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

P2Y12 inhibition should be started at the time of NSTEMI diagnosis – No!

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 definition

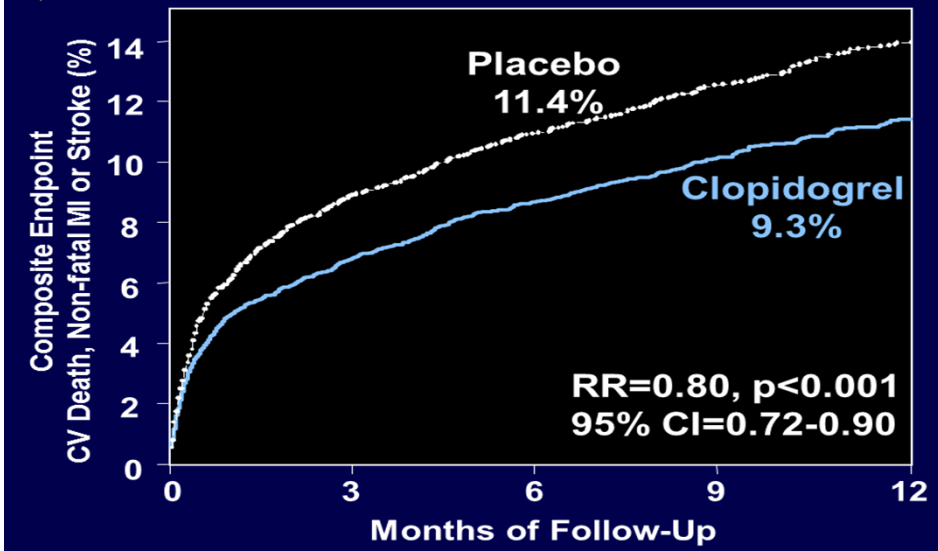
*The term "pretreatment" refers to the **initiation** of a treatment ($P2Y_{12}$ inhibitor) either in the ambulance, an emergency department, in the coronary care unit, or in the catheterization laboratory **prior to the definition of coronary anatomy**."*

A “concept” born with CURE

… not confirmed with CREDO

ACS

CURE Efficacy



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

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

N=12,562

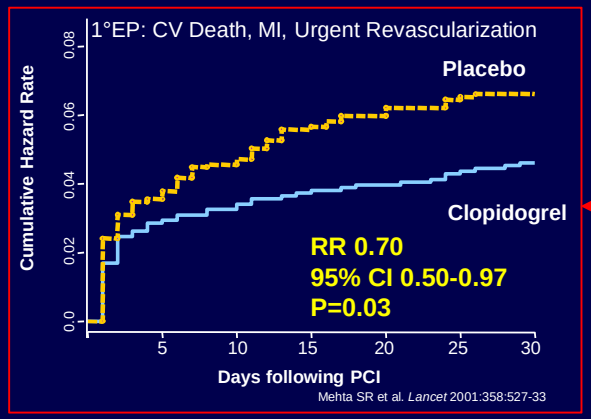
When cath, 10 days waiting …

57% no cath…

?

