

Evolving Genotyping and Platelet Function Testing: Personalized Antiplatelet Therapy, Possible in Real Practice? - Pro

*Transcatheter Cardiovascular Therapeutics
Asian Pacific 2011*

April 28, 2011

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Disclosure Statement

AstraZeneca: research grant support through BWH

Bristol-Myers Squibb / sanofi-aventis Joint Venture: research grant support through BWH; scientific advisory boards

Daiichi-Sankyo: research grant support through BWH

Daiichi-Sankyo / Lilly Partnership: scientific advisory boards

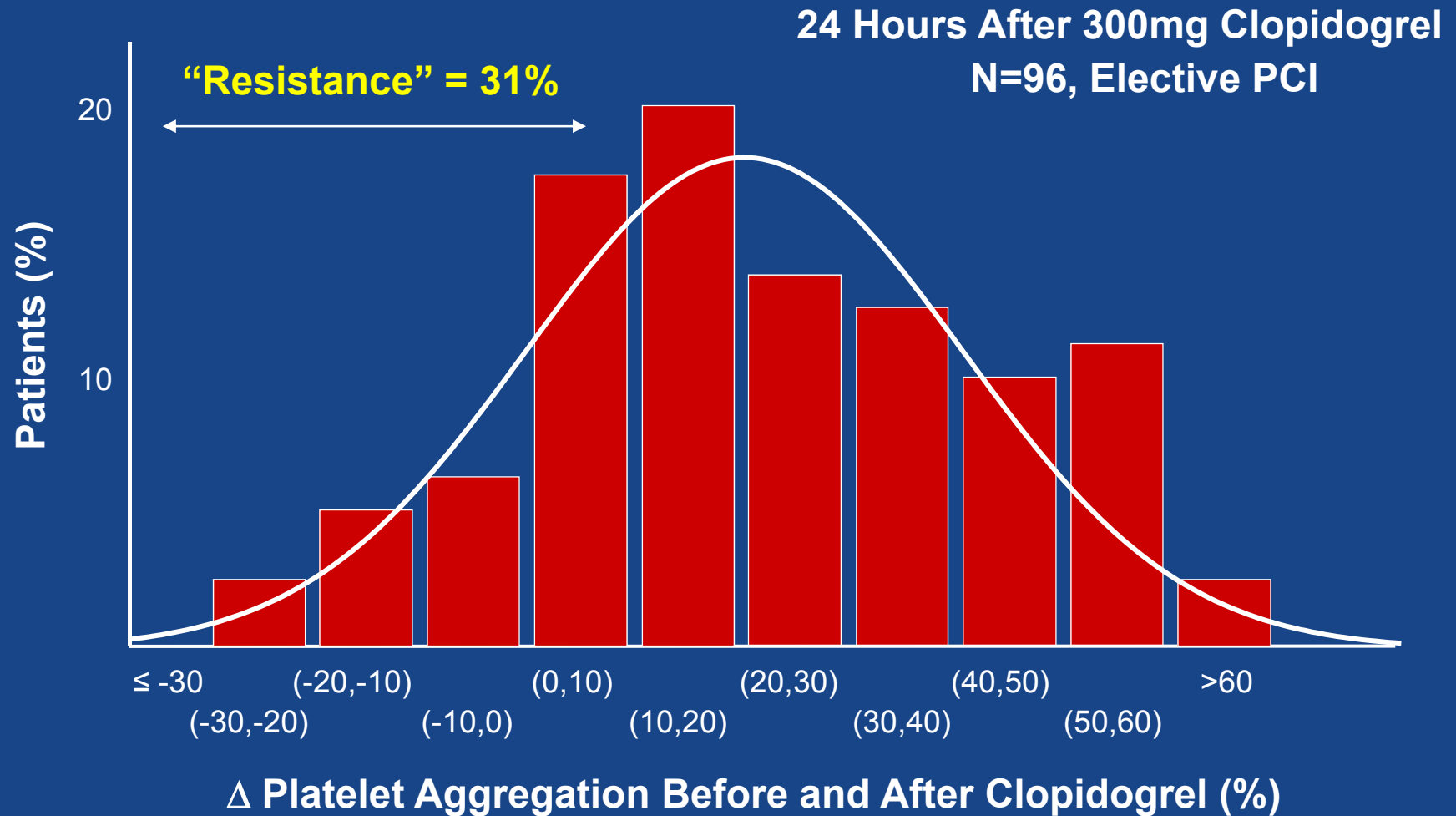
Eli Lilly: honoraria for education presentations

