Comprendre le pourquoi du traitement antithrombotique dans le SCA

C. Bal*, L. Drouet*

J-G Dillinger, P. Henry****

E. Houdart * ,D. Calvet ****, JL Mas******

L. Drouet

*Consultation hémostase thromboses antithrombotiques
Laboratoire Hématologie & IVS
**service de cardiologie
***service de neuroradiologie Hôpital Lariboisière
****service de neurologie Hôpital Sainte Anne

Centre de Référence et d'Education des AntiThrombotiques d'Ile de France

Laboratoire Hématologie et CREATIF
& Consultation hémostase, thromboses, anti-thrombotiques
Laboratoire Thrombose et Athérosclérose * IVS
hôpital Lariboisière

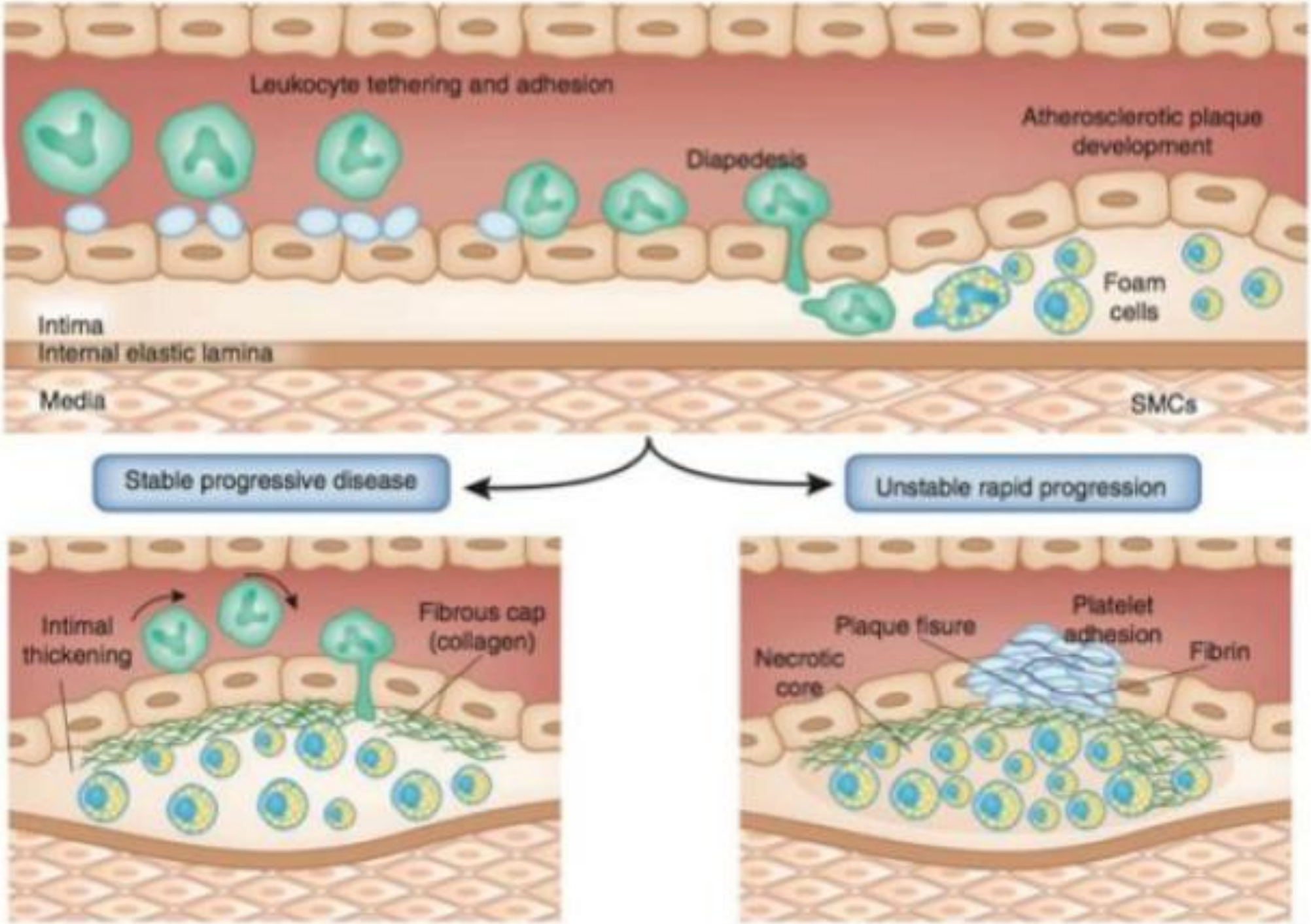
creatif.lrb@lrb.aphp.fr
01 42 81 12 13 (24/24 7/7)
Fax : 01 49 95 63 97
01 49 95 80 78

