P2Y12 Preloading Prior to PCI

Should it be standard of care in 2016?

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8 minutes
21 slides

Disclosures

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- Biomet - Covidien

Consulting/Advisory Boards

- Medtronic - Astra-Zeneca
- Eli Lilly

DJC: 4/16

ACC/AHA 2011 Guidelines
Preloading of Anti-Platelet Therapy prior to PCI

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting.

Options include:

a. Clopidogrel 600 mg (ACS and non-ACS patients).

b. Prasugrel 60 mg (ACS patients).

c. Ticagrelor 180 mg (ACS patients).

Levine GN et al. JACC 2011; 58: e44-122

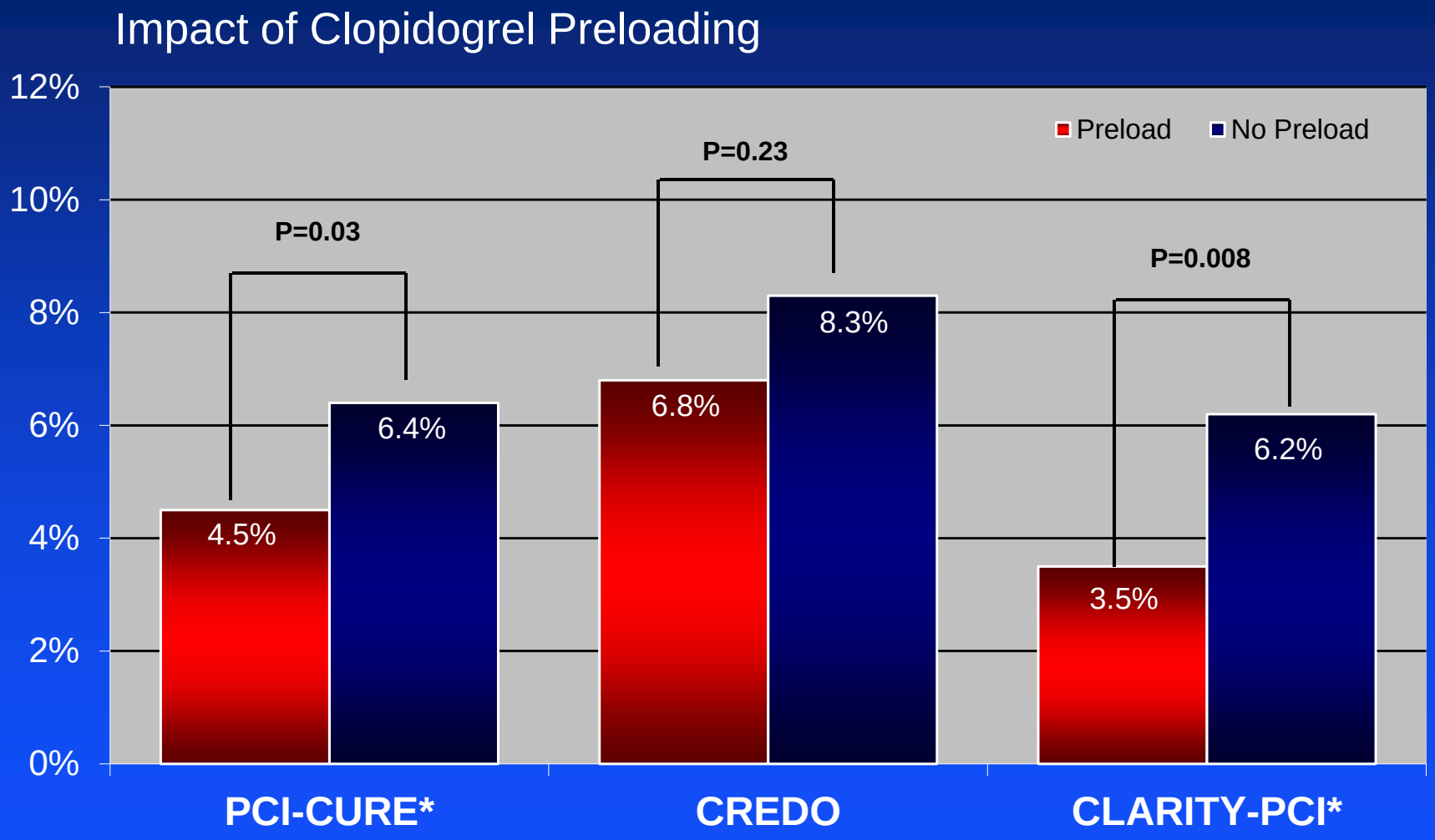
ESC 2010 Guidelines
Preloading of Anti-Platelet Therapy prior to PCI

Elective PCI				
Antiplatelet therapy		Class[a]	Level[b]	Ref.[c]
	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
STEMI				
Antiplatelet therapy				
	ASA	I	B	55, 94
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C	—

Wijns W et al. Eur Heart J 2010; 31: 2501-55

Where do the guidelines come from?

