IIb/IIIa inhibitors in STEMI

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iSTEMI treatment options

- Aspirin
- Heparin/ enoxaparin
- Bivalirudin
- P2Y12 blockers – Clopidoger/Prasugrel/Ticagrelor
- IIb/IIIa Inhibitors – Tirofiban/Eptifibatide
- Thrombus aspiration - 6F/7F
- Intracoronary drugs
- Stents – BMS, DES, MGAURD

2011 ACCF/AHA/SCAI Guideline for PCI

Table 13. Recommendations for Antiplatelet and Antithrombin Pharmacotherapy at the Time of PCI

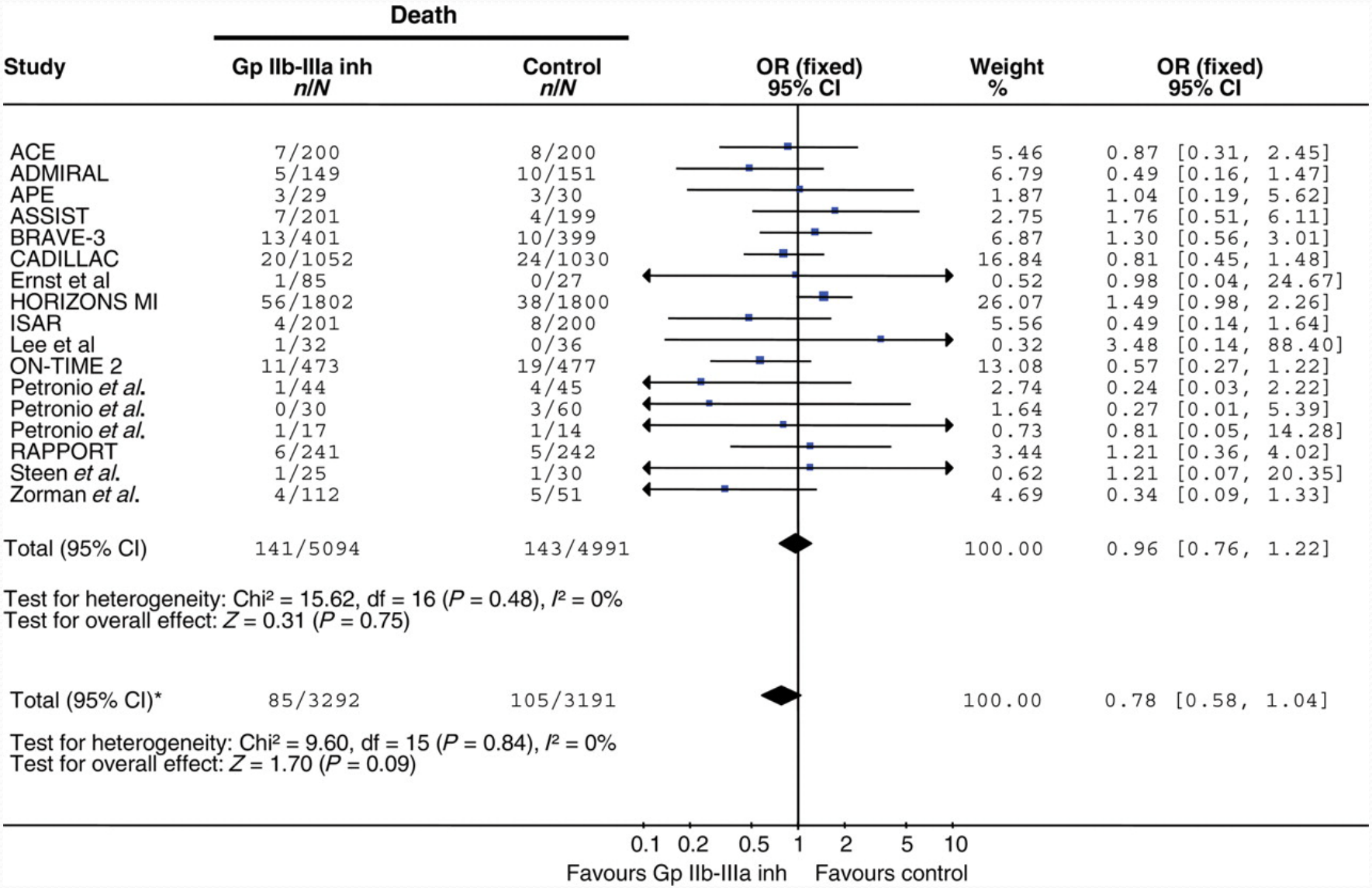
	COR	LOE	References	Relevant Caveats/Comments
Oral antiplatelet agents				
Aspirin	I	B	301–304,560–563	N/A
$P2Y_{12}$ inhibitors	I	A	564–568	• A loading dose of a $P2Y_{12}$ inhibitor should be given to patients undergoing PCI with stenting.
• Clopidogrel	I	B	564–566	• 600-mg loading dose now recommended.
• Prasugrel	I	B	567	• Contraindicated in patients with prior TIA/CVA: ***Class III: Harm; LOE: B.*** • Generally not recommended in patients >75 y of age (Section 5.7.2). • Consideration of using a lower maintenance dose in patients weighing <60 kg suggested by FDA (Section 5.7.2).
• Ticagrelor	I	B	568	• Issues of patient compliance may be especially important.
GP IIb/IIIa inhibitors (abciximab, double-bolus eptifibatide, high-bolus dose tirofiban)				
• No clopidogrel pretreatment	STEMI: IIa	A	584–590	• UA/NSTEMI recommendation applies to those with high-risk features. • GPI use in STEMI may be most appropriate in those with large anterior MI and/or large thrombus burden. • IC abciximab administration in STEMI: ***Class IIb; LOE: B.*** • Precatheterization laboratory GPI administration in STEMI: ***Class III: No Benefit; LOE: B.*** • Recommendations apply to those not at high risk for bleeding complications.
	UA/NSTEMI: I	A	613–618	
	SIHD: IIa	B	619–621	
• Clopidogrel pretreatment	STEMI: IIa	C	584–590	
	UA/NSTEMI: IIa	B	616,619	
	SIHD: IIb	B	619,622–624	
Antithrombin agents				
UFH	I	C	N/A	• Dosing based on whether or not GPI was administered.
Bivalirudin	I	B	625,637–645	• Lower bleeding rates associated with bivalirudin are mitigated when used concomitantly with a GPI.
Enoxaparin	IIb	B	646–650	• Recommendations apply to administration of IV enoxaparin at the time of PCI for those who have not received prior antithrombin therapy or who have received "upstream" SC enoxaparin therapy for UA/NSTEMI. • An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients who have received <2 therapeutic SC doses (eg, 1 mg/kg) or received the last SC enoxaparin dose 8 to 12 h before PCI: ***Class I; LOE: B.*** • Patients treated with SC enoxaparin within 12 h of PCI should not receive additional treatment with UFH during PCI ("stacking"): ***Class III: Harm; LOE: B.***
Anti-Xa inhibitors				
Fondaparinux	III: Harm	C	651,652	• PCI should not be performed with fondaparinux as the sole antithrombin agent in patients treated with upstream fondaparinux. An additional anticoagulant with anti-IIa activity should be administered.

