For at risk ACS patients, Early Use of GPI

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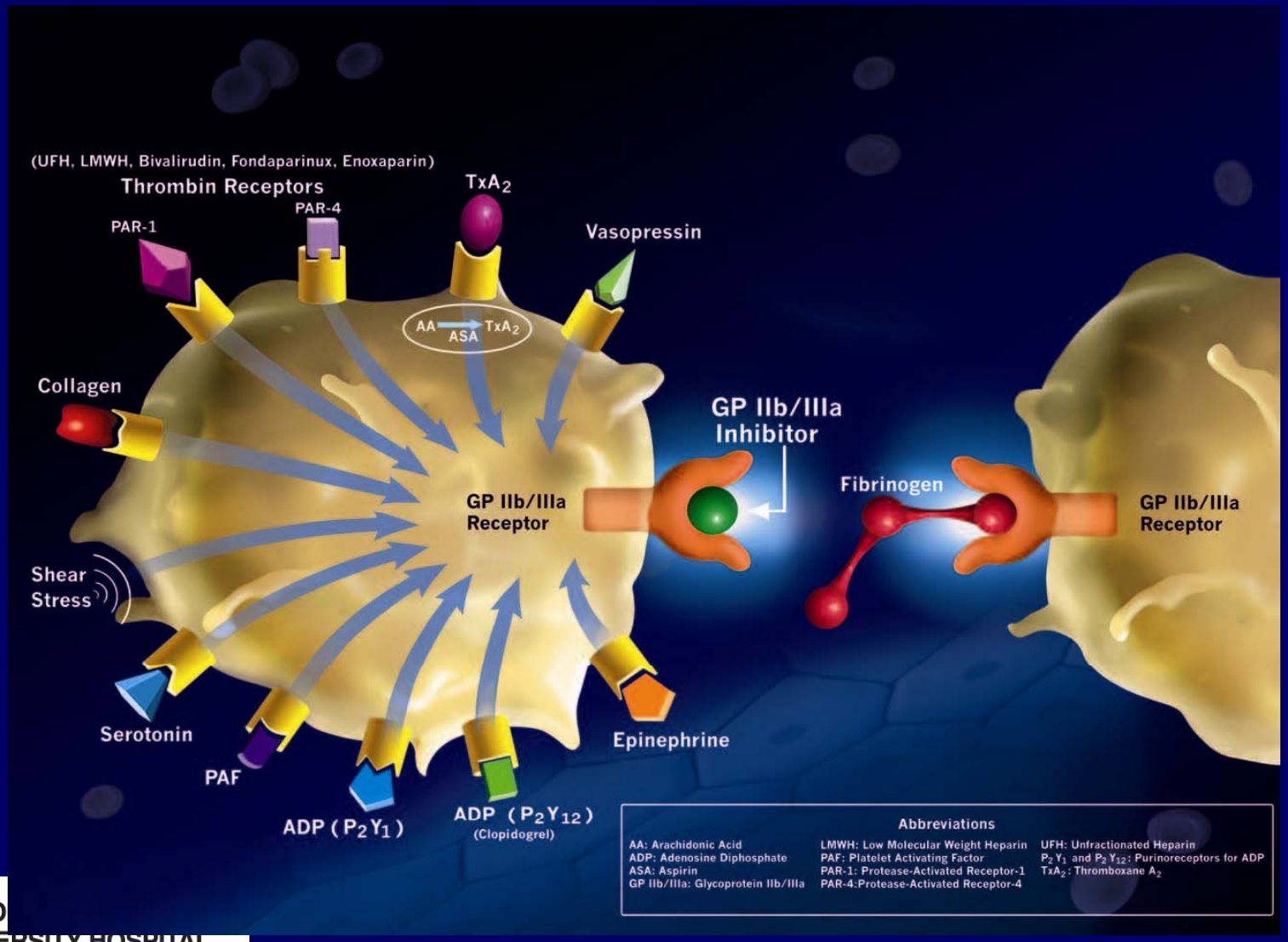
Disclosure

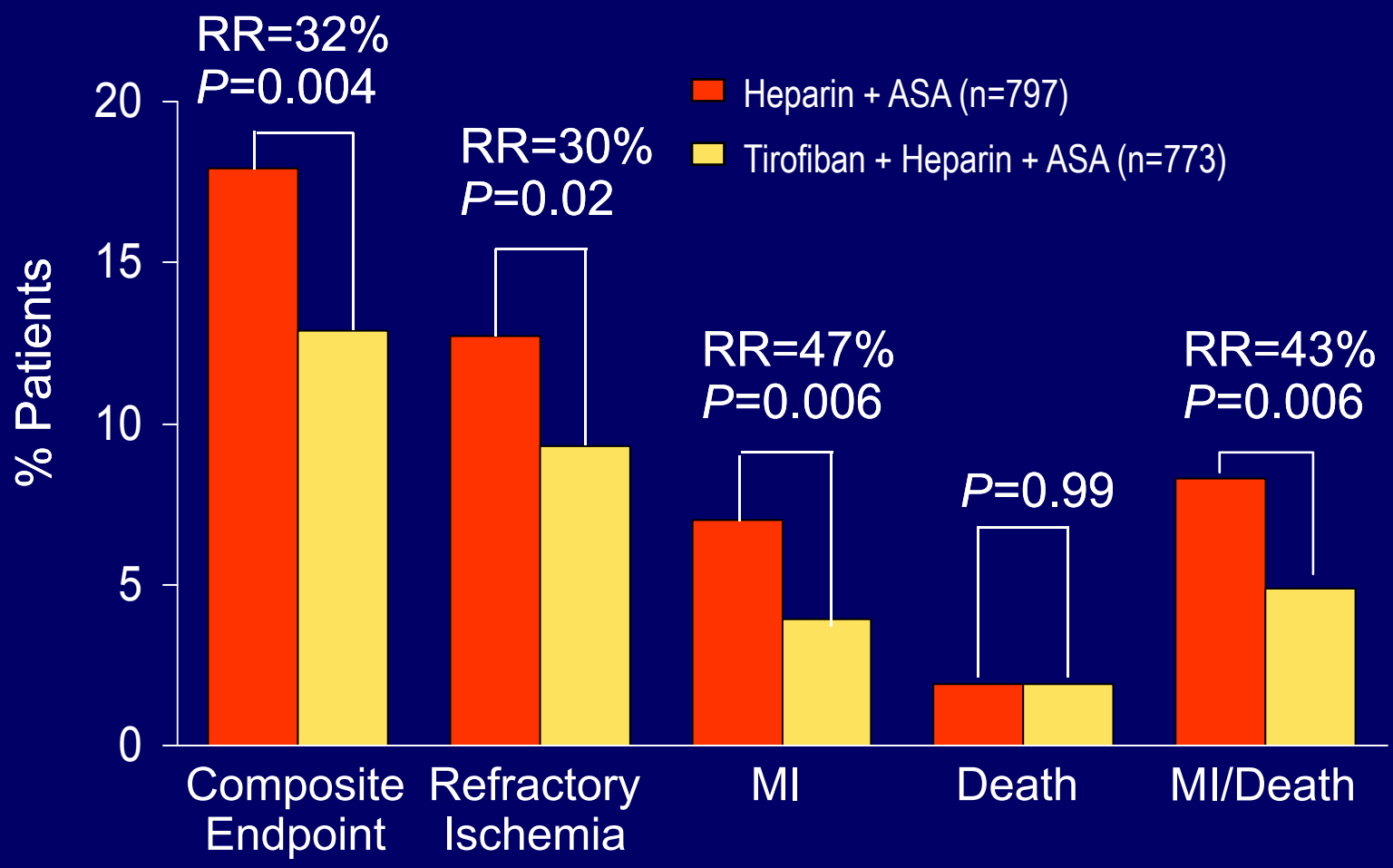
- Nothing.

Mechanism of Action of GP IIb/IIIa Inhibitor



Schneider DJ, Aggarwal A. Expert Rev Cardiovasc Ther. 2004 Nov;2(6):903-13

PRISM-PLUS: Event Reductions at 7 Days



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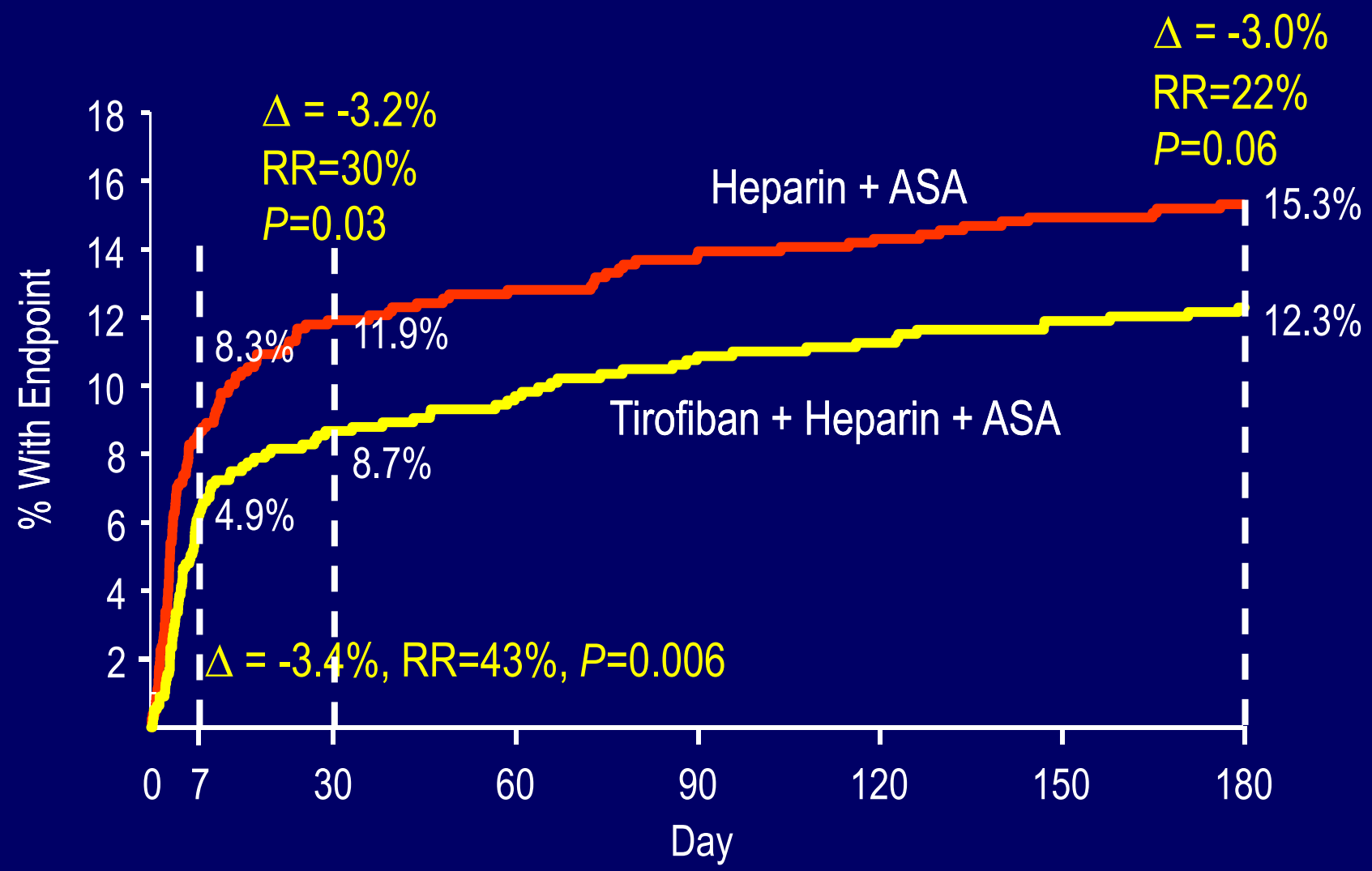
The PRISM-PLUS Study Investigators. *N Engl J Med*. 1998;338:1488-1497.

PRISM-PLUS: Combined MI/Death (180 Days)



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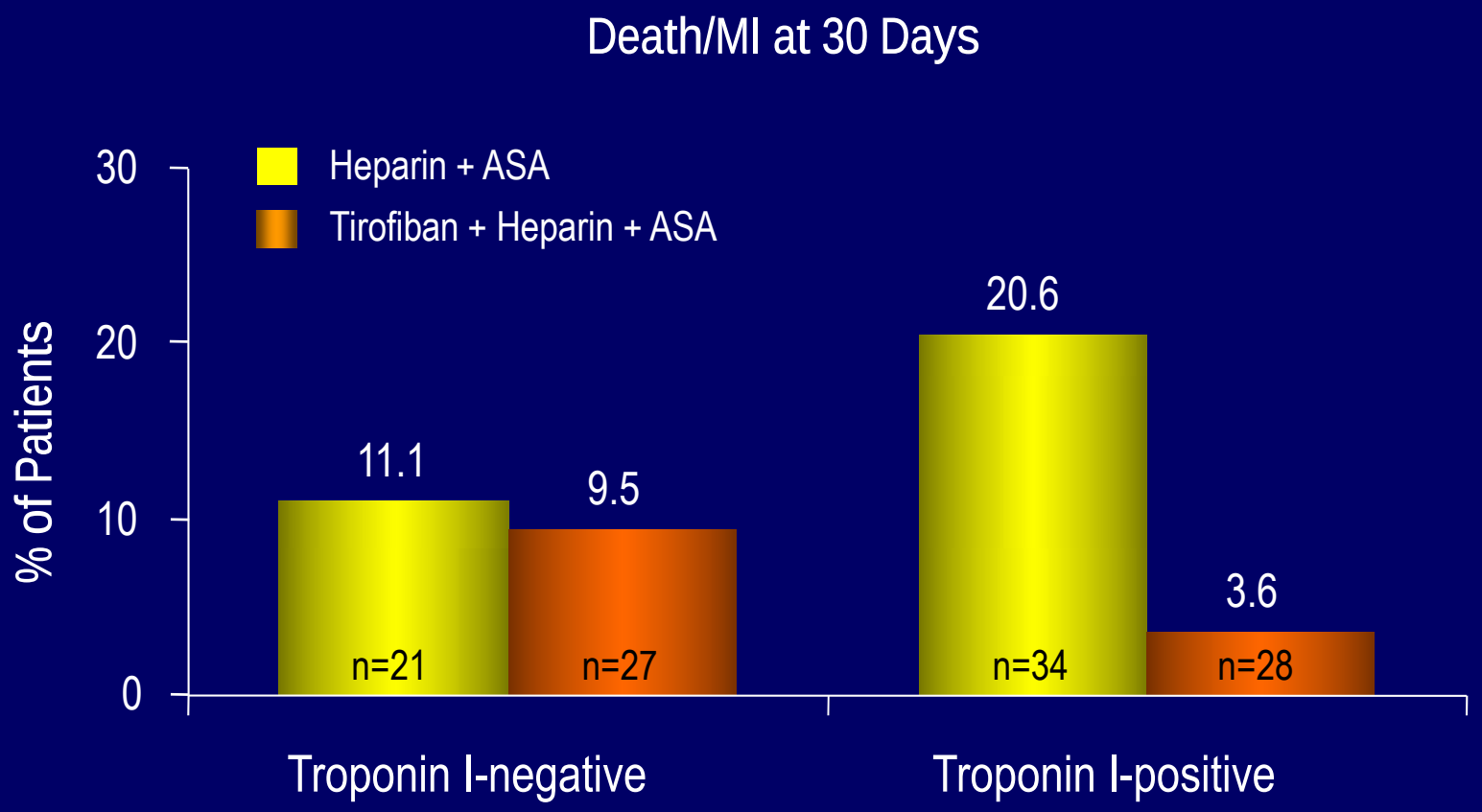
The PRISM-PLUS Study Investigators. *N Engl J Med*. 1998;338:1488-1497

PRISM-PLUS: With Elevated Troponin I



TnI cut point >0.5 ng/mL; 56% of patients TnI positive during the first 24 hours following randomisation.

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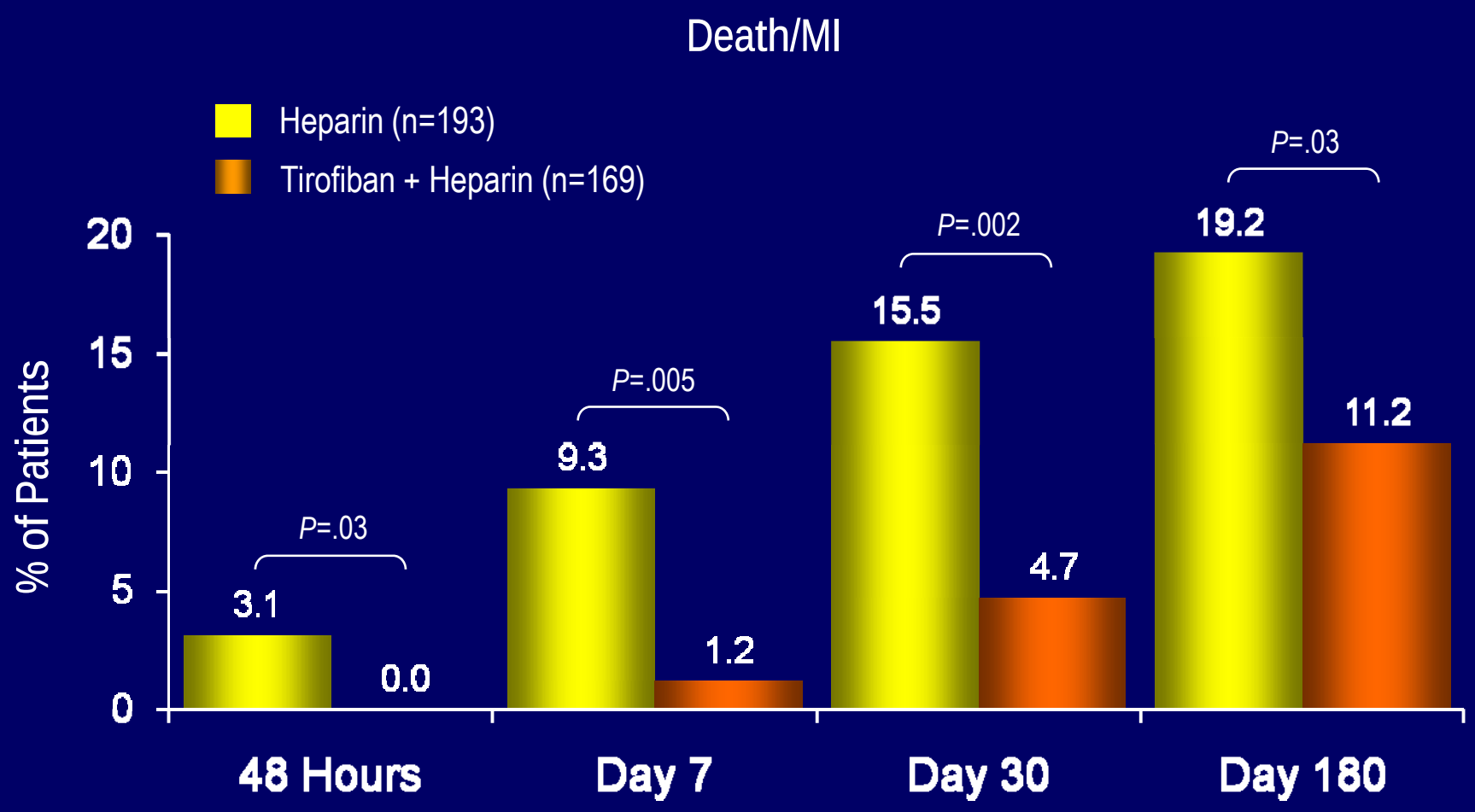
Januzzi JL, et al. *J Thromb Thrombolysis.* 2001;11(3):211-215.

