Standard vs. High-Dose Clopidogrel According to Platelet Function Testing after PCI: Results of the GRAVITAS Trial

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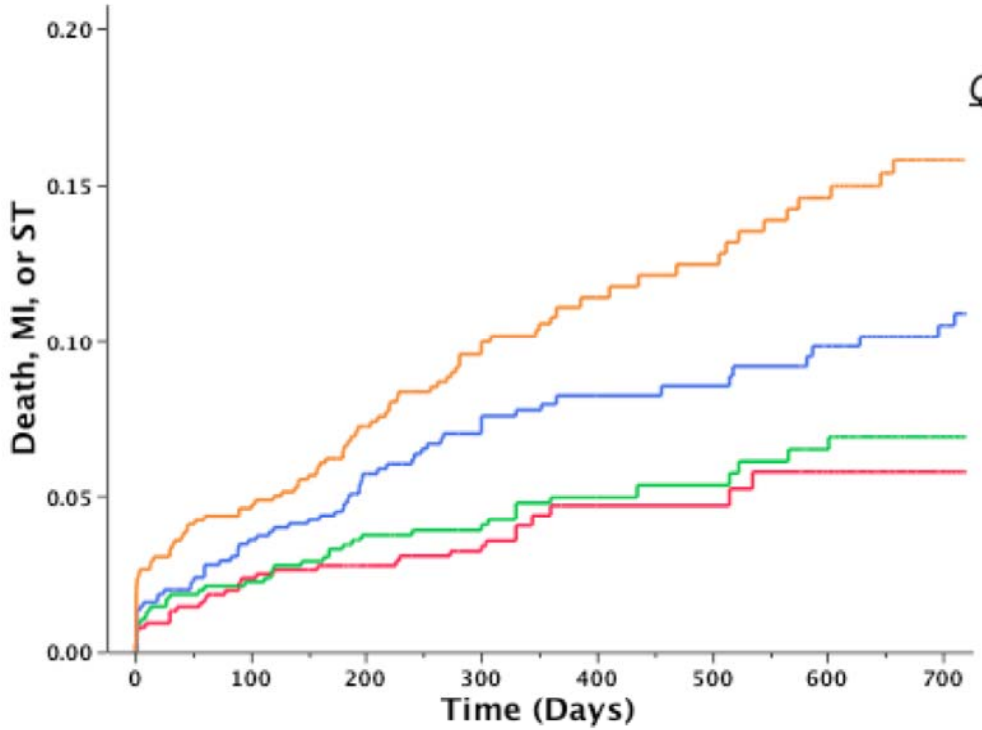
Meta-Analysis of OTR and Ischemic Events Post-PCI: Increasing Risk With Greater Residual Reactivity

N=3,041



Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

No. at risk				
Q1	765	639	179	169
Q2	761	611	249	237
Q3	757	595	294	271
Q4	758	588	252	224

P-values adjusted for multiple comparisons

Brar S, ACC 2011 (in press)

