

# Noninvasive Evaluation of Coronary Artery Disease:

## Selecting the Right Test for the Right Patient

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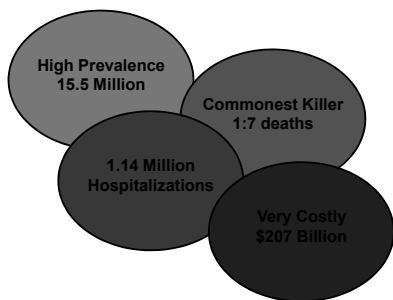
## Drug List

Generic Drug Name	US Trade Name
adenosine	Adenocard
atorvastatin	Lipitor
dipyridamole	Persantine
dobutamine	Dobutrex
lisinopril	Zestril
naproxen	Aleve
regadenoson	Lexiscan

## Learning Objectives

- Describe the physiological basis of stress testing
- Identify the types of noninvasive cardiac imaging tests along with their indications and contraindications
- Discuss the risk-benefit considerations of radionuclide imaging (RNI) for patients with cardiovascular disease factors
- Apply appropriate use criteria (AUC) to select the right test for the right patient.

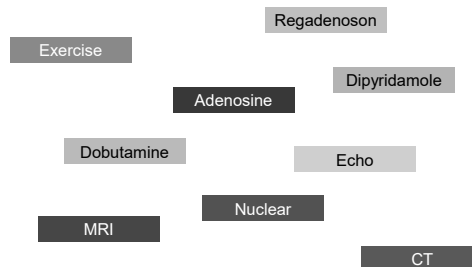
## Prevalence and Impact of CHD in the US



CHD = coronary heart disease.  
Mozaffarian D, et al. *Circulation*. 2016;133(4):e38-360.

## Evaluation of Suspected CAD: Complexity of Decision Making

Many Test Choices!



CAD = coronary arterial disease.

## Evaluation of Suspected CAD: Complexity of Decision-making

### Evolution of the Appropriate Use Criteria:

- Single Modality → Multi-modality (2013)
- Lists multiple "appropriate" test, but does not rank order

Indication Text	Exercise ECG	Stress RNI	Stress Echo	Stress CMR	Calcium Scoring	CCTA	Invasive Coronary Angiography
1 • Low pre-test probability of CAD • ECG interpretable AND able to exercise	A	R	M	R	R	R	R
2 • Low pre-test probability of CAD • ECG uninterpretable OR unable to exercise		A	A	M	R	M	R
3 • Intermediate pre-test probability of CAD • ECG interpretable AND able to exercise	A	A	A	M	R	M	R
4 • Intermediate pre-test probability of CAD • ECG uninterpretable OR unable to exercise		A	A	A	R	A	M
5 • High pre-test probability of CAD • ECG interpretable AND able to exercise	M	A	A	A	R	M	A
6 • High pre-test probability of CAD • ECG uninterpretable OR unable to exercise		A	A	A	R	M	A

A = appropriate; M = may be appropriate; R = rarely appropriate.  
Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## Evaluation of Suspected CAD: Complexity of Decision-making

### Regulatory Requirements:

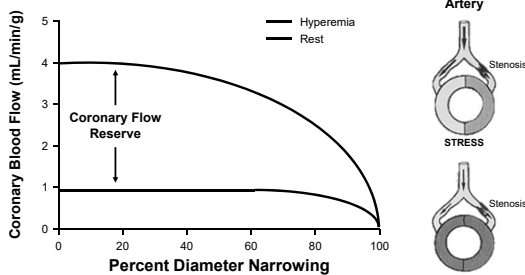
#### Patient Access to Medicare Act (PAMA, 2014):

- Requires referring physicians to consult a decision support tool based on appropriate use criteria (AUC) when referring patients for advanced imaging tests
- Expected implementation January 2018

<https://www.congress.gov/bills/113th-congress/house-bill/4302/text>. Accessed September 23, 2016. Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## Why Stress Test to Diagnose CAD?

### The Physiology of Stress Testing



Adapted from Libby PP, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8<sup>th</sup> ed. Chap. 16. Philadelphia: Elsevier Science; 2007. Gould K L. *Am J Cardiol*. 1978;41:267-78.

