Αντίσταση στην αντιαιμοπεταλιακή θεραπεία

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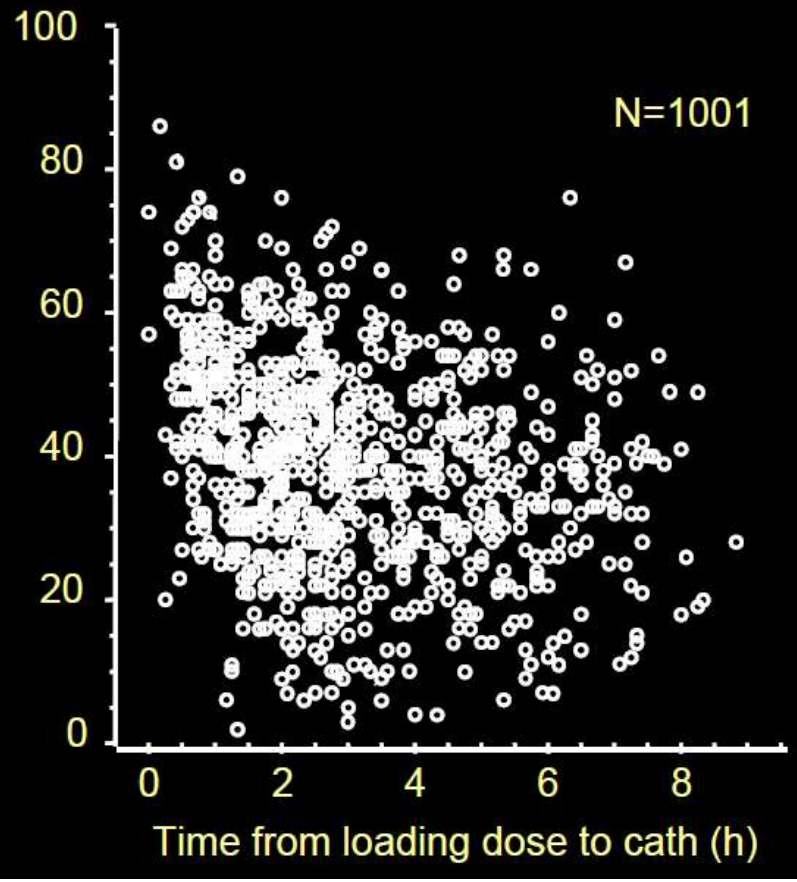
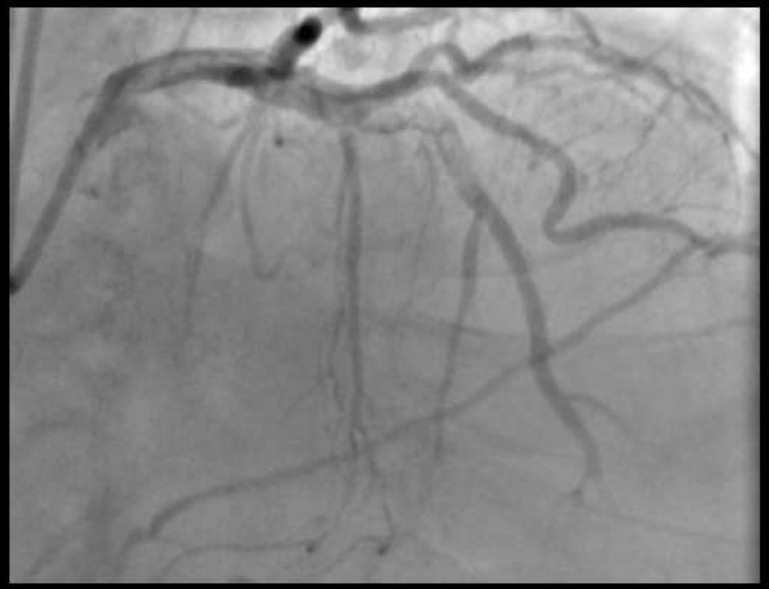
The Problem: Clopidogrel Response Variability and Thrombotic Events after Stent Implantation



Stentthrombosis of DES in mid LAD



Different Mechanism of Late Stent Thrombosis: A Post-Mortem Study

174 autopsies with DES – 127 patients (73%) died > 30 days after PCI

Underlying Causes of Thrombosis of DES

Prolapse of Necrotic Core

Mechanical

Inflammation

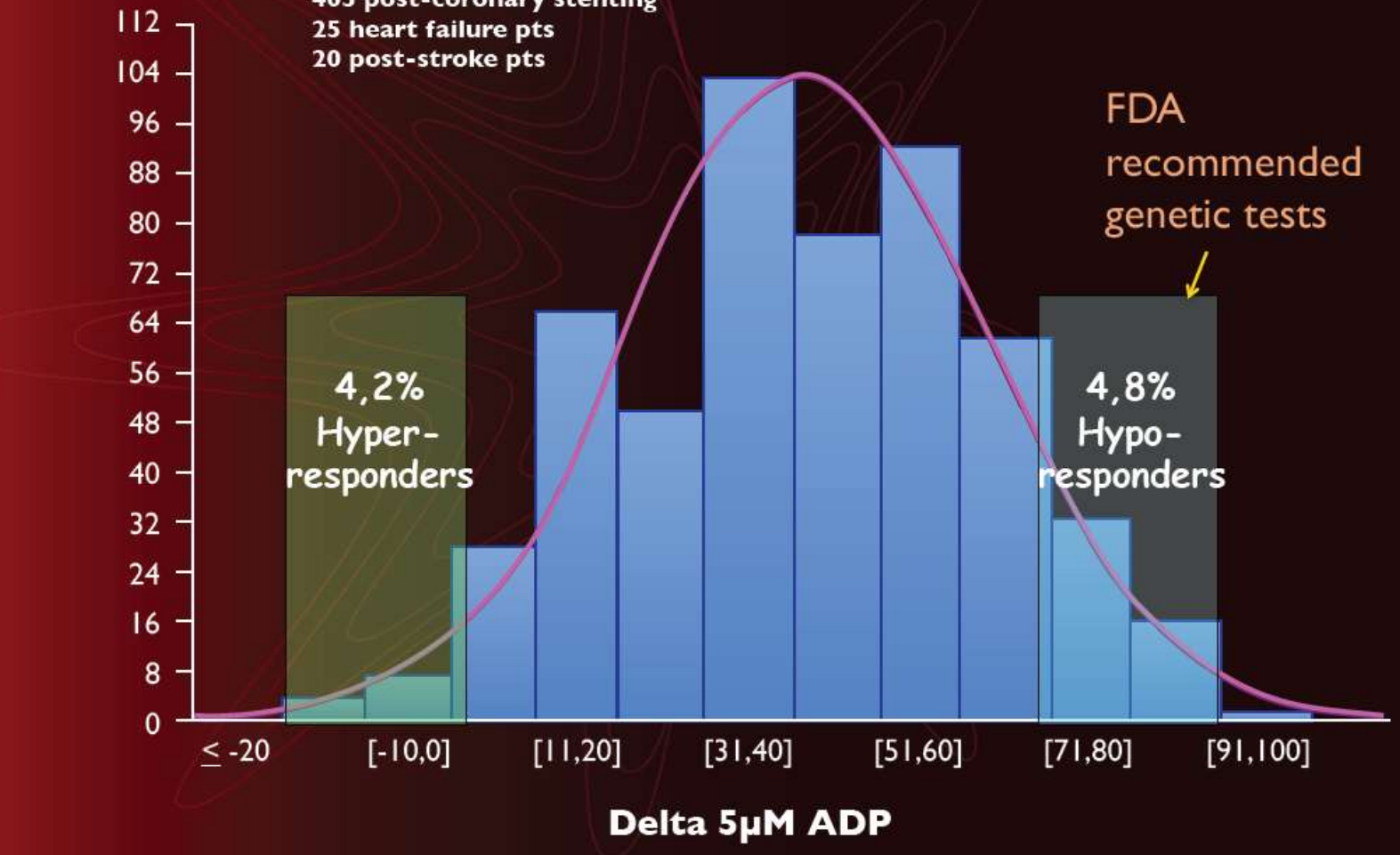
	SES	PES	p Value
Early thrombosis (<30 days), n	11*	13*	
AMI, penetration/prolapse of necrotic core	1	5	0.17
Bifurcation	3	2	0.63
Long/overlapping stents	1	0	0.46
Medial rupture/dissection	3	4	1.00
Malapposition	0	1	1.00
Others†	3	1	0.30
Late thrombosis (≥30 days), n	16*	25*	
AMI, penetration of necrotic core	5	5	0.47
Bifurcation	1	9	0.06‡
Long/overlapping stents	0	2	0.50
Underexpansion	1	1	1.00
Isolated uncovered struts	2	1	0.55
Localized hypersensitivity reaction	7	0	0.0005‡
Malapposition from excessive to fibrin	0	7	0.03‡

Nakazawa, Vermani et al; JACC 2011

Variability in platelet response after standard dosing of clopidogrel

ΙΝΣΤΙΤΟΥΤΟ ΘΡΟΜΒΩΣΗΣ ΑΙΜΟΣΤΑΣΗΣ

Studied population
94 volunteers
405 post-coronary stenting
25 heart failure pts
20 post-stroke pts