ESC Guidelines for the Imanagement of STEMI (2012)

Table 12 Periprocedural antithrombotic medication in primary percutaneous coronary intervention

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B	133, 134
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A	135, 136
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B	109
• Ticagrelor.	I	B	110
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C	-
GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.	IIa	C	-
Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.	IIb	B	137–141
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B	127, 128, 137, 142
Options for GP IIb/IIIa inhibitors are (with LoE for each agent):			
• Abciximab		A	137
• Eptifibatide (with double bolus)		B	138, 139
• Tirofiban (with a high bolus dose)		B	140, 141
Anticoagulants			
An injectable anticoagulant must be used in primary PCI.	I	C	-
Bivalirudin (with use of GP IIb/IIIa blocker restricted to bailout) is recommended over unfractionated heparin and a GP IIb/IIIa blocker.	I	B	124
Enoxaparin (with or without routine GP IIb/IIIa blocker) may be preferred over unfractionated heparin.	IIb	B	122
Unfractionated heparin with or without routine GP IIb/IIIa blocker must be used in patients not receiving bivalirudin or enoxaparin.	I	C	I
Fondaparinux is not recommended for primary PCI.	III	B	118
The use of fibrinolysis before planned primary PCI is not recommended.	III	A	127, 143

Glycoprotein IIb-IIIa inhibitors and mortality benefits at 30 day follow-up,



De Luca G et al. Eur Heart J 2009;30:2705-2713

Are IIb/IIIa inhibitors still relevant in the era of the new P2Y12 blockers

Pharmacokinetics

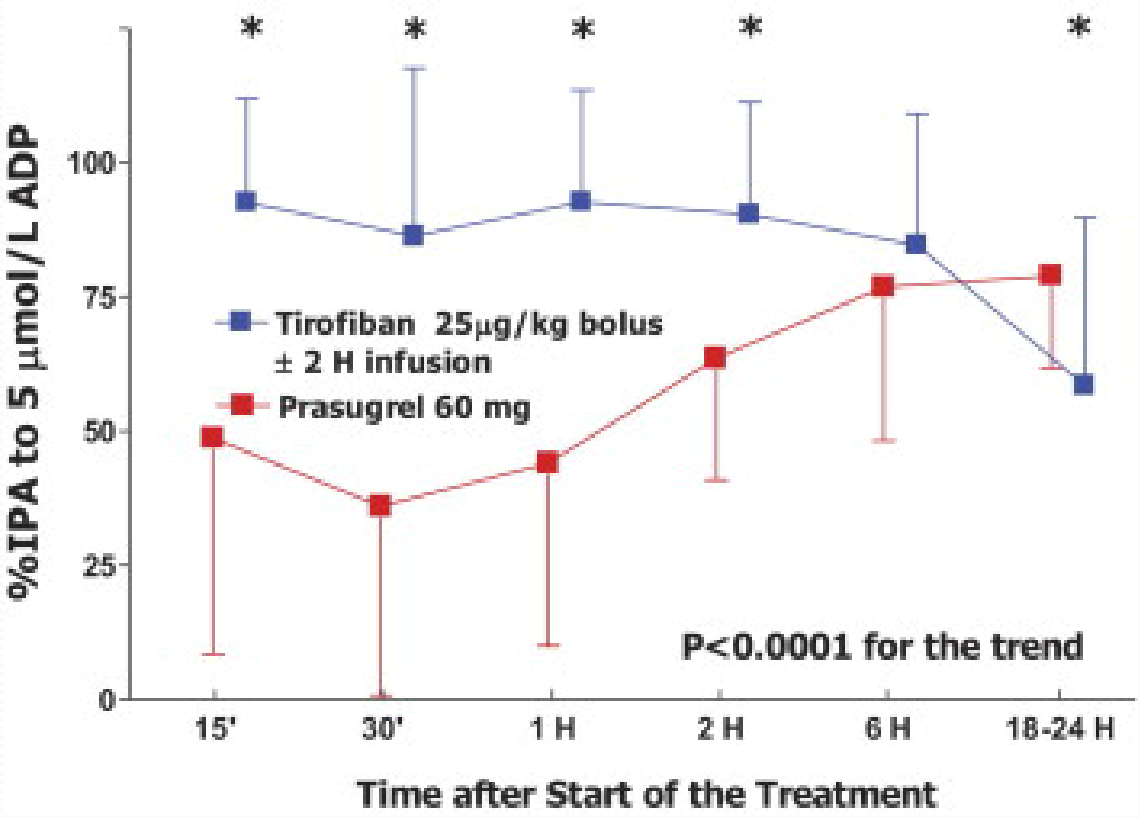
Maximal inhibition of platelet aggregation :

