AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
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Rule Out Ischemia: A Case-Based Overview of Current Stress/Imaging Techniques and Implications for Chest Pain Patients in the Emergency Department

Many patients present to the emergency department with possible angina. Their response to stress testing would help the emergency physician with disposition. Which test should be ordered? Other patients present to the emergency department with chest pain and have a history of some type of negative stress/imaging study, but how good are these tests, and how long after a negative test do the results remain valid? Using a case-based presentation, the lecturer will answer these questions by reviewing the various types of stress/image tests, their indications, and their interpretation in emergency department patients.

- Identify the types of stress/imaging studies available for the evaluation of emergency department patients.
- Describe the indications for each test.
- Discuss the negative and positive predictive values, and diagnostic accuracy of these tests.
- Formulate a strategy for interpreting previous stress/imaging test results in an emergency department patient with chest pain.

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FACULTY

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RULE OUT ISCHEMIA: A CASE-BASED OVERVIEW OF CURRENT STRESS/IMAGING TECHNIQUES AND IMPLICATIONS FOR CHEST PAIN PATIENTS IN THE ED

OR

THE STORY IS ATYPICAL, THE ECG IS NONDIAGNOSTIC, AND CARDIAC ENZYMES/MARKERS ARE NEGATIVE. NOW WHAT DO I DO?

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COURSE OBJECTIVES

- Identify the types of stress/imaging studies available for the evaluation of emergency department patients.
- Describe the indications for each test.
- Discuss the negative and positive predictive values and diagnostic accuracy of these tests.
- Formulate a strategy for interpreting previous stress/imaging test results in emergency department patients with chest pain.

CASE REVIEW

Illustrative cases based on explicit criteria for testing developed using RAND/UCLA expert panel method (Delphi or "structured group judgement").[1] Is testing in a given case:

1. Necessary?
2. Appropriate but not necessary?
3. Uncertain appropriateness?
4. Inappropriate?

Which noninvasive test would you use, given the advantages and limitations of each?

The diagnostic utility of the various noninvasive tests to detect coronary artery disease has been well established. The study populations recruited for most studies have been composed almost exclusively of white males with stable angina pectoris and a high pretest likelihood of disease. Recently, past investigations have been criticized for "workup bias".[2] The diagnostic utility of a test is dependent upon the prevalence of the disease in the study population. In the case of coronary artery disease, prevalence is dependent primarily upon age and sex. The value of noninvasive testing in the typical ED population with chest pain that we encounter daily has not been well studied.

Some pretest probabilities of >75% stenosis of one or more coronary arteries in a primary care setting.

Patient Problem	Pretest Probability
Symptomless	
Female 30-39 yo	0.3%
60-69 yo	8%
Male 30-39 yo	2%
60-69 yo	12%
Non-anginal chest pain	
Female 30-39 yo	1%
60-69 yo	19%
Male 30-39 yo	5%
60-69 yo	28%
Atypical angina	
Female 30-39 yo	4%
60-69 yo	54%
Male 30-39 yo	22%
60-69 yo	67%
Typical angina pectoris	
Female 30-39 yo	26%
60-69 yo	91%
Male 30-39 yo	70%
60-69 yo	94%

Performance of a test with sensitivity of 60% and specificity of 90% in populations with a variable prevalence of coronary artery disease.

Prevalence	1%	10%	50%	90%
PPV	6%	40%	86%	98%
FP Rate	94%	60%	14%	2%
NPV	99%	95%	70%	20%
FN Rate	1%	5%	30%	80%

PPV = Positive predictive value; FP = false positive; NPV = negative predictive value; FN = false negative

The diagnostic values of the various noninvasive tests for coronary artery disease which are quoted by cardiologists apply to the population of patients that they care for. Those "numbers" do not necessarily apply to the emergency department population. During this lecture, I will attempt to define our population, namely, the patient with suspected unstable angina pectoris or a non-Q wave myocardial infarction, and review the application of common noninvasive tests for CAD in this population. What the cardiologist tells us is not what has been demonstrated in our population and the negative predictive value of a test is more important than its sensitivity and specificity.

