First Large-Scale Platelet Function Evaluation in an Acute Coronary Syndromes Trial: The TRILOGY ACS — Platelet Function Substudy

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www.clinicaltrials.gov Identifier: NCT00699998

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Conflict of Interest Disclosures

Disclosures for all authors listed within the manuscript

Sponsor

Eli Lilly and Daiichi Sankyo

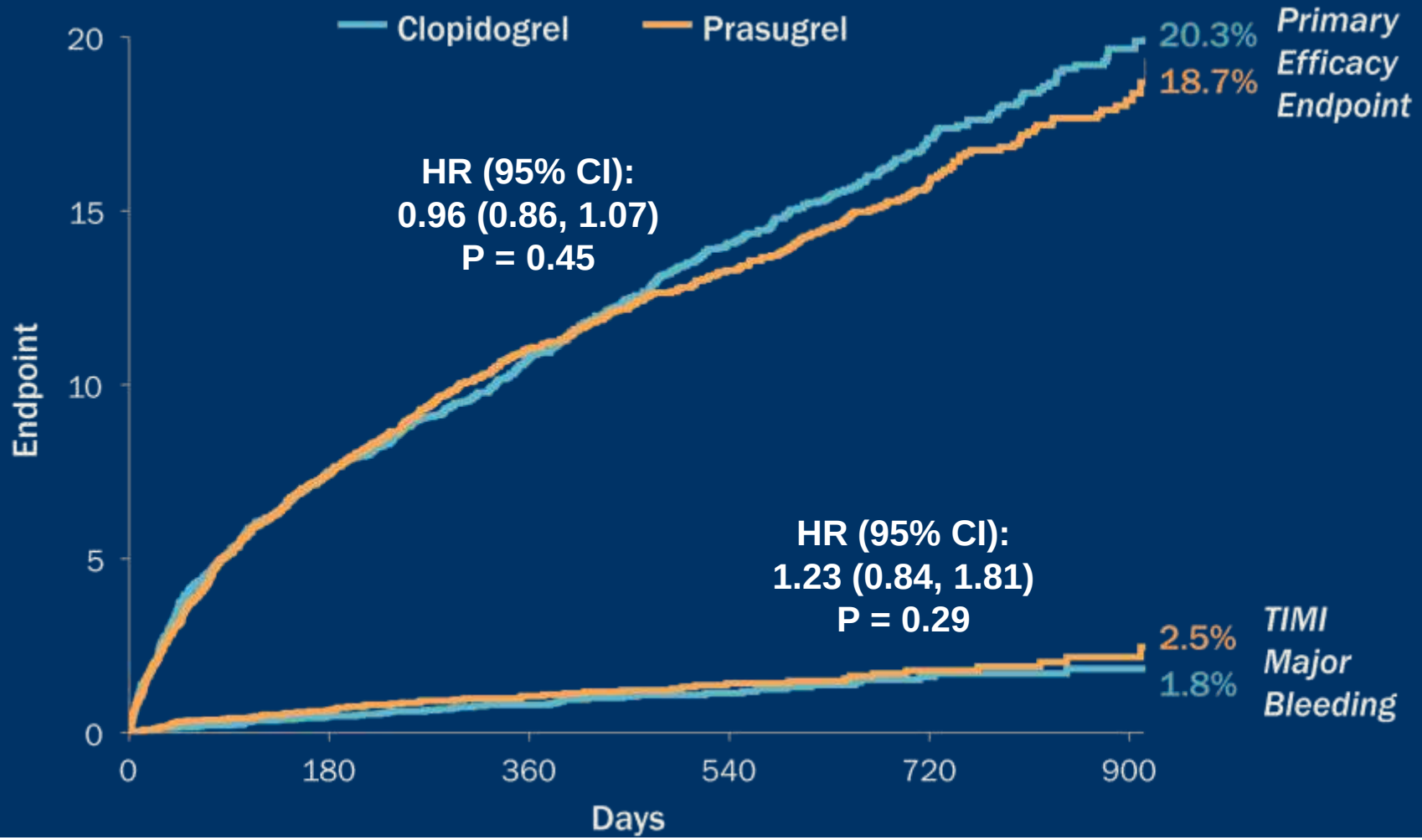
Background

- High platelet reactivity (HPR) to ADP is associated with ischemic risk in stable PCI patients.[1]
- **Few** studies have evaluated time-dependent relationships of platelet reactivity with ischemic event occurrence.
- A large platelet function substudy has not previously been embedded within an ACS trial to inform clinical outcomes.
- **No** information available on platelet function and ischemic events occurrence in ACS patients managed medically without revascularization.
- **No** information on PD effect of 5-mg vs. 10-mg prasugrel doses in ACS patients.

1. Gurbel PA et al. *Thromb Haemost.* 2012;108:12–20.

Primary Efficacy Endpoint (CV Death, MI, Stroke) and TIMI Major Bleeding Through 30 Months

(Overall TRILOGY population)



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

Objectives

- To characterize differences in platelet reactivity [VerifyNow P2Y12 reaction units (PRU)] between prasugrel vs. clopidogrel over time.
- To delineate the relationship of platelet reactivity with ischemic endpoint occurrence.
- To determine a threshold for high platelet reactivity (HPR) to discriminate between patients with and without ischemic event occurrence.