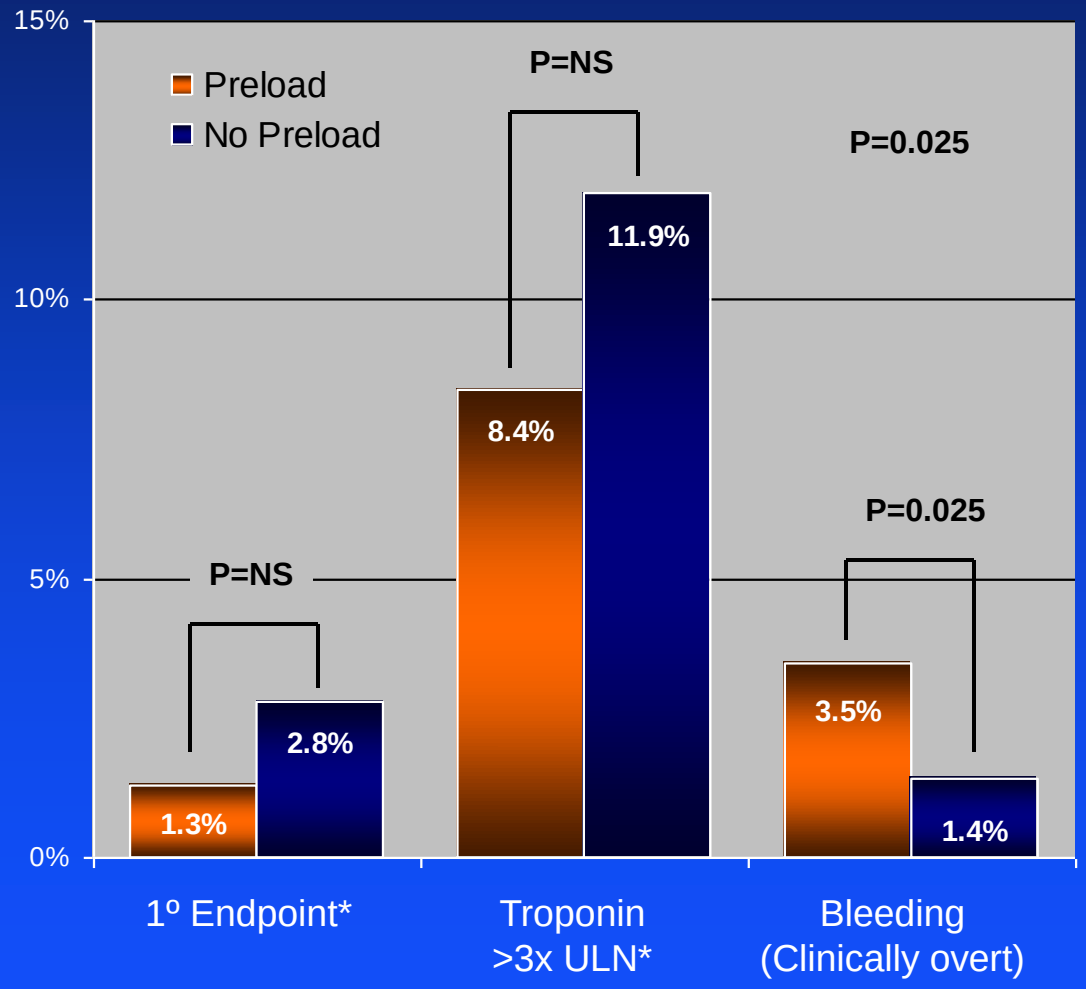
Where do the guidelines come from?
Early clinical trials



Limitations of Early Studies

- Most studies are not true randomized trials but rather post-randomization subgroup analyses of RCTs
- Variable use of loading doses in control groups→ may have exaggerated benefit
- Prolonged delay to PCI not consistent with current practice patterns

PRAGUE-8

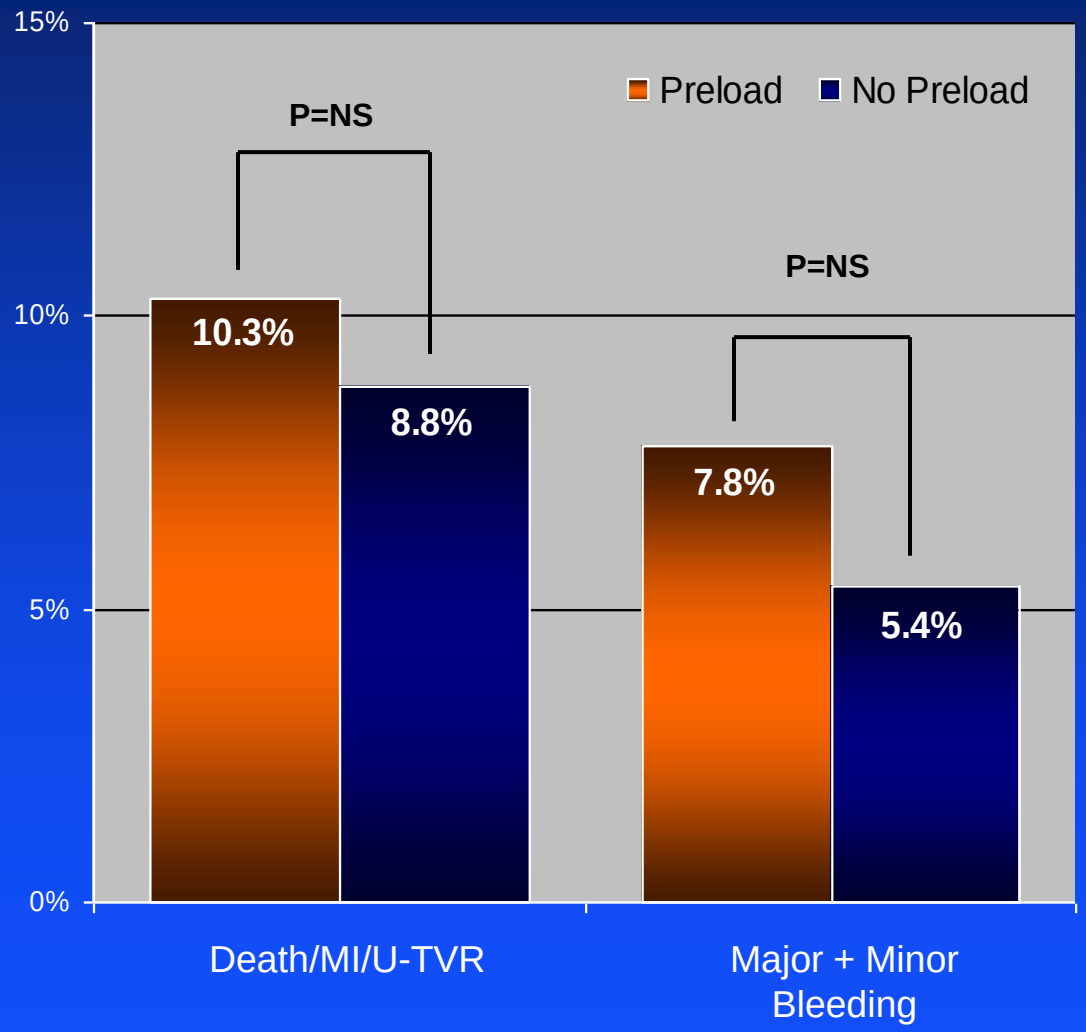


- 1028 patients with stable CAD undergoing cath
- Randomized to:
  - *Preloading: clopidogrel 600 mg 6 hrs prior to cath*
  - *Cath lab loading: 600 mg in lab immediately prior to PCI*
- 1º endpoint: Death, MI, stroke, or U-TVR at 7 days

