POCT in the Management of Antiplatelet Therapy – Patient Response, Treatment Optimization and Personalized Medicine

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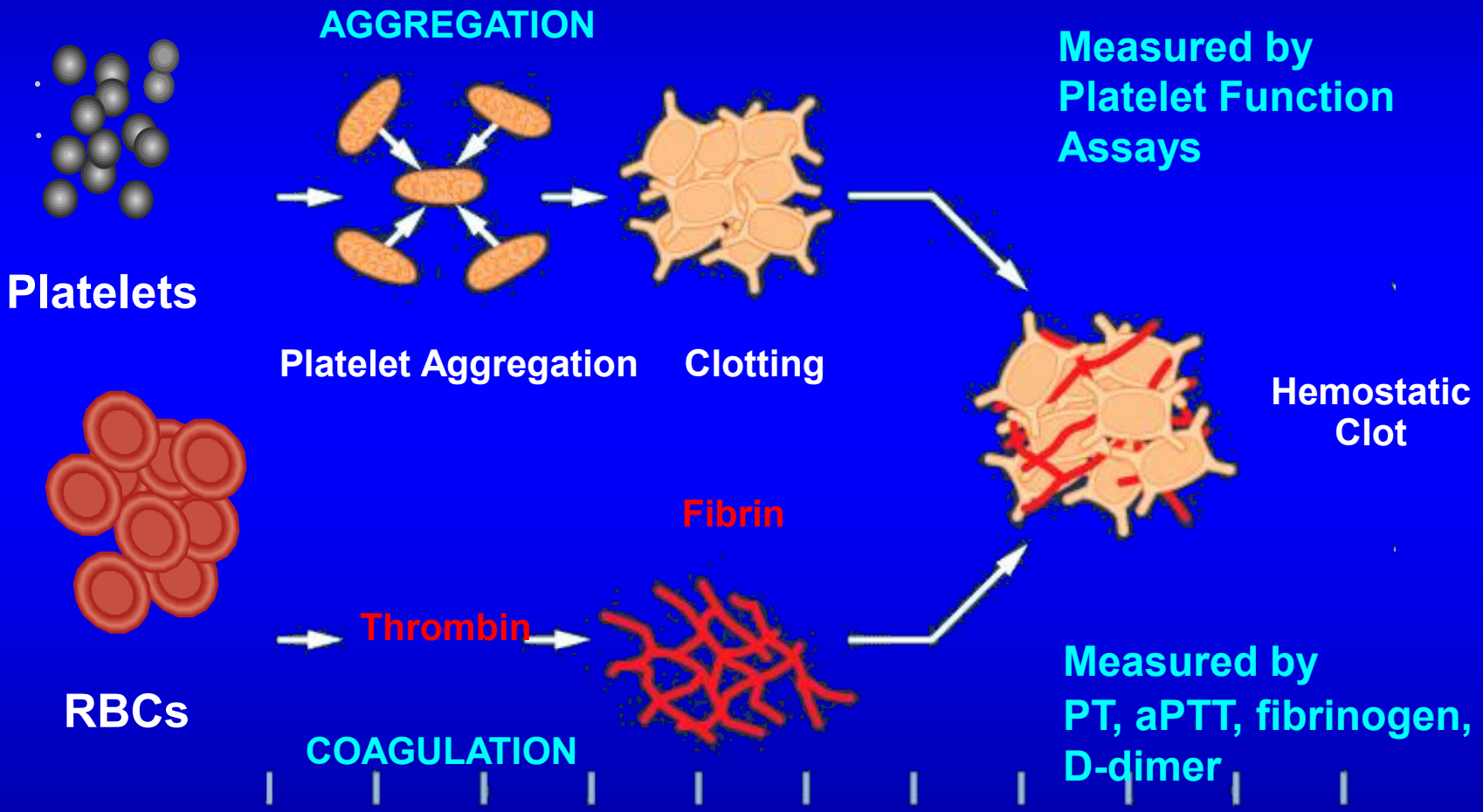
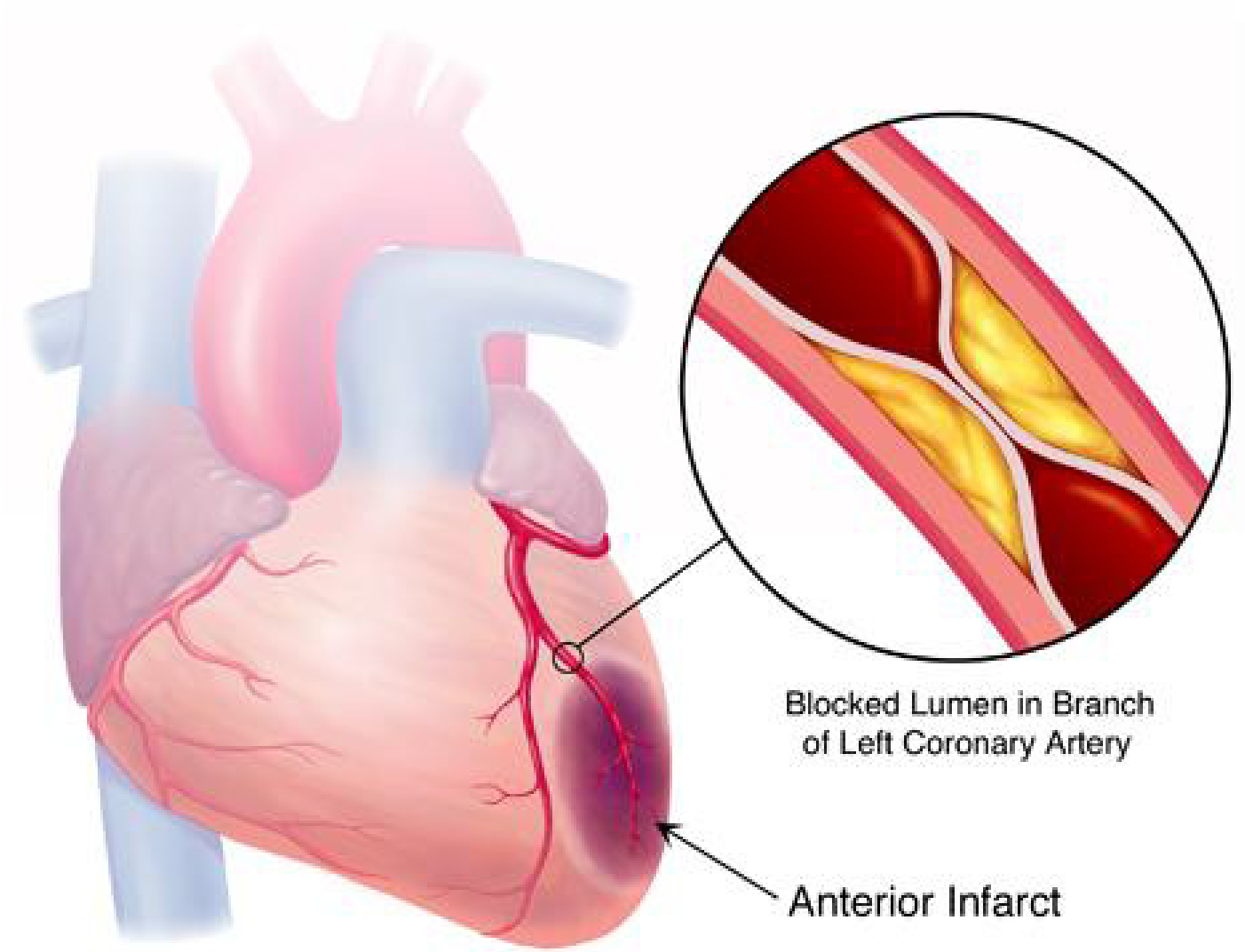
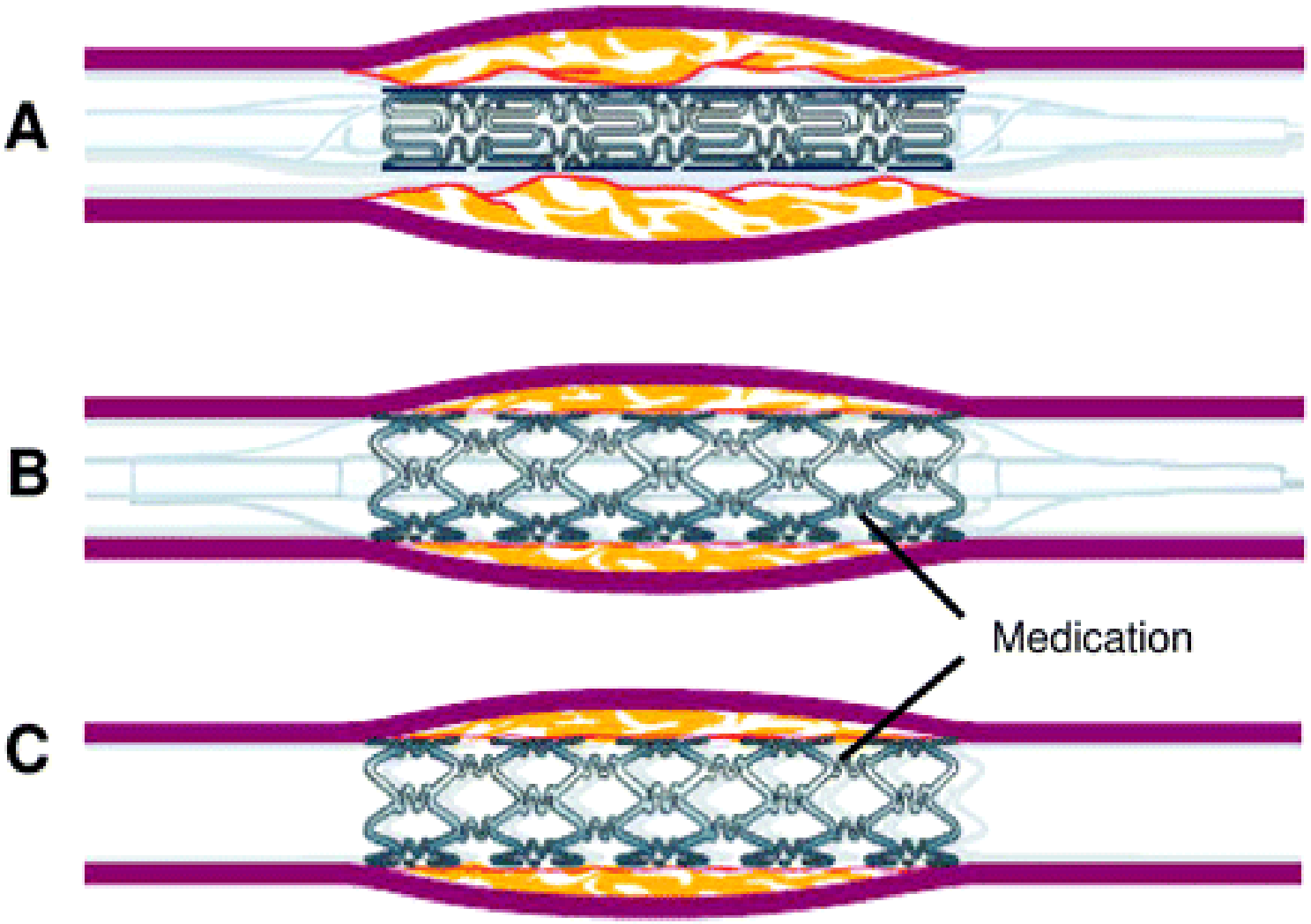
Goals and Objectives

- After reviewing the material you should gain an understanding of the variability in patient response to antiplatelet therapy
- Studies will be presented that will help you understand the importance of platelet reactivity testing on patient outcomes
- A discussion of methods of analysis will enable you to be aware of methods to measure platelet reactivity in response to antiplatelet medications
- Review emerging data showing the clinical utility of assessing response and practical impact on therapy

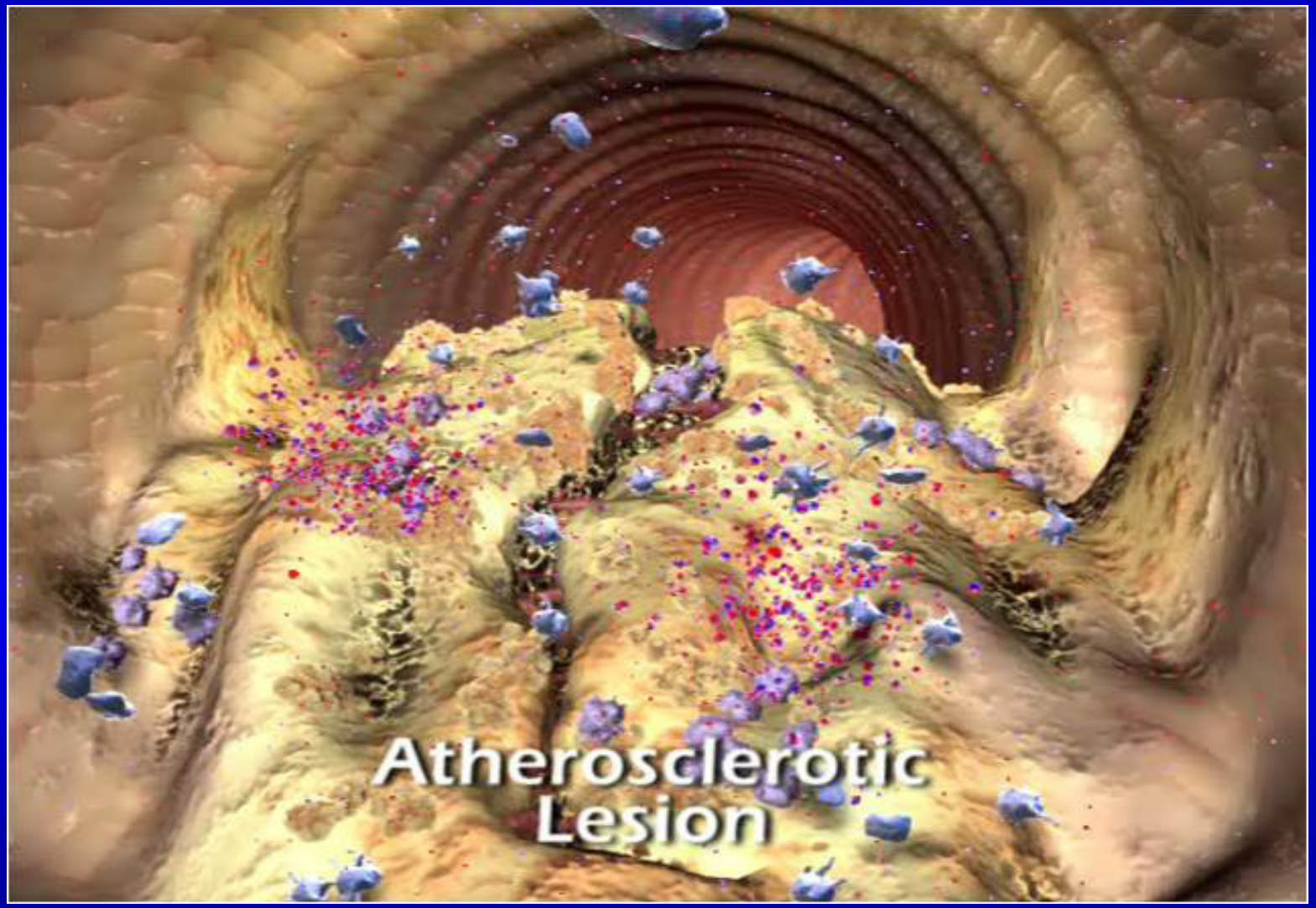
Hemostasis is achieved thru both platelet aggregation and coagulation