Nanosphere: research reagents through BWH

sanofi-aventis: research grant support through BWH; scientific advisory boards

Schering-Plough: research grant support through BWH

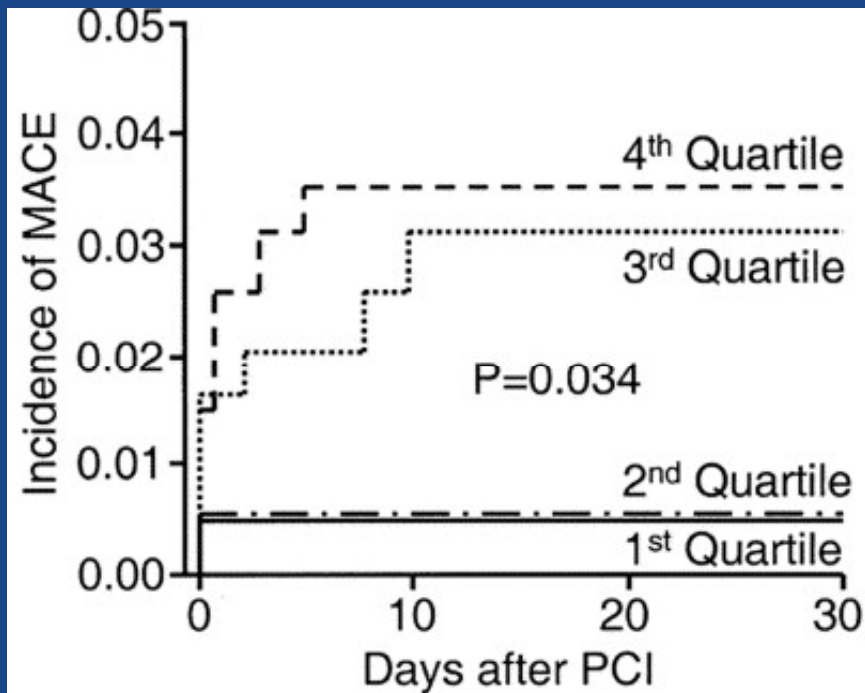
Variable Response to Clopidogrel



“Resistance” = $\leq 10\%$ Δ platelet aggregation

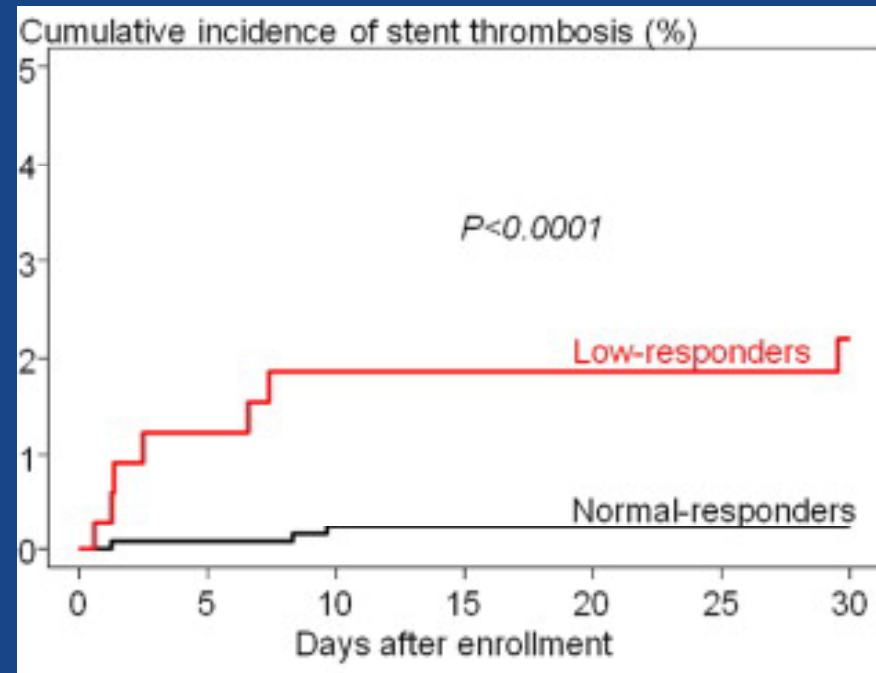
Platelet Reactivity and Outcomes

MACE



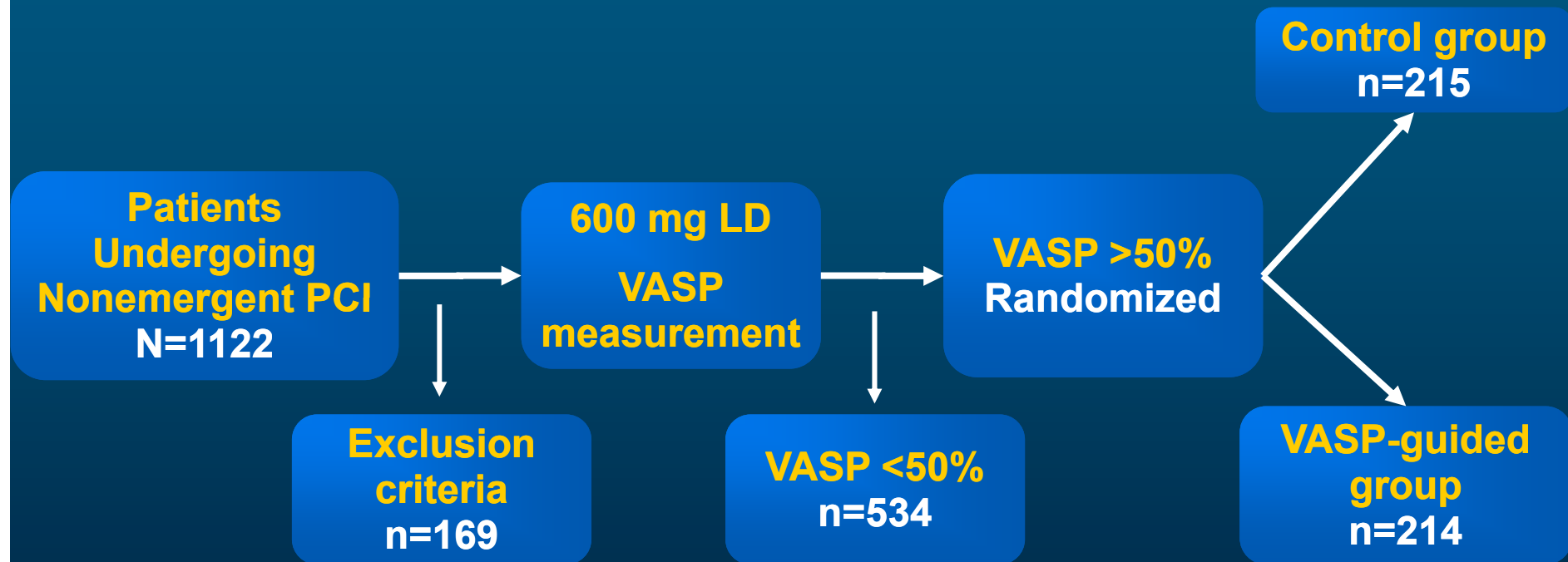
Hochholzer W et al., *JACC* 2006;48:1742-1750

Stent Thrombosis



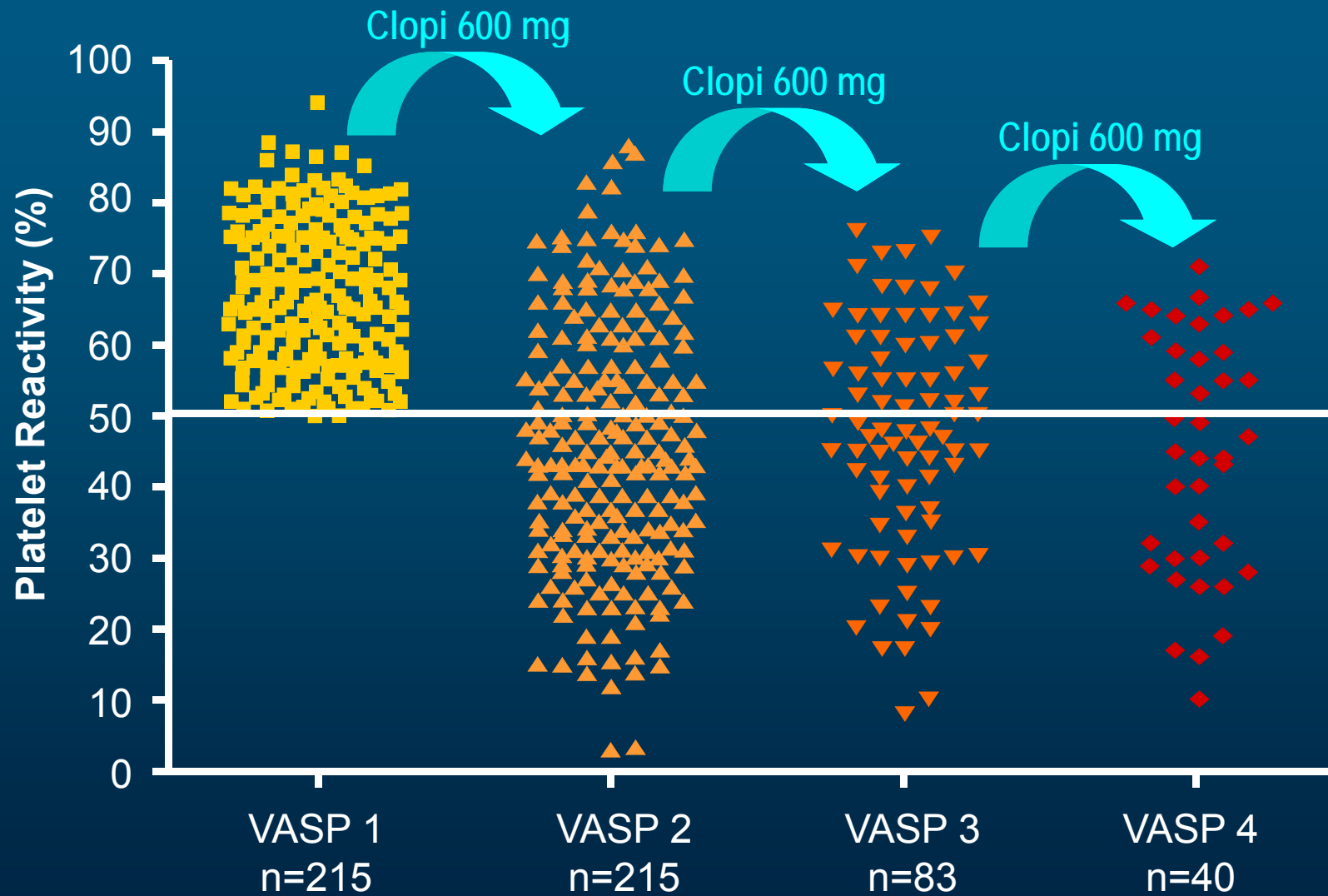
Sibbing D et al., *JACC* 2009;53:849-856

Platelet Responsiveness and VASP Guided Therapy Study Design



VASP=Vasodilator-Stimulated Phosphoprotein Phosphorylation.
Bonello et al. *Am J Cardiol.* 2009;103:5-10.