- Clopidogrel 600mg: 4-6 hours
- Prasugrel 60mg: 2-6 hours
- Ticagrelor 180mg: 2-4 hours
- IIb/IIIa Inhibitors: 10-20min

Li et al, Platelets 2009, Teng et al, Eur J Clin Pharmacol. 2010, Steinhubl et al, Circulation 2001

Prasugrel Versus Tirofiban Bolus in STEMI

The FABOLUS PRO trial

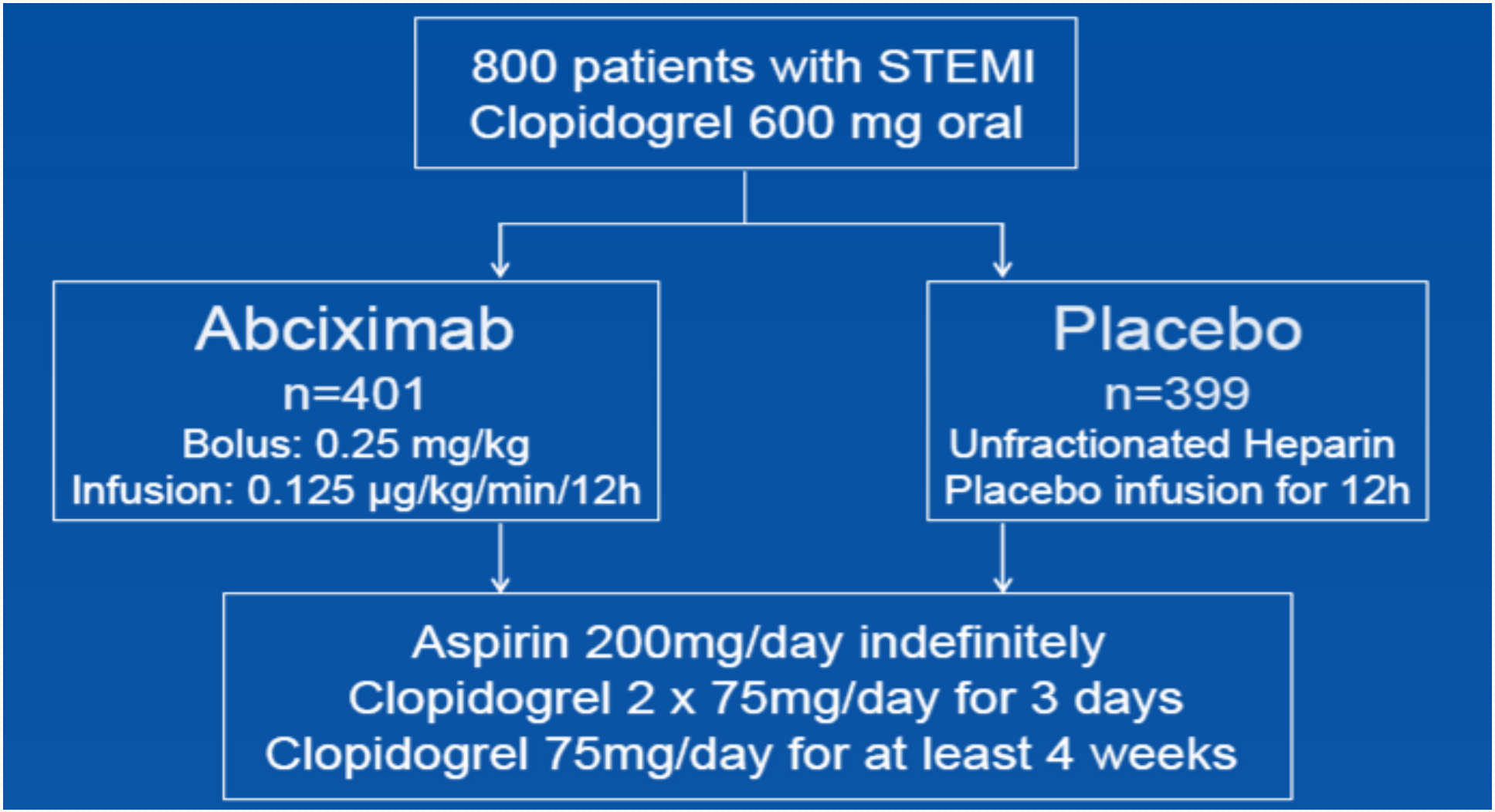


JACC Cardiovasc Interv. 2012 Mar;5(3):268-77

