Variability in Responsiveness to Antiplatelet Therapy

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1. What do we know about it?
2. How do we define it?
3. What causes it?
4. What do we do about it?

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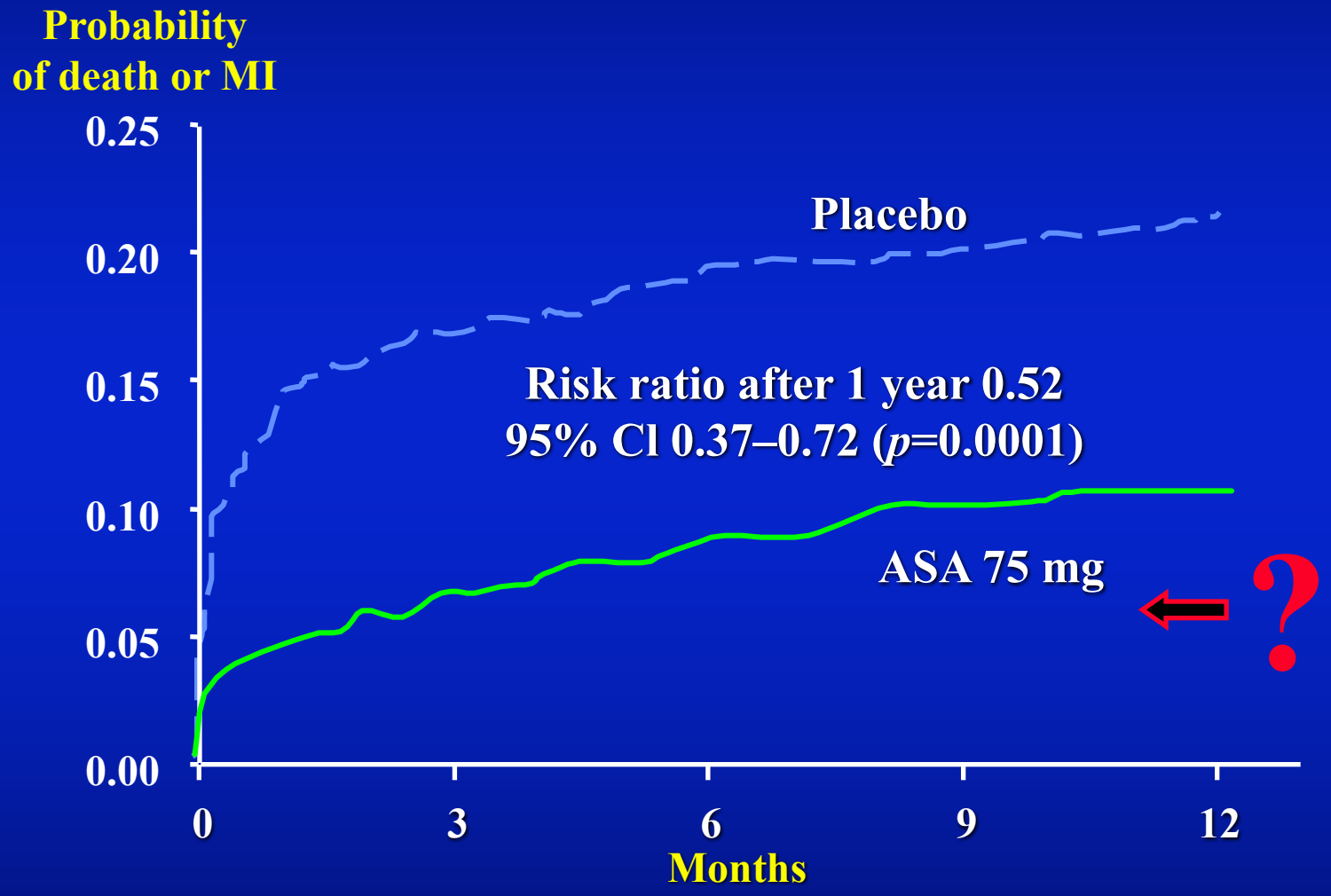
Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina

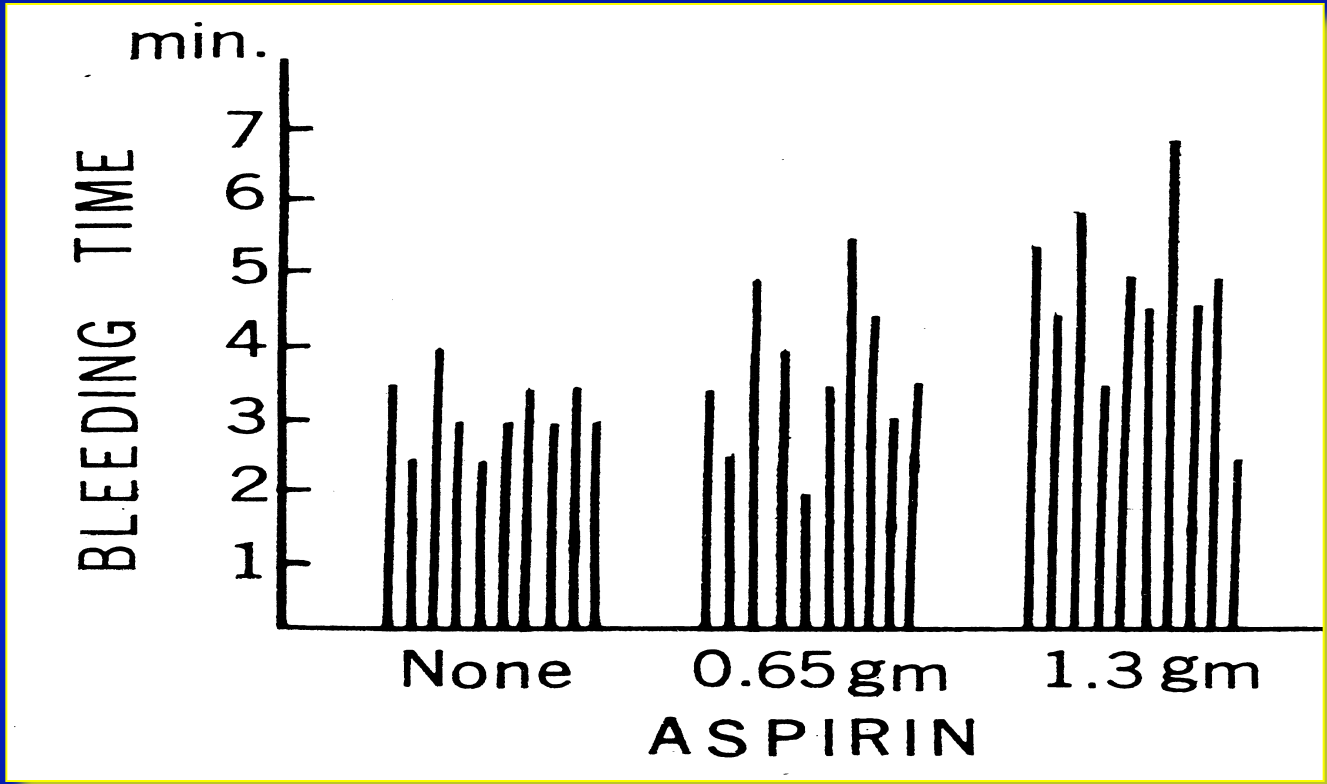


Wallentin LC et al *JACC* 1991;18:1587–1593

People still have events while on ASA!

Do all patients respond in the same way?

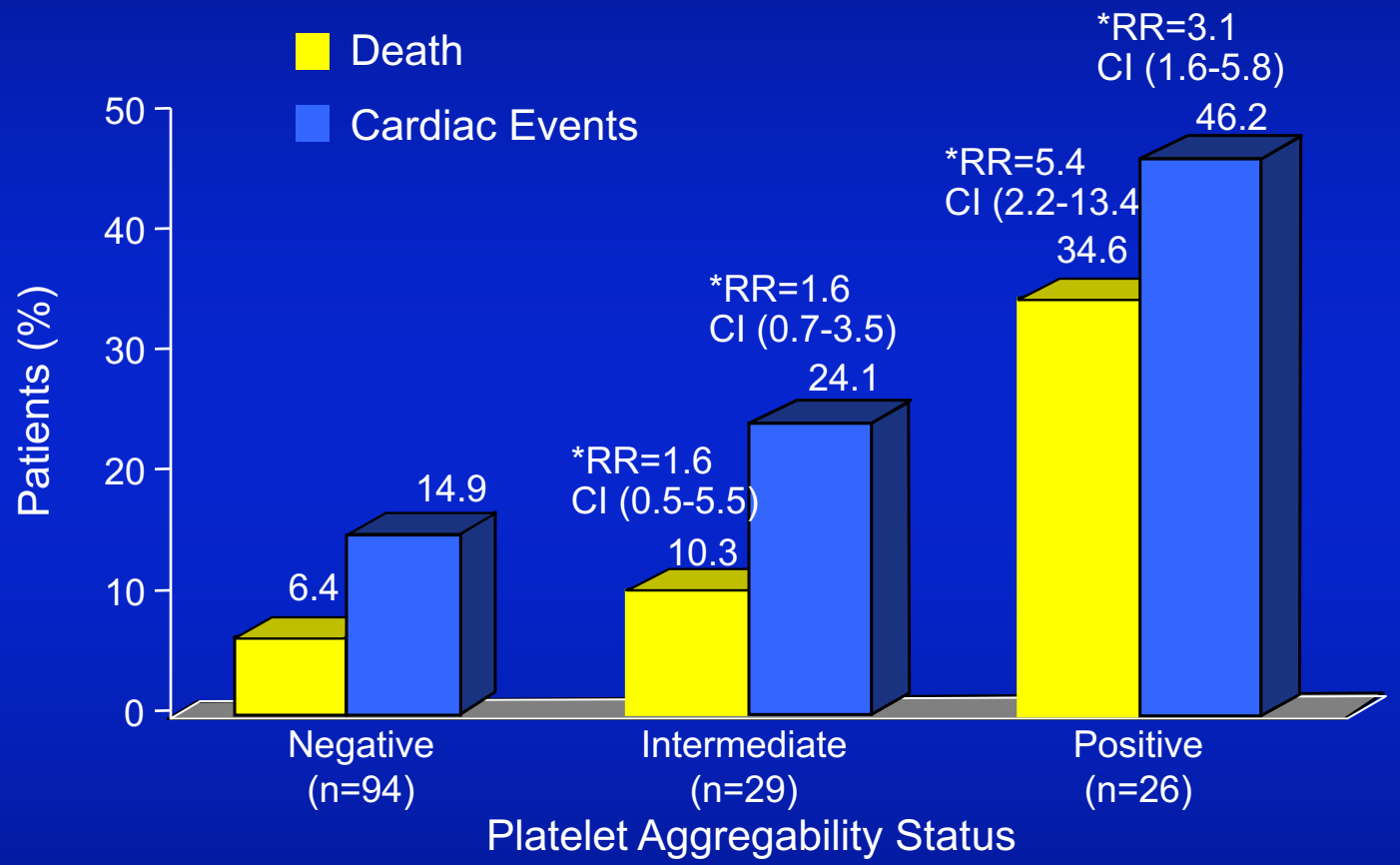
Inter-Individual Variability in Response to ASA



N=10

Quick AJ.
American Journal of Medical Science
Sept 1966:265-9

Platelet Hyperreactivity Following ACS Predicts 5-Year Outcomes



*Relative risk compared to group with negative aggregation.

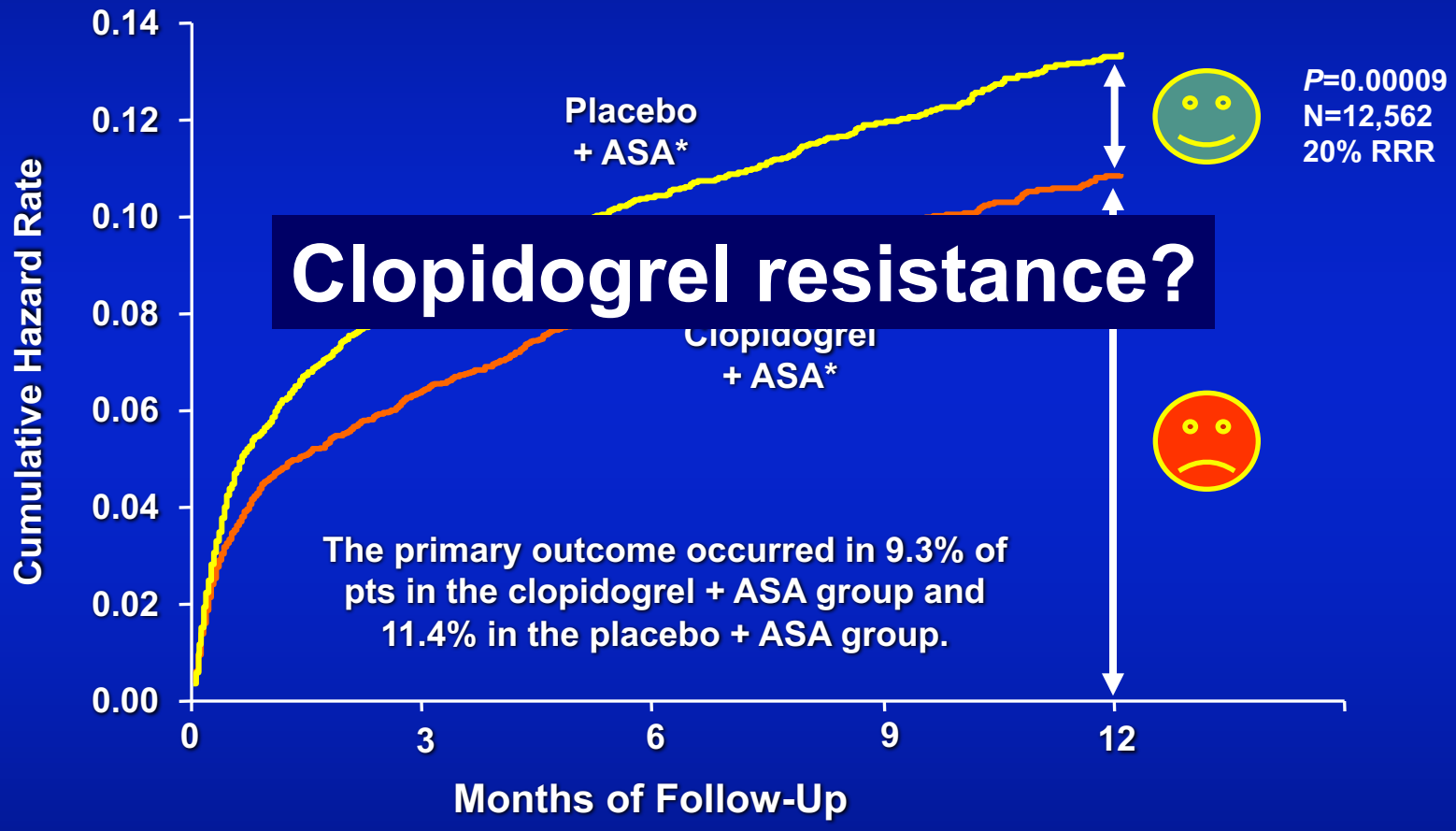
Trip MD, et al. *N Engl J Med.* 1990;322:1549-1554.

ASA Resistance: Long-term Clinical Studies

Pts	ASA dose	Test	F/U	End-point	Results
Stroke[1] (n=180)	1500 mg	Plt Reactivity	24 m	Stroke/MI/ Vascular death	10-fold lower risk in ASA responders
PVD[2] (n=100)	100 mg	Whole blood Agregometry	18 m	Arterial Occlusion	87% higher risk in ASA-R
CVD/CVA[3] (n=53) TIA	100 mg	PFA-10	>60 m	Recurrent CVA/ TIA	Recurrent CVA 34% ASA-R vs. 0% no recurrent events
Subgroup HOPE[4] (n=967)	75-325 mg	Urinary 11-dehydro TX B2	5 yrs	MI/Stroke/ CVDeath	1.8 times higher risk in upper vs. lower quartile
CVD[5] (n=326)	325 mg	Optical platelet aggregation	679±185 days	Death/MI/CVA	24% ASA-R vs. 10% ASA-S [HR 3.12 (95% CI 1.1-8.9, p=0.03)

1. Grotemeyer KH, et al. *Thromb Res* 1993; 71:397-403
2. Mueller MR, et al. Thromb Haemost 1997; 78:1003-1007
3. Grundmann K, et al. *J Neurol* 2003; 250: 63-66
4. Eikelboom JW, et al. *Circulation* 2002; 105:1650-1655
5. Gum PA, et al. *J Am Coll Cardiol* 2003; 41:961-965

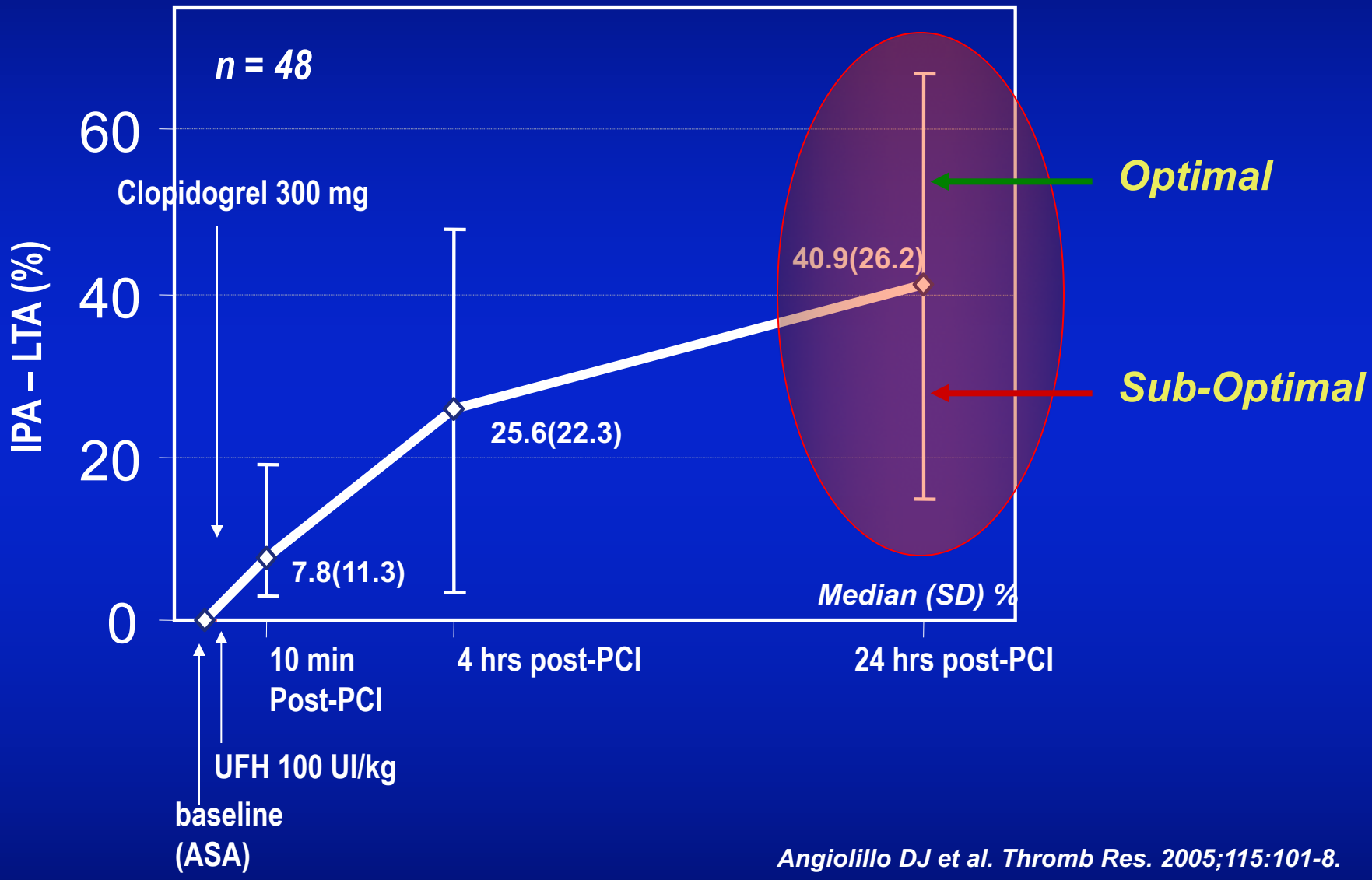
Primary Endpoint—MI/Stroke/CV Death



*Other standard therapies were used as appropriate.

