SOCIEDAD PARAGUAYA DE CARDIOLOGIA

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XIV Jornadas SOLACI
5º Región Cono Sur
12 / 13 de Mayo 2011

DES y resistencia plaquetaria: implicancia clínica

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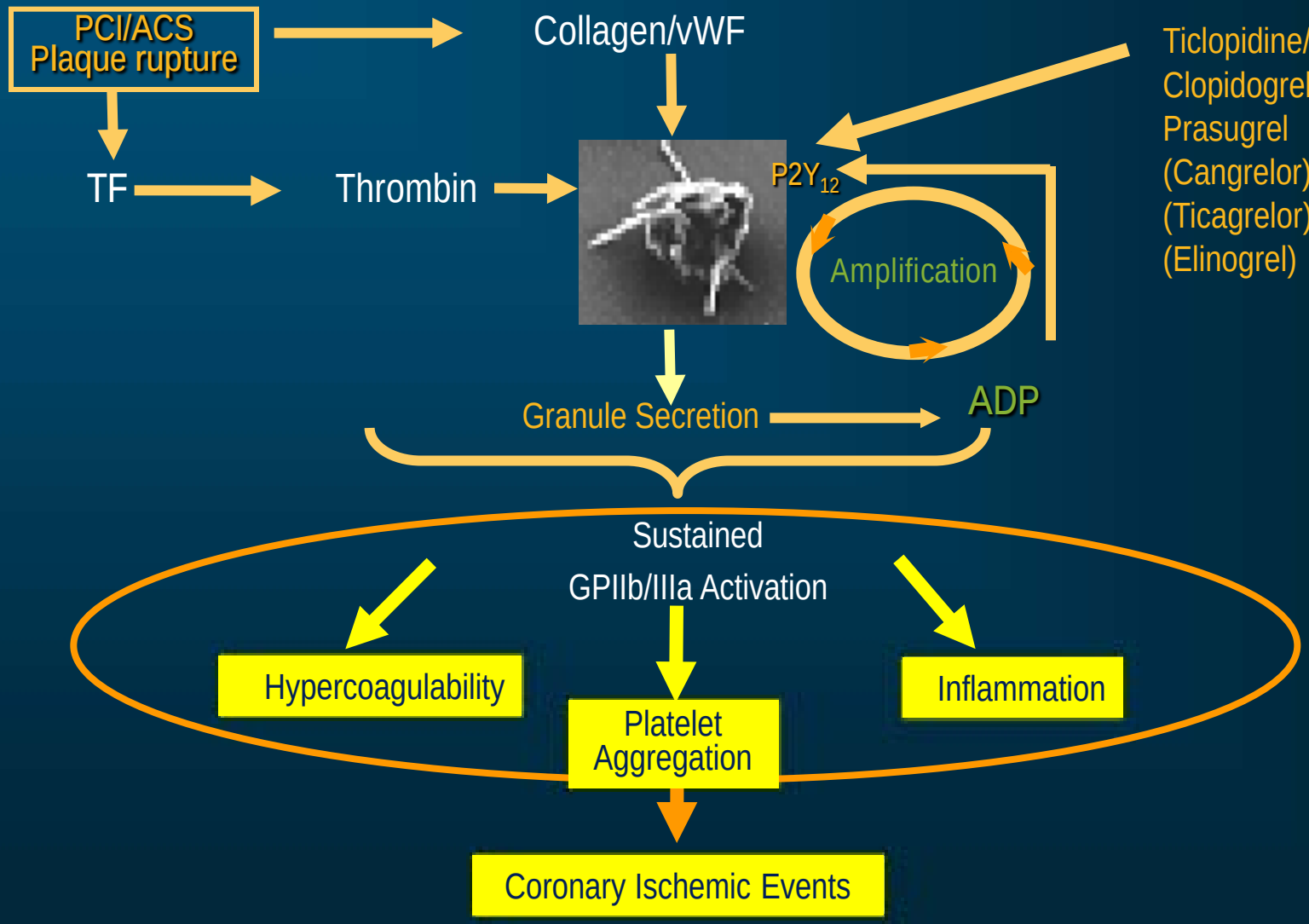
Cardiólogo Intervencionista
Santa Cruz - Bolivia

- Fisiopatología SCA - Plaquetas
- Farmacología de los antiplaquetarios

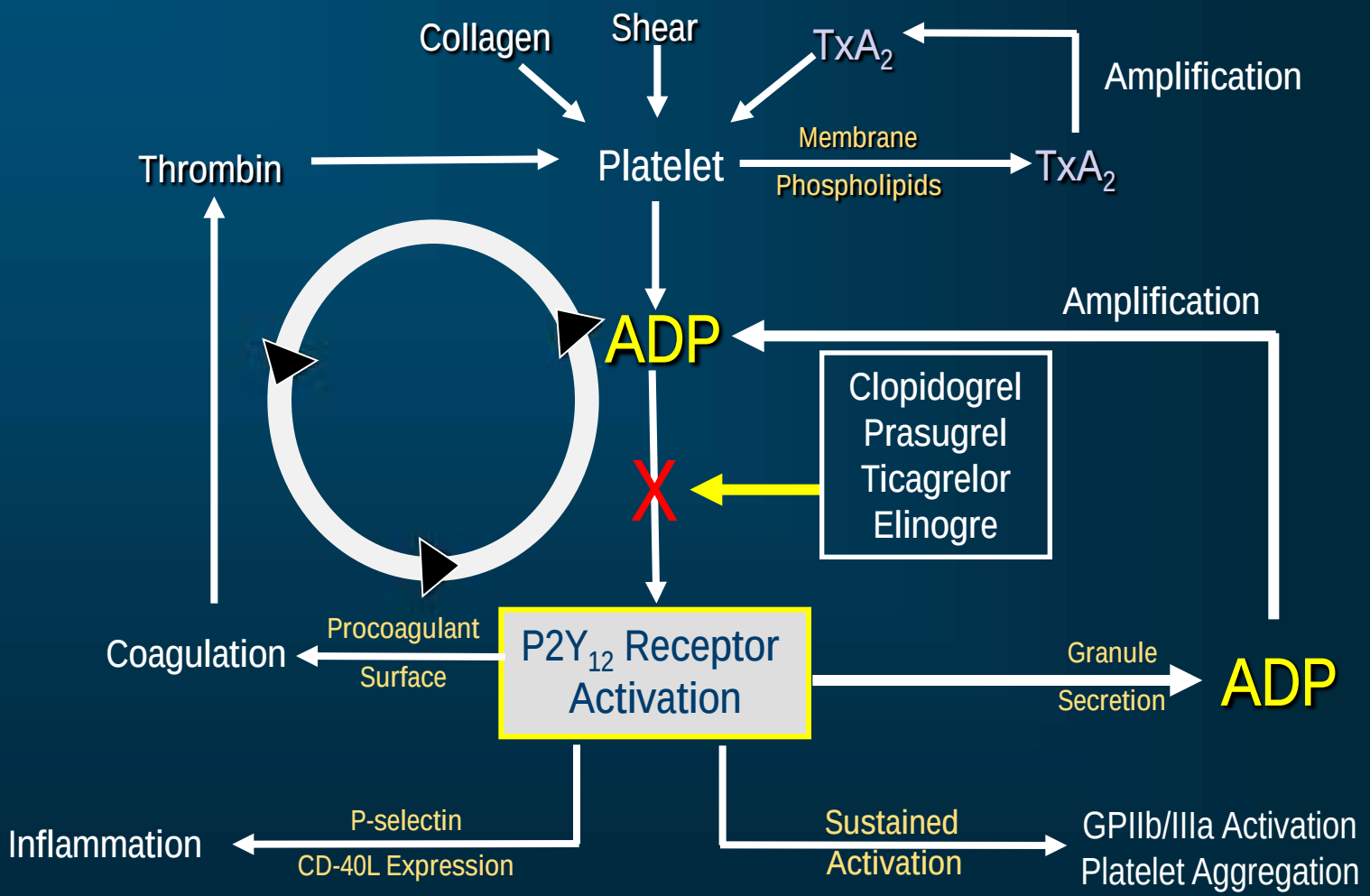
Coronary Ischemic/Thrombotic Events-

A "Platelet-centric" Problem!!!!



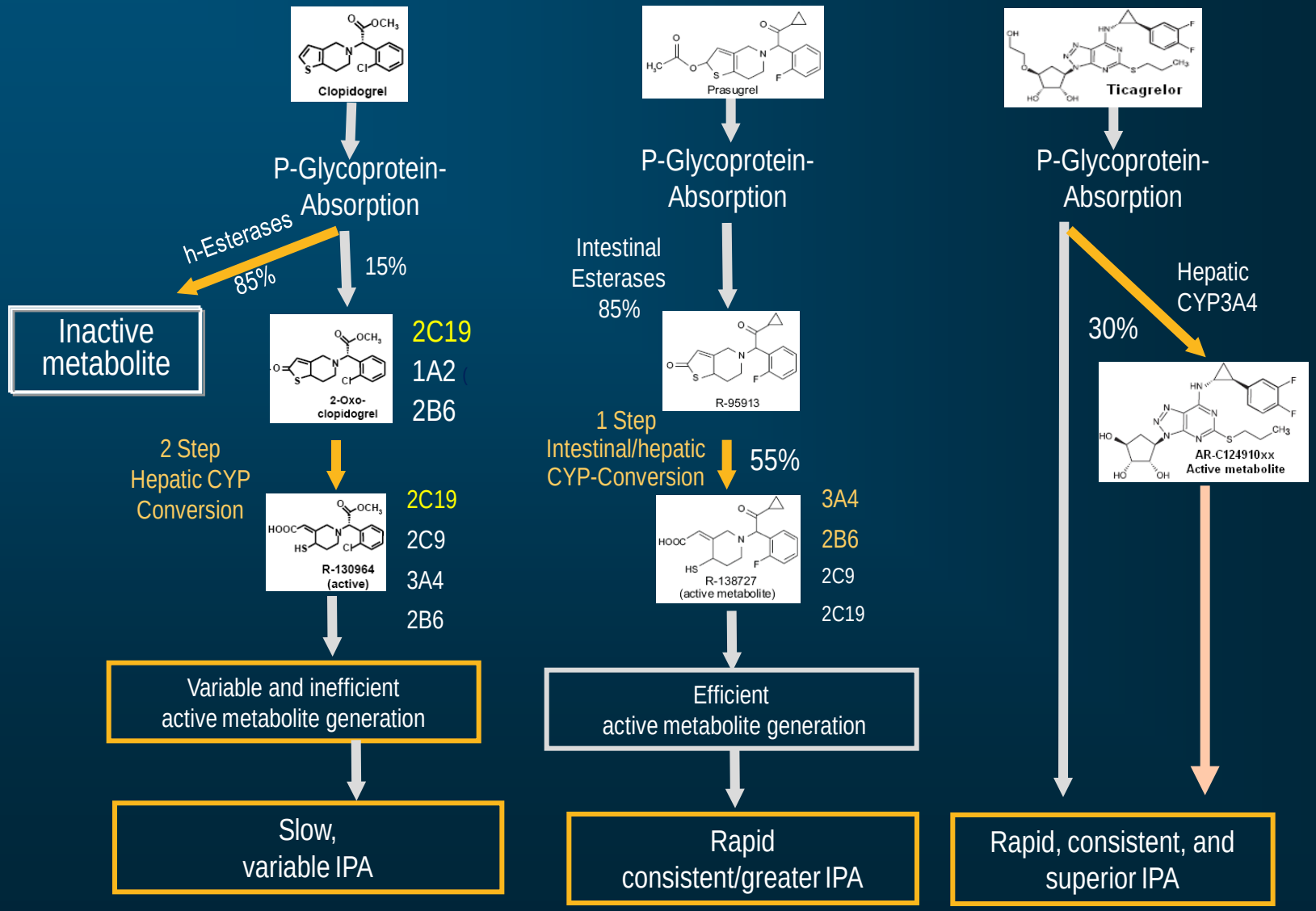
Gurbel PA et al. *Rev Cardiovasc Med*. 2006;7:S20-S28.

$P2Y_{12}$ – A Pivotal Platelet Receptor

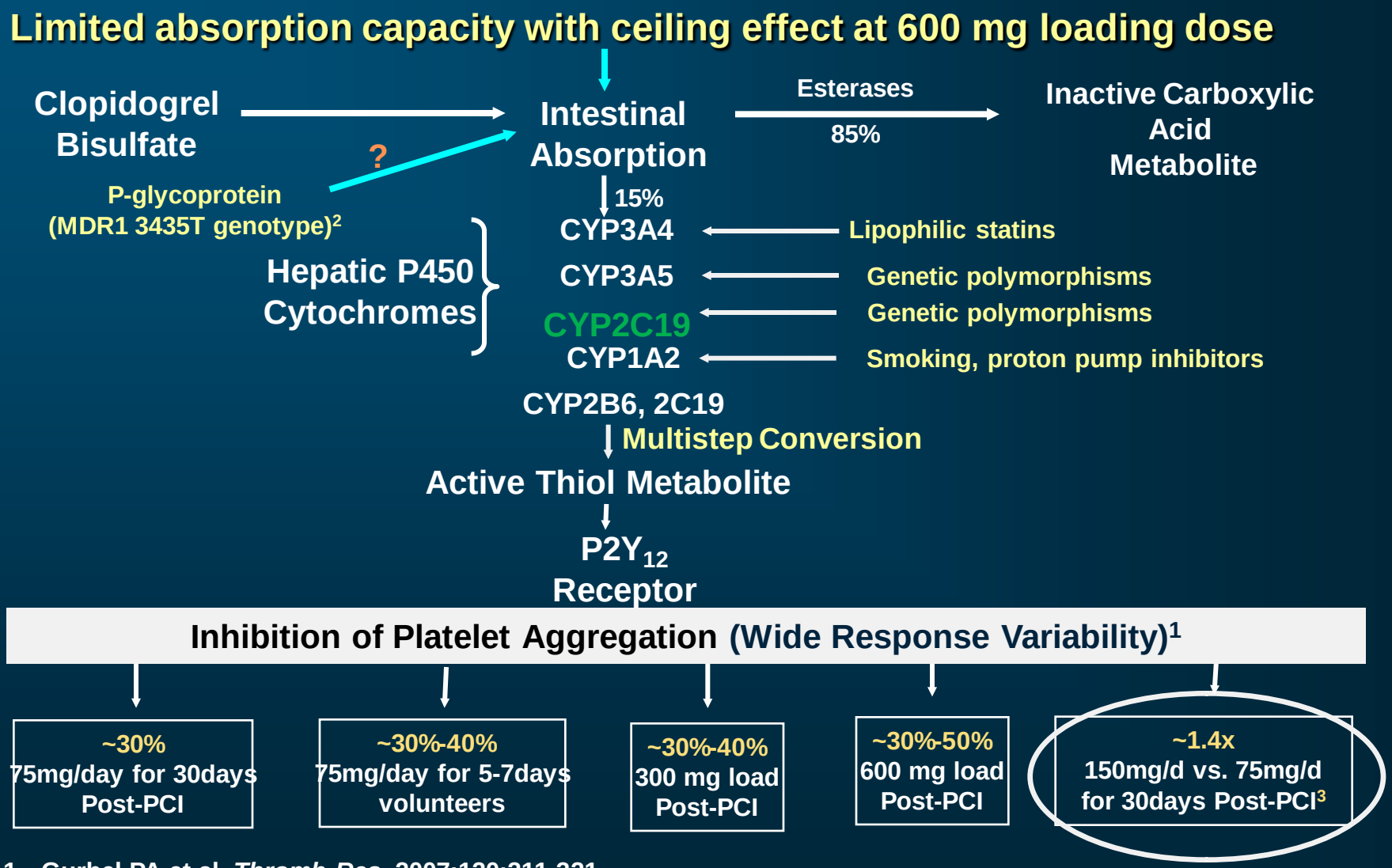


Adapted from:
Gurbel PA et al. *Rev Cardiovasc Med*. 2006;7:S20-S28.

