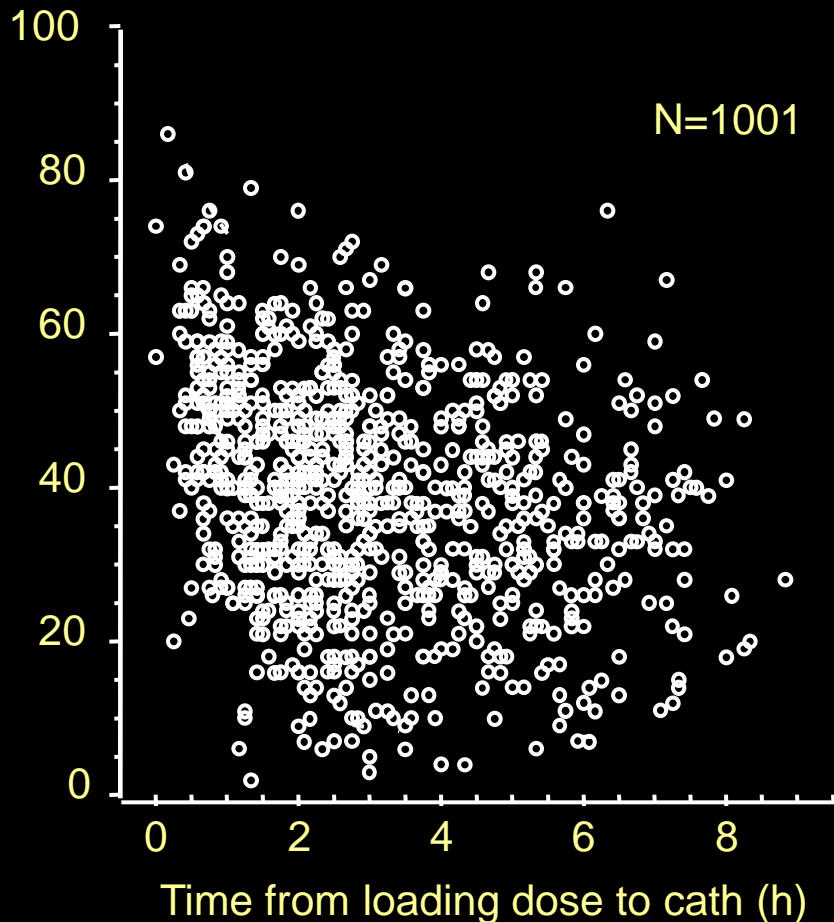

**Primary Results of The Gauging
Responsiveness with A VerifyNow
Assay - Impact on Thrombosis And
Safety Trial**

**GRAVITAS
AHA 2010**

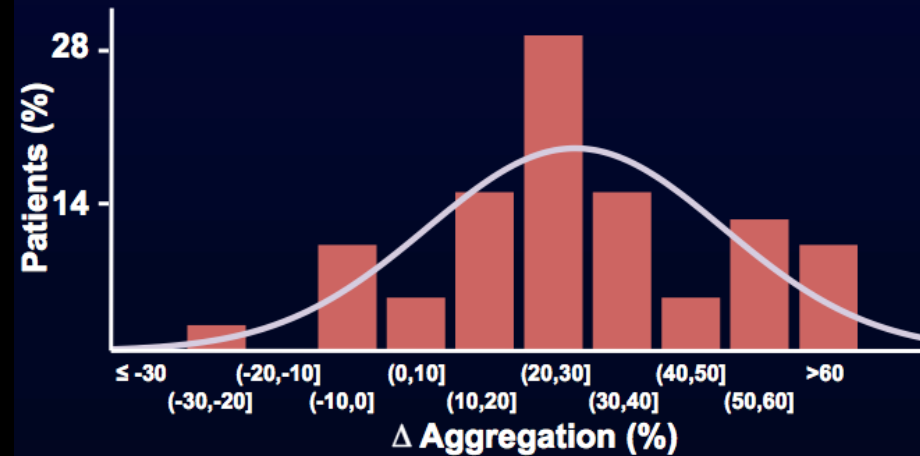
Matthew J. Price, MD
On behalf of the GRAVITAS Investigators

Platelet Reactivity Varies Widely Among Patients on Clopidogrel

Maximal aggregation 5 $\mu\text{mol/L}$ ADP (%) following 600 mg loading dose



Change in ADP-Induced Platelet Aggregation 75 mg chronic dosing



Point-of-Care Platelet Function Testing: Current Status

- At least 7 studies involving more than 3,000 patients have concluded that high residual (on-clopidogrel) platelet reactivity measured by the VerifyNow P2Y12 test is associated with poor clinical outcomes after PCI.
- A treatment strategy for patients with high residual platelet reactivity has not been tested in a large, randomized, clinical trial.

