ASSENT- 4 PCI

The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction

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Hotline 06 sep 2005
ESC Congress 2005 Stockholm

Facilitated direct PCI for STEMI

The goal of combined pharmaco-mechanical reperfusion is to maximize myocardial salvage

- by reducing the treatment delay
- by providing higher patency rates of the IRA
- by improving microcirculatory flow
- by reducing reocclusion and (re)intervention rates

Solid conceptual rationale for “combo” therapy !

A great Clinical Trial is one that …

1. provides a clear-cut answer to the question
2. raises new questions
3. influences the practice of medicine

ASSENT- 4 PCI certainly meets all three of these criteria

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Full-dose fibrinolysis upstream of primary PCI does not facilitate mechanical reperfusion

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Instead, clinical outcome is worse with combined pharmaco-mechanical reperfusion

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Instead, clinical outcome is worse with combined pharmaco-mechanical reperfusion

Benefit from earlier reperfusion is offset by increased rate of peri-procedural ischemic complications and stroke

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ASSENT- 4 PCI

	TNK + PCI	PCI alone
Onset to TNK bolus	153 (105, 225)	
TNK to 1st balloon	104 (82, 135)	
Onset to 1st balloon	263 (212, 340)	256 (200, 335)

ASSENT- 4 PCI

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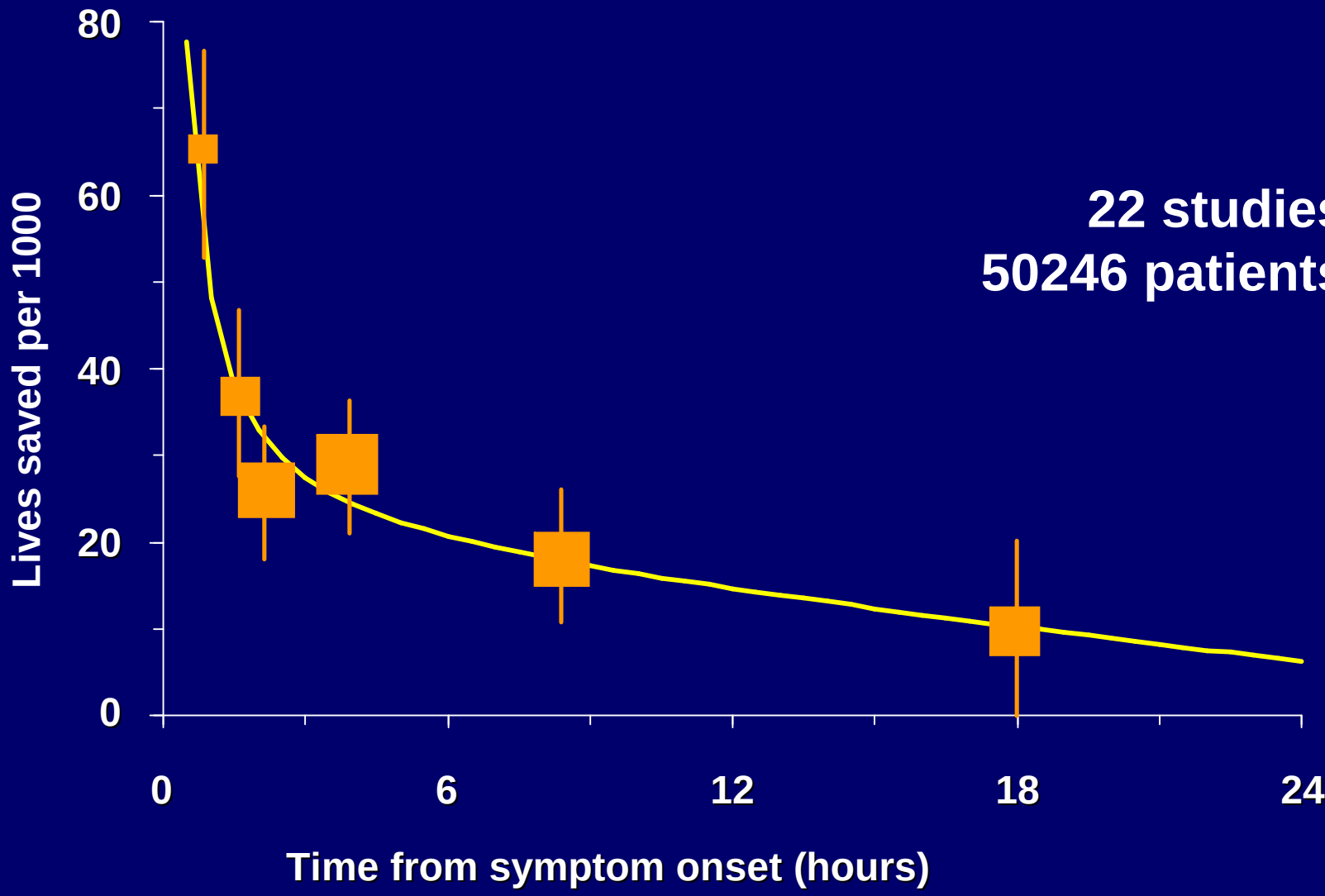
TNK to 1st balloon	104 (82, 135)	
Onset to 1st balloon	263 (212, 340)	256 (200, 335)

Reperfusion delay was reduced by an estimated 1 hour with TNK-facilitated PCI

Treatment of Heart Attacks by Reperfusion

Time Saves Myocardium and Muscle Is Life !



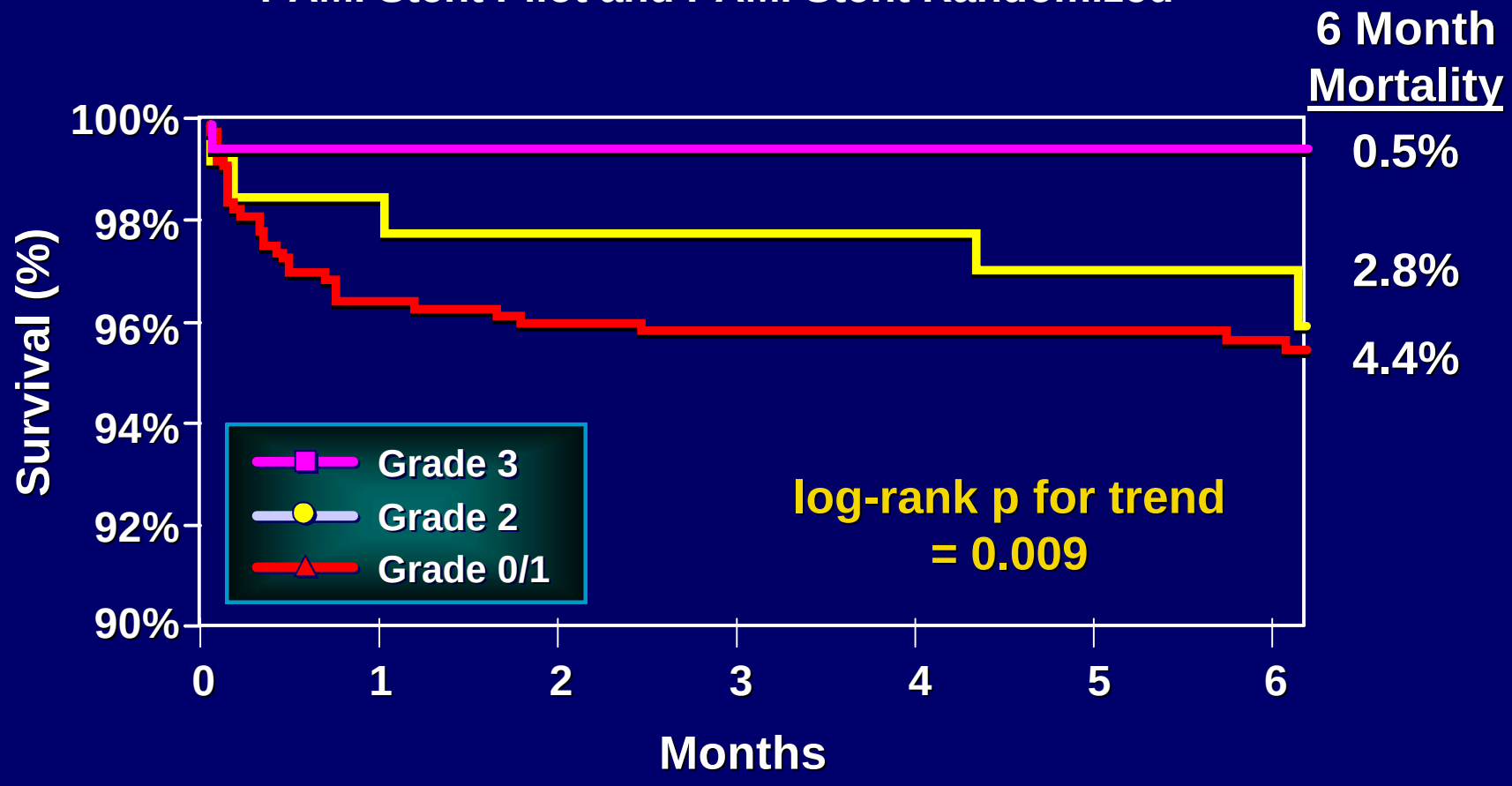
Lancet, 1996

ASSENT- 4 PCI

	TNK + PCI	PCI alone
Onset to TNK bolus	153 (105, 225)	
TNK to 1st balloon	104 (82, 135)	
Onset to 1st balloon	263 (212, 340)	256 (200, 335)
TIMI 2 + 3 prior to PCI	64.4 %	28.1 %
TIMI 2 + 3 post PCI	95.3 %	97.6 %
GP IIb/IIIa inhibitors	9.8 %	53.5 %

Effect of Pre-procedural TIMI Flow on Late Mortality after Primary PCI

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



Stone, et.al. Circulation 2001; 104 (6): 636-641.

Do fibrinolytics promote a prothrombotic milieu in the context of insufficient platelet inhibition?

Such prothrombotic state might cause higher peri-procedural ischemic complications with “facilitated PCI”

TIMI II A	12.8 vs 6.8 %
ECSG	17.0 vs 3.0 %
SAMI	10.3 vs 1.6 %
PRAGUE	7.0 vs 1.0 %
ASSENT-4 PCI	**10.4 vs 3.0 %**

Facilitated direct PCI for STEMI

Options for Pharmacological Treatment Upstream of Direct PCI

Fibrinolytic agents

Antiplatelet drugs

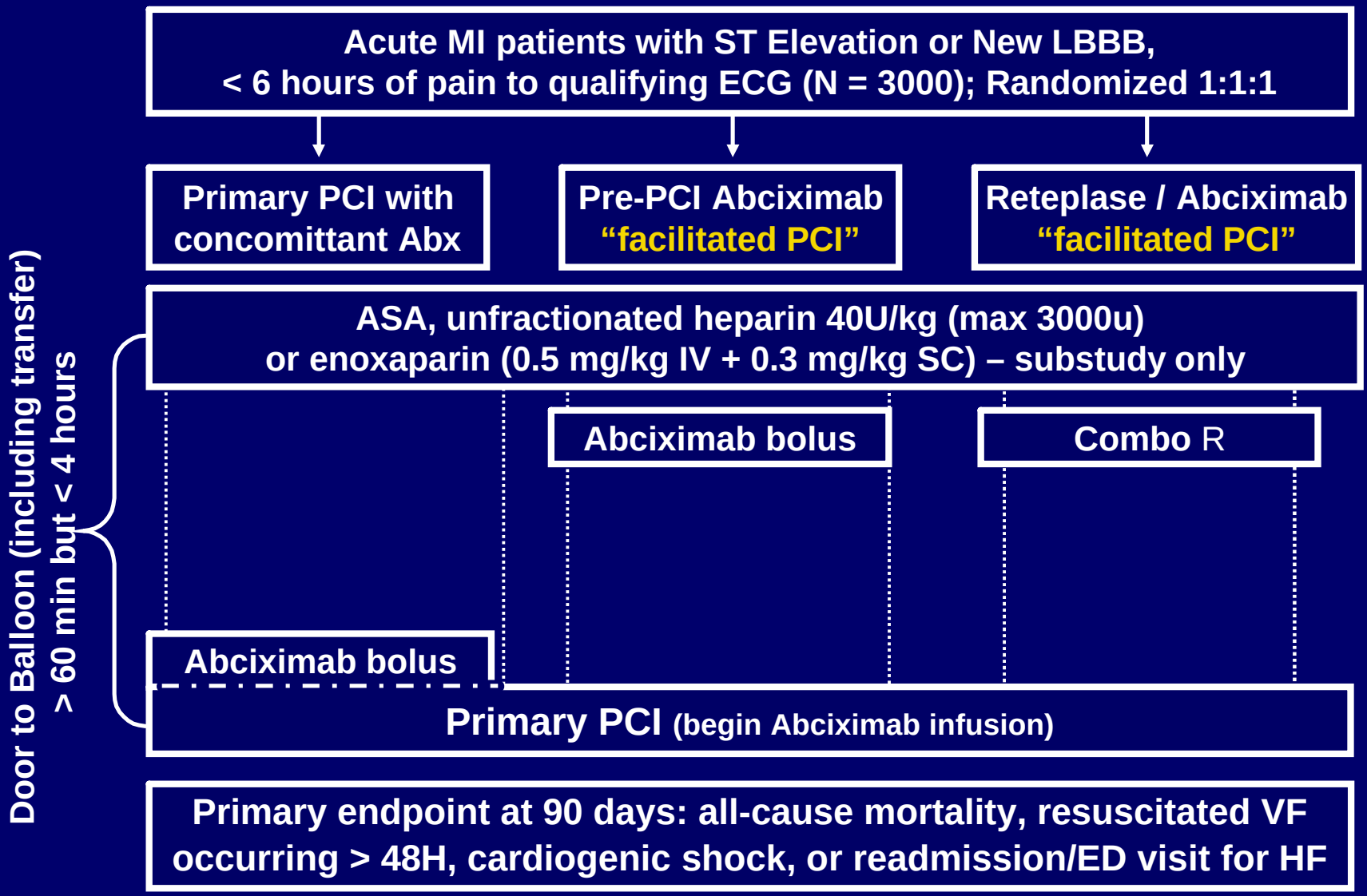
- **Glycoprotein IIb/IIIa inhibitors**
- **Clopidogrel**

Anticoagulants

- **LMWH / UFH**
- **Direct Thrombin Inhibitors**

Combinations of any of the above

FINESSE: Study Design



A great Clinical Trial is one that …

1. provides a clear-cut answer to the question
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ASSENT-4 PCI
Lessons for Clinical Practice

- When PCI is not available, reperfusion therapy using fibrinolytic agents is indicated (I a)