GP IIb/IIIa Inhibitors after clopidogrel loading- Trials after 2005

- BRAVE-3
- On-TIME 2
- Horizons-AMI
- ASSIST

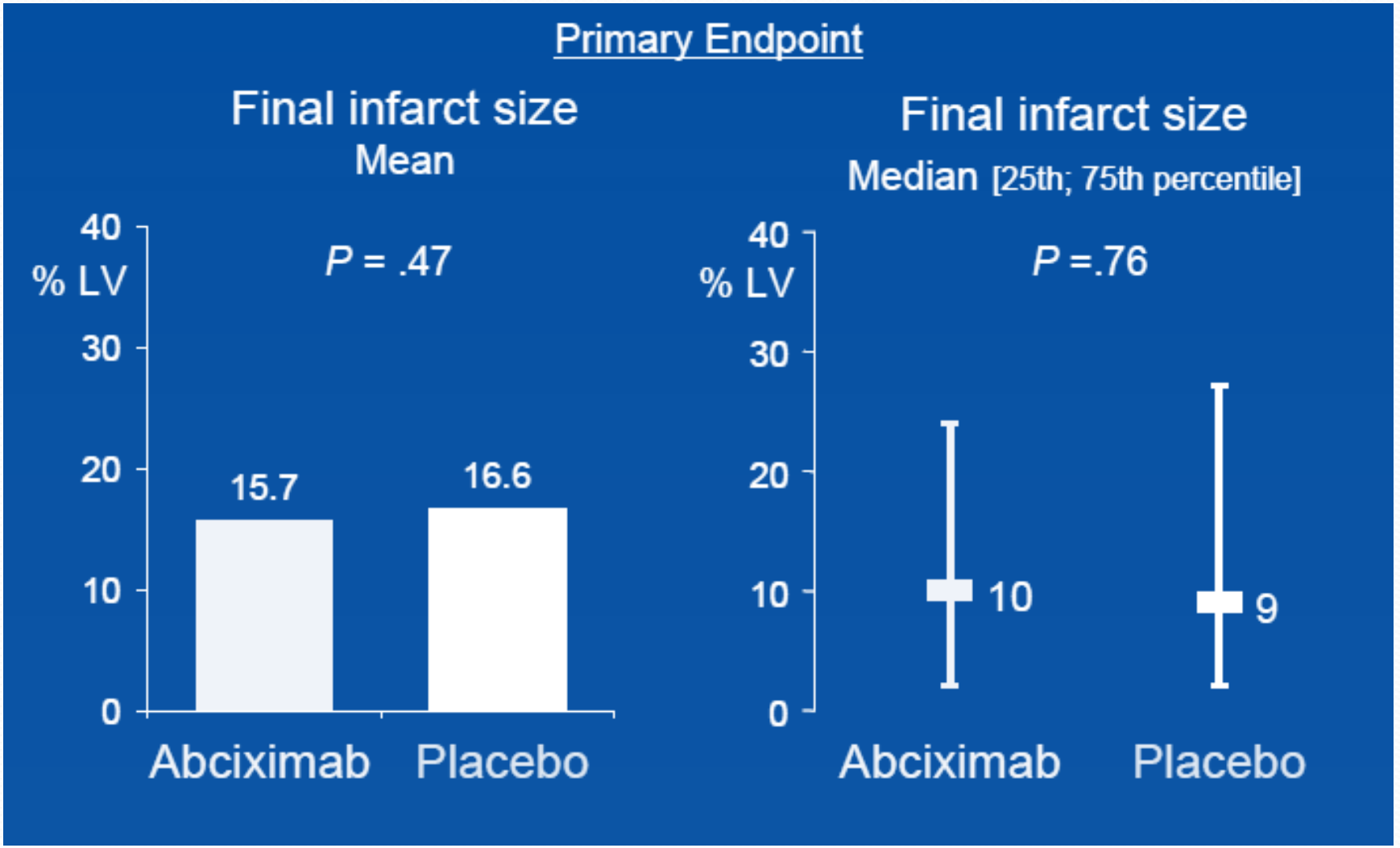
IBRAVE-3 trial



Primary Endpoint: infarct size assessed by SPECT

Mehilli J et al. Circulation 2009;119:1933-1940

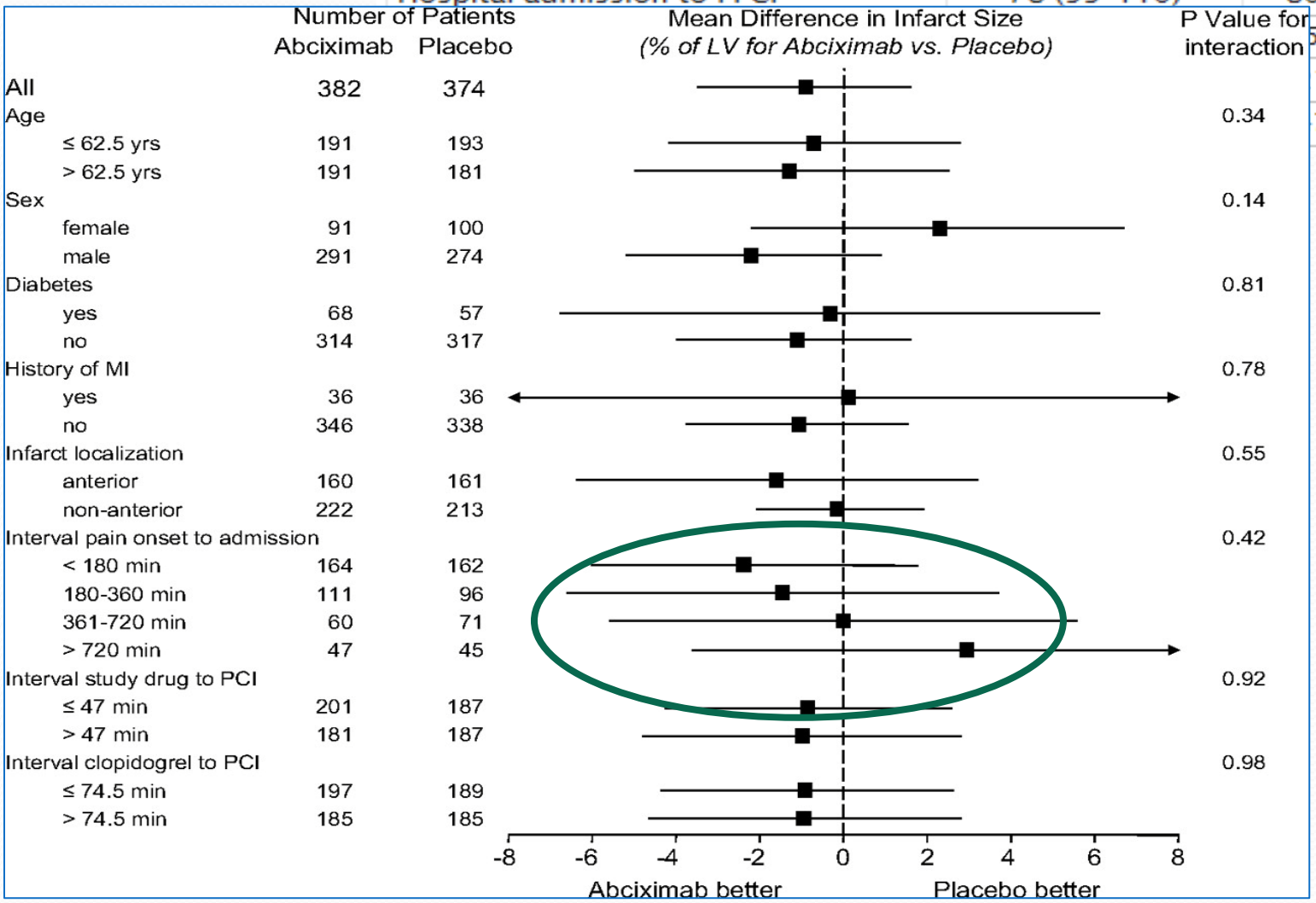
BRAVE-3 trial



Mehilli J et al. Circulation 2009;119:1933-1940

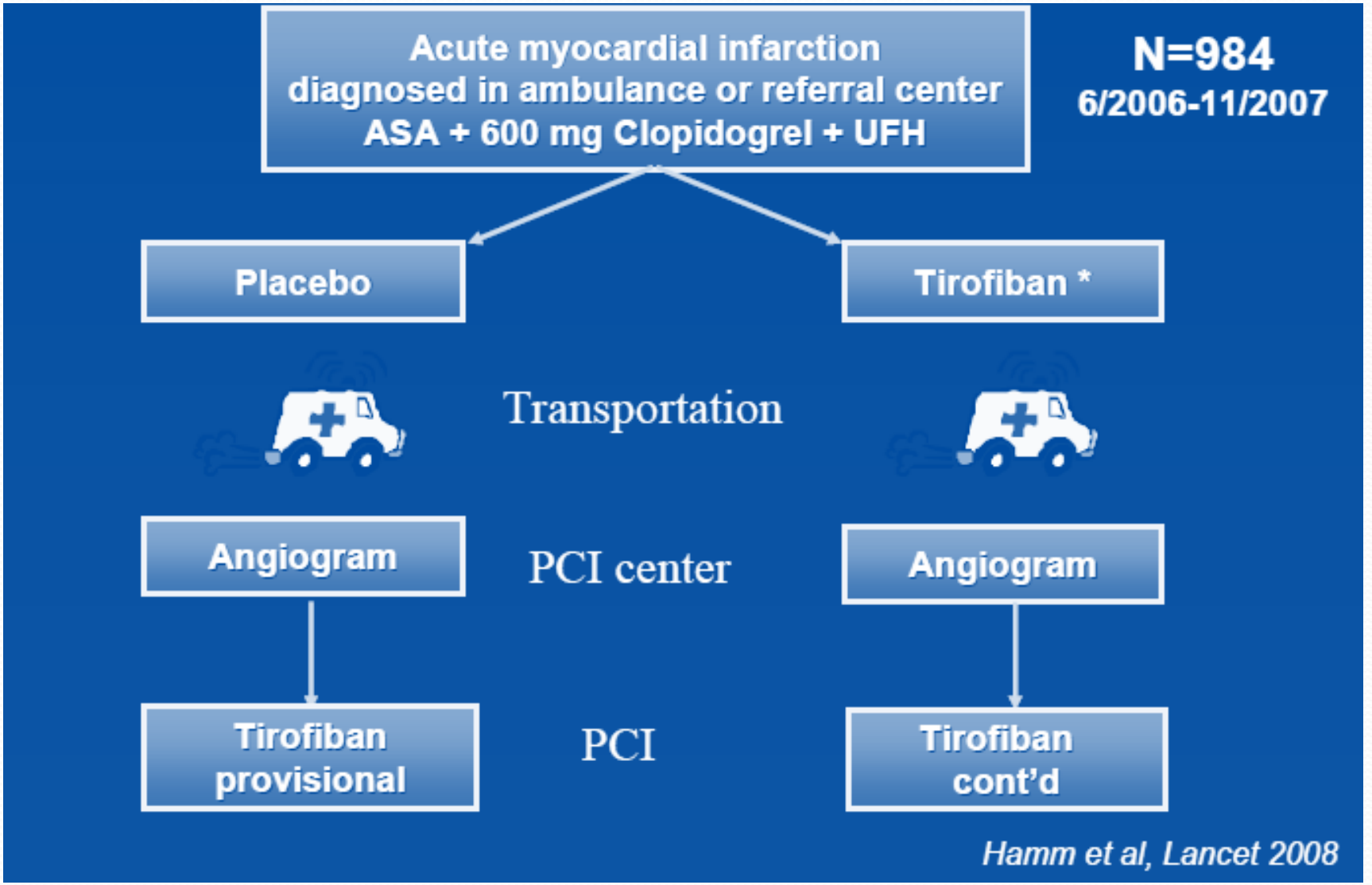
BRAVE-3 Treatment times

Time Intervals	Median (Interquartile Range), min		
	Abciximab (n=401)	Placebo (n=399)	*P*
Symptom onset to hospital admission	210 (110–420)	216 (110–468)	0.68
Symptom onset to study drug	255 (140–465)	260 (135–515)	0.77
Symptom onset to PPCI	302 (190–540)	315 (189–585)	0.67
Hospital admission to PPCI	78 (59–110)	80 (58–110)	0.77
		5 (53–105)	0.77
		1 (12–38)	0.65
		7 (27–69)	0.54