PRISM-PLUS: With Diabetes



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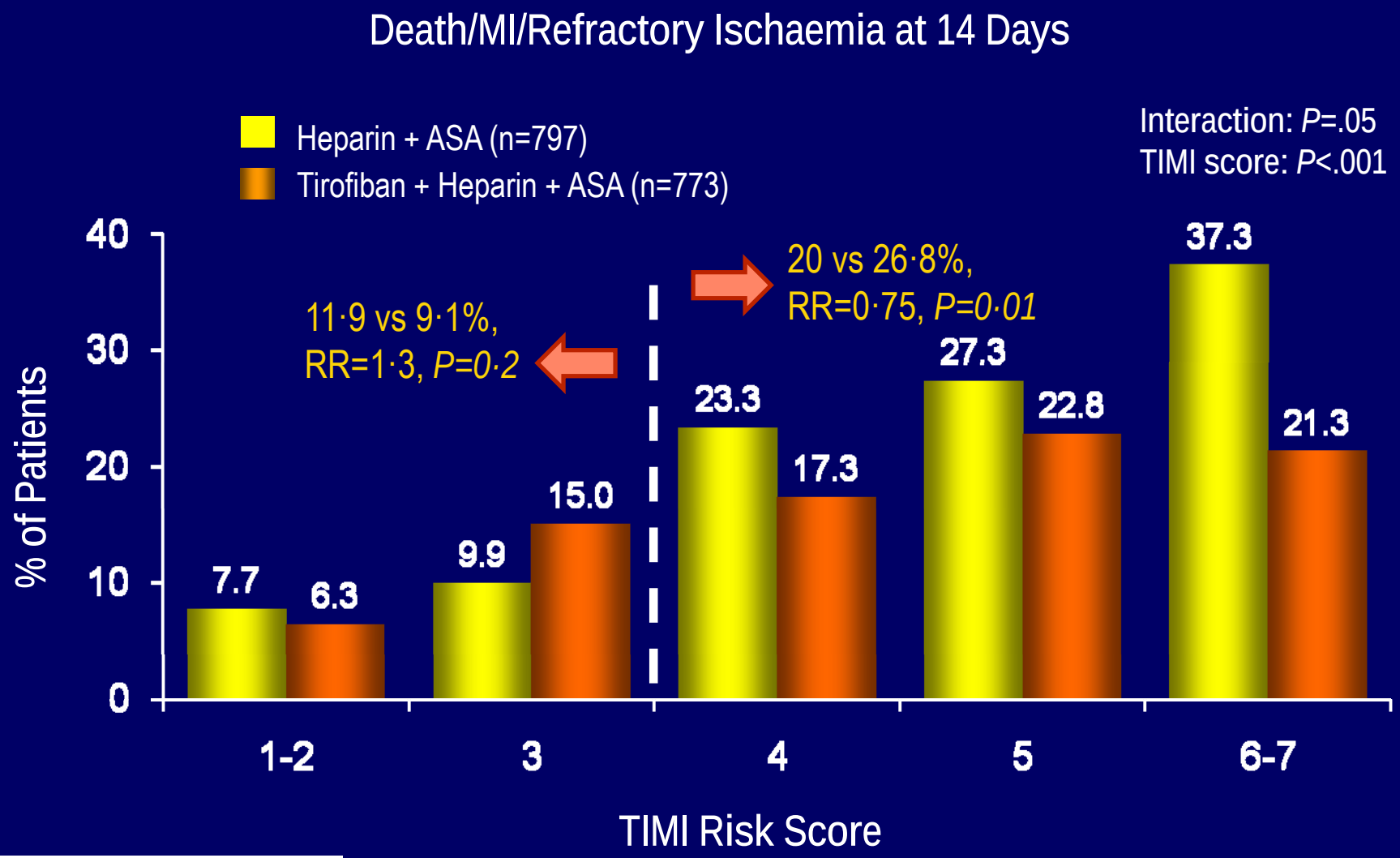
Théroux P, et al. *Circulation*. 2000;102(20):2466-2472.

PRISM-PLUS: TIMI Risk Score



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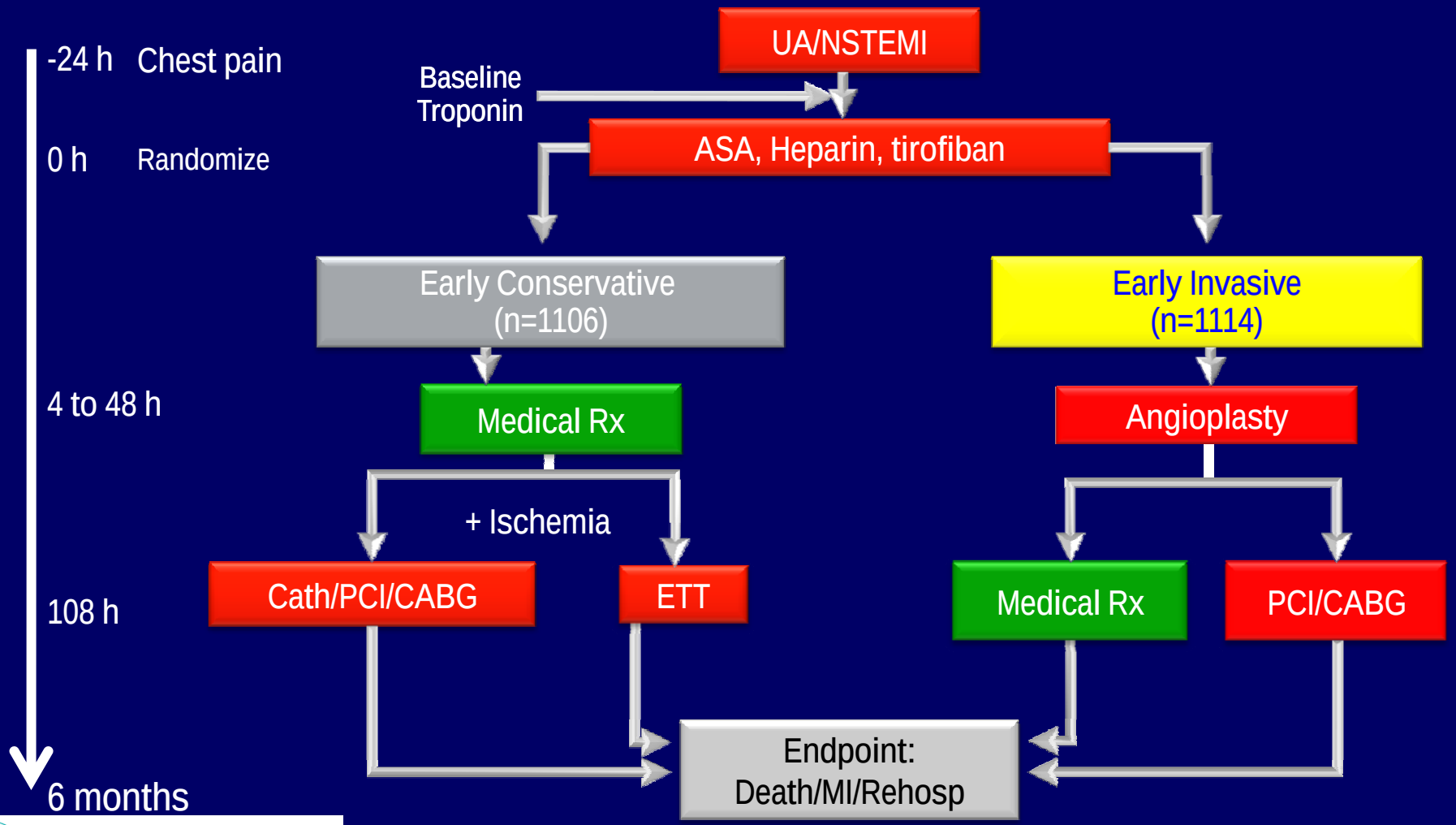
Morrow DA, et al. *Eur Heart J.* 2002;23(3):223-229.

TACTICS-TIMI 18: Study Design



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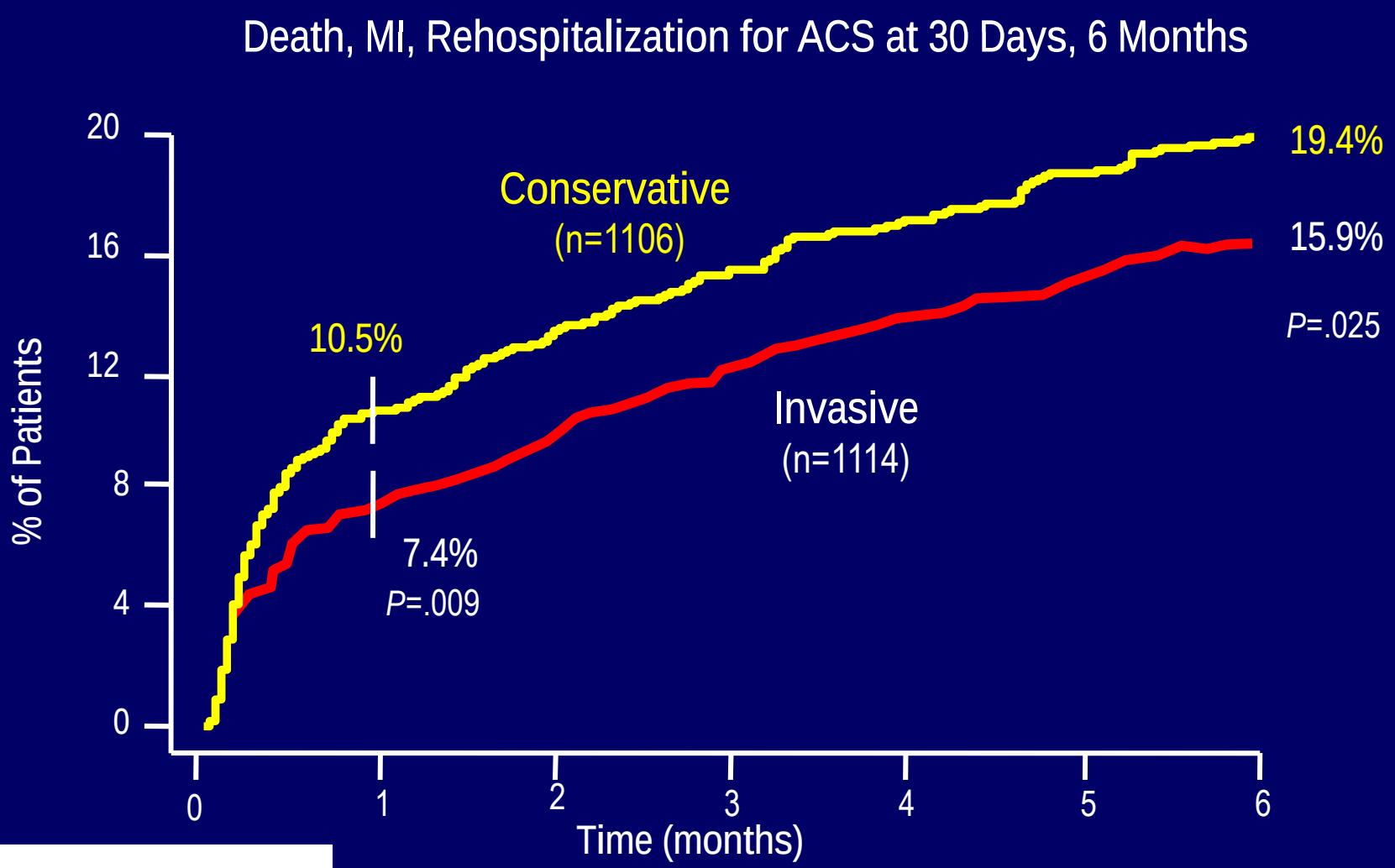
Adapted from Cannon CP, et al. *Am J Cardiol.* 1998;82(6):731-736.

TACTICS-TIMI 18: Primary Endpoint



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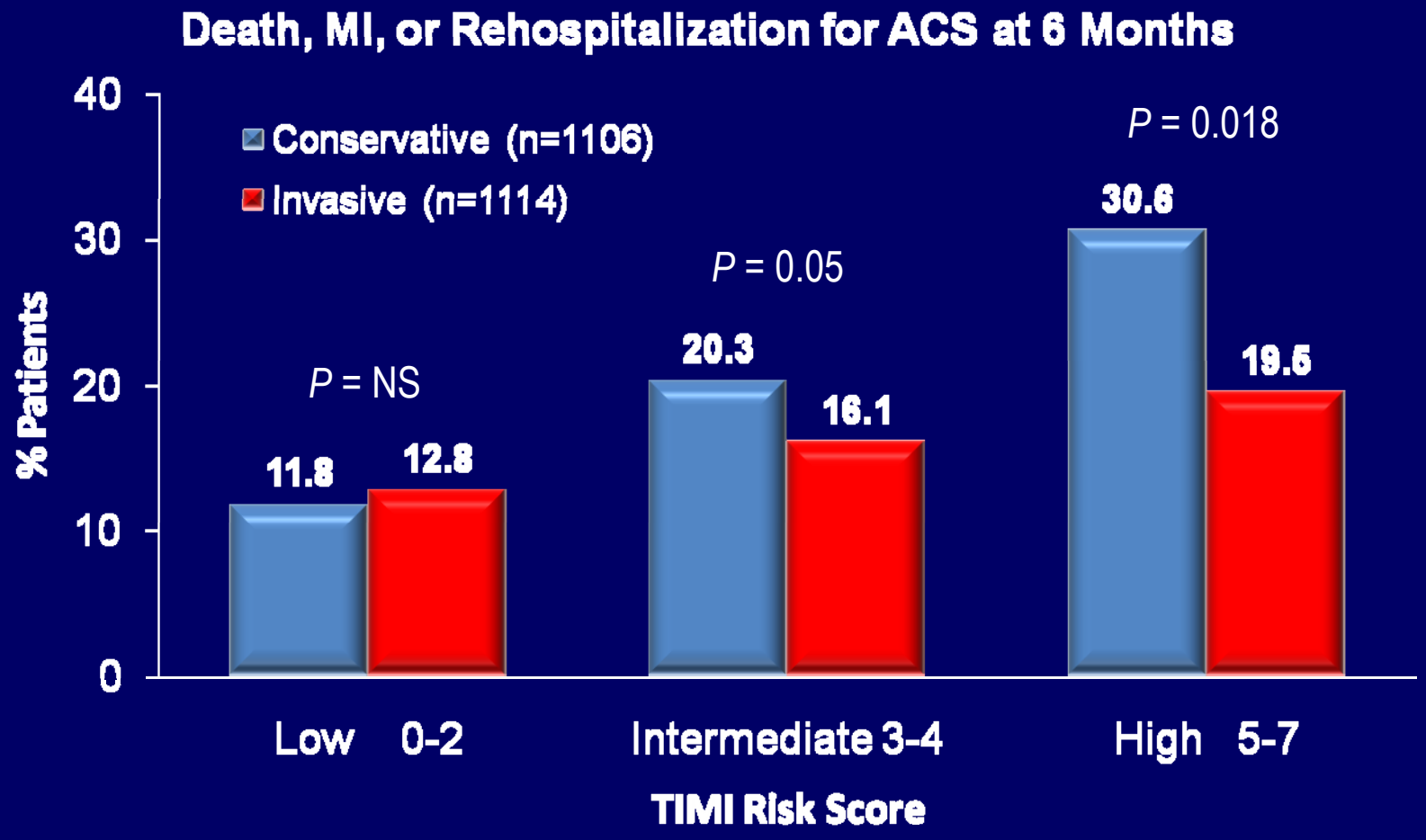
Cannon CP, et al. *N Engl J Med.* 2001;344(25):1879-1887.

TACTICS-TIMI 18: Tirofiban Plus Early Invasive in Intermediate and High Risk



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Cannon CP, et al. *N Engl J Med.* 2001;344:1879-1887.

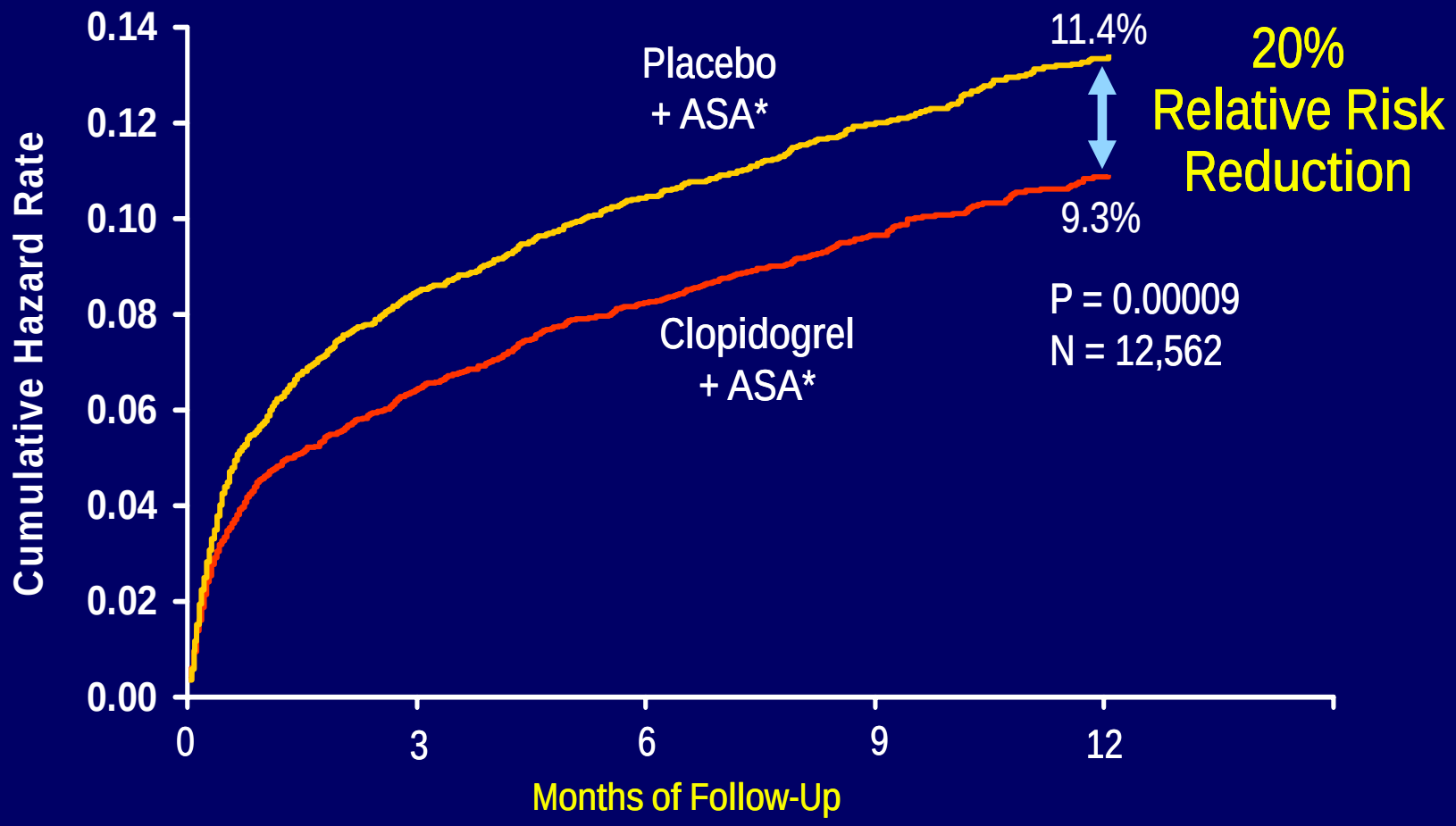
Cannon CP. *J Am Coll Cardiol.* 2003;41:43S– 48S

Benefits of Tirofiban in UA/NSTEMI patients

- Tirofiban significantly reduced short and long-term clinical events, especially in high risk patients with intermediate or high TIMI risk scores, diabetes or elevated troponin I level.

