

Focused Update on Acute Coronary Syndrome



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Scope of Problem (2004 stats)

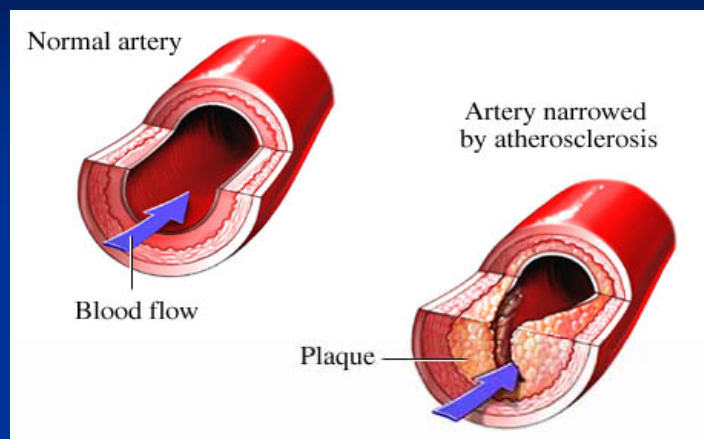
- **CHD one of the leading cause of death**
- **1,200,000 new & recurrent coronary attacks per year**
- **38% of those who with coronary attack die within a year of having it**
- **Annual cost > \$300 billion**



Objectives

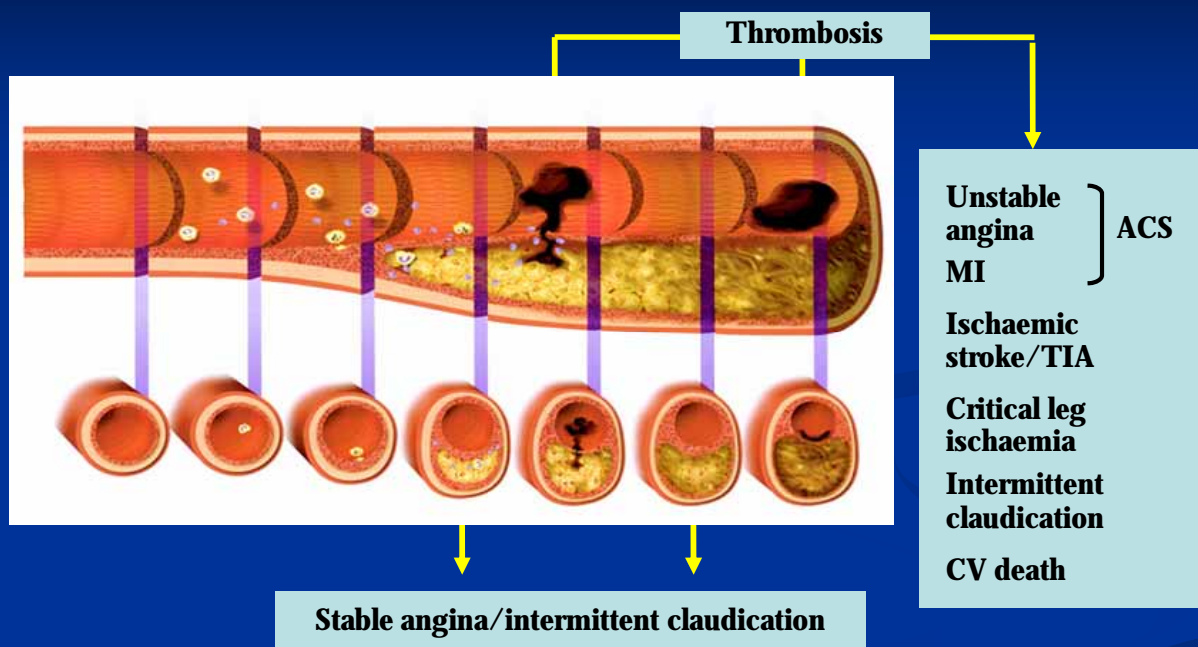
- **Define & delineate acute coronary syndrome**
- **Review Management Guidelines**
 - **Unstable Angina / NSTEMI**
 - **STEMI**
- **Review secondary prevention initiatives**

Coronary Artery Disease



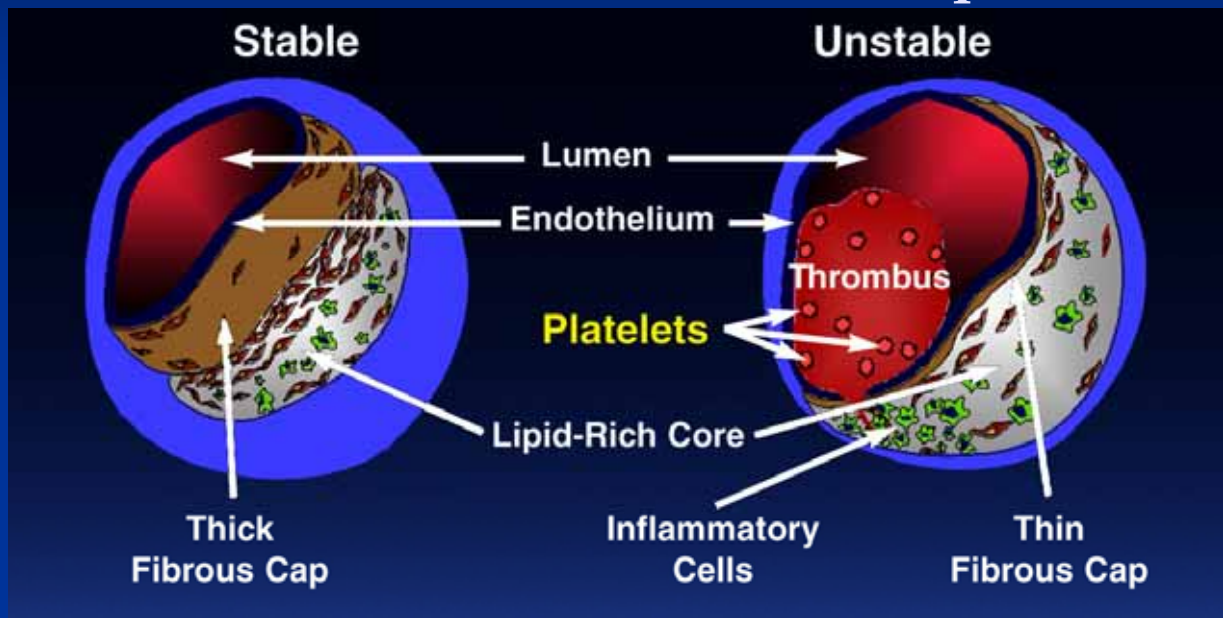
- **Development of cholesterol rich plaque within the walls of the coronary arteries (atherosclerosis) is the pathological process which underlies coronary artery disease**
- **Clinical Manifestation of this generic condition is varied**

Pathologic Progression to Atherothrombosis



MI=myocardial infarction; ACS=acute coronary syndromes; TIA=transient ischemic attack; CV=cardiovascular

Atherothrombosis: Thrombus Superimposed on Atherosclerotic Plaque



Adapted from Falk E, et al. Circulation. 1995;92:657-671.

Acute Coronary Syndromes

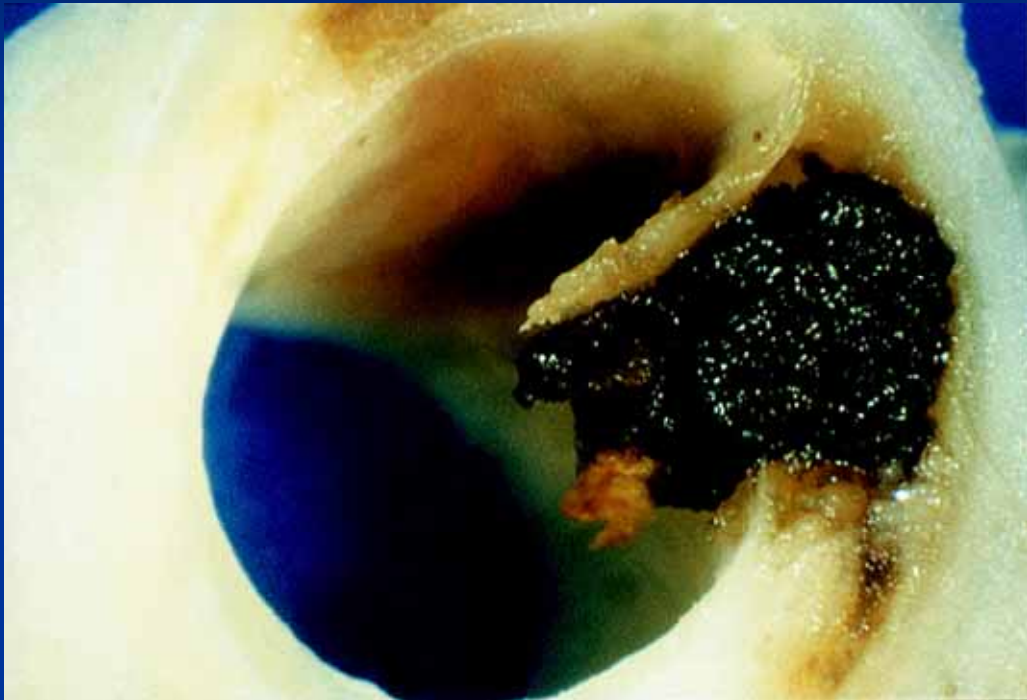
- **Unstable Angina**
- **Non-ST-Segment Elevation MI (NSTEMI)**
- **ST-Segment Elevation MI (STEMI)**