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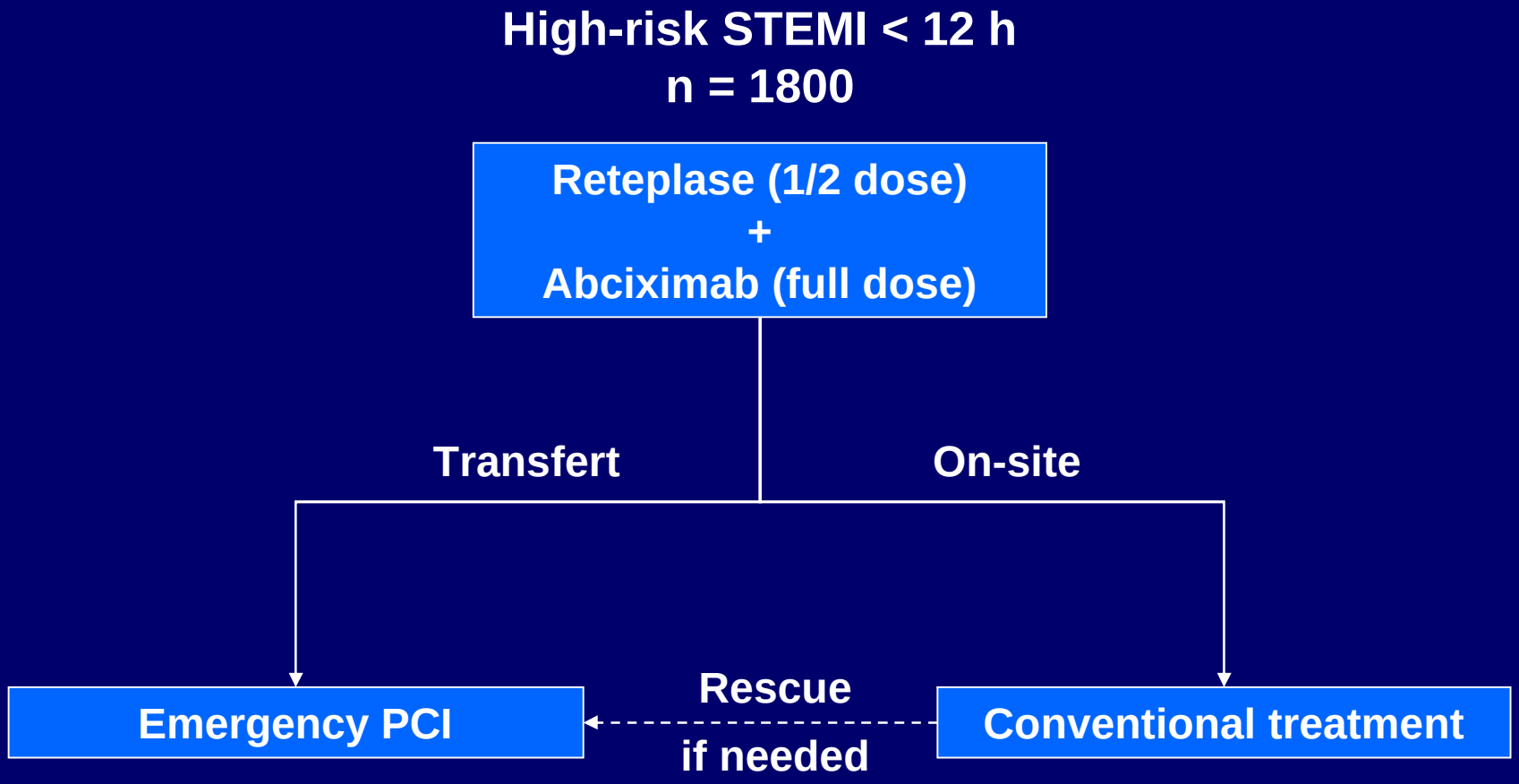
Lessons for Clinical Practice

- When PCI is not available, reperfusion therapy using fibrinolytic agents is indicated (I a)

- Where primary PCI is available, it should be offered to patients presenting with STEMI (I a)

- Primary PCI with procedural delay up to 2 hours after first medical contact is not facilitated by upstream full-dose fibrinolysis

CARESS in AMI: Study Design



Primary endpoint: mortality, re-infarction, ischemia at 30 days

Di Mario et al.

ASSENT- 4 PCI

Onset to TNK bo

TNK to 1st ballo

Onset to 1st ball

GP IIb/IIIa inhibit

TIMI 2 + 3

Histologic analysis

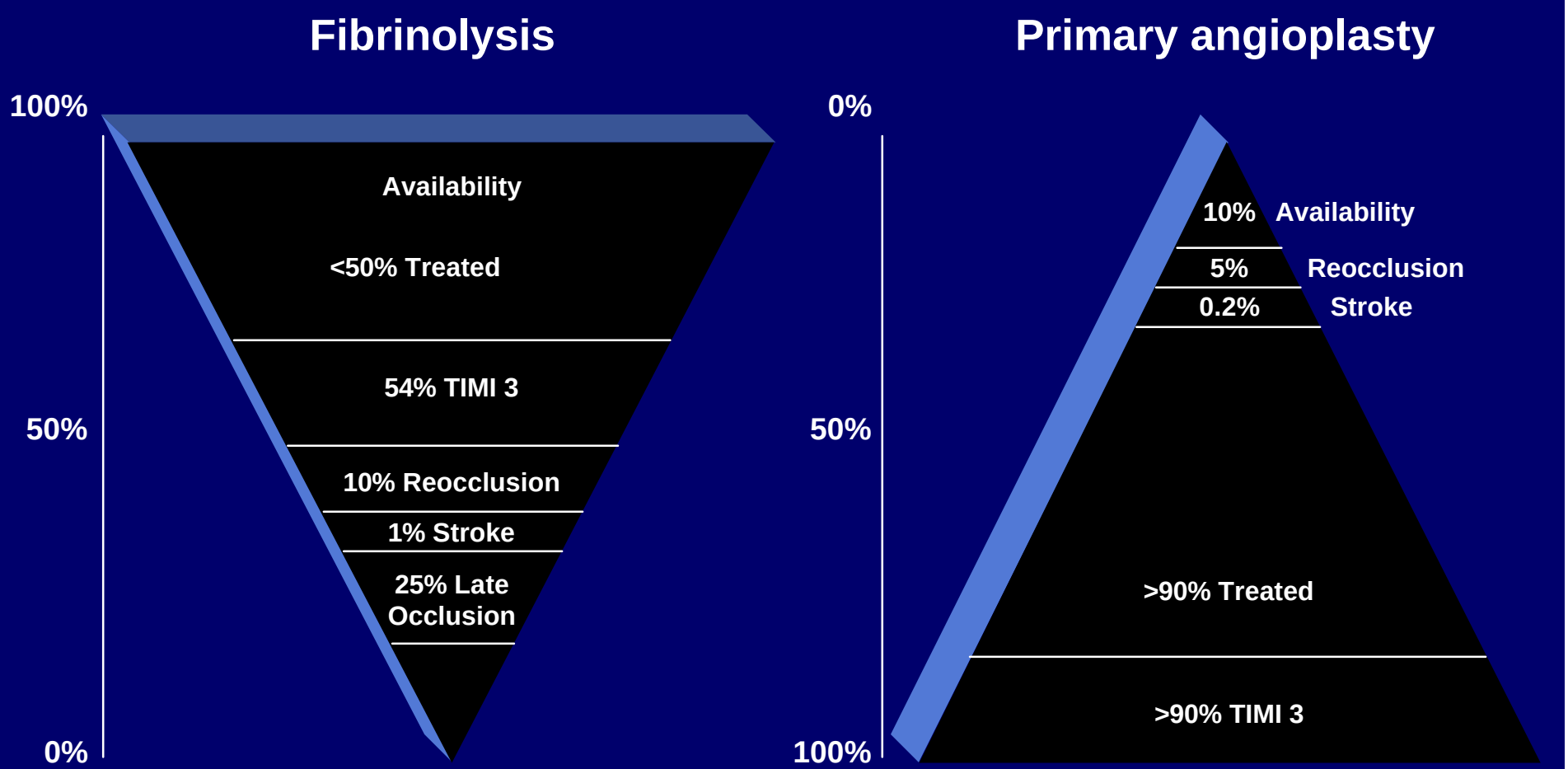
- Necrotic core
- fibrin
- foam cells
- cholesterol clefts

Distal embolization	**11.1 %**	**12.8 %**


Relationship Between Microvascular Obstruction and Event-free Survival
Event-Free Survival (%)*
100
80
60
40
20
0
No Microvascular Obstruction
Microvascular Obstruction
p < 0.01
0
5
10
15
20
25
Months
*Clinical course without CV death, CHF, or CVA
Wu KC, et al. Circulation 1998;97;765-772

Fibrinolysis and primary angioplasty:

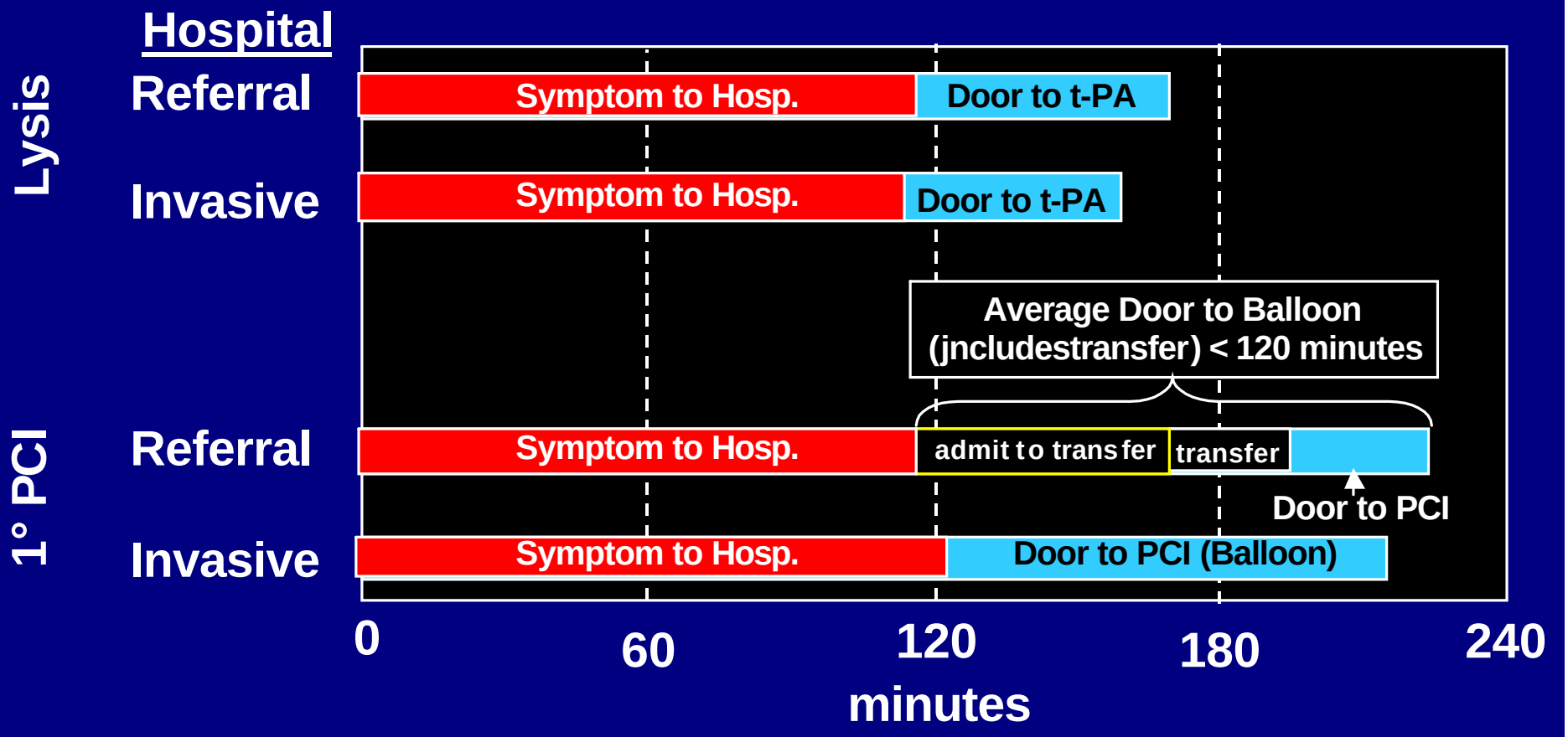
Differences between *"availability" and "efficacy"*

