Acute Coronary Syndromes Education for Healthcare Providers

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NSTEMI – 2 Types

- ACS:
  - Chest pain related to a progressively enlarging intracoronary thrombus.
- Supply-demand infarct:
  - Small amount of myocardial damage caused by increased stress on the heart from tachycardia, hypoxemia, severe hypotension or hypertension.
  - Patient usually has severe underlying coronary artery disease.
  - Can rarely occur even in the context of normal coronary arteries such as with severe psychological stress, also known as Takotsubo cardiomyopathy.

Vignette 1 – Supply-demand MI

- 51yo female with type 2 diabetes, peripheral vascular disease, toe amputations, asthma, coronary artery disease. Had multiple cardiac catheterizations. Last one a year previously which demonstrated 100% chronically occluded right coronary and 60% occlusion branch of circumflex artery.

- Admitted with dyspnea, probable pneumonia with asthma exacerbation.

- Initial Troponin I in ER was 1.87ng/ml, subsequent TnI on floor was 2.7ng/ml. These values were mildly elevated.

- She has chronic anemia Hematocrit=31.6.

- The pt was heparinized, beta-blocker dose increased and she was given antibiotics.

- She was referred for cardiac catheterization 2 days after admission.

ECG unchanged from baseline.

Shows non-specific ST-T changes.
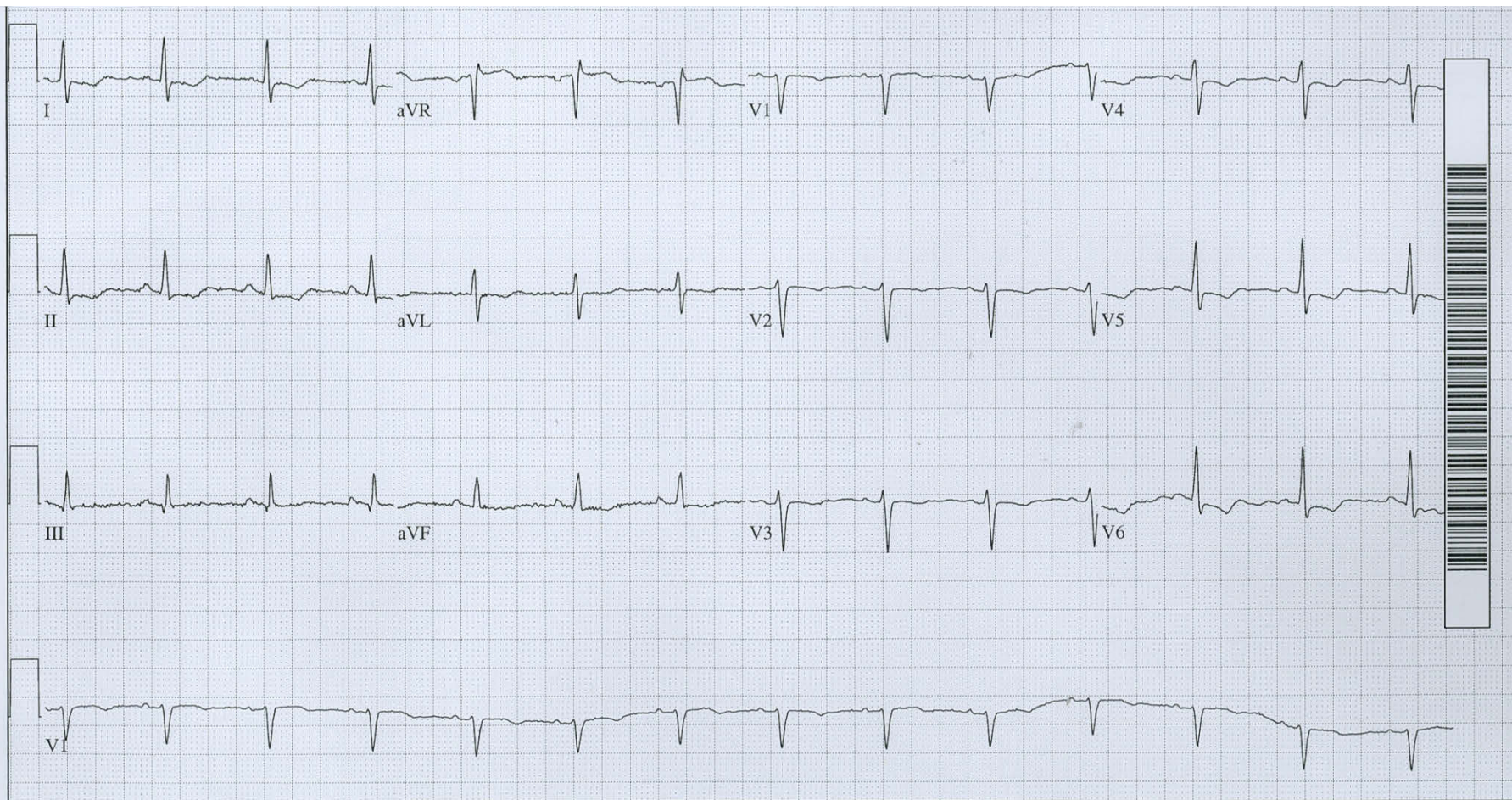
Type 2 - NSTEMI

- Cardiac catheterization demonstrated unchanged coronary anatomy.
- Supply-demand myocardial infarction was related to hypoxemia from pneumonia/asthma.
- She was discharged shortly thereafter on medical therapy and was doing well for several years.
- **Do not need to anticaogulate for supply-demand myocardial infarction.**

The Diagnosis of UA/NSTEMI (ACS not supply-demand)

Cannon CP. J Thrombolysis 1995;2:205–18. (Adapted)
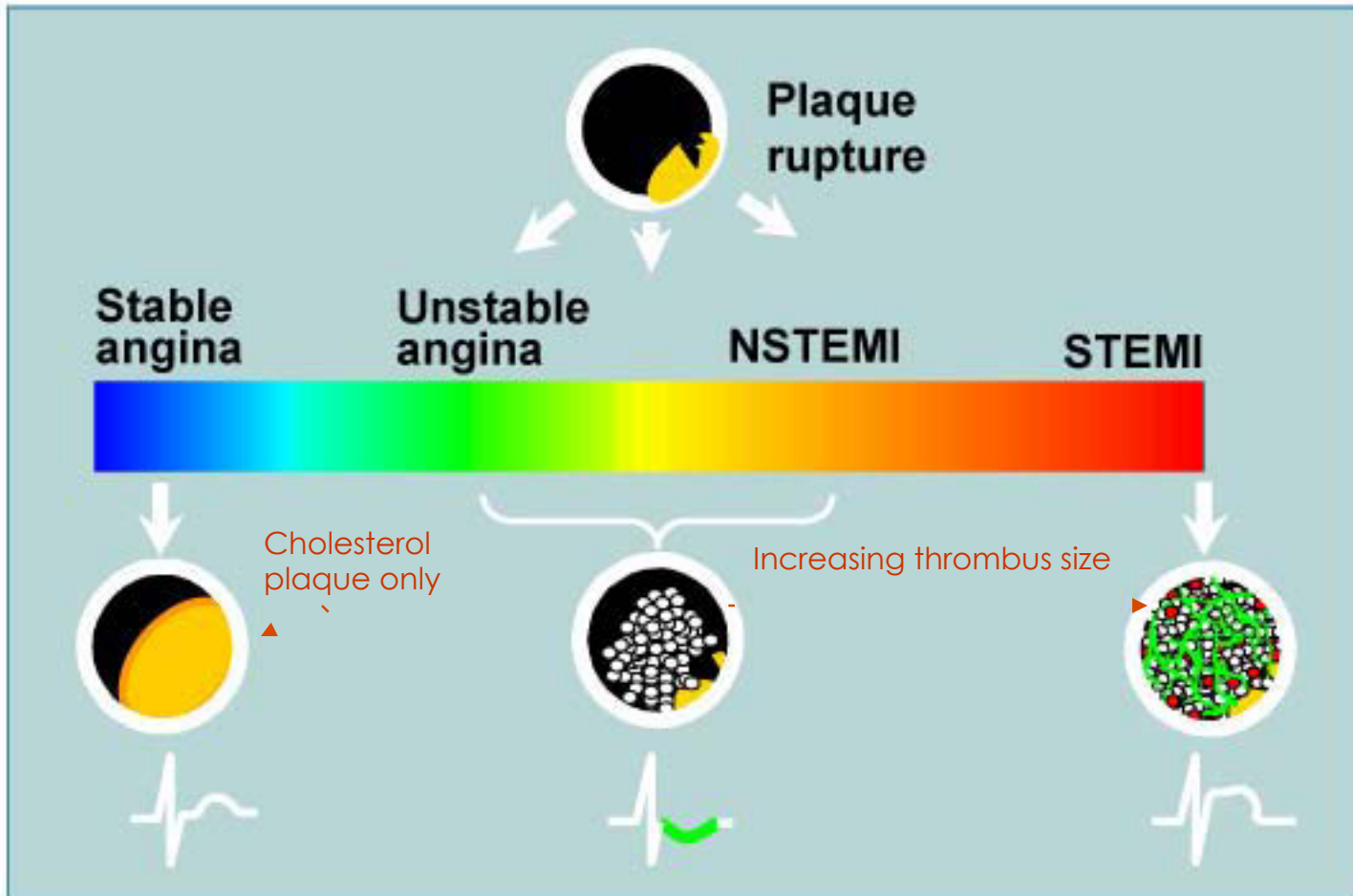
The Diagnosis of UA/NSTEMI (Cont.)
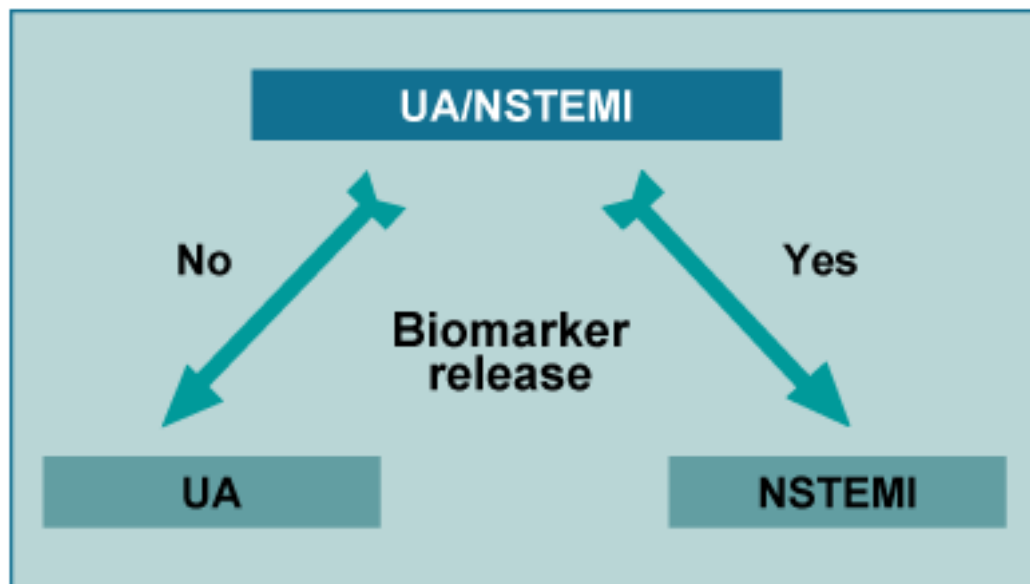
"Once it has been established that no biochemical marker of myocardial necrosis has been released (with a reference limit of the 99th percentile of the normal population), the patient with ACS may be considered to have experienced UA."

ACS = acute coronary syndrome

Braunwald E et al. ACC/AHA Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed April 2002.

Please see important safety information in this presentation and full prescribing information available at this presentation

Initial Evaluation of Chest Pain

- Clinical presentation for typical cardiac chest pain:
  - Crushing, aching, viselike, pressure.
  - Radiates to neck, jaw, left arm, back.
  - Dyspnea, nausea, vomiting, diaphoresis, syncope/pre-syncope can be associated or be only presenting symptoms – atypical presentation.
  - 20%-60% of acute myocardial infarctions are silent or atypical → particularly in diabetics, elderly and women.

Initial Evaluation of Chest Pain

- **Risk factors are very important:**
  1. Age (>45 for men and 55 for women).
  2. Sex (male preponderance).
  3. Diabetes.
  4. Hypertension.
  5. Hypercholesterolemia
  6. Smoking.
  7. Family history of premature coronary artery disease (<55 for 1st degree male relative or 65 for 1st degree female relative).
- Also important are prior characteristics of chest pain, prior history of coronary artery disease and ECG findings.

# Acute Myocardial Infarction (AMI)

- ECG
  - Only 40-50% of pts with AMI have ST-segment elevation.
  - Look for Q-waves, ST-depression, inverted T-waves, flat ST-segments.
  - A patient with a totally normal ECG has very low probability (<4%) of having AMI.

Vignette 2 – STEMI

- 42yo male with history of hypothyroidism. Began having chest pain around 7AM.
- Ambulance arrived on premises within 30 minutes of start of chest pain.
- Initial ECG in ambulance normal.
- Subsequent ECG revealed anterior ST elevation.
- Received angioplasty/stent 100% occlusion of the left anterior descending coronary, patient given abciximab (GP2b/3a inhibitor) in cardiac catheterization laboratory.
- Patient regained near normal LV function by 3 weeks post-AMI.

