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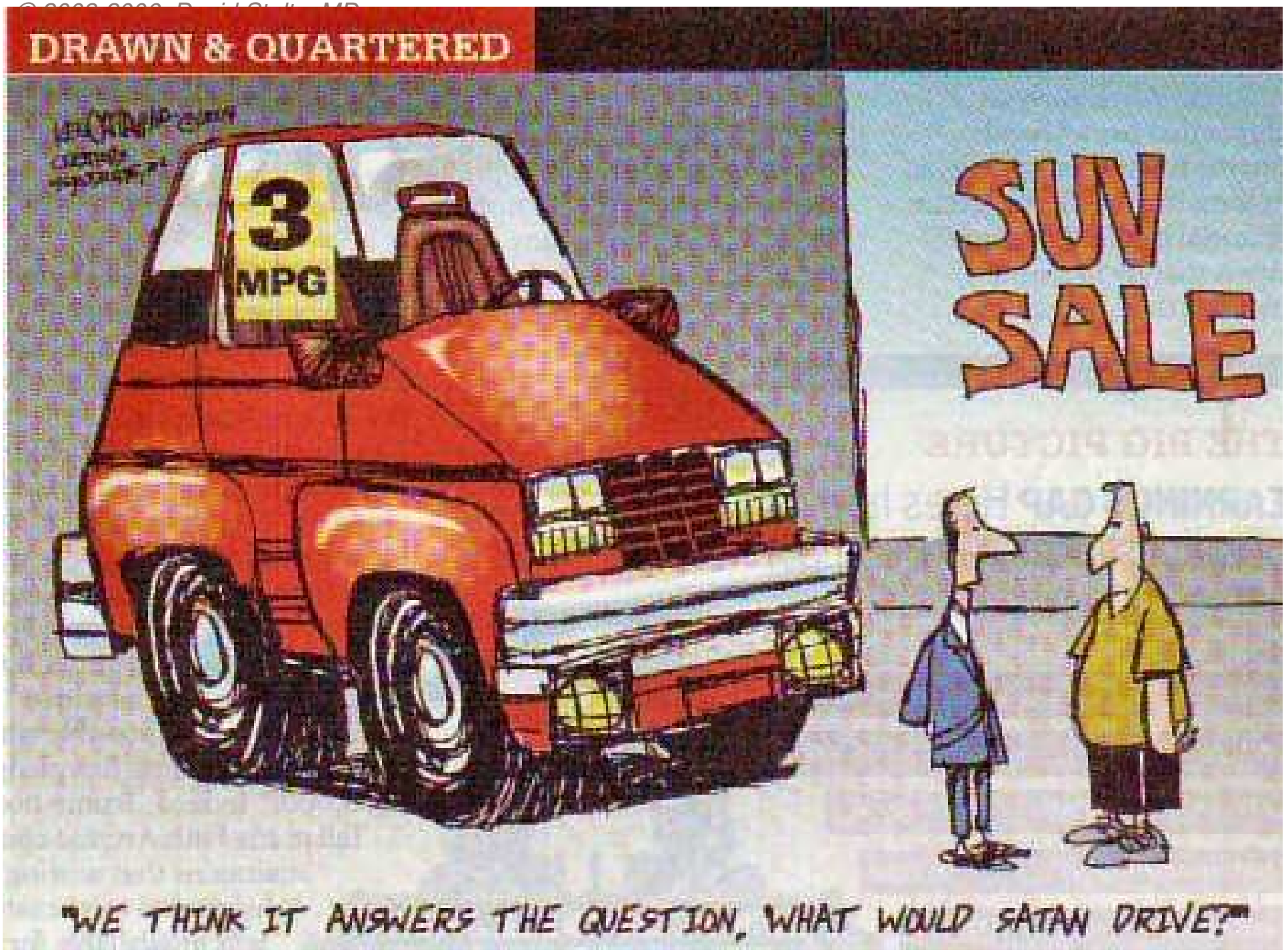

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Cardiac Stress Testing

and Statistics

David Stultz, MD

Cardiology Fellow, PGY 5

July 12, 2004

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Objectives of Conference

- Who needs a stress test?
- What types of tests are available?
  - Brief Overview, focus on Exercise Stress Test
- How is the information used clinically?
- How to apply basic biostatistics to clinical decision making

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Scope of Disease

- Coronary heart disease is the leading cause of death in the US
- More than 700,000 deaths in year 2000

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Cardiac Risk Factors
H&P is useful

- Angina
  - Unstable if onset is new or if pattern has changed in past month
  - Typical Angina
    1. Substernal Chest Pain that is
    2. Provoked by exertion or emotional stress and
    3. Relieved by rest and/or nitroglycerin
- Traditional cardiac risk factors
  - Age, Smoking, DM, Family history, dyslipidemia
- Nontraditional risk factors
  - Obesity, metabolic syndrome, CRP, lipid fractions, sedentary lifestyle, etc
- Physical exam
  - Carotid bruit, peripheral bruit

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Noninvasive options

- Exercise EKG
- Nuclear Imaging
- Stress echocardiography
- Electron Beam CT
- PET
- MRI

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Costs of Testing

	2000 Medicare Total Relative Value Units	1998 Medicare # performed
Treadmill Exercise Test	3.12	533,000
Stress Echocardiography	6.16 (+ doppler charge)	353,942
Stress SPECT myocardial perfusion imaging	17.79 (+ isotope charge)	1,362,210
LHC with left Ventriculography and coronary angiography	65.58	901,625

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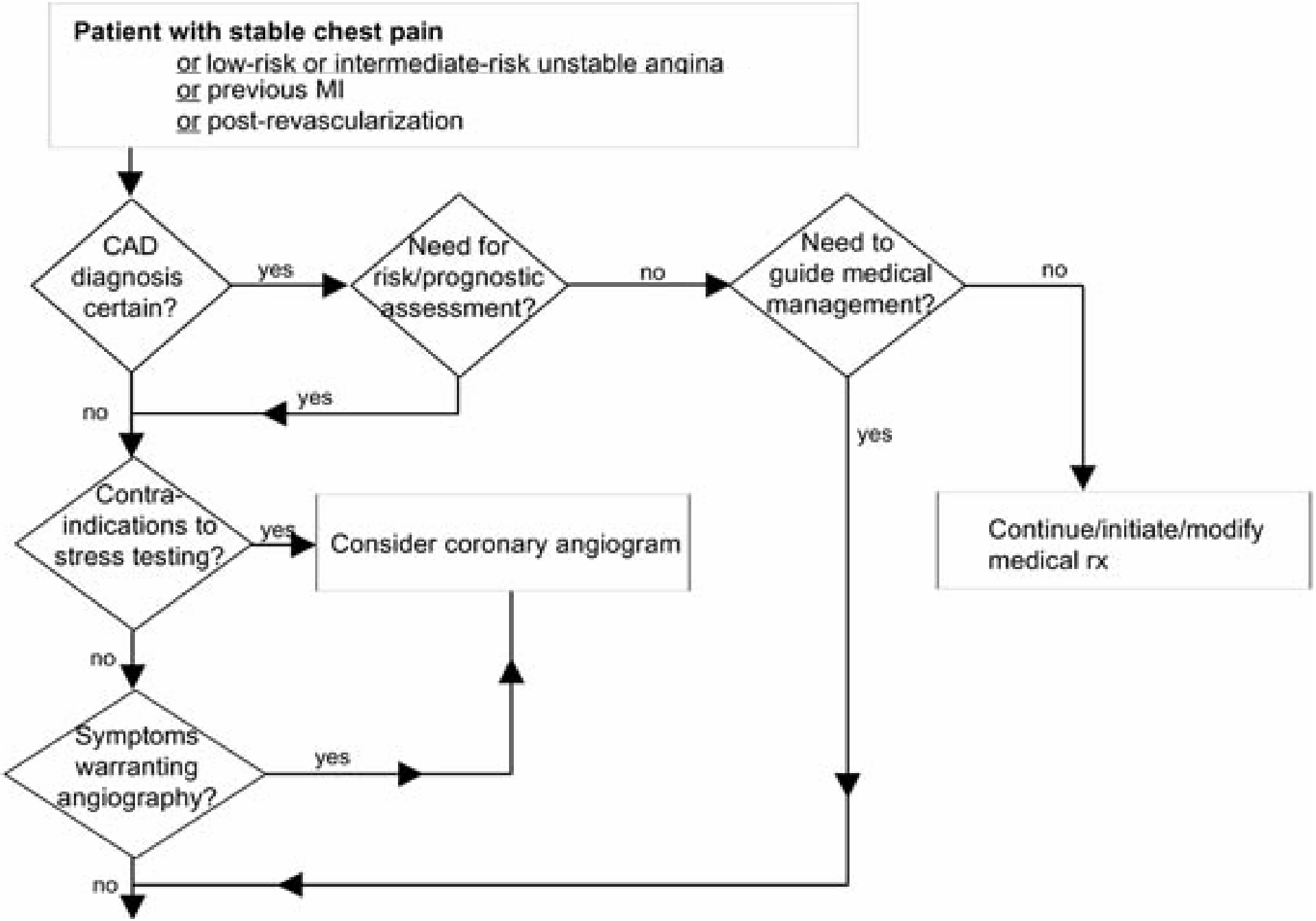
Who Needs a Stress Test?

