ARCISPEDALE SANTA MARIA NUOVA
AZIENDA OSPEDALIERA REGGIO EMILIA
Regione Emilia-Romagna

10° Symposium on Advances in Cardiac Diseases

Antiplatelet therapies in acute coronary syndromes: new trials and guidelines

Stefano Savonitto
Divisione di Cardiologia
Arcispedale S. Maria Nuova
Reggio Emilia

Antithrombotic therapies in ACS

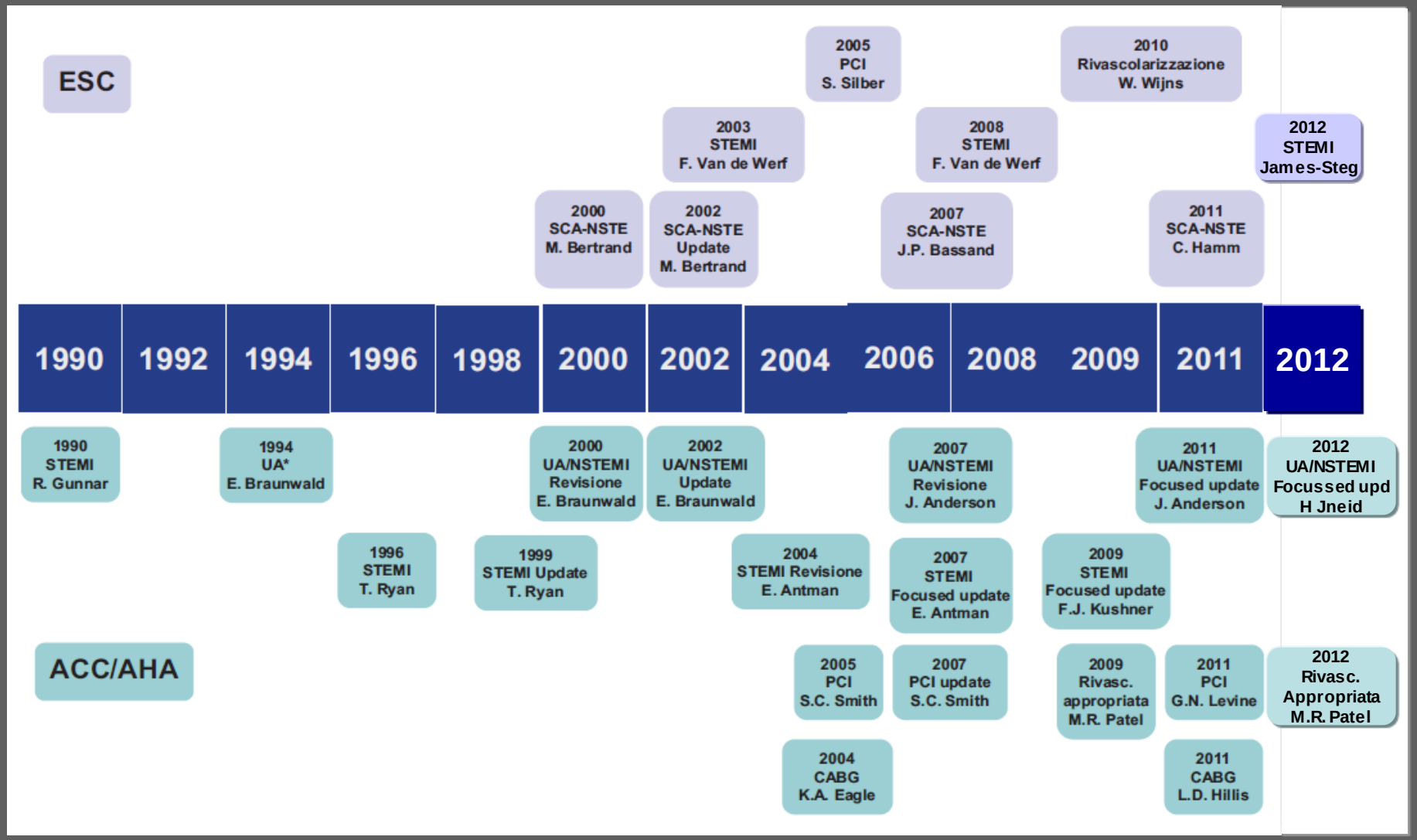
year 2007
- aspirin
- clopidogrel
- GPIIb/IIIa RB
- UFH
- enoxaparin

year 2012
- aspirin
- clopidogrel
- prasugrel
- ticagrelor
- GPIIb/IIIa RB
- UFH
- enoxaparin
- fondaparinux
- bivalirudin

year 2014?
- aspirin
- clopidogrel
- prasugrel
- ticagrelor
- vorapaxar
- GPIIb/IIIa RB
- cangrelor
- rivaroxaban
- UFH
- enoxaparina
- fondaparinux
- bivalirudina

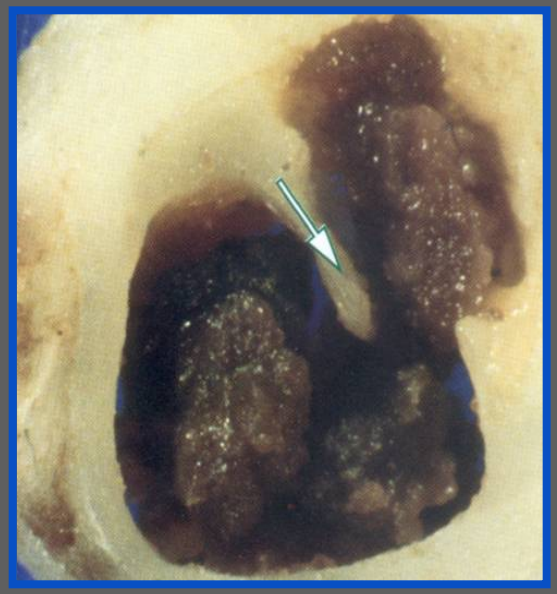
Antiplatelet
Anticoagulant

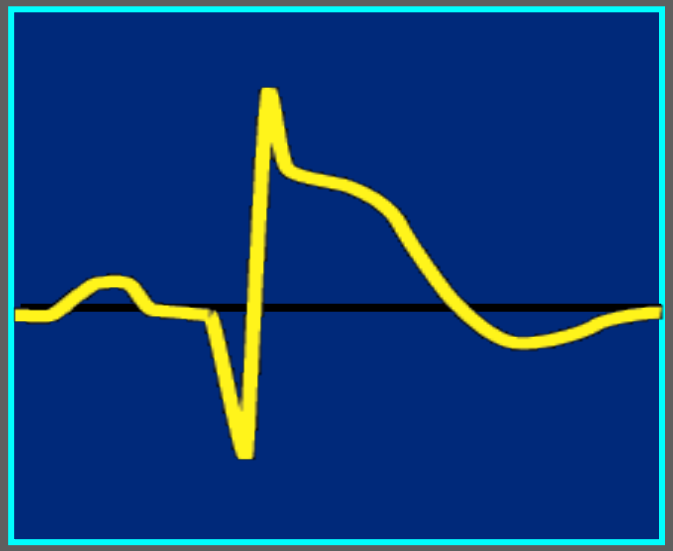
The fast pace of Practice Guidelines



Modif da Savonitto S. GIC 2012;13:157

ACS with persistent ST-segment elevation

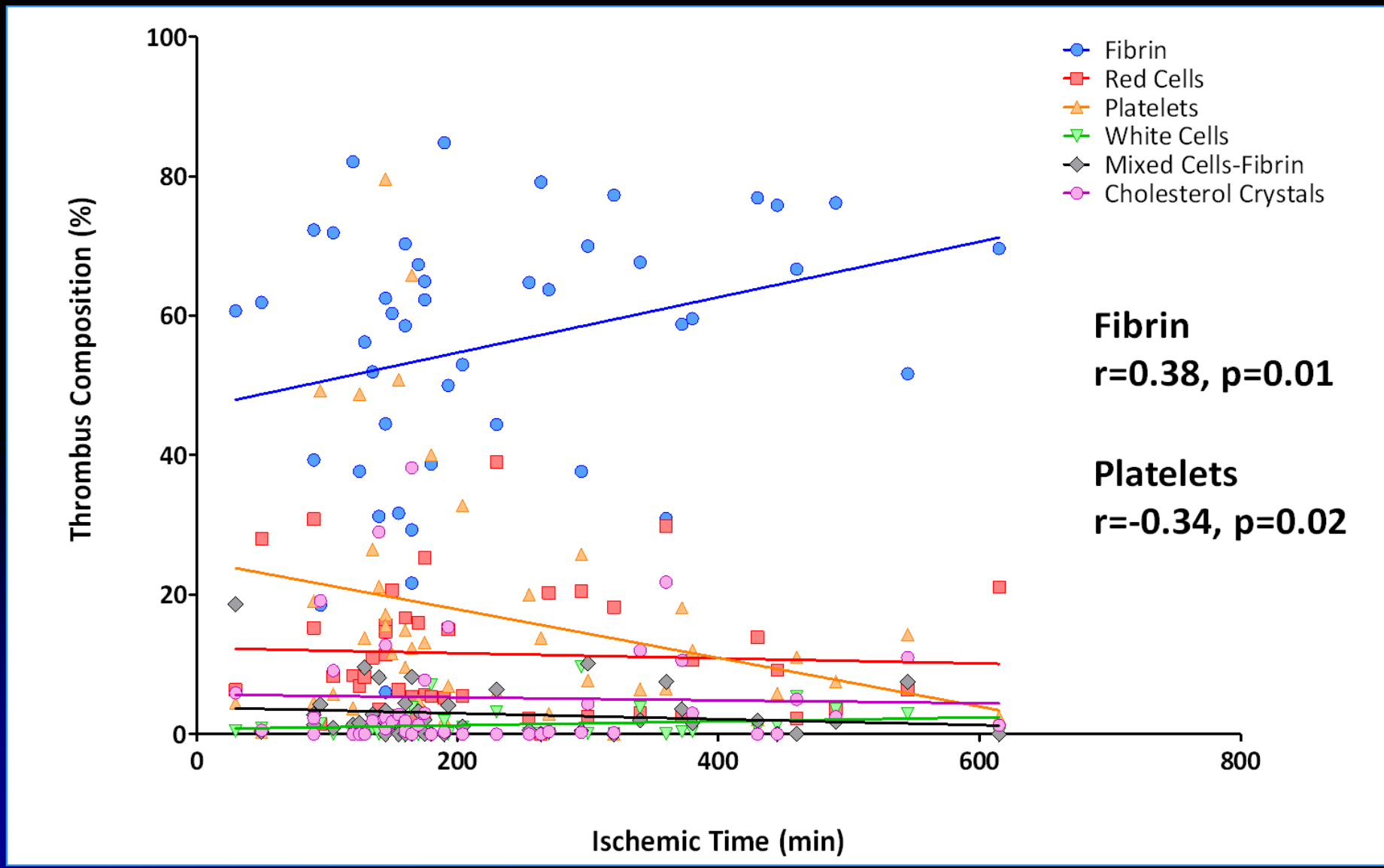




Silvain J. JACC 2011;57:1359

Influence of Time

Dynamic thrombus formation



Time from symptom onset to reopening of the IRA and myocardial salvage

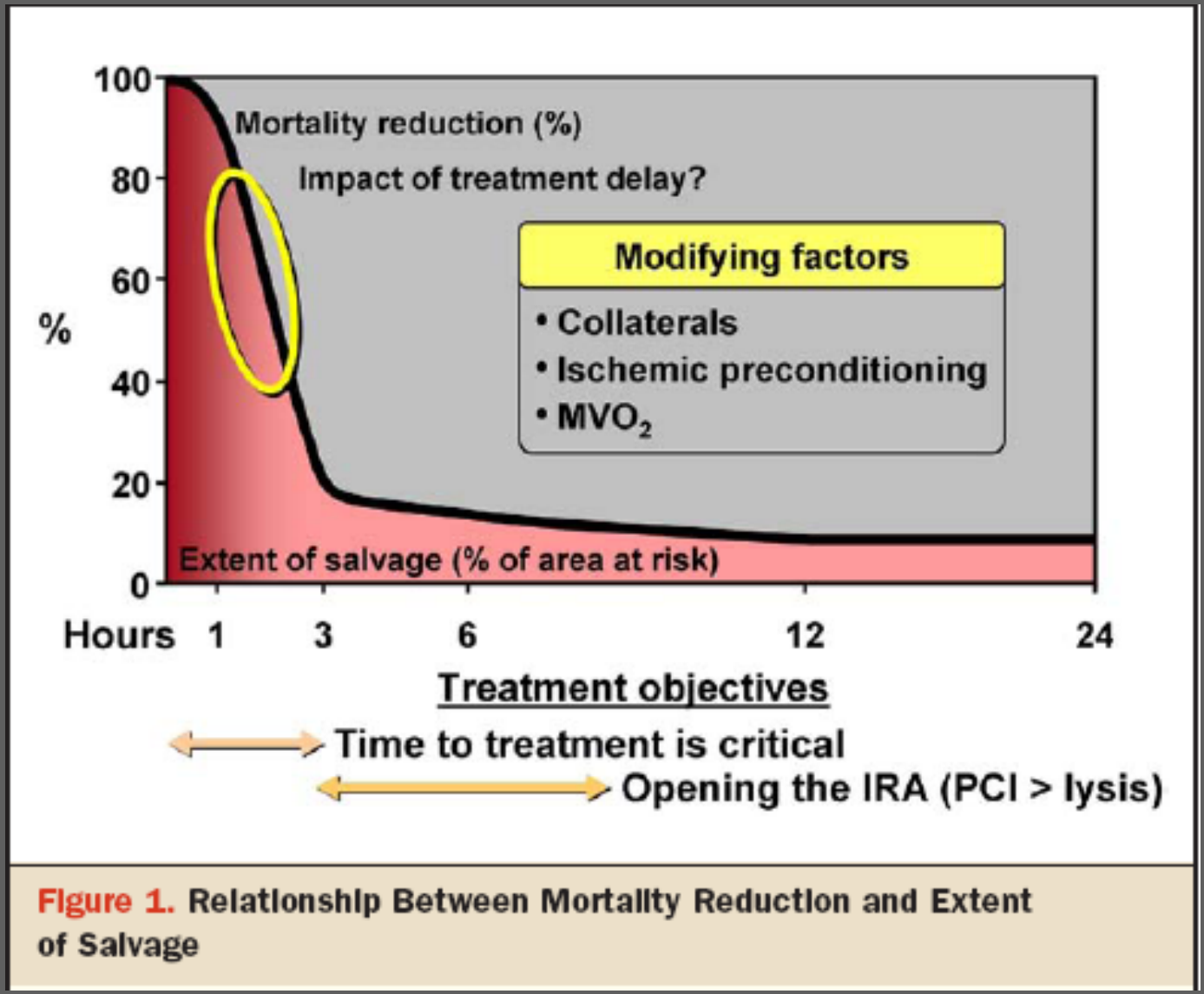
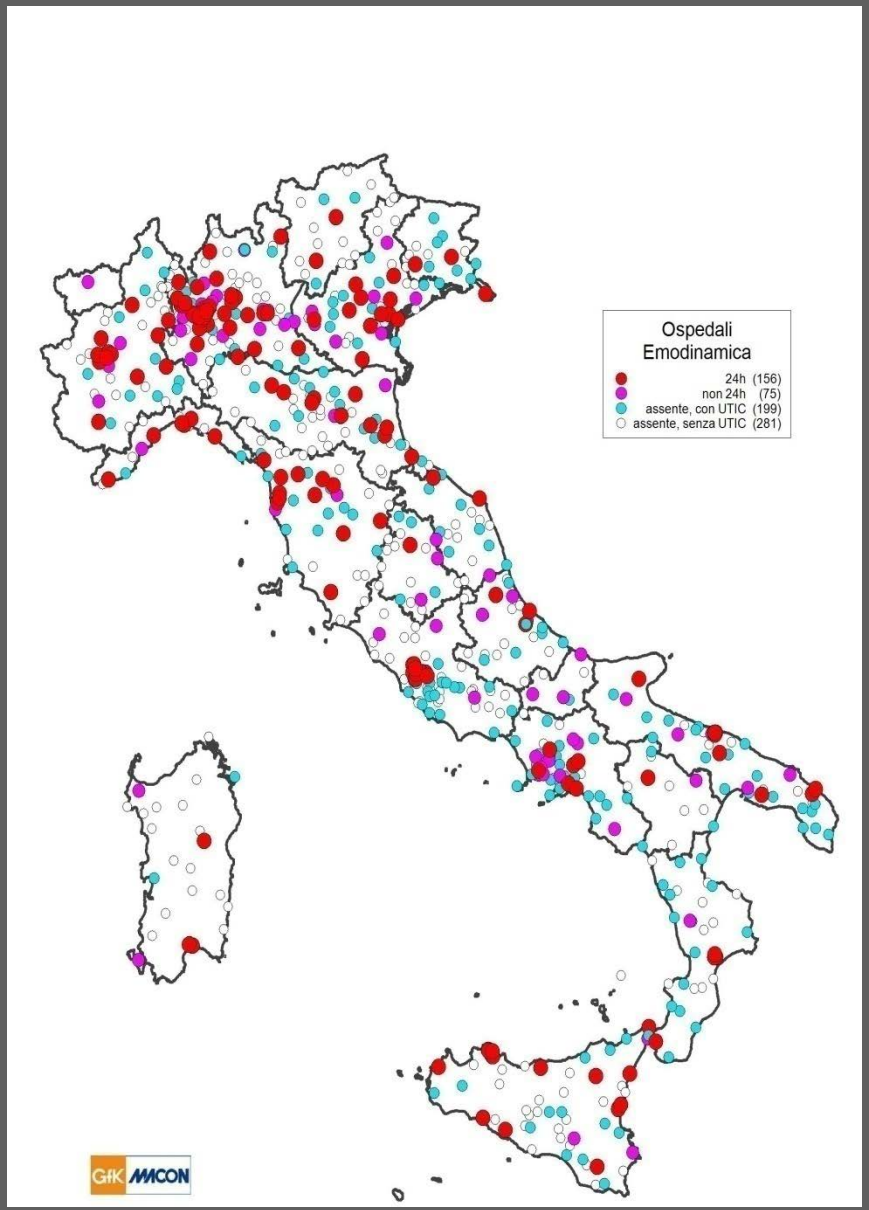


Figure 1. Relationship Between Mortality Reduction and Extent of Salvage

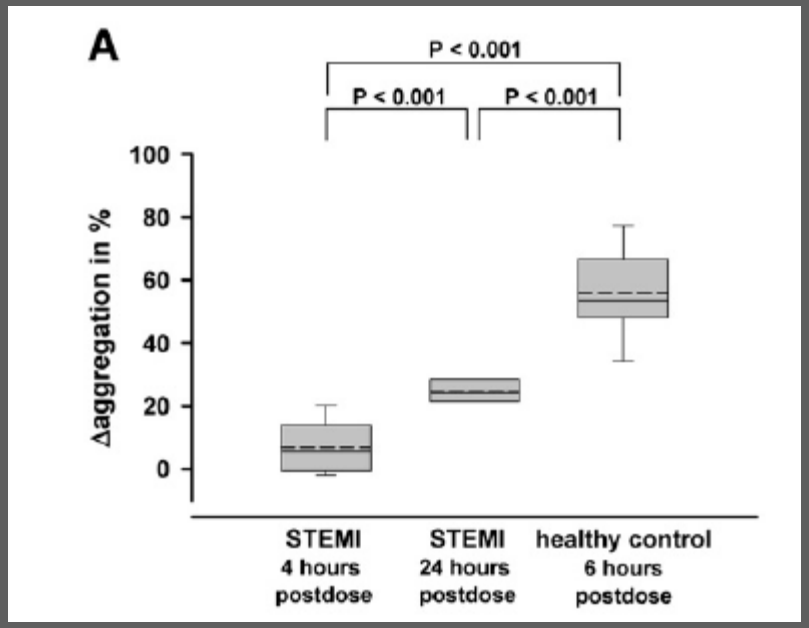
Italian PCI network 2010: 213/262 Cath Lab 24/24 hrs



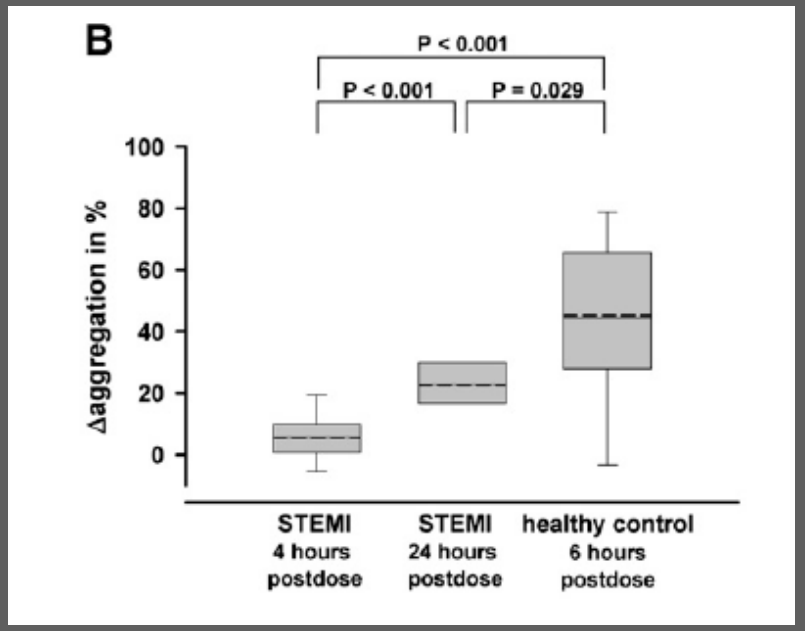
Impaired bioavailability of clopidogrel in STEMI patients

Heestermans A, et al Thrombosis Research 2008;122:776-781

5 μmol/l ADP

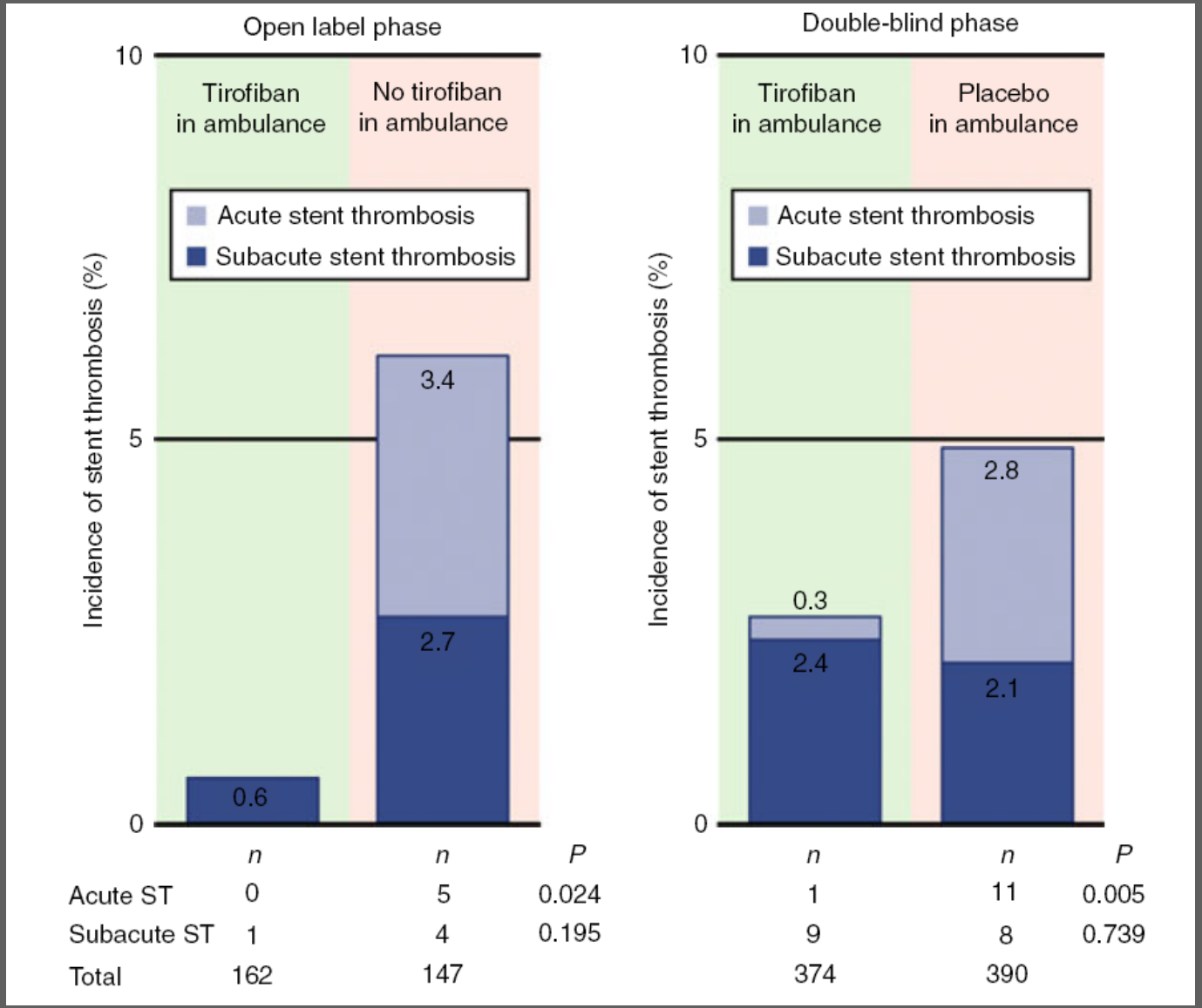


20 μmol/l ADP



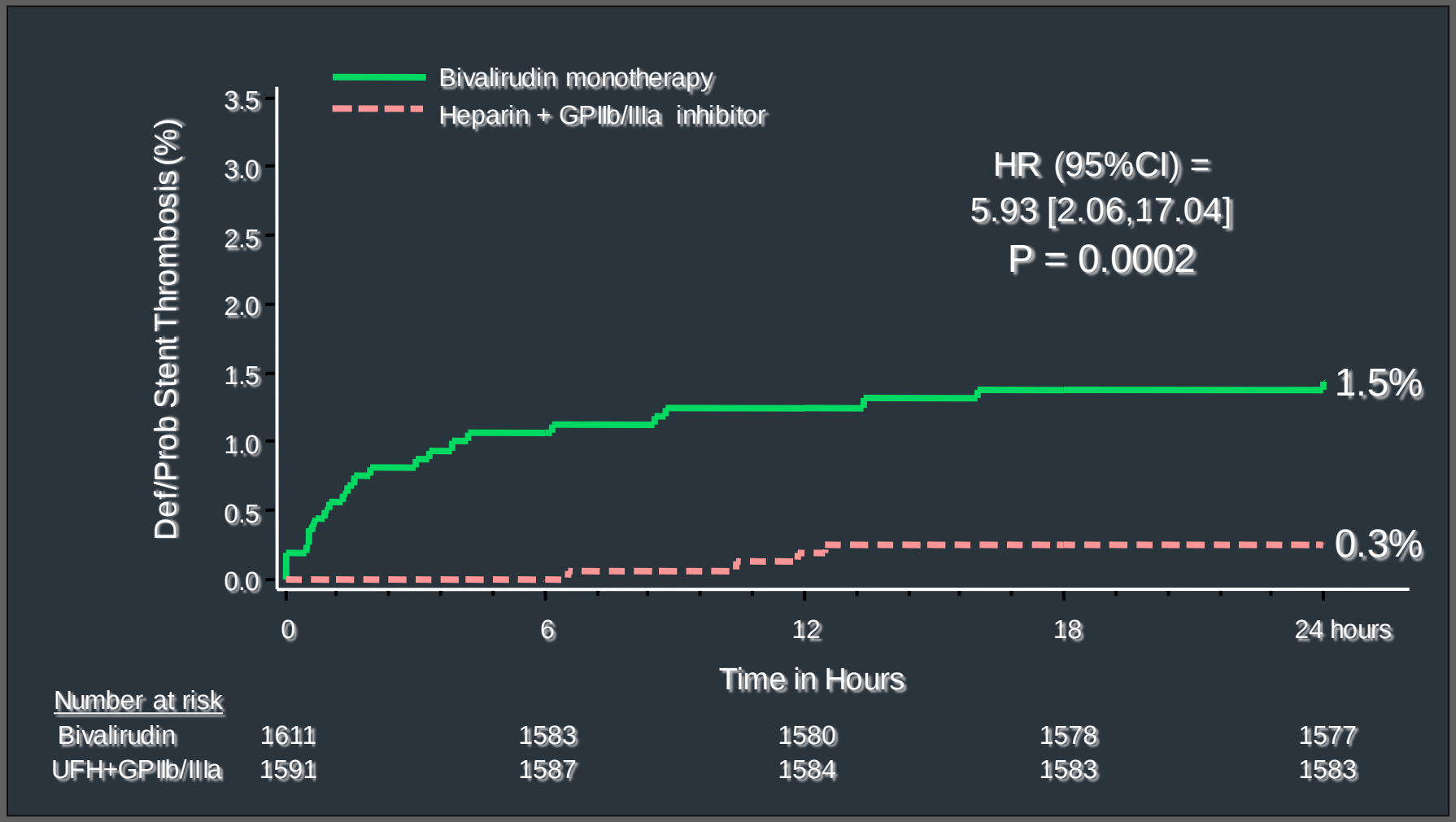
Comparison of changes in platelet aggregation induced between STEMI patients (n=9) and healthy controls (n=10) after a 600 mg clopidogrel loading dose.