Initial ECG in ED demonstrates T-wave peaking and ST-elevation in precordial leads (known as tombstoning) consistent with acute anterior wall myocardial infarction.
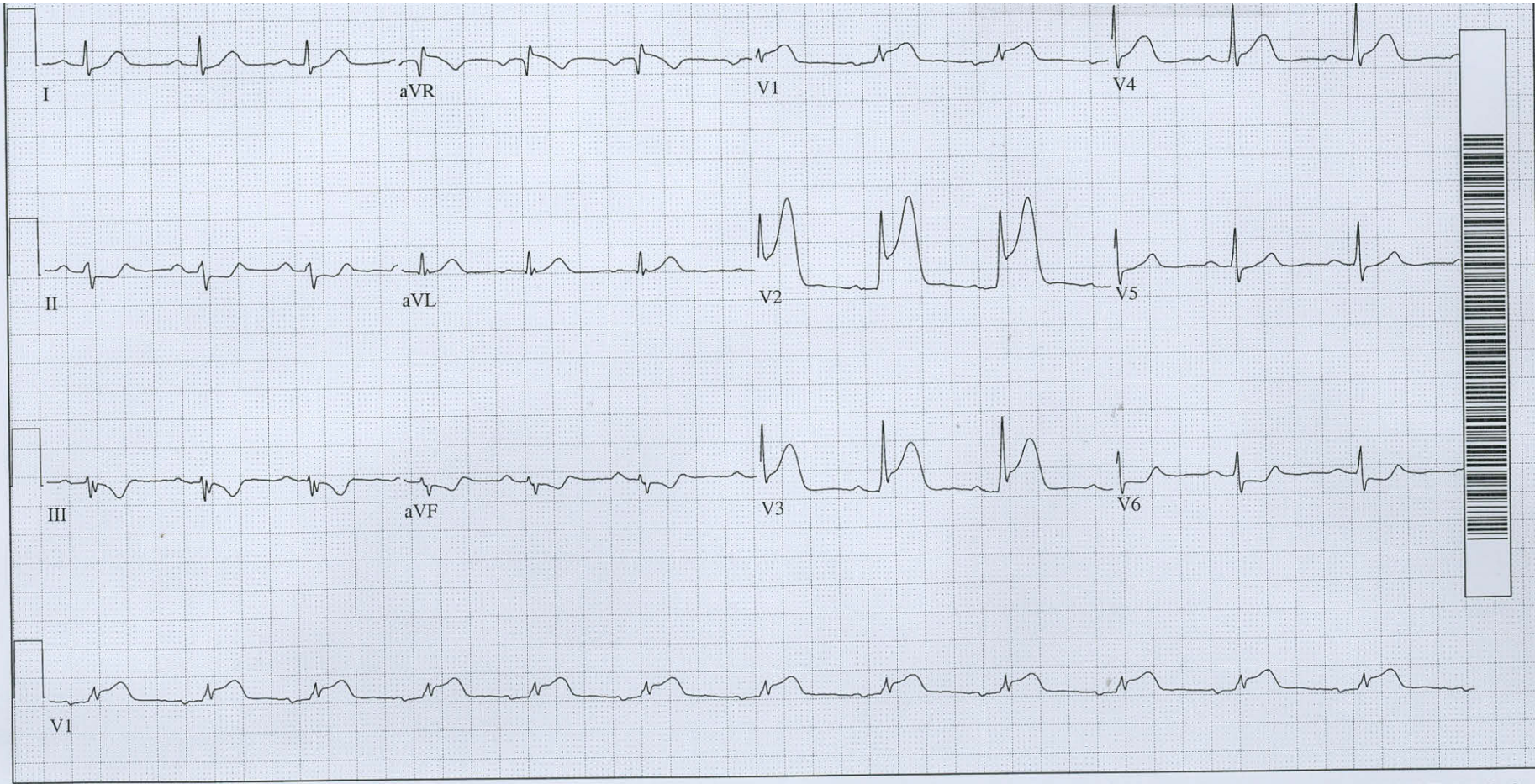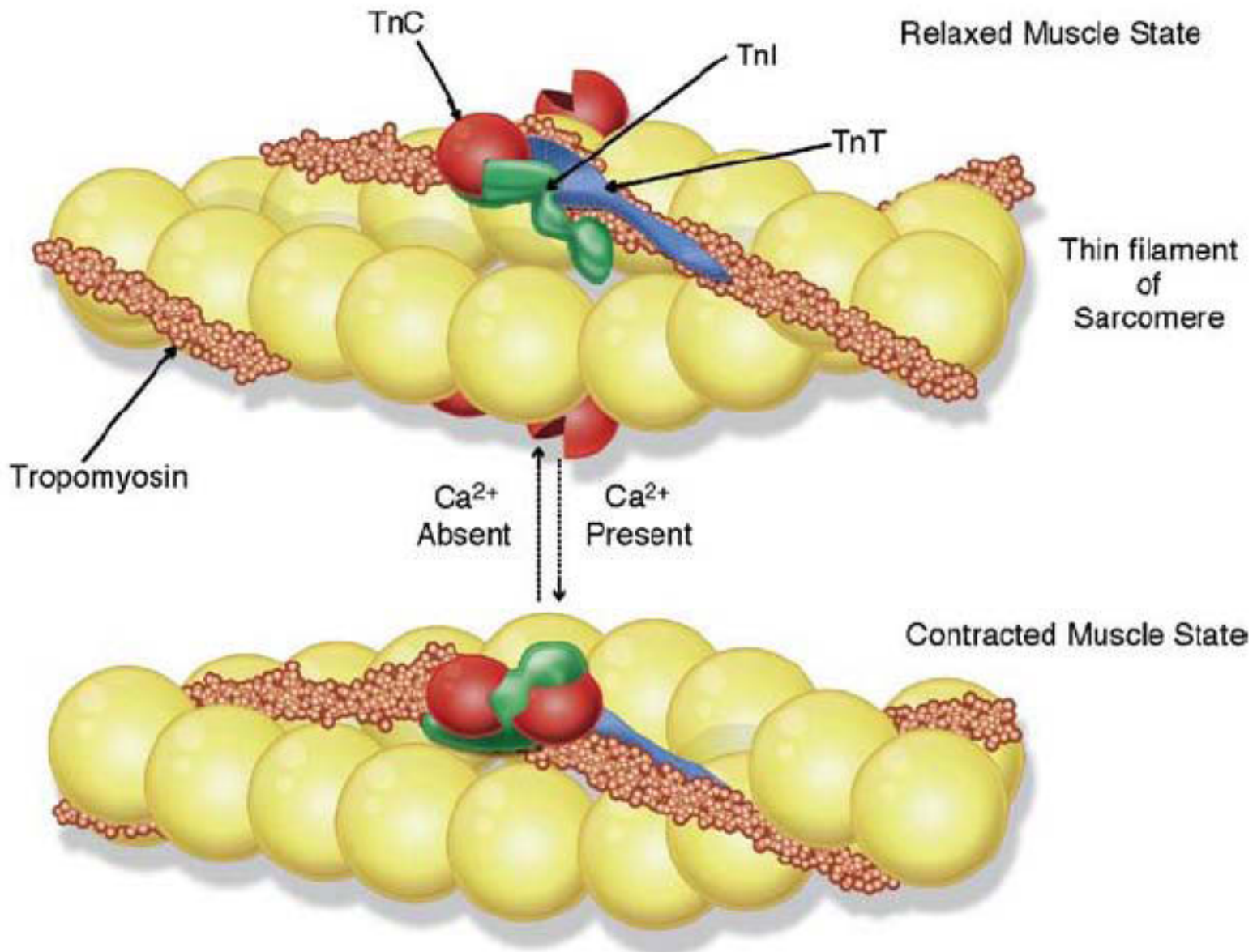
After successful reperfusion, Q-waves appear immediately and ST-segment elevation improves dramatically.
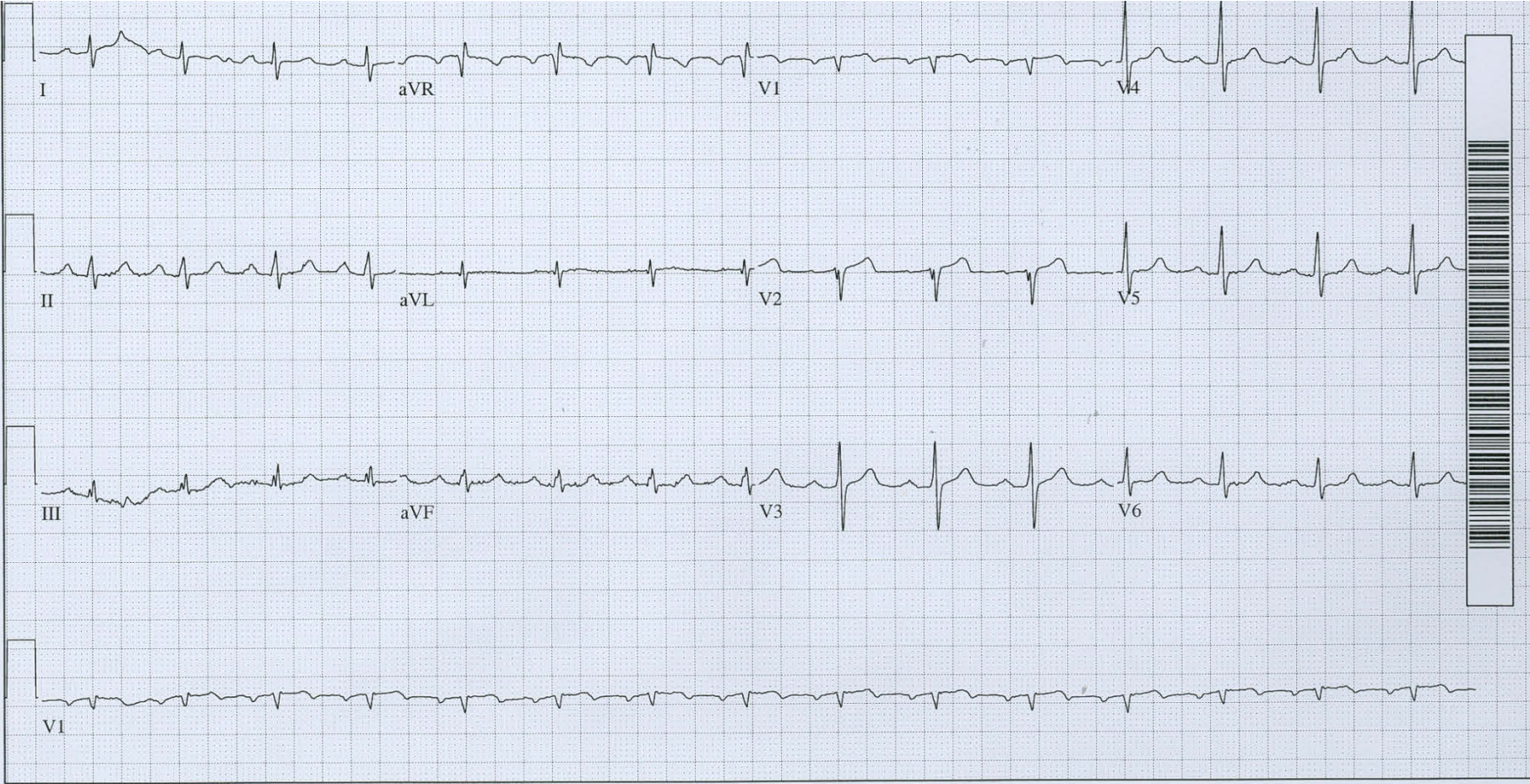
Acute Coronary Syndromes

- Cardiac markers
  - Troponins are cardiac-specific and are extremely sensitive.
  - CPK-MB elevation often occurs in the context of muscle breakdown and means nothing if the troponin is negative.

TnC

TnI

TnT

Relaxed Muscle State

Thin filament of Sarcomere

Tropomyosin

Ca²⁺ Absent

Ca²⁺ Present

Contracted Muscle State

Troponins are contractile elements of cardiomyocytes.

Acute Coronary Syndromes

- TIMI risk score (Total of 7 points)
  - Age $\geq$ 65
  - 3 or more CAD risk factors
  - Prior stenosis > 50%
  - ST deviation on ECG
  - $\geq$ 2 anginal events in 24 hours
 - ASA use in last 7 days
  - Elevated cardiac markers

Acute Coronary Syndromes

- Pitfalls:
  - Young (smokers), language barrier, elderly, women, diabetics, atypical presentations, pre-existing GI problems….
- FYI: the average age of the STEMI patient at Upstate is 45. Statistics show that 80% of STEMI patients under the age of 50 are smokers!
- **Tip: persistent severe chest pain without ECG changes is an aortic dissection until proven otherwise. Consider CT scan of chest.**
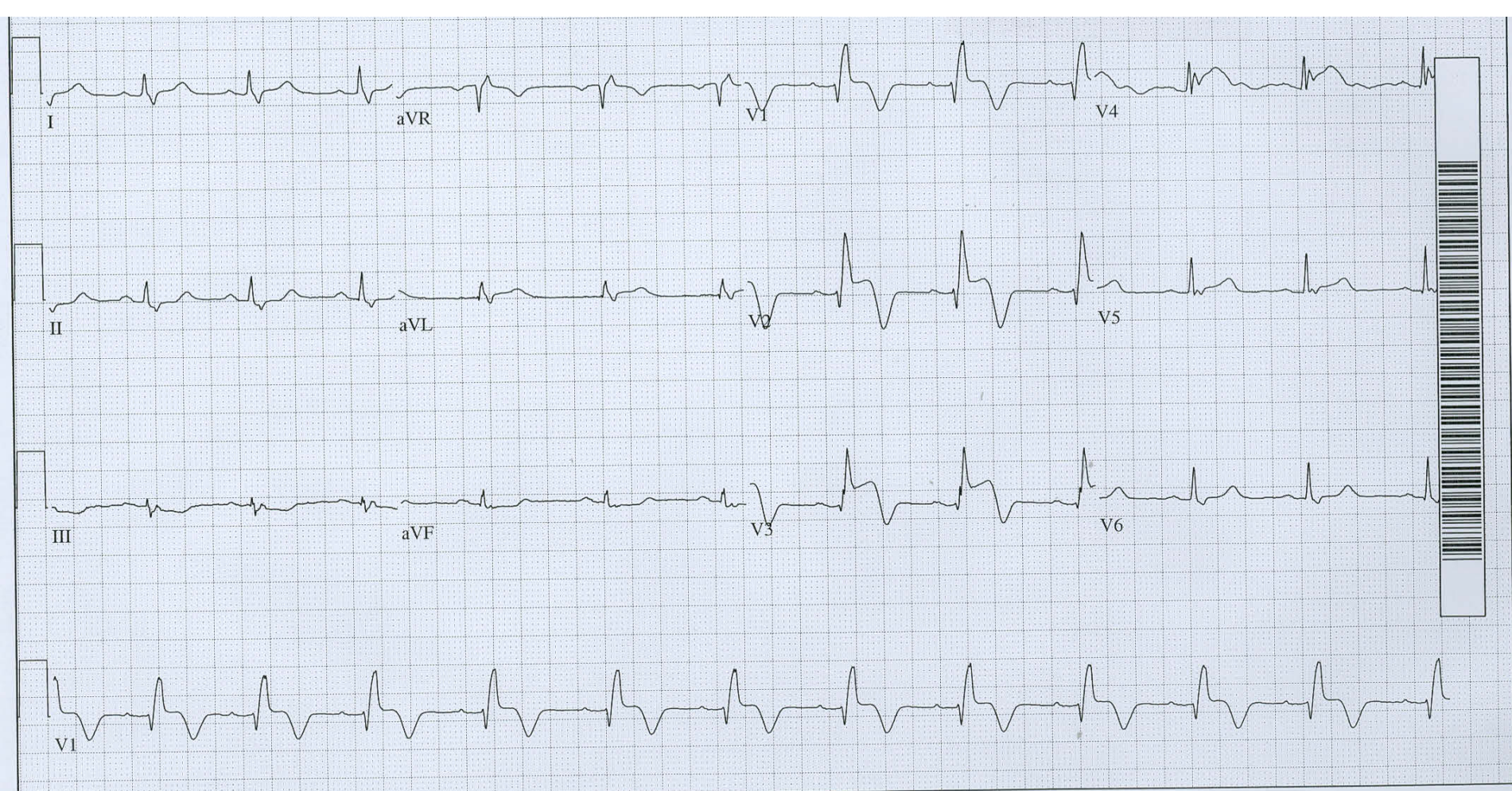
Vignette 3 – Young Smoker

- 34 yo female pre-menopausal smoker.
- Presented to ED within one hour of chest pain, was radiating to back.
- Had vomiting with some blood.
- Initial ECG non-diagnostic.
- Enzymes initially negative.
- Sent for CT scan of chest to rule-out esophageal pathology.
- Patient had persistent C.P.
- ECG not repeated for 4 hours.

This ECG demonstrates peaked T-waves V1-V3 and mild ST-depression infero-laterally. Although non-diagnostic, it is suggestive of ACS.
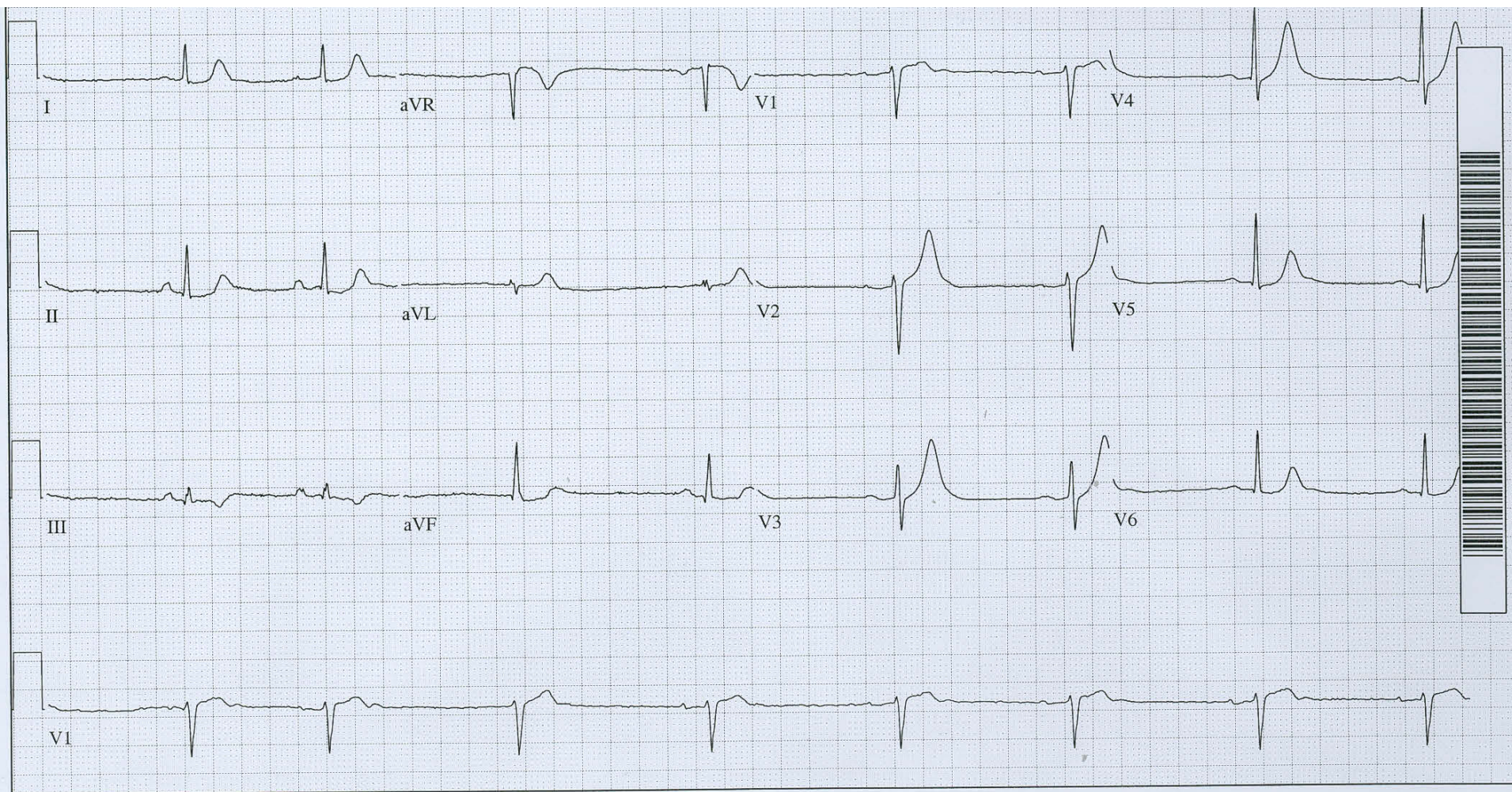
ECG was not repeated until 4 hours later and now reveals Q-waves in V1-V3 as well as marked ST-elevation in the precordial leads, T-wave inversion and a right bundle branch block. The patient was found to have a 100% occluded anterior coronary at catheterization which was stented. **ECGs should be repeated every 15-30 minutes during ongoing chest pain to look for evolution of changes.**


25mm/s   10mm/mV   150Hz   005E   12SL 229   CID: 1

SID: WARREN EID:19 EDT: 09:45 15–MAR–2004 ORDER:

Page 1 of 2

ST depression is just as worrisome as ST elevation. This patient presented in cardiogenic shock and had a 100% occluded left main coronary.

