ST ELEVATION MYOCARDIAL INFARCTION

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MAIN TOPICS

- **Adjuncts to thrombolysis**
- **Pre hospital thrombolysis**
- **PCI for STEMI**
- **The approach to reperfusion**
- **Guidelines – based pharmacotherapy**

ADJUNCTS TO LYSIS – ANTI THROMBOTIC THERAPY

Protocol Design

STEMI < 6 h
Lytic eligible

ASA

Lytic choice by MD
(TNK, tPA, rPA, SK)

Double-blind, double-dummy

ENOX

< 75 y: 30 mg IV bolus
SC 1.0 mg / kg q 12 h (Hosp DC)

≥ 75 y: No bolus
SC 0.75 mg / kg q 12 h (Hosp DC)

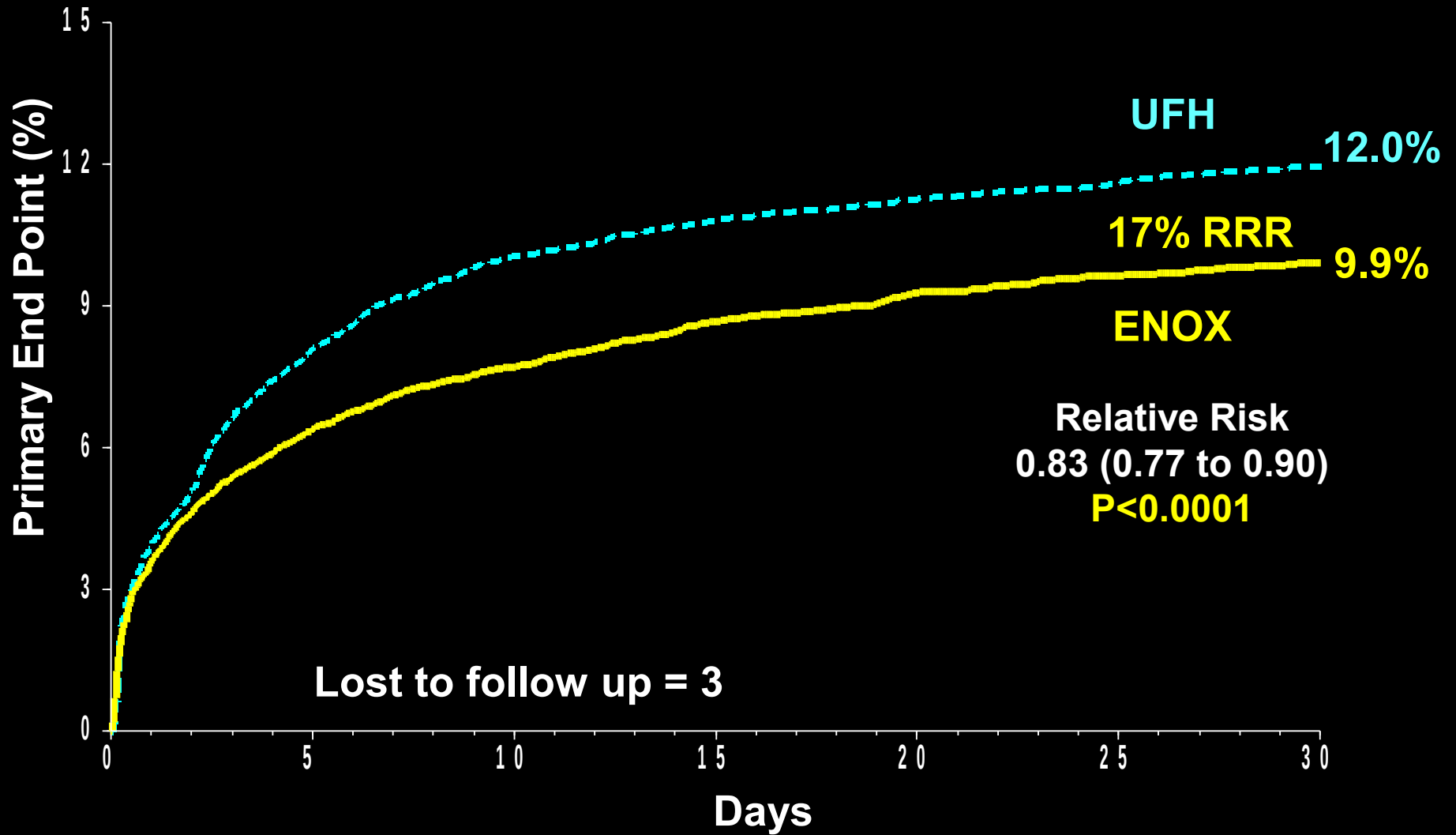
CrCl ≤ 30: 1.0 mg / kg q 24 h

UFH

60 U / kg bolus (4000 U)
Inf 12 U / kg / h (1000 U / h)
Duration: at least 48 h
Cont'd at MD discretion

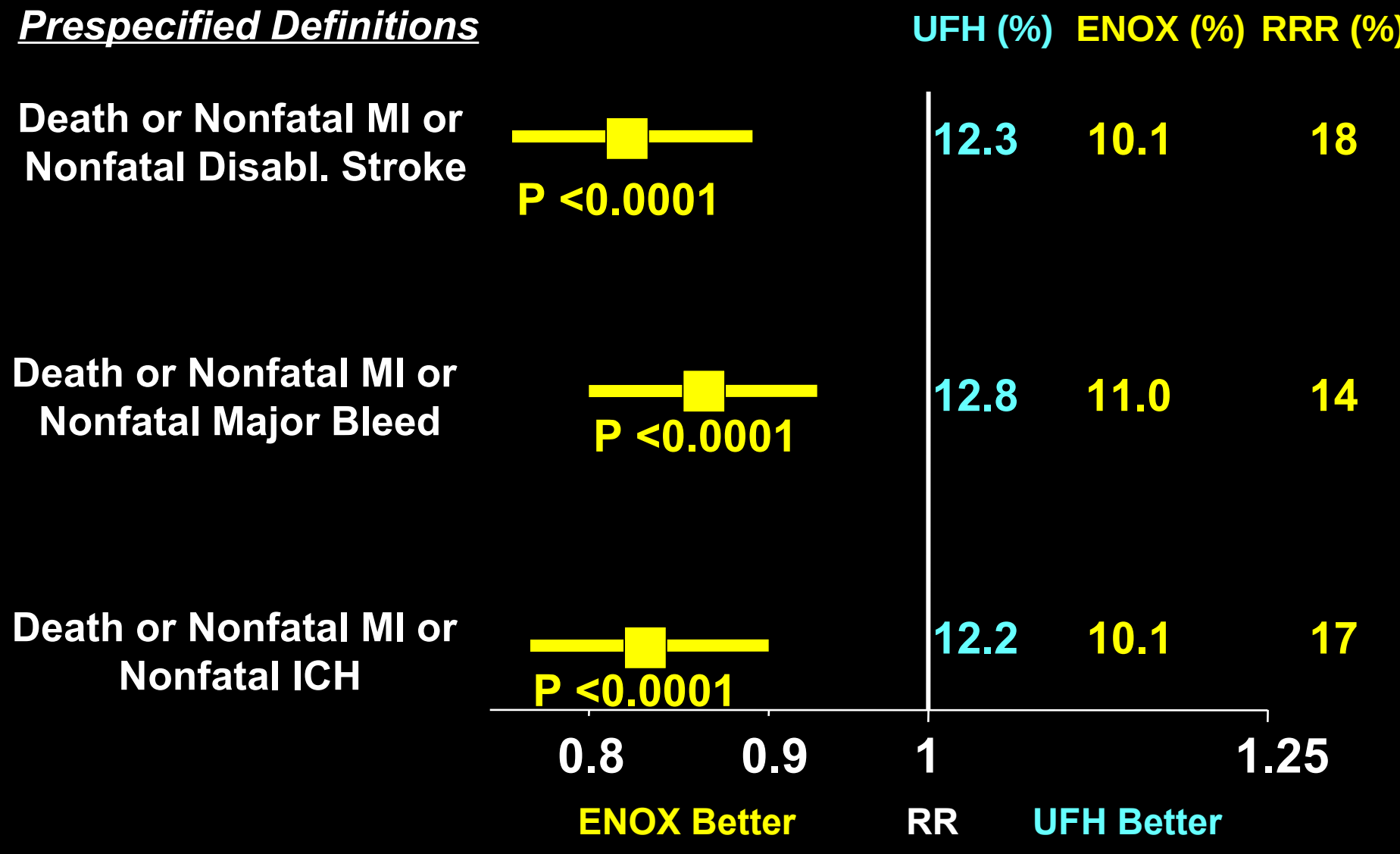
Day 30
1° Efficacy Endpoint: Death or Nonfatal MI
1° Safety Endpoint: TIMI Major Hemorrhage

Primary End Point (ITT)
Death or Nonfatal MI



Net Clinical Benefit at 30 Days

Prespecified Definitions

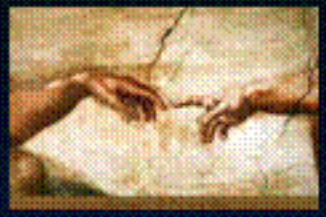


Clinical Implication

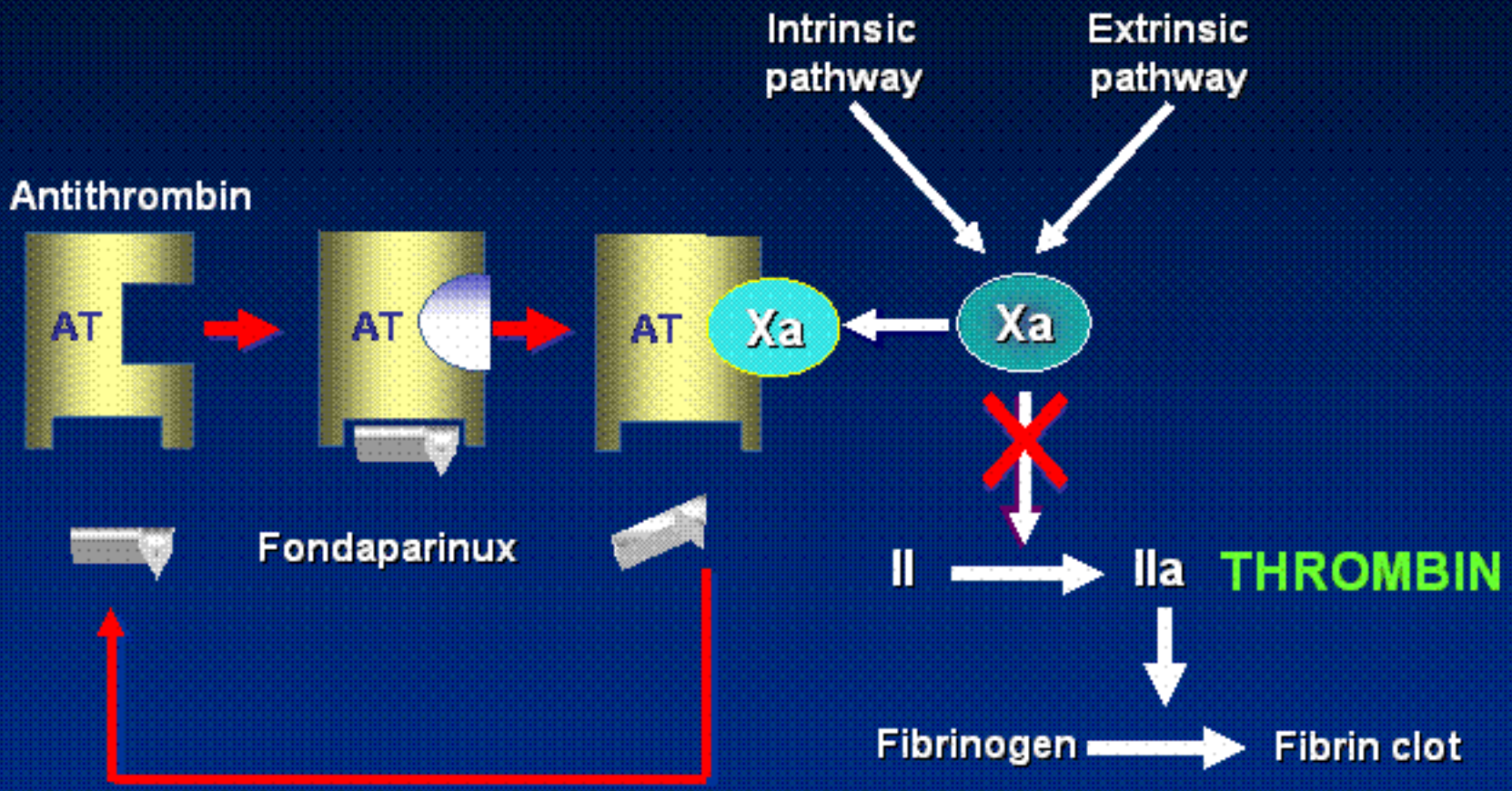
A strategy of **ENOX** is clearly preferable to the current standard of **UFH** as the antithrombin to support fibrinolysis, the most common form of reperfusion for STEMI used worldwide.

Is that clearly so?

- **EXTRACT did not convincingly show that Enoxaparin is superior to UFH while the 2 agents are actually administered.**
- **Only 23% of patients in EXTRACT had PCI. It is unlikely that with early PCI, as currently recommended, a significant difference exists between the 2 agents.**

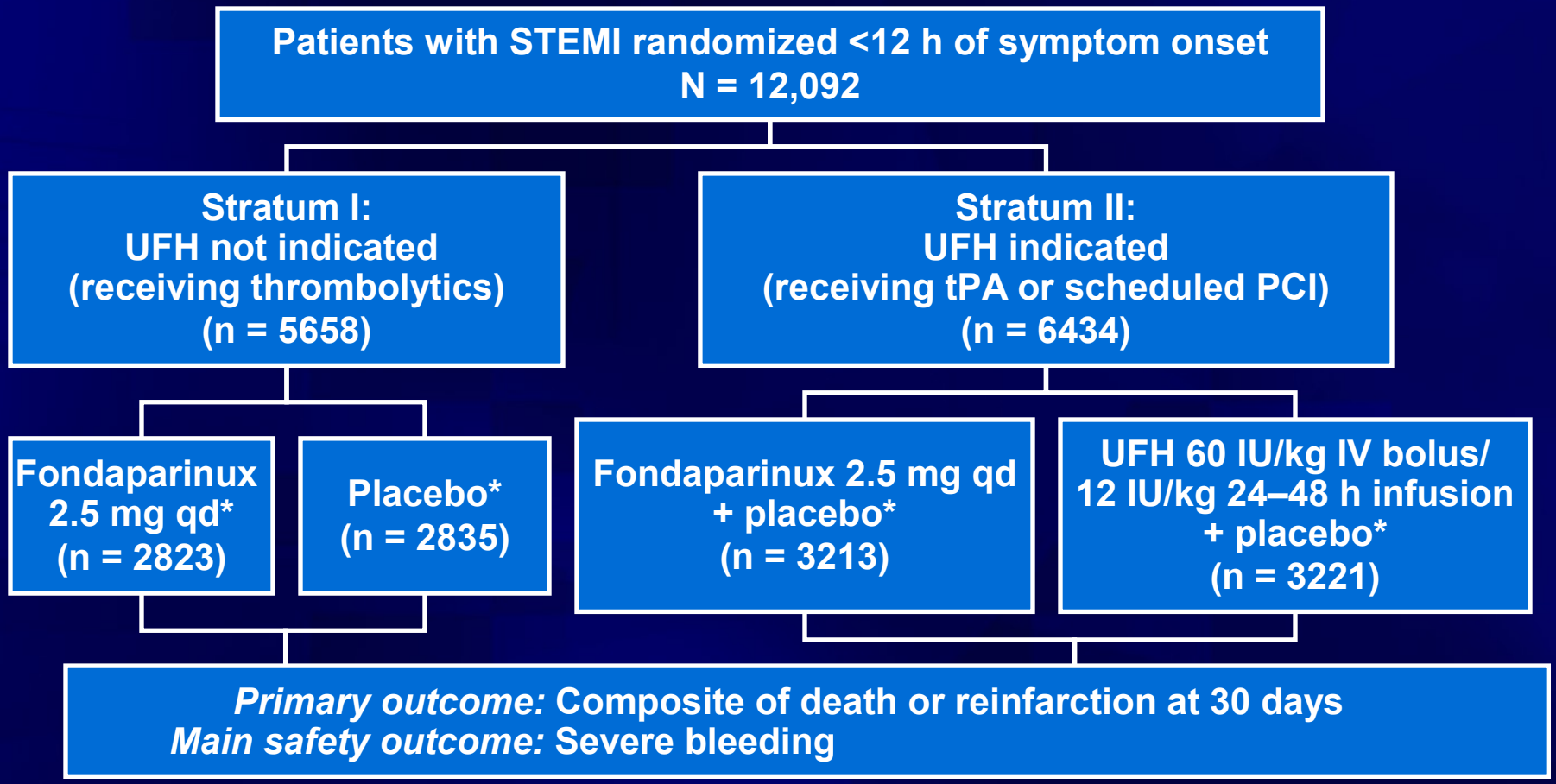


Fondaparinux: A Synthetic Factor Xa Inhibitor



Adapted with permission from Turpie AGG et al. *N Engl J Med.* 2001;344:619.

OASIS-6: Study design

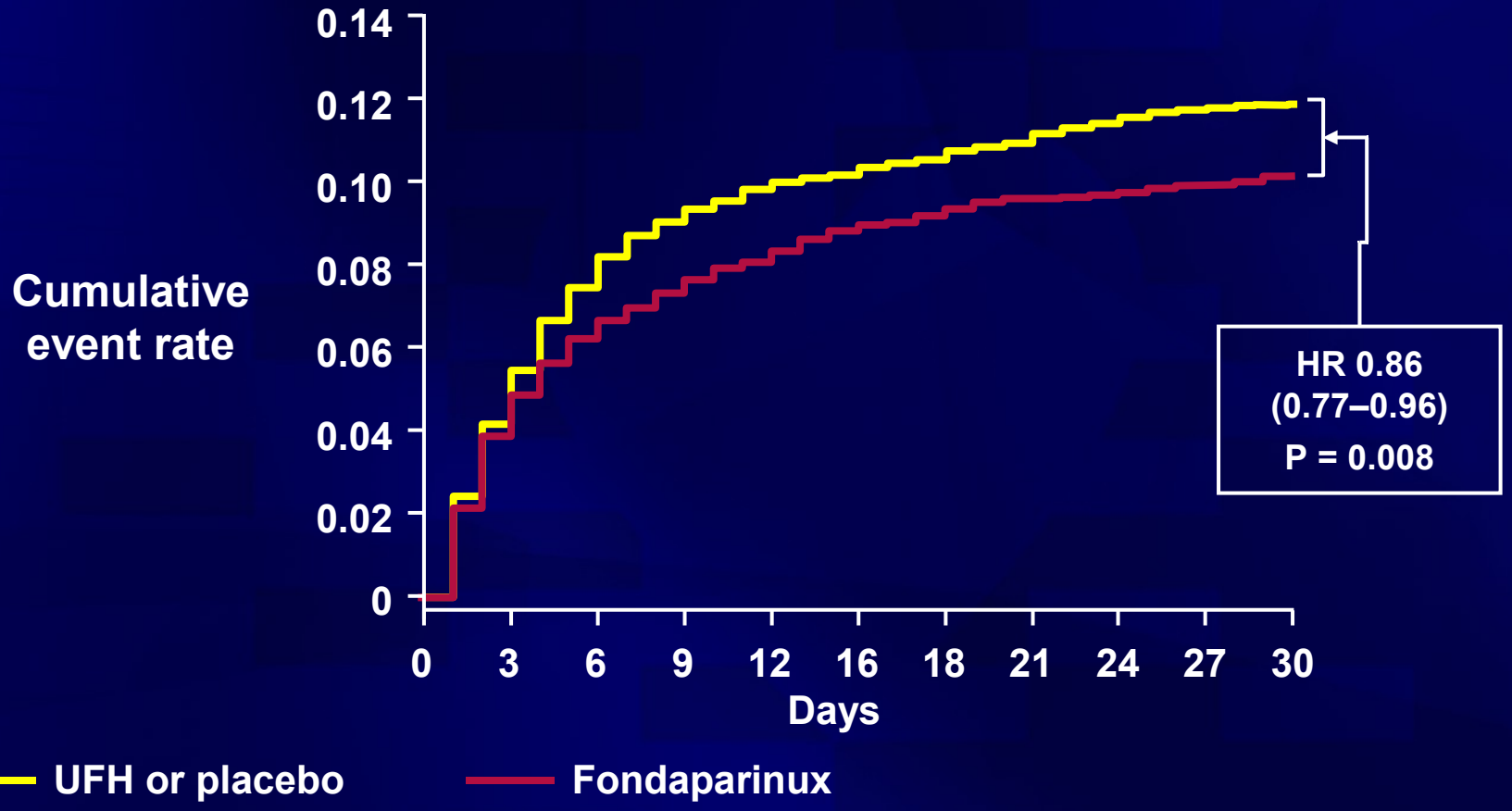


*Up to 8 days (or earlier discharge)

OASIS-6 Trial Group. *JAMA*. 2006;295:1519-30.

OASIS-6: Treatment effect on primary efficacy outcome at 30 days

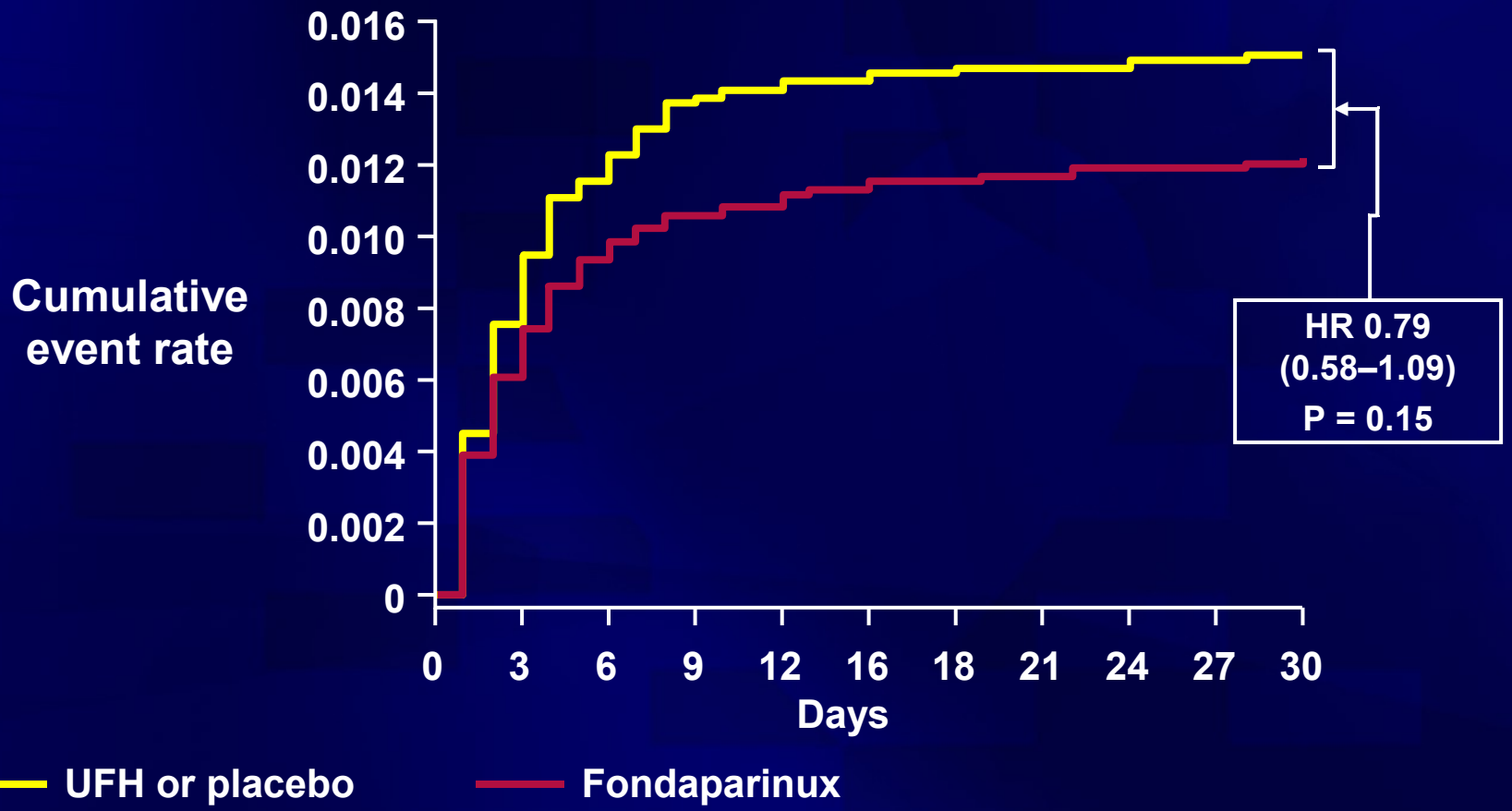
Composite of death, MI



OASIS-6 Trial Group. *JAMA*. 2006;295:1519-30.

OASIS-6: Severe bleeding at 30 days

Modified TIMI criterion



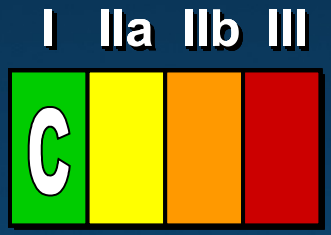
OASIS-6 Trial Group. *JAMA*. 2006;295:1519-30.

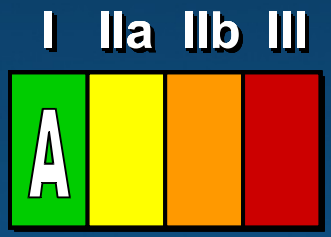
OASIS-6: Summary

- Fondaparinux demonstrated a moderate reduction in mortality and reinfarction vs UFH/placebo
- Unlike other antithrombotic agents (eg, LMW heparin, direct thrombin inhibitors, intravenous antiplatelet agents), fondaparinux reduced deaths and reinfarction without increased bleeding or hemorrhagic stroke
- There appears to be little advantage in using fondaparinux as the initial treatment in patients undergoing primary PCI

OASIS-6 Trial Group. *JAMA*. 2006;295:1519-30.