Similar pathophysiology

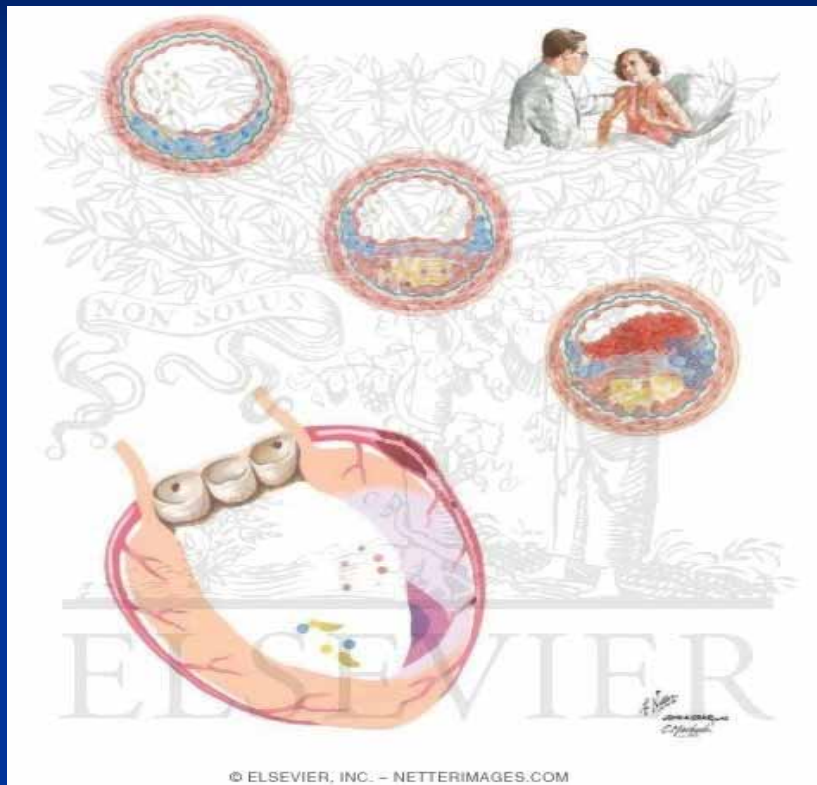
Similar presentation and early management rules

STEMI requires evaluation for acute reperfusion intervention

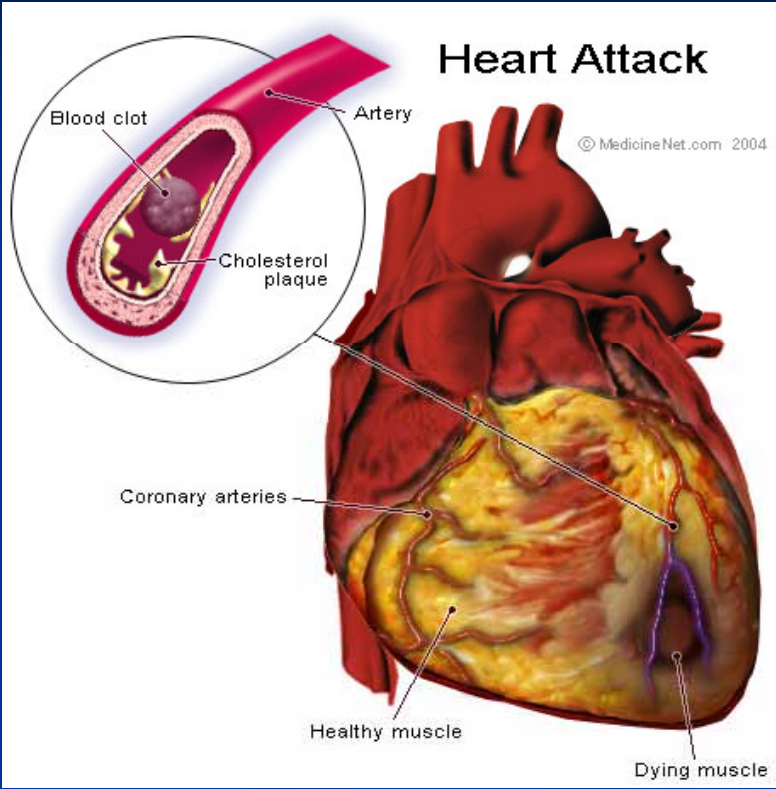
Ruptured Plaque



Non-ST elevation MI



ST Elevation MI



Diagnosis of Acute MI STEMI / NSTEMI

- **At least 2 of the following**
 - **Ischemic symptoms**
 - **Diagnostic ECG changes**
 - **Serum cardiac marker elevations**



Diagnosis of Angina

- **Typical angina—All three of the following**
 - **Substernal chest discomfort**
 - **Onset with exertion or emotional stress**
 - **Relief with rest or nitroglycerin**

- **Atypical angina**
 - **2 of the above criteria**

- **Noncardiac chest pain**
 - **1 of the above**

Diagnosis of Unstable Angina

- **Patients with typical angina - An episode of angina**
 - **Increased in severity or duration**
 - **Has onset at rest or at a low level of exertion**
 - **Unrelieved by the amount of nitroglycerin or rest that had previously relieved the pain**
- **Patients not known to have typical angina**
 - **First episode with usual activity or at rest within the previous two weeks**
 - **Prolonged pain at rest**

Unstable Angina

**Non occlusive
thrombus**

**Non specific
ECG**

**Normal cardiac
enzymes**

NSTEMI

**Occluding thrombus
sufficient to cause
tissue damage & mild
myocardial necrosis**

**ST depression +/-
T wave inversion on
ECG**

**Elevated cardiac
enzymes**

STEMI

**Complete thrombus
occlusion**

**ST elevations on
ECG or new LBBB**

**Elevated cardiac
enzymes**

**More severe
symptoms**

Acute Management



- **Initial evaluation & stabilization**
- **Efficient risk stratification**
- **Focused cardiac care**

Evaluation

- Efficient & direct history
 - Initiate stabilization interventions
- } Occurs simultaneously

Plan for moving rapidly to indicated cardiac care

**Directed Therapies
are
Time Sensitive!**

Chest pain suggestive of ischemia



Immediate assessment within 10 Minutes

Initial labs and tests

- 12 lead ECG
- Obtain initial cardiac enzymes
- electrolytes, cbc lipids, bun/creat, glucose, coags

Emergent care

- IV access
- Cardiac monitoring
- Oxygen
- Aspirin
- Nitrates

History & Physical

- Establish diagnosis
- Read ECG
- Identify complications
- Assess for reperfusion

Focused History

■ Aid in diagnosis and rule out other causes

- Palliative/Provocative factors
- Quality of discomfort
- Radiation
- Symptoms associated with discomfort
- Cardiac risk factors
- Past medical history - especially cardiac

■ Reperfusion questions

- Timing of presentation
- ECG c/w STEMI
- Contraindication to fibrinolysis
- Degree of STEMI risk

Targeted Physical

■ Examination

- Vitals
- Cardiovascular system
- Respiratory system
- Abdomen
- Neurological status

■ Recognize factors that increase risk

- Hypotension
- Tachycardia
- Pulmonary rales, JVD, pulmonary edema,
- New murmurs/heart sounds
- Diminished peripheral pulses
- Signs of stroke

ECG assessment

ST Elevation or new LBBB
STEMI

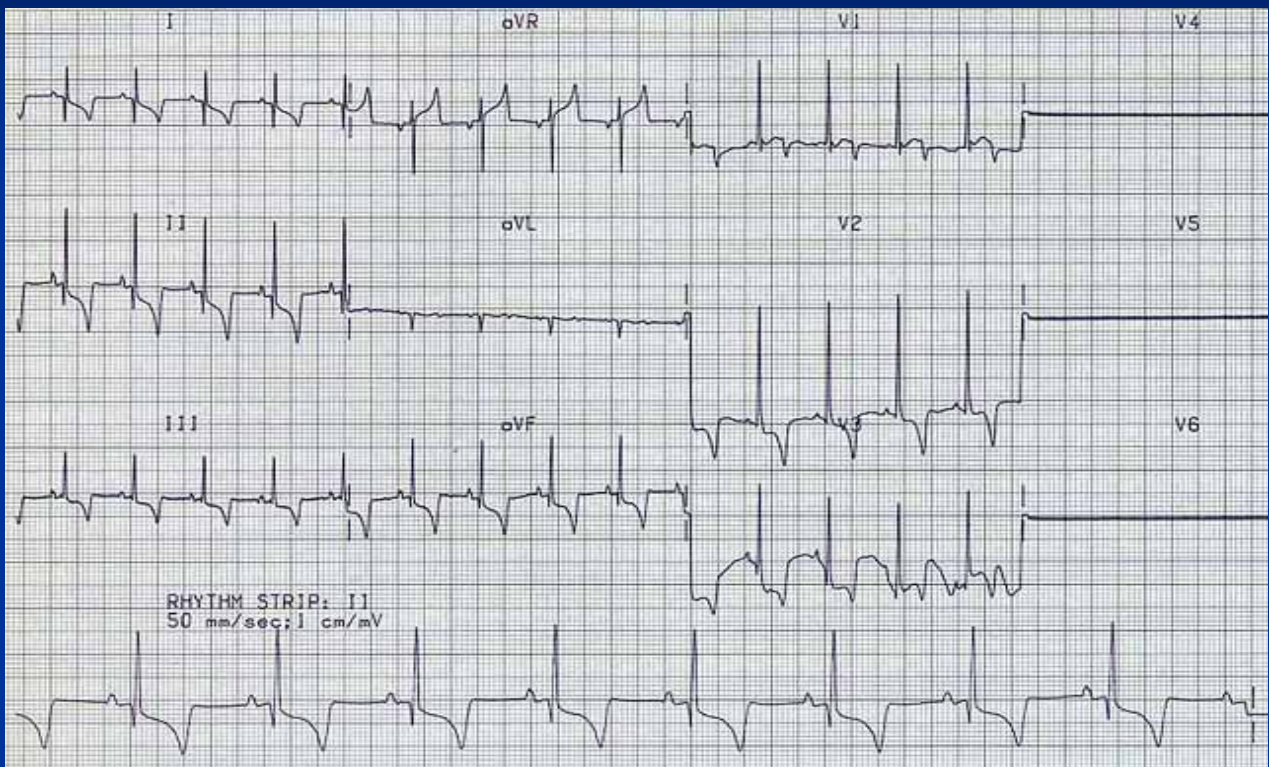
ST Depression or dynamic
T wave inversions
NSTEMI