Mehilli J et al. Circulation 2009;119:1933-1940

On-TIME 2: Study Design



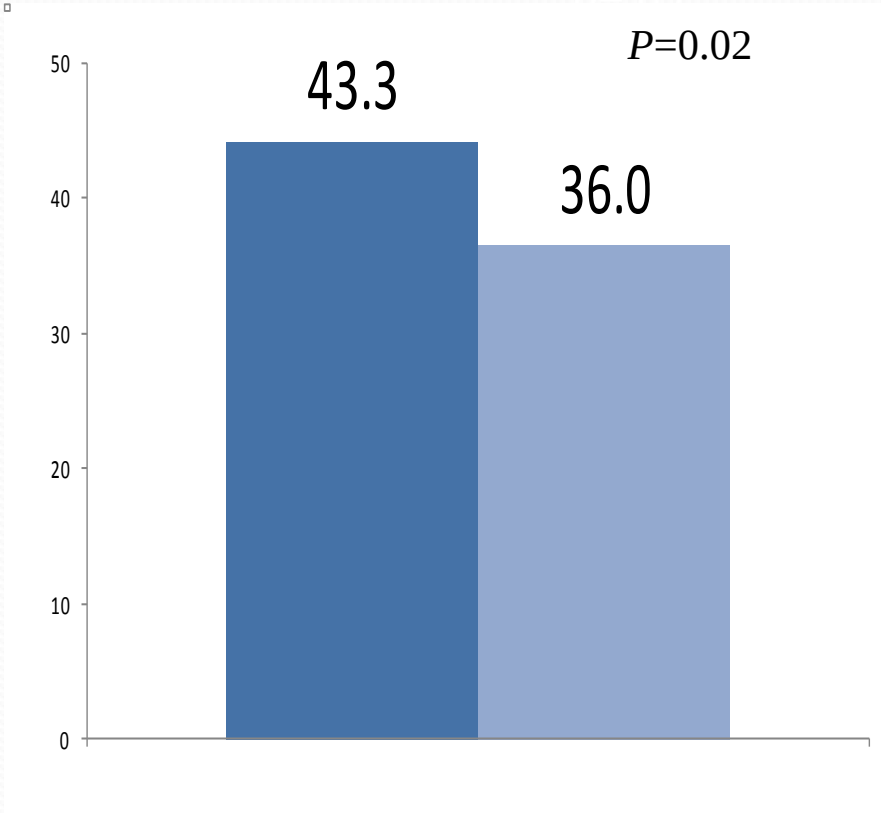
Primary endpoint – ST segment resulution

