Does The Efficacy of Bivalirudin During PCI Depend on Clopidogrel Pre-treatment?

Matthew J. Price MD, FACC
Director, Cardiac Catheterization Laboratory
Scripps Clinic
La Jolla, CA

ACC/AHA Guideline Revision

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction)

Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons

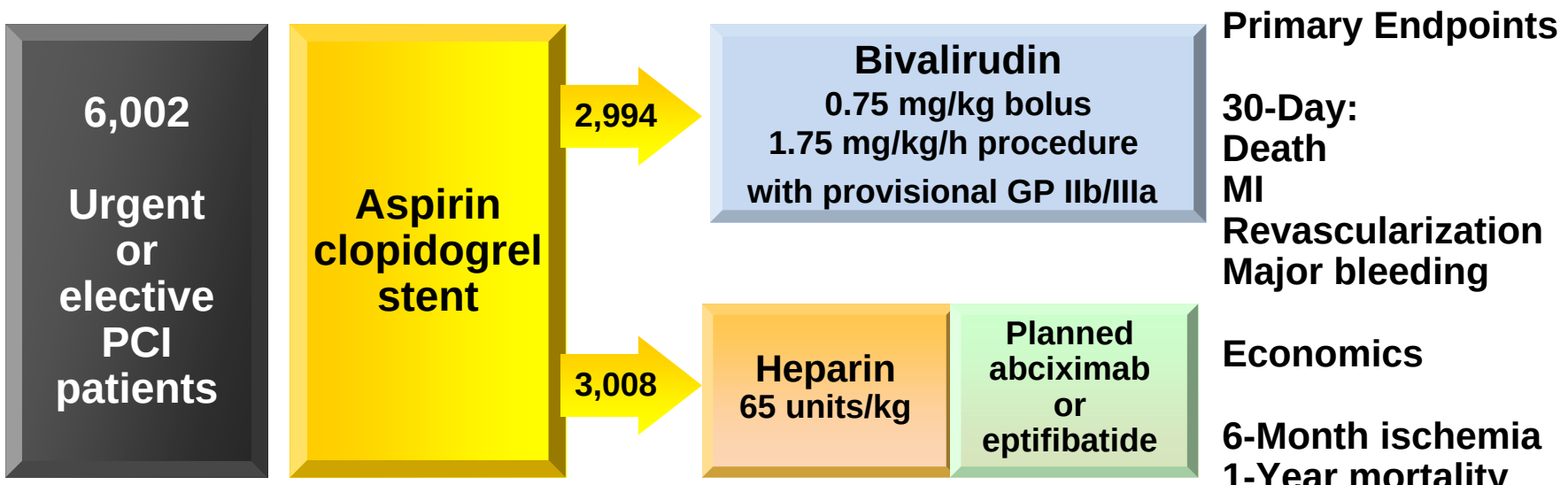
Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine

IIa Recommendation

For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an intravenous GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier than planned catheterization or PCI. (Level of Evidence: B)

REPLACE-2 Trial Design

Randomized, double-blind, active-controlled trial

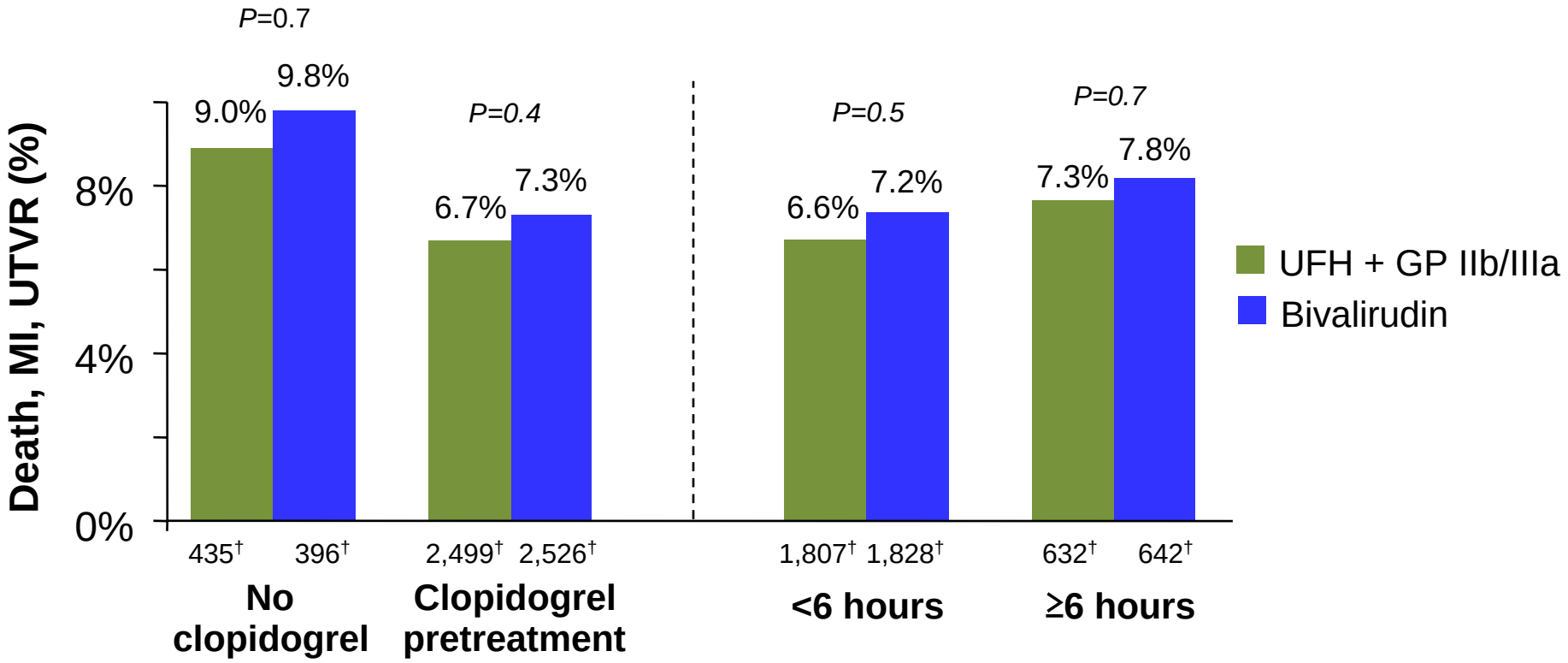


Secondary composite end point=death, MI, or urgent revascularization.

Clopidogrel 300-mg encouraged 2 to 12 hrs before PCI

REPLACE 2: Results Stratified By Clopidogrel Tx

No Differential Benefit Between Heparin/GPI and Bival

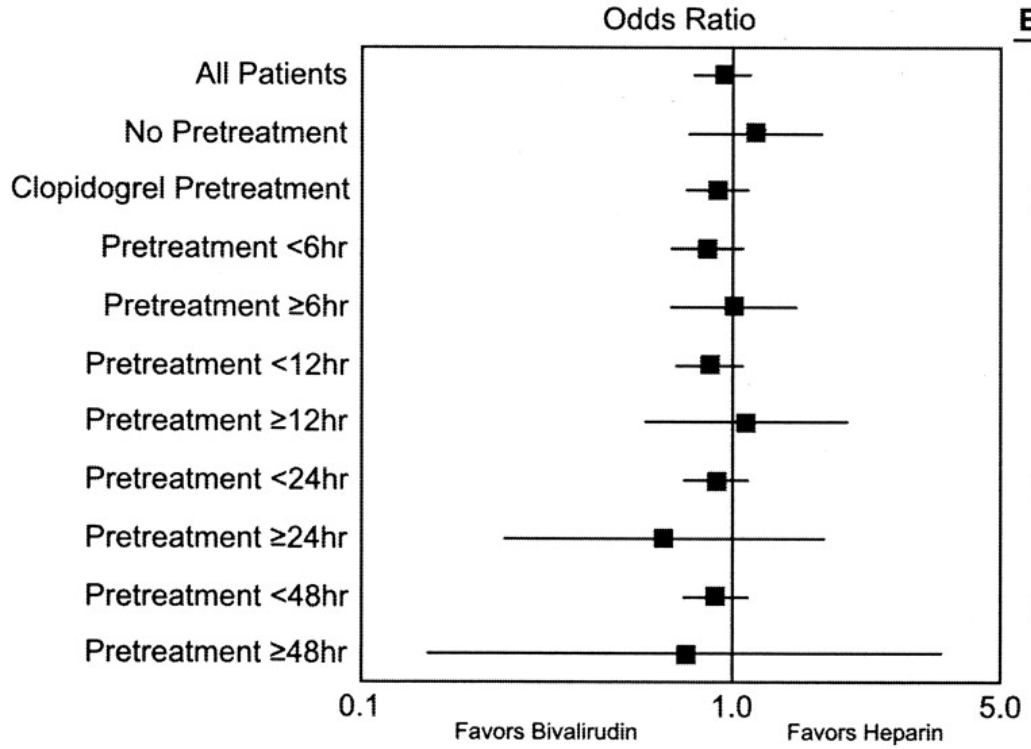


~85% of patients in each arm received clopidogrel pre-PCI.