GRAVITAS: Primary Hypothesis

- High-dose clopidogrel for 6 months is superior to standard-dose clopidogrel for the prevention of adverse CV events after PCI in patients with high residual reactivity.

Trial Organization

Trial Leadership:

Matthew J. Price (Chair), Peter B. Berger, Christopher P. Cannon, J.F Tanguay (Canada PI), Paul S. Teirstein, Eric J. Topol

Sponsor:

Accumetrics (Project Leader, Jeffrey R. Dahlen)

Study Drug:

Provided by BMS/sanofi aventis through an investigator-initiated grant to Scripps Advanced Clinical Trials

Data Center and Site Management:

Synteract (Carlsbad, CA)

Data Safety and Monitoring Board:

David P. Faxon (chair), E Magnus Ohman, Charles S. Davis

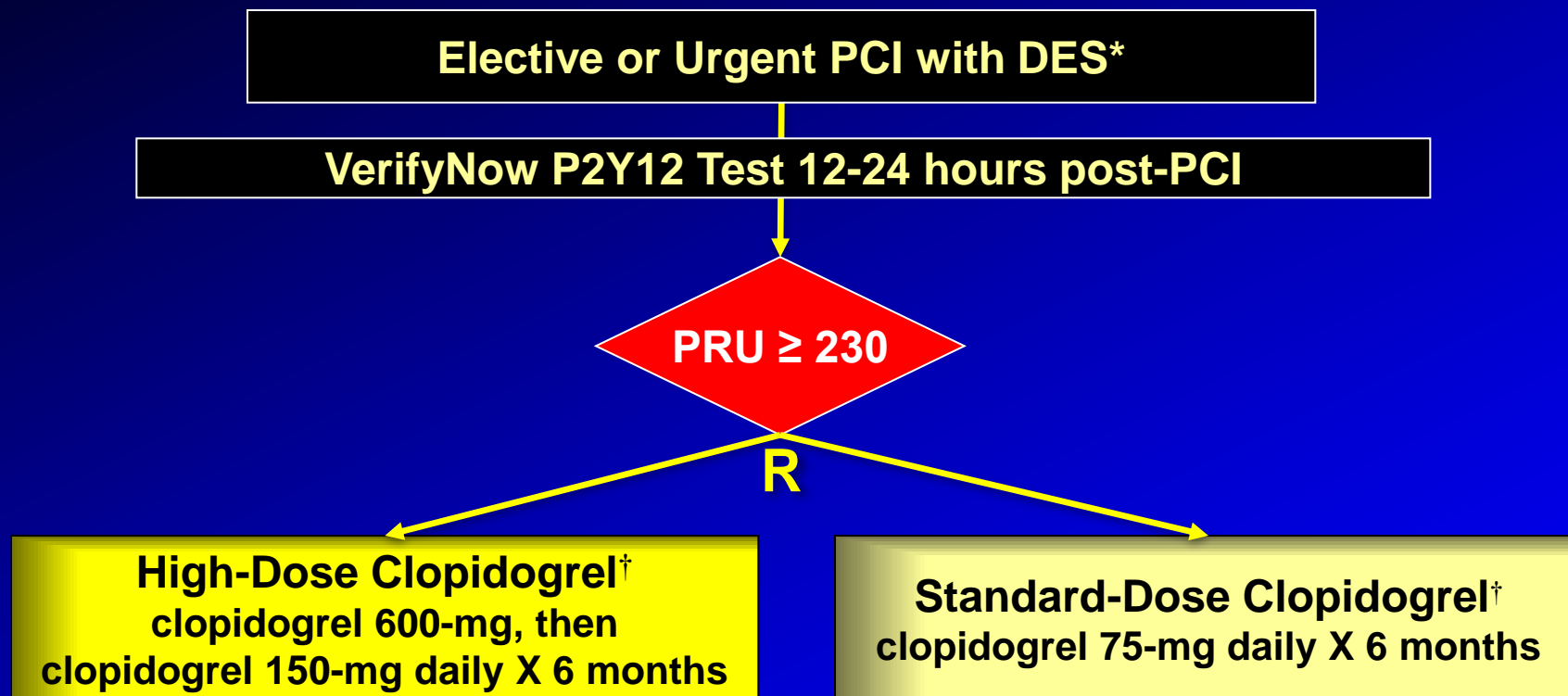
Special Thanks: Robert Hillman

Principal Investigators/Study Sites (Top 40 of 83)

