Case Presentation

Why and How Should We Switch Clopidogrel to Prasugrel?

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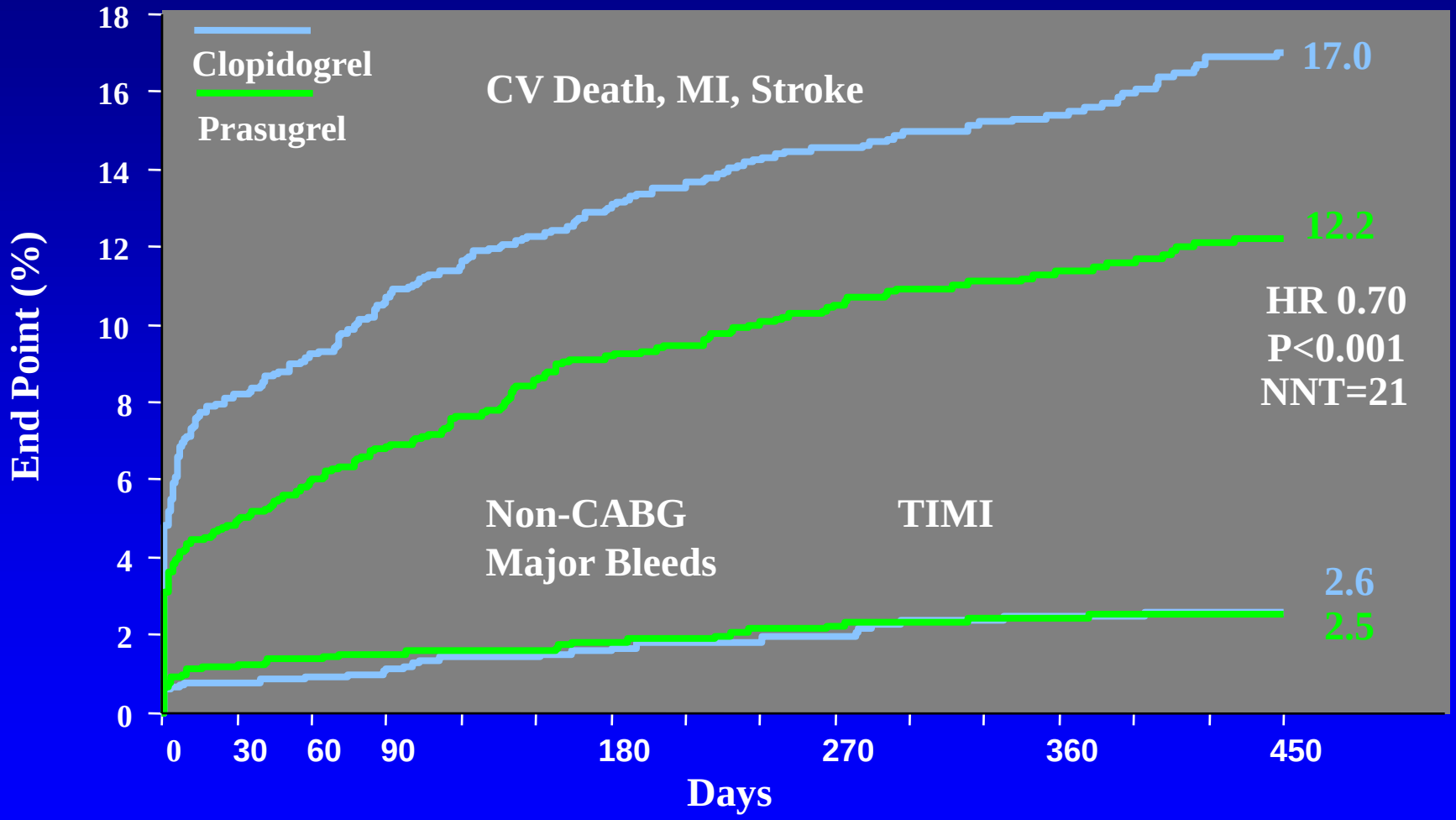
Case Description

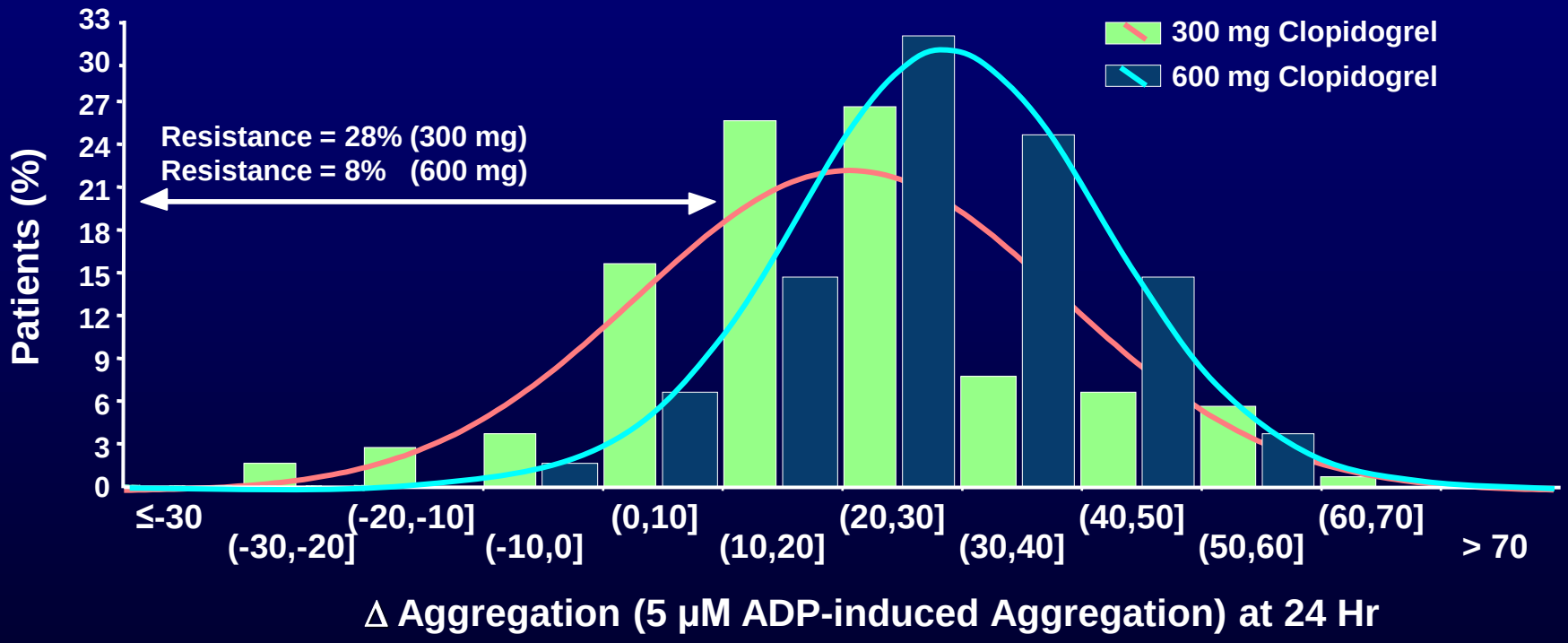
- A 67 Y. Old Pt. admitted to IM with anginal CP.
- **DM, HTN, HLP.**
- First Tn I – negative.
- Clopidogrel 600 mg.
- Second TnI – elevated.
- Transferred to Cardiology Dept on the afternoon, Scheduled for cath the next morning.

TRITON-TIMI 38: Diabetic Subgroup Analysis (n=3,146)



CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; NNT= Number Needed to Treat; TIMI=Thrombolysis In Myocardial Infarction

Clopidogrel Response Variability: Increase the Dose (300 mg vs. 600 mg)



Gurbel PA et al. *J Am Coll Cardiol.* 2005;45:1392-1396.

What should the cardiology fellow do?

- Continue clop. MD & wait for cath results
- Load immediately with prasugrel 60 mg
- Load immediately with prasugrel 30 mg
- Start prasugrel 10 mg w/o loading
- Ticagrelor?

Trials Comparing IPA Following the Switch from Clopidogrel to Prasugrel or to Ticagrelor

- TABF (healthy volunteers)
- PRINCIPLE-TIMI 44 (elective PCI)
- ACAPULCO (NSTE-ACS patients undergoing PCI)
- SWAP (recent ACS history)
- TRIPLET (ACS patients undergoing PCI)