~20% were pretreated > 6 hours prior to PCI.

REPLACE 2: Results Stratified By Clopidogrel Tx

No Differential Benefit On Net Clinical Events

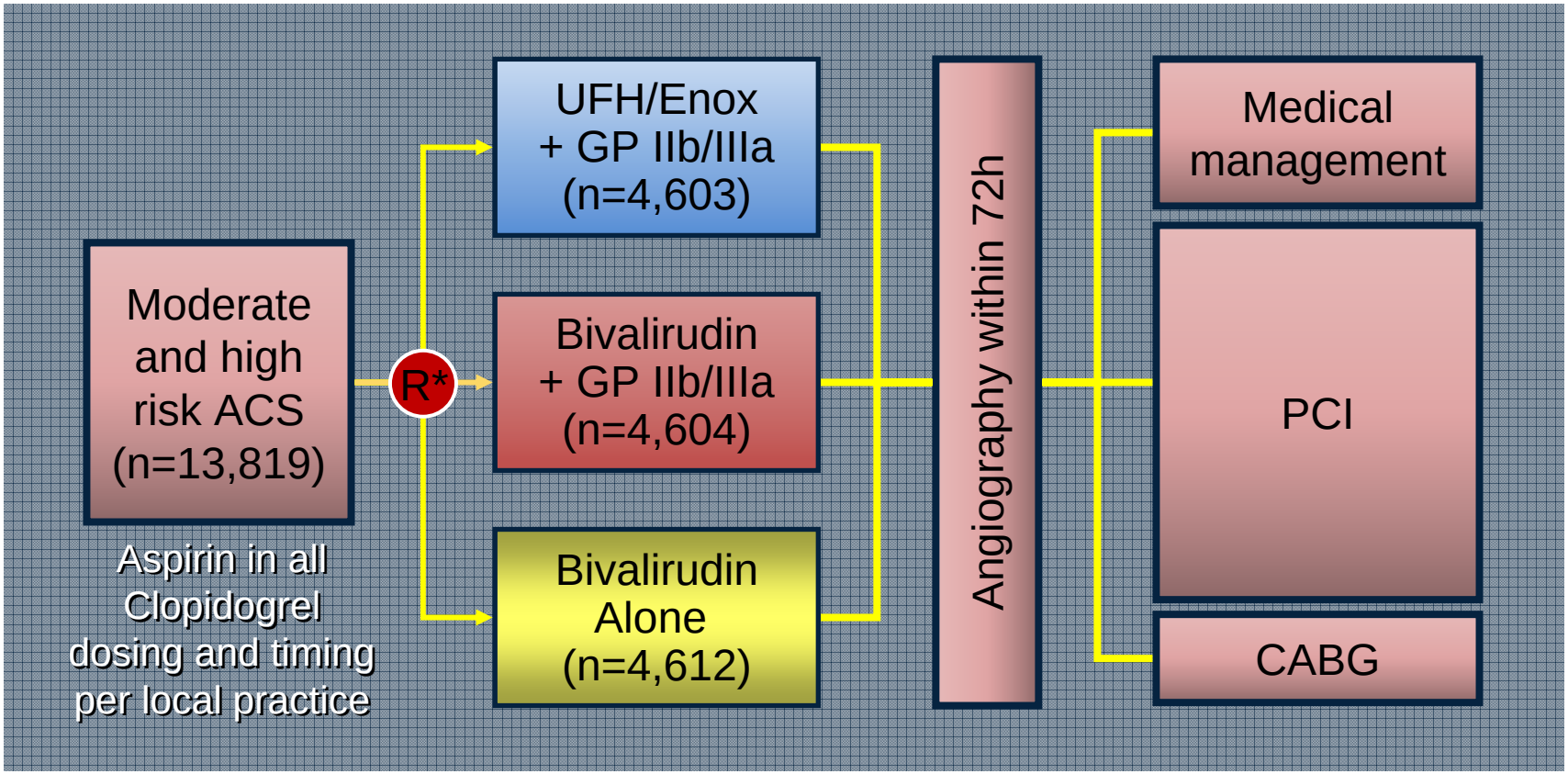


	Bivalirudin Group	Heparin Group	P value
All Patients	275/2975 (9.2%)	299/2991 (10.0%)	0.324
No Pretreatment	51/396 (12.9%)	51/435 (11.7%)	0.612
Clopidogrel Pretreatment	219/2526 (8.7%)	243/2500 (9.7%)	0.198
Pretreatment <6hr	155/1828 (8.5%)	181/1808 (10.0%)	0.111
Pretreatment ≥6hr	57/642 (8.9%)	57/632 (9.0%)	0.930
Pretreatment <12hr	189/2226 (8.5%)	217/2207 (9.8%)	0.121
Pretreatment ≥12hr	23/244 (9.4%)	21/233 (9.0%)	0.876
Pretreatment <24hr	205/2368 (8.7%)	227/2334 (9.7%)	0.205
Pretreatment ≥24hr	7/102 (6.9%)	11/106 (10.4%)	0.367
Pretreatment <48hr	209/2437 (8.6%)	234/2406 (9.7%)	0.167
Pretreatment ≥48hr	3/33 (9.1%)	4/33 (12.1%)	1.00

Saw J, J Am Coll Cardiol. 2004;44:1194-1199.

ACUITY Study Design
First Randomization

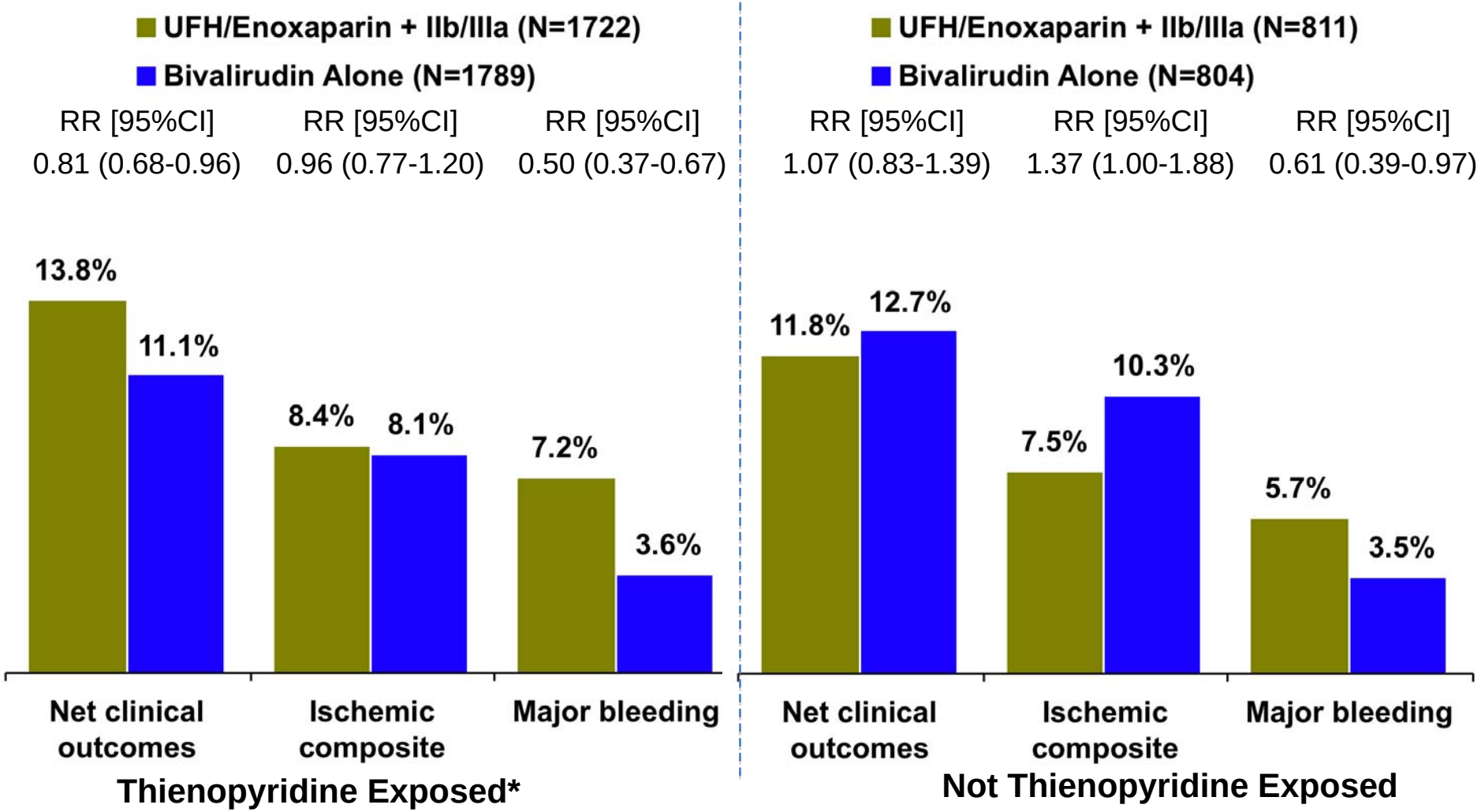
Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)



