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

When should we start a $P2Y_{12}$ inhibitor in patients with an acute coronary syndrome?

G. Montalescot

Dr. Montalescot reports research Grants to the Institution or Consulting/Lecture Fees from ADIR, Amgen, AstraZeneca, Bayer, Berlin Chimie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, Cardiovascular Research Foundation, Celladon, CME Resources, Daiichi-Sankyo, Eli-Lilly, Europa, Elsevier, Fédération Française de Cardiologie, Fondazione Anna Maria Sechi per il Cuore, Gilead, ICAN, Janssen, Lead-Up, Menarini, Medtronic, MSD, Pfizer, Sanofi-Aventis, The Medicines Company, TIMI Study Group, WebMD.

The concept…

Definition of Pre-treatment

ER-CU

- **Working diagnosis** of ACS
- **Invasive strategy** decided
- On aspirin + anticoagulation

→ $P2Y_{12}$ antagonist given before coronary visualization

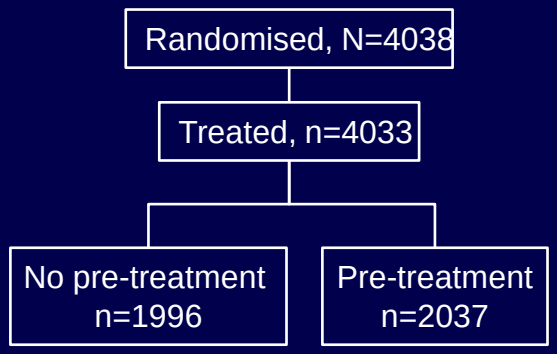
Cath Lab

- **PCI → benefit expected**
- Medical treatment → **?**
- CABG → **no benefit expected**
- Other diagnosis (pericarditis, aortic dissection, heart failure, LVH, pulmonary embolism, GI ulcer, pancreatitis...) → **harm expected**

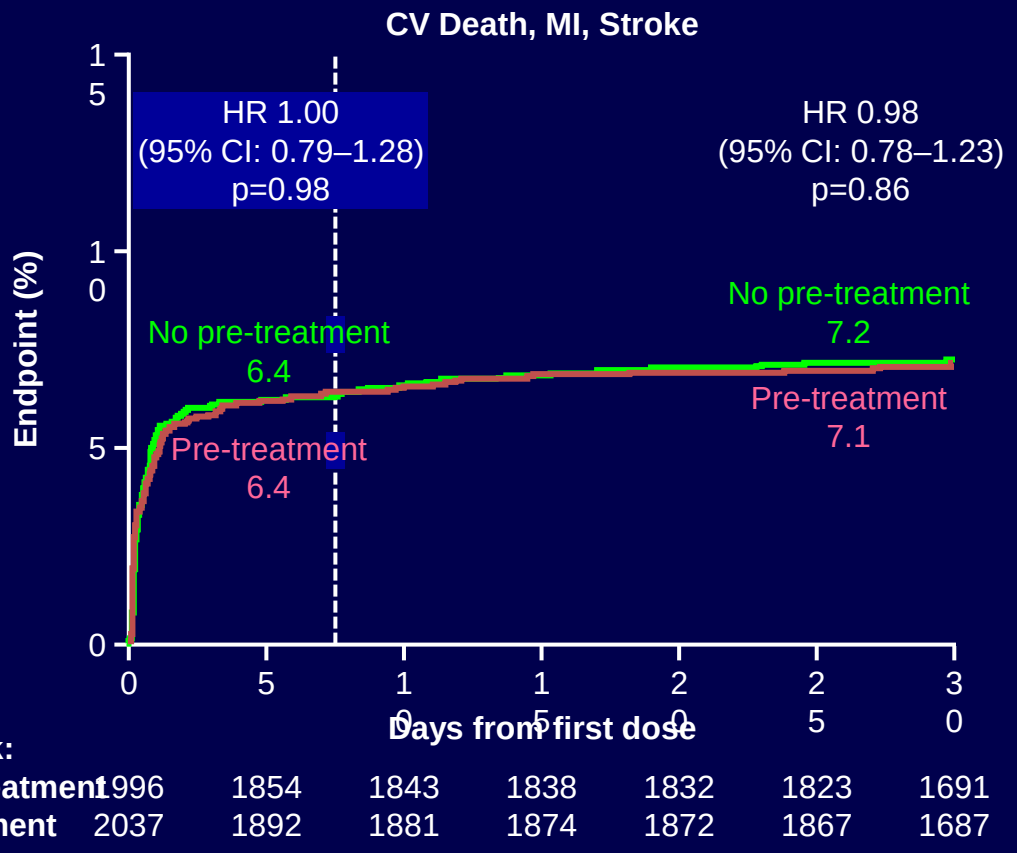
The concept…was never proved

ACCOAST: The only prospective trial in NSTEMI to investigate pre-treatment with a $P2Y_{12}$-receptor antagonist

A comparison of prasugrel at the time of percutaneous coronary intervention (PCI) or as pre-treatment at the time of diagnosis in patients with non-ST elevation myocardial infarction



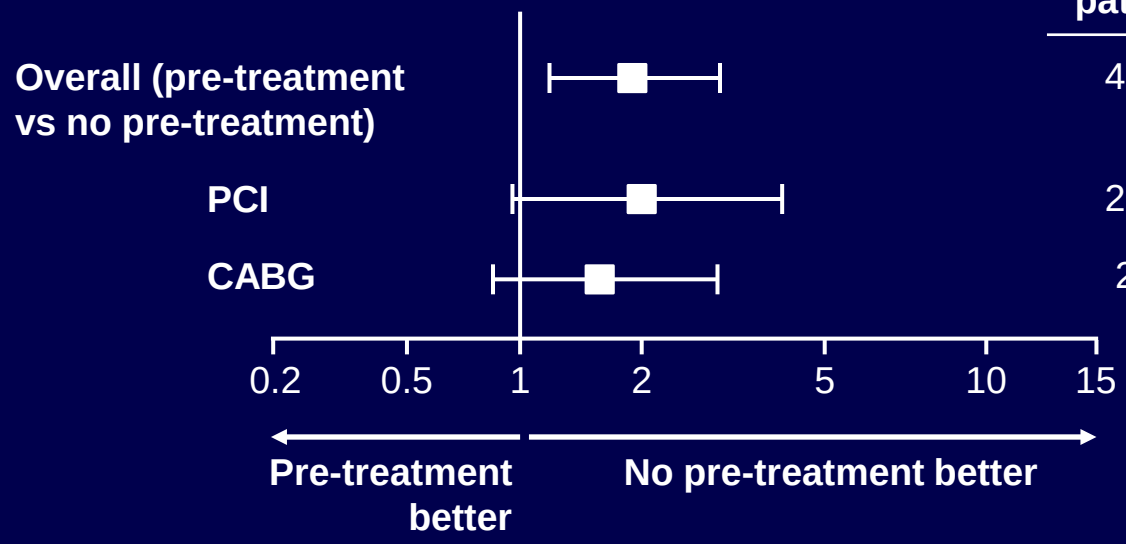
The rate of the primary efficacy endpoint (death from CV causes, MI, stroke, urgent revascularisation, or glycoprotein inhibitor rescue therapy) through Day 7, did not differ significantly between the groups (HR 1.02; 95% CI: 0.84–1.25; p=0.81)



Montalescot et al. *N Engl J Med* 2013;369:999–1010

ACCOAST: Pre-treatment showed similar efficacy but an increase in TIMI major bleeding

The rate of TIMI major bleeding episodes through Day 7 was increased with pre-treatment (HR 1.90; 95% CI: 1.19–3.02; p=0.006)

