First Large Scale Platelet Function Evaluation in a Major Clinical Trial: The TRILOGY ACS — Platelet Function Substudy

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Conflict of Interest Disclosures

Disclosures for all authors listed within the manuscript

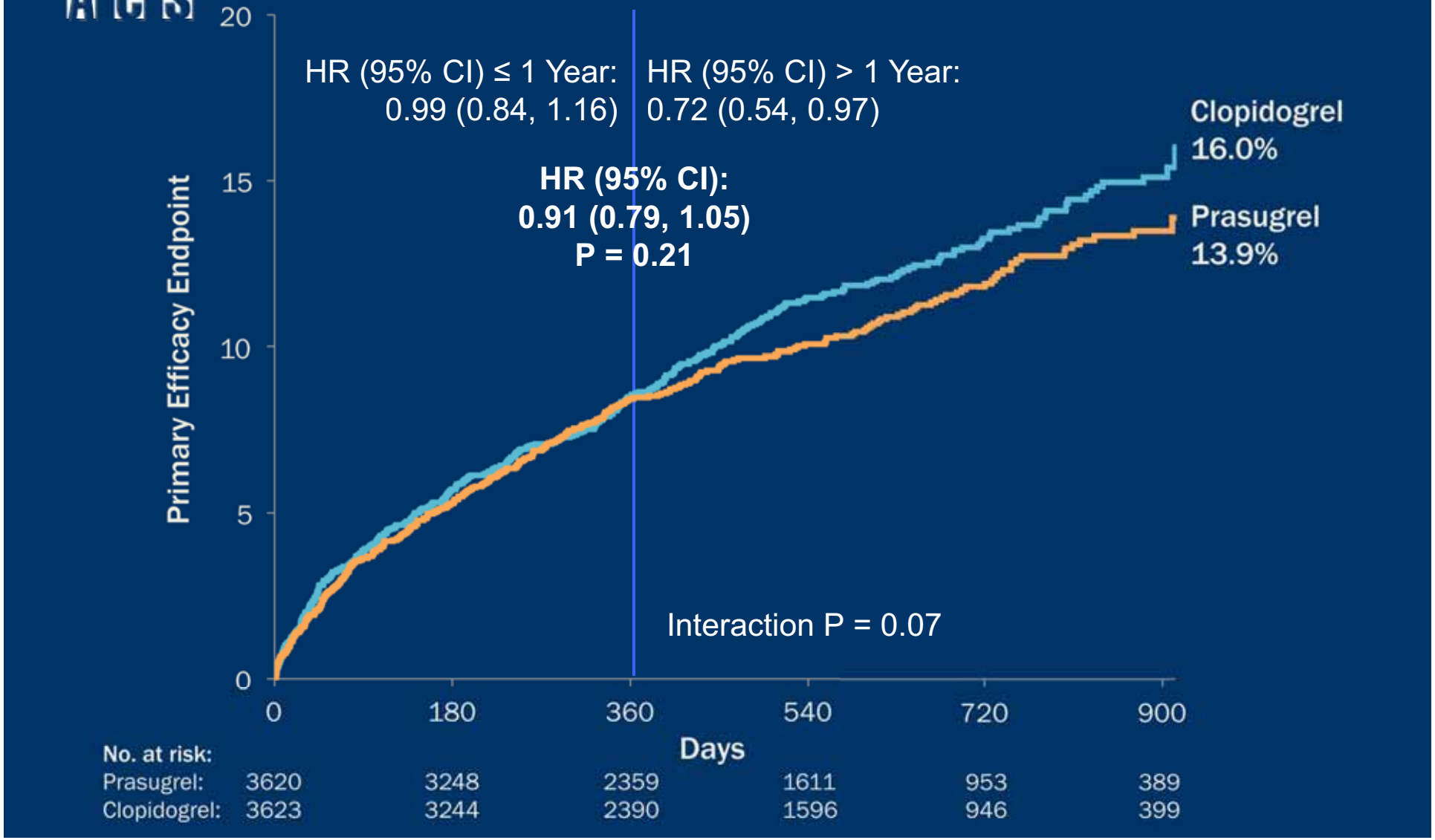
Background

- 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 **never** been embedded within an ACS trial.
- **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 prasugrel dose in ACS patients.

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

TRILOGY ACS Main Results

(Age < 75 years)



Platelet Function Substudy Design

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

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

Aspirin < 100 mg (strongly recommended) **for all**

↓

PFS: 2690 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 participants with no 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 between prasugrel vs. clopidogrel over time.
- To delineate the relationship of platelet reactivity with ischemic endpoint occurrence.
- To determine a threshold for HPR to discriminate between patients with and without ischemic event occurrence.