Statistical Analysis

- Relationship of PRU with ischemic events:
  - Cox models regressing time-to-first-event on PRU
    1) *PRU as time-varying covariate (per 60-unit increase)*
    2) *Imputation for missing PRUs*
  - Cox models with a 30-day landmark, with HPR defined by:
    > 208 PRU (prespecified based on PCI studies: GRAVITAS and ADAPT-DES)

    > 178 PRU (based on ROC analysis from current database)
  - Model variables derived from:
    - GRACE 6-month mortality risk score
    - TRILOGY specific variables (diabetes, angio pre-rand., current smoking, baseline meds., ASA dose, prior CABG, clop. strata).

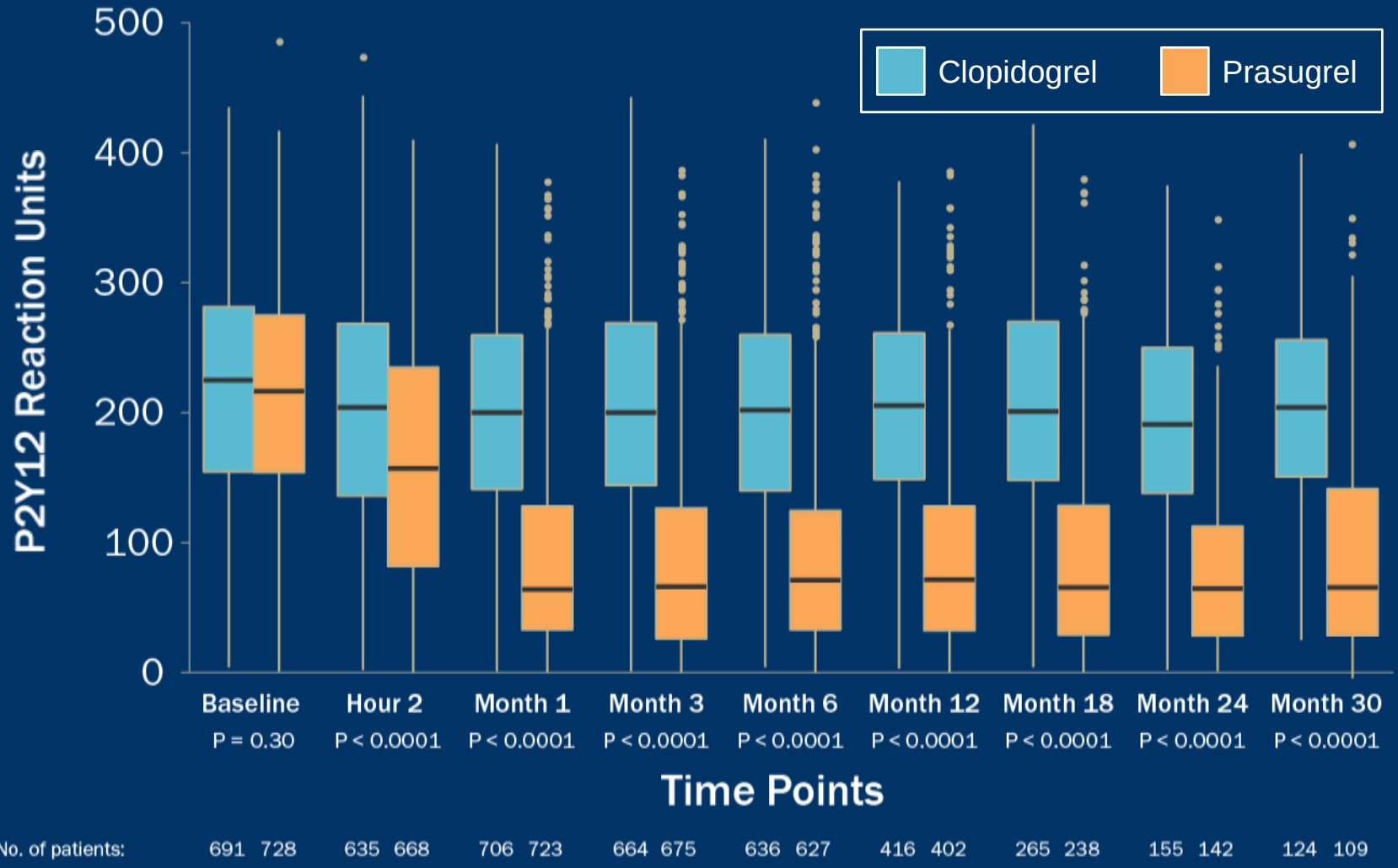
Baseline Characteristics

	PFS and non-PFS Populations		PFS Population by Study Drug	
	Included in PFS (N = 2564)	Not included in PFS (N = 6762)	Prasugrel (N = 1286)	Clopidogrel (N = 1278)
Age ≥ 75 years—%	20.1	23.2	19.0	21.2
Female sex—%	39.1	39.2	38.3	39.9
Weight < 60 kg—%	15.6	14.8	15.5	15.6
Unstable angina—%	32.9	29.0	33.4	32.4
NSTEMI—%	67.1	71.0	66.6	67.6
Diabetes mellitus—%	37.0	38.4	35.8	38.2
Current/recent smoking—%	19.7	20.1	19.4	19.9
GRACE risk score	122 (105–140)	121 (105–139)	120 (104–139)	122 (106–140)
Creatinine clearance—mL/min	74 (55–97)	72 (53–96)	74 (55–97)	74 (56–96)
Statin—%	82.2	83.8	82.3	82.1
Proton-pump inhibitor—%	23.7	25.7	23.6	23.9
Angiography prior to randomization—%	38.7	42.3	38.3	39.2