## Indications for Stress Testing

- **Diagnosis of CAD**
  - Estimating the probability of obstructive CAD
- **Risk Stratification in known or suspected CAD** (Estimating the risk of death or nonfatal MI)
  - Low risk <1% per year
  - Intermediate risk 1–3% per year
  - High risk >3% per year

Gibbons RJ, et al. *J Am Coll Cardiol*. 1997;30:260-311.

## Who to Test? Asymptomatic Patients

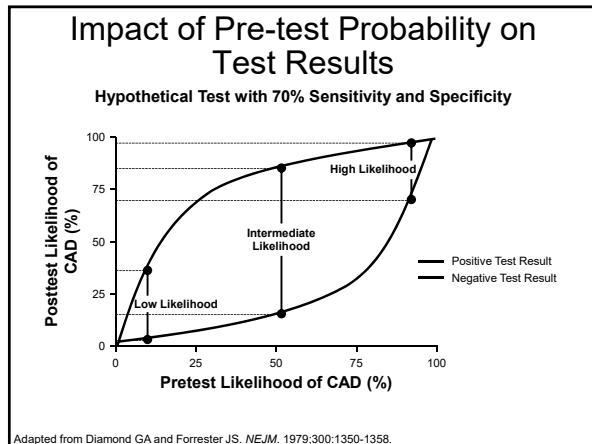
- Stress testing is generally not indicated
- May consider in high-risk patients
  - e.g., > 2% annual risk, CACS > 400 and diabetes

CACS = coronary artery calcium score.  
Greenland P, et al. *Circulation*. 2010;122:e584-636.

## Who to Test? Symptomatic Patients

- Test based on pre-test probability of CAD
- Low probability: No testing
- Intermediate probability
  - Highest yield of testing
- High probability
  - May test for risk stratification or management planning (not diagnosis)

Diamond GA and Forrester JS. *NEJM*. 1979; 300:1350-1358.



### Determination of Pre-Test Probability

Age Group	Typical Angina	Atypical Angina	Non-anginal Chest Pain
♂ 30-39	Intermediate	Intermediate	Low
♂ 40-49	High	Intermediate	Low
♂ 50-59	High	Intermediate	Intermediate
♂ 60-69	High	Intermediate	Intermediate
♀ 30-39	Intermediate	Very low	Very low
♀ 40-49	Intermediate	Low	Very low
♀ 50-59	Intermediate	Intermediate	Low
♀ 60-69	High	Intermediate	Intermediate

■ High >90%    □ Intermediate 10-90%    ■ Low <10%    □ Very low <5%

Adapted from Diamond GA and Forrester JS. *NEJM*. 1979;300(24):1350-1358.

- ### Typical vs Atypical Angina
- **Typical angina**
    - Substernal chest pain or discomfort
    - Provoked by exertion or emotional stress
    - Relieved by rest and/or nitroglycerin
  - **Atypical angina**
    - Meets 2 of the above criteria
  - **Nonanginal chest pain**
    - Meets 1 or none of the above criteria
- Herman LK, et al. *Am J Cardiol*. 2010;105(11):1561-4. Fox K, J, Sechtem U, et al. *Eur Heart J*. 2006; 27(11):1341-81.

- ### Who to Refer to Cardiology
- Typical angina, particularly if new onset of severe symptoms, rest pain, or accelerated angina
- Mieres JH, et al. *Am Fam Physician*. 2007;75:1219-28.

- ### The Anatomy of a Stress Test
- |   |   |
|---|---|
| <b>Stressor</b> <ul style="list-style-type: none"> <li>• Exercise</li> <li>• Pharmacologic vasodilator <ul style="list-style-type: none"> <li>– Adenosine</li> <li>– Regadenoson</li> <li>– Dipyridamole</li> </ul> </li> <li>• Pharmacologic inotrope <ul style="list-style-type: none"> <li>– Dobutamine</li> </ul> </li> </ul> | <b>Imaging</b> <ul style="list-style-type: none"> <li>• ECG, Nuclear, or Echo <ul style="list-style-type: none"> <li>– Exercise stress</li> </ul> </li> <li>• MPI (nuclear) or MRI <ul style="list-style-type: none"> <li>– Pharmacologic stress</li> </ul> </li> <li>• MPI (nuclear), MRI, or Echo <ul style="list-style-type: none"> <li>– Dobutamine stress</li> </ul> </li> </ul> |
|---|---|
- ECG = electrocardiogram; Echo = echocardiogram; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging.

