EYE ON ACS TRIALS: Making the Right Choice

No Benefits, Possible Harm:

The ACCOAST trial

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Mount Sinai Heart

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below. These relationships may lead to bias in my presentation.

Affiliation/Financial Relationship	Company
• Grant/Research Support (Institutional)	• The Medicines Co., AZ, BMS, Lilly/Daiichi Sankyo
• Advisory Board	• Janssen (J+J),
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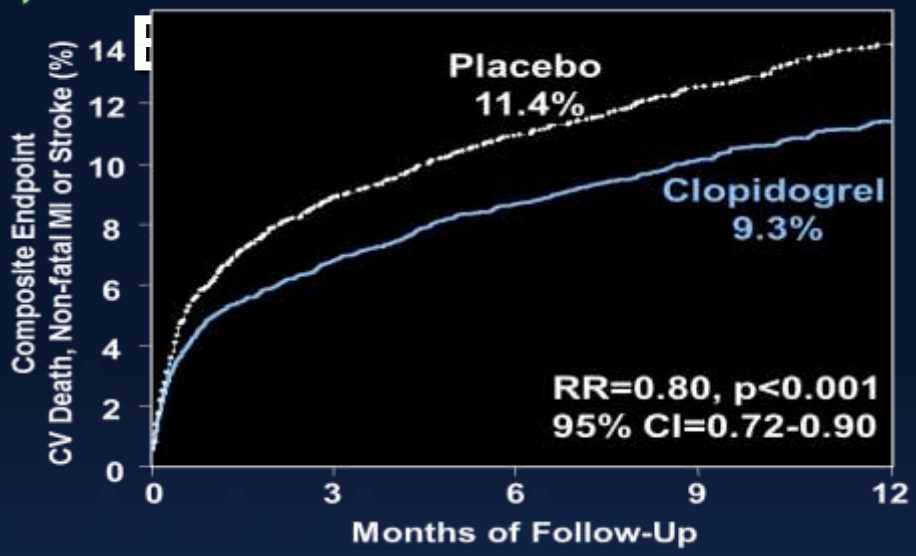
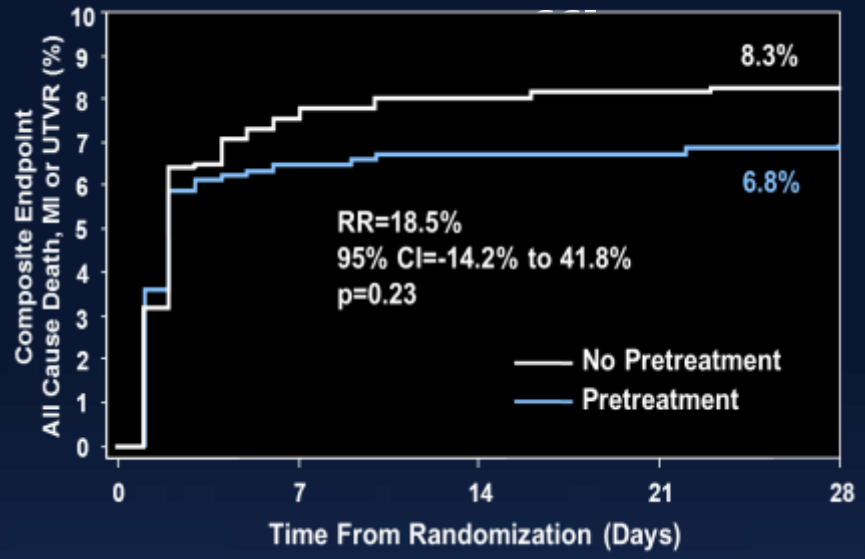
ACS