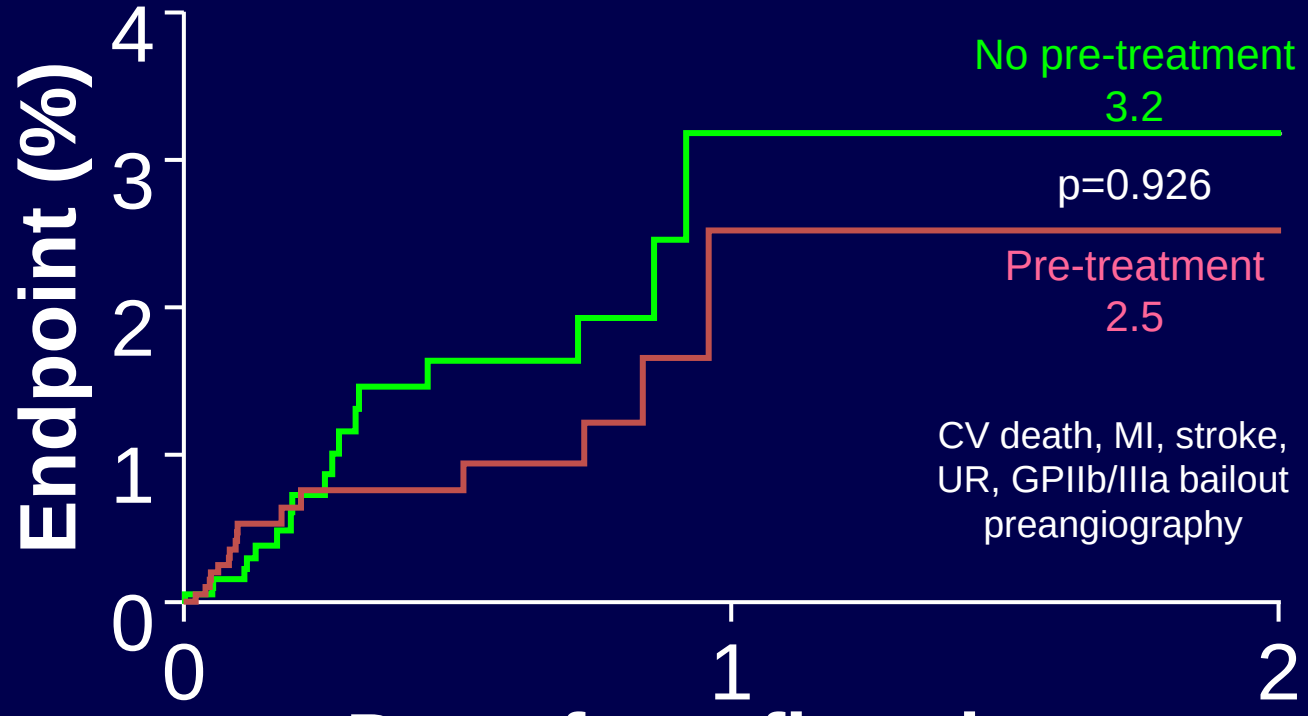


	Total patients	Pre-tx n (%)	No pre-tx n (%)	Hazard Ratio (95% CI)
Overall (pre-treatment vs no pre-treatment)	4033	52 (2.55)	27 (1.35)	1.90 (1.19–3.02)
PCI	2781	22 (1.57)	11 (0.80)	1.98 (0.96–4.09)
CABG	238	25 (20.66)	16 (13.68)	1.59 (0.85–2.98)

Montalescot et al. *N Engl J Med* 2013;369:999–1010 (suppl)

ACCOAST: Is there a risk of waiting angio to treat?

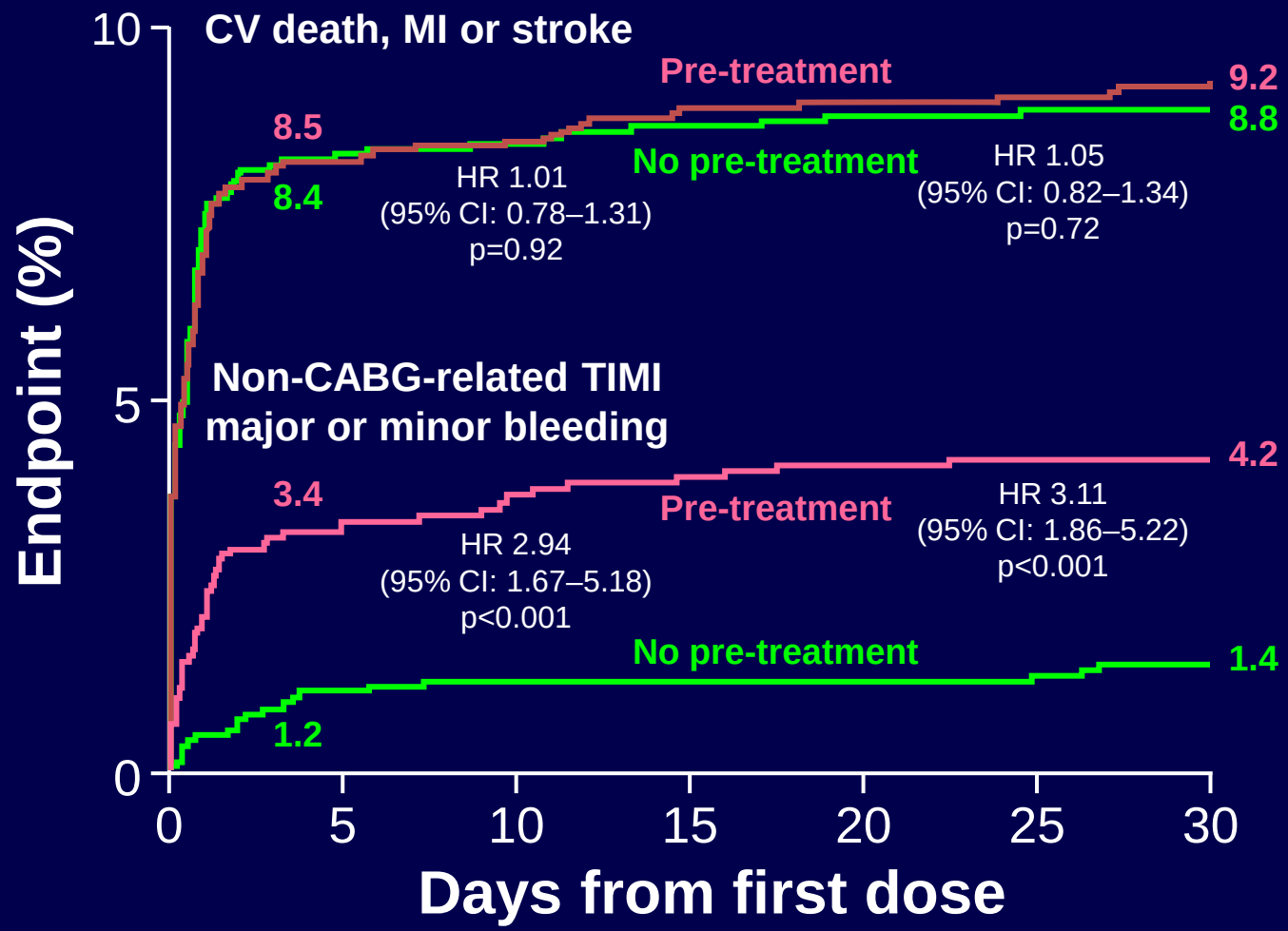
Primary efficacy endpoint prior to angiography



No. at risk:			
No pre-treatment	1981	134	134
Pre-treatment	2014	113	113

Montalescot G et al – ACCOAST Unpublished data

ACCOAST: Are the results different for PCI patients?

