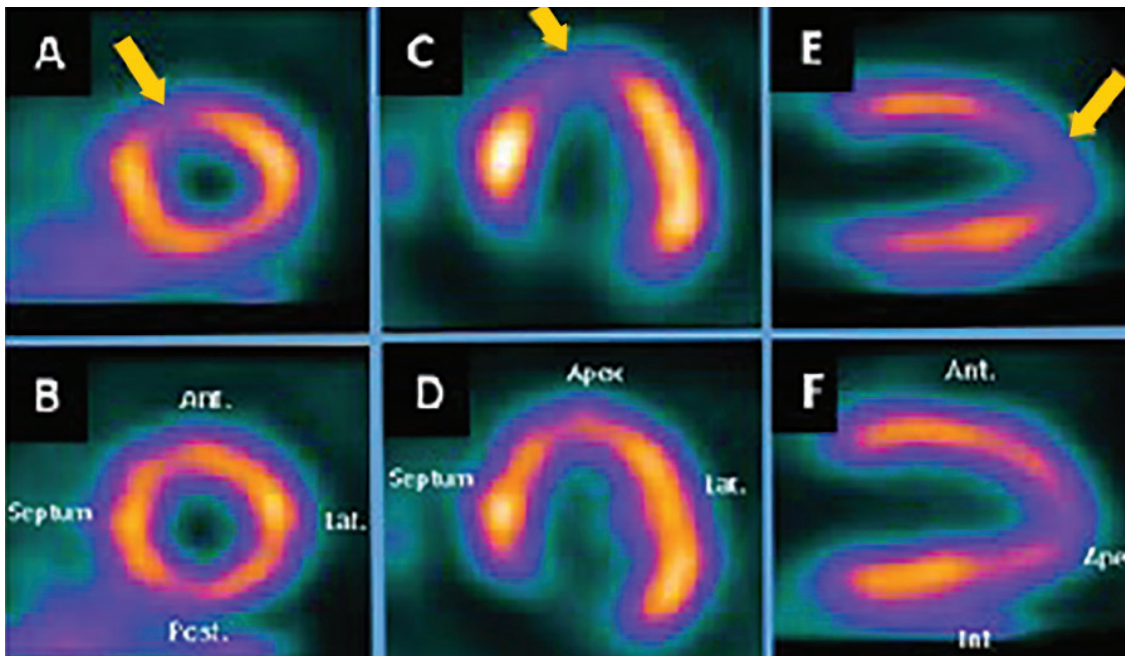
Myocardial blood flow and myocardial flow reserve offer a quantitative assessment of myocardial perfusion<sup>35</sup> and, in some cases, may help identify the presence of microvascular disease. Some centers routinely include these measures on clinical PET reports, and similar quantitative measures may also be available for SPECT in the future.

A systematic review reported sensitivity and specificity of SPECT for the diagnosis of CAD of 82% and 76%, respectively, and 91% and 89% for PET, with the difference accounted for by superior spatial resolution and attenuation correction of PET.<sup>36</sup> SPECT is considered more sensitive than stress echocardiography but less specific. PET is generally accepted as the most accurate noninvasive functional test for ischemia.

MPI provides clinically helpful prognostic information. For those with normal MPI results, the 2-year clinical event rate for cardiac death or myocardial infarction is less than 1%.<sup>37</sup> The presence of perfusion defects is prognostic for clinical myocardial infarction and mortality.

MPI is useful in symptomatic patients with suspected CAD to show the presence or absence of ischemia (**Figure 2**), as well as in those with known CAD to evaluate if stenosis is functionally significant. In addition,

**Positron emission tomography is generally accepted as the most accurate noninvasive functional test for ischemia**



**Figure 2.** Single-photon emission CT myocardial perfusion imaging in a 62-year-old man with diabetes and a 2-month history of dyspnea shows moderate left anterior descending coronary artery ischemia. Panels A, C, and E are poststress images that show perfusion defects in the apex, apical septum, and apical anterior wall (arrows). Panels B, D, and F show relatively normal perfusion at rest at the corresponding levels.

those with impaired LV systolic function may also have viability concurrently assessed during MPI imaging, particularly with FDG-PET techniques, which may help guide revascularization decisions. Those with left bundle-branch block may be suitable candidates for regadenoson pharmacologically induced SPECT or PET (as an ECG exercise stress test would be nondiagnostic). For obese patients, PET MPI is the superior modality.

