18TH CARDIOVASCULAR SUMMIT
TCTAP2013
APRIL 23-26
COEX, SEOUL, KOREA

Is *Potent Oral $P2Y_{12}$ Inhibitor* Enough to Prevent Thrombotic Events in High-risk PCI Patients?

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Disclosures

Research Grants/Support

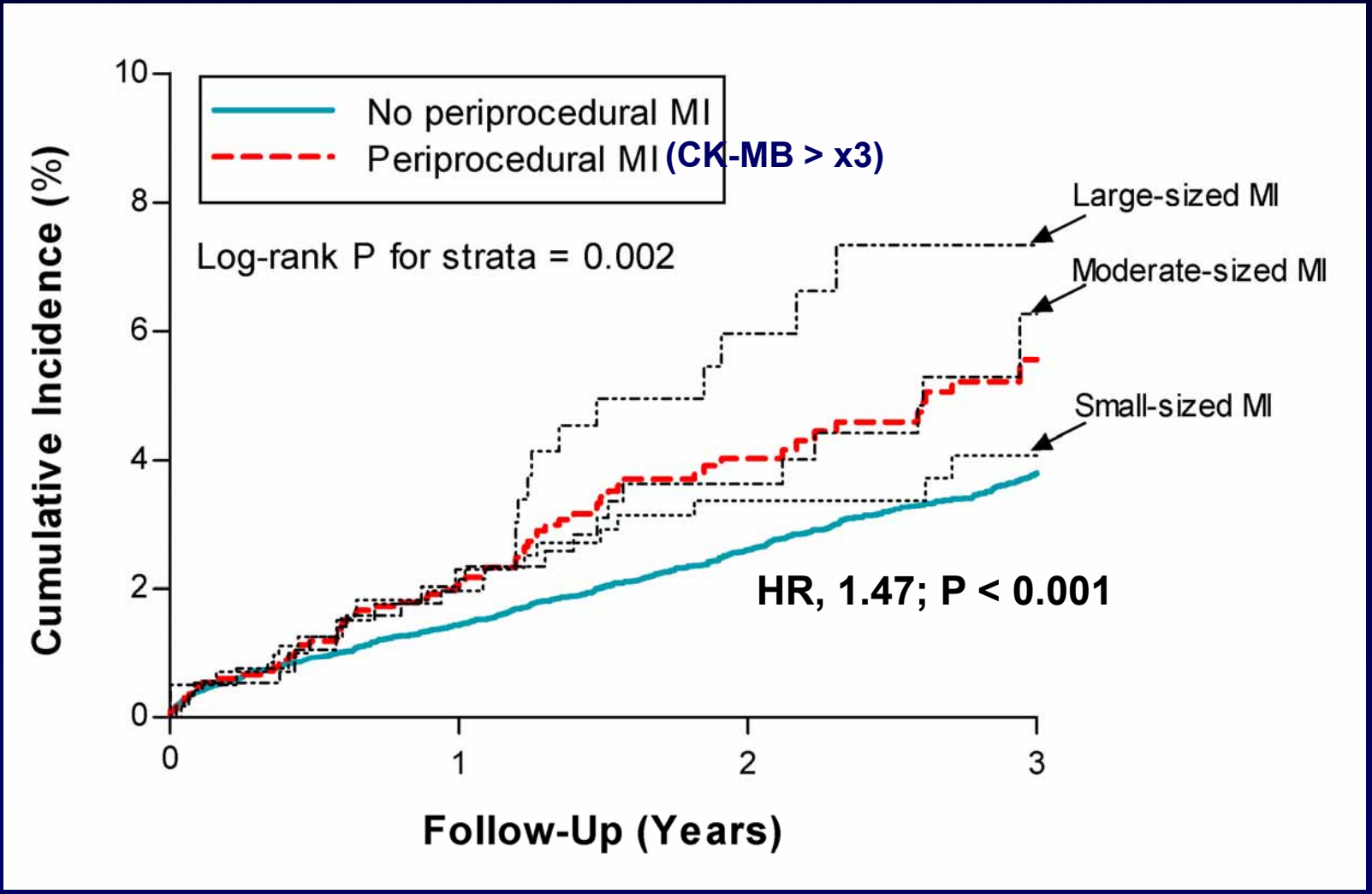
- Otsuka
- Accumetrics
- Boehringer-Ingelheim
- Haemonetics
- Dong-A Pharmaceutical
- Han-Mi Pharmaceutical

Honoraria/Consulting

- Otsuka
- Sanofi-Aventis
- Daiichi Sankyo Inc
- Astrazeneca
- Nanosphere
- Haemonetics
- Han-Dok Pharmaceutical

3-Year Mortality According to Periprocedural MI

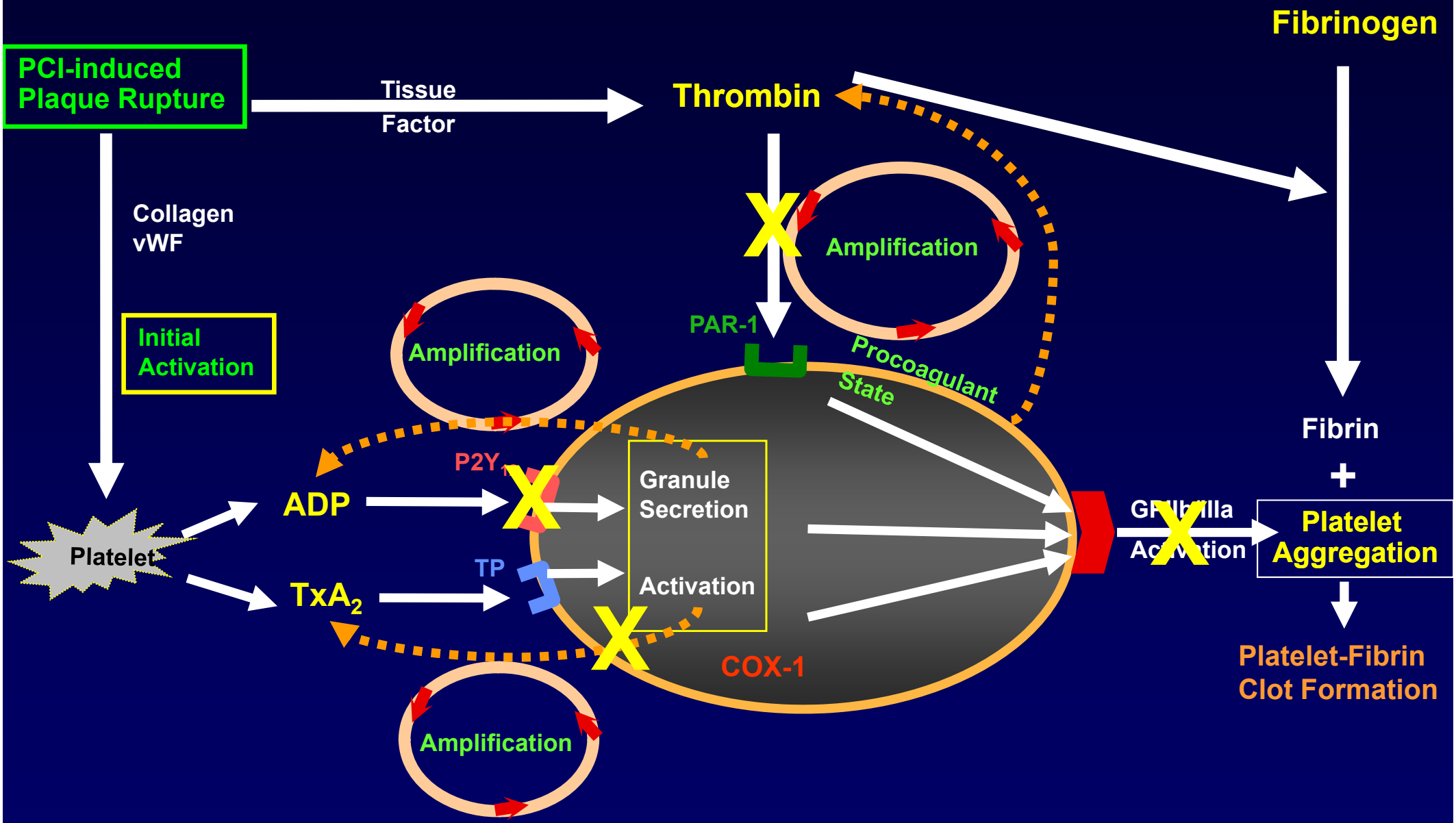
23,604 pts from 8 Korean RCTs and 3 registries **(ASP+CLPD)**



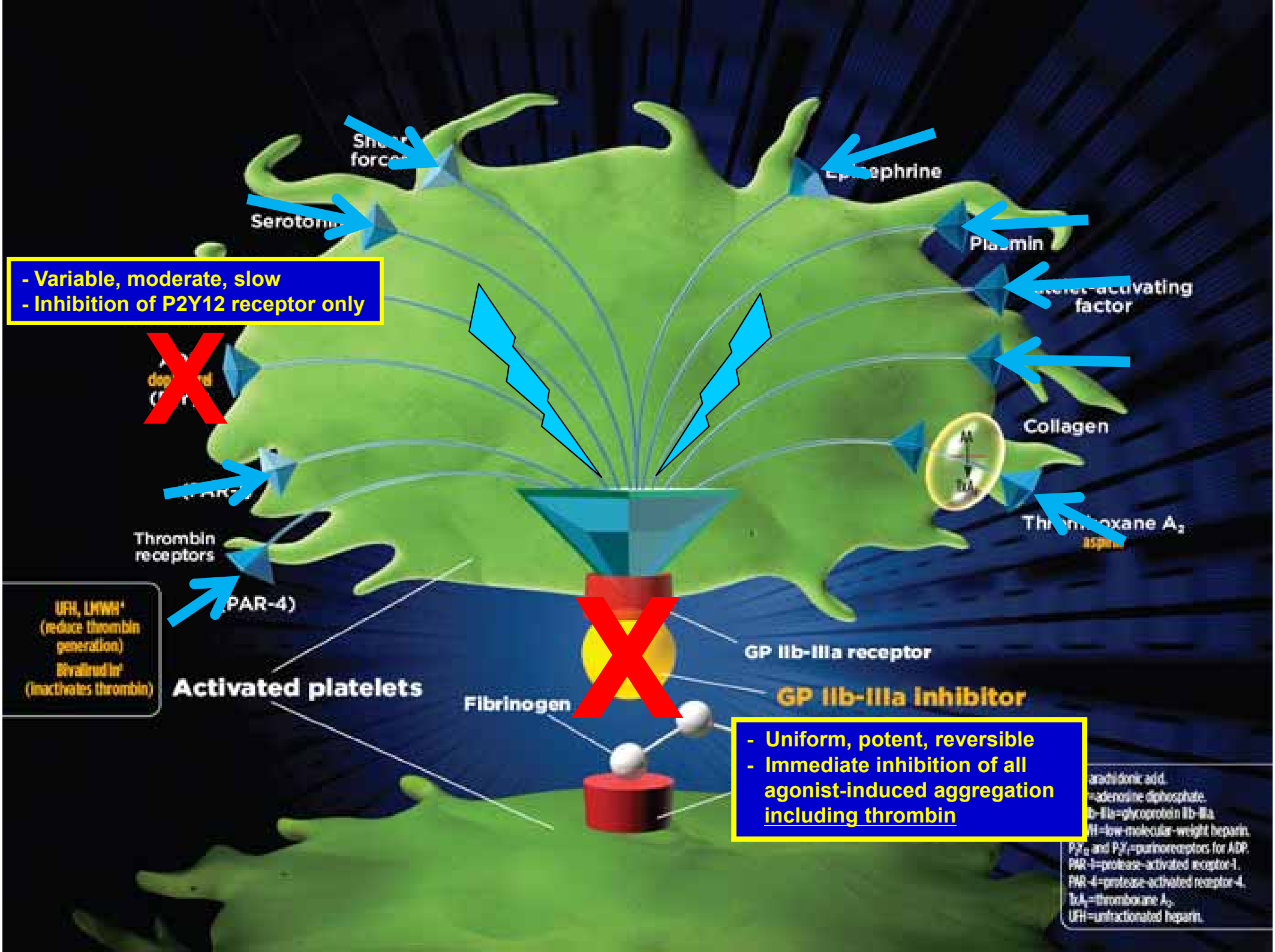
** **HR, 1.20; p = 0.01**: Adjusted for study, age, sex, DM, history of MI, PVD, CKD, ACS, EF, MVD, LM disease, bifurcation disease, stent type, and # stents.

Park DW et al. *Eur Heart J* 2013;Feb 12.

Post-PCI Thrombosis is a Platelet-centric Event:
Ischemic Outcomes Reduced Best by Most Potent and Reliable Agents

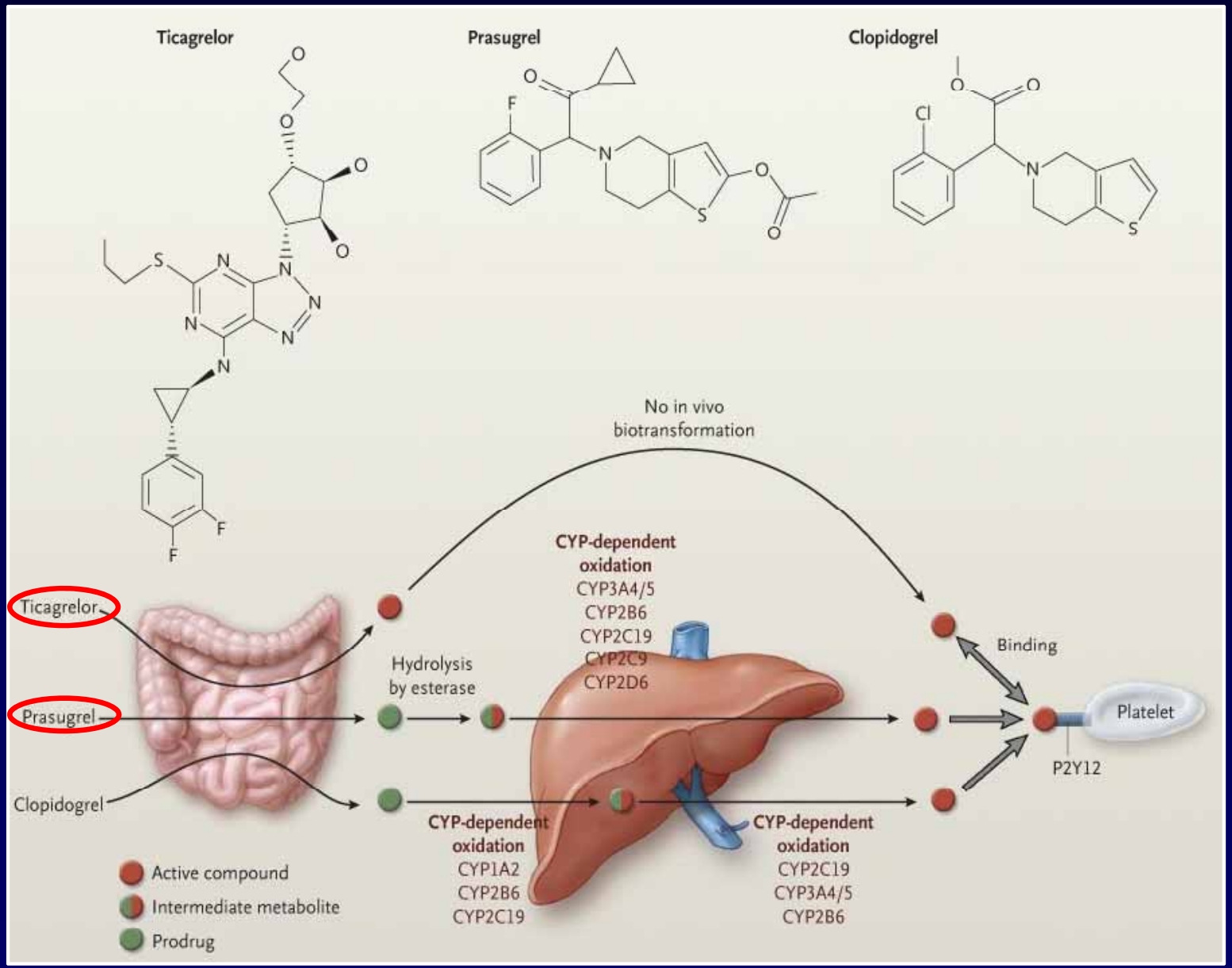


Adapted from Gurbel PA et al. *J Am Coll Cardiol.* 2007;50:1822-34


- Variable, moderate, slow
- Inhibition of P2Y12 receptor only
Shear force
Epinephrine
Serotonin
Plasmin
factor
Collagen
Thrombin receptors
(PAR-4)
UFH, LMWH*
(reduce thrombin generation)
Bivalirudin*
(inactivates thrombin)
Activated platelets
Fibrinogen
GP IIb-IIIa receptor
GP IIb-IIIa inhibitor
- Uniform, potent, reversible
- Immediate inhibition of all agonist-induced aggregation including thrombin
UFH=unfractionated heparin.

