Glycoprotein IIb/IIIa Inhibitors: Update 2009

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OUTLINE

- GP IIb/IIIa inhibitors – pharmacokinetic and pharmacodynamic properties
- Eptifibatide – history, dosing, major studies
- ACS and PCI trials
- Contemporary trials, including compariosn vs. bivalirudin
- Special populations
- Conclusions and implications

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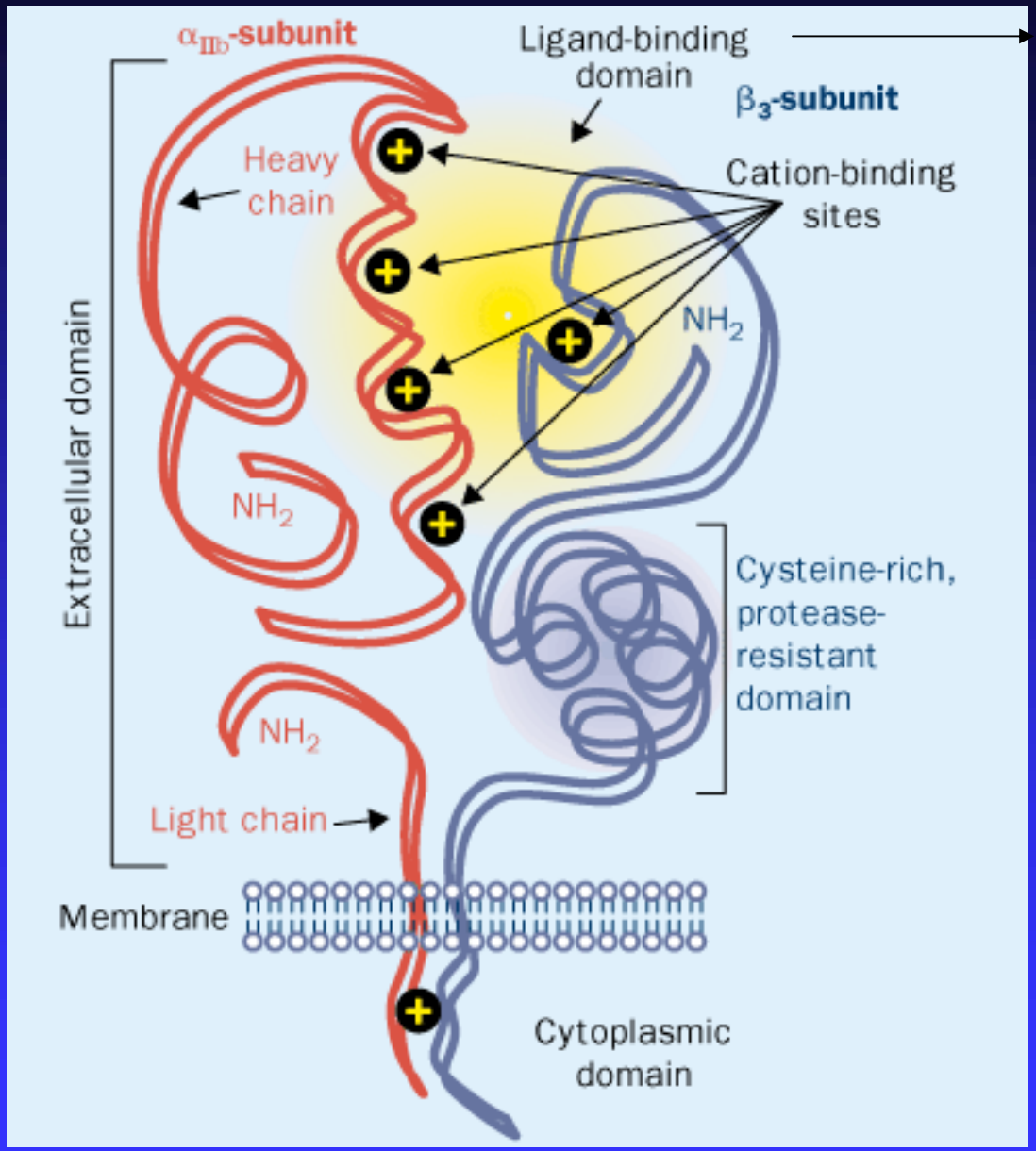
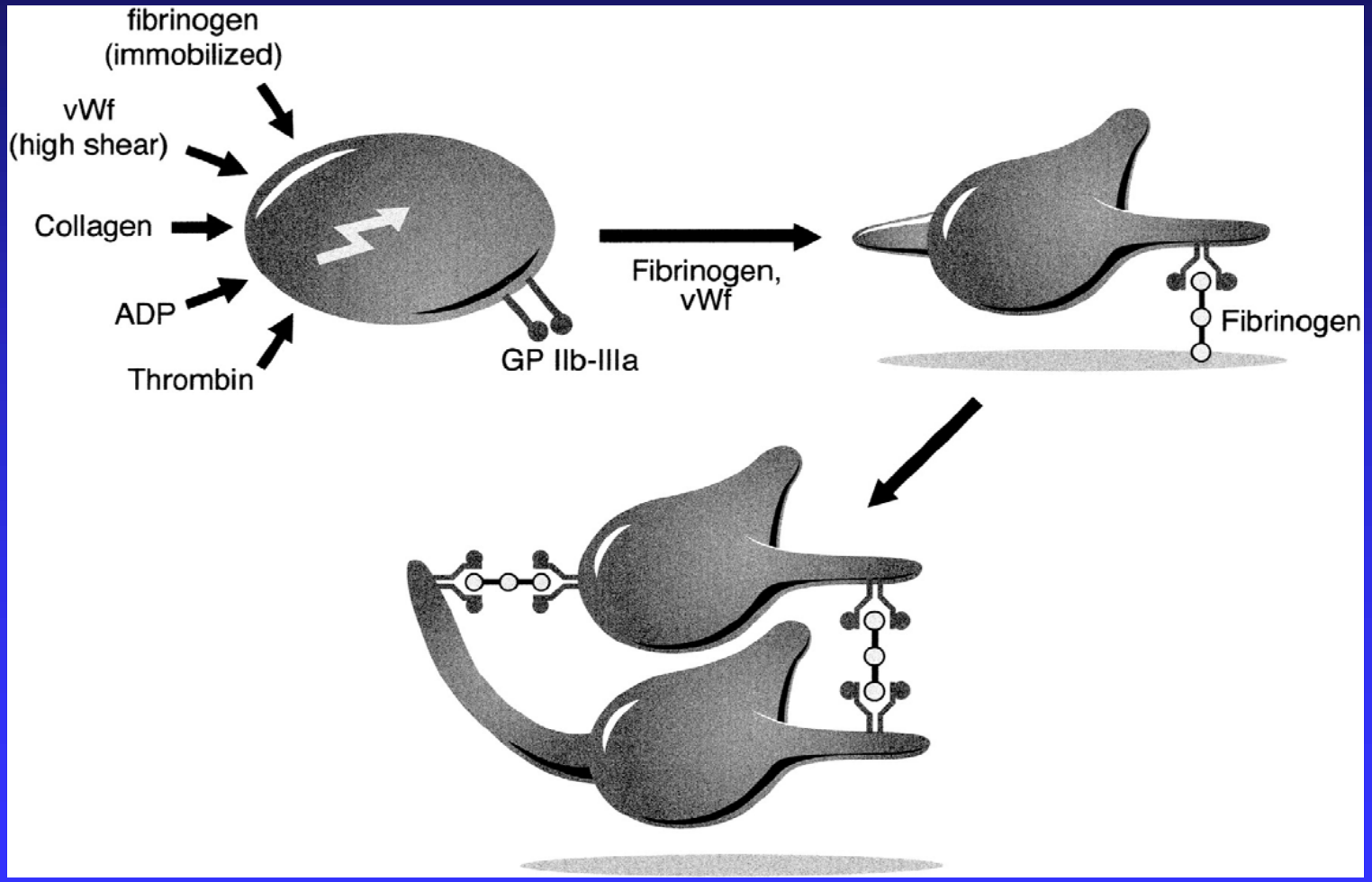
Schematic depiction of integrin $\alpha_{IIb}\beta_3$



Interacts with RGD sequence on ligands

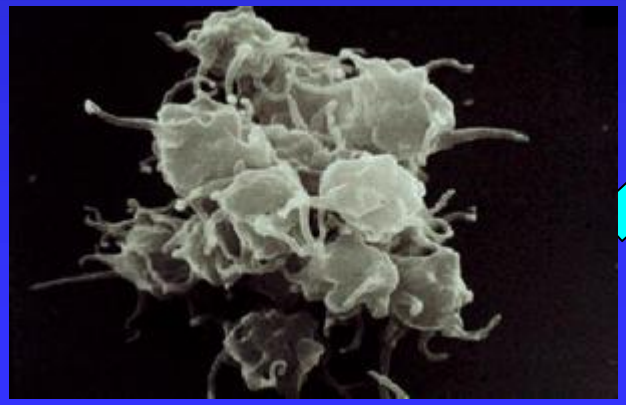
Both subunits are a product of a single gene located on chrom. 17

GP IIb/IIIa Receptor Activation



Platelet Activation - 2004

Thrombin -Induced Platelet Activation



release of over 300 proteins that act in a autocrine and paracrine fashion to modulate cell signaling. Some are pro-thrombotic, others pro-inflammatory, others regulate cell proliferation, and many are of unknown function.

Coppinger JA. Blood 2004;103:2096-2104

GP IIb/IIIA Inhibitors

- **Abciximab (ReoPro®)** – the first inhibitor developed and approved for clinical use.

  Chimeric monoclonal antibody – 7E3, the murine constant region was replaced by its human counterpart

- **Eptifibatide (Integrilin®)** – synthetic cyclic hepta-peptide derived from a sequence found in the venom of the southeastern pygmy rattlesnake

- **Tirofiban (Aggrastat®)** – synthetic small molecule with structure similar to that of the RGD sequence of the snake venom echistatin