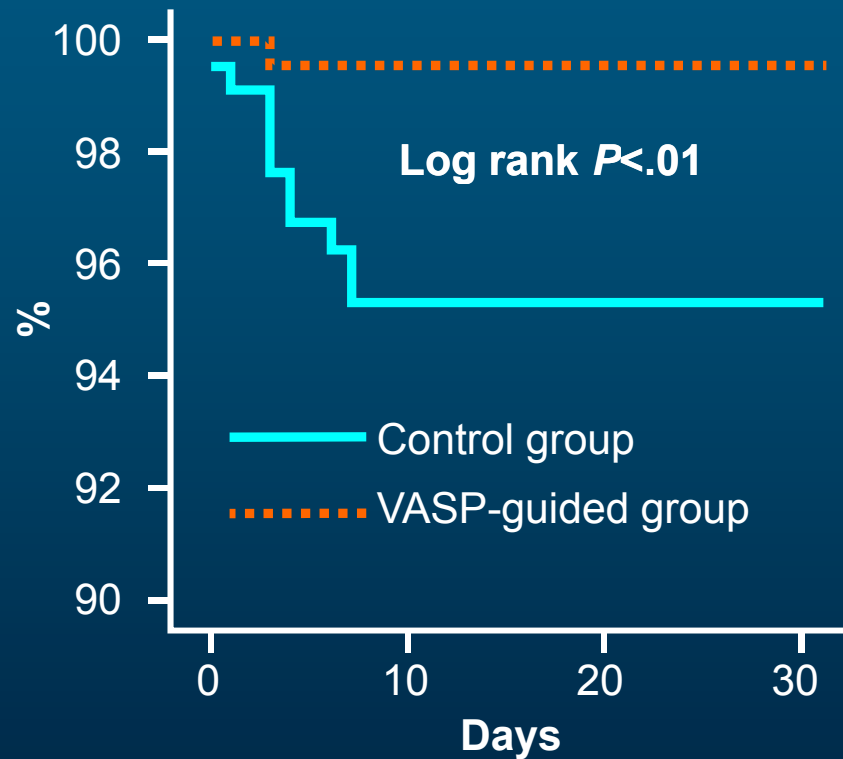
Platelet Activity by Clopidogrel Doses



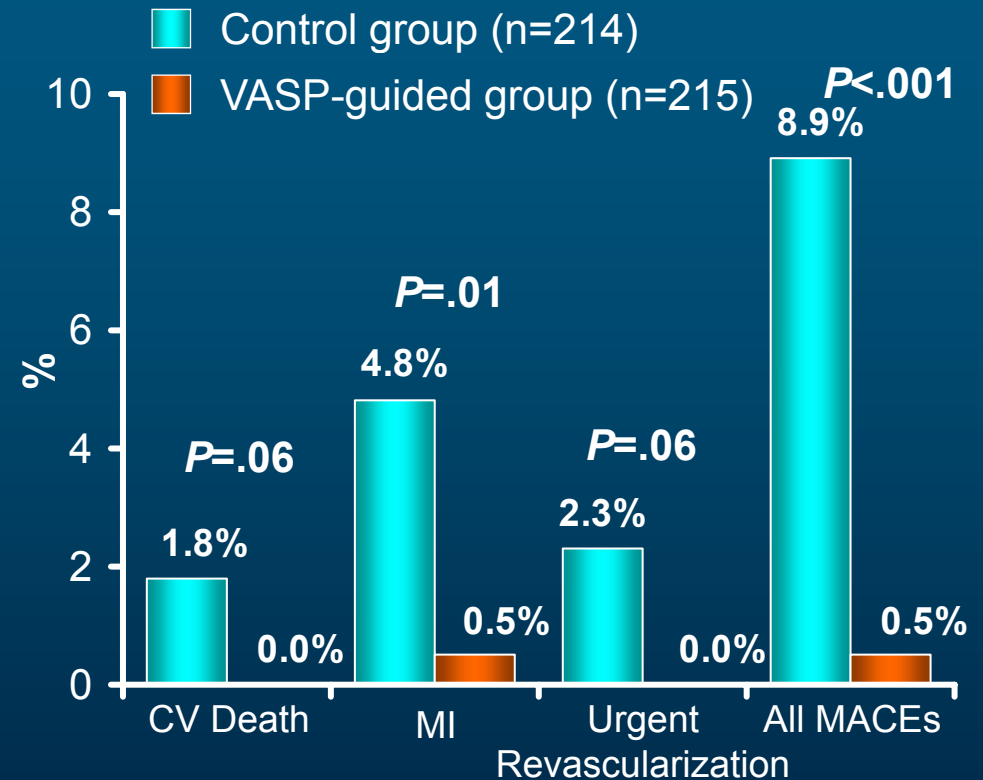
VASP 1 to 4=VASP index after the initial to fourth LD. Bonello et al. *Am J Cardiology*. 2009;103:5-10.

VASP-Guided PCI

Kaplan-Meier Curve of Freedom of Definite Stent Thrombosis Survival According to Groups