Available Strategies of $P2Y_{12}$ Inhibition

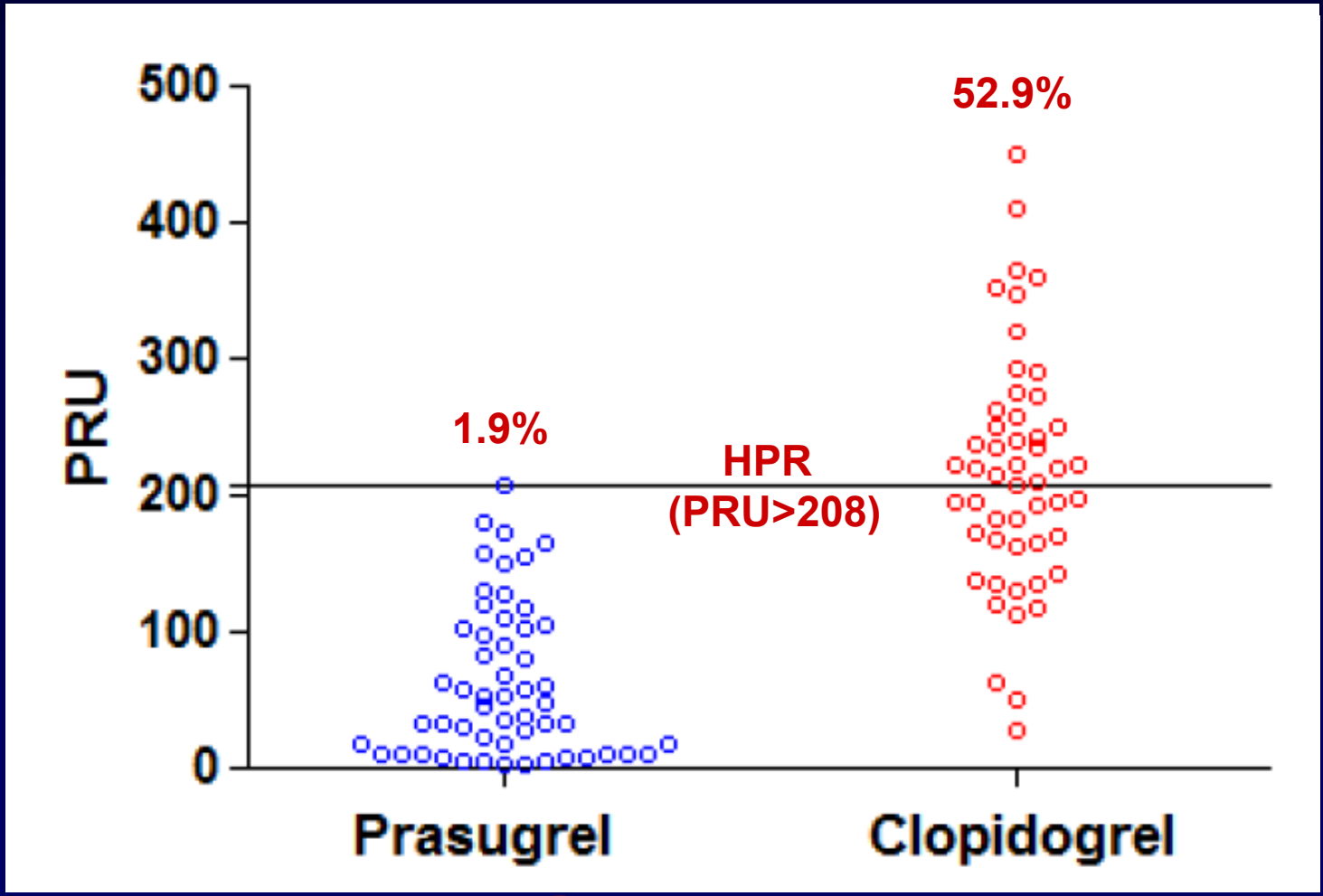
Therapeutic profile not affected by *CYP*, *ABCB1* genetic variation



Schömig A. *N Engl J Med* 2009;361:1108-1111.

Prasugrel vs. Clopidogrel in Stable CAD Patients

Prasugrel 60 mg LD vs. Clopidogrel 600 mg LD (> 12hr before PCI)



PMI (Troponin I): 23% vs. 44% *P* = 0.035

Hamilos et al. *ESC 2012*.

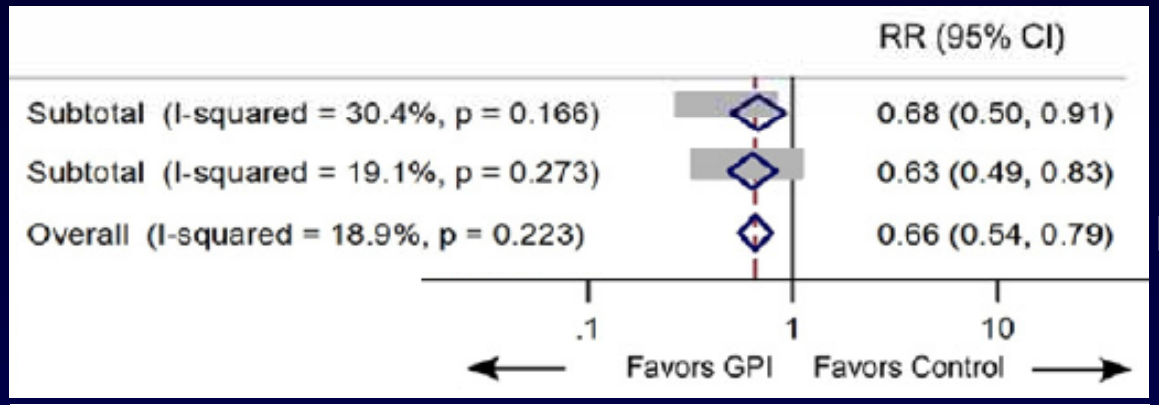
GPIIb/IIIa Inhibitors

Elective PCI in Era of Routine Stents and Thienopyridines: Meta-Analysis

22 studies, n=10,113 patients, routine use of thienopyridines; 30-day outcomes

30-day MI

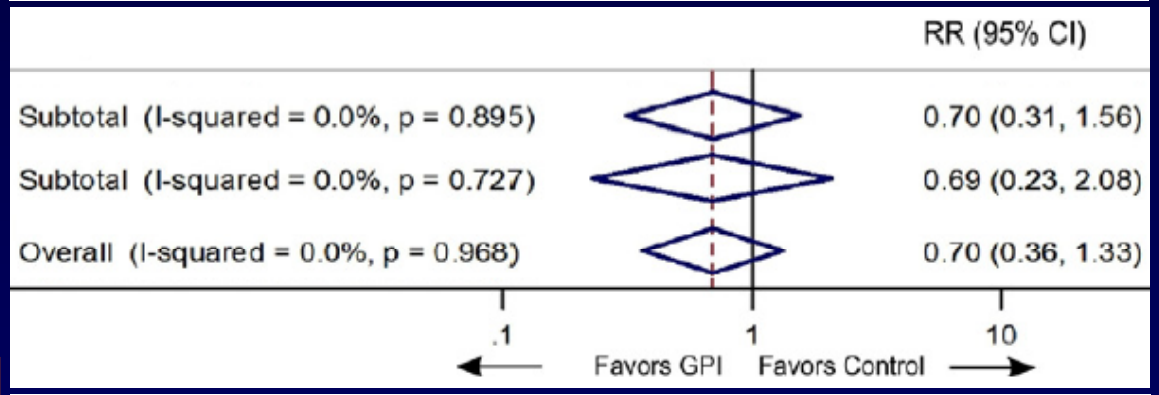
Abciximab
Small Molecule
Overall



p<0.0001

30-day Mortality

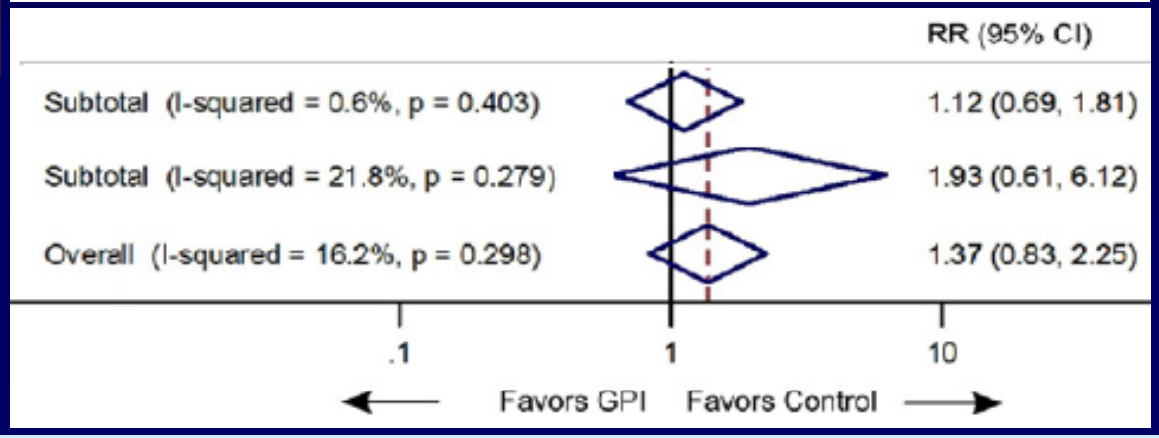
Abciximab
Small Molecule
Overall



p=0.27

30-day Major Bleeding

Abciximab
Small Molecule
Overall



p=0.22

Minor Bleeding (GPI vs. control) = 3.0 vs. 1.7%, RR=1.70, p<0.001

Winchester DE et al. *J Am Coll Cardiol*. 2011;57:1190-9

Personalized GPIIb/IIIa Inhibitor Therapy: 3T/2R Study

Aspirin + Clopidogrel
UFH or Bivalirudin

HPR patients

n = 147 CLPD NR (< 40% inhibition)

n = 23 ASA NR (ARU > 550)

n = 93 ASA and CLOP NR

~ 70%: stable CAD

1:1
Double Blind

Tirofiban*

Bail-out Placebo

Placebo

Bail-out Tirofiban

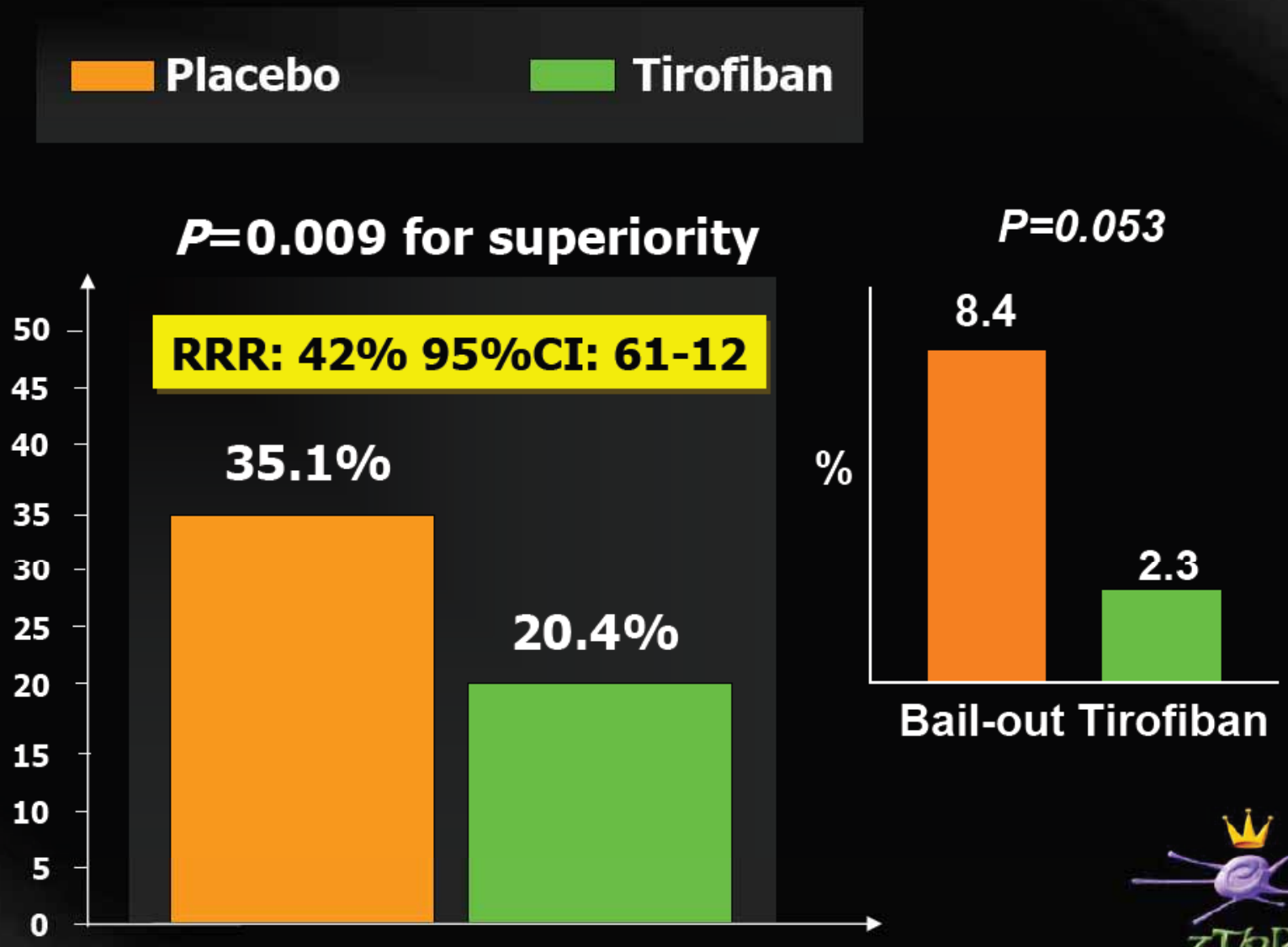
Blood sampling: Hb, PLT, Tp; CK-MB mass @ 6, 12, 18 or 24 hrs
Clinical F-UP: 30-d, 4, 8 and 12 months