GRAVITAS: Primary Hypothesis

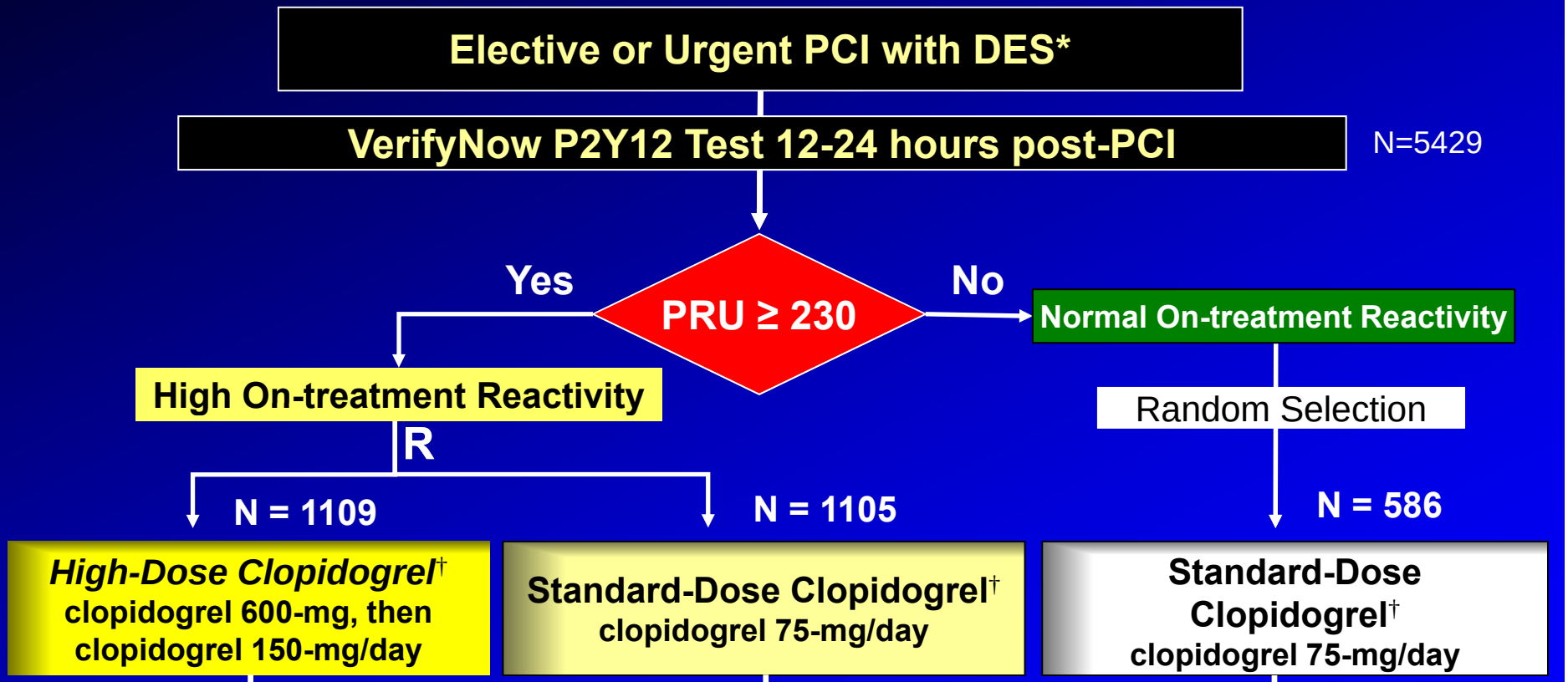
- High-dose clopidogrel for 6 months is superior to standard-dose clopidogrel for the prevention of adverse CV events after PCI in patients with high residual reactivity.

Price MJ, AHA 2010

GRAVITAS

Price MJ et al , JAMA 2011

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

Procedural Characteristics of the Randomized Groups

Characteristic	High-Dose Clopidogrel (N=1109)	Standard-Dose Clopidogrel (N=1105)
Indication for PCI		
Stable angina or ischemia	60%	60%
UA, no ST depression	24%	24%
NSTE-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

Price MJ, AHA 2010

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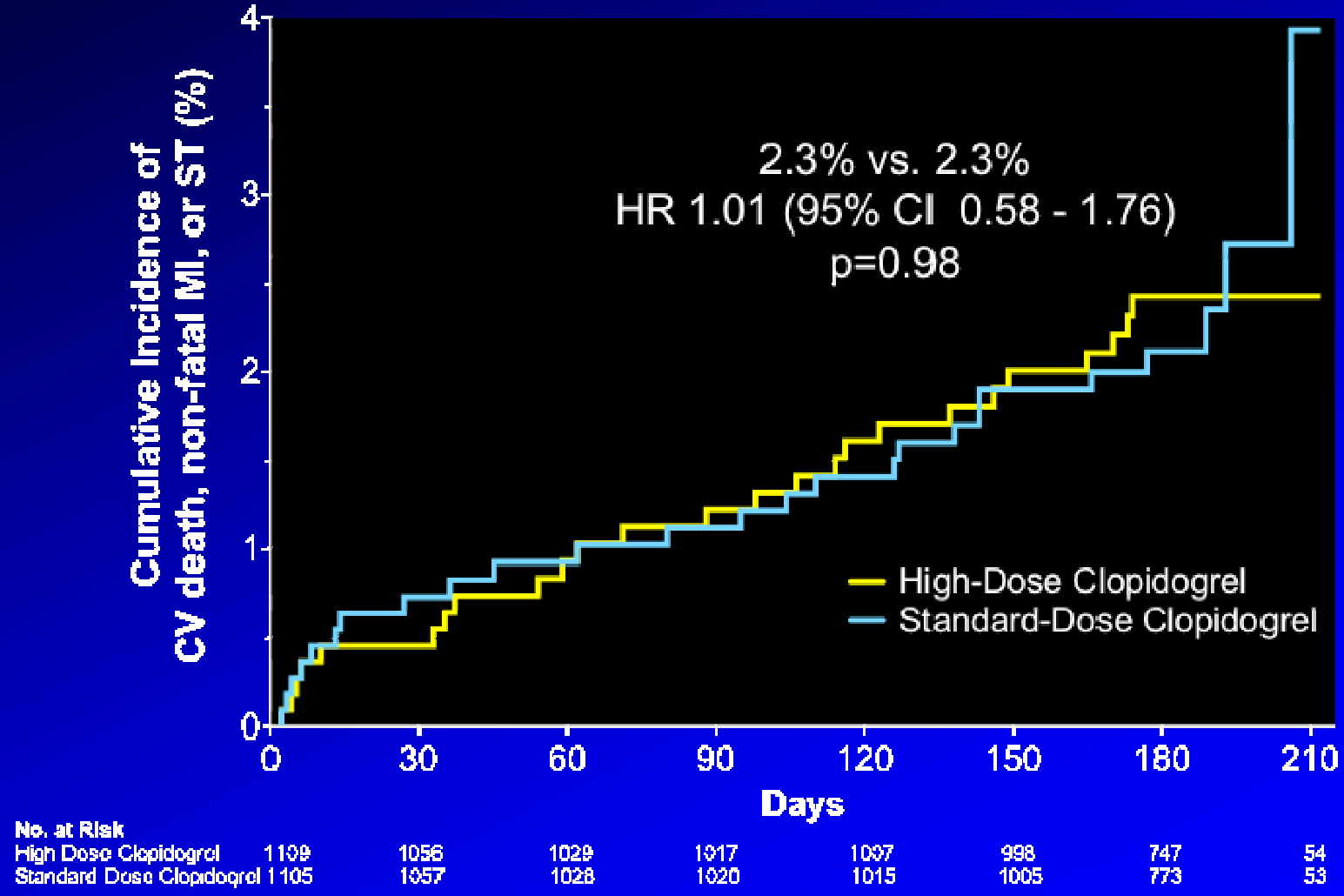
Primary Endpoint: CV Death, MI, Stent Thrombosis