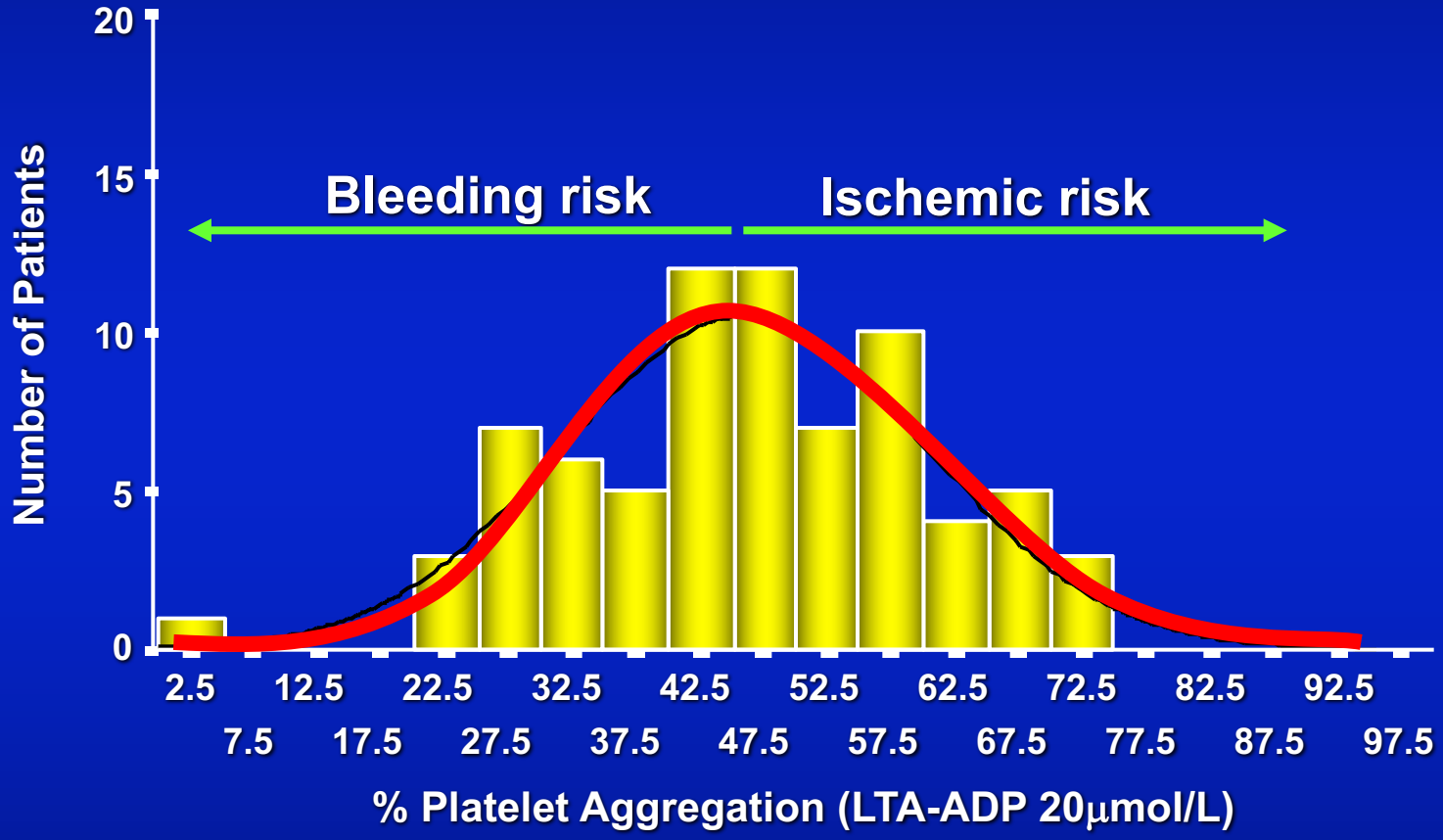
Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

Clopidogrel Response Variability following Loading Dose Administration



Angiolillo DJ et al. Thromb Res. 2005;115:101-8.

Individual Response Variability to Dual Antiplatelet Therapy in the *Steady State Phase* of Treatment



Adapted from Angiolillo DJ et al. *Am J Cardiol.* 2006;97:38-43.

Clinical Relevance of Clopidogrel Non-responsiveness

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.*

Clinical Relevance of Clopidogrel Non-responsiveness

Stent Thrombosis

	N	Functional Parameter	Clinical Relevance
Mueller et al. Thromb Haemost 2003	105	↓inhibition of platelet aggregation	Stent thrombosis
Barragan et al. CCI 2003	36	↑$P2Y_{12}$ reactivity ratio (VASP-levels)	Stent thrombosis
Gurbel et al. JACC 2005	120	↑$P2Y_{12}$ reactivity ratio; ↑platelet aggregation; ↑stimulated GPIIb/IIIa expression	Stent thrombosis
Ajzenberg et al. JACC 2005	49	↑shear-induced platelet aggregation	Stent thrombosis
Buonamici et al JACC 2007	804	↑ platelet aggregation	Stent thrombosis

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

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Definition(s) of "APT Resistance?"

The fact that some patients may experience recurrent vascular events despite the use of APT should be properly defined as "*treatment failure*" rather than "*APT resistance*" (multiple pathways mediate thrombotic events).

APT Resistance/Non-responsiveness = Failure to inhibit the target

APT Resistance/Non-responsiveness ≠ Clinical failure

Platelet Function Tests

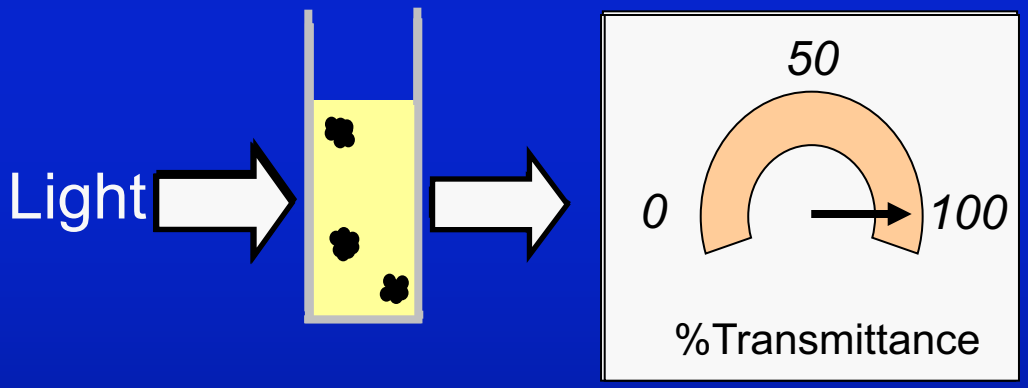
- **Platelet Aggregation**
  - Light transmittance aggregometry (LTA) ← *gold standard*
  - Impedance platelet aggregation
- **Flow Cytometry**
  - GPIIb/IIIa receptor activation
  - P-selectin expression
  - Monocyte-platelet aggregates
  - Vasodilator-associated stimulated phosphoprotein (VASP)
- **Point-of-care**
  - Ultegra rapid platelet function analyzer (VerifyNow)
  - Thromboelastagraph (TEG)
  - PFA-100
  - Plateletworks
  - Cone and plate(let) analyzer (IMPACT)
- **Genetic testing**

adapted from Angiolillo DJ et al. J *Am Coll Cardiol*. 2007

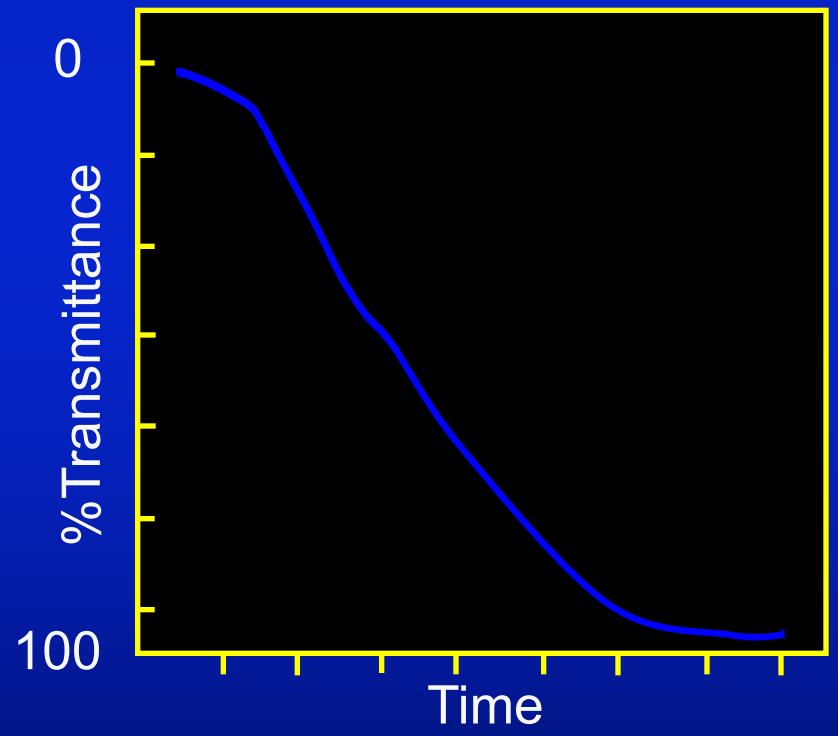
Light Transmittance Aggregometry

Test of platelet aggregation

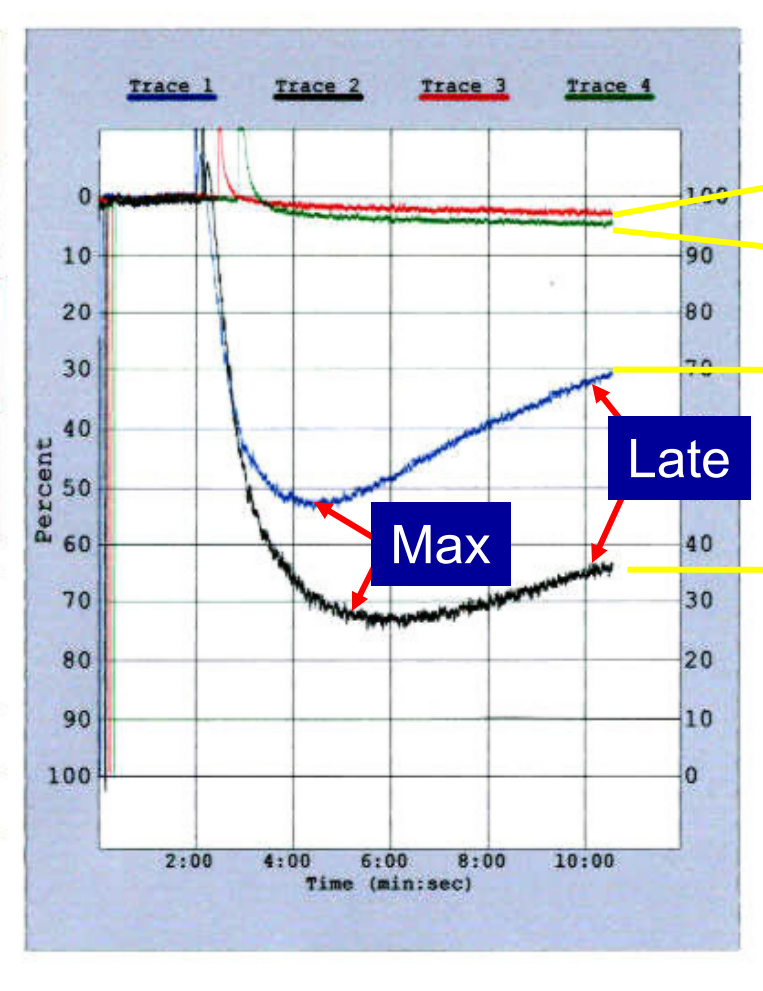
- Agonist (e.g., ADP, collagen, arachidonic acid, epinephrine) added to platelet rich plasma
- Platelet aggregation is monitored by change in light transmittance



Agonist added at Time=0



Light Transmittance Aggregometry



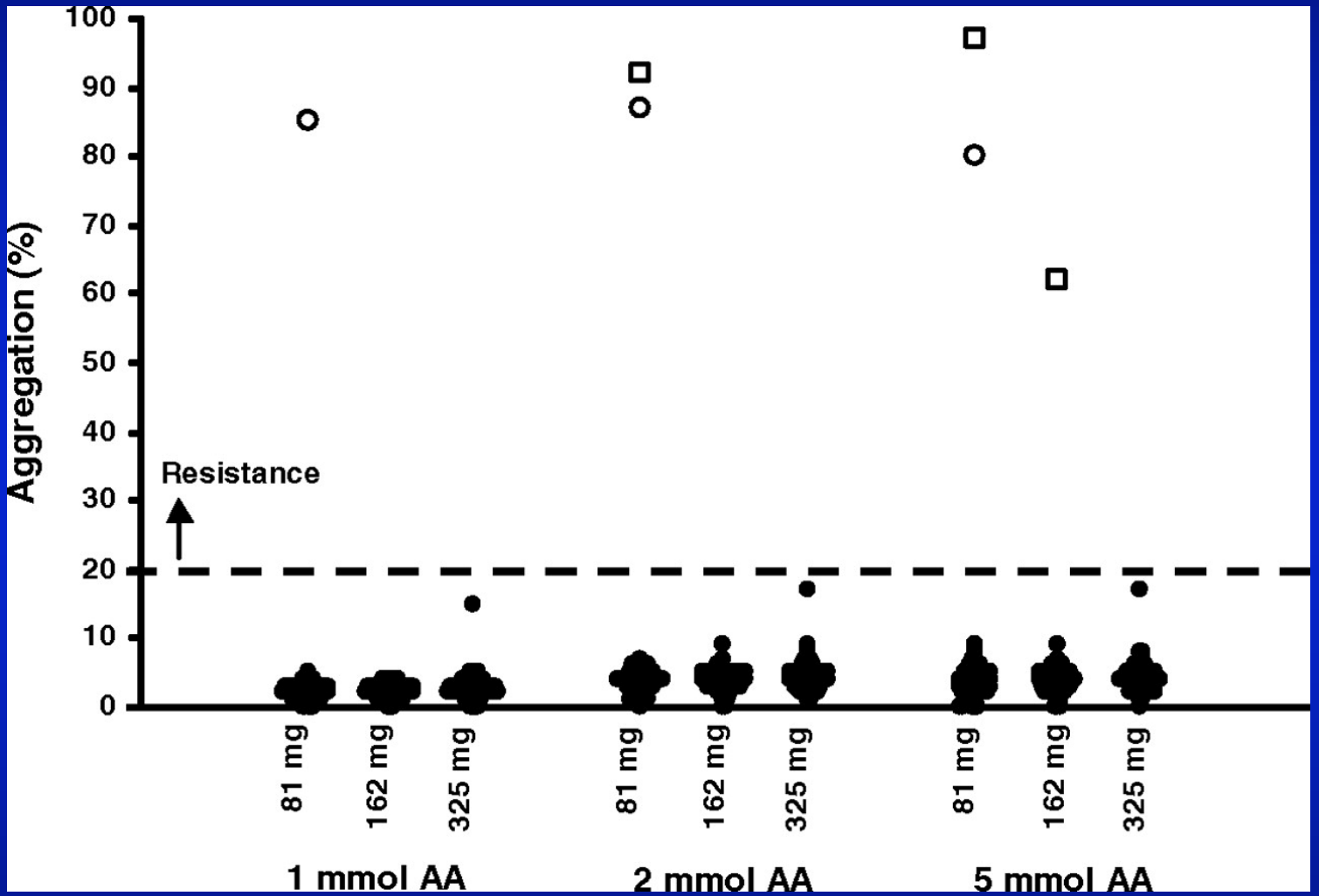
1 mM AA = 2%

2 mM AA = 4%

5 µM ADP = 54%

20 µM ADP = 74%

ASPECT study: Individual platelet aggregation data measured after stimuli by 3 concentrations of AA by LTA at 3 different doses of aspirin



Gurbel, P. A. et al. Circulation 2007;115:3156-3164

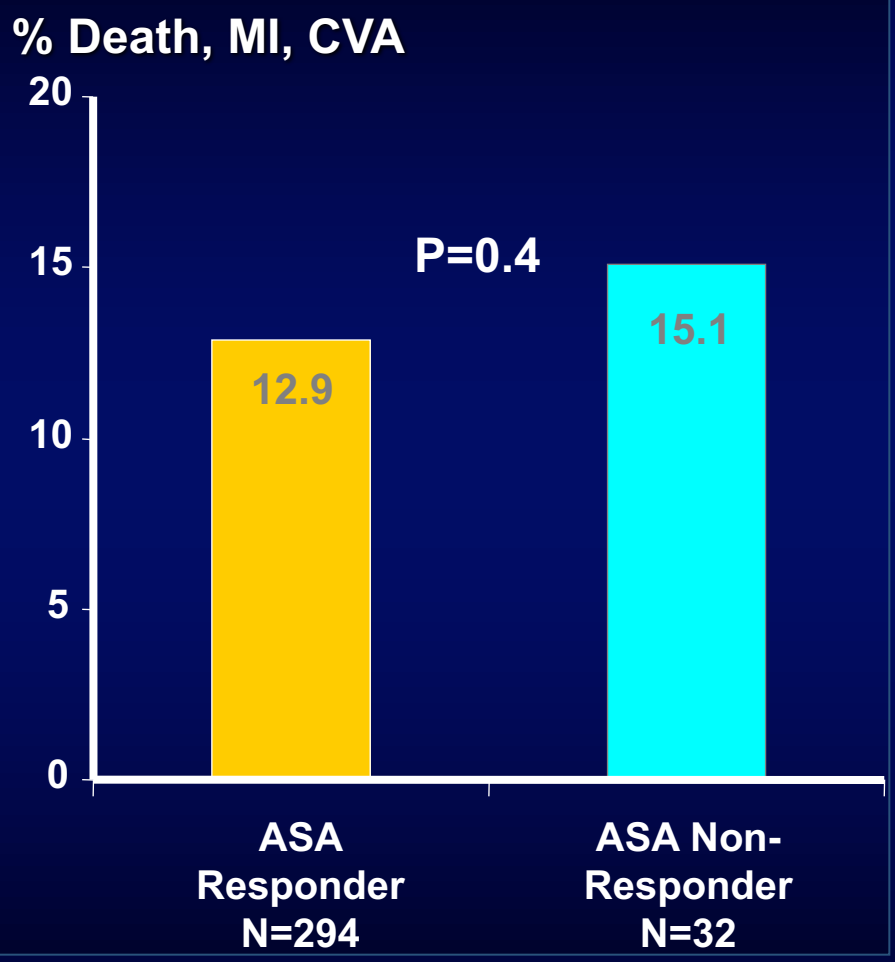
ASPECT study: Effects of Assay and Dose on Measurement of Aspirin Resistance

