EUROPEAN HEART HOUSE

Anti-Thrombotic Therapy – Update 2017

Thursday 23 February – Saturday 25 February, 2017

Pretreatement with oral P2Y12 inhibitors in NSTEMI and STEMI
- in favour -

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Recommendations on Timing of $P2Y_{12}$ Inhibitor and GPI Initiation in Guidelines for NSTE-ACS

Title	Recommendation	Class	LOE
United States			
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Segment–Elevation Acute Coronary Syndromes[12]	A loading dose of a $P2Y_{12}$ receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting	I	A
	In patients with high-risk features (eg, elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI	I	A
	In patients with high-risk features (eg, elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI	IIa	B
2011 ACCF/AHA/SCAI guideline for PCI[10]	In patients with high-risk features (eg, elevated troponin level) not treated with bivalirudin and not adequately pretreated with clopidogrel, it is useful at the time of PCI to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) in patients treated with UFH	I	A
	In patients with high-risk features (eg, elevated troponin level) treated with UFH and adequately pretreated with clopidogrel, it is reasonable at the time of PCI to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban)	IIa	B
Europe			
2011 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[9]	A $P2Y_{12}$ inhibitor (should be administered) as soon as possible	I	A
2014 ESC/EACTS guidelines for myocardial revascularization[11]	Pretreatment with prasugrel in patients in whom coronary anatomy not known, is not recommended	III	B
	Pretreatment with GPI in patients in whom the coronary anatomy is not known, is not recommended	III	A

Capodanno D, Angiolillo DJ. Circ Cardiovasc Interv. 2015

Recommendations on Timing of $P2Y_{12}$ Inhibitor and GPI Initiation in Guidelines for STEMI

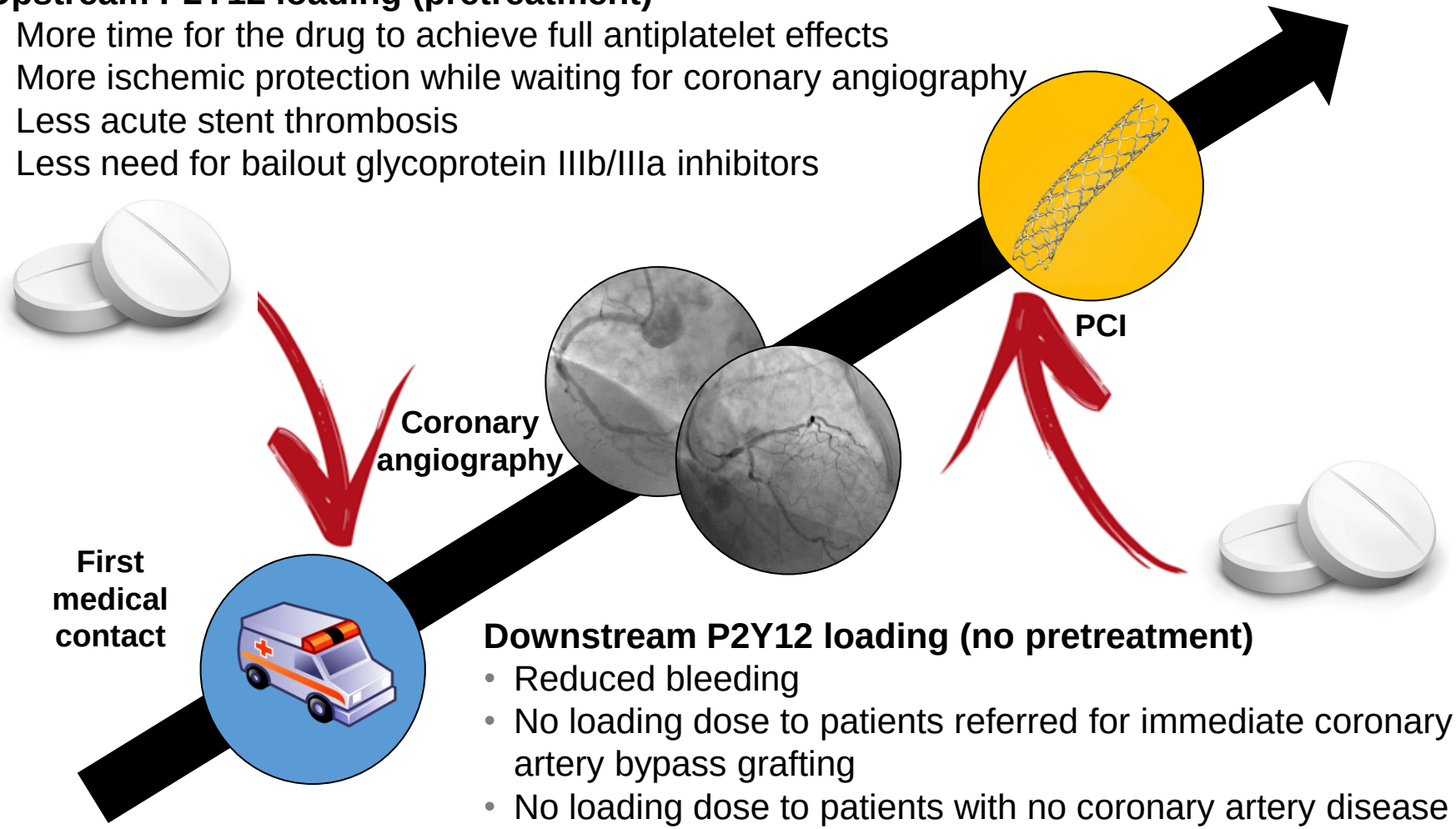
Title	Recommendation	Class	LOE
United States			
2013 ACCF/AHA Guideline for the Management of STEMI[14]	A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI	I	B
	It may be reasonable to administer intravenous GPI receptor antagonist in the precatheterization laboratory setting (eg, ambulance and ED) to patients with STEMI for whom primary PCI is intended	IIb	B
2011 ACCF/AHA/SCAI guideline for PCI[10]	In patients undergoing primary PCI treated with UFH, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban), in patients not pretreated with clopidogrel	IIa	A
	In patients undergoing primary PCI treated with UFH, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban), in patients pretreated with clopidogrel	IIa	C
	Routine precatheterization laboratory (eg, ambulance or emergency department) administration of GPI as part of an upstream strategy for patients with STEMI undergoing PCI is not beneficial	III	B
Europe			
2012 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[13]	A combination of DAPT with aspirin and an adenosine diphosphate receptor blocker as early as possible before angiography	…	…
	Upstream use of a GPI (vs in-laboratory use) may be considered in high-risk patients undergoing transfer for primary PCI	IIb	B
2014 ESC/EACTS guidelines for myocardial revascularization[11]	It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact	I	B
	Upstream use of a GPI (vs in-laboratory use) may be considered in high-risk patients undergoing transfer for primary PCI	IIb	B