- ### Noninvasive Tests for Suspected CAD Symptoms
- #### Noninvasive Cardiac Imaging Tests
- Treadmill ECG (no imaging)
  - Stress nuclear (Myocardial perfusion imaging)
  - Stress echo
  - Stress MRI
  - CT coronary angiography (direct visualization of the coronary arteries without stress testing)

## Absolute Contraindications

### Exercise Stress

1. Acute MI (<4 days)
2. High-risk unstable angina
3. Decompensated HF
4. Hypertensive emergency (BP >200/100 mm Hg)
5. Symptomatic cardiac arrhythmias
6. Severe symptomatic aortic stenosis
7. Acute pulmonary embolism
8. Acute aortic dissection
9. Severe pulmonary hypertension

Avoid in patients with LBBB, unless functional capacity is highly desired.

LBBB = left bundle branch block.  
Henziolova MJ, et al. *J Nucl Cardiol*. 2016;23:606-39.

## Absolute Contraindications

### Dobutamine Stress

1. Acute MI (<4 days)
2. High risk unstable angina
3. Left ventricular outflow obstruction
4. Hypertensive emergency (BP >200/100 mm Hg)
5. History of ventricular tachycardia
6. Severe symptomatic Aortic stenosis
7. Aortic dissection or aortic aneurysms

Avoid in patients on beta-blockers or those with atrial fibrillation or LBBB.

Henziolova MJ, et al. *J Nucl Cardiol*. 2016;23:606-39.

## Absolute Contraindications

### Vasodilator Stress

(Adenosine, Dipyridamole and Regadenoson)

1. Unstable acute MI
2. Known hypersensitivity
3. Active bronchospasm
4. High degree A-V block without pacemaker
5. Resting hypotension (systolic BP <90 mm Hg)
6. Caffeine or other methylxanthine use
7. Recent use of dipyridamole containing medications: for adenosine or regadenoson use

Henziolova MJ, et al. *J Nucl Cardiol*. 2016;23:606-39.

## Exercise Testing

- Most physiological stressor
  - A good functional capacity indicates excellent prognosis and overall health
- Use exercise stress preferentially
- Safety: 1:10,000 deaths, 2:10,000 cardiac arrests

Gibbons L, et al. *Circulation*. 1989;80:846-852. Gibbons RJ, et al. *J Am Coll Cardiol*. 1997;30:260-311.

## Indications for EST (without imaging) Class I

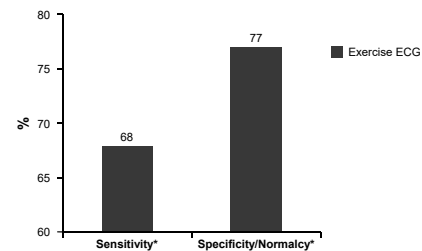
Adult patients (including those with complete RBBB or less than 1 mm of resting ST ↓) with an intermediate pretest probability of CAD, based on gender, age, and symptoms

- Appropriate in patients **able to exercise**, with an **interpretable ECG**, and **intermediate** probability of CAD
- **Not** appropriate:
  - Low probability and high probability
  - >1mm ST depression at baseline, **LBBB**, paced, pre-excitation (OK in RBBB, <1mm ST)

EST = exercise stress test; RBBB = right bundle branch block.  
Gibbons RJ, et al. *J Am Coll Cardiol*. 1997;30:260-311.

## Sensitivity and Specificity of Exercise ECG for CAD

\*Compared to Observed CAD with Cardiac Catheterization



\*Compared to observed CAD with cardiac catheterization.  
Lee TH, et al. *N Engl J Med*. 2001;344:1840-1845.

## Prognostic Value of Exercise ECG CASS Study – Medical Treatment Limb

- 4000 patients with EST
- Only Stage I with >1.0 mm ST↓
  - 12% of patients
  - **5% mortality/year**
- Stage III or higher with <1.0 mm ST↓
  - 34% of patients
  - **<1% mortality/year**
- **Patients with excellent exercise tolerance (>10 METs) have good prognosis regardless of coronary anatomy**

EST = exercise stress test; MET = metabolic equivalent (unit of measurement).  
Weiner DA, et al. *J Am Coll Cardiol.* 1984;3:772-779.