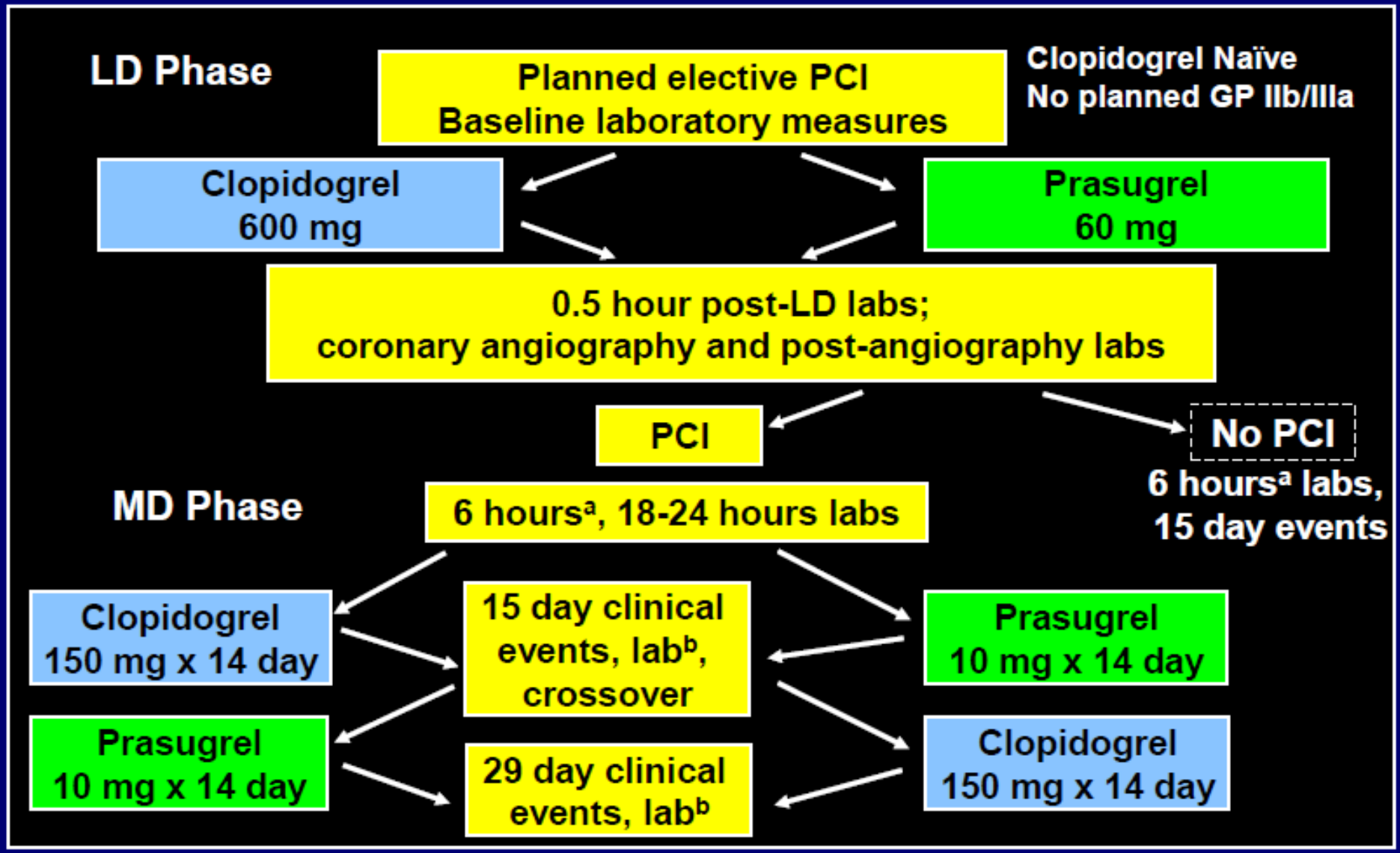
- RESPOND
- *PLATO (pre specified subgroup analysis)□*

- *There have been no studies powered to evaluate the clinical safety and efficacy of switching from clopidogrel to prasugrel*

□ *No IPA data available*

Study Design

PRINCIPLE
TIMI 44

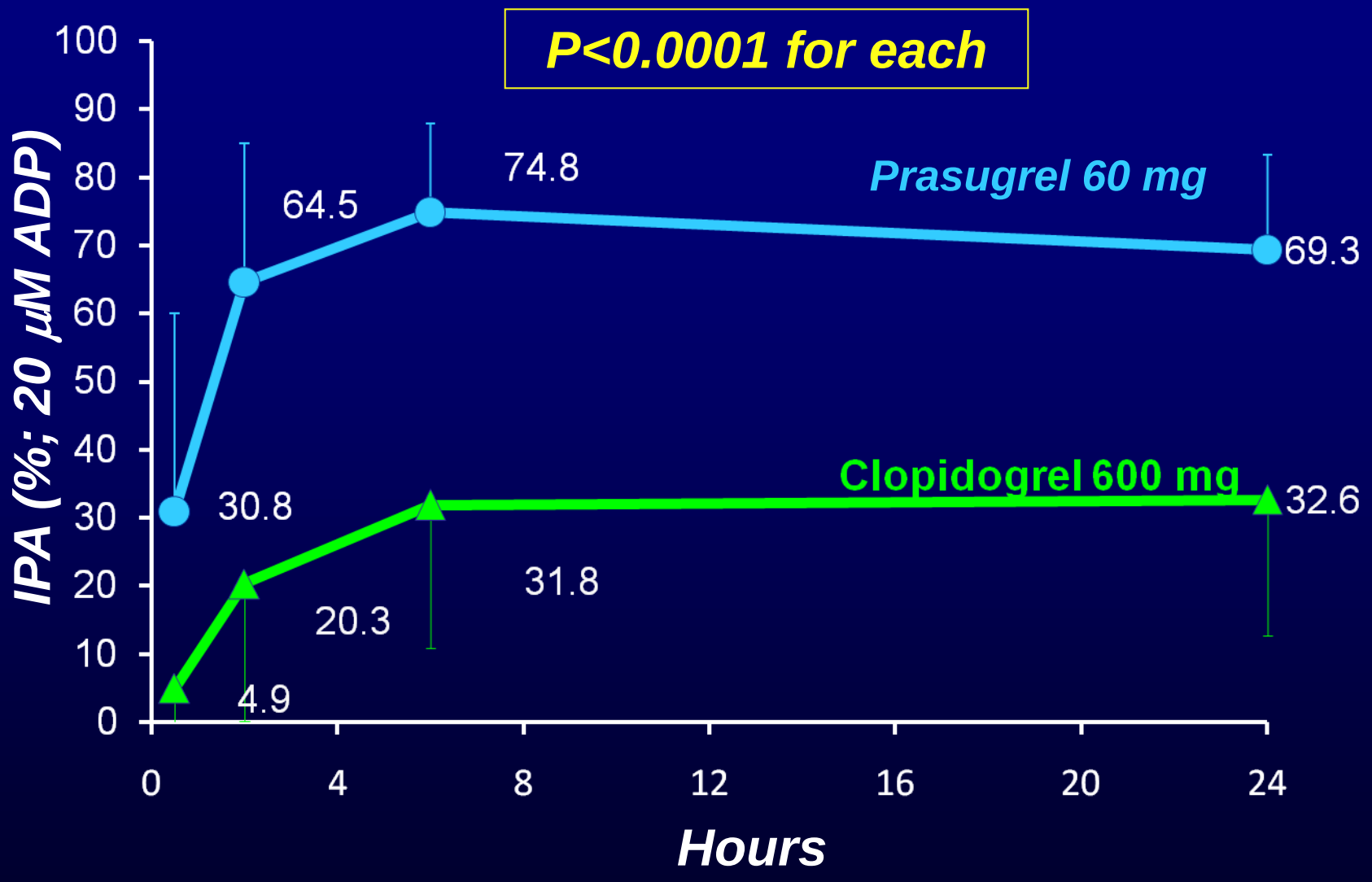


Primary end points: [a]LD phase 6 hours IPA (20 µM ADP); [b]MD phase 15 day and 29 day IPA (20 µM ADP). ADP=Adenosine Diphosphate; GP=Glycoprotein; IPA=Inhibition of Platelet Aggregation; LD=Loading Dose; MD=Maintenance Dose; PCI=Percutaneous Coronary Intervention

