ANTITHROMBOTIC THERAPY in the CATH LAB

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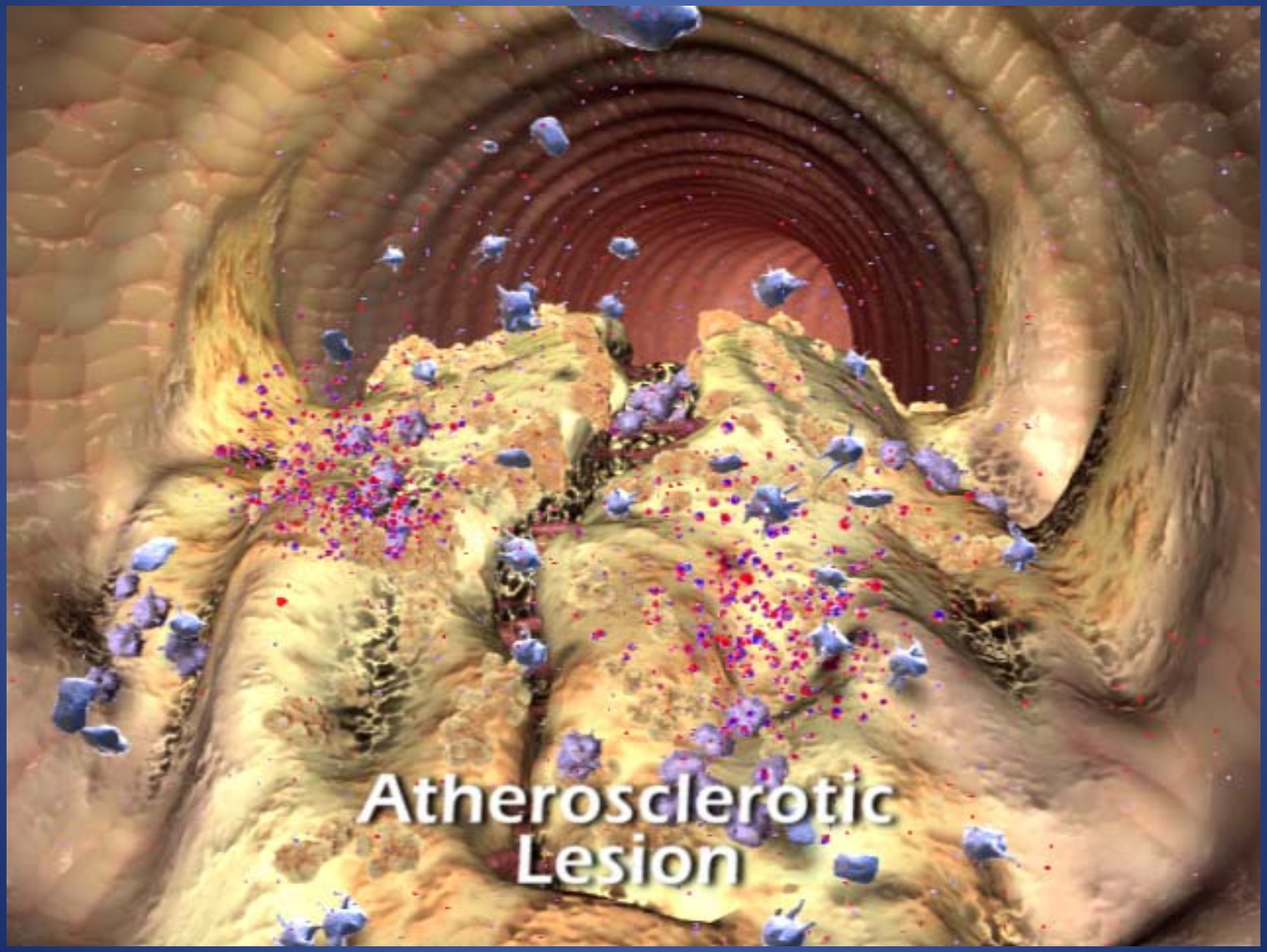
Memorial Regional Hospital

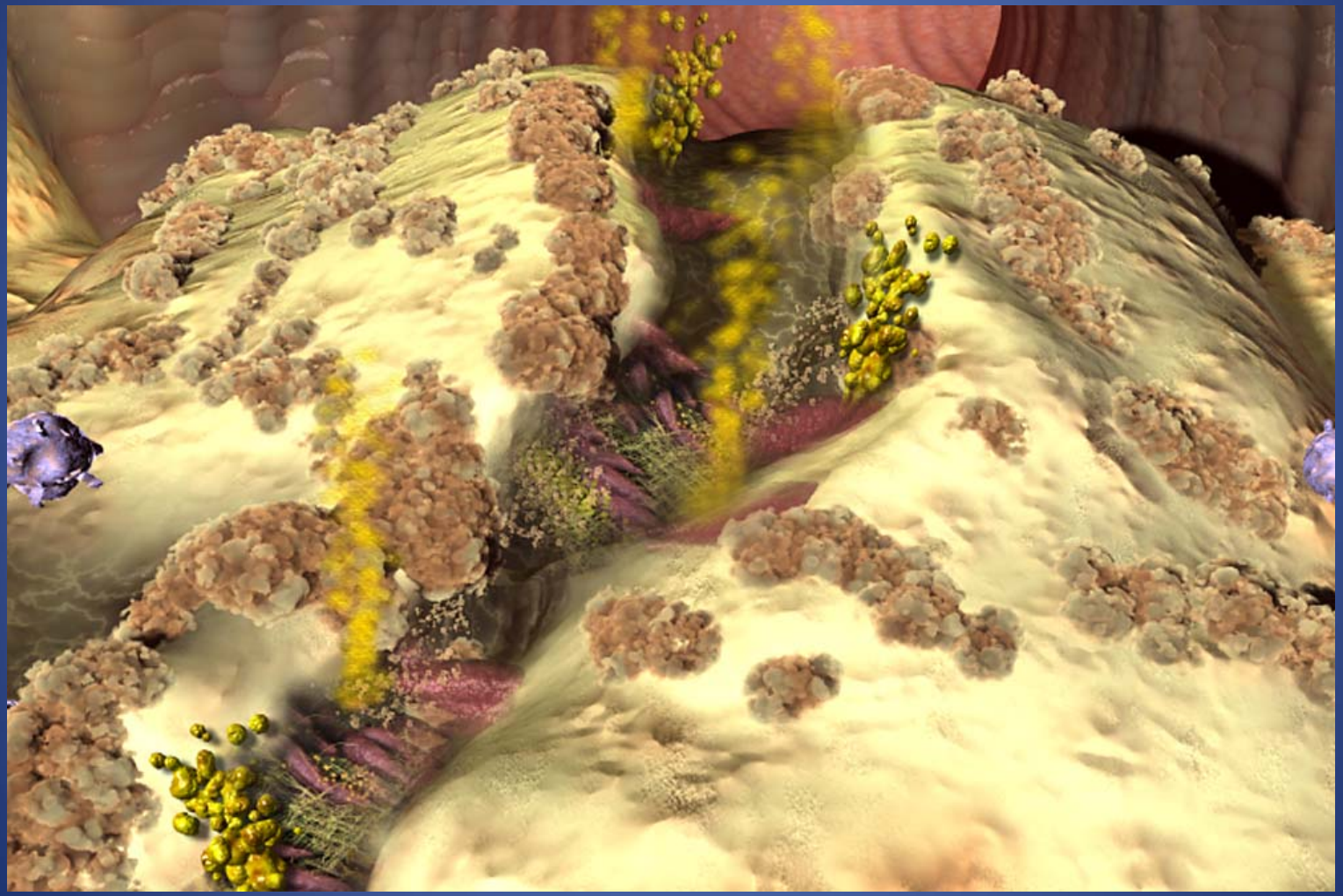
Oct 10, 2009

Unstable Plaque: Basis of ACS



Platelet Cascade: Initiation

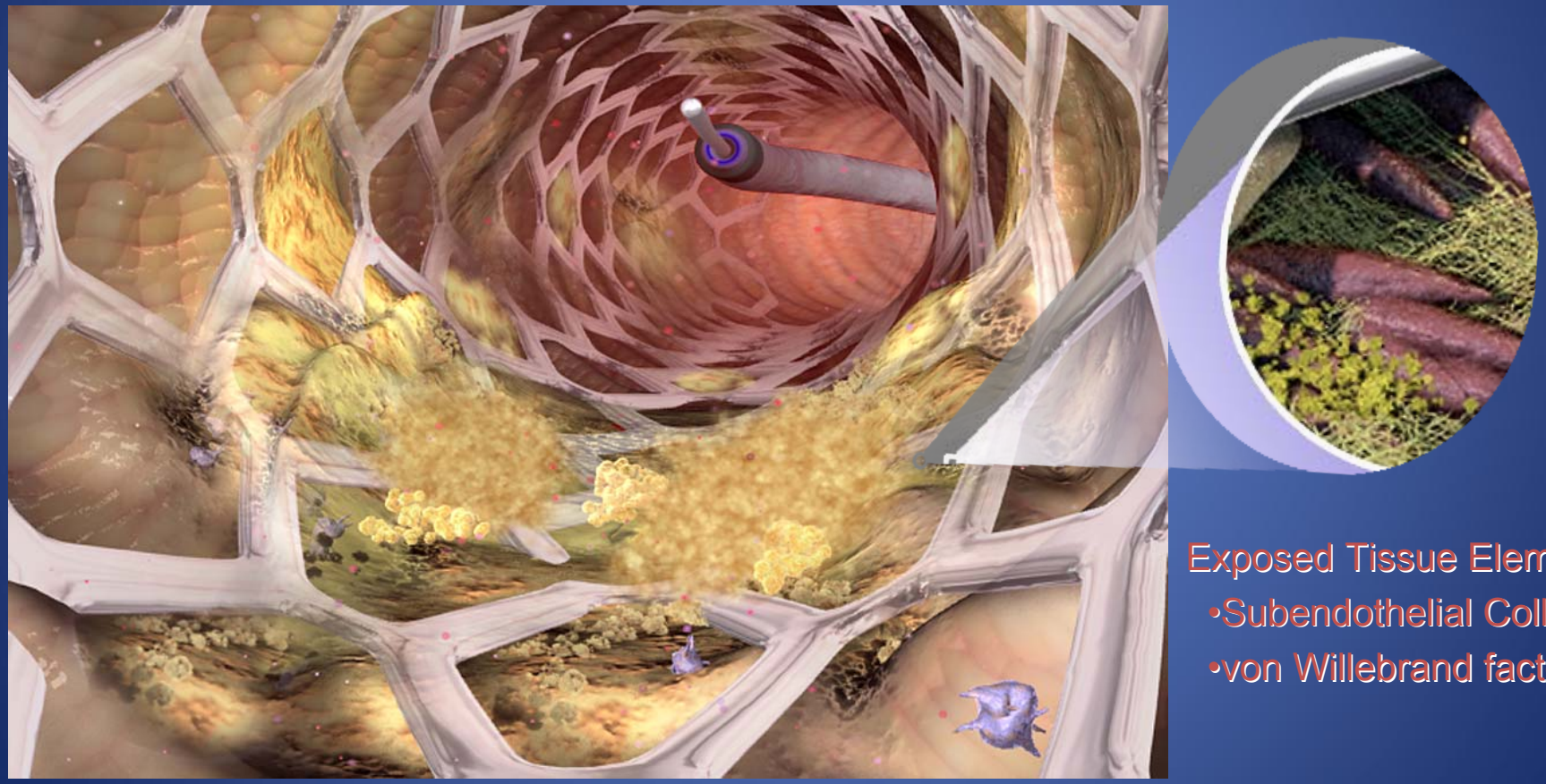
Vascular Damage: Plaque rupture, erosion or calcium nodules



Spontaneous plaque rupture

Platelet Cascade: Initiation

Vascular Damage: Percutaneous coronary interventions

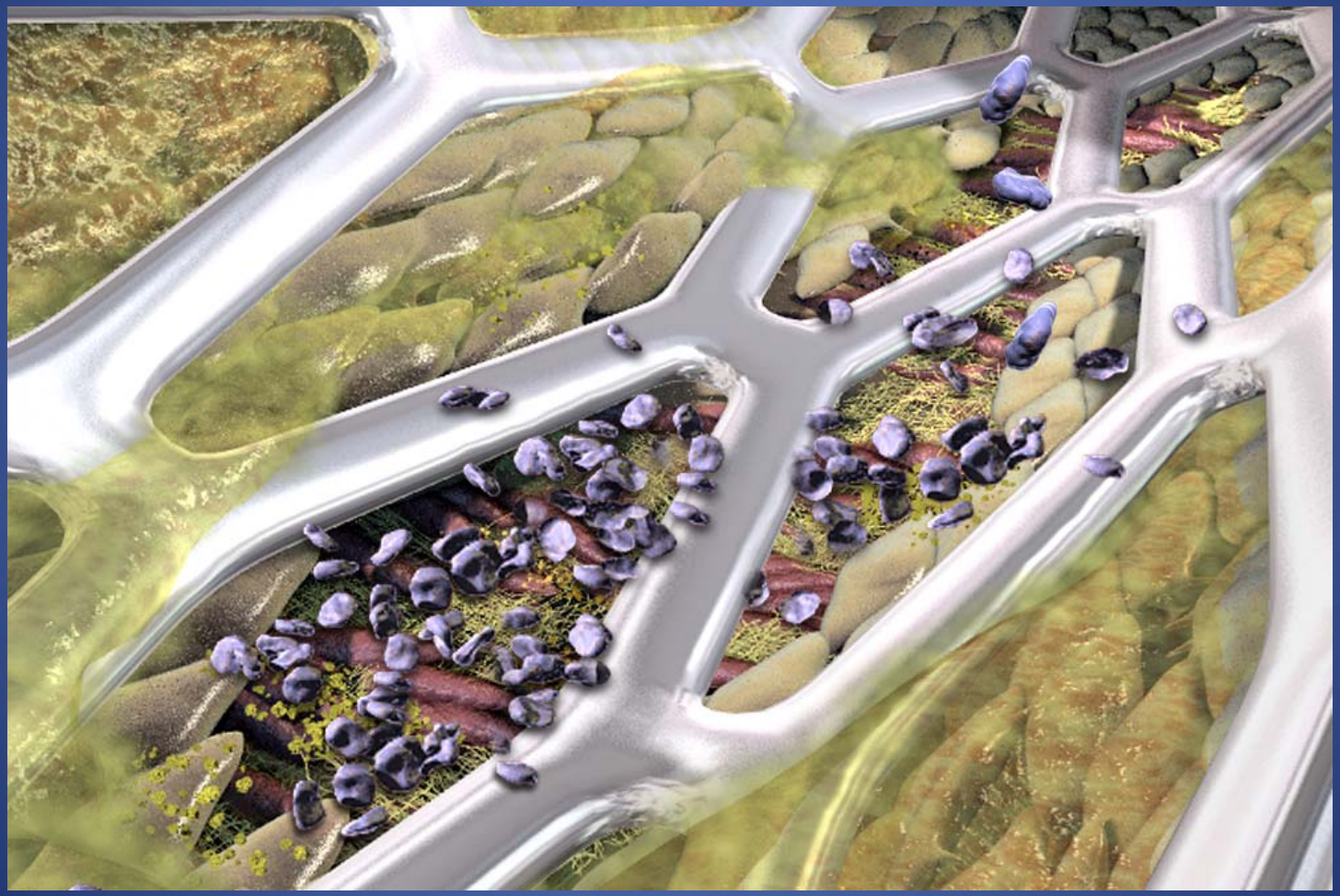


Exposed Tissue Elements

- Subendothelial Collagen
- von Willebrand factor

Platelet Cascade: Adhesion

Immediate Platelet recruitment and adhesion at the site of injury…

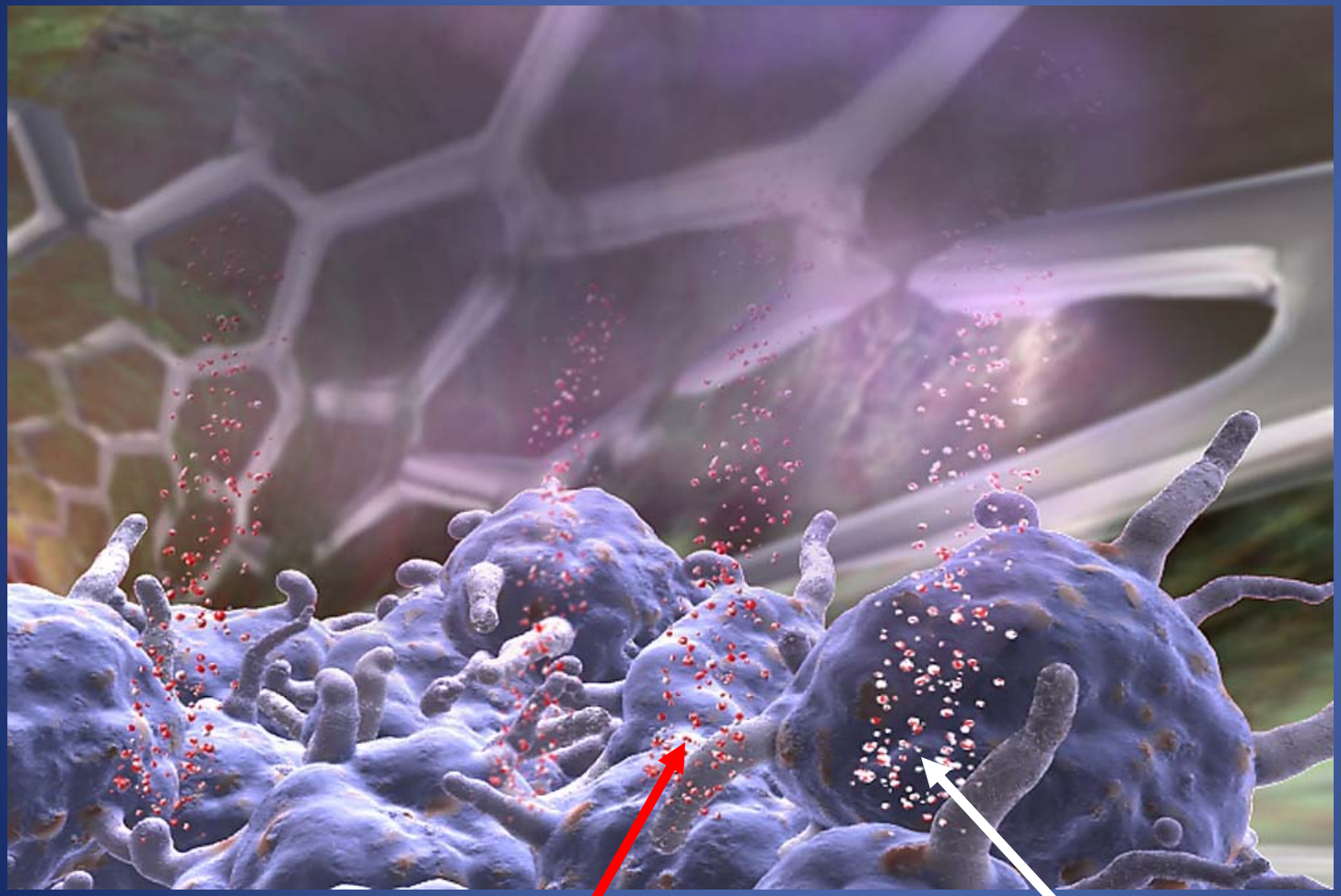


…forming a monolayer.

Platelet Cascade: Activation

Adhesion leads to activation

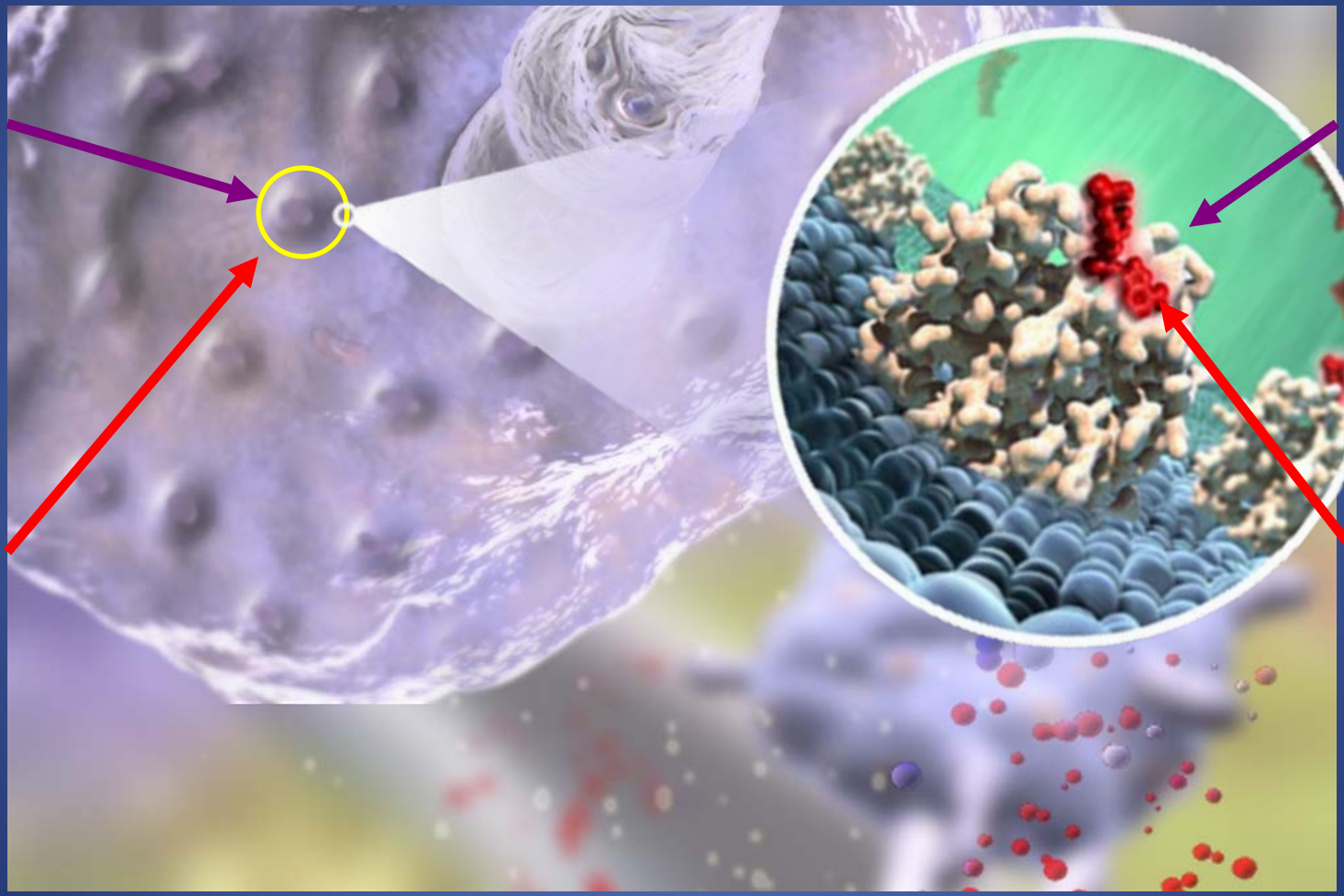
Platelet Cascade: Release of Activators



- ADP and other activators are released through degranulation

- Thromboxane A_2 is generated via cycloxygenase

Platelet Cascade: Surface Receptors

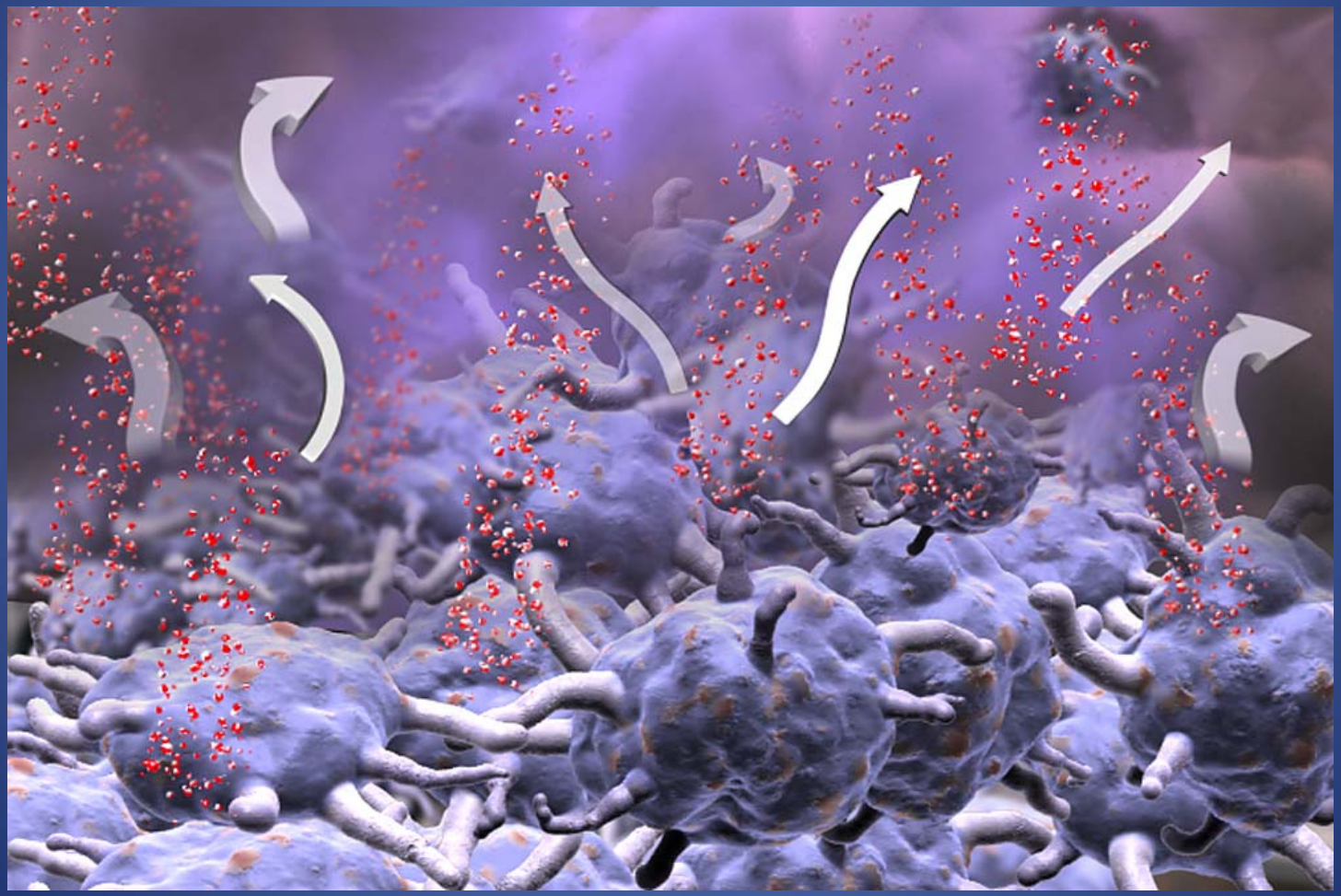


Circulating Platelets

Platelet Cascade: Amplification of Platelet Activation

Platelet activation accelerates…

…resulting in platelet aggregation.

