ESC 2011

Platelet Reactivity on Clopidogrel Therapy and CV Outcomes after PCI: A Time-Dependent Pharmacodynamic Analysis of the GRAVITAS trial

Matthew J. Price MD, Dominick J. Angiolillo MD, PhD, Paul S. Teirstein MD, Elizabeth Lillie PhD, Steven V. Manoukian MD, Peter B. Berger MD, Jean-François Tanguay MD, Christopher P. Cannon MD, and Eric J. Topol MD

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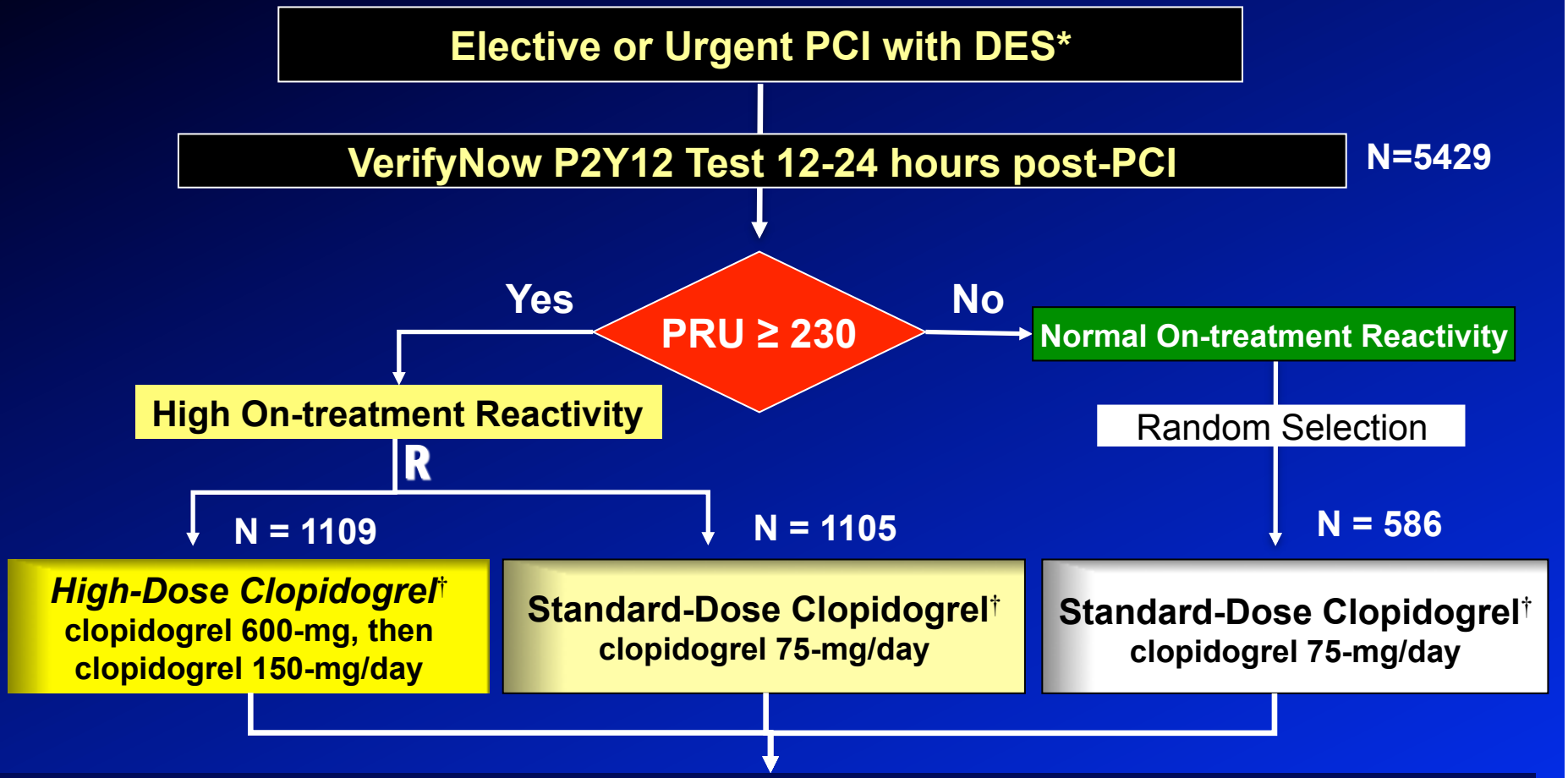
Disclosures:

• Grant support: BMS/sanofi aventis, Accumetrics, Quest Diagnostics

• Honoraria/Consulting/Speaking fees: BMS/sanofi aventis, DSI/Lilly, AstraZeneca, Medicure

Price MJ et al , JAMA 2011

GRAVITAS Study Design



Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs
†placebo-controlled All patients received aspirin (81-162mg daily)

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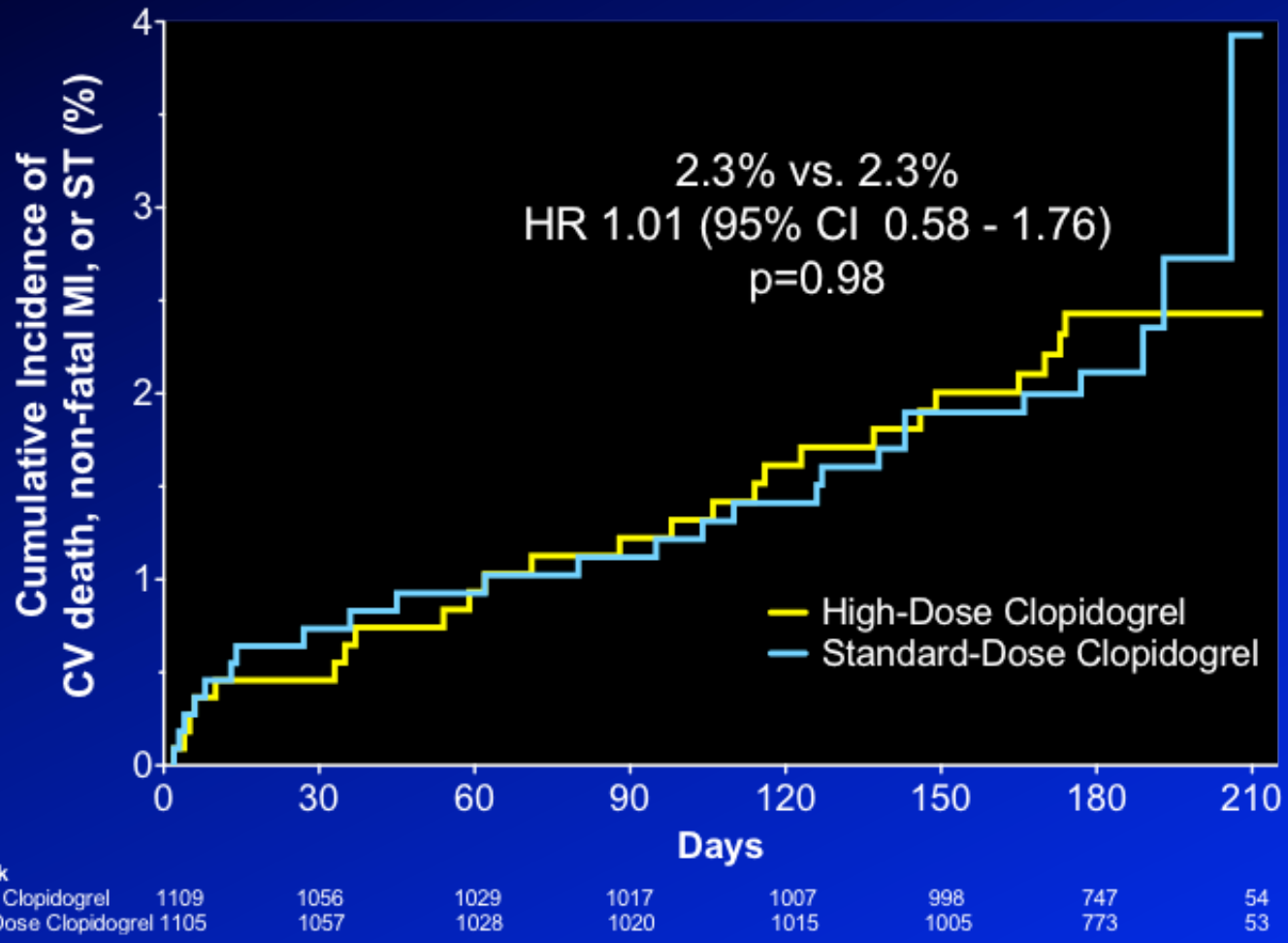
Primary Endpoint: CV Death, MI, Stent Thrombosis



No. at Risk								
High Dose Clopidogrel	1109	1056	1029	1017	1007	998	747	54
Standard Dose Clopidogrel	1105	1057	1028	1020	1015	1005	773	53

Observed event rates are listed; P value by log rank test.