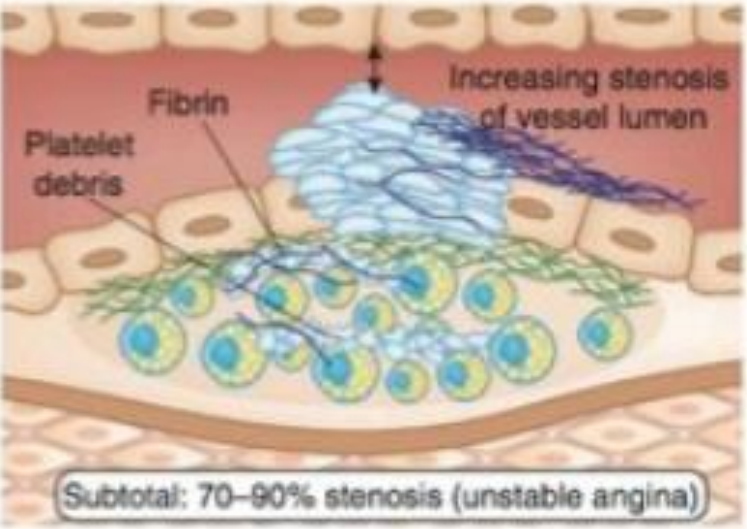
Université Paris VII

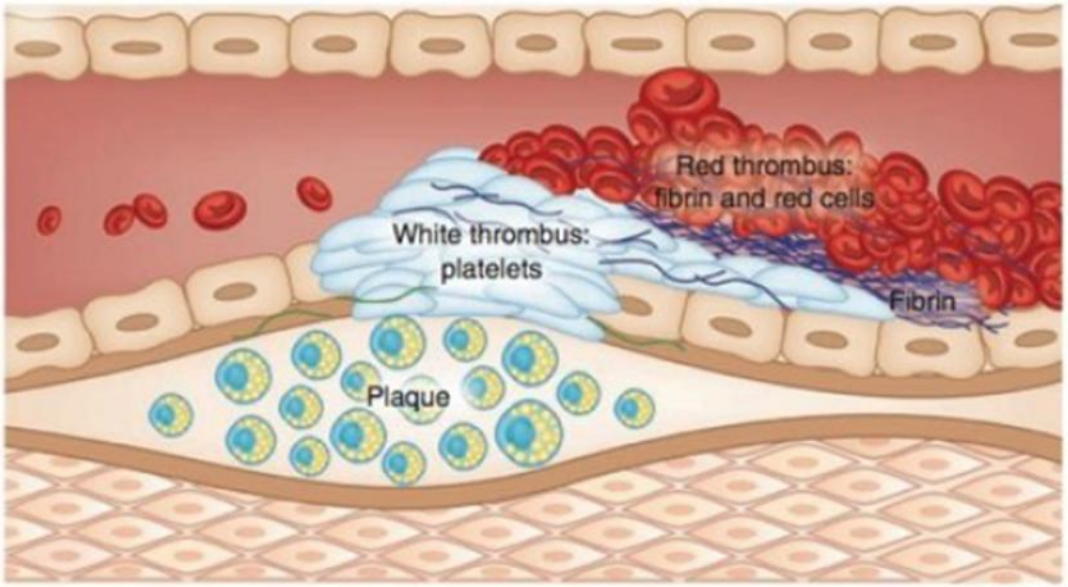
UMRS937

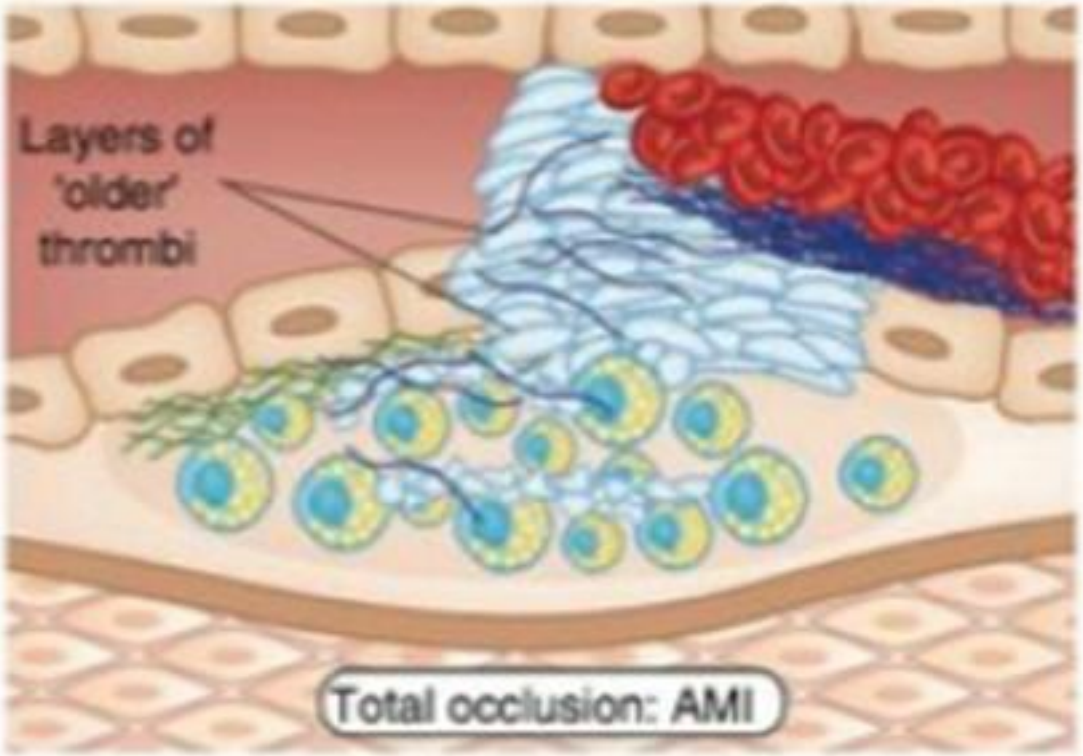
Comprendre le pourquoi du traitement antithrombotique dans le SCA

l’histoire naturelle du SCA

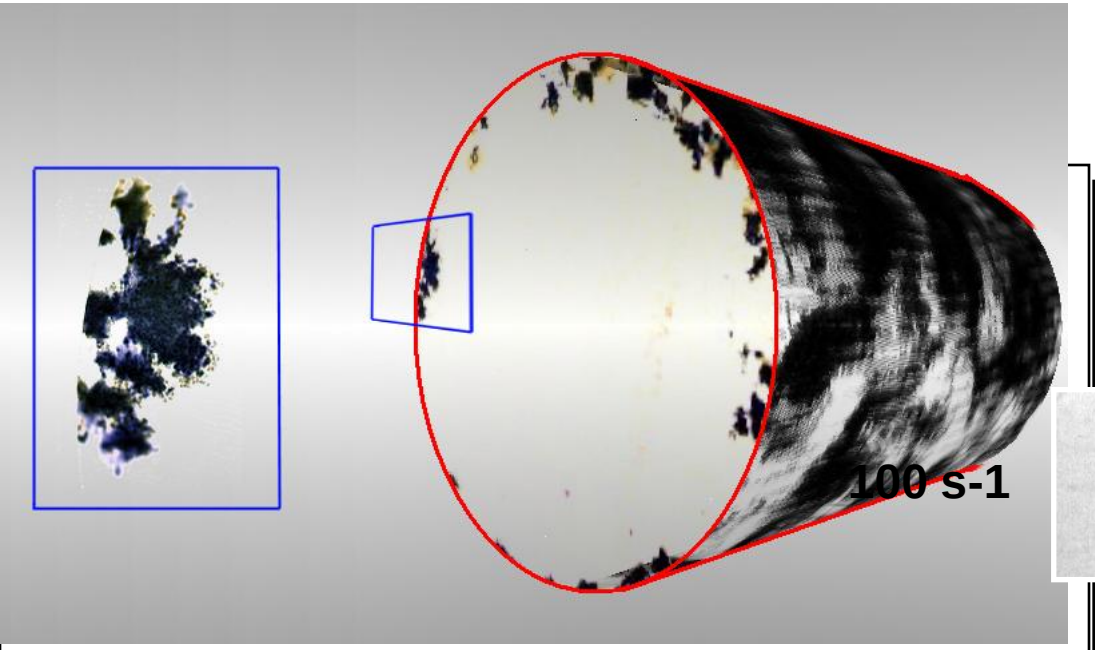

Leukocyte tethering and adhesion
Atherosclerotic plaque development
Diapedesis
Foam cells
Intima
Internal elastic lamina
Media
SMCs
Stable progressive disease
Unstable rapid progression
Intimal thickening
Fibrous cap (collagen)
Plaque fisure
Platelet adhesion
Necrotic core
Fibrin