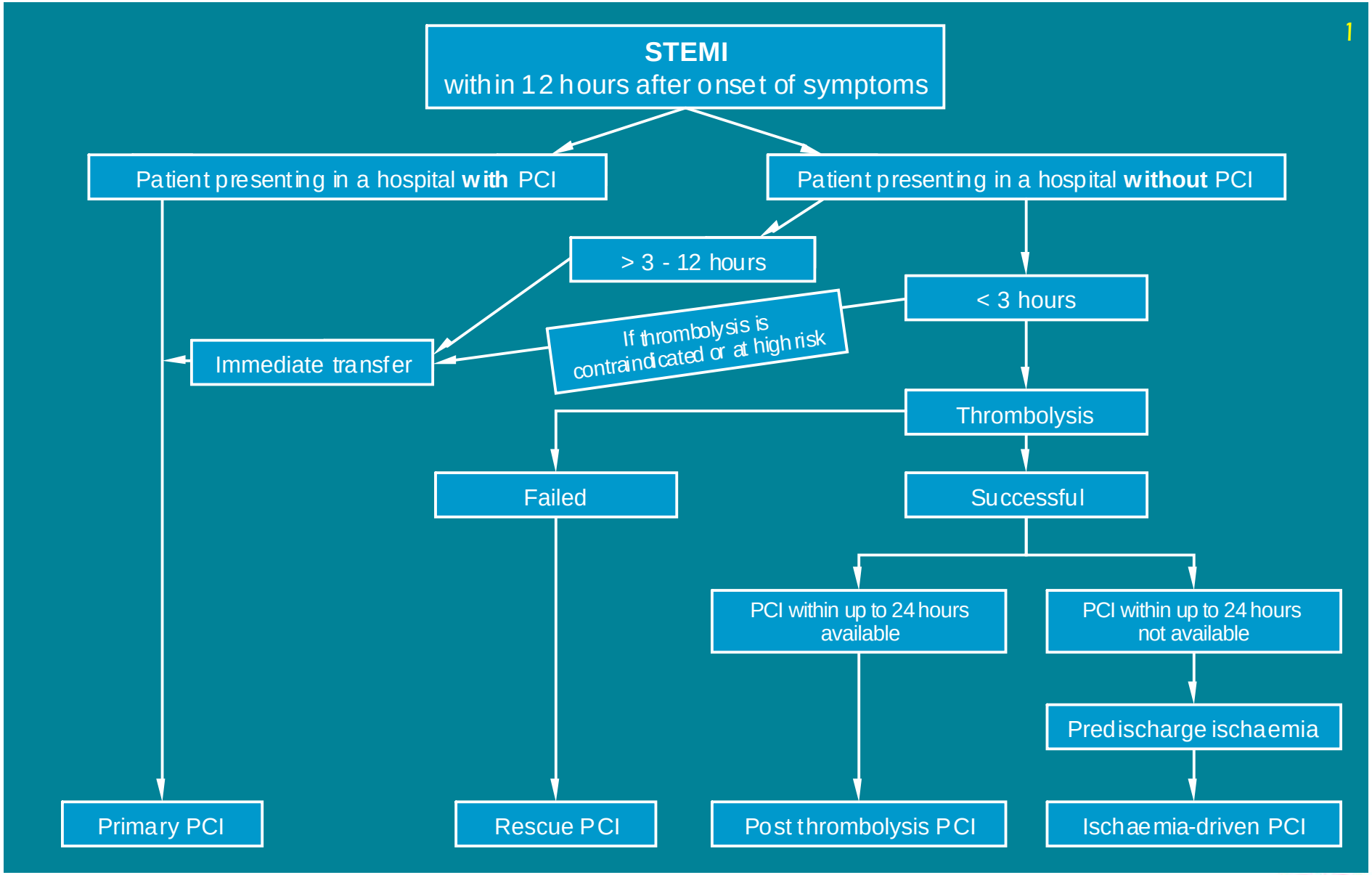


Ribichini & Wijns HEART 2002;88:298

WW3214

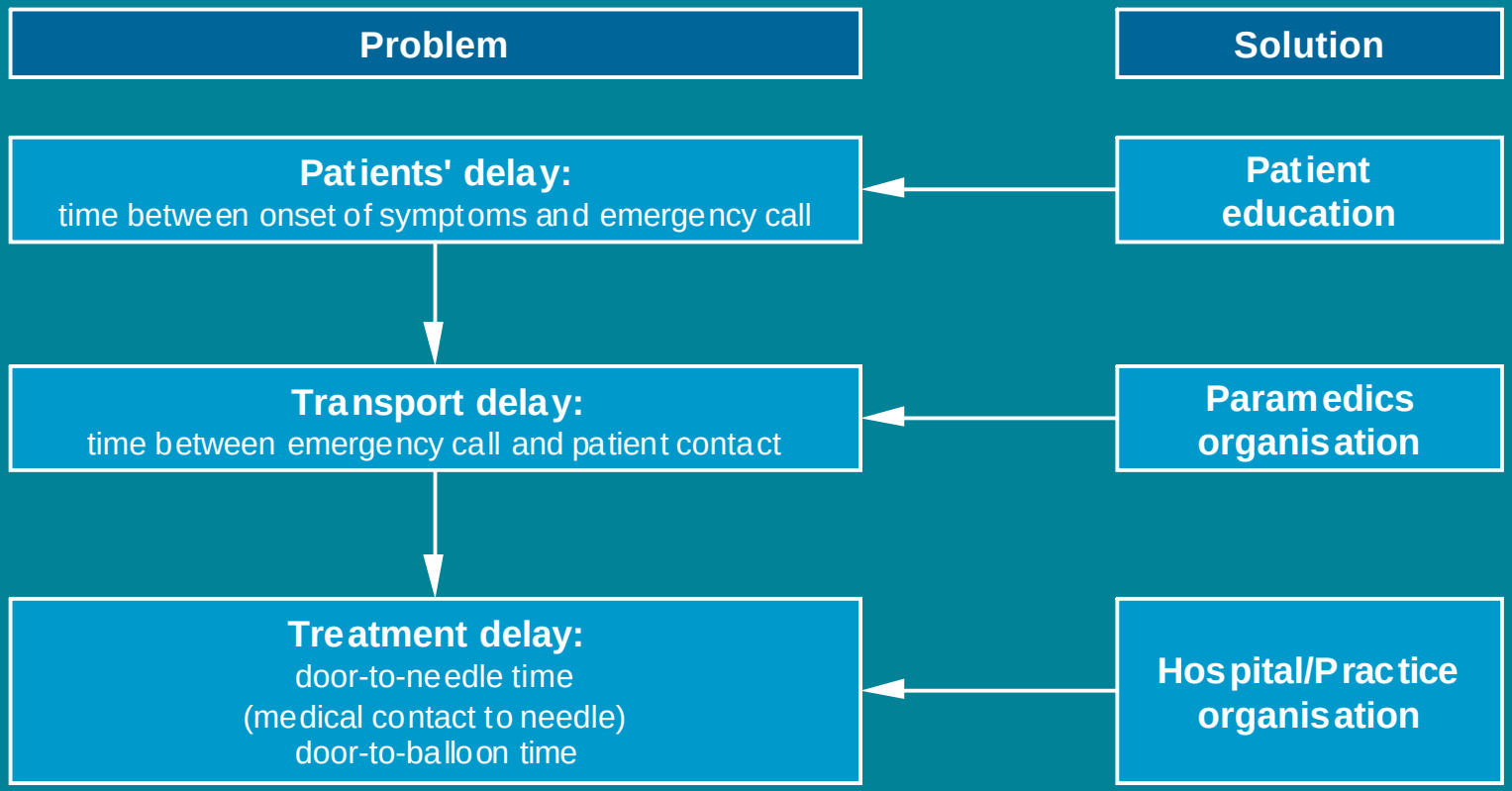
DANAMI-2 - Time from Symptom Onset to Admission and Time from Door to Rx





EUROPEAN SOCIETY OF CARDIOLOGY

Minimisation of Time Delays for Direct PCI in STEMI



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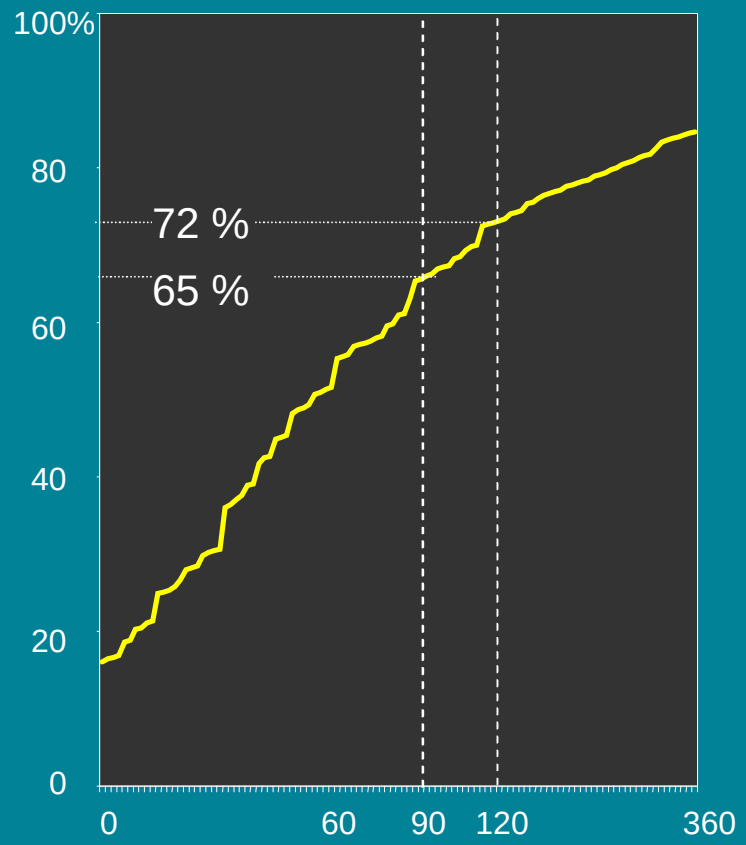
Primary PCI for STEMI
In-Hospital Delays



Primary PCI is the preferred treatment if performed < 90 minutes after first medical contact

EHJ 2003;24:28-66

Delay unknown in 29 %

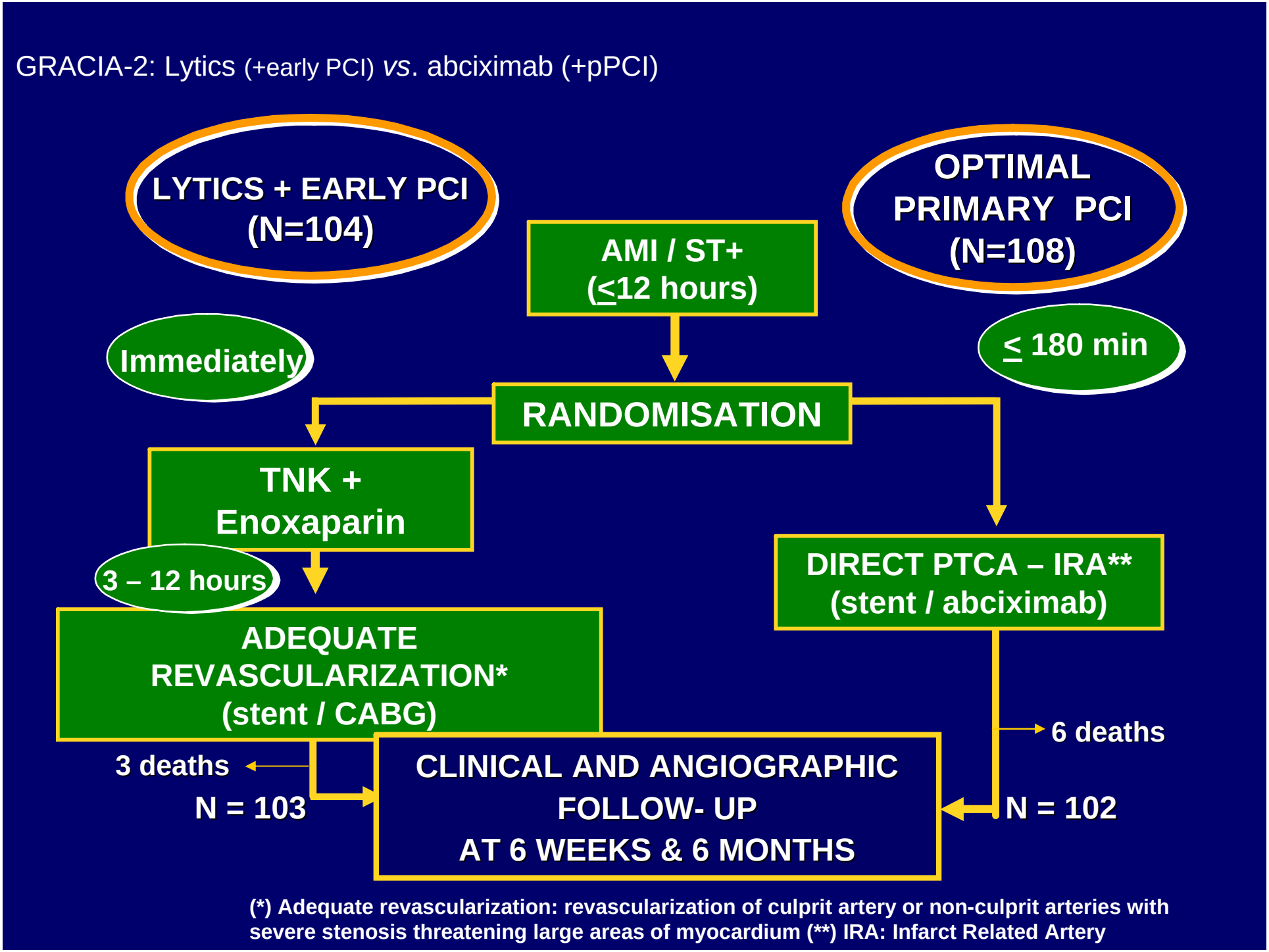
Euro Heart Survey Revascularization 1

EUROPEAN SOCIETY OF CARDIOLOGY

Transfer for Primary PCI vs Lysis

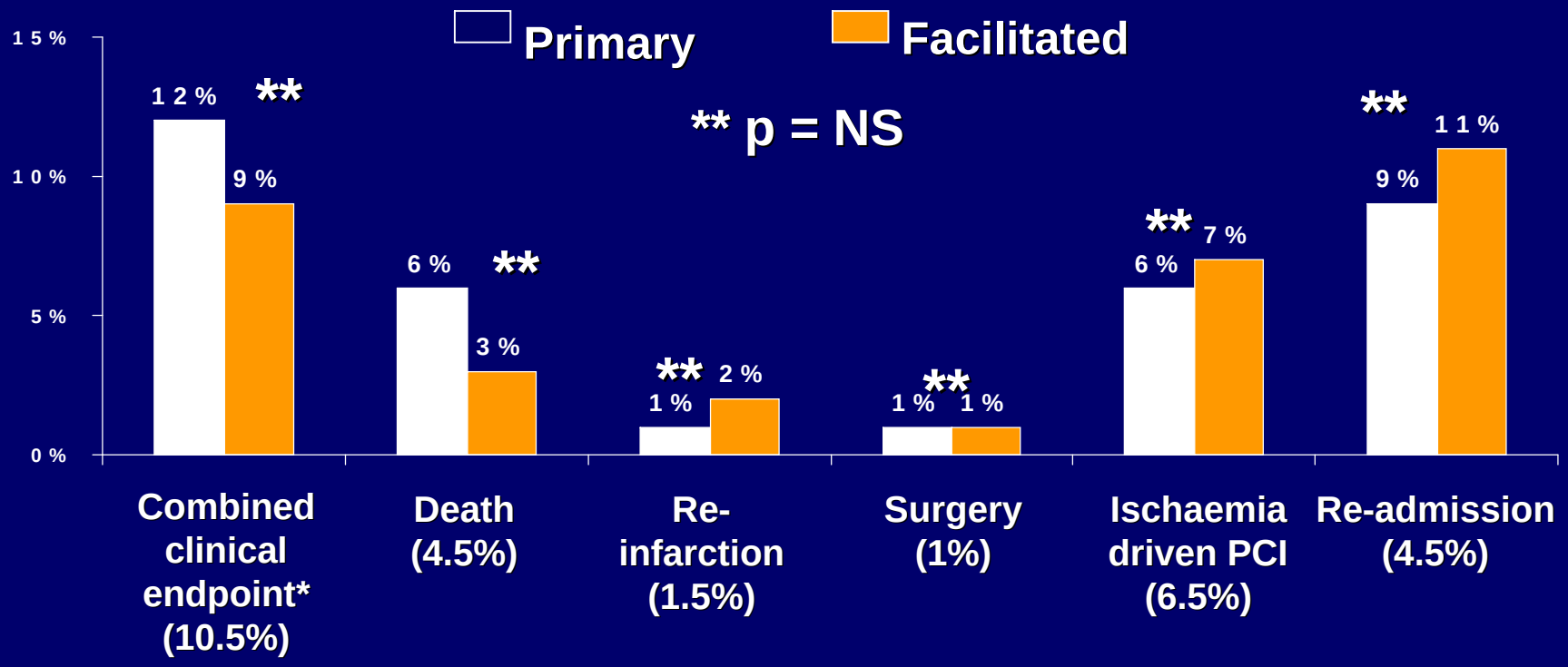
	Limburg	Prague-1	Prague-2	Air-PAMI	DANAMI-2
n	224	300	850	138	1572
STEMI	< 6 h	< 6 h	< 12 h	< 12 h	< 12 h
Lytic R/	Alteplase	SK	SK	SK or t-PA	Alteplase
% stenting	21	79	63	34	93
Transfert time	< 30	35	48 ± 20	33 ± 29	20 - 45
1^{ary} endpoint	death, MI	death, MI, stroke	death	death, MI, stroke	death, MI, stroke
Results	16 / 8	23 / 8	10 / 6.8	13.6 / 8.4	**14 / 8**

GRACIA-2: Lytics (+early PCI) *vs*. abciximab (+pPCI)



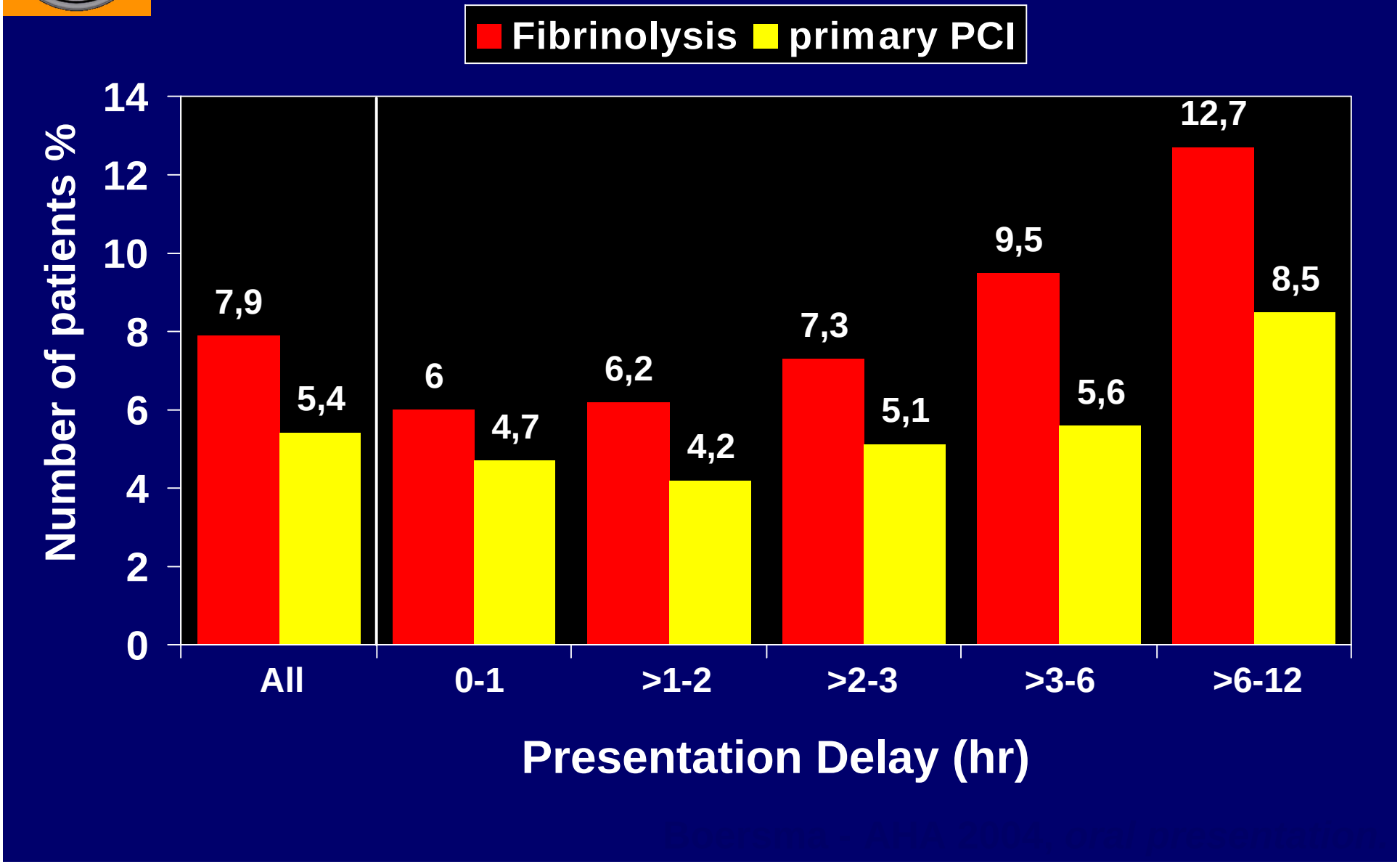
(*) Adequate revascularization: revascularization of culprit artery or non-culprit arteries with severe stenosis threatening large areas of myocardium (**) IRA: Infarct Related Artery

