ST ELEVATION MYOCARDIAL INFARCTION

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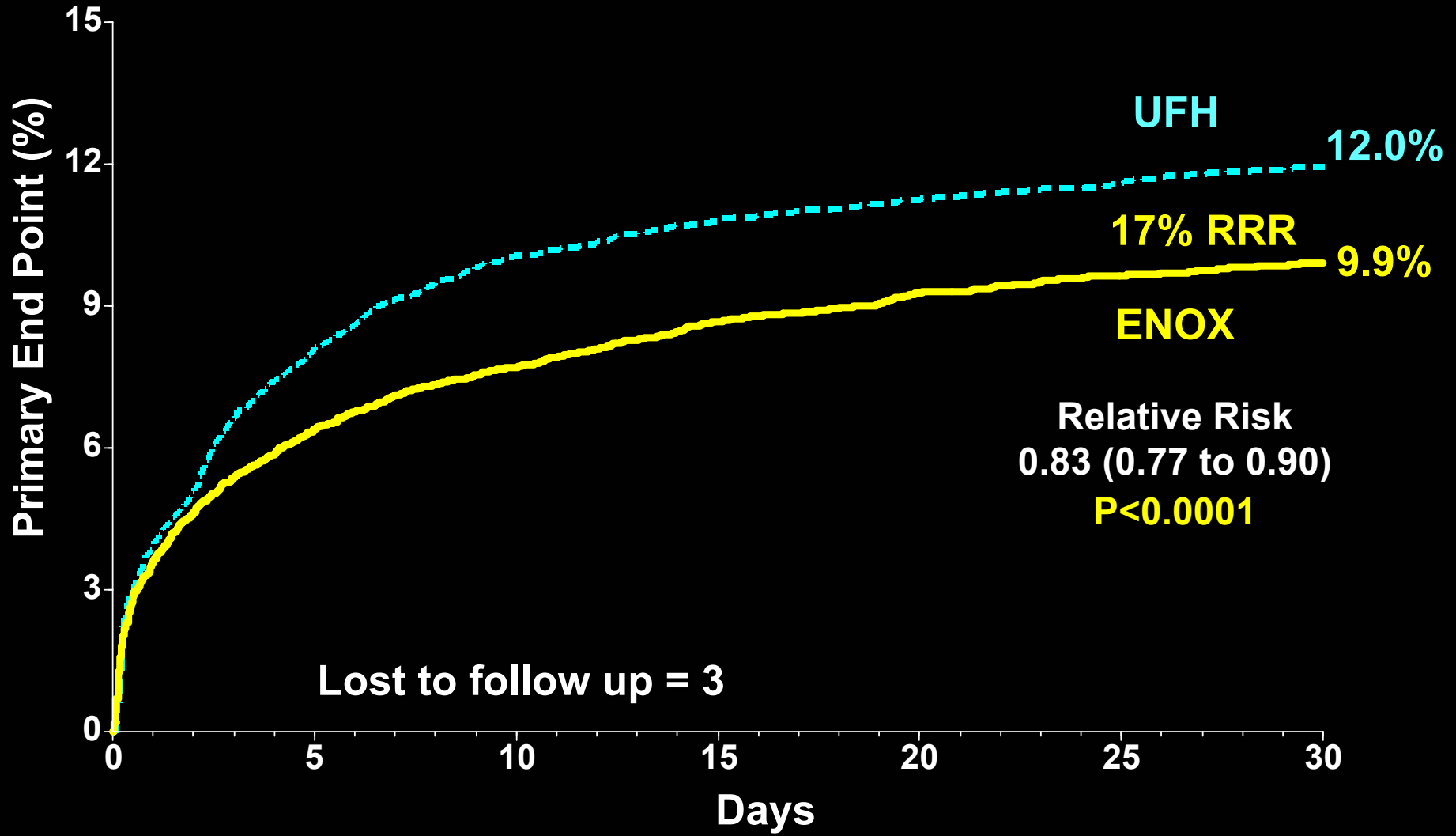
MAIN TOPICS

- **Adjuncts to thrombolysis**
- **Pre hospital thrombolysis**
- **PCI and reperfusion strategies**
- **Pharmacological support of PCI**
- **Guidelines – based pharmacotherapy**

ADJUNCTS TO LYSIS – ANTI THROMBOTIC THERAPY

Primary End Point (ITT)
Death or Nonfatal MI



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?

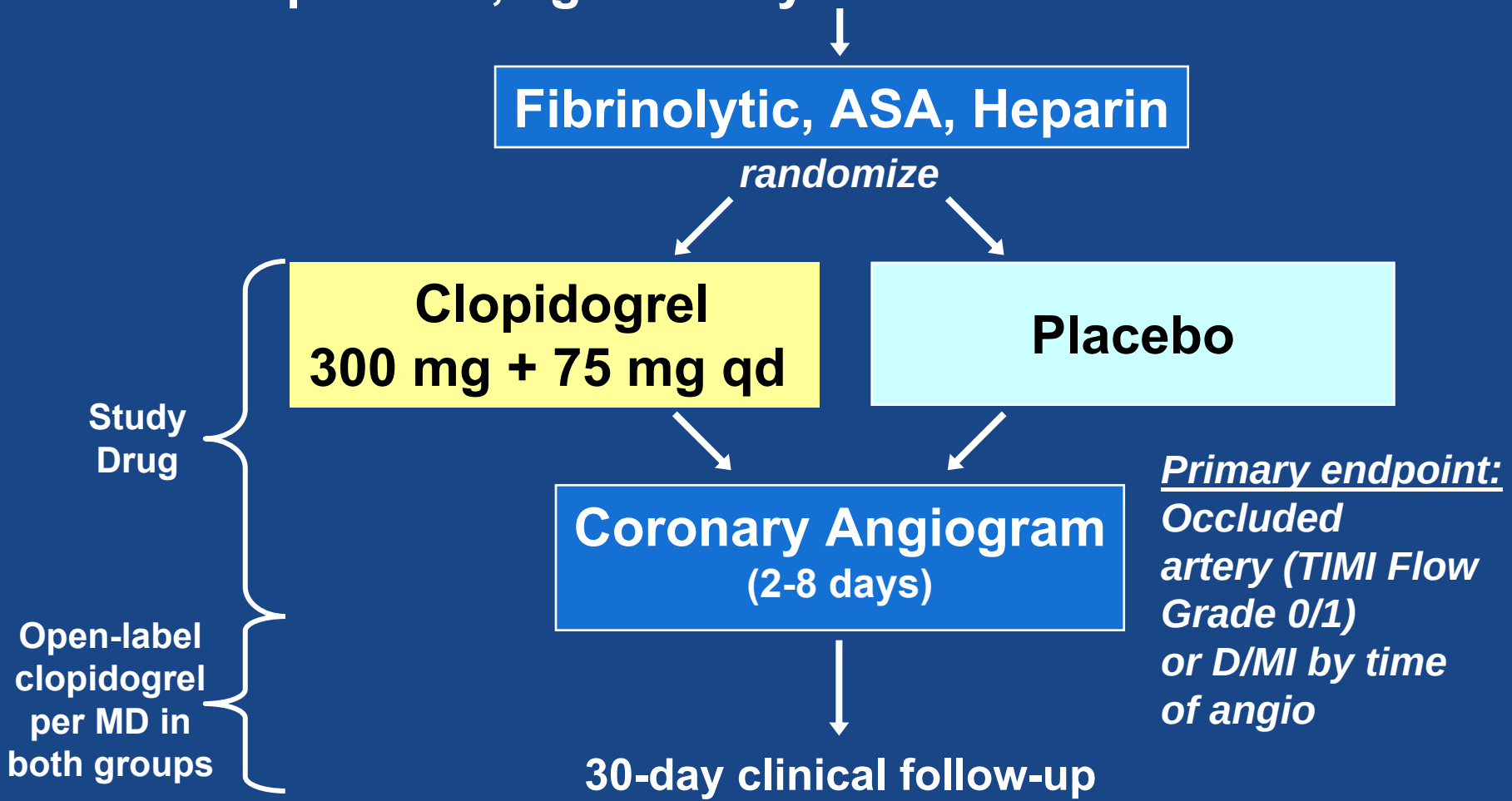
- **EXTRACT did not convincingly show that Enoxaparin is superior to UFH while the 2 agents are actually administered.**
- **Only 23% of patients in EXTRACT had PCI. It is unlikely that with early PCI, as currently recommended, a significant difference exists between the 2 agents.**

ADJUNCTS TO LYSIS – CLOPIDOGREL

CLARITY TIMI 28

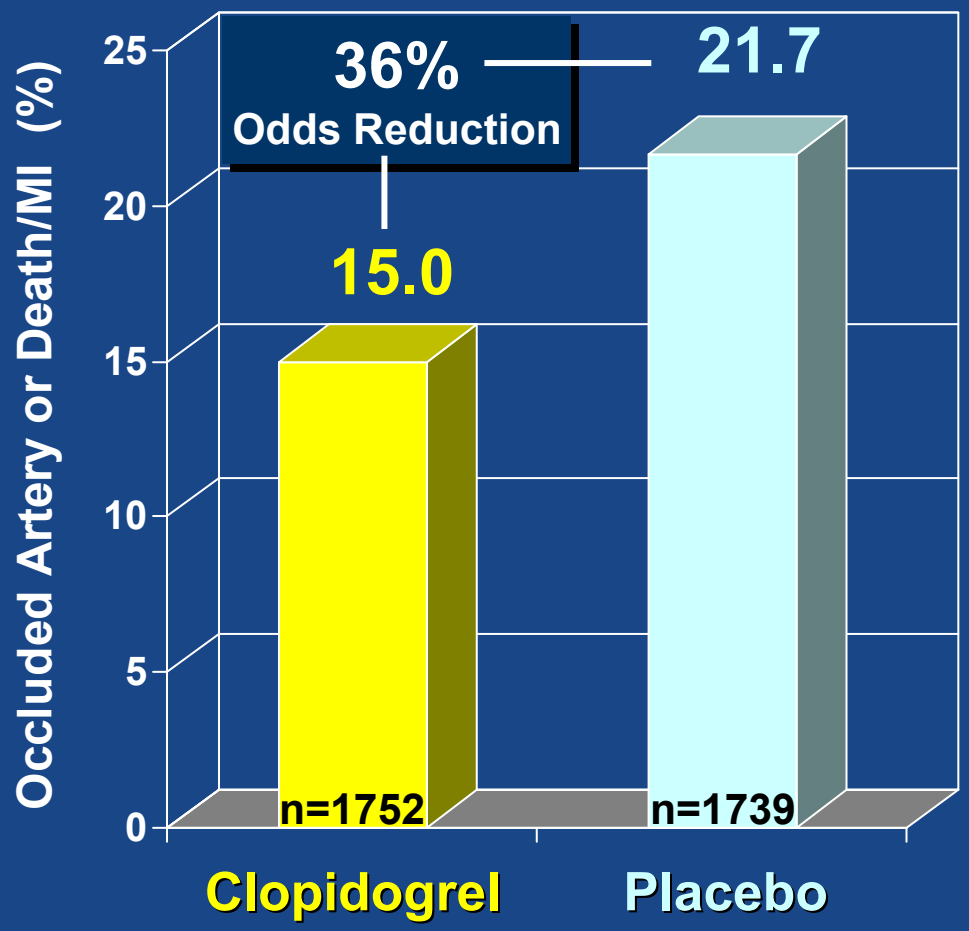
Study Design

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



CLARITY TIMI 28

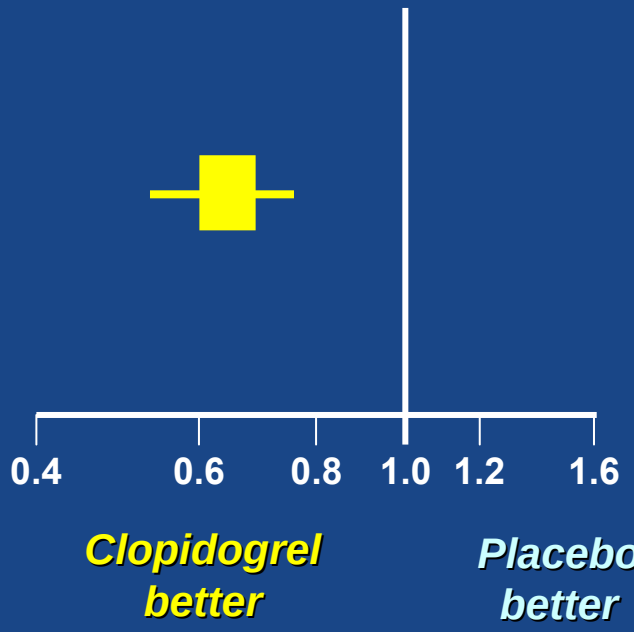
Primary Endpoint: Occluded Artery (or D/MI thru Angio/HD)



Odds Ratio 0.64

(95% CI 0.53-0.76)

P=0.00000036



CLARITY TIMI 28

Bleeding

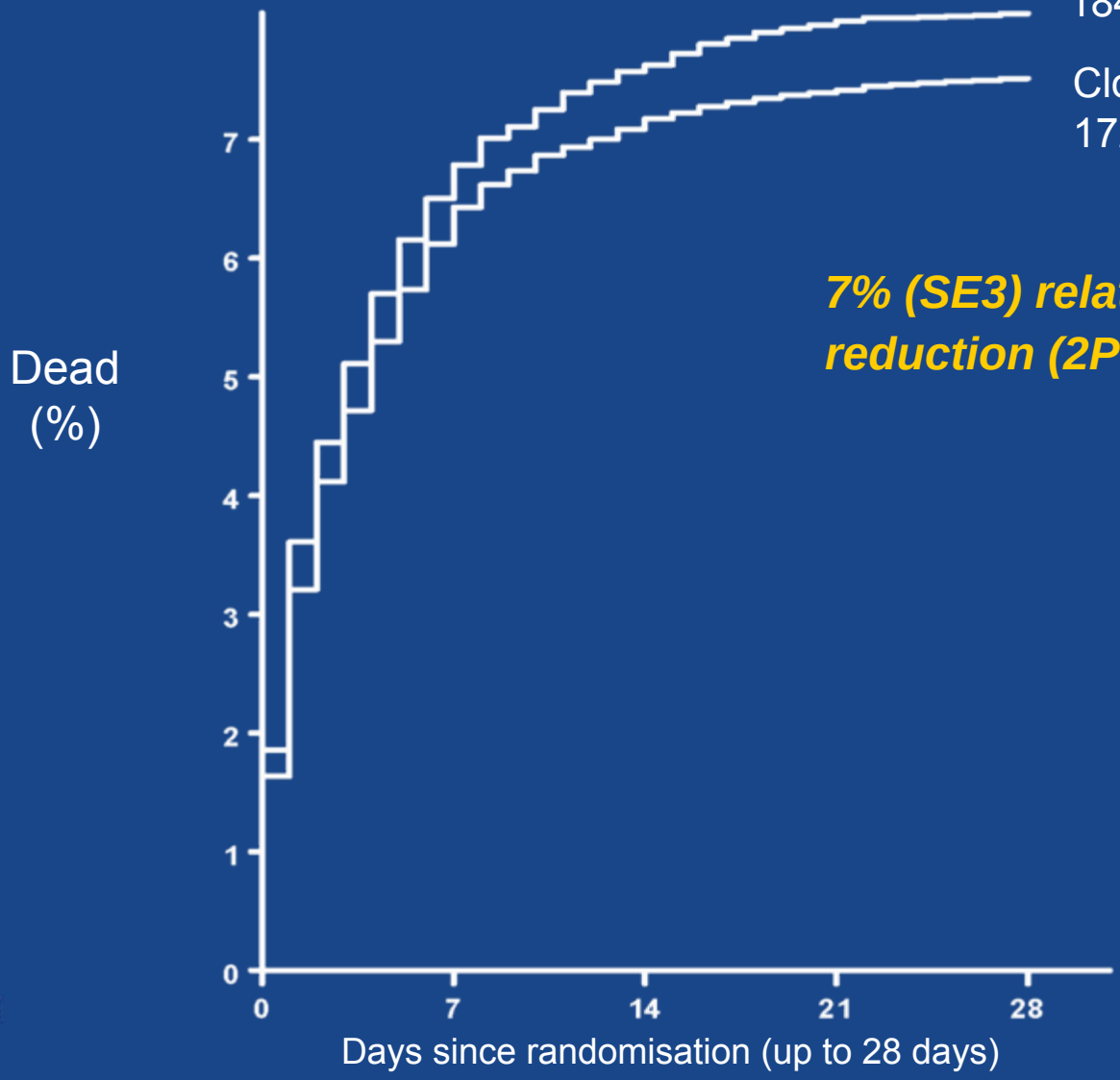
Outcome	Clopidogrel (%)	Placebo (%)	P value
Through angiography			
TIMI major (Hgb ↓ >5 g/dL or ICH)	1.3	1.1	NS
TIMI minor (Hgb ↓ 3-5 g/dL)	1.0	0.5	NS
Intracranial hemorrhage	0.5	0.7	NS
Through 30 days			
TIMI major	1.9	1.7	NS
In those undergoing CABG	7.5	7.2	NS
CABG w/in 5 d of study med	9.1	7.9	NS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

COMMIT: 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

What is the optimal drug combination to support thrombolysis?

- **Enoxaparin for 8d is better than 2d of UFH**
  - **If PCI is planned within 3-24 h post lysis, probably no advantage for enoxaparin over UFH.**
- **Fondaprinux not proved better than UFH.**
- **Clopidogrel reduces mortality**

ESC GUIDELINES FOR ANTI THROMBOTIC CO-THERAPY WITH LYSIS

	CLASS	LOE
ASPIRIN LOADING+MAINTENANCE	I	B
CLOPIDOGREL (+LOADING IF AGE<75)	I	B
WITH tPA, rPA, TNK: Enoxaparin (IV bolus if <75). UFH if enoxaparin not available	I	A
WITH SK: IN ADDITION TO ENOXAPARIN AND UFH AS ABOVE: FONDAPRINUX BOLUS + SC	IIa	B

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

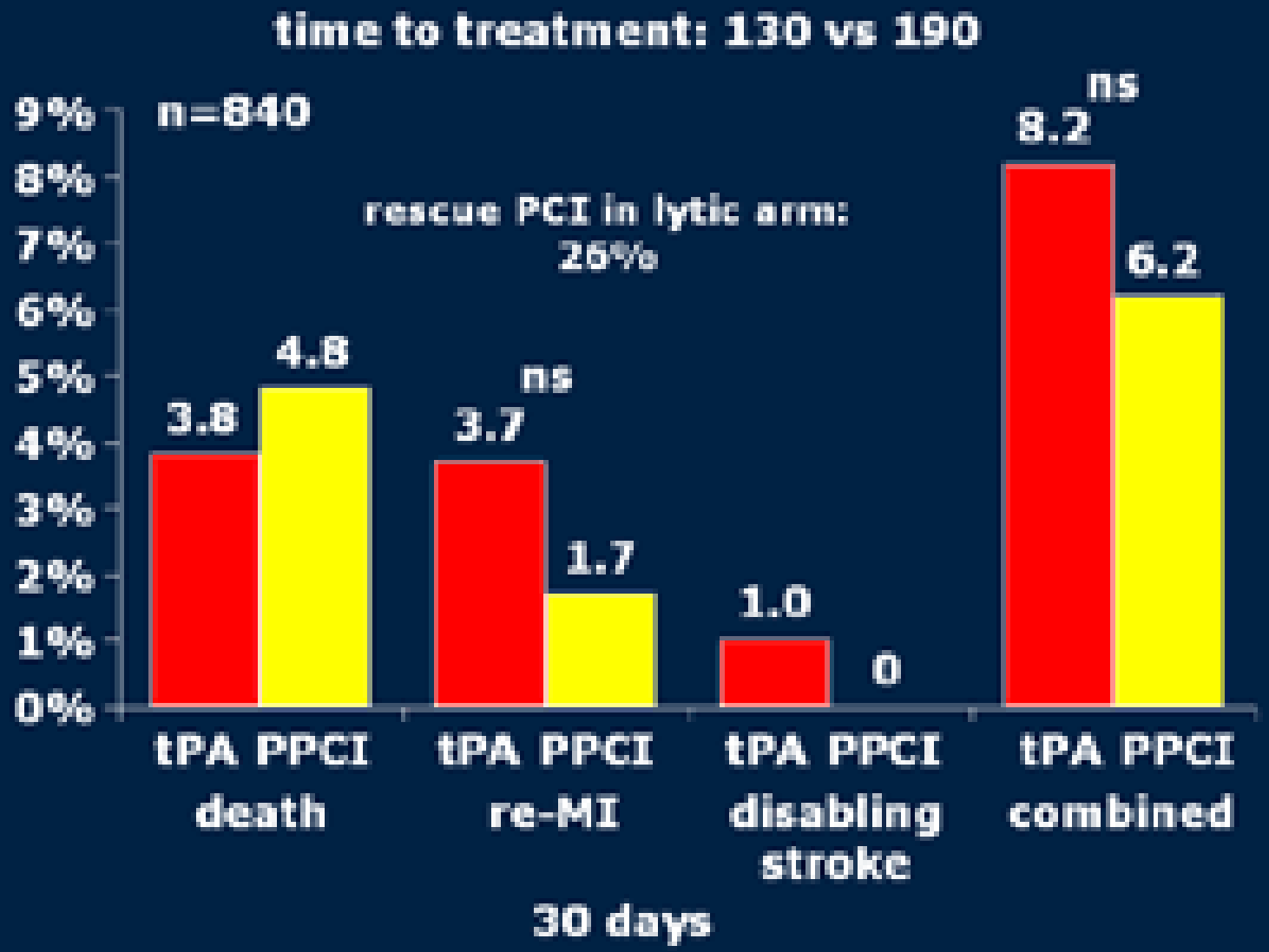
1200 ST elevation AMI patients

randomized, multicentered trial

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

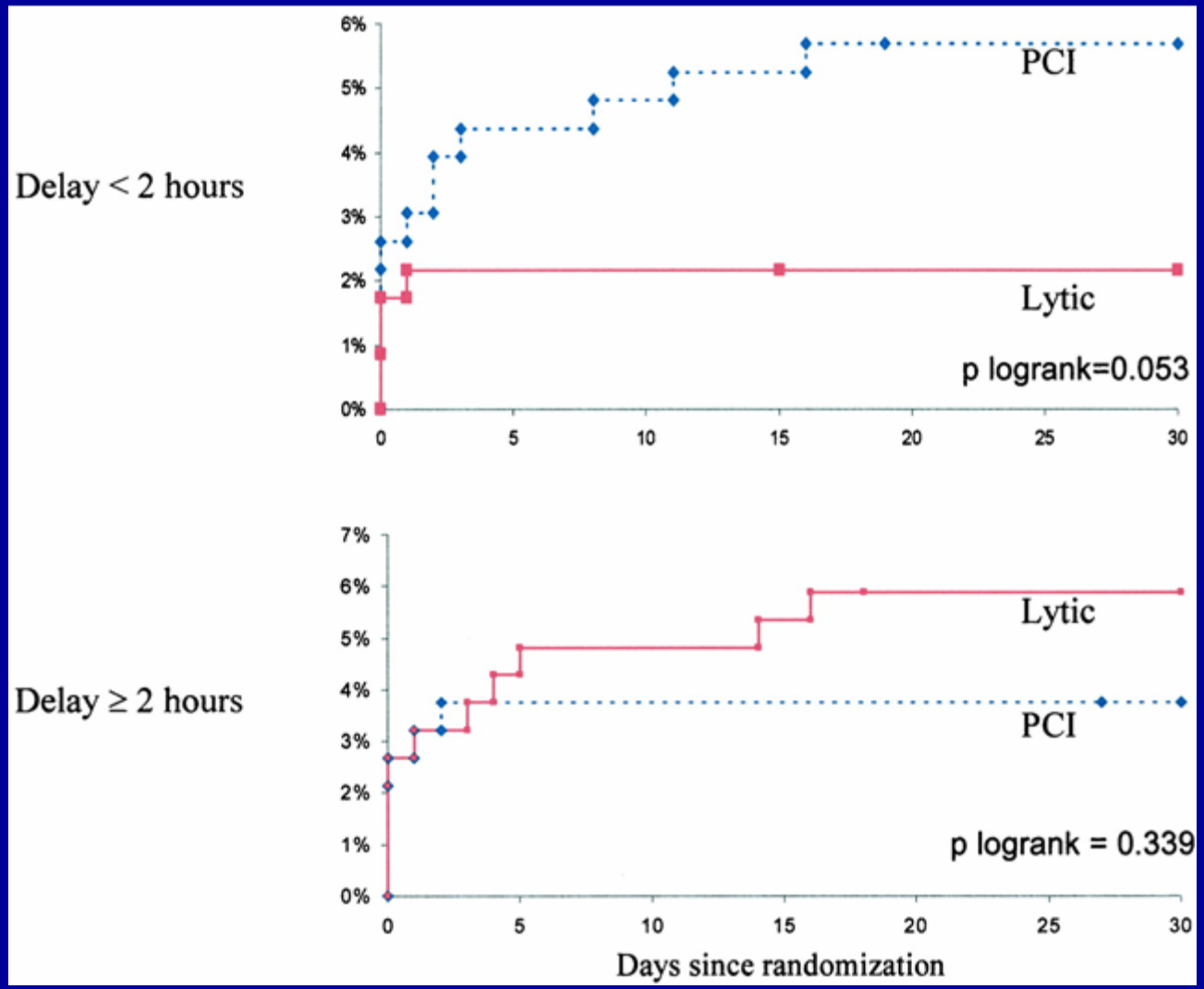
Bonnefoy E, et al. *Lancet* 2002;360(9336):825-9