Price MJ et al, JAMA. 2011;305(11):1097-1105

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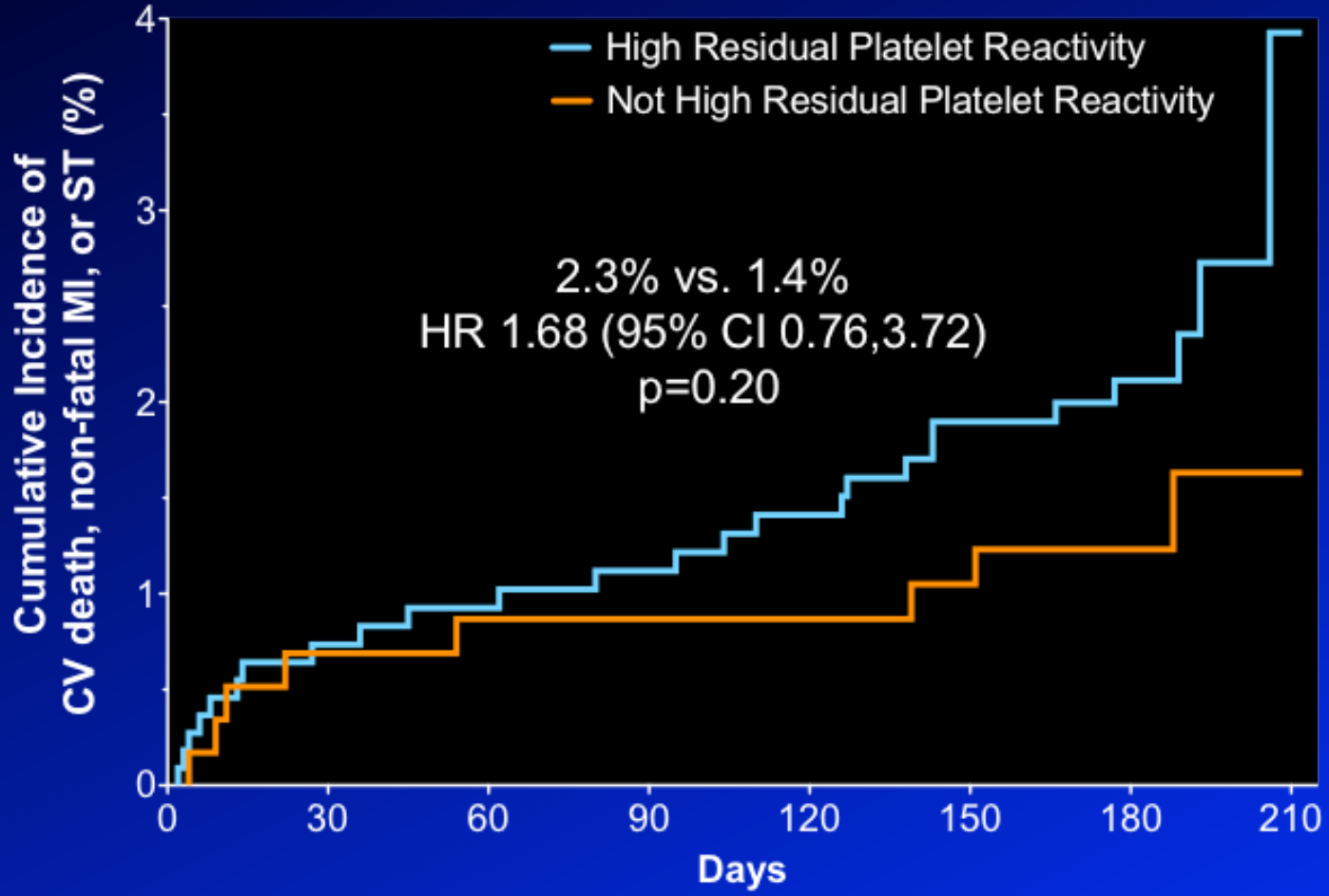
Secondary Comparison: High vs. Not High Reactivity Treated with Clopidogrel 75-mg daily



No. at Risk								
High Residual Reactiivty	1105	1057	1028	1020	1015	1005	773	53
Not High Residual Reactivity	586	565	552	551	549	546	415	19

Observed event rates are listed. P value by log-rank test.

