Do GP IIb/IIIa inhibitors still make sense?

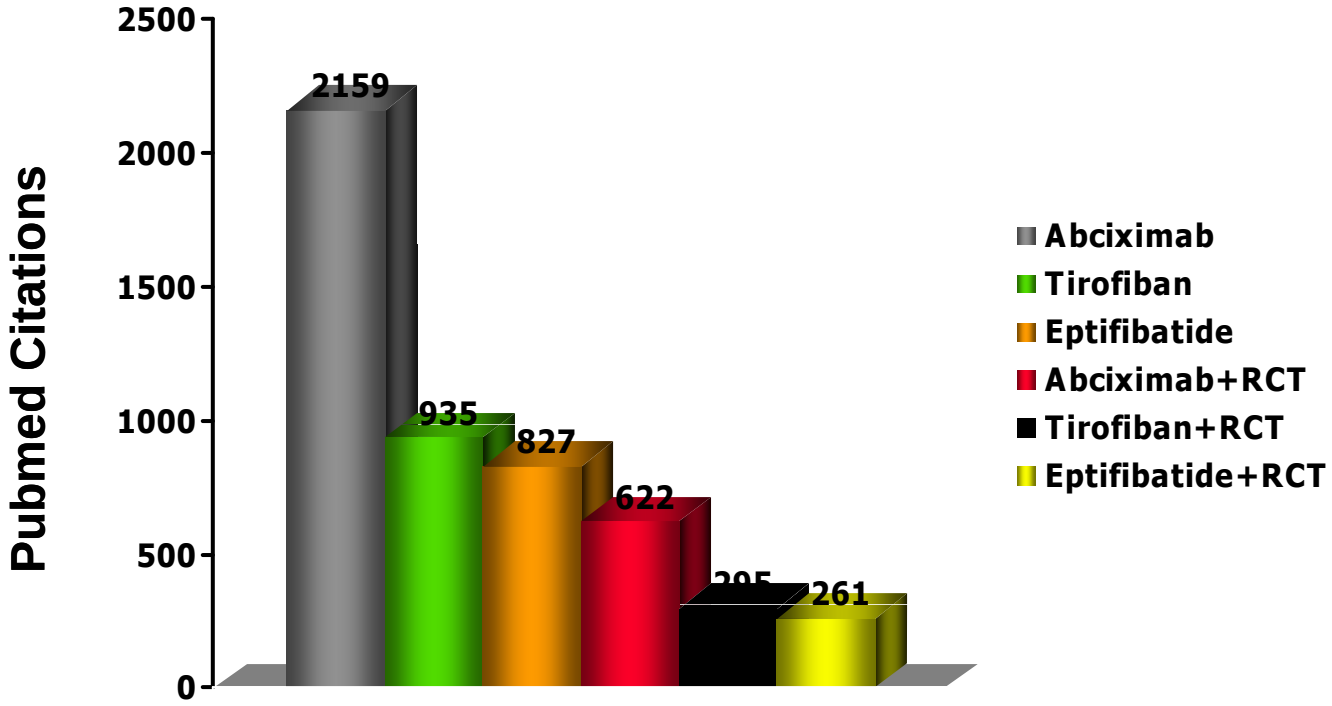
GB Danzi

Ospedale Maggiore Policlinico

Milano

GP IIb/IIIa Antagonists:
A "mature" class of drugs

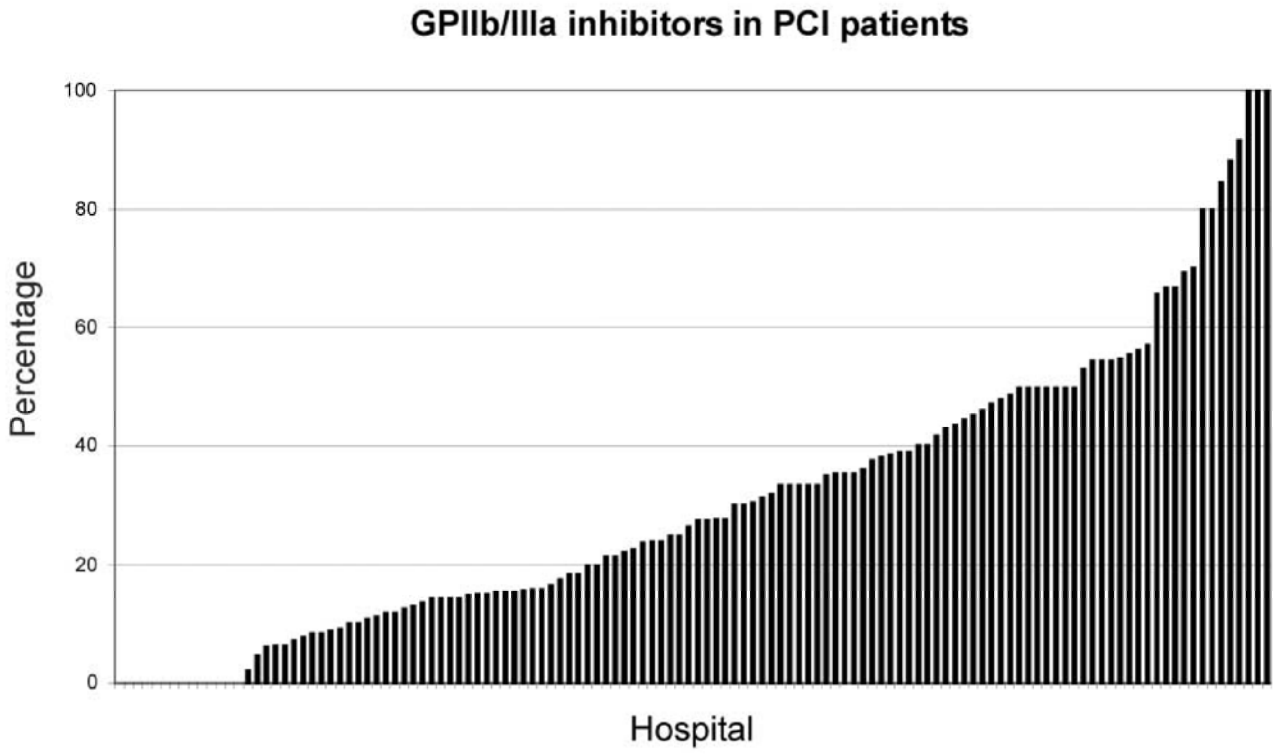
Marketed in the mid or late 90'



http://www.ncbi.nlm.nih.gov/pubmed/ accessed on 25th April 2010

Confusion in Coronary Reperfusion

Use of Gp IIb/IIIa inhibitors in Euro Heart Survey on coronary revascularisation



27% of all PCI

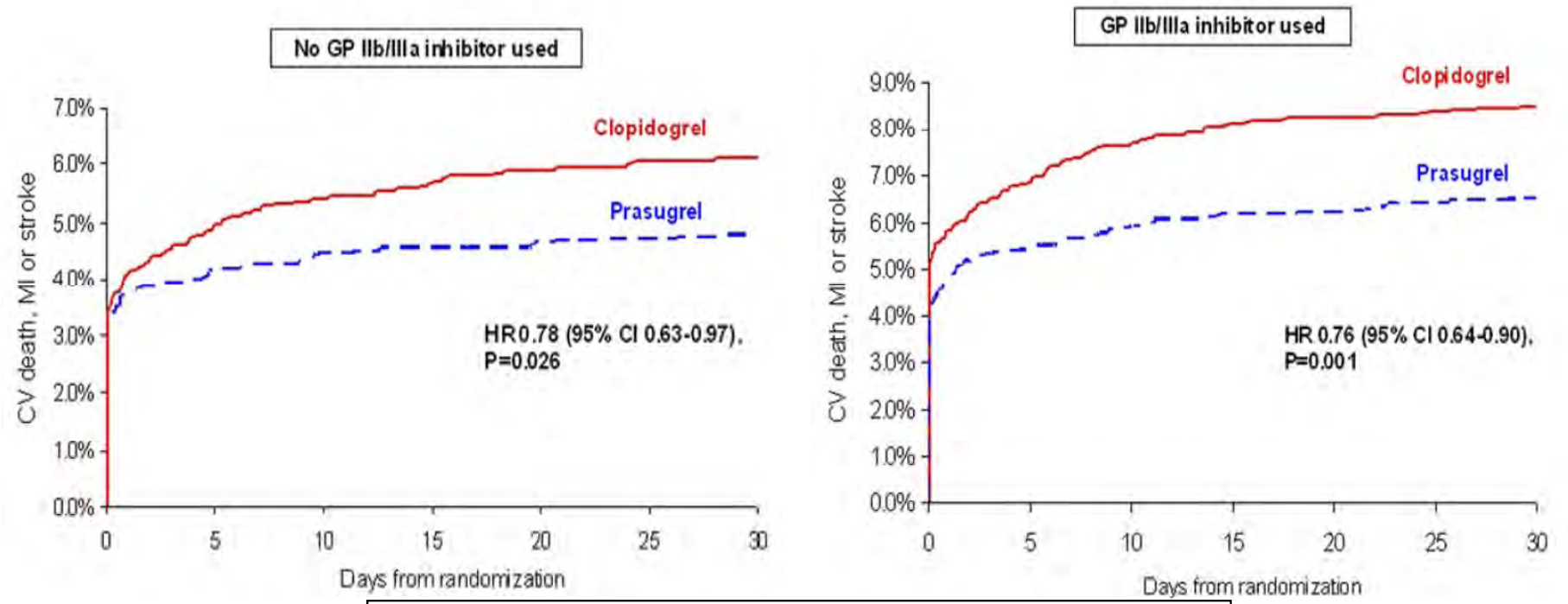
46% of PPCI

32% of PCI in NSTEMI

Lenzen MJ *European Heart J* 2005; 26:1169–1179

TRITON–TIMI 38 Trial

The Efficacy and Safety of Prasugrel With and Without a GPIs in Patients With ACS Undergoing PCI



GPI used in 55% of recruited patients

O'Donoghue M *J Am Coll Cardiol 2009;54:678–85*

PLATO: GP IIb/IIIa

Treated with GP IIb/IIIa during index hospitalization

Outcomes	Ticagrelor	Clopidogrel	HR (95% CI)	$P_{interaction}$
CV death, MI, stroke (n = 5062)	10.0	11.1	0.90 (0.76-1.07)	.41
Major bleeding (n = 5028)	10.1	10.1	0.99 (0.83-1.19)	.57

GP IIb/IIIa use: 26%
Bivalirudin use: 2%

Wallentin L, N Engl J Med. 2009;361:1045-1057.

Do GP IIb/IIIa inhibitors still make sense?

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

STEMI				
Antiplatelet therapy				
	ASA	I	B	55, 94
	Clopidogrel[c] (with 600 mg loading dose as soon as possible)	I	C	—
	Prasugrel[d]	I	B	246, 252
	Ticagrelor[d]	I	B	248, 253
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)			
	Abciximab	IIa	A	55, 94
	Eptifibatide	IIa	B	259, 260
	Tirofiban	IIb	B	55, 94
	Upstream GPIIb–IIIa antagonists	III	B	86
Anticoagulation				
	Bivalirudin (monotherapy)	I	B	255
	UFH	I	C	—
	Fondaparinux	III	B	256

European Heart Journal
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

Why ?