CAPTIM primary endpoint



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

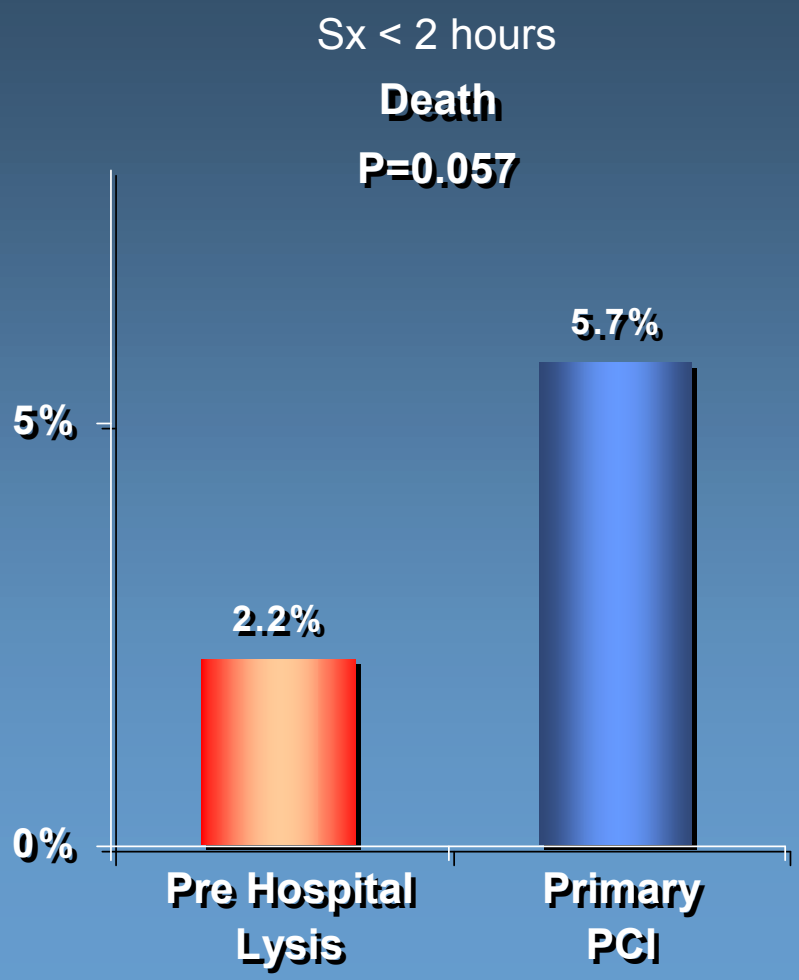
CAPTIM: TIME TO TREATMENT AND MORTALITY

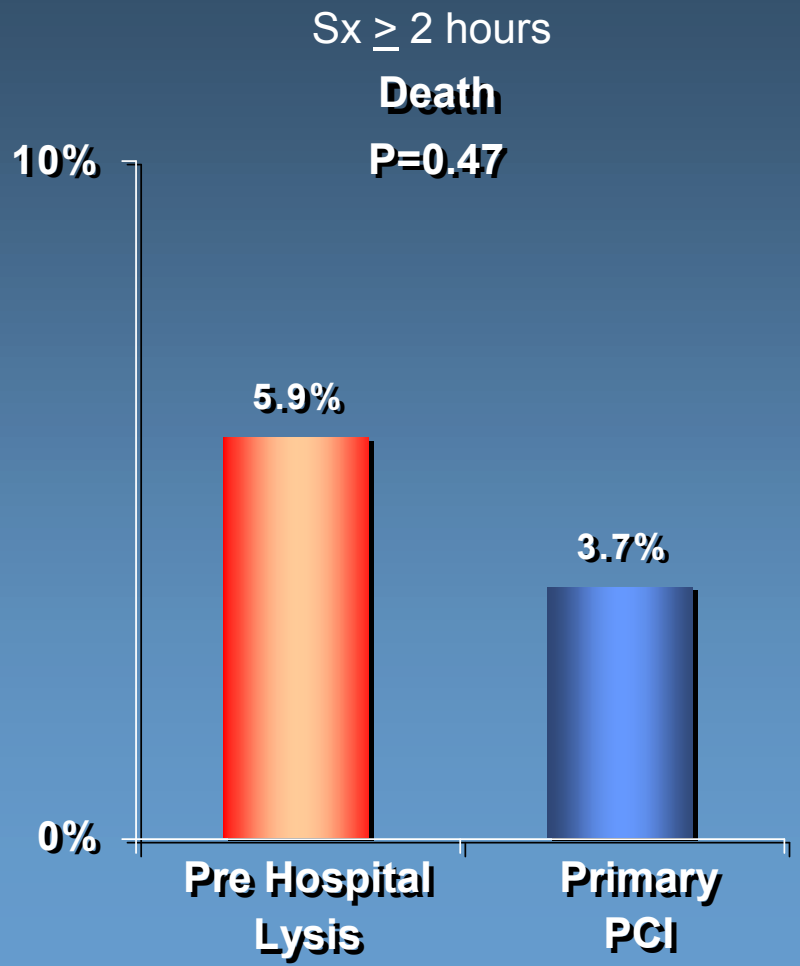


Steg, P. G. et al. Circulation 2003;108:2851-2856

Circulation

CAPTIM 1 Year Results

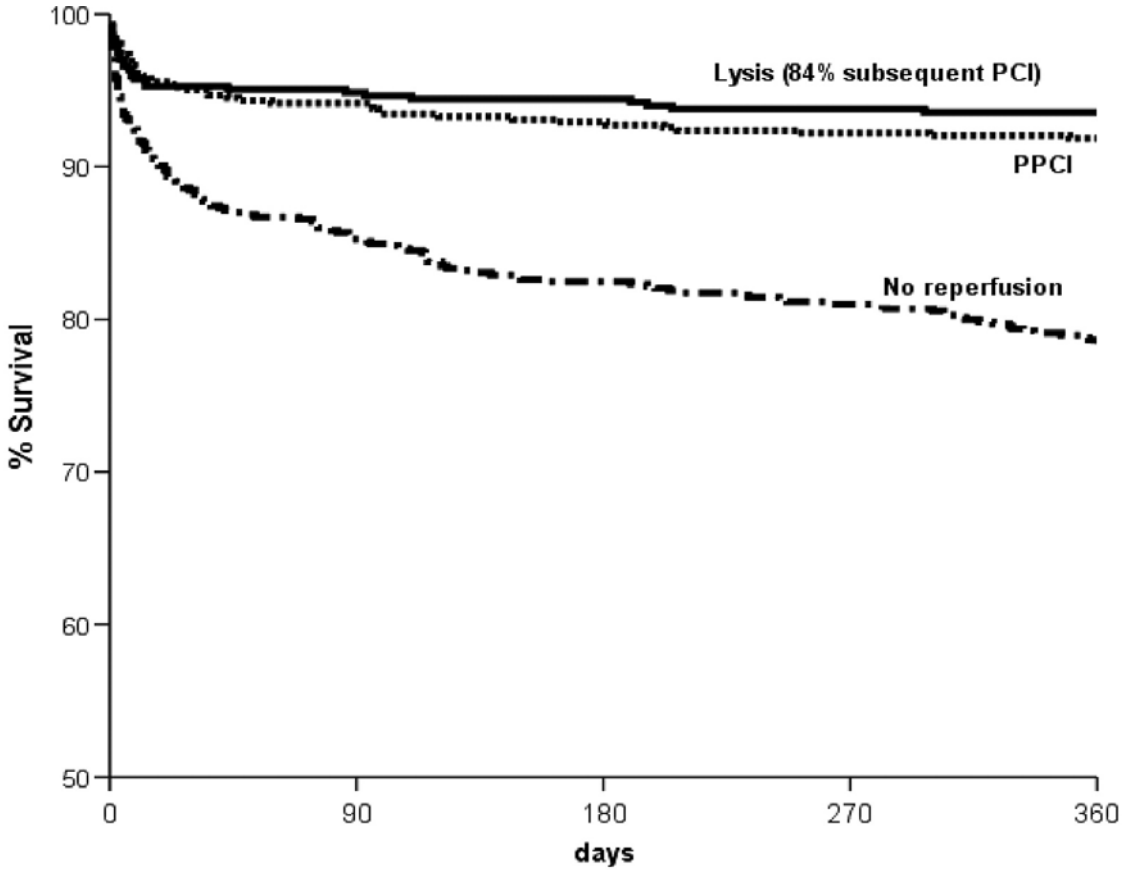




GW Symposium, AHA 2002

French FAST AMI registry:
One-year survival according to use and type of reperfusion therapy

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

Danchin, N. et al. Circulation 2008;118:268-276

Circulation

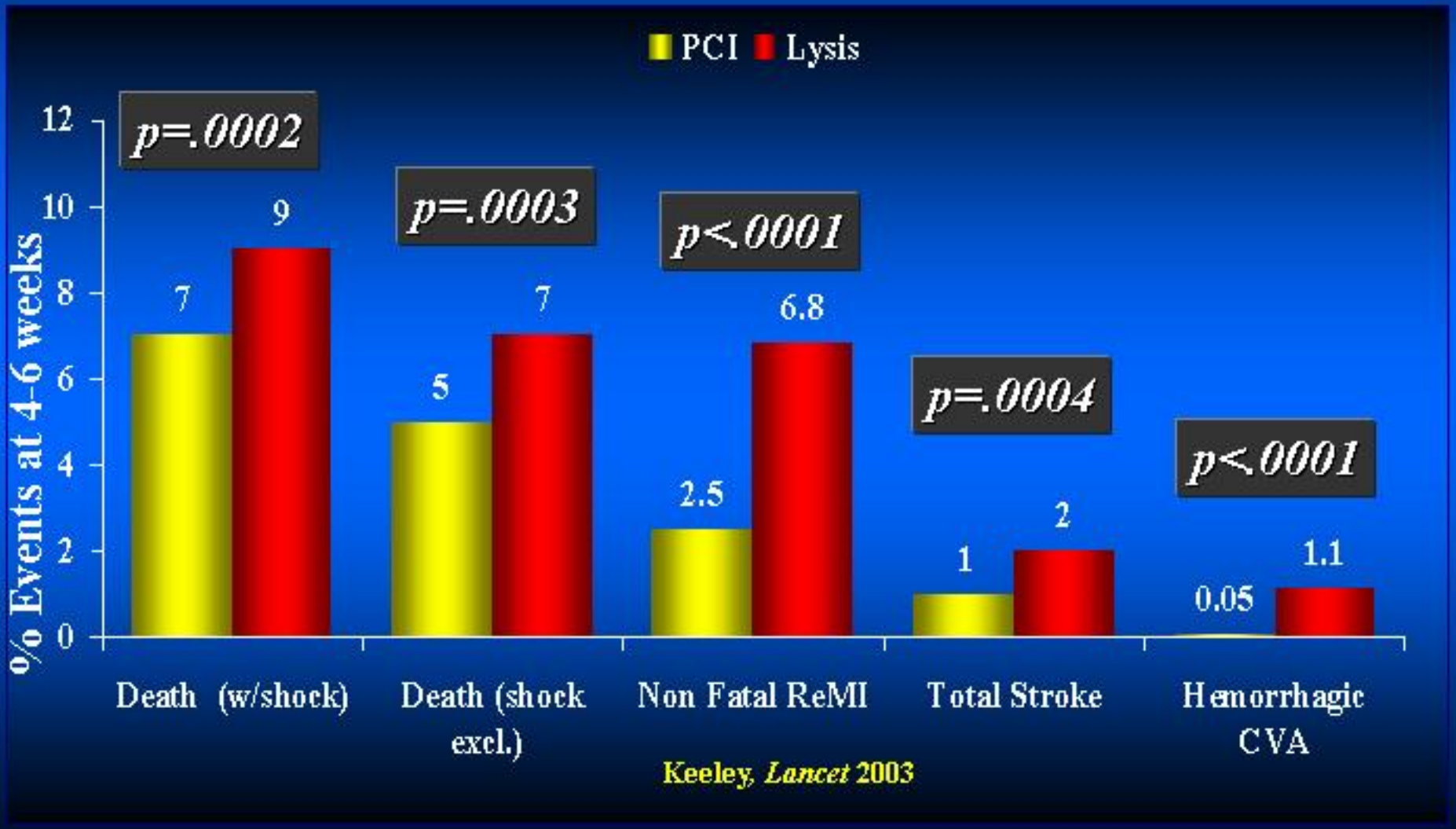
Conclusion

- **Pre-hospital lysis is as good as primary PCI, provided "rescue" procedures are available.**
- **In early comers, pre hospital lysis is probably better than primary PCI**

PCI and reperfusion strategies

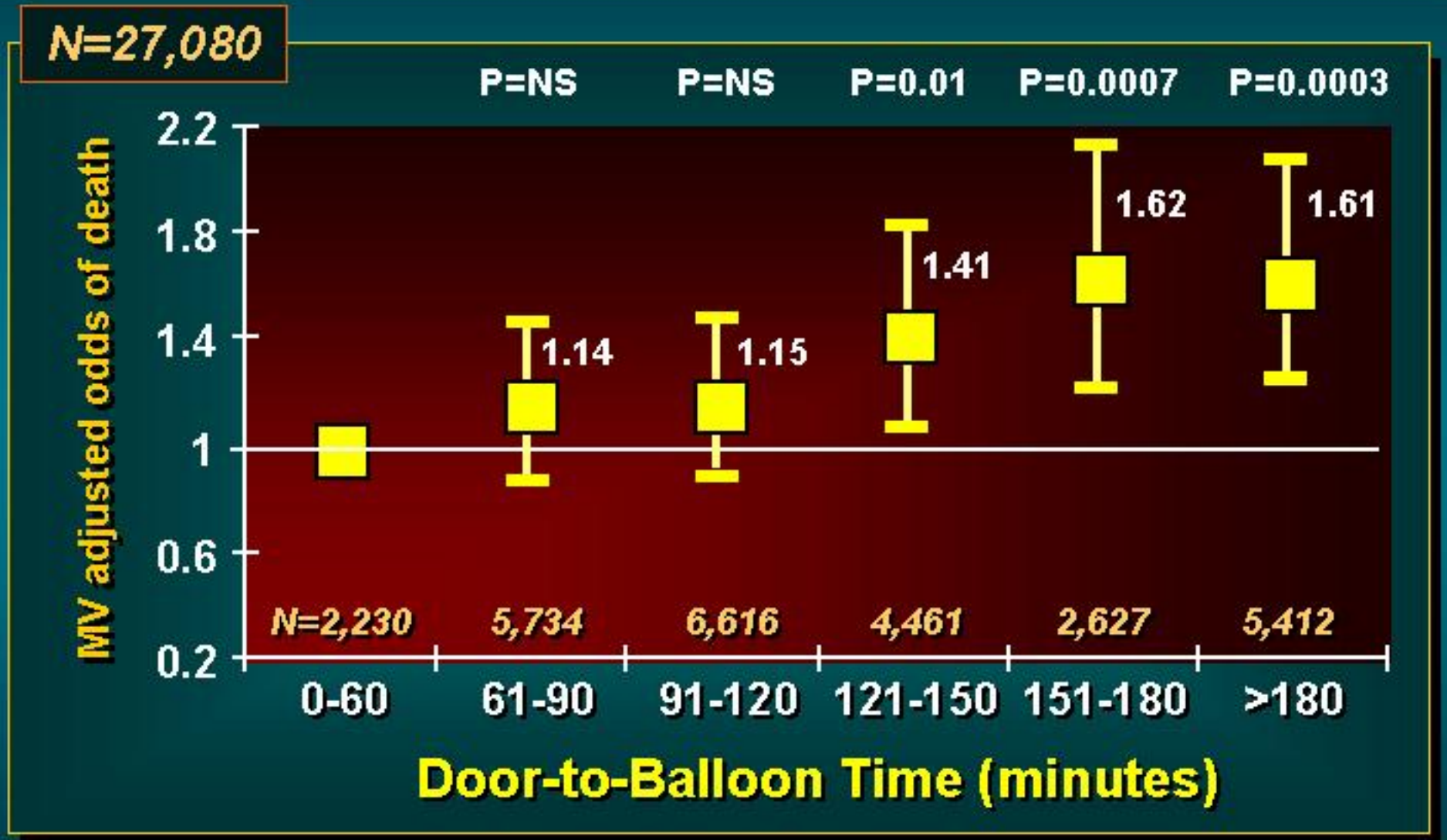
- **Primary PCI Vs. thrombolysis**
- **Transfer to primary PCI**
- **Facilitated primary PCI**
- **Rescue PCI for failed lysis**
- **Routine post lysis PCI**
- **Routine delayed PCI post non reperfused MI**

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

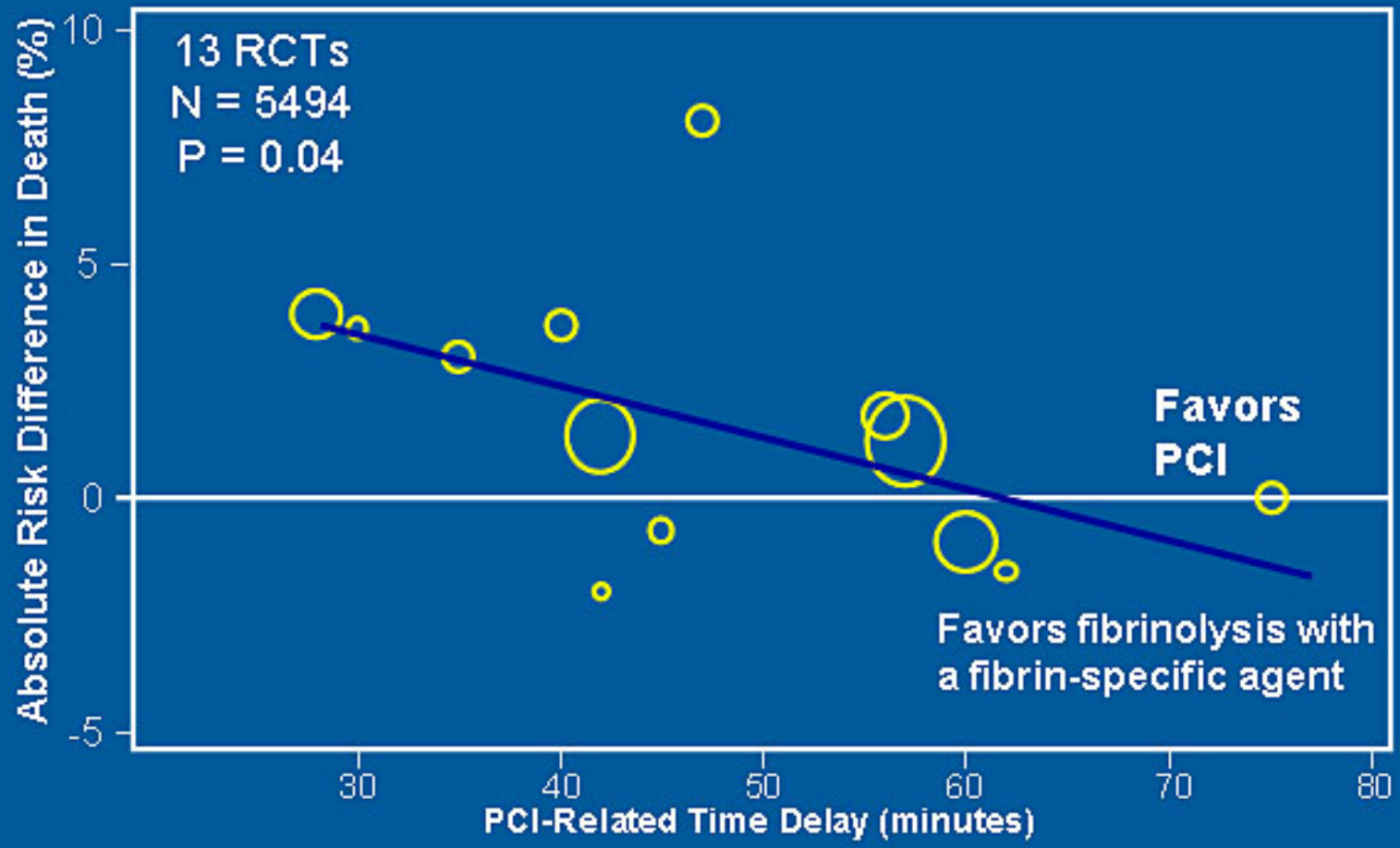


Keeley, *Lancet* 2003

NRMI-2 Primary PCI



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

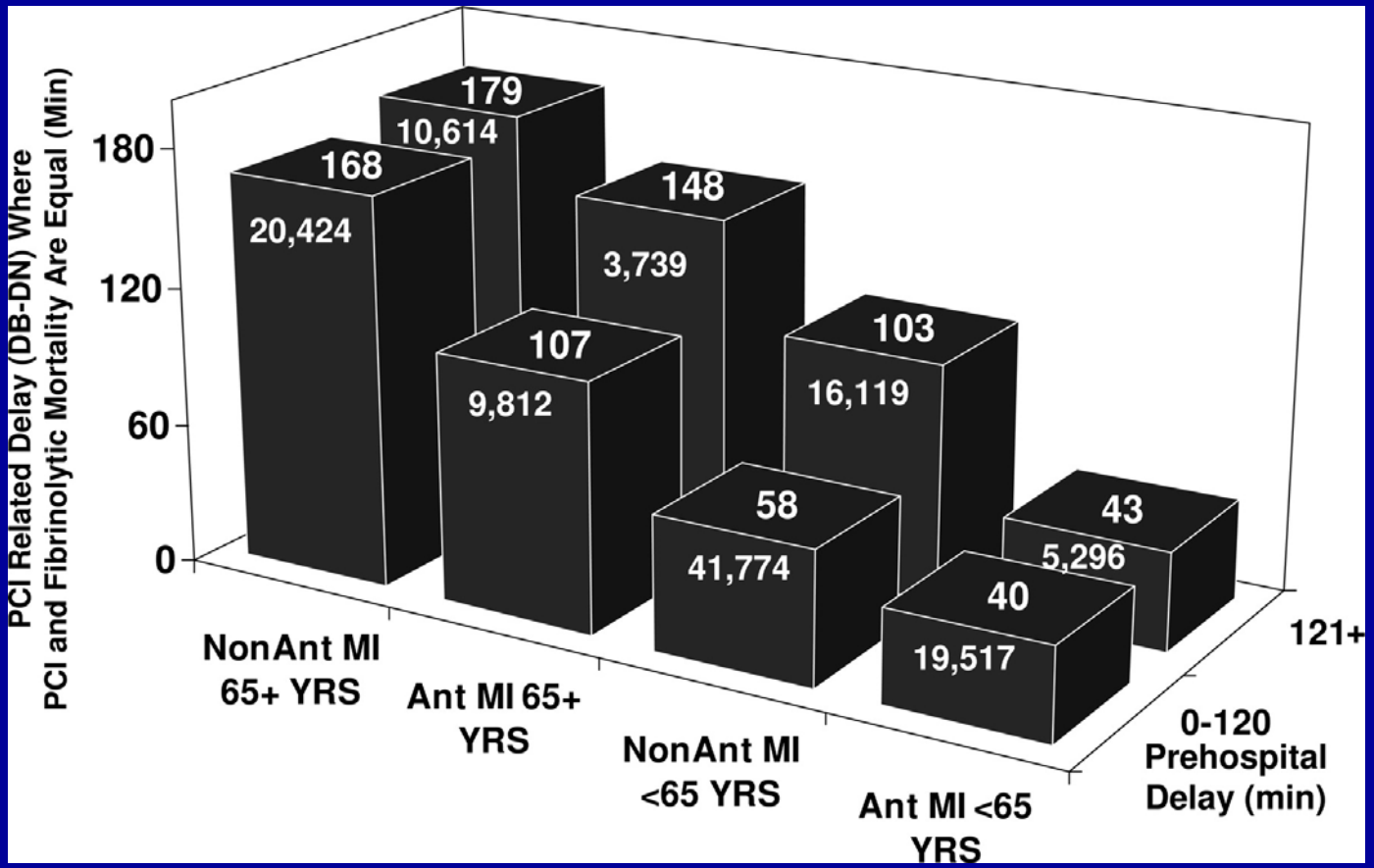


Nallamothu and Bates. Am J Cardiol 2003;92:824.

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

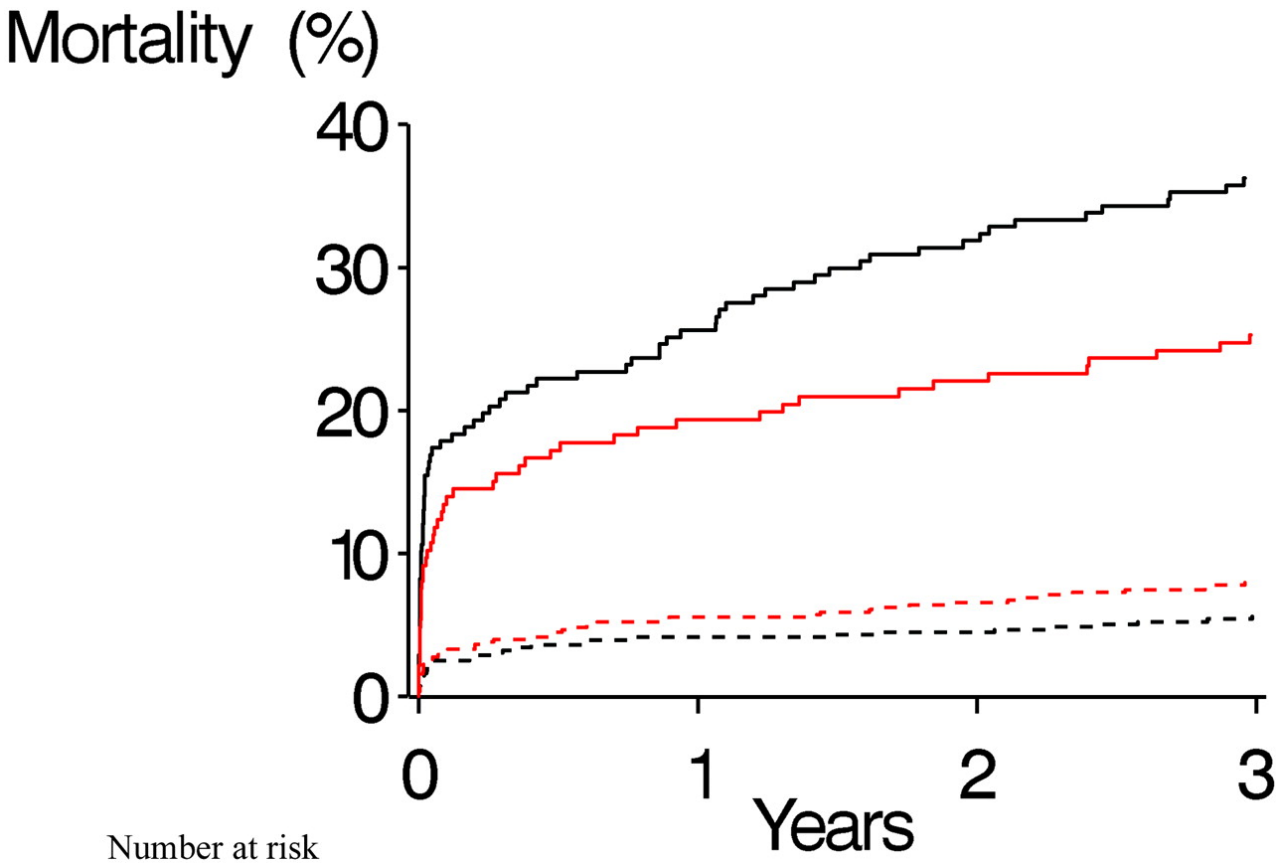
American Heart Association. Learn and Live.