- What can cardiac catheterization and revascularization achieve?
  - Main benefit is symptomatic relief*
- USPSTF recommends AGAINST routine screening in asymptomatic, low risk patients
- Stress testing should be employed in symptomatic patients
  - May be used for patients in certain occupations such as pilots, heavy equipment operators, etc. based on clinical risk factors

*ACS, 3VD, Left Main disease derive mortality benefit


Patient with stable chest pain
or low-risk or intermediate-risk unstable angina
or previous MI
or post-revascularization
CAD diagnosis certain?
yes
Need for risk/prognostic assessment?
no
Need to guide medical management?
no
yes
no
yes
Contra-indications to stress testing?
yes
Consider coronary angiogram
Continue/initiate/modify medical rx
no
Symptoms warranting angiography?
yes
no

ACC 2002

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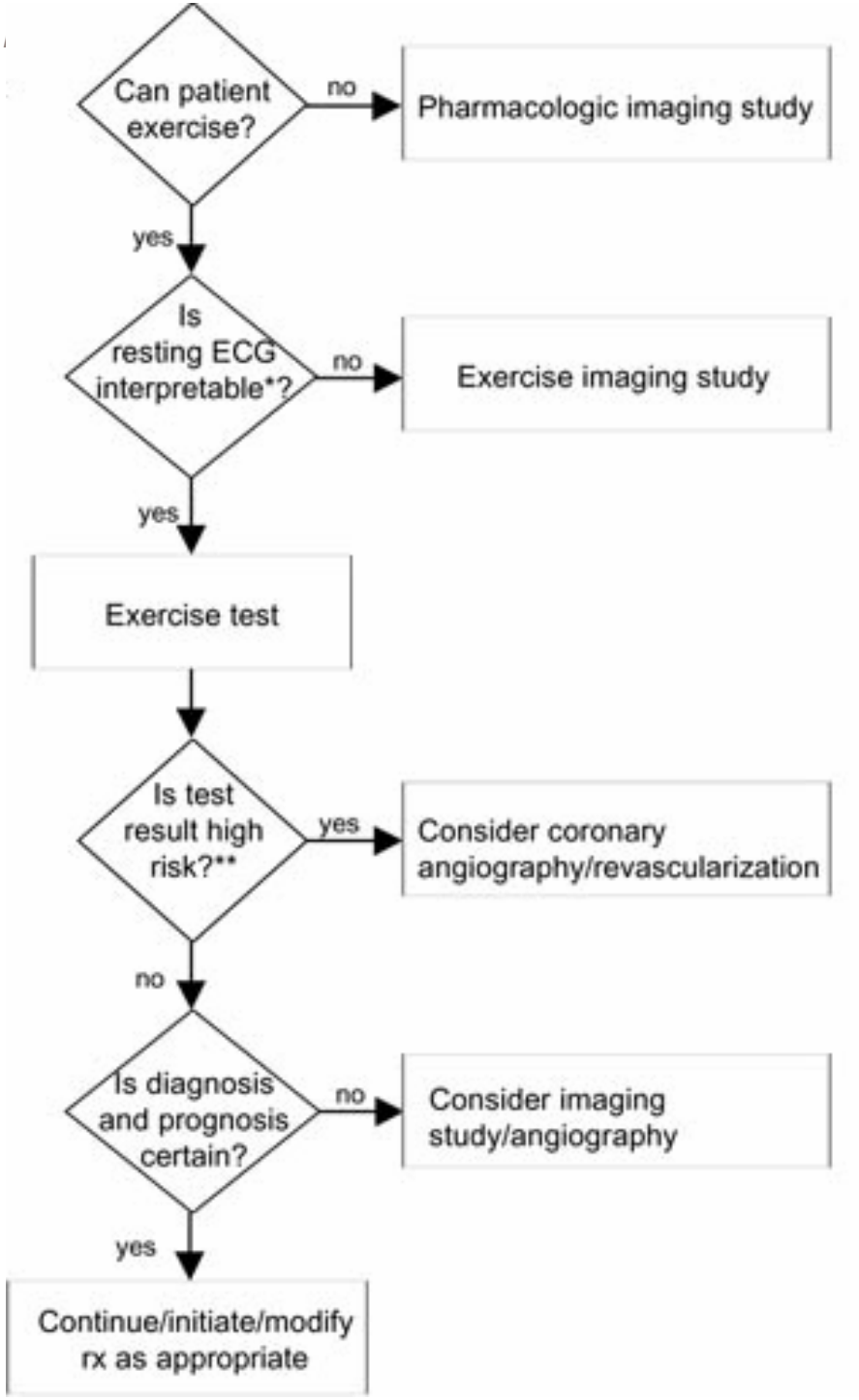

ACC 2002

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ACC Indication Classification

- **Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
- **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
  - **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.
  - **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

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Indications for Exercise Stress Testing (Diagnosis of CAD)

- **Class I**
  - Adult patients (including those with complete right bundle-branch block or less than 1 mm of resting ST depression) with an intermediate pretest probability of CAD on the basis of gender, age, and symptoms (specific exceptions are noted under Classes II and III below).
- **Class IIa**
  - Patients with vasospastic angina.
- **Class IIb**
  - High pretest probability of CAD by age, symptoms, and gender.
  - Low pretest probability of CAD by age, symptoms, and gender.
  - Patients with less than 1 mm of baseline ST depression and taking digoxin.
  - Patients with electrocardiographic criteria for left ventricular hypertrophy (LVH) and less than 1 mm of baseline ST depression.

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Risk Assessment and Prognosis in Patients with history or symptoms of CAD

Class I

1. Patients undergoing initial evaluation with suspected or known CAD, including those with complete right bundle-branch block or less than 1 mm of resting ST depression.
2. Patients with suspected or known CAD presenting with significant change in clinical status.
3. Low-risk unstable angina patients 8 to 12 hours after presentation without active ischemic or heart failure symptoms.
4. Intermediate-risk unstable angina patients 2 to 3 days after presentation without active ischemic or heart failure symptoms.

Class IIa

Intermediate-risk unstable angina patients with normal cardiac markers at 6-12 hours and repeat ECG without significant changes.

Class IIb

1. Patients with the following resting ECG abnormalities:
- Pre-excitation (Wolff-Parkinson-White) syndrome
- Electronically paced ventricular rhythm
- 1 mm or more of resting ST depression
- Complete left bundle-branch block or QRS duration greater than 120 ms.

2. Patients with a stable clinical course who undergo periodic monitoring to guide treatment.

Adapted from ACC 2002

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Indications for Asymptomatic Patients

Class I - None

Class IIa

1. **Evaluation of asymptomatic persons with diabetes mellitus who plan to start vigorous exercise.**

Class IIb

1. **Evaluation of pt with multiple risk factors as a guide to risk-reduction therapy.**
2. **Evaluation of asymptomatic men older than 45 and women older than 55:**
   - **Who plan to start vigorous exercise (especially if sedentary) or**
   - **Who are involved in occupations in which impairment might impact public safety or**
   - **Who are at high risk for CAD due to other diseases (e.g., peripheral vascular disease and chronic renal failure)**

Adapted from ACC 2002

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Non-indications for Exercise Stress Testing (Class III)

- Patients with the following baseline ECG abnormalities:
  - Pre-excitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - Greater than 1 mm of resting ST depression
  - Complete left bundle-branch block
- Patients with known CAD or prior MI; however, ischemia and risk can be determined by testing
- Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization.
- High-risk unstable angina patients
- Routine screening of asymptomatic men or women.

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TABLE 10G–4 ACC/AHA Guidelines for Exercise Testing to Diagnose Obstructive Coronary Artery Disease

	Indication
Class I (indicated)	Adult patients (including those with complete right bundle branch block or less than 1 mm of resting ST depression) with an intermediate pretest probability of CAD on the basis of gender, age, and symptoms (specific exceptions are noted under Classes II and III below).
Class IIa (good supportive evidence)	Patients with vasospastic angina.
Class IIb (weak supportive evidence)	1. Patients with a high pretest probability of CAD by age, symptoms, and gender. 2. Patients with a low pretest probability of CAD by age, symptoms, and gender. 3. Patients with less than 1 mm of baseline ST depression and taking digoxin. 4. Patients with electrocardiographic criteria for left ventricular hypertrophy and less than 1 mm of baseline ST depression.
Class III (not indicated)	1. Patients with the following baseline ECG abnormalities: • Preexcitation (Wolff-Parkinson-White) syndrome • Electronically paced ventricular rhythm • Greater than 1 mm of resting ST depression • Complete left bundle branch block 2. Patients with a documented myocardial infarction or prior coronary angiography demonstrating significant disease who have an established diagnosis of CAD; however, ischemia and risk can be determined by testing.

CAD = coronary artery disease.

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TABLE 10G–11 ACC/AHA Guidelines for Exercise Testing Before and After Revascularization

	Indication
Class I (indicated)	1. Demonstration of ischemia before revascularization. 2. Evaluation of patients with recurrent symptoms that suggest ischemia after revascularization.
Class IIa (good supportive evidence)	After discharge for activity counseling and/or exercise training as part of cardiac rehabilitation in patients who have undergone coronary revascularization.
Class IIb (weak supportive evidence)	1. Detection of restenosis in selected, high-risk asymptomatic patients within the first 12 months after percutaneous coronary intervention. 2. Periodic monitoring of selected, high-risk asymptomatic patients for restenosis, graft occlusion, incomplete coronary revascularization, or disease progression.
Class III (not indicated)	1. Localization of ischemia for determining the site of intervention. 2. Routine, periodic monitoring of asymptomatic patients after percutaneous coronary intervention or coronary artery bypass grafting without specific indications.

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TABLE 13G–1 American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology Guidelines for the Clinical Use of Cardiac Radionuclide Imaging*

Indication	Class I (Indicated)	Class IIa (Good Supportive Evidence)	Class IIb (Weak Supportive Evidence)	Class III (Not Indicated)
Diagnosis of STE acute myocardial infarction		Right ventricular infarction Infarction not diagnosed by standard means–late presentation		Routine diagnosis with ischemia/necrosis already documented clinically
Risk assessment, prognosis, and assessment of therapy after STE acute myocardial infarction	Rest RV/LV function Presence/extent of stress-induced ischemia Detection of infarct size and residual viable myocardium			
Diagnosis, prognosis, and assessment of therapy in patients with unstable angina/NSTEMI	Identification of ischemia in the distribution of the culprit lesion or in remote areas Measurement of baseline LV function Identification of the severity/extent of disease in patients whose angina is satisfactorily stabilized with medical therapy	Identification of the severity/extent of disease in patients with ongoing ischemia but nondiagnostic ECG	Diagnosis of myocardial ischemia in patients when the combination of history and ECG changes is unreliable	
Suspected ACS in the emergency department with nondiagnostic ECG and initial biomarkers	Assessment of risk with rest MPI Stress MPI for diagnosis of CAD after negative biomarkers or normal rest MPI			
Diagnosis of chronic ischemic heart disease	Diagnosis of symptomatic and selected patients with asymptomatic myocardial ischemia Assessment of ventricular performance (rest or exercise) Planning PTCA–identifying lesions causing myocardial ischemia, if not otherwise known Risk stratification before noncardiac surgery in select patients			Screening of asymptomatic patients with low likelihood of disease

Assessment of severity/prognosis/ risk stratification of chronic ischemic heart disease	Assessment of LV performance Identification of extent and severity of ischemia and localization of ischemia† Risk stratification in patients with an intermediate risk Duke Treadmill Score Assessment of functional significance of intermediate coronary stenosis	MPI as the initial test in patients with diabetes or with >20% 10-yr CHD risk	Redefining risk 1–3 yr after initial MPI in patients with stable symptoms	
Assessment of interventions in chronic ischemic heart disease	Assessment for restenosis after PCI (symptomatic) Assessment of ischemia in symptomatic patients after CABG	Assessment 3–5 yr after CABG or PCI in select, high-risk asymptomatic patients	Assessment of drug therapy for myocardial perfusion	Routine assessment of asymptomatic patients after PTCA or CABG
Heart failure	Determination of initial LV and RV performance in heart failure Initial evaluation of LV function in patients receiving chemotherapy with doxorubicin Assessment of myocardial viability in patients with CAD and LV dysfunction without angina	Assessment of the co-presence of CAD in patients without angina	Routine serial assessment of LV and RV function Detection of myocarditis Diagnosis of CAD in hypertrophic cardiomyopathy	
After cardiac transplantation	Assessment of ventricular performance		Detection and assessment of coronary angiopathy	
Valvular heart disease	Initial and serial assessment of LV and RV function		Detection and assessment of function significance of concomitant coronary artery disease	

*Table represents a compilation of recommendations from the 1995 and 2003 guidelines.