	Resistance (n)					
	81 mg	162 mg	325 mg	≥1 Dose	2 Doses	3 Doses
LTA						
1 mmol/L AA	1	0	0	1	0	0
2 mmol/L AA	2	0	0	2	0	0
5 mmol/L AA	2	1	0	2	1	0
2 µg/mL Collagen	12	2	1	14	1	0
5 µmol/L ADP	19	11	10	27	7	3
TEG-1 mmol/L AA	5	3	5	11	2	0
VerifyNow	7	4	4	13	2	0
Urinary 11-dehydro- Thromboxane B_2	31	22	14	42	16	5
PFA-100	32	14	21	42	15	5

Gurbel, P. A. et al. Circulation 2007;115:3156-3164

Clinical Outcomes: Aspirin Responsiveness by Aggregometry And PFA-100

Clinical Outcomes based on PFA-100 Results CEPI-CT≤193 s



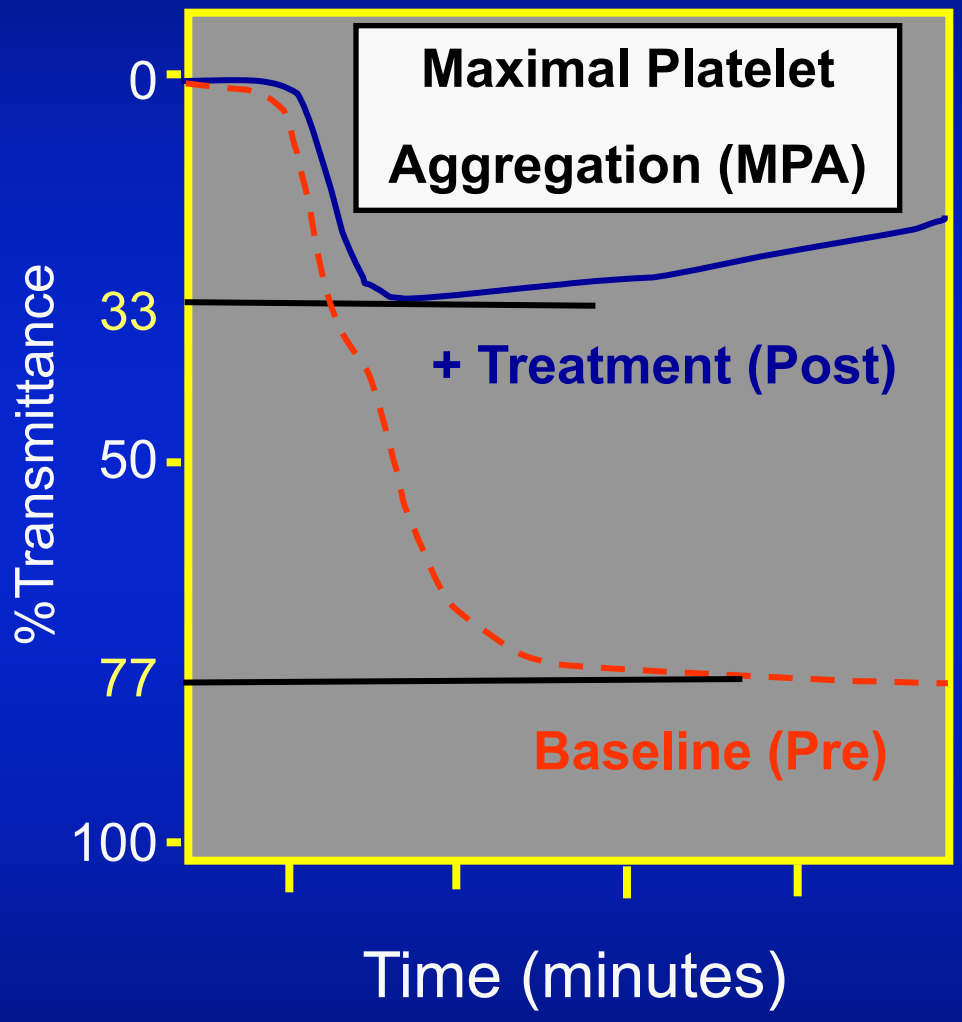
Gum, P. JACC 2003;41:961-5

Light Transmittance Aggregometry

Inhibition of Platelet Aggregation (IPA)

$$IPA = \frac{(MPA_{Pre} - MPA_{Post}) X\ 100\%}{MPA_{Pre}}$$

$$57\% = \frac{(77 - 33)\ X\ 100\%}{77}$$



Definitions of Non/Low – Response using LTA

Gurbel PA et al.,
Circulation 2003

Absolute change in platelet aggregation
ine < 10%

Müller I et al.,
Thromb Haemostas 20

nange in platelet aggregation
ine < 10%

Matetzky S et al.,
Circulation 2004

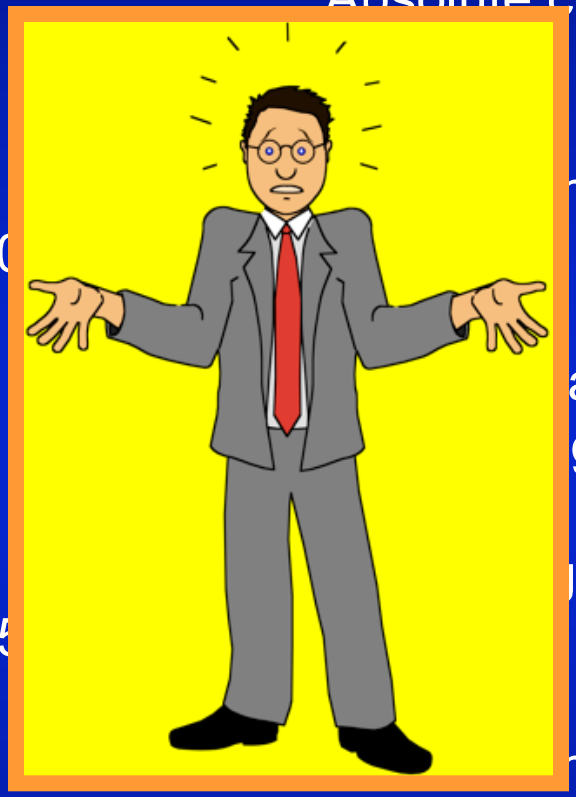
artile of relative reduction of
gregation

Serebruany VL et al.,
J Am Coll Cardiol 2005

gregation 2 standard
below mean

Angiolillo DJ et al.,
Thromb Res 2005

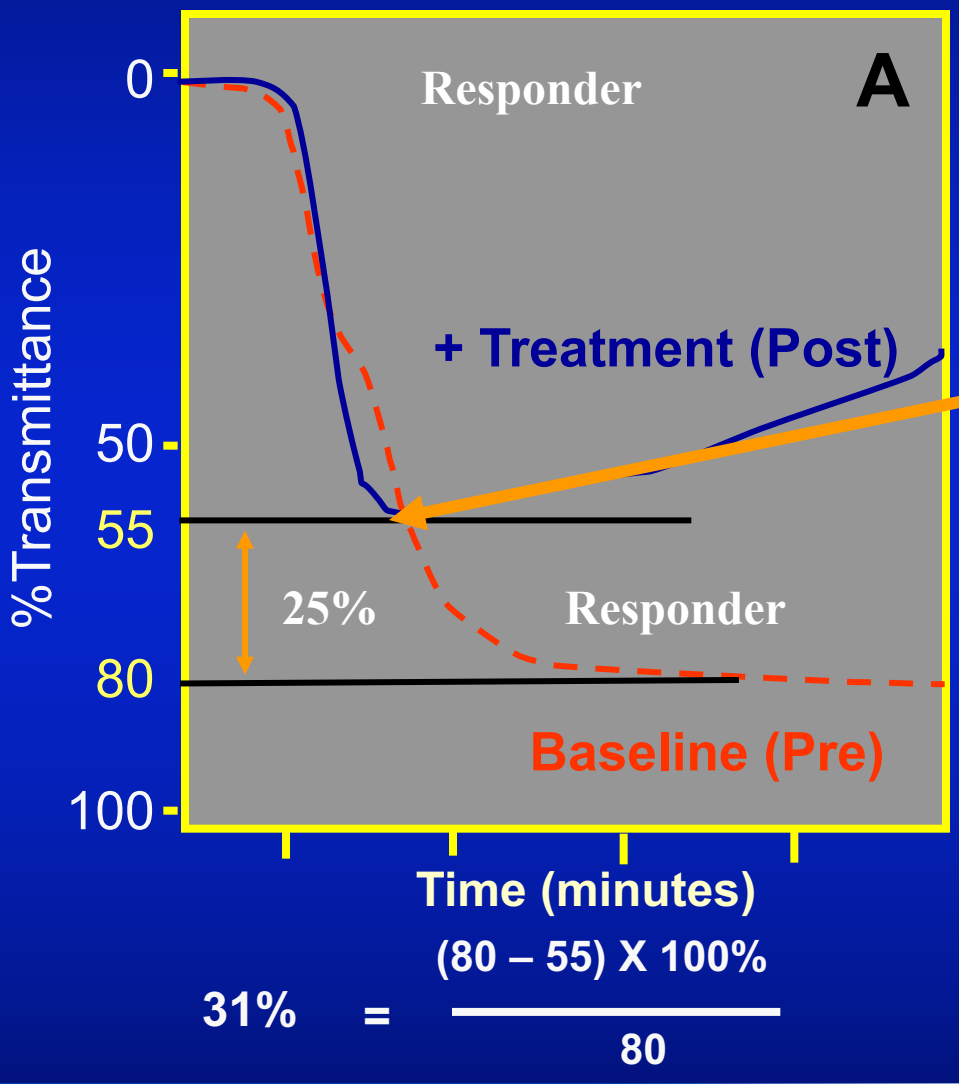
nange in platelet aggregation
from baseline < 40%



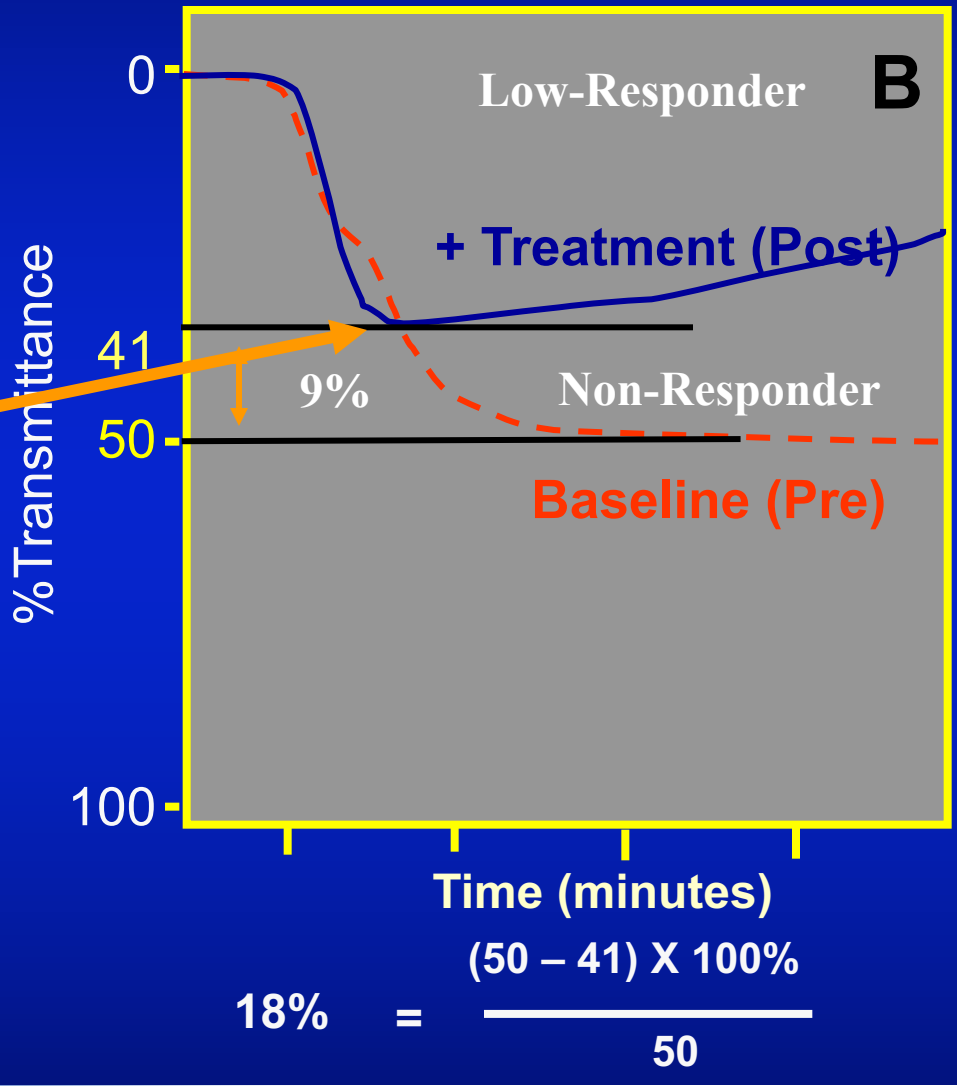
(Variable results also depending on the concentration of ADP used)

Definitions of Non-Response: Which one should we use?

Absolute Change or Relative Change or Post-treatment platelet reactivity?

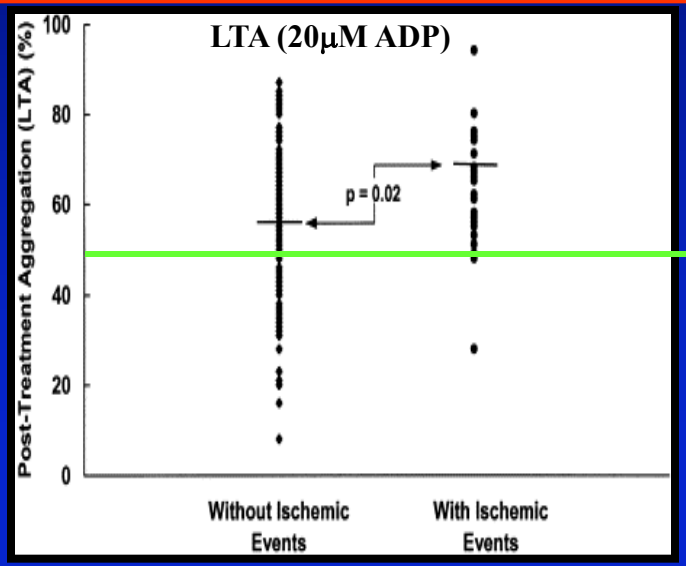


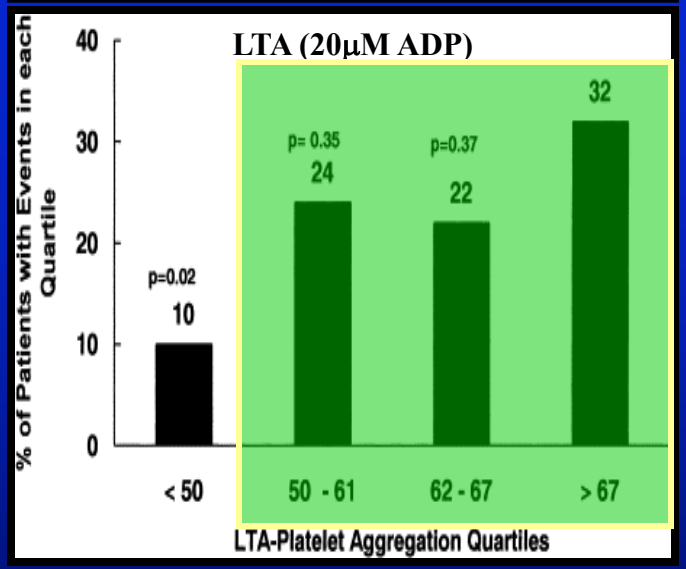
$$31\% = \frac{(80 - 55) \times 100\%}{80}$$



$$18\% = \frac{(50 - 41) \times 100\%}{50}$$

Platelet Reactivity in Patients and Recurrent Events Post-Stenting: Results of the PREPARE POST-STENTING Study



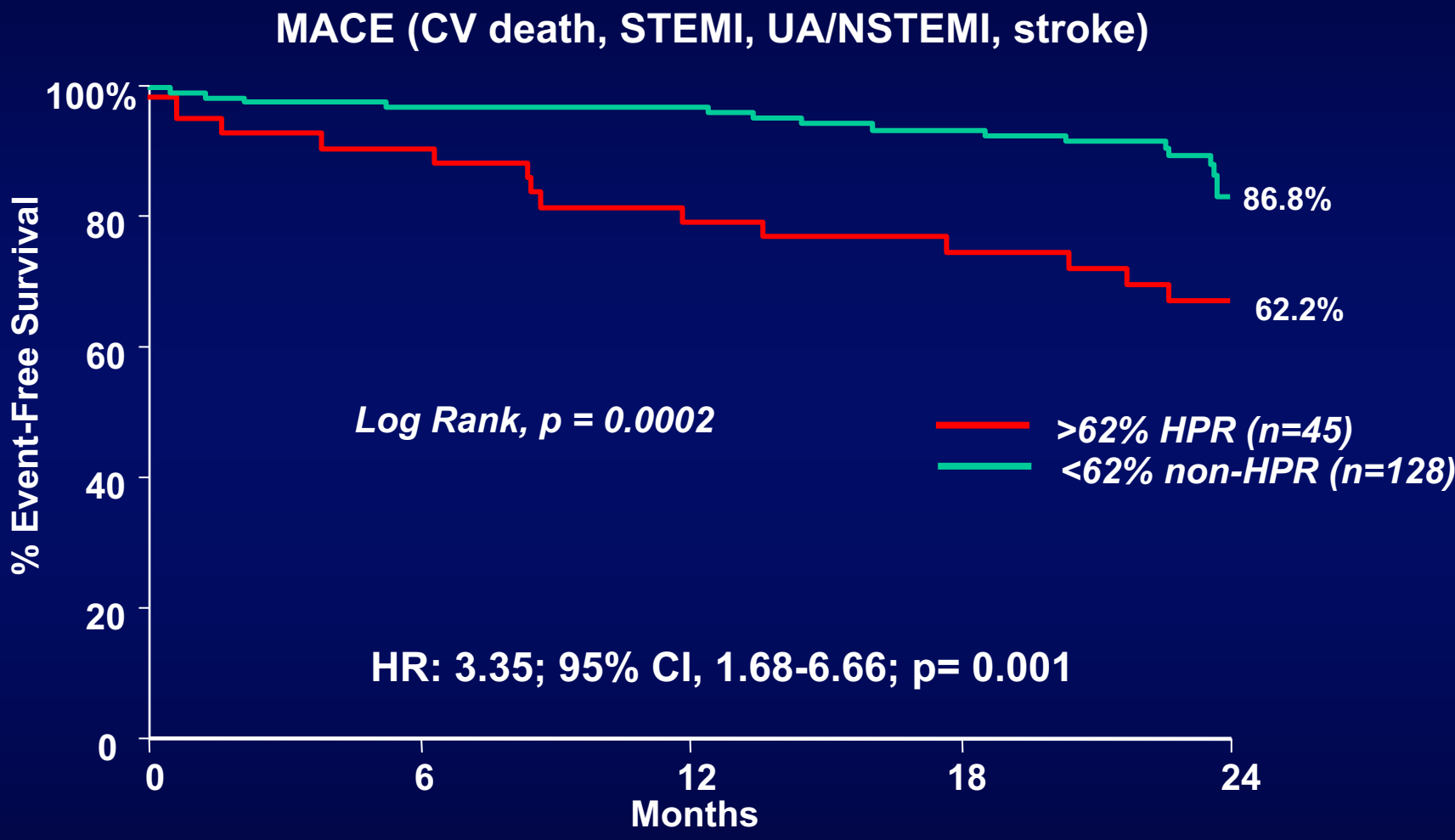


Therapeutic target for $P2Y_{12}$ inhibition (?)