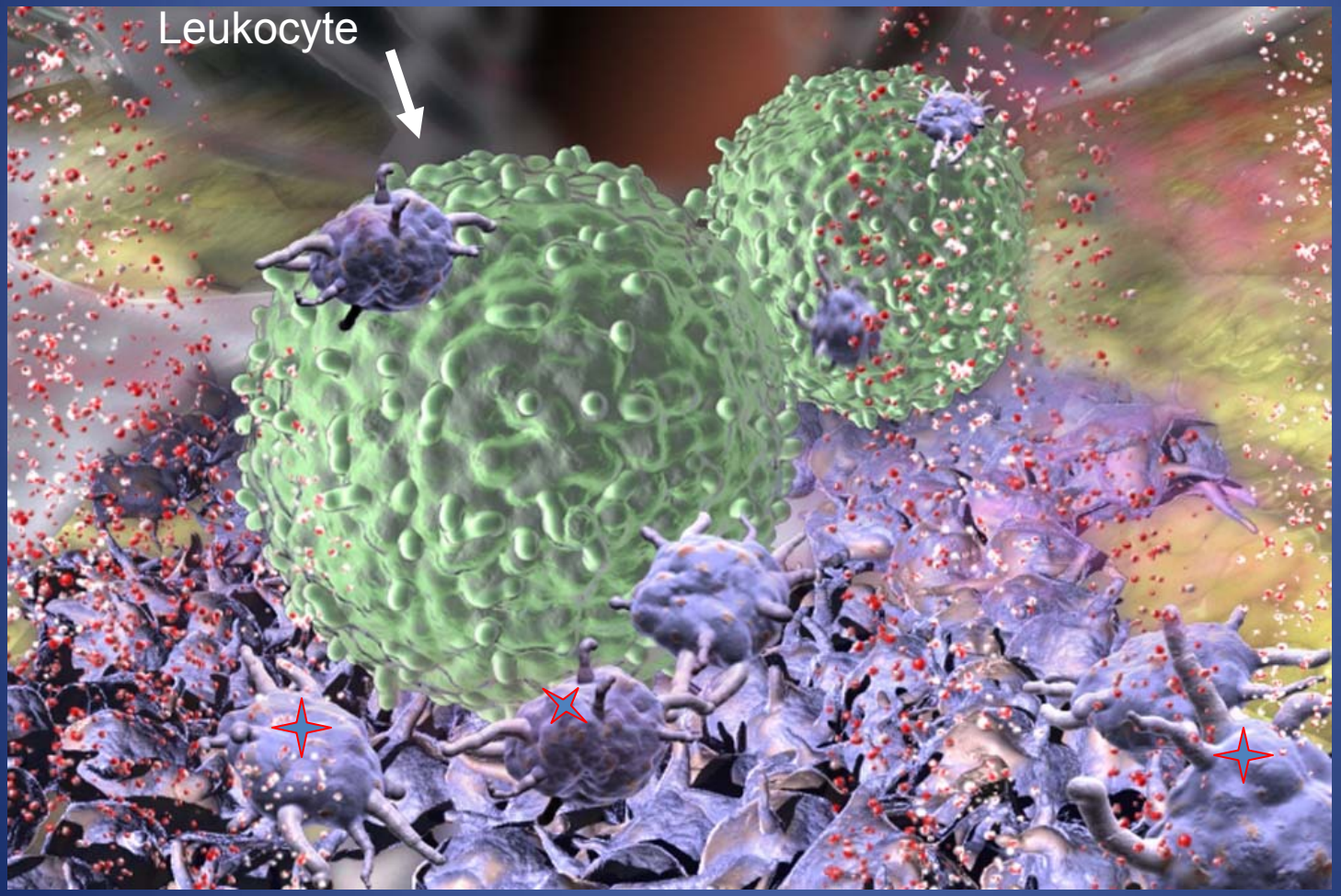


A process that must be managed.

Platelet Cascade: Activation

Triggers Inflammatory Cascade

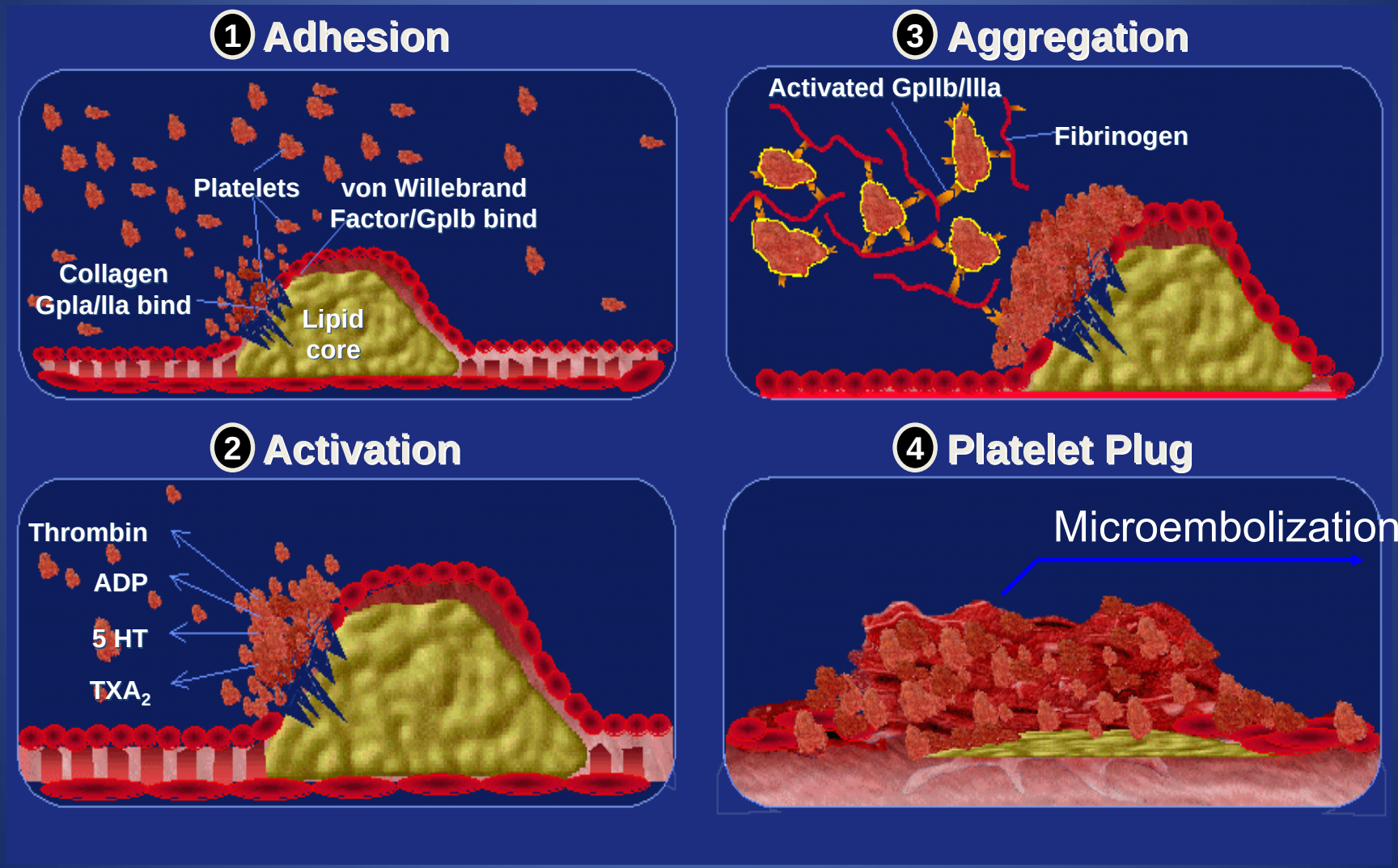
Activated platelets express adhesion receptors for leukocytes



- P-selectin
- CD40 Ligand

Platelet-Leukocyte Conjugates

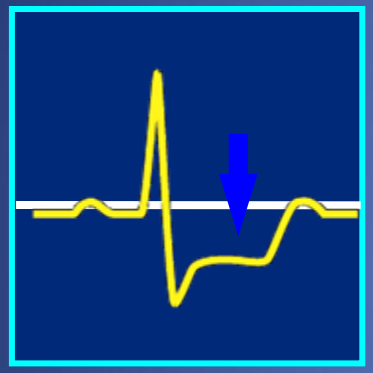
Role of Platelets

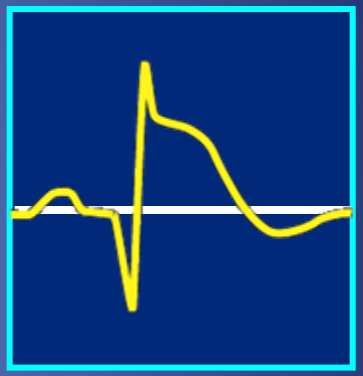


Kumar A et al. *Exp Opin Invest Drugs*. 1997;6:1257–1267.

Acute Coronary Syndromes (ACS)

Acute Coronary Syndromes





UA/NSTEMI

STEMI

1.25 million
admissions per year

0.33 million
admissions per year

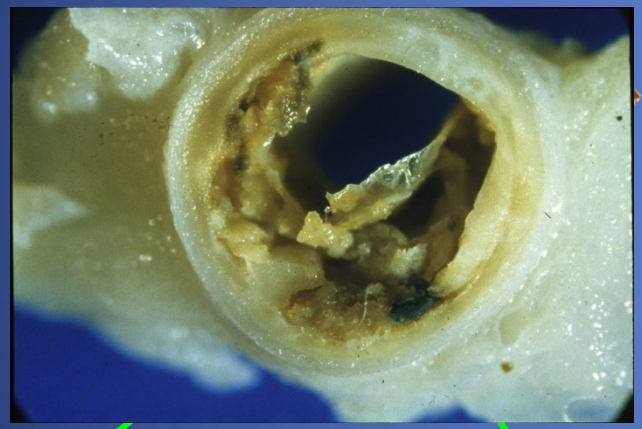
Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69-171.

ACS: Pathology

Vulnerable Plaque

UA/NSTEMI

Partially-occlusive thrombus (primarily platelets)

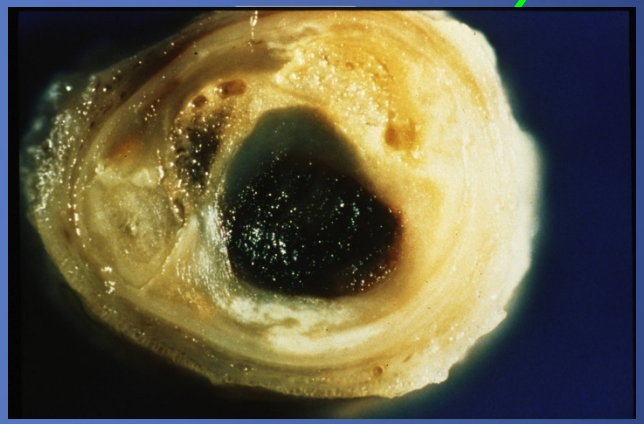


Intra-plaque thrombus (platelet dominated)

Plaque core

STEMI

occlusive thrombus (platelets, red blood cells, and fibrin)



Intra-plaque thrombus (platelet dominated)

Plaque core

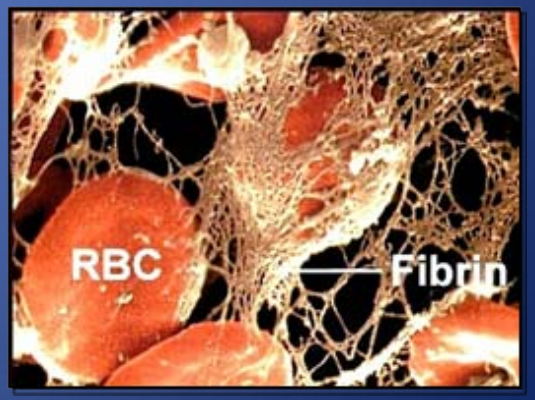
SUDDEN DEATH

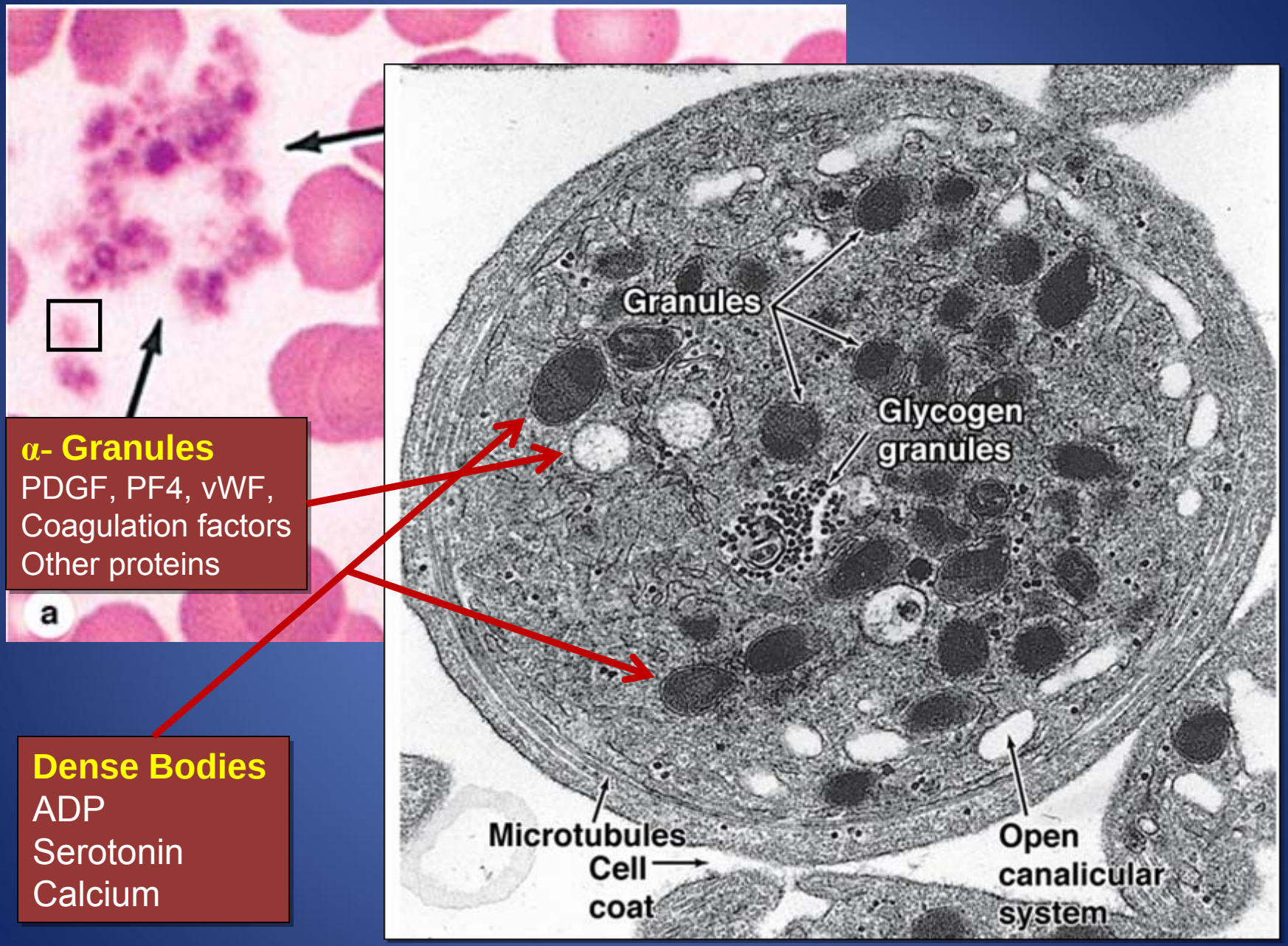
Adapted from Davies MJ. *Circulation.* 1990; 82 (supl II): 30-46.

ANTITHROMBOTIC THERAPY

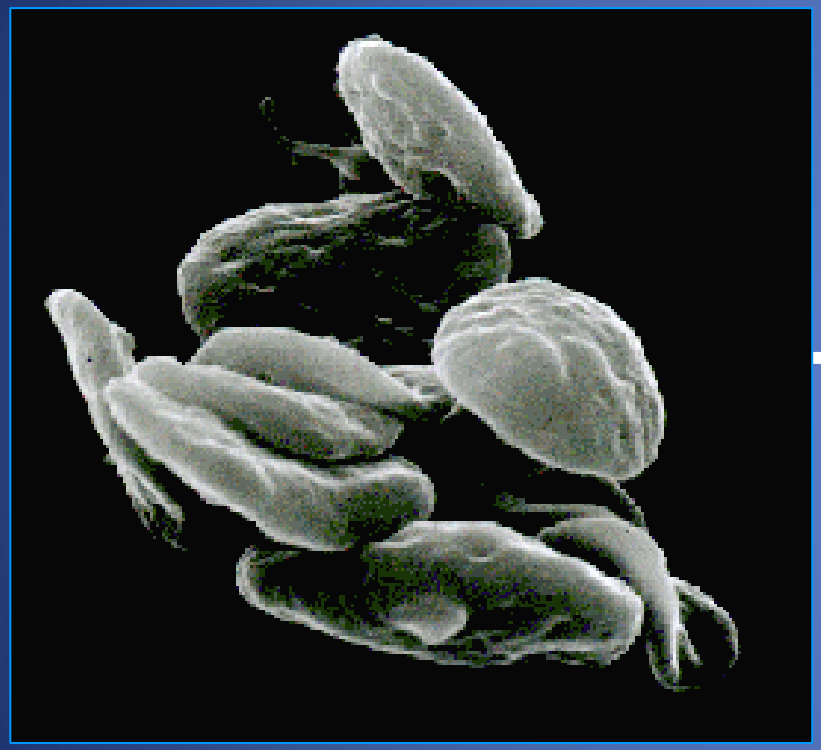
- **ANTIPLATELET THERAPY**
  - ORAL : ASA, Plavix, Effient
  - IV : Reopro, Integrelin, Aggar

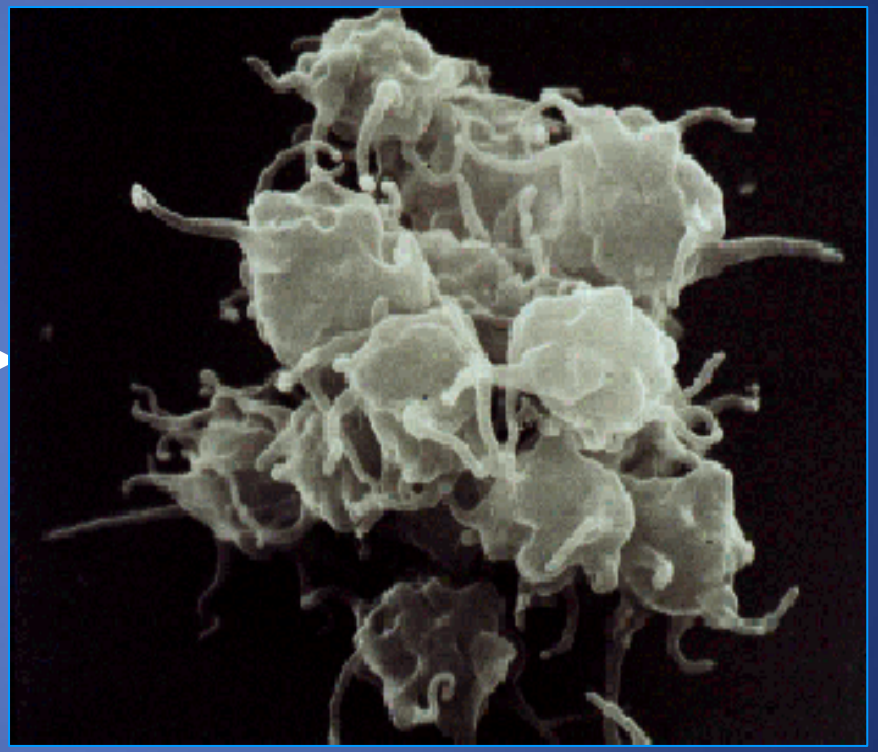
- **ANTITHROMBIN THERAPY**
  - HEPARINS: UFH, LMHW
  - ANGIOMAX




α- Granules
PDGF, PF4, vWF,
Coagulation factors
Other proteins
a
Dense Bodies
ADP
Serotonin
Calcium
Granules
Glycogen granules
Microtubules
Cell coat
Open canalicular system