Anticoagulants





Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours *(Level of Evidence: C)* and preferably for the duration of the index hospitalization, up to 8 days (regimens other than unfractionated heparin [UFH] are recommended if anticoagulant therapy is given for more than 48 hours because of the risk of heparin-induced thrombocytopenia with prolonged UFH treatment). *((Level of Evidence: A*

Anticoagulant regimens with established efficacy :include

UFH *((LOE: C* ♥

Enoxaparin *((LOE:A* ♥

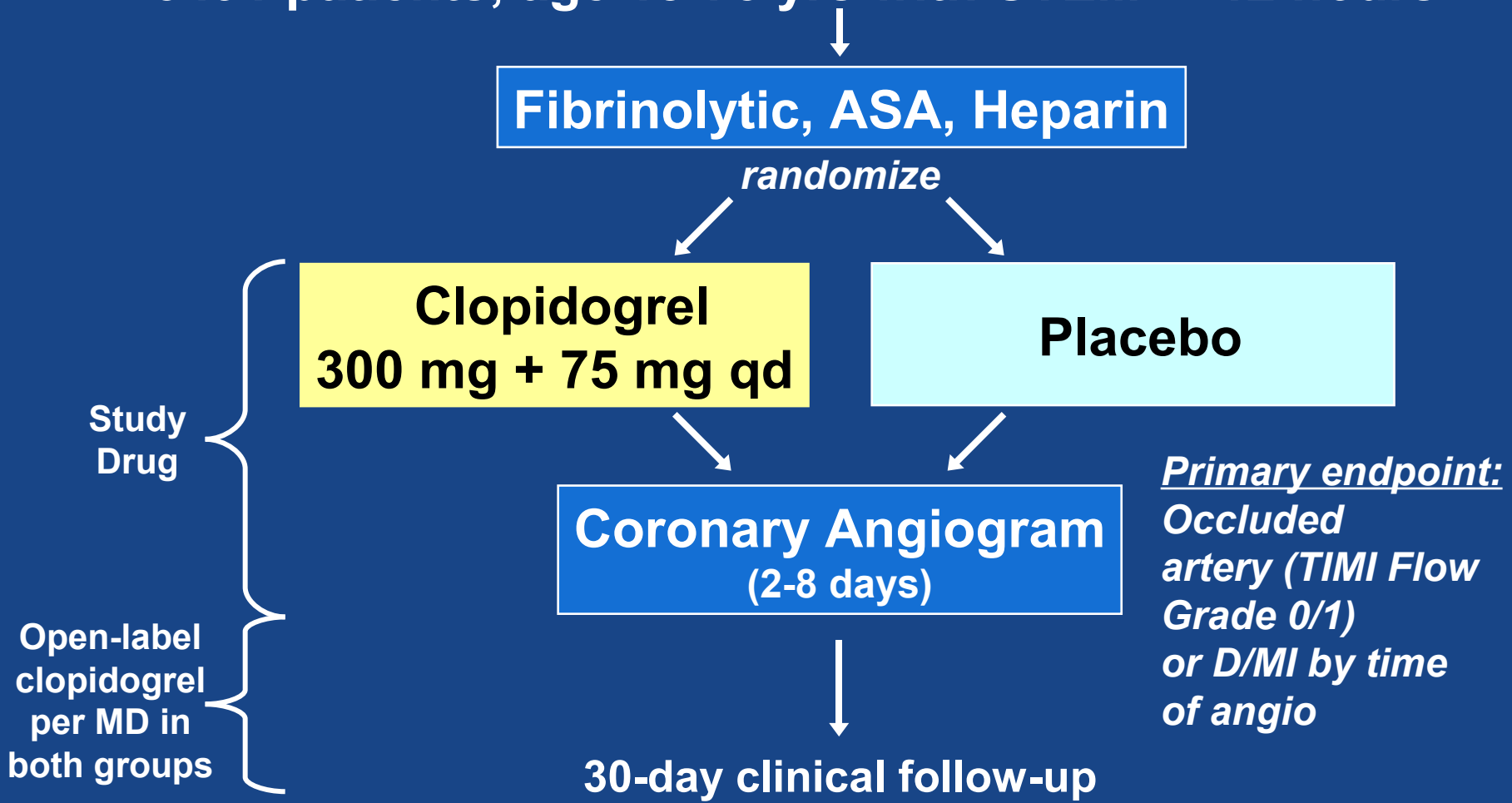
Fondaparinux *((LOE:B* ♥

ADJUNCTS TO LYSIS – CLOPIDOGREL

CLARITY TIMI 28

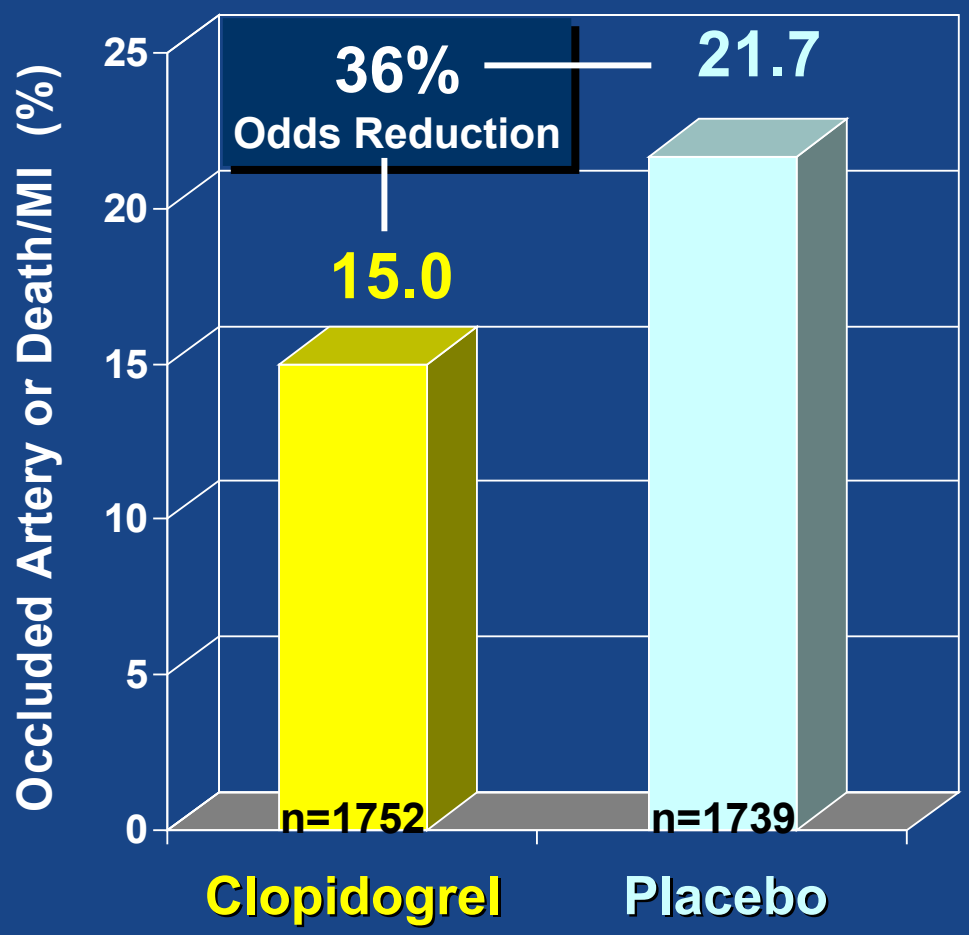
Study Design

Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 yrs with STEMI < 12 hours



CLARITY TIMI 28

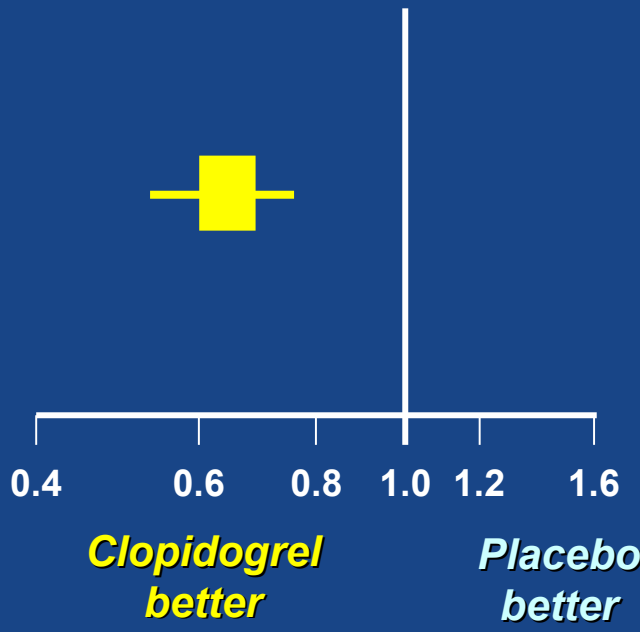
Primary Endpoint: Occluded Artery (or D/MI thru Angio/HD)



Odds Ratio 0.64

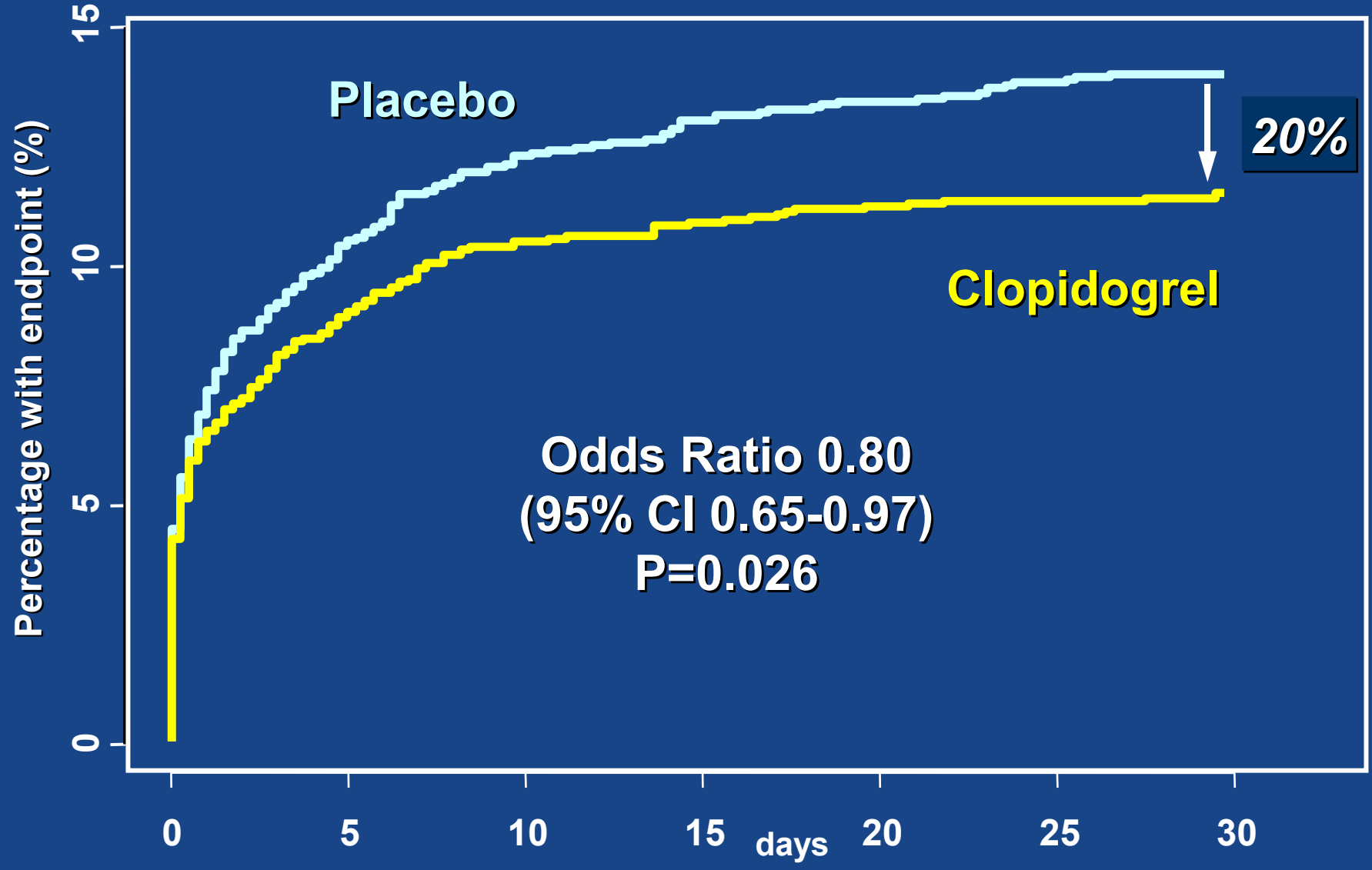
(95% CI 0.53-0.76)

P=0.00000036



CLARITY TIMI 28

CV Death, MI, RI → Urg Revasc



CLARITY TIMI 28

Bleeding

Outcome	Clopidogrel (%)	Placebo (%)	P value
Through angiography			
TIMI major (Hgb ↓ >5 g/dL or ICH)	1.3	1.1	NS
TIMI minor (Hgb ↓ 3-5 g/dL)	1.0	0.5	NS
Intracranial hemorrhage	0.5	0.7	NS
Through 30 days			
TIMI major	1.9	1.7	NS
In those undergoing CABG	7.5	7.2	NS
CABG w/in 5 d of study med	9.1	7.9	NS
TIMI minor	1.6	0.9	NS

COMMIT/CCS-2

(*C*l*O*pidogrel & *M*etoprolol in *M*yocardial *I*nfarction *T*rial)

Designed, conducted, analysed and interpreted independently by COMMIT/CCS-2 collaboration

Sources of funding (US$ 3M):

SanofiAventis/BMS

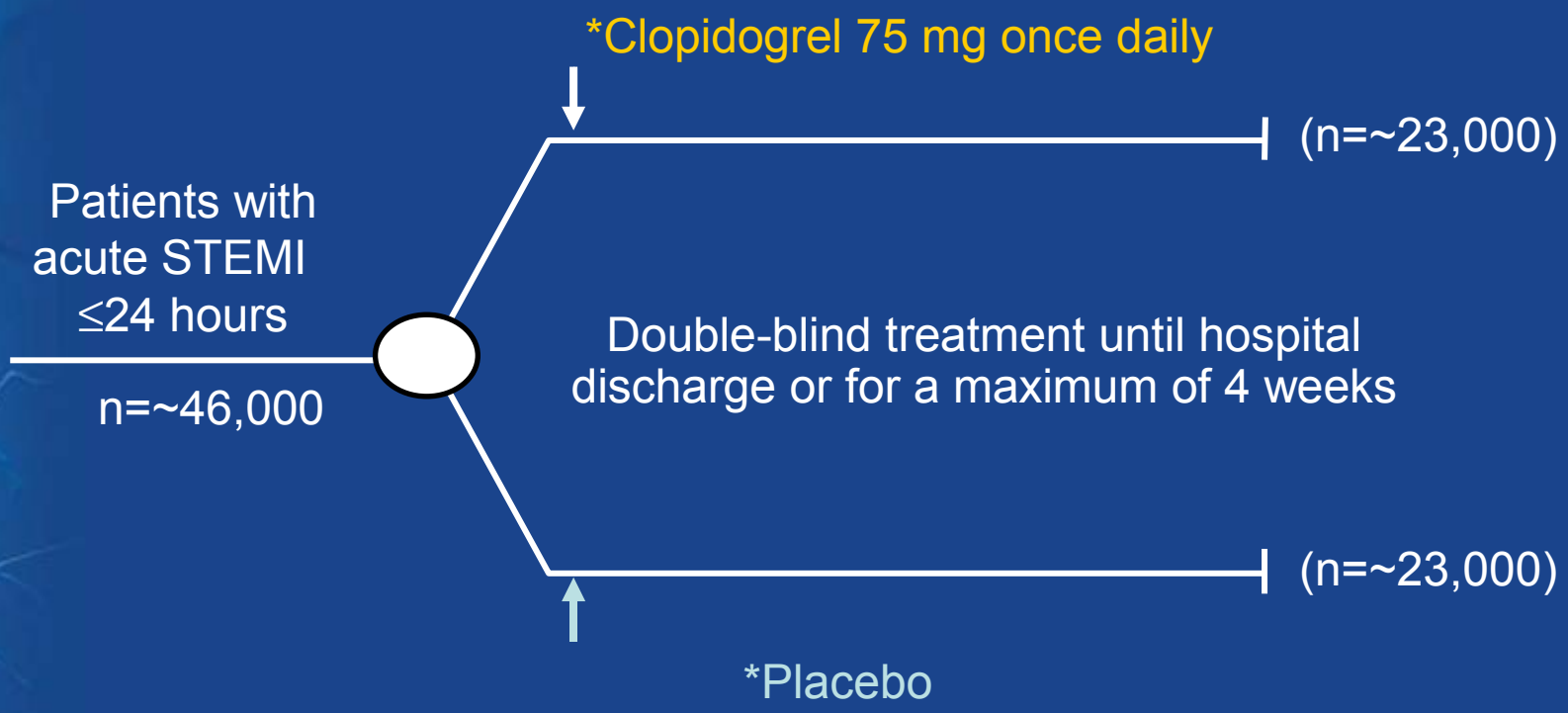
AstraZeneca

British Heart Foundation

UK Medical Research Council

commit CCS-2

Study Design[1]



(X 2 factorial with metoprolol 2)

All patients received a background of ASA 162 mg/day* during the study

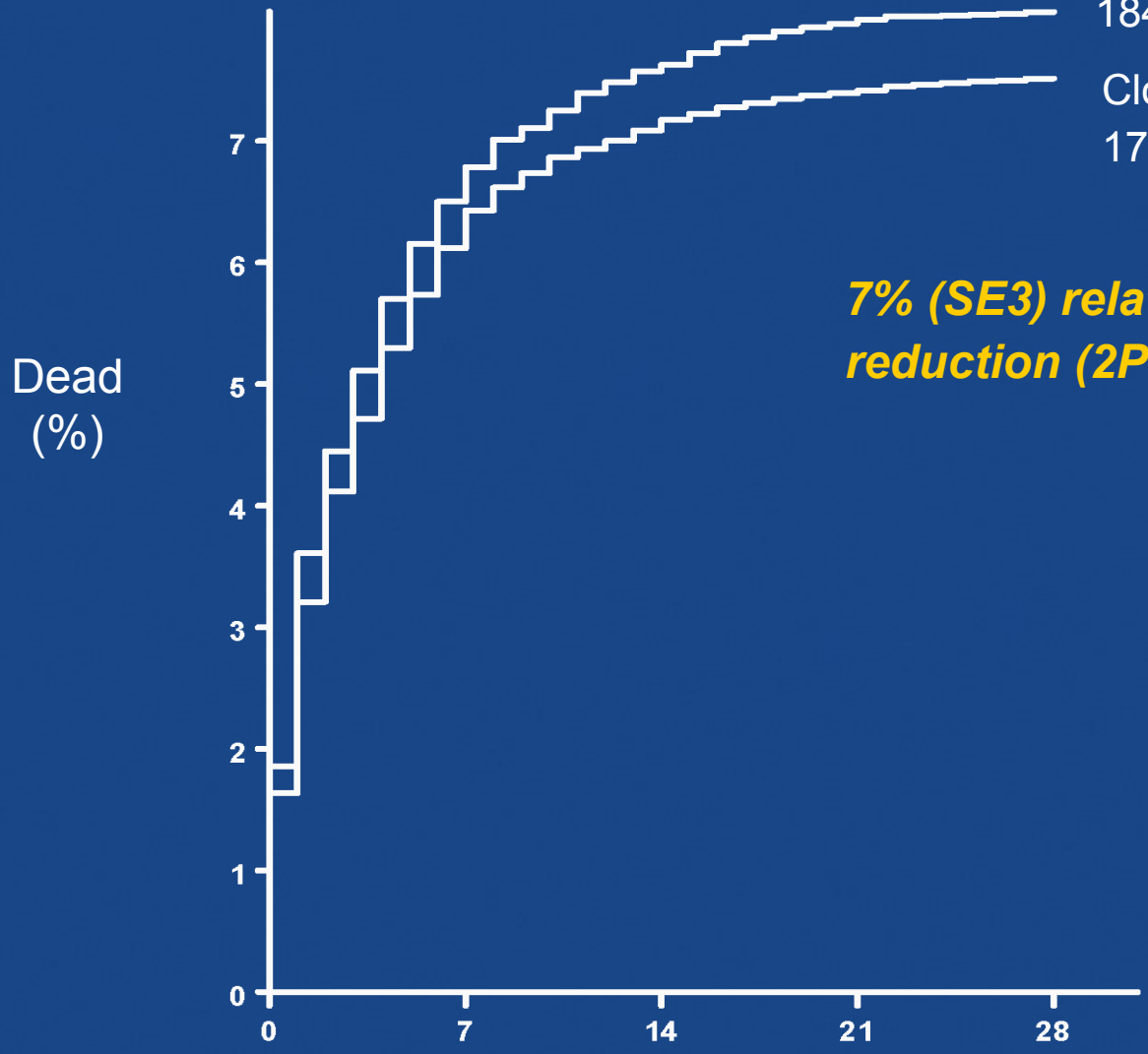
CCS-2 Collaborative Group. J Cardiovasc Risk 2000; 7: 435 .1–.441

COMMIT: Effect of CLOPIDOGREL on Death in hospital

Placebo + ASA:
1846 deaths (8.1%)

Clopidogrel +ASA:
1728 deaths (7.5%)

7% (SE3) relative risk reduction (2P=0.03)



commit CCS-2

COMMIT: Major bleed in hospital

Type	Clopidogrel (n=22,891)	Placebo (n=22,958)
Cerebral		
Fatal	39	40
Non-fatal	16	15
Non-cerebral		
Fatal	36	37
Non-fatal	46	36
Any major bleed	134 *(0.58%)*	124 *(0.54%)*

Thienopyridines

Clopidogrel 75 mg per day orally should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or .do not receive reperfusion therapy

Treatment with clopidogrel should continue .for at least 14 days

What is the optimal drug combination to support thrombolysis?

- **Enoxaparin for 8d is better than 2d of UFH**
  - **If coronary angiography is planned within 3-24 h post lysis, probably no advantage for enoxaparin**
- **Fondaprinux better than placebo but not proved more effective or safer than UFH.**
- **Fondaparinux vs. Enoxaparin - ?**
- **Clopidogrel reduces mortality**

What is the optimal drug combination to support thrombolysis?

- **The safety of clopidogrel + fondaprinux post lysis is uncertain (rare early use of clopidogrel in OASIS 6). Clopidogrel + enoxaparin probably reasonable (30% in CLARITY)**
- **Clopidogrel + enoxaparin is probably the best evidence-based combination when early PCI is not routinely performed.**

Pre hospital lysis

- **Meta analysis of large trials suggests 15-20% reduction in mortality with pre – hospital (vs. hospital based) lysis**
- **Benefit is maximized during first 2 hours (44% reduction).**
- **FFT estimate: benefit declines by 1.6 deaths prevented for 1000 patients treated, for every hour of delay.**

CAPTIM: comparison of angioplasty and prehospital thrombolysis in AMI

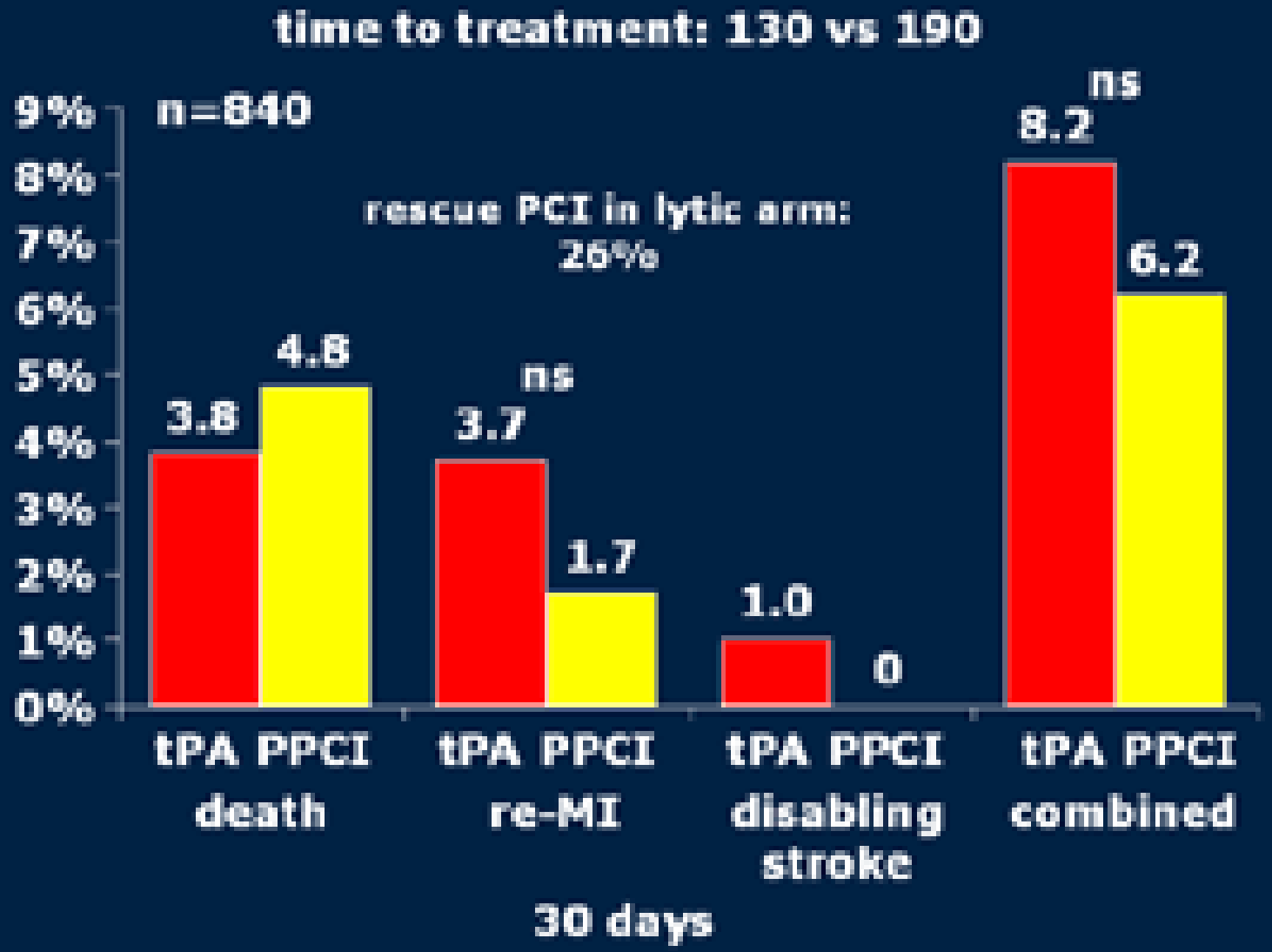
1200 ST elevation AMI patients

randomized, multicentered trial

composite endpoint: all-cause mortality, non-fatal recurrent MI, and non-fatal disabling stroke

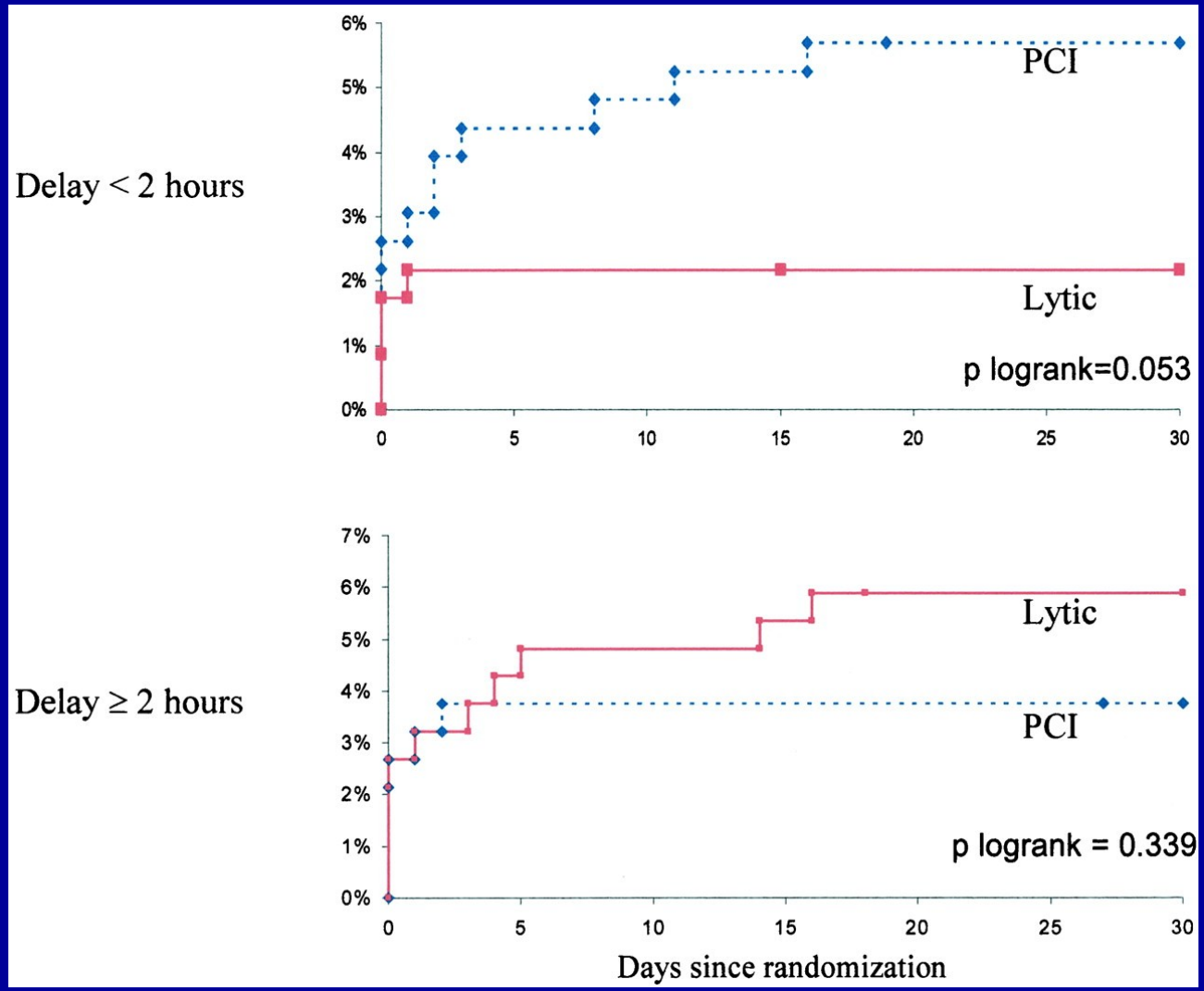
Bonnefoy E, et al. *Lancet* 2002;360(9336):825-9