Non-specific ECG
Unstable Angina

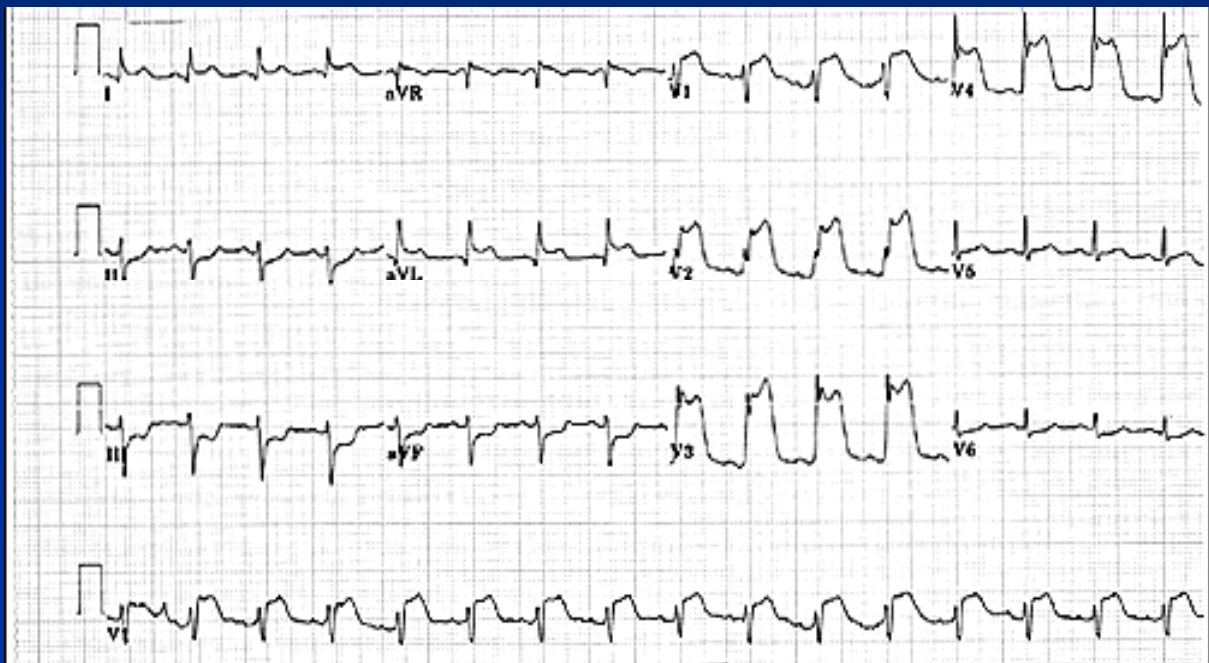
Normal or non-diagnostic EKG



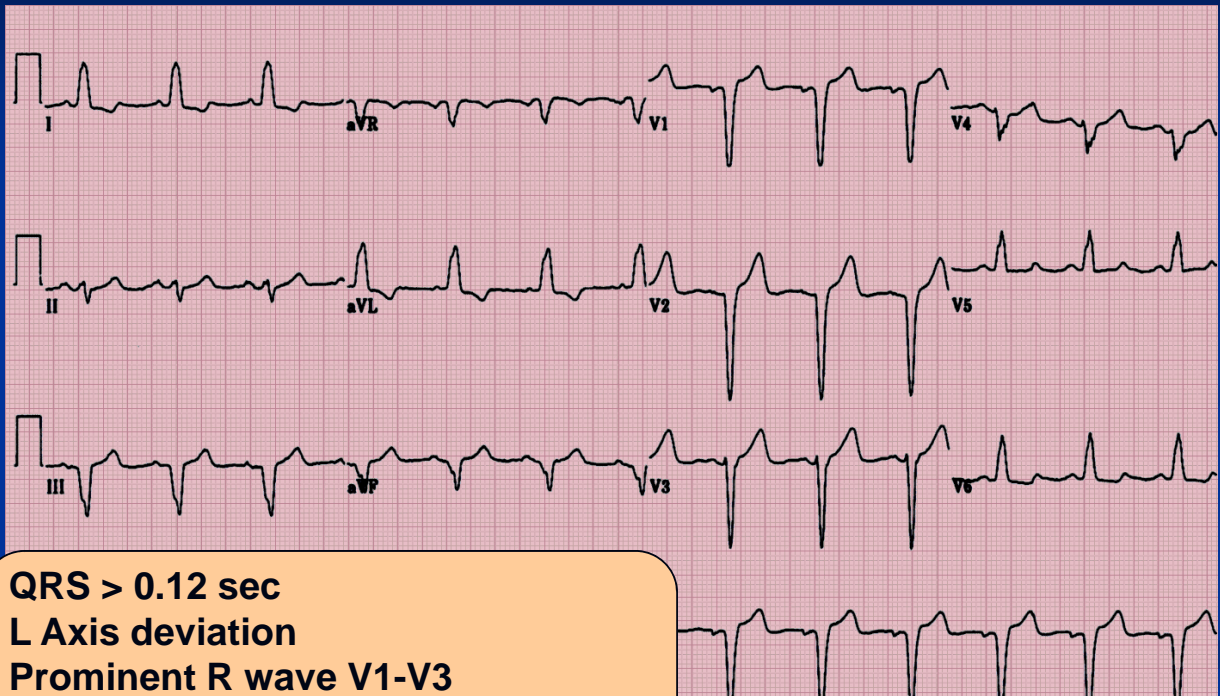
ST Depression or Dynamic T wave Inversions



ST-Segment Elevation MI



New LBBB



QRS > 0.12 sec
L Axis deviation
Prominent R wave V1-V3
Prominent S wave I, aVL, V5-V6
with t-wave inversion

Risk Stratification

Based on initial
Evaluation, ECG, and
Cardiac markers

**STEMI
Patient?**

YES

NO

- **Assess for reperfusion**
- **Select & implement reperfusion therapy**
- **Directed medical therapy**

UA or NSTEMI

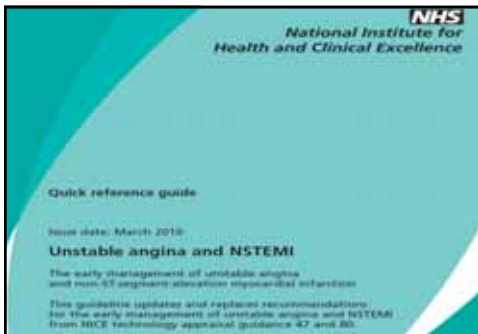
- **Evaluate for Invasive vs. conservative treatment**
- **Directed medical therapy**

Unstable angina/NSTEMI cardiac care

■ Evaluate for conservative vs. invasive therapy based upon:

- Risk of actual ACS
- Risk score to guide therapy and balance benefits of treatment
- ACS risk categories per guidelines





247 Core GRACE & GRACE² Study Sites in 30 Countries*



*30 countries = 16 GRACE² + 7 core GRACE + 7 both

Grace Risk Score

- Age
- Killip Class
- Heart Rate
- SBP
- Creatinine
- ST segment deviation
- Cardiac Arrest at admission
- Elevated cardiac enzymes

The screenshot shows the GRACE ACS Risk Model calculator interface. The window title is "Macromedia Flash Player 7". The interface includes a menu bar (File, View, Control, Help) and a header with the GRACE logo and "ACS Risk Model". There are two tabs: "At Admission (in-hospital/to 6 months)" and "At Discharge (to 6 months)". The "At Admission" tab is active. The form contains several input fields: Age (50-59), HR (70-69), SBP (120-139), Creat. (1.6-1.99), and CHF (III (pulmonary edema)). There are three checkboxes: "Cardiac arrest at admission", "ST-segment deviation", and "Elevated cardiac enzymes/markers", all of which are checked. A table shows the probability of Death and Death or MI for In-hospital and To 6 months. There are "SI Units" and "Reset" buttons. At the bottom, there are links for Calculator, Instructions, GRACE Info, References, and Disclaimer.

Probability of	Death	Death or MI
In-hospital	27%	50%
To 6 months	30%	70%

Cardiac markers

■ Troponin (T, I)

- **Very specific and more sensitive than CK**
- **Rises 4-8 hours after injury**
- **May remain elevated for up to two weeks**
- **As a prognostic marker ?**
- **Troponin T may be elevated with renal dz, poly/dermatomyositis**

■ CK-MB isoenzyme

- **Rises 4-6 hours after injury and peaks at 24 hours**
- **Remains elevated 36-48 hours**
- **Positive if CK/MB > 5% of total CK and 2 times normal**
- **Elevation can be predictive of mortality**
- **False positives with exercise, trauma, muscle dz, DM, PE**

Troponin as a prognostic marker???