Randomization Stratified by pre-angiography thienopyridine use or administration

ACUITY: Influence of Thienopyridine Exposure

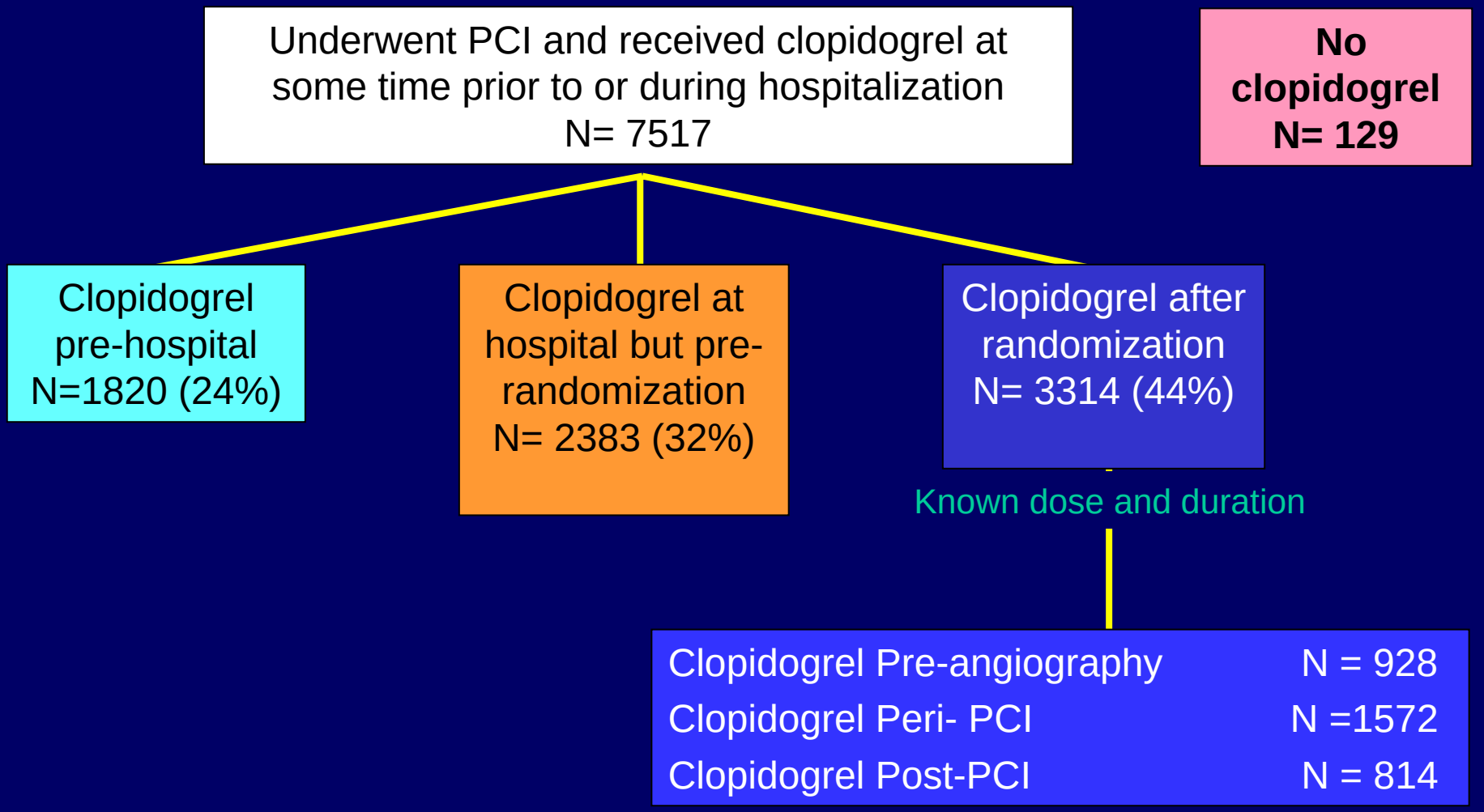
30 Day Primary Endpoint Adverse Events



Interaction P values = 0.17, 0.19 and 0.65 respectively

*Thienopyridine at any time, any dose, up to time of PCI

What is known About Clopidogrel Exposure in ACUITY Patients Pre-PCI



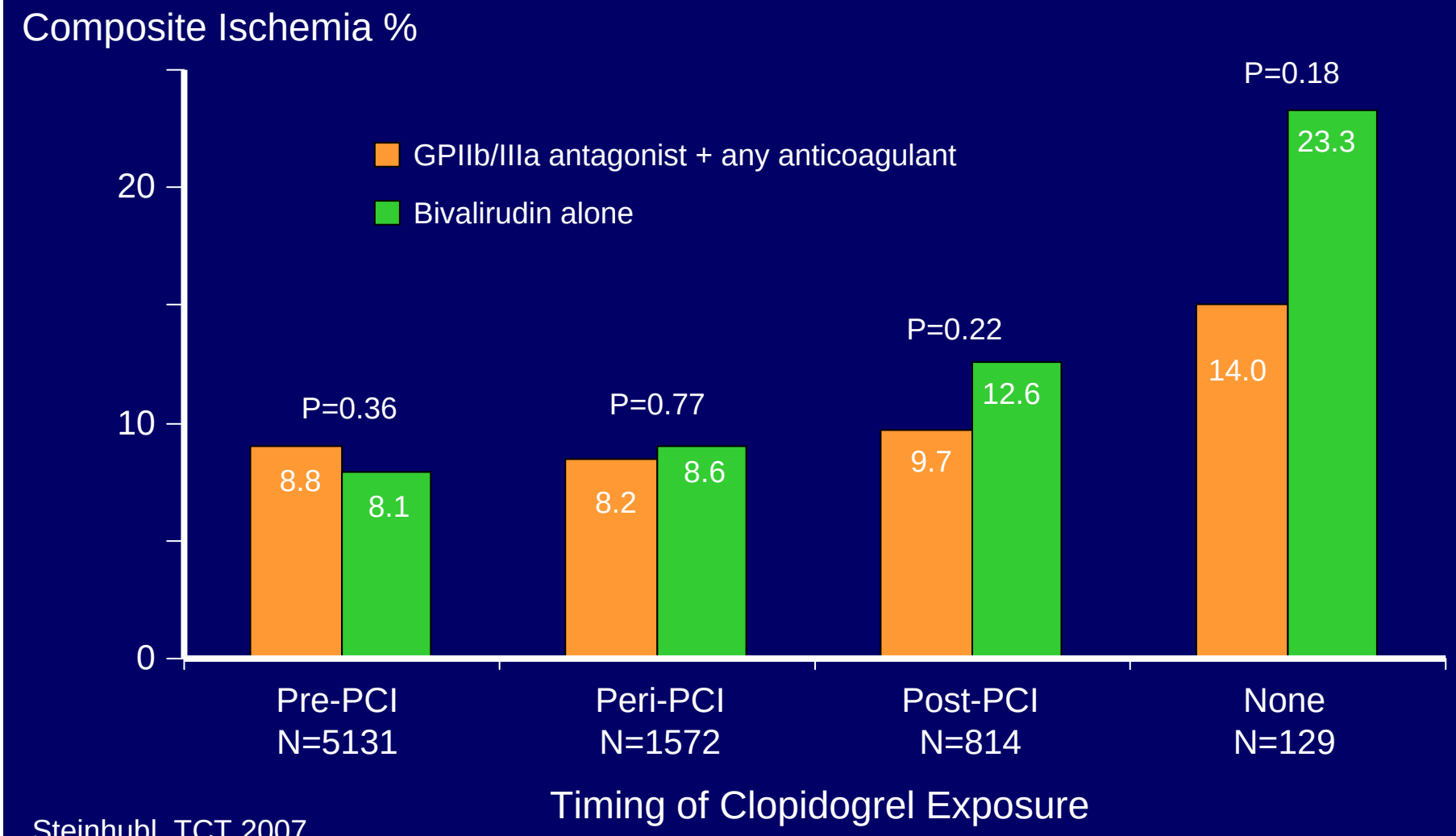
