

# Acute Coronary Syndrome



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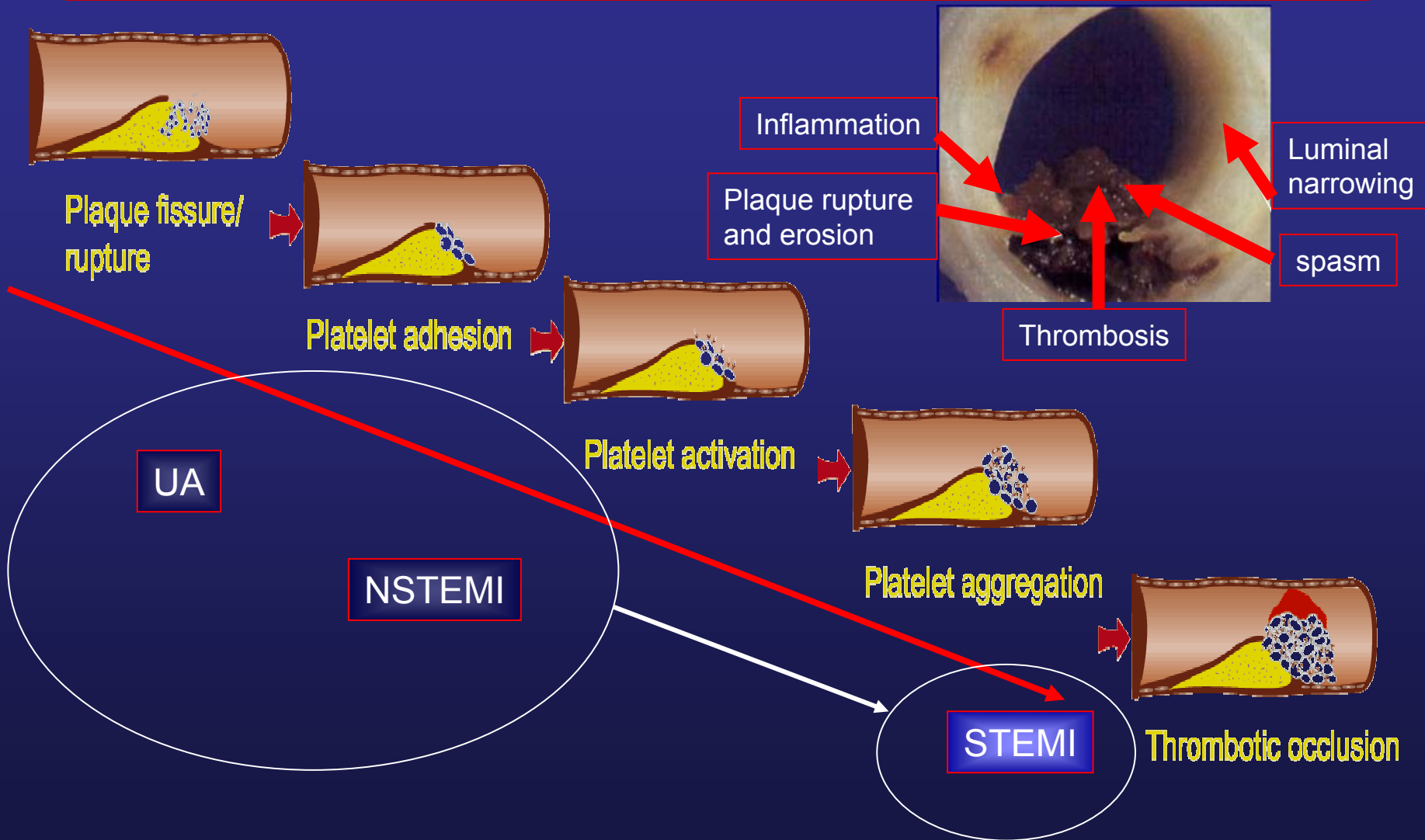
Université de Genève

<http://www.cardiology-geneva.ch>

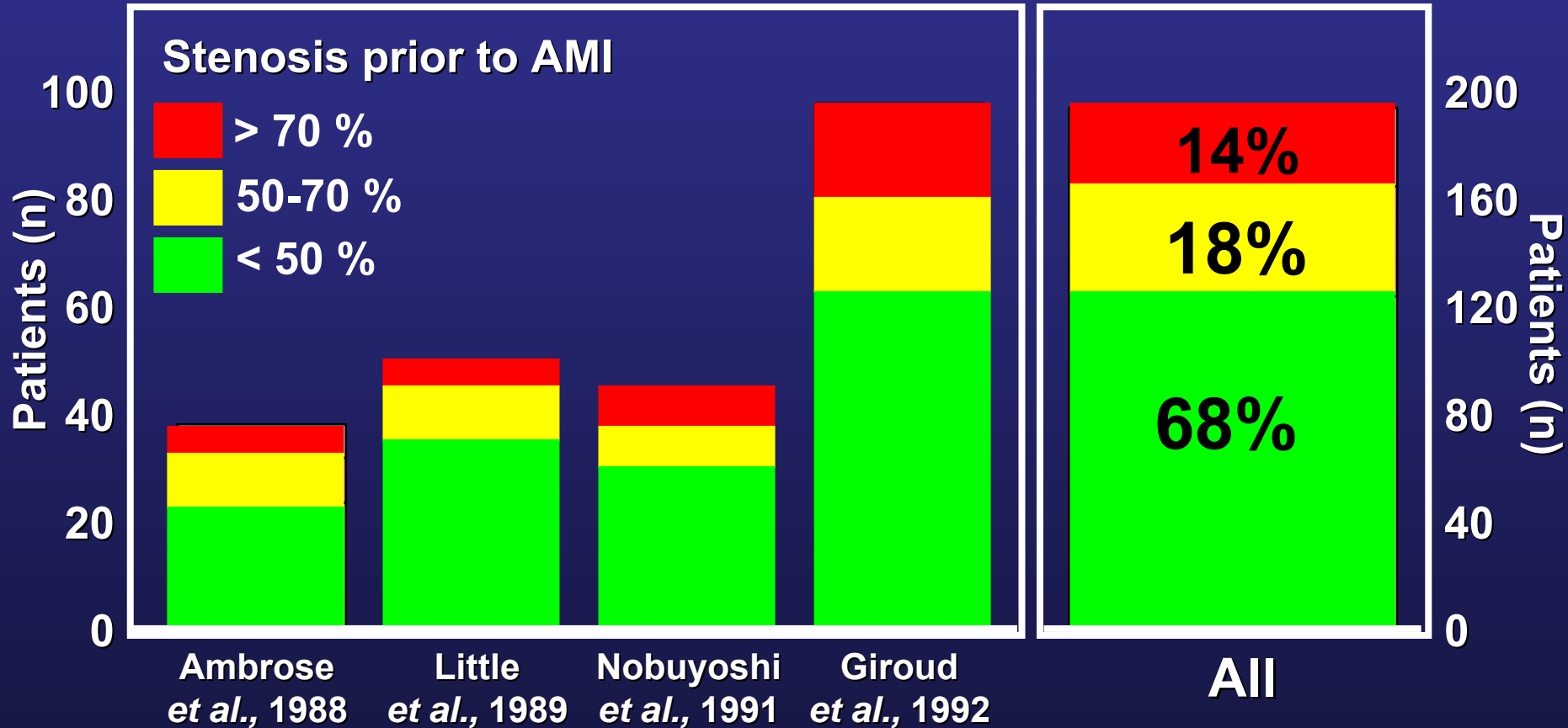
# Acute Coronary Syndrome

- Pathophysiology
- STEMI
- UA and NSTEMI
- Conclusions

# Pathogenesis of ACS



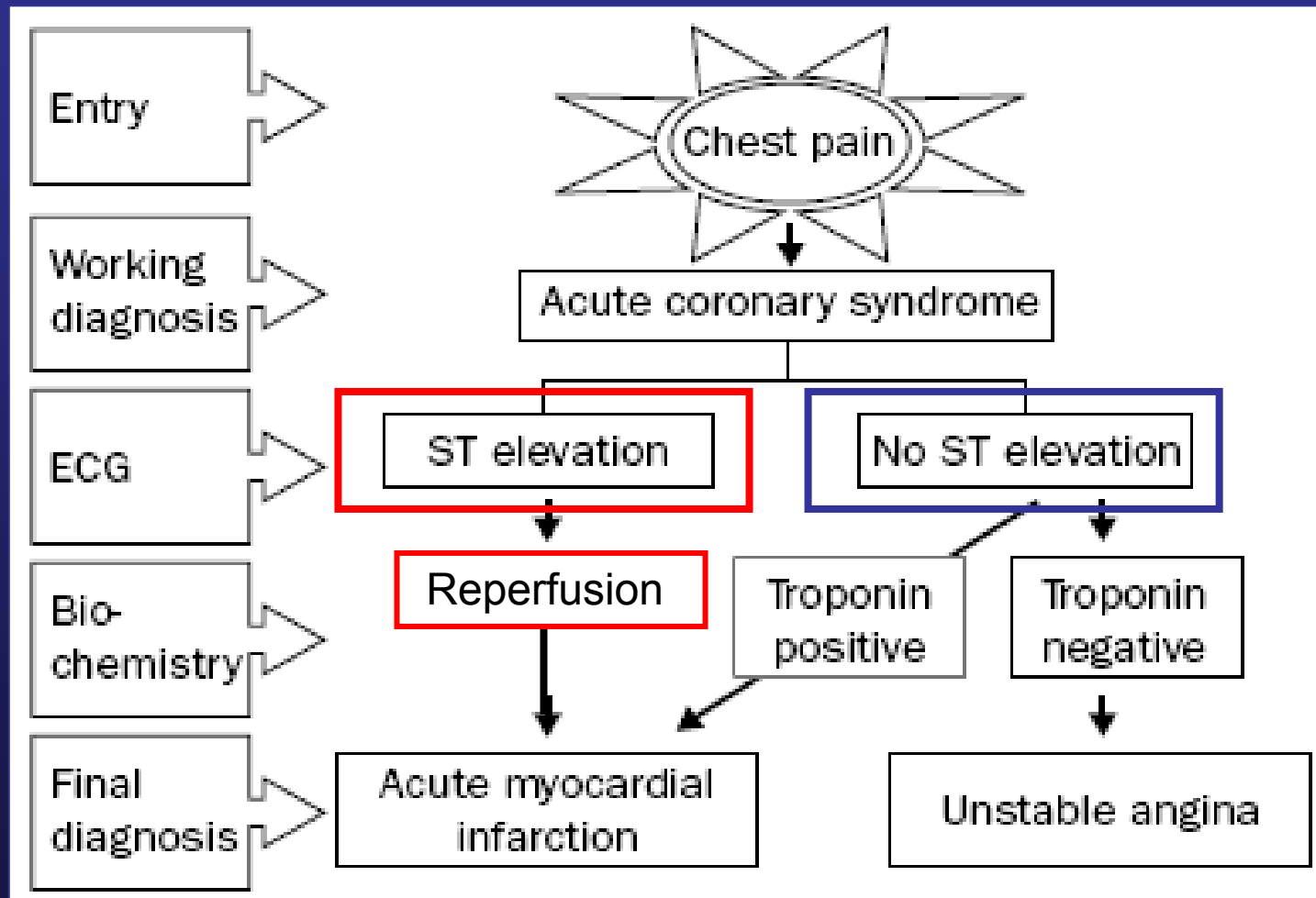
# Evolution to AMI does not depend on the degree of coronary stenosis



# Acute Coronary Syndrome

- Pathophysiology
- STEMI
- UA and NSTEMI
- Conclusions

# Approach of Chest pain



**STEMI**

**=**

**Urgent  
reperfusion**

# Milestones in the Evolution of Thrombolysis in Myocardial Infarction

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			<u>Mortality</u>
<b>1988</b>	<b>ISIS-2</b>	<b>SK</b>	<b>25% ↓</b>
		<b>ASA</b>	<b>23% ↓</b>
<b>1993</b>	<b>GUSTO-1</b>	<b>TPA</b>	<b>14% ↓</b>

# Clinical Impact of Reocclusion after Thrombolysis:

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## Data from the TAMI trials:

- 810 patients, cath 90 min & 7 days later:
- 12.4% reocclusion
- 58% symptomatic
- In-hospital mortality 11.0% vs 4.5% ( $P=0.01$ ).

# Coronary angiography after fibrinolysis :

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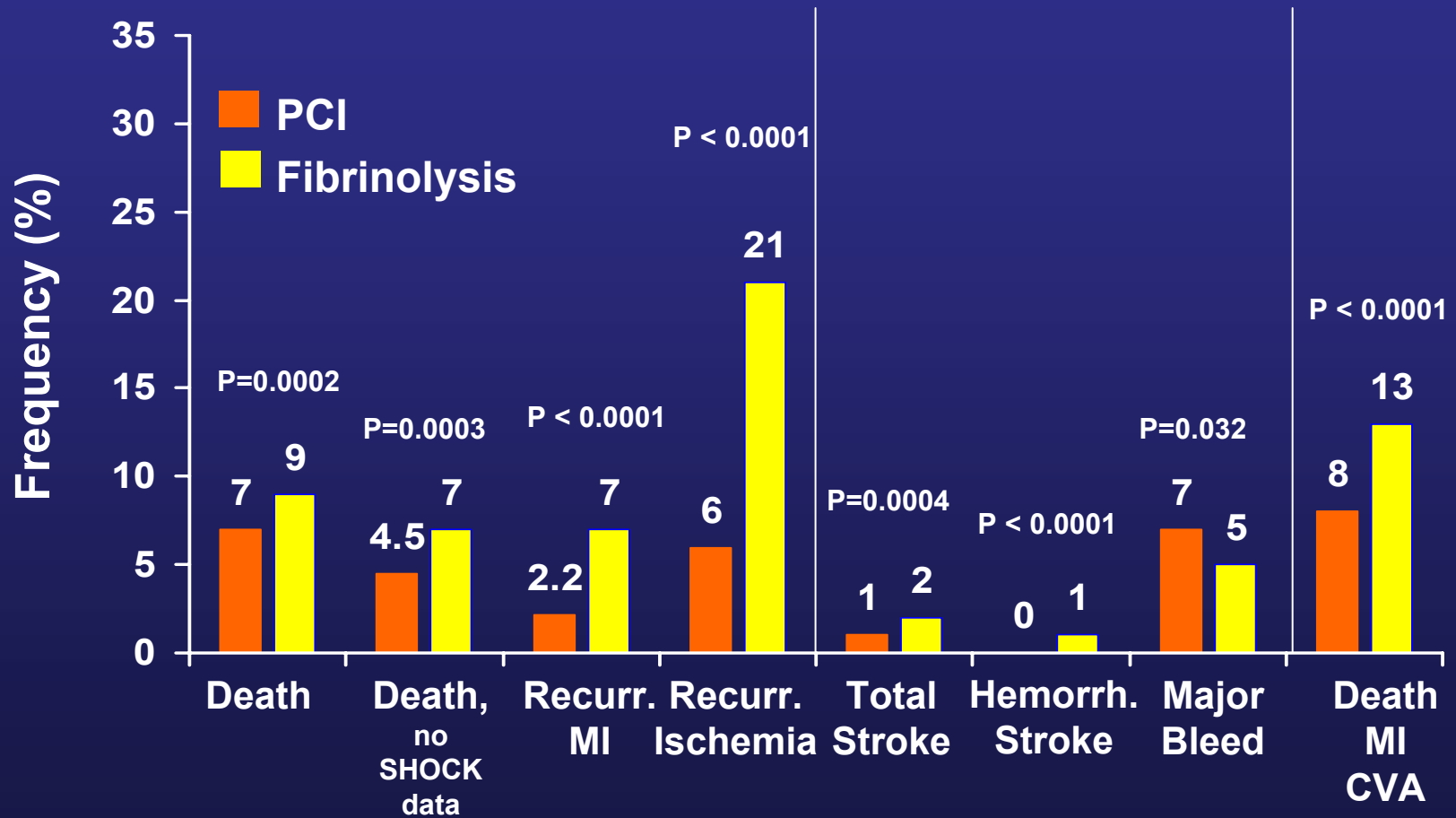
## ⇒ Rescue PCI

if Sx persistence and/or persistence of ST-elevation within  
60 to 90 minutes

## ⇒ Elective angiography and PCI

for all patients after thrombolysis

# PCI vs Fibrinolysis for STEMI: Short Term Clinical Outcomes

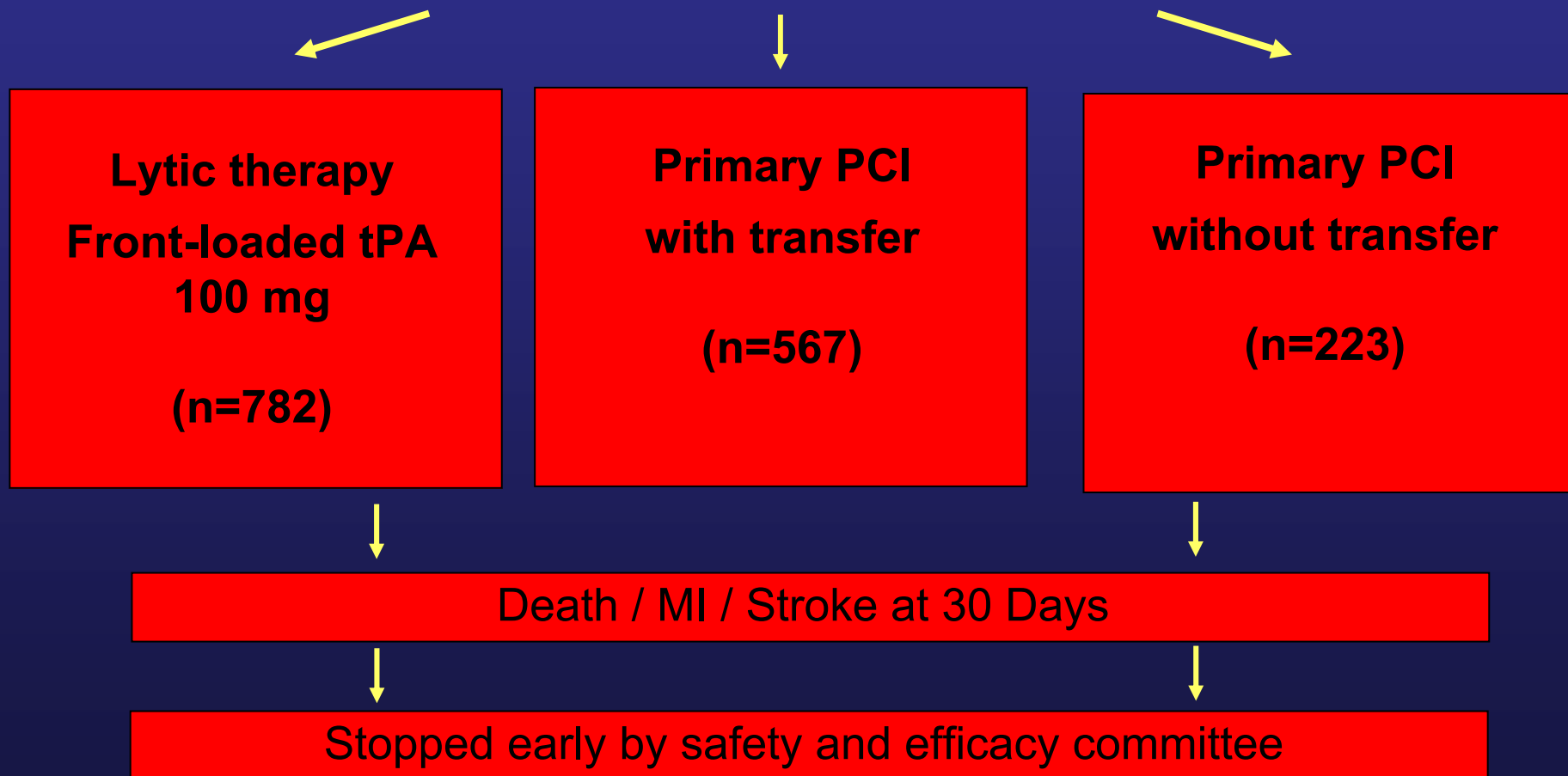


N = 7739



# DANAMI-2: Study Design

High-risk ST elevation MI patients ( $\geq 4$  mm elevation), Sx < 12 hrs  
5 PCI centers (n=443) and 22 referring hospitals (n=1,129), transfer in  $\leq 3$  hrs