Prospective studies with "tailored" treatment regimens warranted !

Gurbel PA et al. J Am Coll Cardiol. 2005; 46: 1820-1826

Optimal ROC determined cut-off value to define MACE in T2DM



Angiolillo DJ et al. JACC 2007; 50: 1541-7.

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Aspirin Resistance –

"More Than Just a Laboratory Curiosity"

Clinical Factors

- Failure to prescribe
- Non-compliance
- Non-absorption
- Interaction with ibuprofen

Cellular Factors

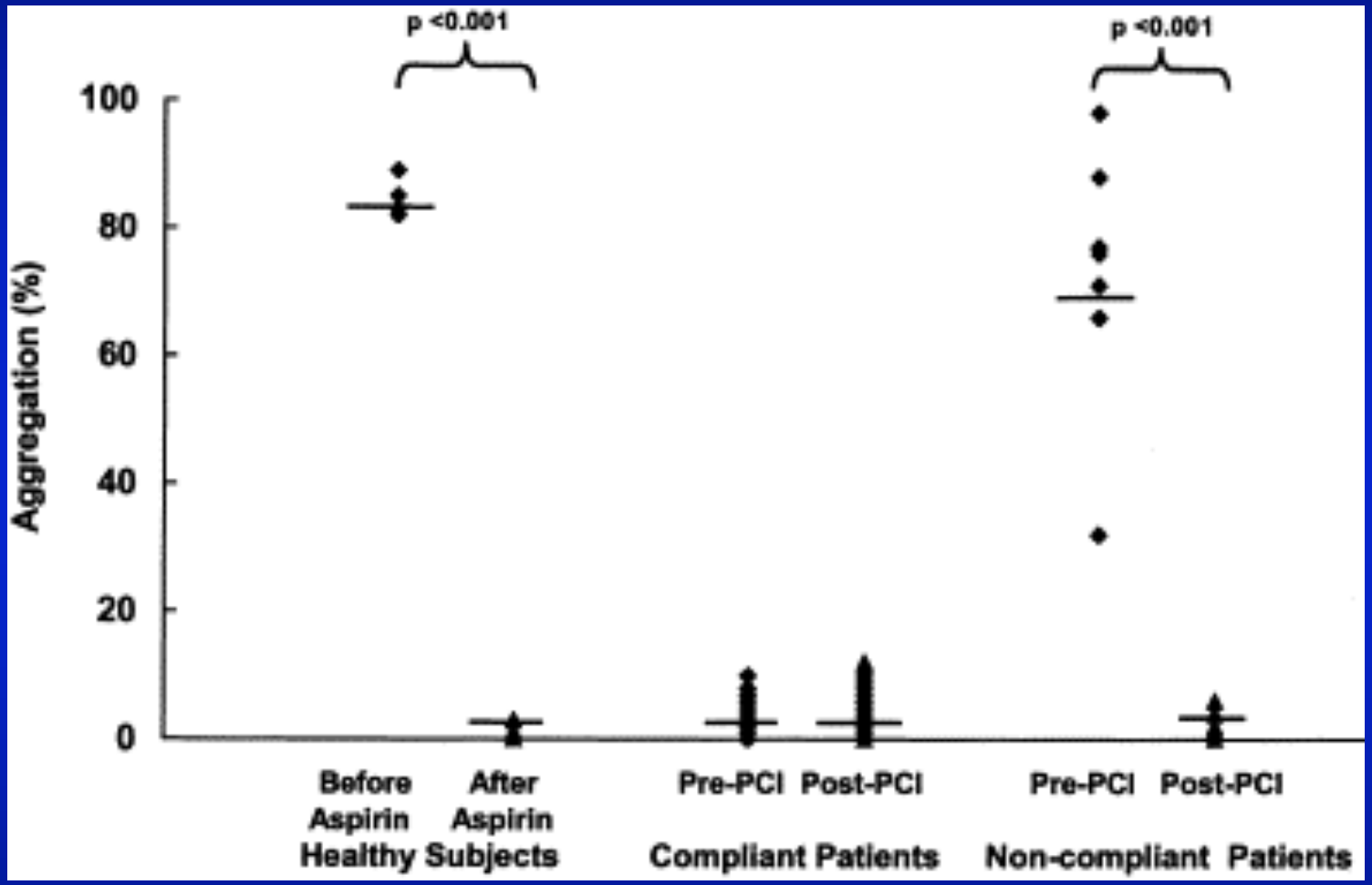
- Insufficient suppression of COX-1
- Over-expression of COX-2 mRNA
- Erythrocyte induced platelet activation
- Increased norepinephrine
- Generation of 8-iso-$PGF_{2\alpha}$

Genetic Polymorphisms

- COX-1
- GPIIIa receptor
- Collagen receptor
- vWF receptor

Bhatt DL. JACC 2004.

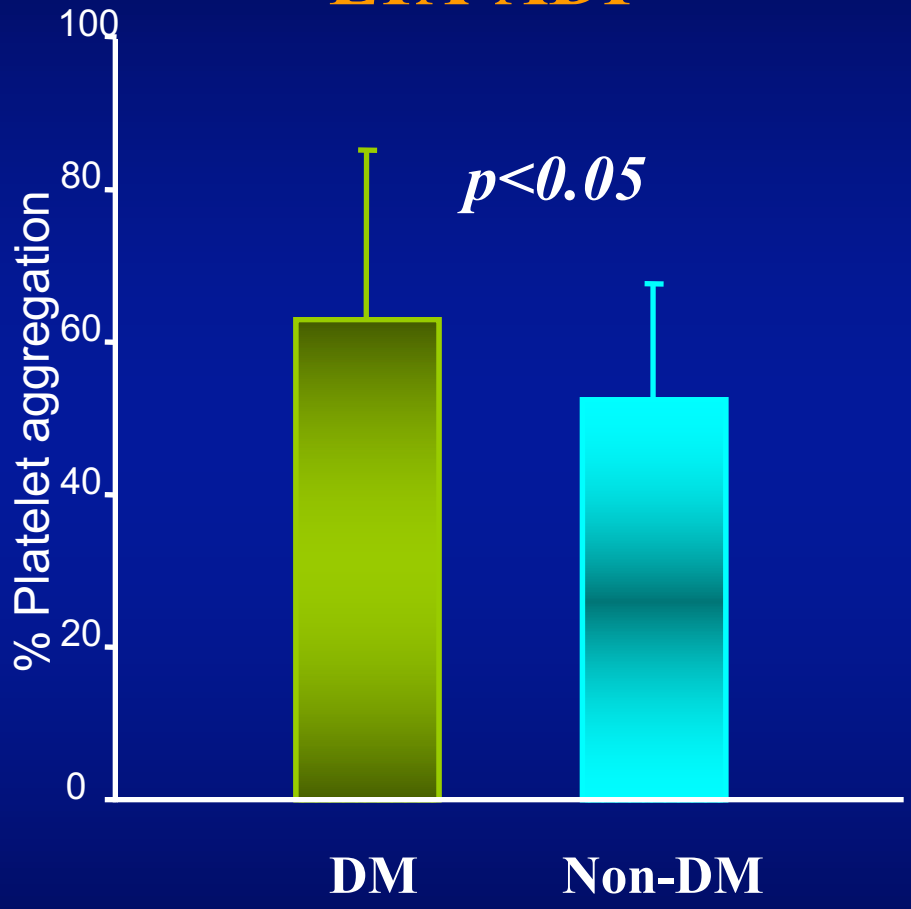
Overestimation of Aspirin Resistance: *Key Role of Compliance*



Tantry U et al. JACC 2005

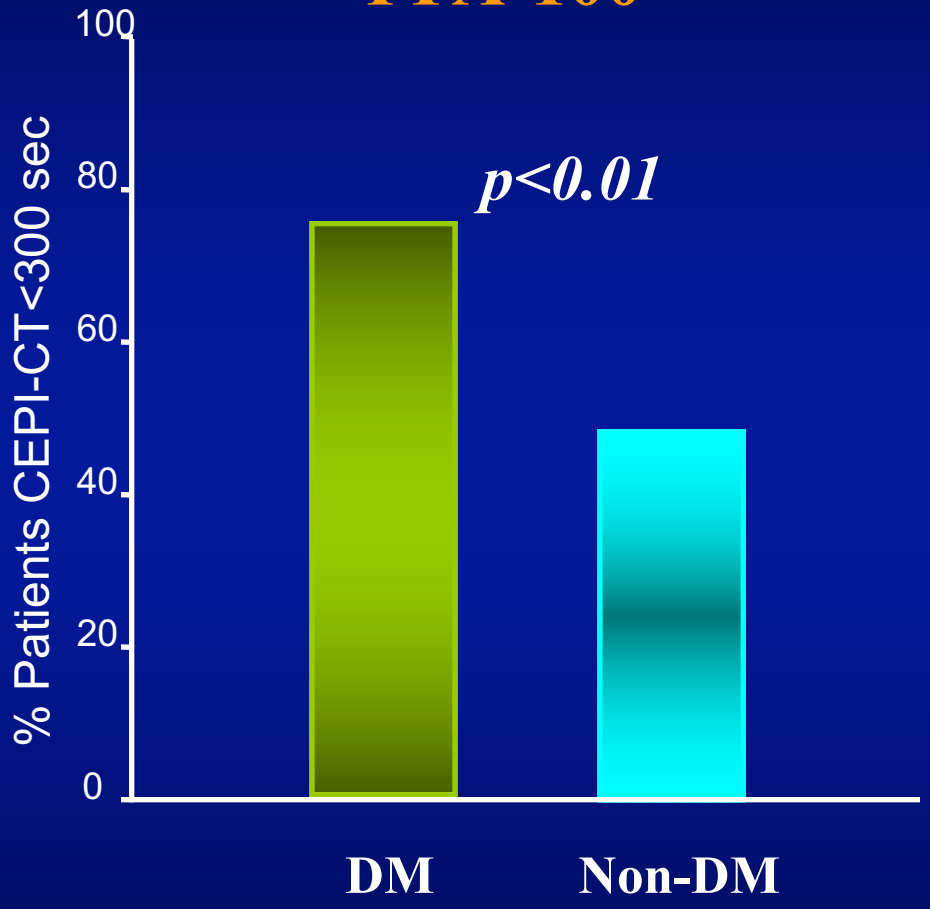
Platelet function (COX-1 independent) in DM vs non-DM on aspirin

LTA-ADP

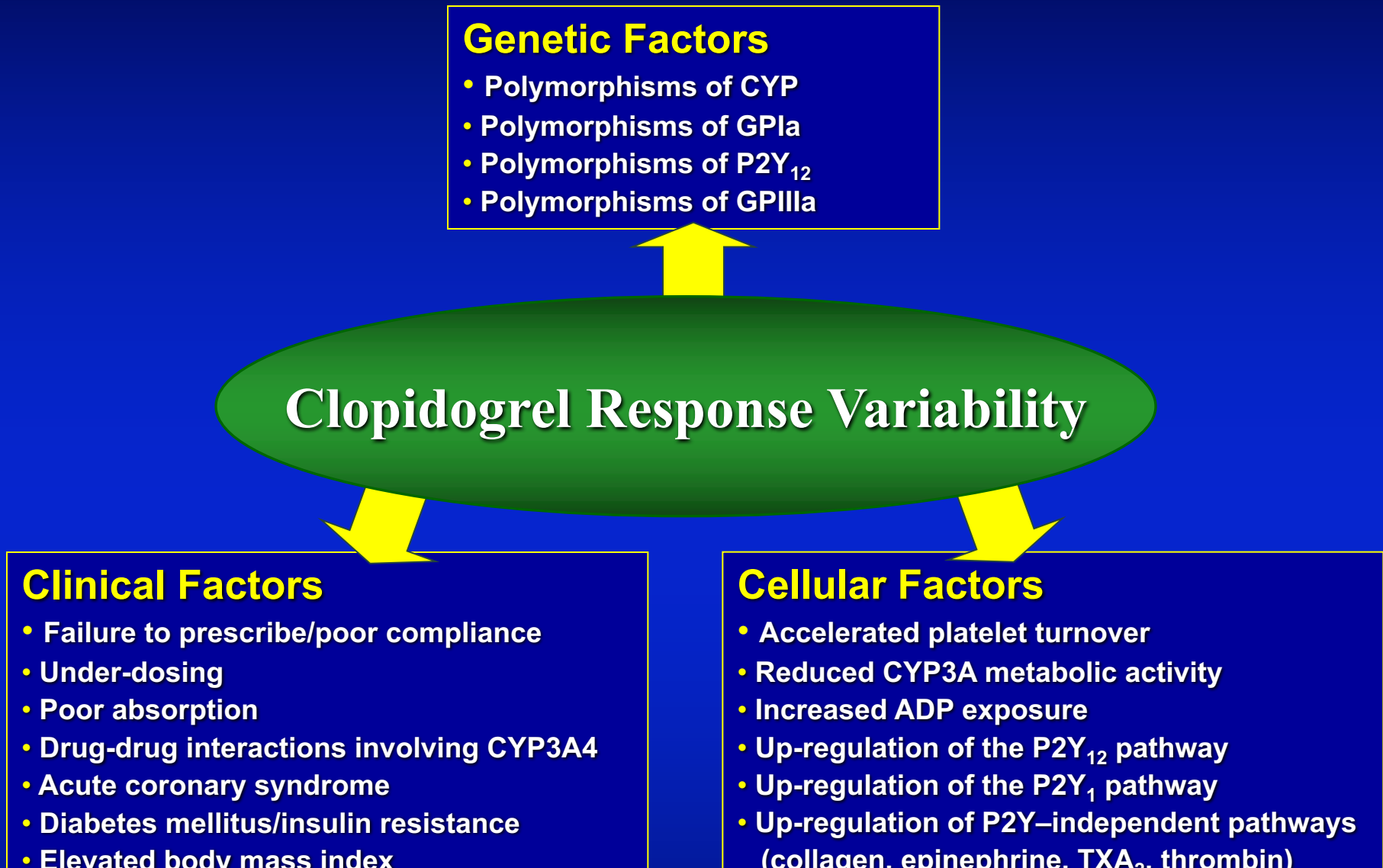


Angiolillo DJ et al. Diabetes 2005; 54:2430-5

PFA-100



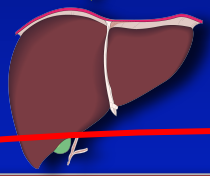
Angiolillo DJ et al. Am J Cardiol 2006; 97:38-43



Angiolillo DJ et al. J Am Coll Cardiol. 2007; 49: 1505-1516 .

Clopidogrel

Pro-drug



Hepatic Metabolism
Cytochrome P450 3A4
(CYP3A4)

Active Metabolite

$P2Y_{12}$ ADP receptor
(irreversible inhibition)

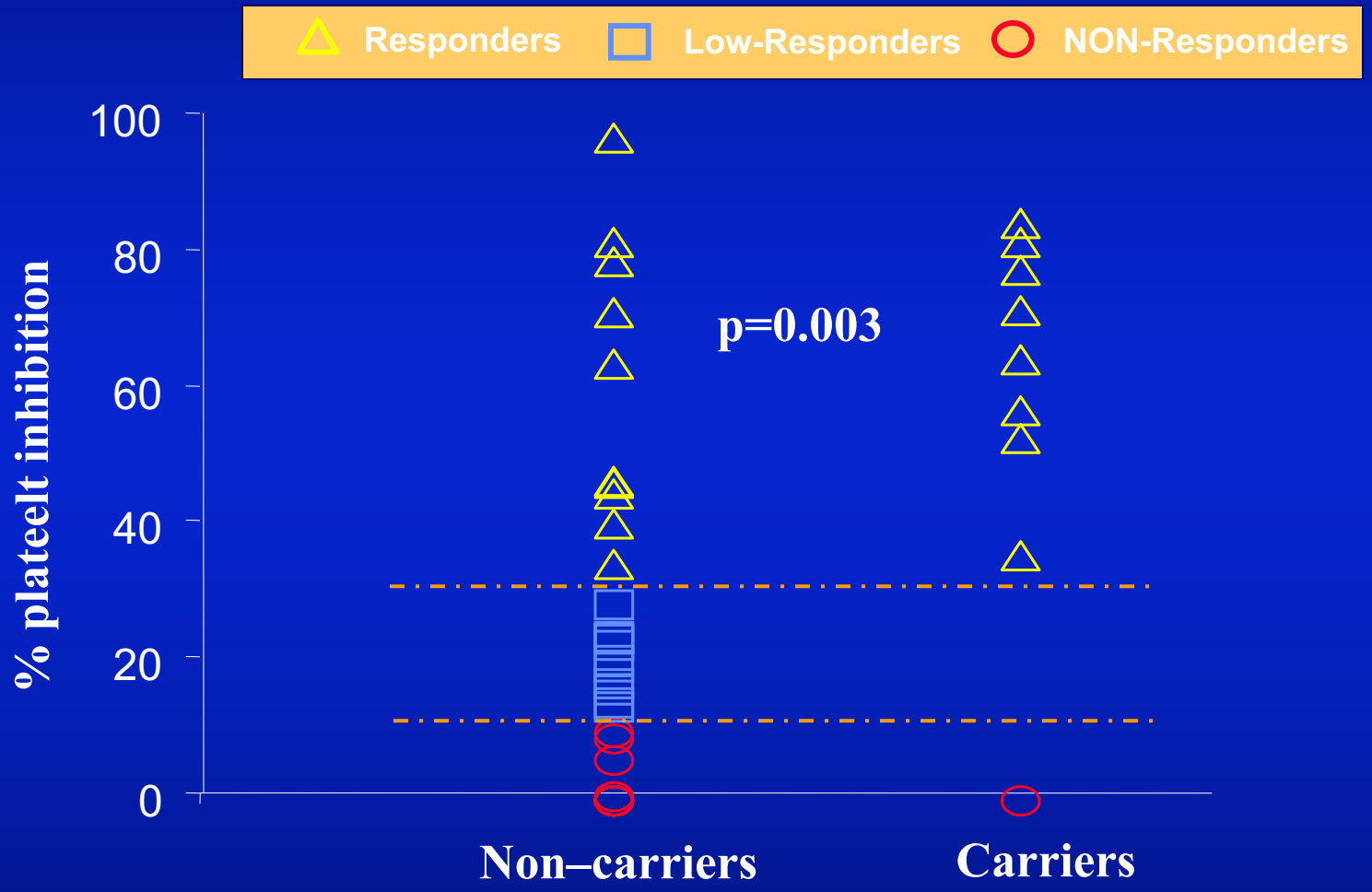
GP IIb/IIIa receptor
(reduced platelet activation)