CURE

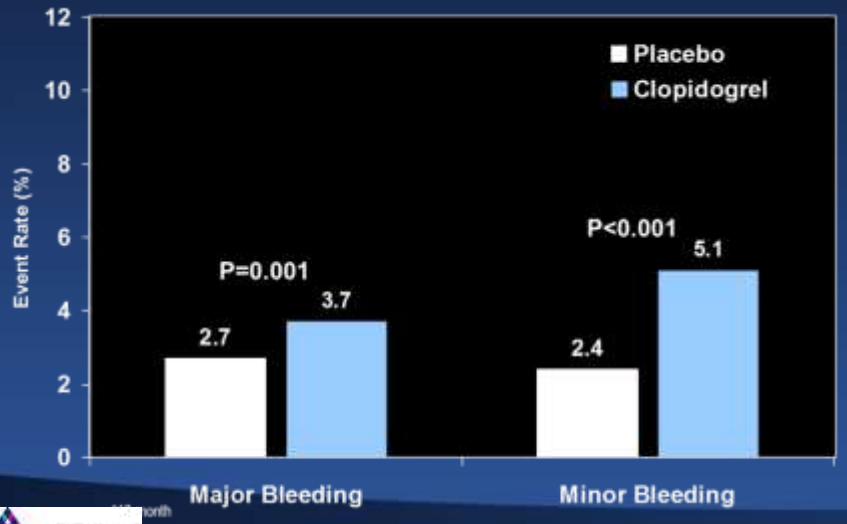


PCI

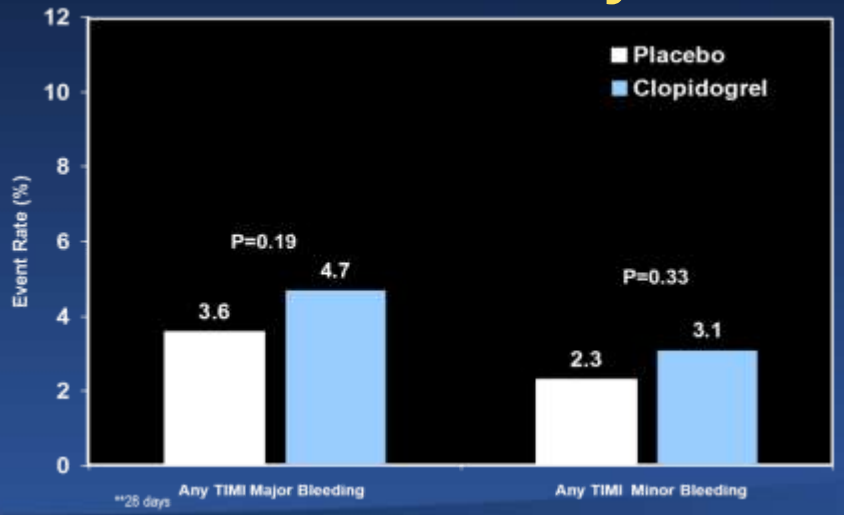
CREDO



CURE Safety*



CREDO Safety**



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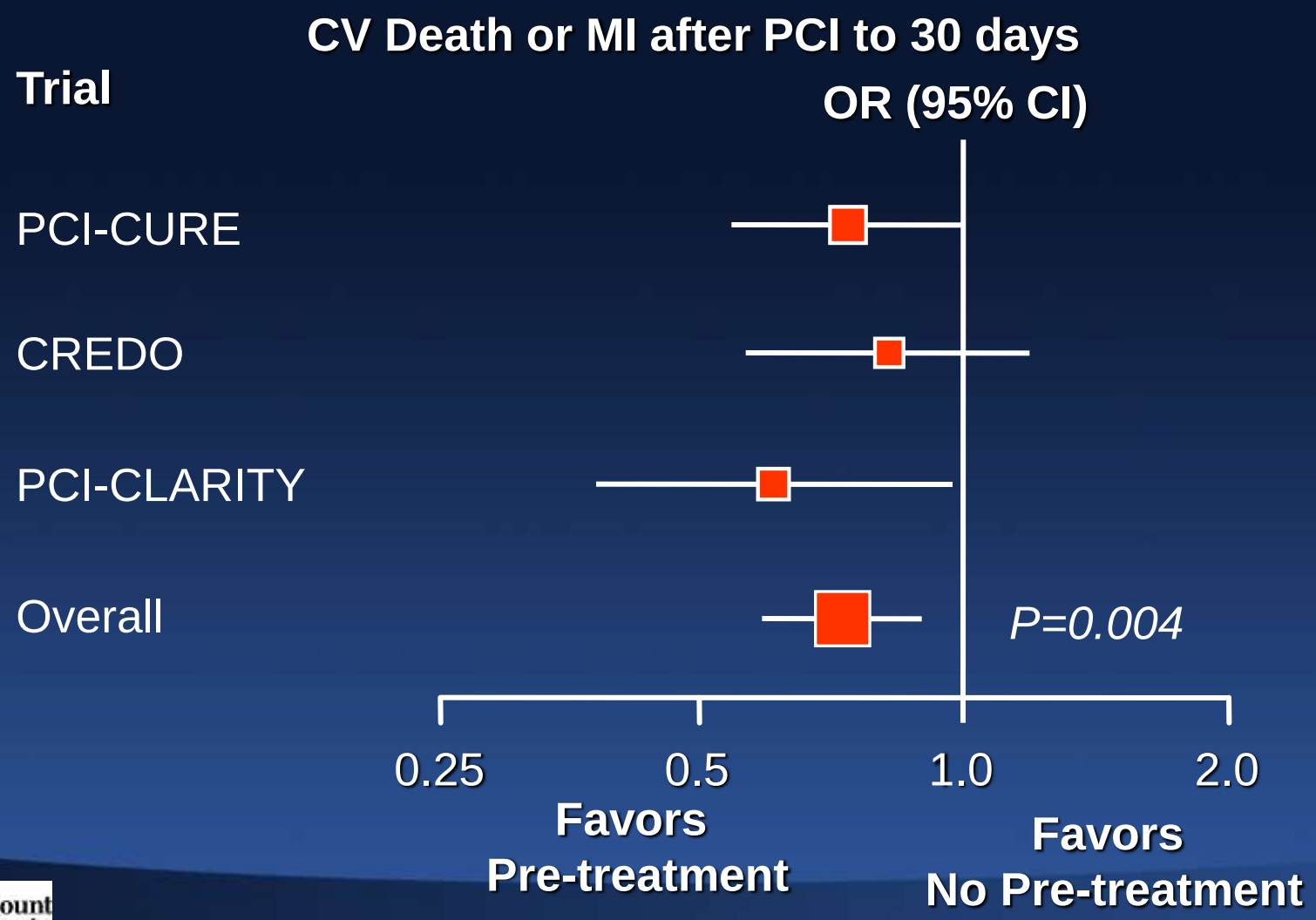
Yusuf S, et al. *N Engl J Med* 2001;345:494-502

Steinhubl SR, et al. *JAMA* 2002;288:2411-2420

PCI Pre-Treatment (With 300 mg load) → Events



Sabatine. et al. *JAMA*. 2005;294:1224-1232

$P2Y_{12}$ Pre-treatment Recommendations

Title	Citation		Class	LOE
2011 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation	European Heart Journal 2011;32:2999–3054	"A $P2Y_{12}$ inhibitor **as soon as possible**" Clopidogrel 600 mg Ticagrelor	I I I	A B B
2010 ESC/EACTS guidelines on myocardial revascularization	European Heart Journal 2010;31:20:2501–2555	"Clopidogrel 600 mg **as soon as possible**"	I	C
2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction	Circulation 2012;126:875–910	*"If invasive strategy, **before** PCI"* Clopidogrel Ticagrelor *Prasugrel	I I	B B
2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention	Circulation 2011;124:e574–651	$P2Y_{12}$ inhibitor Clopidogrel Prasugrel Ticagrelor	I I I I	A B B B

* Prasugrel 60 mg may be considered for administration promptly upon presentation in patients with UA/NSTEMI for whom PCI is planned, before definition of coronary anatomy if both the risk for bleeding is low and the need for CABG is considered unlikely (Level of Evidence: IIb – C)

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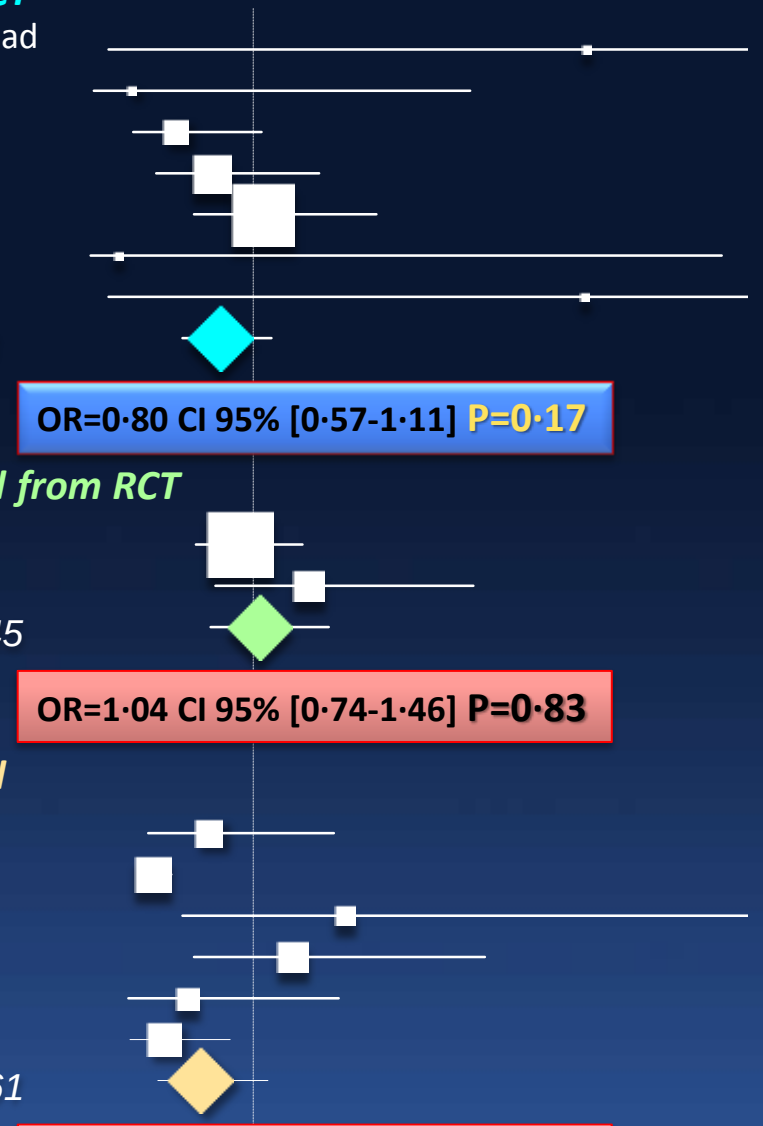
PCI meta-analysis