Reduction of early stent thrombosis with pre-hospital high-dose tirofiban in STEMI



Heestermans AACM
J Thrombosis Haemostasis
2009;7:1612-8

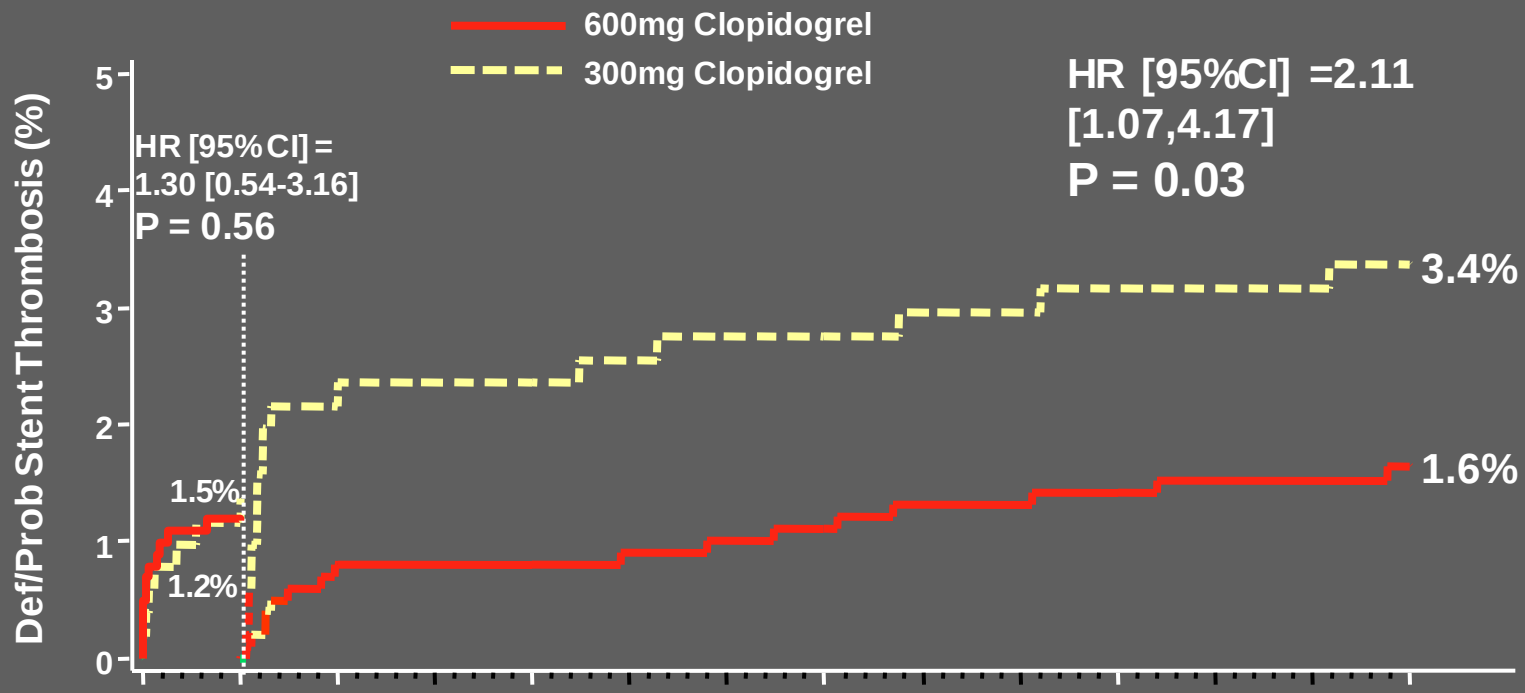
Acute Stent Thrombosis



Dangas G. ACC 2009 Scientific Sessions; March 29, 2009; Orlando, FL.

Clopidogrel Loading in Bivalirudin pts

Stent Thrombosis 1-Day Landmark Analysis

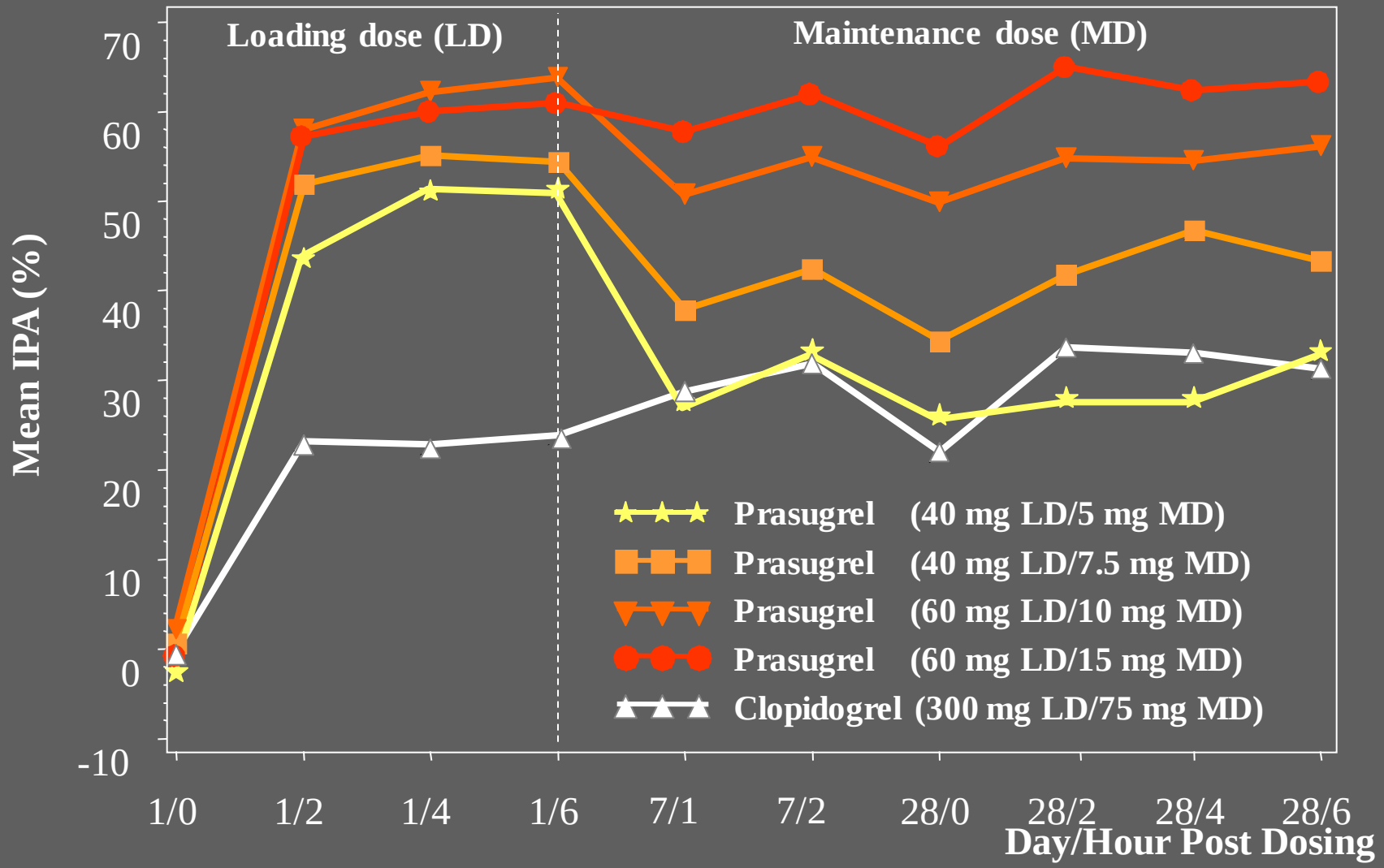


Number at risk

600 mg	1013	1009	990	969	957	943	863
300 mg	519	514	497	486	480	474	430

Dangas G. ACC 2009 Scientific Sessions; March 29, 2009; Orlando, FL.

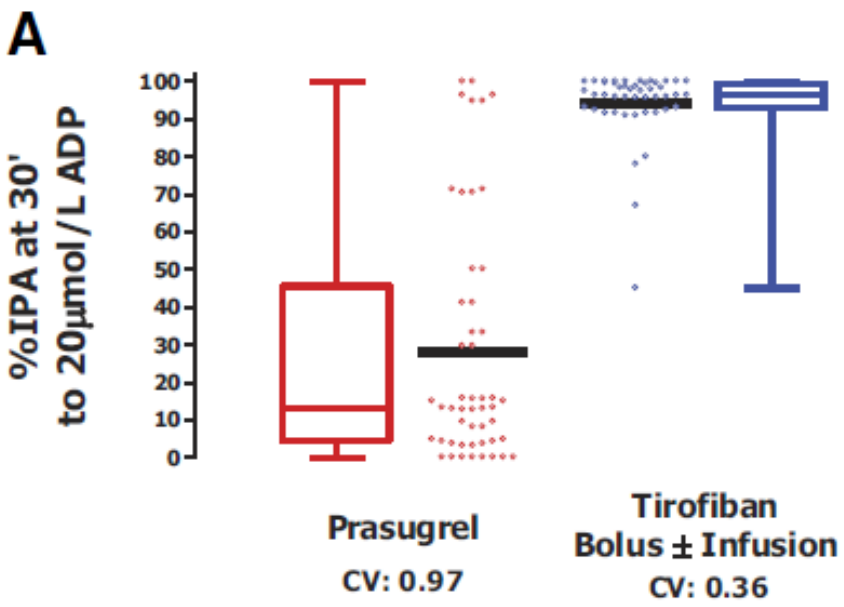
Inhibition of Platelet Aggregation (Stable Atherosclerosis)

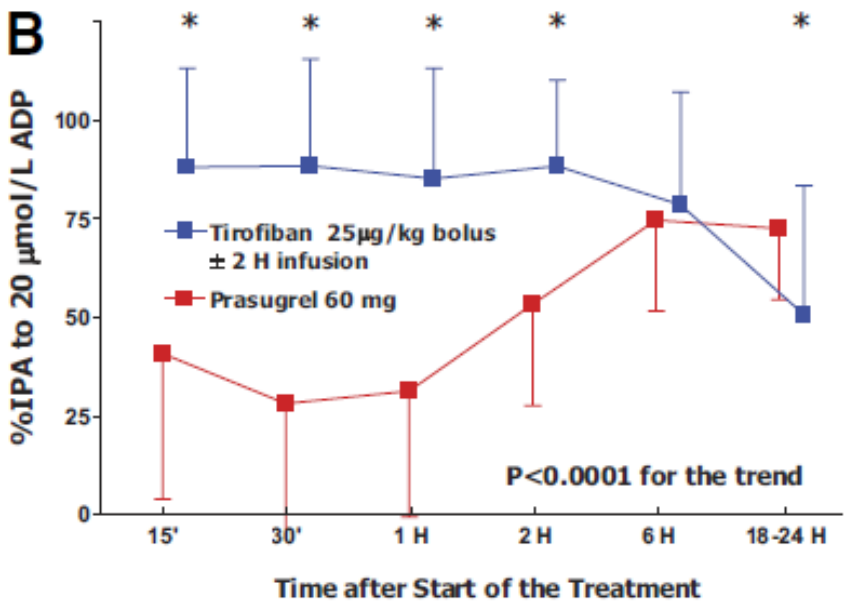


Jernberg, T et al EHJ 2006

Prasugrel vs Tirofiban HBD in PCI for STEMI

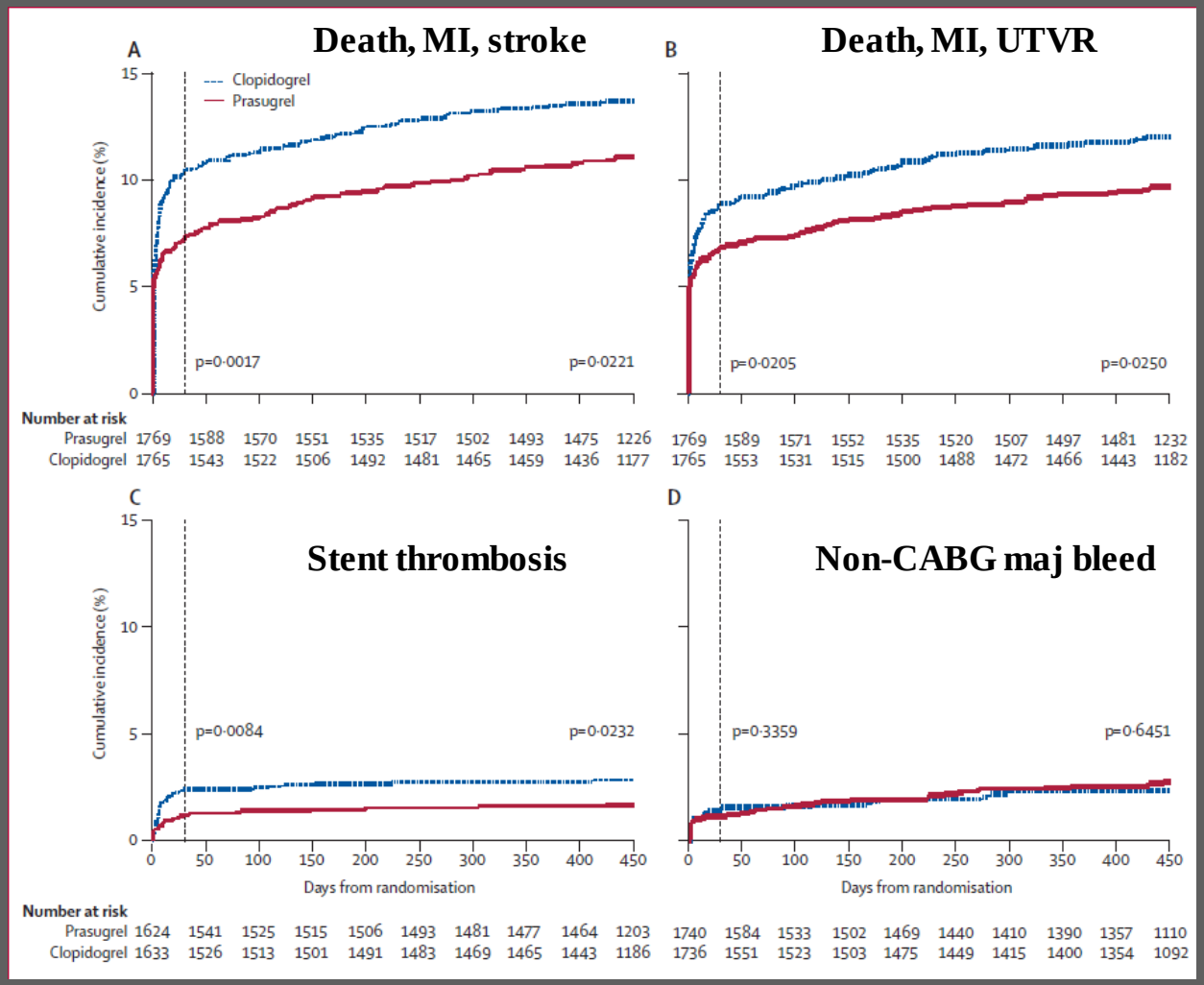
Variability of platelet inhibitory effect 30' after drug administration





Valgimigli M, et al FABOLUS PRO trial]; NCT01336348) (J Am Coll Cardiol Intv 2012;5:268–77)

Prasugrel vs clopidogrel in PCI for STEMI



Montalescot G. Lancet 2009;373:723-31

Prasugrel vs clopidogrel in PCI for STEMI

TRITON TIMI-38

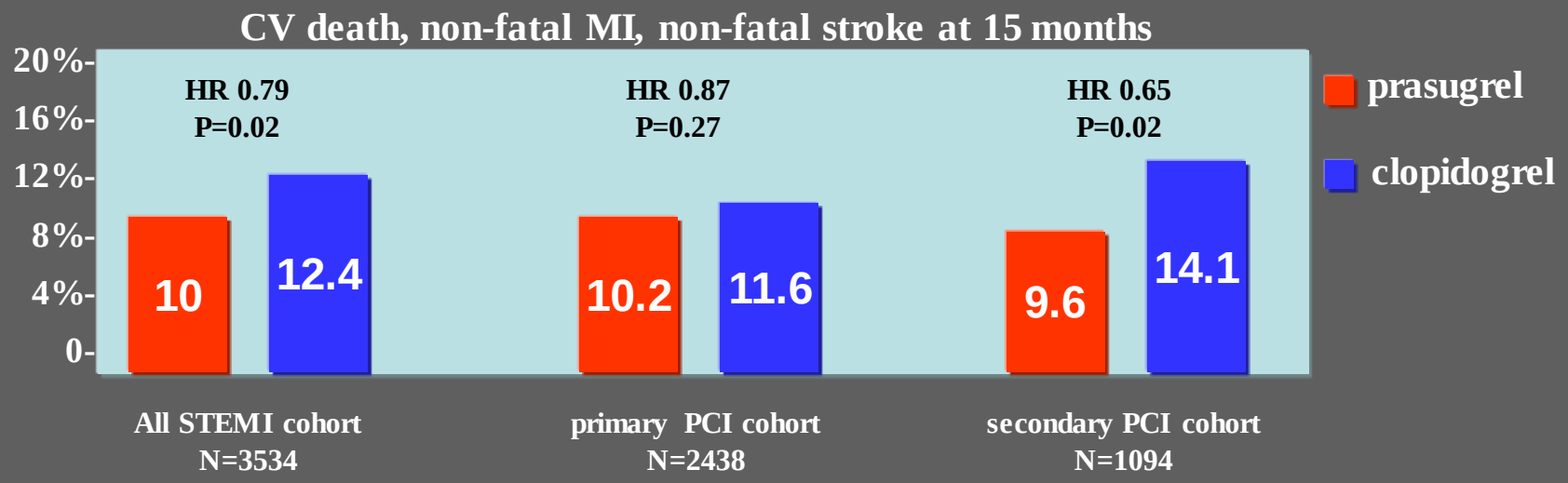
Montalescot G.
Lancet 2009;373:723-31

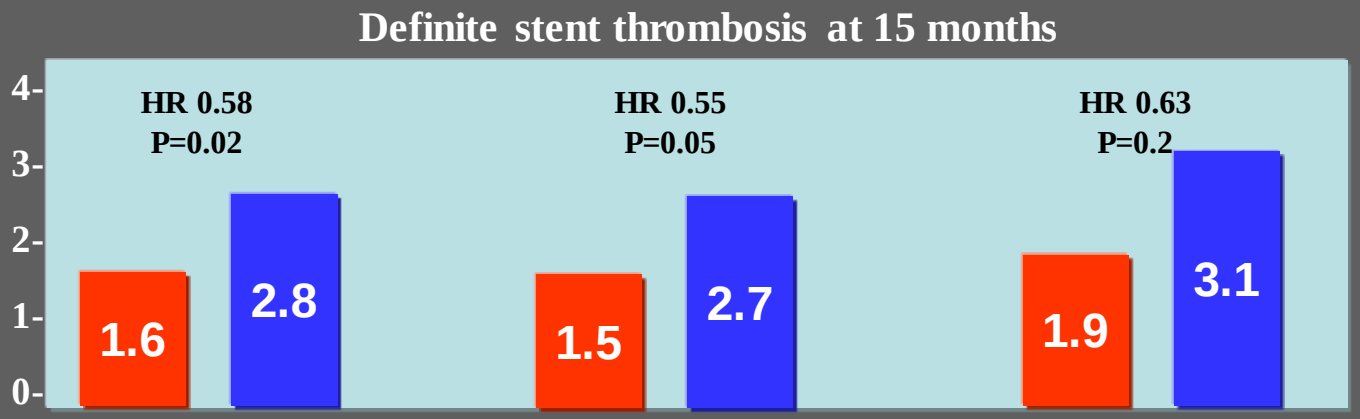
- Time from symptom onset to PPCI 3.8 hours (2438 pts)
- Time from symptom onset to SPCI 47 hours (1094 pts)
- Use of GPI 64% (no difference PPCI vs SPCI)
- Prior lytics: 29% of secondary PCI cohort
- Prasugrel admin. 27% prior and 72% during PCI