GRACIA – 2
6-week clinical outcome

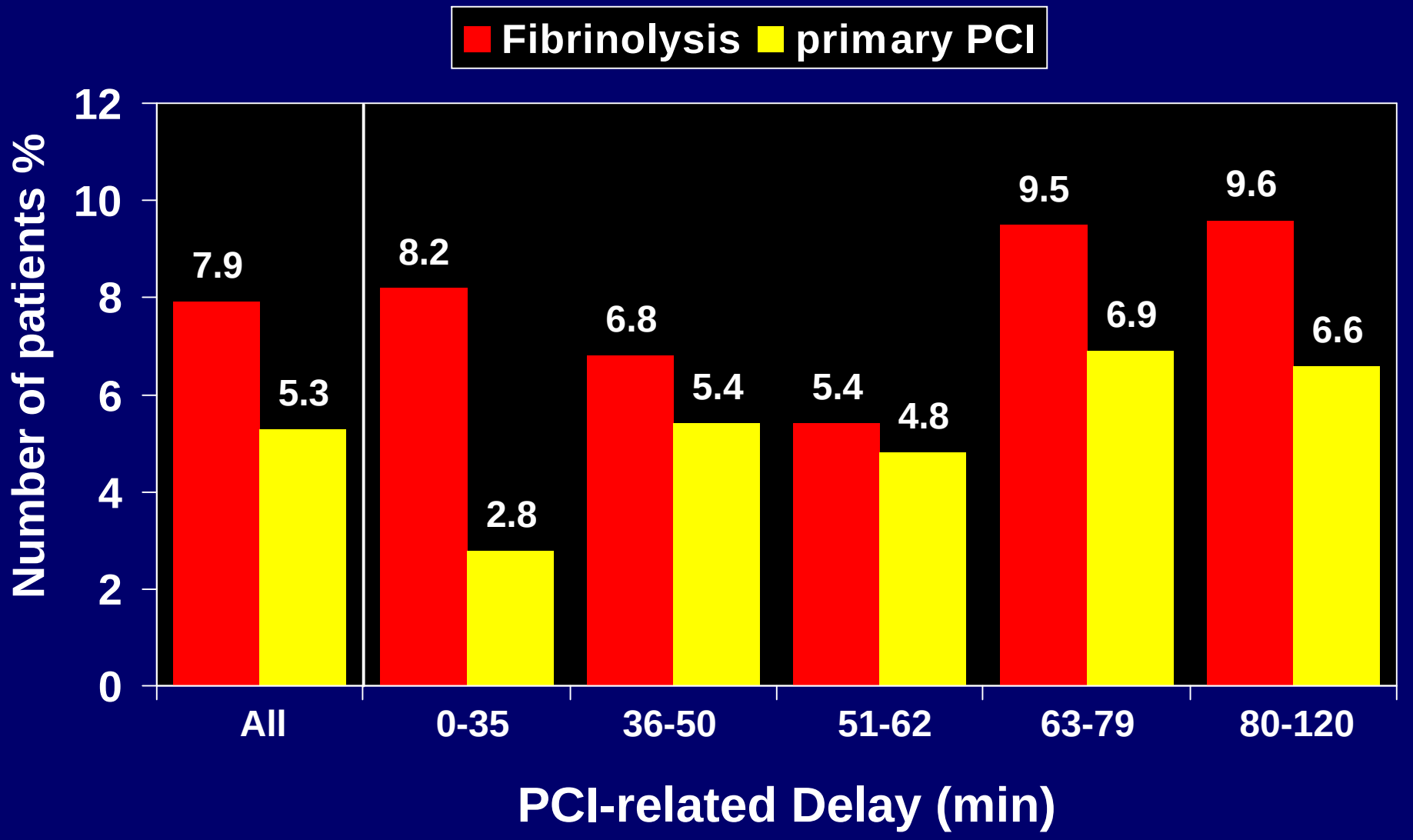


(*) Combined clinical EP: death, nonfatal MI, or ischemia-driven revascularization

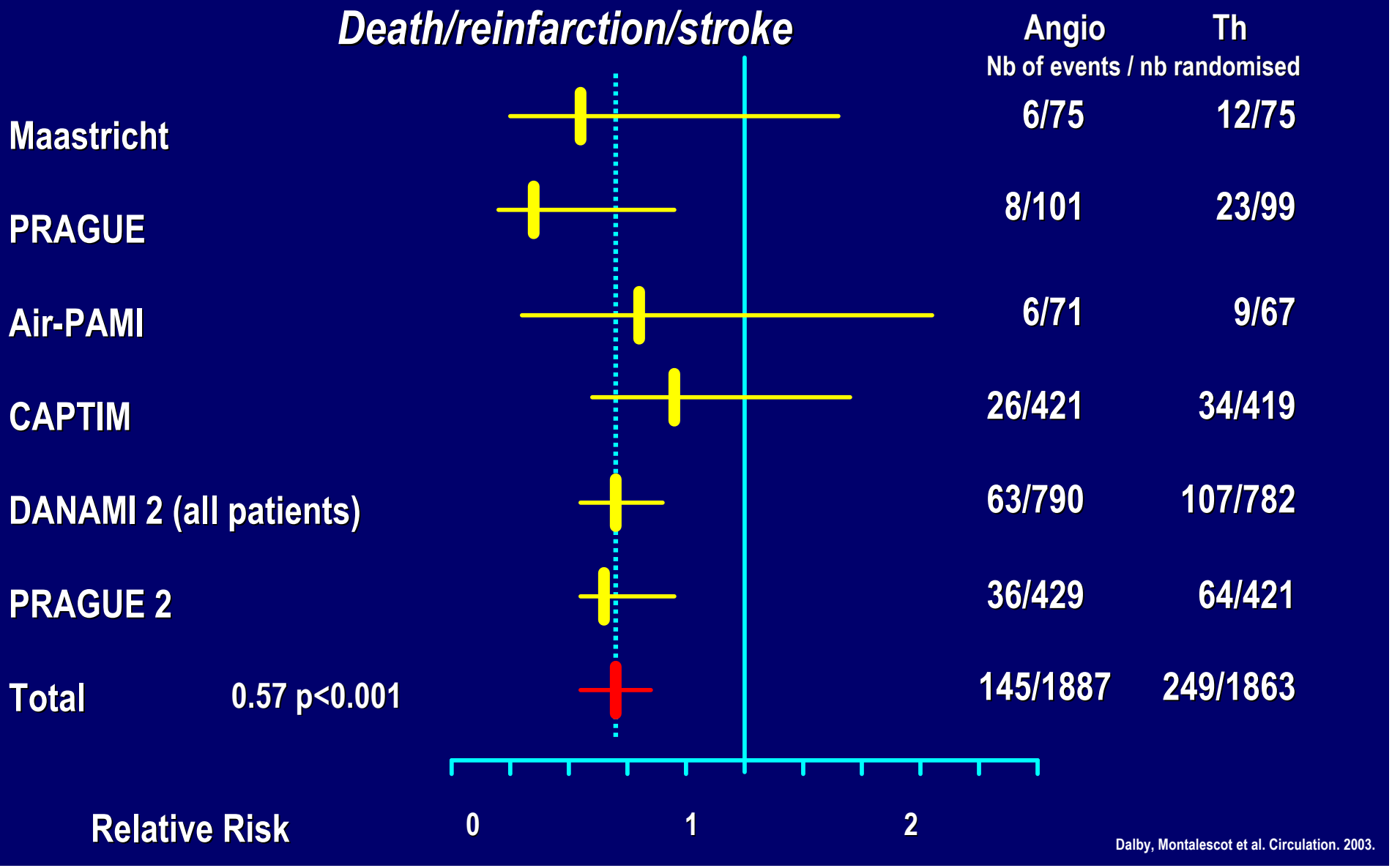
Death At 30 Days – Presentation Delay



Death At 30 Days – PCI-related Delay



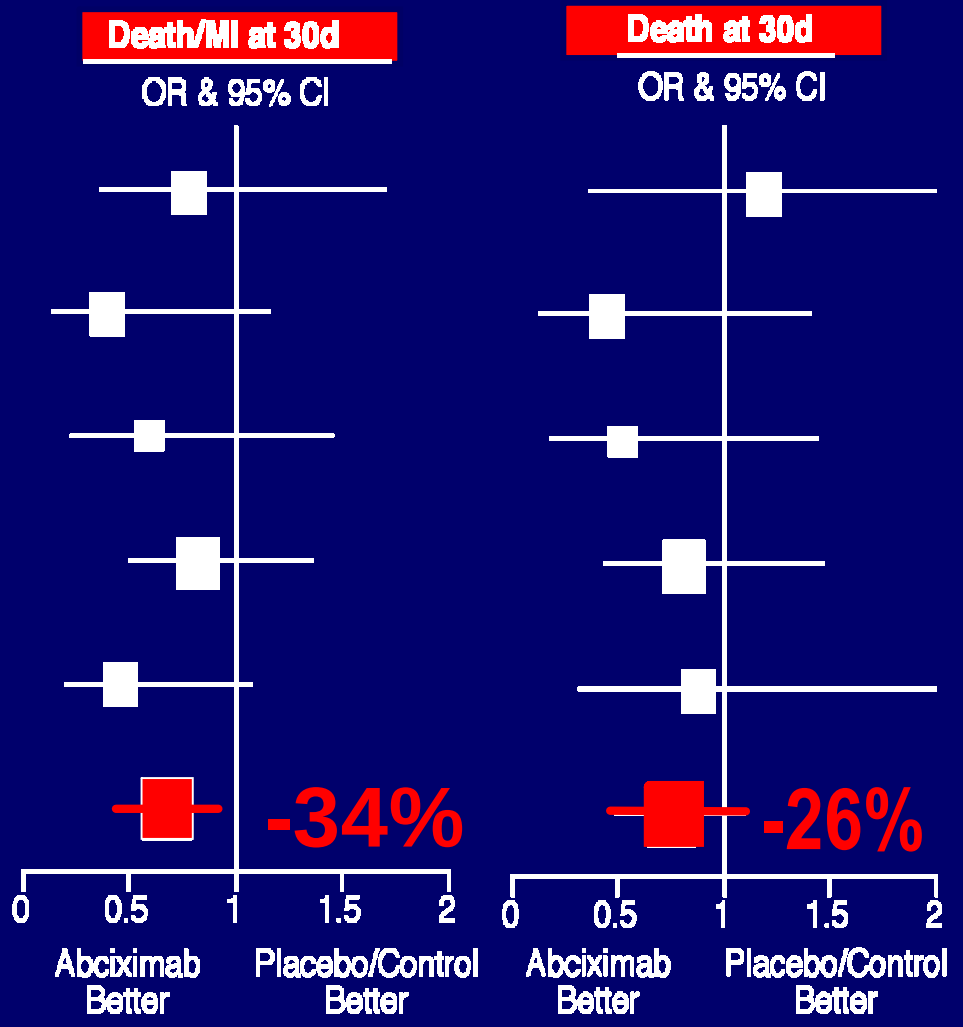
Transfer for PCI > Immediate lysis



Dalby, Montalescot et al. Circulation. 2003.

Abciximab in PCI of STEMI

Trial	Placebo Control	Abciximab
RAPPORT	14/242 (5.8%)	11/241 (4.6%)
ISAR-2	12/200 (6.0%)	5/201 (2.6%)
ADMIRAL	12/151 (7.9%)	7/149 (4.7%)
CADILLAC	33/1030 (3.2%)	28/1052 (2.7%)
ACE	17/200 (8.55%)	8/200 (4.0%)
Pooled	88/1823 (4.8%)	59/1843 (3.2%)



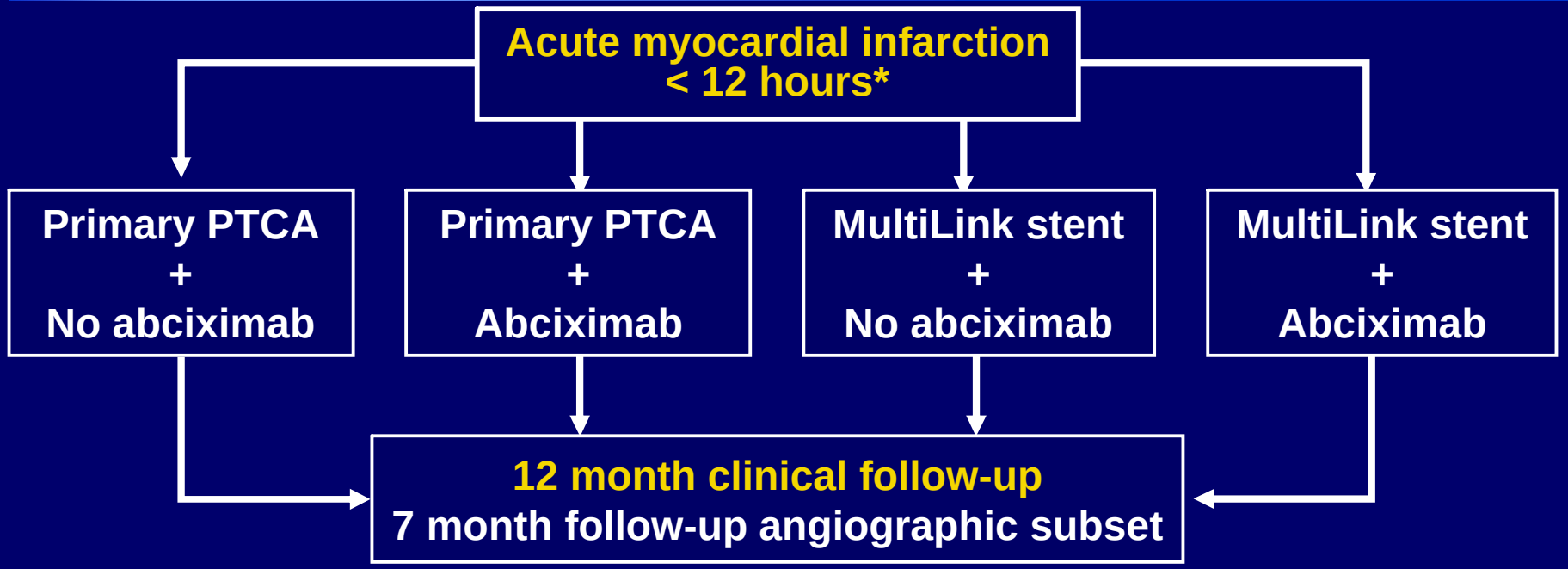
E Topol, FJ Neumann and G Montalescot JACC 2003

Review of Trials Evaluating Primary PCI for the Treatment of AMI

- 1° PTCA vs. lytic therapy
  - PAMI, GUSTO IIb
- Abciximab + 1° PTCA vs. 1° PTCA alone
  - EPIC (post-hoc analysis), RAPPORT
- 1° Stent is vs. 1° PTCA
  - PAMI-STENT
  - CADILLAC
- 1° Stent vs. fibrinolytic monotherapy or combo therapy
  - STOP-AMI, STOP-AMI 2, DANAMI-2, C-PORT
- Abciximab + 1° Stent vs. 1° Stent alone
  - Neumann, ISAR-2, CADILLAC, and ADMIRAL

Primary PCI for AMI

CADILLAC - Protocol Schematic (open label)