* Among 293 pts who underwent PCI

Widimsky P et al. Eur Heart J 2008; 29: 1495-1503

ARMYDA-5 Preload



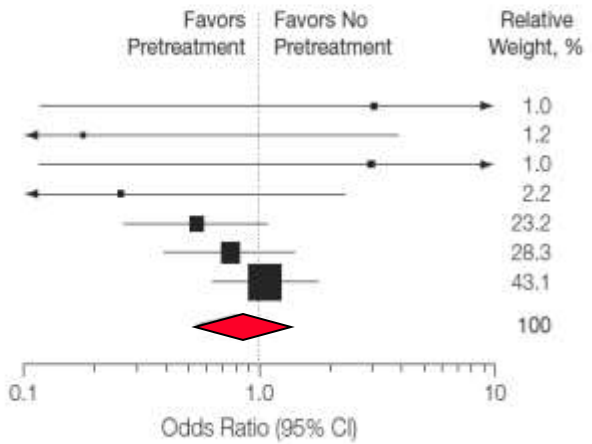
- 409 patients undergoing PCI (36% ACS)
- Randomized to:
  - *Clopidogrel 600 mg given 4-8 hours prior to cath*
  - *Clopidogrel 600 mg in lab immediately prior to PCI*
- 1º endpoint: 30 day death, MI, or U-TVR

Di Sciascio G et al. JACC 2010; 56: 550-7

So does clopidogrel pre-loading do anything?

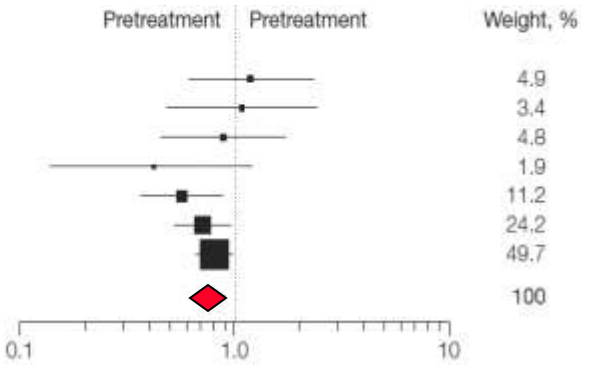
All-Cause Mortality

Source	No. of Events: Pretreatment	No. of Events: No Pretreatment	No. of Patients: Pretreatment	No. of Patients: No Pretreatment	OR (95% CI)
RCTs					
ARMYDA-5 PRELOAD,[17] 2010	1	0	204	205	3.03 (0.12-74.80)
Davlouros et al,[16] 2009	0	2	103	96	0.18 (0.01-3.85)
PRAGUE 8,[18] 2008	1	0	513	515	3.02 (0.12-74.25)
CIPAMI,[7] 2007	1	4	164	171	0.26 (0.03-2.32)
CLARITY PCI,[6] 2005	13	24	933	930	0.53 (0.27-1.05)
CREDO,[3] 2002	18	24	1053	1063	0.75 (0.41-1.40)
PCI CURE,[5] 2001	32	31	1313	1345	1.06 (0.64-1.75)
Overall	66	85	4283	4325	0.80 (0.57-1.11)
					P = .17



MACE

Source	Pretreatment	Pretreatment	Pretreatment	Pretreatment	(95% CI)
RCTs					
ARMYDA-5 PRELOAD,[17] 2010	21	18	204	205	1.19 (0.62-2.31)
Davlouros et al,[16] 2009	15	13	103	96	1.09 (0.49-2.42)
PRAGUE 8,[18] 2008	17	19	513	515	0.89 (0.46-1.74)
CIPAMI,[7] 2007	5	12	164	171	0.42 (0.14-1.21)
CLARITY PCI,[6] 2005	34	58	933	930	0.57 (0.37-0.88)
CREDO,[3] 2002	89	122	1053	1063	0.71 (0.53-0.95)
PCI CURE,[5] 2001	240	292	1313	1345	0.81 (0.67-0.98)
Overall	421	534	4283	4325	0.77 (0.66-0.89)
					P <.001



7 RCTs (n=8608)

Bellemain-Appaix A et al. JAMA 2012; 308: 2507-17

Subgroup Analyses- Clinical Presentation

All-Cause Mortality

	No. of Events		No. of Patients					
	Pretreatment	No Pretreatment	Pretreatment	No Pretreatment	OR (95% CI)	Favors Pretreatment	Favors No Pretreatment	Heterogenity	*P* for Trend χ^2
Presenting feature									
Elective PCI	2	2	820	816	1.12 (0.17-7.27)				
NSTE ACS	50	55	2366	2408	0.93 (0.63-1.36)			2.66	.02
STEMI	14	28	1097	1101	0.50 (0.26-0.96)				