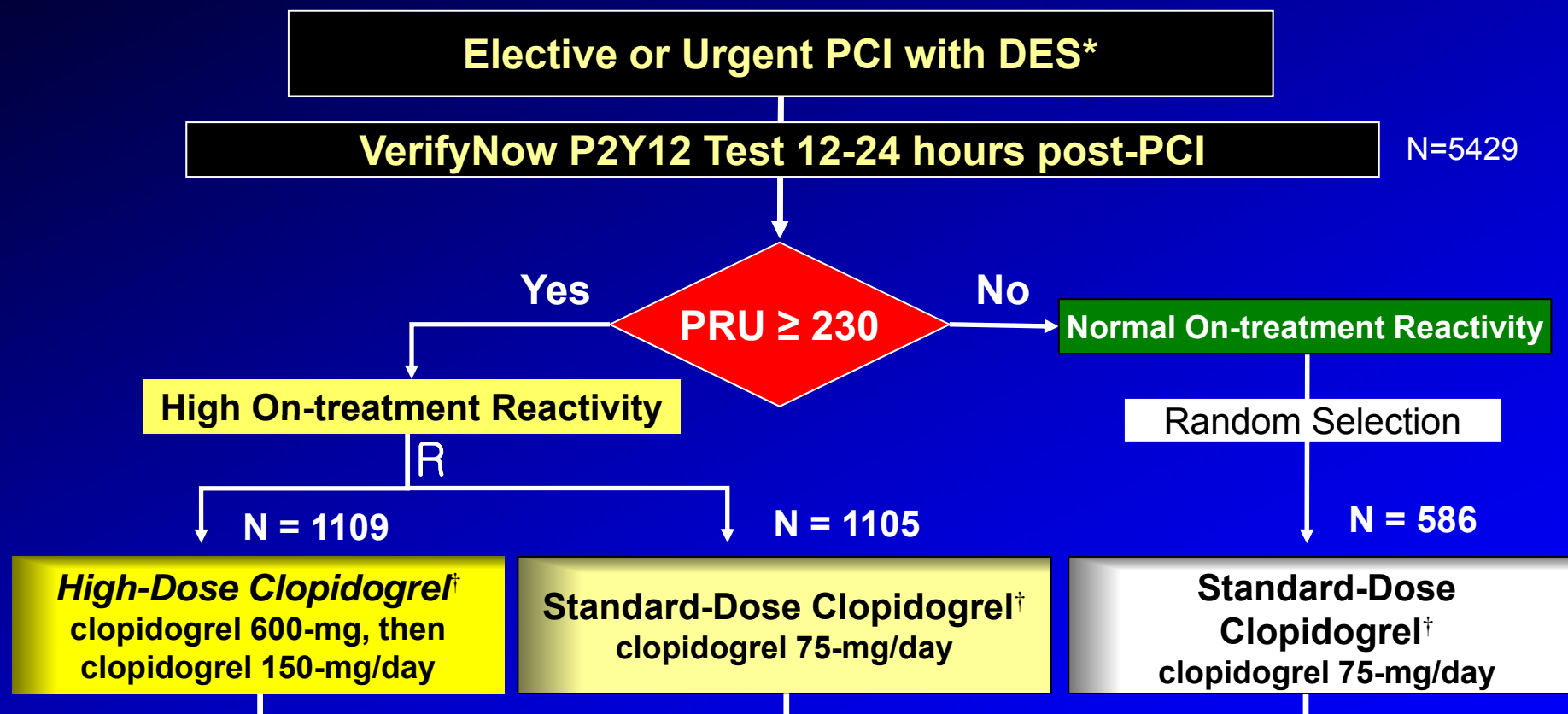
MACEs During 1-Month Follow-up



Loading dose of 600 mg clopidogrel given. Up to 3 additional doses of 600 mg clopidogrel given in VASP-guided group

MACEs=major adverse cardiovascular events.
Bonello et al. *Am J Cardiology*. 2009;103:5-10.

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

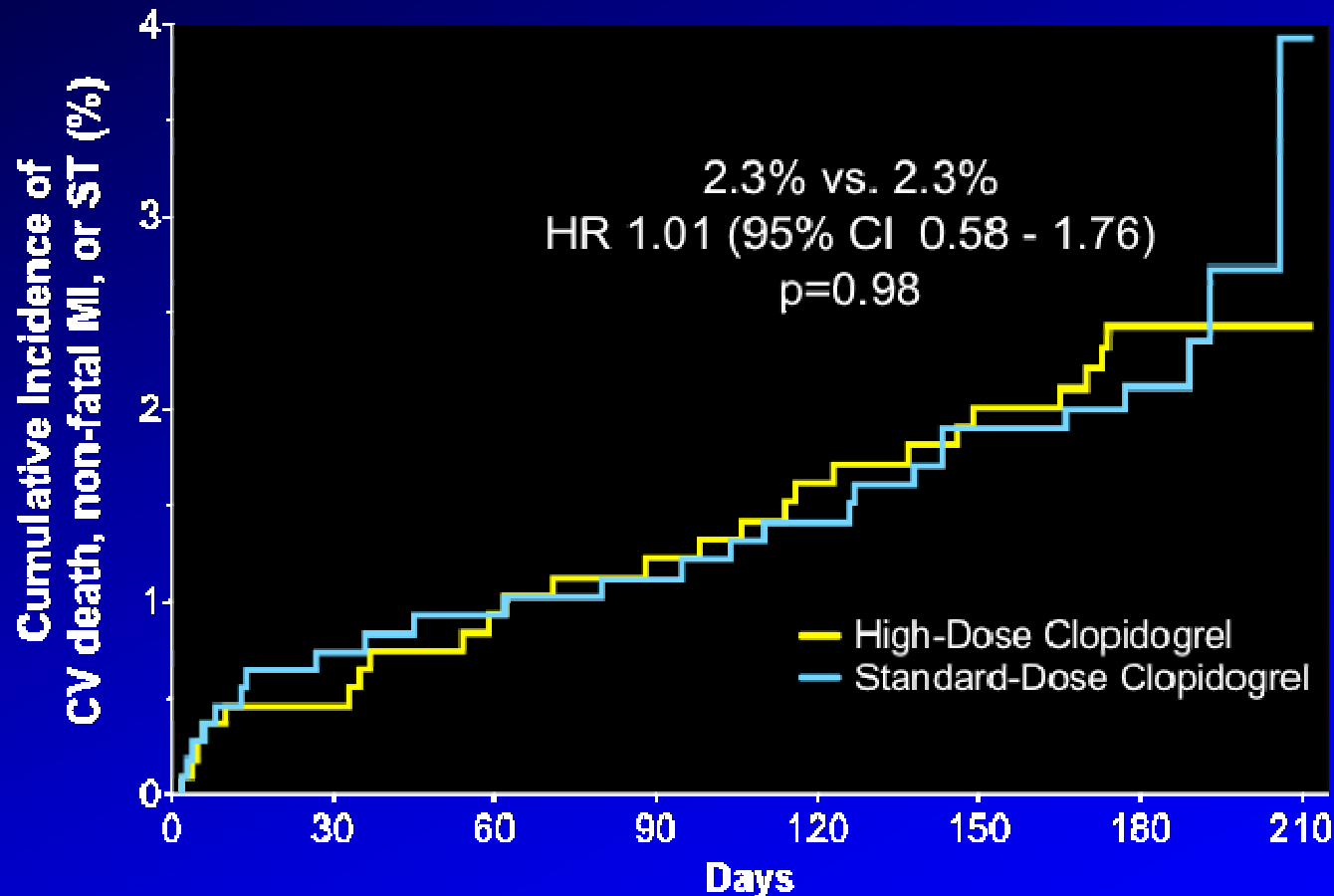
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled

All patients received aspirin (81-162mg daily)

Primary Endpoint: CV Death, MI, Stent Thrombosis



No. at Risk

	0	30	60	90	120	150	180	210
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

GRAVITAS

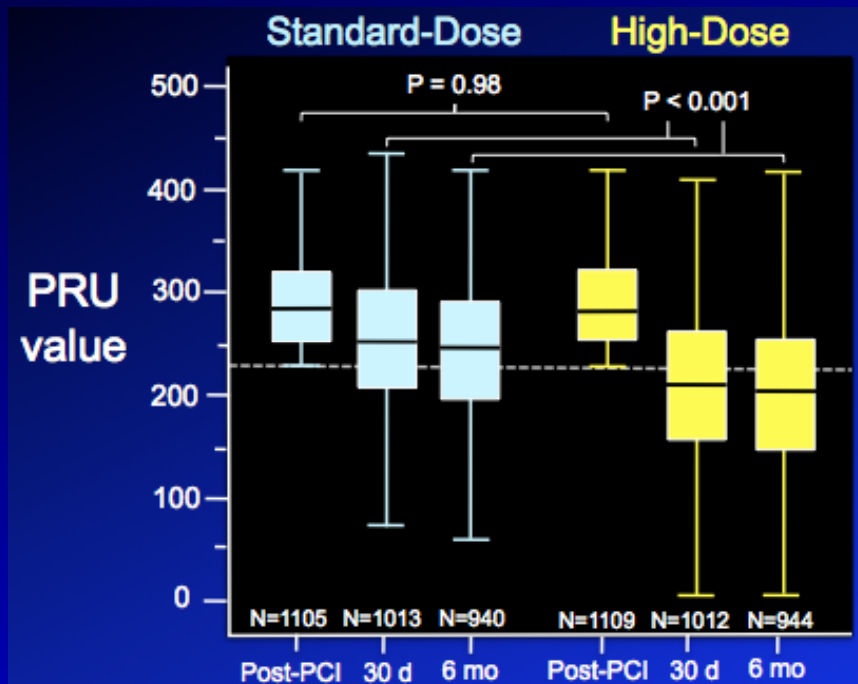
GRAVITAS: Statistical Reasons for a Neutral Result