Platelets





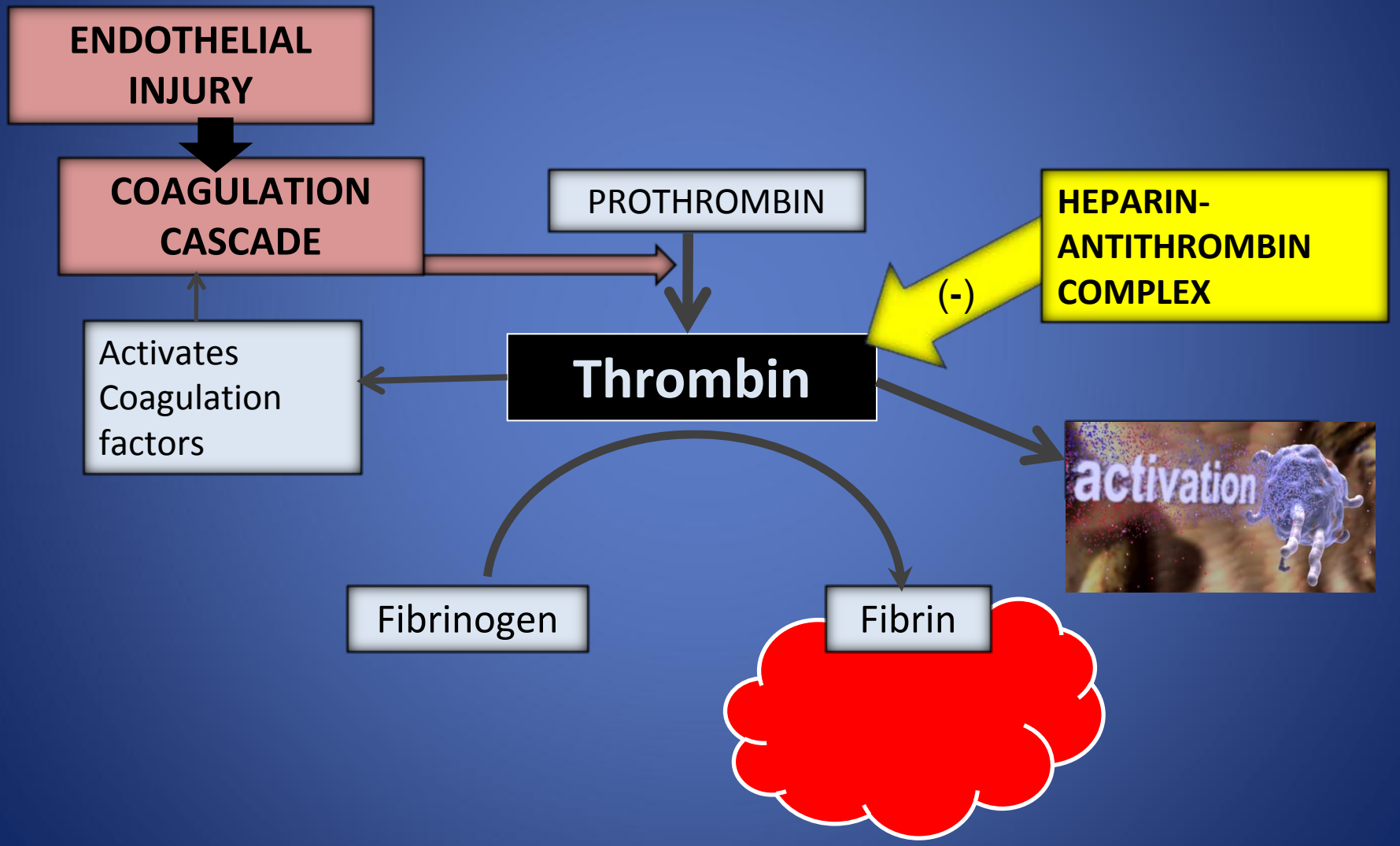
Smooth discoid shape of resting platelets

Spiny spheric shape of activated platelets

High Platelet Reactivity State

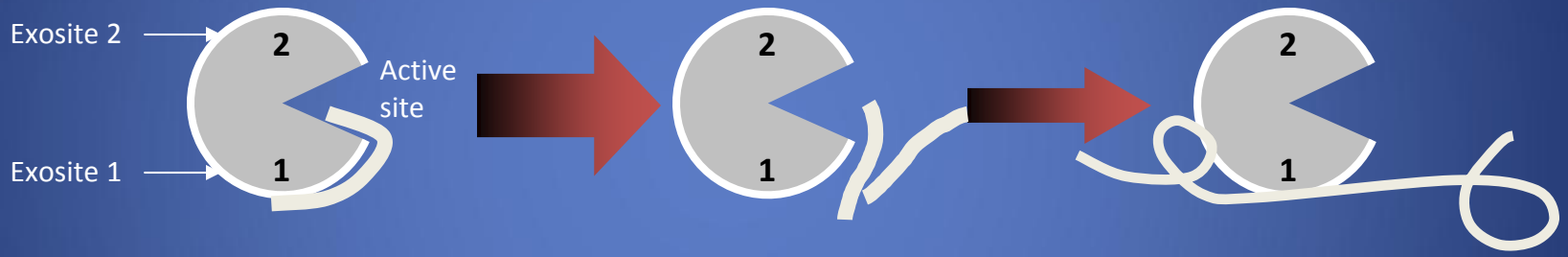
Thrombin :

Plays Central Role in Atherothrombosis



Thrombus formation

Thrombin's receptors and function



Fibrinogen binds to active site and exosite 1

Fibrinogen is cleaved to create fibrin monomers

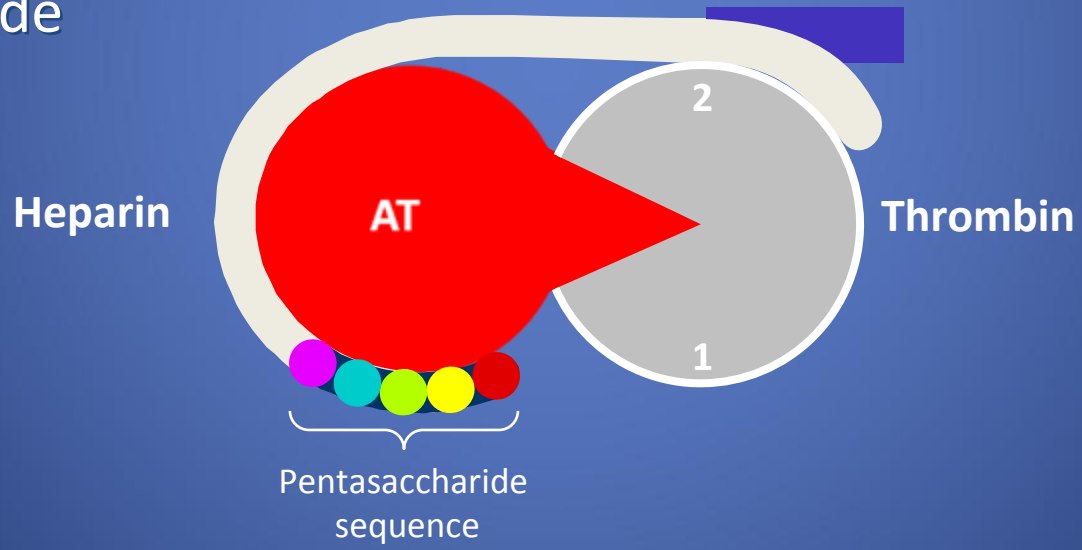
Fibrin monomers polymerize to form fibrin strands

- Proteolytic cleavage of fibrinogen to form fibrin
- Upregulation of coagulation
- Clot stability
- Platelet activation

Heparin mode of action

"Indirect effect", requires Antithrombin

Heparin is long chain of polysaccharide

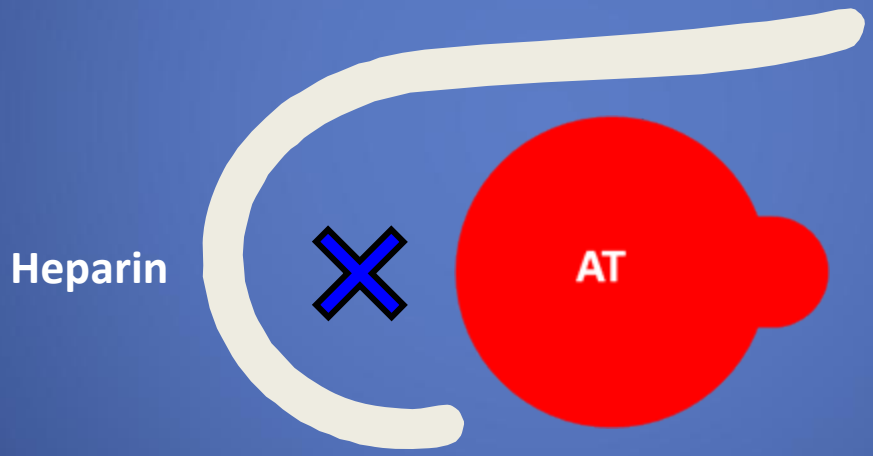


LMWH: Small fragments of heparin

Pentasaccharide is Arixtra

Heparin's limitations

Heparin is heterogeneous and only one-third of heparin chains can combine with AT for thrombin inhibition.

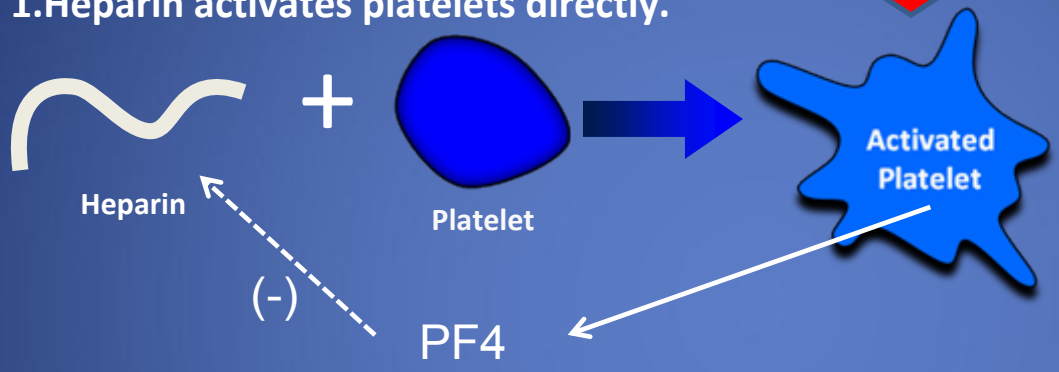


BECAUSE ABOUT 70% of heparin chains lack the correct pentasaccharide sequence needed to interact with AT

Heparin's li ations

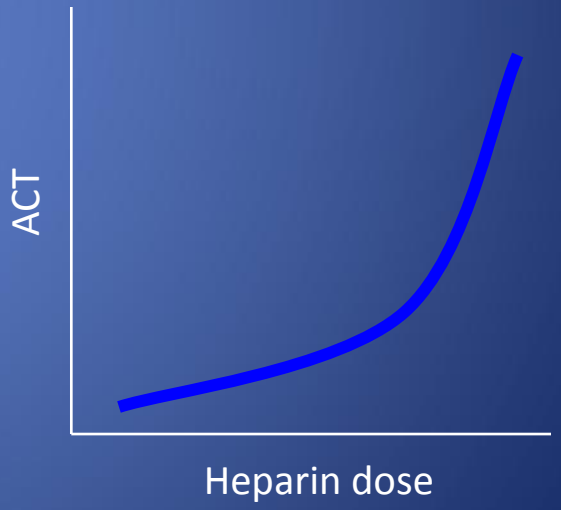
Heparin binds to plasma proteins and cells

1.Heparin activates platelets directly.



2.Heparin can induce an immune response in the form of HIT/HITTS.

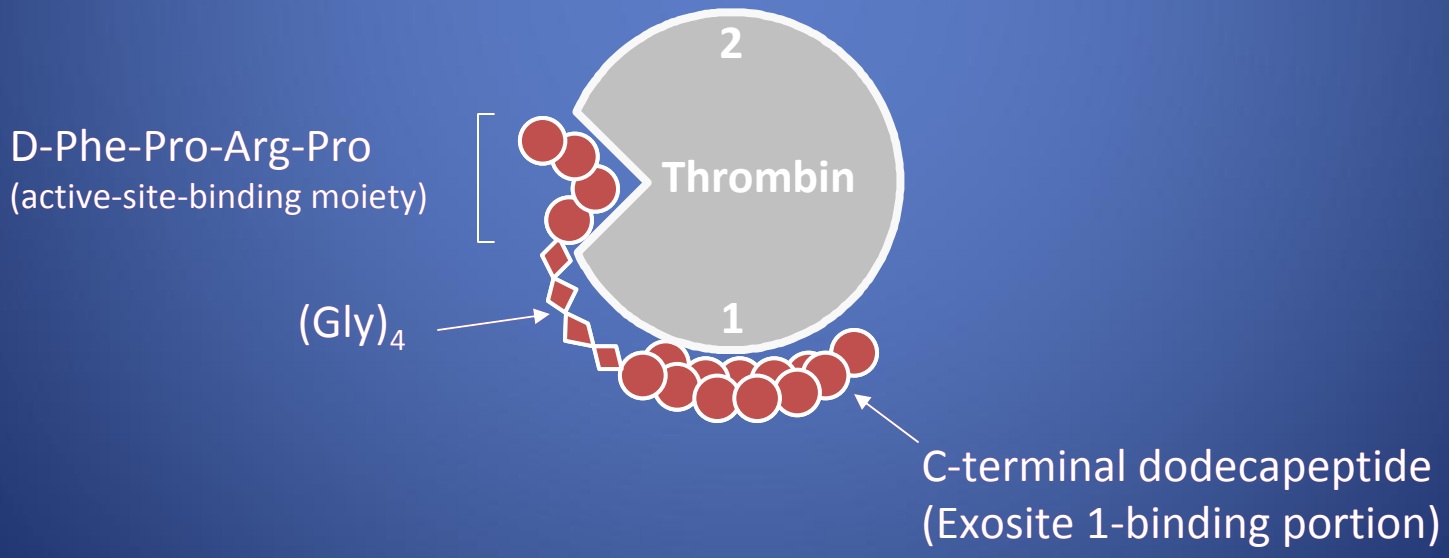
3.Heparin exhibits a nonlinear dose-response.



- Antithrombotic therapy II: Bivalirudin (Angiomax)

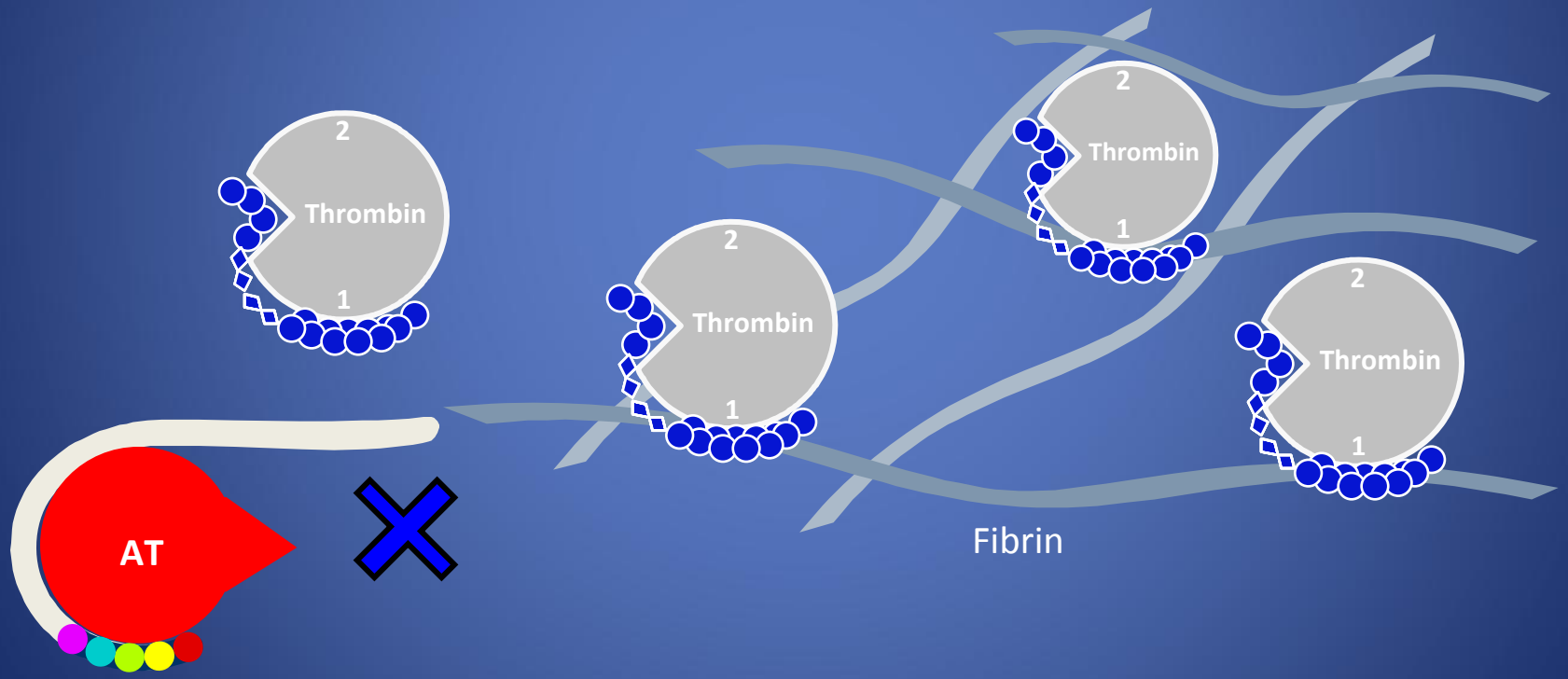
Bivalirudin: Mechanism of Action

Bivalirudin binds bivalently to thrombin's active site and exosite 1 (fibrinogen binding site).

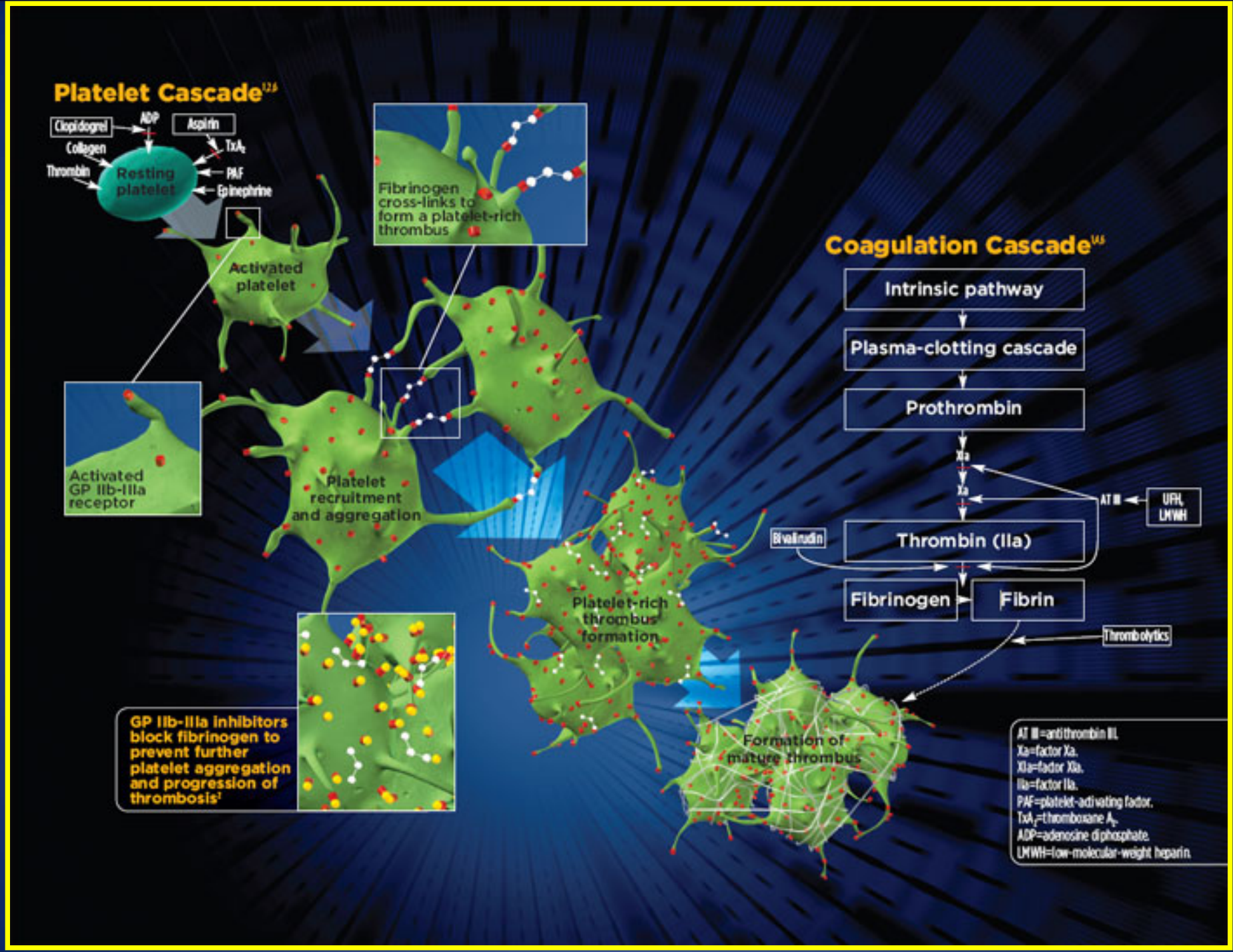


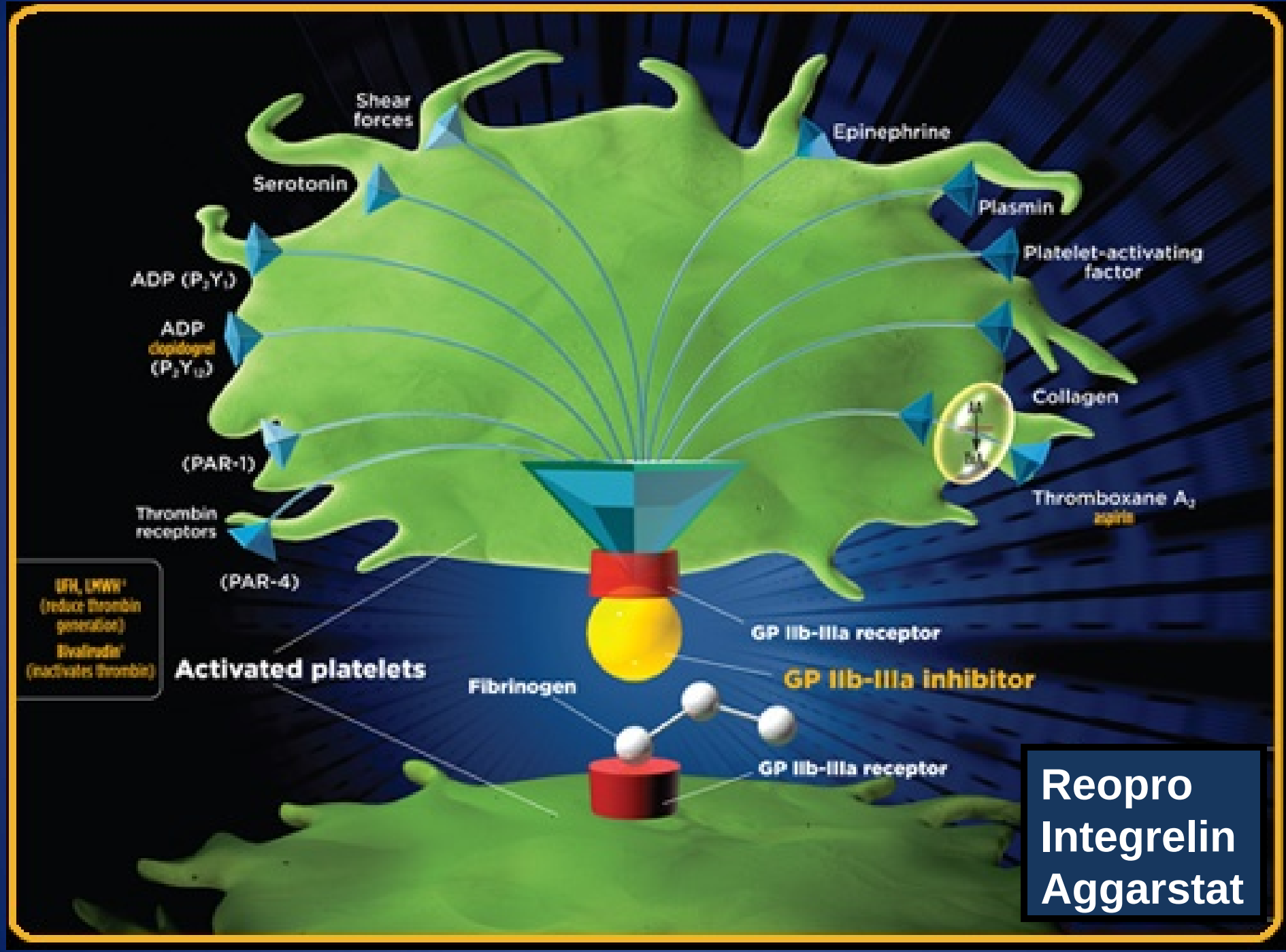
Bivalirudin: Mechanism of Action

Bivalirudin inhibits both fibrin-bound and circulating thrombin.