1° Endpoint -

6 month composite incidence of death, re-MI, disabling stroke, or ischemic TVR

2 Primary Hypotheses -

Stenting, without abciximab will be superior to PTCA without abciximab;
Stenting, without abciximab will be non-inferior to PTCA with abciximab

* excludes cardiogenic shock patients

NEJM 2002; 346: 957-66

STOP AMI-2 Trial design

Abciximab + Stent vs. Combo Rx

AMI < 12 hours
without contraindication for fibrinolysis

1° Stenting
with Abciximab
(n = 81)

Combo Rx without PCI
Abciximab + ↓ Dose t-PA
(n = 81)

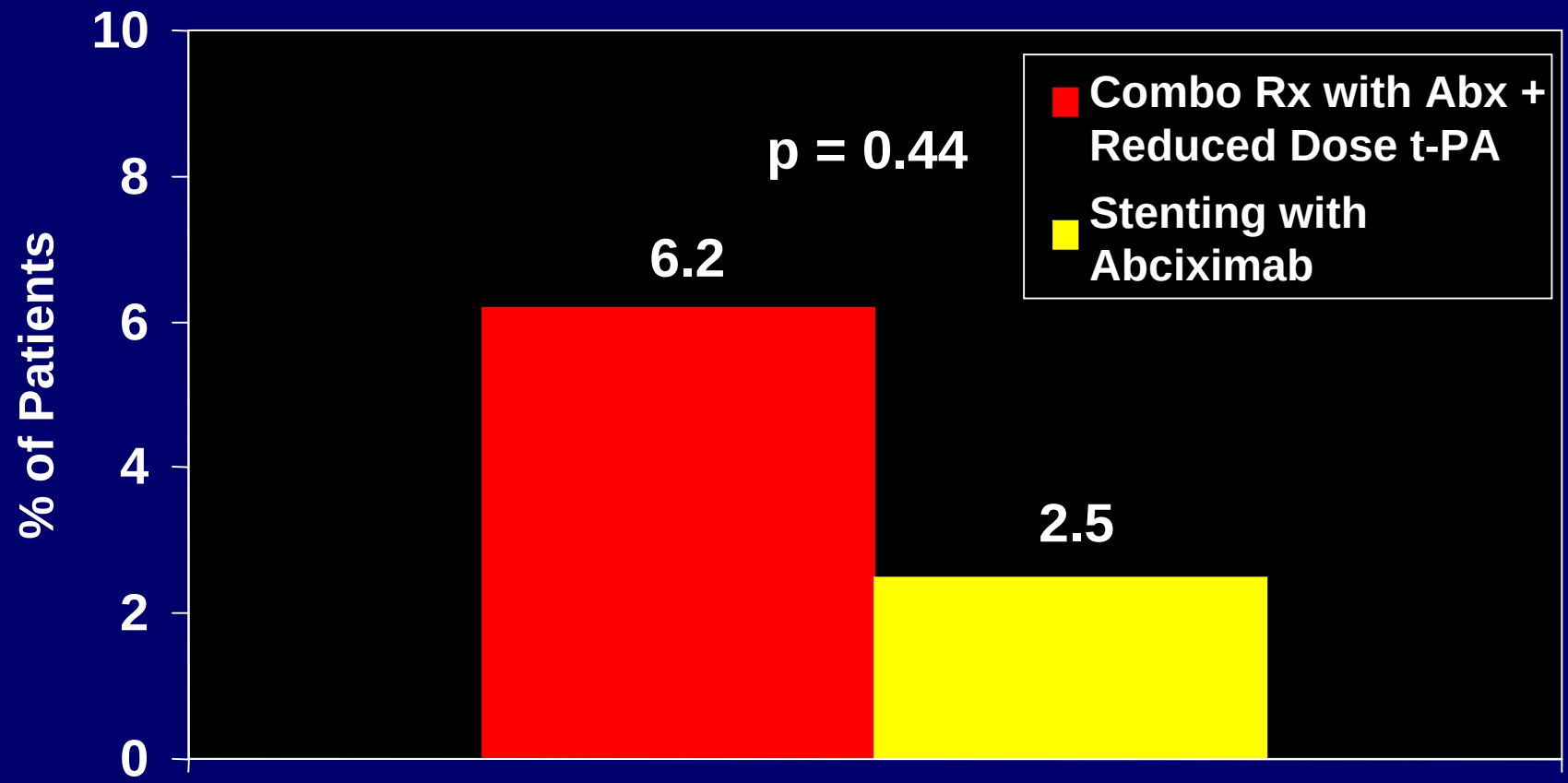
Primary Endpoint: scintigraphic left ventricular myocardial salvage index

Median Door to Needle Time = 35 min
Median Door to Balloon Time = 75 min

Lancet 2002; 359: 920-5

STOP AMI-2 30 Day Mortality

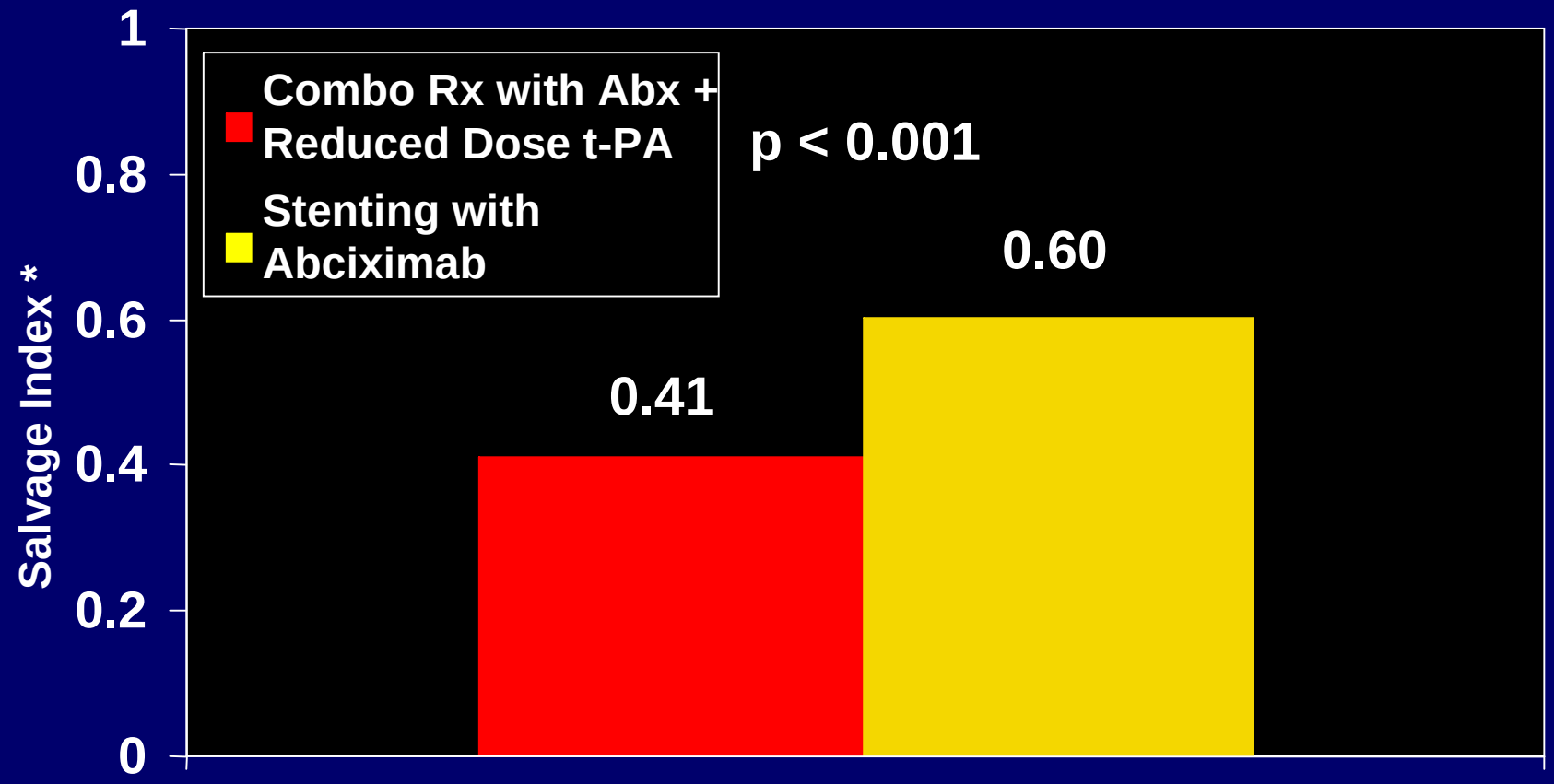
Abciximab + Stent vs. Combo Rx



Lancet 2002; 359: 920-5

STOP AMI-2 1° Endpoint - Salvage Index*

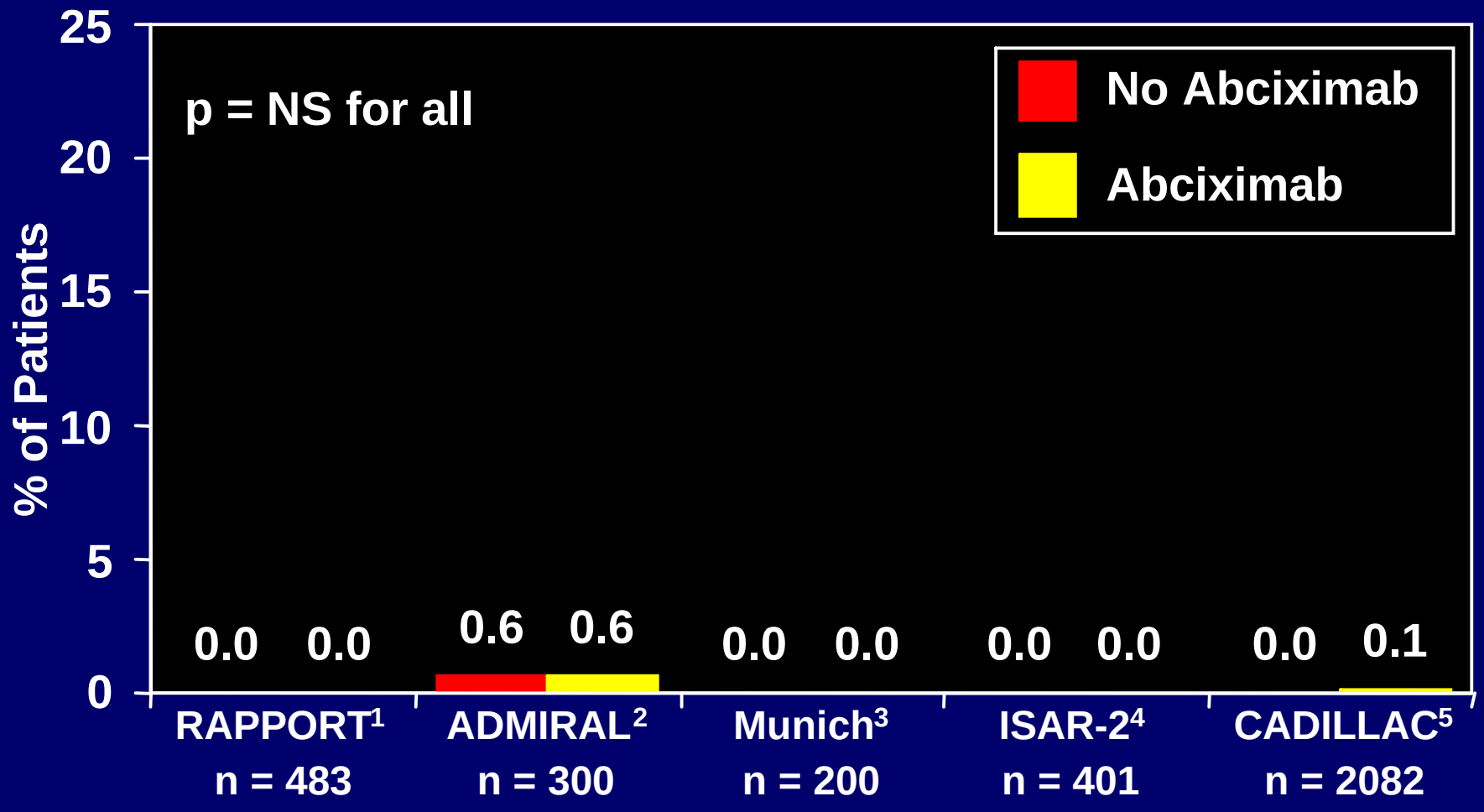
Abciximab + Stent vs. Combo Rx



* % of LV salvaged divided by the % of LV initially compromised by the perfusion defect

Lancet 2002; 359: 920-5

ICH in Randomized Trials



[1] *Circ. 1998; 98:734-41*

[2] *NEJM 2001;344:1895-1903*

[3] *Circ. 1998; 98:2695-2701*

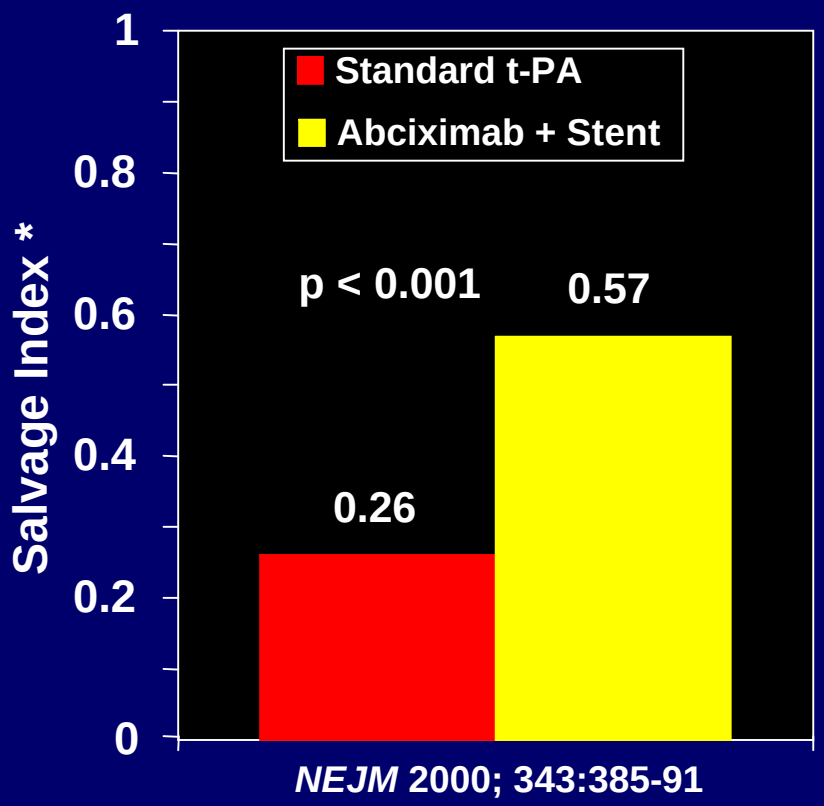
[4] *JACC 2000; 35:915-21*

[5] *NEJM 2002; 346:957-66*

Indicators of Myocardial Salvage

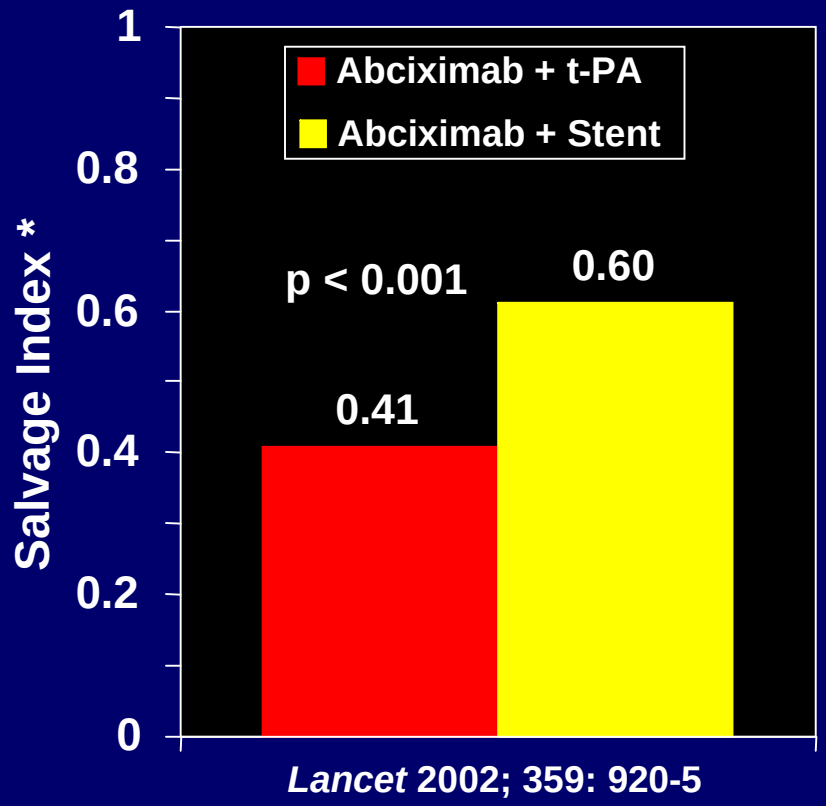
Abciximab + Stent vs. Thrombolysis

STOP AMI



NEJM 2000; 343:385-91

STOP AMI 2



Lancet 2002; 359: 920-5

* % of LV salvaged divided by the % of LV initially compromised by the perfusion defect