Steinhubl, TCT 2007

ACUITY and Clopidogrel Preloading

Method of Analysis of Timing of Clopidogrel

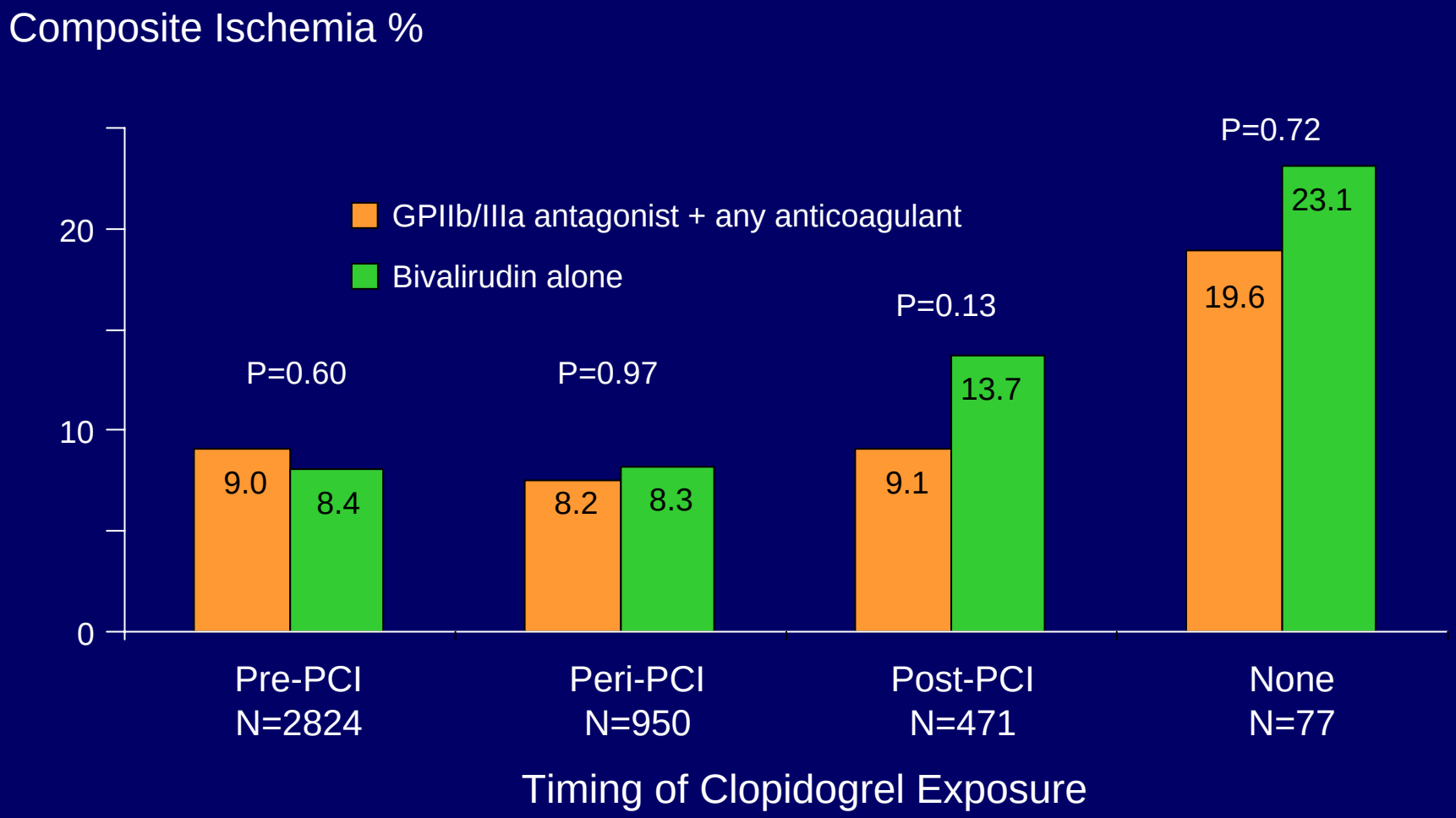
- Timing for the initiation of clopidogrel was *a priori* designated as:
  - **Pre-PCI** if it was initiated at any time prior to the angiogram.
  - **Peri-PCI** if it was initiated after angiography and within 30 minutes of the end of PCI.
  - **Post-PCI** if it was initiated > 30 minutes after PCI