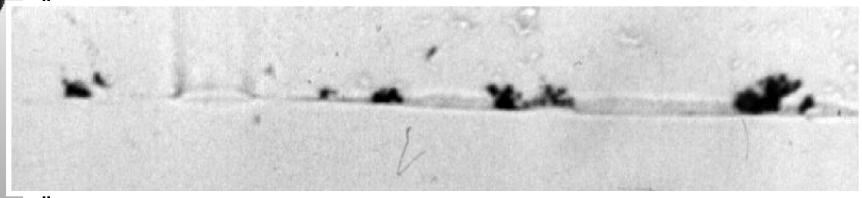

Increasing stenosis of vessel lumen
Fibrin
Platelet debris
Subtotal: 70–90% stenosis (unstable angina)


Red thrombus: fibrin and red cells
White thrombus: platelets
Fibrin
Plaque

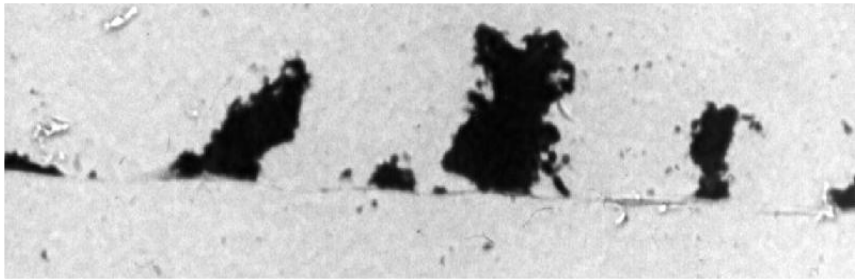