Angiolillo DJ et al. AHA 2004; Angiolillo DJ et al. Thrombosis Research 2005

Modulation of Acute Clopidogrel-induced Antiplatelet Effects

Gene sequence variations of the CYP3A4 enzyme (IVS10+12G>A)

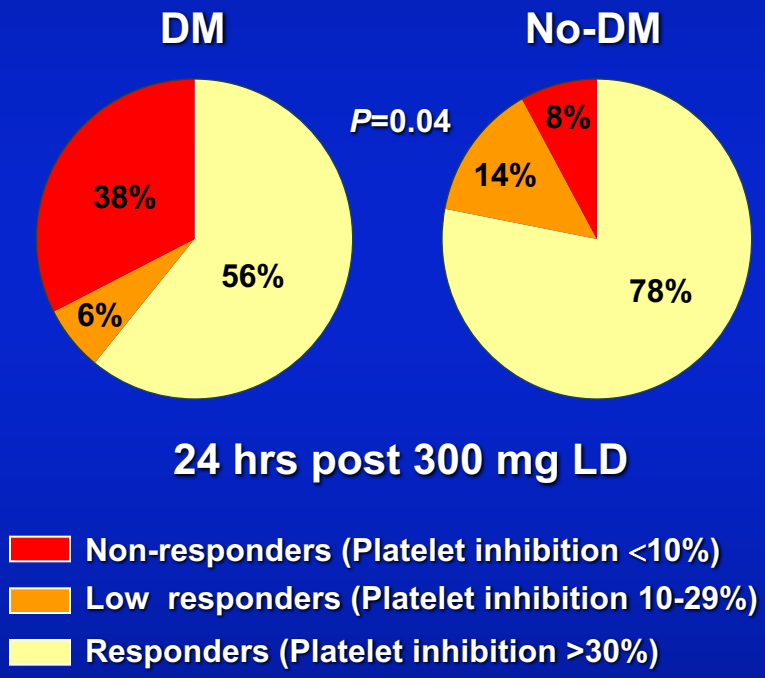
Inhibition of ADP (2μM)–induced GP IIb/IIIa activation following a 300 mg clopidogrel LD



Angiolillo DJ et al. Arterioscler Thromb Vasc Biol. 2006; 26: 1895-1900

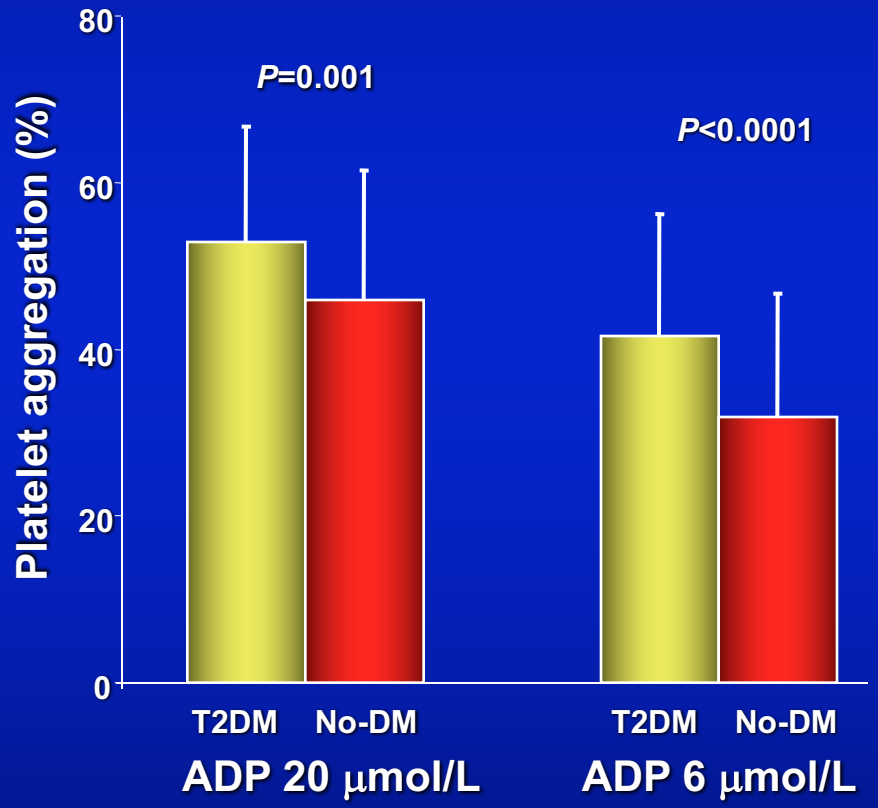
Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

Acute phase of treatment



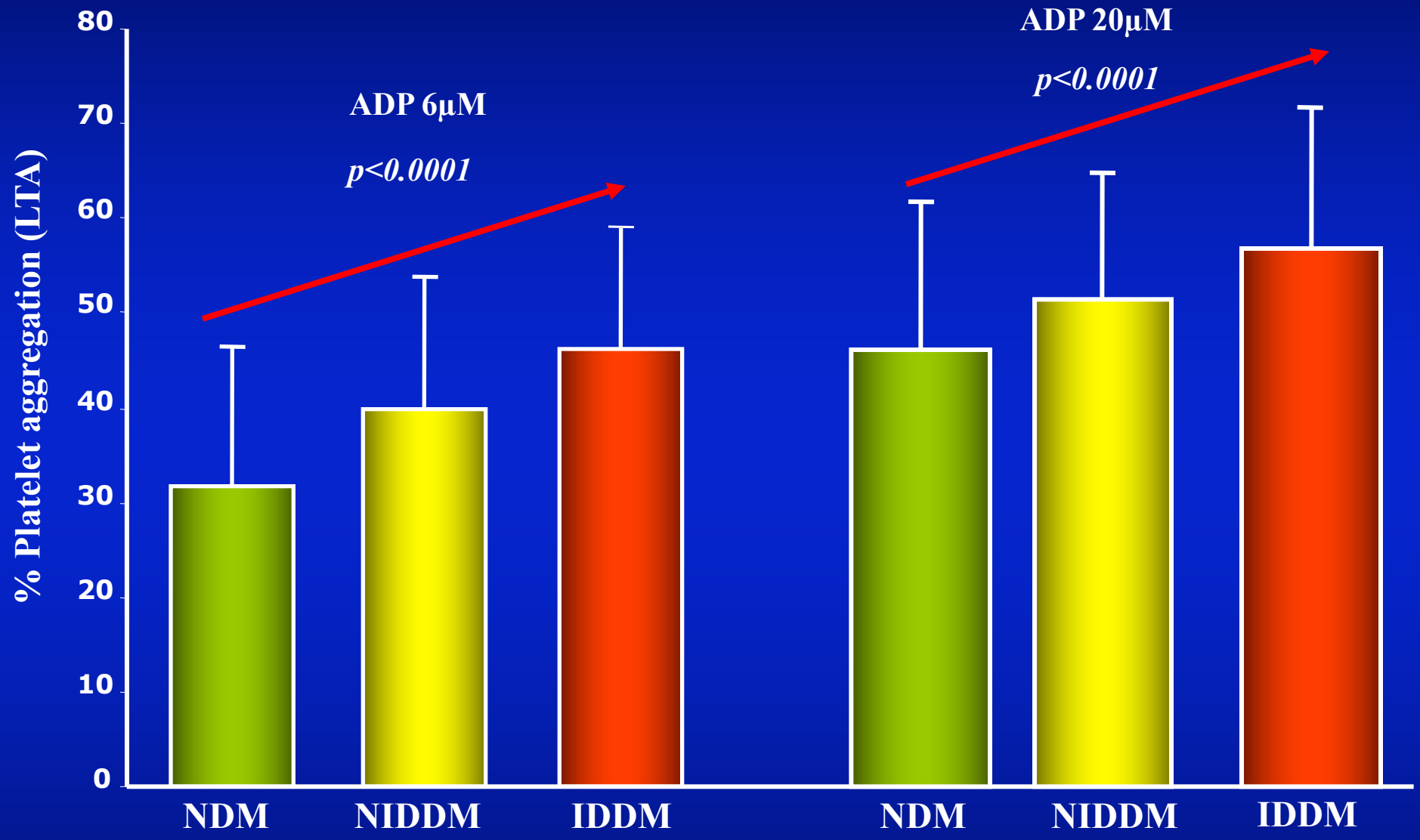
Angiolillo DJ et al. *Diabetes.* 2005;54:2430-5.

Long-term phase of treatment



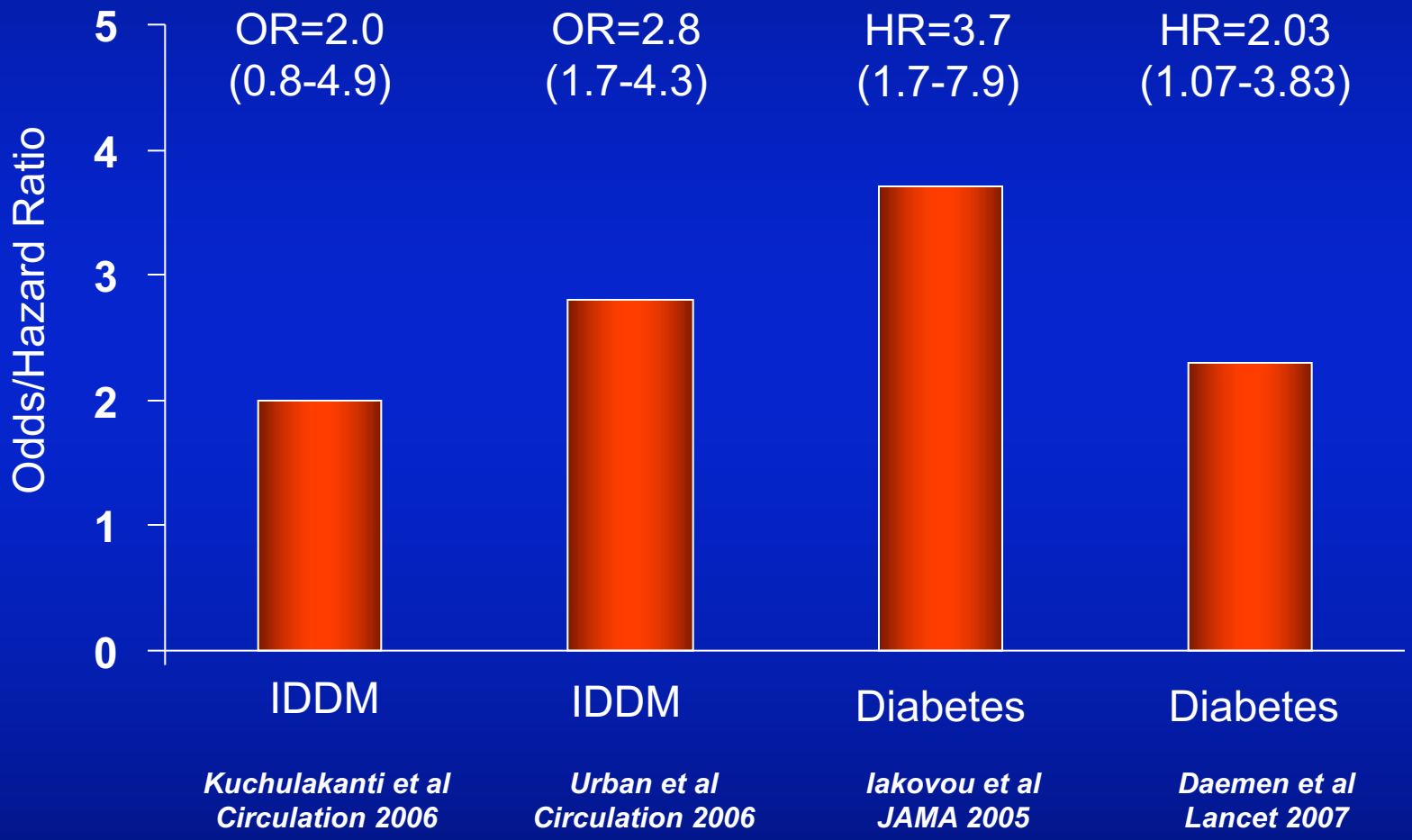
Angiolillo DJ et al. *J Am Coll Cardiol* 2006;48 298-304.

Platelet Function According to Hypoglyemic Treatment



Angiolillo DJ et al. J Am Coll Cardiol 2006; 48: 298-304

Diabetes as Predictor of Stent Thrombosis at One-Year in the Era of DES



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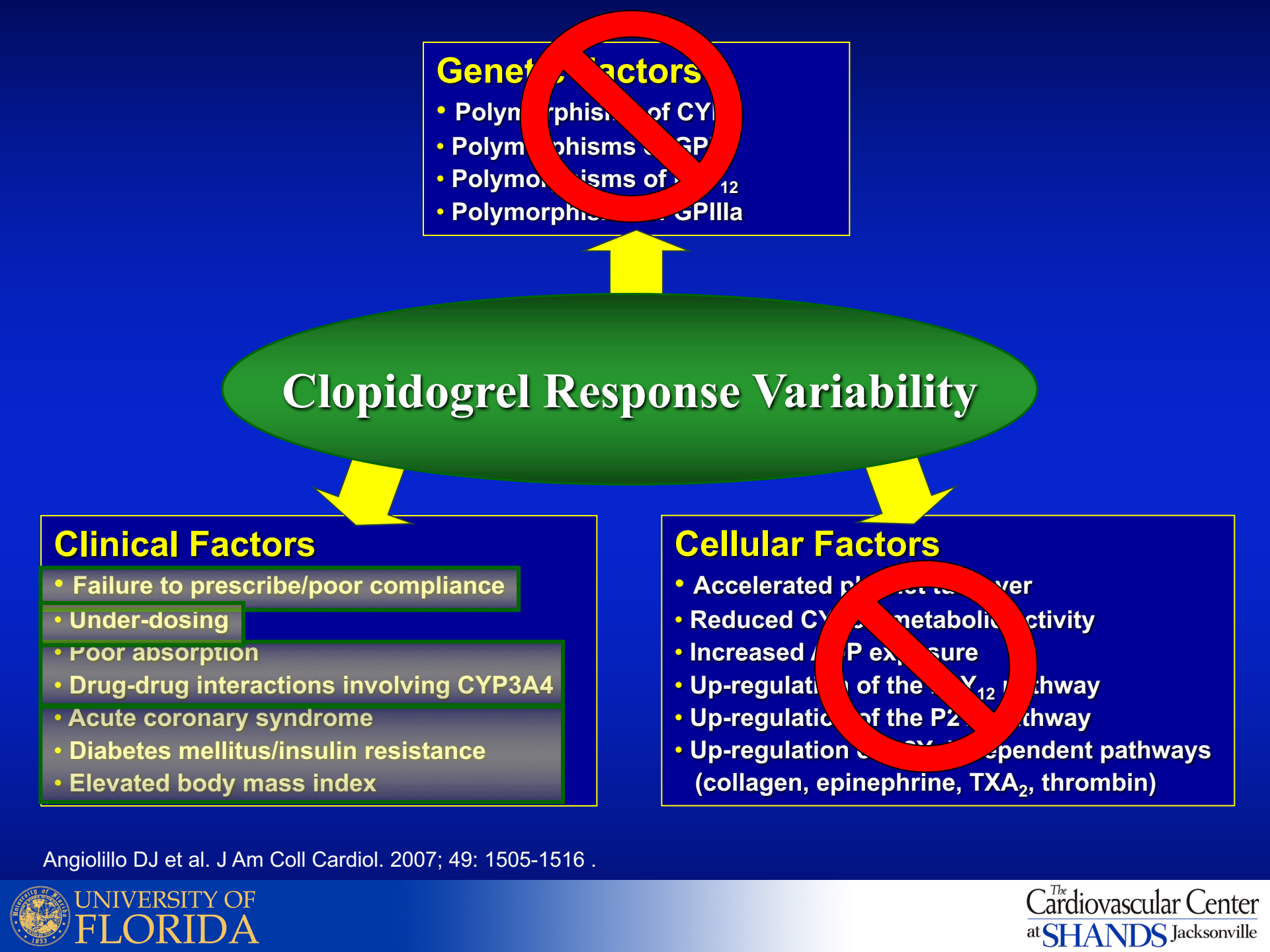
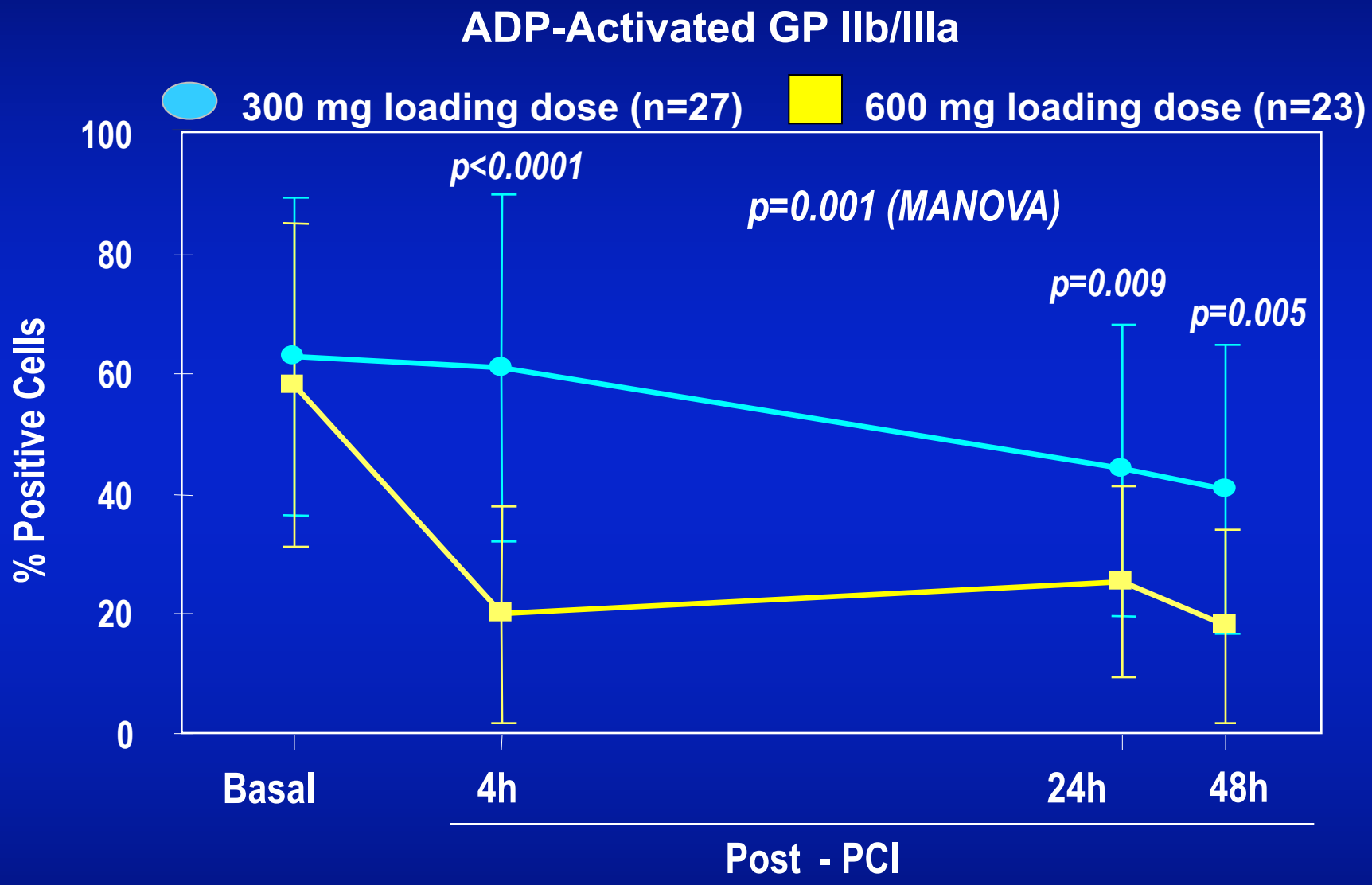
Aspirin Resistant Patient Management

- Educate patient on importance of compliance
- Eliminate interfering substances (ibuprofen)
- Increase aspirin dose (?) (.....*increasing the dose of aspirin does not enhance COX-1 inhibition*)
- Switch to other anti-platelet medications (?) (.....*no evidence that switching to alternative treatment strategies improves outcomes*)



Angiolillo DJ et al. J Am Coll Cardiol. 2007; 49: 1505-1516 .