### Limitations

MPI techniques involve radiation exposure, and there needs to be sufficient clinical value to justify testing. SPECT may be more prone to artifact from diaphragmatic attenuation or gut scatter that may result in false-positive results being identified in the inferior LV wall, particularly in patients who are obese. This is less of an issue with PET.

The main limitations for PET are higher cost and limited availability. Only healthcare facilities with an on-site cyclotron to produce isotopes daily (due to their short half-life) can offer PET imaging.<sup>32</sup>

Finally, a normal result on MPI suggests the absence of obstructive CAD. However, it does not exclude mild to moderate atherosclerosis that may not be contributing to symptoms but nonetheless may warrant aggressive preventive measures. Identifying coronary calcium on CT scout images before an MPI may help flag for the presence of subclinical coronary atherosclerosis.

### CORONARY CT ANGIOGRAPHY

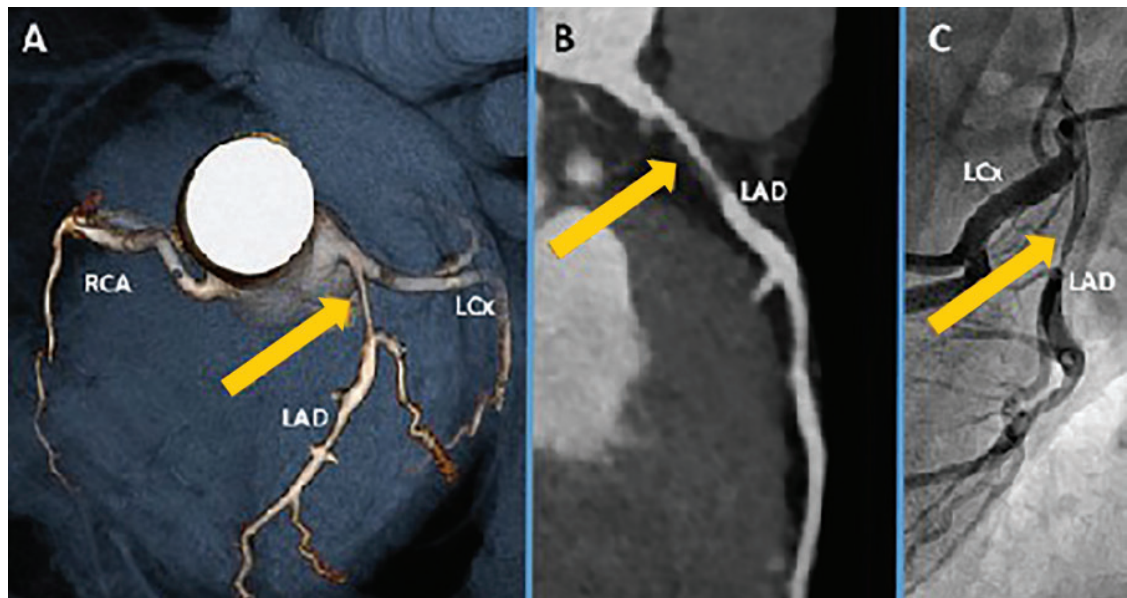
#### Test features

Coronary CT angiography (CCTA) is an anatomic noninvasive modality that can identify and assess the severity of CAD. It differs from stress testing in that it directly visualizes the coronary arteries and can quantify the degree of stenosis and assess plaque characteristics (Figure 3). In contrast, stress testing assesses LV wall-motion abnormalities or perfusion defects to determine if obstructive CAD is present.

Adequate patient preparation is needed to enable high-quality image acquisition and improve accuracy. Ideally, the heart rate needs

**Coronary CT angiography can identify and assess the severity of CAD by quantifying the degree of stenosis and assessing plaque characteristics**





**Figure 3.** Coronary computed tomography angiography in a 40-year-old man who smoked and had a family history of premature coronary artery disease. Panel A is a 3-D rendering showing proximal left anterior descending (LAD) coronary artery stenosis (arrow). Panel B is a multiplanar reconstruction showing proximal LAD coronary artery stenosis with predominantly soft (lipid-laden) noncalcified plaque (arrow). Panel C shows the corresponding LAD lesion (arrow) on coronary catheterization.