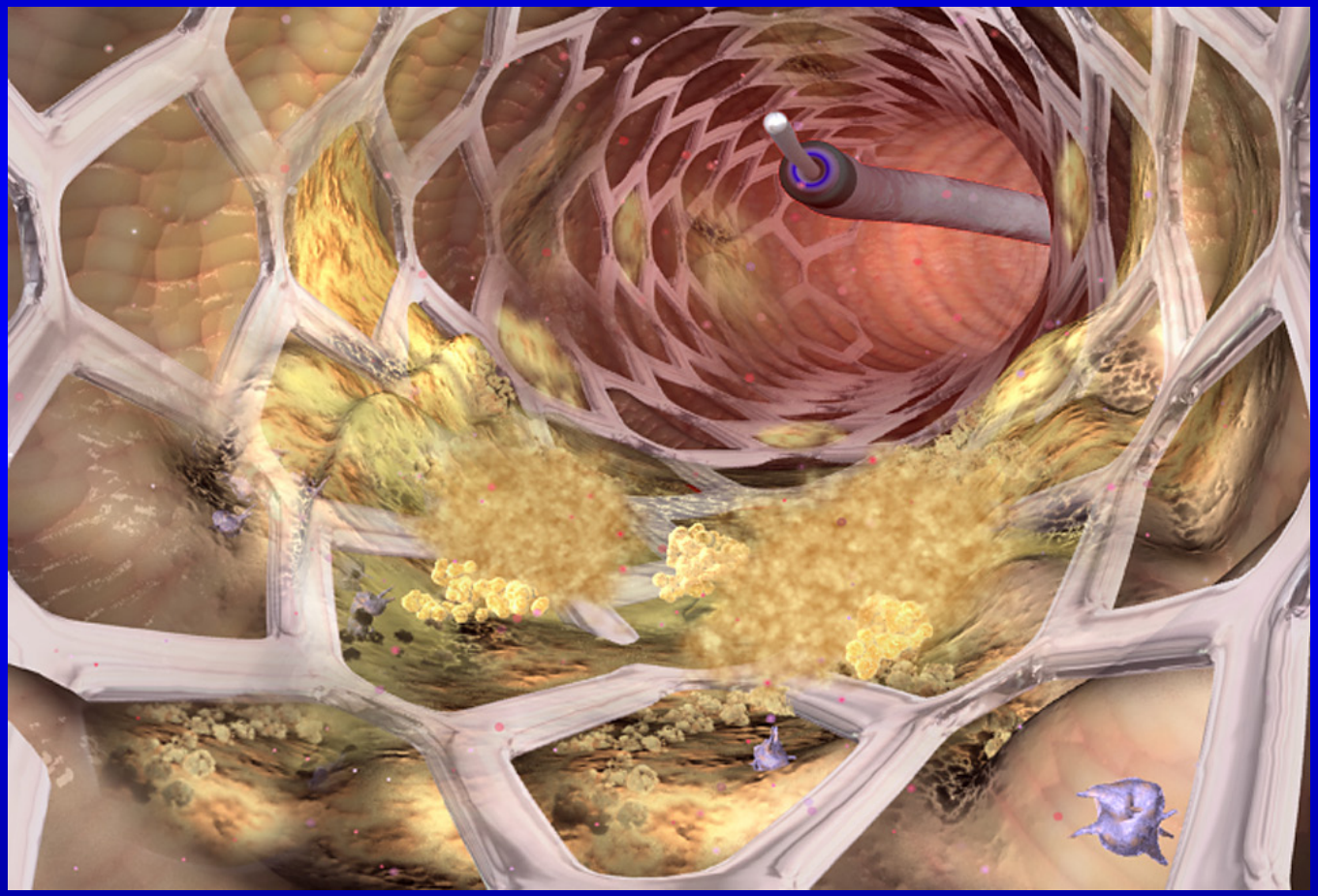

Blocked Lumen in Branch
of Left Coronary Artery
Anterior Infarct


A
B
C
Medication

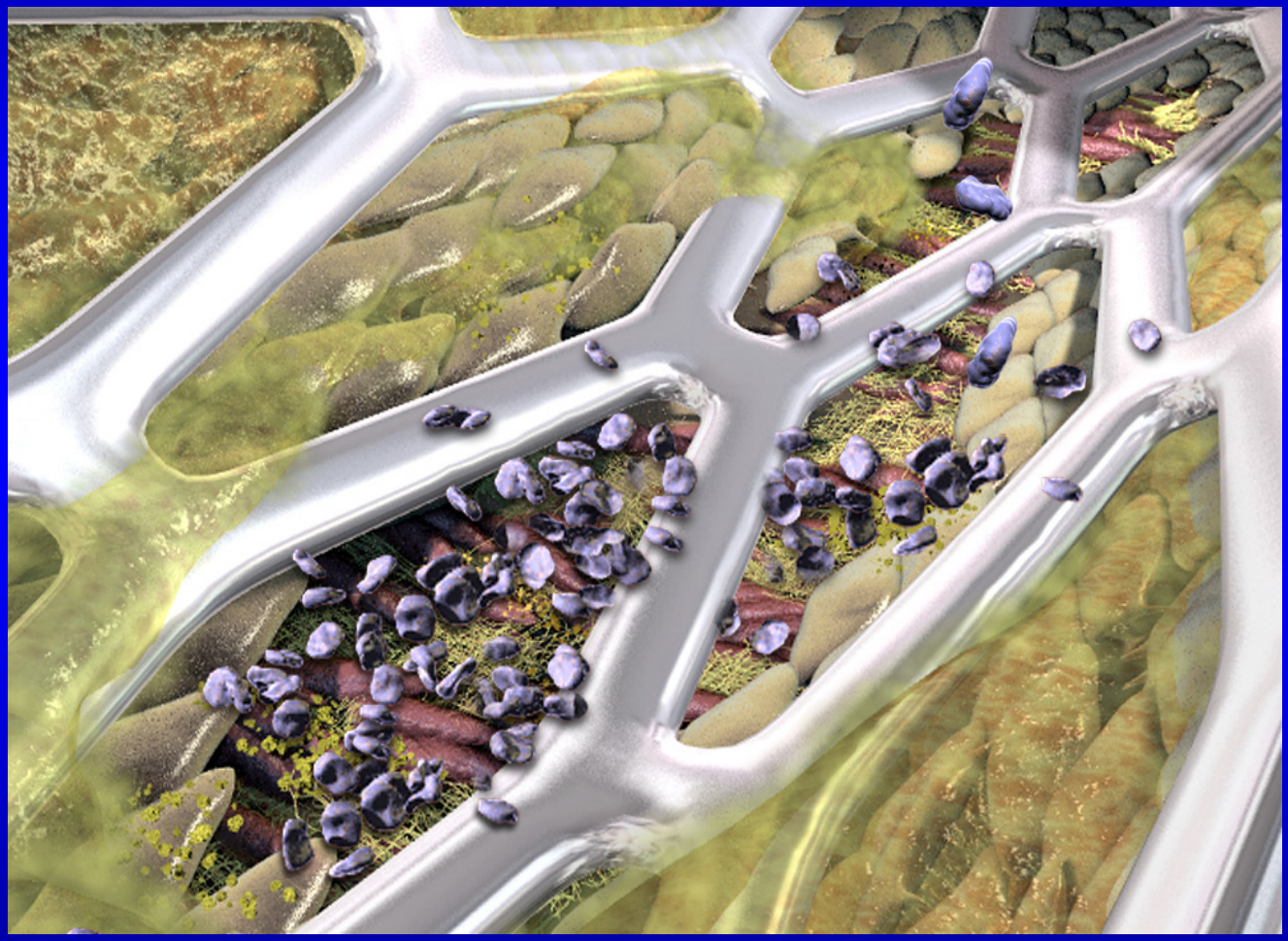
Atherosclerotic Plaque Rupture



Percutaneous Coronary Intervention (PCI) Stent Placement

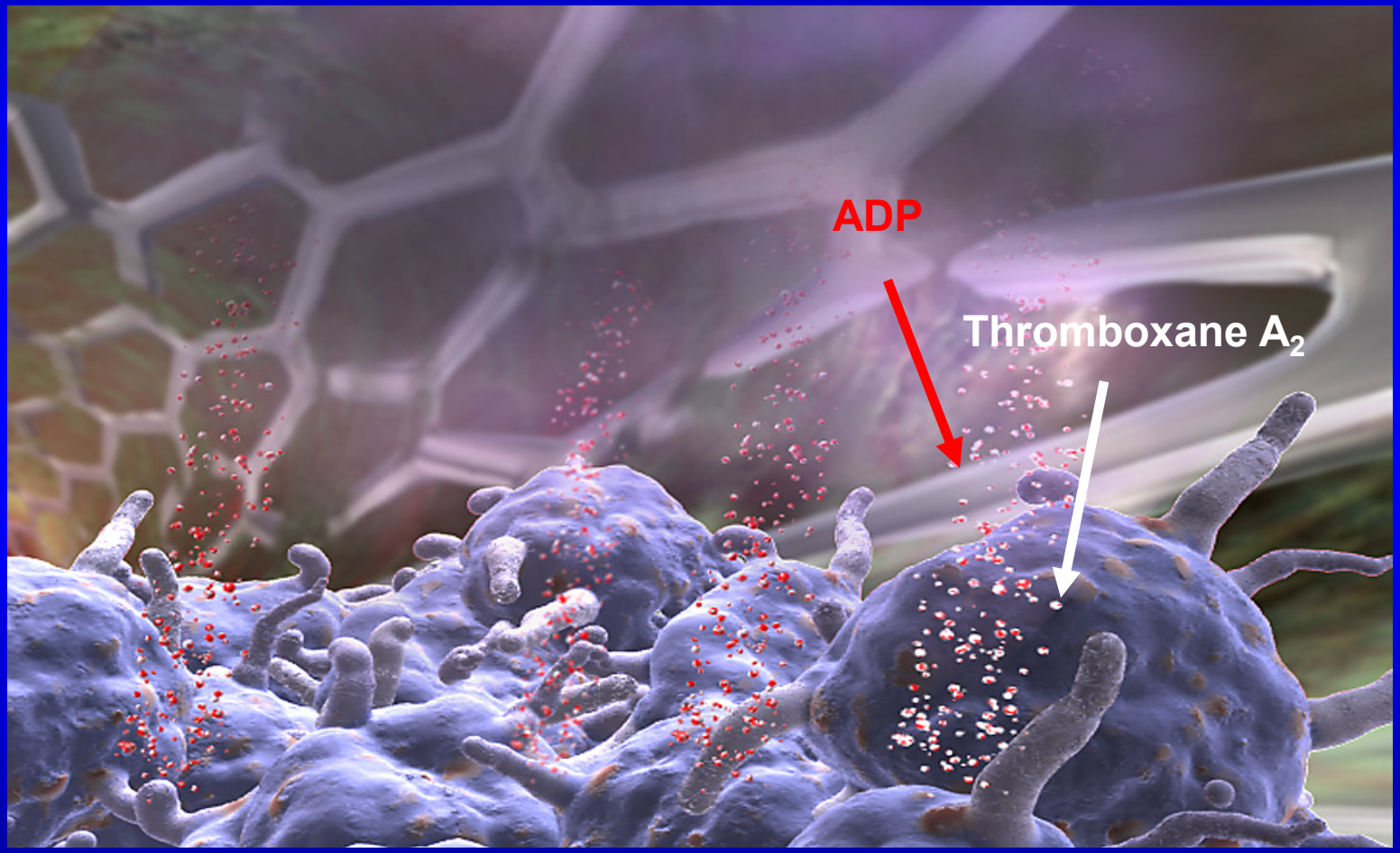


Platelet Cascade: Adhesion



Platelet Cascade: Activation

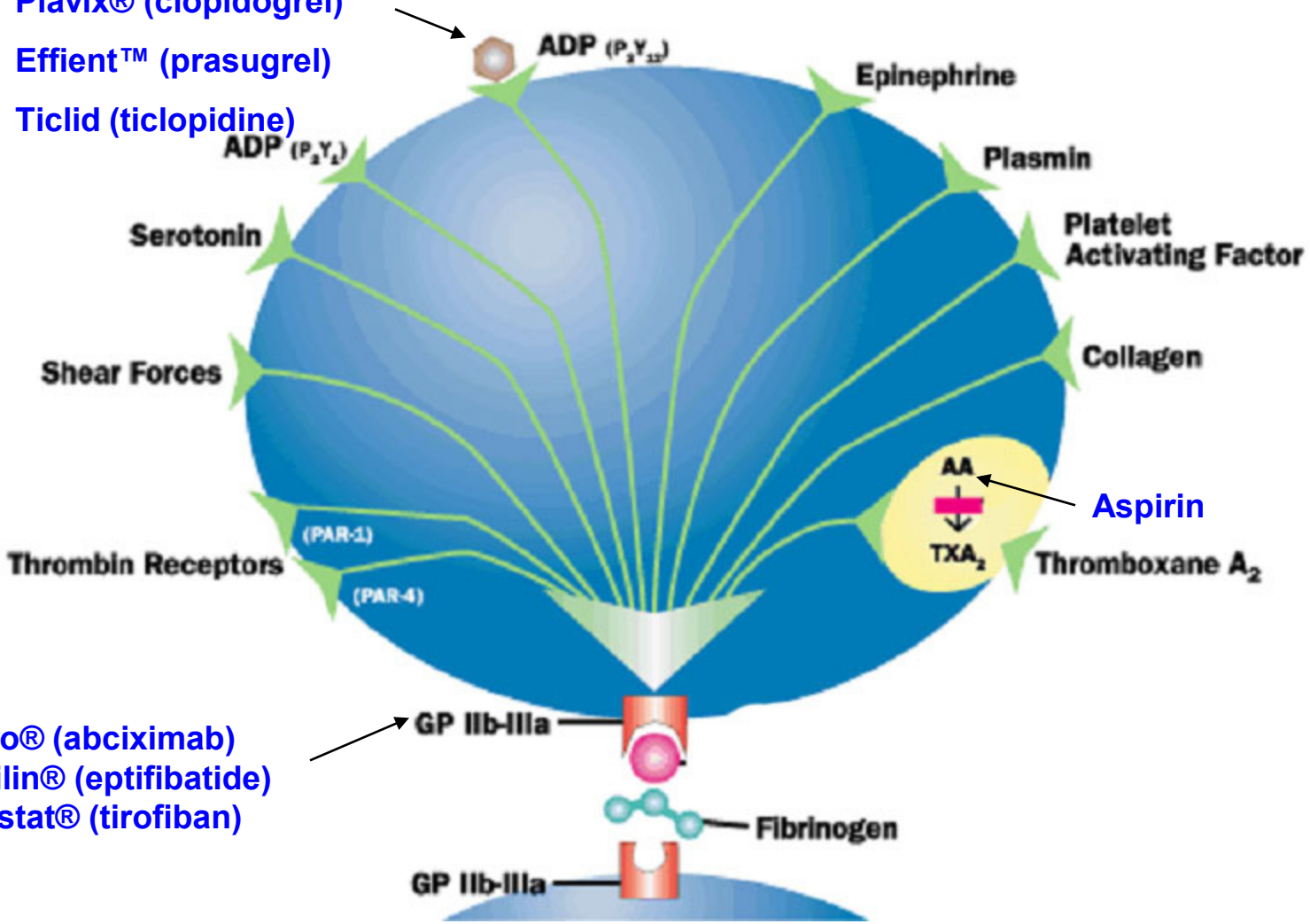
Platelet Cascade: Release of Activators



Plavix® (clopidogrel)

Effient™ (prasugrel)

Ticlid (ticlopidine)