25mm/s   10mm/mV   150Hz   005E   12SL 235   CID: 1
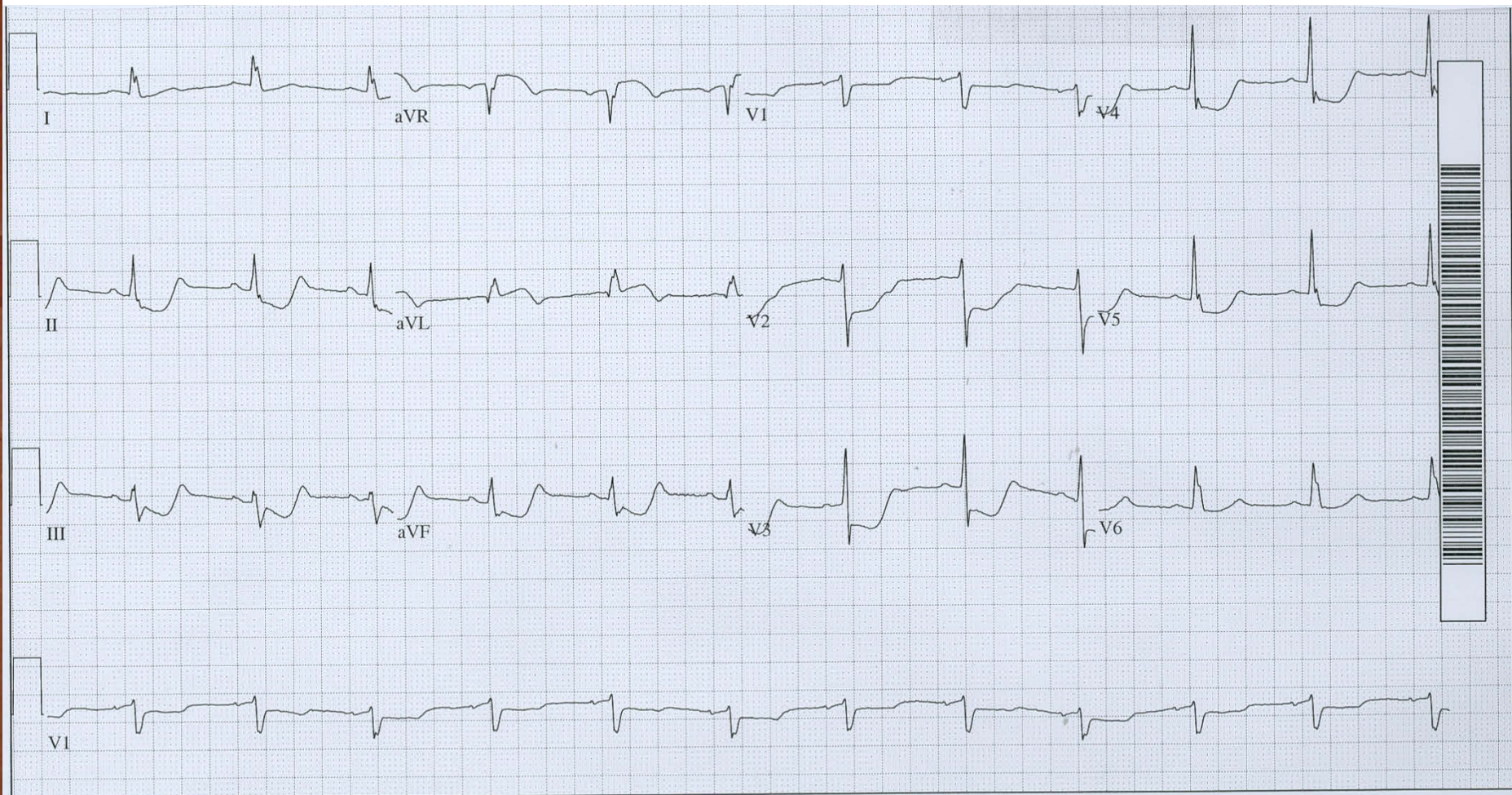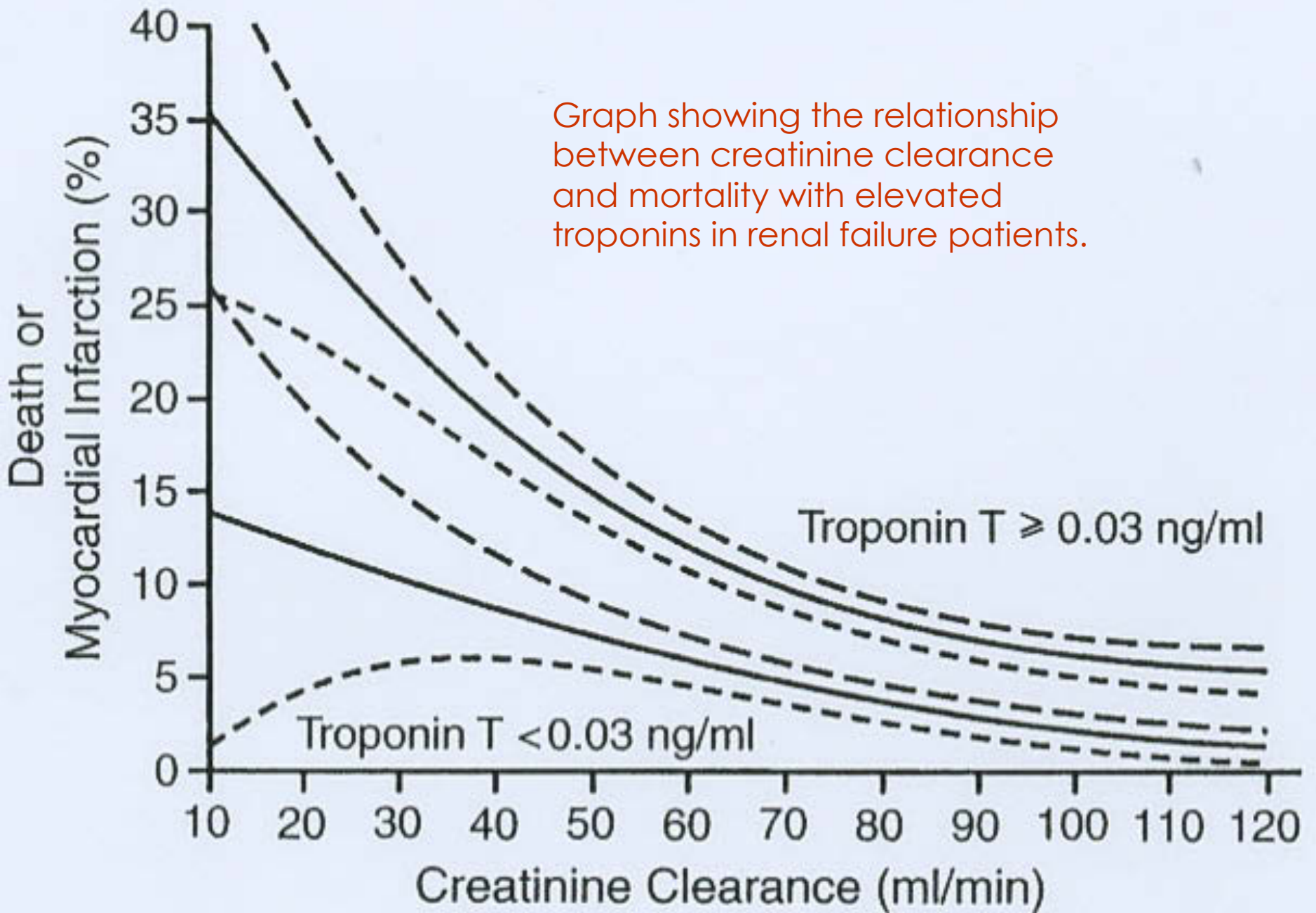
Cardiac Biomarkers

- Most centers rule out patients within 9 to 12 hours of presentation.
- In 2000, definition of AMI changed
  - Any elevation of troponin levels is diagnostic of myocardial infarction.
- Markers appear in blood at different times from symptom onset:
  - Myoglobin → 1-2 hours.
  - CPK-MB → 4 – 6 hours.
  - Troponins → 4 – 6 hours, present up to 2 weeks out from AMI.

A. Myoglobin
B. Troponin after MI
C. CPK-MB
D. Troponin after ACS
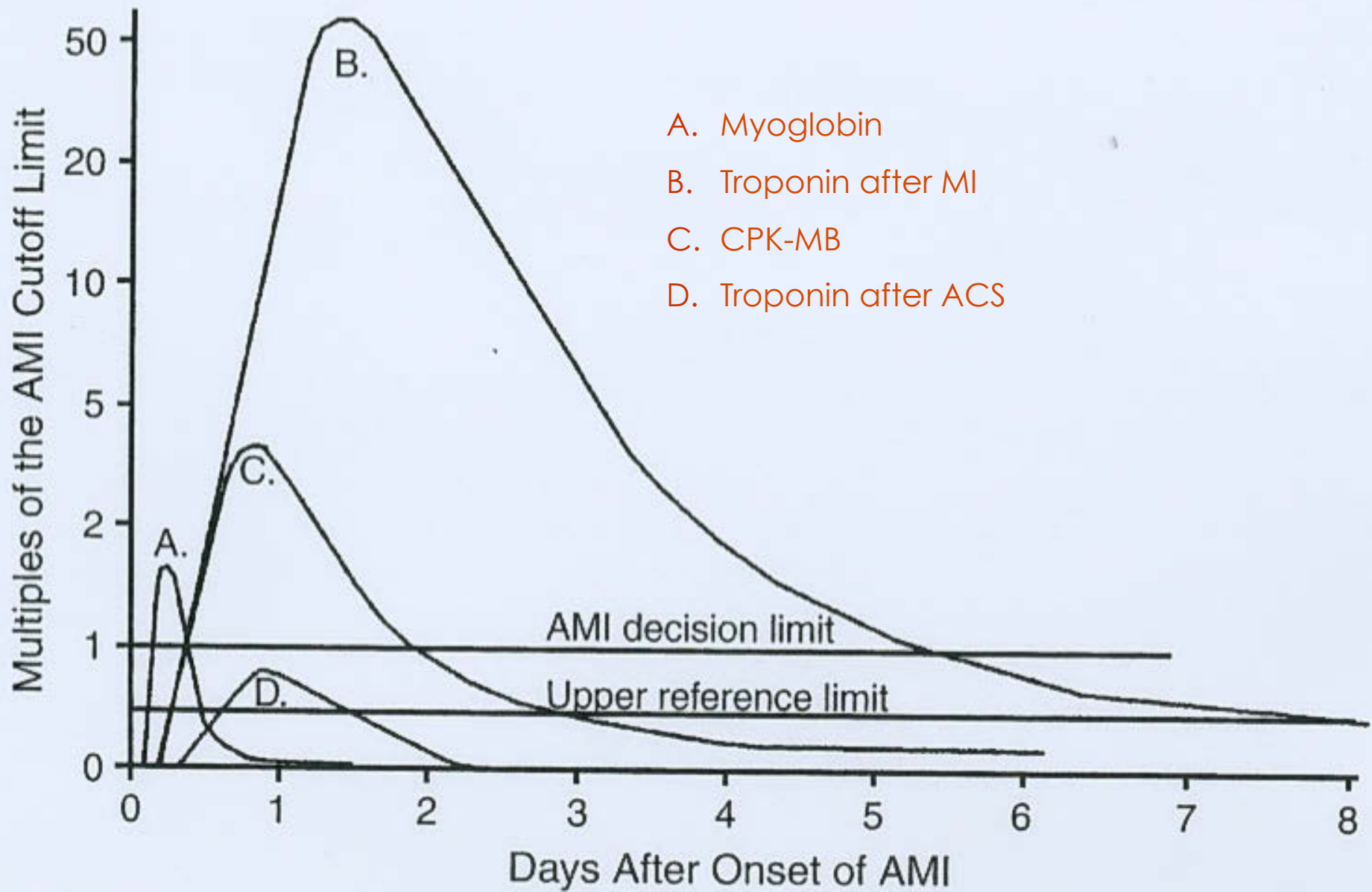
Cardiac Biomarkers

- Myoglobin – not cardiac specific.
- CPK-MB comprises 5% of skeletal muscle.
- Troponins - cTnI/TnT:
  - Can detect 1g myocardial necrosis.
  - Elevated in chronic renal failure.
    - Decreased renal clearance – more with TnT
    - High prevalence of CAD in dialysis patients.
    - Bad prognostic indicator.

Graph showing the relationship between creatinine clearance and mortality with elevated troponins in renal failure patients.

Troponin T ≥ 0.03 ng/ml

Troponin T <0.03 ng/ml

Death or Myocardial Infarction (%)

Creatinine Clearance (ml/min)
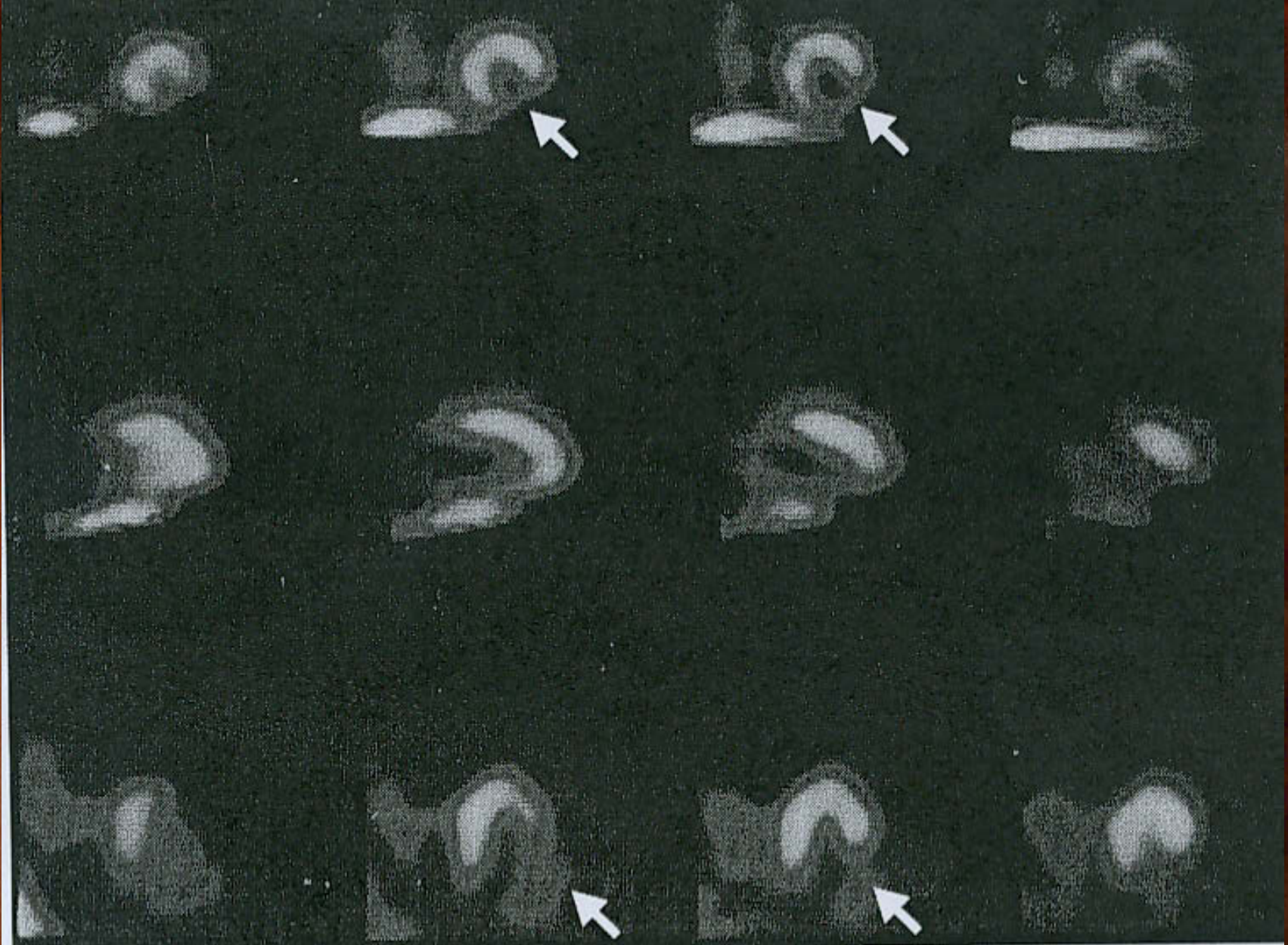
Non-invasive Imaging Techniques

- ECG is often non-diagnostic.
- Cardiac biomarkers take at least 4 hours to become elevated and may be normal.
- Can do serial ECGs and enzymes.
- Can take high-risk patients to cardiac catheterization laboratory.
- What else?

Non-invasive Imaging Techniques

- 2-D echocardiogram
  - 98% negative predictive value for AMI.
  - Operator-dependent and certain patients do not have good windows.
  - Look for wall motion abnormality.
  - Less useful if symptoms resolve prior to arrival in ER or if pre-existing wall motion abnormality.
  - Class I indication by ACC/AHA.
 - Myocardial contrast may help.

- Nuclear perfusion
  - Many centers use resting Tc99 MIBI injection for triage.
  - Can remain abnormal up to two hours after chest pain resolves.
  - 96% sensitive if done during chest pain.
  - Large number of artifacts and patients with prior myocardial infarction cannot be evaluated by this method as they will almost certainly have a perfusion defect.

Single MIBI injection during chest pain demonstrating inferolateral defect.

