Pretreatment with P2Y12 Inhibitors in NSTE-ACS: Selective vs. Routine?

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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),
• Consulting Fees/Honoraria	• Janssen (J+J), Maya Medical,

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ACUTE PHASE

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Pros and Cons of Upstream vs Downstream use of P2Y12 receptor Inhibitors

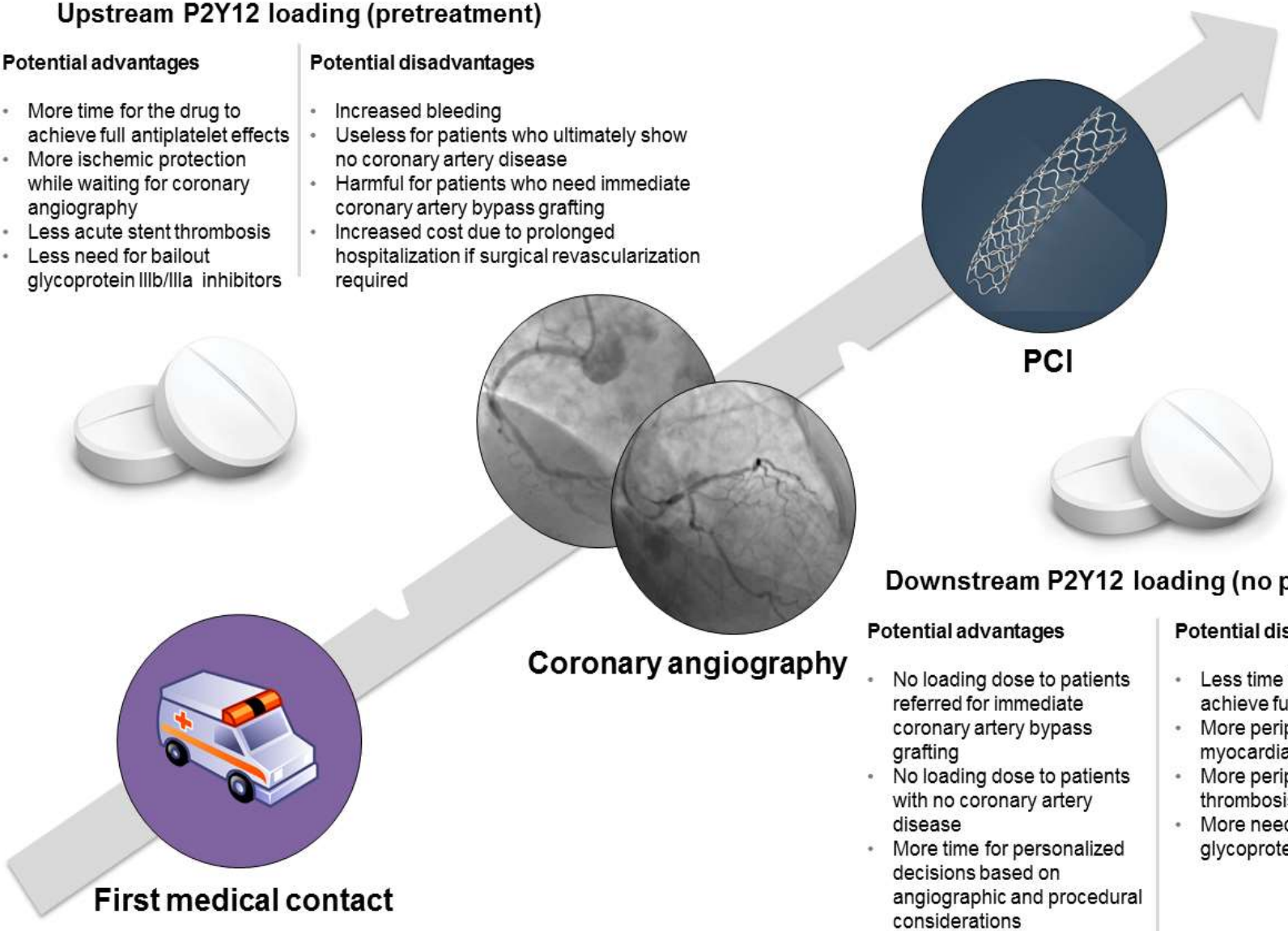
Upstream P2Y12 loading (pretreatment)

Potential advantages

- More time for the drug to achieve full antiplatelet effects
- More ischemic protection while waiting for coronary angiography
- Less acute stent thrombosis
- Less need for bailout glycoprotein IIIb/IIIa inhibitors

Potential disadvantages

- Increased bleeding
- Useless for patients who ultimately show no coronary artery disease
- Harmful for patients who need immediate coronary artery bypass grafting
- Increased cost due to prolonged hospitalization if surgical revascularization required



Downstream P2Y12 loading (no pretreatment)

Potential advantages

- No loading dose to patients referred for immediate coronary artery bypass grafting
- No loading dose to patients with no coronary artery disease
- More time for personalized decisions based on angiographic and procedural considerations