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

DANAMI-2: Mortality rates for low-risk patients treated with fibrinolysis (Fx) (black dashed line) or primary angioplasty (PA) (red dashed line) and high-risk patients treated with fibrinolysis (black solid line) or primary angioplasty (red solid line)



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

Thune, J. J. et al. Circulation 2005;112:2017-2021

Circulation

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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REPERFUSION STRATEGIES – ESC GUIDELINES

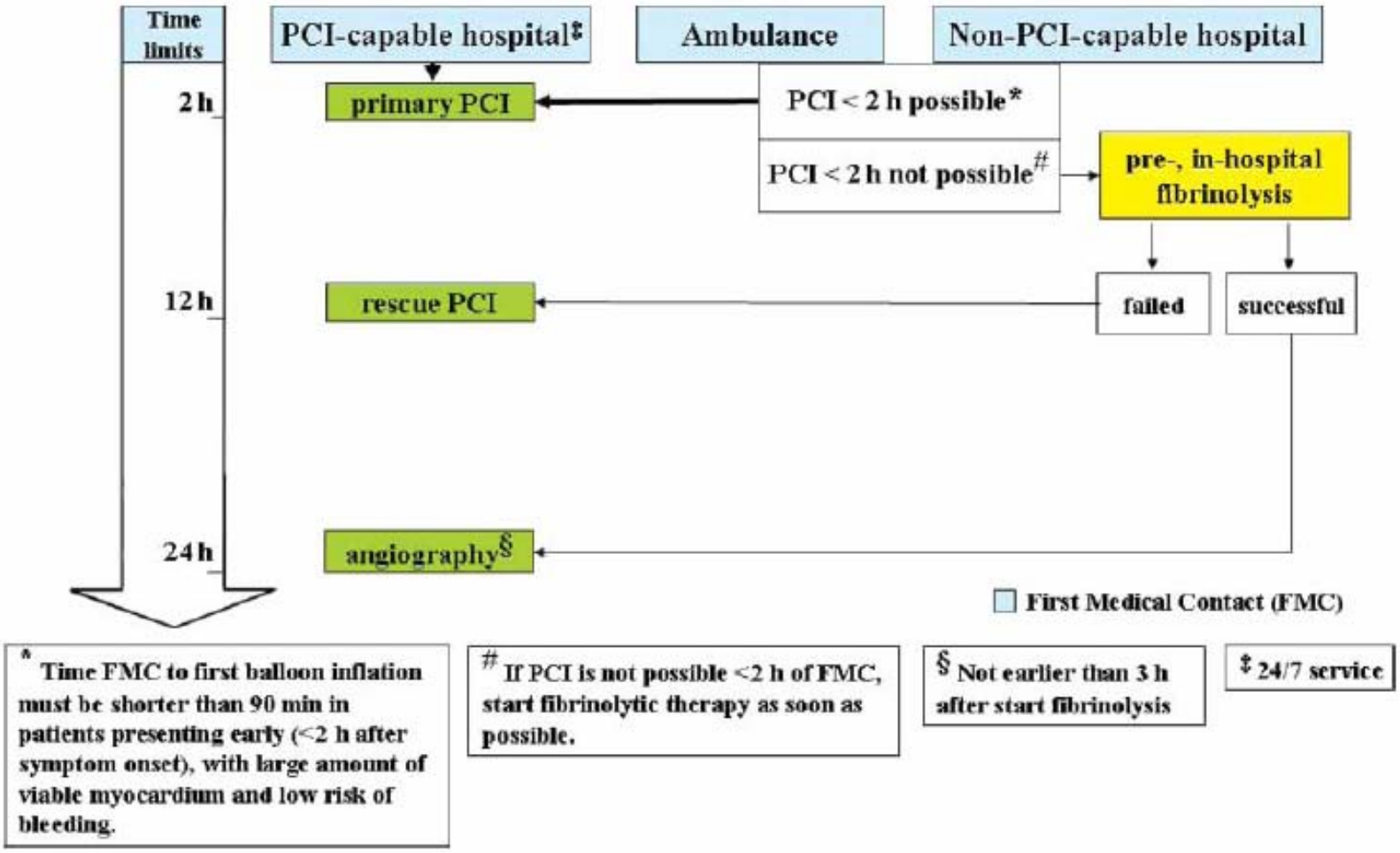
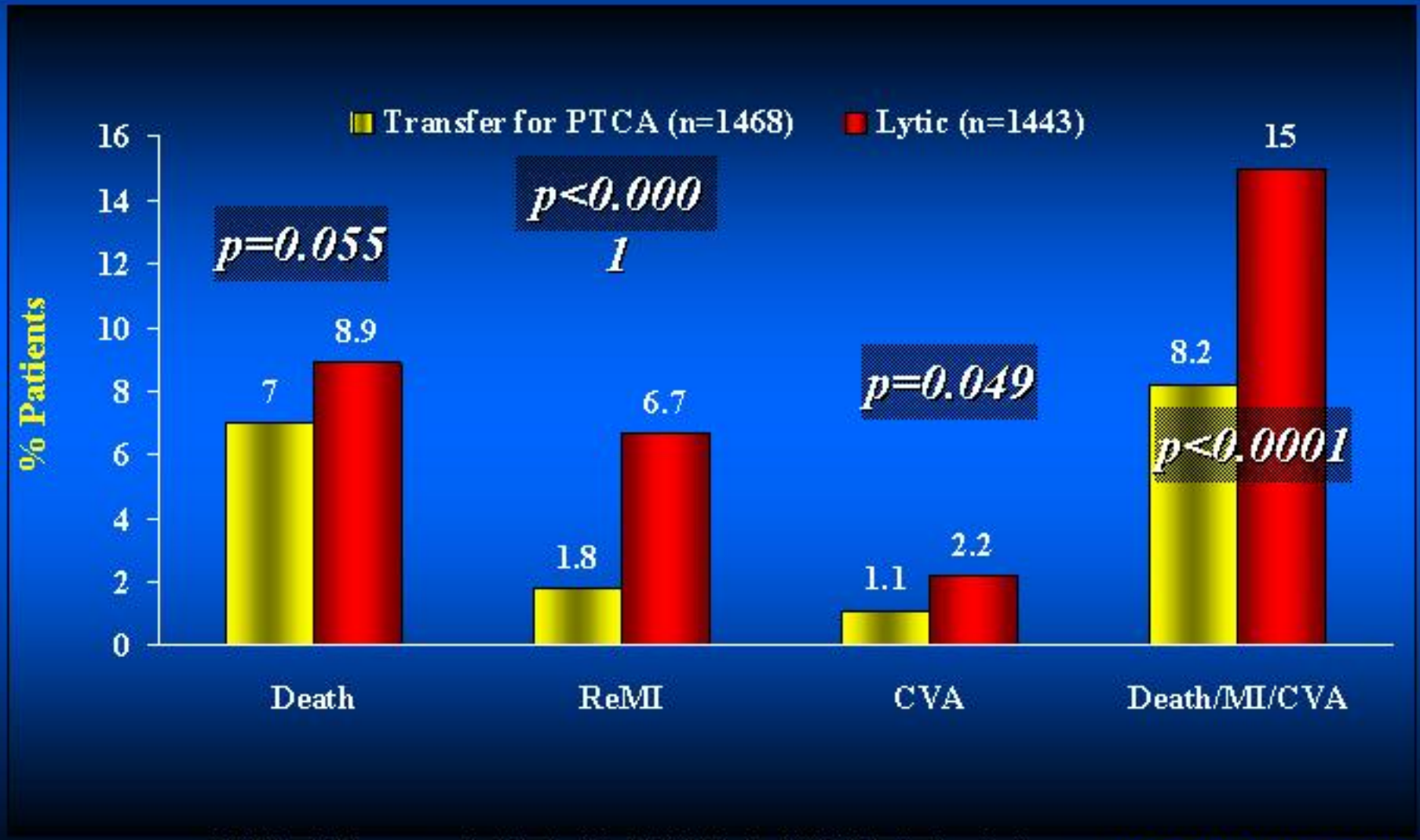


Table 13 Recommendations for reperfusion strategies in ST-segment elevation myocardial infarction patients

	Class[a]	Level[b]	Ref.[c]
Implementation of a well-functioning network based on pre-hospital diagnosis, and fast transport to the closest available primary PCI-capable centre is recommended.	I	A	74, 75
Primary PCI-capable centres should deliver 24 h per day/7 days per week on-call service, be able to start primary PCI as soon as possible and within 60 min from the initial call.	I	B	76, 82, 102–105
In case of fibrinolysis, pre-hospital initiation by properly equipped EMS should be considered and full dose administered.	IIa	A	81
With the exception of cardiogenic shock, PCI (whether primary, rescue, or post-fibrinolysis) should be limited to the culprit stenosis	IIa	B	96, 106, 107
In PCI-capable centres, unnecessary intermediate admissions to the emergency room or the intensive care unit should be avoided.	III	A	94, 108, 109
The systematic use of balloon counterpulsation, in the absence of haemodynamic impairment, is not recommended.	III	B	96, 97

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

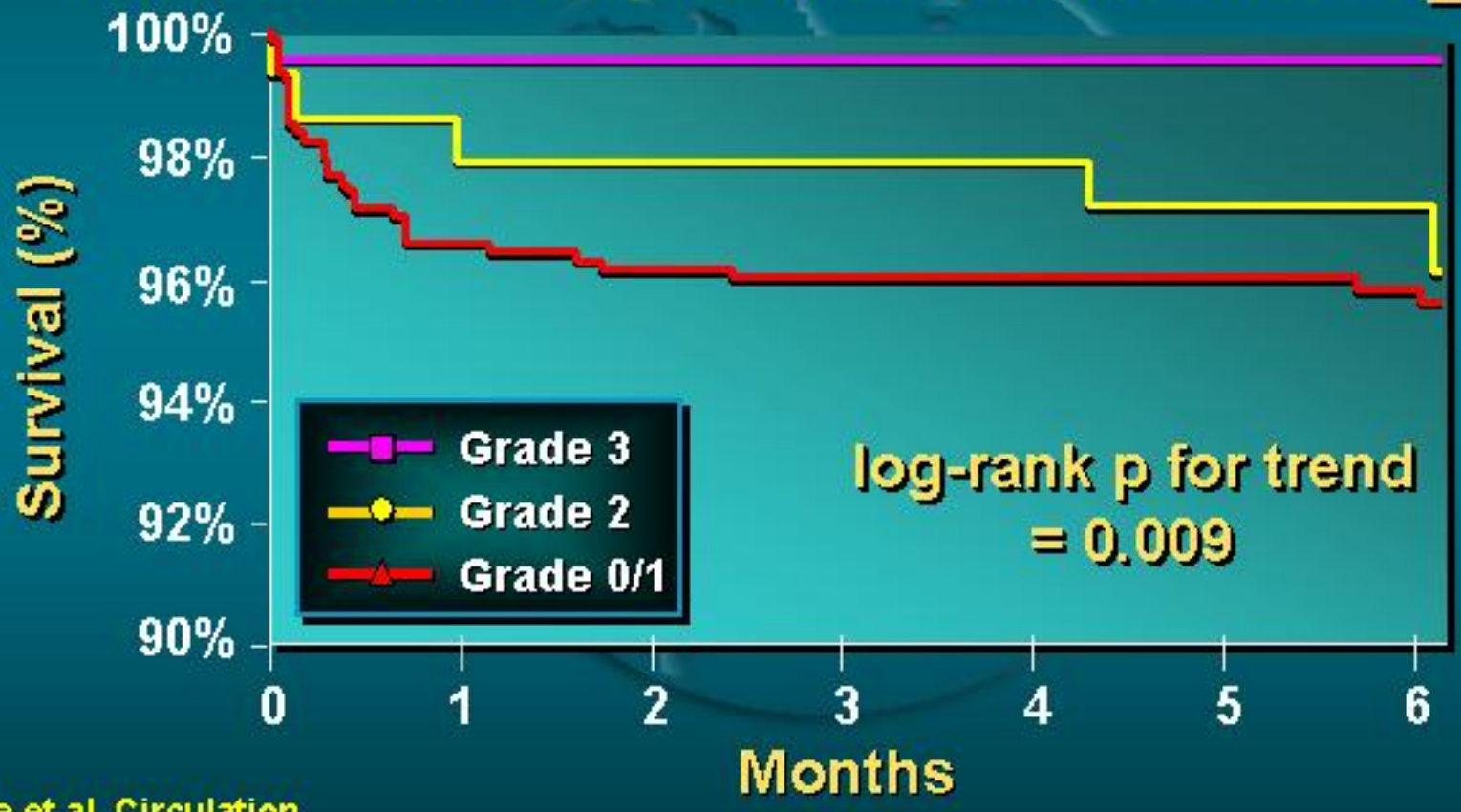
Relationship between delay in transferring patients for primary PCI and one-year mortality

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.

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

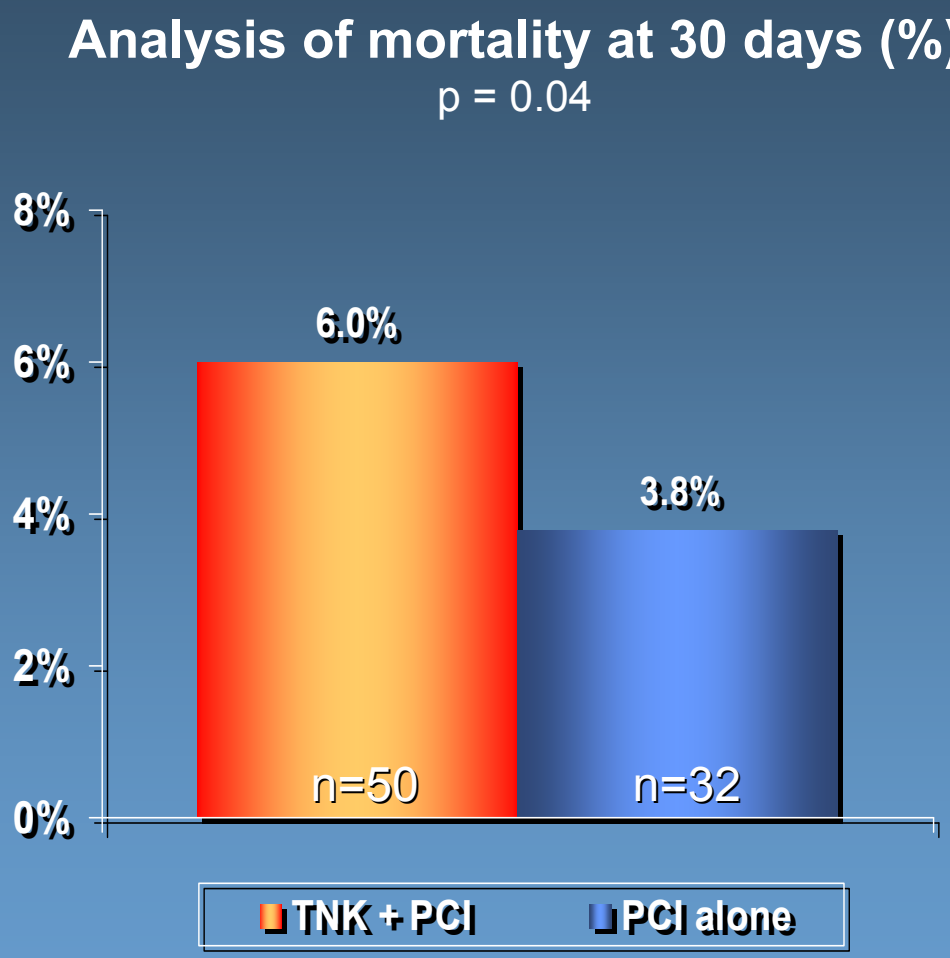
Full-dose TNK + Primary PCI
60 IU/kg, maximum 4000 IU
n=829
GP IIb/IIIa inhibitors allowed only for bail out use

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: Mortality at 30 days



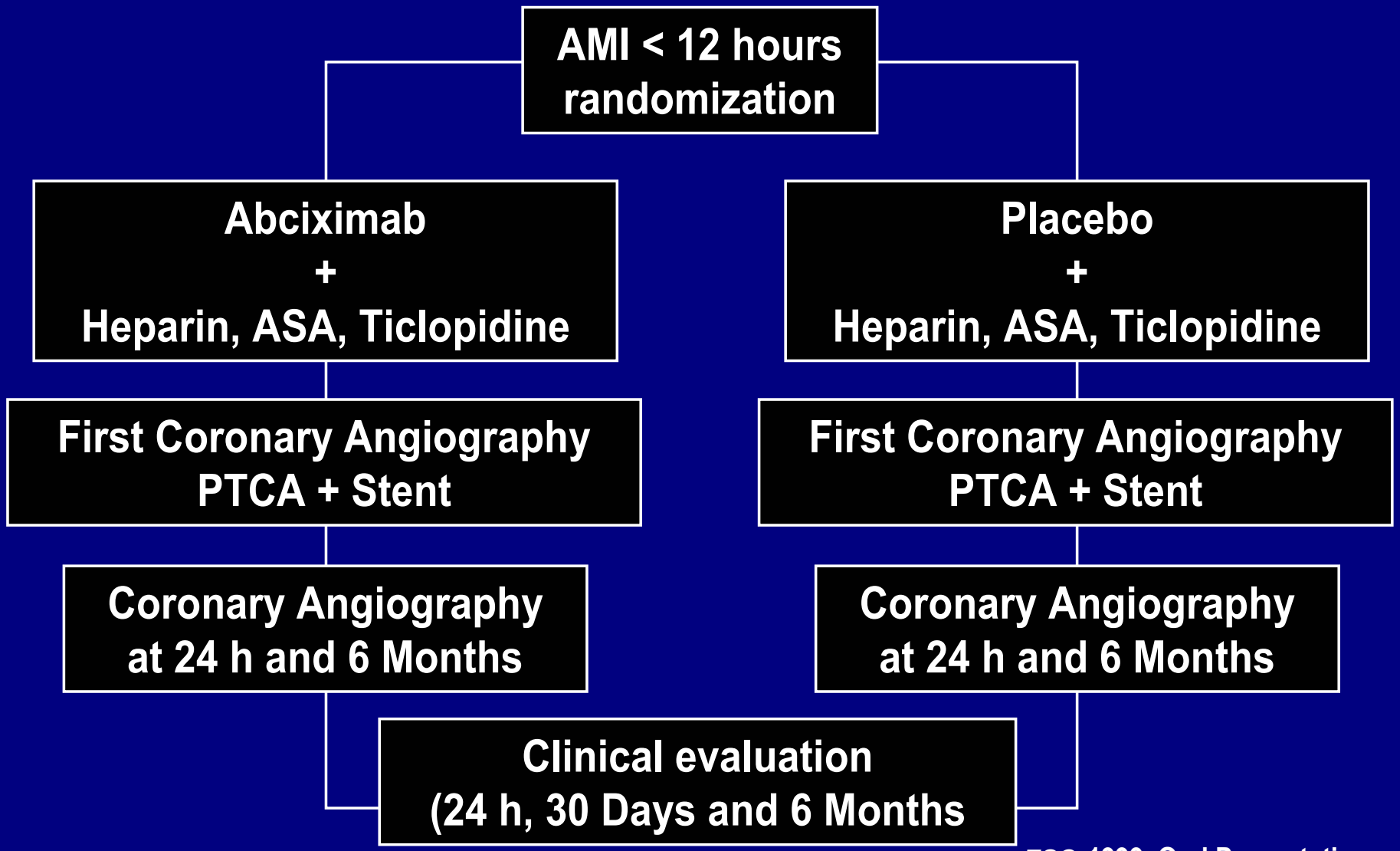
- The primary endpoint of mortality was higher in the TNK + PCI treatment group compared with the PCI alone group (6.0% vs 3.8%, p=0.04) at 30 days

Presented at ESC 2005

FACILITATION BY IIb/IIIa ANTAGONISTS

ADMIRAL

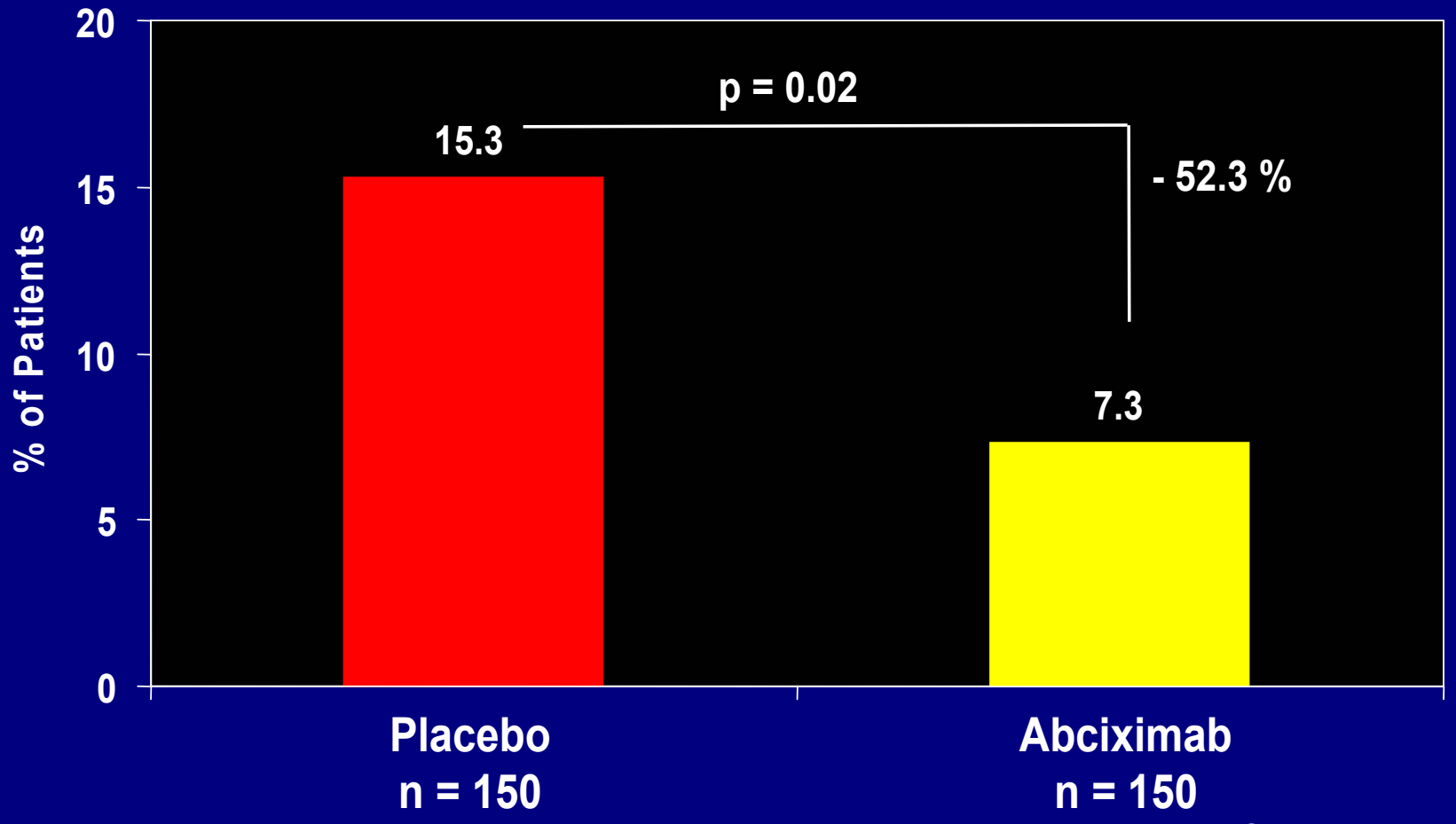
Design



ESC 1999, Oral Presentation

Primary Endpoint (30 days)

Death, Recurrent MI, Urgent TVR



ESC 1999, Oral Presentation

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

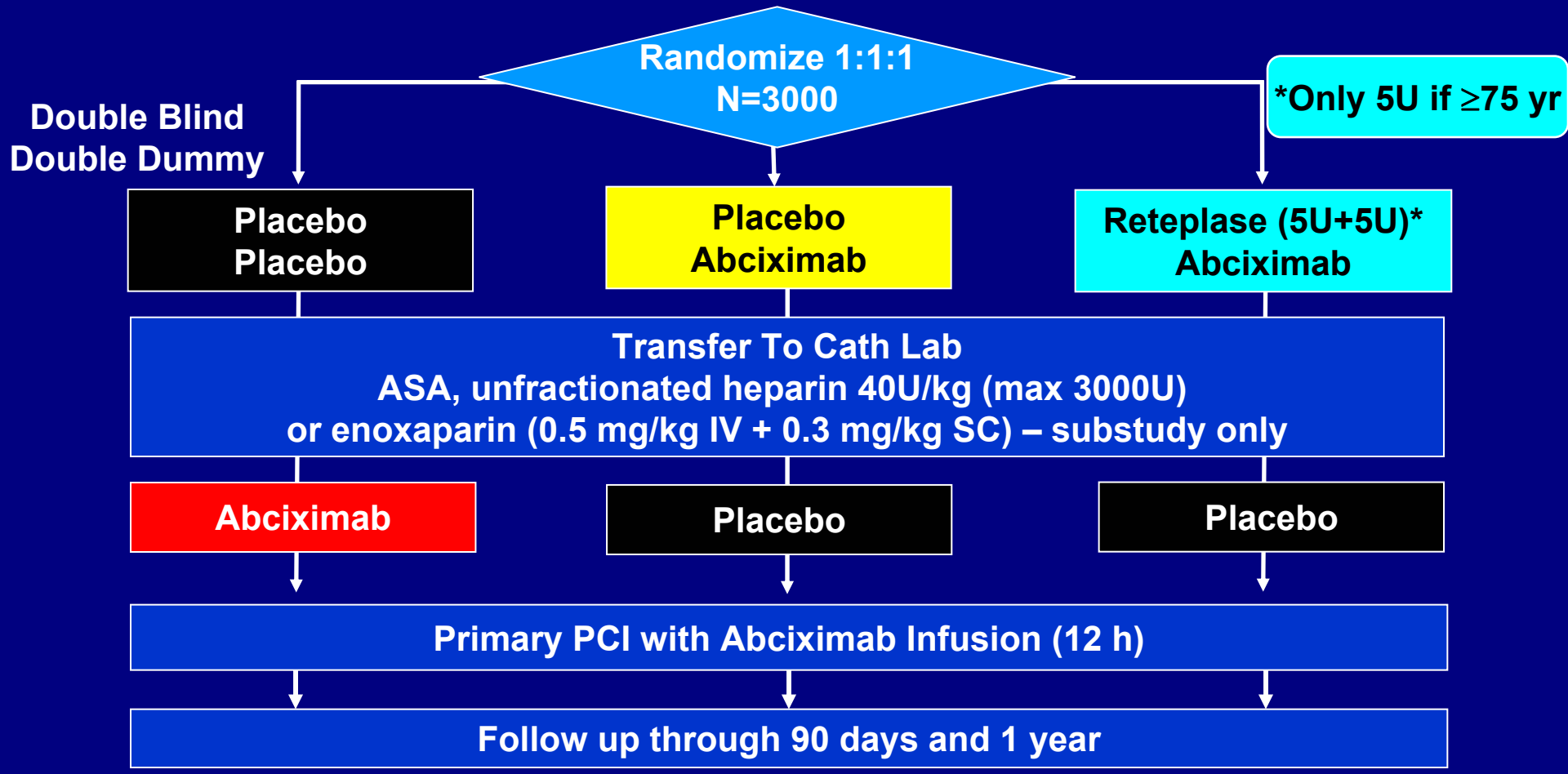
AHA 2007

Conflicts: research grant Centocor/Lilly/Cordis

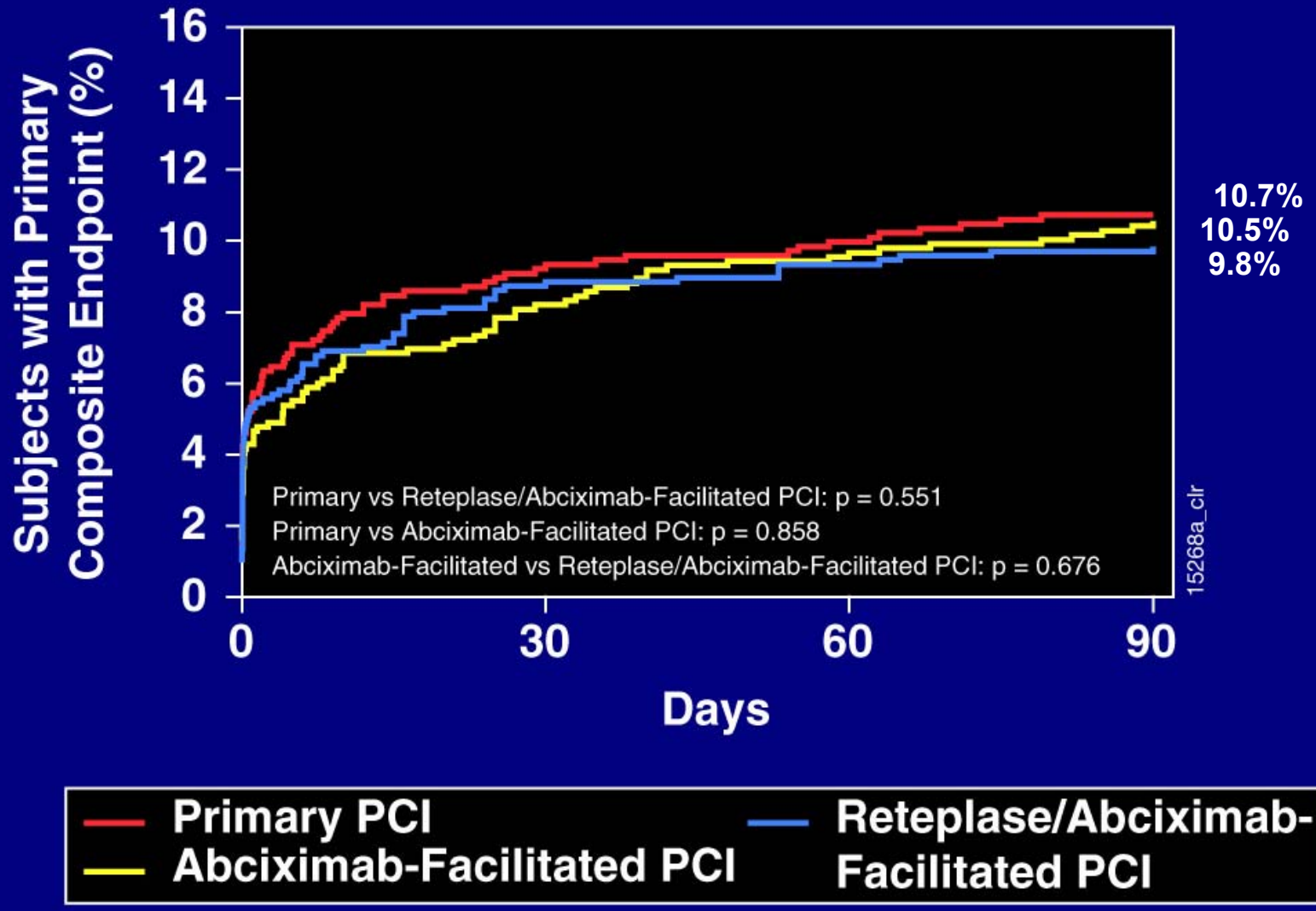
FINESSE: Study Design

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

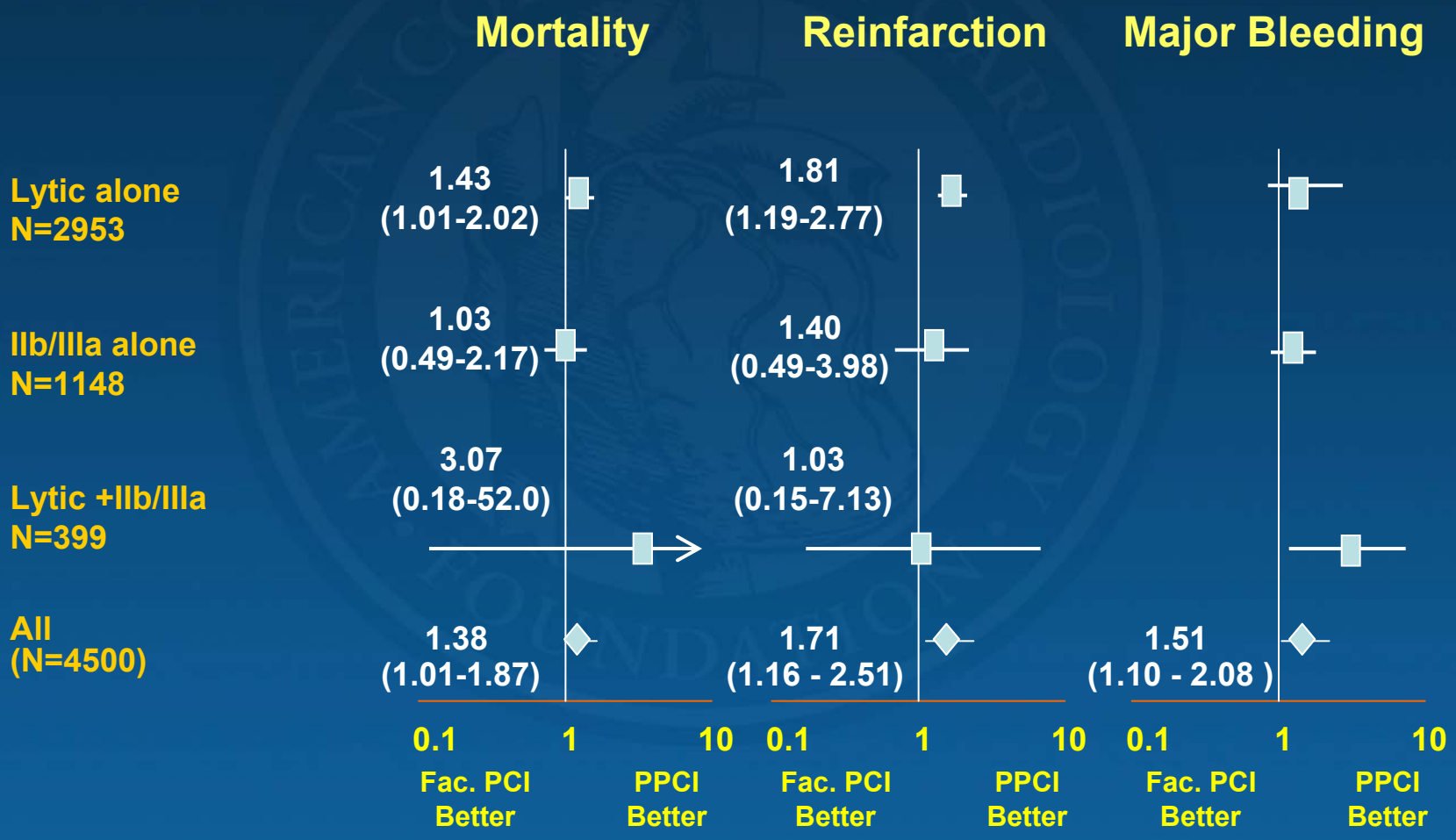
Presenting at Hub or Spoke with estimated time to Cath between 1 and 4 hours