30-Day Ischemic Outcomes Based on Antiplatelet Therapy



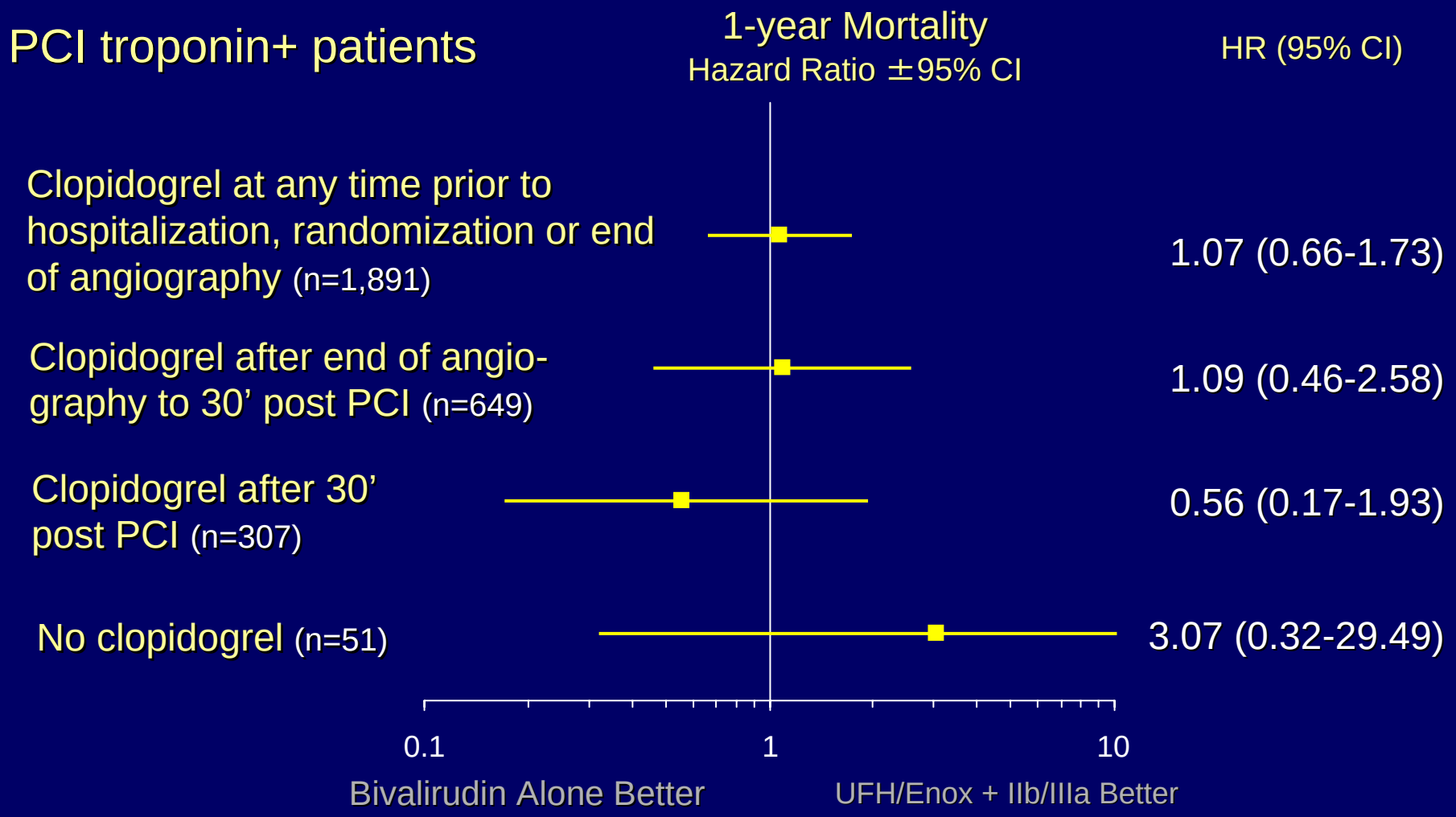
Steinhubl, TCT 2007

30-Day Ischemic Outcomes in Troponin Positive Patients Only



Steinhubl, TCT 2007

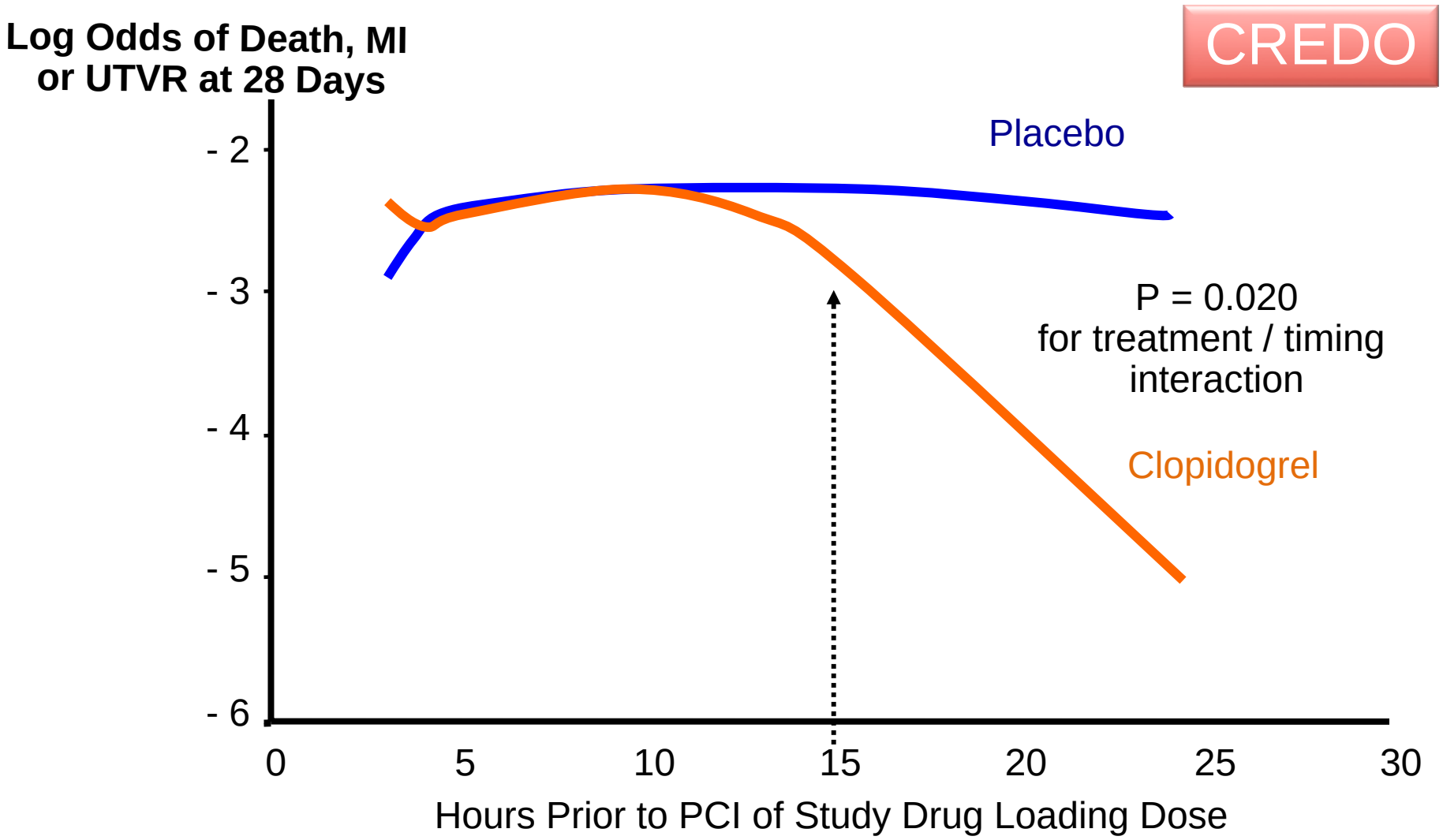
ACUITY PCI: Impact of Timing of Clopidogrel Administration on 1 Yr Mortality (Tn + patients)



White et al, JACC 2008

What dose and duration is an adequate preload?