Prasugrel vs clopidogrel in PCI for STEMI

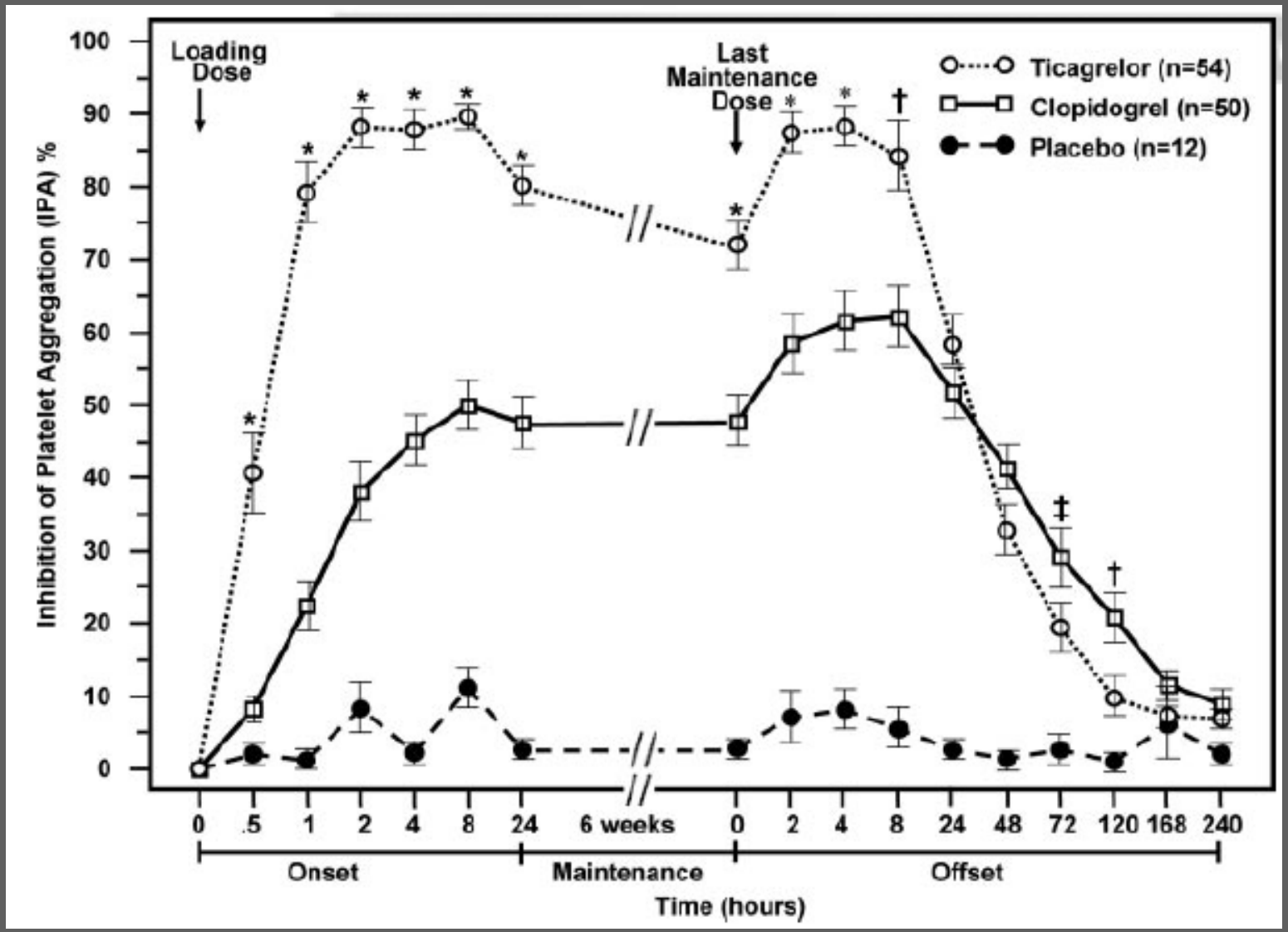
TRITON TIMI-38

Montalescot G.
Lancet 2009;373:723-31



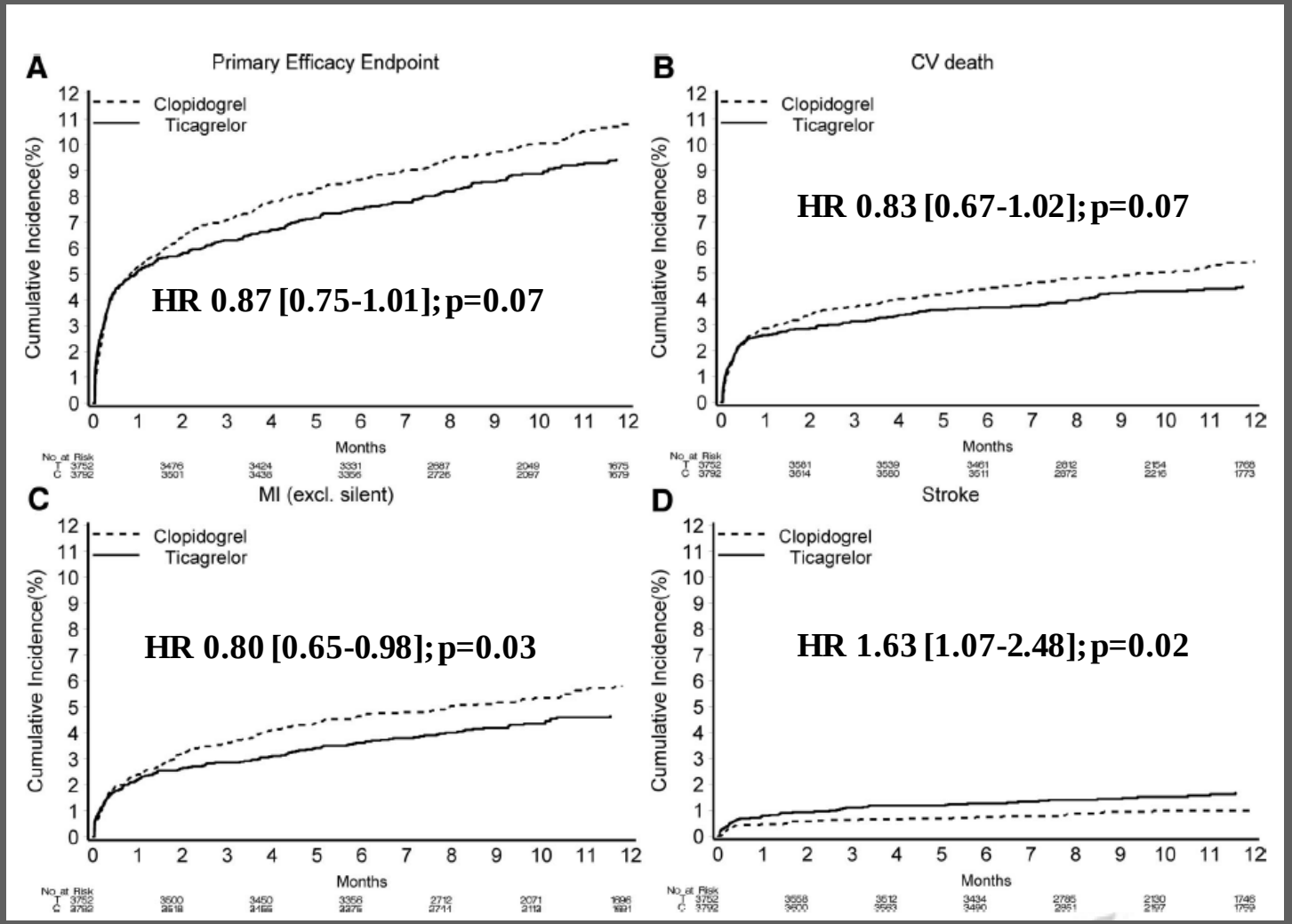


Ticagrelor vs clopidogrel: time course of IPA by 20 μM/L ADP



Gurbel P. Circulation 2009;120:2577–85

Ticagrelor vs clopidogrel in STEMI Intended for primary PCI (n=7,544)



Steg PG. Circulation 2010;122:2131

Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention

A Platelet Inhibition and Patient Outcomes (PLATO) Trial Subgroup Analysis

Delay from pain to random: 5.3h (3-11)

	Ticagrelor (n=4201)	Clopidogrel (n=4229)	P*
Underwent coronary angiography, n (%)	3496 (93.2)	3554 (93.7)	0.35
Underwent primary PCI within 12 h of randomization, n (%)	2706 (72.1)	2733 (72.1)	0.98
Underwent PCI during index admission, n (%)	3061 (81.6)	3097 (81.7)	0.93
Open-label clopidogrel prerandomization, n (%)			
None	2124 (56.6)	2104 (55.5)	0.78
75 mg (50–150 mg)	158 (4.2)	171 (4.5)	
300 mg (151–449 mg)	669 (17.8)	692 (18.3)	
600 mg (≥450)	801 (21.3)	823 (21.7)	
Gp IIb/IIIa inhibitor from index event to randomization	1300 (34.6)	1351 (35.7)	0.35

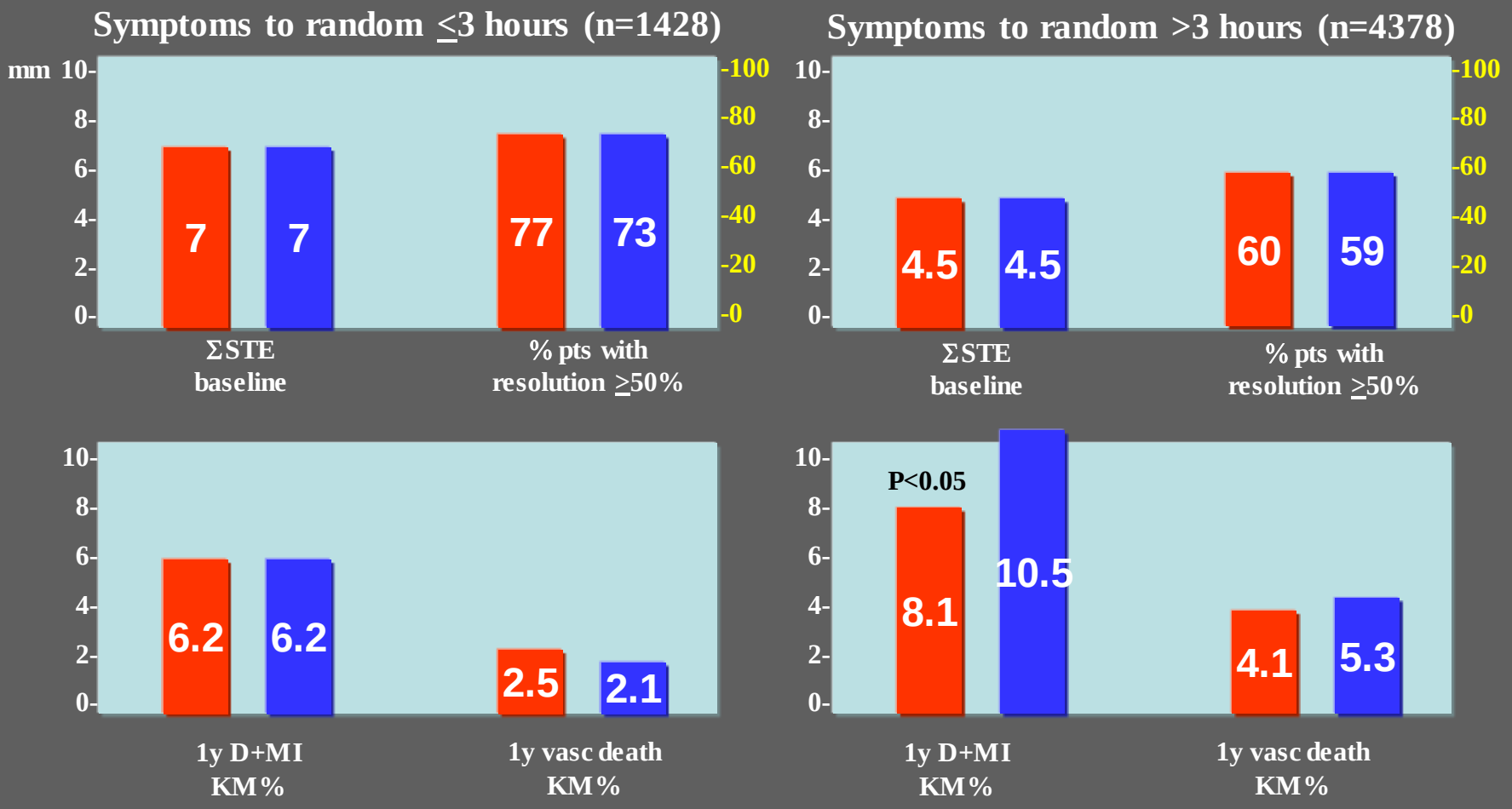
43%

Steg PG. Circulation 2010;122:2131

Ticagrelor vs clopidogrel in STEMI
ECG data and outcome according to time from symptoms

PLATO

ticagrelor clopidogrel



Armstrong PW; Circulation. 2012;125:514-21

Ticagrelor vs clopidogrel in STEMI
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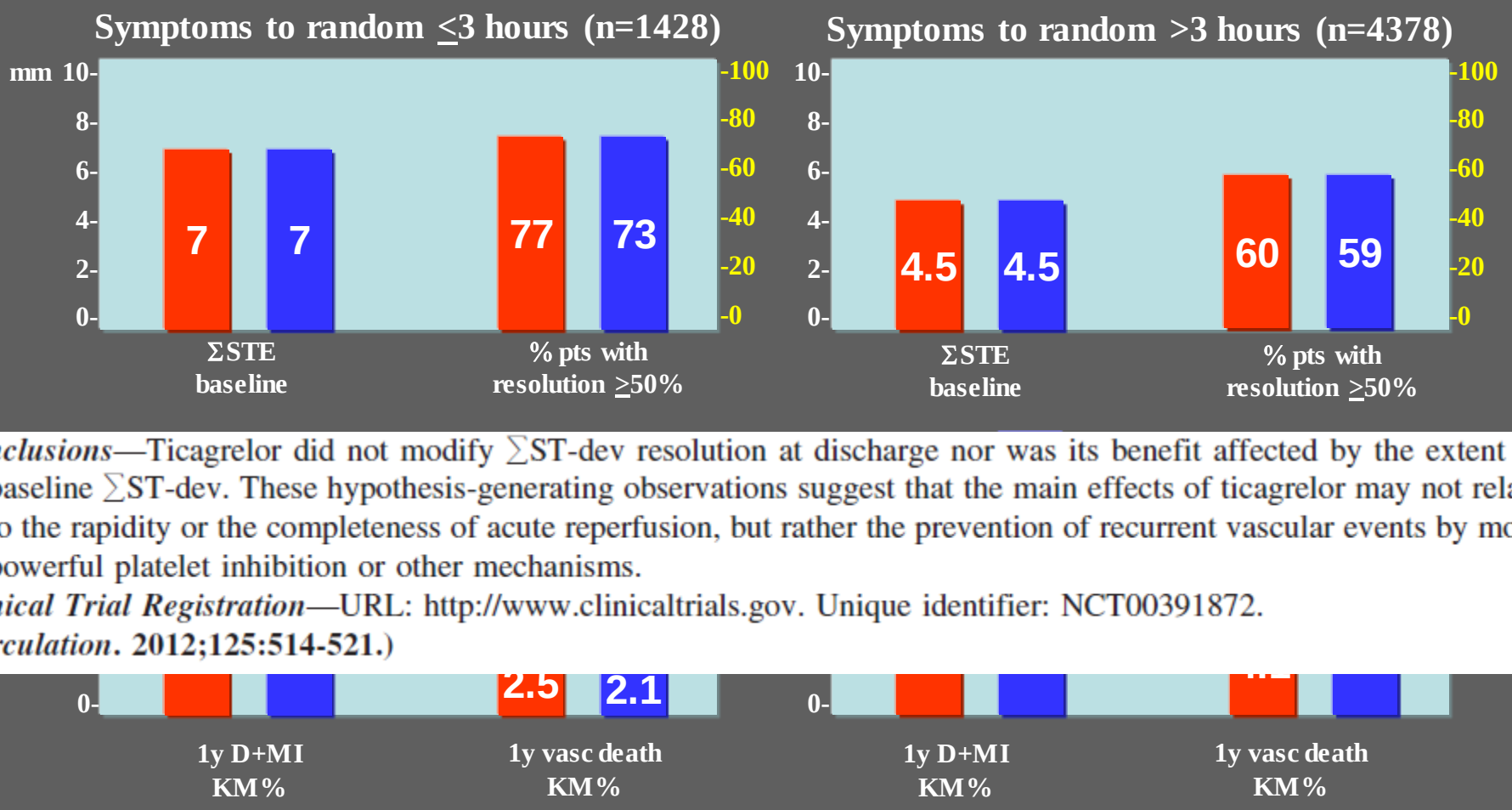
PLATO

ticagrelor clopidogrel



Conclusions—Ticagrelor did not modify ∑ST-dev resolution at discharge nor was its benefit affected by the extent of baseline ∑ST-dev. These hypothesis-generating observations suggest that the main effects of ticagrelor may not relate to the rapidity or the completeness of acute reperfusion, but rather the prevention of recurrent vascular events by more powerful platelet inhibition or other mechanisms.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00391872.

(*Circulation*. 2012;125:514-521.)

Armstrong PW; Circulation. 2012;125:514-21

Pre-H vs In-H ticagrelor in STEMI with planned PPCI
The ATLANTIC STUDY (NCT01347580)

N=1770

STEMI pts planned for PPCI
(symptom onset <6 h and time to balloon <120 min)

Time frame
September 2011
February 2013

R

Pre-hospital ticagrelor loading dose (180 mg) followed by in-H matching placebo

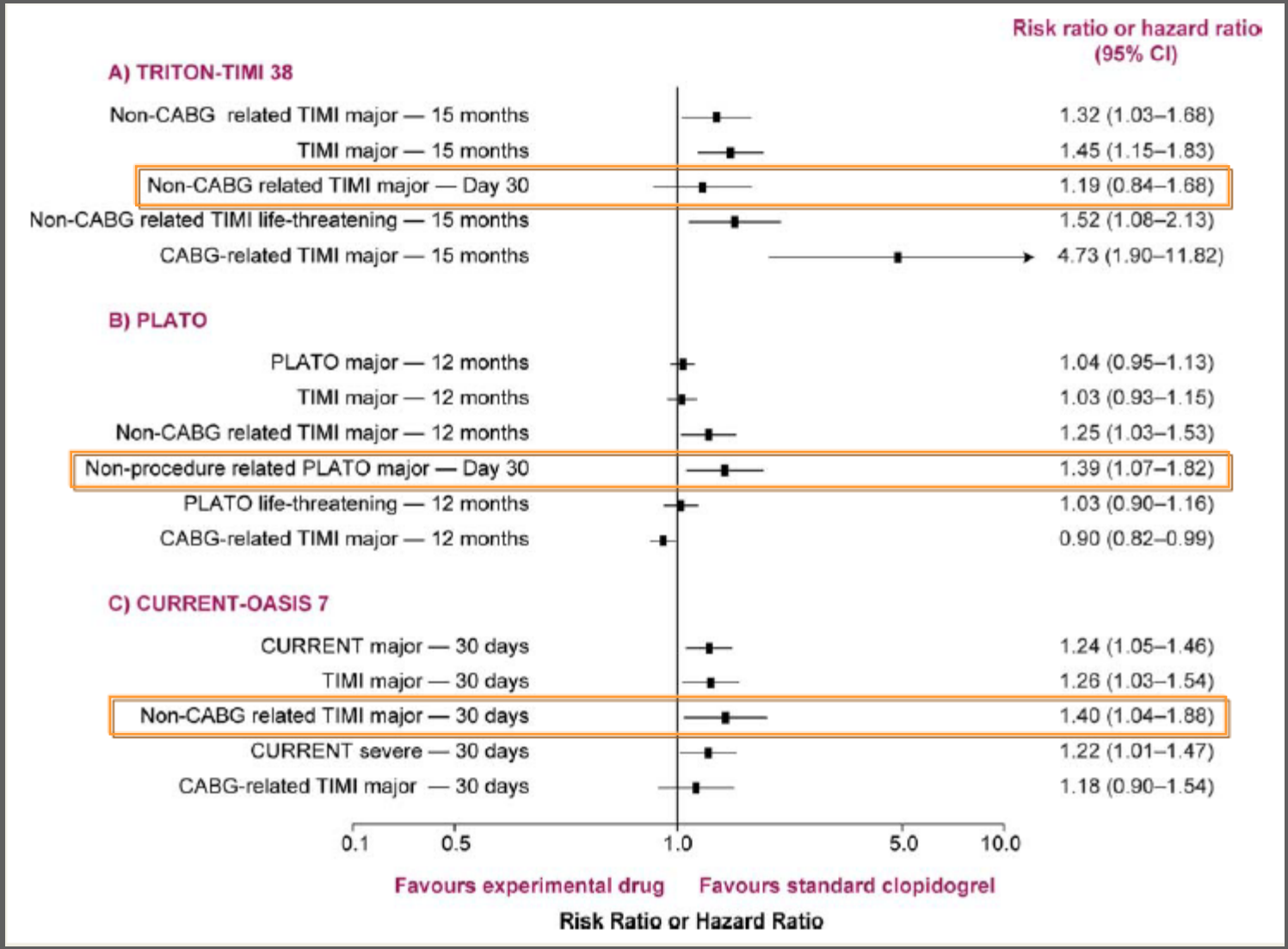
Pre-hospital placebo followed by ticagrelor loading dose (180 mg) in-H

Primary endpoint: IRA TIMI flow grade 3 at initial angiography
ST-segment resolution up to pre-PCI ≥70%

Secondary EP: 30-day death, MI, urgent revasc, stent thrombosis, life threatening bleeding, major and minor bleeding

P.I. Gilles Montalescot

Focus on bleeding rates at 30 days across clopidogrel/comparator trials



Quinlan DJ. Eur Heart J 2011;32:2256-65

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

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

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

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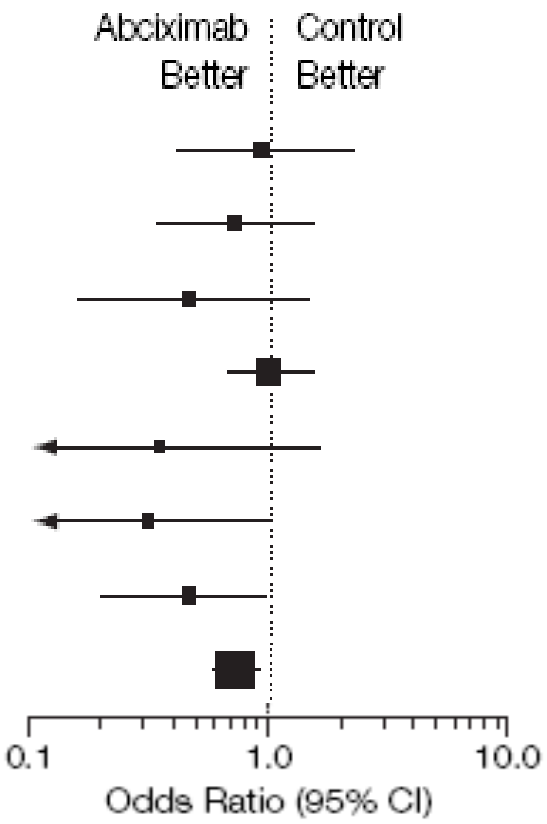
• Tirofiban (with a high bolus dose)		B	140, 141

Abciximab for primary PCI in STEMI significant mortality reduction

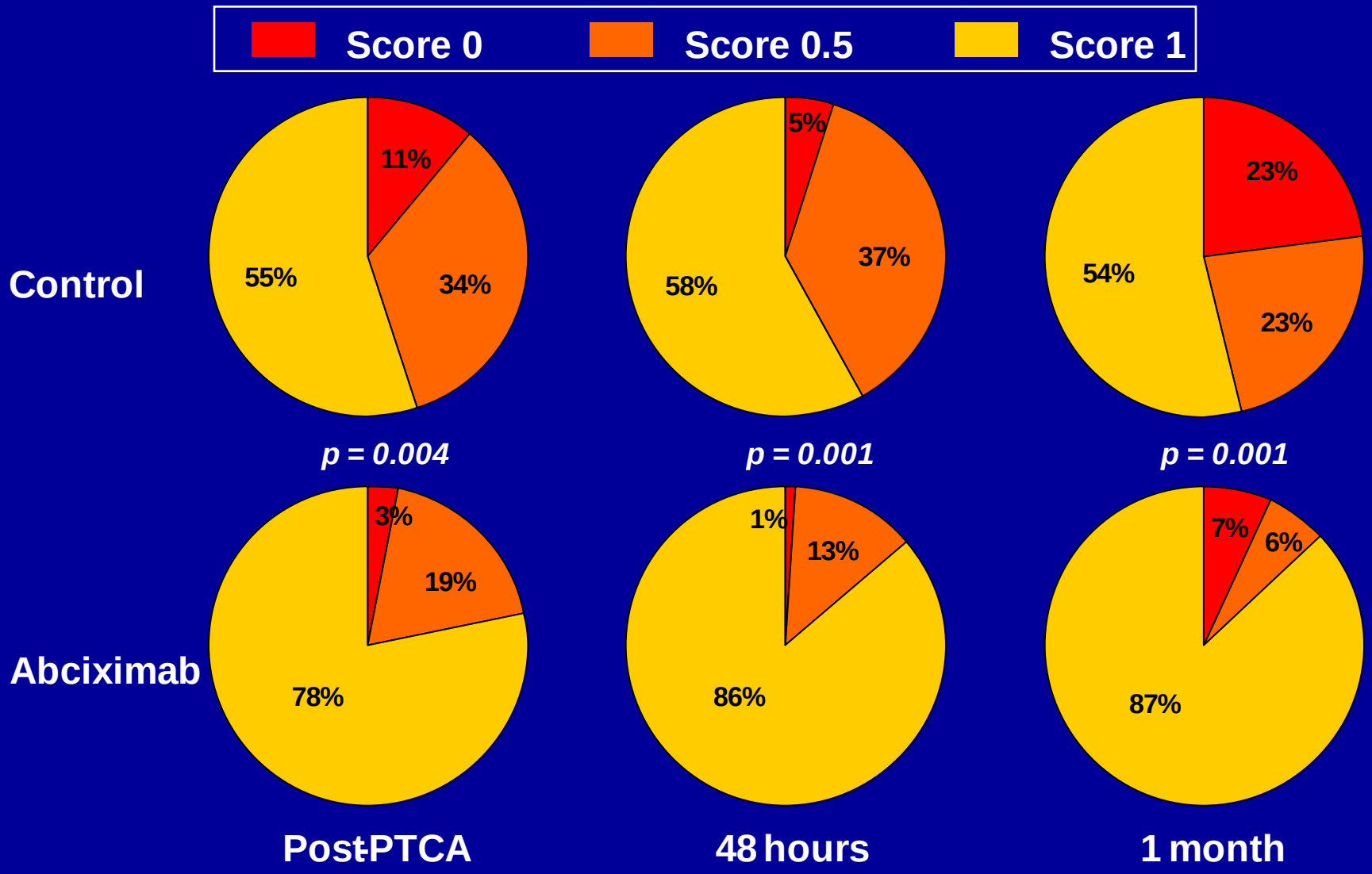
	No. of Deaths/Total (%)		
	Control (n = 14 145)	Abciximab (n = 12 297)	*P* Value
RAPPORT[14*]	11/242 (4.5)	10/241 (4.1)	.83
ISAR-2[8]	17/200 (8.5)	12/201 (6.0)	.33
ADMIRAL[10*]	11/151 (7.3)	5/149 (3.4)	.13
CADILLAC[2]	45/1030 (4.4)	44/1052 (4.2)	.83
Petronio et al[14*]	6/45 (13.3)	2/44 (4.5)	.15
Zorman et al[16*]	7/51 (13.7)	5/112 (4.5)	.04
ACE[18]	21/197 (10.5)	10/197 (5.0)	.04
Primary PCI	118/1916 (6.2)	88/1996 (4.4)	.01