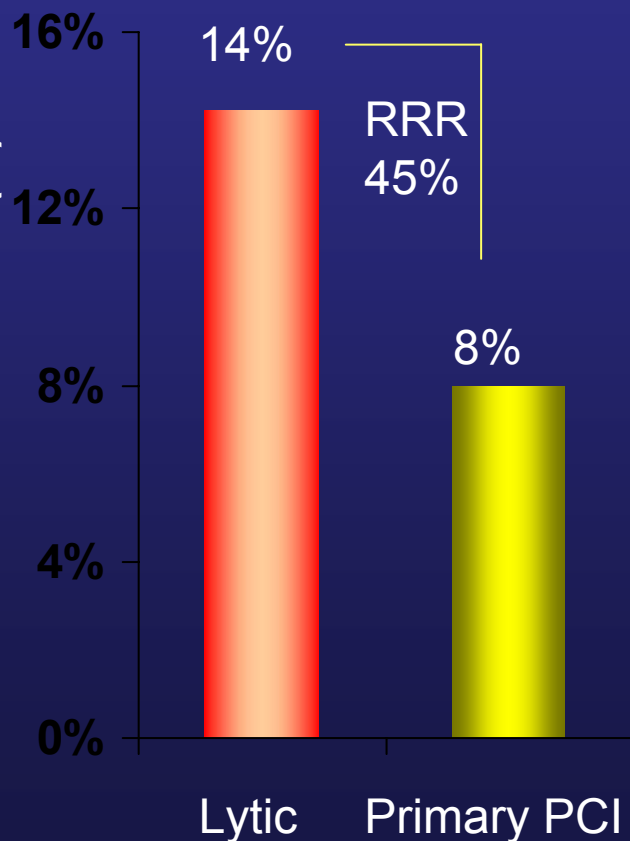




# DANAMI-2

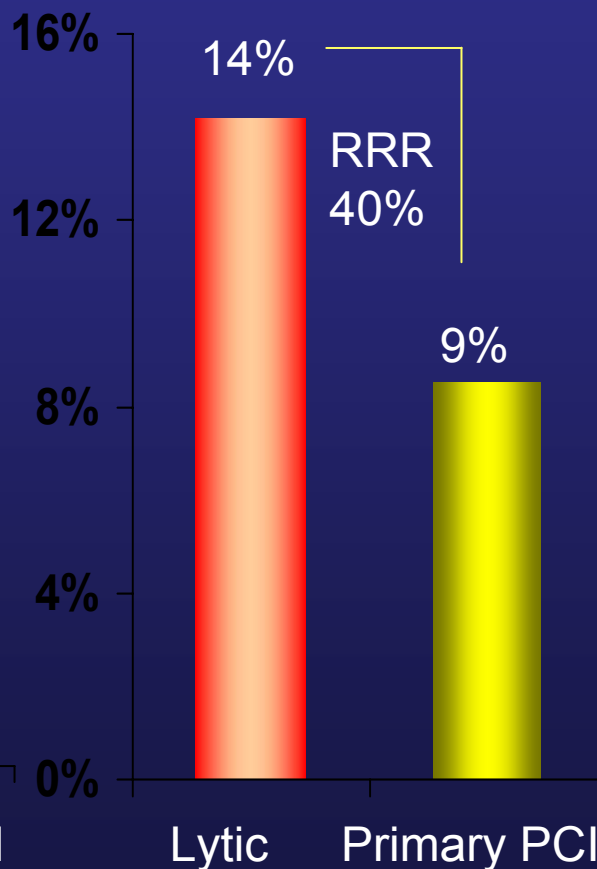
## Combined

P=0.0003



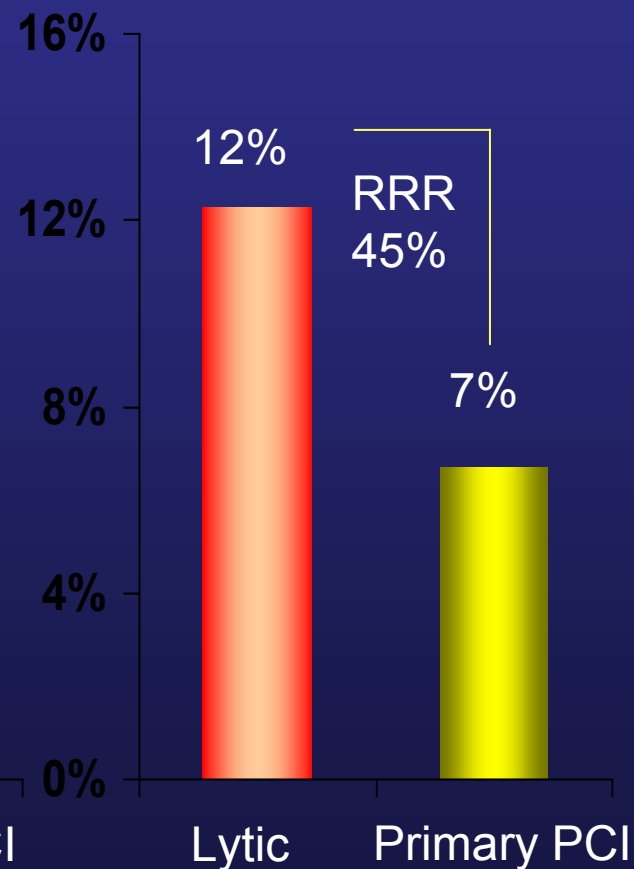
## Transfert sites

P=0.002

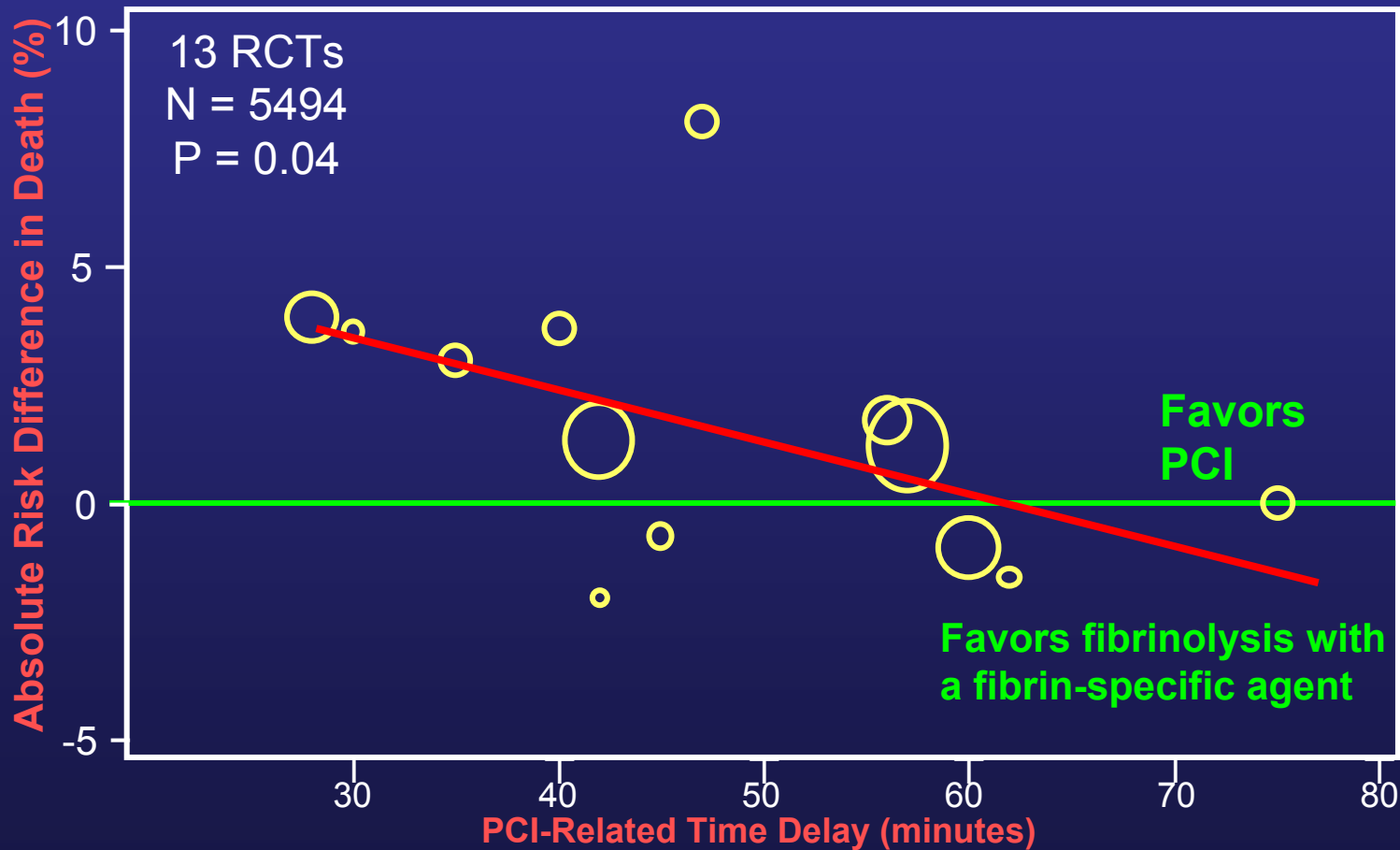


## Non-Transfert sites

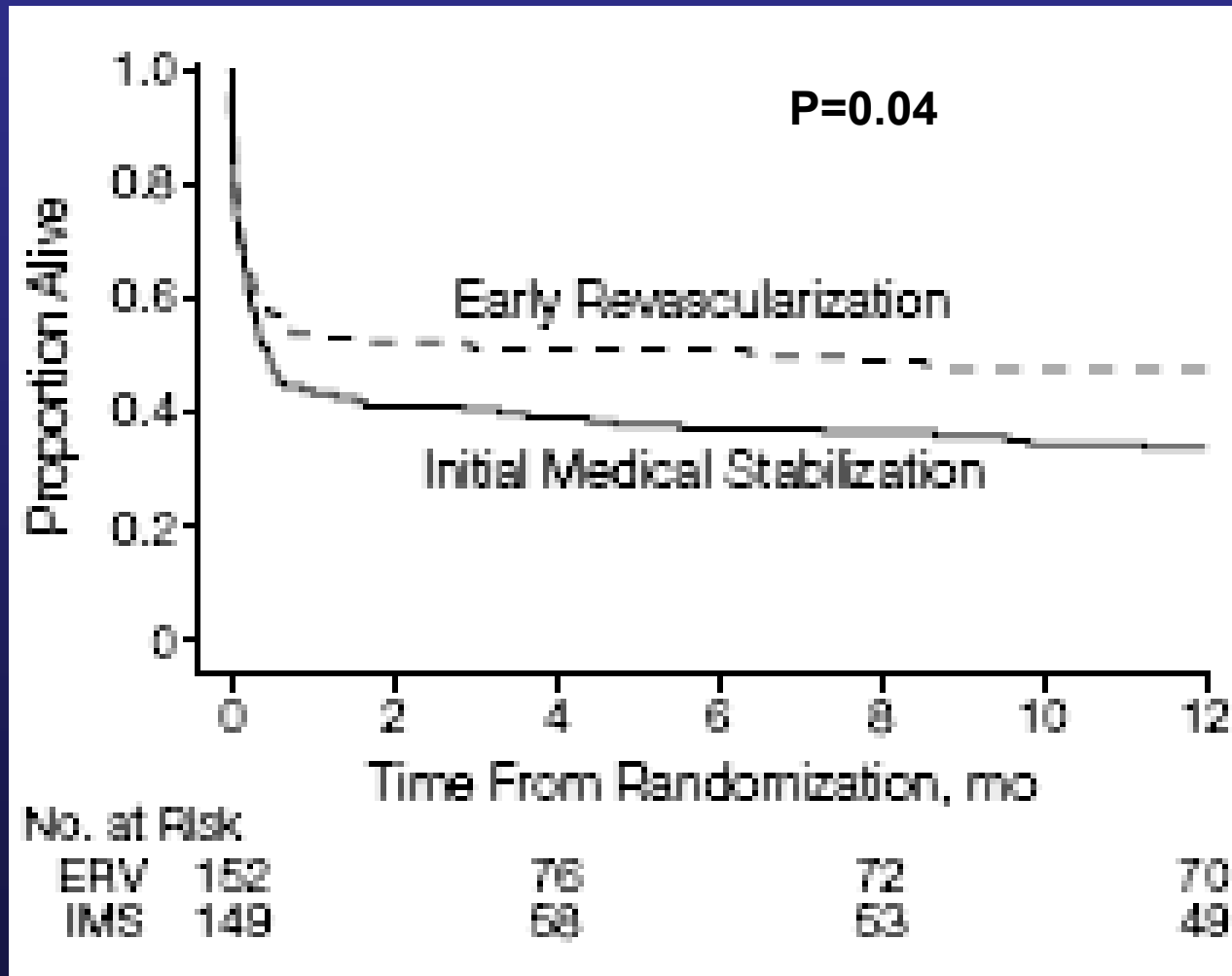
P=0.048



# PCI versus Fibrinolysis with Fibrin-Specific Agents: Is Timing (Almost) Everything?



# Shock Trial : one year follow up



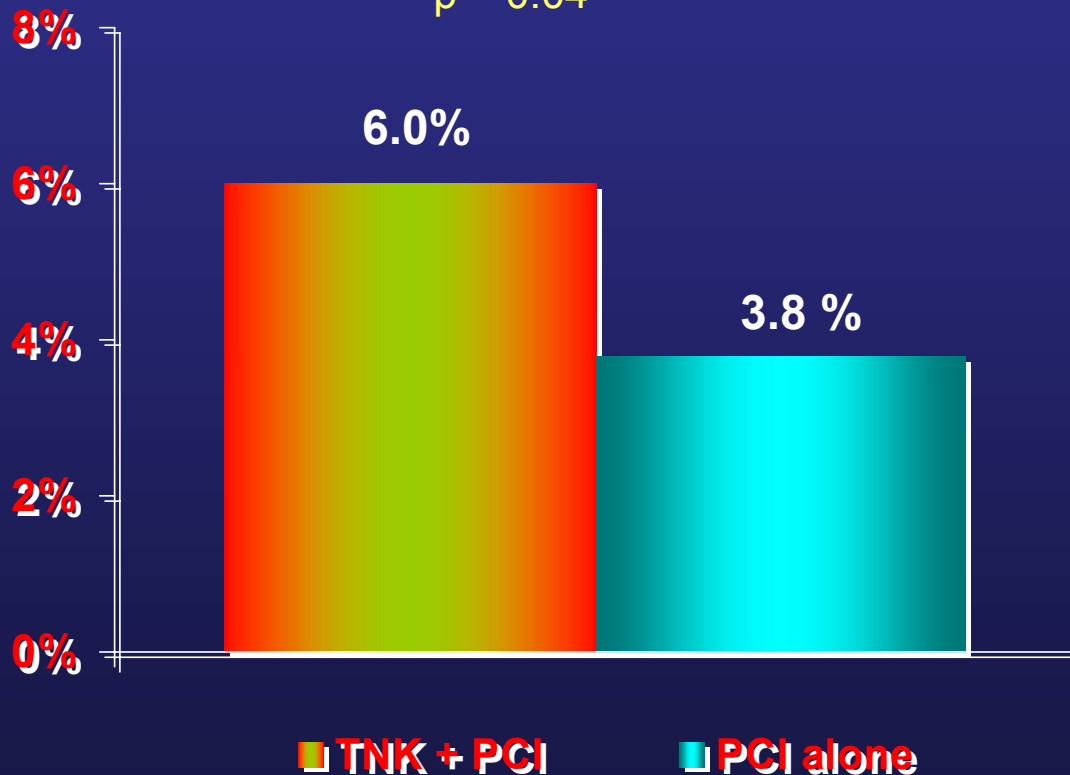
Facilitated angioplasty ?