## EST Indicators of Adverse Prognosis

- <6 METs of exercise
- Failure to increase SBP to 120 mm Hg
- Decrease in BP of 10 mm Hg during exercise
- Downsloping ST segment  $\geq 2$  mm at <6 METs involving 5 leads, persisting 5 min into recovery
- ST segment elevation
- Angina at low exercise workloads
- Sustained (>30 sec) or symptomatic VT

VT = ventricular tachycardia.  
Morrow K, et al. *Ann Intern Med.* 1993;118(9):689-695.

## MPI Nuclear Stress Testing

- IV injection of a radioactive compound (tracer) that is taken up by cardiac muscle in proportion to coronary blood flow
- Produces a 3-D map of myocardial perfusion

MPI = myocardial perfusion imaging.  
Beller GA. *Adv Intern Med.* 1997;42:139-201.

## Myocardial Perfusion Imaging (MPI)

### • Stress Modalities

- Exercise
- Pharmacologic:
  - Vasodilators (dipyridamole, adenosine, regadenoson)
  - Dobutamine

### • Tracers

- Tc-99m-based tracers (Tc-99m sestamibi and Tc-99m tetrofosmin)
- Thallium-201

Beller GA. *Adv Intern Med.* 1997;42:139-201.

## Pharmacologic Stress Agents

### Advantages

- Dipyridamole
  - Long experience, most commonly used
- Adenosine
  - Long experience, most commonly used
- Regadenoson
  - **Well tolerated with low SE**, selective for coronary vasculature, bolus administration, can be used in asthma and COPD patients with caution
- Dobutamine
  - Can use in patients with asthma or bronchospasm

### Disadvantages

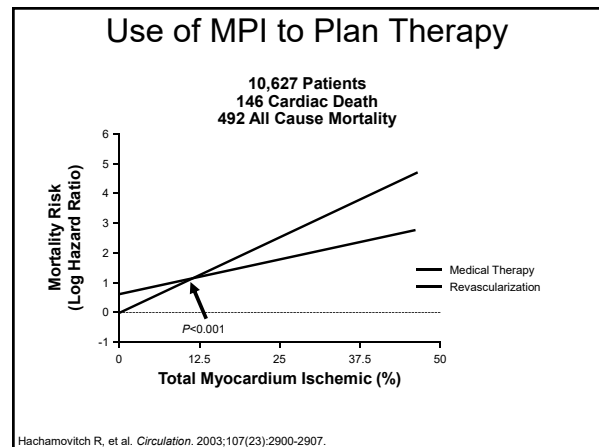
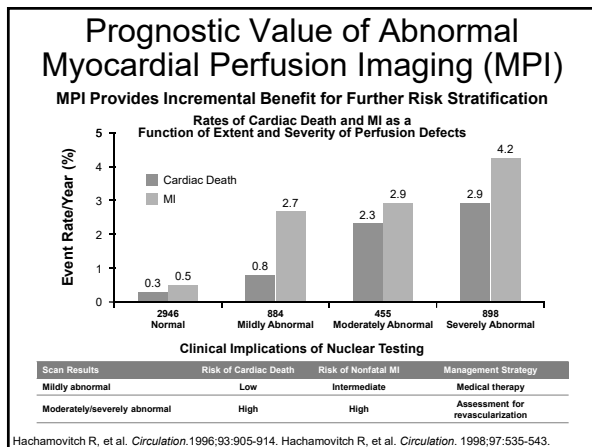
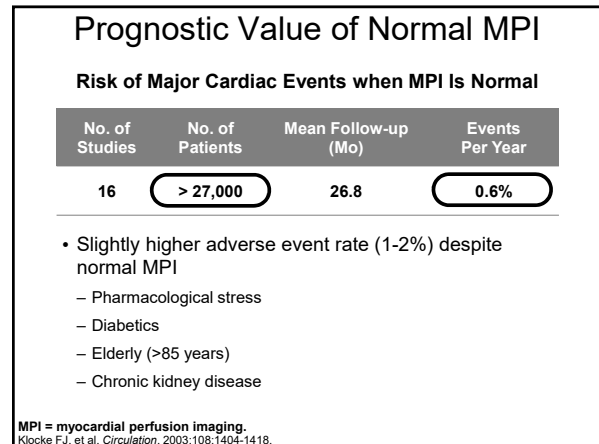
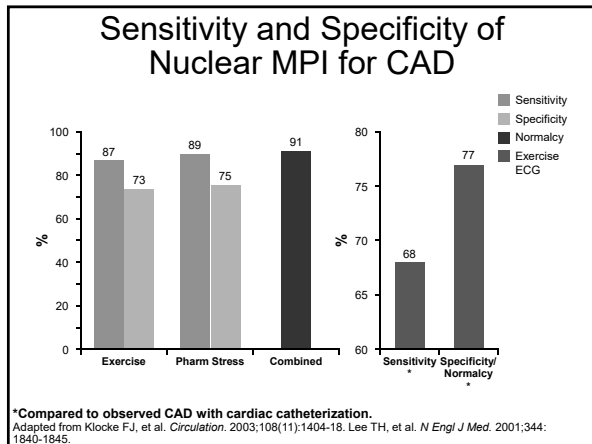
- Dipyridamole
  - Long duration of action, **poorly tolerated with frequent SE**, long infusion time
- Adenosine
  - Short duration of action, requires continuous infusion, **poorly tolerated with frequent SE**, contra-indicated in asthma or COPD patients
- Regadenoson
  - Use with caution in patients with asthma or COPD
- Dobutamine
  - Long duration of action, can cause ischemia and arrhythmia