CAPTIM primary endpoint



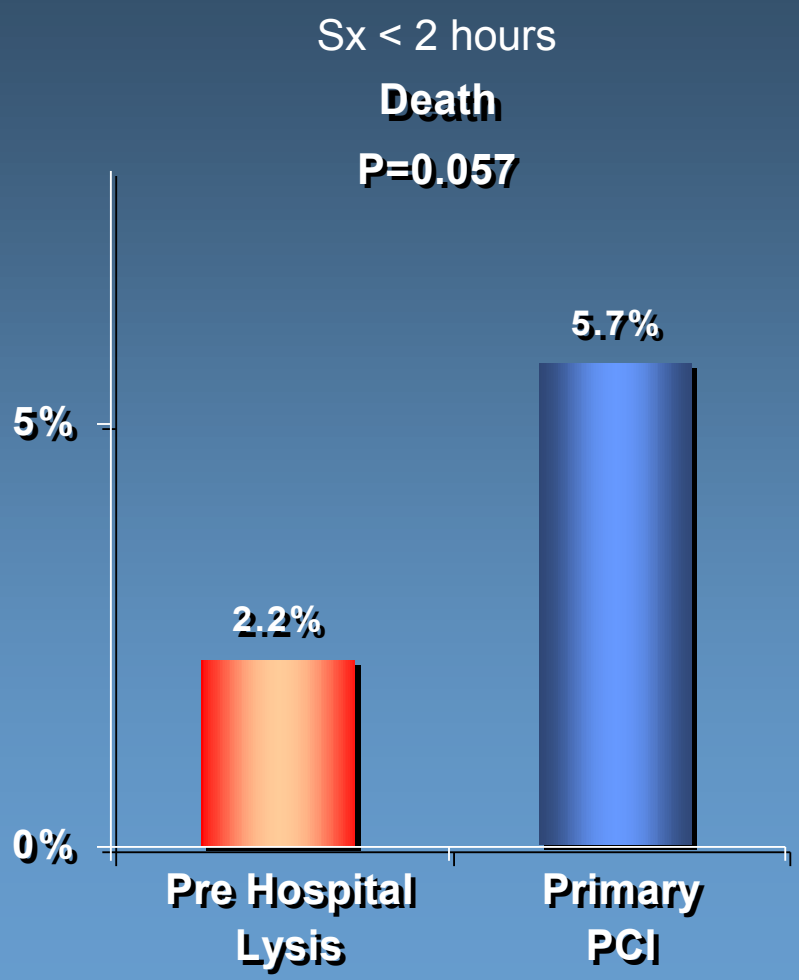
Bonnefoy E, et al. *Lancet* 2002;360(9336):825-9

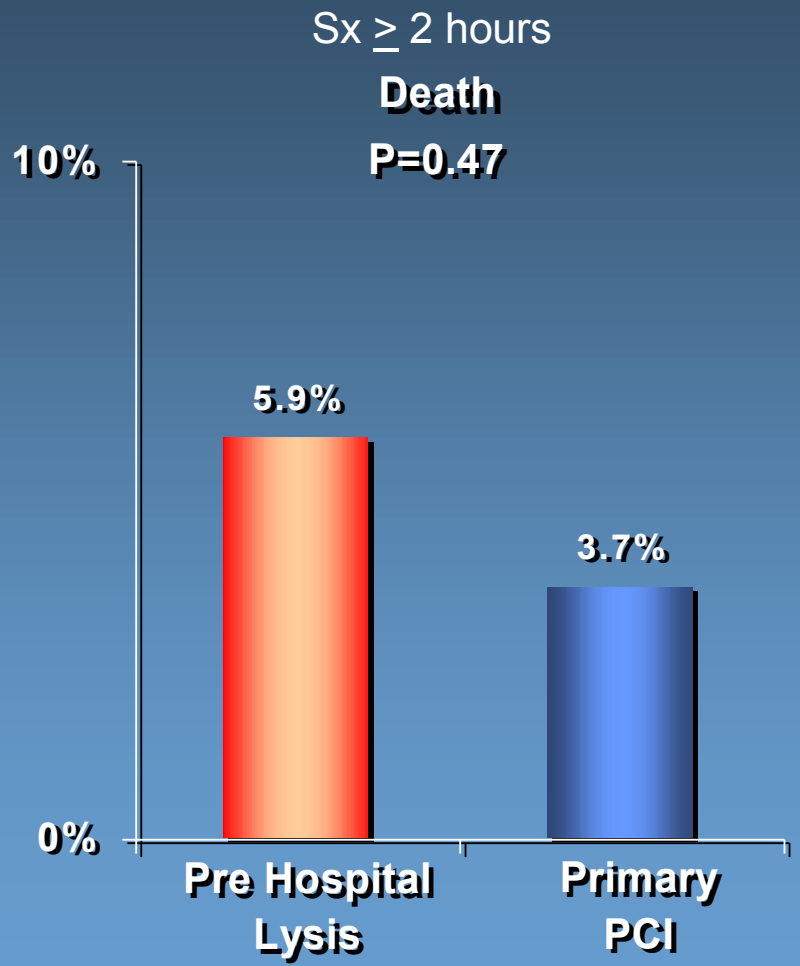
CAPTIM: TIME TO TREATMENT AND MORTALITY



Steg, P. G. et al. Circulation 2003;108:2851-2856

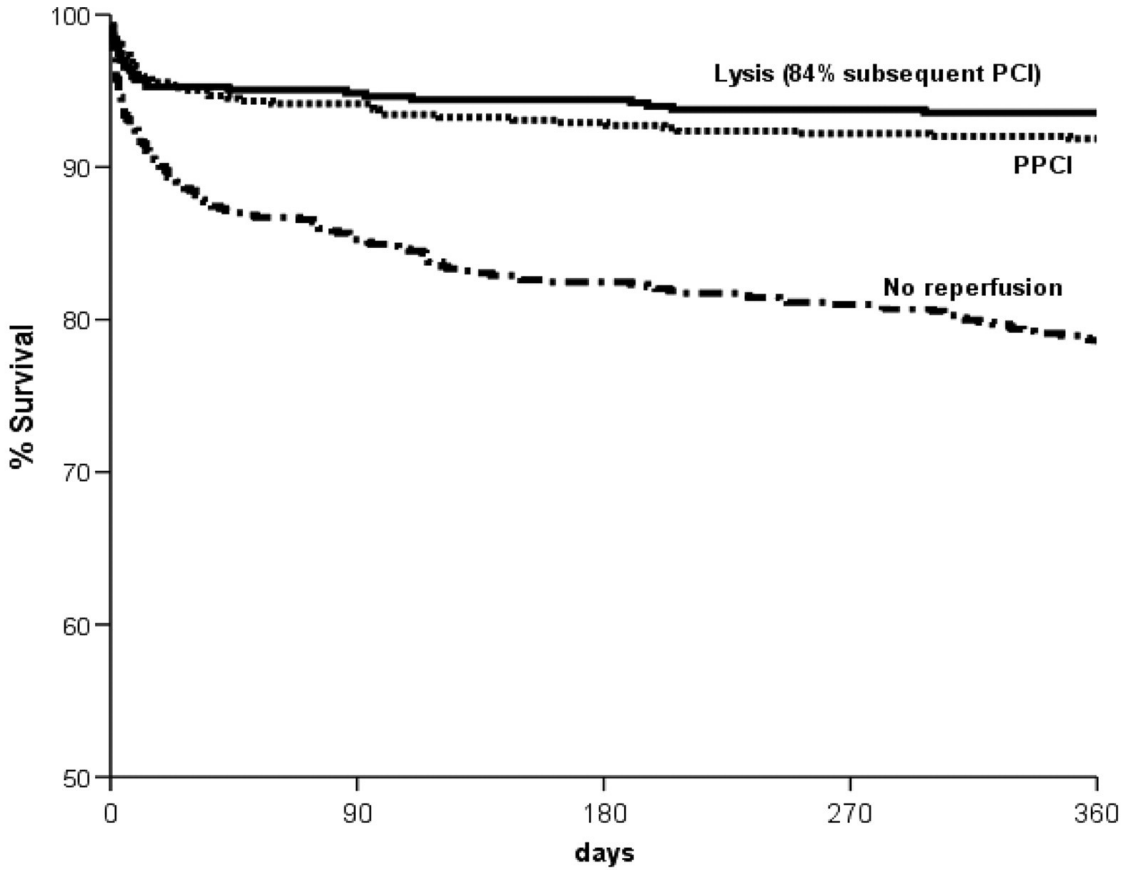
CAPTIM 1 Year Results





GW Symposium, AHA 2002

Lysis: 2/3 pre hospital, 70% treated <3h



# at risk				
No reperfusion	581	562	552	534
Thrombolysis	440	437	434	433
PPCI	529	522	518	512

Long-term Outcome of Primary Percutaneous Coronary Intervention vs Prehospital and In-Hospital Thrombolysis for Patients With ST-Elevation Myocardial Infarction

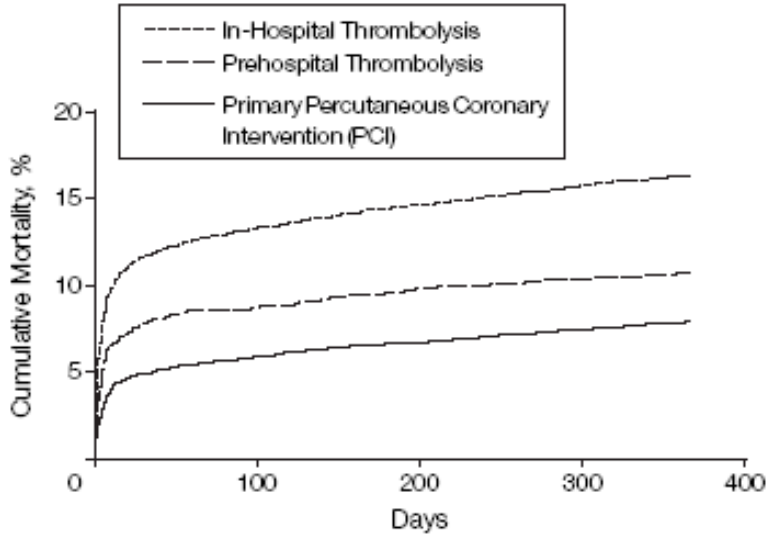
JAMA. 2006;296:1749-1756

Ulf Stenestrand, MD, PhD
Johan Lindbäck, MSc
Lars Wallentin, MD, PhD
for the RIKS-HIA Registry

Context Whether the superior results of percutaneous coronary intervention (PCI) reported in clinical trials in which patients with ST-segment elevation myocardial infarction (STEMI) received reperfusion treatment can be replicated in daily practice has been questioned, especially whether it is superior to prehospital thrombolysis (PHT).

Objective To evaluate the outcome of different reperfusion strategies in consecu-

Figure 2. Unadjusted Cumulative Mortality During the First Year After the Index Event Admission



N=26,205

PCI>pre hospital lysis>hospital lysis @ 30d, 1 year $p<0.05$

Prehospital Issues

- Prehospital 12-lead ECG by ACLS
- Prehospital fibrinolysis

Reperfusion "checklist" by ACLS providers that is relayed with the ECG to a predetermined medical control facility and/or receiving hospital

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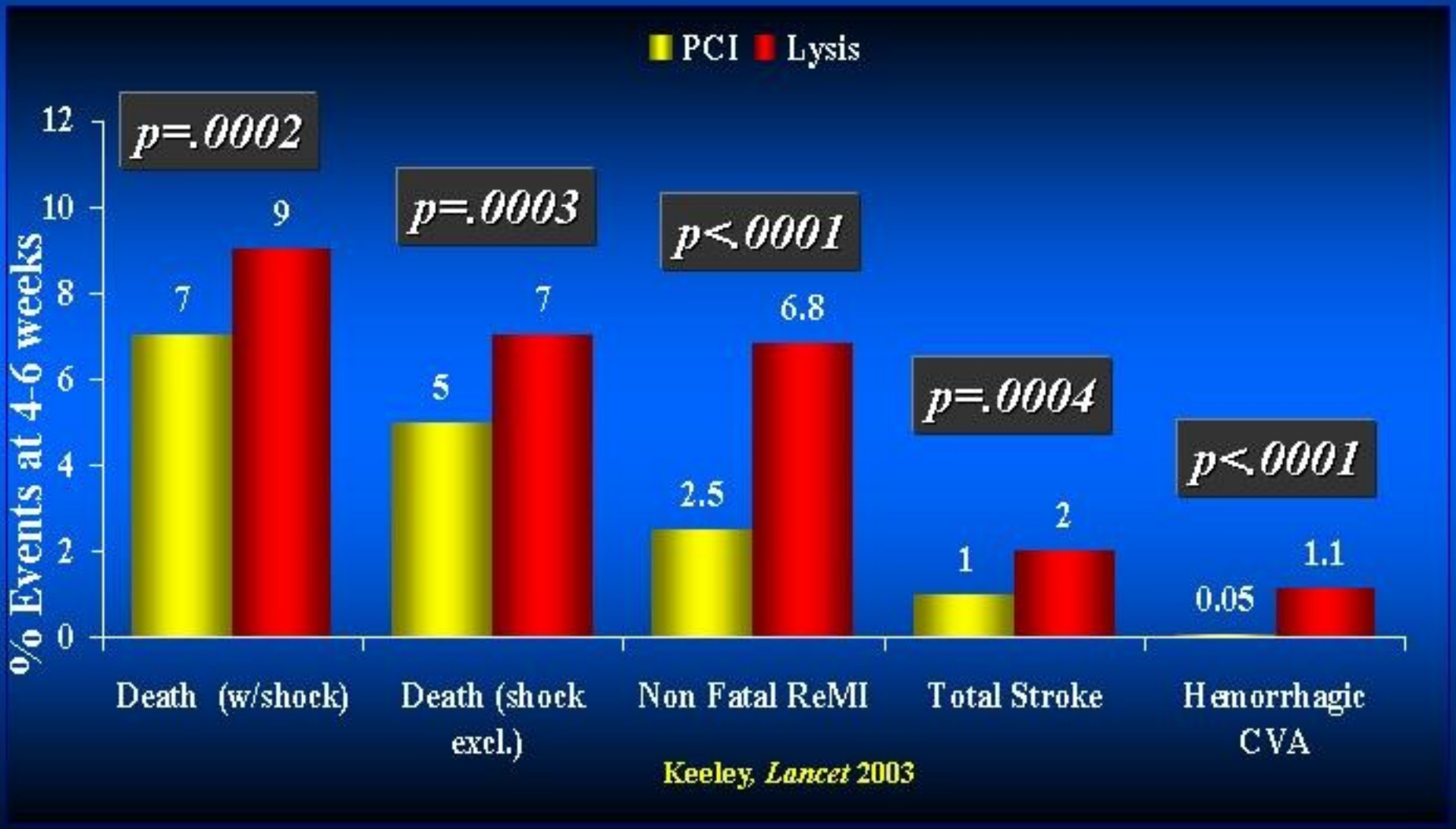
PCI FOR STEMI

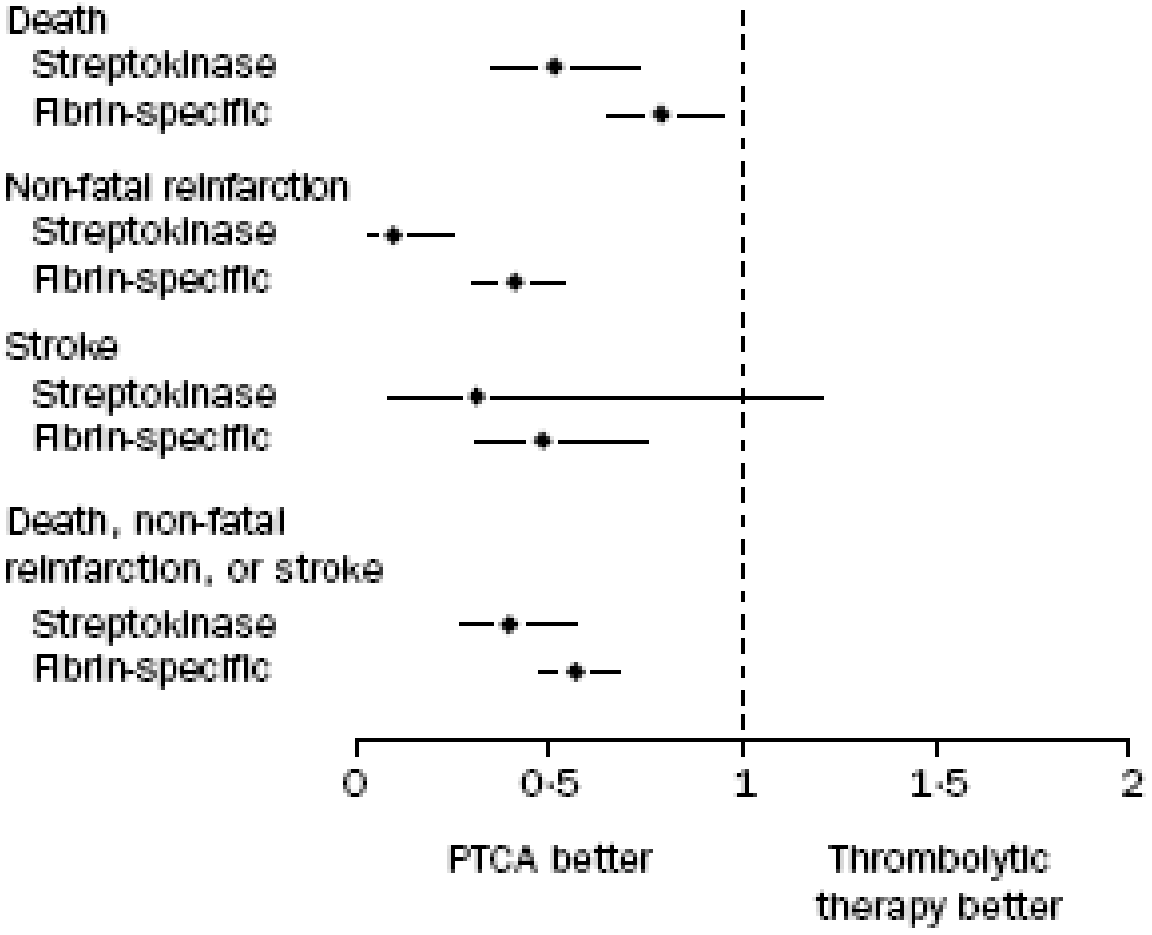
- **Primary PCI Vs. thrombolysis**
- **Transfer to primary PCI**
- **Facilitated primary PCI**
- **Rescue PCI for failed lysis**
- **Routine post lysis PCI**
- **Routine delayed PCI post non reperfused**

Meta-Analysis of 23 Randomized Trials of PCI vs Lysis (n=7739)

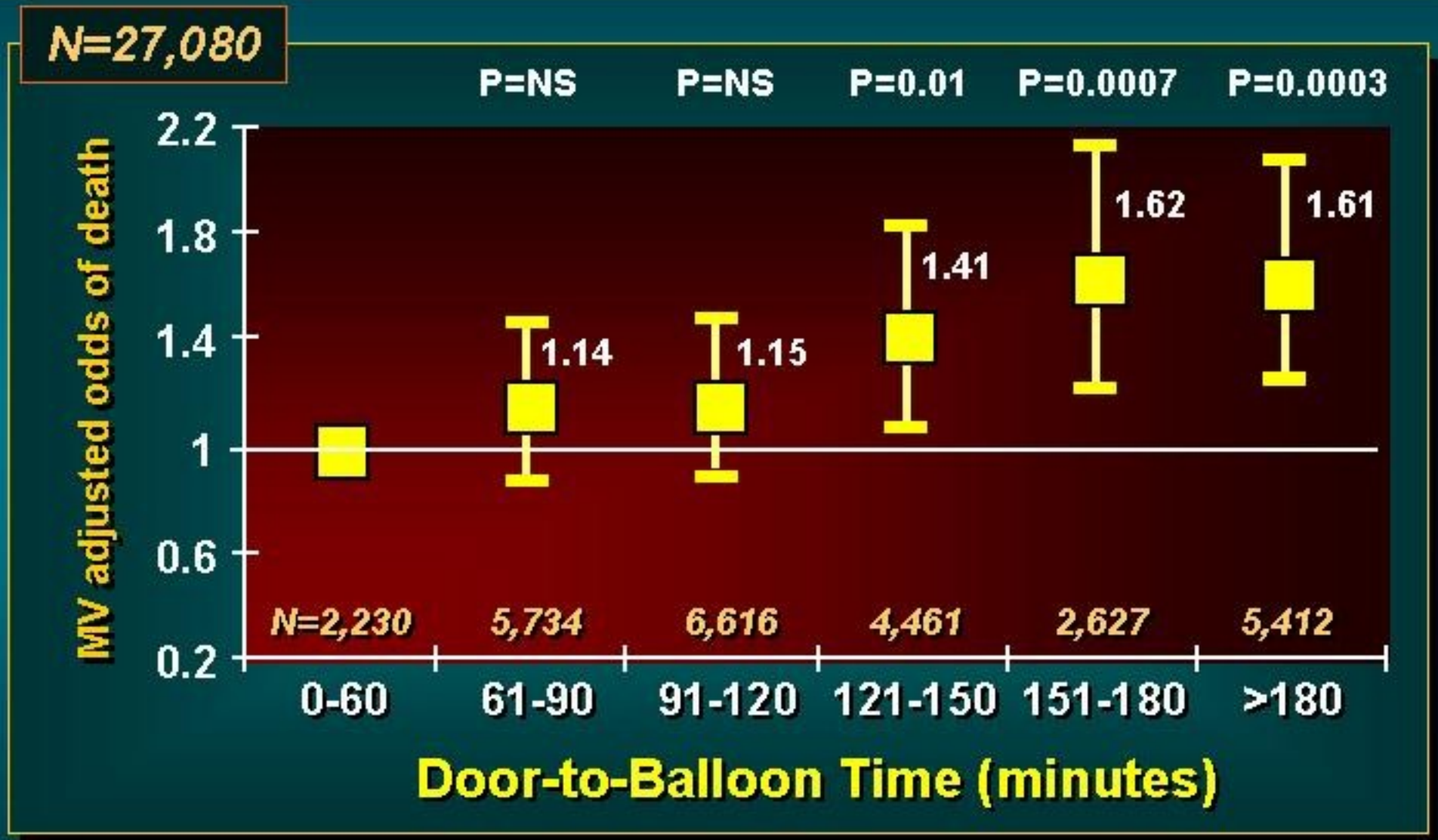


Keeley, *Lancet* 2003

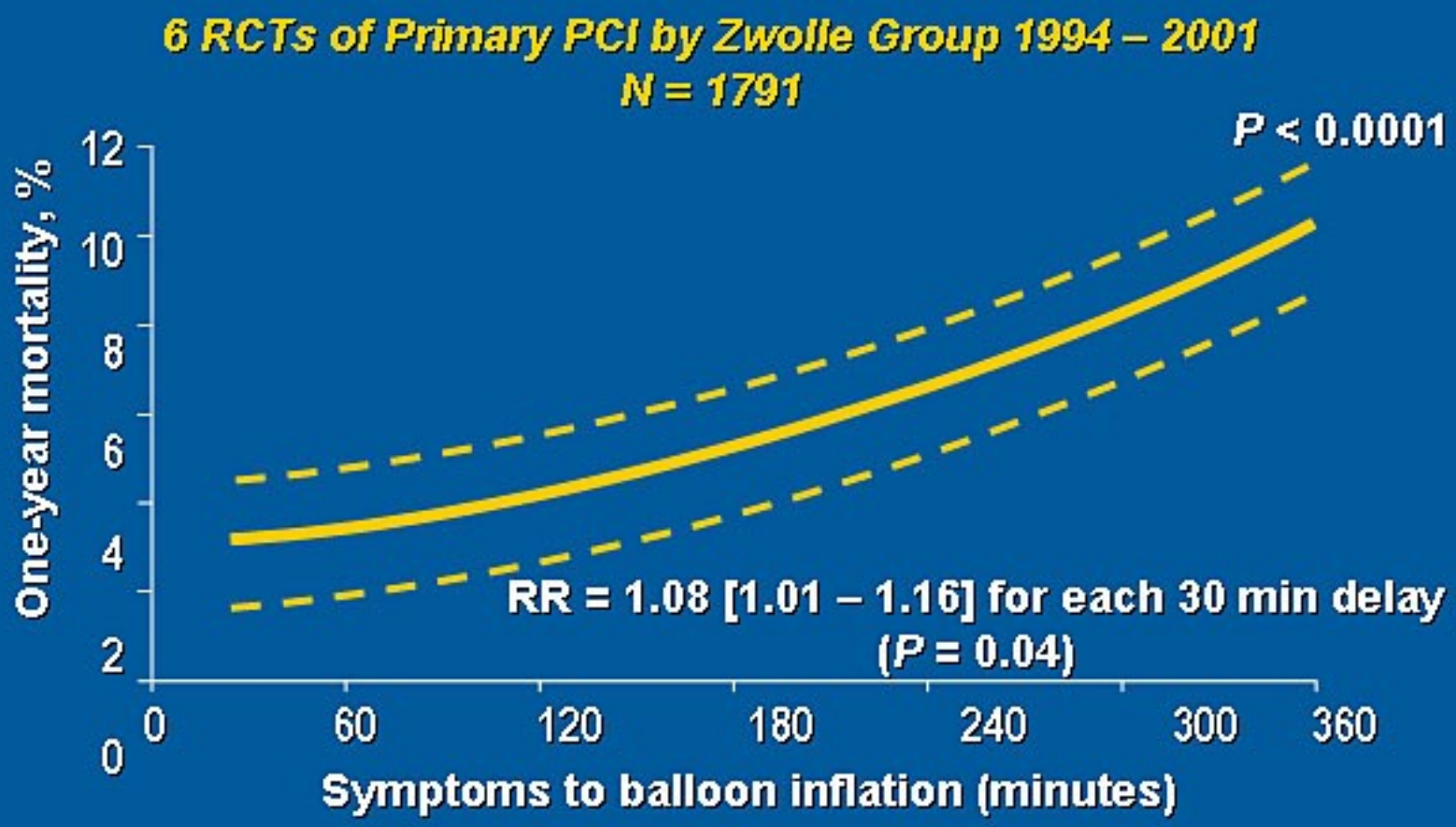
PCI VS. LYSIS: META – ANALYSIS OF 23 TRIALS



NRMI-2 Primary PCI



Symptom Onset to Balloon Time and Mortality in Primary PCI for STEMI



DeLuca et al. Circulation 2004;109:1223.