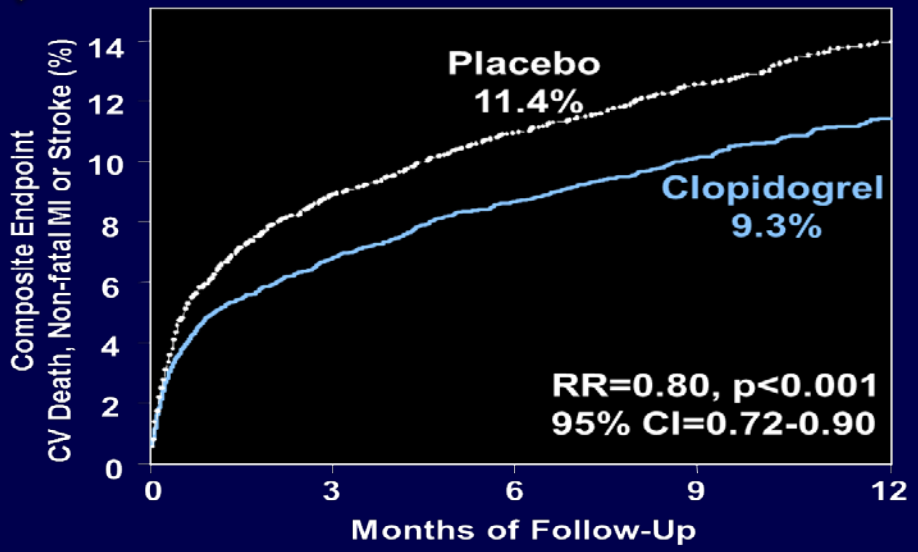


Montalescot et al. *J Am Coll Cardiol* 2014;64:2563–71

The controversy…

ACS

CURE Efficacy

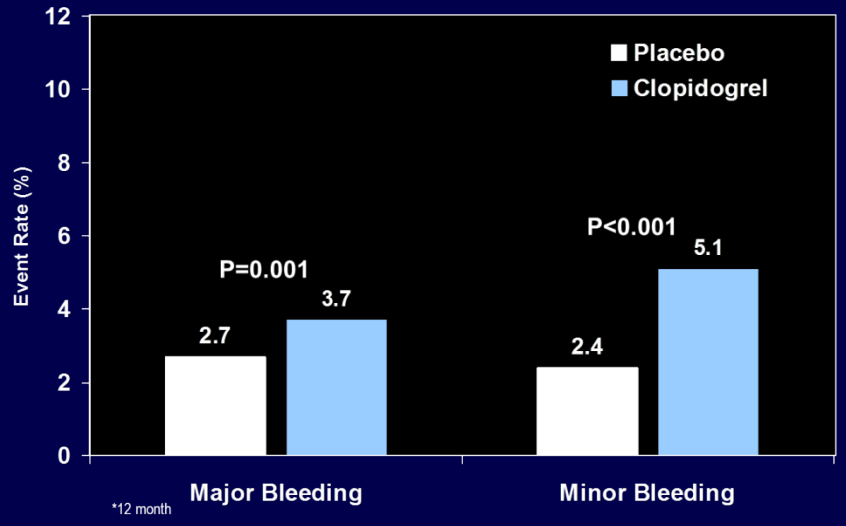


Our study primarily included centers in which there was no routine policy of early use of invasive procedures, since such a policy would have led to a high rate

57% no cath…

20% PCI

CURE Safety*



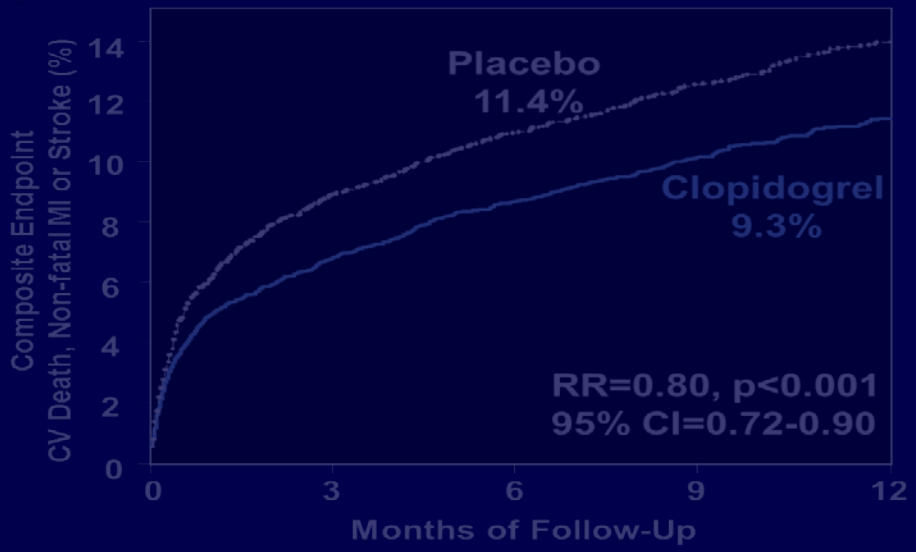
A total of 71 patients in the clopidogrel group (1.1 percent) and 126 patients in the placebo group (2.0 percent) received thrombolytic therapy (relative risk, 0.57; 95 percent confidence interval, 0.43 to 0.76; P<0.001); 369 patients in the clopidogrel group (5.9