SE = side effects.  
Sotnick EH. *J Nucl Med Technol.* 2009;37:14-25. Golzar Y, et al. *Int J Chron Obstruct Pulmon Dis.* 2014;9:129-37. Buhr C, et al. *Vasc Health Risk Manag.* 2008;4(2):337-40. Leppo JA. *J Nucl Cardiol.* 1996;3(6 Pt 2):S22-6.

## Indications for MPI

- Diagnosis of CAD
  - Patients who cannot exercise or have confounding changes on the baseline ECG (LBBB, LVH, digitalis, pre-excitation, >1mm ST depression at baseline)
- Risk stratification in symptomatic patients with known or suspected CAD
- Assessment of myocardial viability
- Detecting post PCI or CABG ischemia
- Assessing the functional significance of coronary stenosis

MPI = myocardial perfusion imaging; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PPM = permanent pacemaker; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.  
Klocke FJ, et al. *Circulation.* 2003;108:1404-1418.



### Considerations for Radionuclide Imaging

- Pros**
  - Widely available, large amount of supporting data, >4 decades of clinical experience
  - Quantitative and highly reproducible data, excellent prognostic capability
  - No contraindications (renal failure, atrial fibrillation, cardiac devices, inability to lie flat) — anyone can have a nuclear scan!
- Cons**
  - Stress testing
  - Radiation

### Non-Nuclear Imaging Techniques for Diagnosing CAD

Timothy Wong, MD

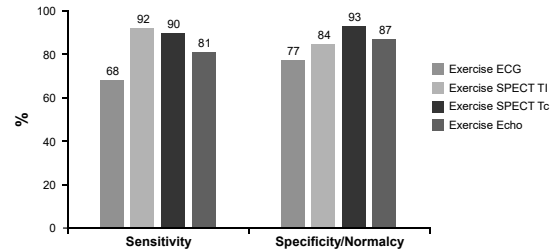
## Stress Echocardiography

- Based on principle that ischemic myocardium becomes hypokinetic
  - Baseline echo to identify regional wall motion
  - Immediate post-stress echo to look for changes in wall motion
- Exercise or pharmacologic (dobutamine) stress
- **Ischemia = change in wall motion with stress**

Douglas PS, et al. *J Am Coll Cardiol.* 2011;57:1126-1166.

## Sensitivity and Specificity of Non-Invasive Tests for CAD

Compared to Observed CAD with Cardiac Catheterization



SPECT = single-photon emission computed tomography;  
Lee TH, et al. *N Engl J Med.* 2001;344:1840-1845.