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M. Robbins (Nashville, TN)
P. Teirstein (La Jolla, CA)
K. Garratt (New York, NY)
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GRAVITAS Study Design



Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo

Key Safety Endpoint: GUSTO Moderate or Severe Bleeding 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)

GRAVITAS

Inclusion and Exclusion Criteria

Major Inclusion Criteria

- DES for the treatment of stable or unstable CAD*

Major Exclusion Criteria

- Bleeding event or other major complication prior to platelet function testing
- Recent glycoprotein IIb/IIIa inhibitor

* STEMI pts were permitted after a protocol modification during the trial

Power Analysis: Sample Size Estimate

- Assumptions:
 - An event rate of 5% in patients on standard-dose clopidogrel at 6-months
 - 50% risk reduction with high-dose clopidogrel
 - 2200 patients needed to provide 80% power at a two-sided 0.05 significance level

GRAVITAS Patient Flow

5429 patients screened with VerifyNow P2Y12
12-24 hours post-PCI

2214 (41%) with high residual
platelet reactivity
(PRU \geq 230)

3215 (59%) without high
residual platelet reactivity
(PRU $<$ 230)

Clopidogrel
High Dose
N=1109

Clopidogrel
Standard Dose
N=1105

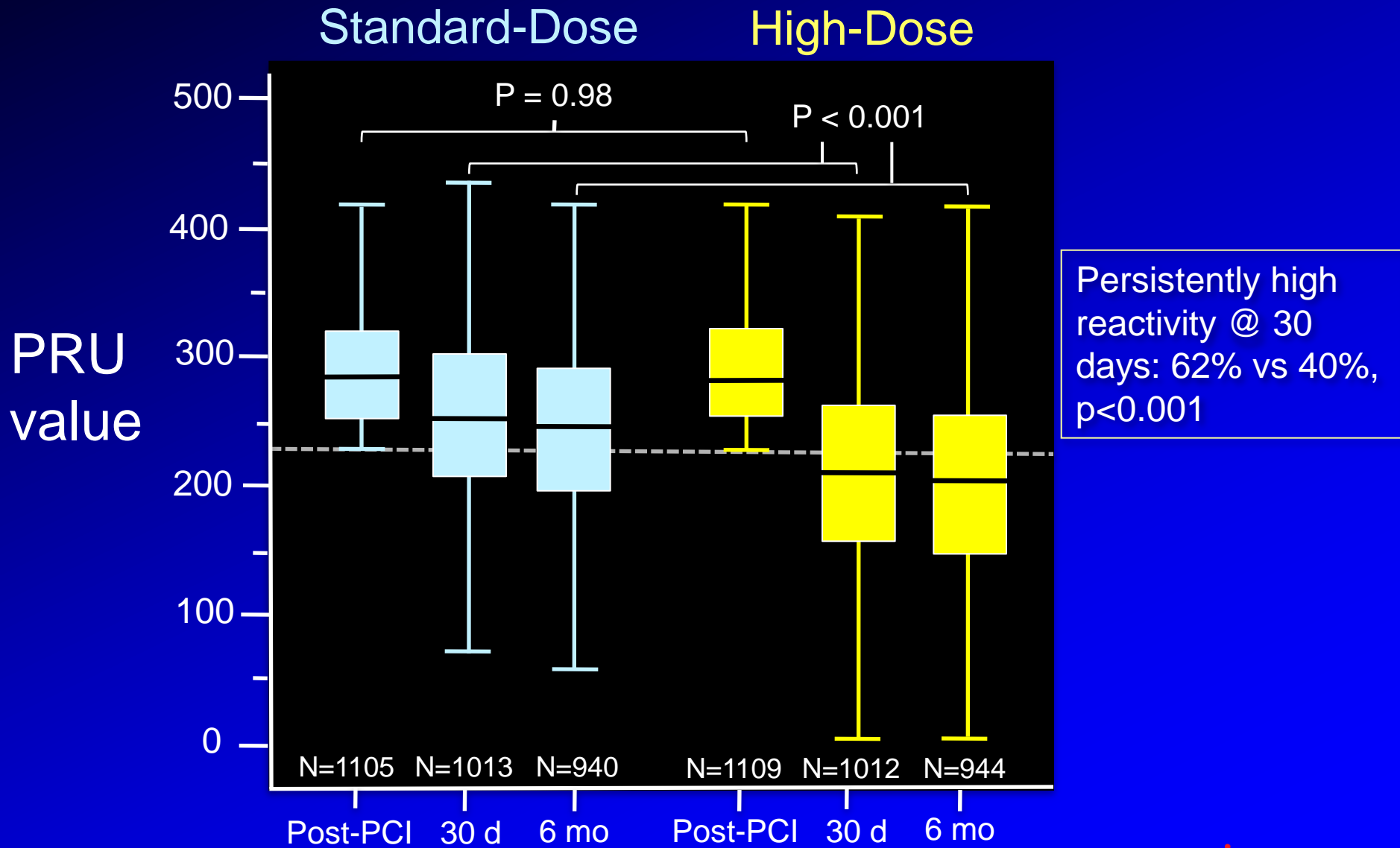
Baseline Characteristics of the Randomized Groups