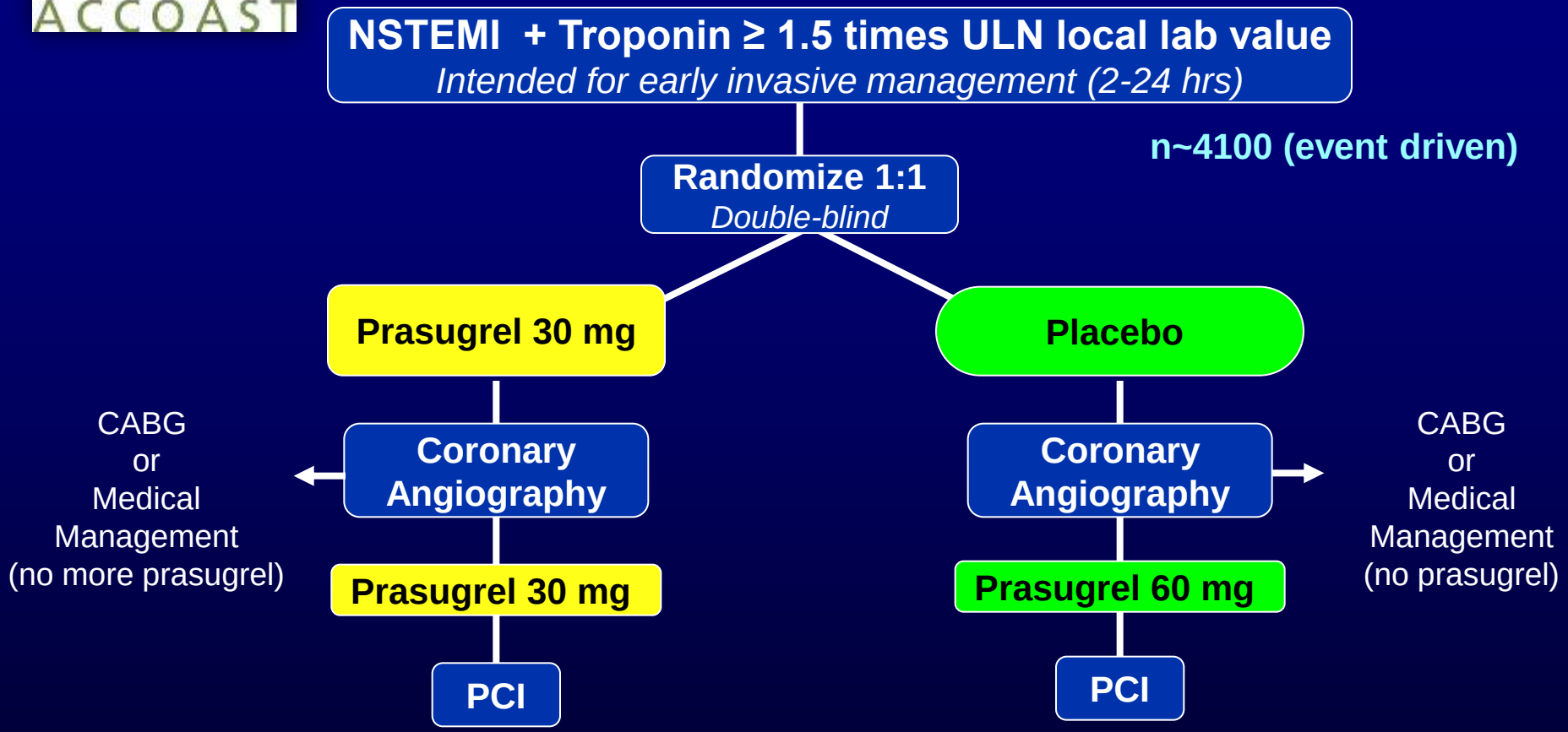
Major Cardiovascular Events

	No. of Events		No. of Patients					
	Pretreatment	No Pretreatment	Pretreatment	No Pretreatment	OR (95% CI)	Favors Pretreatment	Favors No Pretreatment	Heterogenity	*P* for Trend χ^2
Presenting feature									
Elective PCI	53	50	820	816	1.05 (0.70-1.57)				
NSTE ACS	329	414	2366	2408	0.78 (0.66-0.91)			5.1	.08
STEMI	39	70	1097	1101	0.54 (0.36-0.81)				
Loading dose									

Bellemain-Appaix A et al. JAMA 2012; 308: 2507-17

What about the newer agents?