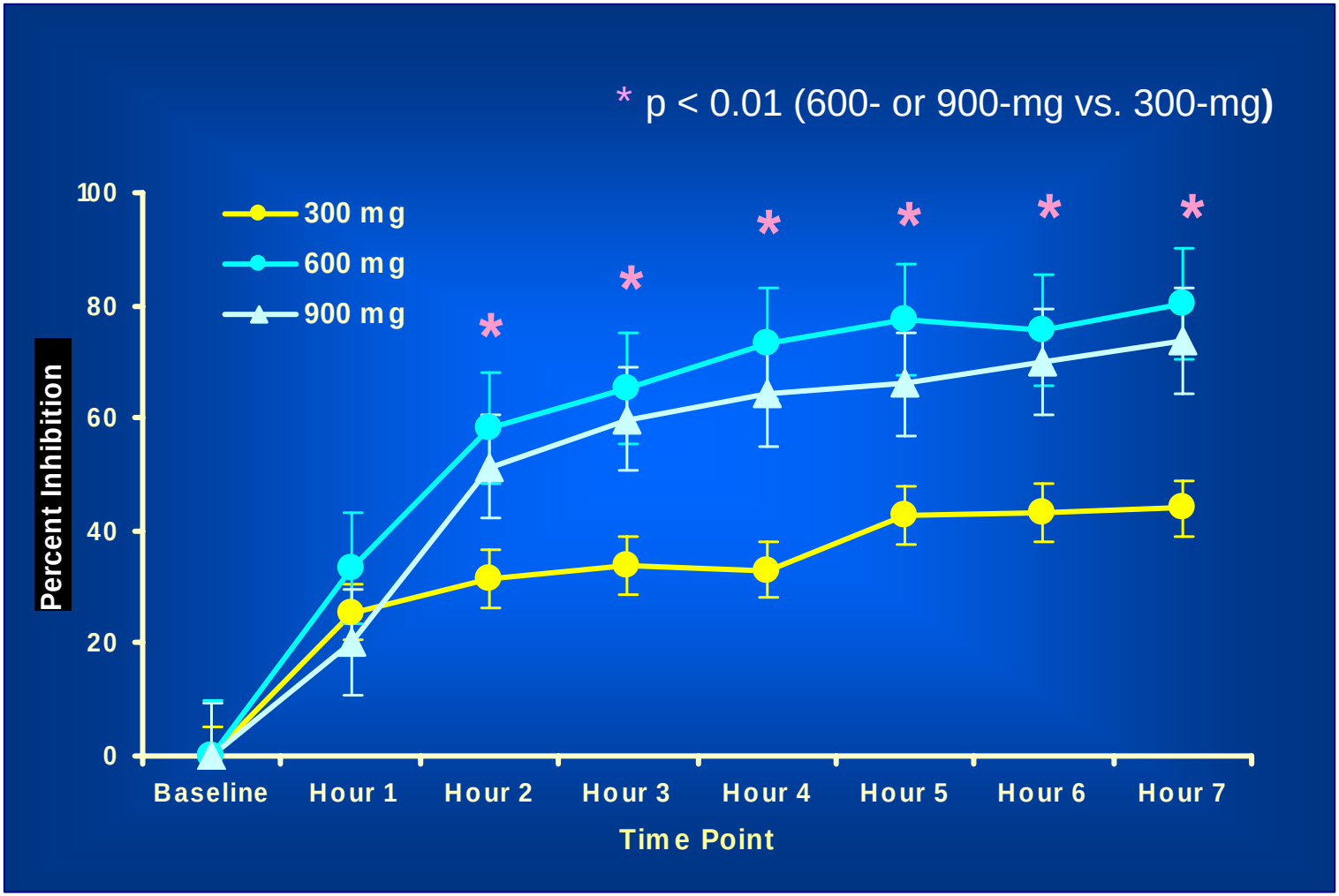
Analysis of the CREDO trial



Steinhubl et al, Am. Coll. Cardiol. 2006;47;939-943

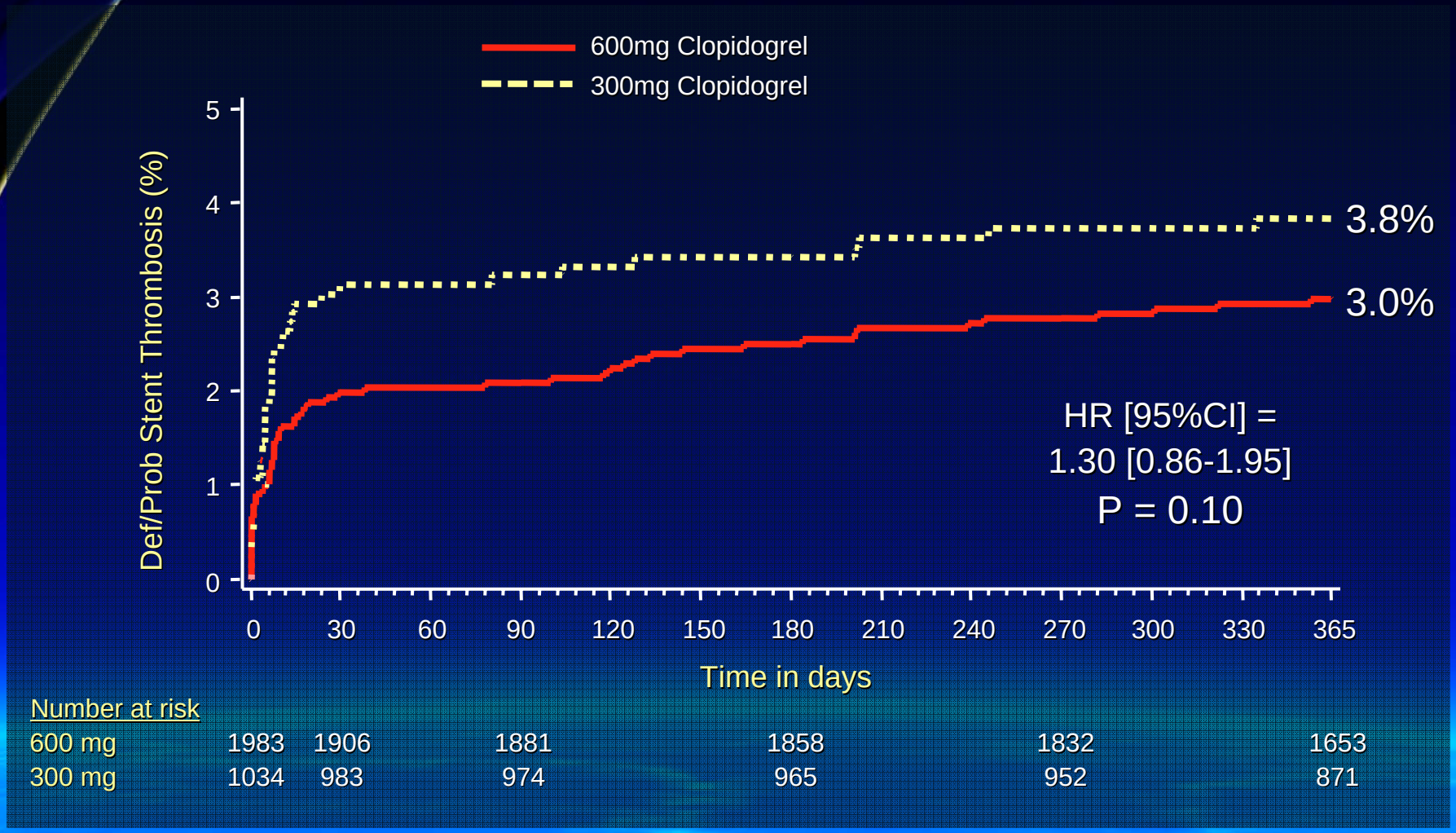
What dose and duration is an adequate preload?

Time to inhibition for different clopidogrel loading doses



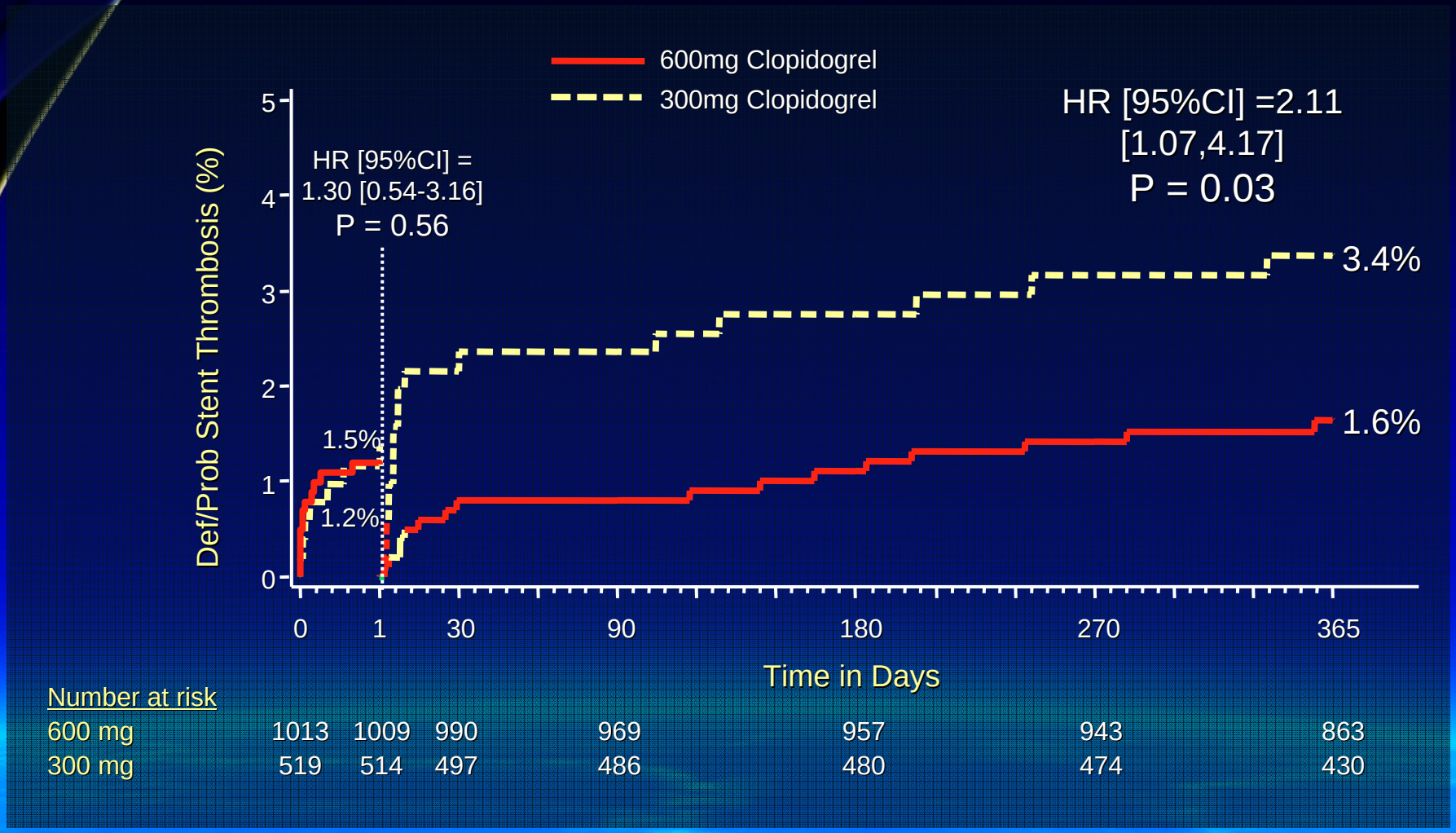
Price MJ, Am J Cardiol 2006;98(5):681-4

1-Year Stent Thrombosis: Impact of Clopidogrel Loading Dose (all pts)



HORIZONS AMI

Stent Thrombosis 1-Day Landmark Analysis: Impact of Clopidogrel Loading (Bivalirudin)