High Clopidogrel Loading Dose Regimen

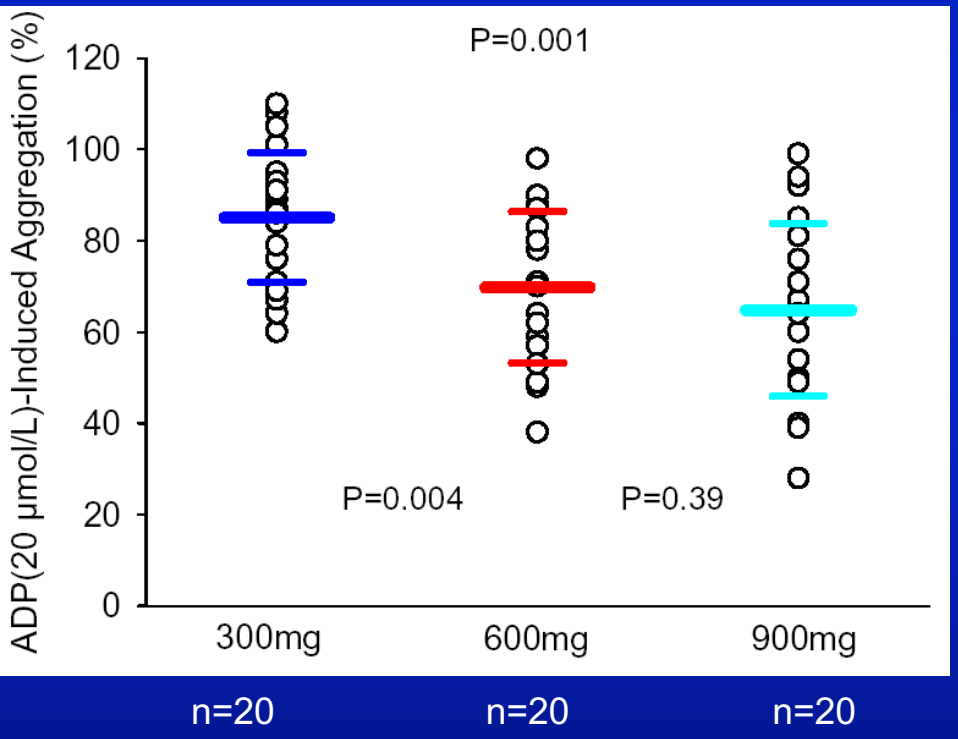


Angiolillo DJ, et al. Eur Heart Journal 2004;25:1903-10.

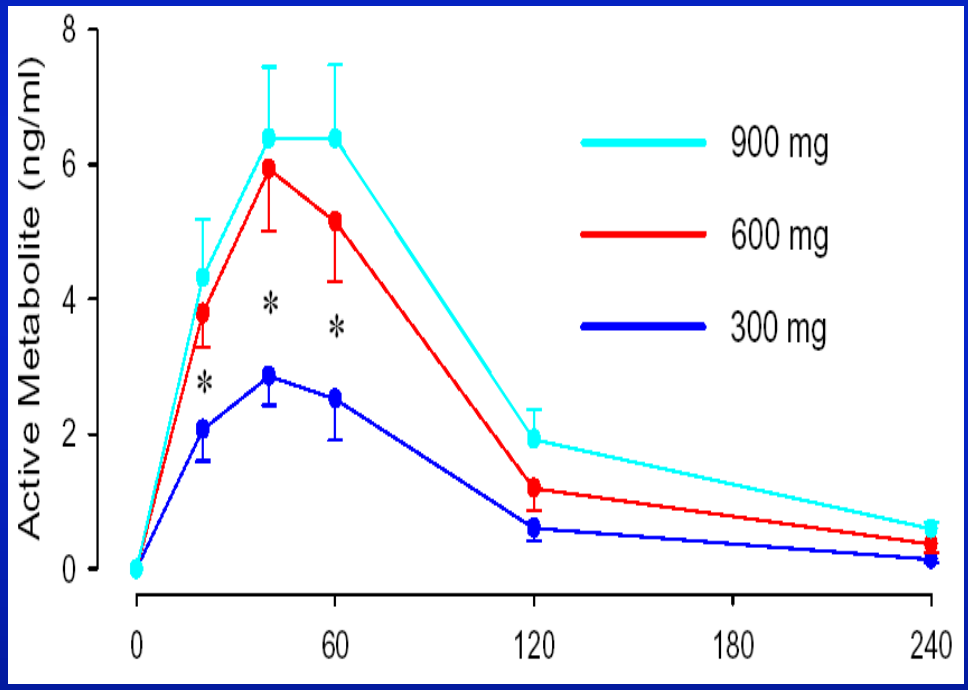
ISAR-CHOICE

Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect

Platelet Aggregation



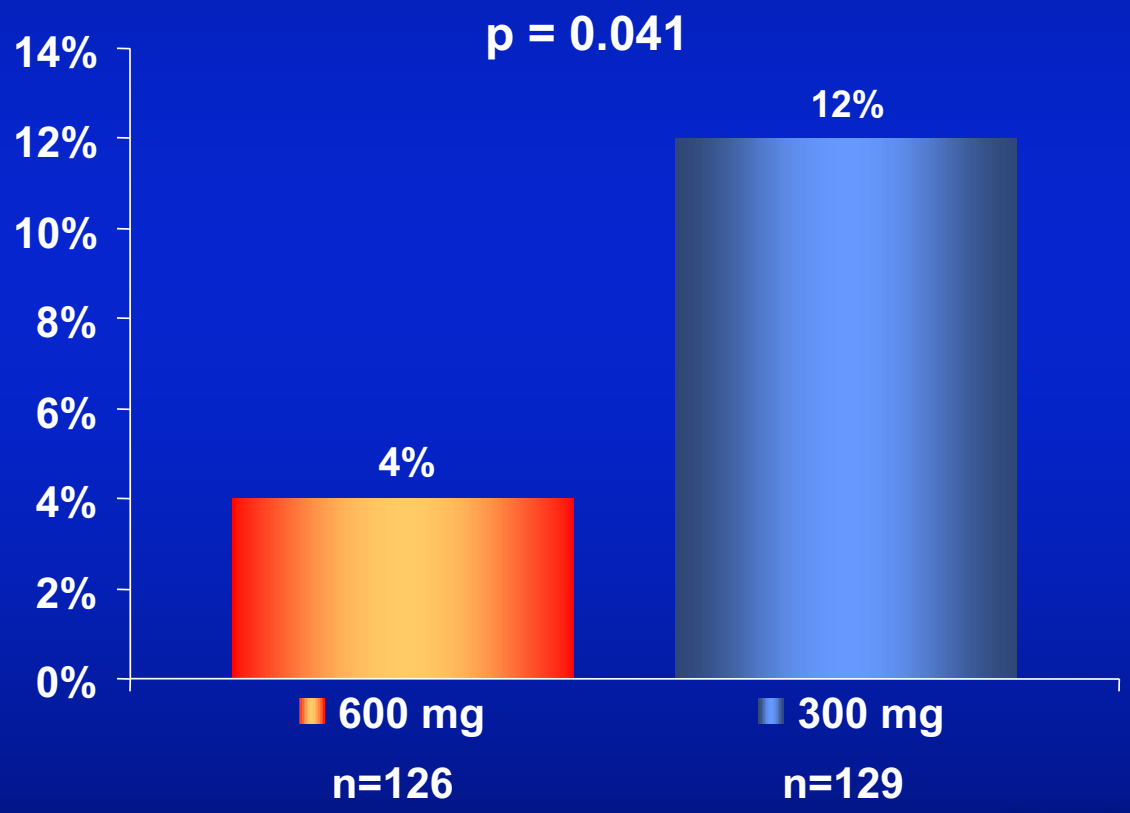
Active metabolite



Von Beckerath N et al. Circulation 2005; 112:2946-50

ARMYDA-2 Trial: Primary endpoint

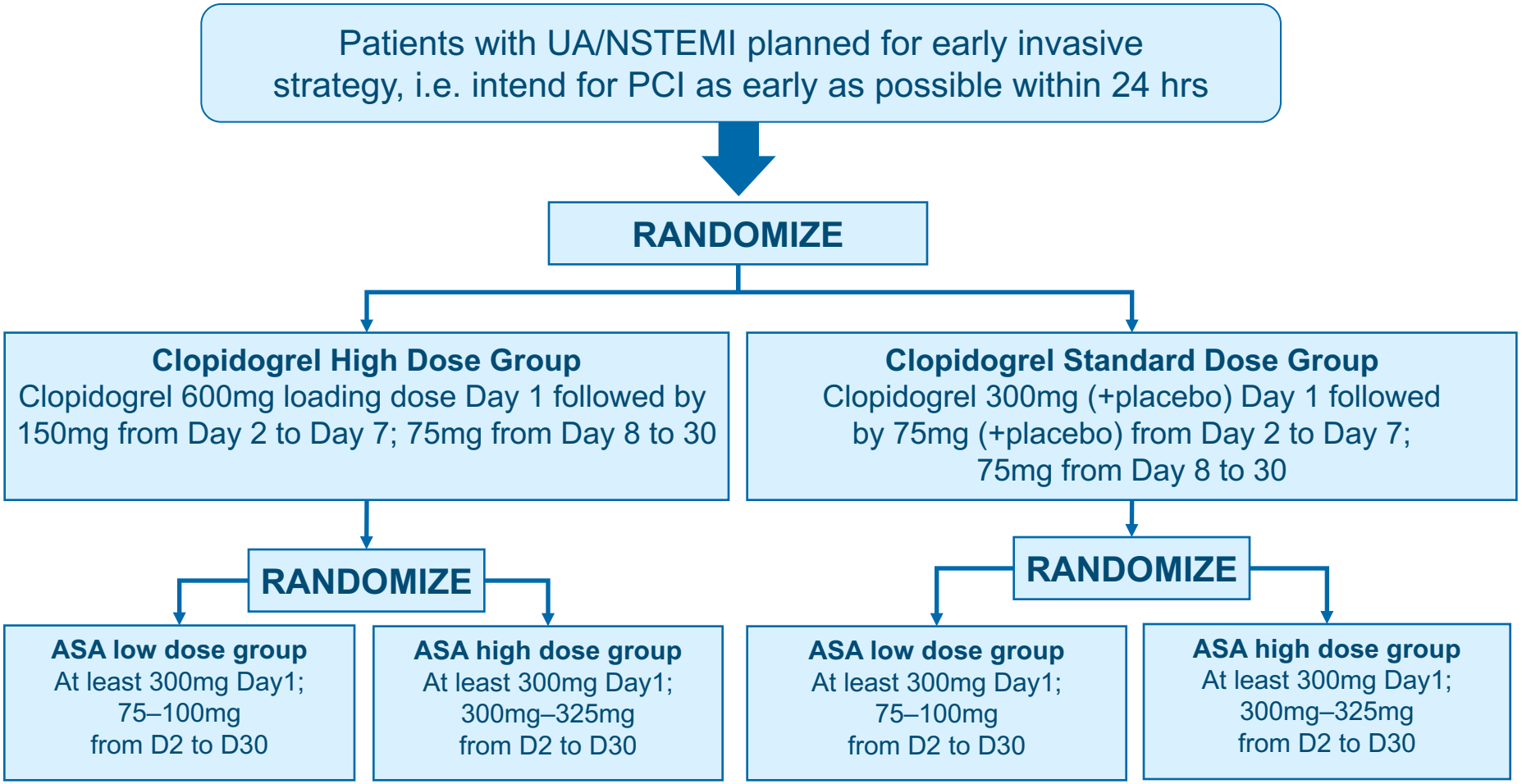
Primary Composite of death, MI, and TVR at 30 days



Patti G et al. Circulation 2005

CURRENT/OASIS 7

Clopidogrel optimal loading dose **U**sage to **R**educe **R**ecurrent **E**ve**NT**s/**O**ptimal **A**ntiplatelet **S**trategy for **I**nterventio**NS**

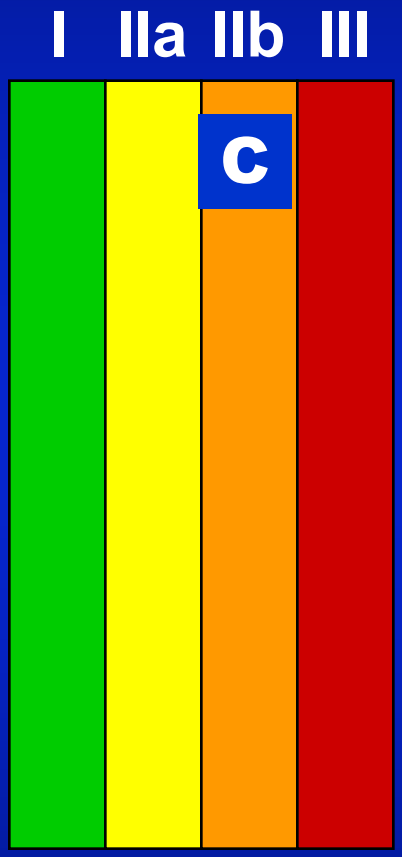


PCI: Percutaneous coronary intervention
UA/NSTEMI: Unstable angina/non-ST-segment elevation myocardial infarction

CURRENT

ACC/AHA/SCAI 2005 Guideline Update for PCI

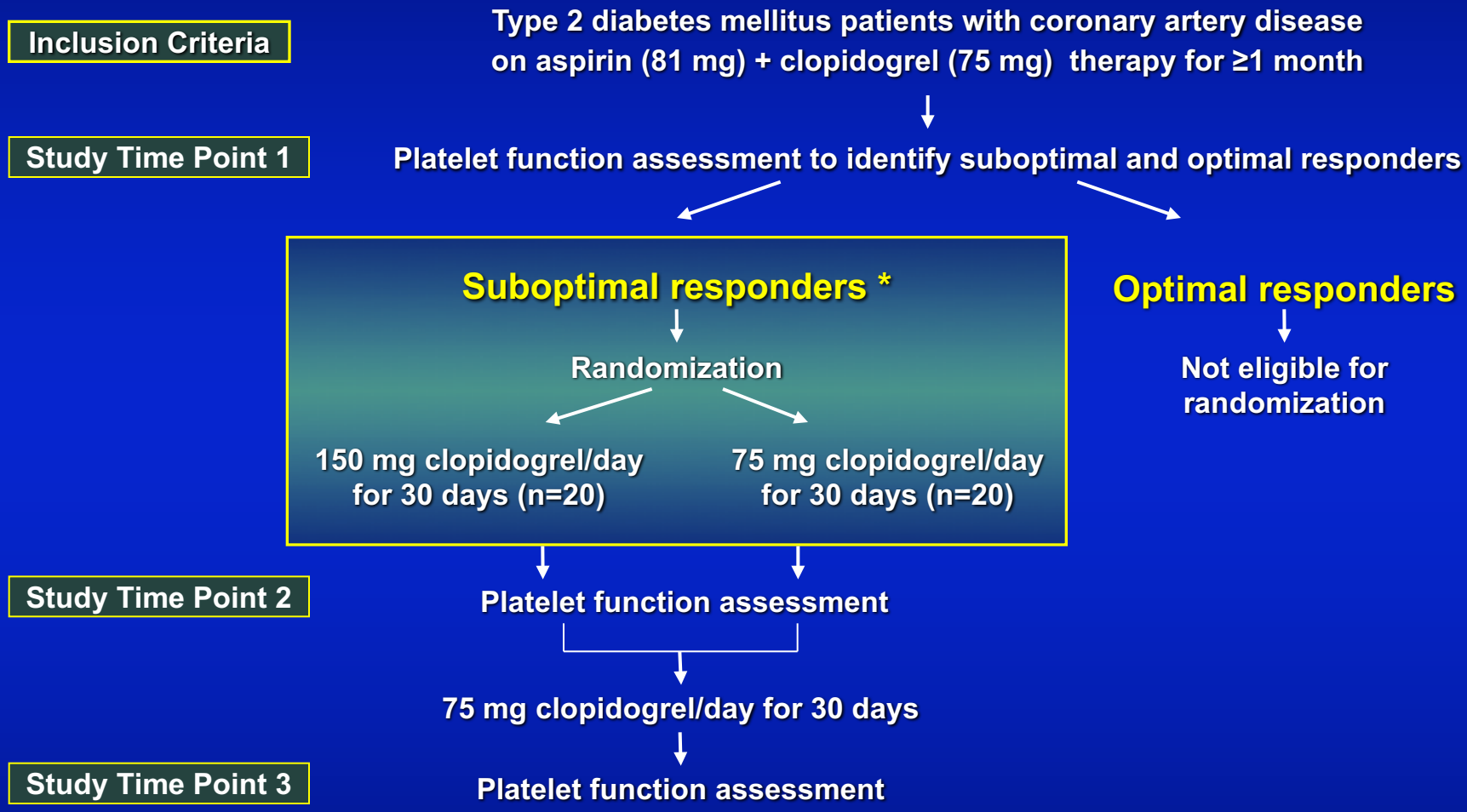
Oral Antiplatelet Adjunctive Therapies



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.