When cath, 10 days waiting …

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

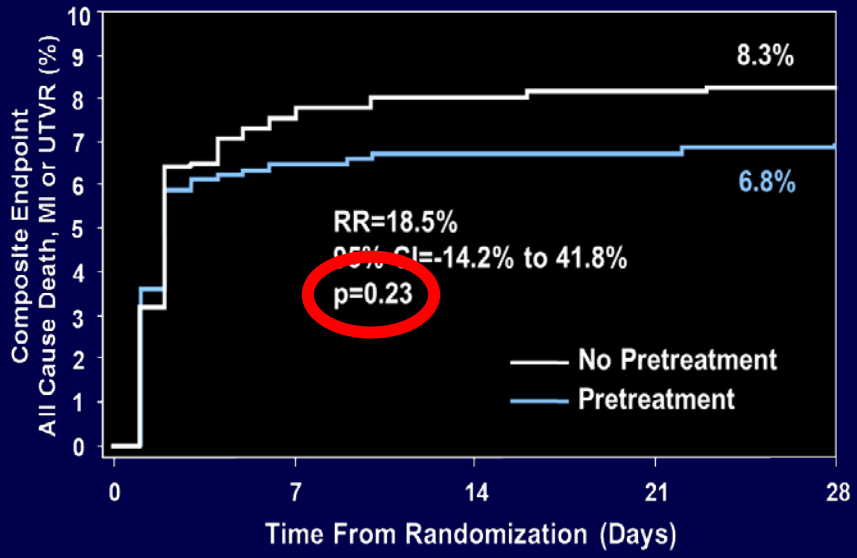
ACS

CURE Efficacy



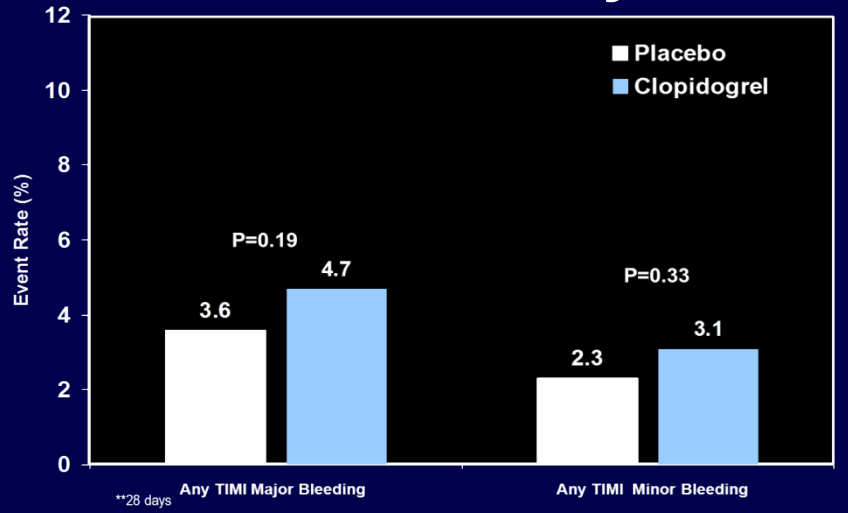
PCI

CREDO Efficacy



CURE Safety*

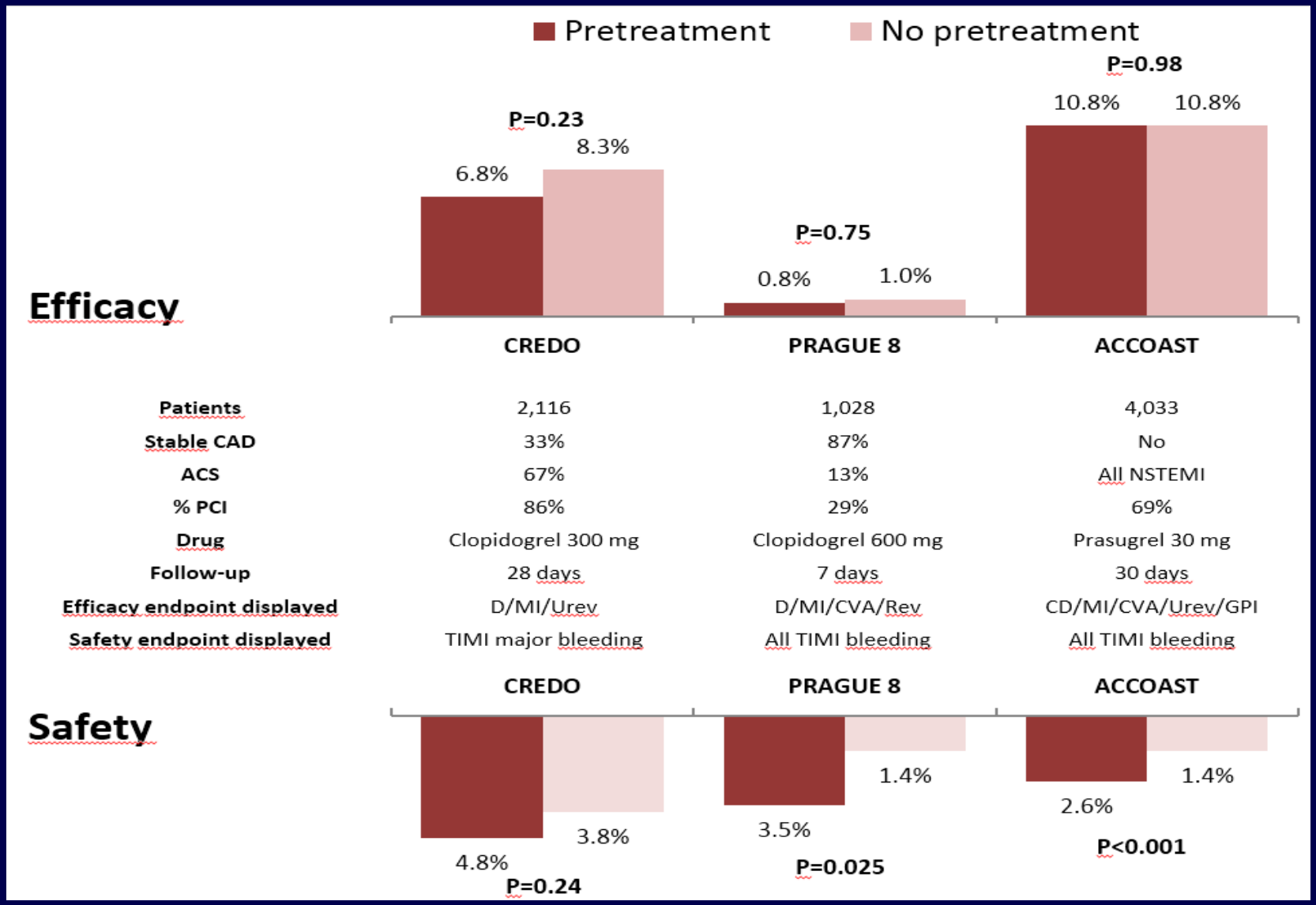
CREDO Safety**



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

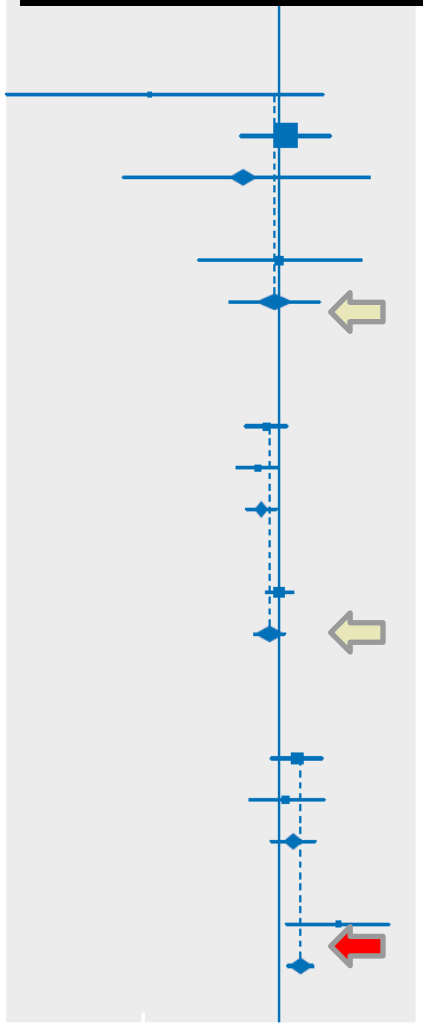
Steinhubl SR, et al. *JAMA* 2002;288:2411-2420

Studies of pretreatment with oral $P2Y_{12}$ receptor inhibitors in patients with stable CAD and NSTE-ACS



Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015

Randomized studies only (PCI patients)