*: 25 μg/kg in 3 mins, followed by an 14-24 hour infusion at 0.15 μg/kg/min

3T/2R

Primary Endpoint

Tp >3×ULN w/in 48 hs

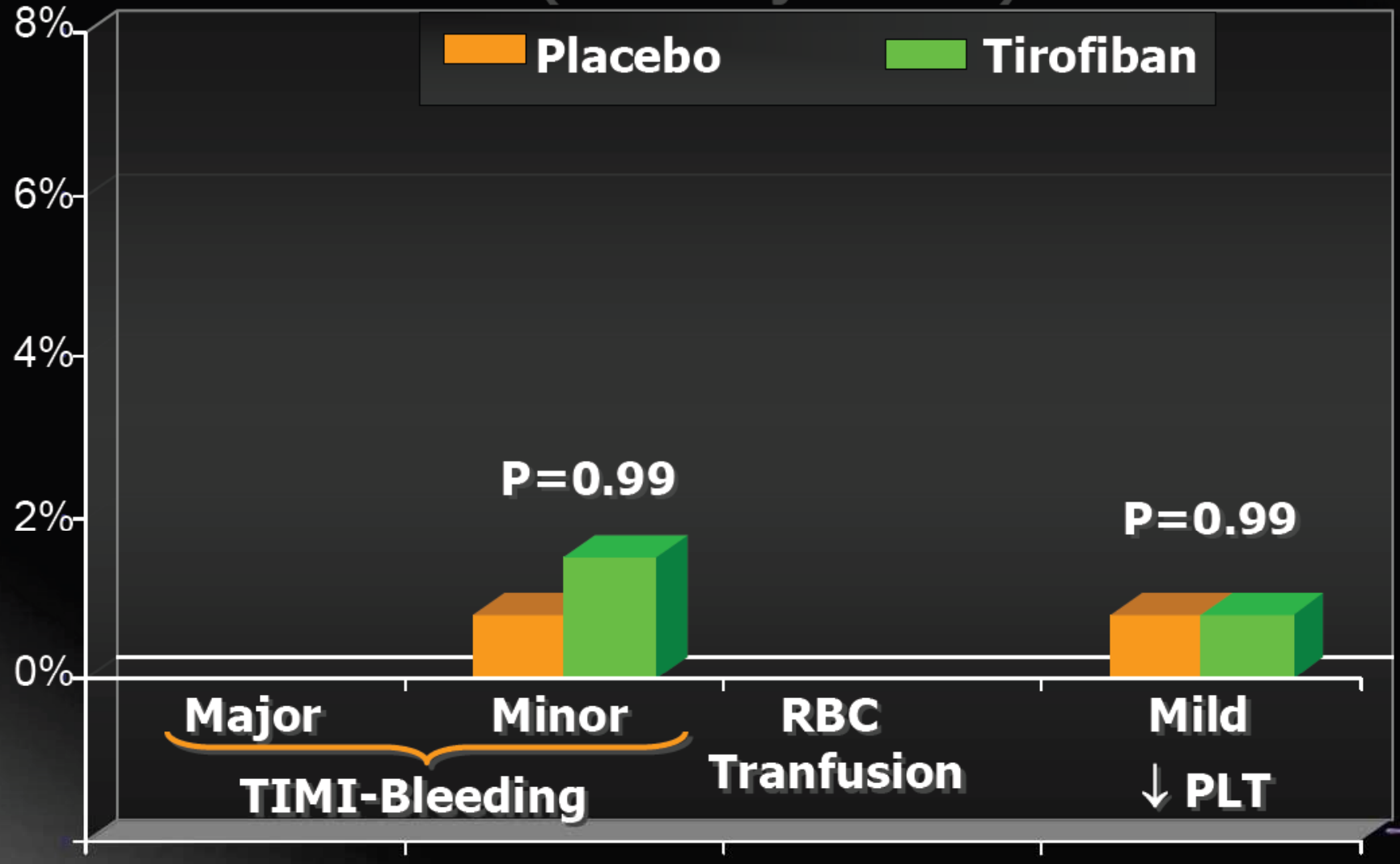


Valgimigli M et al. *Circulation* 2009;119:3215-22.

30-Day Outcomes

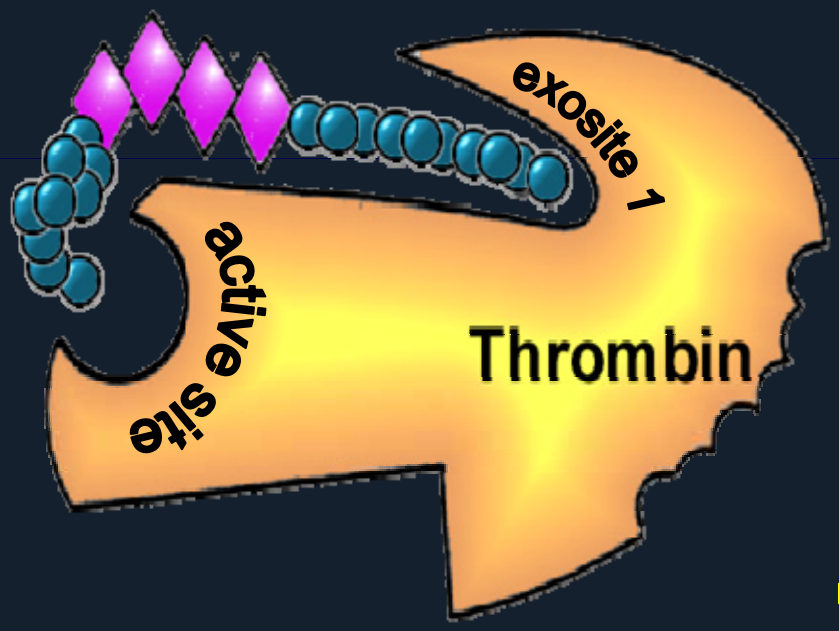
Safety Endpoints

(DSMB adjudicated)



Bivalirudin

Bivalent Synthetic Direct Thrombin Inhibitor



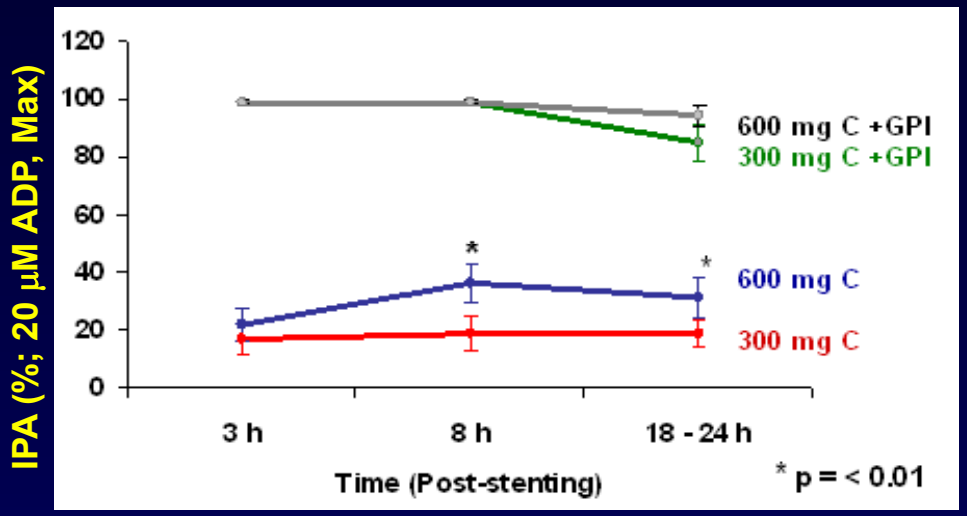
- Specifically inhibits
  - Fluid phase thrombin
  - Clot-bound thrombin
  - Thrombin-mediated platelet aggregation (blocks activation of PAR-1 and PAR-4 receptors): **weak potency**
- Reversible
- $T_{0.5}$ 25 minutes

Topol EJ: Textbook of Interventional Cardiology

Pharmacodynamics of P2Y12 Inhibitor vs. GPI vs. Bivalirudin

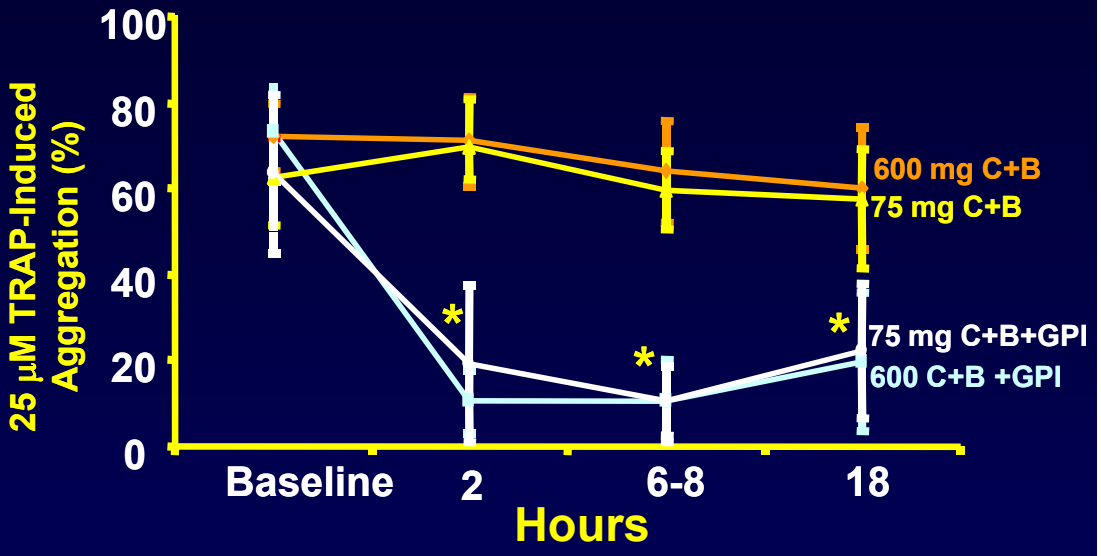
CLEAR PLATELETS-1

Gurbel PA et al.
Circulation. 2005;111:1153-9



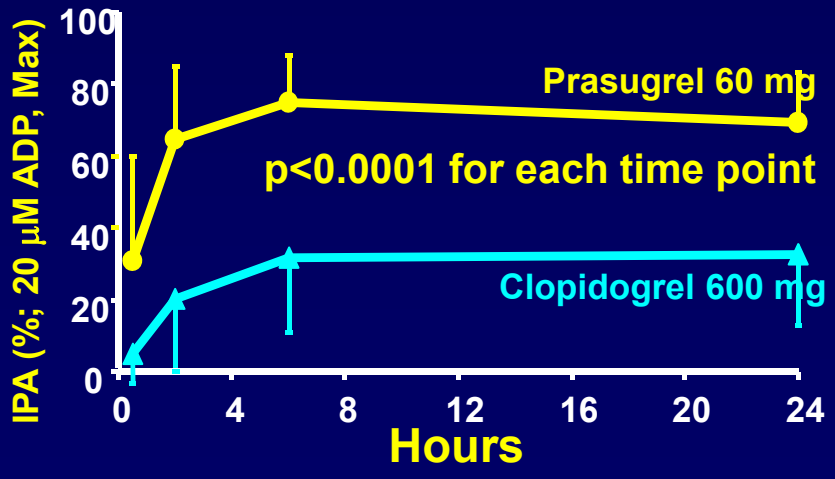
CLEAR PLATELETS-2

Gurbel et al.
J Am Coll Cardiol. 2009;53:648-57



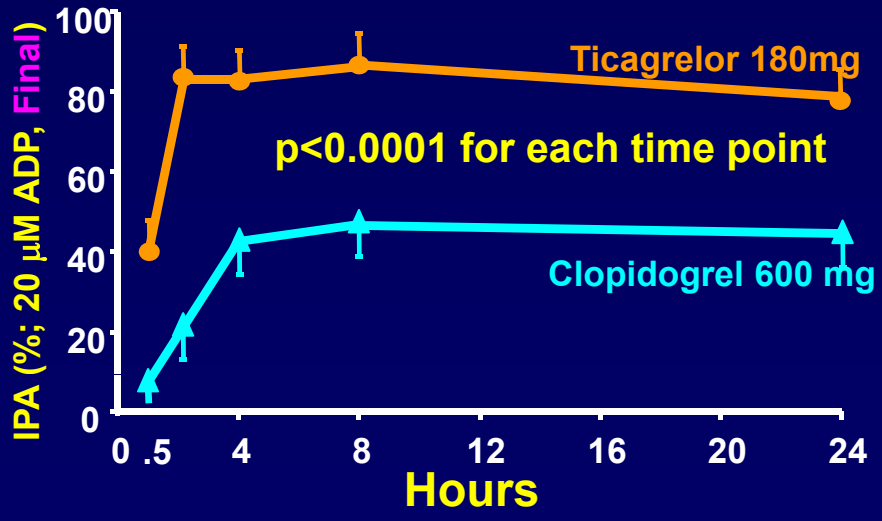
PRICIPLE TIMI-44

Wiviott SD et al,
Circulation. 2007;116:2923-32.



ONSET/OFFSET

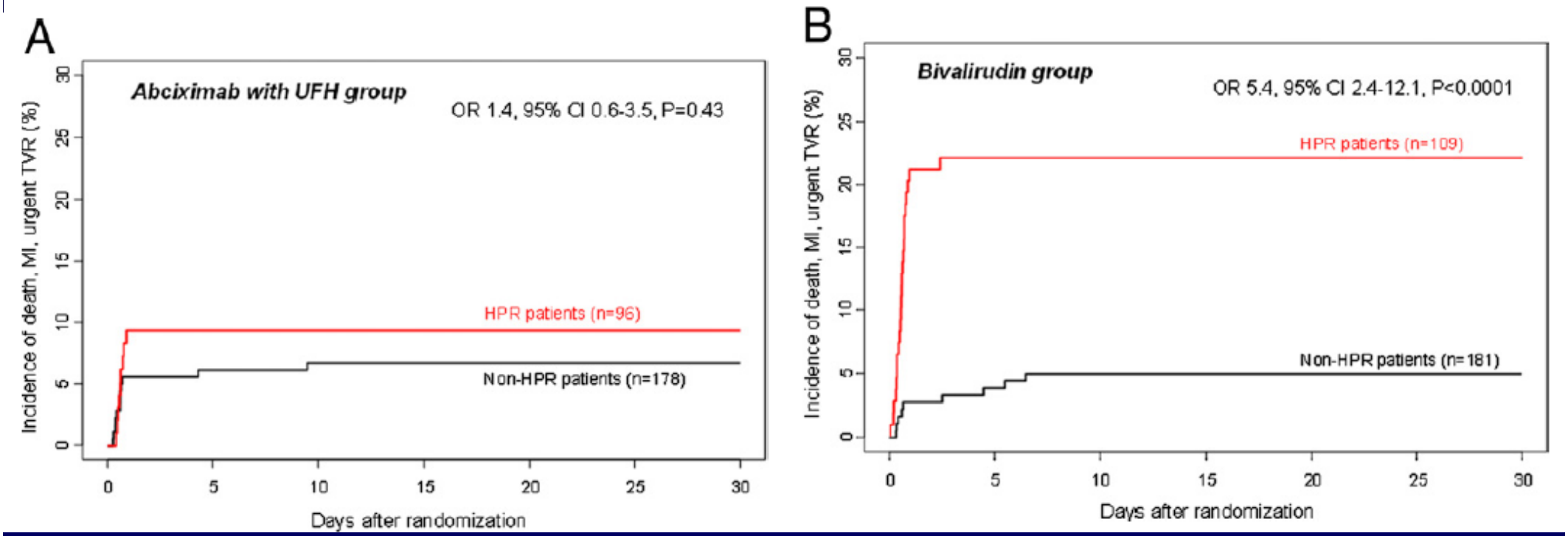
Gurbel PA et al,
Circulation. 2009;120:2577-85