**No!**

# ASSENT – 4 PCI trial: Mortality at 30 days

## Analysis of mortality at 30 days (%)

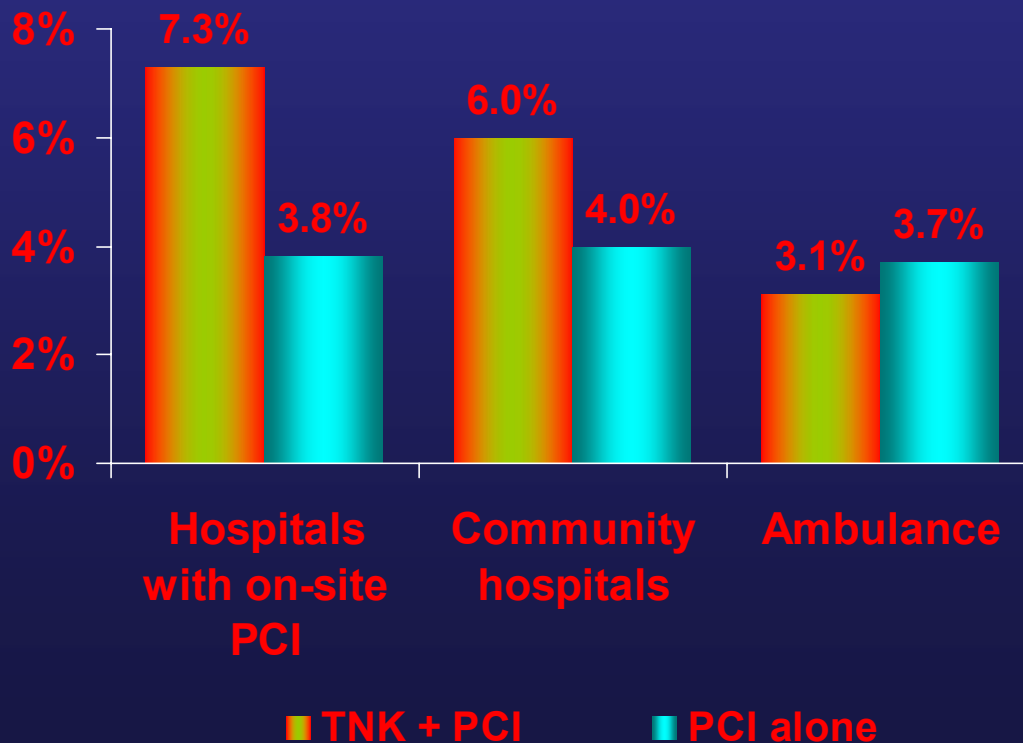
$p = 0.04$



The primary endpoint of mortality was higher in the TNK + PCI treatment group compared with the PCI alone group (6.0% vs 3.8%,  $p=0.04$ ) at 30 days

# ASSENT – 4 PCI trial: Mortality Subgroup Analysis

Subgroup analysis of mortality based on site of randomization (%)

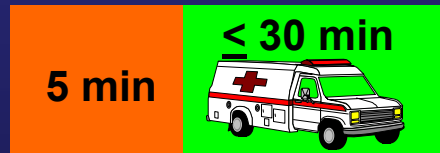
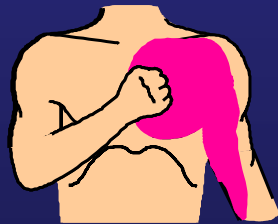


The greatest mortality difference by treatment group was seen in hospitals with on-site PCI (7.3% vs 3.8%), with less difference in community hospitals (6.0% vs 4.0%), and a shift in direction for patients enrolled in the ambulance (3.1% vs 3.7%)

# Reperfusion

■ Patient    ■ Transport

## Goals



Triage Plan



Hospital PCI:  
Door-to-Balloon  
within 90 min.



Inter-Hospital  
Transfer

Hospital fibrinolysis:  
Door-to-Needle  
within 30 min.



# Contraindications and Cautions for Fibrinolysis in STEMI

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## Absolute

## Contraindications

- ♥ Any prior intracranial hemorrhage
- ♥ Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- ♥ Known malignant intracranial neoplasm (primary or metastatic)
- ♥ Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours

NOTE: Age restriction for fibrinolysis has been removed compared with prior guidelines.

# Contraindications and Cautions for Fibrinolysis in STEMI

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## Absolute

## Contraindications

- ♥ Suspected aortic dissection
- ♥ Active bleeding or bleeding diathesis (excluding menses)
- ♥ Significant closed-head or facial trauma within 3 months

# Contraindications and Cautions for Fibrinolysis in STEMI

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## Relative Contraindications

- ♥ History of chronic, severe, poorly controlled hypertension
- ♥ Severe uncontrolled hypertension on presentation (SBP > 180 mm Hg or DBP > 110 mm Hg)
- ♥ History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications
- ♥ Traumatic or prolonged (> 10 minutes) CPR or major surgery (< 3 weeks)

# Contraindications and Cautions for Fibrinolysis in STEMI

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## Relative Contraindications

- ♥ Recent (< 2 to 4 weeks) internal bleeding
- ♥ Noncompressible vascular punctures
- ♥ For streptokinase/anistreplase: prior exposure (> 5 days ago) or prior allergic reaction to these agents
- ♥ Pregnancy
- ♥ Active peptic ulcer
- ♥ Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

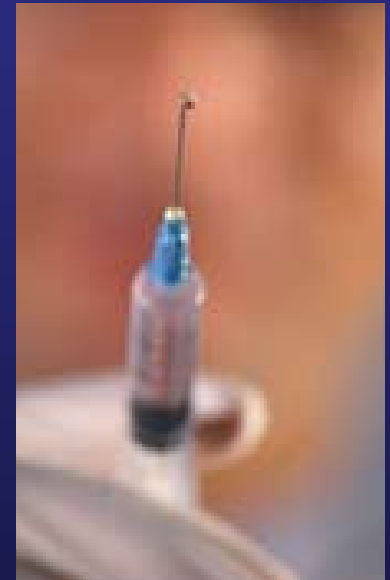
# Reperfusion Options for STEMI Patients

## Step 2: Select Reperfusion Treatment.

*If presentation is < 3 hours and there is no delay to an invasive strategy, there is a **preference for PCI.***

### Fibrinolysis generally preferred

- ♥ *Early presentation (  $\leq 3$  hours from symptom onset and *delay to invasive strategy*)*
- ♥ *Invasive strategy not an option*
  - Cath lab occupied or not available
  - Vascular access difficulties
  - No access to skilled PCI lab
- ♥ *Delay to invasive strategy*
  - Prolonged transport
  - Door-to-balloon more than 90 minutes
  - > 1 hour vs fibrinolysis (fibrin-specific agent) now



# Reperfusion Options for STEMI Patients

## Step 2: Select Reperfusion Treatment.

*If presentation is < 3 hours and there is no delay to an invasive strategy, there is a preference for PCI.*

### Invasive strategy generally preferred

- ♥ *Skilled PCI lab available with surgical backup*
  - Door-to-balloon < 90 minutes
  
- ♥ *High Risk from STEMI*
  - Cardiogenic shock, Killip class  $\geq 3$
  
- ♥ *Contraindications to fibrinolysis, including increased risk of bleeding and ICH*
  
- ♥ *Late presentation*
  - > 3 hours from symptom onset
  
- ♥ *Diagnosis of STEMI is in doubt*



# Summary of Pharmacologic Rx: *Ischemia*

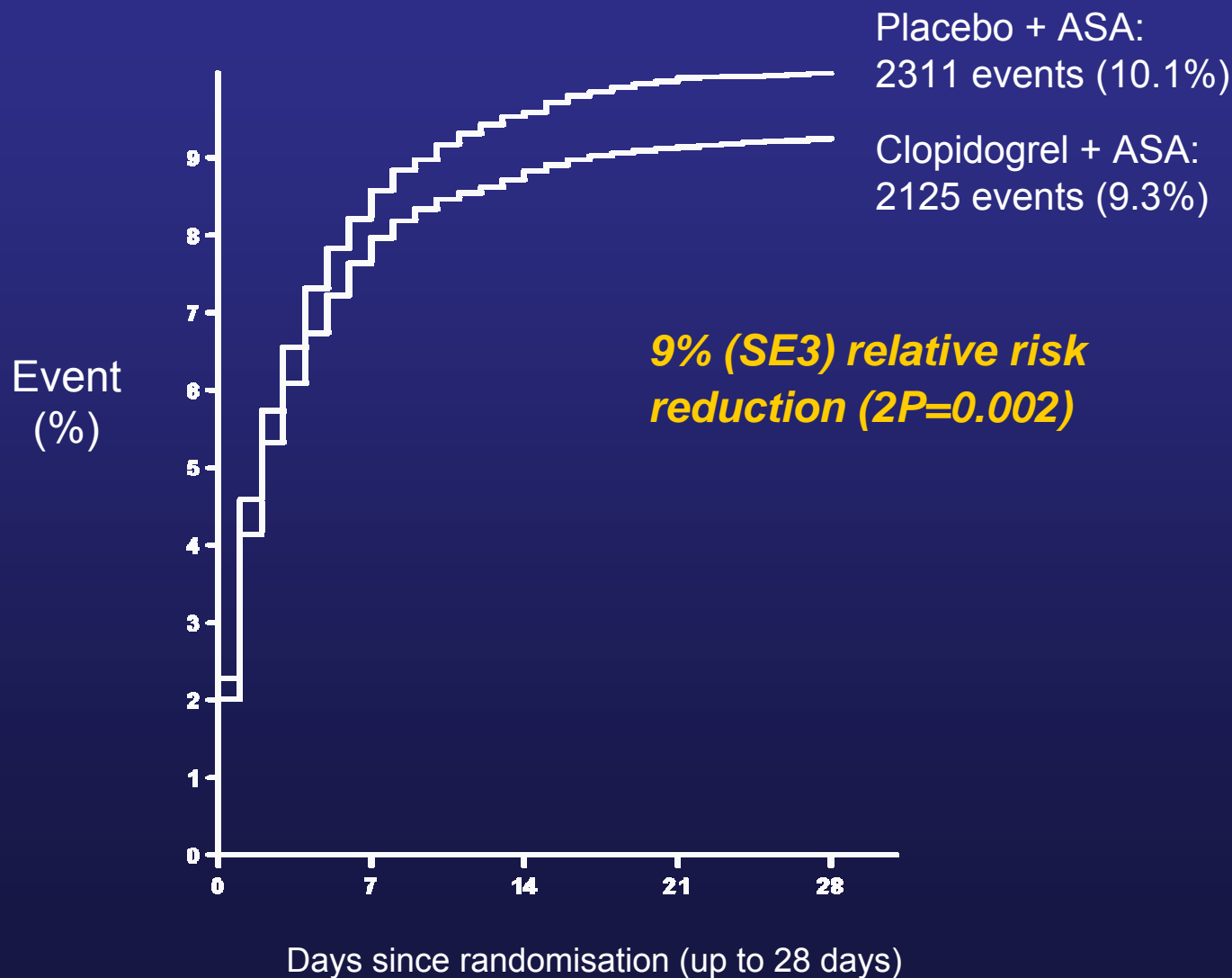
	1st 24 h	During Hosp	Hosp DC + Long Term
<i>Aspirin</i>	162-325 mg chewed	75-162 mg/d p.o.	75-162 mg/d p.o.
<i>Fibrinolytic</i>	tPA, TNK, rPA, SK		
<i>IIb/IIIa inhib</i>	ABCX, Tirofiban, Eptifibatide		
<i>UFH</i>	60U/kg (4000) 12 U/kg/h (1000) aPTT 1.5 - 2 x C	aPTT 1.5 - 2 x C	
<i>Beta-blocker</i>	Oral daily	Oral daily	Oral daily

# Summary of Pharmacologic Rx: *LVD, Sec. Prev.*,

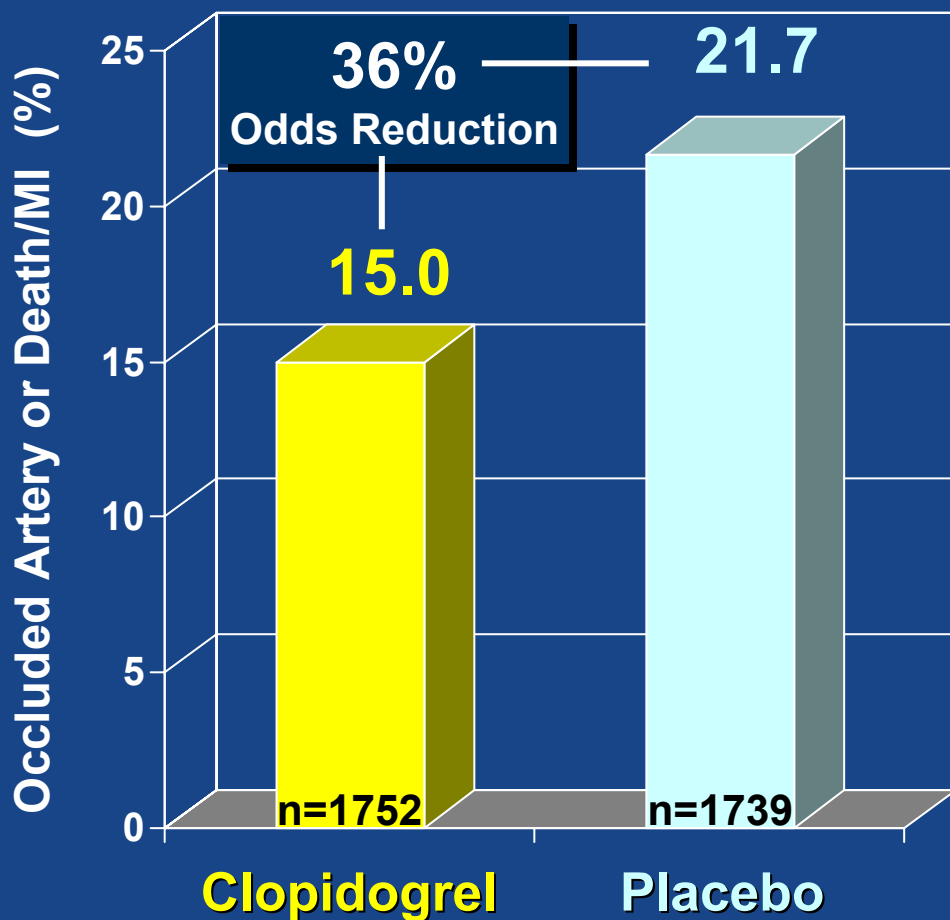
	1st 24 h	During Hosp	Hosp DC + Long Term
<i>ACEI</i>	Anterior MI, Pulm Cong., EF < 40	Oral Daily	Oral Daily Indefinitely
<i>ARB</i>	ACEI intol., HF, EF < 40		
<i>Aldo Blocker</i>		No renal dysf, K <sup>+</sup> ≤ 5.0 mEq/L On ACEI, HF or DM	Same as during Hosp.
<i>Statin</i>	Start early w/o lipid profile	Indefinitely, LDL << 2.6	Indefinitely, LDL << 2.6

# COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke

n=45'851

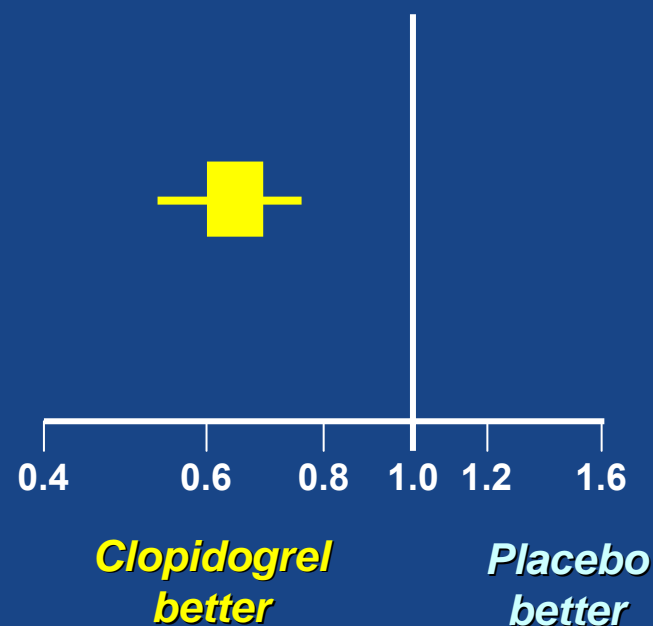


# Primary Endpoint: Occluded Artery (or D/MI thru Angio/HD)



**Odds Ratio 0.64**  
(95% CI 0.53-0.76)

***P=0.00000036***



# Persistent ST-elevation MI without PCI facility

Physical examination, ECG monitoring, Blood samples

**STEMI**

Heparin, ASA, Fibrinolytics,  
Clopidogrel\*, Betablockers, Nitrates, Statins

**High risk**

**Low risk**

LV EF, Ischemia assessment

**High risk**

**Intermediate risk**

**Low risk**

**Cor. Angiography**

**Significant angina**

**Suitable anatomy for PCI or CABG**

**Med tx**

**Revascularization**

\* Unless a CABG is planned within 5 days.