Death

	Events / Size, Clopidogrel Pretreatment	No Pretreat	OR [CI 95%]	Relative Weight [%]
Randomized CT				
ARMYDA5 Preload	1/204	0/205	3·03 [0·12-74·80]	1·0%
CIPAMI	1/164	4/171	0·26 [0·03-2·32]	2·2%
CLARITY PCI	13/933	24/930	0·53 [0·27-1·05]	23·2%
CREDO	18/1053	24/1063	0·75 [0·41-1·40]	28·3%
PCI CURE	32/1313	31/1345	1·06 [0·64-1·75]	43·1%
Davlouros et al.	0/103	2/96	0·18 [0·01-3·85]	1·2%
PRAGUE 8	1/513	0/515	3·02 [0·12-74·25]	1·0%
All *N=8,608*	66/4283	85/4325	0·80 [0·57-1·11]	100%
Observational from RCT				
ACUITY PCI	105/3511	49/1515	0·92 [0·65-1·30]	68·2%
REPLACE 2	114/5087	14/832	1·34 [0·77-2·34]	31·8%
All *N=10,945*	219/8598	63/2347	1·04 [0·74-1·46]	100%
Observational				
Amin et al.	13/923	19/990	0·73 [0·36-1·49]	16·2%
Dorler et al.	209/4879	110/1076	0·39 [0·31-0·50]	24·0%
Fefer et al.	12/217	6/166	1·56 [0·57-4·25]	11·9%
Feldman et al.	18/467	18/574	1·24 [0·64-2·41]	17·0%
Szuk et al.	6/1481	18/2679	0·60 [0·24-1·52]	12·9%
Chan et al.	76/4477	12/332	0·46 [0·25-0·86]	17·8%
All *N=18,261*	334/12444	183/5817	0·68 [0·42-1·09]	100%



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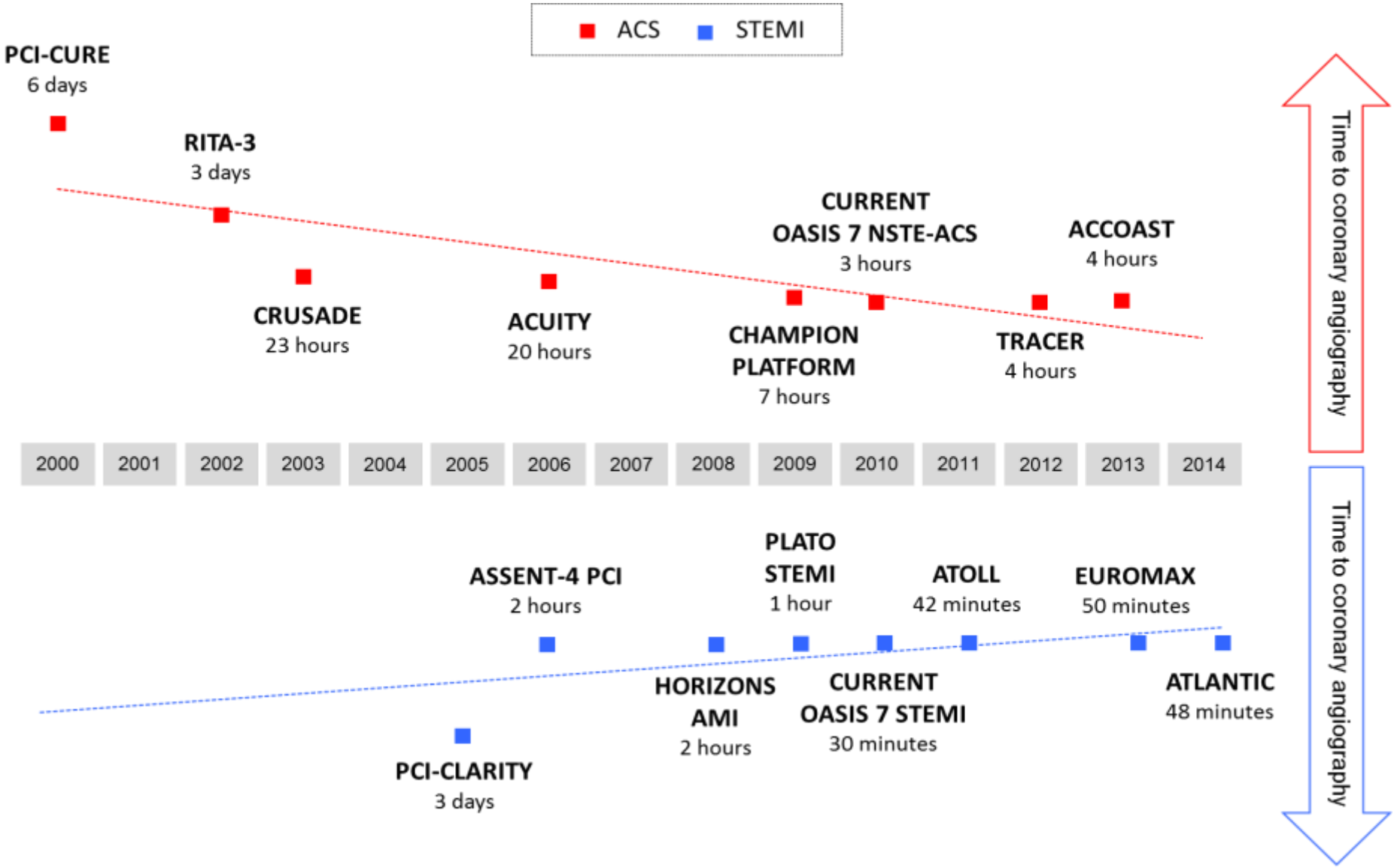
Bellemain-Appaix A et al. *JAMA* 2012;308:2507-2516

Pretreatment with Antiplatelet Drugs in Invasively Managed Patients With CAD: Time from hospital admission or first medical contact to coronary angiography in studies of ACS & STEMI



Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015 [in press]

ACCOAST

A Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pretreatment At the time of diagnosis in patients with non-ST-elevation MI