Metabolism of $P2Y_{12}$ Receptor Blockers



Mechanism of Clopidogrel Response Variability



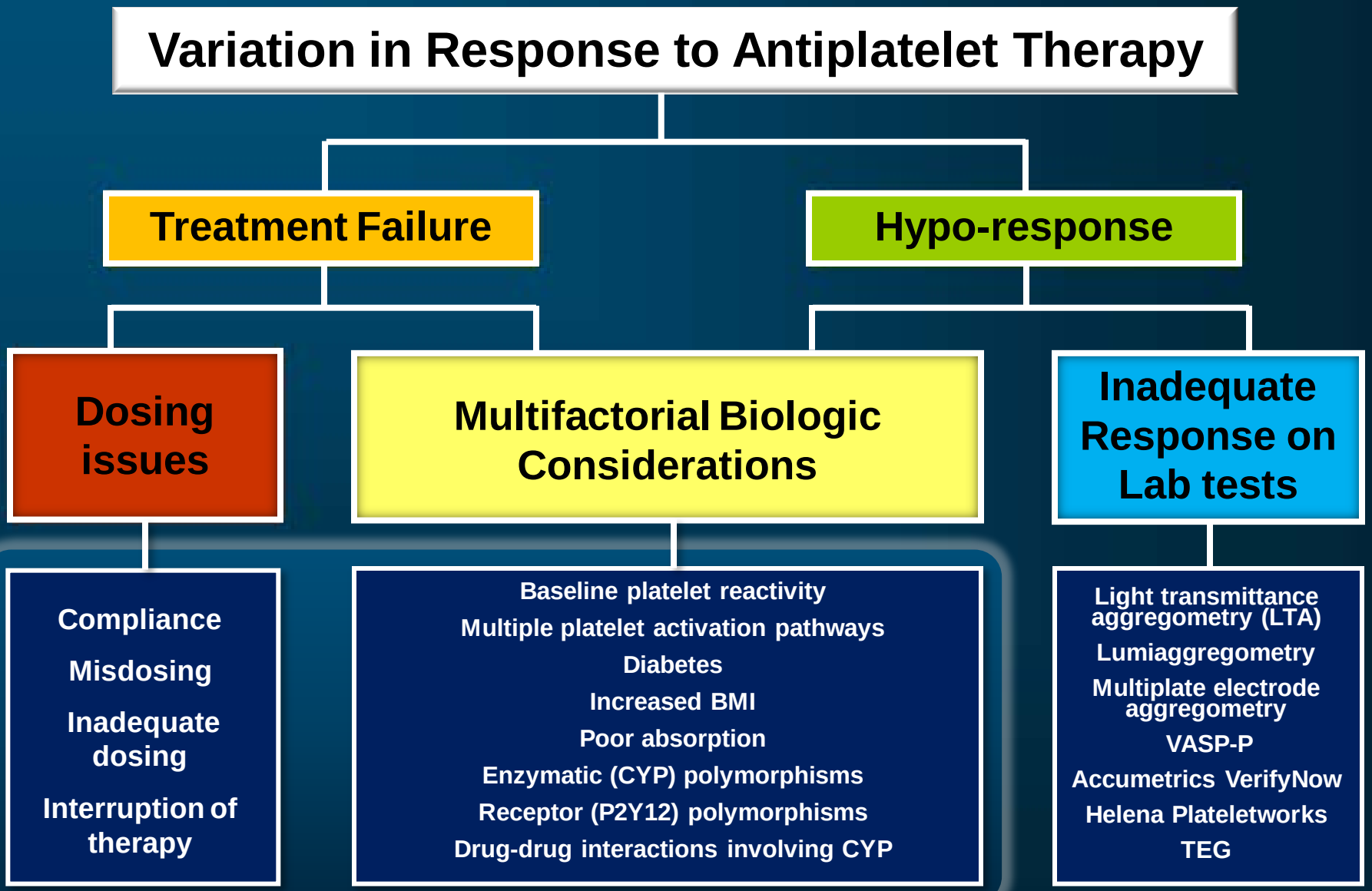
1. Gurbel PA et al. *Thromb Res*. 2007;120:311-321.
2. Taubert et al. *Clin Pharmacol*. 2006;80:486-501.
3. von Beckerth et al. *Eur Heart J*.2007;28:1814-1819.

Resistencia ?
Variabilidad de respuesta

Como podemos medir ?

- Pruebas genéticas
- Pruebas de laboratorio
- Incapacidad para prevenir eventos trombóticos (IMPLICANCIA CLINICA)

Thienopyridine response variability



Resistencia ?
Variabilidad de respuesta

Como podemos medir ?

- Pruebas genéticas
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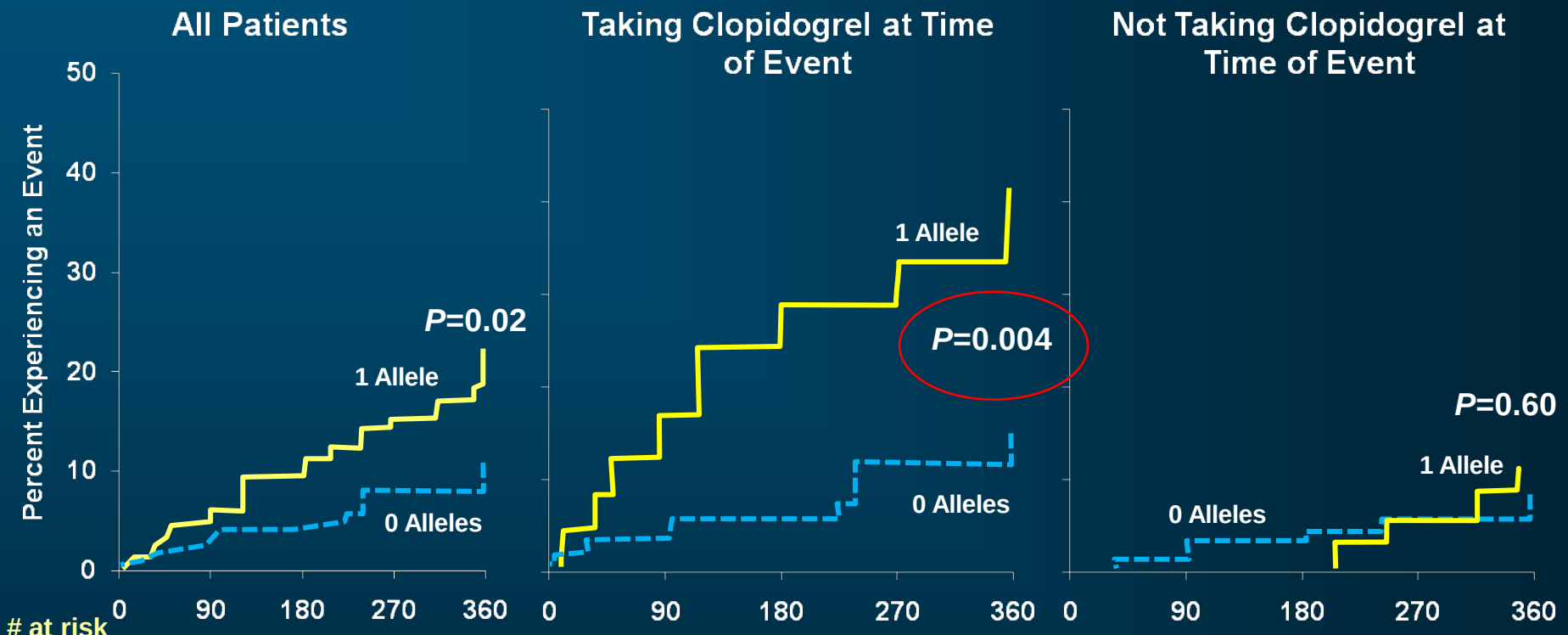
- Incapacidad para prevenir eventos trombóticos (IMPLICANCIA CLINICA)

Association of CYP2C19*2 Alleles With Outcomes*

Sinai Hospital of Baltimore Study



# at risk									
# CYP2C19*2 Alleles									
0	158	154	150	143	66	64	92	90	88
	144	143		58	57		87	85	
1	67	61	55	27	23	18	40	38	38
	53	50		17	15		35	33	

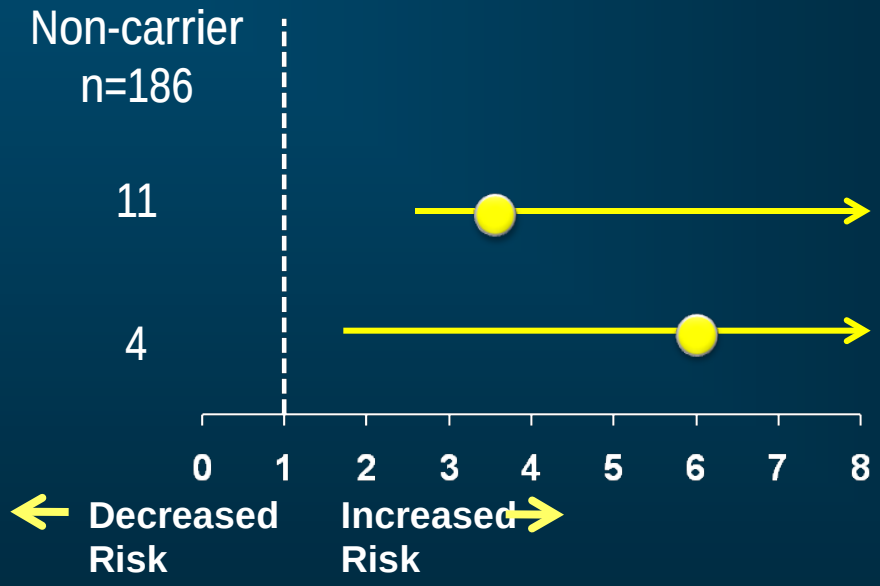
* Myocardial infarction (MI), ischemic stroke, definite stent thrombosis, unplanned target or non-target vessel revascularization, hospitalization for chest pain with evidence of ischemia on electrocardiogram and no evidence of MI as measured by troponin I value, and death secondary to any cardiovascular cause

Shuldiner AR et al. *JAMA*. 2009;302:849-857.

Allelic CYP2C19*2 Variant Associated With Increased MACE Post-MI

*Carriers of CYP2C19*2 vs Non-carriers*

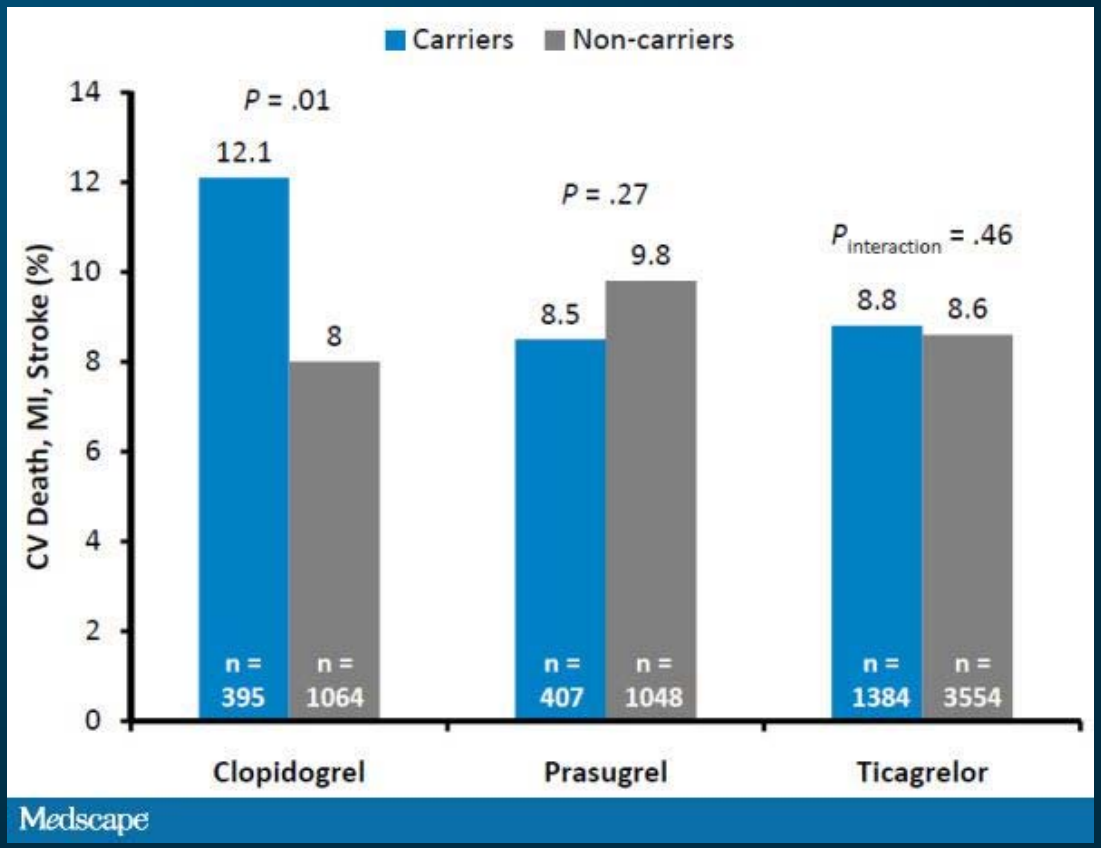
Outcome	Number of Events: Carrier n=73	Number of Events: Non-carrier n=186	HR (95% CI)	*P*-Value
Primary Endpoint†	15	11	5.38 (2.32-12.47)	<0.0001
Definite Stent Thrombosis	8	4	6.04 (1.75-20.80)	0.004



*2 = genetic functional variant 681 G>A
† Death, Myocardial infarction (MI), and urgent coronary revascularization
MI survivors aged < 45 years exposed to clopidogrel for > 1 month (median exposure 1.07 years)

Collet JP et al. *Lancet*. 2009;373:309-317.

Subestudio Genético de TRITON-TIMI 38 y PLATO



CV death, MI, stroke in CYP2C19*2 carriers and noncarriers treated with clopidogrel and prasugrel in TRITON-TIMI 38 and ticagrelor in PLATO

Resistencia ?
Variabilidad de respuesta

Como podemos medir ?