# Acute Coronary Syndrome

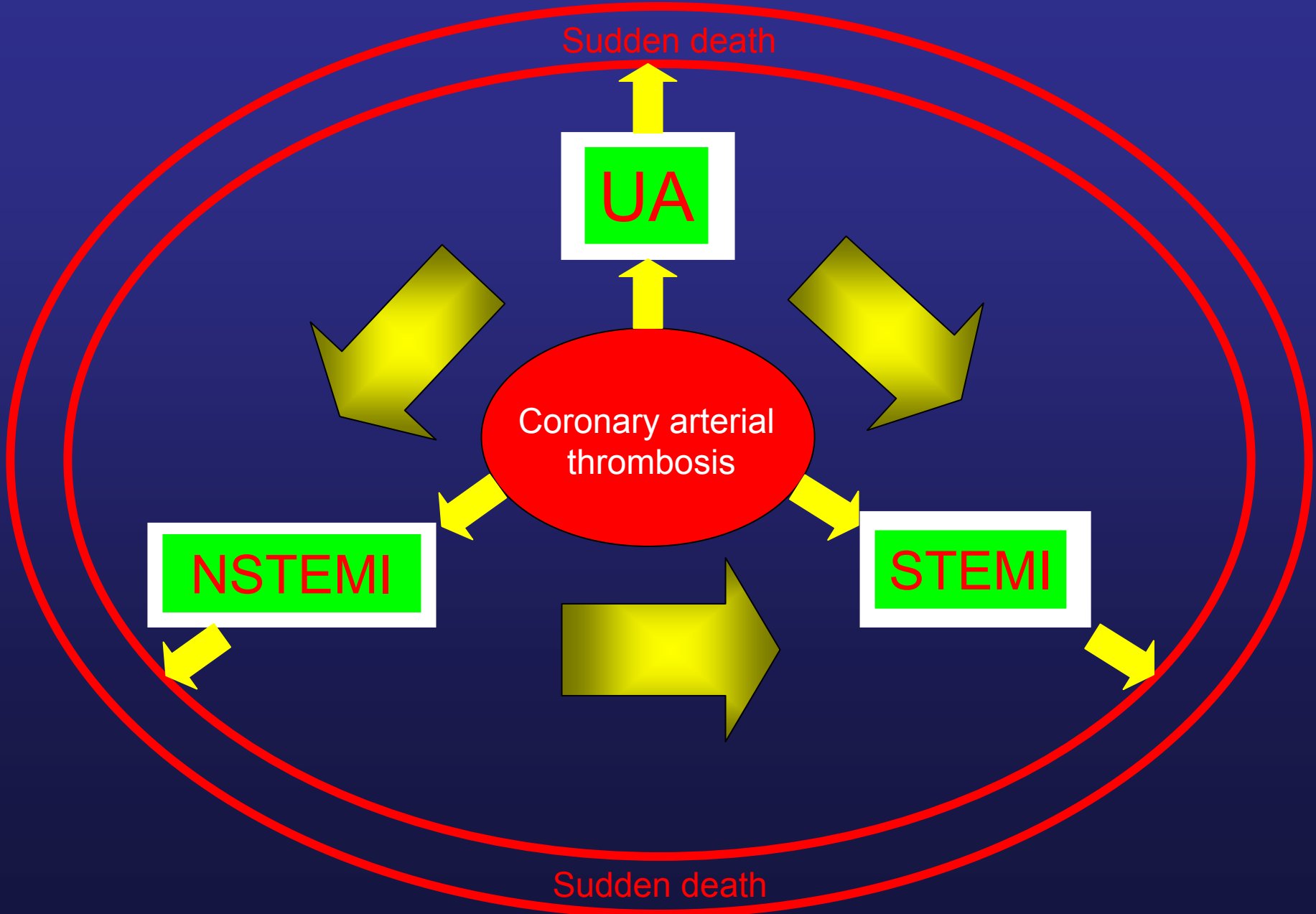
- Pathophysiology
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**UA / NSTEMI**

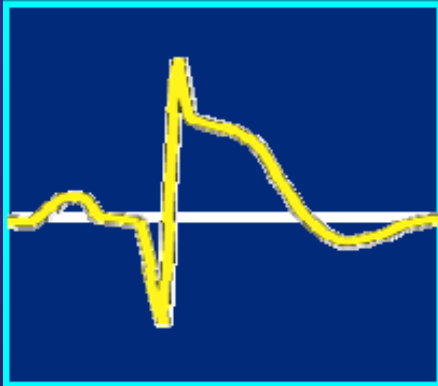


**Risk  
stratification**

# Acute Coronary Syndromes

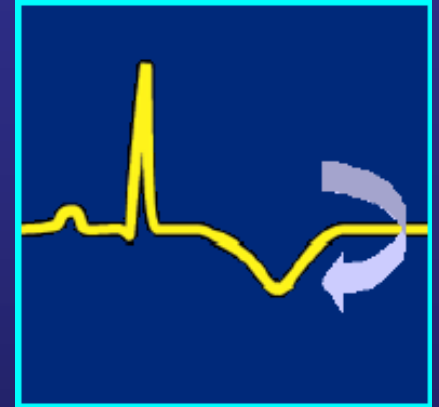
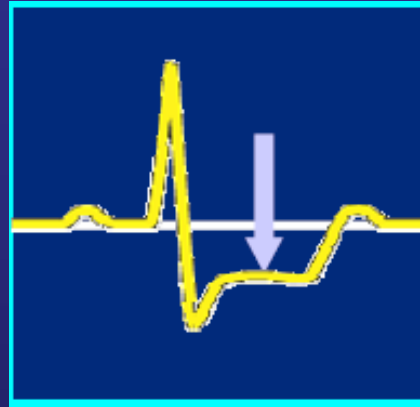


ACS with persistent ST-segment elevation



Troponin or CK-mb elevated

ACS without persistent ST-segment elevation

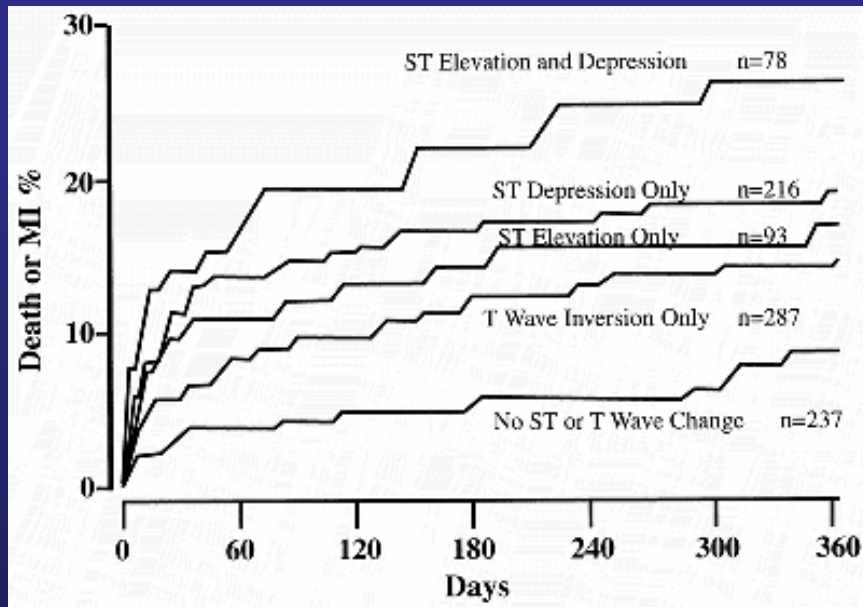


Troponin elevated or not

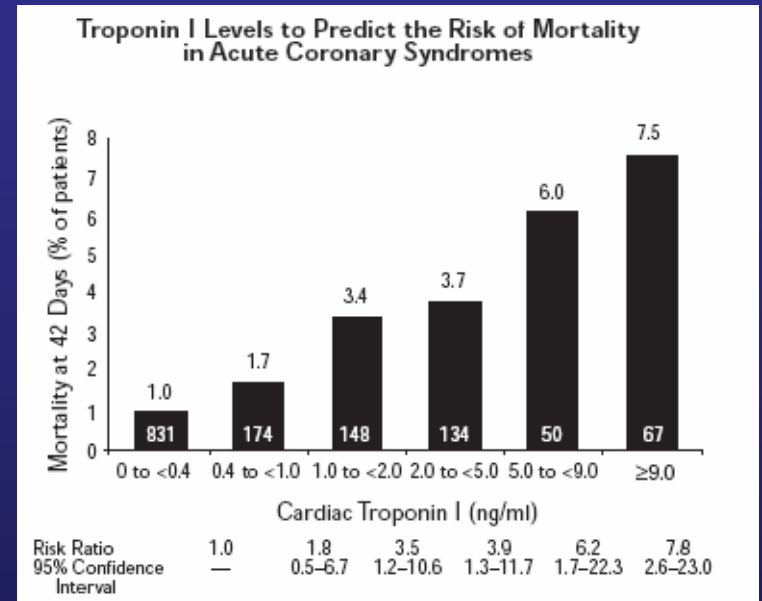
Myocardial infarction

Unstable angina

# Risk stratification : ECG, Troponin



J Intern Med 1993; 234:293-301



N Engl J Med 1996;335:1342

Cardiac enzymes or troponins rise  
 =  
 myocardial infarction

Eur Heart J 2000; 21: 1502-13.

# Criteria for acute, evolving or recent MI

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

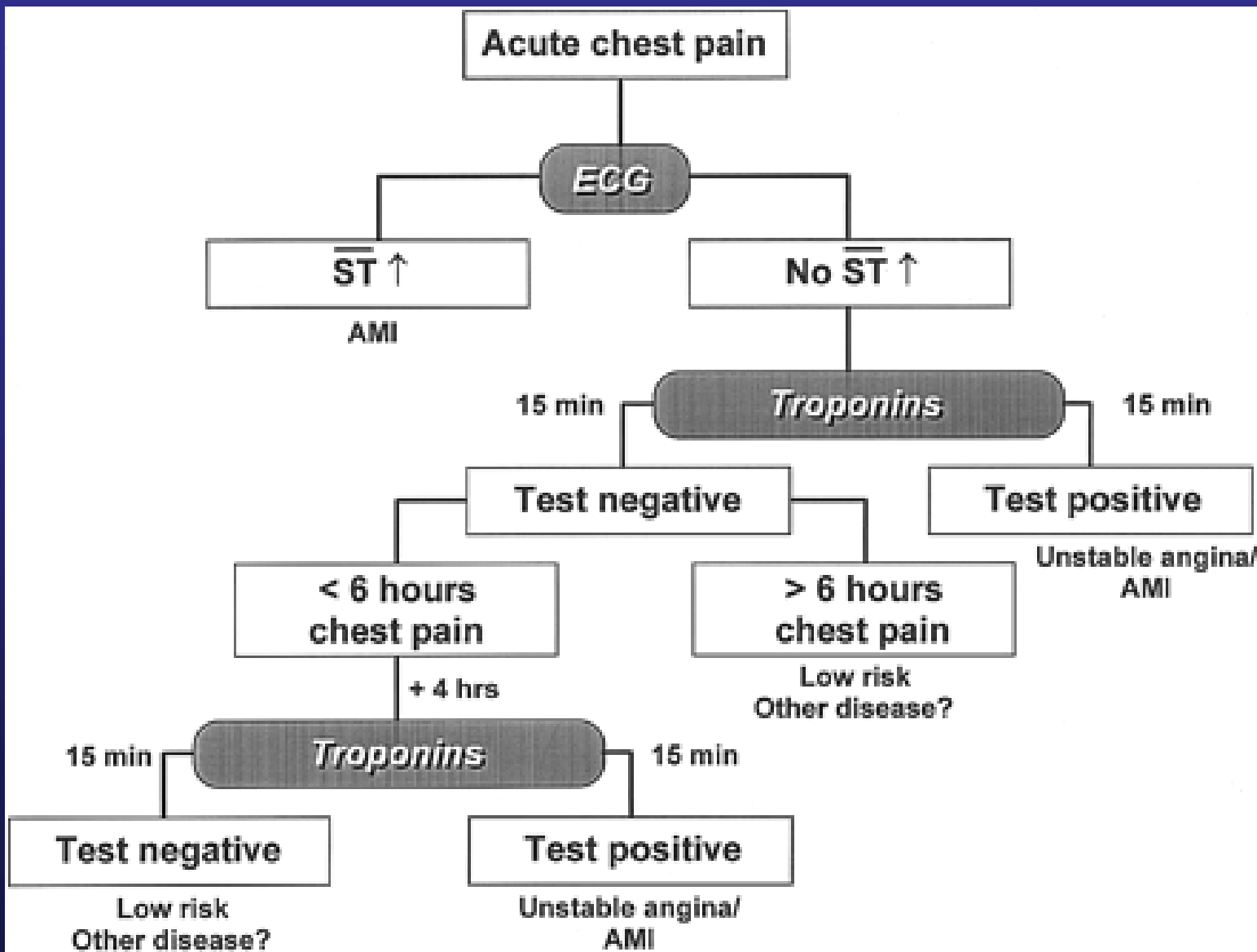
- (1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  - (a) ischemic symptoms;
  - (b) development of pathologic Q waves on the ECG;
  - (c) ECG changes indicative of ischemia (ST segment elevation or depression); or
  - (d) coronary artery intervention (e.g., coronary angioplasty).
- (2) Pathologic findings of an acute MI.

# Criteria for established MI

Any one of the following criteria satisfies the diagnosis

foreestablished MI:

- (1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
- (2) Pathologic findings of a healed or healing MI.



# Braunwald classification UA

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<i>Classification</i>	<b>A. Secondary</b> <i>unstable angina</i>	<b>B. Primary</b> <i>unstable angina</i>	<b>C. Postinfarction</b> <i>(&lt; 2 weeks) unstable angina</i>
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**I New onset of severe  
or accelerated angina**

**No rest pain**

**IA**

**IB**

**IC**

**II Subacute rest angina**

**(> 48 hours ago)**

**IIA**

**IIB**

**IIC**

**III Acute rest angina**

**(within 48 hours)**

**IIIA**

**IIIB**

**IIIC**

# Summary of the Risk Stratification : Risk of Progression to Death and MI

## High-risk patients

**Hemodynamic instability**

**Majors arrhythmias (VF, VT)**

**Pulmonary edema secondary to  
ischemia**

**New or worsening MR murmur**

**S3 or worsening rales**

**Dynamic ECG ST/T changes**

**Early post infarction UA**

**Prolonged or Reccurent chest pain**

**Elevated troponin levels**

**Diabetes**

**\*history of revascularization**

**Age>75 ans**

**Tachycardia / Bradycardia**



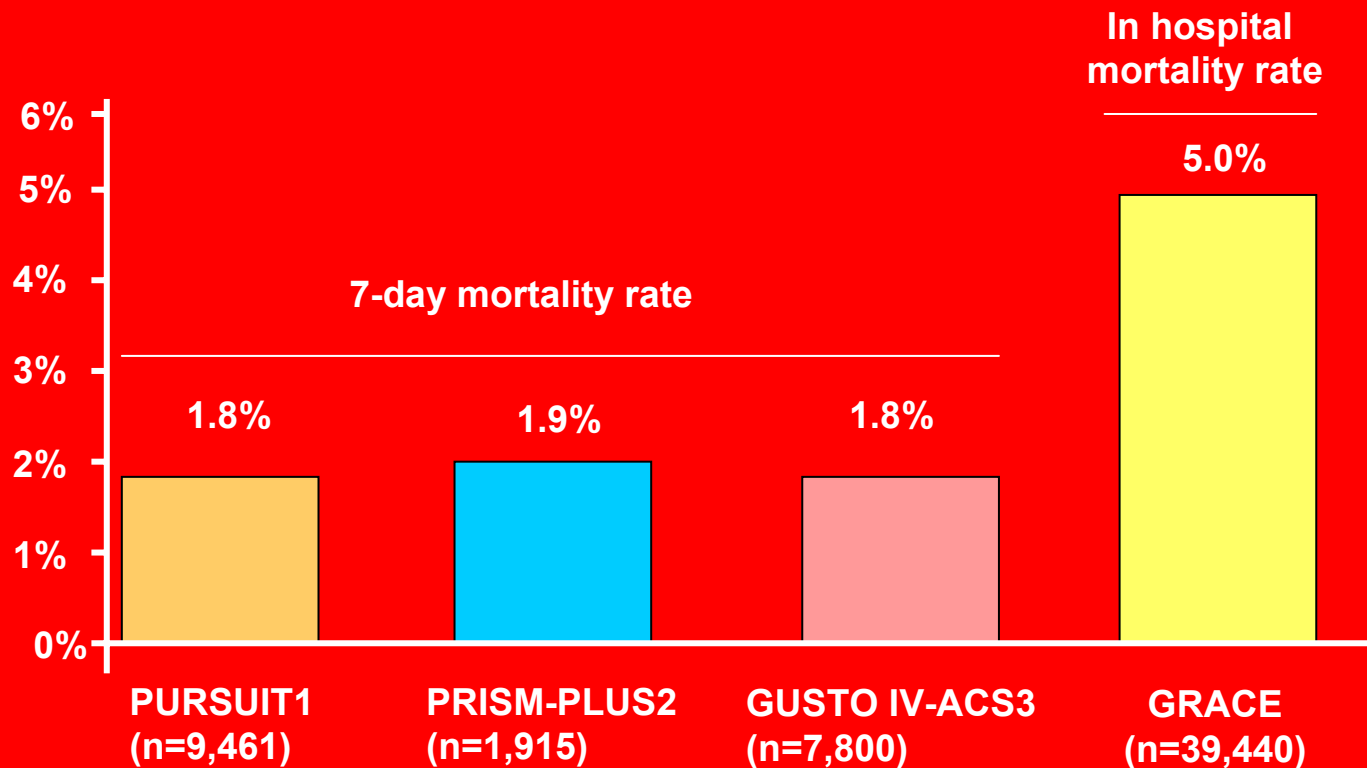
# Summary of the Risk Stratification : Risk of Progression to Death and MI

## Low-risk patients

- ✓ No recurrence of chest pain within observational period
- ✓ No ST-segment depression  
Negative T waves, Flat T waves, Normal ECG
- ✓ No elevation of troponin or others biochemical markers
- ✓ Troponin twice negative



# Mortality rate in High Risk ACS: clinical trials and real life



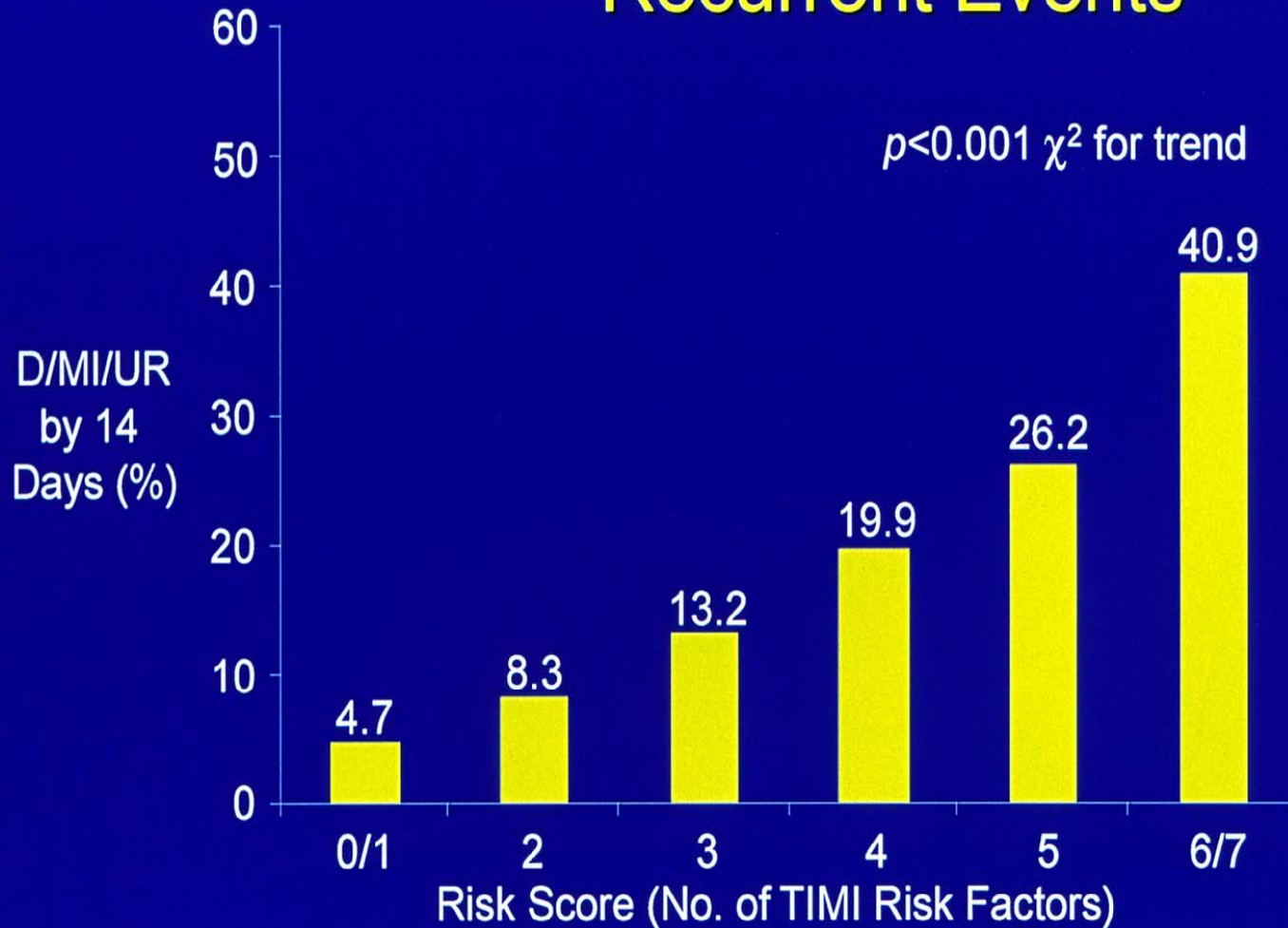
1. The pursuit Trial Investigators. *N Engl J Med* 1998
2. The PRISM-PLUS Study Investigators. *N Engl J Med* 1998
3. The GUSTO IV-ACS Investigators. *Lancet* 2001
4. GRACE. *Am J Cardiol* 2003;92(9):1031-6



# Outcome of “Low-risk” Patients with ACS

- Presentation with UA in the absence of dynamic ECG changes, no troponin elevation, no arrhythmia nor hypotension
- Abnormal ECG in 38%,
- 27% stress test, 37% echo, 52% angio
- 6 month outcome:
  - 23% readmission
  - 12% revascularized
  - 3% deaths
- **“Low-risk” is not no risk**

# Number of TIMI Risk Factors Predicts Short-Term Recurrent Events



## TIMI Risk Factors

- Age  $\geq 65$  yr
- $\geq 3$  CAD risk factors
- Known CAD
- Aspirin in past 7 days
- Recent ( $< 24$  h) severe angina
- ST deviation  $\geq 0.5$  mm
- $\uparrow$  Cardiac markers



D=death, MI=myocardial infarction, UR=urgent revascularization.

