“Terapia Antiaggregante nella SCA”

Stresa, Maggio 2015

Renato Valenti

Cardiologia Invasiva 1 - AOUC - Firenze.

Overall

6.0

Cardiovascular disease

3.9

overall

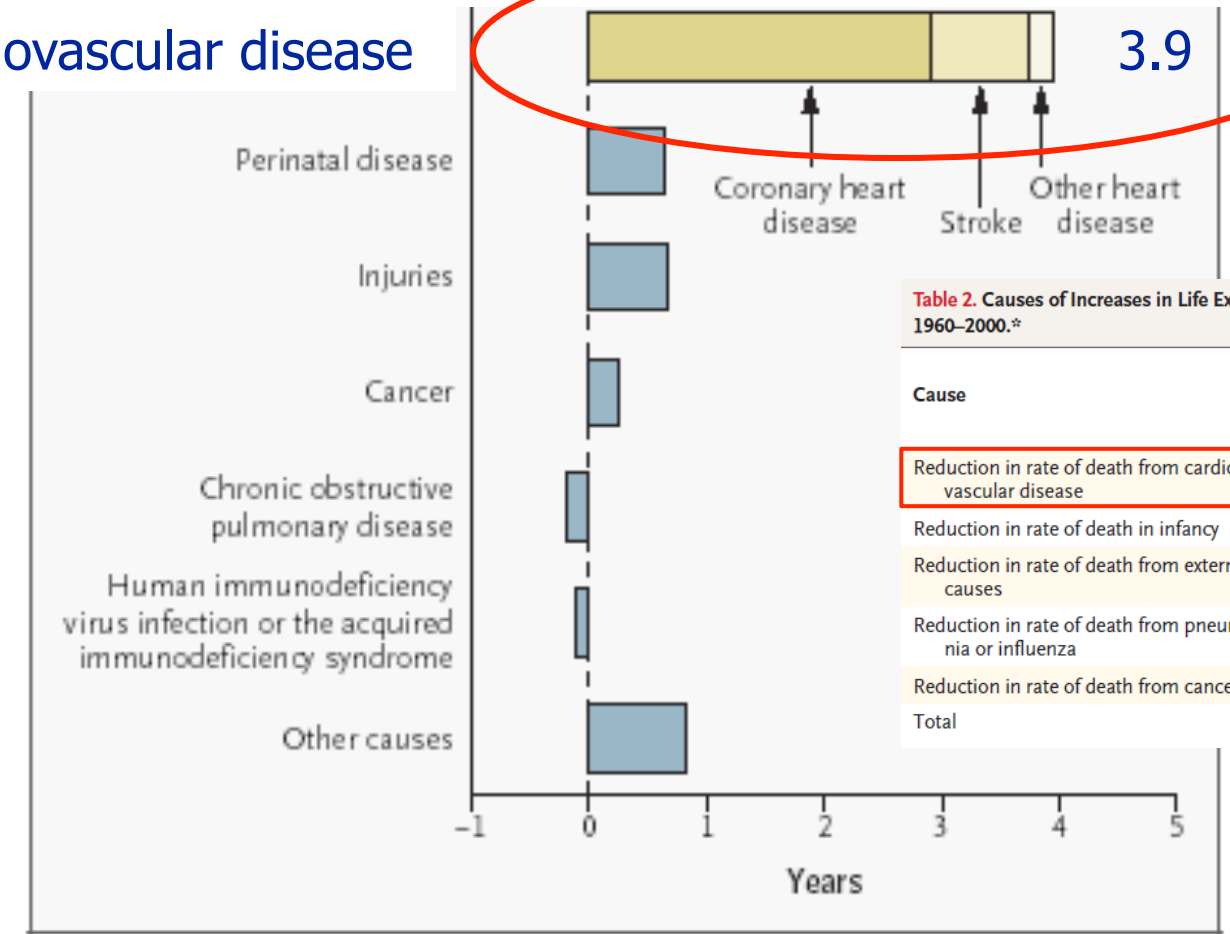


Table 2. Causes of Increases in Life Expectancy among Newborns, 1960–2000.*

Cause	Increase in Life Expectancy	Relative Contribution
	yr	%
Reduction in rate of death from cardiovascular disease	4.88	70
Reduction in rate of death in infancy	1.35	19
Reduction in rate of death from external causes	0.36	5
Reduction in rate of death from pneumonia or influenza	0.28	4
Reduction in rate of death from cancer	0.19	3
Total	6.97	100

N Engl J Med 2006

Figure 1. Change in U.S. Life Expectancy between 1970 and 2000.

Between 1970 and 2000, life expectancy in the United States increased by 6.0 years overall, with 3.9 years of the increase due to reductions in mortality from cardiovascular causes. The data are from the Centers for Disease Control and Prevention.

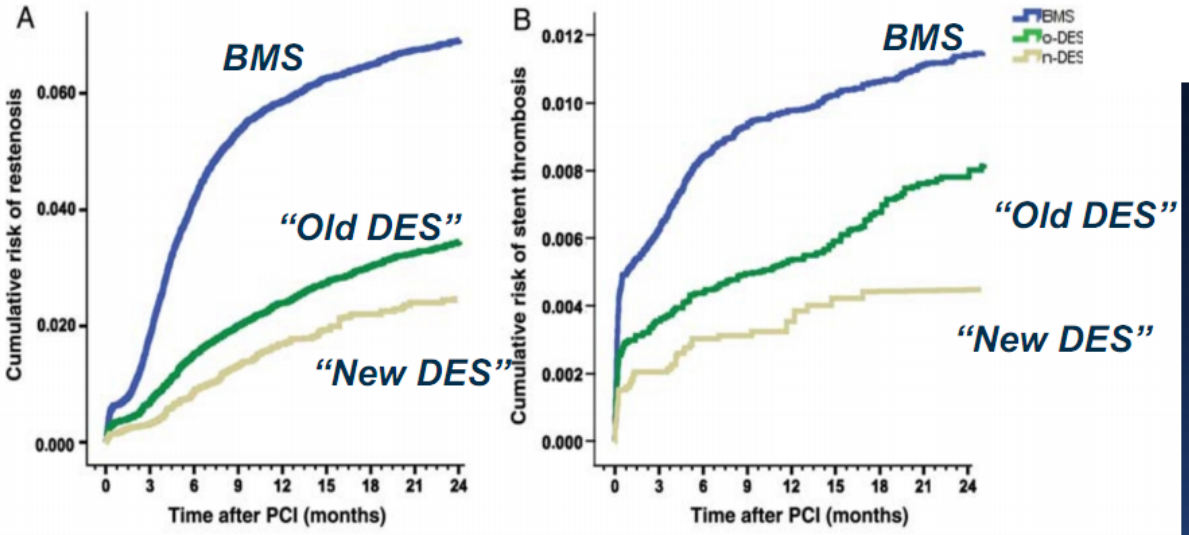
N Engl J Med 2003

New Generation of DES are Associated with a Better Clinical Outcome

SCAAR Registry (94,384 pts)

Adjusted Risks of Adverse Events at 2 yrs

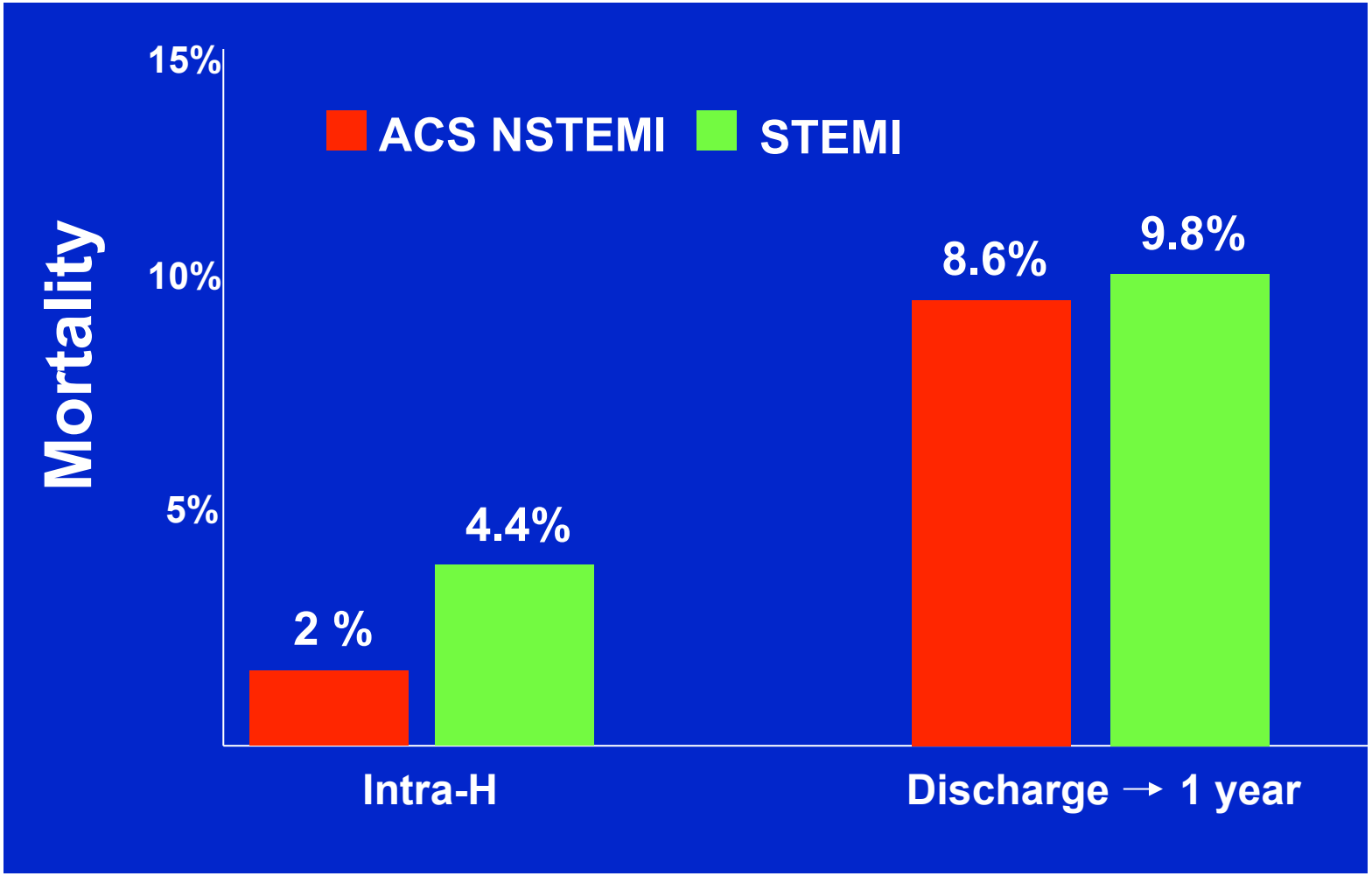
Restenosis *Definite Stent Thrombosis*



n at risk	0 months	6 months	12 months	18 months	24 months
BMS	64631	56070	47968	40539	32698
o-DES	19202	17862	16014	13517	10533
n-DES	10551	8092	4188	2005	847

Sarno et al. Eur Heart J 2012

IN-ACS Outcome Registry



Rizzello V et al. Acute Card Care 2012

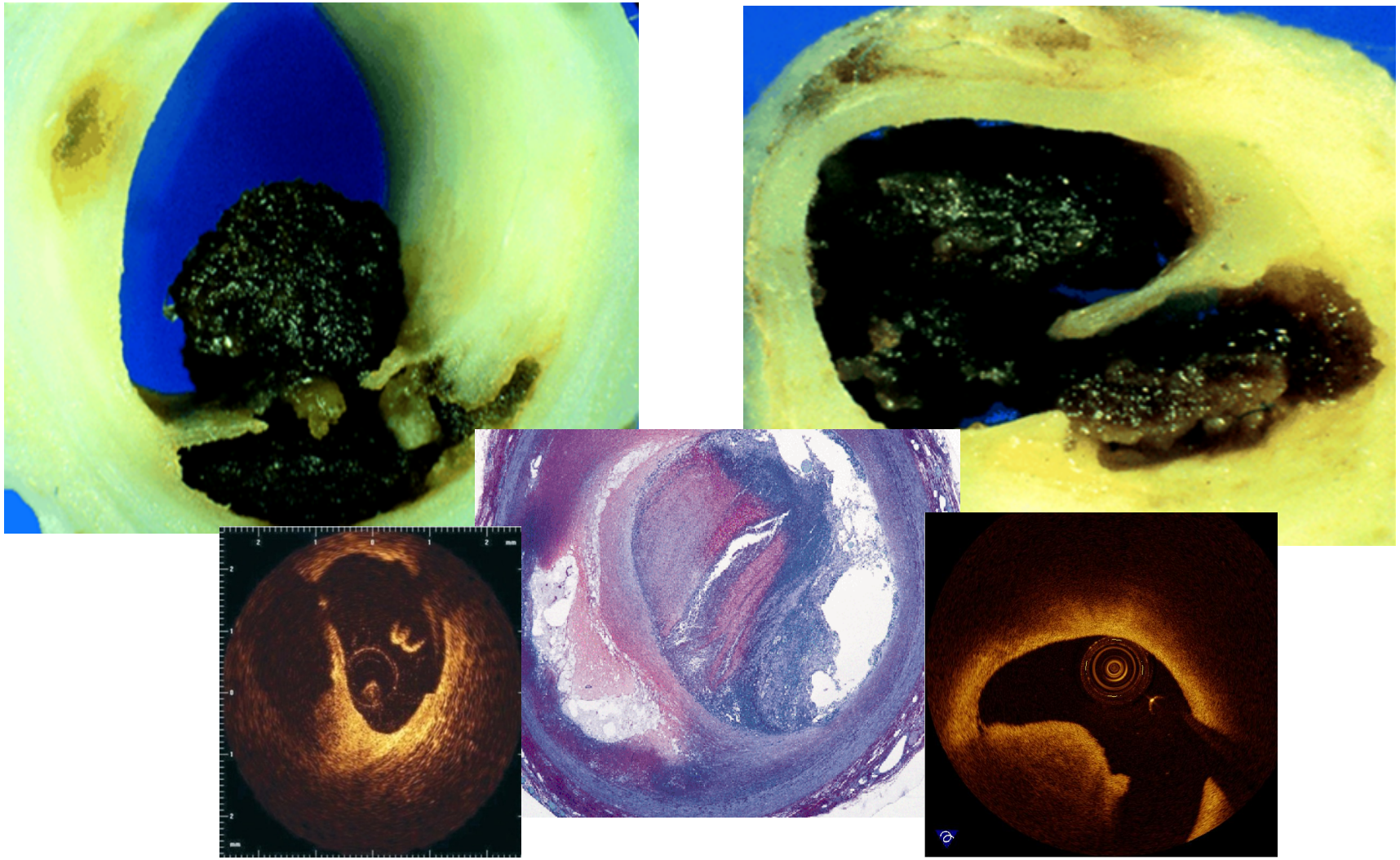
Current Key Points for Antiplatelet Therapy