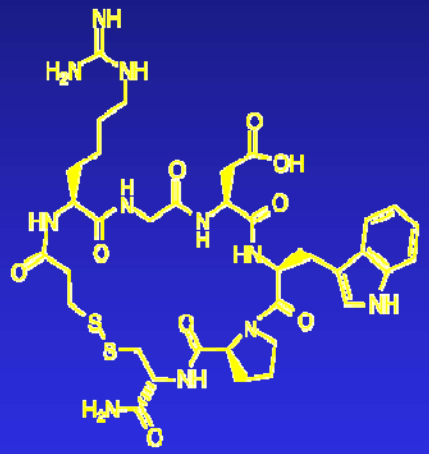
GP IIbIIIa inhibitors

Antibody

- abciximab

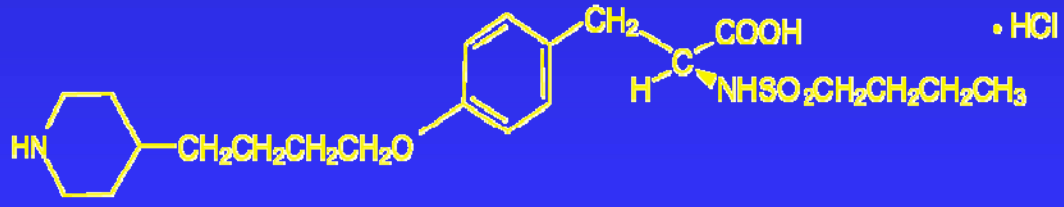
Cyclic peptide

- eptifibatide



Nonpeptide

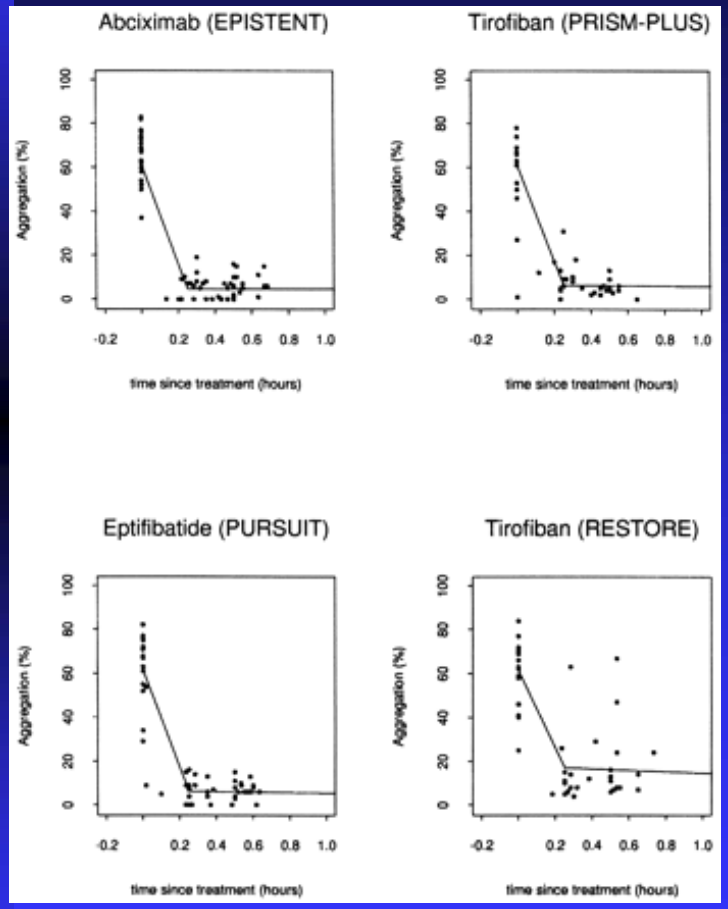
- tirofiban HCl
  (Aggrastat®, Merck)

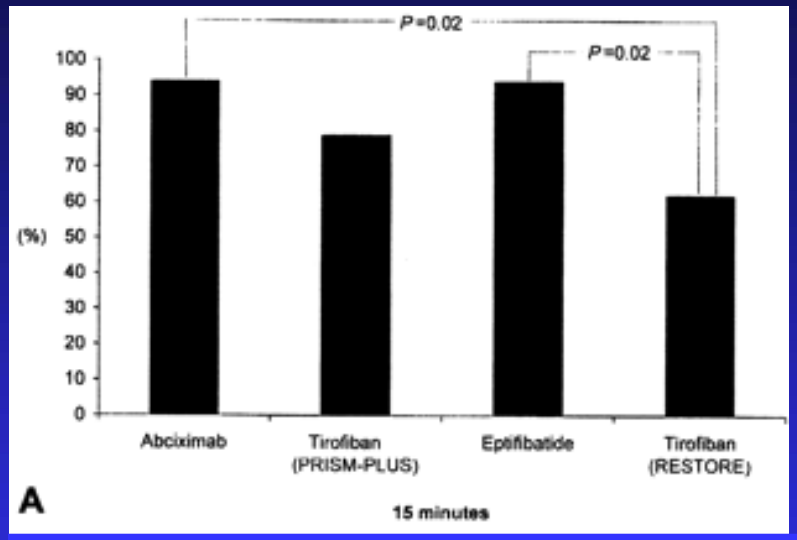


Glycoprotein IIb/IIIa Receptor Antagonists

	Abciximab	Tirofiban	Eptifibatide
Pharma	Fab portion of chimeric monoclonal antibody	Synthetic non-peptide	Cyclic heptapeptide
Plasma ½ life	30 minutes	1.8 hours	2.5 hours
Specificity	Not specific	Highly specific	Highly specific
Dose	0.25 mcg/kg bolus followed by 0.125 mcg/kg/min drip (max 10 mcg/min) for 12-24 hours	0.4 mcg/kg/min for 30 minutes followed by 0.1 mcg/kg/min drip for 48-96 hours	180 mcg/kg bolus (x2) followed by 2.0 mcg/kg/min drip for 18-24 hours

COMPARE Study – early platelet aggregation





Proportion of patients (%), in whom >80% inhibition of 20 µmol/L ADP-induced PA was achieved

73 ACS pts planned for PCI
Samples drawn in PPACK

Batchelor WB et al Circulation 2002

GOLD Study

- 485 patients undergoing a PCI with planned use of 1 of the 3 approved GP IIb/IIIa inhibitors
- Platelet function evaluated at various time points by RPFA correlated to clinical endpoints – MACE at 30 days
- Platelet inhibition at 10 min and MACE:
  ≥ 95% inhibition ⇒ 6.4% MACE
  < 95% inhibition ⇒ 14.4% MACE (p=0.006)
- Platelet inhibition at 8 hrs and MACE:
  ≥ 70% inhibition ⇒ 8.1% MACE
  < 70% inhibition ⇒ 25% MACE (p=0.009)

Steinhubl et al, Circulation 2001; 103: 2572-2578

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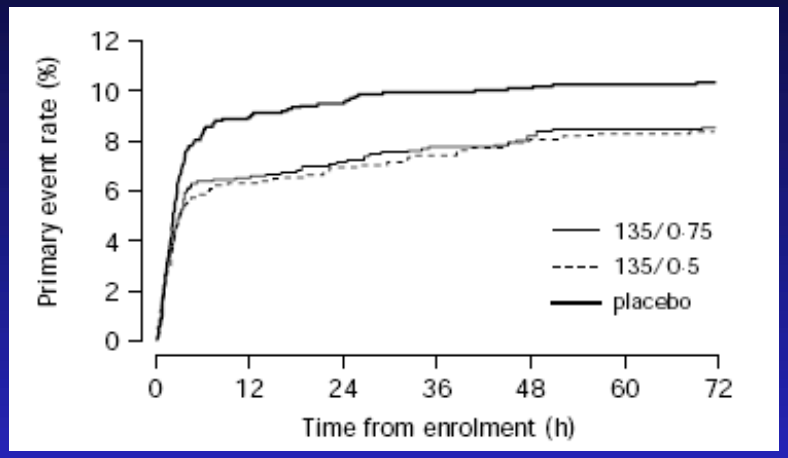
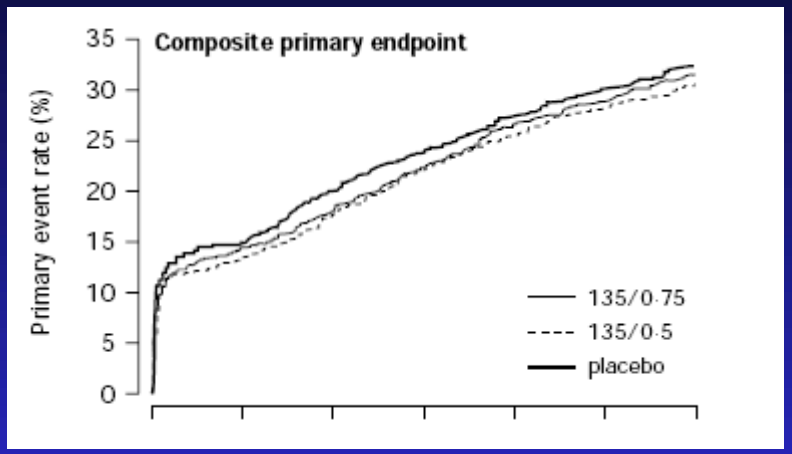
IMPACT – 2 - *Lancet 1997*

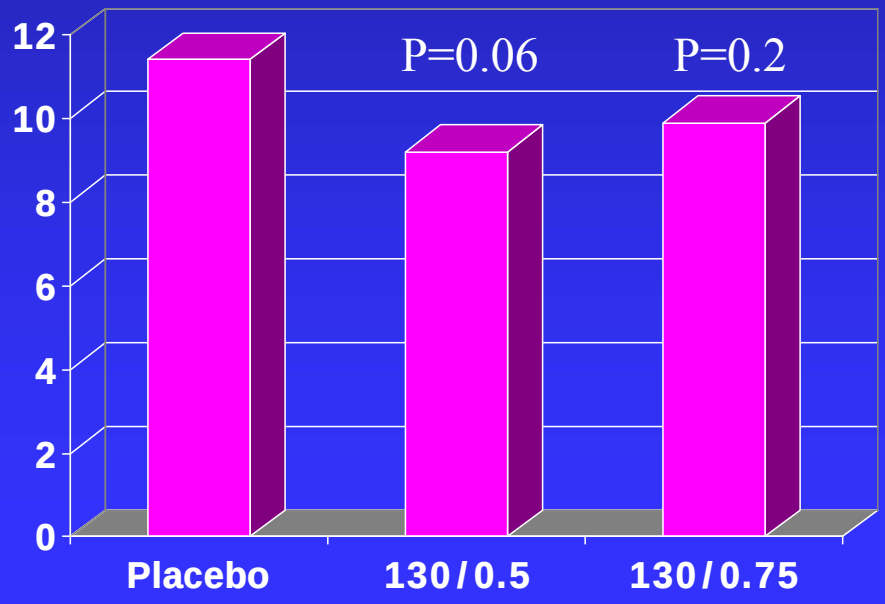
- 4010 patients undergoing elective, urgent, or emergency PCI
- Randomized to: placebo, eptifibatide (135 µg/kg followed by 0.75 µg/kg/min infusion for 20-24 hrs), eptifibatide (135 µg/kg followed by 0.5 µg/kg/min inf. for 20-24 hrs)
- 92% - balloon angioplasy alone (POBA)
- Mean ACT during the procedure 350-365 sec
- 84% - received heparin after the procedure