CURE Study

Primary End Point: MI/Stroke/CV Death



*Other standard therapies were used as appropriate.

The CURE Trial Investigators. N Engl J Med. 2001;345:494-502.

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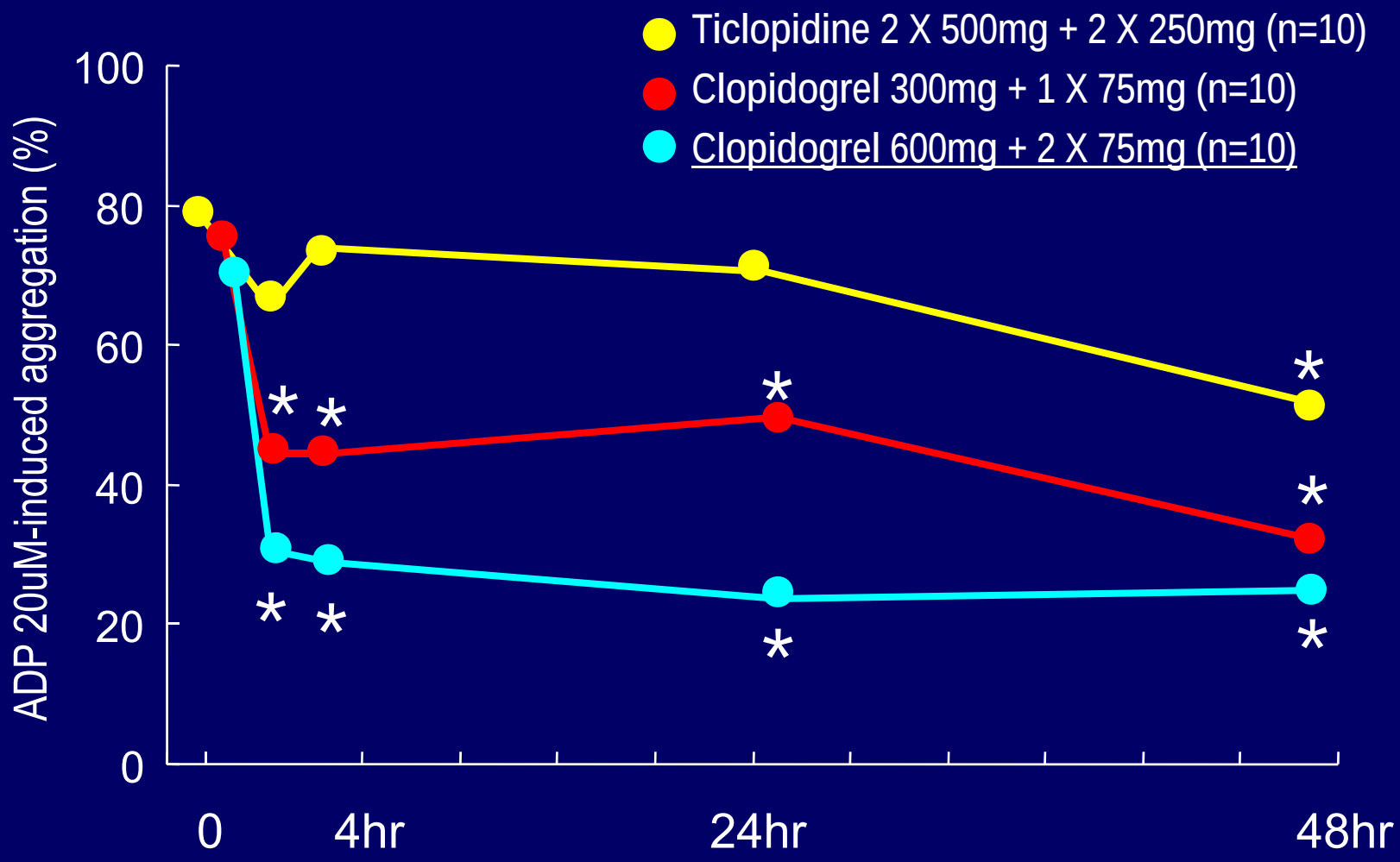
Dose Response of Clopidogrel

Inhibition of platelet aggregation in early period after PCI



* p<0.05 compared to starting concentration

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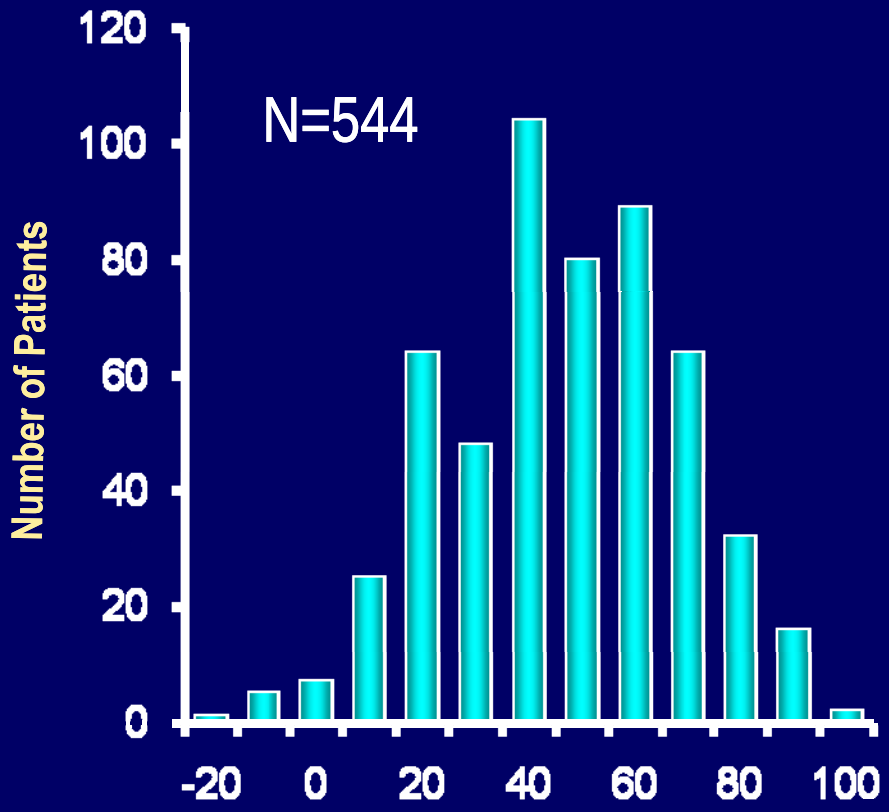
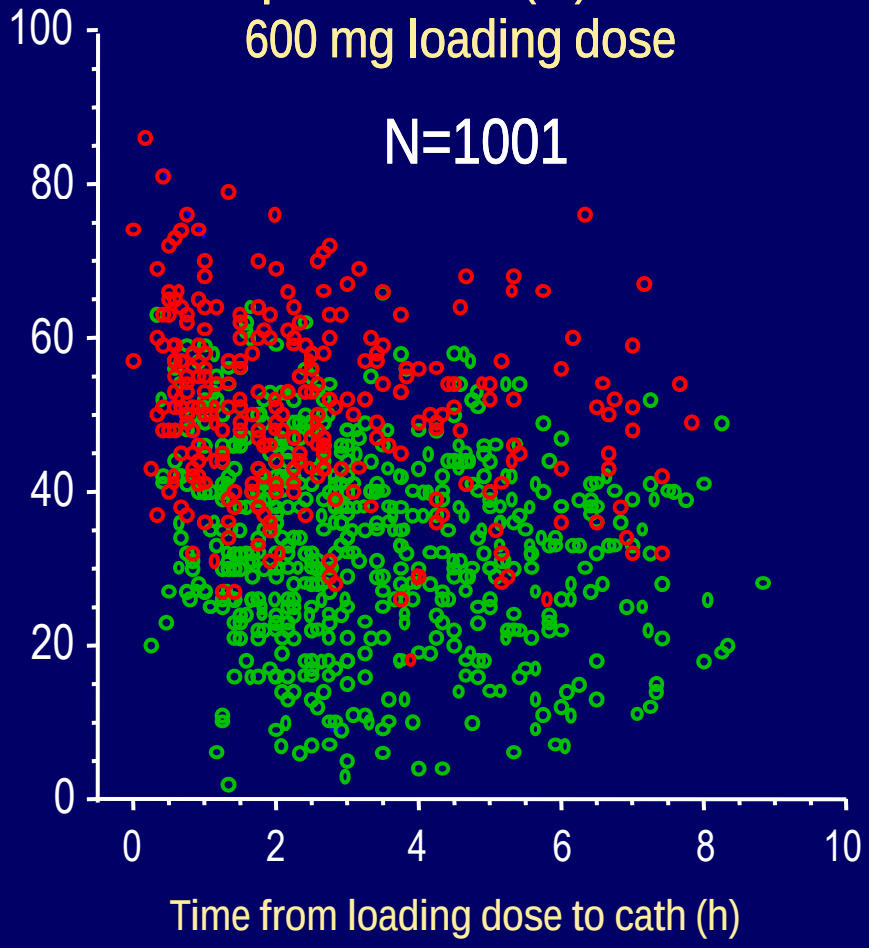
Müller et al, Heart 2001;85:92

Clopidogrel Response Variability

Change in 5 µmol/L ADP-induced platelet aggregation with 75 mg chronic dosing



Maximal aggregation to 5 µmol/L ADP (%) after 600 mg loading dose



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Serebruany V et al. JACC 2005;45:246-51

Hochholzer W et al. Circ 2005;11:2560-4

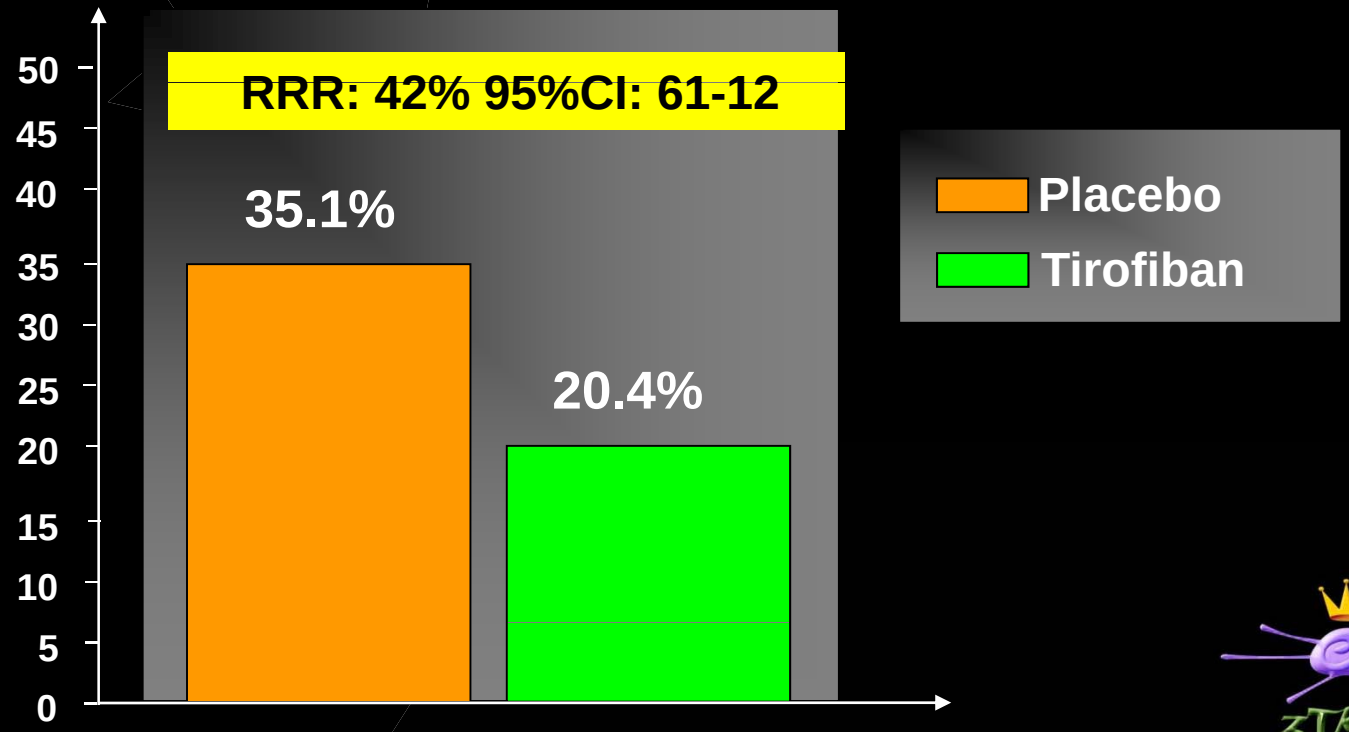
Tailoring Treatment with Tirofiban in patients showing Resistance to aspirin and/or Resistance to clopidogrel

Patients with stable, unstable low risk CAD undergoing elective PCI being ASA and/or clopidogrel resistance using Verify Now

Primary Endpoint

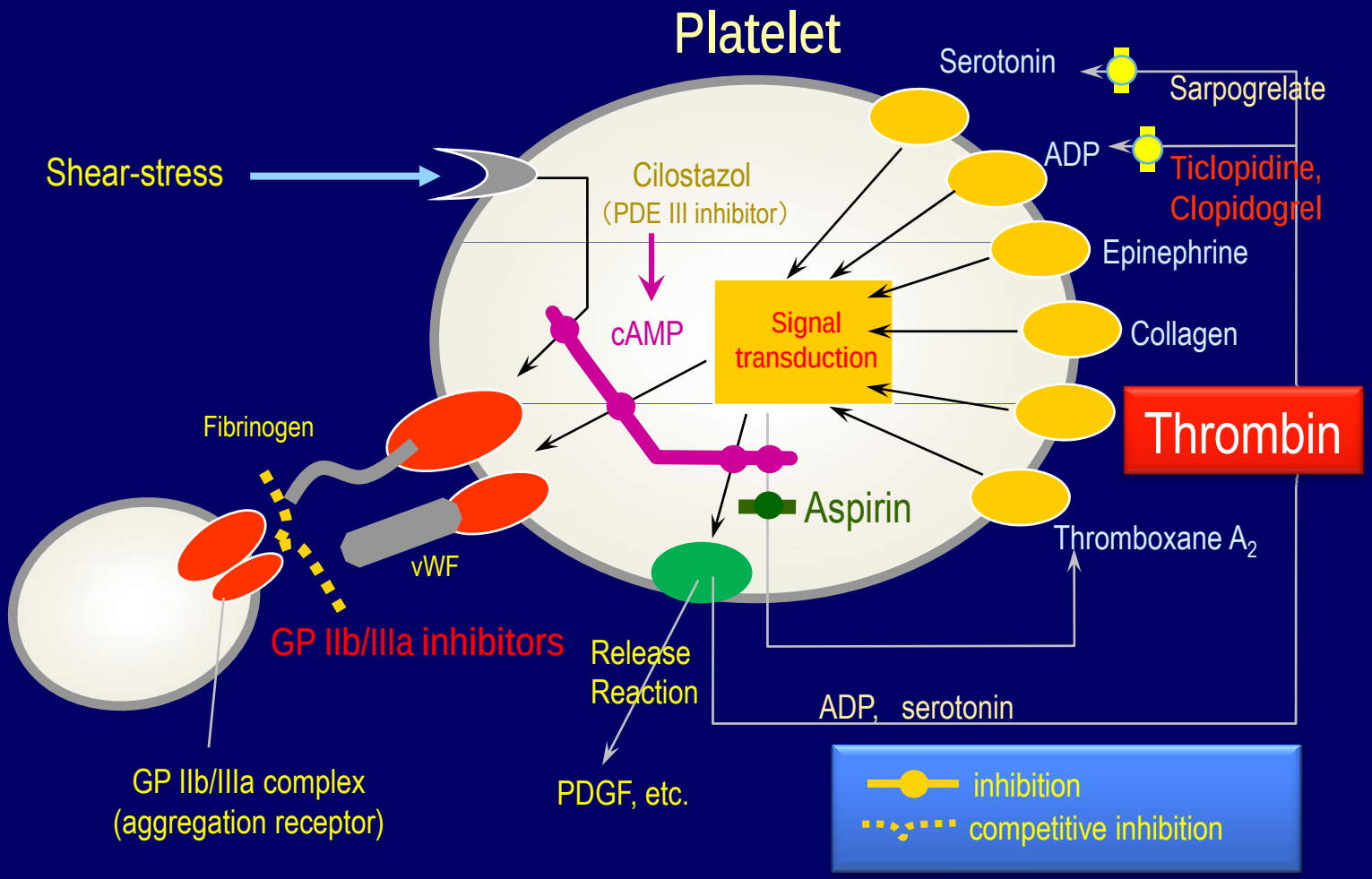
Tp >3×ULN w/in 48 hs

***P*=0.009 for superiority**



Valgimigli M et al Circulation 2009; 119: 3215-22.

Activating Pathways in Platelet



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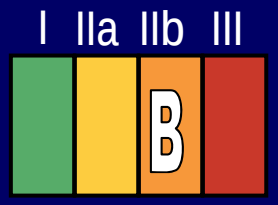
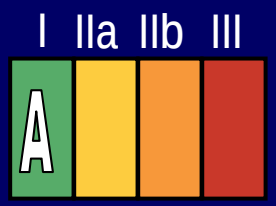
Takao Nishi and Yukio Kimura. J Synthetic Organic Chemistry (Japan). 1999;57(12);1108-1115

Intravenous Antiplatelet Therapy: SIHD, 2011.



In patients undergoing elective PCI with stent implantation treated with UFH and adequately pretreated with clopidogrel, it might be reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban).