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

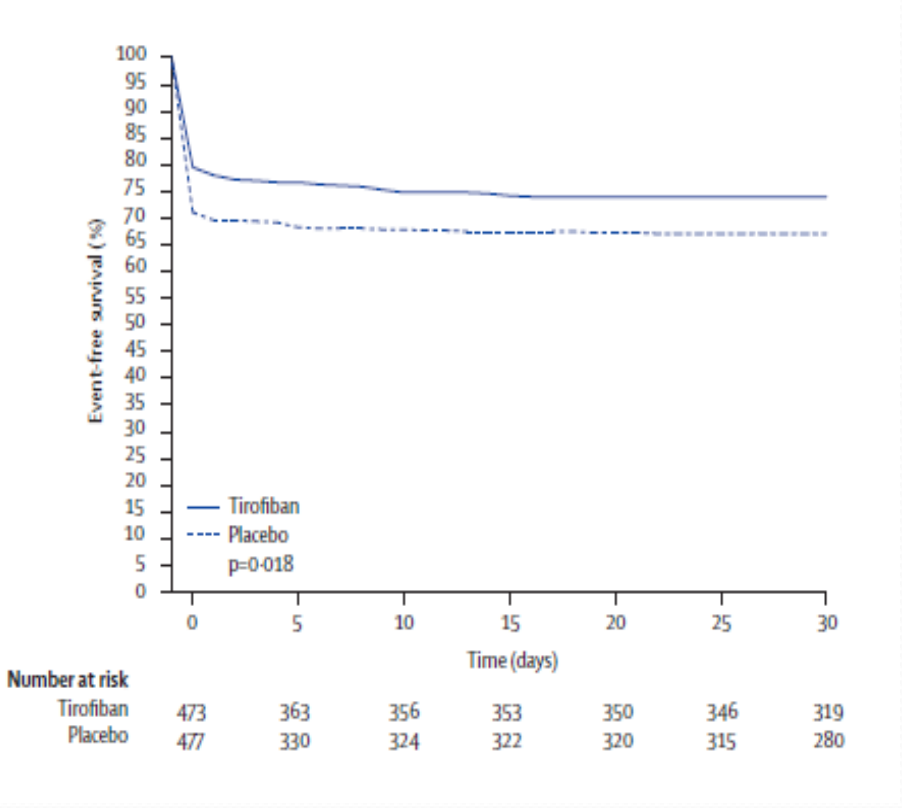
On-TIME 2: Outcomes

Primary outcome

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



Clinical Outcomes at 30 Days

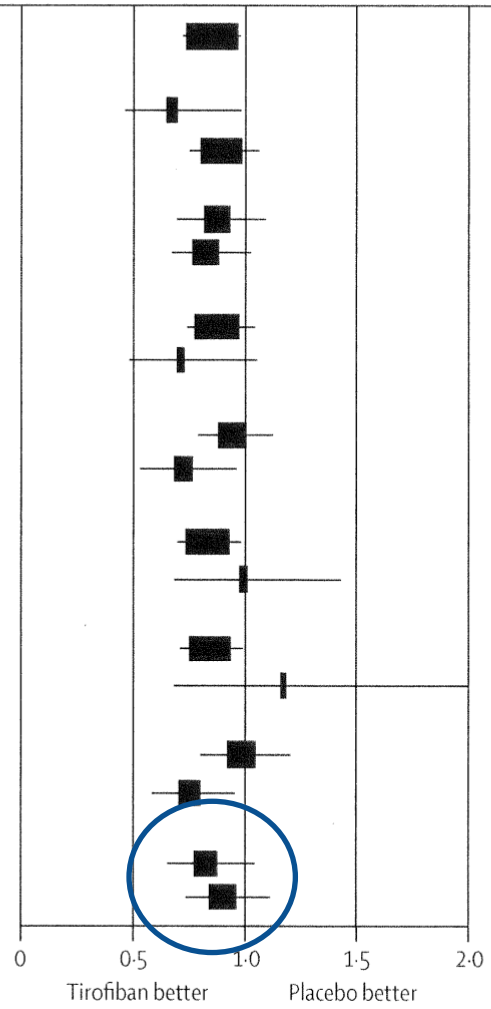


Median time from symptom onset to admission – 75 minutes

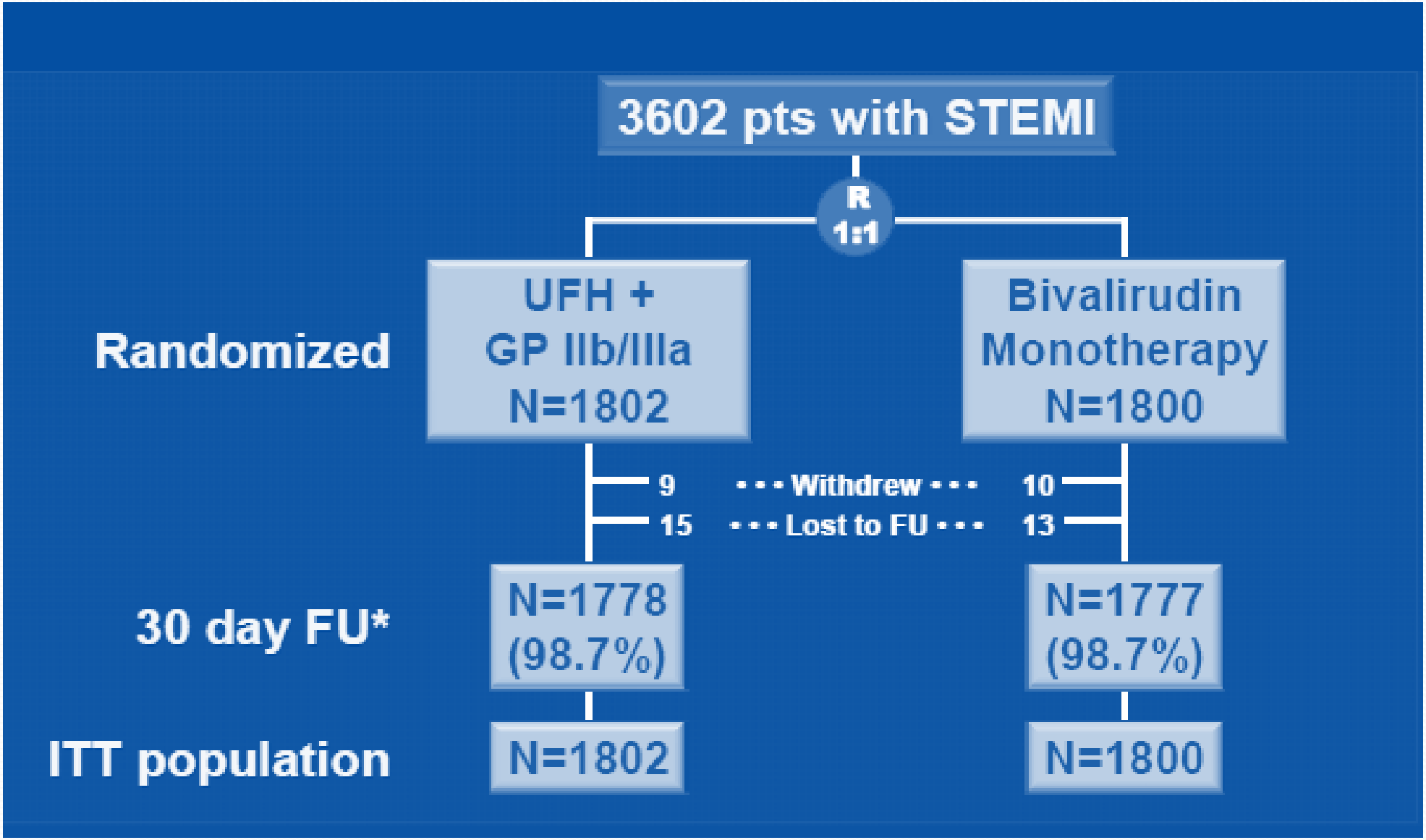
van 't Hof AWJ, et al. *Lancet* 2008;16;372(9638):537-46