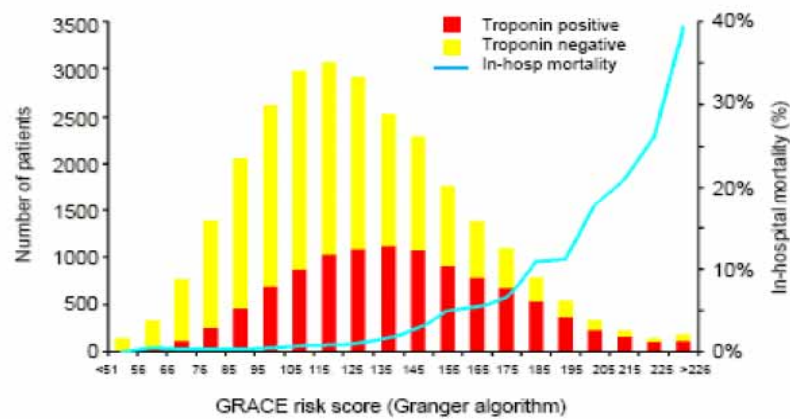


Figure 2-1. This bar chart describes the distribution of (left axis) troponin positive (red bars) and troponin negative (yellow bars) patients according to category of GRACE risk score (ranging from 51 to 226) among 27,406 patients with non-ST elevation acute coronary syndrome in the GRACE registry. The blue curve (right axis) depicts the observed hospital mortality rates.

Management Strategies

- Offer Coronary angiography with in 96 hours of admission to patients with intermediate or higher risk.
- Conservative management to low risk patients with option of angiography if ischemia recurs or is demonstrated

Antiplatelets Therapy

- **Aspirin:** recommended to all patients unless contraindicated. Initiate with a loading dose of 300 mg
- **Clopidogrel:** recommended to patients with risk score of more than 1.5% at 6 months. Loading dose of 300 mg and therapy to be continued for 1 year
- **Glycoprotein IIb/IIIa inhibitors:**
Consider eptifibatide or tirofiban for intermediate or high risk patients in whom angiogram is planned within 96 hours.
Aciximab to be considered only as adjunct during PCI

Antithrombin therapy

- **Fondoparinaux:** recommended if not planned for coronary angio in 24 hours, unless there is high bleeding risk in patients with creat < 265 micromoles/l
- **Unfractionated Heparin:** if planned for angio in 24 hours and also recommended in patients with creatinine >265 micromoles/l with weight adjustment
- **Direct Thrombin inhibitors such as Bivalirudin** can be offered to intermediate and high risk patients going for interventional procedures as an alternative to the combination of GPI with heparin

Fondaparinux(Arixtra)

- Synthetic pentasaccharide, selectively binds antithrombin III with greater affinity than heparin and cause inhibition of Factor X
- Dose of 2.5 mg once daily
- Not advised if Creat more than 265 Micromoles/l
- During PCI additional UFH should be administered because of the Risk of catheter thrombosis

Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators

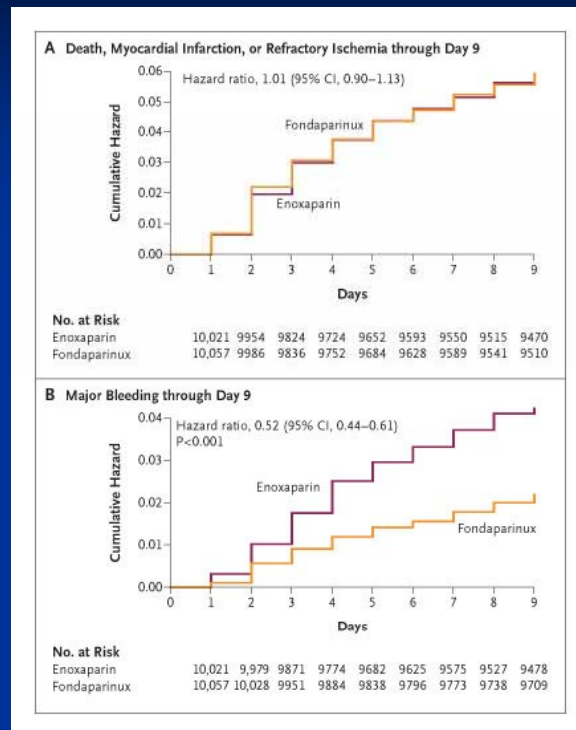
N Engl J Med
Volume 354;14:1464-1476
April 6, 2006

- **Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long term mortality and morbidity**



The NEW ENGLAND
JOURNAL of MEDICINE

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



The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators *N Engl J Med* 2006;354:1464-1476



The NEW ENGLAND
JOURNAL of MEDICINE

Bivalirudin(angiomax)

- **Direct inhibitor of soluble and clot bound thrombin**
- As an alternate for heparin and GPI combo for intermediate and high risk patients scheduled for coronary angiography with in 24 hours

Original Article

Bivalirudin for Patients with Acute Coronary Syndromes

Gregg W. Stone, M.D., Brent T. McLaurin, M.D., David A. Cox, M.D., Michel E. Bertrand, M.D., A. Michael Lincoff, M.D., Jeffrey W. Moses, M.D., Harvey D. White, M.D., Stuart J. Pocock, Ph.D., James H. Ware, Ph.D., Frederick Feit, M.D., Antonio Colombo, M.D., Philip E. Aylward, M.D., Angel R. Cequier, M.D., Harald Darius, M.D., Walter Desmet, M.D., Ramin Ebrahimi, M.D., Martial Hamon, M.D., Lars H. Rasmussen, M.D., Hans-Jürgen Rupprecht, M.D., James Hoekstra, M.D., Roxana Mehran, M.D., E. Magnus Ohman, M.D., for the ACUITY Investigators

Conclusion

- In patients with moderate- or high-risk acute coronary syndromes who were undergoing invasive treatment with glycoprotein IIb/IIIa inhibitors, bivalirudin was associated with rates of ischemia and bleeding that were similar to those with heparin
- Bivalirudin alone was associated with similar rates of ischemia and significantly lower rates of bleeding

N Engl J Med
Volume 355(21):2203-2216
November 23, 2006



The NEW ENGLAND
JOURNAL of MEDICINE

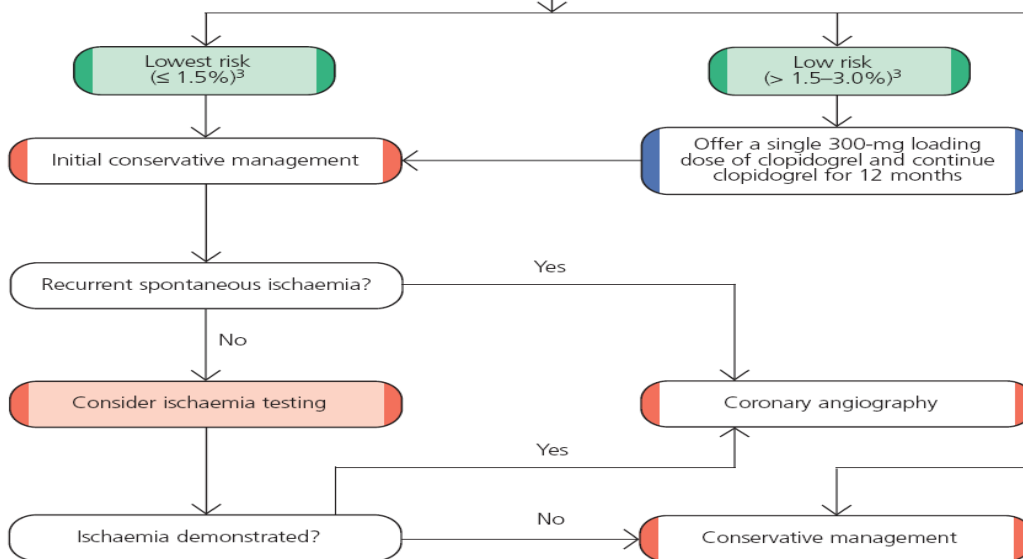
Directed Medical Therapy MONA + BAH

- **MORPHINE**
- **OXYGEN**
- **NITROGLYCERINE**
- **Aspirin**
- **BETABLOCKER**
- **ACE-I/ARB**
- **HEPARIN**

The early management of unstable angina and NSTEMI

- Offer a single loading dose of 300 mg aspirin and continue aspirin indefinitely
- Offer fondaparinux to patients without a high bleeding risk unless angiography is planned within 24 hours
- Offer unfractionated heparin if angiography is likely within 24 hours
- Carefully consider choice and dose of antithrombin for patients with a high bleeding risk (see box B)
 - Consider unfractionated heparin, with dose adjusted to clotting function, if creatinine > 265 micromoles per litre

Use established scoring system such as GRACE (see box A) to predict 6-month mortality and assess risk of future adverse cardiovascular events². Assess bleeding risk (see box B) and pertinent comorbidity before considering treatments and at each stage of management



Intermediate risk
(> 3.0–6.0%)³

High risk
(> 6.0–9.0%)³

Highest risk
(> 9.0%)³

- Offer a single 300-mg loading dose of clopidogrel⁴ and continue clopidogrel for 12 months
- Balance potential reduction in ischaemic risk with risk of bleeding and consider:
 - adding a GPI (eptifibatide or tirofiban), or
 - bivalirudin as an alternative to the combination of a heparin plus a GPI if the patient is not on fondaparinux or a GPI and angiography is scheduled within 24 hours of admission