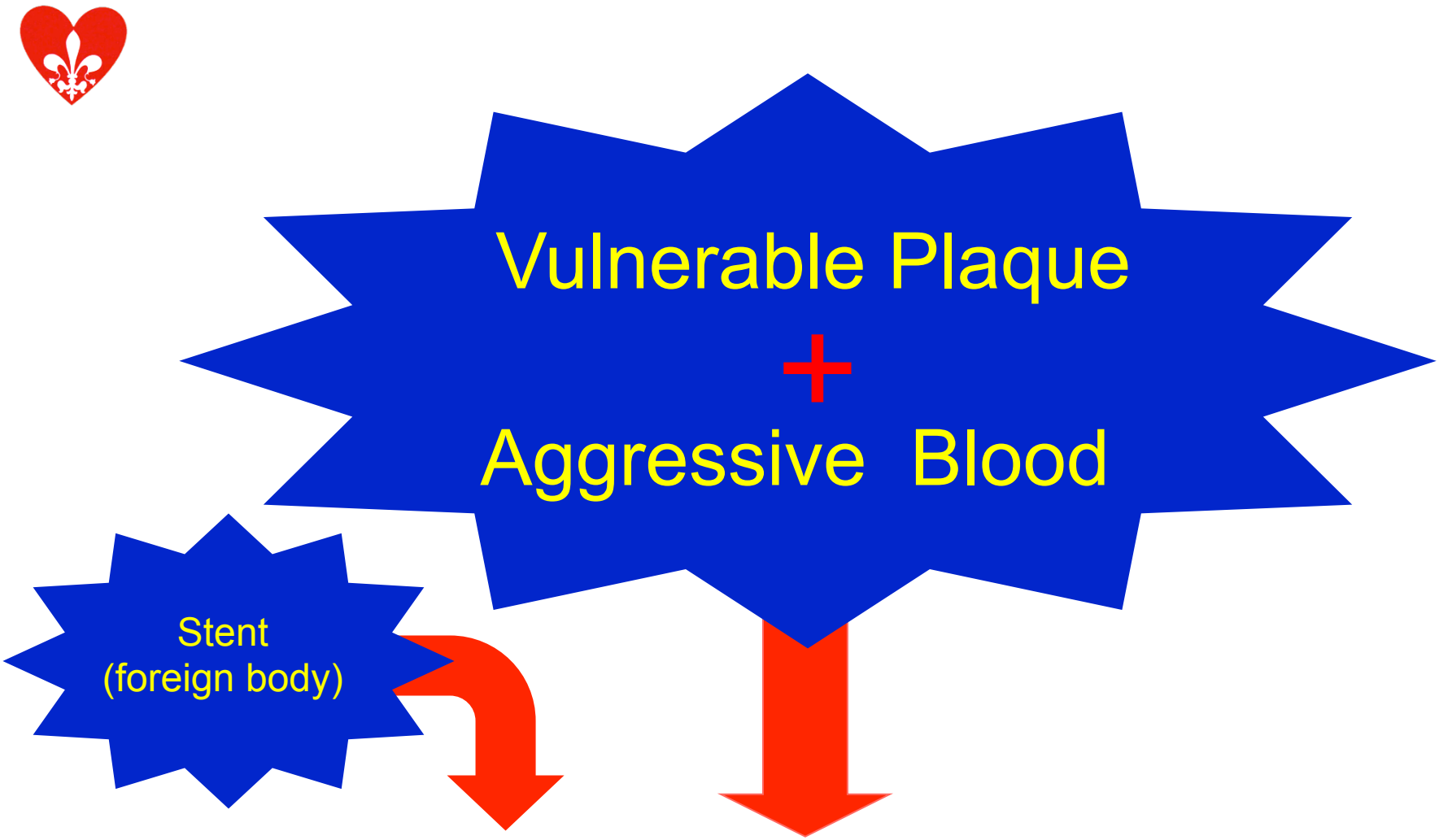
- Rationale for the antiplatelet therapy
- The difficult balance of “Ischemic” & “Bleeding” reduction
- Antiplatelet pretreatment for PCI (STEMI & other settings)
- The “SWITCH” among antiplatelet therapies
- Prolonged DAPT

Plaque Rupture with Thrombosis

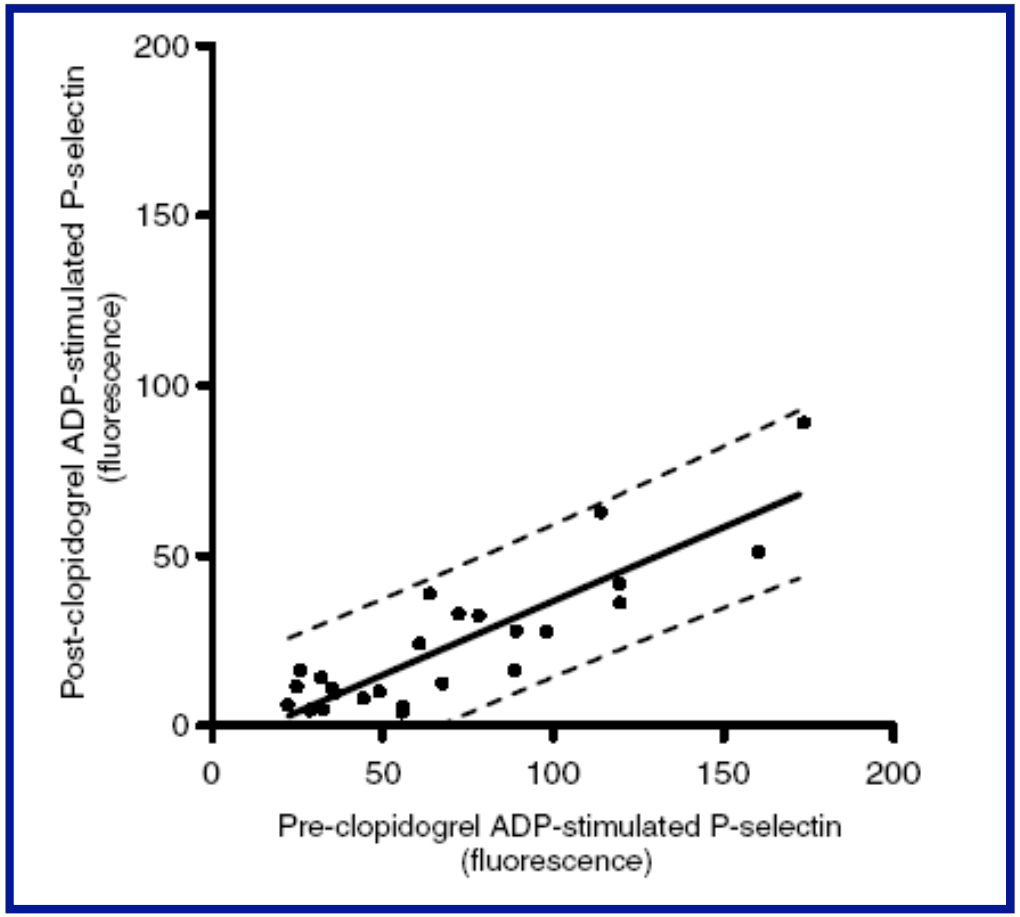
NSTEMI - UA

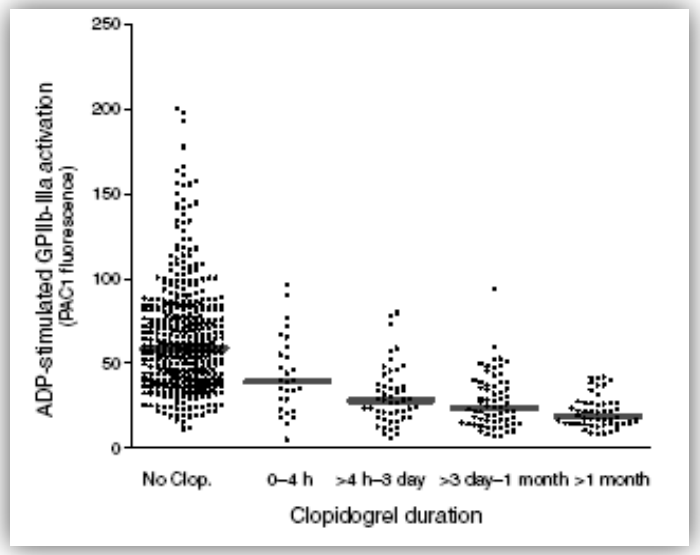
ST Elevaton MI




Vulnerable Plaque
+
Aggressive Blood
Stent
(foreign body)
Vulnerable Patient

Baseline Platelet Reactivity Affects Post-Treatment Platelet Reactivity





Michelson AD, et al. J Thromb Haemost 2007;5:75–81.

ORIGINAL CONTRIBUTION

High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events Among Patients With Acute Coronary Syndromes Undergoing PCI

Guido Parodi, MD
Rossella Marcucci, MD
Renato Valenti, MD
Anna Maria Gori, BS
Angela Migliorini, MD
Betti Giusti, BS
Piergiovanni Buonamici, MD
Gian Franco Gensini, MD
Rosanna Abbate, MD
David Antoniucci, MD

Context High residual platelet reactivity (HRPR) in patients receiving clopidogrel has been associated with high risk of ischemic events after percutaneous coronary intervention (PCI).

Objective To test the hypothesis that HRPR after clopidogrel loading is an independent prognostic marker of risk of long-term thrombotic events in patients with acute coronary syndromes (ACS) undergoing an invasive procedure and antithrombotic treatment adjusted according to the results of platelet function tests.

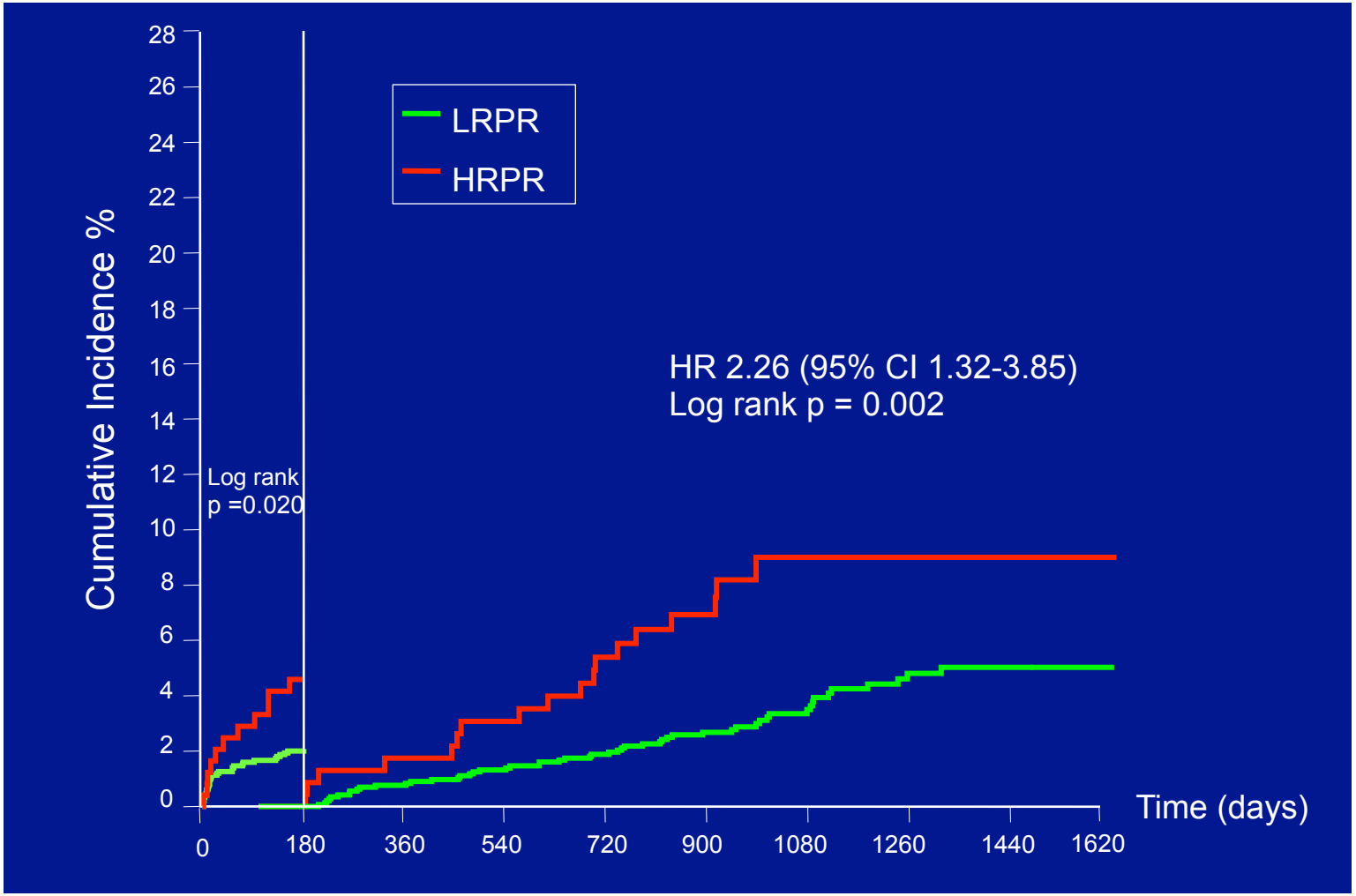
Design, Setting, and Patients Prospective, observational, referral center cohort study of 1789 consecutive patients with ACS undergoing PCI from April 2005 to April 2009 at the Division of Cardiology of Careggi Hospital, Florence, Italy, in whom platelet reactivity was prospectively assessed by light transmittance aggregometry.