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

PRINCIPLE TIMI 44

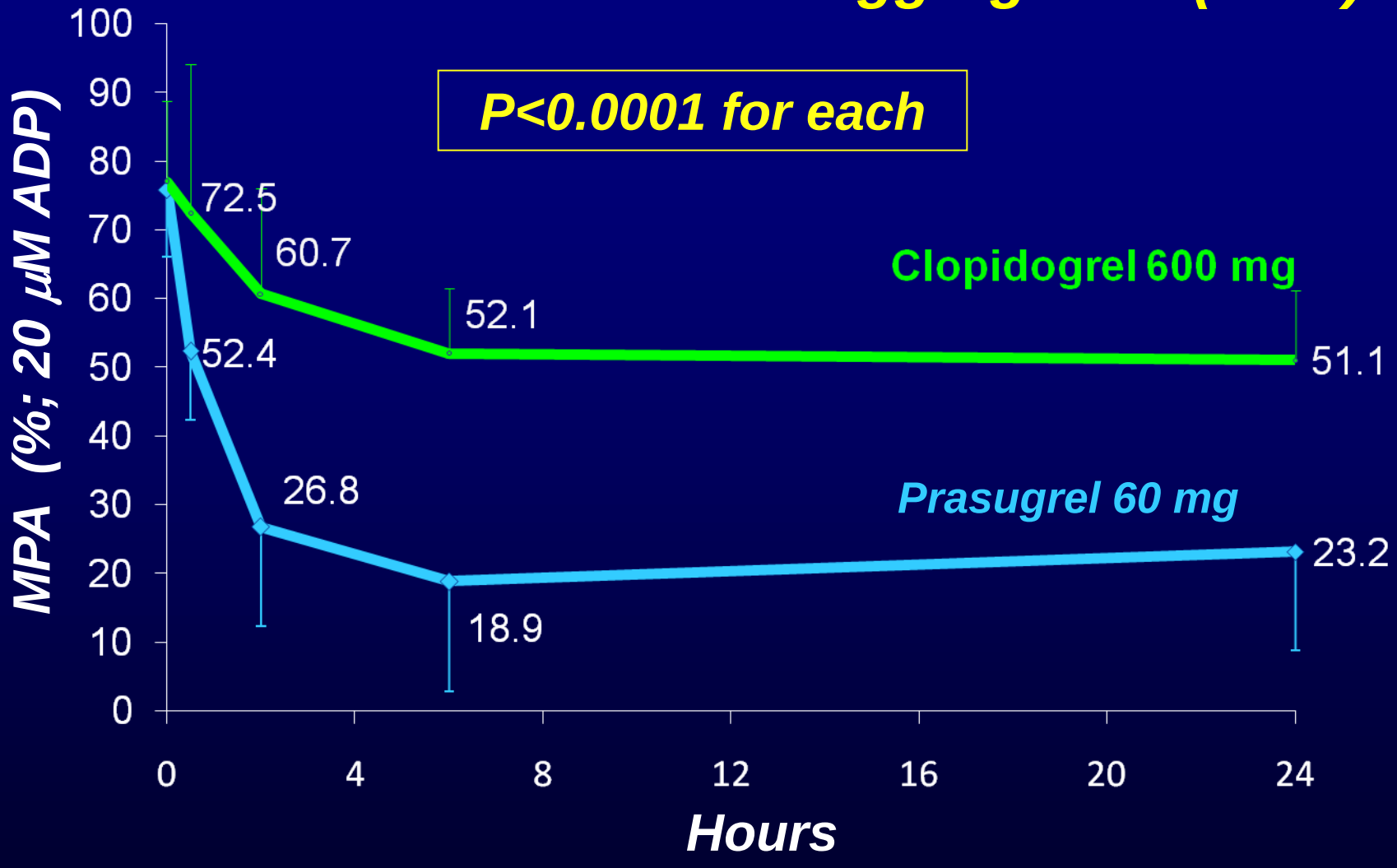
PRIMARY EP Acute Phase: IPA 20 uM ADP



Wiviott SD et al, Circulation 2007

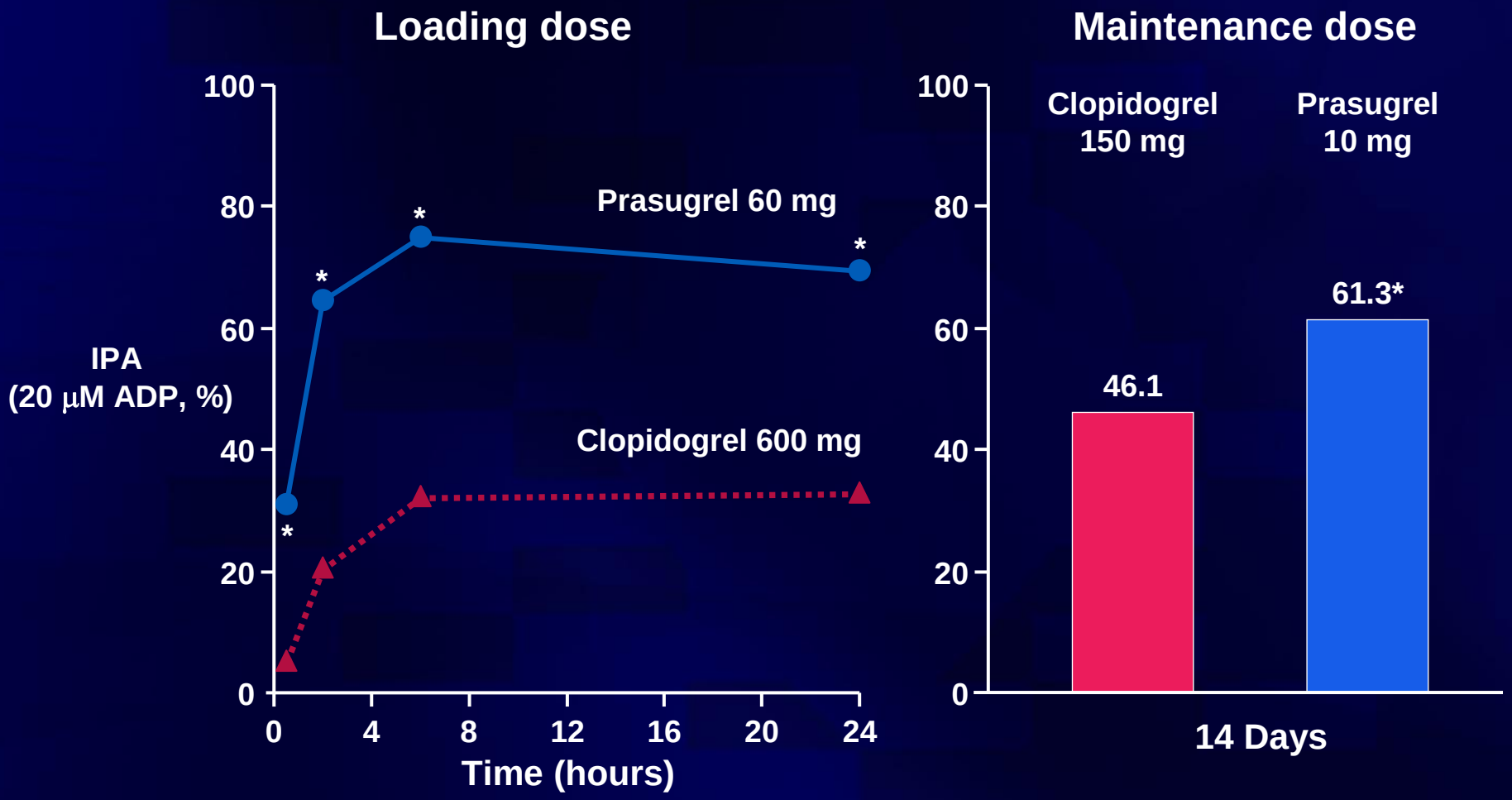
PRINCIPLE TIMI 44

Maximal Platelet Aggregation (MPA)



Wiviott SD et al, Circulation 2007

PRINCIPLE-TIMI 44: Inhibition of platelet aggregation with loading and maintenance doses



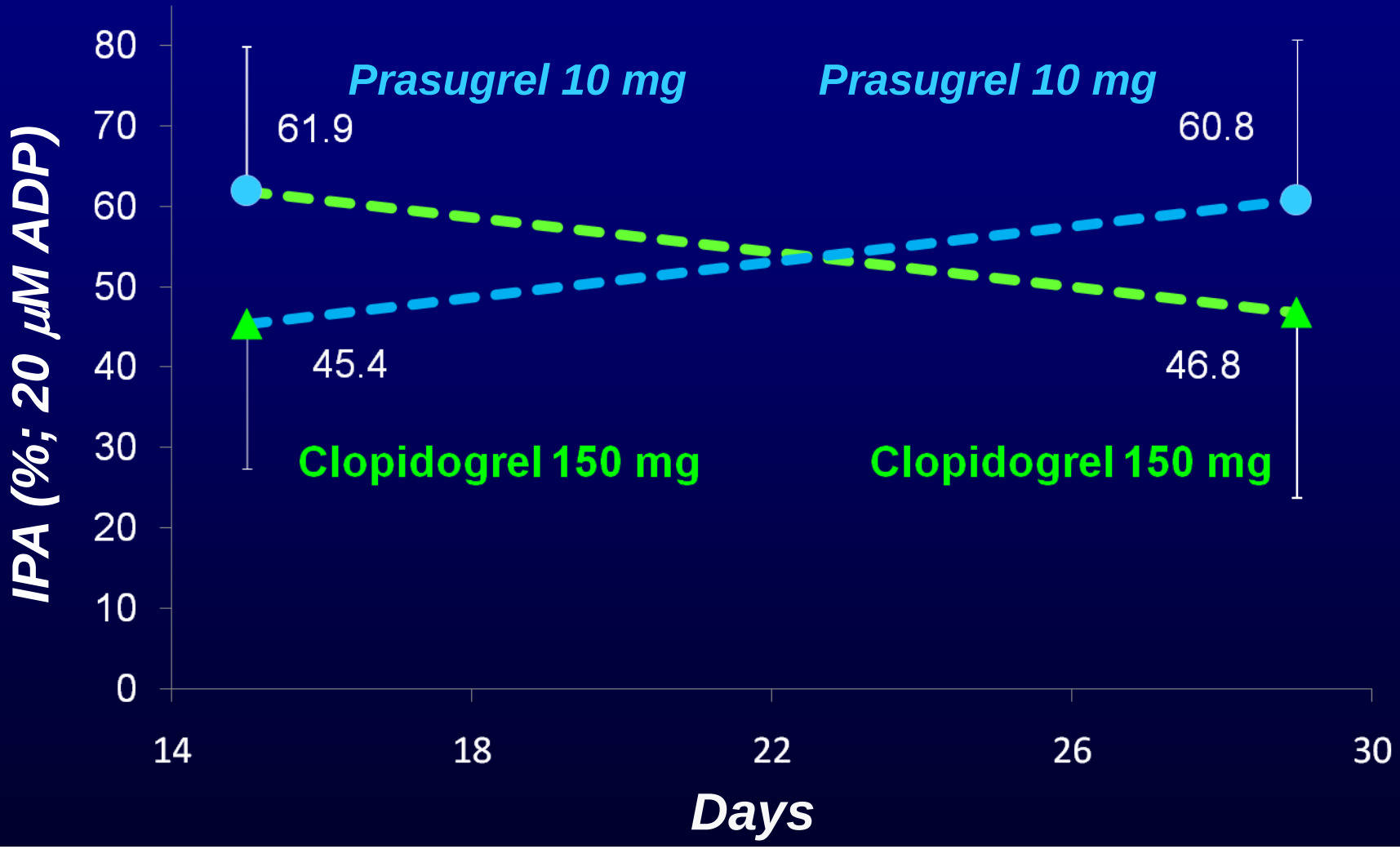
*P < 0.0001 vs clopidogrel
IPA = inhibition of platelet aggregation

Wiviott SD et al. *Circulation.* 2007;116:2923-32.

PRINCIPLE TIMI 44

PRIMARY EP Chronic Phase: IPA 20 uM ADP

Difference Between Treatments: 14.9 [95% CI 10.6 – 19.3], P<0.0001



Wiviott SD et al, Circulation 2007

American Heart Association
Learn and Live

SWitching Anti Platelet Study (SWAP)

Patient eligible for enrollment 30 – 330 days post an ACS
(Must be prescribed clopidogrel 75 mg qd)

↓

Clopidogrel 75 mg qd x 13 -15 days
Baseline platelet function studies at end of clopidogrel run-in