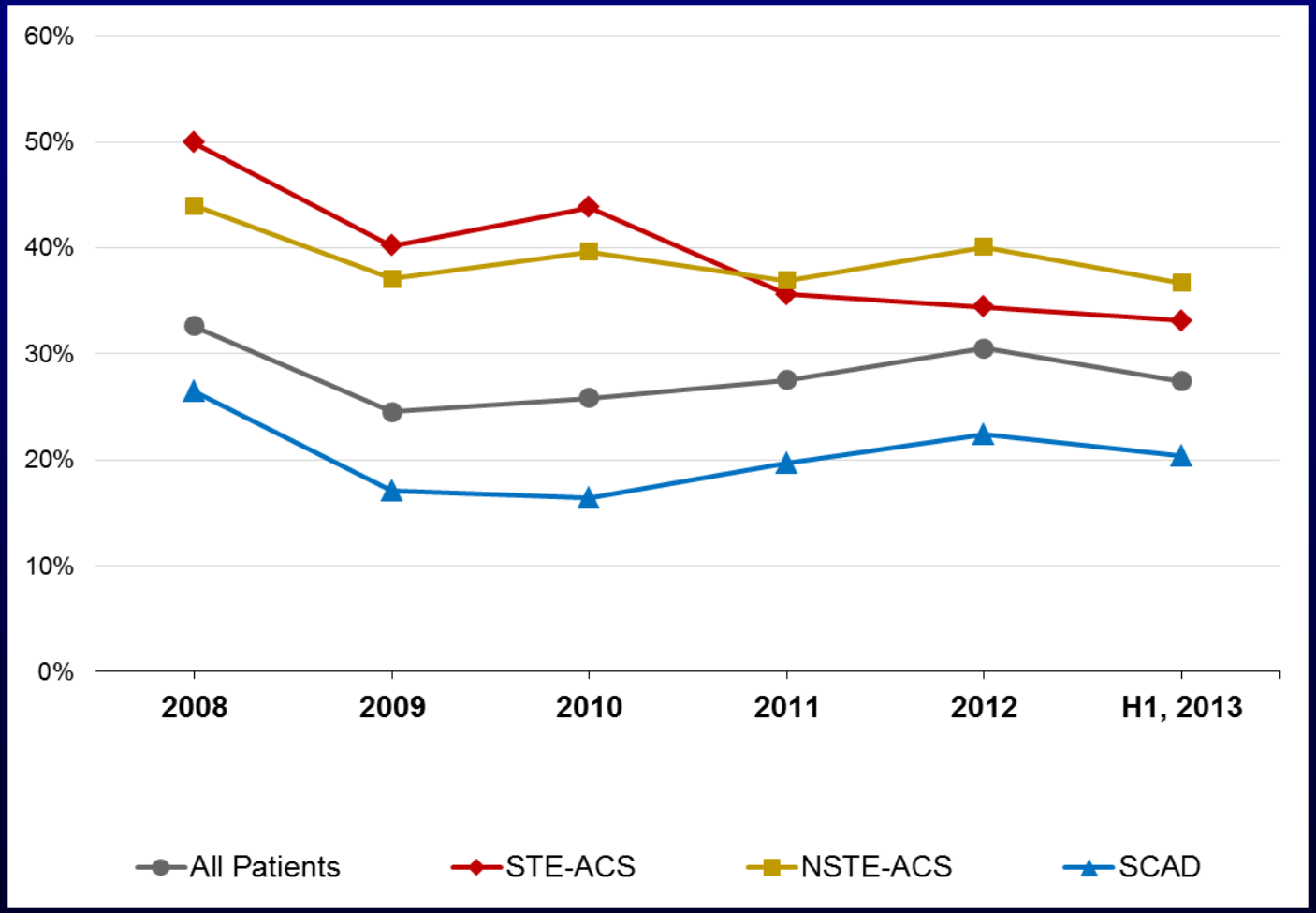
Potential disadvantages

- Less time for the drug to achieve full antiplatelet effects
- More periprocedural myocardial infarction
- More periprocedural stent thrombosis
- More need for bailout glycoprotein IIb/IIIa inhibitors

Capodanno D, Angiolillo DJ. Expert Rev Cardiovasc Ther. 2016

Prevalence of Pretreatment with P2Y12 receptor inhibitors According to Clinical Presentation

Electronic medical records from the US Cerner *Health Facts*® database of adults (n=37,964) who underwent LHC with or without PCI between January 2008 and June 2013 and who received a loading dose of clopidogrel, prasugrel, or ticagrelor at any time from 48 hours before the start of procedure up to 6 hours after.



Fan W et al. Am J Cardiol 2016 (in press)

American College of Cardiology Foundation/American Heart Association guidelines

2005 Focused Update PCI
A loading dose of clopidogrel should be administered *before PCI is performed* (Class I, LOE A)

2007 Focused Update PCI
A loading dose of clopidogrel, generally 600 mg, should be administered *before or when PCI is performed* (Class I, LOE C)

2007 NSTE-ACS
- Initial invasive strategy. Antiplatelet therapy with clopidogrel in addition to aspirin should be initiated *before diagnostic angiography* (Class I, LOE A)
- Initial conservative strategy. Clopidogrel should be added to aspirin *as soon as possible after admission* (Class I, LOE A)

2007 Focused Update STEMI
Clopidogrel should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy (Class I, LOE A)

2009 Focused Update STEMI/PCI
- STEMI. At least 300 to 600 mg of clopidogrel should be given *as early as possible before or at the time of primary or nonprimary PCI* (Class I, LOE C). Prasugrel 60 mg should be given *as soon as possible* for primary PCI (Class I, LOE B)
- Initial invasive strategy in NSTE-ACS: clopidogrel (*before or at the time of PCI*) (Class I, LOE A) or prasugrel (*at the time of PCI*) (Class I, LOE B) is recommended as a second antiplatelet agent

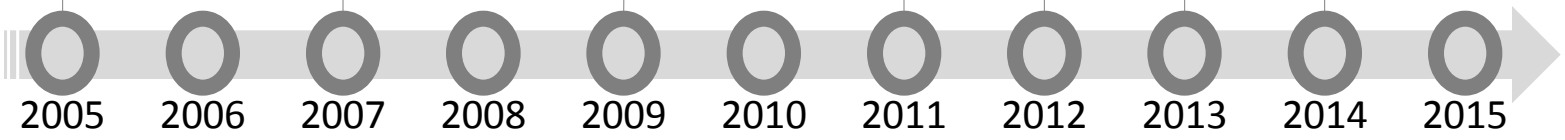
2011 Focused Update PCI
A loading dose of a P2Y12 receptor inhibitor should be given to patients undergoing PCI with stenting. Options are: clopidogrel 600 mg (Class I, LOE A); prasugrel 60 mg (Class I, LOE B), ticagrelor 180 mg (Class I, LOE B)

2011 Focused Update NSTE-ACS
- Initial invasive strategy. *Before PCI*: clopidogrel (Class I, LOE B). *At the time of PCI*: clopidogrel if not started before PCI (Class I, LOE A), prasugrel (Class I; LOE B)
- Initial conservative strategy. Clopidogrel should be added to aspirin *as soon as possible after admission* (Class I, LOE A)

2012 Focused Update NSTE-ACS
- Initial invasive strategy. *Before PCI*: clopidogrel (Class I, LOE B), ticagrelor (Class I, LOE B). *At the time of PCI*: clopidogrel if not started before PCI (Class I, LOE A), prasugrel (Class I, LOE B), ticagrelor (Class I, LOE B)
- Initial conservative strategy. Clopidogrel or ticagrelor should be added to aspirin *as soon as possible after admission* (Class I, LOE B)

2013 STEMI
A loading dose of a P2Y12 receptor inhibitor should be given *as early as possible or at time of primary PCI*. Options include clopidogrel 600 mg (Class I, LOE B), prasugrel 60 mg (Class I, LOE B), ticagrelor 180 mg (Class I, LOE B)

2014 NSTE-ACS
A loading dose of a P2Y12 receptor inhibitor should be given *before the procedure* in patients undergoing PCI with stenting (Class I, LOE A)



Capodanno D, Angiolillo DJ. Expert Review Cardiovasc Therapy 2016

European Society of Cardiology guidelines

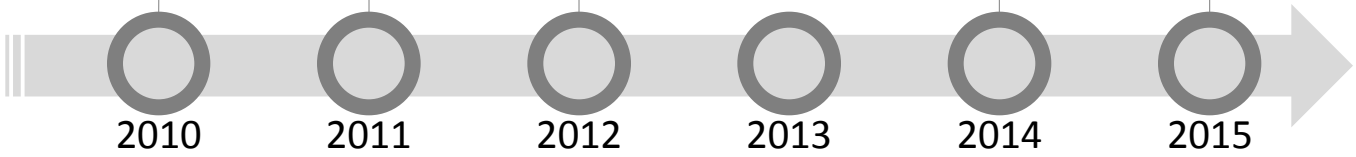
2010 Myocardial revascularization
NSTE-ACS. Clopidogrel (with 600 mg loading dose *as soon as possible*) (Class I, LOE C)

2011 NSTE-ACS
A P2Y12 inhibitor should be added to aspirin *as soon as possible*, unless there are contraindications such as excessive risk of bleeding (Class I, LOE A)