†Exercise MPI in patients with baseline ECG abnormalities, vasodilator pharmacologic stress MPI in patients who cannot exercise adequately or who have LBBB or paced rhythm.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = coronary heart disease; ECG = electrocardiographic; LBBB = left bundle branch block; LV = left ventricular; MPI = myocardial perfusion imaging; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RV = right ventricular; STE = ST segment elevation.

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Summary of Indications

- Initial evaluation of suspected or known CAD
- Symptomatic patients with Intermediate likelihood of CAD
- Low-Medium risk Unstable Angina with negative EKG and cardiac enzymes
- Asymptomatic Diabetics starting vigorous exercise
- Asymptomatic Men >45, Women >55 in high risk occupation or starting vigorous exercise

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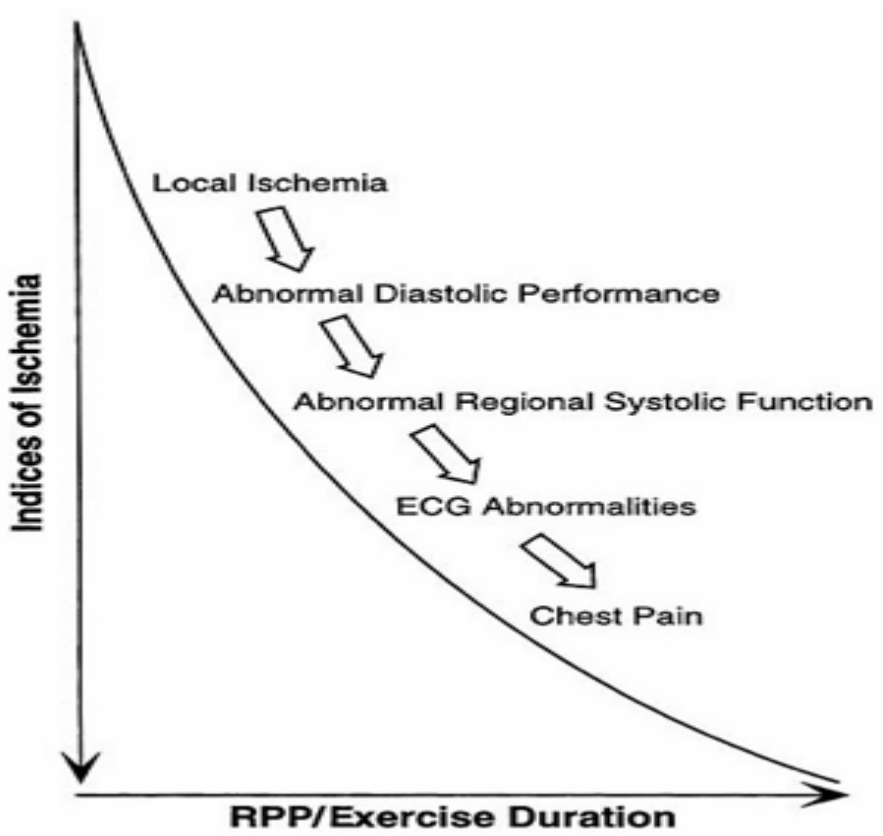
Ischemic Cascade



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Exercise EKG

The basic “stress test”

- Patient exercises on treadmill or bicycle
  - Bruce protocol common for treadmill
    - Start at 1.7 mph at 10% grade
    - Increase about 0.8 mph and 2% every 3 minutes
- EKG monitoring performed throughout
- Patient must achieve 85% of maximum predicted HR for valid results
  - Max HR = 220 - Age

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Positive EKG Stress

- PQ segment used as reference baseline
- Identify J point as junction of QRS complex and ST segment
- Measure ST changes 60-80 ms after J point
- ≥0.1mm of ST depression that is horizontal or downsloping
- 0.1mm ST depression with upsloping may be equivocal

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ACC 2002

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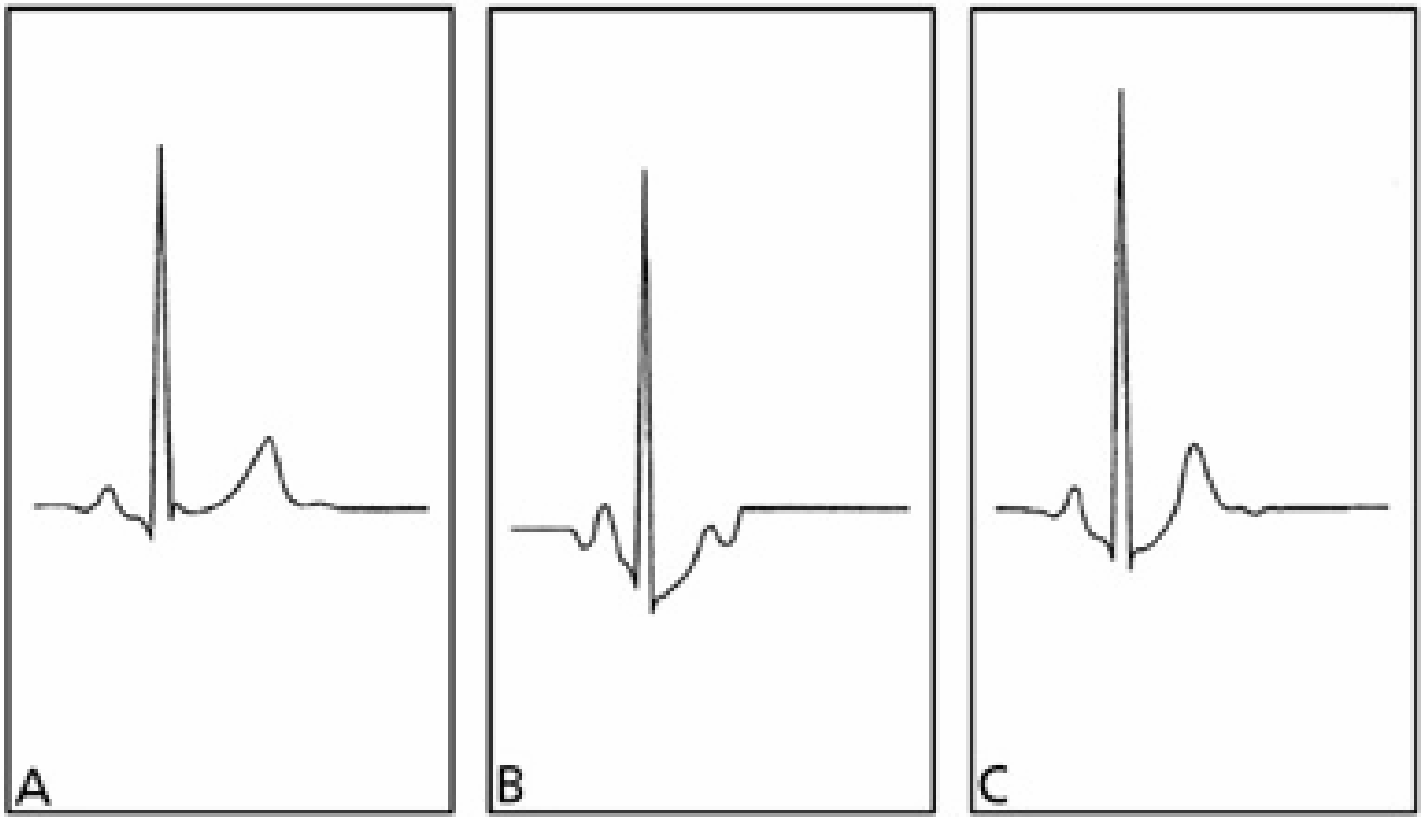
Healthy Subject EKG Progression



- A = Pre-test
- B = Maximal Stress with J point depression and ST upsloping
- C = Recovery

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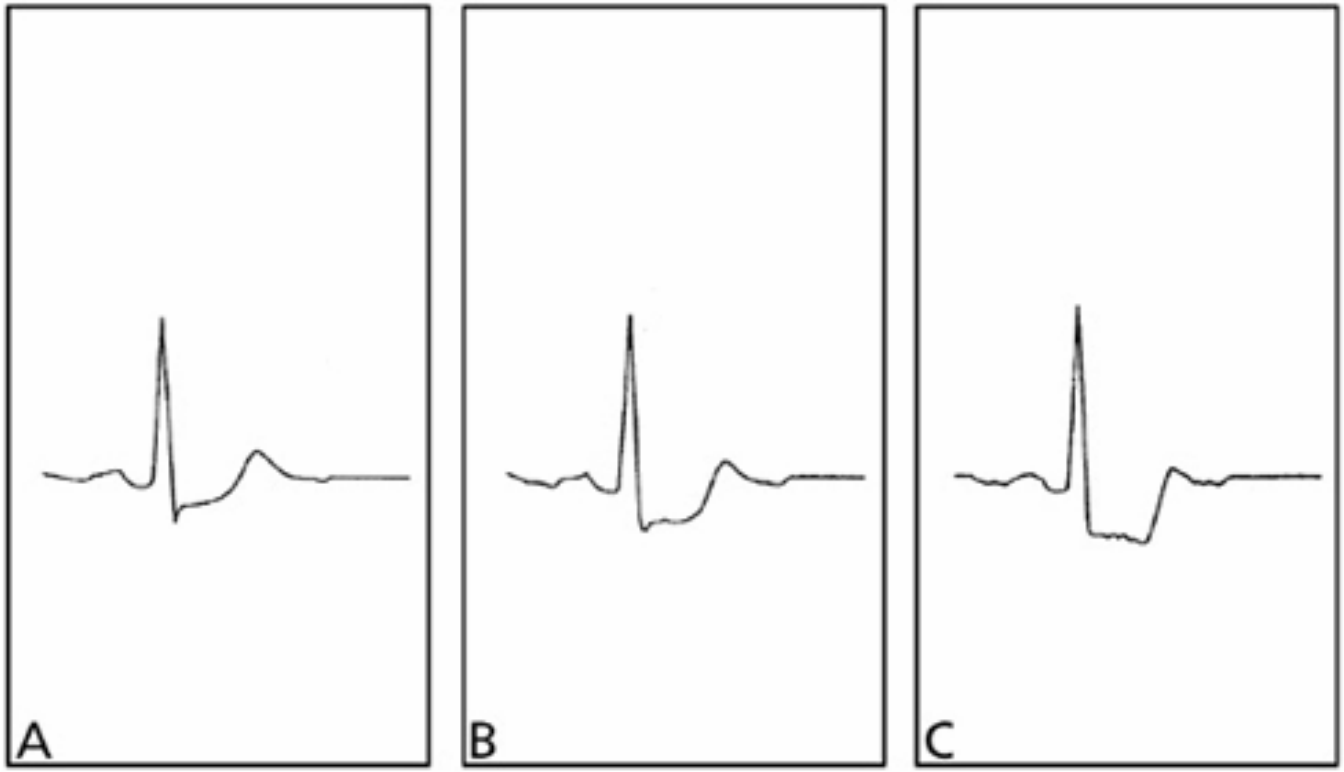
Comparison of ST segment response