Impact of Bivalirudin vs. Abciximab in NSTEMI Patients with HPR

ISAR-REACT 4 Platelet Substudy

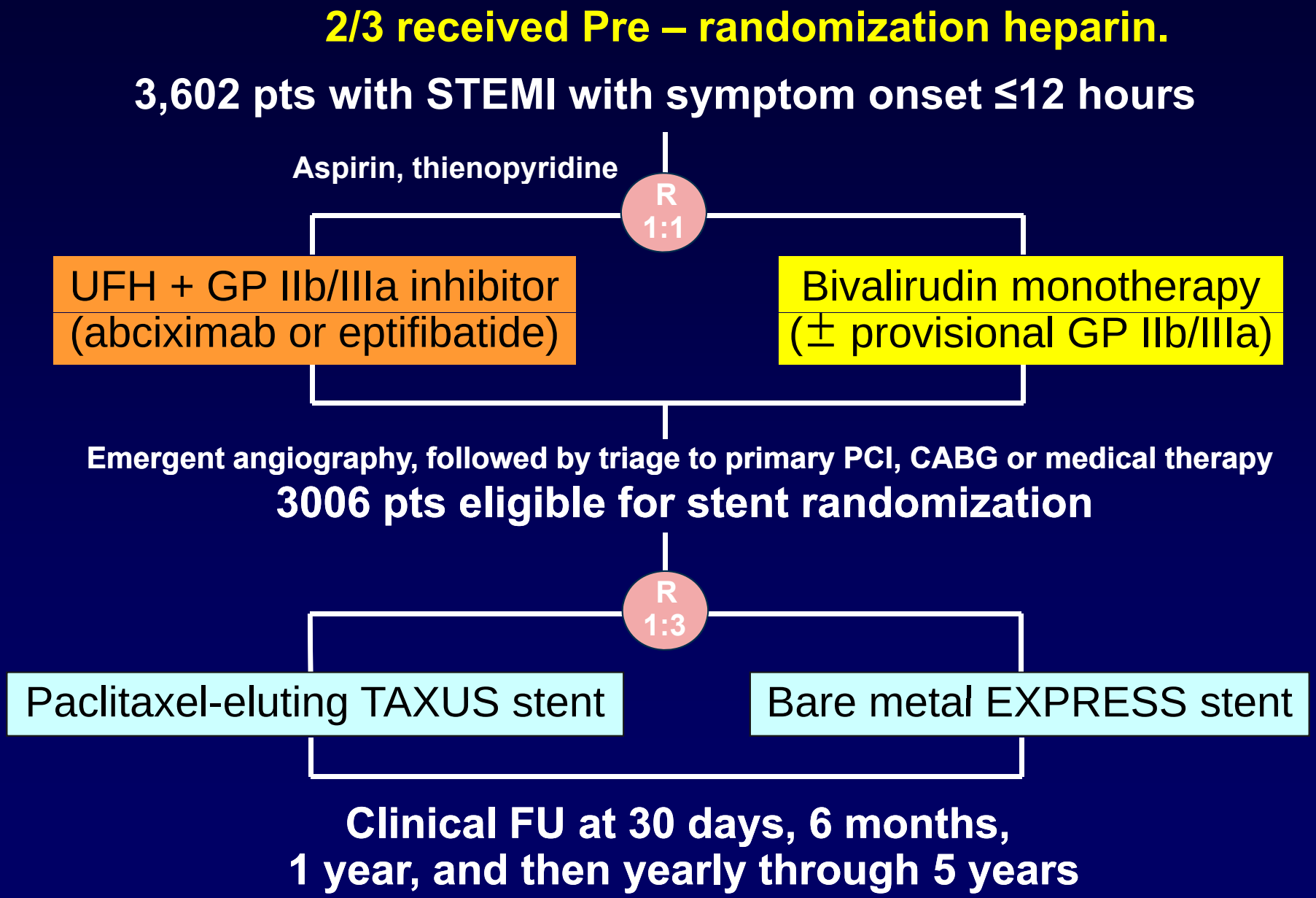
HPR: Multiplate ≥ 468 AU x min



*** Bivalirudin: no protective effect on post-PCI events in AMI**

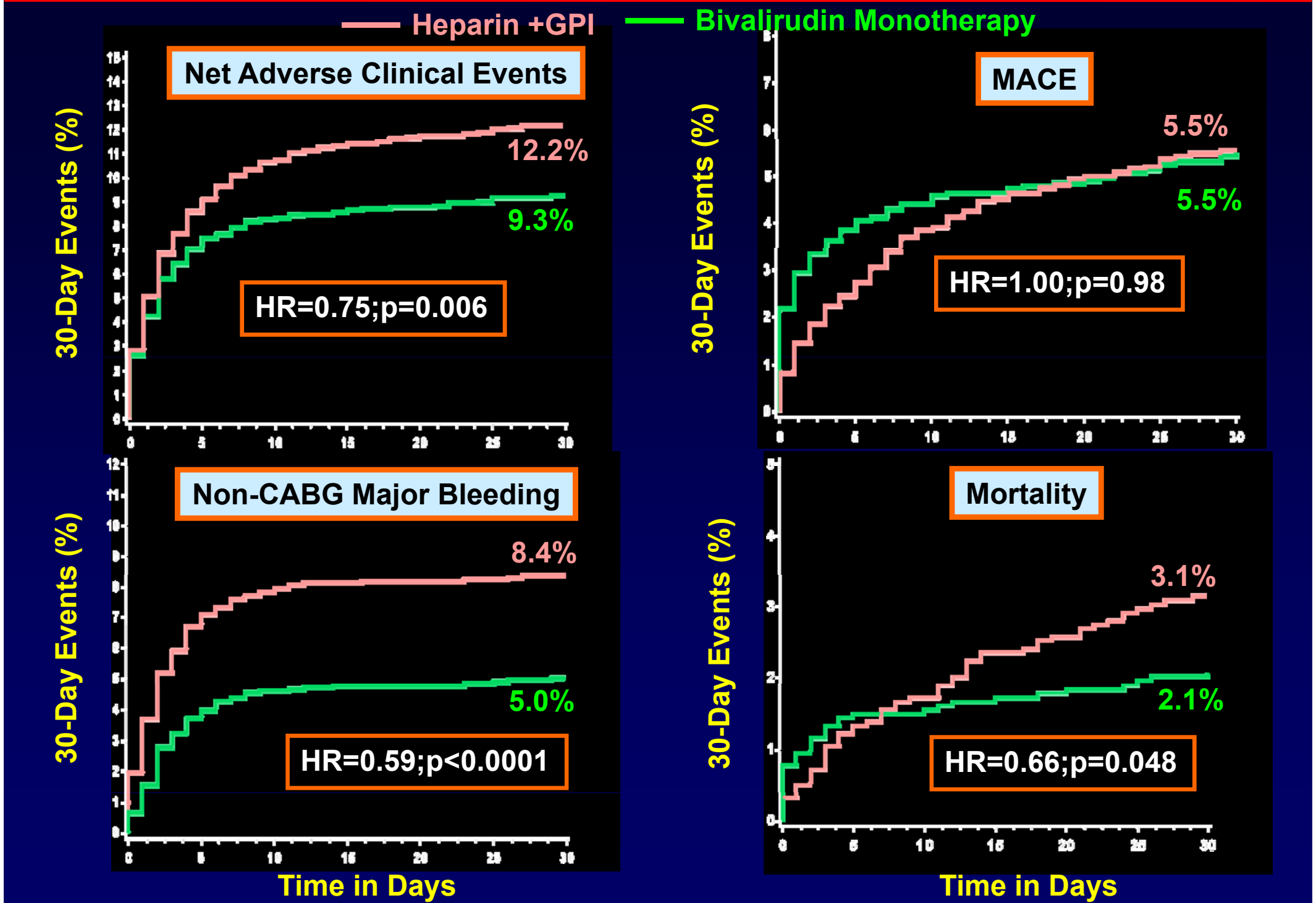
Sibbing et al. *J Am Coll Cadiol* 2012;60:369-77.

Impact of Bivalirudin vs. Abciximab+Heparin in STEMI Patients (HORIZONS-AMI)

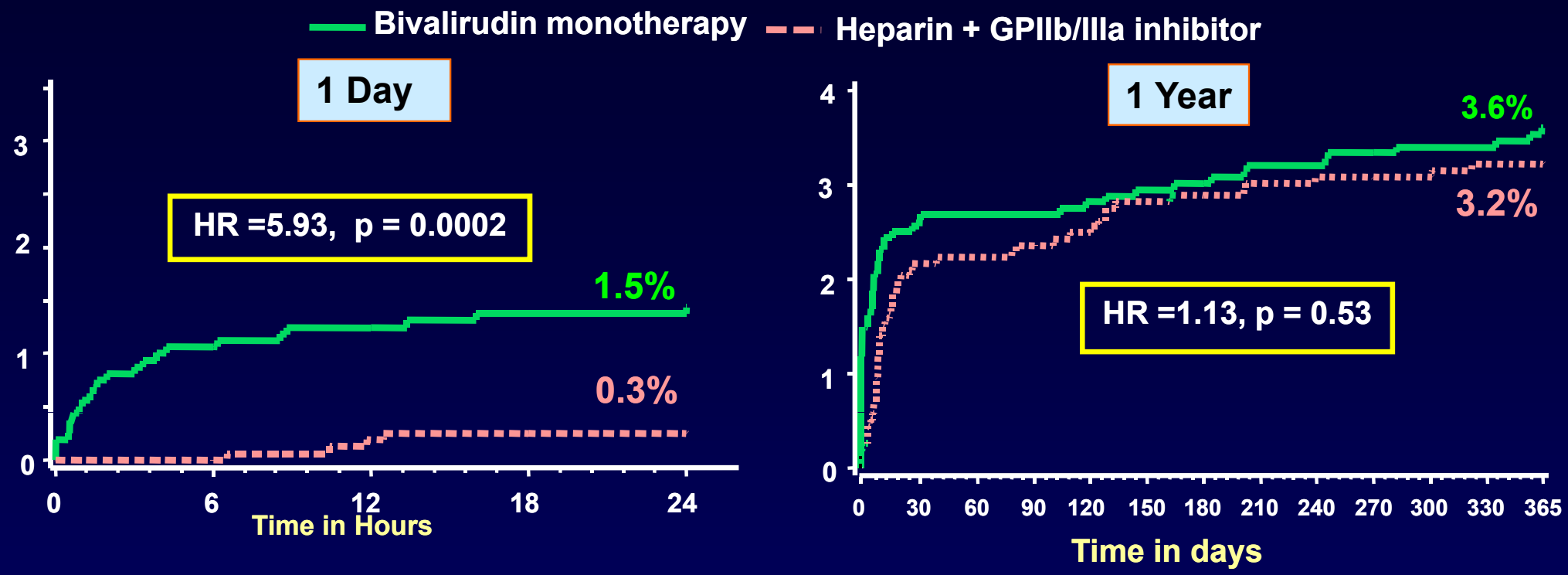


Stone GW. *New Engl J Med.* 2008;358:2218-30.

HORIZON AMI: Primary Outcome Measures

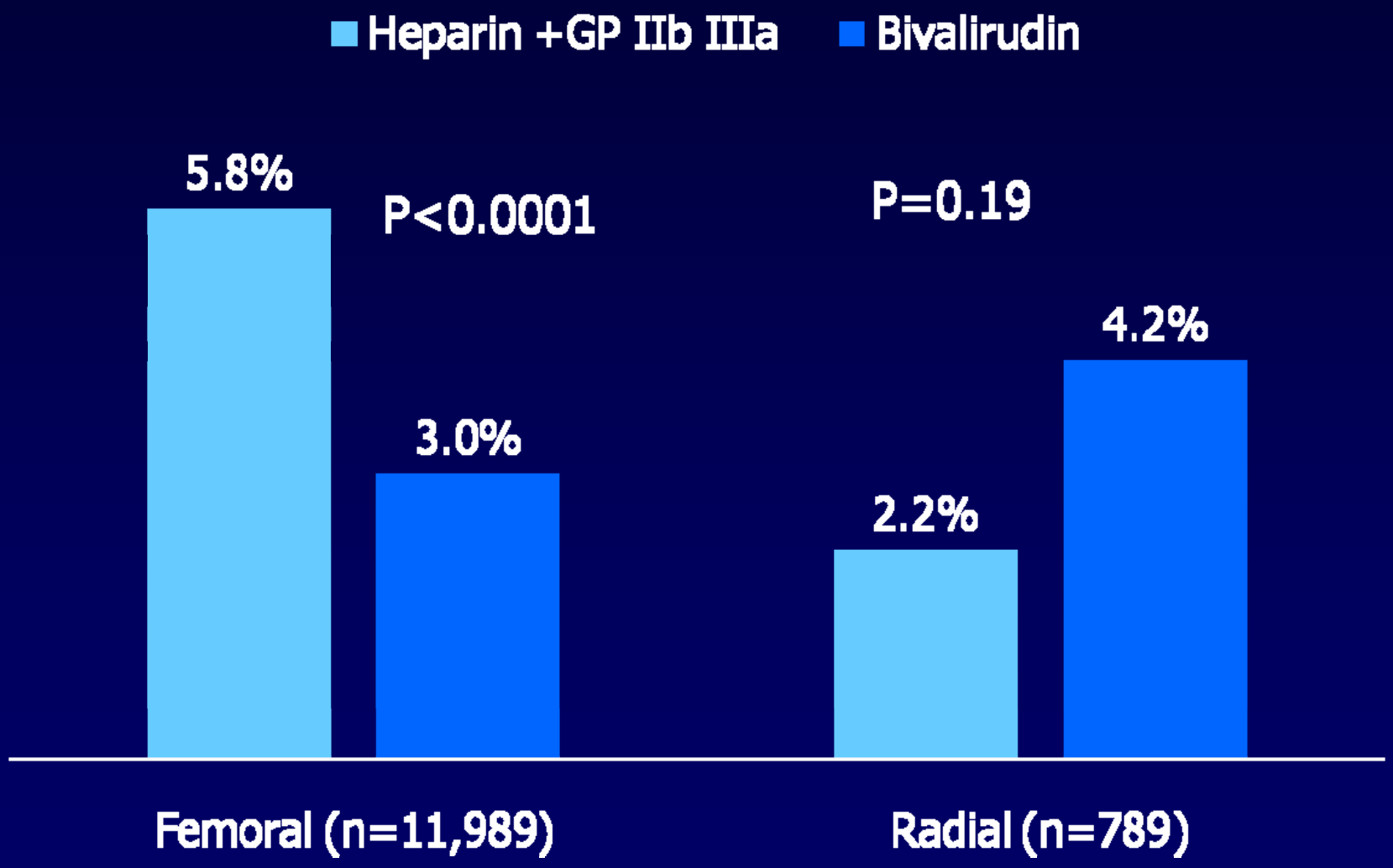


Definite /Probable Stent Thrombosis in HORIZONS-AMI



* Bivalirudin: less MACE driven by less bleeding
  more early stent thrombosis/PMI
* How to maximize the benefit of GPI treatment?
  - radial approach
  - bolus or short-time infusion

ACUITY Trial: Bivalirudin reduces Major bleeding only in femoral access



Hamon M, et al. EuroIntervention. 2009;5:115-20.