Primary Endpoint



Meta-analysis: Facilitated PCI vs Primary PCI



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

ACC/AHA 2007 STEMI Guidelin

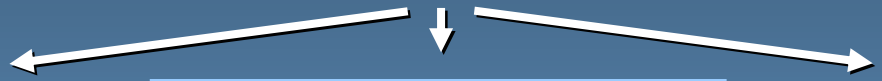
Conclusions

- 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

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

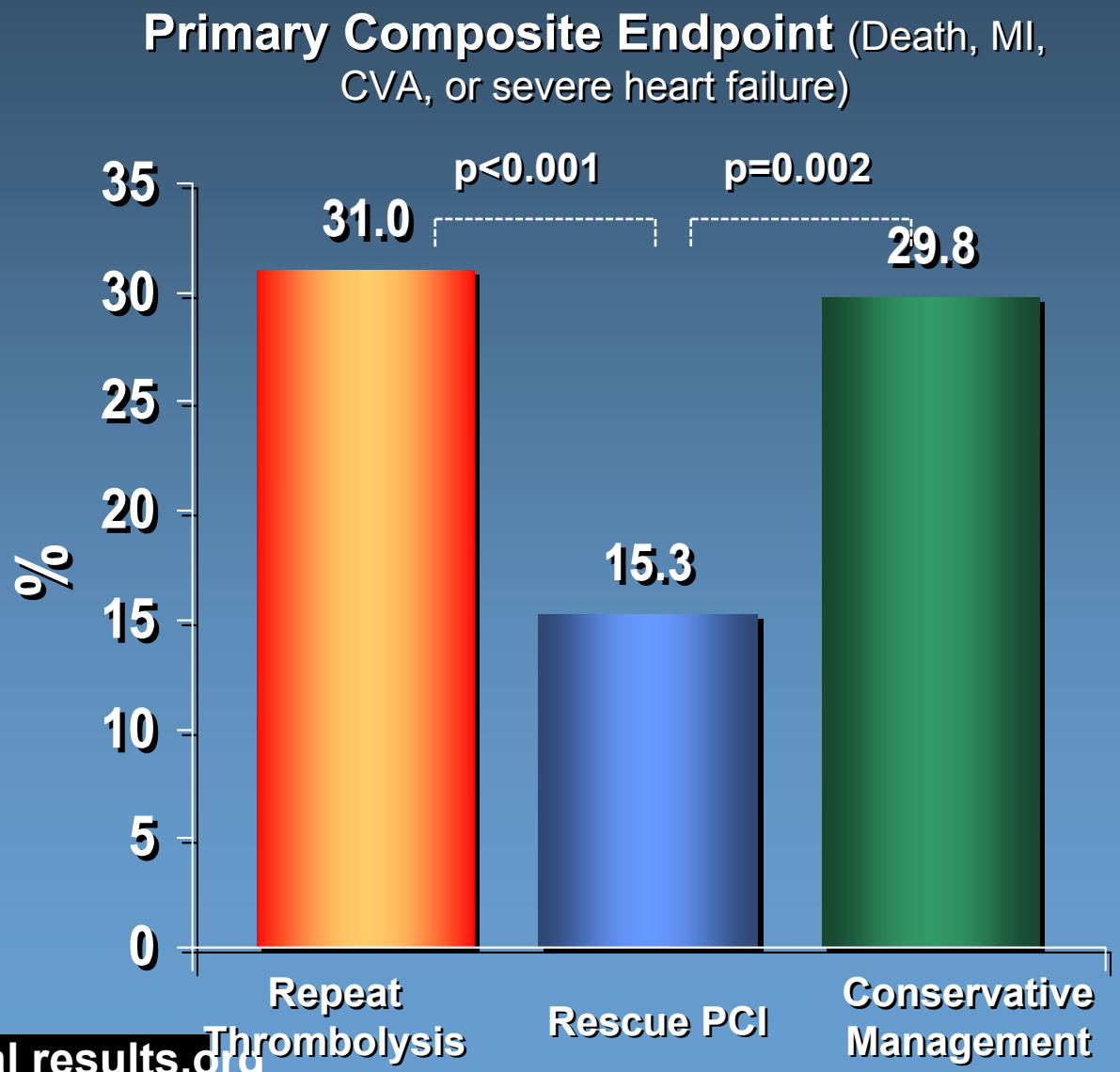
n=141

Primary Endpoint:

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

Presented at AHA 2004

REACT: 6 month results



Transfer AMI

'High Risk' ST Elevation MI within 12 hours of symptom onset

TNK + ASA + Heparin / Enoxaparin + Clopidogrel

Community Hospital Emergency Department

"Pharmacoinvasive Strategy"
Urgent Transfer to PCI Centre

"Standard Treatment"

Assess chest pain, ST↑ resolution at 60-90 minutes after randomization

Failed Reperfusion*

Successful Reperfusion

PCI Centre Cath Lab

Cath / PCI within 6 hrs regardless of reperfusion status

Cath and Rescue PCI ± GP IIb/IIIa Inhibitor

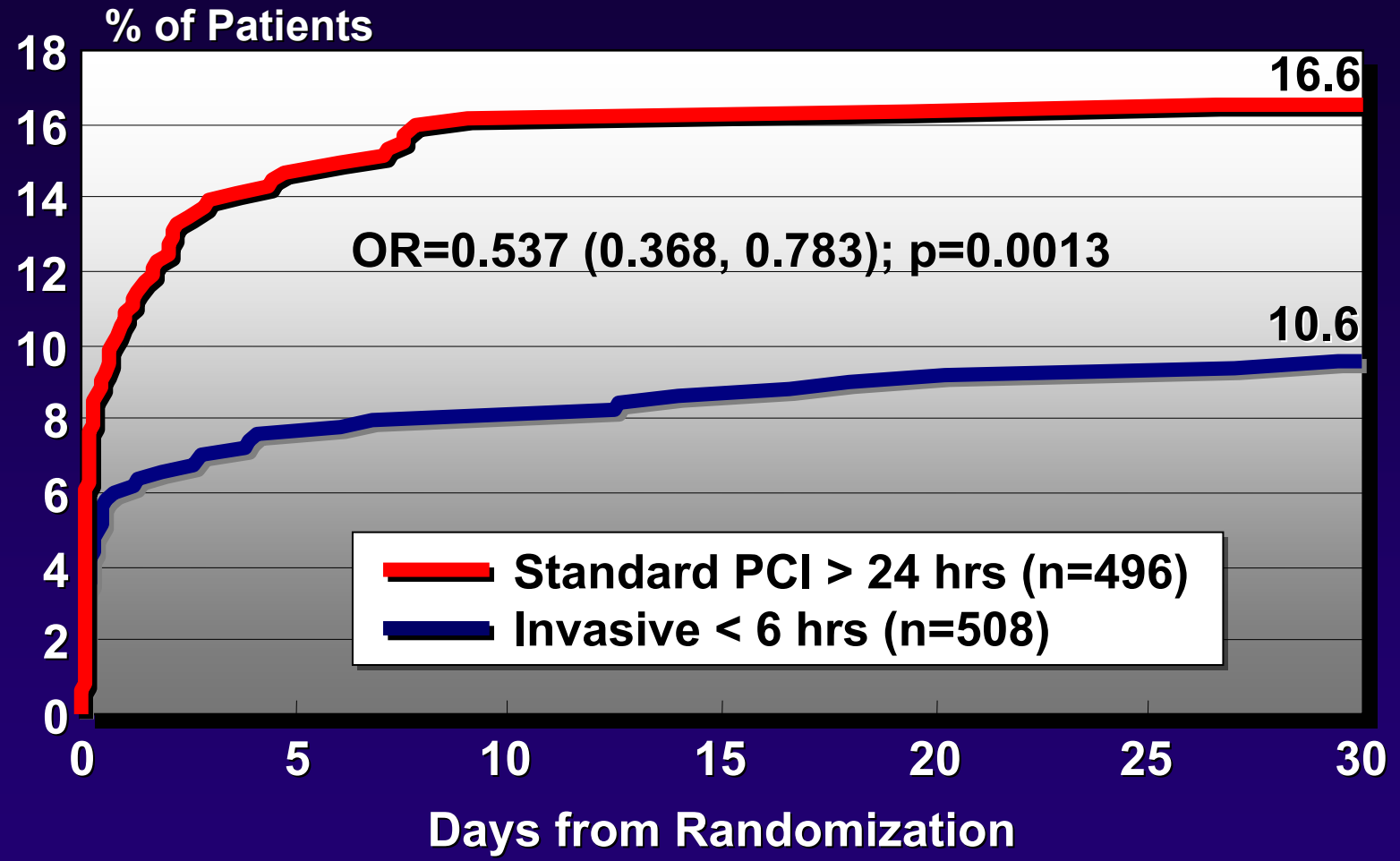
Elective Cath ± PCI > 24 hrs later

Repatriation of stable patients within 24 hrs of PCI

* ST segment resolution < 50% & persistent chest pain, or hemodynamic instability

Randomization stratified by age (≤75 vs. > 75) and by enrolling site

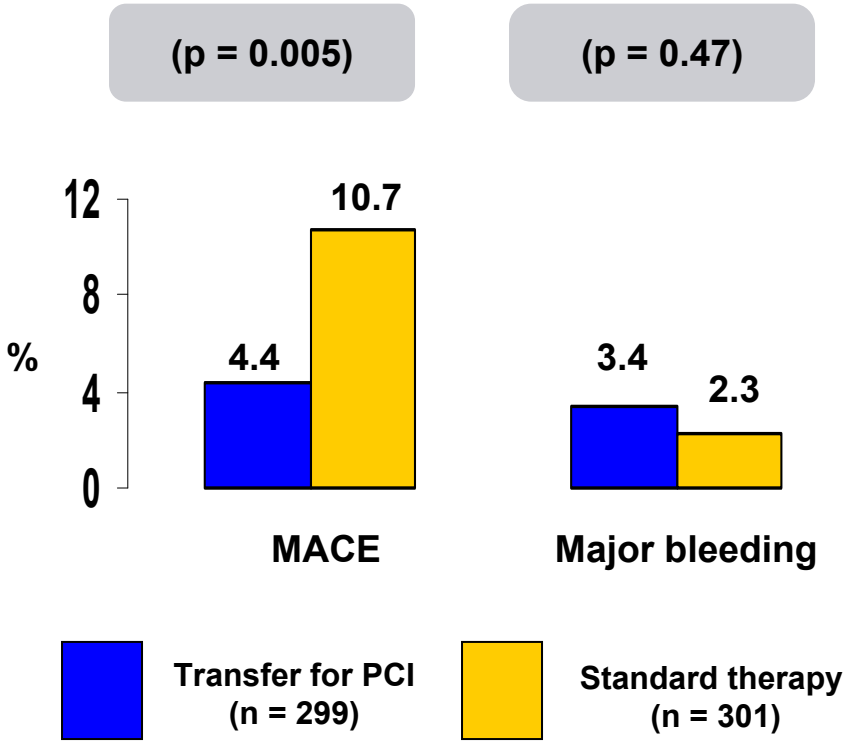
Primary Endpoint: 30-Day Death, re-MI, CHF, Severe Recurrent Ischemia, Shock



n=496	422	415	415	414	414	412
n=508	468	466	463	461	460	457

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

Benefit driven by reduction in refractory ischemia

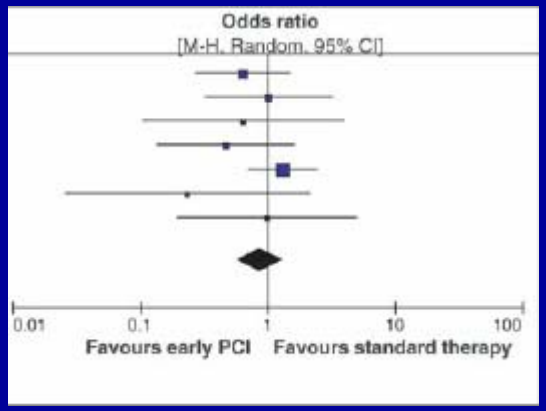
Di Mario C, et al. Lancet 2008;371:559-68

European Heart Journal (2010) **31**, 2156–2169
doi:10.1093/eurheartj/ehq204

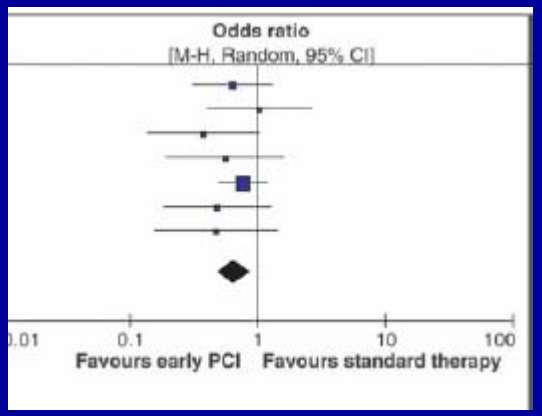
CLINICAL RESEARCH
Interventional cardiology

Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis

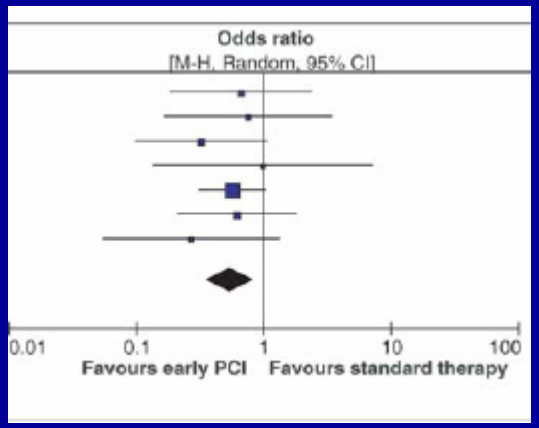
Death



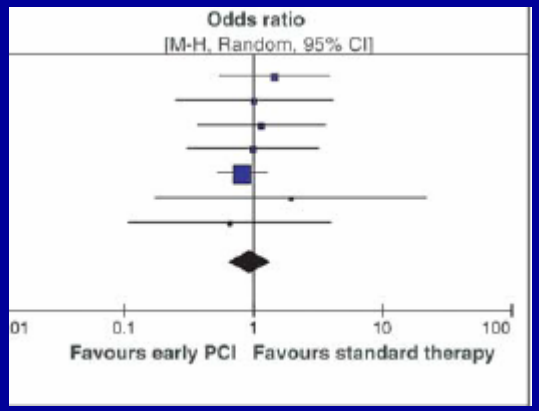
Death/MI



MI



Major bleeding



OAT Trial: Study Design

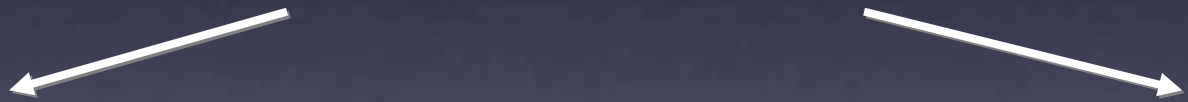
2166 patients with angiography on day 3-28 post-MI revealing total occlusion of the infarct-related artery with poor or absent antegrade flow (TIMI flow grade 0 or 1); and meeting a criterion for increased risk, defined as ejection fraction <50%, proximal occlusion of a major epicardial vessel with a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

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

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



PCI with stenting
n=1082

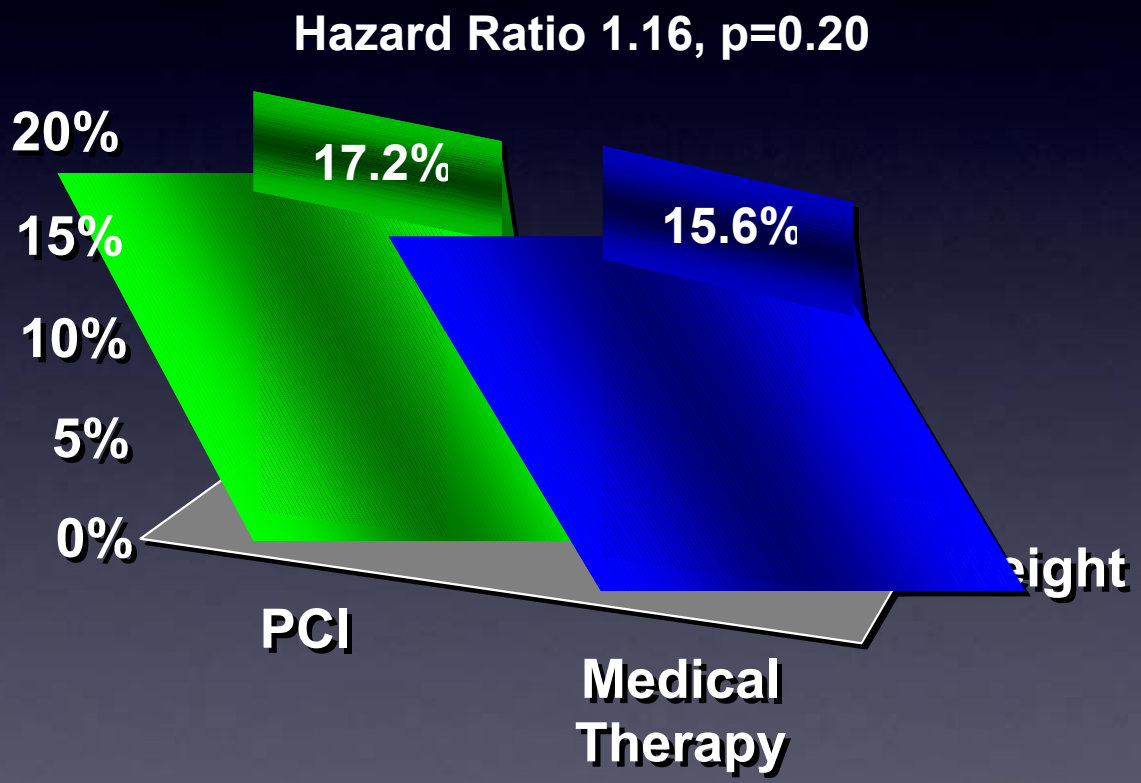
Medical Therapy
n=1084

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

Presented at AHA 2006

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).

Presented at AHA 2006

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.

Presented at AHA 2006

ESC Guidelines

Table 11 Angiography during hospital stay after fibrinolytic therapy and in patients who did not receive reperfusion therapy

Recommendations	Class[a]	Level[b]
Evidence of failed fibrinolysis or uncertainty about success: immediate	IIa	B
Recurrent ischaemia, reocclusion after initial successful fibrinolysis: immediate	I	B
Evidence of successful fibrinolysis: within 3–24 h after start of fibrinolytic therapy	IIa	A
In unstable patients who did not receive reperfusion therapy: immediate	I	C
In stable patients who did not receive reperfusion therapy: before discharge	IIb	C

Table 14 Recommendations for percutaneous coronary intervention in ST-segment elevation myocardial infarction

Indication	Time from FMC	Class[a]	Level[b]	Ref.[c]
Primary PCI				
Is recommended in patients with chest pain/discomfort <12 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible and at any rate <2 h from FMC[d]	I	A	83, 84, 94
Should be considered in patients with ongoing chest pain/discomfort >12 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible	IIa	C	—
May be considered in patients with history of chest pain/discomfort >12 h and <24 h + persistent ST-segment elevation or previously undocumented left bundle branch block.	As soon as possible	IIb	B	88, 89
PCI after fibrinolysis				
Routine urgent PCI is indicated after successful fibrinolysis (resolved chest pain/ discomfort and ST-segment elevation).	Within 24 h[e]	I	A	77–79
Rescue PCI should be considered in patients with failed fibrinolysis.	As soon as possible	IIa	A	80, 87
Elective PCI/CABG				
Is indicated after documentation of angina/positive provocative tests.	Evaluation prior to hospital discharge	I	B	36, 41–43
Not recommended in patients with fully developed Q wave MI and no further symptoms/ signs of ischaemia or evidence of viability in the infarct related territory.	Patient referred >24 h	III	B	90, 91

[e]In order to reduce delay for patients with no reperfusion, transfer to PCI centre of all post-fibrinolysis patients is recommended.