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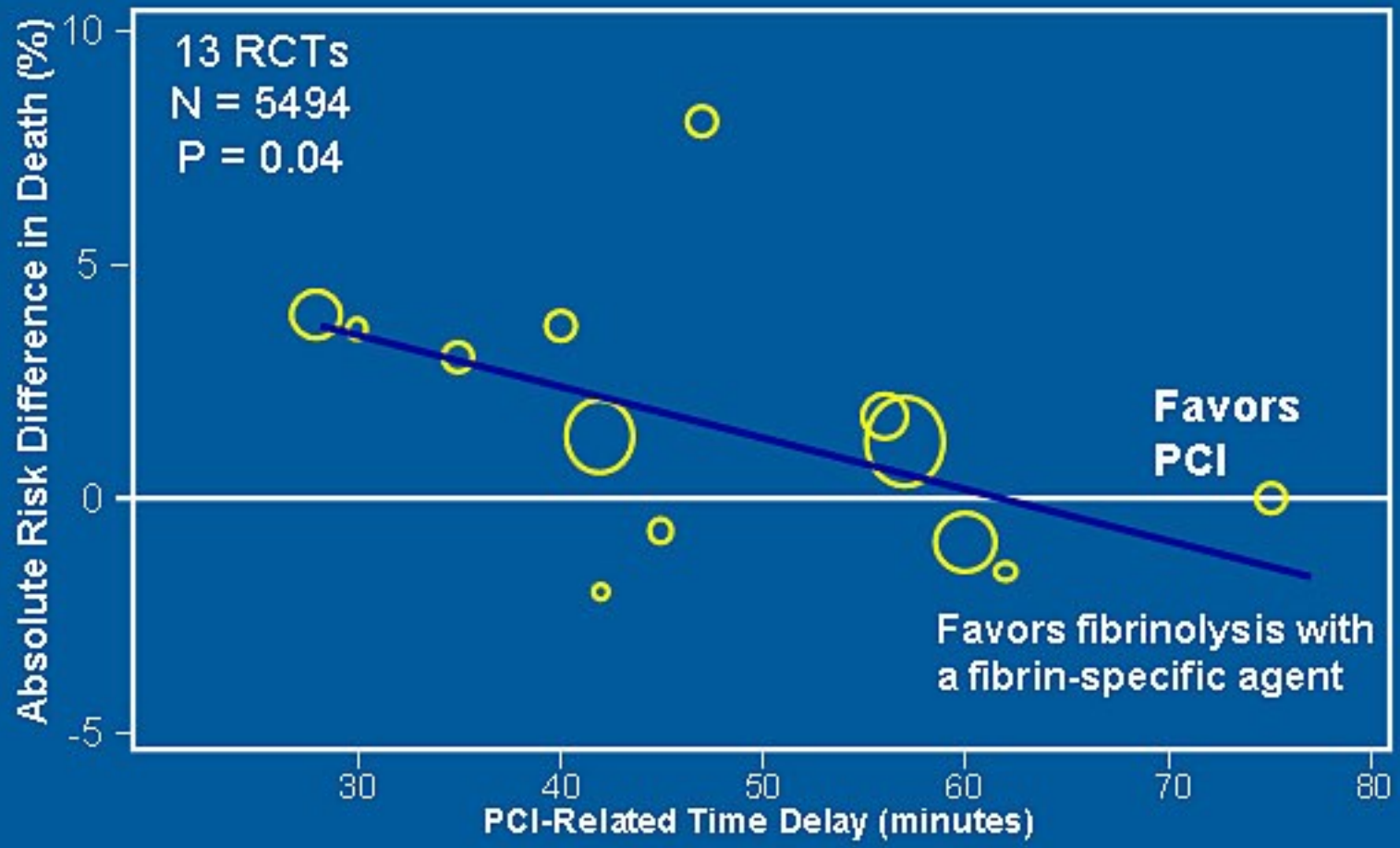
PCI versus Fibrinolysis with Fibrin-Specific Agents: Is Timing (Almost) Everything?



Nallamothu and Bates. Am J Cardiol 2003;92:824.

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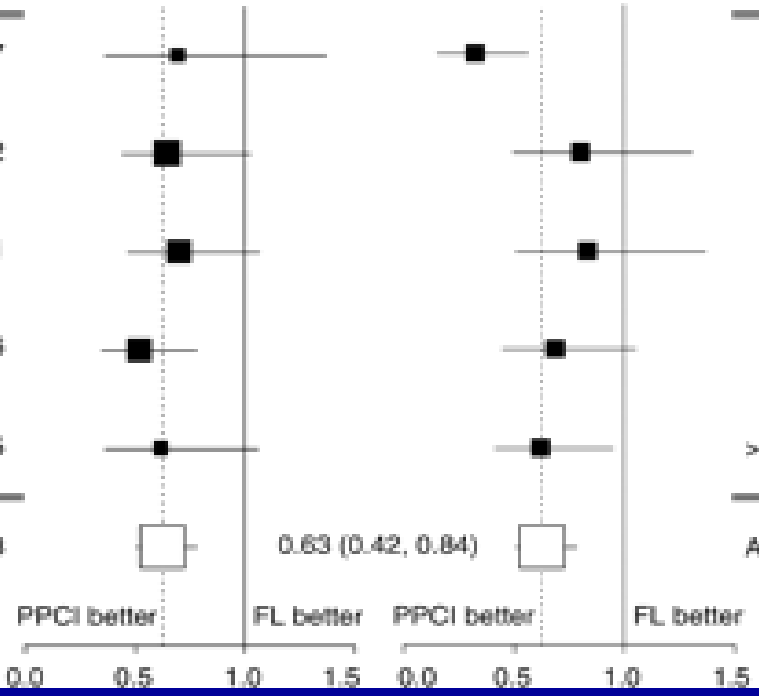
European Heart Journal (2006) 27, 779–788
doi:10.1093/eurheartj/ehl010

Clinical research
Interventional cardiology

Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients

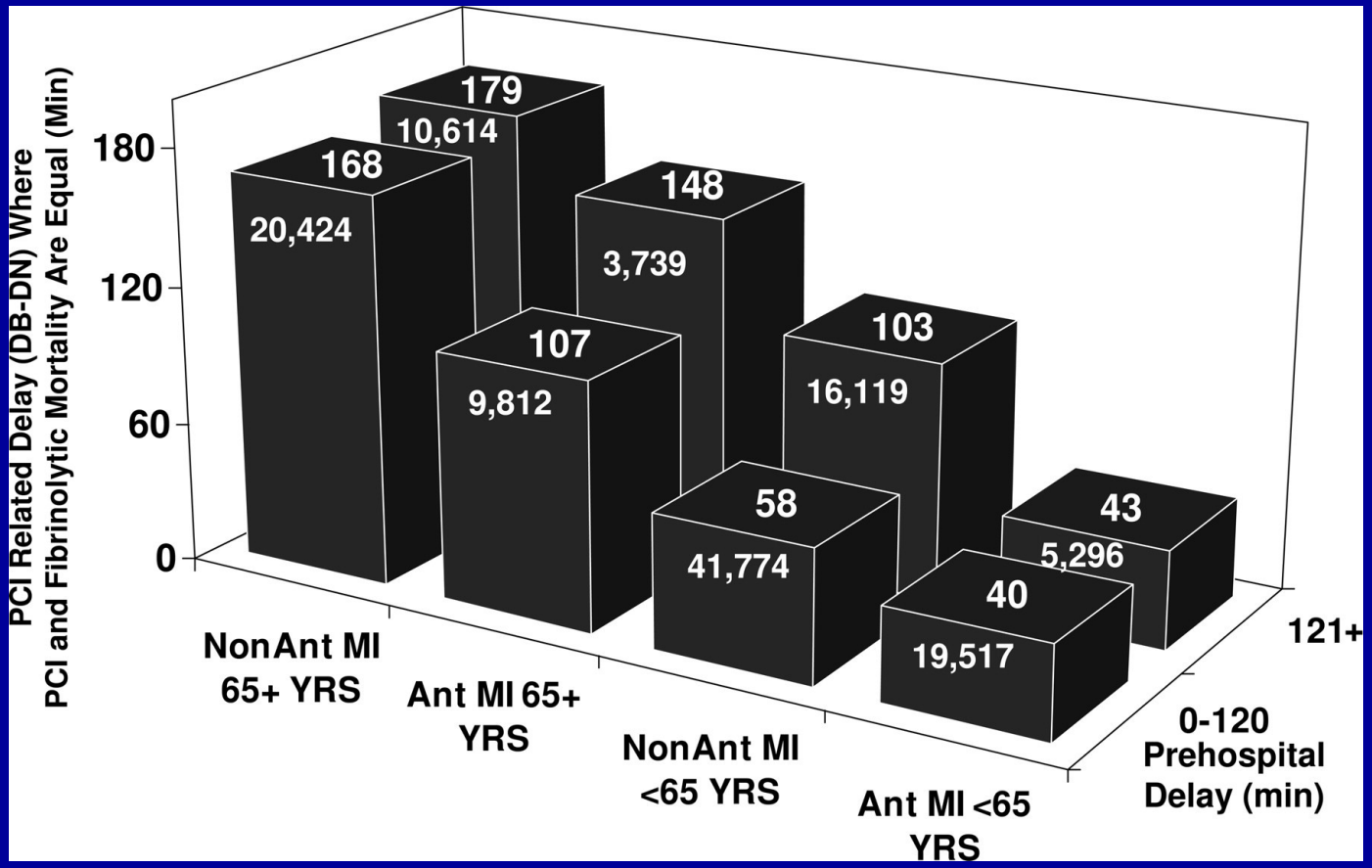
Eric Boersma* and The Primary Coronary Angioplasty vs. Thrombolysis (PCAT)-2 Trialists' Collaborative Group

Presentation delay (h)	Number of patients	30-day death (%) FL	30-day death (%) PPCI
0–1	747	6.0	4.7
>1–2	2000	6.2	4.2
>2–3	1712	7.3	5.1
>3–6	1640	9.5	5.6
>6–12	664	12.7	8.5
All patients	6763	7.9	5.3



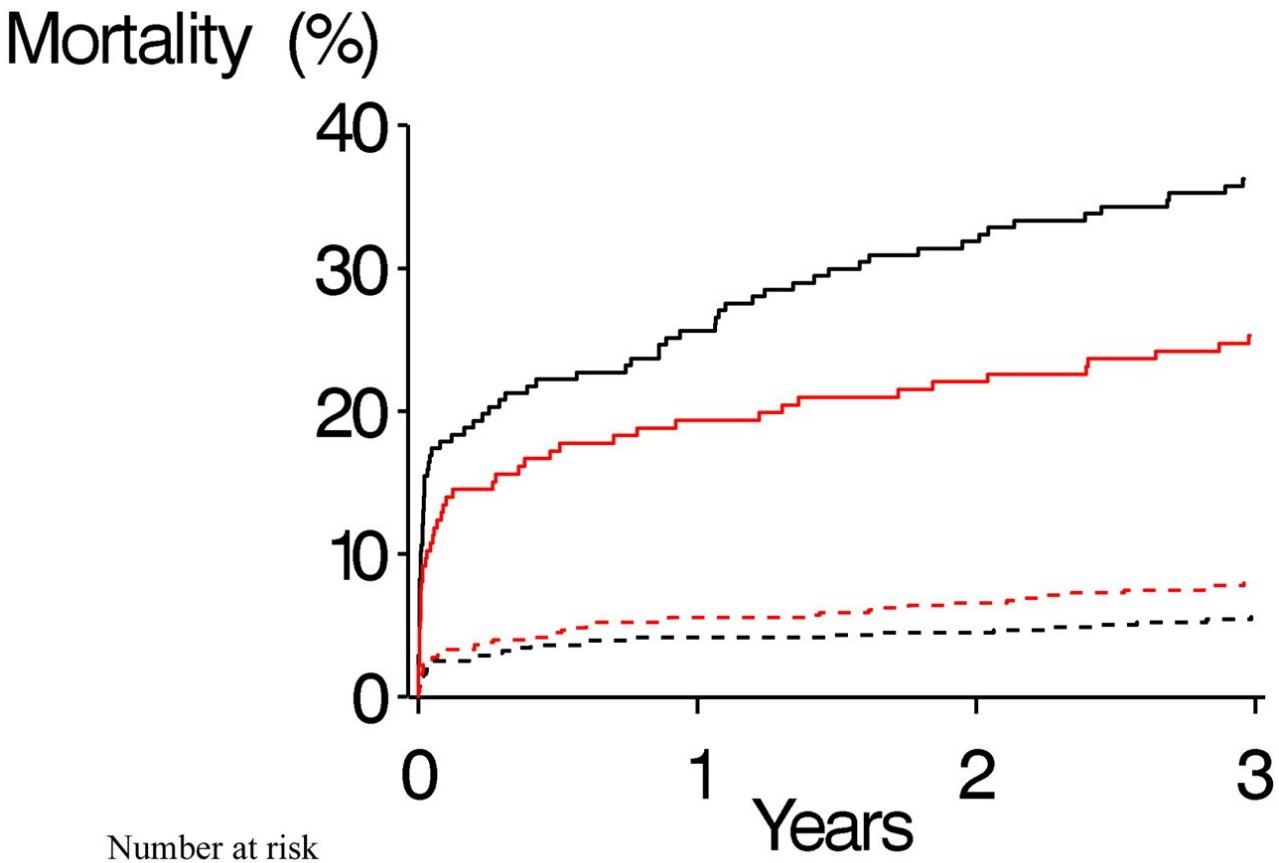
PCI-related delay (min)	Number of patients	30-day death (%) FL	30-day death (%) PPCI
0–35	1417	8.2	2.8
>35–50	1292	6.8	5.4
>50–62	1425	5.4	4.8
>62–79	1280	9.5	6.9
>79–120	1349	9.6	6.6
All patients	6763	7.9	5.3

Adjusted analysis illustrating significant heterogeneity in the PCI-related delay (DB-DN time) for which the mortality rates with primary PCI and fibrinolysis were comparable after the study population was stratified by prehospital delay, location of infarct, and age



Pinto, D. S. et al. Circulation 2006;114:2019-2025

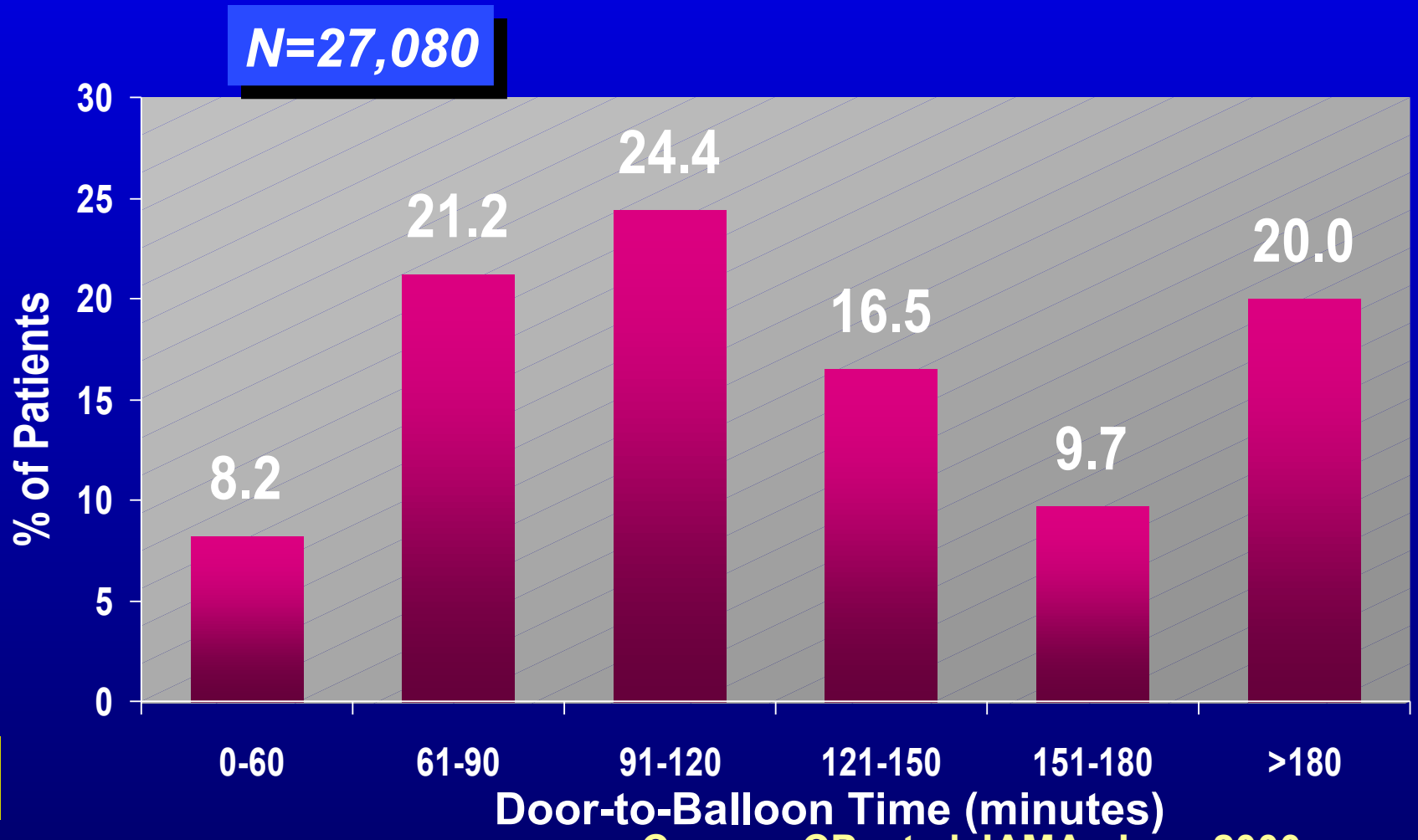
Circulation



Number at risk

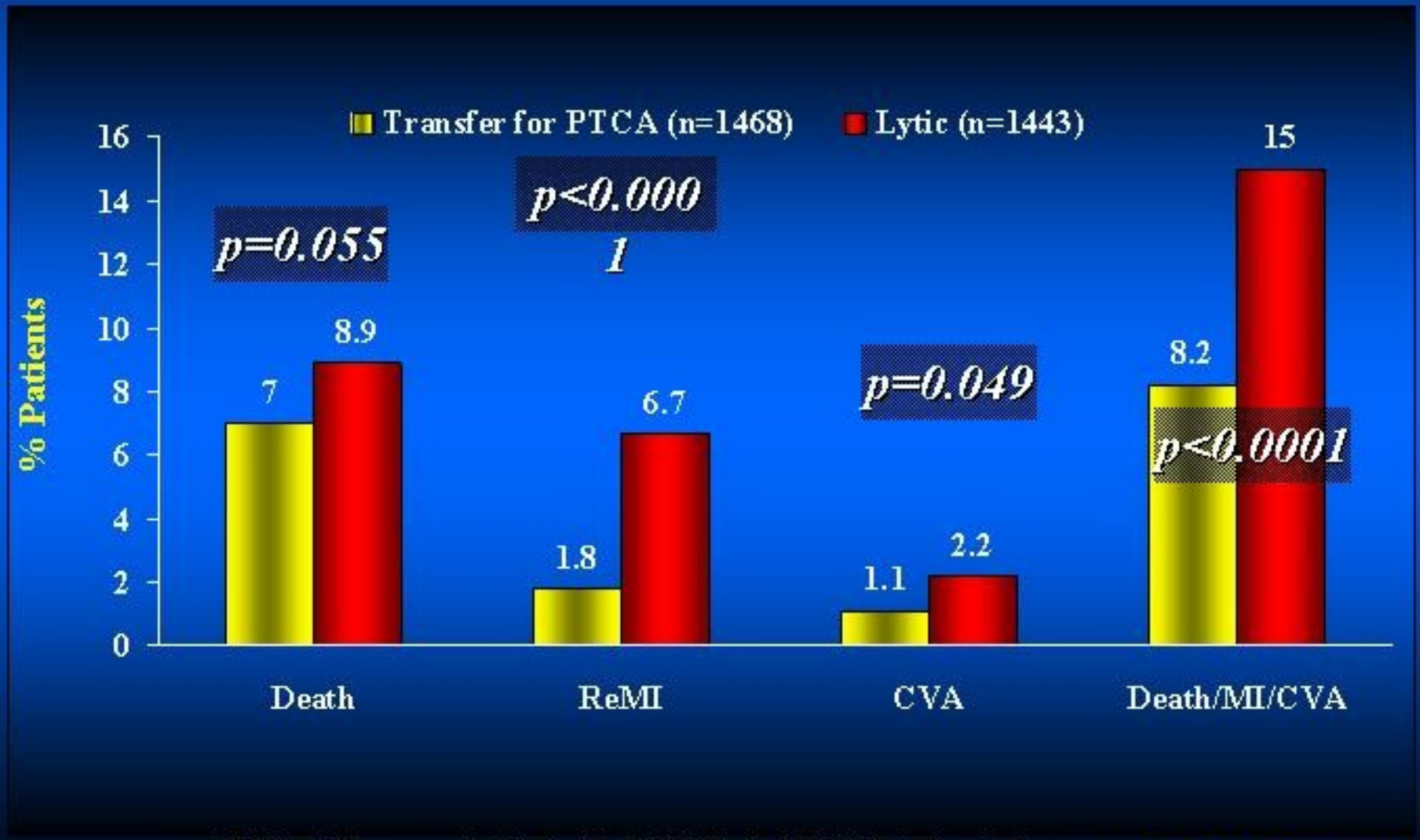
TIMI 0-4	Fx	556	533	531
	PA	578	546	540
TIMI ≥ 5	Fx	207	154	141
	PA	186	150	145

NRMI-2: Primary PCI
Distribution of Door-to-Balloon times



Cannon CP, et al JAMA: June 2000 .

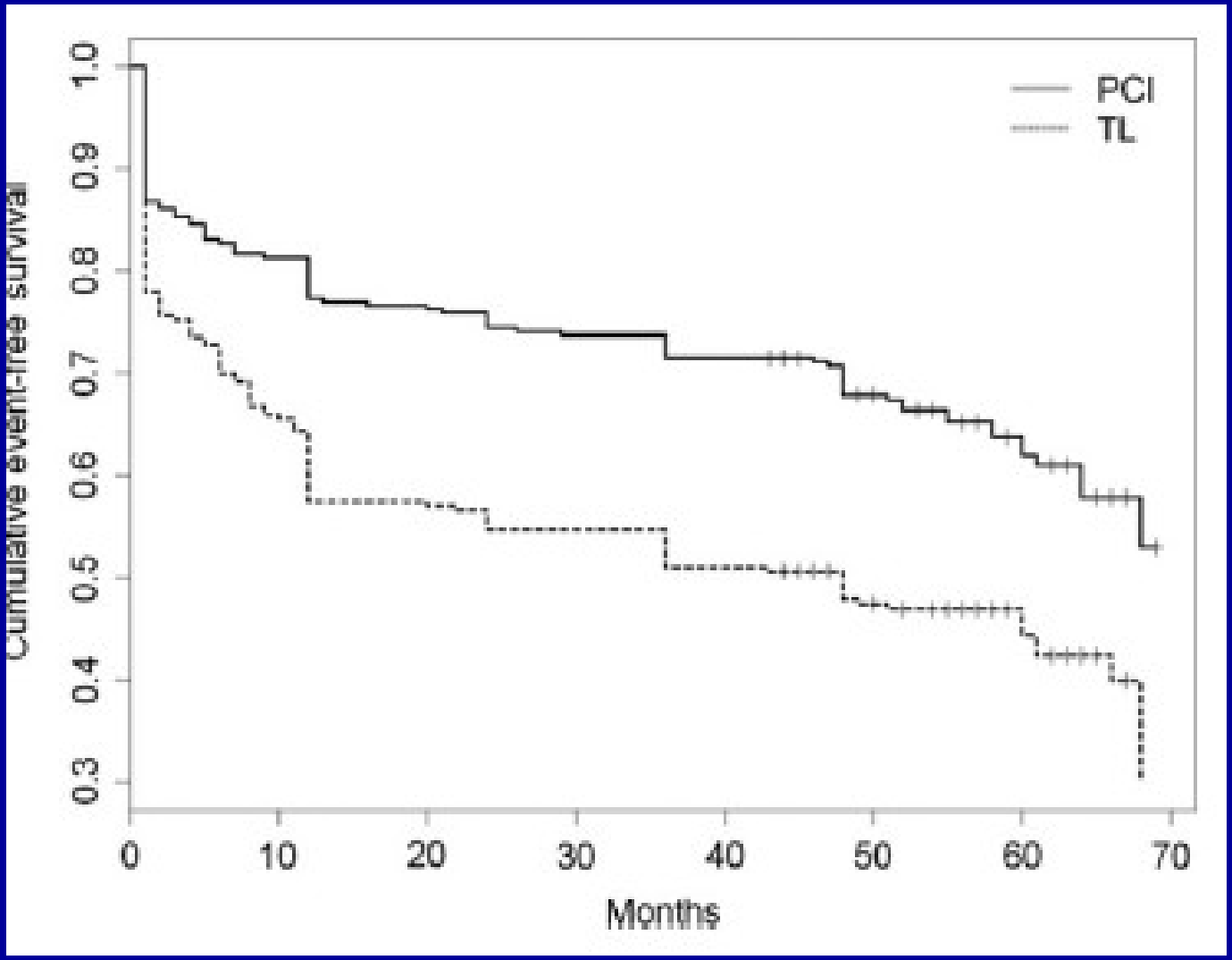
Transfer for Primary PTCA vs On-Site Lytics (Pooled Data from 5 Randomized Trials*)



LIMI, Prague I & II, Air PAMI, DANAMI-II trials

Keeley & Grines, in press

PRAGUE 2 – 5 YEAR FOLLOW UP



Eur Heart J 2007;28:679

Relationship between delay in transferring patients for primary PCI and one-year mortality

Interhospital delay (mins)	<30 (n=94)	30-59 (n=188)	60-89 (n=194)	>90 (n=140)	p
1-y mortality (%)	3.2	6.4	6.2	12.1	0.01

De Luca G et al. *Am J Cardiol* 2005; 95: 1361-1363.

Times to Treatment in Transfer Patients Undergoing Primary Percutaneous Coronary Intervention in the United States

National Registry of Myocardial Infarction (NRMI)-3/4 Analysis

Brahmajee K. Nallamothu, MD, MPH; Eric R. Bates, MD; Jeph Herrin, PhD; Yongfei Wang, MS; Elizabeth H. Bradley, PhD; Harlan M. Krumholz, MD, SM; for the NRMI Investigators

Background—Treatment delays in patients with ST-segment–elevation myocardial infarction (STEMI) transferred for primary percutaneous coronary intervention (PCI) may decrease the advantage of this strategy over on-site fibrinolytic therapy that has been demonstrated in recent clinical trials. Accordingly, we sought to describe patterns of times to treatment in patients undergoing interhospital transfer for primary PCI in the United States.

Methods and Results—We analyzed patients with STEMI undergoing interhospital transfer for primary PCI between January 1999 and December 2002 in the National Registry of Myocardial Infarction. The primary outcome was "total" door-to-balloon time measured from time of arrival at the initial hospital to time of balloon inflation at the PCI hospital. Multivariable hierarchical models were used to assess the relationship of total door-to-balloon time with patient and hospital characteristics. Among 4278 patients transferred for primary PCI at 419 hospitals, the median total door-to-balloon time was 180 minutes, with only 4.2% of patients treated within 90 minutes, the benchmark recommended by national quality guidelines. Comorbid conditions, absence of chest pain, delayed presentation after symptom onset, less specific ECG findings, and hospital presentation during off-hours were associated with longer total door-to-balloon times. Patients at teaching hospitals in rural areas also had significantly longer times to treatment.