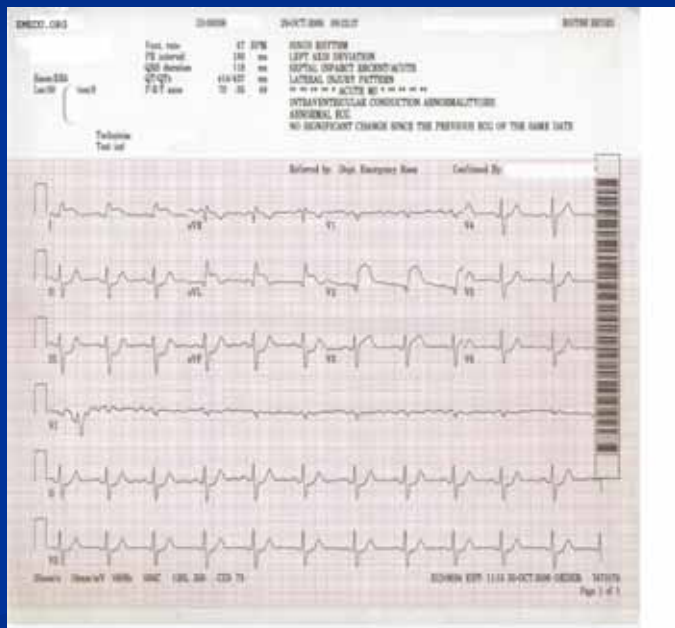
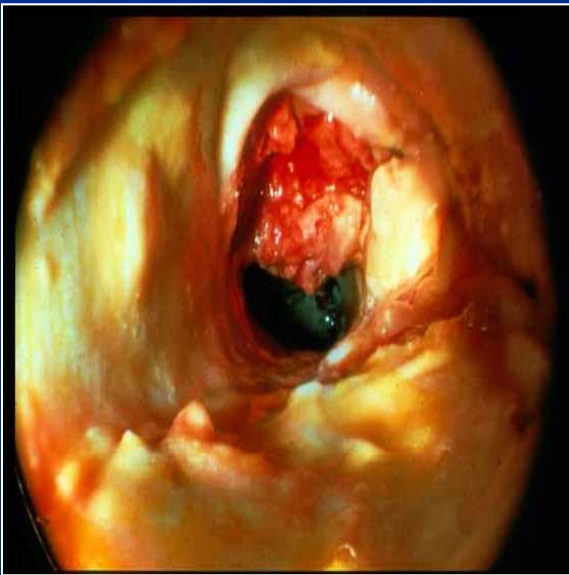
Offer coronary angiography (with follow-on PCI if indicated) within 96 hours of first admission unless contraindicated. Perform as soon as possible if patient is clinically unstable or at high ischaemic risk

Discuss management strategy with interventional cardiologist and cardiac surgeon. Consider angiographic findings, comorbidities and risks and benefits when discussing the choice of revascularisation strategy with the patient

- Percutaneous coronary intervention (PCI)**
- Consider abciximab for patients not on a GPI (eptifibatide, tirofiban)
 - Offer systemic unfractionated heparin (50–100 units/kg) to patients on fondaparinux
 - Consider bivalirudin as an alternative to the combination of a heparin plus a GPI for patients not on a GPI or fondaparinux

- Coronary artery bypass grafting (CABG)**
- Consider stopping clopidogrel 5 days before CABG in patients with low risk of adverse cardiovascular events
 - Discuss with surgeon whether to continue clopidogrel before CABG in patients with intermediate or higher risk of adverse cardiovascular events

Acute ST Elevation Myocardial Infarction



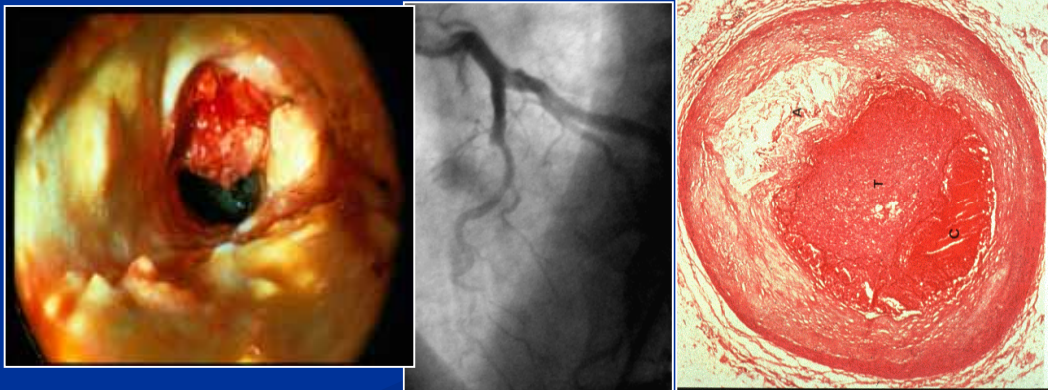
Motto

“Reperfusion therapy for acute myocardial infarction is a milestone achievement in the 20th century cardiology”

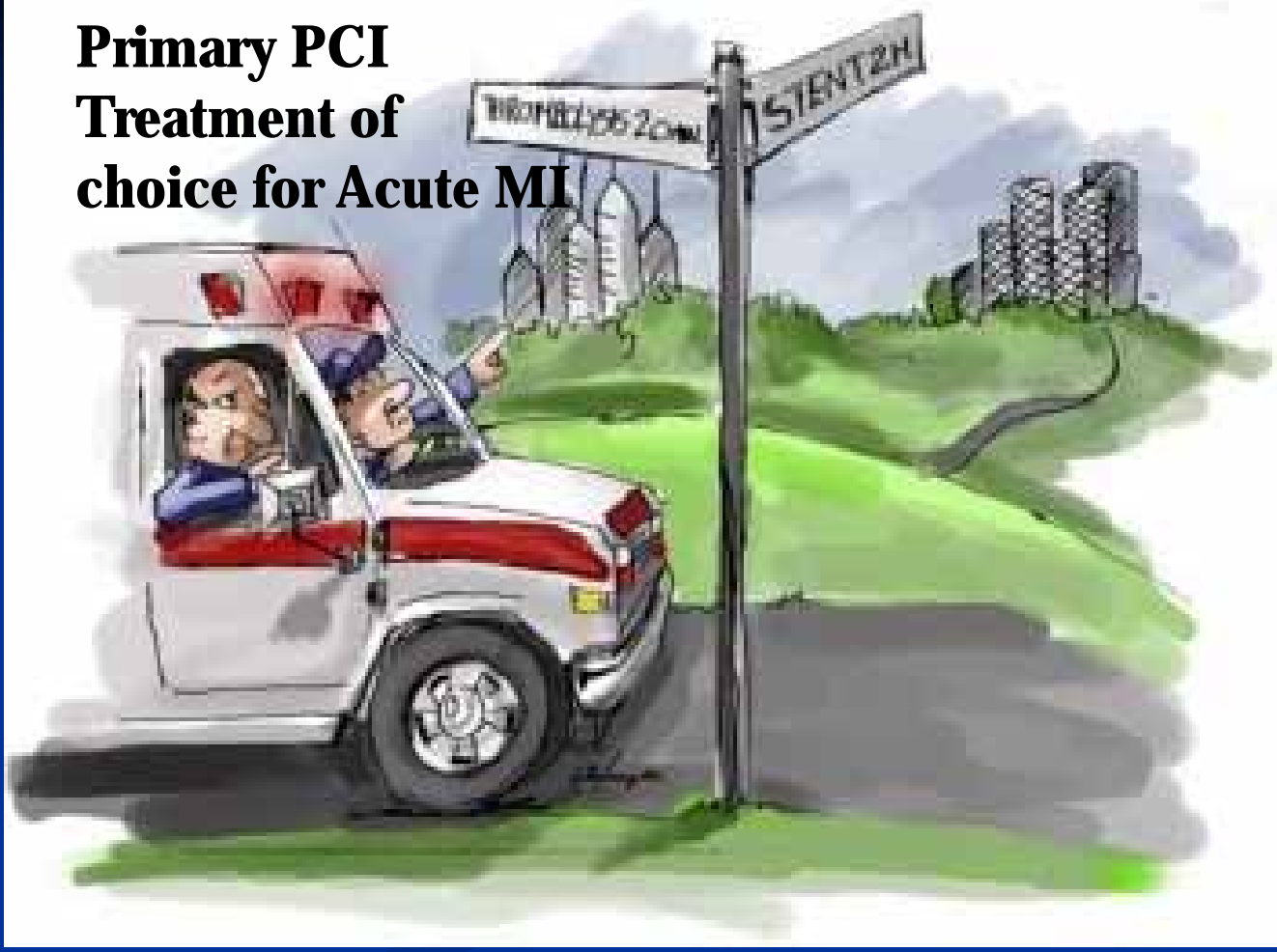
Eugene Braunwald 2002

AIMS OF OUR THERAPY

- To re-establish NORMAL flow in the coronary
- Decrease amount of myocardial necrosis and
 - Preserve LV function
 - Prevent Major adverse cardiac events
 - Treat life threatening complications



**Primary PCI
Treatment of
choice for Acute MI**



Benefits of Direct Angioplasty

- **High Arterial Patency**
- **Earlier Arterial Patency**
- **More Complete reperfusion**
- **Smaller infarction**
- **Better Ventricular function**
- **Fewer CVAs**
- **Improved Mortality**
- **Shorter Hospital stay**
- **Less cost**

Primary PCI

Thrombosaurus Rex

- Success Rate more than 98%
- TIMI 3 flow > 90%
- Complications less than 2%
- Long term mortality better



EXTINCTOPLASE ?

ESC Recommendation on Reperfusion Therapy- Primary PCI

- **Preferred Reperfusion treatment if performed by an experienced team soon as possible after FMC**
- **Time from FMC to Balloon should be <2 hours in any case and < 90 mts in patients presenting early(e.g. < 2 hours) with large infarct and low bleeding risk.**
- **Indicated for patients in shock and with contraindications for fibrinolysis irrespective of time delay.**
- **Rescue PCI: After failed fibrinolysis in patients with large infarcts if performed with in 12 hours.**
- **PCI in stable patients presenting >12-24 hours after symptom onset**



Can a single case ever make a bullet proof argument?

