

# **Update on Evaluating the Patient with Chest Pain**

**Robert L. Jesse, MD, PhD**

Virginia Commonwealth University Health System

Richmond, VA

Veterans Health Administration

Washington, DC

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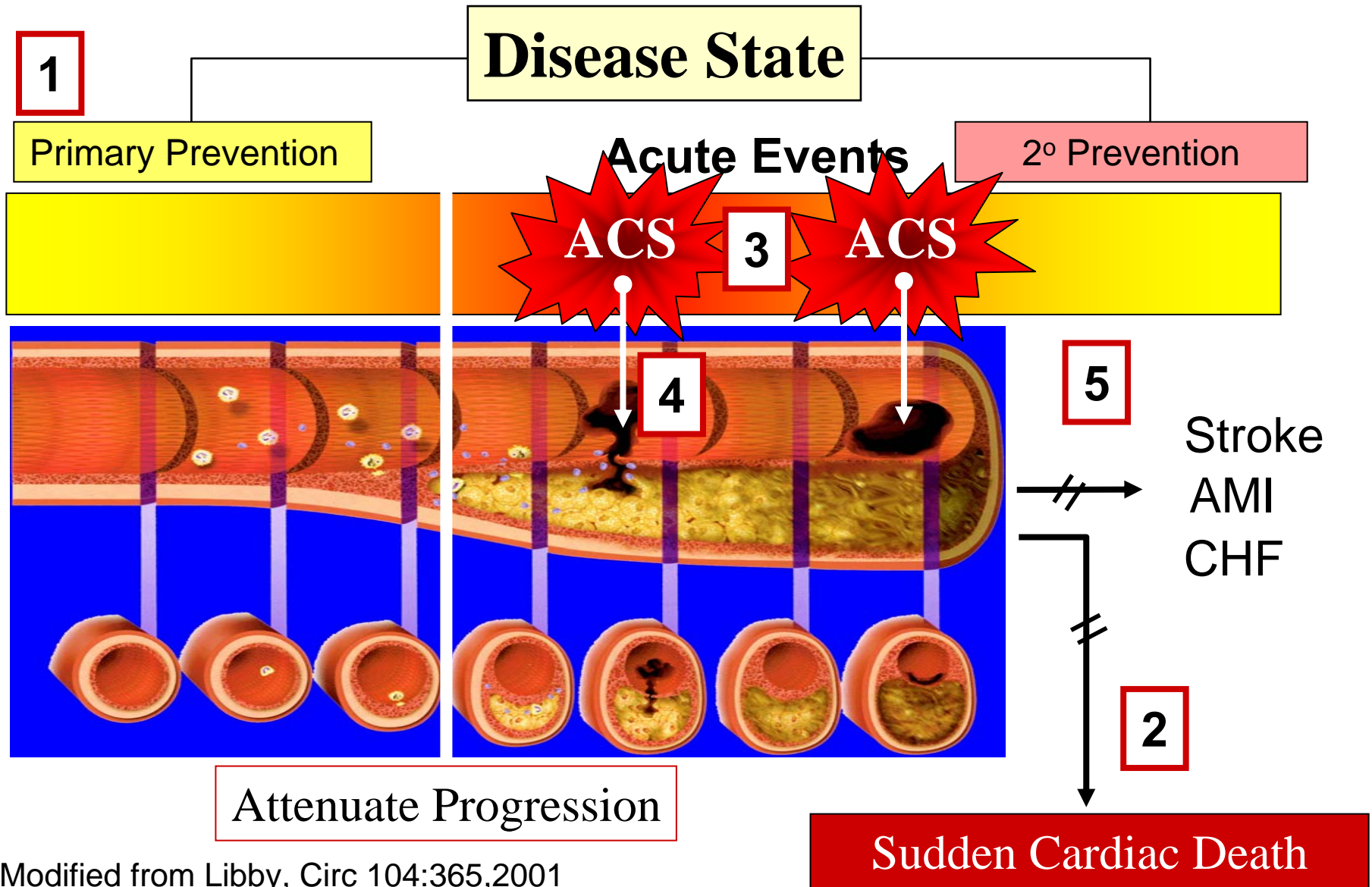


**"You say it's a sharp, stabbing pain. Hmmm  
... sharp ... stabbing pain."**

**"You need a cath."**

*Inflammatory*

# Atherothrombotic Coronary Artery Disease



# Evaluating the Patient with Chest Pain

## What We Really Need to Know

1. Who has coronary heart disease
2. Who is at risk for sudden death
3. Who is at risk for ACS
  - Long-term
  - Short-term
4. Who is having an ACS
5. Is secondary prevention working

# The Biologic Hard Drive



Information about

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Genetic make-up

Current health status

Future health status

# The Biologic Hard Drive

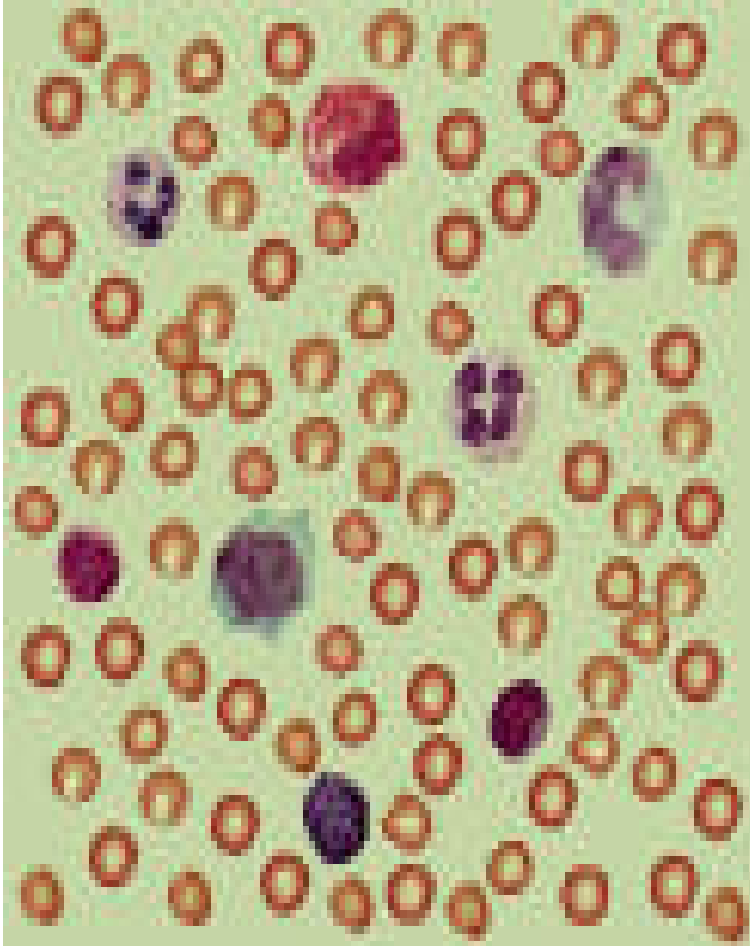


## Potential roles

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- Diagnosis/differential diagnosis
- Risk stratification
- Therapeutic decision-making
- Disease monitoring
- Identification of drug targets
- Better understanding of pathophysiology