Capodanno D, Angiolillo DJ. Circ Cardiovasc Interv. 2015

PROs and CONs of antiplatelet pretreatment

Upstream P2Y12 loading (pretreatment)

- More time for the drug to achieve full antiplatelet effects
- More ischemic protection while waiting for coronary angiography
- Less acute stent thrombosis
- Less need for bailout glycoprotein IIIb/IIIa inhibitors



Downstream P2Y12 loading (no pretreatment)

- Reduced bleeding
- No loading dose to patients referred for immediate coronary artery bypass grafting
- No loading dose to patients with no coronary artery disease
- More time for personalized decisions based on angiographic and procedural considerations

Capodanno D, Angiolillo DJ. Expert Rev Card Ther. 2016

Pretreatment: different scenarios

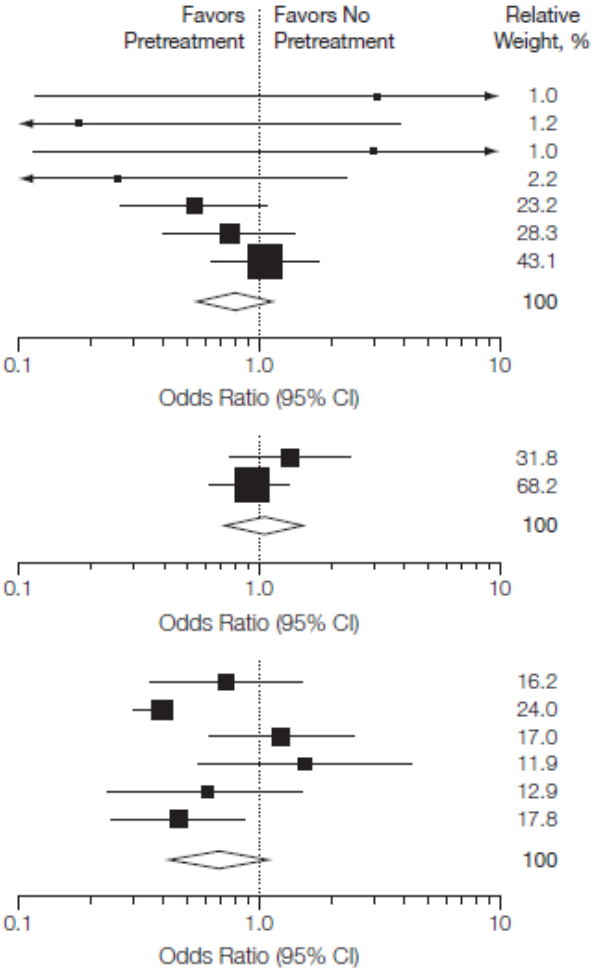
A drug is given…

- in the ambulance
- at the referral hospital
- in the medical emergency department
- in the cardiac intensive care unit,
- in the cath-lab after coronary angiography before PCI

Clopidogrel pretreatment and Mortality

All-Cause Mortality

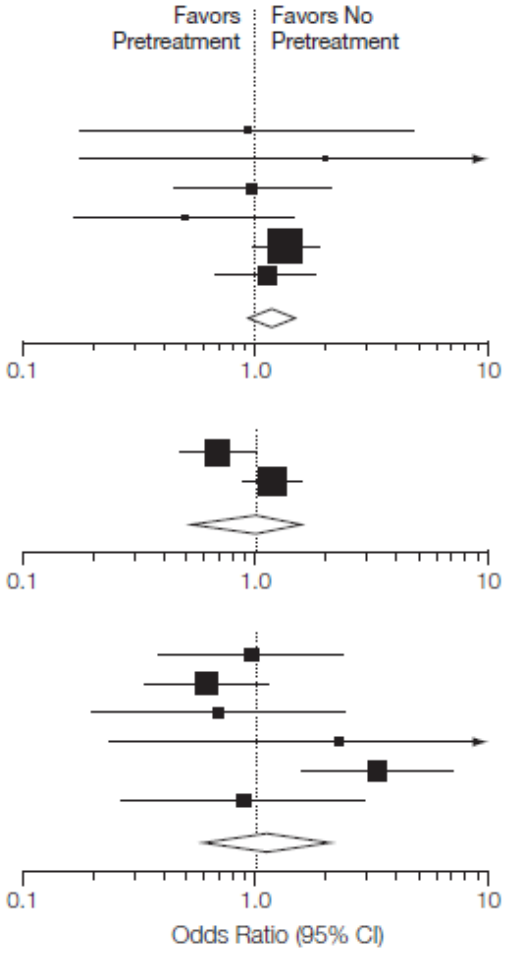
Source	No. of Events: Pretreatment	No. of Events: No Pretreatment	No. of Patients: Pretreatment	No. of Patients: No Pretreatment	OR (95% CI)	Relative Weight, %
RCTs						
ARMYDA-5 PRELOAD,[17] 2010	1	0	204	205	3.03 (0.12-74.80)	1.0
Daviouros et al,[16] 2009	0	2	103	96	0.18 (0.01-3.85)	1.2
PRAGUE 8,[18] 2008	1	0	513	515	3.02 (0.12-74.25)	1.0
CIPAMI,[7] 2007	1	4	164	171	0.26 (0.03-2.32)	2.2
CLARITY PCI,[6] 2005	13	24	933	930	0.53 (0.27-1.05)	23.2
CREDO,[3] 2002	18	24	1053	1063	0.75 (0.41-1.40)	28.3
PCI CURE,[5] 2001	32	31	1313	1345	1.06 (0.64-1.75)	43.1
Overall	**66**	**85**	**4283**	**4325**	**0.80 (0.57-1.11)** $P = .17$	**100**
Observational analyses of RCTs[a]						
REPLACE-2,[19] 2004	114	14	5087	832	1.34 (0.77-2.34)	31.8
ACUITY PCI,[20] 2007	105	49	3511	1515	0.92 (0.65-1.30)	68.2
Overall	**219**	**63**	**8598**	**2347**	**1.04 (0.74-1.46)** $P = .83$	**100**
Observational studies						
Amin et al,[21] 2011	13	19	923	990	0.73 (0.36-1.49)	16.2
Dörler et al,[23] 2011	209	110	4879	1076	0.39 (0.31-0.50)	24.0
Feldman et al,[25] 2010	18	18	467	574	1.24 (0.64-2.41)	17.0
Fefer et al,[24] 2009	12	6	217	166	1.56 (0.57-4.25)	11.9
Szük et al,[26] 2007	6	18	1481	2679	0.60 (0.24-1.52)	12.9
Chan et al,[22] 2003	76	12	4477	332	0.46 (0.25-0.86)	17.8
Overall	**334**	**183**	**12 444**	**5817**	**0.68 (0.42-1.09)** $P = .11$	**100**