PHARMACOLOGIC SUPPORT OF PCI:

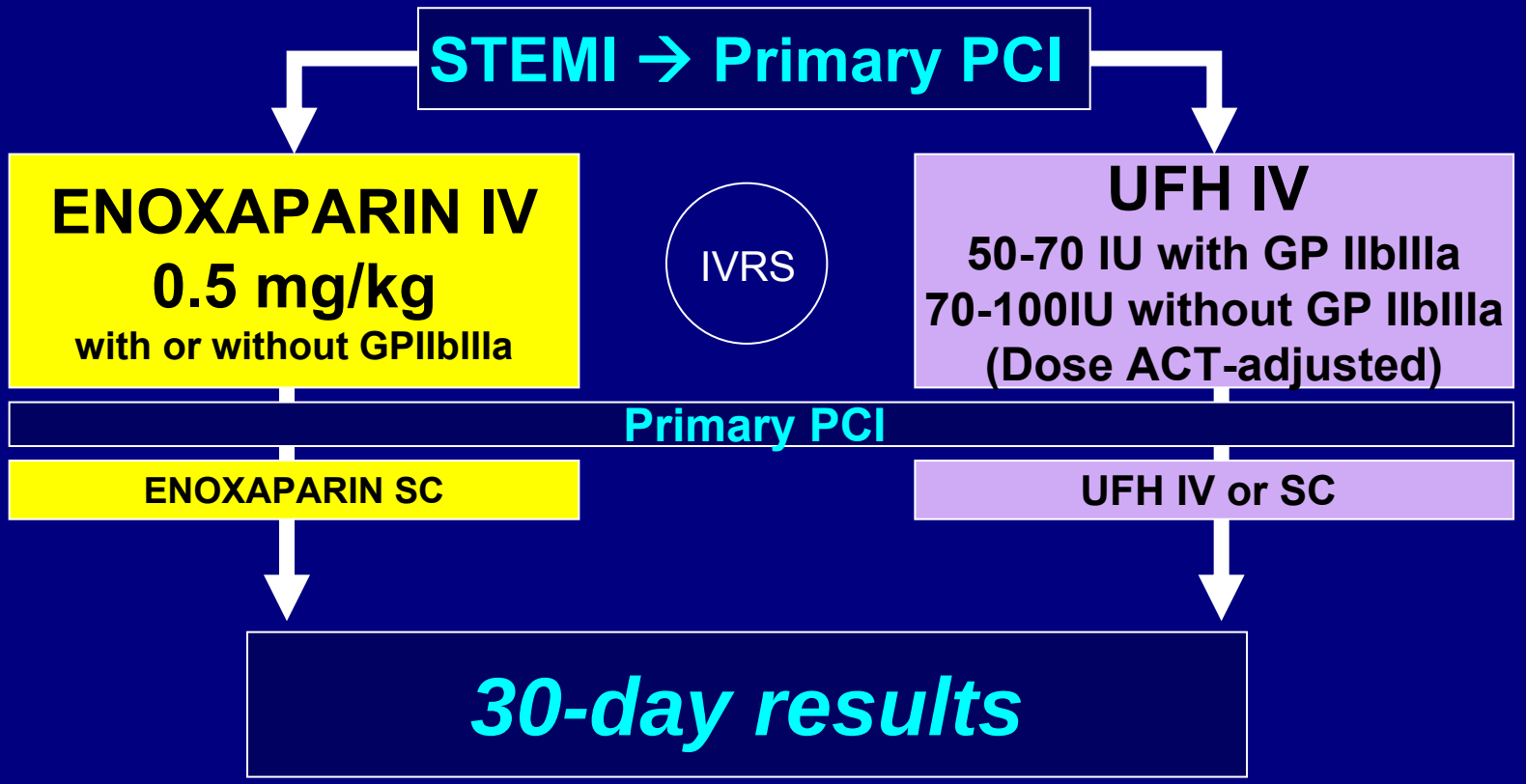
- **Anti thrombotic therapy**
- **Anti platelet therapy**

ANTI THROMBOTIC THERAPY TO SUPPORT PCI IN ACS

- **Unfractionated heparin – standard of care**
- **Fondaprinux – class III**
- **Is enoxaparin useful?**

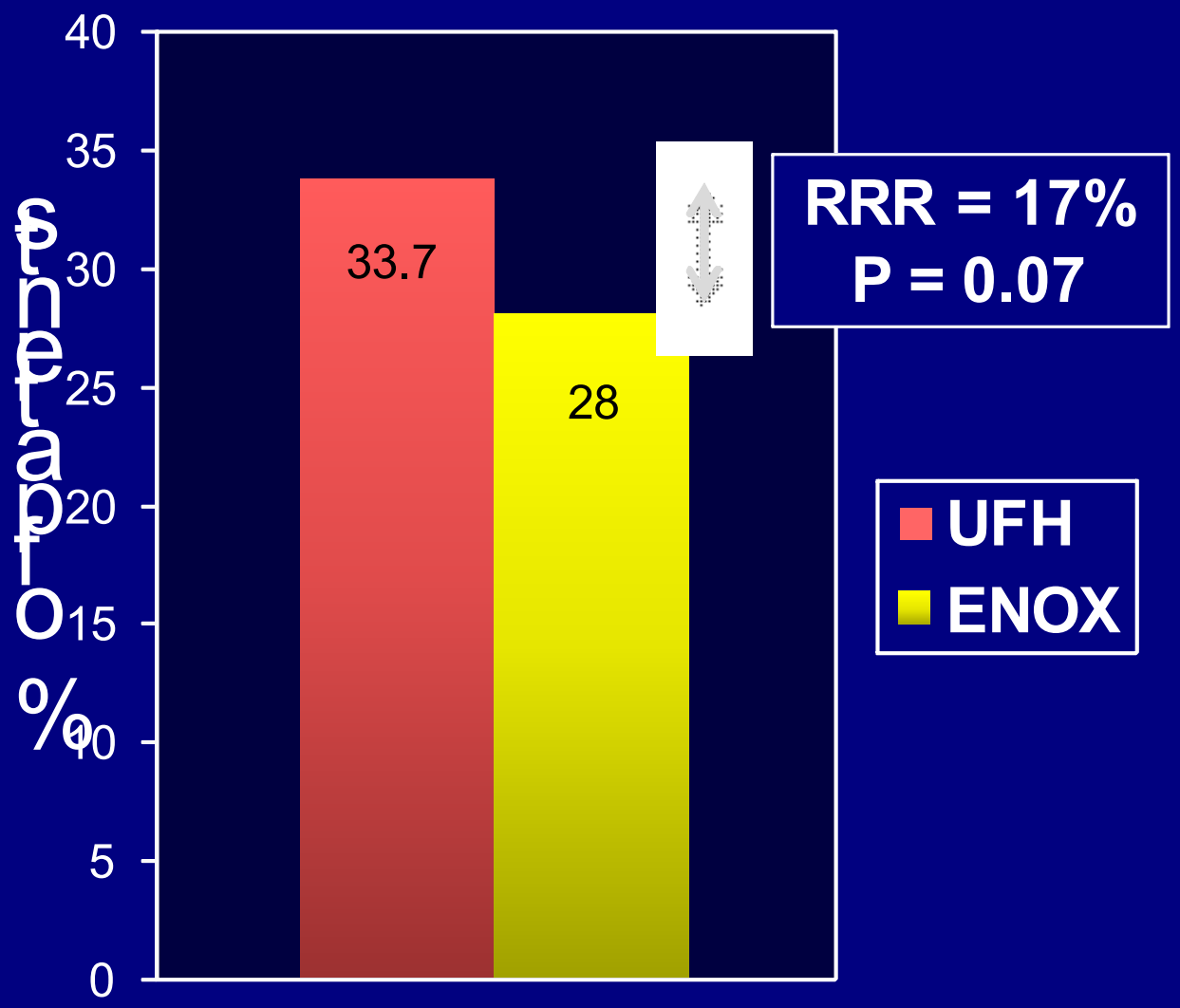
ATOLL Trial design

Randomization as *early* as possible (MICU +++)
Real life population (shock, cardiac arrest included)
No anticoagulation and no lytic **before** Rx
Similar antiplatelet therapy in both groups



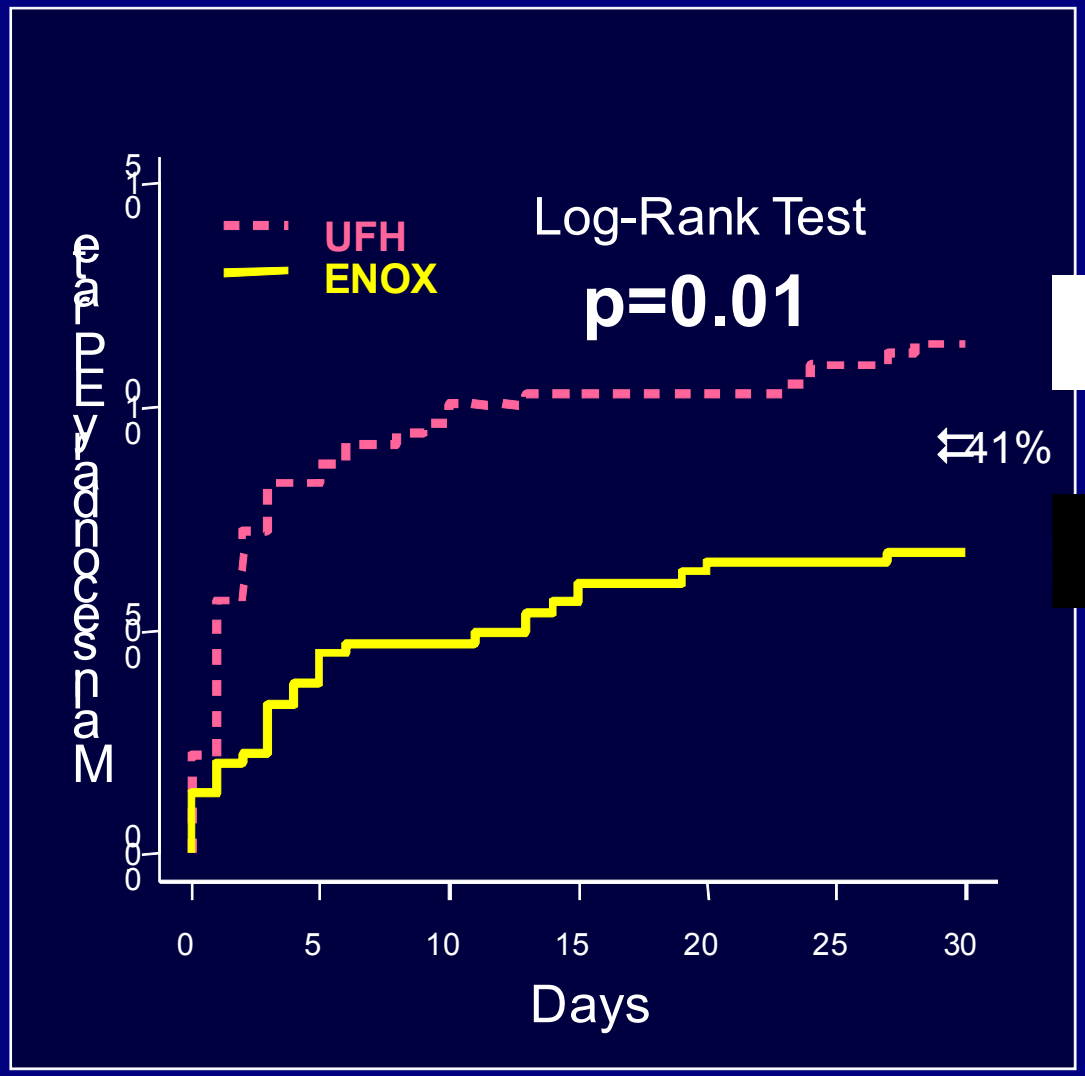
Primary Endpoint

Death, Complication of MI, Procedure Failure or Major Bleeding



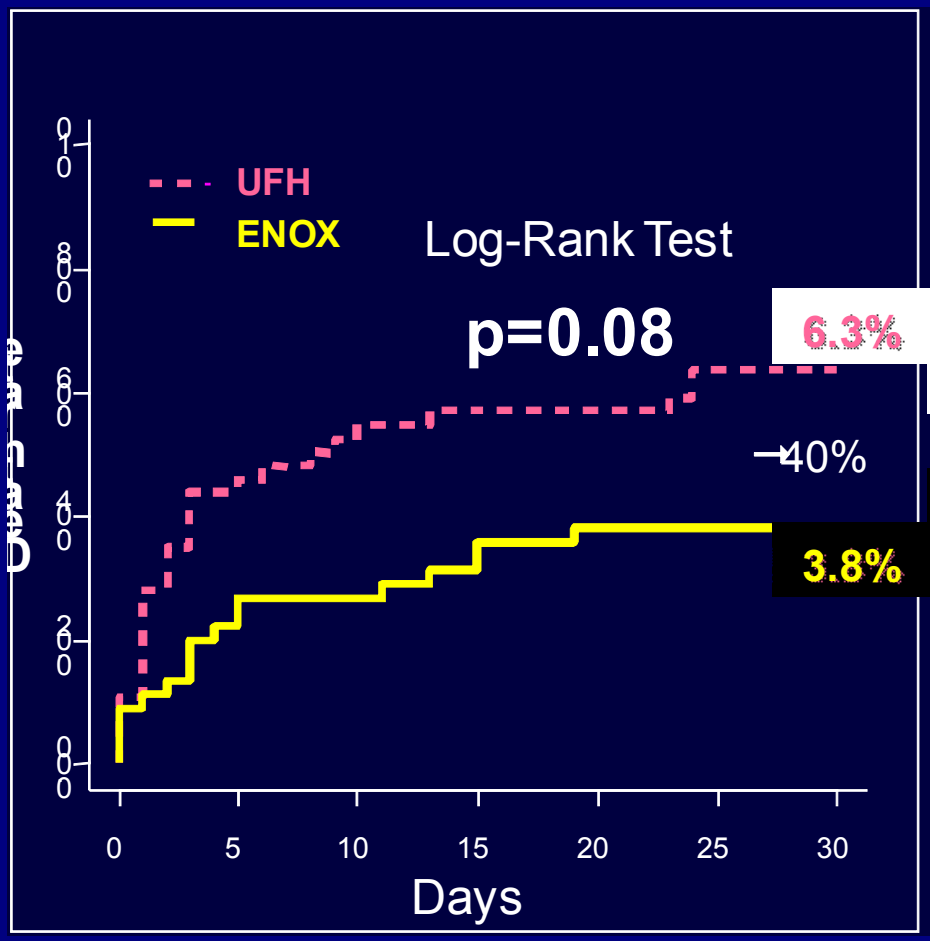
Main Secondary Endpoint (ischemic)

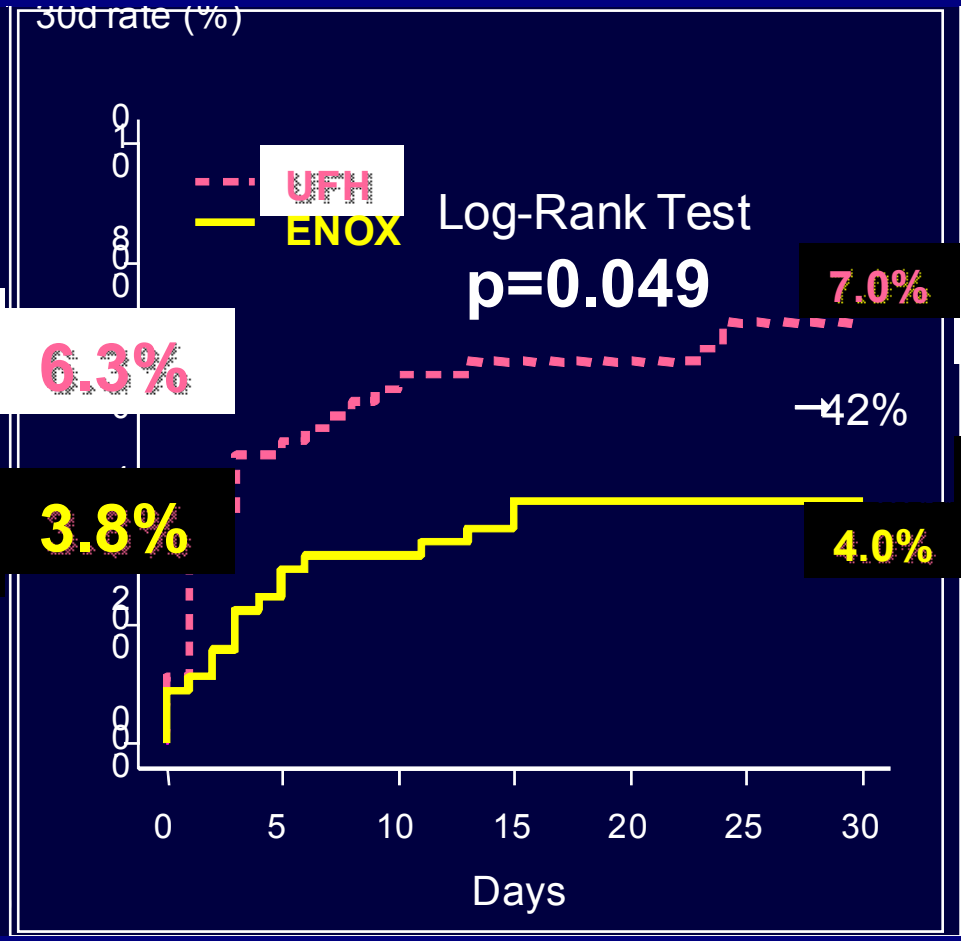
Death, Recurrent MI/ACS or Urgent Revascularization



Death (any)

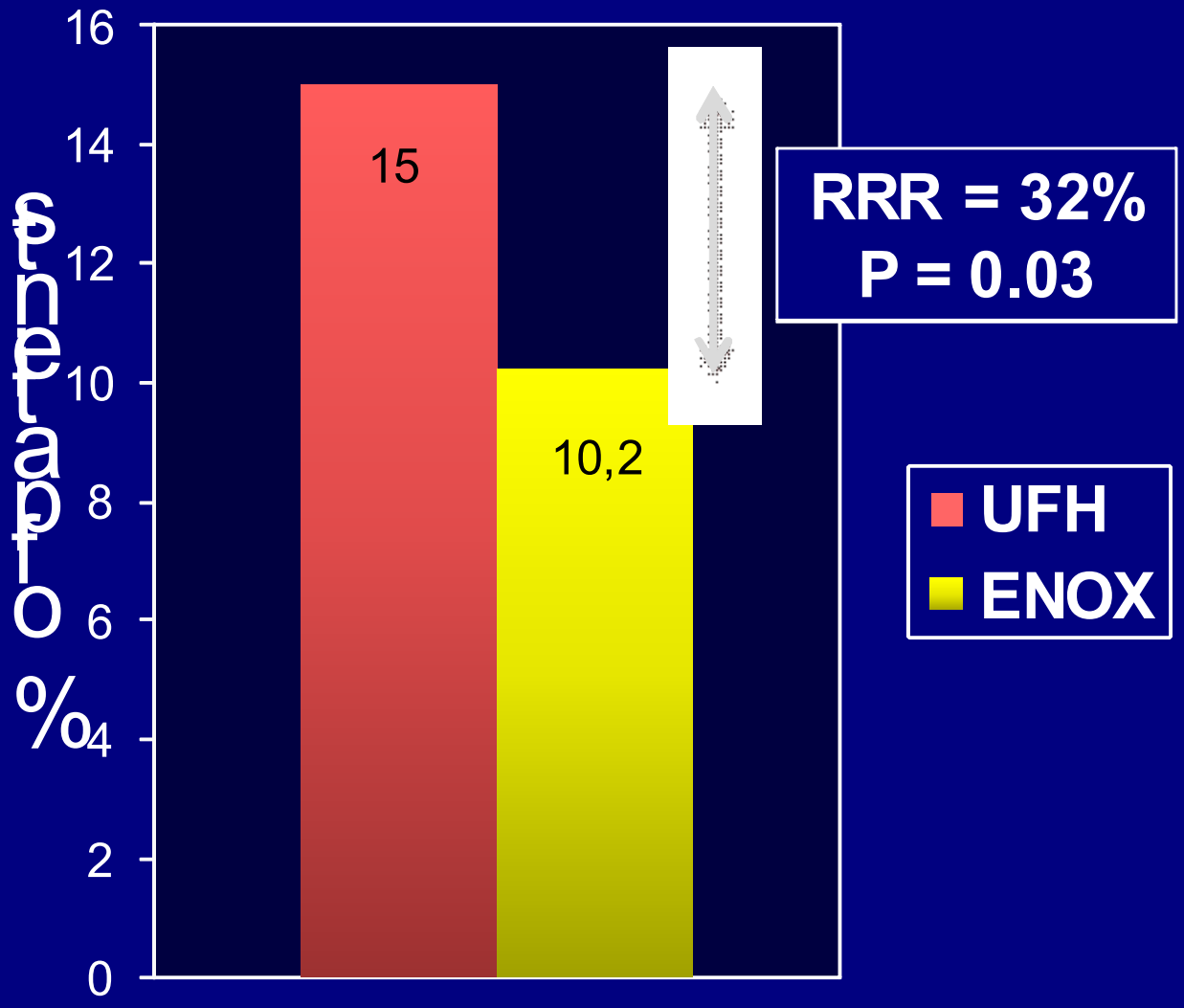
Death *or* resuscitated cardiac arrest





Death, Complication of MI or Major bleeding

Net clinical benefit



HORIZONS AMI

Harmonizing Outcomes with Revascularization and Stents in AMI

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

Aspirin, thienopyridine

R
1:1

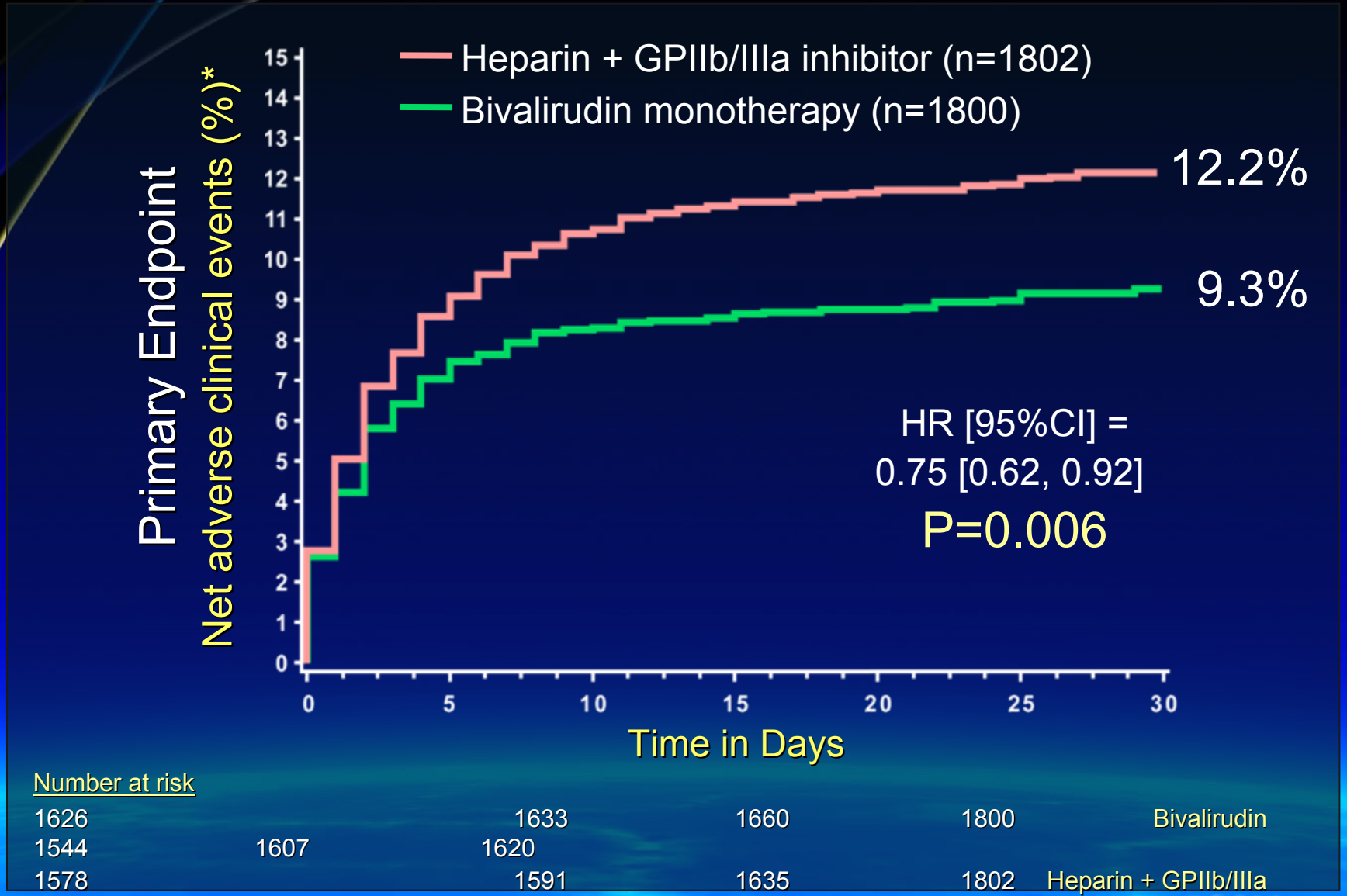
UFH + GP IIb/IIIa inhibitor
(abciximab or eptifibatide)

Bivalirudin monotherapy
(± provisional GP IIb/IIIa)

Pharmacology Arm
Primary Endpoints*
30 Day
Intention to Treat Population

* All stent randomization results are still blinded

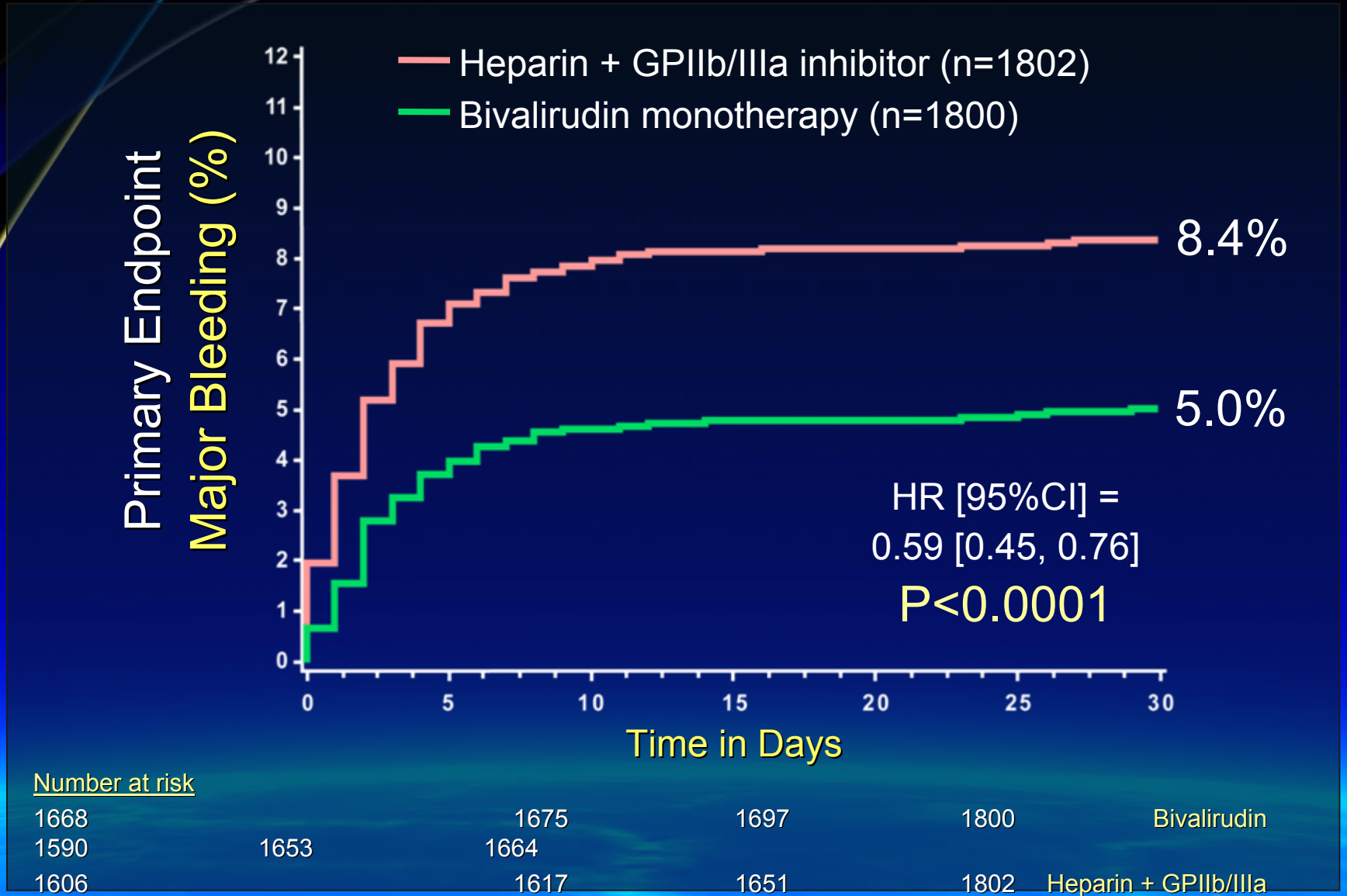
30 Day Net Adverse Clinical Events



*MACE or major bleeding (non CABG)