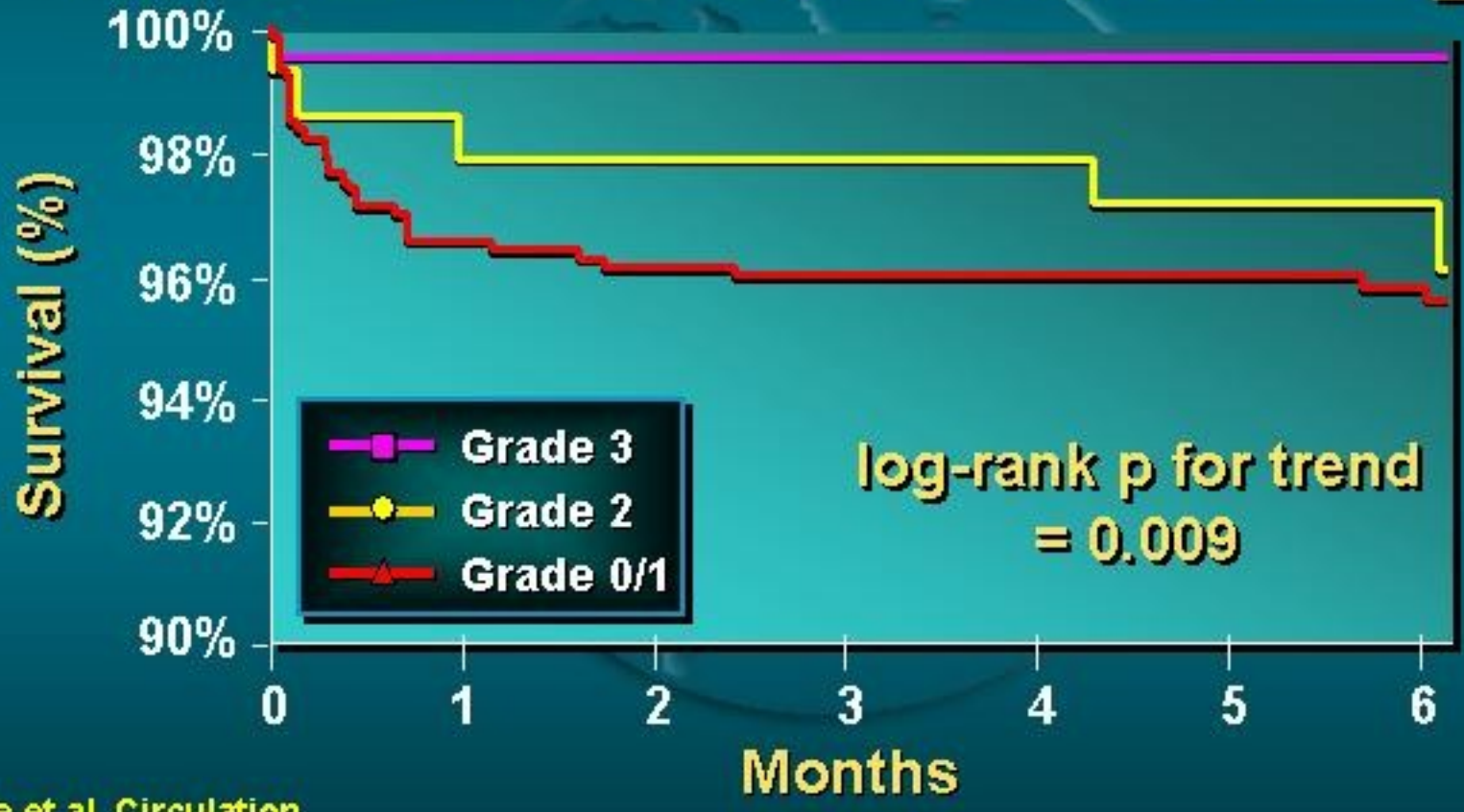
Conclusions—Total door-to-balloon times for transfer patients undergoing primary PCI in the United States rarely achieve guideline-recommended benchmarks, and current decision making should take these times into account. For the full benefits of primary PCI to be realized in transfer patients, improved systems are urgently needed to minimize total door-to-balloon times. (***Circulation***. **2005;111:761-767.**)

Conclusions

- **When transport time does not exceed 60-90 minutes, and a competent team is on standby at the receiving hospital, transfer to PCI is superior to local lysis.**
- **Pre-hospital lysis might be as good as primary PCI, provided "rescue" procedures are available.**

Effect of Pre-Procedural TIMI Flow on Cumulative Late Mortality after Primary PTCA

N = 2,507 pts in PAMI-1, PAMI-2, PAMI Stent Pilot and PAMI Stent Randomized



Stone et al. Circulation

FACILITATION BY THROMBOLYSIS

ASSENT- 4 PCI Trial

1667 patients with STEMI, within 6 hrs; intent to perform primary PCI

Randomized

Mean follow-up: 6 mos (30 days reported to date)

63% of patients received clopidogrel/ticlopidine *during* PCI

Additional UFH was given to 67.4% in the TNK + PCI group and 70.1% in the PCI alone group

Full-dose TNK + Primary PCI

60 IU/kg, maximum 4000 IU

n=829

GP IIb/IIIa inhibitors allowed only for bail out use

Primary PCI

70 IU/kg, no maximum dose

n=838

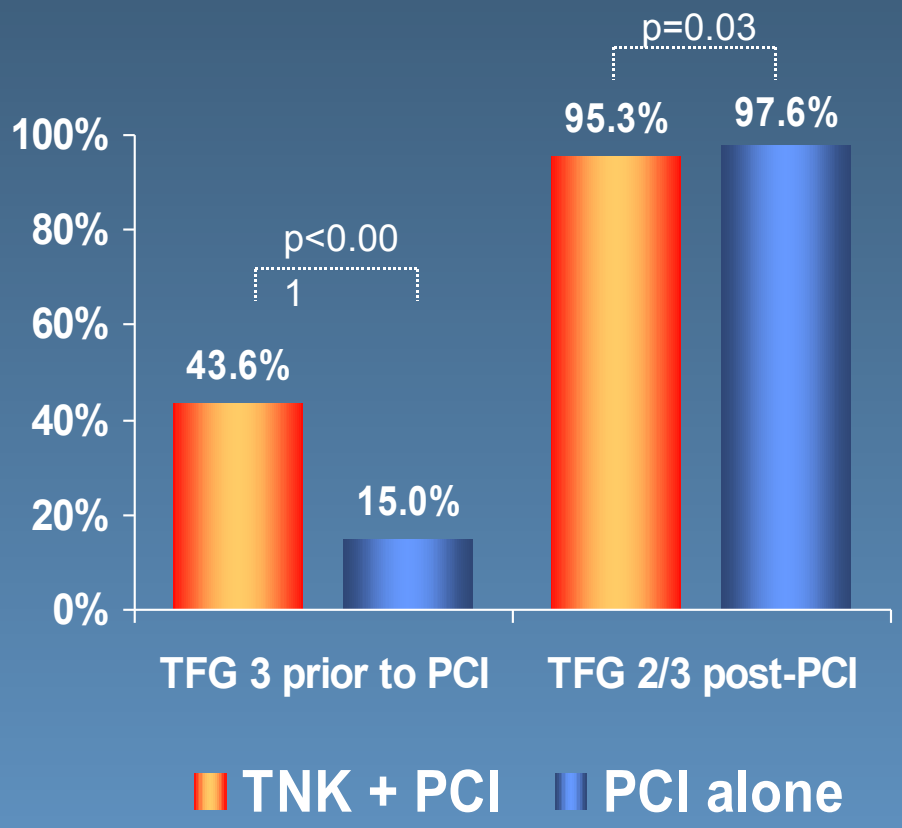
GP IIb/IIIa inhibitors allowed at physician discretion

- Primary Endpoint: Composite of death, shock, or congestive heart failure at 90 days.

Presented at ESC 2005

ASSENT- 4 PCI Trial: TIMI Flow Grade

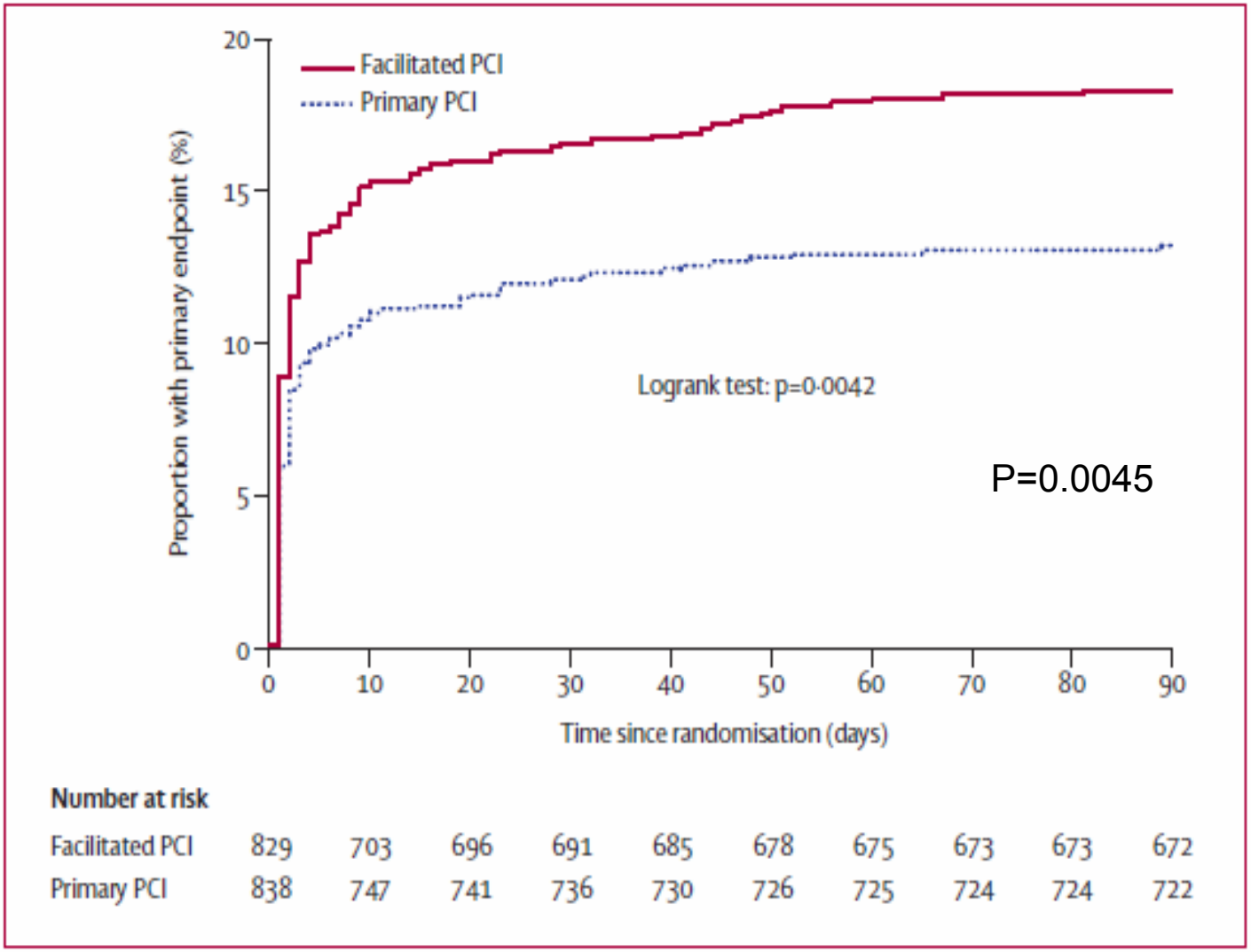
TIMI grade 3 flow prior to PCI and TIMI grade 2/3 flow post-PCI (%)



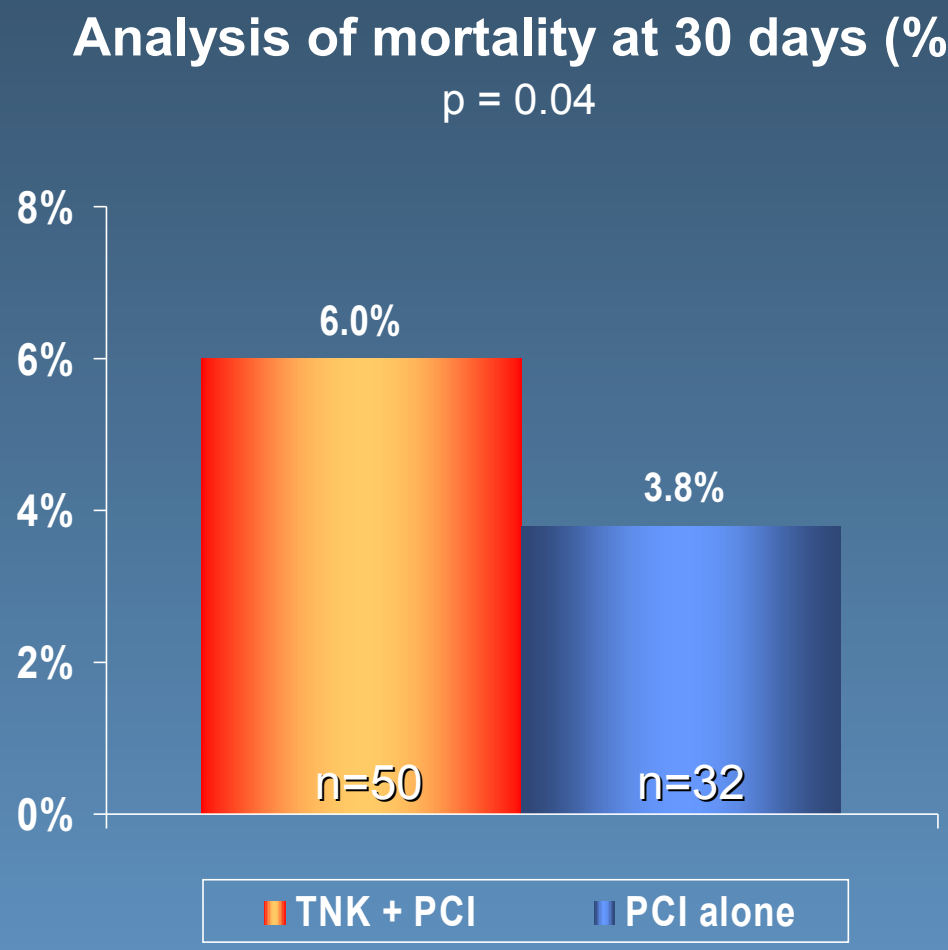
- TIMI grade 3 flow prior to PCI was present more frequently in the TNK + PCI arm (43.6% vs 15.0%)
- TIMI grade 2/3 post-PCI was slightly higher in the PCI alone group (95.3% vs 97.6%)

Presented at ESC 2005

PRIMARY ENDPOINT: DEATH/SHOCK/CHF @ 90 d



ASSENT- 4 PCI Trial: Mortality at 30 days



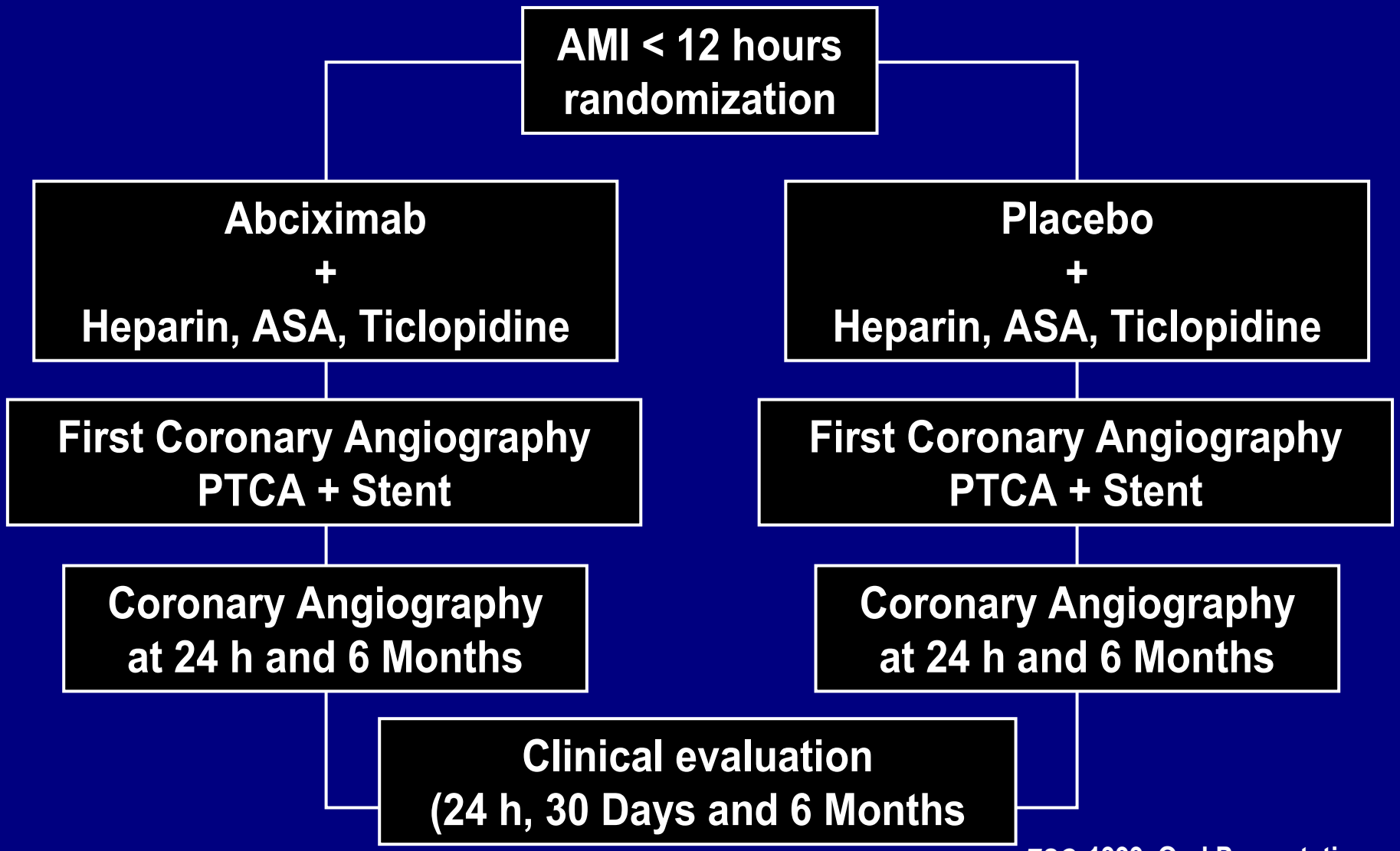
- The primary endpoint of mortality was higher in the TNK + PCI treatment group compared with the PCI alone group (6.0% vs 3.8%, p=0.04) at 30 days

Presented at ESC 2005

FACILITATION BY IIb/IIIa ANTAGONISTS

ADMIRAL

Design

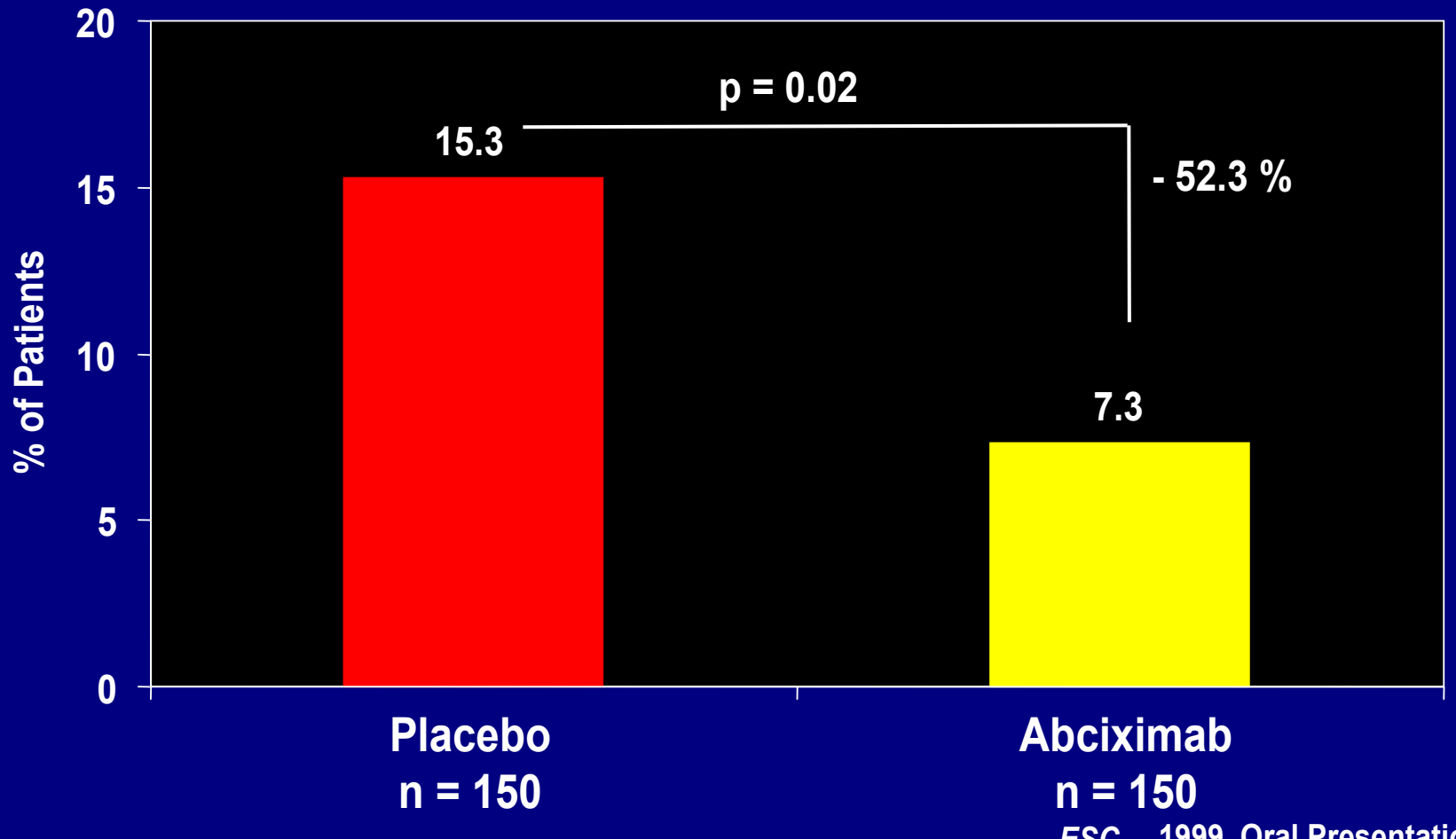


ESC 1999, Oral Presentation

ADMIRAL

Primary Endpoint (30 days)

Death, Recurrent MI, Urgent TVR



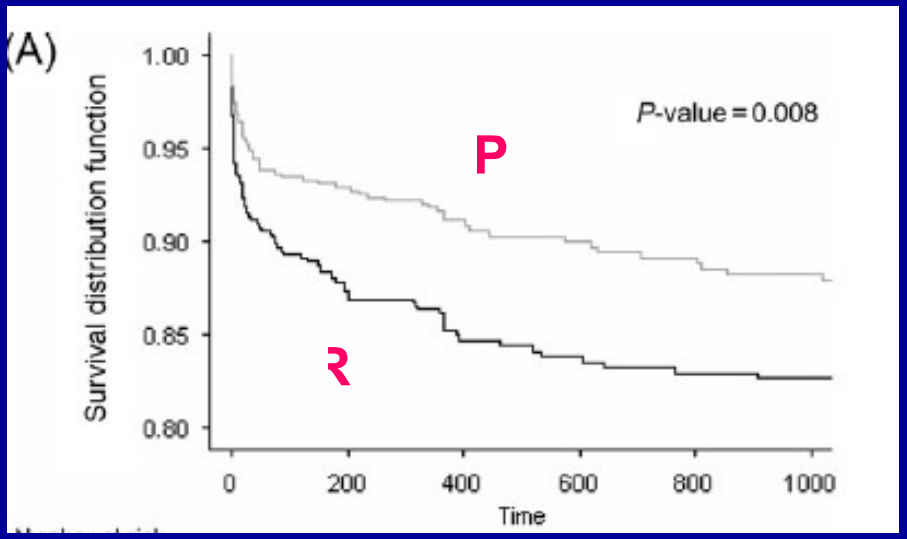
ESC 1999, Oral Presentation

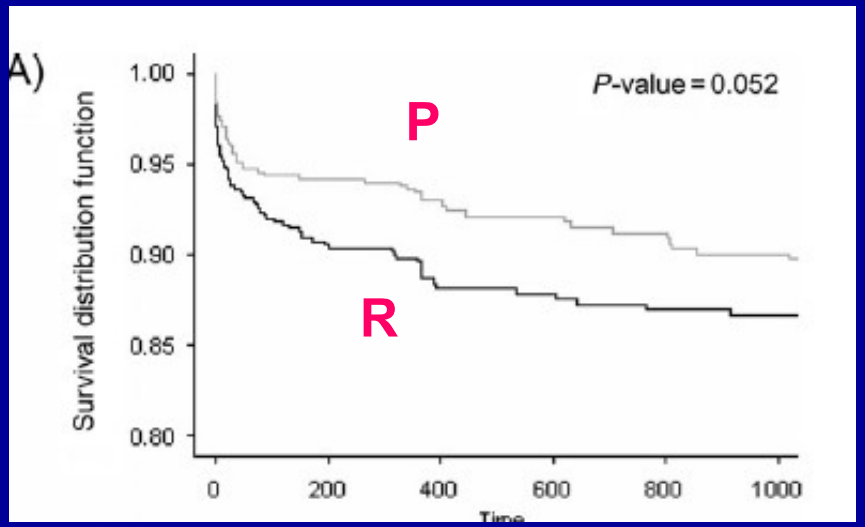
European Heart Journal (2007) 28, 443–449
doi:10.1093/eurheartj/ehl472

Clinical research
Interventional cardiology

Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up

Gilles Montalescot[1]*, David Antoniucci[2], Adnan Kastrati[3], Franz Joseph Neumann[4], Maria Borentain[1], Angela Migliorini[2], Carole Boutron[5], Jean-Philippe Collet[1], and Eric Vicaut[5]





Death/MI

Death

The FINESSE Trial

(Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events)