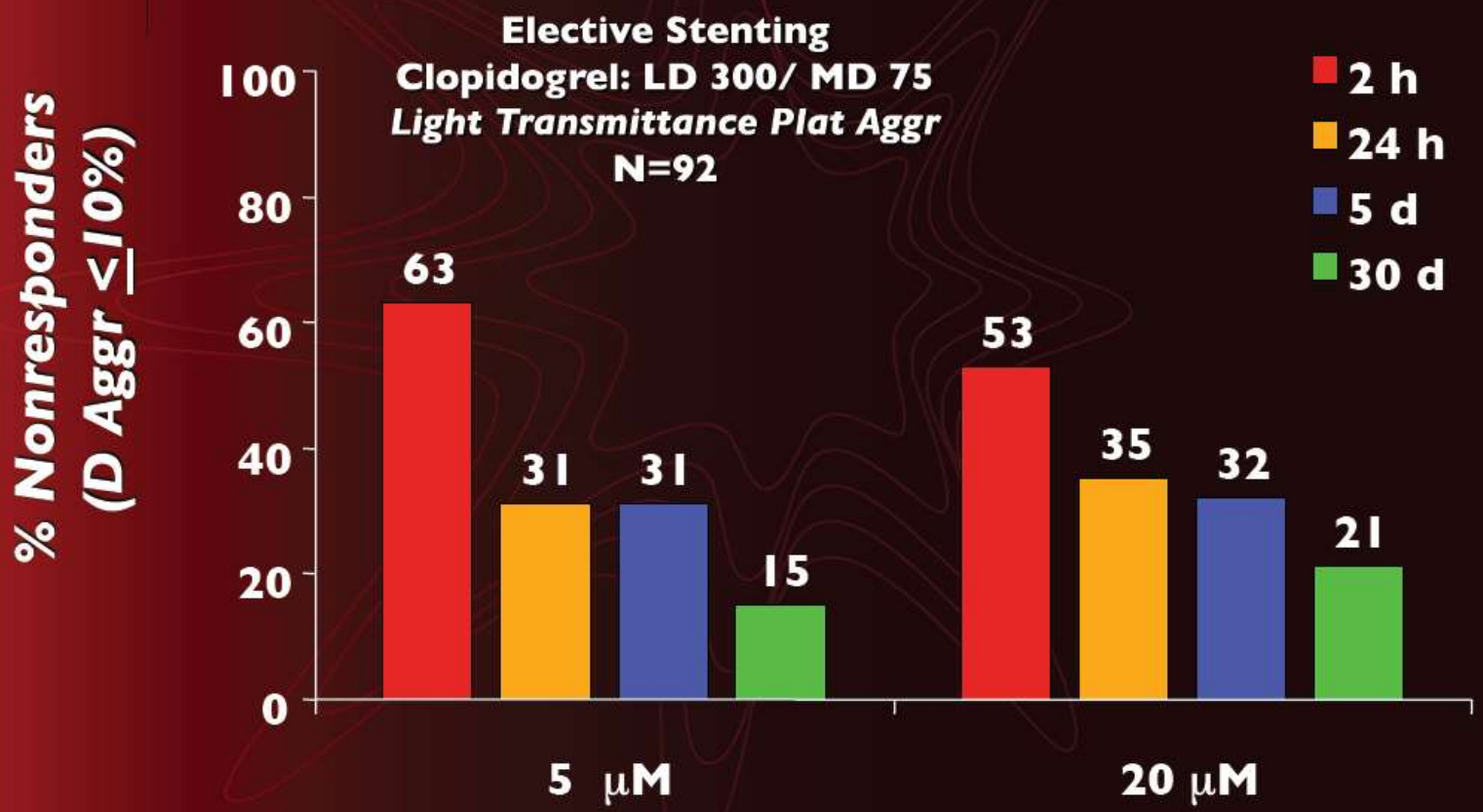


Serebruany et al. *JACC* 2005 ; 45 : 246-251.

Variability of response to clopidogrel: a matter of time?

ΙΝΣΤΙΤΟΥΤΟ ΘΡΟΜΒΩΣΗΣ ΑΙΜΟΣΤΑΣΗΣ

300mg



Gurbel et al. Circulation. 2003;107:2908

Resistance to the Antiplatelet Treatment

Biological resistance

- Failure to demonstrate the effect of the treatment on a specific laboratory test assessing platelet activation

Clinical resistance

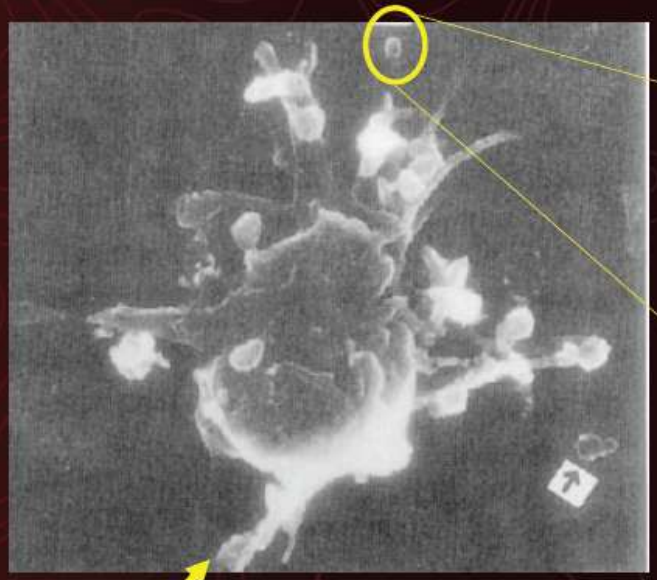
- Recurrent thrombotic episode while the patient is treated with antiplatelet agents

Formation of platelet microparticles

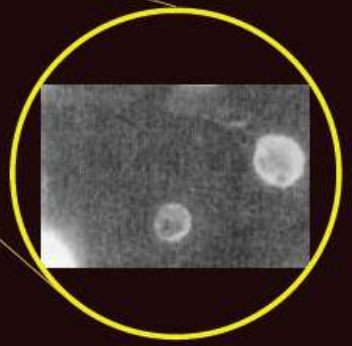
ΙΝΣΤΙΤΟΥΤΟ ΘΡΟΜΒΩΣΗΣ ΑΙΜΟΣΤΑΣΗΣ

Resting platelet

Platelet activation



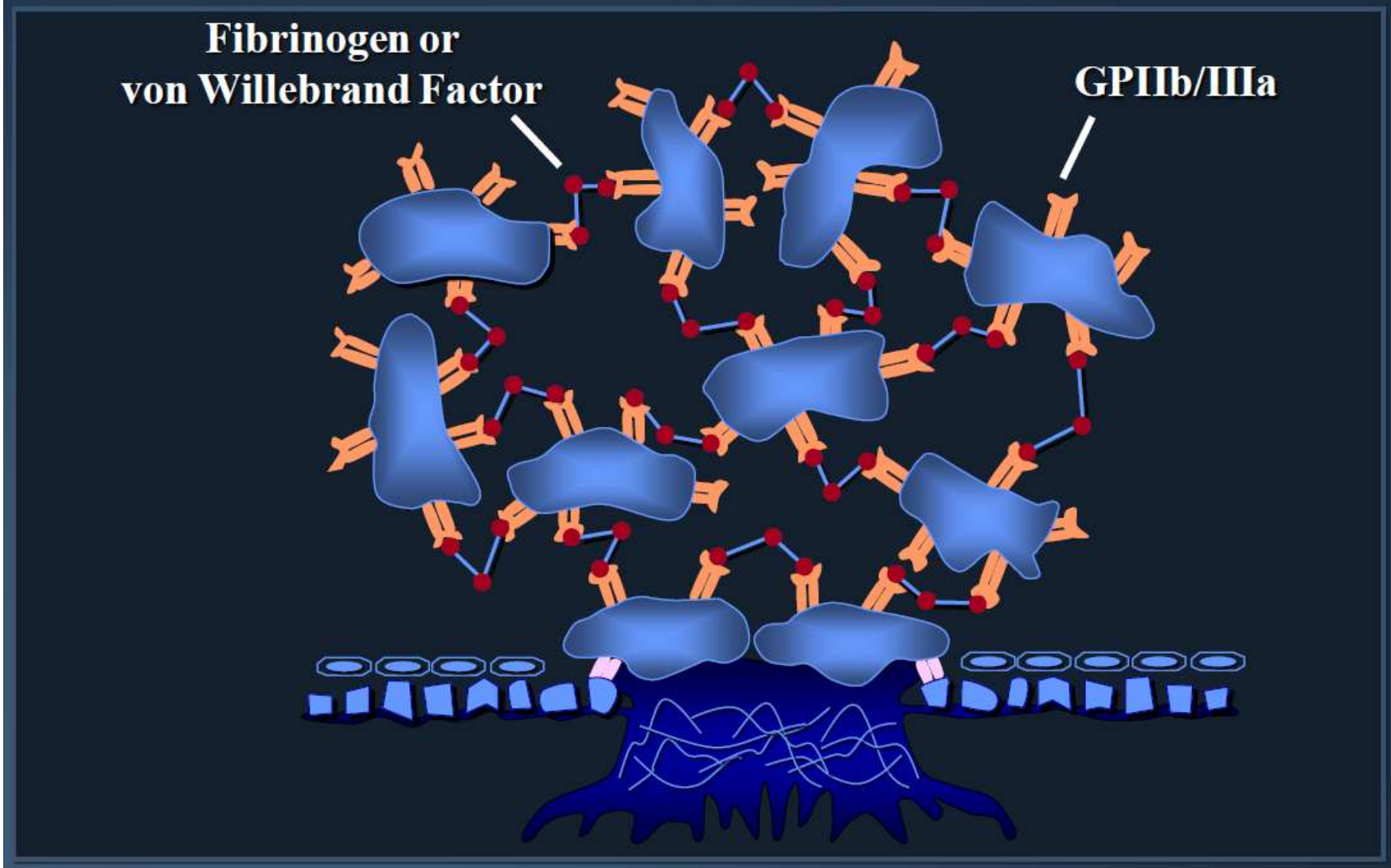
Formation of microparticles



Platelet pseudopodes

Kelton JG, Chest 2005; 127:9S–20S

Aggregation



Antiplatelet agents

ΙΝΣΤΙΤΟΥΤΟ ΘΡΟΜΒΩΣΗΣ ΑΙΜΟΣΤΑΣΗΣ

Inhibitors of Arachidonate pathway

- Aspirin
- Indobufen
- Flurbiprofen
- Triflusal
- Ridogrel
- Picotamide
- S 18886
- Cilostasol