ACCOAST design

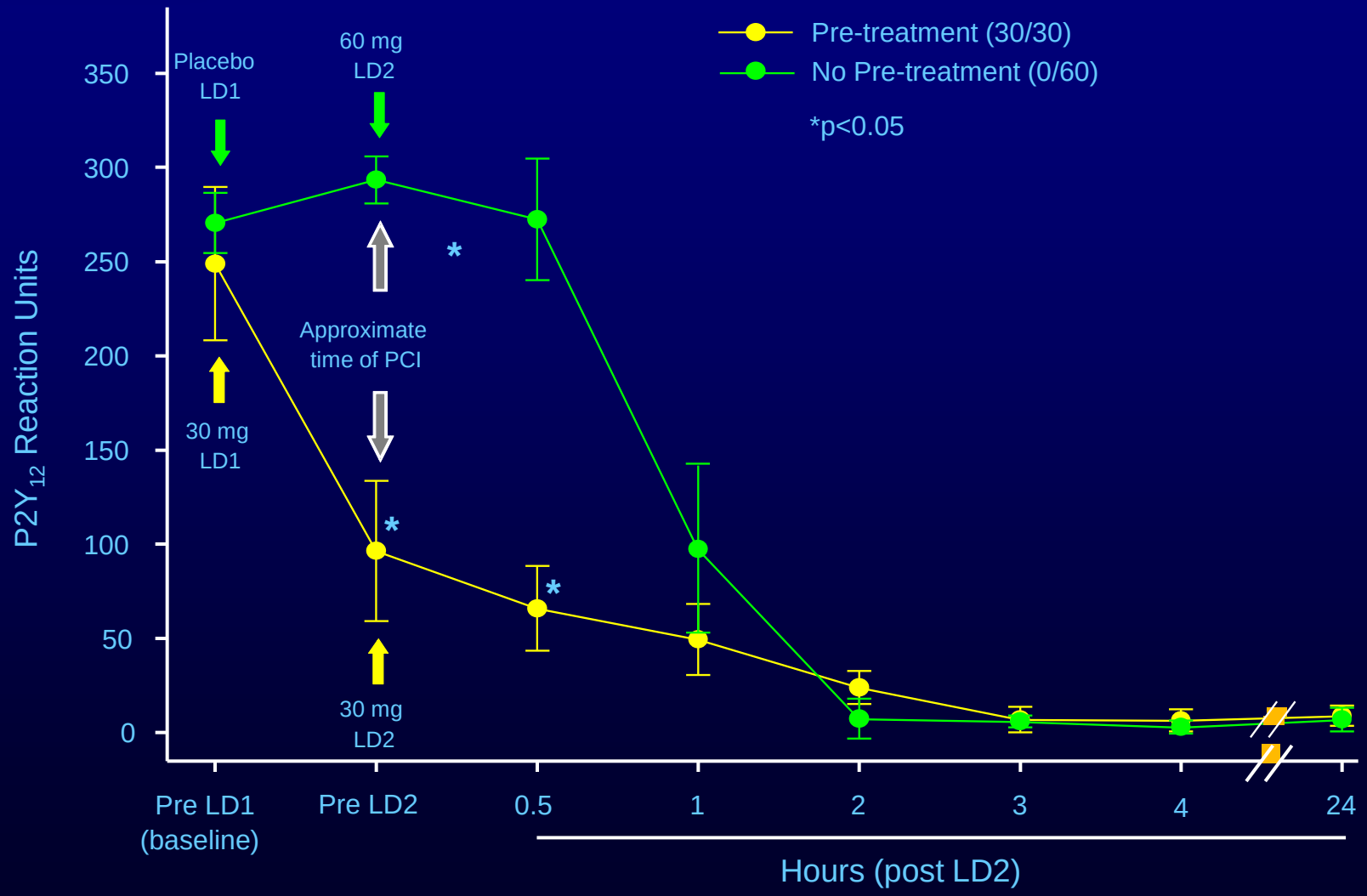


Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

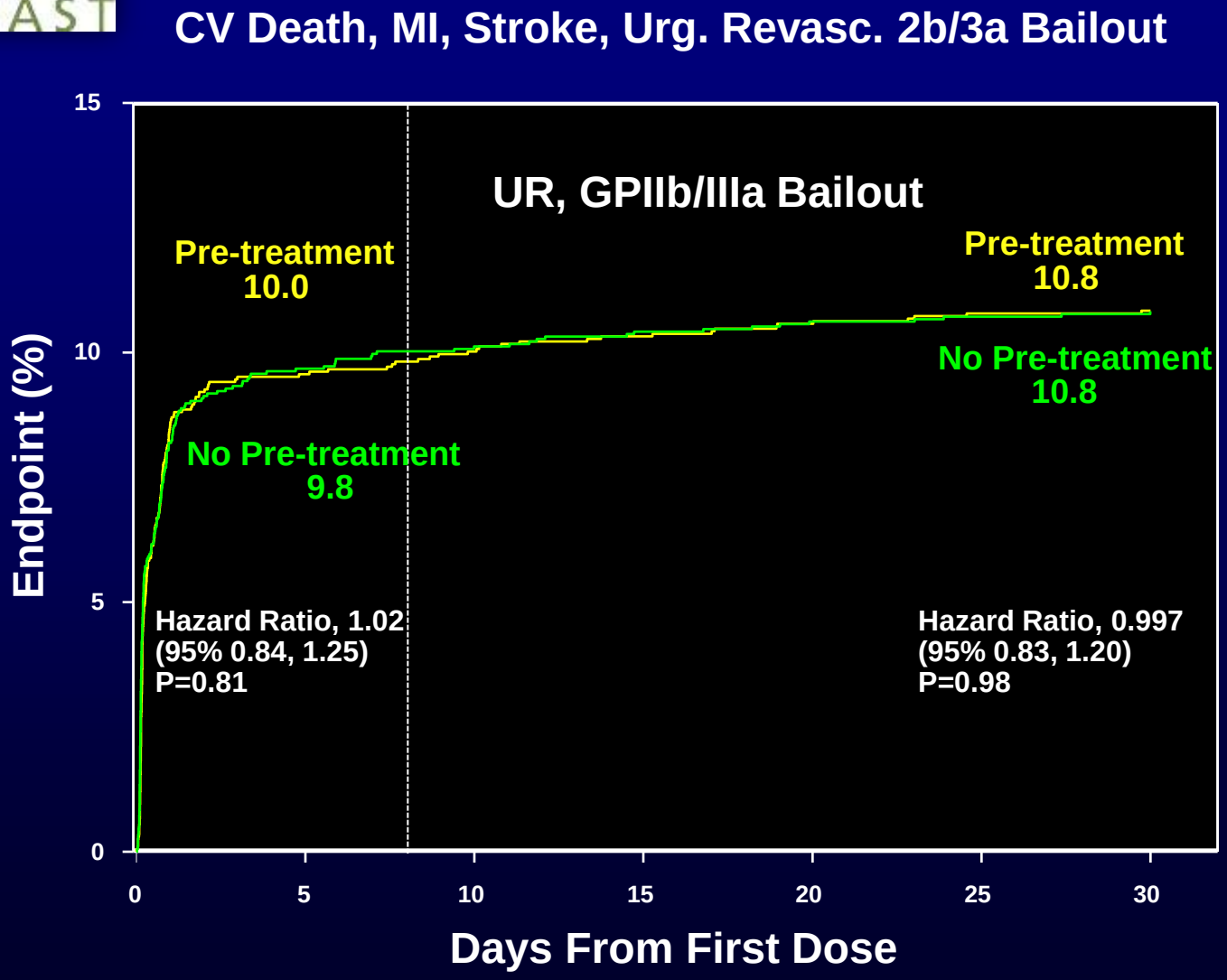
1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