To understand the importance of the population that we will discuss, an understanding of the pathophysiology of unstable angina and its diagnosis, based on currently used practice guidelines, is critical. As emergency physicians our most common dilemma is determining whether a patient has an acute coronary syndrome or not.

CORONARY ARTERY DISEASE IS A CLINICAL SPECTRUM

Three presentations:

- Angina pectoris
- Acute myocardial infarction
- Sudden cardiac death

Only about 10% of patients present with unstable angina as their initial manifestation of CAD.[3]

Patients with CAD tend to "cycle" through phases or stages of acuity:
Stable ↔ unstable ↔ acute infarction

ACUTE CORONARY SYNDROMES

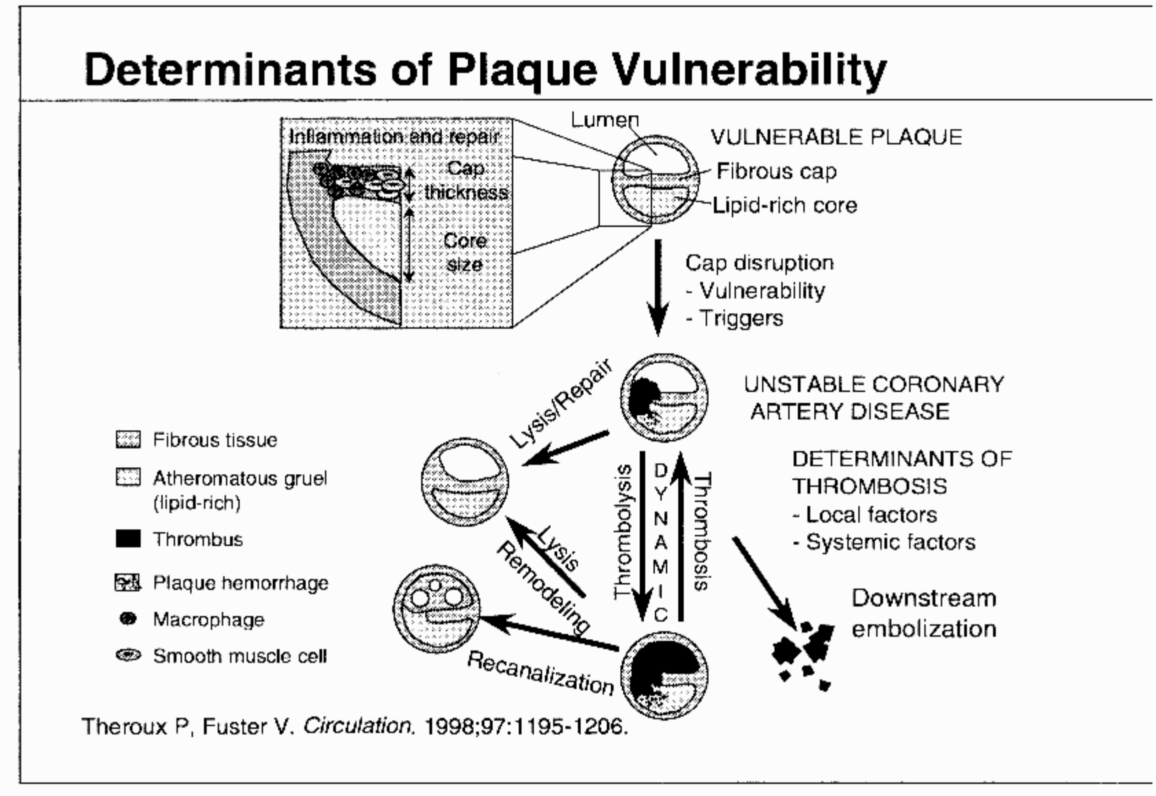
- Unstable angina
- Non-Q wave myocardial infarction
- Reperfusion-eligible myocardial infarction

UNSTABLE ANGINA PECTORIS (USA)

Part of the spectrum of symptomatic CAD which is defined by its:

1. pathophysiology
2. anatomy
3. clinical presentation

- Symptoms are due to a dynamic decrease in O_2 delivery. In stable angina, symptoms due to an increase in 0_2 demand.[4]
- Extent of angiographic CAD is similar to that of patients with stable angina, ie, number of vessels involved, % narrowing, collaterals.
- Major difference is the "culprit lesion:
  -an eccentric, irregular stenosis
  -plaque with fissures, cracks, fibrous cap
  -dynamic interaction of lesion with blood components (platelets, prostaglandins, etc) with changing coronary vasomotor tone
- Platelet adhesion, activation, and aggregation are the final common pathway and inhibiting platelet function is the keystone of therapy.