# Risk Stratification



**Anatomic**

**WBC counts**

**Chemical**

**Creatinine**

**Function**

**aPTT**

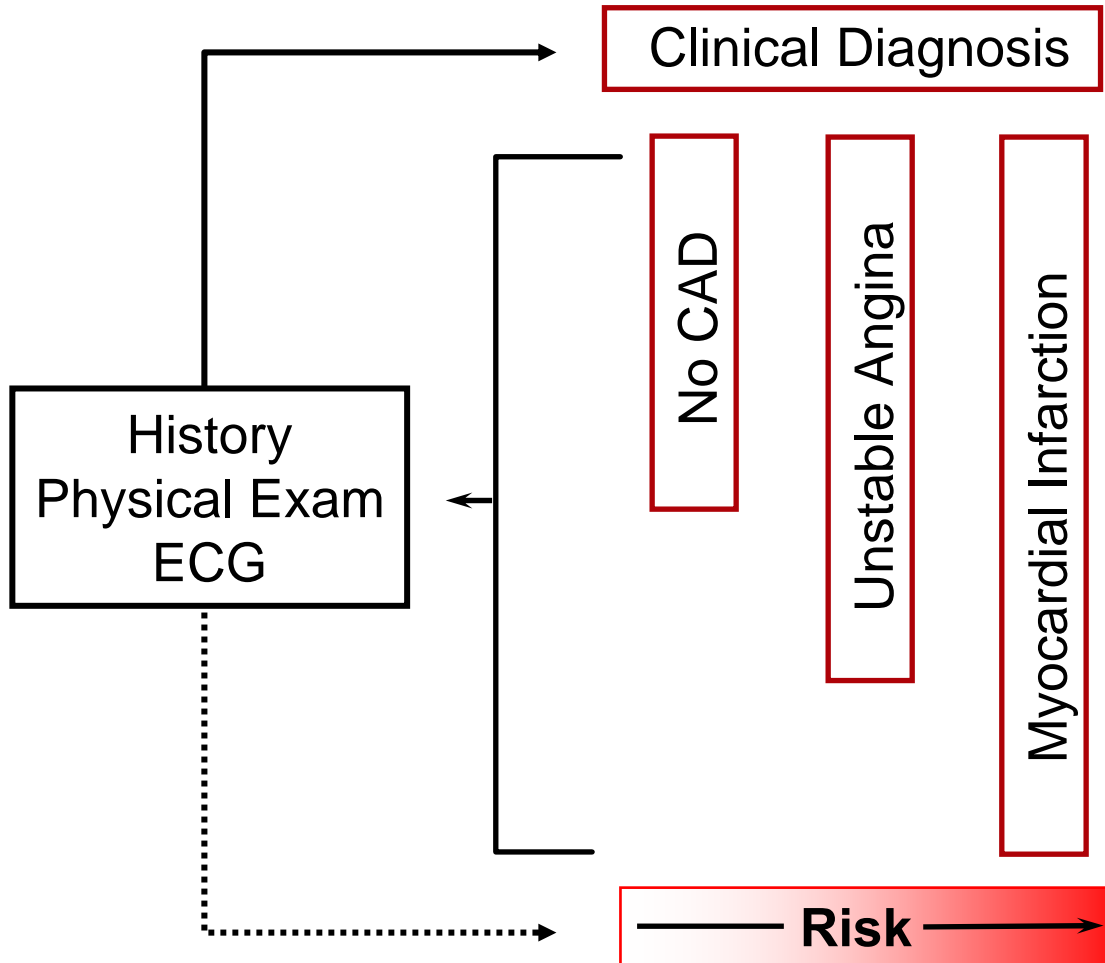
**Genomics**

**Polymorphisms**

**Proteomics**

**Troponin**

# Evaluation of Patients with Suspected ACS

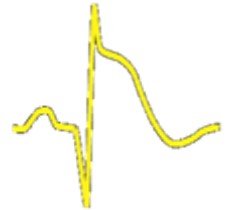


**Sensitivity < 95%**

# Chest Pain Evaluation

## Rule-in ACS

**Rapidly rule-in AMI and initiate therapy**



Rapidly rule-in unstable angina and initiate therapy

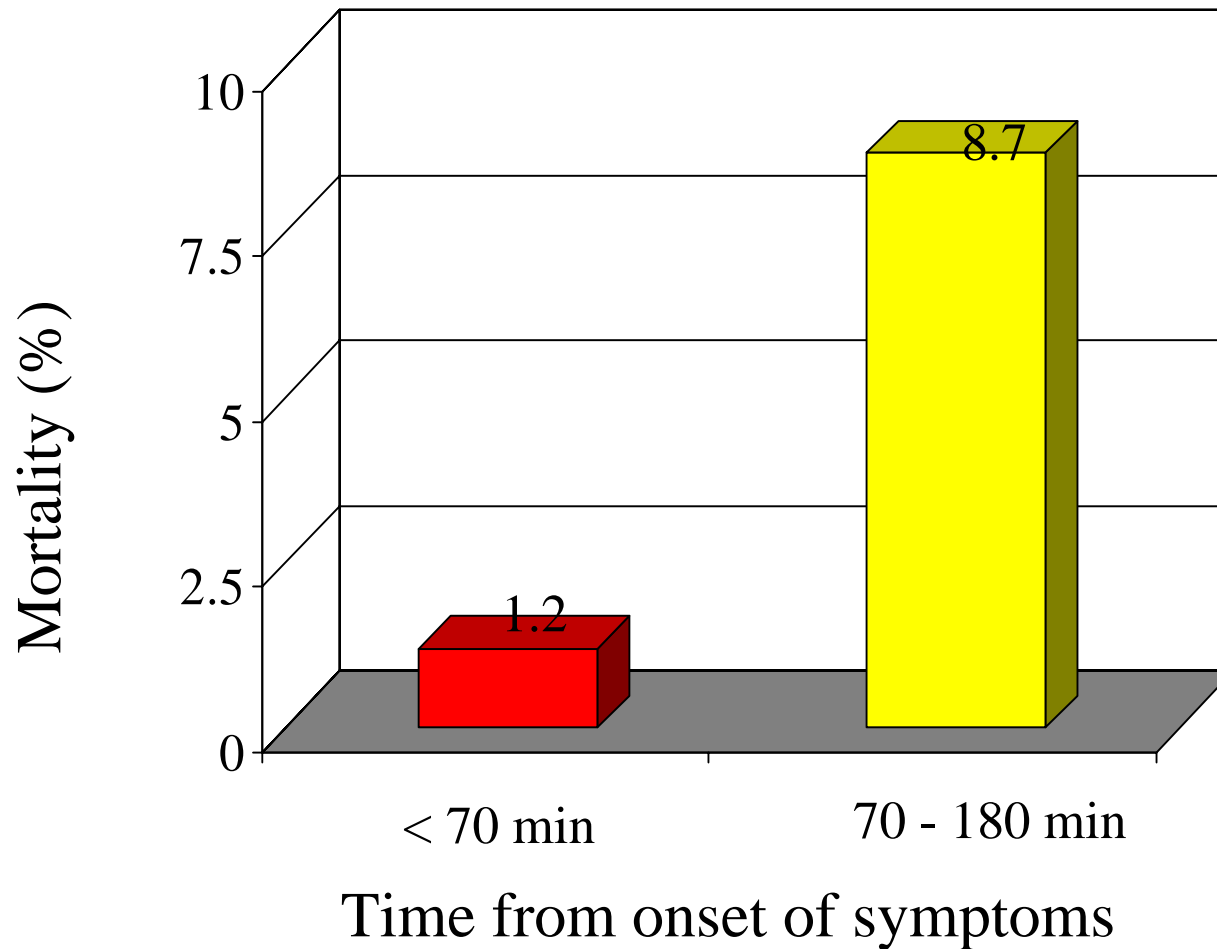
Rule-out acute coronary syndromes

Identify stable coronary disease

Identify high risk individuals

Risk factor modification

# Time to Reperfusion vs Mortality MITI Study



Source: Weaver, JAMA 270:1211-16, 1993

# Chest Pain Evaluation

## Rule-in ACS

Rapidly rule-in AMI and initiate therapy



**Rapidly rule-in unstable angina and initiate therapy**



Rule-out acute coronary syndromes



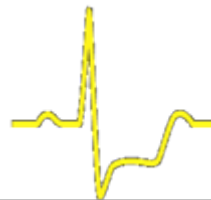
Identify stable coronary disease



Identify high risk individuals

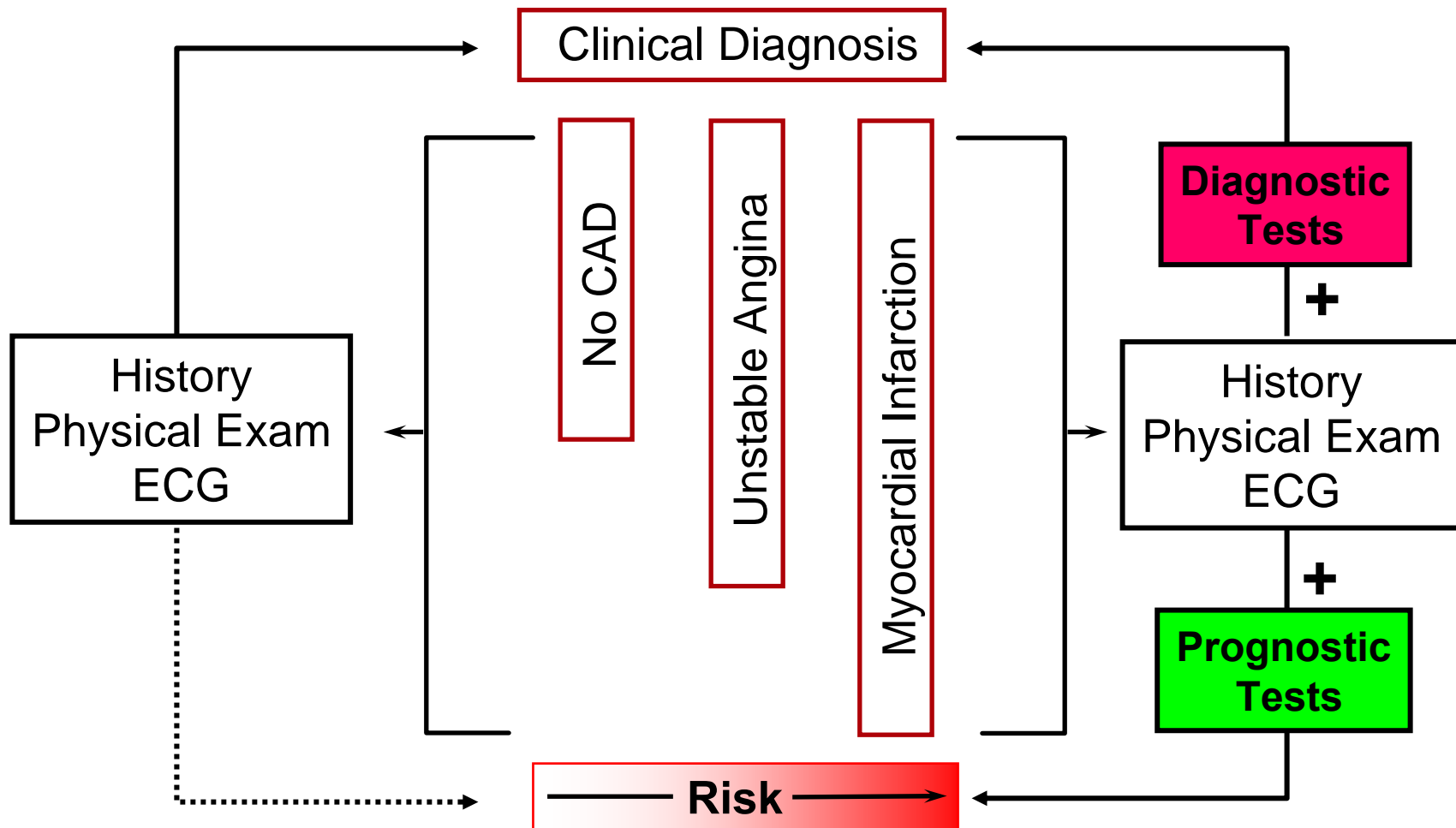


Risk factor modification



Sens 35%

# Evaluation of Patients with Suspected ACS

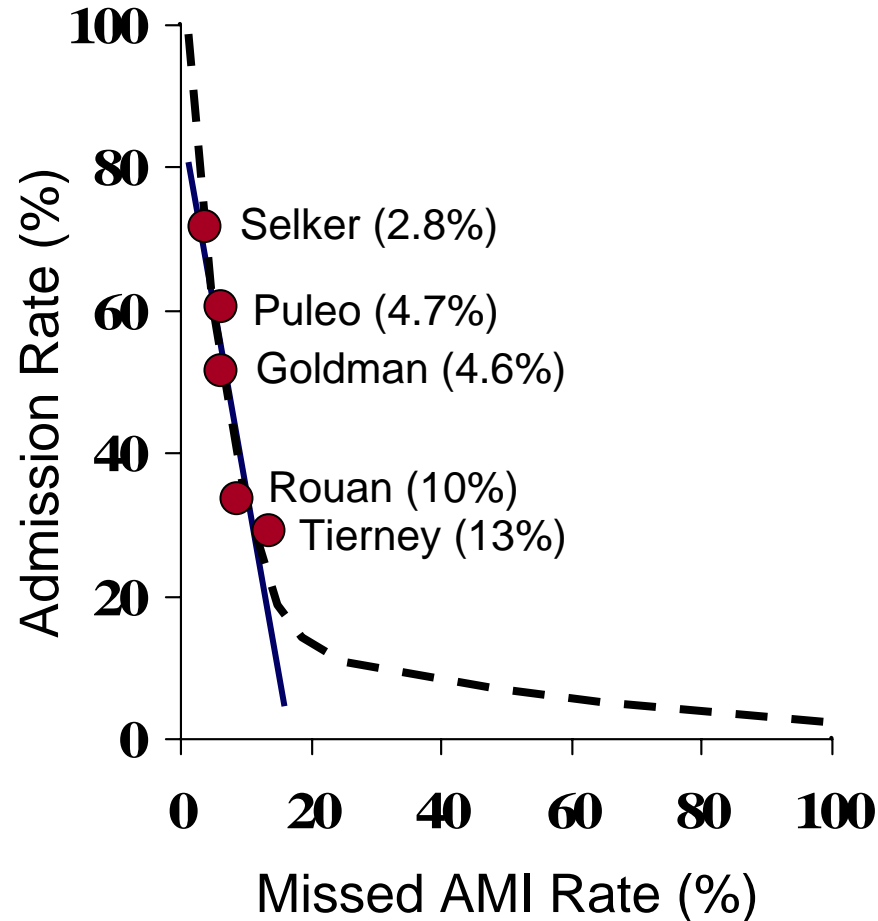


**Sensitivity < 95%**

**Sensitivity > 99%**

# Evaluation of Patients with Suspected ACS

## What Drives the System



# Chest Pain Evaluation

## Rule-in ACS

Rapidly rule-in AMI and initiate therapy



**Rapidly rule-in unstable angina and initiate therapy**



Rule-out acute coronary syndromes



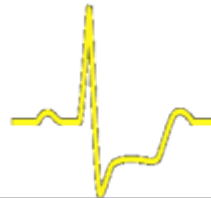
Identify stable coronary disease



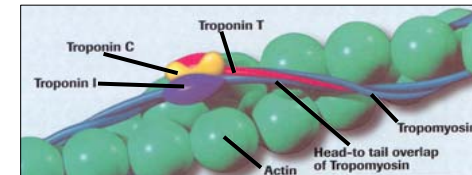
Identify high risk individuals



Risk factor modification



Sens 35%

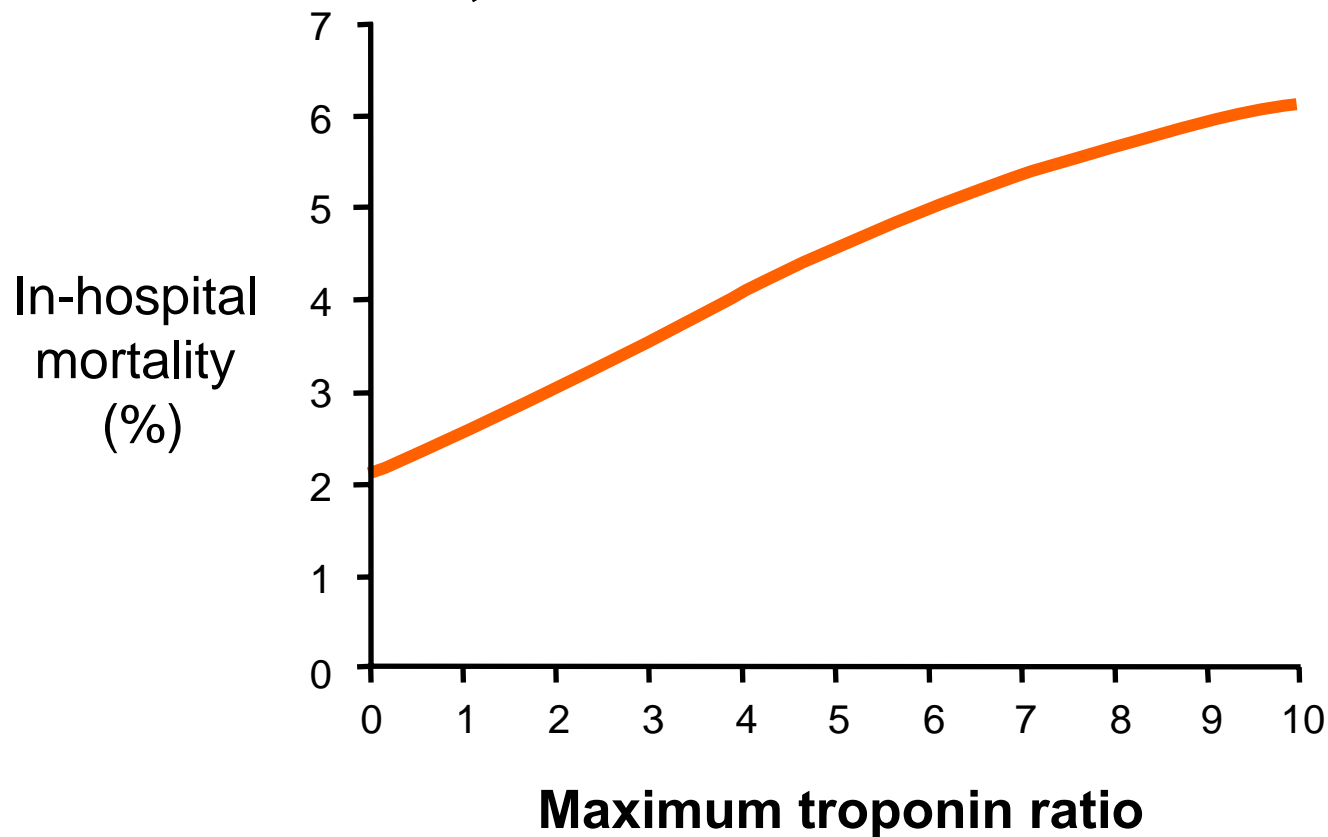


# **Biomarkers in the Clinical Approach to ACS**

1. Identification of risk as a key clinical decision point.

# In-hospital Mortality in NSTEMI Patients is Higher at any Degree of Troponin Elevation

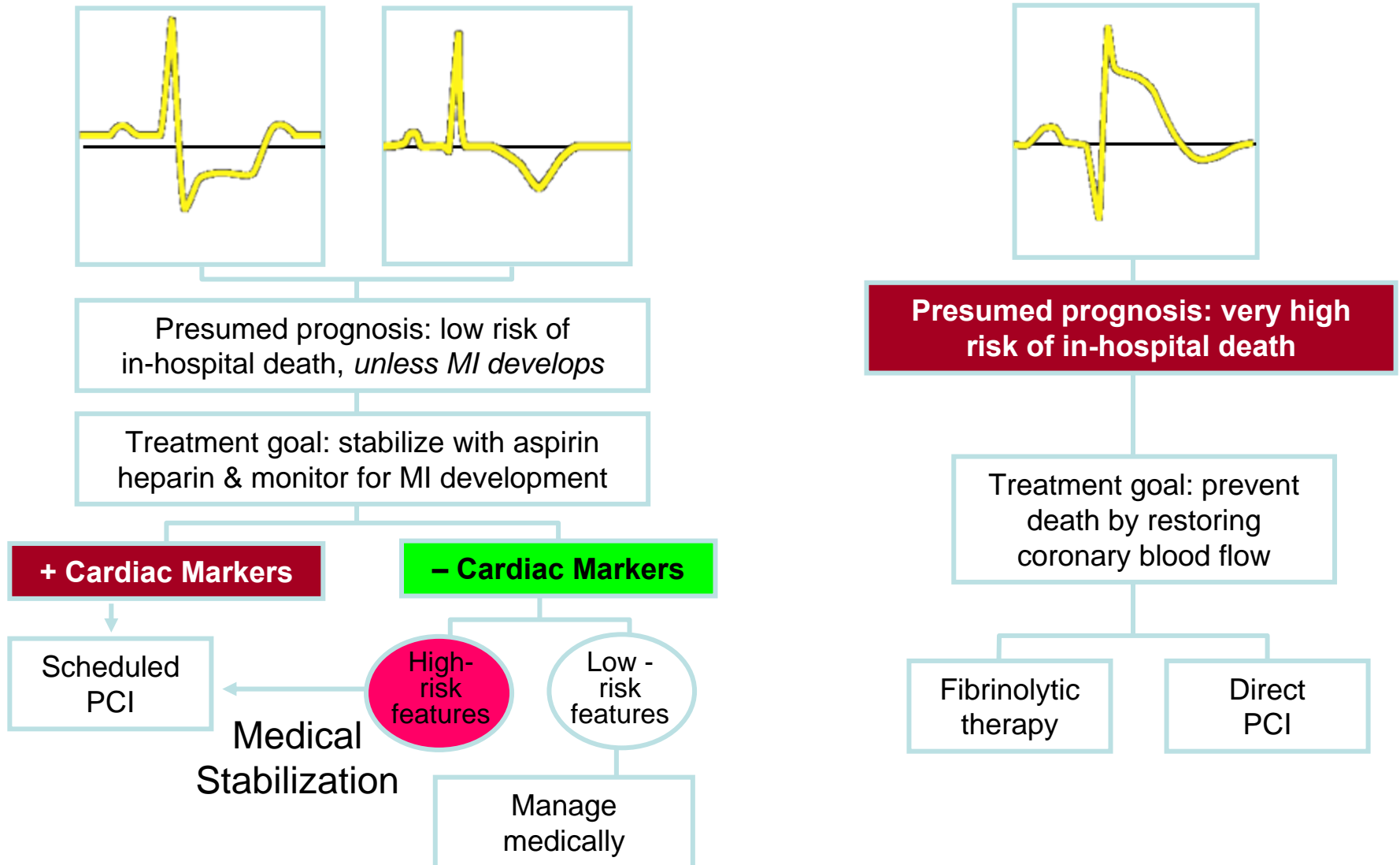
**CRUSADE: N = 23,298**



Reference limit: maximum troponin ratio 0–1x upper limit of normal

Roe MT et al. *Arch Intern Med.* 2005;165:1870-6.

# Current Management of ACS



# Chest Pain Evaluation

## Rule-in ACS

Rapidly rule-in AMI and initiate therapy



**Rapidly rule-in unstable angina and initiate therapy**



Rule-out acute coronary syndromes



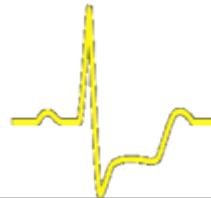
Identify stable coronary disease



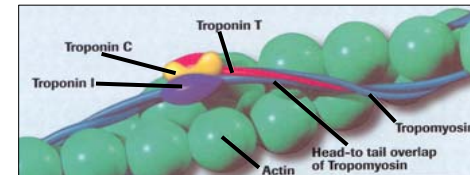
Identify high risk individuals



Risk factor modification

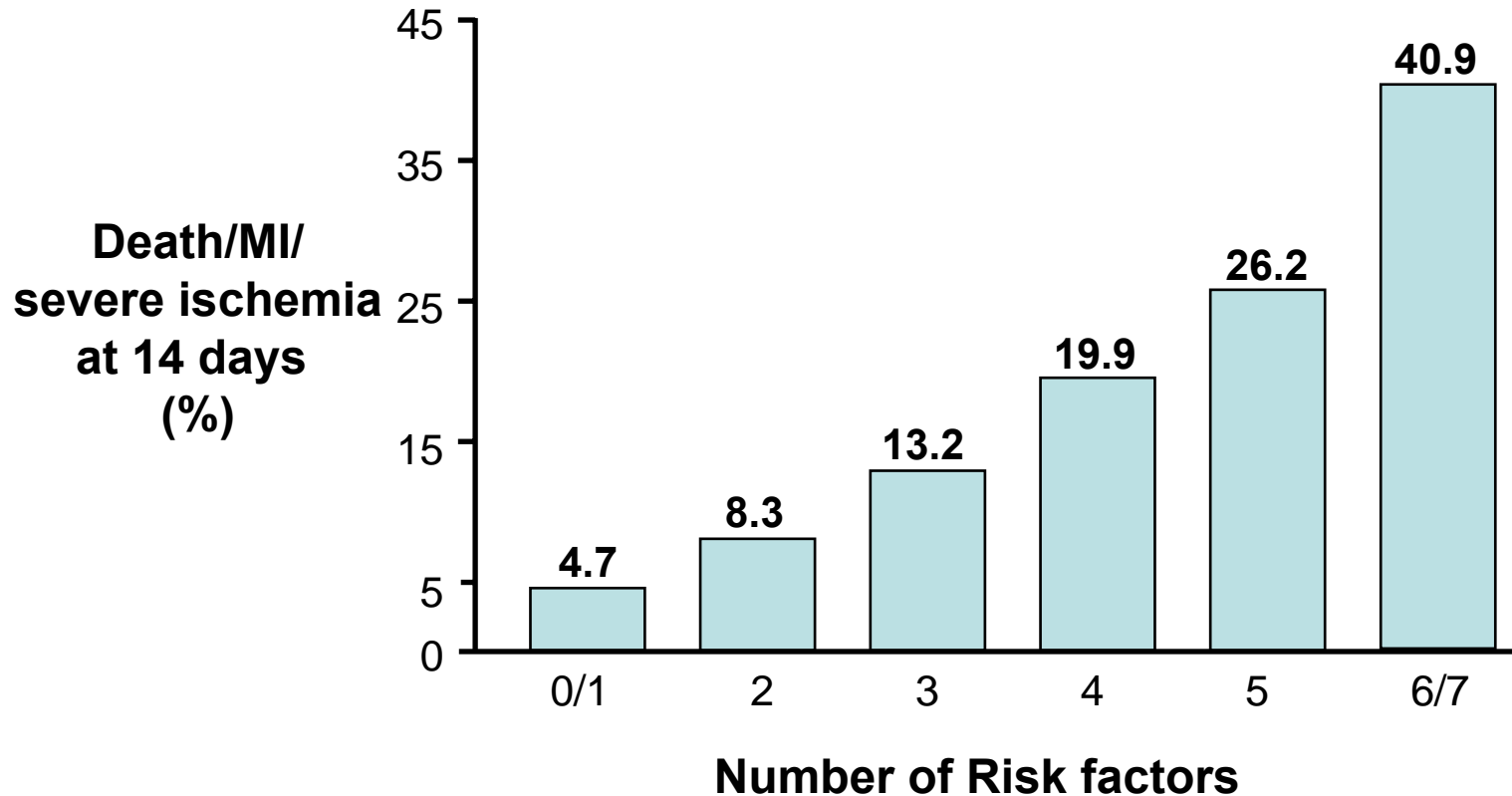


Sens 35%



T<sub>0</sub> Sens 30%

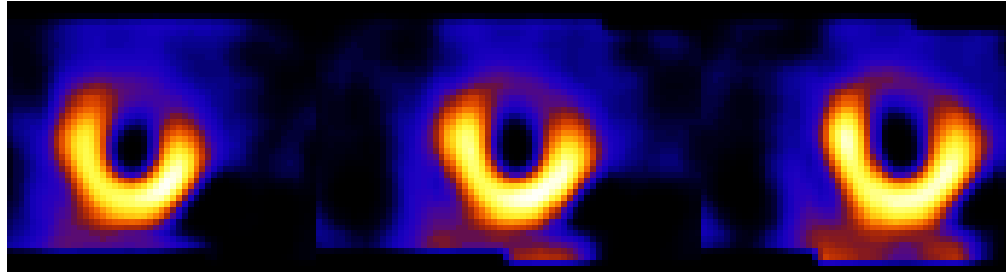
# TIMI risk score in UA/NSTEMI



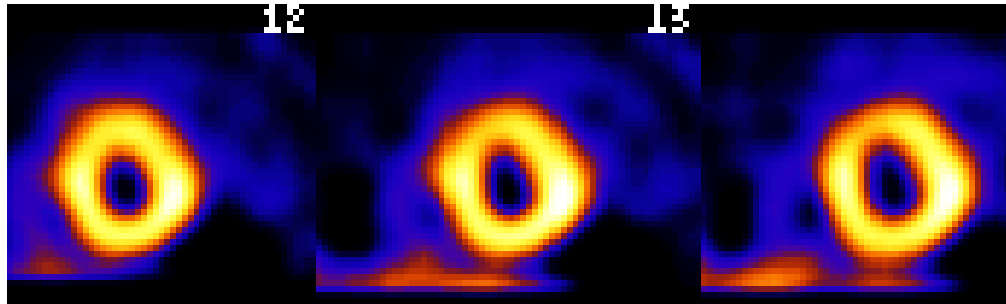
n = 1957 ACS patients

Antman EM et al. *JAMA*. 2000;284:835-42.