Adapted from Smith SC Jr, et al. Available at:
www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf

OPTIMUS Study:
(Optimizing anti-Platelet Therapy In diabetes MellitUS)

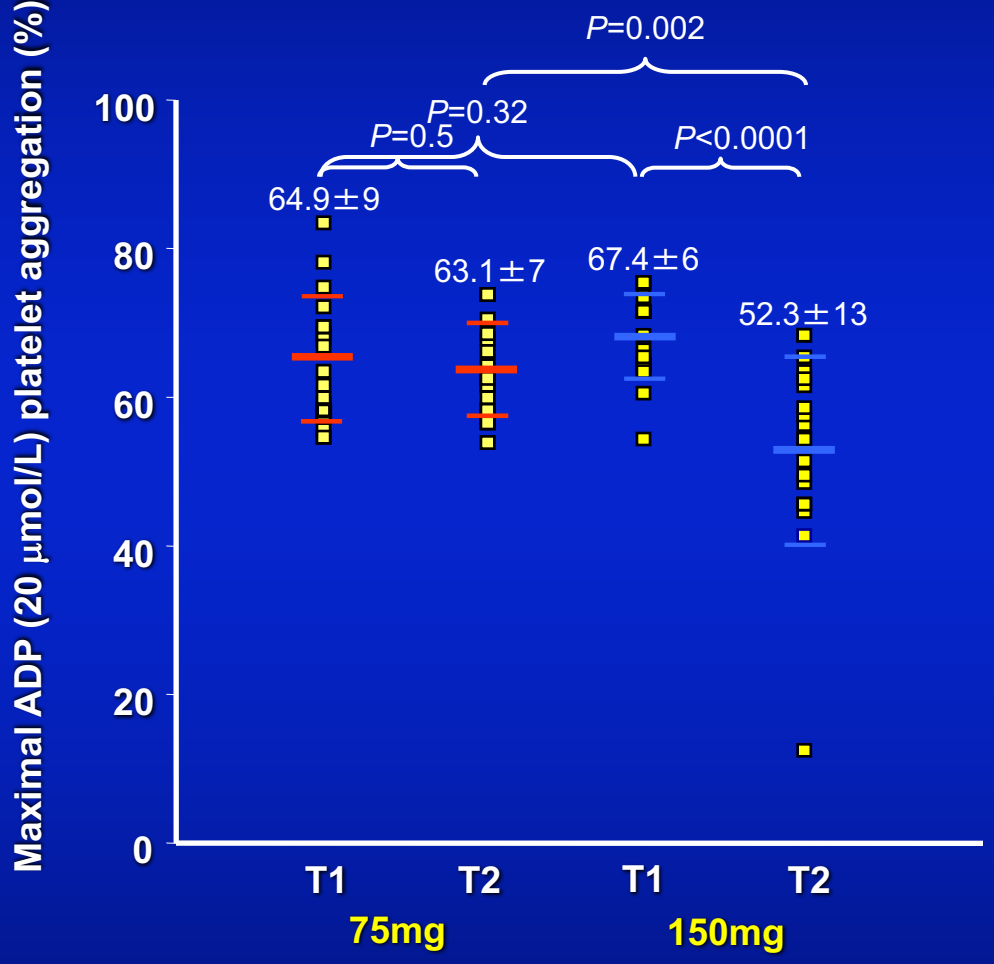


* >50% ADP (20 μmol/L)-induced post-treatment platelet reactivity

Angiolillo DJ et al. *Circulation.* 2007;115:708-16.

OPTIMUS Study:
(Optimizing anti-Platelet Therapy In diabetes MellitUS)

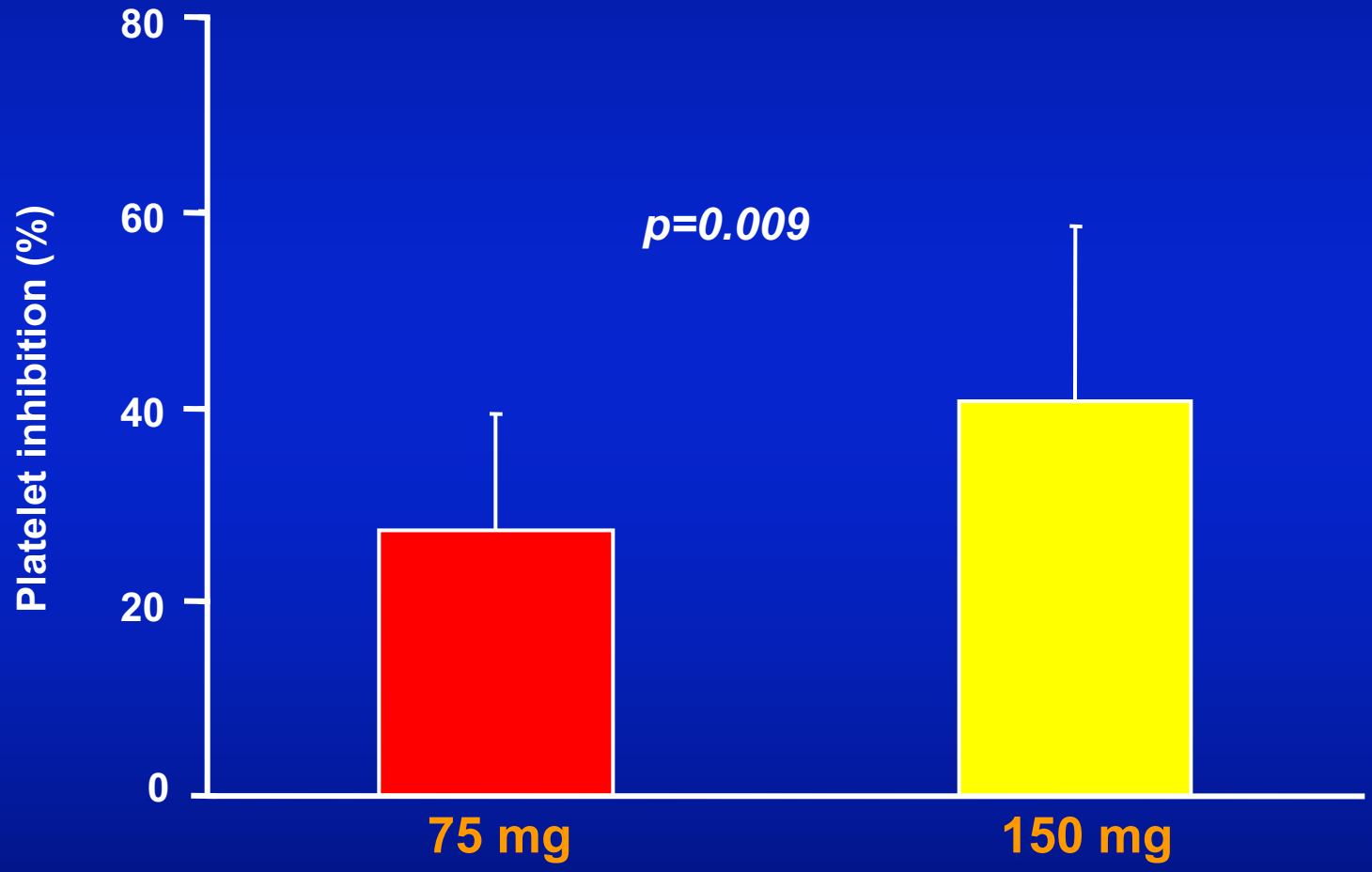
Primary Endpoint: Maximal ADP (20 μmol/L) Platelet Aggregation



Angiolillo DJ et al. *Circulation.* 2007;115:708-16.

Insights into updated ACC/AHA/SCAI 2005 PCI guidelines

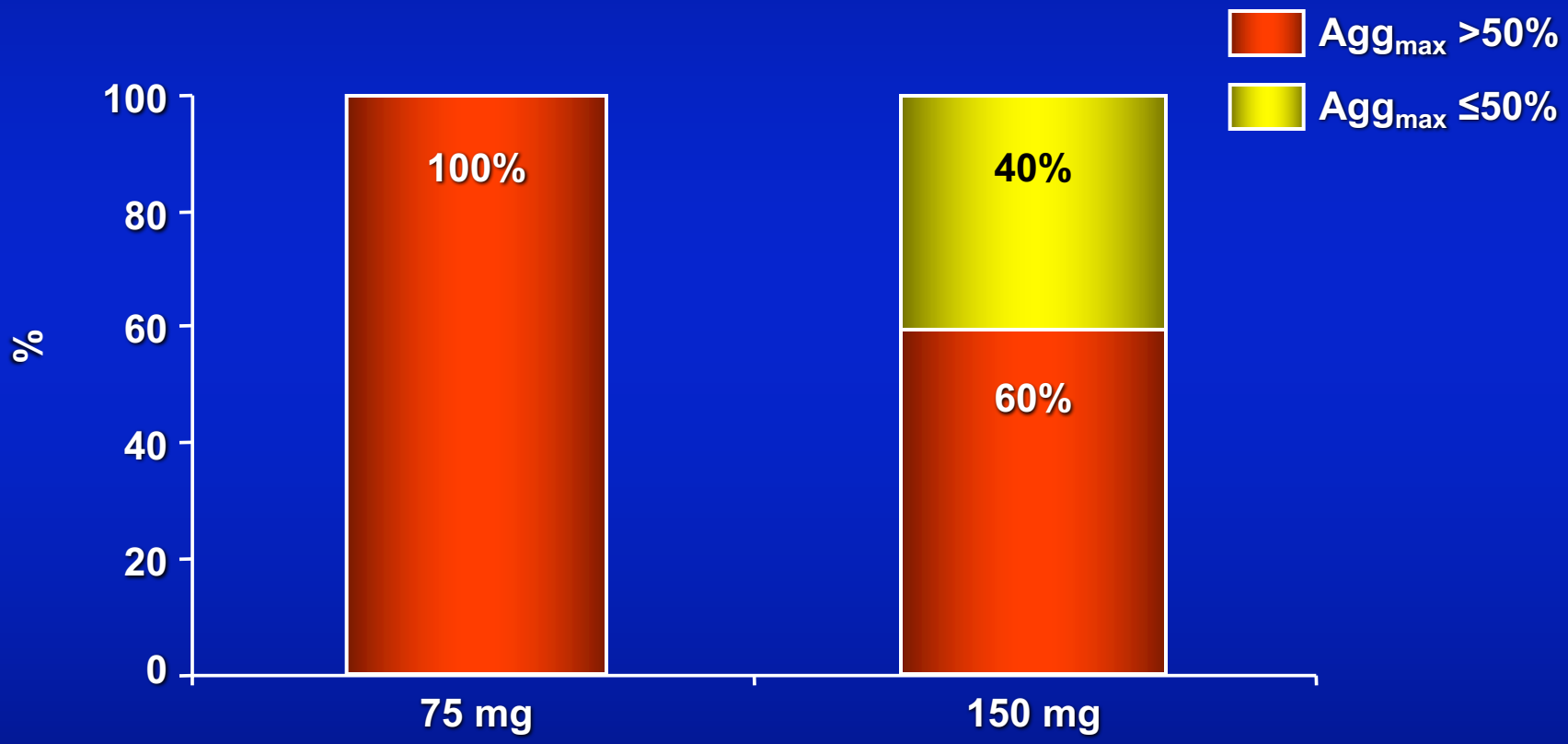
Functional impact of 150mg clopidogrel dosing in patients with <50% inhibition defined by the VerifyNow $P2Y_{12}$ assay (*OPTIMUS substudy*)



Angiolillo DJ et al. *Am J Cardiol.* 2008 (in press).

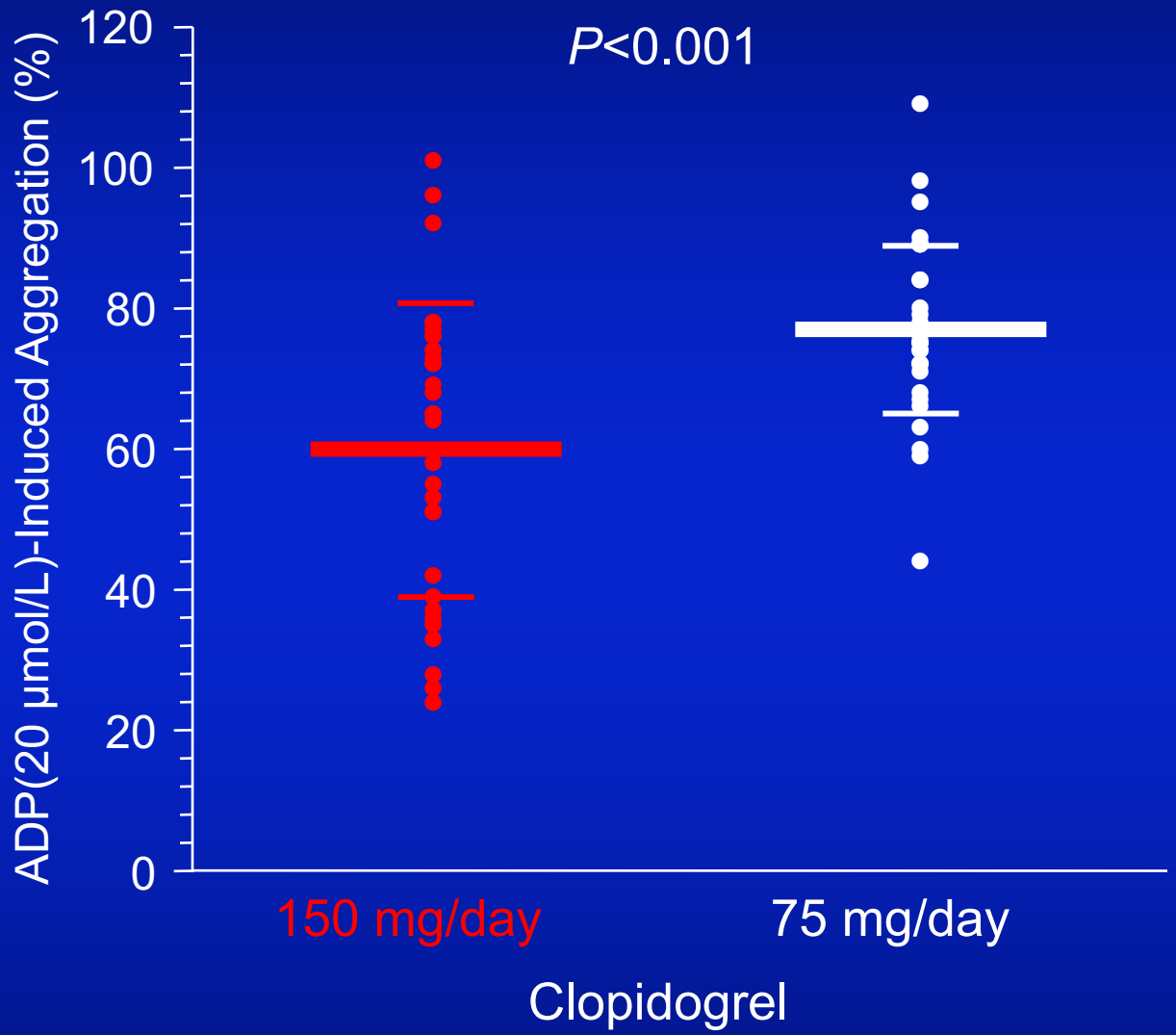
OPTIMUS

Prevalence of Patients Reaching Therapeutic $P2Y_{12}$ Target Levels (20 µmol/L-induced Agg_{max} ≤50%)



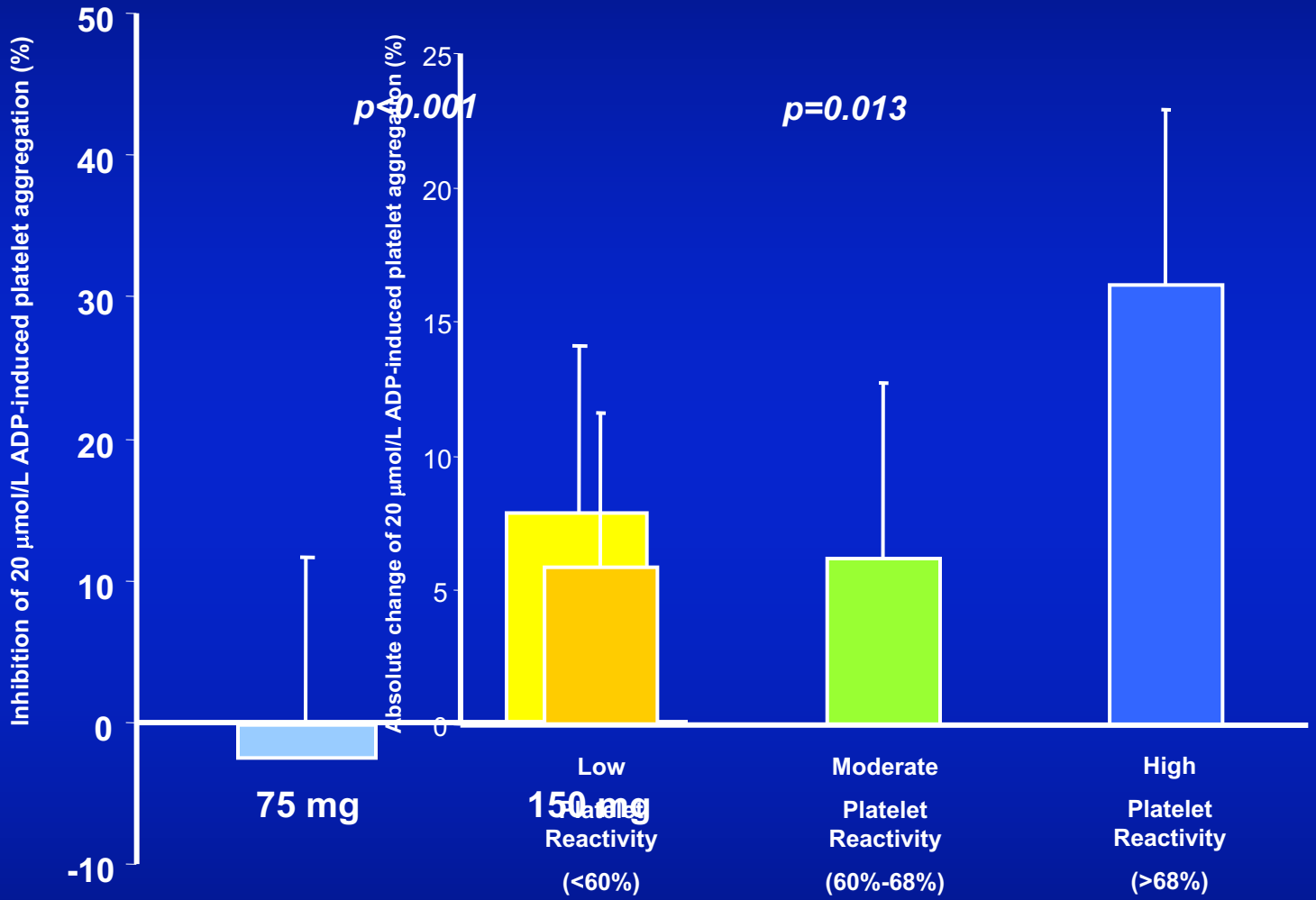
Angiolillo DJ et al. *Circulation.* 2007;115:708-16.

ISAR-CHOICE 2



Von Beckerath N et al. Eur Heart J 2007; 28:1814-9.

Functional impact of 75mg vs 150mg clopidogrel following elective PCI: Results of a Randomized Study



Angiolillo DJ et al. Thromb Haemost 2008 (in press)

Triple versus Dual Antiplatelet Therapy

Role for cilostazol in addition to aspirin and clopidogrel?