Non-invasive Imaging Techniques

- ## CT angiography
  - Electron Beam CT gives calcium score – high calcium score has very good correlation with the presence of CAD and occurrence of subsequent cardiac events.
    - Does not identify thrombosis or the culprit lesion.
  - High resolution CT may be the future
    - Still have technical difficulties with breathing and gating heart beat → Heart rate has to be less than 60/min.
    - Can only see proximal vessels.
    - Significant radiation exposure may preclude the further widespread use of this procedure for ACS diagnosis.
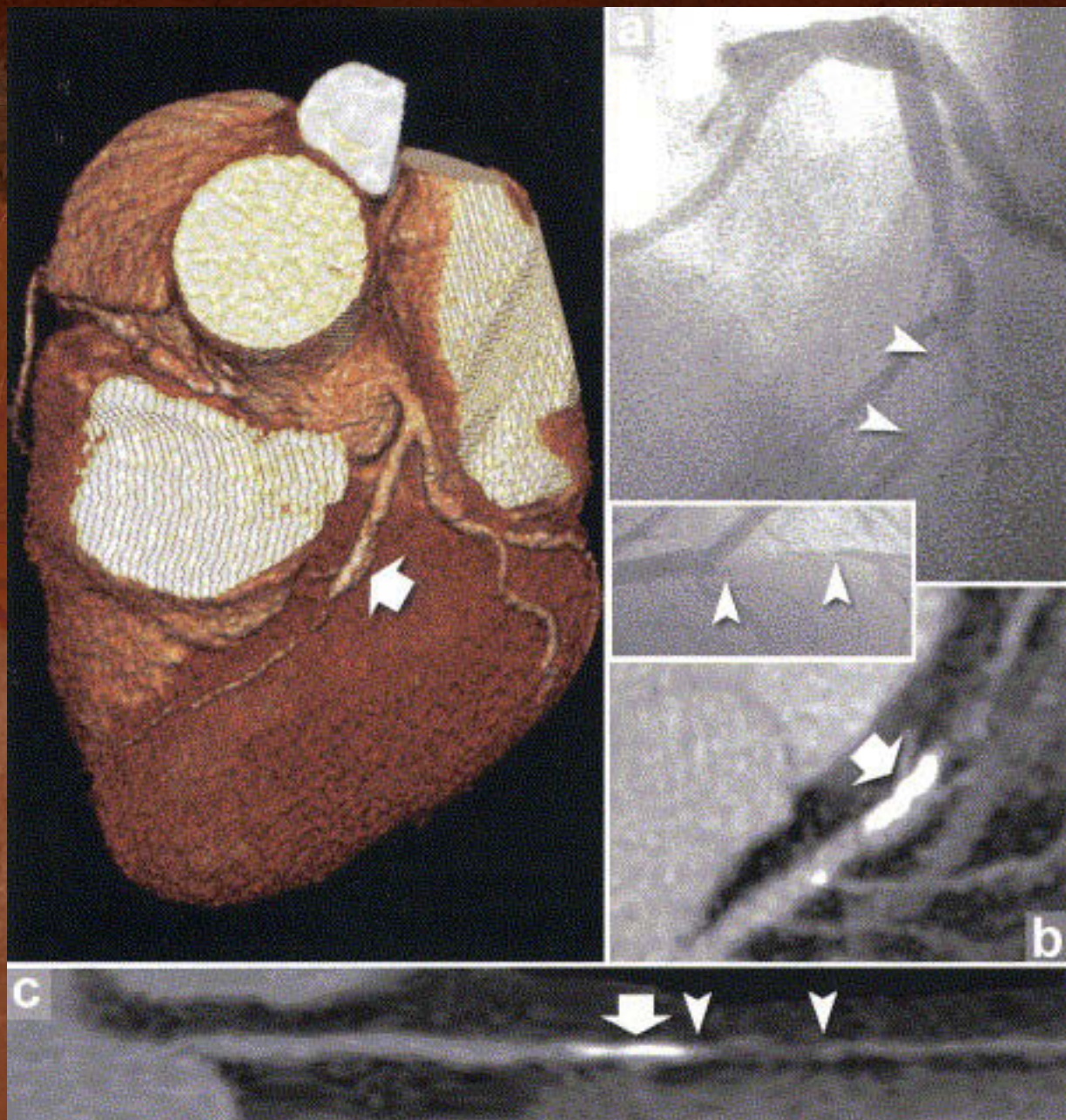
Non-invasive Imaging Techniques

- Stress testing
  - Exercise is better than pharmacologic testing.
  - Not really necessary in every patient with C.P. Much C.P. is obviously non-cardiac.
  - Nuclear stress tests can have a high false positive rate (? 40%) due to artifact. Breast tissue in women, diaphragm in men, motion artifact and prior cardiac events all contribute to a high rate of false positives.
  - Stress echocardiography has less false positives but is not as sensitive as nuclear testing and can miss up to 20% of patients with significant CAD.
  - Pharmacolgic testing with nuclear now uses lexiscan and with echo, dobutamine is the agent of choice.
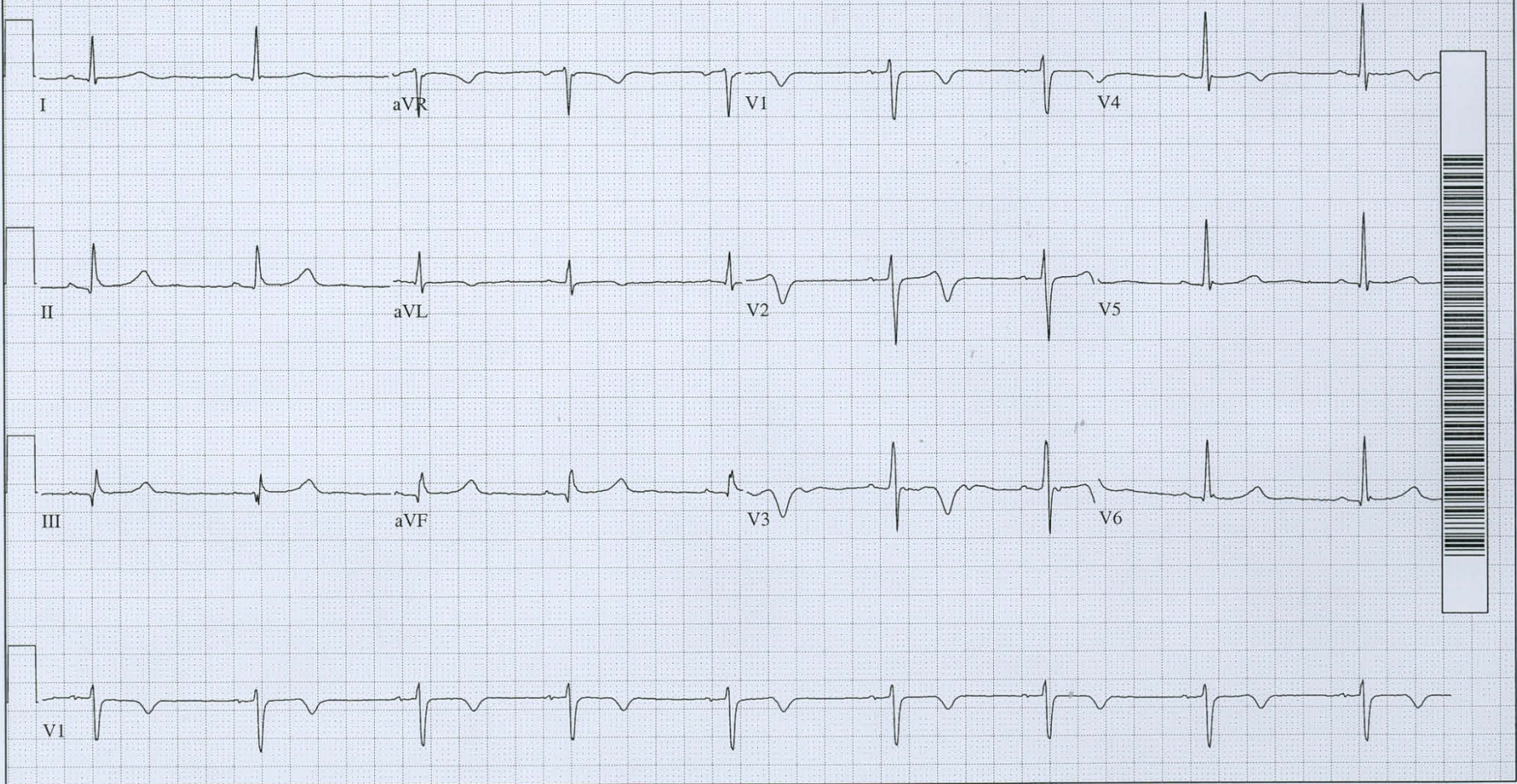
The Acute ECG

- Confounding factors:
  - LBBB – left bundle branch block
  - Paced rhythm
  - LVH – left ventricular hypertrophy
  - Other causes for ST elevation

Vignette 4 – LAD syndrome

- 45 yo male smoker.
- Admitted with pleuritic chest pain on Friday PM.
- Pain was reproducible with chest pressure.
- Ruled out for MI.
- Discharged home without stress test.
- Had severe recurrent pain.
- Returned to ED 3 days later.

ECG at first hospital admission.

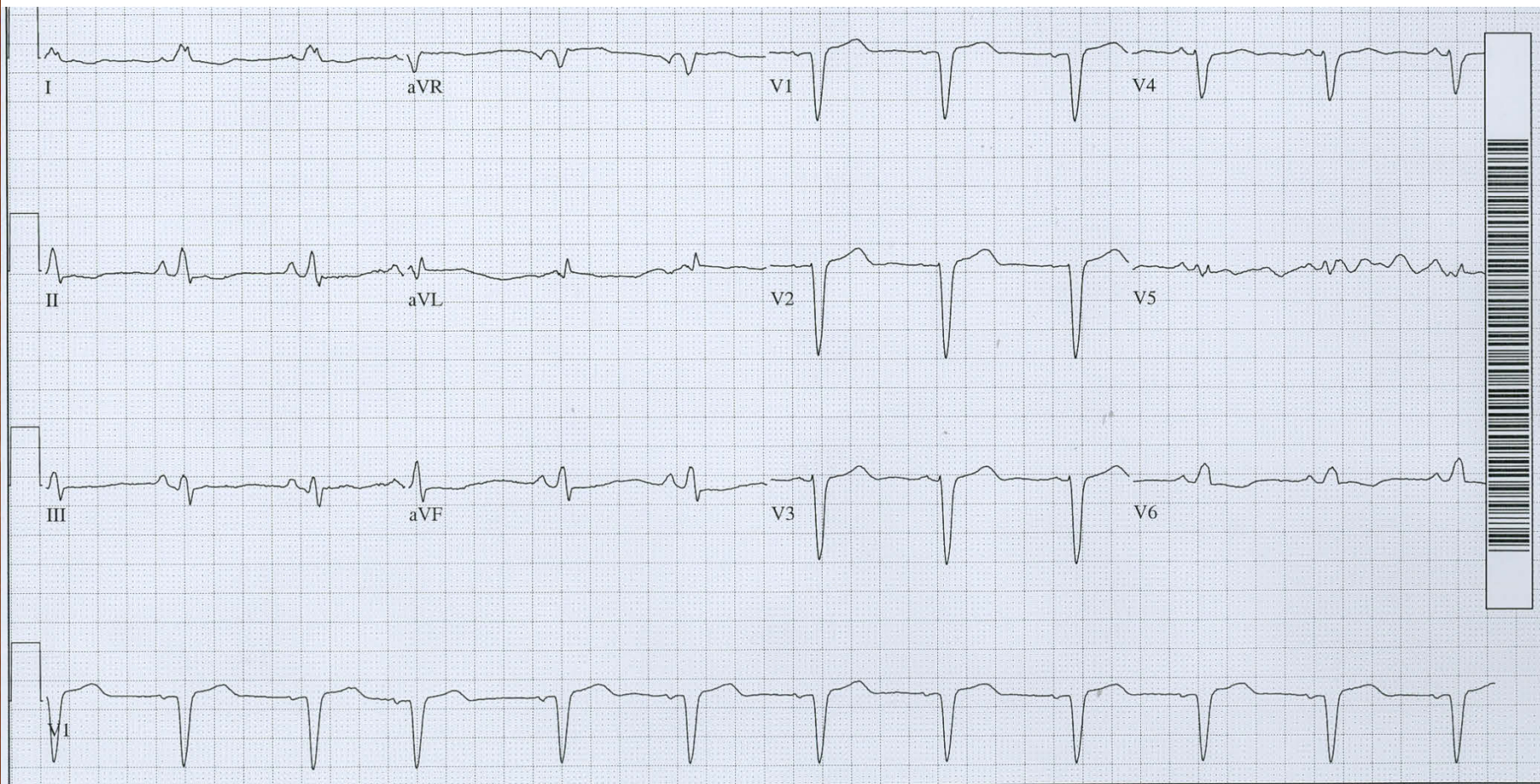There are ischemic-appearing T-waves in V1-V3.

25mm/s   10mm/mV   150Hz   005E   12SL 235   CID: 1

SID: ELLIS EID:28 EDT: 13:03 14–NOV–2005 ORDER: 002400001 ACCOUNT: 96368212

Page 1 of 1

ECG at second hospital admission are now obviously ischemic – deep and symmetrical.

We dubbed this the "slingshot" sign where I used to work in Canada because it "slingshotted" you right into the cath lab.

He was found to have a high-grade proximal anterior coronary lesion which was stented.
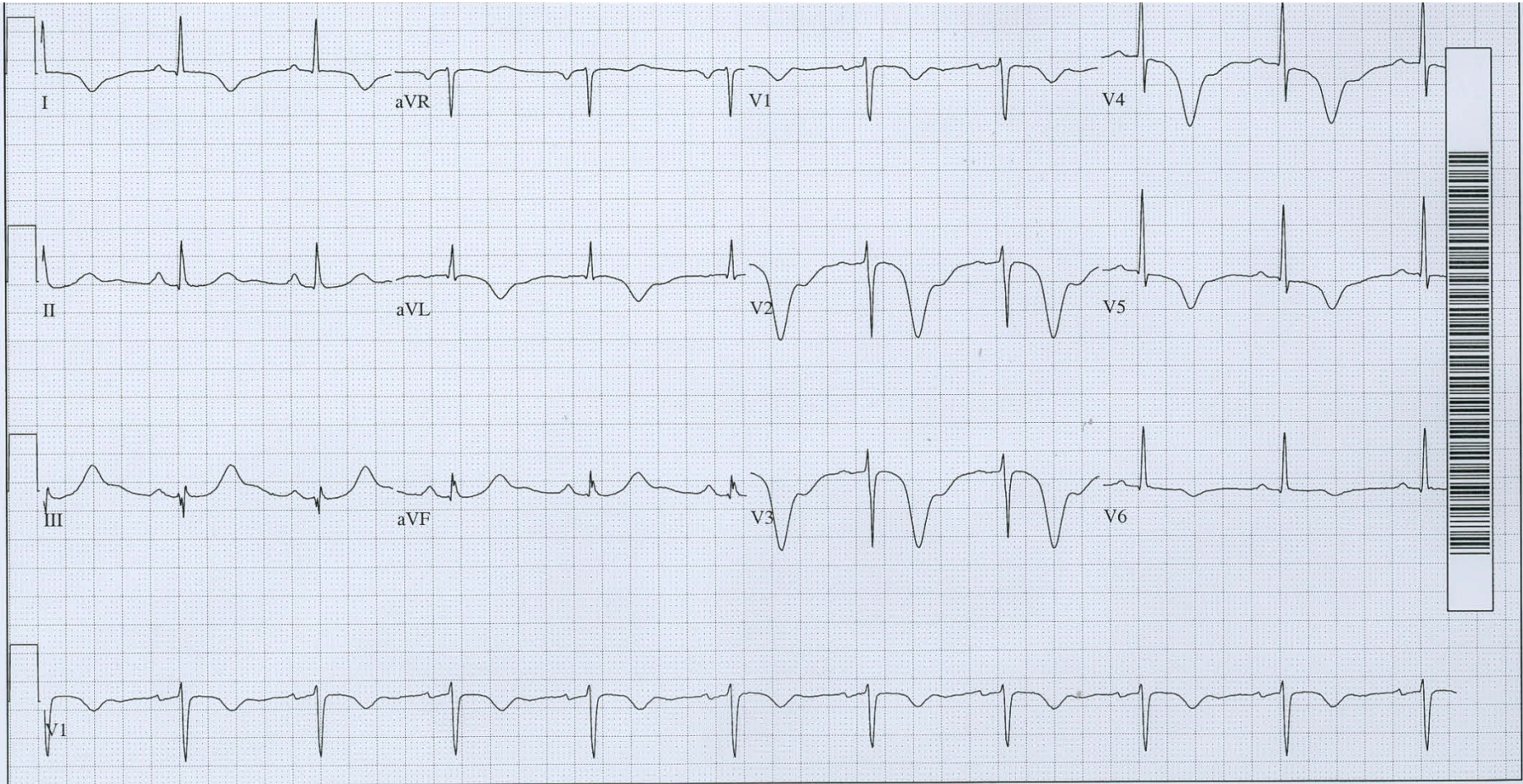
I was asked to perform cardiac catheterization on this patient because of "new" LBBB and chest pain. Her coronaries were normal. LBBB is generally not associated with acute coronary events. It is more likely to be associated with cardiomyopathy or conduction system disease which often becomes evident at a faster heart rate. As demonstrated in vignette 3, RBBB is usually the conduction system abnormality that occurs with AMI.

25mm/s   10mm/mV   150Hz   005E   12SL 235   CID: 1

SID: J.KLINE EID:22 EDT: 11:03 15−FEB−2006 ORDER: 000100001 ACCOUNT: 97443352

Page 1 of 1

This is a patient with a known underlying LBBB who presented with an anterior wall myocardial infarction. Note ST-elevation in V5 concordant with the QRS complex. Any concordant ST-elevation or ST-depression with LBBB is significant. Discordant ST elevation is almost always present with LBBB and usually means nothing. He was found to have a 100% anterior coronary lesion which was stented.