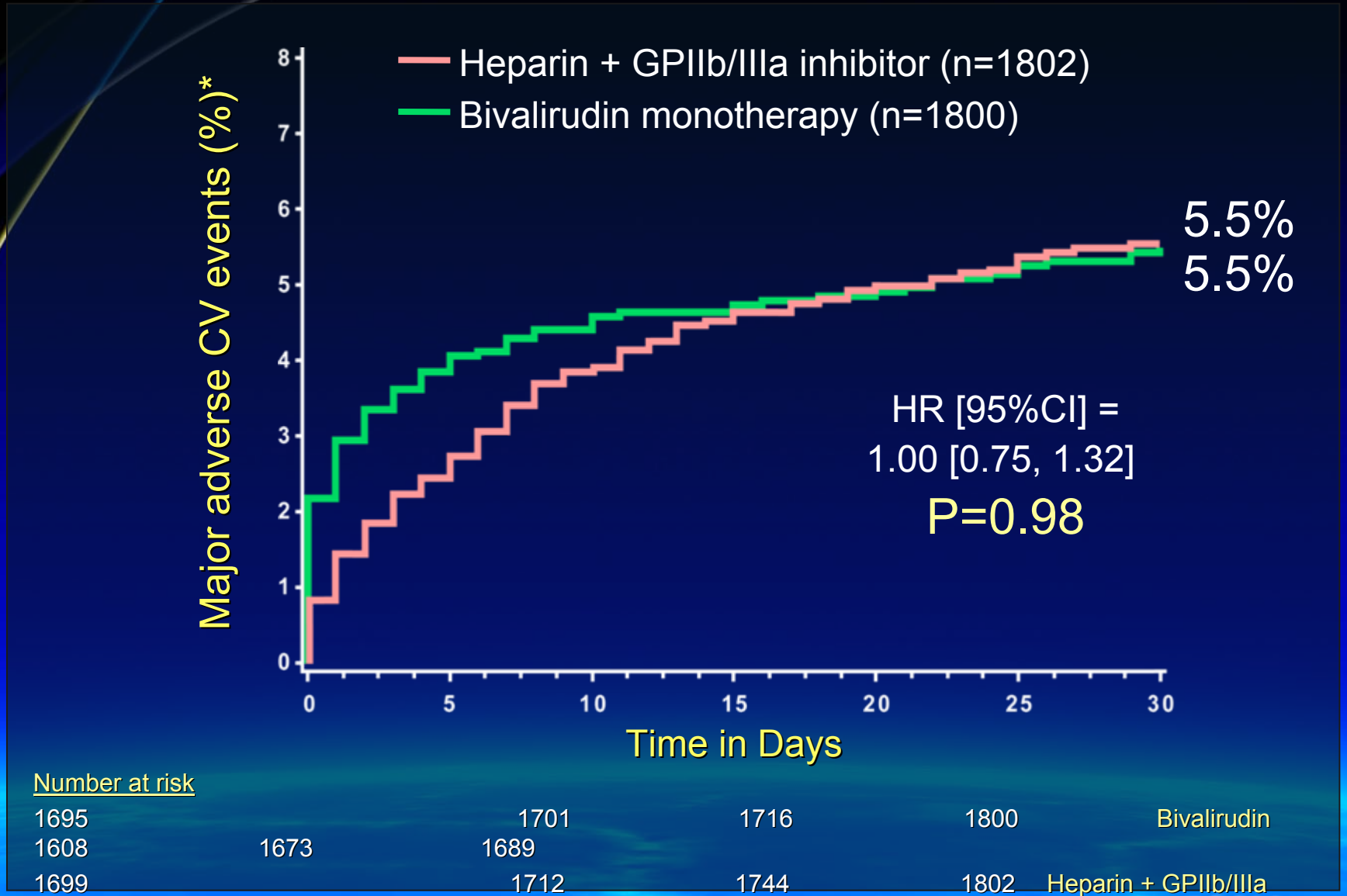
HORIZONS-AMI

30 Day Major Bleeding (non-CABG)



HORIZONS-AMI

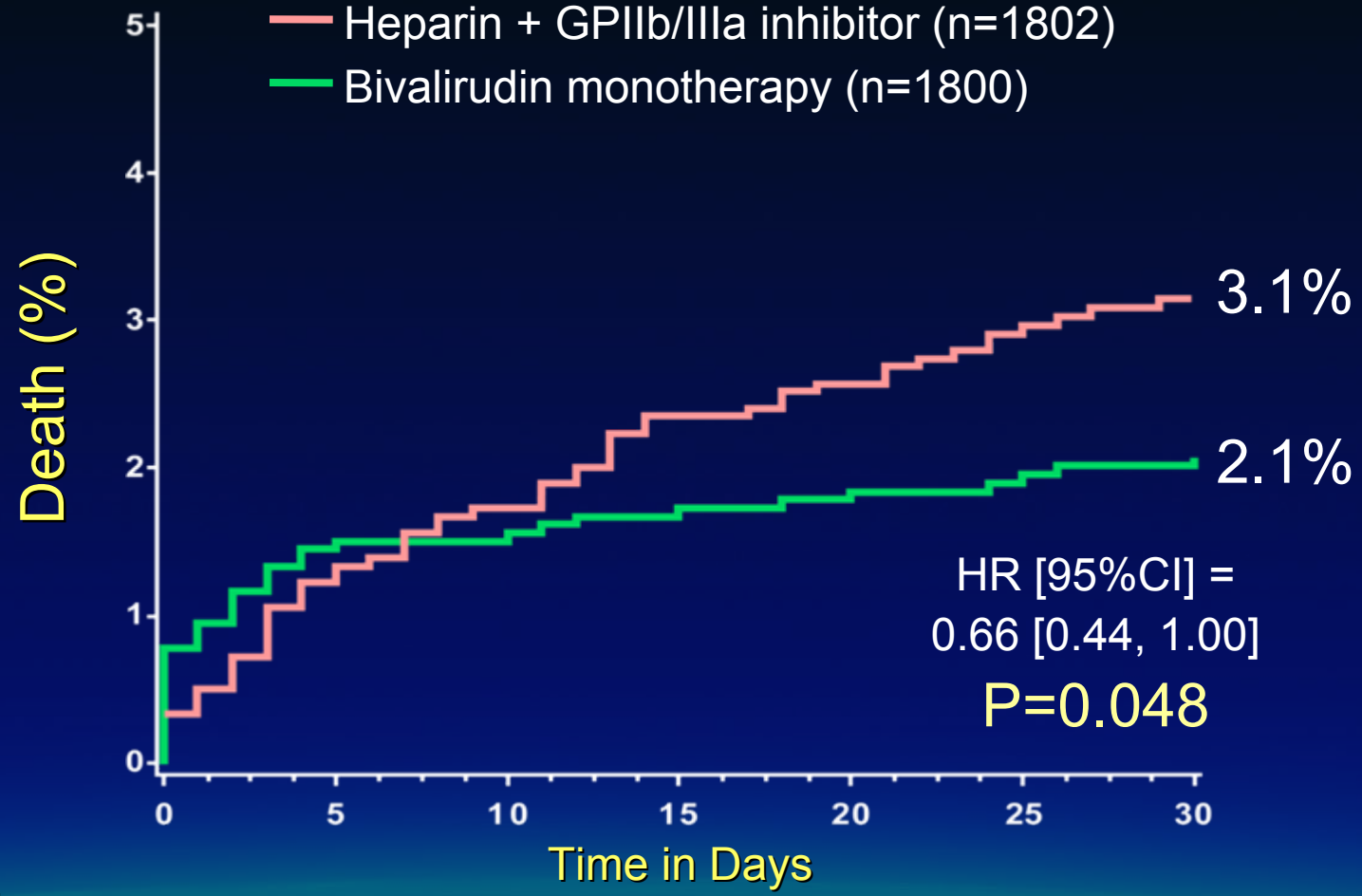
30 Day Major Adverse CV Events



*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

ANTI PLATELET THERAPY TO SUPPORT PCI

- **Aspirin**
- **Clopidogrel, prasugrel, ticagrelor**
- **GP IIb/IIIa receptor antagonists**

Clopidogrel loading before primary PCI

- No controlled data
- Full effect during procedure rarely achieved
- Since most patients will receive a stent (and therefore clopidogrel), since some effect may be present during procedure or early thereafter and in view of the meta - analysis, it is reasonable to load clopidogrel upon diagnosis until further data are available

TRÎTON TIMI·38
STENT ANALYSIS

Main Trial Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,608

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Duration of therapy: 6-15 months

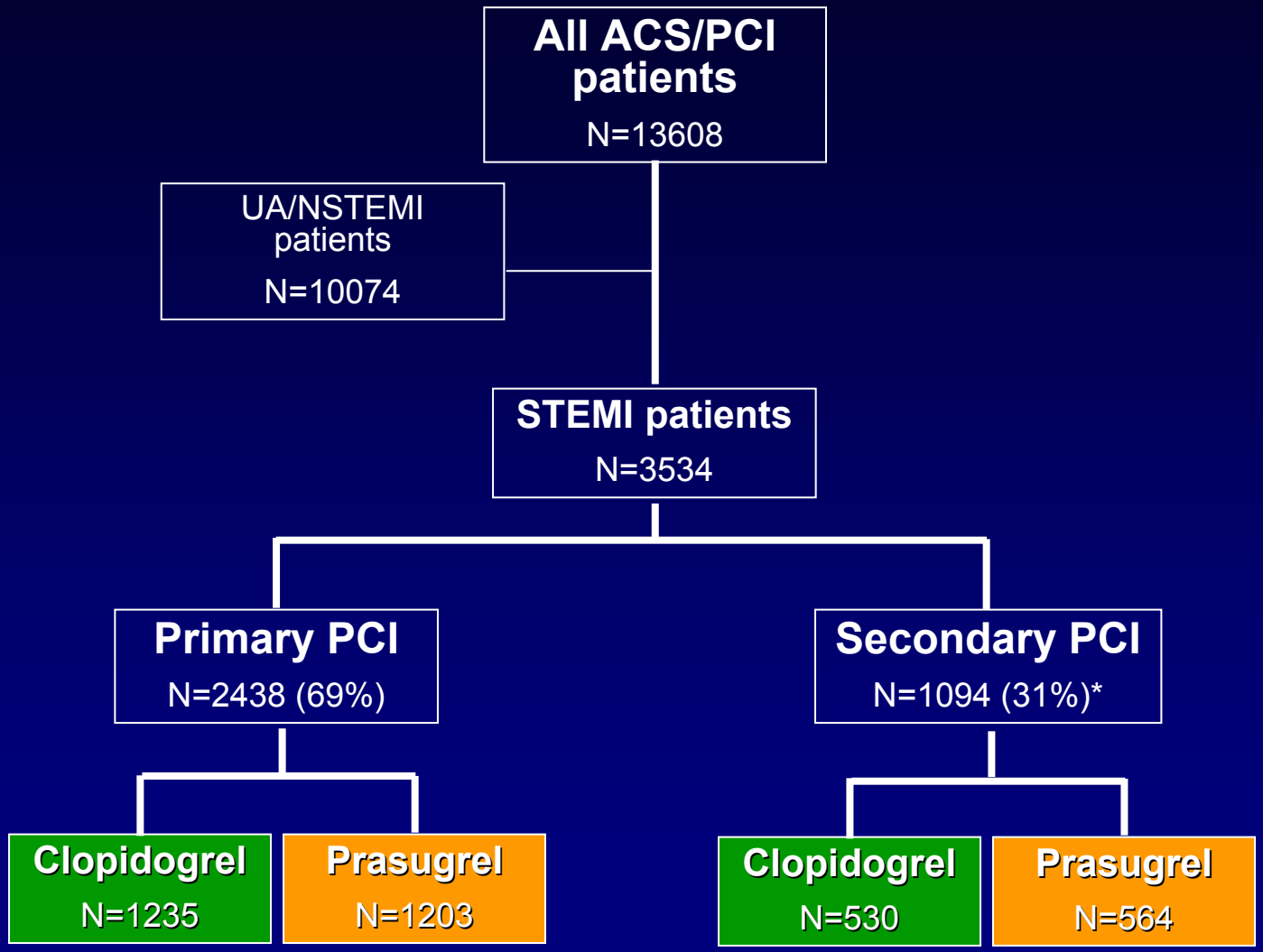
CV death, MI, Stroke 1° endpoint:

Stent Thrombosis 2° endpoint:

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Wiviott SD, Antman EM et al AHJ 2006

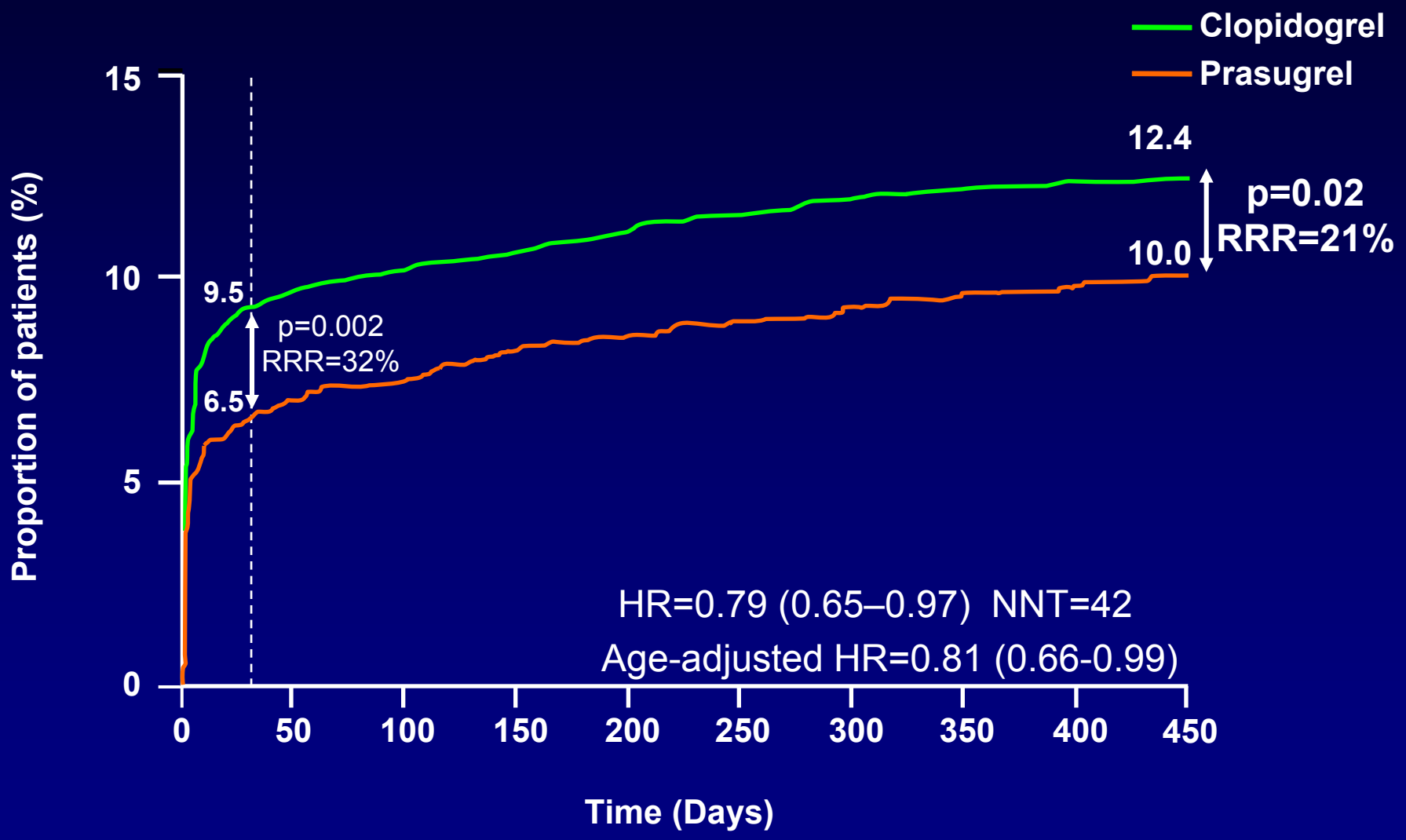
TRITON-TIMI 38 STEMI



* 2 patients were missing data for primary or secondary

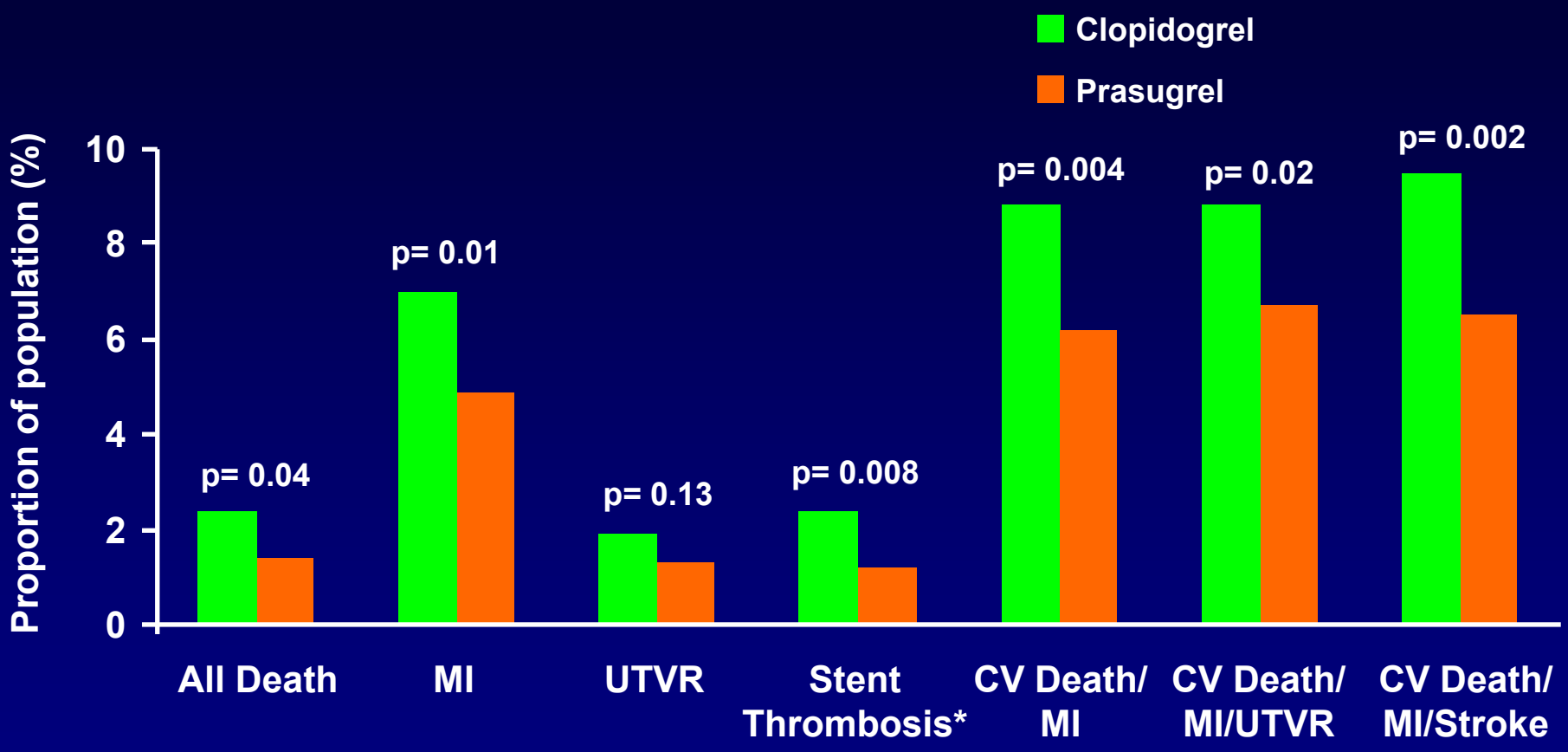
Montalescot et al. ESC 2008

Primary EP (CV death, MI and stroke at 15 months)



Montalescot et al. ESC 2008

Efficacy endpoints at 30 days

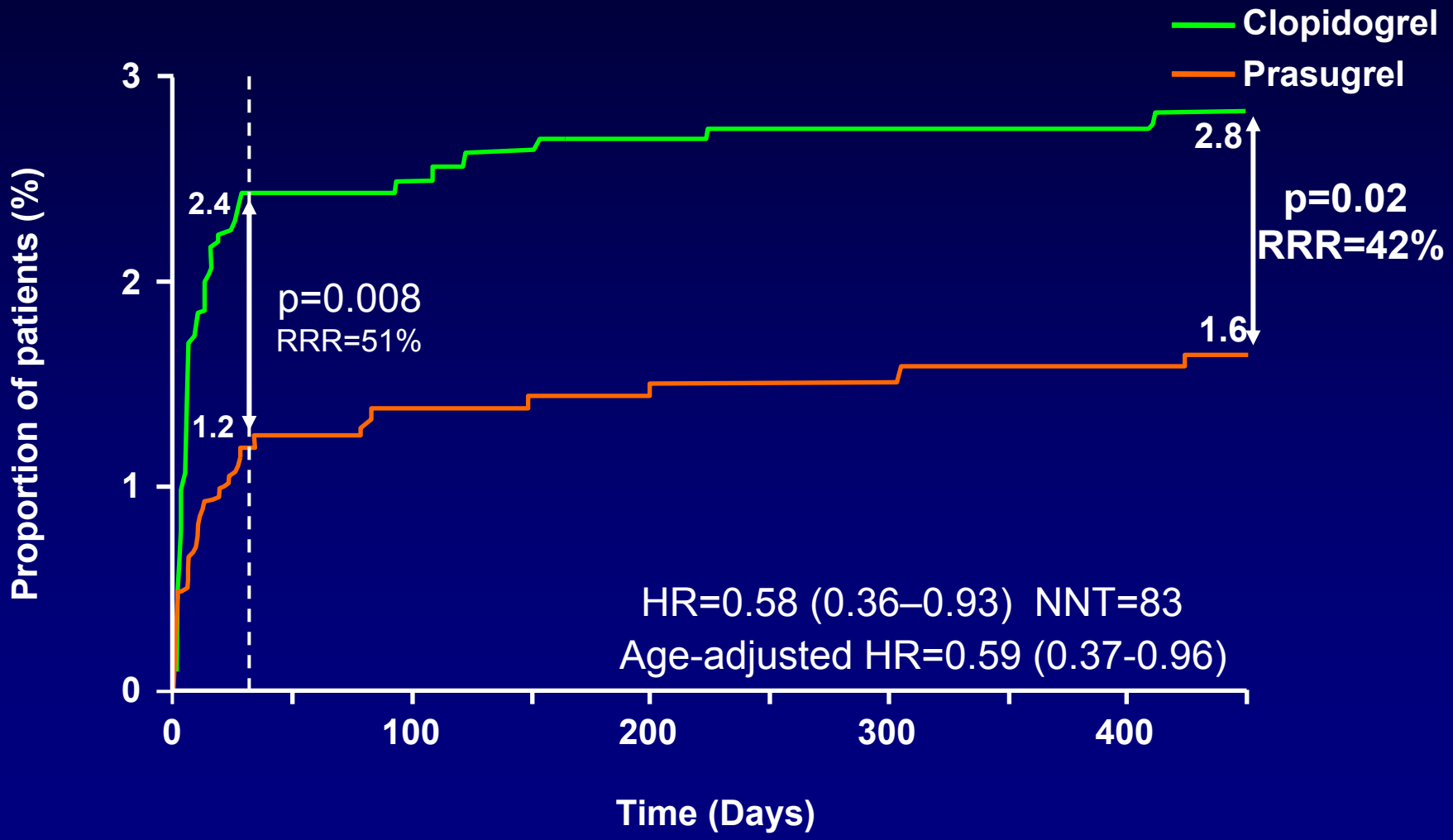


* ARC def/probable

Montalescot et al. ESC 2008

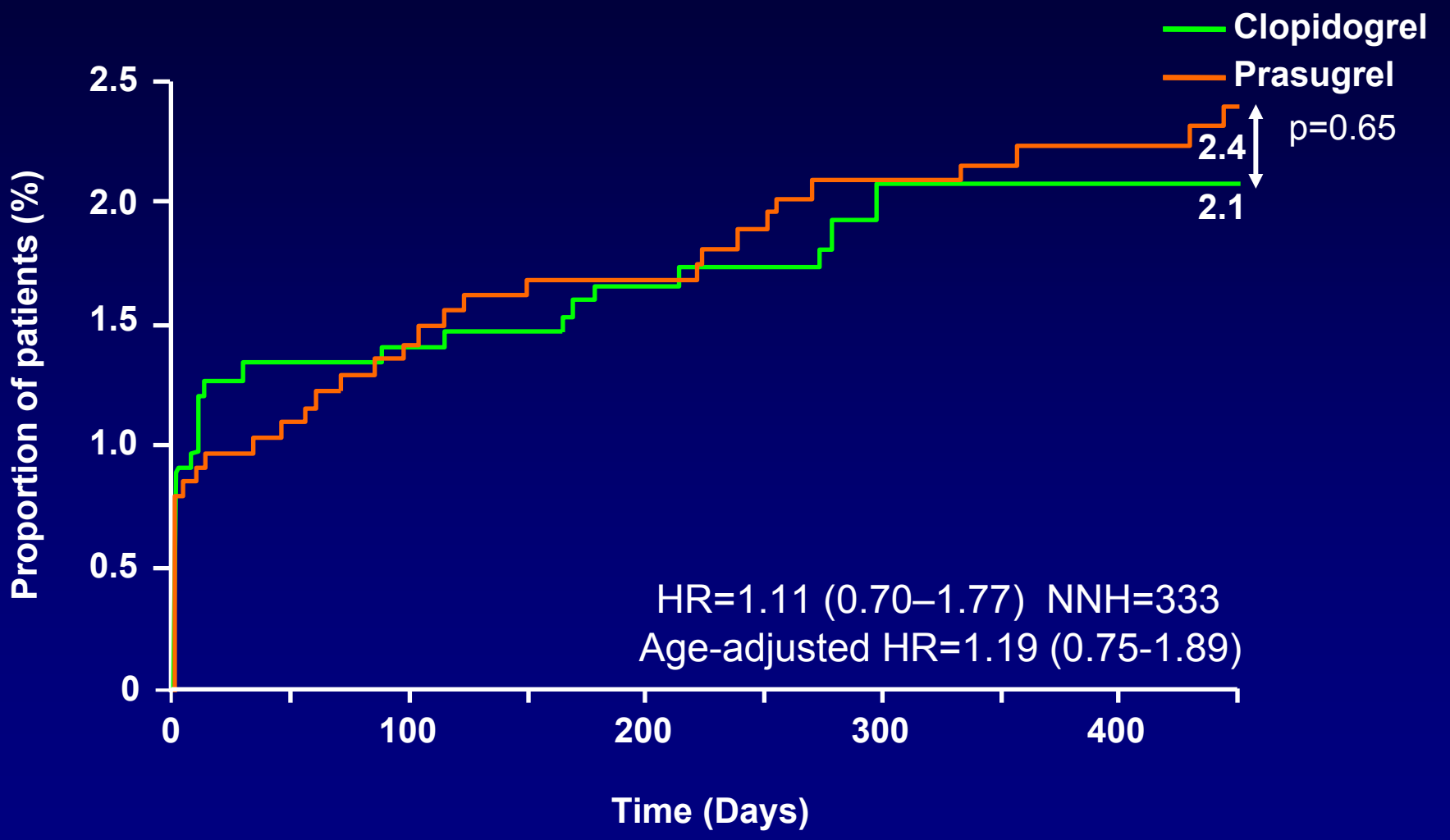
Stent thrombosis

ARC Definite/probable



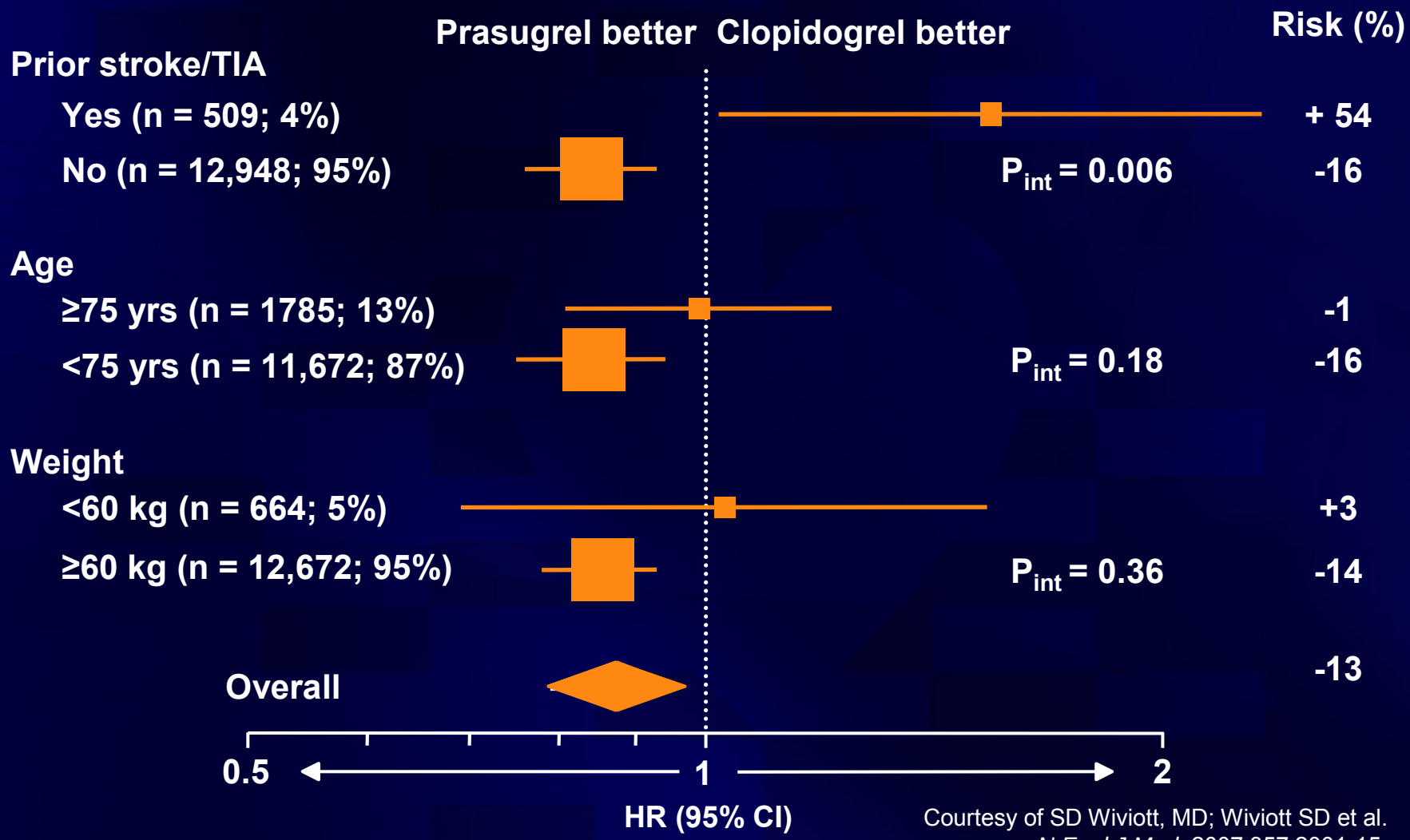
Montalescot et al. ESC 2008

TIMI major non-CABG bleeding



Montalescot et al. ESC 2008

TRITON-TIMI 38 post hoc analysis: Net clinical benefit in subgroups at increased bleeding risk



Courtesy of SD Wiviott, MD; Wiviott SD et al. *N Engl J Med*. 2007;357:2001-15.