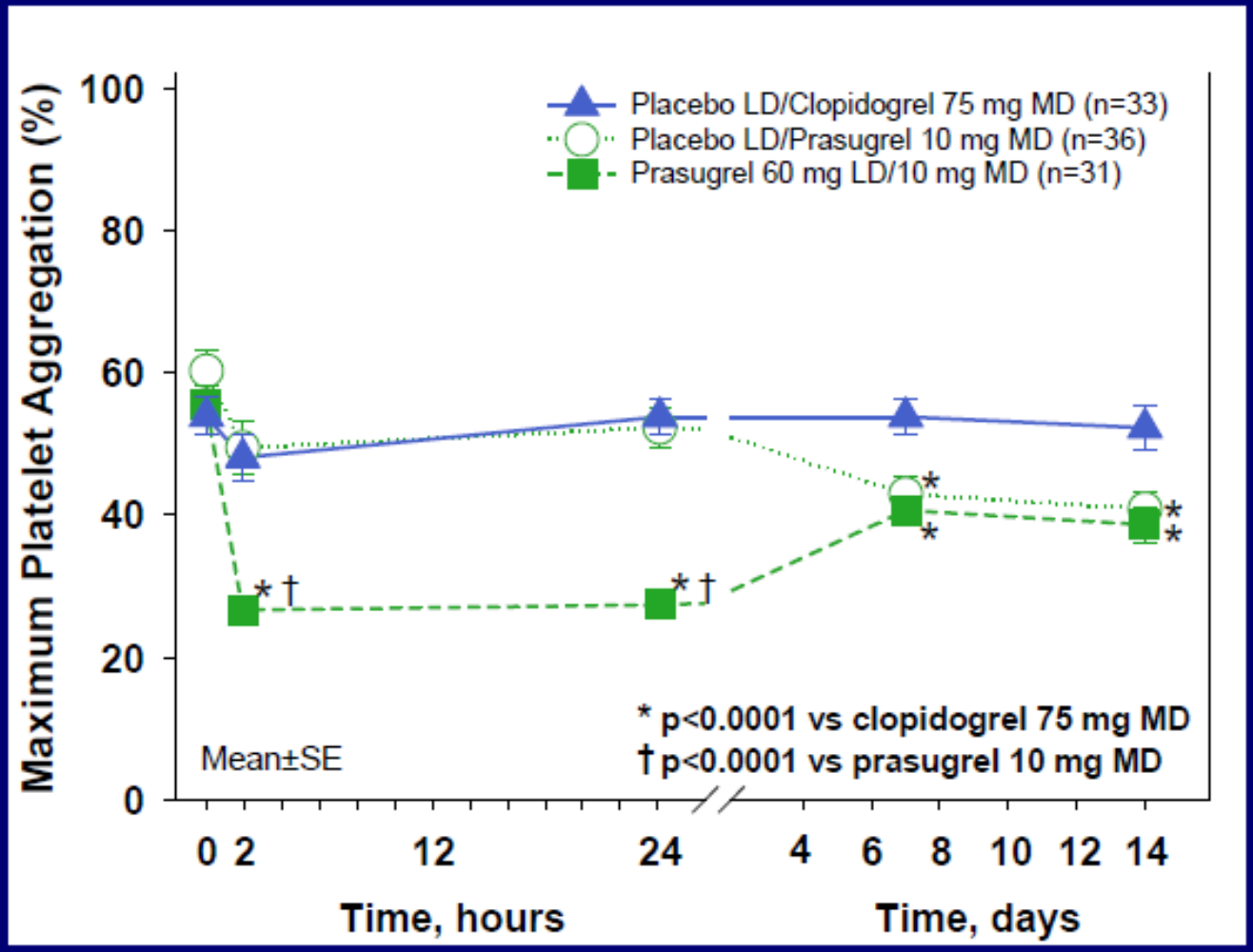
N=33	N=31	N=36
Clopidogrel 75mg qd x 13-15 days	Prasugrel 60 mg loading, 10 mg qd x 13-15 days	Prasugrel 10 mg qd x 13-15 days

↓

Platelet function studies at 2 hours, 24 hours, 7 and 14 days

SWAP: SWITCHING ANTIPLATELET THERAPY

Maximum Platelet Aggregation (20 µM ADP)

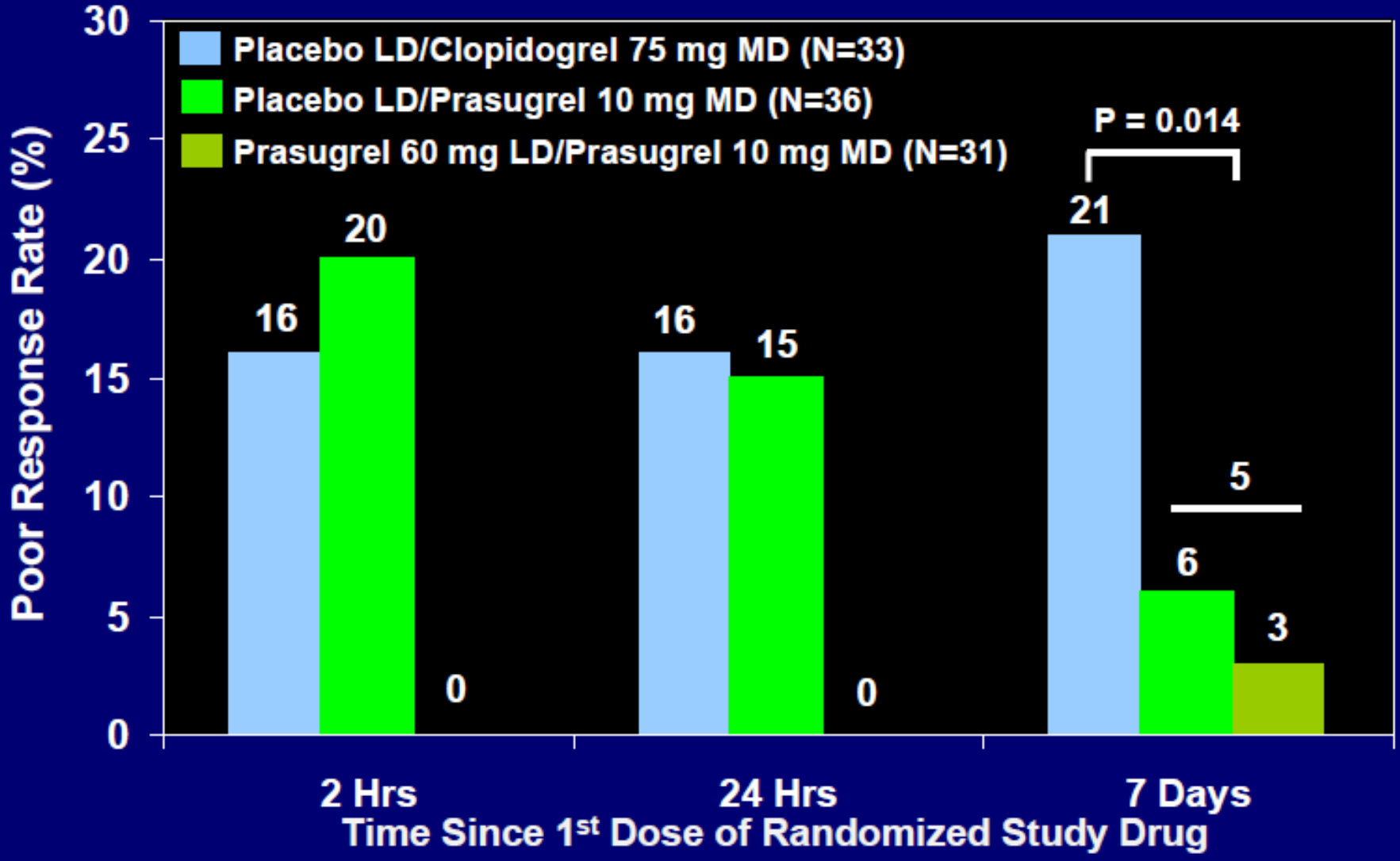


Similar findings obtained with MPA to 5 µM ADP, VASP PRI, and Verify *Now*® PRU

Angiolillo DJ et al. J Am Coll Cardiol 2010; 56:1017-23

SWAP: Poor Response Rates

SWAP

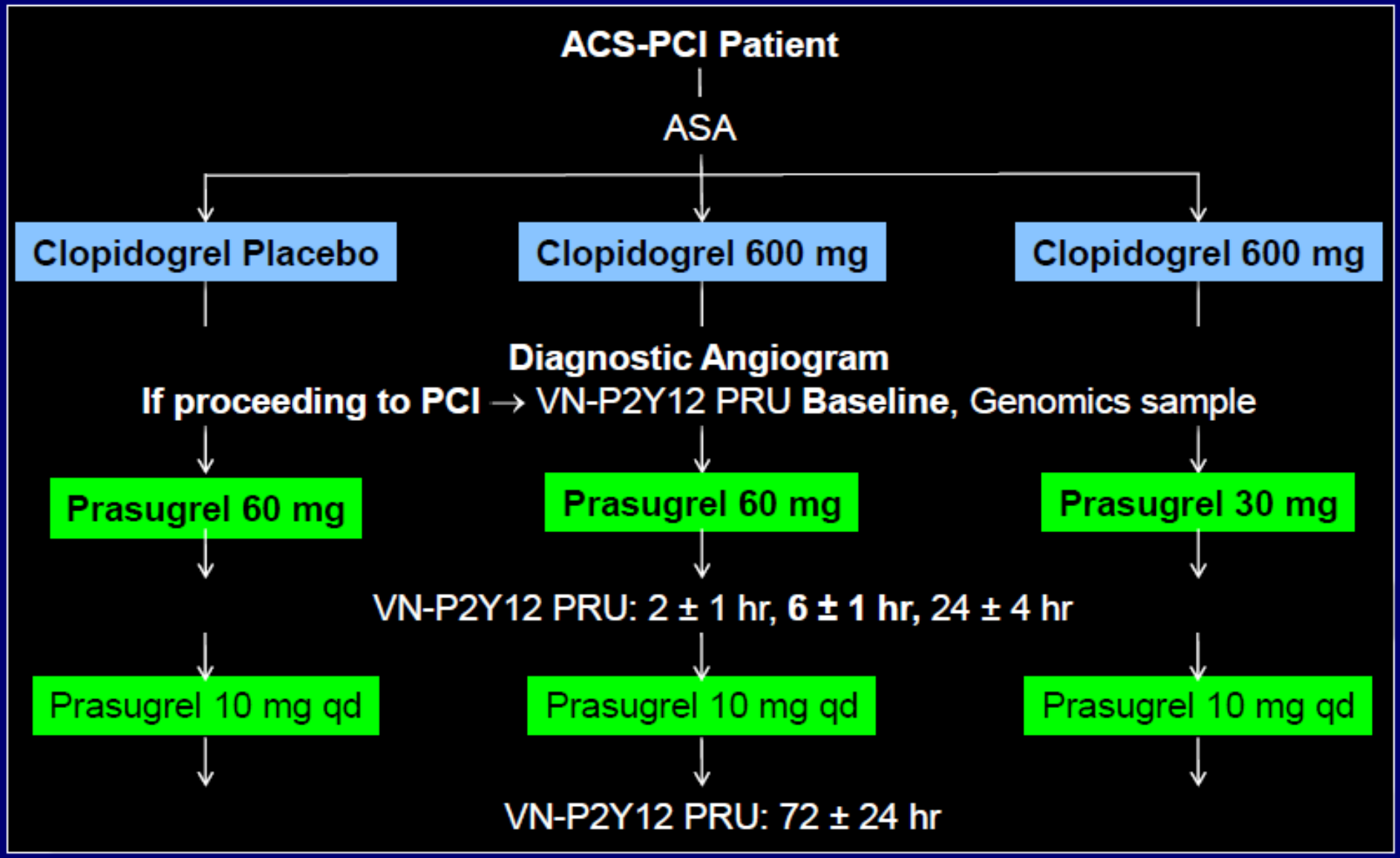


Poor response was defined as patients with MPA > 65% to 20 µM ADP assessed by light transmission aggregometry