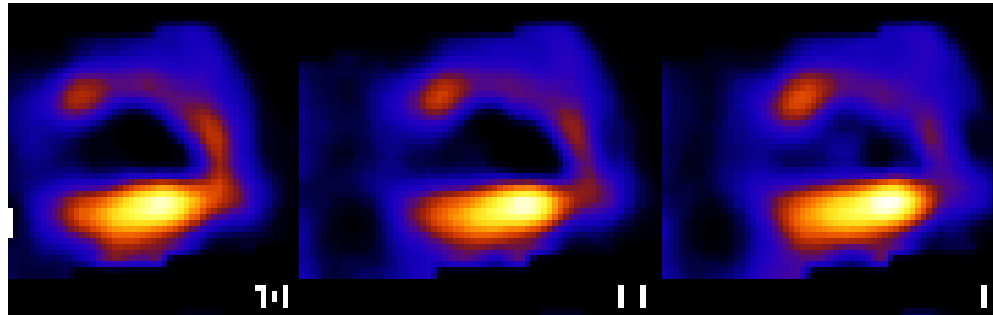
Acute



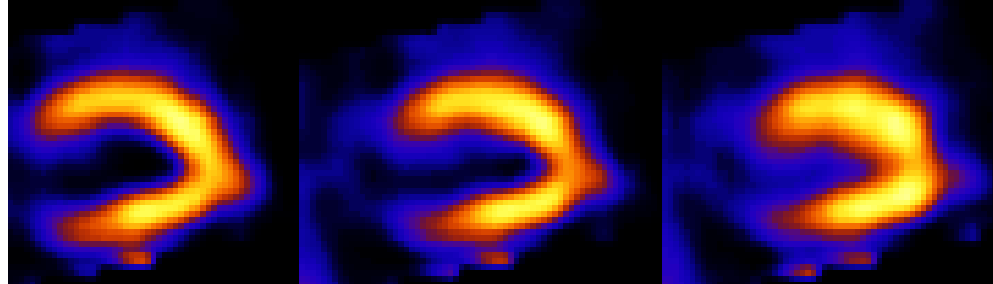
Post PTCA



Acute

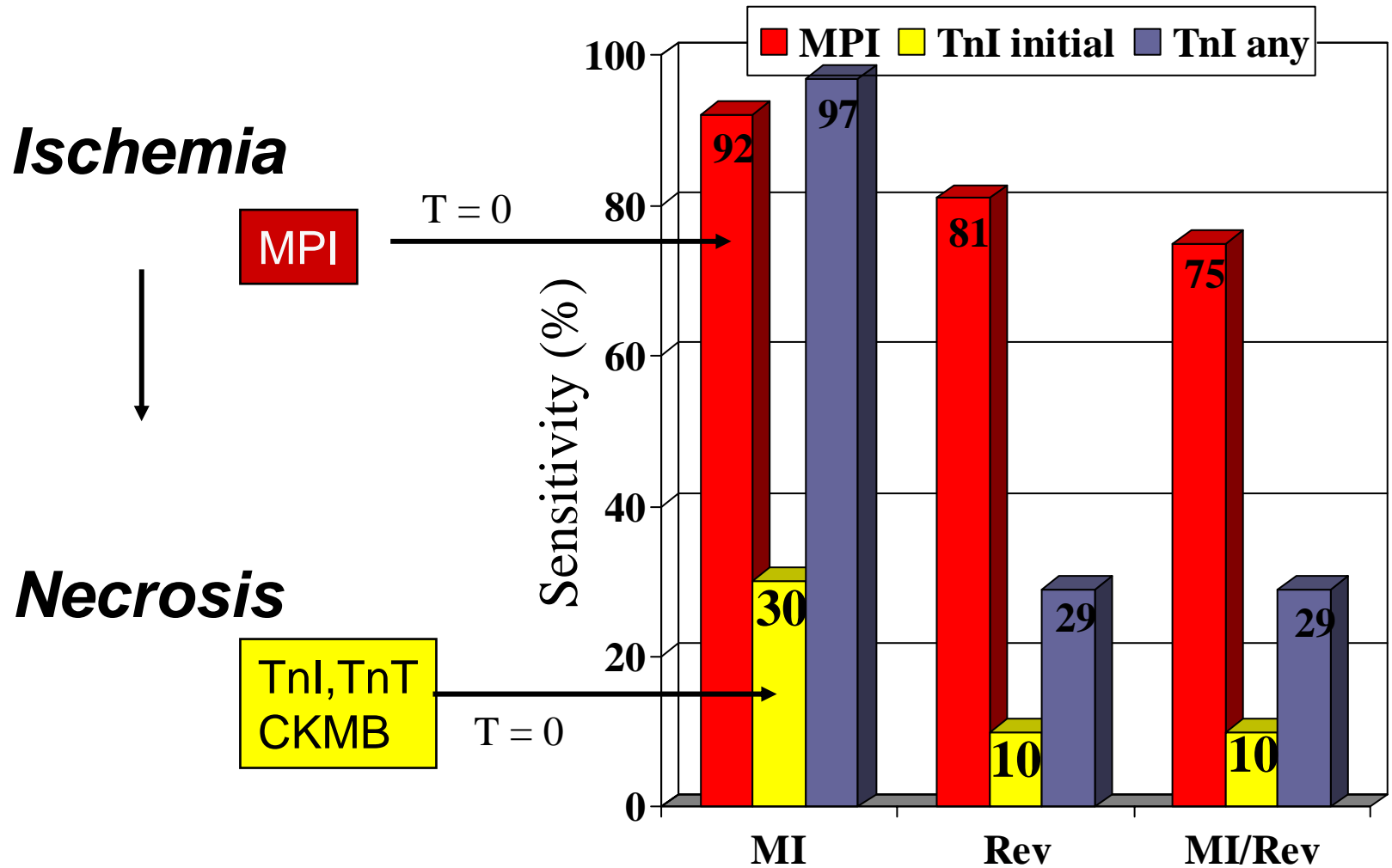


Post PTCA



# Detection of ACS

## Early Sensitivity of MPI vs TnI

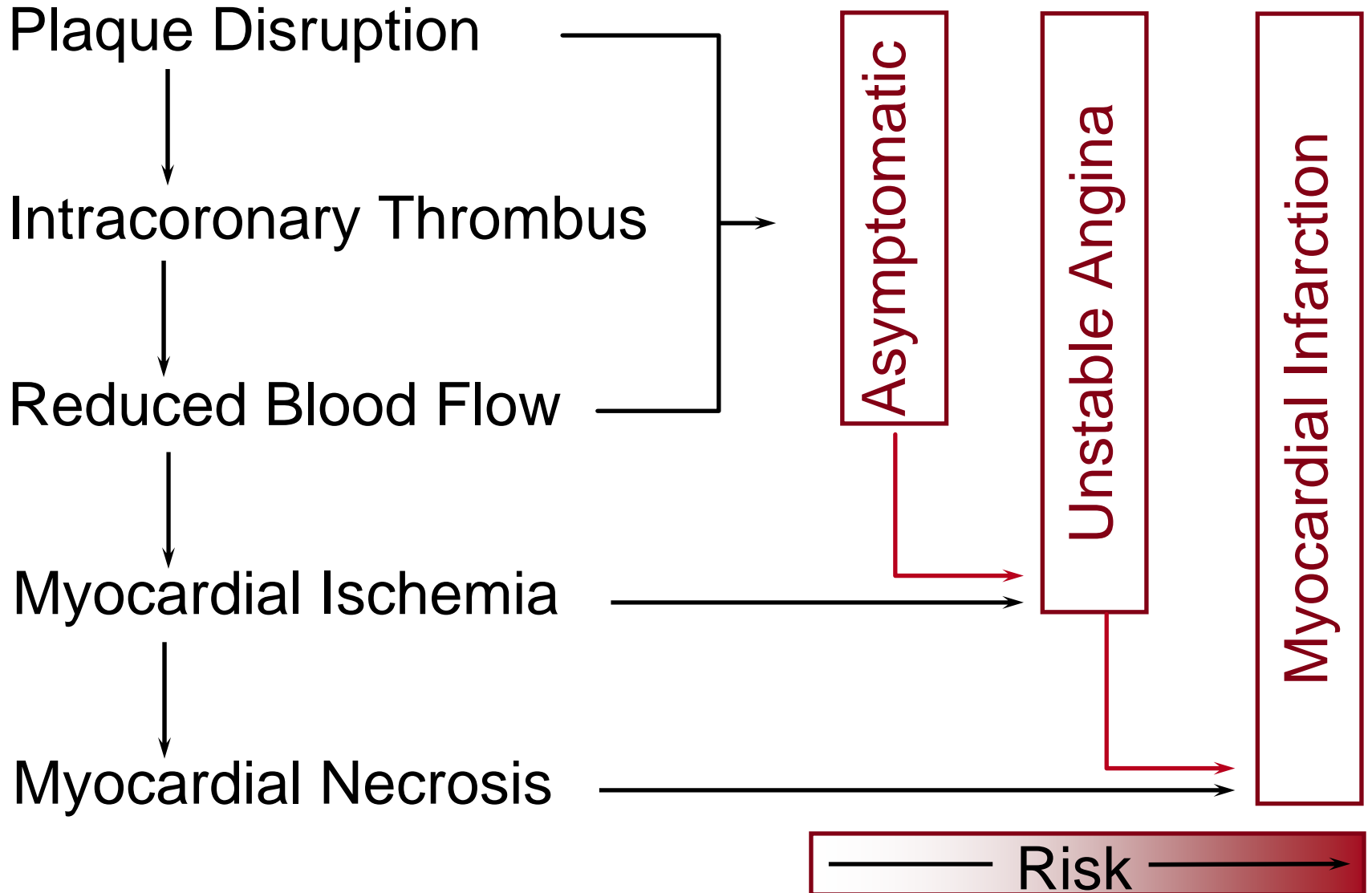


# Biomarkers in the Clinical Approach to ACS

1. Identification of ↑ risk as a key clinical decision point
2. Intelligent Design – targets and strategies

# Pathophysiology

# Clinical Diagnosis



# Pathophysiology

Plaque Disruption



Intracoronary Thrombus



Reduced Blood Flow



Myocardial Ischemia

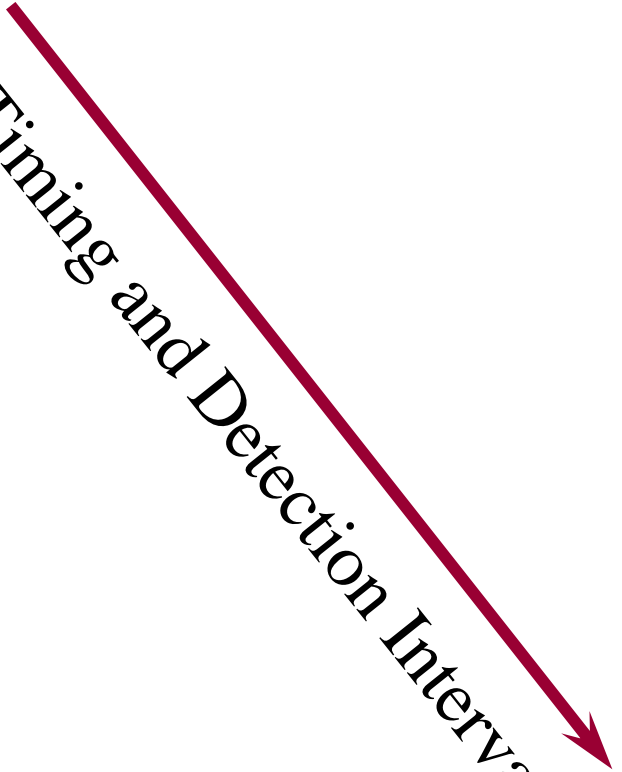


Myocardial Necrosis

Severity of Disease



Timing and Detection Interval



# Pathophysiology

Plaque Disruption

Inflammation

CRP, IL-6, MMP  
Thermography

Biochemical  
Mechanical

Intracoronary Thrombus

Platelet Activation  
Clotting Cascade

P-Selectin, D-Dimer, RPFA  
FPA, TPP, sCD-40 Ligand

Mechanical  
Biochemical

Reduced Blood Flow

Coronary flow

MPI, Angiography  
Flow wire, echo doppler

Imaging  
Mechanical

Myocardial Ischemia

Ischemia

ECG,  
Wall Motion (echo, MPI)  
IMA, BNP, MDA-LDL, FFA

Electrical  
Imaging  
Biochemical

Myocardial Necrosis

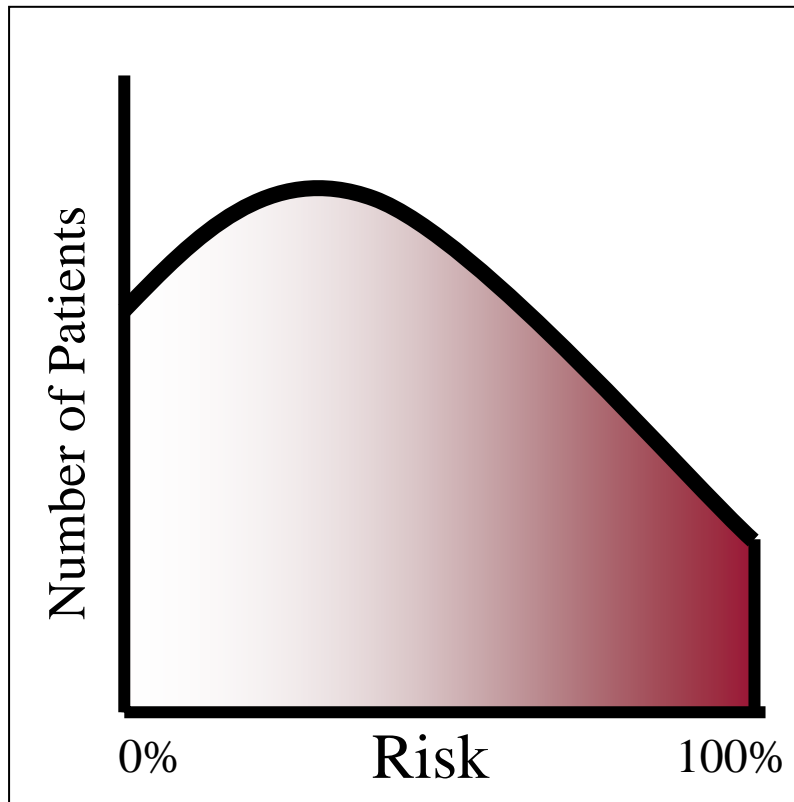
Necrosis  
Scar

TnT, Tnl, CKMB, Myoglobin  
Wall Motion

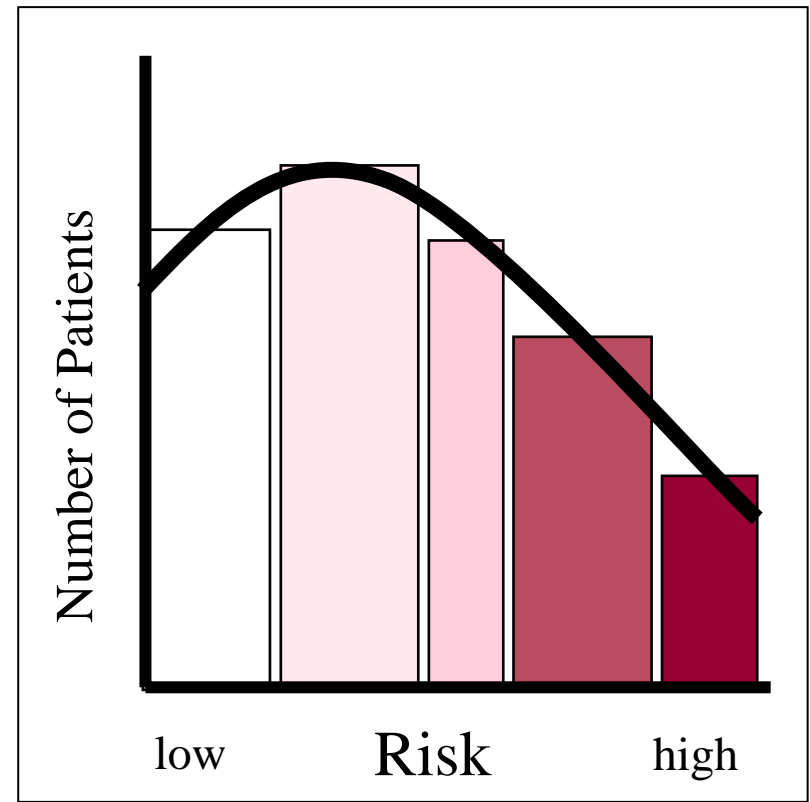
Biochemical  
Imaging

# Evaluation of Patients with Suspected ACS

## Risk as a Discrete and Actionable Value



A. Risk as a Continuous Variable

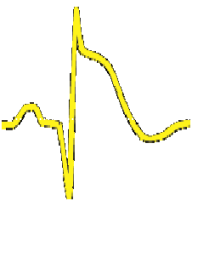
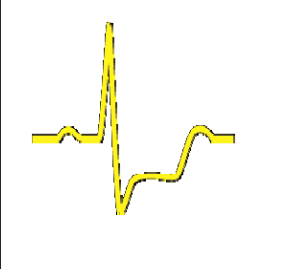
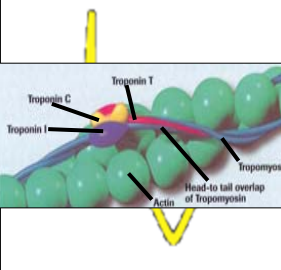
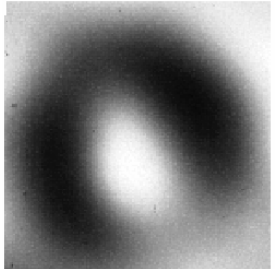


B. Risk as Defined Groups

# Evaluation of Acute Coronary Syndromes

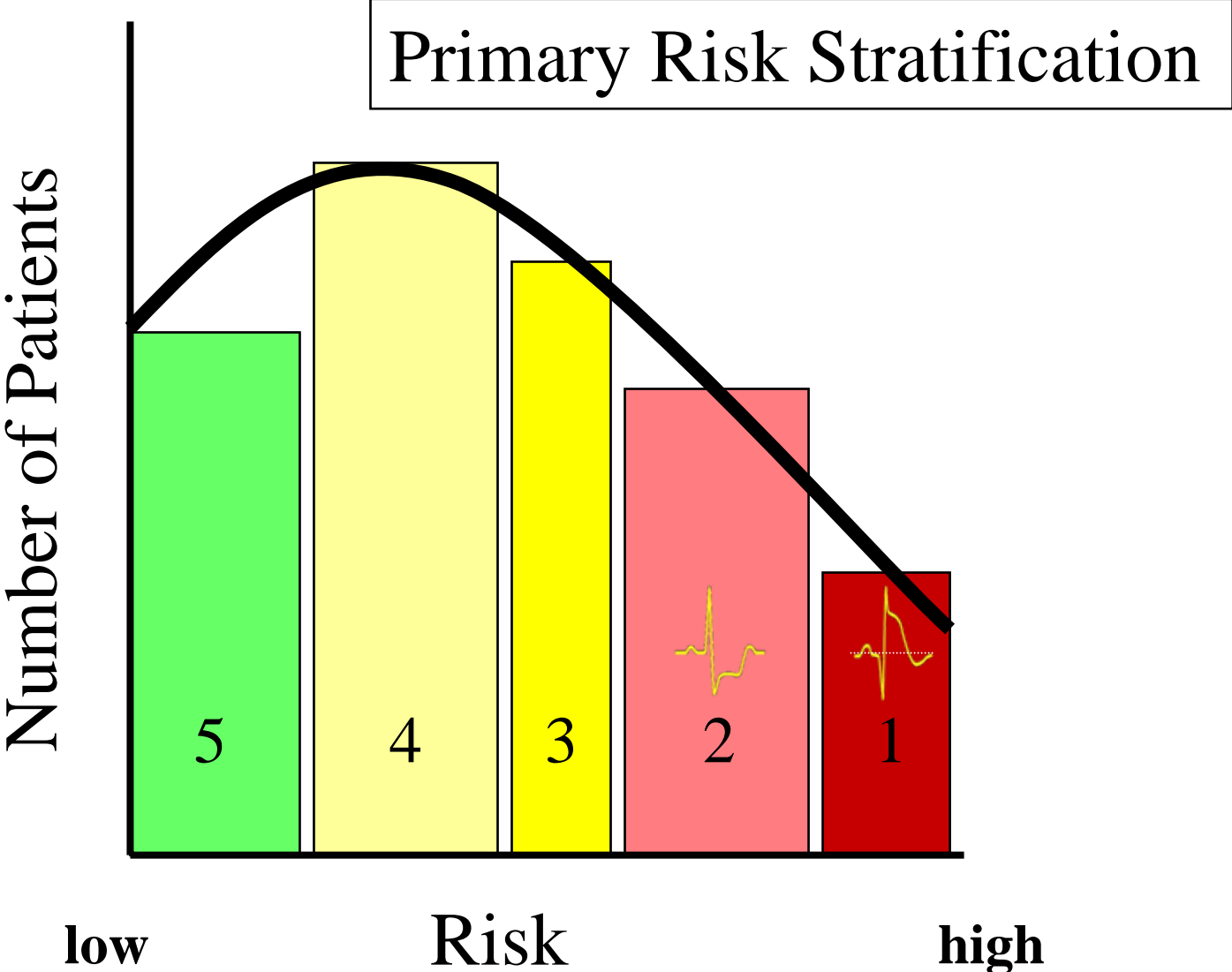
Necrosis is Present

Ischemia is Present

		High	Mod	Low
High				
Mod				
Low				Non ACS

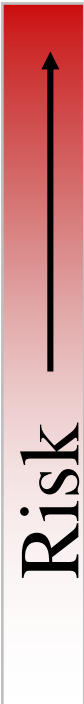
\* AMI = necrosis + ischemia

# Evaluation of Chest Pain



# ACT Strategy for Evaluation and Triage

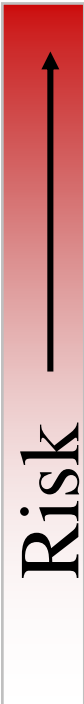
## Risk Based and Goal Driven Strategy



Level	Risk	Goal		Time to Goal
		Primary	Secondary	
1	Very high	Intervention		30 min
2	High	Intervention	Diagnosis	30 min
3	Moderate	Diagnosis	Prevention	8 hours
4	Low	Prognosis	Prevention	3 hours
5	Very low	Alt Diag		N/A

# ACT Strategy for Evaluation and Triage

## Risk Based and Goal Driven Strategy



Level	Risk	Goal		Time to Goal
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1	Very high	Intervention		30 min
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5	Very low	Alt Diag		N/A

# Chest Pain Evaluation

## A Hierarchy of Risk

Rapidly rule-in AMI and initiate therapy



Rapidly rule-in unstable angina and initiate therapy



Rule-out acute coronary syndromes

?