Unstable angina is defined by its clinical presentations:[3]

- Symptoms of angina at rest (usually prolonged > 20 min) within one week of presentation. May be further subdivided into within <48 hrs.
- New onset angina CCSC class II or IV within two months of presentation
- Increasing angina to class III or IV
- Variant angina
- Non-Q-wave myocardial infarction
- Post-MI angina (recurrent pain >24 hrs after acute MI)

Canadian Cardiovascular Society Classification (CCSC) of angina:[5]

Class	Activity Evoking Angina	Normal Activity Limits
I	Prolonged exertion	None
II	Walking > 2 blocks	Slight
III	Walking < 2 blocks	Marked
IV	Minimal or rest	Severe

Likelihood of Significant Coronary Artery Disease in Patients With Symptoms Suggesting Unstable Angina (from *AHCPR Clinical Practice Guideline, 1994)*[3]

High Likelihood (0.85-0.99)	**Intermediate Likelihood (0.15-0.84)**	**Low Likelihood (0.01-0.14)**
Any of the following features:	*Absence of high likelihood features and any of the following:*	*Absence of high or intermediate likelihood features but may have:*
Known hx of CAD (prior MI, PTCA, CABG, SCD)	Definite angina sxs: ♂ < 60, ♀ < 70	Chest pain, probably not angina
Definite angina sxs: ♂ $\geq$ 60, ♀ $\geq$ 70	Probably angina sxs: ♂ > 60, ♀ >70	One risk factor but not diabetes
Hemodynamic Δ's or ECG Δ's with pain	Probably not angina in diabetics or in nondiabetics with $\geq$ two other risk factors	T wave flat or inverted <1 mm in leads with dominant R waves
Variant angina	Peripheral vascular disease	Normal ECG
ST ↑ or ↓ $\geq$ 1 mm*	ST ↓ 0.5-1 mm*	
Marked symmetrical T wave inversion in multiple precordial leads	T wave inversion $\geq$ 1 mm in leads with dominant R waves	

* new changes

Ancillary information:[6]

Clinical features	*Likelihood ratio (for MI)*
Pleuritic chest pain	0.2
Sharp/stabbing	0.3
Positional pain	0.3
Reproducible	0.2
Normal ECG	0.2

Given the low prevalence of disease, which question do I want to answer?

1. Which test should I order to rule out coronary artery disease?
2. Which test should I order to rule out unstable angina pectoris?

NONINVASIVE TESTING IN CORONARY ARTERY DISEASE

- Treadmill exercise stress test **(EST)**
- Single photon emission computed tomograpy **(SPECT) (MIBI scan)**
- Echocardiography **(Echo)**
- Pharmacologic stress testing (with SPECT and Echo)
- Positron emission tomograpy **(PET)**
- Electron beam computed tomography **(EBCT)**

The "Bang for Your Buck"[7,8]

TEST	COST	SENSITIVITY L main All 3 vessel	SPECIFICITY

Treadmill	$110	68%	86%	77%
SPECT*	$574	88%	98%	77%
Echo**	$262	76%	94%	88%

*with exercise
**with exercise or dobutamine/atropine

The above values derived from studies in patients with chronic stable angina or in hospitalized patients admitted to a CCU for chest pain.

The ED patient with chest pain is not the "usual" CAD patient. They are unselected, usually low likelihood patients. In many studies of SPECT and Echo in ED patients, they do not undergo physiologic stress. Your initial selection of the best test based on the above table is probably incorrect.

