ACTION Study Group
Institute of Cardiology
Pitié-Salpêtrière Hospital
Paris - France

Pretreatment with P2Y12 inhibitors prior to PCI: Is it necessary in NSTE-ACS?

Against: little evidence, no benefits!

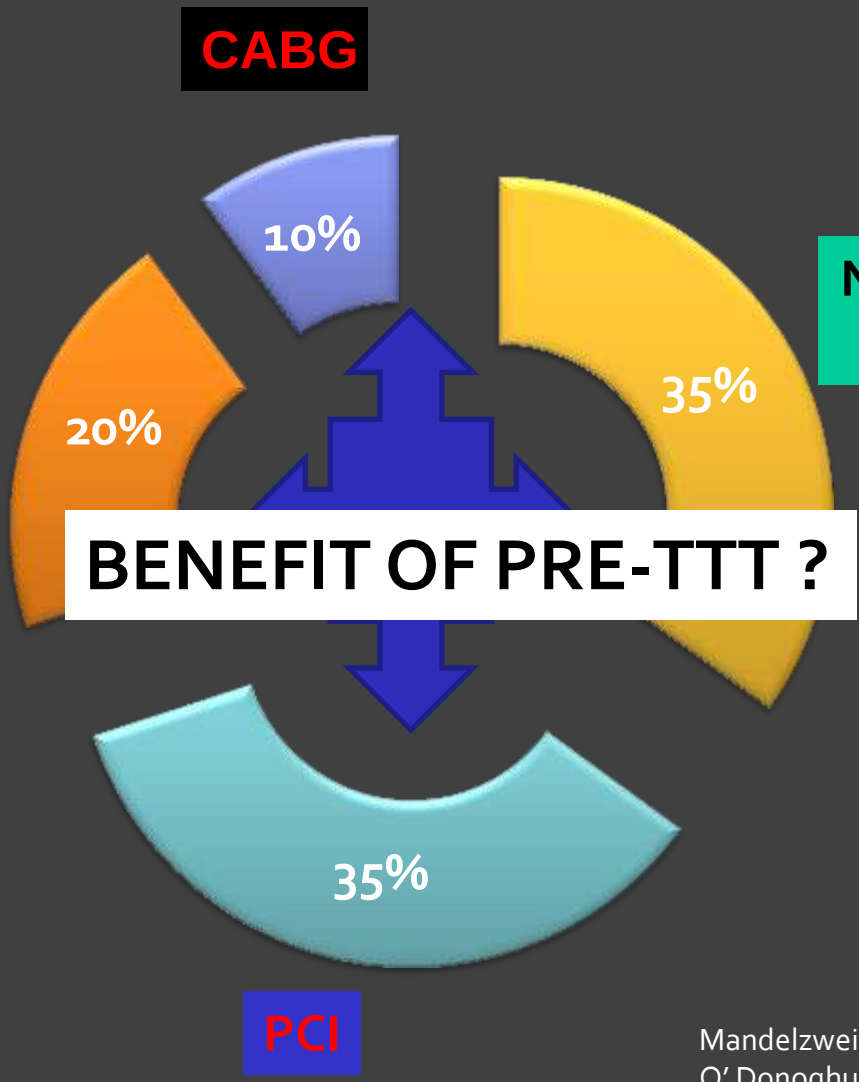
jean-philippe.collet@psl.aphp.fr

COI DISCLOSURE FOR DR. COLLET are available @ http://www.action-coeur.org

NSTE-ACS in the Real World of All-comers

>10% NSTEMI: coro N
>25% chez les femme

ANGIO-No PCI Med TT



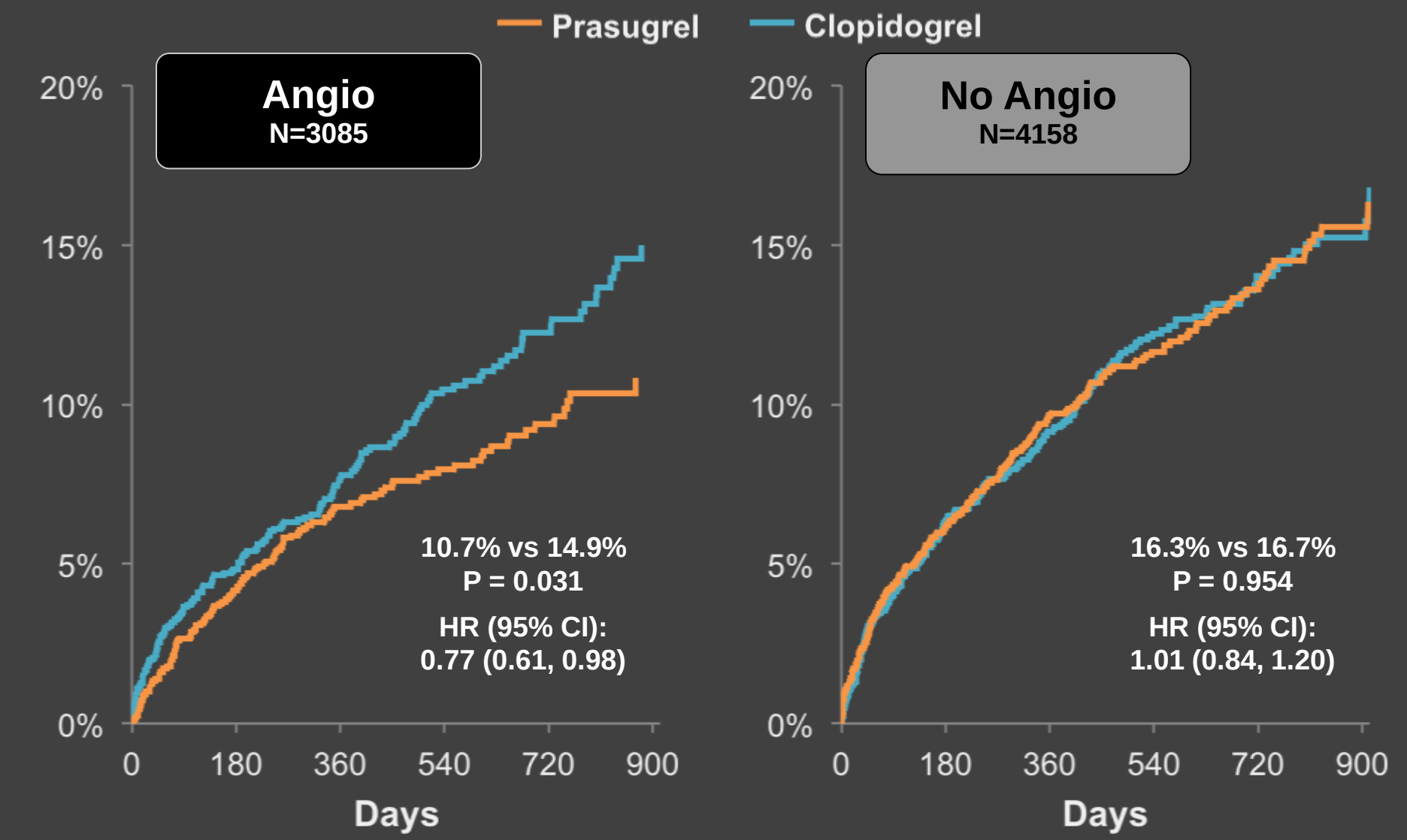
STEMI
-PCI 90%
-CABG 6-8%
-Med 2-4%

SCAD
-PCI 30-80%
-Med 25-60%
-CABG: 10%

Mandelzweig et al., *Eur Heart J. 2006;27:2285-2293*
O' Donoghue et al; *JAMA* 2008; **300:** 71–80.
Patel et al; *Am Heart J* 2006; **152:** 641–47.