-29%



De Luca G, et al. JAMA 2005;293:1759

Distribution of myocardial contrast perfusion scores



Petronio AS, Eur Heart J 2003, 24:67-76

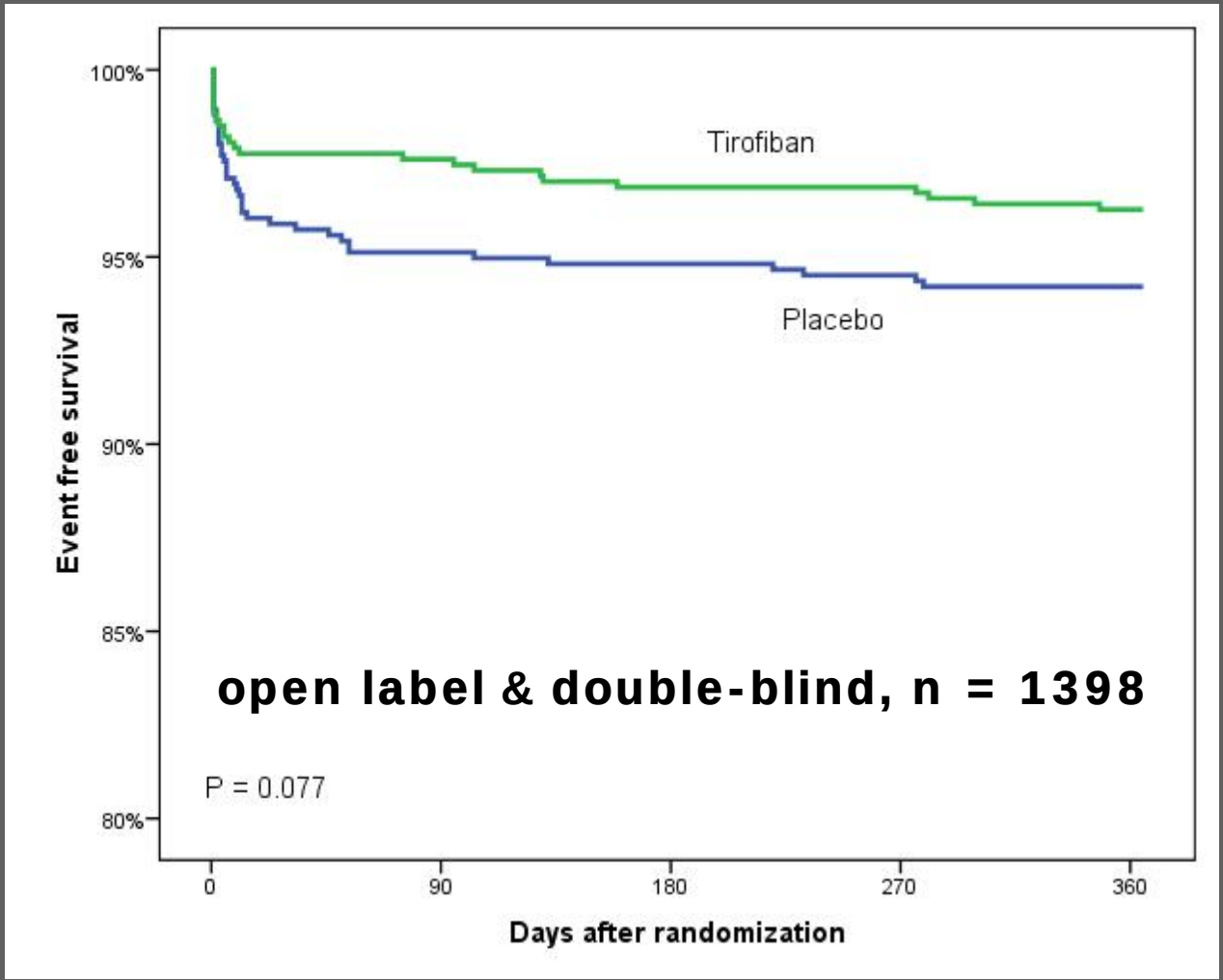
Predictors of no-reflow: the ISAR database

Variable — Data are median [25th; 75th %] or number of patients (%)	No-reflow (n =108)	Reflow (n =1032)	P value
Left ventricular ejection fraction (%)	48.0 [32.8; 56.9]	50.0 [42.0; 58.0]	0.028
Number of narrowed coronary arteries			0.57
1	39 (36.1)	364 (35.3)	
2	29 (26.9)	325 (31.5)	
3	40 (37.0)	343 (33.2)	
Pre-intervention TIMI flow grade			<0.001
0	90 (83.3)	564 (54.6)	
1	5 (4.6)	109 (10.6)	
2	10 (9.3)	189 (18.3)	
3	3 (2.8)	170 (16.5)	
Vessel size (mm)	3.02 [2.65; 3.34]	2.93 [2.58; 3.25]	0.28
Type of intervention			0.96
Stenting	88 (81.5)	843 (81.7)	
Balloon angioplasty	20 (18.5)	189 (18.3)	
Pre-procedural abciximab therapy	84 (77.8)	800 (77.5)	0.95

Ndrepepa J et al. Circ Cardiovasc Interv. 2010;3-27-33

All-Cause Mortality 1-Year

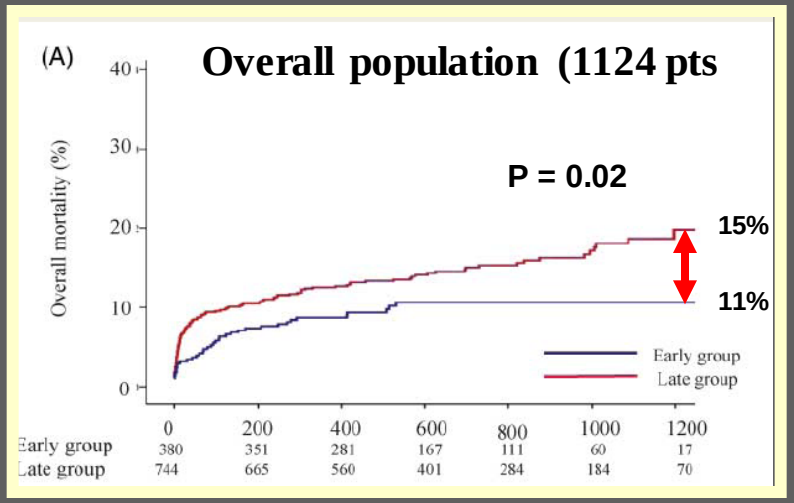
On-TIME-2



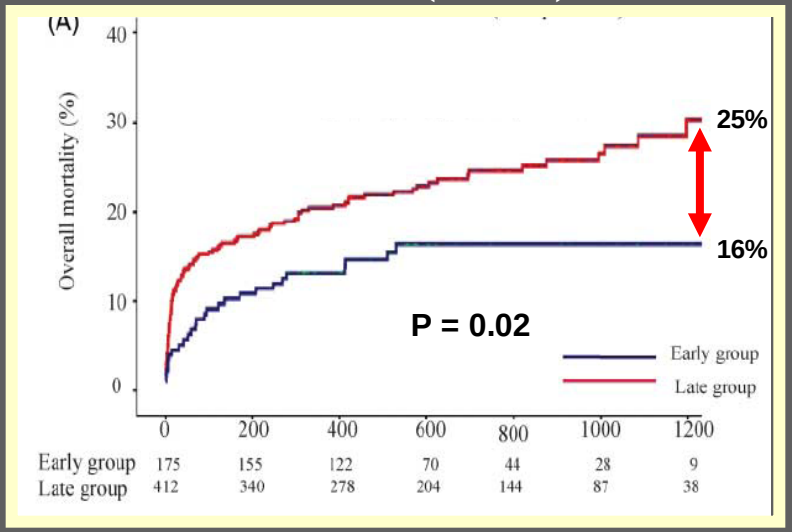
Ten Berg J. J Am Coll Cardiol. 2010;55:2446-55.

Long-Term Mortality:
Median Time = 20 Months

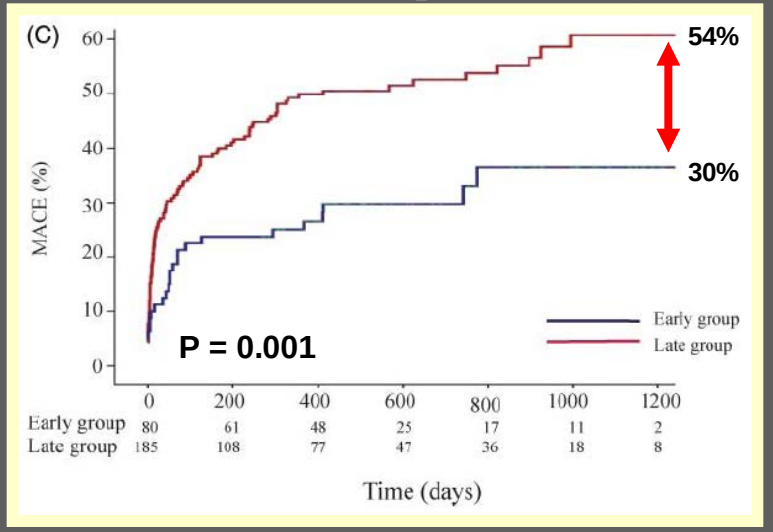
Late group
Early group



TIMI Risk Index > 25 (n = 587)



Killip Class >1 (n = 265)

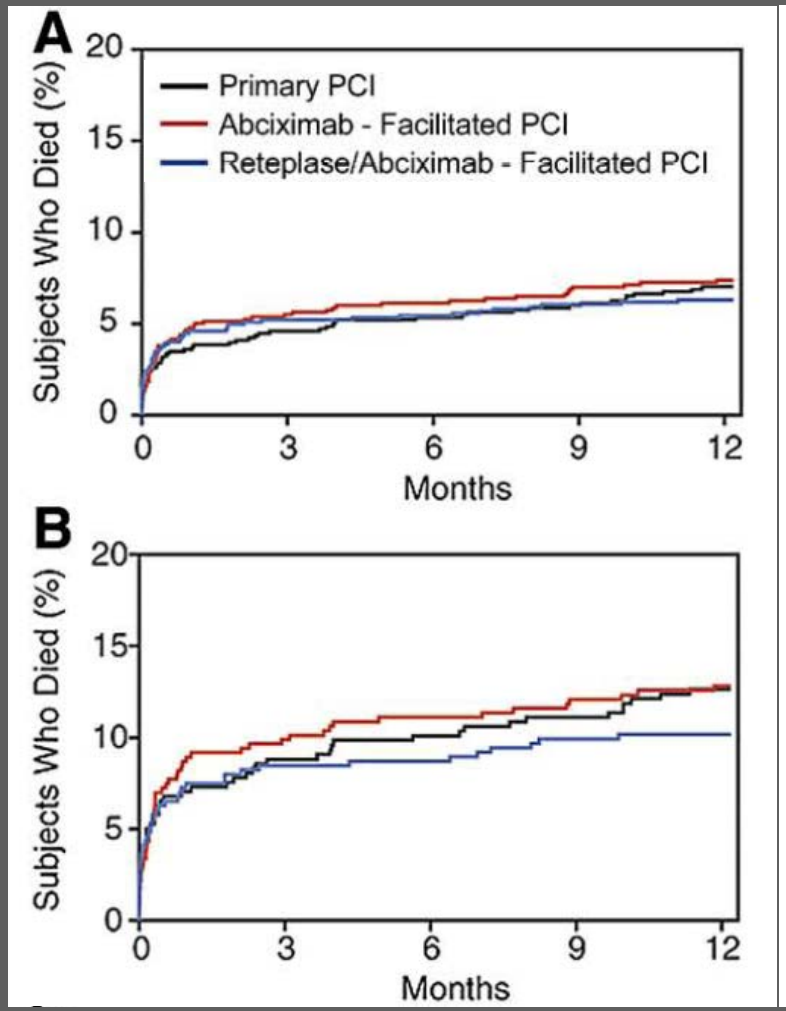


Ortolani P. Eur Heart J 2009;30, 33–43

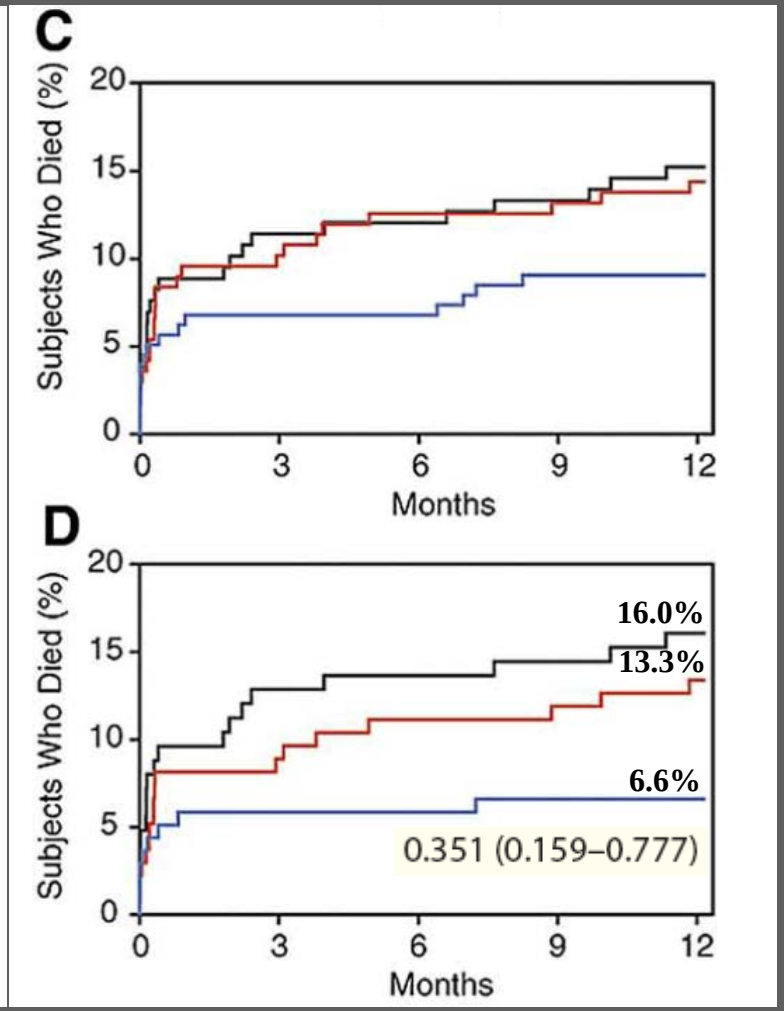
Benefit of facilitated PPCI in high-risk patients presenting at non-PCI centers

1-year mortality

A: all pts
N= 2,452



B: TRS≥3
N= 1,229



C: TRS≥3 spoke site
N= 502

D: TRS≥3 spoke site symptom to rand. ≤ 4h
N= 397

Herrmann HC. JACC Intv 2009;2:917-24

Time from symptom onset to reopening of the IRA and myocardial salvage

ON TIME 2 Ortolani FINESSE

EDITORIAL COMMENT JACC Intv 2010;3: 1292-4

Pharmacological Facilitation of Coronary Intervention in ST-Segment Elevation Myocardial Infarction

Time Is of the Essence*

Bernard J. Gersh, MB, ChB, DPhil,†
Gregg W. Stone, MD‡

Rochester, Minnesota; and New York, New York

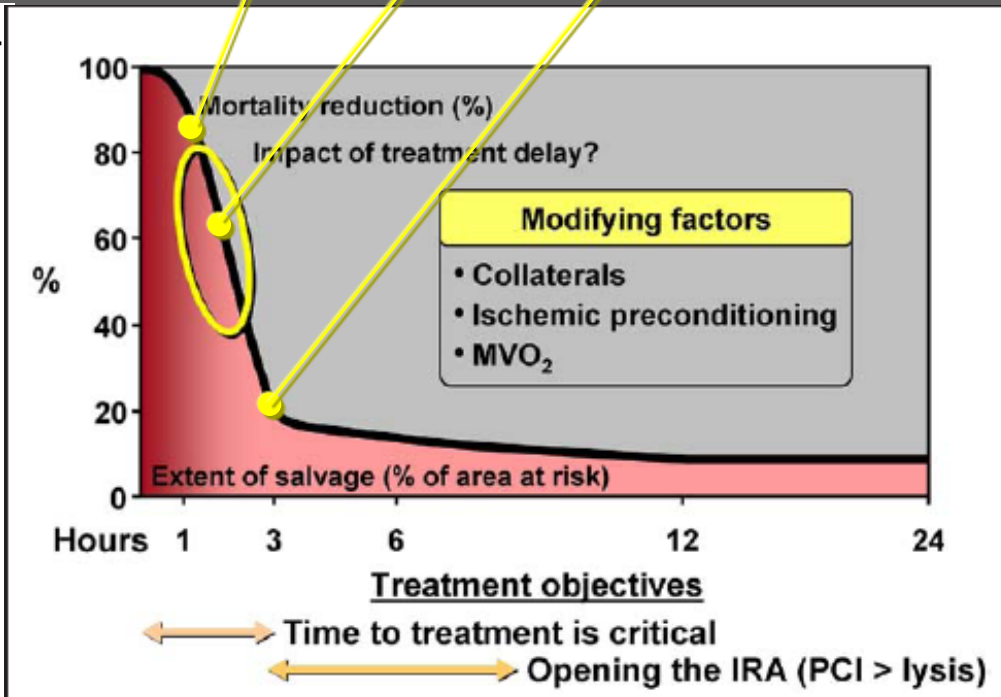
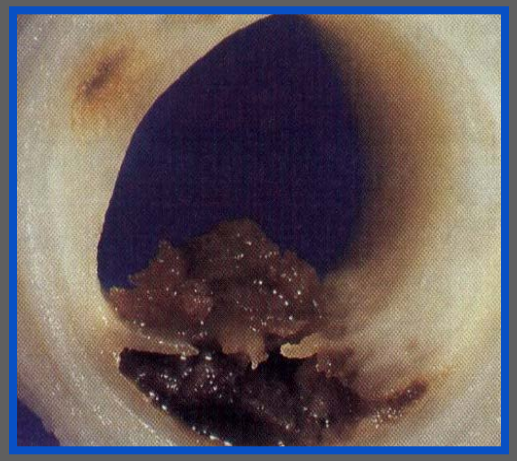
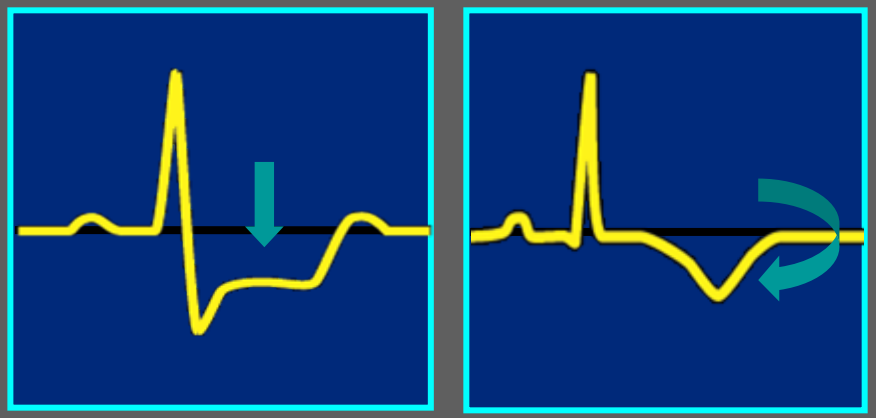


Figure 1. Relationship Between Mortality Reduction and Extent of Salvage

"Educating the public to seek treatment at an early stage… is likely to reduce mortality to a greater degree than pharmacological facilitation before PCI, although translation of this goal to reality in a community setting is and will continue to be extremely difficult."

ACS <u>without</u> persistent ST-segment elevation

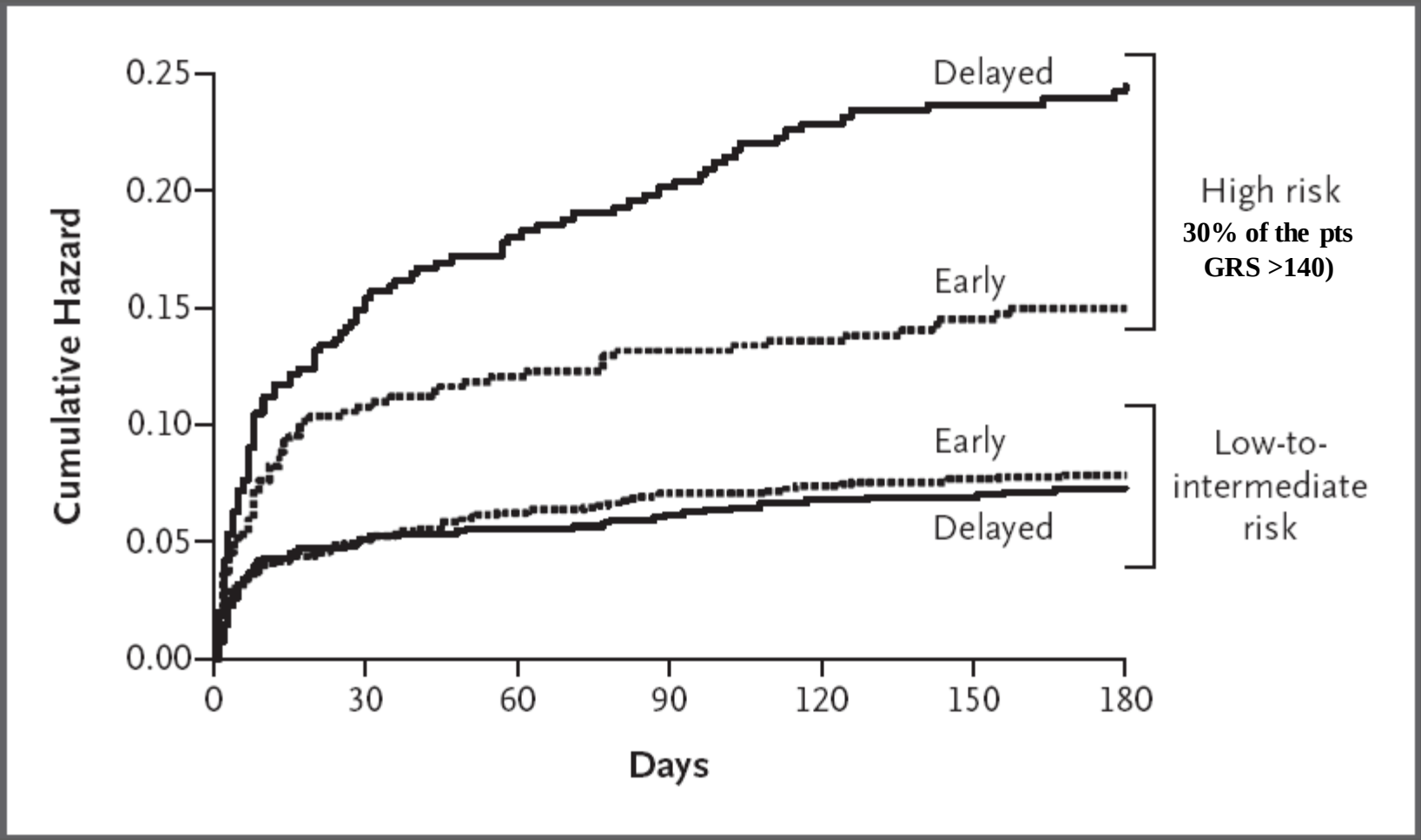




Troponins elevated or not

Impact of early intervention in HR pts With NSTEACS: the TIMACS study

Risk of Death, MI or stroke



Mehta SR, NEJM 2009;360:2165-75

Impact of early intervention in HR pts With NSTEACS: the TIMACS study

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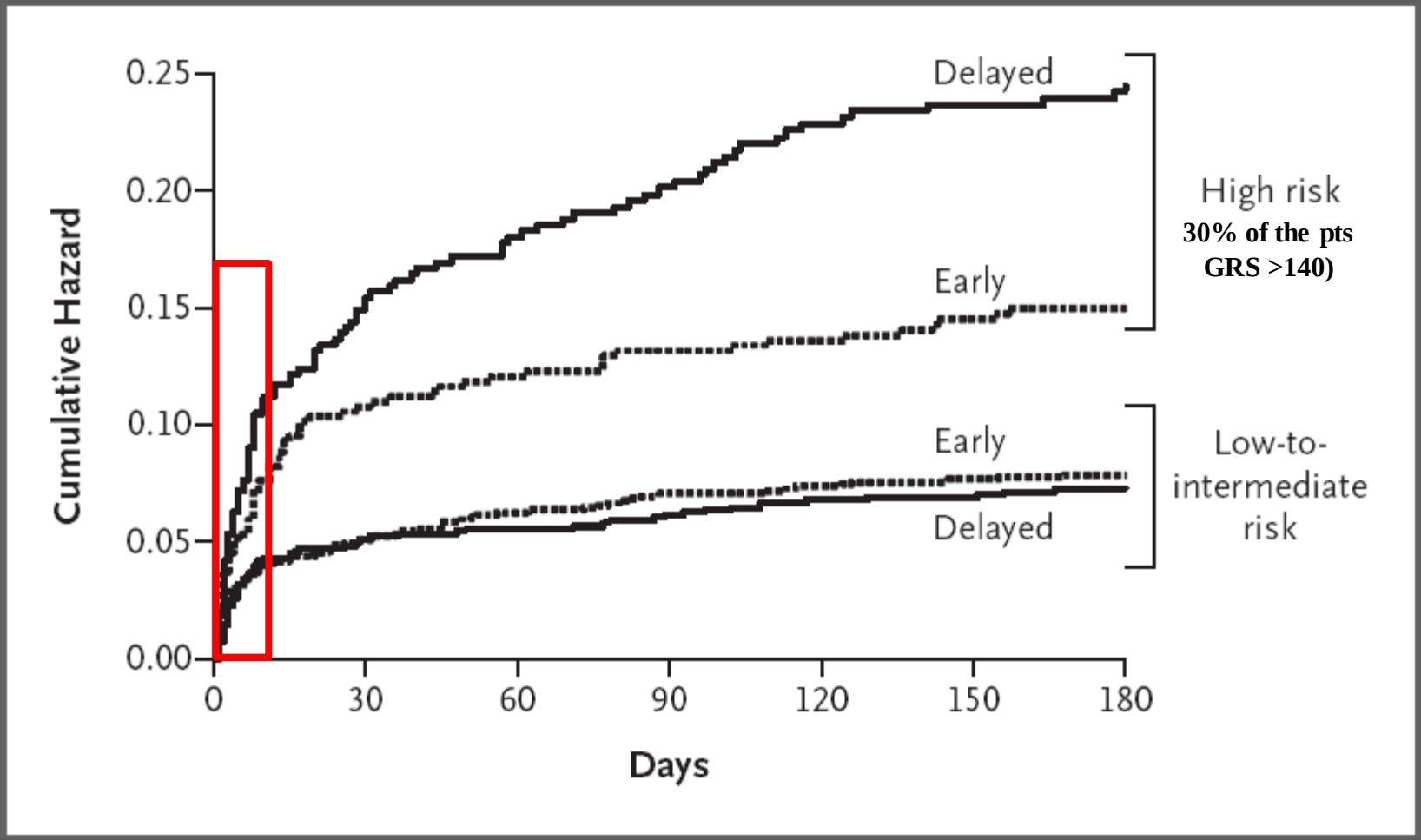
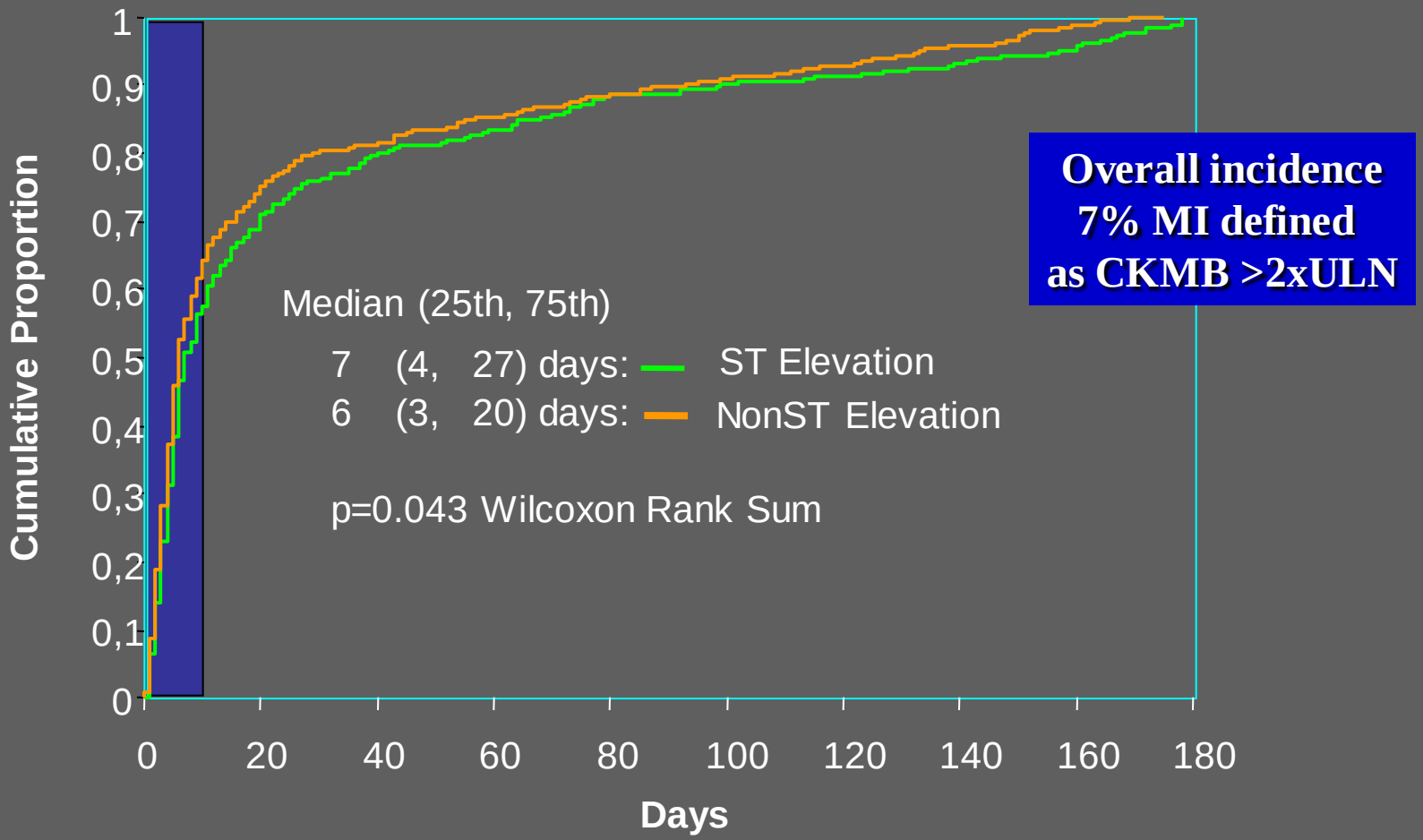