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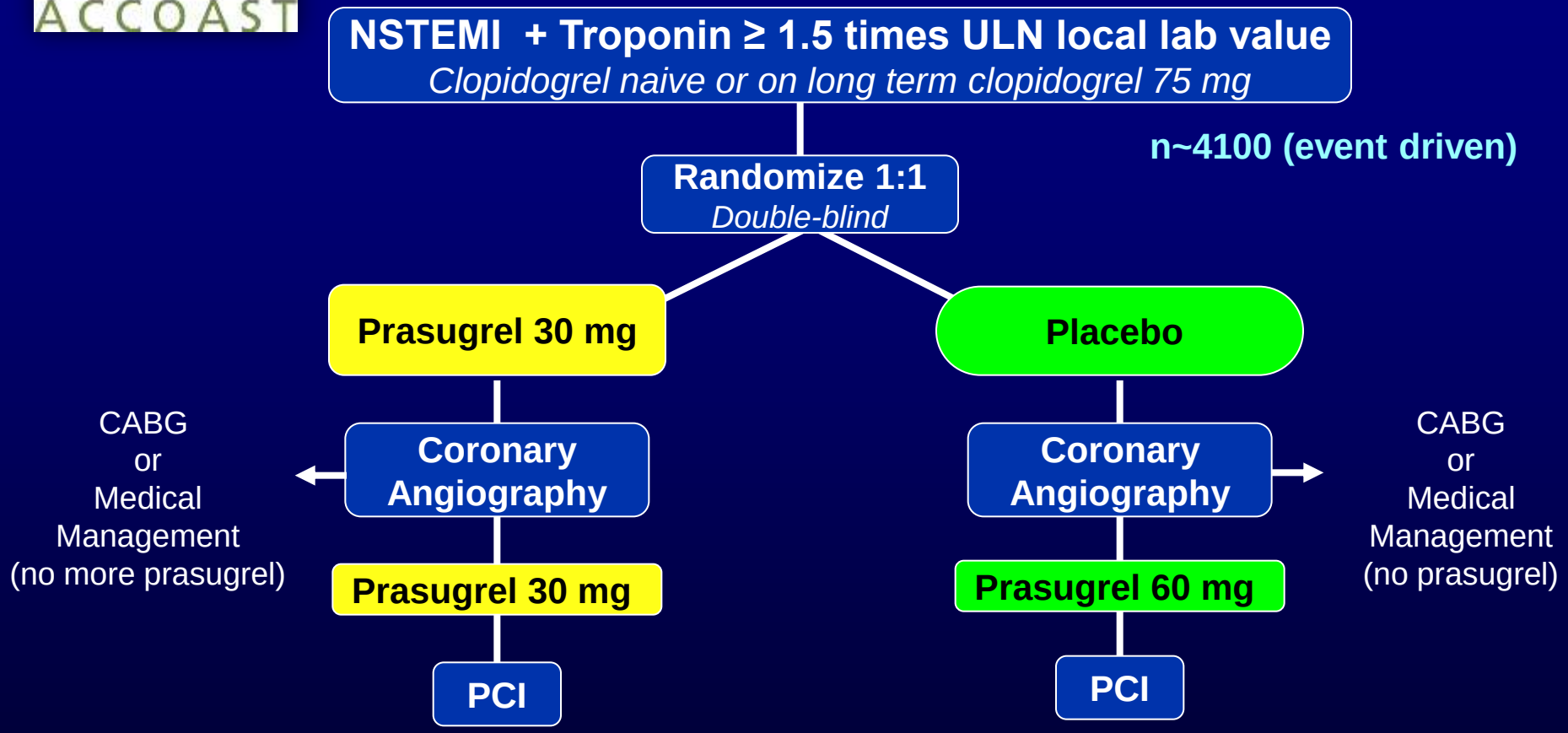
TRIAL RATIONALE

- Pre-treatment with aspirin and a $P2Y_{12}$ antagonist has been a class I recommendation and common practice for the treatment of NSTE-ACS

- However, no trial has ever randomized patients presenting with NSTE-ACS, invasively managed, to pre-treatment with clopidogrel, prasugrel or ticagrelor *vs.* no pre-treatment.

ACCOAST design



Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

<u>1° Endpoint:</u> CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

Montalescot G et al. *Am Heart J* 2011;161:650-656

Baseline Characteristics

Characteristics	Pre-treatment (N =2037)	No Pre-treatment (N =1996)
Age (mean, yrs)	64	64
Female sex (%)	27	28.0
Weight (mean, kg)	82	82
BMI ≥ 30 (%)	29	28
CV risk factors (%)		
Diabetes mellitus	20	20
Dyslipidemia	45	45
Hypertension	63	61
Current smoker	34	33
Region of enrolment (%)		
Eastern Europe/Israel	42	42
Western Europe/Canada	58	58

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Baseline Characteristics

Characteristics	Pre-treatment (N =2037)	No Pre-treatment (N =1996)
GRACE score (%)		
<140	76	78
≥140	24	22
CRUSADE score (median)	34	34
Timing (hr)		
→Symptom onset to 1st LD, median	14.6	15.2
→ 1st LD to coronary angiogram, median	4.4	4.2
Access (%)[ll]		
Femoral	57	57
Radial	43	43