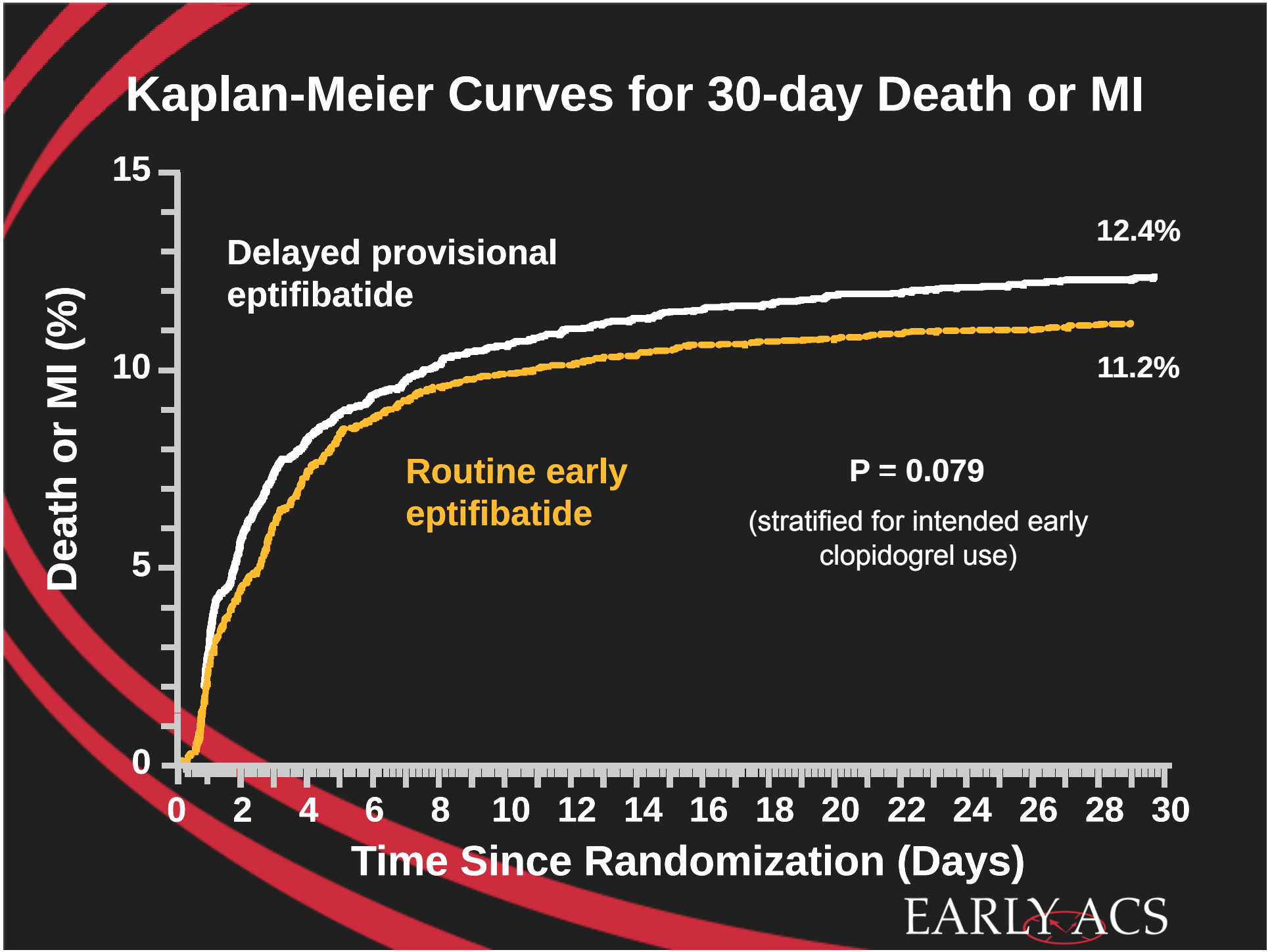
Intravenous Antiplatelet Therapy : UA/NSTEMI, 2011.



In UA/NSTEMI patients with high-risk features (e.g., elevated troponin level) not treated with bivalirudin and not adequately pretreated with clopidogrel, it is useful at the time of PCI to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) in patients treated with UFH.

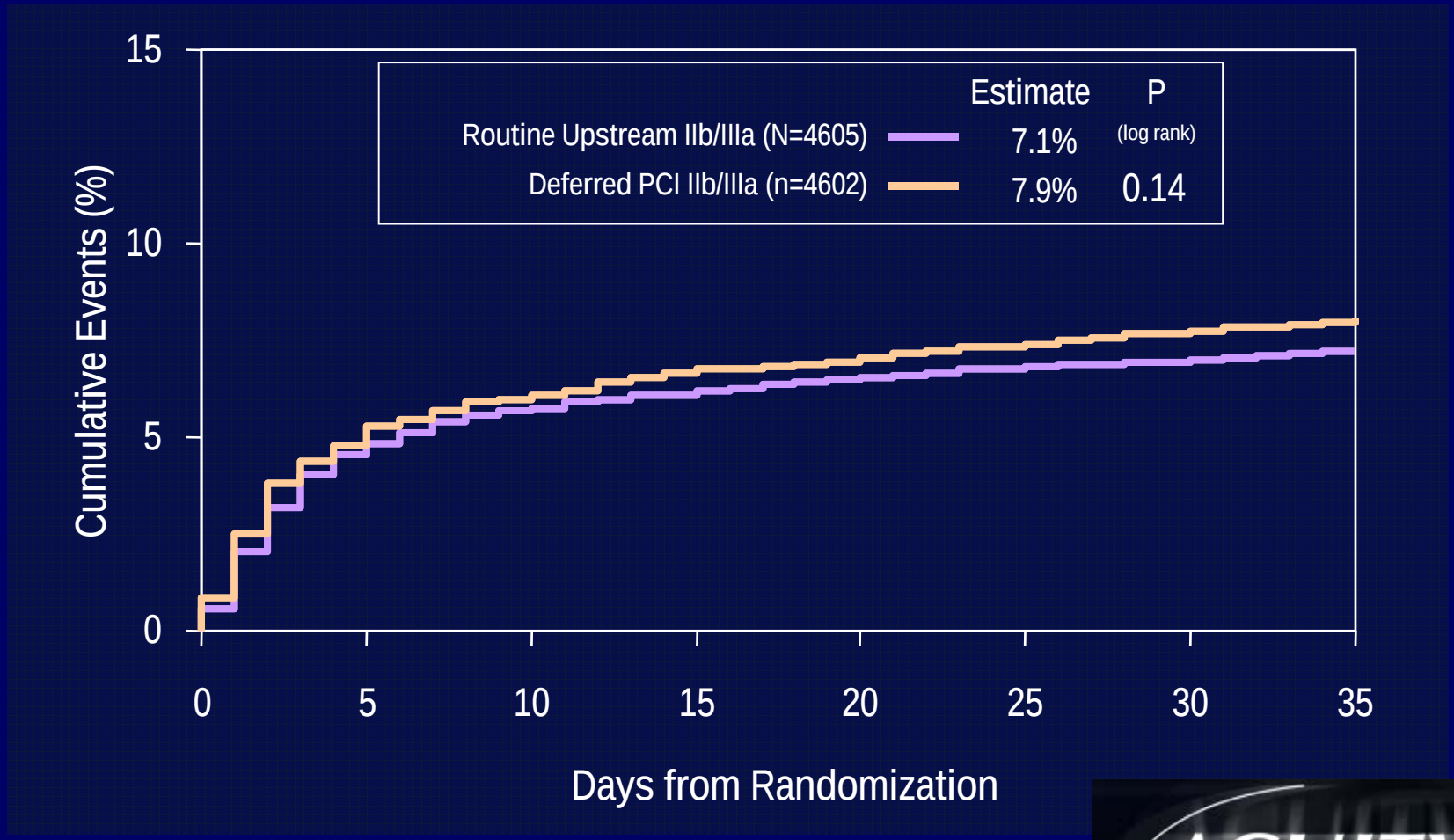
Optimal timing of initiation:
Routine upstream use vs. Deferred provisional use

Kaplan-Meier Curves for 30-day Death or MI



Ischemic Composite Endpoint

Upstream IIb/IIIa vs. Selective IIb/IIIa



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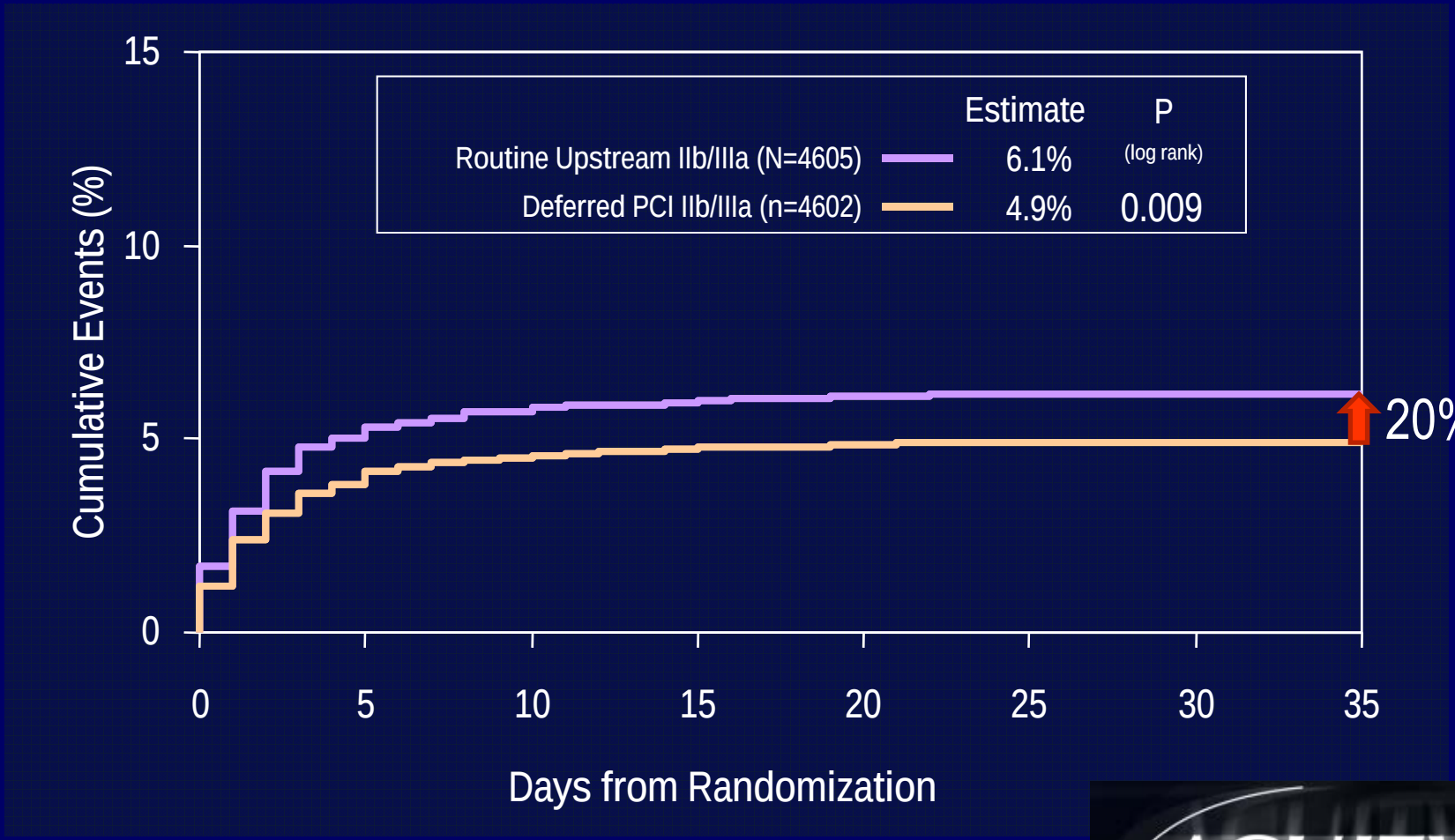
JAMA. 2007;297:591-602

ACUITY TIMING

Major Bleeding Endpoint

Upstream IIb/IIIa vs. Selective IIb/IIIa



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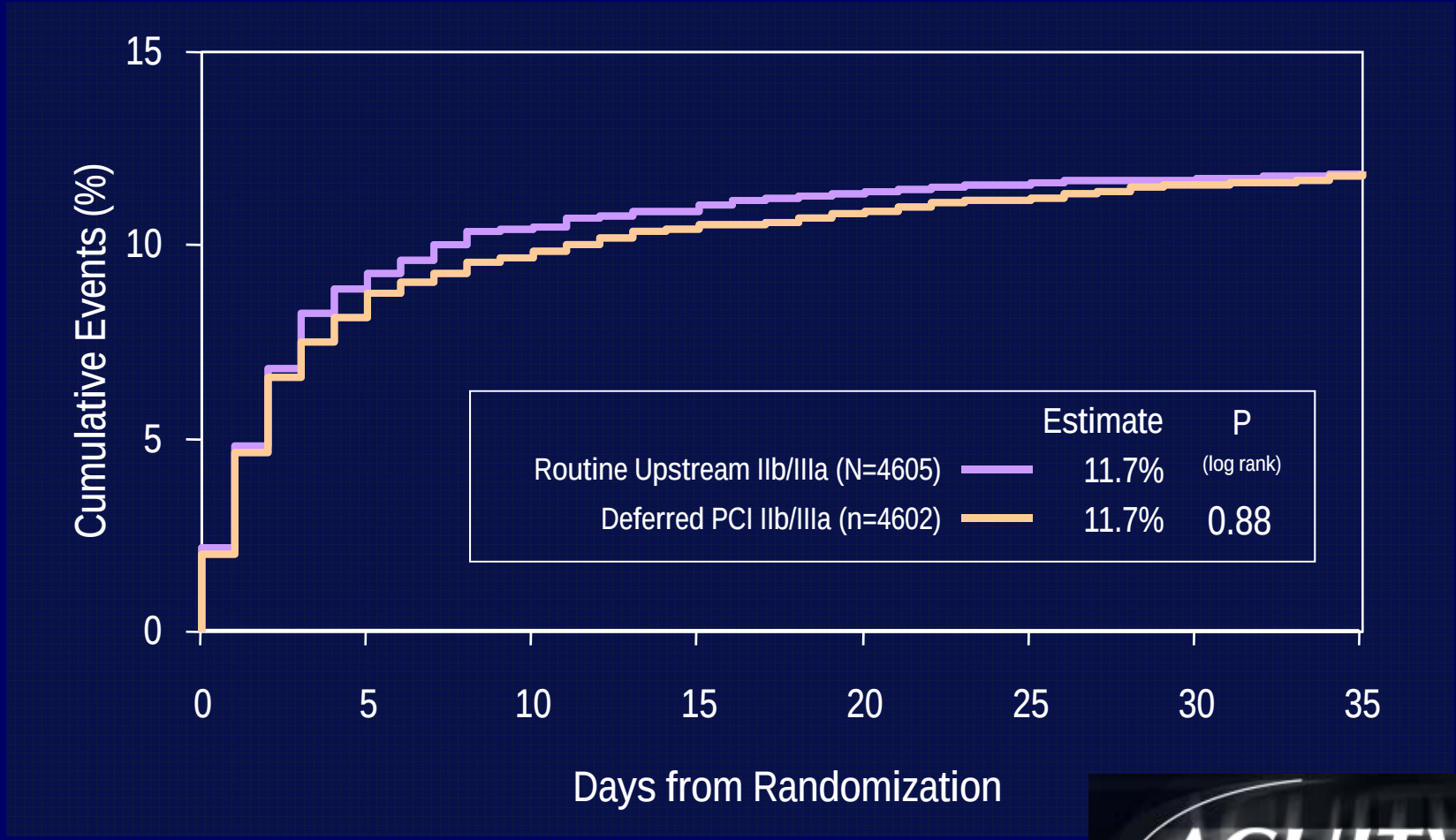
JAMA. 2007;297:591-602

ACUITY TIMING

Net Clinical Outcome Composite Endpoint

Routine upstream IIb/IIIa vs. Deferred IIb/IIIa



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JAMA. 2007;297:591-602

ACUITY TIMING

Early use of GPI in UA/NSTEMI

- Data from EARLY-ACS and ACUITY timing trial highlights the potential bleeding risk of routine upstream GPI.

- The use of GPI should be undertaken when the benefit of GPI surpass the risk of bleeding (eg, elevated cardiac biomarkers, diabetes or age < 75).

Tirofiban in STEMI

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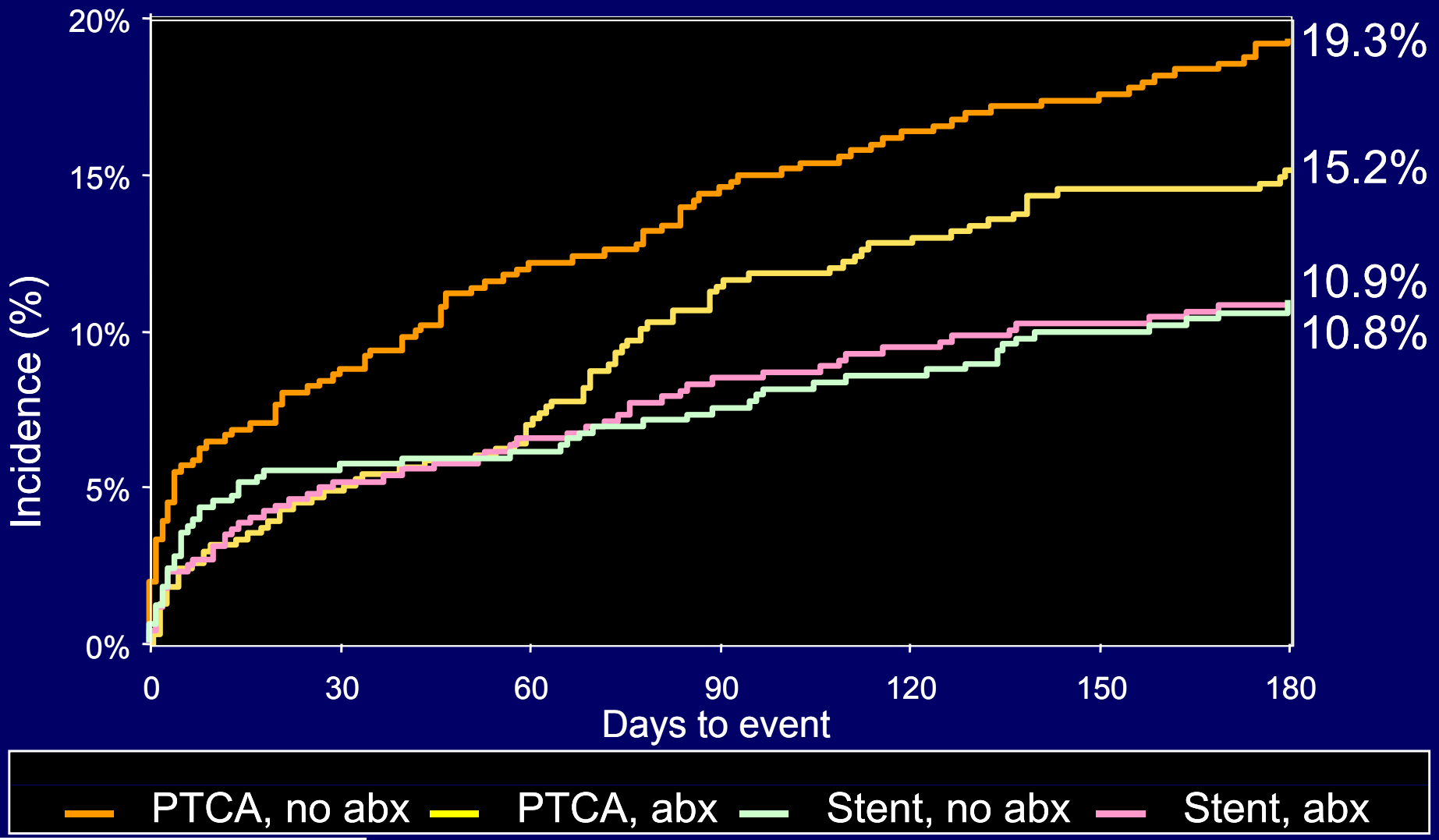
CADILLAC