Mr P

Previously fit 75 yr old

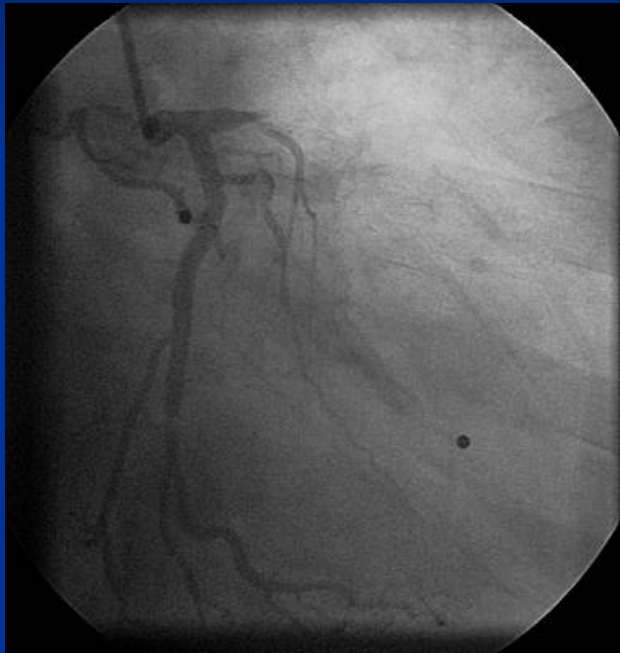
Presented with 3 hr h/o chest pain to local A&E: ST elevation

0100 Rx: aspirin + Streptokinase

0315 Call to Cardiologist continued pain; no ST resolution

0530 On cath lab table..... Systolic 95, pulmonary oedema

This is just one case..... What does it tell us?

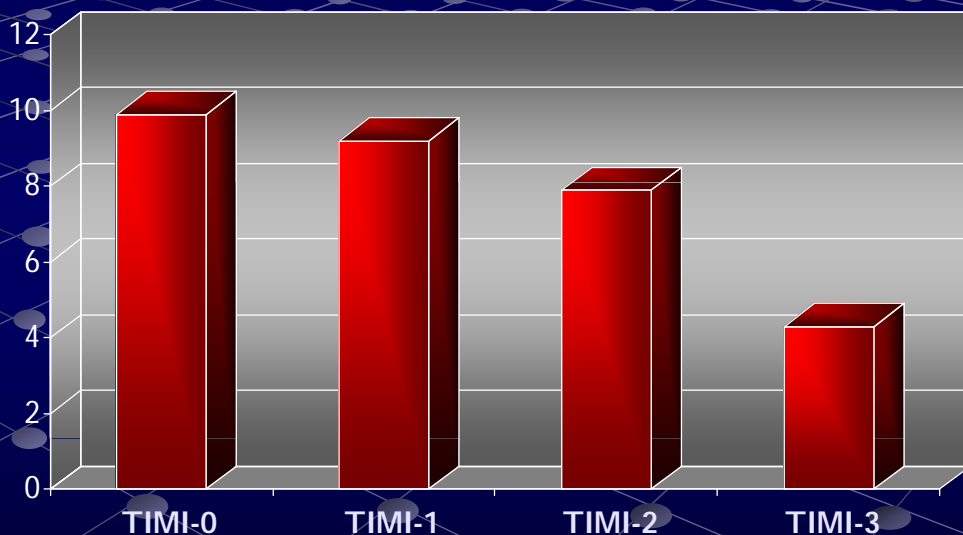


- In the current era of interventional cardiology this patient has had a second best and inferior treatment
- Its time we delivered PPCI to the majority of the patients

So what's wrong with thrombolysis?

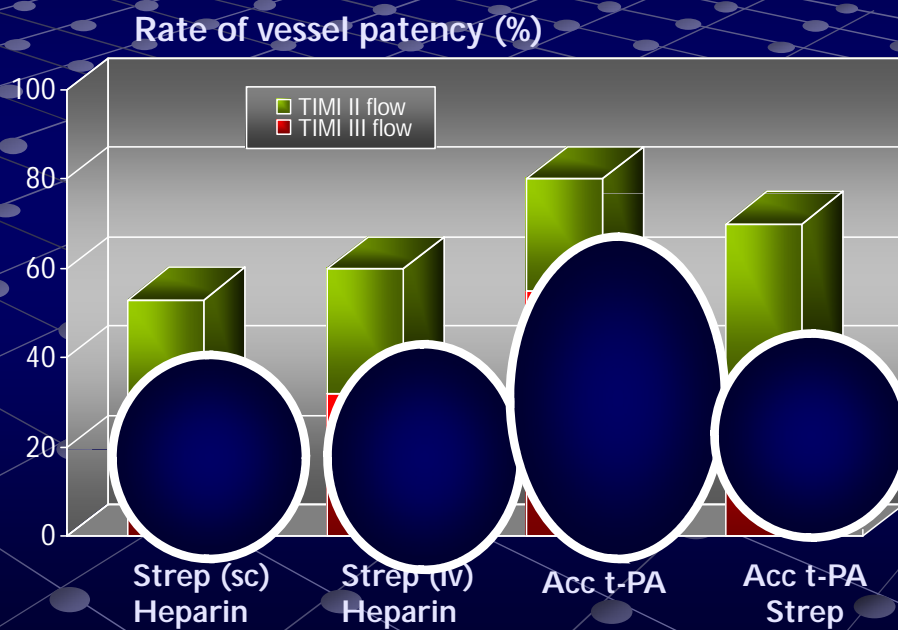
Infarct vessel patency status at 90 minutes related to mortality at 30 days in the GUSTO-I angiographic trial

Mortality (%) at 30 days



Infarct vessel patency at 90 minutes

Patency of infarct-related arteries in patients treated with thrombolysis



Target of AMI therapy = TIMI 3 flow

<u>GUSTO-1</u>	<u>90 min TIMI III</u>
SK	29%
tPA	54%

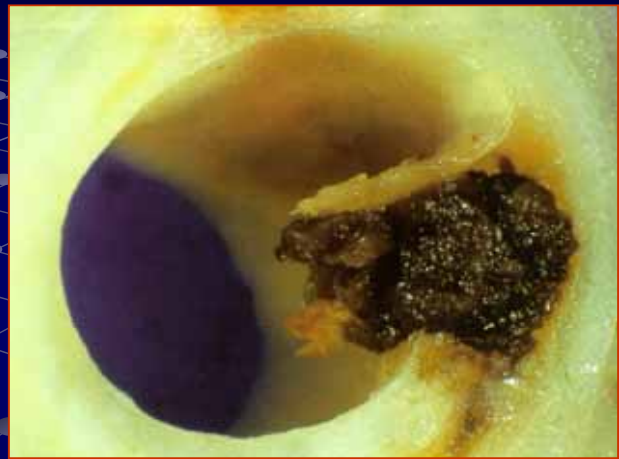
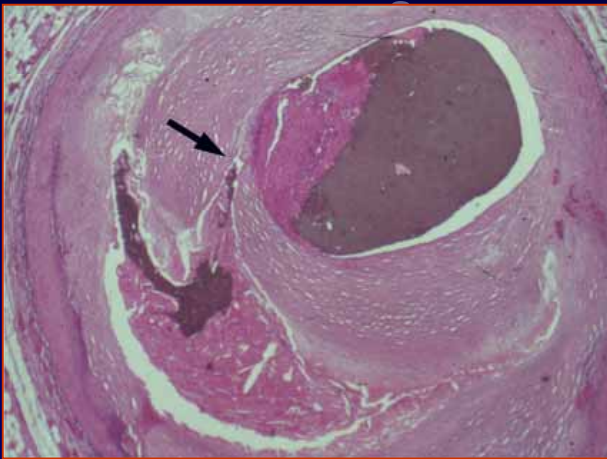
	<u>30 day mortality</u>
TIMI 0/1	8.9%
TIMI 2	7.2%
TIMI 3	4.4%

□ Prehospital discharge reocclusion of IRA 12-32% in patients successfully treated with thrombolysis *Am J Cardiol 1998;82:554-8*

□ 12.3% IRA reocclusion rate in 733 patients after successful thrombolysis.....

Reocclusion "silent" in almost 50% *Circulation 1990;82:781-91*

Thrombolysis addresses only the clot.....
NOT the Ruptured plaque-fissure



That's why so many patients need

- "Rescue PCI"
- Subsequent revascularisation on the admission or later

That's why current ESC guidelines recommend routine
PCI within 24 hours of "successful" thrombolysis
Eur Heart Journal 2005;26:804-847

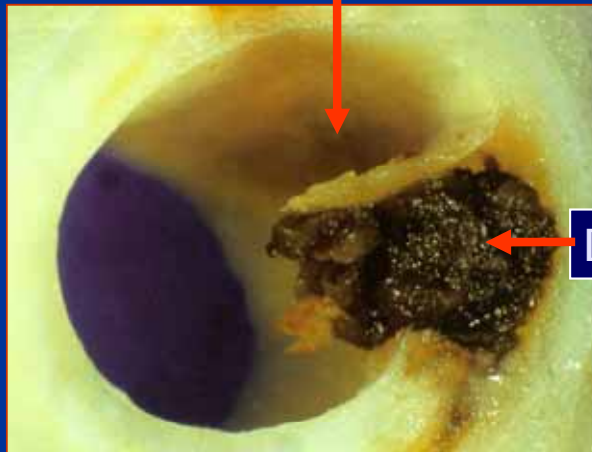
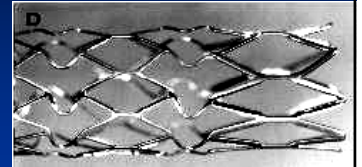
Bottom Line About Thrombolysis

- ❑ 30% reocclusion of the IRA in first 30 days after thrombolysis
- ❑ TIMI 3 flow only achieved in 30-70% of patients
- ❑ In "real life" registries, 30% of STEMI patients ineligible for thrombolysis and total of 48% NOT thrombolysed!!
- ❑ For every 50 STEMI patients treated with PPCI vs. thrombolysis:....
1 life is saved and 2 other major complications (stroke or reinfarction)
Prevented
- ❑ Requirement for revasc in group Rxed by thrombolysis is
70% at 1 year!!!