Median On-Treatment PRU Through 30 Months

< 75 years and ≥ 60 kg

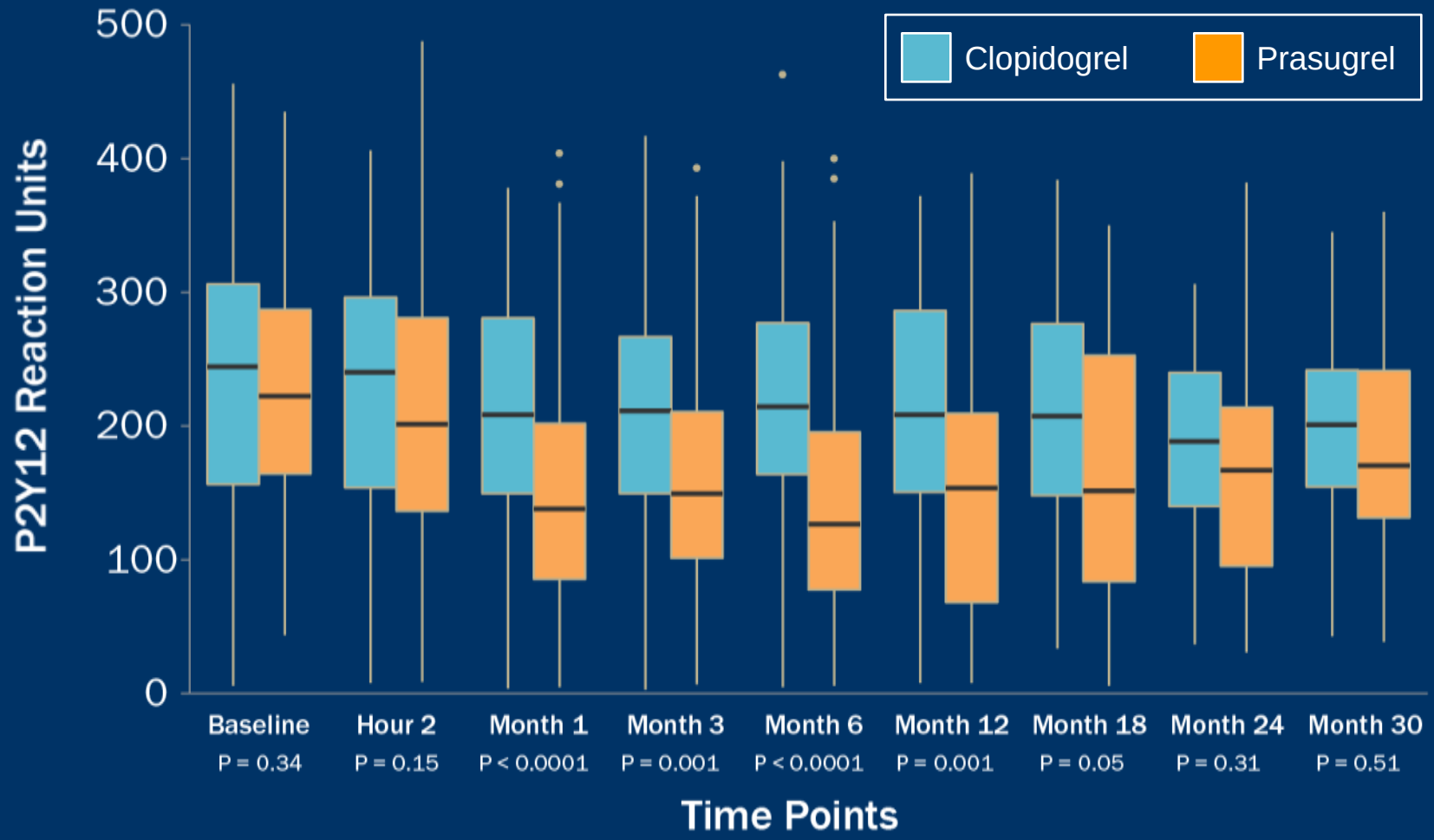
Clopidogrel 75 mg/day vs. **Prasugrel 10 mg/day**