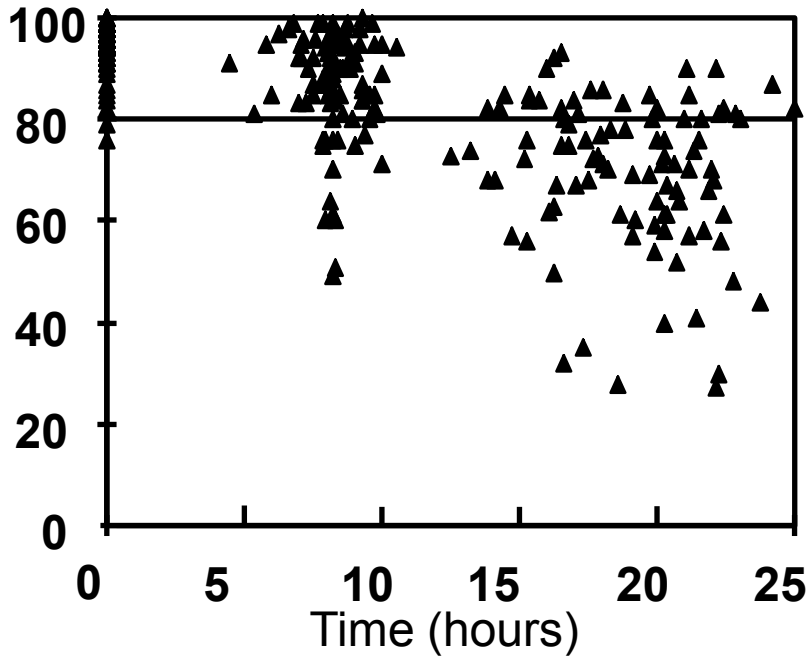


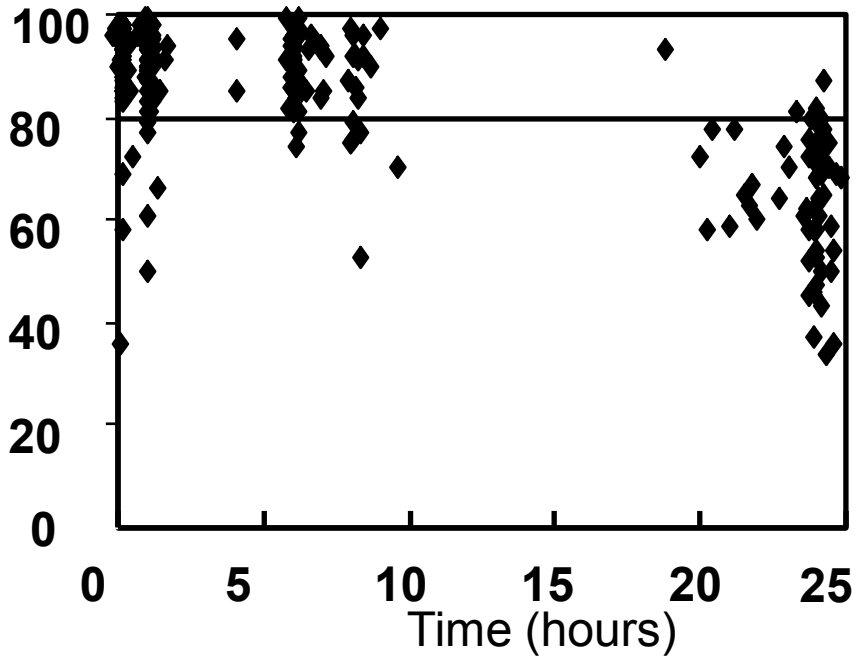
Aspirin

ReoPro® (abciximab)
Integrilin® (eptifibatide)
Aggrastat® (tirofiban)

Studies have shown substantial interpatient variability of platelet inhibition when using GP IIb/IIIa inhibitors during PCI

Abciximab platelet inhibition during and following standard bolus and infusion



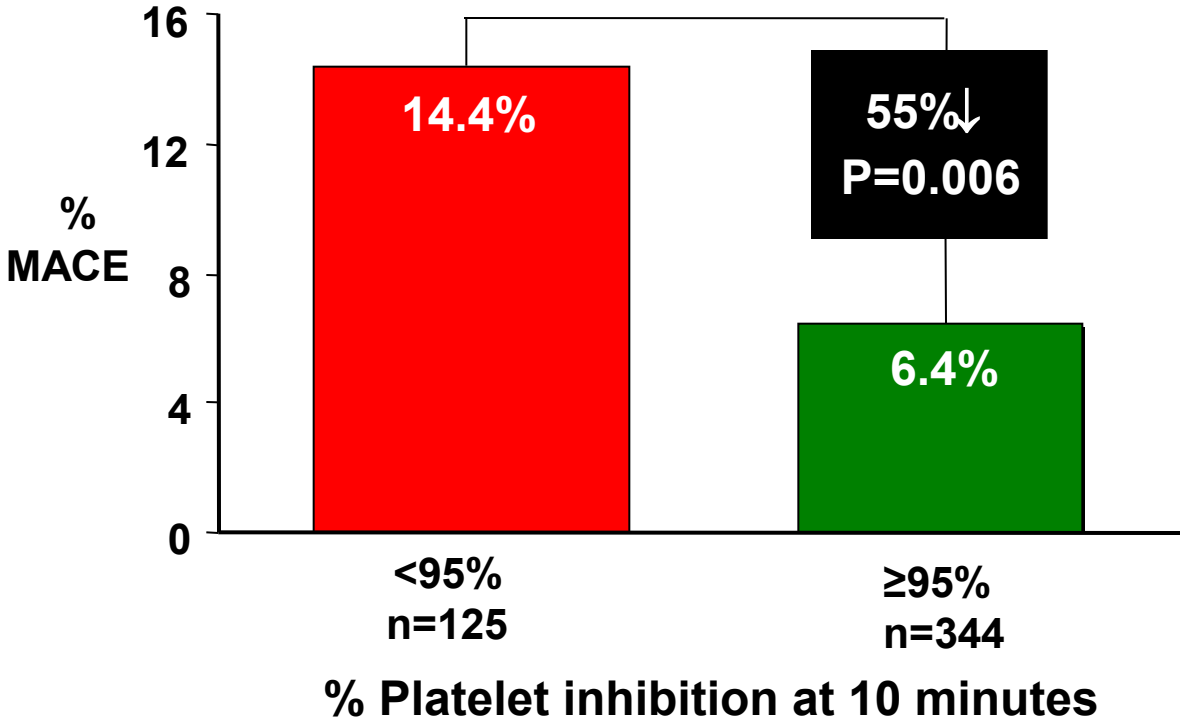


Steinhubl SR et al. *Circulation* 1999;100:1977-1982

Kereiakes DJ et al. *J Thrombosis and Thrombolysis* 1999;7:265-275

GOLD study was the first direct correlation of platelet function to clinical outcome

500 patients undergoing PCI with a IIb/IIIa antagonist

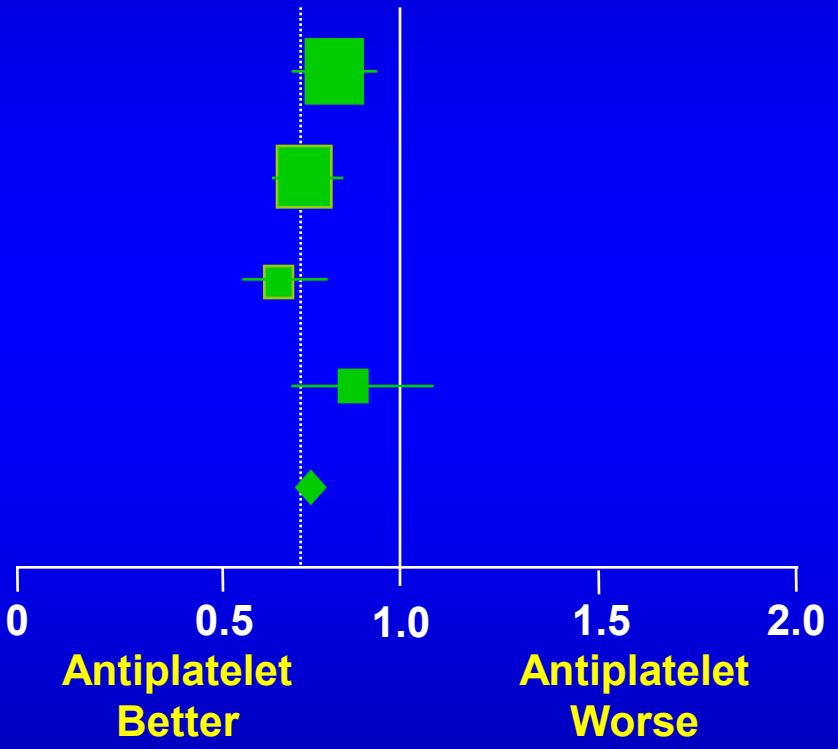


MACE = Death, Q-wave MI, Urgent TVR, Non-Q-wave MI (CKMB >3x ULN)

Steinhubl SR et al. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention. *Circulation* 2001;103:2572-2578.

ATC: Efficacy of Aspirin at Various Doses in Reducing Vascular Events* in High-Risk Patients

Aspirin (mg daily)	No. of Trials	% Odds Reduction
500-1500	34	19
160-325	19	26
75-150	12	32
<75	3	13
Any aspirin	65	23



*Vascular events included nonfatal MI, nonfatal stroke, and death from vascular causes.

Treatment effect *P*<.0001

Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71-86.

Krasopoulos, BMJ, 2008

- 20 studies, 2930 patients with CV disease. Compliance confirmed in 14 studies.
- 28% (810) ASA resistant
- ASA regime on most 75 – 325 mg/day, 6 included adjunct antiplatelet therapy
- Higher in women ($p<0.001$) and patients with previous renal impairment ($p<0.03$)

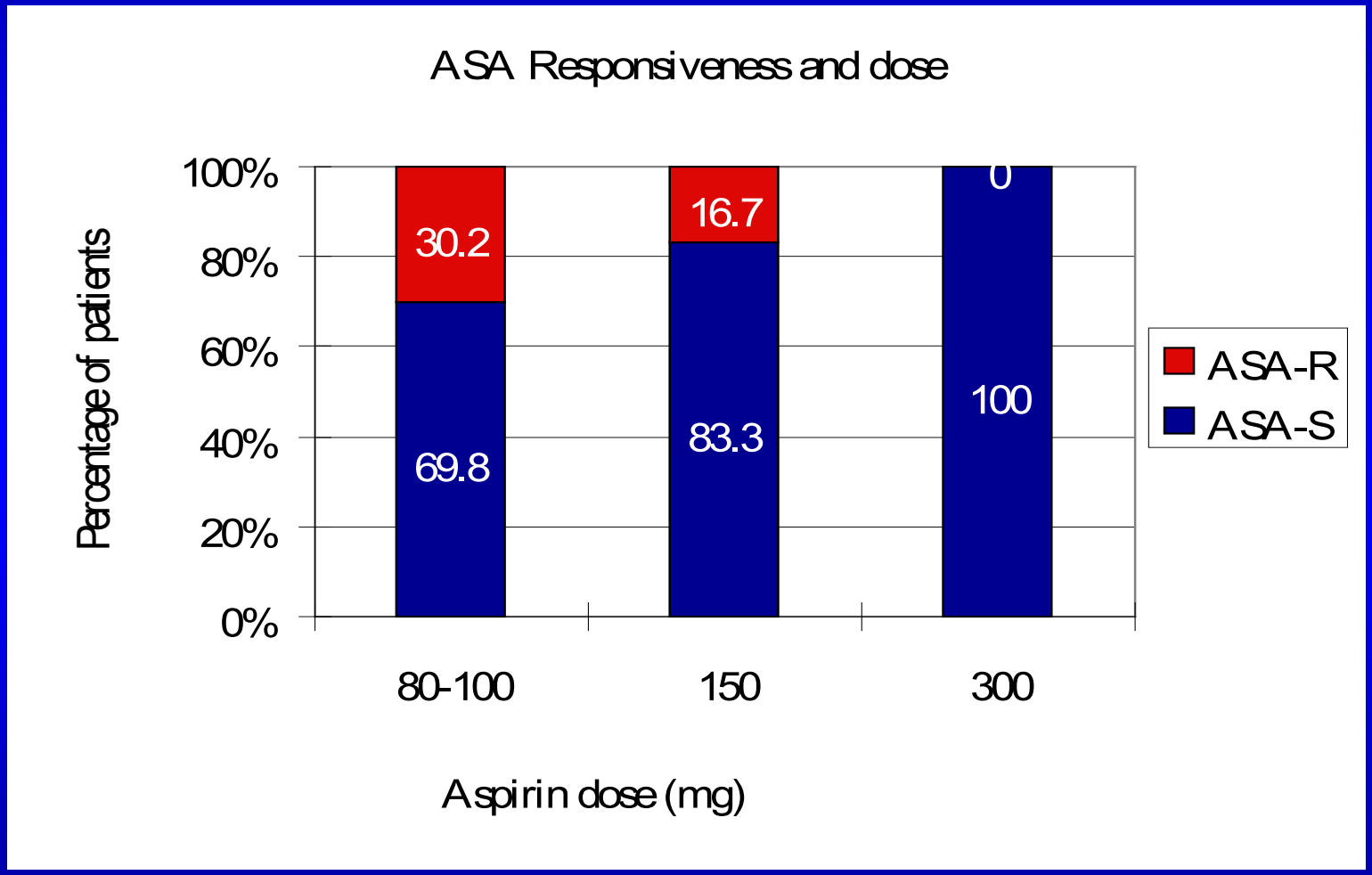
Meta Analysis Results

CV Outcome	Odds Ratio	95% CI	p
All CV events*	3.85	3.08 – 4.80	<0.001
Death	5.99	2.28 – 15.72	<0.003
ACS	4.06	2.96 – 5.56	<0.001
Graft Failure	4.35	2.26 – 8.37	<0.001
New Cerebral Event	3.78	1.25 – 11.41	<0.02

* Death, Stroke, MI, ACS

Krasopoulous et al, *BMJ* published online 17 Jan 2008

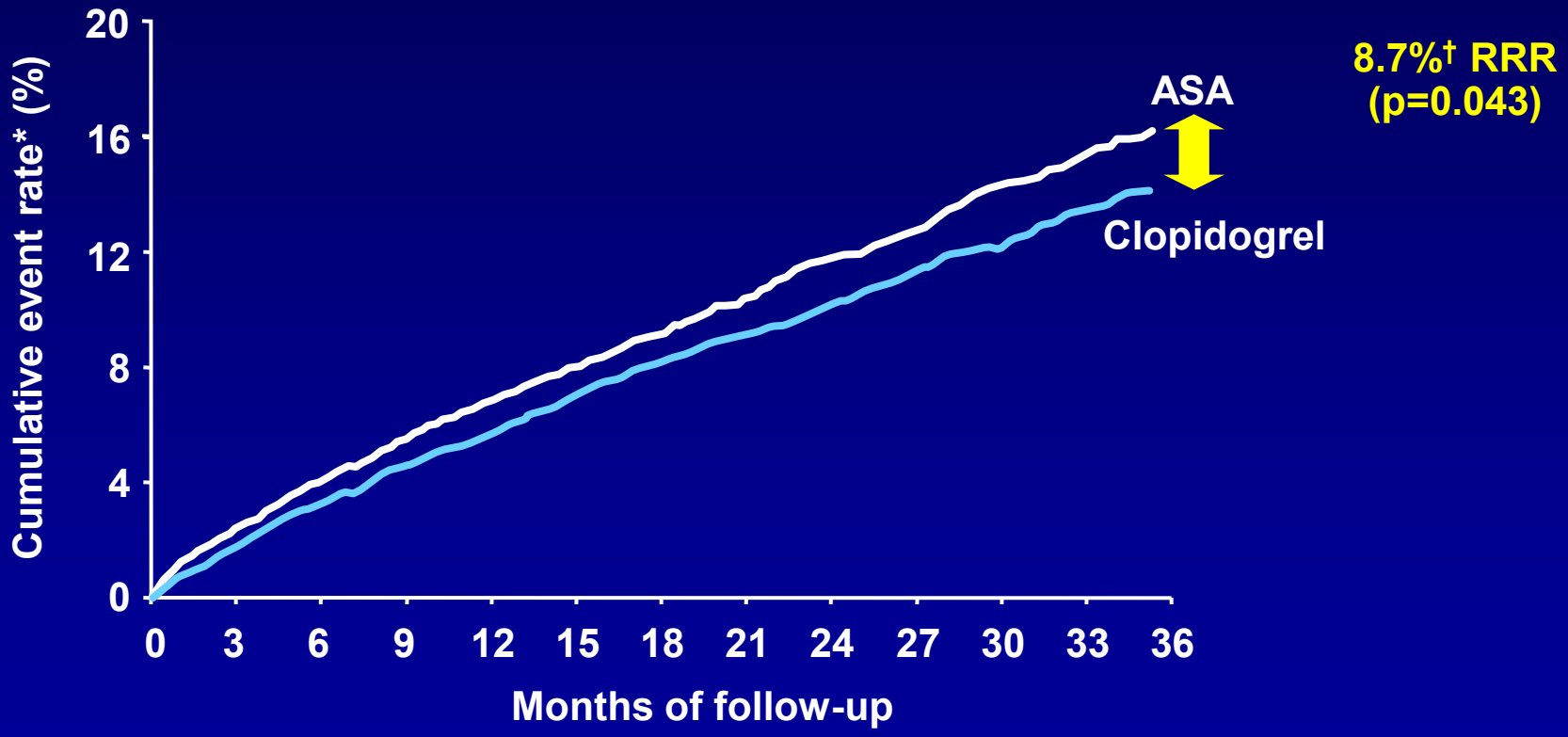
Aspirin non-responsiveness decreases with increasing dose



Lee et al. Low-dose aspirin increases, Aspirin resistance. American Journal of Medicine, July 2005.

CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent ischemic stroke, recent MI or symptomatic PAD

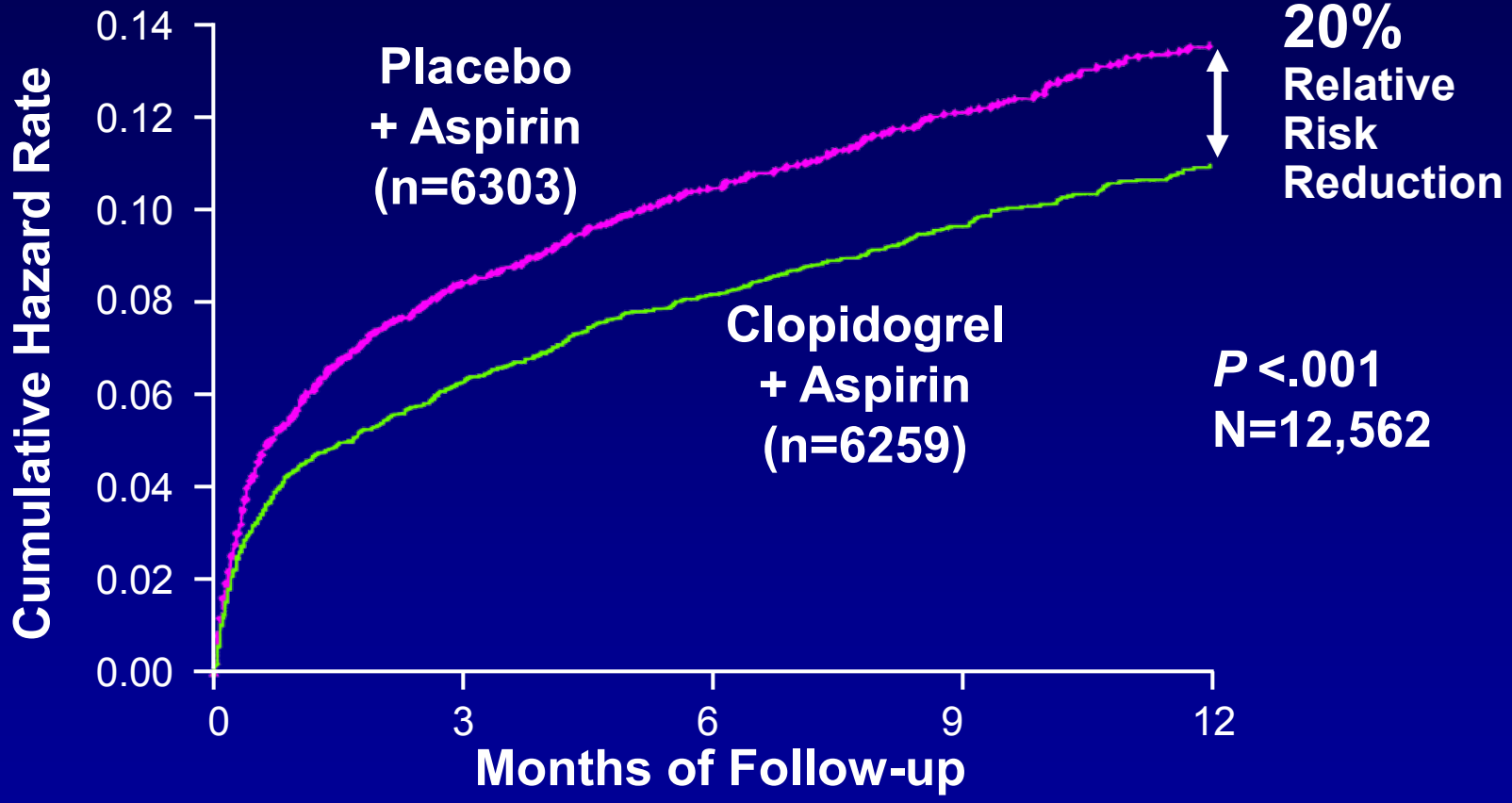


*MI, ischemic stroke or vascular death

†Intent-to-treat analysis (n=19,185) MI within 35 days, ischemic stroke within 6 mo, PAD

CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339.

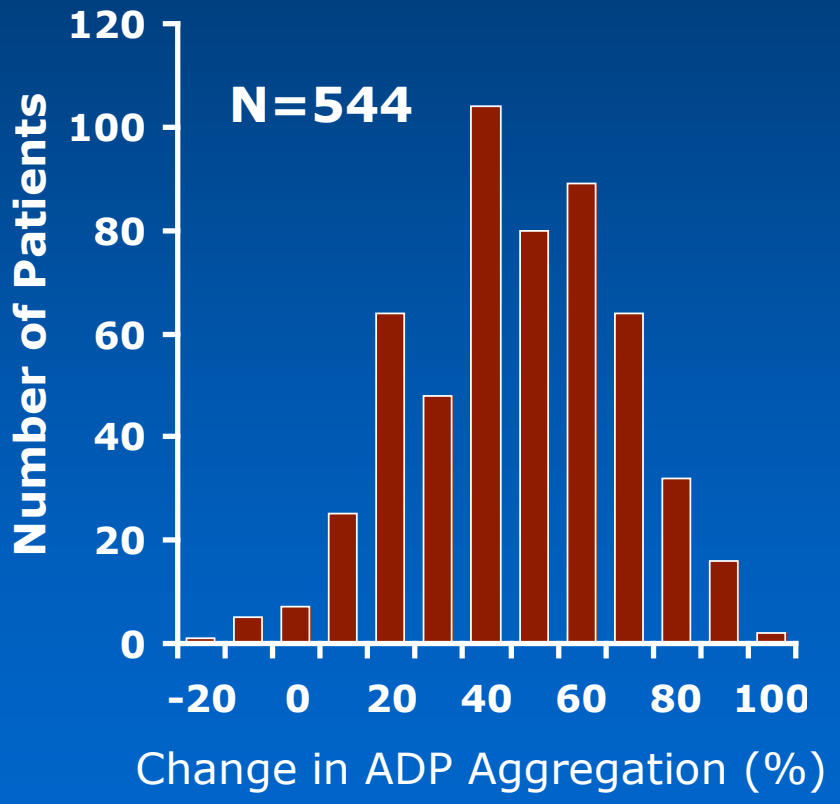
CURE Study: Primary End Point: MI/Stroke/CV Death



Yusuf S, et al. *N Engl J Med.* 2001;345:494-502. 12,562 ACS non-STEMI patients presenting within 24 hours of of onset of most recent chest pain episode or symptons consistent with ischemia