LCx = left circumflex artery; RCA = right coronary artery

**Coronary CT angiography can identify plaque features that suggest the plaque is more vulnerable to rupture**

to be less than 60 beats per minute, although less than 70 beats per minute is acceptable on more advanced scanners. A beta-blocker or calcium channel blocker may be administered orally or intravenously to help achieve the target heart rate.

Sublingual nitroglycerin is given just before scanning to help dilate the coronary arteries and improve the image quality. Then an iodinated contrast agent is administered through an IV line in the cubital fossa, and CT images are acquired with ECG gating. To reduce radiation exposure, it is preferable to use a prospective acquisition protocol for CCTA scans in which images are obtained at a point in end diastole (or sometimes end systole) when cardiac and coronary motion is least, thus reducing motion artifact.

#### Diagnostic and prognostic features

Images are reconstructed and analyzed for the presence, degree, and location of coronary stenosis. Plaque composition (whether calcified, noncalcified, or mixed) and high-risk plaque features, if present, are also reported. The So-

ciety of Cardiovascular CT recommends using the CAD reporting and data system to standardize CCTA reports.<sup>38</sup> It categorizes coronary segments as having no stenosis, minimal (0%–24%), mild (25%–49%), moderate (50%–69%), or severe (70%–99%) stenosis, or total occlusion (100%).<sup>38</sup>

High-risk plaque features include low Hounsfield unit attenuation (signifying more lipid-laden plaque), high plaque volume, positive remodeling (plaque extending outwards from the vessel wall and not just into the lumen), or spotty calcification within the plaque. These features suggest that plaque is more vulnerable to rupture and, thus, the patient has a greater likelihood of clinical events such as myocardial infarction.<sup>39</sup> These features are mandated for clinical reporting in the Society of Cardiovascular CT guidelines.<sup>38</sup>

Numerous meta-analyses have confirmed the diagnostic accuracy of CCTA, including reported sensitivity of 99% and specificity of 89%.<sup>40</sup> As such, it has excellent negative predictive value and can accurately rule out CAD. The European Society of Cardiology 2019

guidelines give CCTA a class 1 indication to assess for (or rule out) CAD in symptomatic patients with low to intermediate cardiovascular risk, and a class IIa indication if functional testing is not diagnostic or is equivocal.<sup>3</sup> UK guidelines recommend CCTA as first-line testing for evaluating stable chest pain.<sup>41</sup>

CCTA results are prognostic. Patients with obstructive CAD identified by CCTA have worse outcomes than those with nonobstructive CAD,<sup>42</sup> who, in turn, have a higher clinical event rate than those without CAD. CCTA is useful clinically, as it may identify patients with nonobstructive CAD (such as 50% stenosis), which a stress test would call normal, as nonobstructive lesions are not flow-limiting.

In addition, identification of nonobstructive CAD by CCTA offers an opportunity for aggressive risk factor modification, including statin therapy.<sup>43</sup> CCTA can be also used for the assessment of coronary artery bypass graft patency, and is excellent in the assessment of suspected anomalous coronary arteries.

Although CCTA is predominately used for anatomic coronary assessment, techniques such as fractional flow reserve CT (FFR-CT) and stress perfusion imaging by CT are now available to determine the functional significance of a moderate coronary lesion (eg, whether a 50% to 70% stenosis on CT is flow-limiting or nonobstructive). FFR-CT has additional costs, and the images are sent off-site for analysis. In addition, CT perfusion requires higher radiation and contrast doses and longer scan time, limiting its widespread adoption.

Another advance is surrogate imaging markers for inflammation such as attenuation in coronary perivascular fat on CCTA, which may be predictive of cardiac mortality and thus may play a clinical role in prevention.<sup>44</sup> Anticipated developments in artificial intelligence and radiomic assessment are expected to enhance automated image evaluation and quantitative assessment of CCTA, with improvements in workflow and diagnostic accuracy.<sup>45</sup> These are expected to have a significant impact on clinical practice.