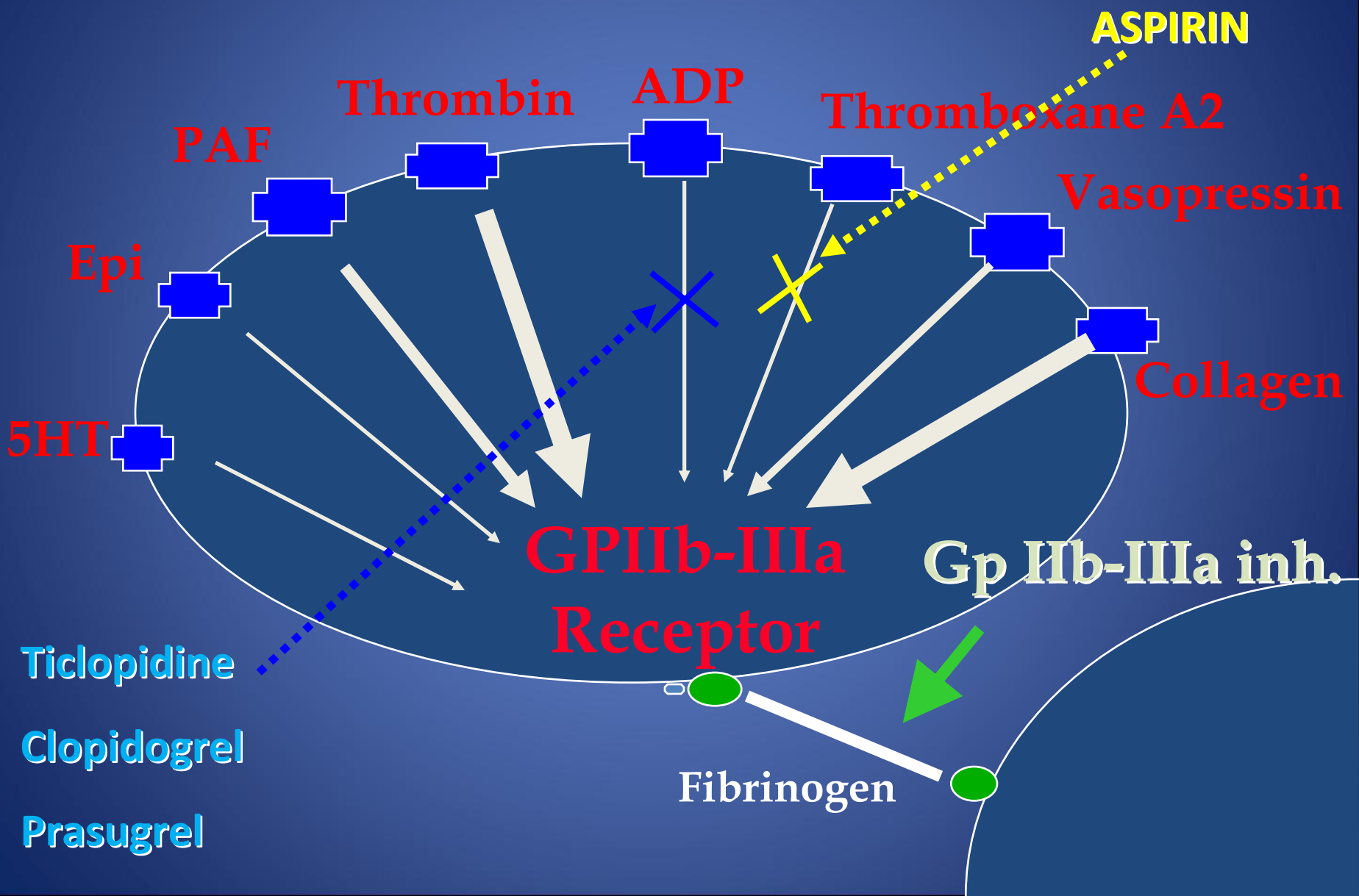


- Antithrombotic therapy III: IIb/IIIa Receptor Blockers


Platelet Cascade[1,2,5]
Clopidogrel
ADP
Aspirin
Collagen
TxA_2
Thrombin
Resting platelet
PAF
Epinephrine
Activated platelet
Fibrinogen cross-links to form a platelet-rich thrombus
Activated GP IIb-IIIa receptor
Platelet recruitment and aggregation
Platelet-rich thrombus formation
Formation of mature thrombus
GP IIb-IIIa inhibitors block fibrinogen to prevent further platelet aggregation and progression of thrombosis[3]
Coagulation Cascade[1,5]
Intrinsic pathway
Plasma-clotting cascade
Prothrombin
Xa
Xa
AT III
UFH, LMWH
Bivalirudin
Thrombin (IIa)
Fibrinogen
Fibrin
Thrombolytics
AT III=antithrombin III.
Xa=factor Xa.
XIa=factor XIa.
IIa=factor IIa.
PAF=platelet-activating factor.
TxA_2=thromboxane A_2.
ADP=adenosine diphosphate.
LMWH=low-molecular-weight heparin.

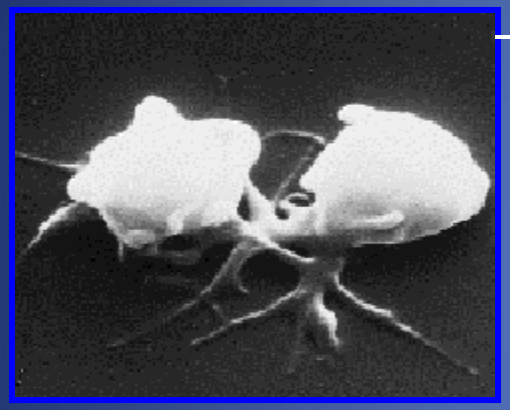

Shear forces
Epinephrine
Serotonin
Plasmin
Platelet-activating factor
ADP (P_2Y_1)
ADP
clopidogrel
(P_2Y_{12})
Collagen
(PAR-1)
Thrombin receptors
Thromboxane A_2
aspirin
(PAR-4)
UFH, LMWH
(reduce thrombin generation)
Bivalirudin
(inactivates thrombin)
Activated platelets
GP IIb-IIIa receptor
GP IIb-IIIa inhibitor
Fibrinogen
GP IIb-IIIa receptor
Reopro
Integrelin
Aggarstat

Multiple Pathways of Platelet Activation



Platelets: An Hemostatic and Inflammatory Cell

Inflammatory Modulators Produced by Activated Platelets



- Platelet-derived growth factor
- Platelet factor 4
- CD 154 (CD40L)
- RANTES*
- Thrombospondin
- Transforming growth factor-β
- Nitric oxide

*Regulated on activation, normal T-cell-expressed and -secreted.

Libby P et al. *Circulation*. 2001:103:1718-1720.

Thrombocytopenia due to Gp IIb/IIIa Receptor Antagonists

- Thrombocytopenia is a class effect. Trend to be more common with abciximab (Reopro).
- Severe thrombocytopenia (< 50K):
  - Tirofiban / Eptifibatide: 0.2-1.2%
  - Abciximab: 1%. Re-exposure up to 4%
- Types:
  - Pseudo-thrombocytopenia (in vitro platelet clumping). Occurred in 2.1% of abciximab treated patients. Explain 1/3 of cases of low platelet counts.
  - Immune-mediated reaction.

Pseudo-thrombocytopenia

Lavander: EDTA
Green: Heparin
Blue: Citrate

Antithrombotic therapy III:

Aspirin

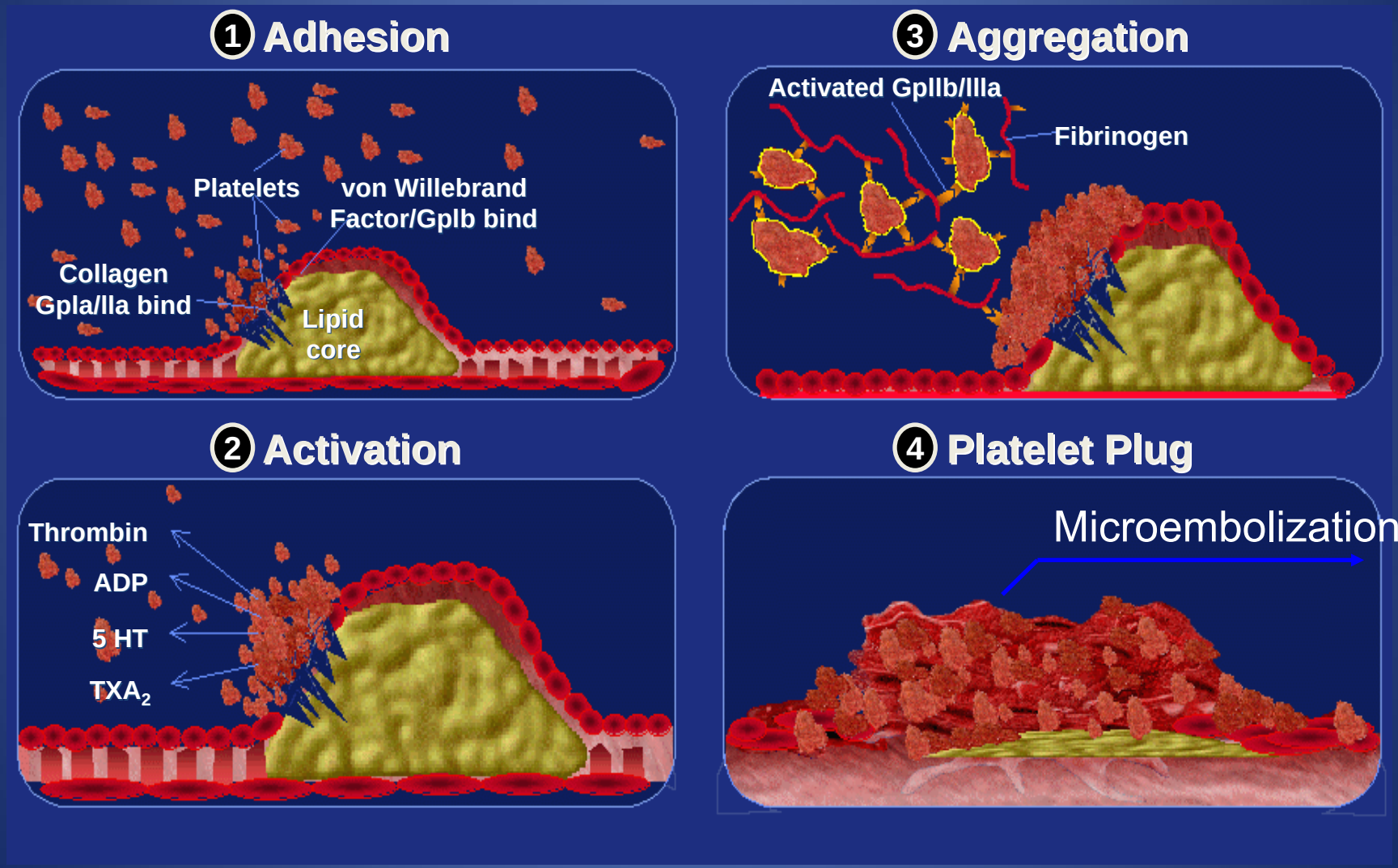
Thienopiridines

Control of Platelet Aggregation

The key to control platelet aggregation is…

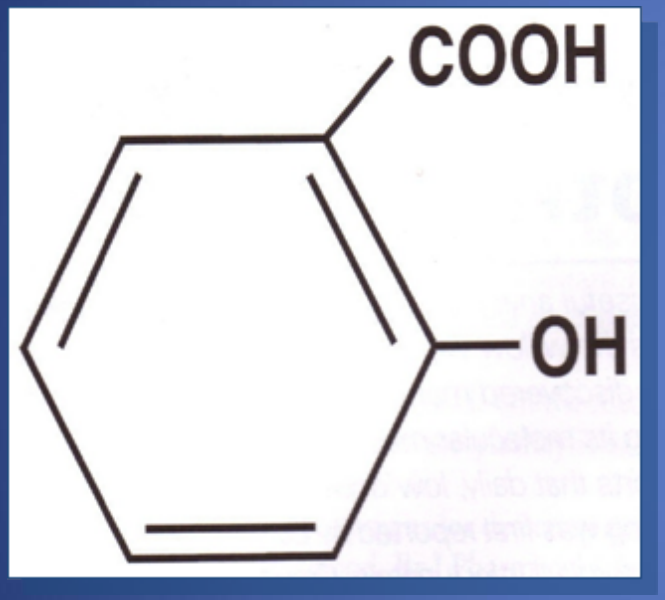
…to manage platelet ACTIVATION over time.

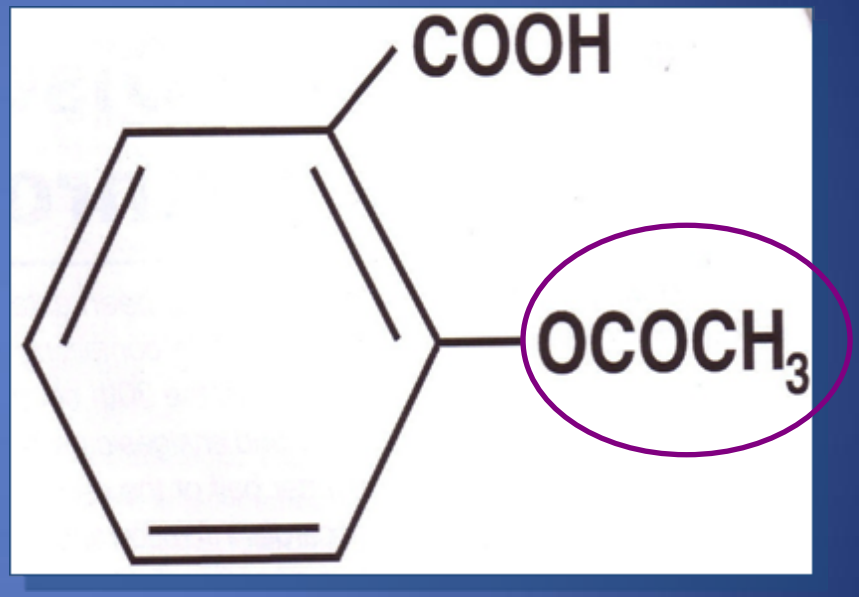
Role of Platelets



Kumar A et al. *Exp Opin Invest Drugs*. 1997;6:1257–1267.

From Willow bark and other plants



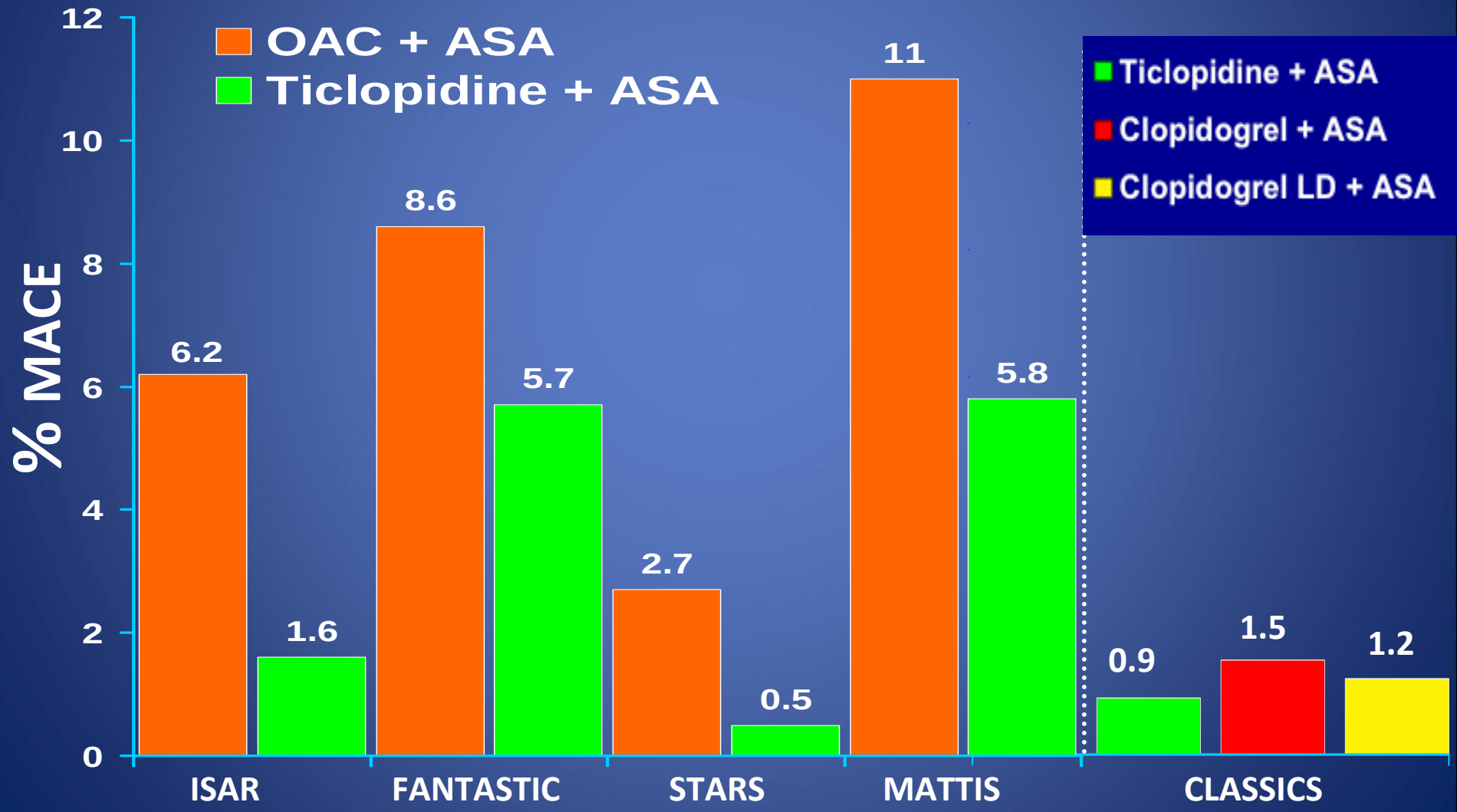


SALICYLIC ACID → **ACETYLSALICYLIC ACID (ASPIRIN)**

Bayer Lab in 1897

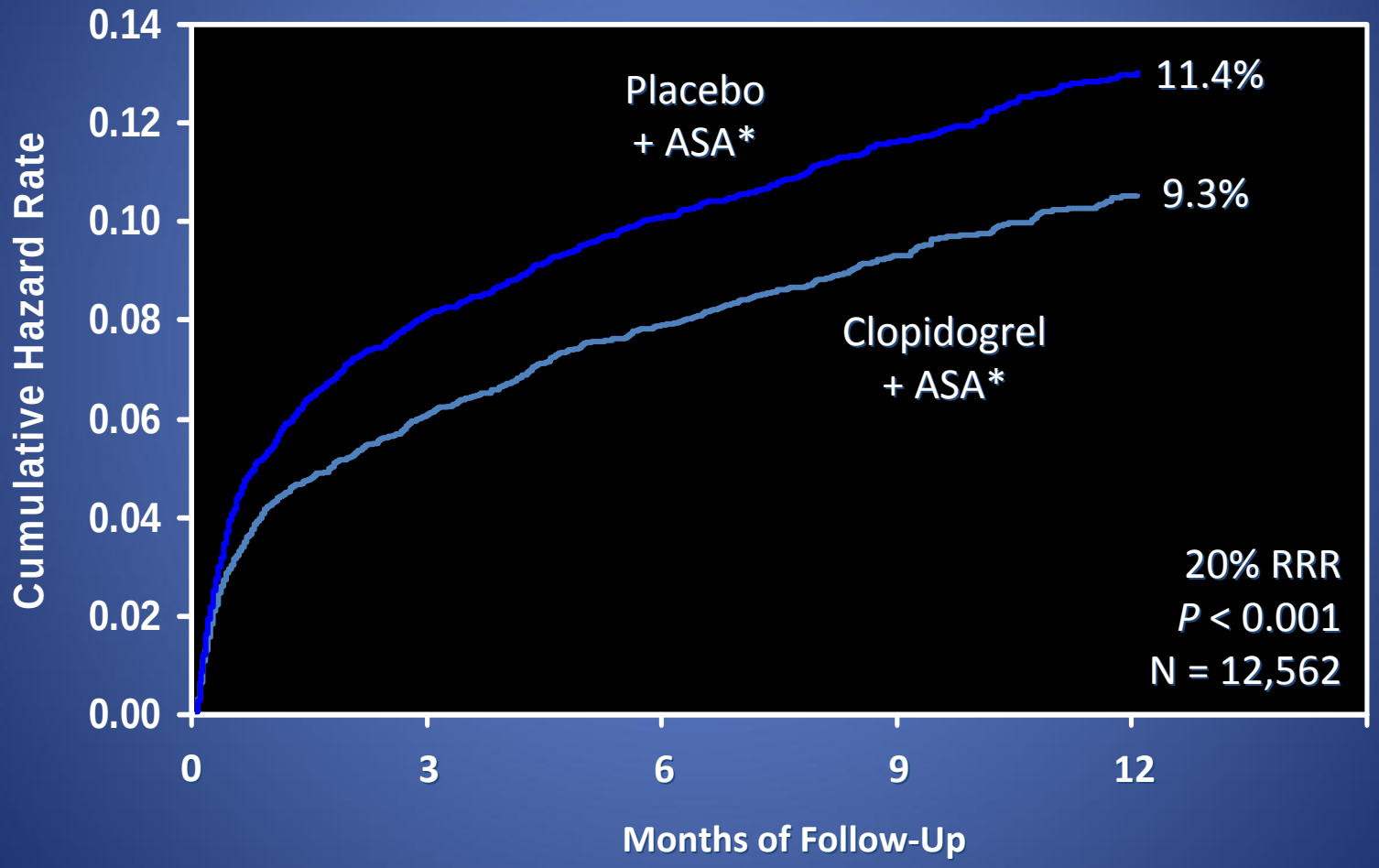
Circ 102: 624,2000

Dual Antiplatelet Rx for PCI



Acute Coronary Syndromes

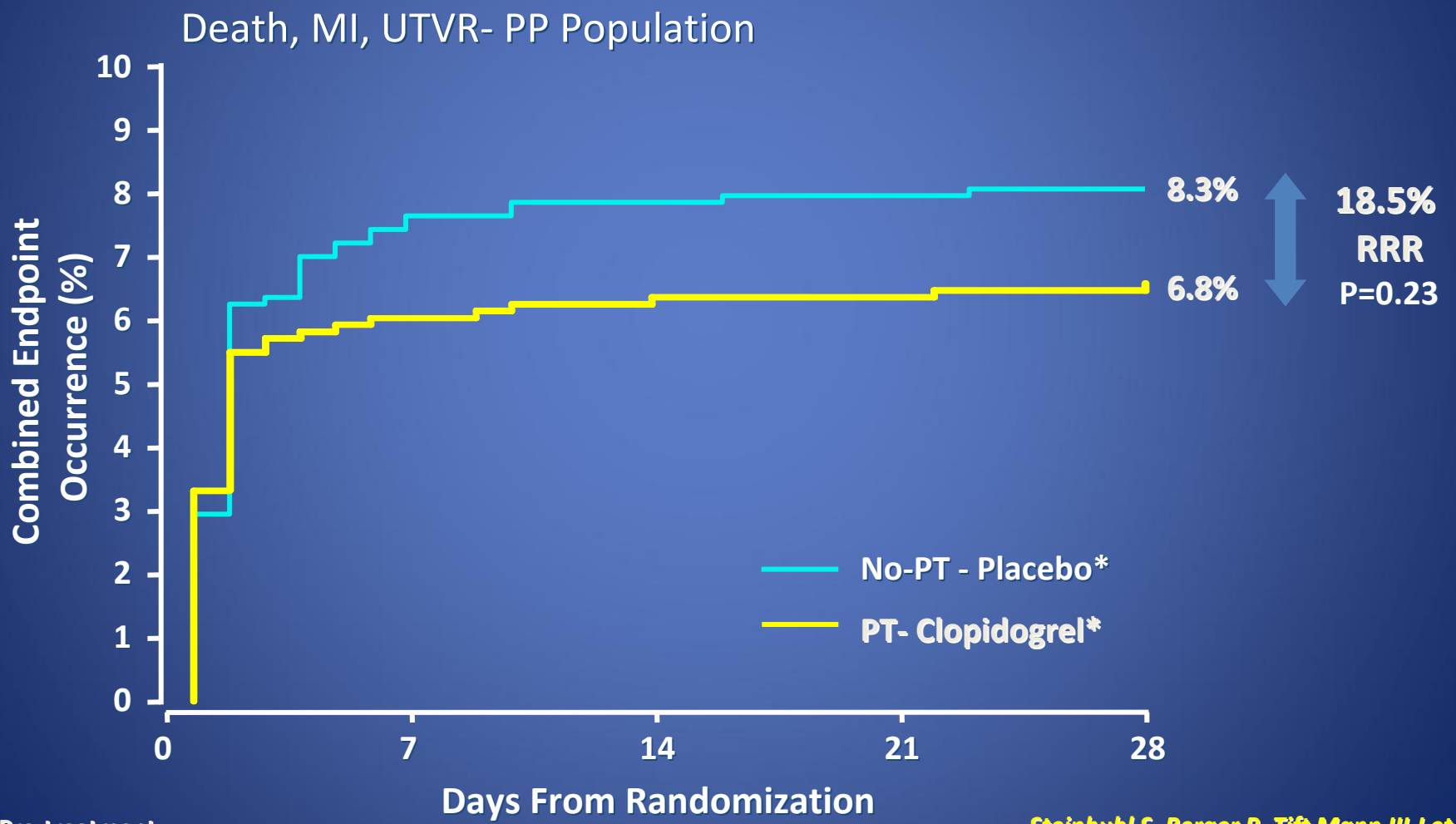
Primary End Point - MI/Stroke/CV Death



* In combination with standard therapy

The CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.