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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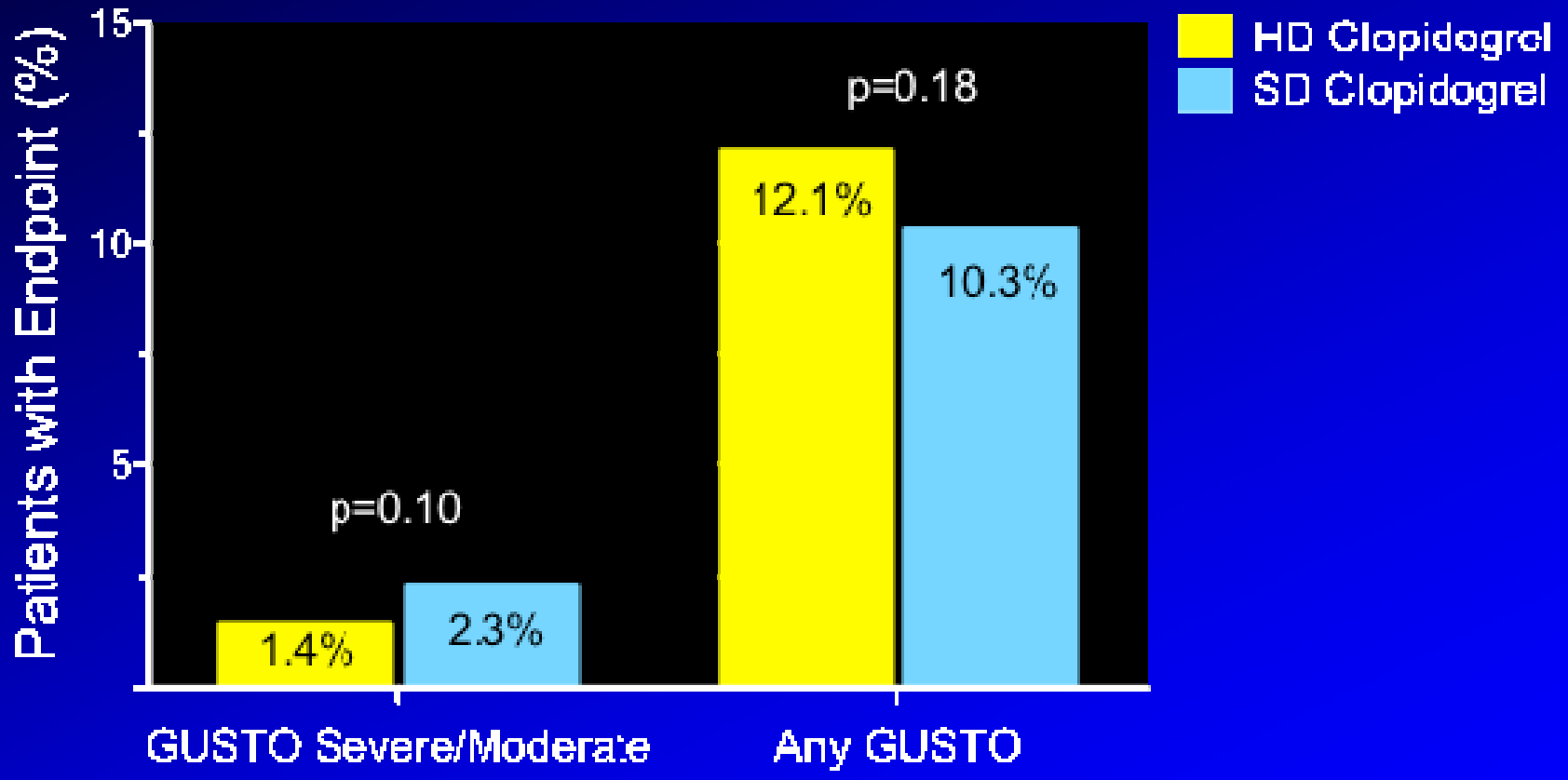
Price MJ et al , JAMA 2011