Seconday Endpoint - MACE at 6 Months



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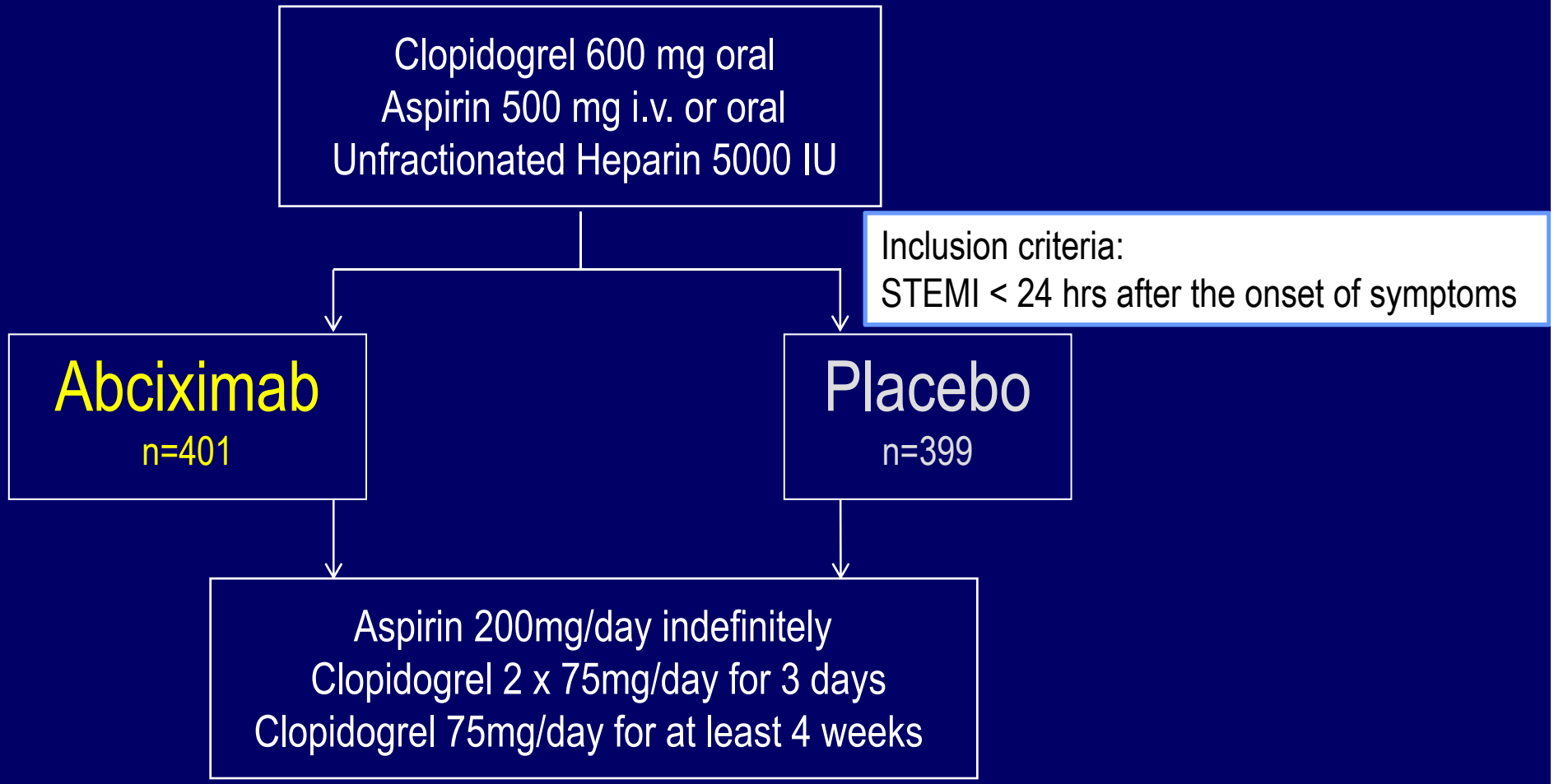
Stone et al. Circ 2000; 102: II-664

Brave 3 Trial: Study Design



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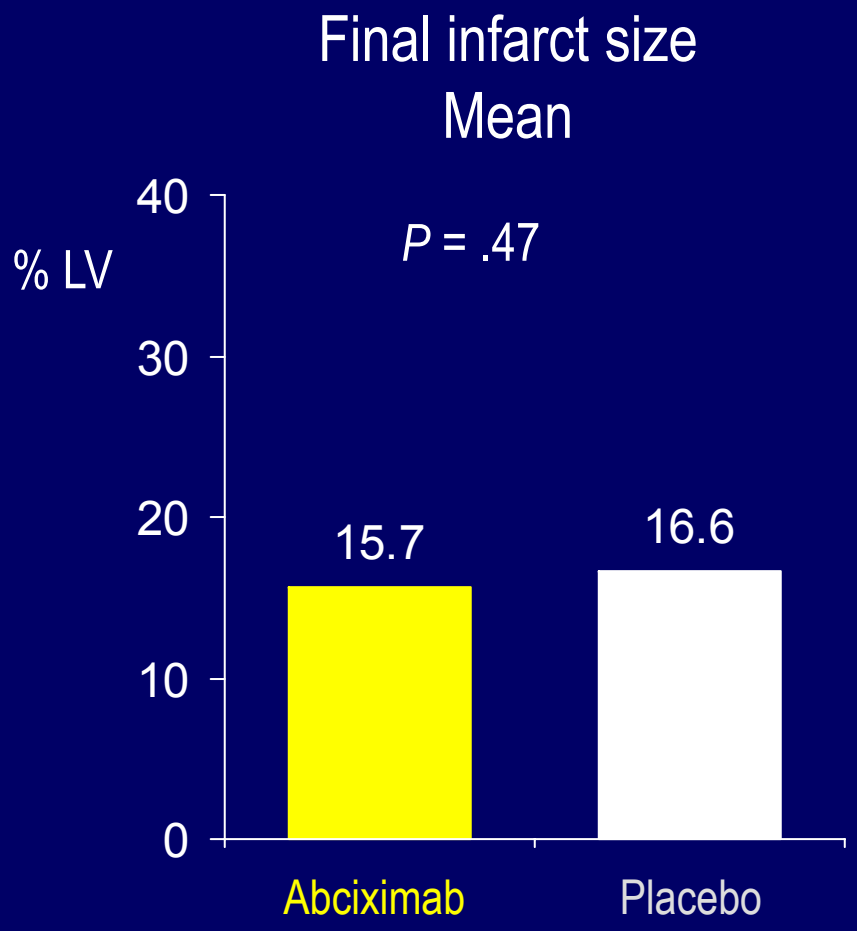
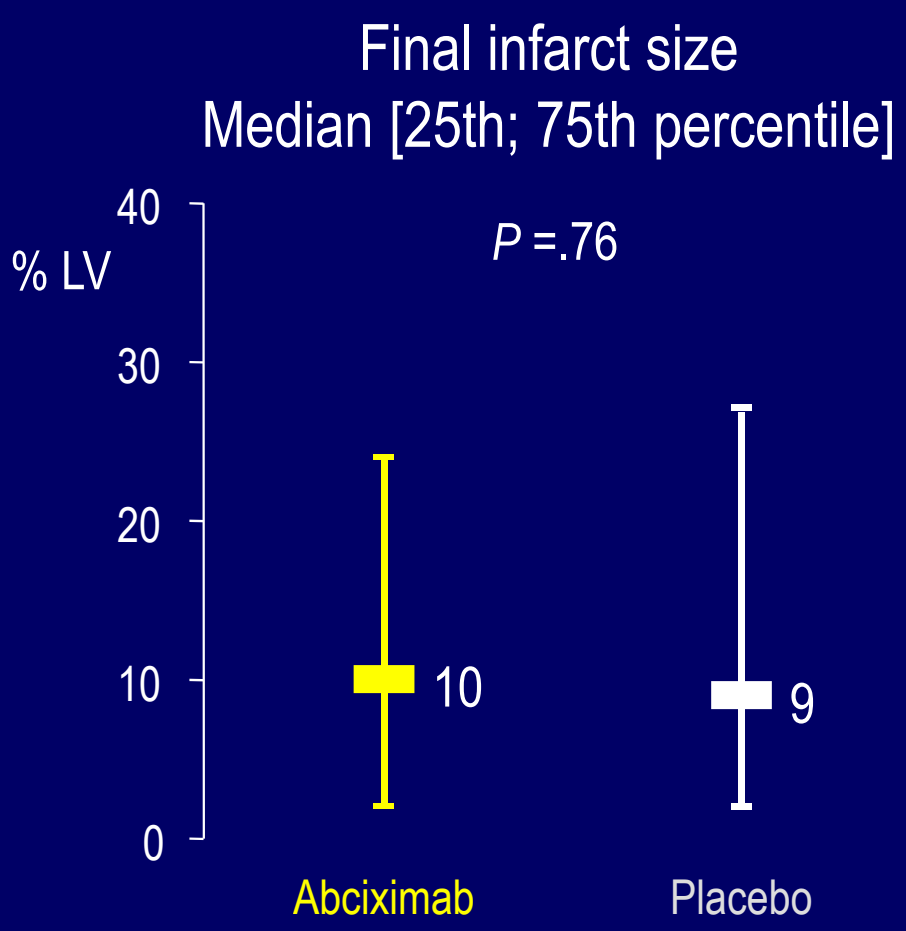
Circulation. 2009;119:1933-40.

Primary Endpoint





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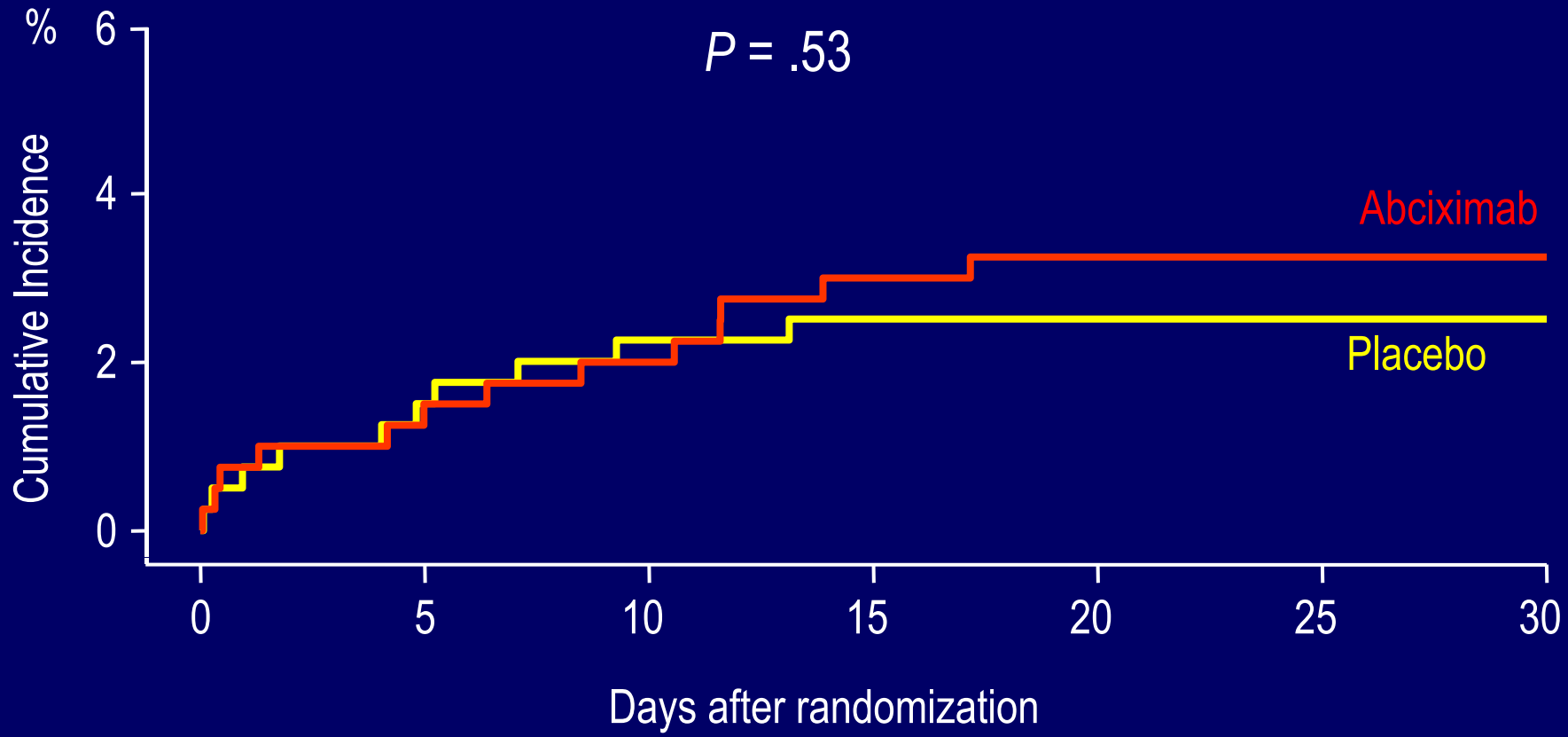
Circulation. 2009;119:1933-40.

30-Day Mortality

Onset of symptom to Abciximab time > 200 minutes



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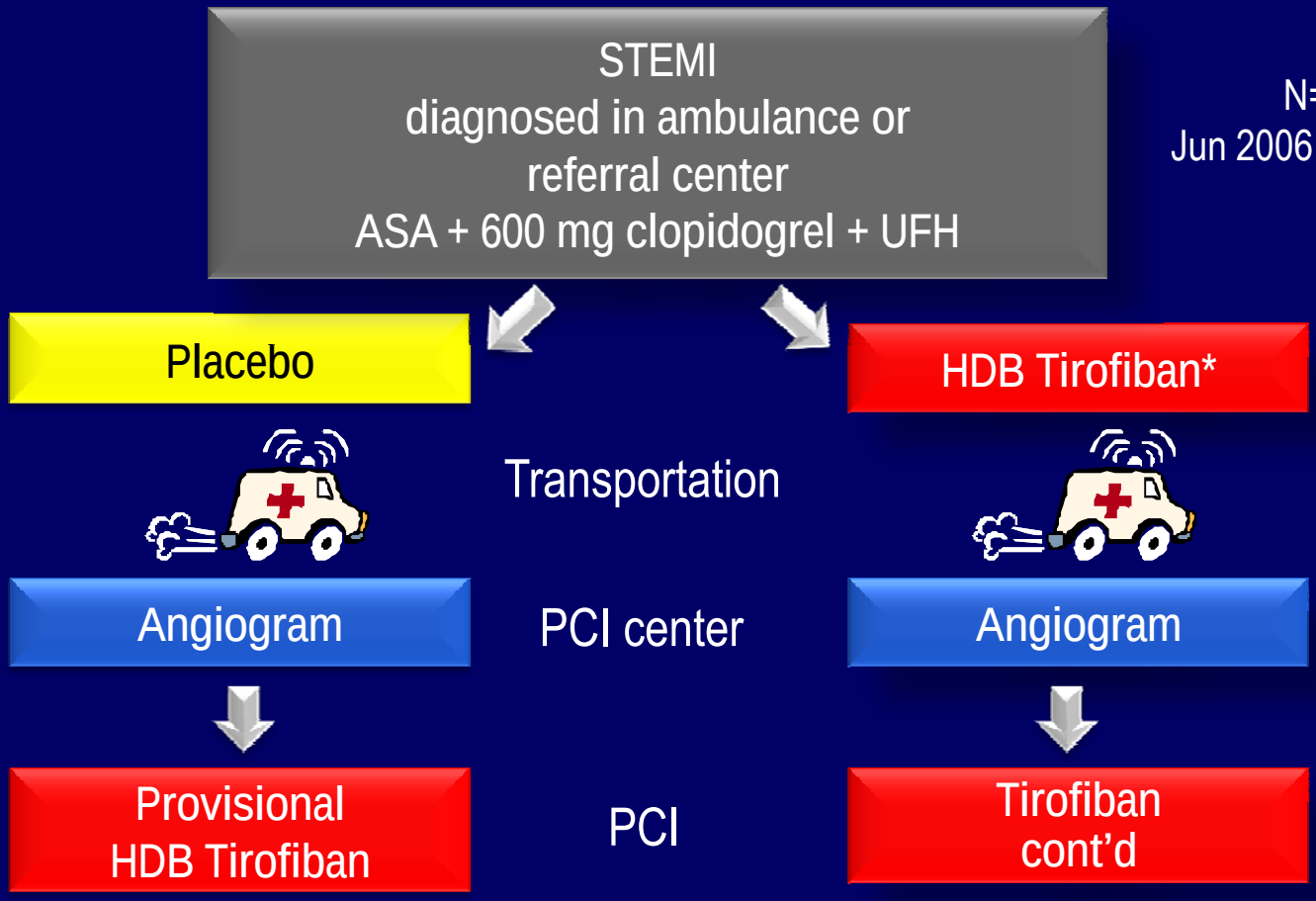
Circulation. 2009;119:1933-40.

On-TIME 2: Study Design



*Bolus: 25 µg/kg and 0.15 µg/kg/min infusion.