- Pruebas genéticas
- Pruebas de laboratorio
- Incapacidad para prevenir eventos trombóticos (IMPLICANCIA CLINICA)

Métodos para medir la actividad plaquetaria

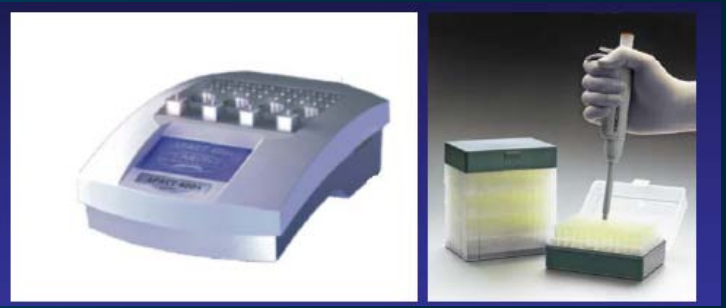
Method	Ease of Use	Normal Platelet Reactivity	High Platelet Reactivity
Light transmittance aggregometry (ADP as agonist)	Requires trained technicians, time and labor intensive	5 µmol/L ADP: **< 42.9%** aggregation 20 µmol/L ADP: **< 64.5%** aggregation	**≥ 42.9%** aggregation≥ **64.5%** aggregation
VerifyNow® $P2Y_{12}$ Assay	Point-of-care test, fully automated	**< 236 PRU**	**≥ 236 PRU**
Plateletworks® Assay (using ADP tubes)	Point-of-care test, semi-automatedHighly time dependent (≤ 10 min)	< 80.5% aggregation	≥ 80.5% aggregation
IMPACT-R™ Assay (with and without ADP prestimulation)	Extensive sample handling	Without ADP: < 8.4% surface coverageWith ADP: < 3.0% surface coverage	≥ 8.4% surface coverage ≥ 3.0% surface coverage
Dade® PFA* (with collagen/ADP cartridge)	Point-of-care test	<116 closure time (sec)	≤ 116 closure time (sec)
Innovance® PFA P2Y*	Point-of-care test	< 299 sec	≥ 299 sec
VASP-P	Requires dedicated lab	**≤ 50% PRI**	**>50% PRI**

ADP = adenosine diphosphate; PFA = platelet function analysis; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction unit; VASP-P = vasodilator-stimulated phosphoprotein phosphorylation

Platelet function testing: Common testing devices

Light transmittance aggregometry (LTA)

- Historical standard
- Aggregation based, platelet rich plasma (PRP)
- ADP peak platelet aggregation
- Central laboratory, trained technicians
- Time consuming



VerifyNow® P2Y12 assay

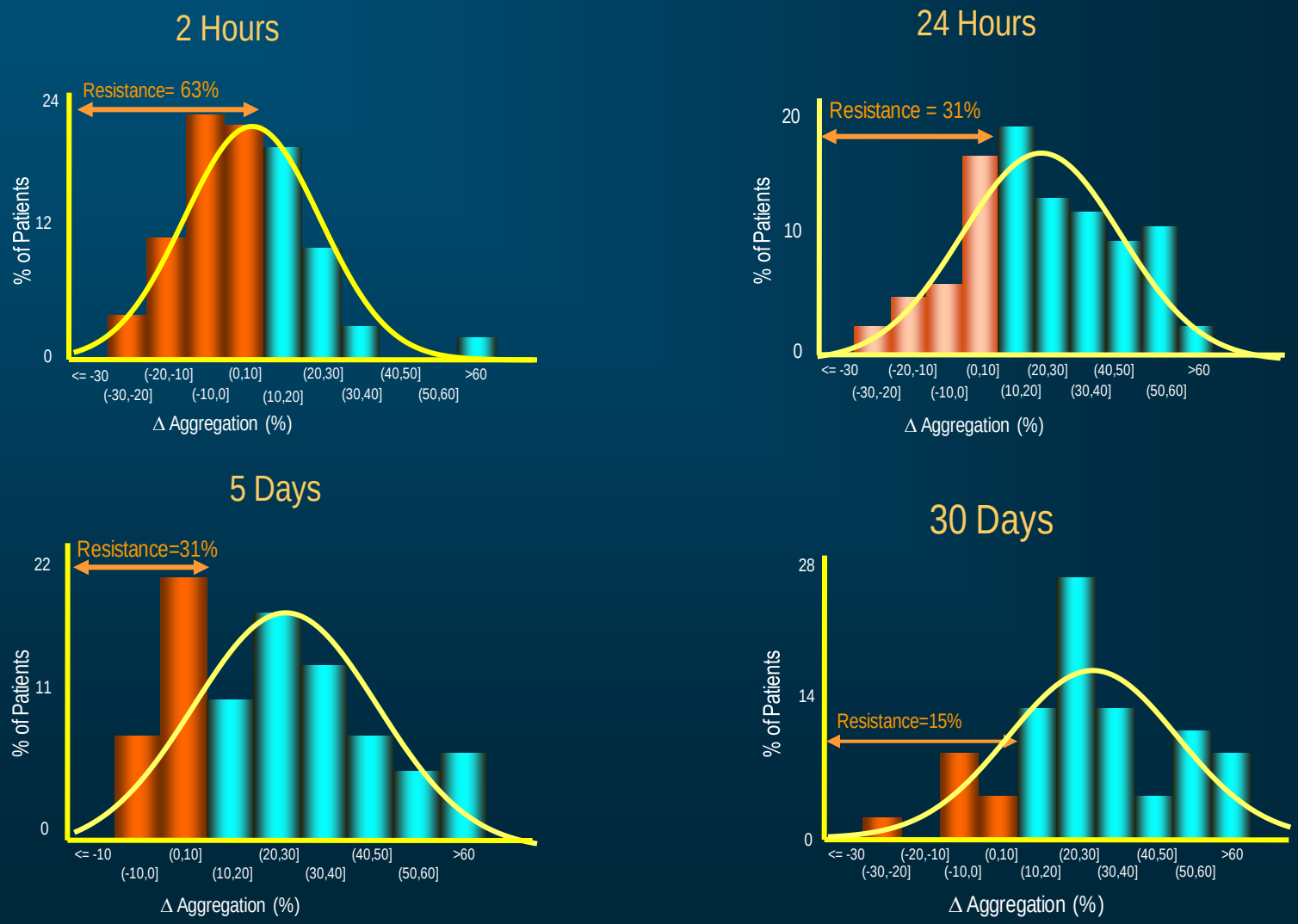
- Aggregation based, whole blood
- Bedside test. fully automated

Multiplate® (MULTIple PLATElet) function analyzer

- Aggregation based, whole blood
- Bedside test. fully automated
- Sensitive for aspirin, ADP receptor inhibitor, GP IIb/IIIa antagonists

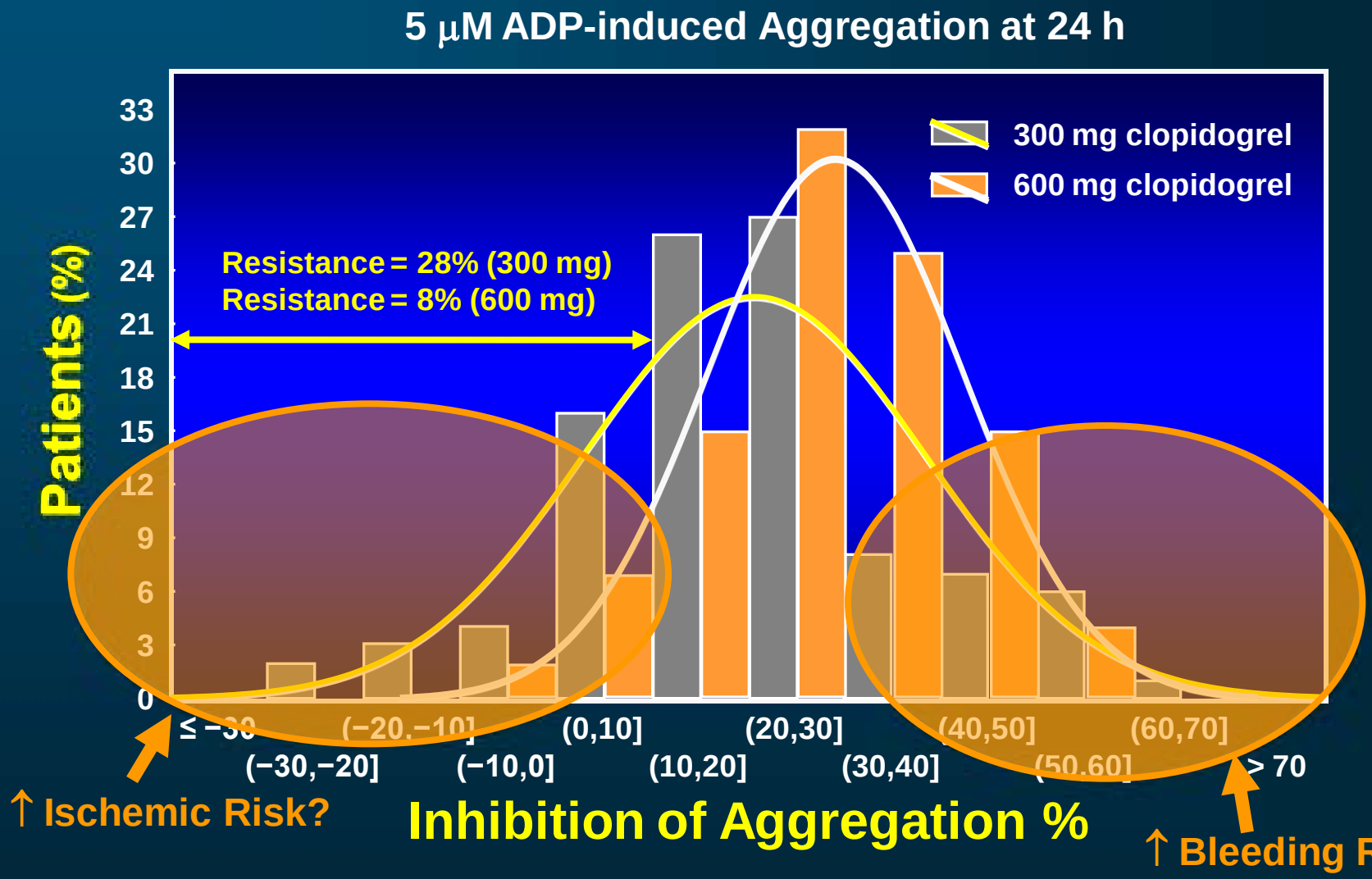
Variability in Inhibition:

The First Clopidogrel Resistance Study (300 mg)



Gurbel et al. *Circulation*. 2003;107:2908-2913.

Variability of Response to Clopidogrel



Gurbel et al. *Circulation.* 2003;107:2908-2913.
Gurbel et al. *J Am Coll Cardiol.* 2005;45:1392-1396.

Resistencia ?
Variabilidad de respuesta

Como podemos medir ?

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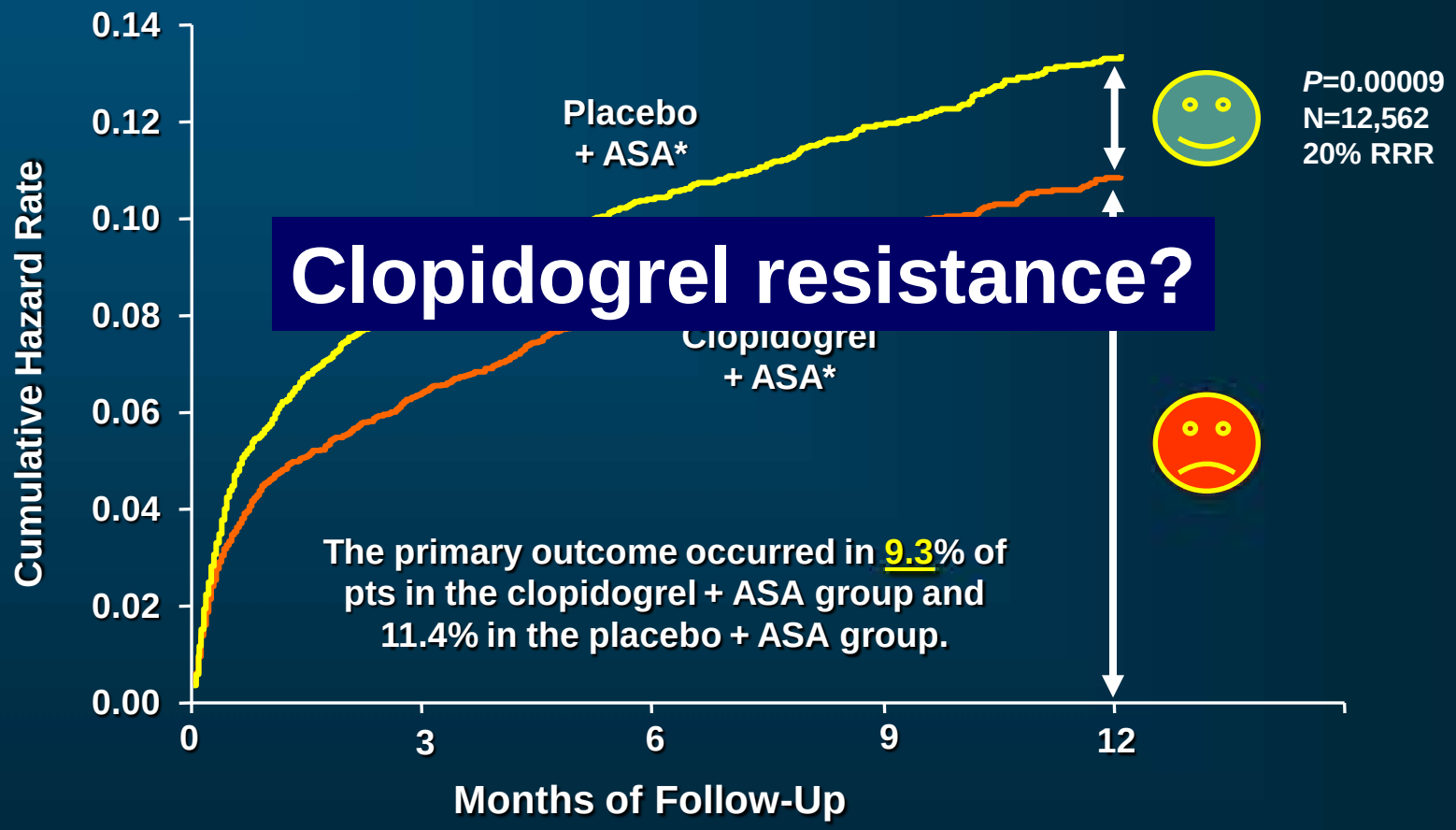
- Pruebas de laboratorio
- Incapacidad para prevenir eventos trombóticos (IMPLICANCIA CLINICA)

Primary Endpoint—MI/Stroke/CV Death



*Other standard therapies were used as appropriate.

Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

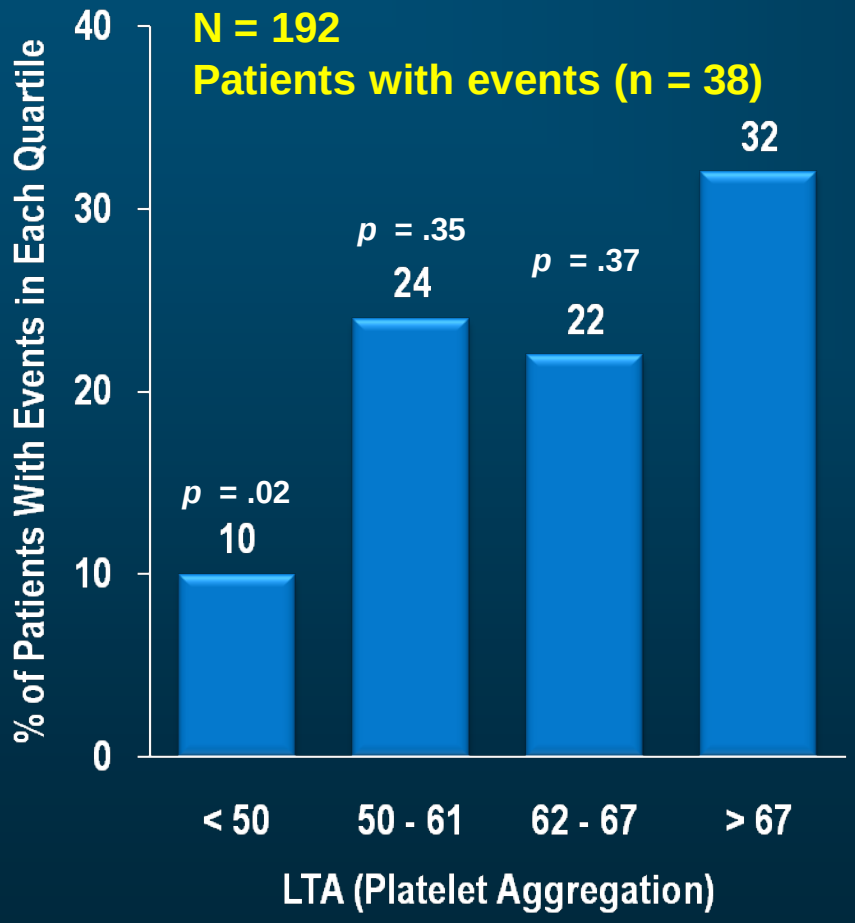
Post-Stent Ischemic Events and Periprocedural Infarction

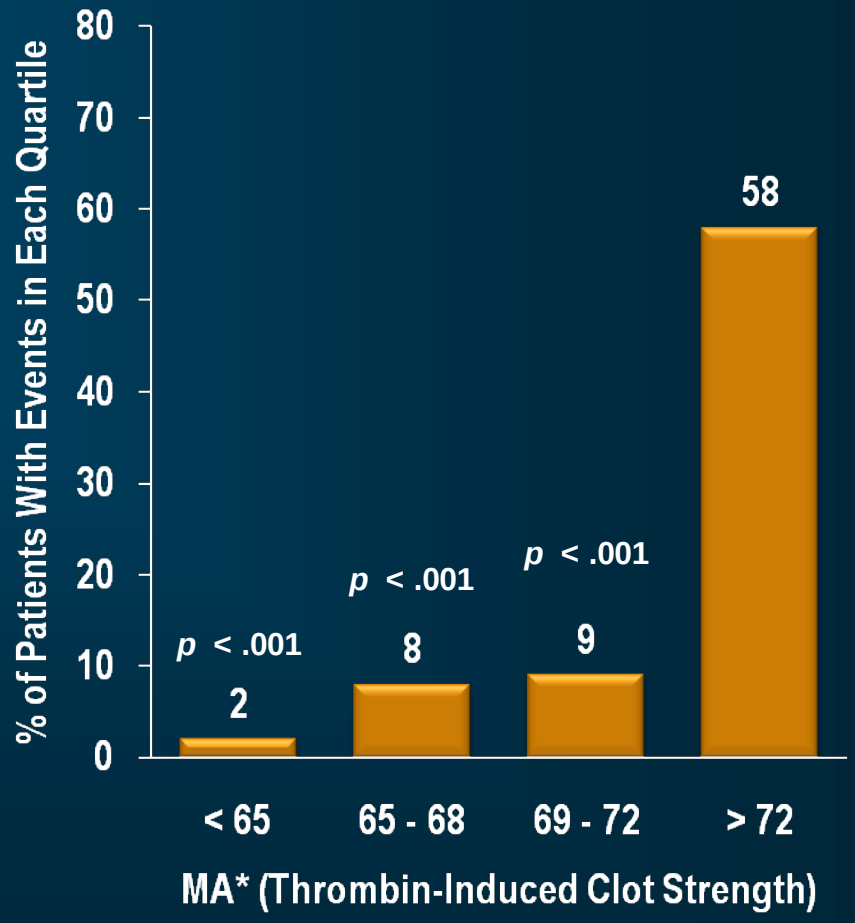
	N	Functional Parameter	Clinical Relevance
Matezky et al. Circulation 2004	60	↑ platelet aggregation (4th quartile)	Post-primary PCI ischemic events (6 months)
Gurbel et al. JACC 2005	192	↑ periprocedrual platelet aggregation	Post-PCI ischemic events (6 months)
Gurbel et al. Circulation 2005	120	↑ periprocedrual platelet aggregation	Myonecrosis and inflammation marker release
Cuisset et al. J Thromb Haemost 2006	106	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Lev et al. JACC 2006	120	↑ clopidogrel/aspirin-resistant patients	Post PCI-myonecrosis
Cuisset et al. JACC 2006	292	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Hocholzer et al. JACC 2006	802	↑ platelet aggregation (3rd & 4th quartiles)	Post-PCI ischemic events (30 days)
Geisler et al. Eur Heart J 2006	379	↓ platelet inhibition	Post-PCI ischemic events (3 months)
Bliden et al. JACC 2007	100	↑ platelet aggregation	Post-PCI ischemic events (12 months)
Angiolillo et al. JACC 2007	173	↑ platelet aggregation (4th quartile)	Ischemic events (24 months)

adapted from Angiolillo DJ et al. *Am J Cardiov Drugs.* 2007.

Target Goals of Platelet Reactivity and Clot Strength

PREPARE Post-Stenting Study

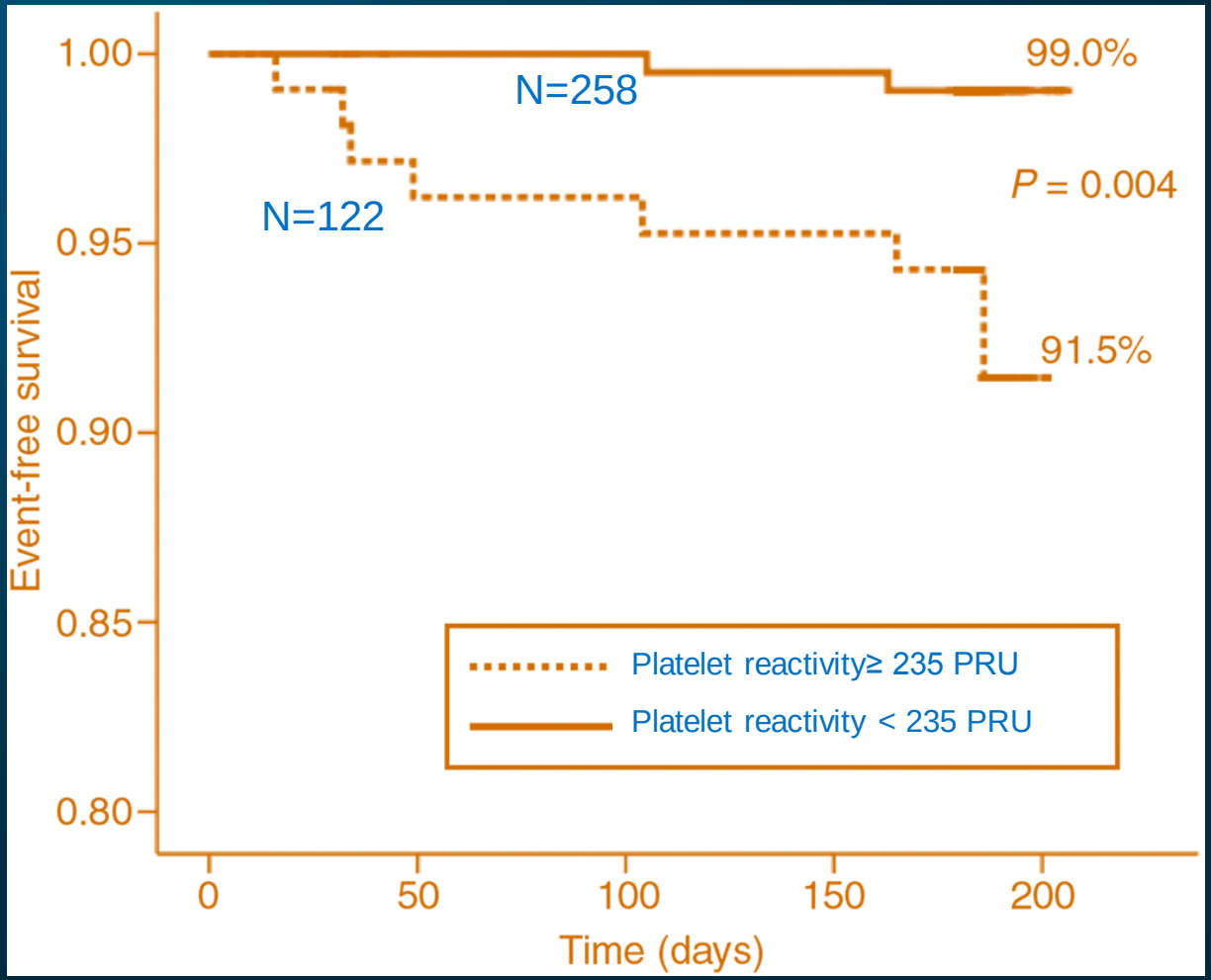




Gurbel PA, et al. *J Am Coll Cardiol*. 2005;46:1820-6.

LTA = Light Transmittance Aggregometry
* As measured by the Thrombelastograph (TEG) Hemostasis Analyzer

Scripps Clinic: Event Free survival in DES patients with and without high post-treatment reactivity (HPR)

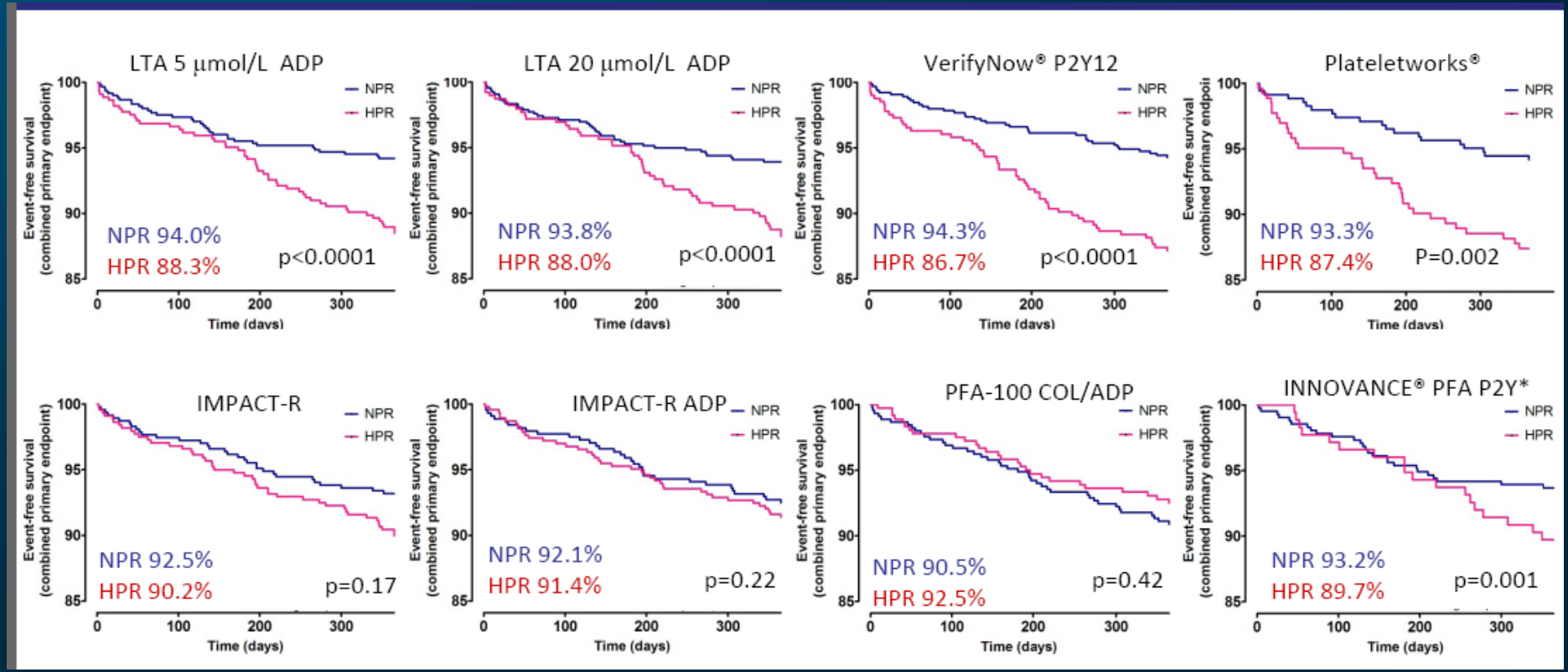


Event – Composite of CV death, MI, or stent thrombosis
HPR – PRU ≥ 235

Price MJ et al . EHJ. 2008; 29, 992–1000

POPULAR:
Survival free from primary endpoint

Primary Endpoint – Composite of death, MI, definite stent thrombosis, or stroke



Breet N et al . JAMA. 2010; 303: 754-762

TRITON TIMI·38
STENT ANALYSIS

Prasugrel Compared to Clopidogrel in Patients with Acute Coronary Syndromes Undergoing PCI with Stenting: the TRITON - TIMI 38 Stent Analysis

Stephen D. Wiviott, Elliott M. Antman, Ivan Horvath, Matyas Keltai, Jean-Paul R. Herrman, Frans van de Werf, William Downey, Benjamin M. Scirica, Sabina A. Murphy, Carolyn H. McCabe, Eugene Braunwald