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

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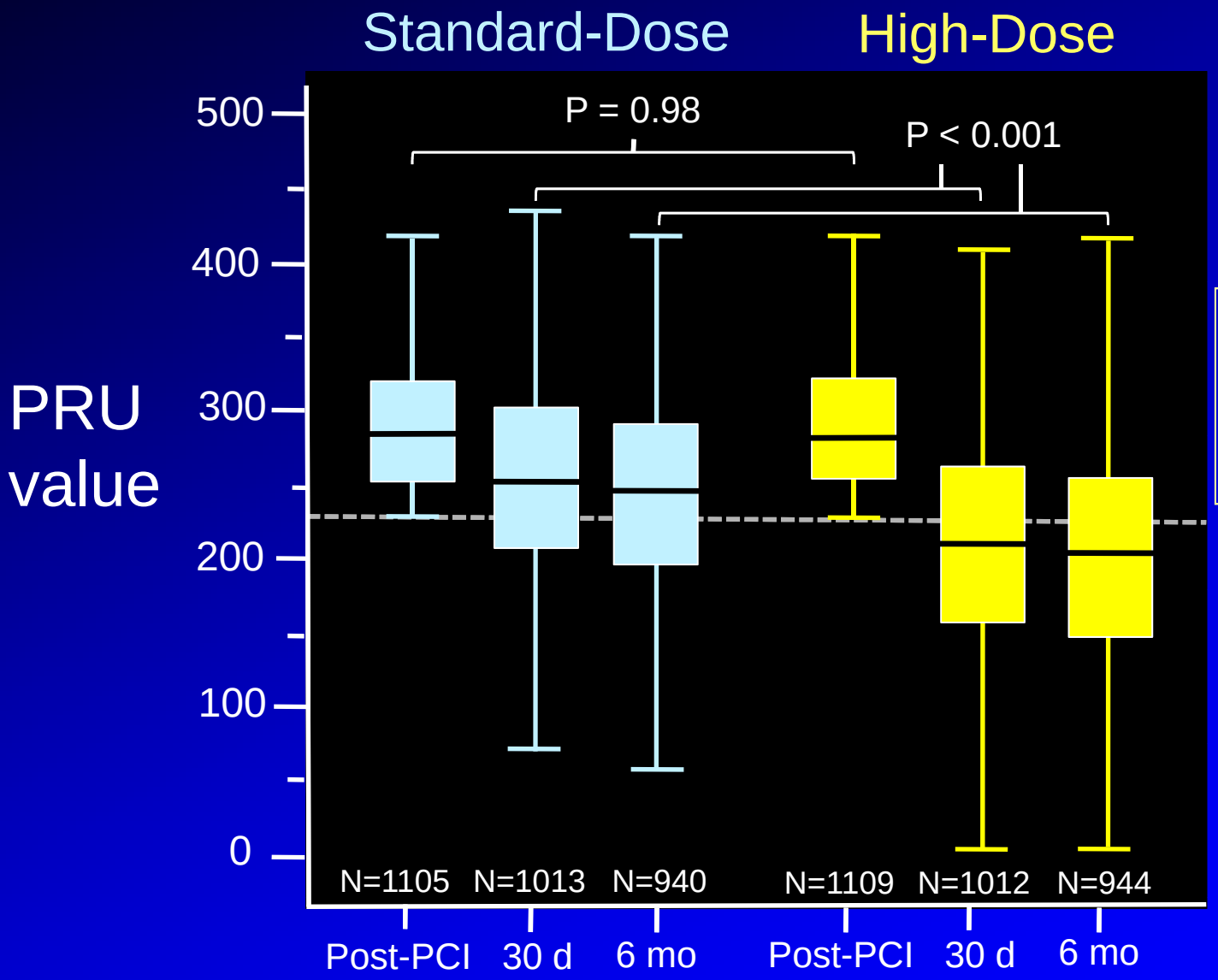
Pharmacodynamics: Effect of SD vs HD Clopidogrel