IMPACT – 2 - *Lancet 1997*



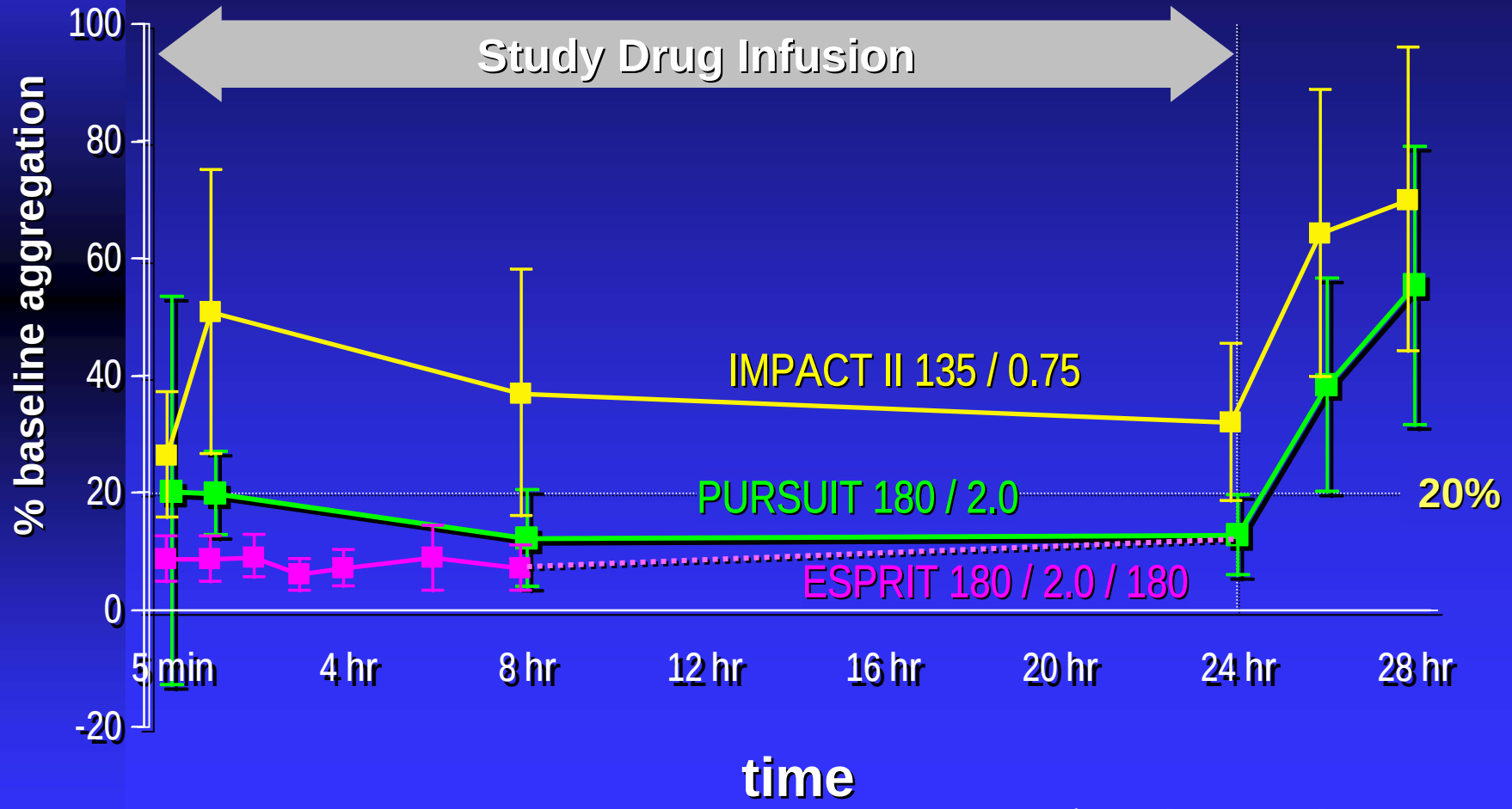


Primary endpoint: 30 day composite occurrence of death, MI, unplanned surgical or repeat PCI., or coronary stent implantation for abrupt closure



Eptifibatide with ADP / PPACK

Inhibition of platelet aggregation

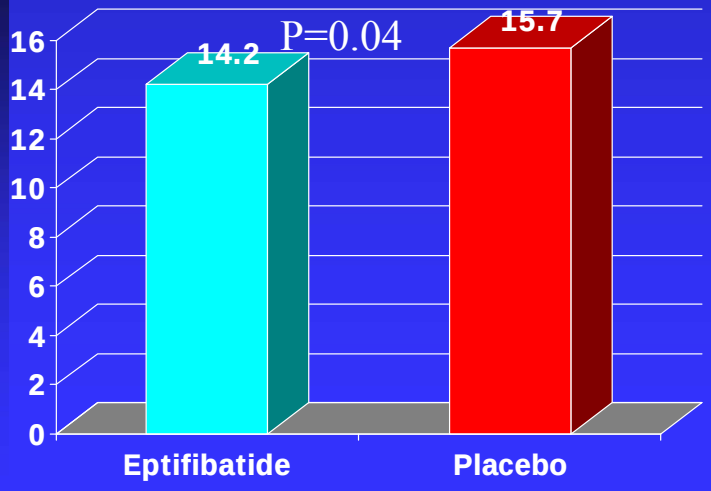


PRIDE study, *Tcheng et al AJC 2001*

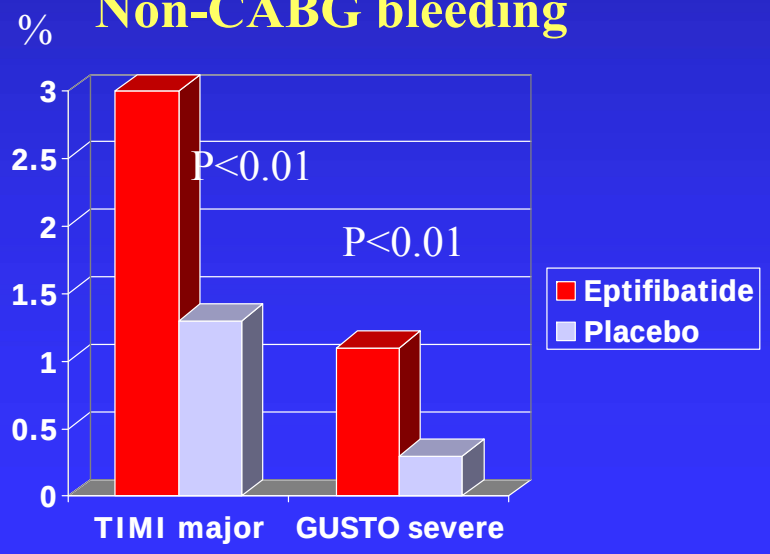
PURSUIT – *NEJM 1998*

- 10,948 patients with ACS (non-ST elevation)
- Performed 1995-1997
- Eptifibatide (180 µg/kg followed by 2 µg/kg/min up to 72-96 hrs!) vs. placebo

Primary endpoint: death or non fatal MI at 30 days



Non-CABG bleeding



PURSUIT – cont.

- Aspirin – 93% of pts, heparin – 90%
- Ticlopidine – used very rarely – considered for pts intolerant to aspirin
- Cardiac cath – 59-60% of pts
- PCI: 23-25% of pts (stents used in 50% of them)
- CABG: 14% of pts
- Revasc performed 72-96 hrs after enrollment

⟶not really relevant for current practice

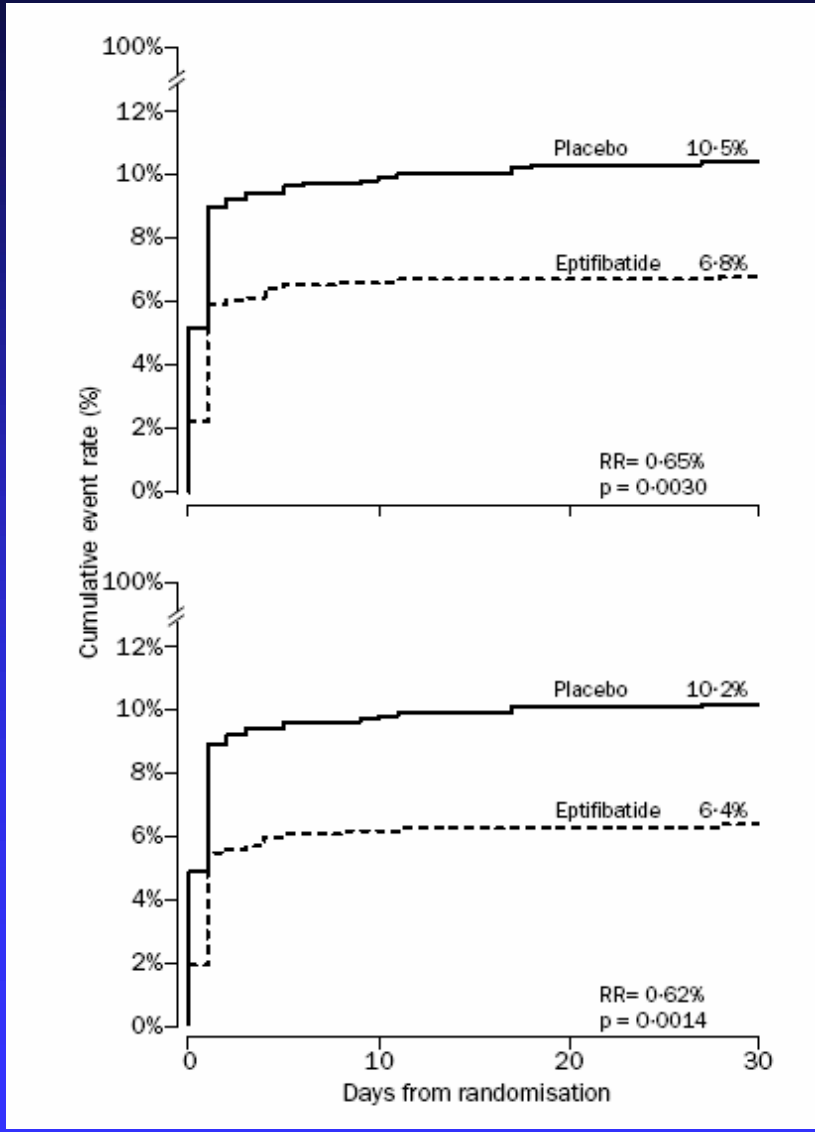
ESPRIT – *Lancet 2000, JAMA 2002*

- 2064 pts planned for PCI of a native coronary artery with stenting
- Conducted 1999-2000
- Almost 20% of pts had an ACS within 48 hrs of enrollment; **rest (~80%) – stable pts**
- Eptifibatide (two 180 µg/kg boluses 10 min apart, followed by 2 µg/kg/min for 18-24 hrs) vs. placebo
- 97% had at least 1 stent placed during PCI
- 97% received a thienopyridine – mainly clopidogrel (without preloading)
- Median ACT = 268 sec