SCAI – ACCi2 2008
Chicago, Illinois

TRITON TIMI-38
STENT ANALYSIS

Main Trial Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ **N= 13,608**

Double-blind

CLOPIDOGREL 300 mg LD/ 75 mg MD	**PRASUGREL** 60 mg LD/ 10 mg MD

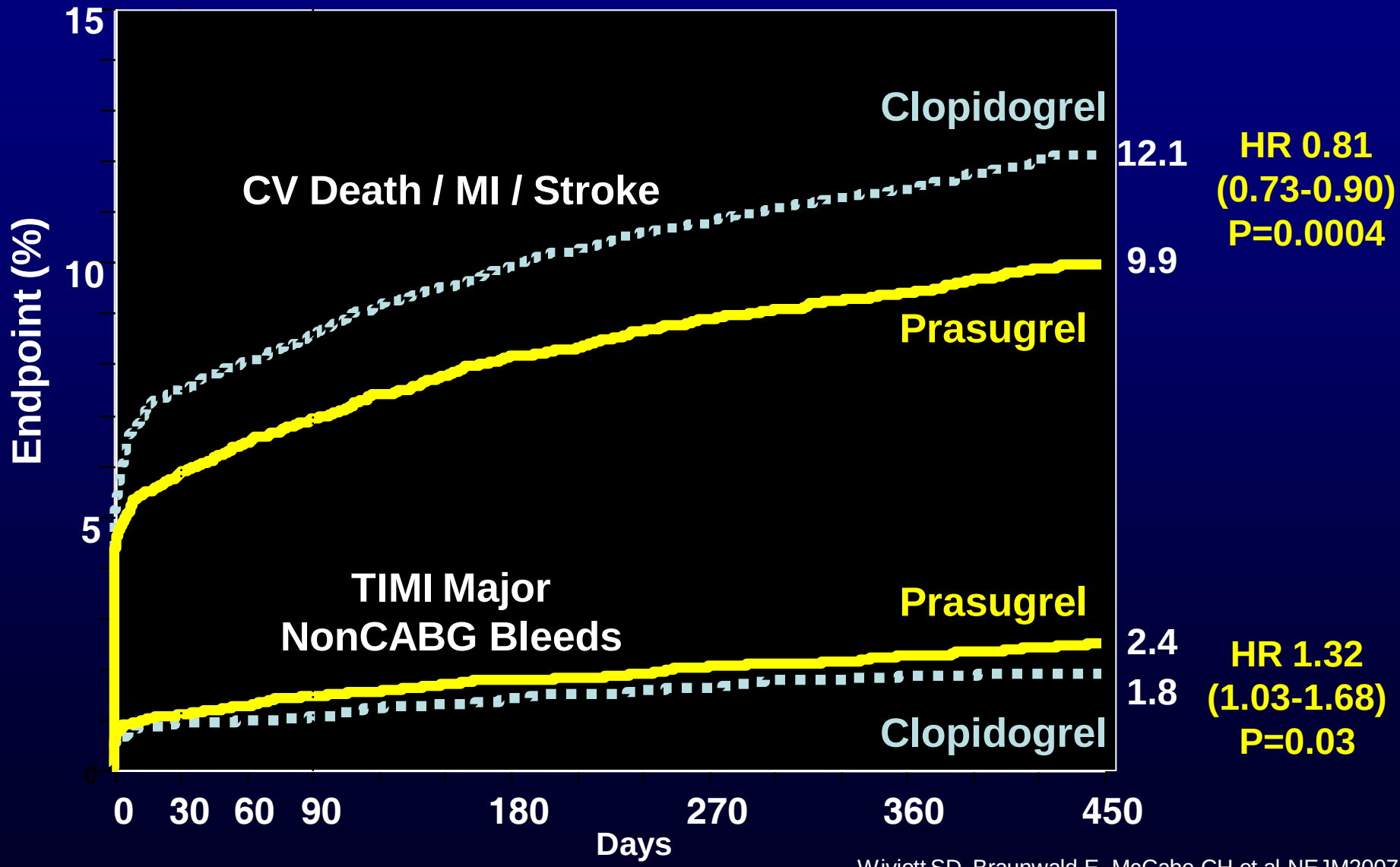
Duration of therapy: 6-15 months

1º endpoint:	CV death, MI, Stroke
2º endpoint:	Stent Thrombosis
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds

Wiviott SD, Antman EM et al AHJ 2006

TRITON TIMI-38

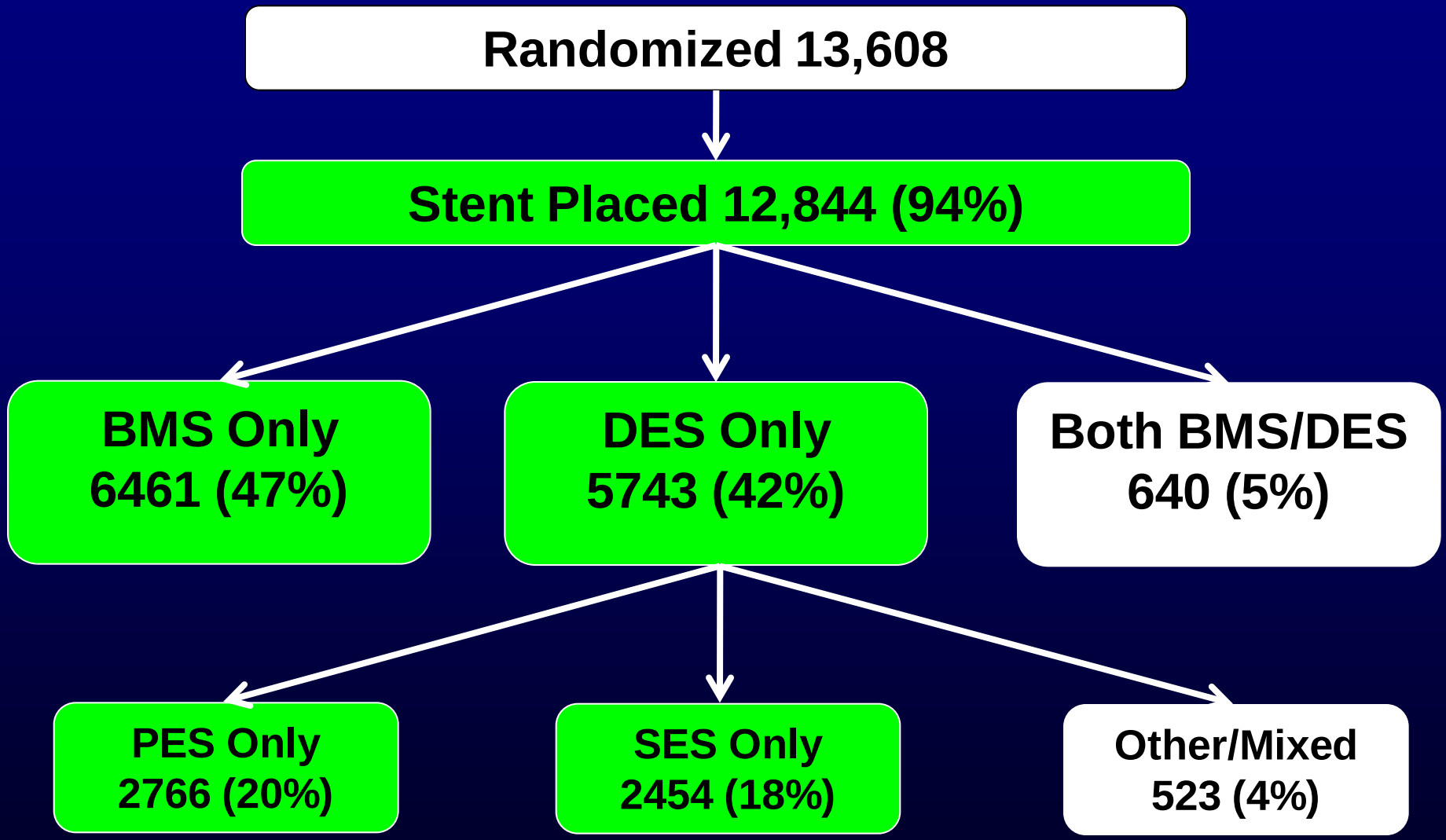
Main Trial: Primary Results



Wiviott SD, Braunwald E, McCabe CH et al NEJM2007

TRITON TIMI-38
STENT ANALYSIS

Patient Population



TRÎTON TIMI·38
STENT ANALYSIS

ARC ST Definitions

Blinded CEC review of using source documents incl imaging reports:

Definite: total occlusion w/in or < 5 mm of the stent or thrombus w/in or< 5 mm of the stent AND a clinical syndrome <48 h.

Probable: unexplained death ≤ 30 days or MI in stented territory w/o angiographic confirmation ST AND w/o alternative cause

Possible: unexplained death > 30 days following stenting

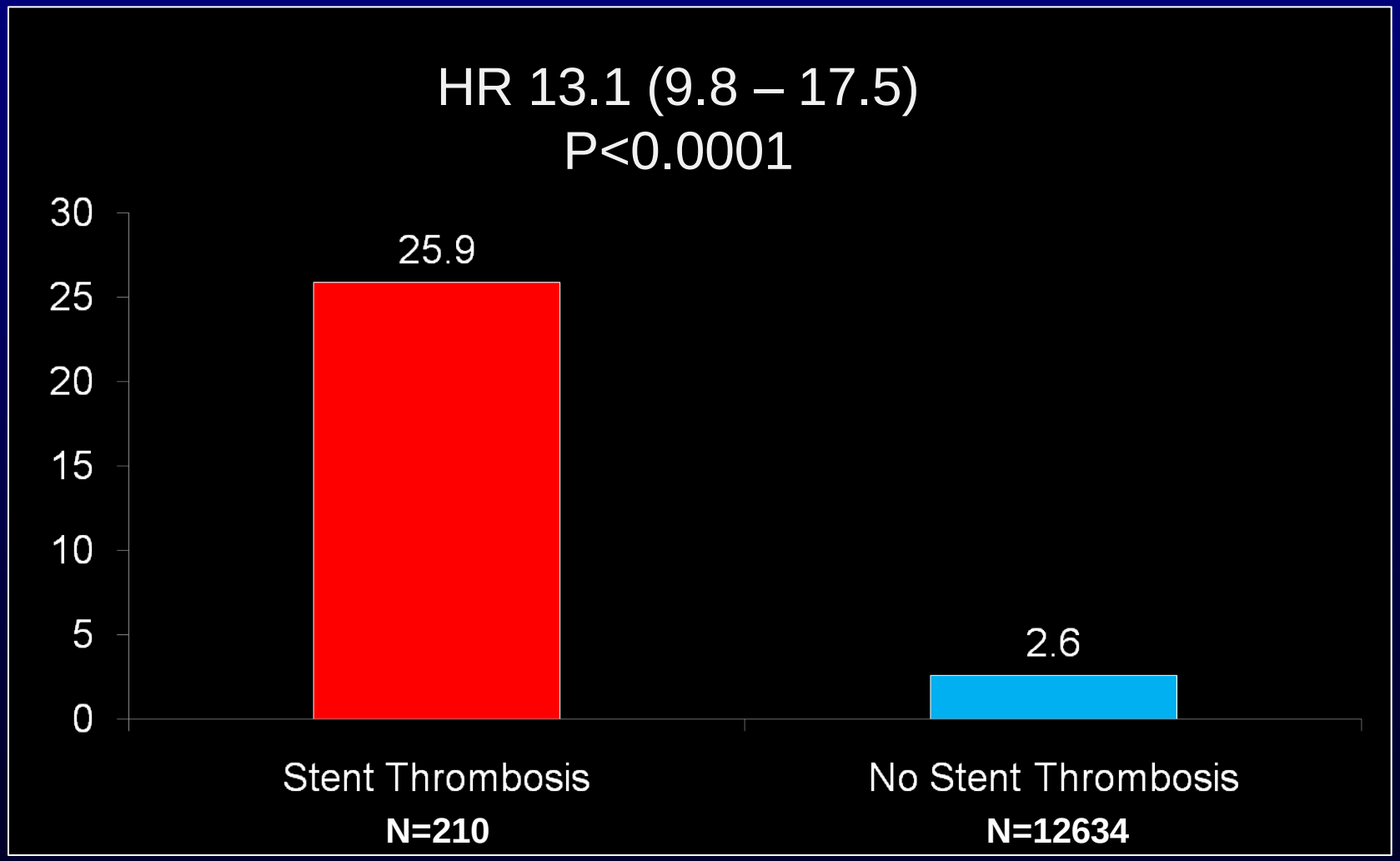
Early: 0 – 30 days after randomization
Late > 30 days after randomization (landmark analysis)

Based on ARC Definitions Mauri L et al NEJM 2007

TRÎTON TIMI·38
STENT ANALYSIS

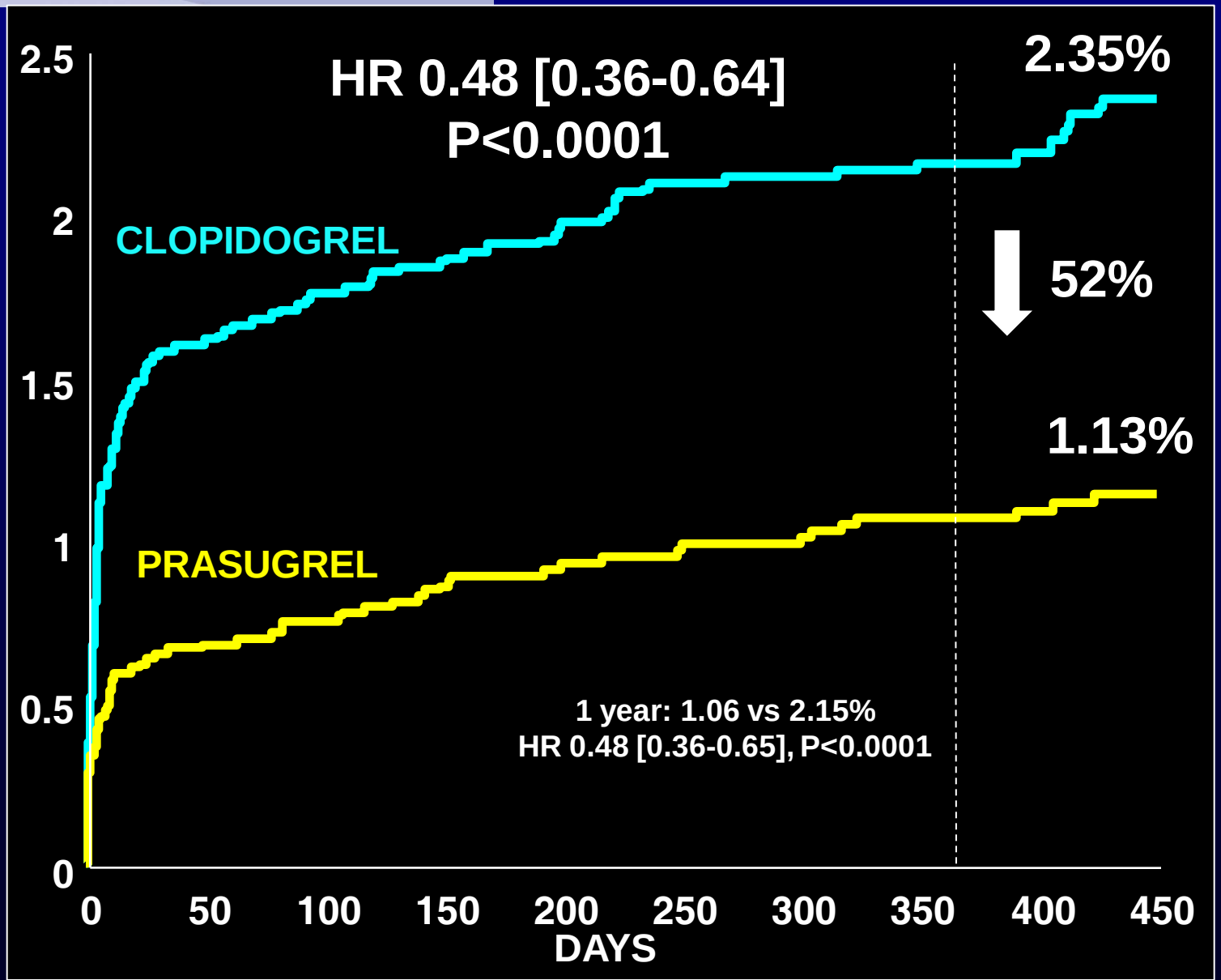
Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis



TRITON TIMI·38
STENT ANALYSIS

Definite/Probable ST: Any Stent (N=12844)



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STENT ANALYSIS

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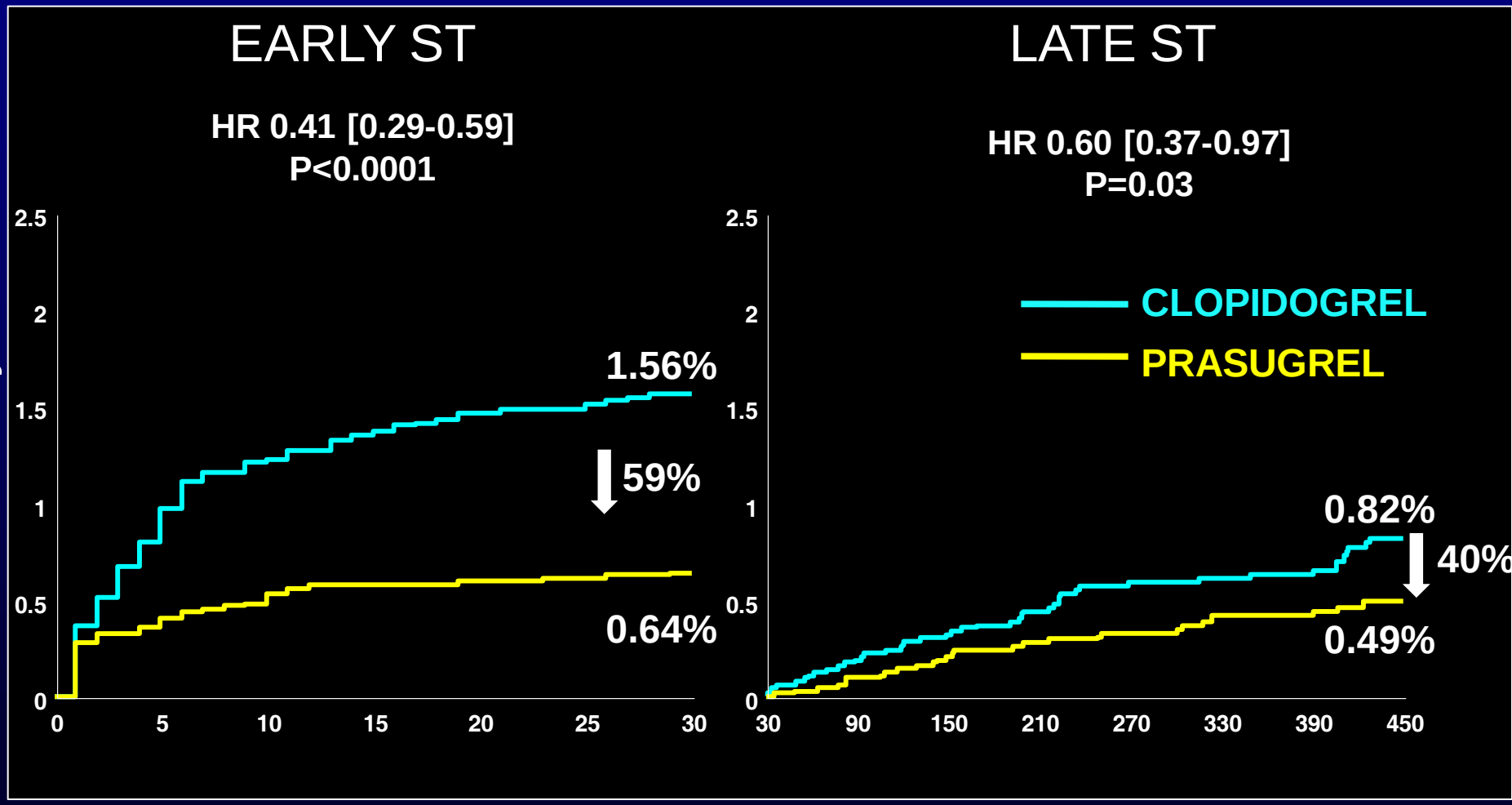
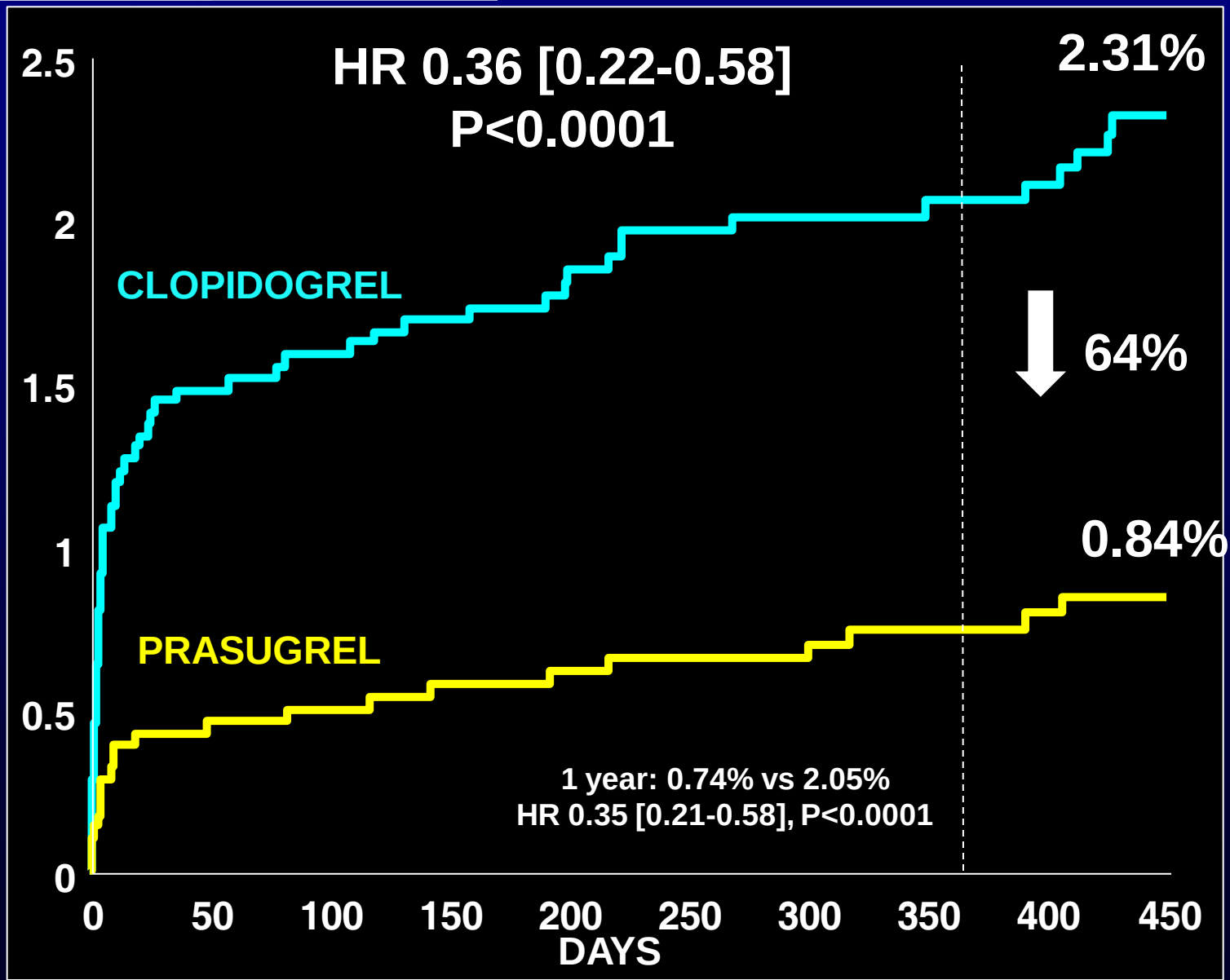


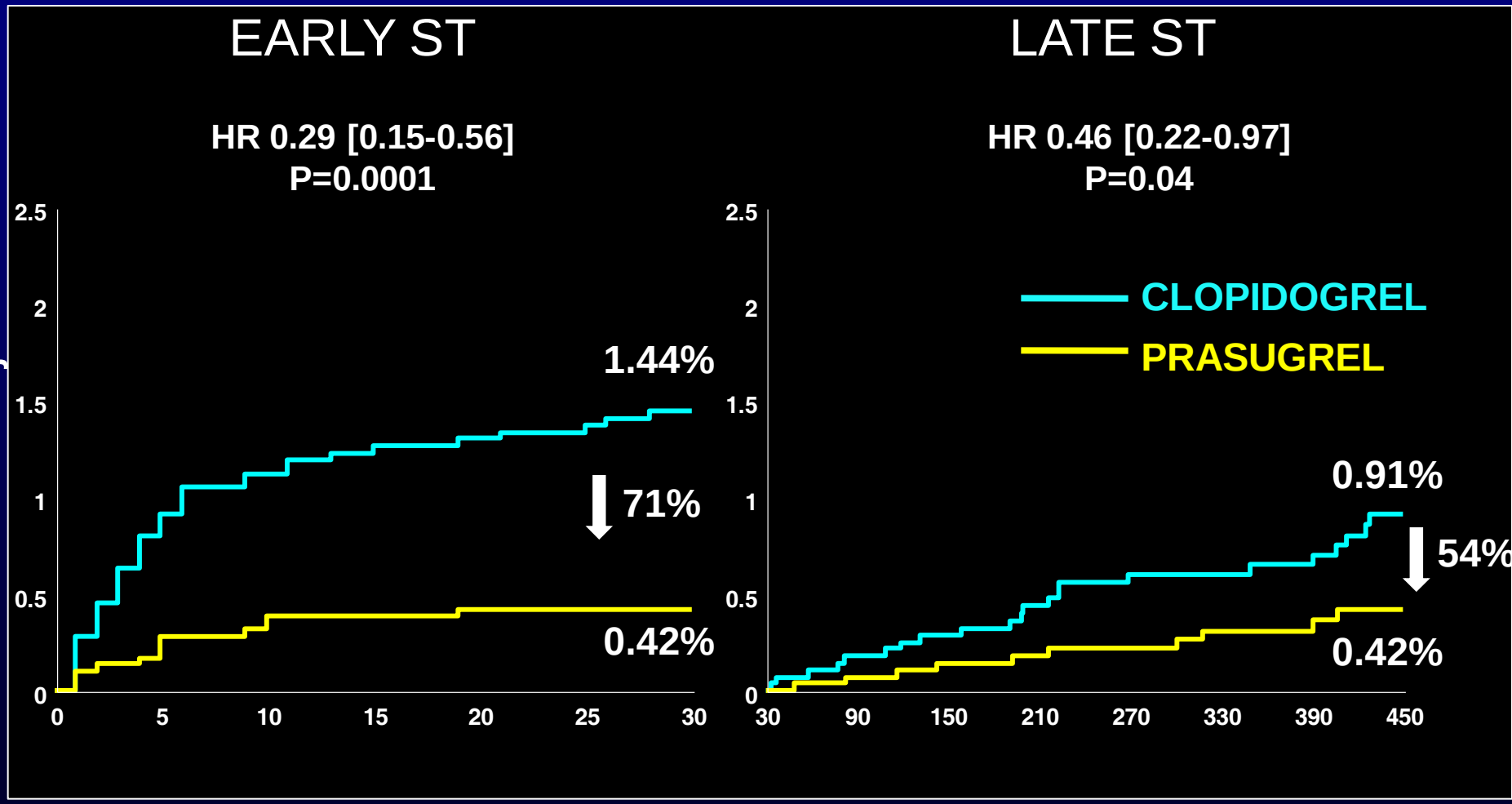
TRITON TIMI·38
STENT ANALYSIS

Definite/Probable ST: DES Only (N=5743)



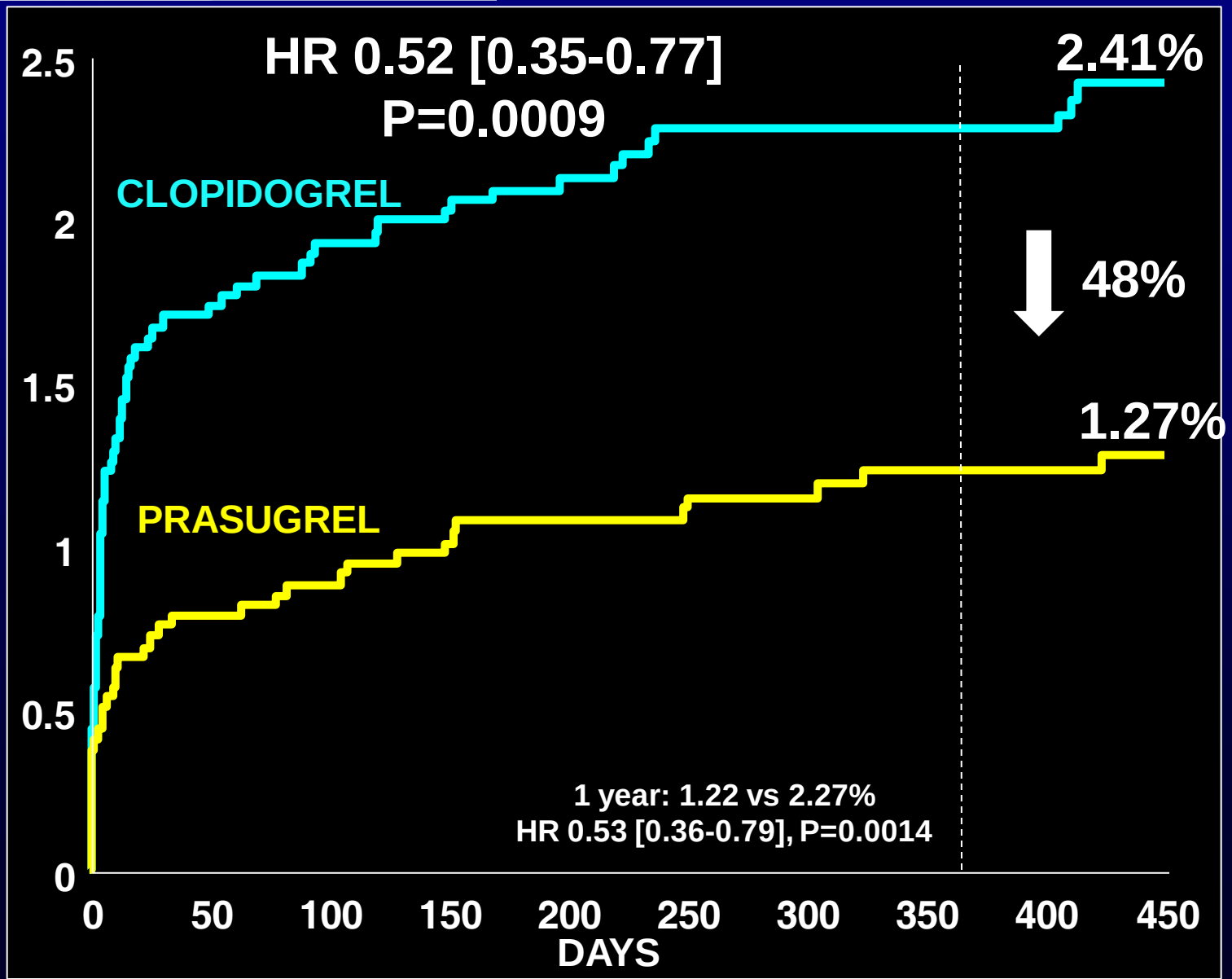
TRITON TIMI·38
STENT ANALYSIS

Definite/Probable ST: DES Only (N=5743)