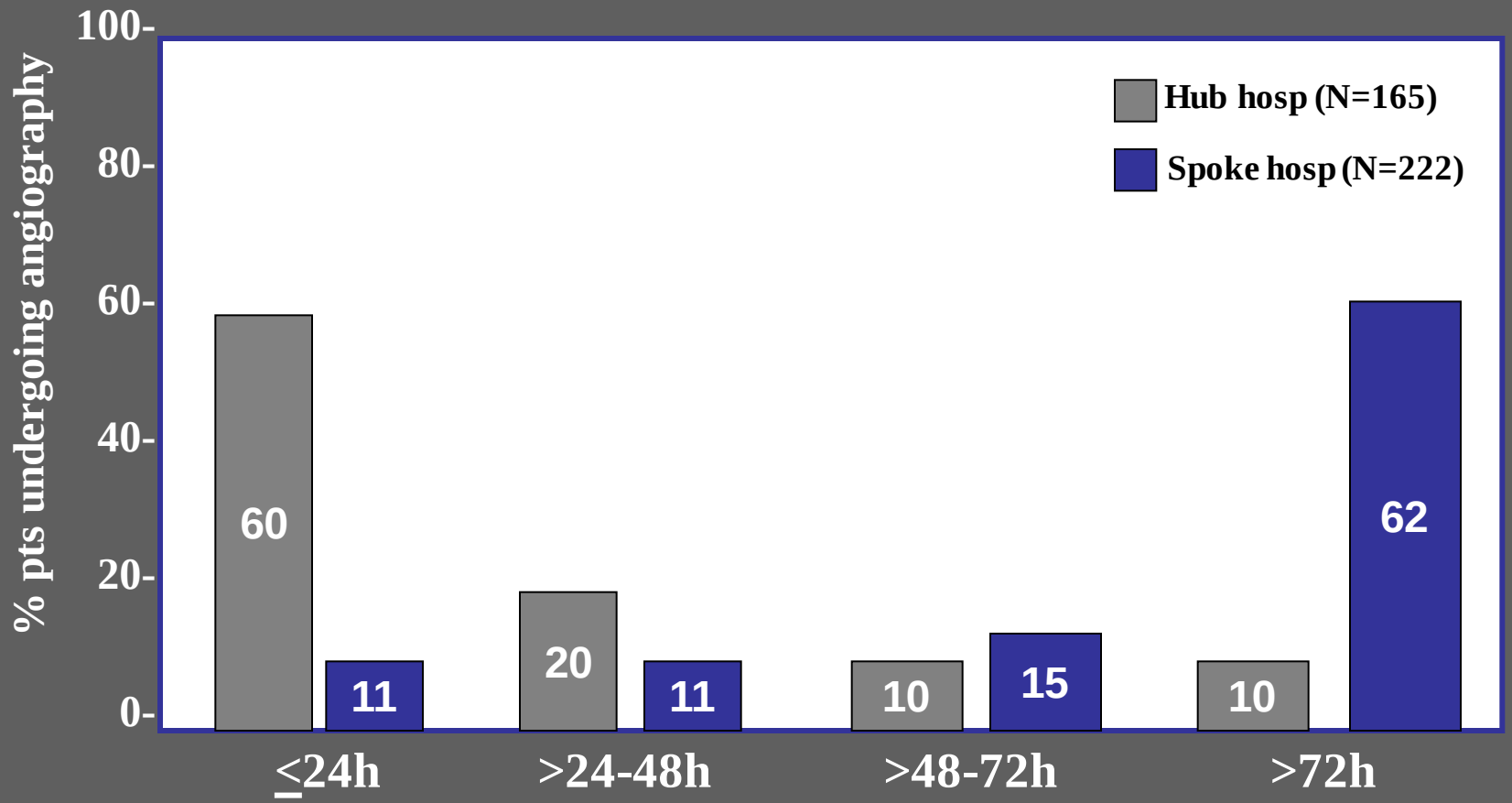
Mehta SR, NEJM 2009;360:2165-75

Cumulative Distribution of Time to (re)MI in ACS: the GUSTO IIb study



Savonitto S, JACC 2002;39:22-9

Time to angiography among NSTEACS pts
In hub and spoke hospitals of the Reggio Emilia province



Savonitto S et al. GIC 2012;13:157-68

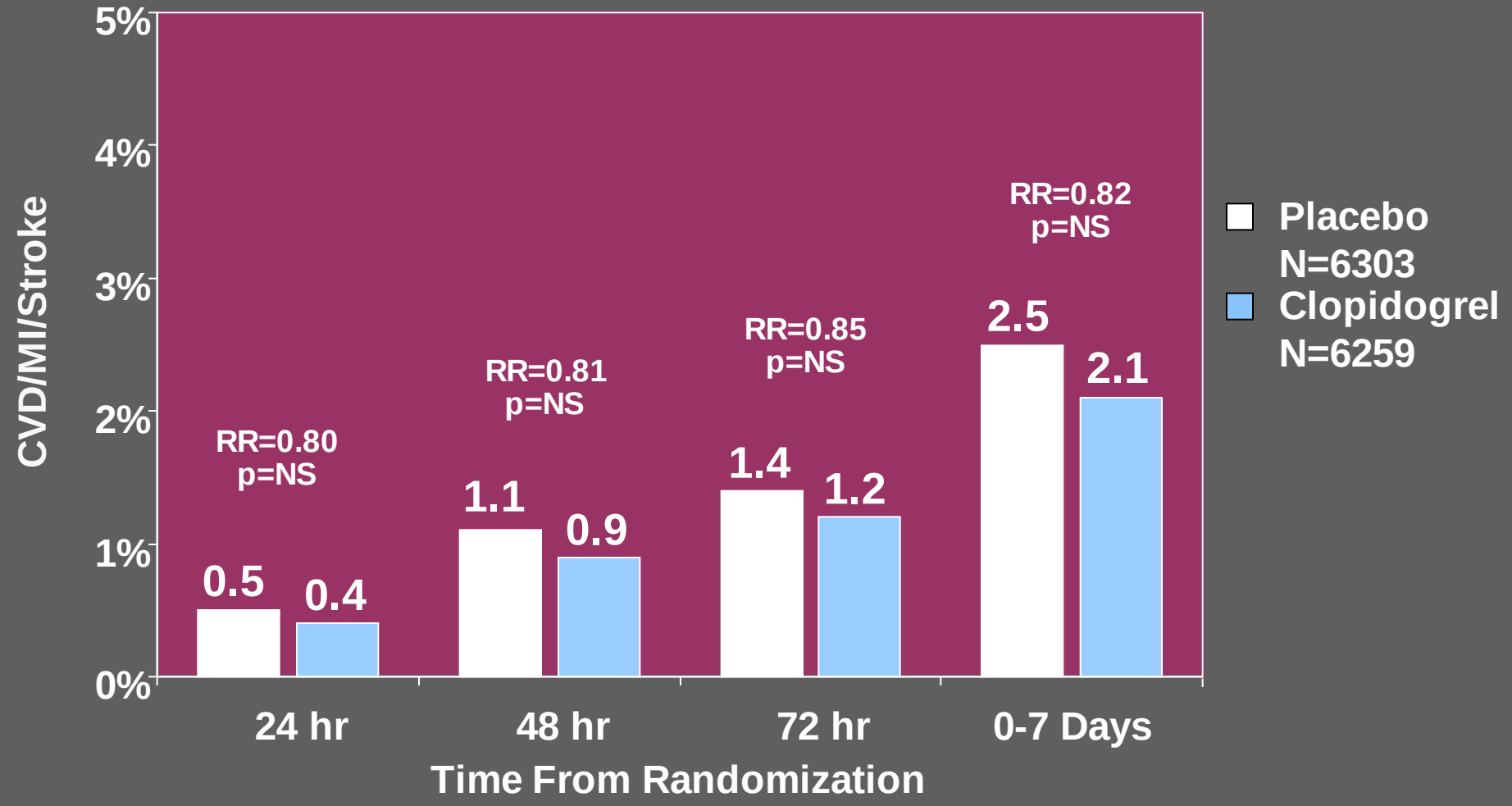
Contemporary recommendations on Antiplatelet therapy in NSTEACS PCI

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

European Heart Journal
doi:10.1093/eurheartj/ehq277

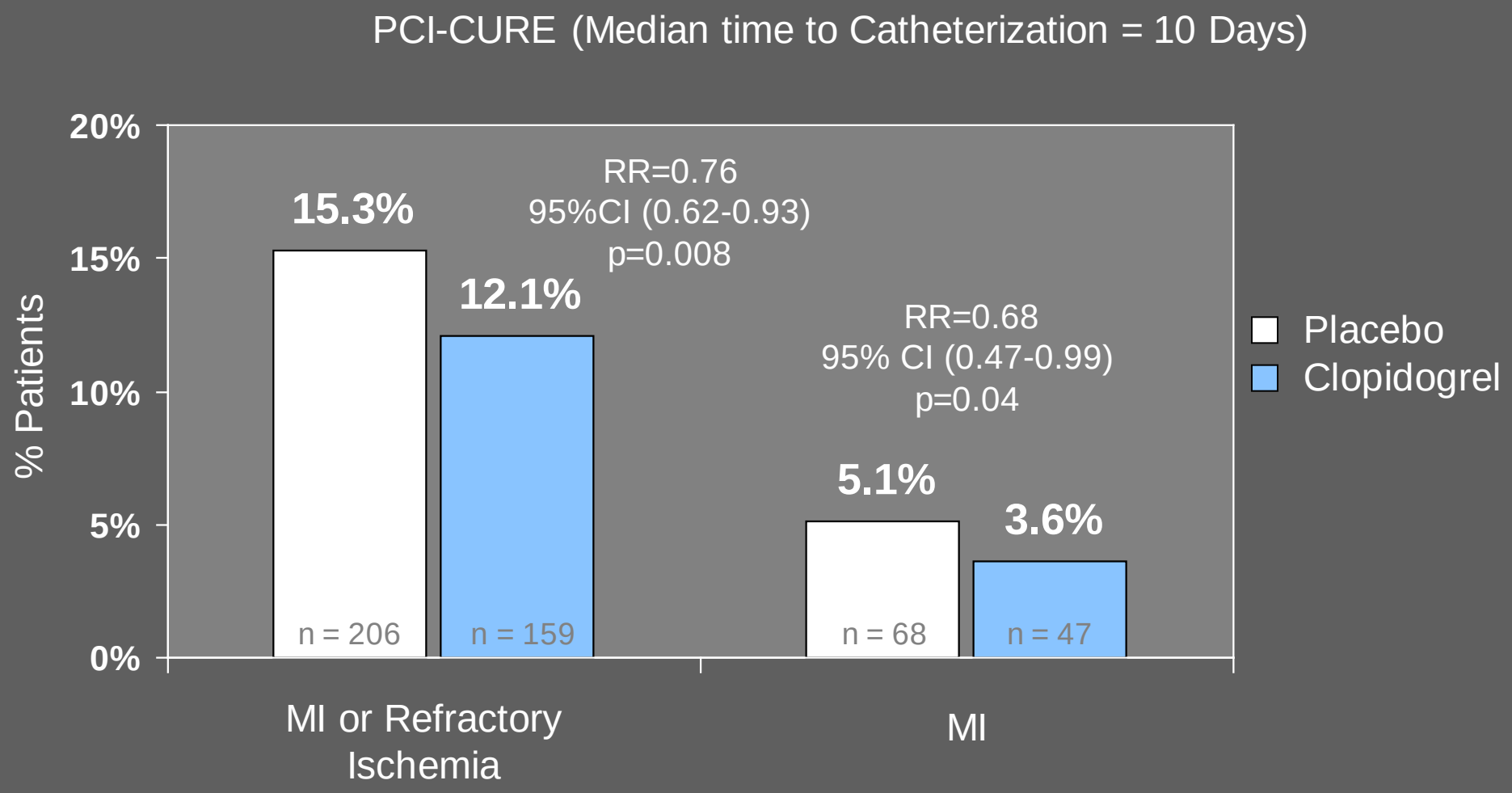
ESC/EACTS GUIDELINES

CURE: Early Impact of Clopidogrel in UA/NSTEMI



Yusuf S. Circulation 2003;107:968

Clopidogrel Pretreatment: Events in UA/NSTEMI Before Cardiac Catheterization



Mehta SR et al. *Lancet* 2001;358:527-533

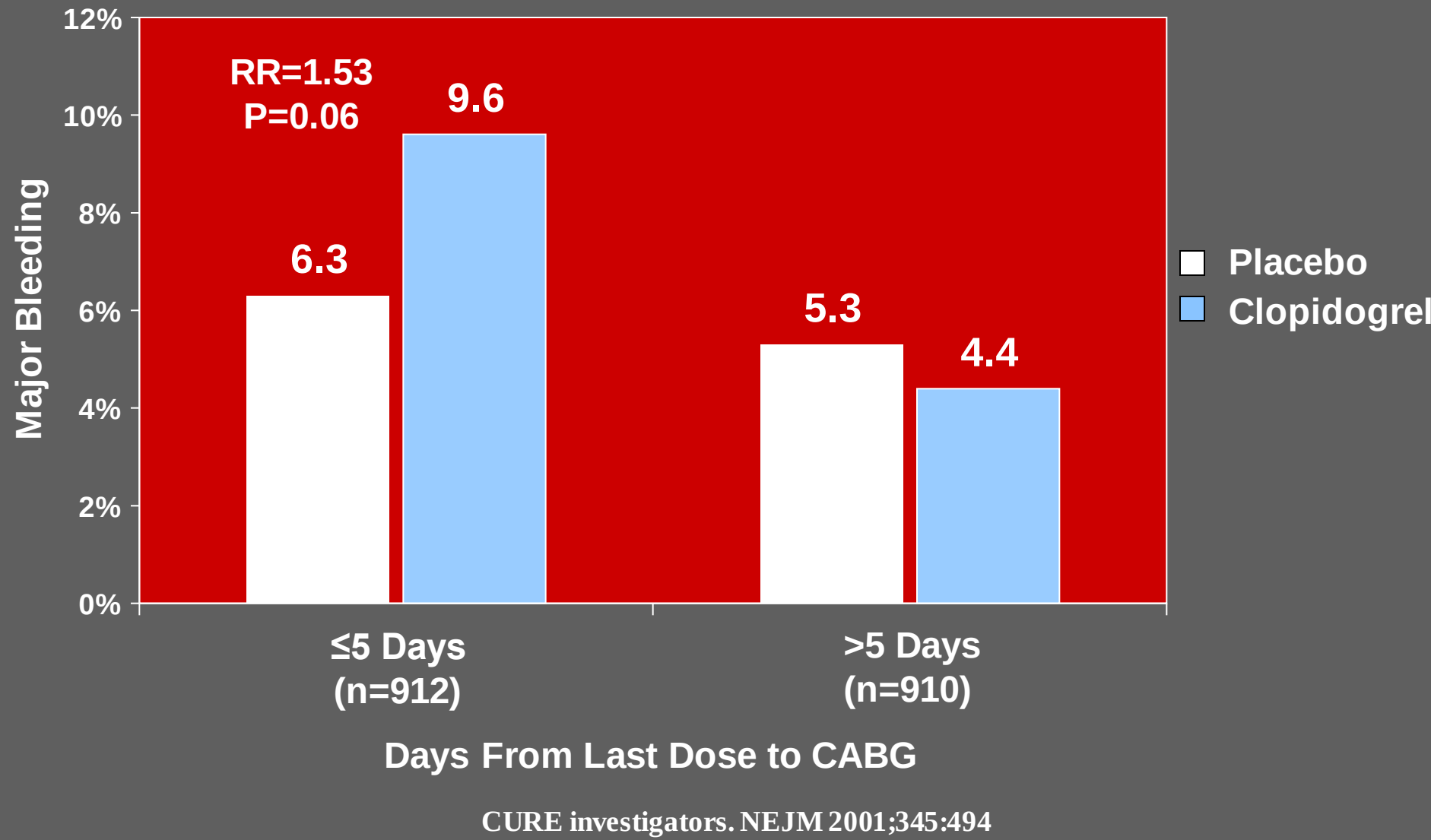
Clopidogrel: Double vs Standard Dose Primary Outcome and Components

CURRENT

Yusuf S, NEJM 2010

	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	4.5	3.9	0.85	0.74-0.99	0.036	0.016
No PCI (2N=7855)	4.2	4.9	1.17	0.95-1.44	0.14	
Overall (2N=25,087)	4.4	4.2	0.95	0.84-1.07	0.370	
MI						
PCI (2N=17,232)	2.6	2.0	0.78	0.64-0.95	0.012	0.025
No PCI (2N=7855)	1.4	1.7	1.25	0.87-1.79	0.23	
Overall (2N=25,087)	2.2	1.9	0.86	0.73-1.03	0.097	
CV Death						
PCI (2N=17,232)	1.9	1.9	0.96	0.77-1.19	0.68	1.0
No PCI (2N=7855)	2.8	2.7	0.96	0.74-1.26	0.77	
Overall (2N=25,087)	2.2	2.1	0.96	0.81-1.14	0.628	
Stroke						
PCI (2N=17,232)	0.4	0.4	0.88	0.55-1.41	0.59	0.50
No PCI (2N=7855)	0.8	0.9	1.11	0.68-1.82	0.67	
Overall (2N=25,087)	0.5	0.5	0.99	0.70-1.39	0.950	

CURE: CABG Bleeding

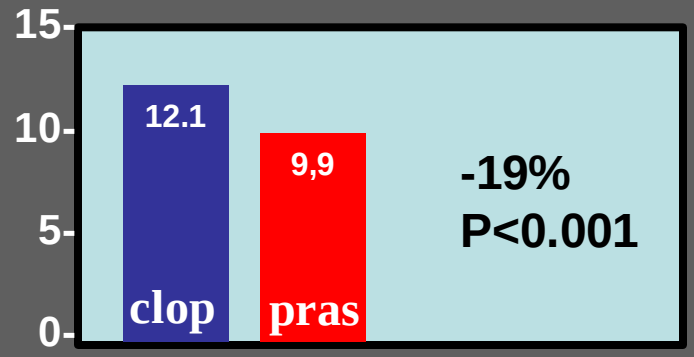


CURE investigators. NEJM 2001;345:494

New P2Y12 inhibitors in ACS: ischemic endpoints

PRASUGREL

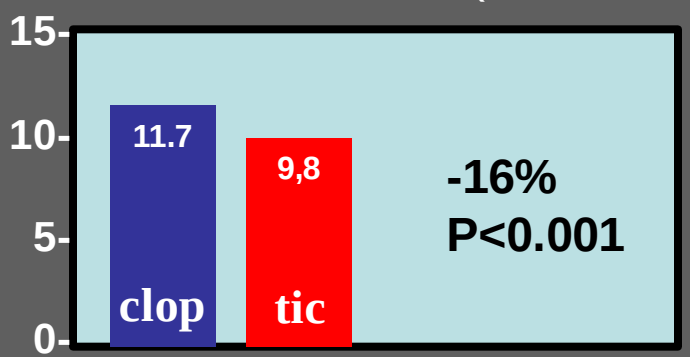
TRITON OVERALL (n=13,608)



Wiviott S. NEJM 2007

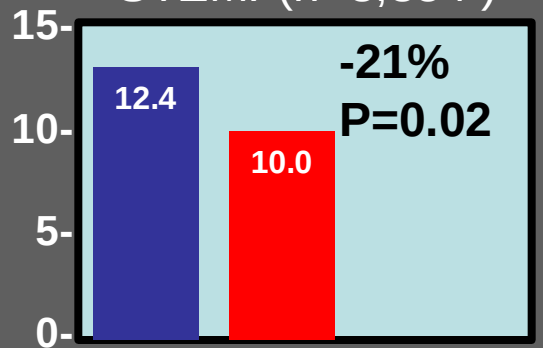
TICAGRELOR

PLATO OVERALL (n=18,624)



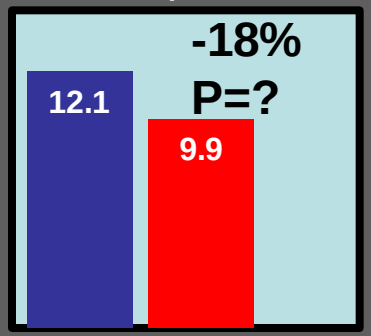
Wallentin L. NEJM 2009

STEMI (n=3,354)



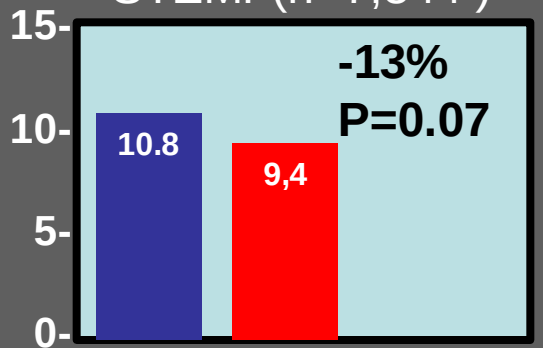
Montalescot G. Circ 2008

NSTE (n=10,074)



?

STEMI (n=7,544)



Steg G. Circ 2010

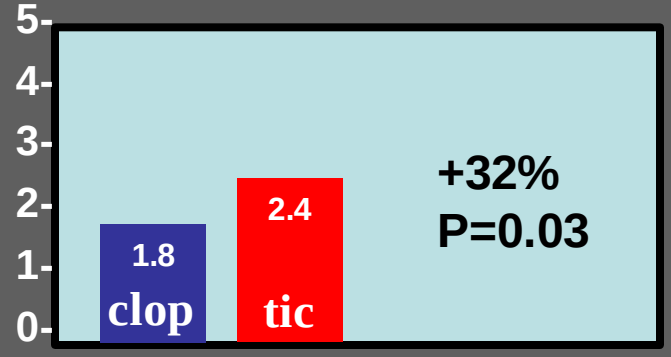
NSTE (n=11,067)

?