## Prognostic Value of Stress Echo vs Stress MPI

- Exercise echo and MPI improve diagnostic and prognostic power of clinical variables including stress ECG
- Comparable prognostic information
- Choice of echo or MPI depends on several factors, including availability, feasibility, expertise, and cost considerations

Olmos LJ, et al. *Circulation.* 1998;98:2679-86.

## Key Points

- Use exercise with stress MPI or echocardiography when possible
- Prepare patient – no caffeine, anti-anginal
- Similar diagnostic and prognostic data with MPI and echo, but incremental to clinical data alone
- Choice between MPI and echo?
  - Use what your Center does best

## Cardiac Magnetic Resonance Imaging

## Stress CMR

- Pharmacologic: dobutamine or vasodilator
- Treadmill exercise: very few centers
- Components of stress CMR:
  - Wall motion
  - Myocardial perfusion: administration of non-iodinated, gadolinium-based contrast

CMR = cardiac magnetic resonance.

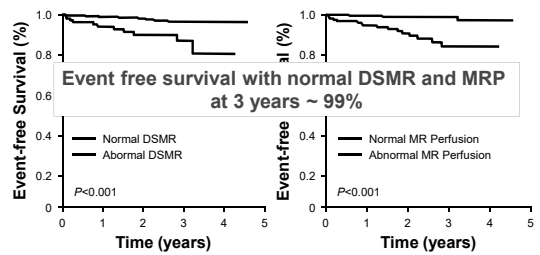
## Performance of CMR for Detecting CAD

### CE-MARC study

- 676 patients: largest study to date
- CAD:  $\geq 70\%$  anatomical stenosis on angiography
- Sensitivity: 87%
- Specificity: 83%
- Positive predictive value: 77%
- Negative predictive value: 91%

CMR = cardiac magnetic resonance.  
Greenwood JP, et al. *Lancet*. 2012;379(9814):453-460.

## CMR: Prognostic Value



461 symptomatic patients; CMR for perfusion (adenosine) and WM (dobutamine);  
Outcomes: cardiac death or nonfatal MI; median follow-up 2.3 years

WM = wall motion; MI = myocardial infarction; MRP = magnetic resonance perfusion; DSMR = dobutamine stress magnetic resonance.  
Jahnke C, et al. *Circulation*. 2007;115(13):1769-1776.

## Key Points

- High spatial resolution providing good structural data
- **Cannot use in severe renal insufficiency or in the presence of metallic implant**
- Limited availability and expertise

## Cardiac CT Angiography (CCTA)

## Cardiac CTA

### • Indication

- Evaluation of patients with intermediate pre-test probability for CAD

### • Contraindications

- Tachycardia (typically heart rate  $\sim 50-60$  bpm required), arrhythmia, or severe kidney dysfunction

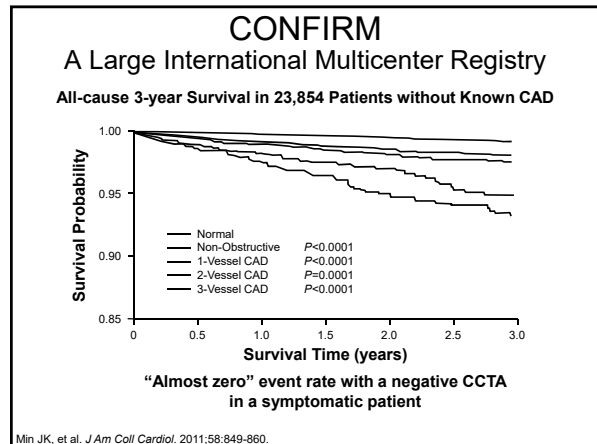
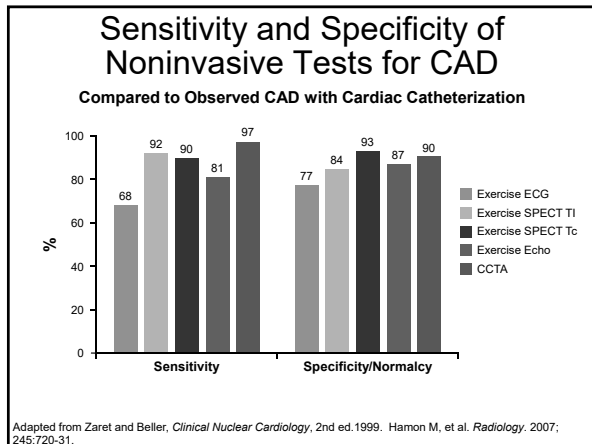
## CCTA and Invasive Angiography: Meta-analysis