FOCUSED LITERATURE REVIEW (<u>not</u> a systematic review or meta-analysis, maybe a critically appraised topic or "CAT")

- The first study
- The largest study
- The best study
- The study of interest to emergency physicians
- Sensitivity/specificity stated or raw data provided for calculations

ECHOCARDIOGRAPHY[9]

<u>Advantages</u>:

- Noninvasive
- Portable
- Can be done at rest
- Accepted definition of abnormal: regional wall motion abnormality (may be a post-infarct scar, an acute MI, or acute ischemia)
- Detects an early sign of myocardial ischemia which may precede ECG Δ's

<u>Disadvantages:</u>

- Technical expertise required for image acquisition and interpretation (translation: you need a cardiologist)
- An adequate study cannot be performed in about 20% of the population
- Cannot distinguish between acute vs chronic contractile abnormalities
- Limited experience in the ED management of chest pain patients

<u>*Sasaki et al, Am Heart J, 1986*[10]</u>

46 patients, equivocal sxs of cardiac ischemia, nondiagnostic ECGs. Rest echo in 18 patients during pain and in 28 patients after pain resolution. Patients were excluded if other causes for wall motion abnormality were known. All patients had subsequent angiography, EST, or radionuclide study.

Rule in rate 33%.
In patients with chest pain during echo, sensitivity for AMI or CAD = 89%; specificity = 100%.

In patients without chest pain, sensitivity for AMI or CAD = 64%; specificity = 93%.

Peels et al, Am J Cardiol, 1990[11]

43 nonconsecutive patients with acute chest pain suggestive of cardiac ischemia, nondiagnostic or normal ECGs. Patients with known CAD excluded. Rest echo during pain. Angiography in some patients within the subsequent 3 weeks.

Rule in rate 30%.
Sensitivity for AMI = 92%; specificity = 53%
Sensitivity for ischemia/CAD = 88%; specificity 78%

Sabia et al, Circulation, 1991[12]

180 patients presenting within 4 hrs of pain onset. Chest pain without an obvious cause (?). Negative cardiac enzymes. Included patients with diagnostic and non-diagnostic ECGs. No other study performed to confirm CAD diagnosis.

Rule in rate for acute MI was 21%. Rest Echo **sensitivity for AMI = 92%, specificity for AMI = 57%.** Greatest value was identifying patients at risk for in-hospital complications.

Gibler et al, Ann Emerg Med, 1995[13]

1,101 patients, sxs suggestive of acute coronary syndrome, serial markers, continuous 12 lead ECG ST segment monitoring for 9 hours, echo, and exercise testing.

Rule in rate 1.2%, final dx unstable angina in 3% (overall acute coronary syndrome incidence 4%)
Echo data in 901 patients
Sensitivity for cardiac disease = 47%; specificity for cardiac disease = 99%

Summary of published studies

- Widely divergent, selected, small study populations with rule in rates of 1-33%.
- Pain during study appears to impact sensitivity
- No clear evidence that rest echo adds anything to serial marker determinations and observation alone.
- Utility of stress echo not evaluated

Can we draw any conclusions?

- **In high risk groups (high “rule in” or event rate), sensitivity 89-92%, specificity 53-100%.**

- Subendocardial, non-Q infarcts most often missed.
- **In low risk groups, sensitivity 47%, specificity 99%**
- Rest echo not sufficiently sensitive to be of clinical use in the low probability, low risk population with suspected acute coronary syndrome
- Possible value: LBBB, LVH with 2° ST-T wave changes

RADIONUCLIDES[14]

Thallium (^{201}Tl)

- Low photon energy (68-83 keV)
- Low-radiation background scatter (low count density = poor image)
- Long half life (73 hrs)
- Rapid washout from myocardium and redistribution
- Must scan soon after injection

Technetium-99m Sestamibi ("MIBI scan)

- Higher photon energy (140 keV)
- Higher emission energy = less scatter
- Short half life (6 hrs)
- Minimal redistribution
- Imaging can be delayed 1-4 hrs

MIBI scan is now the preferred perfusion imaging method. High quality images can be obtained with delayed scanning (can inject during pain, image when pain free). Images are better in the obese patient. However, due to early hepatic uptake and biliary excretion, liver disease may decrease image quality.

There is limited experience with nuclear imaging in emergency department patients with suspected ACS (chest pain, "R/O MI", unstable angina). Existing literature deals with patients admitted to the CCU and later discharged or low risk ED patients with chest pain, usually as part of a "chest pain unit protocol". Studies are generally divided between those that use MIBI for diagnosis and those that use it for risk stratification.