Statistical Analysis

- **Baseline characteristics:**
  Continuous variables : ANOVA F test or Kruskal-Wallis
  Categorical variables: χ^2 test or exact test

- **Relationship of PRU values with risk of an ischemic event (primary efficacy endpoint, all-cause death, and all MI events):**
  Cox model regressing time-to-first-event on PRU was fit with 3 separate approaches:

  - PRU treated as time-varying covariate -most recent PRU used when estimating the relationship of PRU at each fail-time during the study period.
  - To determine whether PRU values measured 30 days after randomization predicted risk, a Cox model landmarked at 30 days regressing time-to-first-event on PRU was fit.
- - Multiple imputation techniques used with both modeling procedures to account for potential bias induced by missing PRU values at all timepoints except for Mo. 30.

- Variables: GRACE 6-mo mortality risk score, and variables specific to TRILOGY trial

Statistical Analysis (continued)

- **The relationship of dichotomous determinations of HPR on risk of an event:** A Cox model regressing time-to-first-event on HPR status was fit. HPR = >208 PRU [1], and >178 (ROC analysis of continuous 30-day PRU data with the primary efficacy endpoint).

- Kaplan-Meier event rates for the primary efficacy endpoint, MI, all cause death starting at the 30-d landmark time period through 30 mo were compared among participants with and without HPR using the >208 cut-point.

- Adjusted and unadjusted analyses performed for primary efficacy endpoint, MI, all cause death

- Significance level $p<0.05$. All analyses performed at Duke Clinical Research Institute, using SAS 9.3 and R 2.14.1.