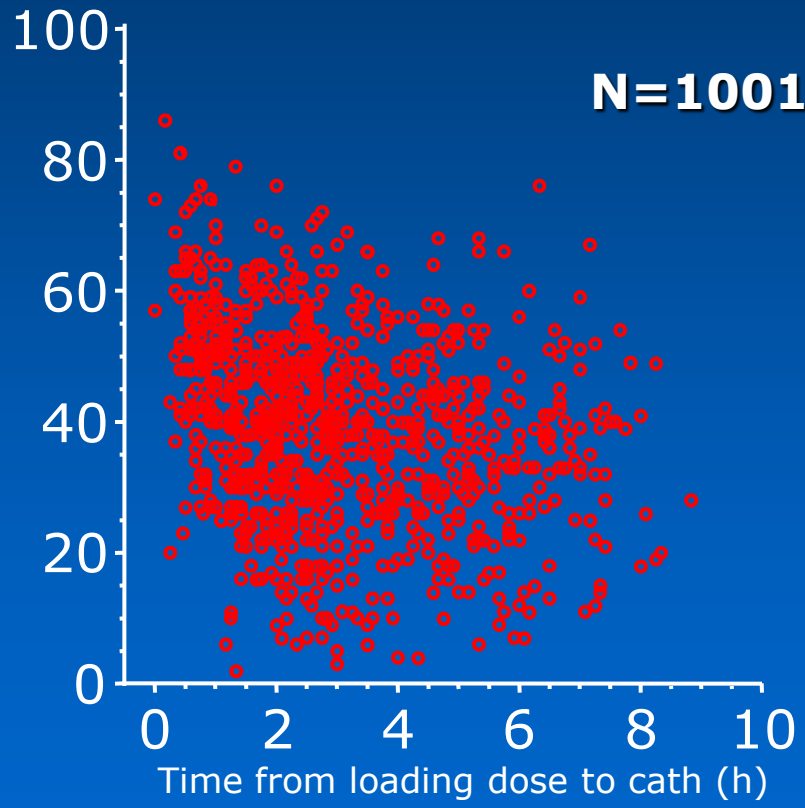
Variability in Plavix® Response

Change in ADP-Induced Platelet Aggregation 75 mg chronic dosing



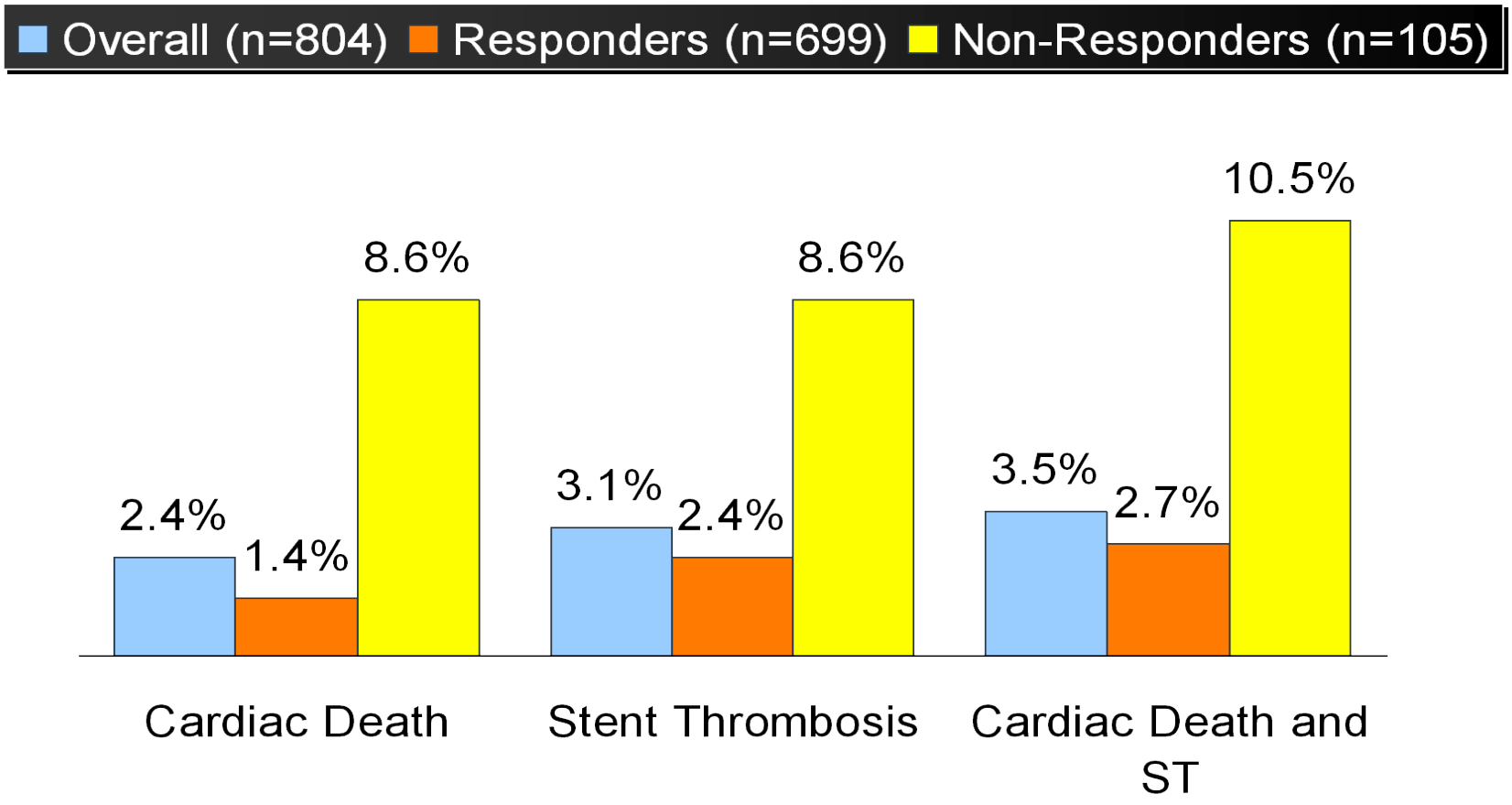
Serebruany. J Am Coll Cardiol. 2005

Maximal aggregation 5 µmol/L ADP (%) following 600 mg loading dose



Hochholzer W et al., Circulation 2005

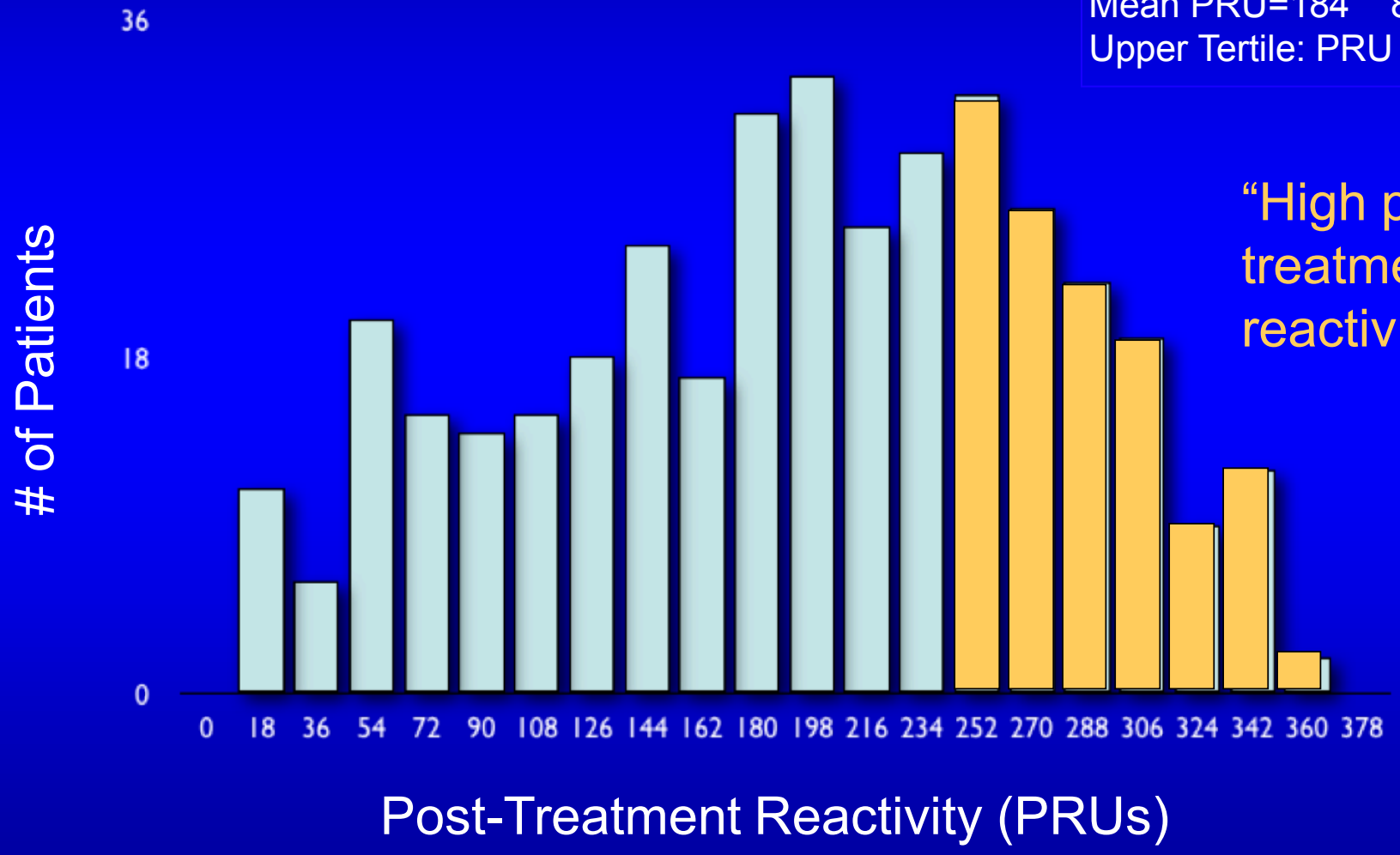
The Reclose Study: 6 Month Outcomes After DES Implantation Stratified By Post-Plavix ADP-mediated Platelet Reactivity to 600 mg loading dose clopidogrel



Buonamici et al, JACC, June 2007

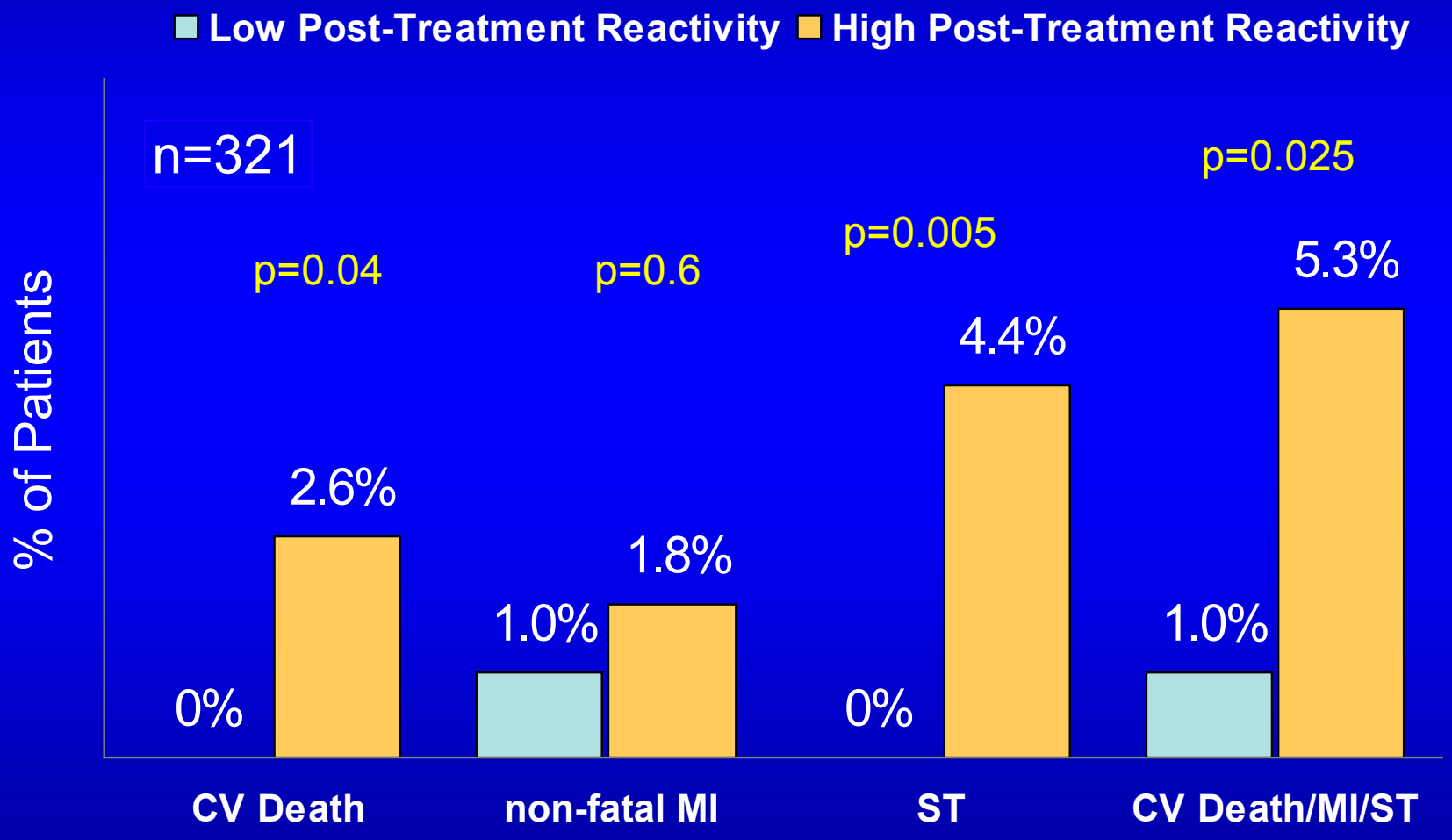
Distribution of Post-Treatment Reactivity (n=380)

Mean PRU=184 85
Upper Tertile: PRU > 231



Price et al, Eur Heart J, 2008

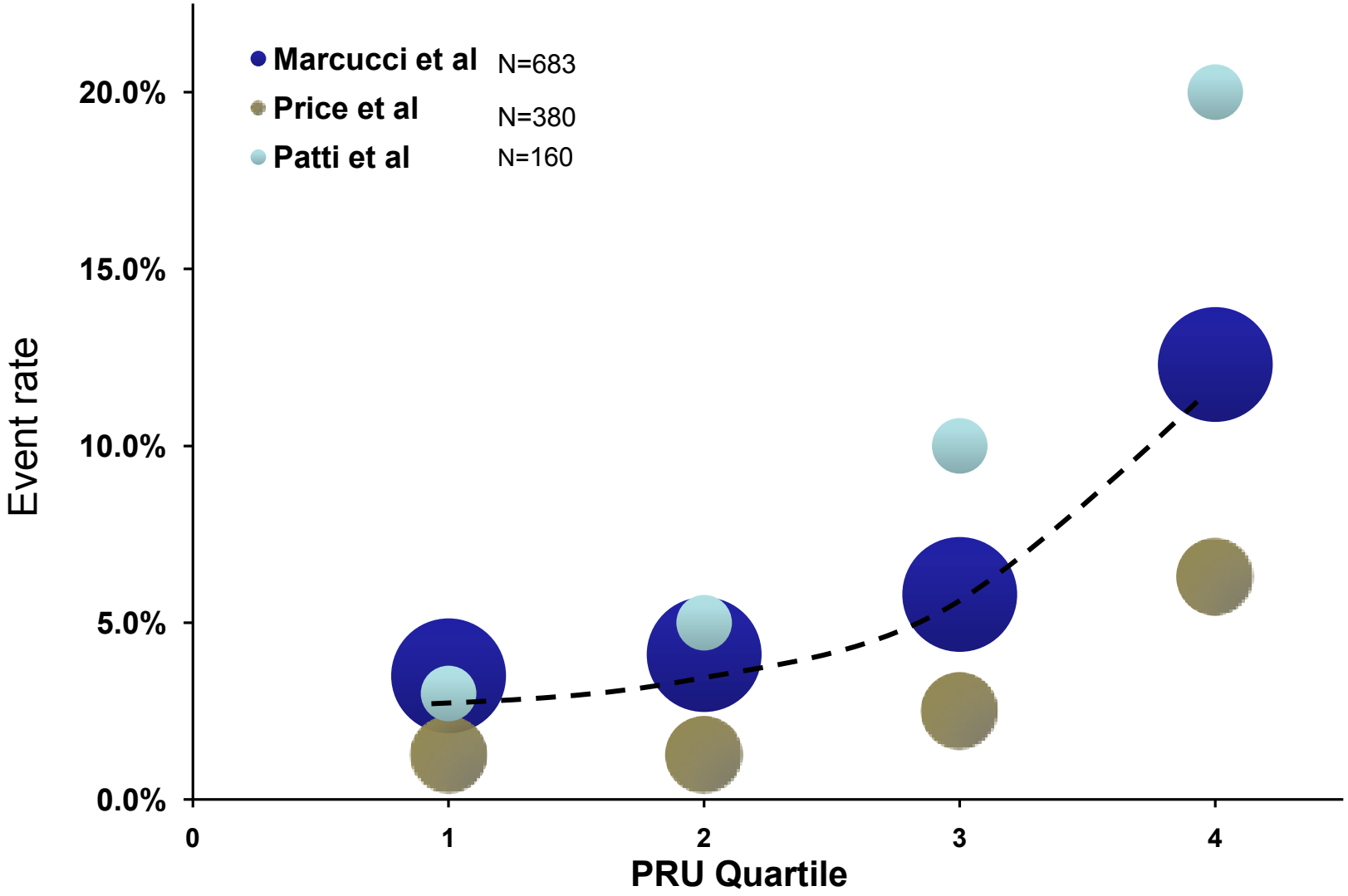
Out-of-hospital 6 Month Outcomes Stratified By Reactivity In Patients On Consistent Clopidogrel Therapy At 6 months*



*on clopidogrel at 30 day & 6 month FU, or reached an endpoint on clopidogrel by 6 month FU

Increasing Risk With Greater Residual Reactivity

Event Rates In Prospective PCI Studies Stratified By PRU Quartile

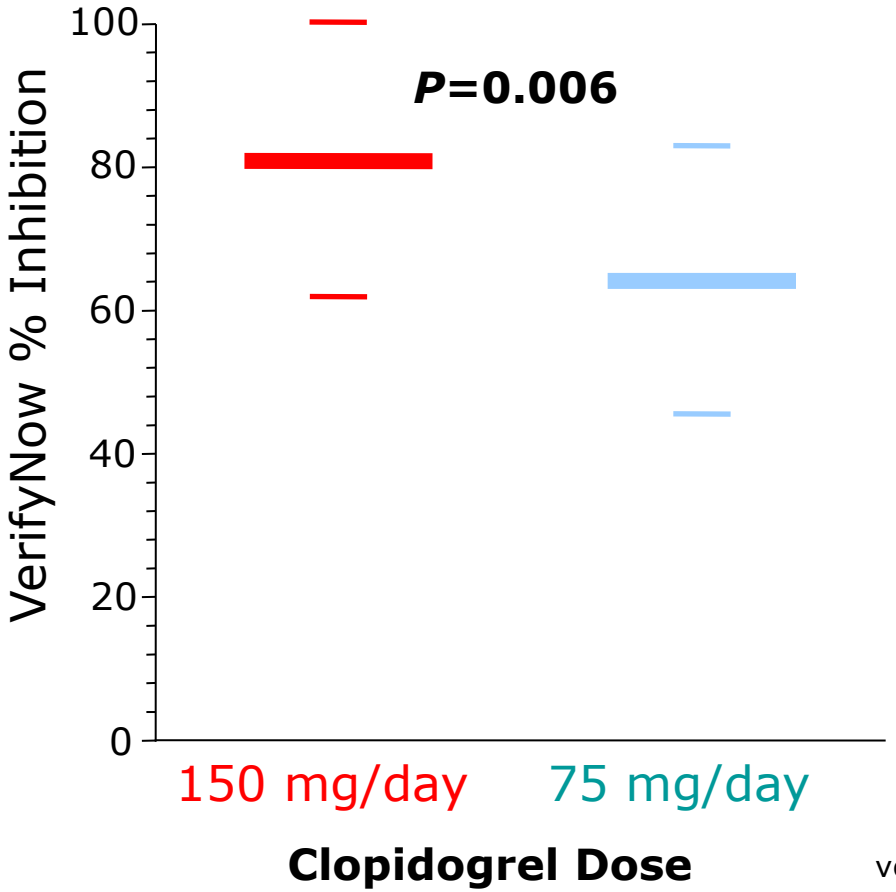


Patti, G. et al. J Am Coll Cardiol 2008;52:1128-1133

Price MJ et al. Eur Heart J 2008; 29:992-1000 Marcucci et al, Circulation 2009

ISAR-CHOICE 2

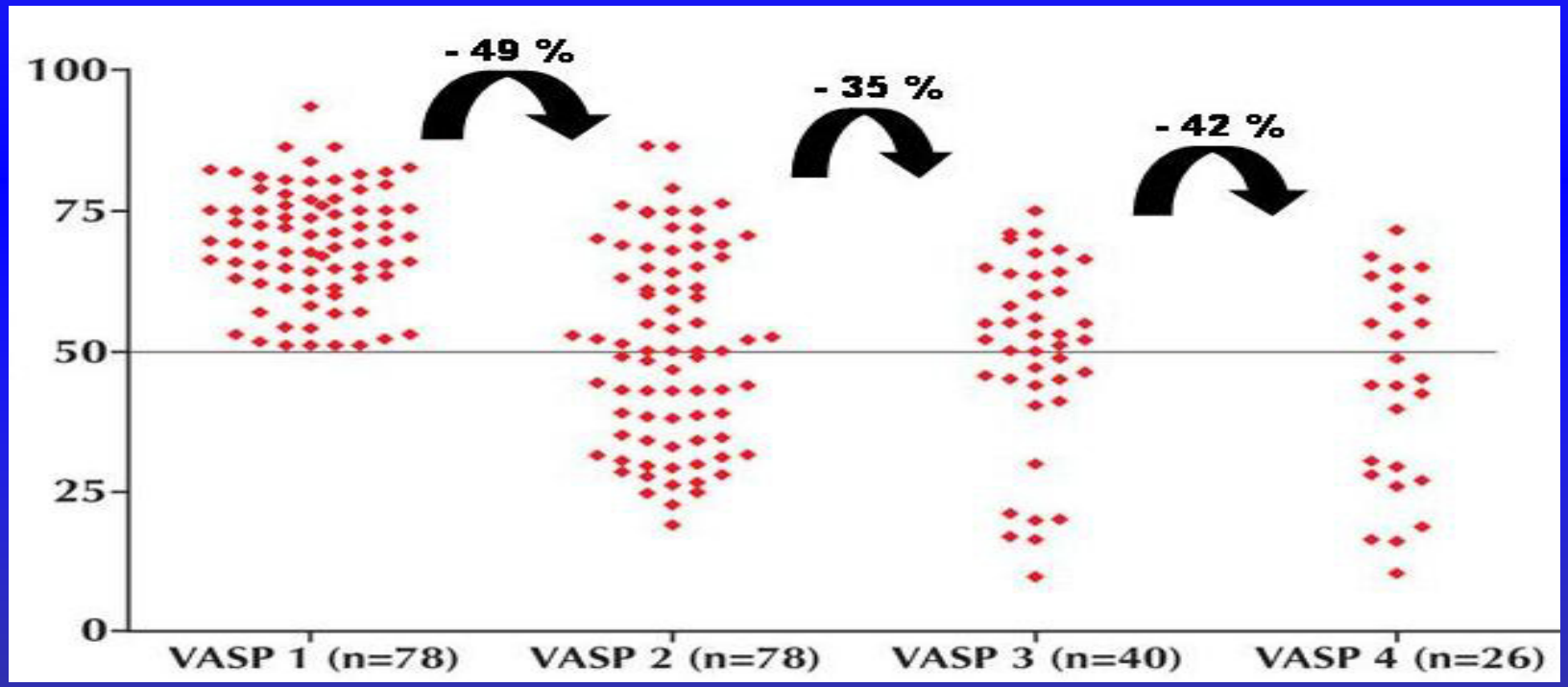
Doubling the Daily Dose of Clopidogrel After PCI Improves Inhibition At 30 Days