Persistently high reactivity @ 30 days: 62% vs 40%, p<0.001

ITT population

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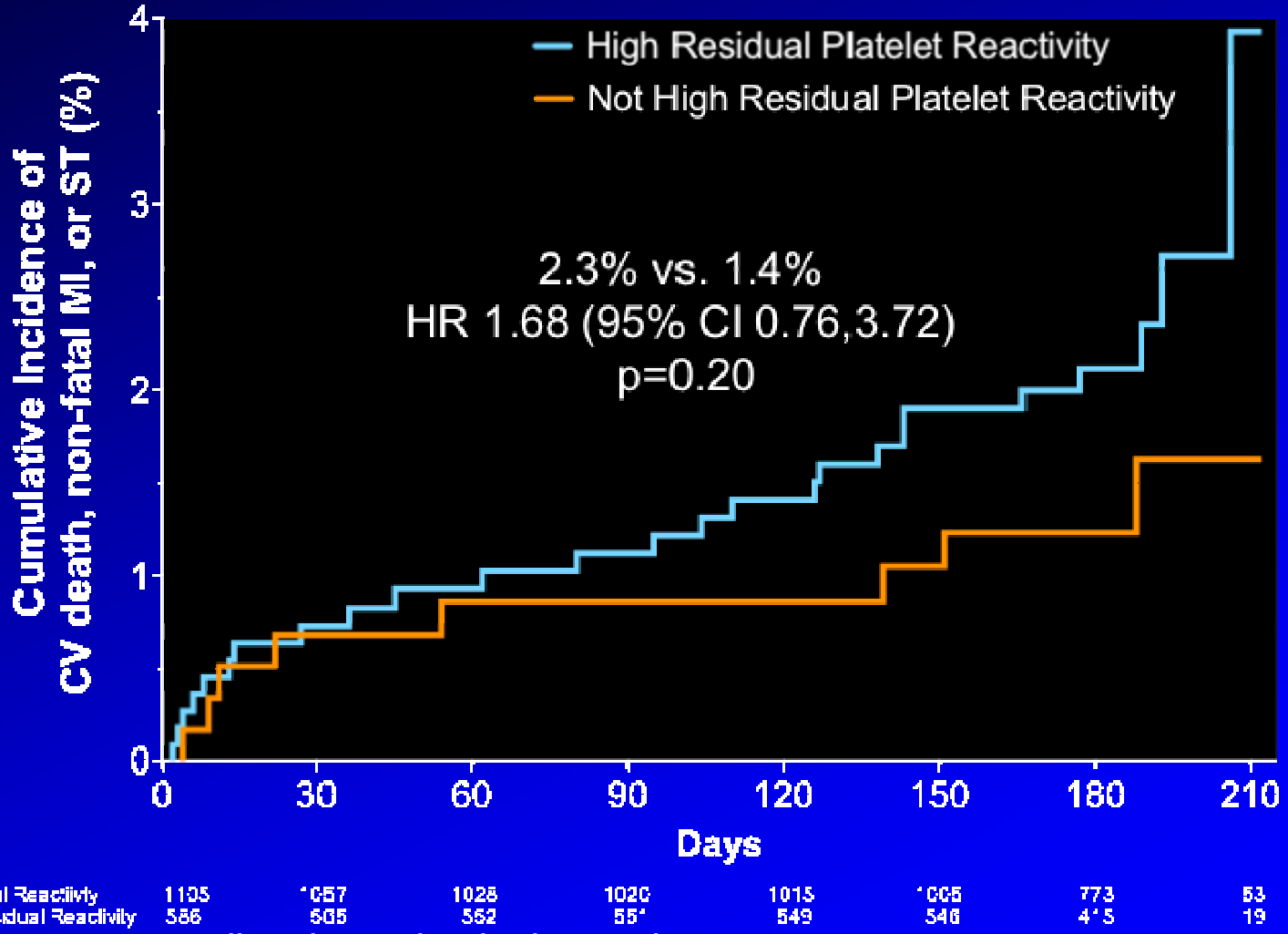
Price MJ et al, JAMA. 2011;305(11):1097-1105