- A = Slowly Upsloping ST segment depression
- B = Horizontal ST segment depression
- C = ST depression with downsloping

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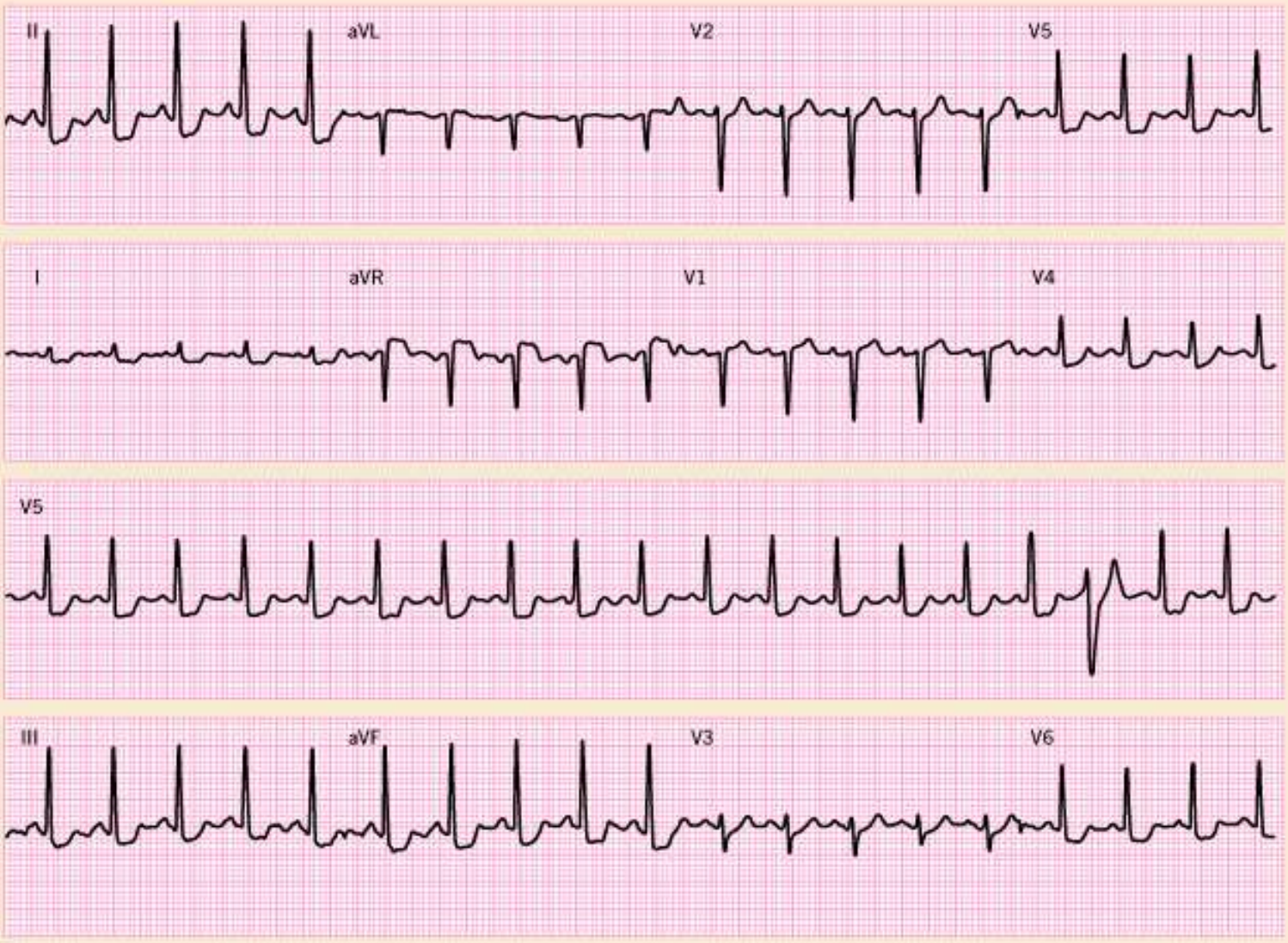
ABNORMAL EXERCISE ECG WITH MARKED HORIZONTAL ST-SEGMENT DEPRESSION



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DiMarco

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Duke Treadmill Score for Prognosis

- Exercise time (minutes) – 5 x (ST change in mm) – 4 x (angina index) [0=no angina, 1=nonlimiting angina, 2=angina stops test]
- <= -11 = high risk, >5% annual CV mortality
- >=5 = low risk, <0.5% annual CV mortality

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Absolute Contraindications for Exercise

- Acute myocardial infarction in past 2 days
- Unstable angina not addressed by medical therapy
- Uncontrolled, significant arrythmia
- Symptomatic severe aortic stenosis
- Uncontrolled CHF
- Acute PE
- Acute myocarditis or pericarditis
- Acute aortic dissection

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Relative Contraindications for Exercise

- Significant left main coronary disease
- Moderate valvular stenosis
- Electrolyte abnormalities
- Severe hypertension (SBP >200 or DBP >110)
- HOCM
- High degree AV block
- Pt inability or refusal to exercise

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Patients who should not have EKG only

- These lead to uninterpretable EKG or have high rate of false positives
  - Left Bundle Branch Block
  - Wolf-Parkinson-White (Ventricular pre-excitation)
  - Left Ventricular hypertrophy with strain
  - Ventricular pacing
  - Digoxin use

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Exercise EKG

- 1 in 2500 risk of death or MI[1]
- Sensitivity about 68%, Specificity about 77%[2] (using 50% stenosis by cath as gold standard)
- Functional capacity assessed by METS
- BP expected to rise with exercise
- Poor heart rate recovery (HR decrease <12bpm 2 minutes after peak exercise) has negative prognosis
- Location of ST depressions does not anatomically localize coronary lesions

1 DiMarco
2 Gianrossi

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Exercise testing in Females

- Increased incidence of false positives compared to males[1]
  - CASS data shows sensitivity similar for women (76%) and men (78%)
  - However, specificity for women (64%) lower than for men (73%)
- Functional information is important
  - Females achieving 7.5 METS have same 20 year mortality prognosis with or without ST depression[2]

1 Wiener
2 Mora

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Nuclear Stress Test

- Basic concepts
  - Images the heart at rest and stress
  - Compare images to determine if coronary perfusion is reduced with stress
  - Scar areas revealed by lack of perfusion at rest
  - Gating techniques allow calculation of ejection fraction

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Nuclear Stress Testing

- Choice of stress agents
  - Exercise
  - Pharmacological
    - Dobutamine
      - β-1 agonist which increases contractility, cardiac index, and oxygen consumption
    - Vasodilators
      - Adenosine
        - » Direct vasodilator
      - Dipyridamole (Persantine)
        - » Indirect vasodilator (enhances endogenous adenosine)

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Nuclear Stress Testing

- Choice of Imaging Agents
  - Thallium-201
    - K+ analogue
  - Technitium-99m
    - Sestamibi (Cardiolite)
    - Tetrofosmin (Myoview)
    - Improved image resolution due to higher energy
      - Obesity