Characteristic	High-Dose Clopidogrel (N=1109)	Standard-Dose Clopidogrel (N=1105)
Residual platelet reactivity, median (IQR)	282 PRU (255 - 320)	283 PRU (255 - 321)
Age, mean \pm SD	64 \pm 11	64 \pm 11
Male sex	65%	65%
Diabetes Mellitus	44%	47%
Myocardial infarction	30%	29%
PCI	50%	45%
Cr Cl < 60 ml/min	40%	42%
Proton-Pump Inhibitor	30%	30%
Peri-procedural clopidogrel		
Naïve/Clopidogrel 600-mg load	53%	53%
Clopidogrel 75 mg/d > 7d	39%	37%
Clopidogrel Load + 75mg/d < 7d	8%	10%

Procedural Characteristics of the Randomized Groups

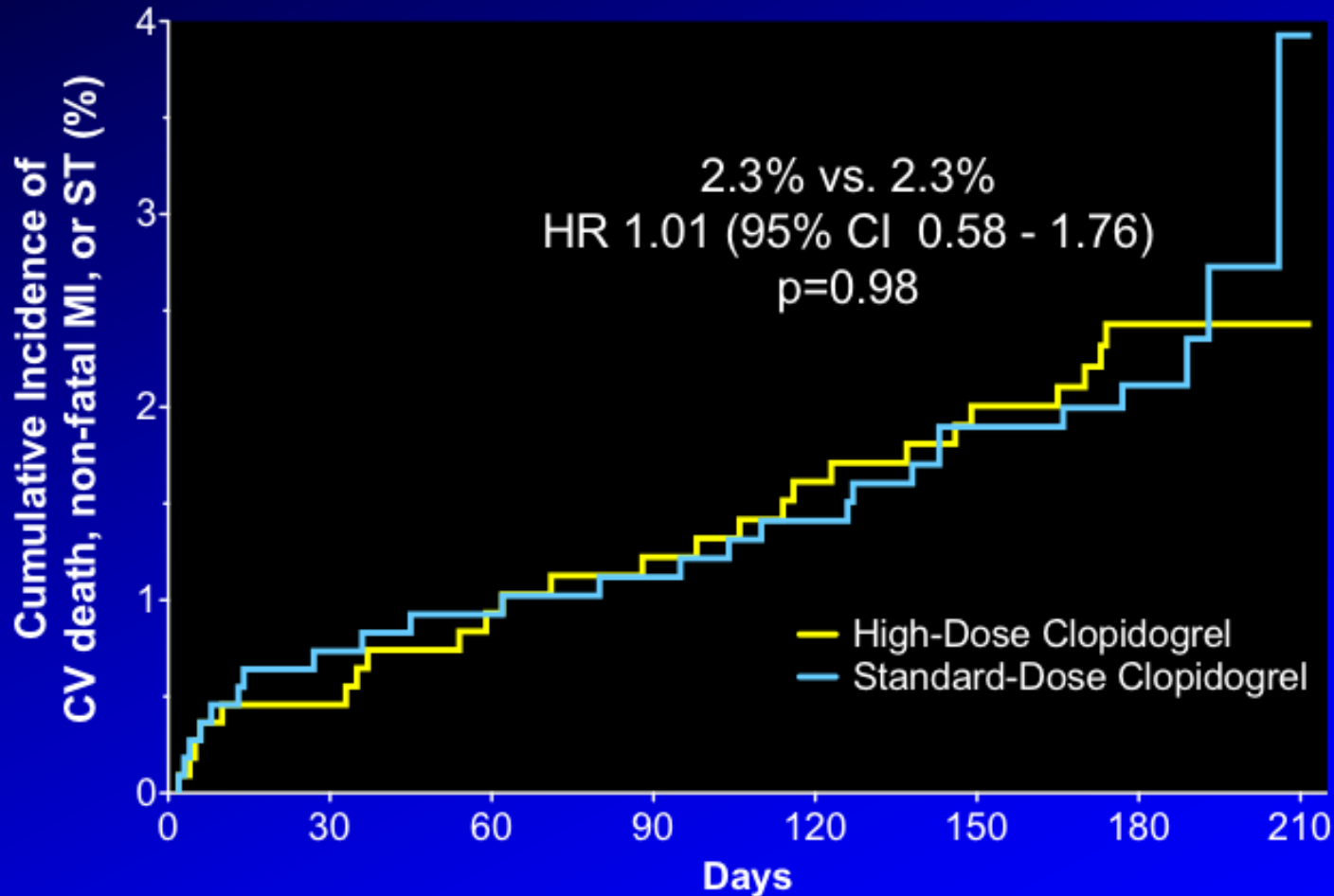
Characteristic	High-Dose Clopidogrel (N=1109)	Standard-Dose Clopidogrel (N=1105)
<i>Indication for PCI</i>		
Stable angina or ischemia	60%	60%
UA, no ST depression	24%	24%
NSTEMI-ACS		
UA, ST-dep, biomarker (-)	5%	5%
Cardiac biomarker (+)	10%	10%
ST-elevation MI	0.5%	0.2%
Treated lesions/patient	1.4 ± 0.6	1.4 ± 0.7
Stents/Patient	1.7 ± 1.0	1.6 ± 1.0
Total stented length (mm)	30 ± 23	29 ± 21