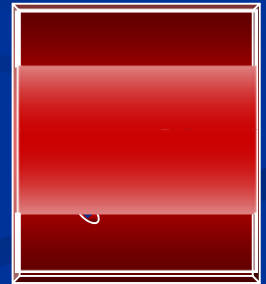
Strategies in Treatment of STEMI

Stent the Mechanical Obstruction (stenosis)



Dissolve the Clot

Reduce the Inflammatory Response



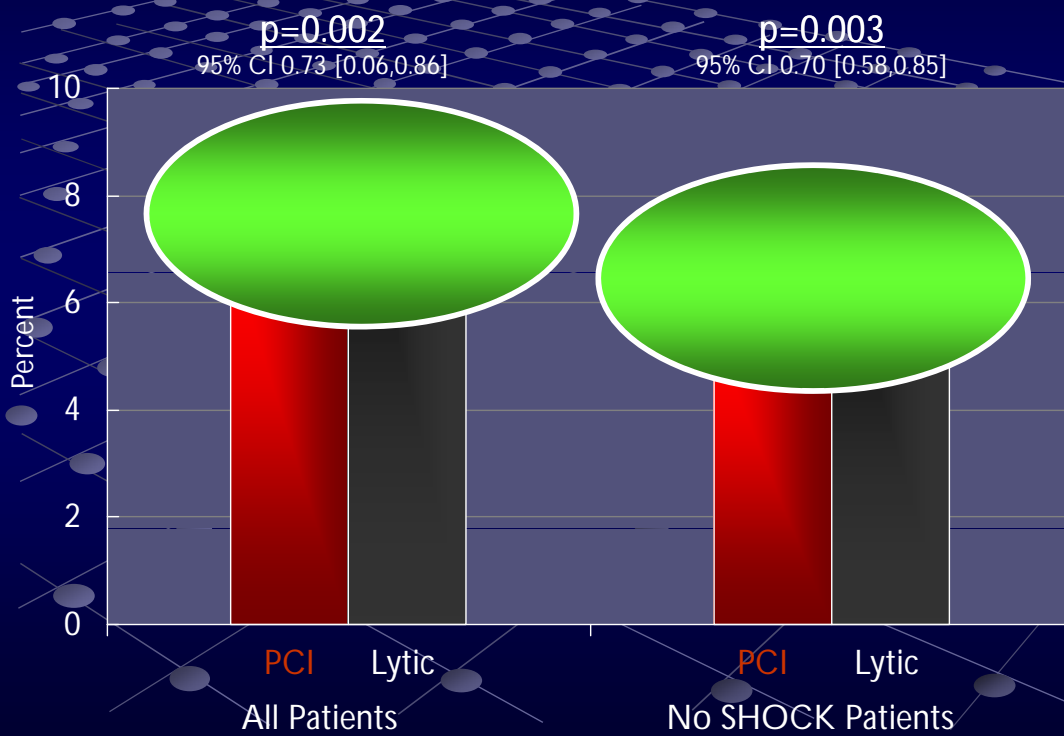


**Primary Coronary Angioplasty versus
Thrombolysis for Acute Myocardial Infarction**

Keeley EC, Boura JA, Grines CL

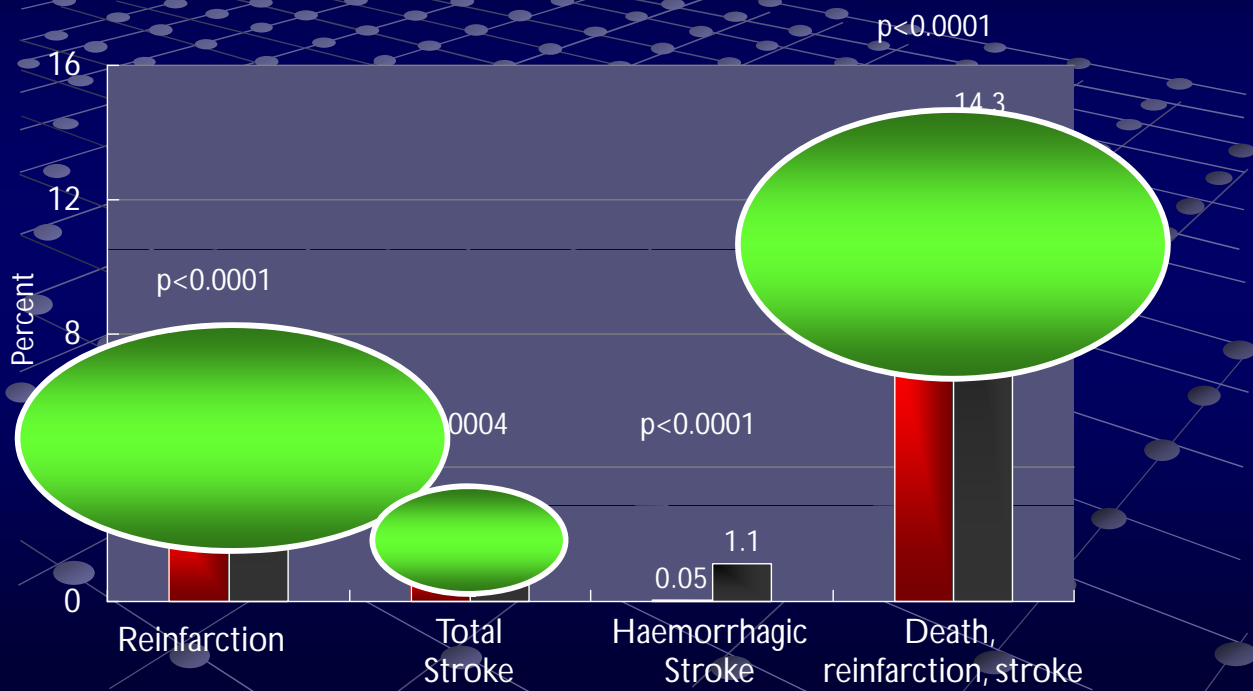
Lancet 2003;361:1304-1305

Primary PCI vs. Thrombolysis Mortality



Lancet 2003;361:13-20

Primary PCI vs. Thrombolysis Short Term Complications



Lancet 2003;361:13-20

Primary angioplasty vs. Thrombolysis

Type of Thrombolytic Used

Death

Streptokinase
Fibrin Specific

Non-fatal reinfarction

Streptokinase
Fibrin Specific

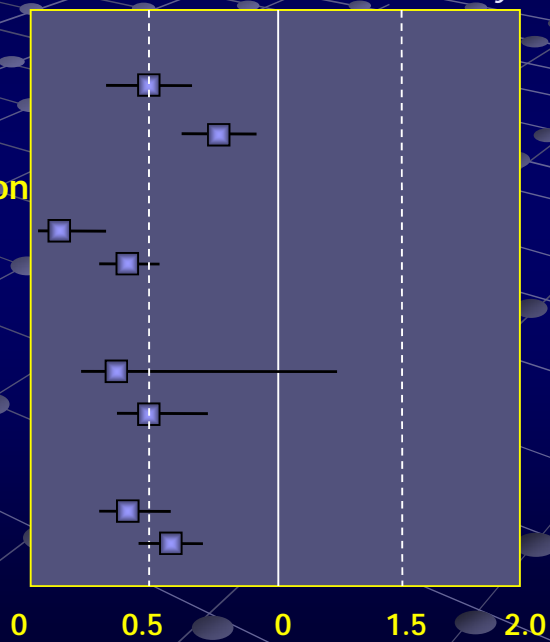
Stroke

Streptokinase
Fibrin Specific

All complications

Streptokinase
Fibrin Specific

Favours PCI *Favours Lytic*



Primary angioplasty vs. Thrombolysis Length of Stay

Streptokinase

Akhras

Zwolle

t-PA

Gibbons

PAMI

Accelerated t-PA

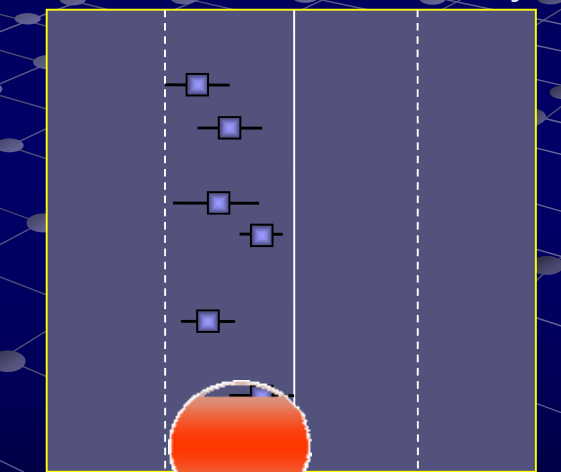
Ribichini

Streptokinase/t-PA

AirPAMI

Favours PCI

Favours Lytic



-10

-5

0

+5

+10

Days

p=0.0002

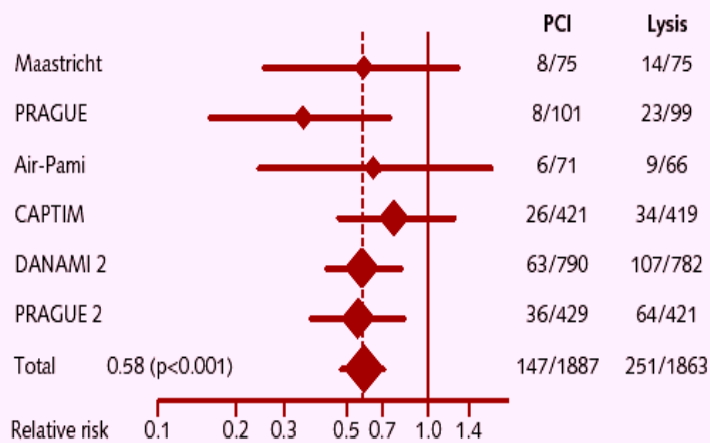
95% CI -2.42 [-3.59, -1.25]

What to do in a hospital with out cath lab ?