---

---

Fail-safe

Identify stable coronary disease



Identify high risk individuals



Risk factor modification

Fail-safe

Sens > 99%

# Pathophysiology

Plaque Disruption

Inflammation

CRP, IL-6, MMP  
Thermography

Biochemical  
Mechanical

Intracoronary Thrombus

Platelet Activation  
Clotting Cascade

P-Selectin, D-Dimer, RPFA  
FPA, TPP, sCD-40 Ligand

Mechanical  
Biochemical

Reduced Blood Flow

Coronary flow

MPI, Angiography  
Flow wire, echo doppler

Imaging  
Mechanical

Myocardial Ischemia

Ischemia

ECG,  
Wall Motion (echo, MPI)  
IMA, BNP, MDA-LDL, FFA

Electrical  
Imaging  
Biochemical

Myocardial Necrosis

Necrosis  
Scar

TnT, Tnl, CKMB, Myoglobin  
Wall Motion

Biochemical  
Imaging

# Biomarkers in the Clinical Approach to ACS

1. Identification of  $\uparrow$  risk as a key clinical decision point
2. Intelligent Design – targets and strategies
3. Utilization of markers within the context of systematic protocols and pathways

# Diagnostic Strategies for ACS

## Negative

Rule out  
Low  
Low  
High Sensitivity

Throughput

Deferred cost

Missed AMI

## Focus

Goal  
Prevalence  
Risk  
Performance

Outcome

Financial basis

Error effect

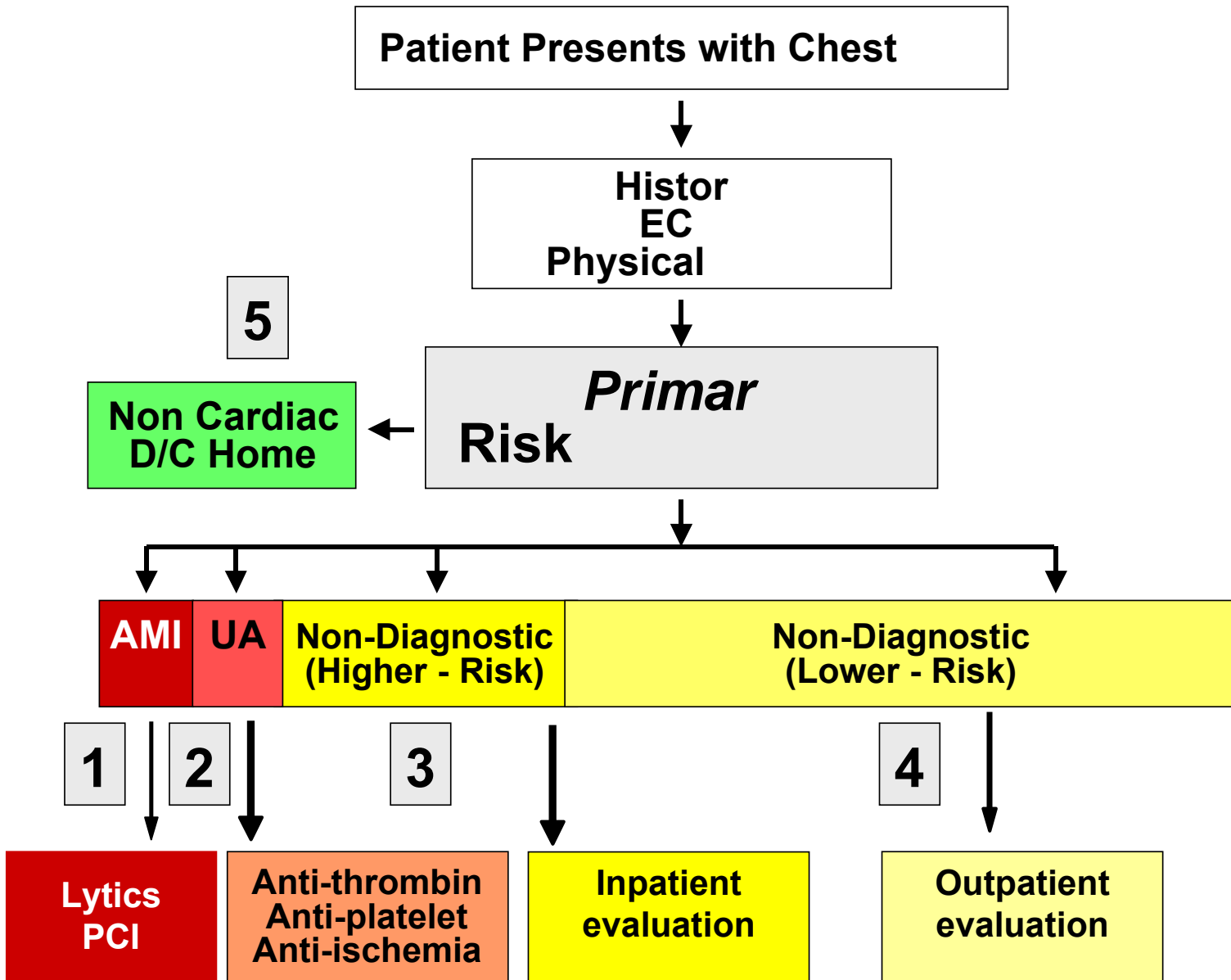
## Positive

Rule in  
High  
High  
High specificity

Appropriate care

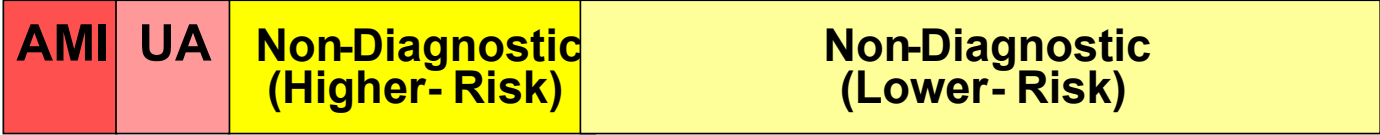
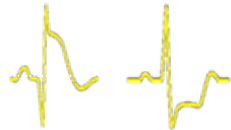
Incurred cost

Unneeded care



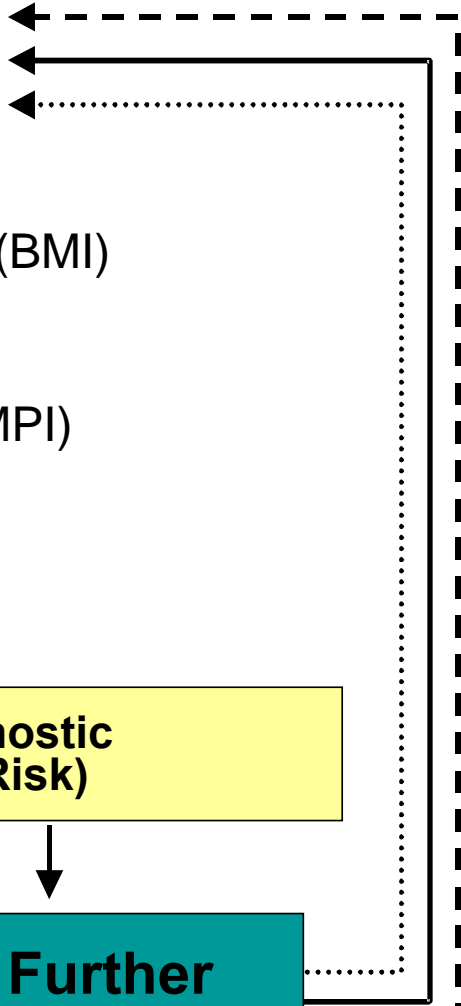
# Secondary Risk

- Biochemical markers of Ischemia (BMI)
- Serial troponin/CKMB (Tn)
- Serial ECG
- Myocardial Perfusion imaging (MPI)
- Stress testing
- Echocardiography
- Angiography