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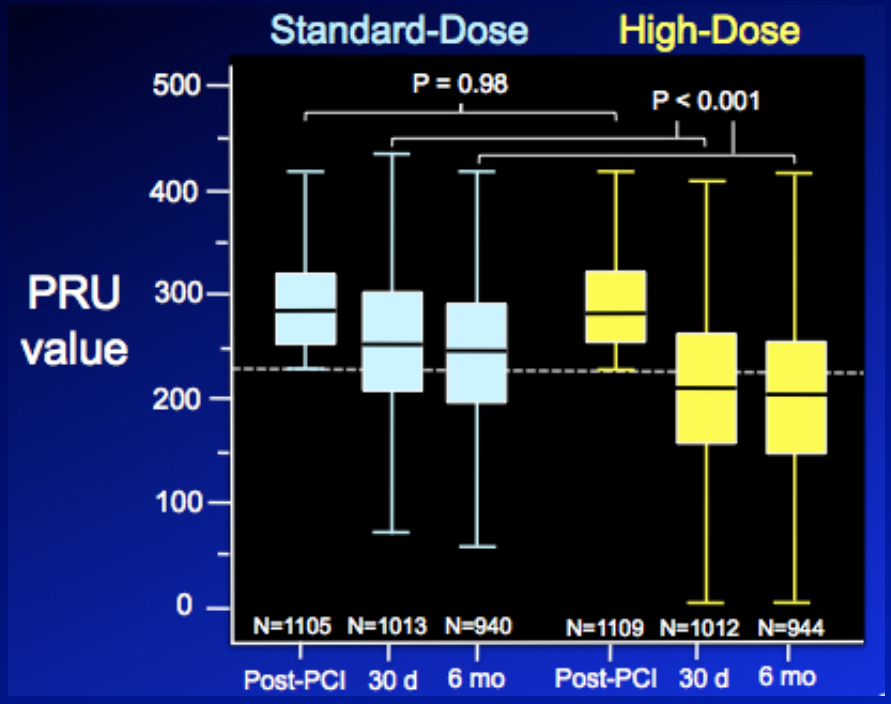
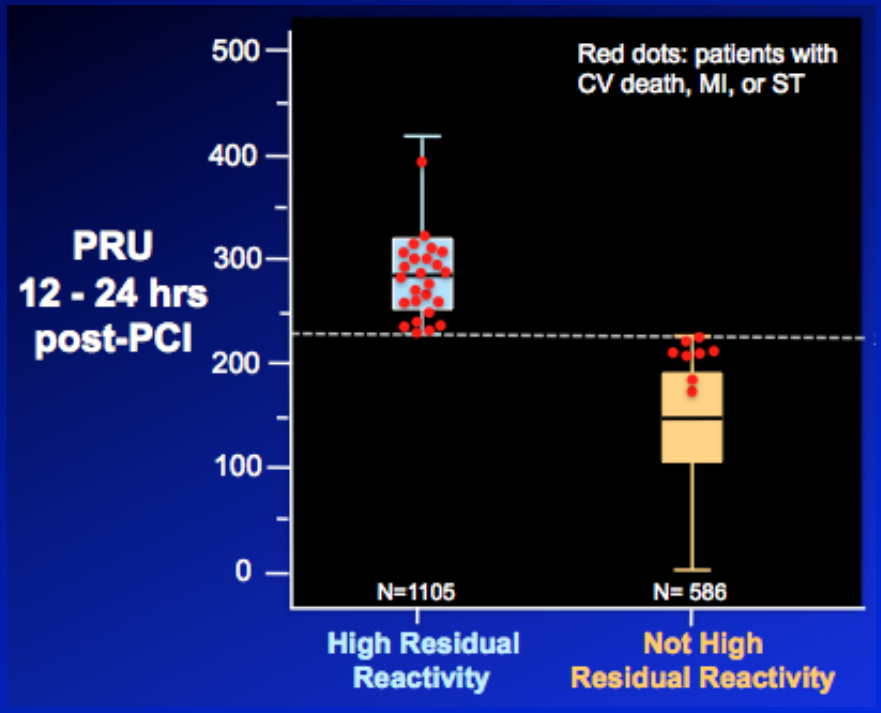
Price MJ et al, JAMA. 2011;305(11):1097-1105