Trial	Treatments	N	Events	RRR
TRITON-TIMI 38	Prasugrel vs Clopidogrel	13,608	1424	19%
PLATO	Ticagrelor vs Clopidogrel	18,624	1878	16%
CURRENT (PCI)	Clopi 600/150 vs 300/75* for 7 days	25,086 (17,263)	1079 (722)	6% (14%)
GRAVITAS	Clopi 600/150 vs 75 in patients with HRPR (41%)	2214	Targeted 68	Targeted 50%

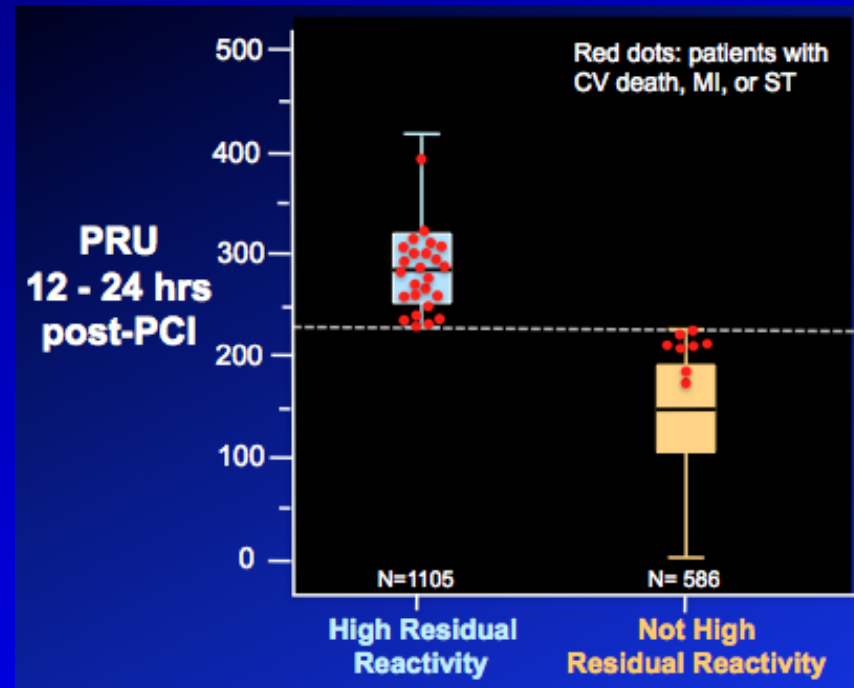
GRAVITAS	Event Rate	RRR	Power
As Designed	5.0%	50%	82%
Achieved Rate	2.3%	50%	~50%
Achieved Rate & ↓ RRR	2.3%	25%	~12%