CURRENT Study Design, Flow and Compliance

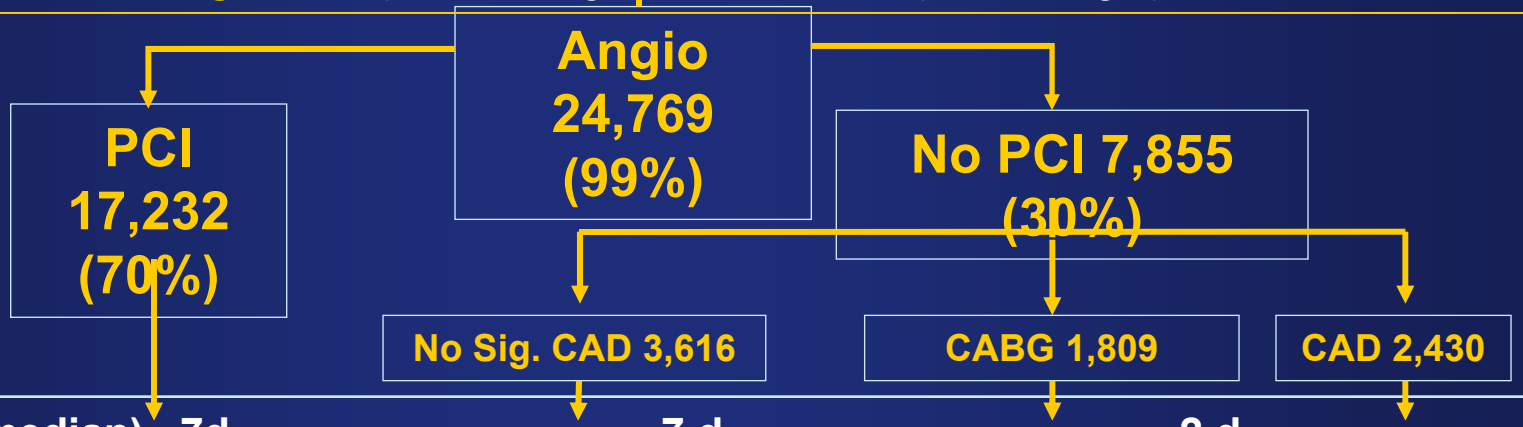
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ Planned Early (<24 h) Invasive Management with **intended PCI**
- ✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)



Compliance:

Clop in 1st 7d (median) 7d

7d

7 d

2 d

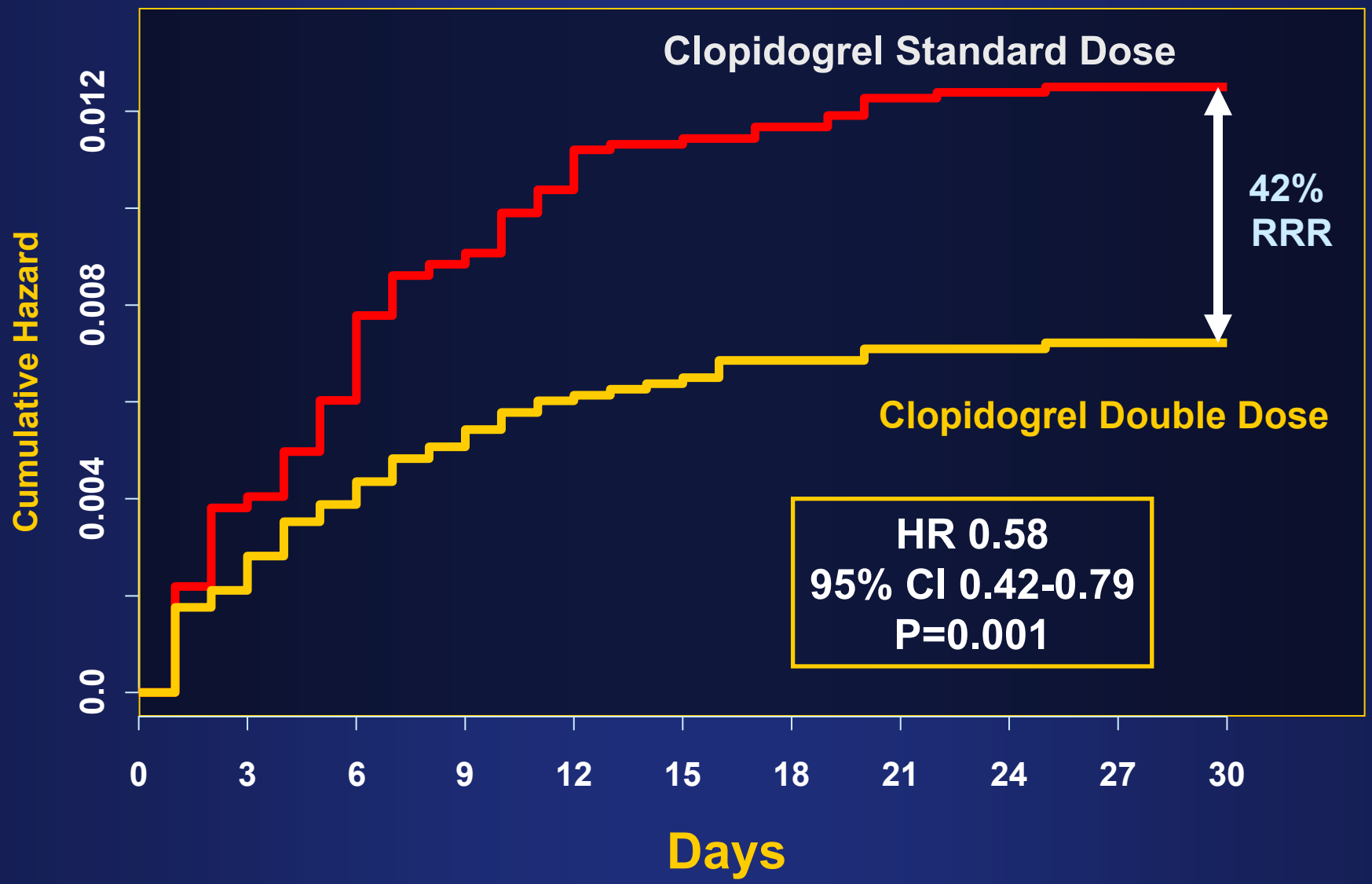
Efficacy Outcomes: CV Death, MI or stroke at day 30
Stent Thrombosis at day 30

Safety Outcomes: Bleeding (CURRENT defined Major/Severe and TIMI Major)

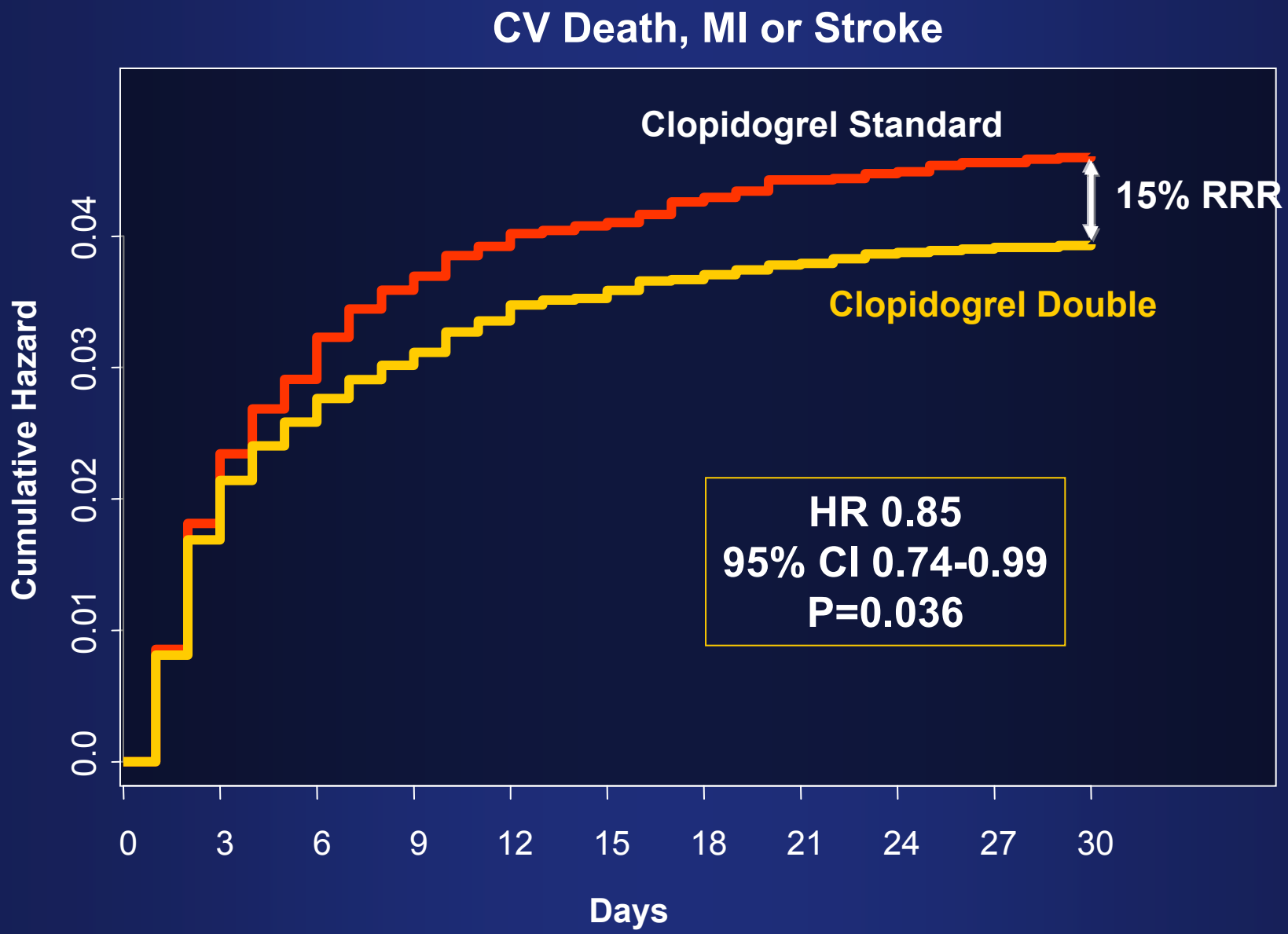
Key Subgroup: PCI v No PCI

Complete Followup 99.8%

Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)



Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients

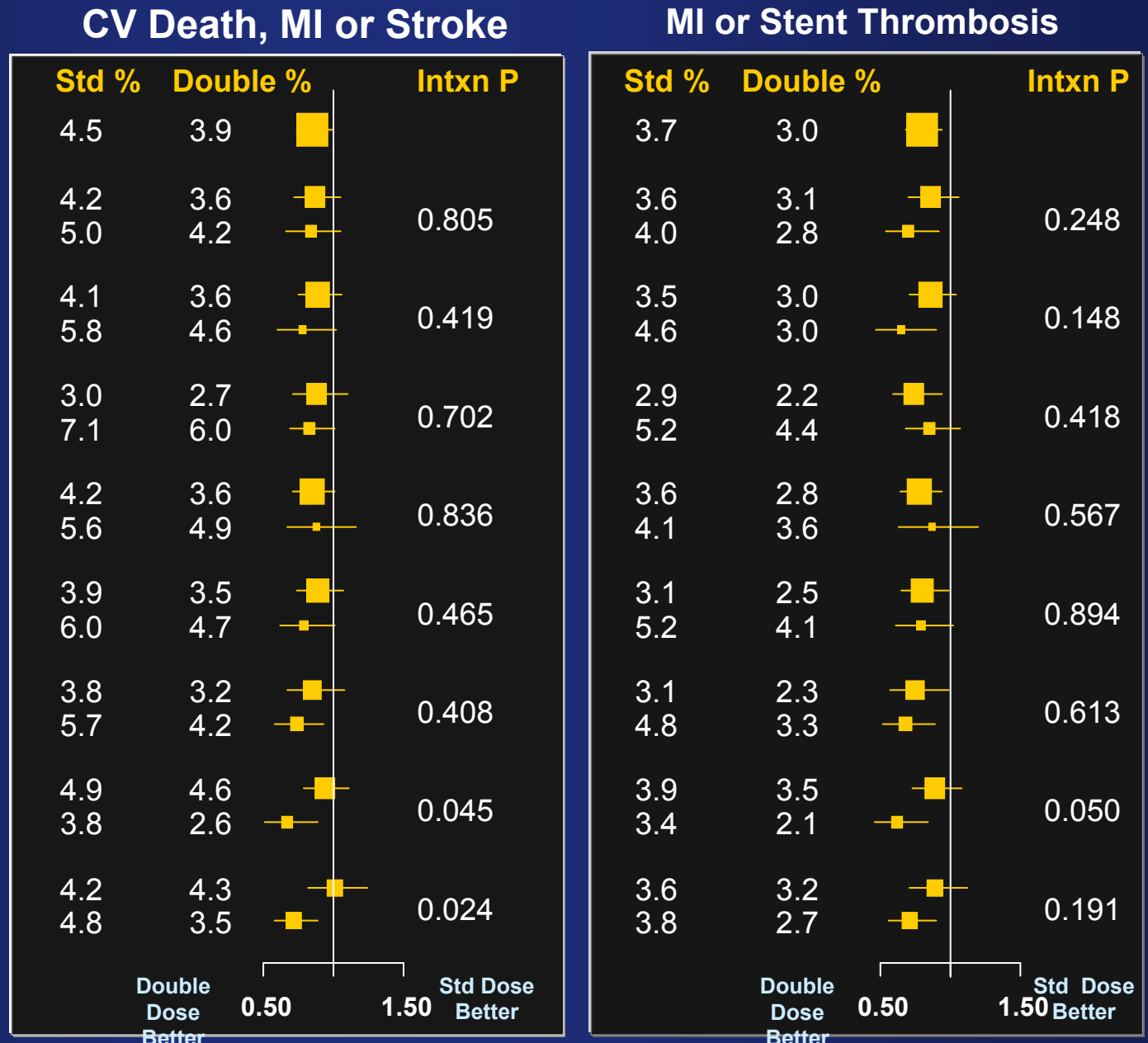


Clopidogrel Double vs Standard Dose Bleeding PCI Population

	Clopidogrel				
	Standard N= 8684	Double N=8548	Hazard Ratio	95% CI	P
TIMI Major[1]	0.5	0.5	1.06	0.70-1.61	0.79
CURRENT Major[2]	1.1	1.6	1.44	1.11-1.86	0.006
CURRENT Severe[3]	0.8	1.1	1.39	1.02-1.90	0.034
Fatal	0.15	0.07	0.47	0.18-1.23	0.125
ICH	0.035	0.046	1.35	0.30-6.04	0.69
RBC transfusion ≥ 2U	0.91	1.35	1.49	1.11-1.98	0.007
CABG-related Major	0.1	0.1	1.69	0.61-4.7	0.31

[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units

Clopidogrel: Double v Standard Dose PCI Cohort Subgroups



PLATO STEMI

Ticagrelor compared with clopidogrel in patients with acute coronary syndromes
the PLATelet Inhibition and patient Outcomes trial

Outcomes in patients with STEMI and planned PCI

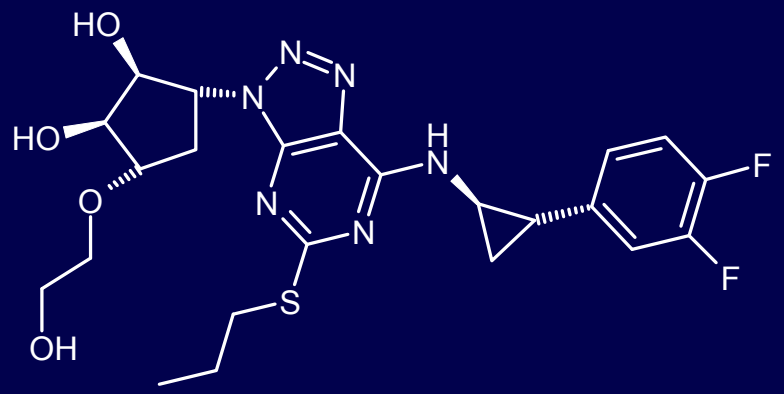
Ph.Gabriel Steg*, Stefan James, Robert A Harrington, Diego Ardissino, Richard C. Becker, Christopher P. Cannon, Håkan Emanuelsson, Ariel Finkelstein, Steen Husted, Hugo Katus, Jan Kilhamn, Sylvia Olofsson, Robert F. Storey, Douglas Weaver, Lars Wallentin, for the PLATO study group

*Unité INSERM U-698
Hôpital Bichat – Claude Bernard
Université Paris VII – Denis Diderot

The PLATO trial was funded by AstraZeneca

Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist

PLATO



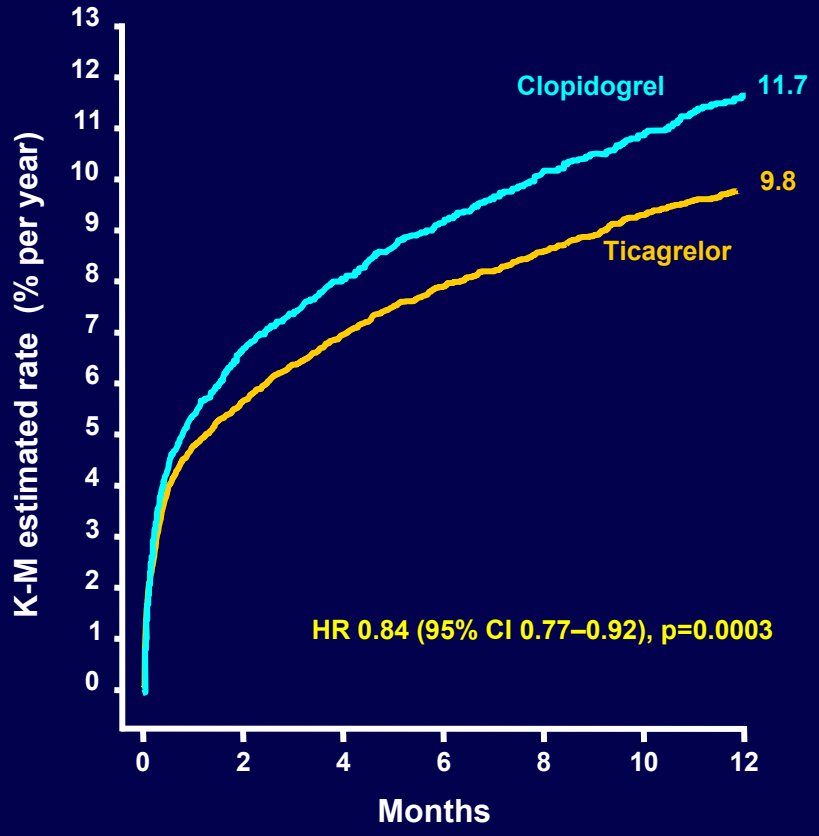
Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - **Not a pro-drug; does not require metabolic activation**
  - **Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor**
  - **Greater inhibition of platelet aggregation than clopidogrel**
- **Reversibly bound**
  - **Degree of inhibition reflects plasma concentration**
  - **Faster offset of effect than clopidogrel**
  - **Functional recovery of circulating platelets within ~48 hours**

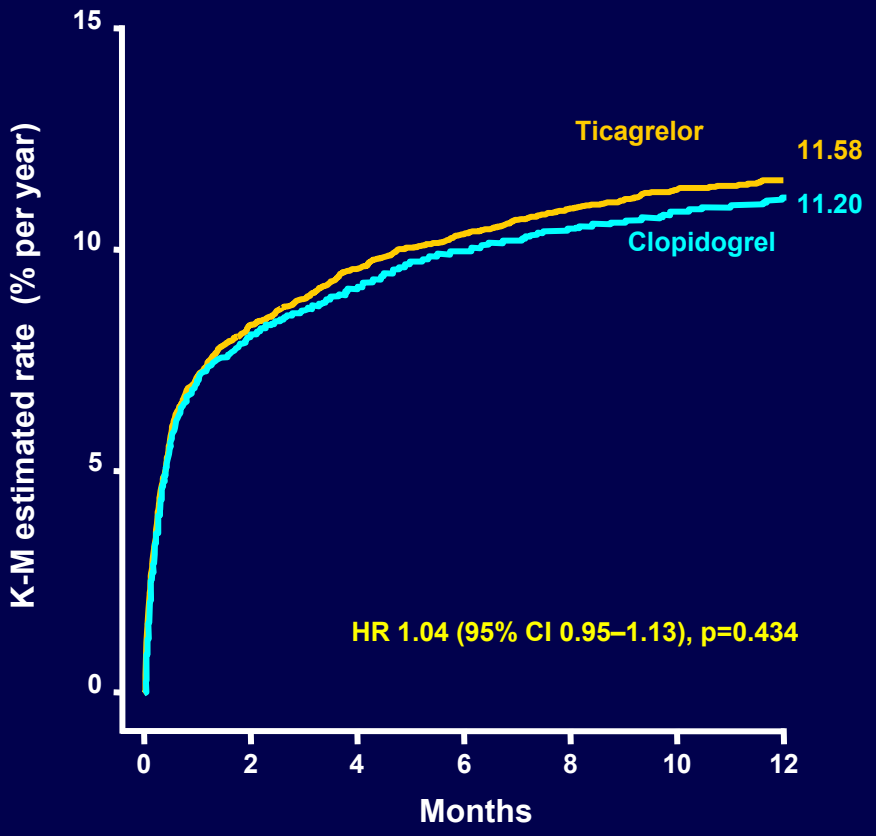
PLATO main endpoints

PLATO

Primary efficacy endpoint



Primary safety endpoint



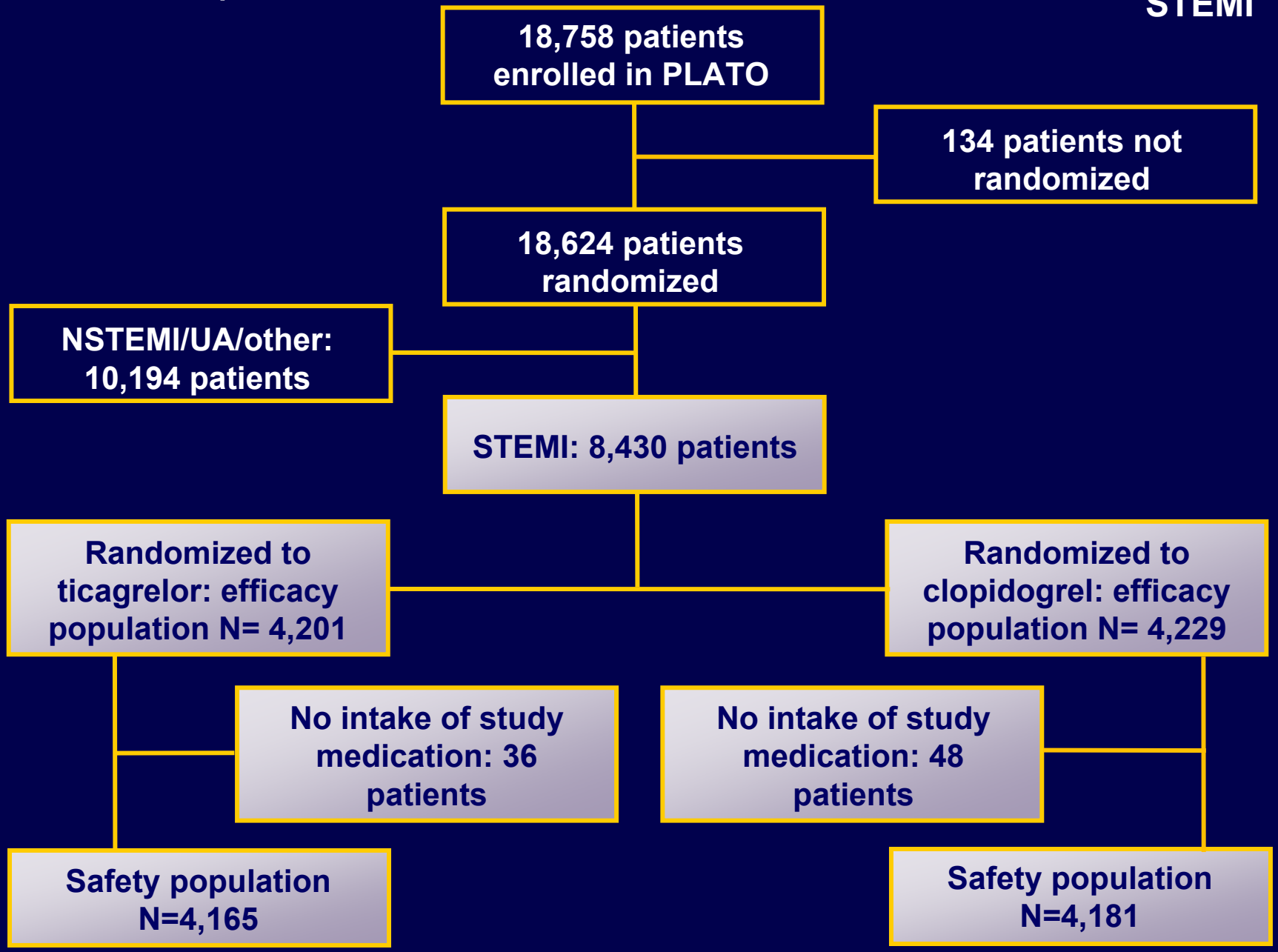
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

9,235	7,246	6,826	6,545	5,129	3,783	3,433
9,186	7,305	6,930	6,670	5,209	3,841	3,479