2012 STEMI
Patients undergoing primary PCI should receive a combination of dual antiplatelet therapy with aspirin and an adenosine diphosphate receptor blocker, *as early as possible* before angiography

2014 Myocardial revascularization
NSTE-ACS. Pretreatment with prasugrel in patients in whom coronary anatomy not known, is not recommended (Class III, LOE B)
STEMI. It is recommended to give P2Y12 inhibitors *at the time of first medical contact* (Class I, LOE B)

2015 NSTE-ACS
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known (Class III, LOE B).
As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated

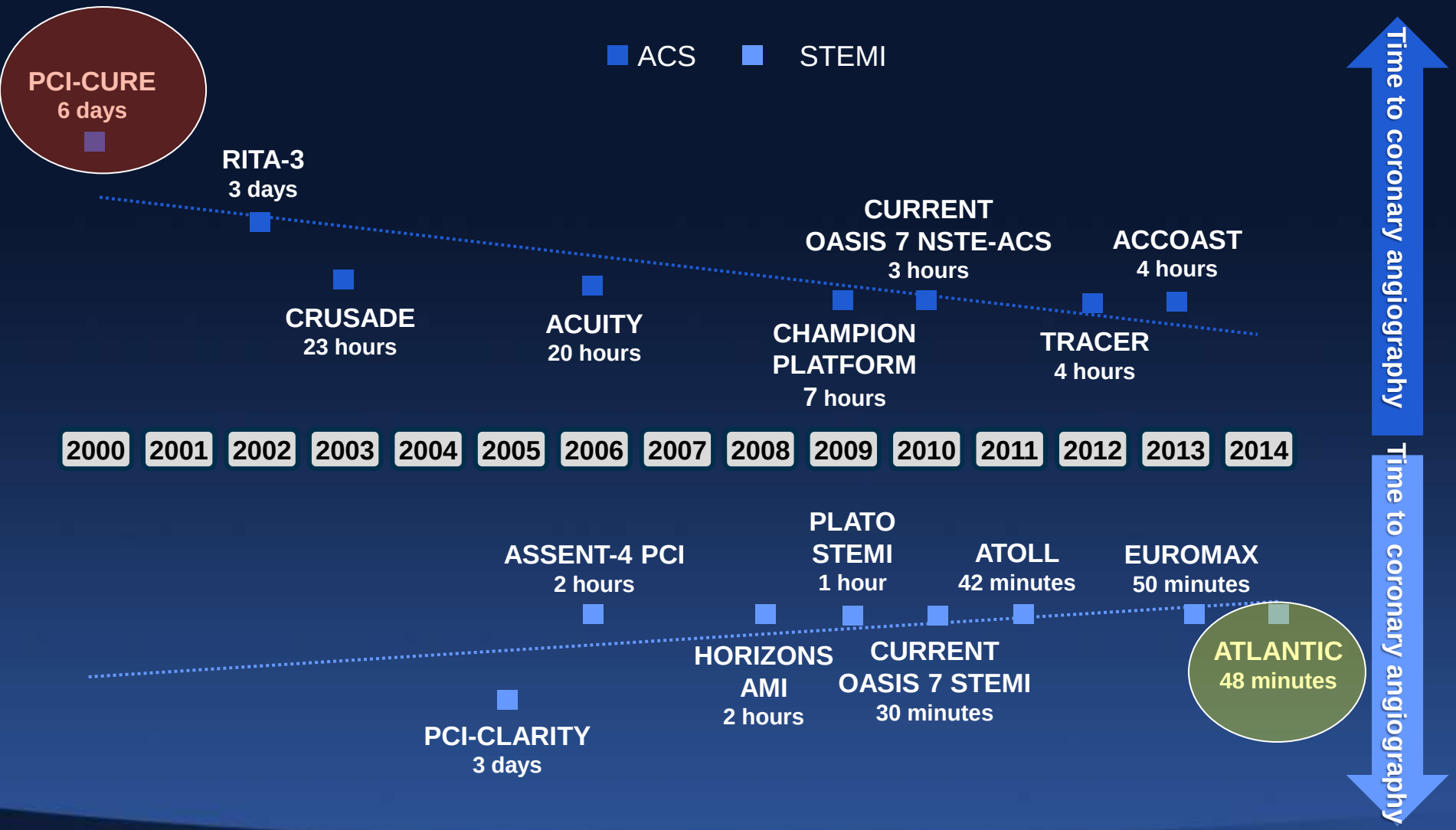


Capodanno D, Angiolillo DJ. Expert Review Cardiovasc Therapy 2016

Timing of $P2Y_{12}$ Inhibitor Initiation

- As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated.
- Based on the ACCOAST results, pretreatment with prasugrel is not recommended.

Time from Hospital Admission or First Medical Contact to Coronary Angiography in Studies of ACS & STEMI



ACS=acute coronary syndrome, STEMI=ST segment elevation myocardial infarction

Capodanno D, Angiolillo DJ. *Circ Cardiovasc Interv.* 2015;8:e002301.

Issues with Oral DAPT Pre-loading Before PCI

1. Stable CAD: Increased bleeding, no evidence of benefit
2. NSTEACS: Increased bleeding, some evidence of benefit in PCI triage subgroup, but requires 5-7 day delay in CABG subgroup (~10% of patients)
3. STEMI: No data, but delayed absorption, not active in first 2-4 hours