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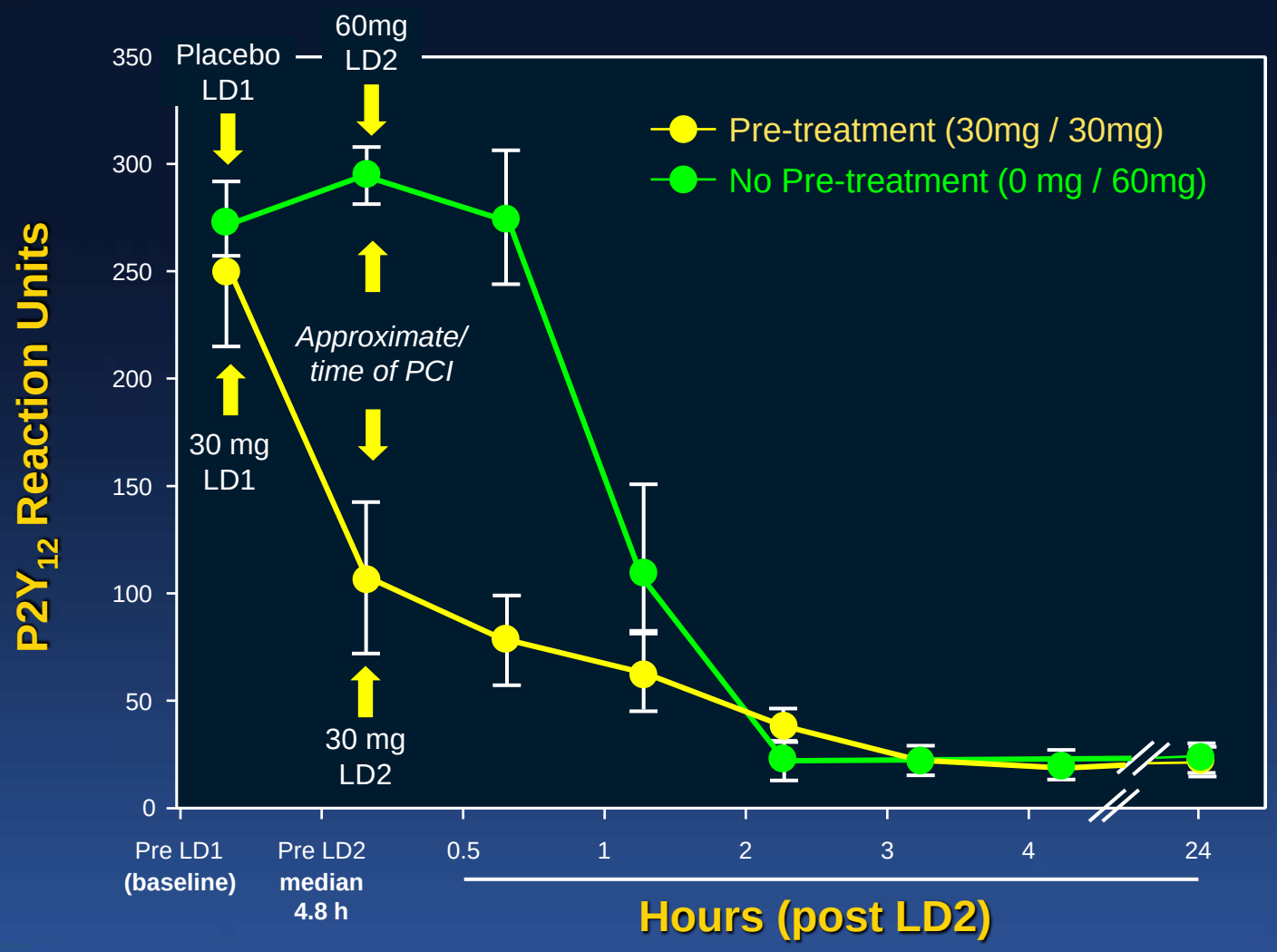
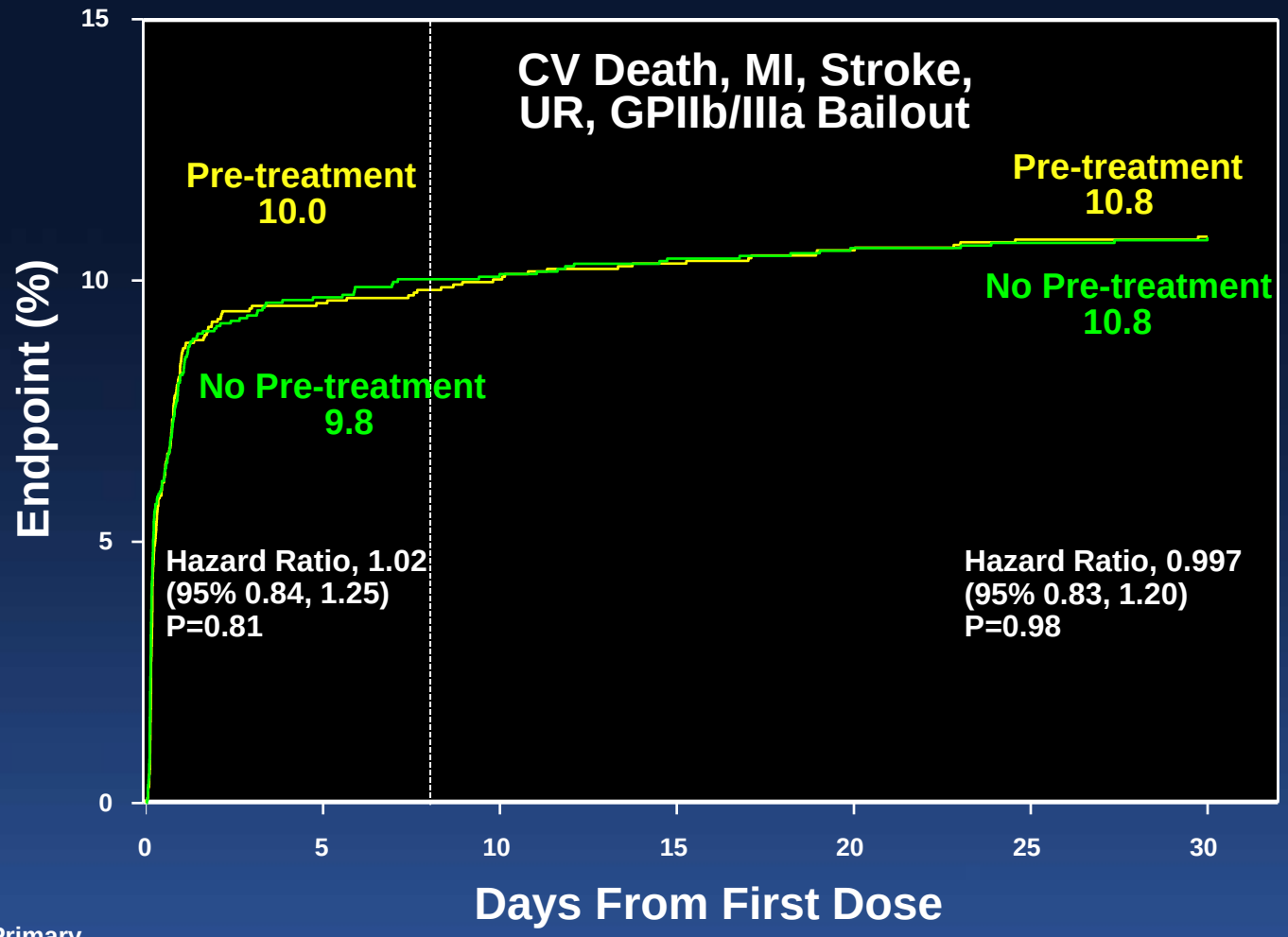
Pharmacodynamic Substudy
(n=23)



Montalescot G et al. *NEJM* 2013

1° Efficacy End Point @ 7 + 30 days (All Patients)



No. at Risk, Primary Efficacy End Point:

No pre-treatment	1996	1788	1775	1769	1762	1752	1621
Pre-treatment	2037	1821	1809	1802	1797	1791	1616

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Major Efficacy Endpoints

End Point	Pretreatment (N=2037)	No Pretreatment (N=1996)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
7 Days				
Death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout: primary end point	203 (10.0)	195 (9.8)	1.02 (0.84–1.25)	0.81
Death				
From any cause	8 (0.4)	10 (0.5)	0.78 (0.31–1.98)	0.61
From cardiovascular cause	7 (0.3)	10 (0.5)	0.69 (0.26–1.80)	0.44
Myocardial infarction	119 (5.8)	109 (5.5)	1.07 (0.83–1.39)	0.60
Stroke	8 (0.4)	10 (0.5)	0.78 (0.31–1.98)	0.60
Urgent revascularization	22 (1.1)	26 (1.3)	0.83 (0.47–1.46)	0.52
Glycoprotein IIb/IIIa bailout	76 (3.7)	78 (3.9)	0.96 (0.70–1.31)	0.79
30 Days				
Death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout	219 (10.8)	216 (10.8)	0.997 (0.83–1.20)	0.98
Death from cardiovascular causes, myocardial infarction, or stroke	144 (7.1)	144 (7.2)	0.98 (0.78–1.23)	0.86
Death from cardiovascular causes or myocardial infarction	135 (6.6)	130 (6.5)	1.02 (0.80–1.30)	0.88
Death from cardiovascular causes, myocardial infarction, or urgent revascularization	157 (7.7)	146 (7.3)	1.06 (0.85–1.33)	0.62
Death from cardiovascular causes	14 (0.7)	22 (1.1)	0.62 (0.32–1.22)	0.16
Myocardial infarction	126 (6.2)	116 (5.8)	1.07 (0.83–1.37)	0.62

