Cardiovascular Imaging to Risk-Stratify in Chronic Angina

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The location, extent, and severity of obstructive coronary artery disease impact cardiovascular risk and mortality in independent and profound ways. Cardiovascular imaging modalities allow physicians to better define the anatomy and physiology of coronary obstructive disease. Conventional coronary angiography remains the most commonly used modality to define coronary anatomy. Computed tomography coronary angiography represents an important innovation, particularly by allowing coronary anatomy to be assessed in a noninvasive fashion. Stress myocardial perfusion imaging with single-photon emission computed tomography is a valuable prognostic tool. Stress testing, echocardiography, and stress myocardial radionuclide perfusion can all play important roles in risk stratification. Stress echocardiography is particularly useful in the clinic, due to the relatively low cost of equipment acquisition and the ability to image without exposure to radiation. The emerging modality of cardiac positron emission tomography offers the prospect of improved resolution, accurate quantification of blood flow, and shorter examination times.
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Key words: Cardiovascular risk • Coronary angiography • Stress myocardial perfusion imaging • Echocardiography • Stress myocardial nuclear perfusion • Cardiac positron emission tomography

As interventional and imaging cardiologists, one of the more difficult decisions to be made is whether to intervene and "rock the boat" in the natural course of chronic angina, a stable condition. The term *chronic* characterizes the past clinical character of the condition, though not necessarily the future. The challenge in the management of these patients is to look forward and differentiate the lower risk patient who will do well, or even better, with medical therapy from the higher risk patient in whom a revascularization option should be considered. With cardiovascular imaging modalities, we can better define the anatomy and physiology of coronary obstructive disease. Proper employment of these techniques seems to allow us to better distinguish the risk that an individual patient will suffer from a major adverse cardiovascular event.

This article will examine use of cardiovascular imaging modalities such as conventional coronary angiography (CCA), computed tomography coronary angiography, stress testing, echocardiography, stress myocardial nuclear perfusion, and cardiac positron emission. It will also consider how results from these tests might influence therapeutic decisions.

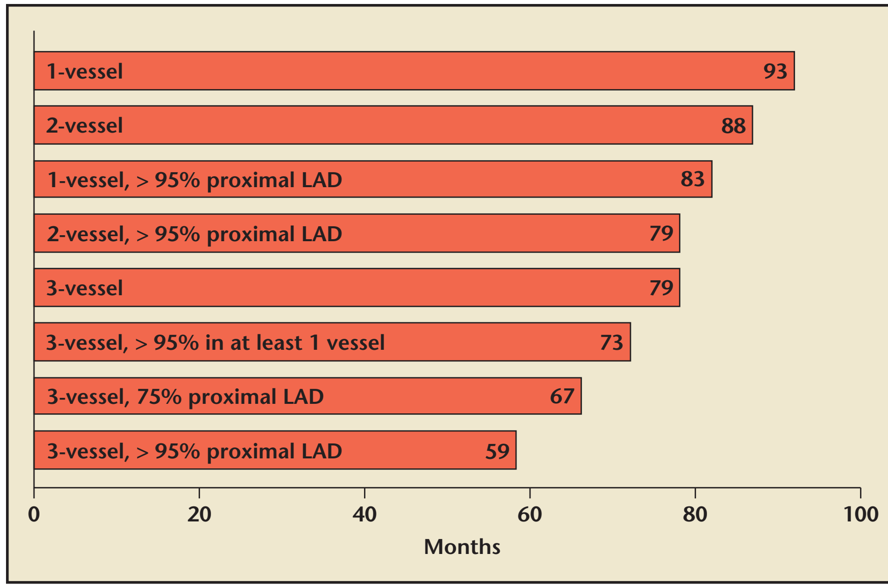

Figure 1. *Five-year survival ranges from 93% in patients with single-vessel disease to as low as 59% in patients with triple-vessel disease that includes a greater than 95% stenosis in the proximal left anterior descending (LAD) artery. Reprinted with permission from Morrow DA and Gersh BJ.[1]*