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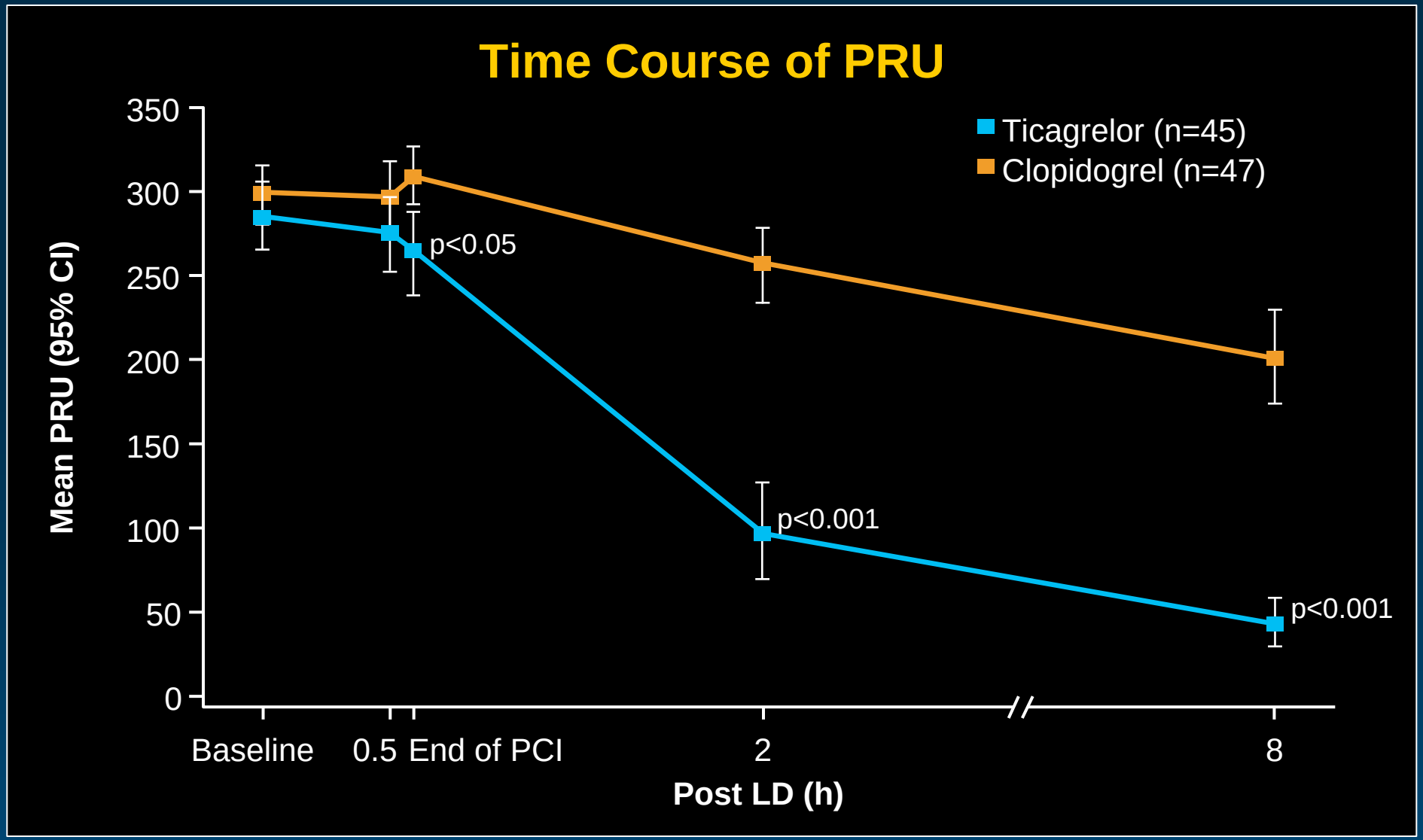
Ticagrelor: Trials of Pre-treatment vs No pre-treatment in NSTE-ACS

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.

Ad-Hoc PCI Trial

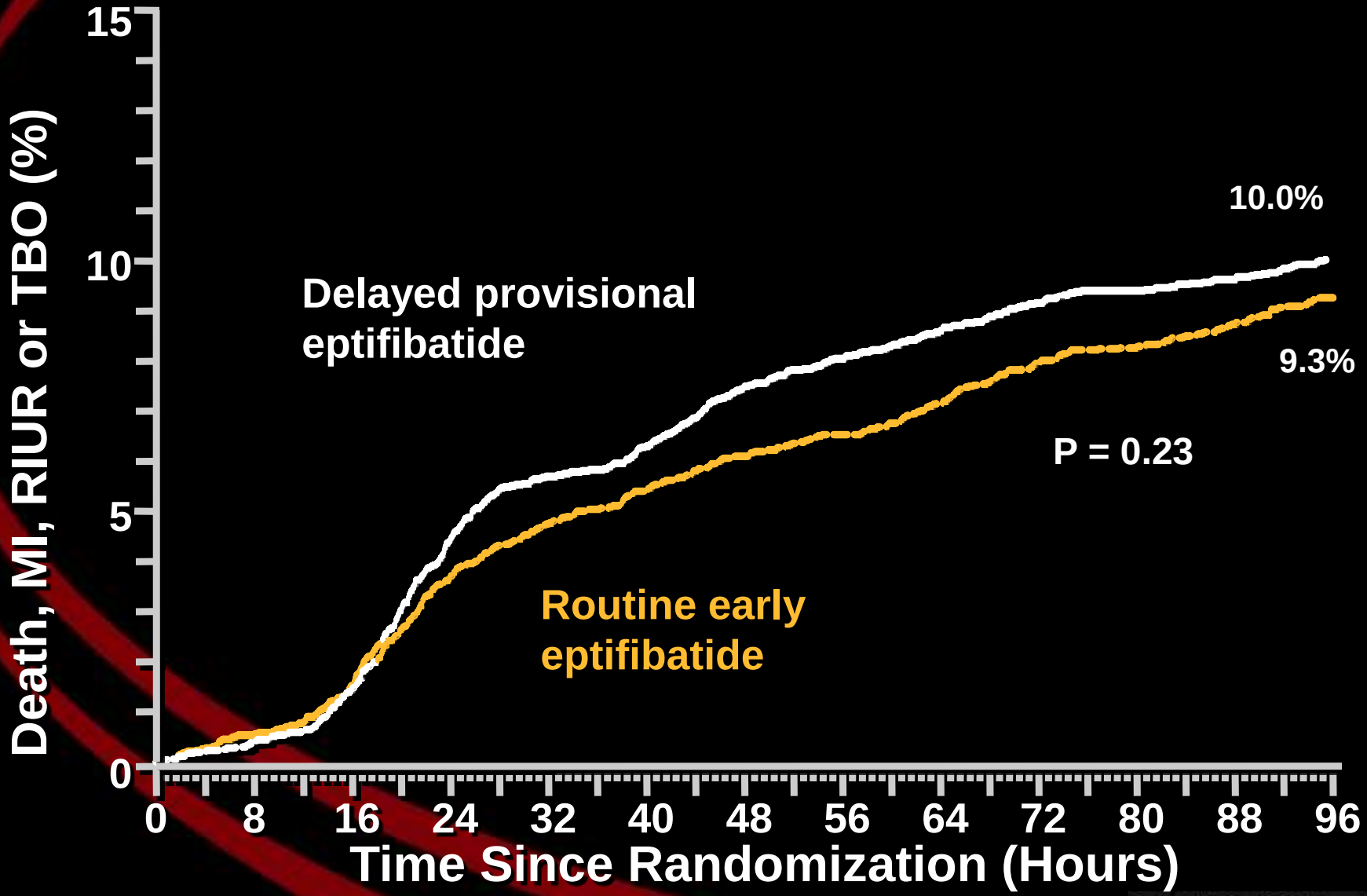


Angiolillo DJ & Mehran R. JACC 2016;67:603-13.