Early Effects of Pre-treatment with Clopidogrel – 28 Day Results



PT = Pre-treatment

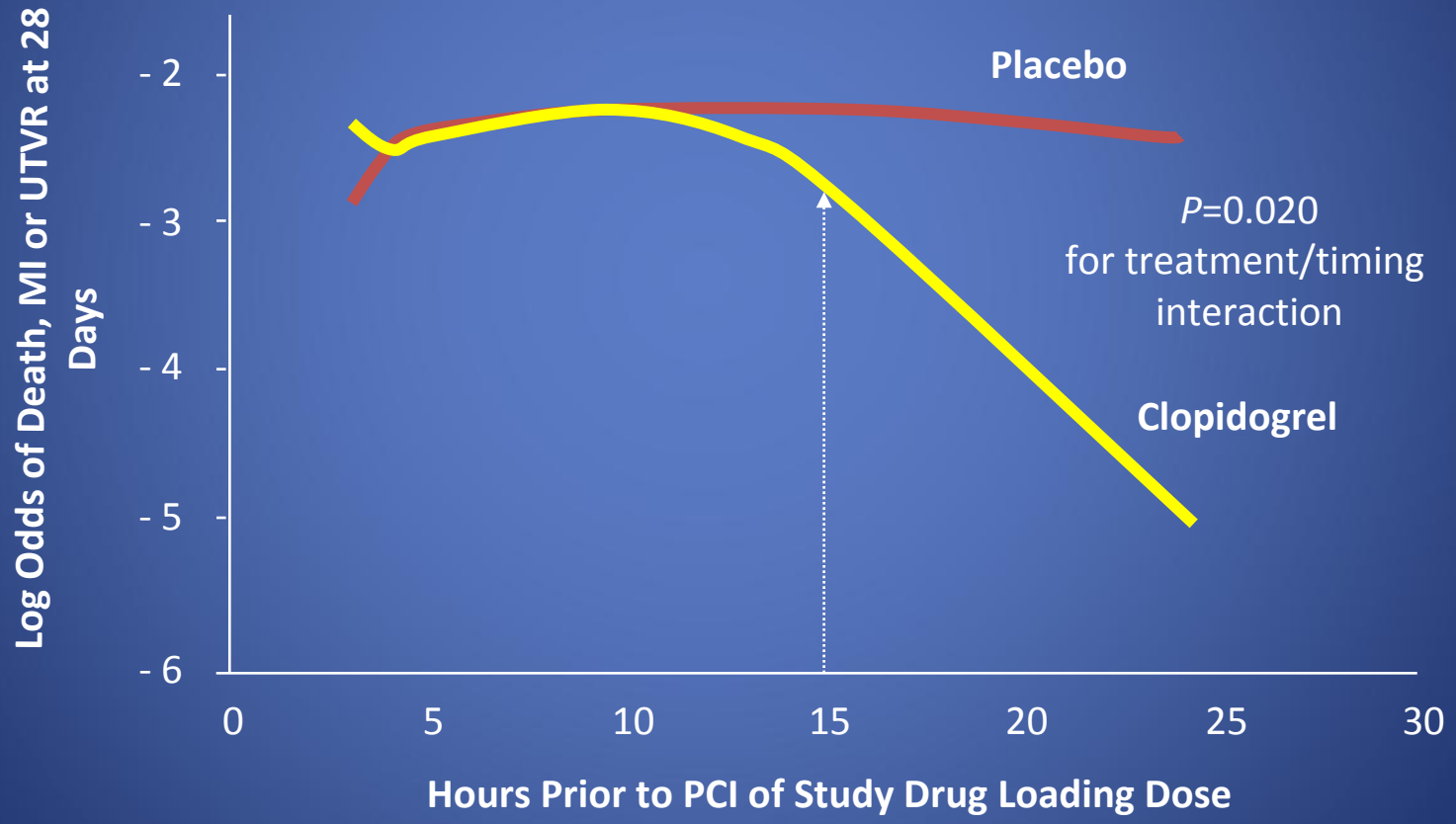
*Plus ASA and other standard therapies

Steinhubl S, Berger P, Tift Mann III J et al.

JAMA. 2002;Vol 288,No 19:2411-2420.

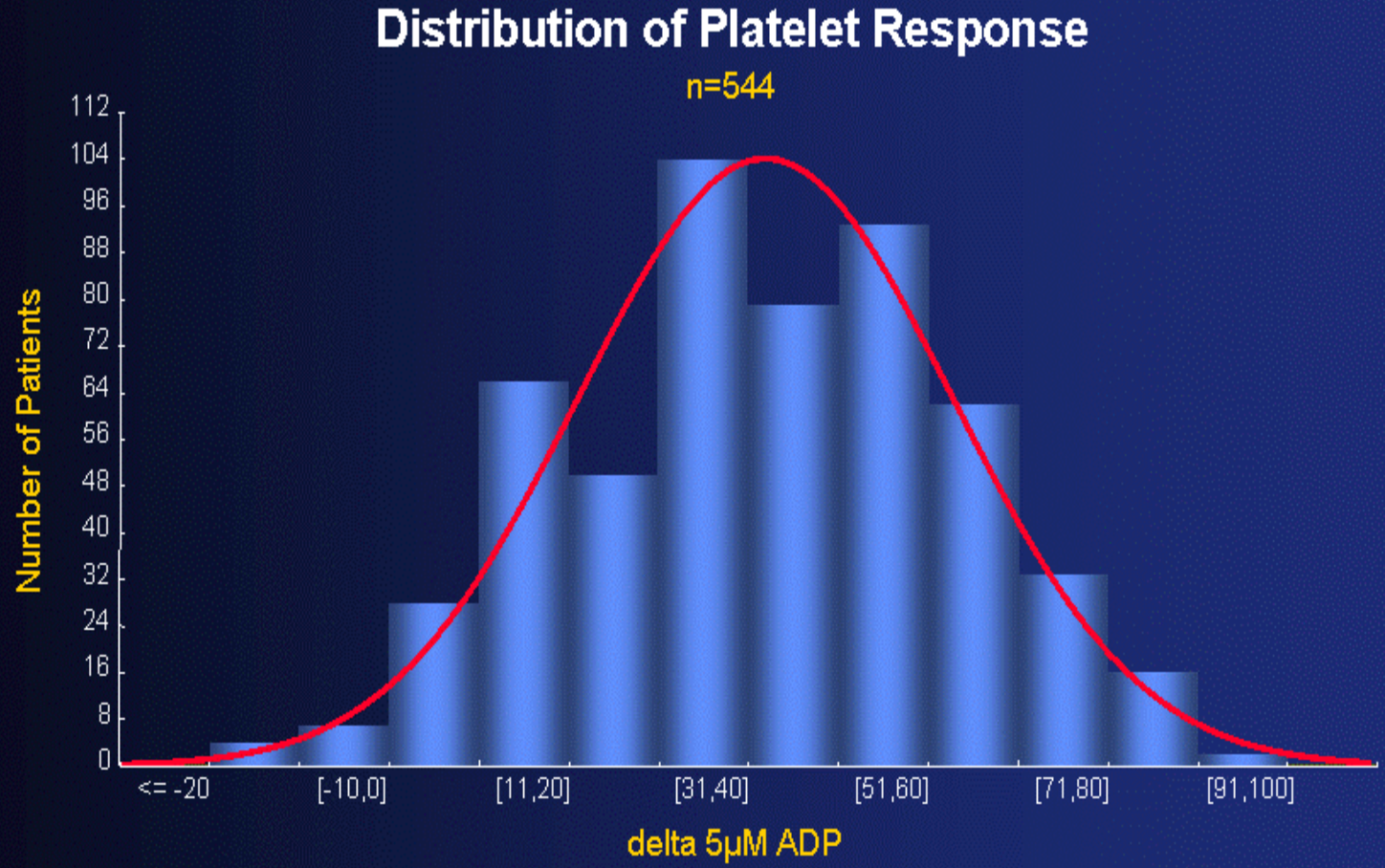
CREDO: Clopidogrel Loading

Dose Timing and Risk of MACE



Steinhubl, et al

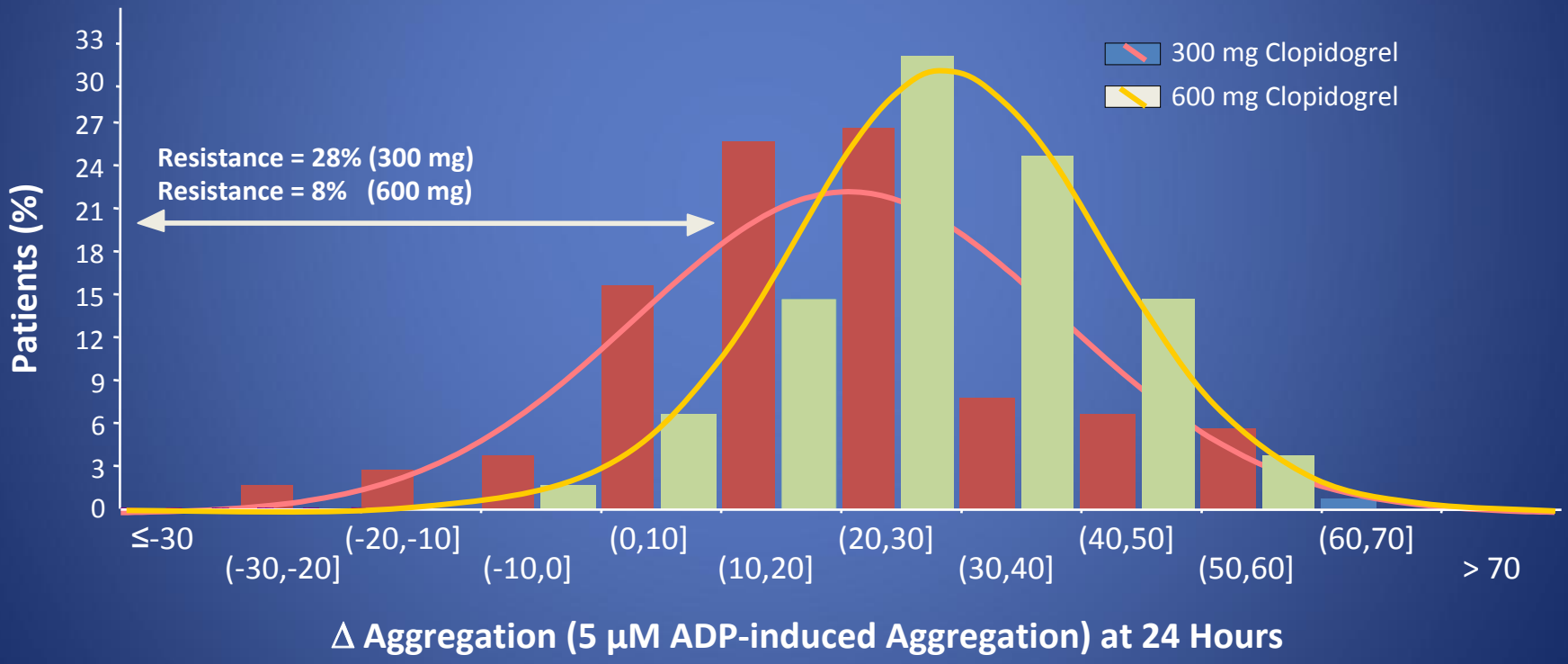
Platelet Reactivity to Clopidogrel Follows a Normal, Bell-Shaped Distribution*



* Response of 544 individuals follows a normal bell-shaped distribution. Only 4.2% of patients are two standard deviations below the mean and might be considered hypo-responders.
Serebruany VL, et al. *J Am Coll Cardiol*. 2005;45:246-251.

PLAVIX backup slide.

Increase the Dose of Clopidogrel: (300 mg vs 600 mg)



Gurbel PA, et al. *J Am Coll Cardiol.* 2005;45:1392-1396.

ESC
Aug 30, 2009

CURRENT

OASIS-7

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

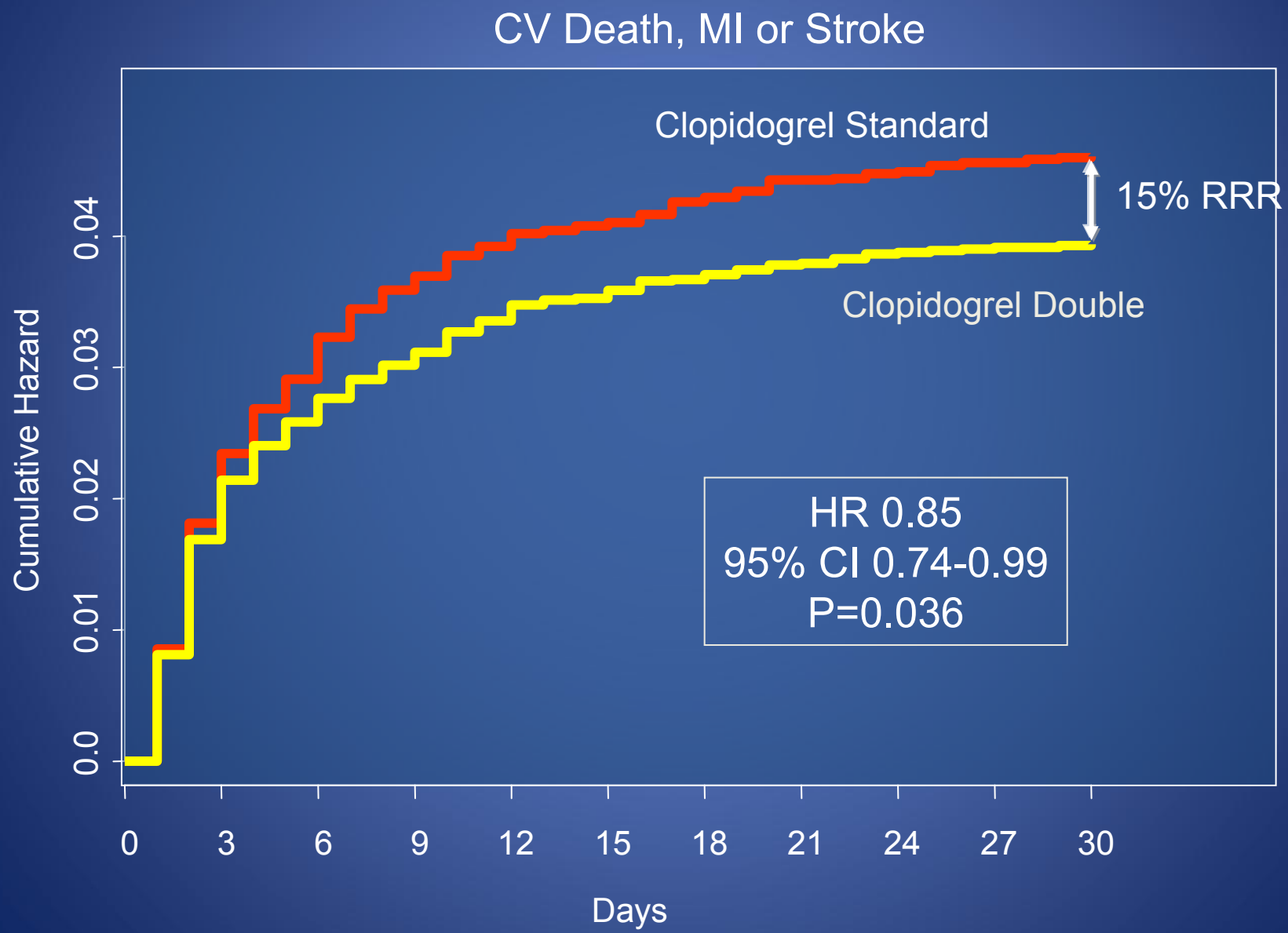
- ✓ Planned Early (<24 h) Invasive Management with intended PCI
- ✓ Ischemic ECG Δ (80.8%) or ↑ cardiac biomarker (42%)

Double-dose CLOPIDOGREL
600 mg loading
150 mg/d x 7d then 75 mg/d

Vs

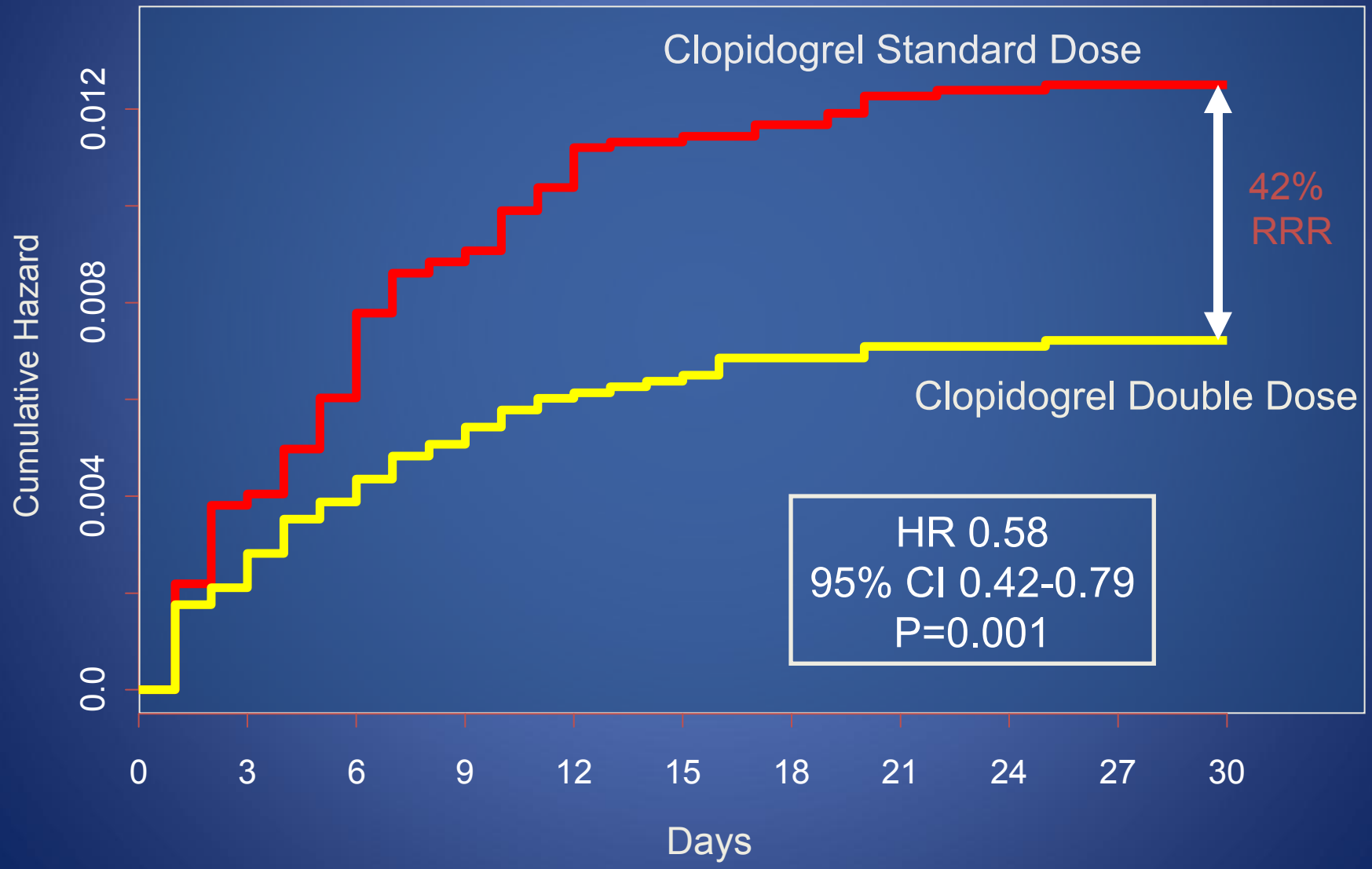
Standard dose CLOPIDOGREL
(300 mg then 75 mg/d)

Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients



CURRENT

Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)



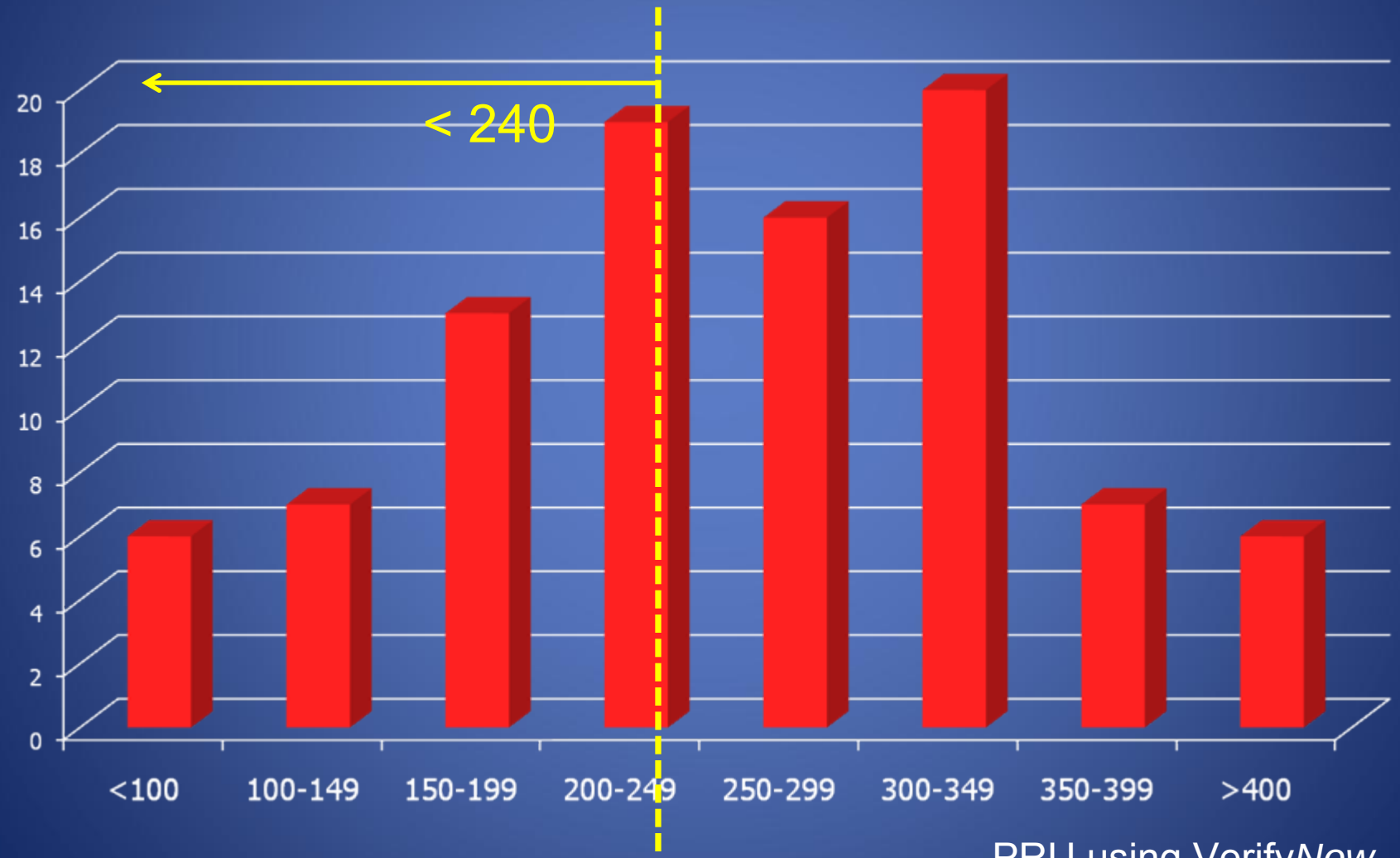
Study population: CCL MRH

Verify Now P2Y12

- All Patients taking Plavix on a chronic basis or patients who were loaded the day before with 300 or 600
- March /April 2000
- N= 94