25mm/s   10mm/mV   150Hz   005E   12SL 235   CID: 1

SID: LOPEZ EID:17 EDT: 10:28 22−OCT−2004 ORDER:
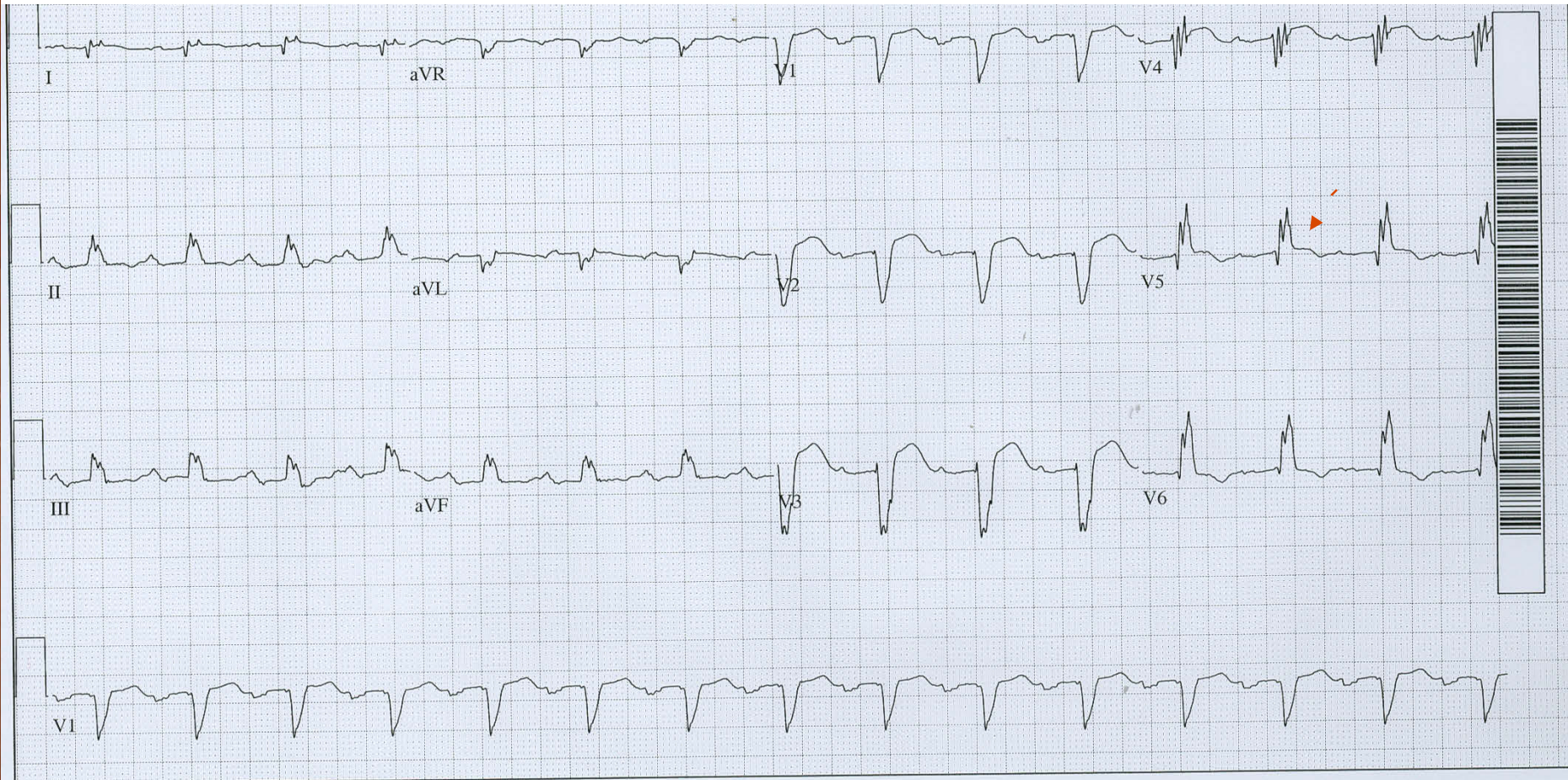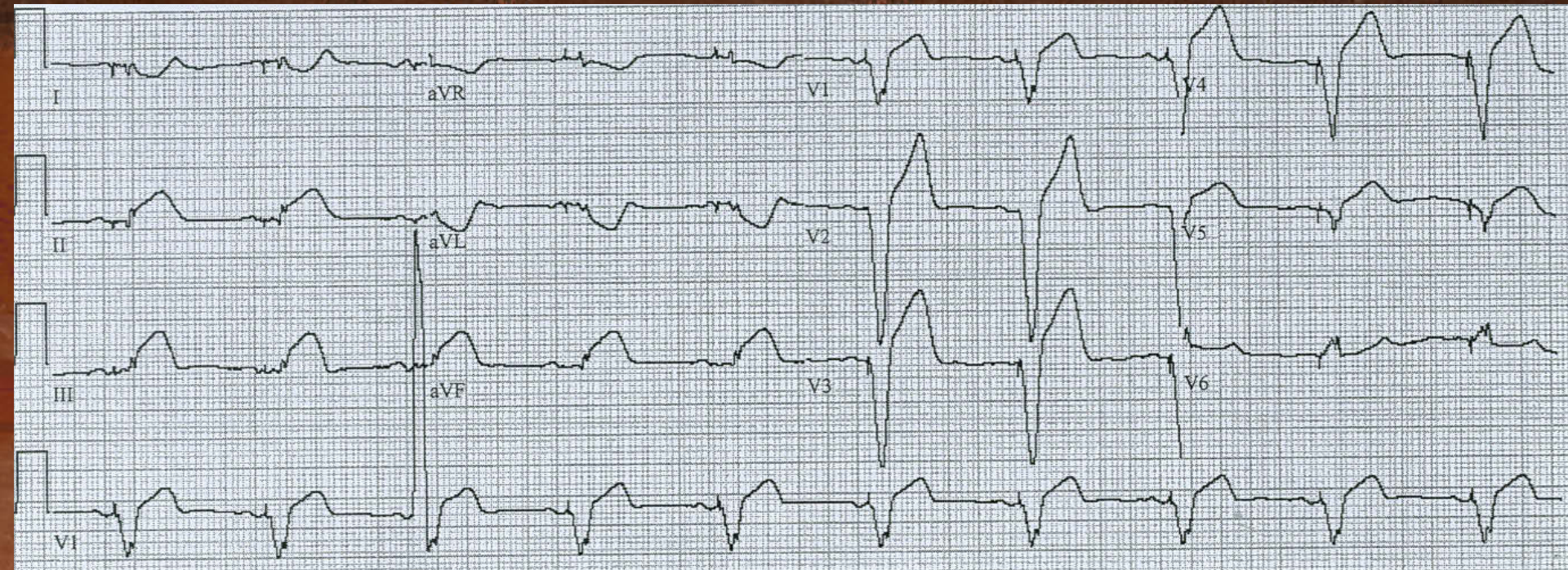
This is a paced rhythm with an inferior wall myocardial infarction. Right ventricular pacing gives an LBBB pattern. Note the concordant ST-elevation in II, III and aVF.
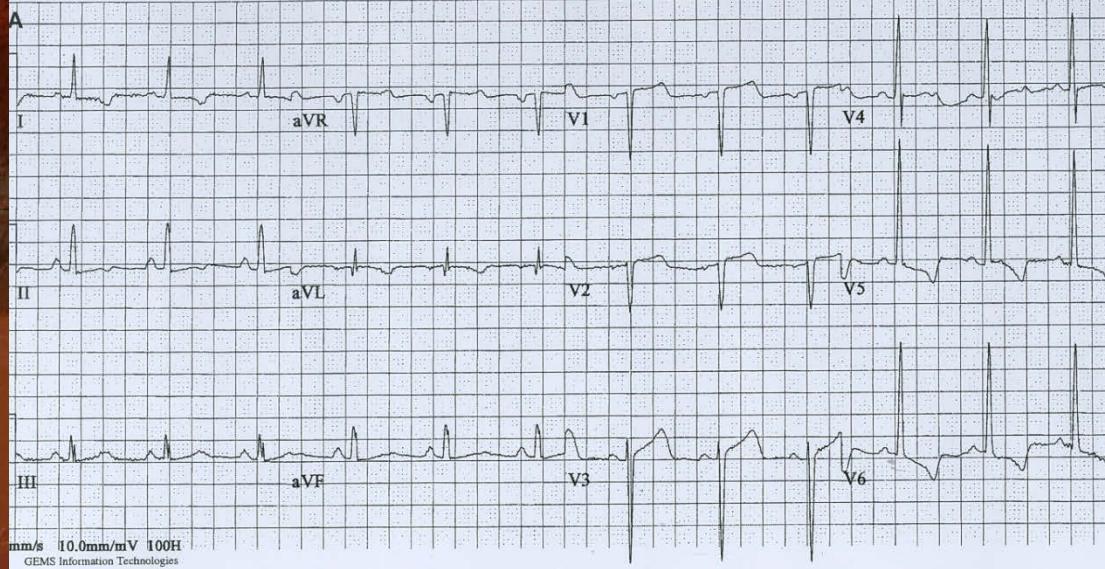
LVH is the most common cause of ST elevation on an ECG. Both these ECGs belong to the same patient with LVH. The bottom ECG is during an anterior wall myocardidal infarction.
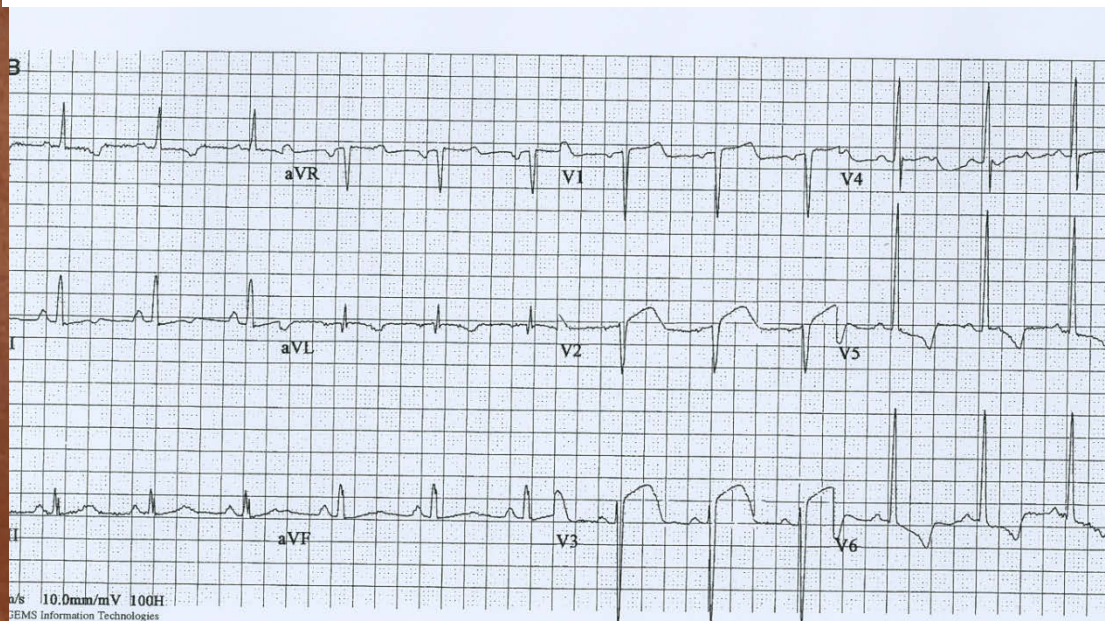
Treatment in ED

- ASA – 160 to 325mg chew and swallow.
- Oxygen
- Establish IV.
- Beta-blockers – Metoprolol 5mg IV q 5 min x 3 doses → only give if patient hypertensive and tachycardic. Can induce shock if BP borderline. Can cause atrioventricular block, particularly with inferior wall MI.
- Nitrates – can resolve some chest pain and ECG changes. Does not affect mortality. More important to proceed ASAP to cardiac catheterization laboratory.

Treatment

- Anticoagulation
  - Heparin – probably of benefit in addition to ASA. Only better than placebo after meta-analysis of all the studies dating from 1980s. Should give weight-based.
  - Low Molecular Weight Heparin - LMWH
    - Only enoxaparin an fondaparinux show benefit over heparin.
    - More factor Xa selective.

Treatment

- LMWH
  - More predictable anticoagulant effect.
  - No need for PTT.
  - Binds to clot bound thrombin.
  - Enoxaparin – 1mg/kg sc BID.
  - Fondaparinux 2.5mg sc daily.
  - Not all LMWH are equal.

SYNERGY trial evaluated enoxaparin vs unfractionated heparin and revealed decreased events if the patient was continued on LMWH through the stent procedure.
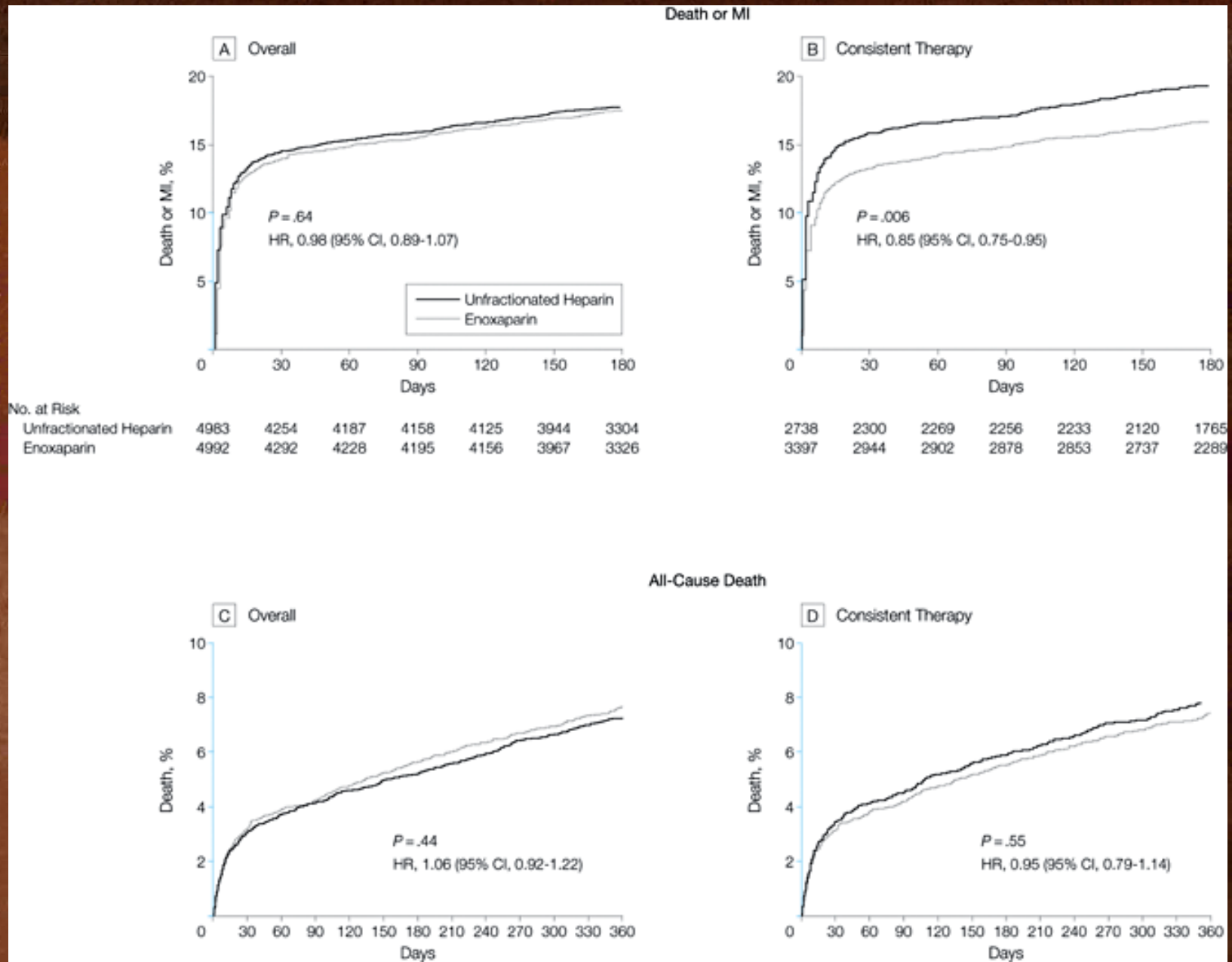
Study Design:
Randomized, Double Blind

Patients with NSTE ACS, Chest discomfort < 24 hours
2 of 3: Age>60, ST Segment Δ, ↑ cardiac markers

Exclude
Age < 21
Any contra-ind to Enox
Hem stroke< 12 mo.
Creat> 3 mg/dL/265 umol/L

ASA, Clop, GP IIb/IIIa,
planned Cath/PCI as per
local practice

Randomize

Fondaparinux
2.5 mg sc once daily

N=20,000

Enoxaparin
1 mg/kg sc twice daily

PCI <6 h: IV Fonda 2.5 mg
without IIb/IIIa, 0 with IIb/IIIa
PCI> 6 h: IV Fonda 2.5 mg with
and 5.0 mg without IIb/IIIa

PCI< 6 h, No additional UFH
PCI >6 h, IV UFH
With IIb/IIIa 65 U/kg
Without IIb/IIIa 100 U/kg

Outcomes

Primary: **Efficacy**: Death, MI, refractory ischemia at 9 days
Safety: Major bleeding at 9 days
Risk benefit: Death, MI, refractory ischemia, major bleeds 9 days
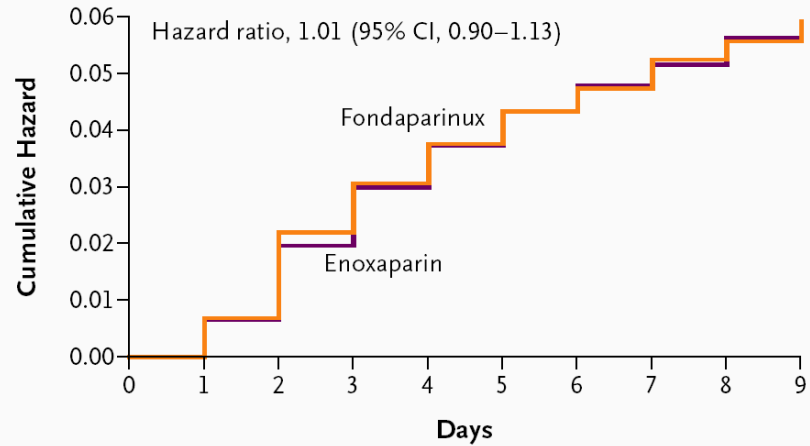**Secondary**: Above & each component separately at day 30 & 6 months
Hypothesis: First test non-inferiority, then test superiority

A Death, Myocardial Infarction, or Refractory Ischemia through Day 9

Hazard ratio, 1.01 (95% CI, 0.90–1.13)

Fondaparinux

Enoxaparin

No. at Risk									
Enoxaparin	10,021	9954	9824	9724	9652	9593	9550	9515	9470
Fondaparinux	10,057	9986	9836	9752	9684	9628	9589	9541	9510

B Major Bleeding through Day 9

Hazard ratio, 0.52 (95% CI, 0.44–0.61)
P<0.001

Enoxaparin
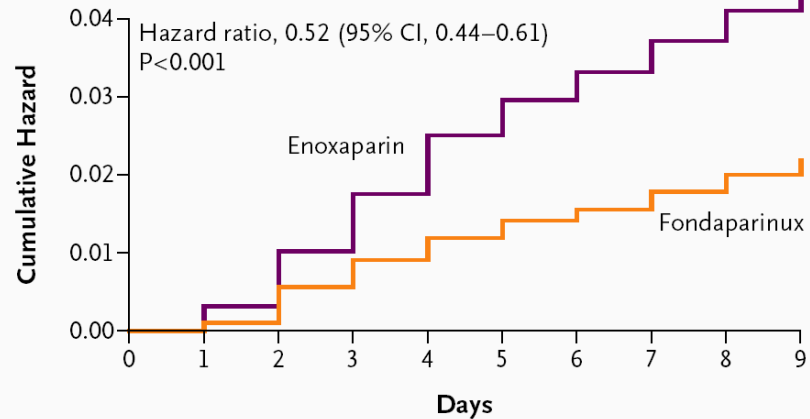
Fondaparinux

No. at Risk									
Enoxaparin	10,021	9,979	9871	9774	9682	9625	9575	9527	9478
Fondaparinux	10,057	10,028	9951	9884	9838	9796	9773	9738	9709

Figure 1. Cumulative Risks of Death, Myocardial Infarction, or Refractory Ischemia (Panel A) and of Major Bleeding (Panel B) through Day 9.