1. Gurbel PA et al. *Circulation.* 2012;125:1276-1287

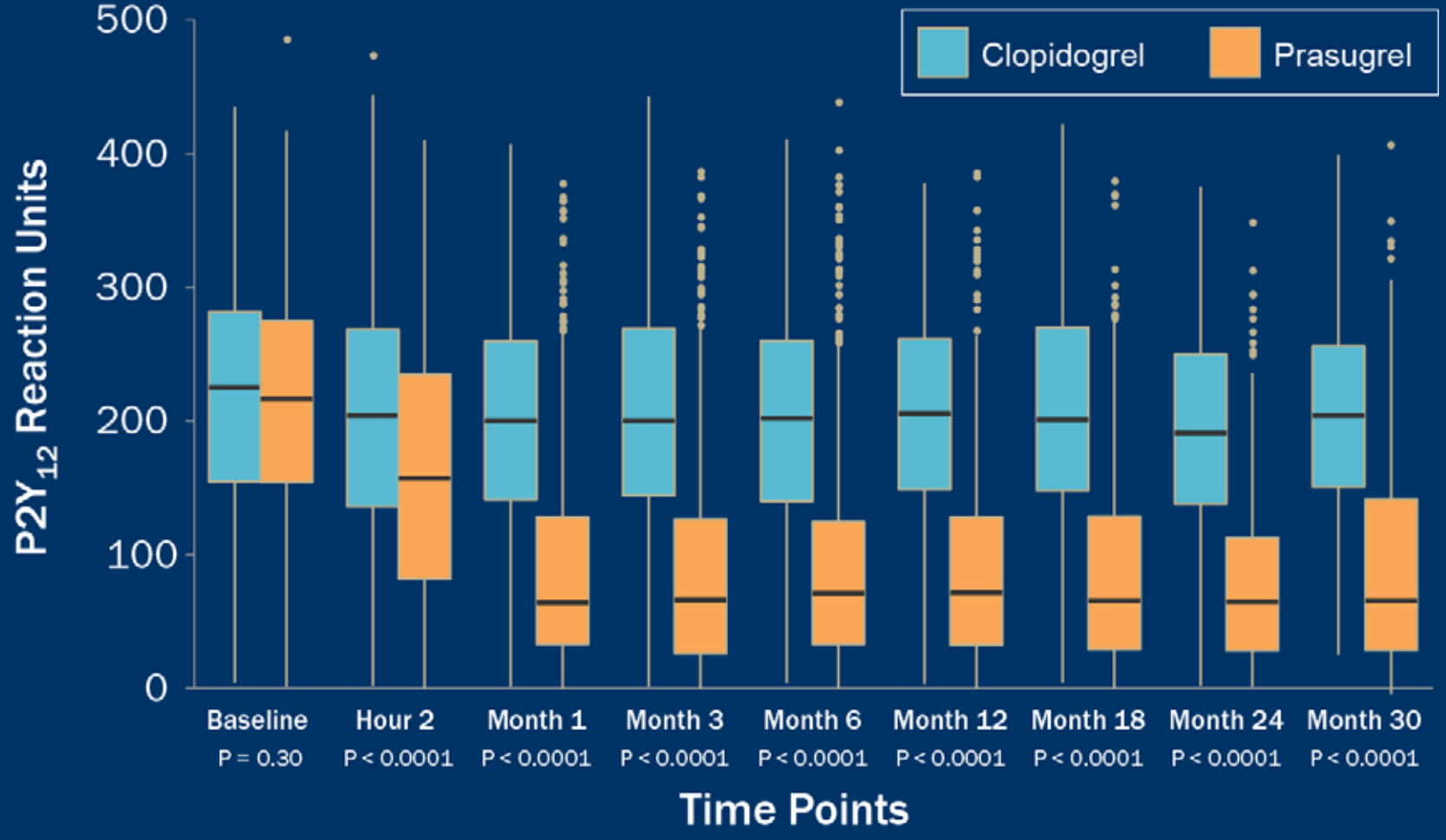
Baseline Characteristics

	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

On-Treatment PRU Through 30 Months

< 75 years and ≥ 60 kg

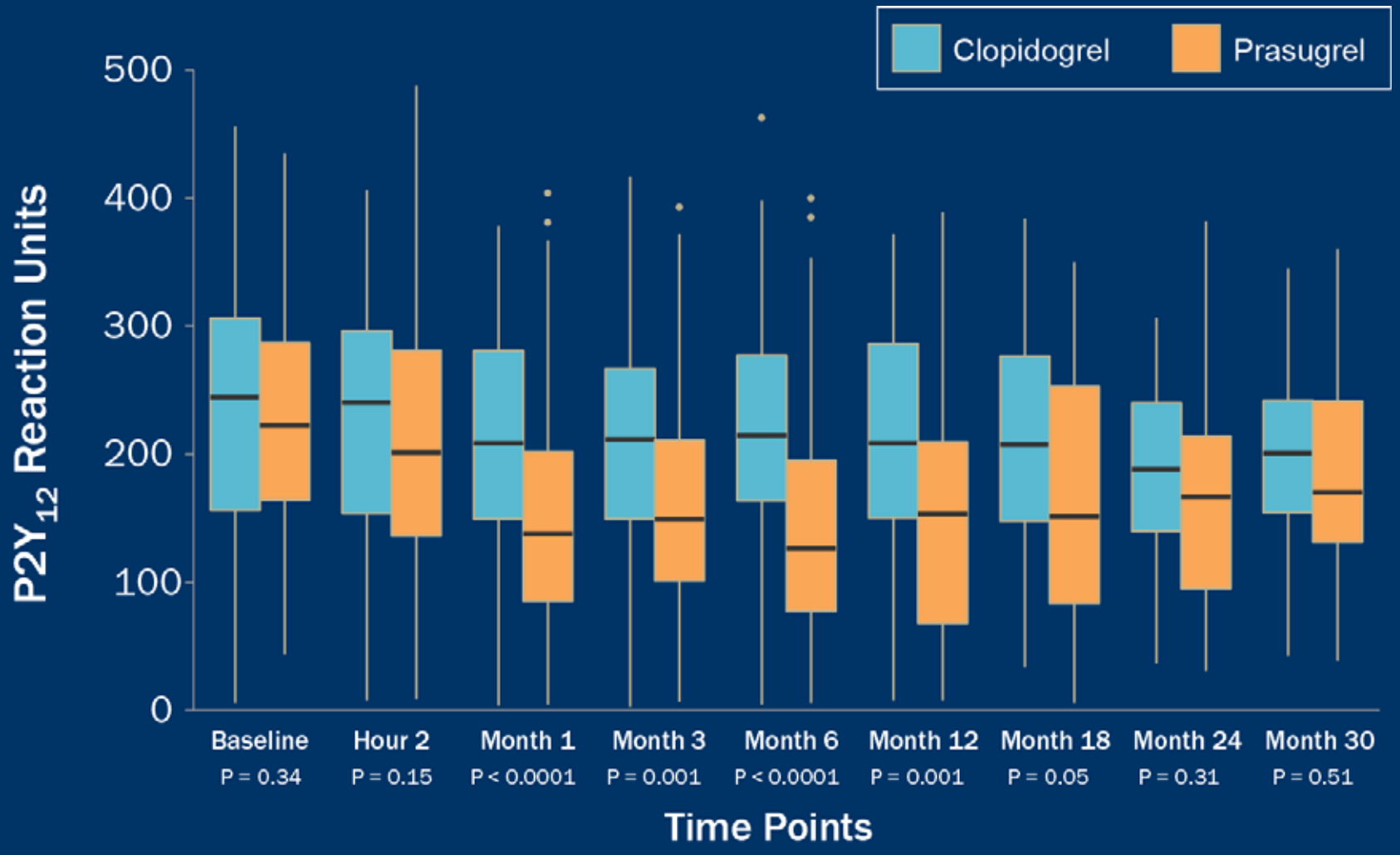
Clopidogrel 75 mg/day vs. **Prasugrel 10 mg/day**