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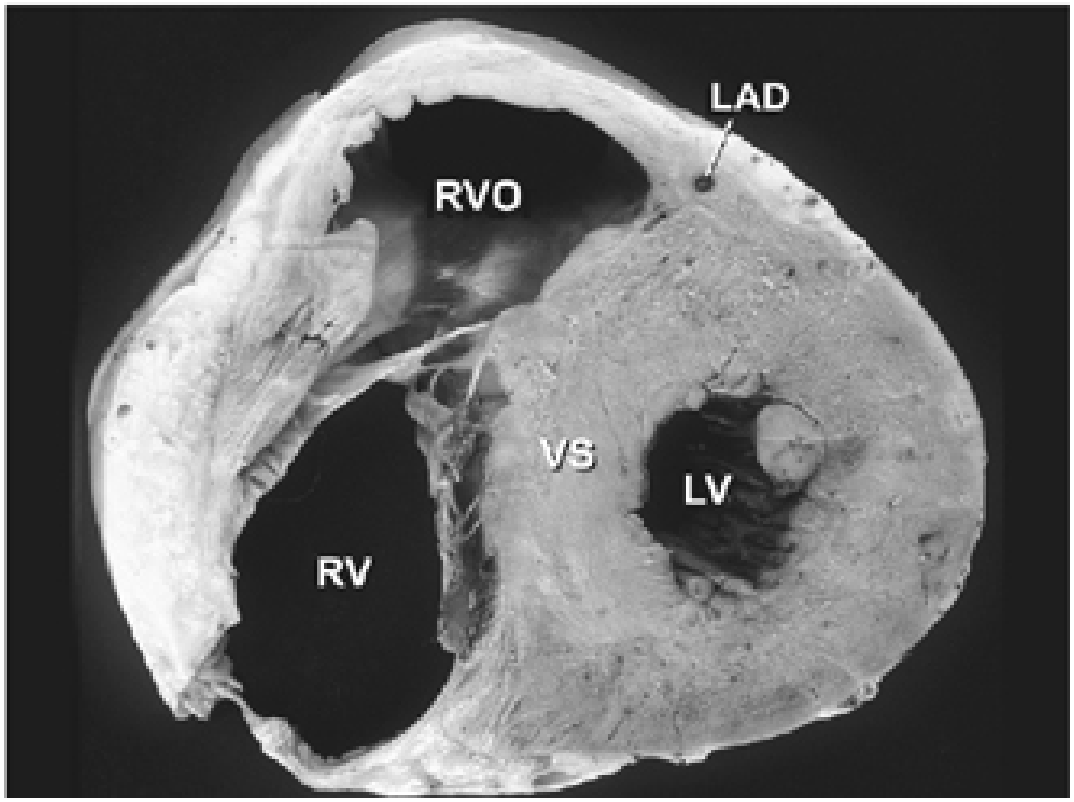
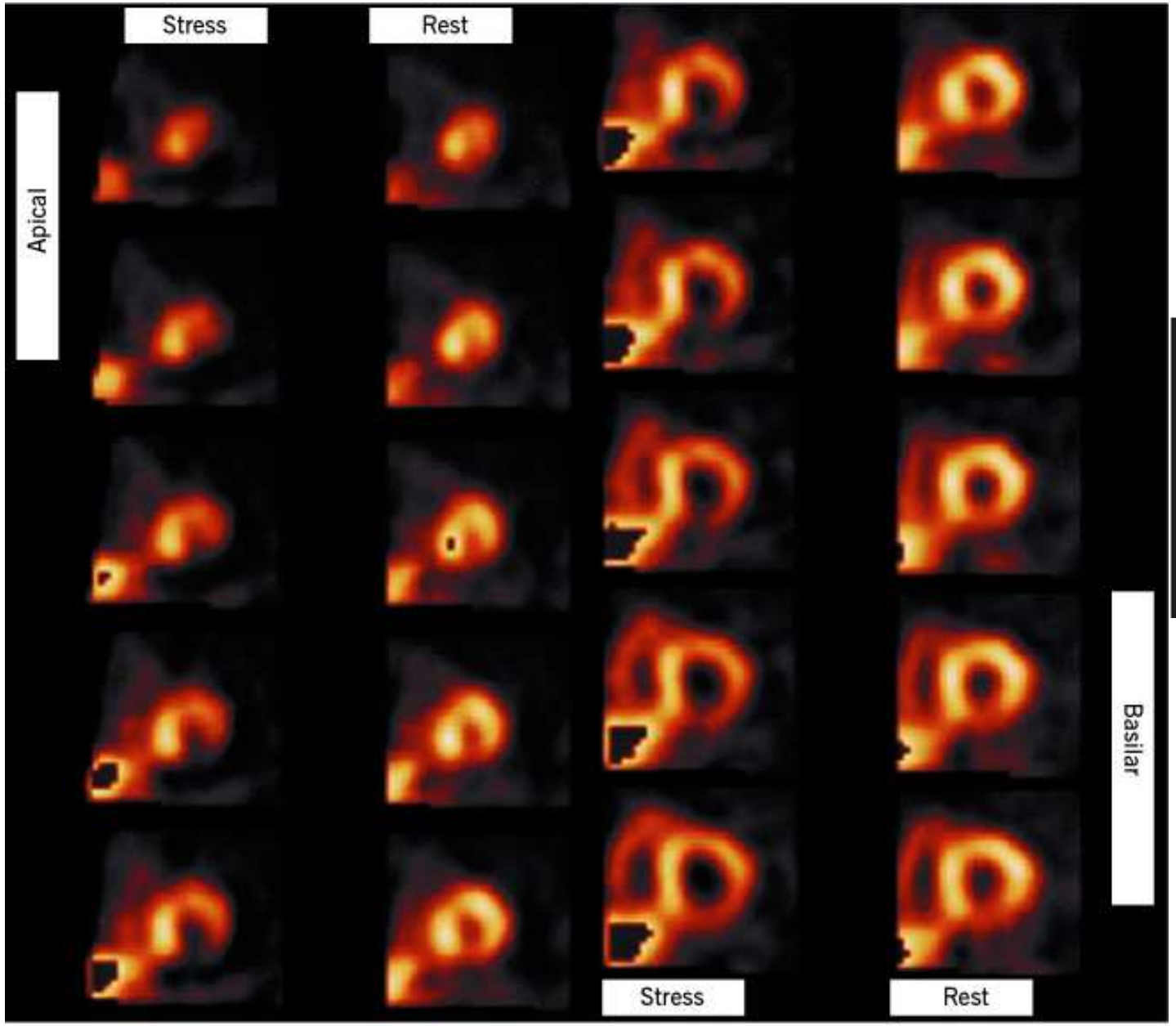
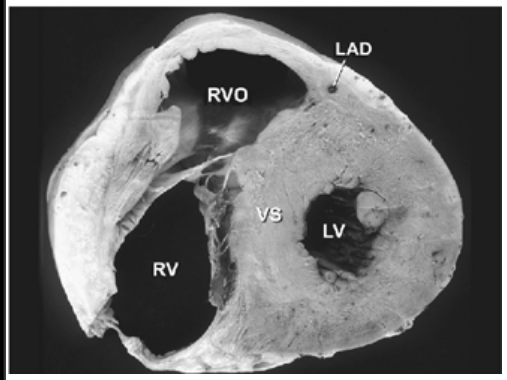
Short axis View of the Heart







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DiMarco
Hurst

Reversible ischemia of anterior, lateral, and inferior walls with LV dilitation

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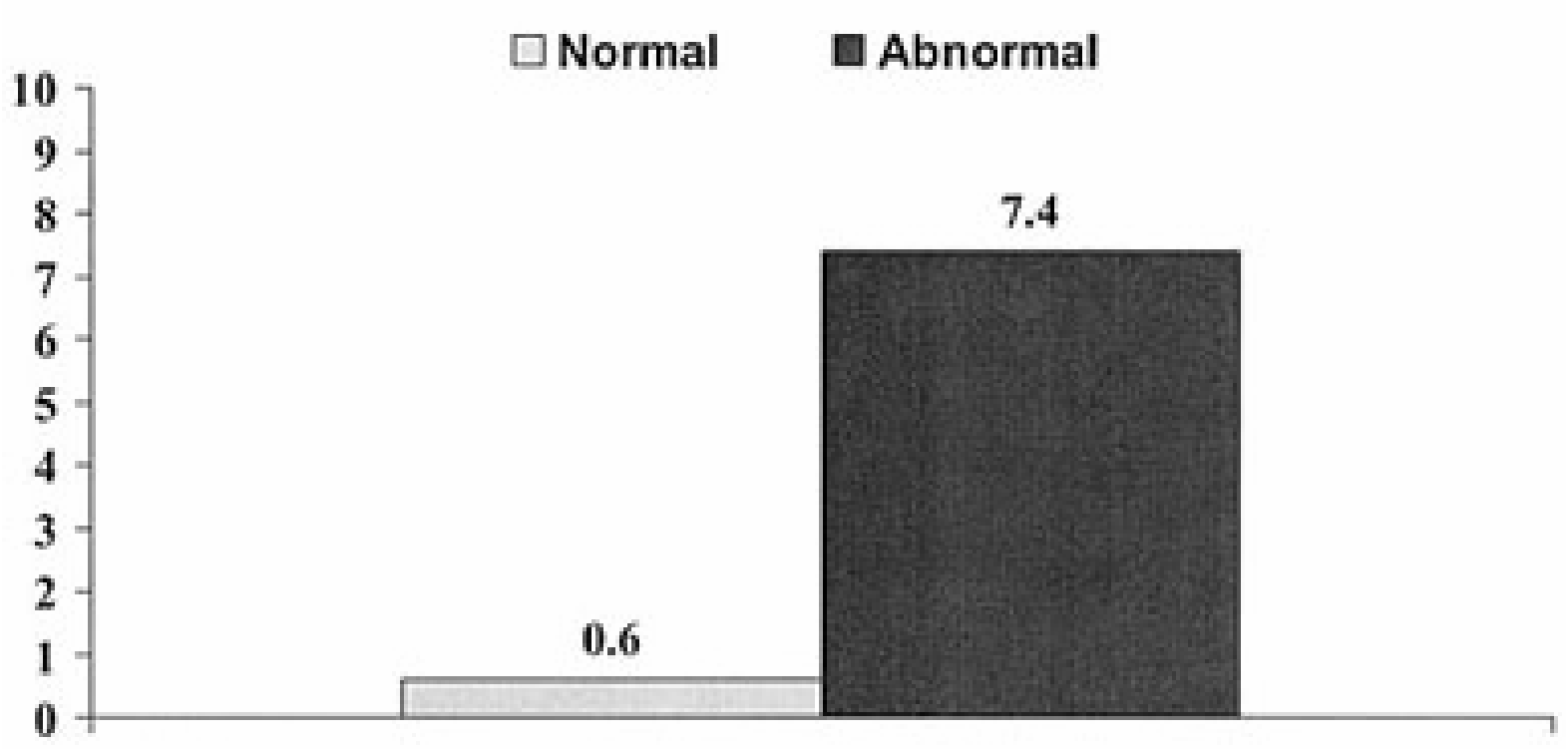
Prognosis