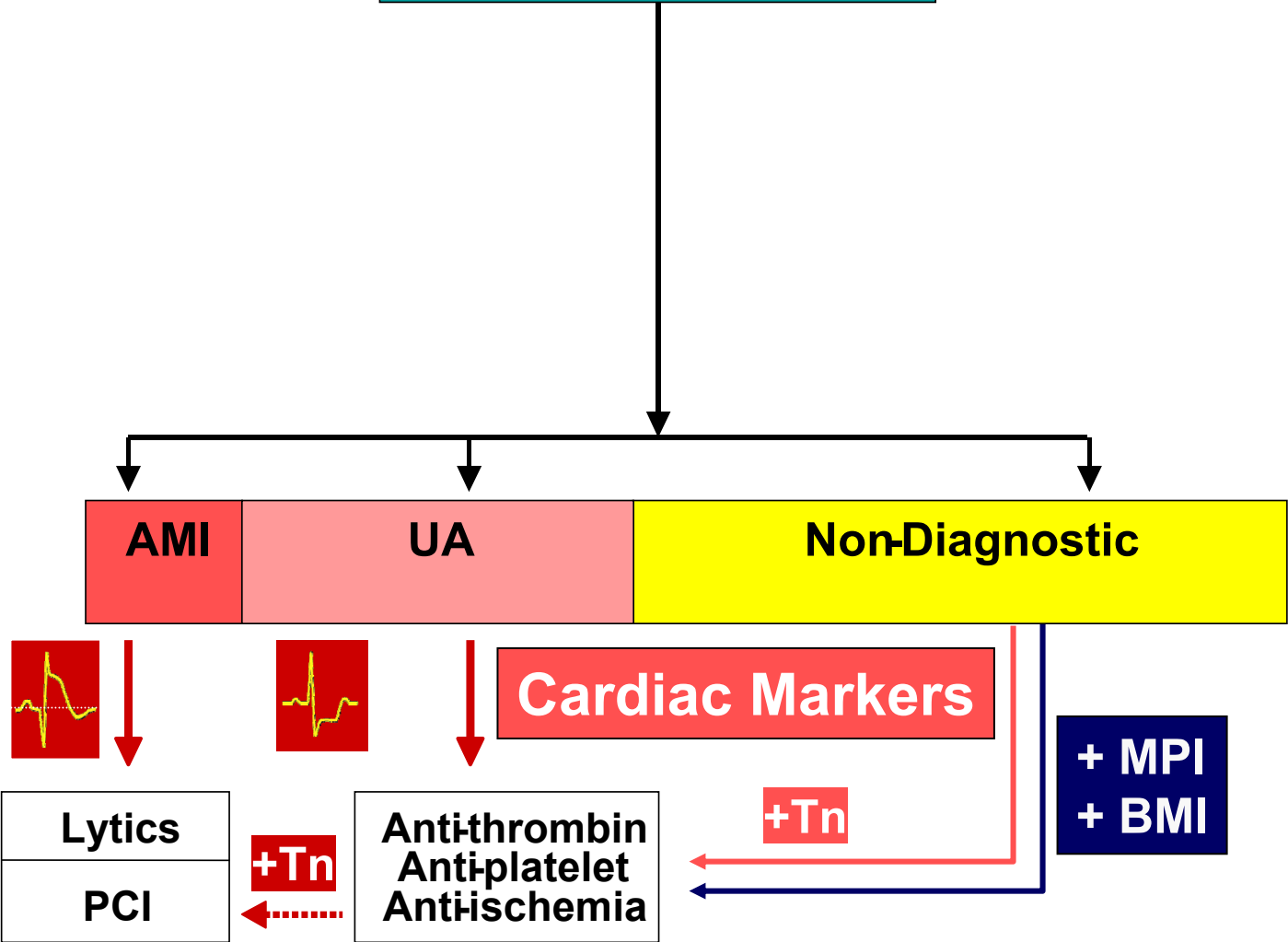


**Treat**

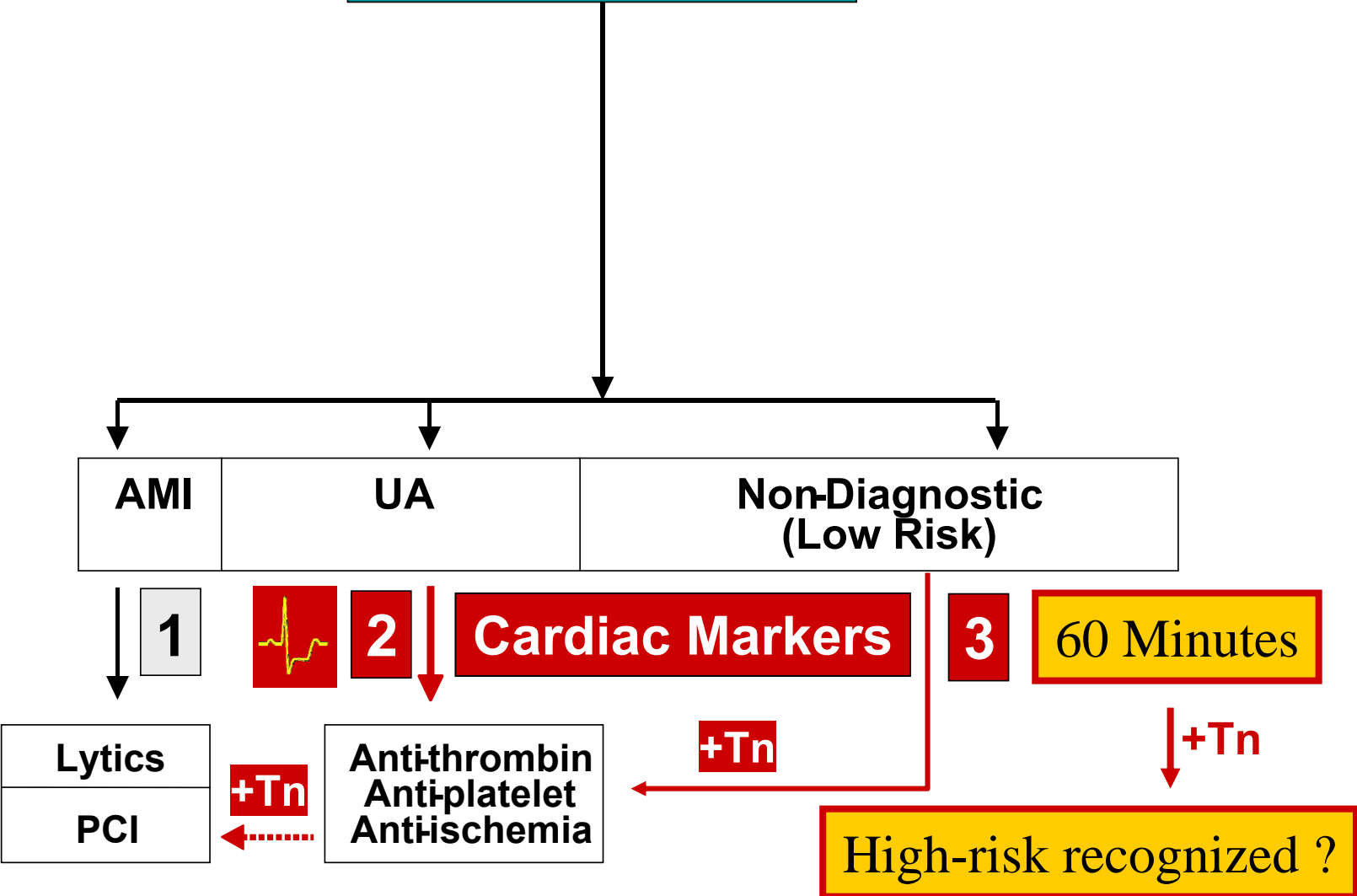
**Further Assessment**



# Secondary Risk

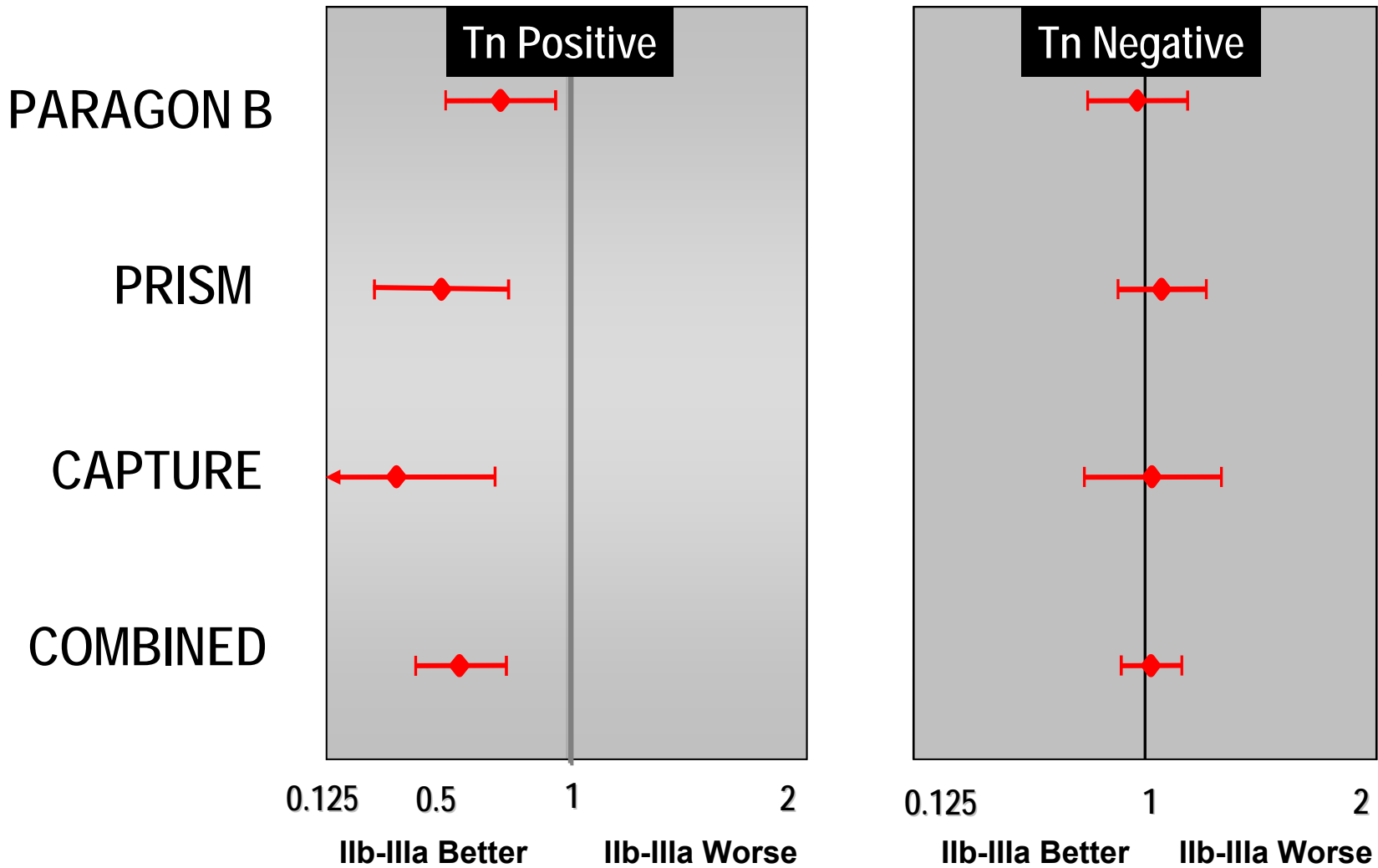


# Secondary Risk



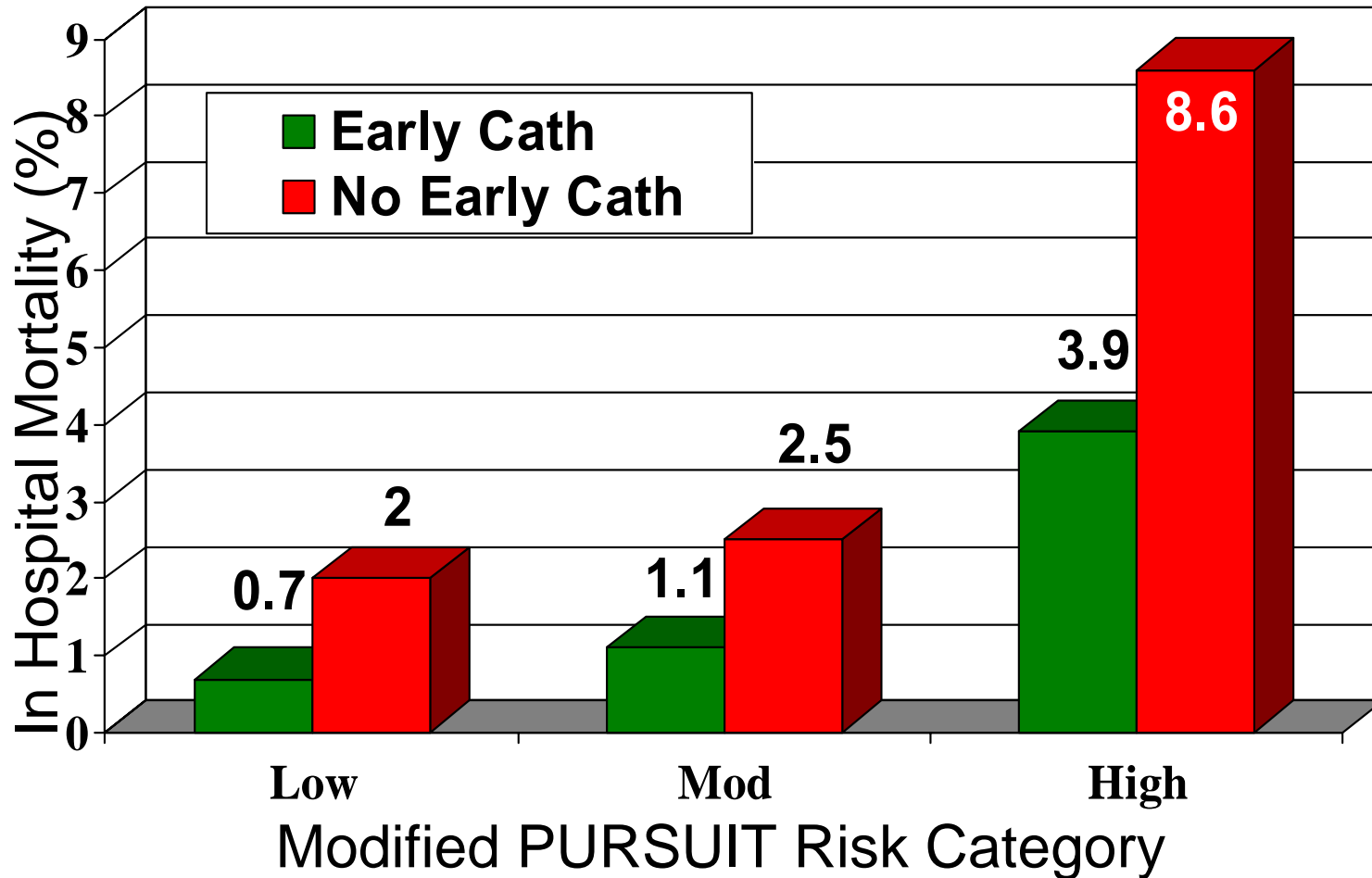
# Benefits of GP IIb-IIIa Inhibition

## Outcome by Troponin Status in NSTEMI ACS



# CRUSADE

## Mortality vs Early Catheterization



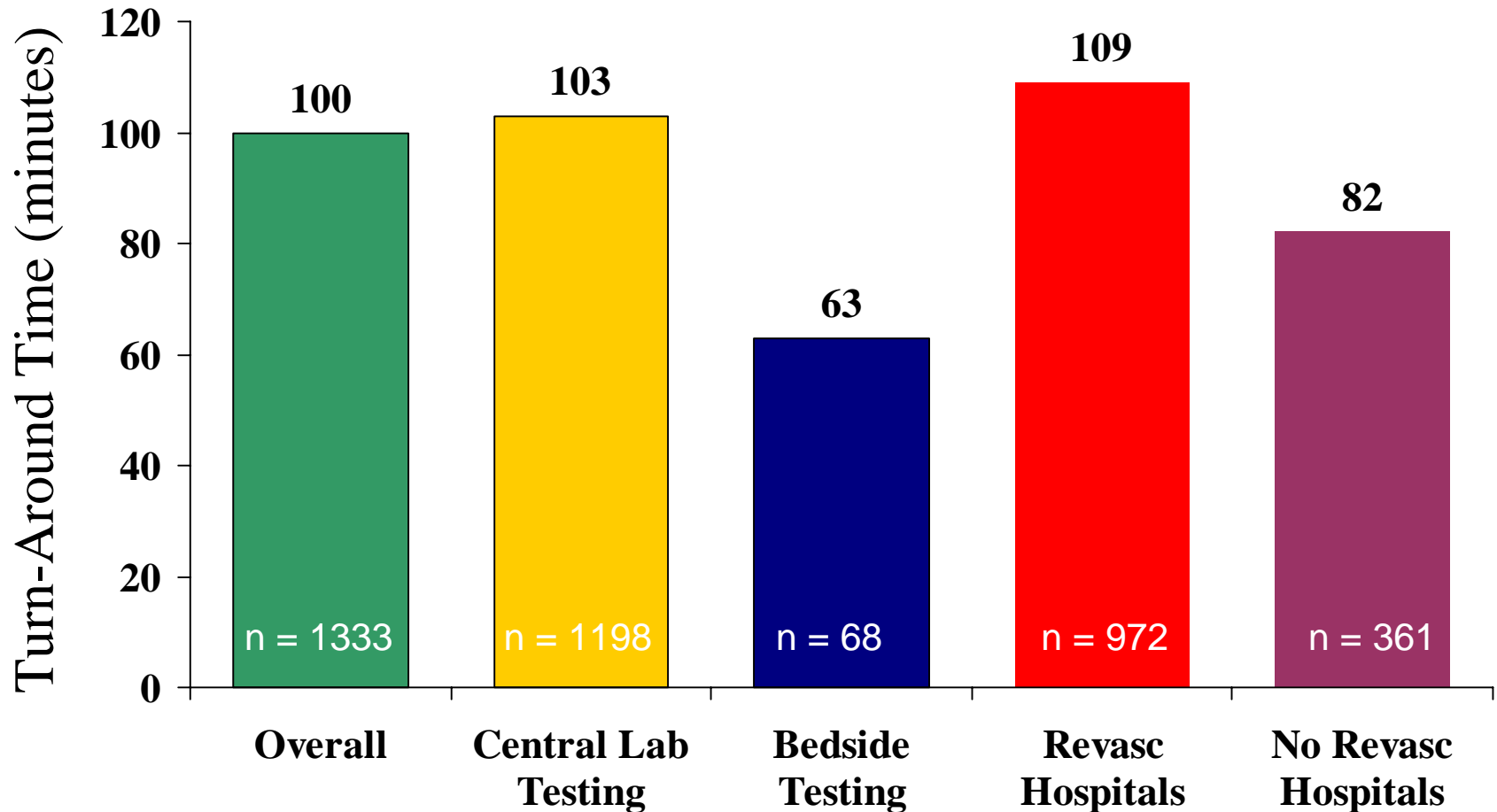
# System Performance Measures

## Troponin Turn-Around Time

- Troponin identifies patients who are at higher risk for poor outcomes and who will benefit most from many treatments
- ACC/AHA and NACB/AACC recommend 60 minute turnaround for troponin

# Troponin Turnaround Times in the ED

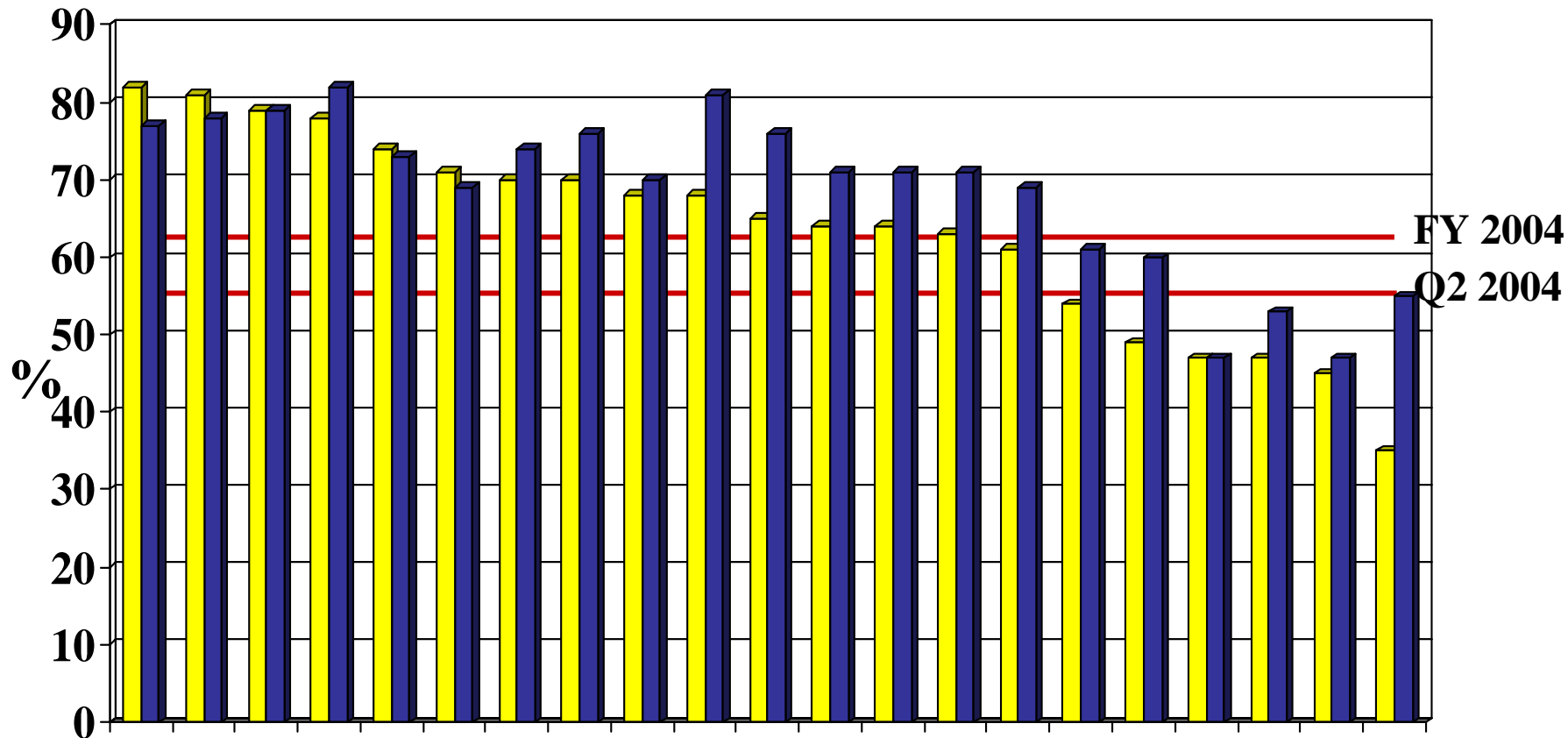
## 26 U.S. CRUSADE Hospitals



Vein-to-brain = time from blood draw until troponin results reach the physician

# VHA Performance Measures

## Troponin Turnaround < 60 Min

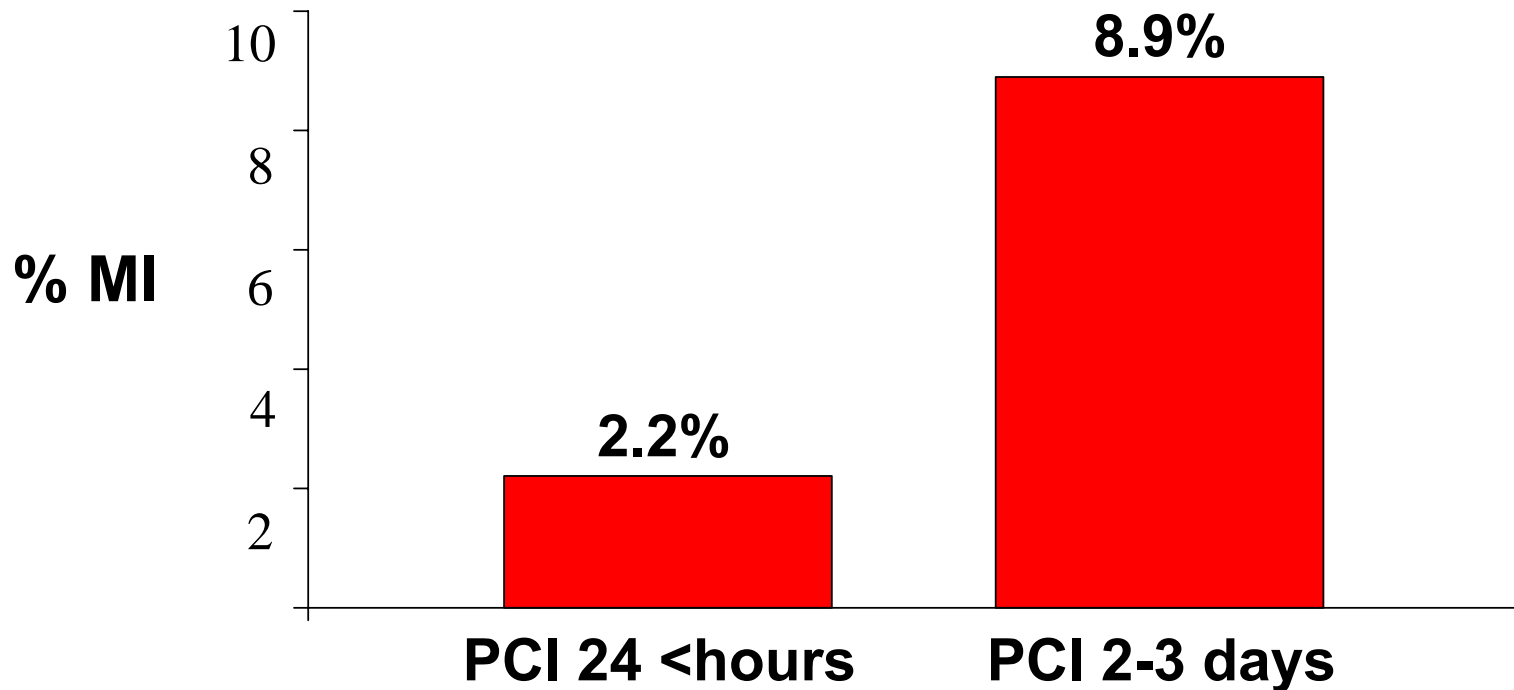


By VISN

The explicit goal in ACS must be to identify high risk patients early and to prevent any necrosis !

# Incidence of MI Prior to PCI

## Patients with Non-ST Elevation ACS



Post-randomization analysis





# Predictive Value of CRP in Unstable Angina

## Early and Late outcomes relative to TnI

- Capture Study n=447
  - High risk ACS pts
  - All underwent PCI
  - F/u for 6 months
- CRP (Behring) } baseline
- TnT (Elecsys) }

\**TnT predicts early events*

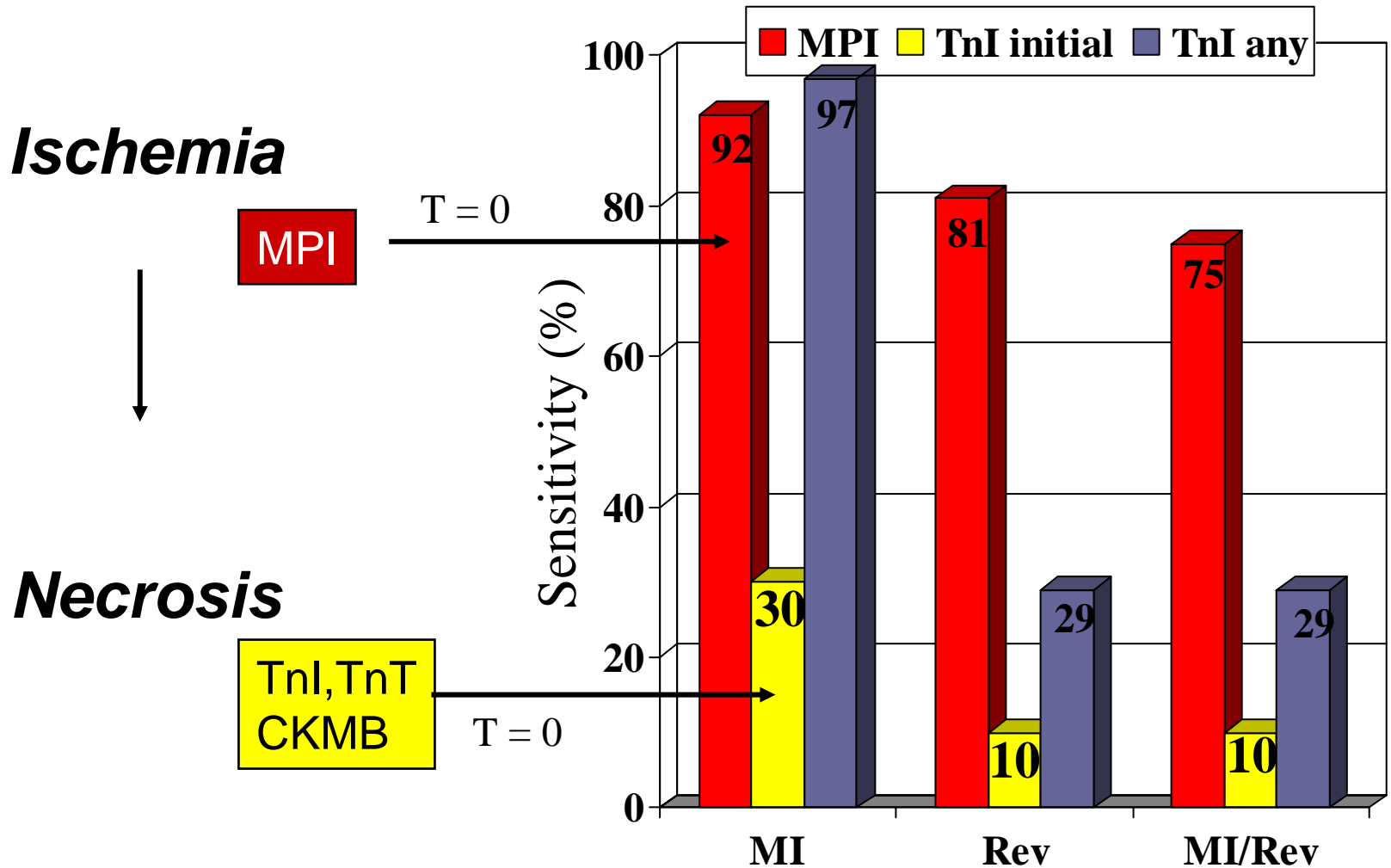
\**CRP predicts late events*

Heeschen, JACC. 35:1535-1542, 2000

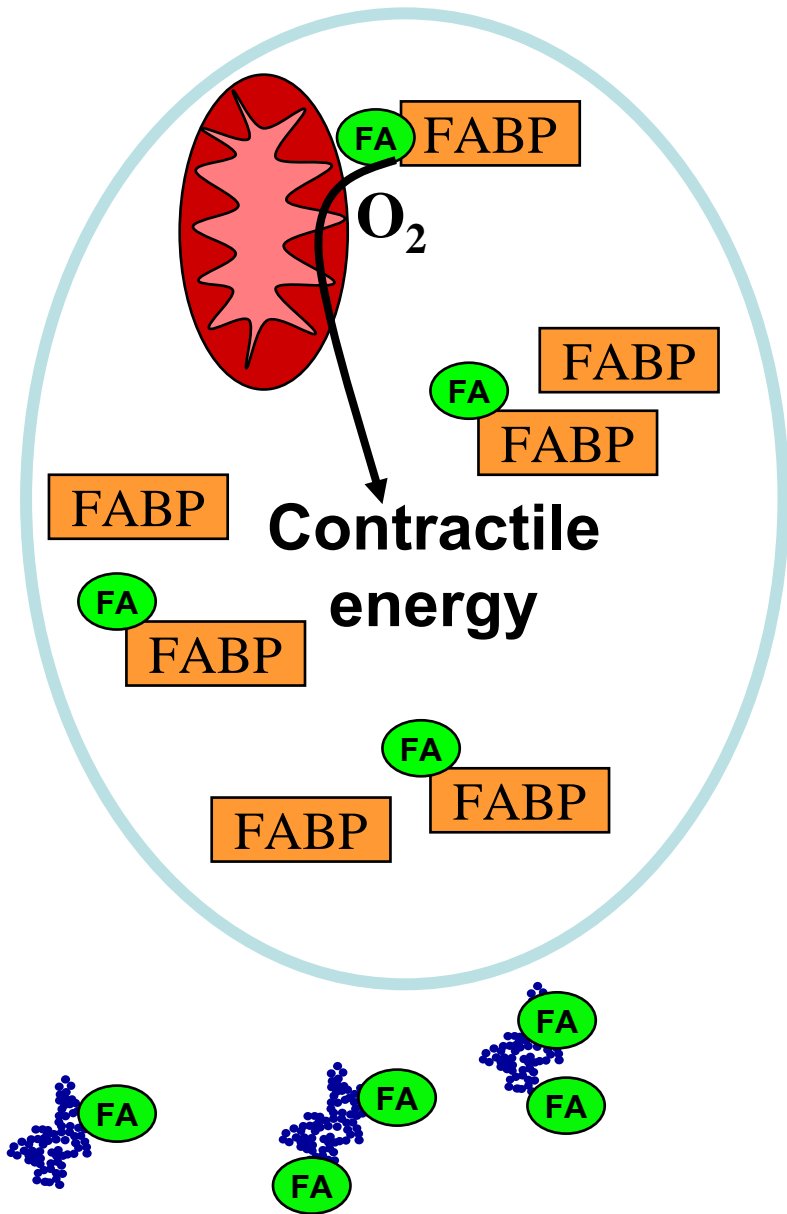
	<u>Death/AMI</u>		
	Yes	no	<i>p</i>
48 hrs			
<b>TnI +</b>	<b>17.4</b>	<b>4.2</b>	<b>.001</b>
CRP +	10.3	8.4	.41
6 mo			
<b>CRP +</b>	<b>18.9</b>	<b>9.5</b>	<b>.003</b>
<hr/>			
	<u>Restenosis</u>		
6 mo			
TnI +	3.0	4.5	.49
<b>CRP +</b>	<b>7.0</b>	<b>2.3</b>	<b>.03</b>