Pre-treatment vs No pre-treatment

A problem not just with P2Y12 inhibitors

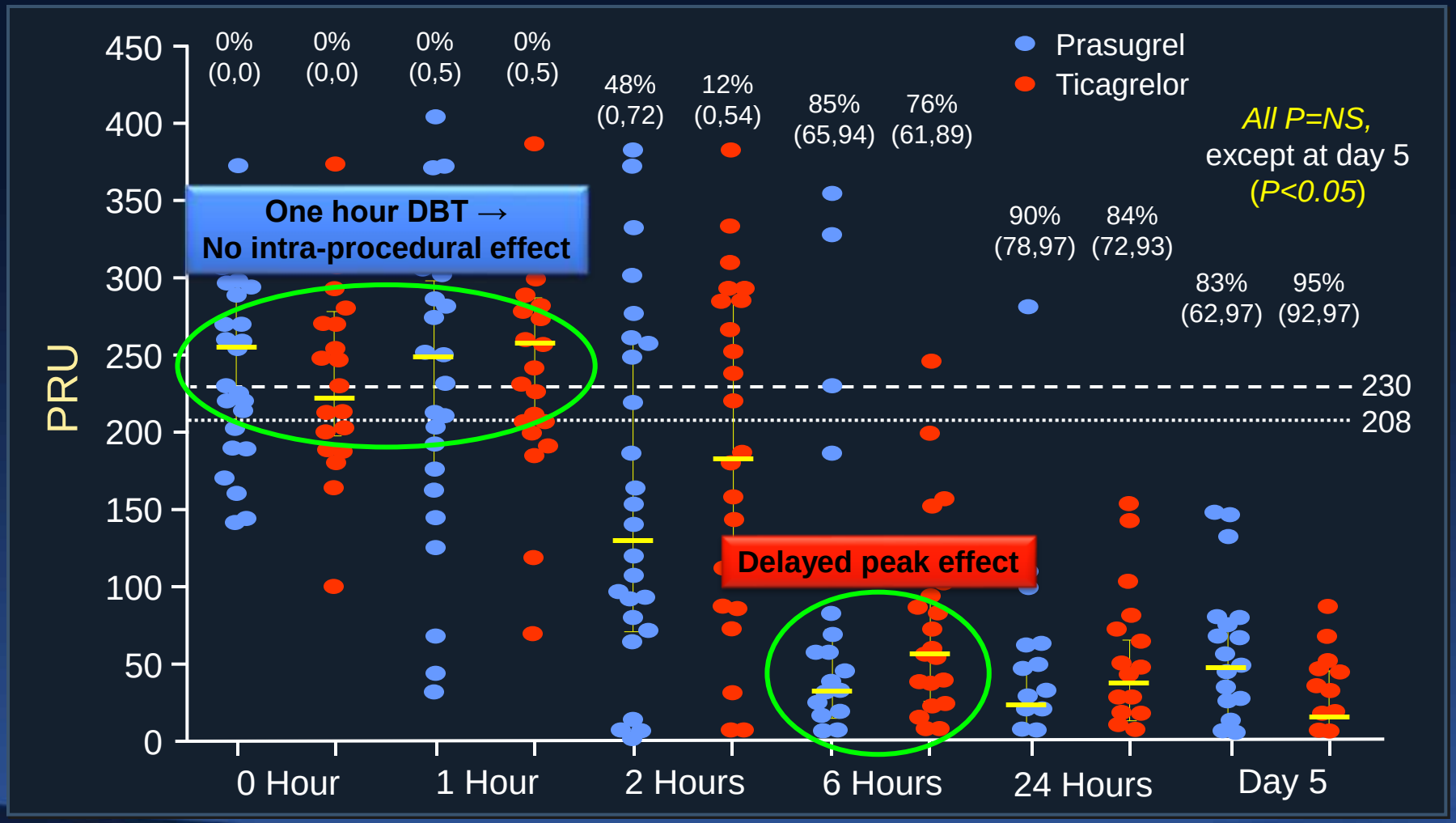
EARLY-ACS Trial: Primary Endpoint



EARLY ACS

Issues with Oral DAPT (Ticagrelor or Prasugrel) Pre-Loading in STEMI

- Delayed absorption
- PD effect no evident in the first 4-6 hours
- Contemporary times to CA are short
- Increased platelet activation in STEMI



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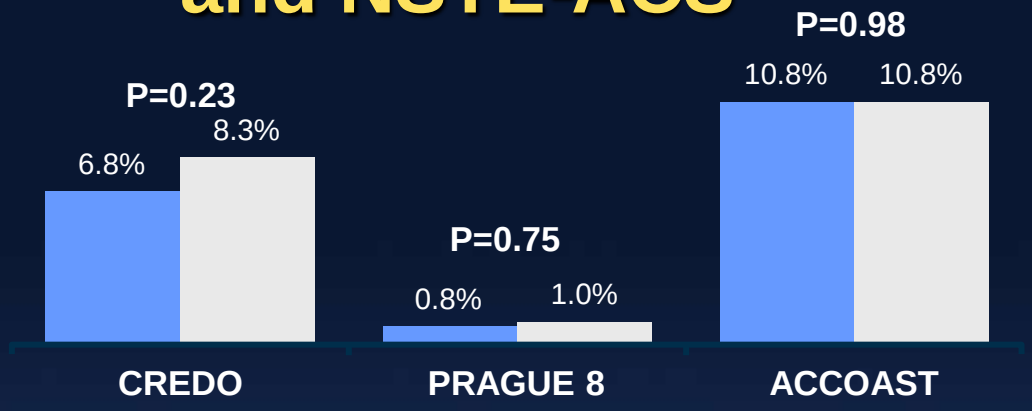
Alexopoulos D et al. *Circ Cardiovasc Interv.* 2012;5:797-804

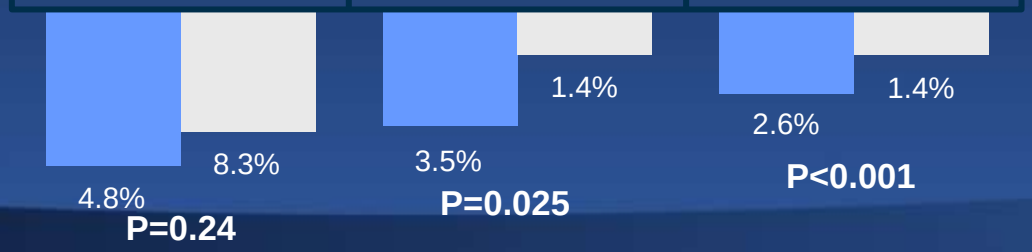
Studies of Pretreatment with Oral P2Y12 Receptor Inhibitors in Patients with Stable CAD and NSTE-ACS

Efficacy



	CREDO	PRAGUE 8	ACCOAST
Patients	2,116	1,028	4,033
Stable CAD	33%	87%	No
ACS	67%	13%	All NSTEMI
% PCI	86%	29%	69%
Drug	Clopidogrel 300 mg	Clopidogrel 600 mg	Prasugrel 30 mg
Follow-up	28 days	7 days	30 days
Efficacy endpoint displayed	D/MI/Urev	D/MI/CVA/Rev	CD/MI/CVA/Urev/GPI
Safetyendpoint displayed	TIMI major bleeding	All TIMI bleeding	All TIMI bleeding