Coronary Angiography

The location(s), extent, and severity of obstructive coronary artery disease impact cardiovascular risk and mortality in independent and profound ways. Five-year survival ranges from 93% in patients with single-vessel disease to as low as 59% in patients with triple-vessel disease that includes a stenosis exceeding 95% in the proximal left anterior descending (LAD) artery (Figure 1).[1] Even among patients with triple-vessel disease, there is a wide difference in survival, ranging from 59% to 79%, based in large part on the presence or absence and severity of disease in the proximal segment of the LAD artery. The ability to rule out high-risk coronary anatomy (left main coronary artery and proximal LAD disease) can allow for more appropriate triage to medical therapy, with high-risk patients referred for consideration for revascularization. CCA remains the most commonly used modality to define coronary anatomy. As adjuncts to CCA, fractional flow reserve and intravascular ultrasound can add to the diagnostic capabilities of angiography by providing additional physiologic and anatomic information. These approaches are particularly useful in lesions of intermediate severity. Fractional flow reserve provides the ability to perform a physiologic assessment of a coronary artery stenosis during the course of CCA and complements the ability to characterize a coronary artery stenosis above and beyond angiographic appearance. The use of fractional flow reserve improves the outcome of patients with multivessel disease who are undergoing coronary stent placement.[2] Intravascular ultrasound can also be a useful adjunct to help define the severity of intermediate lesions observed on CCA. A luminal area of less than 4.0 mm^2 has a sensitivity and specificity of 80% to 90% in identifying those coronary stenoses that are severe enough to cause inducible ischemia with stress myocardial perfusion single-photon emission computed tomography (SPECT).[3] Computed tomography coronary angiography (CTCA) represents an important innovation, particularly by allowing coronary anatomy to be assessed in a noninvasive fashion.[4] This approach avoids the small but inherent risk associated with CCA, particularly at the vascular access site.[5] Evaluation of coronary anatomy outside of the cardiac catheterization laboratory also helps avoid the "occulo-stenotic reflex," which can lead, in some cases, to unnecessary revascularization of lesions of intermediate severity. CTCA has been demonstrated to have a high degree of accuracy in determining stenosis severity as compared with CCA.[6] CCTA has also been shown to add significant prognostic value to clinical risk assessments, such as the Framingham risk model, in defining the risk of major cardiac adverse events.[7] An additional benefit of CTCA is its potential ability to characterize plaque morphology by assessing for positive remodeling and lower computed tomography density of plaque.[8] This information may be able to define the acuity of the lesion, and thus lead to either intensification of medical therapy or use of device therapy. CTCA is an incredibly powerful diagnostic tool to assist in the risk stratification of patients with chronic stable angina.

Stress testing, echocardiography (with and without stress testing), and stress myocardial nuclear perfusion can all play important roles in stratification of patients with coronary artery disease into high risk (> 3% 1-year mortality) and low risk (< 1% 1-year mortality) categories (Table 1).[9] Stress myocardial perfusion imaging (MPI) with SPECT is a valuable prognostic tool for the evaluation of patients with coronary artery disease. It is well established that MPI with ^{201}Tl, ^{99m}Tc-sestamibi, and ^{99m}Tc-tetrofosmin has been found to provide incremental information for risk assessment in patients who have coronary artery disease or who are at risk.[10-13] Although studies have not confirmed a relationship between an abnormal SPECT scan and cardiovascular death, they do show that the extent of abnormalities is associated with incremental risk (Figure 2).[14]

Table 1
Risk Stratification With Cardiac Imaging

High Risk (> 3% annual mortality rate)

1. Severe resting left ventricular dysfunction (LVEF < 35%)
2. High-risk treadmill score (≤ −11)
3. Severe exercise left ventricular dysfunction (exercise LVEF < 35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with left ventricular dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with left ventricular dilation or increased lung update (thallium-201)
8. Echocardiographic wall motion abnormality (involving > 2 segments) developing at a low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min)
9. Stress echocardiographic evidence of extensive ischemia

Intermediate Risk (1% to 3% annual mortality rate)

1. Mild/moderate resting left ventricular dysfunction (LVEF of 35% to 49%)
2. Intermediate-risk treadmill score (−10 to +4)
3. Stress-induced moderate perfusion defect without left ventricular dilation or increased lung intake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤ segments

Low Risk (< 1% annual mortality rate)

1. Low-risk treadmill score (score ≥ +5)
2. Normal or small myocardial perfusion defect at rest or with stress*
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress*

*Although the published data are limited, patients with these finding will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting left ventricular dysfunction (LVEF < 35%).
LVEF, left ventricular ejection fraction.
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The prognostic value of MPI has also been found to be relevant in the outpatient setting, where the most potent independent risk factors for cardiovascular events in order of importance are: transient ischemic dilation, extent of reversibility, post-stress ejection fraction, extent and severity of the stress perfusion defect, and whether the overall test was normal or abnormal.[15] MPI can also play a role in determining the relative benefit of medical therapy versus a revascularization approach in patients with coronary artery disease. In a retrospective evaluation of patients who underwent MPI, there was no benefit of revascularization compared with medical therapy, except among patients whose scans showed a high ischemic burden (> 20% of the myocardium).[16]

The nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial evaluated the effectiveness of percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) as compared with OMT alone in the reduction of ischemic burden and its relationship to cardiac event rates.[17] The substudy entry criteria included patients with medically stable angina, a stenosis of 70% or more in at least 1 major coronary artery, and ischemia on MPI. The primary endpoint, reduction in ischemic myocardium of 5% or more on a 6- to 18-month MPI, was more frequent with PCI plus OMT than with OMT alone (33% vs 18% [P = .0004]). The results of the substudy also suggest that ischemia reduction

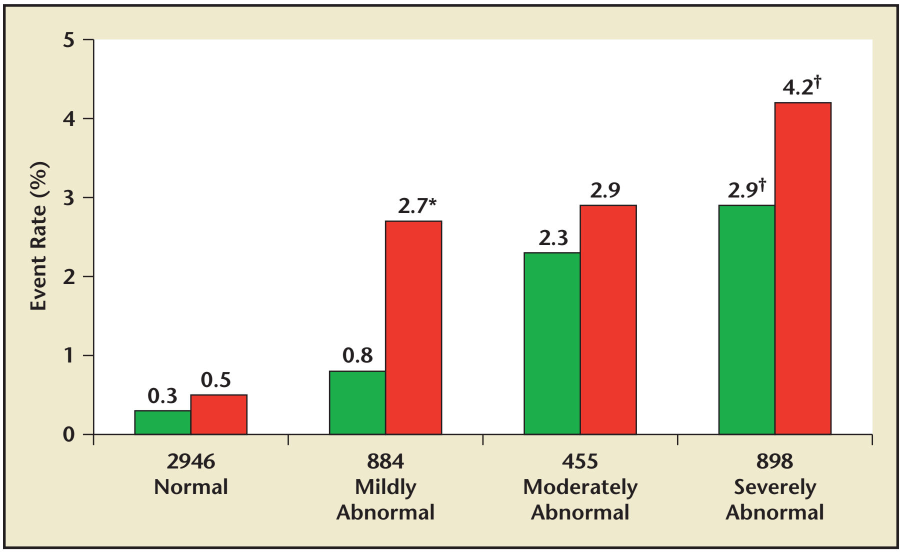

Figure 2. *Rates of cardiac death (red bars) and myocardial infarction (green bars) as a function of myocardial perfusion scan result. *Statistically significant increase in rate of myocardial infarction vs cardiac death within scan category. †Statistically significant increase as a function of scan result. Reprinted with permission from Hachamovitch R, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction.* Circulation. *1998;97(6):535-543.*[14]

of 5% or more may be associated with a significantly lower risk of death and myocardial infarction (MI), whether treatment is with OMT alone or with OMT plus PCI. Therefore, the extent of residual ischemia at follow-up imaging may be predictive of clinical outcomes. Follow-up stress imaging may prove to be valuable in assessing residual ischemia in patients on OMT and thereby identifying residual risk, which can lead to either further intensification of medical therapy or consideration for revascularization.