### Limitations

CCTA involves exposure to ionizing radiation. It requires an iodinated contrast agent, which needs premedication in patients with

iodine allergy. And its use is limited in those with renal insufficiency.

CCTA is generally less useful for evaluating coronary stents because of blooming artifact from the metal struts, limiting its ability to assess for in-stent restenosis unless the stent is large in caliber.

Arrhythmias, including atrial fibrillation and ectopy, make it more difficult to obtain a quality image, requiring adjustment of protocols. More rapid heart rate also reduces image quality.

Heavy calcification can result in segments being uninterpretable for stenosis, potentially limiting the utility of CCTA in elderly or dialysis patients. Patients unable to adequately hold their breath would not be suited for CCTA.

## CORONARY ARTERY CALCIUM SCORE

### Test features

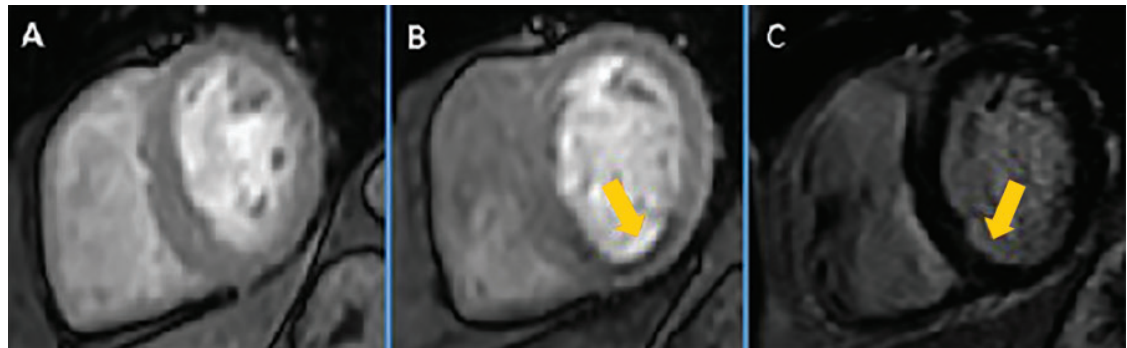
A coronary artery calcium (CAC) score is widely accepted and used for CAD risk stratification in *asymptomatic* patients. It is a surrogate marker for the presence and the burden of CAD as it quantifies coronary calcification and, hence, the extent of atherosclerotic disease. It involves rapid CT scan acquisition without contrast, with the field of view focused on the heart. Axial slices with 3-mm thickness are acquired prospectively with ECG gating in mid to late diastole. The CAC Agatston score takes into account the amount and density of calcium, with more than 130 Hounsfield units or at least 3 adjacent voxels needed to generate a numeric score.<sup>46</sup>

### Diagnostic and prognostic features

There are strong data to support the prognostic value of CAC, and it enhances risk stratification incremental to traditional clinical cardiovascular risk factors.<sup>47</sup> In absolute terms, a calcium score of 0 is associated with excellent prognosis; scores in categories of 1 to 99, 100 to 299, and 300 and above are associated with respective increased risks of mortality.<sup>47</sup> However, risk prediction is often reported as a percentile with adjustment for age, sex, and ethnicity.

The CAC score may be useful in the clinical decision-making process for patients who are asymptomatic with borderline (5%–7.5%) or intermediate (7.5%–20%) 10-year risk ac-

**A coronary artery calcium score is used for CAD risk stratification in asymptomatic patients**



**Figure 4.** Stress cardiac magnetic resonance imaging in a 67-year-old woman with diabetes and chest pain shows normal perfusion at rest (A). Panel B shows a poststress image with a perfusion defect in the inferior and inferoseptal segments (arrow), suggestive of ischemia in the right coronary artery territory. Panel C is a delayed gadolinium-enhanced image showing mild subendocardial enhancement (arrow) in the corresponding region, consistent with a small area of scar.