Interventions All patients received 325 mg of aspirin and a loading dose of 600 mg of clopidogrel followed by a maintenance dosage of 325 mg/d of aspirin and 75 mg/d

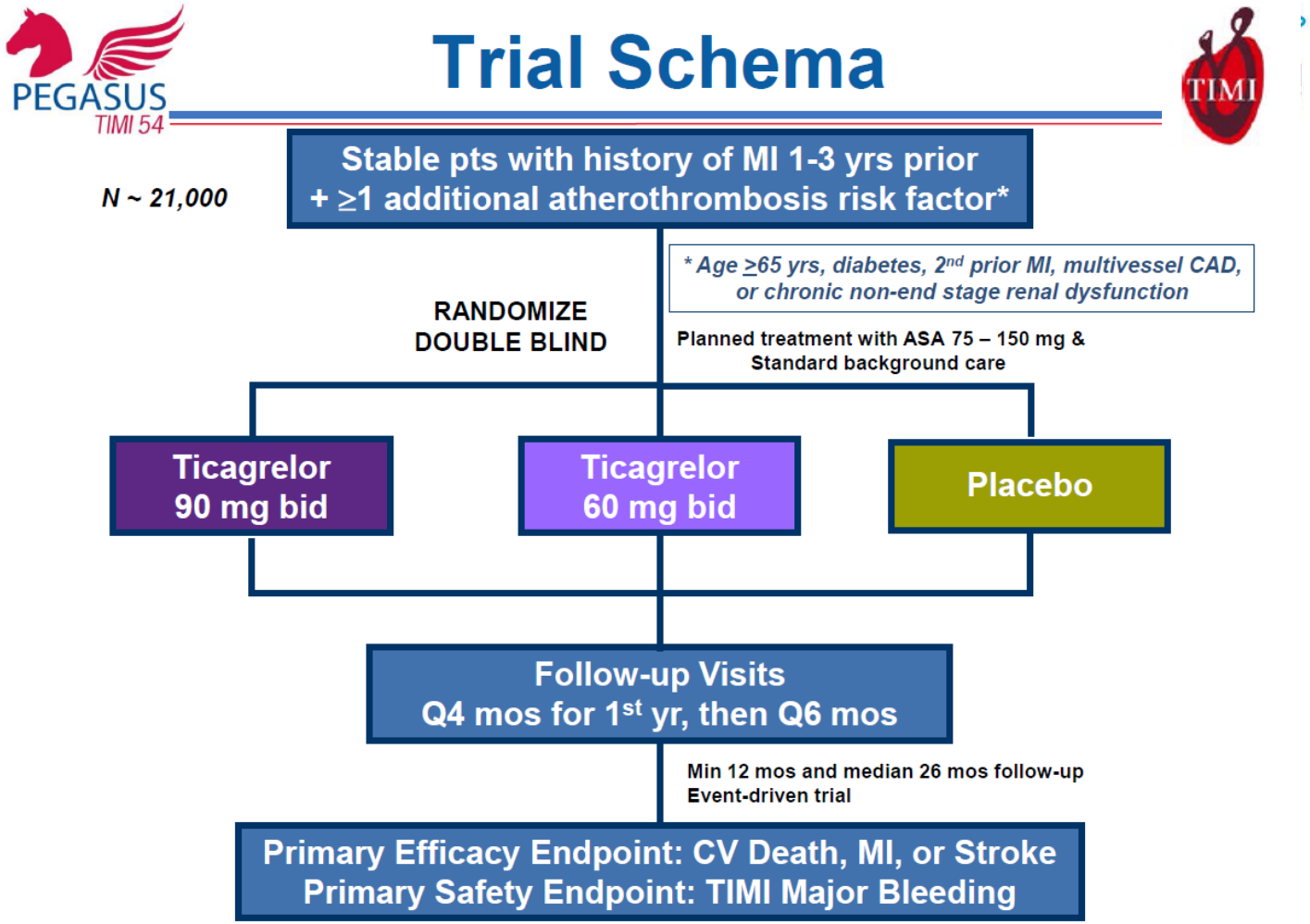
Trial Registration clinicaltrials.gov Identifier: NCT01231035

JAMA. 2011;306(11):1215-1223 www.jama.com

Cardiac Mortality in RECLOSE2-ACS



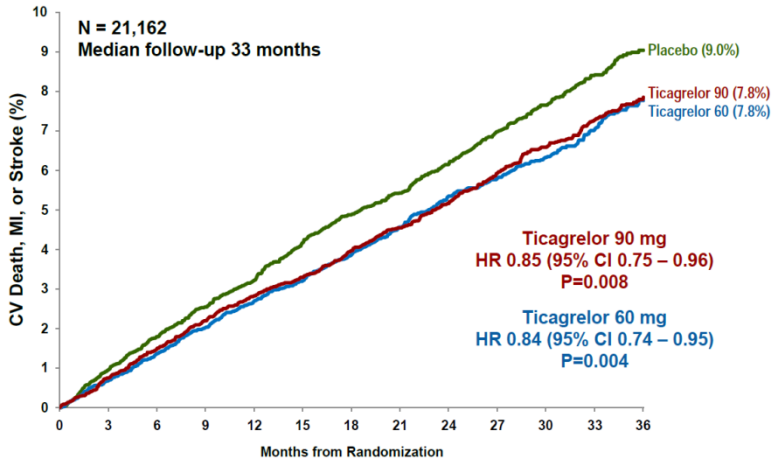
PEGASUS: Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction



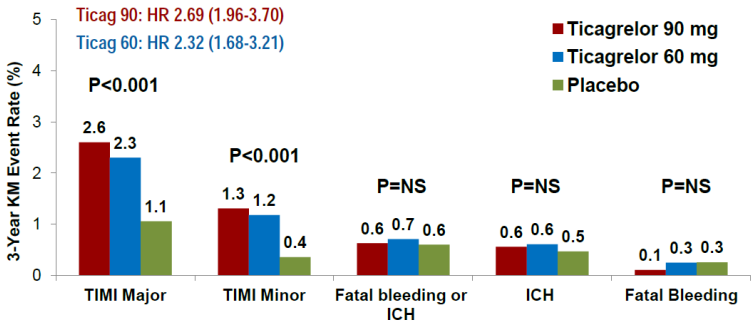
Bonaca MP et al . Am Heart J 2014

PEGASUS Trial: Outcome

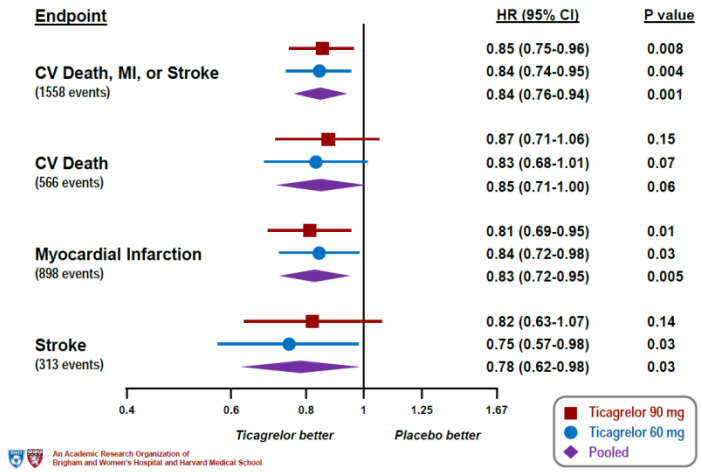
Primary Endpoint



Bleeding



Components of Primary Endpoint



Other Efficacy Outcomes

Outcome	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)	Ticagrelor 90 vs Placebo p-value	Ticagrelor 60 vs Placebo p-value
	3-yr KM rate (%)				
Coronary Death, MI, or Stroke	7.0	7.1	8.3	HR 0.82 P=0.002	HR 0.83 P=0.003
Coronary Death or MI	5.6	5.8	6.7	HR 0.81 P=0.004	HR 0.84 P=0.01
Coronary Death	1.5	1.7	2.1	HR 0.73 P=0.02	HR 0.80 P=0.09
Death from any cause	5.2	4.7	5.2	HR 1.00 P=0.99	HR 0.89 P=0.14

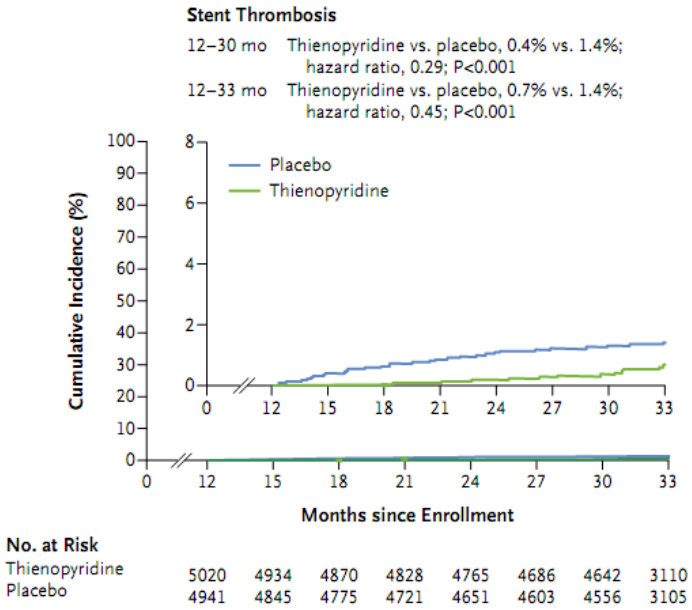
Bonaca MP et al. N Engl J Med. 2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

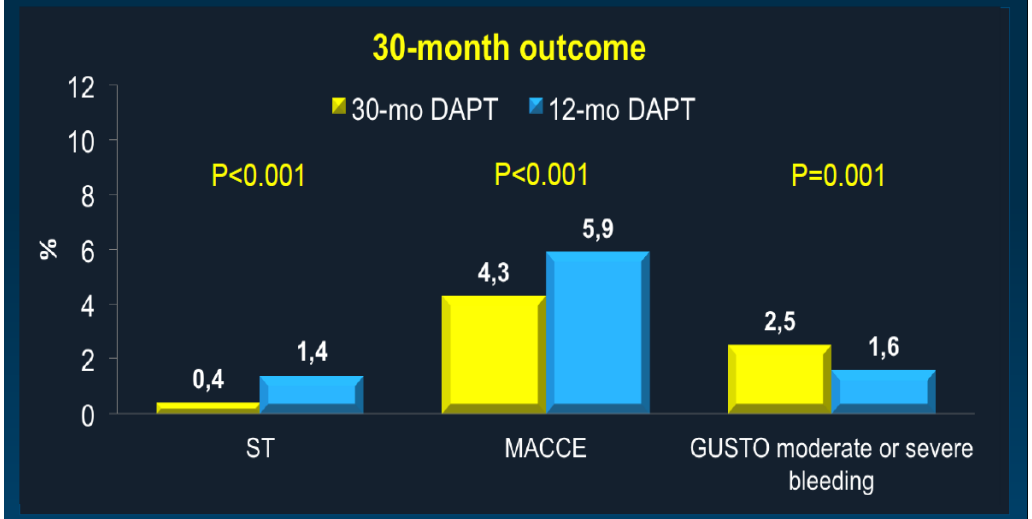
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massa



DAPT: 30 months versus 12 months of DAPT after PCI

9961 patients with DES after 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin with no events randomly assigned to continue thienopyridine treatment or to receive placebo



55% of the MI benefit was not related to stent thrombosis

Ticagrelor and non P2Y12 Effects
Pleiotropic action and drug interaction

In PLATO, ticagrelor slightly but significantly reduced the incidence of cardiovascular (4.0% vs. 5.1%) and total (4.5% vs. 5.9%) mortality compared with clopidogrel, whereas no significant reduction in cardiovascular (2.1% vs. 2.4%) or total (3.0% vs. 3.2%) mortality was observed with prasugrel versus clopidogrel in TRITON (3,4). In addition, a greater incidence of dyspnea and ventricular pauses was observed with ticagrelor (3).