Stent thrombosis @ 30 days (Lee SW et al JACC 2006)

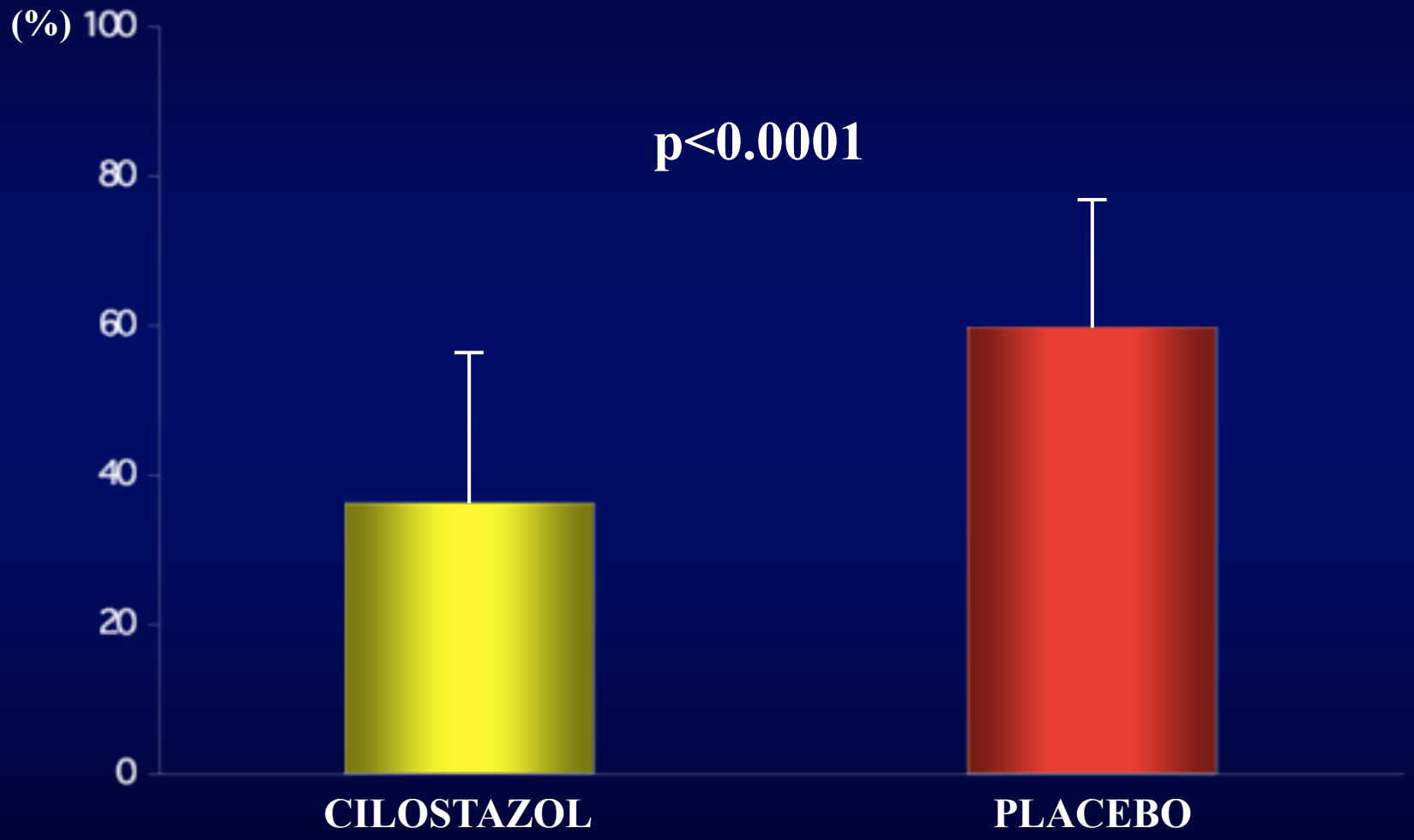
Triple therapy vs dual therapy

9/1597 (0.5%) vs 1/1415 (0.1%) p=0.024

DECLARE-Long Study: Triple therapy significantly reduced late loss at 6 months after DES implantation and the occurrence of TLR and major adverse cardiac events in patients with long coronary lesions (Lee SW et al Am J Cardiol 2007).

Primary Endpoint

$P2Y_{12}$ reactivity index (PRI)



Angiolillo DJ et al. TCT 2007

Novel $P2Y_{12}$ ADP receptor antagonist

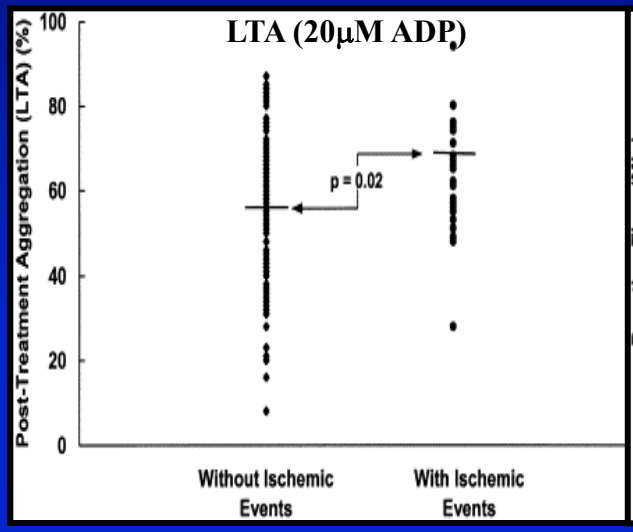
Drug	Type	Route	Action	Dose	Mean platelet inhibition (time required)	Trials (phase III)
Prasugrel (CS-747)	Thienopyridine (3rd generation) - requires hepatic conversion to active metabolite	Oral	Irreversible binding	60 mg loading dose, 10 mg maintenance dose	≈ 70% (< 1 hour)	TRITON
Cangrelor (ARC-669931MX)	ATP analogue-Direct inhibition	Parenteral	Competitive binding	4 µg/kg/min	≈ 95% (few minutes)	CHAMPION
AZD-6140	Cyclopetyl-triazolopy-rimidine-Direct inhibition	Oral	Competitive binding	90 mg/twice daily	≈ 95% (2-4 hours)	PLATO

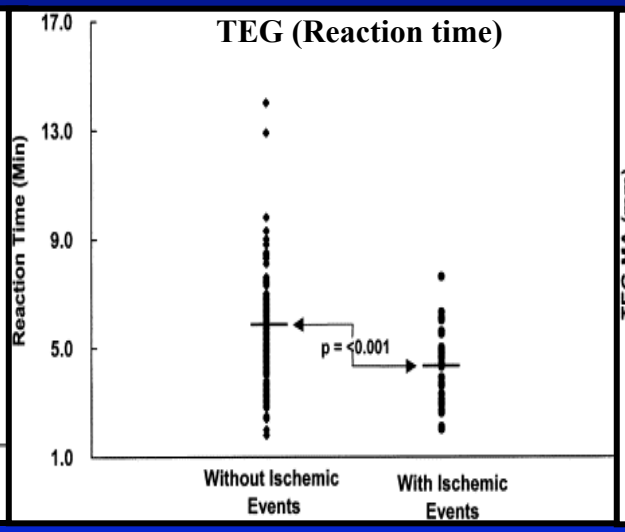
More potent and less variability!!

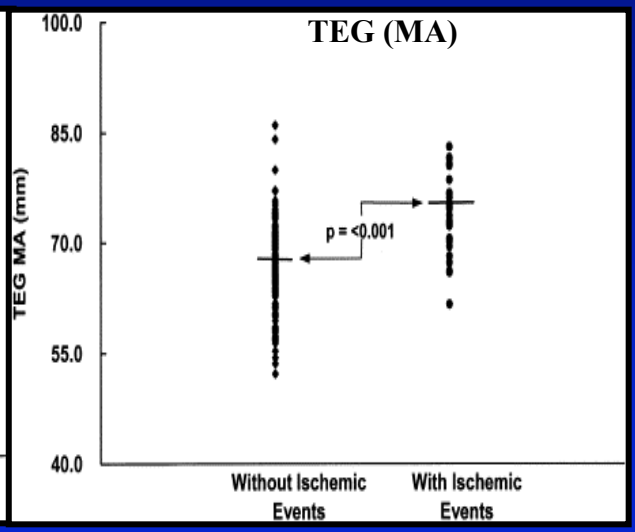
Angiolillo DJ et al. J *Am Coll Cardiol.* 2007.

Is it all about the platelet?

Insights from the PREPARE POST-STENTING Study





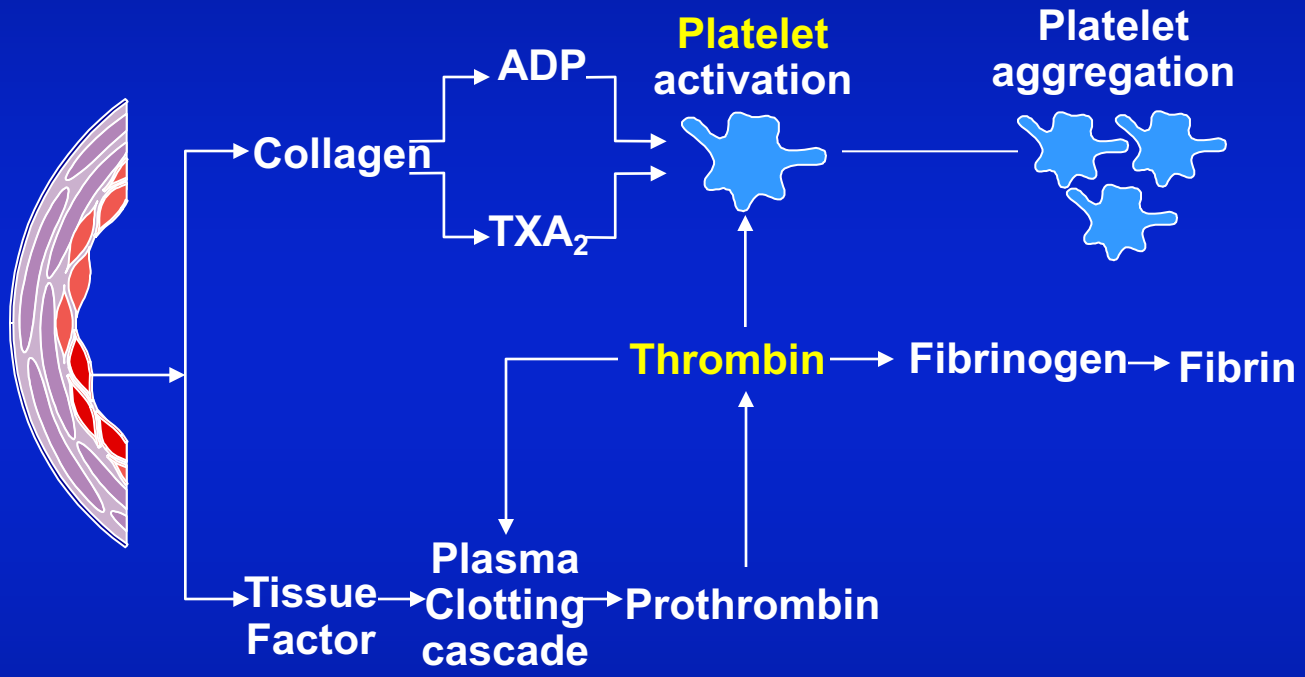


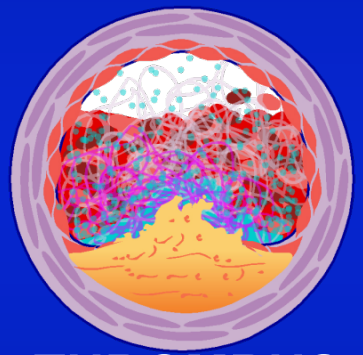
- High platelet reactivity, rapid fibrin formation and clot strength are risk factors for ischemic events after PCI.
- Clot strength is the most predictive.
- These findings may explain the occurrence of events despite treatment with COX-1 and $P2Y_{12}$ inhibitors, <u>suggesting the need to address thrombin inhibition</u> during and after PCI

Gurbel PA et al. J Am Coll Cardiol. 2005; 46: 1820-1826

Thrombus Formation

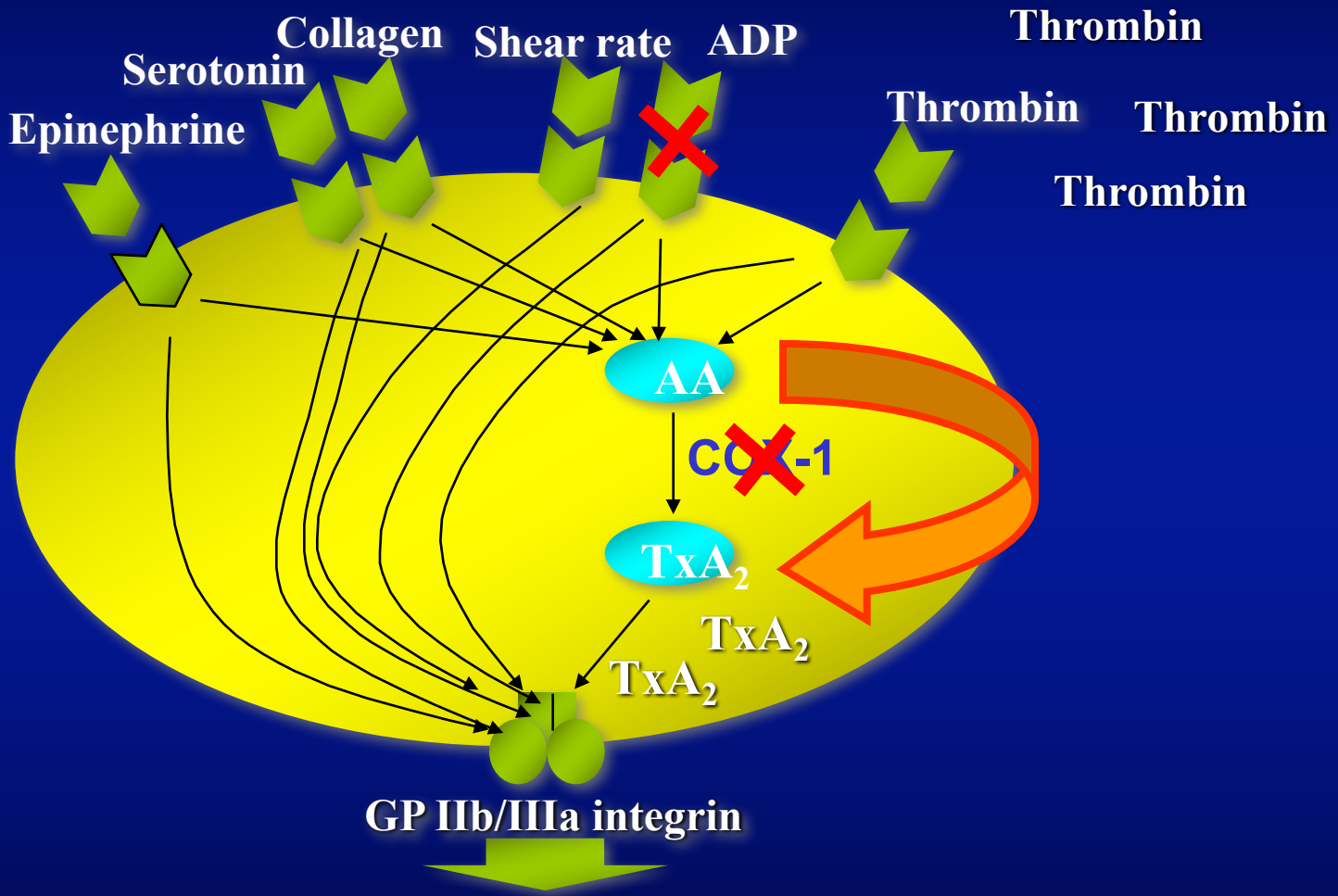
Two key elements: cellular (platelets) and plasmatic (coagulation factors)





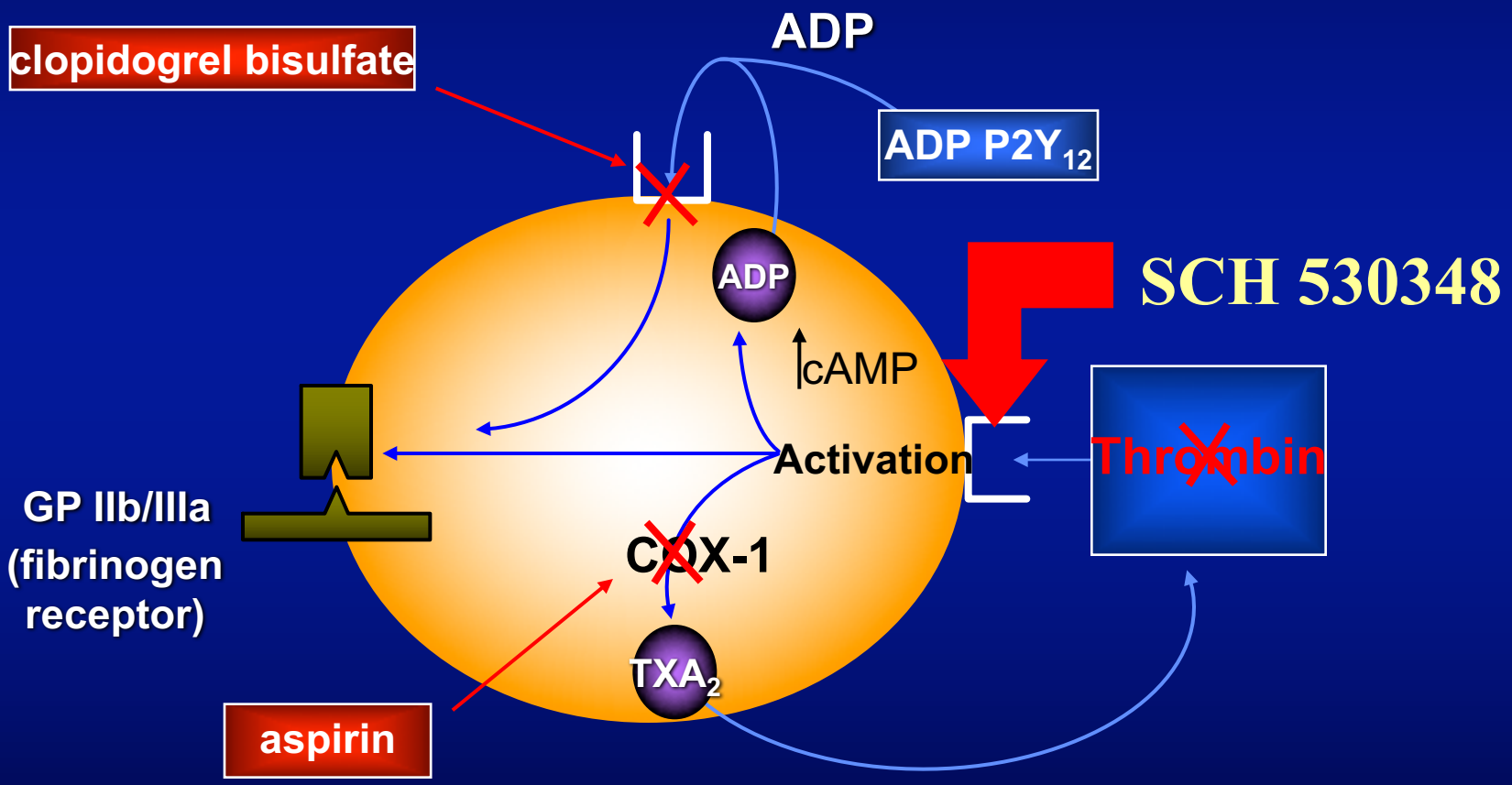
THROMBUS

Platelet Stimuli



Oral Anti-PAR-1 receptors

TRA-PCI trial



adapted from Schafer AI. *Am J Med*. 1996;101:199-209.