The hazard ratios are for the fondaparinux group as compared with the enoxaparin group. CI denotes confidence interval.
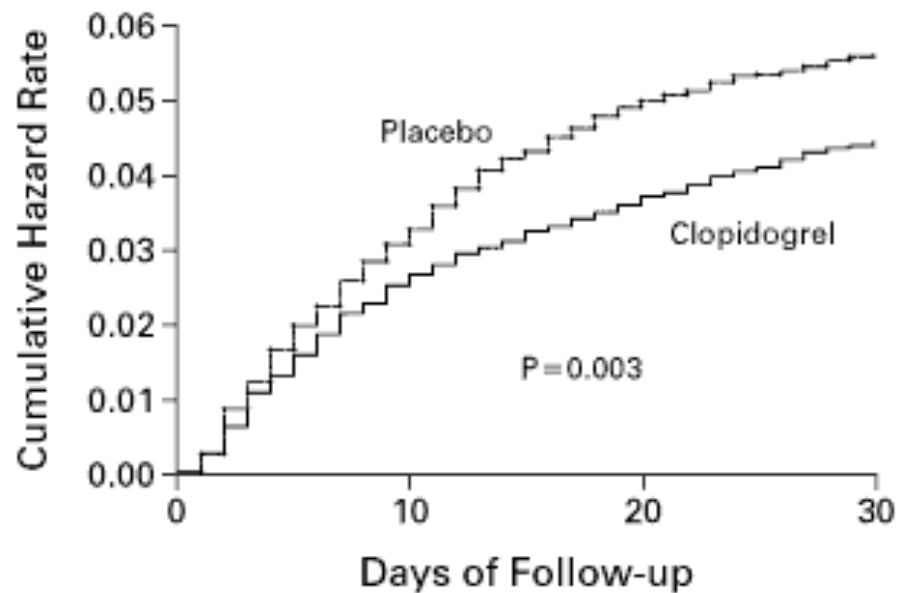
Treatment

- Clopidogrel/Prasugrel
  - Block ADP mediated platelet aggregation.
  - Good for stenting and for long-term treatment → may be multiple vulnerable plaques which can rupture.
  - Event rate post-ACS is 6-8% per year.
  - Also good acutely.

CURE trial (n=12652)
Plavix is class I indication in ACS.
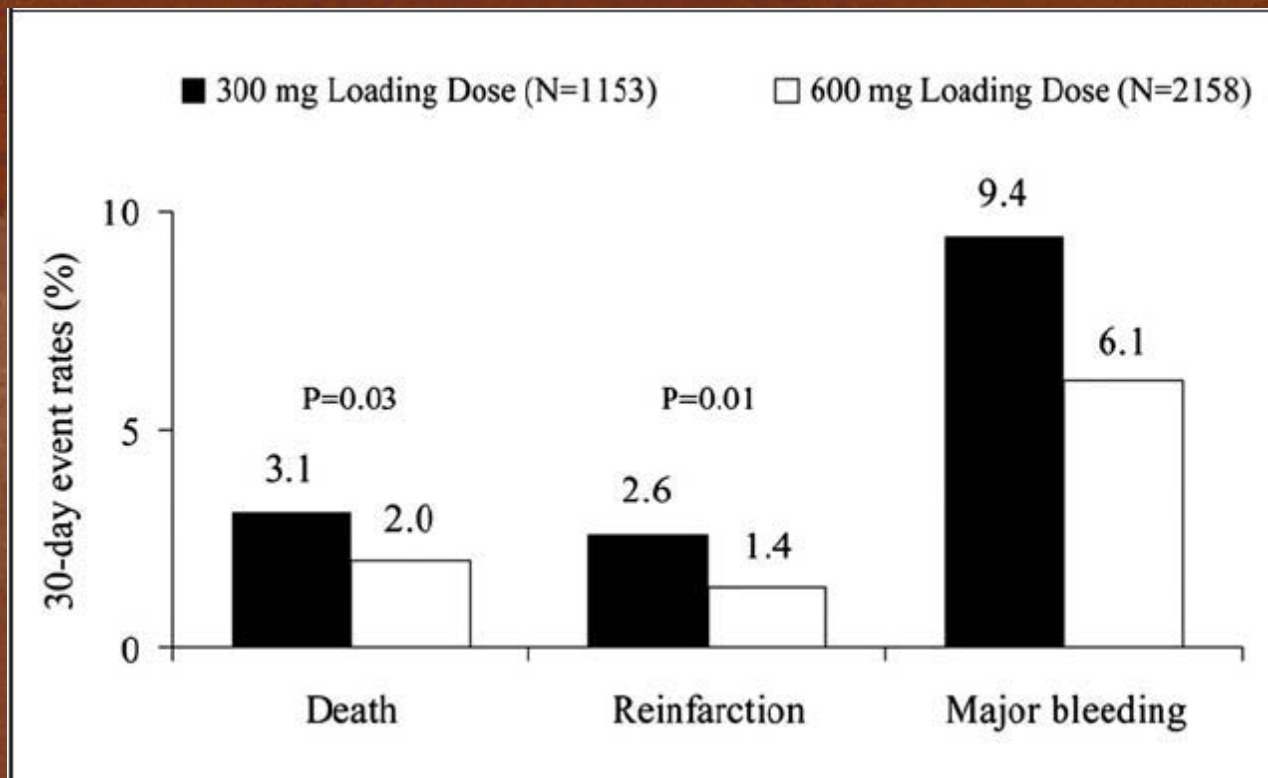## 300mg loading dose.

HORIZONS –AMI trial recently showed a Clopidogrel 600mg loading dose better than 300 mg in patient with AMI heading to the cath lab.

Role of Clopidogrel Loading Dose in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Angioplasty

Results From the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial
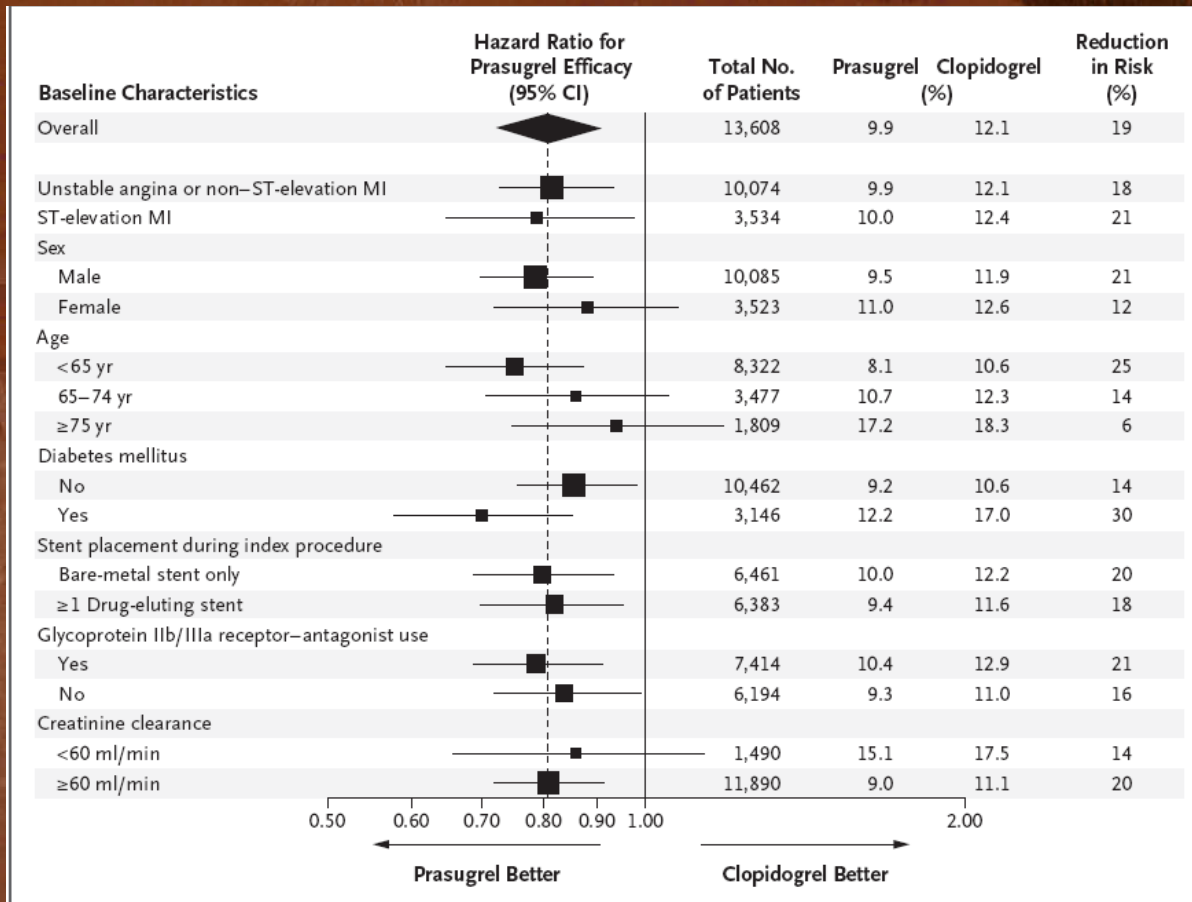
- 300 mg Loading Dose (N=1153)
- 600 mg Loading Dose (N=2158)

30-day event rates (%)

Event	P value	300 mg	600 mg
Death	P=0.03	3.1	2.0
Reinfarction	P=0.01	2.6	1.4
Major bleeding		9.4	6.1

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

N Engl J Med 2007;357:2001-15.

TRITON trial showed benefit of Prasugrel over clopidogrel for ACS if patient < 75 yrs and weight > 60 Kg. Prasugrel had higher bleeding rates particularly in the elderly .

Baseline Characteristics	Hazard Ratio for Prasugrel Efficacy (95% CI)	Total No. of Patients	Prasugrel (%)	Clopidogrel (%)	Reduction in Risk (%)
Overall		13,608	9.9	12.1	19
Unstable angina or non–ST-elevation MI		10,074	9.9	12.1	18
ST-elevation MI		3,534	10.0	12.4	21
Sex					
Male		10,085	9.5	11.9	21
Female		3,523	11.0	12.6	12
Age					
<65 yr		8,322	8.1	10.6	25
65–74 yr		3,477	10.7	12.3	14
≥75 yr		1,809	17.2	18.3	6
Diabetes mellitus					
No		10,462	9.2	10.6	14
Yes		3,146	12.2	17.0	30
Stent placement during index procedure					
Bare-metal stent only		6,461	10.0	12.2	20
≥1 Drug-eluting stent		6,383	9.4	11.6	18
Glycoprotein IIb/IIIa receptor–antagonist use					
Yes		7,414	10.4	12.9	21
No		6,194	9.3	11.0	16
Creatinine clearance					
<60 ml/min		1,490	15.1	17.5	14
≥60 ml/min		11,890	9.0	11.1	20

0.50 0.60 0.70 0.80 0.90 1.00   2.00

← Prasugrel Better   Clopidogrel Better →

Treatment

- Glycoprotein 2b/3a inhibitors
  - Eptifibatide, tirofiban for UA/NSTEMI useful if given upstream from PCI for ACS.
  - Alternatively abciximab can be given in the lab for UA/NSTEMI.
  - Abciximab only adjunctive therapy recommended for STEMI.

# TACTICS TIMI-18 – upstream Tirofiban for ACS before PCI
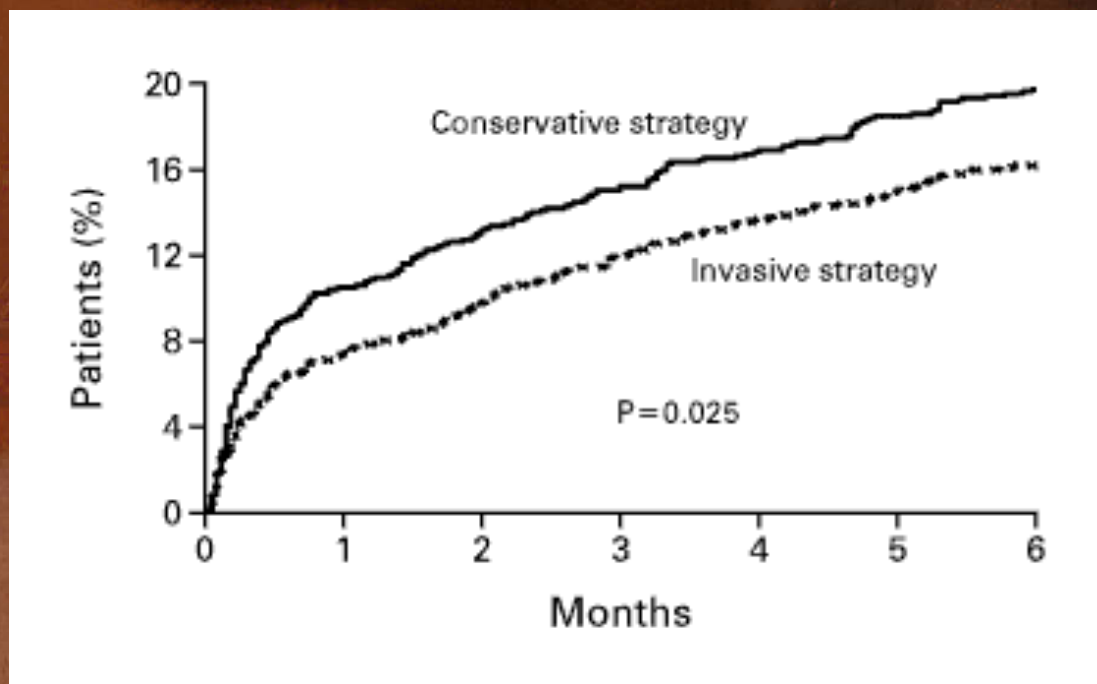
This study is why the vast majority of patients with ACS proceed to the cath lab. More recent data shows a selectively invasive strategy may be just as good with intervention only if recurrent events on appropriate medical therapy.