Bellemain-Appaix A on behalf of the ACTION study, Lancet 2012; 308: 2507-17

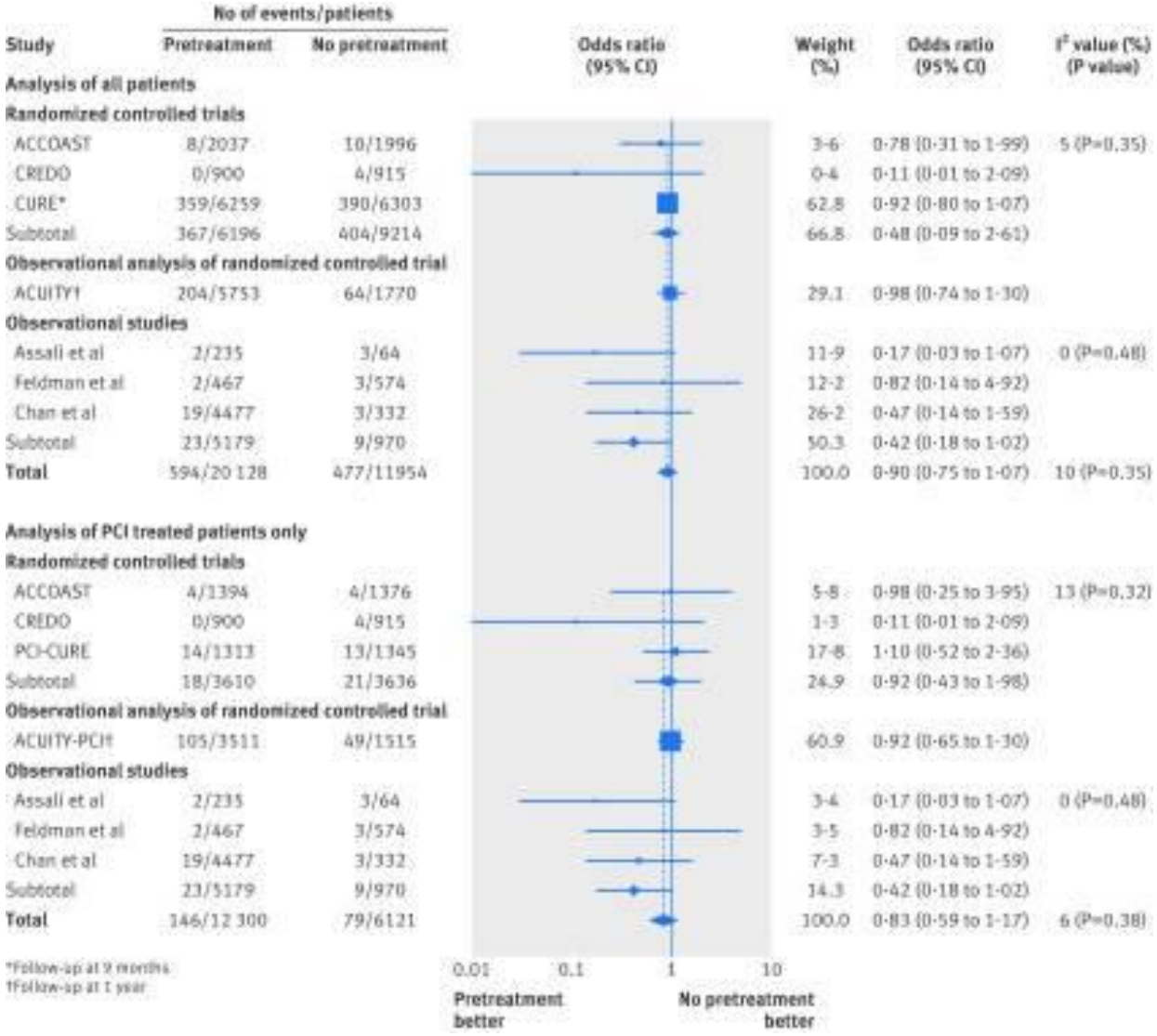
Clopidogrel pretreatment and Major Bleeding

Source	Major Bleeding: No. of Events, Pretreatment	Major Bleeding: No. of Events, No Pretreatment	Major Bleeding: No. of Patients, Pretreatment	Major Bleeding: No. of Patients, No Pretreatment	OR (95% CI)	Relative Weight, %
RCTs						
ARMYDA-5 PRELOAD,[17] 2010	0	0	204	205	Not Estimable	—
Davlouros et al,[16] 2009	3	3	103	96	0.93 (0.18-4.72)	2.2
PRAGUE 8,[18] 2008	2	1	513	515	2.01 (0.18-22.26)	1.0
CIPAMI,[7] 2007	14	15	164	171	0.97 (0.45-2.08)	10.0
CLARITY PCI,[6] 2005	5	10	933	930	0.50 (0.17-1.46)	5.0
CREDO,[3] 2002	93	71	1053	1063	1.35 (0.98-1.87)	56.3
PCI CURE,[5] 2001	36	33	1313	1345	1.12 (0.69-1.81)	25.4
Overall	**153**	**133**	**4283**	**4325**	**1.18 (0.93-1.50)**	**100**
					P=.18	
Observational analyses of RCTs[a]						
REPLACE-2,[19] 2004	152	38	5051	881	0.69 (0.48-0.99)	47.7
ACUITY PCI,[20] 2007	190	70	3511	1528	1.19 (0.90-1.58)	52.3
Overall	**342**	**108**	**8562**	**2409**	**0.92 (0.54-1.57)**	**100**
					P=.75	
Observational studies						
Amin et al,[21] 2011	9	10	923	990	0.96 (0.39-2.39)	18.9
Dörler et al,[23] 2011	42	15	4879	1076	0.61 (0.34-1.11)	23.6
Feldman et al,[25] 2010	4	7	467	574	0.70 (0.20-2.41)	14.5
Fefer et al,[24] 2009	3	1	217	166	2.31 (0.24-22.44)	6.6
Szük et al,[26] 2007	20	11	1481	2679	3.32 (1.59-6.95)	21.4
Chan et al,[22] 2003	36	3	4477	332	0.89 (0.27-2.90)	15.1
Overall	**114**	**47**	**12 444**	**5817**	**1.13 (0.58-2.19)**	**100**
					P=.72	