**Stress cardiac MRI compares favorably with established noninvasive tests in terms of accuracy for detecting CAD**

cording to the atherosclerotic cardiovascular disease (ASCVD) risk calculator, and in whom the benefit of a statin is in question.<sup>6</sup> The 2019 American College of Cardiology/American Heart Association guidelines recommend initiating a statin in patients with diabetes or in those age 40 to 75 with an ASCVD risk above 7.5% over 10 years.<sup>6</sup> In this latter group, the CAC score may be used to re-stratify the risk either up or down and better guide statin initiation. For example, a patient with borderline or intermediate ASCVD risk and a CAC score of 0 would not be started on a statin. However, if the CAC score were above 100 (or  $\geq$  75th percentile for age/sex/race), then the risk would be re-stratified up, clearly defining a patient who would benefit from a statin.<sup>6</sup>

#### Limitations

It must be stressed that although the CAC score has use in prognostication in asymptomatic patients, if anginal-equivalent symptoms are being evaluated, then the CAC score has no role as it cannot determine whether a calcified coronary plaque is stenotic, and other tests would need to be considered.

### ■ STRESS CARDIAC MAGNETIC RESONANCE IMAGING

#### Test features

Stress cardiac magnetic resonance imaging (MRI) is a promising modality, with advantages such as good spatial and temporal resolu-

tion, wide field of view, and ability to acquire images in different planes.<sup>48</sup> It uses gadolinium contrast rather than iodinated contrast and does not use ionizing radiation. MRI perfusion images can be assessed for perfusion defects (Figure 4), just as is done with nuclear MPI before and after stress. In addition, cine images from MRI can be assessed for regional wall-motion abnormalities as is done with stress echocardiography. MRIs also provide morphologic information including quantification of ventricular and valvular function.<sup>49</sup> However, current technology limits MRI anatomic assessment of the coronary arteries in adults to visualization of only the proximal portions.

#### Diagnostic and prognostic features

Stress cardiac MRI compares favorably with established noninvasive modalities in terms of accuracy for detecting CAD. Studies show stress-induced wall-motion abnormality imaging by MRI has a sensitivity of 83% and specificity of 86%.<sup>48</sup> Perfusion imaging with MRI has a sensitivity of 91% and specificity of 81%.<sup>48</sup>

Stress cardiac MRI that is negative for ischemia has prognostic value and is associated with very low risk of cardiovascular death and myocardial infarction (less than 1% combined rate per annum).<sup>50</sup>

#### Limitations

Stress cardiac MRI is relatively new and is the least frequently used compared with the other modalities discussed. Its availability and



access may be limited, with practical experience still nascent and limited in most centers. Other potential limitations include cost and long duration of scanning, which may be intolerable for those with significant claustrophobia or inability to hold their breath. It may be contraindicated in those with metal devices or prostheses, or in those with severe renal dysfunction due to risk of nephrogenic systemic fibrosis.<sup>51</sup>

## ■ APPROPRIATE USE CRITERIA

Appropriate-use criteria (AUC) guidelines are available for each imaging modality. They summarize the evidence and provide broad recommendations for given clinical scenarios by way of categorization as appropriate, may be appropriate, inappropriate, or rarely appropriate.

In 2019, a group of healthcare societies released consensus AUC guidelines for cardiac multimodality imaging including stress testing that address appropriateness of test selection in broad categories.<sup>9</sup> The 2014 AUC guidelines, however, are more focused on testing for CAD and give more of a detailed and extensive list of scenarios for appropriate use,<sup>10</sup>

although additional evidence has accrued since then. Nevertheless, both guidelines are useful in improving understanding for appropriate test selection. Ultimately, AUC guidelines cannot determine a single best test, and a physician must take into account the whole clinical picture and test features when making a selection.

## ■ TAKE-HOME MESSAGE

Both stress testing with ECG, echocardiography, nuclear perfusion imaging, and MRI and anatomical evaluation with coronary CT provide details for evaluating CAD in at-risk patients. Results can help in risk stratification and assist with prognostication. Appropriate test selection is based on the patient's clinical picture, including the nature of symptoms, the risk profile, the clinical question being asked, and the strengths and limitations of the testing modality. Other factors that may influence test selection include local expertise, availability and access to a given modality, cost, and patient preference. ■

## ■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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