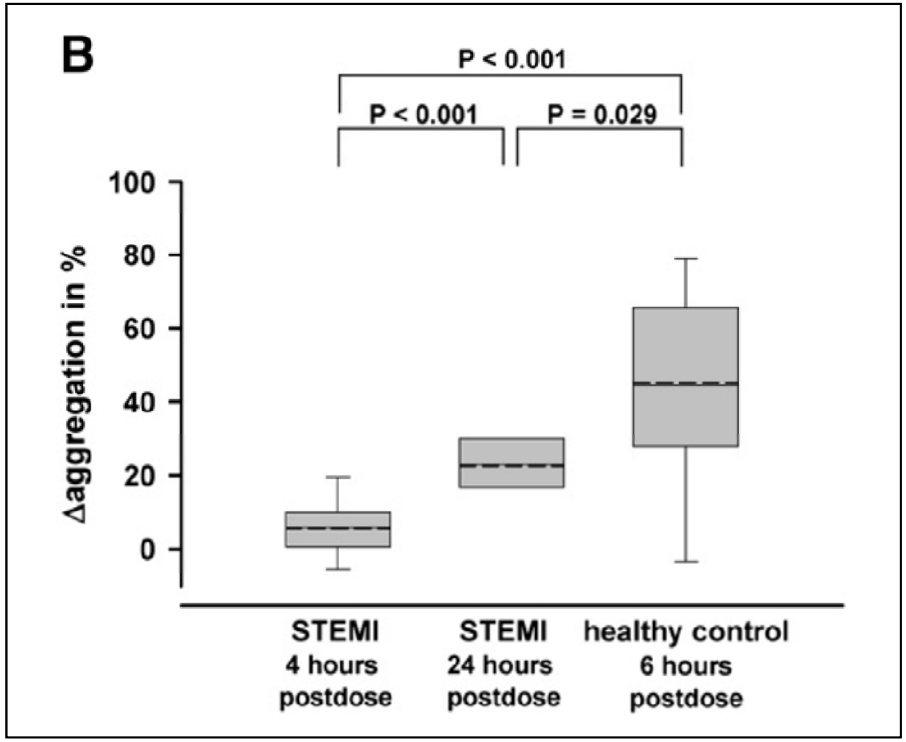
Bleeding Risk !

Do we still need GPI once dual Antiplatelet Tx is on board ??

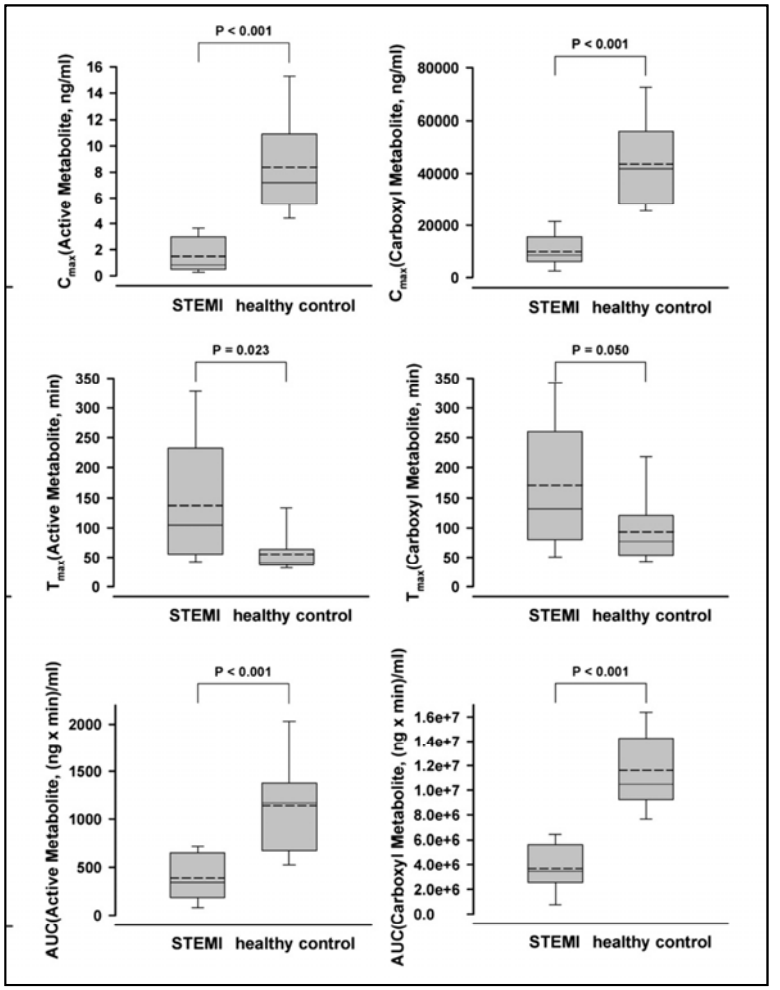
Do GP IIb/IIIa inhibitors still make sense?