New P2Y12 inhibitors in ACS: non-CABGmajor bleeding

PRASUGREL

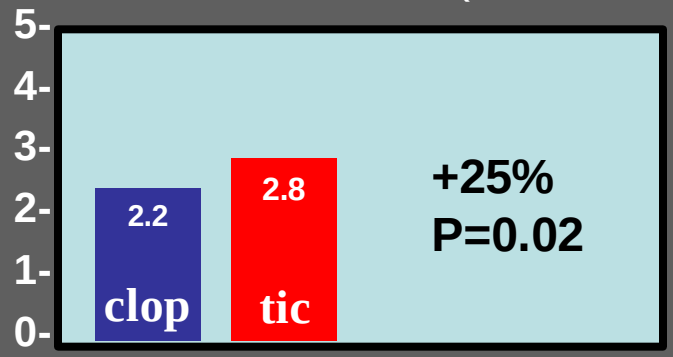
TRITON OVERALL (n=13,608)



Wiviott S. NEJM 2007

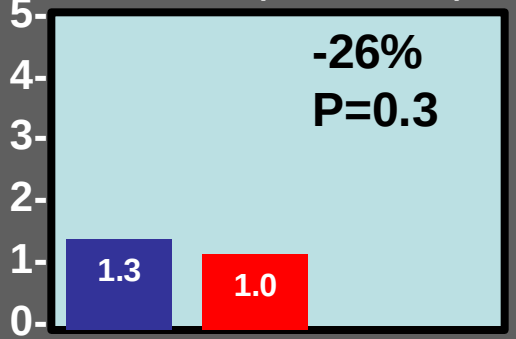
TICAGRELOR

PLATO OVERALL (n=18,624)



Becker RC. EHJ 2011

STEMI (n=3,354)

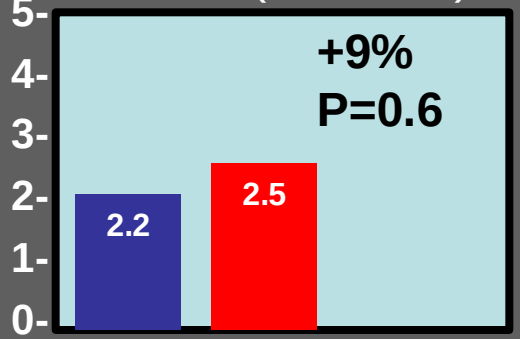


Montalescot G. Circ 2008

NSTE (n=10,074)

?

STEMI (n=7,544)

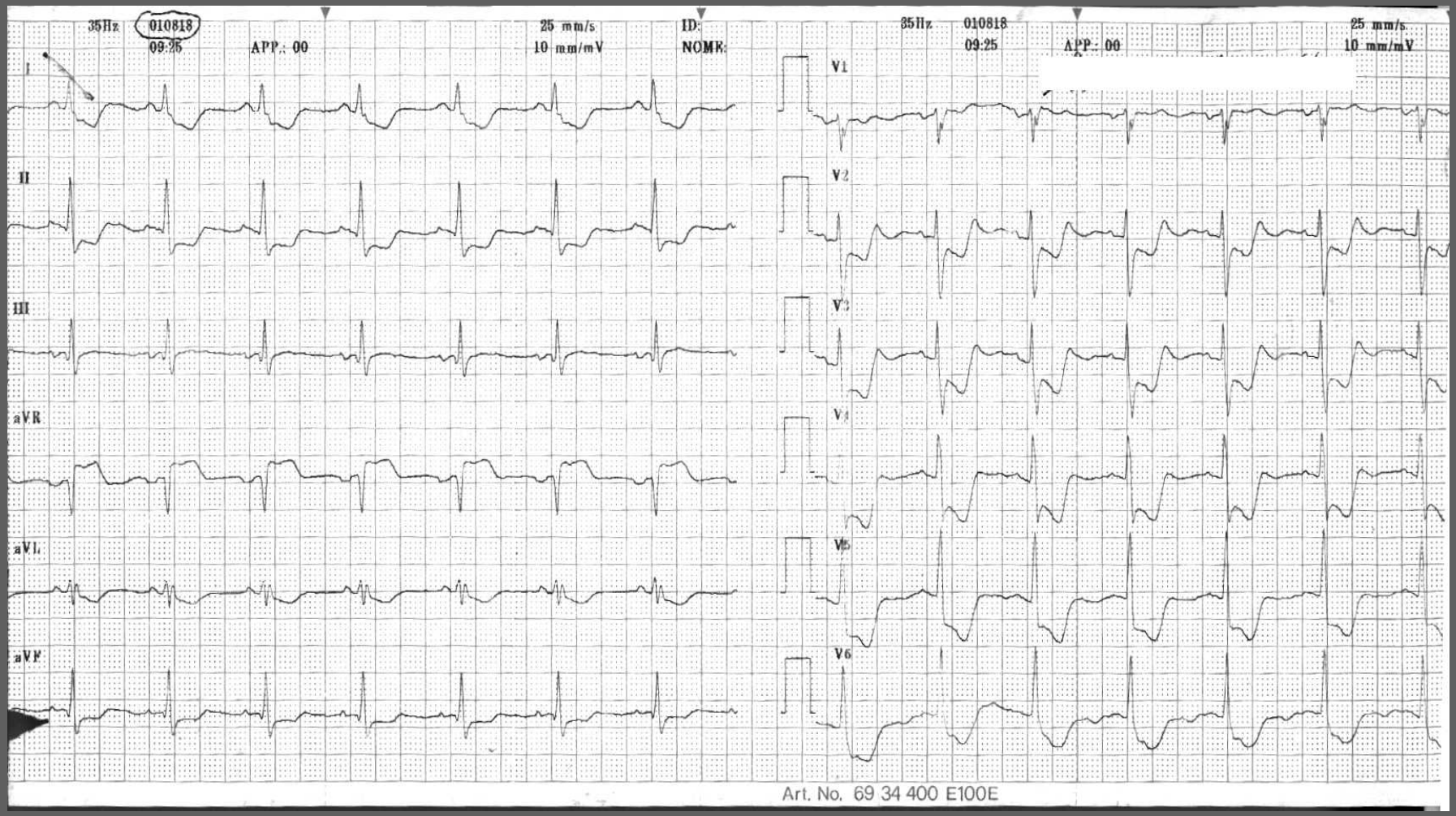


Steg G. Circ 2010

NSTE (n=11,067)

?

How would you treat this patient?



ACUITY: Invasive Management

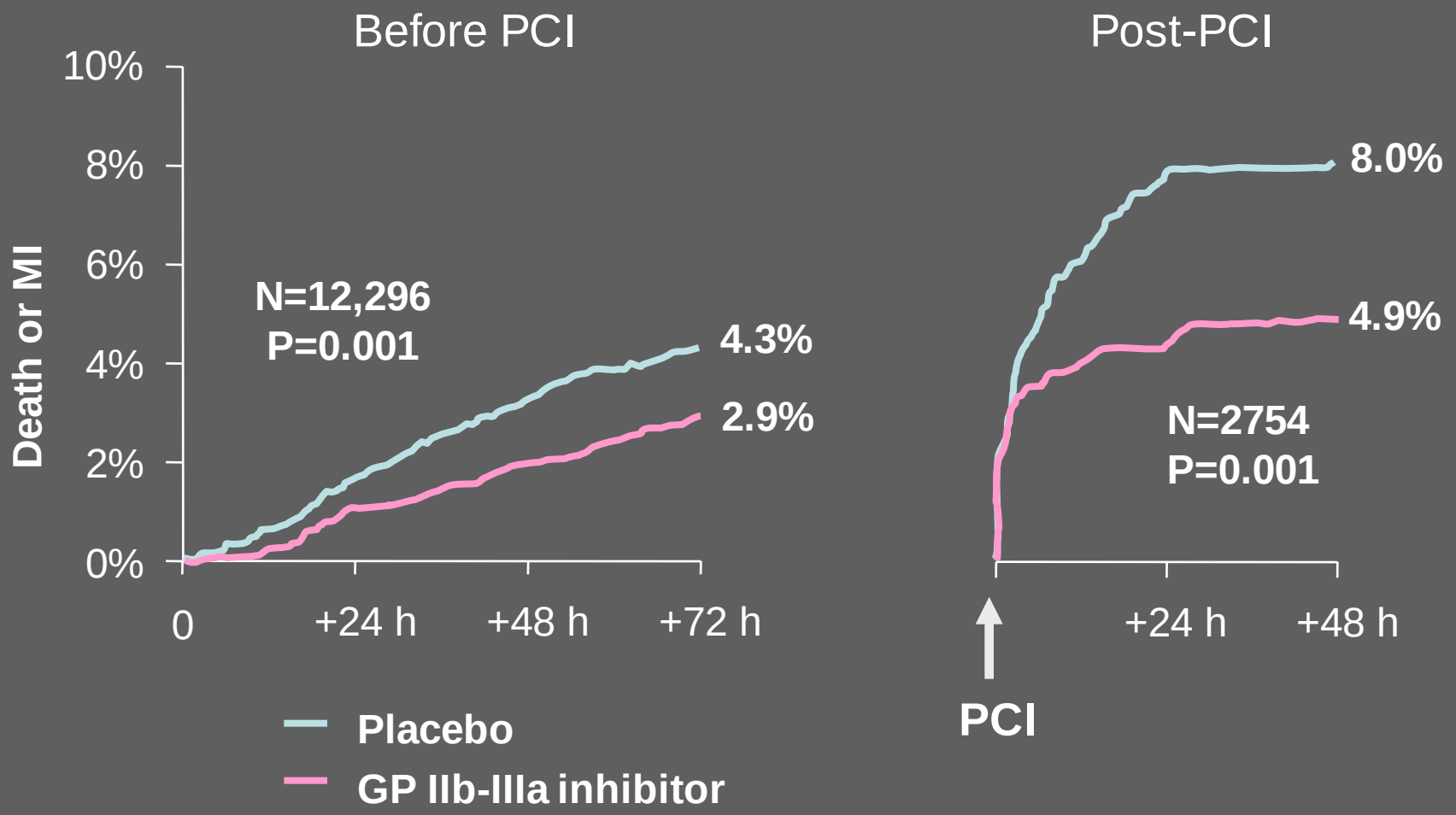
	UFH/Enoxaparin + GP IIb/IIIa (N=4,603)	Bivalirudin + GP IIb/IIIa (N=4,604)	Bivalirudin alone (N=4,612)
Angiography	99.2%	98.8%	98.9%
Adm. to angio (h)	19.7 (7.0-29.3)†	19.5 (7.0-28.2)†	19.8 (7.3-29.0)†
Drug* to angio/interv (h)	5.6 (1.6-22.5)†	5.0 (1.4-21.4)†	5.2 (1.5-22.5)†
Actual procedure			
PCI	55.6%	56.7%	56.8%
CABG	11.9%	10.8%	10.6%
Medical therapy	32.4%	32.5%	32.6%

†median (IQR)

Stone GW. NEJM 2006;355:2203

GP IIb-IIIa Blockade Before and After PCI:
CAPTURE, PURSUIT, PRISM-PLUS

Boersma E, et al. Lancet. 2002;359:189-198.



The NEW ENGLAND JOURNAL of MEDICINE

Giugliano RP. N Engl J Med 2009;360:2176-90

ORIGINAL ARTICLE

Early versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes

Robert P. Giugliano, M.D., S.M., Jennifer A. White, M.S., Christoph Bode, M.D., Paul W. Armstrong, M.D., Gilles Montalescot, M.D., Basil S. Lewis, M.D., Arnoud van 't Hof, M.D., Lisa G. Berdan, P.A., M.H.S., Kerry L. Lee, Ph.D., John T. Strony, M.D., Steven Hildemann, M.D., Enrico Veltri, M.D., Frans Van de Werf, M.D., Ph.D., Eugene Braunwald, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and L. Kristin Newby, M.D., M.H.S., for the EARLY ACS Investigators*

What Early ACS really showed?

The initial sample size (10,500 patients) provided a power of 85% to detect a 22.5% relative reduction in the rate of the primary efficacy end point in the early-eptifibatide group, as compared with the delayed-eptifibatide group, assuming a 96-hour event rate of 5.8% in the latter group. This sample size preserved a power of 85% to detect a 15% reduction in the rate of death or myocardial infarction at 30 days in the early-eptifibatide group. The executive committee regularly reviewed pooled event rates in a blinded fashion. Since the rate of the observed composite primary end point was nearly twice the initial projection (5.2%) after the enrollment of 6822 patients, the executive committee recommended a sample-size reduction to 9500 patients, which provided a power of 98% for the composite primary end point and 81% for the composite secondary end point.

PE: D+MI+ recurrent ischemia requiring urgent revasc, or thrombotic bailout at 96 h

SE: D+MI at 30 days

One prespecified interim efficacy analysis was conducted after approximately 50% of the patients had been enrolled. O'Brien–Fleming stopping boundaries were generated for between-group comparisons, with a one-sided nominal alpha level of 0.0026. Thus, the final primary analysis compared the study groups at a two-sided alpha level of 0.048. The protocol specified a step-down testing procedure, requiring that the test of the primary end point be significant before the key secondary end point was tested (also at an alpha level of 0.048).

What Early ACS really showed?

2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)

The primary endpoint (a 30-day composite of all-cause death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours) occurred in 9.3% of patients in the early therapy arm versus 10.0% of patients in the provisional GP IIb/IIIa inhibitor therapy arm (OR: 0.92; 95% CI: 0.80 to 1.06; P=0.23). Secondary endpoint (all-cause death or MI within 30 days) event rates were 11.2% versus 12.3% (OR: 0.89; 95% CI: 0.79 to 1.01; P=0.08).

Giugliano RP. N Engl J Med 2009;360:2176-90

30-day Primary Efficacy Results after shrinking the power

	Early Eptifibatide (n=4722)	Delayed Eptifibatide (n=4684)	OR (95% CI)	P
death or MI	11.2	12.3	0.89 (0.79–1.01)	0.079
Death	2.8	2.6	1.10 (0.86–1.41)	0.46
Myocardial infarction	9.5	10.6	0.88 (0.77–1.01)	0.073
Death, MI, RI req urg revasc	12.5	13.8	0.89 (0.79–1.01)	0.065
RI req urg revasc	2.4	2.9	0.80 (0.62–1.03)	0.083

Giugliano RP. N Engl J Med 2009;360:2176-90

Strategy During First 96 Hours

Randomization N=9406

Medical Only	N=3490
PCI	N=5389
CABG	N=519

Early Eptifibatide (N=4718)
Total Events = 439

- Medical Only (N=1784) Total Events = 71
- CABG (N=268) Pre-CABG Events = 33 Post-CABG Events = 52
- PCI (N=2666) Pre-PCI Events = 82 Post-PCI Events = 201

Delayed Provisional Eptifibatide (N=4680)
Total Events = 469

- Medical Only (N=1706) Total Events = 71
- CABG (N=251) Pre-CABG Events = 22 Post CABG Events = 46
- PCI (N=2723) Pre-PCI Events = 87 Post-PCI Events = 243

Total Events on Medical Treatment = 71 + 82 +33

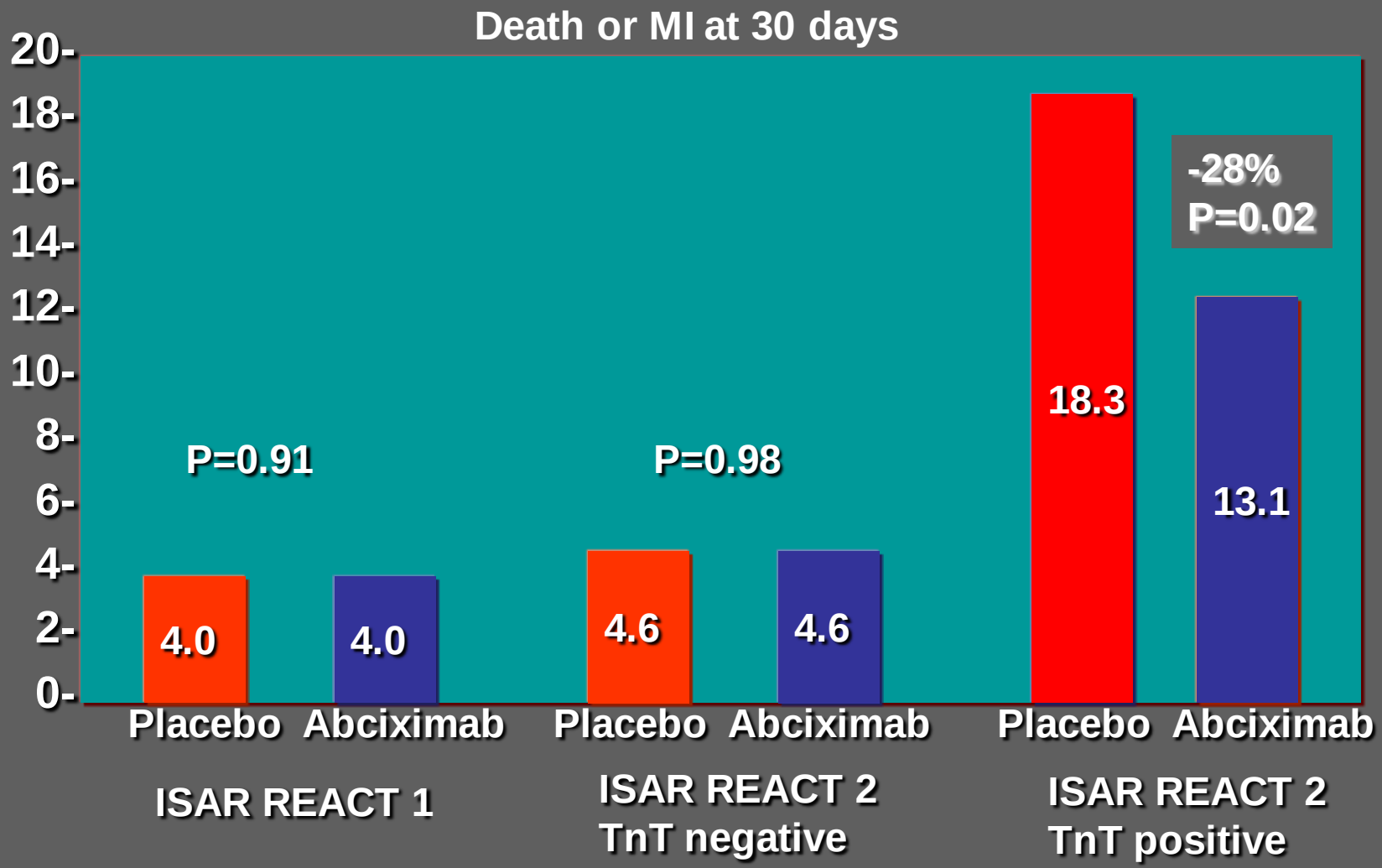
Group	Events	Risk	Rate
Medical	186	4718	4.1%
Post PCI	201	2584	8.0%
Post CABG	52	235	23.4%

-24%

Total Events on Medical Treatment = 71 + 87 + 22

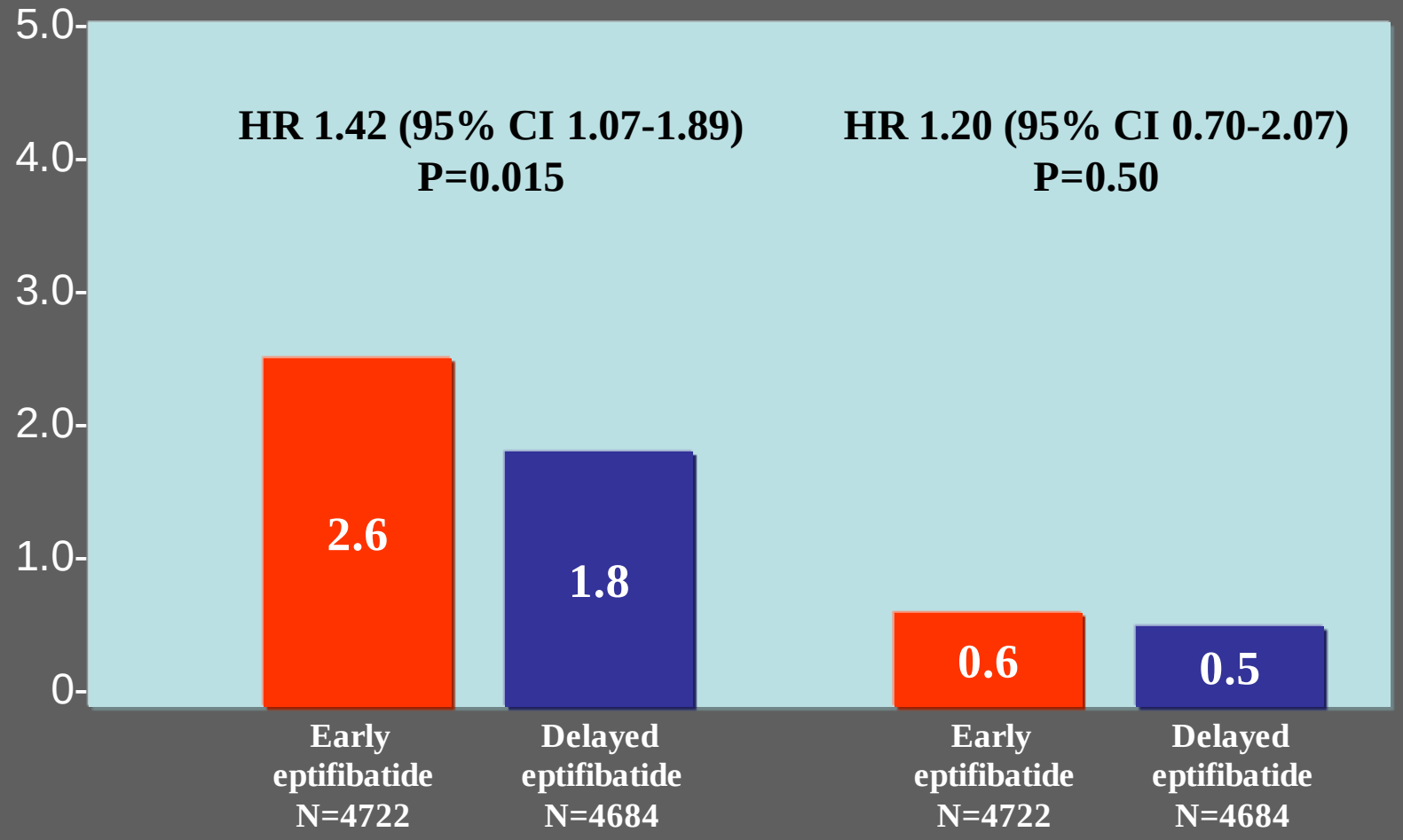
Group	Events	Risk	Rate
Medical	180	4680	4.0%
Post PCI	243	2636	10.5%
Post CABG	46	229	20.6%

Impact of abciximab on top of ASA and clopidogrel



Kastrati A, NEJM 2004, JAMA2006

Major bleeding



Giugliano RP. N Engl J Med 2009;360:2176-90

Contemporary recommendations on Antiplatelet therapy in NSTEACS PCI

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
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	Abciximab (with DAPT)	I	B	249
	Tirofiban, Eptifibatide	IIa	B	55
	Upstream GPIIb–IIIa antagonists	III	B	65

European Heart Journal
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

ACC/AHA NSTEACS Guidelines

Table 2. Recommendations for Antiplatelet Therapy

2012 Focused Update Recommendations

Class I

1. Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.[59–66] *(Level of Evidence: A)*
2. A loading dose followed by daily maintenance dose of either clopidogrel[13,67,68] *(Level of Evidence: B)*, prasugrel* (in PCI-treated patients)[7] *(Level of Evidence: C)*, or ticagrelor†[9] *(Level of Evidence: C)* should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major GI intolerance.
3. Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected (Appendix 6) should receive dual antiplatelet therapy on presentation.[13,16,45,69] *(Level of Evidence: A)* Aspirin should be initiated on presentation.[59,61–66] *(Level of Evidence: A)* The choice of a second antiplatelet therapy to be added to aspirin on presentation includes 1 of the following (note that there are no data for therapy with 2 concurrent $P2Y_{12}$ receptor inhibitors, and this is not recommended in the case of aspirin allergy):

   Before PCI:

   - Clopidogrel[13,16] *(Level of Evidence: B)*; or
   - Ticagrelor†[9] *(Level of Evidence: B)*; or
   - An IV GP IIb/IIIa inhibitor.[45,50,51,70,71] *(Level of Evidence: A)* IV eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors.[50,51] *(Level of Evidence: B)*

   At the time of PCI:

   - Clopidogrel if not started before PCI[13,16] *(Level of Evidence: A)*; or
   - Prasugrel*[7] *(Level of Evidence: B)*; or
   - Ticagrelor†[9] *(Level of Evidence: B)*; or
   - An IV GP IIb/IIIa inhibitor.[46,50,51] *(Level of Evidence: A)*

ACC/AHA NSTEACS Guidelines

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2. A loading dose followed by daily maintenance dose of either clopidogrel[13,67,68] *(Level of Evidence: B)*, prasugrel* (in

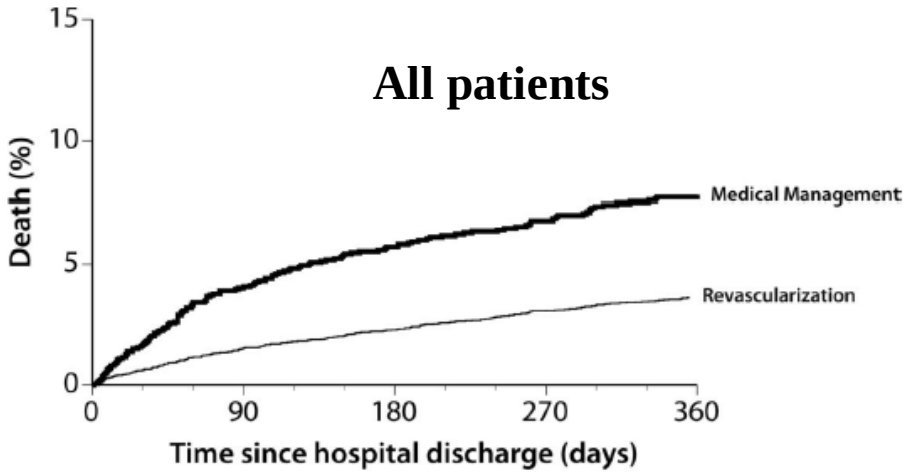
Although early GP IIb/IIIa inhibitor therapy as dual antiplatelet therapy also reduced complications after PCI, supporting its continued role in patients undergoing PCI,[49,53,54,56,58] these 2 most recent studies[56,57] more strongly support a strategy of selective rather than routine upstream use of GP IIb/IIIa inhibitor therapy as part of triple antiplatelet therapy.