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

Pharmacodynamic sub-study

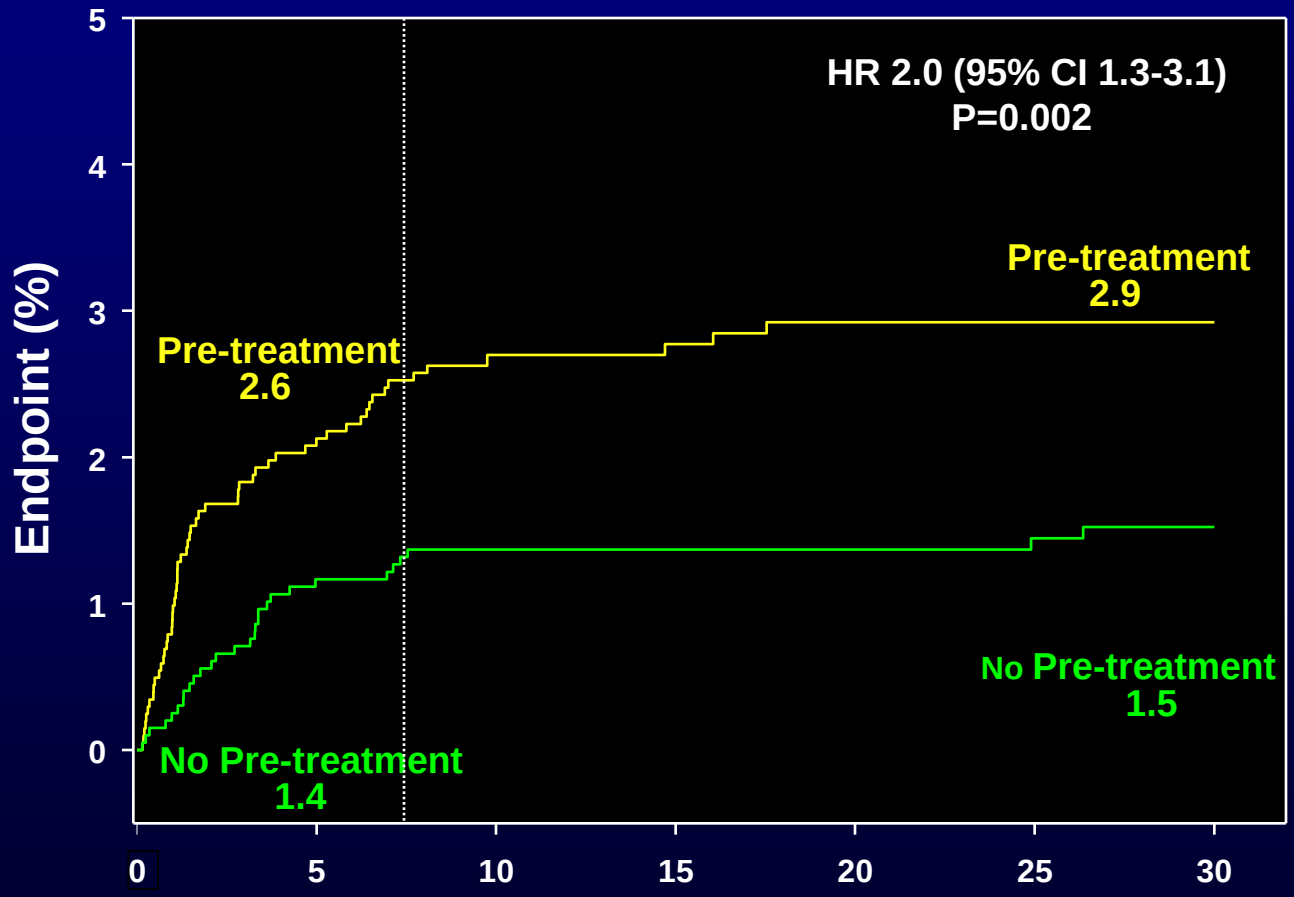


1° Efficacy End Point



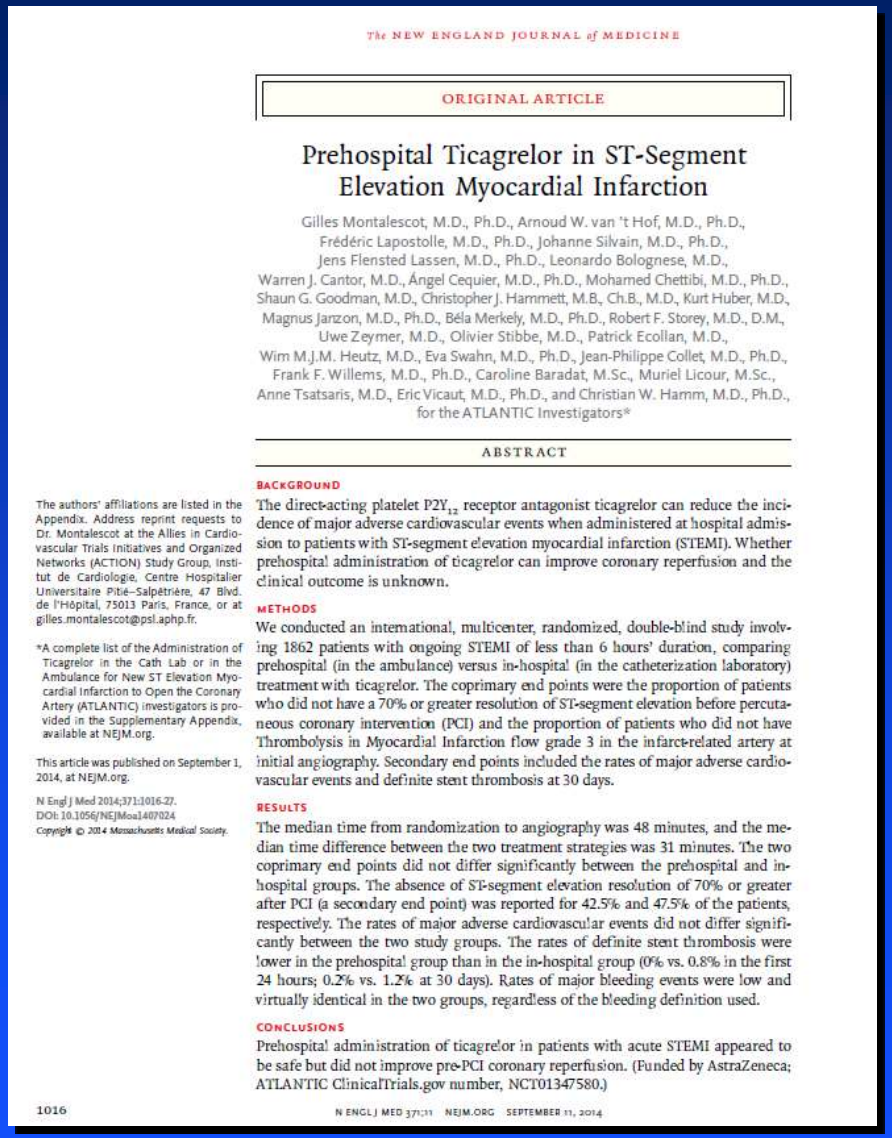
Montalescot G, et al. NEJM 2013;369:999-101

TIMI Major Bleeding



Montalescot G, et al. NEJM 2013;369:999-101

Ticagrelor Preloading



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND

The direct-acting platelet $P2Y_{12}$ receptor antagonist ticagrelor can reduce the incidence of major adverse cardiovascular events when administered at hospital admission to patients with ST-segment elevation myocardial infarction (STEMI). Whether prehospital administration of ticagrelor can improve coronary reperfusion and the clinical outcome is unknown.