LD=Loading Dose; MD=Maintenance Dose; MPA=Maximal Platelet Aggregation

TRIPLET
TReatment with Prasugrel Loading dose with or without prior clopidogrEl in acs paTients

Study Design



IPA=Inhibition of Platelet Aggregation; LD=Loading Dose; PRU=P2Y12 Reaction Units

Adapted from http://www.clinicaltrials.gov/ trial number NCT0115738

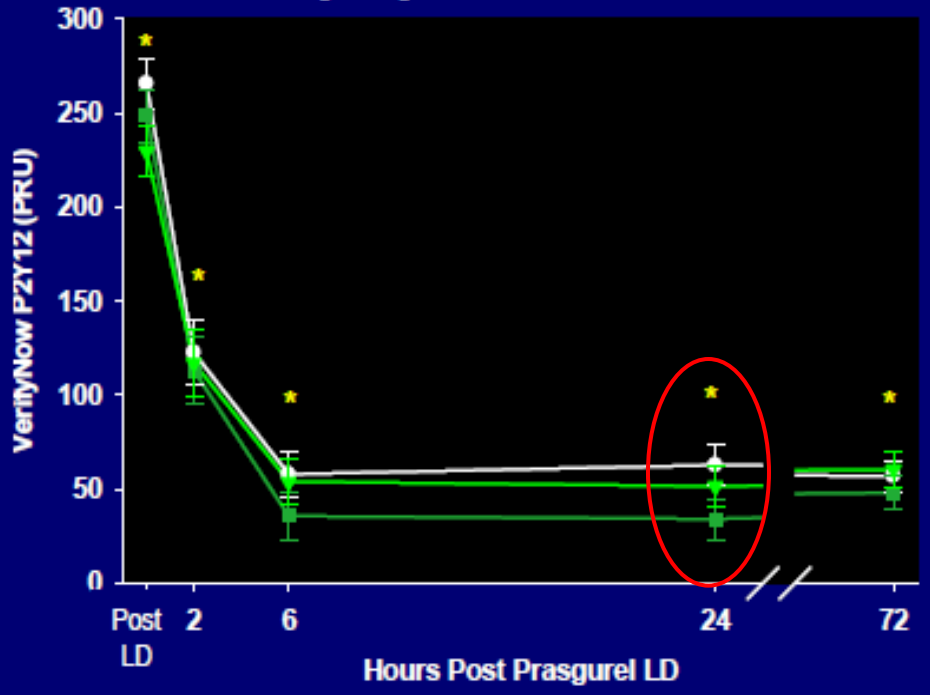
Safety of Reloading Prasugrel in Addition to Clopidogrel Loading in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Joshua P. Loh, MBBS, Lakshmana K. Pendyala, MD, Hironori Kitabata, MD, PhD, Rebecca Torguson, MPH, Fang Chen, PhD, Kenneth M. Kent, MD, PhD, Lowell F. Satler, MD, William O. Suddath, MD, Augusto D. Pichard, MD, and Ron Waksman, MD*

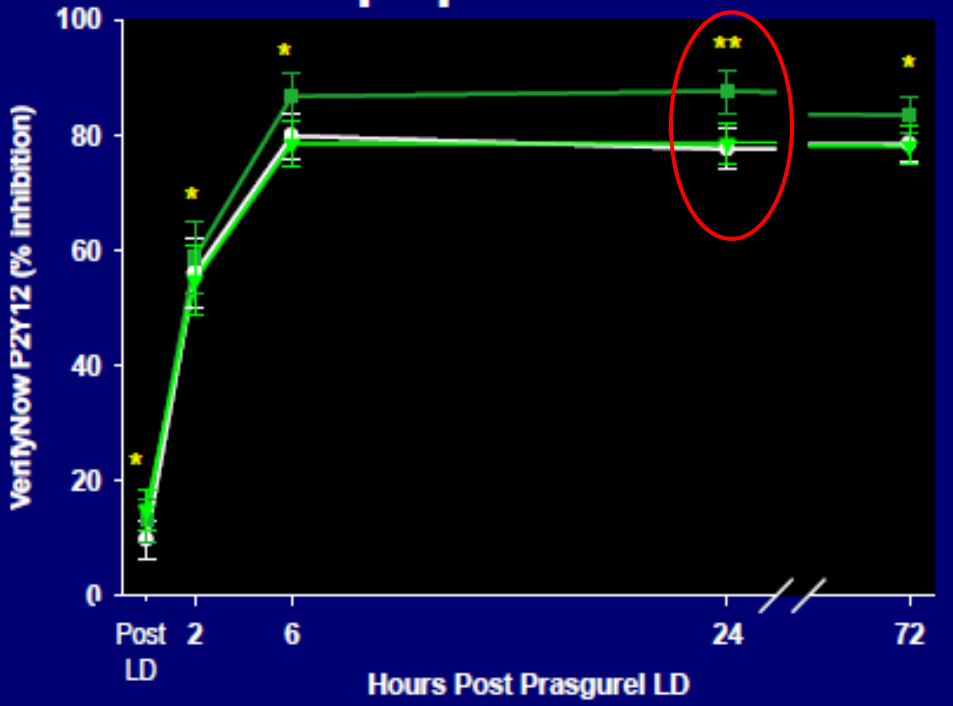
Patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) commonly receive a loading dose of either clopidogrel or prasugrel, in addition to aspirin. The present study aimed to assess the safety of reloading prasugrel in patients who had initially received a loading dose of clopidogrel compared to prasugrel loading alone. The study included a cohort of 606 consecutive patients with acute coronary syndrome who had received a 60-mg loading dose of prasugrel before PCI. These patients were then categorized into clopidogrel preloading (300 or 600 mg) followed by prasugrel reloading (CP-load group, n = 90) and prasugrel loading only (P-load group, n = 516). Both groups received a 10-mg maintenance dose of prasugrel after PCI. The primary end point was in-hospital Thrombolysis In Myocardial Infarction-defined major bleeding. The secondary end points were other in-hospital bleeding complications and major cardiovascular events. Patients in the CP-load group compared to the P-load group were younger, with lower rates of cardiovascular risk factors. Significantly more patients in the CP-load group presented with biomarker-positive myocardial infarction (80.0% vs 30.6%, p ≤0.001) and cardiogenic shock (5.6% vs 1.4%, p = 0.022). No significant differences (p = NS) were seen in Thrombolysis In Myocardial Infarction major bleeding (2.6% vs 2.8%), Thrombolysis In Myocardial Infarction major or minor bleeding (12.2% vs 7.0%), the need for blood transfusion (2.6% vs 2.1%), and vascular complications (1.3% vs 2.0%) between groups. The CP-load group experienced more in-hospital major adverse cardiac events (5.6% vs 1.6%, p = 0.031), urgent coronary artery bypass grafting (3.3% vs 0.2%, p = 0.011), and longer hospital and intensive care unit stays. In conclusion, preloading with clopidogrel should not be prohibitive to reloading with prasugrel in patients presenting with acute coronary syndrome and undergoing PCI with respect to bleeding and vascular complications. (Am J Cardiol 2013;111:841–845)

Time Course: Pharmacodynamic Population

PRU (LS mean), PD population



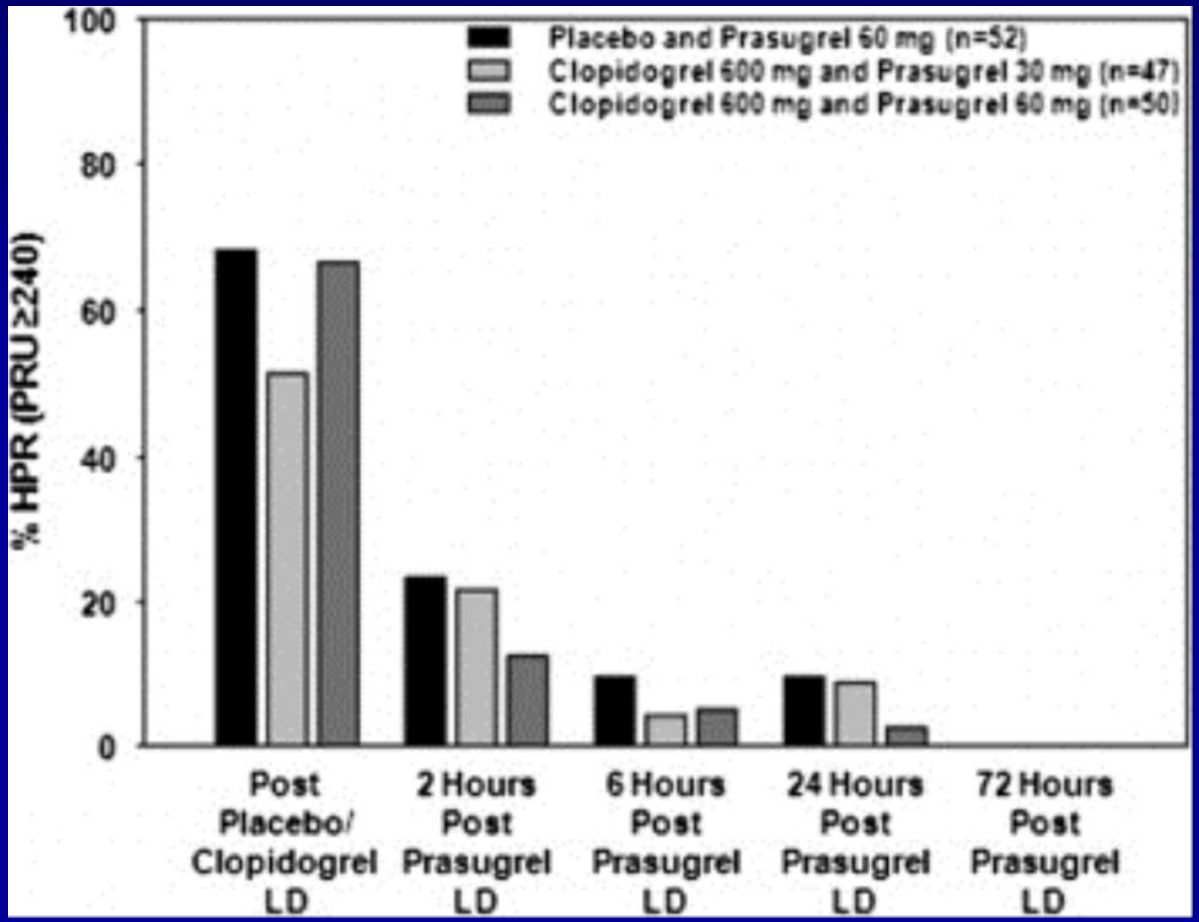
% Inhibition (LS mean), PD population



Placebo and Prasugrel 60 mg/10 mg
Clopidogrel 600 mg and Prasugrel 60 mg/10 mg
Clopidogrel 600 mg and Prasugrel 30 mg/10 mg