- 28 studies, N=2024 patients
- 16- and 64-slice CT compared to coronary angiography
- 50% coronary stenosis is positive

	Slice	Sens (95% CI)	Spec (95% CI)	PPV	NPV
<b>Patient</b>	64	97% (97, 100)	90% (89, 98)	93%	96%
<b>Segment</b>	64	88% (88, 97)	96% (96, 97)	79%	98%

CCTA = cardiac computed tomography angiography; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval.  
Hamon M, et al. *Radiology*. 2007;245:720-31.





### Which Test to Use? Comparative Effectiveness

	Nuclear	Echo	CT	MRI
Wide availability	+	+	±	
Exercise	+	+	n/a	
Dobutamine	+	+	n/a	+
Vasodilator	+		n/a	+
Independent of body habitus	+			+
Use with metal implants	+	+	+	
Use in renal failure	+	+		
Use in atrial fibrillation	+	±		±
Provides structural information		+	+	+

+ = Yes; ± = moderate or with caution.  
Courtesy of Prem Soman, MD.

### What are “appropriate use criteria” and why should I care?

### Appropriate Use Criteria (AUC)

- AUC are evidence-based guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decision for a specific clinical condition.
- Determines whether a test ordered will be covered or not
- Appropriate diagnostic or therapeutic procedure:
  - Expected benefits – *survival* or *health outcomes* (symptoms, functional status, QOL) exceed the expected negative consequences (AE + downstream testing)
- Based on:
  - Available evidence + collective expert judgment

QOL = quality of life; AE = available evidence.  
Hendel RC, et al. *Circulation*. 2009;119:e561-e587. <http://www.acr.org/quality-safety/appropriateness-criteria>. Accessed September 28, 2016. Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

### Appropriate Use Criteria cont'd

Not intended to adjudicate individual cases, but rather to define patterns of care

Original Rating	2013 Rating
Appropriate	Appropriate (A)
Uncertain	May be appropriate (M)
Inappropriate	Rarely appropriate (R)

**AUC App**  
<https://itunes.apple.com/us/app/appropriate-use-criteria-auc/id391068250?mt=8>

Hendel RC, et al. *Circulation*. 2009;119:e561-e587. Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## Appropriate Use Criteria cont'd

**Appropriate Use Criteria (AUC)**

**AUC App**  
<https://itunes.apple.com/us/app/appropriate-use-criteria-auc/id391068250?mt=8>

Indication Category

APPROPRIATE Indications  
 UNCERTAIN Indications  
 INAPPROPRIATE Indications

Test Your Knowledge  
 Resources  
 Framingham Risk Calculator

**Not intended to adjudicate individual cases, but rather to define patterns of care**

Original Rating	2013 Rating
Appropriate	Appropriate (A)
Uncertain	May be appropriate (M)
Inappropriate	Rarely appropriate (R)

Hendel RC, et al. *Circulation*. 2009;119:e561-e587. Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## AUC Methodology

- Step 1:** Writing panel of experts develops a group of typical clinical scenarios after review of the literature and guidelines
- Step 2:** Rating by panel (13–15 imaging, clinical and health policy experts) — Delphi method (RAND Corp)
  - Independent scoring
  - Face-to-face meeting and attempt at consensus
  - Final independent scoring
  - 1–3 (R), 4–6 (M), 7–9 (A)
- Step 3:** Review panel

**AUC = appropriate use criteria.**  
 Farell MB. *J Nuc Med Technol*. 2012;40:81. Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## Case 1

- TJ is a 56-year-old male with PCI to the mid-LAD 3 years ago for exertional angina. He is currently on optimal medical therapy for his hypertension and dyslipidemia. He is doing well with an active lifestyle and no symptoms.
- He wants to know if he needs a stress test.