Primary Efficacy Endpoint to 30 Months

(Age < 75 years)

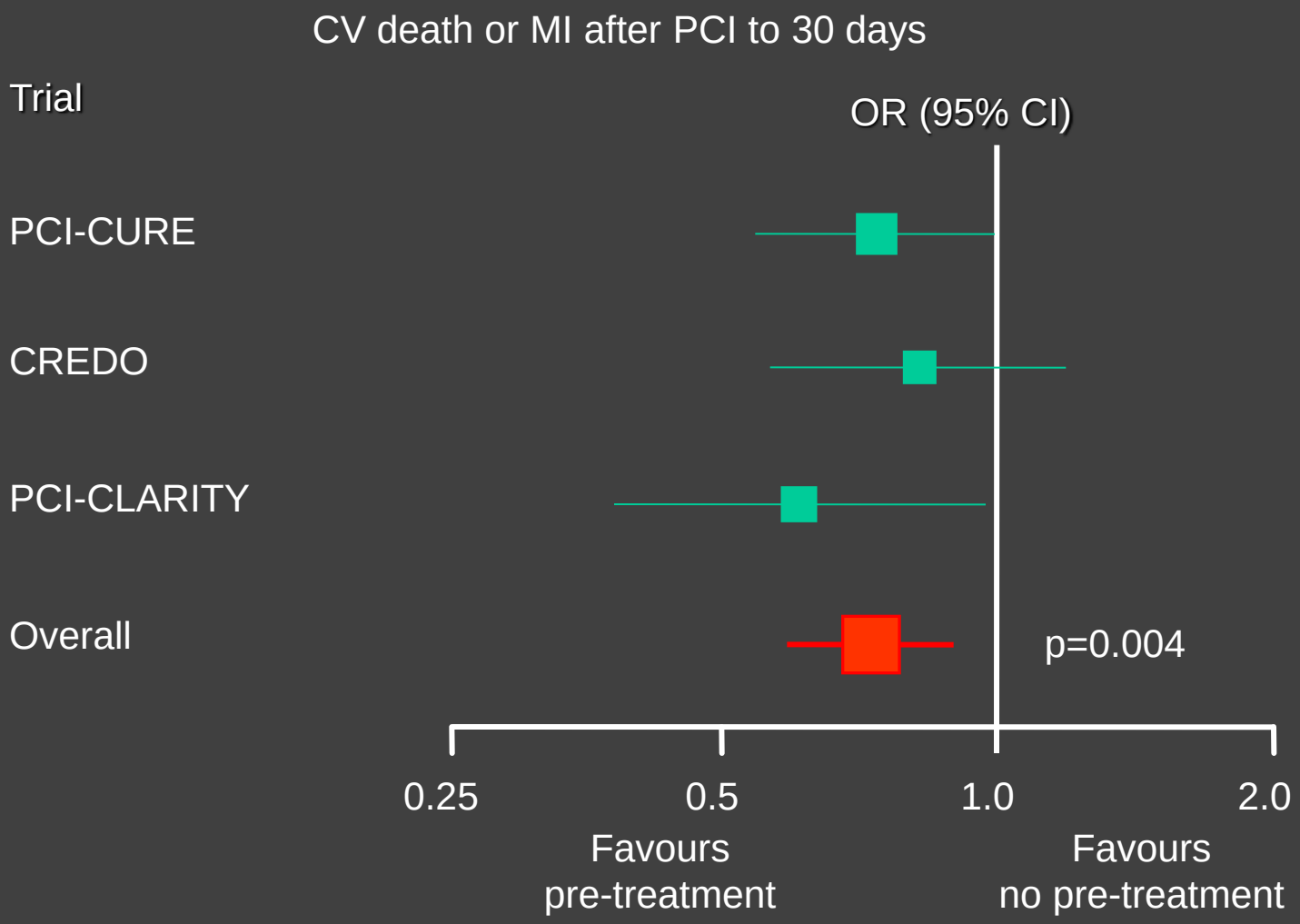


P interaction = 0.08

***Lancet* 2013; 382: 605–13**

Revisiting the concept of Pre-treatment with $P2Y_{12}$ antagonists ?

PCI pre-treatment (with 300 mg Load) → Events

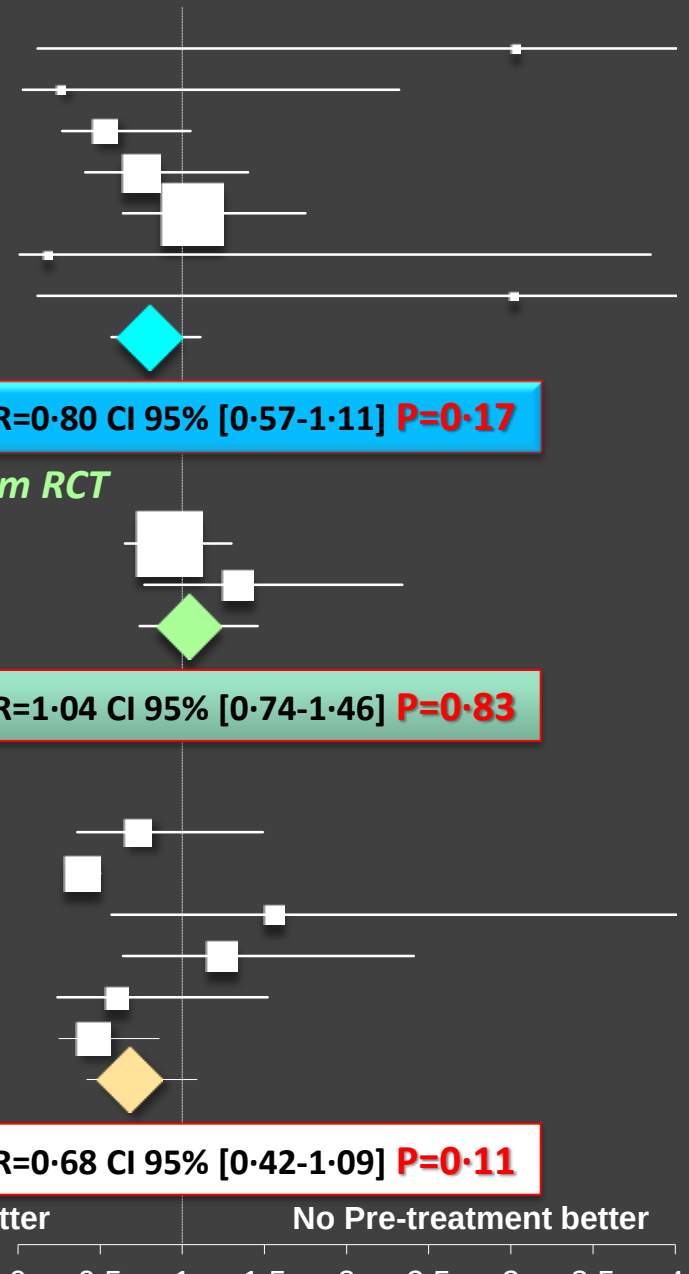


Sabatine. et al. JAMA. 2005;294:1224-1232

P2Y12 Pre-treatment ESC 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 P2Y12 inhibitor **as soon as possible"**	I	A
		Clopidogrel 600mg	I	B
		Ticagrelor	I	B
2010 ESC/EACTS guidelines on myocardial revascularization	European Heart Journal 2010;31:20:2501–2555	"Clopidogrel 600mg **as soon as possible"**	I	C