Median On-Treatment PRU Through 30 Months

< 75 years and < 60 kg

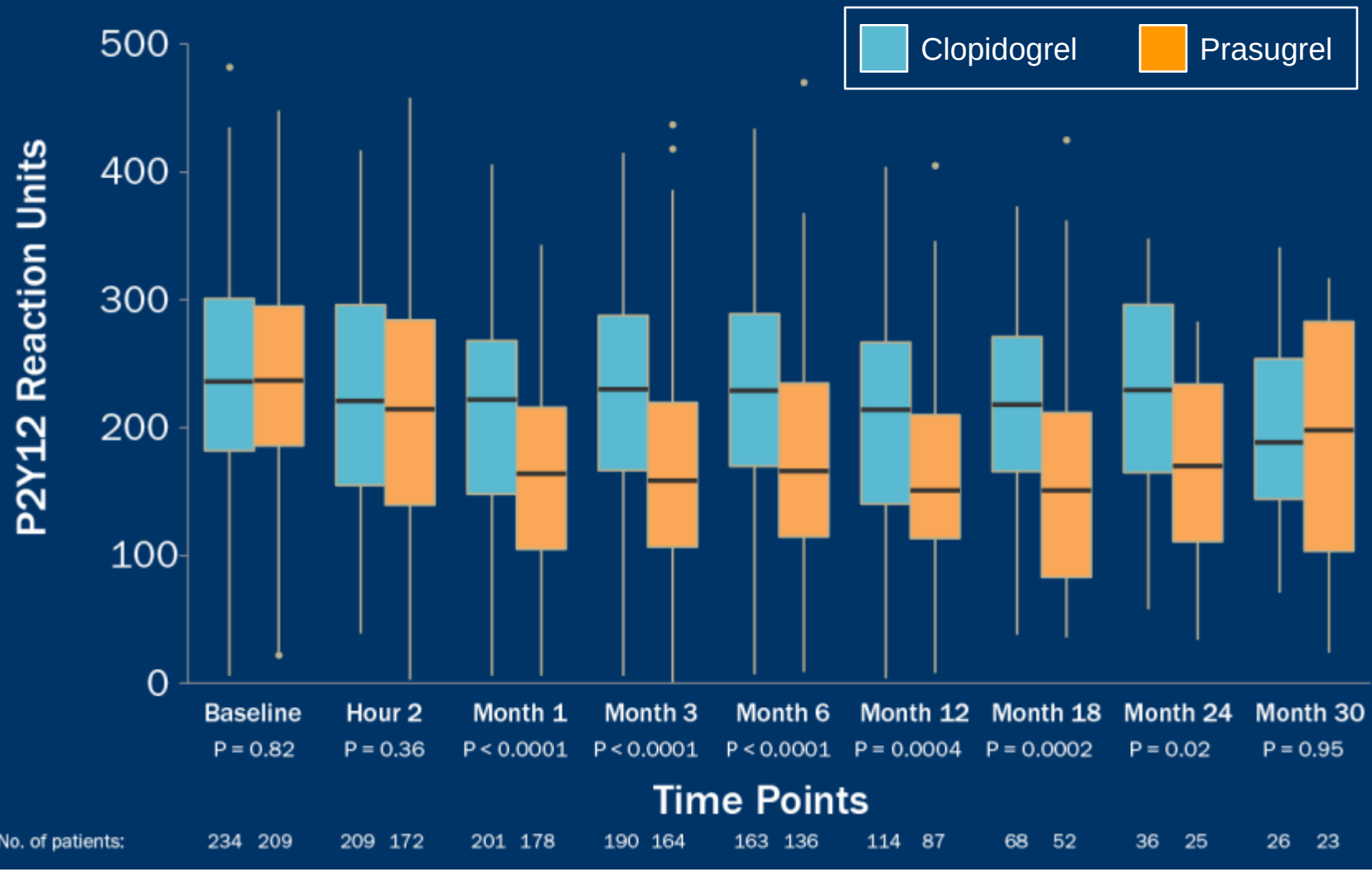
Clopidogrel 75 mg/day vs. **Prasugrel 5 mg/day**