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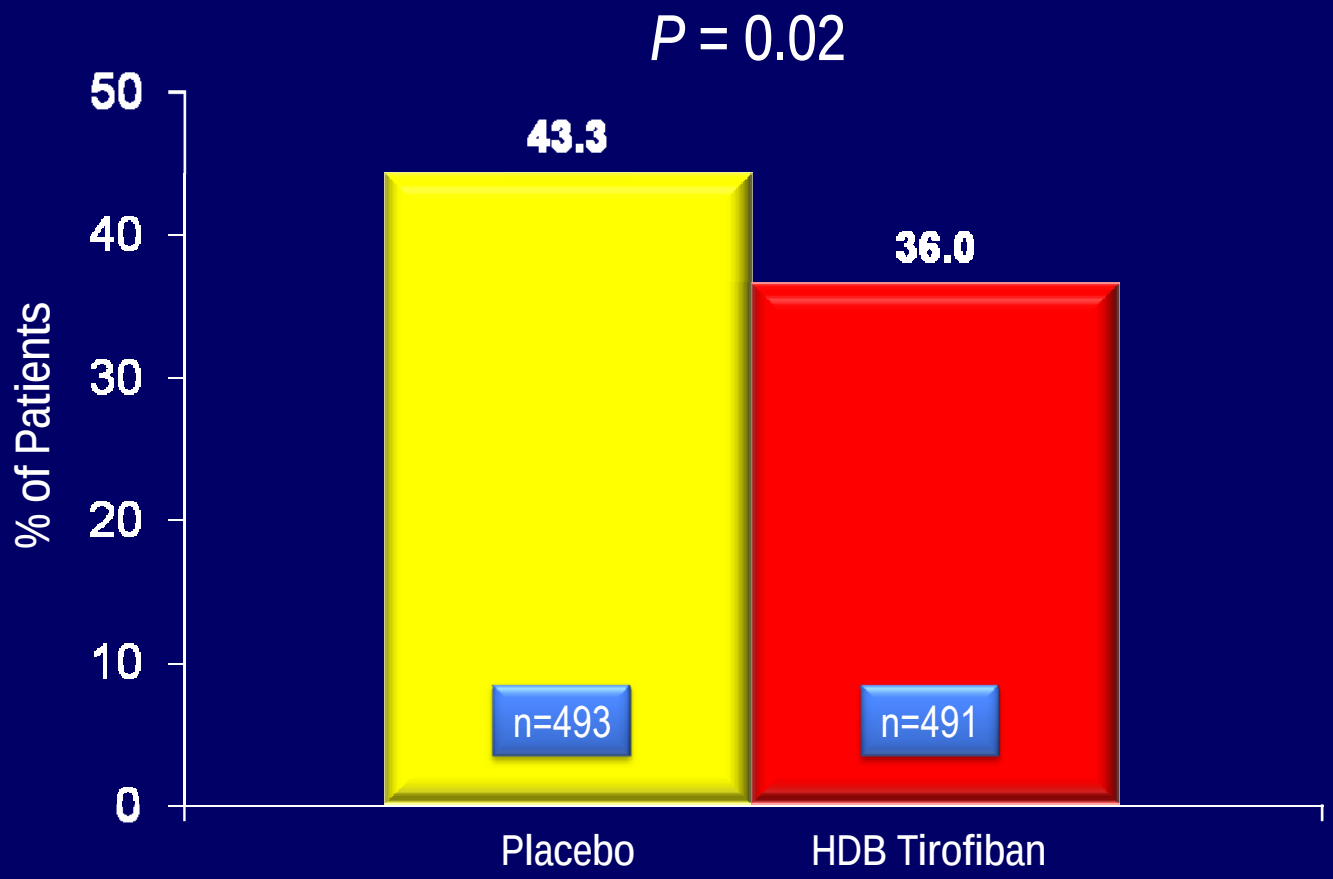
van 't Hof AWJ, et al. *Lancet* 2008;16;372(9638):537-46

ST-Segment > 3 mm Deviation 1 Hour Post-PCI



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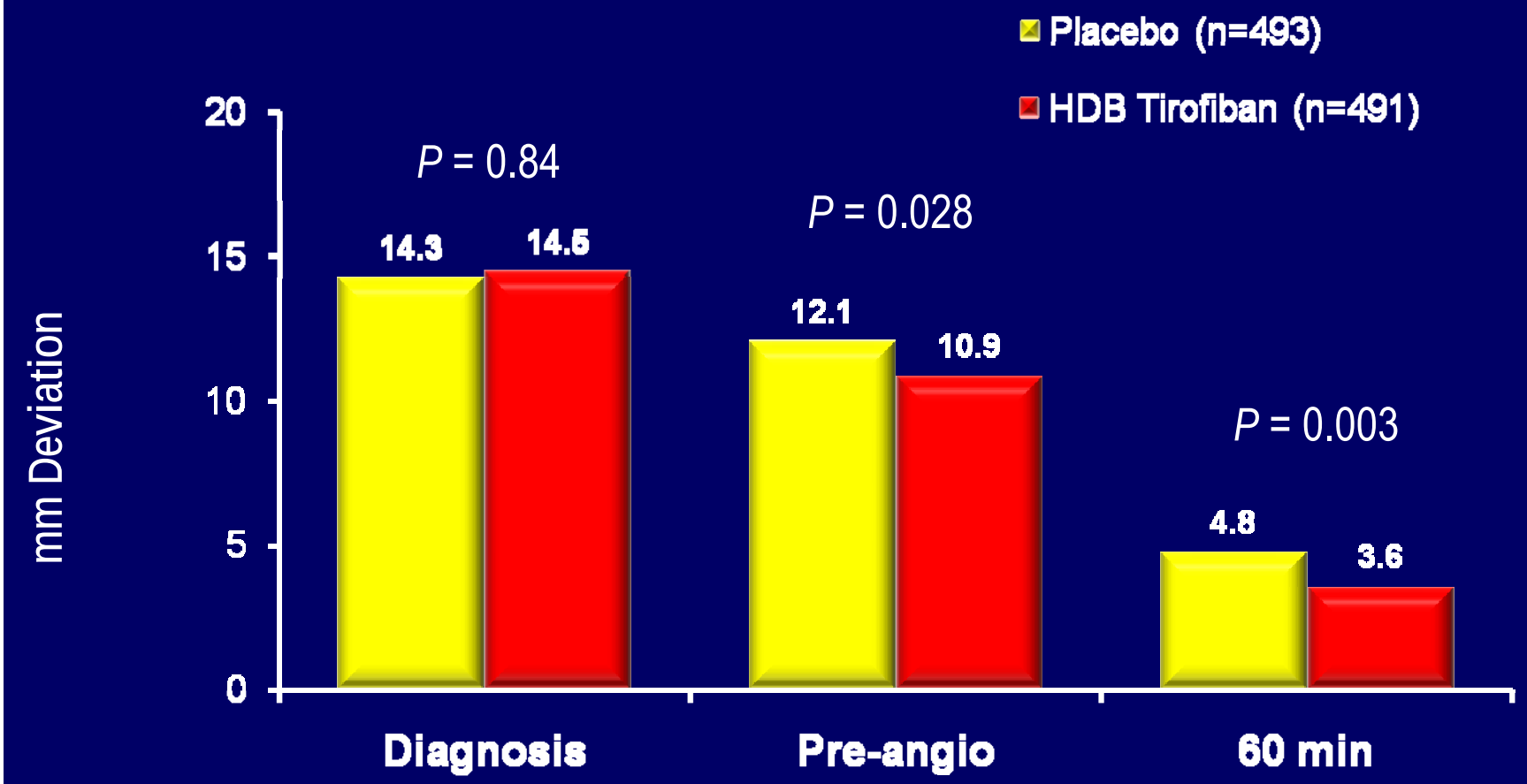
van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

ST Deviation Over Time



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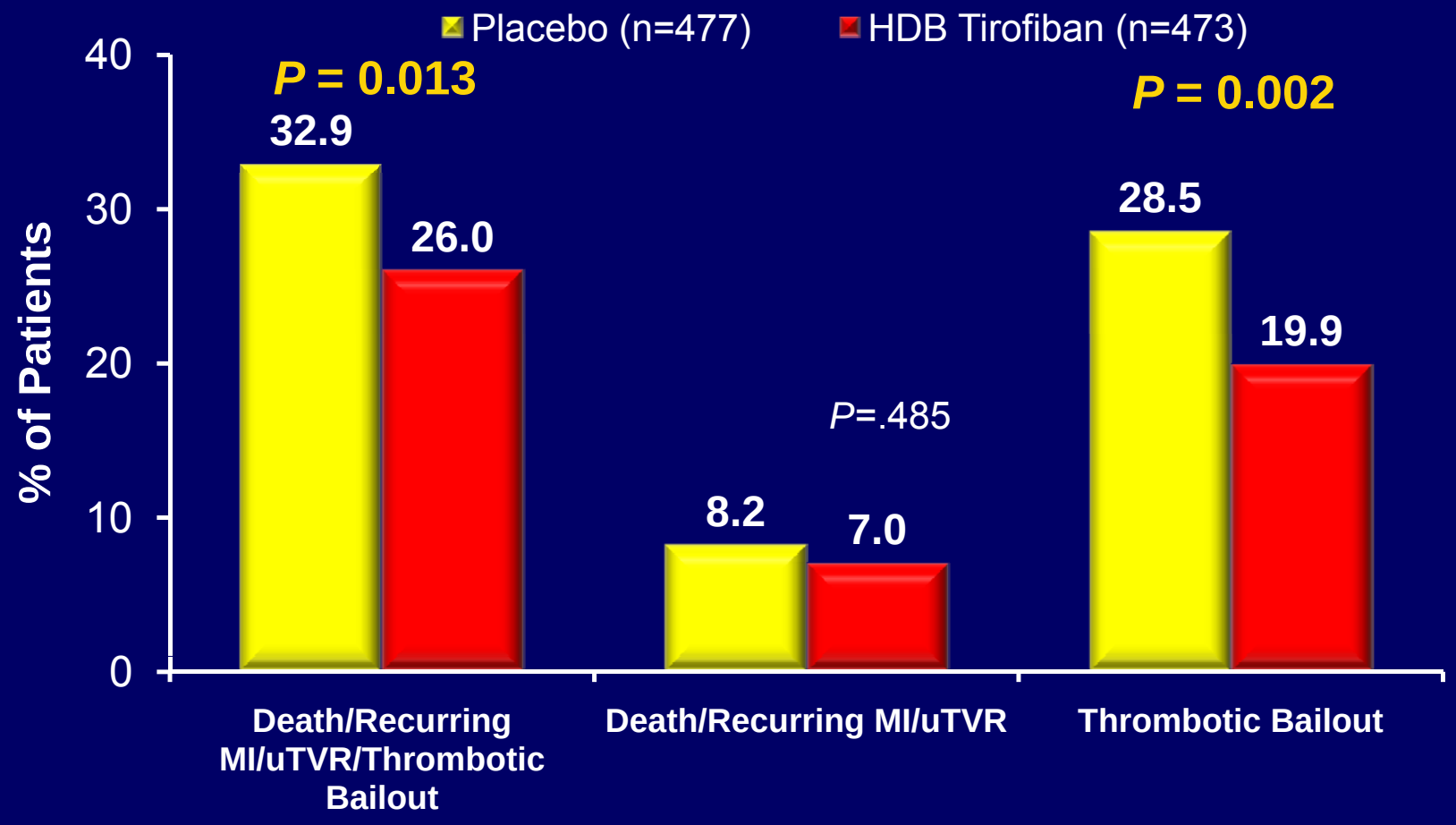
van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

Outcomes at 30 Days



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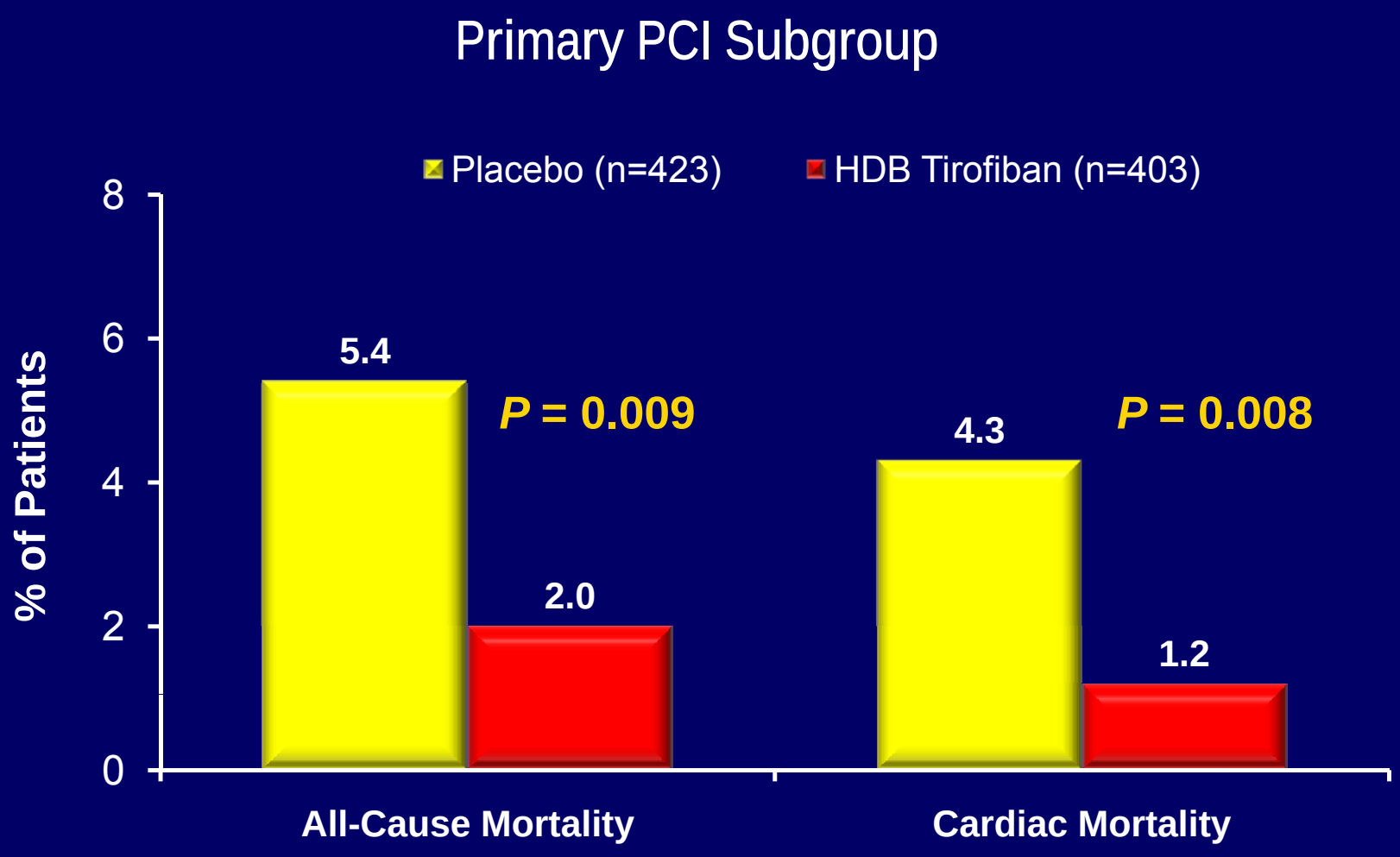
van 't Hof AWJ, et al. *Lancet* 2008;372(9638):537-46

Mortality at 1 Year



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J Am Coll Cardiol. 2010;55:2446–55

Early vs. Late GPI use in Primary PCI of STEMI

Figure 2. Odds Ratios for Thrombolysis in Myocardial Infarction (TIMI) Grade 3 Flow With Early vs Late Administration of Glycoprotein IIb/IIIa Inhibitors

Study	Agent	No. of Events/Total No. Early Administration	Late Administration
On-TIME[9]	Tirofiban	46/243	36/244
TIGER-PA[10]	Tirofiban	16/50	5/50
Cutlip et al[11]	Tirofiban	9/28	6/30
Zorman et al[12]	Abciximab	9/56	1/56
ERAMI[14]	Abciximab	4/36	3/38
Overall		84/413	51/418

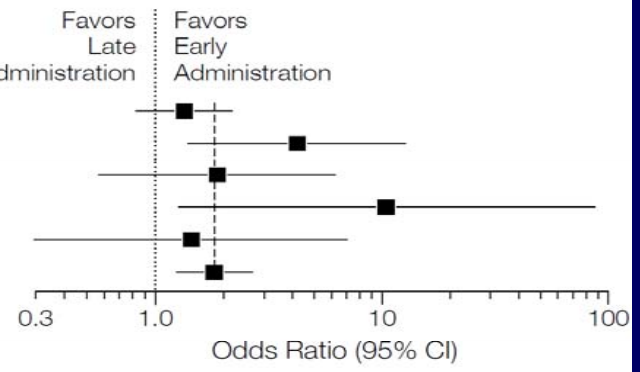
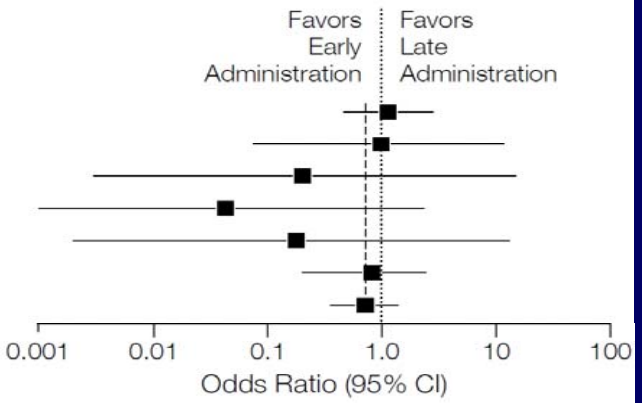


Figure 3. Odds Ratios for Mortality With Early vs Late Administration of Glycoprotein IIb/IIIa Inhibitors

Study	Agent	No. of Events/Total No. Early Administration	Late Administration
On-TIME[9]	Tirofiban	11/245	9/244
TIGER-PA[10]	Tirofiban	1/50	1/50
Cutlip et al[11]	Tirofiban	0/28	1/30
Zorman et al[12]	Abciximab	0/56	5/56
REOMOBILE[13]	Abciximab	0/52	1/48
ERAMI[14]	Abciximab	4/36	5/38
Overall		16/467	22/466



JAMA. 2004;292:362-366

IV GPIIb/IIIa Inhibitors

Pharmacology

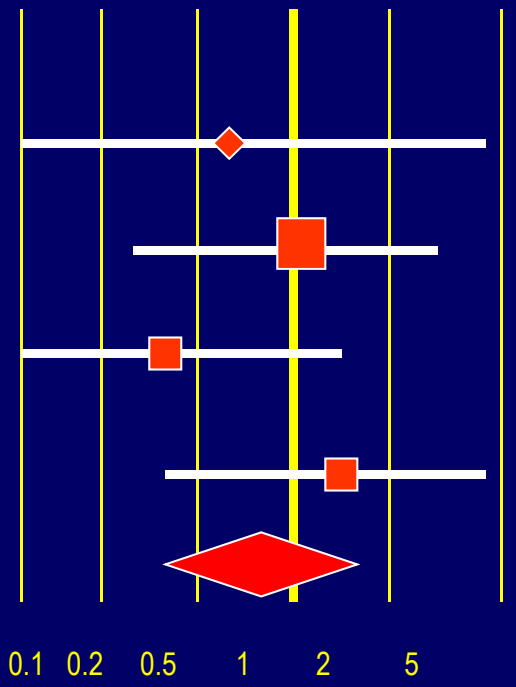
	Eptifibatide	Tirofiban	Abciximab
Molecular weight	~800	~500	~50,000
Stoichiometry *drug-to-receptor ratio*	>>100:1	>>100:1	~1.5:1
Binding	Competitive	Competitive	**High affinity**
Half life plasma biologic	~2-2.5 hr plasma	~2-2.5 hr plasma	~10-15 min **12-24 hr**
Clearance	Renal	Renal	proteolysis

- Bleeding risk: similar across the drugs
- Thrombocytopenia: Eptifibatide =Tirofiban < Abciximab

Use of Glycoprotein IIb/IIIa Receptor Antagonists in STEMI

Study Name	Year	Statistics	p-value	Death/Total	
				SM GPI	Abciximab
Valgimigli	2005	0.667 (0.11-4.09)	0.661	2/87	3/88
EVA-AMI	2007	1.017 (0.36-2.86)	0.974	8/226	7/201
MULTISTRATEGY	2008	0.438 (0.13-1.44)	0.173	4/372	9/372
FATA	2008	1.367 (0.43-4.35)	0.596	7/351	5/341
overall		*0.843 (0.46-1.55)*	*0.584*		

OR and 95% CI of 30-day Mortality



Gurm et al. Small Molecule GP IIb/IIIa Inhibitors primary PCI. *Circ Cardiovas Intervent.* 2009;2:230-2236.