Death



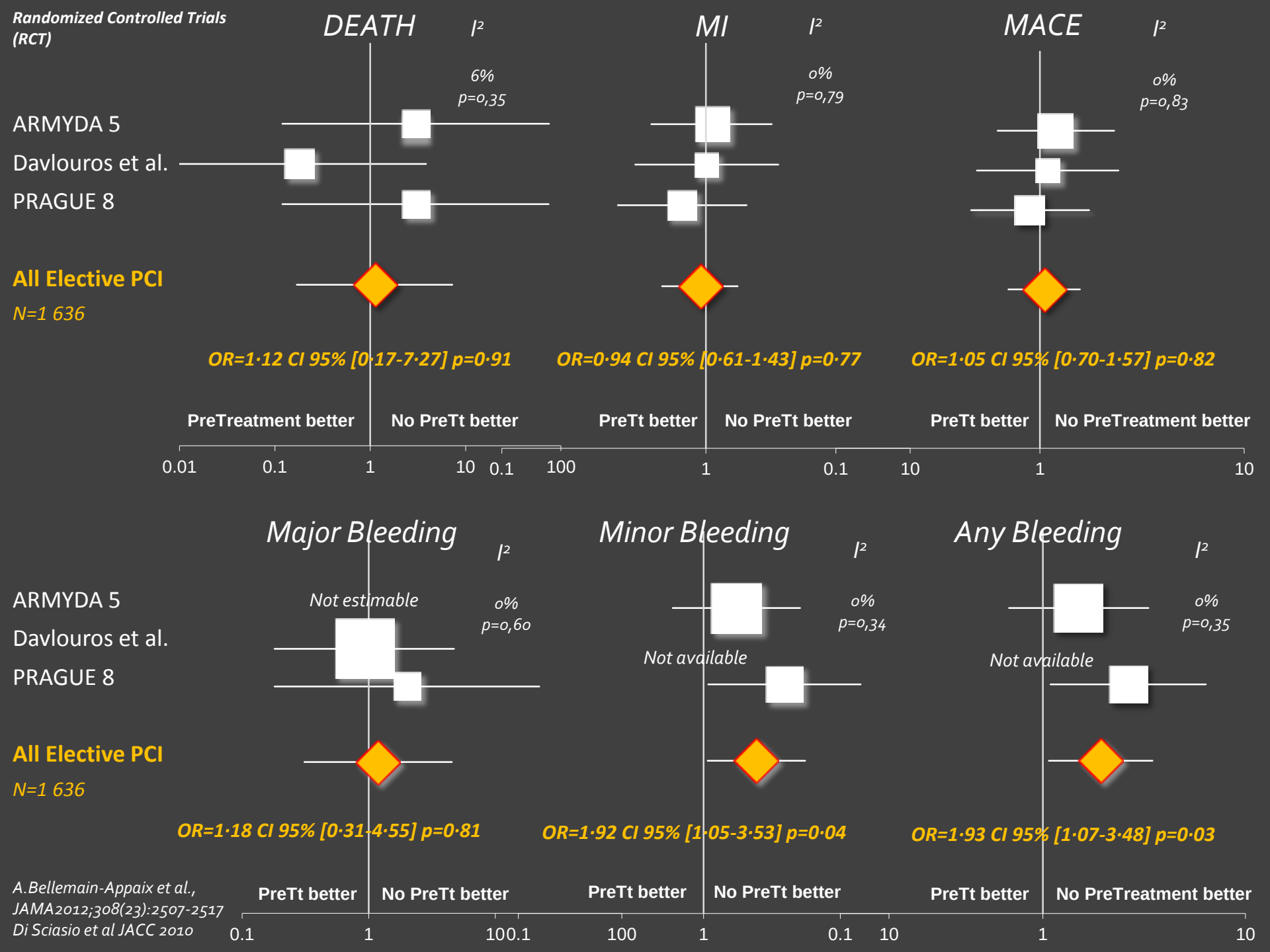
	Events / Size, Clopidogrel Pretreatment	Events / Size, Clopidogrel No Pretreat	OR [CI 95%]	Relative Weight [%]
Randomized CT				
ARMYDA5 Preload	1/204	0/205	3·03 [0·12-74·80]	1·0%
CIPAMI	1/164	4/171	0·26 [0·03-2·32]	2·2%
CLARITY PCI	13/933	24/930	0·53 [0·27-1·05]	23·2%
CREDO	18/1053	24/1063	0·75 [0·41-1·40]	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%
OR=0·80 CI 95% [0·57-1·11] P=0·17				
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%
OR=1·04 CI 95% [0·74-1·46] P=0·83				
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%
OR=0·68 CI 95% [0·42-1·09] P=0·11				

Pre-treatment better **No Pre-treatment better**

0 0.5 1 1.5 2 2.5 3 3.5 4

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

Randomized Controlled Trials (RCT)



A.Bellemain-Appaix et al., JAMA2012;308(23):2507-2517
Di Sciasio et al JACC 2010

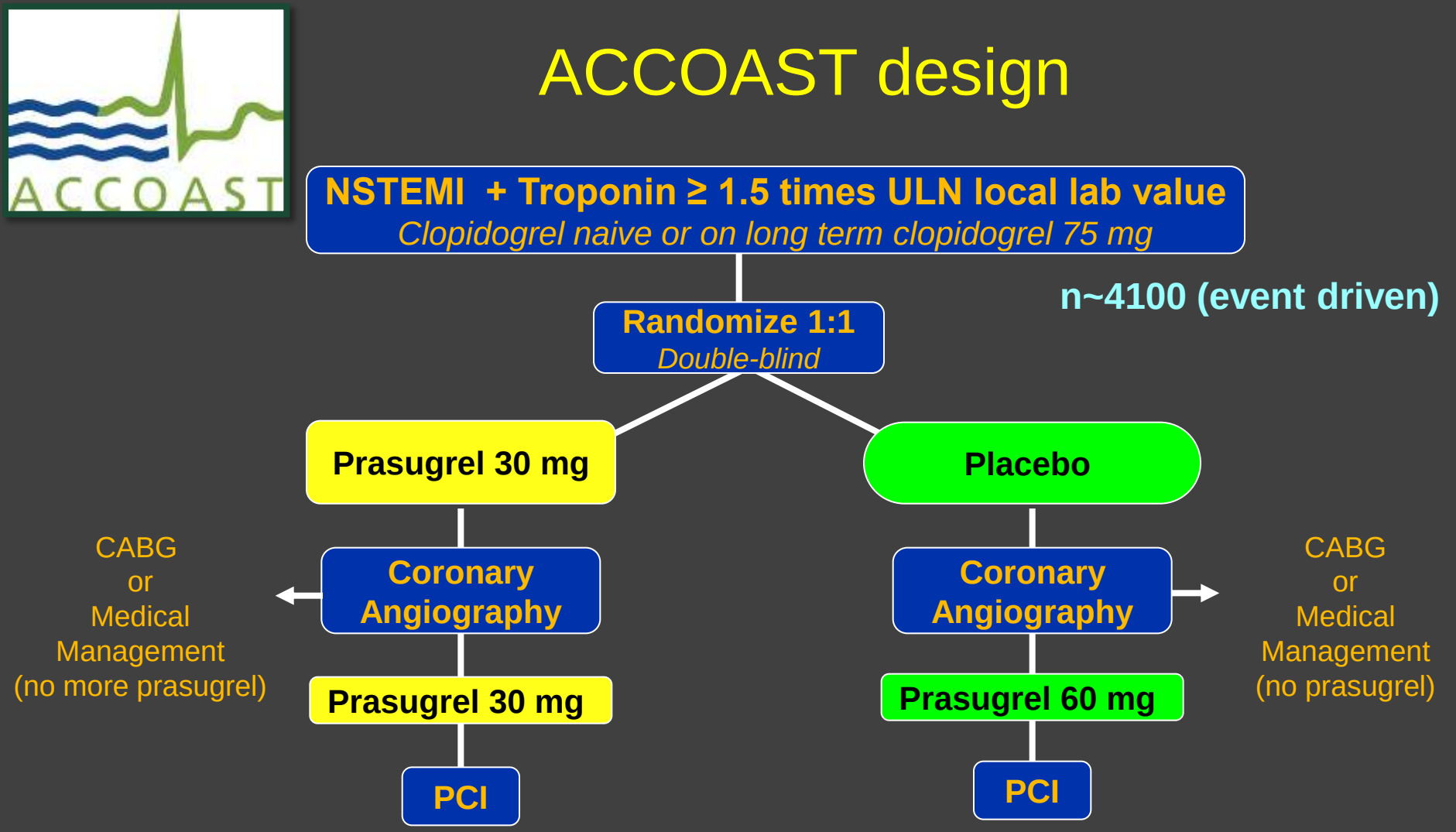
CONCLUSIONS:
Clopidogrel pre-treatment in NSTEMI-PCI