von Beckerath, Eur Heart J 2007

Loading Dose Adjustment: VASP Assay

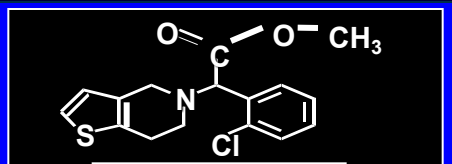
- Each additionnal bolus of 600 mg of clopidogrel decreased the number of patients with low response from 35 to 49%.
- Despite 2400 mg of clopidogrel 11 (14%) patients remained low-responders.



Bonello L. et al, Eur Heart J 2008

WHY?

Thienopyridines: Formation of Active Metabolite

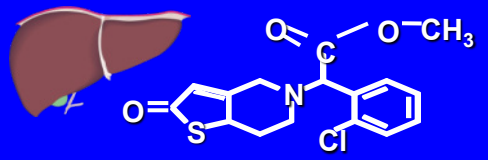


Clopidogrel

85% Inactive Metabolites

CYPs:
1A2
2C19
2B6

Oxidation (Cytochrome P450)

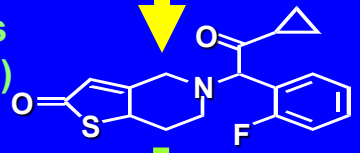


CYPs:
3A
2C19
2C9
2B6

Active Metabolite

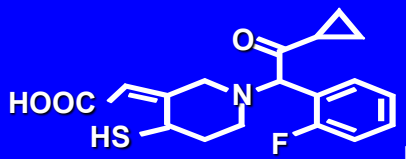
Prasugrel

Hydrolysis (Esterases)



CYPs:
3A
2B6
2C9
2C19

Oxidation (Cytochrome P450)



Active Metabolite

What is the probability that an individual has this genetic variant?

The Plavix package insert was recently updated to include the information regarding the frequency of the genetic variants that may contribute to decreased response as 26% in the white population, 33% in the black population, and 64% in the Asian population.

Omeprazole reduces antiplatelet effect of clopidogrel

Gilard M, Arnaud B, Cornily J-C, et al

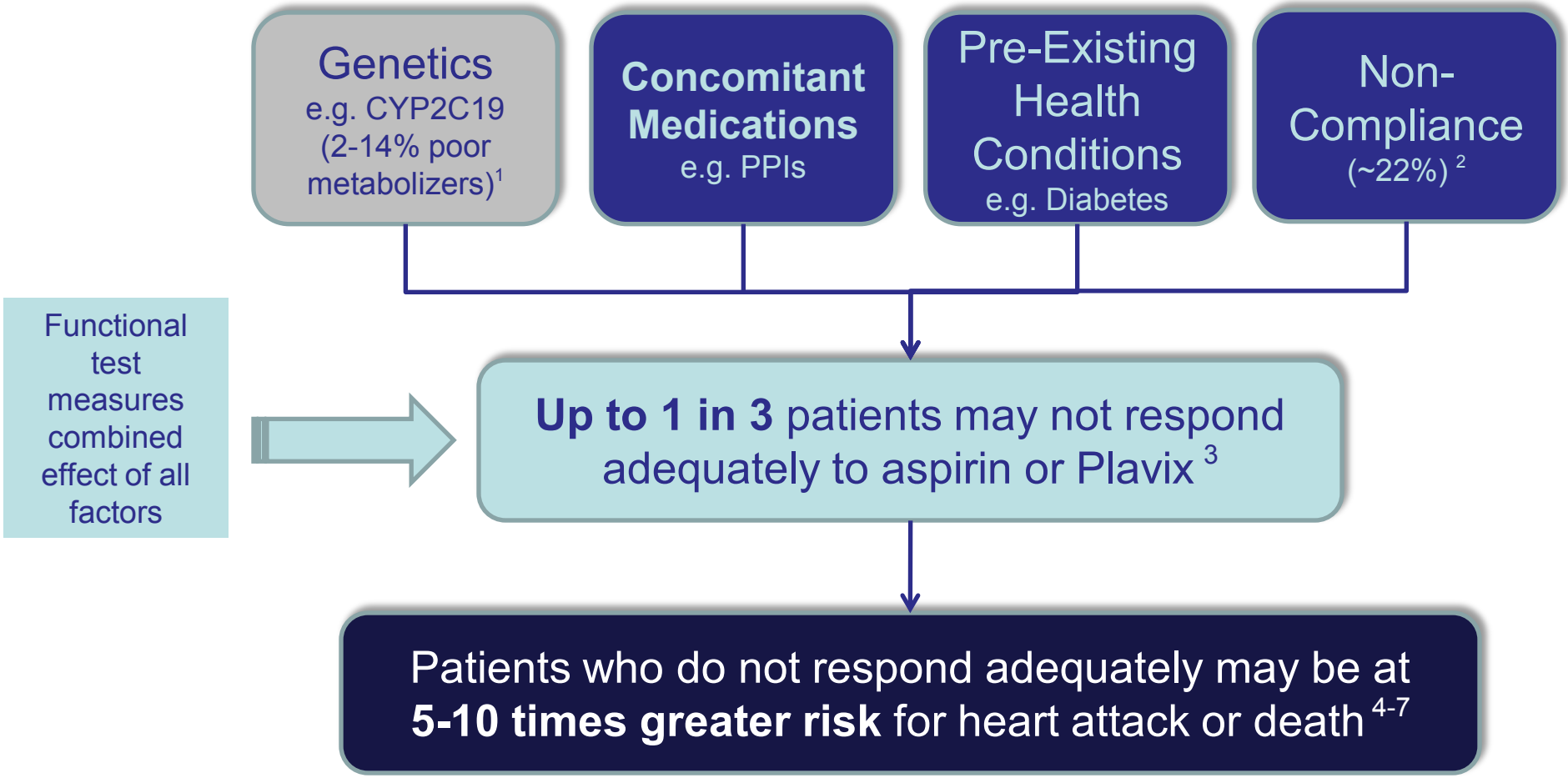
Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study.

J Am Coll Cardiol 2008;51:256–60.

Conclusion

There is more than a fourfold greater chance of being a clopidogrel "bad responder" when patients were treated with omeprazole.

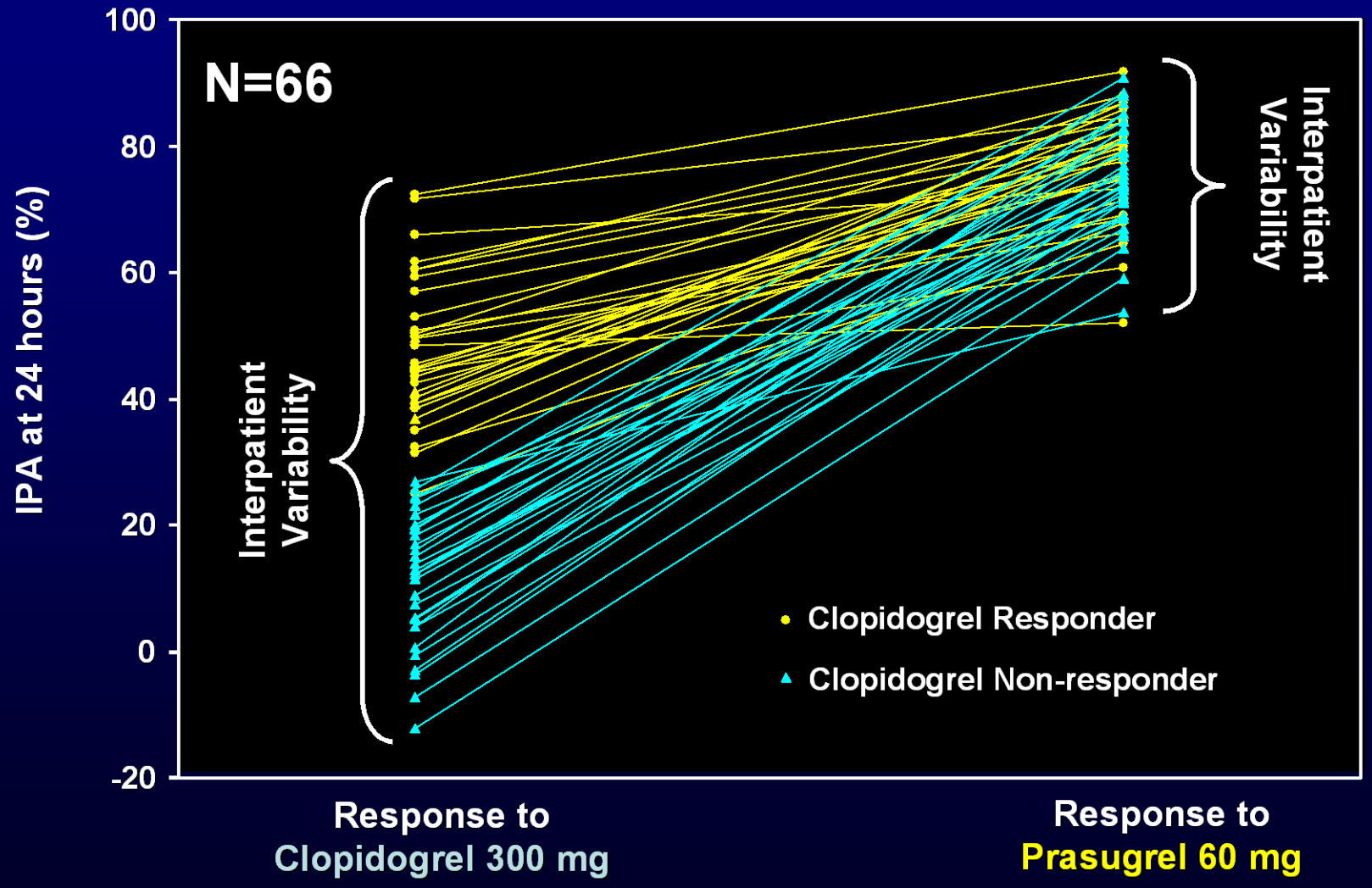
Inadequate Response to Antiplatelet Medications: Many Factors Can Contribute



References
1. US FDA at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm Accessed 3-13-10.
2. Serebruany, V. et al. *Am Heart J. 2009;158:925–932.*
3. Dupont, AG. et al. *Thrombosis Research. 2009 May;124(1):6-13.*
4. Patti, G. et al. *J Am Coll Cardiol. 2008; 52:1128–33.*
5. Marcucci, R. et al. *Circulation. 2009;119(2):237-42*
6. Cuisset, T. et al. *Am J Cardiol. 2008 Jun 15;101(12):1700-3*
7. Price, MJ. et al. *Eur Heart J. 2008 Apr;29(8):992-1000*

TRITON TIMI·38

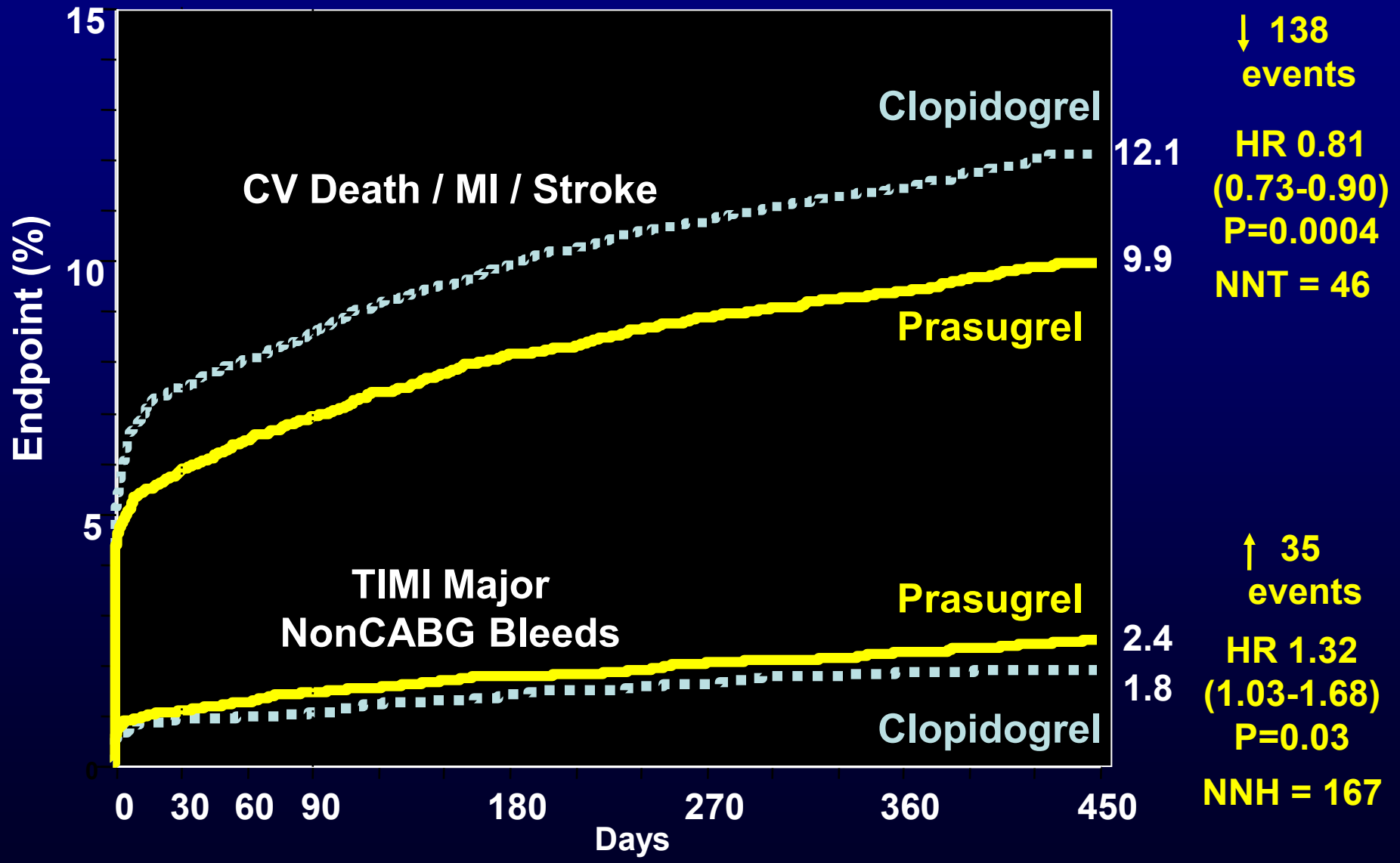
Healthy Volunteer Crossover Study



From Brandt JT AHJ 153: 66e9,2007

TRÎTON TIMI·38

Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

P2Y12 Treatment Regimes

- Clopidogrel 75 mg daily or 300 mg bolus with maintenance dose of 75 mg daily. (CAPRIE, CURE) Note: This is the FDA approved dosing for clopidogrel. Discussion of other regimes is off-label.
- Clopidogrel 600 mg bolus with maintenance dose of 75 mg daily (Most common current practice)
- Clopidogrel 600 mg bolus followed by 150 mg for 7 days then 75 mg daily (OASIS-7 presented at ESC 2009, TCT 2009)
- Prasugrel, 60 mg loading dose followed by 10 mg daily. Note Black Box Warning. (Triton TIMI-38 and 44)
- Prasugrel, 60 mg loading dose followed by 5 mg daily (patient <60 kg). Per package insert, t*he effectiveness and safety of the 5 mg dose have not been prospectively studied.*
- Ticlopidine (STARS) (used if clopidogrel option required)
- Refer to Surgeon
- Combination