GRAVITAS: Pharmacodynamics

PD effect of study drug in pts with high OTR



CV Events in Pts Treated with 75 mg



- In patients with high on-treatment reactivity (OTR) after PCI, there was substantial variability over time in the pharmacodynamic responses to study drug.
- Patients with low levels of OTR after PCI appeared to have few (if any) CV events.

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Price MJ, AHA 2010

GRAVITAS: Objective of Time-Varying Analysis

- *The objective of this analysis* was to explore the relationship between on-treatment platelet reactivity over the course of the GRAVITAS trial and the risk of subsequent CV events.

Methods

- All 3 study arms were pooled given lack of clinical efficacy in the overall trial.
- *High on-treatment reactivity (OTR)* was defined as:
  - OTR > 230 PRU (pre-specified)
  - OTR > 208 PRU (post-hoc, based on data available *after* GRAVITAS began enrolling)
- Primary Endpoint: CV death, MI, and ST

Statistical Methods

- Cox proportional hazards regression used to test associations between predefined cut-offs and outcomes, using OTR as a *time-varying covariate* (measured 12-24 hrs and 30 days after PCI).
- Models built for the association between:
  - *OTR and outcome at 60 days* (ie, 30 days after the 1 month follow-up platelet function test)
  - *OTR and outcome at 6 months* (end of follow-up)
- Multivariate time-dependent Cox regression used to adjust for clinical and procedural characteristics associated with outcome.

Patient Flow: On-Treatment Reactivity (OTR) Over The Course of GRAVITAS

2796 Patients (99.9%) Eligible for Analysis

Baseline (12-24 hrs)	501 with OTR <208 PRU 2295 with OTR ≥208 PRU	588 with OTR <230 PRU 2208 with OTR ≥230 PRU
30±7 days	1156 with OTR <208 PRU 1397 pts OTR ≥208 PRU	1448 with OTR <230 PRU 1105 pts OTR ≥230 PRU

4 patients (0.1%) lost to follow-up

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On-Treatment Reactivity As A Time-Varying Covariate: Unadjusted Hazard of CV death, MI, and ST

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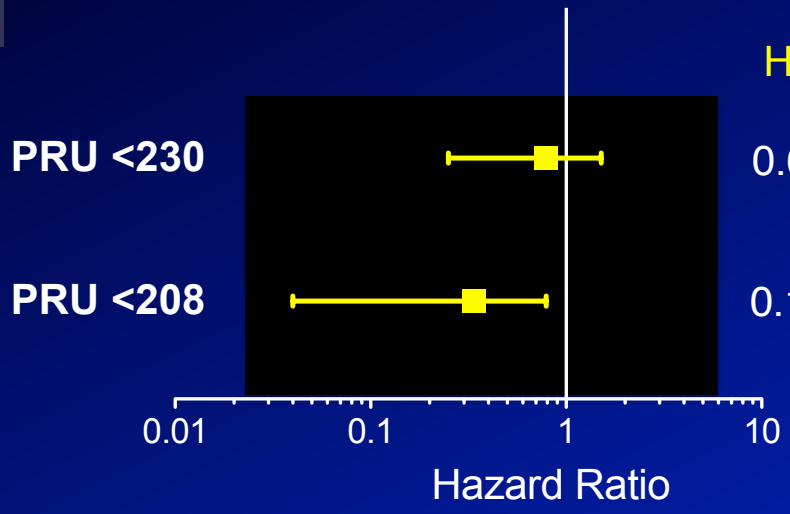
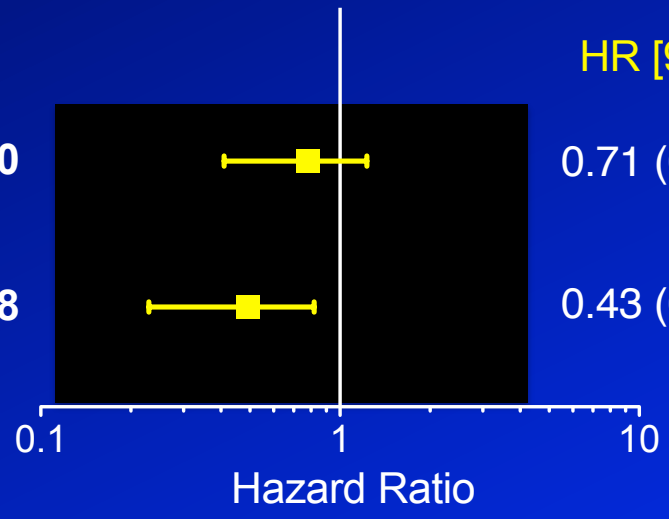
60 days