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



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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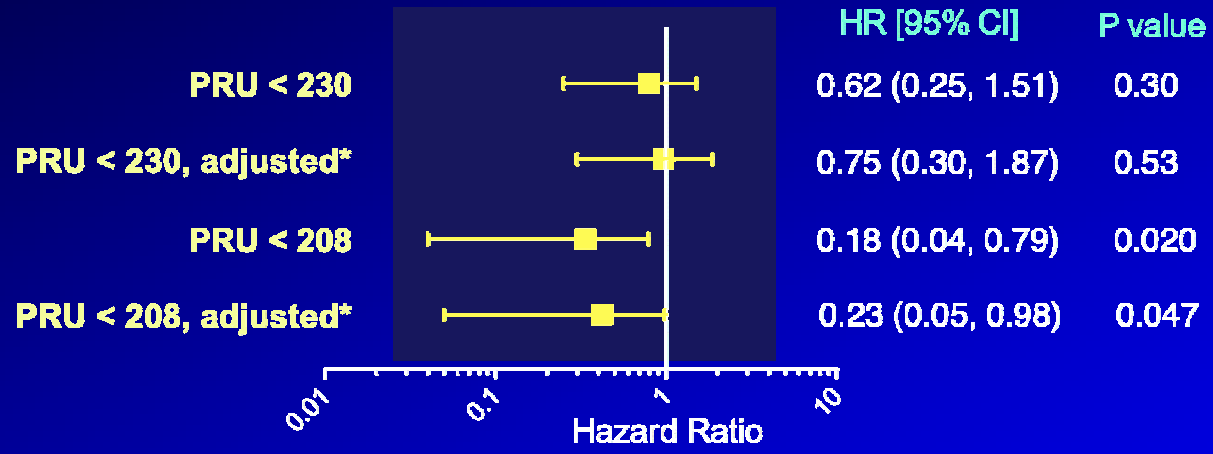
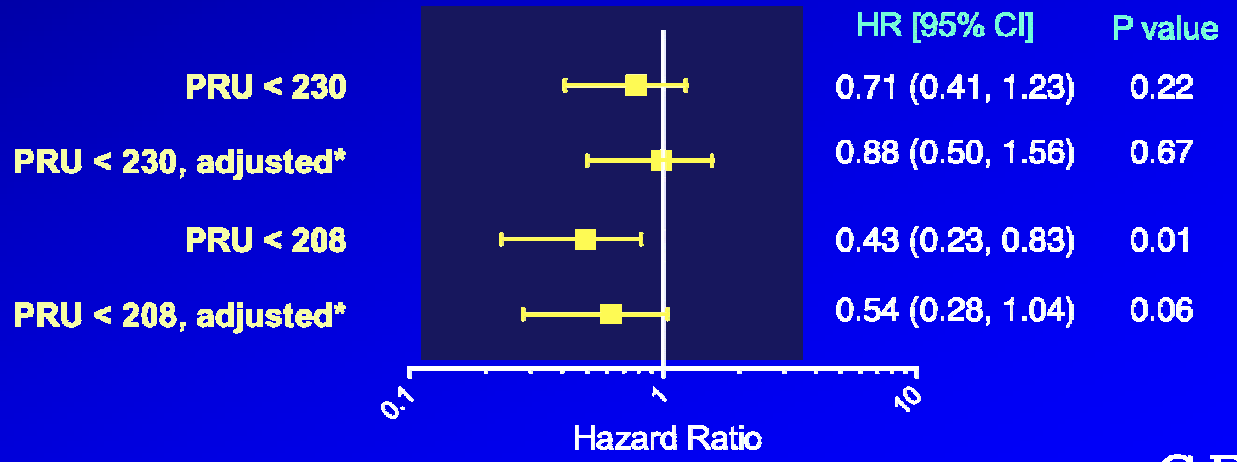
GRAVITAS: Hazard of Primary Endpoint According To *Achieved* OTR (Baseline or 30 days)

CV Death, MI or ST at 60 Days

N=2796



CV Death, MI or ST at 6 Months



Cox regression using OTR as a time-varying covariate
Price MJ et al, *in submission*

GRAVITAS

GENOTYPE INFORMATION & FUNCTIONAL TESTING

Results: Influence of *PON1*, *CYP2C19*, and *ABCB1* on the Primary Endpoint

P < 0.0013 for statistical significance

On-Treatment Reactivity at Screening (12-24 hrs post-PCI) N=1013

SNP	R^2	
PON1 Q192R	0.2%	P = 0.42
*CYP2C19*2*	6.5%	P = 2.2 x 10^{-15}
*CYP2C19*17*	0.5%	P = 0.08
ABCB1 3435 C→T	0.1%	P = 0.61