Wallentin et al., New Eng J Med. 2009;361:1045–1057

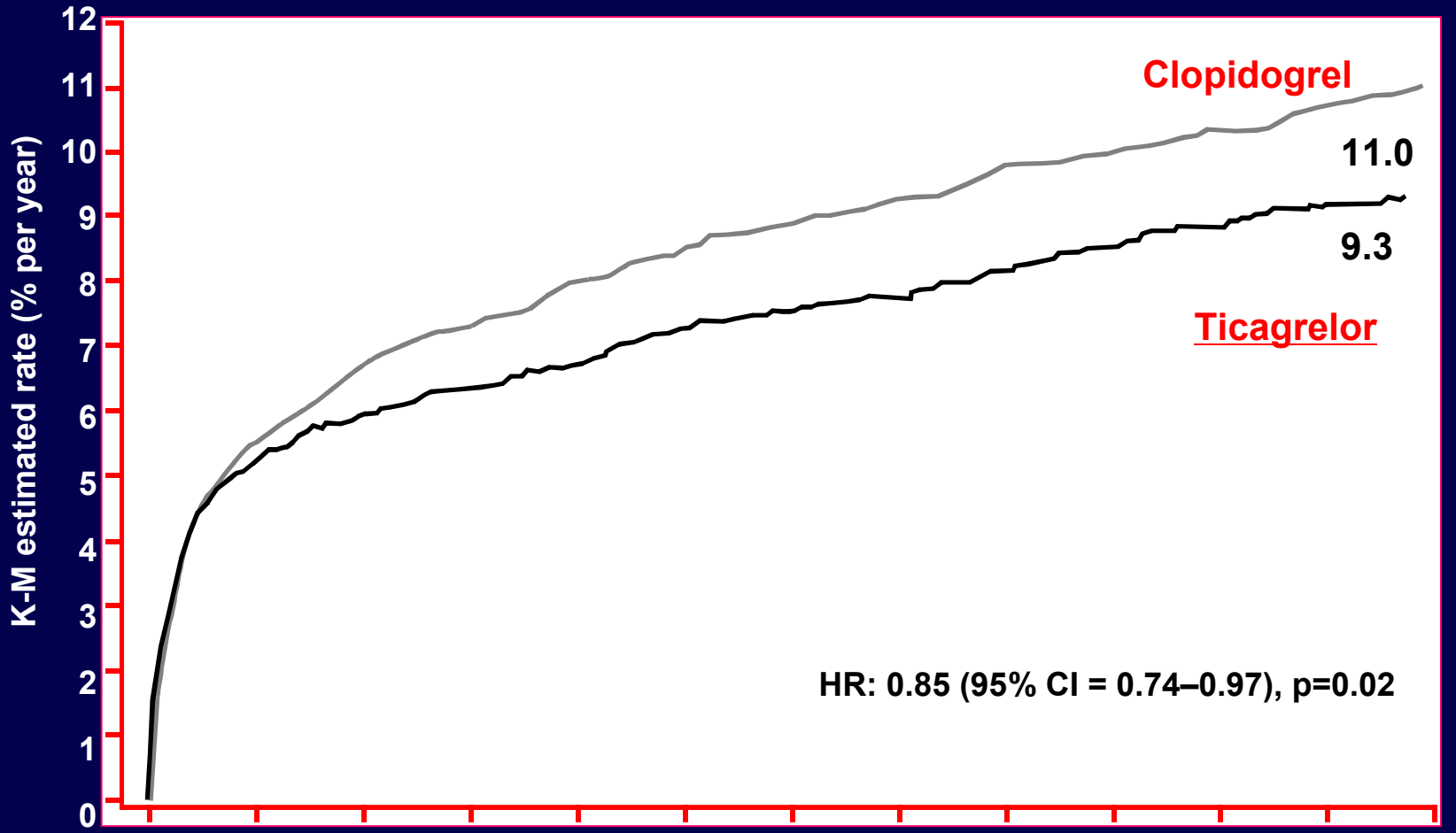
Patient disposition

PLATO
STEMI



Primary endpoint: CV death, MI or stroke

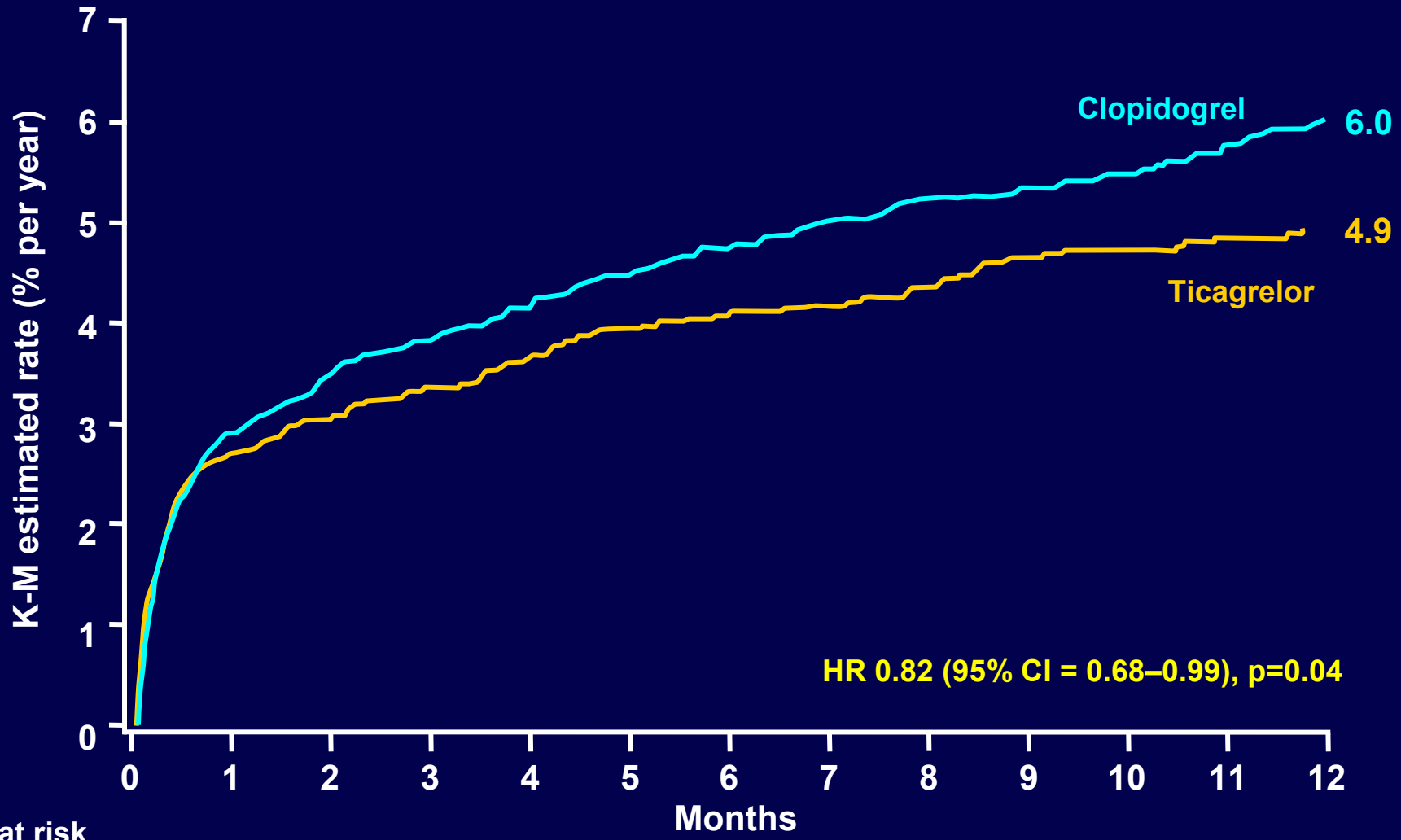
PLATO
STEMI



No. at risk							
Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868

All cause mortality

PLATO
STEMI



No. at risk							
Ticagrelor	4,201	4,005	3,962	3,876	3,150	2,413	1,993
Clopidogrel	4,229	4,029	3,989	3,912	3,195	2,471	1,980

Stent thrombosis (as per ARC definitions)*

PLATO STEMI

	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Definite	1.6	2.5	0.61 (0.42–0.87)	0.01
Probable or definite	2.5	3.6	0.69 (0.52–0.92)	0.01
Possible, probable, or definite	3.2	4.4	0.73 (0.56–0.94)	0.02

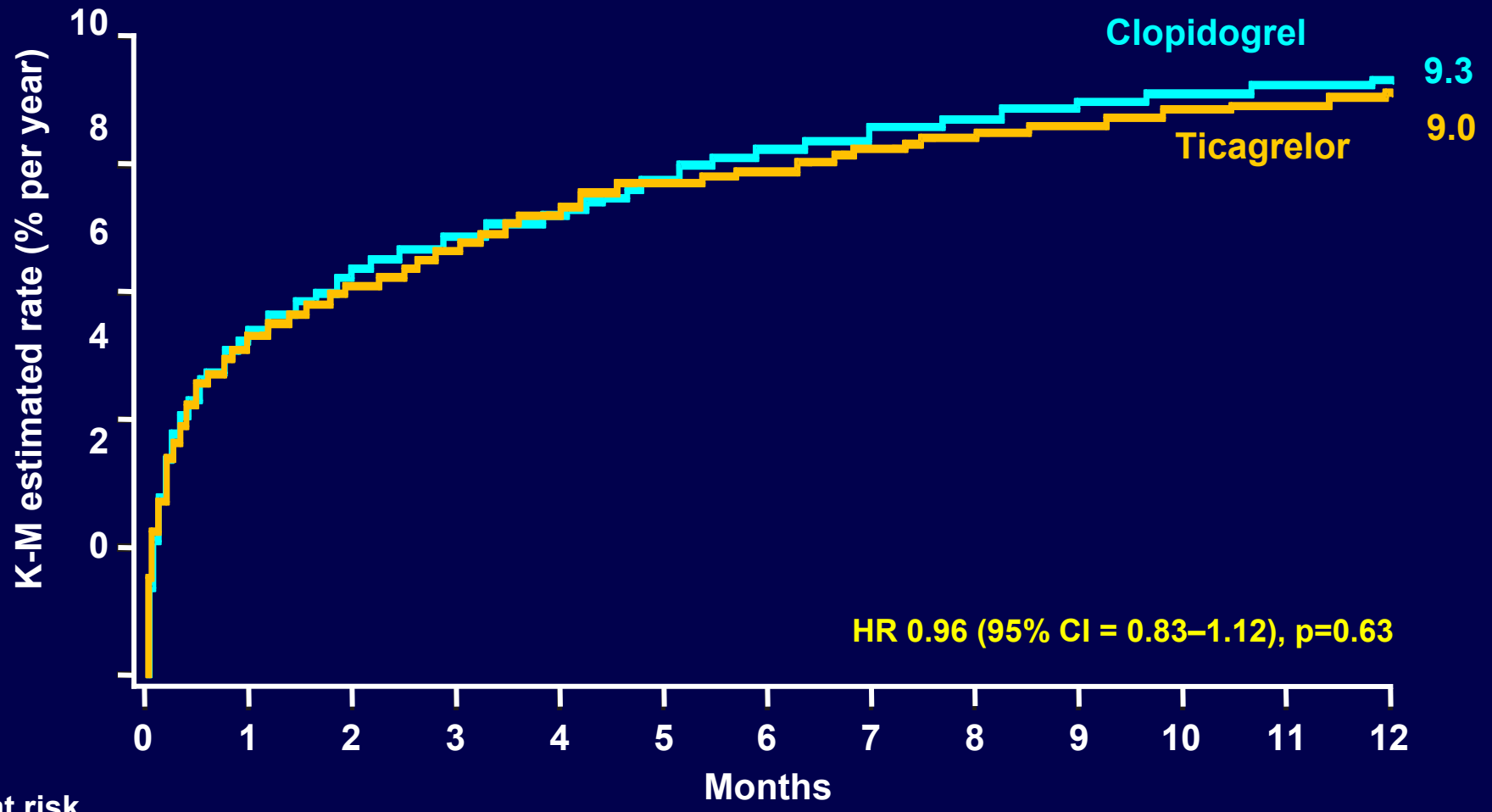
Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

*Cutlip et. al., Circulation. 2007;115:2344–2351

†By univariate Cox model

Primary safety event: major bleeding

PLATO
STEMI



No. at risk							
Ticagrelor	4,165	3,431	3,254	3,137	2,440	1,786	1,640
Clopidogrel	4,181	3,430	3,297	3,159	2,441	1,804	1,635

Other findings

PLATO STEMI

All patients	Ticagrelor (n=4,165)	Clopidogrel (n=4,181)	p-value*
Dyspnoea, %			
Any	12.9	8.3	<0.0001
Requiring discontinuation of study treatment	0.5	0.1	0.0003
Bradycardia-related events, %			
Bradycardia	4.6	4.9	0.57
Pacemaker placement	1.2	1.0	0.35
Syncope	1.0	0.8	0.35
Heart block	1.0	0.9	0.82

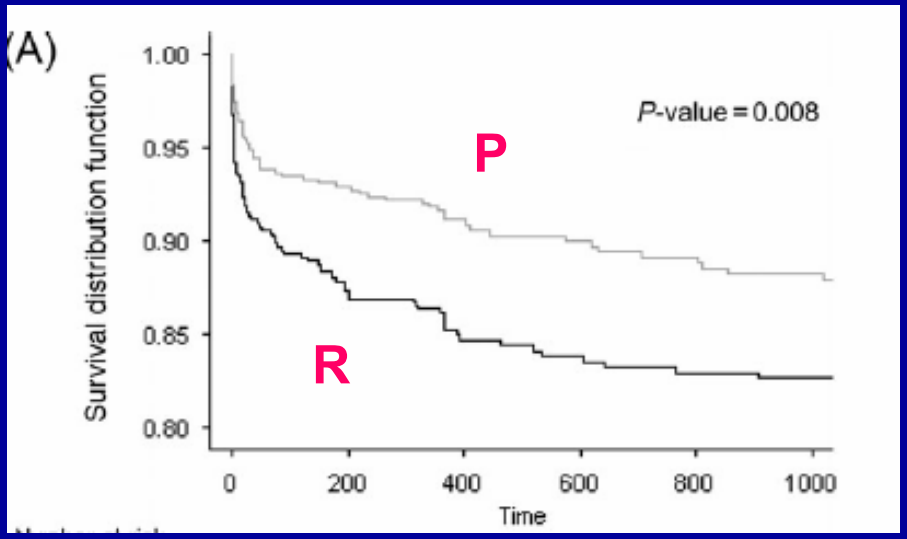
* Fisher's exact test

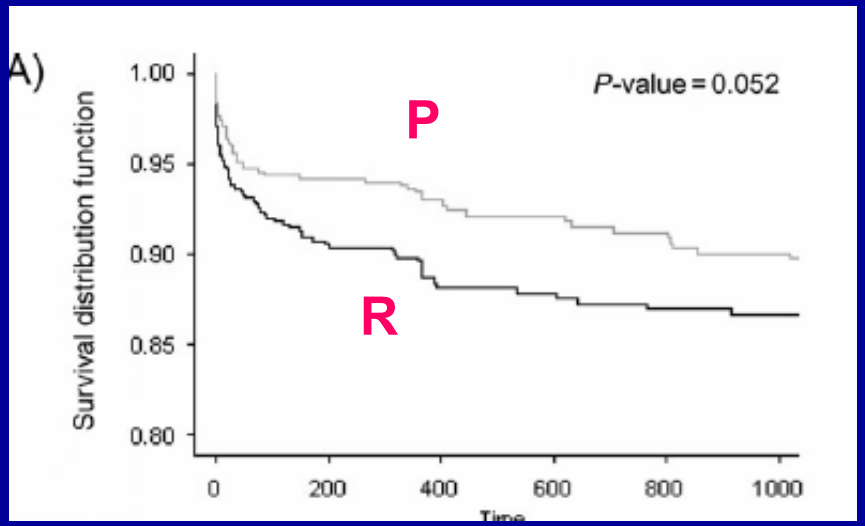
European Heart Journal (2007) 28, 443–449
doi:10.1093/eurheartj/ehl472

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

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

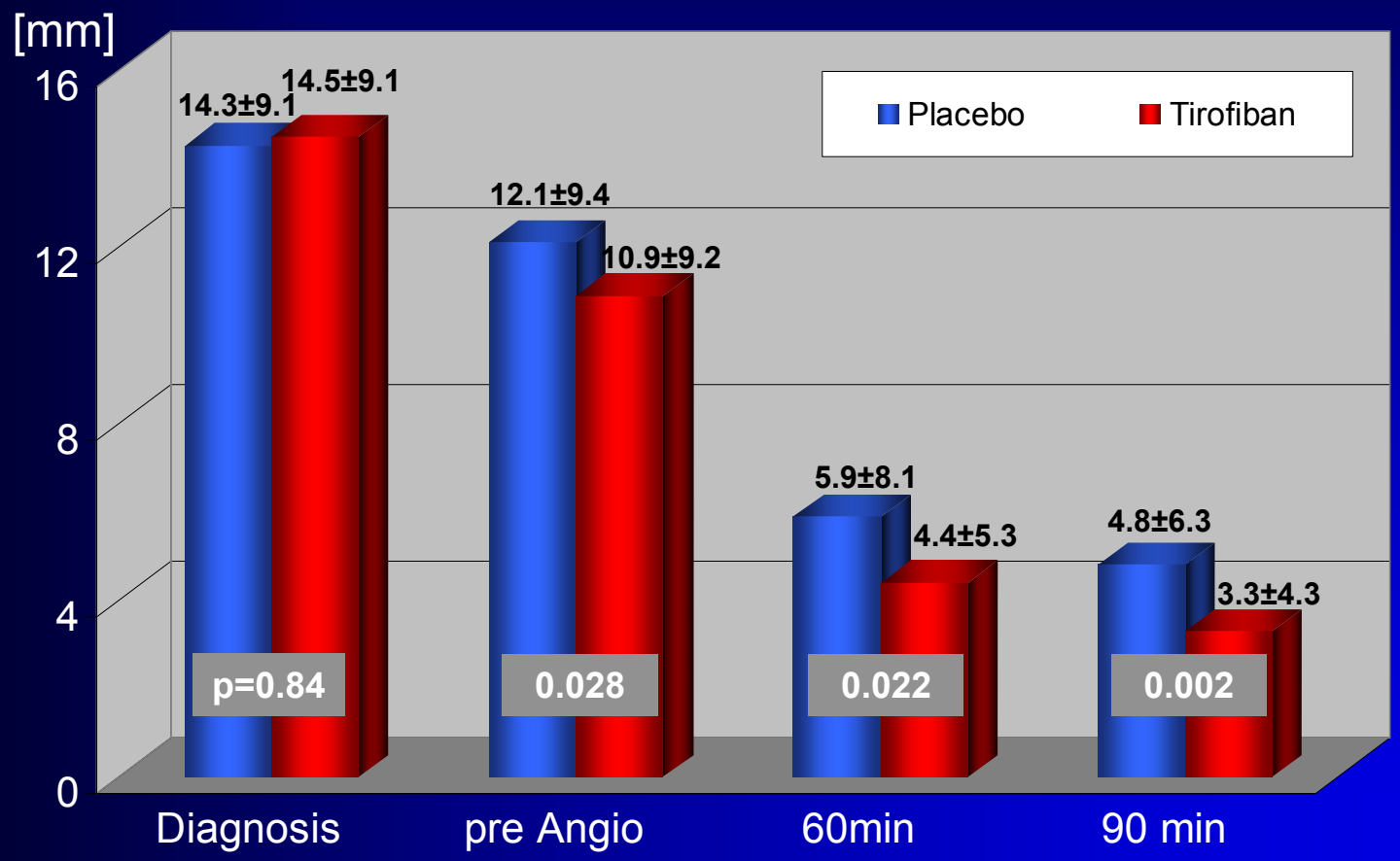
PCI

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.

Cumulative ST- Deviation over Time



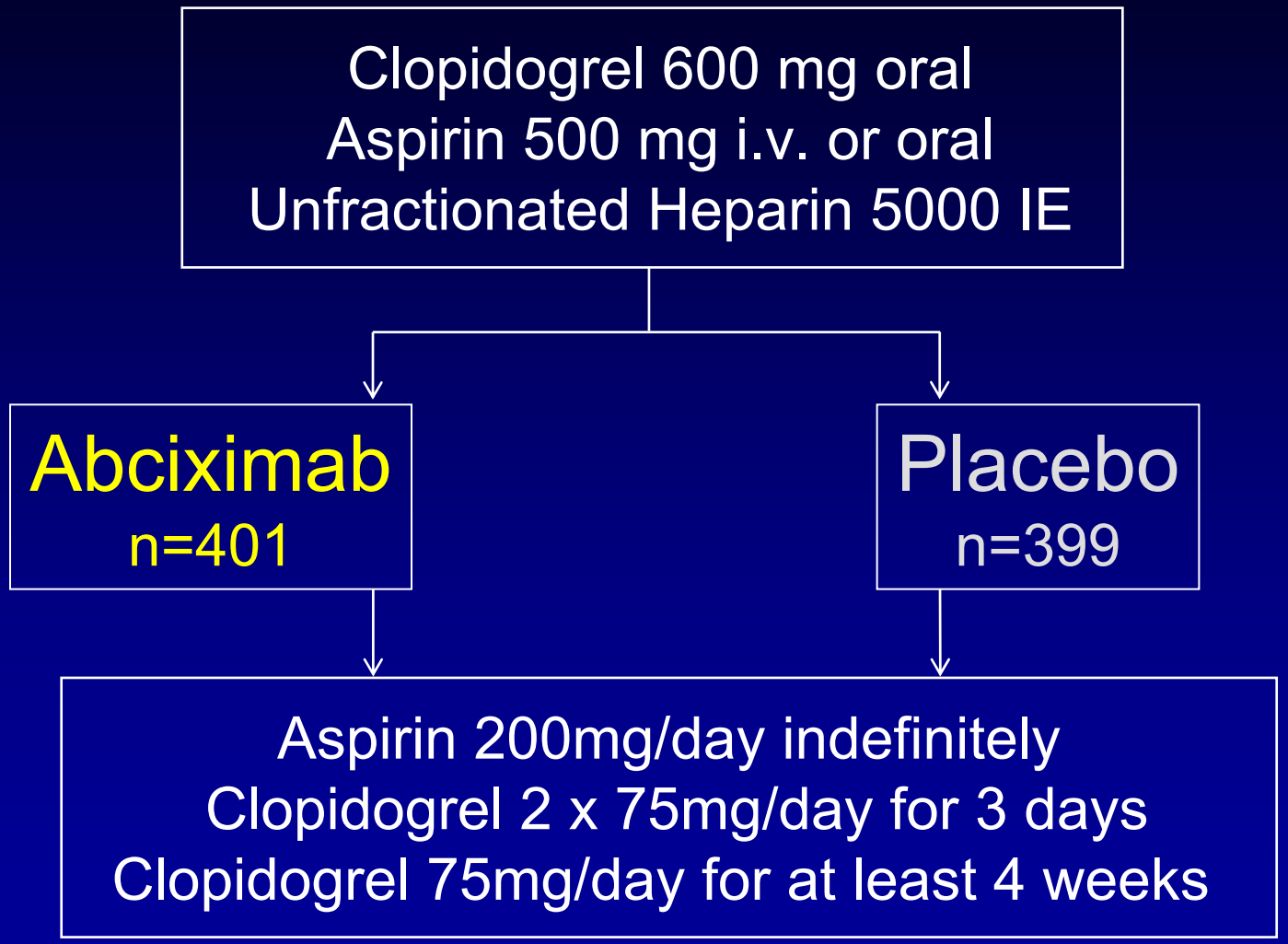
Hamm CW et al. Abstract 413-5. Presented April 1, 2008, at the American College of Cardiology 57th Annual Meeting in Chicago, IL.

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.

Study Therapy
BRAVE-3 (randomized, double-blind, multicenter)

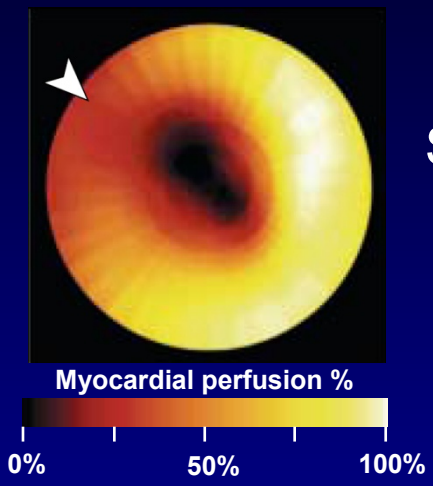


BRAVE-3

Endpoints

Primary endpoint:

- Final infarct size (% of the left ventricle)



SPECT study (5-7 days after randomization)

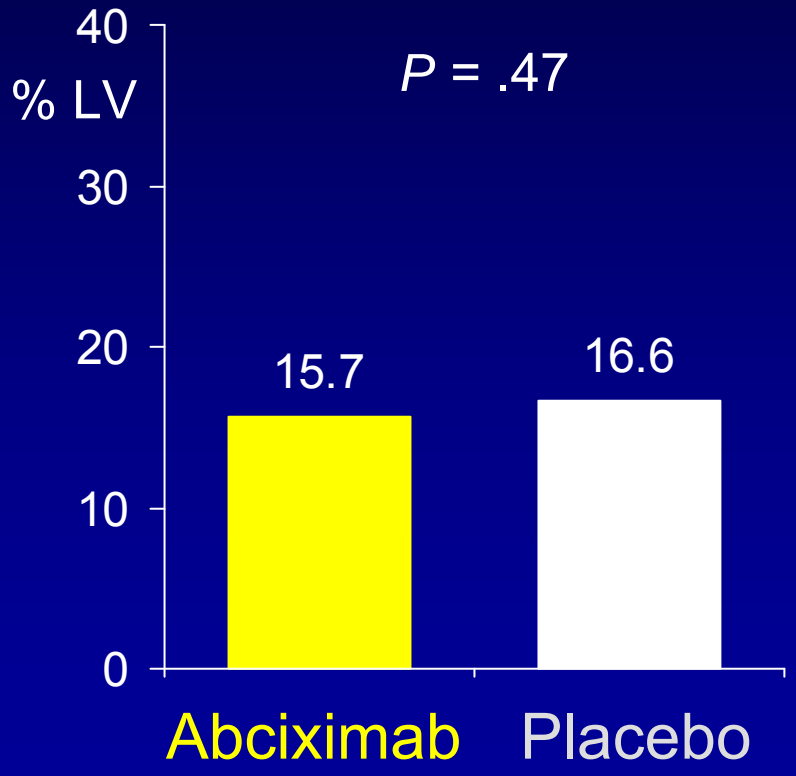
Secondary endpoints:

- Death
- Myocardial reinfarction
- Urgent revascularization
- Stroke
- Major and minor bleedings (TIMI criteria)
- Profound thrombocytopenia

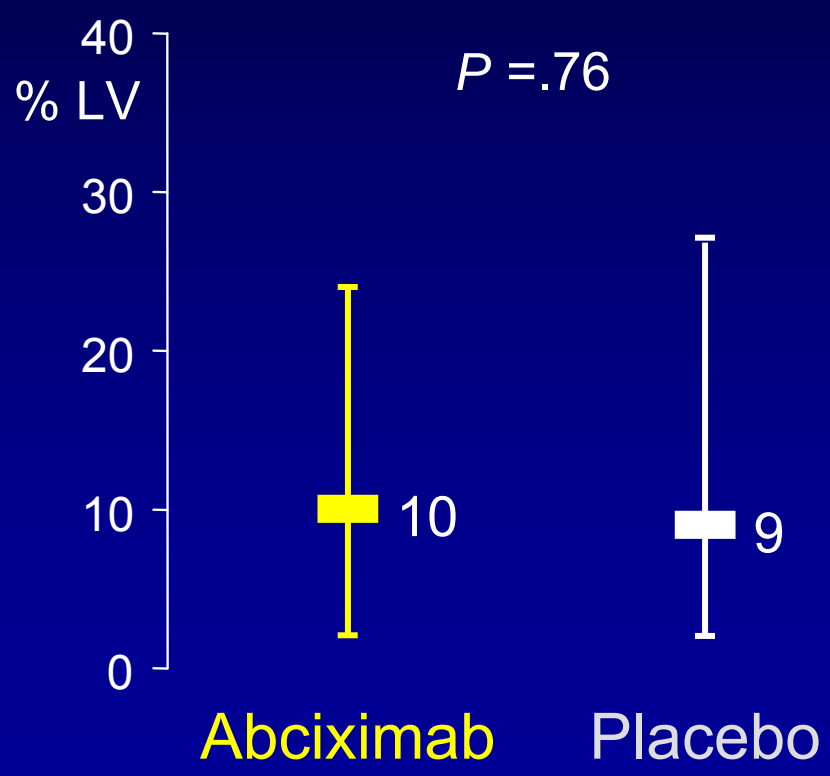
Primary Endpoint

BRAVE-3

Final infarct size
Mean



Final infarct size
Median [25th; 75th percentile]



So is there a role for GP IIb/IIIa blockers on top of clopidogrel loading in STEMI?

- ON TIME 2 and BRAVE 3 seem to be contradictory.
- Both studies did not use hard clinical endpoints.
- BRAVE 3 accepted patients up to 24h, possibly too late to modify infarct size.

2010 ESC REVASC. GUIDELINES

Anti thrombotic therapy in primary PCI for STEMI

Antiplatelet therapy				
	ASA	I	B	55, 94
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C	—
	Prasugrel[d]	I	B	246, 252
	Ticagrelor[d]	I	B	248, 253
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)			
	Abciximab	IIa	A	55, 94
	Eptifibatide	IIa	B	259, 260
	Tirofiban	IIb	B	55, 94
	Upstream GPIIb–IIIa antagonists	III	B	86
Anticoagulation				
	Bivalirudin (monotherapy)	I	B	255
	UFH	I	C	—
	Fondaparinux	III	B	256

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	