Safety



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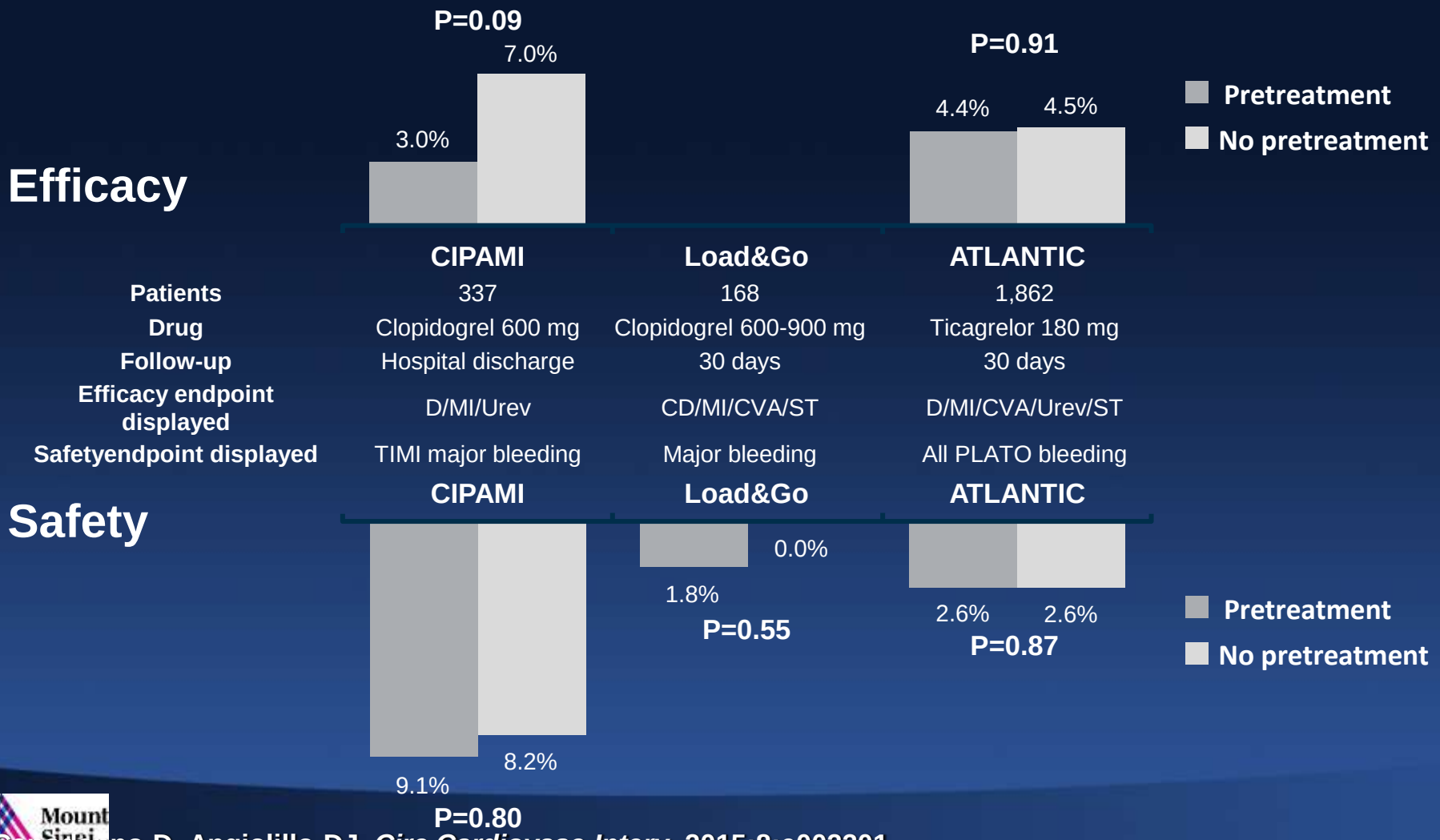
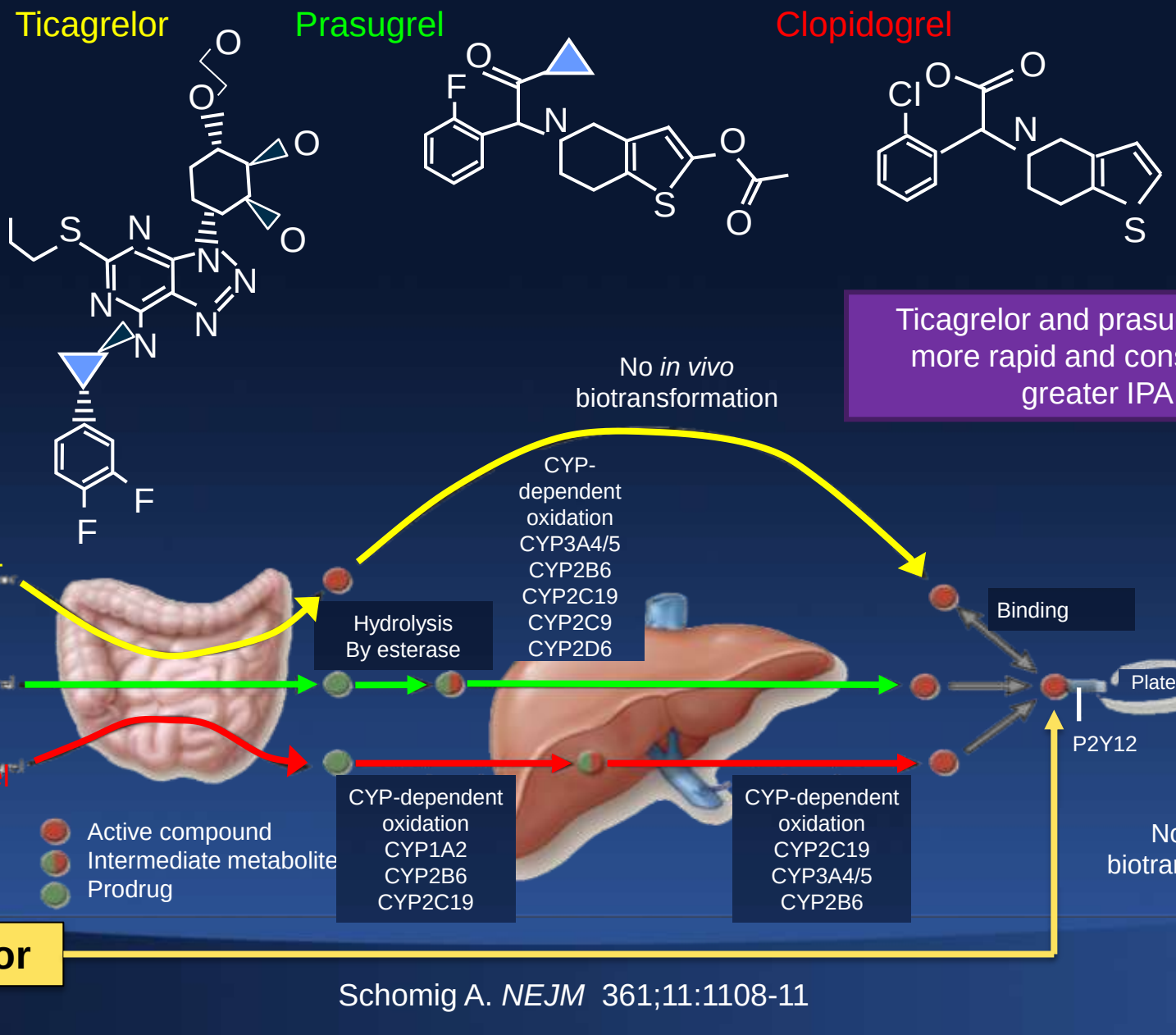
Capodanno D, Angiolillo DJ. Circ Cardiovasc Interv. 2015;8:e002301.