Yes It Is feasible to transfer for PCI

Figure 1. Transfer for primary PCI versus immediate thrombolysis in AMI: A meta-analysis. Data show the ratio of number of events to number of randomized patients.



Air PAMI: Air Primary Angioplasty in Myocardial Infarction; CAPTIM: Comparison of Angioplasty and Prehospital Thrombolysis In Acute Myocardial Infarction; DANAMI-2: Danish Trial in Acute Myocardial Infarction-2. Reproduced with permission from [35].

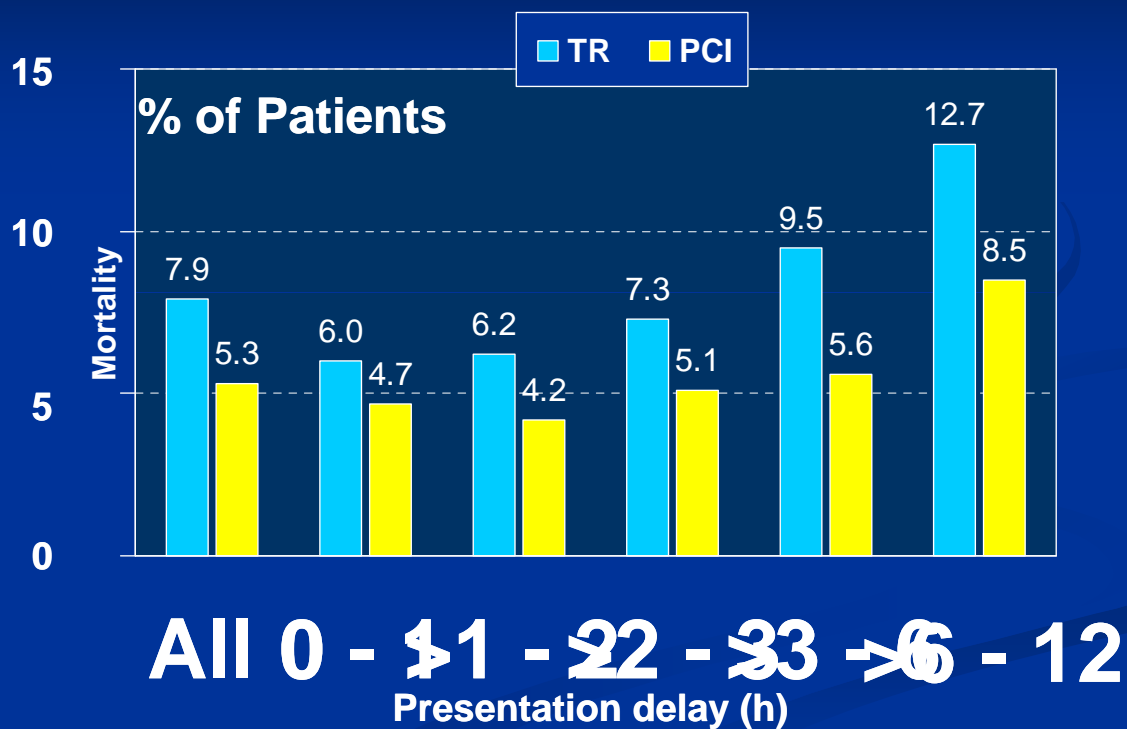
Does Time Matter?

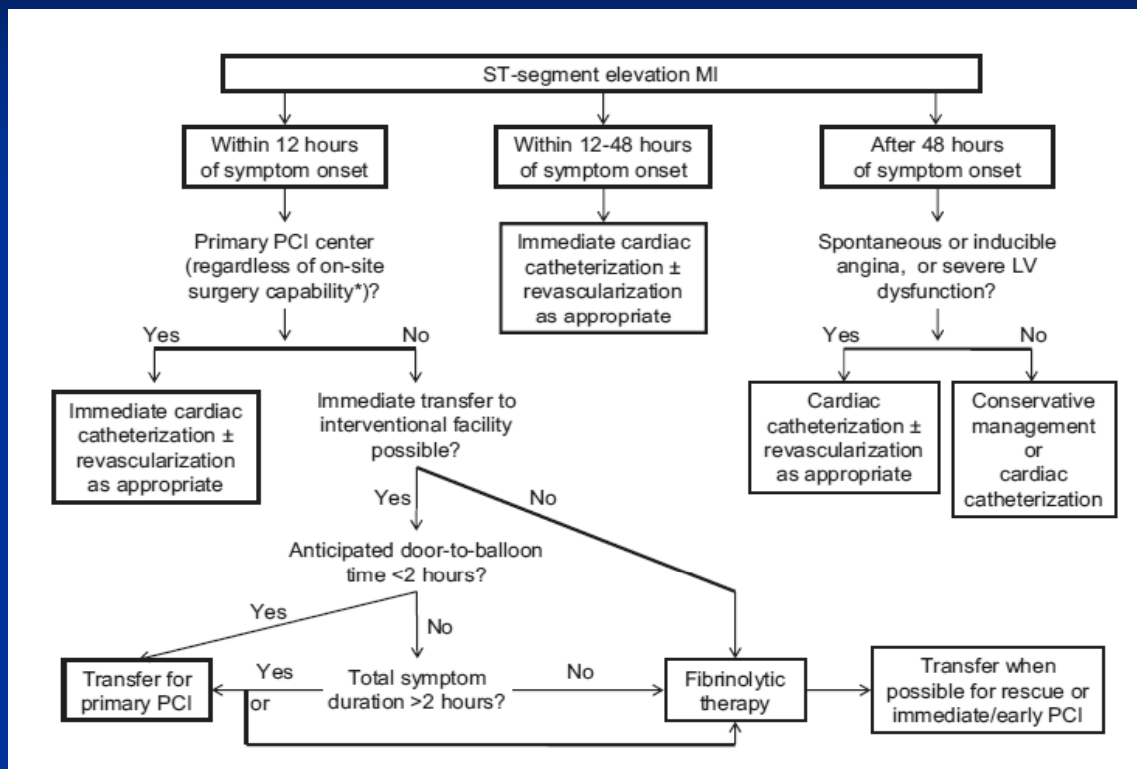
Individual Patient Data-based Meta-analysis of Primary PCI versus Fibrinolysis in Acute Myocardial Infarction Randomized Trials

**Eric Boersma, R John Simes,
Cindy L Grines, Cynthia M Westerhout**

**On behalf of the Primary Coronary Angioplasty versus
Thrombolysis (PCAT)-2 Collaborators**

30 day mortality





- ✓ If 60% of STEMI patients have angiography & PCI already...
Regardless of thrombolysis
- ✓ If ESC guidelines now recommend PPCI for ALL our STEMI pts
- ✓ If ESC guidelines recommend angiography & PCI for even the
successfully thrombolysis treated STEMI patients within 24 hrs
- ✓ If 70% of patients treated with thrombolysis
(who don't get in patient PCI) need angio & PCI within 1 year,
having had further outpatient tests first.....
- ✓ If PPCI patients can go home 2 days earlier than thrombolysed...

**Then to provide PCI at the time of STEMI presentation, when
most heart muscle is saved and mortality reduced, is easily the
right option**

SUMMARY

- ✓ PPCI reduces mortality, reinfarction & heart failure
- ✓ Thrombolysis does not address the stenosis
- ✓ Most patients who are thrombolysed now have angio± PCI during their current admission
- ✓ ESC Guidelines suggest that almost all should
- ✓ 70% of thrombolysed patients who go home have angio/PCI within a year of discharge

LET'S DELIVER THE RIGHT TREATMENT AT THE
RIGHT TIME FOR OUR PATIENTS

Secondary Prevention disease management

■ Blood Pressure

- Goals < 140/90 or <130/80 in DM /CKD
- Maximize use of beta-blockers & ACE-I

■ Lipids

- LDL < 70 ; TG < 150
- Maximize use of statins; consider fibrates/niacin first line for TG>500; consider omega-3 fatty acids

■ Diabetes

- A1c < 7%

Secondary prevention behavioral intervention

■ Smoking cessation

- Cessation-class, meds, counseling

■ Physical Activity

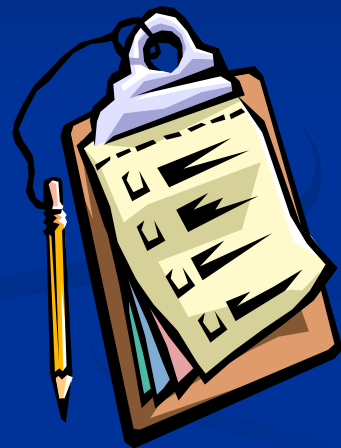
- Goal 30 - 60 minutes daily
- Risk assessment prior to initiation

■ Diet

- DASH diet, fiber, omega-3 fatty acids
- <7% total calories from saturated fats

Medication Checklist after ACS

- **Antiplatelet agent**
 - **Aspirin* and/or Clopidogrel**
- **Lipid lowering agent**
 - **Statin***
 - **Fibrate / Niacin / Omega-3**
- **Antihypertensive agent**
 - **Beta blocker***
 - **ACE-I* / ARB**
 - **Aldactone (as appropriate)**



Summary

- **ACS includes UA, NSTEMI, and STEMI**
- **Management guideline focus**
 - **Immediate assessment/intervention (MONA+BAH)**
 - **Risk stratification (UA/NSTEMI vs. STEMI)**
 - **RAPID reperfusion for STEMI (PCI vs. Thrombolytics)**
 - **Conservative vs Invasive therapy for UA/NSTEMI**
- **Aggressive attention to secondary prevention initiatives for ACS patients**
 - **Beta blocker, ASA, ACE-I, Statin**