Discontinuation of Antiplatelet Medications

Safety and Bleeding Management

Patients on Plavix® have increased risk of bleeding

- During CABG surgery, patients on Plavix® received 3.5X more blood products[1]
- Blood loss in first 24 hours after surgery was almost 2X when comparing patients off Plavix <4 days vs. patients off Plavix ≥5 days[2]
- Associated with higher postoperative bleeding and morbidity and mortality[3]
- 10X greater rate of re-operation[4]

[1]Chen et al. *J Thorac Cardiovasc Surg* 2004;128:425-31

[2]Chu et al. *Ann Thorac Surg* 2004;78:1536-41

[3]Ascione et al. *Ann Thorac Surg* 2005;79:1210-6.

[4]Hongo et al. *J Am Coll Cardiol* 2002;40:231-7

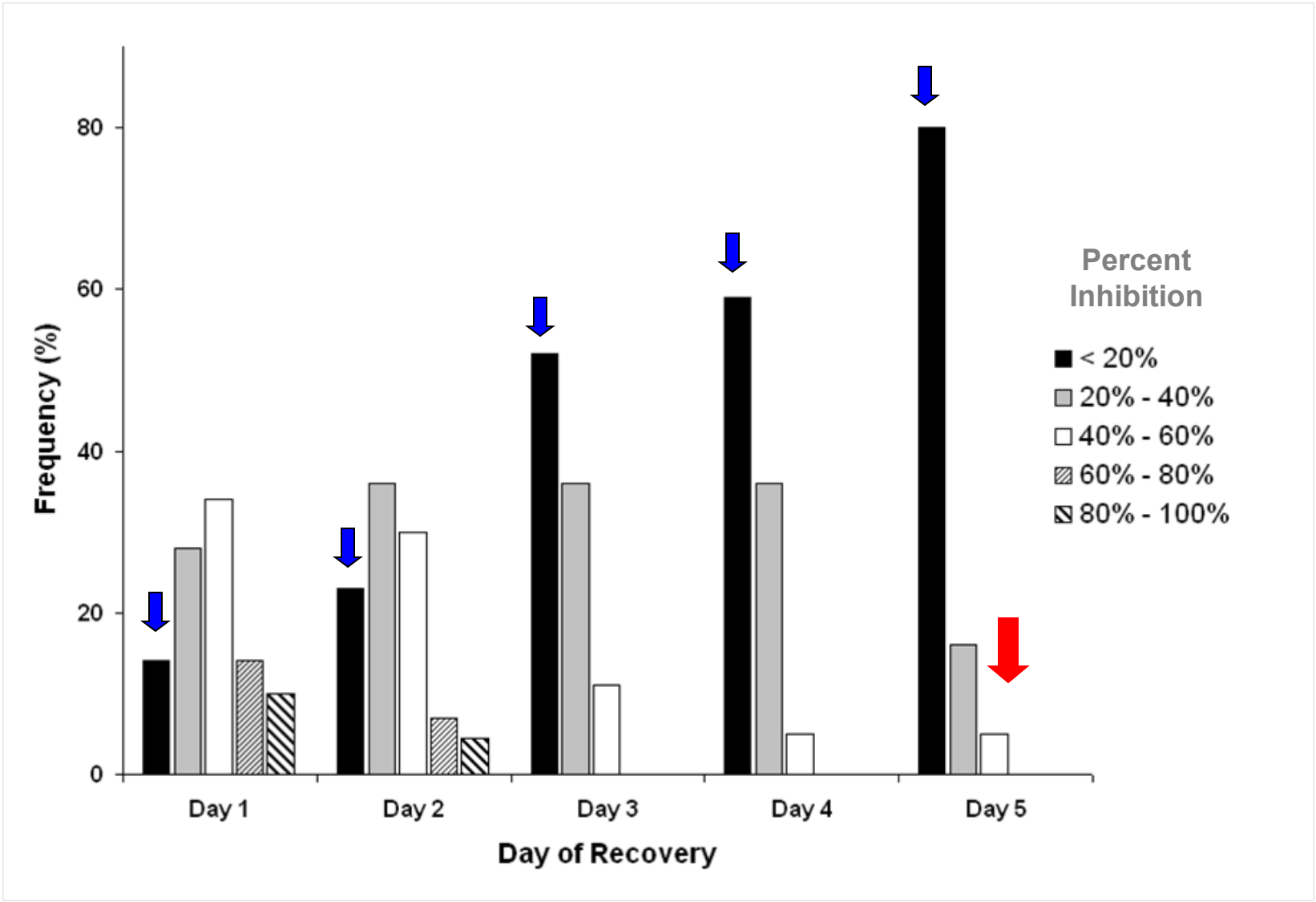
As % platelet inhibition increases, so does the need for transfusions

ADP aggregometry % inhibition	# pts	Last Plavix dose days (range)	Platelet transfusion		RBC transfusion (# units)
			Incidence (%)	# units	
>60%	12	2.0 0.4 (1-5)	92*	16.6 2.8*	5.8 1.0*
40-60	17	2.5 0.5 (1-6)	35	3.4 1.2	2.2 0.5
<40%	14	2.3 0.4 (<1-5)	21	1.7 1.0	1.7 0.4

*p<0.05 compared with 40-60% and <40%

Chen et al. Clopidogrel and bleeding in patients undergoing elective CABG. *J Thorac Cardiovasc Surg* 2004;128:425-31.

Frequency Distribution of Platelet Inhibition After Cessation of Daily Clopidogrel Therapy



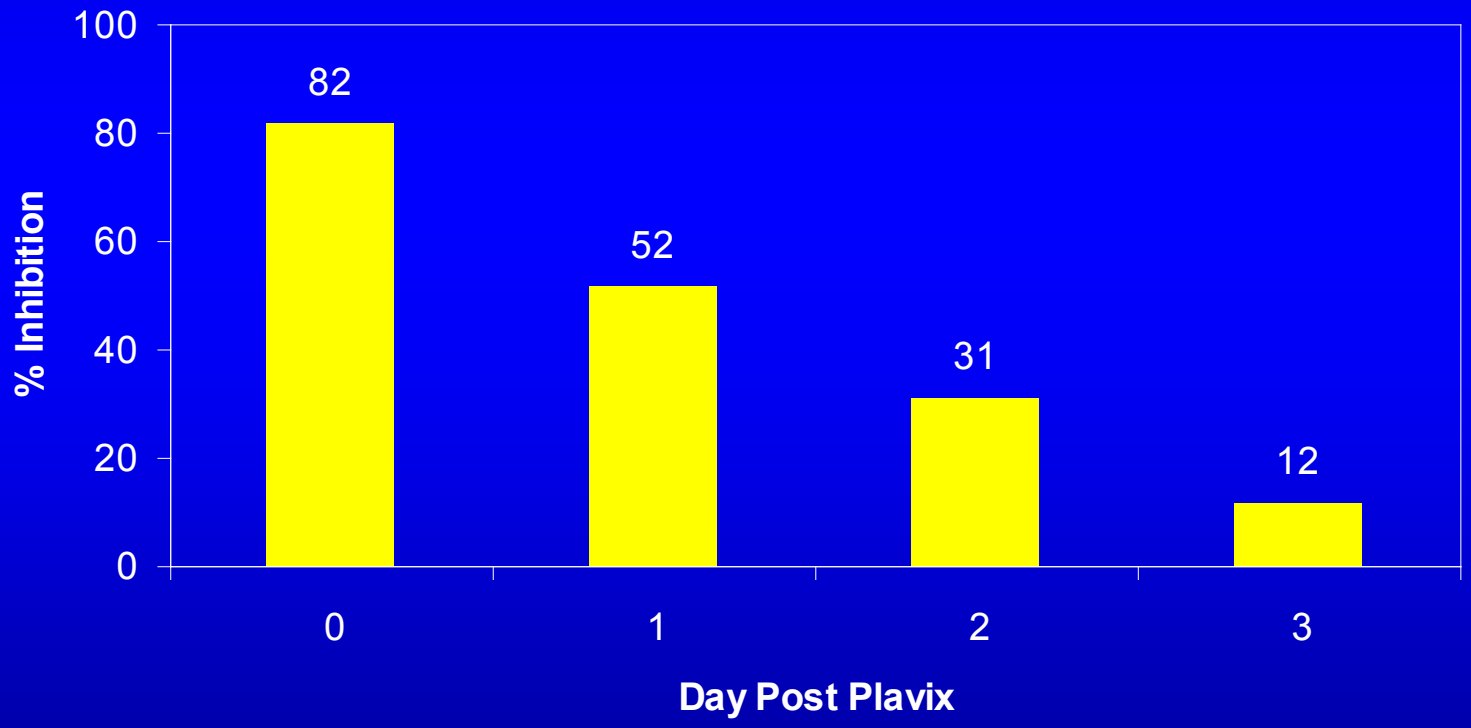
A Multimodal Approach for the Reduction of Allogeneic Blood Products Following Coronary Artery Bypass Grafting Utilizing Transcollation™ Technology

Shankha Biswas, MD; Bradford Ray, NRABT
Riverside Community Hospital, Riverside, CA

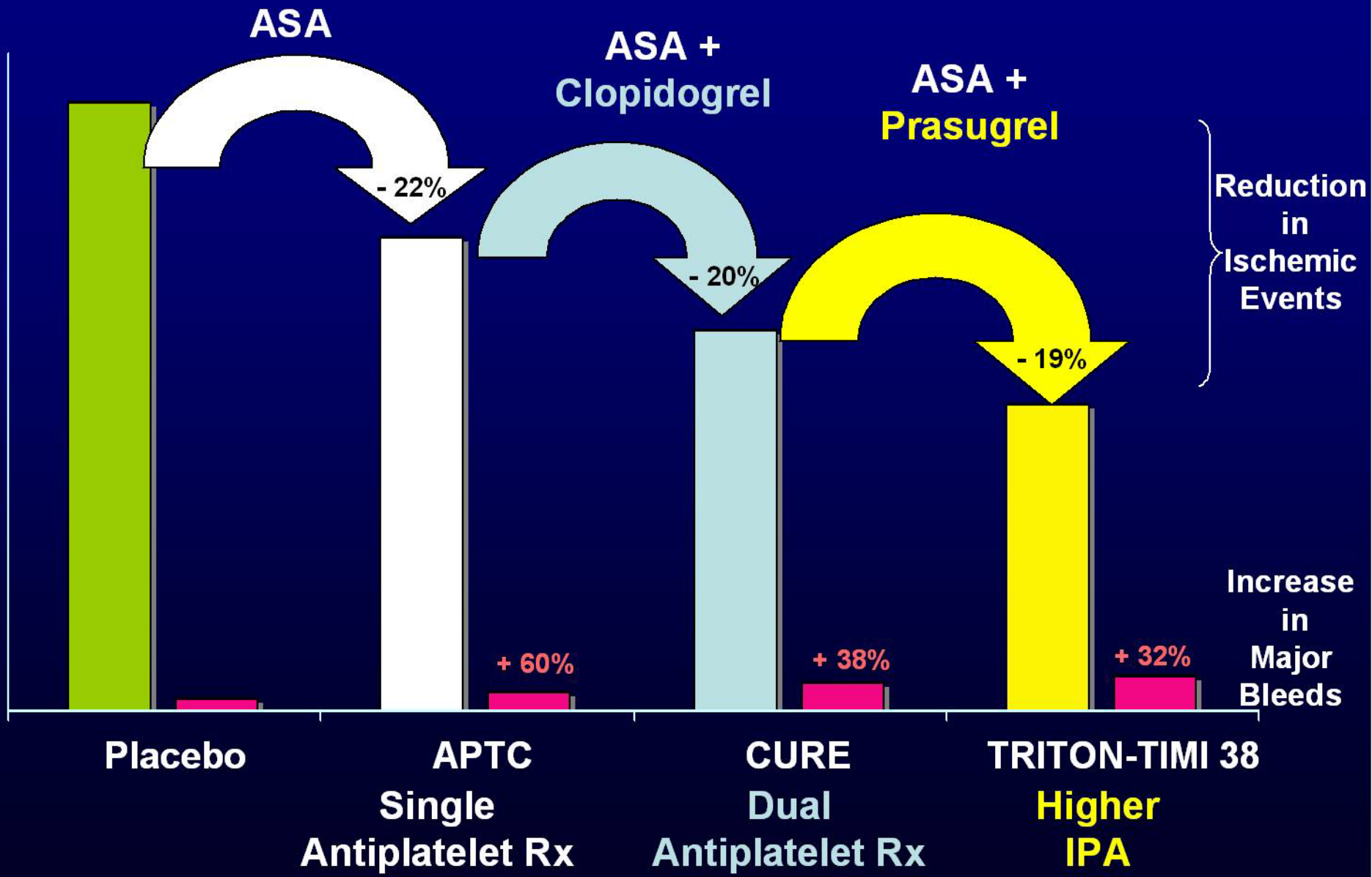
Cardiac Surgery Center Experience

46% Reduction of Exposure to allogenic blood products
47% Reduction of prevelance of allogenic blood transfusions
66% Reduction in RBC exposure
88% Reduction in platelet exposure
86% Reduction in Fresh Frozen Plasma
76% Reduction in Average Number of Units Transfused

Case Study: Female in ER with Hip Fracture would have been admitted for 7 days post-plavix prior to surgery. Able to perform surgery on third day post Plavix.



Antiplatelet Therapy in ACS



What Assay Should I Choose and Why?

Laboratory Measurements of Antiplatelet Effect

- Fibrin Formation Based Assay
  - Bleeding Time (POC)
  - TEG (POC or Lab)
- Aggregation Based Assays
  - Light transmission aggregometry (Lab)
  - Accumetrics VerifyNow (POC or Lab)
  - Plateletworks (POC or Lab)
- Shear-Based Platelet Function Assay (Dade) (Rarely POC – mainly Lab)
- Urine thromboxane metabolite (Aspirinworks) (POC)

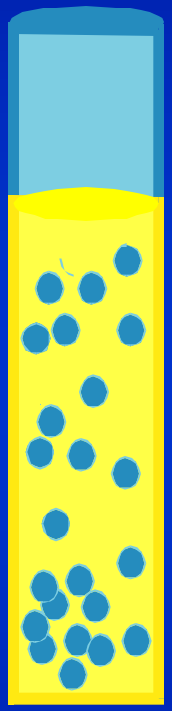
Bleeding Time

- First described in 1901
- Involves touching a piece of filter paper to the edge of a controlled, superficial wound.
- Previously used extensively for pre-operative evaluation of bleeding risk, but subsequent found to have no correlation with bleeding events.
- It is influenced by aspirin therapy.