Change in On-Treatment Reactivity at 30 days N=714

SNP	R^2	
PON1 Q192R	0%	P = 0.71
*CYP2C19*2*	5.1%	P = 1.4 x 10^{-5}
*CYP2C19*17*	1.2%	P = 0.02
ABCB1 3435 C→T	0%	P = 0.40

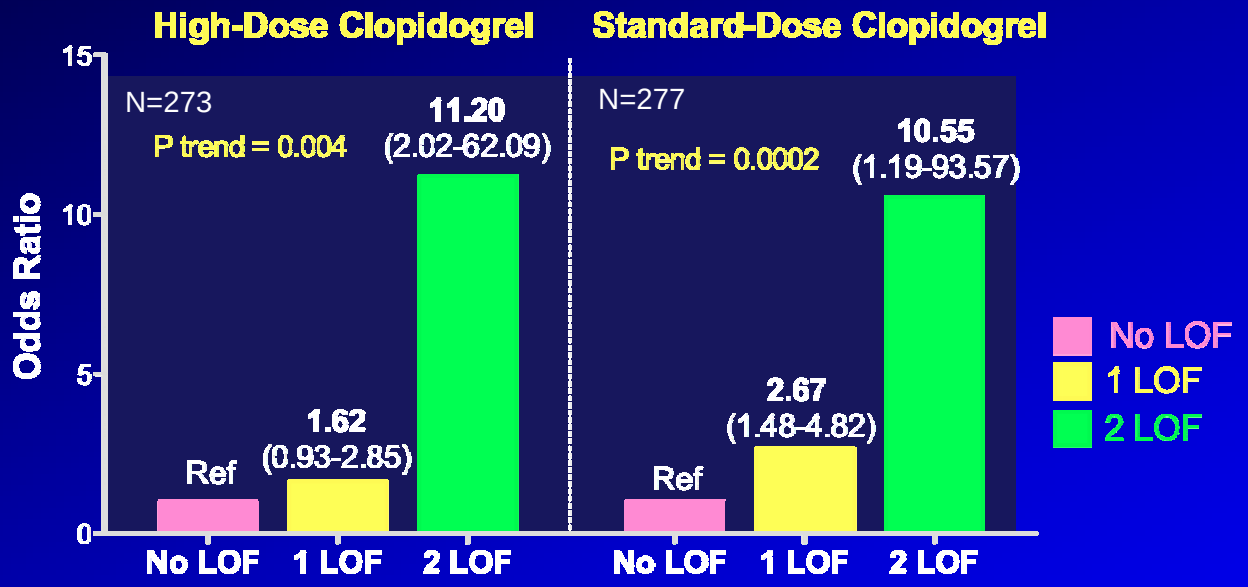
Co-dominant model, adjusted for tx and characteristics associated with OTR.

GRAVITAS

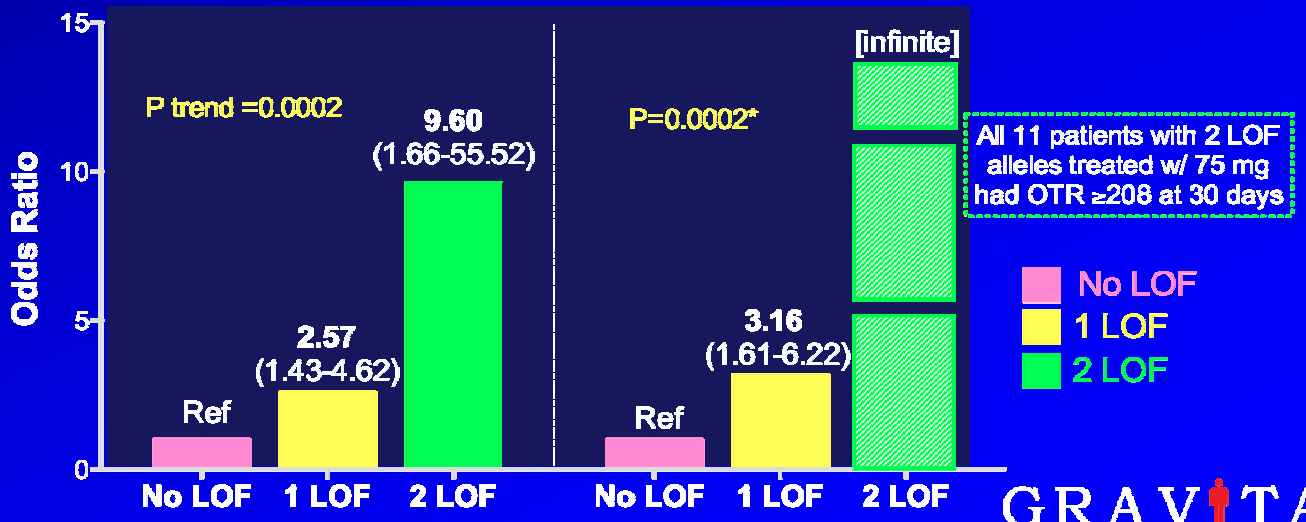
Gift
GENOTYPE INFORMATION & FUNCTIONAL TESTING

CYP2C19 LOF Allele Is Associated With Higher Risk of Persistently High OTR at 30 Days Regardless of Dose