Studies of Pretreatment with Oral $P2Y_{12}$ Receptor Inhibitors in Patients with STEMI Undergoing Primary PCI



Capodanno D, Angiolillo DJ. *Circ Cardiovasc Interv.* 2015;8:e002301.

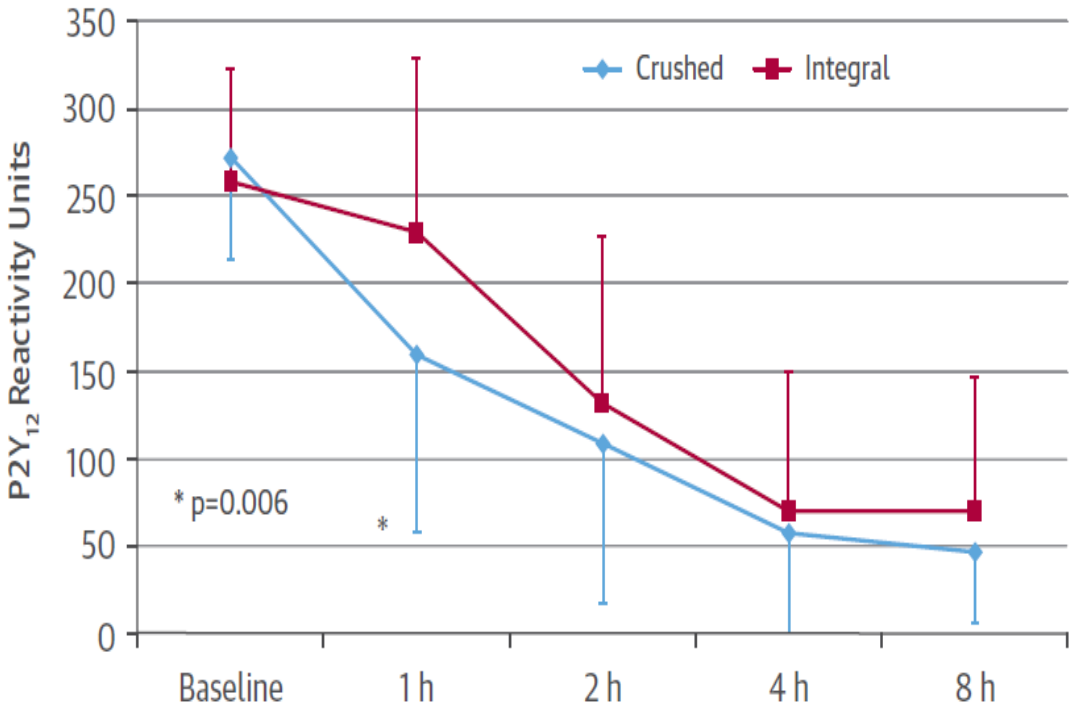
Metabolism of P2Y12 Receptor Blockers



Schomig A. *NEJM* 361;11:1108-11

Crushed ticagrelor tablet administration in STEMI patients is feasible and provides earlier platelet inhibition compared with standard integral tablets - The MOJITO Study -

FIGURE 1 Platelet Inhibition Over Time

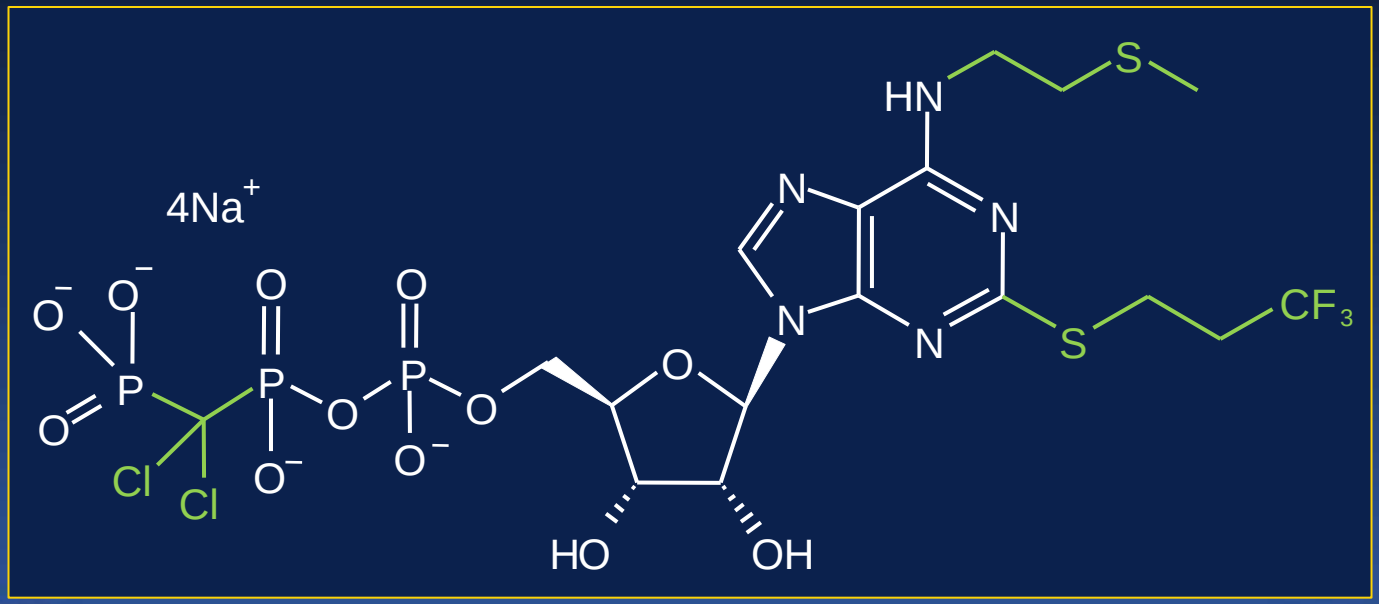


Platelet reactivity was assessed at baseline, 1, 2, 4, and 8 h after a 180-mg ticagrelor loading dose in patients treated by crushed tablets **(diamonds)** or integral tablets **(squares)**. Data are expressed as mean ± SD.