ESPRIT – 30 day results *(Lancet 2000)*

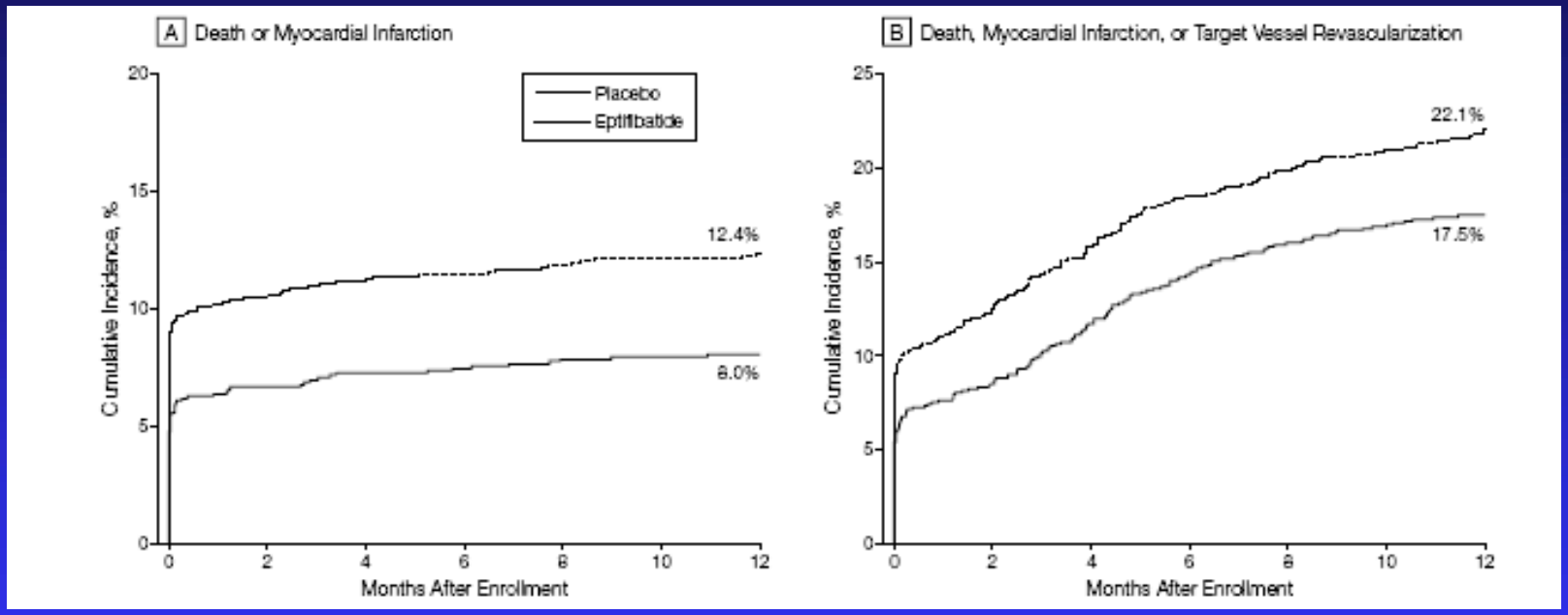
Death/MI

Death/MI/
urgent TVR



Major bleeding:
1.3% vs. 0.4%
(eptif vs. placebo)
P=0.03

ESPRIT – 1 year results *(JAMA 2002)*



Hazard ratio, 0.63; *P*=.001

Hazard ratio, 0.76; *P*=.007

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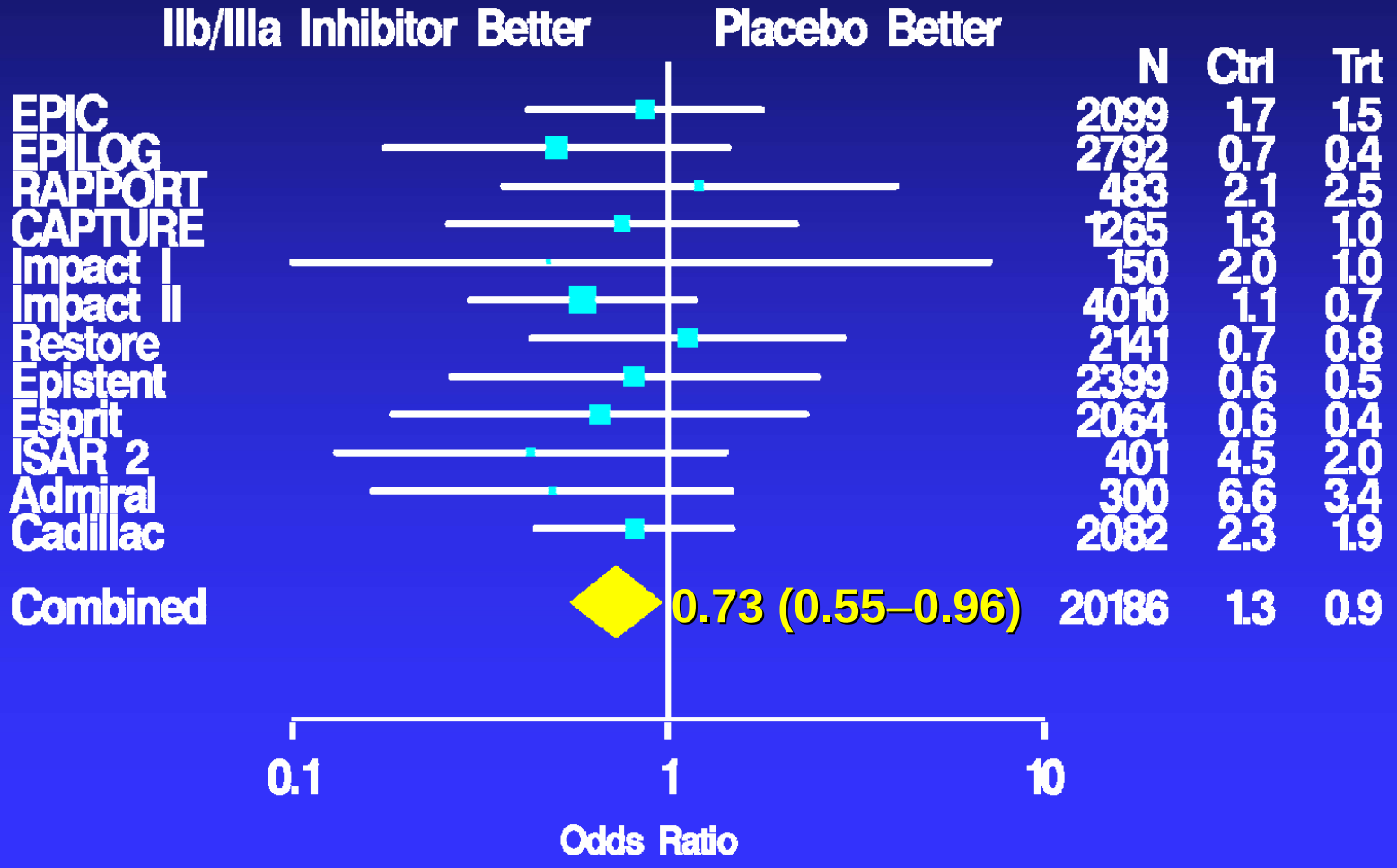
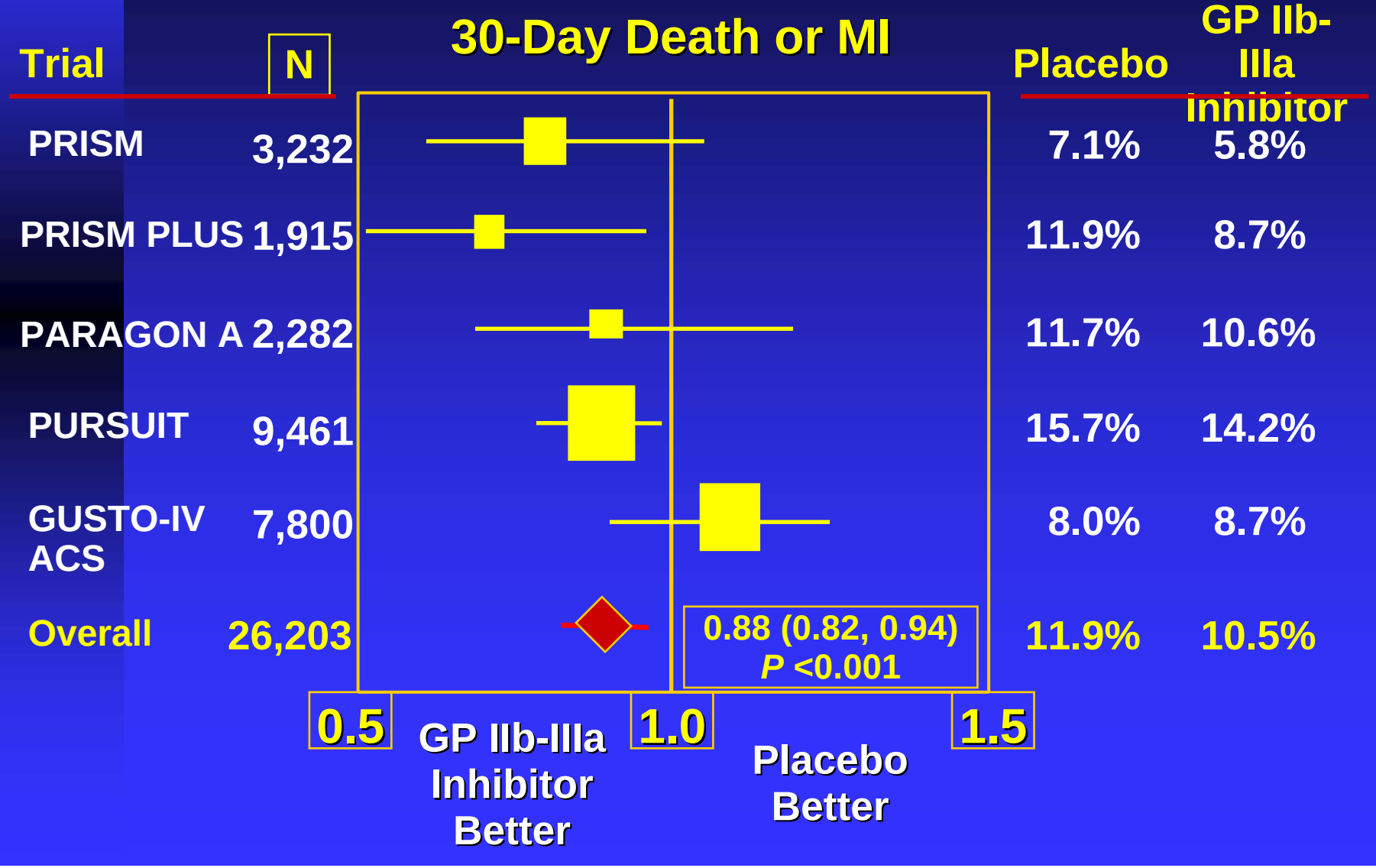
PCI Trials - 30-Day Mortality

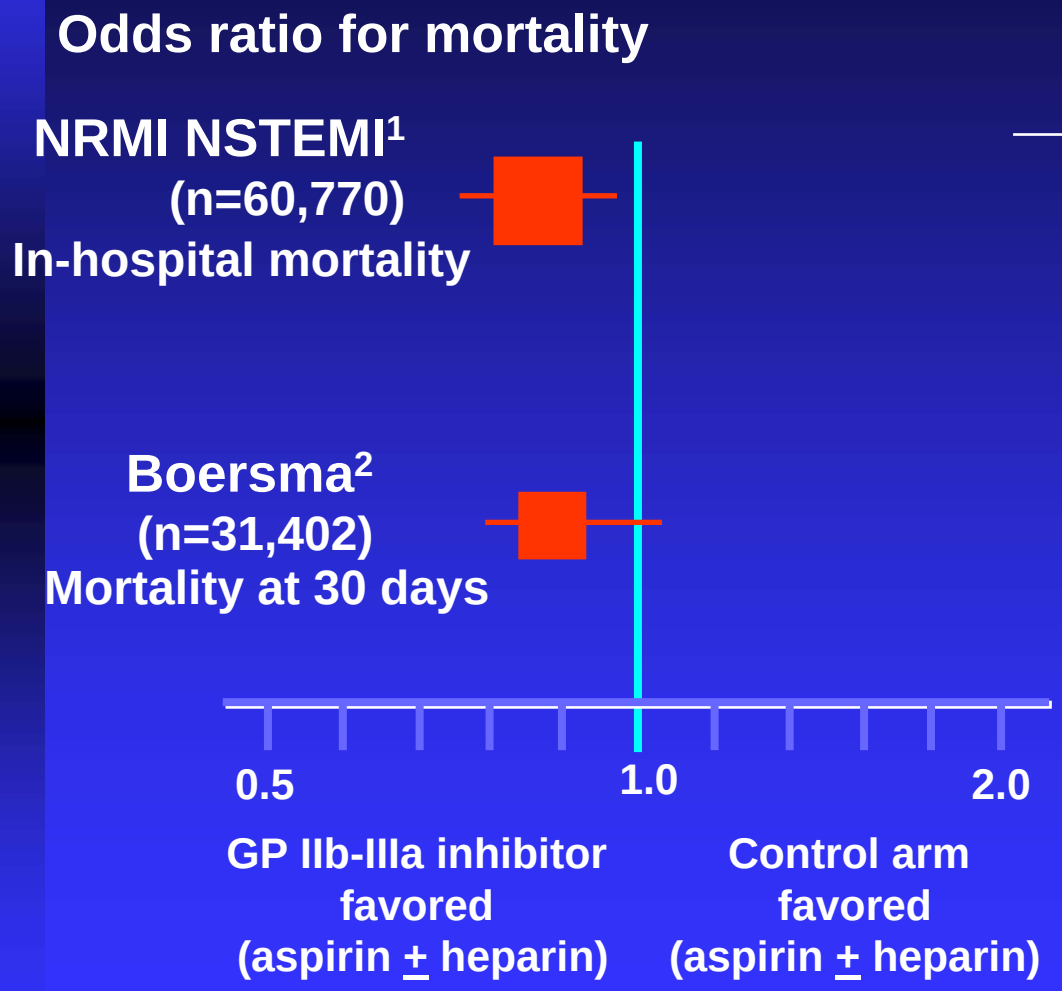


Am J Cardiol 2003;92:651-5

GP IIb/IIIa Inhibition in ACS



Meta-Analysis of Risk-Adjusted Mortality in GP IIb-IIIa Inhibitor NSTE ACS Trials



	Odds Ratio	95% CI
NRMI NSTEMI[1] (n=60,770) In-hospital mortality	0.88	0.79,0.97
Boersma[2] (n=31,402) Mortality at 30 days	0.91	0.81,1.03

NRMI=National Registry of Myocardial Infarction

[1]Peterson ED, et al. *J Am Coll Cardiol.* 2003;42(1):45-53.
[2]Boersma E, et al. *Lancet.* 2002;359:189-198.