Evidence supporting the upstream use of clopidogrel in pPCI

Impaired bioavailability of clopidogrel in STEMI



Active Metabolite **Inactive Metabolite**

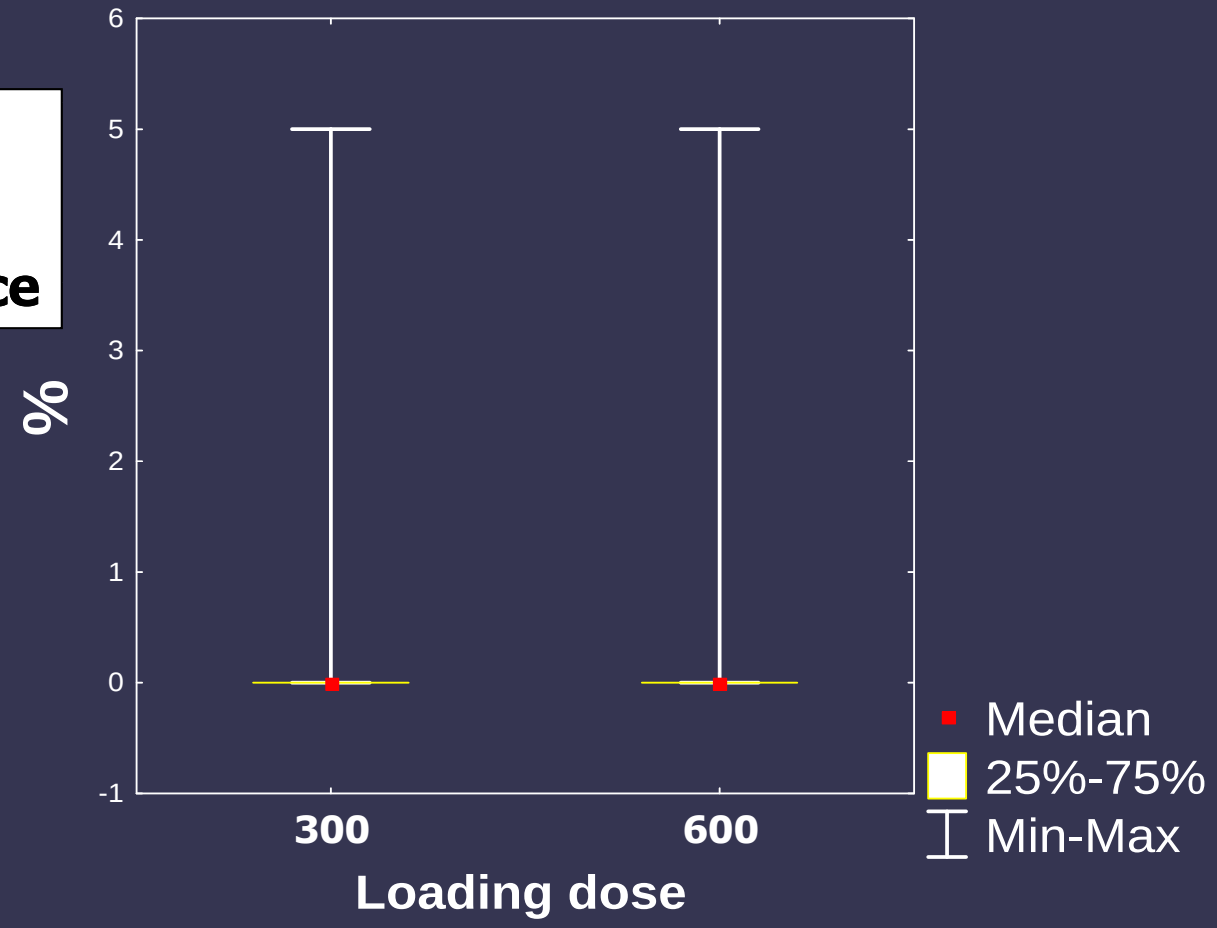


Heestermans A *Thrombosis Research* 2008; 122: 776

Surrogate evidence linking upstream clopidogrel to potential improved outcome

145 pts with STEMI
Loaded with mainly
600 mg in the ambulance

- **55 minutes**
- **IQR: 30-80’**
- **Range: 22-212’**

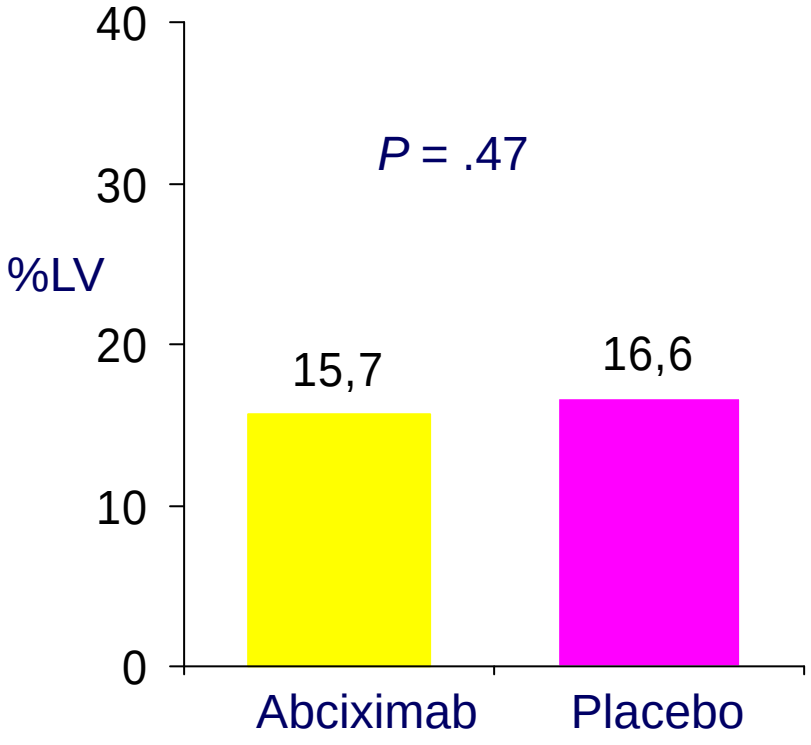


Courtesy of Marco Valgimigli

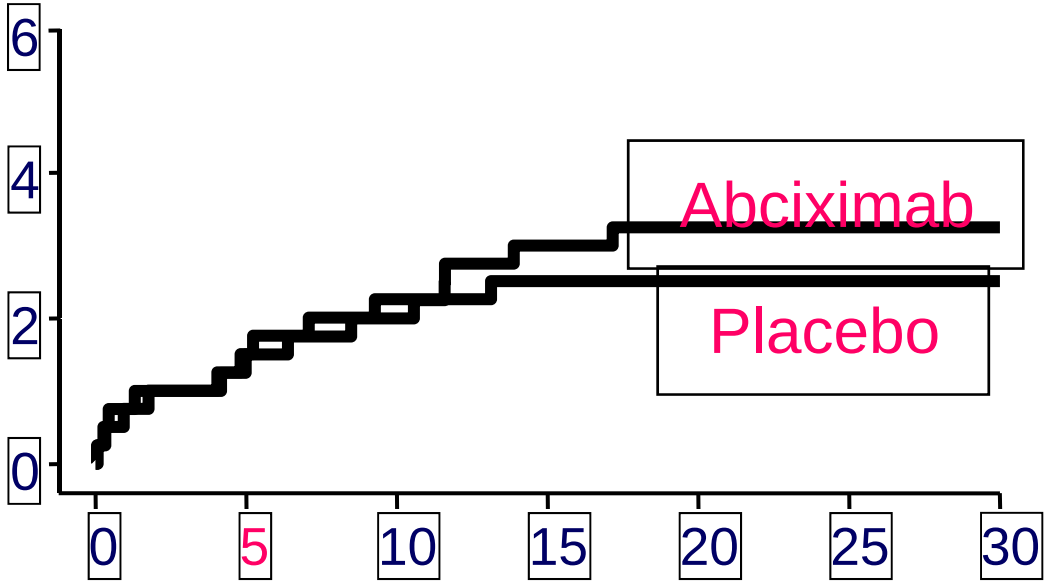
BRAVE-3: Abciximab+600 mg Clopidogrel

800 pts recruited within 24 hours from symptoms onset

Primary Endpoint
Final infarct size
Mean



Secondary Endpoint
Death at 30 days



Mehilli J *Circulation* 2009;119:1933

BRAVE-3: Abciximab+600 mg Clopidogrel

	Median (Interquartile Range), min	
Time Intervals*	Abciximab (n=401)	Placebo (n=399)
Symptom onset to hospital admission	210 (110–420)	216 (110–468)
Symptom onset to study drug	255 (140–465)	260 (135–515)
Symptom onset to PPCI	302 (190–540)	315 (189–585)
Hospital admission to PPCI	78 (59–110)	80 (58–110)
Clopidogrel loading to PPCI	73 (54–104)	75 (53–105)
Clopidogrel loading to study drug	23 (13–41)	21 (12–38)

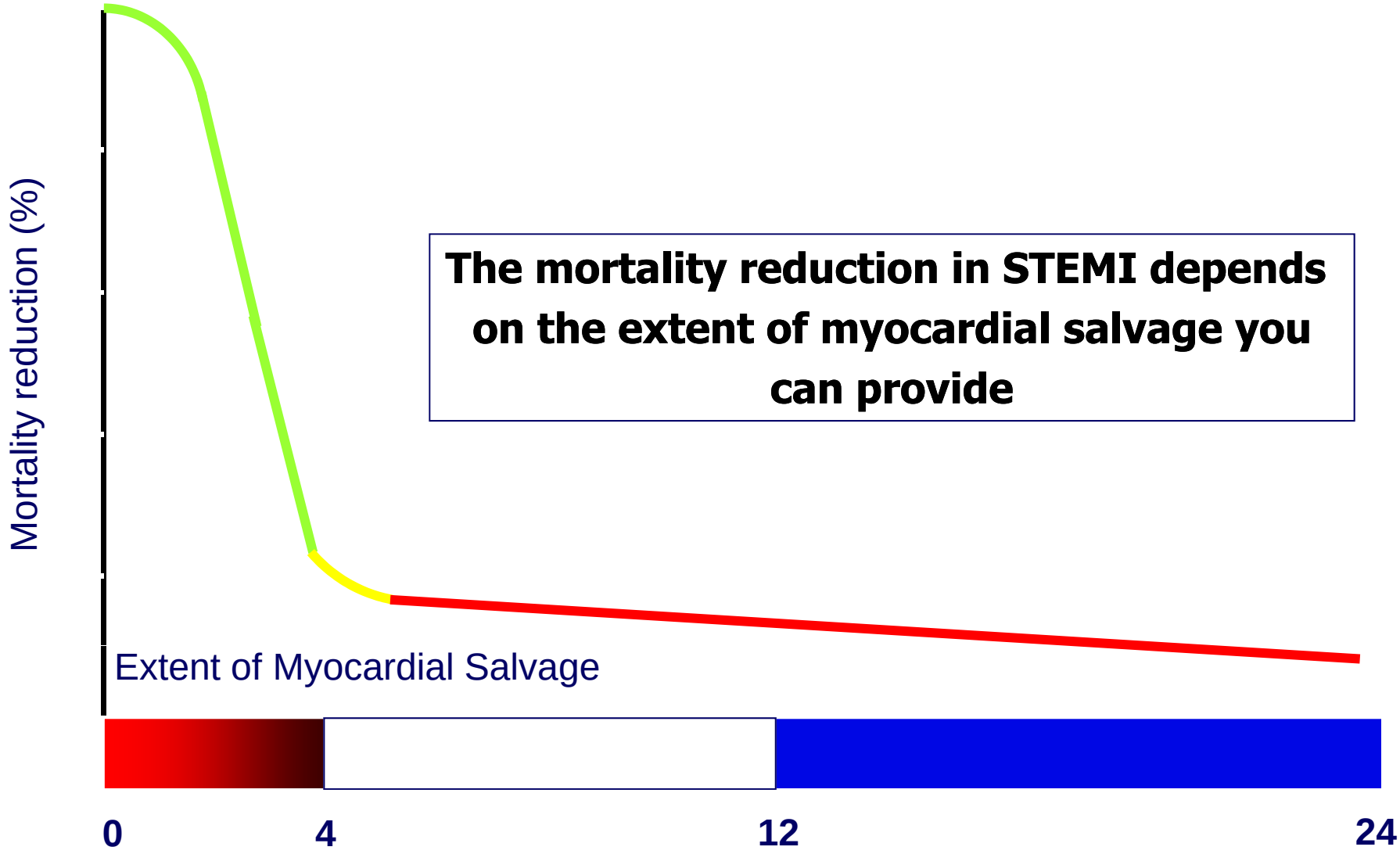
>50% pts received drug >4 hour delay

>50% pts received PCI >5 hour delay

Mehilli J *Circulation* 2009;119:1933

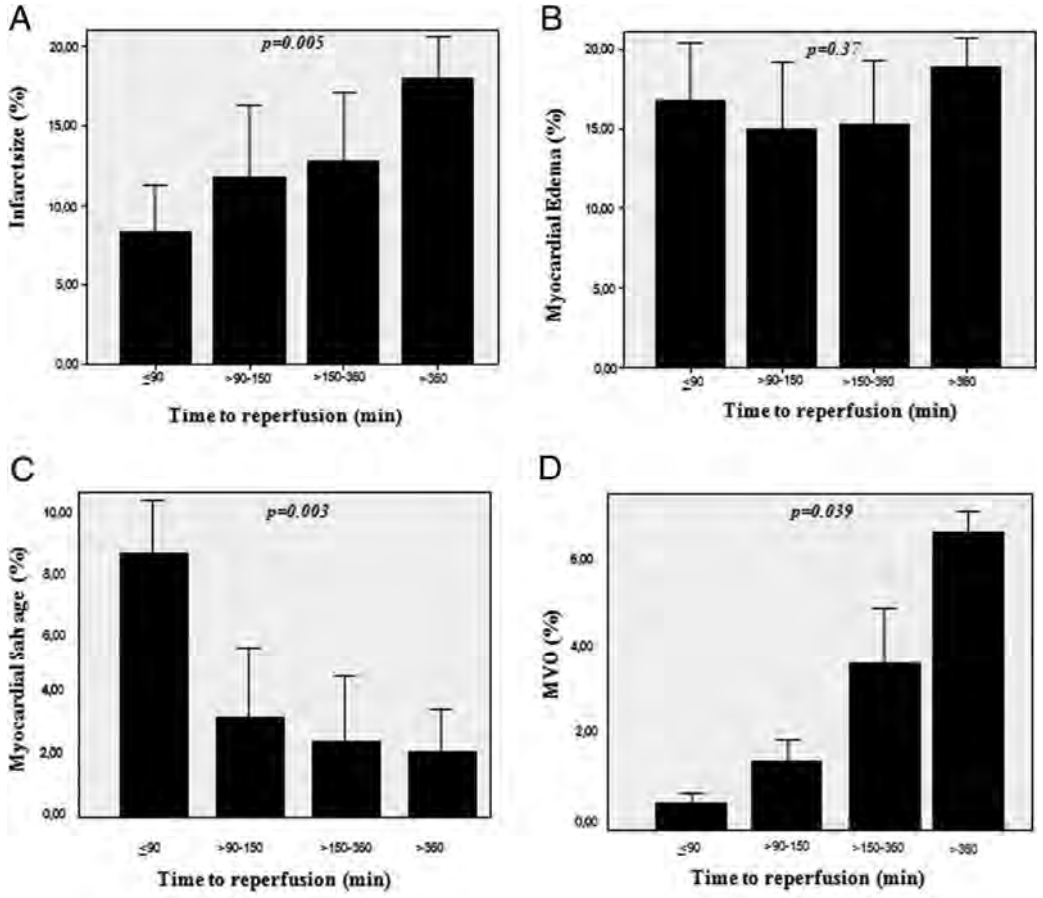
Time-to-Tx and myocardial salvage

Gersh B *JAMA* 2005; 293: 979



Myocardium at Risk – Infarct size

STEMI patients stratified by delay of treatment



1. Pts reperfused early (<90 min) have smaller IS and microvascular damage, and larger *salvaged myocardium*
2. Pts presented later (>360 min) have larger IS and MVO and very limited ,if any, *salvaged myocardium*
3. The presence and extent of salvaged myocardium decreased when reperfusion occurred > 90 min

Francone M, *J Am Coll Cardiol* 2009;54:2145

Do GP IIb/IIIa inhibitors still make sense?