Antman E et al. *JAMA*. 2000;284:835.

[www.timi.org/files/riskscore/risk\\_home.htm](http://www.timi.org/files/riskscore/risk_home.htm)

# Tools to assess the risk stratification



[www.outcomes.org/grace](http://www.outcomes.org/grace)

## A Validated Prediction Model for All Forms of Acute Coronary Syndrome

Estimating the Risk of 6-Month Postdischarge Death in an International Registry

**Conclusions** The GRACE 6-month postdischarge prediction model is a simple, robust tool for predicting mortality in patients with ACS. Clinicians may find it simple to use and applicable to clinical practice.

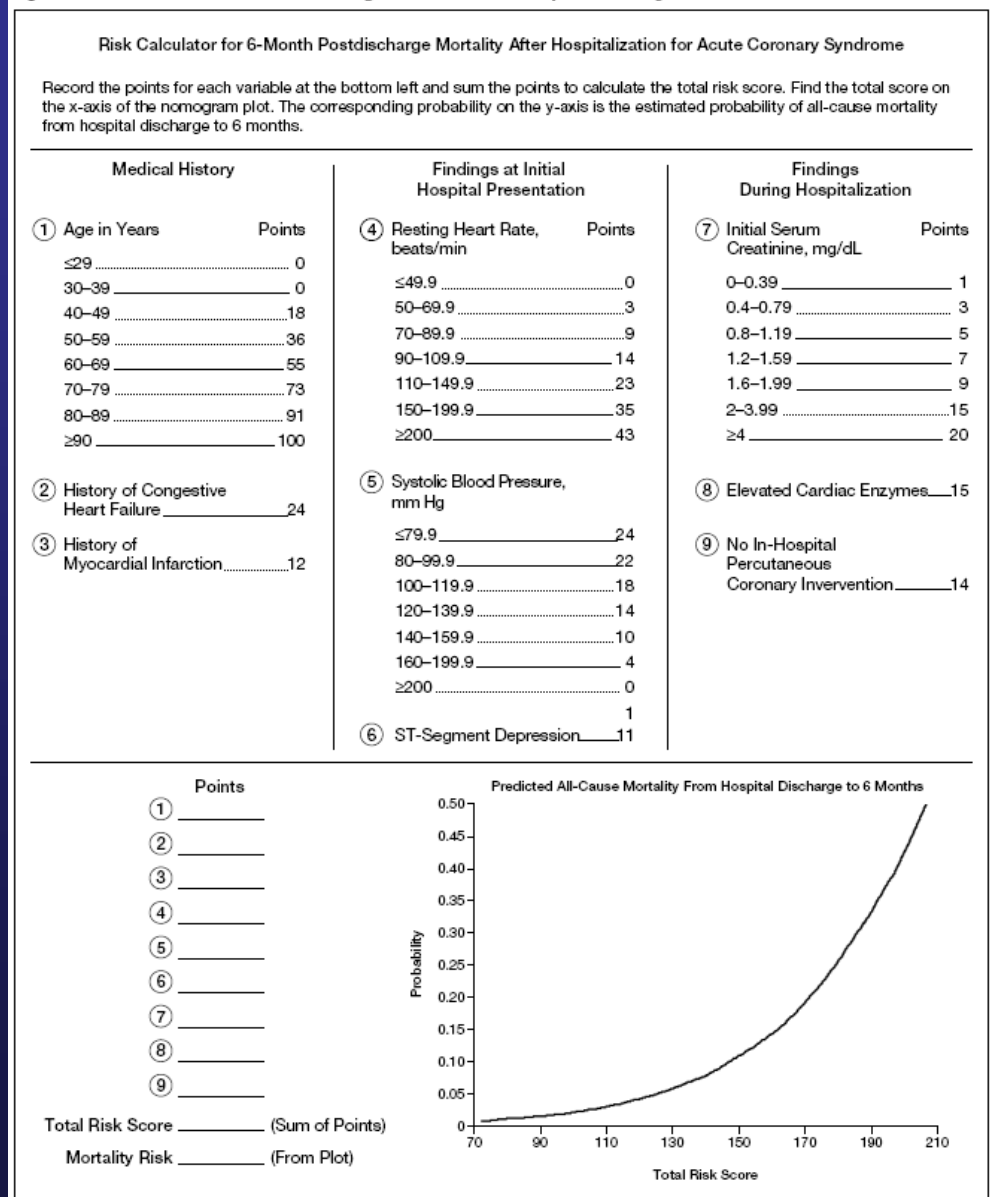
JAMA. 2004;291:2727-2733

www.jama.com

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- \_\_\_\_\_  
for the GRACE Investigators



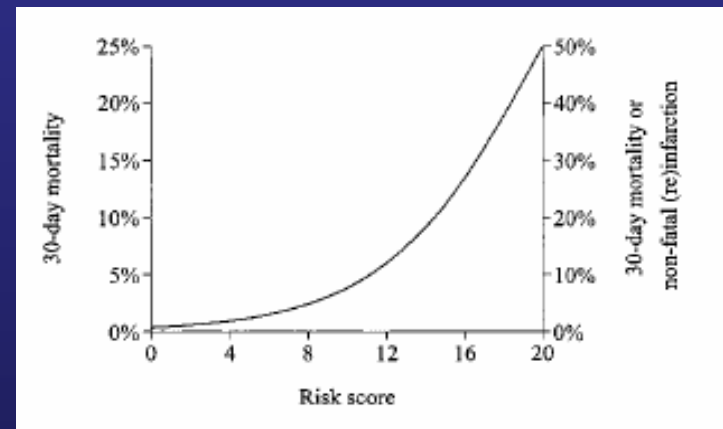
Figure 2. GRACE Prediction Score Card and Nomogram for All-Cause Mortality From Discharge to 6 Months



# Tools to assess the risk stratification

## PURSUIT RISK SCORE

		Score	
		Mortality only	Mortality or infarction
Age (year)	50	0	8 (11)
	60	2 (3)	9 (12)
	70	4 (6)	11 (13)
	80	6 (9)	12 (14)
Gender	Female	0	0
	Male	1	1
Worst CCS-class in previous 6 weeks	No angina; I or II	0	0
	III or IV	2	2
Heart rate (bpm)	80	0	0
	100	1 (2)	0
	120	2 (5)	0
Systolic blood pressure (mmHg)	120	0	0
	100	1	0
	80	2	0
Signs of heart failure (rales)	No	0	0
	Yes	3	2
ST-depression on presenting ECG	No	0	0
	Yes	3	1



American Heart Association® 

*Learn and Live* SM

Acute Coronary Syndrome W/O  
persistent ST-segment elevation

Treatment

# ACS without persistent ST-segment elevation

Treatment options :

- Anti-ischemic
- Antithrombotic therapy
- Urgent PCI



# Class I Recommendations for anti-ischemic therapy



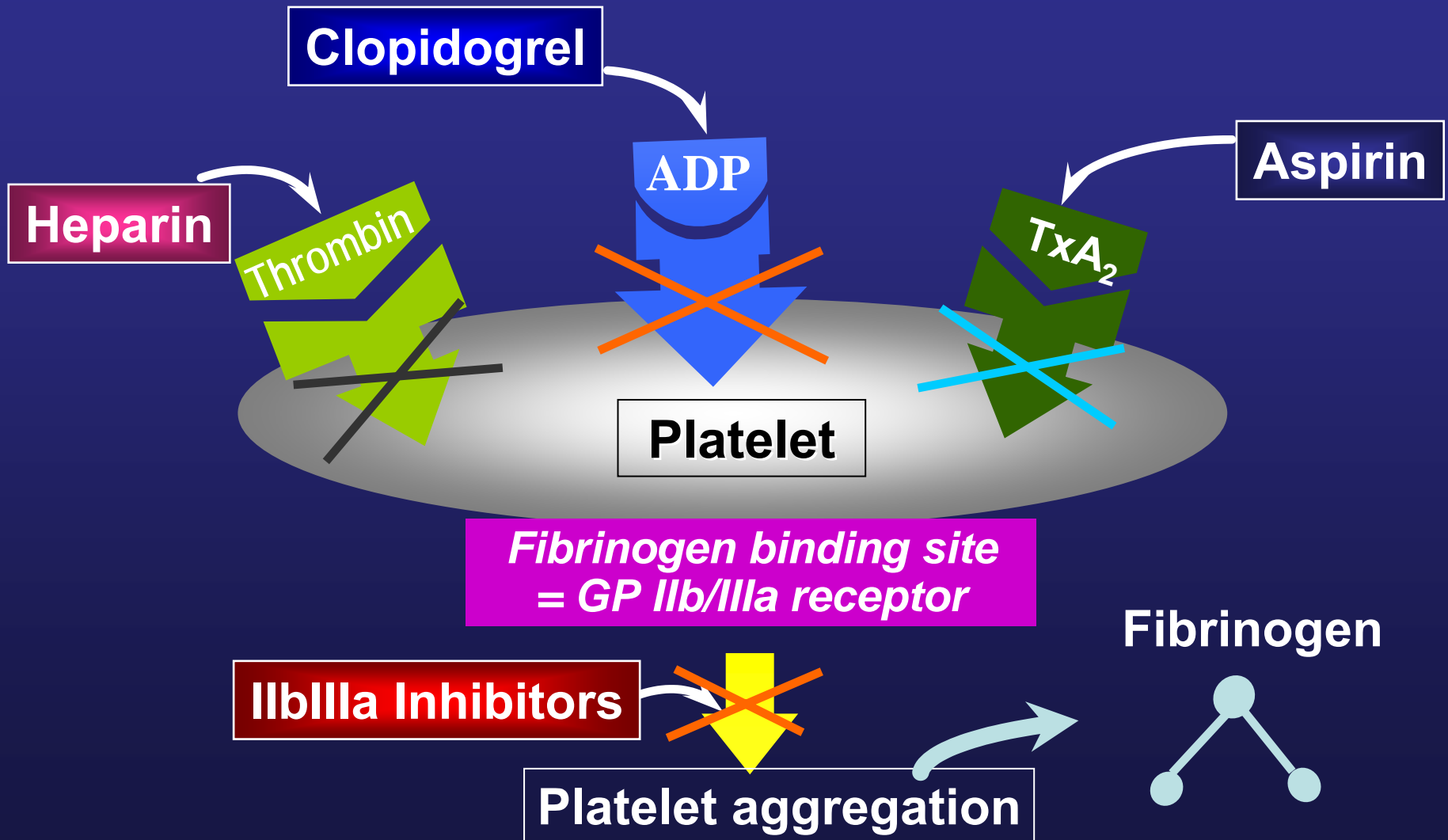
Continuing Ischemia/Other Clinical High-Risk Features <sup>‡</sup>		Level of evidence
Present	Absent	
Bed rest with continuous ECG monitoring		C
Supplemental O <sub>2</sub> to maintain Sao <sub>2</sub> >90%		C
NTG IV		C
Beta-blockers, oral or IV	Beta-blockers, oral	B
Morphine IV for pain, anxiety, pulmonary congestion		C
IABP if ischemia or hemodynamic instability persists		B
ACEI for control of hypertension or LV dysfunction, after MI	ACEI for control of hypertension or LV dysfunction, after MI	B

# ACS without persistent ST-segment elevation

Treatment options :

- Anti-ischemic
- Antithrombotic therapy
- Urgent PCI

# Antiplatelet and Anticoagulation therapy



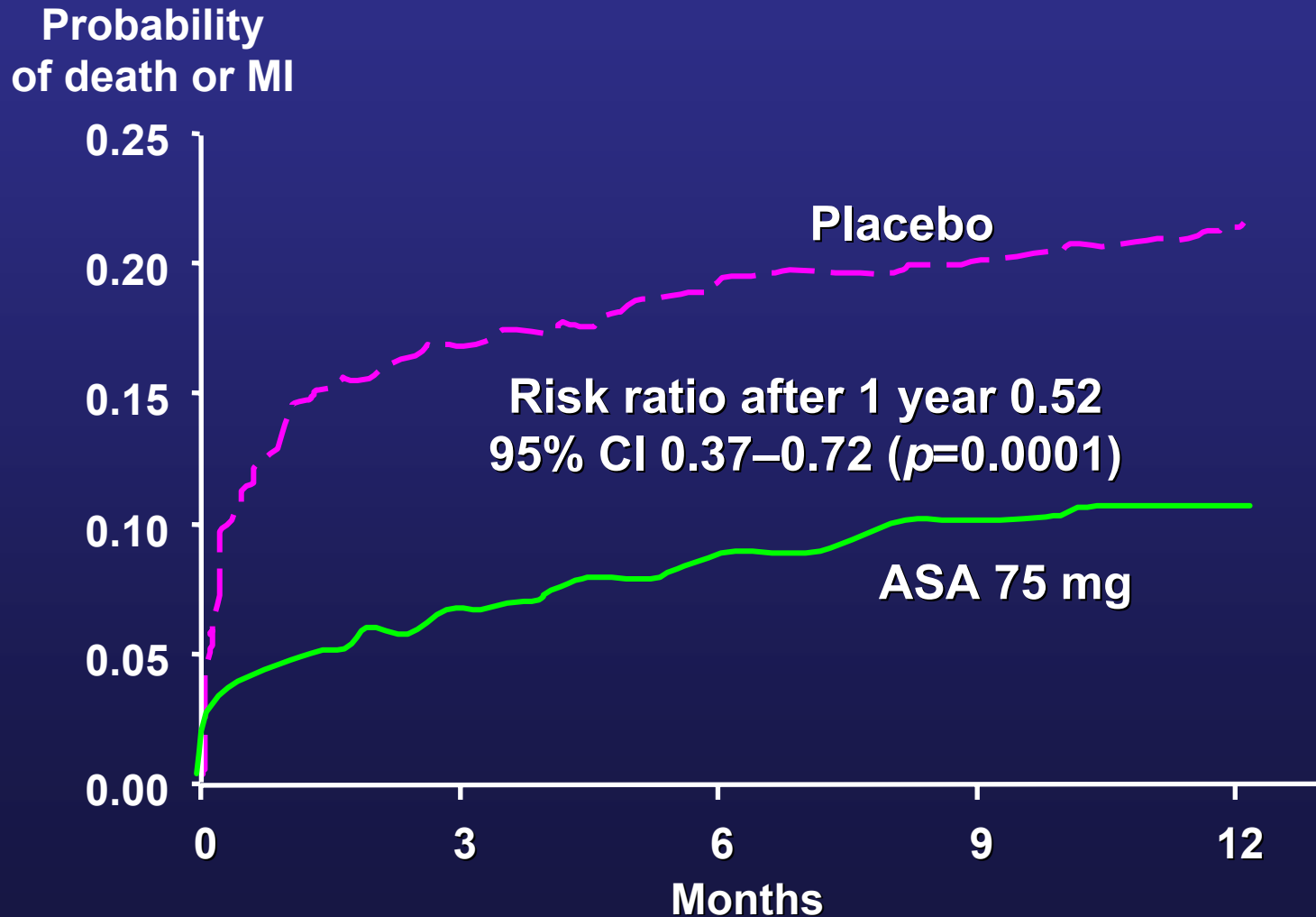
# ACS without persistent ST-segment elevation

Treatment options :