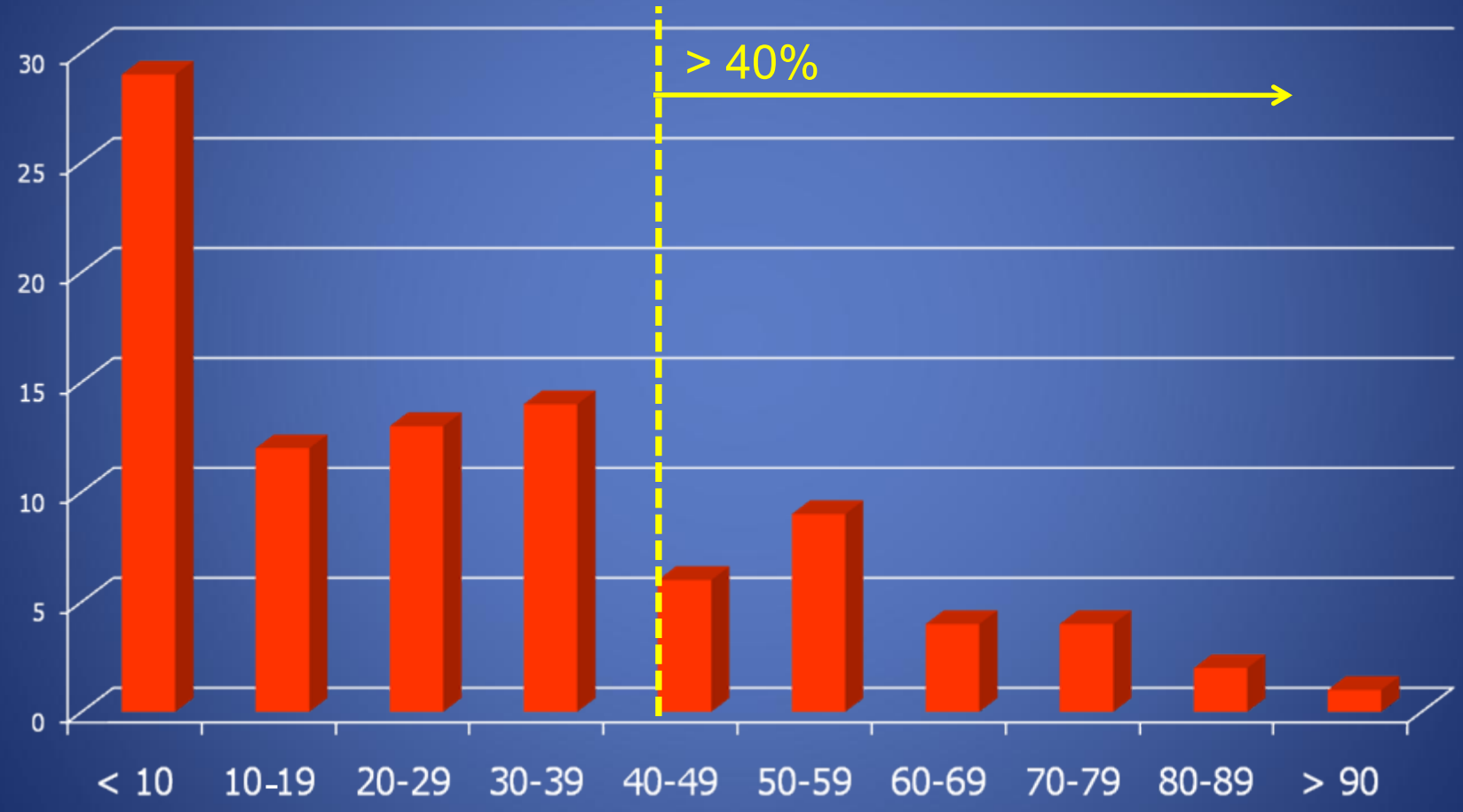
P2Y12 Reactivity on Clopidogrel:

PRU (n=94)



PRU using Verify*Now*

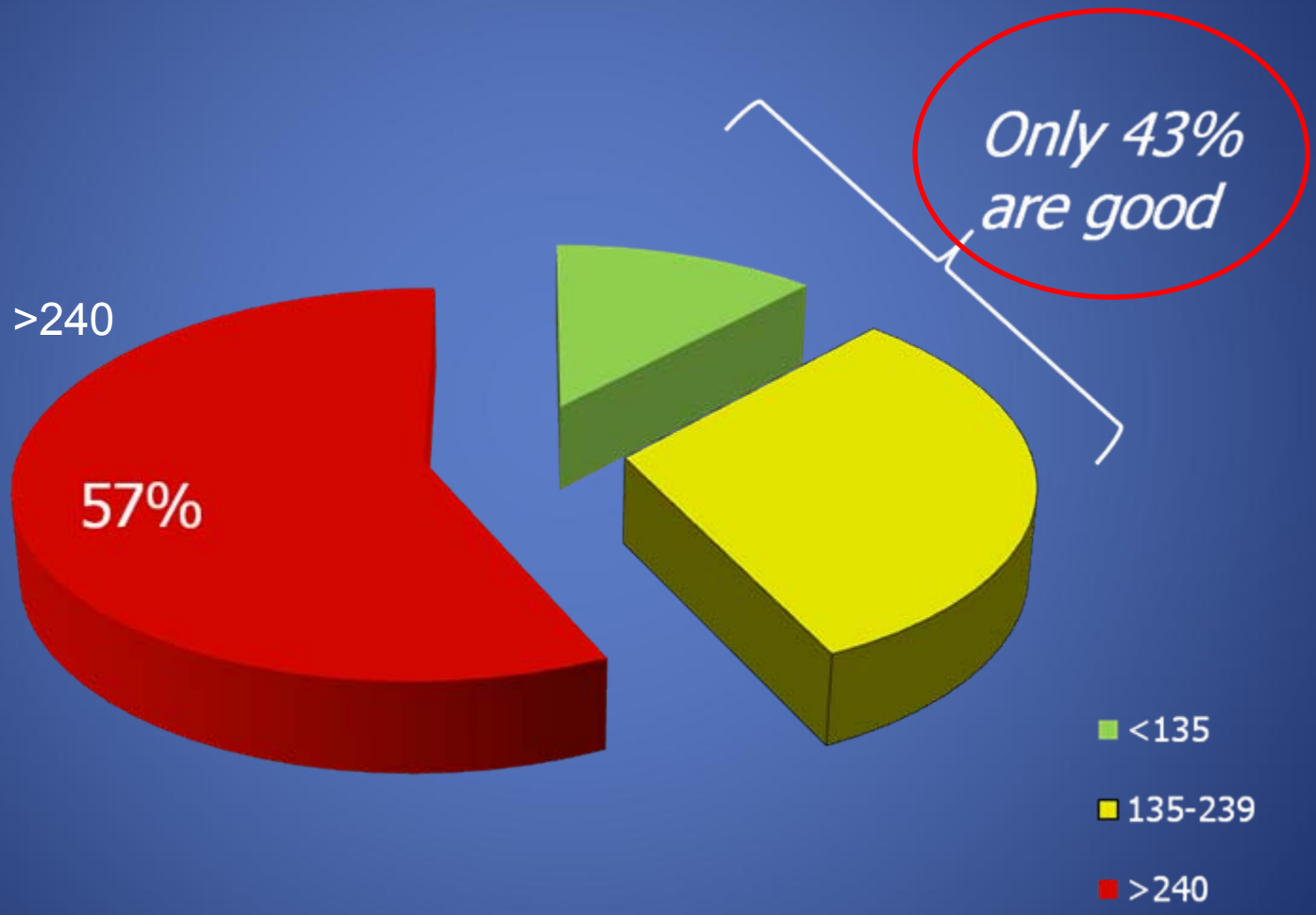
P2Y12 Reactivity on Clopidogrel % Inhibition (n=94)



% Inhibition by VerifyNow

VerifyNow P2Y12 Inhibition: MRH

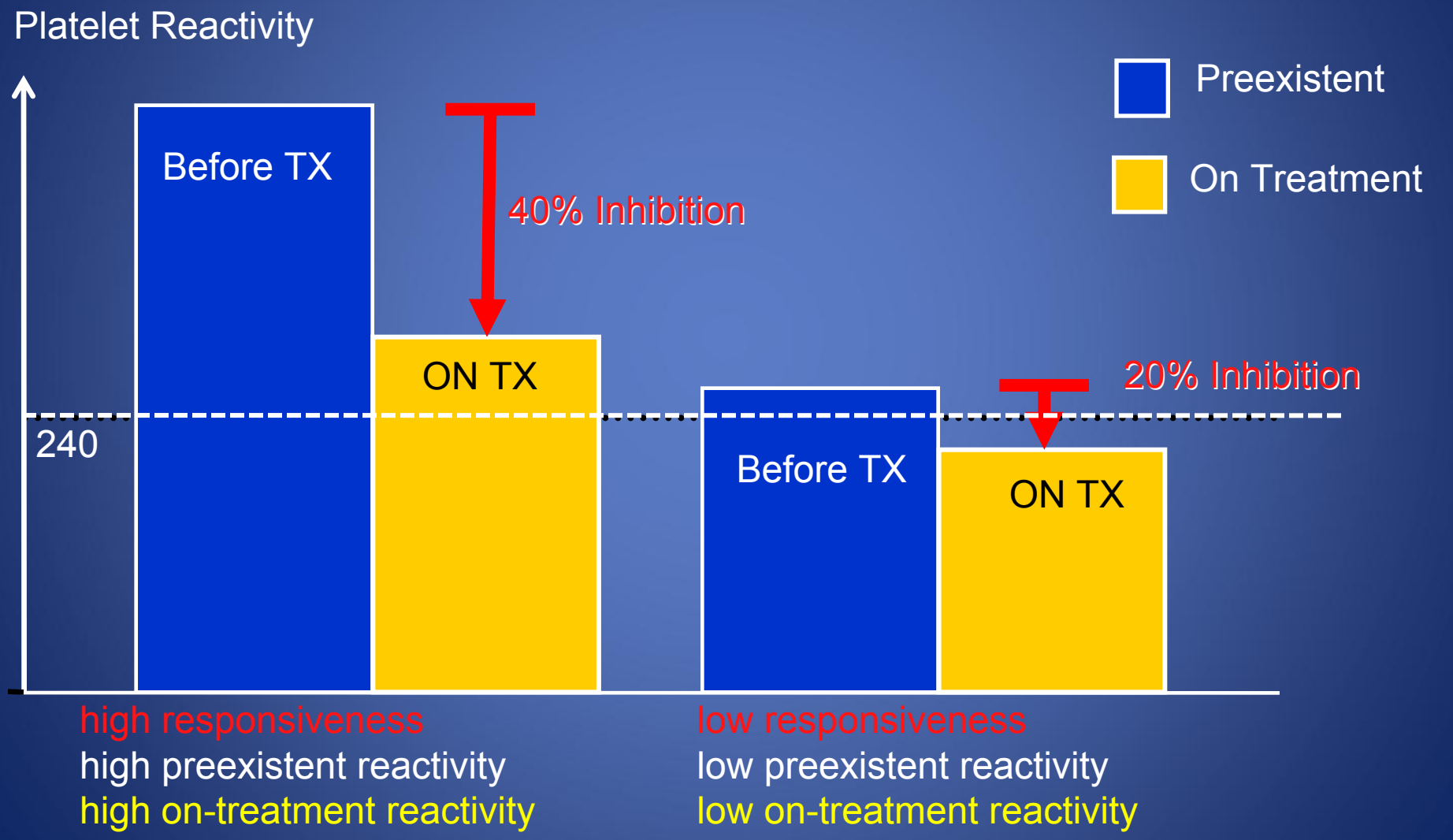
PRU GOAL < 240



% Inhibition or absolute platelet reactivity?

Although probably BOTH are important, the absolute residual platelet reactivity has been associated with outcomes.

Role of Preexistent Platelet Aggregation
- Responsiveness vs. On-Treatment Reactivity -



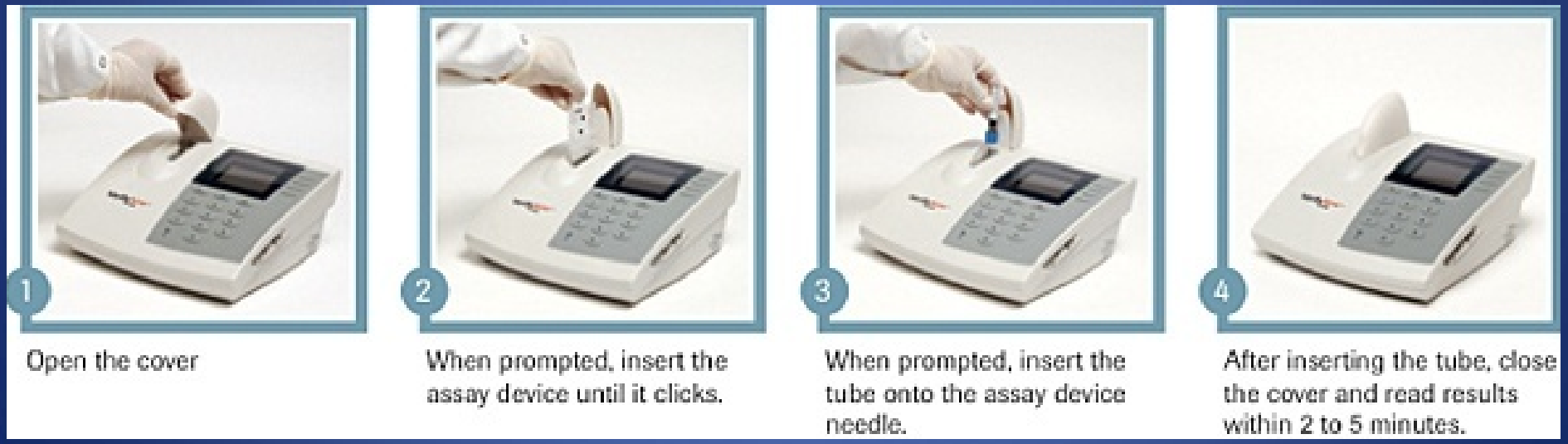
Platelet testing
Background

- “One size fits all”: WRONG CONCEPT
- Variable baseline platelet reactivity
- Response to antiplatelet therapy is variable
- Residual platelet reactivity is related to thrombotic complications in PCI risk and risk of bleeding from CABG

Platelet Aggregation: VerifyNow™

Easy to Use

- Whole blood, small sample volume.
- No sample preparation
- Results in 2-5 minutes
- Point of care device: MRH CATH LAB AND CENTRAL LAB



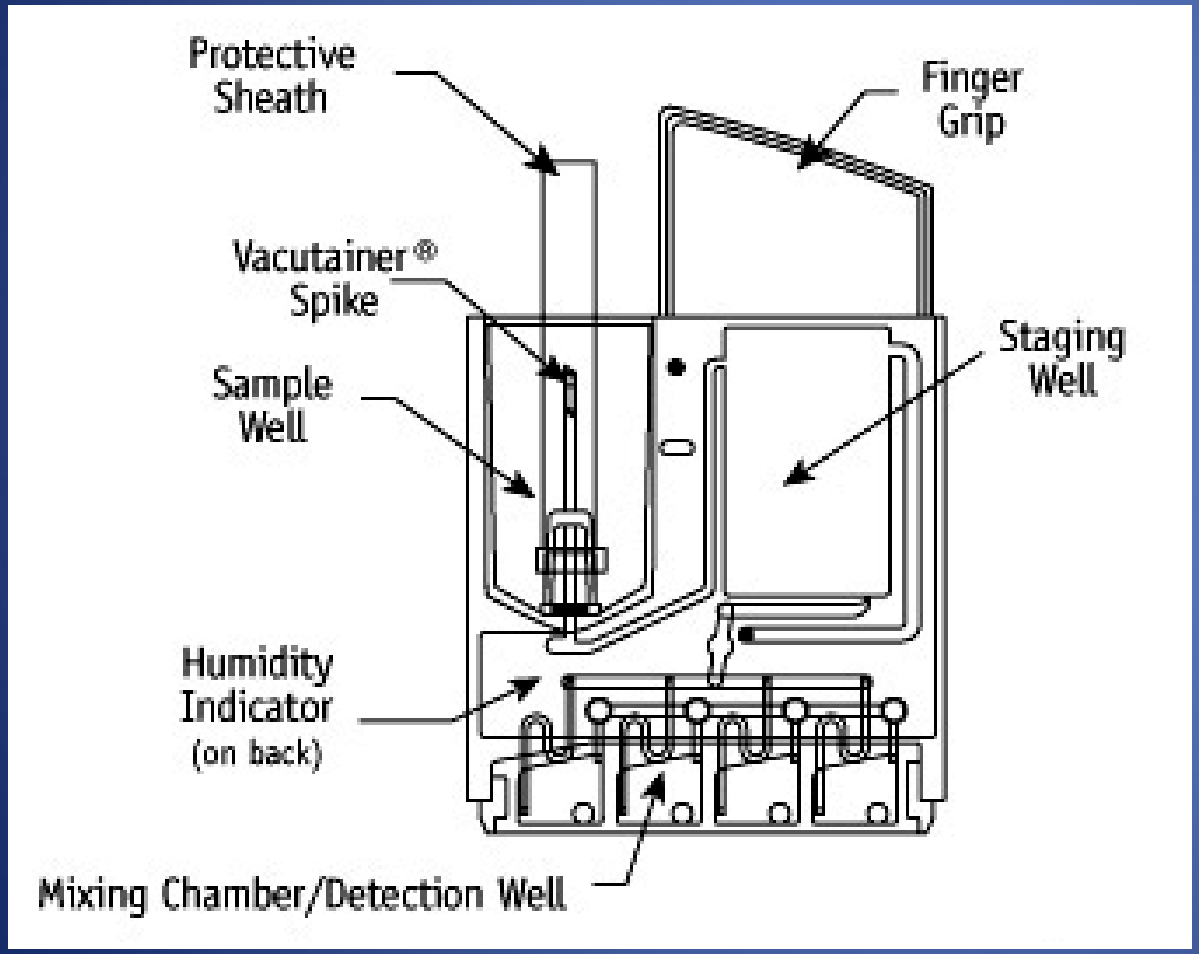
ASSAYS

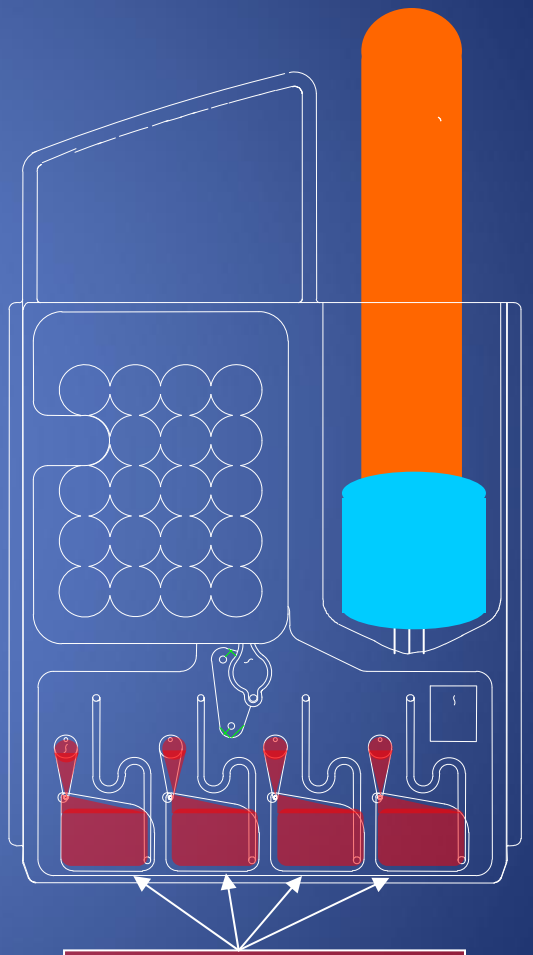
VerifyNow P2Y12

VerifyNow Aspirin

VerifyNow IIb/IIIa

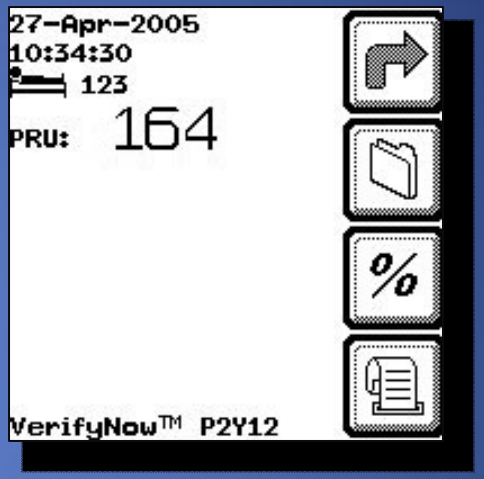
VerifyNow®


Protective Sheath
Finger Grip
Vacutainer® Spike
Staging Well
Sample Well
Humidity Indicator (on back)
Mixing Chamber/Detection Well

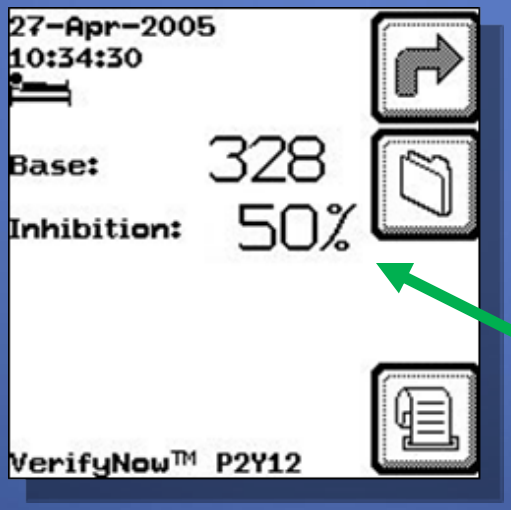

Mixing Chambers/ Detection Well

VerifyNow® P2Y12 Result Calculations

ADP-mediated platelet activation determines the PRU value



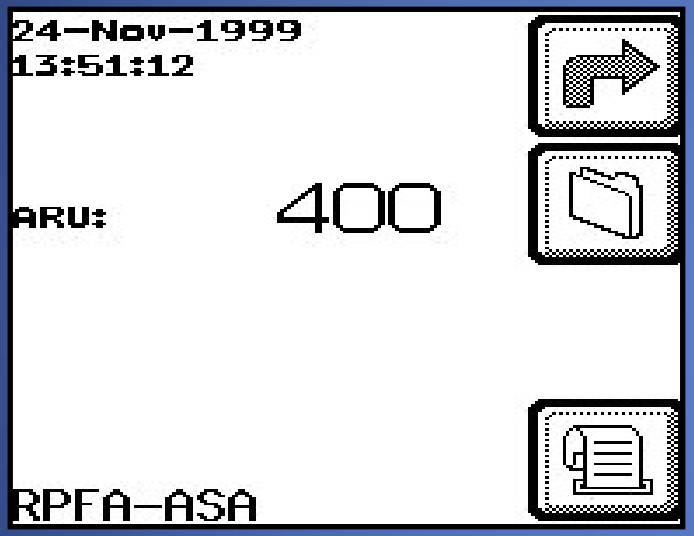
TRAP-mediated platelet activation approximates Baseline PRU



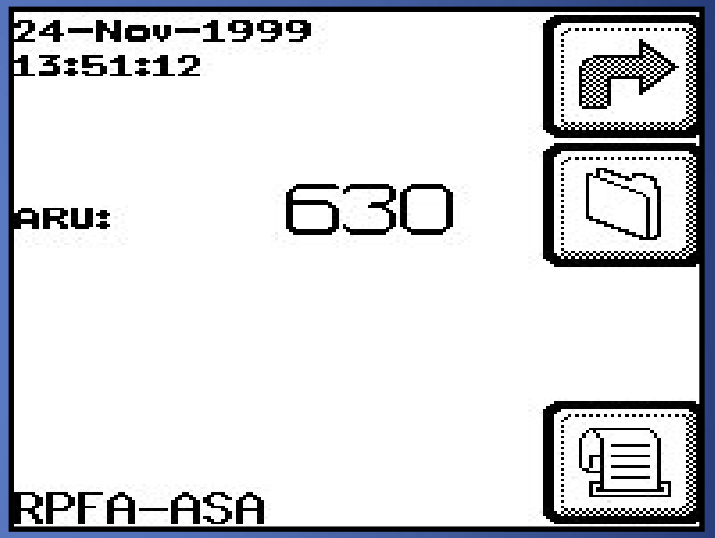
Clopidogrel-induced % platelet inhibition

$$= \frac{\text{Baseline PRU} - \text{Post-PRU}}{\text{Baseline PRU}} \times 100$$

Results are based on the extent of platelet aggregation measured and are reported in Aspirin Reaction Units (ARU)



If result is **<550** ARU, then platelet dysfunction has been detected, indicating that **Aspirin IS working**.