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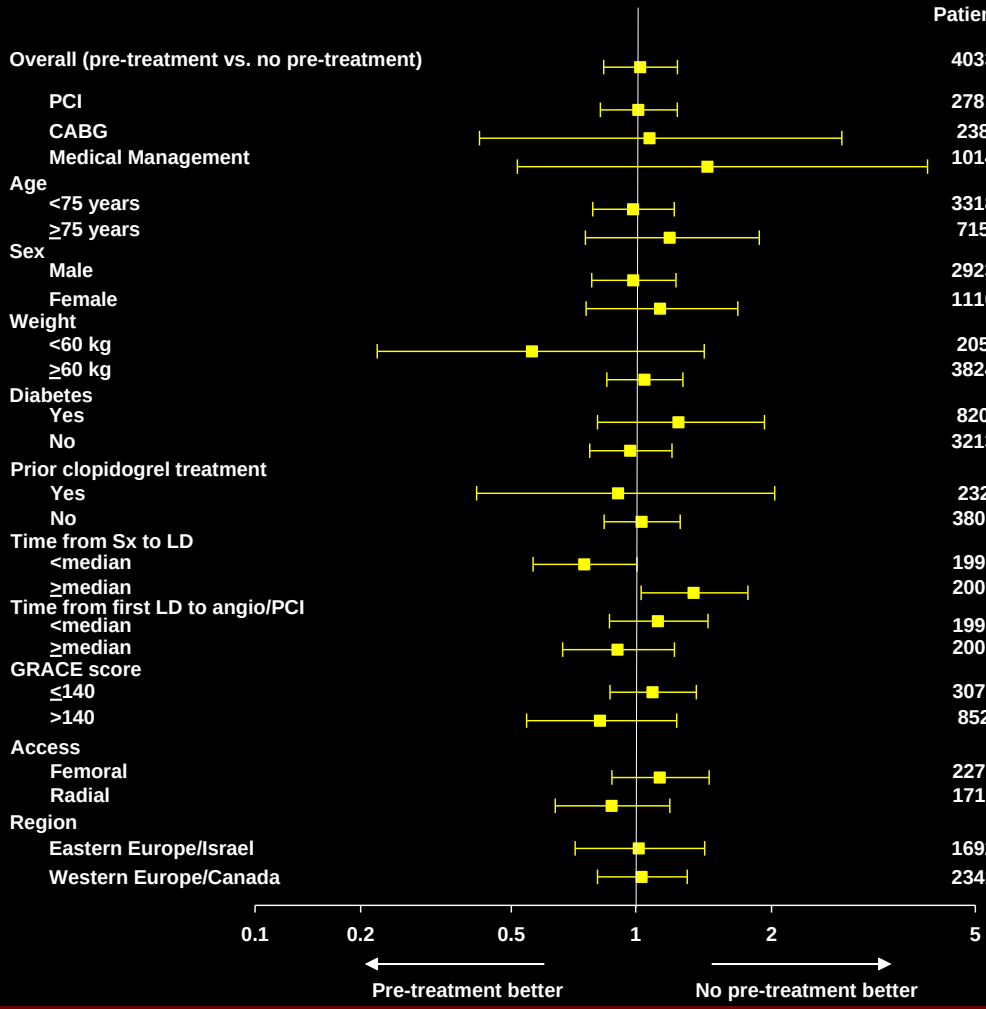
Montalescot G et al. *NEJM* 2013

1° Efficacy Endpoint Through 7 Days for Prespecified Subgroups (All Patients)



	Total Patients	Pre-tx n (%)	No Pre-tx n (%)	Hazard Ratio (95% CI)	Interaction P-value†
Overall (pre-treatment vs. no pre-treatment)	4033	203 (9.97)	195 (9.77)	1.02 (0.84, 1.25)	
PCI	2781	185 (13.21)	181 (13.11)	1.01 (0.83, 1.25)	0.54
CABG	238	9 (7.44)	8 (6.84)	1.08 (0.42, 2.79)	
Medical Management	1014	9 (1.74)	6 (1.20)	1.45 (0.52, 4.09)	
Age					
<75 years	3318	160 (9.62)	162 (9.79)	0.99 (0.79, 1.23)	0.45
≥75 years	715	43 (11.53)	33 (9.65)	1.20 (0.76, 1.88)	
Sex					
Male	2923	152 (10.24)	149 (10.36)	0.99 (0.79, 1.24)	0.54
Female	1110	51 (9.24)	46 (8.24)	1.14 (0.76, 1.70)	
Weight					
<60 kg	205	7 (6.80)	12 (11.76)	0.56 (0.22, 1.43)	0.20
≥60 kg	3824	195 (10.09)	183 (9.68)	1.05 (0.86, 1.28)	
Diabetes					
Yes	820	46 (11.14)	37 (9.09)	1.25 (0.81, 1.93)	0.30
No	3213	157 (9.67)	158 (9.94)	0.97 (0.78, 1.21)	
Prior clopidogrel treatment					
Yes	232	11 (9.82)	13 (10.83)	0.91 (0.41, 2.03)	0.76
No	3801	192 (9.97)	182 (9.70)	1.03 (0.84, 1.26)	
Time from Sx to LD					
<median	1990	84 (8.24)	105 (10.82)	0.76 (0.57, 1.01)	0.004
≥median	2008	119 (11.91)	90 (8.92)	1.36 (1.03, 1.78)	
Time from first LD to angio/PCI					
<median	1998	120 (12.07)	109 (10.86)	1.13 (0.87, 1.46)	0.30
≥median	2003	82 (8.02)	86 (8.77)	0.91 (0.67, 1.23)	
GRACE score					
≤140	3079	154 (10.05)	143 (9.24)	1.09 (0.87, 1.37)	0.24
>140	852	44 (9.73)	47 (11.75)	0.82 (0.55, 1.24)	
Access					
Femoral	2276	125 (10.96)	111 (9.77)	1.14 (0.88, 1.47)	0.21
Radial	1711	76 (8.75)	83 (9.86)	0.88 (0.64, 1.20)	
Region					
Eastern Europe/Israel	1692	66 (7.65)	63 (7.60)	1.02 (0.72, 1.43)	0.93
Western Europe/Canada	2341	137 (11.67)	132 (11.31)	1.03 (0.81, 1.31)	

*Hazard ratio not evaluated for <10 events.
†Interaction p-value is from a Cox proportional hazards model with treatment, subgroup, and the treatment-by-subgroup interaction as fixed effects; PCI includes 11 patients with PCI + CABG.