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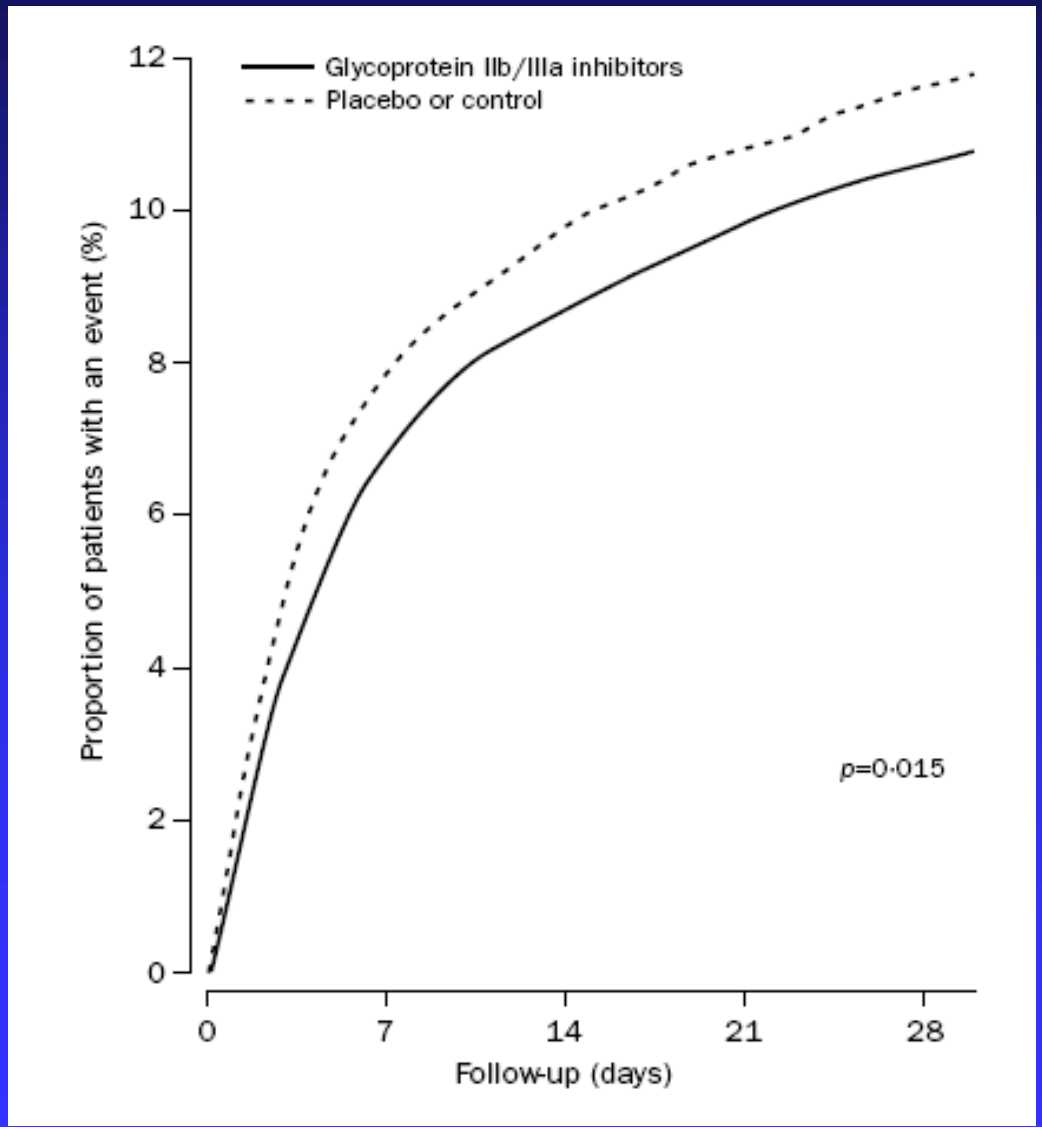
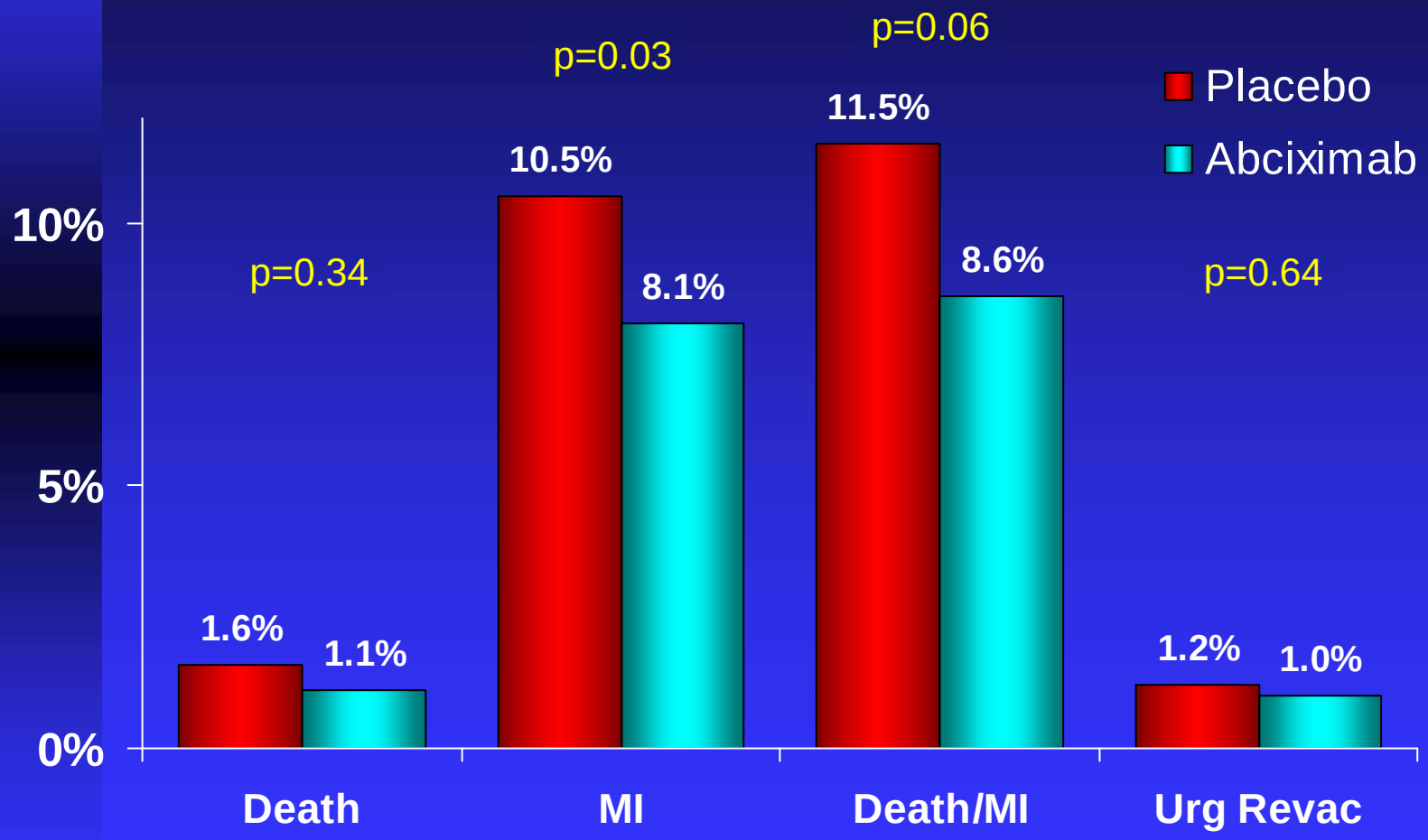


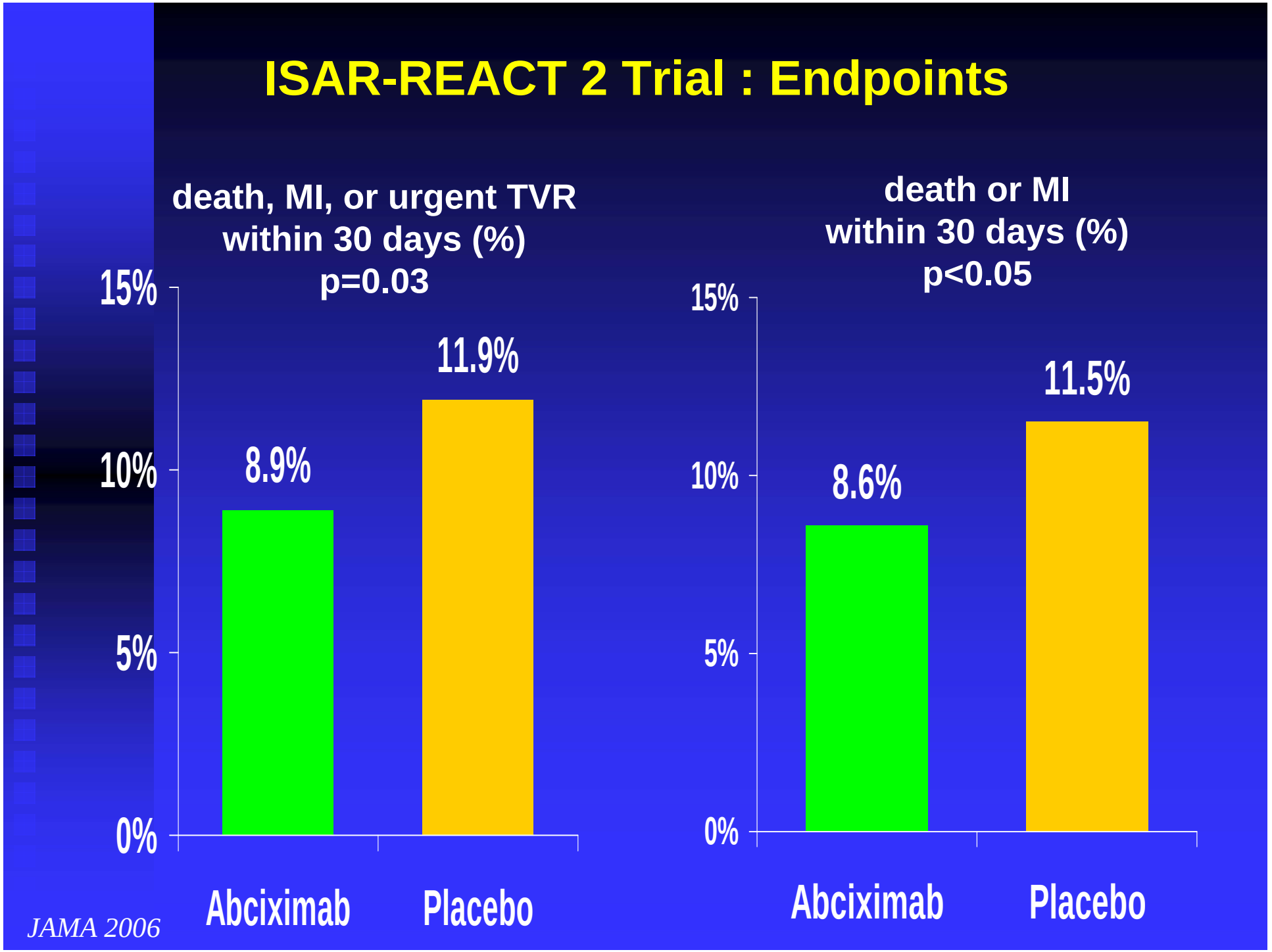
Boresma et al, Lancet 2002

ISAR-REACT 2
High-risk ACS Patients – 30 Days



JAMA 2006;295:1531-38

ISAR-REACT 2 Trial : Endpoints



JAMA 2006

ACC/AHA 2007 Guideline Update for the Management of NSTE-ACS

4. For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)* or an intravenous GP IIb/IIIa inhibitor. *(Level of Evidence: A)* Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor. *(Level of Evidence: B)*