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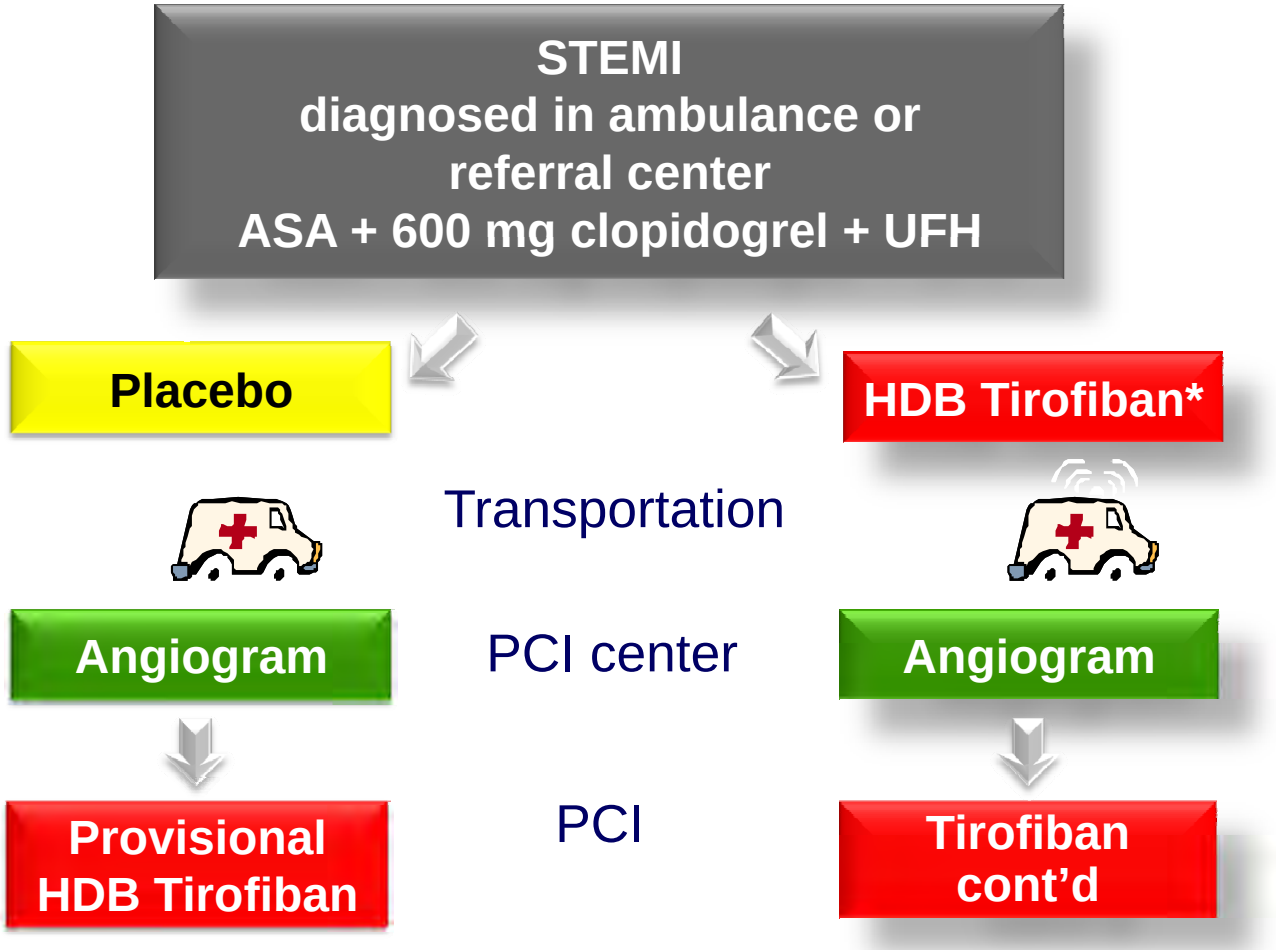
	Fondaparinux	III	B	256

European Heart Journal
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

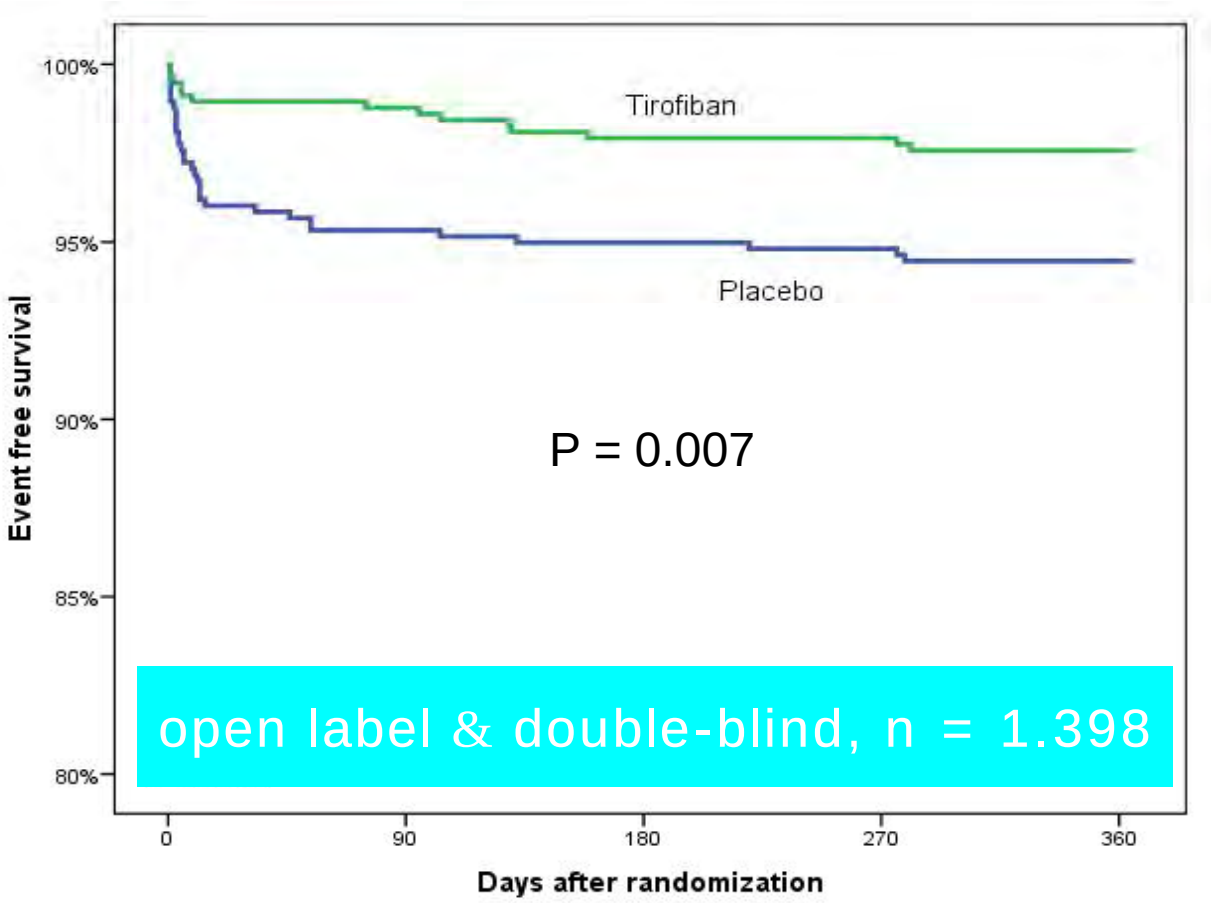
On-TIME 2: Study Design



van 't Hof AWJ, *Lancet* 2008 16;372

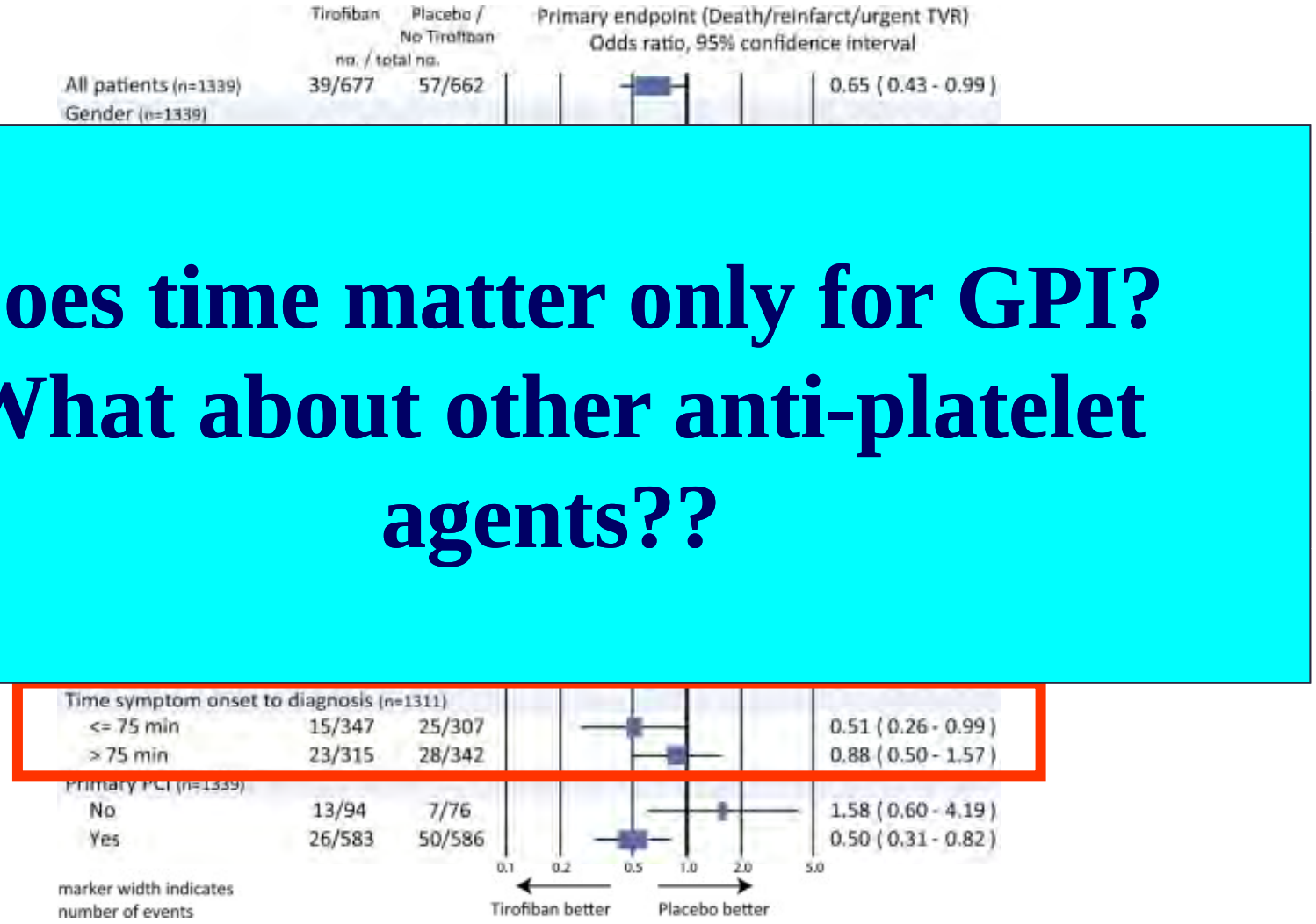
ON-TIME 2 Trial

1 Year Survival: Patients with Primary PCI



Ten Berg JM, *J Am Coll Cardiol* 2010;55:2446

ON-TIME 2 Trial: Subgroup analysis

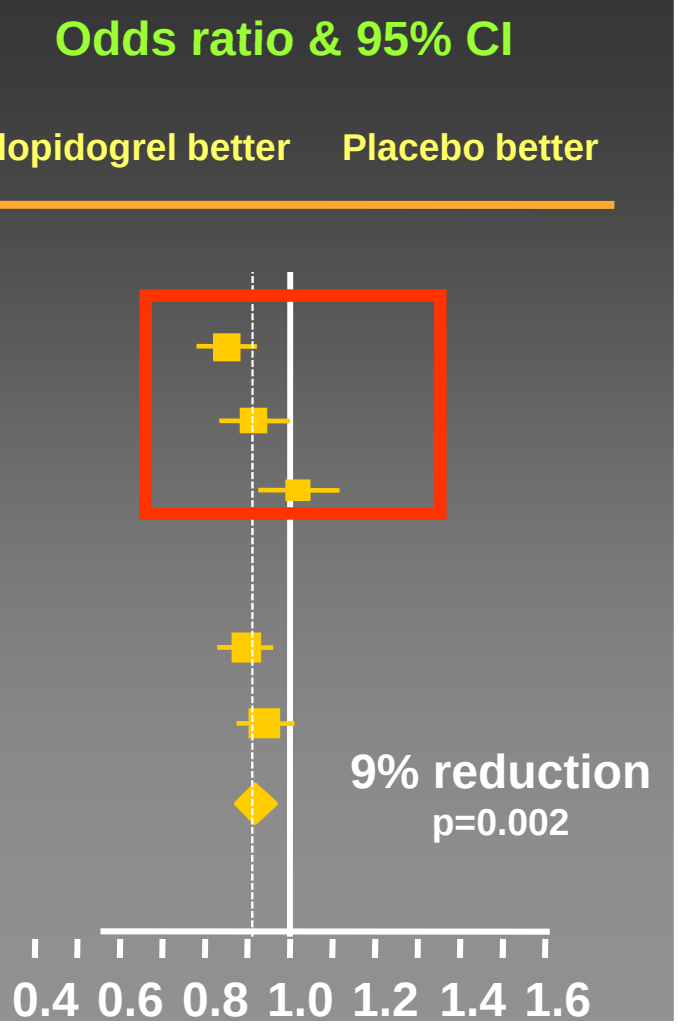


Does time matter only for GPI? What about other anti-platelet agents??