Layers of 'older' thrombi
Total occlusion: AMI

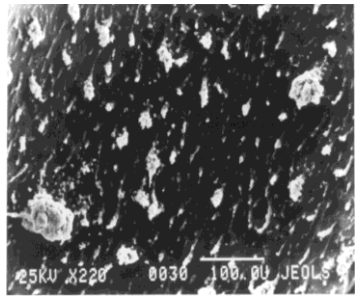
Dépendant du flux sanguin



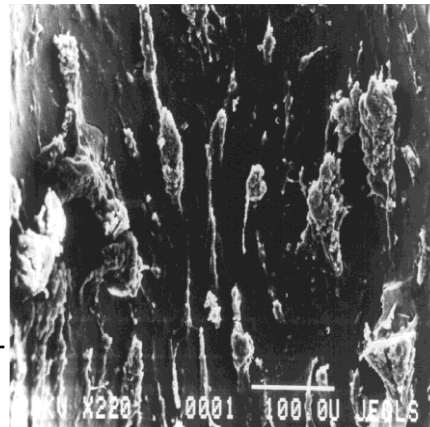


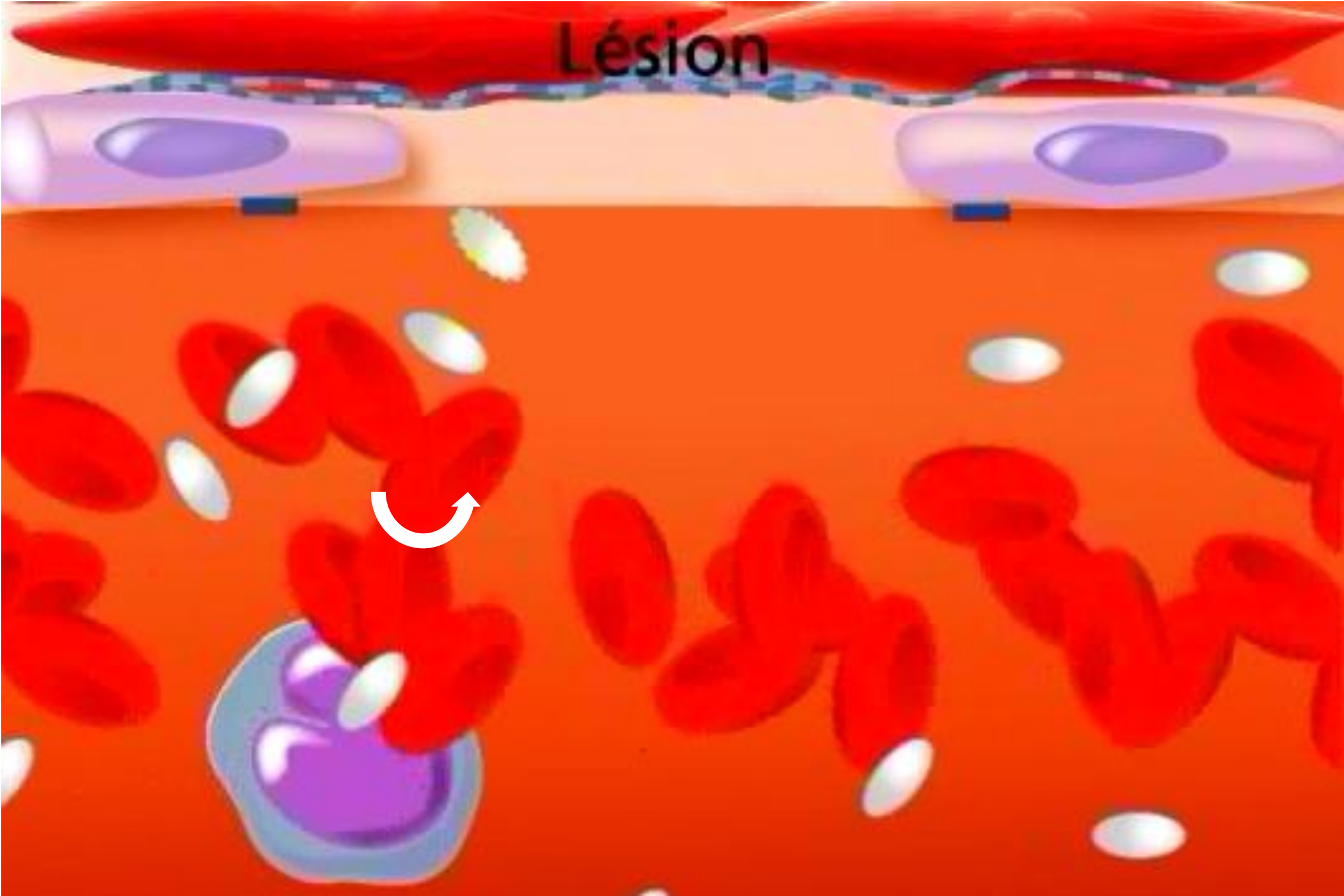
650 s-1

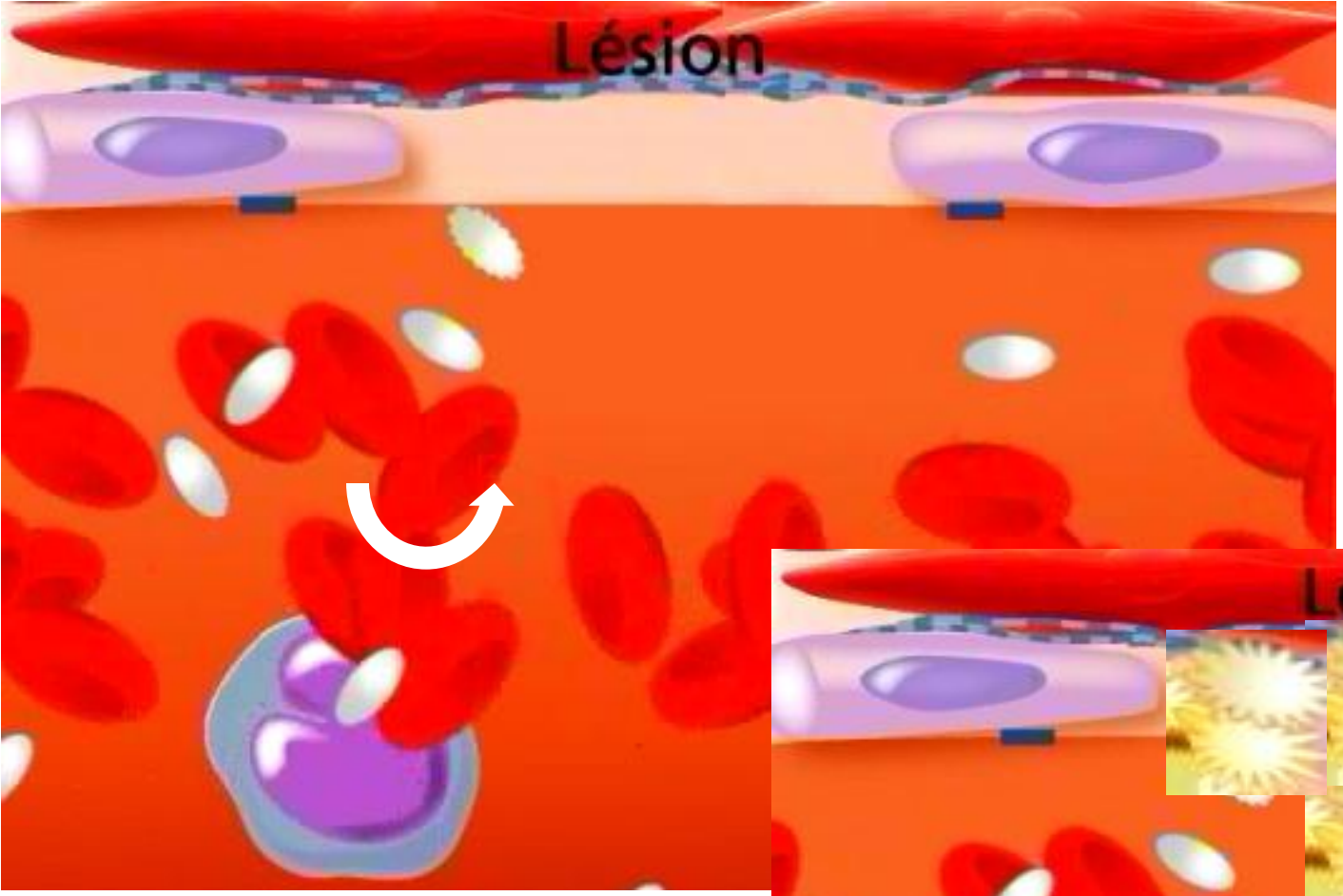