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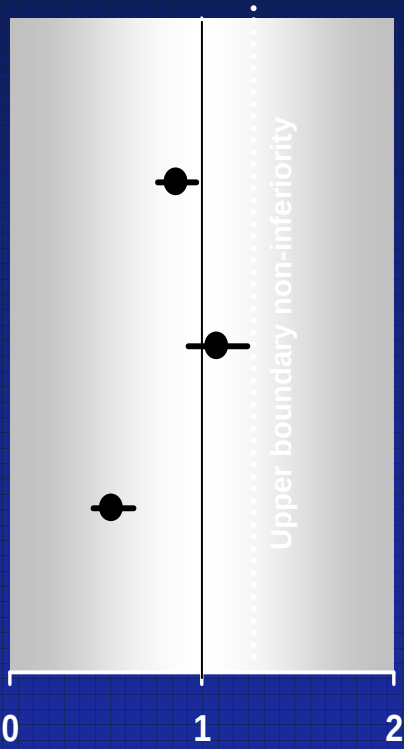
ACUITY – High risk ACS, 30 days endpoint

UFH/Enoxaparin + GPI vs. Bivalirudin Alone

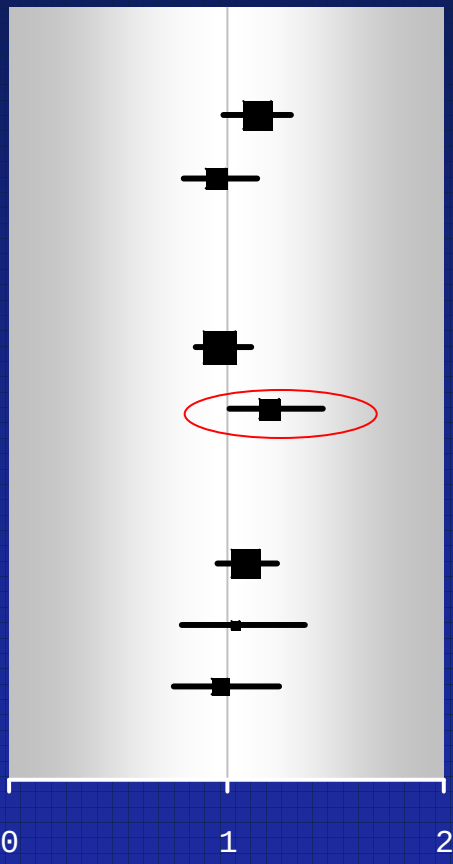
Primary endpoint	Bival alone	UFH/Enox + IIb/IIIa	RR (95% CI)	p value (non inferior) (superior)
Net clinical outcome	10.1%	11.7%	0.86 (0.77-0.97)	<0.001 0.015
Ischemic composite	7.8%	7.3%	1.08 (0.93-1.24)	0.01 0.32
Major bleeding	3.0%	5.7%	0.53 (0.43-0.65)	<0.001 <0.001



Stone GW et al. NEJM 2006;355:2203-16

ACUITY - Composite Ischemia at 1-Year

UFH/Enoxaparin + GPIIb/IIIa vs. Bivalirudin alone



	1 yr KM estimate Bival alone	UFH/Enox + IIb/IIIa	HR (95% CI)	P_{int}
Biomarkers (CK/Trop)				
Elevated (n=5072)	17.7%	16.4%	1.14 (0.99-1.30)	0.11
Normal (n=3402)	14.6%	16.1%	0.95 (0.80-1.14)	
Pre Thienopyridine				
Yes (n=5751)	16.2%	17.2%	0.97 (0.86-1.11)	0.07
No (n=3305)	16.4%	14.3%	1.20 (1.01-1.44)	
Actual Treatment				
PCI (n=5179)	19.8%	19.2%	1.09 (0.96-1.23)	
CABG (n=1040)	21.1%	20.7%	1.04 (0.79-1.36)	0.67
Medical (n=2994)	9.0%	9.6%	0.97 (0.76-1.24)	

Stone GW et al. NEJM 2006;355:2203-16

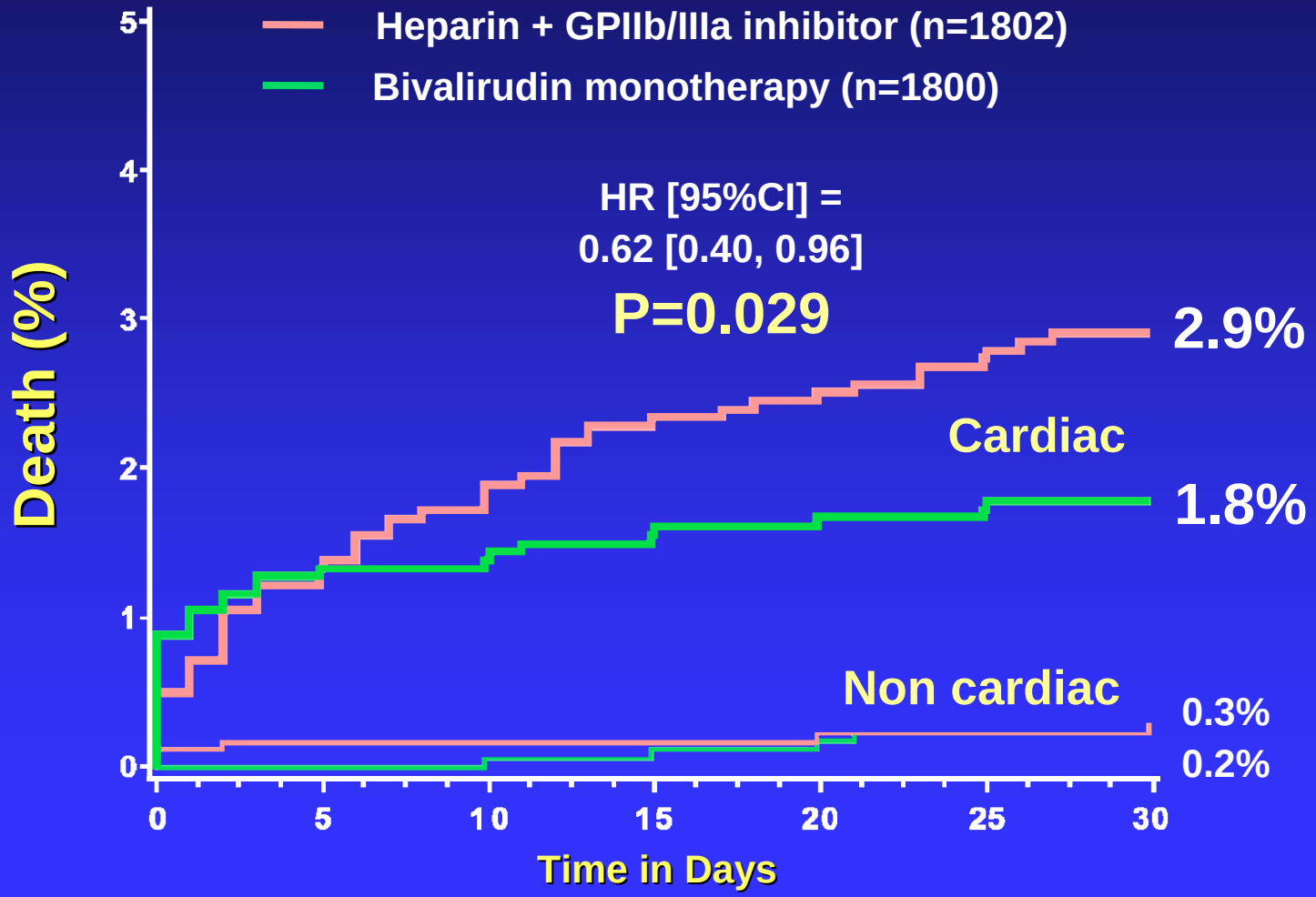
HORIZONS: STEMI pts, 30 days endpoint

Outcome	Bivalirudin (%)	Heparin+GP IIb/IIIa blocker (%)	Relative risk (95% CI)	p
Major bleeding	4.9	8.3	0.60 (0.46–0.77)	<0.001
Net adverse clinical events	9.2	12.1	0.76 (0.63–0.92)	0.005
MACE	5.5	5.5	1.00 (0.75–1.32)	0.98
Death from cardiac causes	1.8	2.9	0.62 (0.40–0.95)	0.03
Death from all causes	2.1	3.1	0.66 (0.44–1.00)	0.047

Stone GW et al. *N Engl J Med* 2008; 358:2218-2230.

HORIZONS 30 Day Mortality:

Cardiac and Non Cardiac



Stone et al, NEJM 2008

HORIZONS: Stent thrombosis results

Outcome	Bivalirudin (%)	Heparin+GP IIb/IIIa blocker (%)	p
Stent thrombosis within 30 d	2.5	1.9	0.30
Acute (<24 h)	1.3	0.3	<0.001
Subacute (24 h–30 d)	1.2	1.7	0.28

Stone GW et al. *N Engl J Med* 2008; 358:2218-2230.

BRIEF-PCI Rationale

- Dual anti-platelet oral therapy with aspirin and clopidogrel – almost 100% of pts undergoing PCI
- High dose clopidogrel loading (600 mg) is often used, well tolerated and has rapid onset of action
- Routine use of coronary stents reduces abrupt vessel closure
- Prolonged 18-hour eptifibatide infusion may not be necessary