Conclusions

Abciximab + Stent vs. Thrombolysis

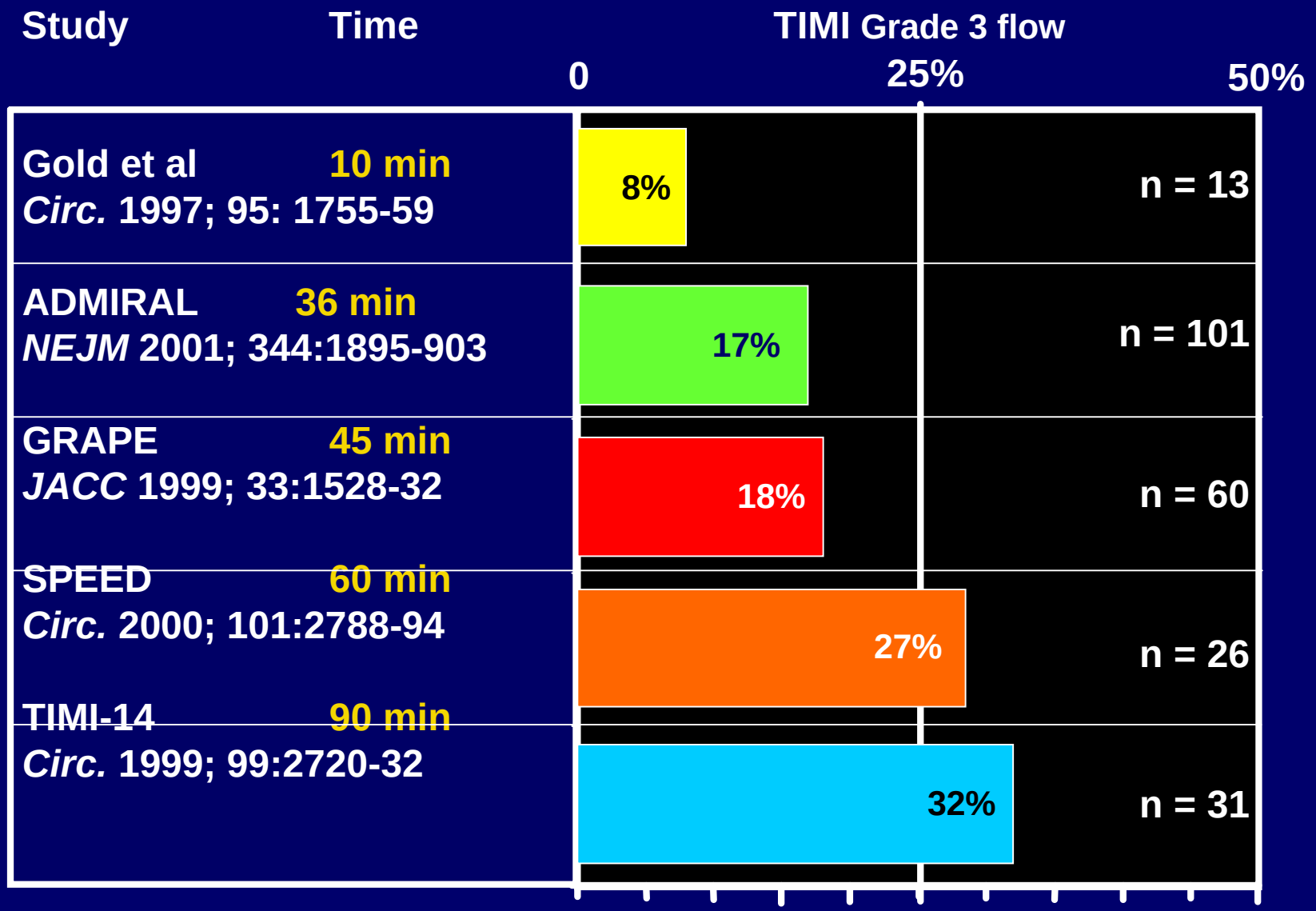
- **The addition of abciximab to 1/2 dose fibrinolysis in STOP-AMI 2 appears to enhance myocardial salvage achieved with fibrinolysis alone when compared with data from STOP-AMI 1.**

- **An interventional reperfusion strategy based on stenting with abciximab appears to be superior to pharmacologic lysis with either standard fibrinolysis or combination therapy.**

Lancet 2002; 359: 920-5

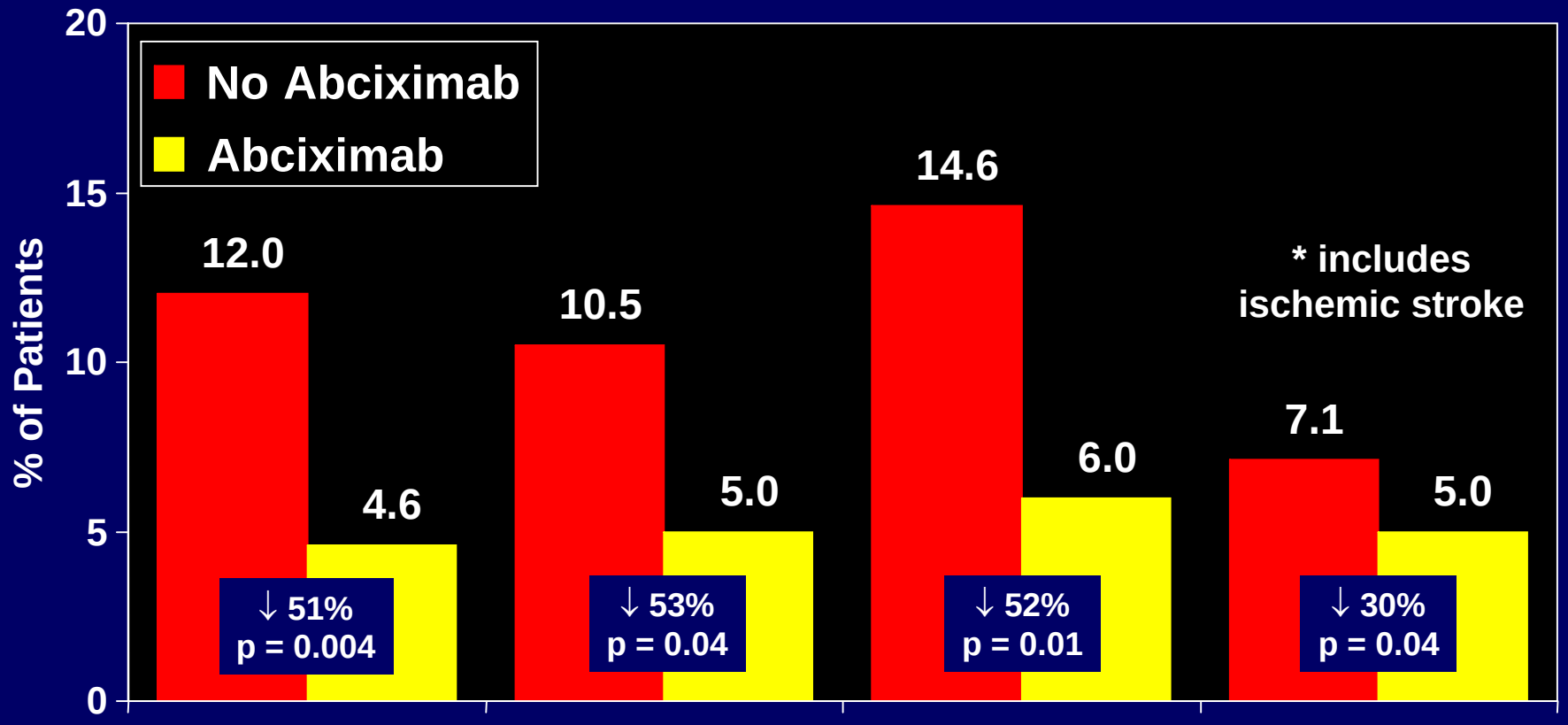
Dethrombosis

Ability of Abciximab to Cause Dethrombosis



30 Day Composite Endpoint

Death, MI or Urgent TVR



Circ 1998; *98:734-41*

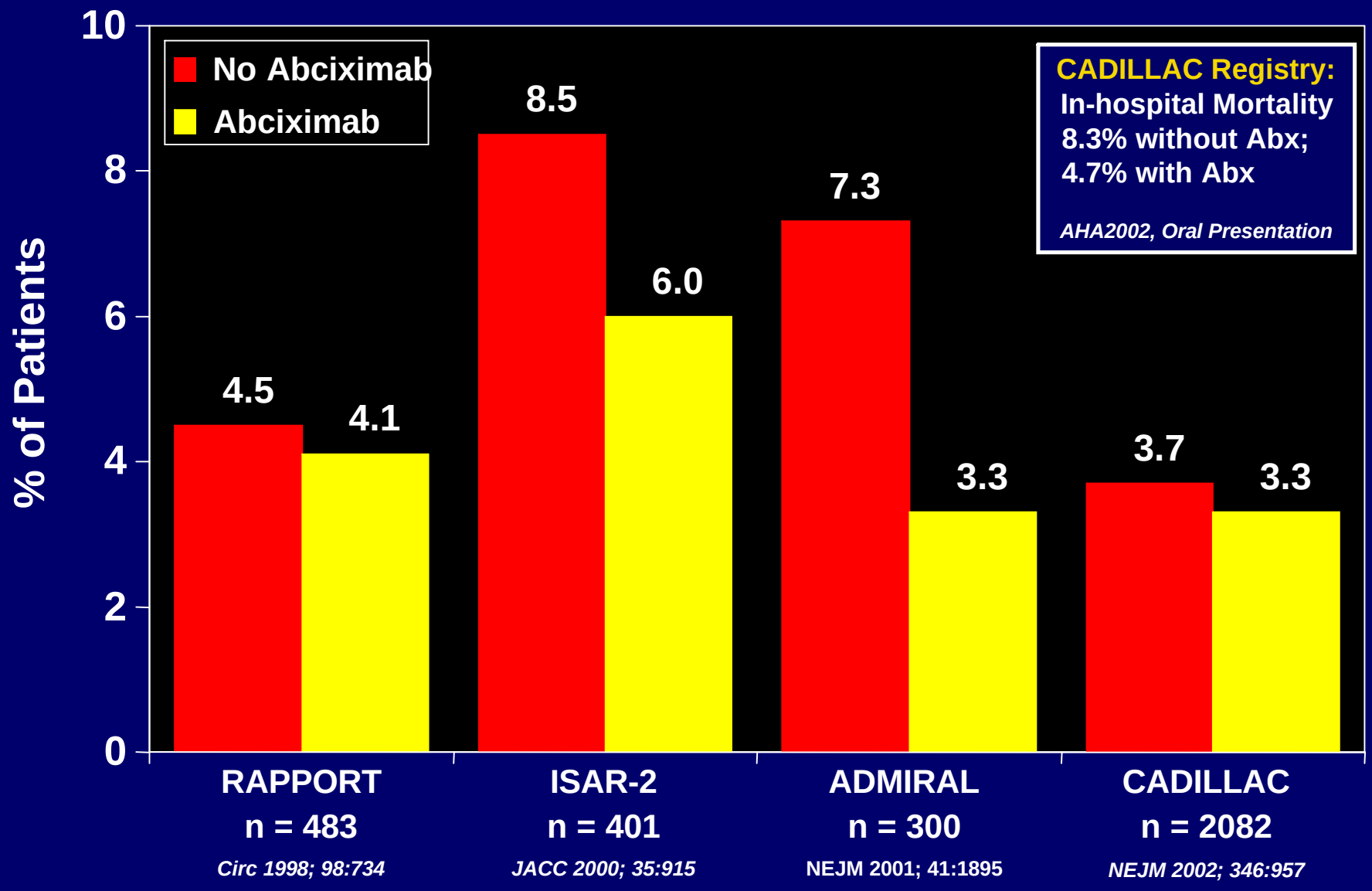
JACC 2000; *35:915-21*

NEJM 2001; 41:1895-03

TCT 2000; Oral Pres.

Primary PCI for AMI

6 Month Mortality in Primary PCI Trials



Summary of Conclusions from Primary PCI Trials for the Treatment of AMI

- 1° PTCA is superior to lytic therapy
  - PAMI, GUSTO IIb
- Abciximab + 1° PTCA is superior to 1° PTCA alone
  - EPIC (post-hoc analysis), RAPPORT
- 1° Stent is superior to 1° PTCA
  - PAMI-STENT
  - CADILLAC
- 1° Stent is superior to thrombolysis
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- Abciximab + 1° Stent is superior to 1° Stent alone
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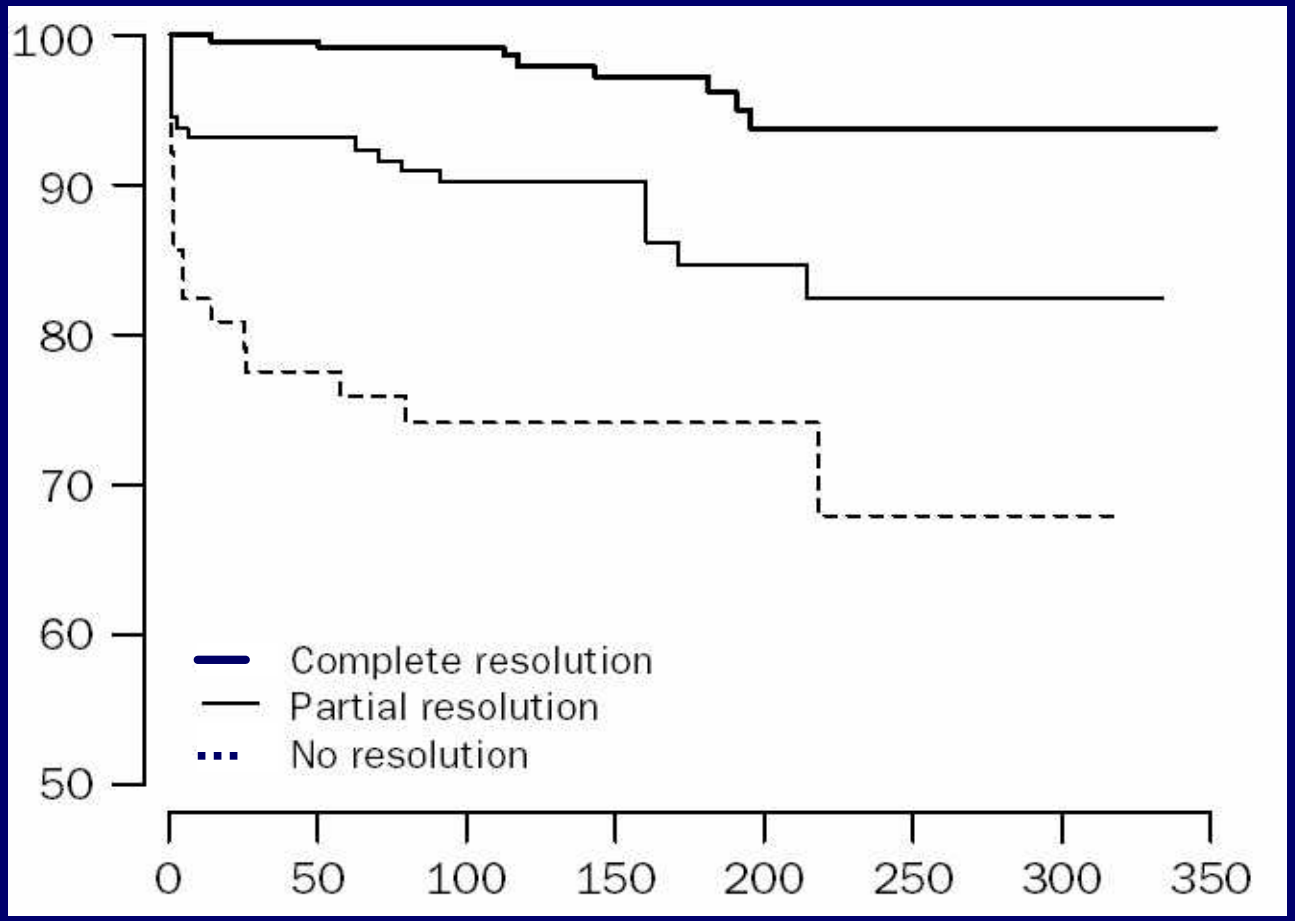
Mortality in Relation to ST-resolution (ECG) 1 hour after Successful p-PCI



Van't Hof, et.al. Lancet 1997;350:615-619.