2600 s-1

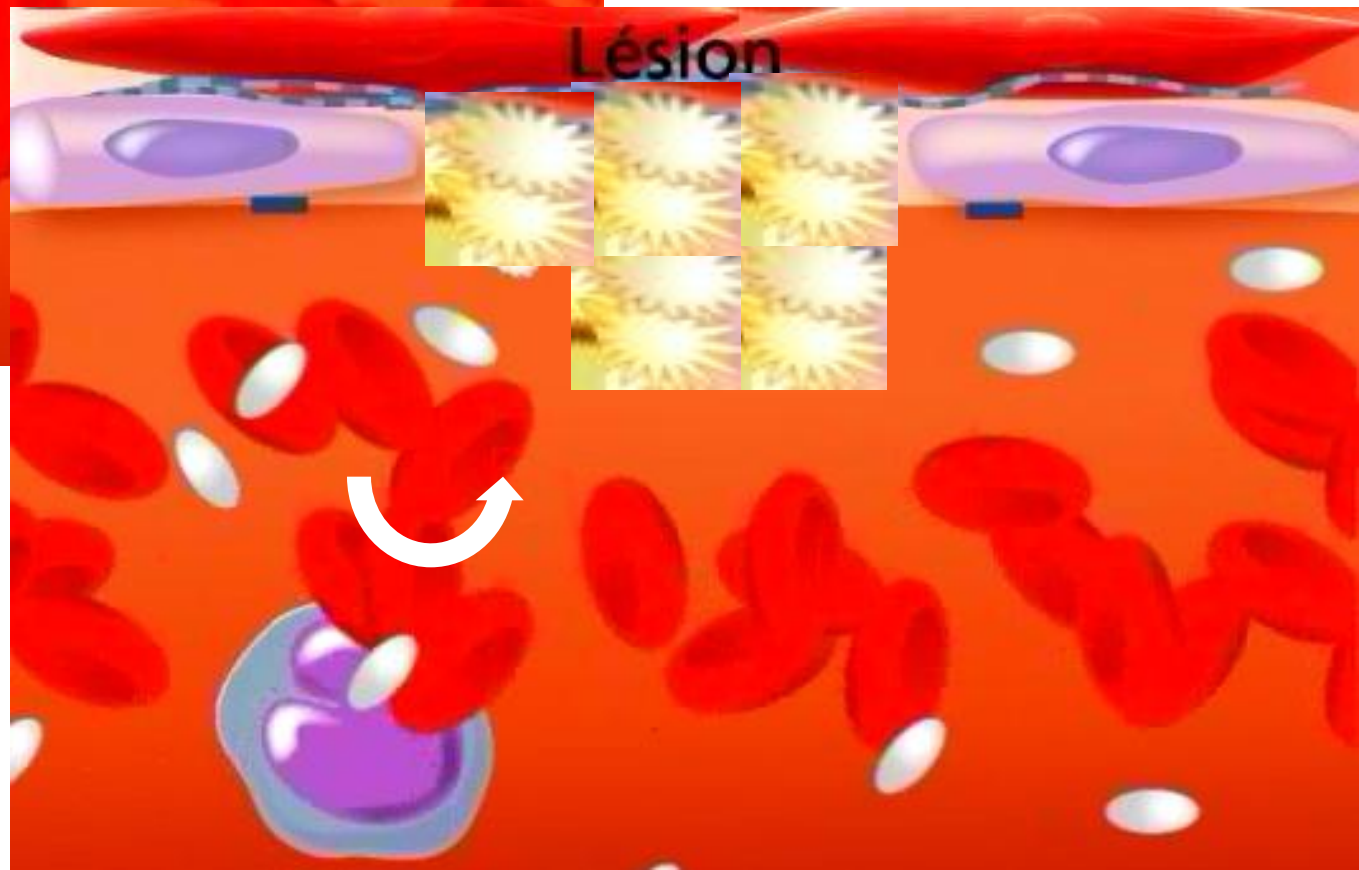


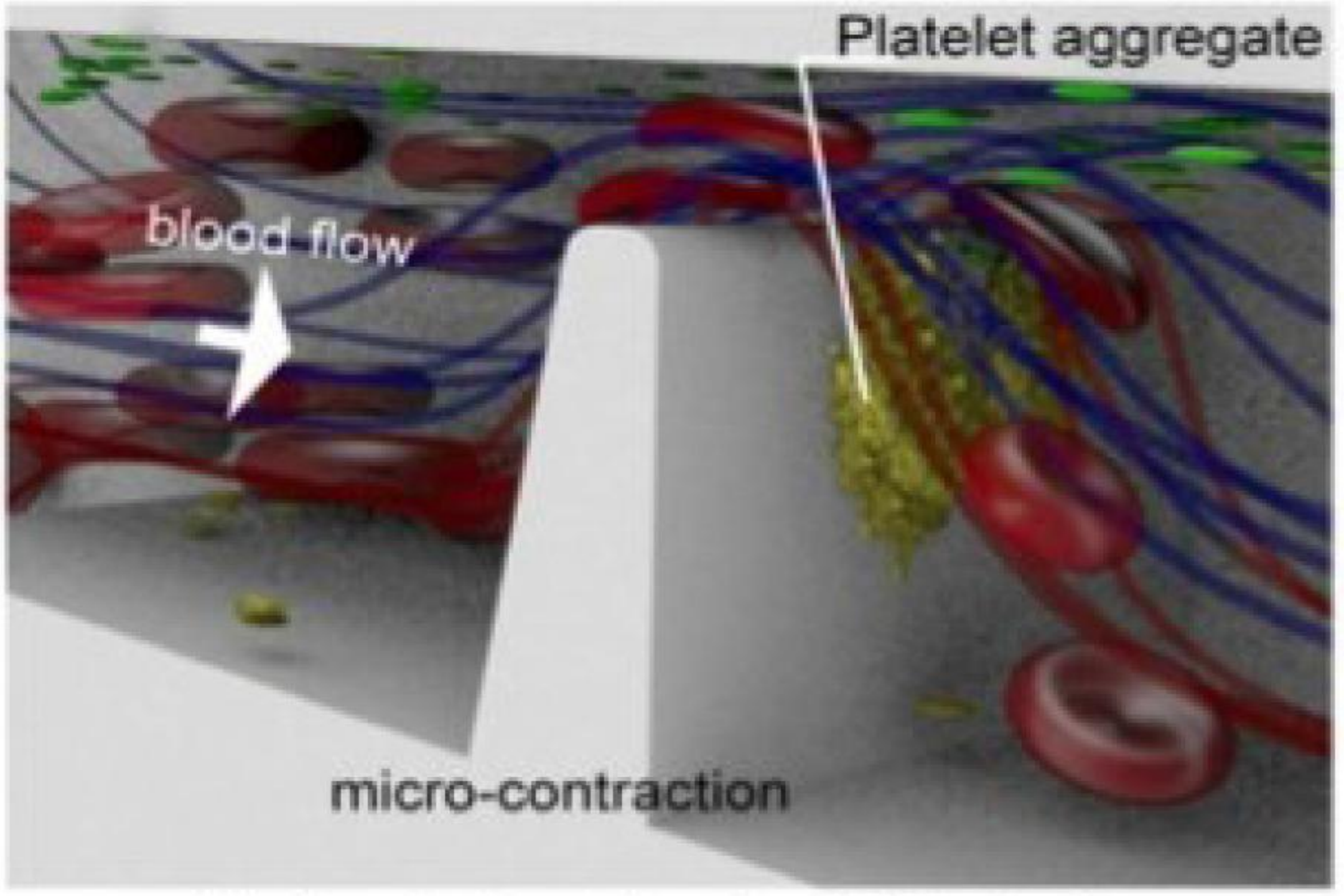

Lésion



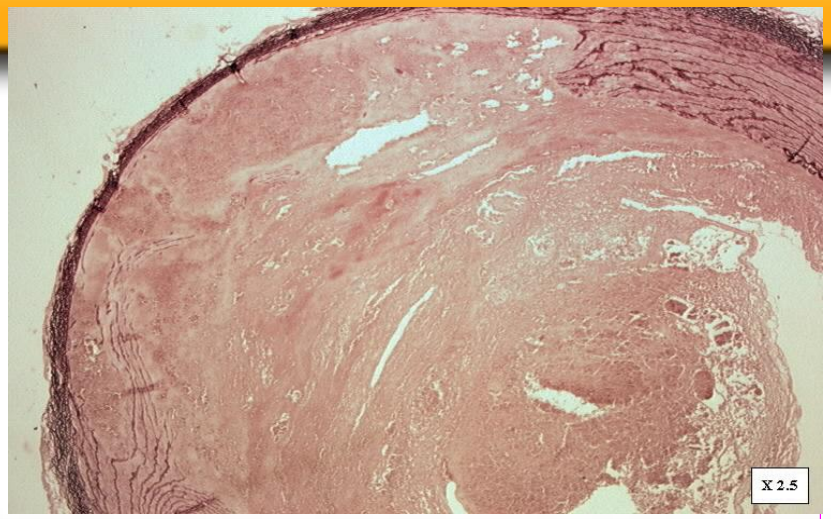
Dépendant du flux sanguin

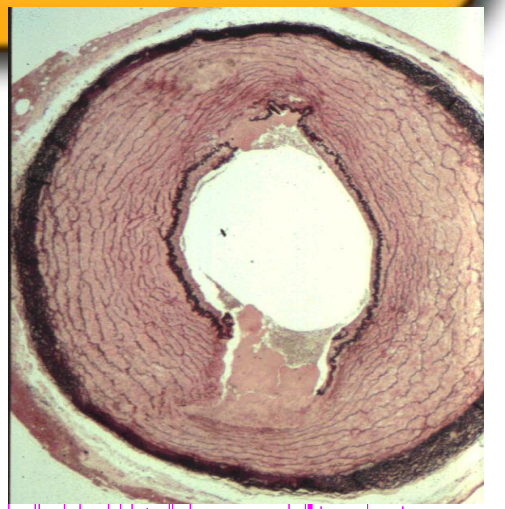
à cause des GR

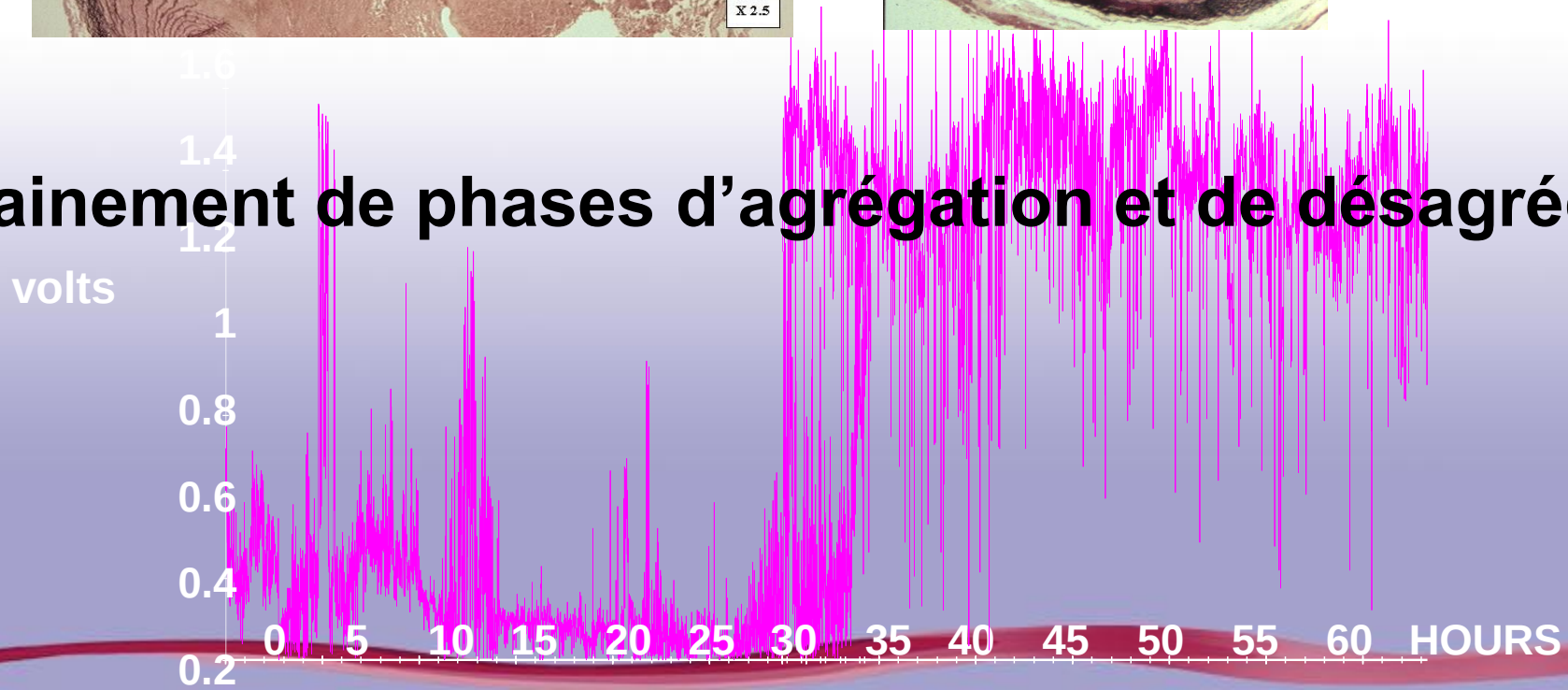