Bellemain-Appaix A on behalf of the ACTION study, Lancet 2012; 308: 2507-17

Mortality after the ACCOAST trial …



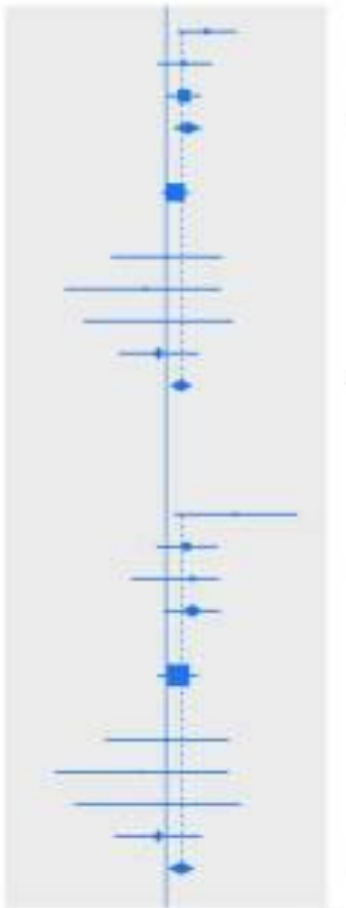
Study	No of events/patients: Pretreatment	No of events/patients: No pretreatment	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)	I^2 value (%) (P value)
Analysis of all patients						
Randomized controlled trials						
ACCOAST	8/2037	10/1996		3·6	0·78 (0·31 to 1·99)	5 (P=0.35)
CREDO	0/900	4/915		0·4	0·11 (0·01 to 2·09)	
CURE*	359/6259	390/6303		62·8	0·92 (0·80 to 1·07)	
Subtotal	367/6196	404/9214		66·8	0·48 (0·09 to 2·61)	
Observational analysis of randomized controlled trial						
ACUITY†	204/5753	64/1770		29·1	0·98 (0·74 to 1·30)	
Observational studies						
Assali et al	2/235	3/64		1·9	0·17 (0·03 to 1·07)	0 (P=0.48)
Feldman et al	2/467	3/574		1·2	0·82 (0·14 to 4·92)	
Chan et al	19/4477	3/332		2·6	0·47 (0·14 to 1·59)	
Subtotal	23/5179	9/970		5·3	0·42 (0·18 to 1·02)	
Total	594/20 128	477/11954		100·0	0·90 (0·75 to 1·07)	10 (P=0.35)
Analysis of PCI treated patients only						
Randomized controlled trials						
ACCOAST	4/1394	4/1376		5·8	0·98 (0·25 to 3·95)	13 (P=0.32)
CREDO	0/900	4/915		1·3	0·11 (0·01 to 2·09)	
PCI-CURE	14/1313	13/1345		17·8	1·10 (0·52 to 2·36)	
Subtotal	18/3610	21/3636		24·9	0·92 (0·43 to 1·98)	
Observational analysis of randomized controlled trial						
ACUITY-PCI†	105/3511	49/1515		60·9	0·92 (0·65 to 1·30)	
Observational studies						
Assali et al	2/235	3/64		3·4	0·17 (0·03 to 1·07)	0 (P=0.48)
Feldman et al	2/467	3/574		3·5	0·82 (0·14 to 4·92)	
Chan et al	19/4477	3/332		7·3	0·47 (0·14 to 1·59)	
Subtotal	23/5179	9/970		14·3	0·42 (0·18 to 1·02)	
Total	146/12 300	79/6121		100·0	0·83 (0·59 to 1·17)	6 (P=0.38)

*Follow-up at 9 months
†Follow-up at 1 year

Bellemain-Appaix A on behalf of the ACTION study, BMJ 2014; 349: g6269

Major Bleeding after the ACCOAST trial …

Study	No of events/patients: Pretreatment	No of events/patients: No pretreatment	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)	I^2 value (%) (P value)
Analysis of all patients						
Randomized controlled trials						
ACCOAST*	52/2037	27/1996		9·5	1·91 (1·20 to 3·05)	0 (P=0.40)
CREDO*	50/1053	38/1063		11·3	1·34 (0·87 to 2·07)	
CURE	125/6259	95/6303		28.9	1·33 (1·02 to 1·74)	
Subtotal	227/9349	160/9362		49.7	1·43 (1·16 to 1·76)	
Observational analysis of randomized controlled trial						
ACUITY	258/5753	128/3304		44·7	1·16 (0·94 to 1·45)	
Observational studies						
Assali et al	26/235	7/64		2·7	1·01 (0·42 to 2·45)	0 (P=0.89)
Feldman et al	4/467	7/574		1·4	0·70 (0·20 to 2·41)	
Chan et al	36/4477	3/332		1·5	0·89 (0·27 to 2·90)	
Subtotal	66/5179	17/970		5.5	0·89 (0·48 to 1·65)	
Total	551/20 281	305/13 636		100.0	1·27 (1·10 to 1·47)	0 (P=0.52)
Analysis of PCI treated patients only						
Randomized controlled trials						
ACCOAST†	19/1397	7/1376		5·4	2·70 (1·13 to 6·44)	25 (P=0.27)
CREDO†	50/1053	38/1063		21·9	1·34 (0·87 to 2·07)	
PCI-CURE	21/1313	19/1345		10·4	1·13 (0·61 to 2·12)	
Subtotal	90/3763	64/3784		37.7	1·45 (0·97 to 2·15)	
Observational analysis of randomized controlled trial						
ACUITY-PCI	188/3511	70/1528		51.5	1·18 (0·89 to 1·56)	
Observational studies						
Assali et al	26/235	7/64		5·2	1·01 (0·42 to 2·45)	0 (P=0.89)
Feldman et al	4/467	7/574		2·7	0·70 (0·20 to 2·41)	
Chan et al	36/4477	3/332		2·9	0·89 (0·27 to 2·90)	
Subtotal	66/5179	17/970		10.8	0·89 (0·48 to 1·65)	
Total	344/12 453	151/6282		100.0	1·23 (1·00 to 1·50)	0 (P=0.58)