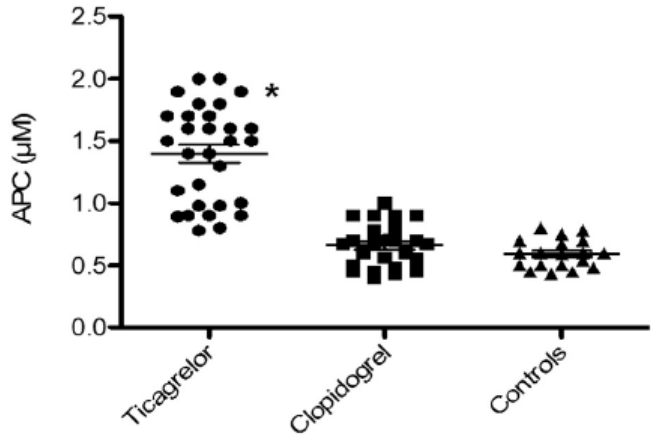
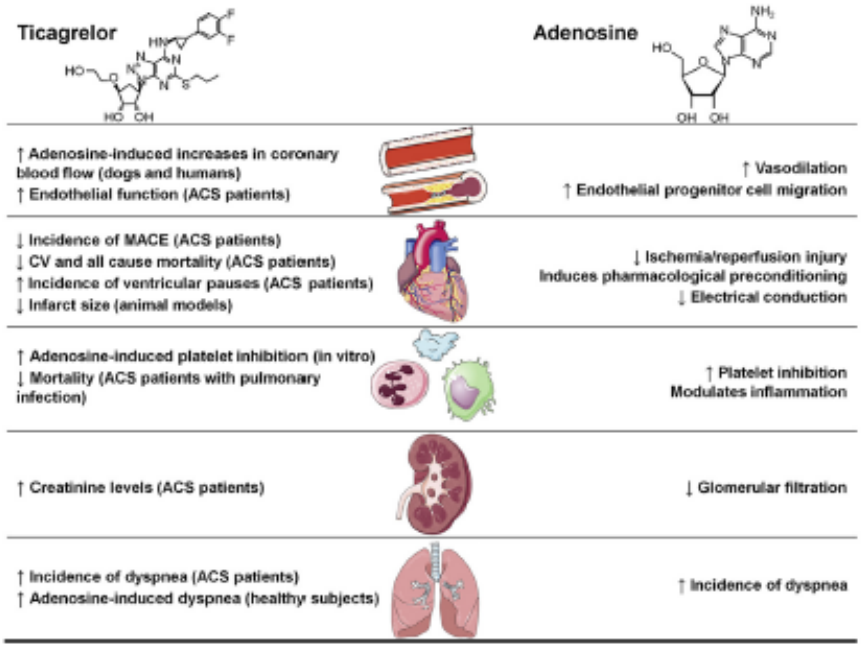


Figure 1 Comparisons of APC in Ticagrelor, Clopidogrel, and Control Groups

*Indicates $p < 0.01$ for ticagrelor group versus control group or clopidogrel group. APC = adenosine plasma concentration.

Bonello L et al. J Am Coll Cardiol 2014

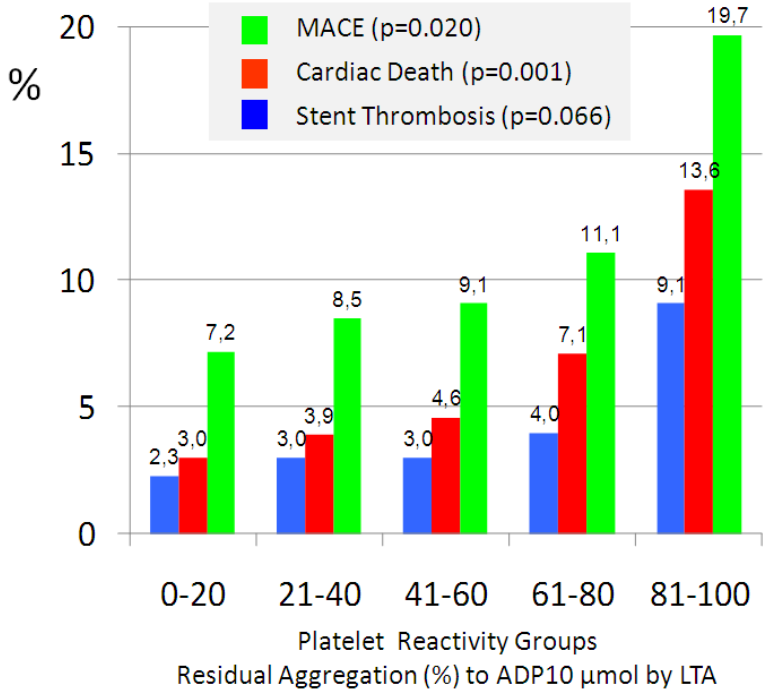


Selection of Effects Mediated by Ticagrelor and Adenosine

Cattaneo M et al. J Am Coll Cardiol 2014

Platelet Reactivity Parallels Ischaemic and Bleeding Events

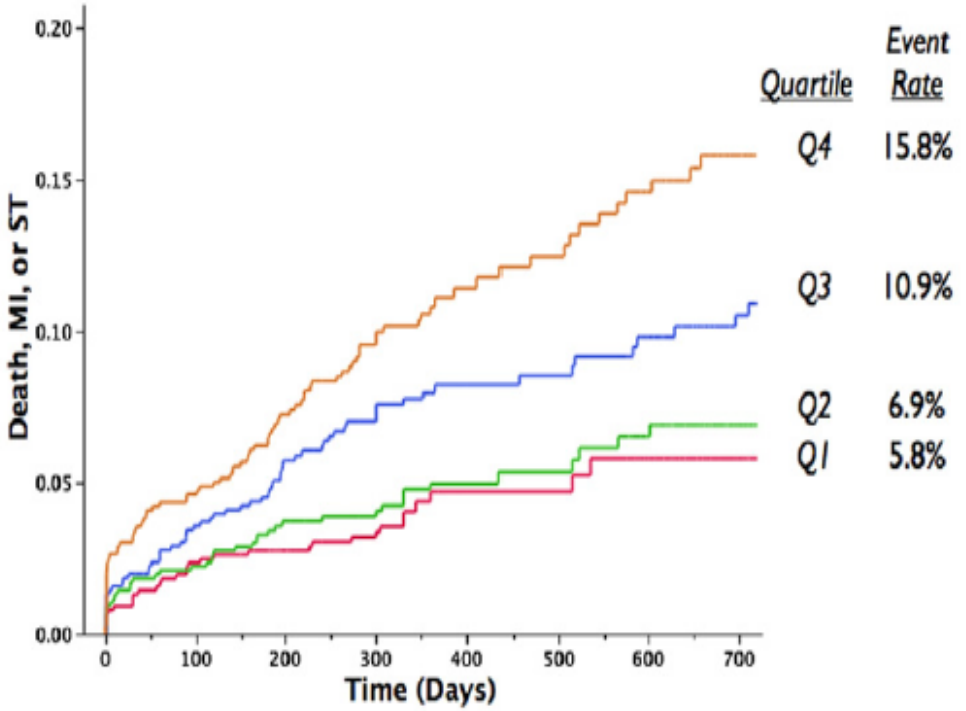
Two-Year Outcome
Insights from the RECLOSE2-ACS Study



Valenti R. et al. J Am Coll Cardiol. 2012;60(17_S)
J Am Coll Cardiol 2011;58:1945-54

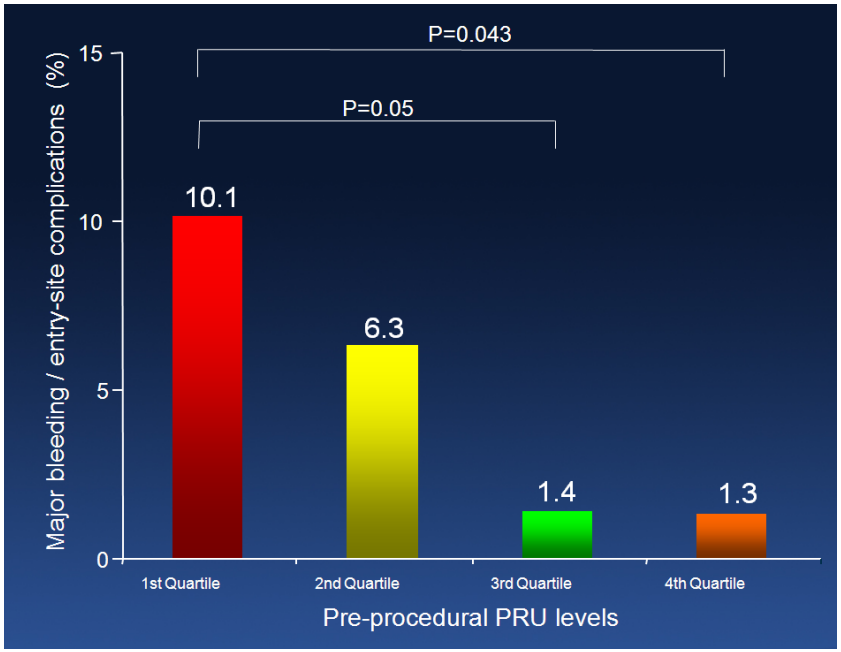
Impact of Platelet Reactivity on Clinical Outcomes After Percutaneous Coronary Intervention

A Collaborative Meta-Analysis of Individual Participant Data



Platelet Reactivity Parallels Ischaemic and Bleeding Events

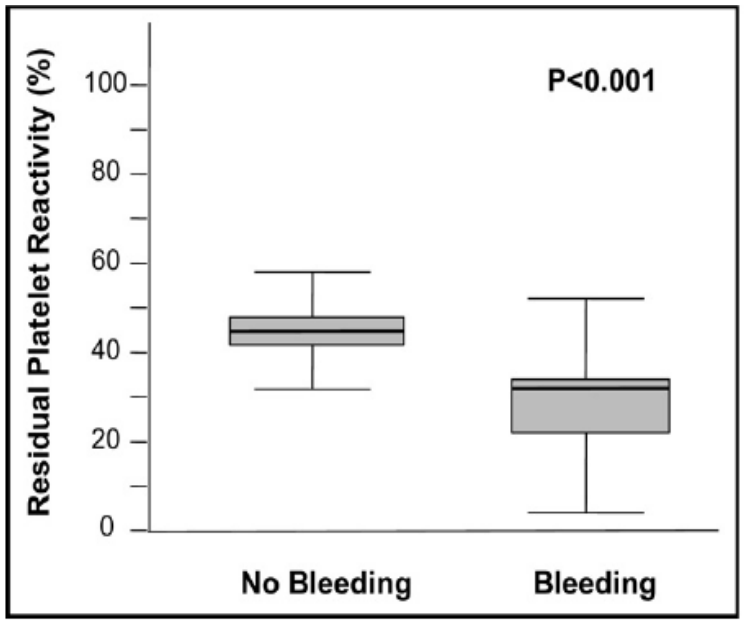
ARMYDA BLEEDS



Patti G et al. Am J Cardiol 2011;107:995-1000

Residual Platelet Reactivity, Bleedings, and Adherence to Treatment in Patients Having Coronary Stent Implantation Treated With *Prasugrel*

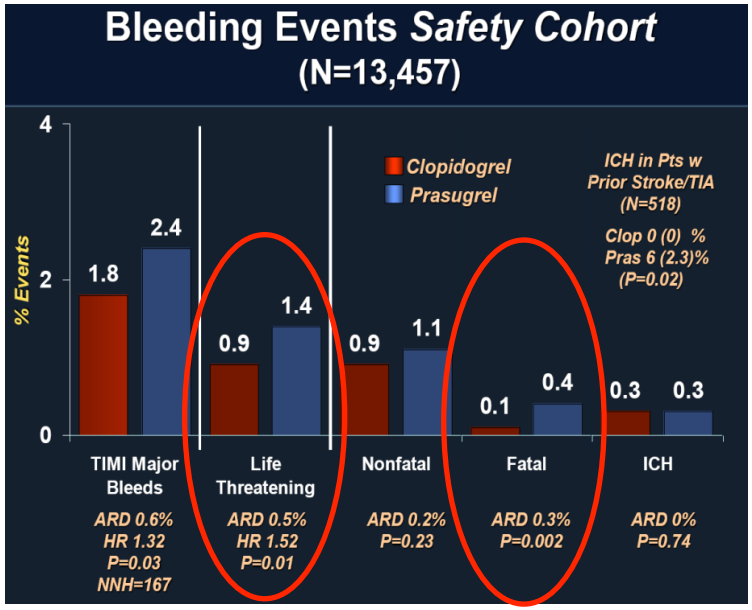
Guido Parodi, MD, PhD*, Benedetta Bellandi, MD, Francesco Venditti, MD, Nazario Carrabba, MD, Renato Valenti, MD, Angela Migliorini, MD, Silvia Grassellini, RN, Erica Ramazzotti, RN, and David Antoniucci, MD

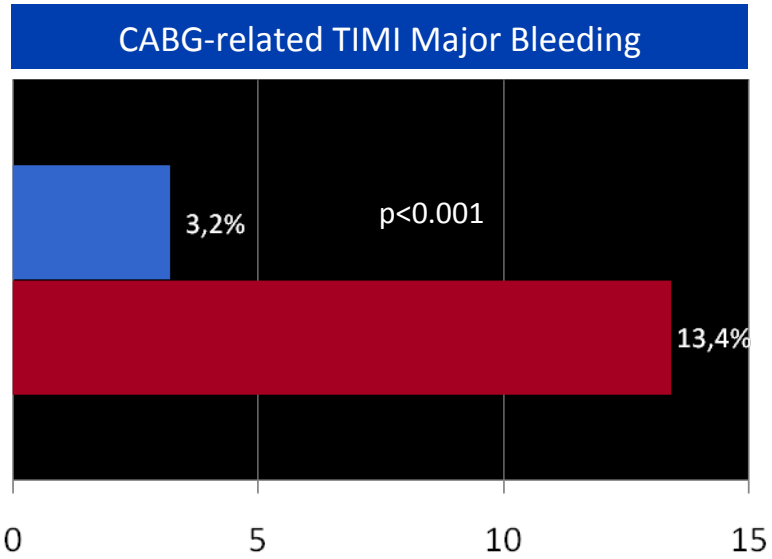


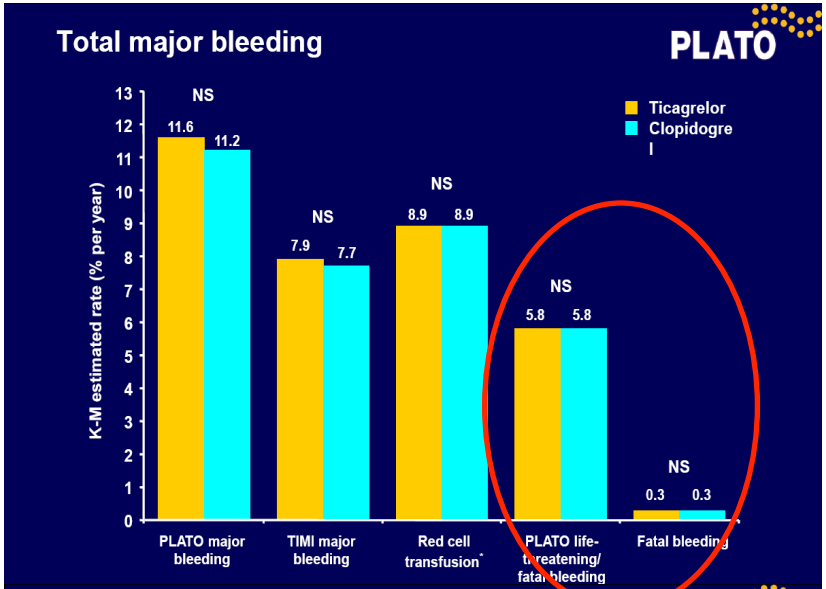
At multivariable analysis female gender (odds ratio 2.20, 1.08 to 4.45, p = 0.029) and low residual platelet reactivity (odds ratio 0.91, 0.88 to 0.95, p = 0.001) were the only independent predictors of bleeding events.