METHODS

We conducted an international, multicenter, randomized, double-blind study involving 1862 patients with ongoing STEMI of less than 6 hours' duration, comparing prehospital (in the ambulance) versus in-hospital (in the catheterization laboratory) treatment with ticagrelor. The coprimary end points were the proportion of patients who did not have a 70% or greater resolution of ST-segment elevation before percutaneous coronary intervention (PCI) and the proportion of patients who did not have Thrombolysis in Myocardial Infarction flow grade 3 in the infarct-related artery at initial angiography. Secondary end points included the rates of major adverse cardiovascular events and definite stent thrombosis at 30 days.

RESULTS

The median time from randomization to angiography was 48 minutes, and the median time difference between the two treatment strategies was 31 minutes. The two coprimary end points did not differ significantly between the prehospital and in-hospital groups. The absence of ST-segment elevation resolution of 70% or greater after PCI (a secondary end point) was reported for 42.5% and 47.5% of the patients, respectively. The rates of major adverse cardiovascular events did not differ significantly between the two study groups. The rates of definite stent thrombosis were lower in the prehospital group than in the in-hospital group (0% vs. 0.8% in the first 24 hours; 0.2% vs. 1.2% at 30 days). Rates of major bleeding events were low and virtually identical in the two groups, regardless of the bleeding definition used.

CONCLUSIONS

Prehospital administration of ticagrelor in patients with acute STEMI appeared to be safe but did not improve pre-PCI coronary reperfusion. (Funded by AstraZeneca; ATLANTIC ClinicalTrials.gov number, NCT01347580.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Montalescot at the Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION) Study Group, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié–Salpêtrière, 47 Blvd. de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.aphp.fr.

*A complete list of the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 1, 2014, at NEJM.org.

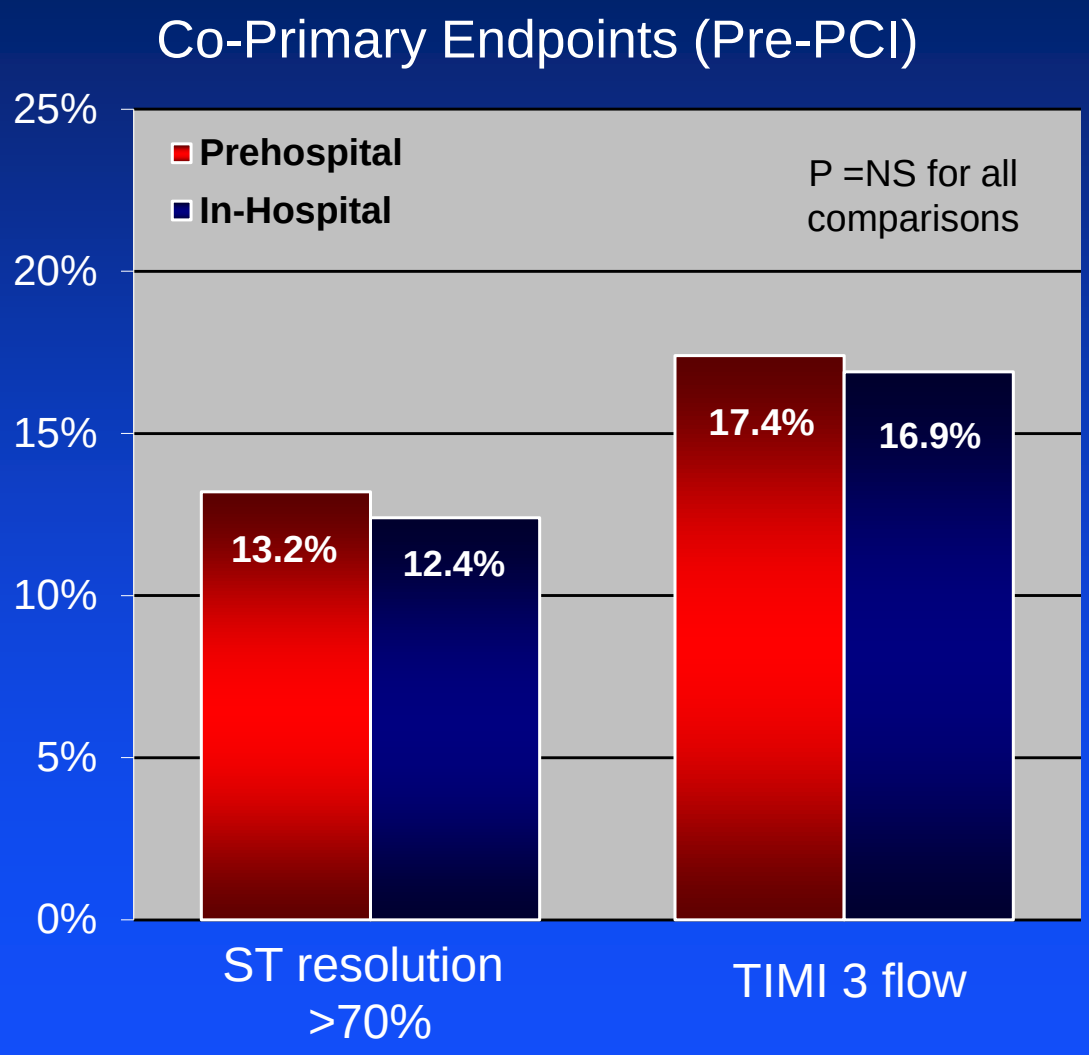
N Engl J Med 2014;371:1016-27.
DOI: 10.1056/NEJMoa1407024