Annual Rate of Death or MI with Normal and Abnormal SPECT scans using Tc-99m

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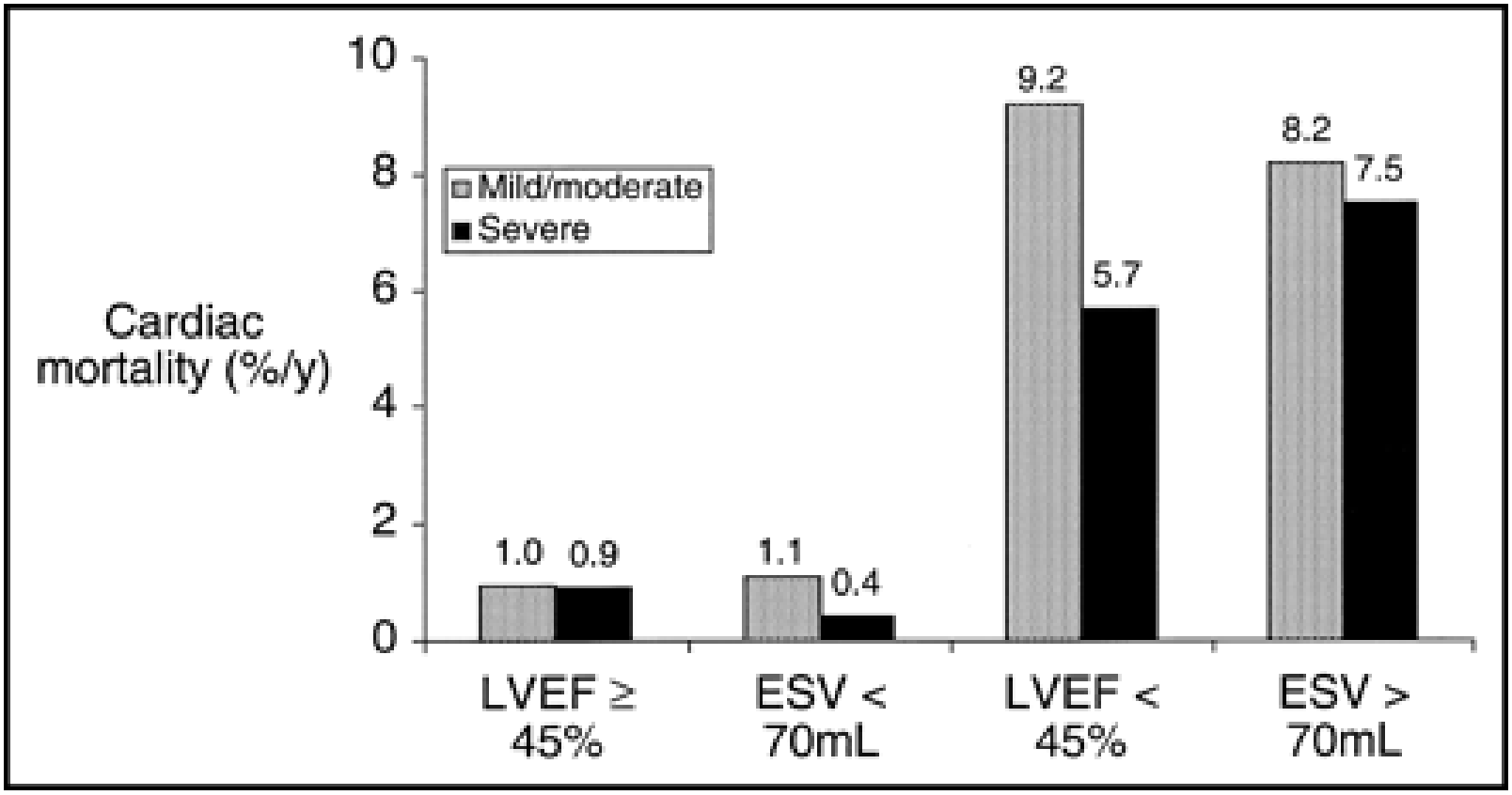
Gated SPECT Ejection Fraction as a Prognostic Marker



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Nuclear Stress Testing

- Overall sensitivity 88%, specificity 85%
- Adenosine and dipyrimadole are contraindicated in bronchospastic disease

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Stress Echocardiography

- Basic Principles
  - Imaging the heart at stress and rest
  - Evaluate for wall motion abnormalities at stress
  - Can identify akinetic scar areas
  - Dependent on adequate acoustic windows

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Stress Echocardiography

- Pick a method of stress
  - Exercise
  - Dobutamine
- 81% Sensitivity, 92% specificity for at least 50% stenosis by angiography

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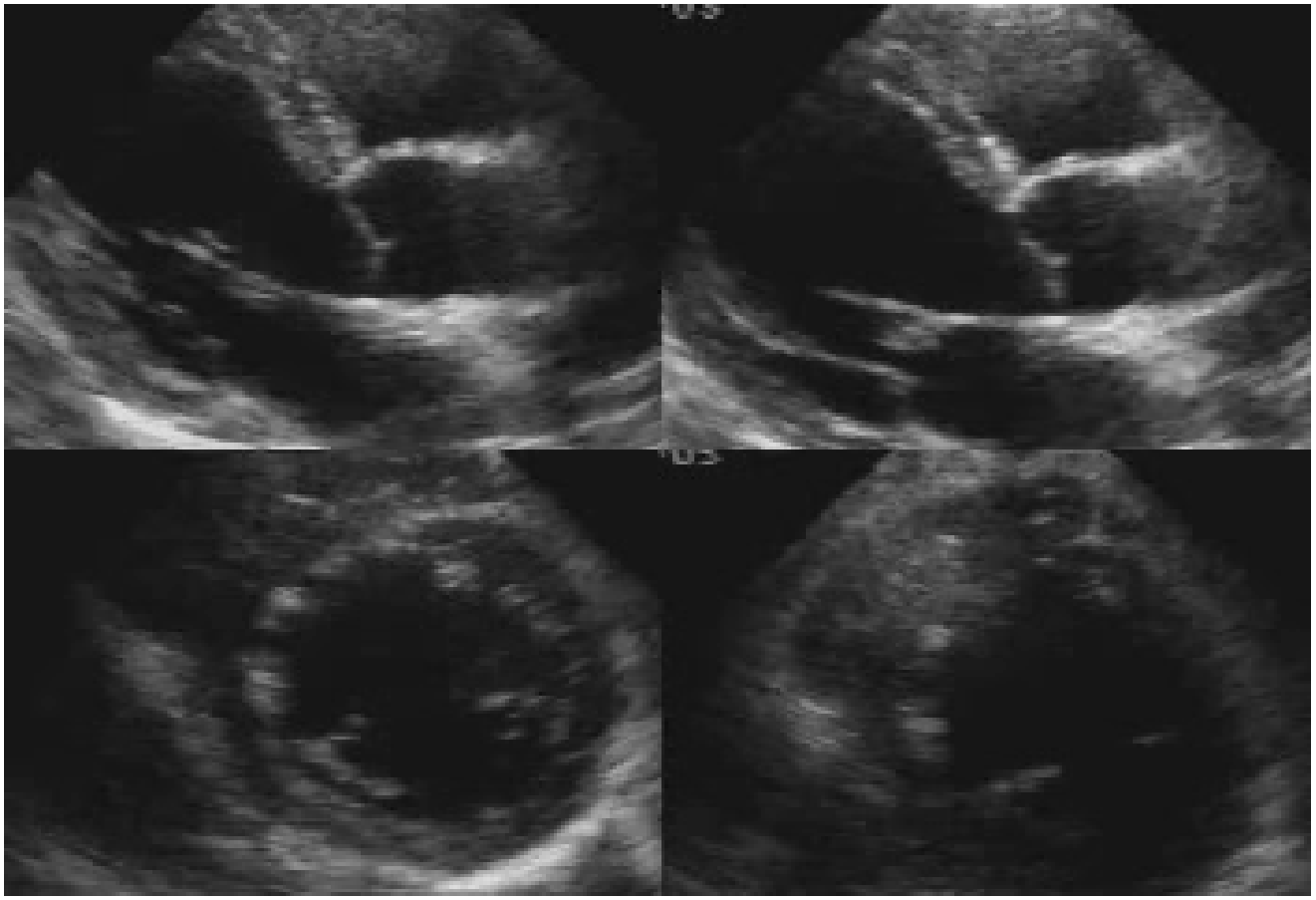

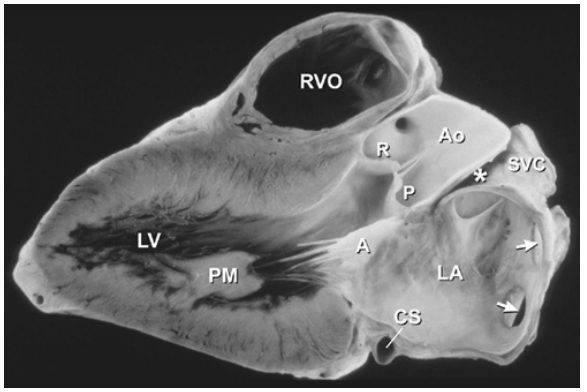

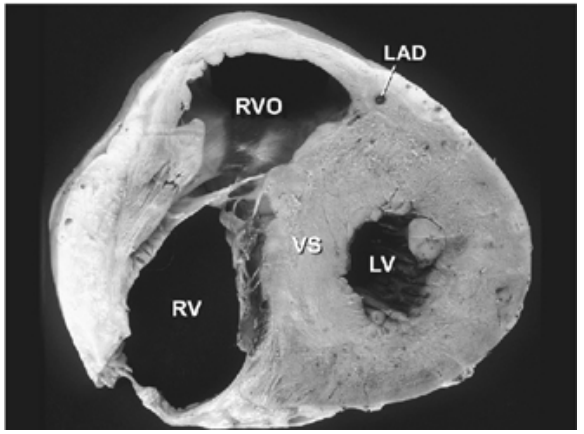

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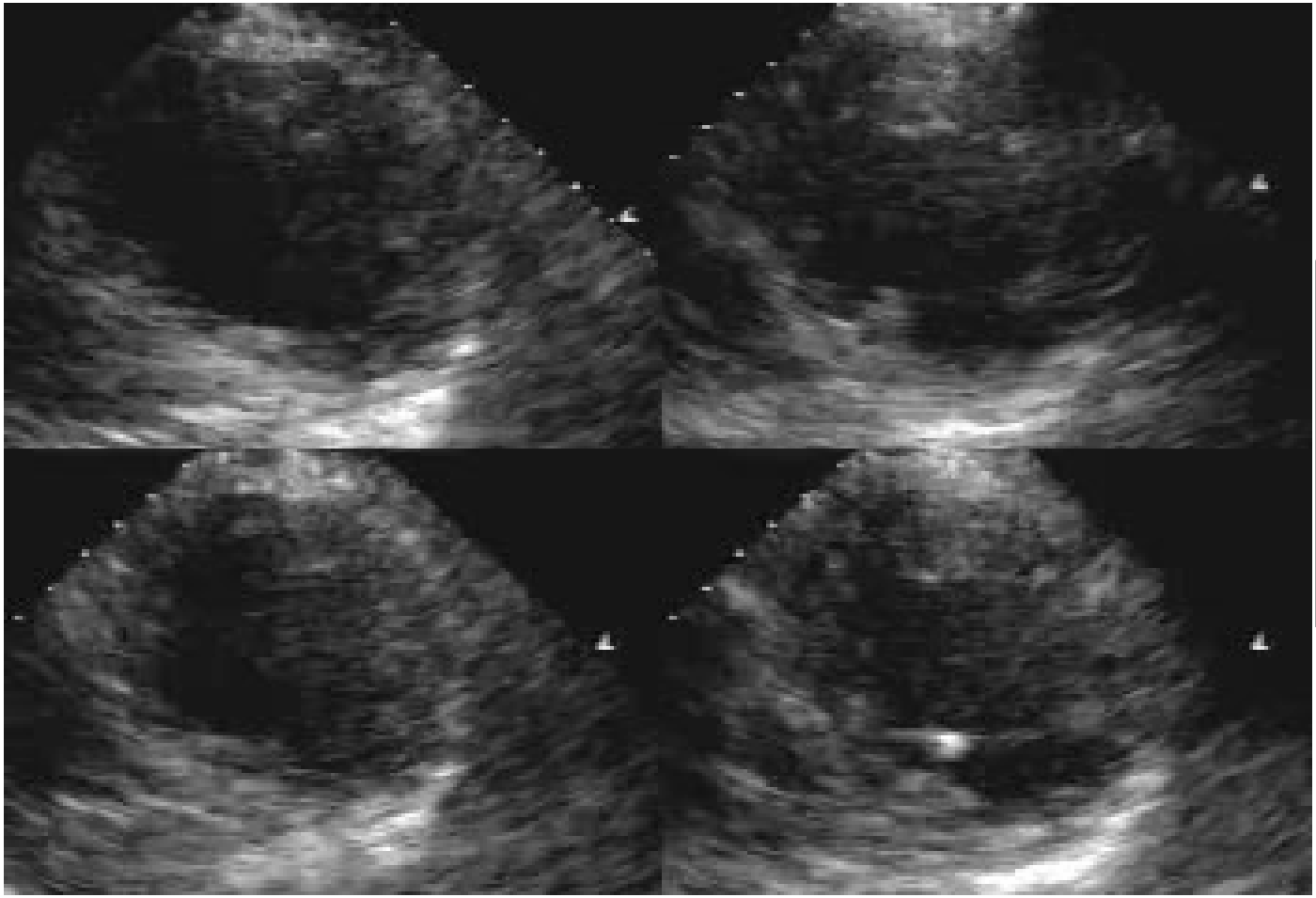