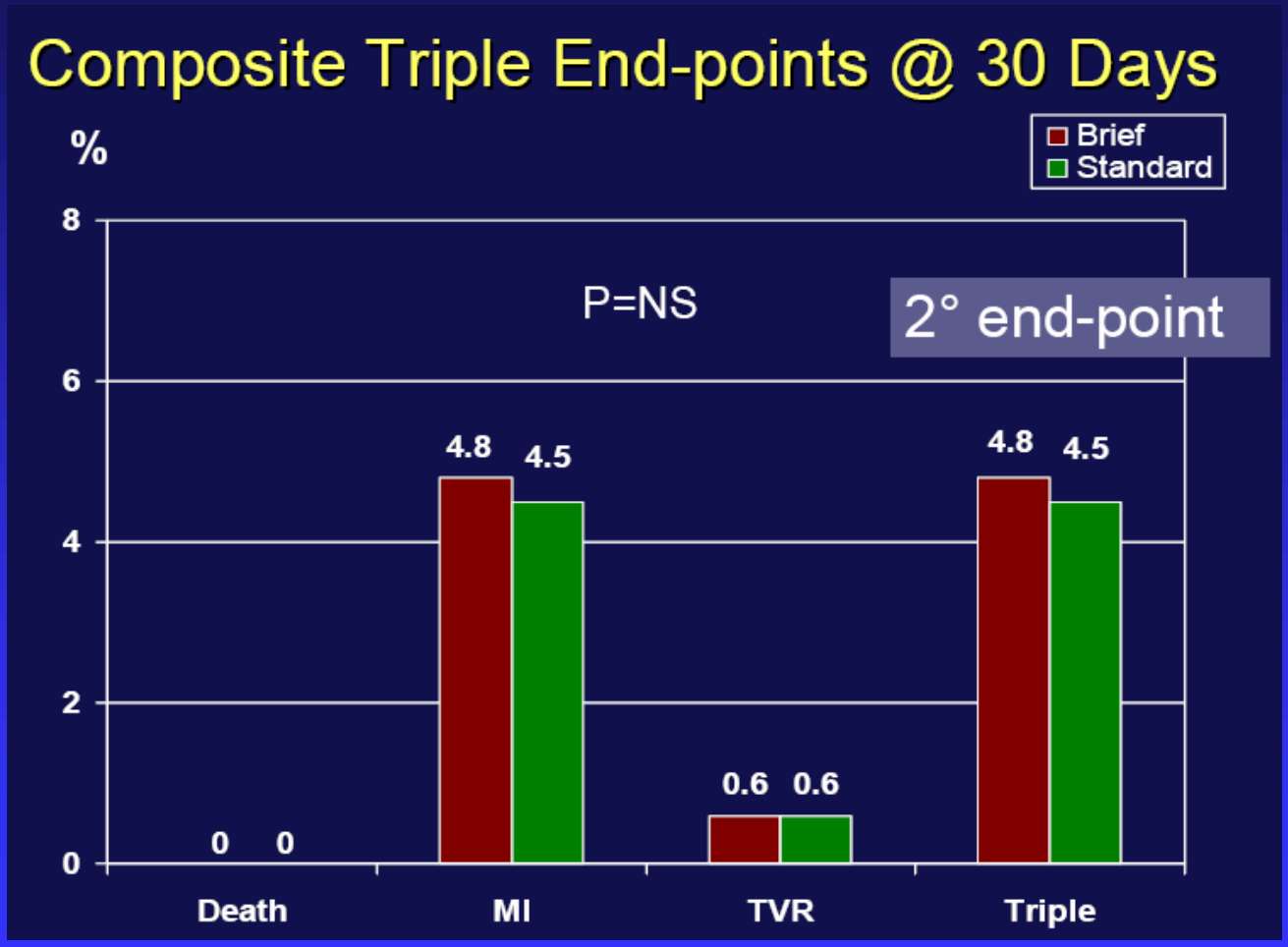
Fung et al, JACC 2009

BRIEF-PCI

- 624 pts with ACS > 48 hrs or stable angina (non emergent pts)
- Uncomplicated PCI with stenting, performed under the coverage of eptifibatide
- TIMI-3 flow, no dissection or thrombus post procedure
- Randomization after successful PCI
- 67% pts received clopidogrel pre-treatment - dose dependent on timing
- Randomized to brief (< 2hrs) vs. 18 hrs of eptifibatide maintenance

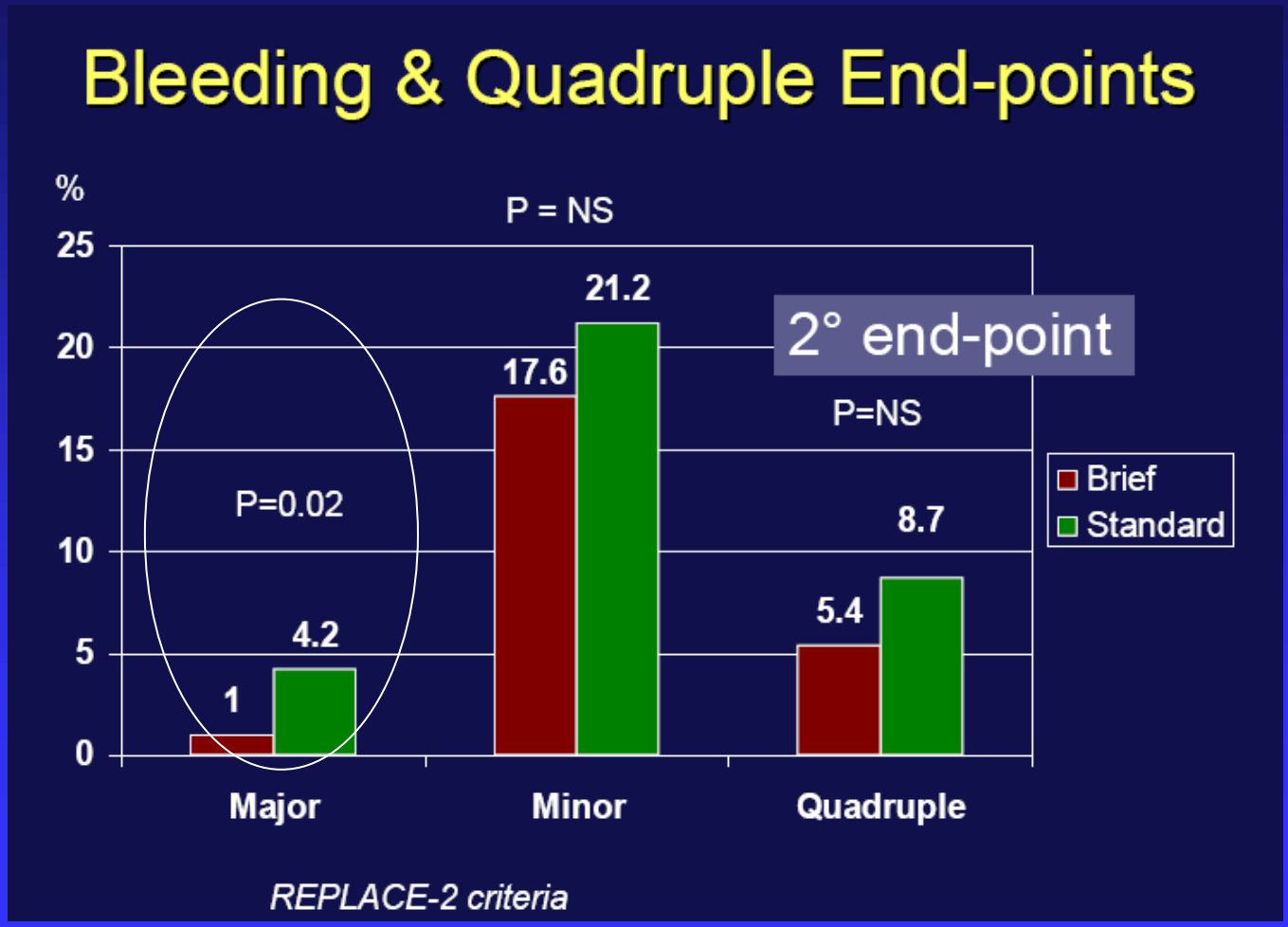
Fung et al, JACC 2009

BRIEF-PCI - cont



No differences in markers of myonecrosis

BRIEF-PCI - cont



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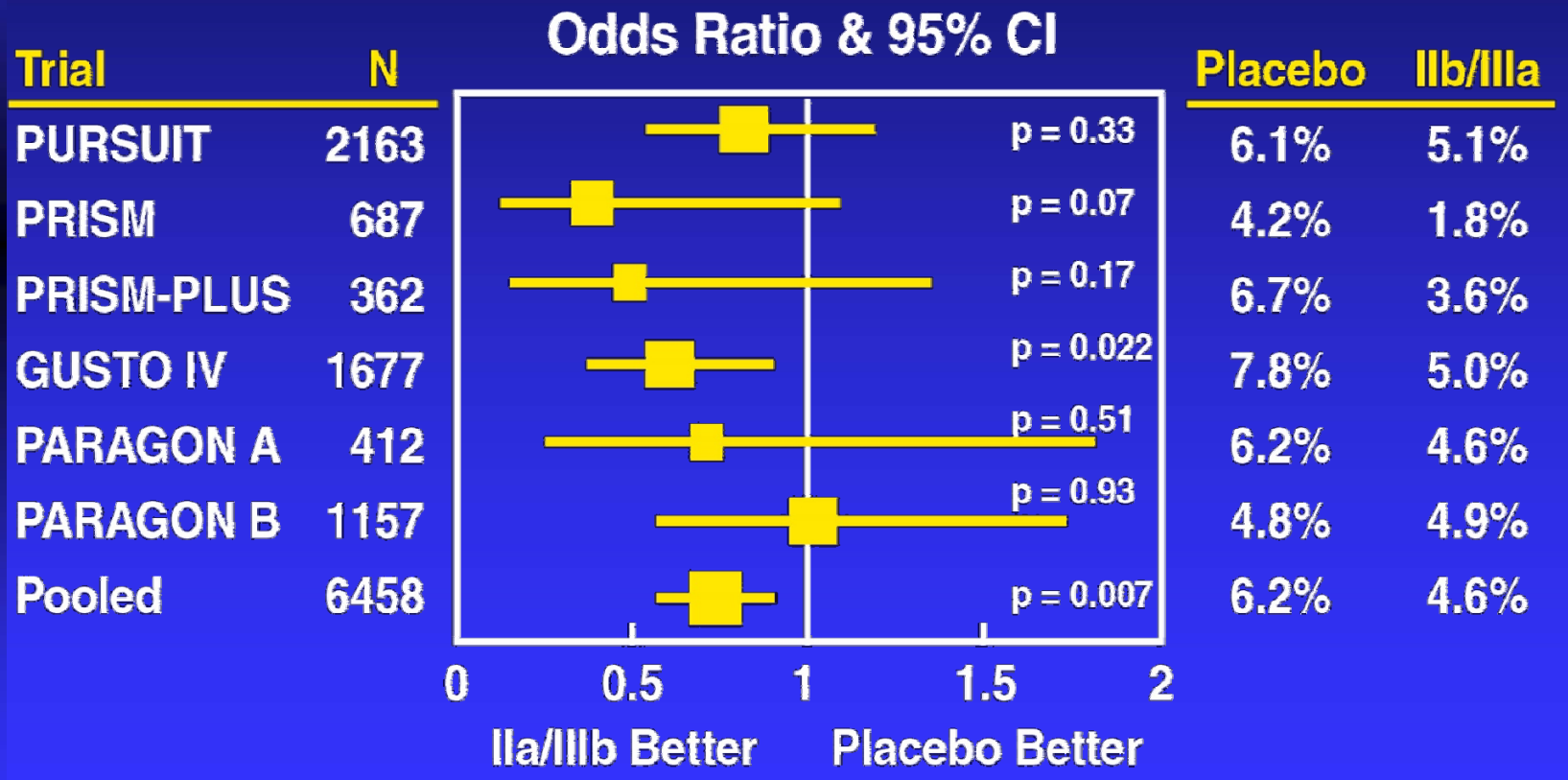
GP IIb/IIIa Inhibitors Reduce Mortality in Pts With Diabetes