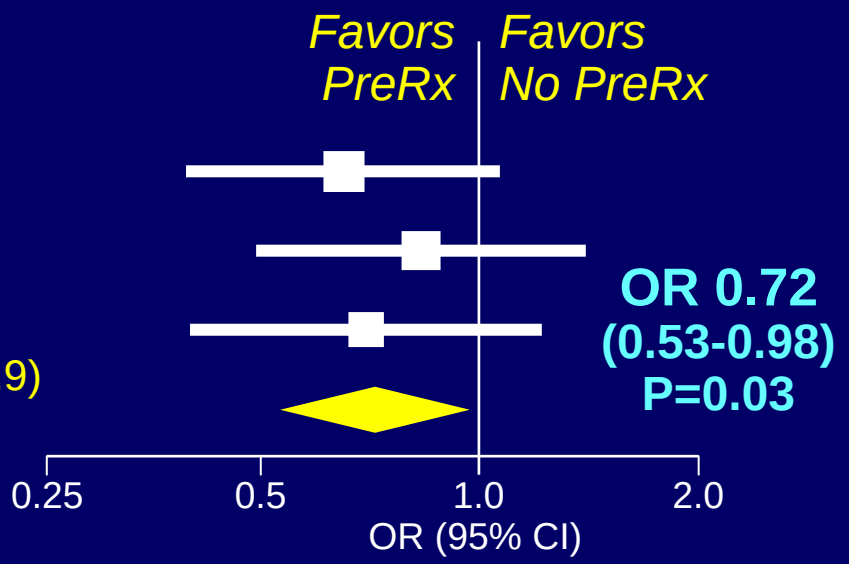
HORIZONS-AMI

Efficacy of Clopidogrel Pre-treatment in Patients Receiving GpIs: Combined Analysis PCI-CURE, CREDO and PCI-CLARITY

CV Death, MI, or Stroke Following PCI

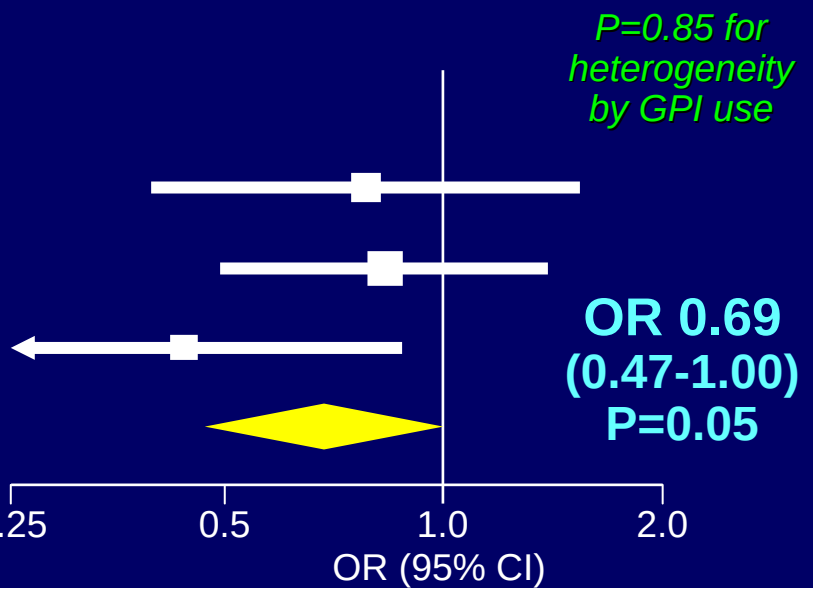
Without GPI

Trial	Clop PreRx	No PreRx
PCI-CURE	27/1039 (2.6)	39/988 (3.9)
CREDO	26/473 (5.5)	34/519 (6.6)
PCI-CLARITY	22/639 (3.4)	30/615 (4.9)
OVERALL	75/2151 (3.5)	103/2122 (4.9)



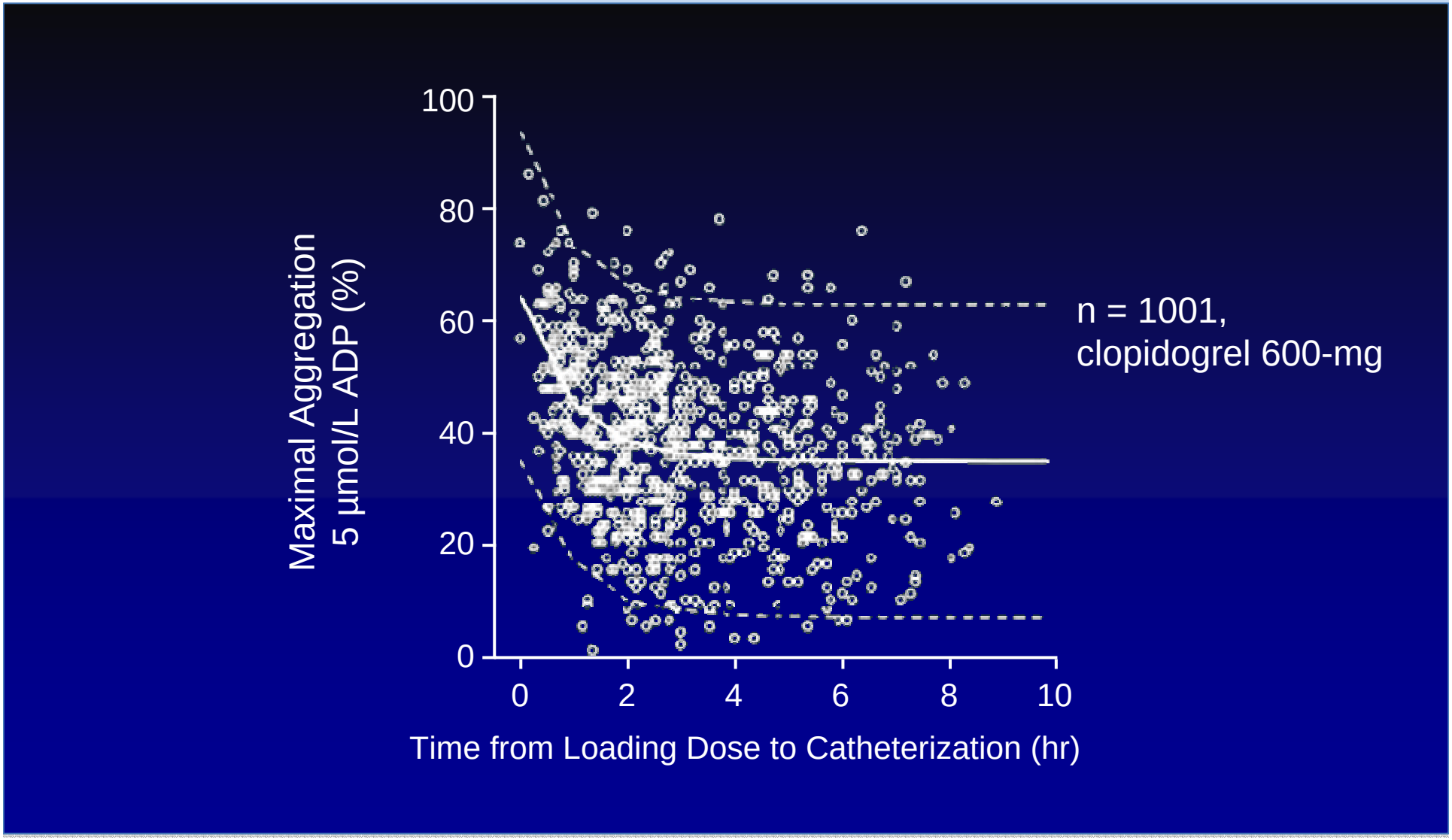
With GPI

Trial	Clop PreRx	No PreRx
PCI-CURE	14/274 (5.1)	23/357 (6.4)
CREDO	29/427 (6.8)	32/396 (8.1)
PCI-CLARITY	12/288 (4.2)	28/310 (9.0)
OVERALL	55/989 (5.6)	83/1063 (7.8)