N=2,658

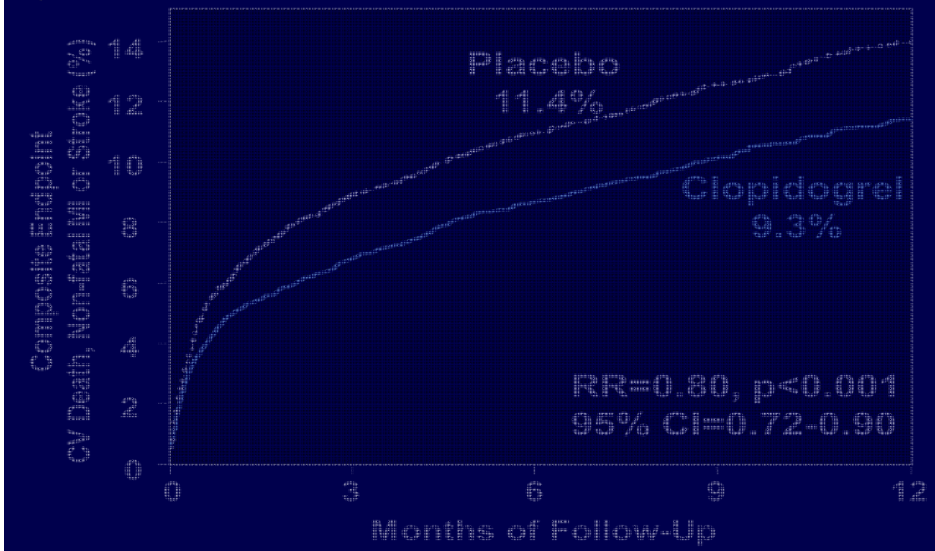
20% PCI



Mehta SR et al. *Lancet* 2001:358:527-33

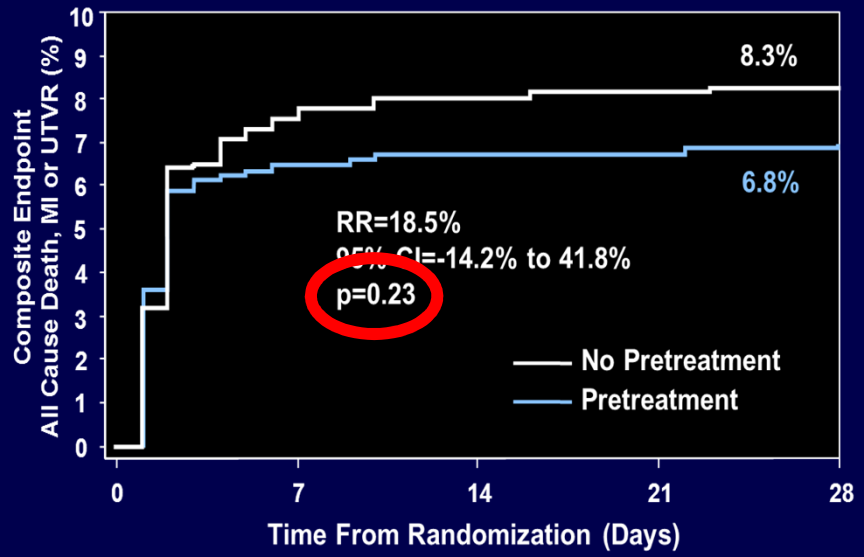
ACS

CURE Efficacy

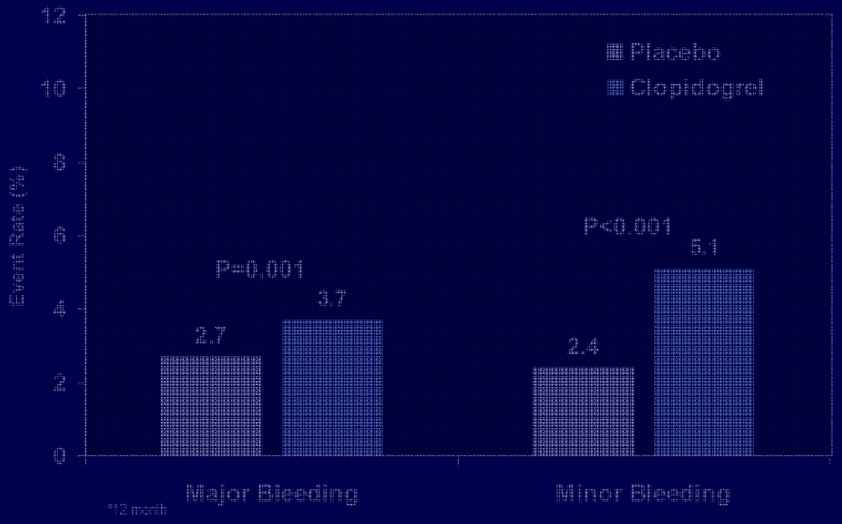


PCI

CREDO Efficacy

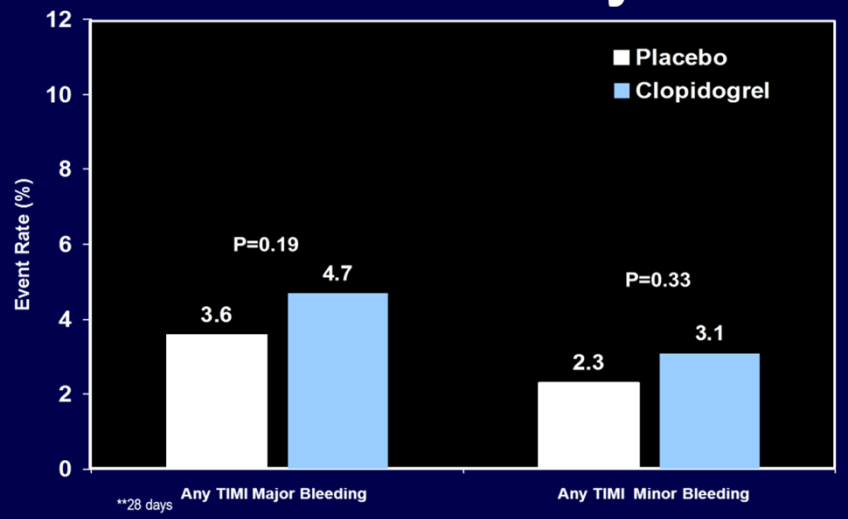


CURE Safety*



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

CREDO Safety**



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

A “concept” invalidated by ACCOAST

ACCOAST

2013

Randomization before angiography (mandatory)

NSTEMI + Troponin ≥ 1.5 times ULN local lab value
Clopidogrel naive or on long term clopidogrel 75 mg

n~4100 (event driven)

Randomize 1:1
Double-blind

Prasugrel 30 mg

Placebo

CABG or Medical Management (no more prasugrel)

Coronary Angiography

Coronary Angiography

CABG or Medical Management (no prasugrel)

Prasugrel 30 mg

Prasugrel 60 mg

PCI

PCI

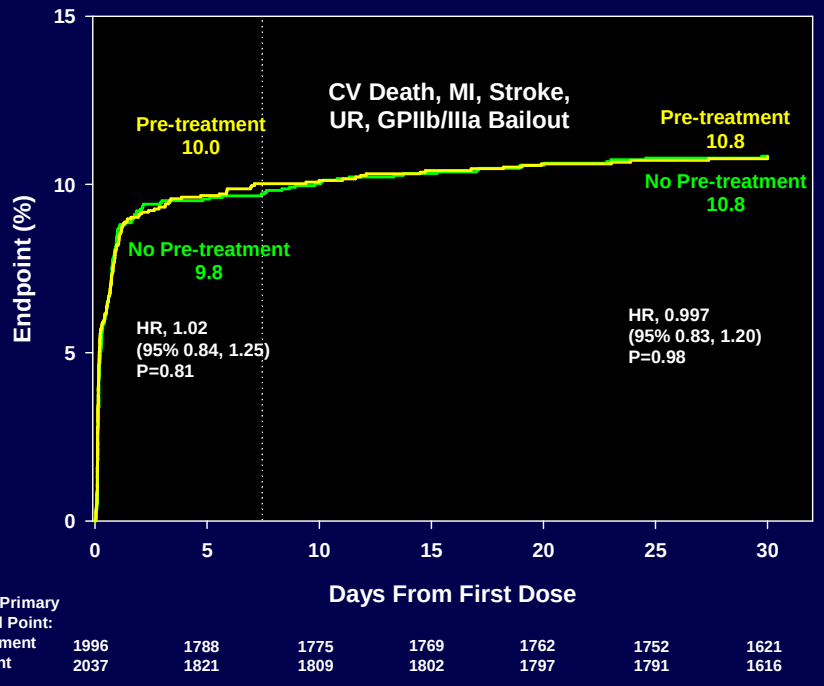
Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

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

The licensed loading dose of prasugrel is 60mg

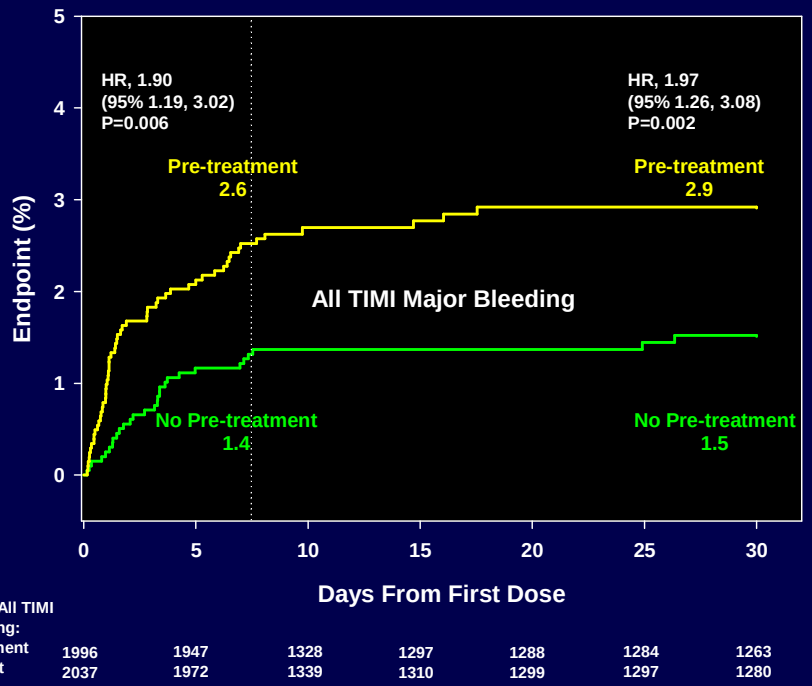
Montalescot G et al. *Am Heart J* 2011;161:650-656