Bolus-only or Short Infusion vs. Prolonged Infusion

Study	BRIEF PCI	EASY	Kini et al
Study Type	RCT, n=624	RCT, n=1005	Retrospective, n=2629
GPI Type	Eptifibatide	Abciximab	Eptifibatide (72%) Abciximab (28)
Study Population	ACS or Stable CAD 32% Troponin^{+}	ACS or Stable CAD 20% Troponin^{+}	ACS or Stable CAD 14% Troponin^{+}
B2/C Coronary Lesion (%)	63%	47%	80%
Duration of Infusion	<2h vs. 18h	bolus only vs. 12h	bolus only vs. 12-18h
Adequate Clopidogrel Load Before PCI (%)	70%	92%	54%

Bolus only or Short Infusion vs. Prolonged Infusion			
Death/MI/Urgent TVR at 30 days	4.8% vs. 4.5%, p=1.0	1.4% vs. 1.8%, p=ns	3.2% vs. 3%, p=0.73
Major Bleeding	1.0% vs. 4.2%, p=0.02	0.8% vs. 0.2% p=ns	0.8% vs. 1.6%; p=0.09
Minor Bleeding	17.6% vs. 21.2%, p=0.31	N/A	1.1% vs. 2.2%; p=0.03

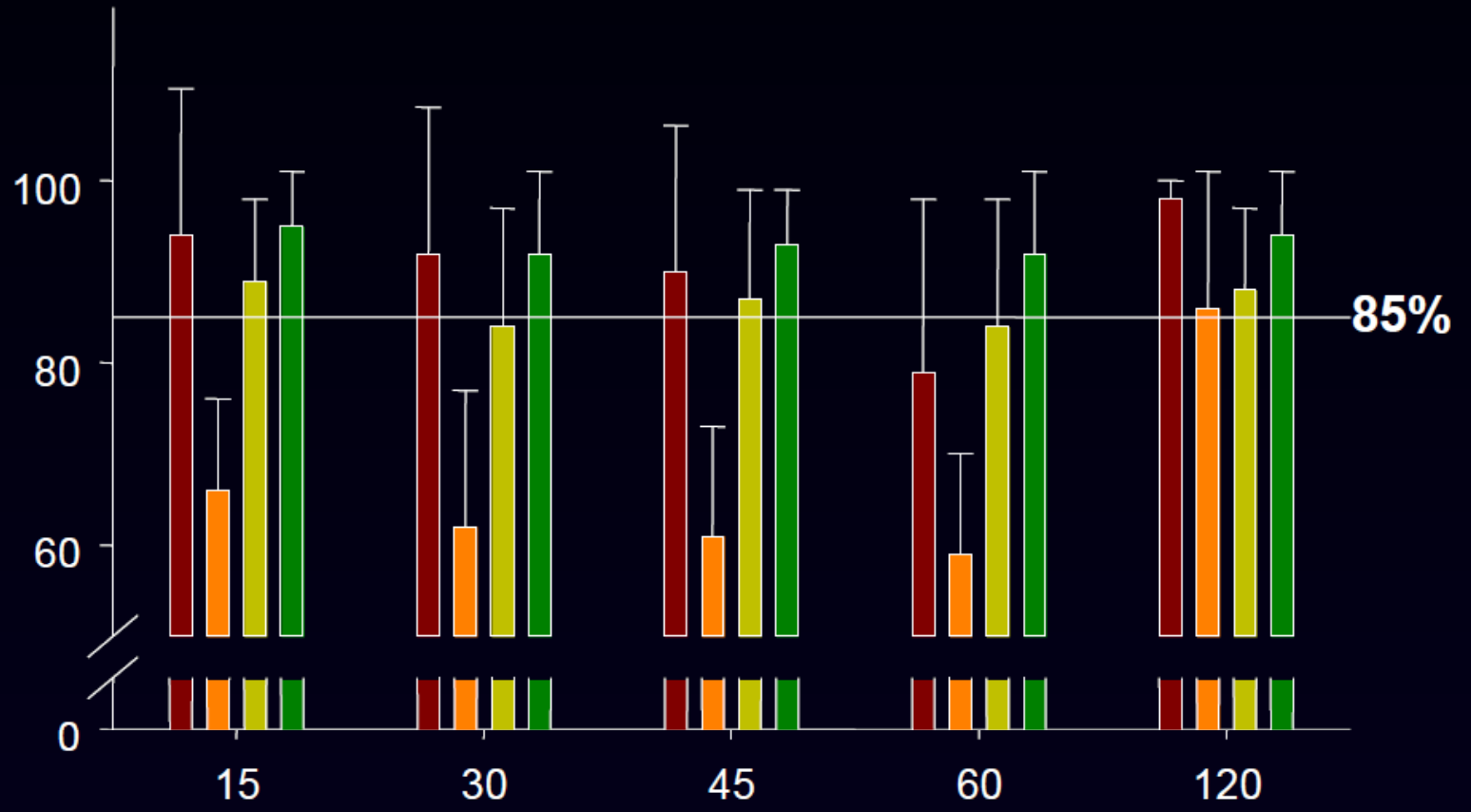
Hanna EB et al. *J Am Coll Cardiol Intv*. 2010;1209-19
Bertard OF et al. *Circulation* 2006;114:2636-43 (EASY)
Fung AY et al. *J Am Coll Cardiol*. 2009;53:837-45 (BRIEF-PCI)
Kini AS et al. *Am Heart J.* 2008;156:513-6

Characteristics of Glycoprotein IIb/IIIa Inhibitors

	Abciximab	Eptifibatide	Tirofiban
Type	Monoclonal antibody fragment	Small molecule (cyclic peptide)	Small molecule (non-peptide)
Platelet-bound half-life	Hours	Seconds	Seconds
Plasma half-life	Minutes	2.5 hours	2.0 hours
Drug-to-receptor ratio	1.5–2.0	250–2,500	>250
Percent of dose in bolus	75%	<2.5%	<2.5%
Cost	€€	€	€
Specificity/Selectivity			
IIb/IIIa	+++	+++	+++
αvβ3	+++	+	
Mac-1	+		
Anticoagulant properties			
↓ *thrombin generation*	++	+	+
↑ *activated clotting time*	30 seconds	20 seconds	0 seconds
Reversibility without platelets	24–48 hours	4 hours	4 hours
Reversibility with platelets	Yes	No	No
Route of elimination (22)	Spleen	Renal (50%)	Renal (40–70%)
Renal dose adjustment (22)	None	CrCl < 50 ml/min; 180 µg/kg/bolus + 1.0 µg/kg/min	CrCl < 30 ml/min; 0.2 µg/kg/min x 30 min + 0.05 µg/kg/min

Kristensen et al. *Thromb Haemost* 2012;107:215-24.

Inhibition of Light Transmission Aggregation Induced by 20 µM ADP after Treatment with Tirofiban or Abciximab



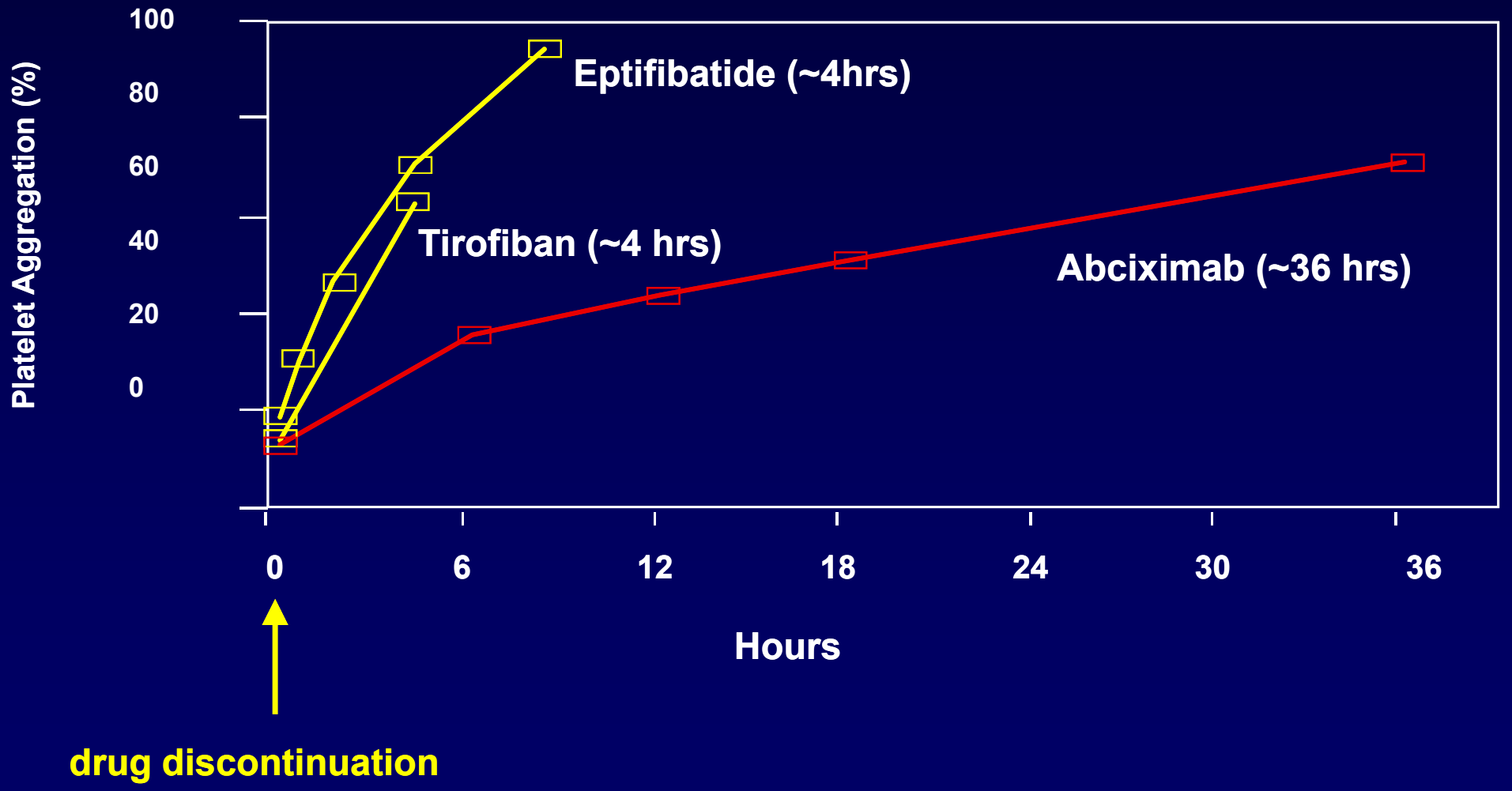
abciximab
tirofiban 10 µg/kg bolus
tirofiban 20 µg/kg bolus
tirofiban 25 µg/kg bolus
} 0.15 ug/kg/min infusion

(High-dose bolus, HDB)

Schneider, Herrmann, et al, Am J Cardiol 2002; 90:1421-1423

Reversibility of Glycoprotein IIb/IIIa Inhibitors

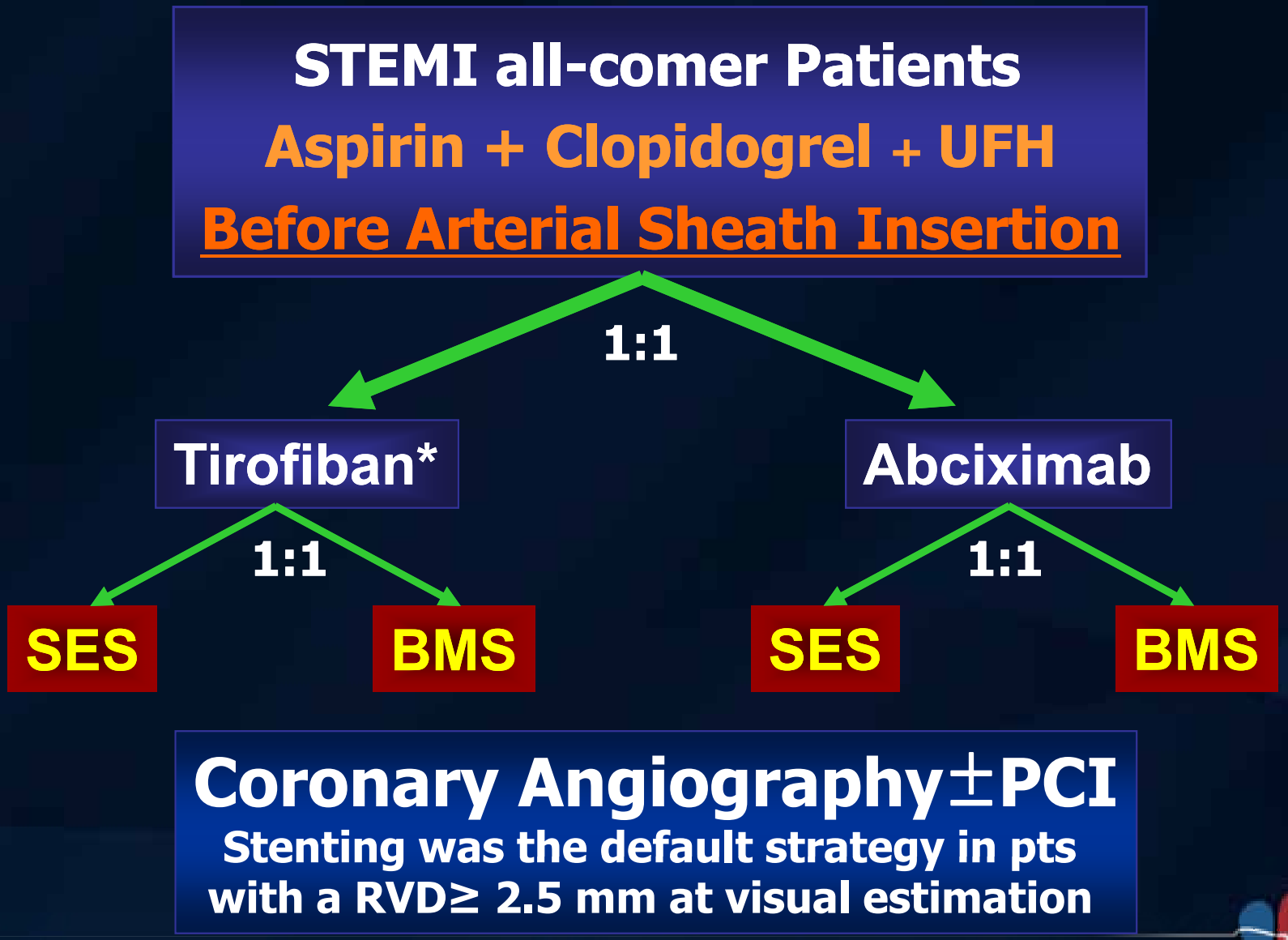
Small Molecules vs. Abciximab



Adapted from Tantry US and Gurbel PA. *Future Cardiol.* 2006;2:343-66.