6 months



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Clinical and Procedural Characteristics Associated With CV Death, MI, and ST at **60 days**: Multivariate Analysis

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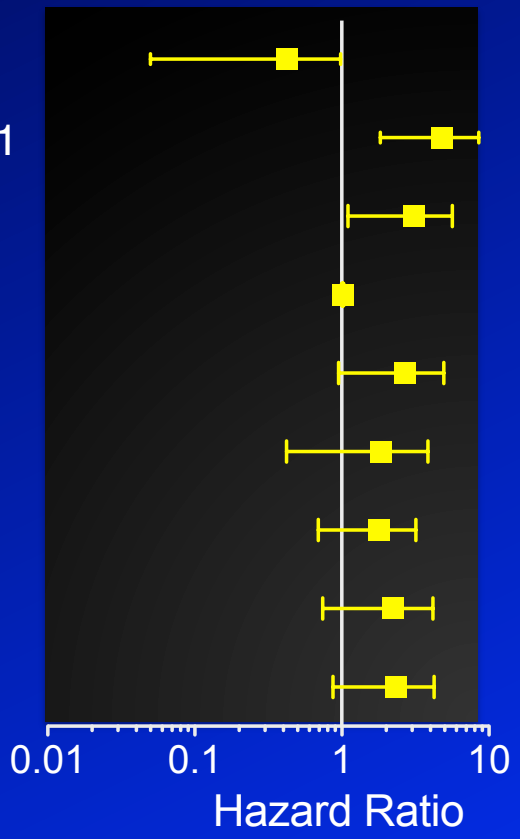
	HR [95% CI]	P
PRU <208	0.23 [0.05, 0.98]	0.047
ACS	3.95 [1.83, 8.53]	<0.001
Diabetes	2.49 [1.10, 5.64]	0.028
Stent Length (per mm)	1.01 [1.01, 1.02]	0.003
Prior MI	2.16 [0.94, 4.93]	0.068
Beta Blocker	1.27 [0.42, 3.85]	0.668
CrCl <60	1.48 [0.69, 3.18]	0.668
Prior PCI	1.76 [0.74, 4.16]	0.201
Prior CABG	1.92 [0.87, 4.23]	0.108



*On-treatment reactivity treated as a time-varying covariate

CrCl = creatinine clearance, ACS = acute coronary syndrome, MI = myocardial infarction

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Clinical and Procedural Characteristics Associated With CV Death, MI, or ST at **6 Months**: Multivariate Analysis

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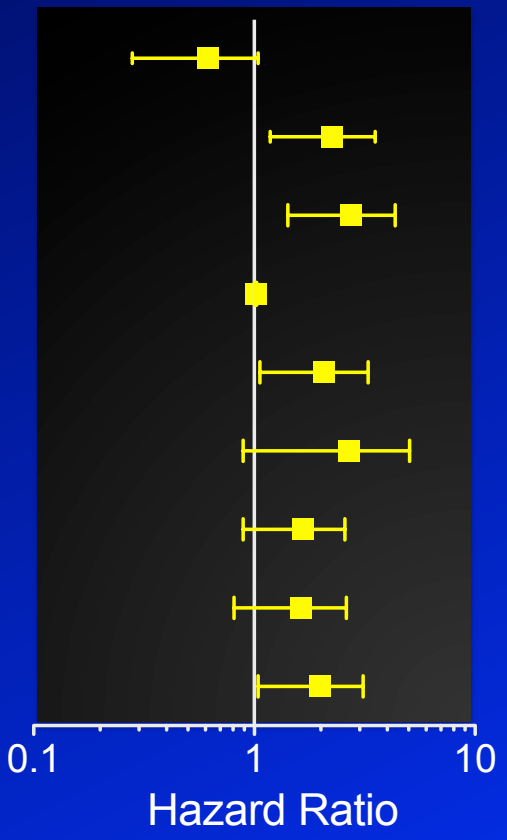
	HR [95% CI]	P
PRU <208	0.54 [0.28, 1.04]	0.065
ACS	2.04 [1.18, 3.53]	0.011
Diabetes	2.48 [1.42, 4.35]	0.002
Stent Length (per mm)	1.01 [1.01, 1.02]	0.001
Prior MI	1.86 [1.06, 3.28]	0.031
Beta Blocker	2.12 [0.89, 5.05]	0.090
CrCl <60	1.52 [0.89, 2.57]	0.123
Prior PCI	1.45 [0.81, 2.61]	0.209
Prior CABG	1.80 [1.04, 3.11]	0.037