- Clopidogrel SPC: patients with impaired response
- Mode of action suggests benefit
- Registry data suggest benefit
- Meta-analysis suggests benefit
- RCTs in lower risk populations failed to show benefit
- Posthoc analysis from one RCT marginally positive
- No evidence from RCT in high risk NSTEMI-PCI

→ ACCOAST is to provide the missing evidence

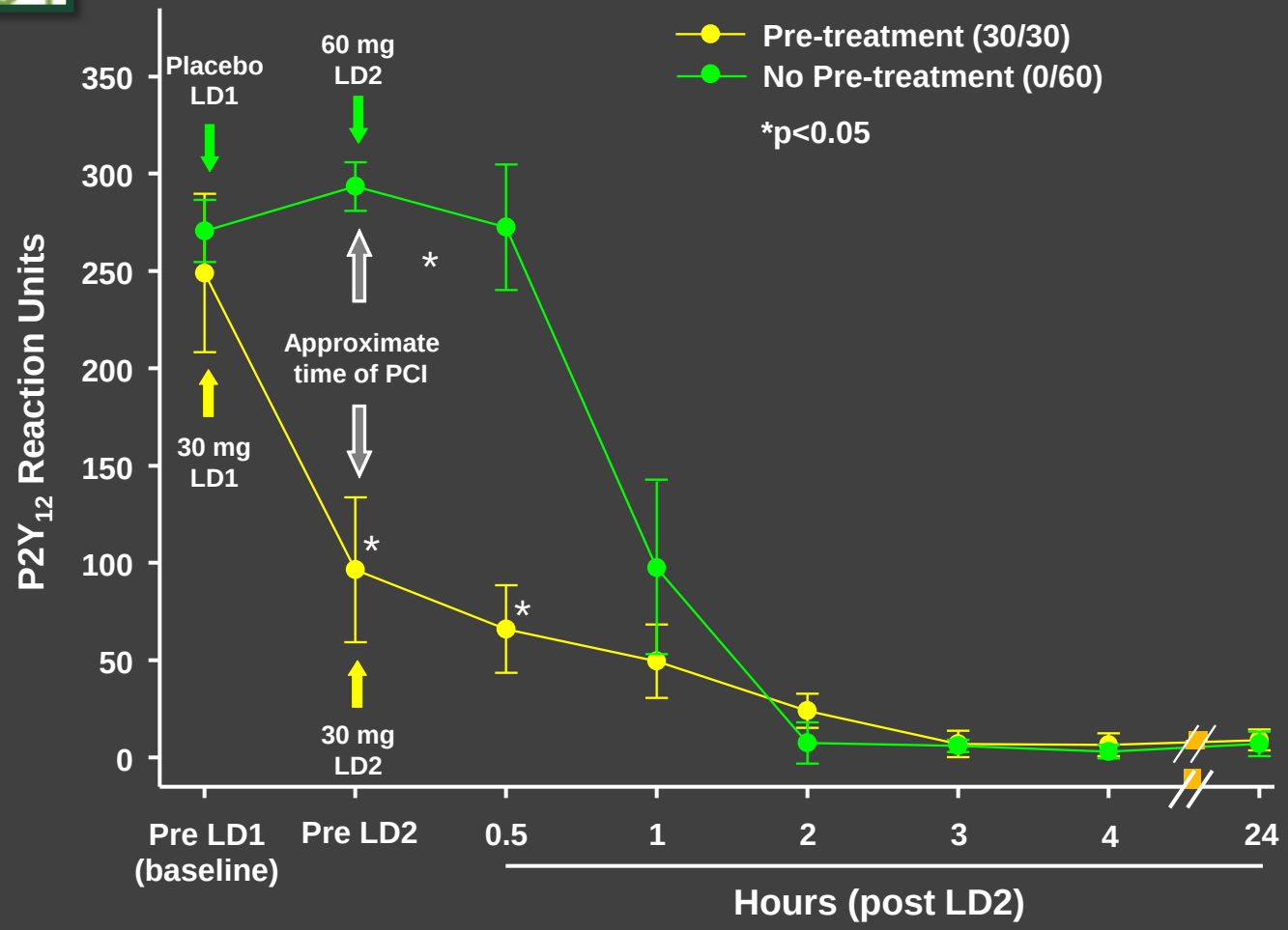
The ACCOAST Trial

ACCOAST design



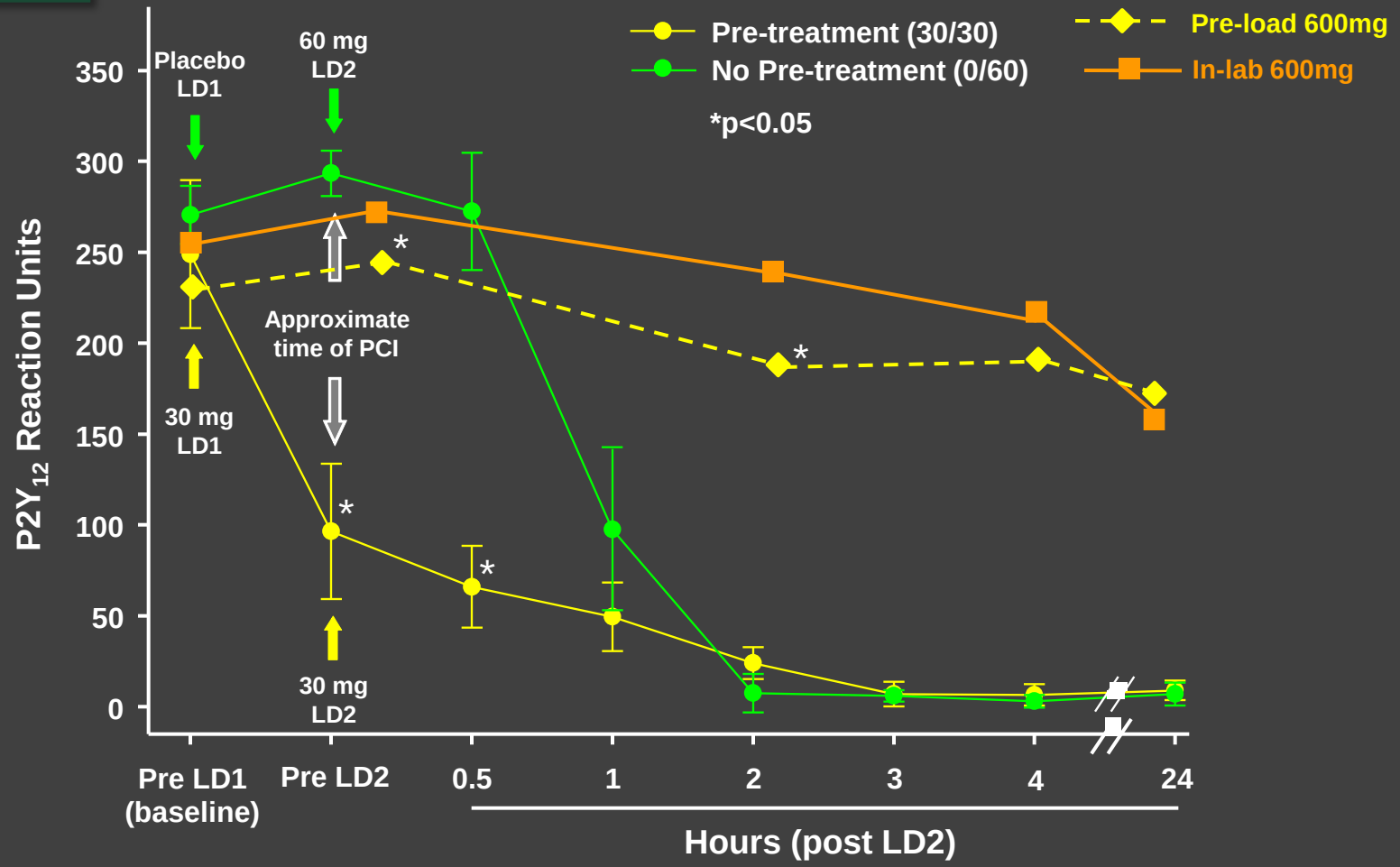
Montalescot G et al. *Am Heart J* 2011;161:650-656