Pharmacological Treatment prior to p-PCI

- **High dose UFH** (HEAP study)
  - No benefit
- **Full dose of lytics followed by PCI** (SWIFT,TIMI IIa,TAMI, ESCG, PRAGUE 1, Maastricht)
  - No benefit
- **Half dose lytics** (PACT)
  - Unanswered (due to study design)
- **Full dose abciximab** (ADMIRAL, ERAMI, BRIDGING study)
  - Suggested Benefit
- **Half dose lytics + full dose abciximab ”combo”** (FINESSE)
  - Under investigation

Topol, Neumann, Montalescot: Editorial

"The data available indicate that early use, before visualization of the coronary arteries, will be associated with the most favorable clinical outcomes.

Although it may be possible to replicate the favorable findings with other IIb/IIIa inhibitors, the only available data to date have been accrued with abciximab.

Unless or until there are new data available, we should regard catheter-based reperfusion with adjunctive abciximab therapy as the preferred reperfusion therapy for acute MI."

JACC 2003;42:1886-1889.

Montalescot: Recommendations PCI

“To date, abciximab is the only GPIIb/IIIa inhibitor proven to be clinically effective in PCI for AMI. Immediate administration of abciximab on first presentation is recommended for AMI patients scheduled for primary PCI.”

Montalescot et.al. Heart 2004; 90: 1-13.

Available Data Early Use ReoPro

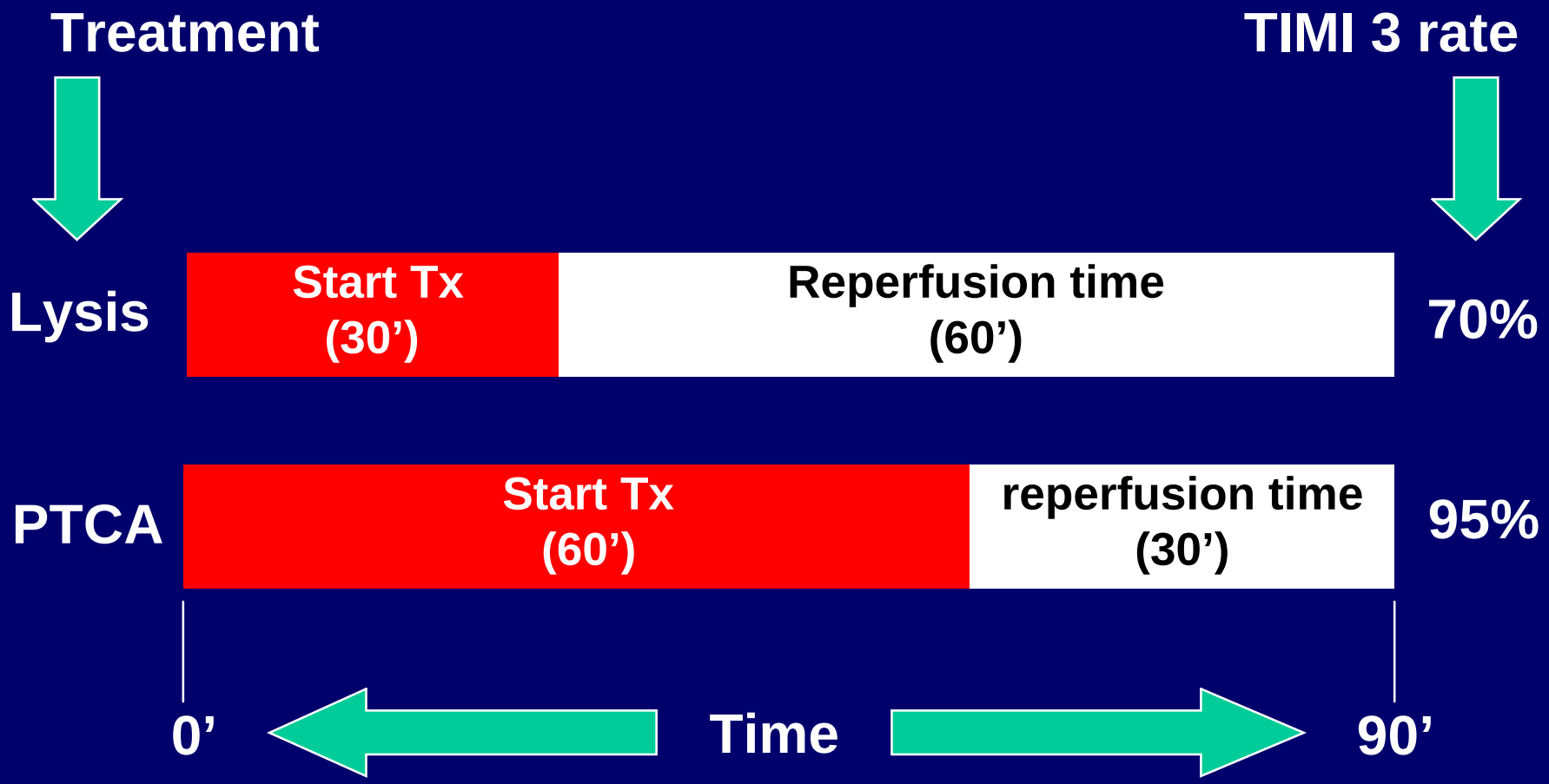
- ADMIRAL
- ReoPro Bridging Study
- ERAMI
- ReoMobile
- Zorman et al
- SWEDES
- Leiden experience
- Nancy Registry
- Bellandi et.al.

Early Start of Abciximab in Primary PCI: Meta-Analysis of Available Evidence from Prospective Trials (n= 602 patients)

Flather et.al. ESC 2004

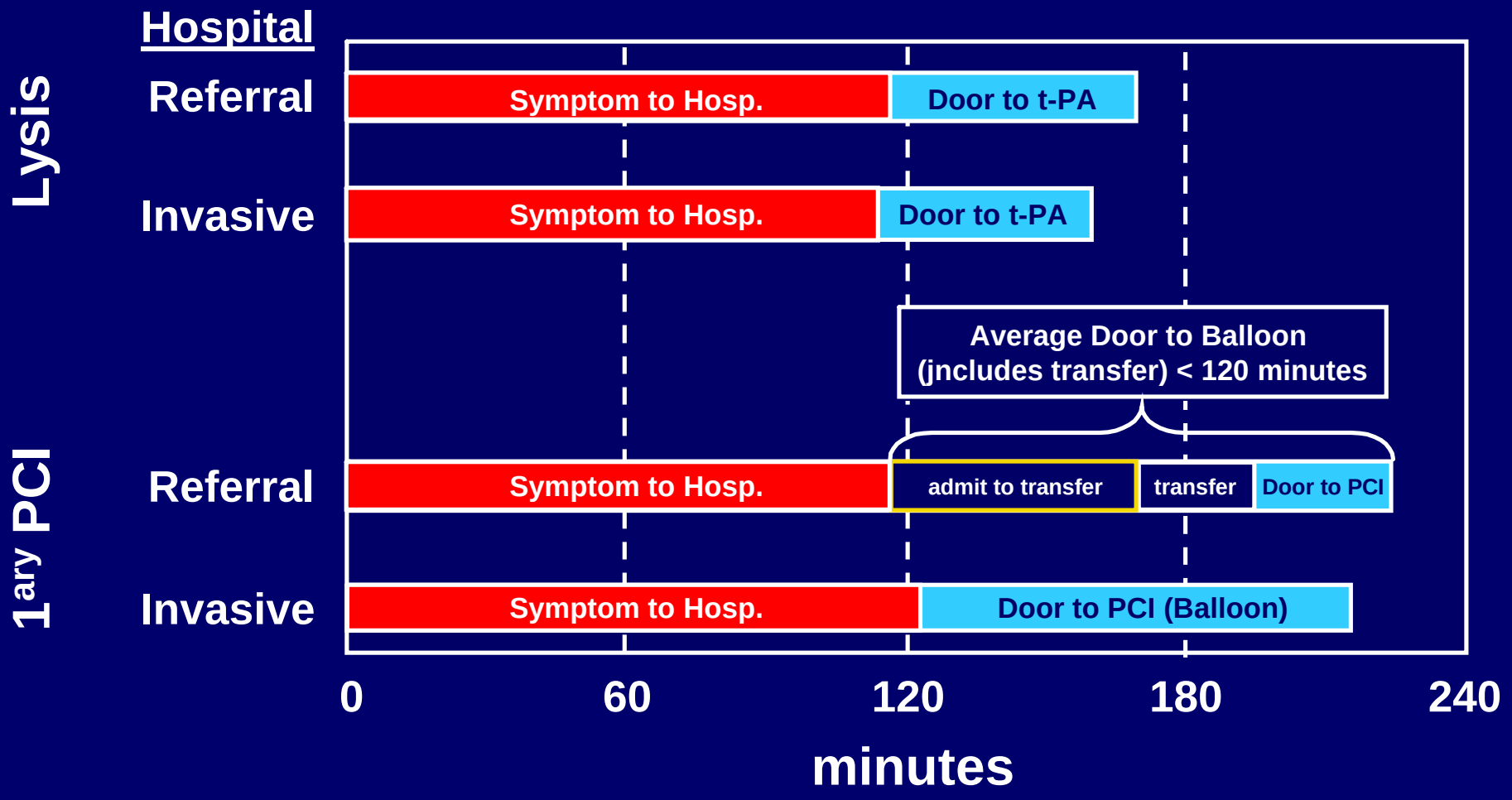
- Primary endpoint: death, re-MI and TVR at 30 days
- Major secondary endpoint: death at 30 days