Median On-Treatment PRU Through 30 Months

≥ 75 years

Clopidogrel 75 mg/day vs. **Prasugrel 5 mg/day**



30-Day PRU Values

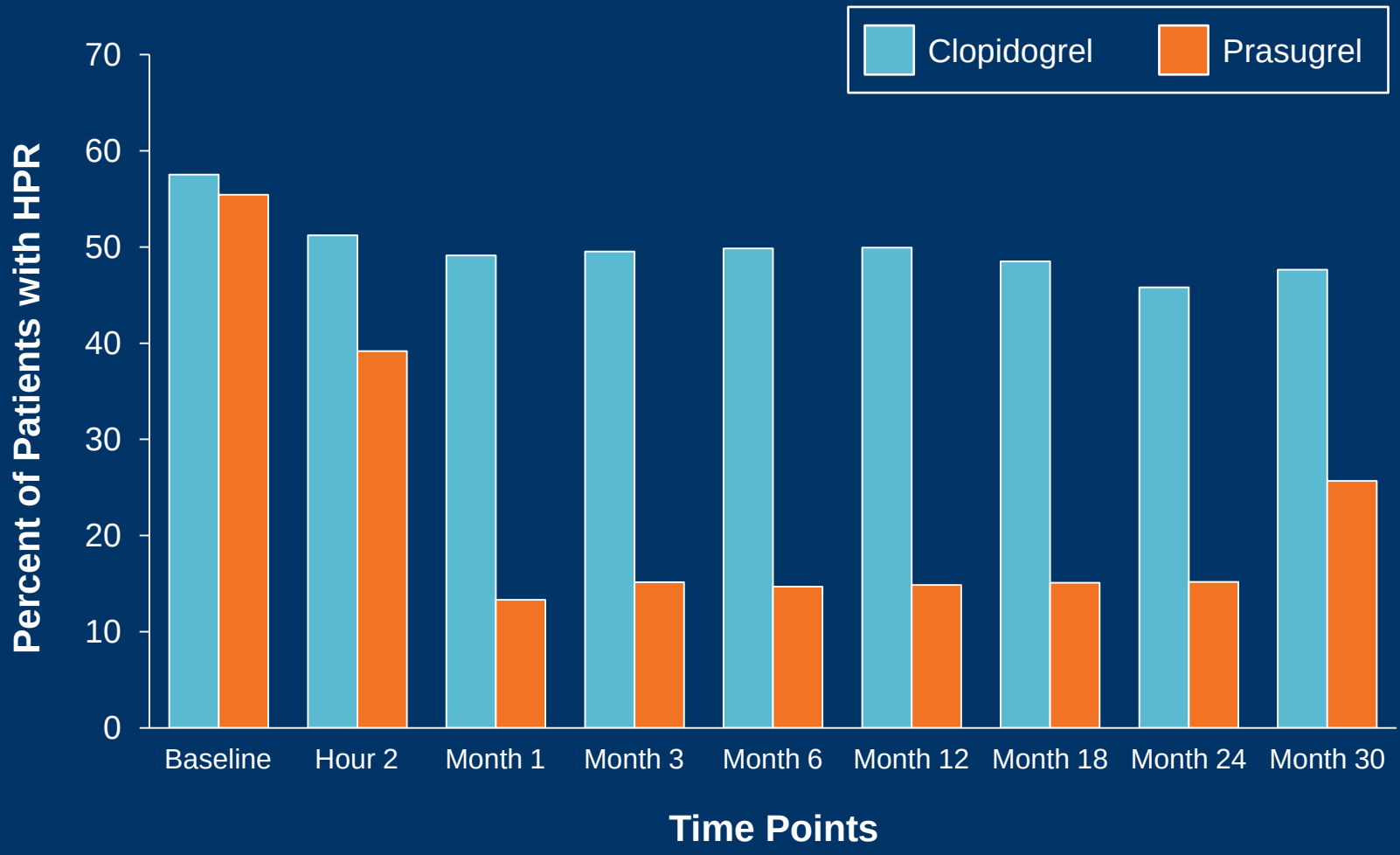
Prasugrel - 10 mg/day vs. 5 mg/day

	10 mg dose	5 mg dose (< 75 years and < 60 kg)	p-value
Median (Interquartile range)	64 (33-128)	139 (86-203)	< 0.001

	10 mg dose	5 mg dose (≥ 75 years)	p-value
Median (Interquartile range)	64 (33-128)	164 (105-216)	< 0.001

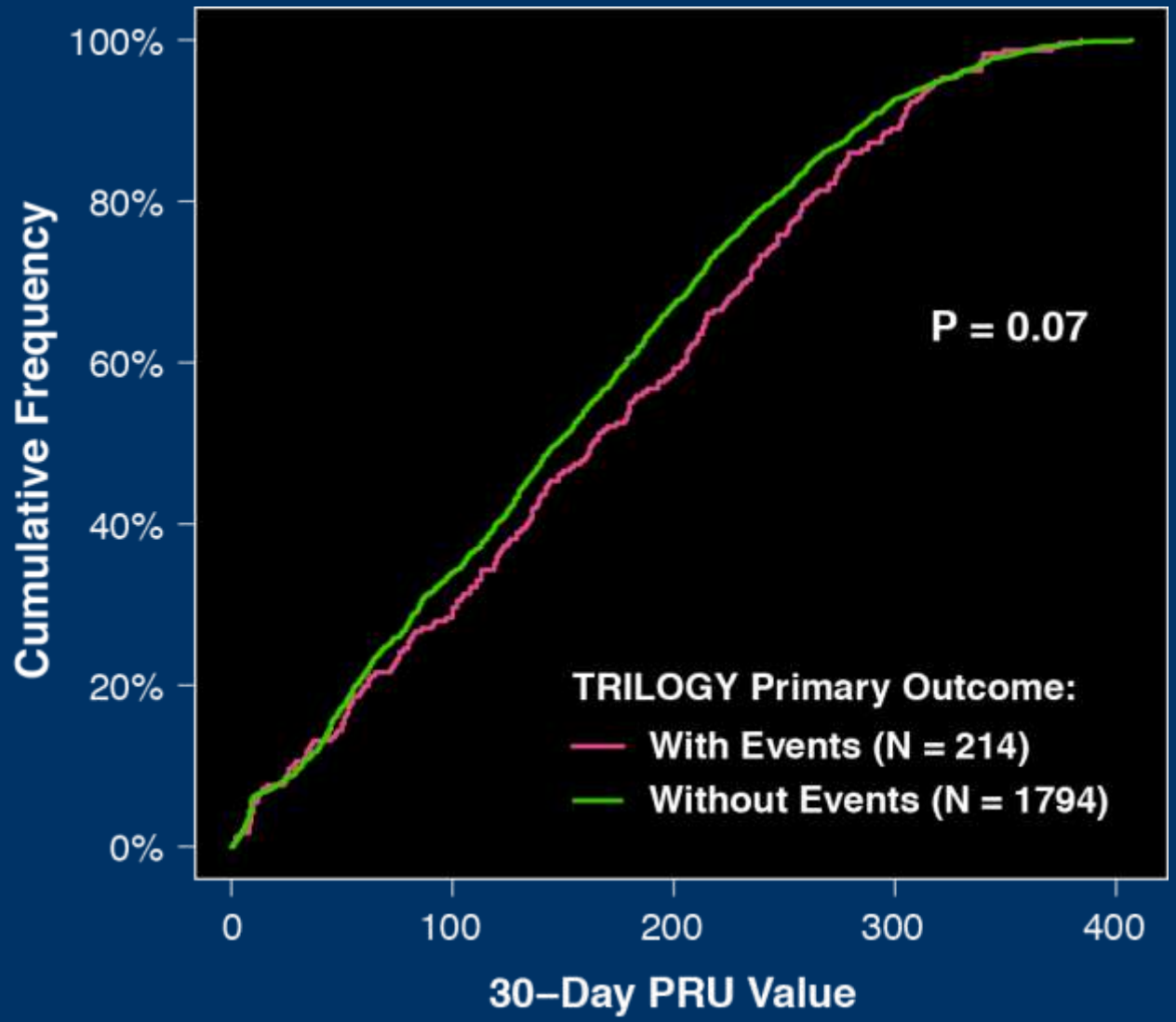
Frequency of High Platelet Reactivity (HPR)