# Detection of Ischemia in ACS

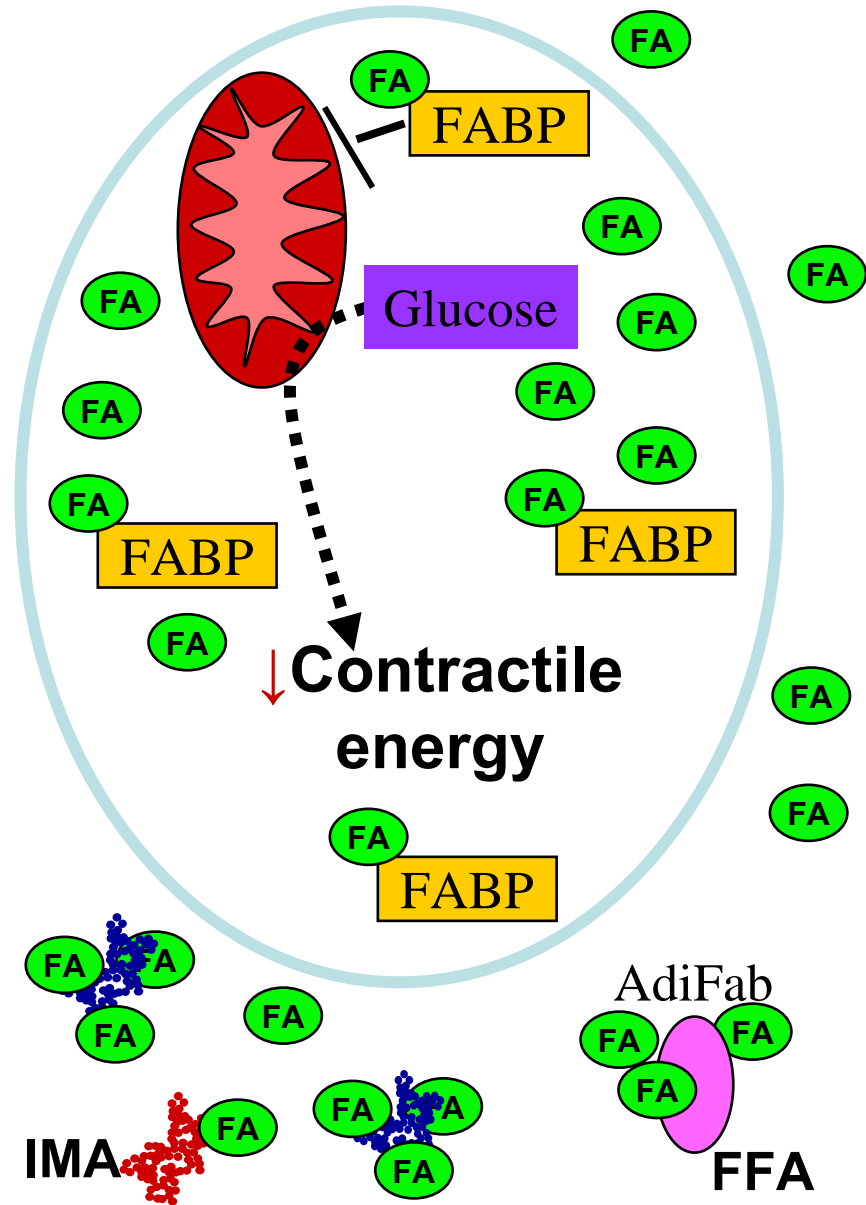
## Early Sensitivity of MPI vs TnI



O<sub>2</sub>



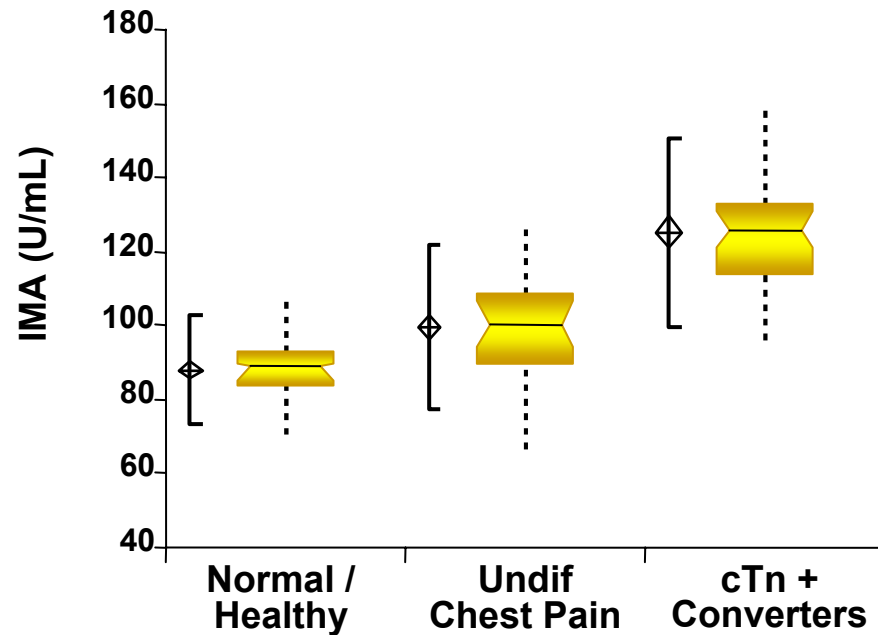
Ischemia



# IMA Values

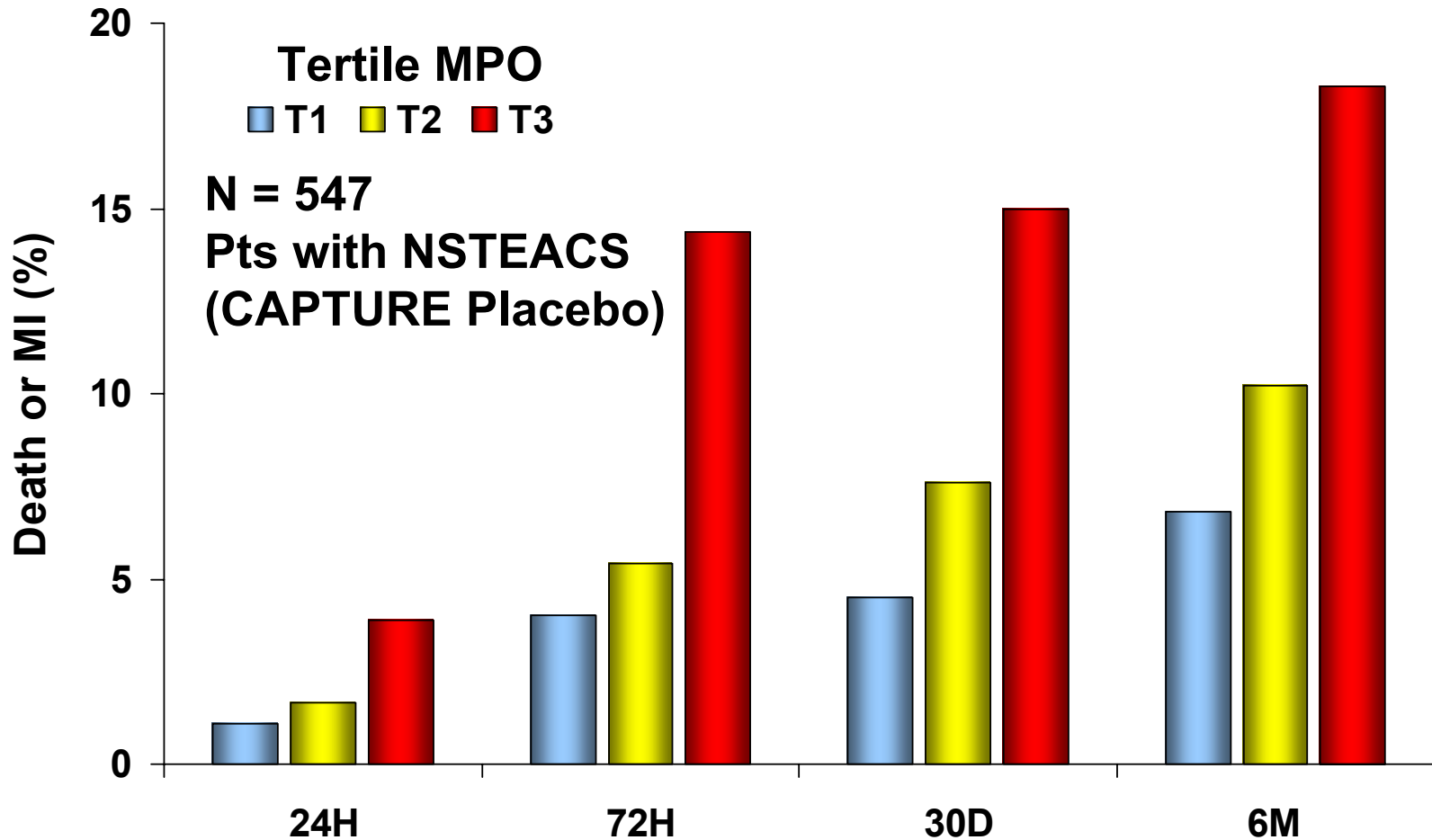
## Normal and Chest Pain Populations

- Median IMA levels were significantly higher in patients with ACS vs NICEP, with UA vs NICEP, and UA vs AMI

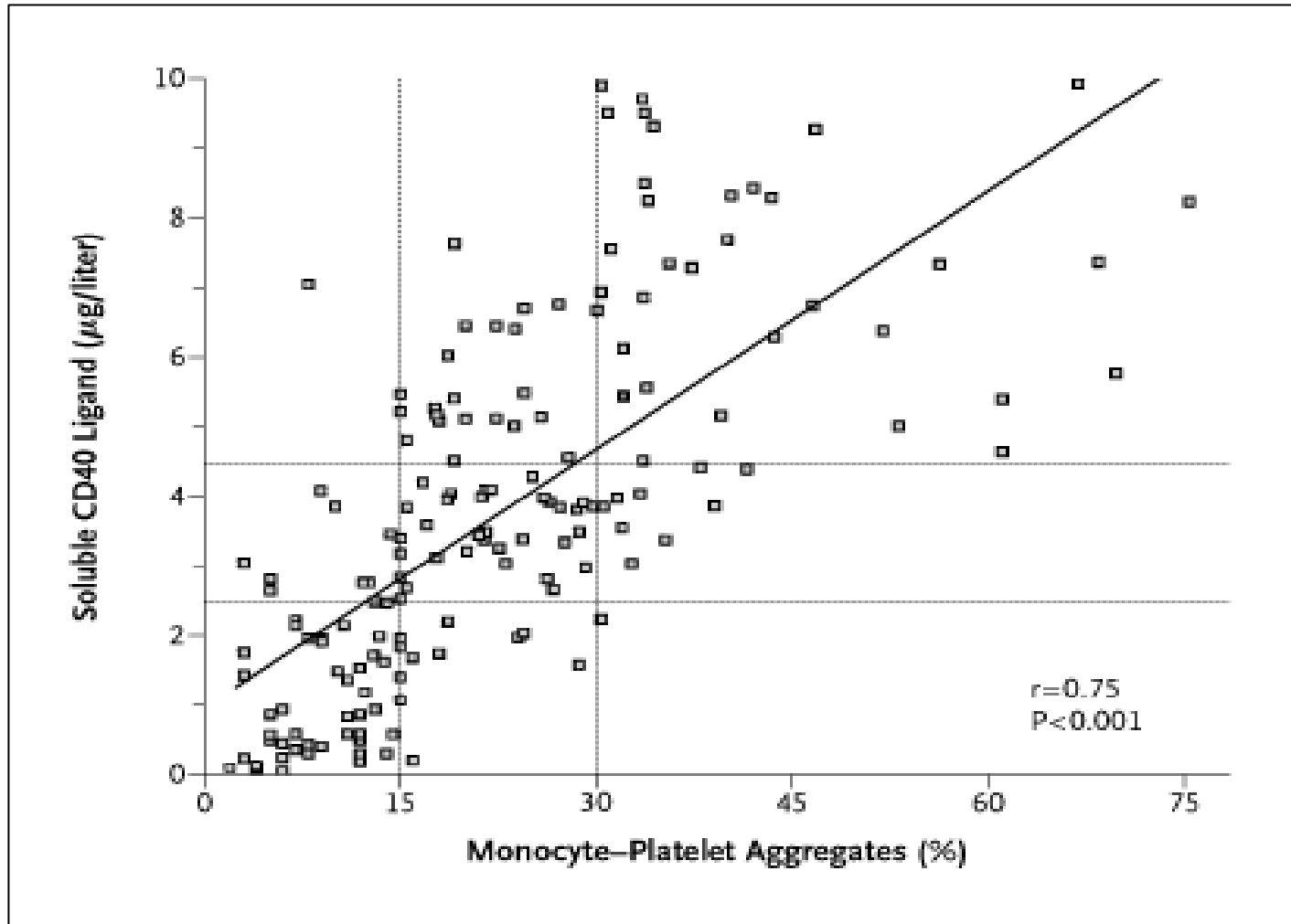


Population	N	Median IMA U/mL	95% CI
Normal/Healthy	69	89.0	85 - 90
Undifferentiated CP	78	100	94 - 107
cTn + Converters	53	126	121-131

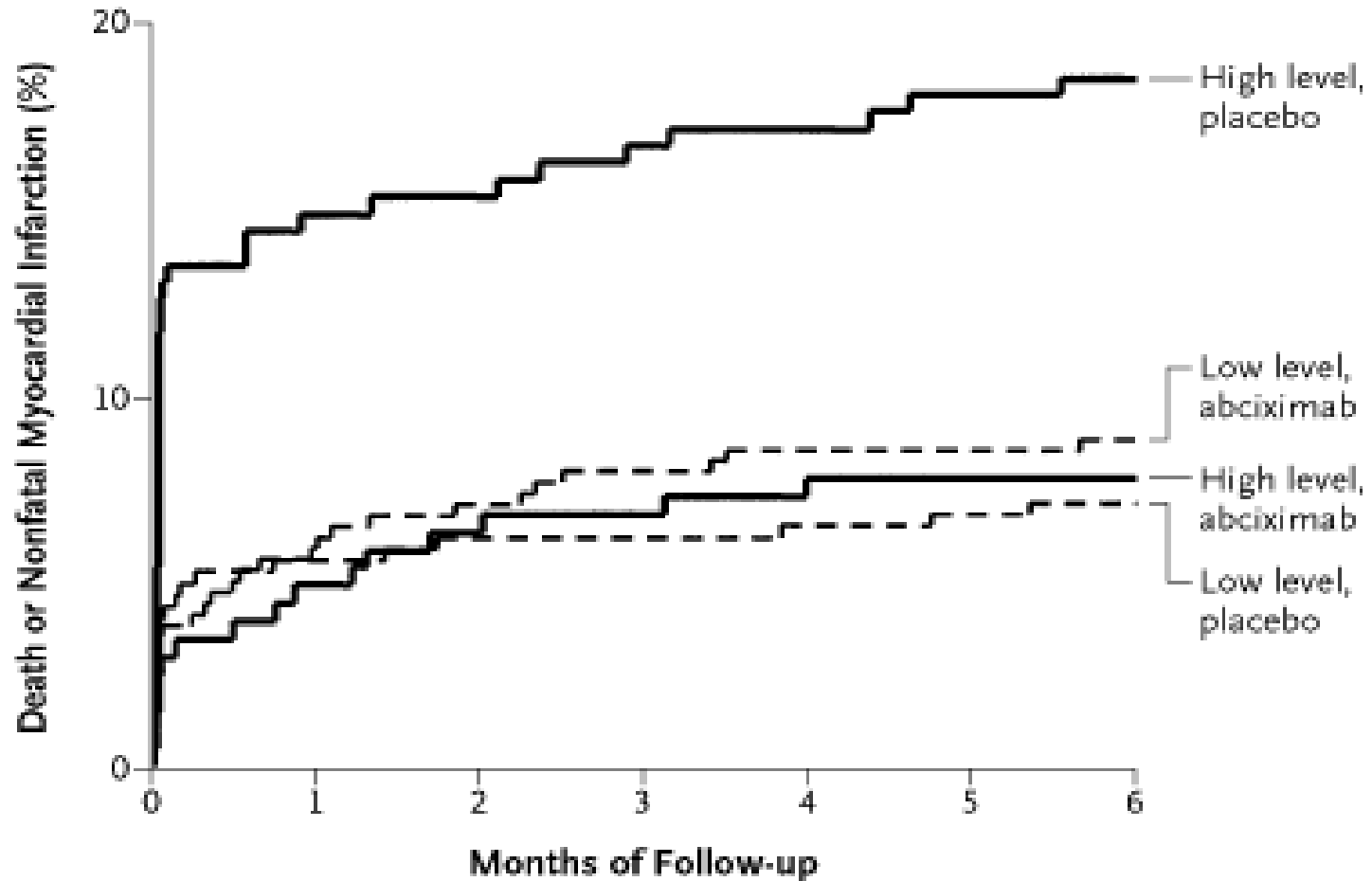
# Myeloperoxidase (MPO) in ACS



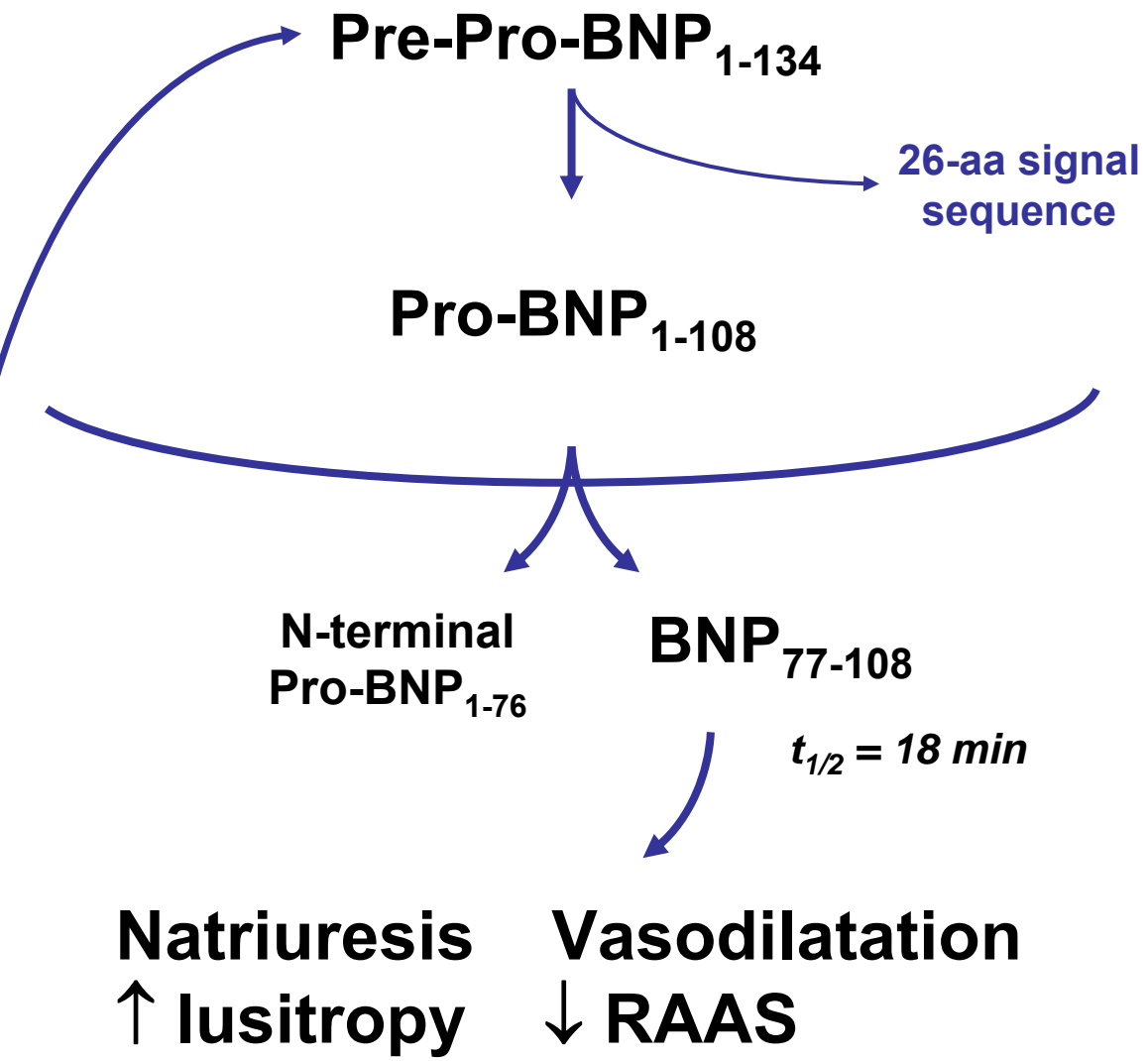
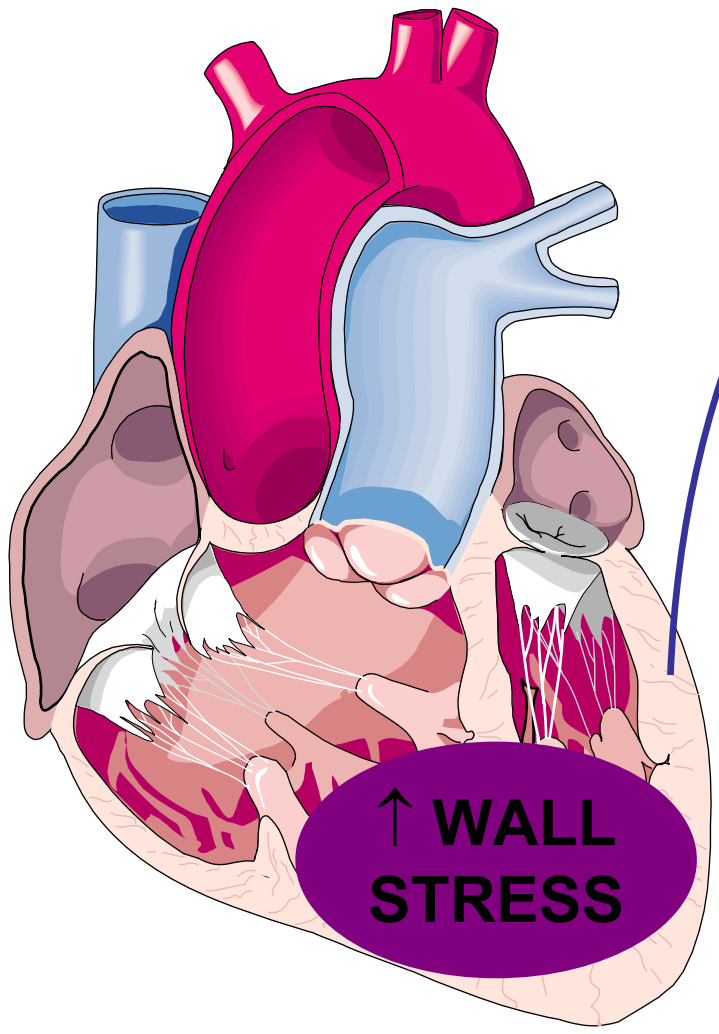
# sCD40 Ligand and Platelet Activation