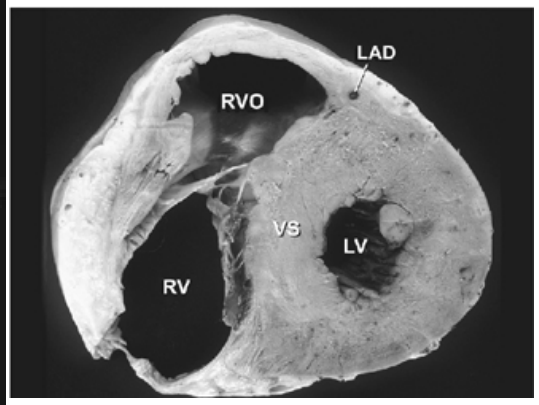

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Other Methods of Stress Imaging

- MRI
  - Dobutamine MRI similar to Dobutamine echo in premise
  - Better imaging, does not depend on acoustic windows
- PET
  - Similar to other nuclear imaging
  - Not widely available

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Electron Beam CT

- Not a stress test
- Noninvasive evaluation of coronary calcification
- ACC 2000 guidelines essentially do not recommend use of EBCT
- USPSTF recommends against using EBCT to screen asymptomatic patients
- Probably best employed in asymptomatic patients – but studies not conclusive on indications or long term prognosis

J Am Coll Cardiol 2000;36:326-40

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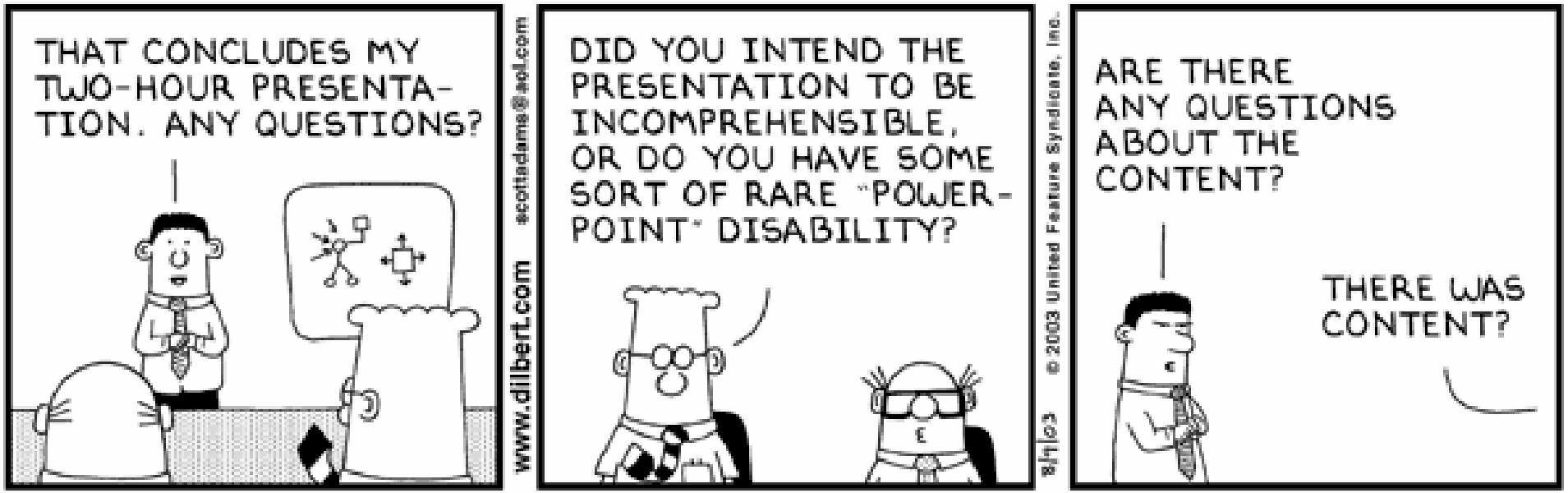
And now on to Stats…



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Biostatistics Lite

- Practical pointers for stats
- This will be included on In-Service and board exams
- A little knowledge goes a long way
- Practically useful for clinical decision making

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Sensitivity, Specificity

- Sensitivity: If a subject has a disease, the chance the test will be positive
- Specificity: If a subject does not have the disease, the chance a test will be negative
- These are independent of the disease prevalence!

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The 2x2 square for the ‘Dave’ test

	Test +	Test -
Disease +	75	25
Disease -	20	80

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	Test +	Test -
Disease +	75 (TP)	25 (FN)
Disease -	20 (FP)	80 (TN)

Sensitivity = TP/(TP + FN)
75/(75 + 25) = 75%

Specificity = TN/(TN + FP)
80/(80 + 20) = 80%

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The Meaning of a Test Result

- What does a positive result mean?
- What does a negative result indicate?
- What is the chance of a false positive/negative?
- The interpretation of a test result depends on the underlying prevalence of disease (pre-test probability)

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An example of the Dave test

- 75% sensitivity, 80% specificity
- There is a 20% prevalence of ‘Dave’ in a population.
  - Patient A tests positive, what is the chance they have the disease?
  - Patient B tests negative, what is the chance they are free of disease?

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Positive and Negative Predictive Value

- PPV = The chance that a positive test means the patient has the disease
- NPV = The chance that a negative test means the patient does not have the disease
- These both depend on the underlying prevalence of the disease (Pre-test likelihood)

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Back to the problem…

- 75% sensitivity, 80% specificity
- 20% prevalence

	Test +	Test -	
Disease +	150	50	200
Disease -	160	640	800
	(310)	(690)	1000

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PPV and NPV

	Test +	Test -	
Disease +	150	50	200
Disease -	160	640	800
	(310)	(690)	1000

PPV = TP/(Total Positives)
150/(150 + 160) = 48%
NPV = TN/(Total Negatives)
640/(50 + 640) = 93%

75% sensitivity
80% specificity
20% prevalence

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50% Prevalence

	Test +	Test -	
Disease +	375	125	500
Disease -	100	400	500
	(475)	(525)	1000

PPV = TP/(Total Positives)
375/(375 + 100) = 79%
NPV = TN/(Total Negatives)
400/(400 + 125) = 76%

75% sensitivity
80% specificity
50% prevalence

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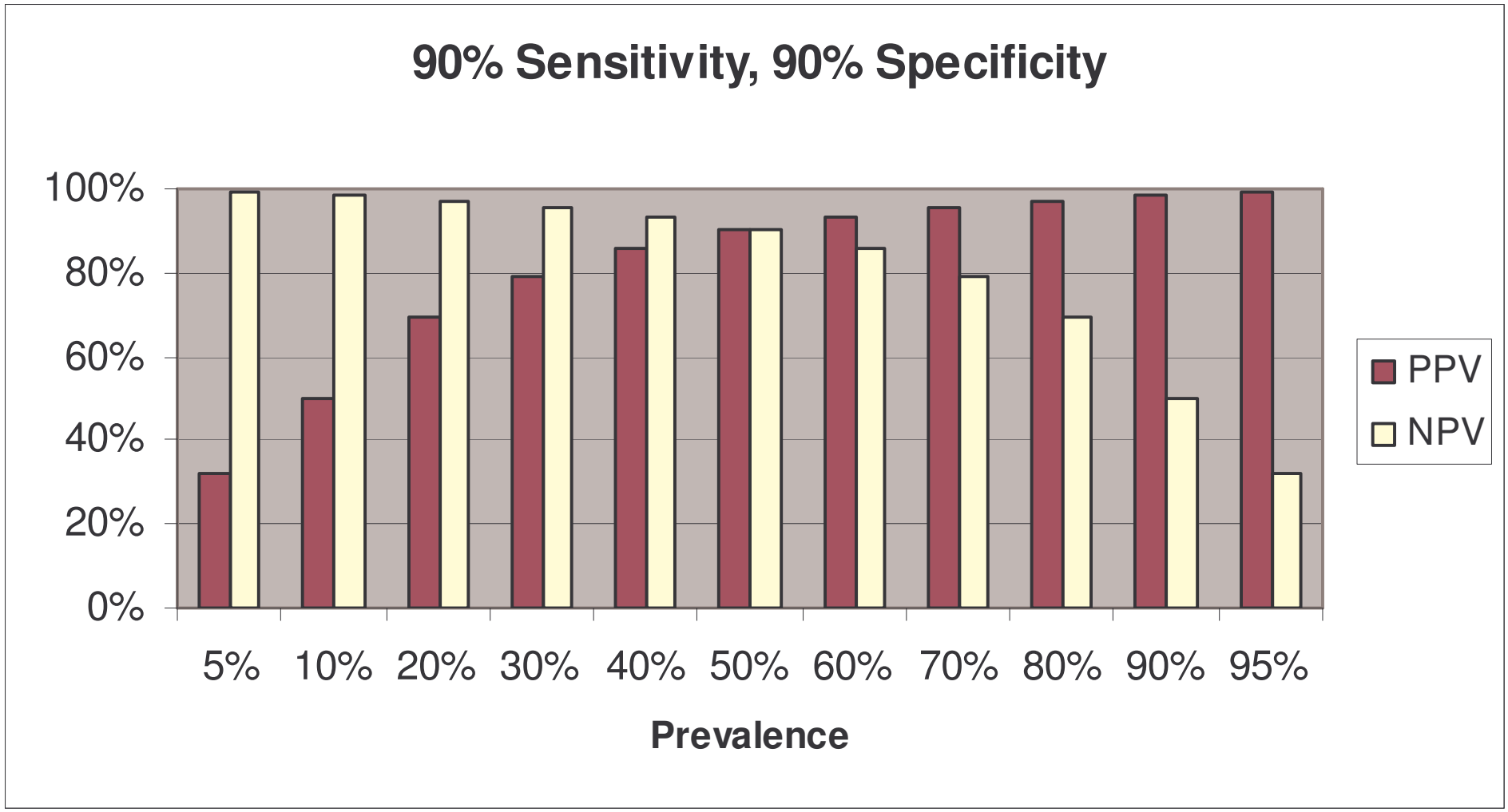
Relationship of PPV and NPV to Prevalence