> 208 PRU Cut-Point



Continuous Frequency Distribution of 30-day PRU:

Relation to Primary Efficacy Endpoint After 30 Days



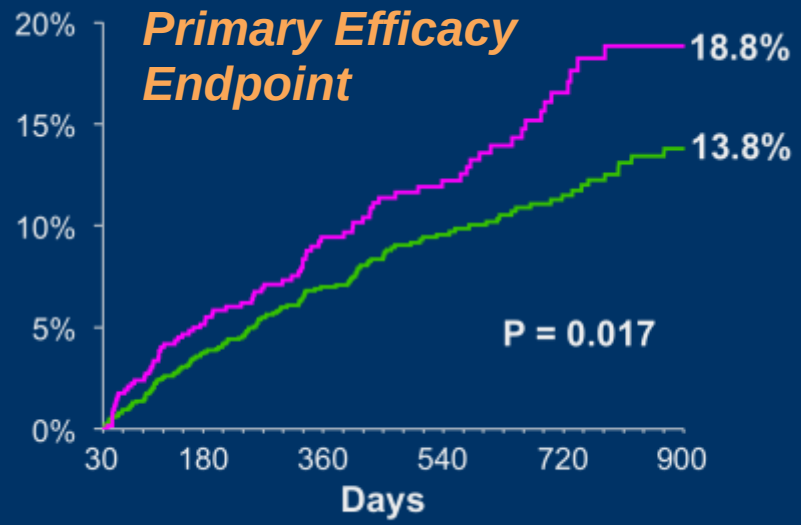
Kaplan-Meier Event Curves: Landmark at 30 Days

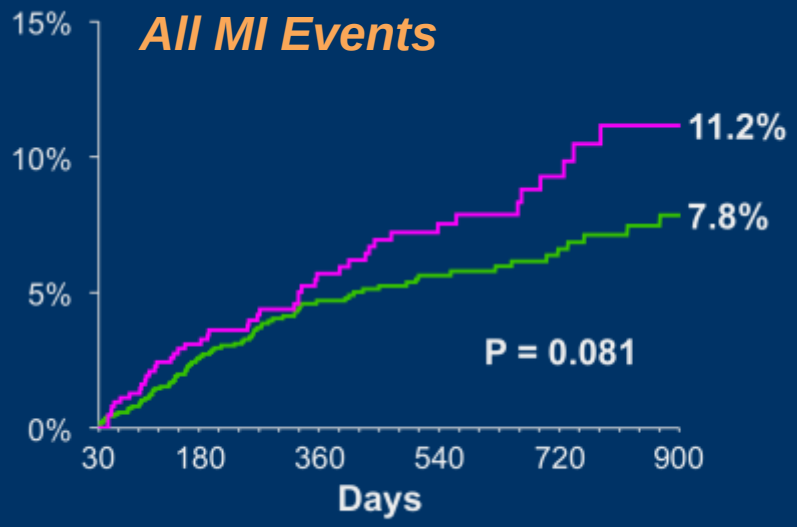
HPR Cut-Point > 208 PRU

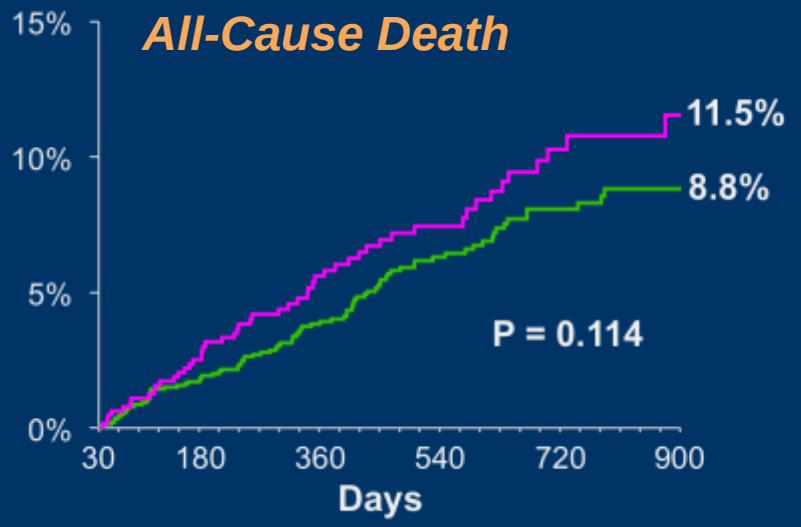
With HPR

Without HPR

The P values for each panel compare the hazard between the two groups throughout the time period represented.