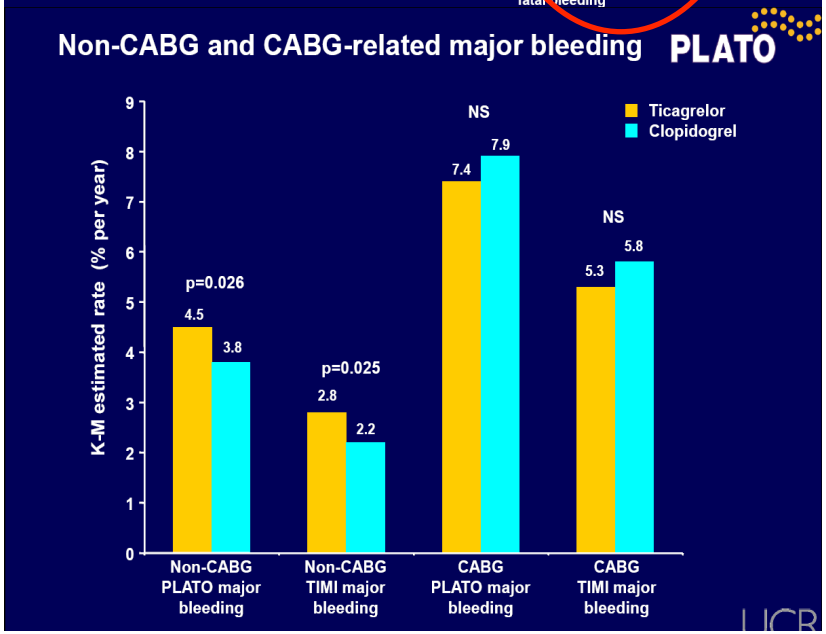
Am J Cardiol. 2012 Jan 15;109(2):214-8

Bleeding Events in TRITON-TIMI 38 & PLATO

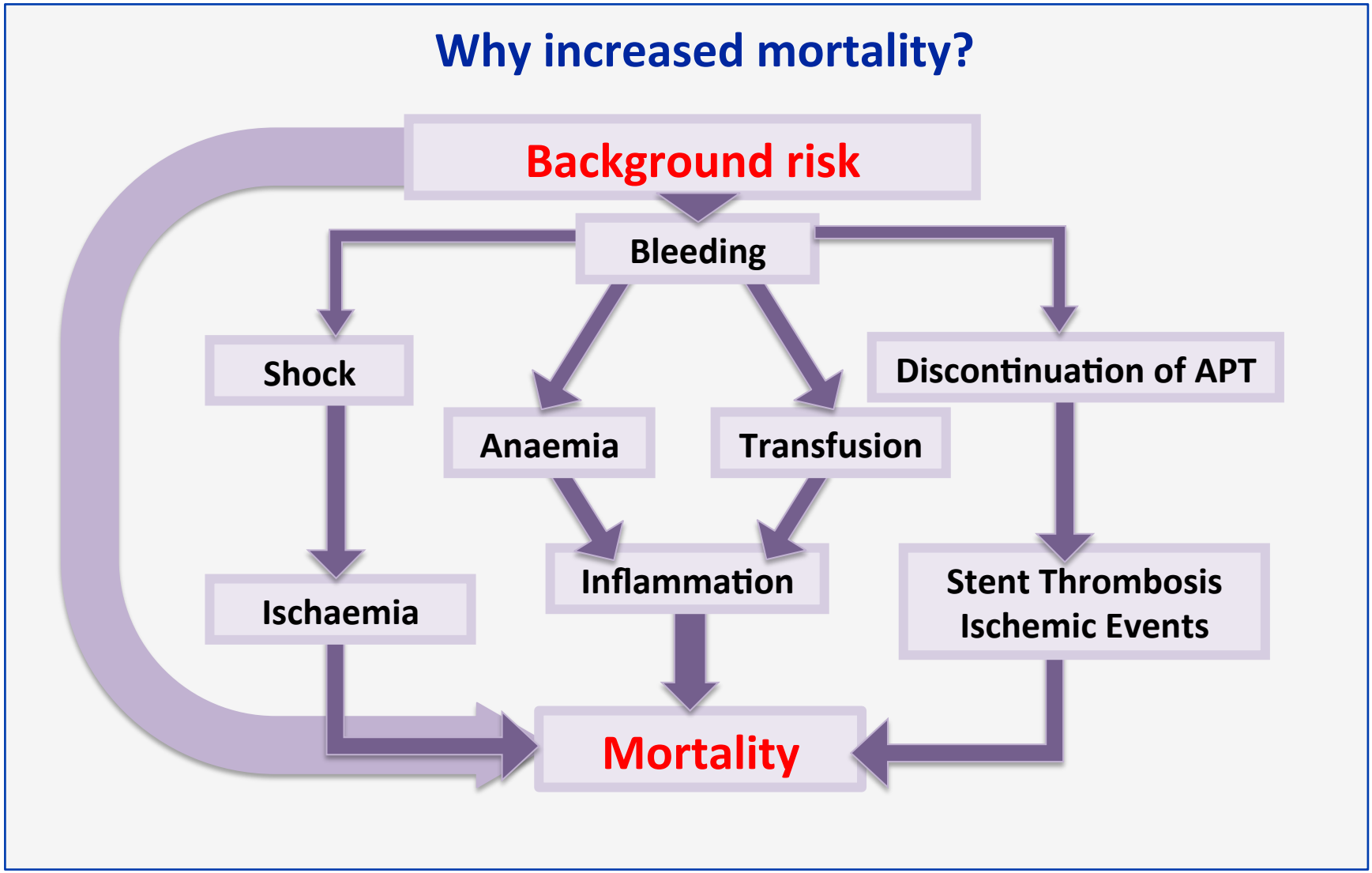




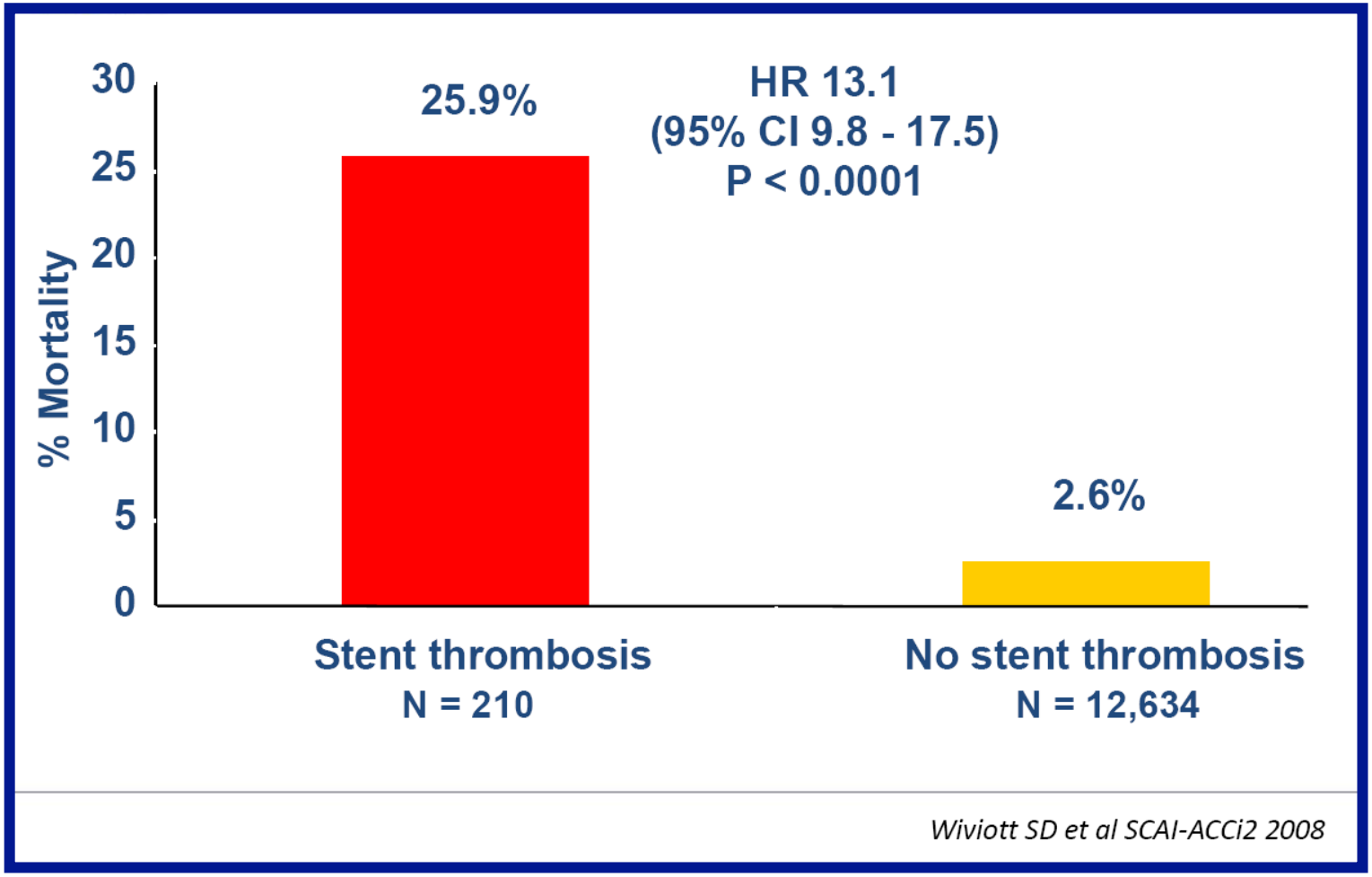




Hypothetical Mechanisms Linking Bleeding and Mortality

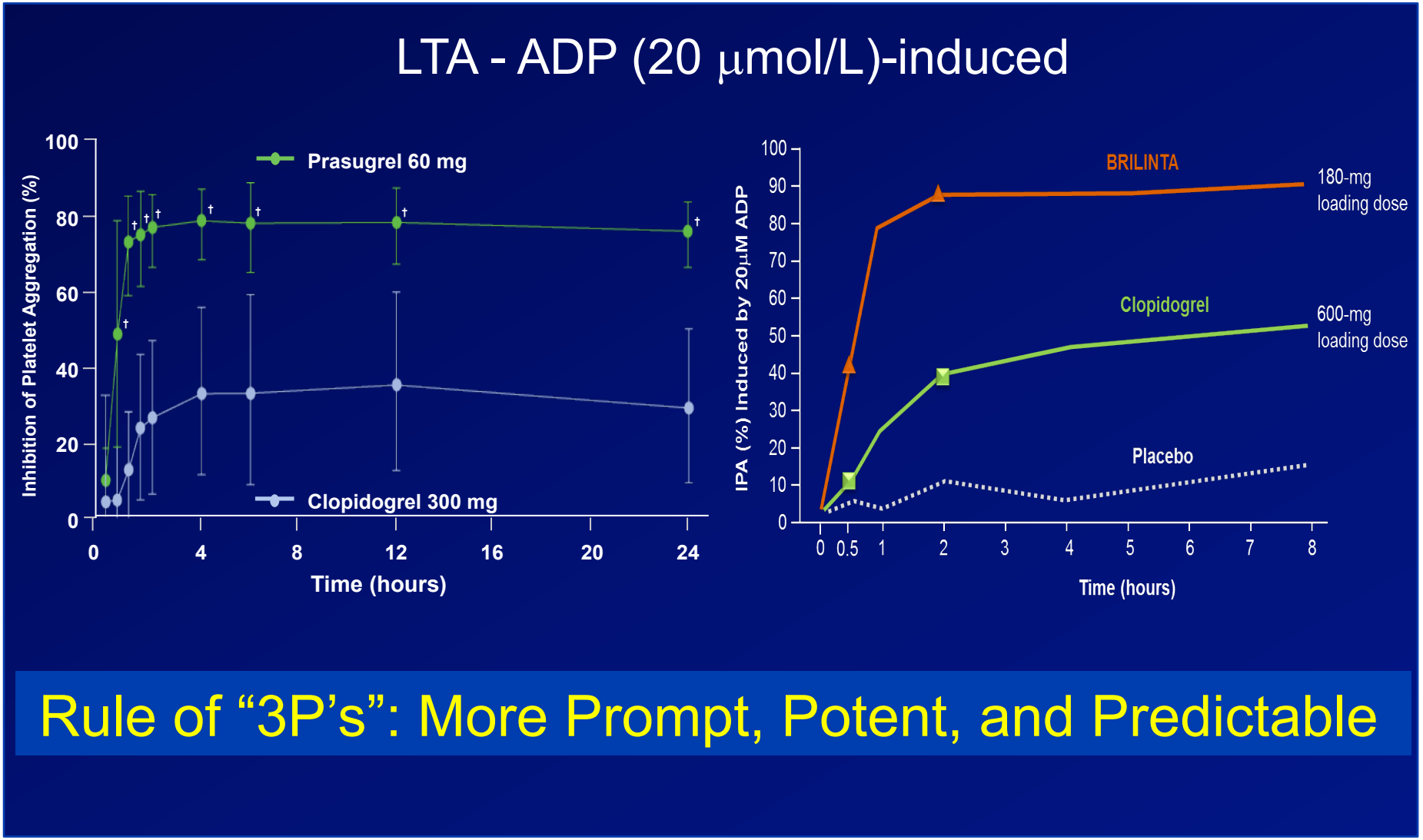


Mortality Following Stent Thrombosis



Damocle' Sword of Stent Thrombosis

Inhibition of Platelet Aggregation



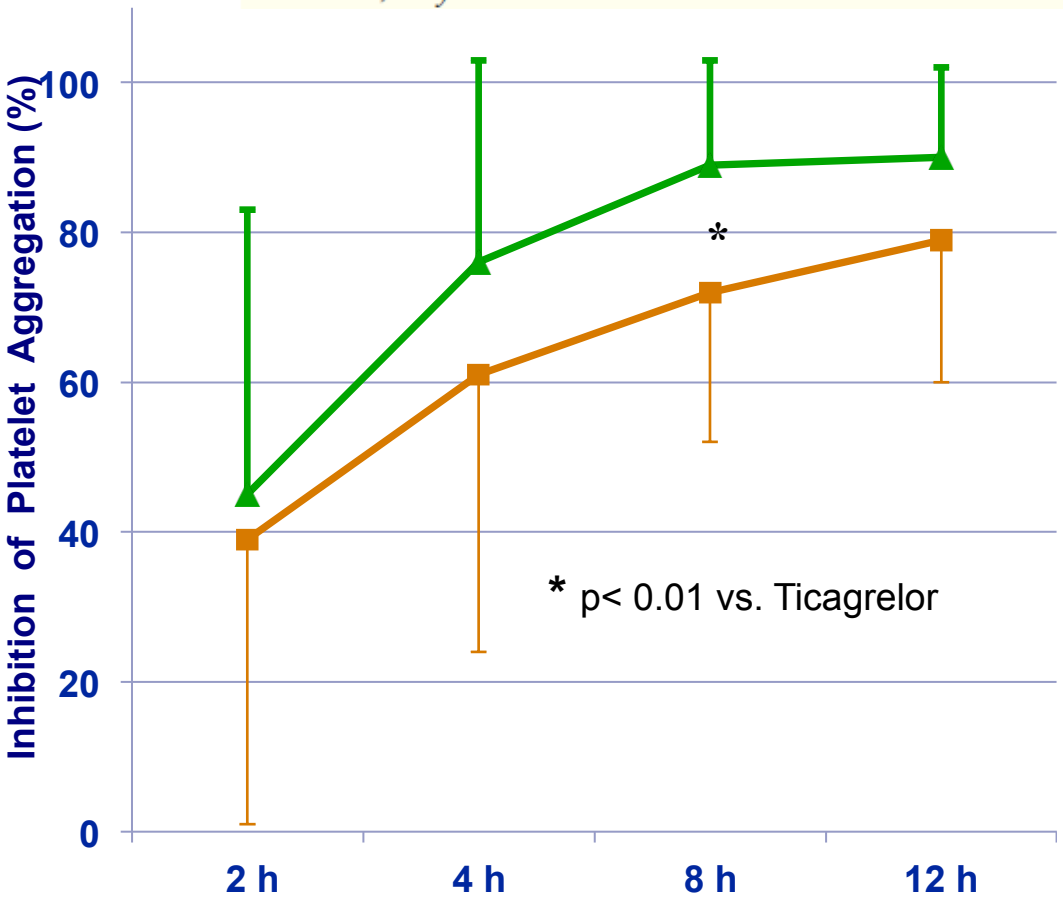
Adapted from Angiolillo

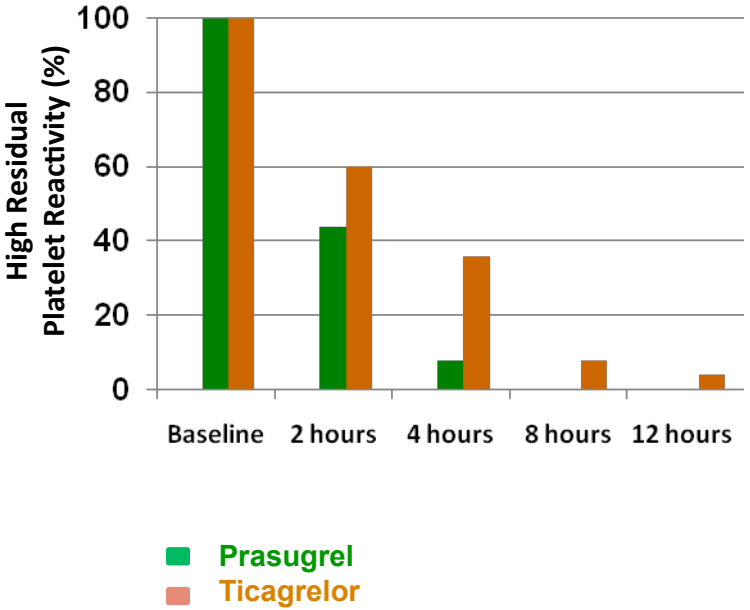
Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients

RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study

Guido Parodi, MD, PHD, Renato Valenti, MD, Benedetta Bellandi, MD, Angela Migliorini, MD, Rossella Marcucci, MD, Vincenzo Comito, MD, Nazario Carrabba, MD, Alberto Santini, MD, Gian Franco Gensini, MD, Rosanna Abbate, MD, David Antoniucci, MD

Florence, Italy