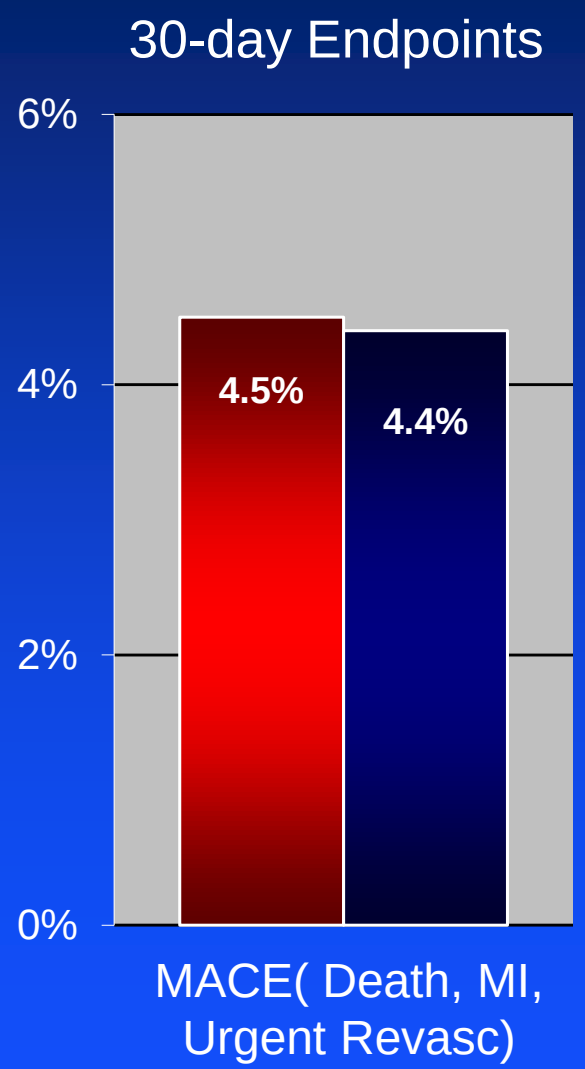
ATLANTIC Trial

- 1862 patients with STEMI randomized to prehospital ticagrelor loading vs. cath lab loading (180 mg PO)
- Co-primary endpoints
  - >70% ST resolution pre-PCI
  - TIMI 3 flow pre PCI

Montalescot G, et al. NEJM 2014;371:1016-27

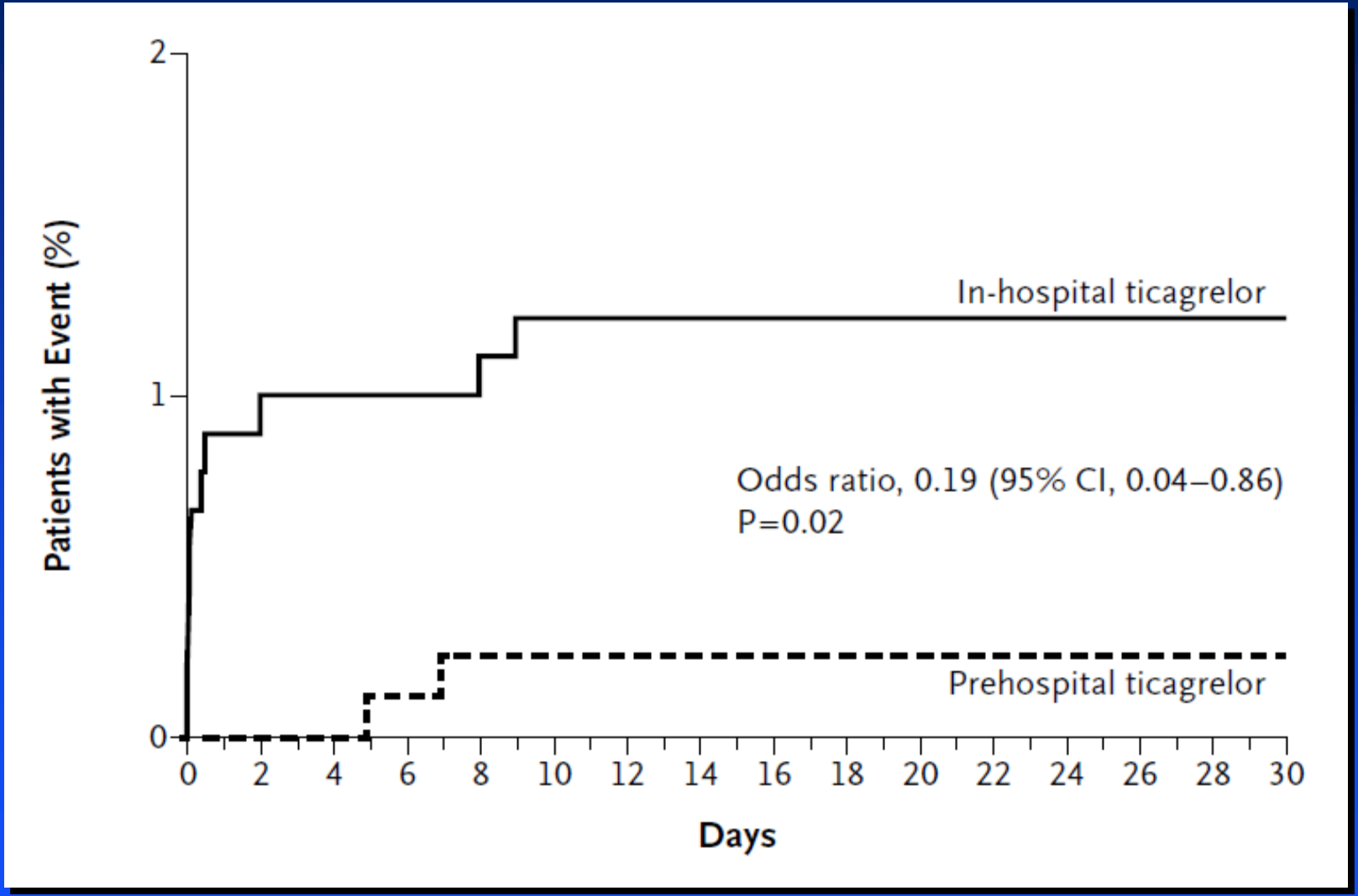
ATLANTIC Trial: Results





Montalescot G, et al. NEJM 2014;371:1016-27

ATLANTIC Trial: Definite Stent Thrombosis



Montalescot G, et al. NEJM 2014;371:1016-27

Summary

- Despite Class I guideline recommendations, data supporting P2Y12 pre-loading prior to PCI are uncertain at best
- Most of the data demonstrating benefit are derived from older trials using conservative management strategies with prolonged treatment delays→ substantial proportion of benefit occurs pre-PCI
- Studies with newer agents (prasugrel, ticagrelor) demonstrate limited benefit as well
- Any potential benefits seem to be confined to the highest risk patients (STEMI, NSTEMI)

Summary

- Despite Class I guideline recommendations, data supporting P2Y12 pre-loading prior to PCI are uncertain at best
-
-
- Any potential benefits seem to be confined to the highest risk patients (STEMI, NSTEMI)

Taken together, these findings suggest that reappraisal of the current ACS and PCI guidelines with respect to pretreatment may be warranted