Primary Efficacy and Safety Endpoints (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

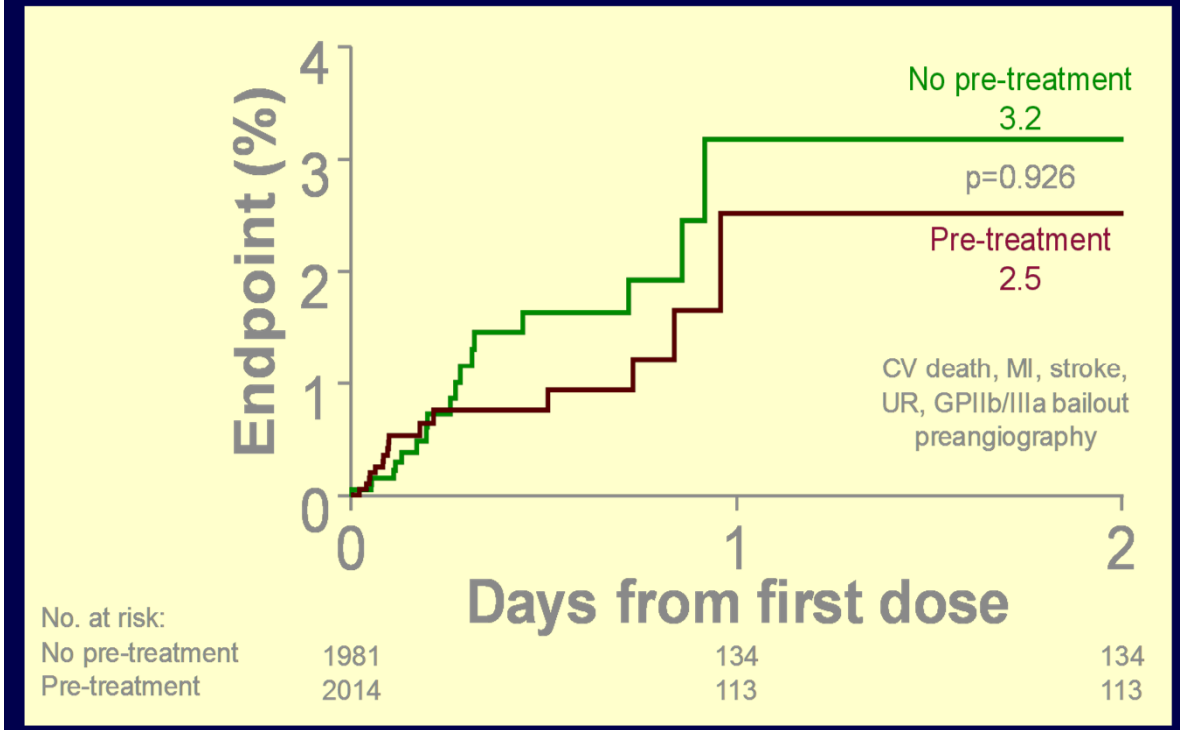


No. at Risk, All TIMI Major Bleeding:

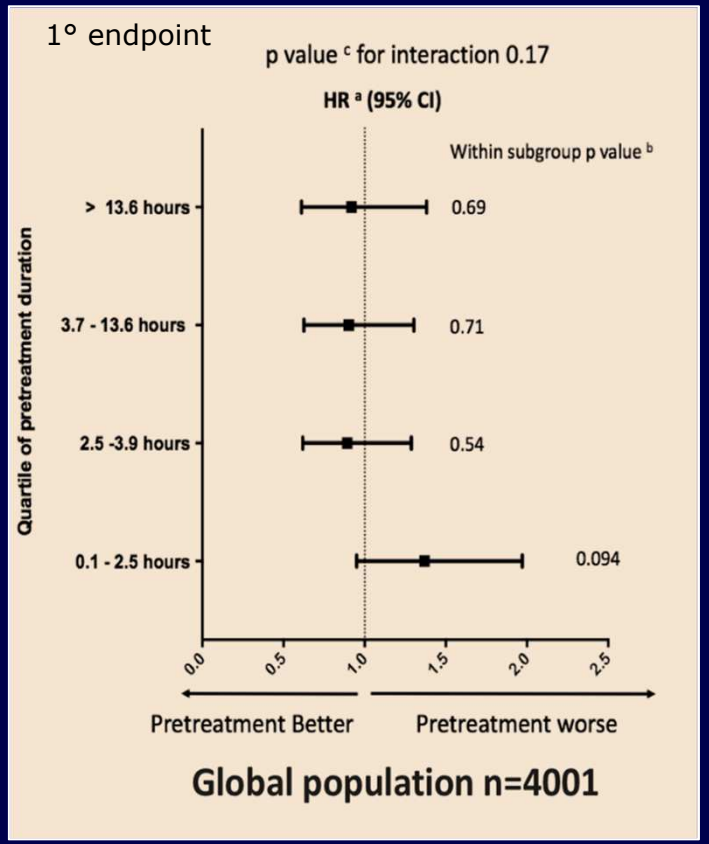
No pre-treatment	1996	1947	1328	1297	1288	1284	1263
Pre-treatment	2037	1972	1339	1310	1299	1297	1280