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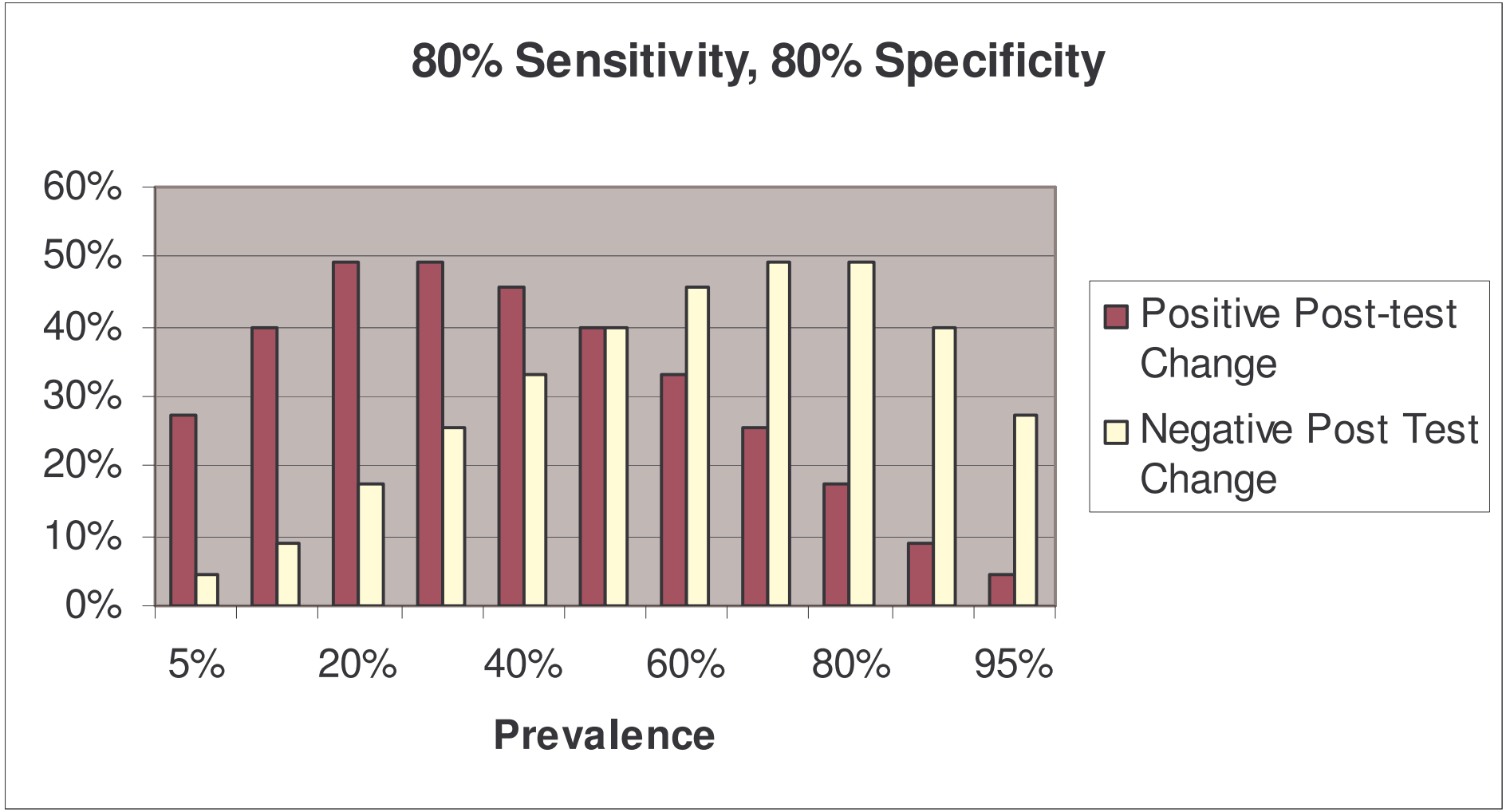
How Much Does the Test Outcome Change Your Prediction?



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Summary of Biostats

- Sensitivity and Specificity are independent of disease prevalence
- Interpretation of test results requires an estimation of disease prevalence/pre-test probability
- Positive and Negative predictive values are dependent on prevalence

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Remember those numbers

	Sensitivity	Specificity
Stress EKG	68%	77%
Stress Echo	81%	92%
Nuclear	88%	90%

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Back to Clinical Use….
Pre Test Probability

Table 4. Pretest Probability of Coronary Artery Disease by Age, Gender, and Symptoms*

Age (y)	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

*No data exist for patients <30 or >69 years, but it can be assumed that prevalence of CAD increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range. High indicates >90%; intermediate, 10%–90%; low, <10%; and very low, <5%.

ACC 2002

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Summary of Stress Testing

- Determine Pre-test likelihood for symptomatic patient based on history
- Stress testing is best used in patients with intermediate pre-test likelihood
- Consider Exercise EKG if patient can exercise and baseline EKG is normal
- If patient cannot exercise or baseline EKG abnormal, consider stress echo or nuclear based on local expertise
- Adenosine and dipyridimole are contraindicated in bronchospastic disease

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ACC 2002 Guideline for Exercise Testing

- Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines).
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Who needs a stress test?

- What benefit can be derived from a catheterization/revascularization
  - Patients with 3 vessel disease or significant Left Main disease obtain 5 year mortality benefit from CABG (10.7%) vs PCI (13.7%) [BARI]
  - Patients with angina obtain symptomatic benefit from revascularization
  - CABG maintains symptomatic benefit longer than PCI
  - Outside the setting of ACS and 3VD/Left Main disease, revascularization has not shown mortality benefit!

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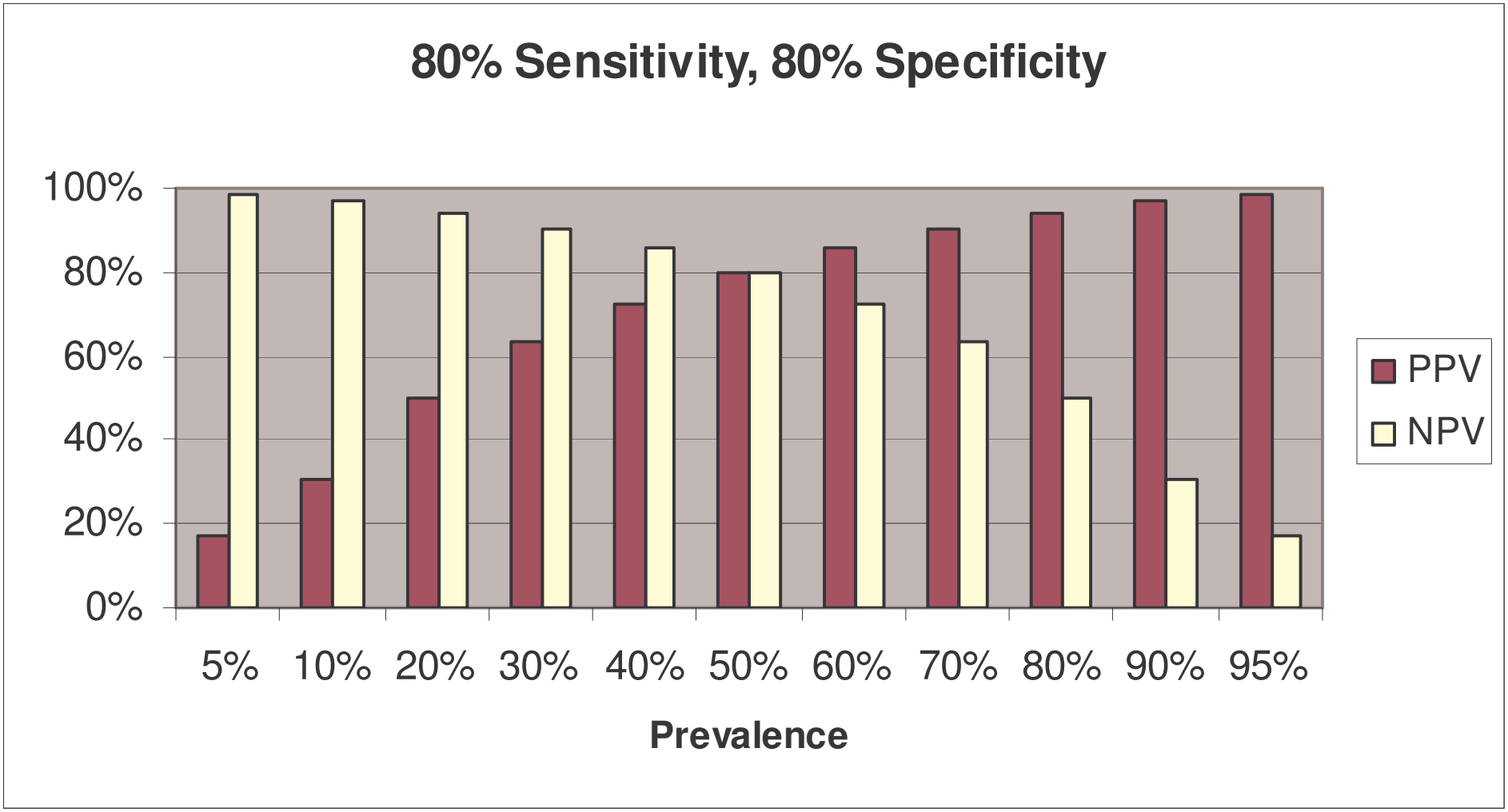

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