Varetto et al, JACC, 1993[15]

64 patients who presented to the ED within 12 hrs of chest pain onset. 28% had sxs that were characterized as atypical pain. All patients had a normal or nondiagnostic ECG. Rest MIBI only; 58% had pain at the time of injection. All patients were admitted to the CCU and followed up for 11 ± 3 months. Study endpoints: MI, death, and revascularization.

A + MIBI was obtained in 30 patients. 13 of these had a MI by enzyme criteria, 17 others underwent angiography. Three angios were negative; thus 3 MIBI's were false positives. **Sensitivity = 100%.**

34 patients had a – MIBI study. None had a MI, and 22 had a – angiogram. **Specificity = 92%.**

Follow-up: No patient with a – MIBI met endpoint criteria compared to 30% in + MIBI group.

Small sample size, selected high-risk population, ie, all patients admitted to the CCU based on clinical grounds which were not stated.

Hilton et al, JACC, 1994[16]

102 nonconsecutive ED patients with "angina-like" chest pain and normal or nondiagnostic ECG. Nearly 1/3 of the study group had undergone an angiogram or treadmill exercise test in the past. All patients underwent rest MIBI study with injection during pain. Study endpoints: cardiac death, nonfatal MI, coronary angioplasty, CABG, or thrombolysis within 90 days.

70/102 (69%) patients had a – MIBI. 23/70 (33%) had a – MIBI and were discharged from the ED. One of these patients had known CAD and had CABG within 90 days.

15/102 (15%) had an equivocal scan and 2/15 (13%) had a "cardiac event". 17/102 (17%) had a + scan and 12/17 (71%) had a cardiac event.

Using only MI as an endpoint: sensitivity = 100%, specificity 78%, and accuracy 100%.

Nonconsecutive patients, small sample size, 1/3 of pts had known CAD, variable pretest probability, revascularization as an endpoint.

Tatum et al, Ann Emerg Med, 1997[17]

438 consecutive patients enrolled over 5 months. Patients classified as probable or possible unstable angina (AHCPR guidelines). 22% had known CAD. Normal or nondiagnostic ECG. Rest MIBI; injection with or without pain. Endpoints: MI, death, and revascularization within 1 year.

Sensitivity for AMI = 100% (95% CI, 64-100).
Specificity for AMI = 78% (95% CI, 74-82).

Event rate at 1 year was 42% for patients with a + MIBI. Event rate at one year, with – MIBI was 3% (revascularization).

Kontos et al, Circulation, 1999[18]

620 patients with low to moderate risk of ACS. Rest MIBI and serial serum markers of AMI. Endpoints: MI within 1 week, + angiogram, or revascularization within 6 weeks.

	SENSITIVITY	SPECIFICITY	ODDS RATIO
MI			
MIBI	92 (81-96)	67 (63-71)	22 (6.2-57)
Troponin I	90 (79-95)	96 (94-98)*	230 (66-590)
Revascularization			
MIBI	81 (69-89)	74 (70-77)	12 (4.7-23)

Troponin I	17 (107-29)*	98 (96-99)*	9.3 (3.6-23)
Combined MI or revascularization MIBI Troponin I	 86 (79-92) 54 (45-63)*	 74 (70-77) 98 (96-99)*	 17 (8.2-30) 52 (25-105)
Combined MI or significant CAD MIBI Troponin I	 82 (75-88) 45 (37-53)*	 75 (70-78) 98 (96-99)*	 13 (7.3-22) 35 (17-69)

Numbers in parentheses indicate 95% CI.
*P<0.001 compared to MIBI

The authors concluded that MIBI and serial troponin I are complimentary. Problems: Wide confidence intervals (especially for sensitivity), population not well defined and included patients with known CAD. Revascularization and angiography used as endpoints.