inhibitors.[...] *(Level of Evidence: B)*

At the time of PCI:

- Clopidogrel if not started before PCI[13,16] *(Level of Evidence: A)*; or
- Prasugrel*[7] *(Level of Evidence: B)*; or
- Ticagrelor†[9] *(Level of Evidence: B)*; or
- An IV GP IIb/IIIa inhibitor.[46,50,51] *(Level of Evidence: A)*

One-year mortality according to actual treatment after angiography

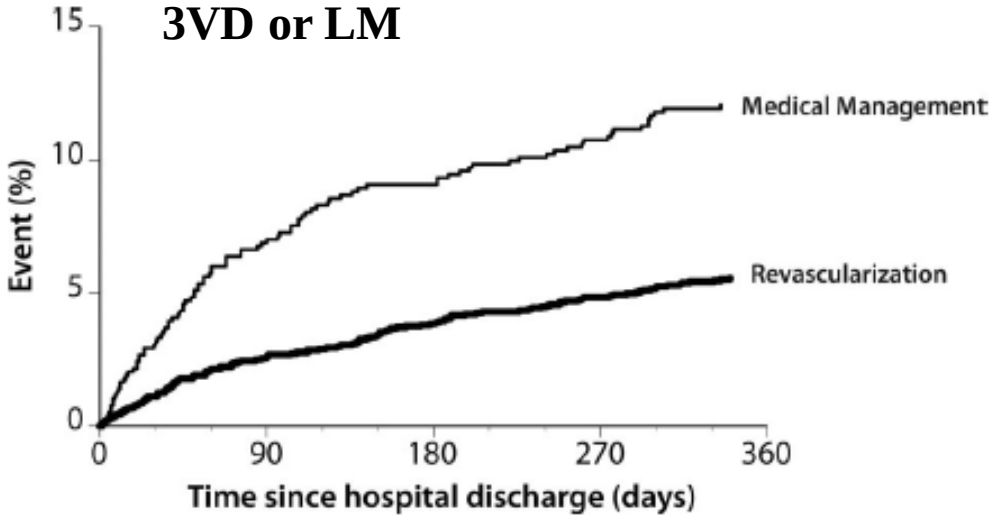


Medical Management					
Deaths	0	70	98	116	133
Number at Risk	1727	1642	1608	1587	1012
Revascularization					
Deaths	0	99	147	198	233
Number at Risk	6498	6315	6252	6194	3489

7.8% vs 3.6%; p<0.0001

12.1% vs 5.6%; p<0.0001

Roe MT. Circ CV Qual Outcomes 2012;5:205

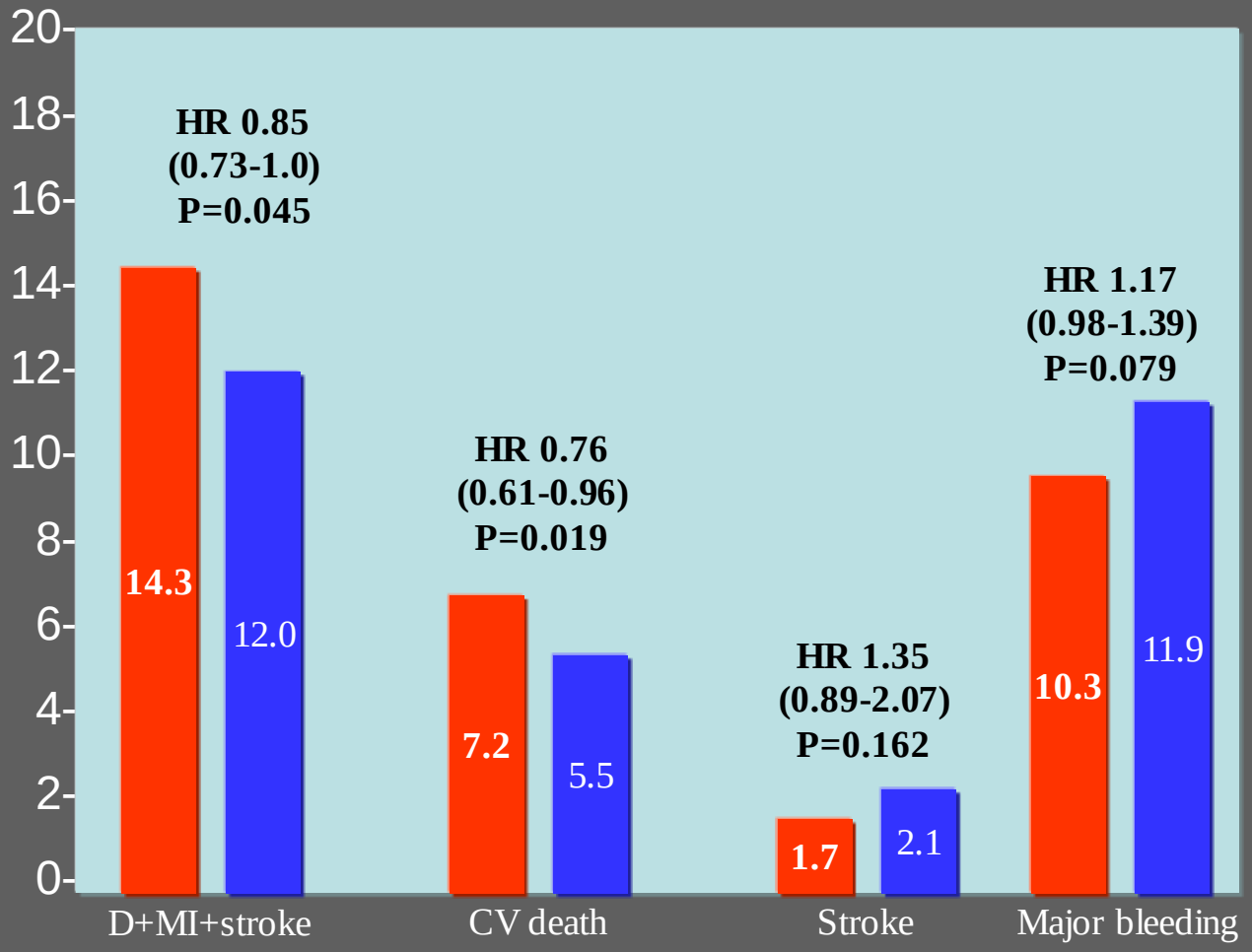


Medications at discharge according to in-H treatment: medical management vs revascularization

Medication, %	MM (n=1766)	Revasc (n=6621)	*P*-Value
Aspirin	93.3	97.2	<0.001
Clopidogrel	58.3	83.3	<0.001
Beta-blockers	83.4	84.4	0.28
ACE inhibitors	67.6	64.5	0.02
ARBs	10.6	8.8	0.02
Statins	85.2	87.0	0.05

Roe MT. Circ CV Qual Outcomes 2012;5:205

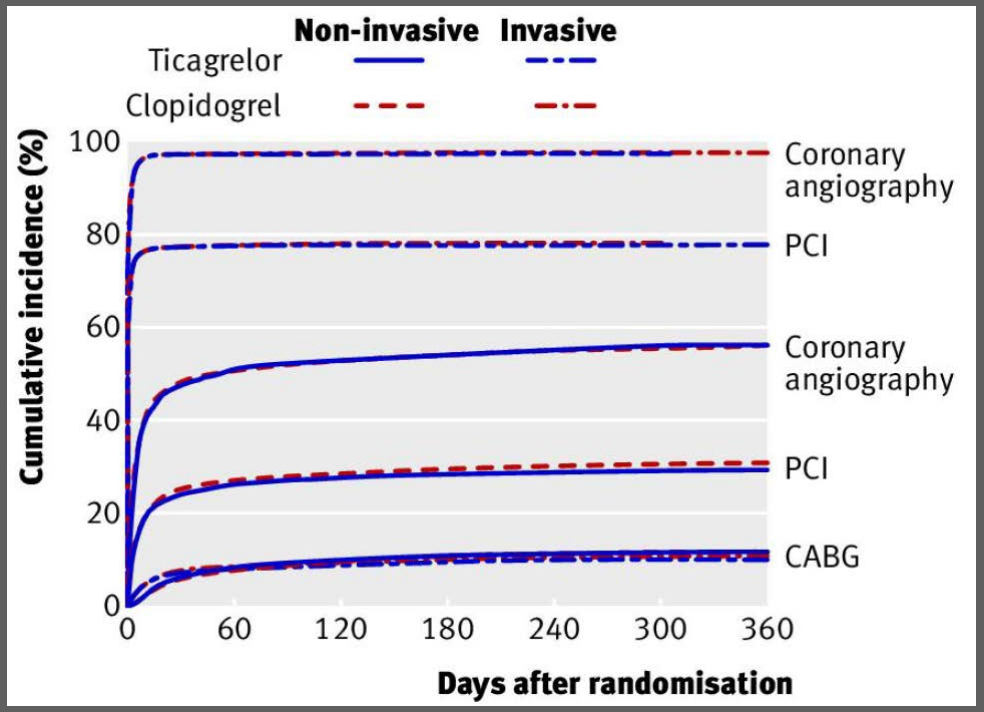
Kaplan Meier estimetes of efficacy and safety endpoints in patients intended for noninvasive management



James S. BMJ 2011; Jun 17;342:d3527. doi: 10.1136/bmj.d3527

Cumulative incidence of coronary angiography, PCI and CABG in patients intended for noninvasive management

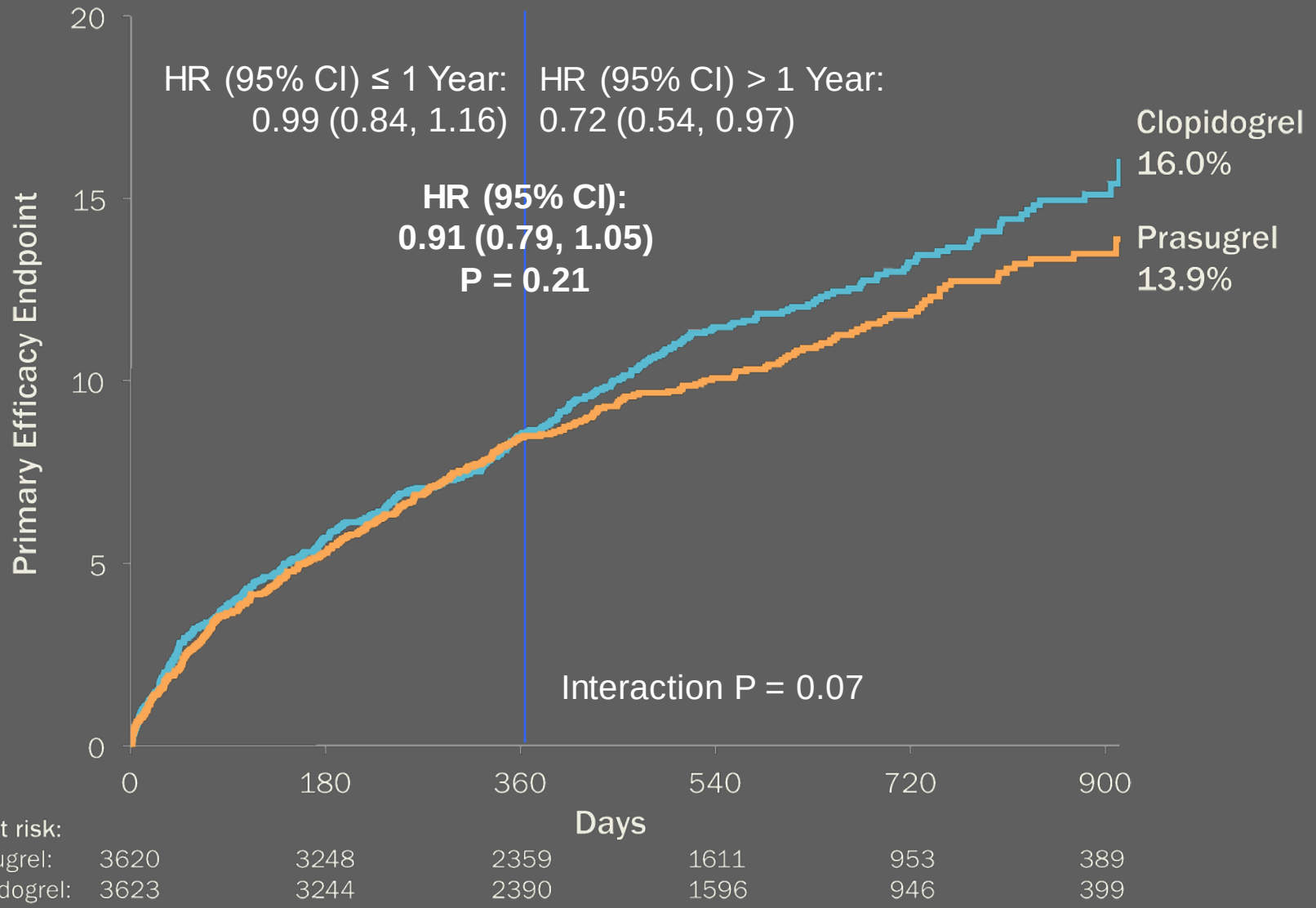
	Intended noninvasive Total (n=5216)	Planned invasive (n=13 408)
STE	8.7 (451/5202)	49.1 (6575/13 380)
NSTE	55.9 (2910/5202)	37.7 (5045/13 380)
UA	35.4 (1841/5202)	13.2 (1760/13 380)



James S. BMJ 2011; Jun 17;342:d3527. doi: 10.1136/bmj.d3527

Primary Efficacy Endpoint to 30 Months

(Age < 75 years)



Titolo: Antiplatelet therapy in ACS

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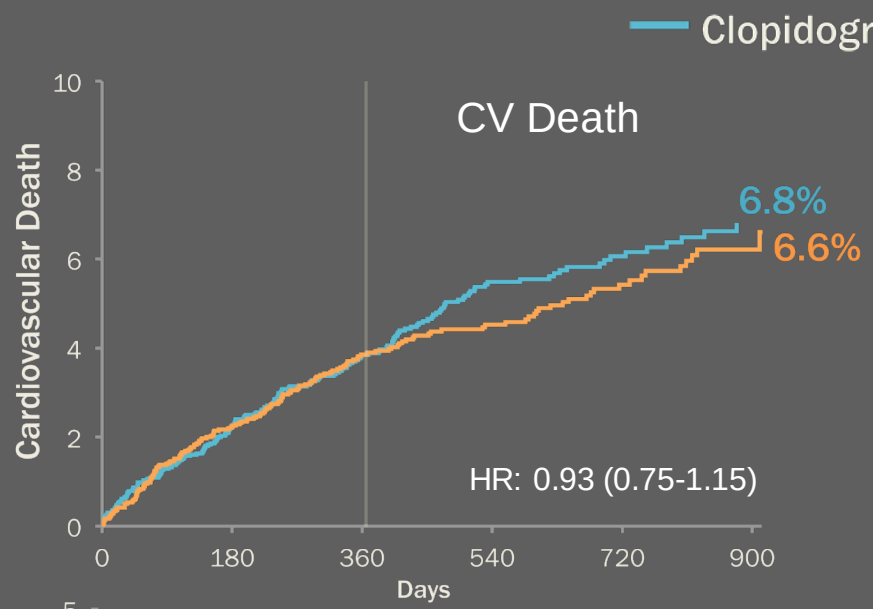
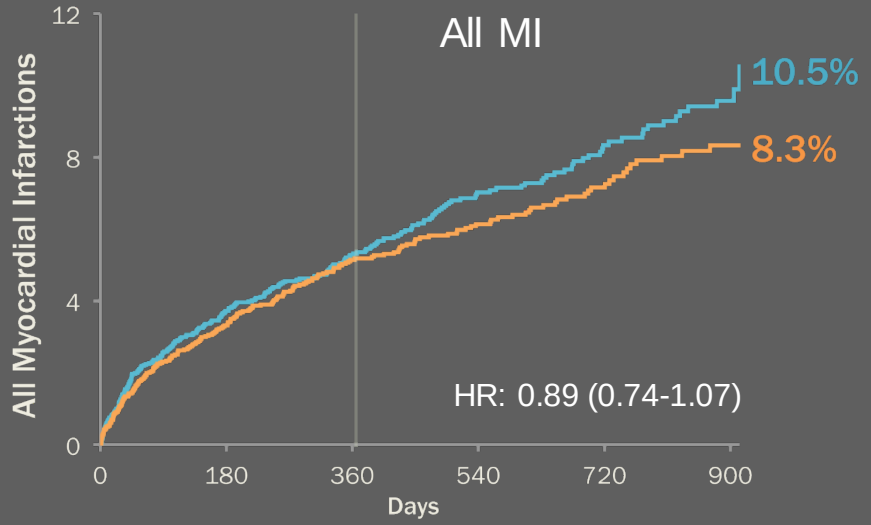
Roe MT. NEJM 2012;367:1297

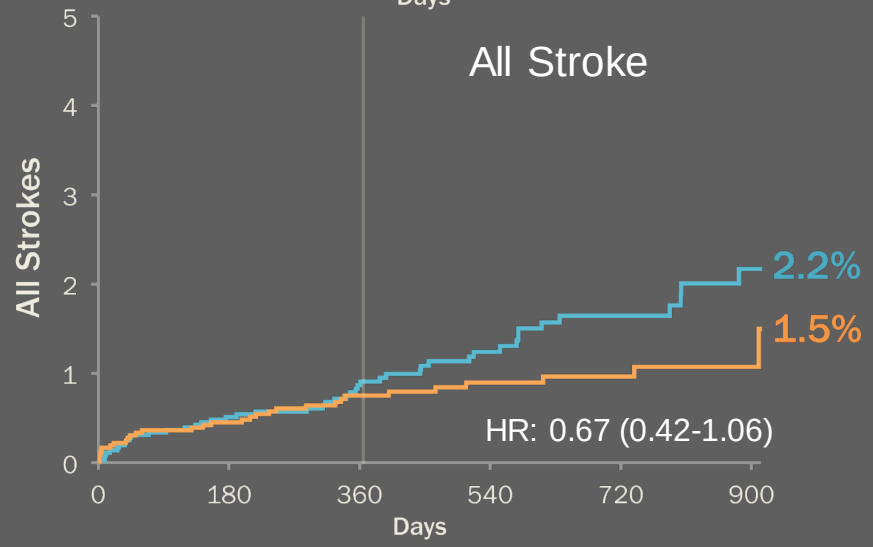
Data: 25 november 2012

Evento: Turin

Efficacy Component Endpoints to 30 Months
(Age < 75 years)







	HR (95% CI) ≤ 1 Year	HR (95% CI) > 1 Year
CV Death	1.00 (0.78, 1.28)	0.75 (0.49, 1.14)
All MI	0.97 (0.78, 1.19)	0.68 (0.46, 0.99)
All Stroke	0.86 (0.50, 1.47)	0.35 (0.14, 0.88)

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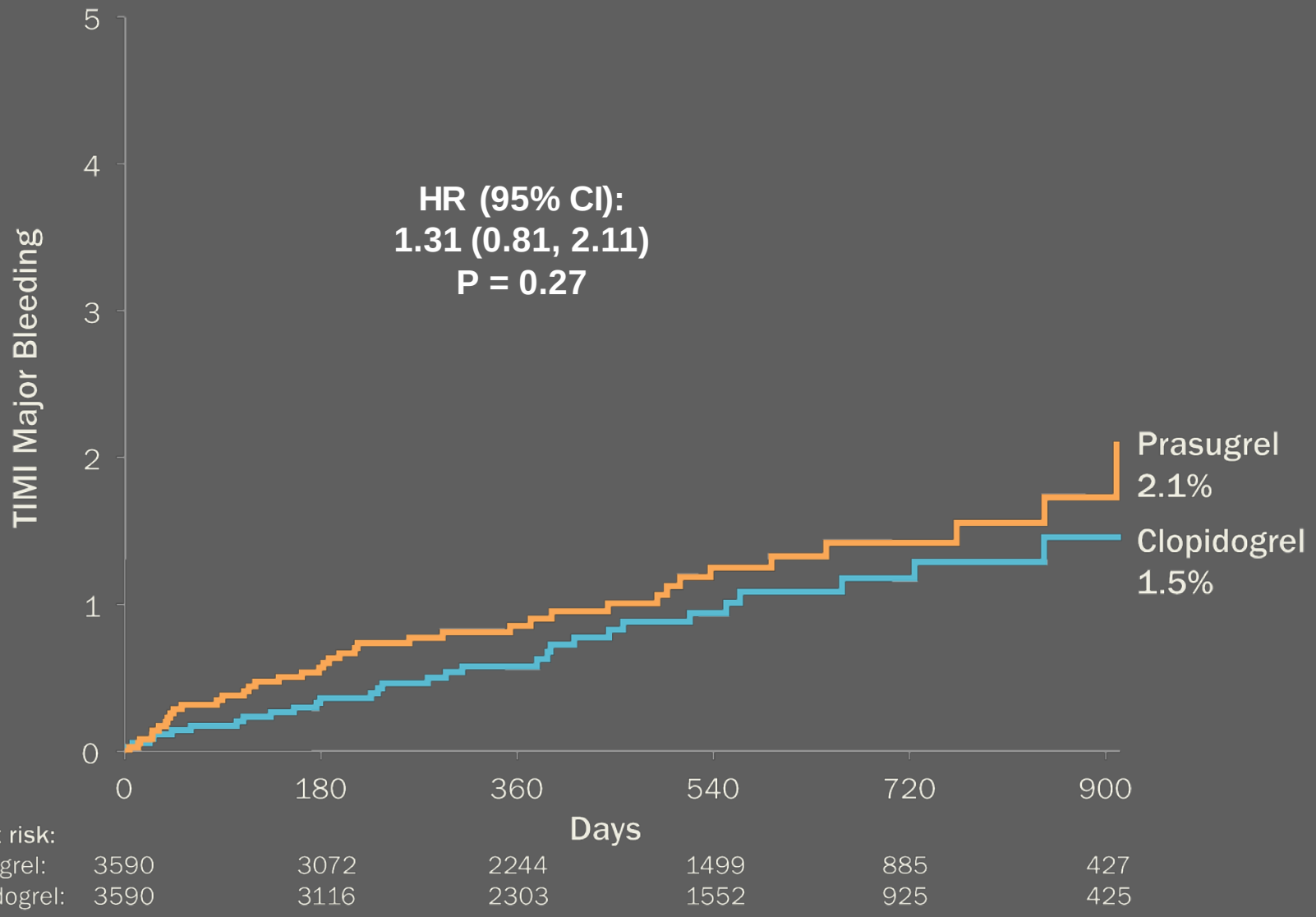
TIMI Major Bleeding to 30 Months
(Age < 75 years)



Roe MT. NEJM 2012;367:1297

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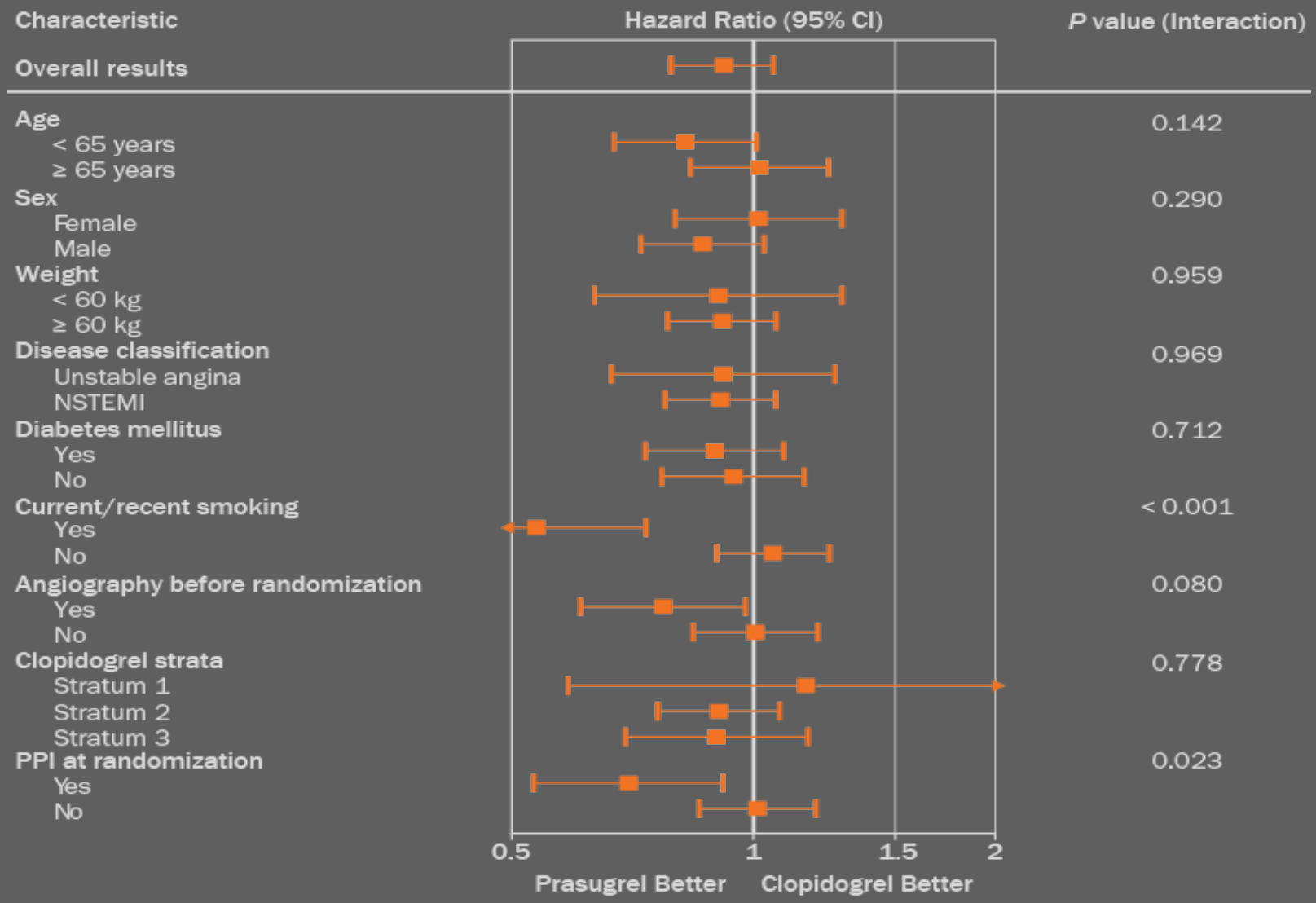
Primary Endpoint - Pre-Specified Sub-Groups