Pharmacodynamics: Effect of SD vs HD Clopidogrel



ITT population

Primary Endpoint: CV Death, MI, Stent Thrombosis

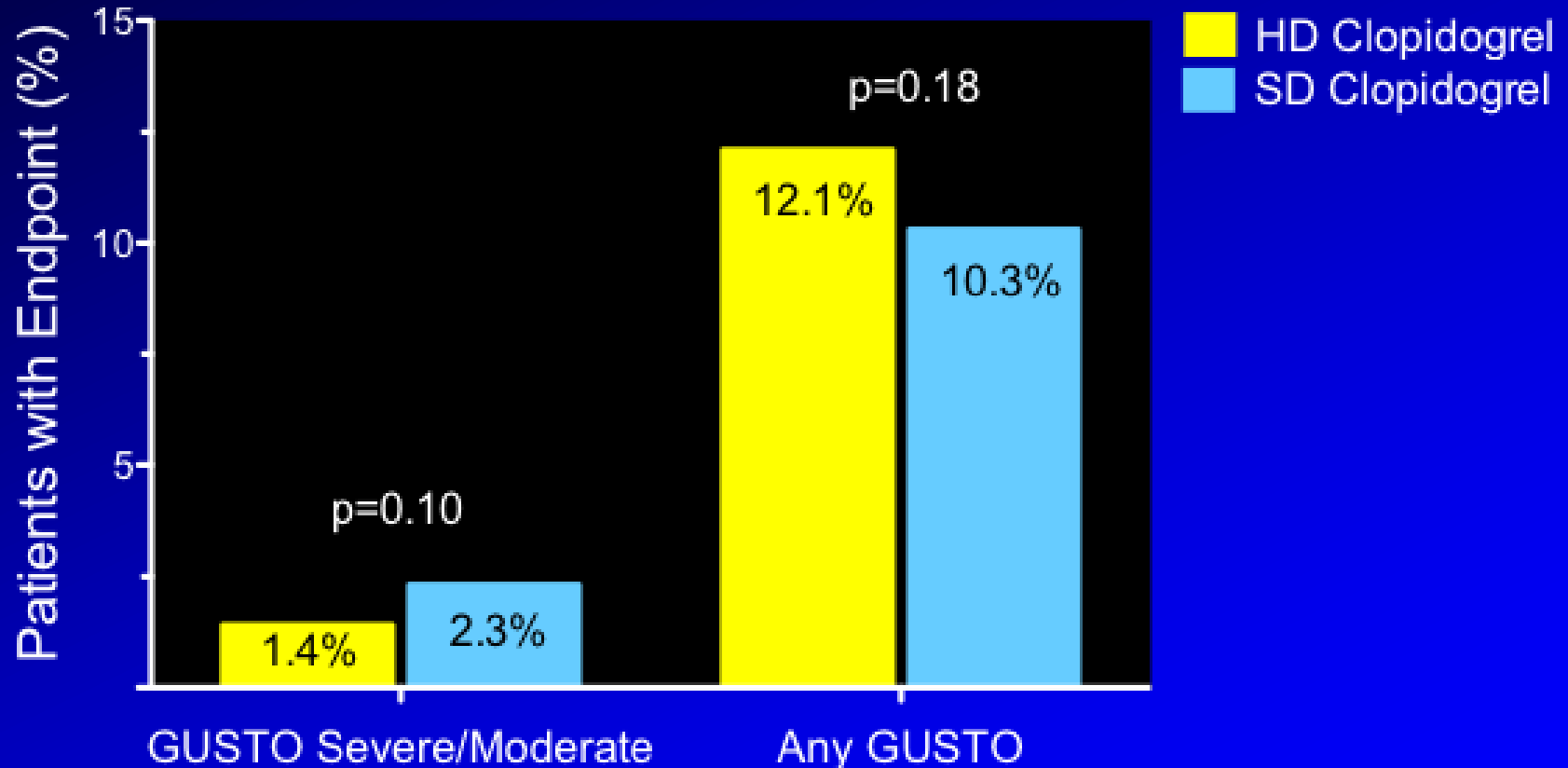


No. at Risk

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.

Bleeding Events: Safety Population



Severe or life-threatening: Fatal bleeding, intracranial hemorrhage, or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention

Moderate: Bleeding that leads to transfusion but does not meet criteria for severe bleeding

P by log rank test; observed event rates listed. HD, high-dose; SD, standard dose

GRAVITAS Patient Flow: Secondary Analysis

5429 patients screened with VerifyNow P2Y12
12-24 hours post-PCI

2214 (41%) with high residual
platelet reactivity
(PRU \geq 230)

3215 (59%) without high
residual platelet reactivity
(PRU < 230)