Abciximab vs. HDB Tirofiban in Primary PCI

Valgimigli et al, JAMA 2008



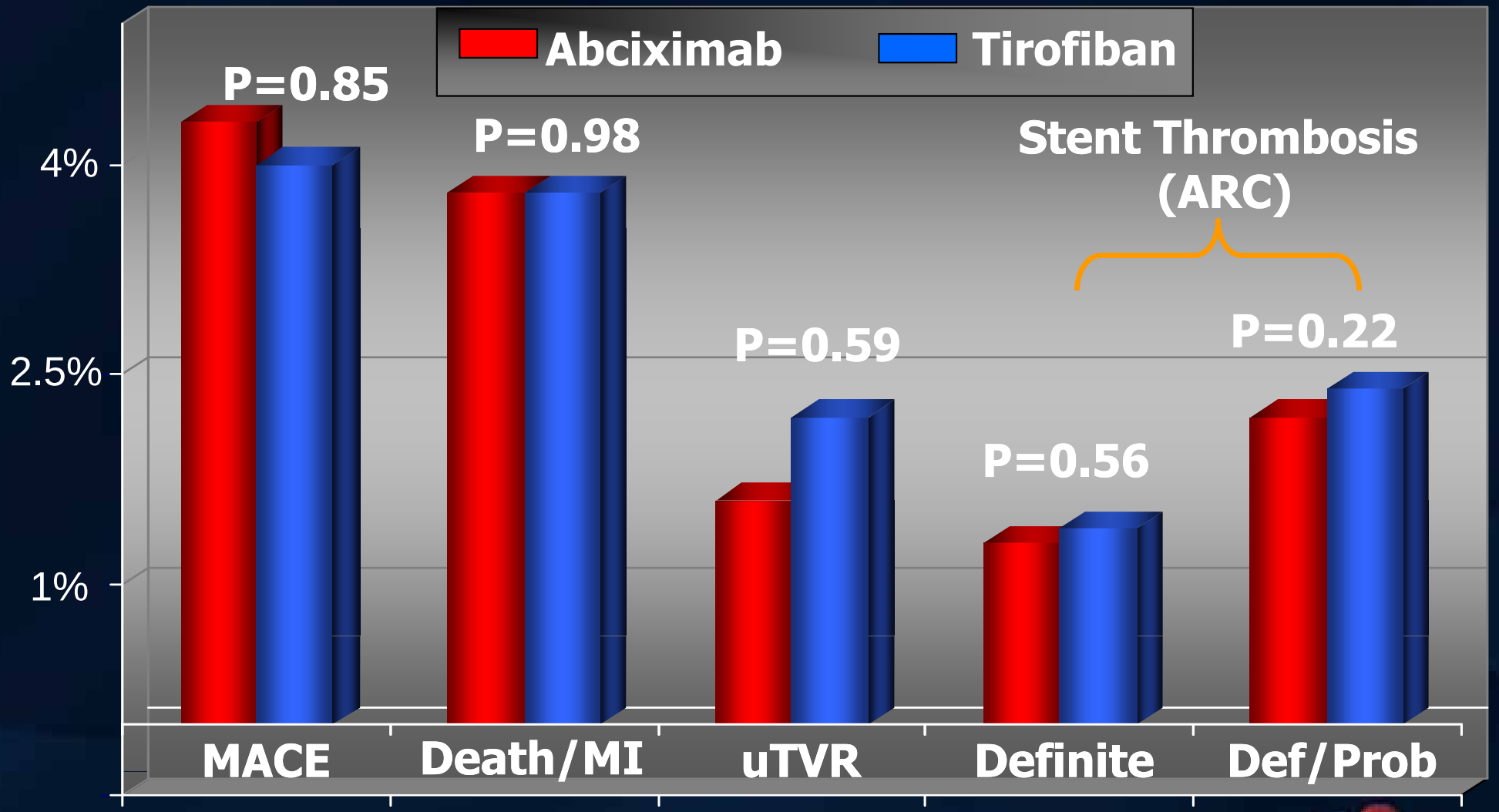
*: given as a bolus of 25 μg/kg, followed by an 18-24 hour infusion at 0.15 μg/kg/min

MULTISTRATEGY

30-Day Outcomes

Efficacy Endpoints

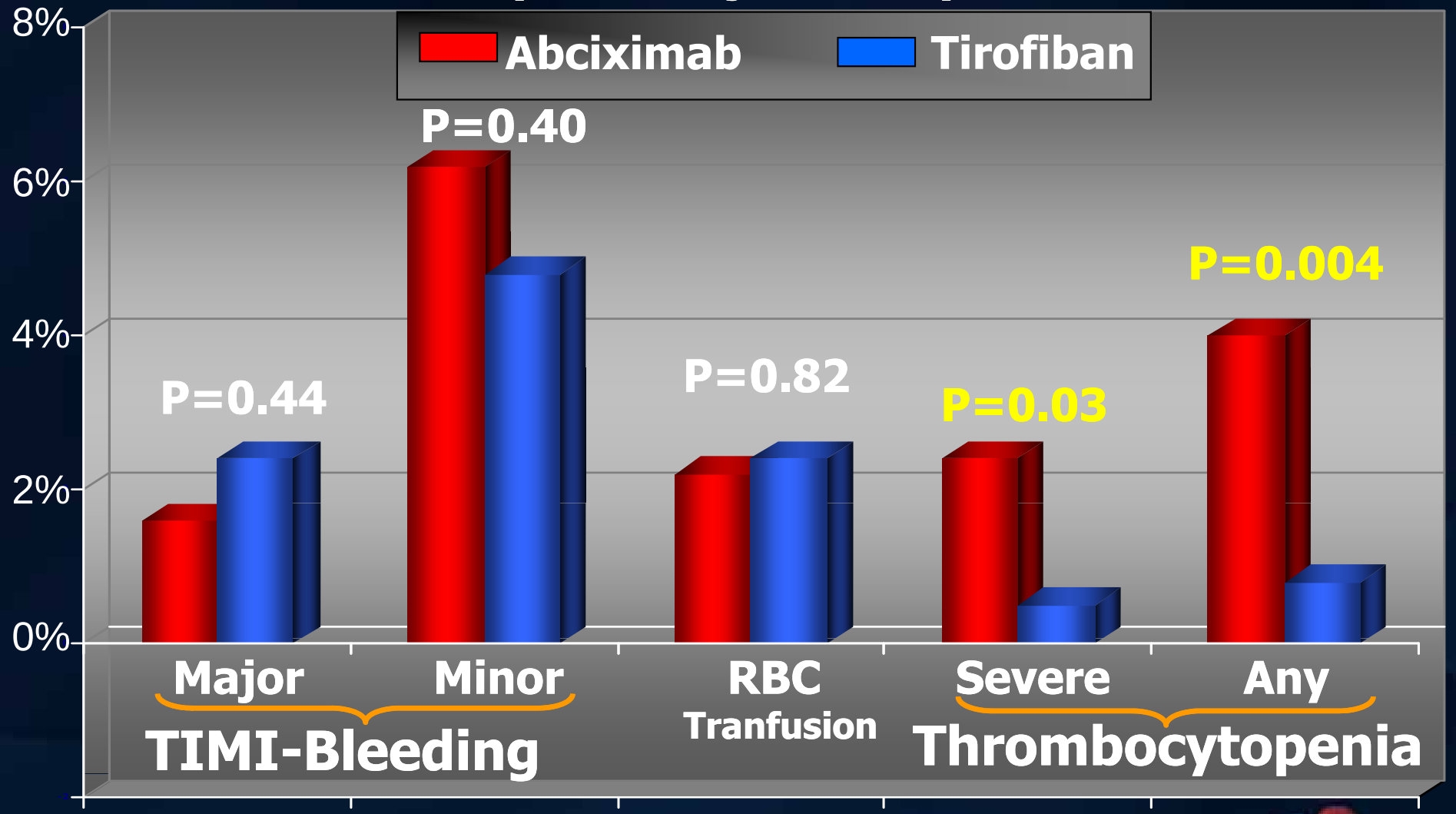
(CEC adjudicated)



30-Day Outcomes

Safety Endpoints

(DSMB adjudicated)

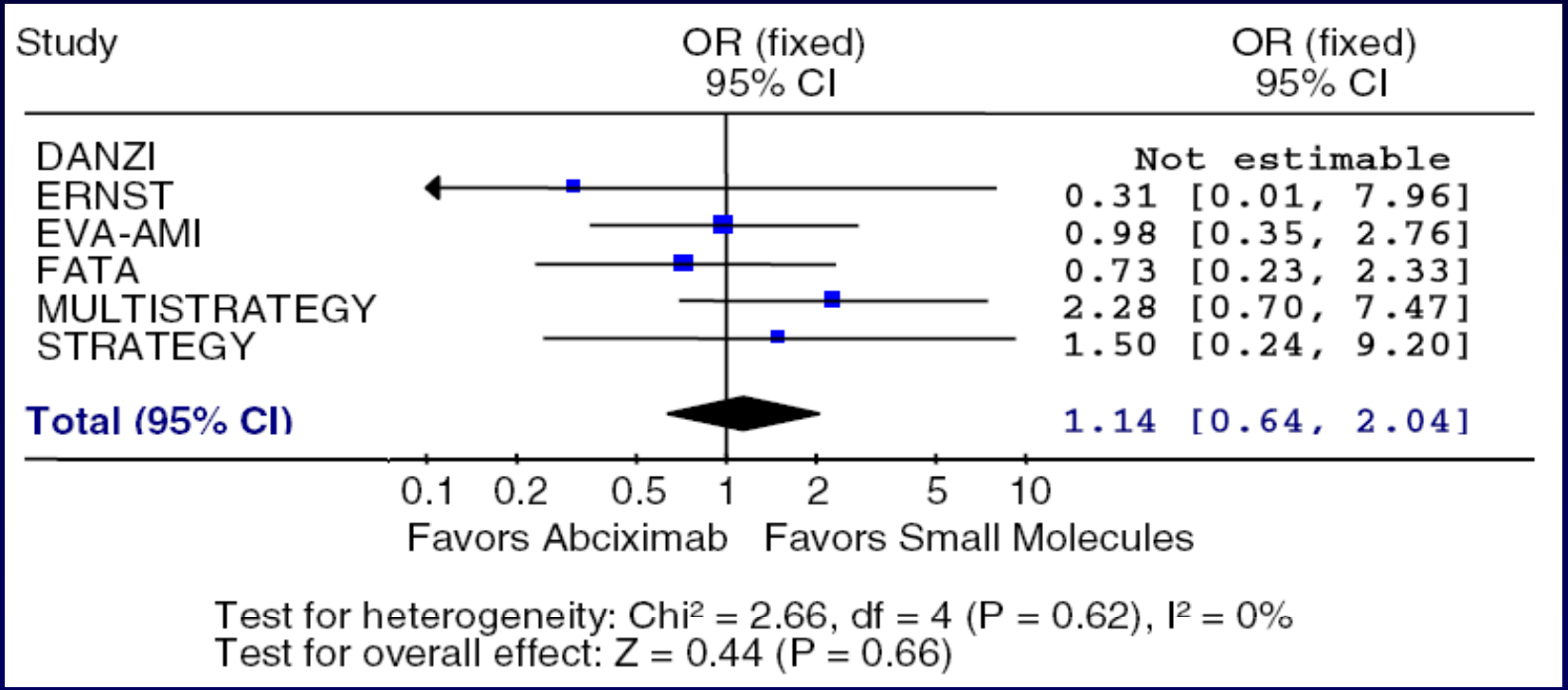


MULTISTRATEGY

Small Molecule vs. Abciximab Administration
Primary PCI: Meta-Analysis

6 RTs, n=1086 abciximab vs. 1115 small molecules (only high-dose bolus and infusion)

30-day Mortality



30-day Secondary Outcomes

	OR (95% CI)
Reinfarction	0.94 (0.44, 2.04)
Post-procedural TIMI flow Grade 3	1.05 (0.80, 1.39)
ST-segment resolution	0.96 (0.78, 1.17)

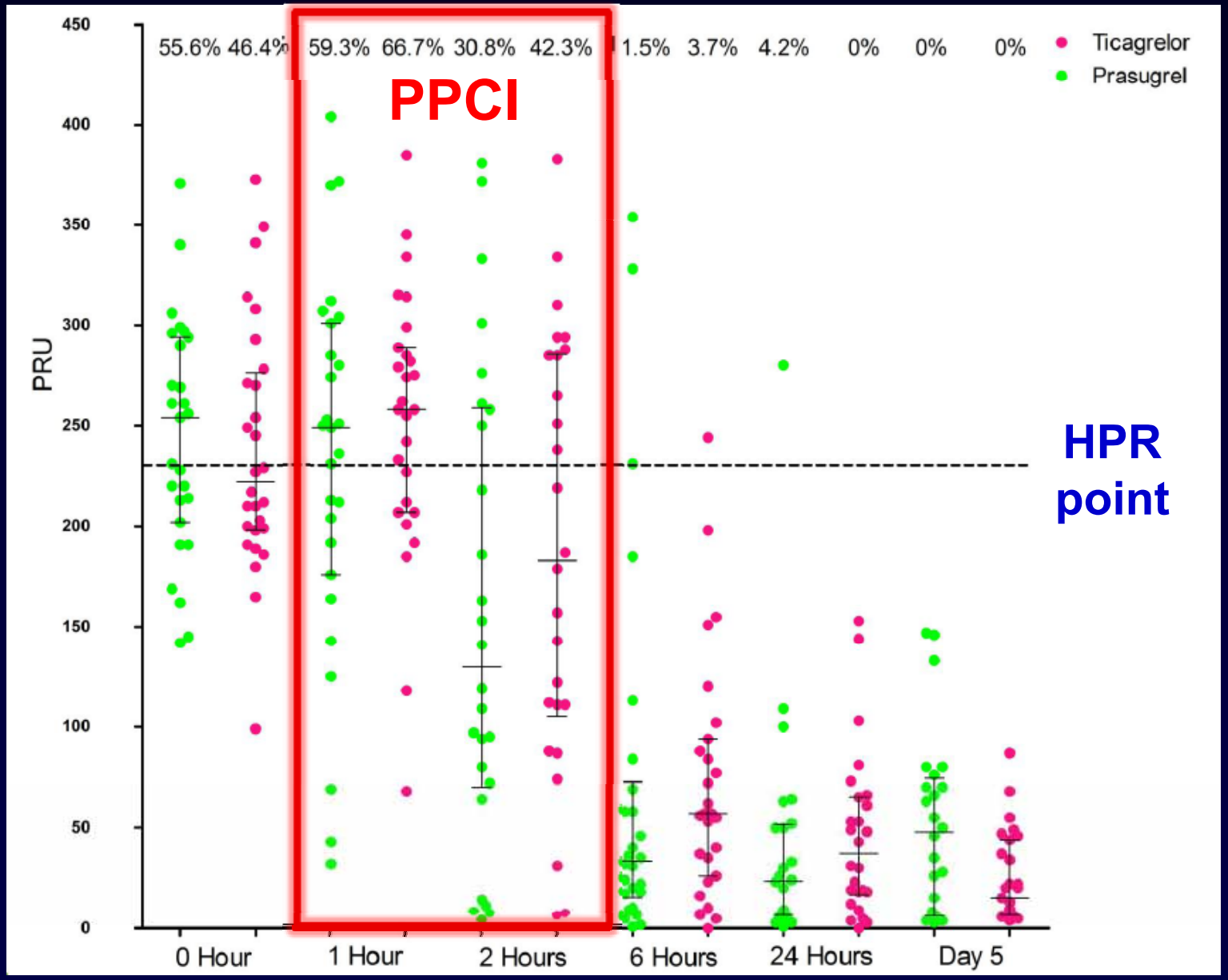
De Luca et al. J Am Coll Cardiol. 2009;53:1668-73

STEMI Pts = "Non-responder to $P2Y_{12}$ Inhibitor"