Ten Berg JM, *J Am Coll Cardiol* 2010;55:2446

Effects of Clopidogrel on Death, Re-MI or Stroke by Time Delay and Fibrinolytic Use

Baseline features	Clopidogrel (n=22,958)	Placebo (n=22,891)
Time delay (hours)		
0–6	776 (9.3%)	904 (10.9%)
7–12	672 (9.7%)	735 (10.7%)
13–24	666 (8.8%)	666 (8.7%)
Fibrinolytic used		
Yes	1005 (8.8%)	1123 (9.9%)
No	1120 (9.7%)	1188 (10.3%)
ALL	2125 (9.3%)	2311 (10.1%)



Chen ZM Oral presentation ACC 2005

Do GP IIb/IIIa inhibitors still make sense?

Guidelines on myocardial revascularization

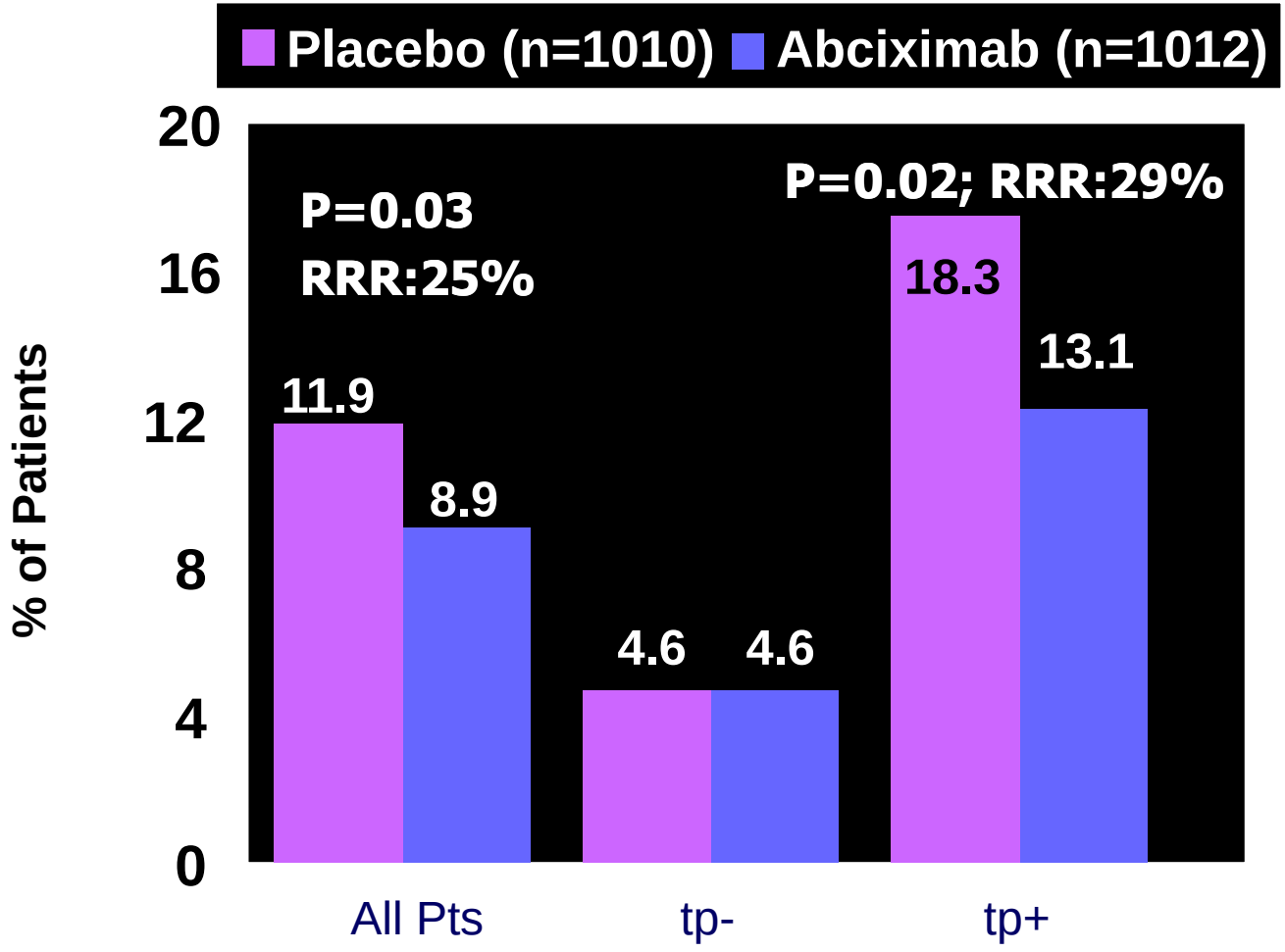
The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

		Class[a]	Level[b]	Ref.[c]
Elective PCI				
Antiplatelet therapy				
	ASA	I	B	55
	Clopidogrel	I	A	55
	Clopidogrel - pretreatment with 300 mg loading dose >6 h before PCI (or 600 mg >2 h before)	I	C	—
NSTE-ACS				
Antiplatelet therapy				
	ASA	I	C	—
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C	—
	Clopidogrel (for 9–12 months after PCI)	I	B	55
	Prasugrel[d]	IIa	B	246,247
	Ticagrelor[d]	I	B	248
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)			
	Abciximab (with DAPT)	I	B	249
	Tirofiban, Eptifibatide	IIa	B	55
	Upstream GPIIb–IIIa antagonists	III	B	65
Anticoagulation				
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C	—
	Bivalirudin (monotherapy)	I	B	251

ISAR-REACT-2

Primary Endpoint at 30 Days

Composite of Death, MI or Urgent TVR



Kastrati A, *JAMA* 2006;350:232-238.

12.2 Non-ST-segment elevation acute coronary syndrome

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

(a) Antiplatelet Therapy

GPIIb–IIIa inhibitors should be used in patients with high ischaemic risk undergoing PCI. The greatest benefit of GPIIb–IIIa inhibitors vs. placebo was demonstrated in earlier RCTs when ADP receptor blockers were not routinely used.[60] The usefulness of upstream eptifibatide, with or without clopidogrel on board, was not confirmed in EARLY-ACS. The lack of benefit was associated with a higher bleeding risk.[65] The selective 'downstream administration' of abciximab in the catheterization laboratory, in combination with a 600 mg clopidogrel loading dose, has been shown to be effective in troponin-positive NSTE-ACS patients[249] and might therefore be preferred over upstream use.

Wijns W, European Heart J doi:10.1093/eurheartj/ehq277

Characteristics of patients with NSTE-ACS at high ischemic risk

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

(1) recurrent resting pain
(2) dynamic ST-segment changes: ***ST- depression***
0.1 mV or transient (,30 min) ST- elevation 0.1 mV
(3) elevated Troponin-I, Troponin-T, or CK-MB levels
(4) haemodynamic instability within the observation period
(5) major arrhythmias (VT, VF)
(6) early post-infarction unstable angina
(7) diabetes mellitus

Silber S, *European Heart J* 2005;26:804

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

9. Special conditions
9.1 Diabetes

9.1.5 Antithrombotic pharmacotherapy

There is no indication that antithrombotic pharmacotherapy should differ between diabetic vs. non-diabetic patients undergoing elective revascularization. In ACS trials, there is no indication that the antithrombotic regimen should differ between diabetic and non-diabetic patients.[65,85,86] Although an interaction between diabetic status and efficacy of GPIIb–IIIa inhibitors was noted in earlier trials without concomitant use of thienopyridines, this was not confirmed in the more recent Early-ACS trial.[65] In the current context of the use of high-dose oral antiplatelet agents, diabetic patients do not benefit from the routine addition of GPIIb–IIIa inhibitors.