## “No Testing” Is an Option!

**ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease**

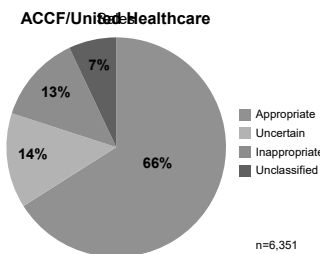
“In fact, although not a rating choice, “no testing at all” may also be considered an option in such low-risk cases since the low pre-test probability alone limits the value of a positive test in determining likelihood of disease and often could then potentially lead to further testing. This is in keeping with the concept that because a test was rated Appropriate or May Be Appropriate, this does not indicate that a test must be performed.”

Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## Distribution of Appropriateness for SPECT

### Inappropriate Tests

- 48%: Low-risk, asymptomatic
- 27%: Pre-op: good functional capacity or low risk symptoms



Hendel RC, et al. *J Am Coll Cardiol*. 2010;55(2):156-62.

## Pre-op Evaluation

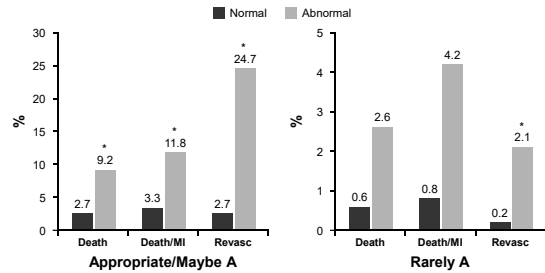
CAD, CHF, CVA, DM, creatinine >2 mg/dL

Indication Text	Exercise ECG	Stress RNI	Stress Echo	Stress CMR	Calcium Scoring	CCTA	Invasive Coronary Angiography
Moderate-to-Good Functional Capacity (≥4 METs) OR No Clinical Risk Factors							
→ 71 • Any surgery	R	R	R	R	R	R	R
Asymptomatic AND <1 Year Post Any of the Following: Normal CT or Invasive Angiogram, Normal Stress Test for CAD, or Revascularization							
→ 72 • Any surgery	R	R	R	R	R	R	R
Poor or Unknown Functional Capacity (<4 METs)							
→ 73 • Low-risk surgery • ≥1 clinical risk factor	R	R	R	R	R	R	R
74 • Intermediate-risk surgery • ≥1 clinical risk factor	M	M	M	M	R	R	R
75 • Vascular surgery • ≥1 clinical risk factor	M	A	A	M	R	R	R
→ 76 • Kidney transplant	M	A	A	M	R	R	M
→ 77 • Liver transplant	M	A	A	M	R	R	M

Refer to pages 12 and 13 for relevant definitions.  
 Wolk MJ, et al. *J Am Coll Cardiol*. 2014;63(4):380-406.

## Performance of MPI based on Appropriateness of Indication

N: 1511, consecutive, community-based MPI  
Follow-up: 27 ± 10 m



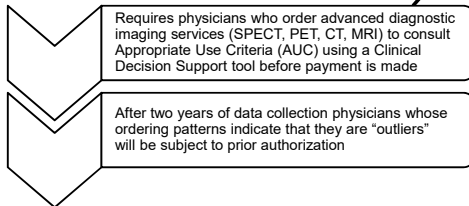
\*Significant difference.  
Doukky R, et al. *Circulation*. 2013;128(15):1634-43.

## Case 2

- RT is 76-year-old male who presents with exertional chest pain of 3-month duration.
- He has long-standing hypertension, which is now well-controlled on a diuretic and amlodipine. He has type-2 DM. Three years ago he had a pacemaker for sick sinus syndrome.
- A recent echocardiogram showed normal LV function but was technically difficult (poor image quality). His ECG shows sinus rhythm and LVH with 1.5 mm ST-segment depression and T-wave inversion.
- You decide to refer him for a stress test.

## Protecting Access to Medicare Act (PAMA) 2014

- “SGR Patch” for 2014
- Included the CMS “AUC Mandate”



SGR = Sustainable Growth Rate formula; CMS = Centers for Medicare and Medicaid Services.  
<https://www.cms.gov/Medicare/Fee-for-Service-Payment/ClinicalLabFeeSched/PAMA-Regulations.html>.  
Accessed September 23, 2016.

## Summary for Optimal Stress Testing

### Optimal patient selection

- Appropriate indication

### Optimal choice of test

- Availability, expertise and contraindications
- In general, performance characteristics are comparable across testing modalities

**“Right test, right patient, right time”**