Light Transmittance Aggregometry

Light Transmittance Platelet Aggregometry

Platelet Rich Plasma (PRP)



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Aggregating Reagent

Arachidonate

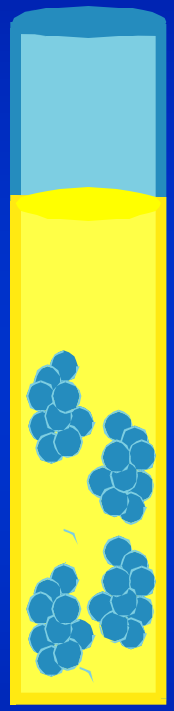
ADP

TRAP

Collagen

Epinenphrine

→

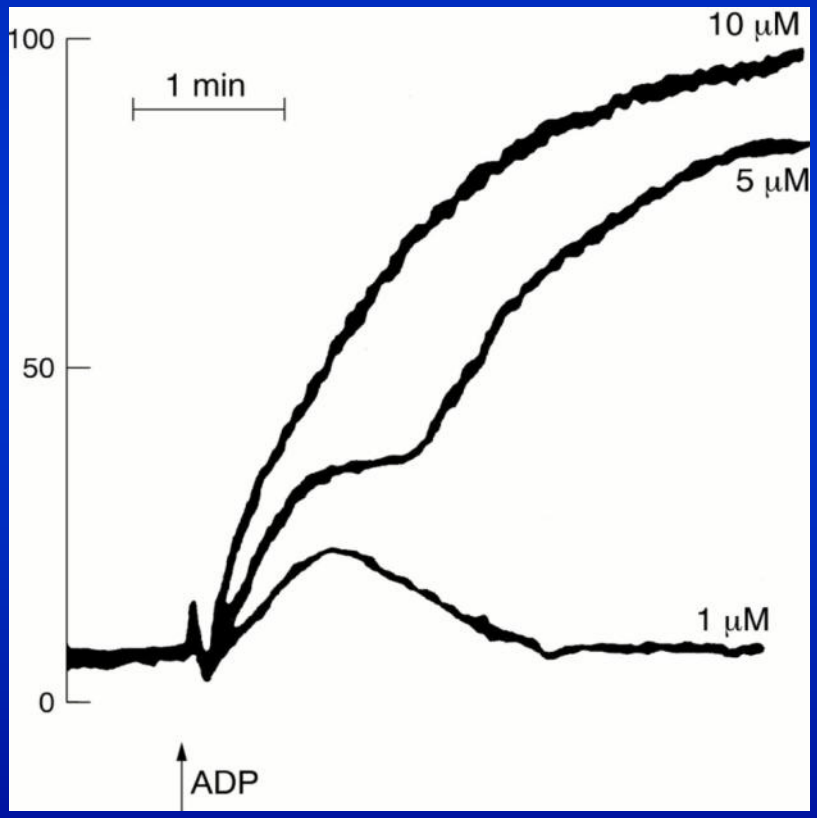


Aggregate Clumping

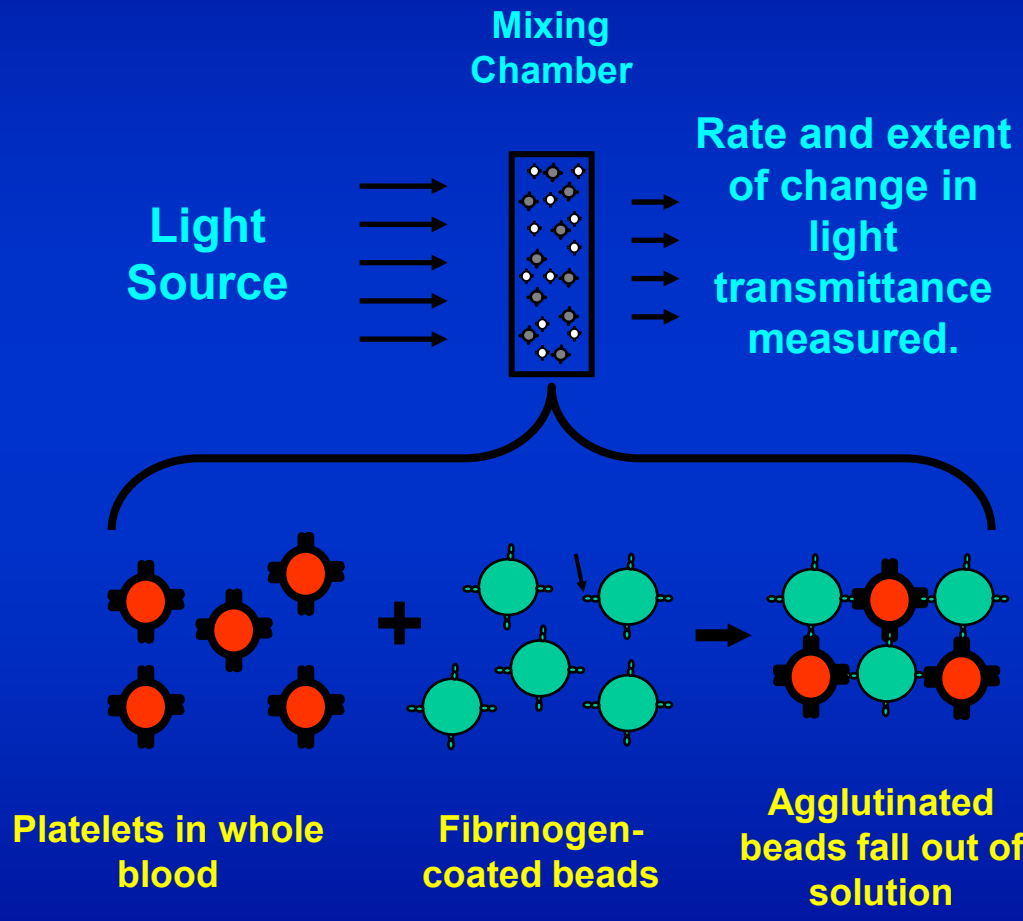
Baseline Light Transmission – the unaggregated platelets in plasma creates a turbid solution that absorbs light

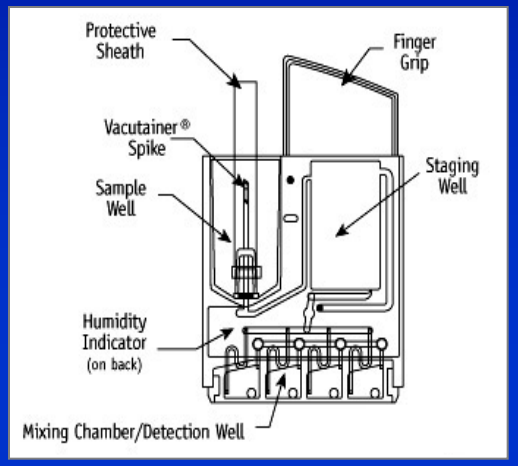
Light transmission increases as platelets aggregate and fall to the bottom of the tube.

Aggregometry Tracing

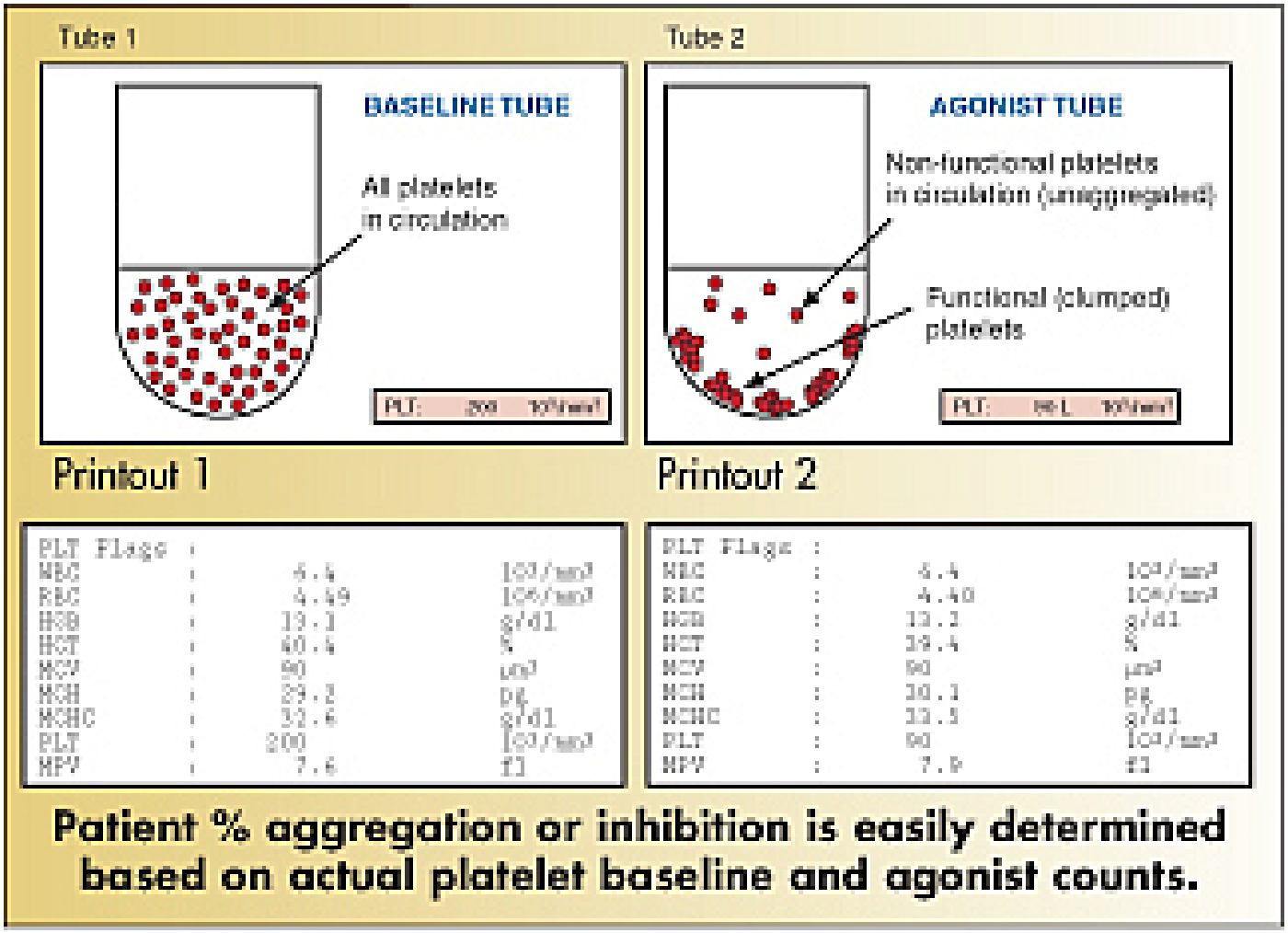


Aggregation –Based Rapid Platelet Function Assay

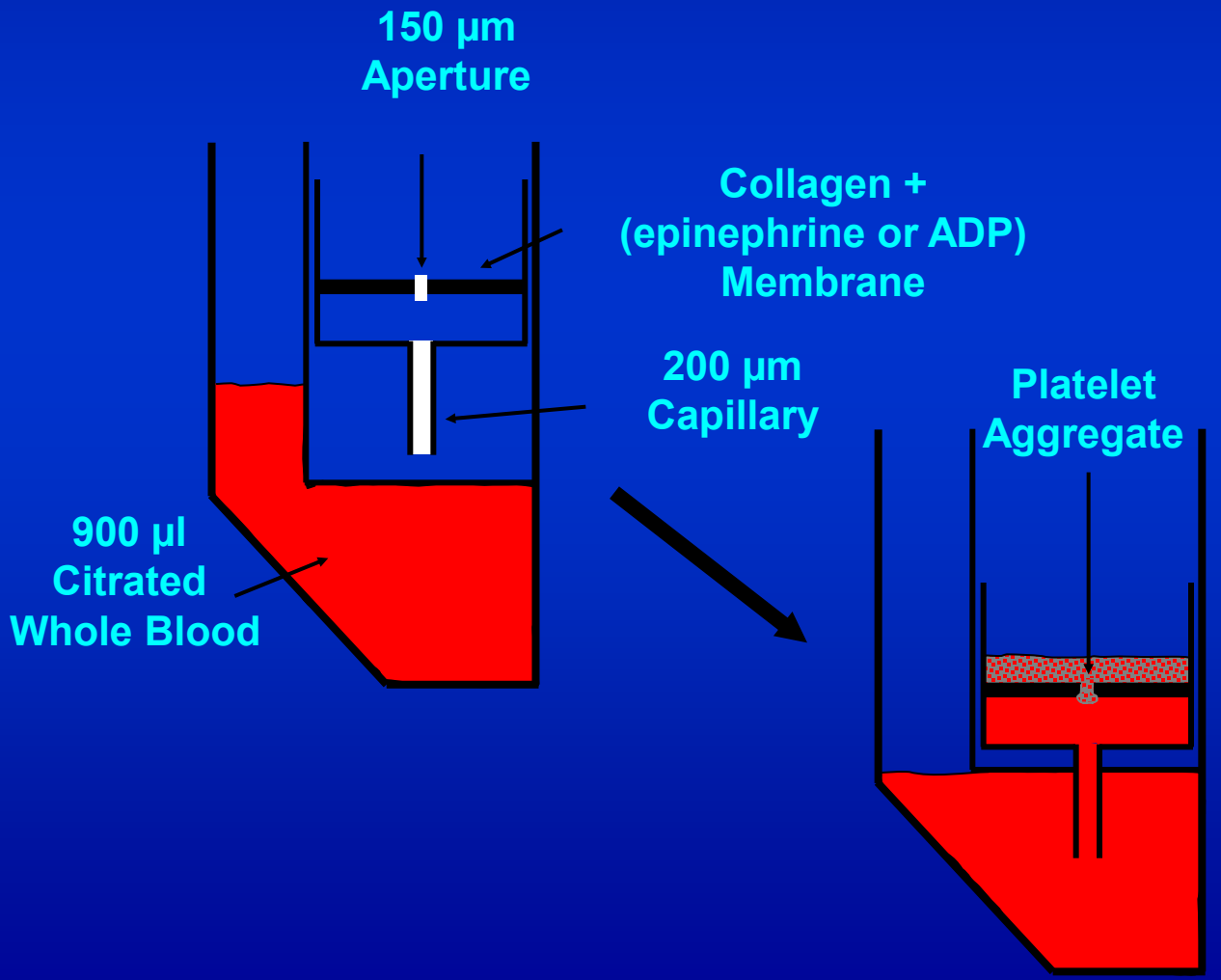




Plateletworks



Shear-Based Platelet Function Assay - PFA-100®



Thromboelastograph (TEG)

Urinary Thromboxane – AspirinWorks

- 11-dehydroxy thromboxane B_2 is the most stable and abundant urinary metabolite of thromboxane A_2, which is synthesized by activated platelets and inhibited by ASA
- Requires only a random urine sample
- Ship to a core reference lab for ELISA testing
- May be other interferences, e.g. medication, obesity – studies pending

Goals of Antiplatelet Therapy

- Right Drug
- Right Dose
- Right Time
- Right Duration
- Right Strategy