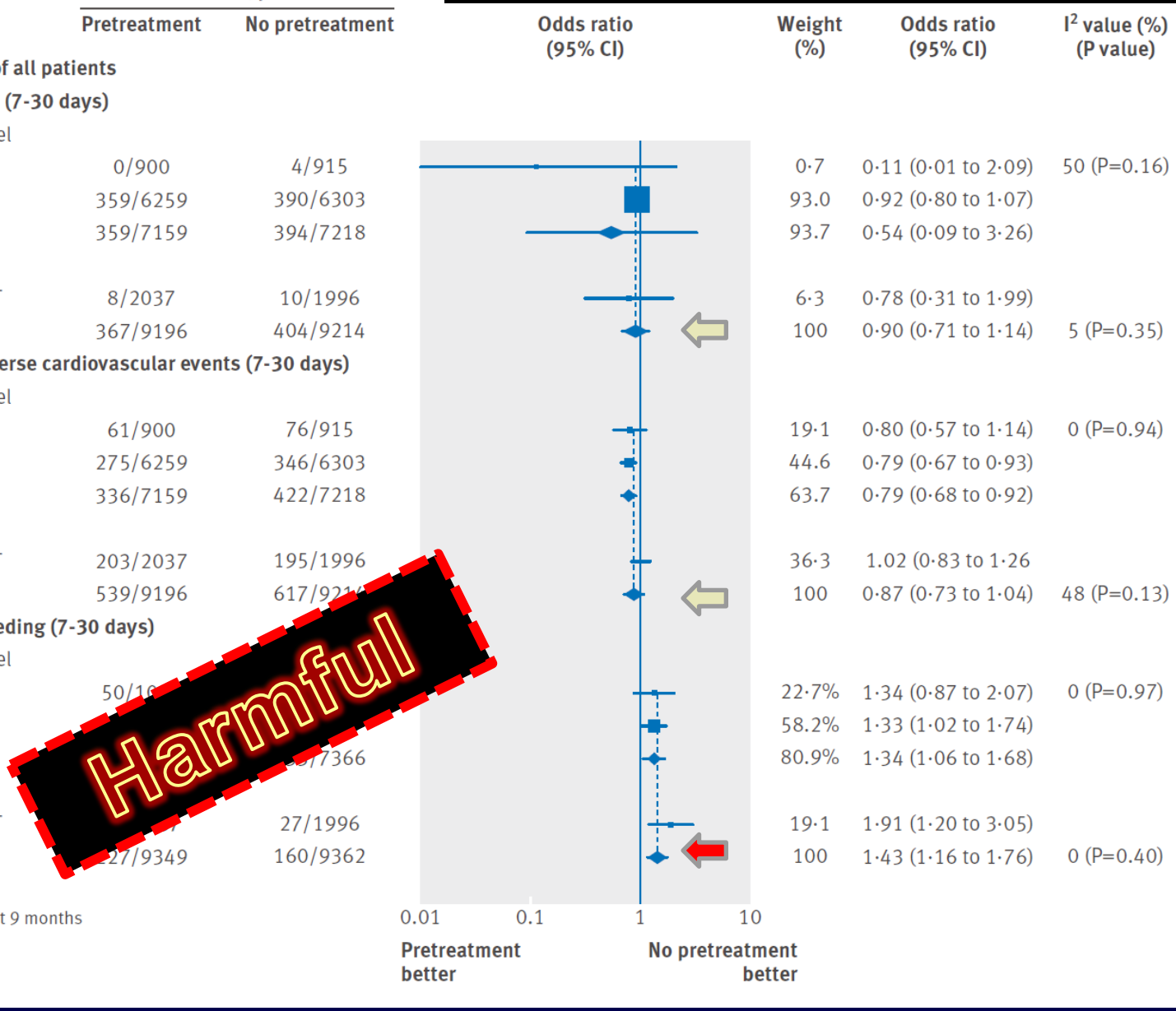


Analysis of PCI treated patients only					
All deaths (7-30 days)					
Clopidogrel					
CREDO	0/900	4/915	36·7	0·11 (0·01 to 2·09)	57 (P=0.13)
CURE*	14/1313	13/1345	56.0	1·10 (0·52 to 2·36)	
Subtotal	14/2213	17/2260	92.7	0·54 (0·07 to 4·53)	
Prasugrel					
ACCOAST	4/1397	4/1376	7·3	0·98 (0·25 to 3·95)	
Total	18/3610	21/3636	100	0·92 (0·43 to 1·98)	13 (P=0.32)
Major adverse cardiovascular events (7-30 days)					
Clopidogrel					
CREDO	61/900	76/915	27·4	0·80 (0·57 to 1·14)	0 (P=0.54)
CURE*	59/1313	86/1345	28.3	0·69 (0·49 to 0·97)	
Subtotal	120/2213	162/2260	55.7	0·74 (0·58 to 0·95)	
Prasugrel					
ACCOAST	183/1397	180/1376	44·3	1.00 (0·80 to 1·25)	
Total	303/3610	342/3636	100	0·85 (0·67 to 1·07)	44 (P=0.17)
Major bleeding (7-30 days)					
Clopidogrel					
CREDO	50/1053	38/1063	51·2	1·34 (0·87 to 2·07)	0 (P=0.66)
CURE*	21/1313	19/1345	30.8	1·13 (0·61 to 2·12)	
Subtotal	71/2366	57/2408	82.0	1·27 (0·89 to 1·82)	
Prasugrel					
ACCOAST	19/1397	7/1376	18·0	2·70 (1·13 to 6·44)	
Total	90/3763	64/37	100	1·45 (0·97 to 2·15)	25 (P=0.27)

*Endpoint at 9 months

Bellemain-Appaix A et al. BMJ 2014

Randomized studies only (All patients)