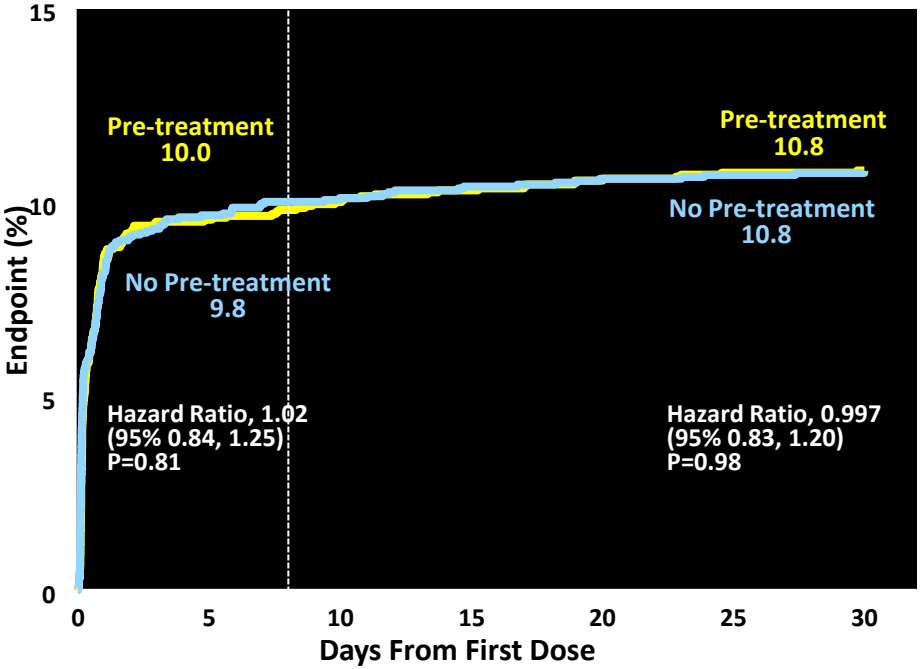
*Coronary artery bypass graft (CABG) and non-CABG
†Non-CABG

Bellemain-Appaix A on behalf of the ACTION study, BMJ 2014; 349: g6269

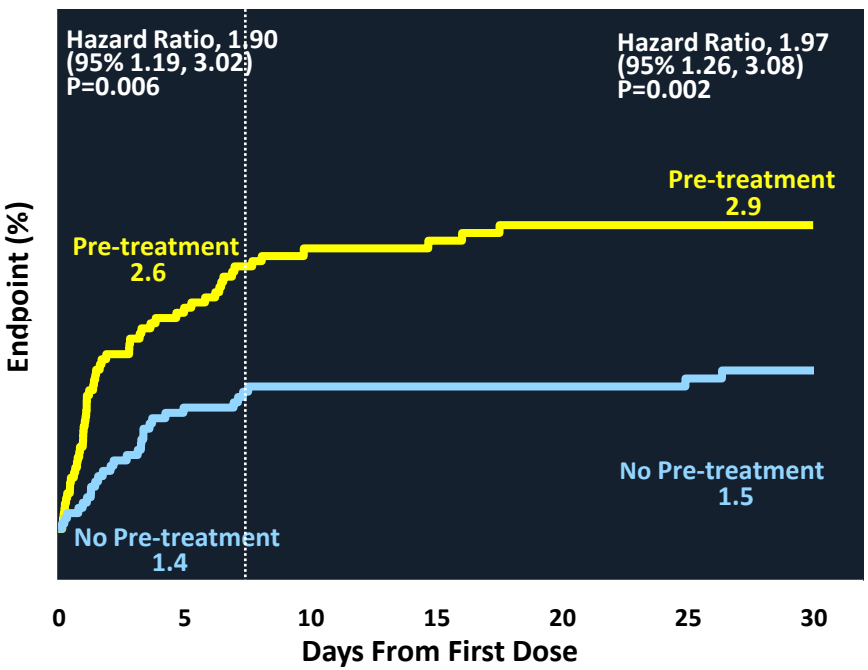
Pretreatment with Prasugrel in NSTE-ACS

ACCOAST: 4033 patients with NSTE-ACS ⇒ coronary angiography within 2 - 48 hours
Randomization to pre- or in-lab treatment with prasugrel