Although PCI plus OMT seemed to be associated with greater reduction in ischemic burden in the nuclear substudy, in the greater COURAGE trial, PCI plus OMT did not lead to a significant reduction in the primary clinical endpoints of death and nonfatal MI or the secondary endpoints of death, MI, or stroke, and hospitalization for acute coronary syndromes compared with OMT alone.[18] The finding of a greater reduction of ischemia in the nuclear substudy is consistent with the COURAGE trial findings of greater reduction in angina severity with PCI plus OMT.

The limitations of the nuclear substudy include the nonrandom comparisons by treatment, the lack of statistical power to evaluate differences in long-term event rates, and the fact that the study population differed from that in the main COURAGE trial.

Stress Echocardiography

Stress echocardiography was introduced in 1979 and has developed into a versatile and accurate technique to evaluate for obstructive coronary artery disease. Stress echocardiography, like SPECT, can be performed with exercise or pharmacologically (Table 2). Stress echocardiography has attributes that make it particularly useful in the clinic, including the relatively low cost of equipment acquisition and the ability to image without exposure to radiation. Its major limitation is the need to have adequate acoustic windows, which can be a challenge in patients who are very thin or obese, or patients who have breast implants or lung disease.

The sensitivity and specificity of exercise echocardiography to determine the presence of obstructive coronary artery disease has been well studied and ranges from 71% to 97% and 64% to 90%, respectively.[19,20] Using the exercise wall motion score index, occurrence of ST-segment change at maximal exercise, and treadmill exercise time, a model has been developed to estimate 5-year risk of death and nonfatal MI from the time of the exercise study.[21,22] Recent reports show that taking into account the presence of resting wall motion abnormalities in addition to the development of new stress-induced wall motion abnormalities adds to the

Table 2
Methodologies to Perform Stress Echocardiography

Exercise
Post-treadmill exercise
Supine bicycle
Upright bicycle
Pharmacologic
Dobutamine infusion (± atropine)
Dipyridamole (± atropine)
Adenosine (± atropine)
Combined dobutamine-dipyridamole
Other
Transesophageal atrial pacing
Transvenous pacing (temporary or permanent)
Ergonovine
Hyperventilation
Cold pressor

Table 3
Appropriateness for Revascularization With Low-Risk Noninvasive Studies in Non-CABG Patients

Low-Risk Findings on Noninvasive Study							Asymptomatic					
Symptoms **Med Rx**							**Stress Test** **Med Rx**					
Class III or IV Max Rx	U	A	A	A	A		High Risk Max Rx	U	A	A	A	A
Class I or II Max Rx	U	U	A	A	A		High Risk No/Min Rx	U	U	A	A	A
Asymptomatic Max Rx	I	I	U	U	U		Int Risk Max Rx	U	U	U	U	A
Class III or IV No/Min Rx	I	U	A	A	A		Int Risk No/Min Rx	I	I	U	U	A
Class I or II No/Min Rx	I	I	U	U	U		Low Risk Max Rx	I	I	U	U	U
Asymptomatic No/Min Rx	I	I	U	U	U		Low Risk No/Min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1 vz disease of prox LAD	2 vz disease; with prox LAD	3 vz disease; no left main		**Coronary Anatomy**	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1 vz disease of prox LAD	2 vz disease with prox LAD	3 vz disease; no left main

CABG, coronary artery bypass grafting; A, appropriate; CTO, chronic total occlusion; I, inappropriate; int, intermediate; max, maximum; med, medical; min, minimum; prox LAD, proximal left anterior descending artery; Rx, treatment; U, uncertain; vz, vessel. Reprinted from *J Am Coll Cardiol*. Volume 53, Issue 6. Patel MR, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization. Pages 530-553.[9] © 2009, with permission from the American College of Cardiology.