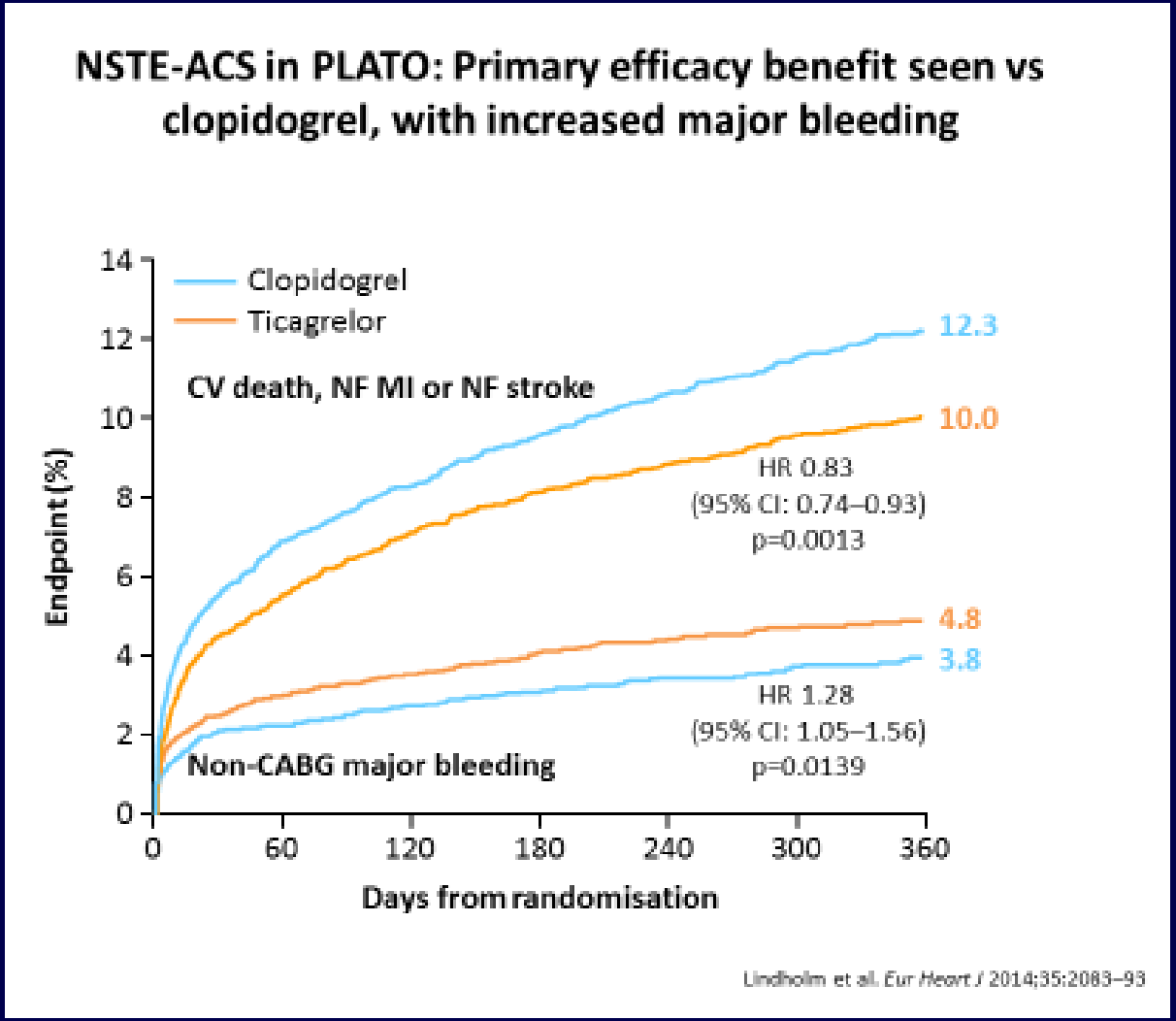


Bellemain-Appaix A et al. BMJ 2014

Ticagrelor in ACS: PLATO

All patients were pretreated before the angiogram…

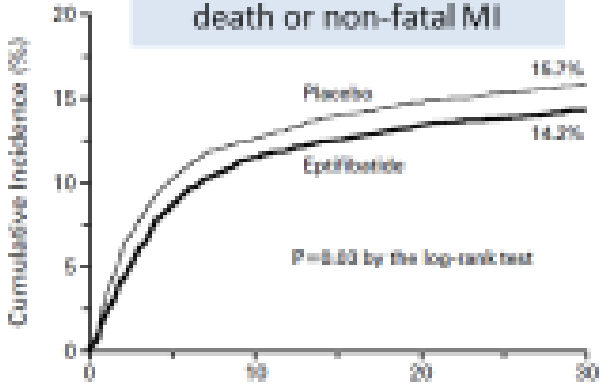
Cath 74%
PCI 46%



The controversy… was seen before

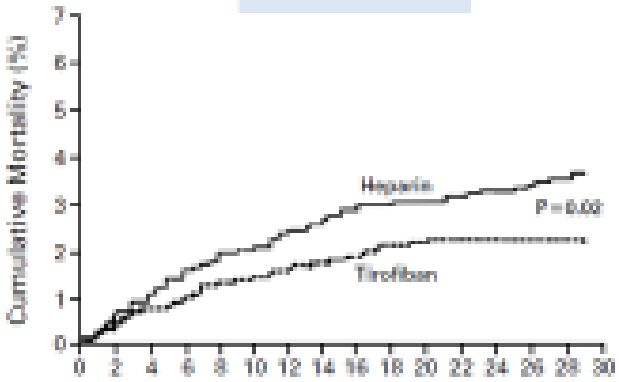
GPIs in NSTE-ACS

PURSUIT:
death or non-fatal MI



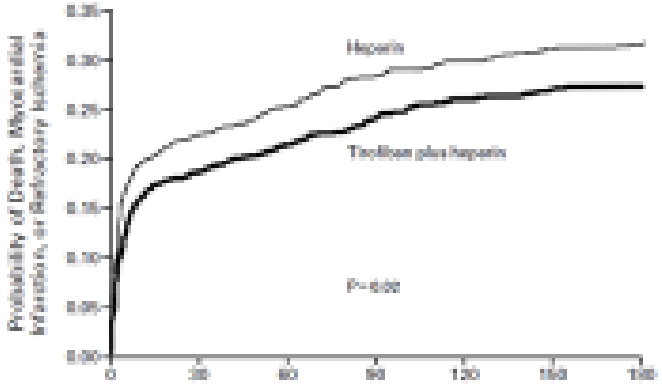
Harrington et al. *N Engl J Med* 1998;339:436–43

PRISM: death



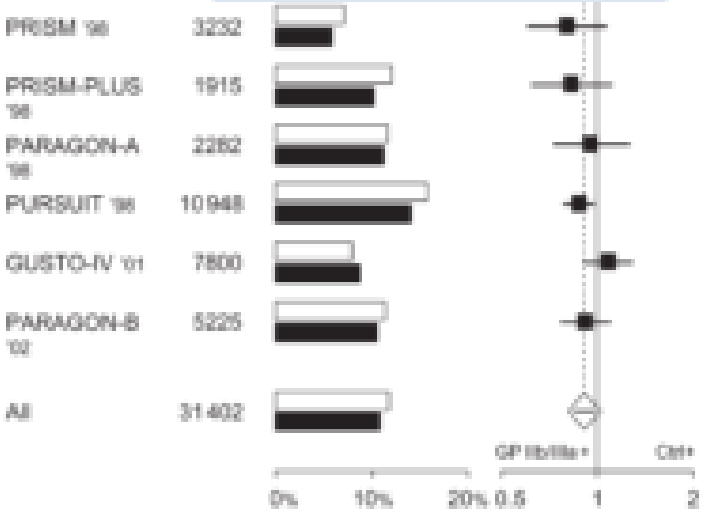
White et al. *N Engl J Med* 1998;338:1488–505

PRISM PLUS:
death, MI, or refractory ischemia



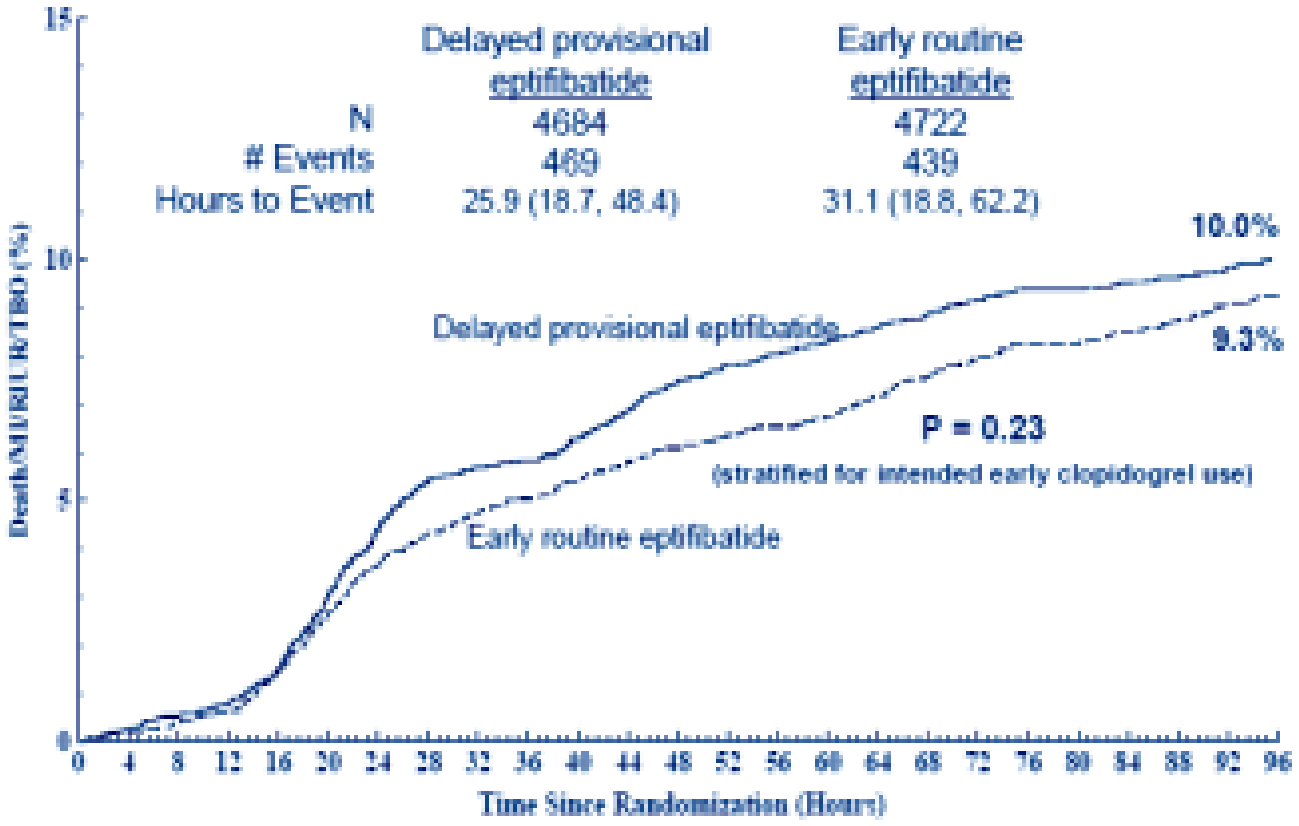
Théroux et al. *N Engl J Med* 1998;338:1488–97