*P=NS at each time point vs. placebo/prasugrel 60 mg, **P=0.049 between the placebo/prasugrel 60 mg group and the clopidogrel 600 mg/prasugrel 60 mg group

Transferring from Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients: High on-Treatment Platelet Reactivity Analysis of the TRIPLET Trial



J Am Coll Cardiol. 2012;60(17_S):. doi:10.1016/j.jacc.2012.08.764

Safety Outcomes

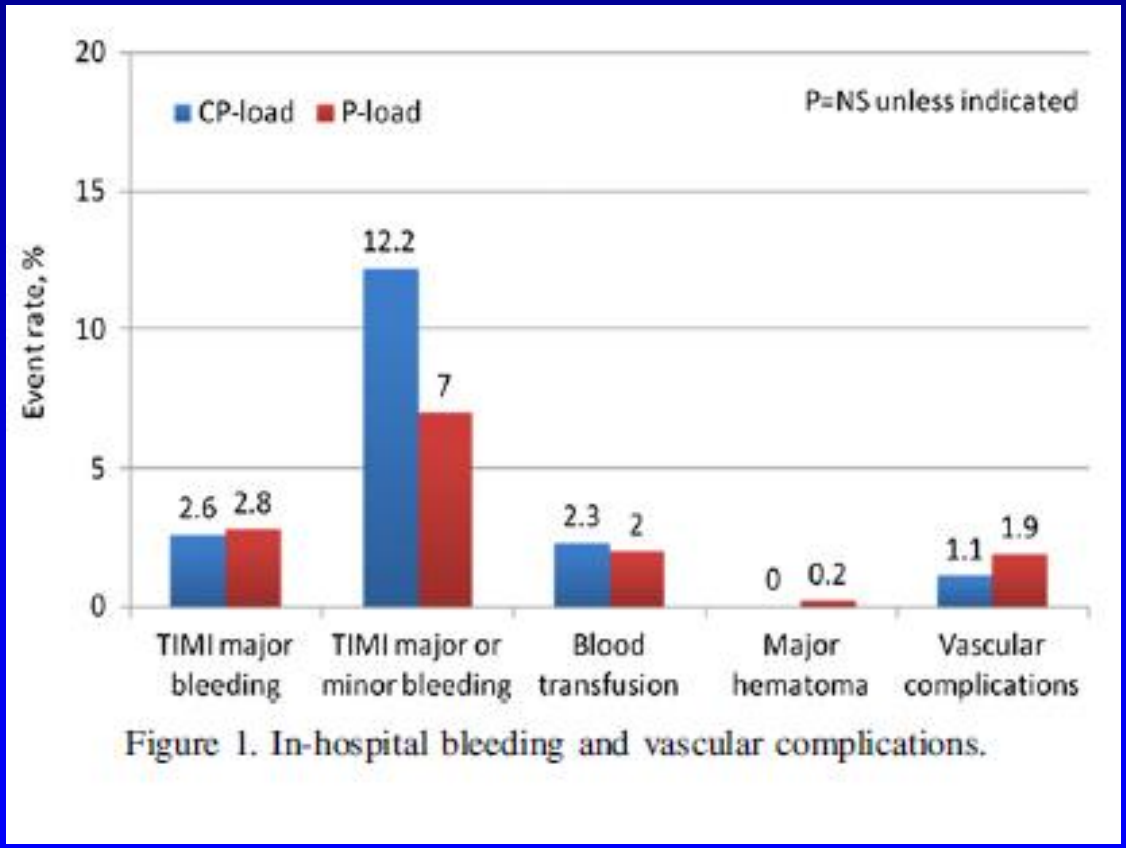


Figure 1. In-hospital bleeding and vascular complications.

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Median Time to Enrollment = 4.5 Days

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel**[1]: 300 mg LD + 75 mg MD
- **Prasugrel**[1]: 30 mg LD + 5 or 10 mg MD

Medical Management Decision ≤ 10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Clopidogrel**[1]: 75 mg MD
- **Prasugrel**[1]: 5 or 10 mg MD

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

Platelet Function Substudy Design

UA/NSTEMI (N = 9326, 52 countries)
planned medical management without revascularization

Prasugrel	vs.	Clopidogrel
10 mg (< 75 years and ≥ 60 kg) 5 mg (≥ 75 years; < 75 years and < 60 kg)		75 mg (for all)

Aspirin ≤ 100 mg (strongly recommended) for all

↓

PFS: 2690 (28% of total) participants from 25 countries

↓

VerifyNow $P2Y_{12}$ Assay
At baseline, at 2 h, and at 1, 3, 6, 12, 18, 24, and 30 mos after randomization

→ 126 without valid PRU measurement excluded from analysis

↓

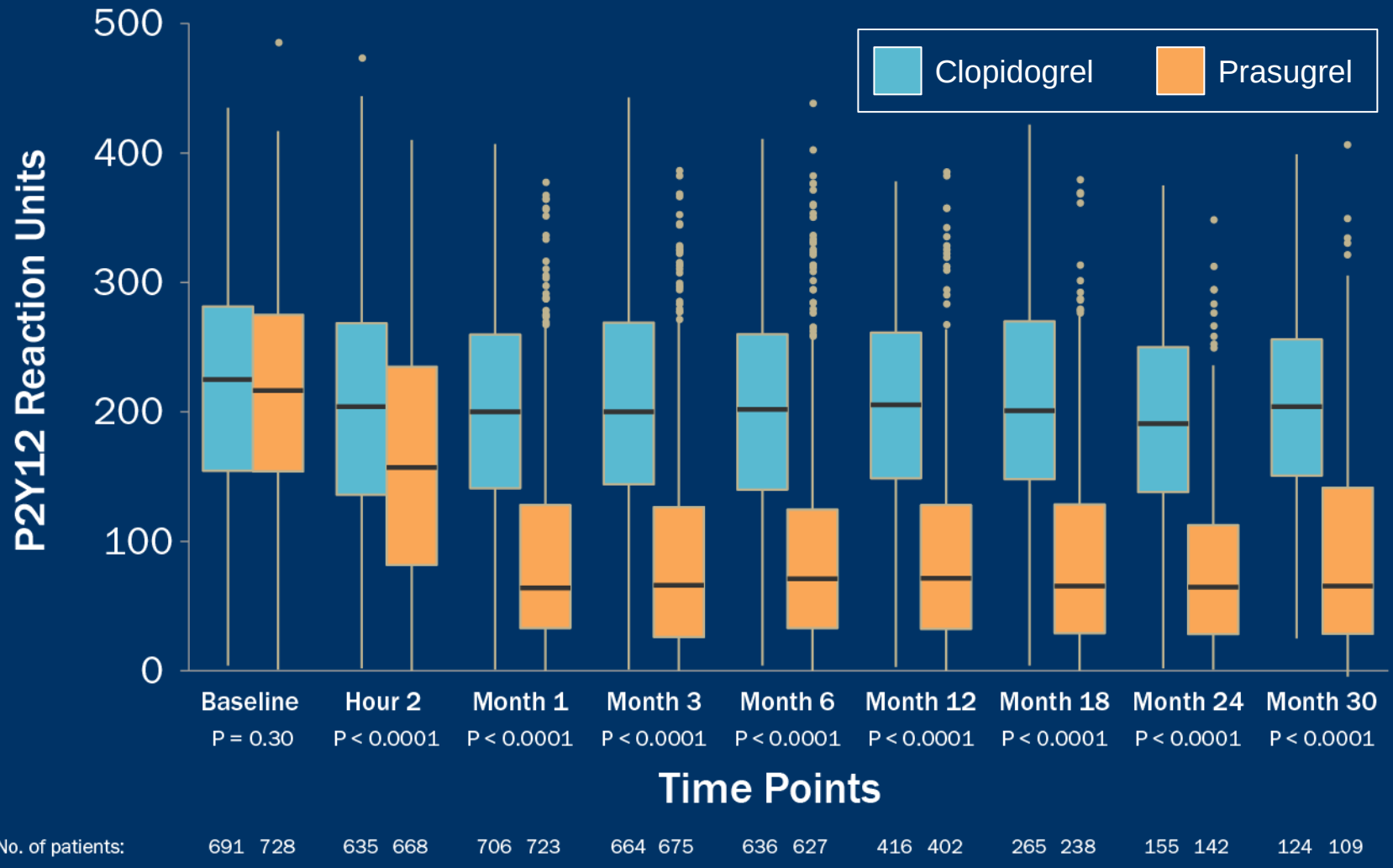
2564 participants (prasugrel, n = 1286 and clopidogrel, n = 1278) included in final analysis

Primary efficacy endpoint: - Composite of CV death, MI, and stroke through 30 months
Key secondary endpoints: - All-cause death
- MI