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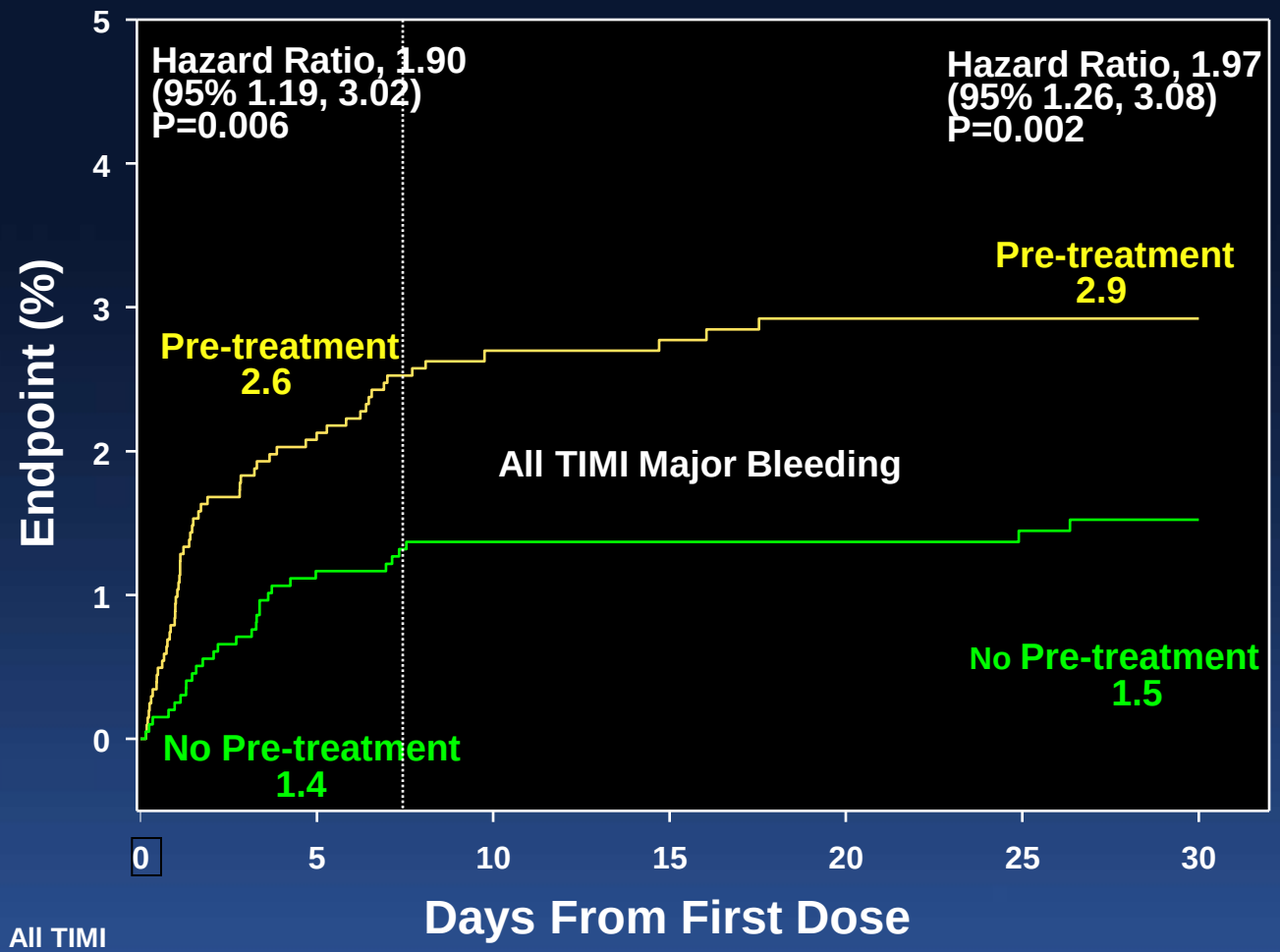
All TIMI (CABG or non-CABG) Major Bleeding (All Treated patients)



No. at Risk, All TIMI Major Bleeding:							
No pre-treatment	1996	1947	1328	1297	1288	1284	1263
Pre-treatment	2037	1972	1339	1310	1299	1297	1280

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Major Bleeding Endpoints

7 Days				
All CABG-related or non–CABG-related TIMI major bleeding: key safety end point	52 (2.6)	27 (1.4)	1.90 (1.19–3.02)	0.006
Non–CABG-related TIMI major bleeding	27 (1.3)	9 (0.5)	2.95 (1.39–6.28)	0.003
Fatal bleeding	1 (<0.1)	0	NE	NE
Life-threatening bleeding	17 (0.8)	3 (0.2)	5.56 (1.63–19.0)	0.002
Type of bleeding†				
Intracranial hemorrhage	0	0	NE	NE
Vascular access-site bleeding	9 (0.4)	2 (0.1)	NE	NE
Gastrointestinal	4 (0.2)	3 (0.2)	NE	NE
Hematuria	1 (<0.1)	0	NE	NE
Pericardial	4 (0.2)	2 (0.1)	NE	NE
Other‡	9 (0.4)	2 (0.1)	NE	NE
Non–CABG-related TIMI major or minor bleeding	61 (3.0)	20 (1.0)	3.02 (1.82–5.01)	<0.001
CABG-related TIMI major bleeding§	25 (20.7)	16 (13.7)	1.59 (0.85–2.98)	0.14
GUSTO moderate or severe, CABG-related or non–CABG-related	70 (3.4)	35 (1.8)	1.98 (1.32–2.97)	<0.001
STEEPLE major bleeding, non–CABG-related	46 (2.3)	18 (0.9)	2.52 (1.46–4.35)	<0.001
STEEPLE minor bleeding, non–CABG-related	58 (2.8)	38 (1.9)	1.50 (1.00–2.26)	0.05
Transfusions¶				
Total, for any reason	41 (2.0)	22 (1.1)	1.84 (1.09–3.08)	0.02
For non–CABG-related TIMI major bleeding	20 (1.0)	7 (0.4)	2.81 (1.19–6.63)	0.01

Montalescot G et al. *NEJM* 2013

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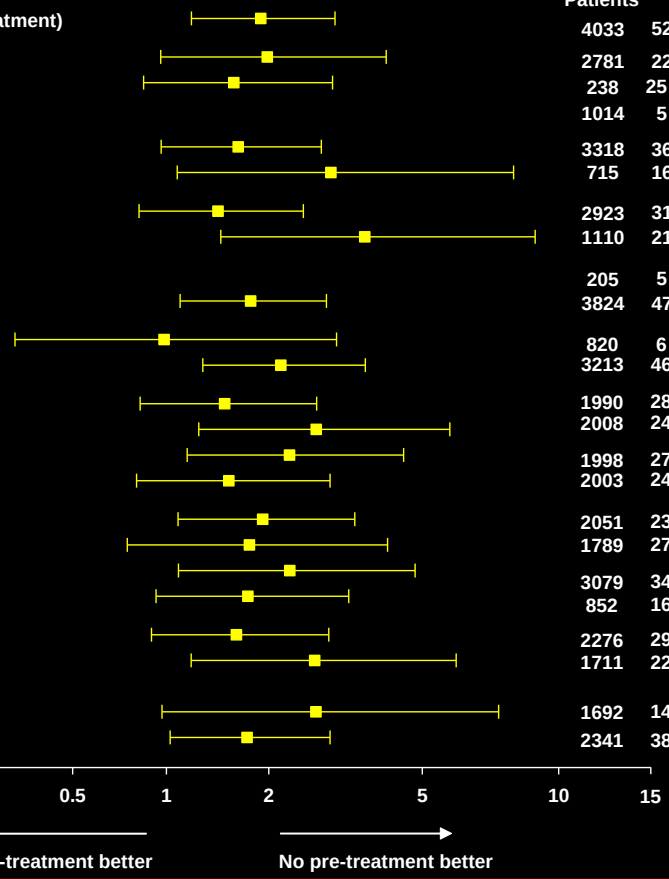
All TIMI Major Bleeding for Prespecified Subgroups Through 7 days (All Treated Patients)