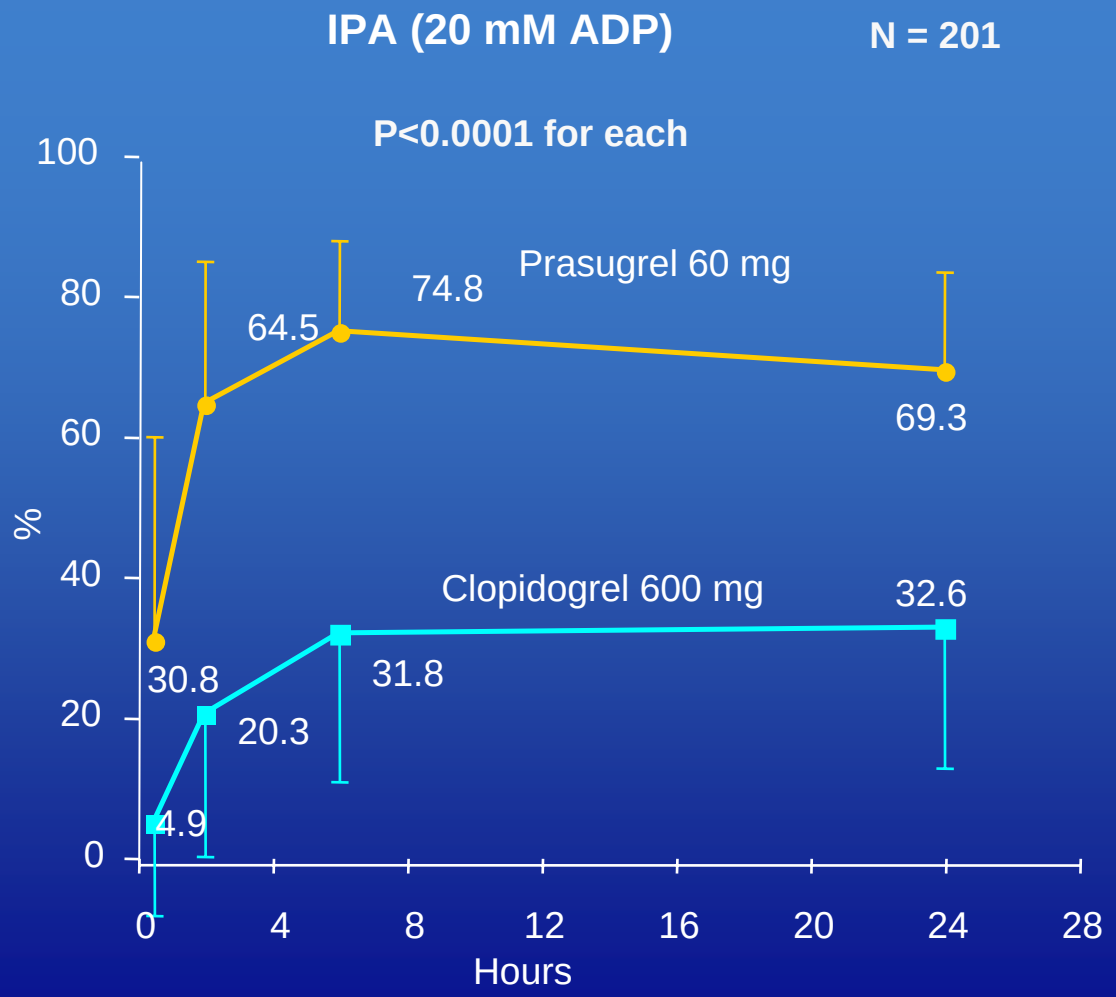
Sabatine MS Am Heart J 2008;155(5):910-917

The Response To A Uniform Dose Of Clopidogrel Is Not Uniform



Hochholzer W et al. Circulation. 2005;111:2560-2564.

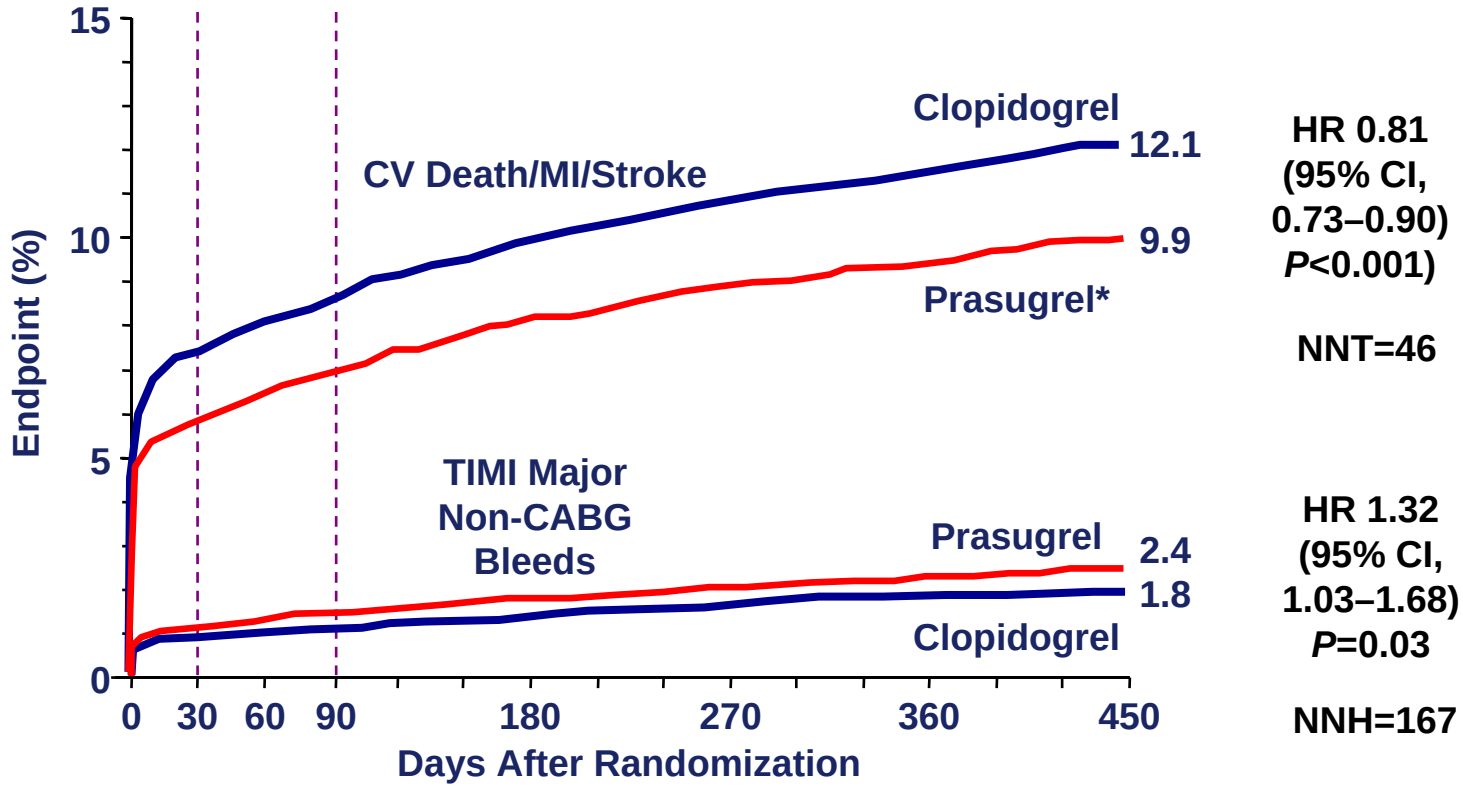
PRINCIPLE TIMI 44: Time and Magnitude of Onset of Inhibition of Prasugrel Compared with 600-mg Clopidogrel



IPA = inhibition of platelet aggregation.

Wiviott SD et al. Circulation. 2007;116:2923-2932.

TRITON-TIMI 38: *Primary Endpoint*



Wiviott SD et al. *N Engl J Med*. 2007;357(20):2001-2015.

Conclusions

- In REPLACE 2, clopidogrel pretreatment did not influence the relative efficacy of bivalirudin versus heparin plus a GPI. However, pretreatment was associated with a trend towards lower clinical events overall.
- In ACUITY, patients who received clopidogrel either prior to, or at the time of, PCI achieved similar ischemic event rates and significantly less bleeding when randomized to bivalirudin alone versus a GPI, irrespective of troponin status.
- There was a trend in ACUITY towards worse ischemic outcomes among patients receiving clopidogrel > 30 min after PCI or no clopidogrel at all.

Conclusions (2)

- Clopidogrel pre-treatment is beneficial whether or not a GPI is used at the time of PCI.
- The desire or ability to pre-treat an ACS patient with clopidogrel prior to PCI should not influence the choice of antithrombotic therapy.
- In the case of ACS, the availability of prasugrel, which provides greater, more consistent, and quicker onset of inhibition then clopidogrel, may make the question of clopidogrel pretreatment moot.