## Antithrombotic therapy

- ASA and Heparin
- Thienopyridines : Clopidogrel
- Anti IIbIIIa

# Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina



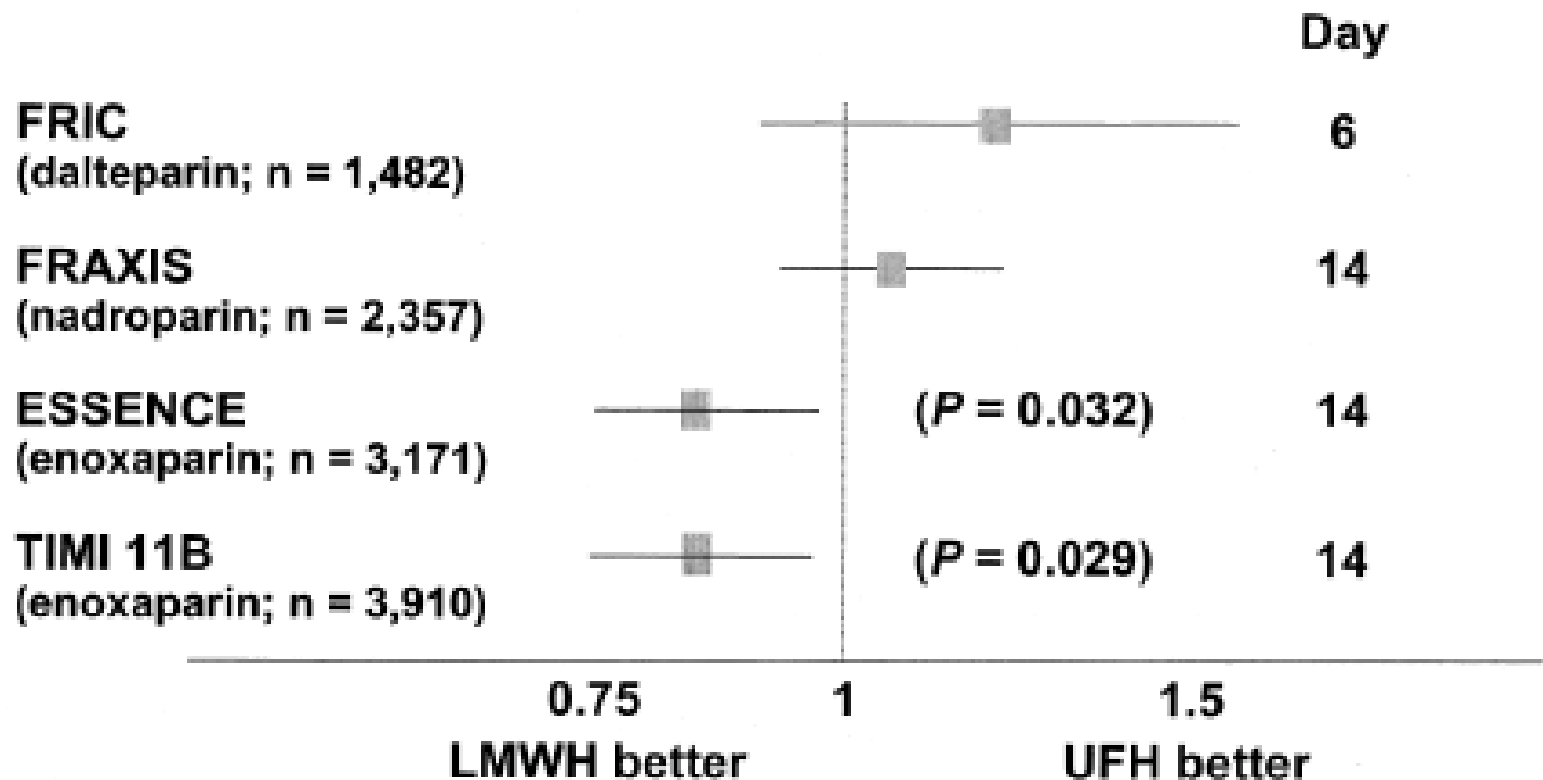
# Heparin trials

Study	Patients	ASA, mg/d	Heparin	Entry Window, h	Follow-up, d	ASA, %	Cardiac Death or Nonfatal MI		
							ASA/Heparin, %	RR Reduction, %	p
RISC <sup>138</sup>	796	75	Bolus q6h	72	5	3.7	1.4	62	NS
					30	4.8	3.8	21	NS
Théroux et al <sup>136</sup>	479	650	Bolus, infusion	24	6	3.3	1.6	52	NS
ATACS <sup>140</sup>	214	162.5	Bolus, infusion	48	5	8.3	3.8	54	NS
Overview <sup>140</sup>								56	<0.05

Low Molecular Weight Heparin

Unfractionated Heparin

# LMWH versus UFH in ACS with conservative strategy



\* Triple endpoint: death, MI, recurrent ischemia ± urgent revascularization.

Klein W. Circulation 1997;96:61-68.

FRAXIS study group. Eur Heart J 1999;20: 1553-62.

Cohen M. N Engl J Med 1997;337:447-52.

Antman EM. Circulation 1999;100:1593-601.

# UF versus LMWH Bleedings

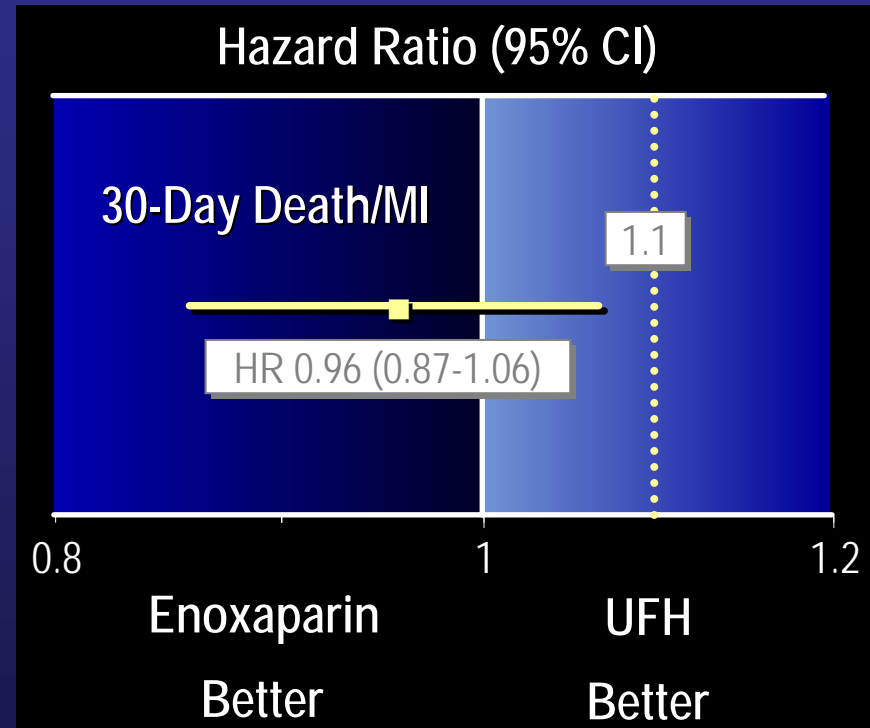
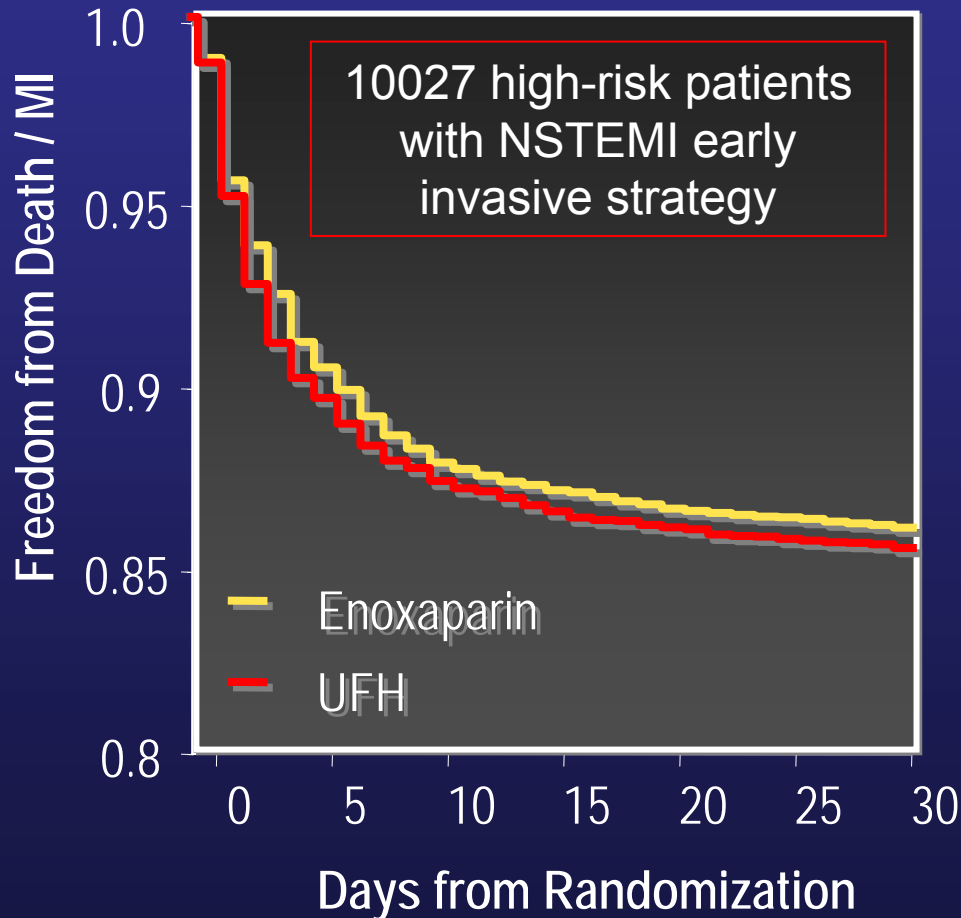
Time Point	Treatment Group		P
	Unfractionated Heparin (n=1936)	Enoxaparin <sup>a</sup> (n=1938)	
72 h			
Major hemorrhage	14 (0.7)	16 (0.8)	0.714
Minor hemorrhage	45 (2.3)	99 (5.1)	<0.001
End of initial hospitalization			
Major hemorrhage	19 (1.0)	29 (1.5)	0.143
Minor hemorrhage	48 (2.5)	176 (9.1)	<0.001

**TIMI IIb. Antman, E. M. et al.  
Circulation 1999;100:1593-1601**

ADVERSE EVENT	TREATMENT GROUP		P VALUE
	UNFRACTIONATED HEPARIN	ENOXAPARIN	
	number (percent)		
Hemorrhage			
Major	107 (7.0)	102 (6.5)	0.57
Minor	110 (7.2)	188 (11.9)	<0.001
Stroke	7 (0.5)	7 (0.4)	
Hemorrhagic	1 (0.1)	0	
Nonhemorrhagic	6 (0.4)	7 (0.4)	
Transient ischemic attack	8 (0.5)	1 (0.1)	
Drop in platelet count of >50% from base line	56 (3.7)	39 (2.5)	0.08

**ESSENCE. Cohen M et al.  
N Engl J Med 1997;337:447-52.**

# Death and MI at 30 Days in the SYNERGY trial

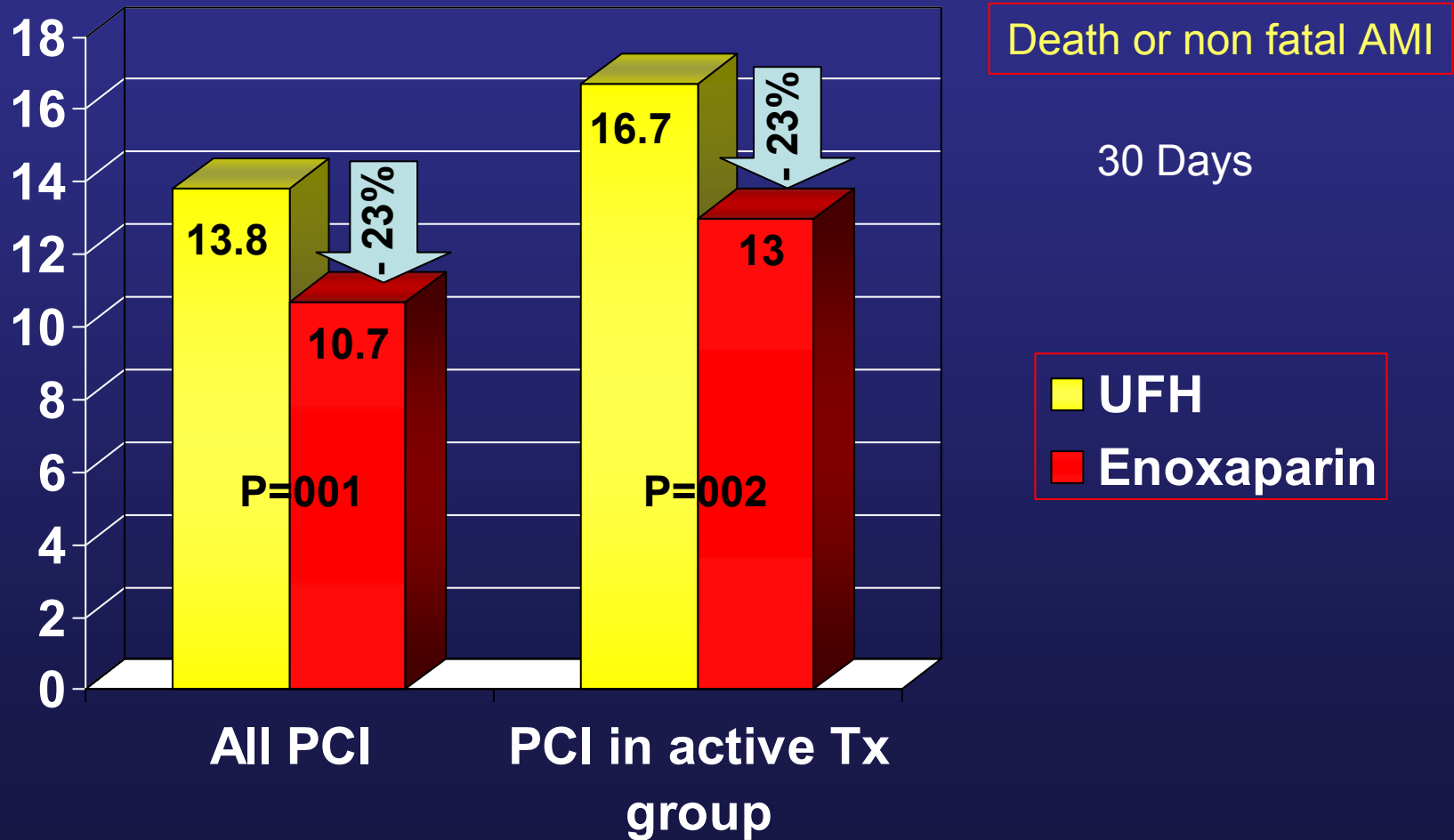


# Bleedings at 30 Days in the SYNERGY trial

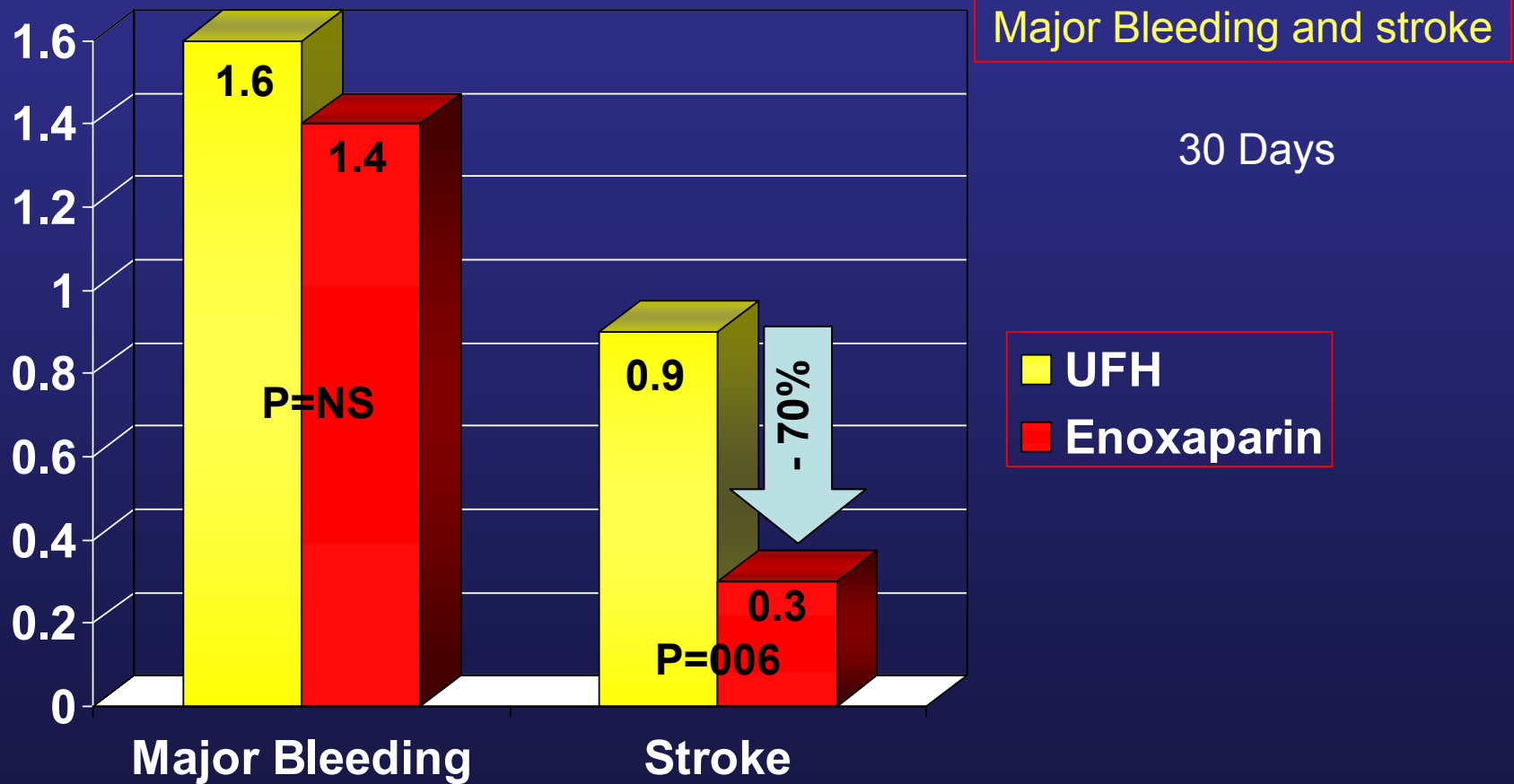
TIMI major bleeding (9.1% vs 7.6%,  $P=.008$ )