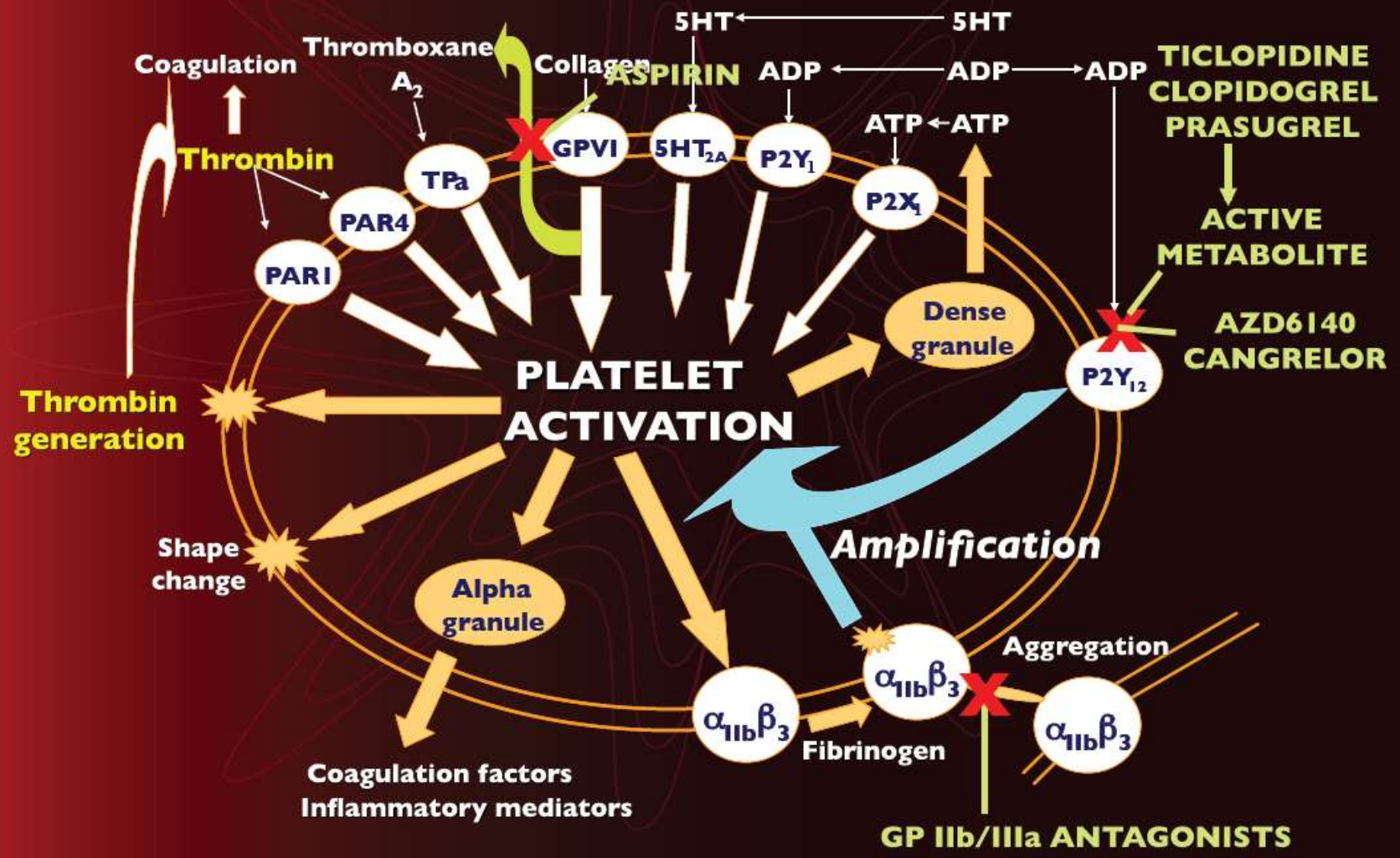
Antagonists of ADP receptor

- Ticlopidin
- Clopidogrel
- Prasugrel
- ticagrelor
- Cangrelor

Antagonists of GP I | b/IIIa

- Abciximab
- Tirofiban
- Eptifibatide

Platelet Activation Mechanisms



Storey RF. *Curr Pharm Des.* 2006;12:1255-59.

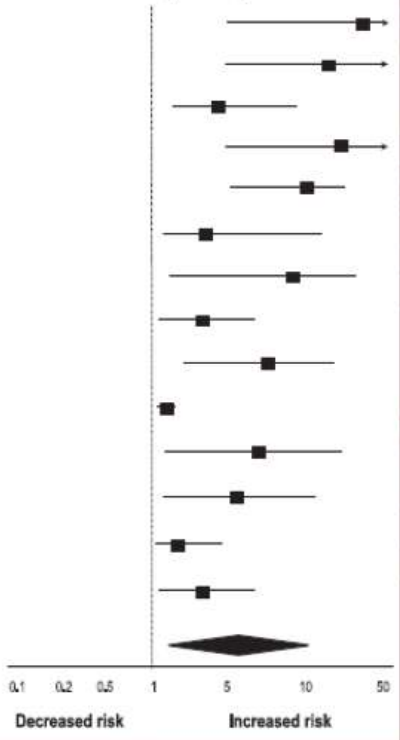
Clopidogrel Landmark Trials

Trial	Patients	Regiment	Composite end-point (AMI,Stroke, CV death)
CAPRIE 1996 Clopidogrel vs Aspirin in pts at risk of Ischemic Events	19185 pts with recent AMI, stroke, PAD	Clopidogrel 75 mg/d vs ASA 325 mg/d	8,7% RRR after 1,9 ys follow up
CURE 2001 Clopidogrel in Unstable angina to prevent recurrent events	12562 pts	ASA 325 mg +clopidogrel 75 mg vs ASA 325 mg+placebo	20% reduction after 9 mo follow up
CREDO 2002 Clopidogrel for the reduction of events during observation	2116 pts with elective PCI	ASA 325 mg +clopidogrel 75 mg vs ASA 325 mg+placebo	27% reduction after 1 y follow up

Clopidogrel non-responsiveness and risk of cardiovascular morbidity

ΙΝΣΤΙΤΟΥΤΟ ΘΡΟΜΒΩΣΗΣ ΑΙΜΟΣΤΑΣΗΣ

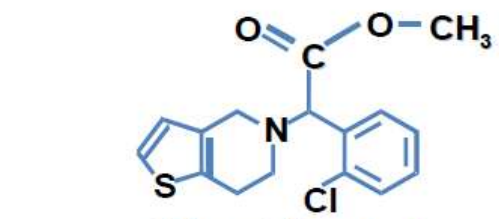
Study	Odds ratio (95%CI)	Weight (%)
Muller et al. 2003[9]	**44.50** (4.47-443.34)	4.4
Matetzky et al. 2004[10]	**38.50** (4.15-357.10)	4.6
Gurbel et al. 2005[11]	**4.95** (2.45-10.02)	8.8
Cuisset et al. 2006[12]	**41.60** (4.75-364.51)	4.7
Cuisset et al. 2006[13]	**13.82** (5.30-36.04)	8.2
Geisler et al. 2006[14]	**3.71** (1.08-12.72)	7.3
Hochholzer et al. 2006[15]	**9.60** (2.09-44.09)	6.4
Buonamici et al. 2007[16]	**3.08** (1.32-7.17)	8.5
Frere et al. 2007[17]	**8.62** (2.31-32.16)	7.1
Blindt et al. 2007[18]	**1.16** (1.01-1.33)	9.9
Price et al. 2007[19]	**7.17** (1.46-35.19)	6.2
Patti et al. 2008[20]	**6.10** (1.50-24.88)	6.8
Wang et al. 2008[21]	**2.44** (1.09-5.46)	8.7
Marcucci et al. 2009[22]	**3.60** (1.46-8.87)	8.4
Total (95% CI)	**5.67 (2.97-10.84)**	**100**



Non responders : 1205 out of 4564 (26%)
higher risk of death and/or ischaemic recurrences
(OR 5.67, 95% CI 2.97 to 10.84; p<0.00001).

Sofi et al Thromb Haemost 2010; 103:

The Generation of Clopidogrel's Active Metabolite is Inefficient and CYP450-dependent

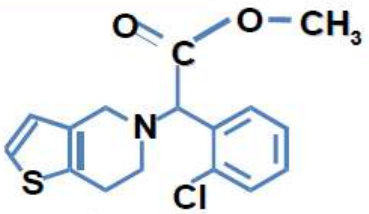


Clopidogrel

Pro-drug

Hydrolysis
(Esterases)

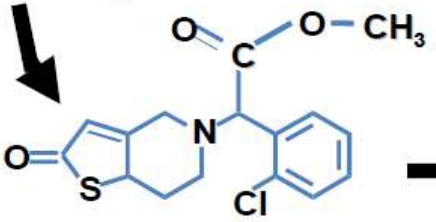
85% Inactive Metabolites

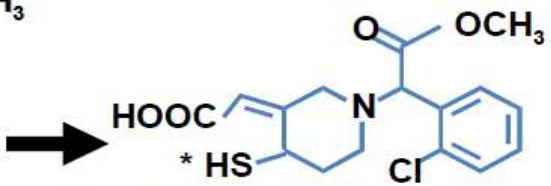


2-Step Oxidation
(Cytochrome P450)

CYP2C19: 45% of 1st, 20% of 2nd

CYP1A2, CYP3A4, CYP3A5, CYP2C9, CYP2B6

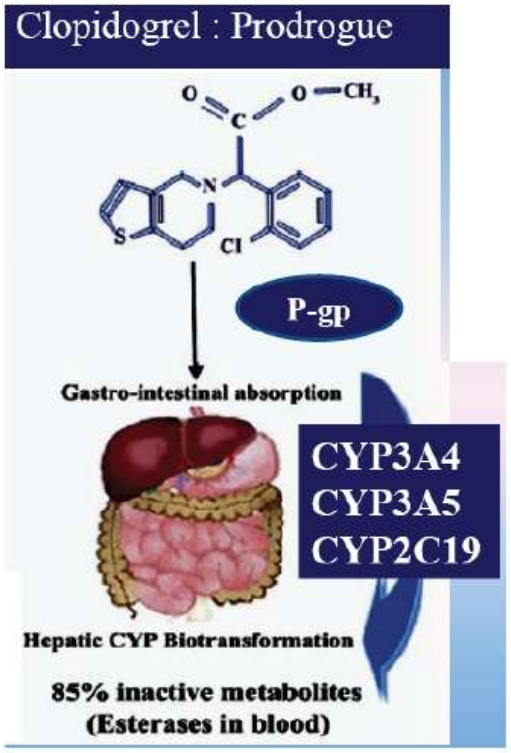




Active Metabolite

Herbert JM, Savi P. *SeminVasc Med* 2003;3(2):113-122.