Wijns W, European Heart J doi:10.1093/eurheartj/ehq277

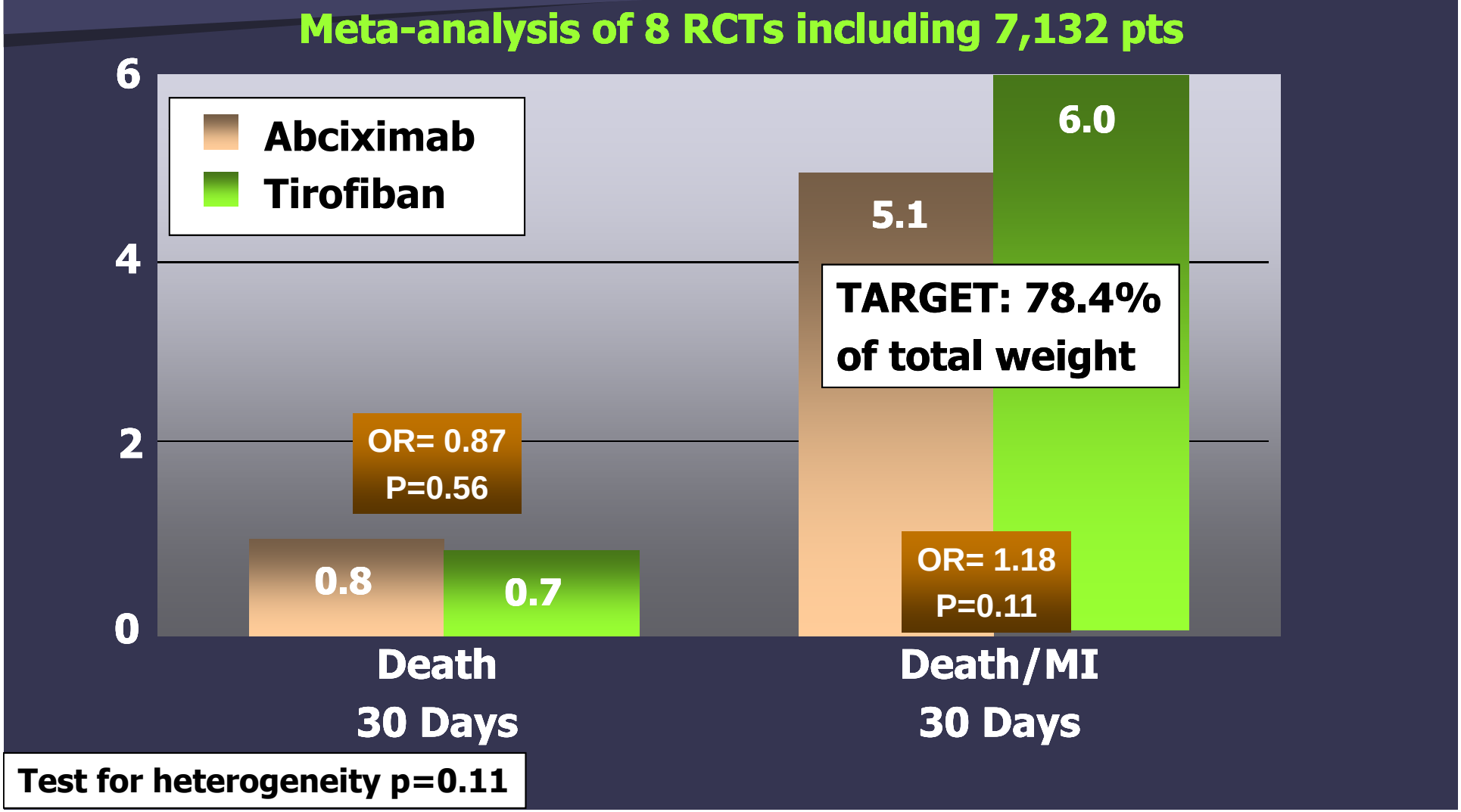
Patient population

31 studies involving
20,006 patients
(12,874 comparing tirofiban
versus heparin plus placebo or bivalirudin
and 7,132 versus abciximab)