META-ANALYSIS: death or MI



Bassand et al. *Eur Heart J* 2007;28:1598-1660

EARLY-ACS: GPI pre-treatment vs. no pre-treatment



TIMI major hemorrhage (2.6% vs.1.8%, P=0.02)

Giugliano RP et al. NEJM 2009;360(21):2176-90

The controversy…in the guidelines

European Heart Journal (2007) 28, 1598–1660
doi:10.1093/eurheartj/ehm161

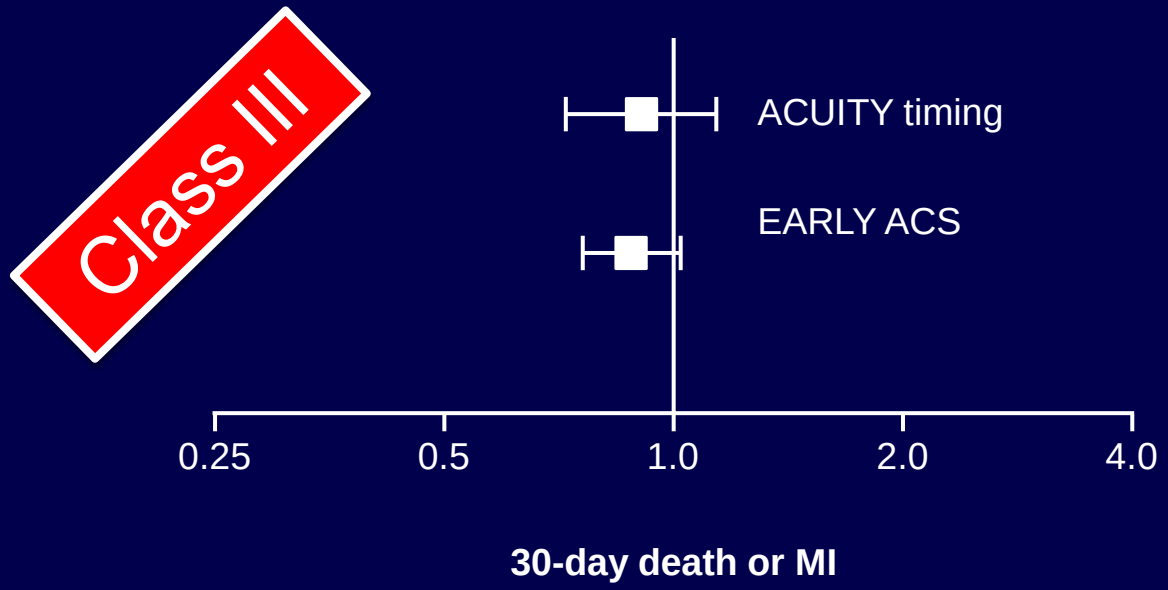
EUROPEAN SOCIETY OF CARDIOLOGY®

Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes

Recommendations for glycoprotein IIbIIIa inhibitors

- In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment is recommended in addition to oral antiplatelet agents (IIa-A).
- In high-risk patients not pre-treated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography (I-A). The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).

GPI pre-treatment in NTE-ACS



Recommendations	Class[a]	Level[b]
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

Windecker et al. *Eur Heart J* 2014;35:2541–619

SCAD Guidelines

Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended.	III	A

Revasc Guidelines

NSTE-ACS: It is recommended to give $P2Y_{12}$ inhibitors at the **time of first medical contact**	I	B
Pretreatment with prasugrel in patients in whom coronary anatomy is not known, is not recommended	III	B

NSTE-ACS Guidelines

A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contra-indications such as excessive risk of bleeds..	I	A
It is not recommended to administer **prasugrel** in patients in whom coronary anatomy is not known.	III	B

DAPT Guidelines

In patients with SCAD **pre-treatment with clopidogrel** may be considered if the **probability of PCI is high.**	IIb	C
Pre-treatment with a P2Y12 inhibitor is generally recommended in patients in whom **coronary anatomy is known** and the decision to proceed to PCI is made as well as in **patients with STEMI**	I	A
In NSTE-ACS patients undergoing invasive management, ticagrelor or clopidogrel if ticagrelor is not an option, should be considered **as soon as the diagnosis is established.**	IIa	C
In NSTE-ACS patients İt is not recommended to administer **prasugrel** in patients in whom coronary anatomy is not known.	III	B

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

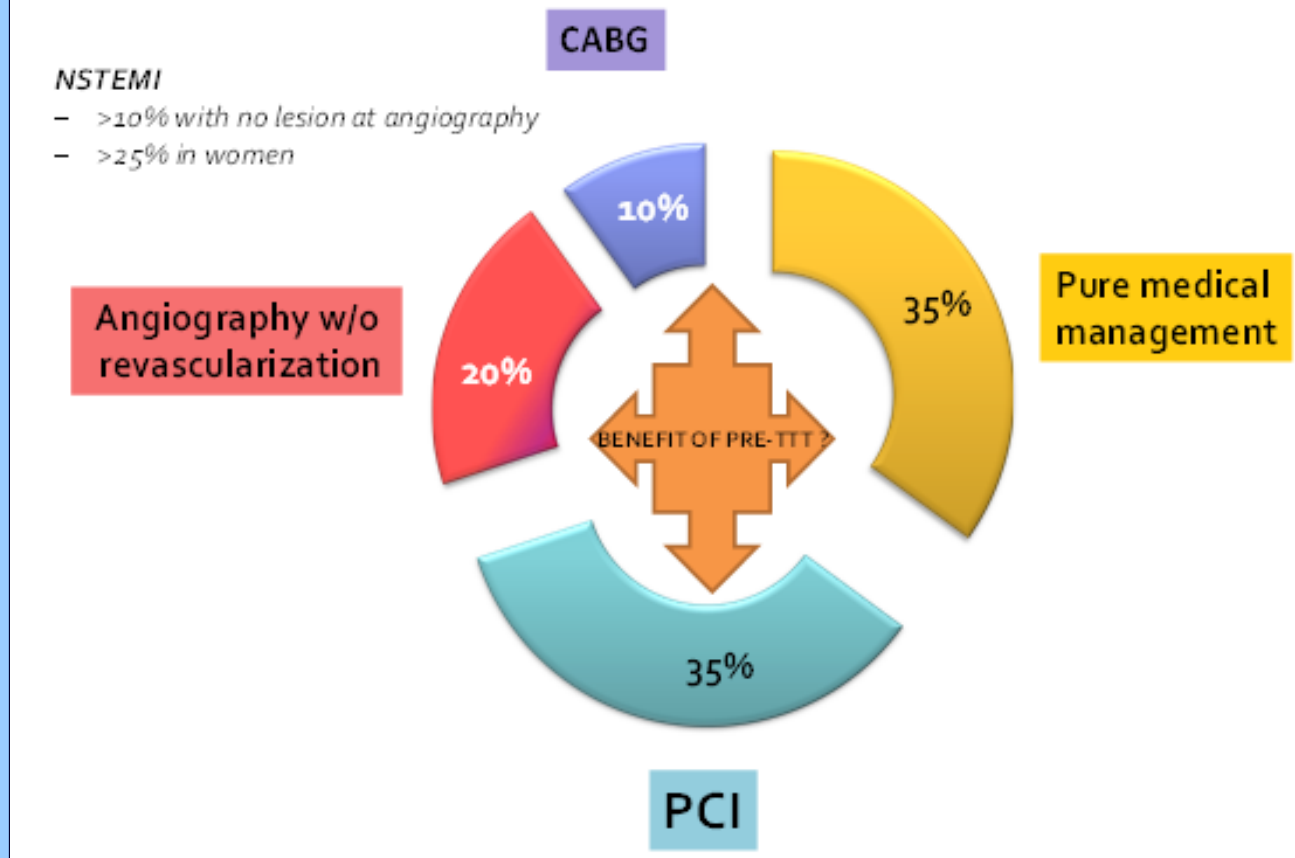
JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

$P2Y_{12}$ inhibitors				
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B	(291)
• $P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: – Clopidogrel – Ticagrelor*	300-mg or 600-mg loading dose, then 75 mg/d 180-mg loading dose, then 90 mg BID	I	B	(289,292) (293,294)
• $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B	(293,296,302, 330,331)
• Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B	(293,294)

Applying the evidence

NSTE-ACS in the Real World of All-Comers

→ Shall we treat them all before the angio?