RADIONUCLIDES IN THE EMERGENCY DEPARTMENT

Summary of published studies:
- Study populations divergent, selected, and included high risk patients
- Revascularization and angiography endpoints are artificial
- <1500 patients studied

Can we draw any conclusions?
- Rest MIBI is feasible if you can keep the agent in the ED and have 24-hr access to a gamma camera and necessary personnel.
- Rest MIBI can detect perfusion defects, both old and new. This can be a problem.
- **Sensitivity is about 95% with wide confidence intervals for CAD or acute MI. MI's are nearly equally well detected with serum markers**. Are we worried about MI or unstable angina?
- If the test is negative, it appears safe to discharge the patient from the ED. The early and late event rates are <1%.

TREADMILL EXERCISE TEST[19]

Advantages:

- Inexpensive
- Readily available
- Does not require technical expertise
- Extensive experience

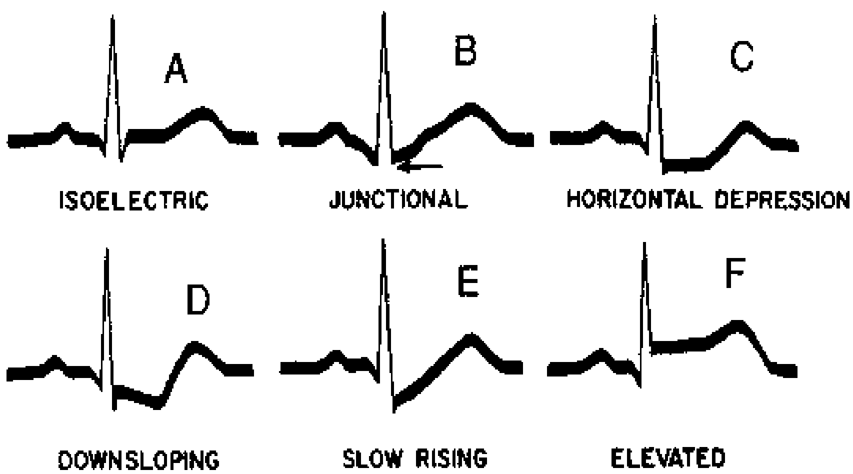
Disadvantages:

- Patient must be able to exercise (attain 85% of age predicted maximum heart rate)
- Must have no baseline ST segment abnormalities
- May be effected by drugs which attenuate heart rate response to exercise or increase exercise tolerance

Definition of a positive test:

- ≥ 1 mm horizontal or downsloping ST-segment depression or an elevation at 80 ms after the J-point
- significant arrhythmias
- ↓ systolic BP of ≥ 10 mm Hg
- significant symptoms

In general, the earlier a positive, the more likely and significant is the degree of CAD. Scoring systems using other indicators have been developed for assessing prognosis.



C, D, and F are positive responses during treadmill exercise testing.

Lewis et al, Am J Cardiol, 1994[20]

93 patients with low probability (5%) of unstable angina or MI. Patients with known CAD excluded. All included patients had sxs suggestive of cardiac ischemia, a normal or nondiagnostic ECG, and single negative CK. Treadmill testing was performed within 1 hr (median) of presentation. Baseline ST segment Δ's did not preclude treadmill testing nor did the presence of chest pain.

64% had a – test and about half of these were discharged home from the ED. All patients with a – test had no further testing.

13% had a + test and 24% an equivocal test. Of the + tests, 50% were false +.

Excluding nondiagnostic tests, sensitivity = 100%, specificity = 91%.

Gibler et al, Ann Emerg Med, 1995[13]

Observation, marker, test protocol (echo and/or treadmill). 791 patients with suggestive history, negative marker, and normal or nondiagnostic ECG. 78% of the eligible population had treadmill testing (high probability patients excluded). Treadmill exercise test performed after 9 hrs of observation. Endpoint was a "cardiac diagnosis" which included MI, USA, PTCA, and CABG).

782/791 (99%) had a – or equivocal test. There were 5 false + and 10 false –.
Sensitivity = 29%
Specificity = 99%
+ predictive value = 44%, Likelihood ratio + = 29
– predictive value = 99%, Likelihood ratio – = 0.72

Low sensitivity most likely due to selected endpoints.

Zalenski et al, Arch Intern Med, 1997[21]

Observation, serial marker, test protocol (treadmill). Disease prevalence 9.5% with all MI's diagnosed by serial markers and ECGs. 224 patients were stressed after 12 hours of observation.