Equivalent time to reperfusion with fibrinolysis or with primary angioplasty



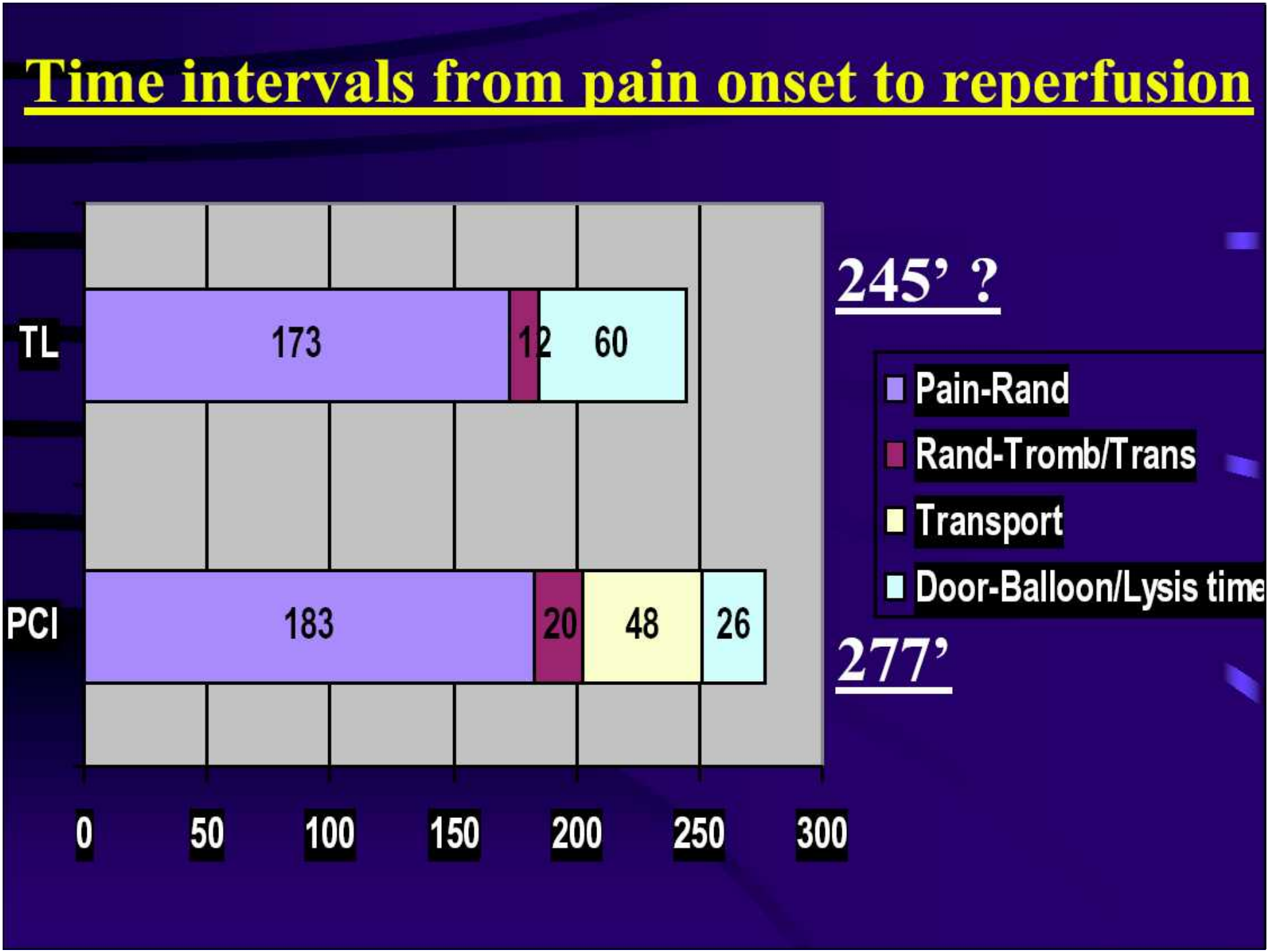
WW3215

DANAMI-2 - Time from Symptom Onset to Admission and Time from Door to Treatment



ACC 2002; Oral presentation

Time intervals from pain onset to reperfusion



ASSENT- 4 PCI - Protocol Design

AMI ST ↑ ≥ 6 mm
if > 70 y: > 70 kg; PCI not possible within 60 min

- Community Hospitals
- Ambulance
- Tertiary Care Hospitals

ASPIRIN
UFH
N=2000 planned

ASPIRIN + TNK-tPA
ENOX
N=2000 planned

Immediate transport to cath lab

- PCI in all pts
- IIb/IIIa at discretion of investigator
- Clopidogrel if stent

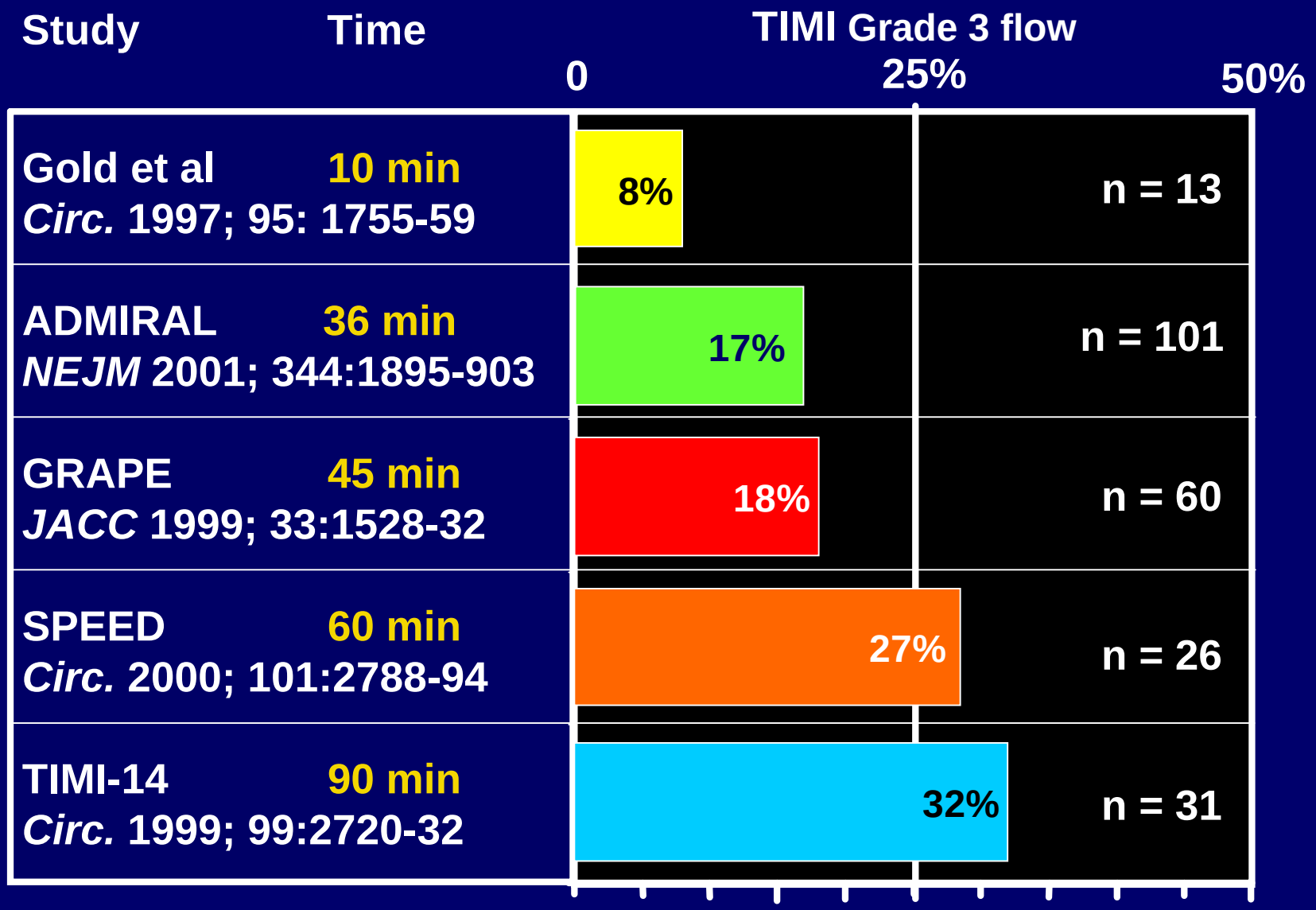
Immediate transport to cath lab

- PCI in all pts
- No IIb/IIIa
- Clopidogrel if stent

Primary Efficacy Endpoint
Death, Heart Failure or Shock up to 90 days

Oral presentation, ESC 2002

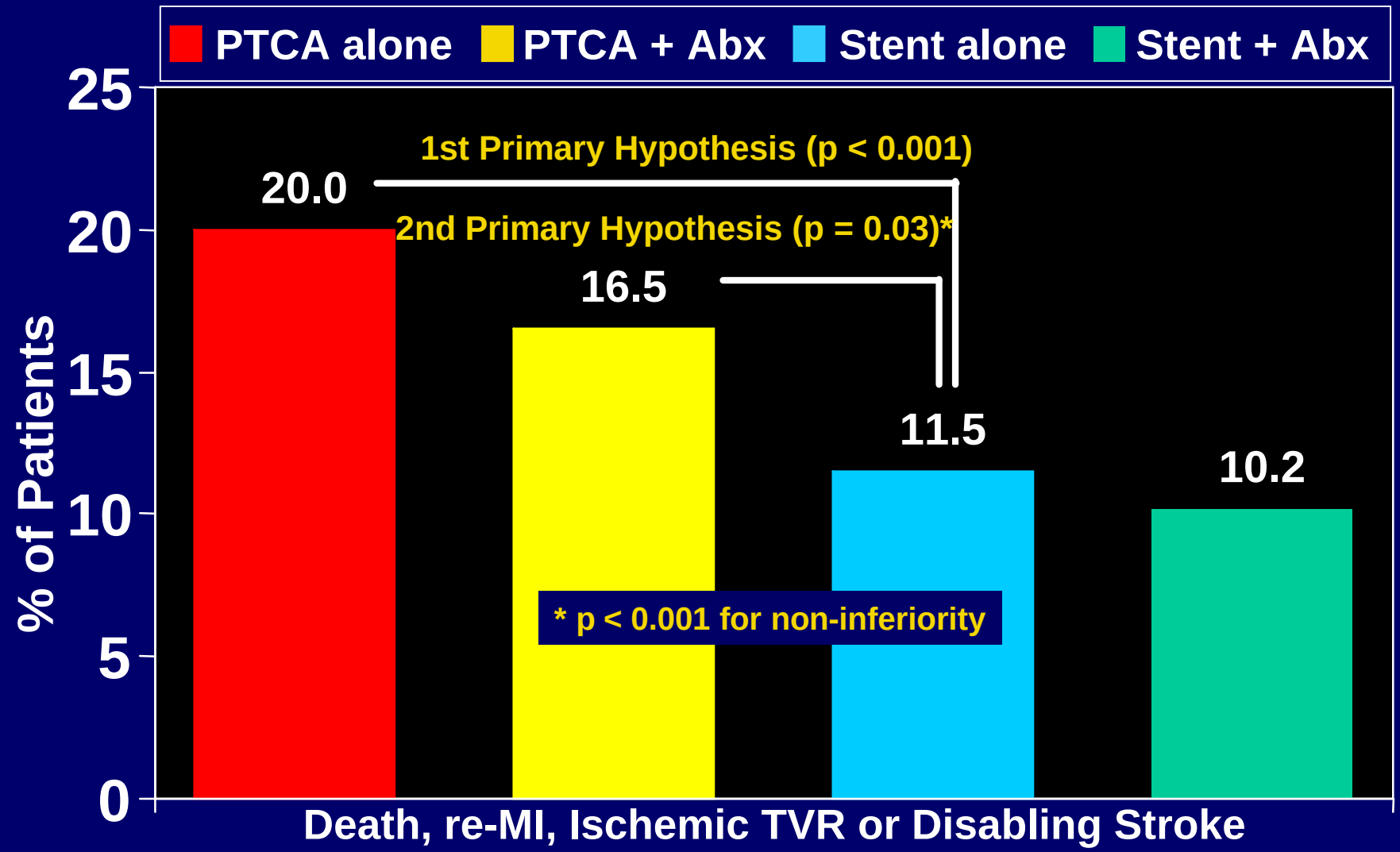
Ability of Abciximab to Cause Dethrombosis



Reperfusion after STEMI
TAKE-HOME MESSAGES

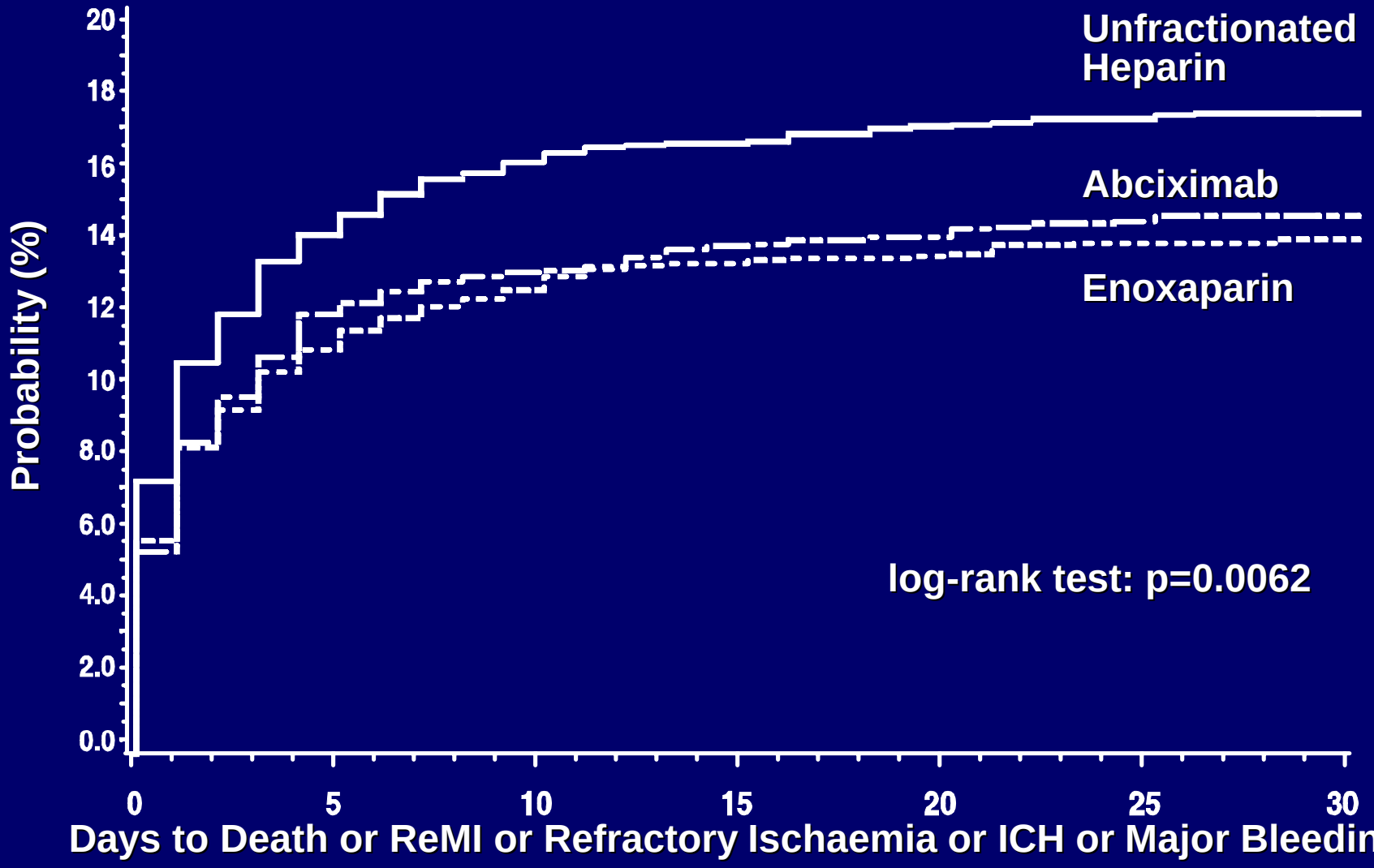
- 1^{ary} PTCA is superior to thrombolysis (meta-analysis)
- 1^{ary} PTCA with Abciximab is superior to 1^{ary} PTCA without (EPIC post-hoc analysis, RAPPORT)
- 1^{ary} stent is superior to 1^{ary} PTCA (PAMI-STENT, CADILLAC)
- 1^{ary} stent is superior to thrombolysis (STOP-AMI, STOP-AMI 2, DANAMI-2, C-PORT)
- 1^{ary} stent with Abciximab is superior to 1^{ary} Stent without (Neumann, ISAR-2, CADILLAC, ADMIRAL)

CADILLAC 1° Endpoint-MACE through 6 months



NEJM 2002; 346: 957-66

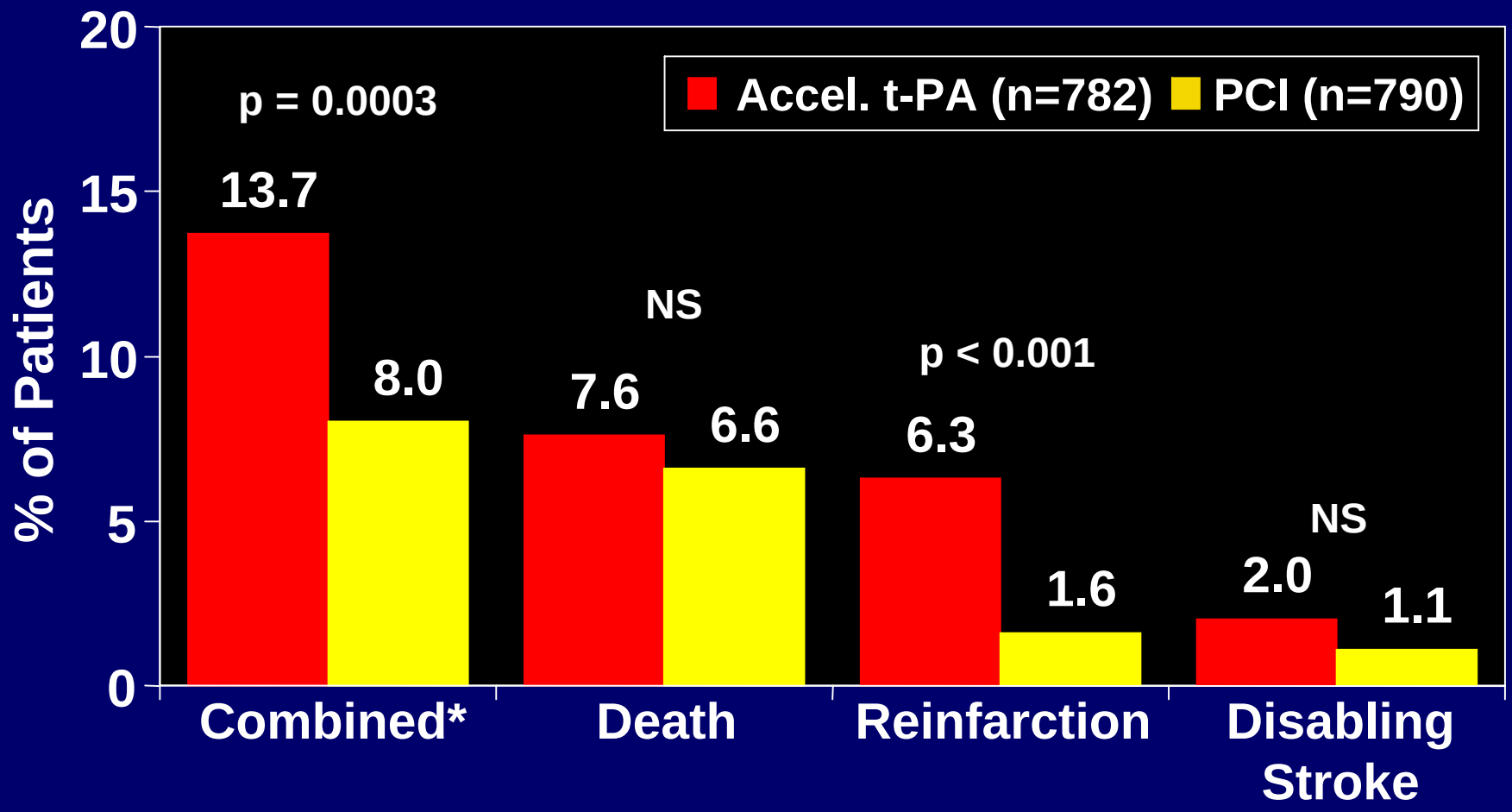
Kaplan-Meier Curves for the Primary Efficacy plus Safety End-point



Primary PCI for AMI

DANAMI-2 - Primary Endpoint through 30 days

All Patients



*Primary Endpoint: Death, Reinfarction, or Stroke

ACC 2002; Oral presentation