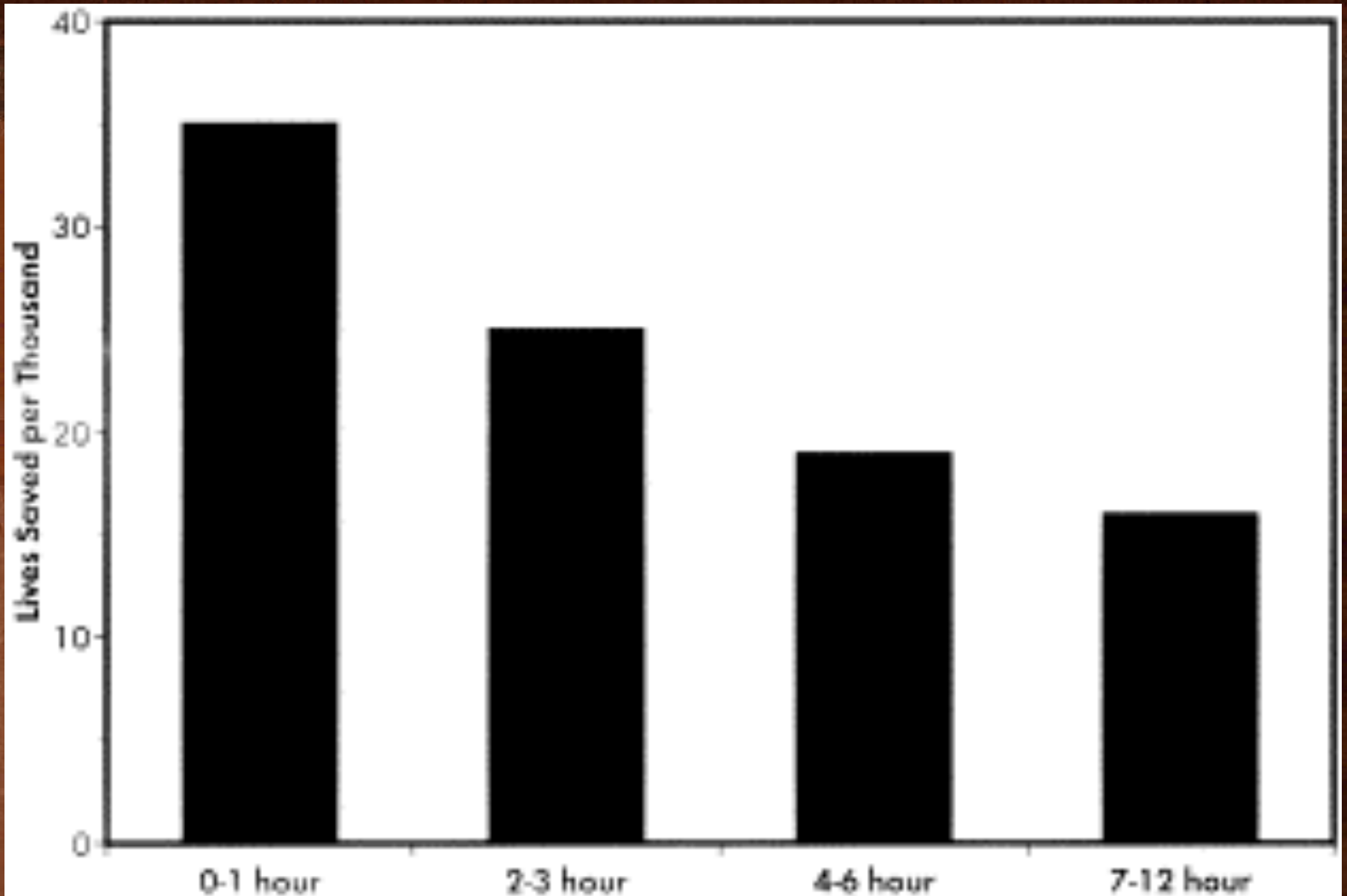# Acute ST-elevation MI

Proximal LAD occlusion.

Thrombolytics showed a ceiling on AMI mortality over time.
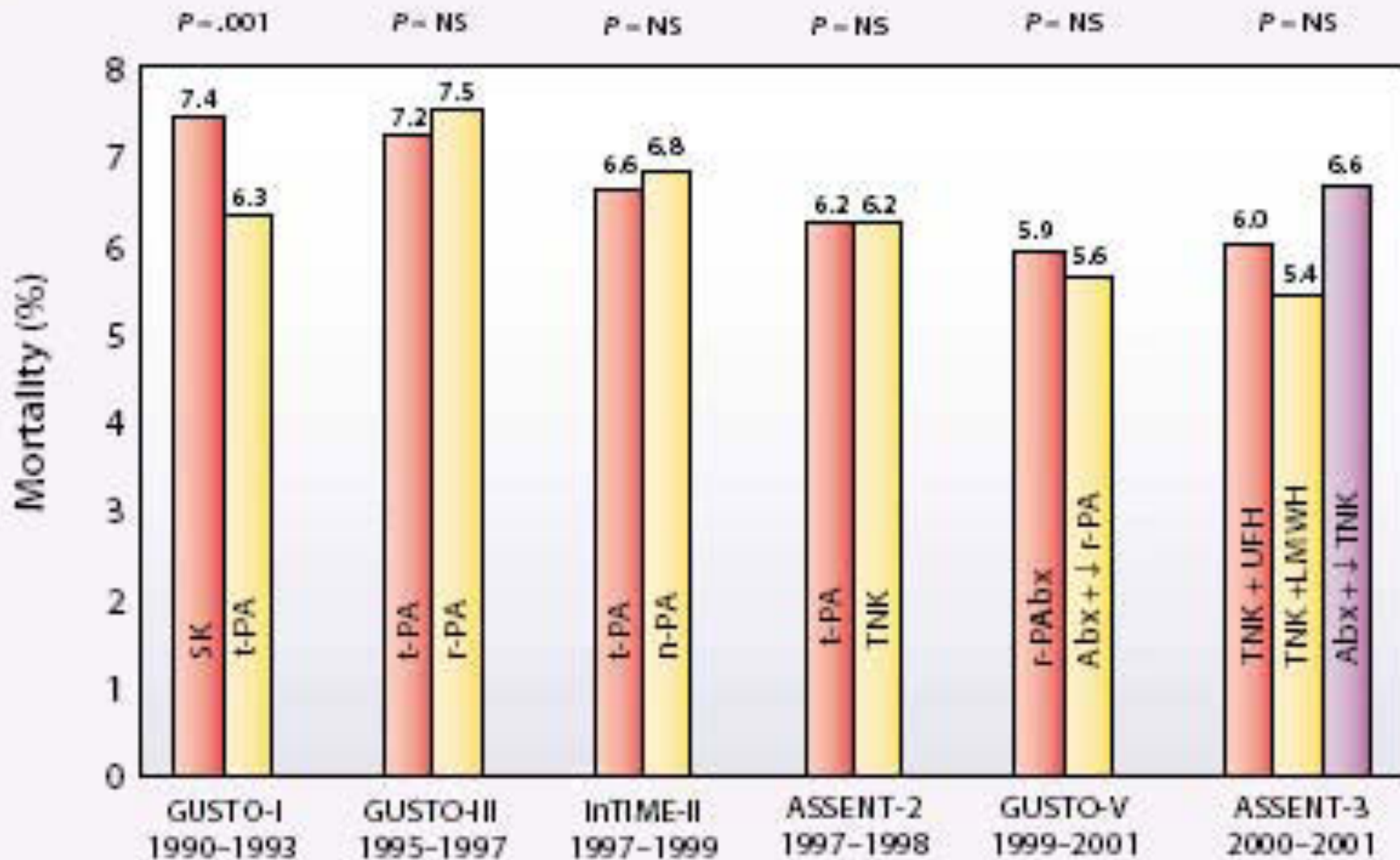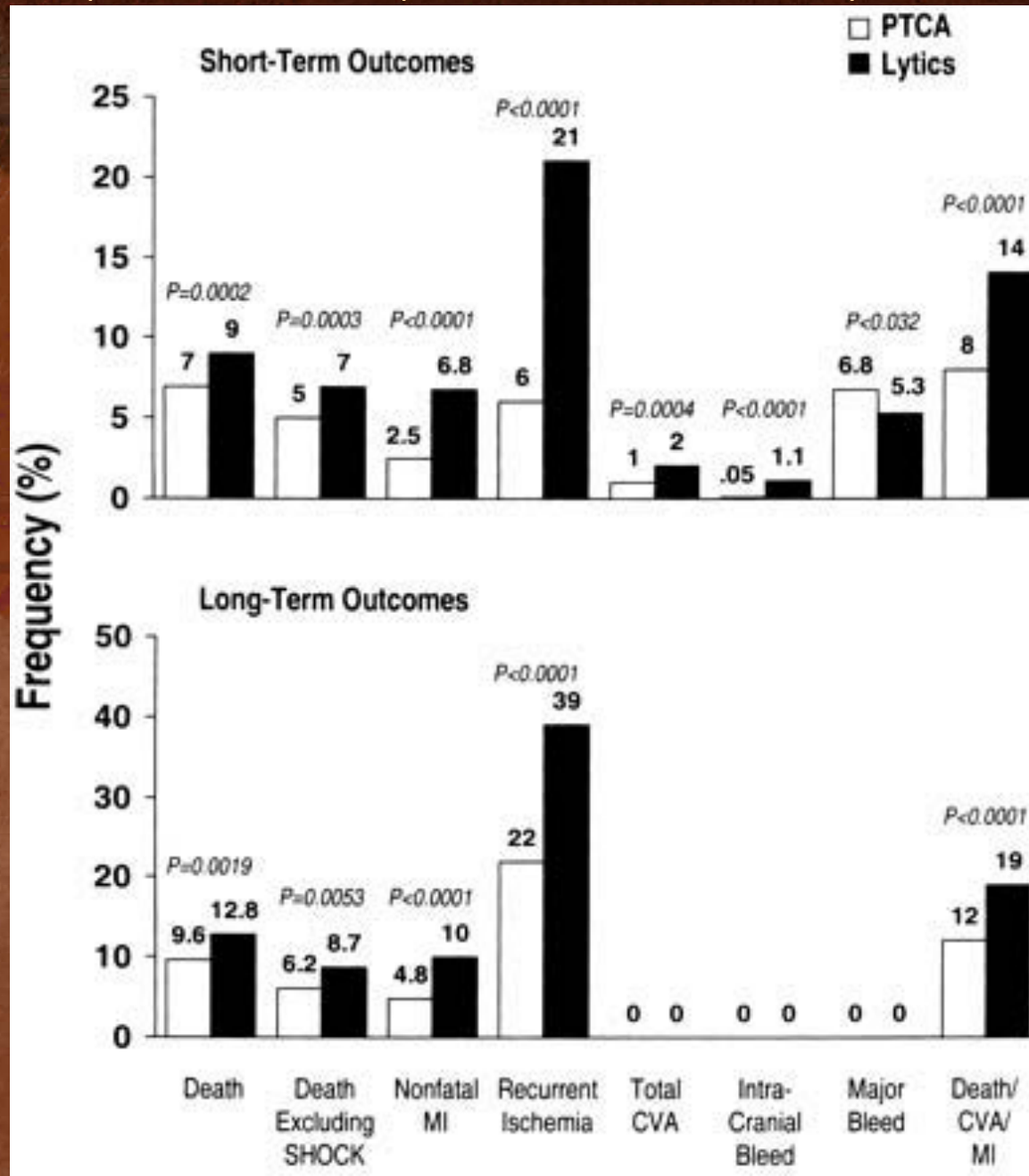
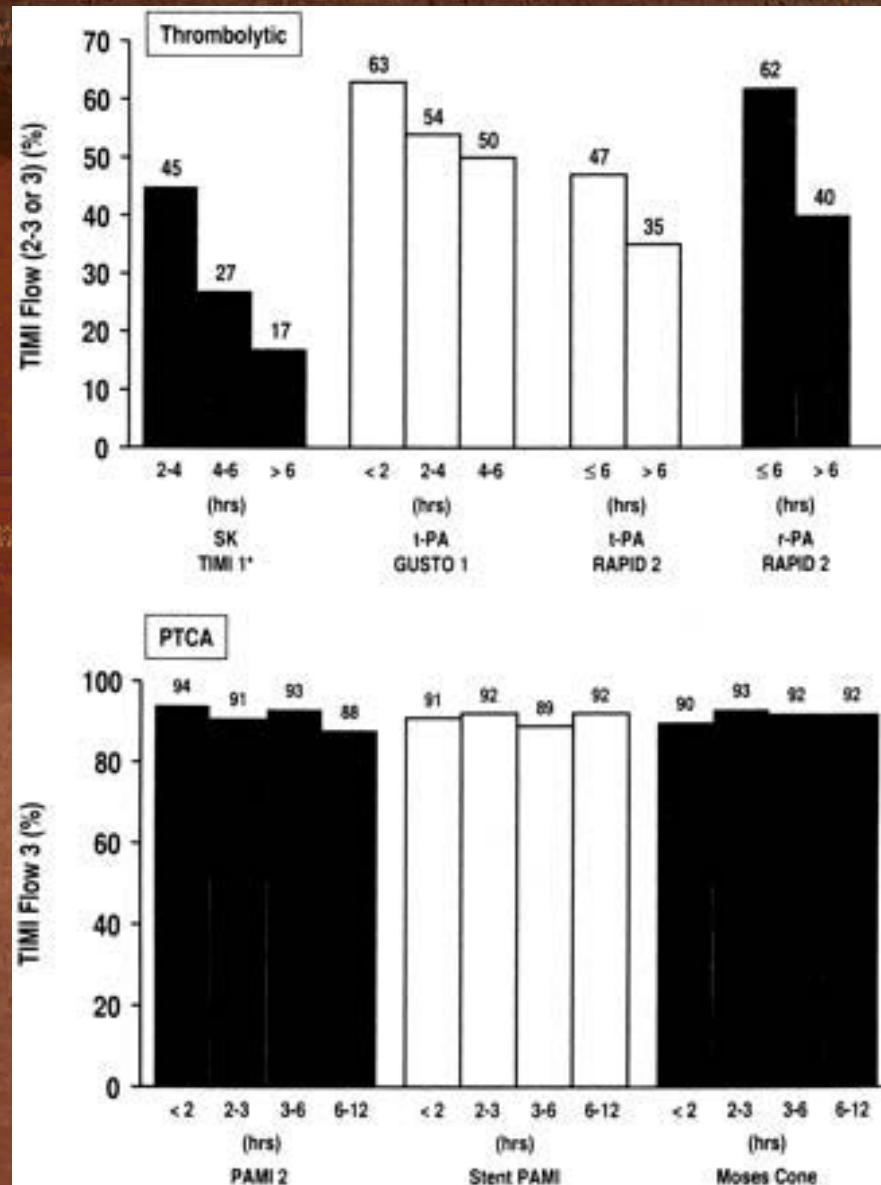# Intracranial Bleeding – big problem resulting in 66% mortality.
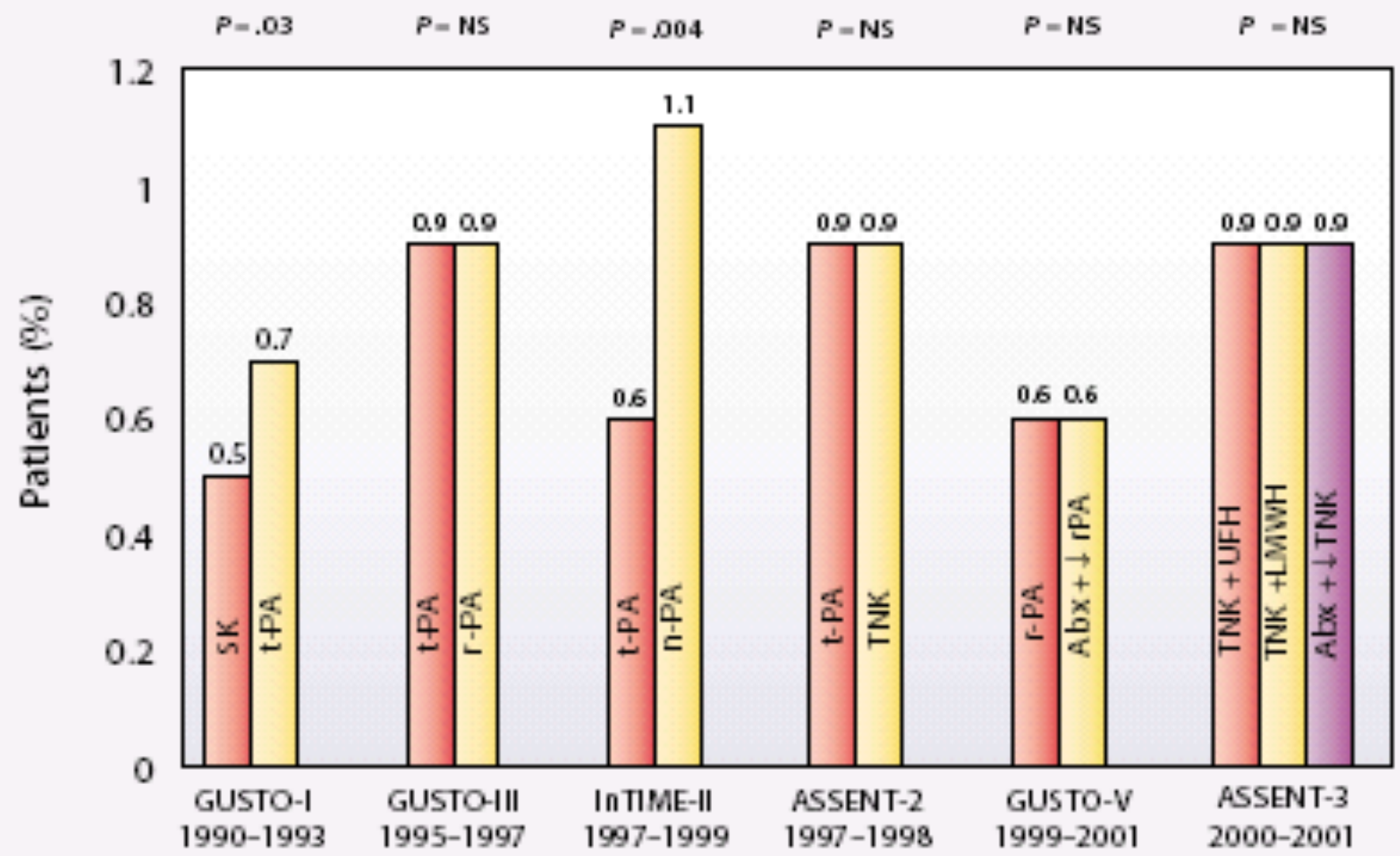
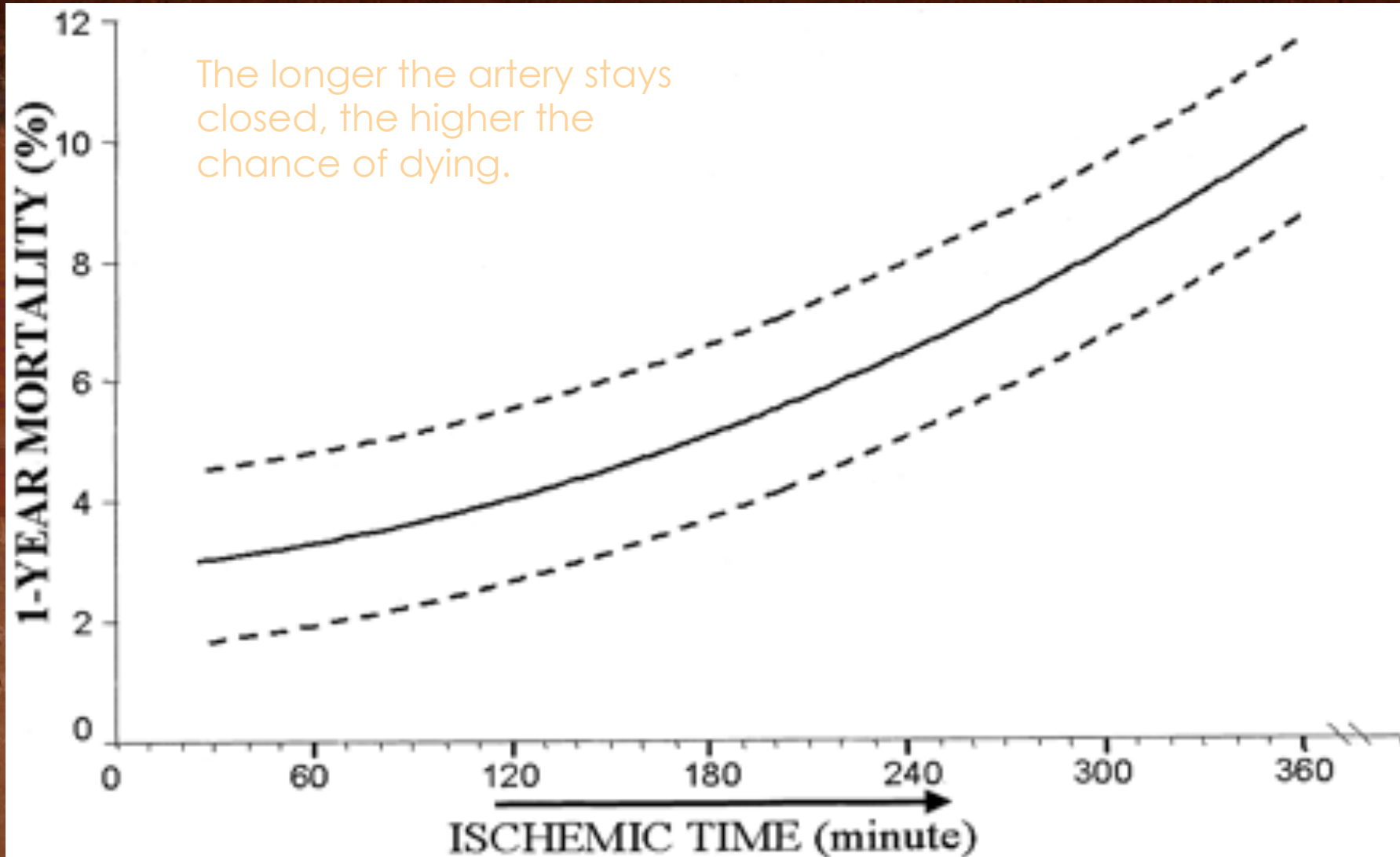The earlier the intervention for AMI, the more lives saved.