Final 90 Day Results in Perspective

Stephen Ellis, MD
for the FINESSE Investigators

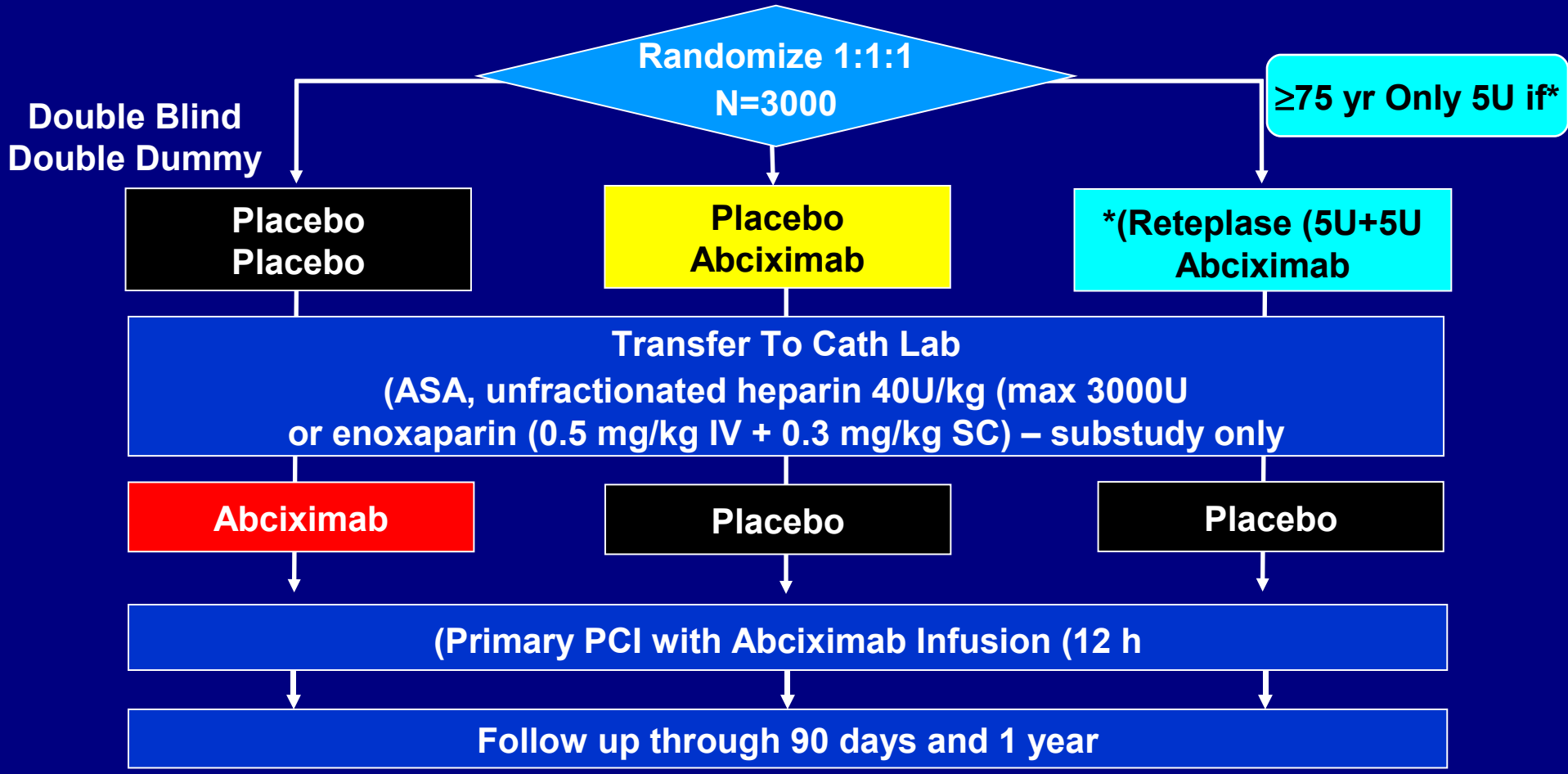
AHA 2007

Conflicts: research grant Centocor/Lilly/Cordis

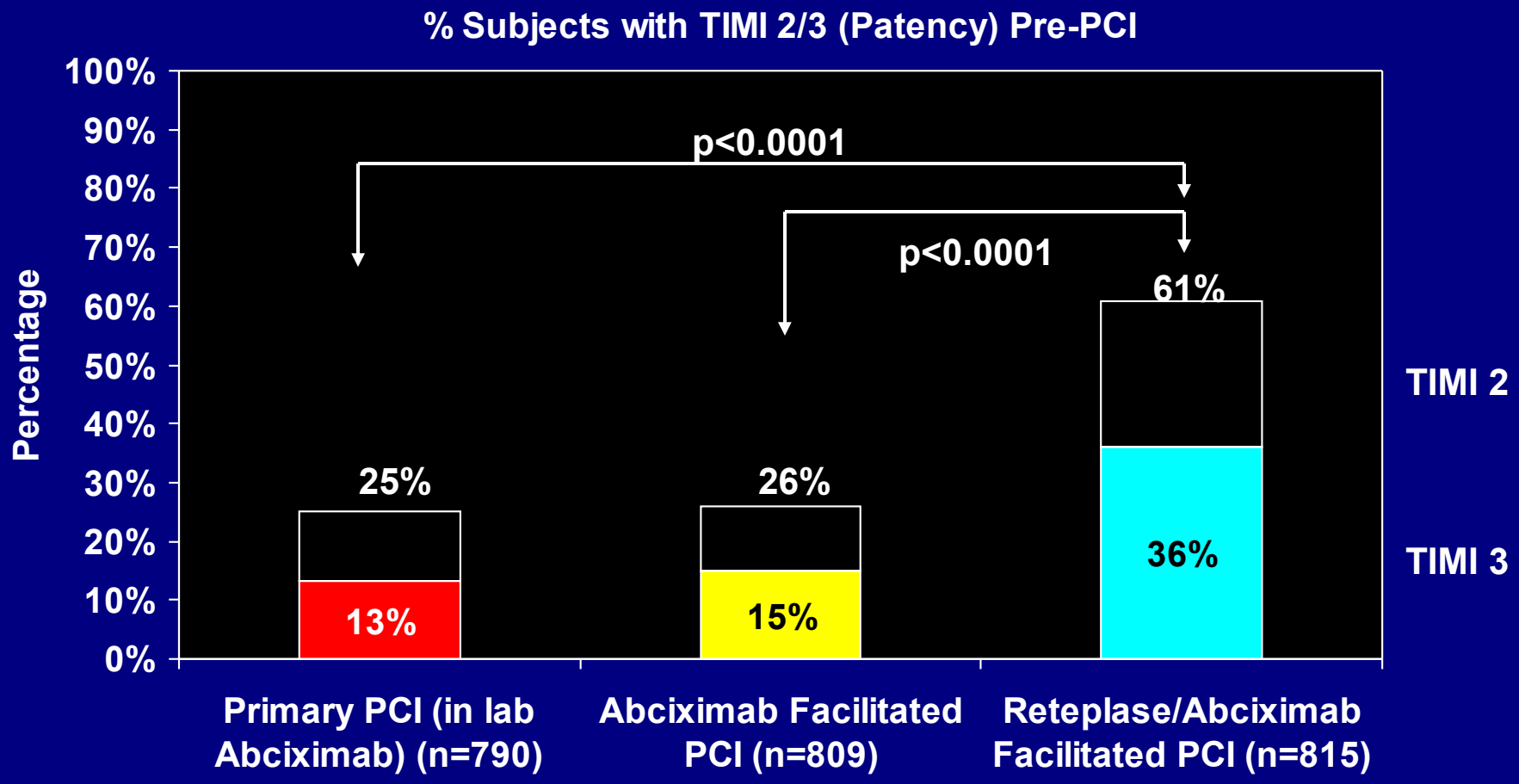
FINESSE: Study Design

Acute ST Elevation MI (or New LBBB) within 6h pain onset

Presenting at Hub or Spoke with estimated time to Cath between 1 and 4 hours



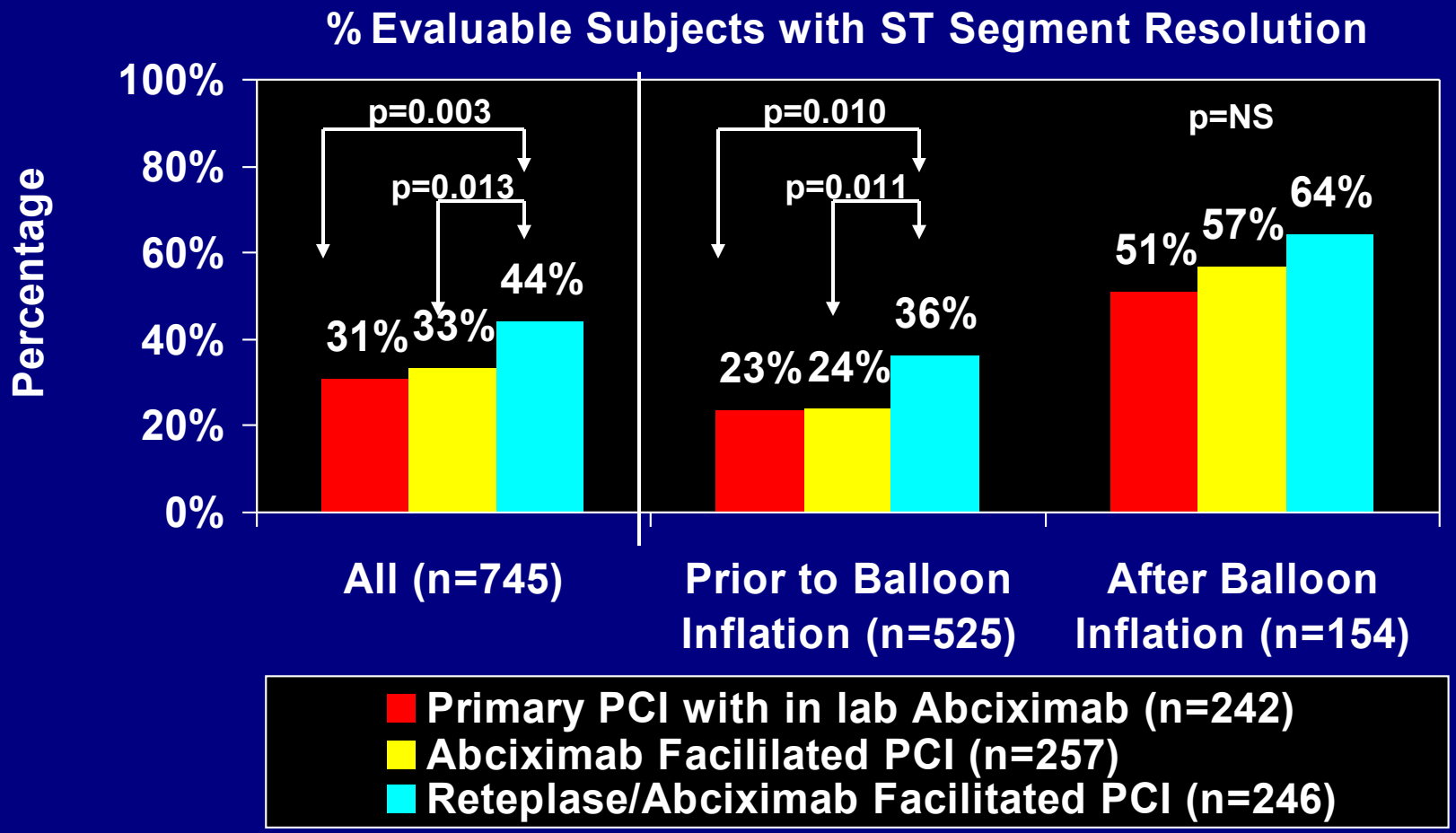
TIMI Flow in IRA Pre-PCI



Ave Time from First Abciximab Bolus to Angiogram In Facilitated Groups:
74min 76min

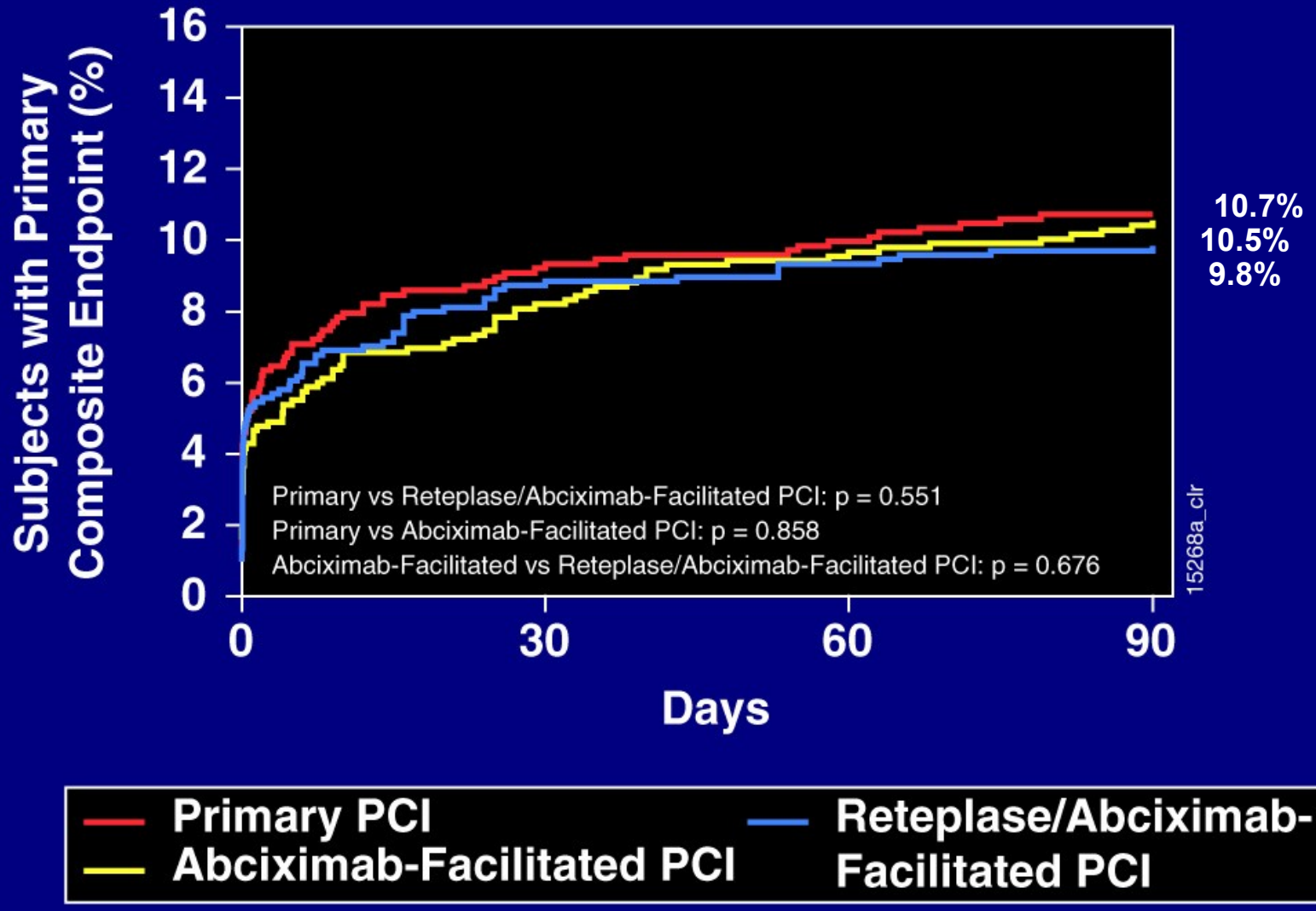
Modified ITT Population with Index PCI: ITT, PCI and any dose of study drug (active or placebo); Investigator assessment

ST Segment Resolution (>70%) at 60-90 Min: Core Lab

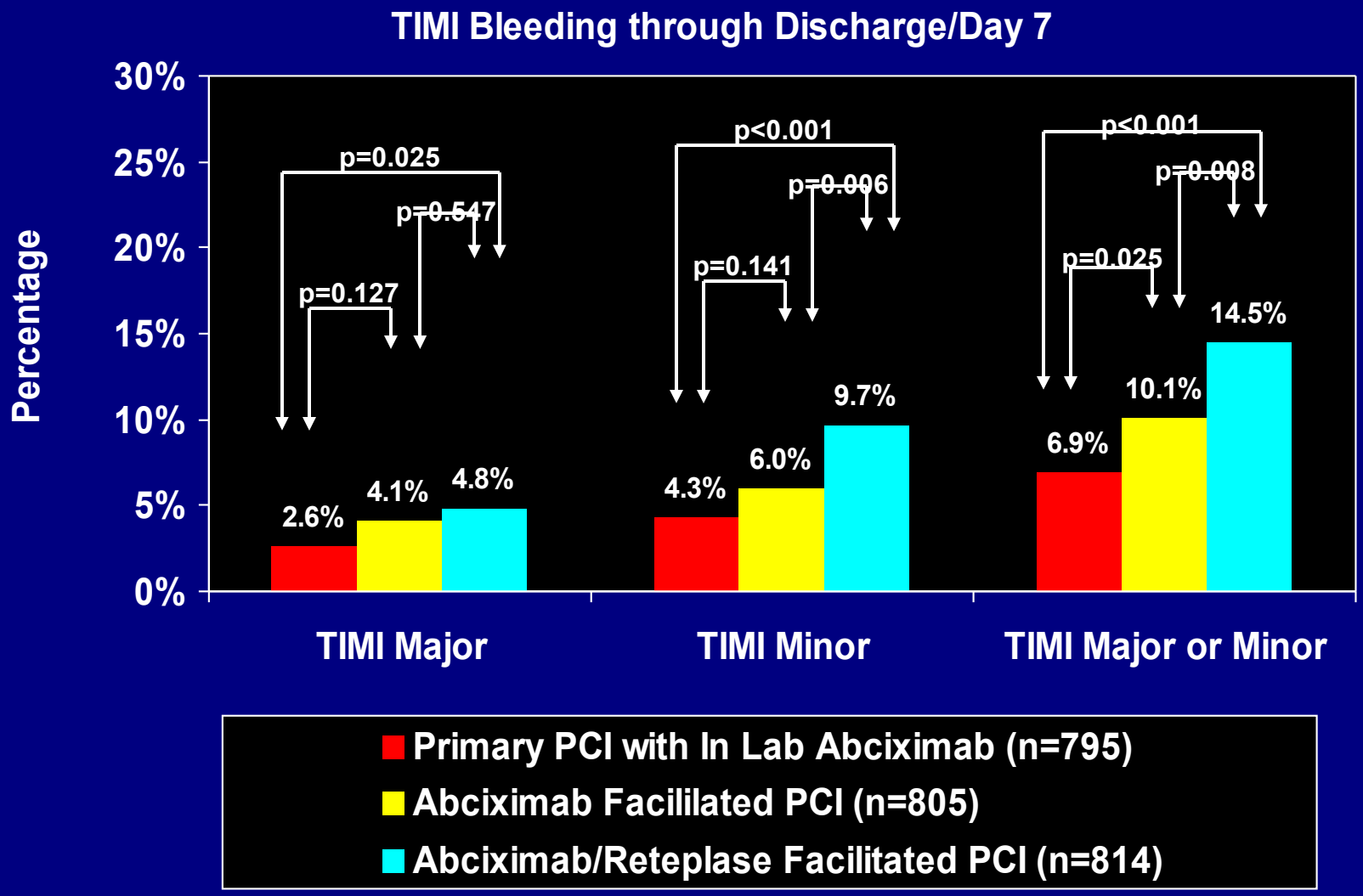


Half of subjects randomly selected for Core Lab over-read*

Primary Endpoint



TIMI Major or Minor Bleeding (nonintracranial) through Discharge/Day7



ON-TIME -2

Acute myocardial infarction diagnosed in ambulance or referral center ASA + 600 mg Clopidogrel + UFH

N=984
6/2006-11/2007

Placebo

*** Tirofiban**

Transportation

Angiogram

PCI center

Angiogram

Tirofiban provisional

PCI

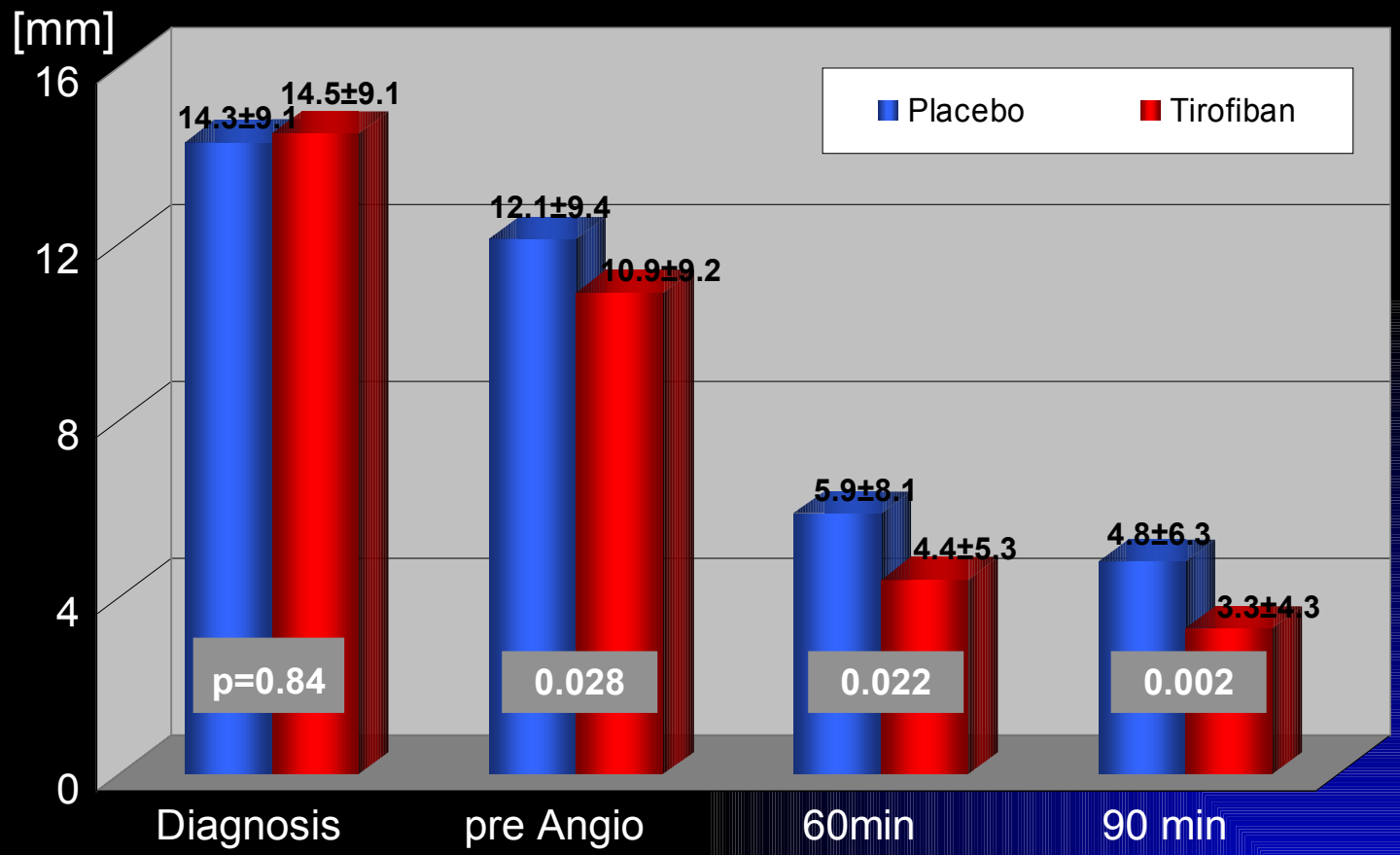
Tirofiban cont'd

Bolus: 25 µg/kg & 0.15 µg/kg/min infusion*

Hamm CW et al. Abstract 413-5. Presented April 1, 2008, at the American College of Cardiology 57th Annual Meeting in Chicago, IL.

On goingT irofibanI nM yocardial InfarctionEvaluation

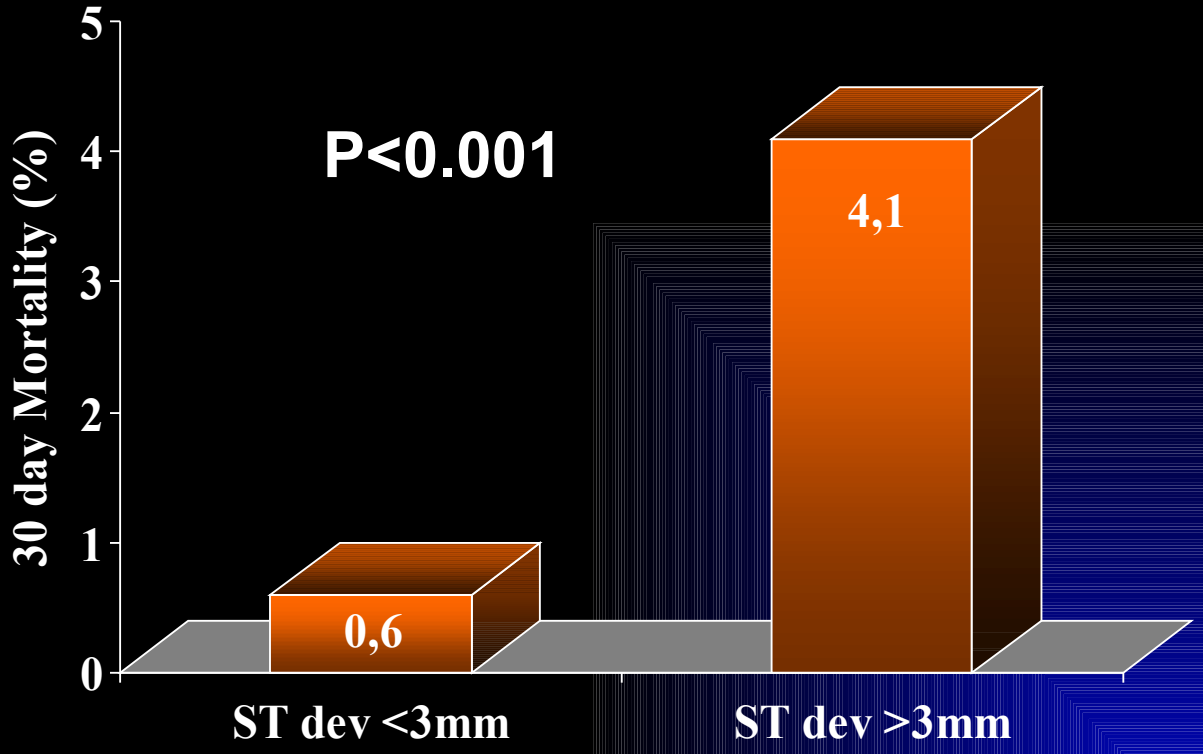
Cumulative ST- Deviation over Time



Hamm CW et al. Abstract 413-5. Presented April 1, 2008, at the American College of Cardiology 57th Annual Meeting in Chicago, IL.

On goingT irofibanI nM yocardial InfarctionEvaluation

Residual ST-Deviation and Mortality



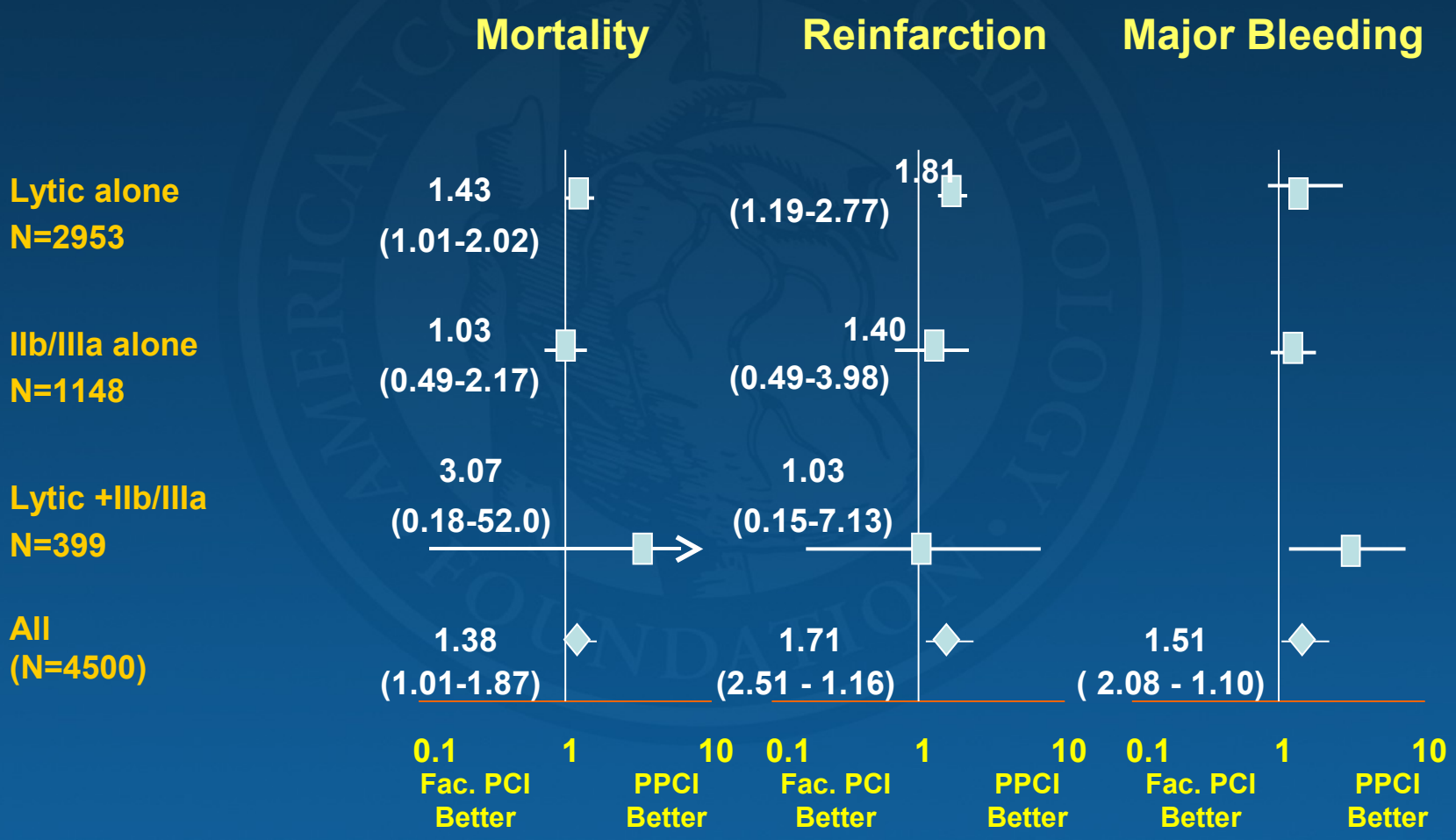
Hamm CW et al. Abstract 413-5. Presented April 1, 2008, at the American College of Cardiology 57th Annual Meeting in Chicago, IL.