CV Death/MI/Stroke/UR/GPI bailout



All TIMI Major Bleeding



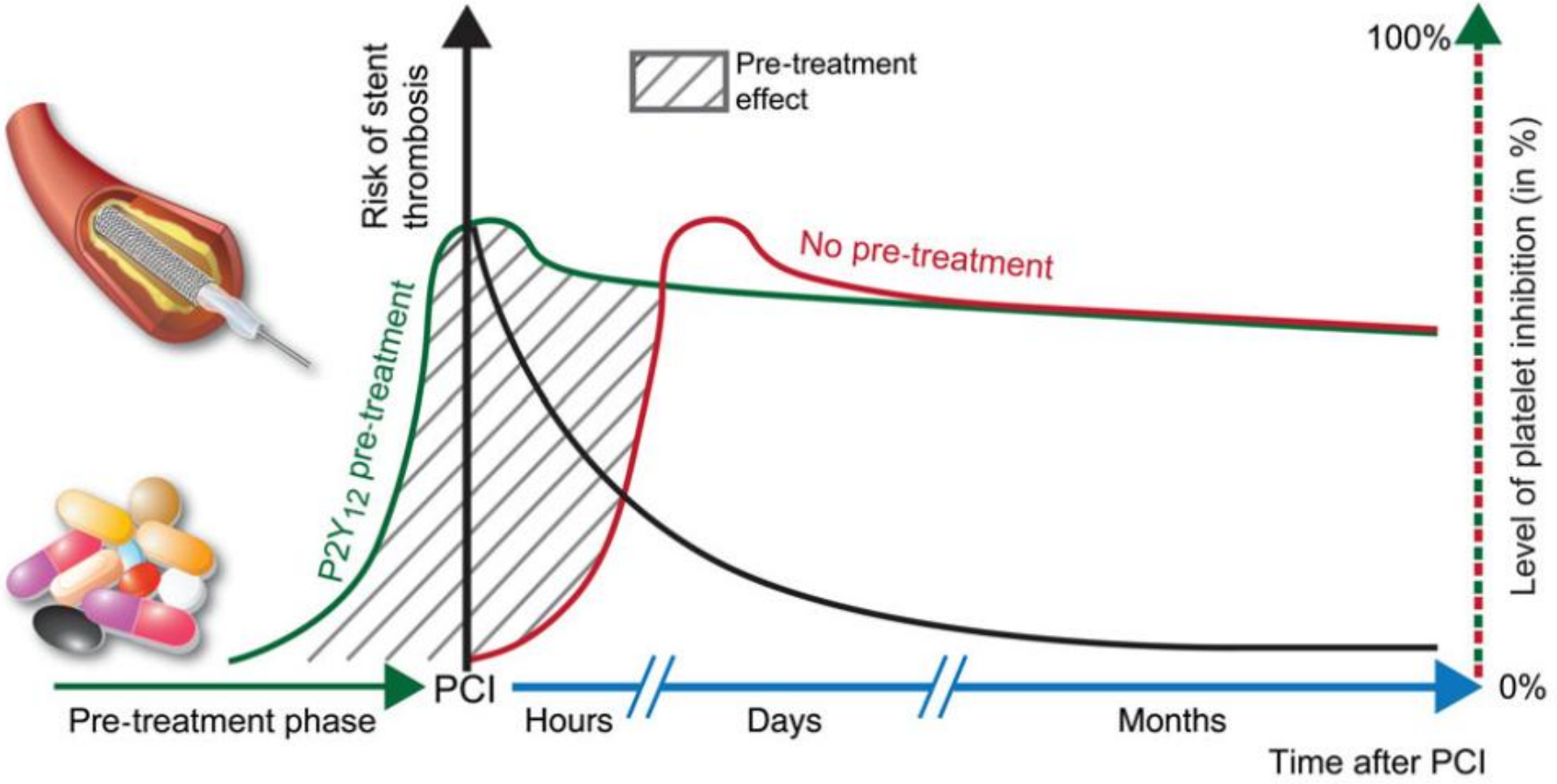
Independent predictors for TIMI major bleeding	HR	95% CI
Pre-treatment with Prasugrel	3.02	1.42–6.43
Femoral access for PCI	2.45	1.11–5.38

Montalescot G, et al. N Engl J Med. 2013;369:999-1010

Pretreatment with Ticagrelor in STEMI

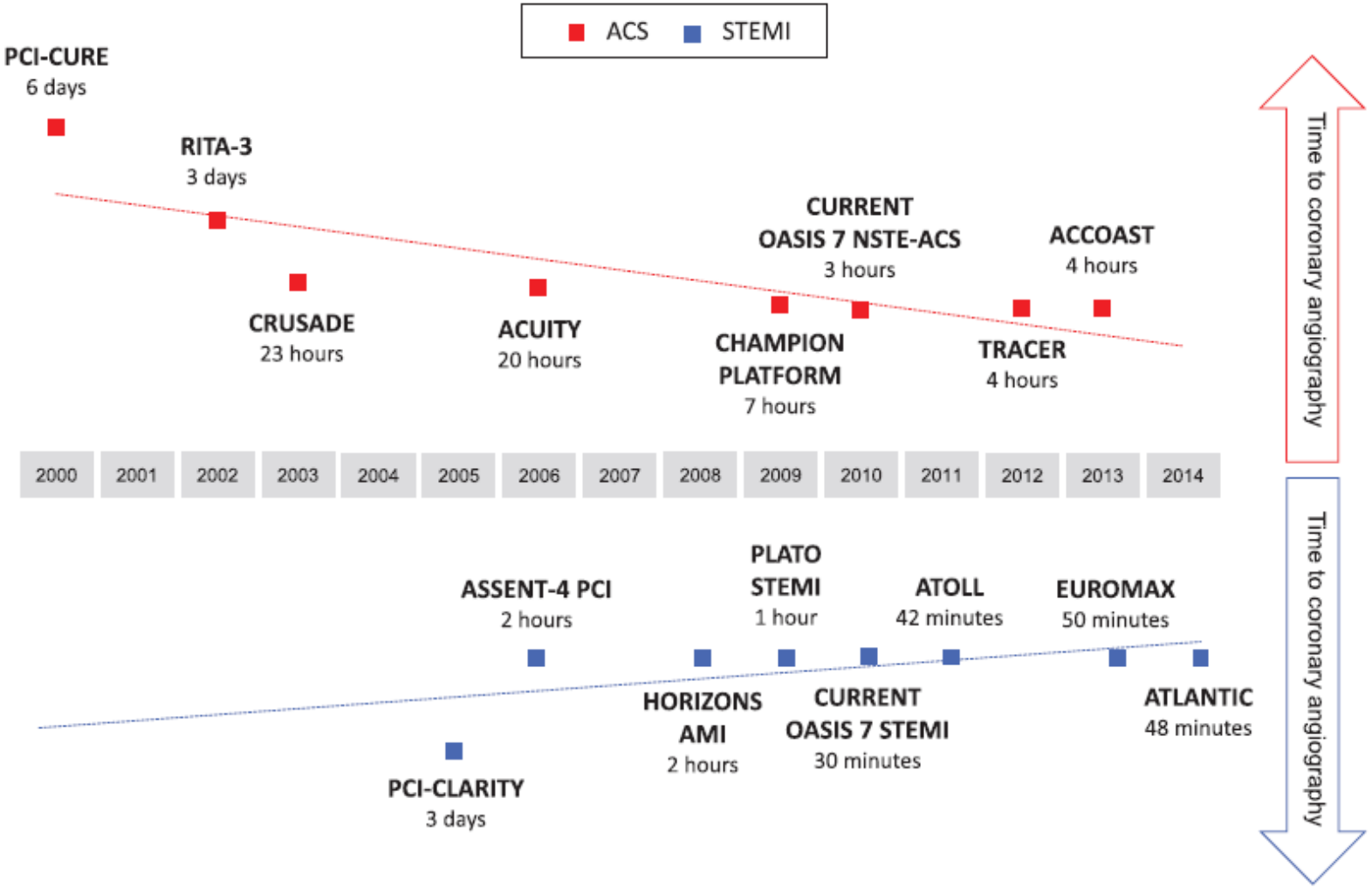
Variable	Prehospital Ticagrelor	In-Hospital Ticagrelor	Odds Ratio (95% CI)	P Value
Ischemic end point				
No. of patients who could be evaluated	906	952		
Composite of death, myocardial infarction, stroke, urgent revascularization, or definite stent thrombosis — no. (%)	41 (4.5)	42 (4.4)	1.03 (0.66 to 1.60)	0.91
Composite of death, myocardial infarction, or urgent revascularization — no. (%)	39 (4.3)	34 (3.6)	1.22 (0.76 to 1.94)	0.42
Stent thrombosis — no. (%)				
Definite at ≤24 hr after index PCI	0	8 (0.8)	—	0.008‡
Definite at 30 days	2 (0.2)	11 (1.2)	0.19 (0.04 to 0.86)	0.02‡
Definite or probable at 30 days¶	21 (2.3)	20 (2.1)	1.11 (0.60 to 2.05)	0.75
Death from any cause — no. (%)	30 (3.3)	19 (2.0)	1.68 (0.94 to 3.01)	0.08
Myocardial infarction — no. (%)	7 (0.8)	10 (1.1)	0.73 (0.28 to 1.94)	0.53
Stroke — no. (%)	4 (0.4)	2 (0.2)	2.11 (0.39 to 11.53)	0.39
Transient ischemic attack — no. (%)	0	1 (0.1)	—	NE
Urgent coronary revascularization — no. (%)	5 (0.6)	8 (0.8)	0.66 (0.21 to 2.01)	0.46
Thrombotic bailout with glycoprotein IIb/IIIa inhibitors — no. (%)	78 (8.6)	100 (10.5)	0.80 (0.59 to 1.10)	0.17