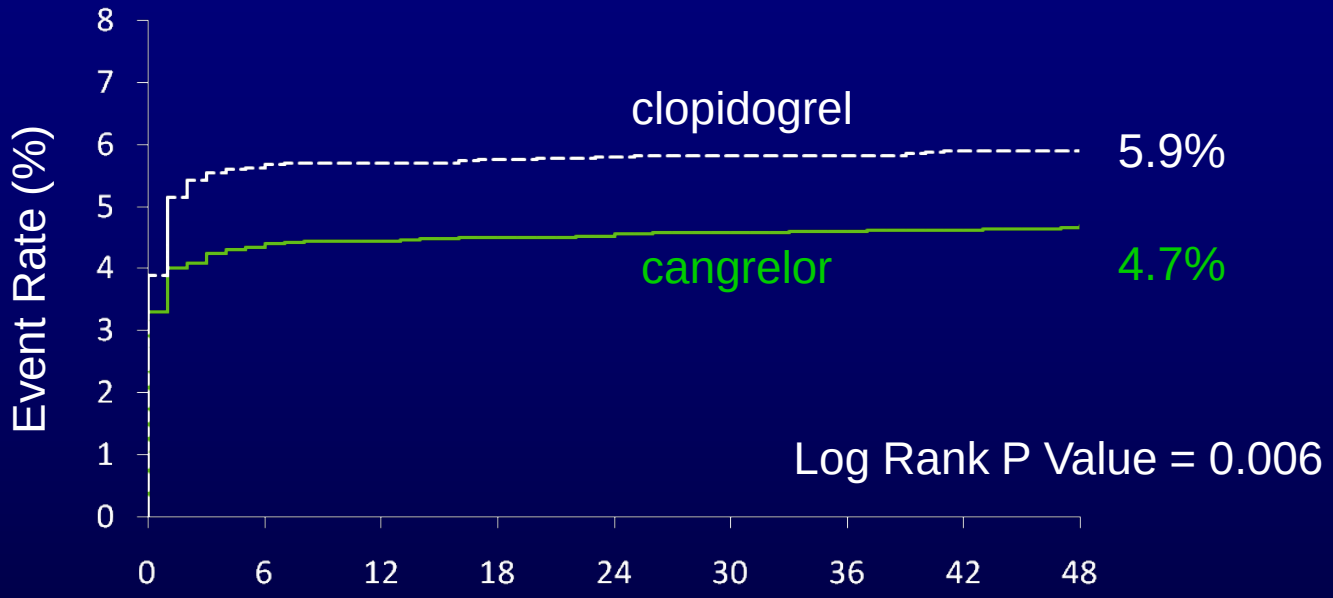
Collet JP et al. Circulation. 2014;130:1904-1914

Clinical situations where administration of antiplatelet therapy is delayed

- Intubated patient
- Vomiting, dysphagia…
- STEMI and limited pre-hospital care
- NSTE-ACS or SCAD → no pre-treatment

CHAMPION-PHOENIX: IV P2Y12 inhibitor cangrelor

Death/ MI/ IDR/ Stent Thrombosis within 48 Hours

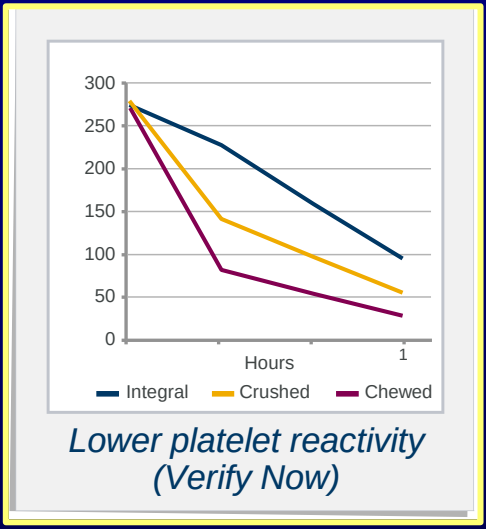


TIMI Major 48h	**0.1%**	**0.1%**	**>0.999**
TIMI Minor 48h	0.2%	0.1%	0.08
Death 48h	**0.3%**	**0.3%**	**0.99**

Bhatt DL et al. N Engl J Med 2013; 368: 1303-1313

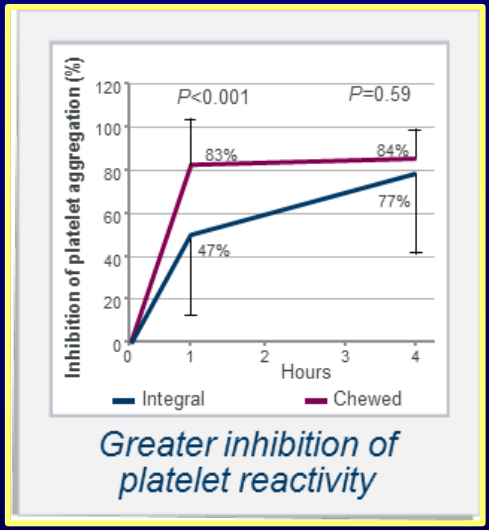
Crushed, chewed *or* orodispersible

Ticagrelor



Lower platelet reactivity (Verify Now)

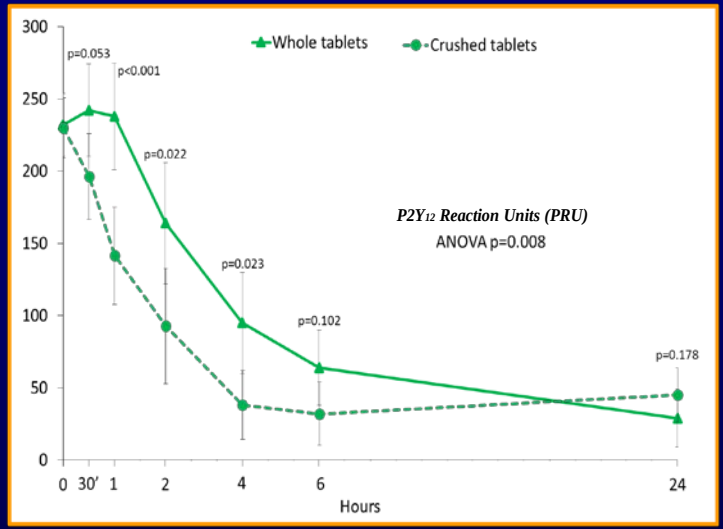
Venetsanos D *et al*.
Thromb Res 2017;149:88–94



Greater inhibition of platelet reactivity

Asher E *et al.*
Thromb Haemost 2017

Prasugrel



Rollini F et al.
JACC 2016

Conclusions

When should we start a $P2Y_{12}$ inhibitor?

- **Guidelines uncertain:** LOE B for prasugrel / LOE C for ticagrelor and clopidogrel
- **Bleeding risk increases** with early administration
- **Ischemic risk reduction is uncertain**

➢ **Early start more justified when long wait (>48hrs) for cath** *or* **no cath strategy**

➢ **Start after angio more justified when expeditive care** ***with*** **preferred use of crushed pills** *or* **IV P2Y12 inhibitor**

Slides available at **www.action-coeur.org**

Action cœur