1. Splanchnic and liver hypoperfusion
   by hemodynamic instability:
   ↓ drug absorption and metabolism

2. Catecholamine release and use:
   ↑ platelet baseline reactivity and turn-over

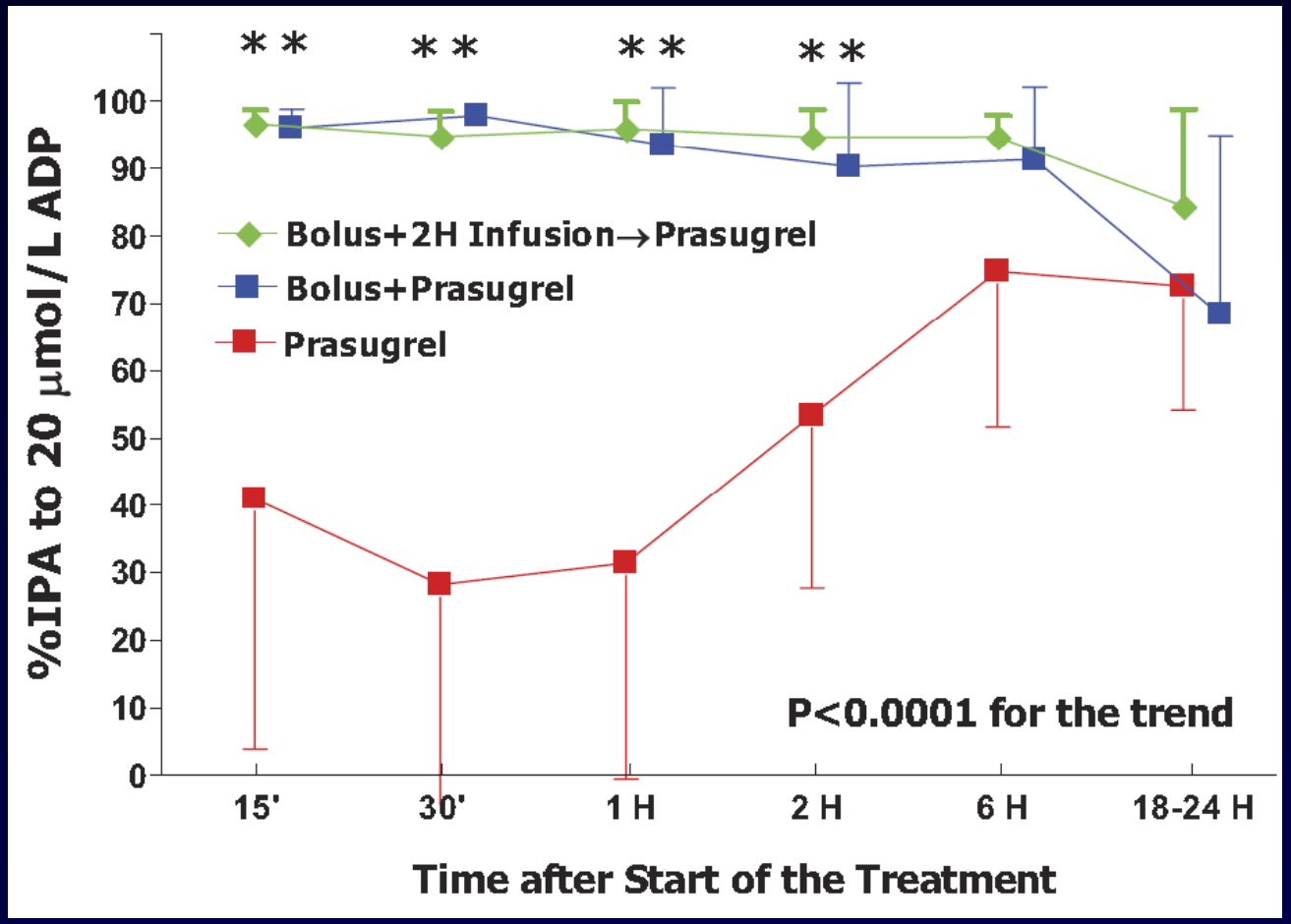
Ticagrelor vs. Prasugrel in STEMI Patients
(180 mg LD/90 mg bid MD vs. 60 mg LD/10 mg QD MD)



Alexopoulos D, et al. Circ CV Interv 2012;5:797-804.

Pharmacodynamic Effect of *Prasugrel Alone* vs. *Prasugrel + HDB Tirofiban Infusion* in STEMI Pts

FABOLUS PRO Study (n = 100): Prasugrel 60mg LD ± Tirofiban 25 µg/kg bolus ± Tirofiban 0.15 µg/kg/min 2 hr infusion



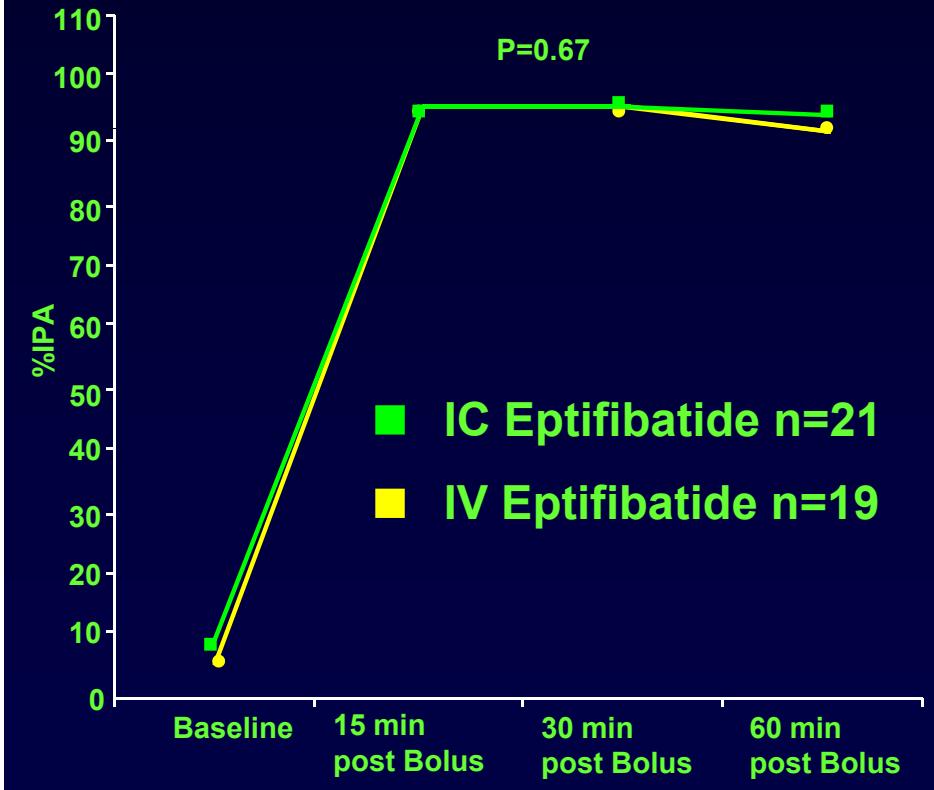
Prasugrel LD + GPI bolus obviates the need of continuous infusion and almost completely abolishes platelet activation.

Valgimigli M, et al. JACC Cardiovasc Interv. 2012;5:268-77.

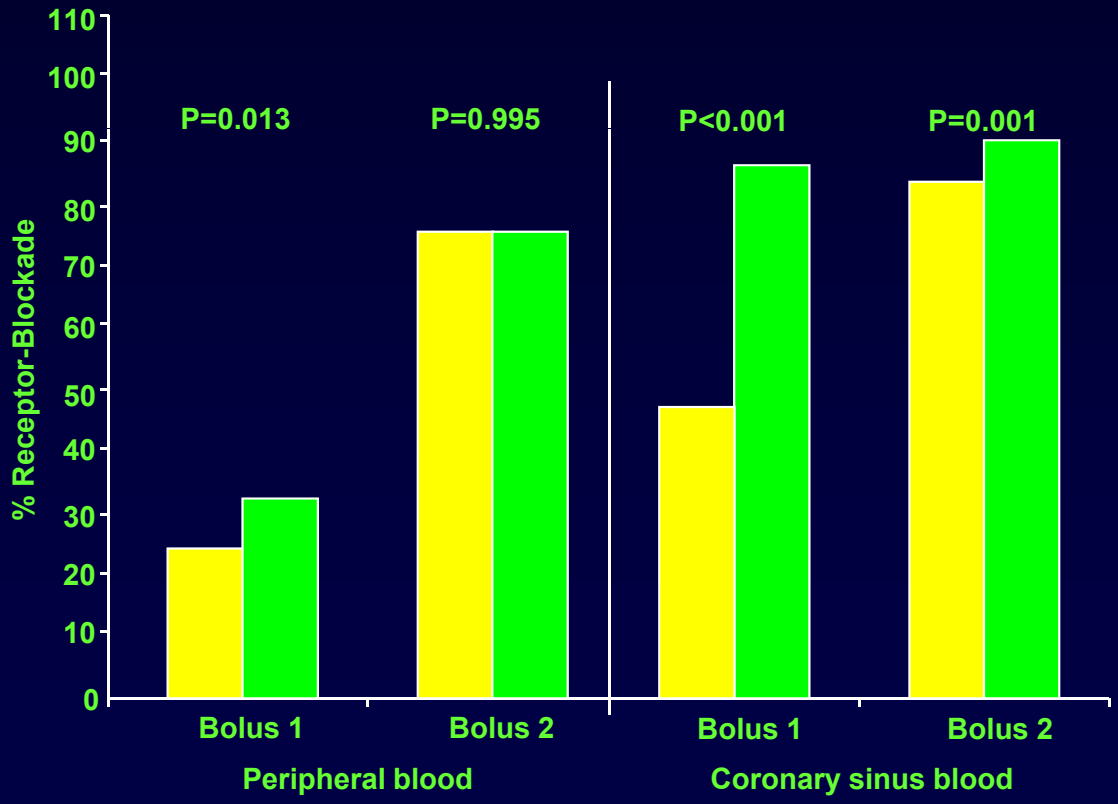
Eptifibatide IC vs. IV in STEMI (ICE Trial)

IC versus IV bolus (2 x Bolus within 10 min. 180 µg/kg Eptifibatide), Followed by 2 µg/kg/min continuous infusion i.v. for 18 h

IPA periphery (20 µmol/L ADP)



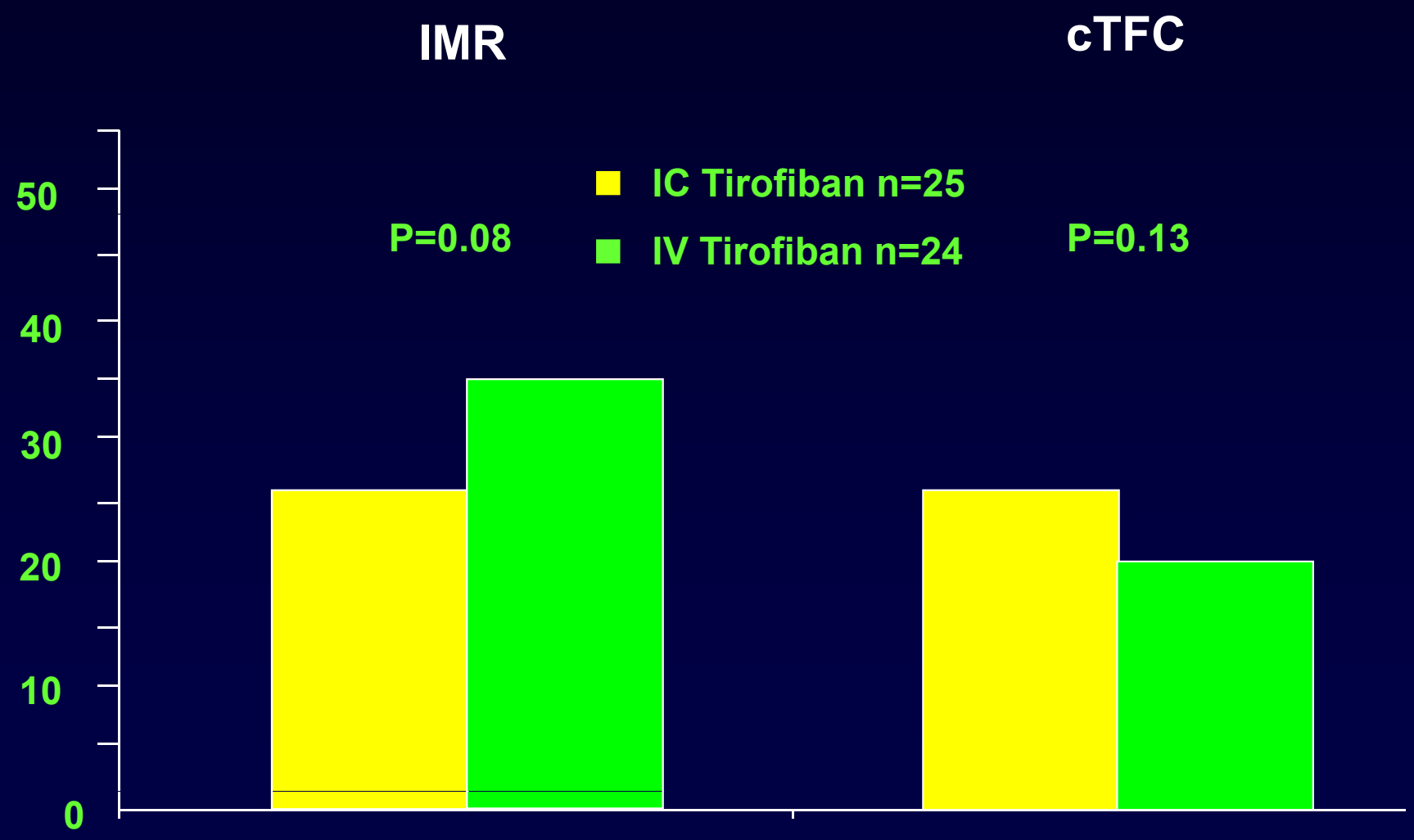
GPIIb/IIIa receptor-blockade



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

IC Bolus-only vs. IV Bolus+Infusion Tirofiban in STEMI Patients

Tirofiban 25 µg/kg IC bolus only versus IV bolus+ 0.15µg/kg/min infusion IV for 18 h

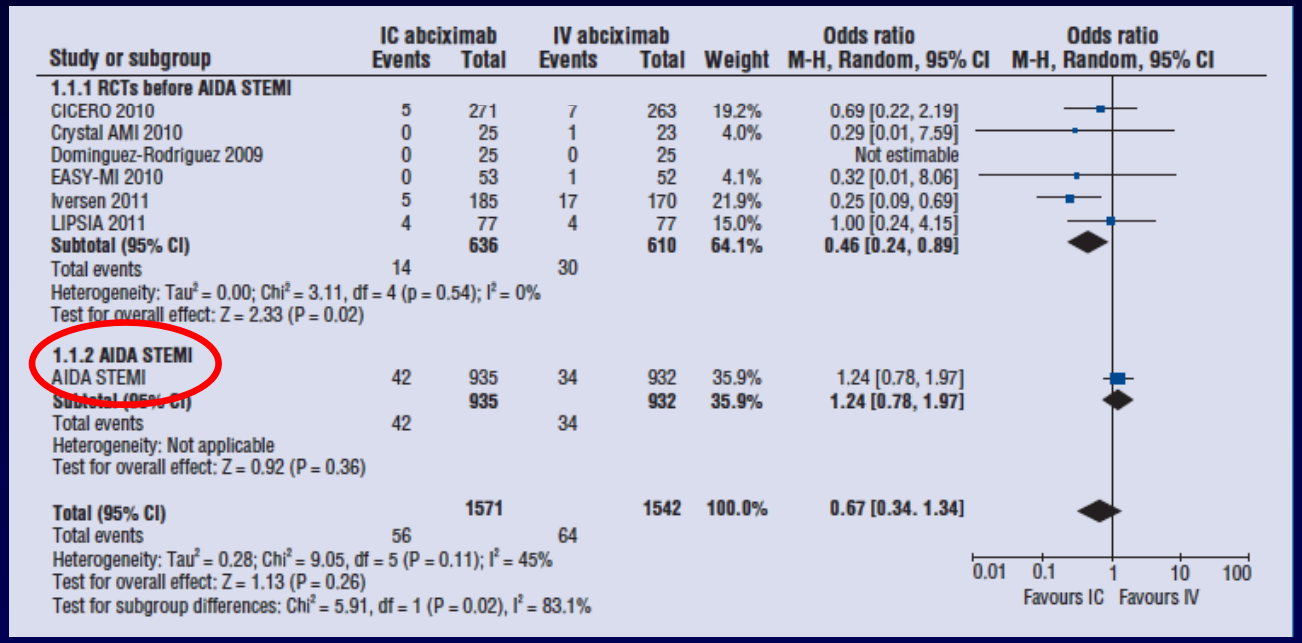


Kirma et al. Cath Cardio Interv 2012;79:59–67.