30-Day Mortality – Diabetic Patients



Roffi et al, Circulation 2001

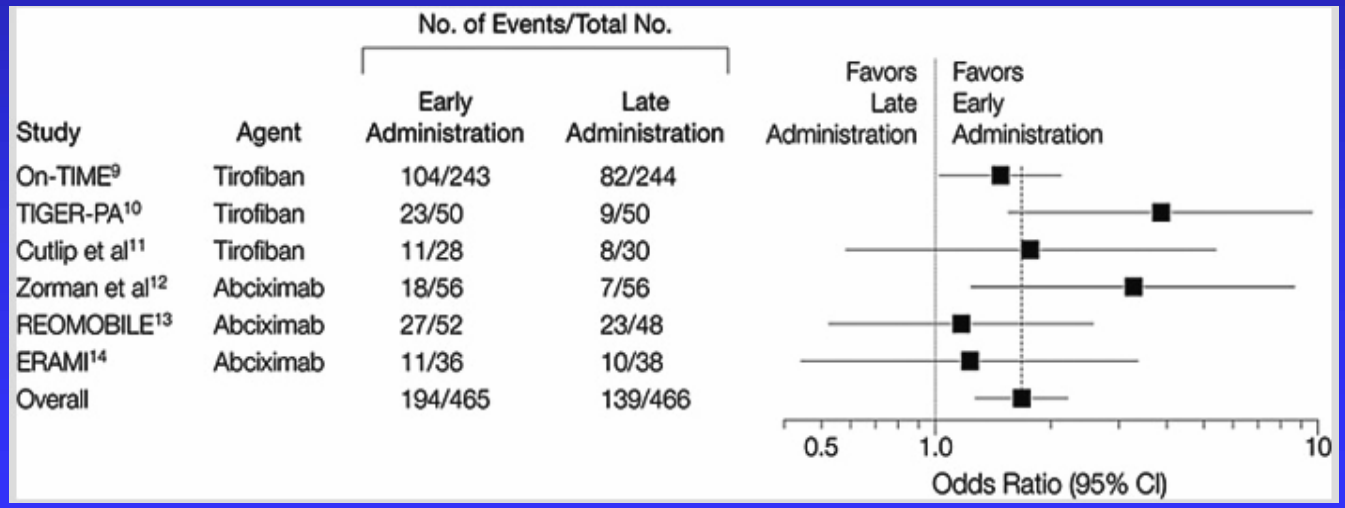
GP IIB/IIIA inhibitors and **Diabetes**

- Meta-analysis of non-STEMI ACS trials with GP IIb/IIIa inhib. (PRISM, PRISM-PLUS, PARAGON, PURSUIT, GUSTO-IV)
- 6,458 diabetic pts → significant **mortality** reduction at 30 dys: 6.2% vs. 4.6% (placebo vs. IIb/IIIa, P=0.007)
- 23,072 non diabetic pts → no survival benefit (3% vs. 3%)
- Main benefit in diabetics among those who underwent PCI (4% vs. 1.2%, P=0.002)

Roffi et al, Circulation 2001

STEMI

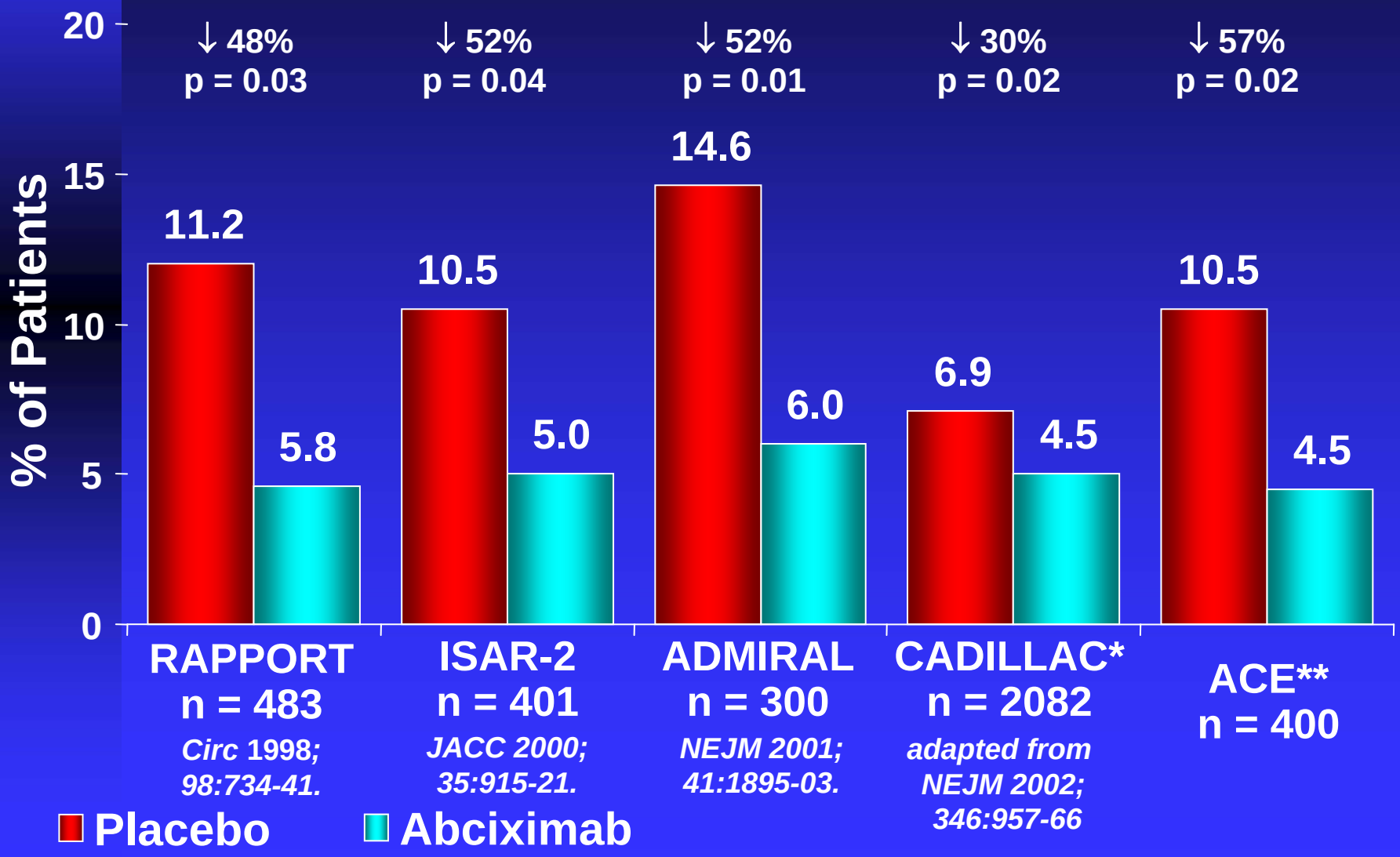
- Majoraty of large GP IIb/IIIa trials with abciximab
- In all trials early administration preferable to late



Montalescot G et al, JAMA. 2004 ;292:362-6

Primary PCI

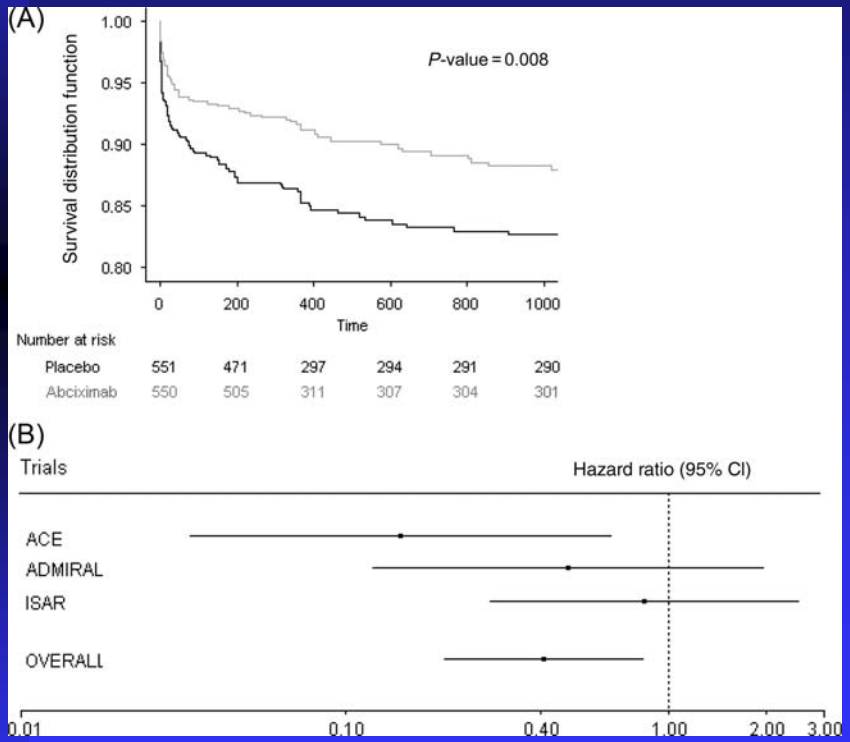
30 Day Death, MI or Urgent TVR



GP IIb/IIIa Inhibitors - Abciximab

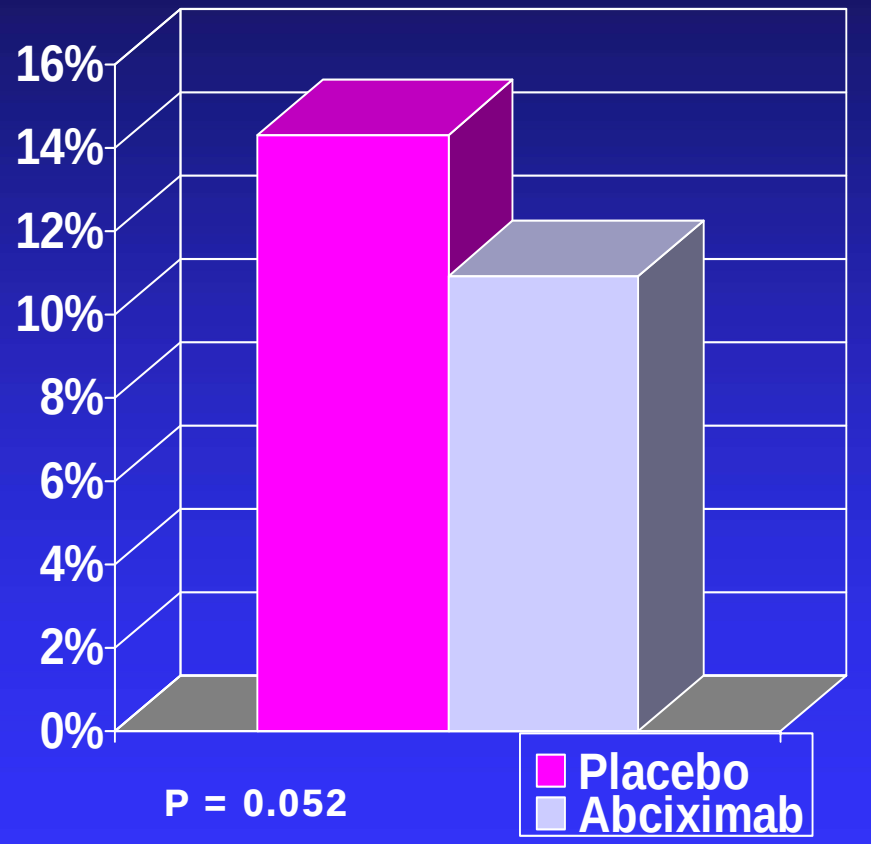
Only trials of PCI with *stenting* that included long-term follow-up

Death or re-infarction over 3 yrs of f/u



P = 0.008

3 year mortality



P = 0.052

Montalescot, G. et al. Eur Heart J 2007 28:443-449

CONCLUSIONS - 1

- GP IIb/IIIa inhibitors still have an important role and are beneficial in **high risk patients**
- Patient groups who appear to benefit the most from GP IIb/IIIa inhibitor therapy:

1. ACS troponin+ (especially STEMI) who undergo PCI
2. Patients with diabetes
3. Patients with ACS who were not preloaded with clopidogrel before the PCI

CONCLUSIONS - 2

- Bleeding complications are definitely an important issue when compared to bivalirudin (or heparin alone). Increase in major bleeding offsets advantages in ischemic complications and can translate to mortality differences (e.g. HORIZONS)

- Bleeding can be reduced by:
  - Shorten infusion time
  - Lower heparin dose
  - Better adjustment for CrCl

THANK YOU