On-Treatment PRU Through 30 Months

≥ 75 years

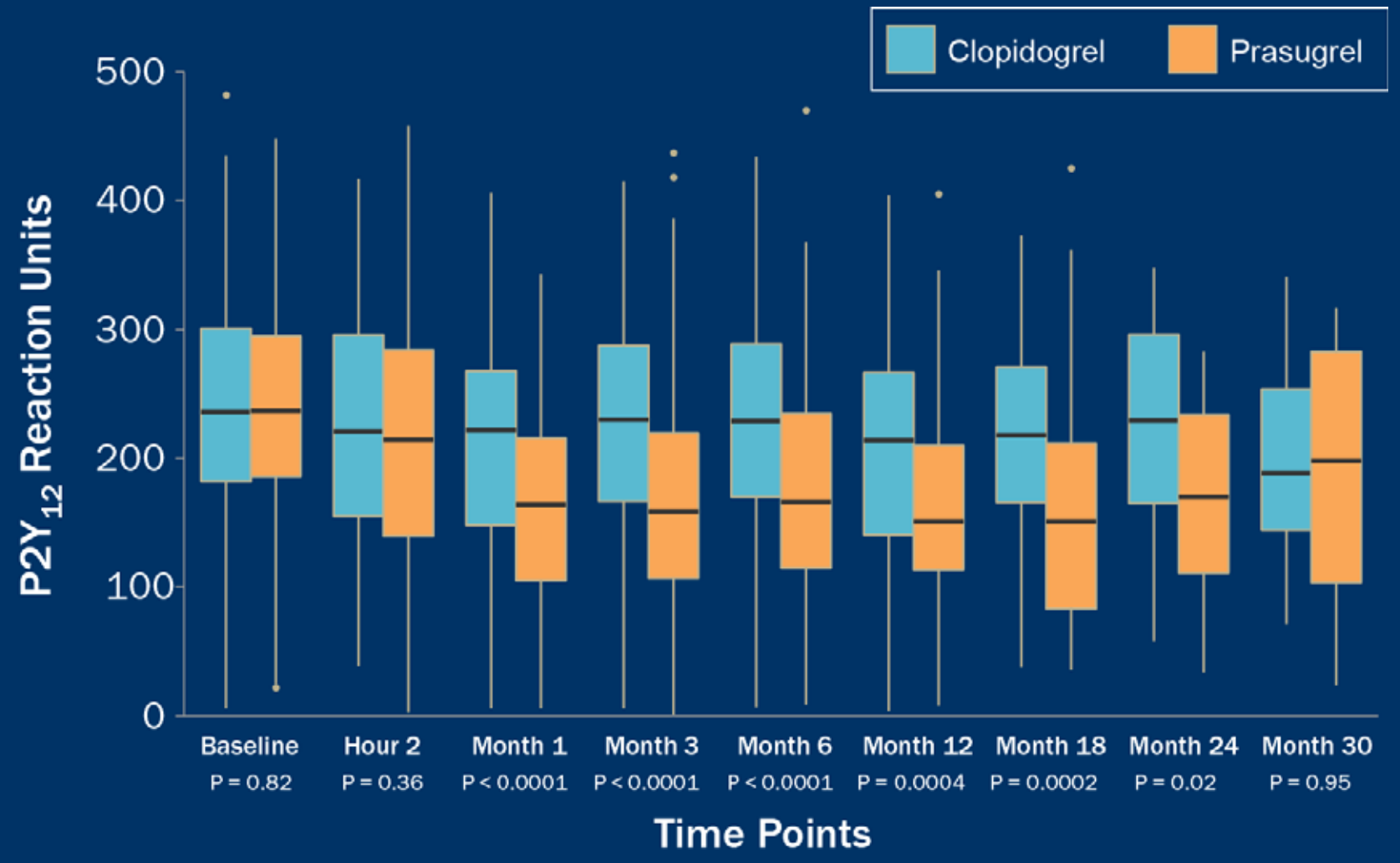
Clopidogrel 75 mg/day vs. **Prasugrel 5 mg/day**