IC vs. IV Abciximab Infusion in STEMI

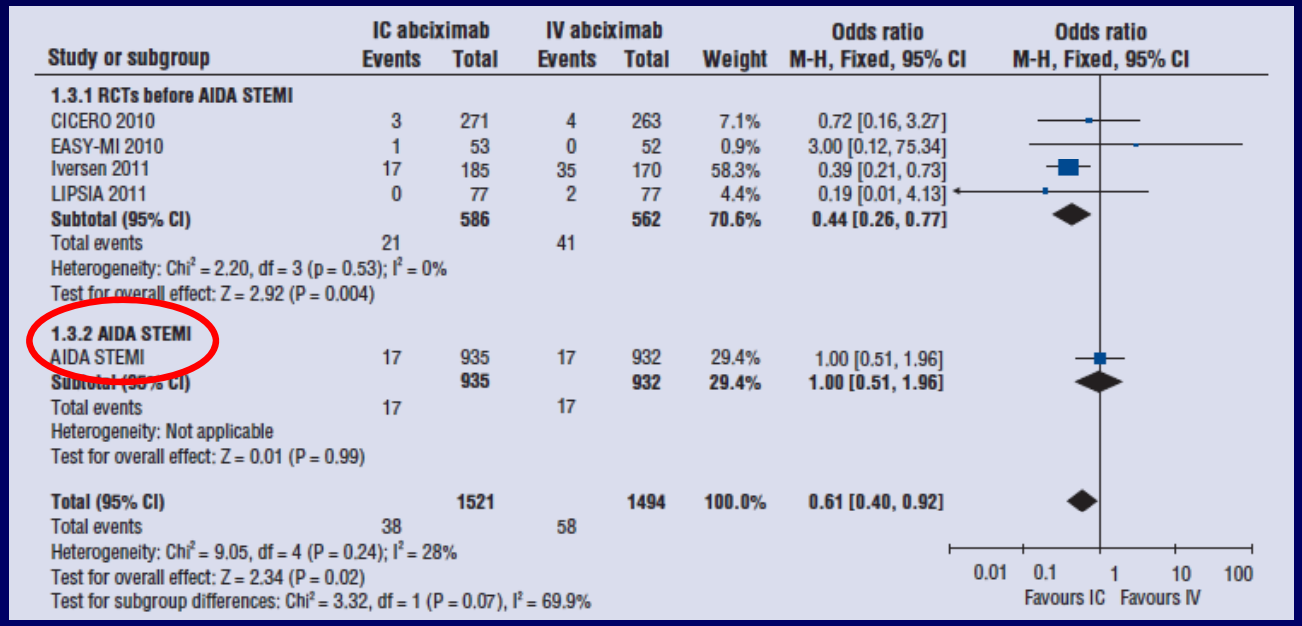
7 studies, n=3,311 patients, median follow-up of 3 months

All-cause Death



Study or subgroup	IC abciximab Events	Total	IV abciximab Events	Total	Weight	Odds ratio M-H, Random, 95% CI
1.1.1 RCTs before AIDA STEMI						
CICERO 2010	5	271	7	263	19.2%	0.69 [0.22, 2.19]
Crystal AMI 2010	0	25	1	23	4.0%	0.29 [0.01, 7.59]
Dominguez-Rodriguez 2009	0	25	0	25		Not estimable
EASY-MI 2010	0	53	1	52	4.1%	0.32 [0.01, 8.06]
Iversen 2011	5	185	17	170	21.9%	0.25 [0.09, 0.69]
LIPSIA 2011	4	77	4	77	15.0%	1.00 [0.24, 4.15]
Subtotal (95% CI)		**636**		**610**	**64.1%**	**0.46 [0.24, 0.89]**
Total events	14		30			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.11$, df = 4 (p = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 2.33 (P = 0.02)						
1.1.2 AIDA STEMI						
AIDA STEMI	42	935	34	932	35.9%	1.24 [0.78, 1.97]
Subtotal (95% CI)		**935**		**932**	**35.9%**	**1.24 [0.78, 1.97]**
Total events	42		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**1571**		**1542**	**100.0%**	**0.67 [0.34. 1.34]**
Total events	56		64			
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 9.05$, df = 5 (P = 0.11); $I^2 = 45\%$						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: $Chi^2 = 5.91$, df = 1 (P = 0.02), $I^2 = 83.1\%$						

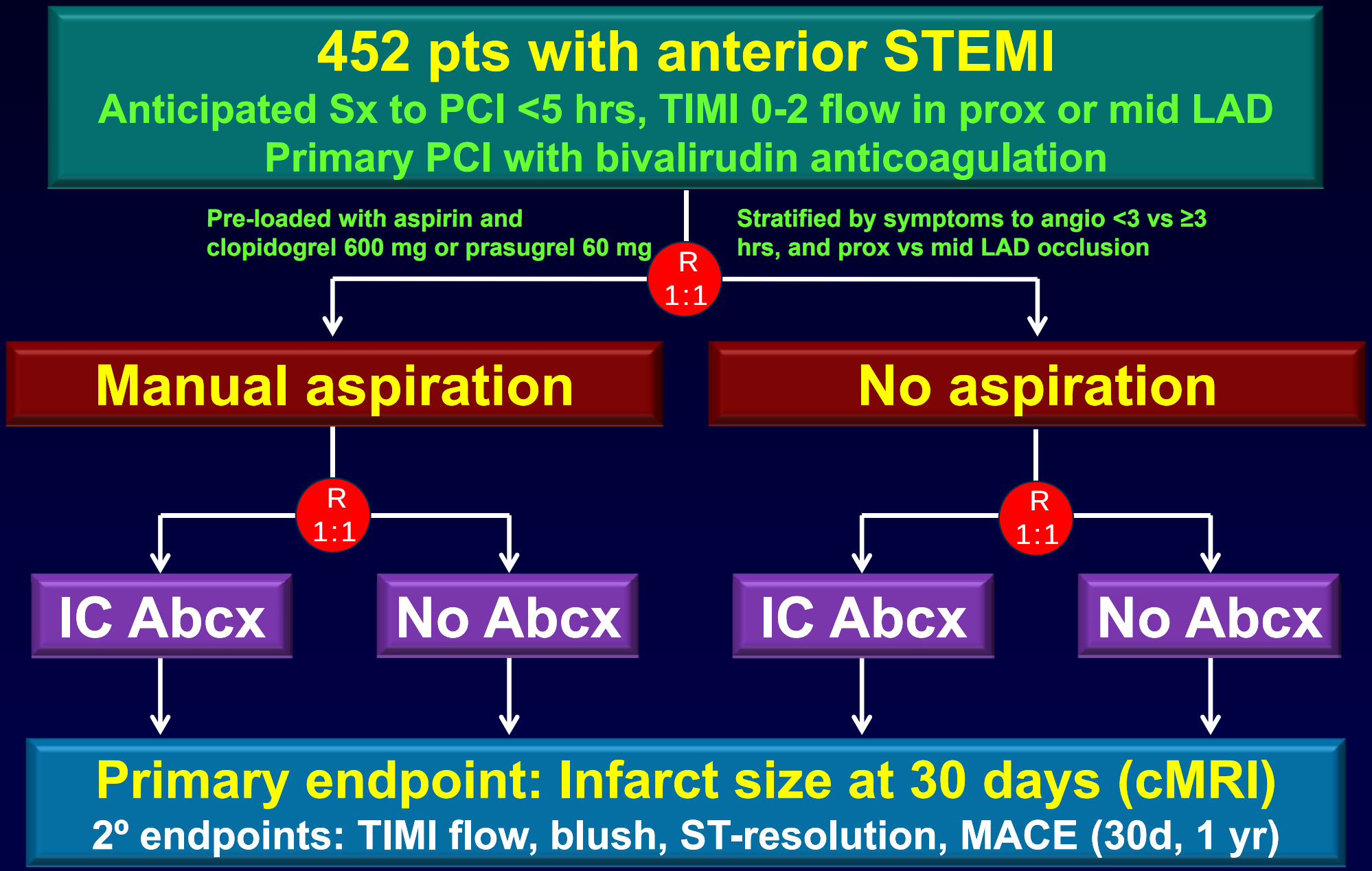
Recurrent MI



Study or subgroup	IC abciximab Events	Total	IV abciximab Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
1.3.1 RCTs before AIDA STEMI						
CICERO 2010	3	271	4	263	7.1%	0.72 [0.16, 3.27]
EASY-MI 2010	1	53	0	52	0.9%	3.00 [0.12, 75.34]
Iversen 2011	17	185	35	170	58.3%	0.39 [0.21, 0.73]
LIPSIA 2011	0	77	2	77	4.4%	0.19 [0.01, 4.13]
Subtotal (95% CI)		**586**		**562**	**70.6%**	**0.44 [0.26, 0.77]**
Total events	21		41			
Heterogeneity: $Chi^2 = 2.20$, df = 3 (p = 0.53); $I^2 = 0\%$						
Test for overall effect: Z = 2.92 (P = 0.004)						
1.3.2 AIDA STEMI						
AIDA STEMI	17	935	17	932	29.4%	1.00 [0.51, 1.96]
Subtotal (95% CI)		**935**		**932**	**29.4%**	**1.00 [0.51, 1.96]**
Total events	17		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**1521**		**1494**	**100.0%**	**0.61 [0.40, 0.92]**
Total events	38		58			
Heterogeneity: $Chi^2 = 9.05$, df = 4 (P = 0.24); $I^2 = 28\%$						
Test for overall effect: Z = 2.34 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 3.32$, df = 1 (P = 0.07), $I^2 = 69.9\%$						

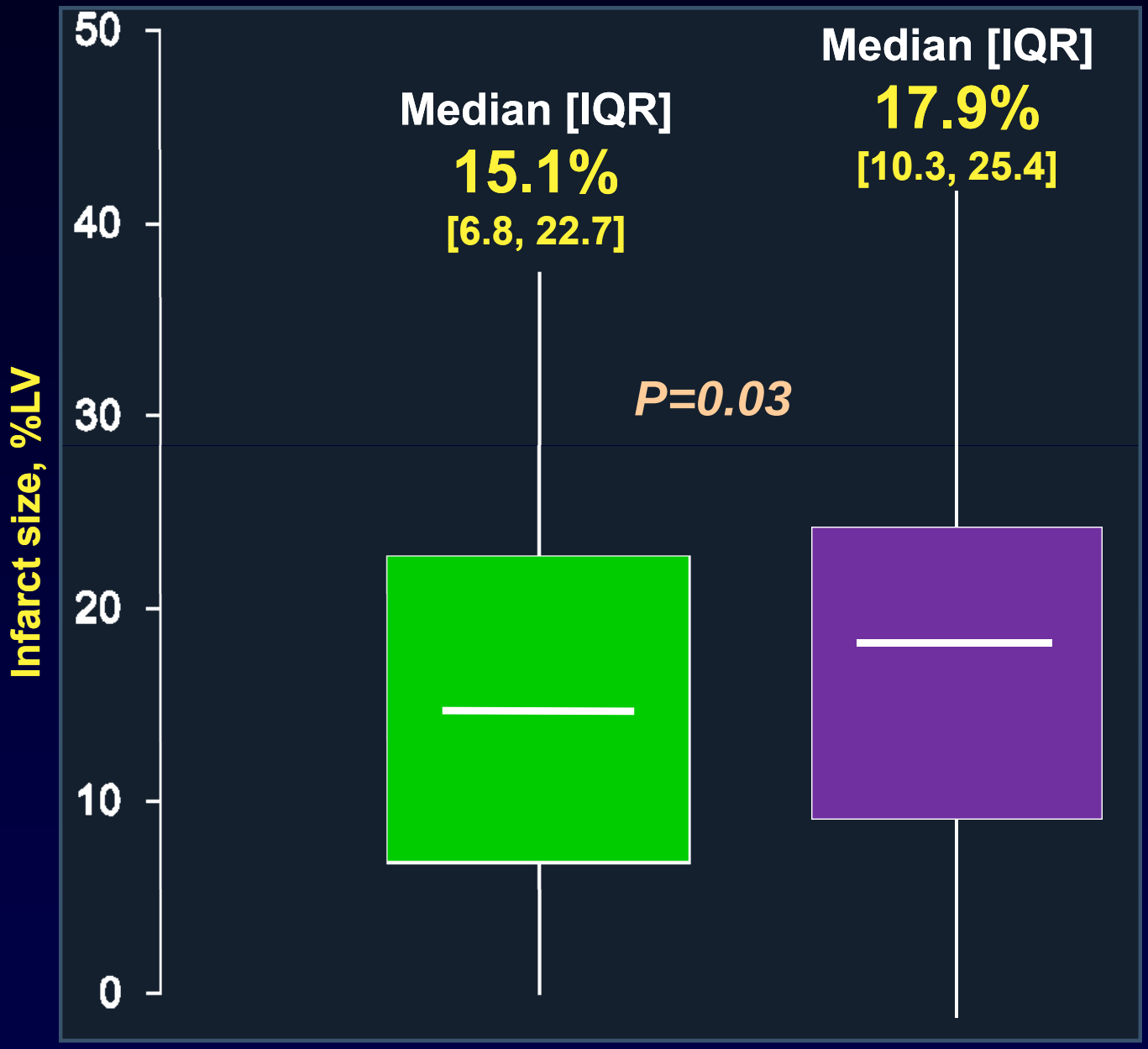
Kubica et al. *Cardiol J* 2012;19:230-42.

INFUSE-AMI Trial



Stone et al. *JAMA* 2012;307:1817-26.

Infarct size at 30 days by CMR



Localized infusion of IC abciximab bolus only through the drug delivery balloon (ClearWay rx) reduced infarct size:

↓15.6% versus no abciximab arms

Stone et al. *JAMA* 2012;307:1817-26.

Conclusions

* Common indications for GPI use during PCI

Clinical setting	Indications
Non-acute patients	No pretreatment with or Poor response to P2Y12 inhibitor
	Bail-out situations (thrombus formation, vessel closure, etc.)
NSTE-ACS	No pretreatment with or Poor response to P2Y12 inhibitor
	High-risk patients (complex lesions, large thrombi, elevated troponin levels).
	Bail-out situations (thrombus formation, vessel closure, etc.)
STEMI	High-risk patients (early phase after antiplatelet therapy LD, complex lesions, large thrombi, haemodynamically compromised patients).

In the era of potent $P2Y_{12}$ receptor inhibitor, GPI bolus (through IC delivery system) +/- short-term IV infusion in high-risk patients:

↓post-PCI ischemic events w/o ↑serious bleeding

Interaction of Haemostatic Components for PCI-related Thrombosis