Genes regulating the effect of thienopyridines (clopidogrel and prasugrel)

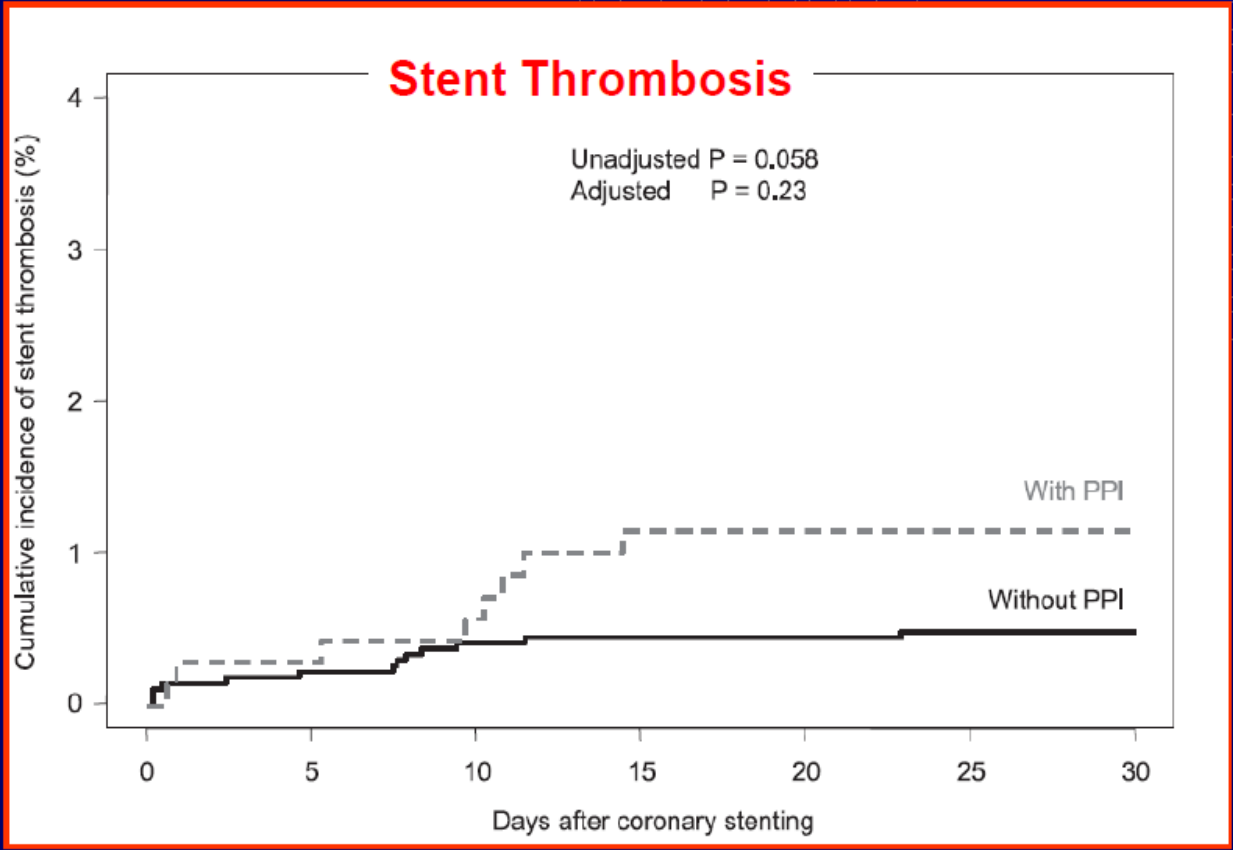


- Intestinal pump
- Physiologic intestinal barrier against the absorption of clopidogrel
- Encoded by the ABCB1 gene
- Relation with GP expression and activity?

- CY3A4, CYP3A5
- CYP2C19
- *2, *3, *4, *5 : decreased function
- *17 : increased metabolism

Stent Thrombosis (within 30 days) and PPI Use

3,338 patients with DES – 698 (21%) treated with PPI
All treated with clopidogrel



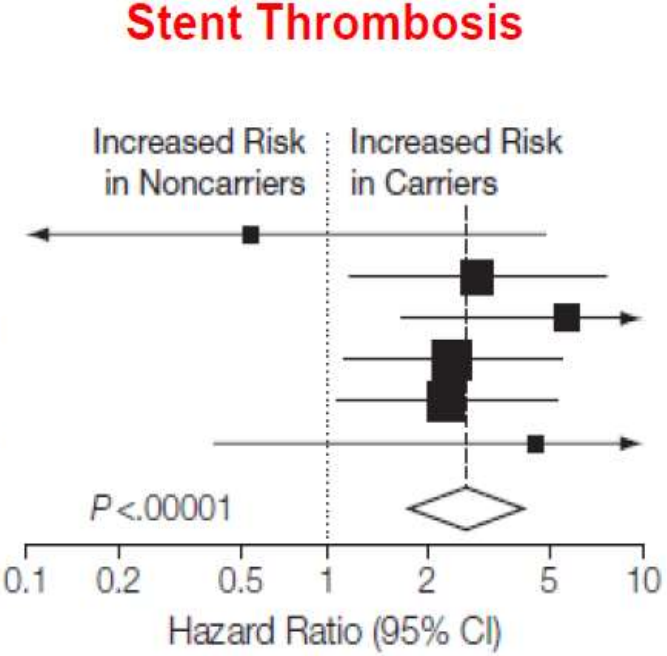
30-day mortality w PPI 2.6% vs w/o 0.9%; adjusted p=0.02

Reduced-Function *CYP2C19* Genotype and Risk of Stent Thrombosis with Clopidogrel: A Meta-Analysis

9,685 patients with PCI – 84 pts with stent thrombosis
72% non-carriers, 26% 1 reduced function allele,
2% 2 reduced function allele

A Carriers of 1 or 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	1 or 2	None	
EXCELSIOR	1/243	4/554	0.57 (0.06-5.09)
TRITON-TIMI 38	9/375	8/1014	3.09 (1.19-8.00)
AFIJI	8/61	4/162	6.04 (1.75-20.82)
RECLOSE	13/247	11/525	2.55 (1.14-5.70)
ISAR	11/680	12/1805	2.45 (1.08-5.55)
CLEAR-PLATELETS	2/68	1/160	4.78 (0.43-52.69)
Overall	44/1674	40/4420	2.81 (1.81-4.37)



Identifying The Patient At High Risk for Clopiodgrel Non-responsiveness: *The Majority of Clopidogrel-response Variability Remains Unexplained by CYP2C19 and Clinical Factors*

N=760, elective PCI after 600-mg clopidogrel

Table 2 Multivariable Linear Regression Model for RPA After Stimulation With 5 μmol/l ADP

	Partial η^2	p Value
*CYP2C19** polymorphism	0.052	<0.001
Age (yrs)	0.010	0.006
Arterial hypertension	0.001	0.386
Diabetes mellitus	0.012	0.003
Body mass index (kg/m^2)	0.010	0.008
Platelets (× 10^9/l)	0.010	0.006
ACE inhibitors	0.001	0.403
Nitrates	<0.001	0.890
Verapamil/diltiazem	0.010	0.006
Previous balloon angioplasty	0.007	0.026
Previous CABG	0.001	0.435
Impaired LV function†	<0.001	0.945
CCS angina class III or IV	0.004	0.081

*Cytochrome P450 2C19 681G>A; †impaired LV function (ejection fraction <55%).
ADP = adenosine diphosphate; RPA = residual platelet aggregation; other abbreviations as in Table 1.

Full regression model could only explain 11.5% of the antiplatelet response

Measuring Platelet Reactivity In Patients Receiving $P2Y_{12}$ Receptor Antagonists

Table 1. Methods to Measure the Effect of Clopidogrel on Platelet Function

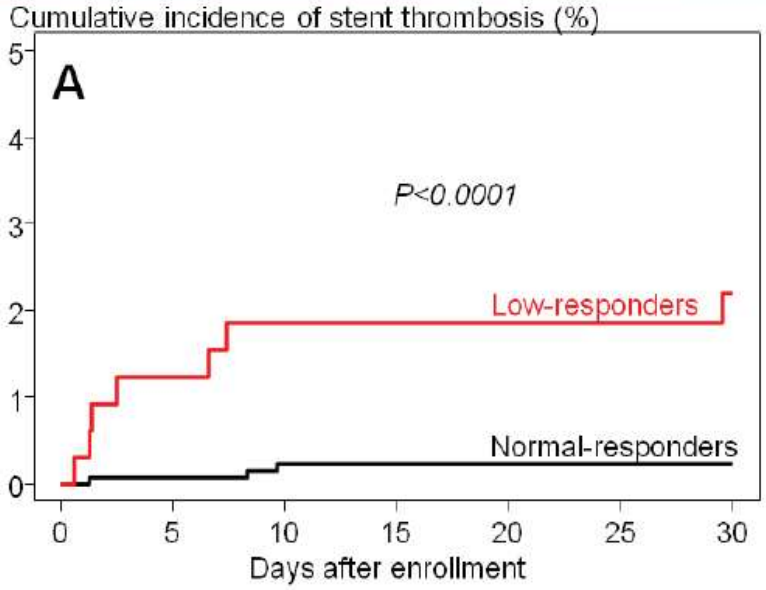
Assay	Methodology	Strengths	Weaknesses
LTA	Transmission of light through platelet-rich sample compared with platelet poor sample after exposure to ADP	Historical reference method	Lack of uniformity in agonist (ADP) concentration; difficult to integrate into clinical practice due to technical complexity
VASP	Phosphorylation status of VASP measured by flow cytometry after incubation with ADP and/or PGE_1	May most accurately reflect $P2Y_{12}$ receptor inhibition	Difficult to integrate into clinical practice due to technical complexity; number of patients with clinical outcome data relatively small
VN P2Y12	Agglutination of fibrinogen-coated beads by platelets in the presence of ADP (20 μmol) and PGE_1	True POC assay; largest number of patients studied with clinical outcomes	Association with clinical outcomes not well studied for surrogate measurement of percent inhibition provided by device without baseline preclopidogrel sample
Multiplate analyzer (MEA)	Change in electrical conductance between a pair of electrodes as platelets adhere after exposure to ADP	Whole-blood assay	Association with clinical outcomes shown only in large single-center study; not currently available in the United States
PlateletWorks	Difference in single-platelet counts by cell counter after stimulation with ADP vs baseline	Whole-blood assay	Association with clinical outcomes from single-center study; results highly depend on time between-sample collection and testing