Resulted from CABG-related events

# PCI-Extract TIMI 25



# PCI-Extract TIMI 25



# ACS without persistent ST-segment elevation

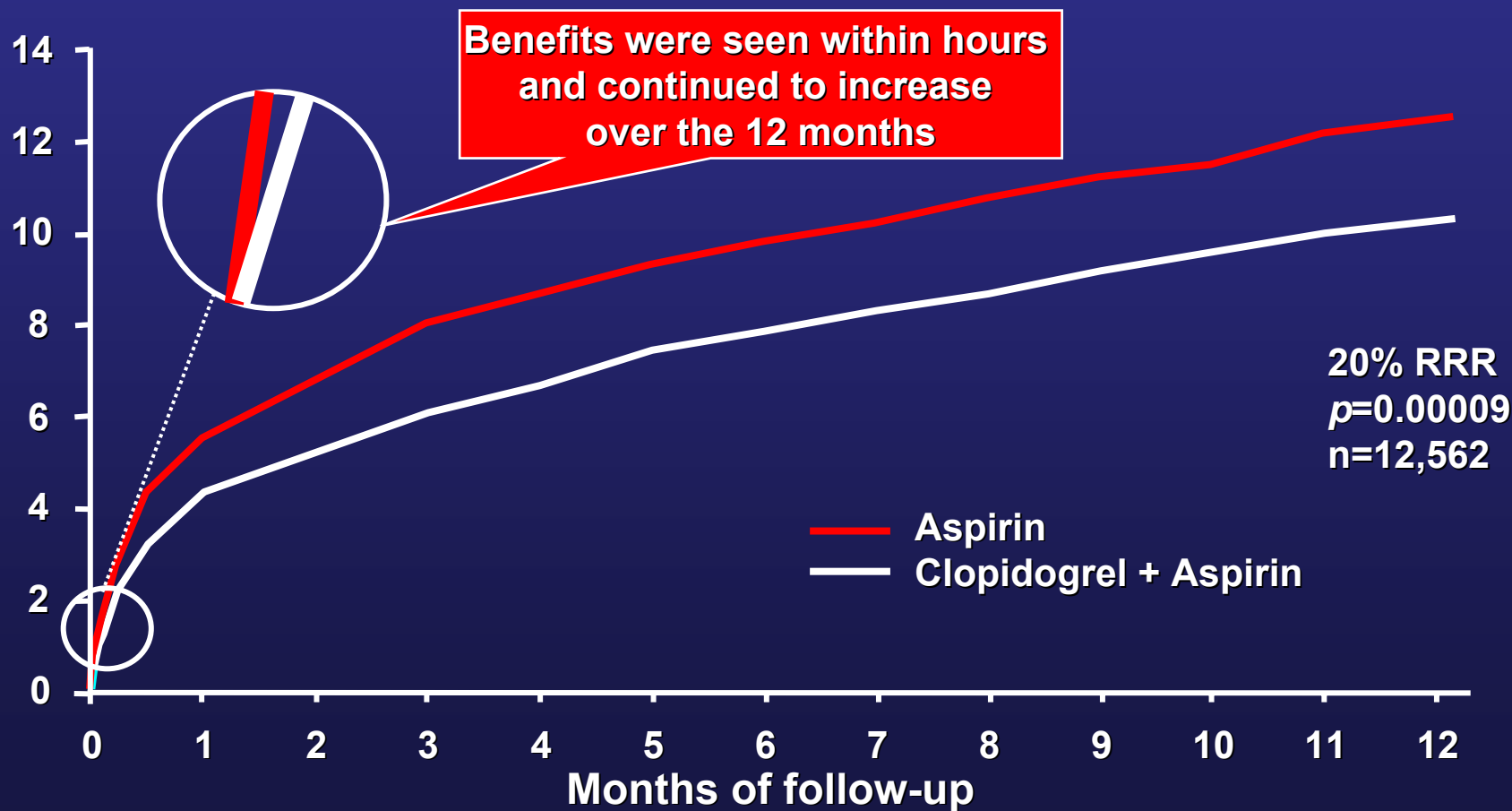
Treatment options :

## Antithrombotic therapy

- ASA and Heparin
- Thienopyridines : Clopidogrel
- Anti IIbIIIa

# CURE: Early & Long-Term Benefits of Clopidogrel

Cumulative Events [%]  
(Cardiovascular Death, Myocardial Infarction, or Stroke)



# CURE: Bleedings

VARIABLE	CLOPIDOGREL GROUP (N= 6259)	PLACEBO GROUP (N= 6303)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
Major bleeding	231 (3.7)	169 (2.7)	1.38 (1.13–1.67)	0.001
Necessitating transfusion of $\geq 2$ units of blood	177 (2.8)	137 (2.2)	1.30 (1.04–1.62)	0.02
Life-threatening	135 (2.2)	112 (1.8)	1.21 (0.95–1.56)	0.13
Fatal	11 (0.2)	15 (0.2)		
Causing 5 g/dl drop in hemoglobin level	58 (0.9)	57 (0.9)		
Requiring surgical intervention	45 (0.7)	43 (0.7)		
Causing hemorrhagic stroke	7 (0.1)	5 (0.1)		
Requiring inotropic agents	34 (0.5)	34 (0.5)		
Necessitating transfusion of $\geq 4$ units of blood	74 (1.2)	60 (1.0)		
Non-life-threatening	96 (1.5)	57 (0.9)	1.70 (1.22–2.35)	0.002
Site of major bleeding				
Gastrointestinal	83 (1.3)	47 (0.7)		
Retroperitoneal	8 (0.1)	5 (0.1)		
Urinary (hematuria)	4 (0.1)	5 (0.1)		
Arterial puncture site	36 (0.6)	22 (0.3)		
Surgical site	56 (0.9)	53 (0.8)		
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75–2.56)	<0.001
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48–1.94)	<0.001

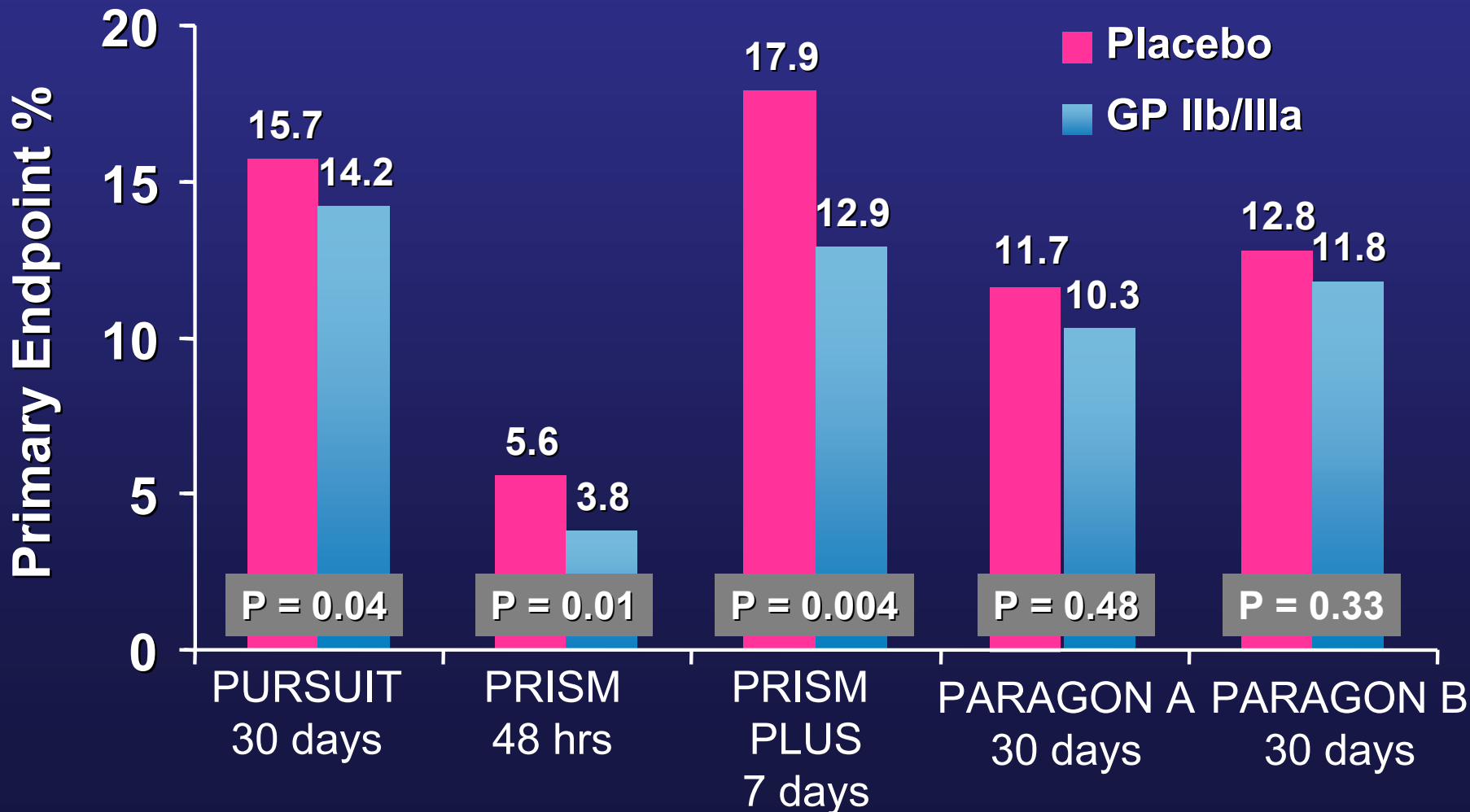
# ACS without persistent ST-segment elevation

Treatment options :

## Antithrombotic therapy

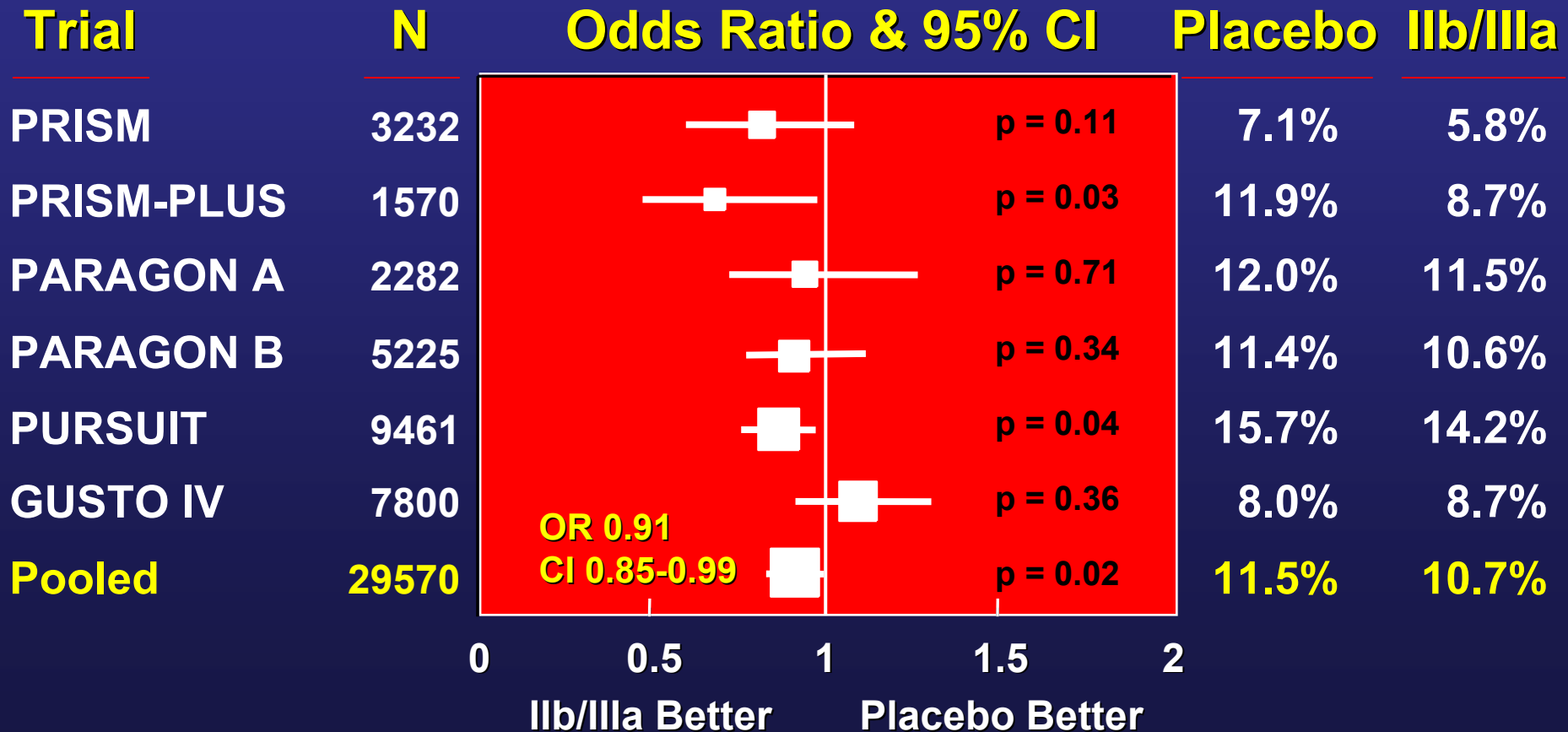
- ASA and Heparin
- Thienopyridines : Clopidogrel
- Anti IIb/IIIa