Table 4
Appropriateness for Revascularization With Intermediate-Risk Noninvasive Studies in Non-CABG Patients

Intermediate-Risk Findings on Noninvasive Study							CCS Class I or II Angina					
Symptoms **Med Rx**							**Stress Test** **Med Rx**					
Class III or IV Max Rx	A	A	A	A	A		High Risk Max Rx	A	A	A	A	A
Class I or II Max Rx	U	A	A	A	A		High Risk No/Min Rx	U	A	A	A	A
Asymptomatic Max Rx	U	U	U	U	A		Int Risk Max Rx	U	A	A	A	A
Class III or IV No/Min Rx	U	U	A	A	A		Int Risk No/Min Rx	U	U	U	A	A
Class I or II No/Min Rx	U	U	U	A	A		Low Risk Max Rx	U	U	A	A	A
Asymptomatic No/Min Rx	I	I	U	U	A		Low Risk No/Min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1 vz disease of prox LAD	2 vz disease with prox LAD	3 vz disease; no left main		**Coronary Anatomy**	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1 vz disease of prox LAD	2 vz disease with prox LAD	3 vz disease; no left main

CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; A, appropriate; CTO, chronic total occlusion; I, inappropriate; int, intermediate; max, maximum; med, medical; min, minimum; prox LAD, proximal left anterior descending artery; Rx, treatment; U, uncertain; vz, vessel. Reprinted from *J Am Coll Cardiol*. Volume 53, Issue 6. Patel MR, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization. Pages 530-553.[9] © 2009, with permission from the American College of Cardiology.

ability to define cardiovascular risk with stress echocardiography.[23]

Future developments in stress echocardiography that may further enhance its diagnostic capabilities include 3-dimensional imaging, contrast echocardiography, and the incorporation of tissue Doppler, myocardial strain, and strain rate imaging.[24]

Stress PET

The emerging modality of cardiac positron emission tomography (PET) offers the prospect of improved resolution, accurate quantification of blood flow (especially important for the better detection of global balanced ischemia), and shorter examination times than the most commonly used technique, myocardial perfusion scintigraphy. For PET imaging, the dominant perfusion tracers used in the clinical setting are *N*-13 ammonia and ^{82}Rb, the latter eluted from a generator. The short-lived cyclotron-produced radionuclide ^{Oxygen}-15 water is another PET perfusion agent that has been used predominantly in the research setting. The sensitivity and specificity of PET MPI appear to be higher than those reported for SPECT.

Although myocardial perfusion PET imaging is an option for all patients requiring stress perfusion imaging, there are identifiable patient groups that are difficult to image with conventional SPECT imaging and are particularly likely to benefit from PET imaging. These groups include obese patients, women, patients with previous nondiagnostic tests, and patients with poor left ventricular function attributable to coronary artery disease who are being considered for revascularization. Myocardial PET perfusion imaging with ^{82}Rb is noteworthy for high efficiency, rapid throughput, and, in a high-volume setting, low operational costs.

Stress Cardiovascular Magnetic Resonance

Stress cardiovascular magnetic resonance (CMR) has several distinct advantages over other stress imaging modalities, including its high contrast, high spatial resolution, and lack of ionizing radiation exposure. For detection of significant coronary artery disease, stress CMR can provide several different strategies, including dynamic first-pass perfusion imaging and stress wall motion imaging. The former images perfusion deficits and the latter images stress abnormalities of regional wall function (motion and/or thickening). In a meta-analysis comparing the ability of these 2 approaches against that of CCA to identify coronary stenoses exceeding 50%, both had similar specificity (perfusion imaging, 81% and stress-induced wall motion abnormalities, 86%) and similar sensitivity (perfusion imaging, 91% and stress-induced wall motion abnormalities, 83%).[25] This sensitivity and specificity compare favorably to those of SPECT (86% and 79%) and stress echocardiography (84% and 82%).[26,27] Another approach to detecting stress-induced myocardial ischemia with CMR uses phosphorus spectroscopy to depict adenosine triphosphate and phosphocreatine. This approach is still considered experimental.[28,29]

Imaging/Cardiac Risk and Therapeutic Decisions

Taking into account the results of nuclear, echocardiography, and magnetic resonance imaging, patients with obstructive coronary artery disease can be stratified into 3 mortality risk groups: high risk (> 3% annual mortality rate), intermediate risk (1% to 3% annual mortality rate), and low risk (< 1% mortality risk) (Table 1). Patients with high-risk characteristics may be good candidates for CCA and considered for revascularization as an adjunct to OMT. Those with low-risk characteristics may be good candidates for continued OMT. Those with intermediate risk may undergo CTCA to define whether they have high-risk coronary anatomy (left main or proximal LAD disease) or lower risk disease. The lack of high-risk characteristics in this intermediate-risk population would seem to make this group suitable for an initial attempt at an OMT approach.