*On-treatment reactivity treated as a time-varying covariate

CrCl = creatinine clearance, ACS = acute coronary syndrome, MI = myocardial infarction

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Achieved Levels of On-Treatment Reactivity at 30-Days Stratified By Randomized Treatment Arm

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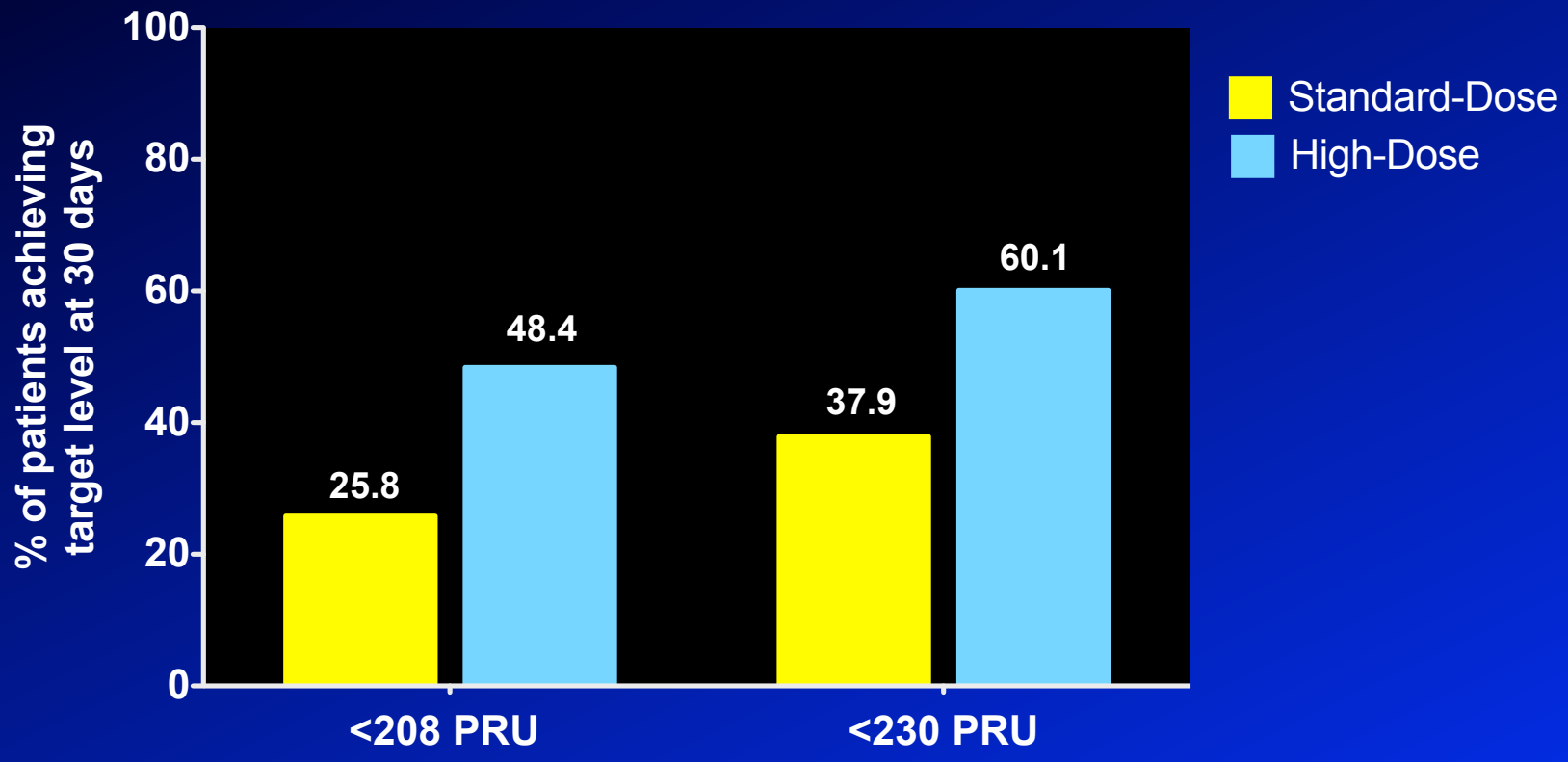