GRAVITAS: Pharmacodynamic Outcomes

Effect of study drug in patients with high OTR



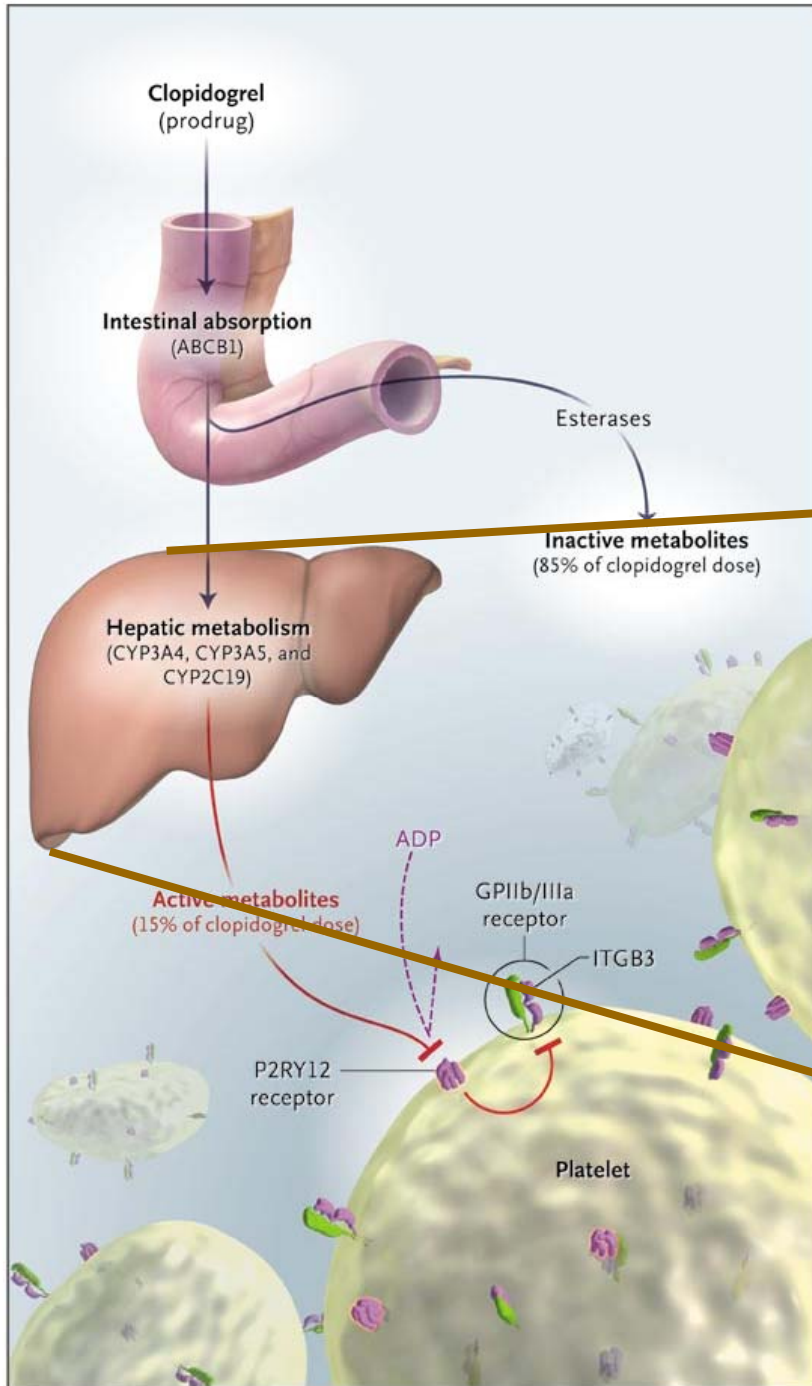
Events in Patients Treated with 75 mg



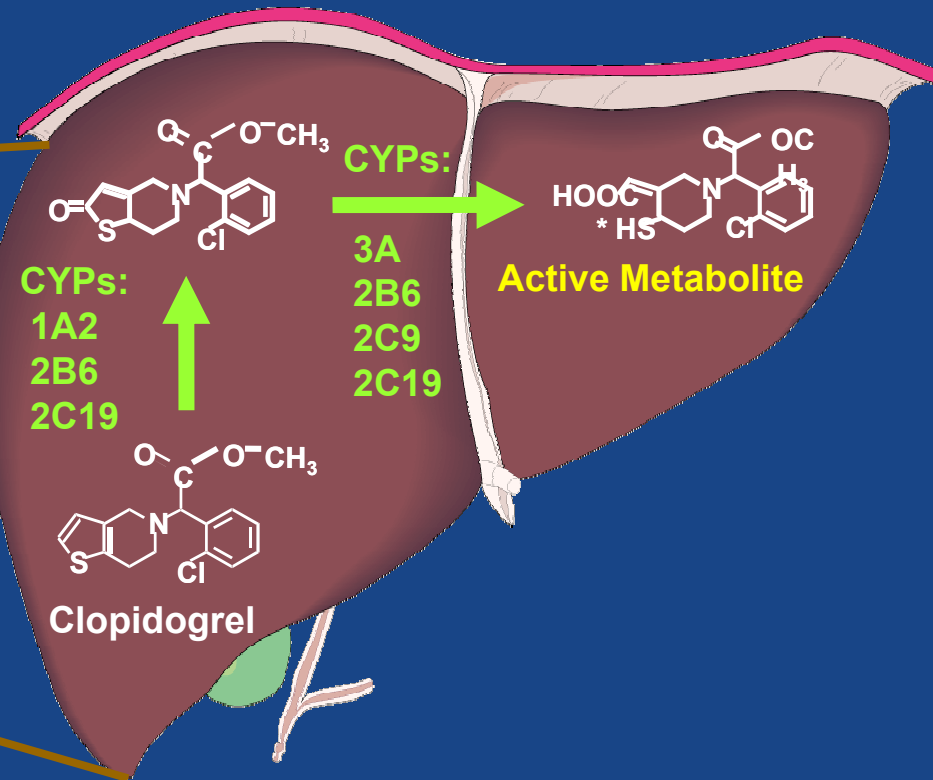
- High-dose provided variable and modest reduction in on-treatment reactivity (OTR)
- Post-hoc: “responders” with events had OTR clustered just below 230 PRU

GRAVITAS: Conclusions

- Underpowered to detect a realistic treatment effect
- Serial platelet function testing may be needed to better discriminate responders & non-responders
- More potent antiplatelet therapy may be needed to differentiate from standard of care
- Other major trials to address value of platelet function testing to tailor antiplatelet therapy:
 - TRIGGER-PCI: clopidogrel vs prasugrel → **TERMINATED**
 - ARCTIC: stnd vs tailored clopidogrel; n=2500; **ONGOING**
 - TARGET-PCI: clopi vs prasugrel; n=1500; **ONGOING**

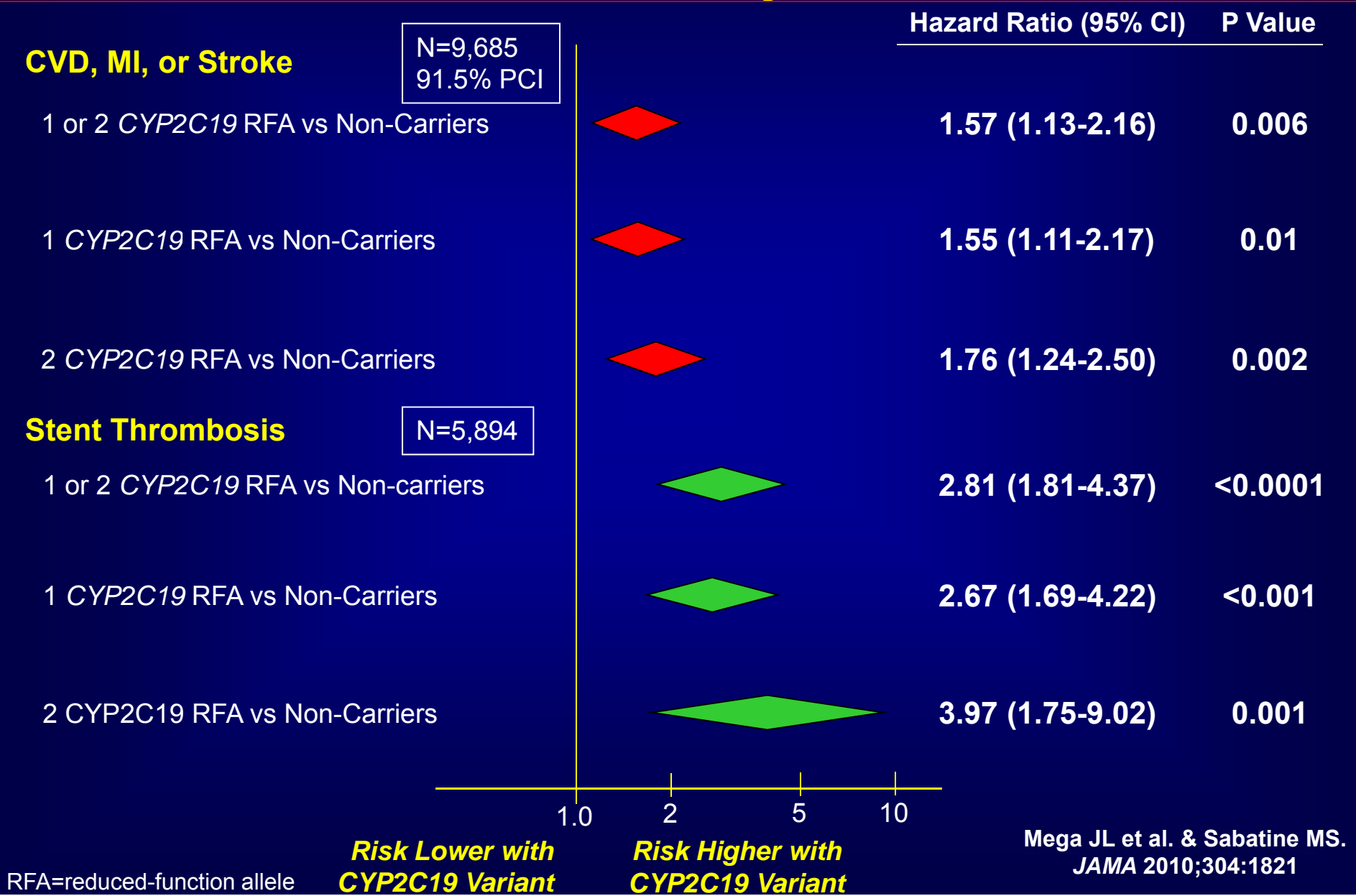


Clopidogrel Metabolism



New Engl J Med 2009;360:363-75.