The course of the level of platelet inhibition



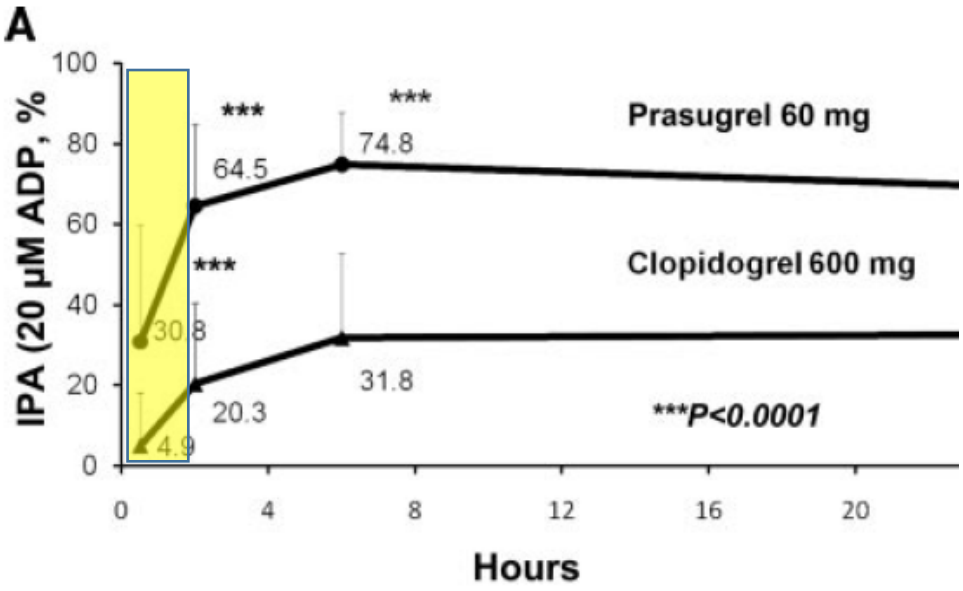
Sibbing et al. Eur Heart J 2016; 37: 1284-95

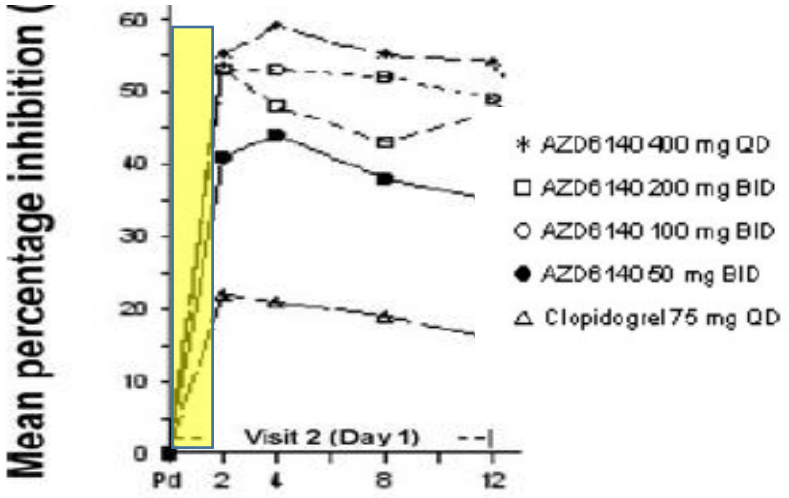
Time from first medical contact to coronary angiography in studies of ACS