Clopidogrel
High Dose
N=1109

Clopidogrel
Standard Dose
N=1105

Clopidogrel
Standard Dose
N=586

Random selection

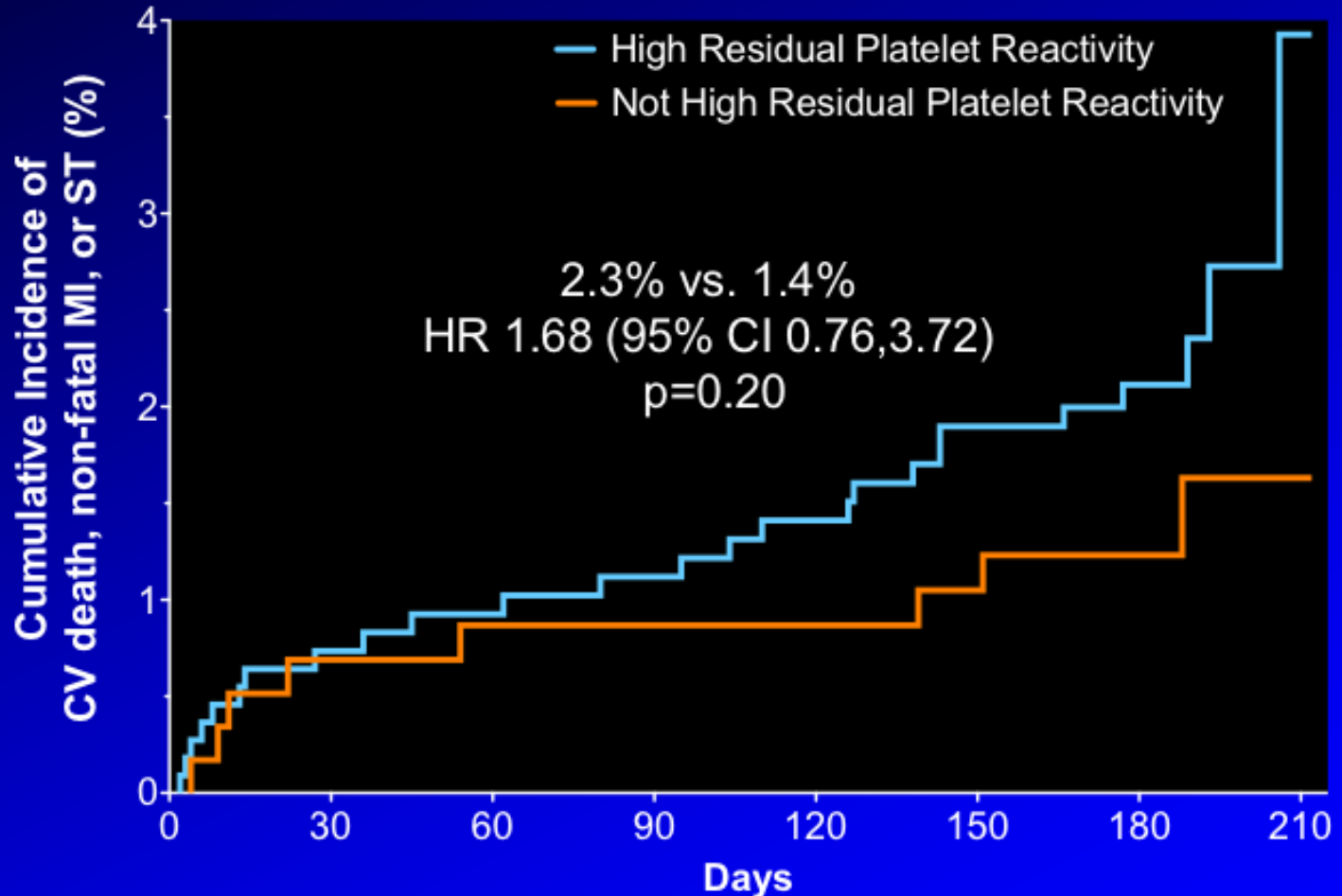
Non-Randomized Comparison

GRAVITAS

Baseline Characteristics: Non-Randomized Comparison

Characteristic	SD – High RPR N=1105	SD – Not High RPR N=586	p
Residual platelet reactivity, median (IQR)	283 PRU (255 - 321)	151 PRU (105 - 191)	<0.001
Age, years	64 ± 11	62 ± 10	<0.001
Male sex	65%	80%	<0.001
Diabetes Mellitus	47%	29%	<0.001
Body mass index (median)	31	29	<0.001
Cr Cl < 60 ml/min	42%	27%	<0.001
Proton pump inhibitor	30%	20%	<0.001
<i>Indication for PCI</i>			0.41
Stable angina or ischemia	60%	56%	
UA, no ST depression	24%	28%	
NSTE-ACS			
UA, ST-dep, biomarker (-)	5%	5%	
Cardiac biomarker (+)	10%	11%	