# Platelet GP IIb/IIIa Inhibition for NSTEMI-ACS Primary Endpoint Results from the 5 Major RCTs

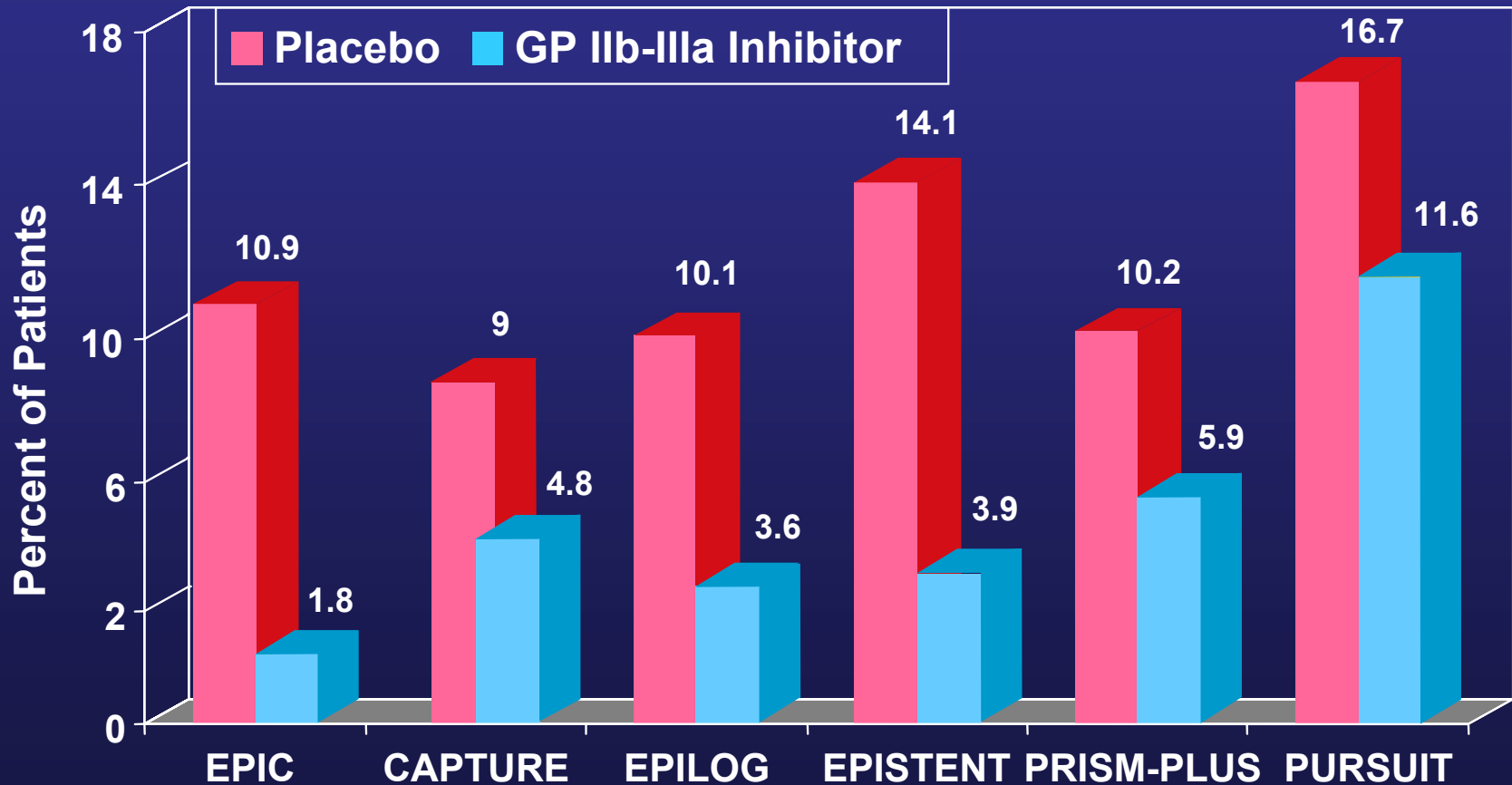


# GP IIb/IIIa and ACS:

## Death / MI at 30 Days

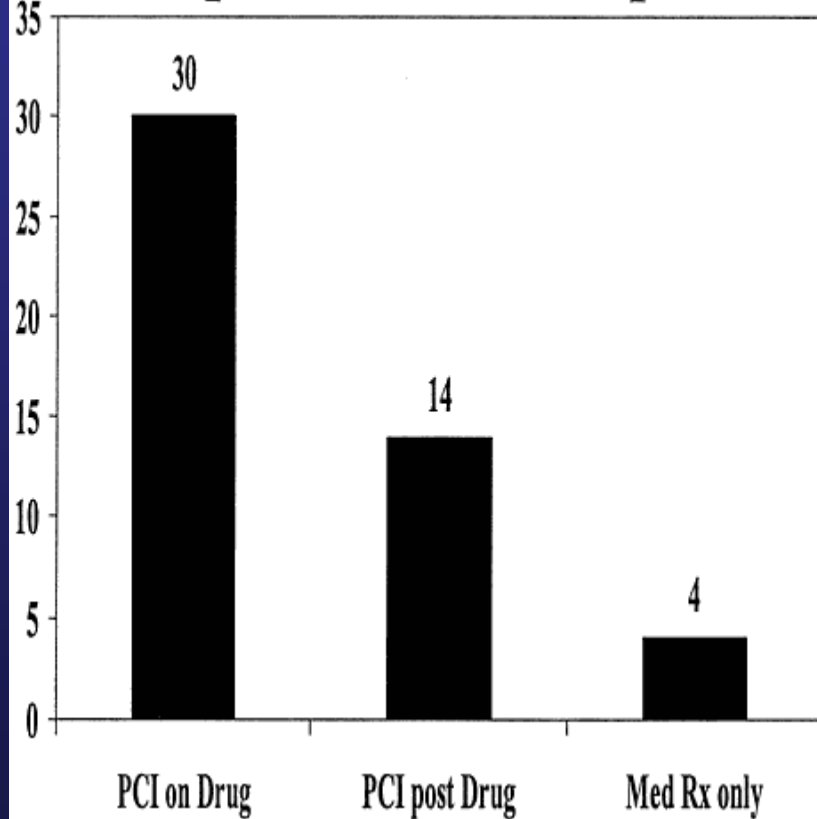


# Benefit of Glycoprotein IIb/IIIa Inhibition Impact in PCI

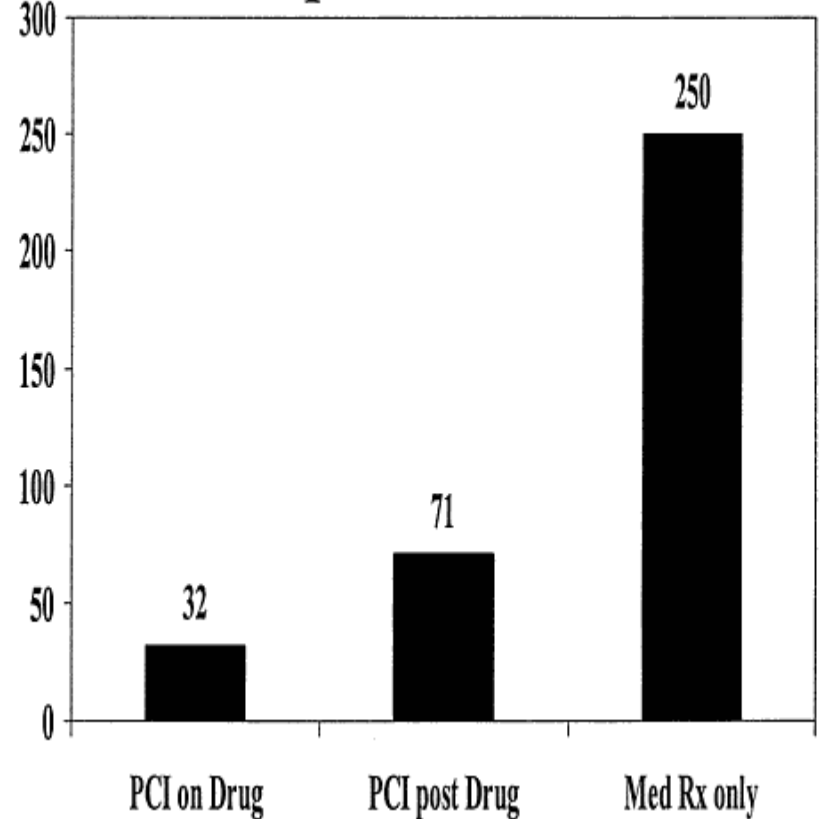


# Anti-IIb/IIIa and PCI

Events prevented /1000 pts Rx



NNT to prevent 1 event



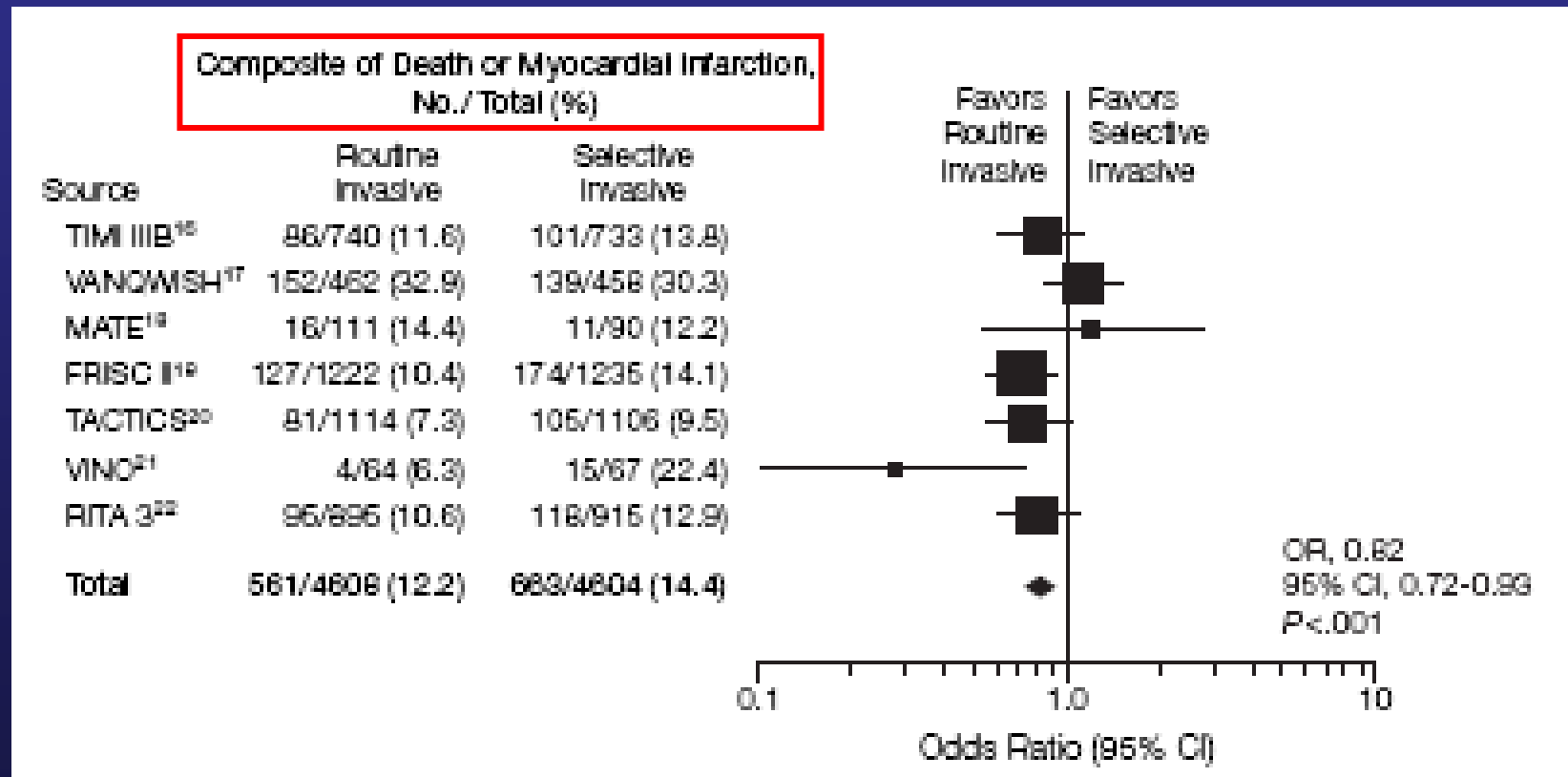
# ACS without persistent ST-segment elevation

Treatment options :

- Anti-ischemic
- Antithrombotic therapy
- Urgent PCI

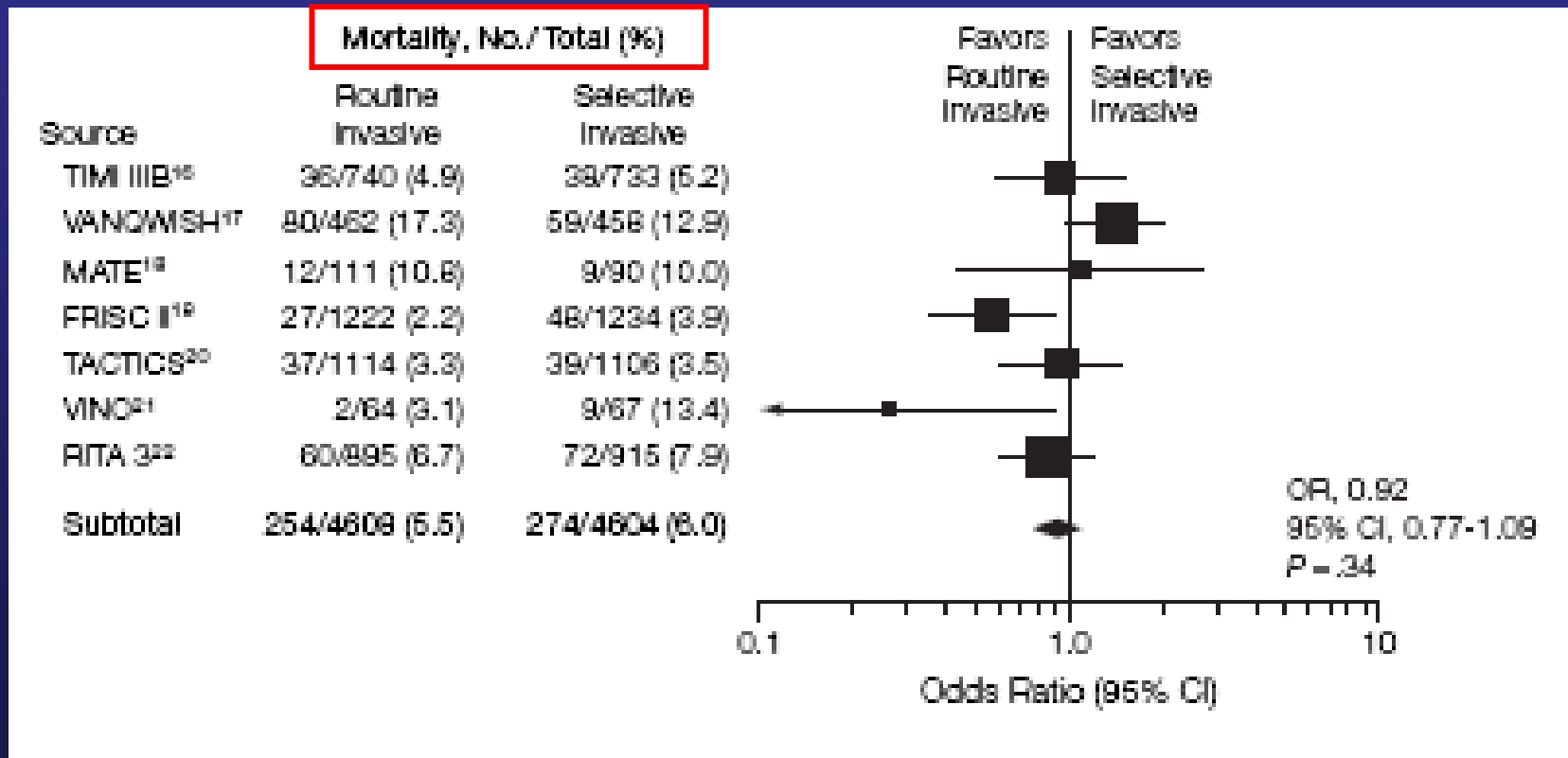
# Early Invasive versus no early invasive

Mean follow-up 17.3 months (range 6-24 months)



# Early Invasive versus no early invasive

Mean follow-up 17.3 months (range 6-24 months)





## **Early Invasive** versus **Selectively Invasive** Management for high risk ACS

- Coronary angiography should be planned as soon as possible, but without undue urgency.
- In most cases coronary angiography is performed within the 48 h, or at least within hospitalization period.

# Evaluation of Prolonged Antithrombotic Pretreatment (“Cooling-Off” Strategy) Before Intervention in Patients With Unstable Coronary Syndromes

## A Randomized Controlled Trial

# ISAR-COOL TRIAL

Franz-Josef Neumann, MD

Adnan Kastrati, MD

Gisela Pogatsa-Murray, MD

Julinda Mehilli, MD

Hildegard Bollwein, MD

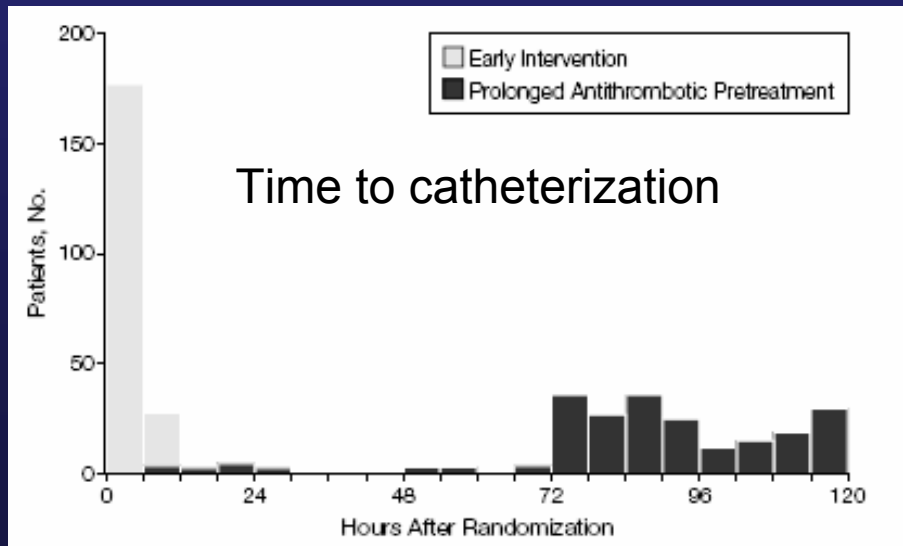
Hans-Peter Bestehorn, MD

Claus Schmitt, MD

Melchior Seyfarth, MD

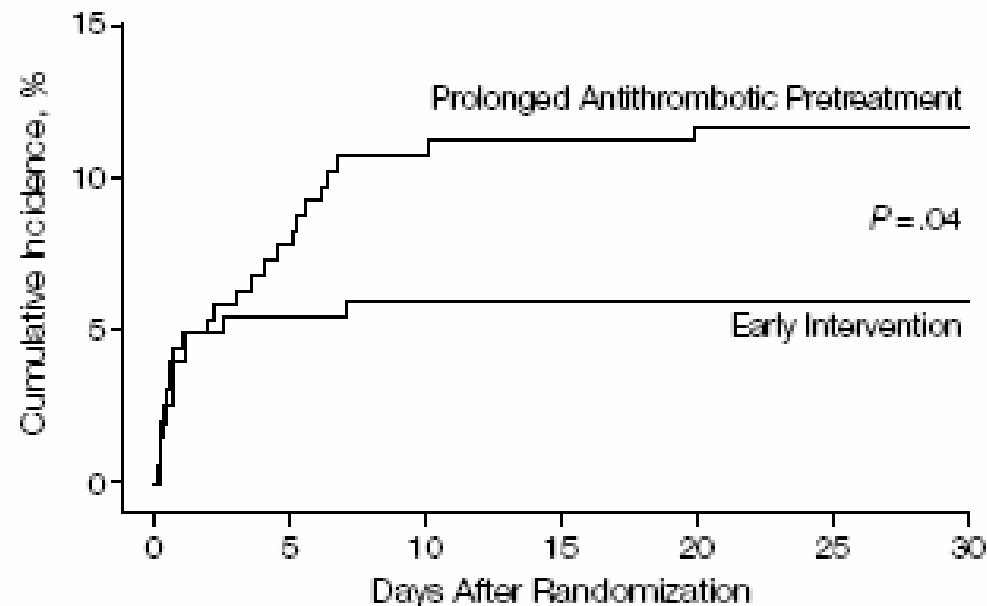
Josef Dirschinger, MD

Albert Schömig, MD



- ASA
- Plavix 600mg bolus
- Tirofiban for all patients (n=410)

# ISAR-COOL: Death/MI at 30 Days



	No. at Risk	0	5	10	15	20	25	30
Prolonged Antithrombotic Pretreatment	207	191	185	184	183	183	183	183
Early Intervention	203	192	191	191	191	191	191	191

**Conclusion** In patients with unstable coronary syndromes, deferral of intervention for prolonged antithrombotic pretreatment does not improve the outcome compared with immediate intervention accompanied by intense antiplatelet treatment.

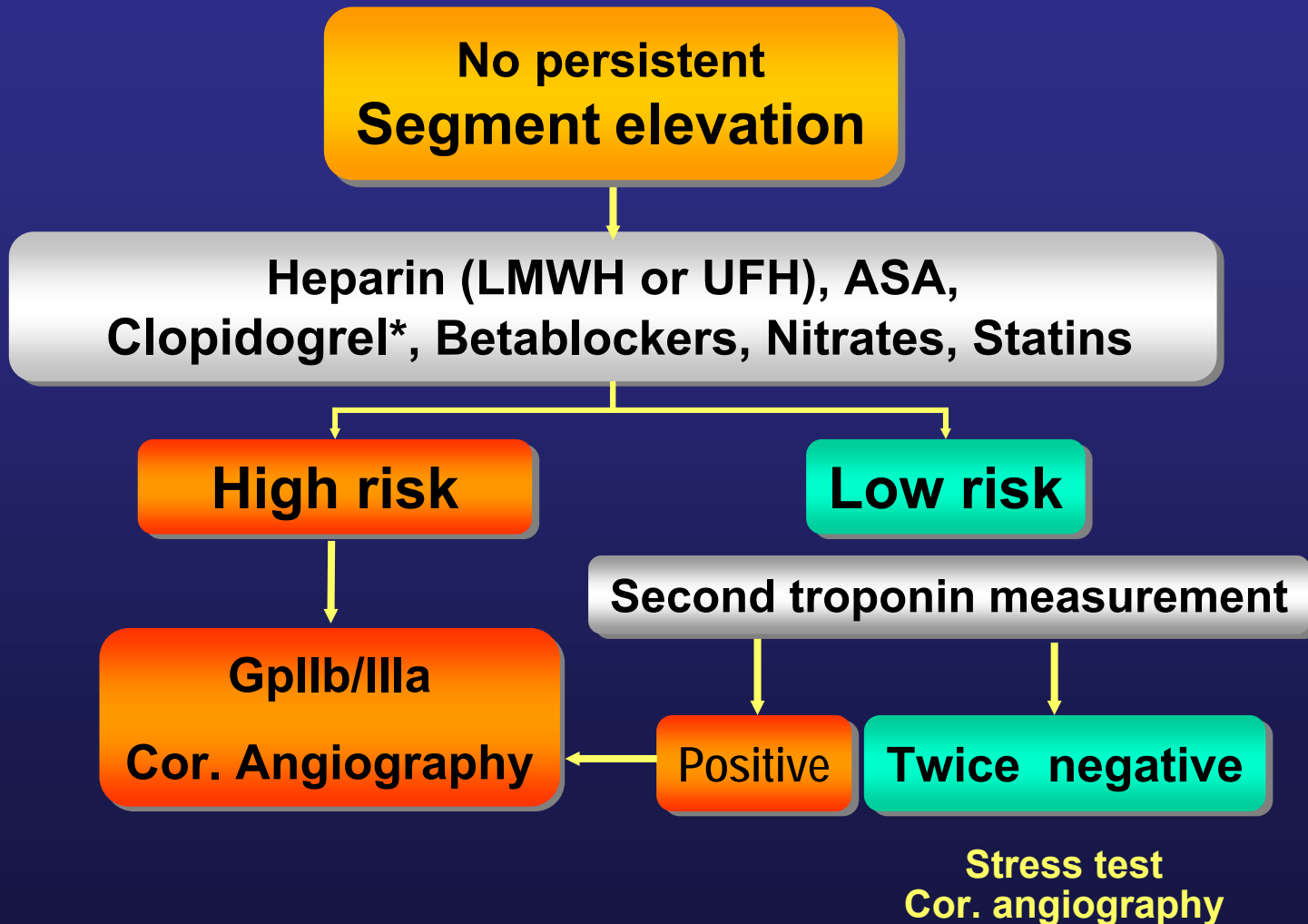
JAMA. 2003;290:1593-1599

www.jama.com

# Clinical Suspicion of ACS



Physical examination, ECG monitoring, Blood samples



\* Unless a CABG is planned within 5 days.

# GRACE: NSTEMI Treatment Strategies

## Worldwide Results from July to December 2001