Valgimigli M *European Heart J* 2009;31:35

Tirofiban vs Abciximab

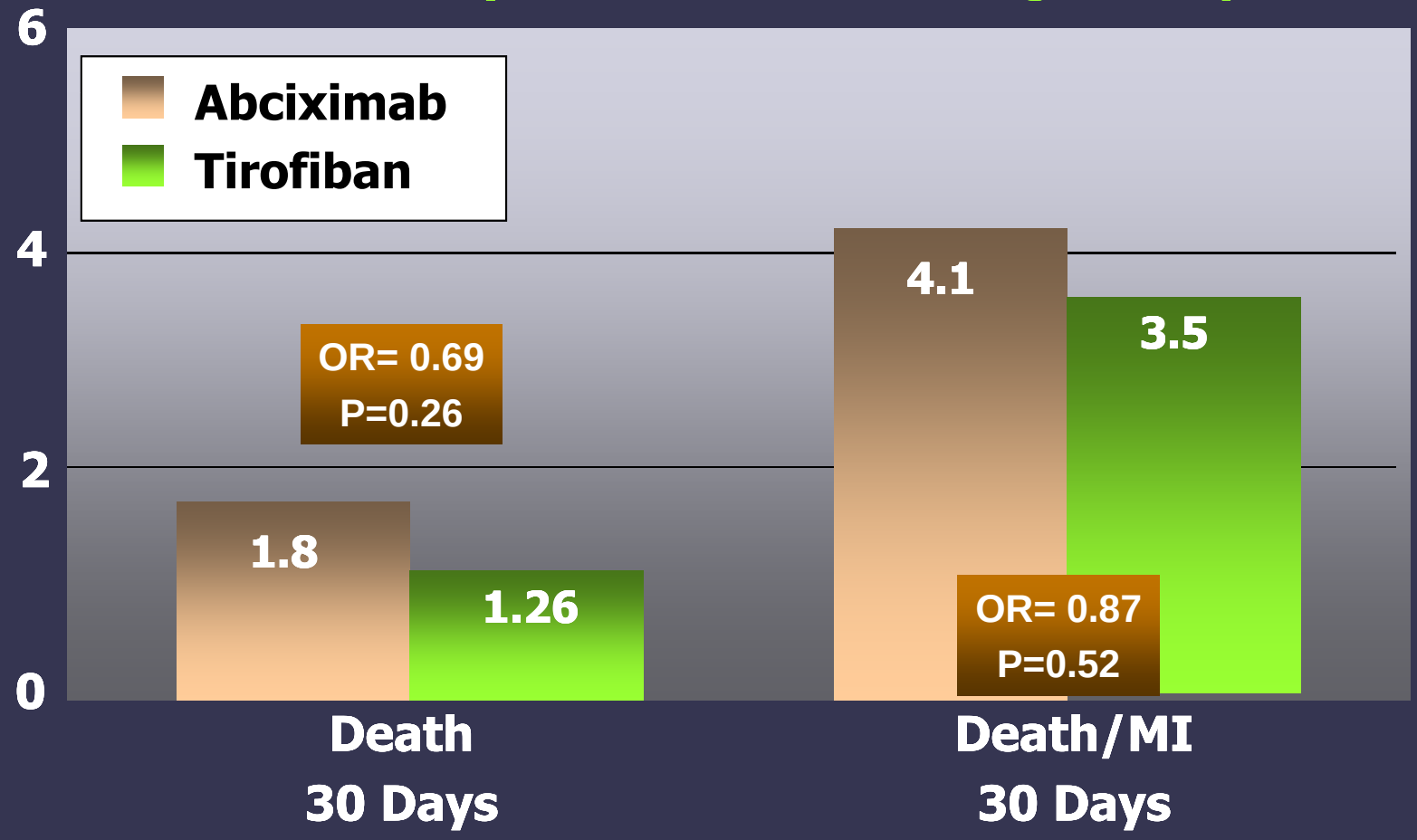
Tirofiban bolus given @ 10μ or 25 μ



Tirofiban vs Abciximab

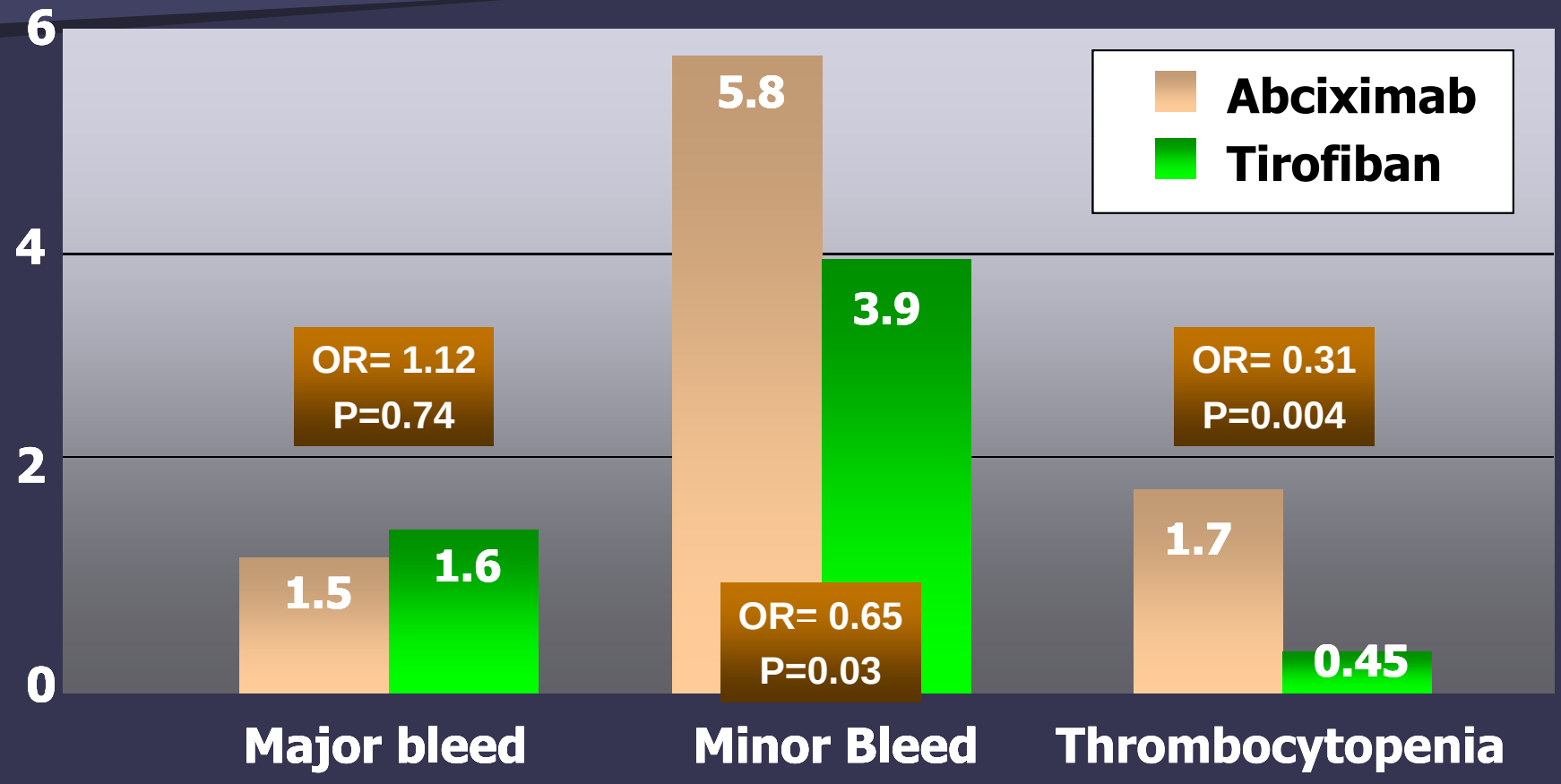
Tirofiban bolus given only @ 25 μ

Meta-analysis of 7 RCTs including 2,213 pts



Tirofiban vs Abciximab

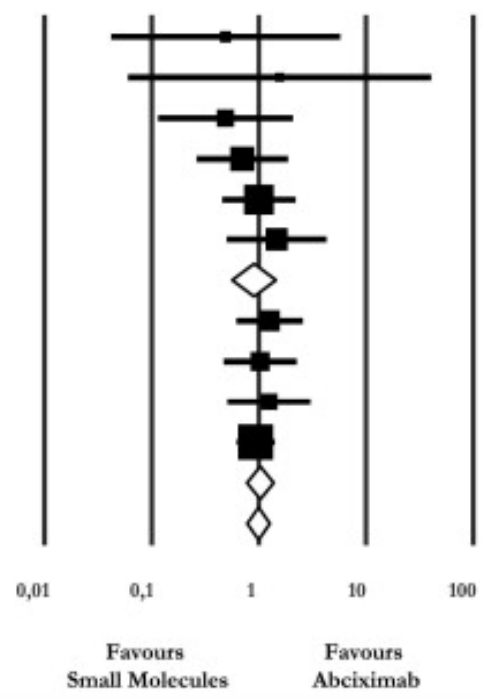
Tirofiban bolus given only @ 25 μ



Small molecules *Vs* Abciximab during PPCI

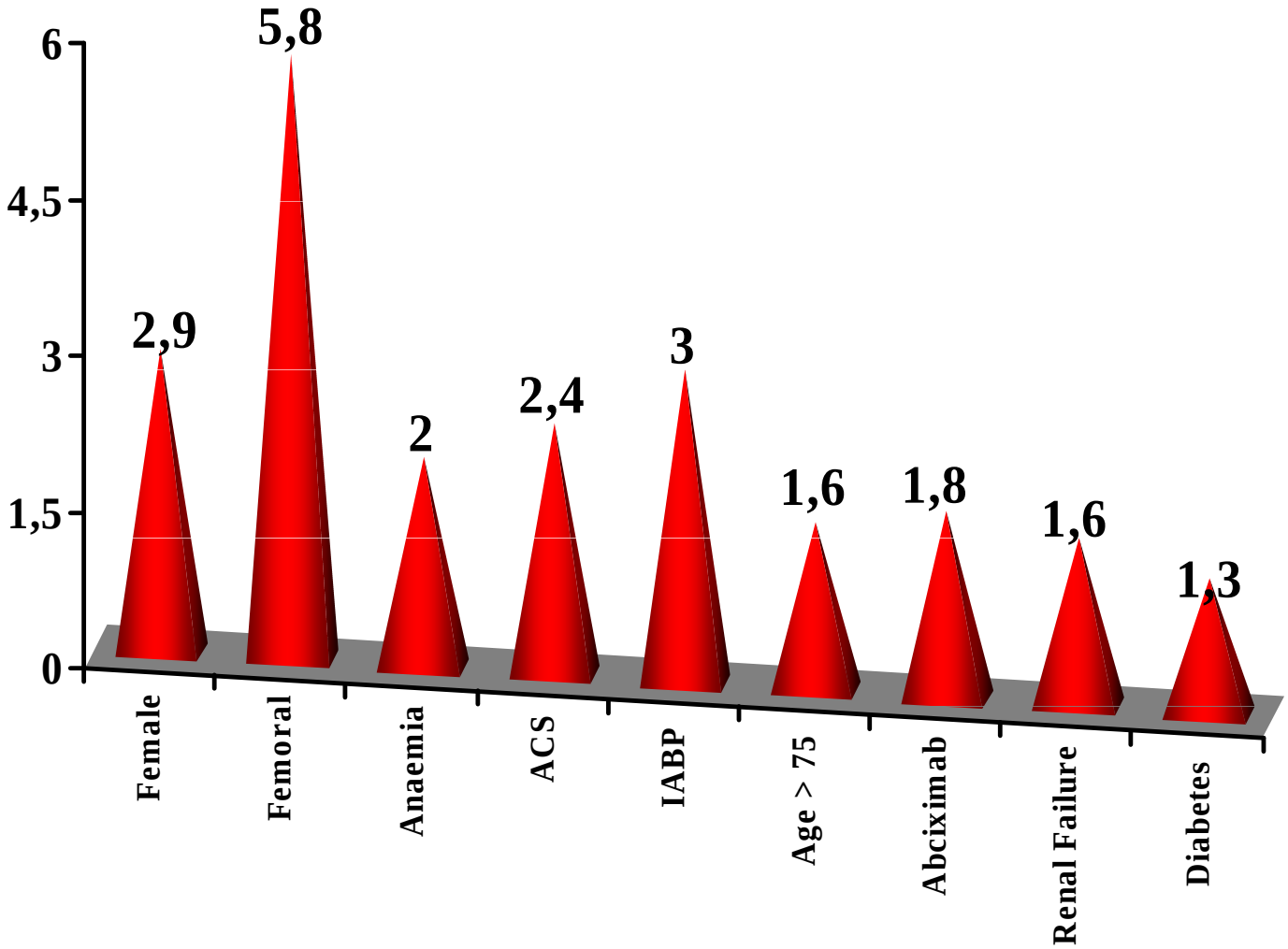
Death and MI at 30-day

Study type	Study name	Small Molecules n/N	Abciximab n/N
RCT	Danzi	1 / 50	2 / 50
RCT	Ernst	1 / 59	0 / 30
RCT	STRATEGY	3 / 87	6 / 88
RCT	EVA-AMI	8 / 226	10 / 201
RCT	Multi STRATEGY	14 / 372	14 / 372
RCT	FATA	9 / 351	6 / 341
RCT subtotal		36 / 1145	38 / 1082
Registry	Raveendran	17 / 249	18 / 327
Registry	Midei	21 / 294	11 / 158
Registry	Lachance	8 / 153	17 / 400
Registry	Gurm	130 / 2812	36 / 729
Registry subtotal		176 / 3508	82 / 1614
Total		212 / 4653	120 / 2696



Ottani F, *Am J Cardiol* 2010;106:167

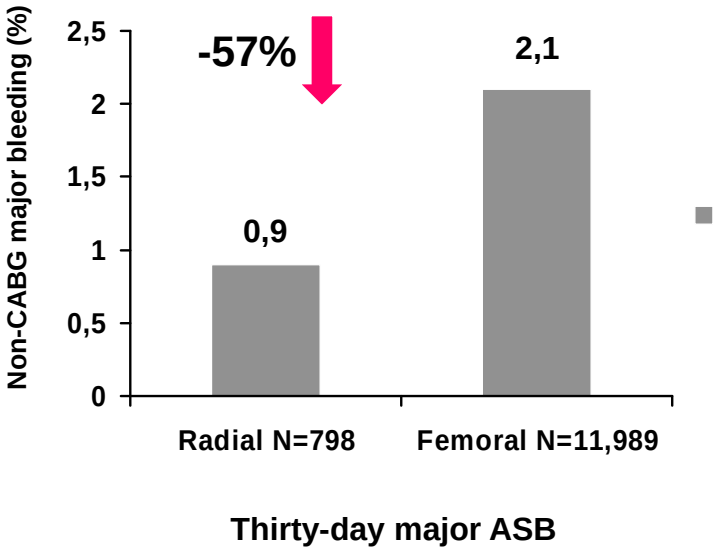
Factors associated to higher incidence of major bleeding



Montalescot G *Heart* 2005;91:89 - Kinnaird *Am J Cardiol* 2003;92:930R - Mehran R *J Am Coll Cardiol* 2010;55:2556–66

Strategies for reducing access site bleeding in ACS

Radial approach



Thirty-day major ASB

Vascular Closure Devices

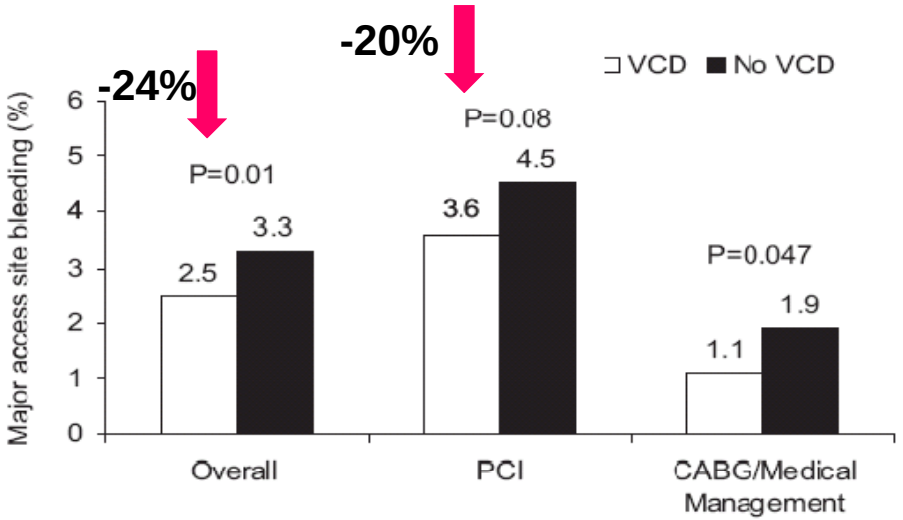
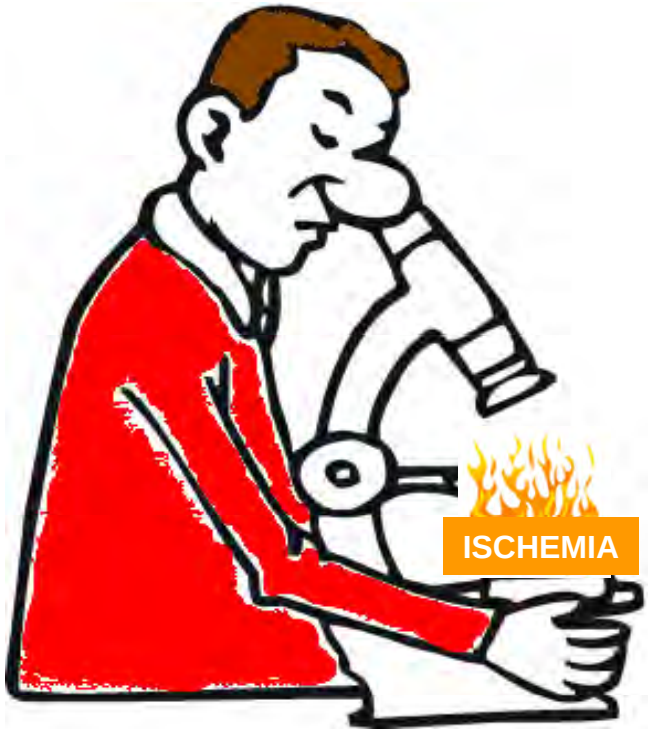


Figure 2. Thirty-day major ASB stratified by VCD use in the overall, PCI, and combined CABG and medical management cohorts.

Hamon M, *Eurointervention* 2009;5:115 Samborn T, *Circ Cardiovasc Interv* 2010;3:57