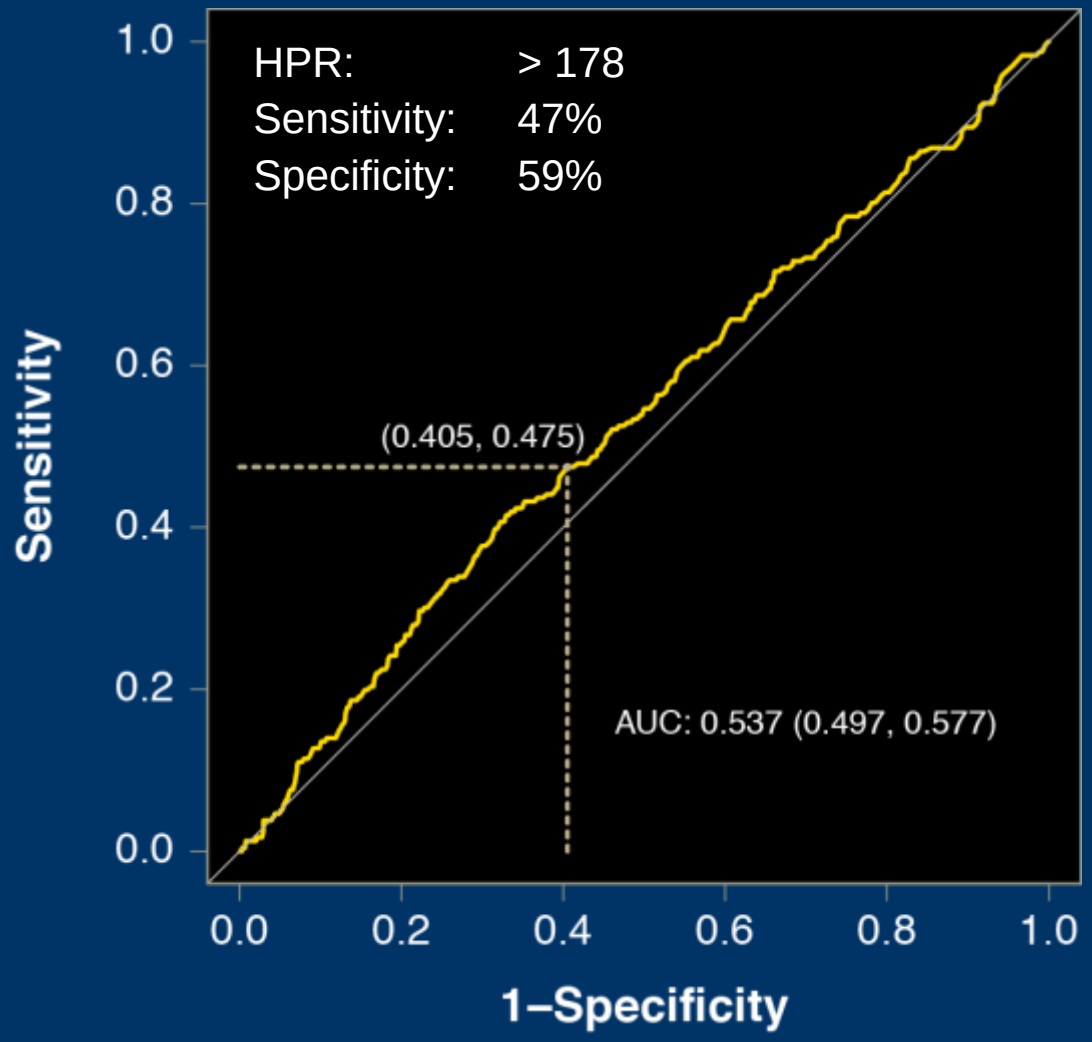






ROC Curve Analysis

Relation of 30-day PRU With Primary Efficacy Endpoint



Relationship of PRU Values with Ischemic Event Occurrence Through 30 Months

	Unadjusted Results		Adjusted Results	
	HR (95% CI)	p-value	HR (95% CI)	p-value
PRU as time-dependent covariate (per 60-unit increase)				
CVD/MI/stroke	**1.09 (1.02-1.16)**	**0.008**	1.03 (0.96-1.11)	0.44
All-cause death	**1.09 (1.01-1.18)**	**0.03**	0.99 (0.90-1.08)	0.79
All MI	1.02 (0.94-1.11)	0.60	0.97 (0.88-1.07)	0.53
30-day HPR PRU cut-point > 208				
CVD/MI/stroke	**1.43 (1.10-1.86)**	**0.01**	1.16 (0.89-1.52)	0.28
All-cause death	1.38 (0.99-1.91)	0.06	1.03 (0.74-1.44)	0.84
All MI	1.37 (0.96-1.95)	0.08	1.13 (0.79-1.62)	0.50
30-day HPR PRU cut-point > 178				
CVD/MI/stroke	**1.35 (1.05-1.73)**	**0.02**	1.13 (0.87-1.45)	0.35
All-cause death	1.27 (0.92-1.75)	0.15	0.99 (0.71-1.38)	0.95
All MI	1.34 (0.96-1.86)	0.09	1.13 (0.80-1.58)	0.49

Limitations

- Formal sample size analyses were not possible for power calculations
- No PRU measurements obtained after 2 hours after start of study drug until 30 days later.
- PRU measurements not in close proximity to clinical event occurrence.