Platelet aggregate
blood flow
micro-contraction

MECHANICAL INJURY TO THE PIG CAROTID THROMBUS EVOLUTION UNTIL PASSIVATION

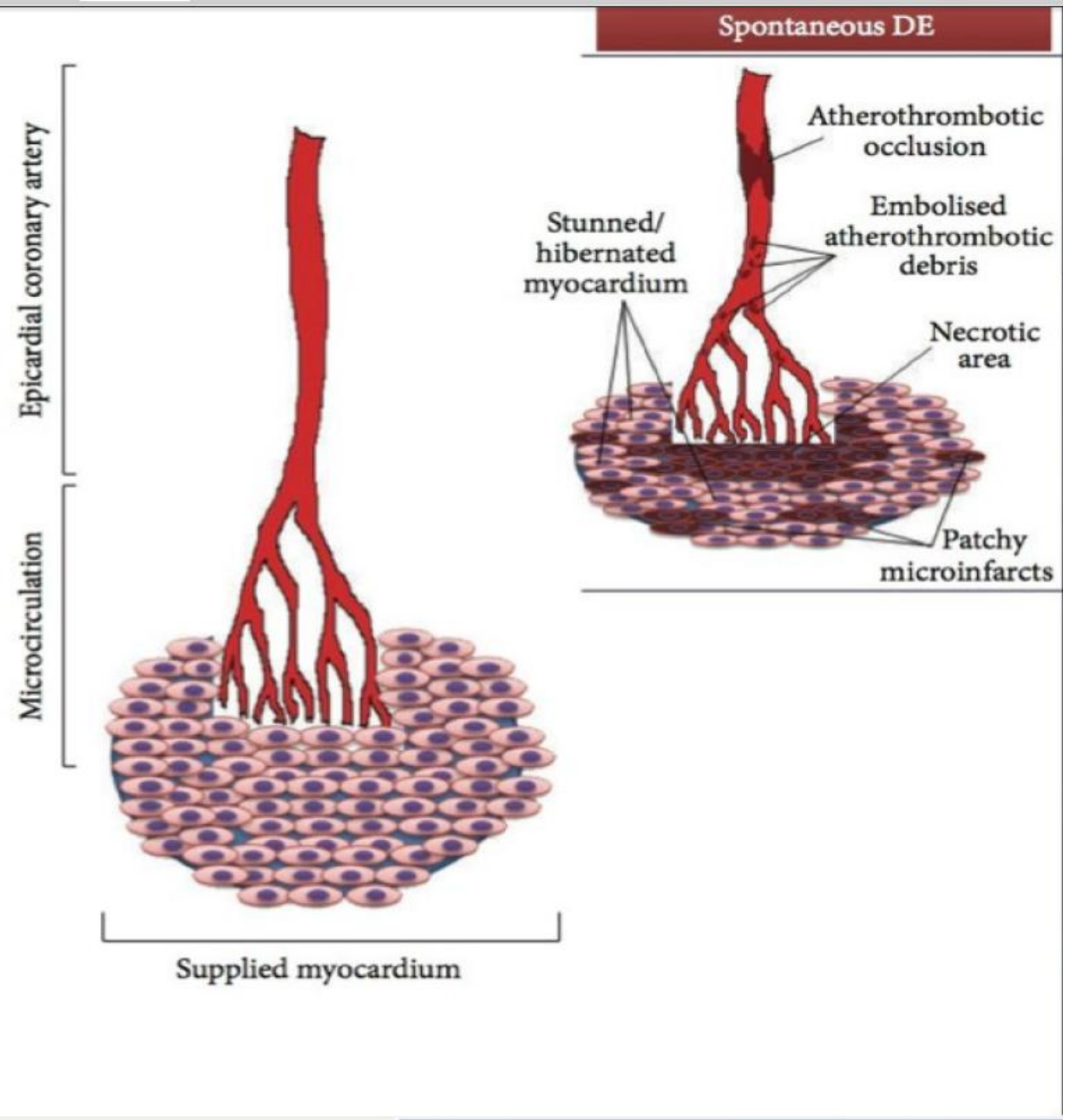






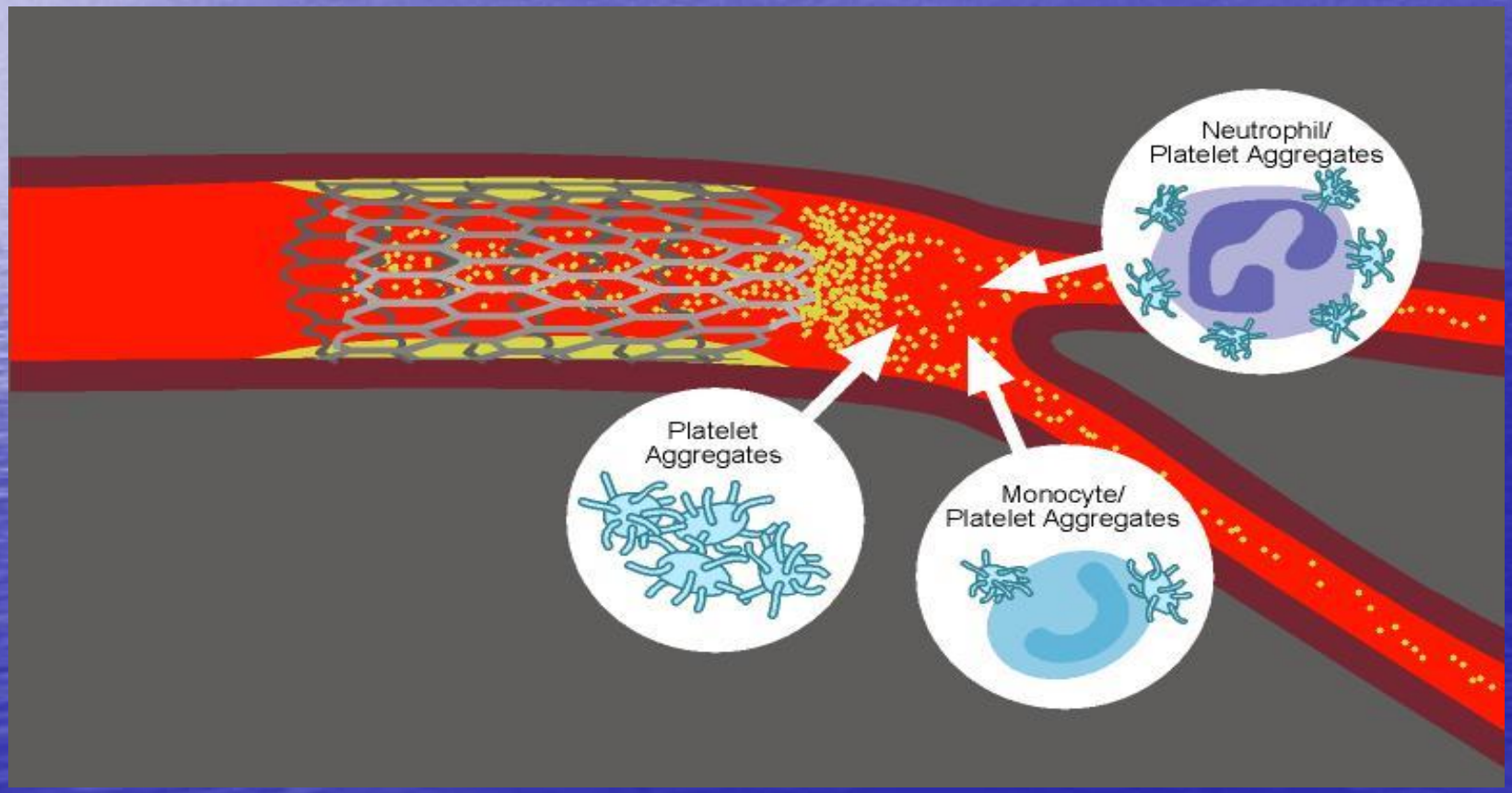
Enchainement de phases d'agrégation et de désagrégation

Platelet Embolus


Spontaneous DE
Epicardial coronary artery
Microcirculation
Supplied myocardium
Atherothrombotic occlusion
Embolised atherothrombotic debris
Stunned/ hibernated myocardium
Necrotic area
Patchy microinfarcts