Sensitivity = 90%, specificity = 50%, negative predictive value = 98%
Likelihood ratio + = 1.82
Likelihood ratio – = 0.20

Kirk et al, Ann Emerg Med, 1998[22]

212 patients with low likelihood (6%) of disease; markers not measured before exercise testing.

11% + tests, about 50% false +. Sensitivity and specificity not provided.

All patients with a negative test and 93% of those with an equivocal test were discharged from the ED. There were no complications at 30 days of follow-up.

Summary of published studies:

- Early or immediate treadmill EST has been studied more extensively than echo or MIBI.
- Generally a low risk population selected
- Sensitivity, specificity, etc not always provided by the investigators and raw data not provided to allow backward calculation. However, it appears that the test has a sensitivity of 90-100% with highly variable specificity.

Can we draw any conclusions?

- Few tests will be +, and about 50% of these will be false +. Admit all + tests and let the cardiologist sort it out.
- A negative test has a high negative predictive value (about 98%)
- The LR of a – test is 0.20
- Patients with a negative or equivocal test have an extremely low rate of short-term events.

Considering the pathophysiology of unstable angina, it is unlikely that someone with USA will have a – stress test.

ACCURACY IN THE ED PATIENT vs REPORTED ACCURACY IN CAD POPULATION

Test	Sensitivity	Specificity
Treadmill		
Overall	68%	77%
ED	90%	50%
SPECT		
Overall	88%	77%
ED	86%	74%
Echo		
Overall	76%	88%
ED	47%	99%

WHICH TEST TO USE[23]

- ***THREADMILL EST:*** No ST segment changes on baseline ECG, not on digoxin. Can still test if patient on beta-blockers or calcium channel blockers.
- ***REST AND EXERCISE SPECT (MIBI) OR ECHO:*** Baseline ST segment changes
- ***DOBUTAMINE ECHO:*** Patient unable to exercise. Dobutamine without echo?

Availability and expertise generally determine which test is done.

UTILITY OF PAST TESTS

- *Angiography:*[22-26]
  -if normal, progression to >50% occlusion is unlikely within 5 years
  -if <50% occlusion, about 30% progress to >50% obstruction at 3 years
  -change in chest pain character and risk factors generally predictive of progression
- *SPECT or treadmill EST:*[27,28]

  <1% cardiac event rate at one year in patients with normal tests

CASE REVIEW

Is testing:

- ❑ **Necessary**
- ❑ **Appropriate but not necessary**
- ❑ **Uncertain appropriateness**
- ❑ **Inappropriate**

Which test would you use?

CASE #1

A 70 yo male with increasingly frequent chest tightness on mild exertion (chest pain duration >10 min) radiating to L shoulder. ECG shows T wave flattening in lateral leads.

CASE #2

A 65 yo female with hypertension who recently had 10 sec of gas-like L chest pain. ECG is normal.

CASE #3

A 71 yo female with mid-chest pain relieved by a friend’s nitroglycerin one week previously. No cardiac risk factors. ECG is normal.

CASE #4

A 65 yo diabetic female with new-onset sharp mid-chest pain at rest lasting 10-15 min. ECG shows LVH with strain pattern.

CASE #5

A 41 yo male with two hours of left chest pain while lying in bed, not relieved by nitroglycerin. No cardiac risk factors. Normal ECG.

CASE #6

A 66 yo female with upper back pain while walking. Past history of diabetes. ECG is normal.

CASE #7

A 53 yo female with no cardiac risk factors with L sided chest pain of <5 min duration that that radiated to her jaw occurring 3 days ago. ECG shows nonspecific T wave changes.

CASE #8

A 49 yo male with R sided chest pain while watching television the previous weekend. No cardiac risk factors. ECG shows nonspecific ST segment and T wave changes.