# sCD40 Ligand

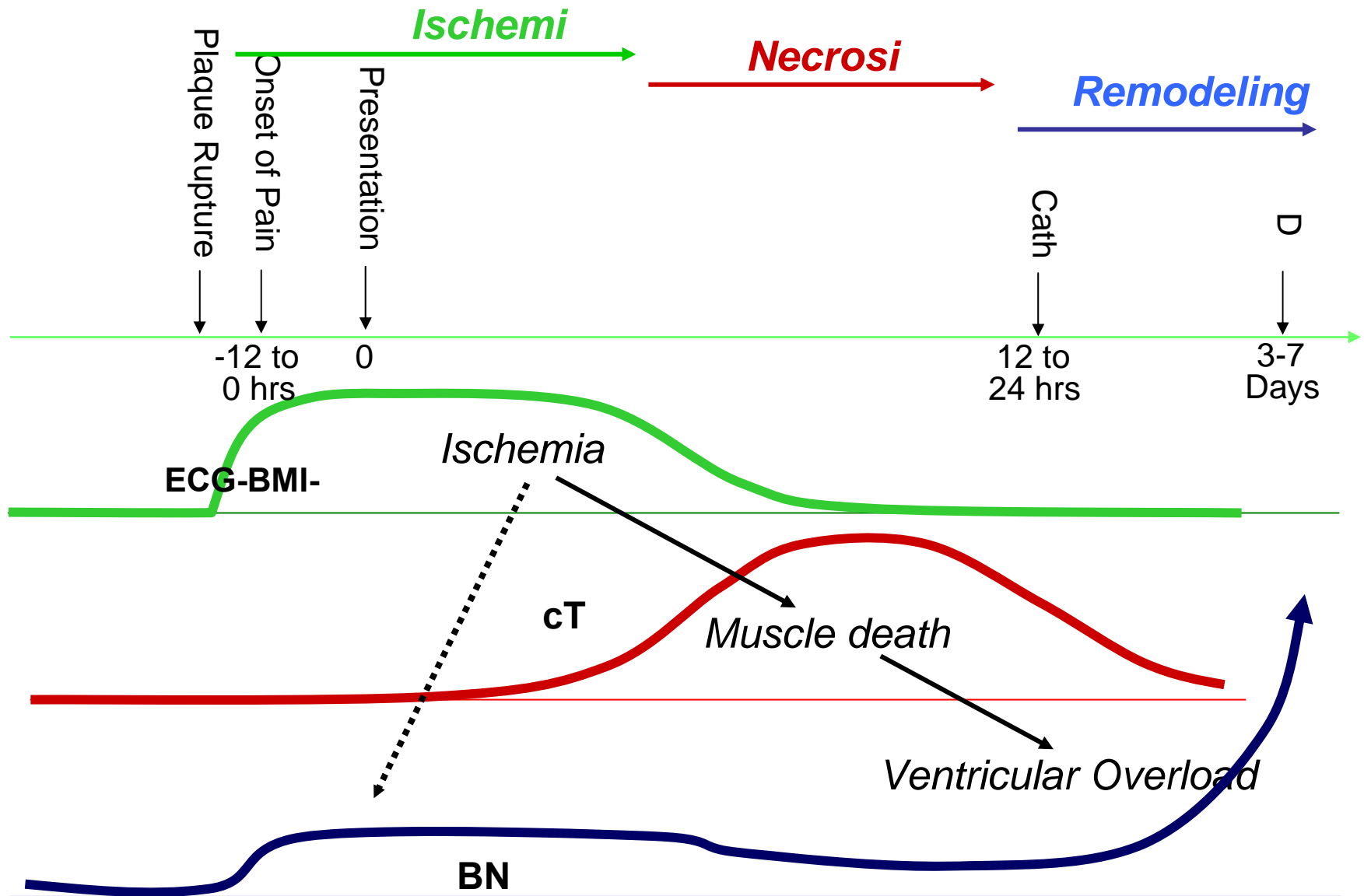


# B-type Natriuretic Peptide (BNP)

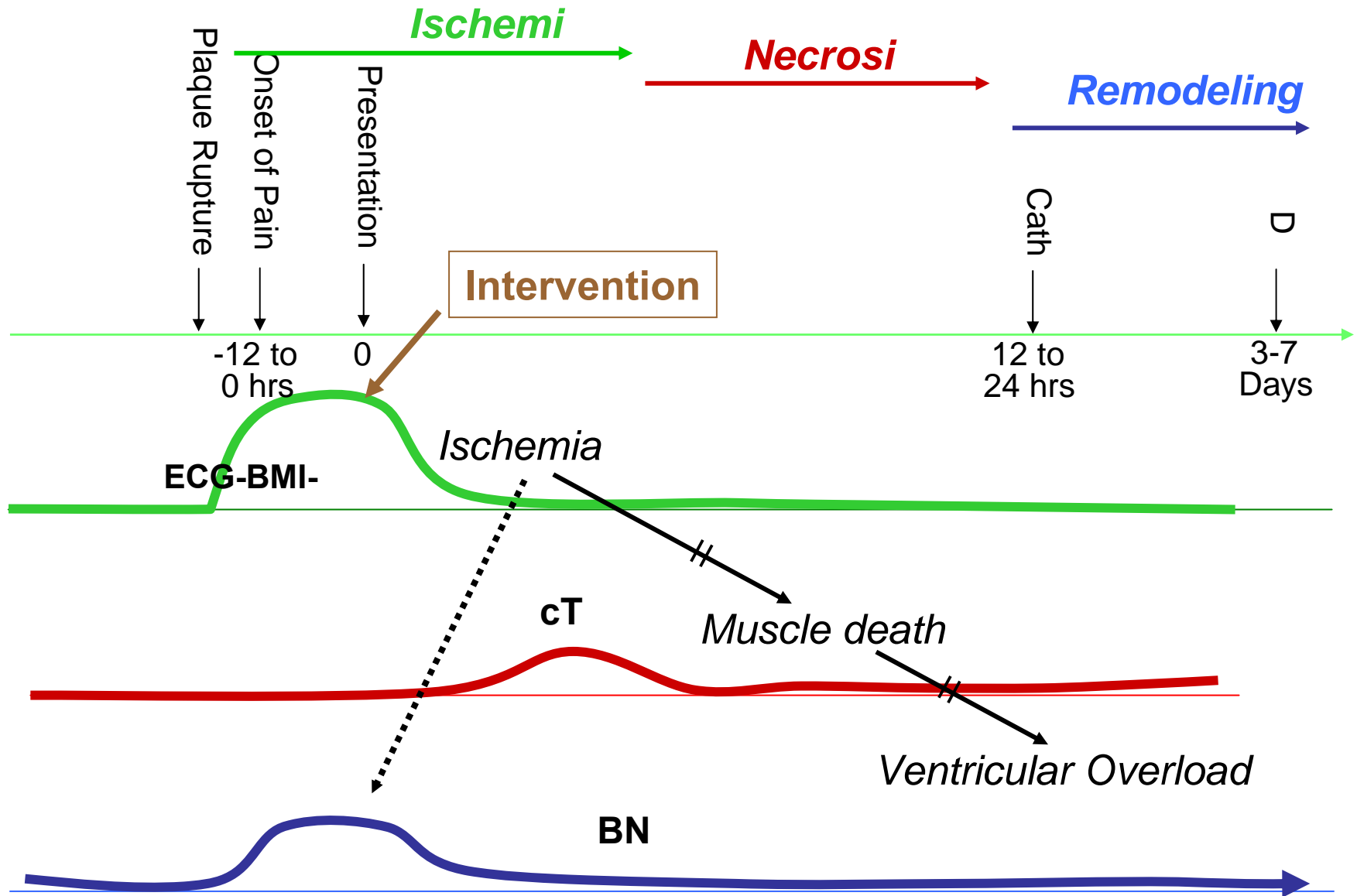




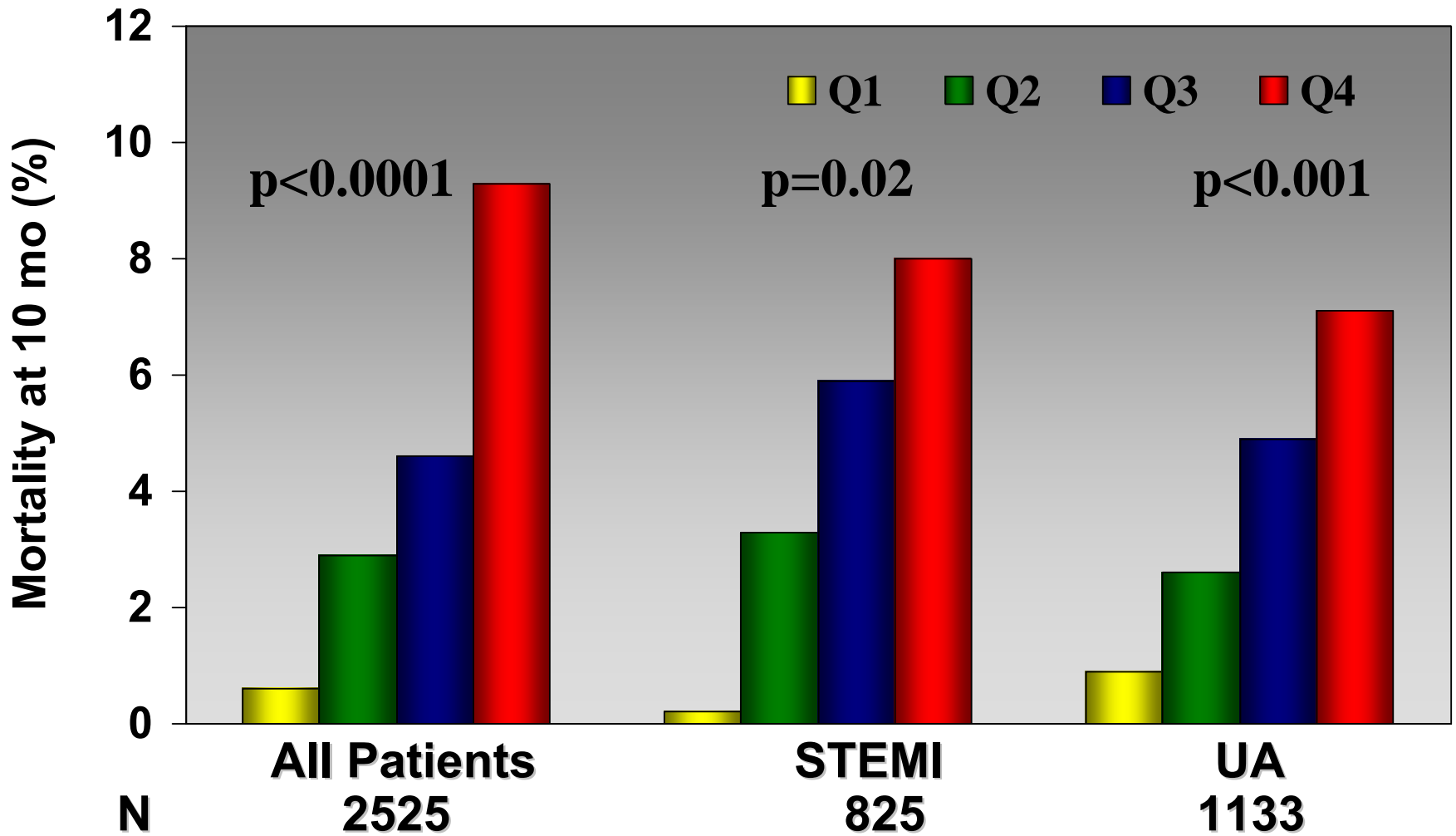
# Acute Coronary Syndromes



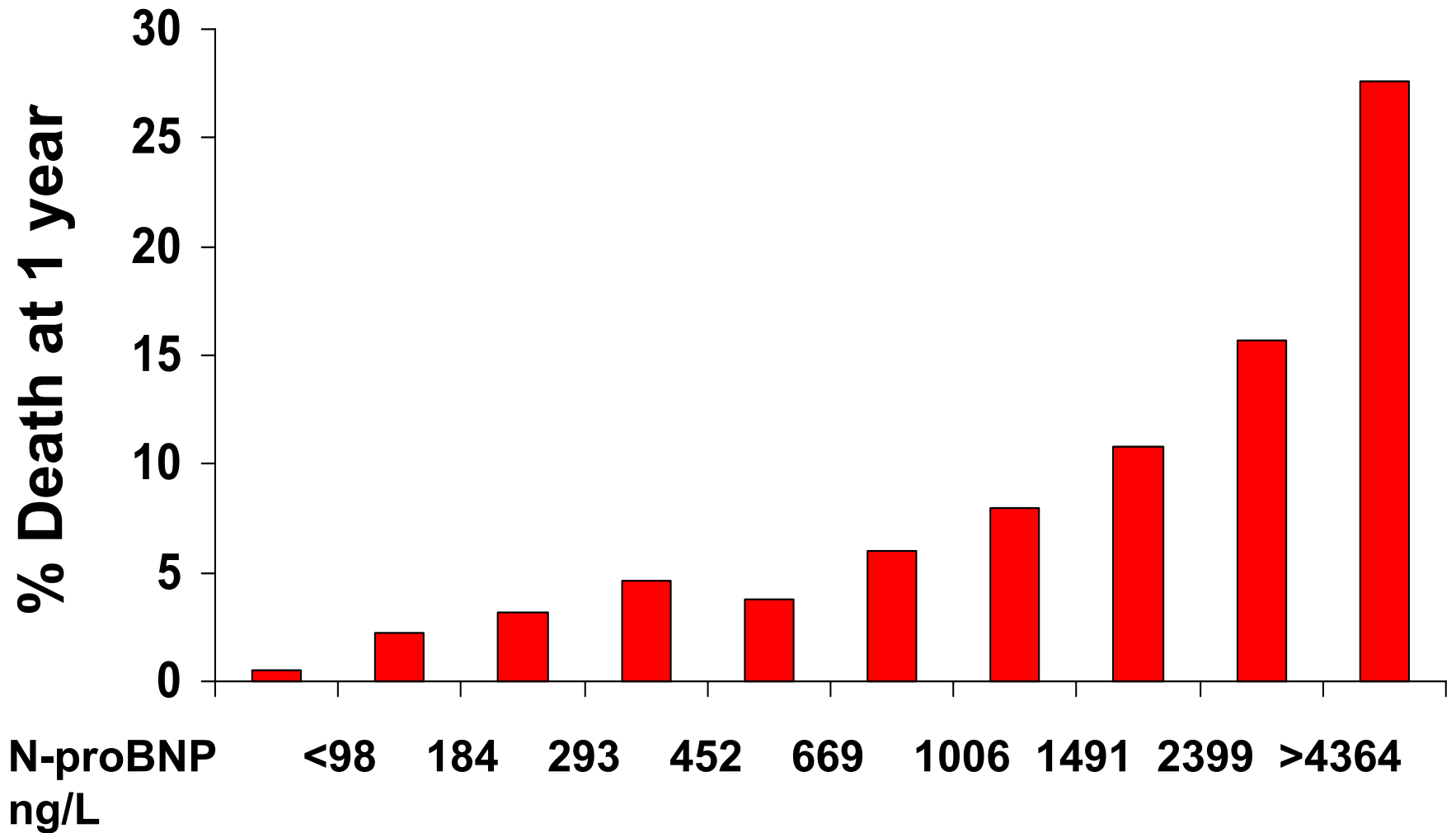
# Acute Coronary Syndromes



# BNP & Risk of Death

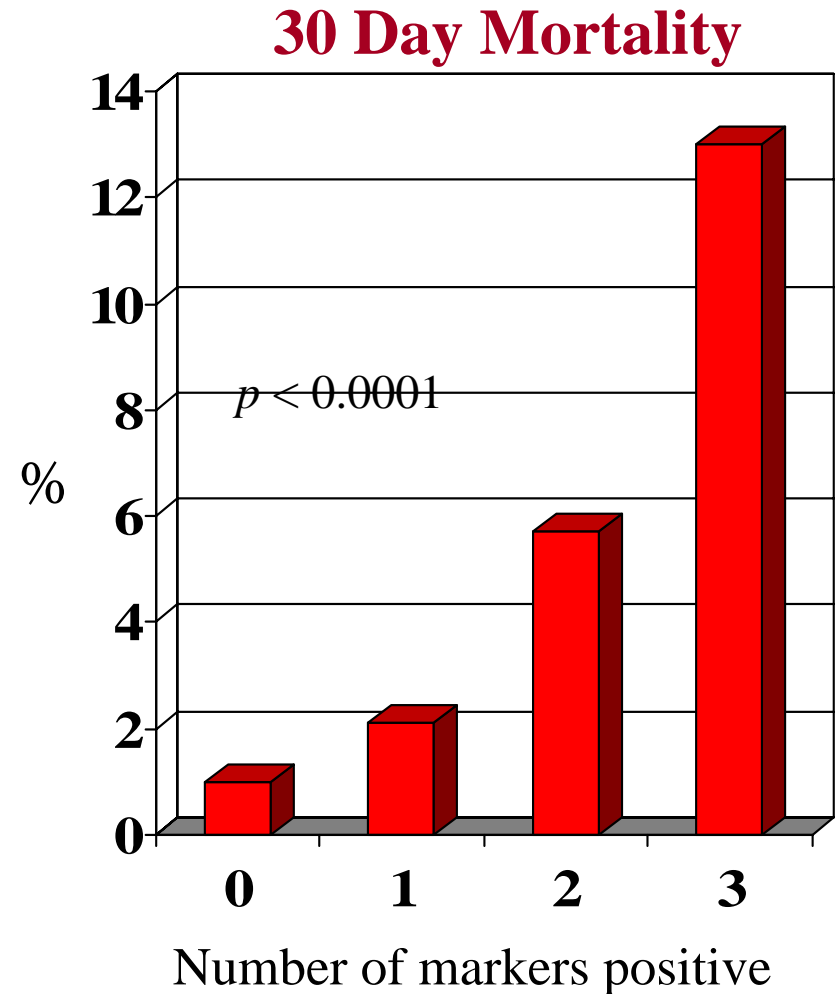


# N-proBNP in ACS



# Multi-marker Risk Stratification in ACS

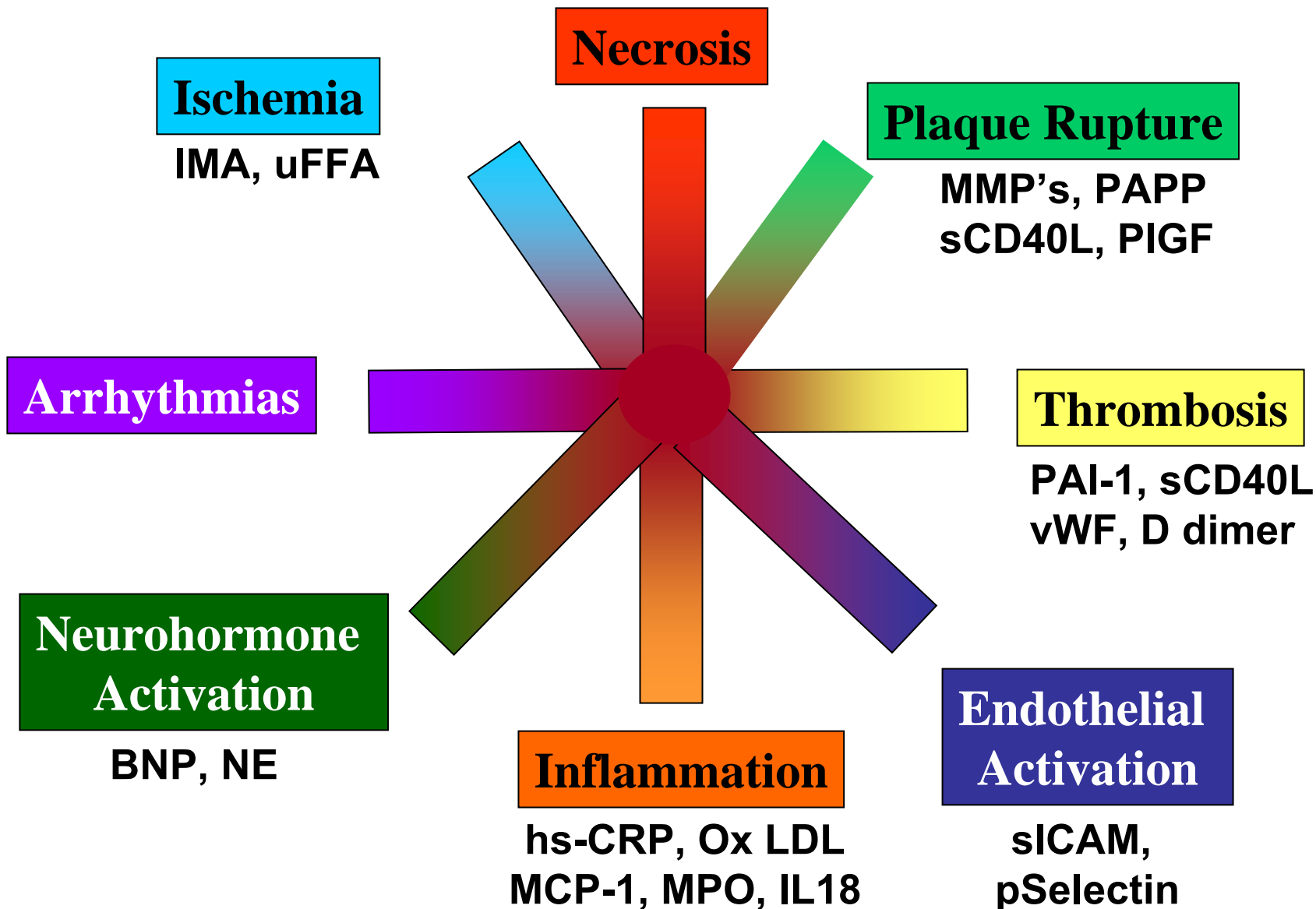
- **TACTICS – TIMI 18**
- **Tnl** – 0.1 ng/mL  
– Bayer ACS
- **hs-CRP** – 1.5 mg/dL  
– Dade-Behring
- **BNP** – 80 pg/mL  
– Biosite





# Potential Biomarker Targets in ACS

cTnT, cTnI, Myo, CKMB, FABP



# Acute Cardiac Care

## What We Need to Detect

- AMI: STEMI (ECG) vs non-STEMI (+Tn)
- Ischemia – ECG (non-STE-ACS) vs -ECG
- Vulnerable plaques – inflammation, MMPs
- Thrombosis
- LV function – more than just LVEF - BNP
- Electrical instability – TWA

# What We Really Need to Know

1. Who has heart disease
2. Who is at risk for sudden death
3. Who is at risk for ACS
  - Long-term
  - Short-term
4. Who is having an ACS
5. LV functional status
6. Is secondary prevention working

# Biomarkers in ACS - Where We Stand

## Summary

- Troponin is precise but limited in use
- Anticipate new markers – approach with caution
  - Its easy to show prognostic value
  - Its hard to show value
- Physiology and Technology are unfolding