On-TIME 2: risk ratios for the primary endpoint

	Tirofiban n/N	Placebo n/N	RR (95% CI)	p value
All patients	172/451	205/455	0·85 (0·72–0·99)	0·035
Sex				
Female	30/107	47/113	0·67 (0·46–0·98)	0·035
Male	142/344	158/342	0·89 (0·75–1·06)	0·194
Age (years)				
≤61·3	84/228	99/234	0·87 (0·69–1·09)	0·230
>61·3	88/223	106/221	0·82 (0·67–1·02)	0·071
Diabetes				
No	150/397	175/404	0·87 (0·74–1·03)	0·111
Yes	22/53	30/51	0·71 (0·48–1·05)	0·078
Location				
Anterior MI	98/168	106/170	0·94 (0·79–1·11)	0·450
Non-anterior MI	54/231	78/240	0·72 (0·53–0·97)	0·028
Killip >1				
No	145/396	173/392	0·83 (0·70–0·98)	0·032
Yes	25/49	29/56	0·99 (0·68–1·43)	0·938
TIMI flow grade before PCI				
0–2	135/329	168/343	0·84 (0·71–0·99)	0·039
3	23/91	18/83	1·17 (0·68–2·00)	0·578
Time start study drug to balloon inflation or angiography (min)				
≤55	98/218	104/226	0·98 (0·80–1·20)	0·822
>55	72/221	93/213	0·75 (0·58–0·95)	0·017
Time symptom onset to diagnosis (min)				
≤ 76	81/234	89/212	0·82 (0·65–1·04)	0·110
> 76	86/202	110/232	0·90 (0·73–1·11)	0·312



HORIZONS - AMI



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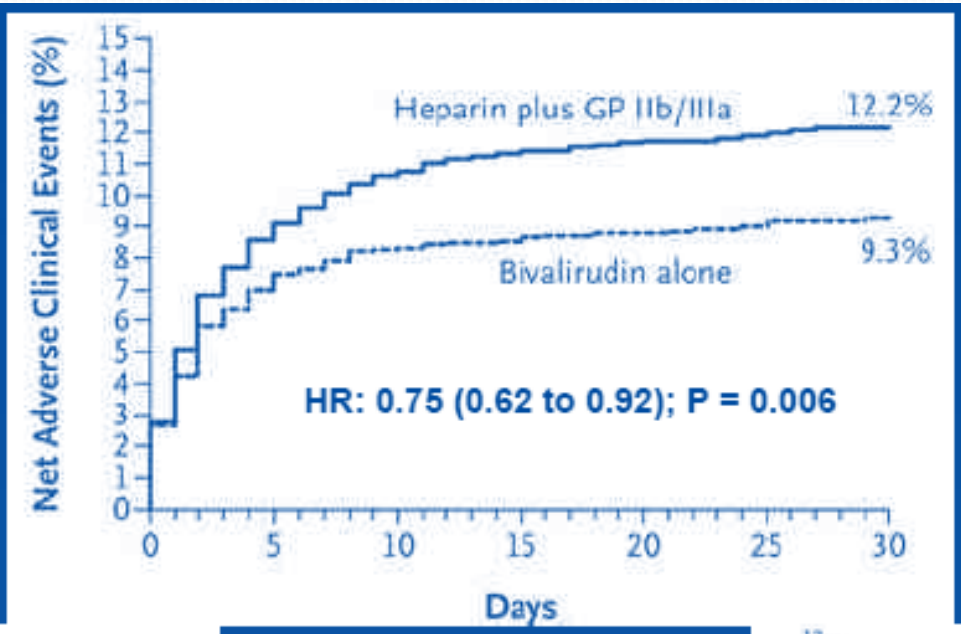

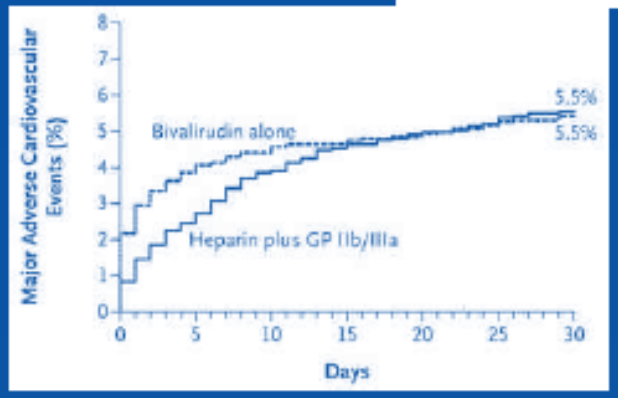

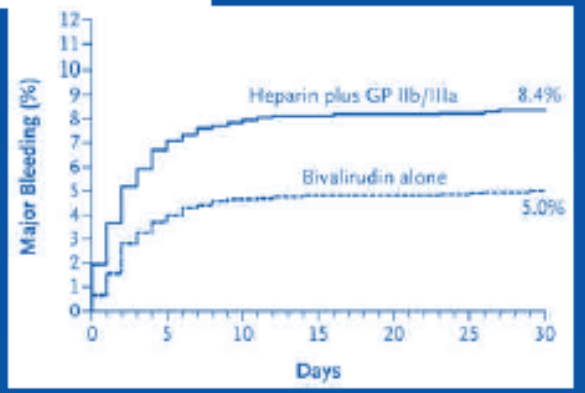

Stone et al, NEJM 2008

iHorizons-AMI

- Absiximab/Eptifibatide were given 12-18 hours post procedure
- Femoral approach

ISummary

- Are GP IIb/IIIa inhibitors still relevant – **YES**
- Greater benefit:

  Early comers < 2 hours

  High risk – Rec. event, DM, MVD, Large thrombus

  Radial approach
- Short term treatment – up to 4-6 hours

ıThank you!