Montalescot G et al. N Engl J Med.2013;369(11):999-1010

Timing? risk of waiting

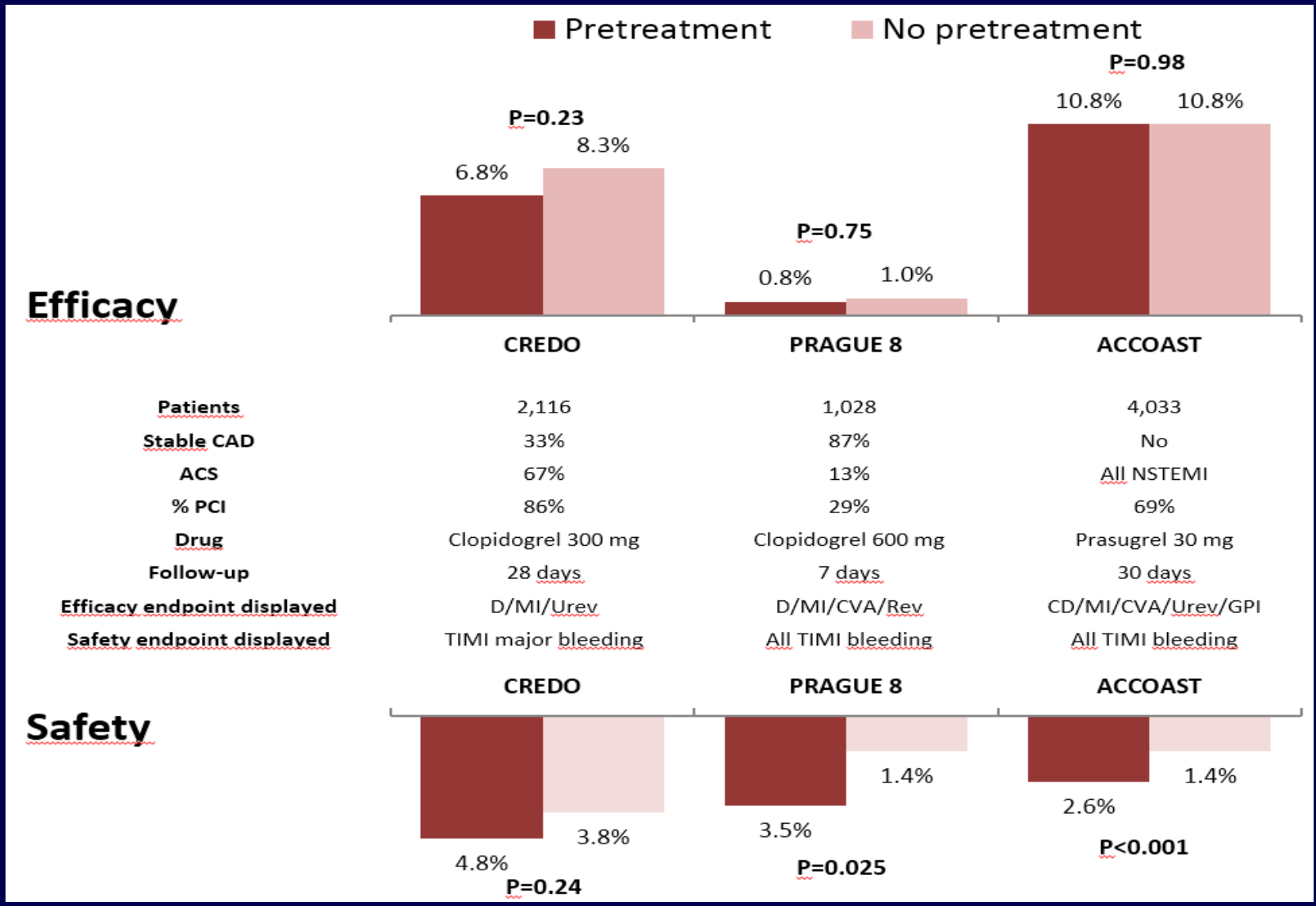


Montalescot et al. *N Engl J Med* 2013;369:999–1010



Silvain et al. ACCOAST-timing, JACC 2018

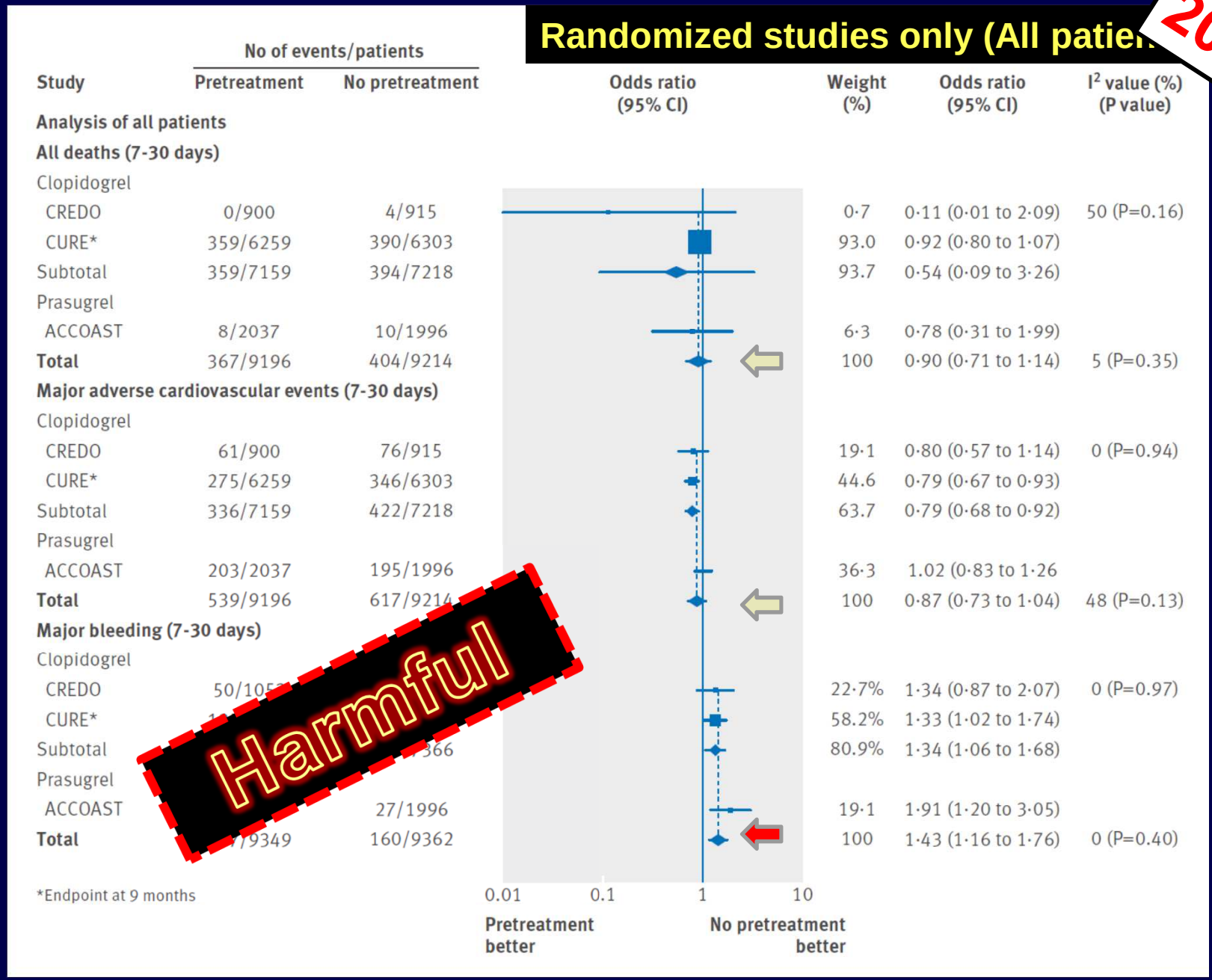
Studies of pretreatment with oral $P2Y_{12}$ receptor inhibitors



Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015

Randomized studies only (All patien

2014



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						
All deaths (7-30 days)						
Clopidogrel						
CREDO	0/900	4/915		0·7	0·11 (0·01 to 2·09)	50 (P=0.16)
CURE*	359/6259	390/6303		93.0	0·92 (0·80 to 1·07)	
Subtotal	359/7159	394/7218		93.7	0·54 (0·09 to 3·26)	
Prasugrel						
ACCOAST	8/2037	10/1996		6·3	0·78 (0·31 to 1·99)	
Total	367/9196	404/9214		100	0·90 (0·71 to 1·14)	5 (P=0.35)
Major adverse cardiovascular events (7-30 days)						
Clopidogrel						
CREDO	61/900	76/915		19·1	0·80 (0·57 to 1·14)	0 (P=0.94)
CURE*	275/6259	346/6303		44.6	0·79 (0·67 to 0·93)	
Subtotal	336/7159	422/7218		63.7	0·79 (0·68 to 0·92)	
Prasugrel						
ACCOAST	203/2037	195/1996		36·3	1.02 (0·83 to 1·26	
Total	539/9196	617/9214		100	0·87 (0·73 to 1·04)	48 (P=0.13)
Major bleeding (7-30 days)						
Clopidogrel						
CREDO	50/105			22·7%	1·34 (0·87 to 2·07)	0 (P=0.97)
CURE*				58.2%	1·33 (1·02 to 1·74)	
Subtotal		366		80.9%	1·34 (1·06 to 1·68)	
Prasugrel						
ACCOAST		27/1996		19·1	1·91 (1·20 to 3·05)	
Total	/9349	160/9362		100	1·43 (1·16 to 1·76)	0 (P=0.40)

Harmful

*Endpoint at 9 months

0.01 0.1 1 10

Pretreatment better

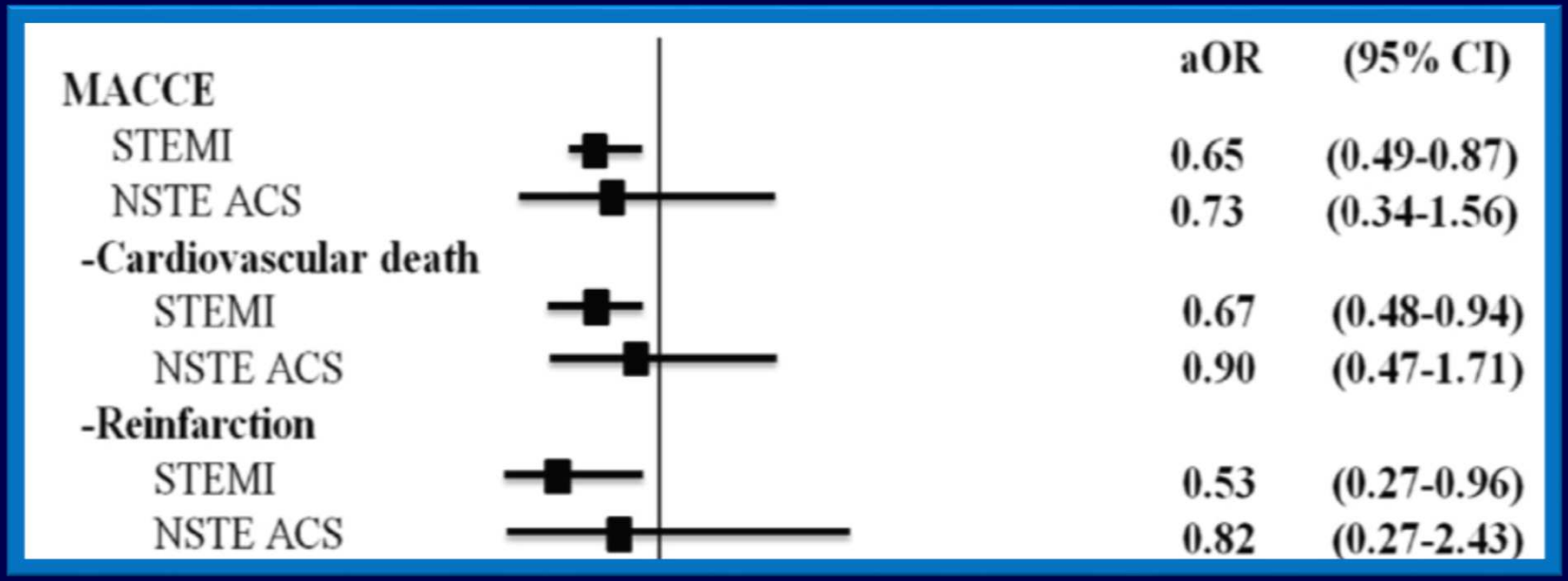
No pretreatment better

Bellemain-Appaix A et al. BMJ 2014

Real life of pre-treatment

2015

ARIAM-Andalucia (M. Amendro-Delia et al)



N=9621

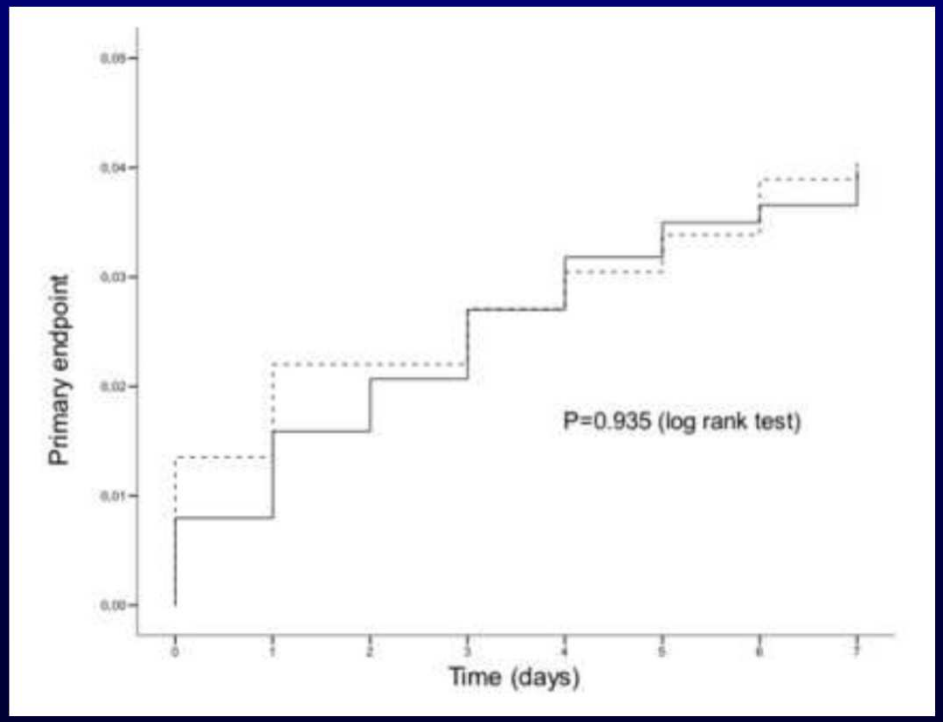
In conclusion, pretreatment with clopidogrel reduced the occurrence of death and thrombotic outcomes at the cost of minor bleeding. Those benefits exclusively affected ST-elevation myocardial infarction cases. The potential benefit of routine upstream pretreatment in patients with non–ST-elevation ACS should be reappraised at the present. (Am J Cardiol 2015;115:1019–1026)