Summary

- Pre-Hospital initiation of tirofiban (HDB) improves ST resolution before and after primary PCI
- Combined secondary clinical endpoint reduced
- No increase in bleeding risk

.Hamm CW et al. Abstract 413-5. Presented April 1, 2008, at the American College of Cardiology 57th Annual Meeting in Chicago, IL.

Meta-analysis: Facilitated PCI vs Primary PCI

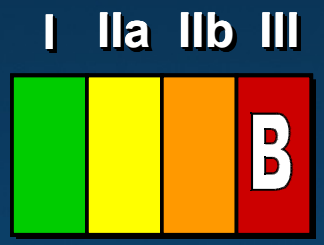


Keeley E, et al. *Lancet* .2006;367:579

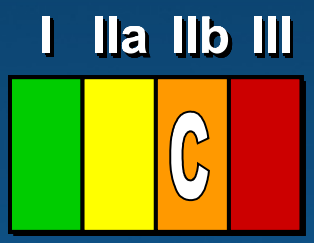
Conclusions

- Administration of lytics or GP IIb/IIIa antagonists prior to primary PCI markedly improves initial flow but has not been shown to improve outcome.
- Thrombolysis facilitation is probably harmful and should not be used.
- IIb/IIIa antagonists probably useful but facilitation may not be better than in lab administration.
- The use of these agents to "facilitate" PPCI may be justified when treatment delays are expected and bleeding risk is low.
- The use of abciximab with primary PCI is a class IIa recommendation in both ESC and ACC/AHA STEMI guidelines

Facilitated PCI



A planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI is not recommended .and may be harmful



Facilitated PCI using regimens other than full-dose fibrinolytic therapy might be considered as a reperfusion :strategy when all of the following are present

,a. Patients are at high risk

b. PCI is not immediately available within 90 minutes, and

c. Bleeding risk is low (younger age, absence of poorly .(controlled hypertension, normal body weight

HORIZONS AMI

Harmonizing Outcomes with Revascularization and Stents in AMI

pts with STEMI with symptom onset ≤12 hours *3400≤

Aspirin, thienopyridine

R
1:1

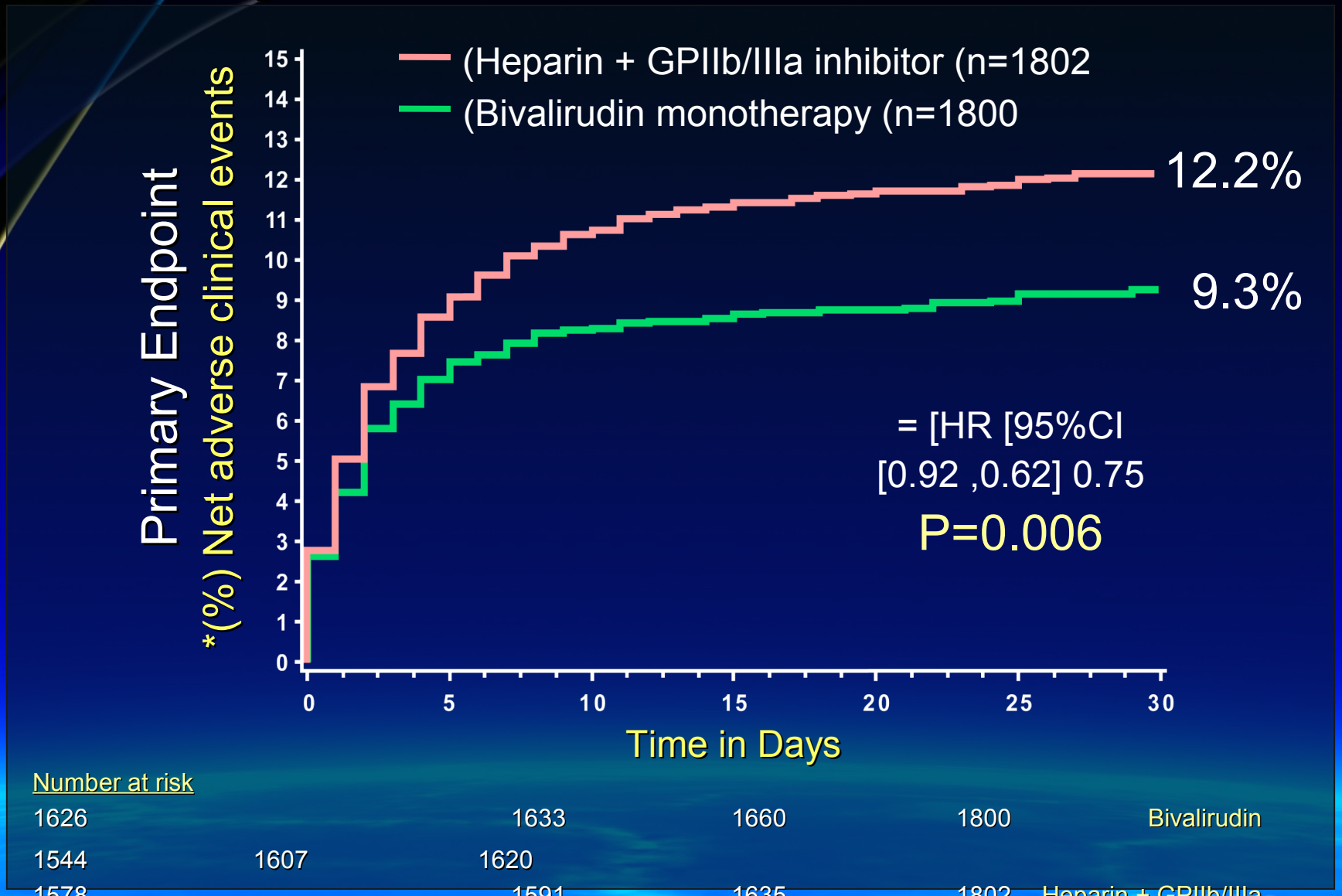
UFH + GP IIb/IIIa inhibitor
(abciximab or eptifibatide)

Bivalirudin monotherapy
(provisional GP IIb/IIIa ±)

Pharmacology Arm
*Primary Endpoints
Day 30
Intention to Treat Population

All stent randomization results are still blinded *

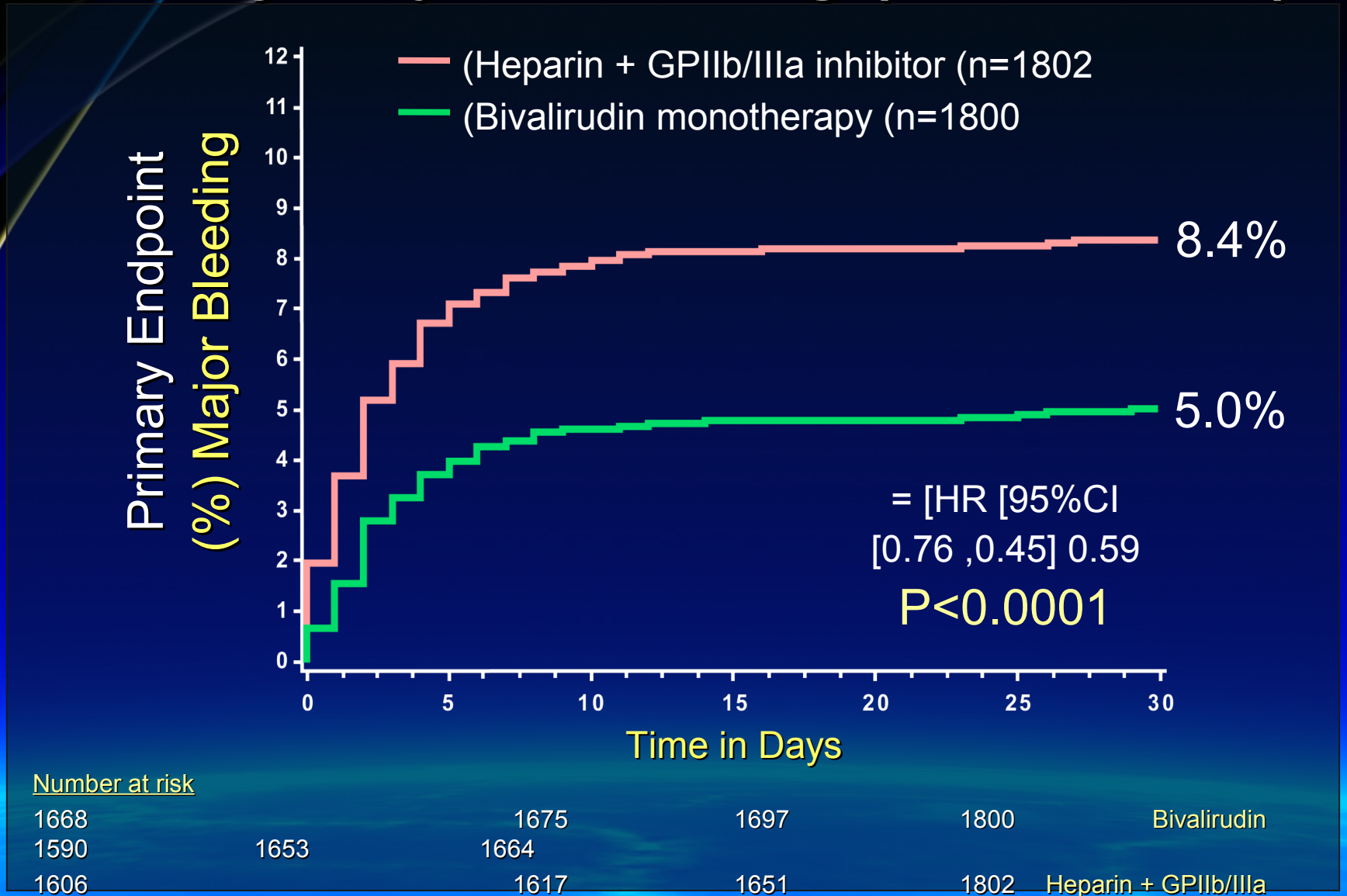
30 Day Net Adverse Clinical Events



(MACE or major bleeding (non CABG)

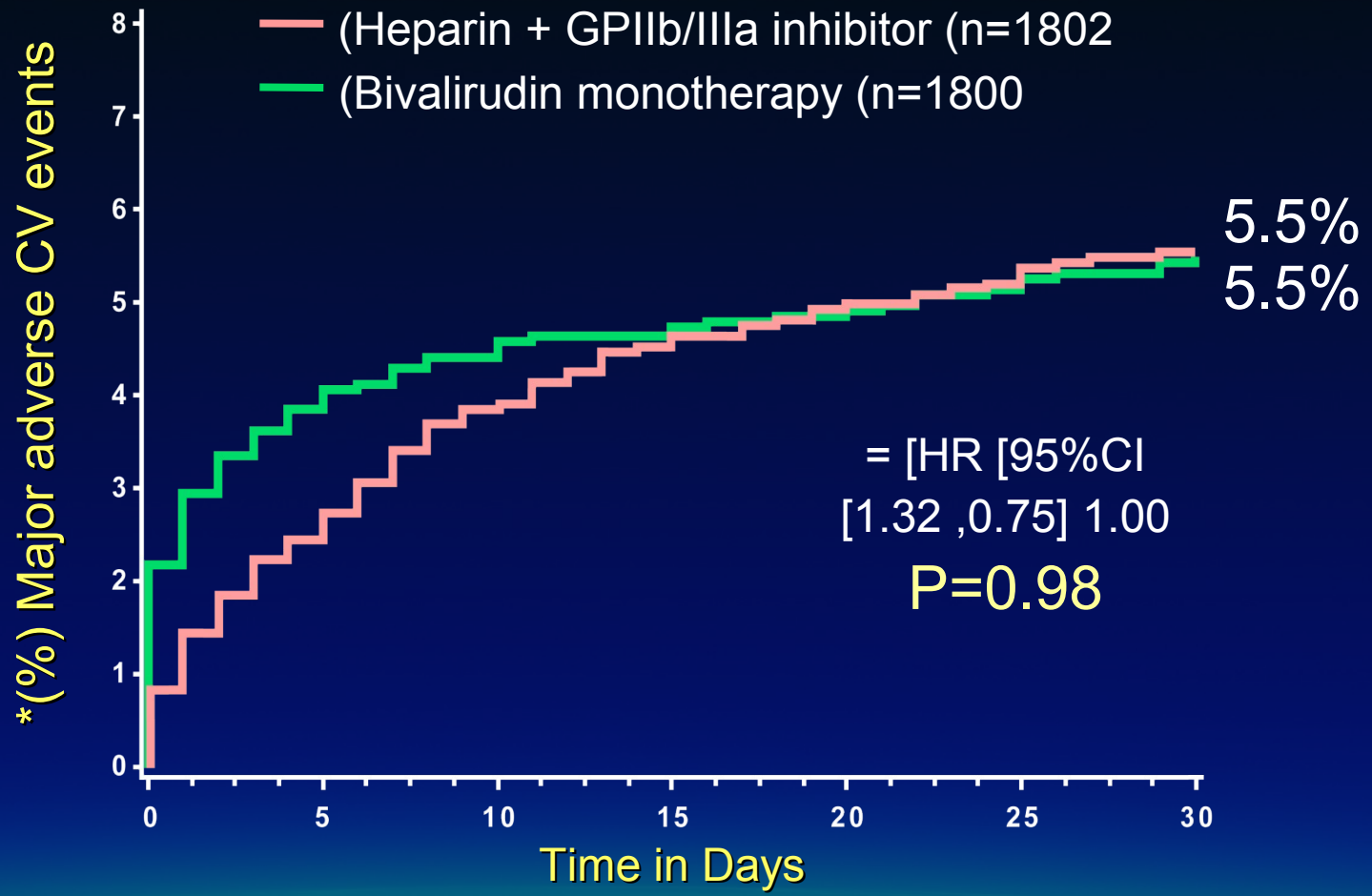
HORIZONS-AMI

30 Day Major Bleeding (non-CABG)



HORIZONS-AMI

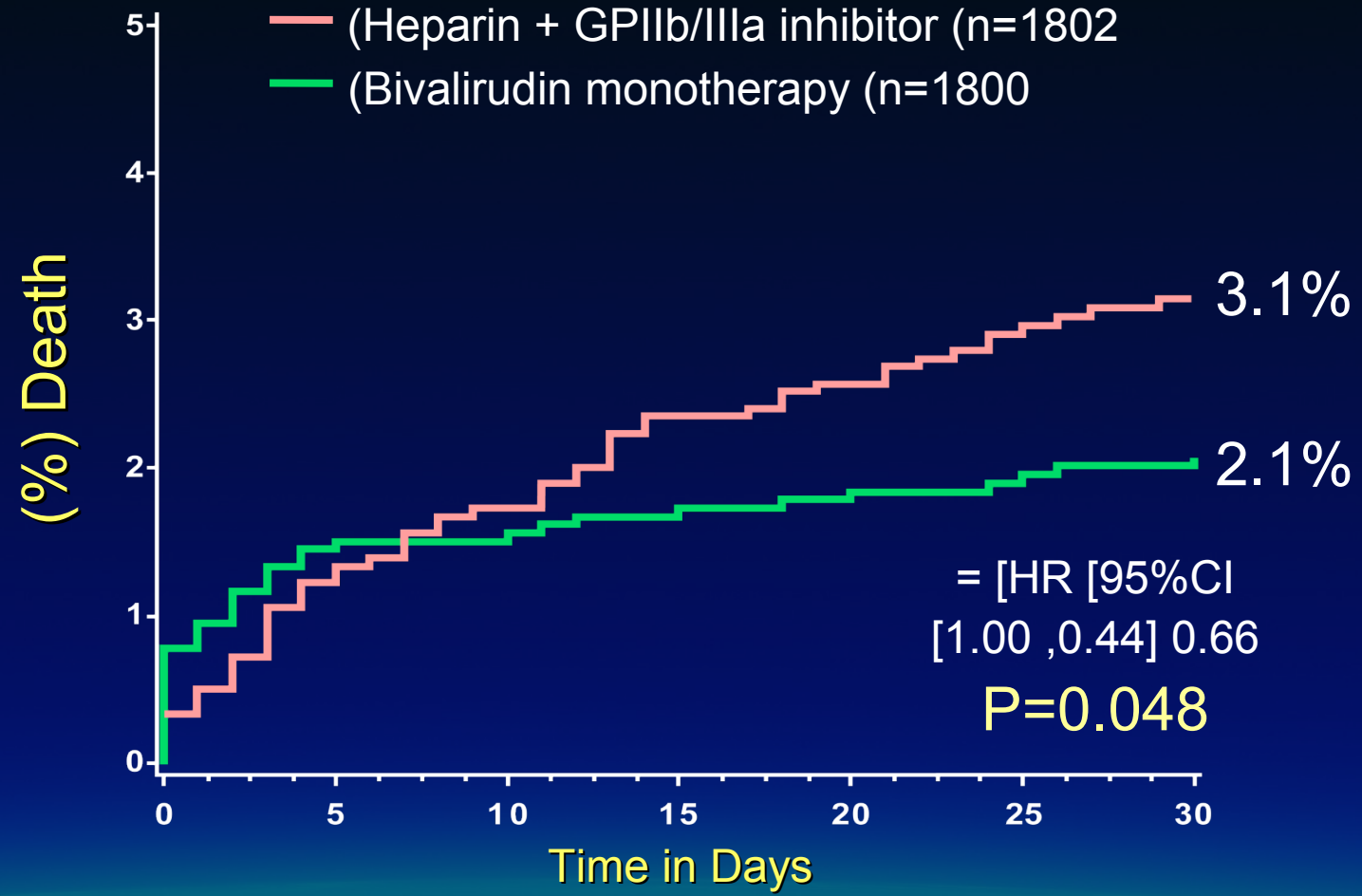
30 Day Major Adverse CV Events



MACE = All cause death, reinfarction, ischemic TVR or stroke*

HORIZONS AMI

30 Day Mortality



Number at risk

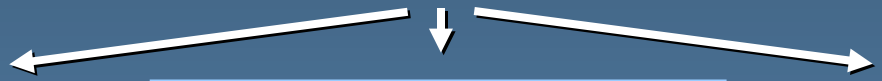
1746	1751	1758	1800	Bivalirudin
1666	1729	1742		
1736	1748	1764	1802	Heparin + GPIIb/IIIa
1630	1707	1728		

HORIZONS-AMI

REACT: 6 month results

427 Acute MI patients with failed thrombolysis

aspirin and thrombolytic therapy within 6 hours of chest pain onset, <50% ST resolution at 90 minutes, 42% anterior infarctions



Repeat Thrombolysis

Accelerated tPA or reteplase

n=142

Rescue PCI

Angiography with or without Revascularization

- n=144

Conservative Treatment

IV Unfractionated Heparin for 24 hours

n=141

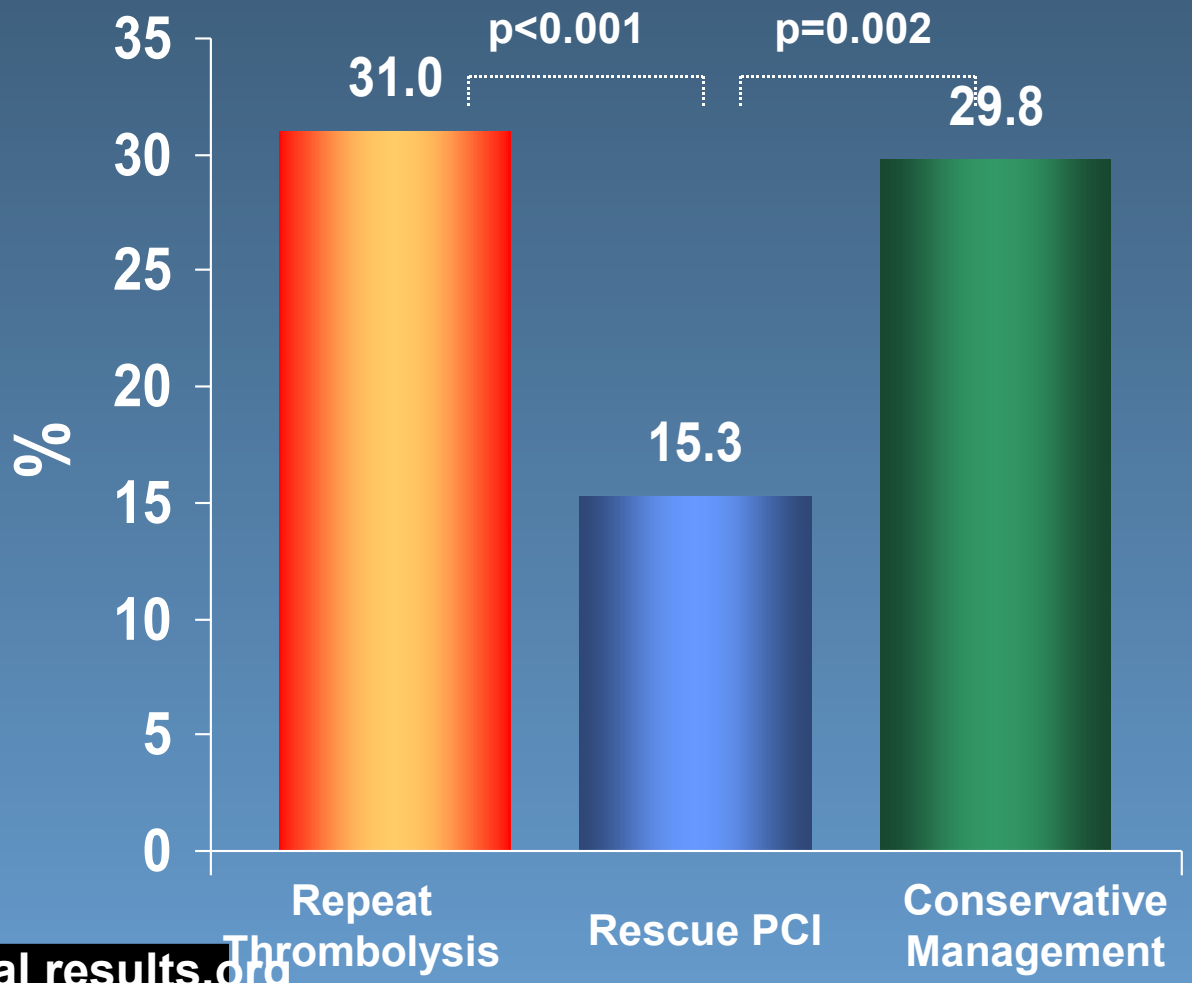
Primary Endpoint:

- **Composite of death, reinfarction, CVA, or severe heart failure at 6 months**

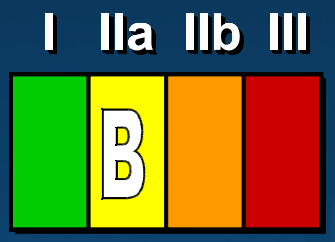
Presented at AHA 2004

REACT: 6 month results

Primary Composite Endpoint (Death, MI, CVA, or severe heart failure)

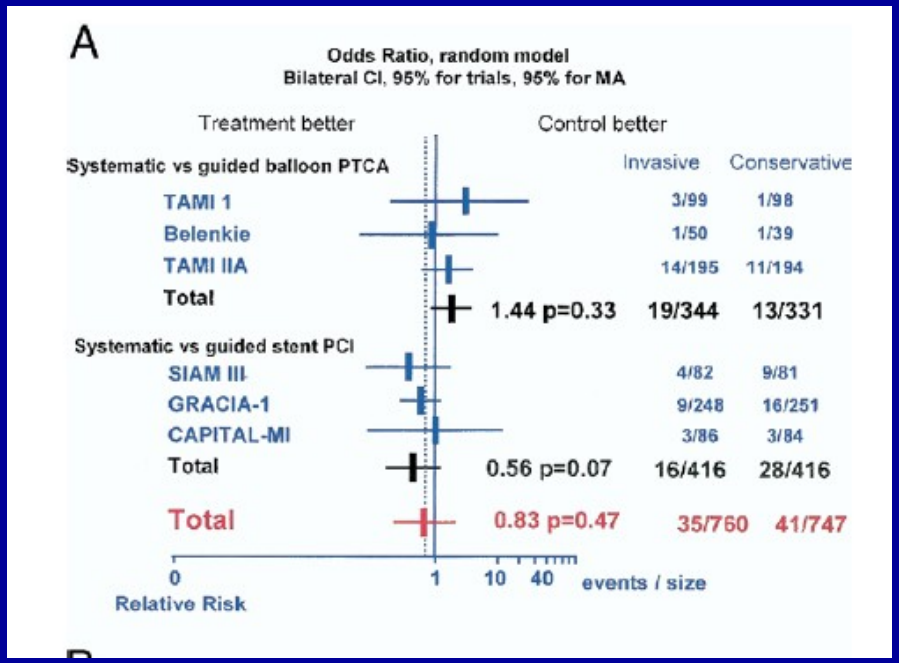


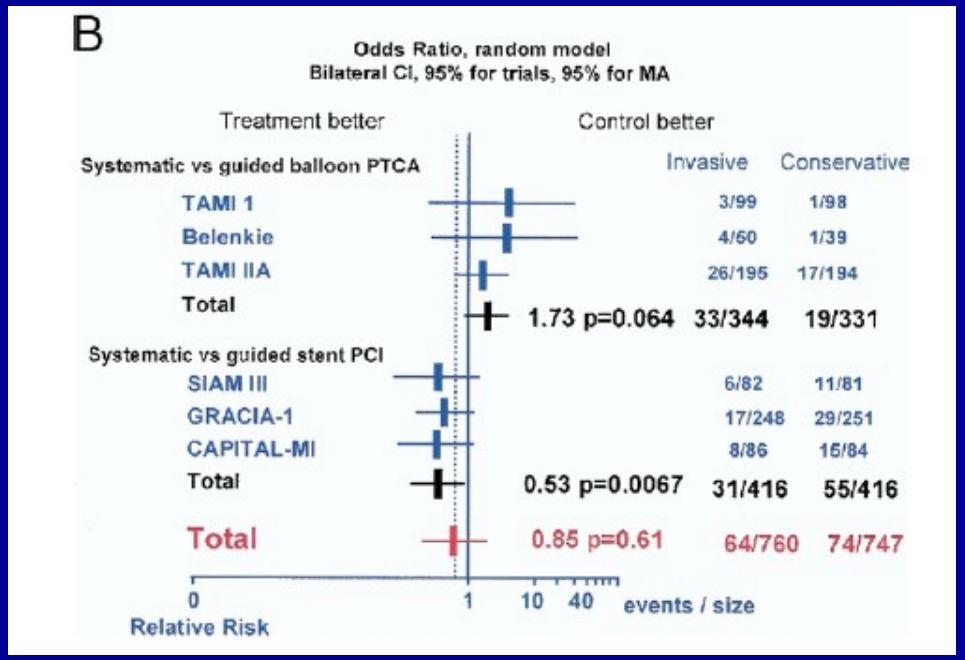
Rescue PCI



A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation < 50% resolved after 90 min following initiation of fibrinolytic therapy in the lead showing the worst initial elevation) and a moderate or large area of myocardium at risk [anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression].