If result is **≥550 ARU** indicating that the anti-platelet effect has not have been achieved or **Aspirin IS NOT working**

Publication of TIMI 38

NEJM, Nov 15, 2007

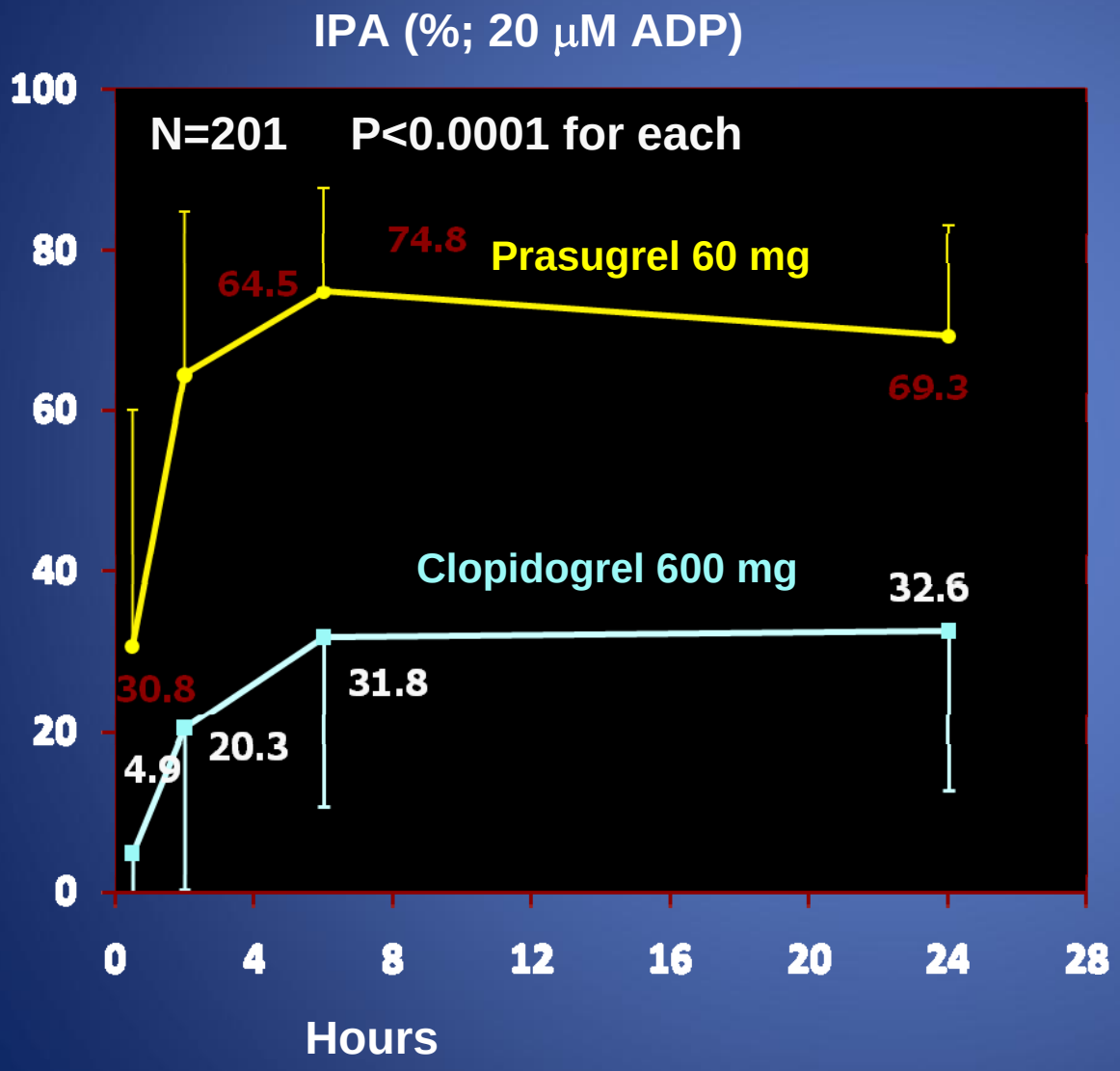
The NEW ENGLAND JOURNAL of MEDICINE

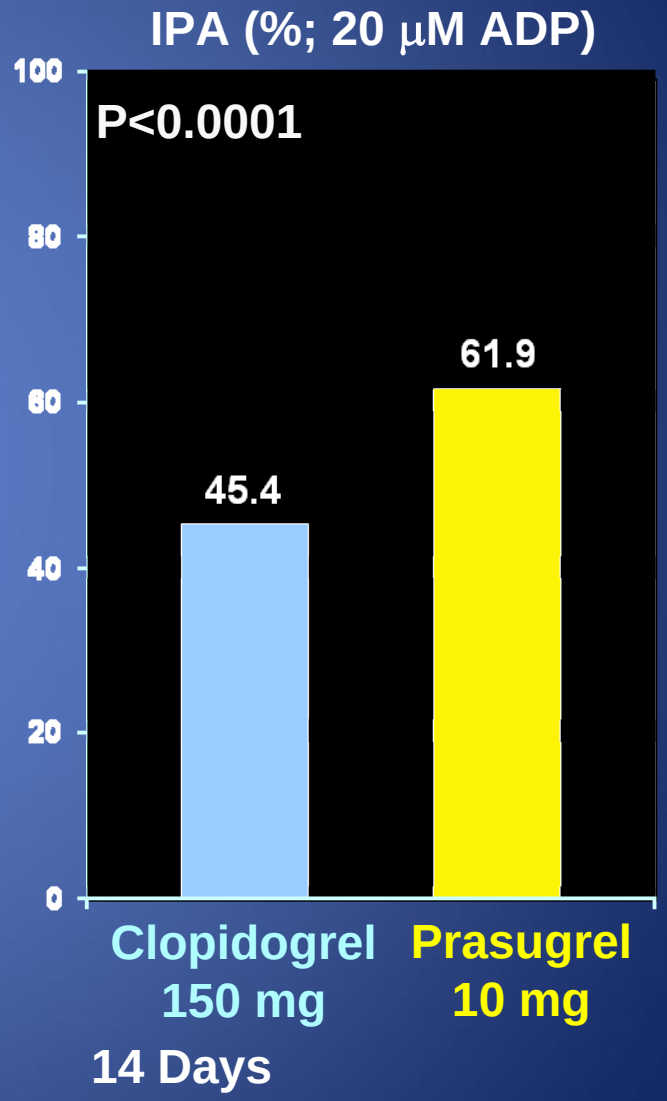
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

Effient (Prasugrel) approved by FDA July 10, 2009

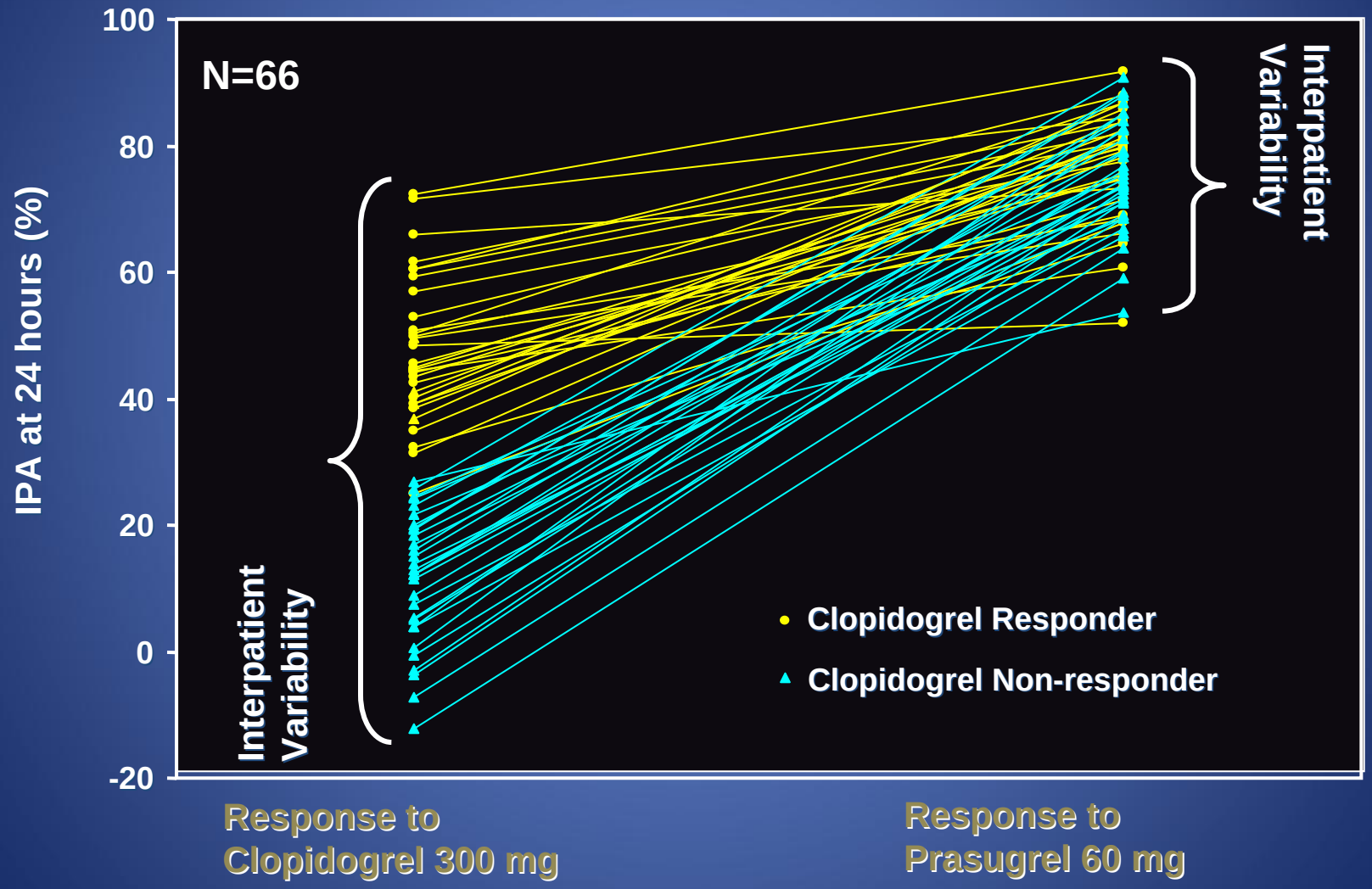
Prasugrel: Comparison with High Dose Clopidogrel





Wiviott et al Circ 2007

Healthy Volunteer Crossover Study



From Brandt JT AHJ 153: 66e9,2007

TRITON-TIMI 38

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ **N= 13,600**

Double-blind

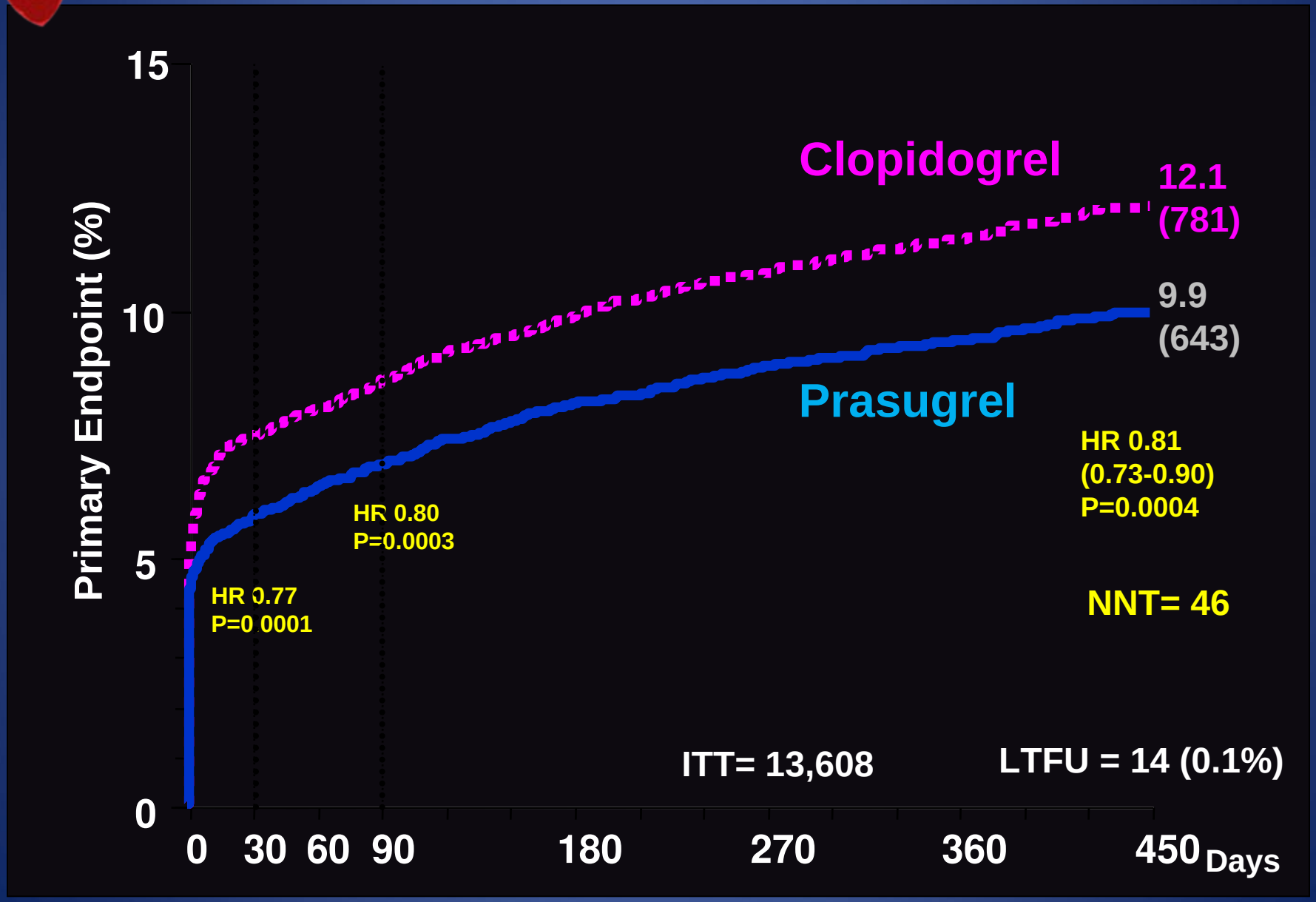
CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

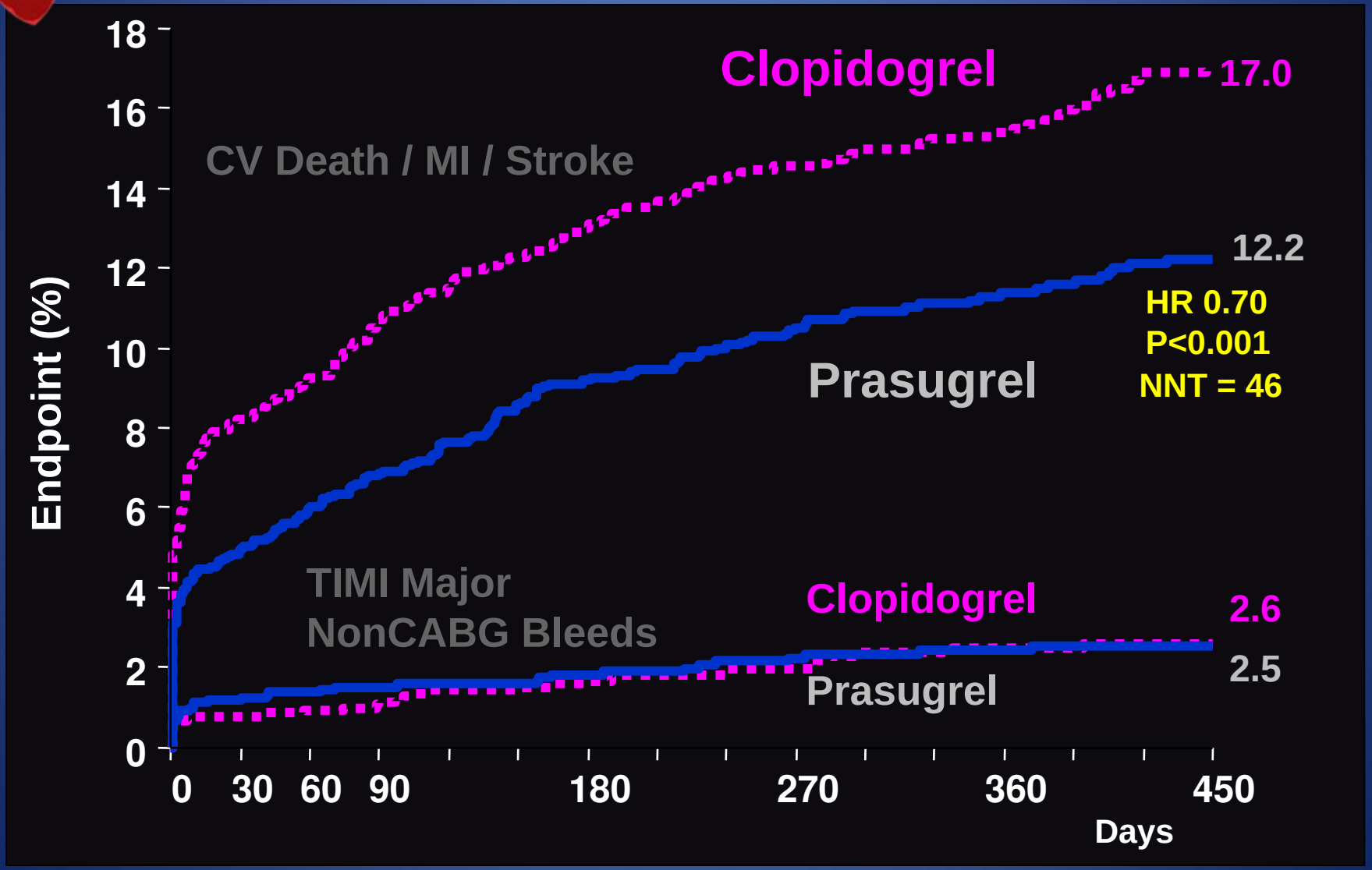
Median duration of therapy - 12 months

1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Rehosp-Rec Isch
	CV death, MI, UTVR
	Stent Thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key Substudies:	Pharmacokinetic, Genomic