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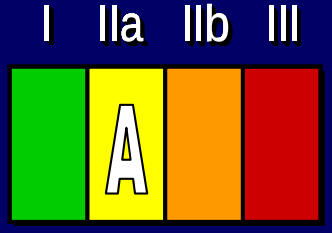
Use of Glycoprotein IIb/IIIa Receptor Antagonists in STEMI

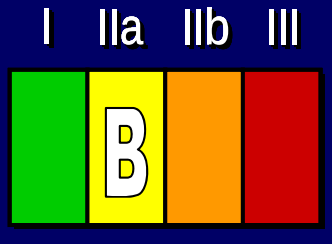
Modified Recommendation

It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists at the time of primary PCI (with or without stenting) in selected patients with STEMI



abciximab

Large anterior MI;
Large thrombus burden;
Inadequate thienopyridine loading



tirofiban and eptifibatide

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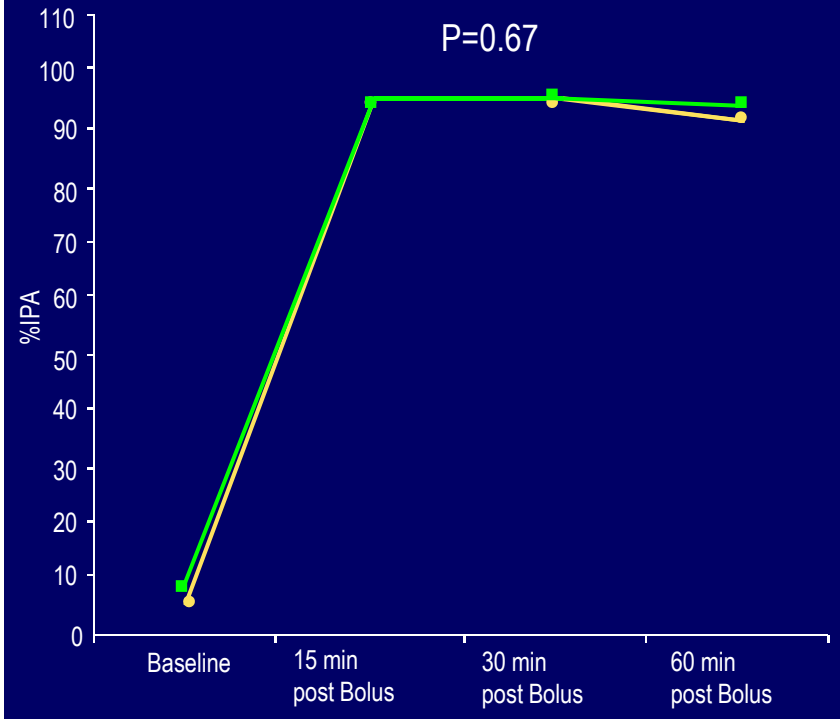
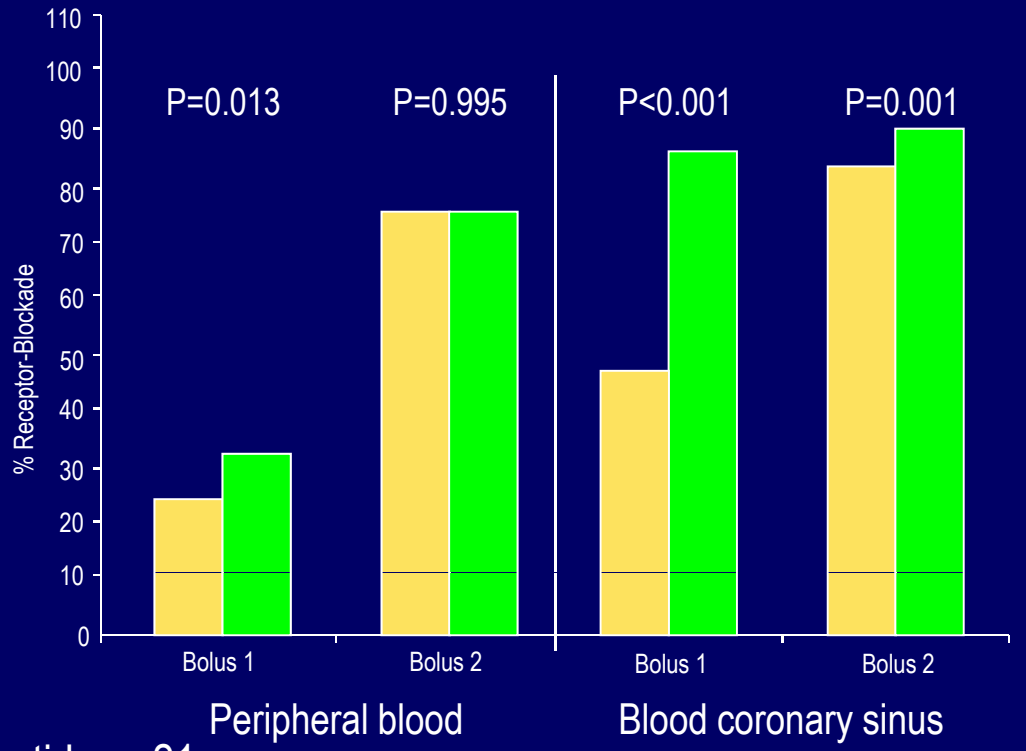
IC vs. IV GPI (ICE-Trial)

2 x Bolus within 10 min. 180 µg/kg Eptifibatide (Buffering with NaBi) i.c. versus i.v.
2 $\mu g/kg^{-1} .min^{-1}$ continuous infusion i.v. for 18 h

IPA periphery (20 µmol/L ADP)



GP IIb/IIIa receptor-blockade



i.c. Eptifibatide n=21

i.v. Eptifibatide n=19

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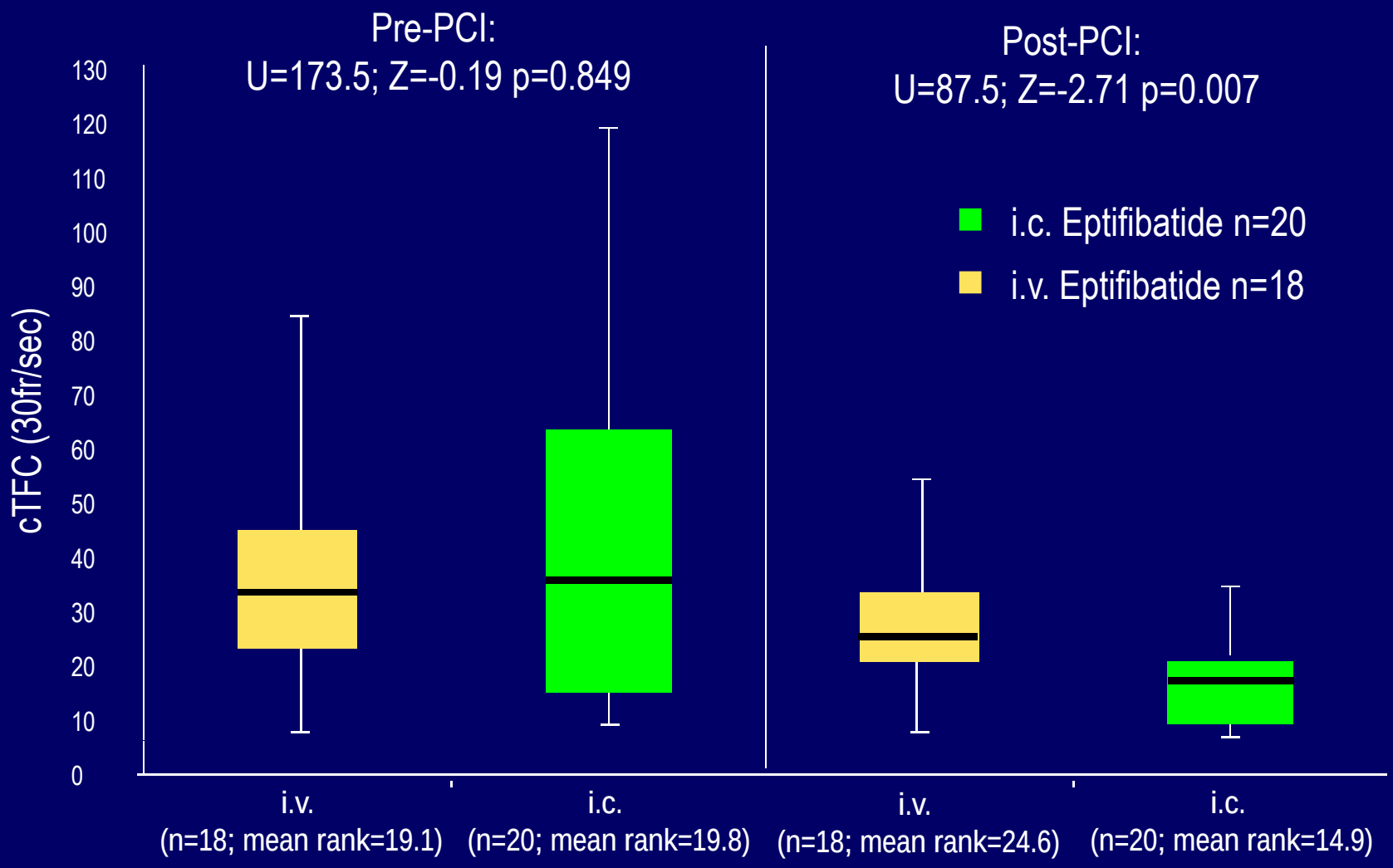
Deibele et al. Circulation 2010;121:784-791

IC Eptifibatide. (ICE-Trial)



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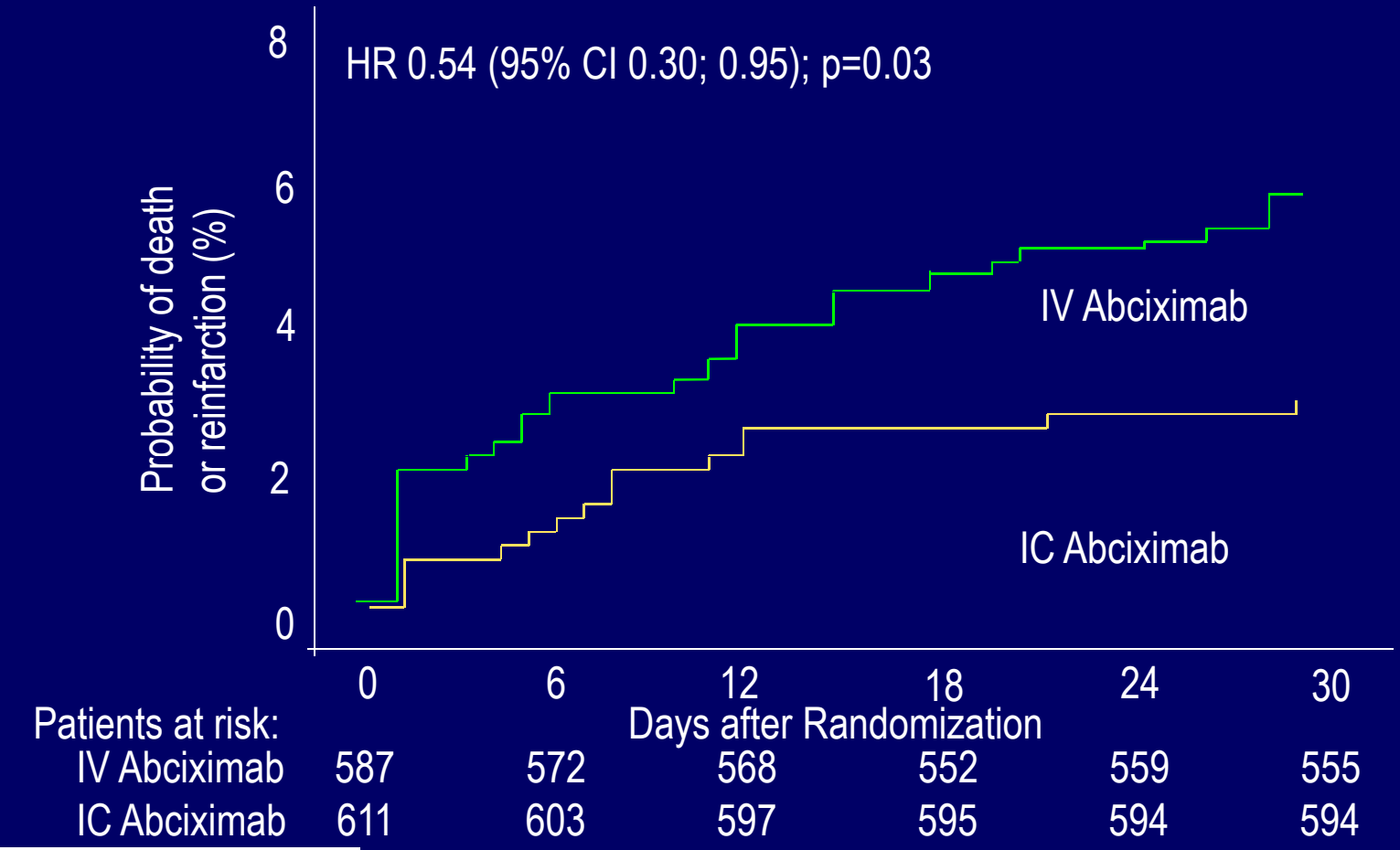
Deibele et al. Circulation 2010;121:784-791

Individual Patient-based Meta-Analysis

5 randomized trials (n = 1198);
individual patient-based meta-analysis
IC Abciximab n = 611
IV Abciximab n = 587



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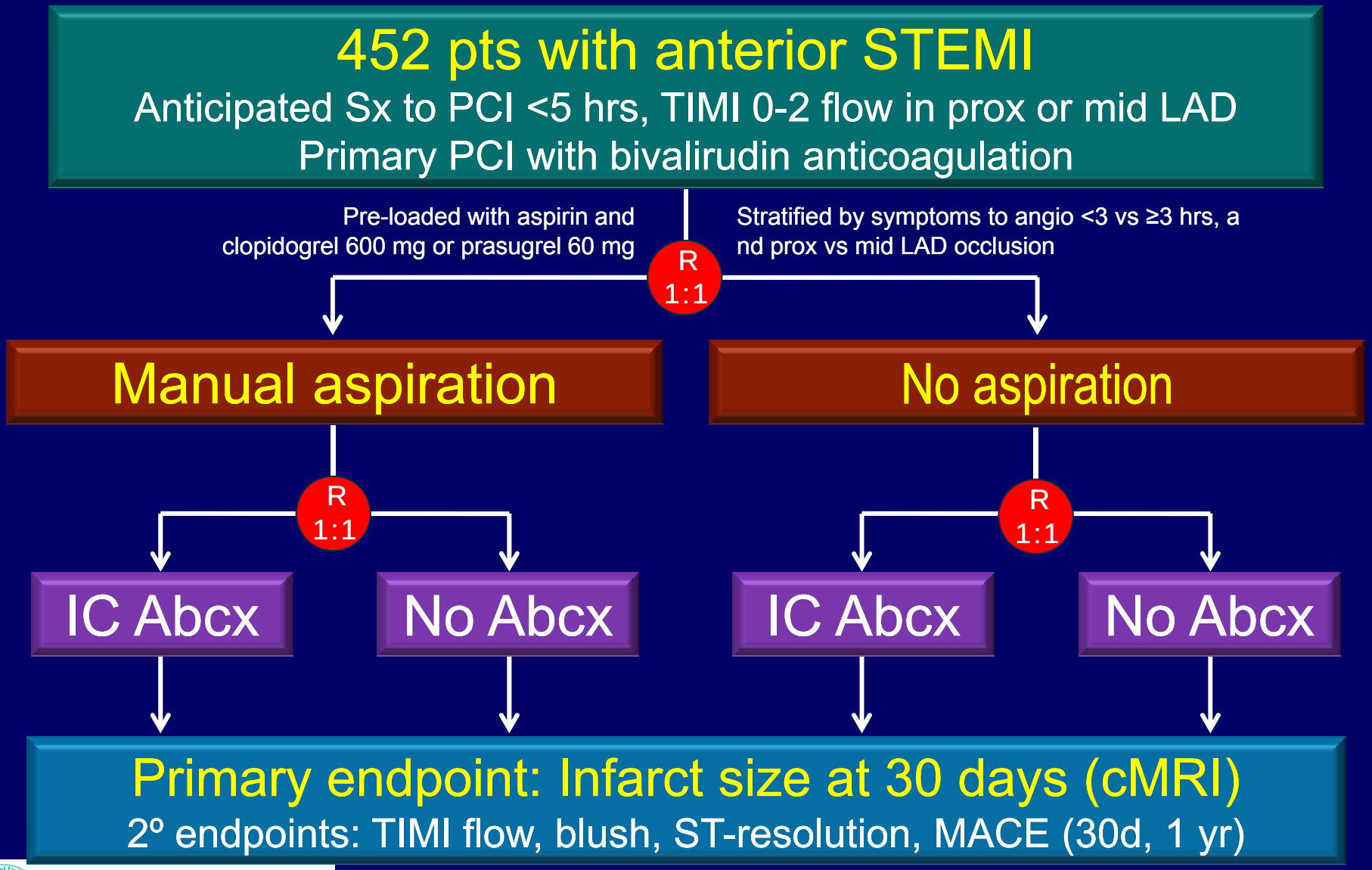
Piccolo, Thiele et al.