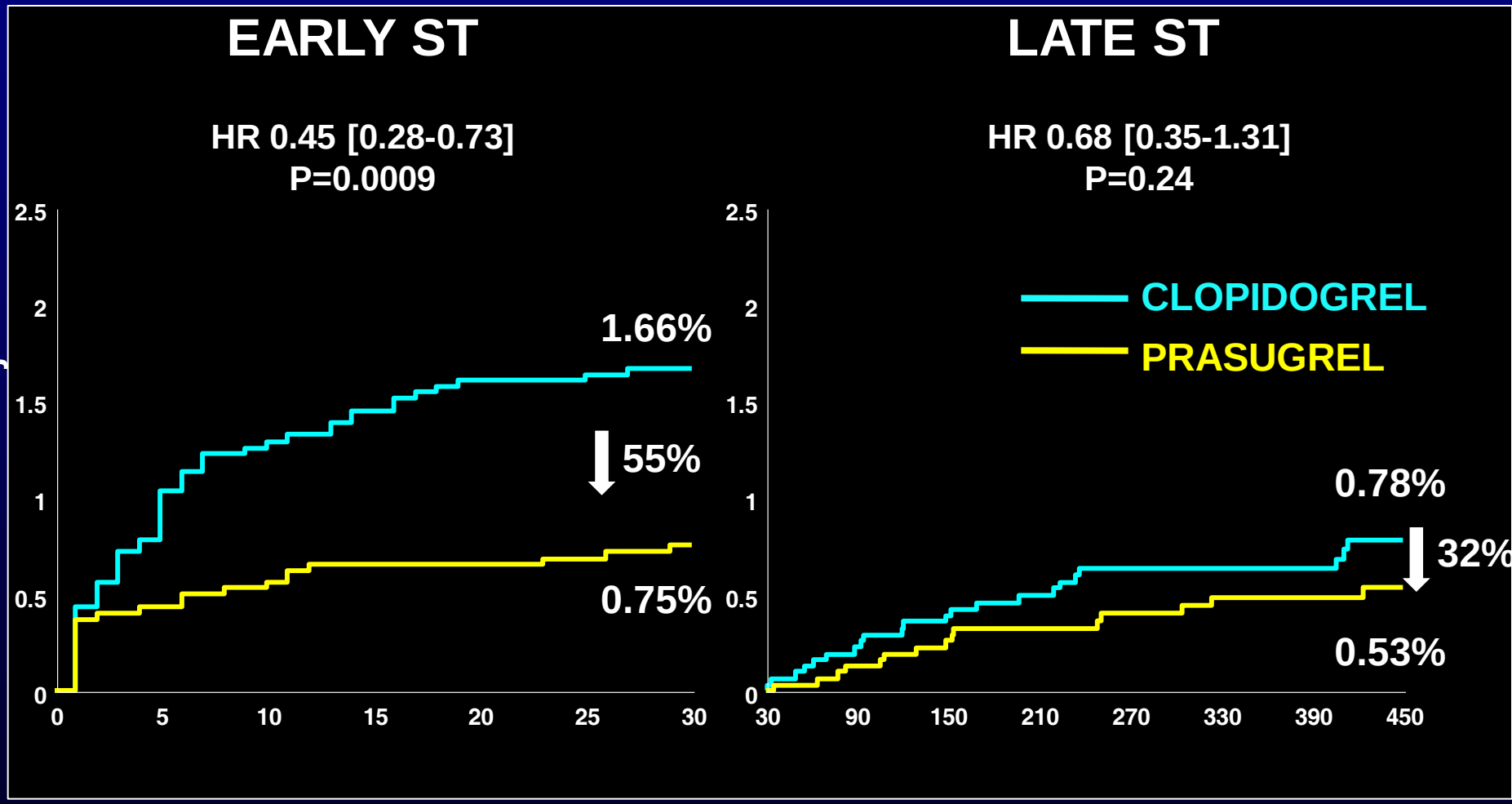
TRITON TIMI·38
STENT ANALYSIS

Definite/Probable ST: BMS Only (N=6461)



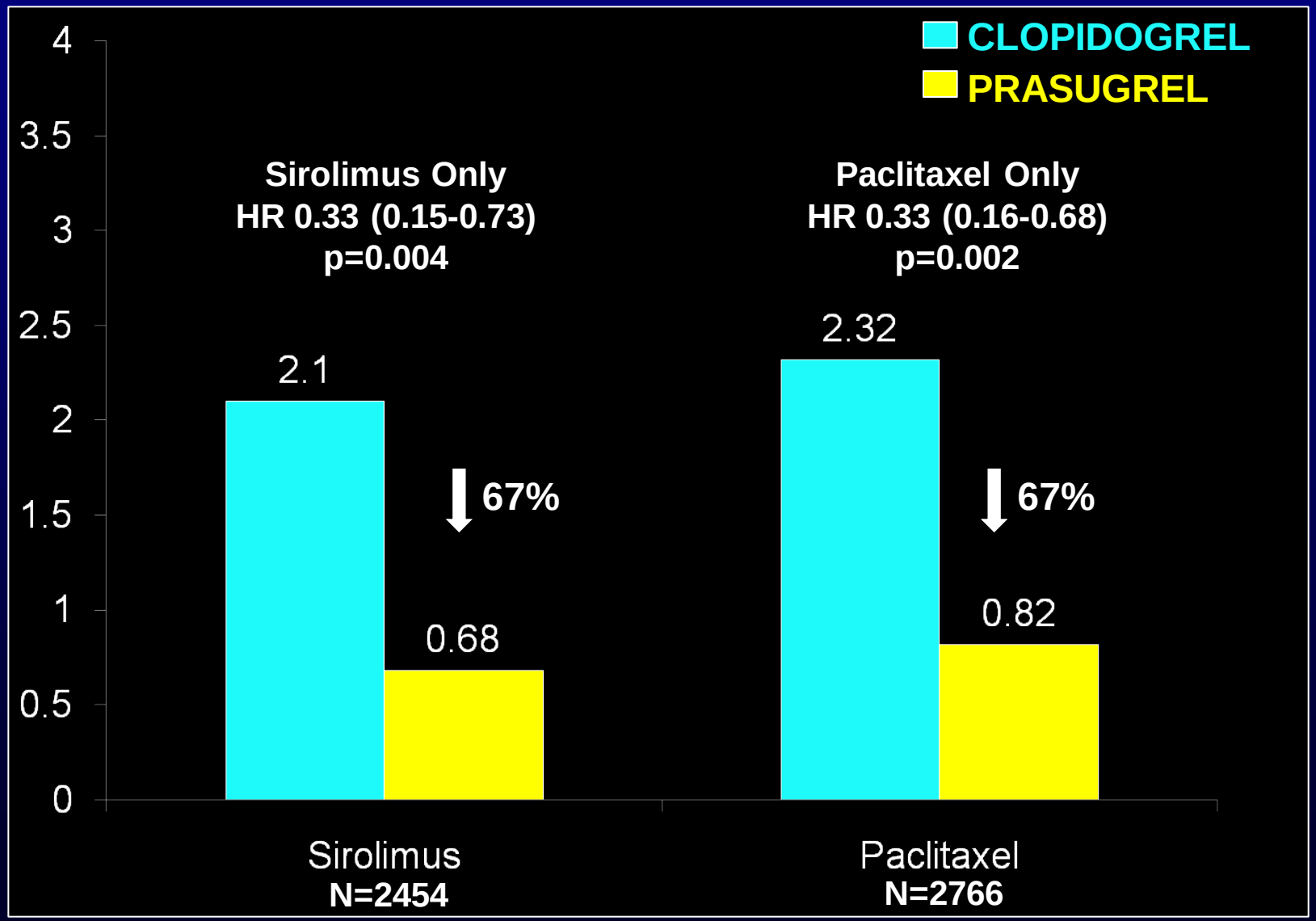
TRITON TIMI·38
STENT ANALYSIS

Definite/Probable ST: BMS Only (N=6461)



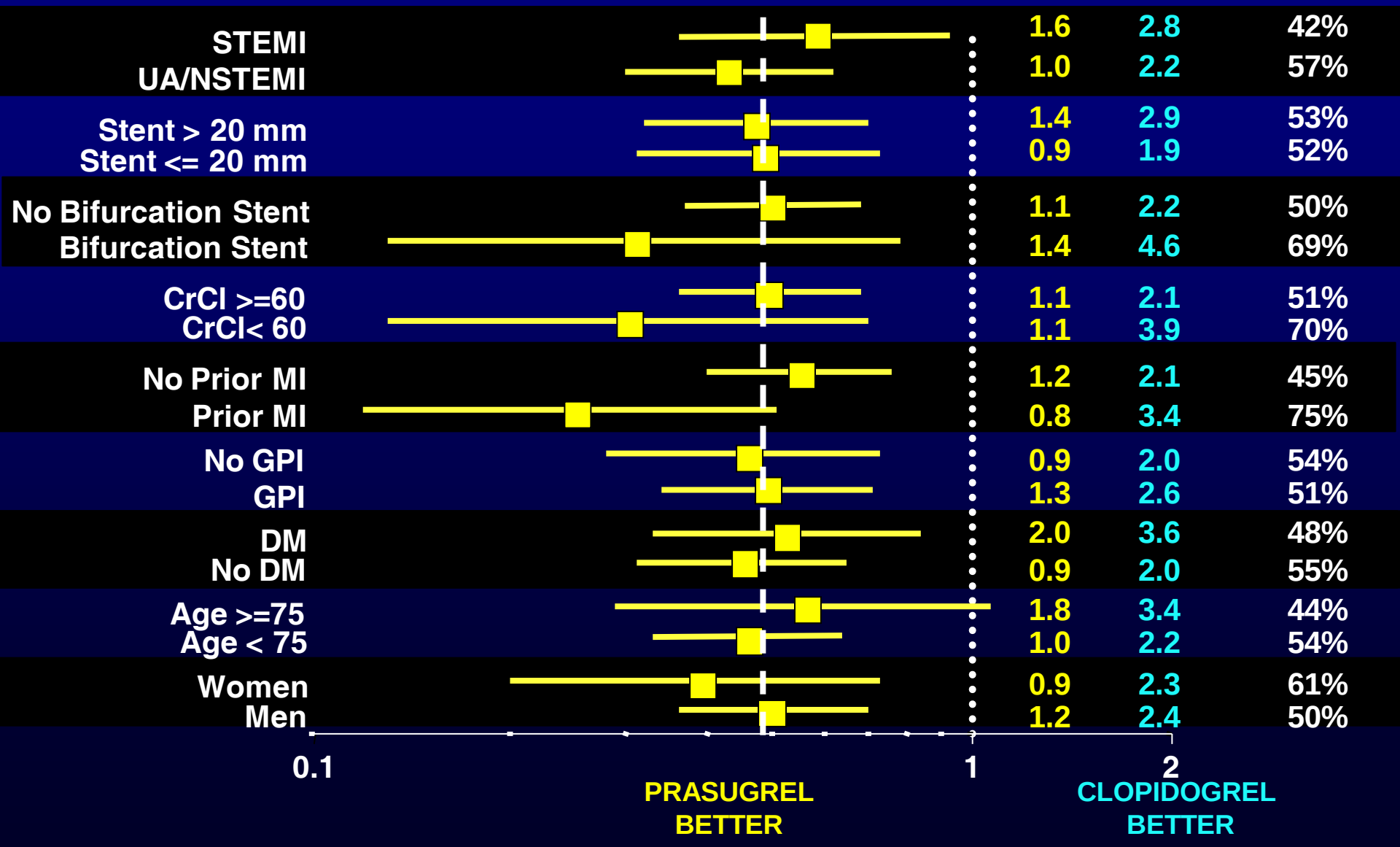
TRITON TIMI·38
STENT ANALYSIS

Stent Thrombosis DES Subtypes
Trial Duration



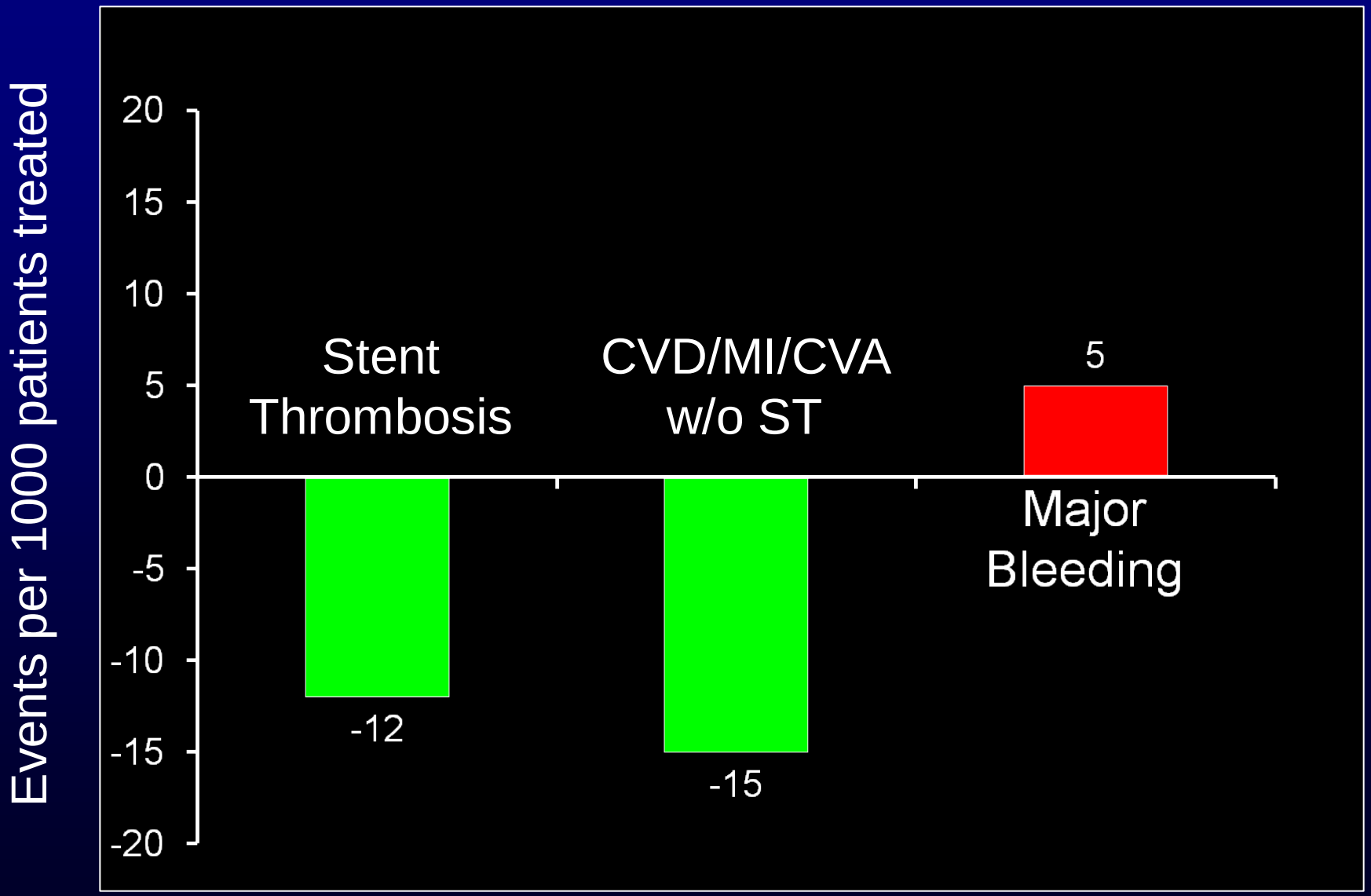
TRÎTON TIMI·38
STENT ANALYSIS

Stent Thrombosis Subgroups



TRÎTON TIMI·38
STENT ANALYSIS

Balance of Efficacy and Safety (Stented Population)