Median On-Treatment PRU Through 30 Months

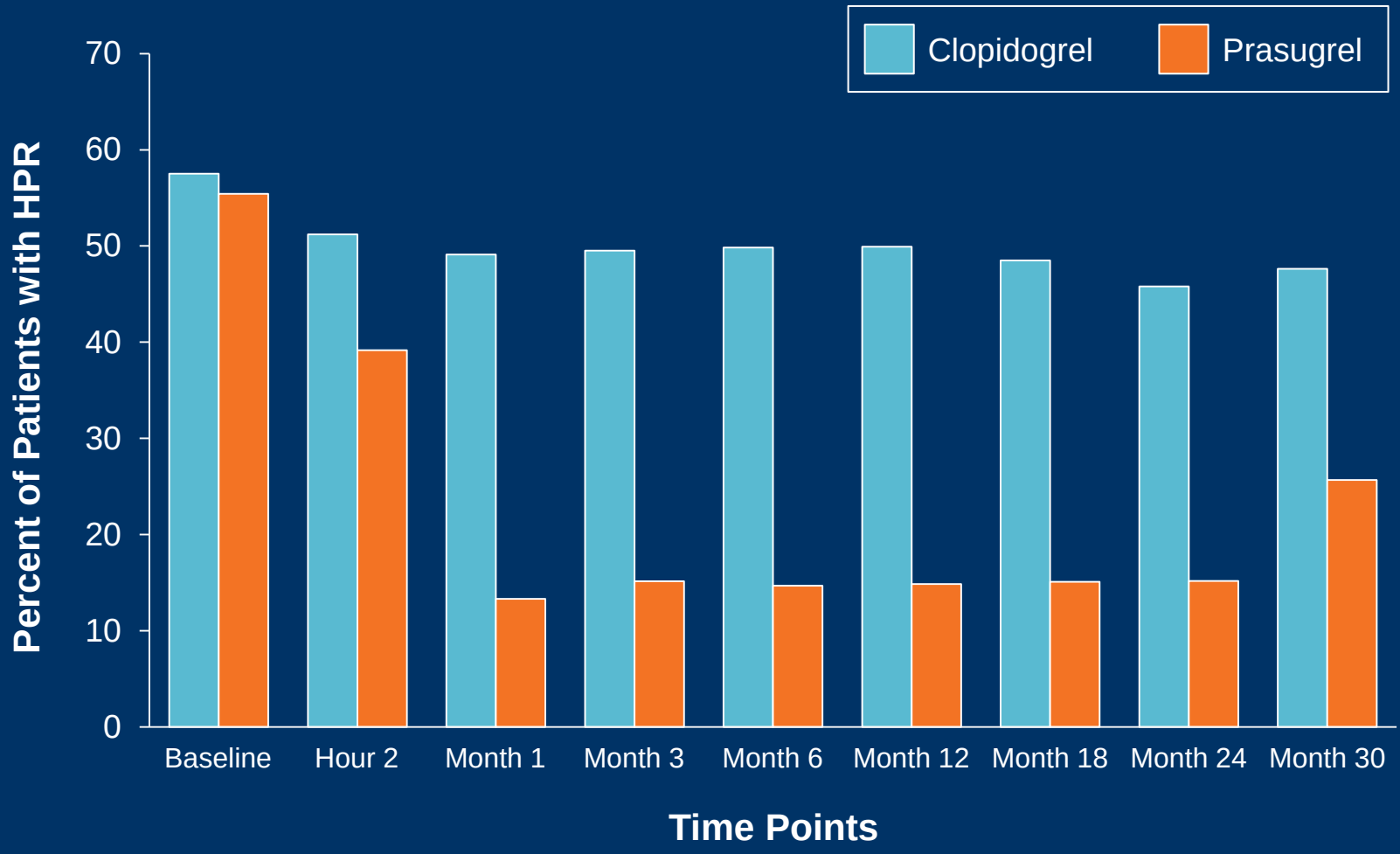
< 75 years and ≥ 60 kg

Clopidogrel 75 mg/day vs. **Prasugrel 10 mg/day**



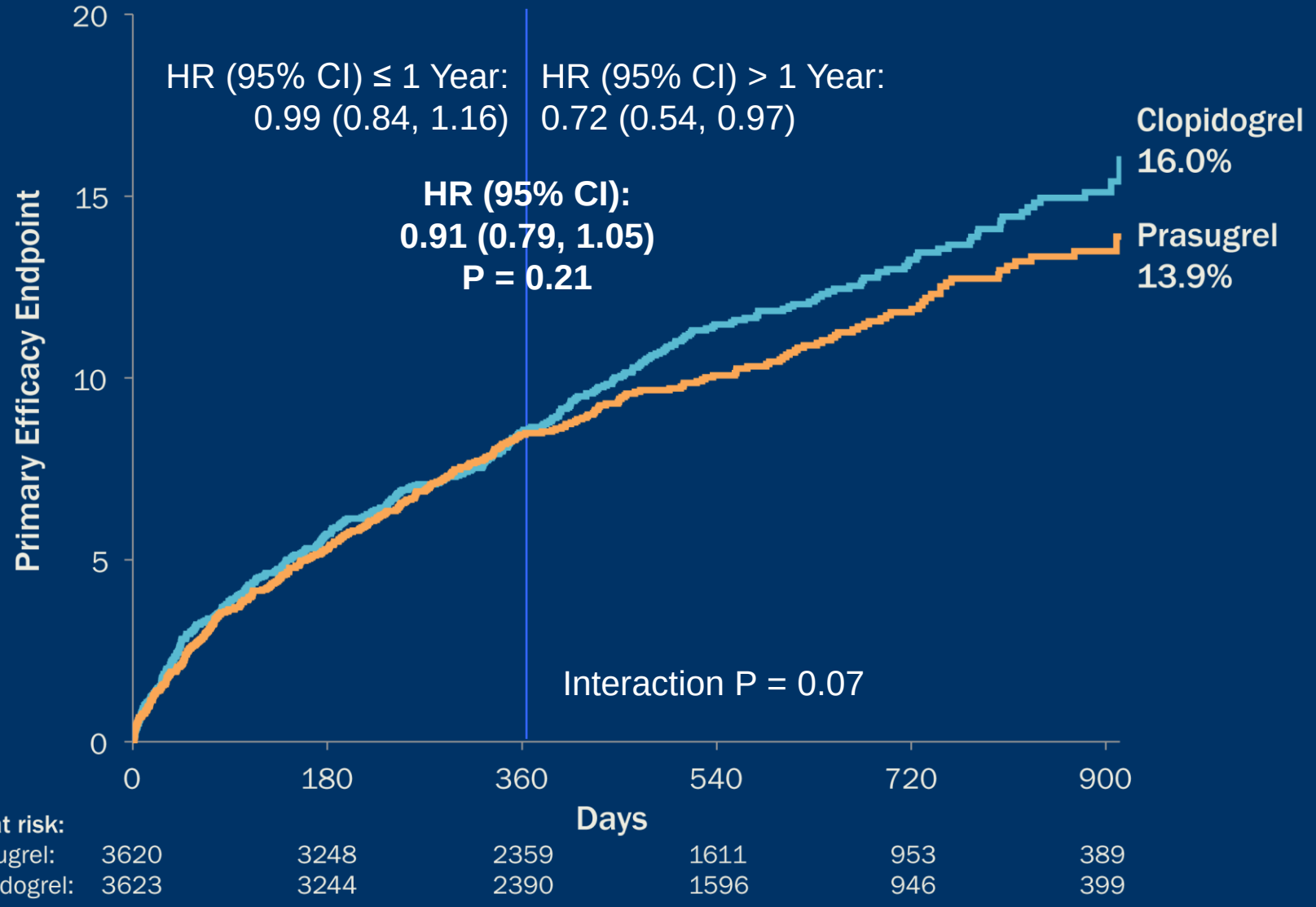
Frequency of High Platelet Reactivity (HPR)

> 208 PRU Cut-Point



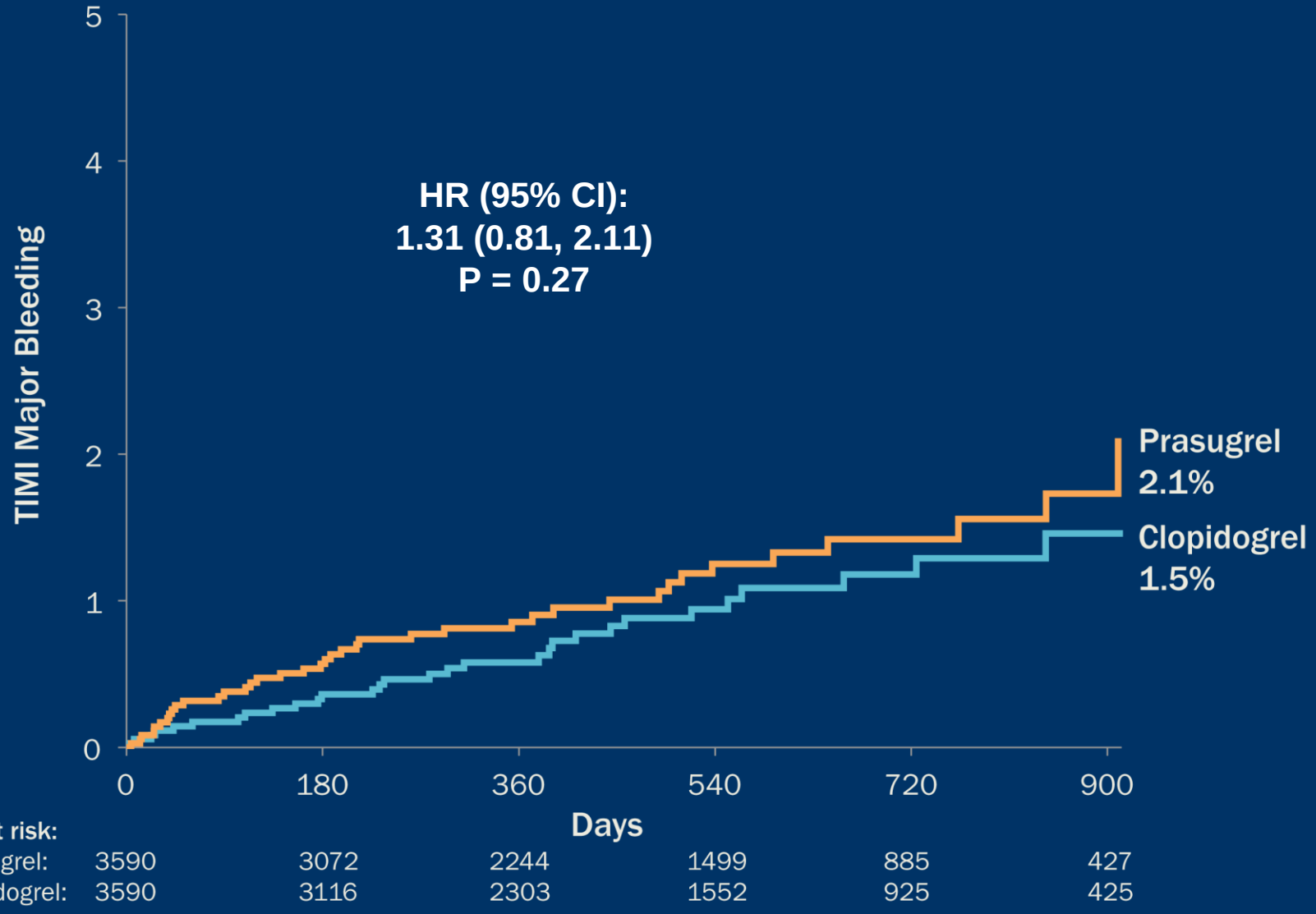
Primary Efficacy Endpoint to 30 Months

(Age < 75 years)