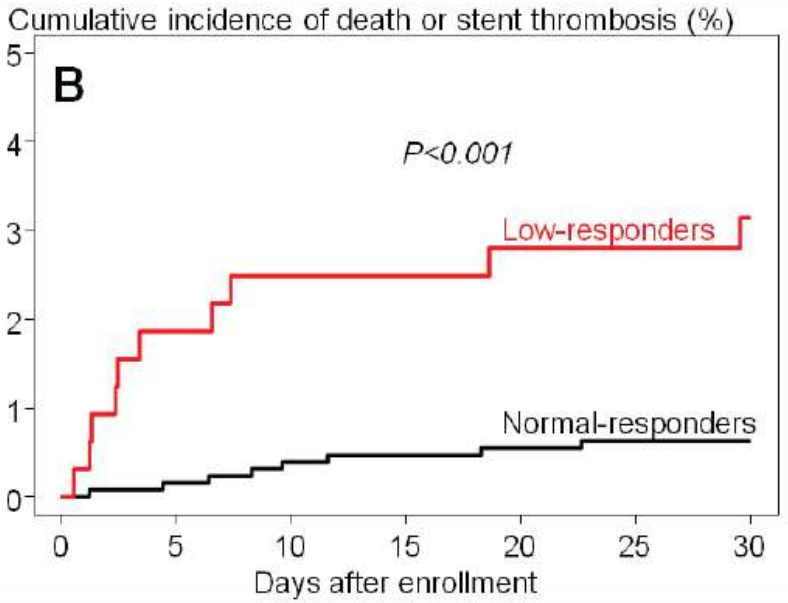
Price MJ, Circ CardiovascInterv, 2010. **3(3): 277-83**

Platelet Reactivity Following Clopidogrel Treatment Assessed With Point-of-Care Multiplate Analysis And Early Drug-Eluting Stent Thrombosis

ΙΝΣΤΙΤΟΥΤΟ ΘΡΟΜΒΩΣΗΣ ΑΙΜΟΣΤΑΣΗΣ

- 1608 consecutive patients with CAD and planned drug-eluting stent implantation
- Before PCI all patients received 600 mg clopidogrel
- The primary endpoint was definite ST at 30 days





Sibbing et al J Am Coll Cardiol. 2009, Mar 10;53(10):849-56.

"Bedside" Platelet Function Testing Can Identify Patients At-Risk For Ischemic Events after PCI

Clinically-Derived Cut-Offs from Prospective Studies:

Study	N	Device	Primary Endpoint	Cutoff	Method	Sens	Spec	NPV
Price et al	**380**	VN P2Y12	6M CV death, MI, ST	**PRU ≥ 235**	ROC curve	78%	70%	99%
Patti et al	**160**	VN P2Y12	30-day CV death, MI, TVR	**PRU ≥ 240**	ROC curve	81%	53%	nr
Marcucci et al	**683**	VN P2Y12	1 yr CV death, MI	**PRU ≥ 240**	ROC curve	61%	70%	96%
Sibbing et al	**1608**	Multiplate Analyzer	30-day Stent thrombosis	**468 AU·min**	ROC curve	70%	84%	nr
Breet et al	**1052**	VN P2Y12	1 yr death, MI, ST, CVA	**PRU ≥ 236**	ROC curve	nr	nr	nr
Campo et al	**826**	VN P2Y12	1 yr death, MI, CVA	**PRU ≥ 208**	ROC curve	69%	76%	nr

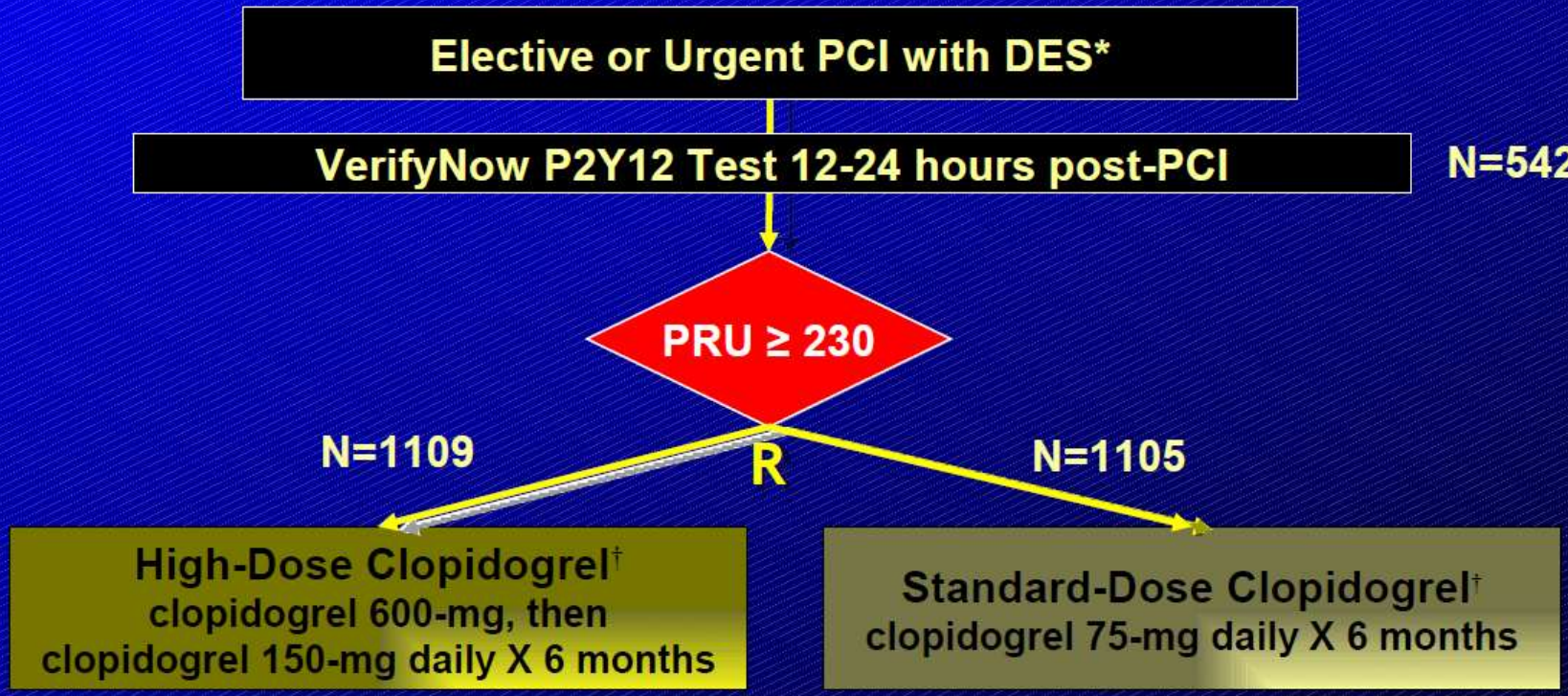
Sibbing et al, J Am Coll Cardiol 2009;53:849-856
Marcucci et al, Circulation 2009; 20;119(2):237-42
Patti, G. et al. J Am Coll Cardiol 2008;52:1128-1133
Price MJ et al. Eur Heart J 2008; 29(8):992-1000
Campo G et al., J Am Coll Cardiol, 2010. 56(18): 1447-55

nr = not reported

Adapted from Price MJ, Circ Cardiovasc Interv 2010 Jun 1;3(3):277-83

Price MJ, AHA 2010

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

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)