(Age < 75 years)



Roe MT. NEJM 2012;367:1297

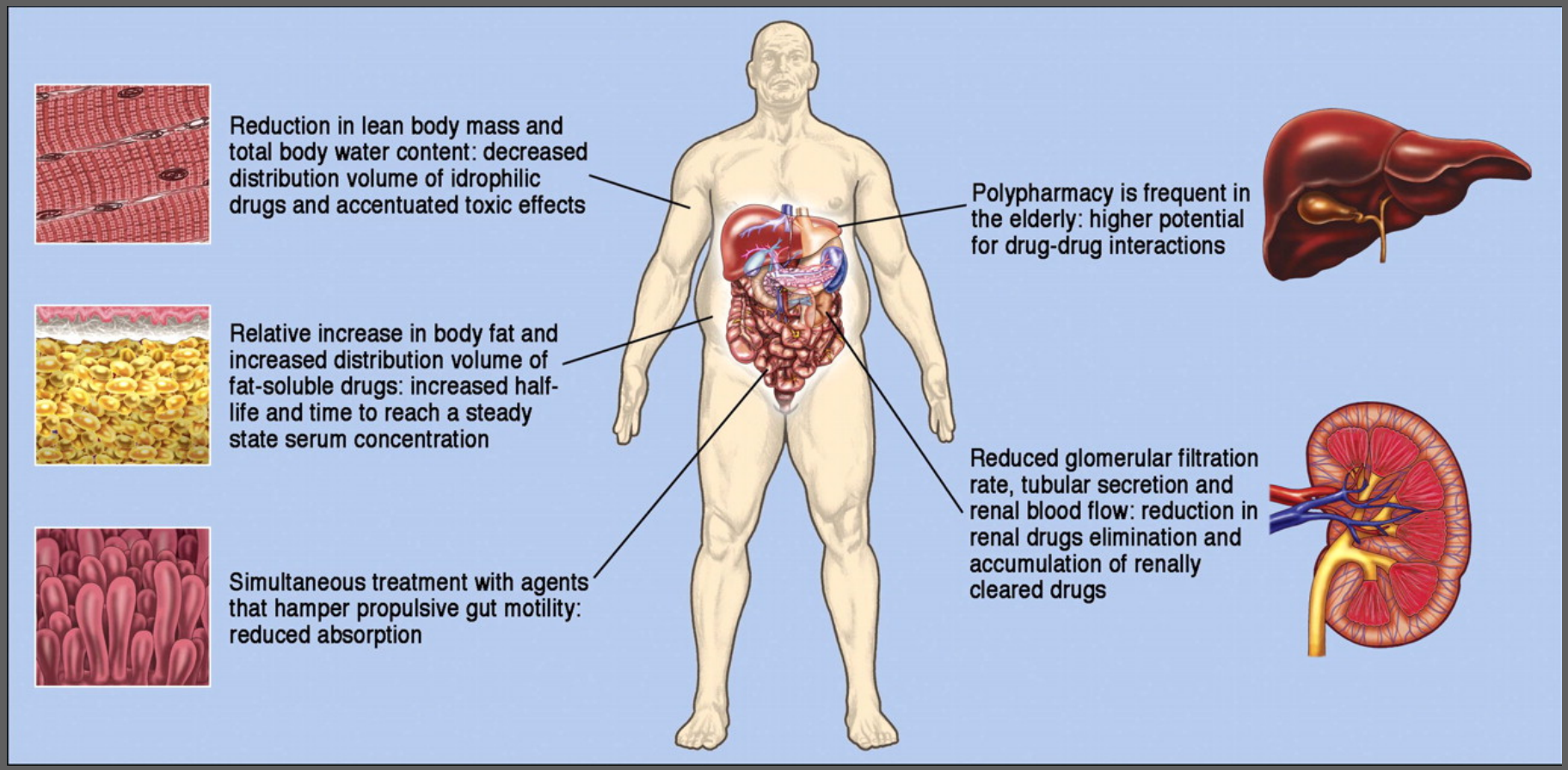
Evaluation of All Ischemic Events Over Time*
(Age < 75 years)

- Lower risk multiple recurrent ischemic events suggested with prasugrel using the pre-specified Andersen-Gill model (HR = 0.85, 95% CI: 0.72–1.00, P=0.04)
- Significant interaction with treatment and time (HR for > 12 mos = 0.64, 95% CI: 0.48–0.86, Interaction P=0.02)

	Prasugrel	Clopidogrel
≥ 1 event	364	397
≥ 2 events	77	109
3–7 events	18	24

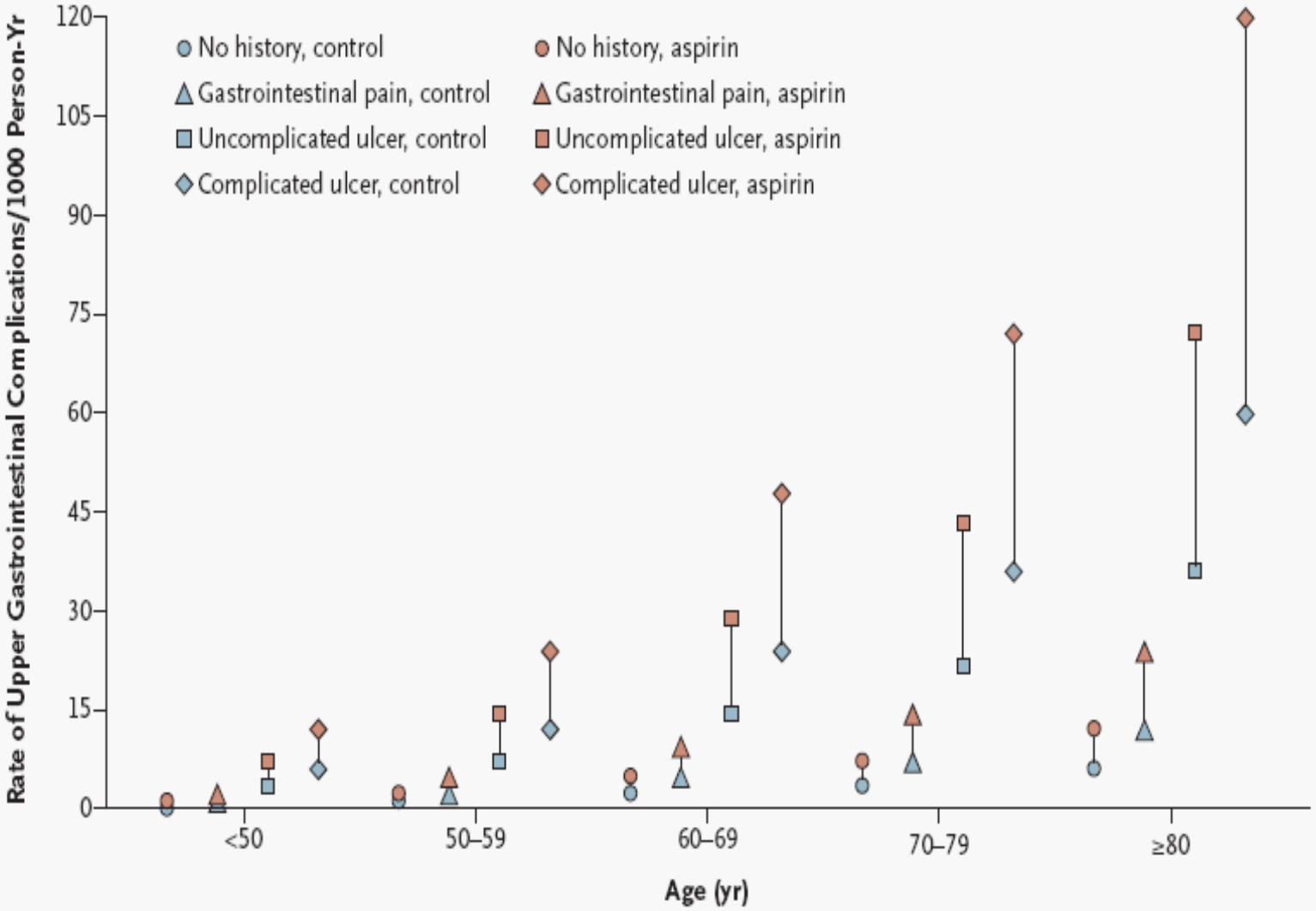
* Pre-specified evaluation of all CV death, MI, or stroke events by treatment

Mechanisms Leading to Pharmacokinetic Variations of Antithrombotic Drug Effects in the Elderly



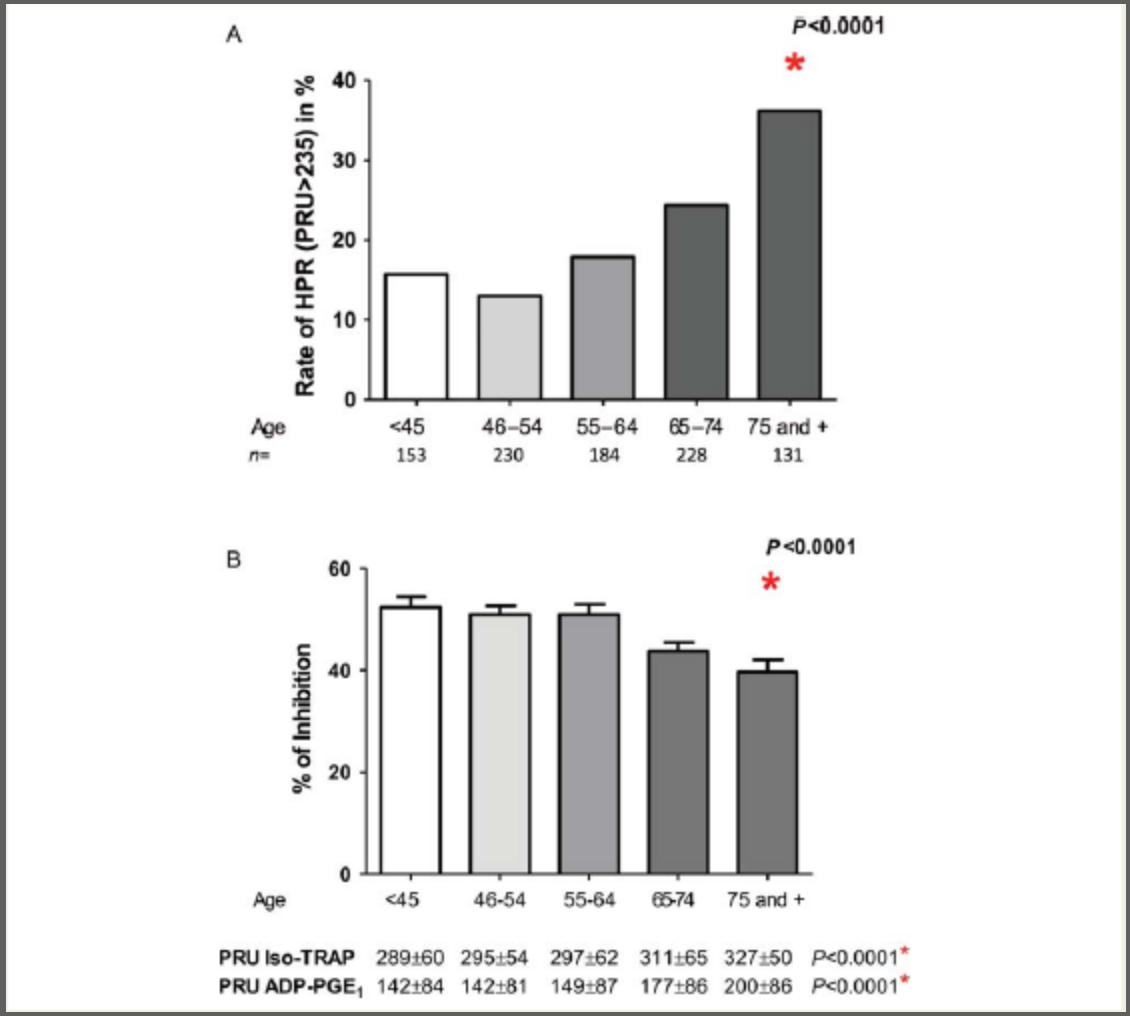
Capodanno & Angiolillo. JACC 2010;56:1683-1692

Excess of upper GI complications with low-dose aspirin Depending on age and previous clinical history



Patrono C. NEJM 2005

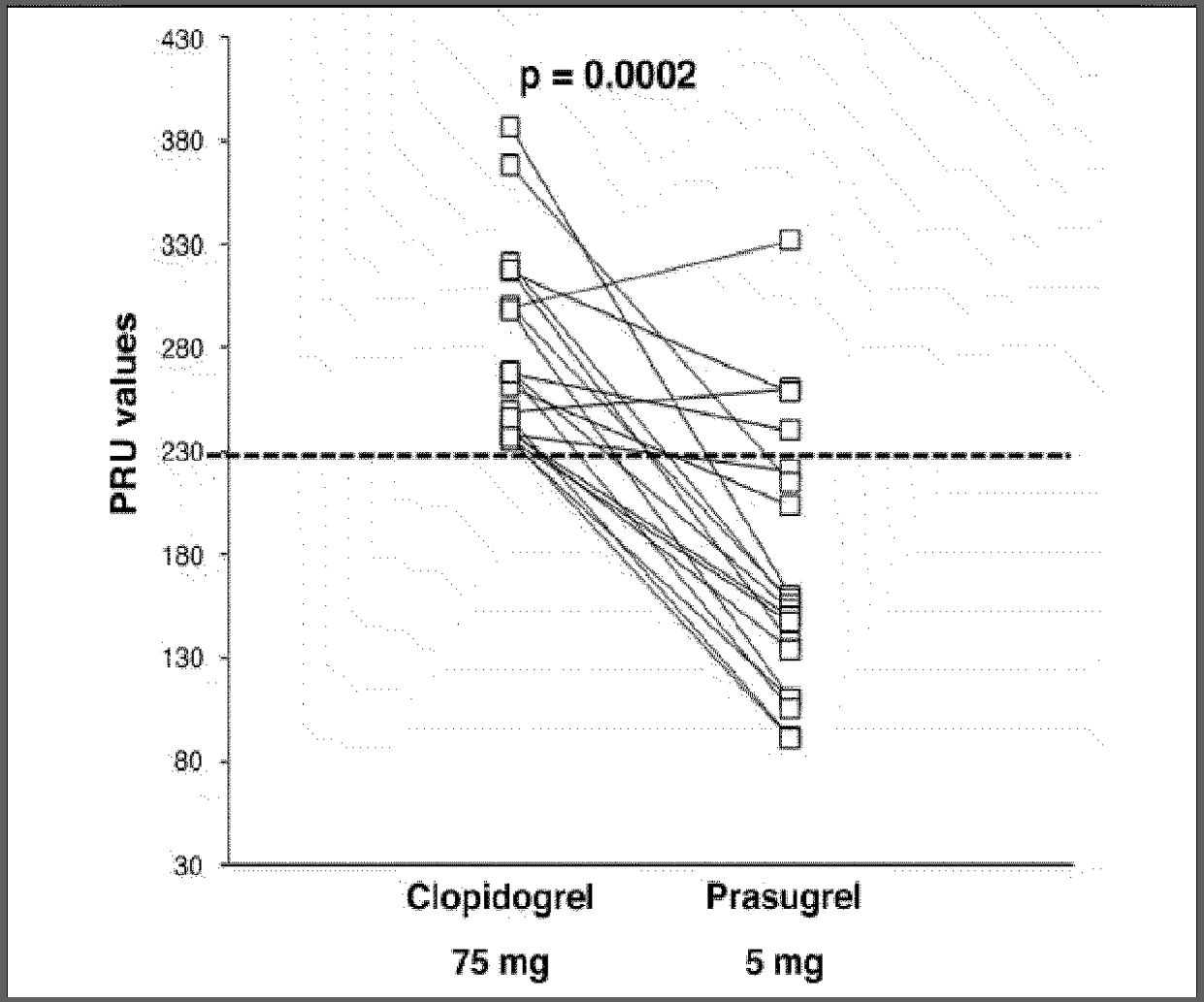
Reduced platelet inhibition on clopidogrel in elderly patients (the SENIOR PLATELET study)



Silvain J. Eur Heart J 2012;33:1241-9

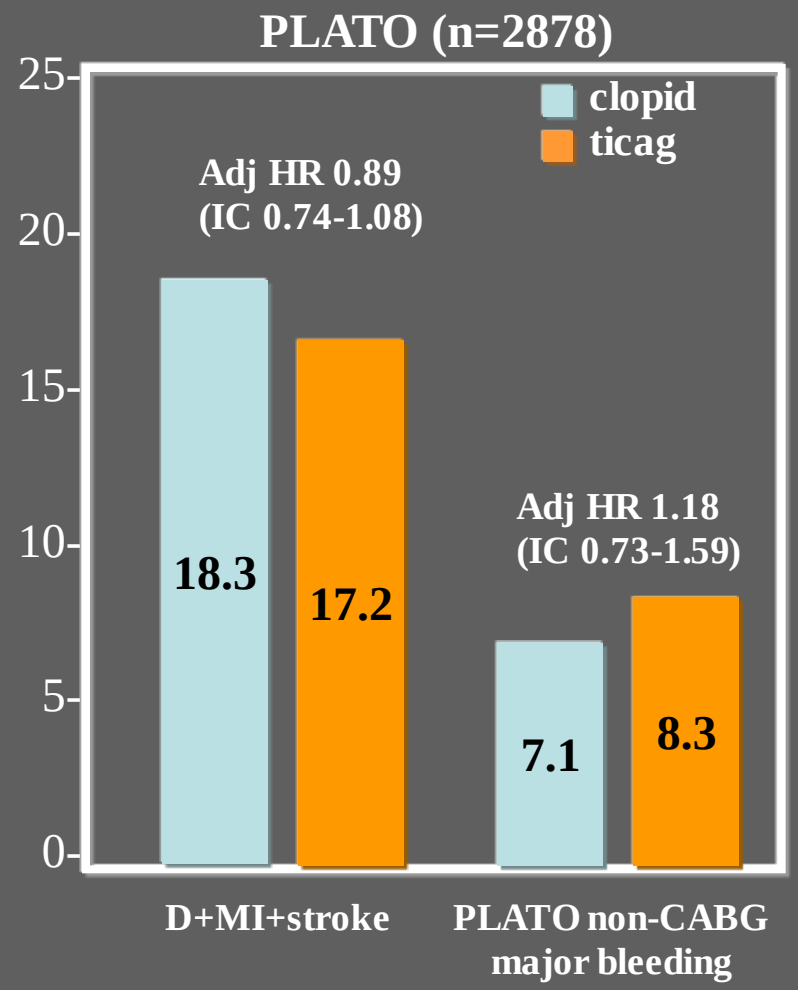
Prasugrel 5 mg improves platelet inhibition in the elderly

(patients on chronic treatment)

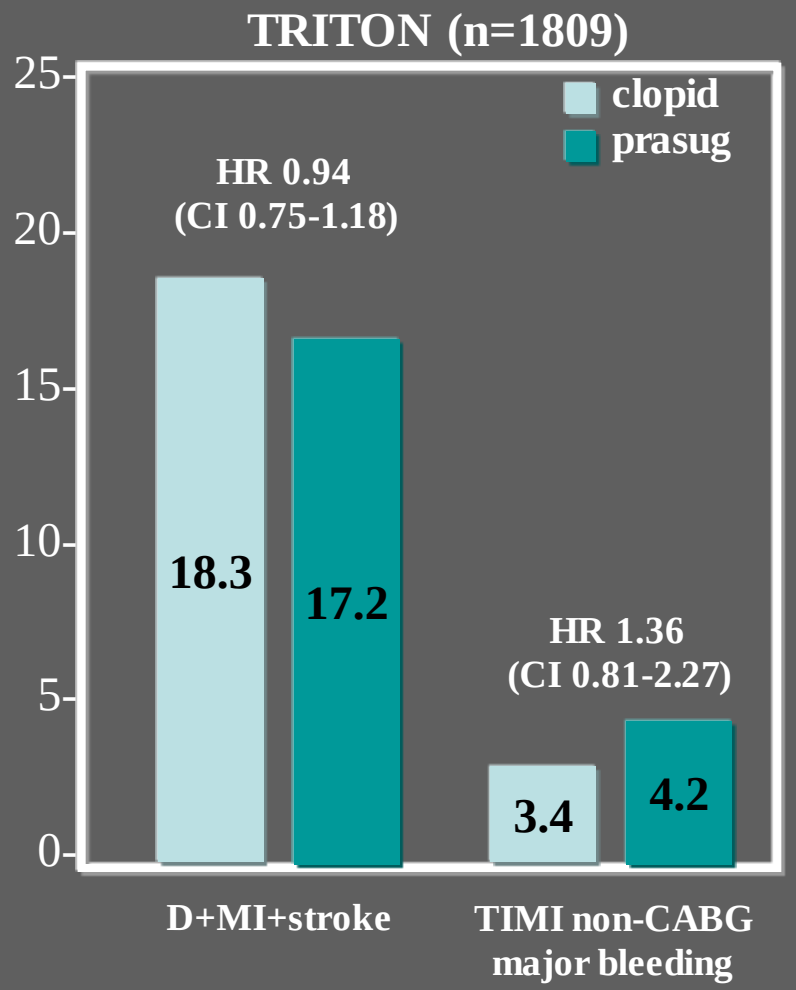


Capranzano P. Thromb Haemost 2011;106:1149-57

Newer antiplatelet treatments compared to clopidogrel in ACS: Patients >75 y.o.



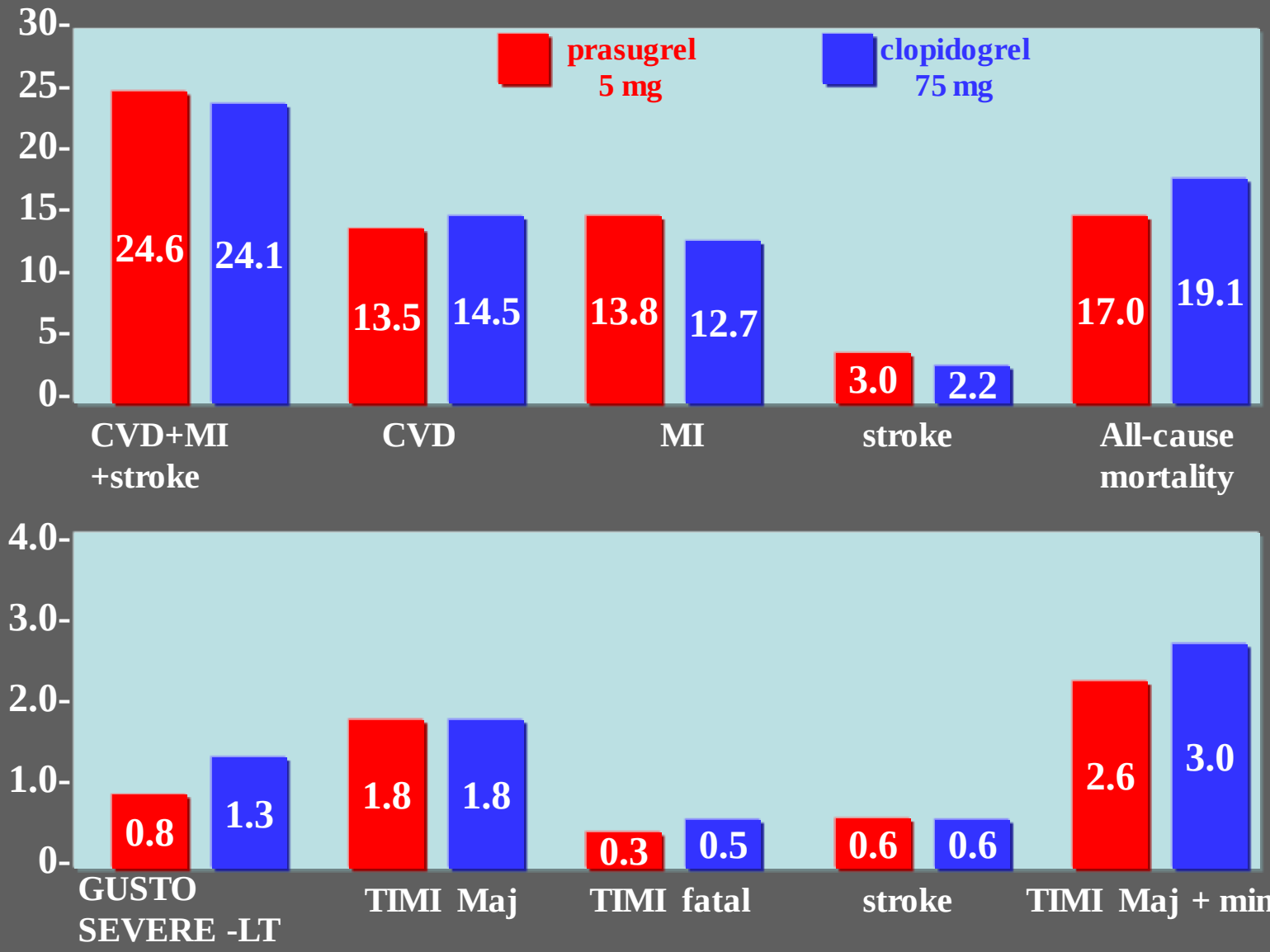
Husted S. Circ CV Qual Outcomes 2012;5:680



Wiviott S. N Engl J Med 2007;357:2001

Overall efficacy and safety in the elderly

Figures derived by subtraction from the main paper



RCT

2,000 patients ≥75 years with ACS treated invasively

web random

Clopidogrel 300+75 mg → **12-month follow-up**

Prasugrel 60+5 mg → **12-month follow-up**

Primary endpoint

the composite of all-cause mortality, myocardial (re)MI, disabling stroke and re-hospitalization for cardiovascular causes or severe bleeding within 12 months

PI: S. Savonitto, S. De Servi

Coordinating Center: IRCCS Arcispedale S. Maria Nuova, Reggio Emilia