	Total Patients	Pre-tx (%)	No Pre-tx (%)	Hazard Ratio (95% CI)	Interaction P-value†
Overall (pre-treatment vs. no pre-treatment)	4033	52 (2.55)	27 (1.35)	1.90 (1.19, 3.02)	
PCI	2781	22 (1.57)	11 (0.80)	1.98 (0.96, 4.09)	0.74
CABG	238	25 (20.66)	16 (13.68)	1.59 (0.85, 2.98)	
Medical Management*	1014	5 (0.97)	0 (0.00)	NE	
Age					
<75 years	3318	36 (2.16)	22 (1.33)	1.64 (0.96, 2.78)	0.31
≥75 years	715	16 (4.29)	5 (1.46)	2.95 (1.08, 8.05)	
Sex					
Male	2923	31 (2.09)	21 (1.46)	1.43 (0.82, 2.49)	0.09
Female	1110	21 (3.80)	6 (1.08)	3.61 (1.46, 8.95)	
Weight					
<60 kg*	205	5 (4.85)	1 (0.98)	NE	0.35
≥60 kg	3824	47 (2.43)	26 (1.37)	1.78 (1.10, 2.87)	
Diabetes					
Yes	820	6 (1.45)	6 (1.47)	0.98 (0.32, 3.05)	0.22
No	3213	46 (2.83)	21 (1.32)	2.16 (1.29, 3.62)	
Time from Sx to LD					
<median	1990	28 (2.75)	18 (1.86)	1.50 (0.83, 2.71)	0.23
≥median	2008	24 (2.40)	9 (0.89)	2.70 (1.25, 5.80)	
Time from first LD to angio/PCI					
<median	1998	27 (2.72)	12 (1.20)	2.28 (1.16, 4.51)	0.41
≥median	2003	24 (2.35)	15 (1.53)	1.54 (0.81, 2.93)	
CRUSADE score‡					
≤median	2051	23 (2.23)	10 (0.98)	2.29 (1.09, 4.81)	0.59
>median	1789	27 (2.97)	15 (1.71)	1.75 (0.93, 3.28)	
GRACE score					
≤140	3079	34 (2.22)	18 (1.16)	1.92 (1.09, 3.41)	0.87
>140	852	16 (3.54)	8 (2.00)	1.76 (0.75, 4.12)	
Access					
Femoral	2276	29 (2.54)	18 (1.58)	1.62 (0.90, 2.91)	0.66
Radial	1711	22 (2.53)	8 (0.95)	2.67 (1.19, 6.00)	
Region					
Eastern Europe/Israel	1692	14 (1.62)	5 (0.60)	2.69 (0.97, 7.47)	0.46
Western Europe/Canada	2341	38 (3.24)	22 (1.89)	1.74 (1.03, 2.94)	

*Hazard ratio not evaluated for <10 events.
†Interaction p-value is from a Cox proportional hazards model with treatment, subgroup, and the treatment-by-subgroup interaction as fixed effects; ‡CRUSADE score is a post-hoc analysis; PCI includes 11 patients with PCI + CABG.

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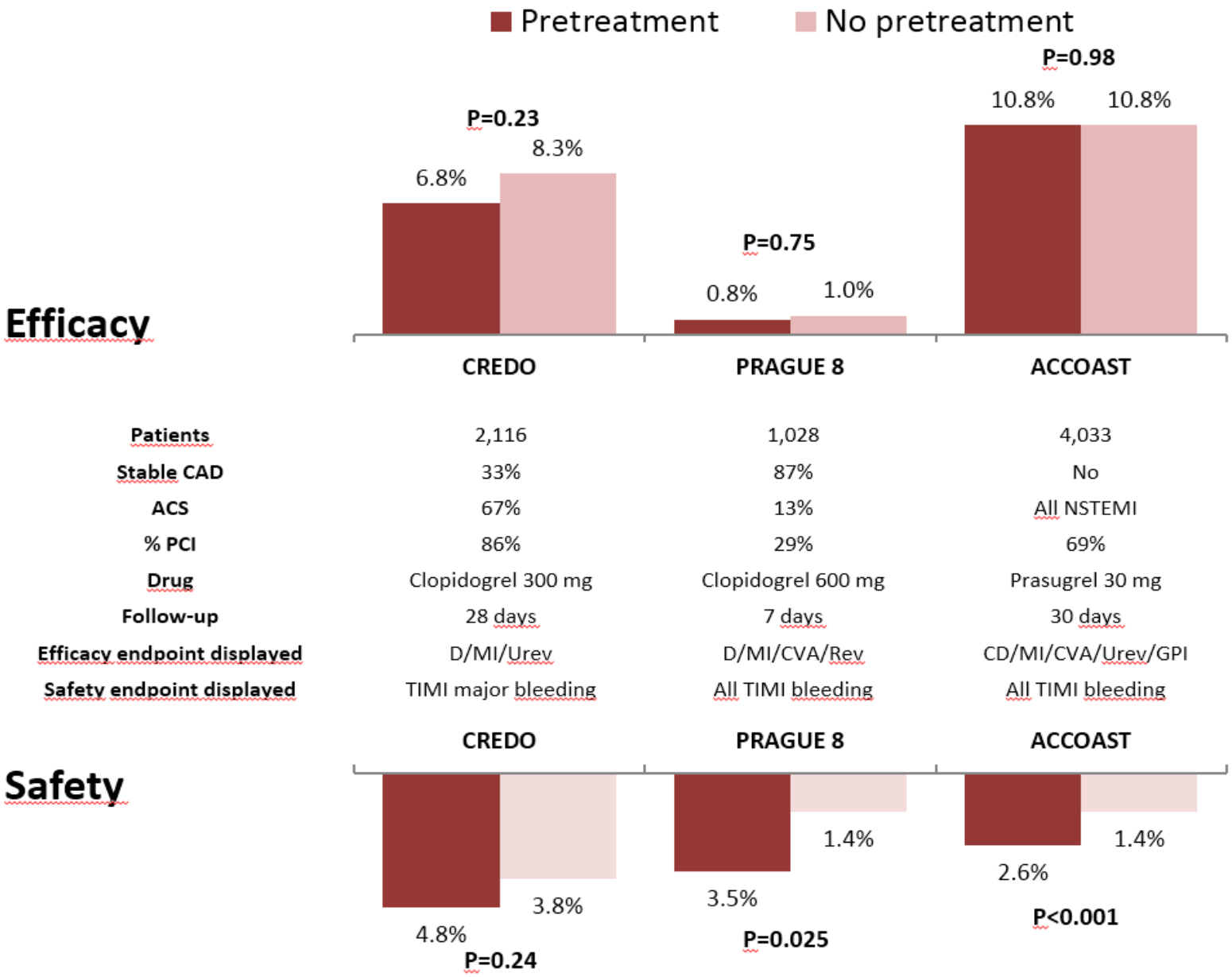
Studies of pretreatment with oral P2Y12 receptor inhibitors in patients with stable CAD and NSTE-ACS



Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015 [in press]

ACCOAST: To Pre-treat or not to?

1. Not effective, and may be harmful to pre-treat patients with Prasugrel
2. Should we selectively favor preloading NSTEMI pts with ticagrelor, or waiting until cath and then starting either prasugrel or ticagrelor for PCI pts? Atlantic also negative!
3. Given these data, how does Cangrelor fit into this scenario?

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Antithrombotic therapy in NSTE-ACS patients undergoing PCI

Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication.	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C
Pre-treatment with prasugrel in patients in whom coronary anatomy is not known is not recommended.	III	B
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.	III	A

A pre-treatment strategy, compared with a delayed administration of ticagrelor, has not so far been tested. In PLATO, all patients had received pre-treatment. Thus, the risk–benefit ratio of pre-treatment using ticagrelor prior to diagnostic coronary angiography is not known.