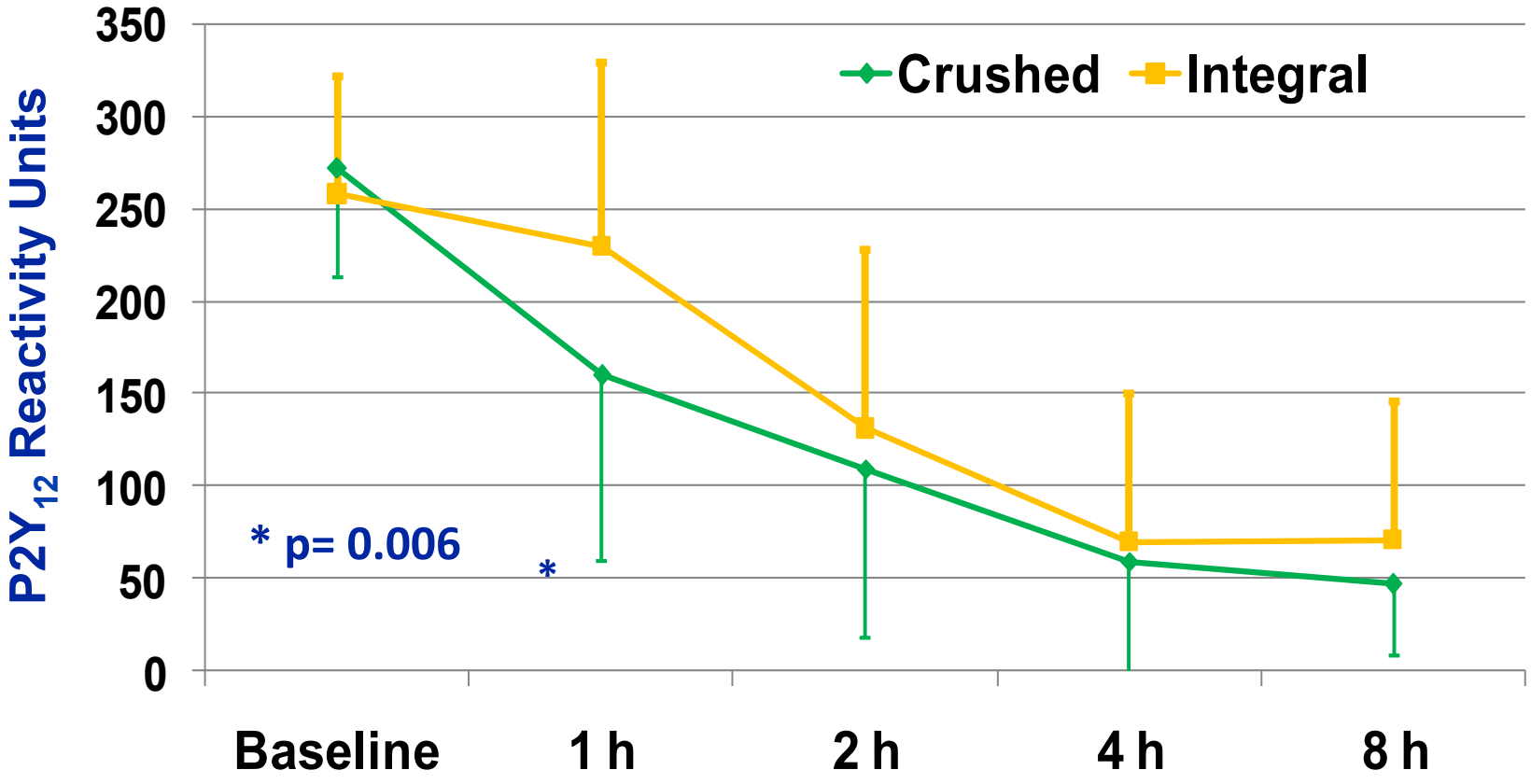




J Am Coll Cardiol 2013;61:1601-6

MOJITO Study

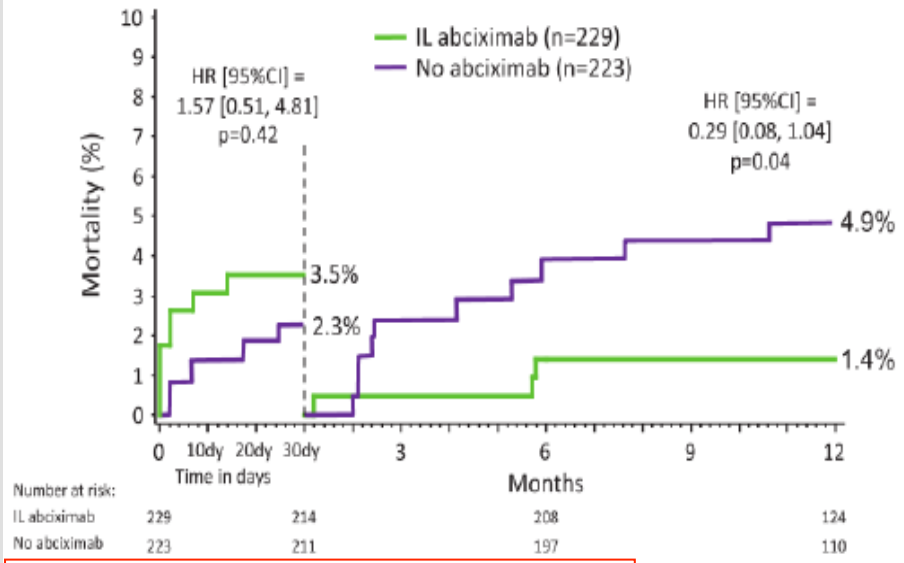
Residual platelet reactivity changes over time

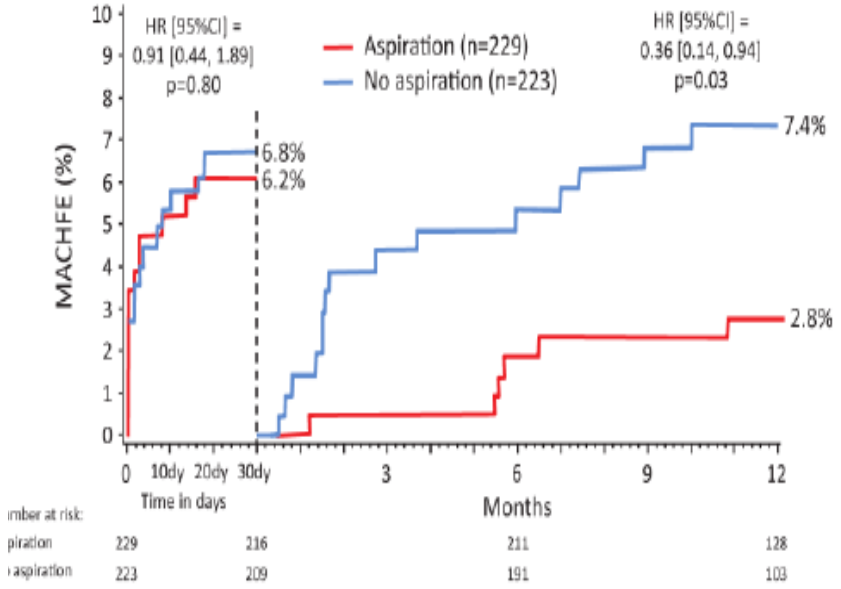


J Am Coll Cardiol 2014

INFUSE-AMI 1-year Outcome

Infarct Size: independent predictor of 1-year mortality
HR 1.11 [1.01-1.22] p= 0.03





WHAT THE STUDY ADDS

- Infarct size is a powerful determinant of late (30-day to 1-year) mortality and heart failure after primary percutaneous coronary intervention in ST-segment–elevation myocardial infarction.
- Treatment with intralesional abciximab may improve late outcomes after primary percutaneous coronary intervention in ST-segment–elevation myocardial infarction, in part by reducing infarct size.
- Although reduced infarct size was not seen with thrombus aspiration, fewer heart failure events and readmissions between 30 days and 1 year may occur after aspiration as well.