Pharmacodynamic sub-study



Data presented as median ± SEM. * p<0.05 relative to the No pre-treatment group.
Pretreatment=Prasugrel 30 mg/Prasugrel 30 mg; No Pre-treatment=Placebo/Prasugrel 60 mg

Pharmacodynamic sub-study



Data presented as median ± SEM. * p<0.05 relative to the No pre-treatment group.
Pretreatment=Prasugrel 30 mg/Prasugrel 30 mg; No Pre-treatment=Placebo/Prasugrel 60 mg

N Engl J Med. 2013 Sep 12;369(11):999-1010

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

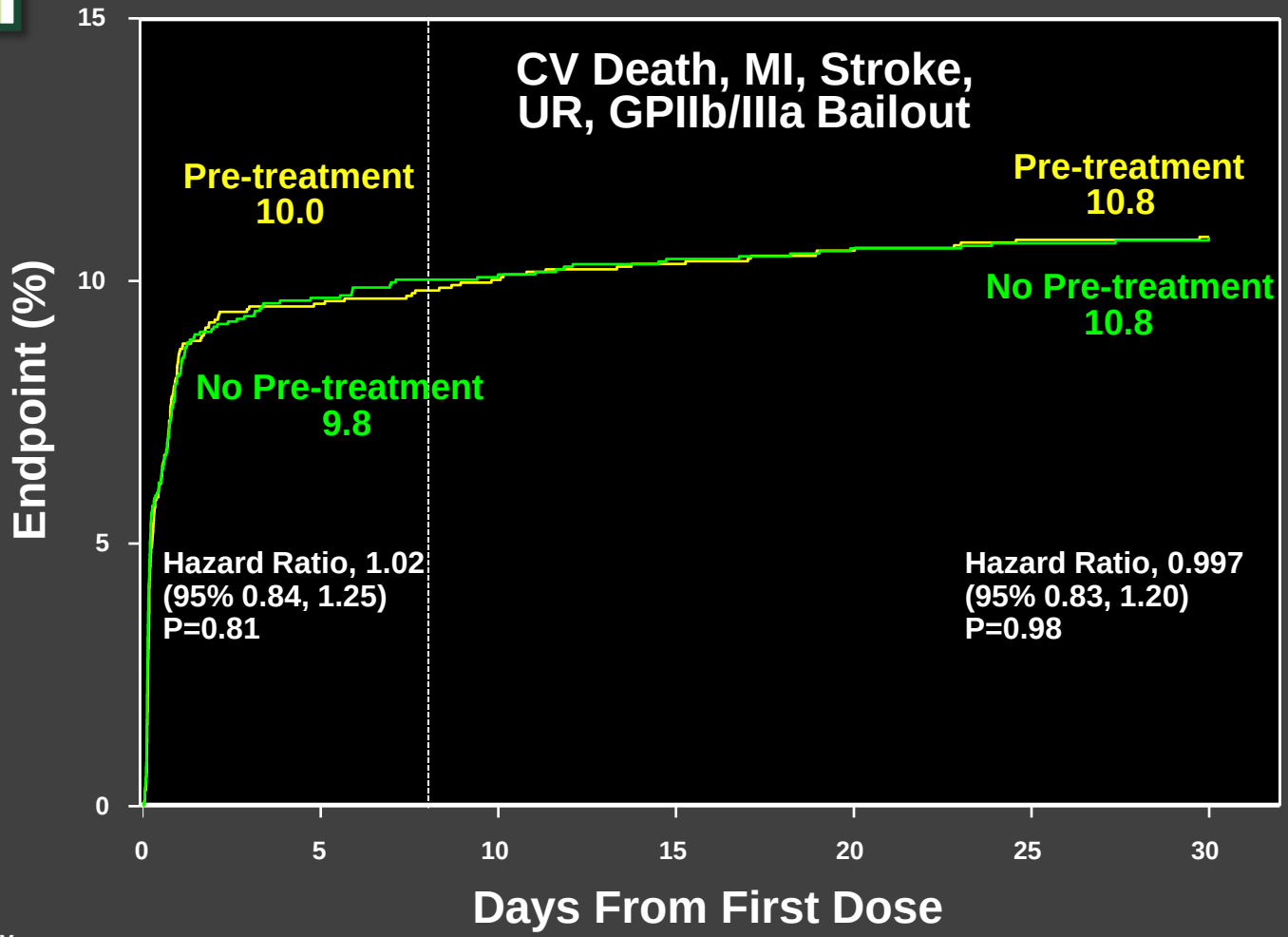
N Engl J Med. 2013 Sep 12;369(11):999-1010

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 (%)‖		
Femoral	57	57
Radial	43	43

N Engl J Med. 2013 Sep 12;369(11):999-1010

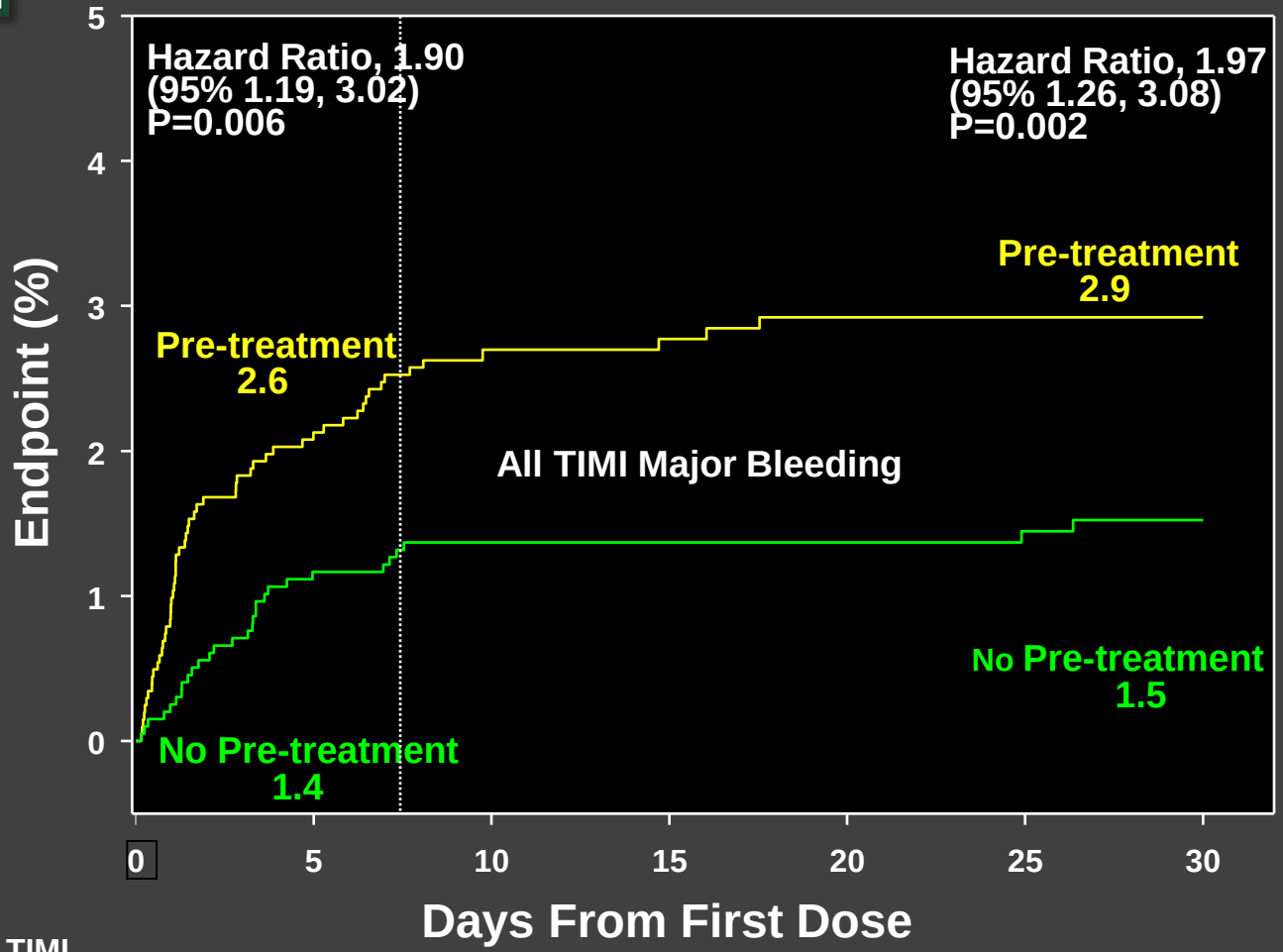
1° Efficacy End Point @ 7 + 30 days (All Patients)