TIMI Major Bleeding to 30 Months

(Age < 75 years)



PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if PPCI planed)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

Study medication

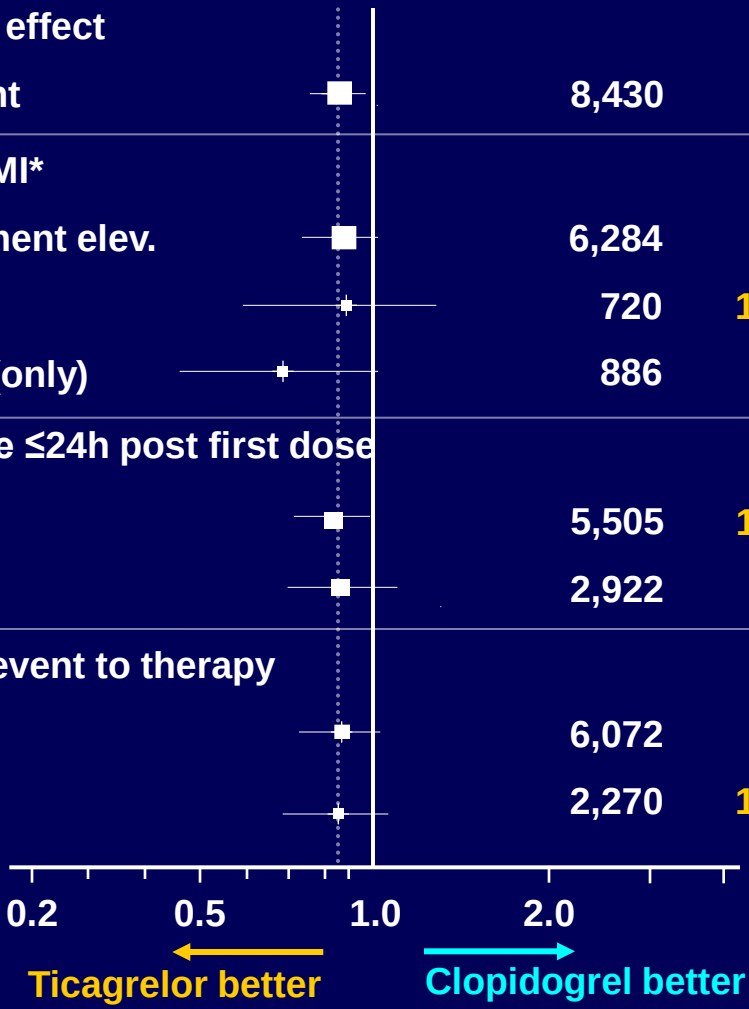
PLATO

Medication	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)
Start of randomised treatment		
Time after start of chest pain, h, median	11.3	11.3
Randomised treatment compliance, %		
Premature discontinuation of study drug	23.4	21.5
Clopidogrel start-up, %		
Clopidogrel in hospital before randomisation	46.0	46.1
Invasive procedures at index hospitalisation, %		
Planned invasive treatment	72.1	71.9
Coronary angiography	81.4	81.5
PCI during index hospitalisation	60.9	61.1
Cardiac surgery	4.3	4.7

Primary efficacy endpoint in selected pre-defined subgroups

PLATO-STEMI

Characteristic	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	p-value (Interaction)
Overall treatment effect					
Primary Endpoint	8,430	9.3	11.0	0.85 (0.74, 0.97)	
Definition of STEMI*					0.49
Persist. ST-segment elev.	6,284	8.9	10.4	0.87 (0.74, 1.02)	
LBBB	720	14.5	14.5	0.89 (0.59, 1.34)	
Final diagnosis (only)	886	8.4	12.5	0.67 (0.44, 1.02)	
Intended clop dose ≤24h post first dose					0.90
300 mg	5,505	10.1	11.9	0.84 (0.71, 0.99)	
600 mg	2,922	7.9	9.3	0.86 (0.67, 1.11)	
Time from index event to therapy					0.89
<12 hours	6,072	8.3	9.5	0.86 (0.73, 1.03)	
≥12 hours	2,270	12.0	14.2	0.85 (0.67, 1.07)	



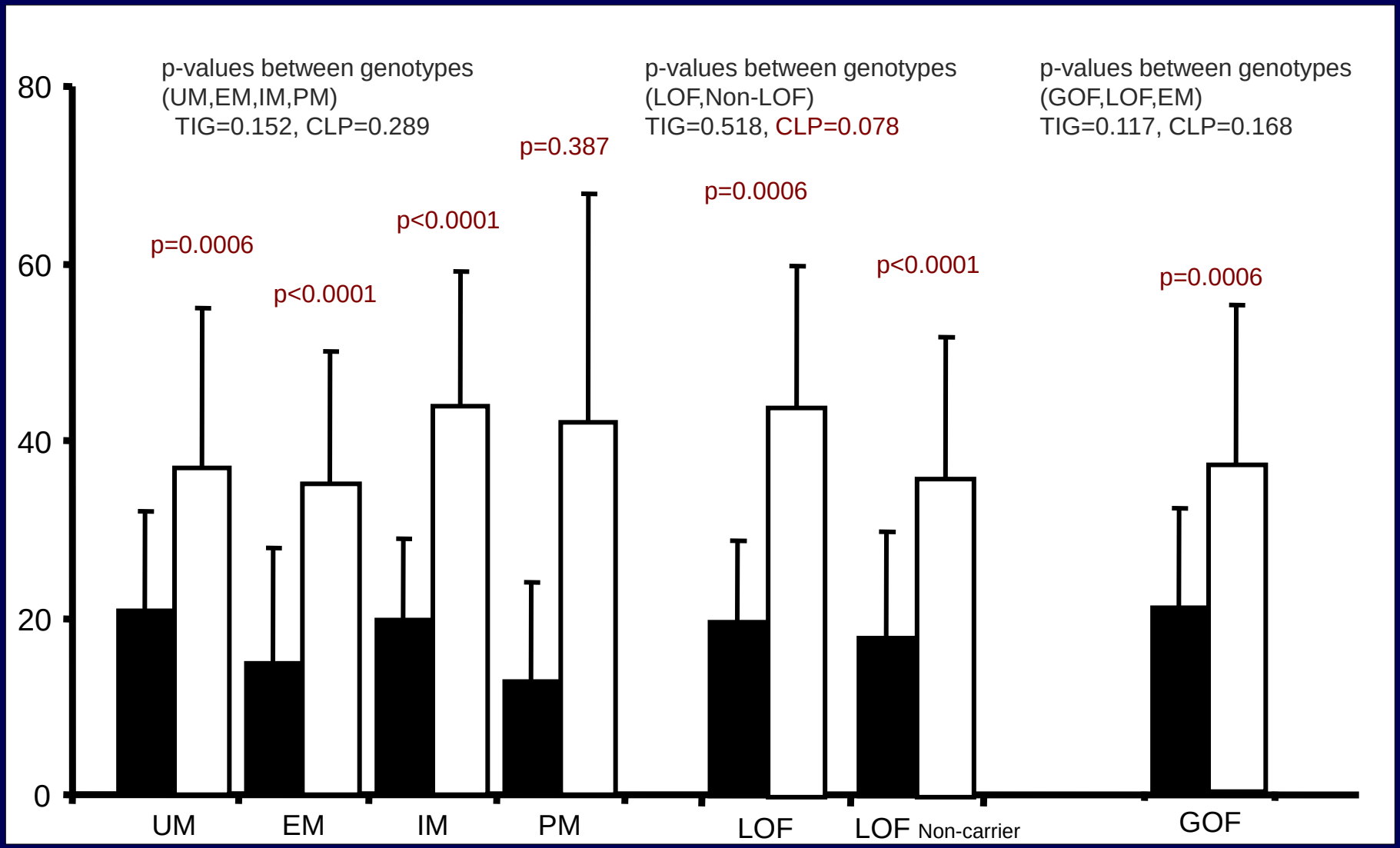
*Patients with LBBB and ST-elevation were classified as LBBB

Gabriel et al. *Circulation. 2010;122:2131-2141.*

5 μM ADP-Induced Aggregation

8 hrs After Loading Dose

PLATO



UM = ultra rapid metabolizer
Extensive metabolizer
Intermediate metabolizer
Poor metabolizer

Ticagrelor Clopidogrel

Wallentin et al. TheLancet 2010; DOI:10.1016/S0140-6736(10)61274-3

What should the cardiology fellow do?

- Continue clop. MD & wait for cath results
- Load immediately with prasugrel 60 mg
- Load immediately with prasugrel 30 mg
- Start prasugrel 10 mg w/o loading
- Ticagrelor?

Addendum

- The patient was loaded with 60 mg prasugrel on admission.
- Taken to cath lab the next morning.
- PCI to LCX with DES.
- Discharge next day.

Thank you for your attention