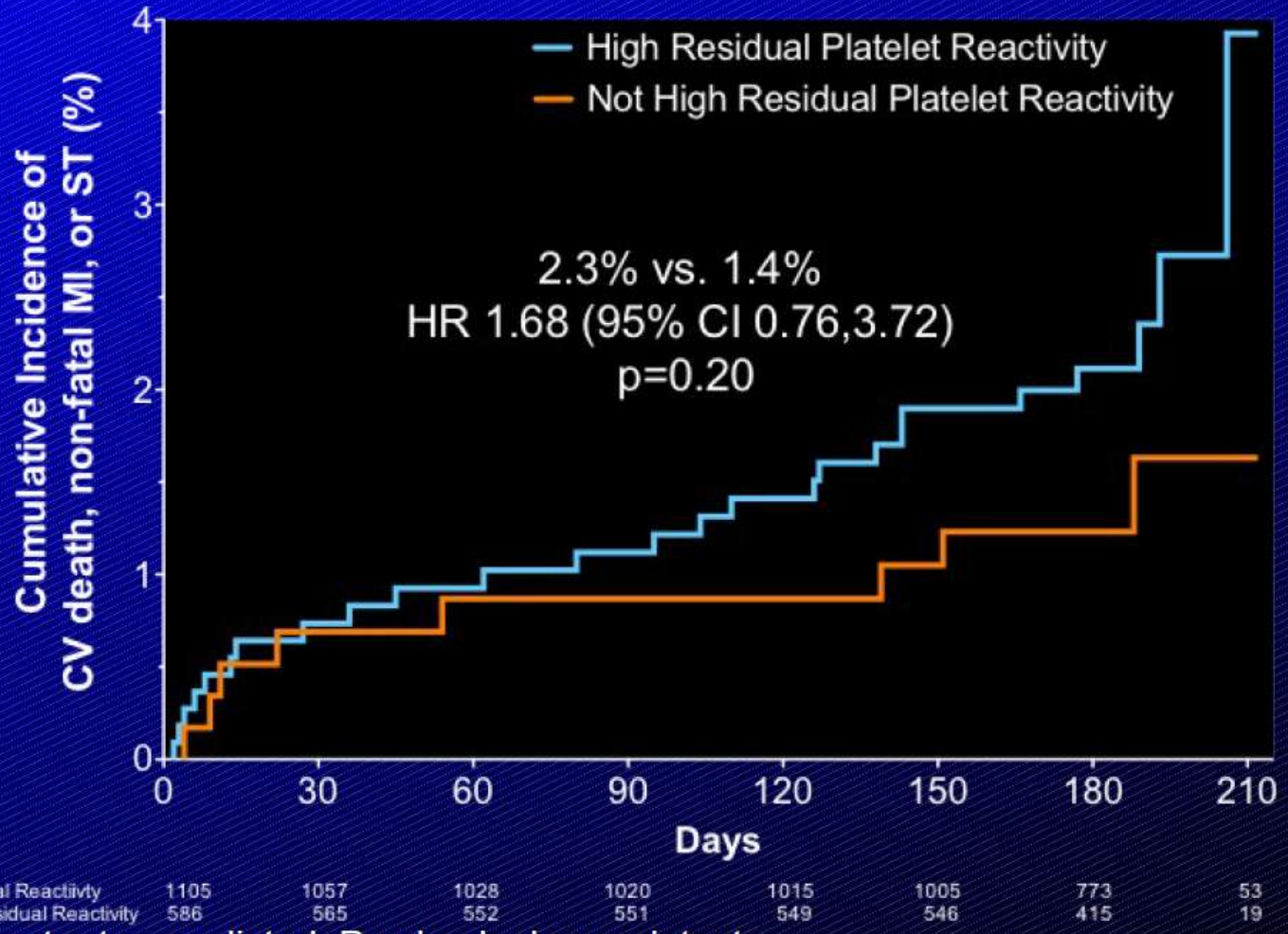
Clopidogrel High Dose N=1109

Clopidogrel Standard Dose N=1105

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

GRAVITAS

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

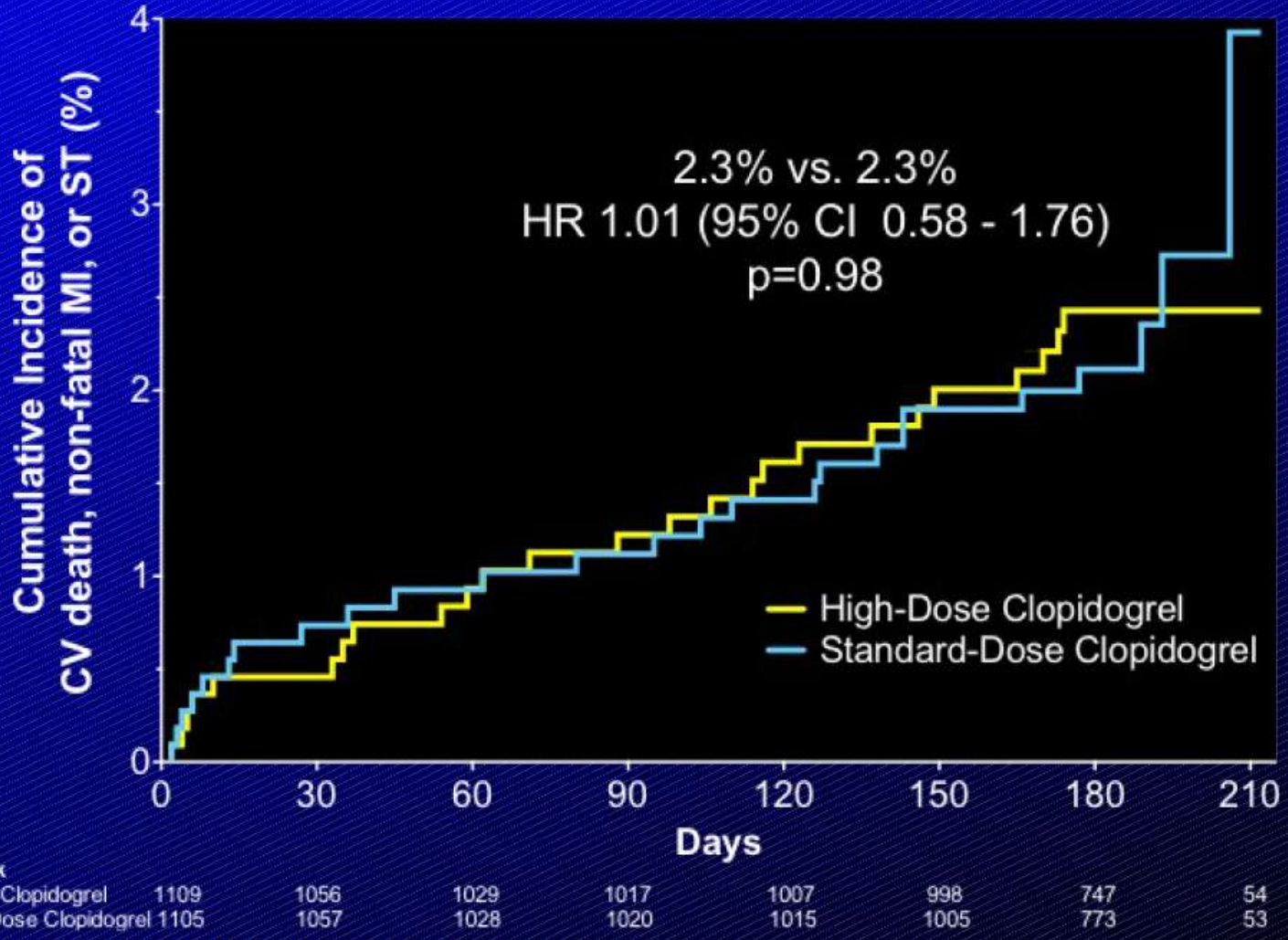


Observed event rates are listed. P value by log-rank test.

Price MJ, AHA 2010

GRAVITAS

GRAVITAS: Standard- vs High-Dose Clopidogrel in Patients with On-Treatment Reactivity ≥ 230 PRU Post-PCI



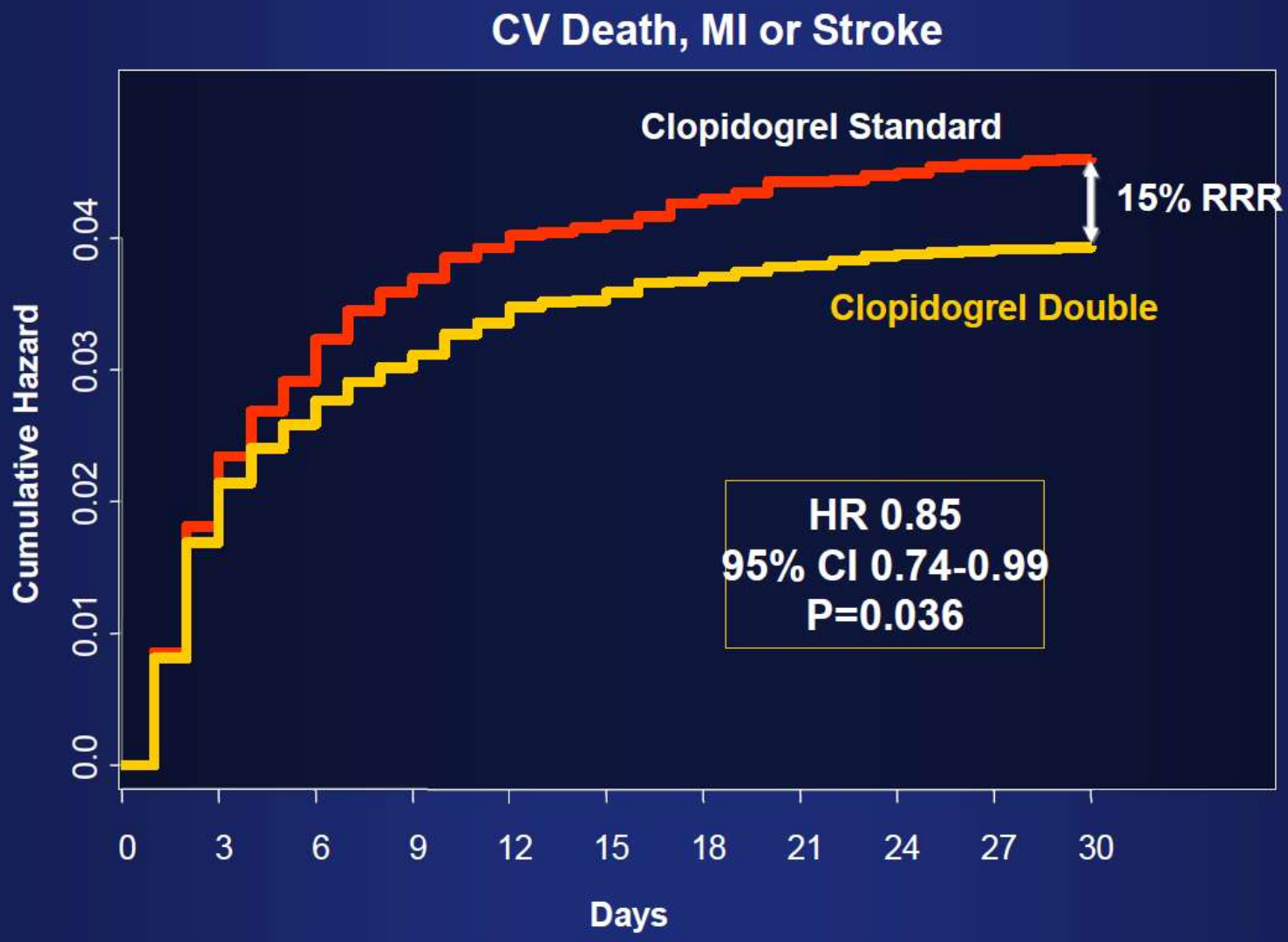
No. at Risk								
High Dose Clopidogrel	1109	1056	1029	1017	1007	998	747	54
Standard Dose Clopidogrel	1105	1057	1028	1020	1015	1005	773	53