Patient with ACS undergoing invasive management

Our past

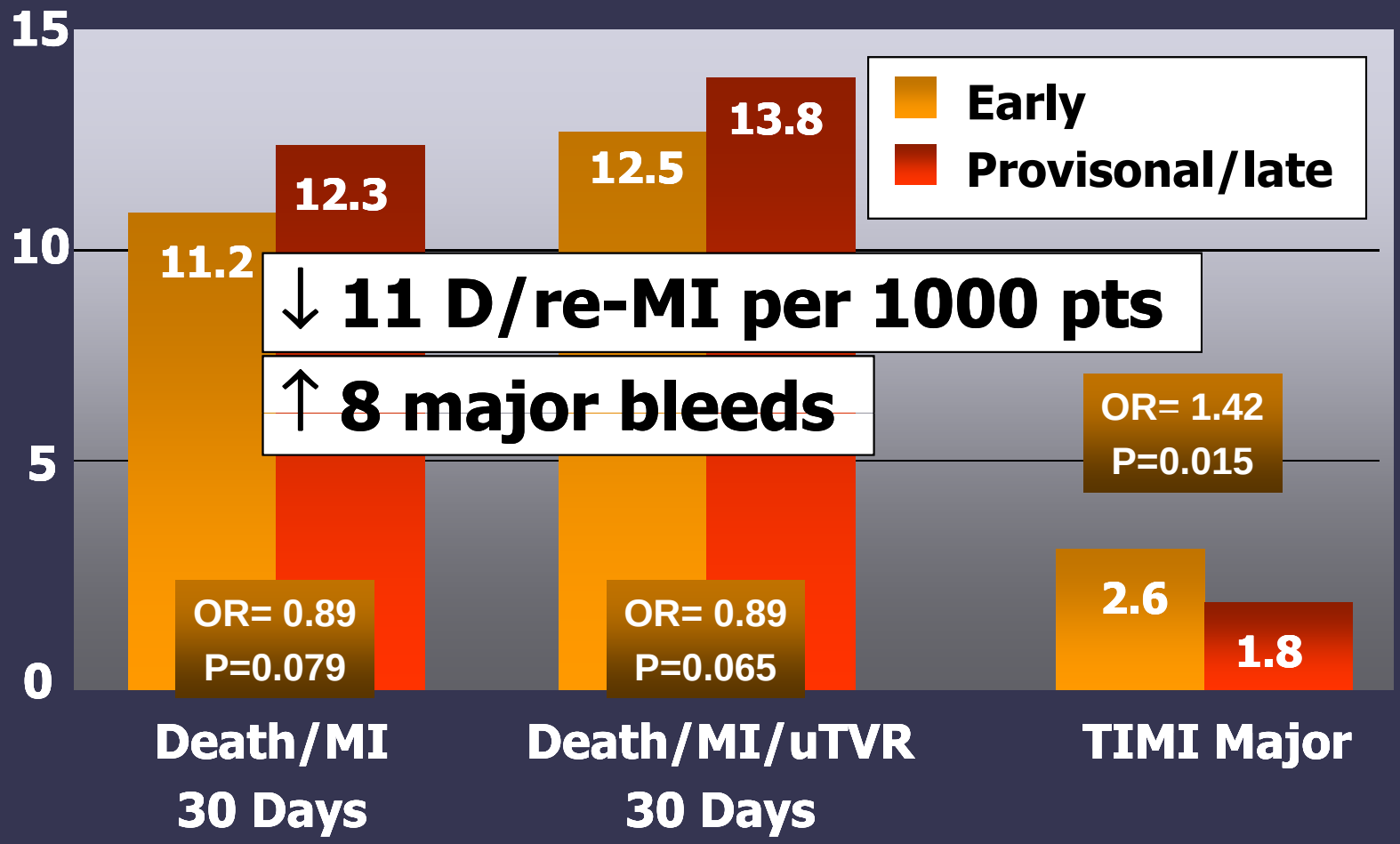


Patient with ACS undergoing invasive management

Our risky present

EARLY ACS

9,406 NSTEACS pts to early eptifibatide vs. provisional late eptifibatide

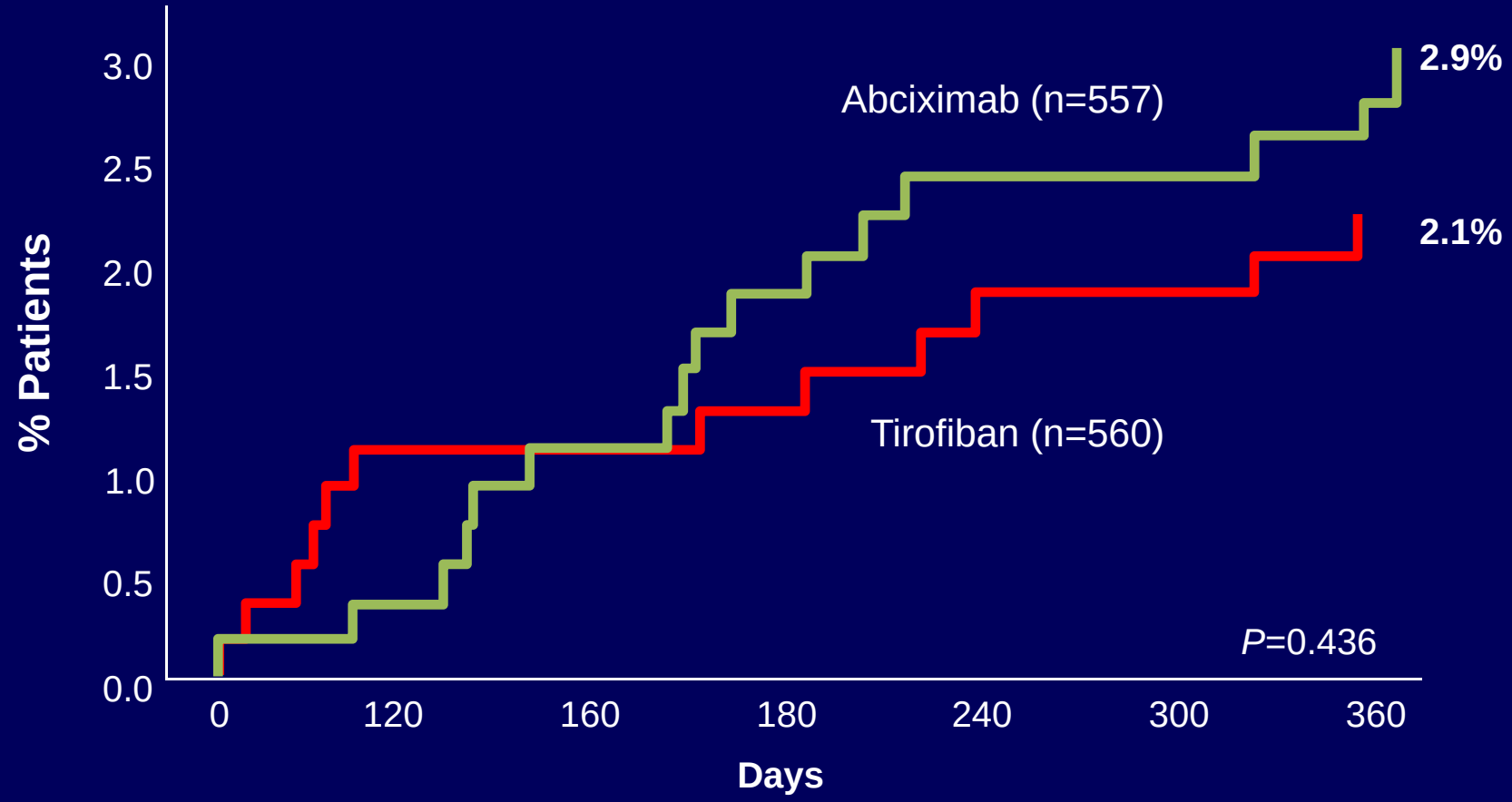


Incidence of the primary end-point and TIMI-major bleeding events in patients who received ticagrelor vs patients who received clopidogrel in the PLATO trial.

Events	Ticagrelor no/total (%)	Clopidogrelno/total (%)	Hazard Ratio (95% C.I.)	p
Primary end point (composite of vascular death, myocardial infarction or stroke)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77-0.92)	<0.001
Major bleedings, TIMI criteria	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93-1.15)	0.57
Non-CABG-related major bleedings, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03-1.53)	0.03

Wallentin and PLATO Investigators, NEJM 2(

TARGET: 1-Year Mortality in Diabetic Patients



Roffi M, et al. *Circulation.* 2002;105(23);2730-2736.

Binocular Vision…

Characteristics of patients with very high ischemic risk

Guidelines on myocardial revascularization

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(1) Refractory angina with associated:

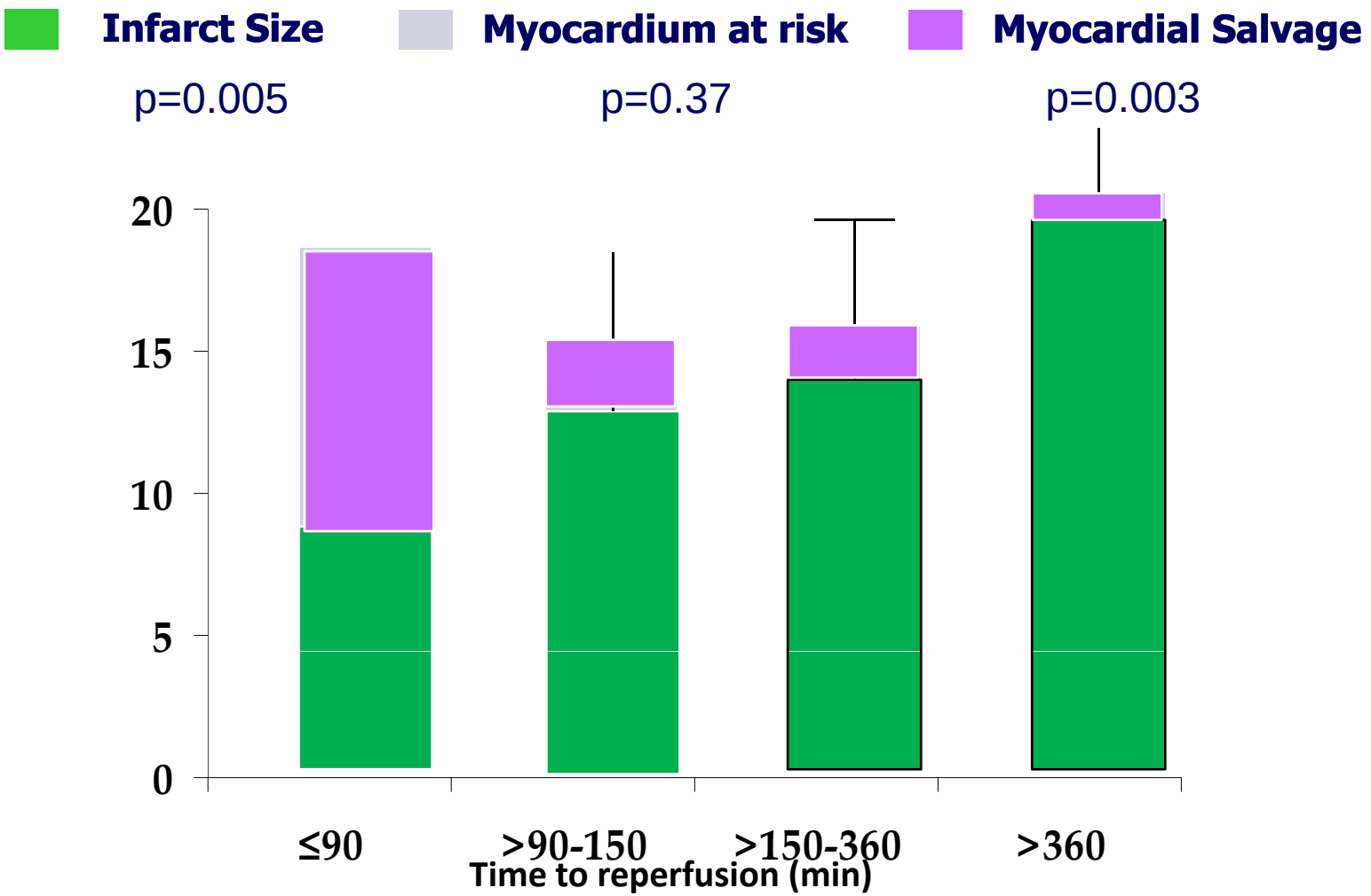
- **heart failure**
- **arrhythmias**
- **hemodynamic instability**

UHF (+ GP IIb/IIIa receptor blocker) IC

Wijns W, European Heart J doi:10.1093/eurheartj/ehq277

Myocardium at Risk – Infarct size

STEMI patients stratified by delay of treatment



Francone M, *J Am Coll Cardiol* 2009;54:2145