TRÎTON TIMI·38
STENT ANALYSIS

Conclusions/Implications

Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting (TRITON-TIMI 38): a subanalysis of a randomised trial

Stephen D Wiviott, Eugene Braunwald, Carolyn H McCabe, Ivan Horvath, Matyas Kaltai, Jean-Paul R Herrman, Frans Van de Werf, William E Downey, Benjamin M Scirica, Sabina A Murphy, and Elliott M Antman for the TRITON–TIMI 38 Investigators

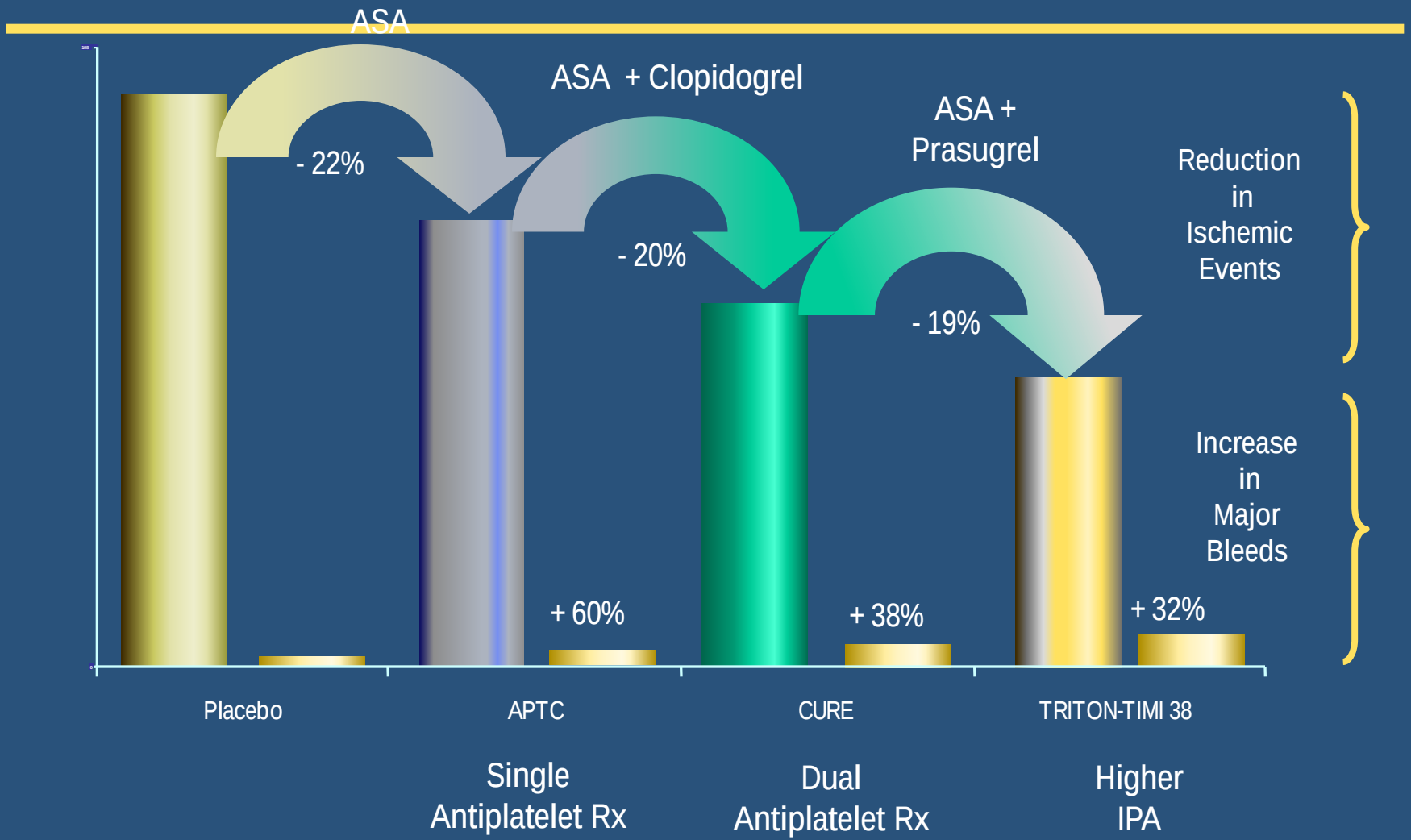
THE LANCET

www.thelancet.com

- Stent Thrombosis is a rare, but devastating complication of PCI associated with a high mortality. Efforts to reduce ST have focused on compliance w/ and duration of ASA/clopidogrel

- Our data indicate that an agent w/ more rapid, consistent, and greater inhibition of platelet aggregation (prasugrel) results in major reductions (~50%) in ST across a broad array of clinical procedural characteristics

Evolution of Antiplatelet Therapy in ACS



APTC. *BMJ.* 1994;308:81-106.
Mehta SR et al. *Lancet.* 2001;358:527-533.

GRAVITAS: Patient flow

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

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

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

Clopidogrel High Dose N=1109

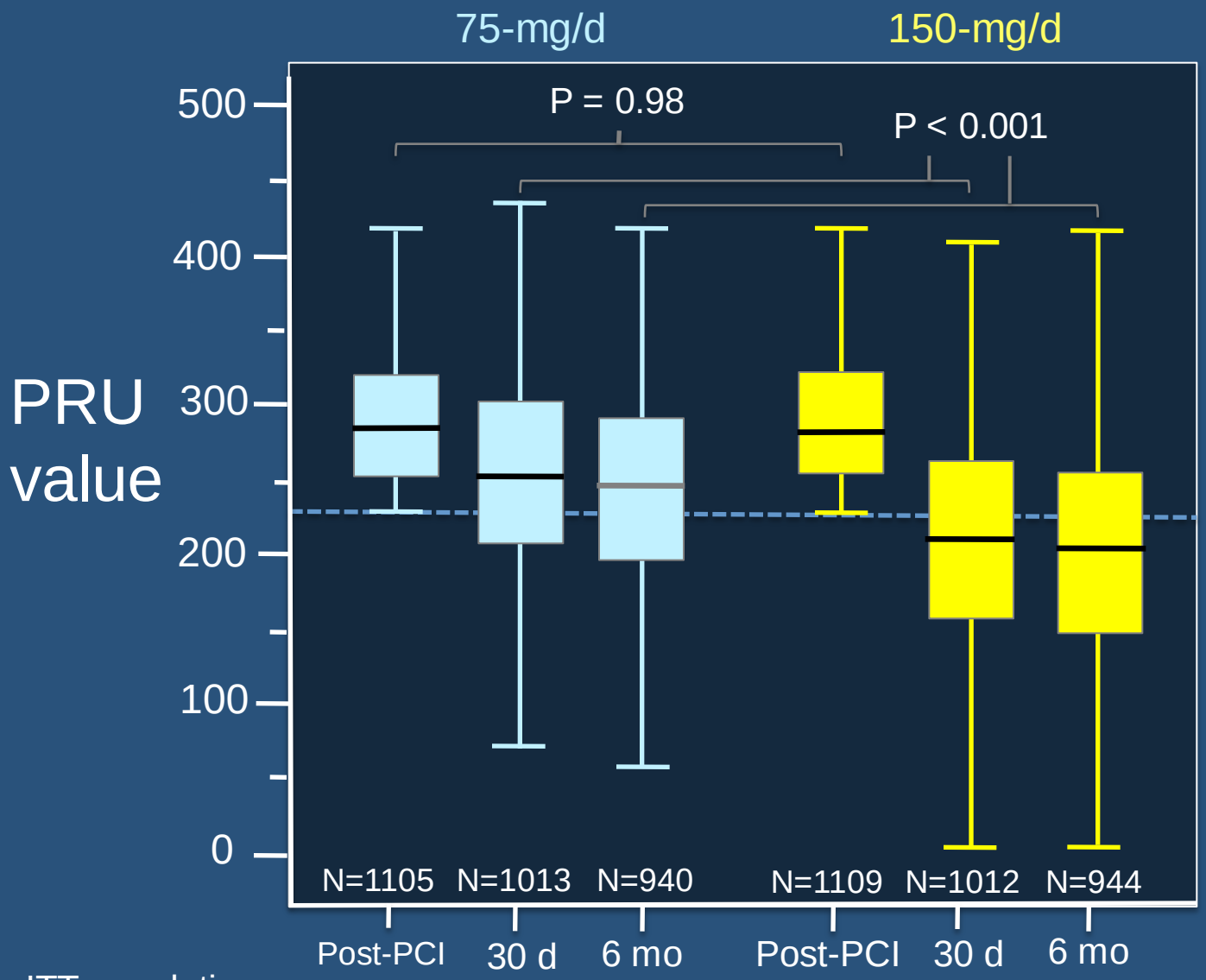
Clopidogrel Standard Dose N=1105

High-Dose Clopidogrel†
clopidogrel 600-mg, then
clopidogrel 150-mg daily X 6 months

Standard-Dose Clopidogrel†
clopidogrel 600-mg, then
clopidogrel 75-mg daily X 6 months

Price. AHA Scientific Sessions, Chicago 2010

GRAVITAS: Pharmacodynamics: Effect of SD vs HD clopidogrel

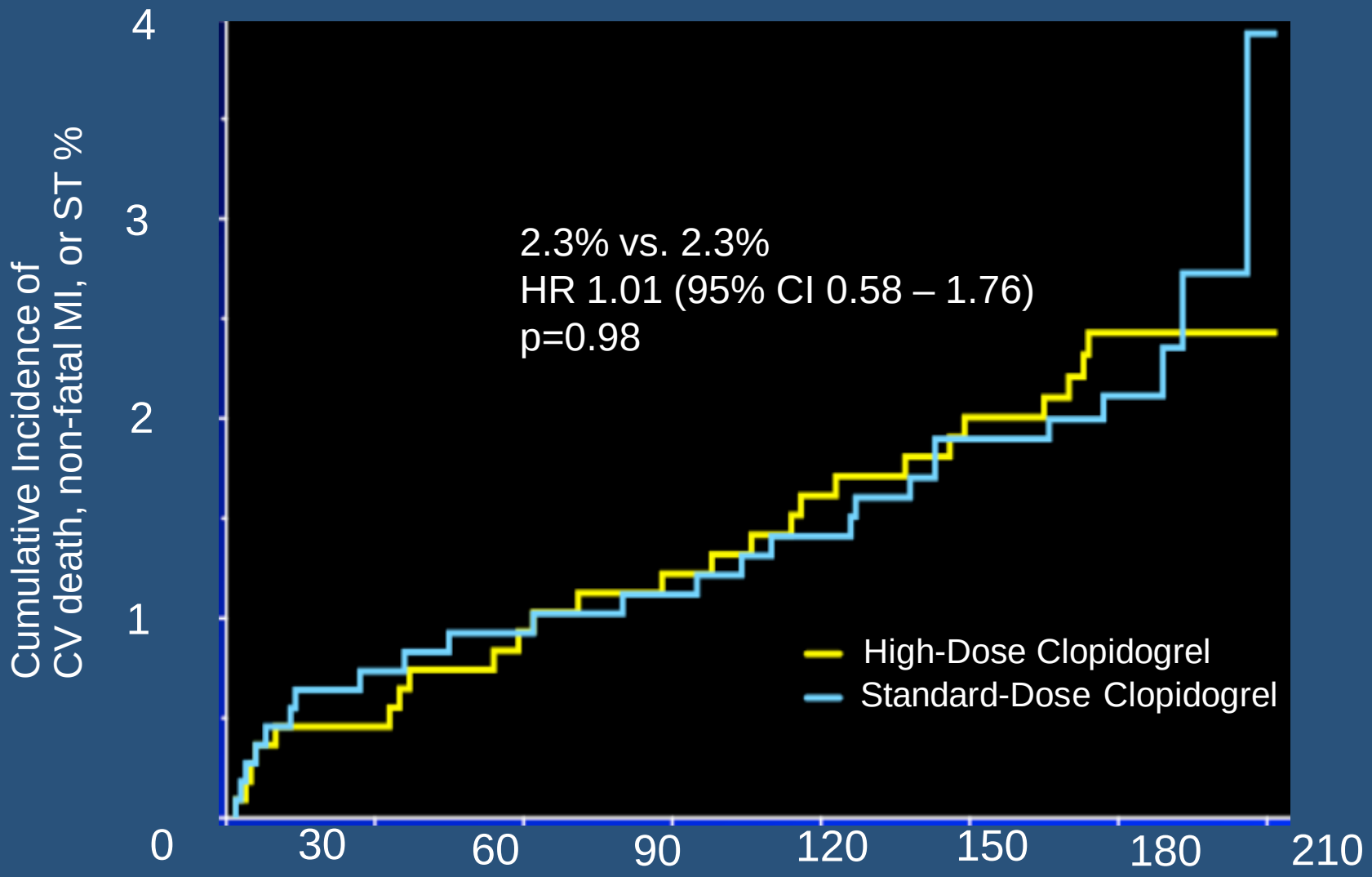


PRU ≥ 230 at 30 days	
Clopidogrel 75mg/d	Clopidogrel 150mg/d
62%	40%
p < 0.001	

ITT population

Price. AHA Scientific Sessions, Chicago 2010

GRAVITAS Trial: Primary Endpoint: CV Death, MI, Stent Thrombosis



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

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

Price et al, AHA 2010

TRIGGER PCI Trial: Study Design

Elective PCI with DES without GP IIb/IIIa use

VerifyNow P2Y12 Test 2-4hrs first clopidogrel MD (75mg)

N= 2150

PRU ≥ 206

All patients received aspirin (81-162mg daily)

R

Prasugrel
Loading dose 60mg, then 10mg daily X 6 months

Placebo LD,then Clopidogrel
75mg daily X 6 months

Primary Efficacy Endpoint: CV Death, Non-Fatal MI at 6 mo
Key Safety Endpoint: Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 3 and 6 months

Trial was halted after 432 pts enrolled because of <2% event rate (projected 7%) in 250 pts reaching 6M mark

Conclusiones

- La variabilidad de la agregación plaquetaria con uso de clopidogrel tiene implicancia clínica.
- En pacientes de alto riesgo trombotico se deberia preferir el uso de prasugrel o ticagrelor o adicionar otro Antiagregante plaquetario EV (Bivalirudina),
- Dar prasugrel una vez que se decida PCI??
- Evitar en > 75 años y < 60 kg, ant ACV.

Gracias

"Take an aspirin every day, but before you swallow it, take it out for a five-mile walk."