	Intralesional Abciximab, Thrombus Aspiration, or Both Therapies (n=340)	No Active Treatment (n=112)	HR [95% CI]	*P* Value
Death	4.5% (15)	10.4% (11)	0.44 [0.20–0.96]	0.03
Reinfarction	0.9% (3)	0.9% (1)	0.98 [0.10–9.45]	0.99
New-onset severe HF	4.2% (14)	10.3% (11)	0.41 [0.19–0.91]	0.02
Rehospitalization for HF	1.6% (5)	7.8% (8)	0.19 [0.06–0.60]	0.001
Stroke	0.9% (3)	2.8% (2)	0.46 [0.08–2.73]	0.38
Clinically driven TVR	3.8% (12)	2.8% (3)	1.26 [0.36–4.47]	0.72
Stent thrombosis*	0.9% (3)	3.8% (4)	0.25 [0.05–1.10]	0.046
MACCE	8.2% (27)	11.2% (12)	0.72 [0.36–1.42]	0.34
MACHFE	9.0% (30)	14.8% (16)	0.61 [0.33–1.12]	0.10

Stone GW et al. Circ Cardiovasc Interv 2013; 6:527-34

ATLANTIC Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

End Point	Prehospital Ticagrelor (N=906)	In-Hospital Ticagrelor (N=952)	Odds Ratio (95% CI)†	P Value†	Difference (95% CI)‡
	no./no. of patients who could be evaluated (%)				
Coprimary end points					
Absence of ST-segment elevation resolution ≥70% before PCI	672/774 (86.8)	722/824 (87.6)	0.93 (0.69 to 1.25)	0.63	−0.008 (−0.041 to 0.025)
Absence of TIMI flow grade 3 in infarct-related artery at initial angiography	681/824 (82.6)	711/856 (83.1)	0.97 (0.75 to 1.25)	0.82	−0.004 (−0.040 to 0.032)
Met one or both coprimary end points					
Both	541/744 (72.7)	571/777 (73.5)	0.96 (0.77 to 1.21)	0.73	−0.008 (−0.052 to 0.037)
One or both	677/719 (94.2)	710/751 (94.5)	0.93 (0.60 to 1.45)	0.75	−0.004 (−0.027 to 0.020)
Secondary end points					
Absence of ST-segment elevation resolution ≥70% after PCI	303/713 (42.5)	353/743 (47.5)	0.82 (0.66 to 1.004)	0.05	−0.050 (−0.101 to 0.001)
Absence of TIMI flow grade 3 in infarct related artery after PCI	135/760 (17.8)	154/784 (19.6)	0.88 (0.68 to 1.14)	0.34	−0.019 (−0.058 to 0.020)
Met one or both secondary end points					
Both	73/763 (9.6)	87/775 (11.2)	0.84 (0.60 to 1.16)	0.29	−0.017 (−0.047 to 0.014)
One or both	339/684 (49.6)	371/703 (52.8)	0.88 (0.71 to 1.09)	0.23	−0.032 (−0.085 to 0.020)

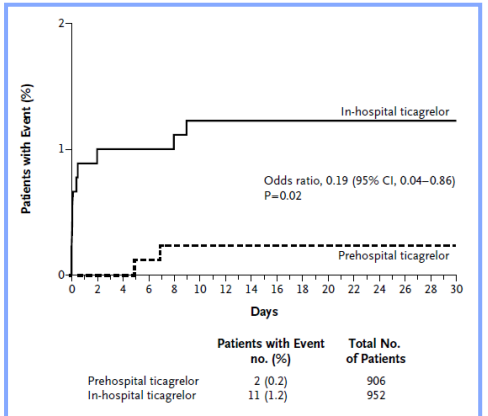
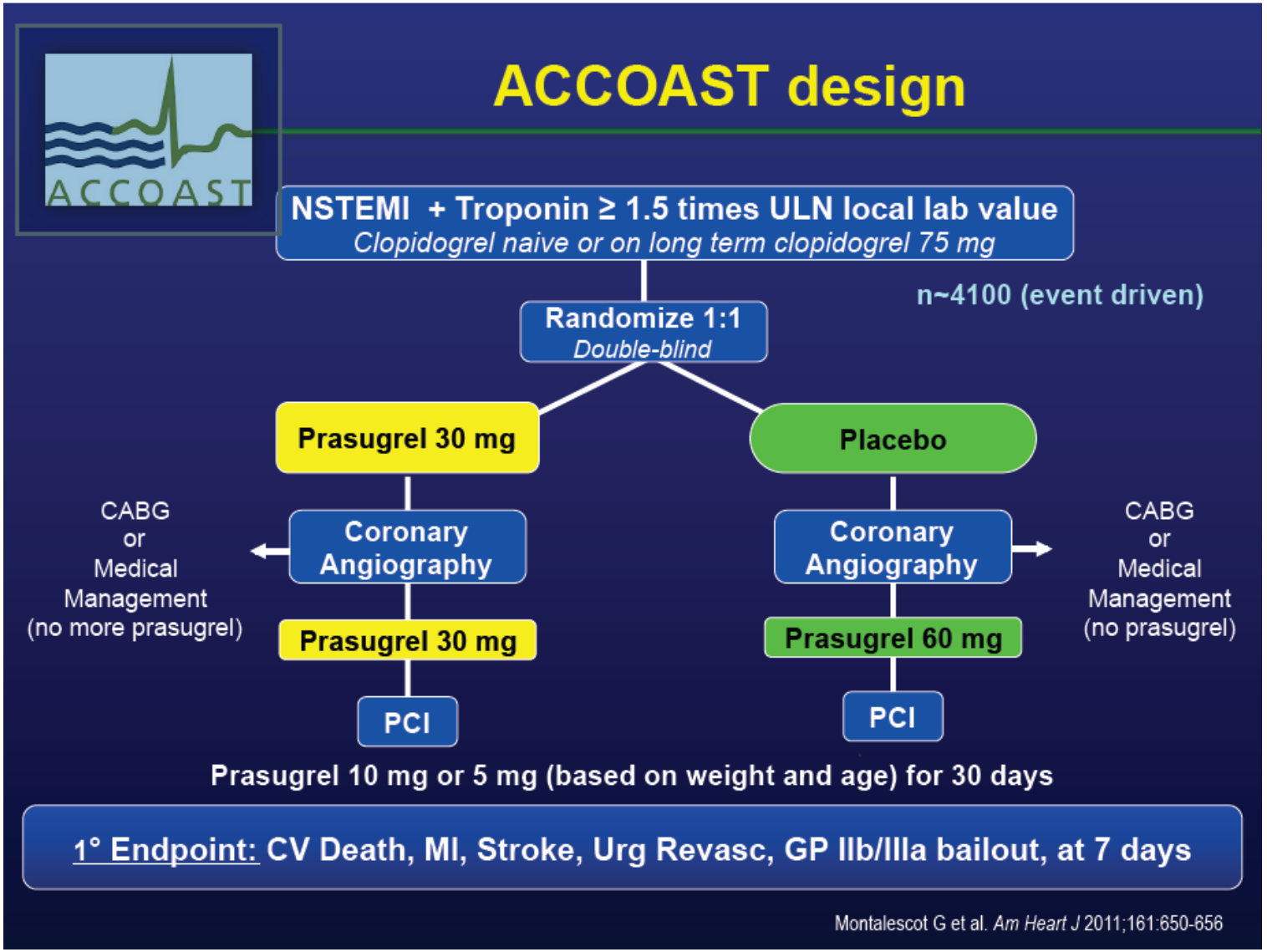
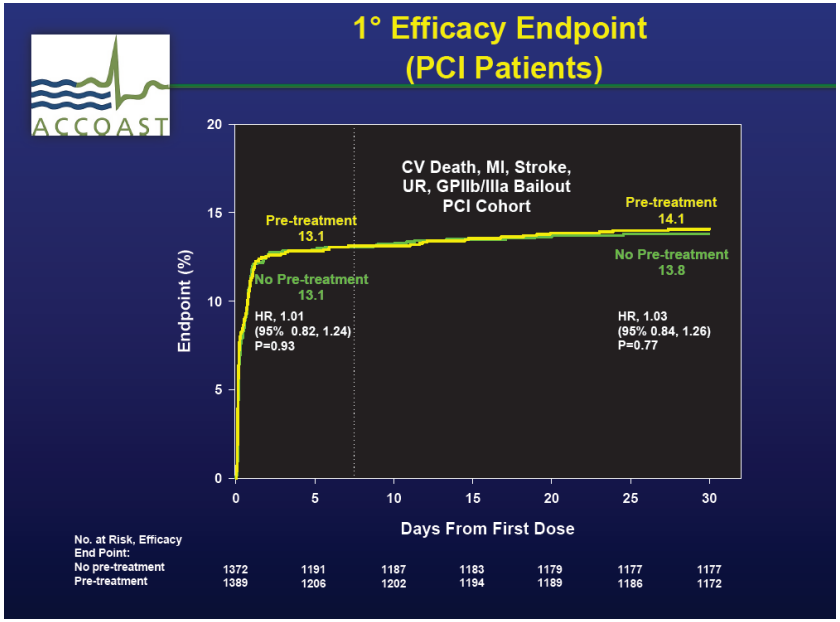


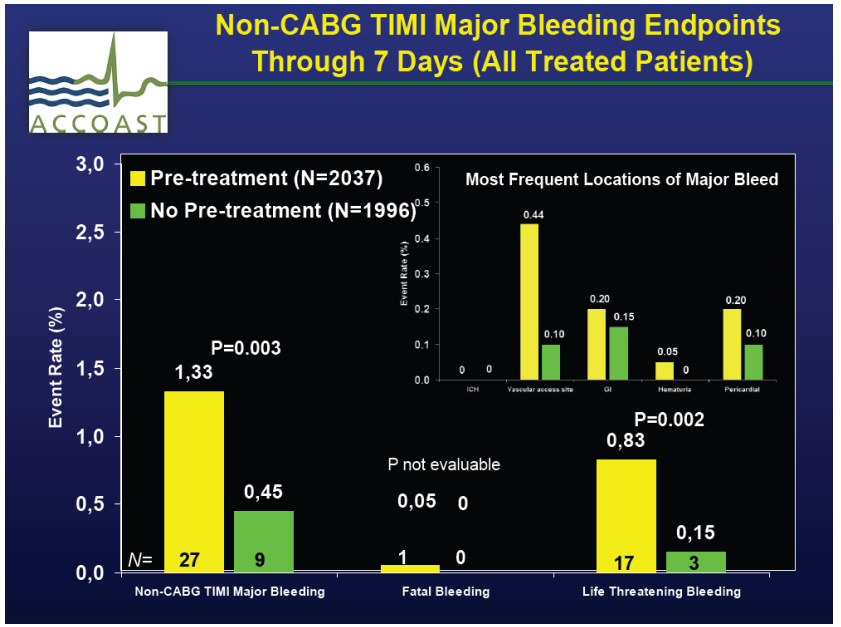
Figure 2. Definite Stent Thrombosis up to 30 Days after Ticagrelor Administration in the Modified Intention-to-Treat Population.

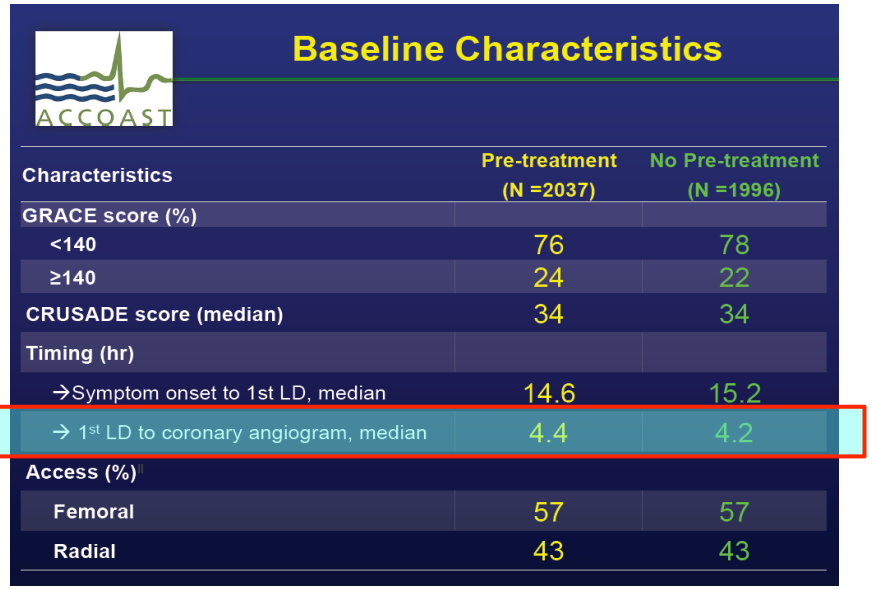
Montalescot G et al. N Engl J Med. 2014;371(11):1016-27


ACCOAST design
ACCOAST
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
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