PRAGUE 18 study

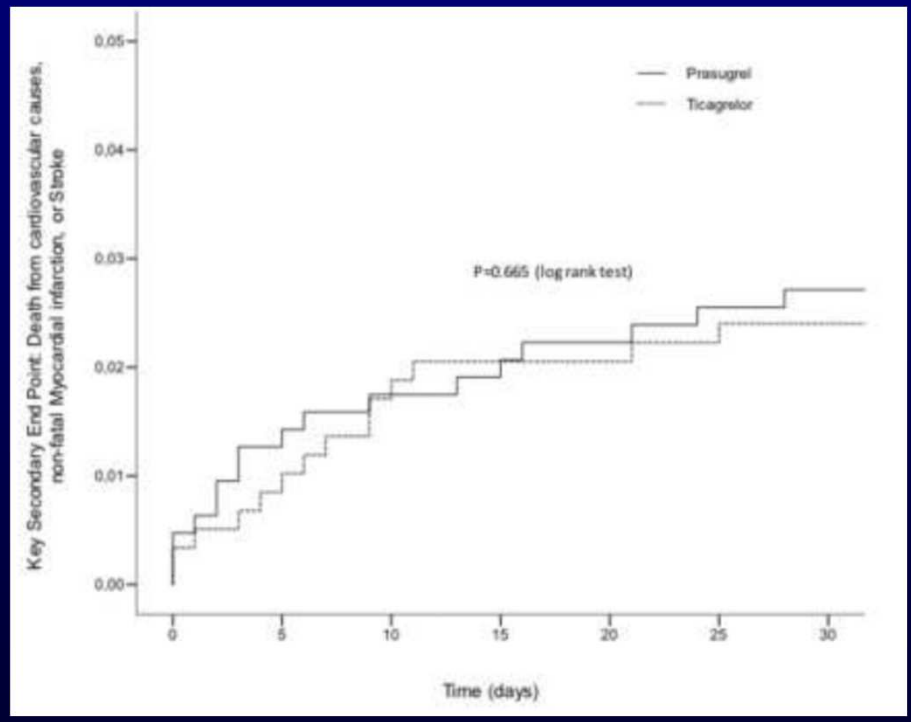
n=1230, prasugrel vs ticagrelor

2016

1° Endpoint
Death, MI, Stroke, urg revasc, MB @D7



Key 2° Endpoint
Death, MI, Stroke @D30



Motovska Z et al. Circ 2016

Meta-analysis of clopidogrel pretreatment in acute coronary syndrome patients undergoing invasive strategy

2017

Ramez Nairooz [a,*], Marco Valgimigli [b], Yogita Rochlani [c], Naga Venkata Pothineni [a], Sameer [illegible]ia [a], Partha Sardar [d], Debabrata Mukherjee [e], Srihari S Naidu [f], David M. Shavelle [g]

International Journal of Cardiology 229 (2017) 82–89

- **Prasugrel and ticagrelor excluded** (= Class I recommendations)
- **PCI patients only** (= post-hoc studies only)
- **Mixing of STEMI and NSTE-ACS** (= mixing of opposite situations)
- **>90% of patients come from registries** (= multiple biases)
- **No loading in no pretreatment arm** of some studies (= no treatment at all)

The Timing of $P2Y_{12}$ Inhibitor Initiation in the Treatment of ACS? Does the Evidence Exist in This Era?☆

Harsh Golwala, Deepak L. Bhatt *

Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, United States

2018

Conclusion

Pretreatment strategy with a $P2Y_{12}$ inhibitor in patients with ACS still remains an area of debate. Randomized trials, which supported their use, are from an older era and precede the state of the art management of patients with ACS including primary PCI for STEMI and a routine early invasive approach for NSTEMI. Pretreatment may be considered in certain groups of patients, such as when there is an expected delay of >48 h for PCI, low bleeding risk, high recurrent ischemic risk, and/or low likelihood of requiring CABG. However, based on the above data, routine pretreatment with oral $P2Y_{12}$ inhibitors may not be an optimal option.