Capodanno D, Angiolillo DJ. Circ Cardiovasc Interv. 2015

Delay to peak platelet inhibition for $P2Y_{12}$ inhibitors

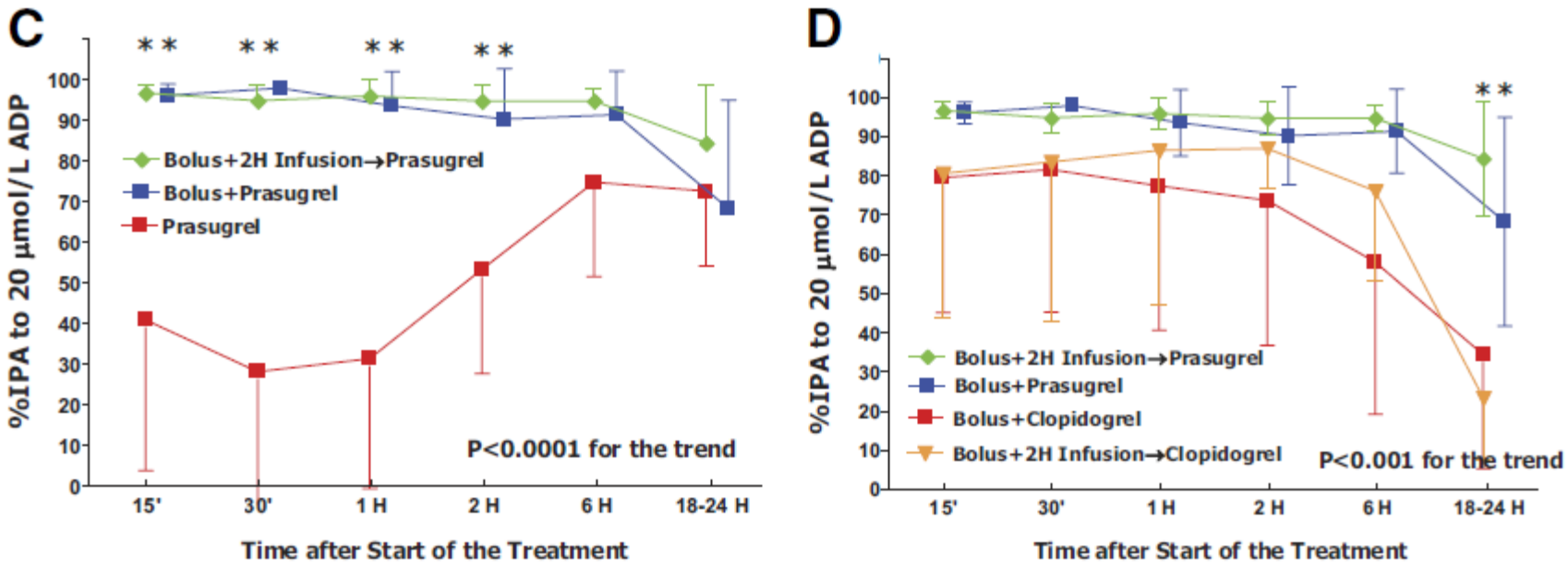




Wiviott SD and PRINCIPLE-TIMI 44 investigators
Circulation. 2007; 116: 2923–32

Husted S et al.
Eur Heart J 2006; 27: 1038–1047

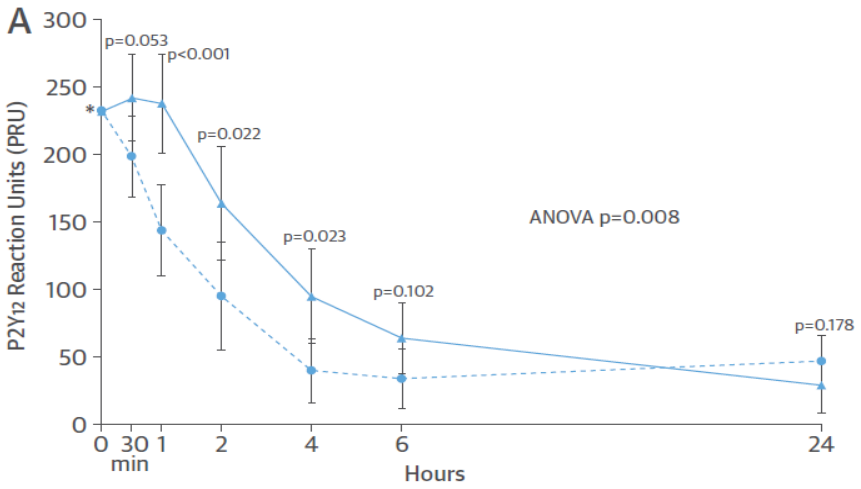
Prasugrel + Tirofiban in PPCI for STEMI



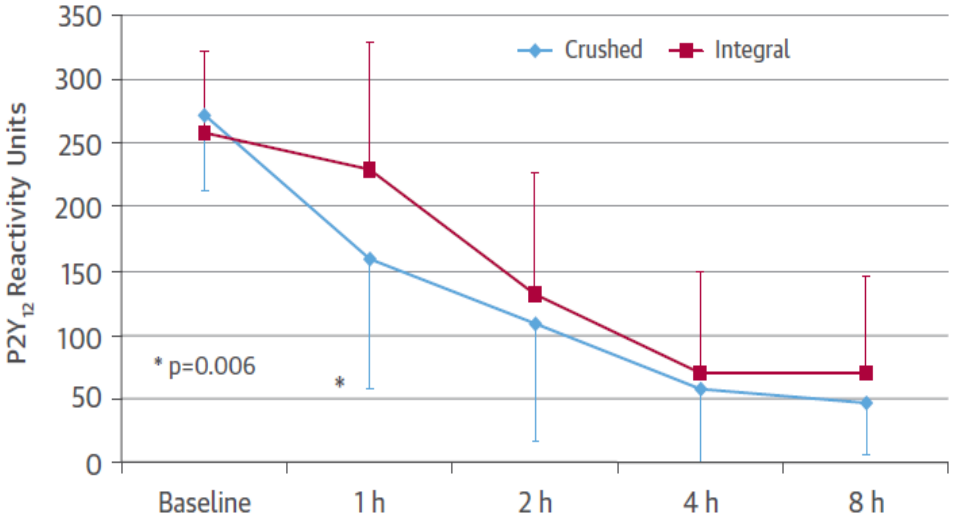
Valgimigli M on behalf of FABULUS PRO; JACC Intv 2012; 5: 268–77

Crushing pills to increase bioavailability of orally administered $P2Y_{12}$ receptor inhibitors

Prasugrel



Ticagrelor



Rollini F and CRUSH investigators
JACC 2016; 67: 1994–2004

Parodi G and MOJITO investigators
JACC 2015; 65: 211-2

As for $P2Y_{12}$ inhibitors pre-treatment…

• No robust data to support	Agreed
• Periprocedural bleeding	Use radial access
• CABG	<5% in most STEMI trials <2% in ATLANTIC
• Incorrect diagnosis	10% of pts did not receive revascularization in ATLANTIC
• Delayed onset of antiplatelet activity	Crush the pills!