HD group, CV events according to PRU <208: HR 0.48 [95%CI, 0.18 to 1.25], P=0.14

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Limitations

- Power to detect significant associations between OTR and clinical outcomes was reduced by:
  - Skewed distribution of population (GRAVITAS by design enrolled and followed more patients with high OTR than lower levels of OTR)
  - Lower-than-expected event rates
- Underpowered to detect clinical efficacy of high-dose clopidogrel according to achieved platelet reactivity.
- Analysis using cut-off of 208 PRU was post-hoc
  - Supporting data for this cut-off after enrollment began
  - Assessing a single additional cut-off minimizes risk of a chance finding

Conclusions

- In GRAVITAS, patients who achieved on-treatment reactivity (OTR) <208 PRU at 12 to 24 hours after PCI or during follow-up had a significantly lower risk of subsequent CV events, even after adjustment for other characteristics.
  - Supports the prognostic utility of serial platelet function testing
  - Provides further support for the ESC 2011 and ACCF/AHA 2011 guideline recommendations

Conclusions

- Less than half of the patients randomly assigned to clopidogrel 150 mg daily achieved this level of OTR.
  - Supports hypothesis that an insufficient pharmacodynamic response may have contributed to the lack of observed clinical effect
- Alternative individualized strategies to improve patient outcomes after PCI merit further consideration.

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The GRAVITAS investigators (Top 40 of 83)

D. Spriggs (Clearwater, FL)
S. Puri (Moline, IL)
M. Robbins (Nashville, TN)
P. Teirstein (La Jolla, CA)
K. Garratt (New York, NY)
O. Bertrand (Quebec, QC)
M. Stillabower (Newark, DE)
J. Aragon (Santa Barbara, CA)
E.D. Nukta (Fairview Park, OH)
J.F. Tanguay (Montreal, QC)
A. Abbas (Troy, MI)
T. Mann (Raleigh, NC)
W. Batchelor (Tallahassee, FL)
P. Gordon (Providence, RI)
M. Schweiger (Springfield, MA)
M. Amine (Tomball, TX)
P. Berger (Danville, PA)
N. Chronos (Atlanta, GA)
D. So (Ottawa, ON)
R. Stoler (Dallas, TX)
S. Marshalko (Bridgeport, CT)
R. Waksman (Washington, DC)
C. O'Shaughnessy (Elyria, OH)
E. Fry (Indianapolis, IN)
D. Angiolillo (Jacksonville, FL)
B. McLaurin (Anderson, SC)
S. Rao (Durham, NC)
R. Gammon (Austin, TX)
Z. Jafar (Poughkeepsie, NY)
G. Wong (Sacramento, CA)
D. Cohen (Kansas City, MO)
J. Robb (Lebanon, NH)
M. Lucca (Duluth, MN)
S. Ward (Erie, PA)
D. Rizik (Scottsdale, AZ)
J. Wang (Baltimore, MD)
R. Minutello (New York, NY)
E. Mahmud (San Diego, CA)
P.K. Cheung (Edmonton, AB)
M. Fugit (Sacramento, CA)

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Platelet Reactivity and Cardiovascular Outcomes After Percutaneous Coronary Intervention

A Time-Dependent Analysis of the Gauging Responsiveness With a VerifyNow $P2Y_{12}$ Assay: Impact on Thrombosis and Safety (GRAVITAS) Trial

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Circulation. 2011;124:1132-1137

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