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

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

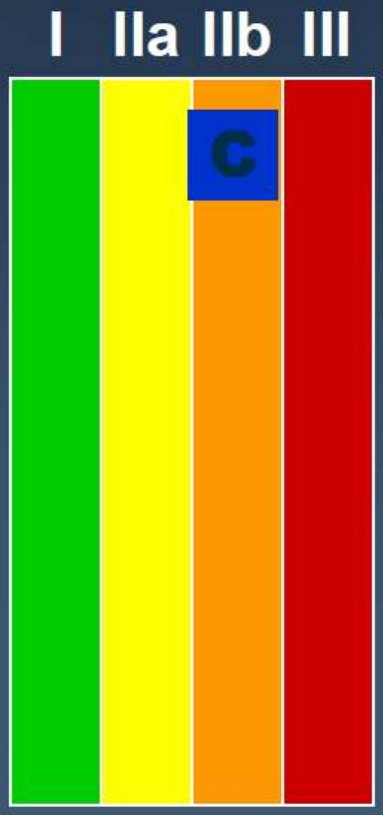
GRAVITAS

Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients

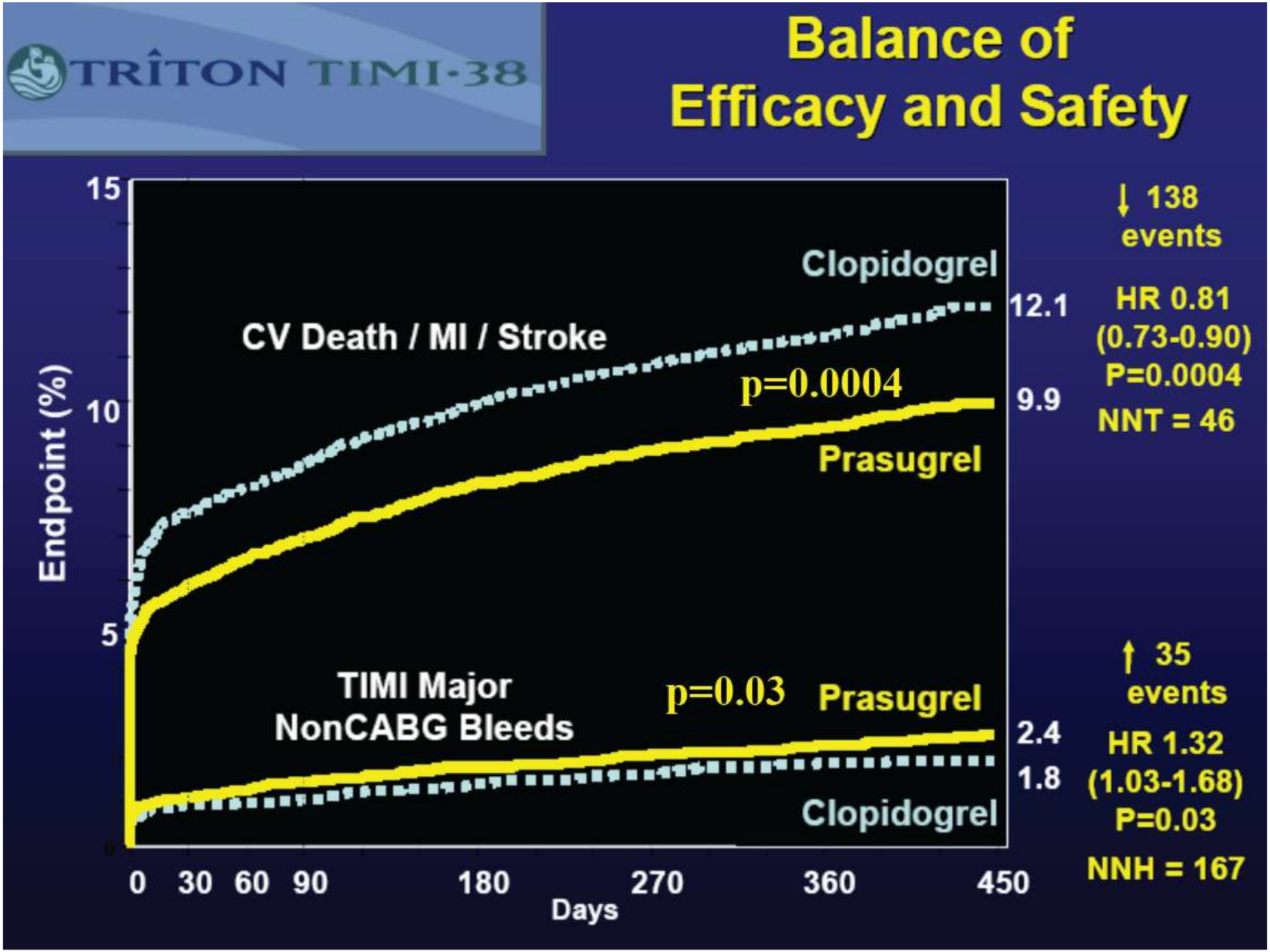


ACC/AHA/SCAI Guideline Update for PCI

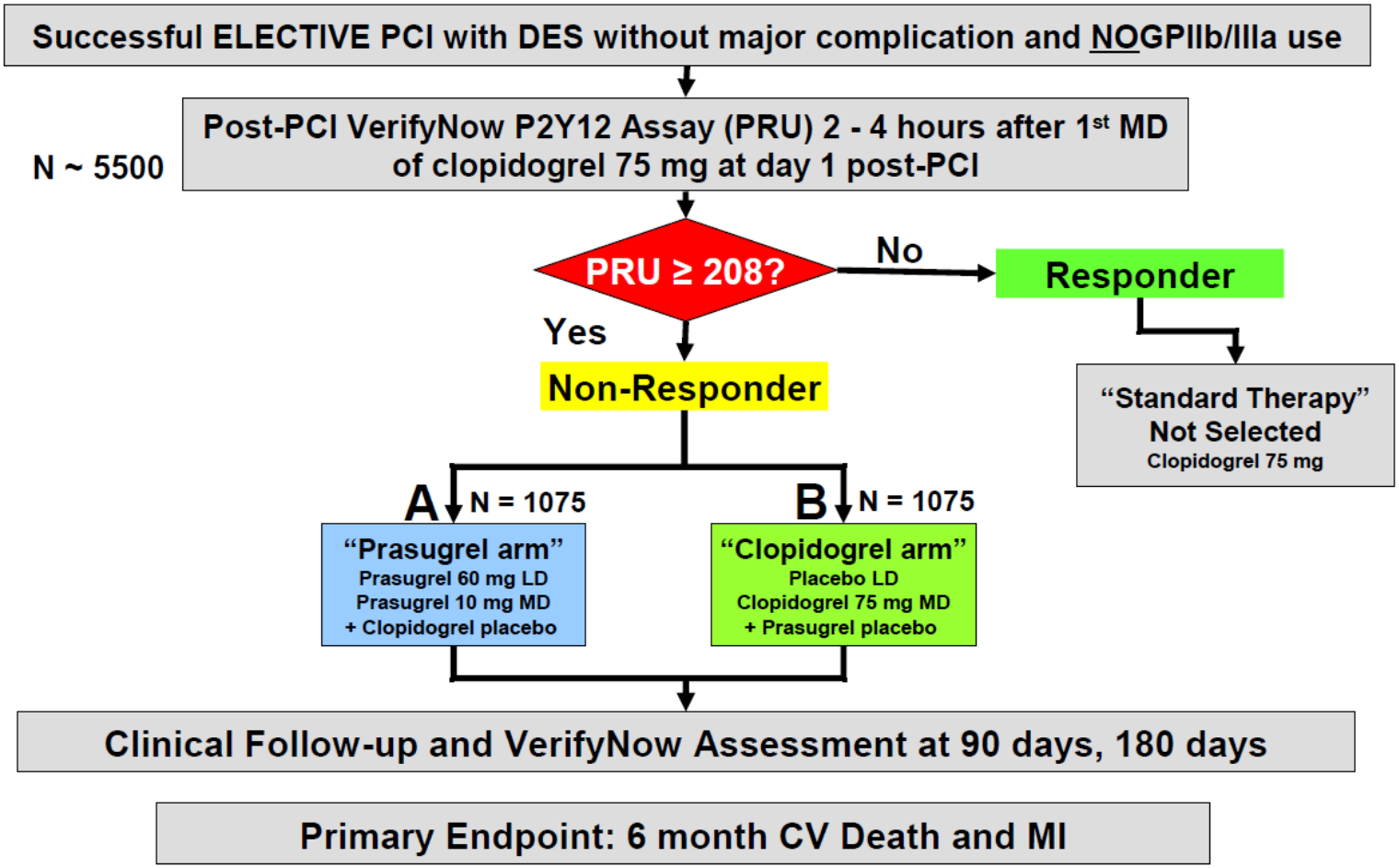
Oral Antiplatelet Adjunctive Therapies



In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated.


TRÎTON TIMI-38
Balance of Efficacy and Safety
Endpoint (%)
15
10
5
0
CV Death / MI / Stroke
Clopidogrel
Prasugrel
p=0.0004
12.1
9.9
↓ 138 events
HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46
TIMI Major NonCABG Bleeds
p=0.03
Prasugrel
Clopidogrel
2.4
1.8
↑ 35 events
HR 1.32
(1.03-1.68)
P=0.03
NNH = 167
0 30 60 90 180 270 360 450
Days