INFUSE-AMI Trial



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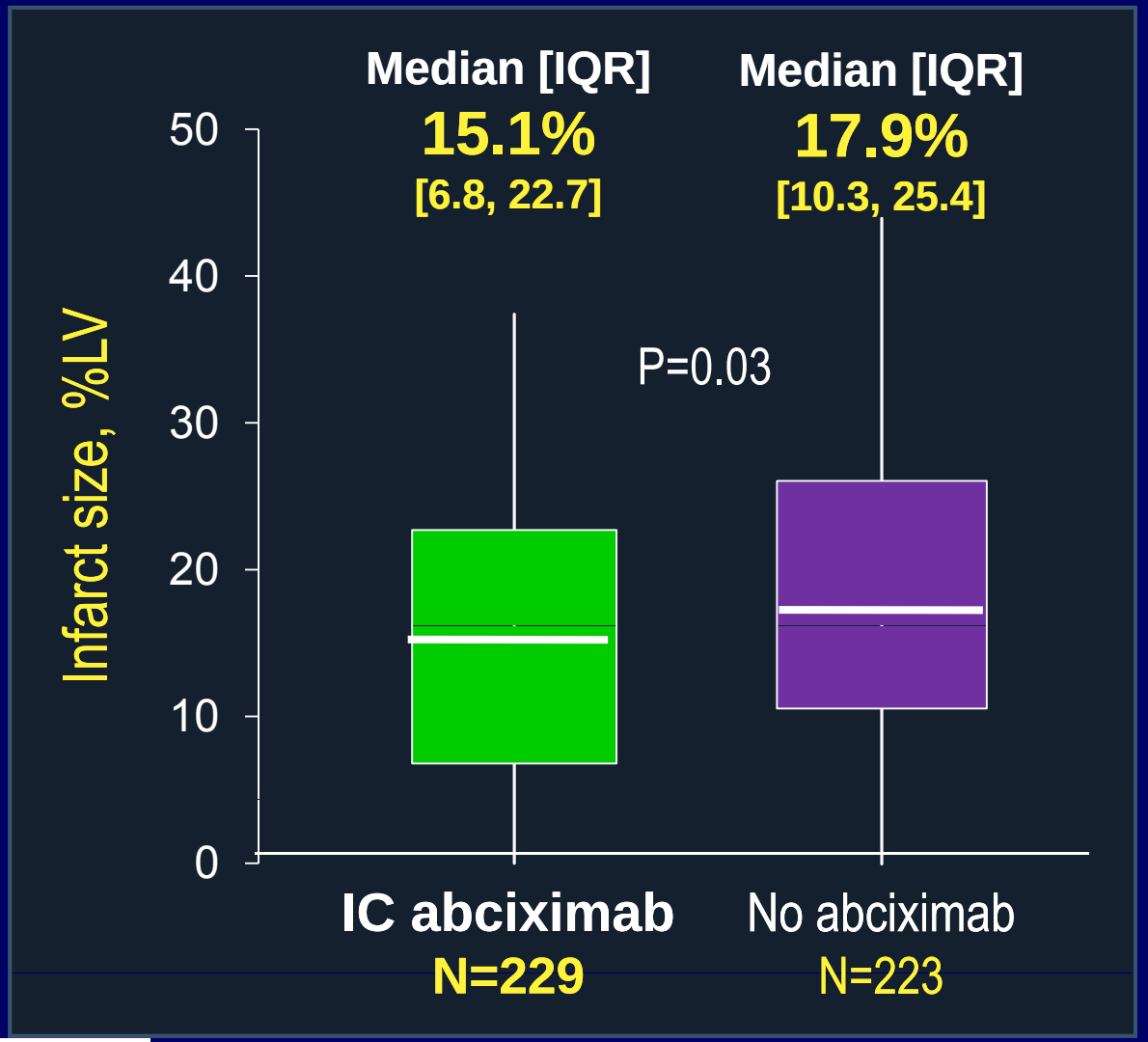
JAMA. 2012, e-pub.

INFUSE-AMI: Infarct size at 30 days*

- Primary endpoint -



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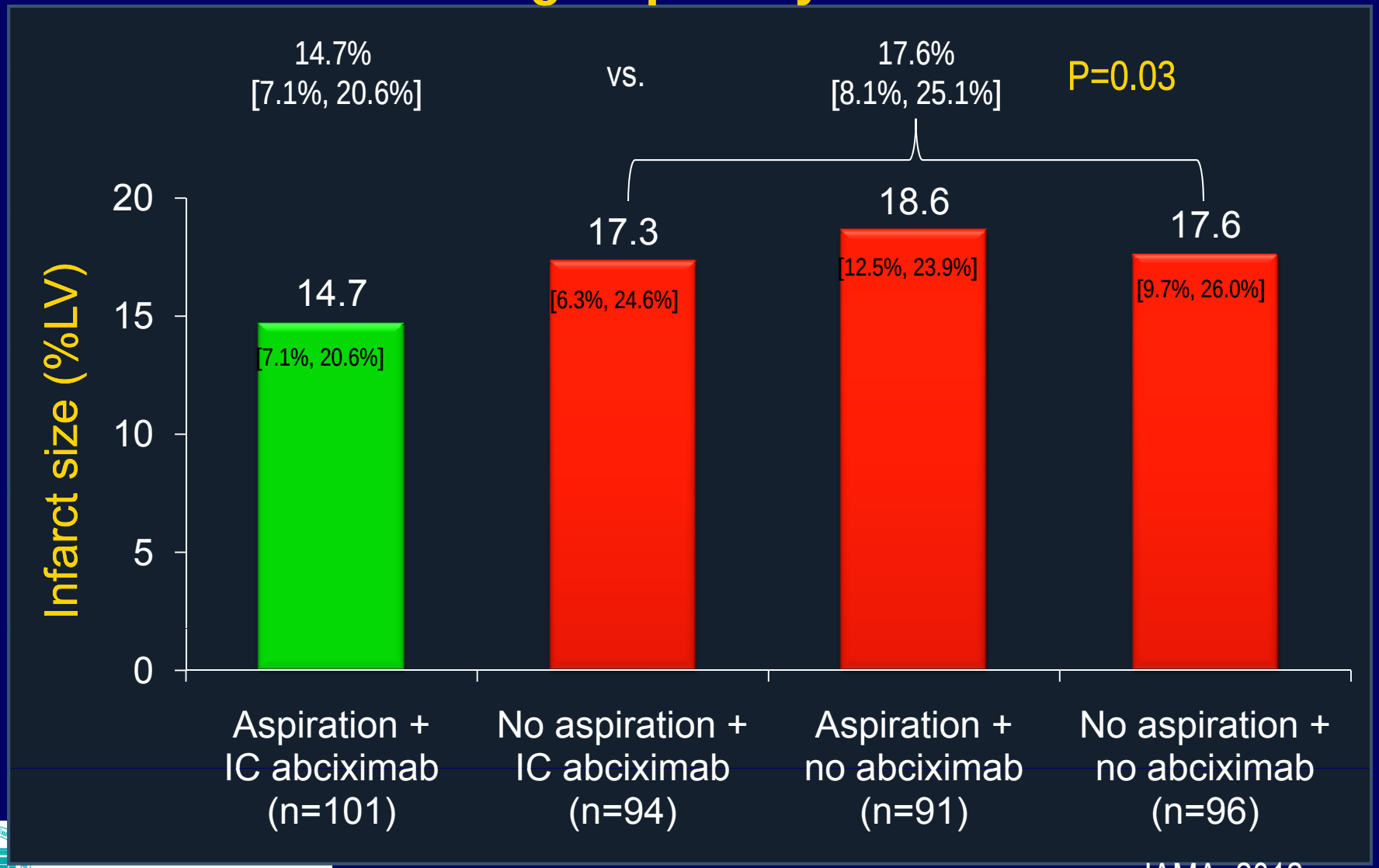
*Core laboratory assessed

JAMA. 2012, e-pub.

INFUSE-AMI: Infarct size at 30 days*

- 4 group analysis -



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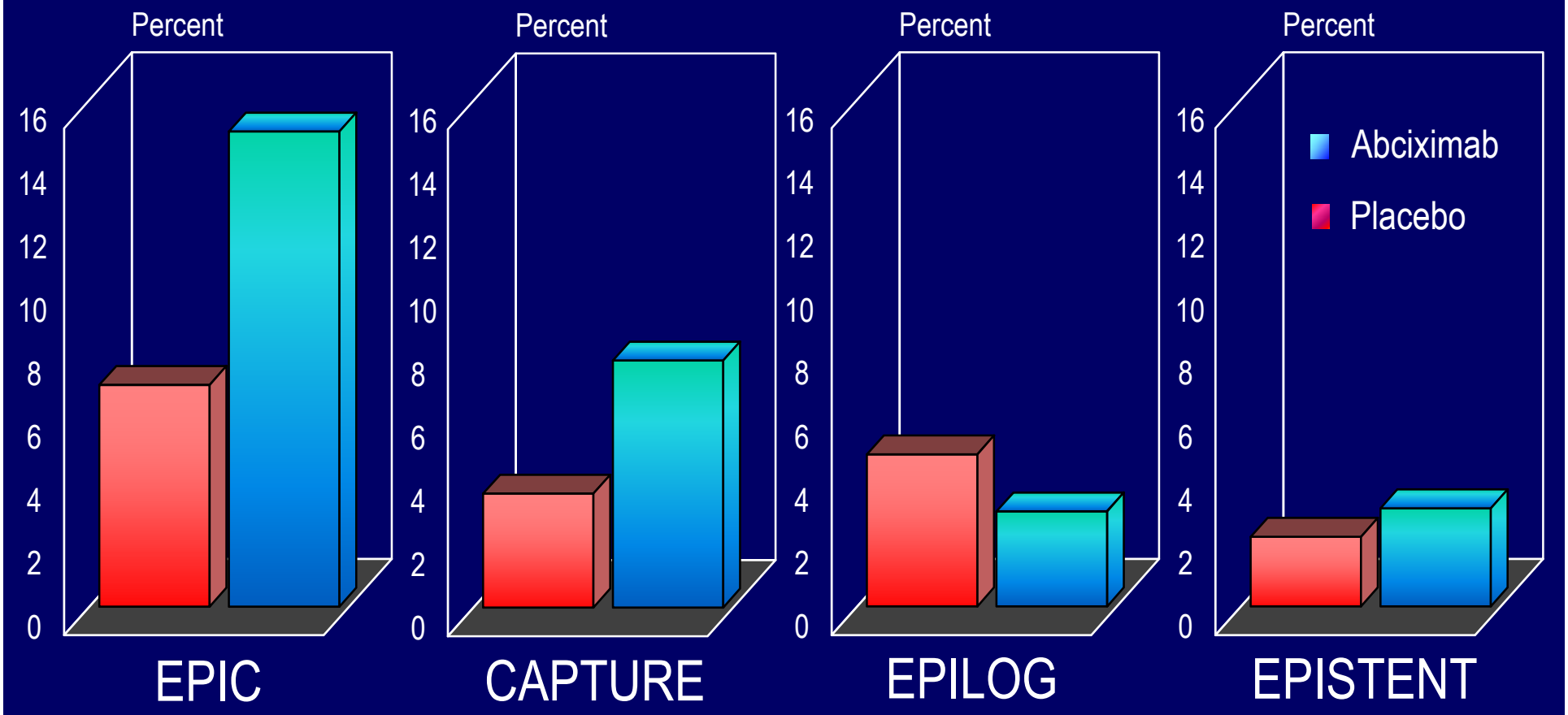
JAMA. 2012, e-pub.

Major Bleeding in Trials of Abciximab

1992-1997

(Includes Peri-CABG Bleeding)



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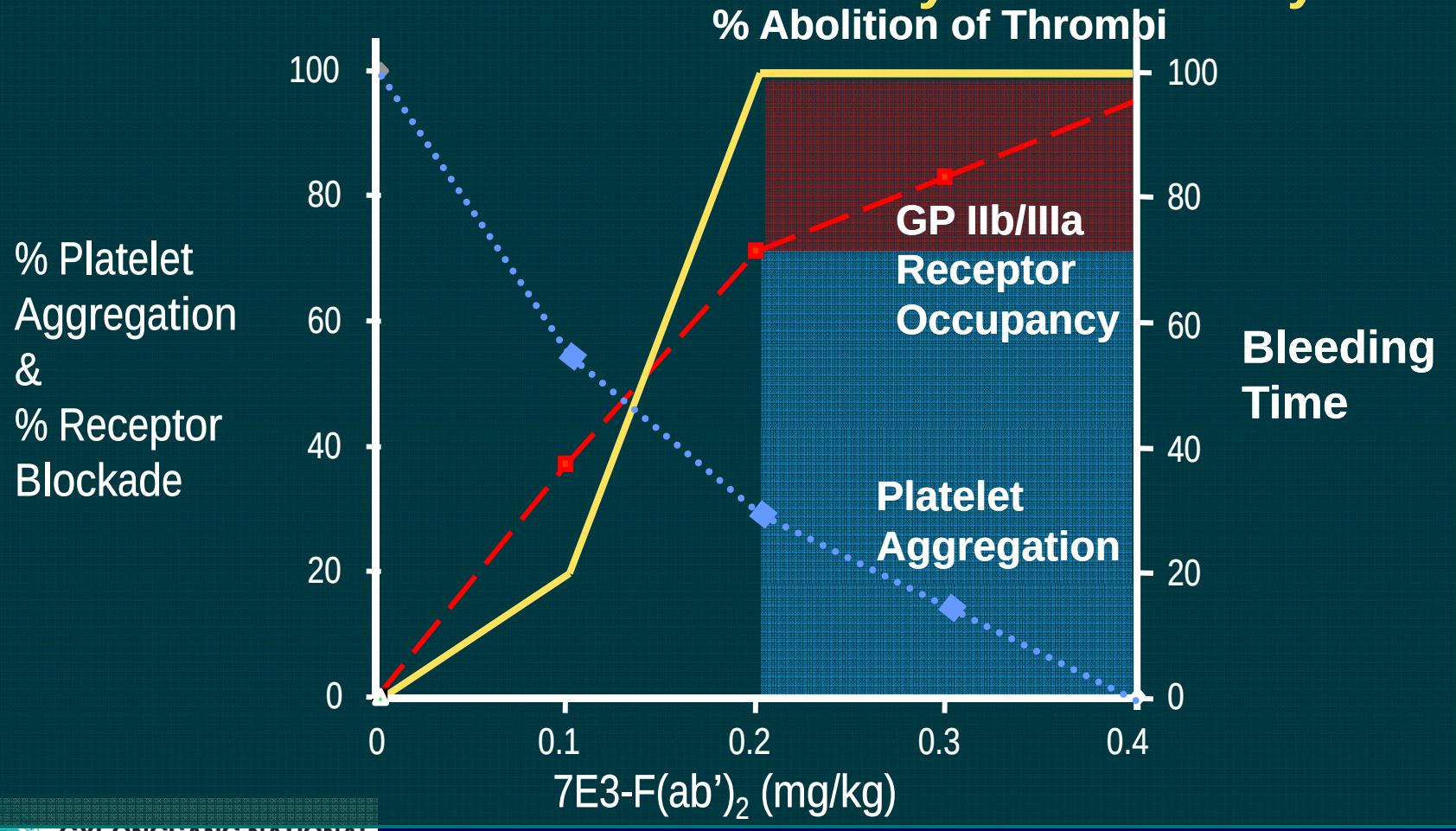
Animal Models – Prevention of Thrombosis with GPIIb/IIIa Antagonists

Folt's model in the monkey carotid artery



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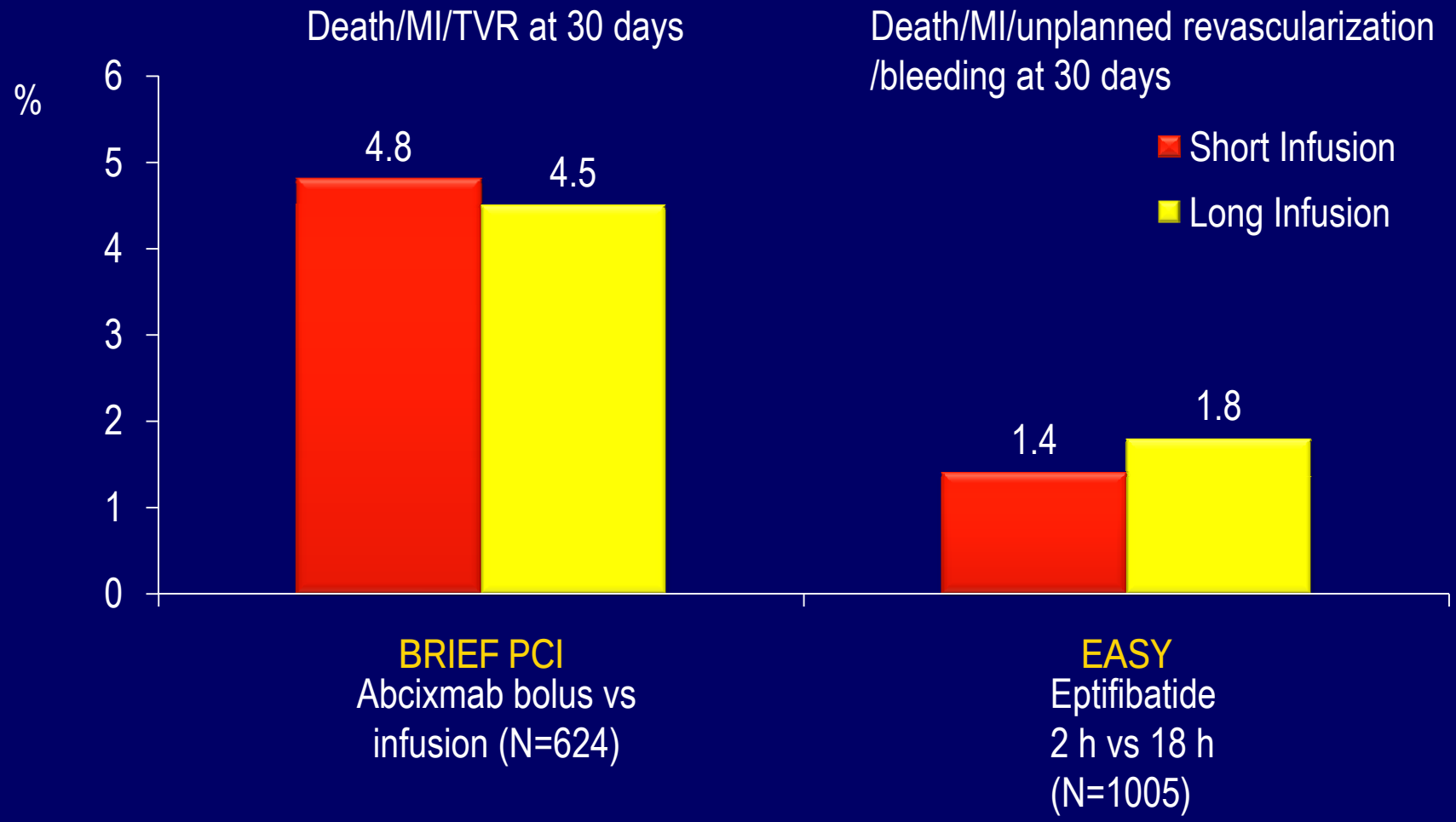
Coller, Circulation 1989;80:1766

Randomized Trials of Short or Bolus infusion vs. Standard Infusion of GPI



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J Am Coll Cardiol. 2009;53:837–45
Circulation. 2006:2636-2643

Summary

- In NSTEMI patients, GPI including tirofiban reduced ischemic outcomes, particularly in those with high-risk features such as positive biomarkers, diabetes and high TIMI risk scores.
- Selective but rather than routine upstream use of GPI may be more practical in the era of dual antiplatelet therapy.
- Pre-hospital use of tirofiban in patients with STEMI reduced the all-cause and cardiovascular mortality in the ontime-2 trial. However, the studies with similar design did not attain the same results and GPI use in this setting may increase the risk of bleeding.
- Intracoronary administration of GPI showed beneficial effects in reducing infarct size, left ventricle myocardial salvage, and composite clinical endpoints in patients with STEMI without tradeoff of bleeding risks.

Glycoprotein IIb/IIIa inhibitors

- When: routine upstream vs. selective downstream use
- For whom: all, ACS, NSTEMI or STEMI
- How: intravenous vs. intracoronary
- What: Abciximab vs. small molecule GPI
- How long

Conclusion

- GPI should be part of appropriate ACS treatment pathways.