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APPENDIX

	Disease Present	Disease Absent	Total
Test Positive	**a**	**b**	**a+b**
Test Negative	**c**	**d**	**c+d**

Total	**a+c**	**b+d**	

Sensitivity = True Positives/True Positives + False Negatives = a/a+c

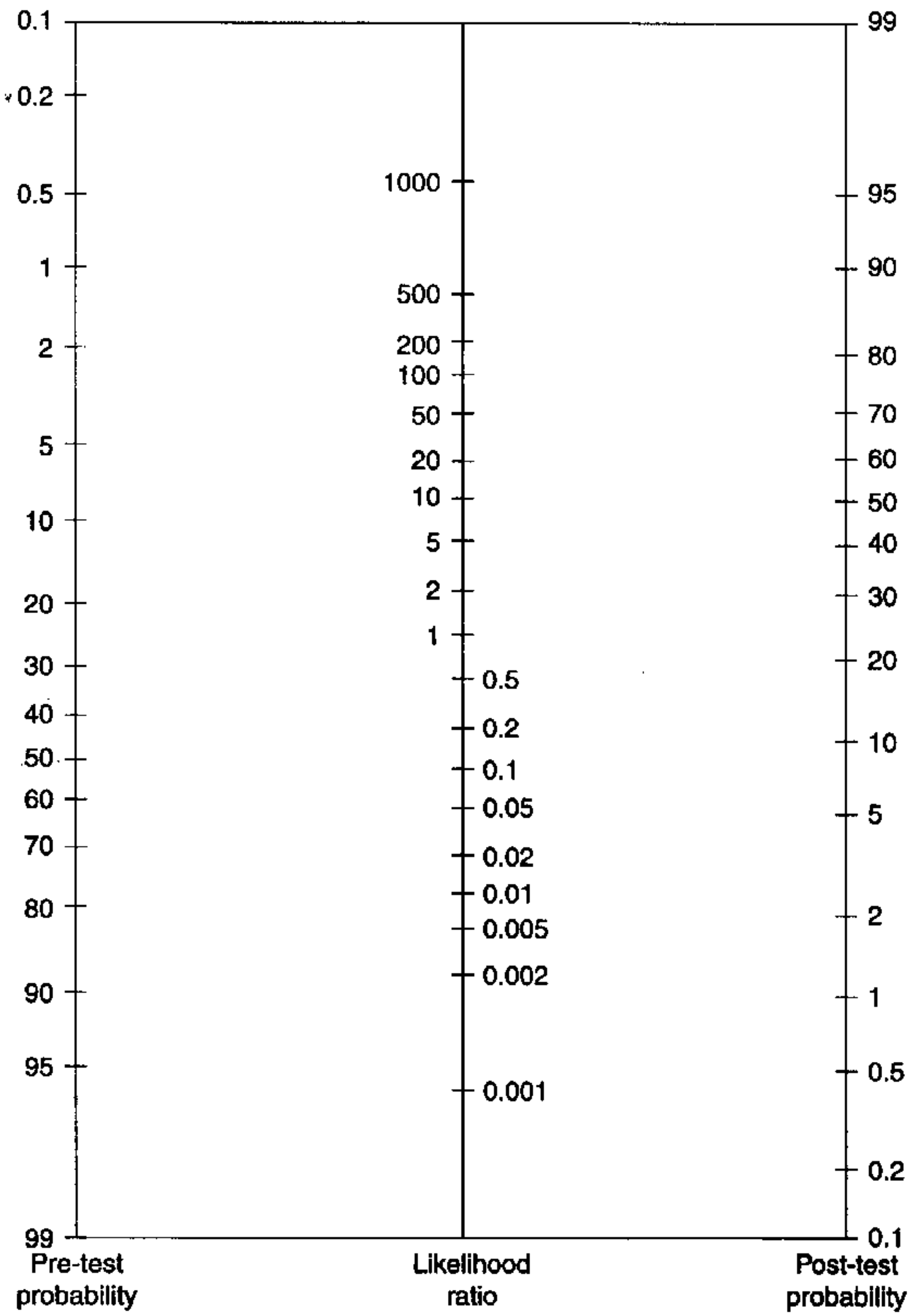
Specificity = True Negatives/True Negatives + False Positives = d/b+d

Positive Predictive Value = True Positive/True Positive + False Positive = a/a+b

Negative Predictive Value = True Negative/True Negative+False Negative = d/d+c

Likelihood ratio + test = sensitivity/1-specificity

Likelihood ratio – test = 1-sensitivity/specificity



Nomogram for interpreting diagnostic test results. (Fagan, N Engl J Med, 1975)