Progress in Cardiovascular Diseases 60 (2018) 471–477

ISAR-REACT 5

2019

STEMI

Randomization

- **Ticagrelor** 180 mg loading
- **Prasugrel** 60 mg loading

Angiography + PCI

- **Ticagrelor** 90 mg 1-0-1
- **Prasugrel** 10 mg 1-0-0#

NSTE-ACS

Randomization

- **Ticagrelor** 180 mg loading
- **Prasugrel** 60 mg loading*

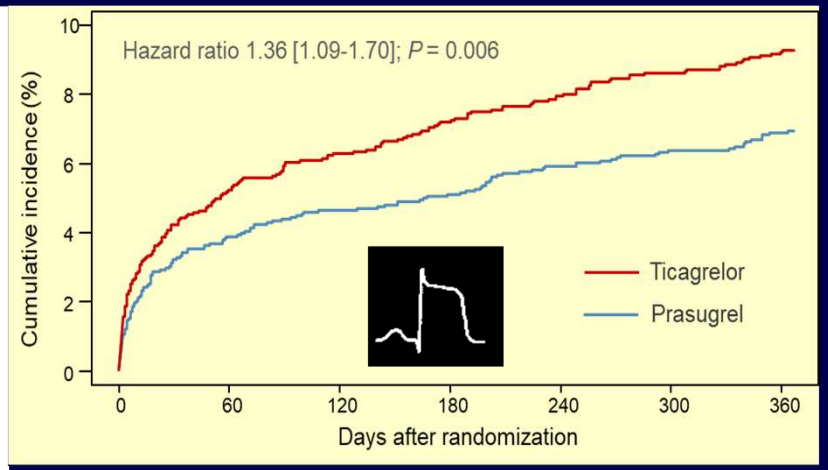
Angiography

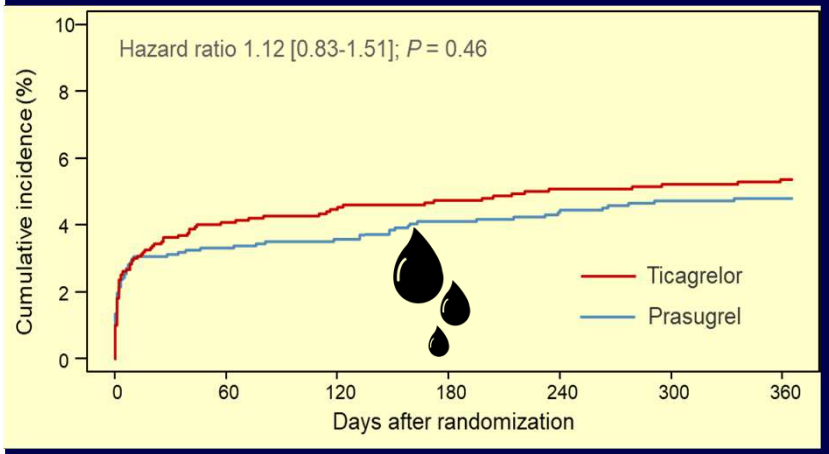
- **Prasugrel** 60 mg loading

PCI

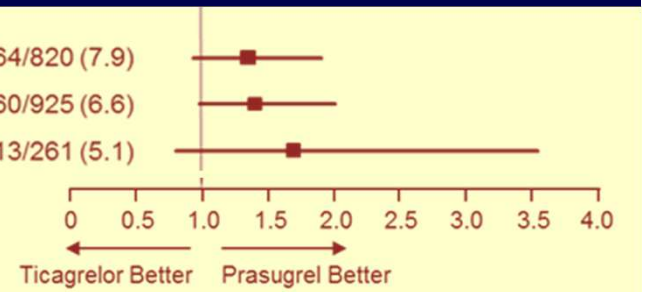
- **Ticagrelor** 90 mg 1-0-1
- **Prasugrel** 10 mg 1-0-0#

Primary Endpoint:
Composite of Death, Myocardial infarction or Stroke at 12 Months After Randomization





Clinical Presentation		
STEMI	83/833 (10.1)	64/820 (7.9)
NSTEMI	81/930 (8.8)	60/925 (6.6)
Unstable Angina	20/249 (8.2)	13/261 (5.1)



A debate also in the guidelines!

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

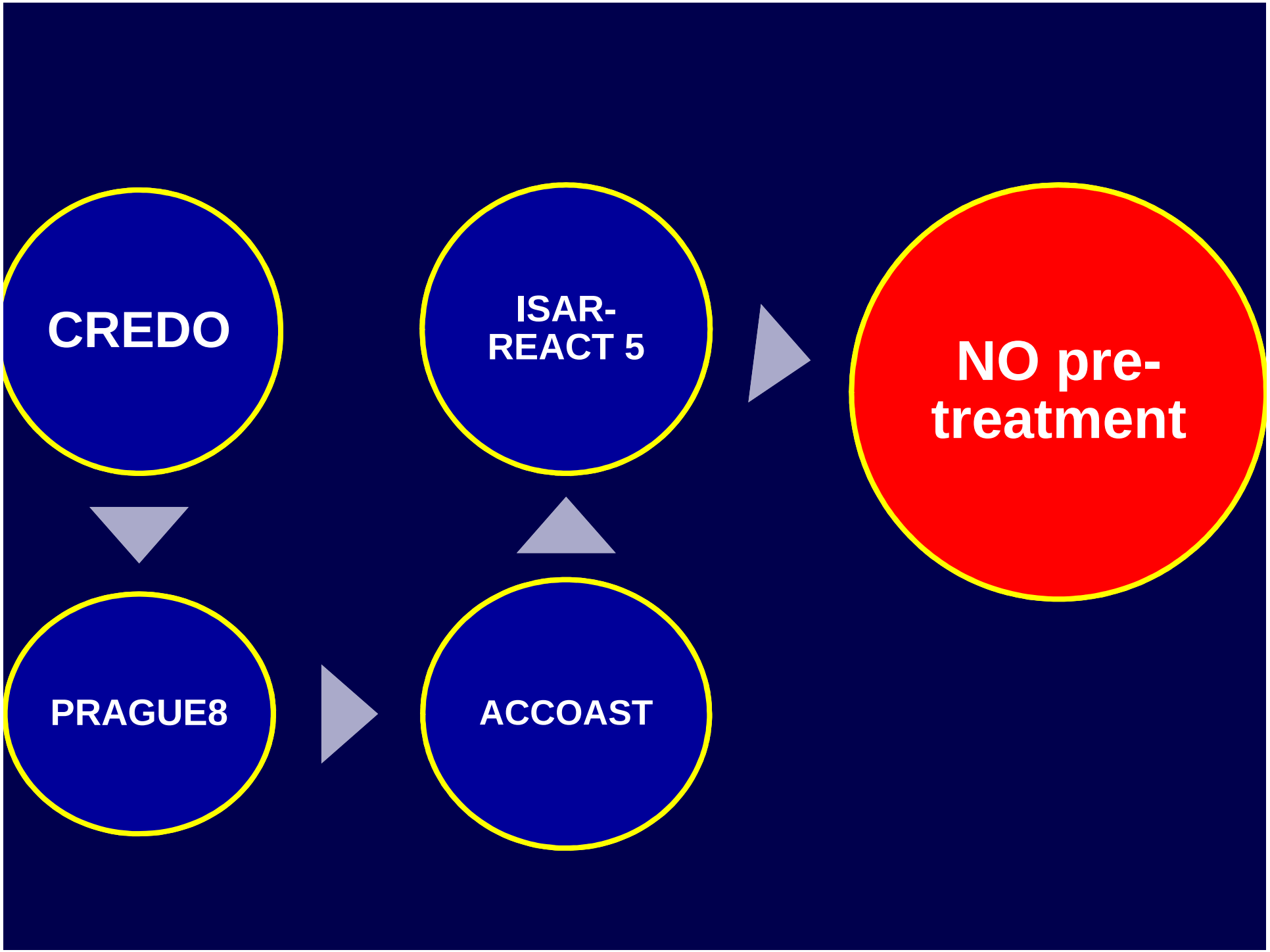
In patients with SCAD **pre-treatment with clopidogrel** may be considered if the **probability of PCI is high.**	IIb	C
Pre-treatment with a P2Y12 inhibitor is generally recommended in patients in whom **coronary anatomy is known** and the decision to proceed to PCI is made as well as in **patients with 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