Conclusions

- **Consistently lower PRU values for prasugrel vs. clopidogrel in all dosing groups.**
  - Attenuated response for 5-mg vs.10-mg prasugrel.
- **Univariate, but <u>not</u> independent association between platelet reactivity and ischemic events in medically managed ACS patients.**
  - Results differ from prior PCI studies.
- **Lack of significant independent association between platelet reactivity and ischemic outcomes may explain comparable clinical outcomes in main TRILOGY ACS.**

Acknowledgements

- USA
- Ukraine
- India
- China
- Bulgaria
- Argentina
- Poland
- Philippines
- Brazil
- Turkey
- Italy
- South Africa
- Germany
- Netherlands
- Canada
- Belgium
- Malaysia
- New Zealand
- Taiwan
- Korea
- United Kingdom
- Singapore
- Australia
- Sweden
- Ireland

**Totals represent number of participants with analyzable PRU measurements.*
A full listing of all participating TRILOGY ACS sites and investigators is available at:
http://www.nejm.org/doi/suppl/10.1056/NEJMoa1205512/suppl_file/nejmoa1205512_appendix.pdf

TRILOGY ACS

ORIGINAL CONTRIBUTION

ONLINE FIRST

Platelet Function During Extended Prasugrel and Clopidogrel Therapy for Patients With ACS Treated Without Revascularization

The TRILOGY ACS Platelet Function Substudy

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For the TRILOGY ACS Platelet Function Substudy Investigators

Context The relationship of platelet function testing measurements with outcomes in patients with acute coronary syndromes (ACS) initially managed medically without revascularization is unknown.

Objective To characterize the differences and evaluate clinical outcomes associated with platelet reactivity among patients with ACS treated with clopidogrel or prasugrel.

Design, Setting, and Patients Patients with medically managed unstable angina or non–ST-segment elevation myocardial infarction were enrolled in the TRILOGY ACS trial (2008 to 2011) comparing clopidogrel vs prasugrel. Of 9326 participants, 27.5% were included in a platelet function substudy: 1286 treated with prasugrel and 1278 treated with clopidogrel.

Interventions Aspirin with either prasugrel (10 or 5 mg/d) or clopidogrel (75 mg/d); those 75 years or older and younger than 75 years but who weighed less than 60 kg received a 5-mg prasugrel maintenance dose.

Main Outcome Measures Platelet reactivity, measured in $P2Y_{12}$ reaction units (PRUs), was performed at baseline, at 2 hours, and at 1, 3, 6, 12, 18, 24, and 30 months after randomization. The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or stroke through 30 months.

Results Among participants younger than 75 years and weighing 60 kg or more, the median PRU values at 30 days were 64 (interquartile range [IQR], 33-128) in the prasugrel group vs 200 (IQR, 141-260) in the clopidogrel group ($P<.001$), a difference that persisted through all subsequent time points. For participants younger than 75 years and weighing less than 60 kg, the median 30-day PRU values were 139 (IQR, 86-203) for the prasugrel group vs 209 (IQR, 148-283) for the clopidogrel group ($P<.001$), and for participants 75 years or older, the median PRU values were 164 (IQR, 105-216) for the prasugrel group vs 222 (IQR, 148-268) for the clopidogrel group ($P<.001$). At 30 months the rate of the primary efficacy end point was 17.2% (160 events) in the prasugrel group vs 18.9% (180 events) in the clopidogrel group ($P=.29$). There were no significant differences in the continuous distributions of 30-day PRU values for participants with a primary efficacy end point event after 30 days (n=214) compared with participants without an event (n=1794; $P=.07$) and no significant relationship between the occurence of the primary efficacy end point and continuous PRU values (adjusted hazard ratio [HR] for increase of 60 PRUs, 1.03; 95% CI, 0.96-1.11; $P=.44$). Similar findings were observed with 30-day PRU cut points used to define high on-treatment platelet reactivity—PRU more than 208 (adjusted HR, 1.16; 95% CI, 0.89-1.52, $P=.28$) and PRU more than 230 (adjusted HR, 1.20; 95% CI, 0.90-1.61; $P=.21$).

Conclusions Among patients with ACS without ST-segment elevation and initially managed without revascularization, prasugrel was associated with lower platelet reactivity than clopidogrel, irrespective of age, weight, and dose. Among those in the platelet substudy, no significant differences existed between prasugrel vs clopidogrel in the occurence of the primary efficacy end point through 30 months and no significant association existed between platelet reactivity and occurrence of ischemic outcomes.

Trial Registration clinicaltrials.gov Identifier: NCT00699998

JAMA. 2012;308(17):doi:10.1001/jama.2012.17312 www.jama.com

PLATELET-RICH THROMBUS FORMATION plays a major role in the occurrence of ischemic events in patients with acute coronary syndromes (ACS).[1] A large body of evidence, primarily based on single ex vivo measurements, demonstrates an association between high on-treatment platelet reactivity to adenosine diphosphate and the occurrence of ischemic events among patients treated with clopidogrel following percutaneous coronary intervention (PCI); however, many questions regarding this association remain unanswered.[2-4]

See related article.

First, few studies have included longitudinal assessments of platelet function to evaluate time-dependent relationships

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JAMA®
The Journal of the American Medical Association

Published online November 4, 2012

Available at:
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