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

N Engl J Med. 2013 Sep 12;369(11):999-1010

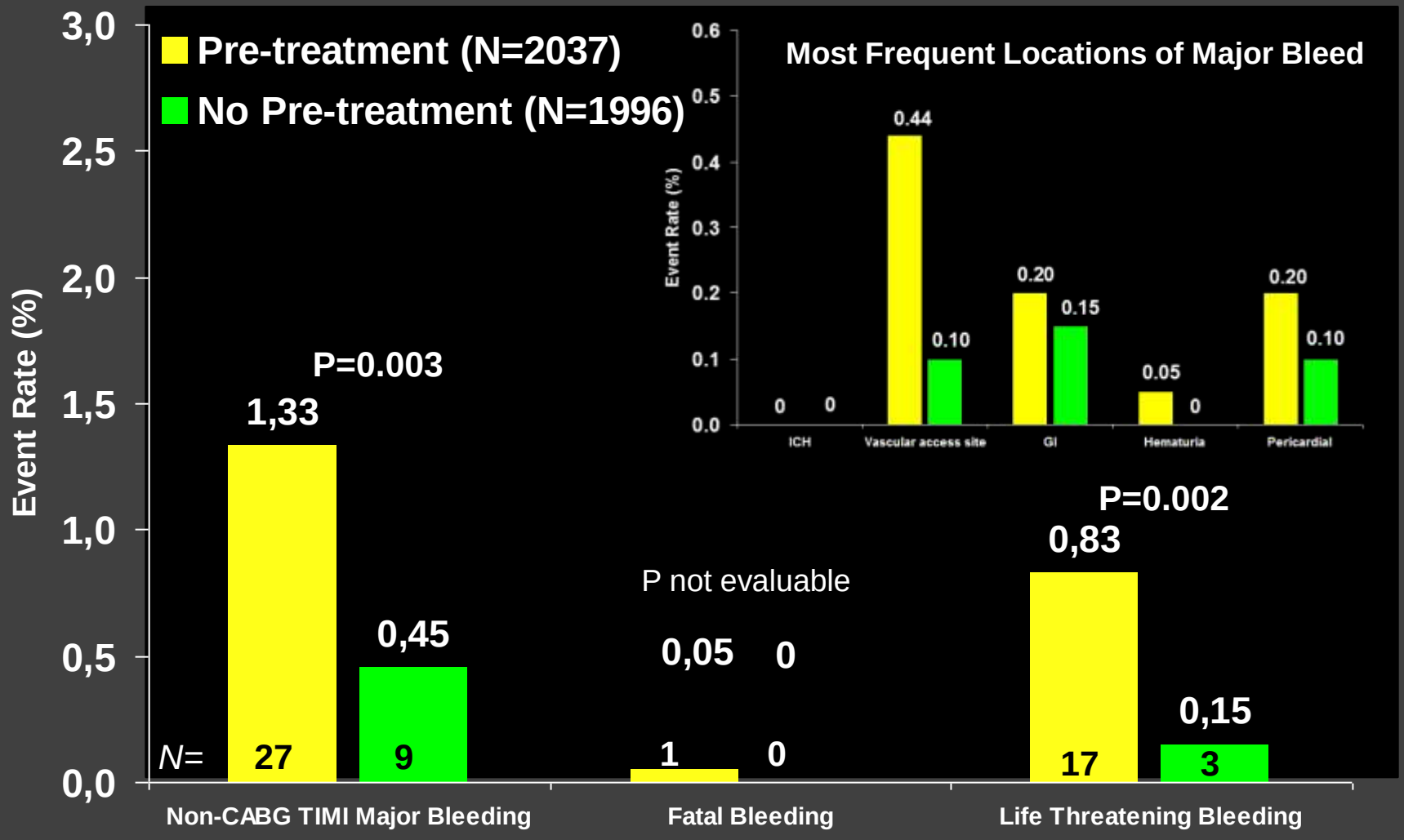
All TIMI (CABG or non-CABG) Major Bleeding (All Treated patients)