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



No. at Risk
High Residual Reactivity
Not High Residual Reactivity

1105

1057

1028

1020

1015

1005

773

53

586

565

552

551

549

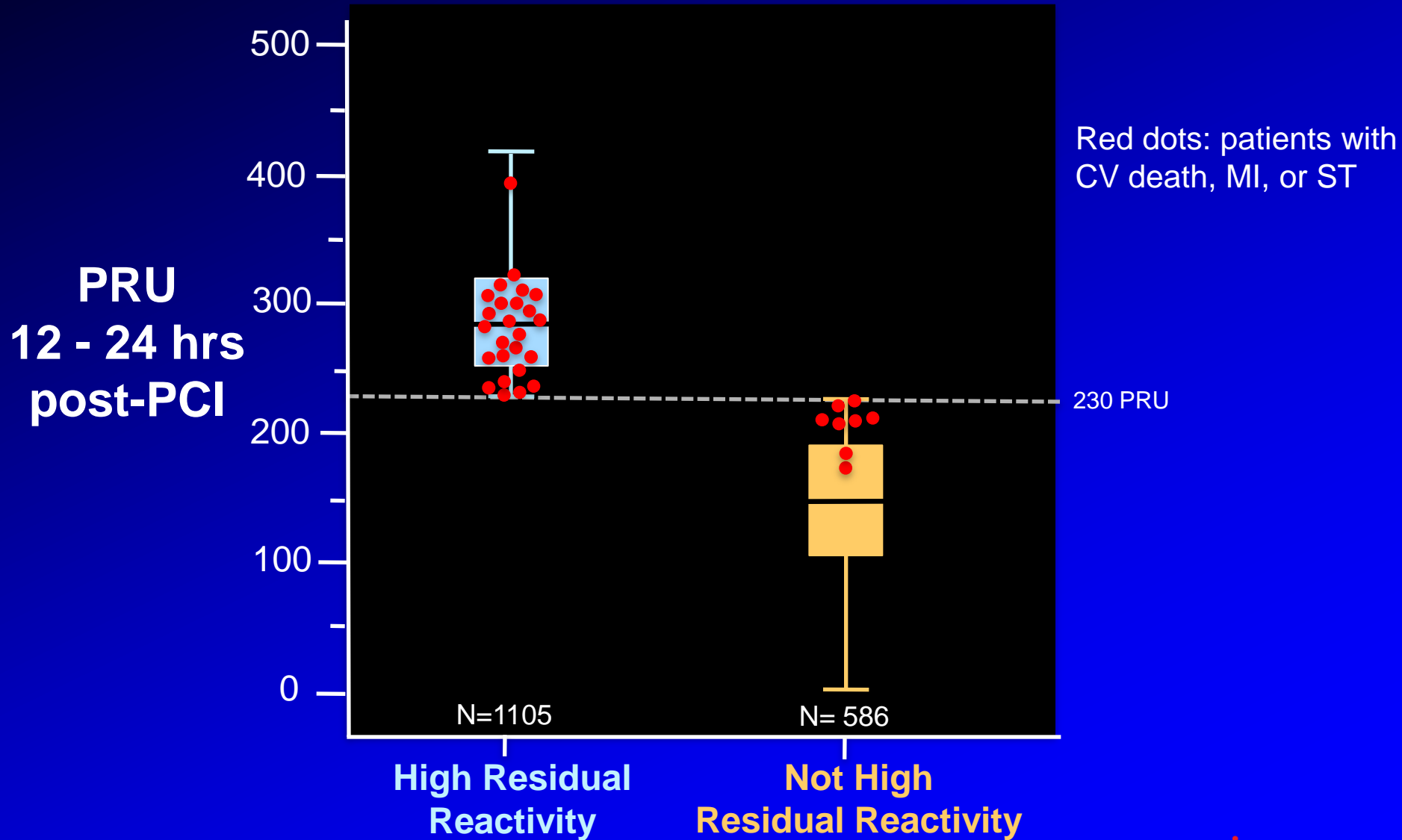
546

415

19

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

CV Events and Post-PCI PRU In Patients With High and Not High Reactivity Treated With Clopidogrel 75-mg Daily



GRAVITAS: Summary

- Compared with standard-dose therapy, high-dose clopidogrel achieved a modest pharmacodynamic effect in patients with high residual reactivity.
- In patients with high residual reactivity measured after PCI, 6-months of high-dose clopidogrel did not reduce the rate of cardiovascular death, non-fatal MI, or stent thrombosis and did not increase GUSTO severe or moderate bleeding.

GRAVITAS: Possible Explanations

- Underpowered: patients low-risk, low event rates?
 - Given HR of 1.01 with more than 2,200 patients, unlikely that a larger trial would show a clinically meaningful benefit
- Pharmacodynamic effect of the intervention was too weak?
 - Stronger intervention and/or goal-directed therapy with serial measurements merit study (TRIGGER-PCI; ARCTIC; TARGET-PCI)

GRAVITAS does not support a treatment strategy of high-dose clopidogrel in patients with high residual reactivity identified by a single platelet function test after PCI.