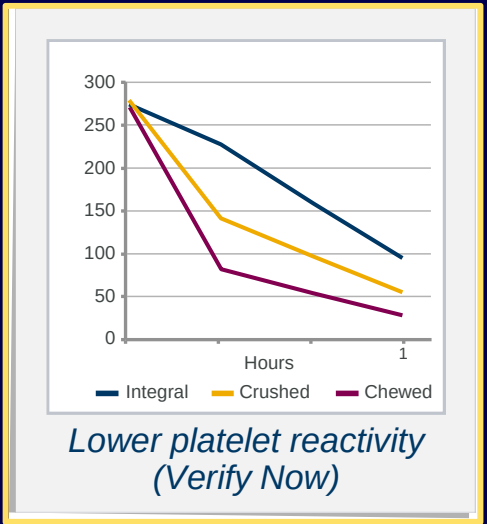
$P2Y_{12}$ inhibitors				
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B	(291)
• $P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: – 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)

Just apply the evidence and use the right options


CREDO
ISAR-REACT 5
NO pre-treatment
PRAGUE8
ACCOAST

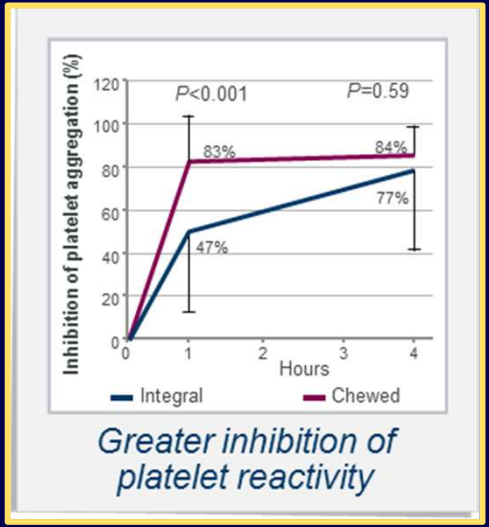
Crushed, chewed *or* orodispersible

Ticagrelor



Lower platelet reactivity (Verify Now)

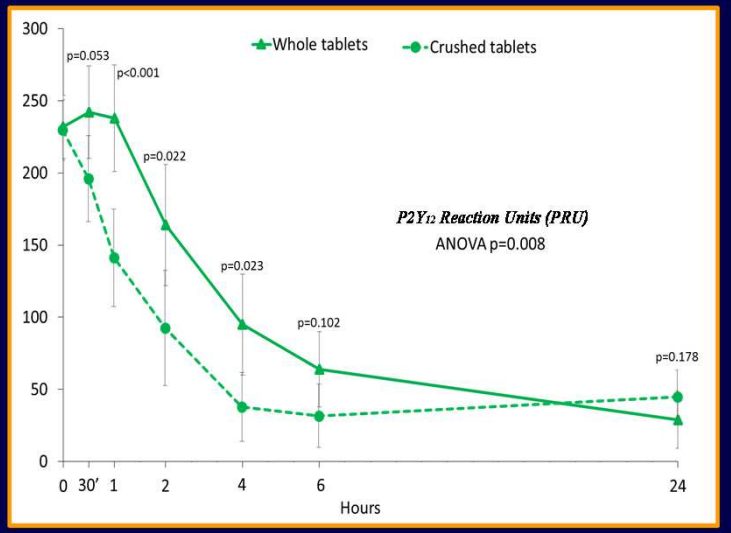
Venetsanos D *et al*.
Thromb Res 2017;149:88–94



Greater inhibition of platelet reactivity

Asher E *et al.*
Thromb Haemost 2017

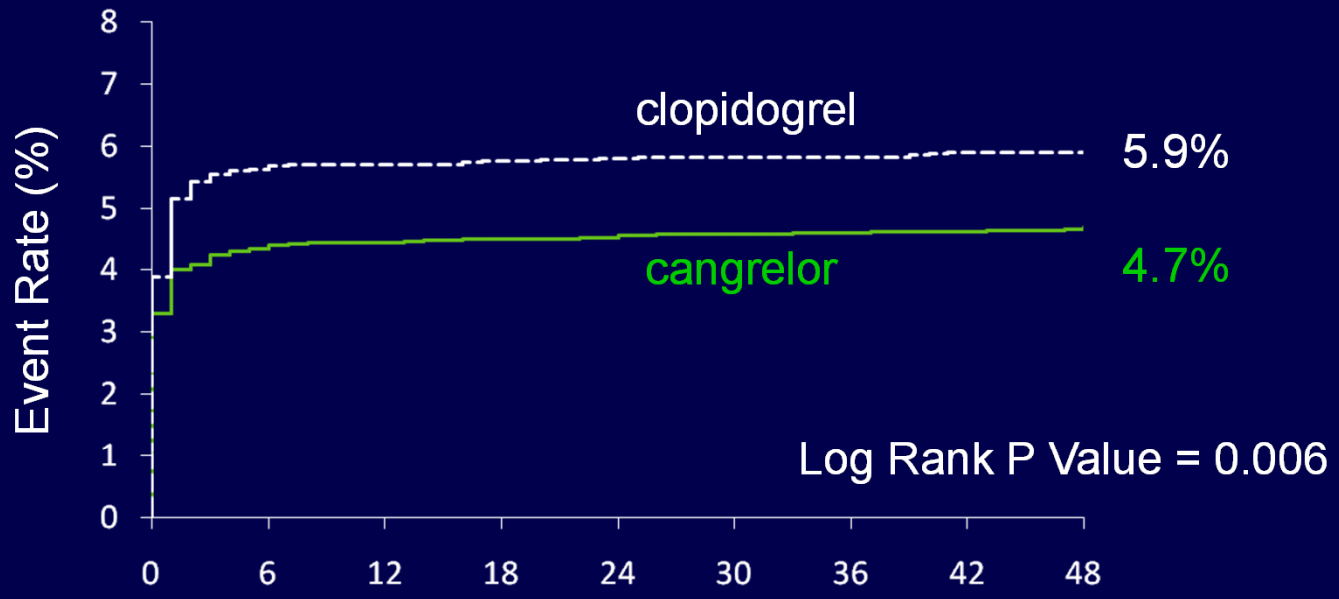
Prasugrel



Rollini F et al.
JACC 2016

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

Conclusions

- Bleeding risk increases with pretreatment
- Ischemic risk is not reduced with pretreatment
- No mortality effect with pretreatment

- **Look first (at coronaries) and Treat (selectively)**
- **Do not Treat (routinely) and Watch (complications)**
- Early start only justified if long wait (>48hrs) for cath *or* no cath strategy

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

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