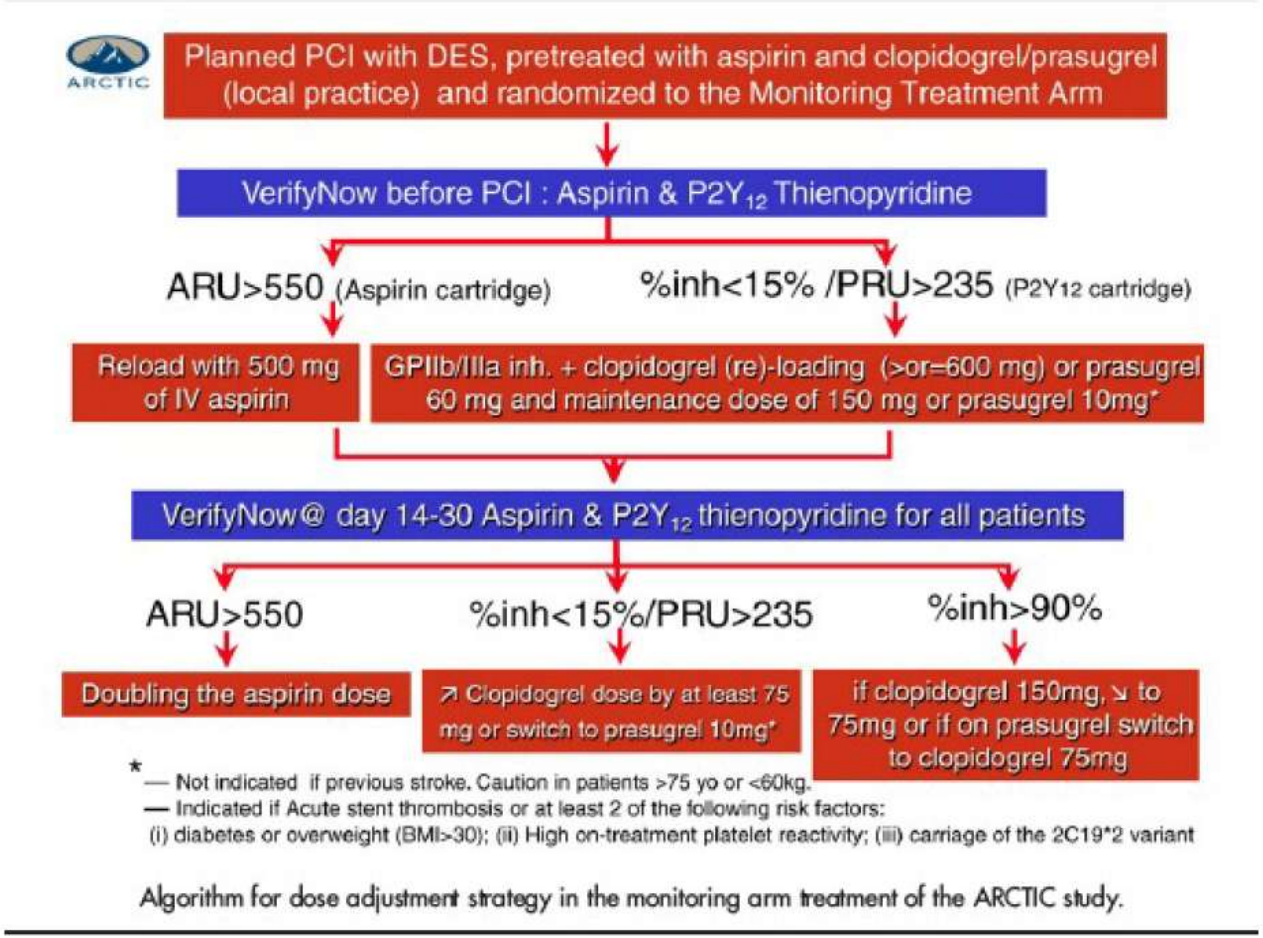
TRIGGER-PCI



ClinicalTrials.gov Identifier: NCT00910299

ARCTIC Trial

N=2500: PFT vs no PFT



Algorithm for dose adjustment strategy in the monitoring arm treatment of the ARCTIC study.

Primary Endpoint: Death, MI, urgent revasc, ST, stroke

Collet JP et al, Am Heart J, 2011. 161(1): 5-12

PLATO study design

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

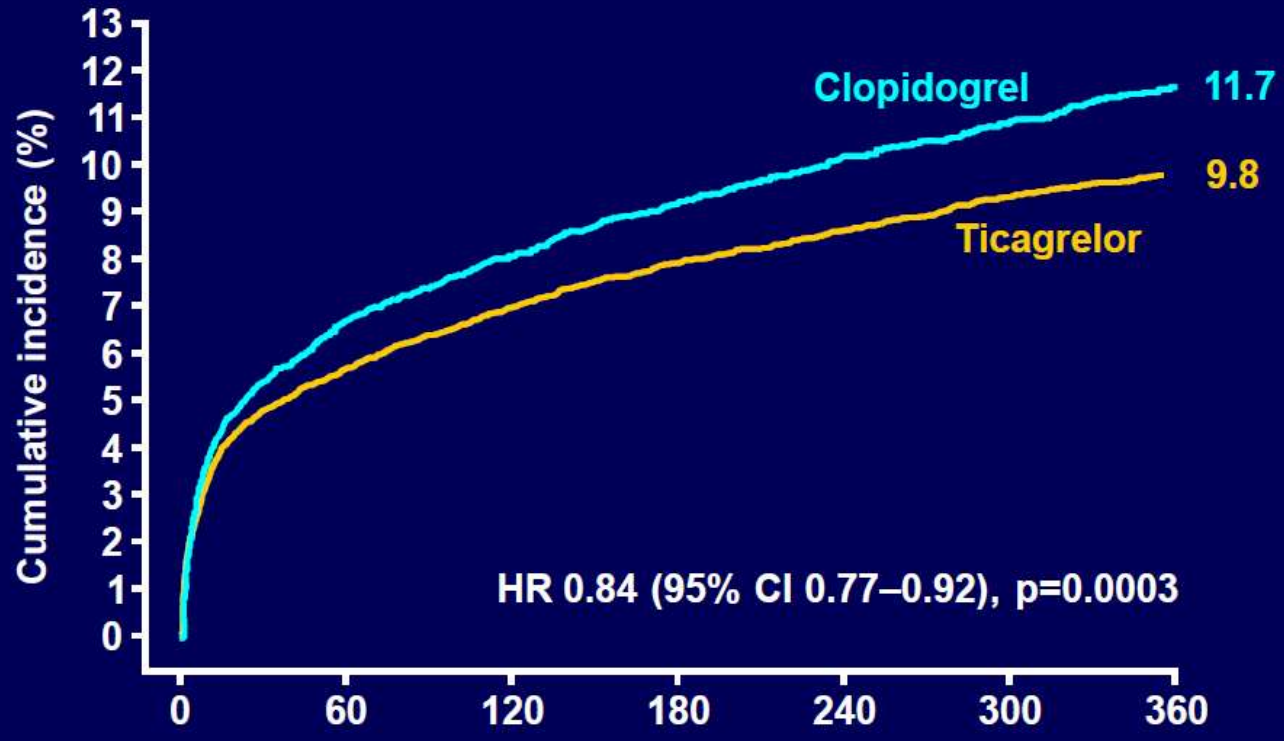
6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

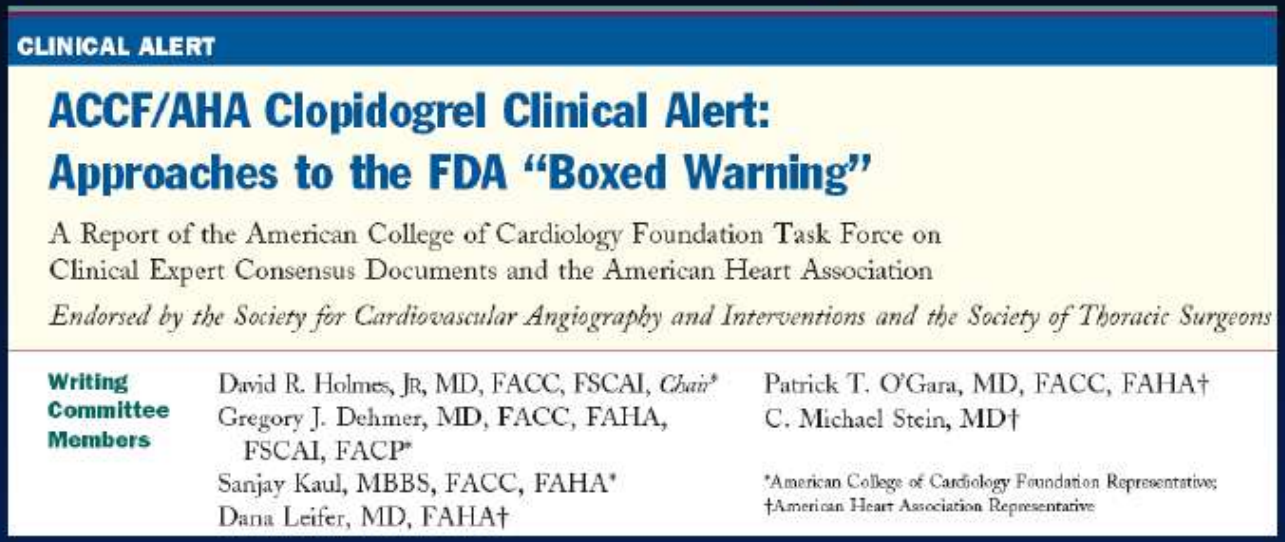
PLATO



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

"Expert Consensus Opinion"



CLINICAL ALERT

ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning"

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

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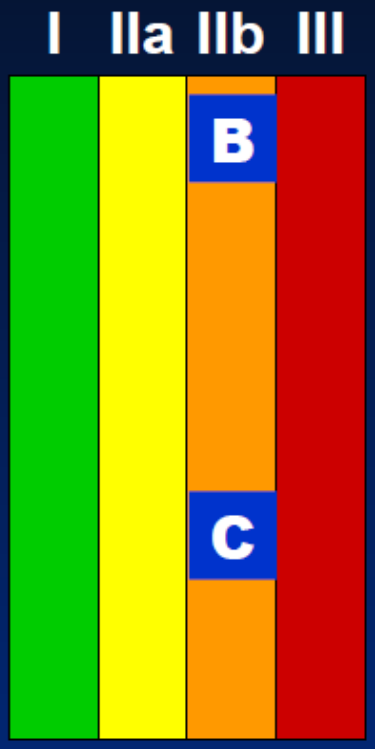
Genetic Testing

Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism ("poor metabolizers") may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes. This might include, among others, patients undergoing elective high-risk PCI procedures (e.g. treatment of extensive and/or very complex disease). If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel for coronary patients, should be considered.

Recommendations for Additional Management of Antiplatelet and Anticoagulant Therapy

New Recommendation



Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management

Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management

Class IIb: Benefit ≥ Risk; ***Treatment may be considered***
Additional studies w/broad objectives needed; additional registry data would be helpful.

Take home messages

- Clinical, genetic and pharmacokinetic factors contribute to the wide variability in response to antiplatelet treatment
- The absolute magnitude of ADP-induced platelet reactivity at the time of PCI is associated with an increased risk of atherothrombotic events or bleeding
- The phenotype of resistance to antiplatelet treatment is a dynamic phenomenon
- There is a need to further define a therapeutic window for oral antiplatelet treatment with clopidogrel or newer agents such as prasugrel.
- For the individual patient undergoing coronary stent placement, the information provided by genetic and platelet function testing may be complementary in improving patients' outcomes
- Optimisation of antiplatelet treatment requires multidisciplinary diagnistic and therapeutic approach