ORs for PRU ≥ 230 at 30 Days



ORs for PRU ≥ 208 at 30 Days



GRAVITAS

Price ACC/i2 2011

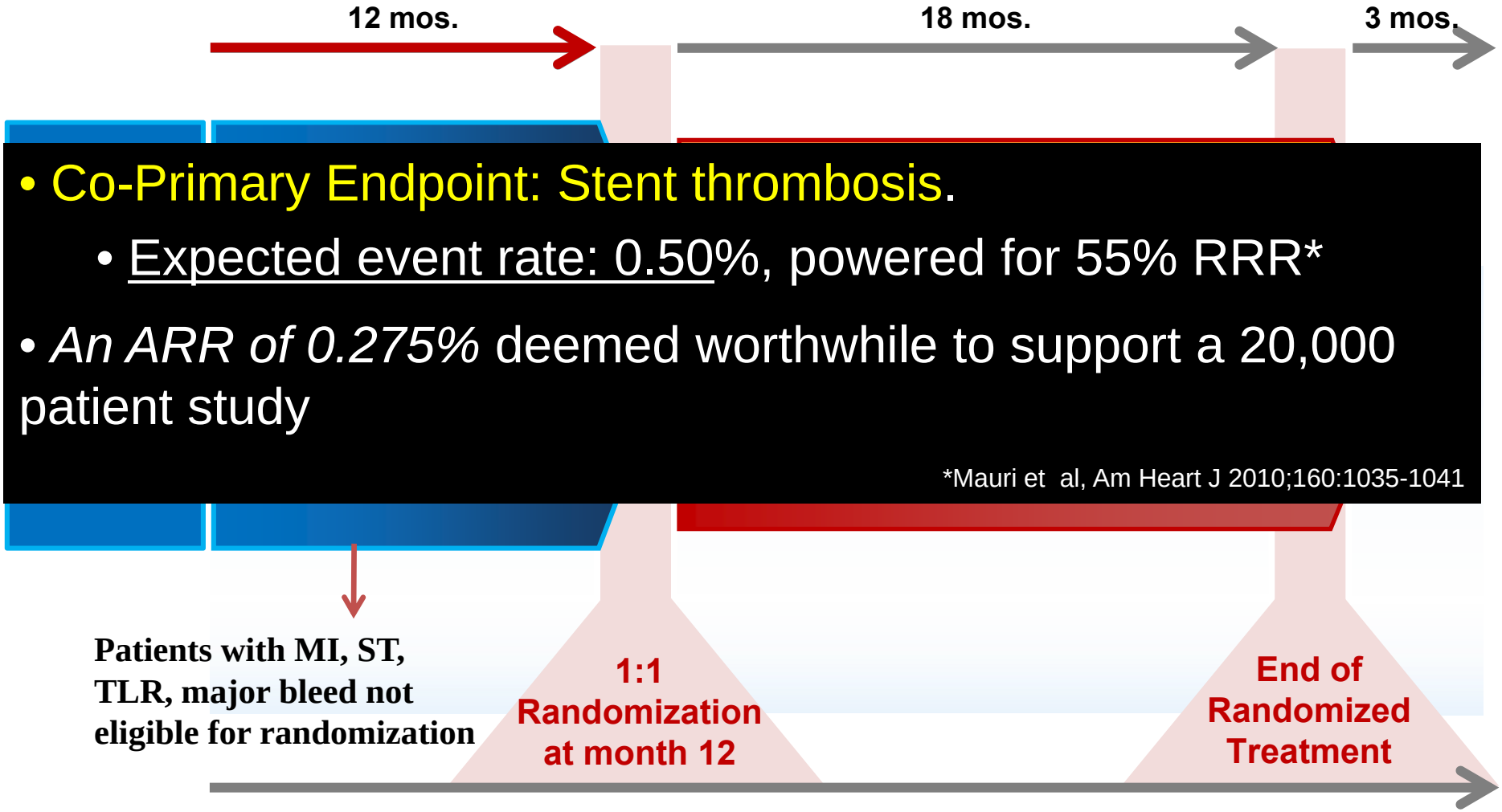
GRAVITAS, TRIGGER-PCI, Low Event Rates, and Platelet Function Testing

- GRAVITAS and TRIGGER-PCI reinforce the observation that event rates after PCI for stable CAD with newer DES and current PCI techniques are quite low.
- Large trials will be needed to prove the efficacy of potent individualized APT in PCI for stable CAD.
- Are the event rates so low in stable patients that platelet function testing is not worthwhile?

Is It Worth Testing Prolonged Dual Antiplatelet Therapy After DES?

DAPT STUDY

Study Design



www.daptstudy.org www.clinicaltrials.gov – NCT00977938

Summary

- In GRAVITAS, double-dose clopidogrel for 6 months was not superior to standard-dose clopidogrel in patients with high reactivity after PCI.
- PD effect of double-dose is variable and influenced by CYP2C19 LOF allele carriage.
- Post-hoc analysis demonstrates that an achieved reactivity < 208 PRU was significantly associated with improved CV outcomes.
- In stable CAD patients with high reactivity but low CV event rates, special consideration may be needed to balance the potential ischemic benefit and bleeding harm with more powerful antiplatelet agents.