CYP2C19 and Treatment with Clopidogrel Predominantly for PCI



Clopidogrel Boxed Warning

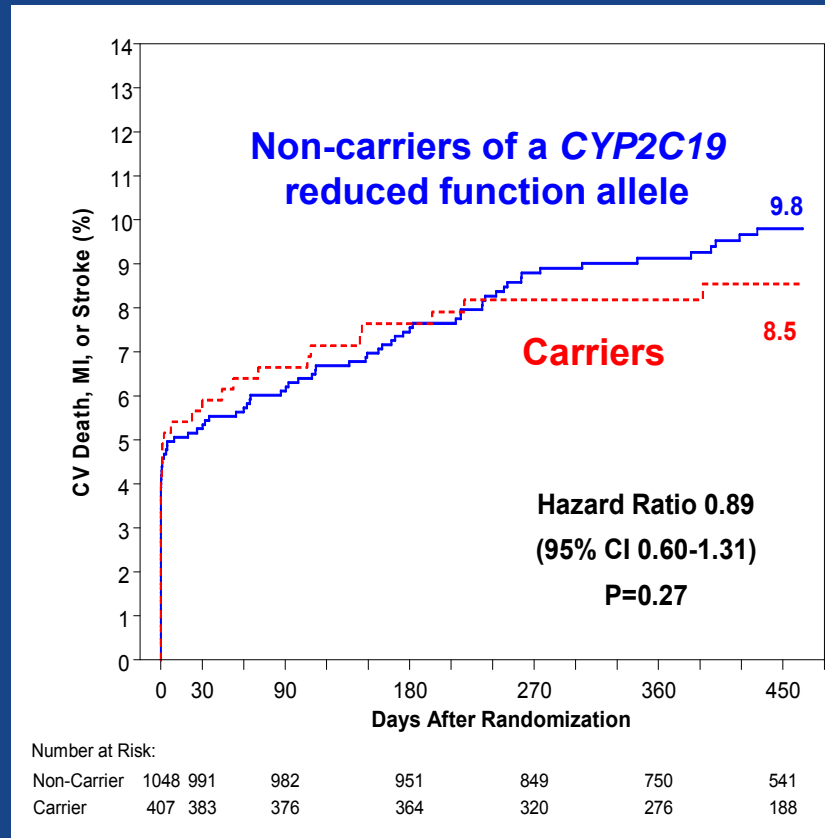
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

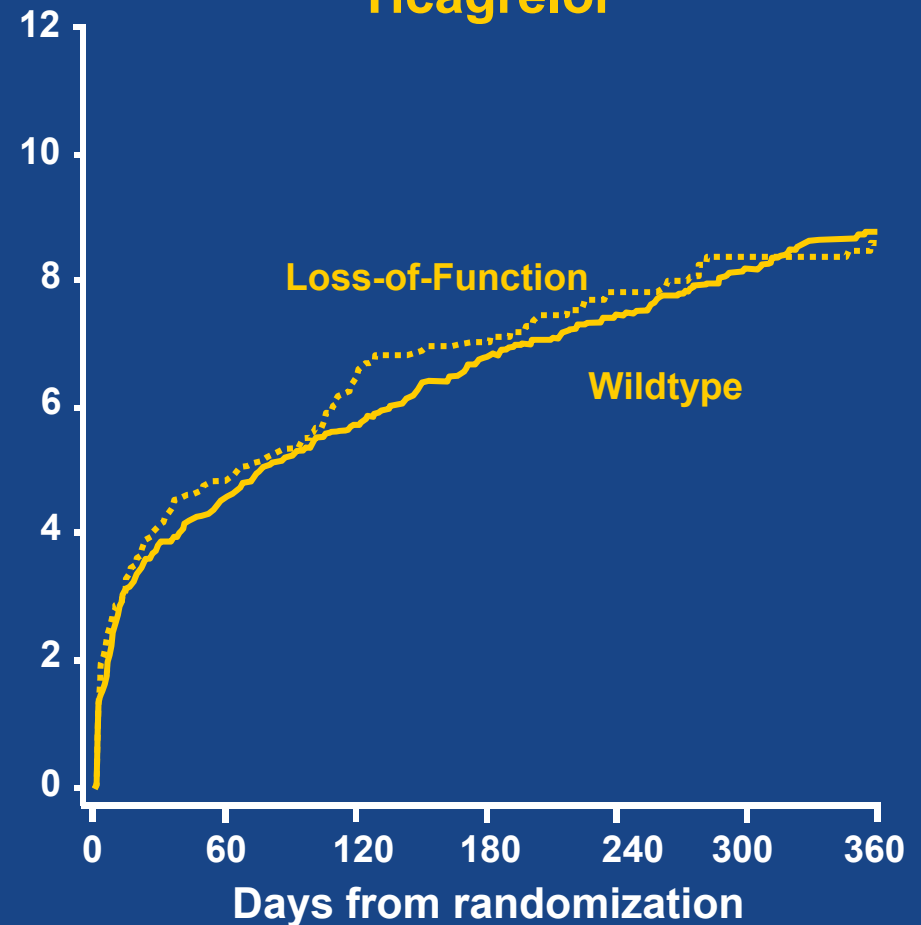
CYP2C19 Genotype Does Not Affect Prasugrel or Ticagrelor

Prasugrel



Mega JL et al. & Sabatine MS.
Circulation 2009;119:2553-60.

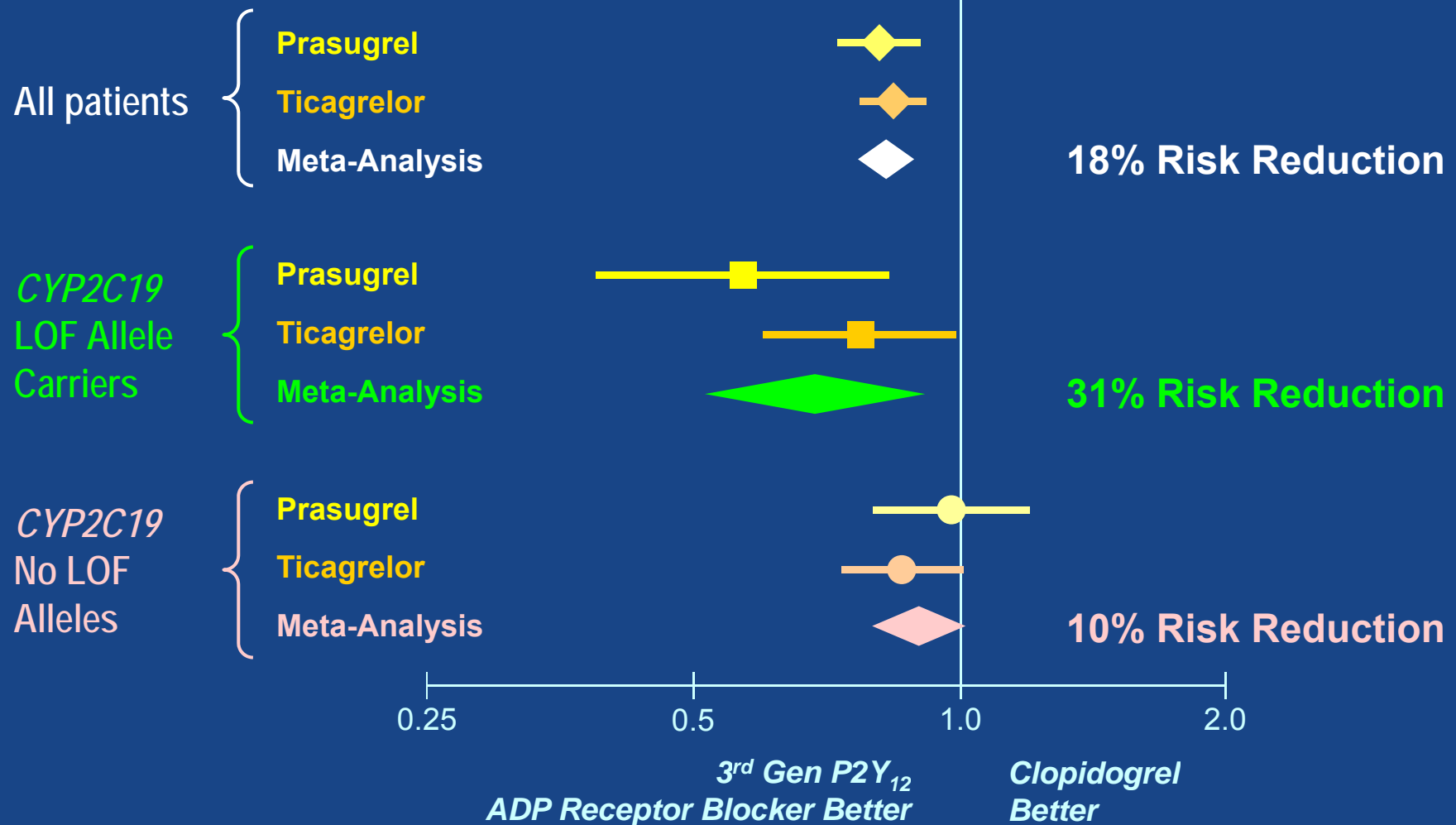
Ticagrelor



Wallentin L et al
Lancet 2010;376:1320

Benefit of 3rd Gen P2Y₁₂ ADP Receptor Blockers vs. Clopidogrel Based on CYP2C19 Genotype