On-Treatment PRU Through 30 Months

< 75 years and < 60 kg

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



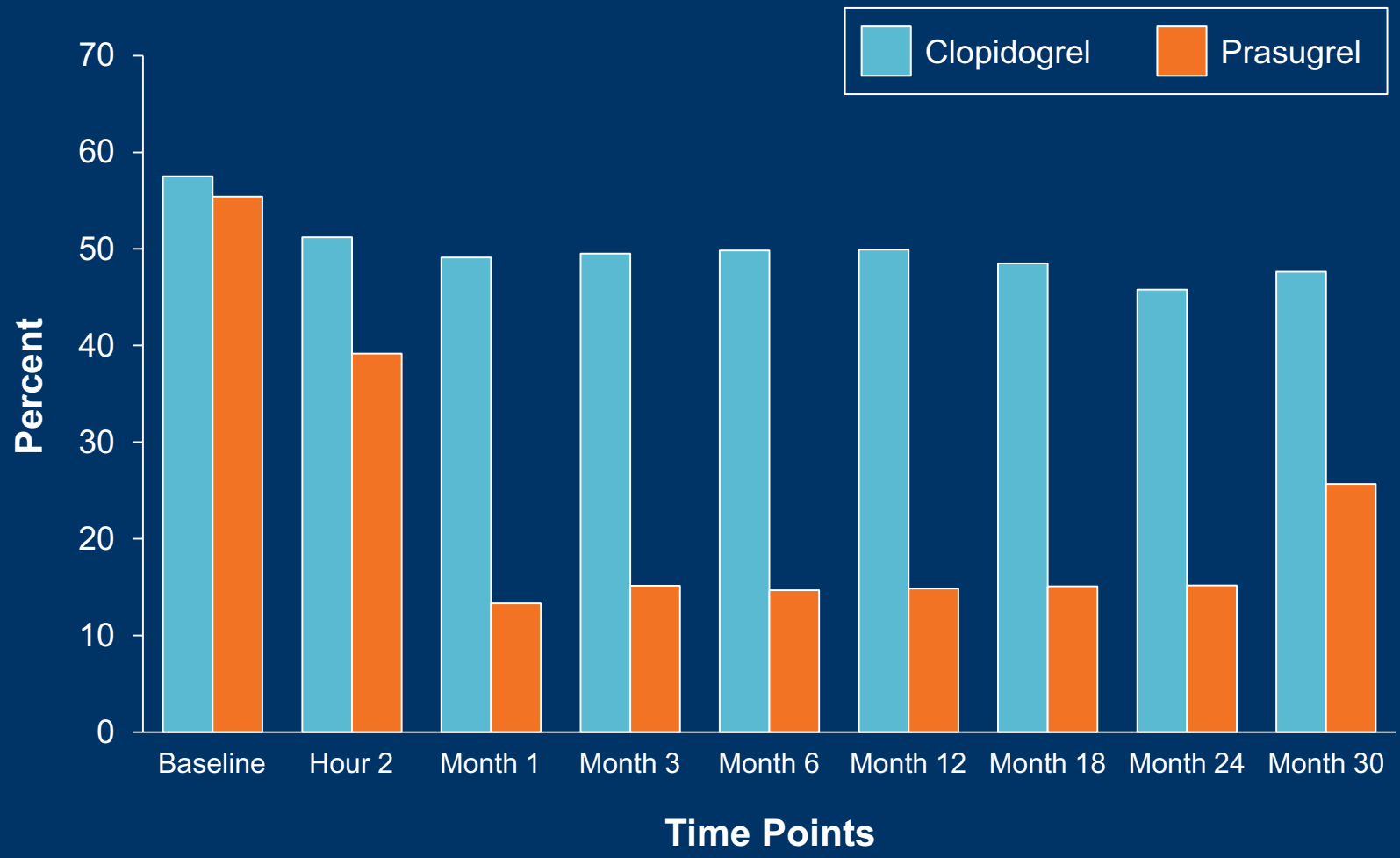
30 Day Median PRU
Prasugrel 10 mg/day vs. 5 mg/day