The 2009 Appropriateness Guidelines for Coronary Revascularization represent a data-based attempt to incorporate clinical angina status, the results of noninvasive imaging, and the relative risk stratification that it provides combined with angiographic data into guidelines for coronary revascularization.[9] Recommendations for patients at low risk, intermediate risk, and high risk are outlined (Tables 3-5).

Conclusion

Cardiac imaging plays a pivotal role in predicting the risk of major cardiovascular events in patients with coronary artery disease, above and beyond clinical presentation. The finding of high-risk characteristics, such as extensive stress-induced left ventricular systolic dysfunction, extensive ischemic deficit stress MPI (SPECT, echocardiography, PET, or magnetic resonance), high-risk angiographic findings (left main or multivessel disease, including the proximal LAD artery), or large residual ischemic burden while on prescribed OMT, may direct consideration for revascularization with PCI or coronary artery bypass grafting. For the majority of patients with chronic stable angina who have their symptoms adequately controlled with OMT and who lack high-risk characteristics on imaging studies, OMT alone appears to be the most prudent approach. ■

Table 5
Appropriateness for Revascularization With High-Risk Noninvasive Studies in Non-CABG Patients

High-Risk Findings on Noninvasive Study					
Symptoms **Med Rx**					
Class III or IV Max Rx	A	A	A	A	A
Class I or II Max Rx	A	A	A	A	A
Asymptomatic Max Rx	U	A	A	A	A
Class III or IV No/Min Rx	A	A	A	A	A
Class I or II No/Min Rx	U	A	A	A	A
Asymptomatic No/Min Rx	U	U	A	A	A
Coronary Anatomy	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1 vz disease of prox LAD	2 vz disease with prox LAD	3 vz disease; no left main

CCS Class III or IV Angina					
Stress Test **Med Rx**					
High Risk Max Rx	A	A	A	A	A
High Risk No/Min Rx	A	A	A	A	A
Int Risk Max Rx	A	A	A	A	A
Int Risk No/Min Rx	U	U	A	A	A
Low Risk Max Rx	U	A	A	A	A
Low Risk No/Min Rx	I	U	A	A	A
Coronary Anatomy	CTO of 1 vz; no other disease	1-2 vz disease; no prox LAD	1 vz disease of prox LAD	2 vz disease with prox LAD	3 vz disease; no left main

CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; A, appropriate; CTO, chronic total occlusion; I, inappropriate; int, intermediate; max, maximum; med, medical; min, minimum; prox LAD, proximal left anterior descending artery; Rx, treatment; U, uncertain; vz, vessel. Reprinted from *J Am Coll Cardiol*. Volume 53, Issue 6. Patel MR, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization. Pages 530-553.[9] © 2009, with permission from the American College of Cardiology.

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Main Points

- The ability to rule out high-risk coronary anatomy (left main coronary artery and proximal left anterior descending disease) can allow for more appropriate triage to medical therapy, with high-risk patients referred for consideration for revascularization.
- Conventional coronary angiography, in combination with fractional flow reserve and intravascular ultrasound, is particularly useful in imaging lesions of intermediate severity.
- In a retrospective evaluation of patients who underwent myocardial perfusion imaging, there was no benefit of revascularization compared with medical therapy, except among patients whose scans showed a high ischemic burden.
- The sensitivity and specificity of exercise echocardiography to determine the presence of obstructive coronary artery disease has been well studied and ranges from 71% to 97% and 64% to 90%, respectively.
- Myocardial positron emission tomography perfusion imaging with ^{82}Rb is noteworthy for high efficiency, rapid throughput, and, in a high-volume setting, low operational costs.
- Stress cardiovascular magnetic resonance has several distinct advantages over other stress imaging modalities, including its high contrast, high spatial resolution, and lack of ionizing radiation exposure.

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