Parodi et al - JACC 2015

Cangrelor

- Direct $P2Y_{12}$ receptor antagonist (non thienopyridine)
  - ATP analogue; MW=800 Daltons
    - Parenteral administration
      - $T_{1/2}$ = 3 to 6 minutes
      - Offset = 60 minutes



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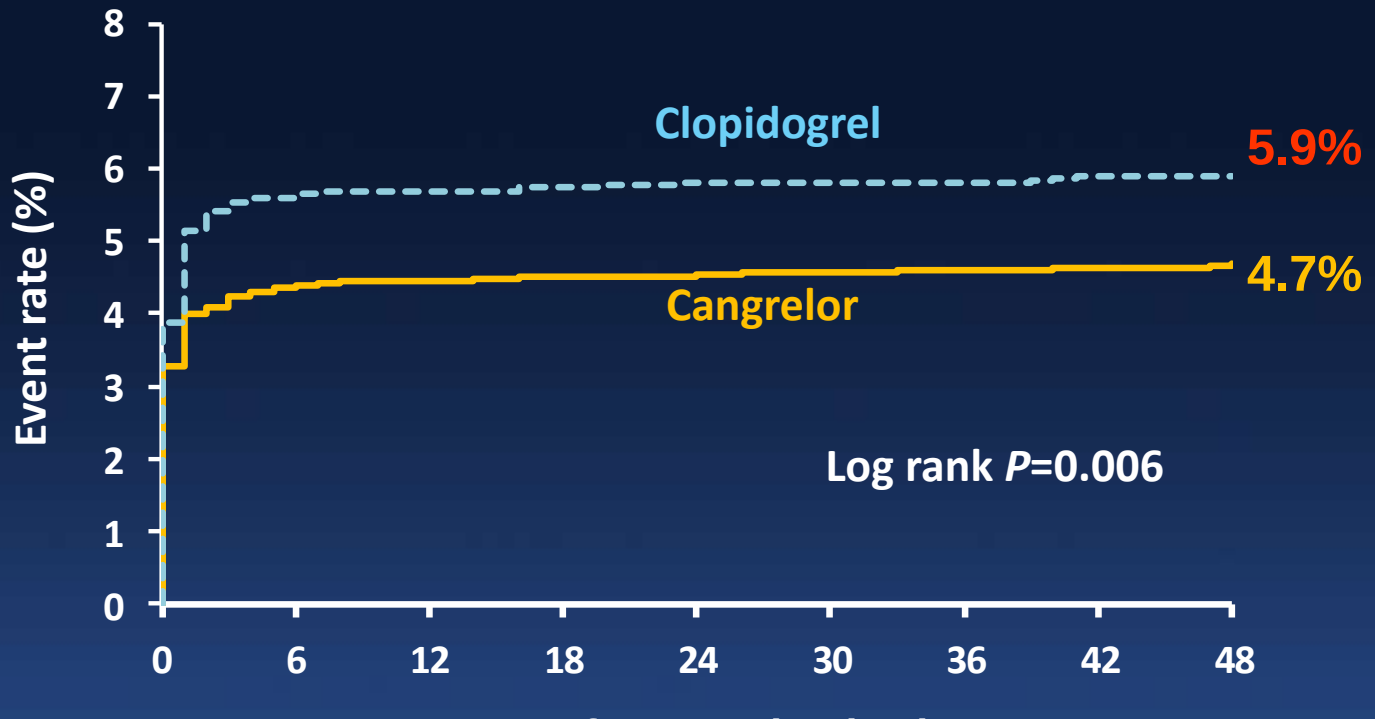
Angiolillo DJ et al. *J Thromb Thrombolysis* 2012;34:44-55

CHAMPION PHOENIX
Death/MI/IDR/Stent Thrombosis within 48 Hours



Patient at risk:

Cangrelor	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel	5470	5162	5159	5155	5152	5151	5151	5147	5147

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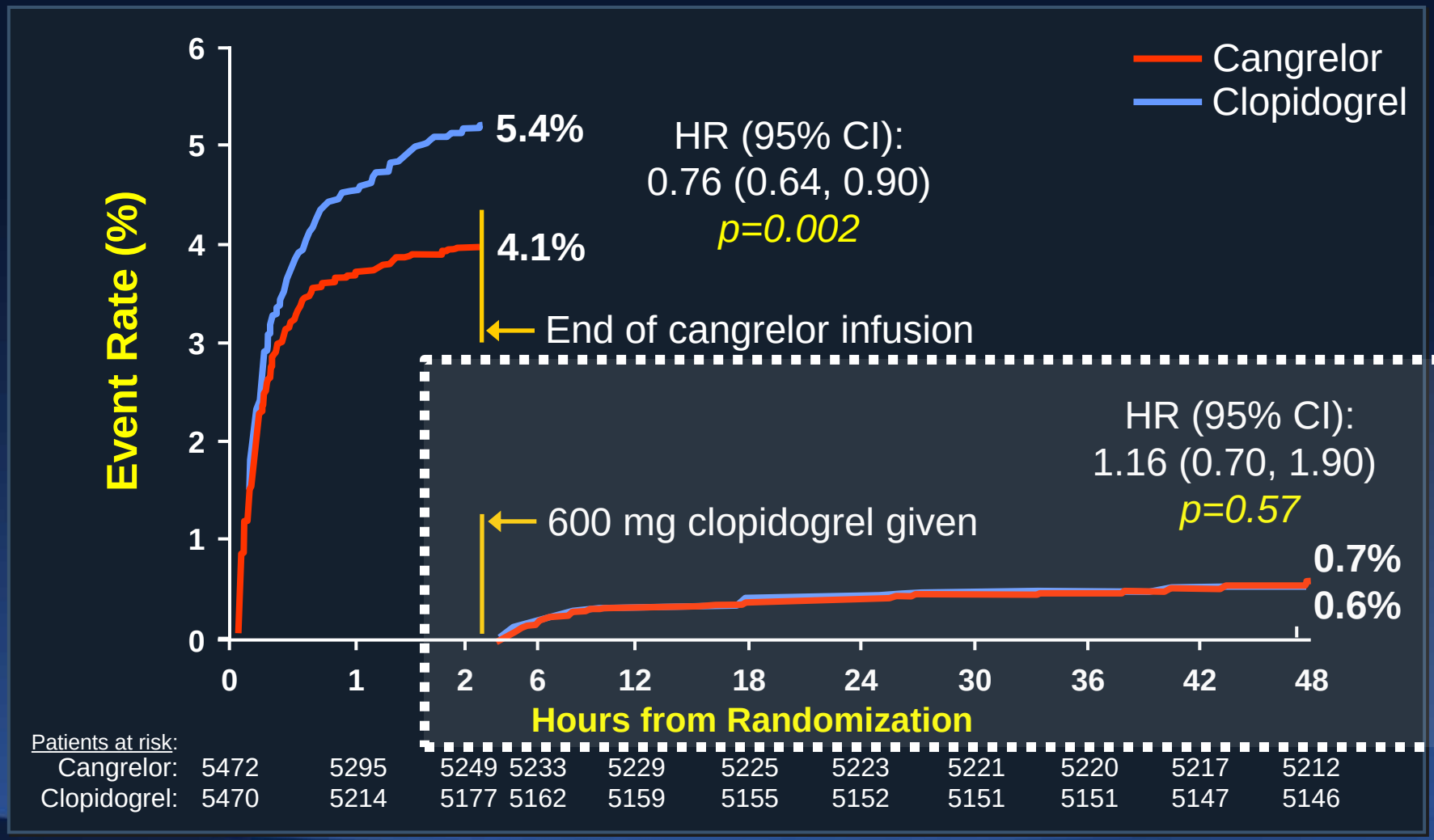
Bhatt DL et al. *N Engl J Med*. 2013;368:1303-1313.

Death, MI, IDR or ST:
Landmark analysis from Phoenix



Which treatment strategy is better for an ACS? Option #1 or #2?

#1

Quick-onset, high-potency, consistent platelet inhibition patway

PCI

Cangrelor

Ticagrelor or Prasugrel

Aspirin

Acute Phase

Chronic Phase

This is the best choice obviously!!

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