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

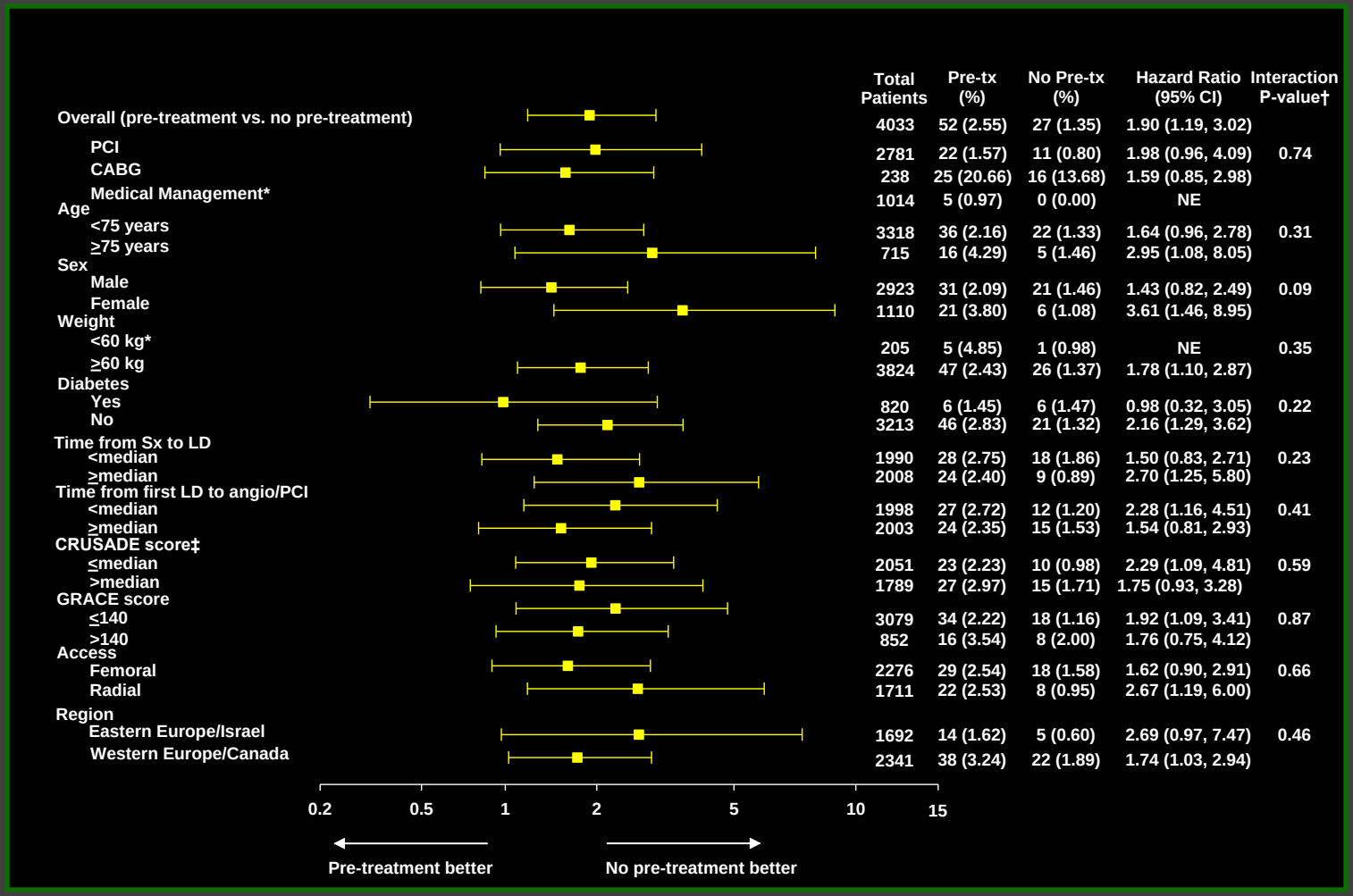
N Engl J Med. 2013 Sep 12;369(11):999-1010

Non-CABG TIMI Major Bleeding Endpoints Through 7 Days (All Treated Patients)



N Engl J Med. 2013 Sep 12;369(11):999-1010

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

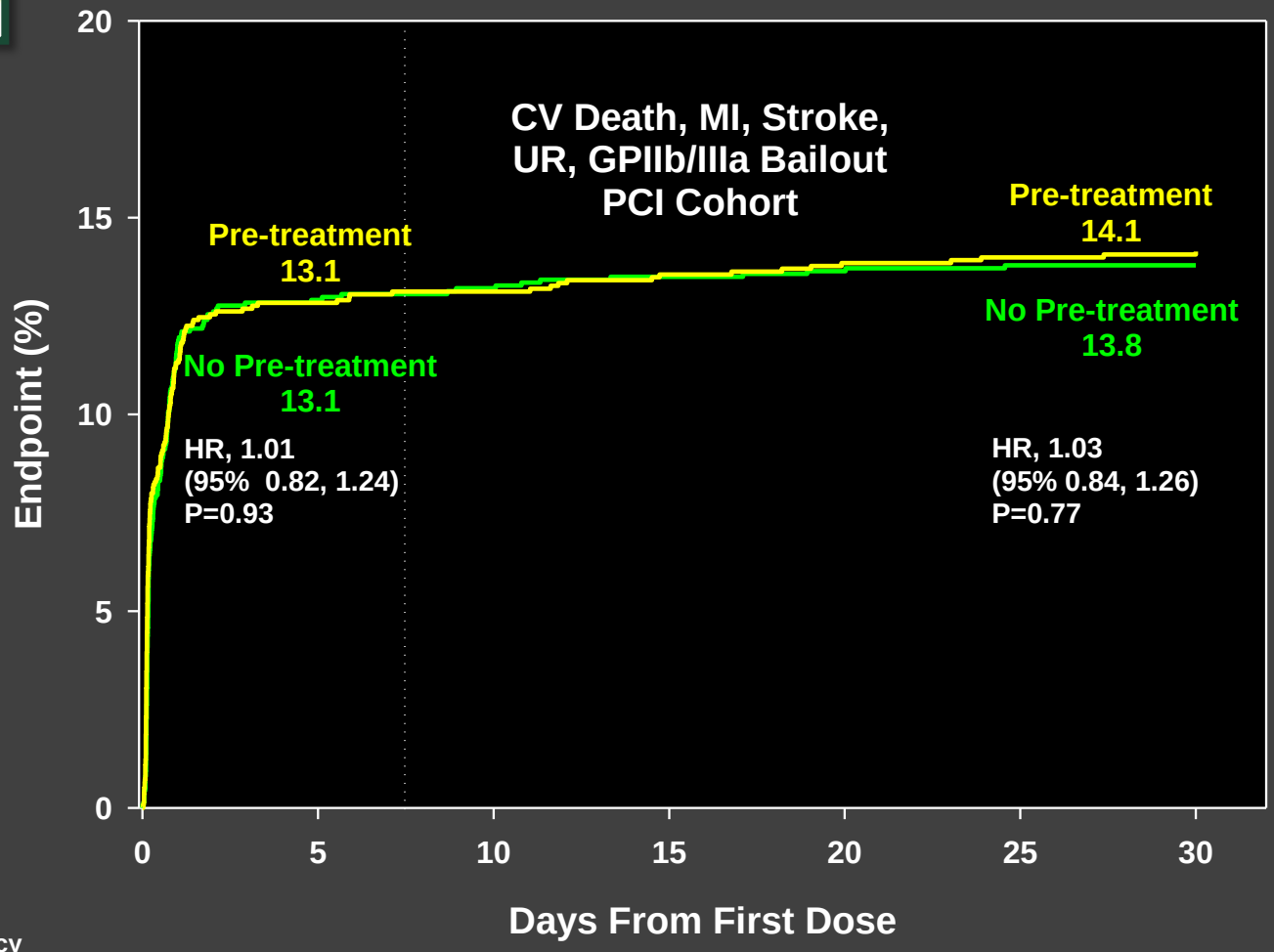


	Total Patients	Pre-tx (%)	No Pre-tx (%)	Hazard Ratio (95% CI)	Interaction P-value†
Overall (pre-treatment vs. no pre-treatment)	4033	52 (2.55)	27 (1.35)	1.90 (1.19, 3.02)	
PCI	2781	22 (1.57)	11 (0.80)	1.98 (0.96, 4.09)	0.74
CABG	238	25 (20.66)	16 (13.68)	1.59 (0.85, 2.98)	
Medical Management*	1014	5 (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.