TIMI 38: Primary Endpoint: CV Death, MI, Stroke



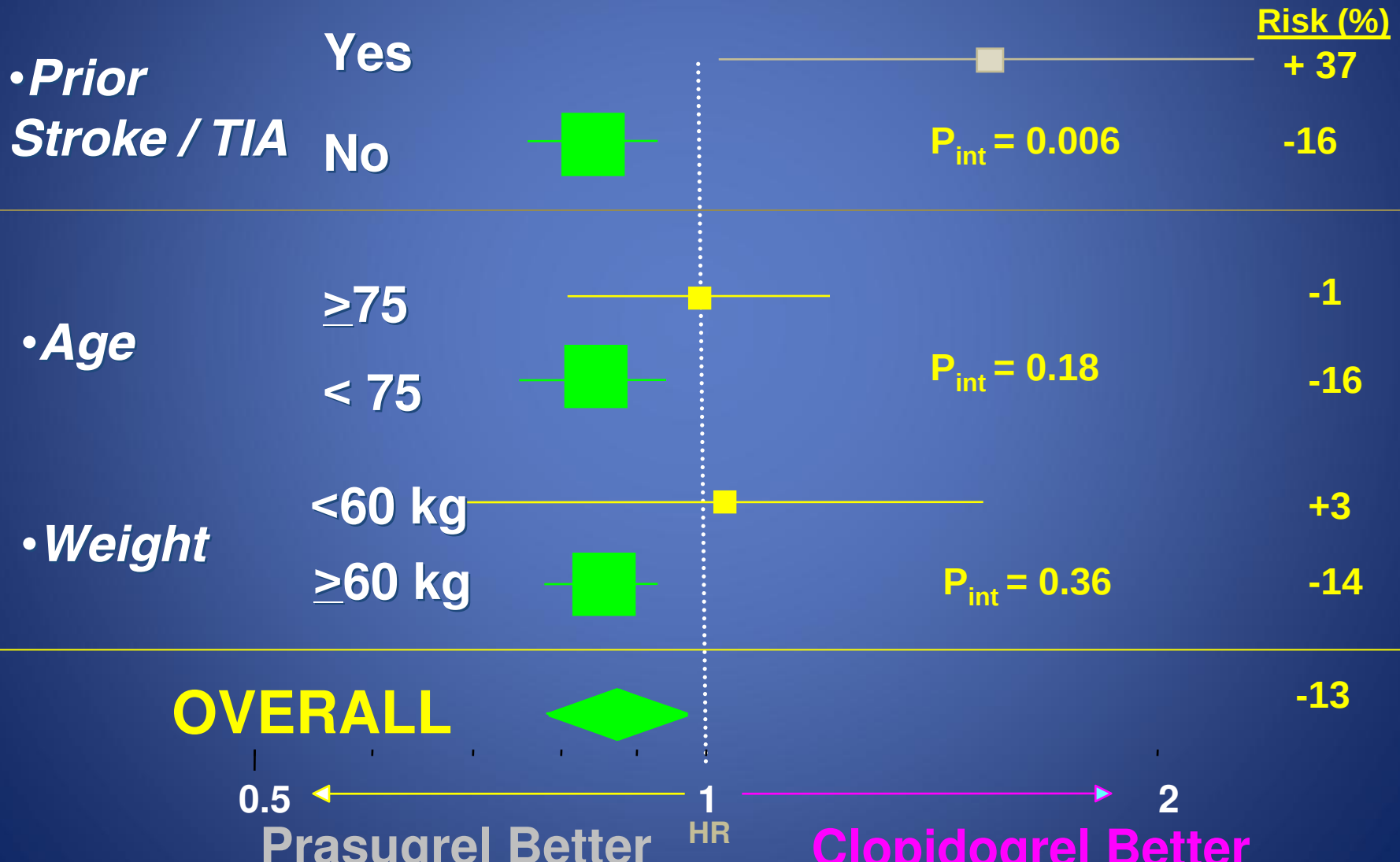
Diabetic Subgroup N=3146



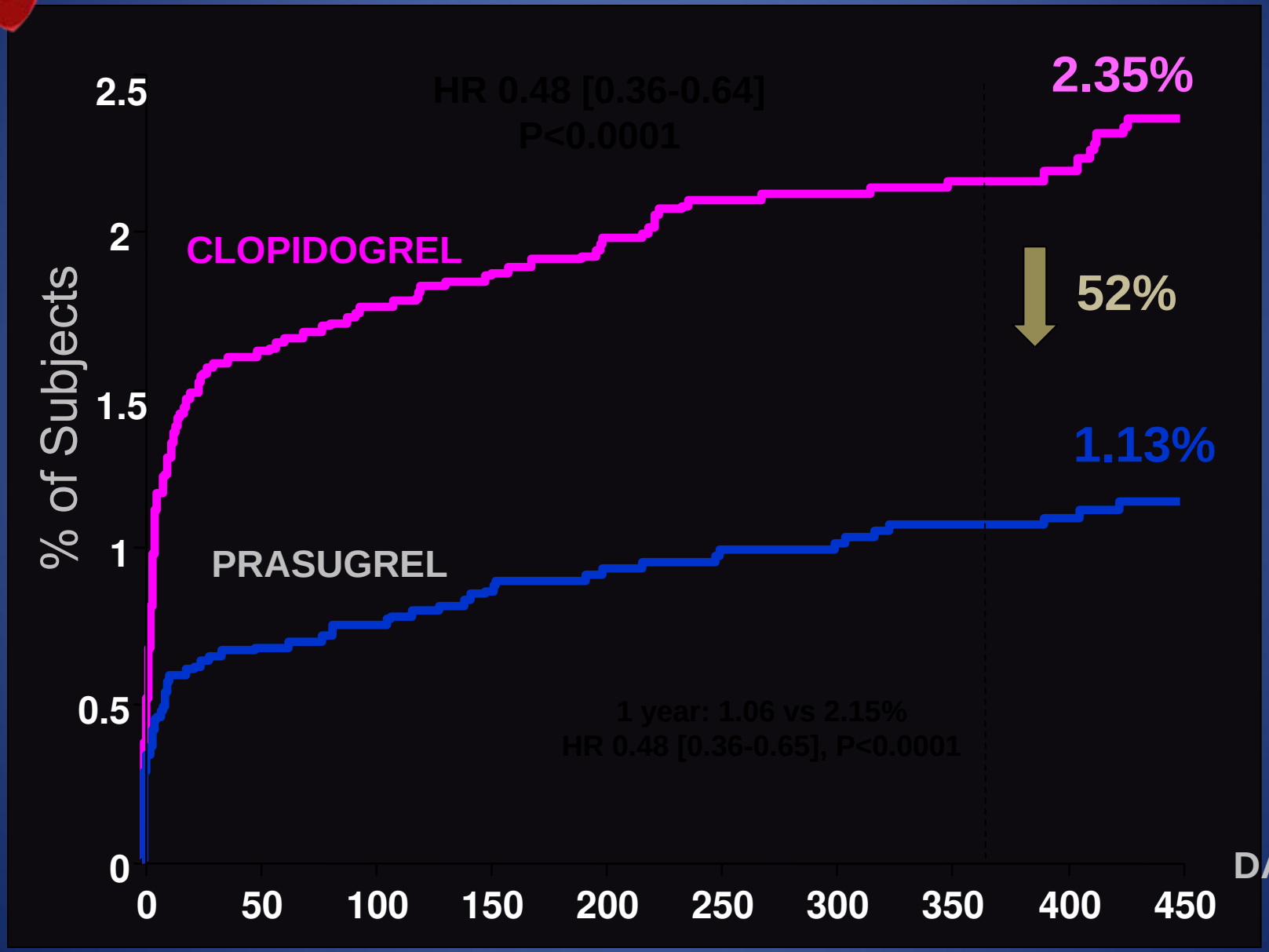
Post-hoc analysis TRITON 38

Net Clinical Benefit

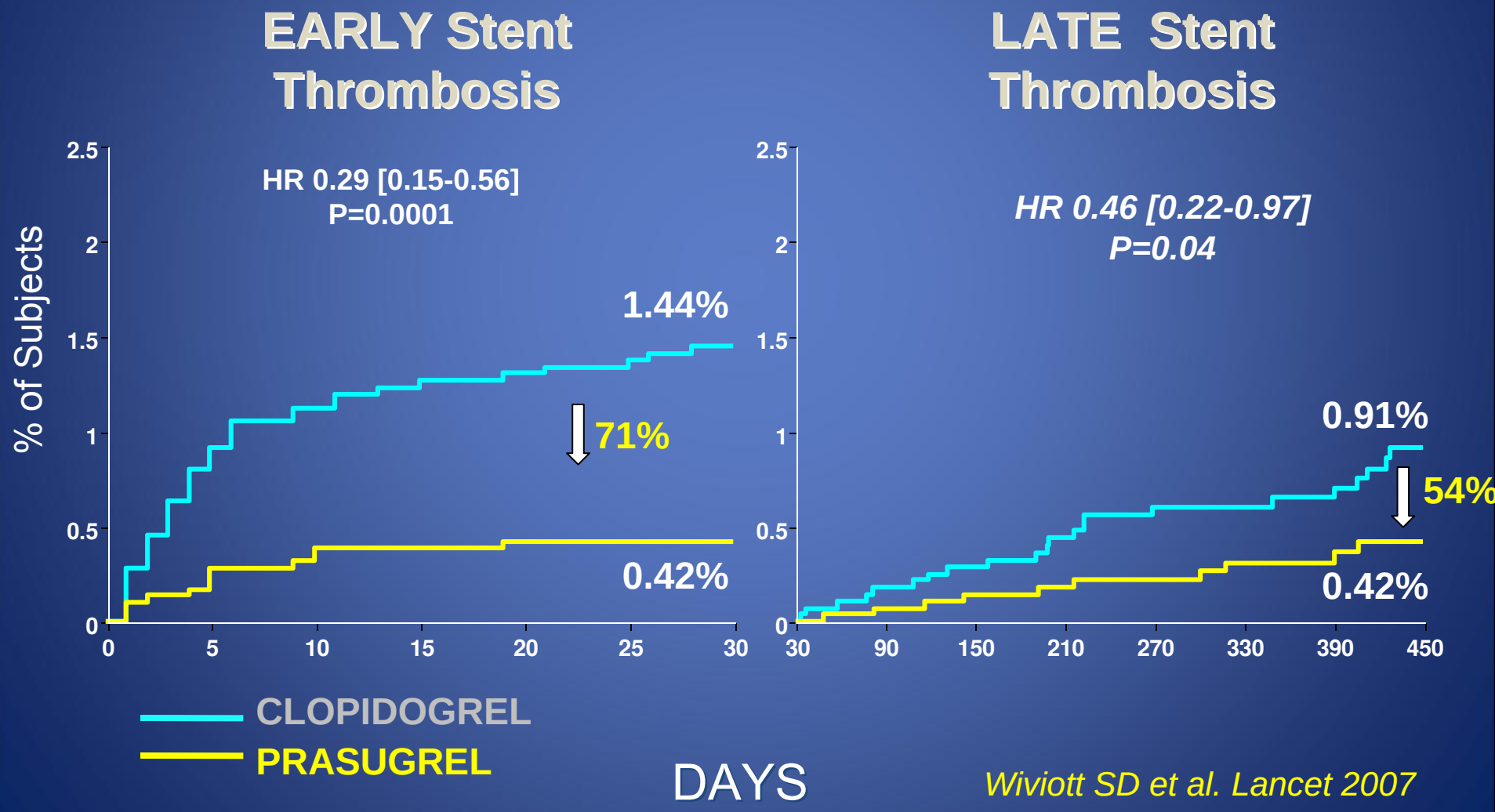
Bleeding Risk Subgroups



Definite/Probable ST: Any Stent (N=12,844)

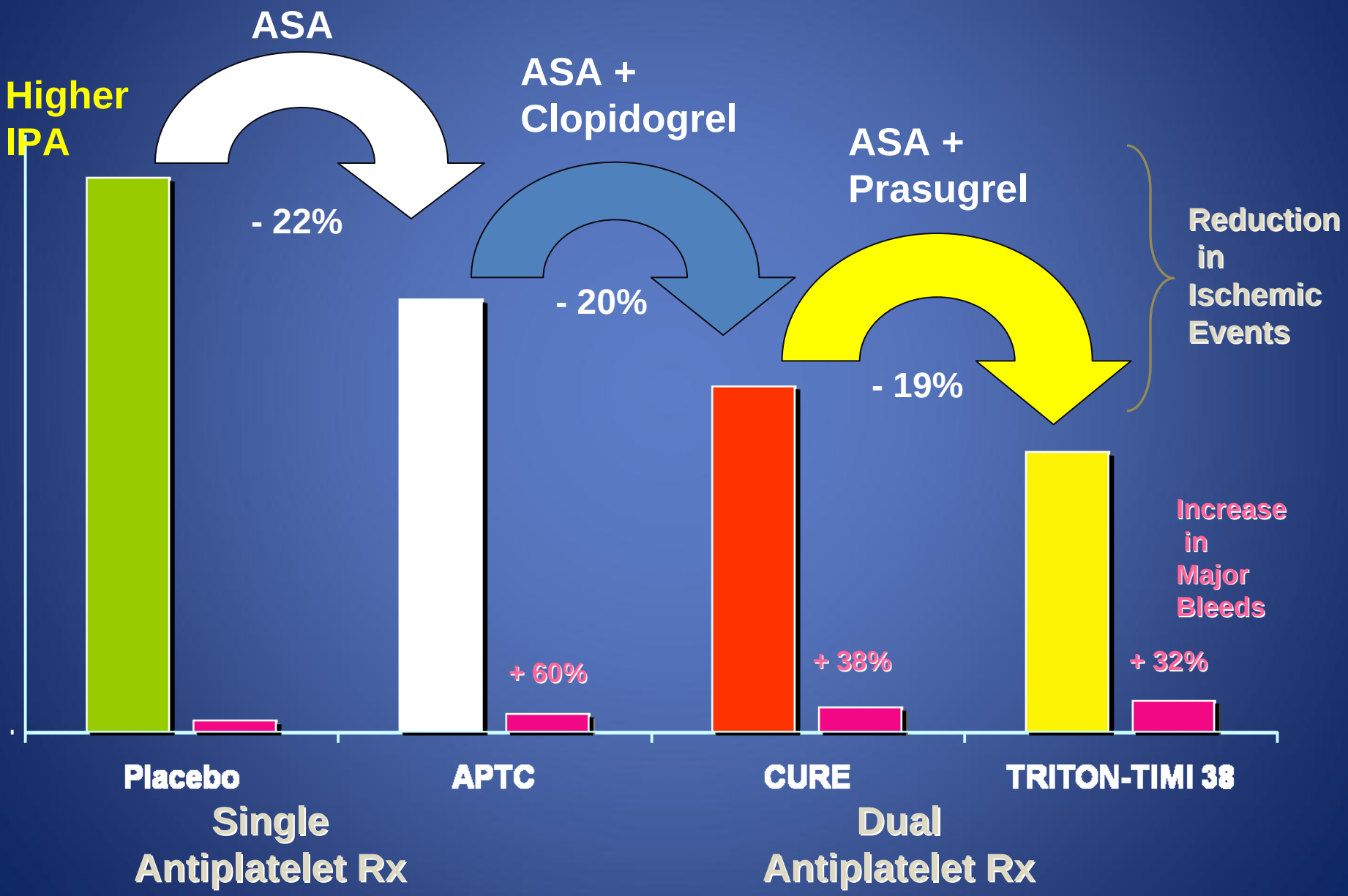


Definite/Probable Stent Thrombosis: DES Only (N=5743)



Wiviott SD et al. Lancet 2007

Antiplatelet Therapy in ACS



UPCOMING REVERSIBLE ADP RECEPTOR INHIBITOR

The NEW ENGLAND JOURNAL of MEDICINE

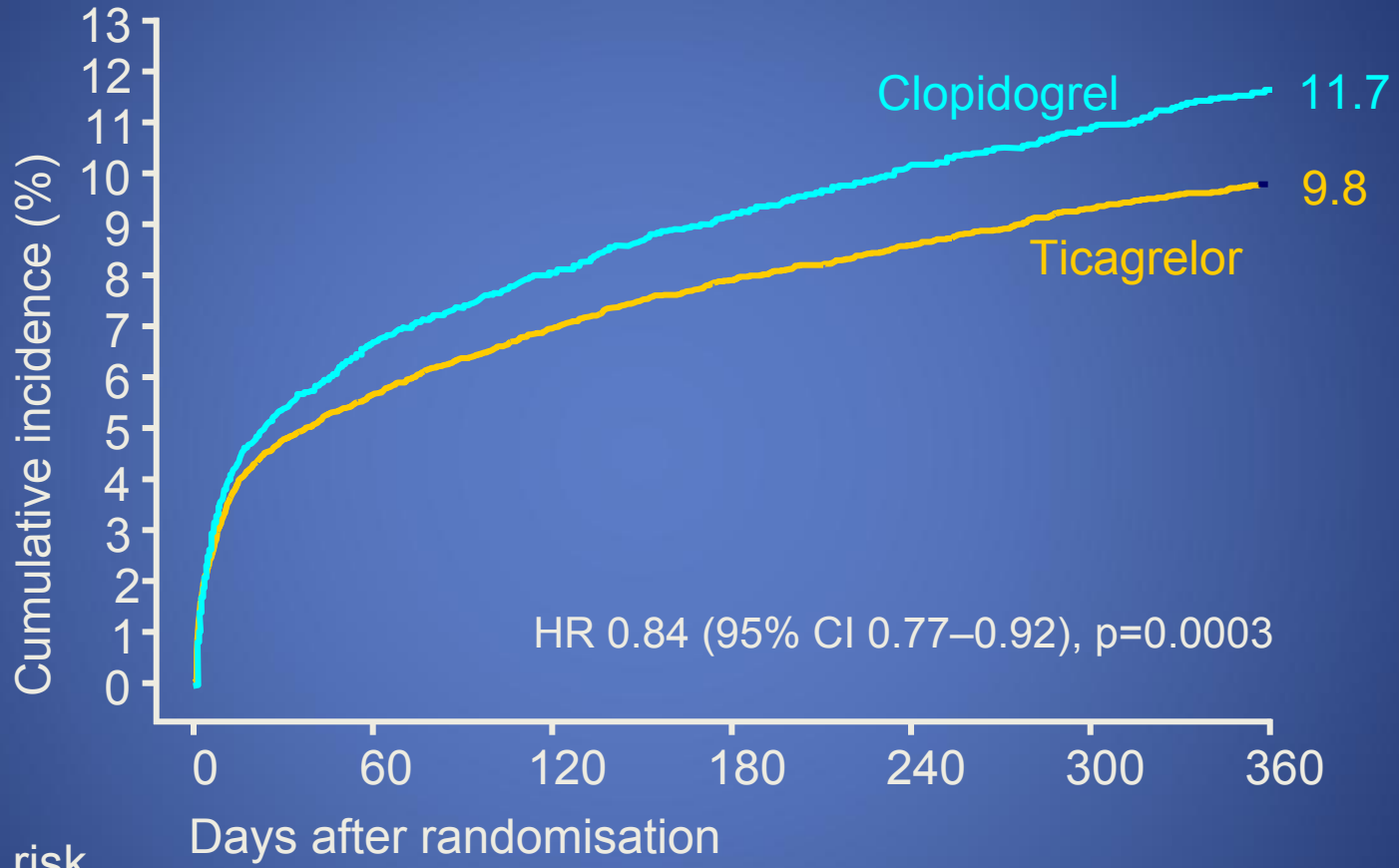
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

August 30, 2009

Composite of CV death, MI or stroke

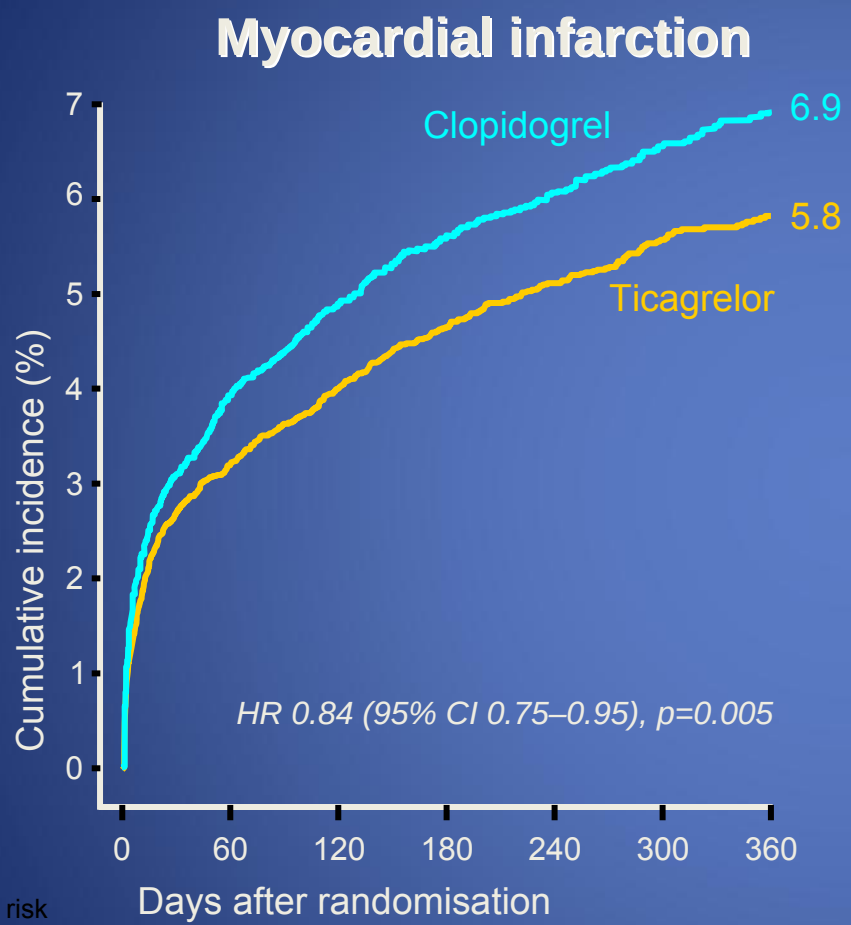
Primary efficacy endpoint

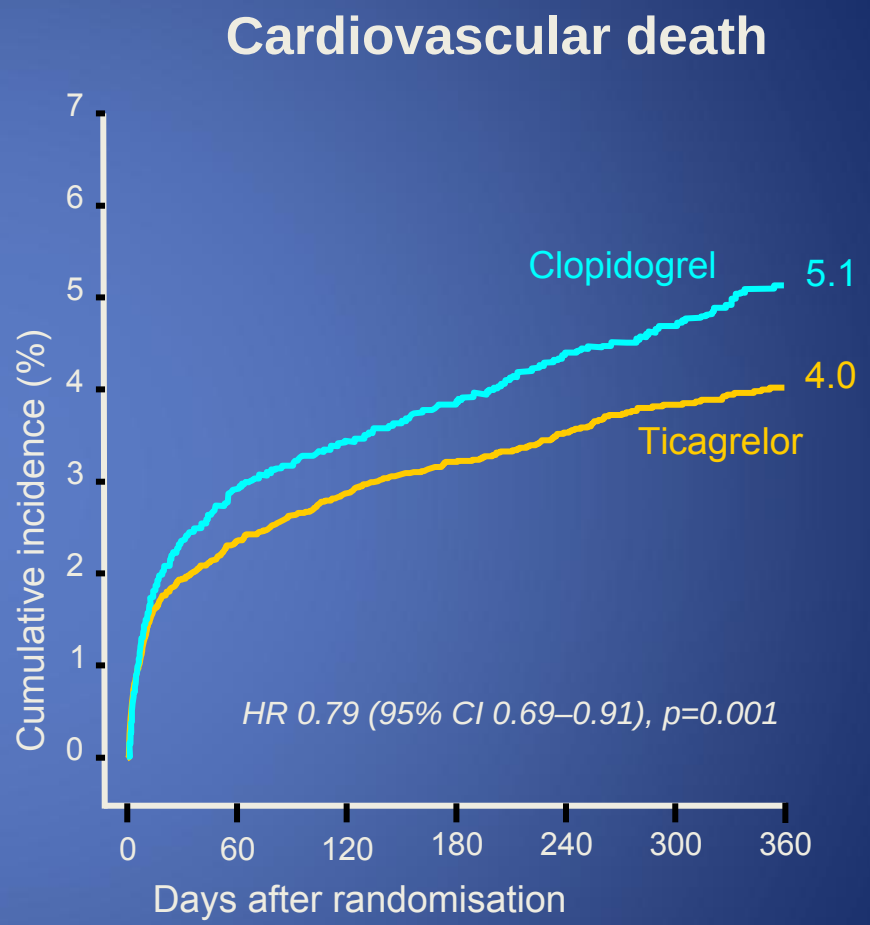


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

Myocardial Infarction and CV death





No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

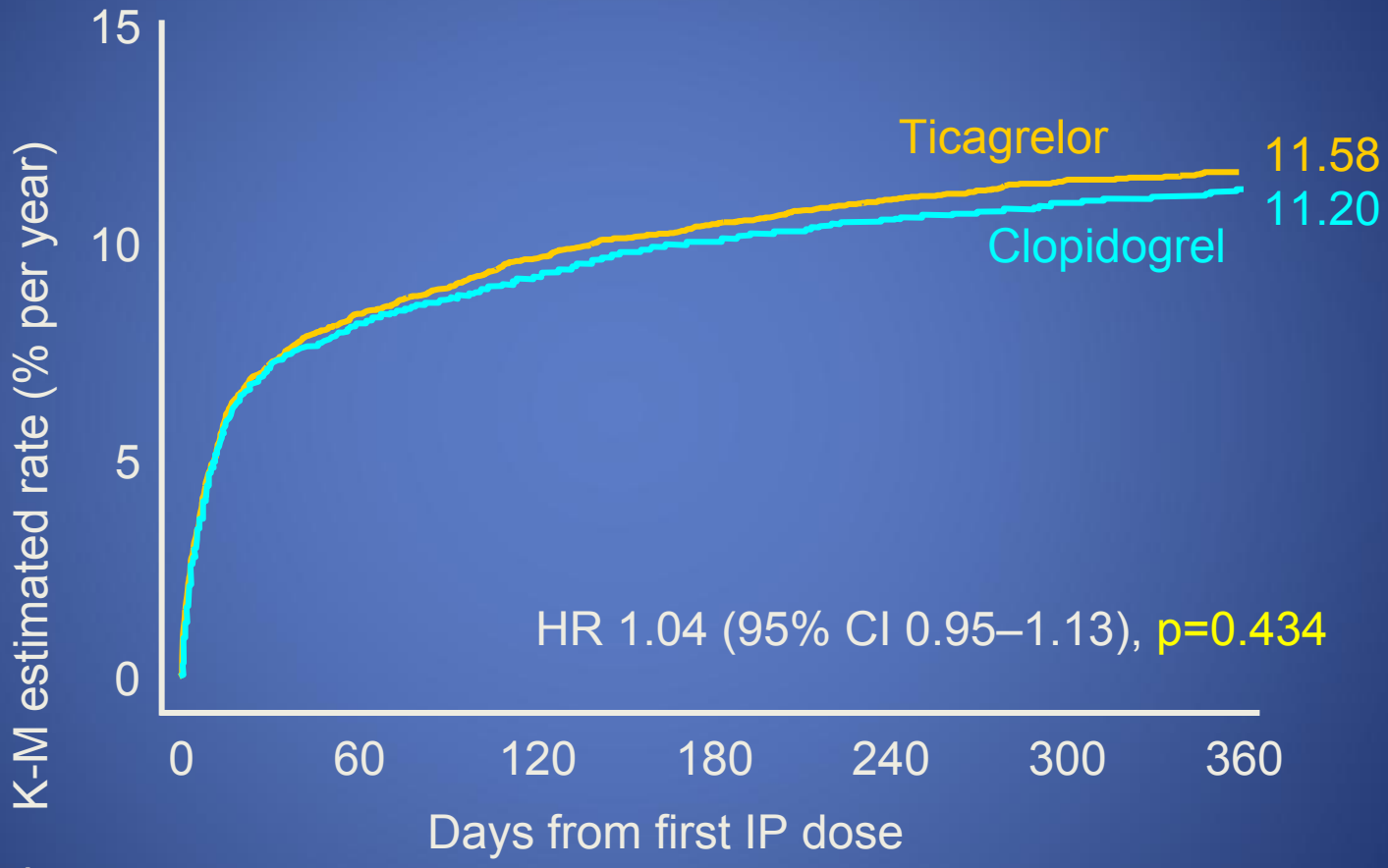
Stent thrombosis

	Ticagrelor (n=5,640)	Clopidogrel (n=5,649)	HR (95% CI)	p value
Stent thrombosis, n (%)				
Definite	71 (1.3)	106 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118 (2.1)	158 (2.8)	0.75 (0.59–0.95)	0.02
Possible, probable, definite	155 (2.8)	202 (3.6)	0.77 (0.62–0.95)	0.01

*Time-at-risk is calculated from first stent insertion in the study or date of randomisation

Major bleeding

Primary safety event



No. at risk

Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479