  - New targets present new challenges
- It just isn't that simple – manage complexity

**#1**  
Bestselling  
Medical  
Book

**All-New  
Edition!**

# CHEST PAIN FOR DUMMIES

PREMIER EDITION

**A Reference  
for Us**

by Bob Jesse

**The Fun and Easy Way  
to Learn about the  
Evaluation and Management  
of Chest Pain**

**Your First Aid Kit for  
Establishing Systematic  
Care Guidelines**

**New Diagnostic  
Technologies**

**ACT** *E.D. and  
Books* *Cardiology  
Compatible*

*Covers Imaging and  
Biochemical Markers*

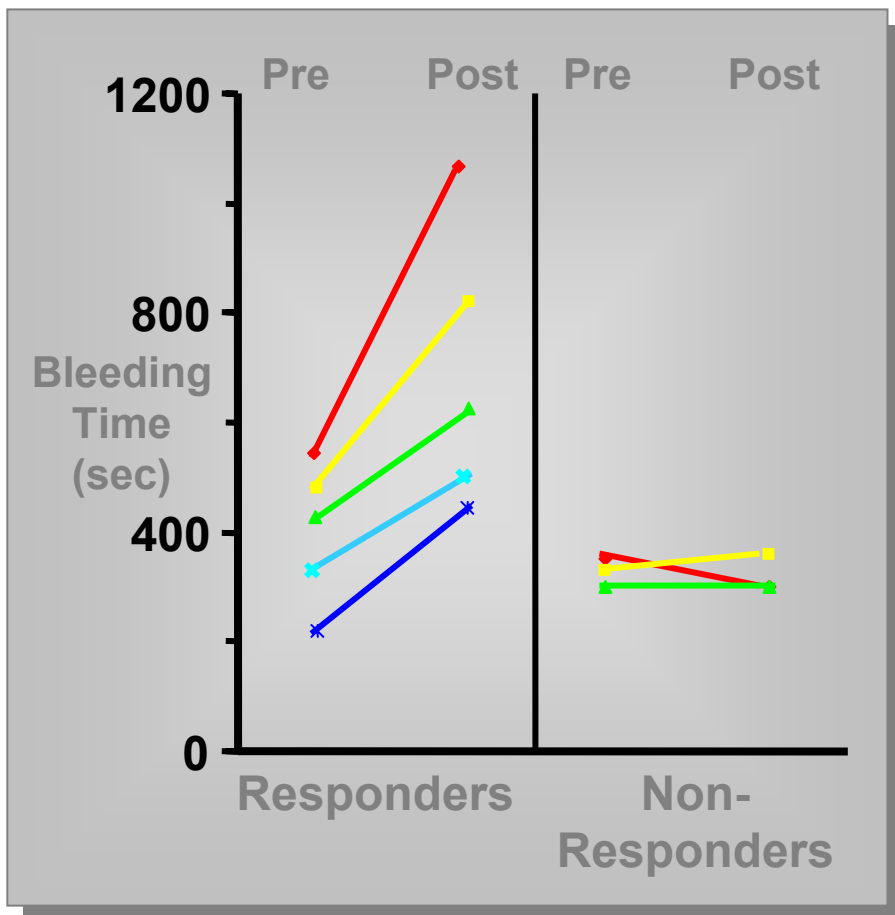
# **Biomarkers for Cardiovascular Disease**

**What's Important ?**

**From an Entirely Different  
Perspective...**

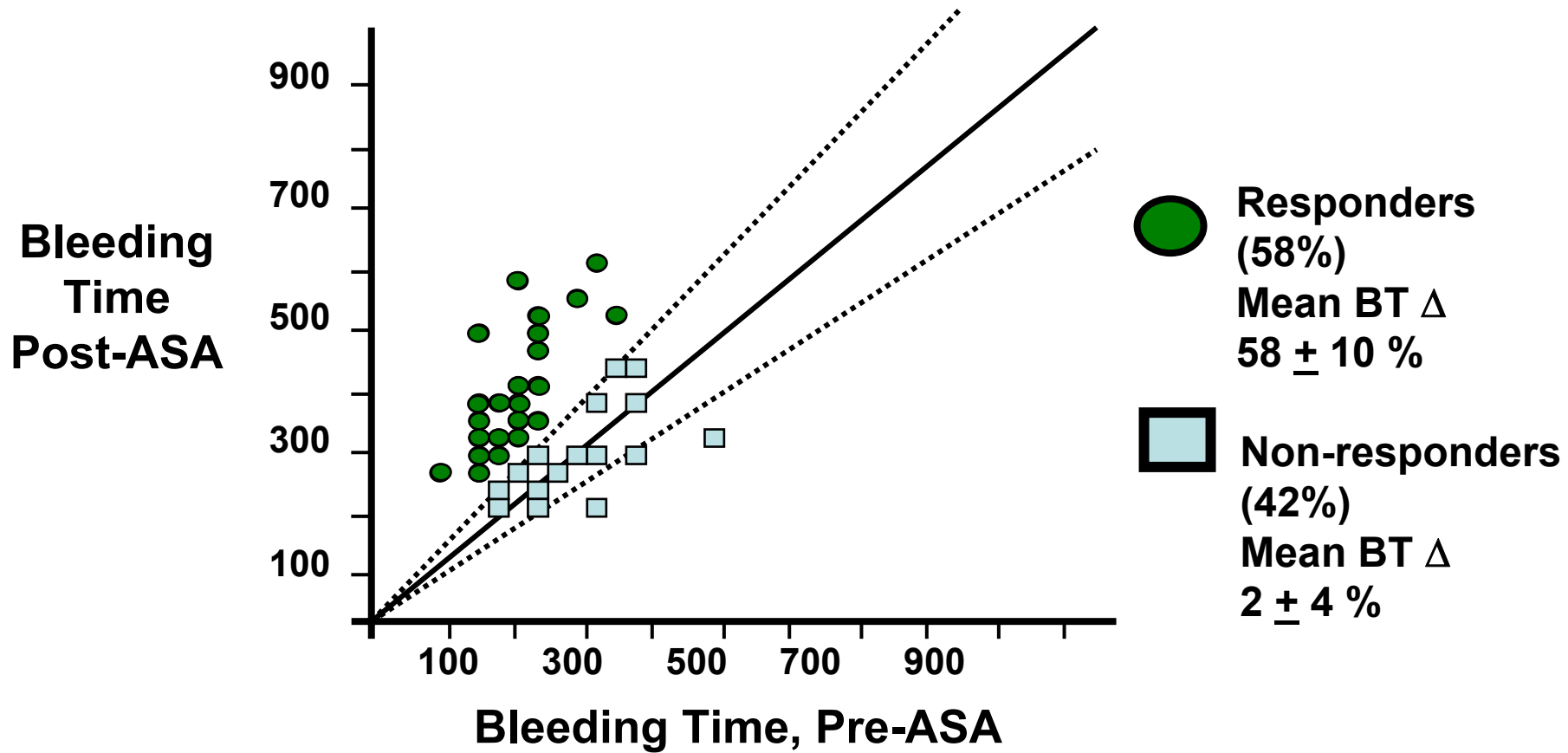
# Aspirin Resistance

## Increased Sensitivity to Collagen



- 8 volunteers, 324 mg ASA
- All with complete COX inhibition.
- ASA nonresponders were more sensitive to collagen than responders.
- No change when repeated 30 months later.

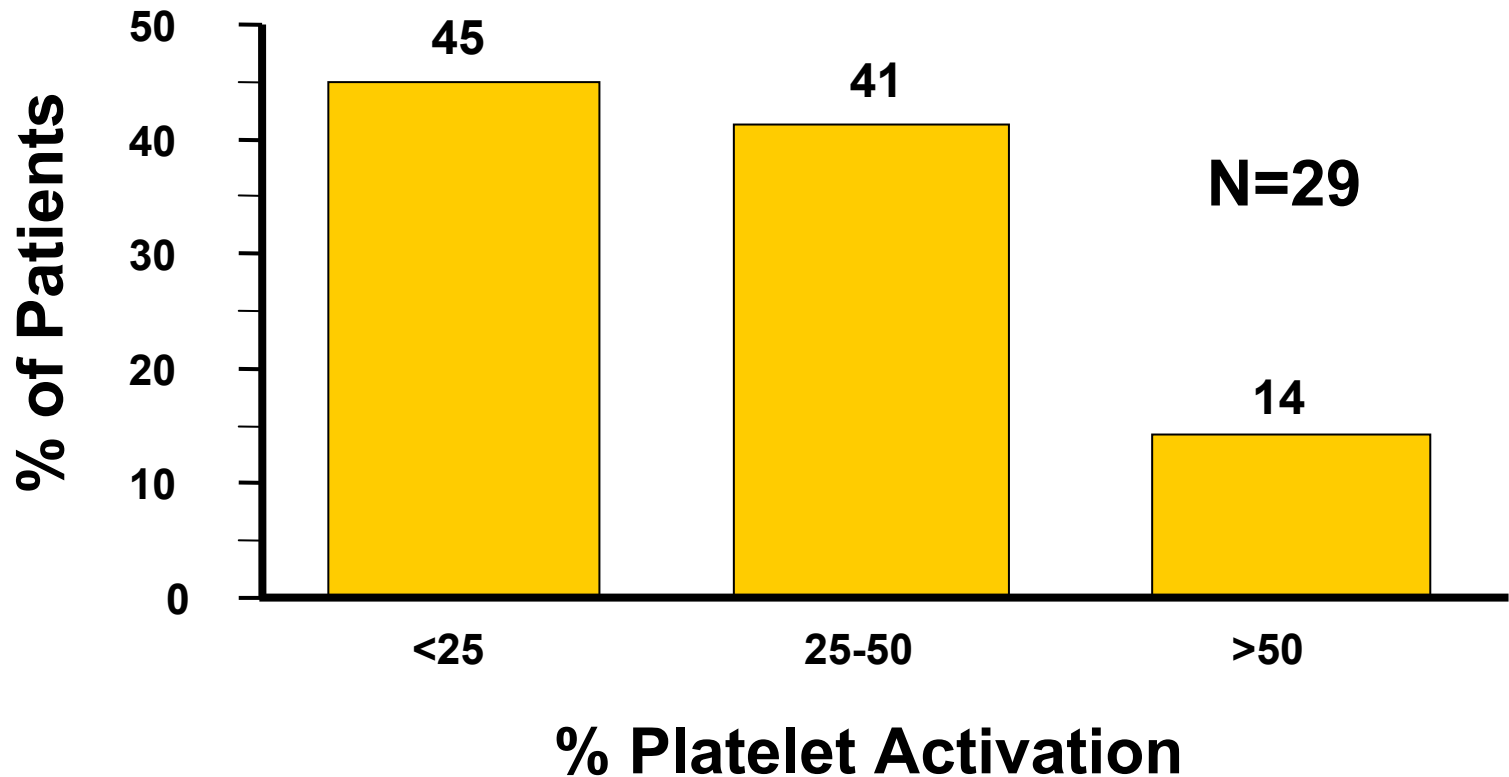
# Variability in Response to Aspirin



# Variable Aspirin Responsiveness

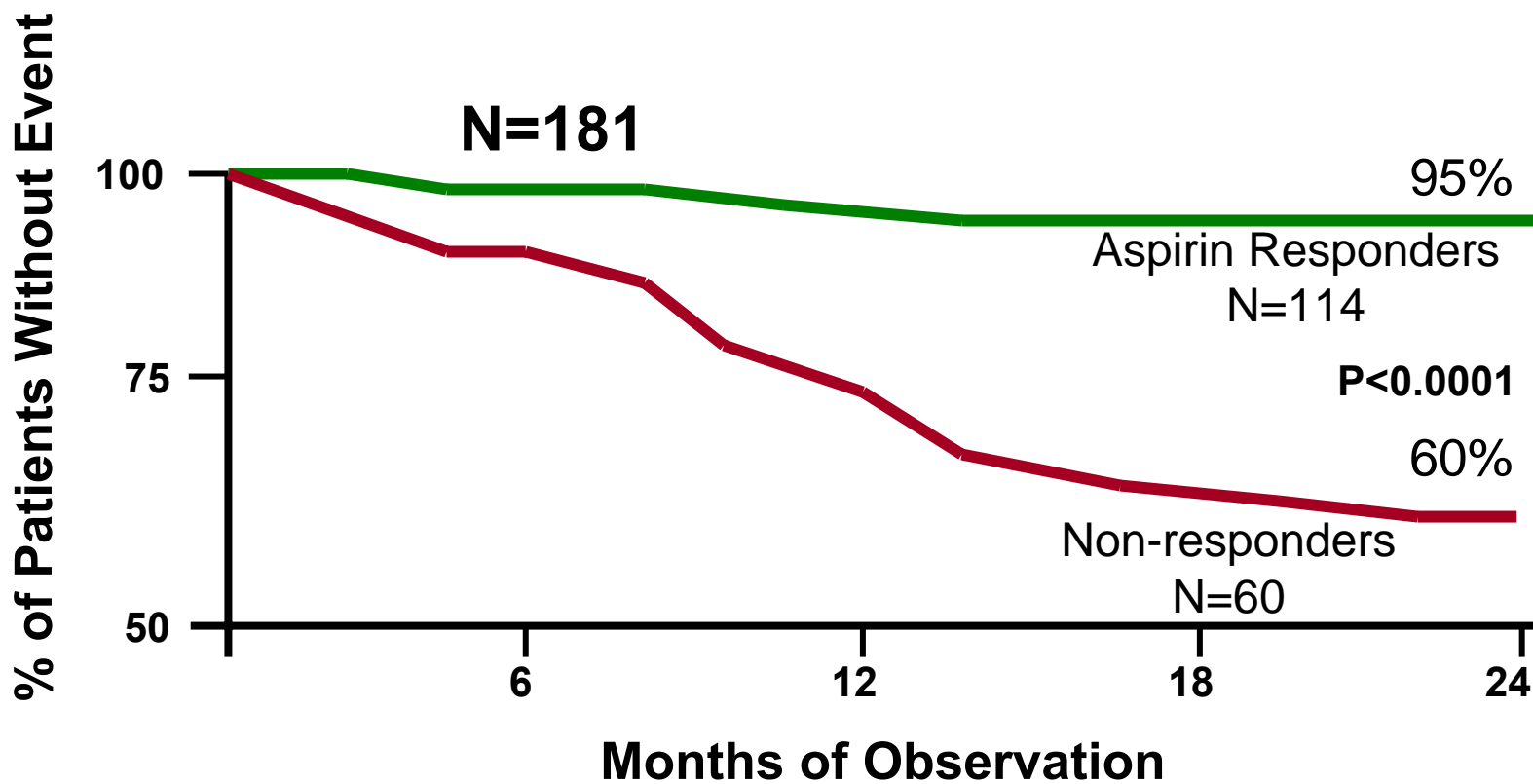
## Platelet Activation by Flow Cytometry

Aspirin, 325 mg QD x 7



# Aspirin Responsiveness vs Outcome

Patients, followed for 24 months post-CVA.  
Aspirin 500 mg TID.



# Is Aspirin Resistance Testing Necessary?



**END**

**[rjesse@hsc.vcu.edu](mailto:rjesse@hsc.vcu.edu)**