HR for CV Death, MI, or Stroke



NEJM 2007;357:2001; NEJM 2009;360:354; Circulation 2009;119:2553; NEJM 2009;361:1045; J Thromb Haemost 2010;8:1678; Lancet 2010;376:1320; Lancet 2011;377:637

Verigene[®] System - CYP2C19 Testing

A **rapid** and **simple** development will enable testing in any hospital catheterization lab.

- Simple, whole blood processing in 3-4 hours
- Multiplexed assay for multiple CYP2C19 genotypes on a single device

Nanosphere

Detail Report

11-20-09 08:01 p.m.

Operator ID: administrator

S/N: 08092057

Session ID: CBS-TP-1786-1.0_112009

See application's package insert for details regarding results.

Sample	Is5-111809-33	Processing completed	11-20-09, 07:55 p.m.
Test	CBS	Analysis completed	11-20-09, 08:01 p.m.
Cartridge	01503991		

Summary

*1	Mut Detected	*2 ¹	-0.01 Heterozygous
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Detail

*1	Mut Detected	*2 ¹	-0.01 Heterozygous
*3 ²	1.00 Wild Type	*4 ²	1.00 Wild Type
*5 ³	1.00 Wild Type	*6 ⁴	1.00 Wild Type
*7 ⁴	1.00 Wild Type	*8 ²	1.00 Wild Type
*9 ²	1.00 Wild Type	*10 ²	1.00 Wild Type
*13 ⁵	1.00 Wild Type	*17 ²	0.93 Wild Type

Genotype Score Ranges

- ¹ - Heterozygous (-0.25 to 0.54)
- ² - Wild Type (0.60 to 1.00)
- ³ - Wild Type (0.69 to 1.00)
- ⁴ - Wild Type (0.55 to 1.00)
- ⁵ - Wild Type (0.70 to 1.00)

Processor Quality Control Status

Processor Module	D:1
Processing Time	189 minutes
Occlusions Corrected	0
Seal Pressure	0.766 psi
Seal Pressure Decay	0.000 psi
Processing Temperature	39.9 C
Failure Status	no failure

Investigational device:
Limited by Federal law to
investigational use - pending FDA clearance

CYP2C19, Plt Agg, & Stent Thrombosis

772 patients undergoing PCI and treated with clopidogrel

	Univariate		Multivariable*	
	OR (95% CI)	P value	OR (95% CI)	P value
CYP2C19 *2 carrier	2.59 (1.15-5.88)	0.02	3.43 (1.01-12.78)	0.047
Residual plt aggregation $\geq 70\%$	3.17 (1.32-7.59)	0.01	3.08 (1.23-7.72)	0.016

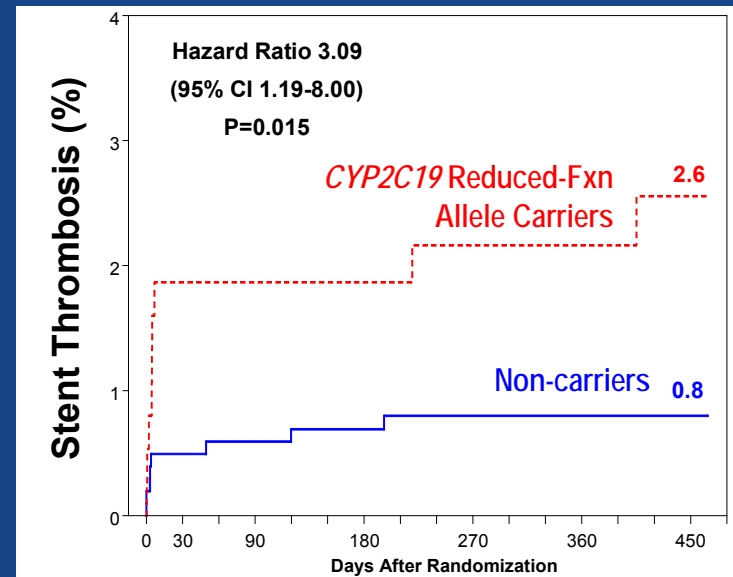
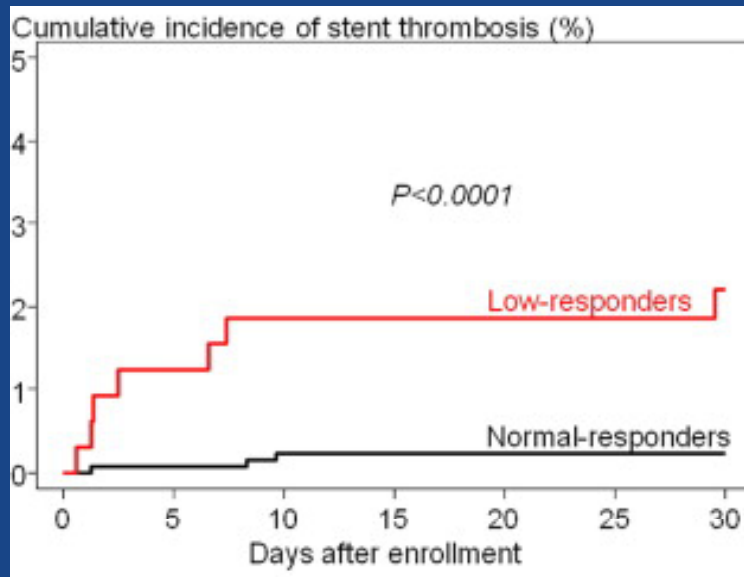
* Model contained CYP2C19, platelet resistance, and clinical factors

Summary

- Platelet function testing & *CYP2C19* genotype predict clinical outcomes in patients treated with clopidogrel
- If one opts to treat all patients with a 3rd generation ADP receptor blocker (prasugrel or ticagrelor), then testing is irrelevant
- But if one wants to use (or, with it going generic this year, is *forced to use*) clopidogrel in some Pts, then tailoring therapy is logical
- We already use clinical factors to identify subsets of patients in whom more potent antiplatelet therapy is particularly efficacious (eg, STEMI, diabetics) or harmful (eg, prior stroke, elderly)
- Tailoring to plt fxn data pre-PCI ↓ stent thrombosis & MACE
- The benefit of tailoring to plt fxn data post-PCI remains unproven
- The benefit of prasugrel & ticagrelor relative to clopidogrel tends to be greater in *CYP2C19* reduced-function variant carriers

Conclusion

Among high-risk patients undergoing stenting, it is reasonable to consider using clinical factors, platelet function testing, and genotyping to guide decision-making with regard to antiplatelet therapy.



If you were a poor responder or a *CYP2C19**2 carrier and had a coronary stent implanted, would you want to go home on clopidogrel 75 mg?