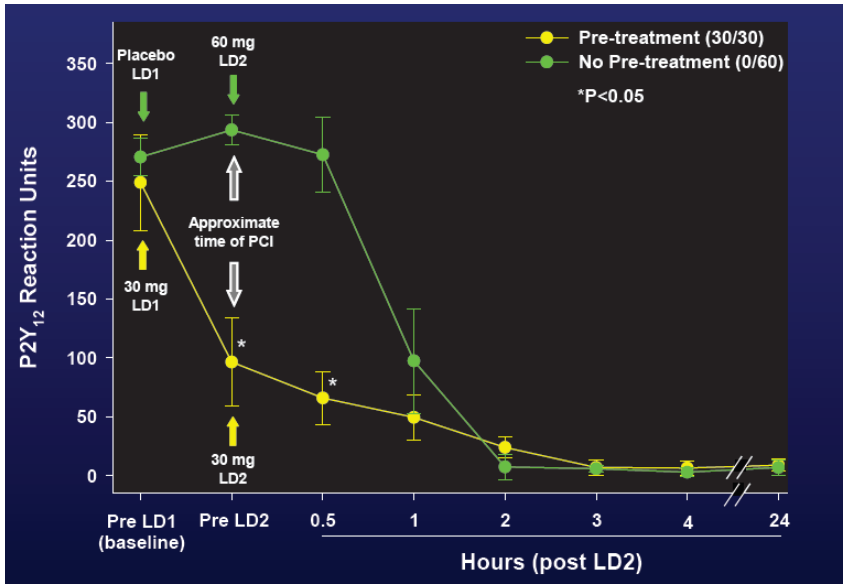
ACCOAST Trial





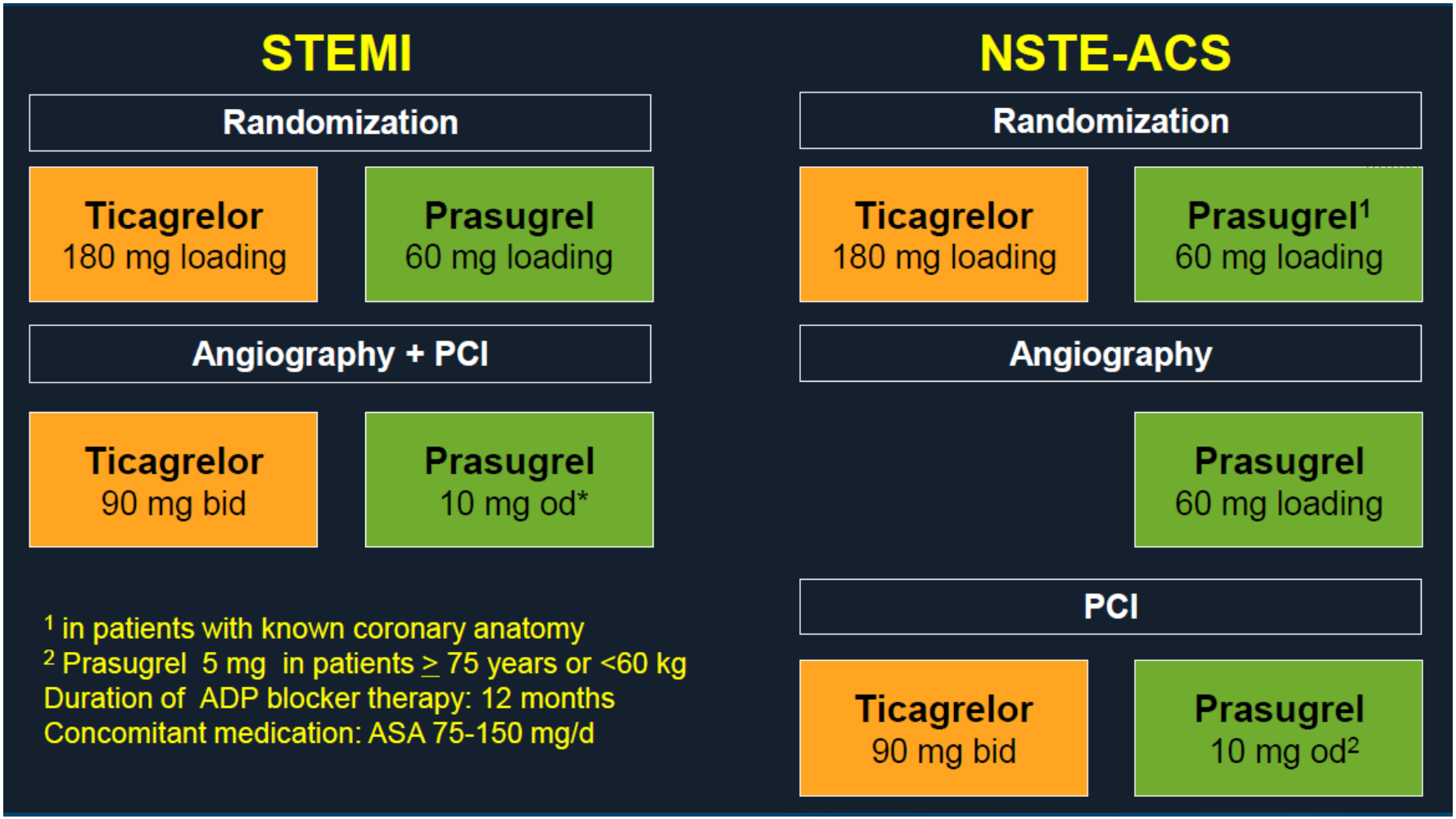


Characteristics	Pre-treatment (N =2037)	No Pre-treatment (N =1996)
GRACE score (%)		
<140	76	78
≥140	24	22
CRUSADE score (median)	34	34
Timing (hr)		
→Symptom onset to 1st LD, median	14.6	15.2
→ 1st LD to coronary angiogram, median	4.4	4.2
Access (%)		
Femoral	57	57
Radial	43	43



Montalescott G et al. N Engl J Med. 2013

ISAR-REACT 5: Ticagrelor vs. Prasugrel



Schulz S et al. J Cardiovasc Transl Res. 2014;7:91-100

Switching of P2Y12 inhibitor in patients with ACS:

Insights from EYESHOT Registry (3 weeks: 2013-2014)

EYESHOT Registry

N = 2585 ACS patients (1707 PCI)

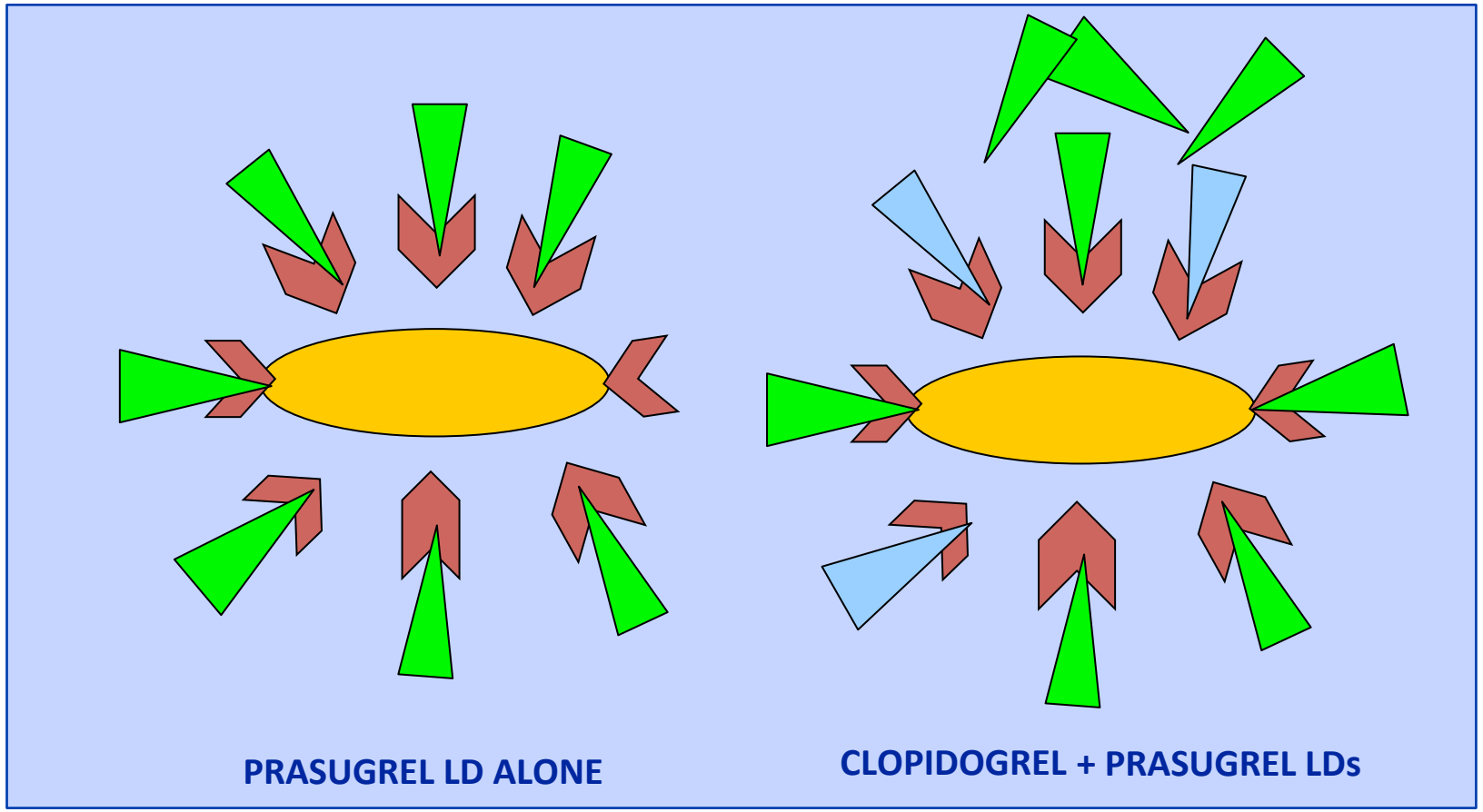
242 (14%) SWITCHING

- **N= 164 (68%) UPGRADE Clop→Tica/Pras**
- **N= 55 (23%) DOWNGRADE Pras/Tica→Clop**
- **N= 23 (9%) CHANGE Tica↔Pras**

Switching of P2Y12 inhibitor mostly represents upgrade from clopidogrel to ticagrelor or prasugrel but it is not frequent practice.

De Luca L et al. Eur Heart J CP 2015

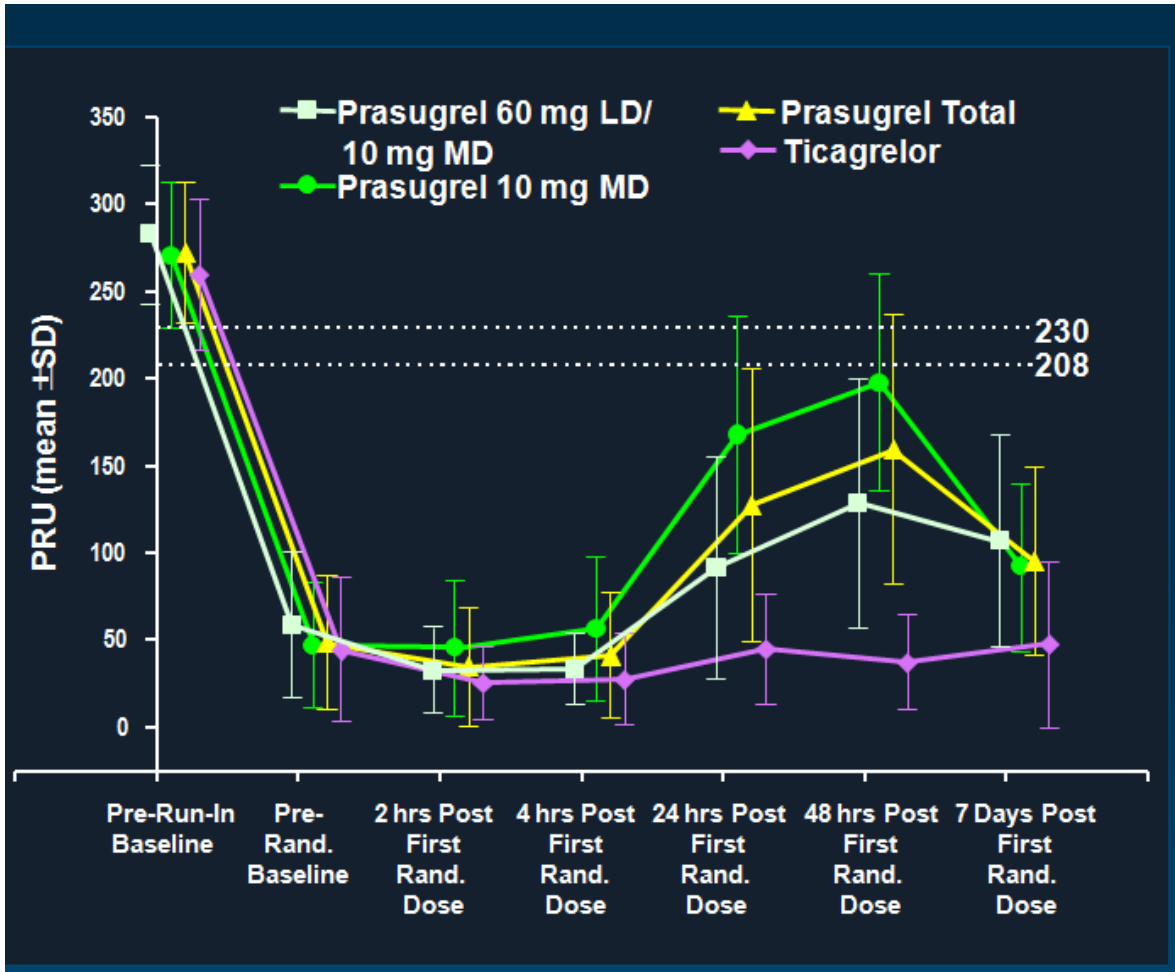
Prasugrel LD Alone vs. Clopidogrel + Prasugrel LDs



AM=Active Metabolite; LD=Loading Dose, PD=Pharmacodynamic

Diodati J and Angiolillo DJ. Circ Cardiovasc Interv 2013; 6(5):567-74

SWAP-2: Ticagrelor to Prasugrel (± LD)



- PRU increased at 24 and 48 hours in the prasugrel MD only group relative to pre-randomization values
- Smaller increase in the prasugrel LD group compared with the prasugrel MD only group
- PRU was higher in the prasugrel total group compared with the ticagrelor group at 7 days post-randomization

Angiolillo D. J Am Coll Cardiol 2014