STUDIES OF ROUTINE EARLY PCI VS. DELAYED OR GUIDED PCI





Death

Death/MI

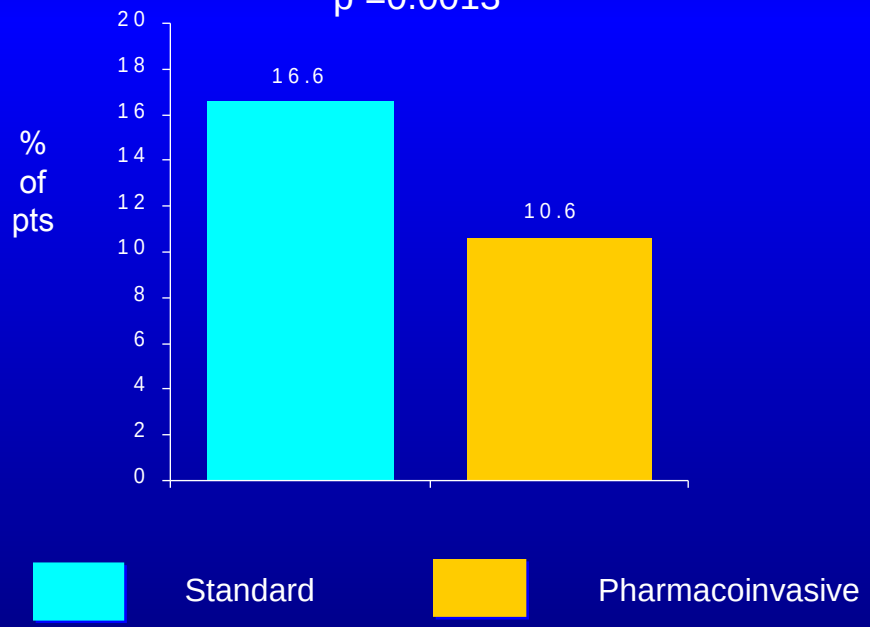
Collet et al, JACC 2006;48:1326

TRANSFER-MI

American Heart Association
Learn and Live

Trial Design: TRANSFER-MI was a randomized study comparing pharmacoinvasive strategy (transfer to PCI center for routine early PCI within 6 hrs) with standard treatment (early transfer only for failed reperfusion) for high-risk STEMI patients receiving thrombolysis at non-PCI centers (N=1,060). The primary endpoint was 30-day composite of death, reinfarction, recurrent Ischemia, CHF, shock.

Day Composite (death, reinfarction, 30
(recurrent ischemia, CHF, shock
OR = 0.537
p =0.0013



Results

- Early PCIwithin 6 hrs after thrombolysis was associated with a 6% absolute reduction in the primary study composite endpoint . Standard 16.6% vs Pharmacoinvasive 10.6% (OR = 0.0013 = 0.537 [.368, 0.783]: p = 0.0013 ((Figure

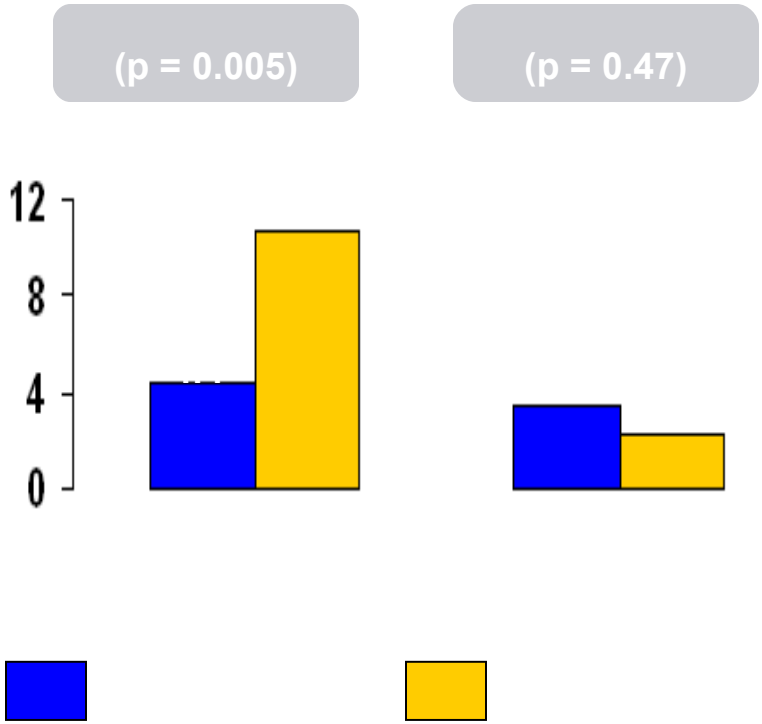
Conclusions

- Challenges findings of older studies regarding timing of fibrinolysis and PCI
- Pharmacoinvasive strategy was safe and effective
- Findings provide important information for shaping future guidelines

Kastrani, K et al. Presented at ACC, 2008.

CARESS-in-AMI

Trial design: STEMI patients admitted to non-PCI hospitals and initially treated with heparin, half-dose reteplase, and abciximab were randomized to immediate transfer for .(urgent PCI (n = 299) or standard therapy with rescue PCI if needed (n = 301



Results

- 86% of the immediate PCI group underwent PCI vs. 30% of the standard care group
- Death, MI, or refractory ischemia at 30 days (4.4% vs. 10.7%, p = 0.005)
- Refractory ischemia (0.3% vs. 4.0%, p = 0.003)

Conclusions

- STEMI patients treated with half-dose lytics and abciximab did better with immediate transfer for PCI
- This approach reduced death, MI, or refractory ischemia at 30 days

Di Mario C, et al. Lancet 2008;371:559-68

OAT Trial: Study Design

patients with angiography on day 3-28 post-MI revealing total occlusion 2166 of the infarct-related artery with poor or absent antegrade flow (TIMI flow grade 0 or 1); and meeting a criterion for increased risk, defined as ejection fraction <50%, proximal occlusion of a major epicardial vessel with a large risk region, or both

Exclusions: NYHA class III or IV heart failure, shock , serum creatinine concentration >2.5 mg/dl, angiographically significant left main or three-vessel coronary artery disease, angina at rest, or severe .ischemia on stress testing

.Randomized

female, mean age 59 years, mean follow-up 3 years, mean EF 48% at baseline 22%

,Concomitant medications: Aspirin, anticoagulation if indicated, ACE inhibitors, beta-blockers and lipid-lowering therapy, unless contraindicated

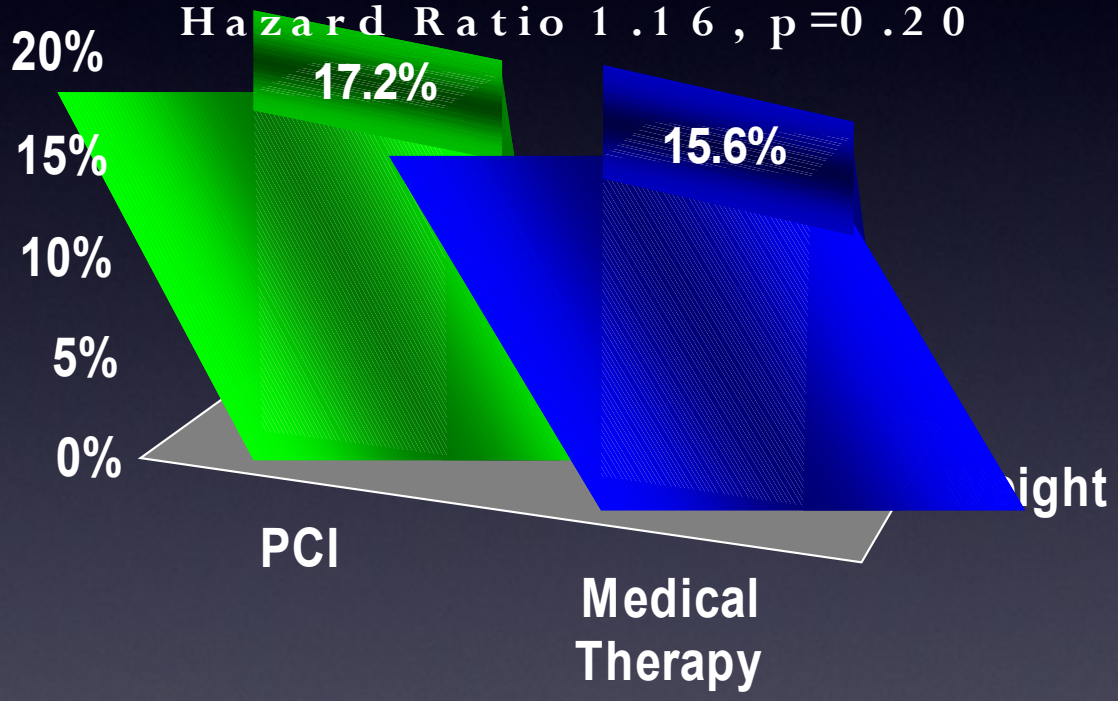
PCI with stenting
n=1082

Medical Therapy
n=1084

Primary Endpoints: Death, MI, or NYHA class IV heart failure

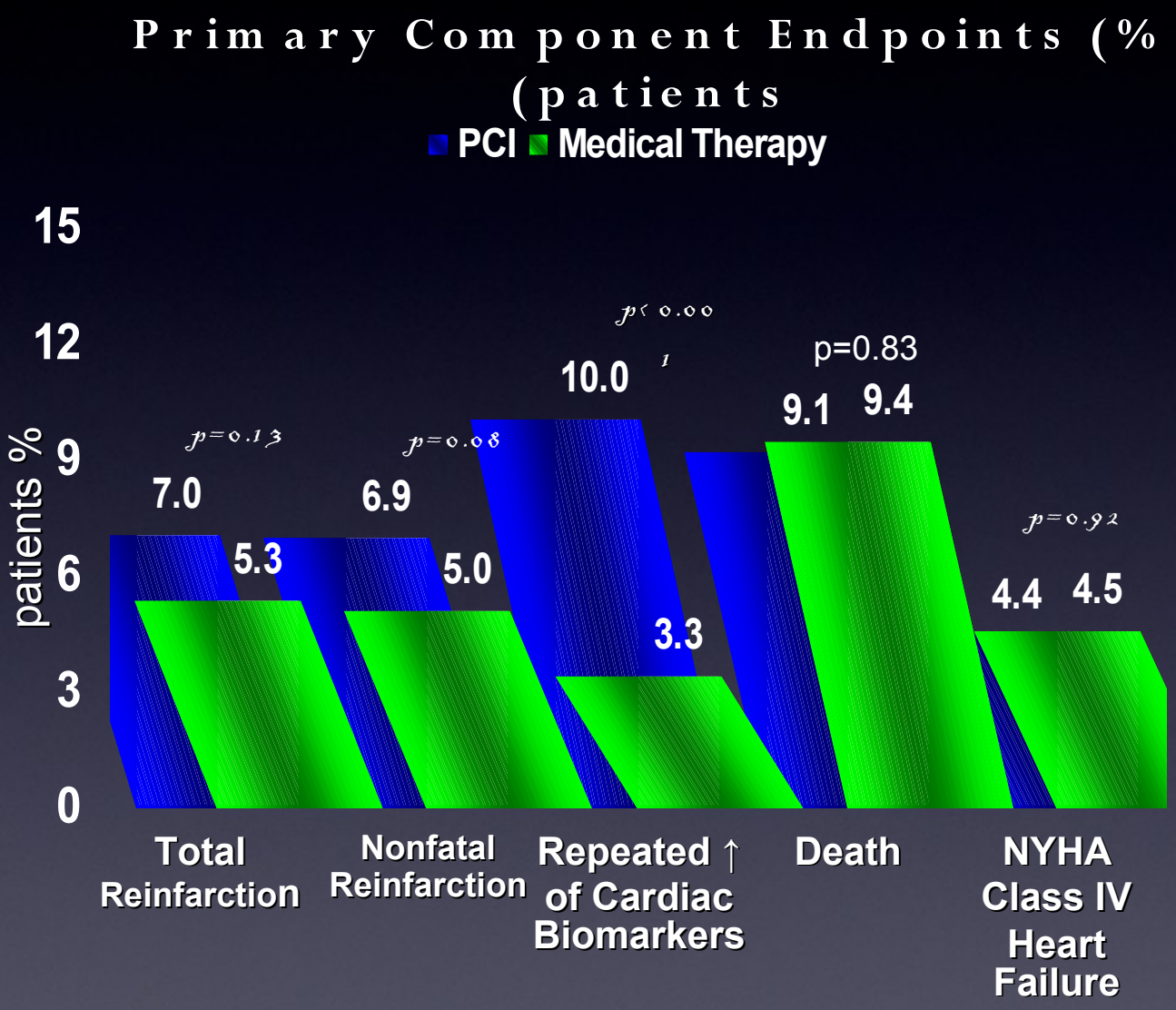
OAT Trial: Primary Endpoint

Primary Endpoint of death, reinfarction, NYHA class IV heart (failure (% patients



The primary endpoint: death, reinfarction, or NYHA class IV heart failure occurred in 17.2% of the PCI group and 15.6% of the medical therapy group (HR 1.16, p=0.20

OAT Trial: Results



- Total reinfarction trended higher in the PCI group (7.0% vs. 5.3%, HR 1.36, p=0.13), as did nonfatal reinfarction (6.9% vs. 5.0%, HR 1.44, p=0.08).

- Repeated elevation of cardiac biomarkers within 48 hours of randomization occurred significantly more frequently in the PCI group (10.0% vs. 3.3%, p< 0.001).

- There was no difference in the individual endpoints of death (9.1% for PCI vs. 9.4% for medical therapy, p=0.83) or NYHA class IV heart failure (4.4% vs. 4.5%, p=0.92) between the treatment groups.

OAT Trial: Summary

In stable, high-risk patients with persistent total occlusion of the infarct-related artery post-MI compared to maximum medical therapy, routine PCI 3-28 days post-MI was not associated with a difference in the composite of death, reinfarction, or NYHA class IV heart failure through a mean follow-up of 3 years.

Despite no reduction in the composite endpoint, PCI was associated with a trend toward higher rates of reinfarction compared with medication therapy.

Myocardial infarctions were not only procedural-related infarcts, but also Q elevation MI occurring throughout follow-up.

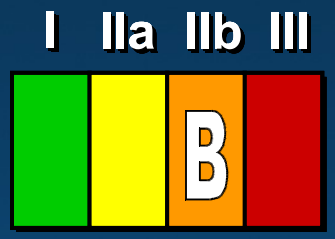
Presented at AHA 2006

Coronary angiography post thrombolysis: Guidelines

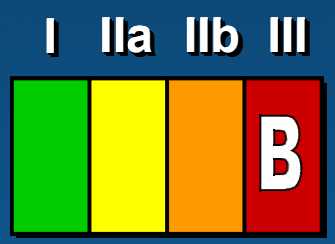
- **ACC/AHA:**
  - Class I/IIA for recurrent or provocable, ischemia, LV dysfunction, hemodynamic compromise
  - Class IIb: Routine post thrombolysis

- **ESC:**
  - Class I as routine post thrombolysis

Late PCI after Fibrinolysis or for Patients Not Undergoing Primary Reperfusion



PCI of a hemodynamically significant stenosis in a patent infarct artery > 24 hours after STEMI may .be considered as part of a invasive strategy



PCI of a totally occluded infarct artery > 24 hours after STEMI is not recommended in asymptomatic patients with 1- or 2-vessel disease if they are hemodynamically and electrically stable and do .not have evidence of severe ischemia

PCI FOR STEMI

- Primary PCI Vs. thrombolysis - yes
- Transfer to primary PCI - yes
- Facilitated primary PCI – with lysis – no, with Reopro - possibly
- Rescue PCI for failed lysis - yes
- Routine early post lysis PCI - yes
- Routine delayed PCI post non reperfused MI - no

Reperfusion Options for STEMI Patients

Step One: Assess Time and Risk.

Time Since Symptom Onset

Risk of STEMI

Risk of Fibrinolysis

Time Required for Transport to a Skilled PCI Lab

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THE APPROACH TO REPERFUSION THERAPY: I – Pre hospital phase

Determine a community policy for STEMI transfer

STEMI < 12h

↓

ASA, UFH

↓

Contact receiving hospital

↓

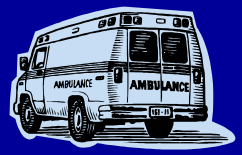
Decide on destination hospital

THE APPROACH TO REPERFUSION THERAPY: I – Pre hospital phase

Time to PCI center≤ time to non PCI center → PCI center

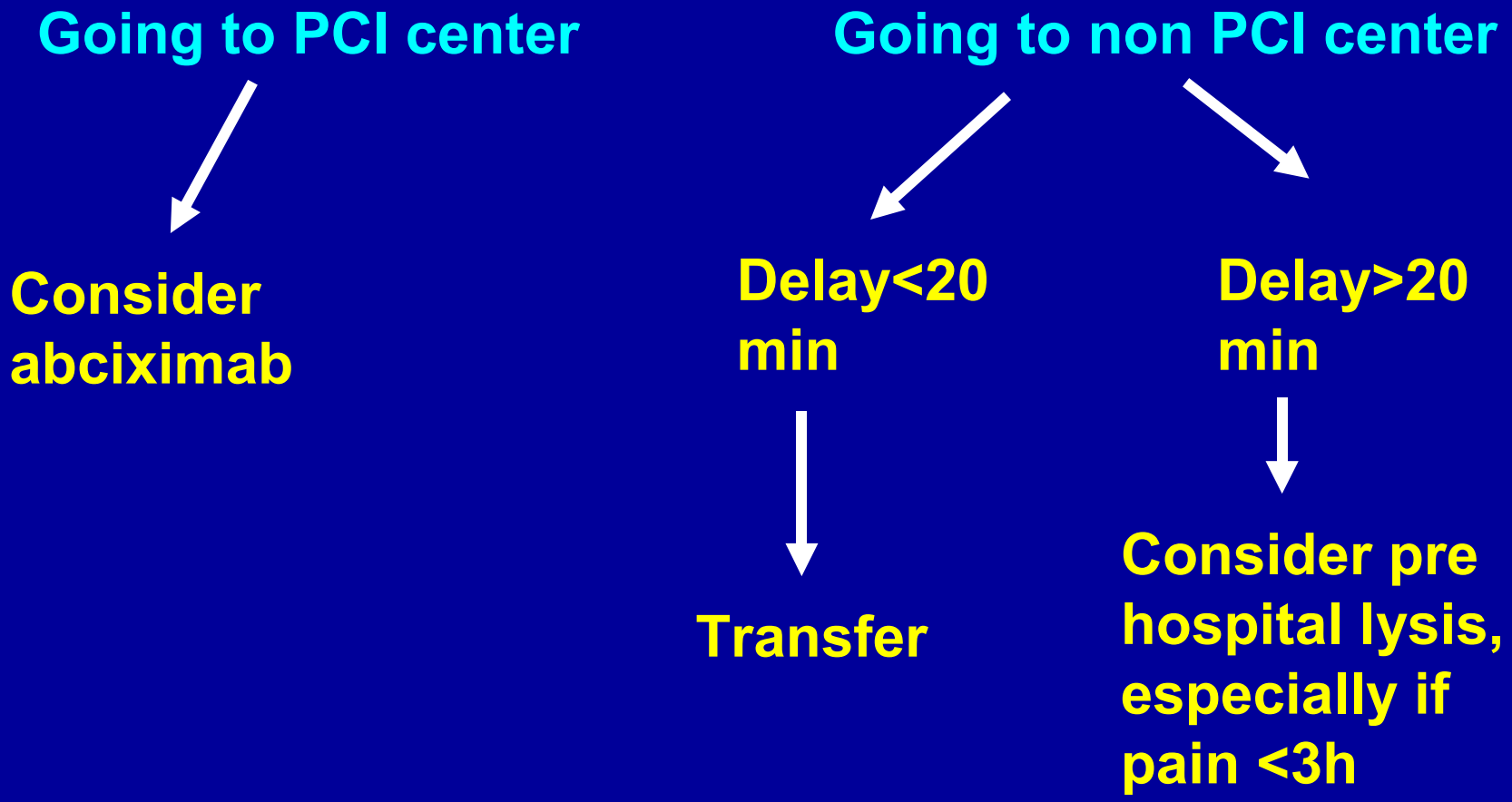
Time to PCI center > time to non PCI center

- Cardiogenic shock, other very high risk → PCI center
- C/I to lysis → PCI center



- Expected time to balloon - time to t-PA ≤60 min
- Not high risk, Expected time to balloon >> time to t-PA → Non PCI center

THE APPROACH TO REPERFUSION THERAPY: I – Pre hospital phase



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 no preference for either strategy.

Fibrinolysis generally preferred

- *Early presentation (≤ 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

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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 no preference for either strategy.

Invasive strategy generally preferred

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

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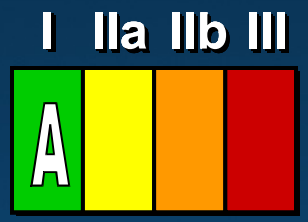
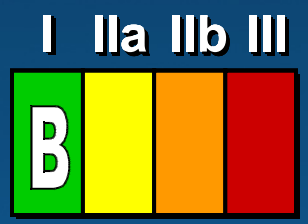
Primary PCI



STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within .90 min of first medical contact as a systems goal



STEMI patients presenting to a hospital without PCI capability, and who cannot be transferred to a PCI center and undergo PCI within 90 min of first medical contact, should be treated with fibrinolytic therapy within 30 min of hospital presentation as a systems goal, unless fibrinolytic therapy is .contraindicated

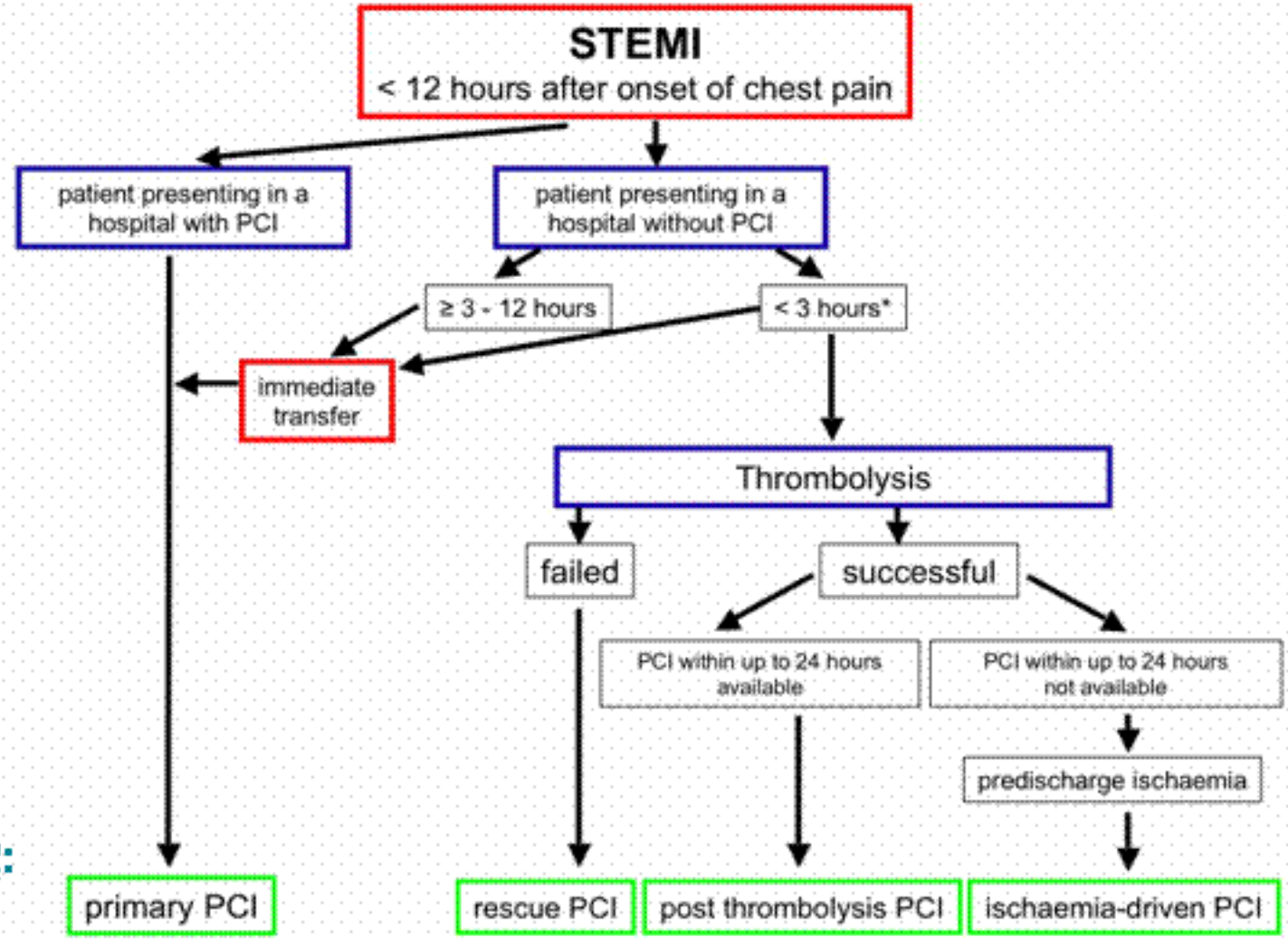


Figure 2:

Within the first 3 hours after onset of chest pain or other symptoms, thrombolysis is a viable alternative to primary PCI. *If thrombolysis is contraindicated or at high risk, immediate transfer for primary PCI is strongly advised. The major rationale for possible preference of primary PCI over thrombolysis within the first 3 hours is stroke prevention. The major rationale for preference of primary PCI over thrombolysis within 3 to 12 hours is to salvage myocardium and to prevent stroke. If thrombolysis is preferred, it should not be considered to be the final treatment. Even after successful thrombolysis, coronary angiography within 24 hours and PCI, if applicable, should be considered.

GUIDELINES - BASED PHARMACOTHERAPY OF STEMI (1)

		ACC/AHA	ESC
ASA		Class I for all, starting on presentation, indefinitely	
UFH			
	With primary PCI	I	
	With t-PA & variants	I	
	With SK if ant. MI, large MI, AF	I	
	Other SK	IIb	IIa
	No reperfusion	IIa, at least 48h	

GUIDELINES - BASED PHARMACOTHERAPY OF STEMI (2)

		ACC/AHA	ESC
LMWH	With lytics	I	
	Anterior MI, large MI, AF	I	
	No reperfusion, low risk	IIa, at least 48h	
Bivalirudin	with PPCI		IIa
Fonda	With lytics	I	IIa (STK)
Abciximab	with PPCI	IIa	
Clopidogrel	Post stenting, lysis, no reperfusion	I	

GUIDELINES - BASED PHARMACOTHERAPY OF STEMI (3)

		ACC/AHA	ESC
ß blockers	Early IV	IIa, if hypertensive	IIb
	Hospital phase	I	
	Hospital phase with heart failure	III	
	Long term, low risk	IIa	I
CCB	Verapamil/diltiazem if ß blockers not tolerated	IIa	II
	With LV dysfunction	III	

GUIDELINES - BASED PHARMACOTHERAPY OF STEMI (4)

		ACC/AHA	ESC
ACE - I		I	
	1ST 24h, low risk	IIa	
STATINS	Any LDL	I	
	LDL > 115 despite diet		I
FIBRATE/ NIACIN	LDL<100+ HDL <40 or TG>500	I	I if HDL <45 + TG>200
WARFARIN	ASA allergy, AF, LV clot	I	
	With ASA if <75	IIa	