Primary PCI had definite benefit over thrombolytics when data were pooled – 2% improvement in mortality.

In addition to intracranial bleeding, thrombolytics are much less efficacious than PCI for reperfusion. TIMI 3 flow is normal flow.

The longer the artery stays closed, the higher the chance of dying.

A Comparison of Coronary Angioplasty with Fibrinolytic Therapy in Acute Myocardial Infarction

Henning R. Andersen, M.D., Torsten T. Nielsen, M.D., Klaus Rasmussen, M.D., Leif Thuesen, M.D., Henning Kelbaek, M.D., Per Thayssen, M.D., Ulrik Abildgaard, M.D., Flemming Pedersen, M.D., Jan K. Madsen, M.D., Peer Grande, M.D., Anton B. Villadsen, M.D., Lars R. Krusell, M.D., Torben Haghfelt, M.D., Preben Lomholt, M.D., Steen E. Husted, M.D., Else Vigholt, M.D., Henrik K. Kjaergard, M.D., and Leif Spange Mortensen, M.Sc., for the DANAMI-2 Investigators*

From this 2003 Danish trial, patients transferred for primary PCI did better than those that received thrombolytics, primarily by a dramatic reduction in re-infarction.

Table 3. Clinical Outcome at 30 Days.

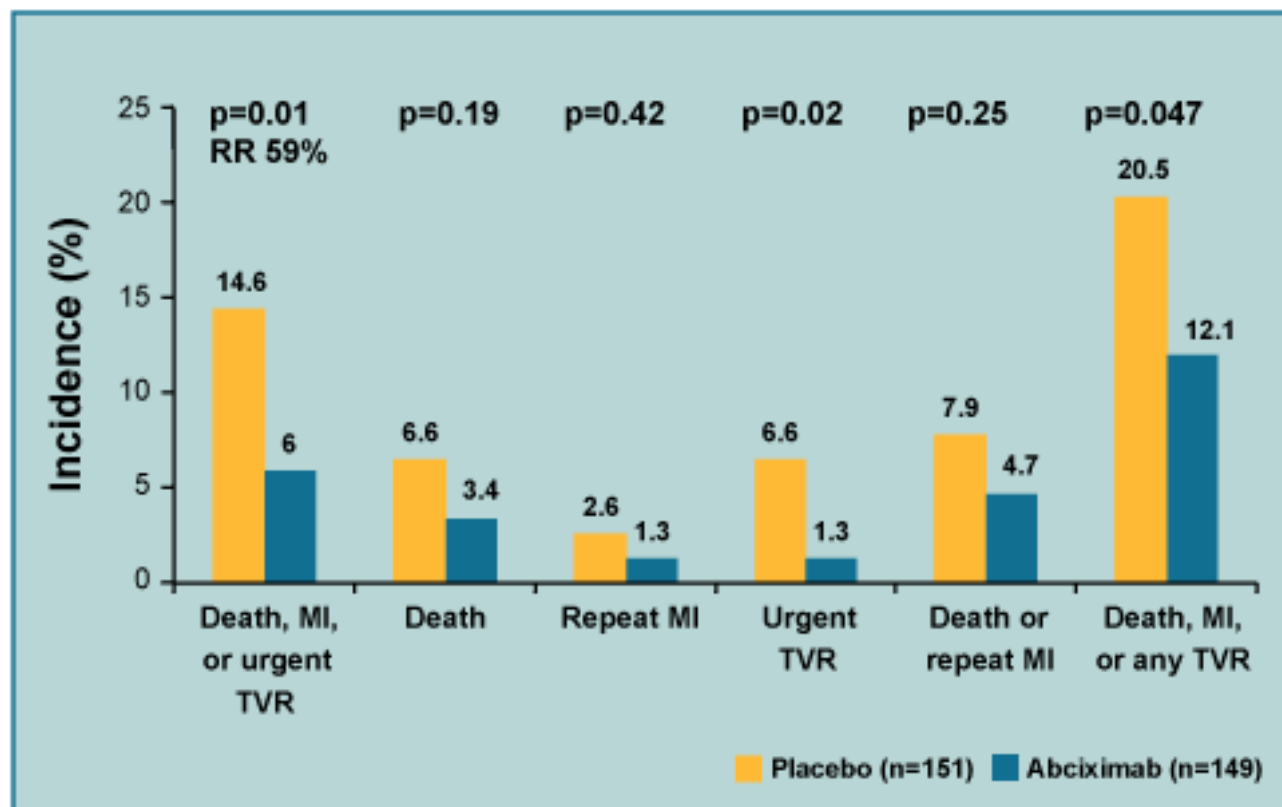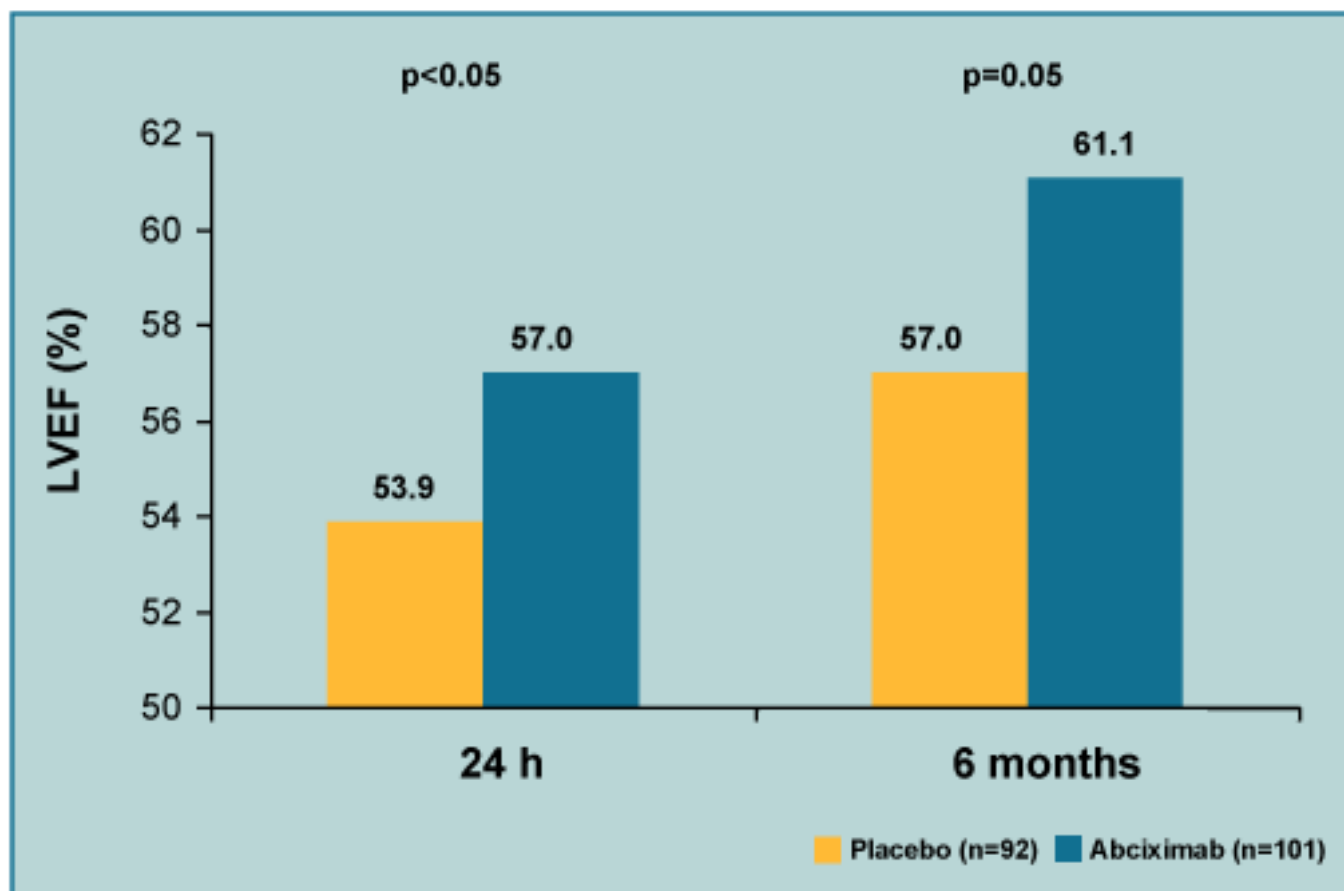| Outcome	Referral Hospitals			Invasive-Treatment Centers			All Hospitals		
	Fibrinolysis Group (N=562)	Angioplasty Group (N=567)	P Value	Fibrinolysis Group (N=220)	Angioplasty Group (N=223)	P Value	Fibrinolysis Group (N=782)	Angioplasty Group (N=790)	P Value
	no. (%)			*no. (%)*			*no. (%)*		
Death	48 (8.5)	37 (6.5)	0.20	13 (5.9)	15 (6.7)	0.72	61 (7.8)	52 (6.6)	0.35
Reinfarction	35 (6.2)	11 (1.9)	<0.001	14 (6.4)	2 (0.9)	0.002	49 (6.3)	13 (1.6)	<0.001
Disabling stroke	11 (2.0)	9 (1.6)	0.64	5 (2.3)	0	0.02	16 (2.0)	9 (1.1)	0.15
Composite end point	80 (14.2)	48 (8.5)	0.002	27 (12.3)	15 (6.7)	0.05	107 (13.7)	63 (8.0)	<0.001
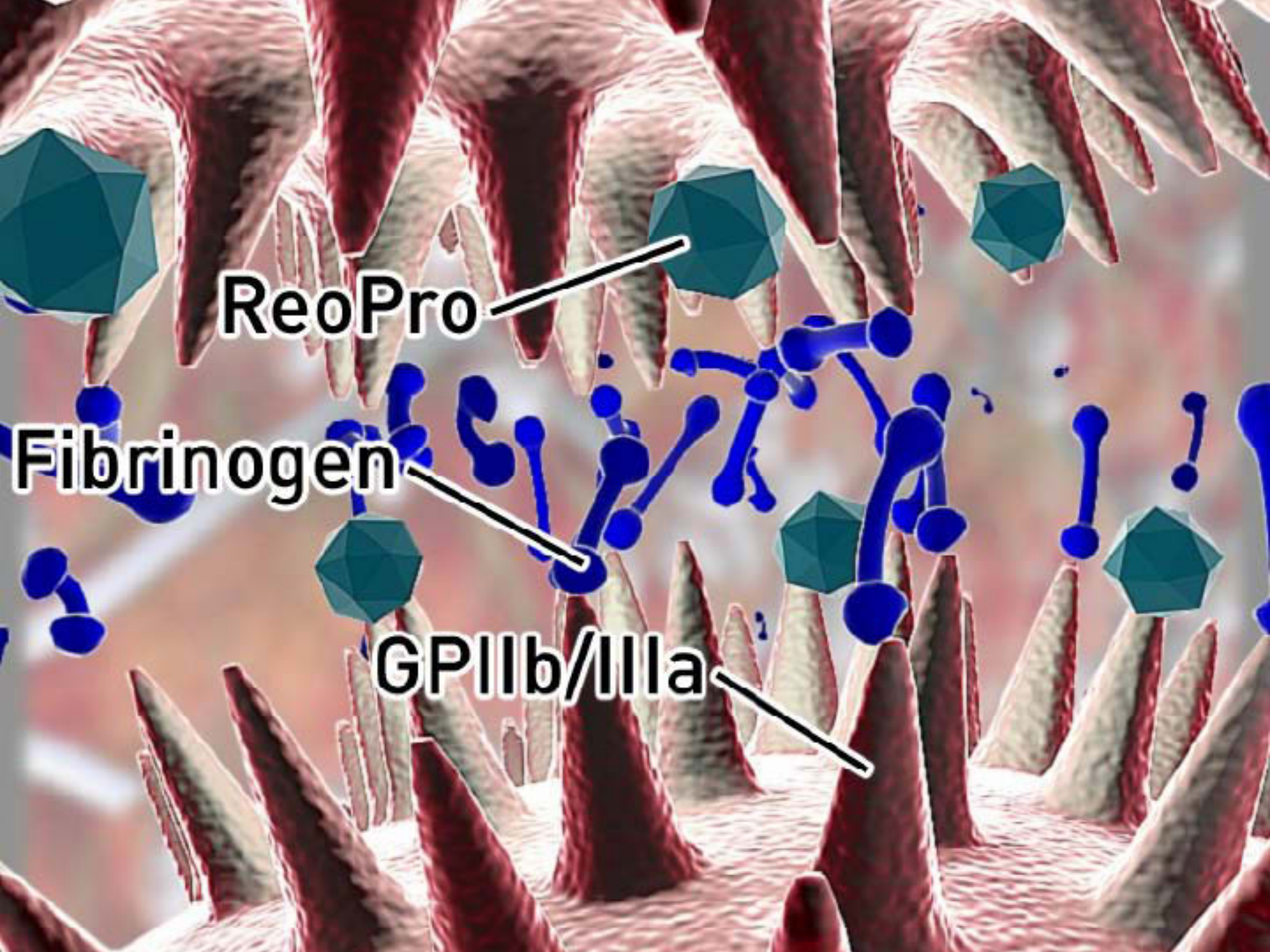
Abciximab

- Also known as Reopro is a glycoprotein 2b/3a receptor antagonist which is often given at the time of an AMI.
- It is the only GP 2b/3a inhibitor with randomized double-blind data showing benefit in AMI.
- It is given in the cath lab.
- It can rarely cause transient thrombocytopenia.

ADMIRAL: 30-Day Clinical Events

1. Montalescot G et al. *N Engl J Med* 2001;344:1895–903.

ADMIRAL: LVEF

1. Montalescot G et al. *N Engl J Med* 2001;**344**:1895–903.

Thrombocytopenia

In clinical trials, patients treated with abciximab were more likely than patients who received placebo to experience decreases in platelet counts (see Readministration)

Moderately lower rates were observed among patients treated with placebo plus standard-dose heparin.

EPILOG and EPISTENT patients treated with abciximab plus low-dose heparin	Patients (%)
Any thrombocytopenia (platelets <100,000 cells/µL)	2.5–3.0
Severe thrombocytopenia (platelets <50,000 cells/µL)	0.4–1.0
Platelet transfusions	0.9–1.1

Conclusions – three critical take home points

- High risk ACS patients benefit most from medical intervention and invasive management.

- Not all enzyme rises are related to thrombus formation.

- Earlier intervention on STEMI with PCI results in improved patient outcomes.