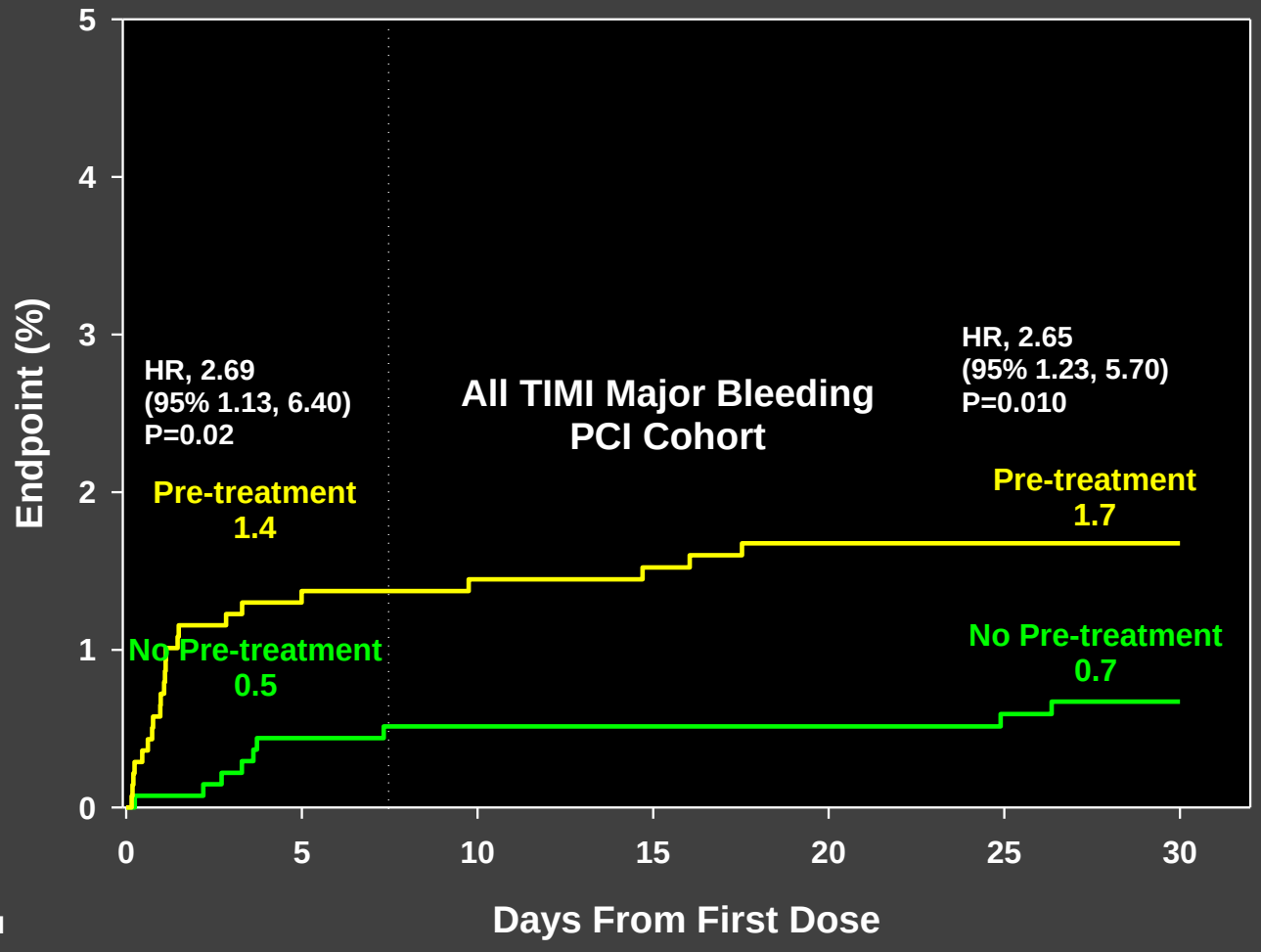
ACCOAST PCI

1° Efficacy Endpoint (PCI Patients)



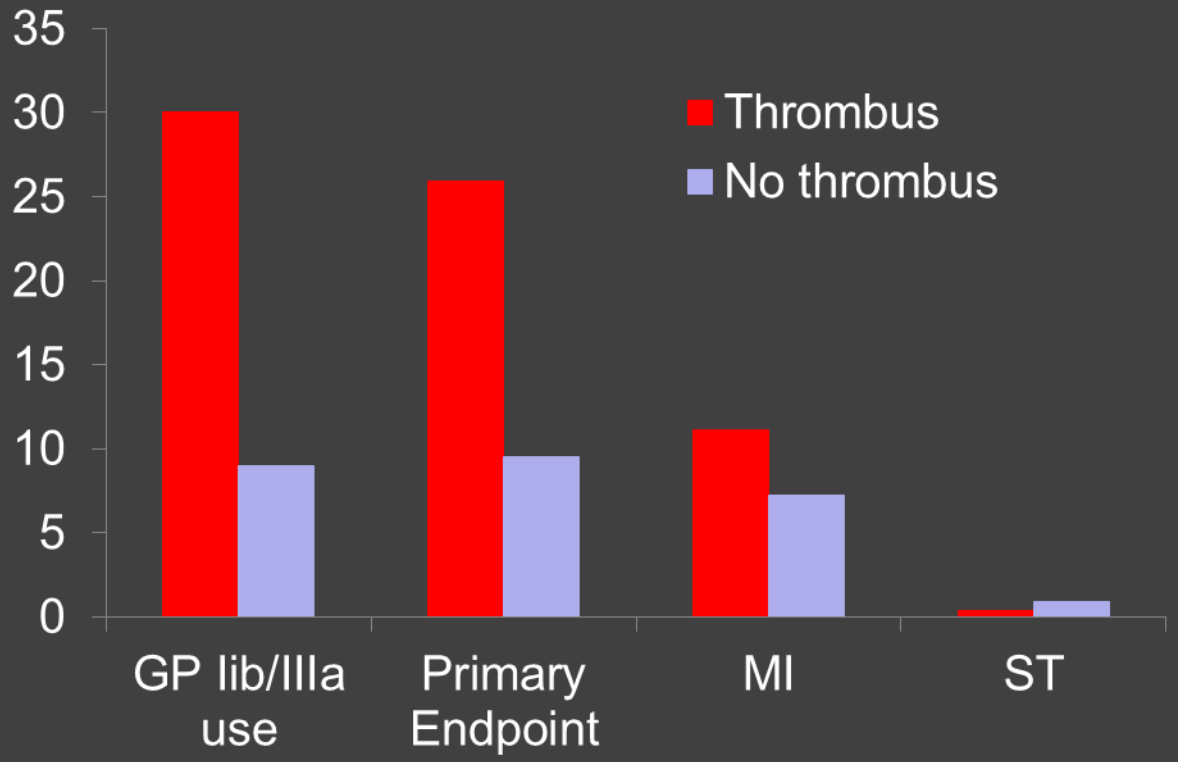
No. at Risk, Efficacy End Point:							
No pre-treatment	1372	1191	1187	1183	1179	1177	1177
Pre-treatment	1389	1206	1202	1194	1189	1186	1172

All TIMI Major Bleeding (PCI Patients)



No. at Risk, All TIMI Major Bleeding:							
No pre-treatment	1372	1356	1302	1280	1272	1268	1249
Pre-treatment	1389	1364	1314	1293	1282	1280	1269

Impact of Visible thrombus



HR 2.61 [2.09-3.25], p<0.001
-Length of procedure (HR: 1·88 (1·49, 2·36) p<0·001,
-number of lesions (HR: 1·24 (1·10, 1·39) p<0·001,
-maximum length of stent (HR: 1·19 (1·04, 1·35) p=0·005),
-and CRUSADE risk score (HR: 1·01 (1·00, 1·02) p=0·023;

CONCLUSIONS

ACCOAST

- In NSTE-ACS invasively managed <48 hours of admission, pre-treatment with prasugrel does not reduce MACE at but increases major bleedings.
- The results are consistent among patients undergoing PCI supporting treatment with prasugrel once the coronary anatomy has been defined.
- No subgroup appears to have a favorable risk/benefit ratio of pre-treatment.
- Reappraisal of routine pre-treatment strategies in NSTE-ACS is needed.

ACCOAST-PCI

- Reinforces the role the angiogram to ascertain the diagnosis of NSTEMI,
- Shows no downside in waiting for the coronary angiogram in patients who will need DAPT for stenting.
- Shows that angiogram provides additional information on the risk of the procedure and the prognosis
- Demonstrates that prasugrel loading after angiogram is not only safer but also effective in this population
- Such strategy gives flexibility and no bleeding risk

NSTEMI

Aspirin 500 mg IV
Enox SQ

Fast transfer to the cathlab (24h) with TNI+ or high-risk features*

NO

Ticagrelor → Cath

Clopidogrel → Cath

YES

Treatement on the table with prasugrel

* At the exclusion of STEMI-like