PRU (10-mg prasugrel dose) lower than:
5-mg dose (< 75 years and < 60 kg) *(P < 0.001)*

and

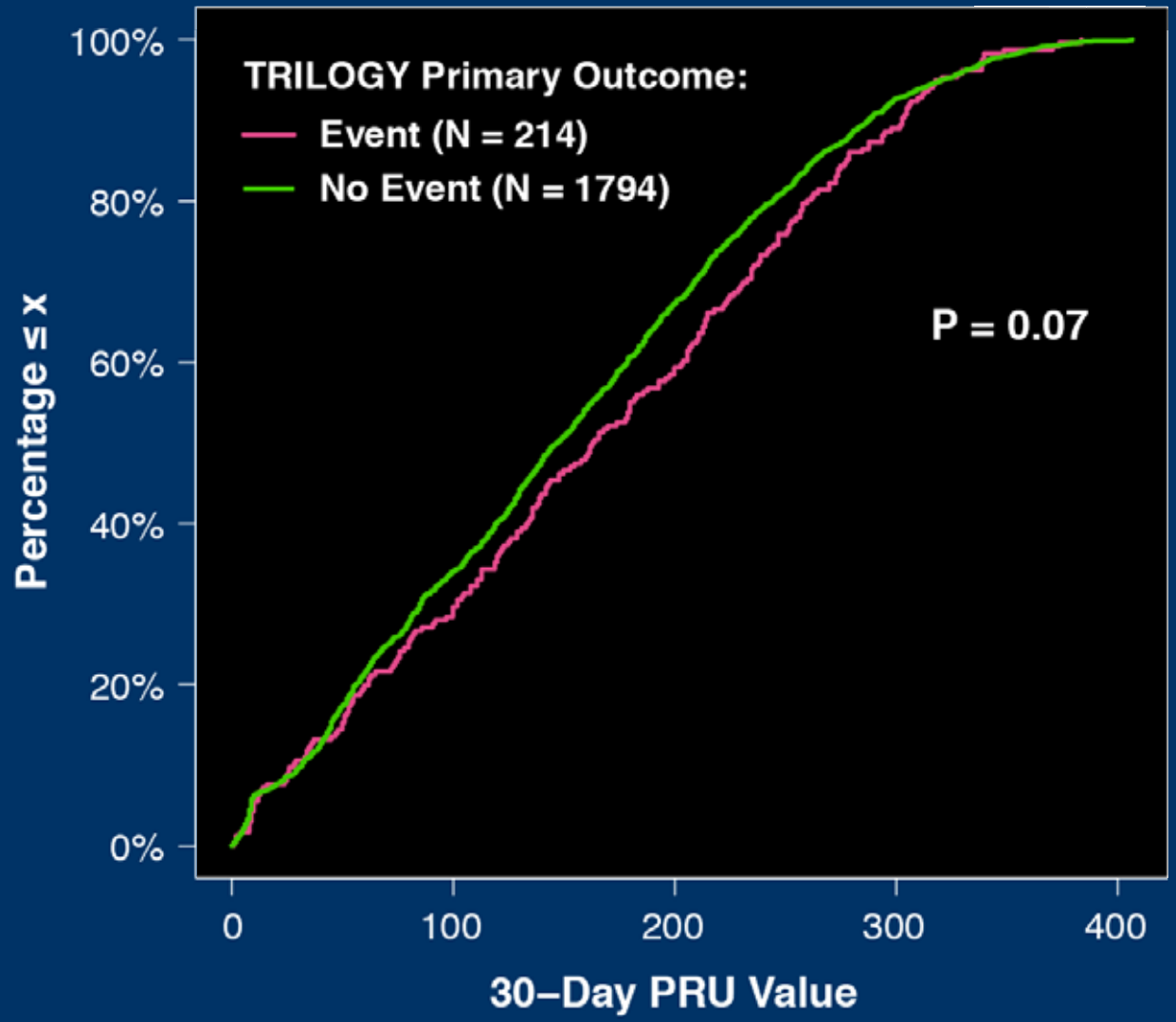
PRU (10-mg prasugrel dose) lower than:
5-mg dose (≥ 75 years) *(P < 0.001)*

Frequency of HPR
> 208 PRU



Continuous Frequency Distribution:

30-day PRU in Patients With vs. Without Events

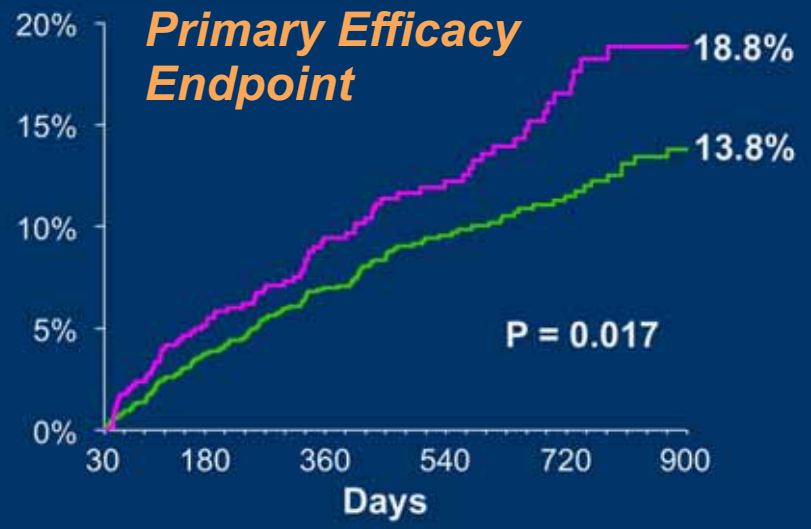


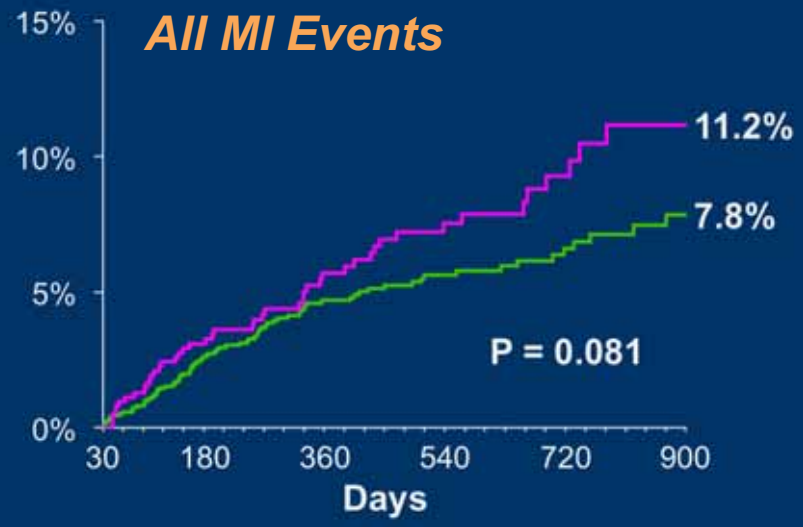
Kaplan-Meier Event Curves:
HPR > 208

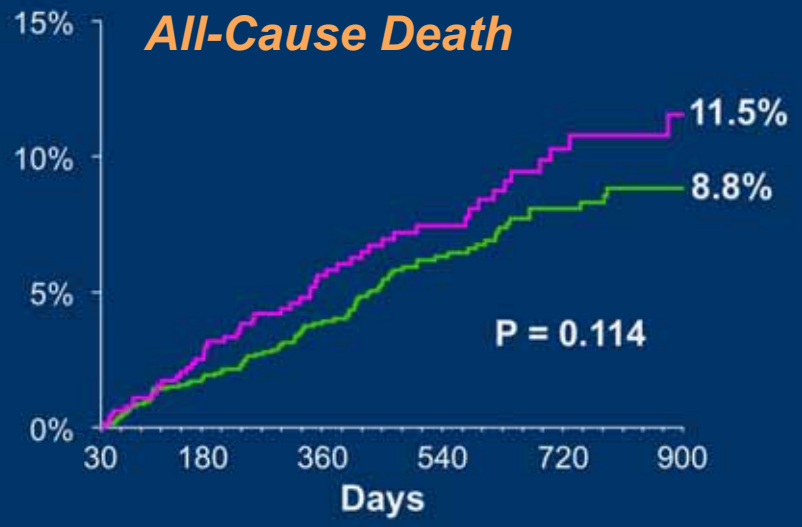
With HPR

Without HPR

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

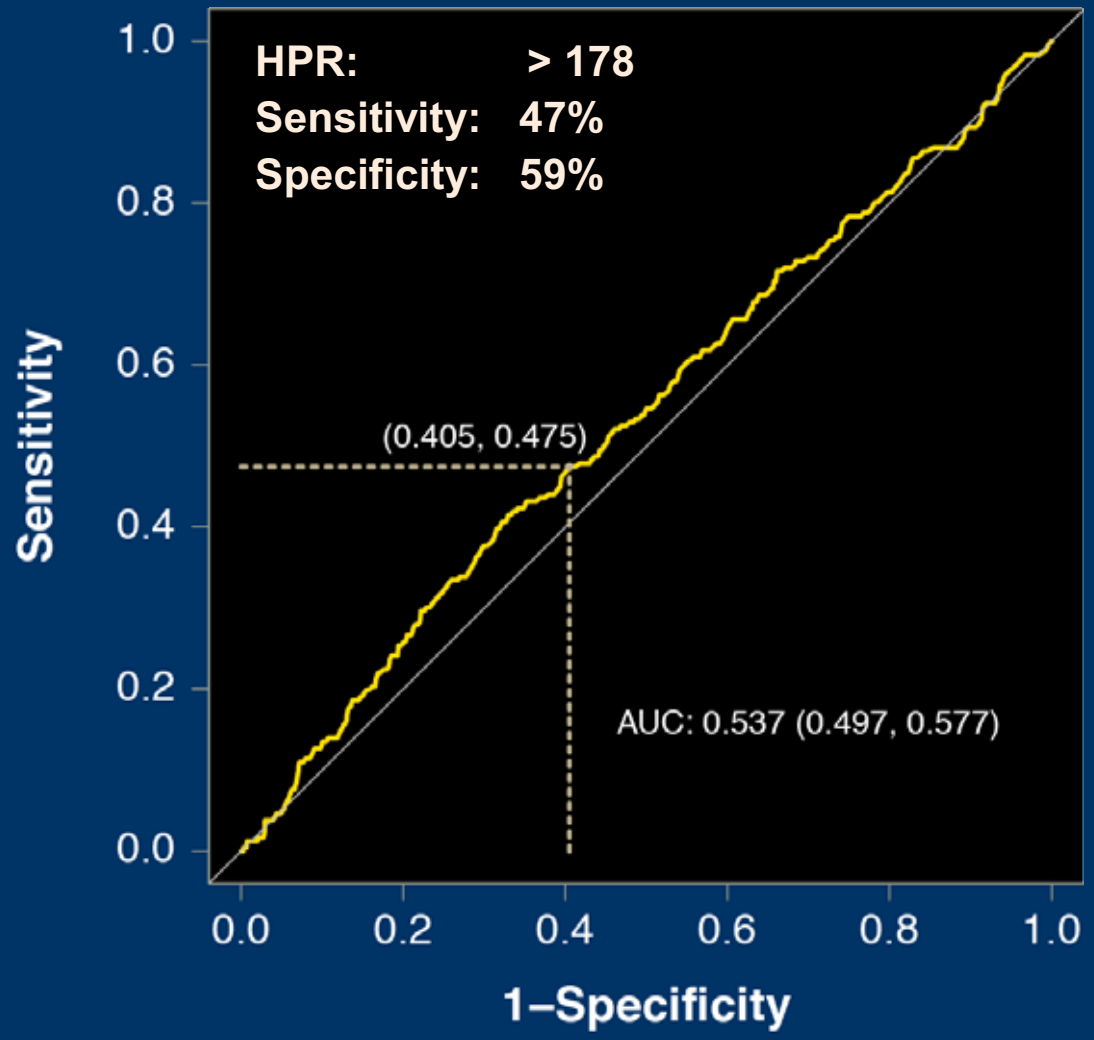






ROC Curve Analysis

Relation of 30-day PRU with primary efficacy endpoint



Risk of On-Treatment PRU vs. Ischemic Event Occurrence Through 30 Months

	Unadjusted Results		Adjusted Results	
	HR (95% CI)	P-value	HR (95% CI)	P-value
PRU as a time-dependent covariate				
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 > ROC-defined value of 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

- No mechanism to do a formal sample size analysis.
- PRU values missing across all time periods:
  - multiple imputation techniques used to account for potential bias induced by missing PRU values.
- Due to logistical issues, only 2-hour PRU measurement made after start of study drug treatment.
- Few measurements after 12 mo do not inform the observation of a late, time-dependent separation of event curves in the main trial.

Conclusions

- Longest longitudinal assessment of on-treatment platelet reactivity for both clopidogrel- and prasugrel-treated patients.
- Consistently greater PD response for prasugrel vs. clopidogrel in all dosing groups.
  - Novel PD data on 5-mg prasugrel: greater PD vs. 75-mg clopidogrel but attenuated PD vs. 10-mg prasugrel.
- Univariate, but not independent association between PRU and HPR cut-points with ischemic event occurrence.
- Lack of significant independent association between platelet reactivity and ischemic outcomes may explain the comparable clinical outcomes in TRILOGY ACS.