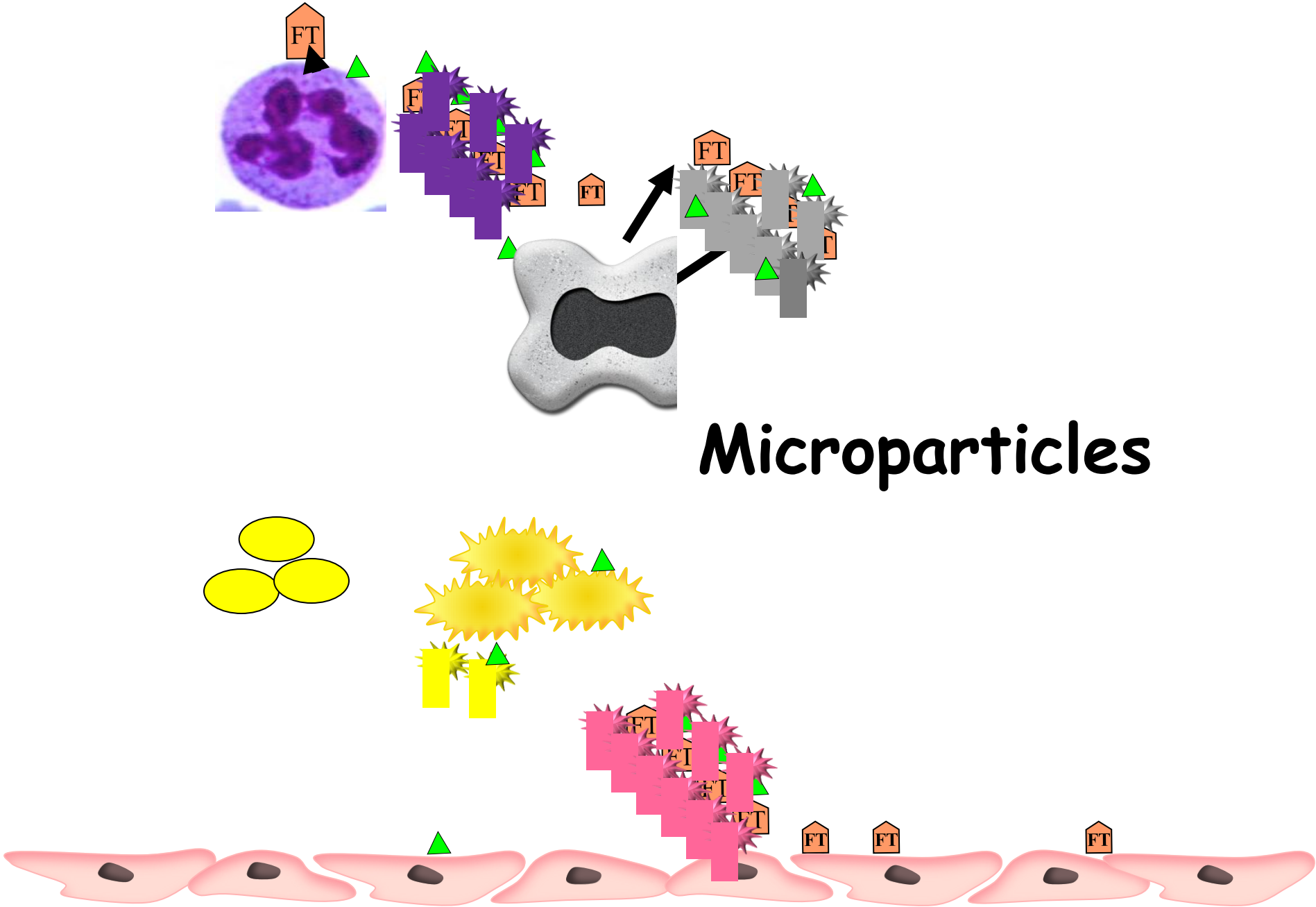
platelets, coagulation but also leucocytes

Microemboli plug microcirculation; activated monocytes and neutrophils implicated in inflammatory response



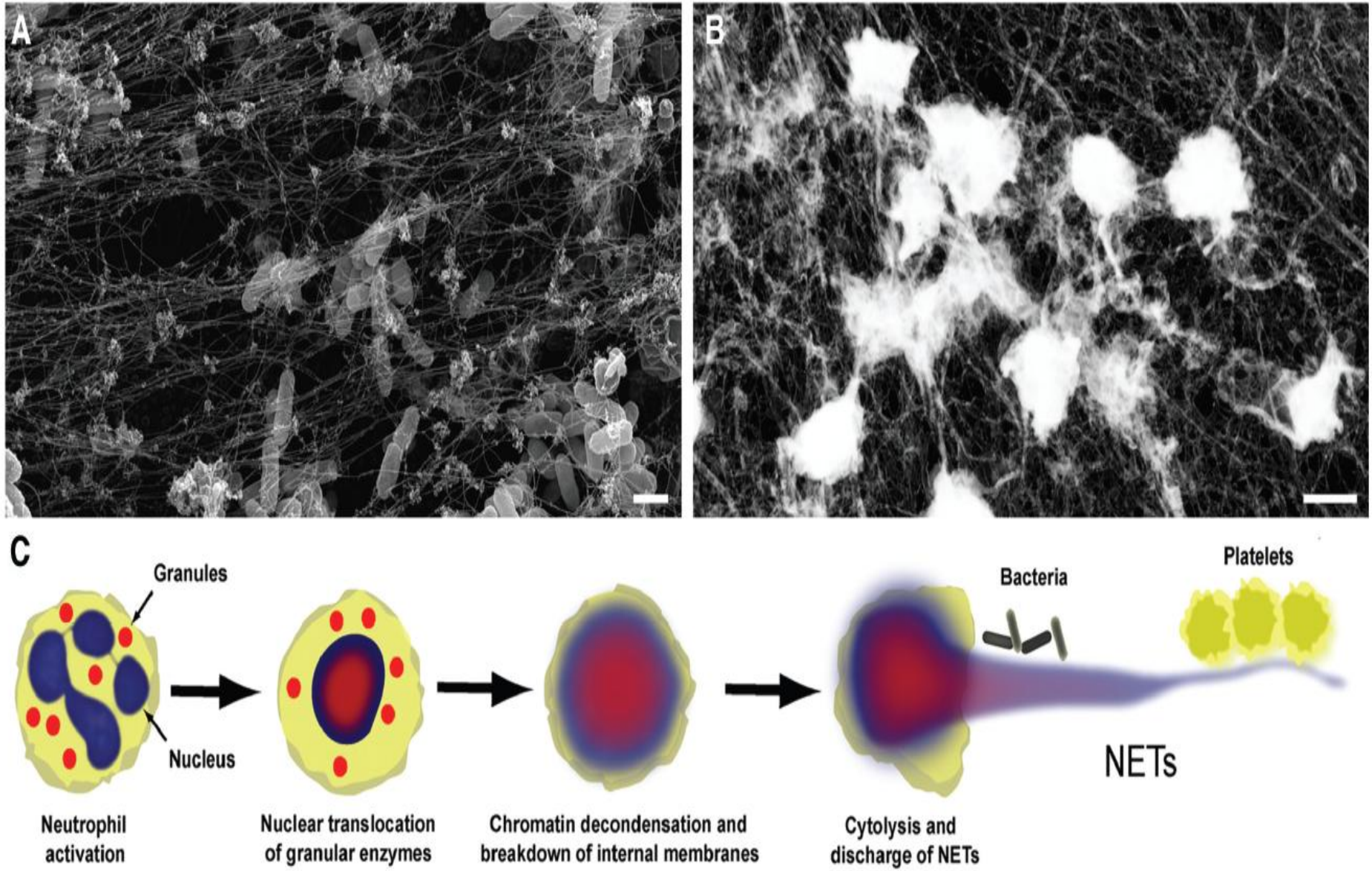
Leucocytes involvement

Limbruno et al, *Circulation*. 2003; 08:171

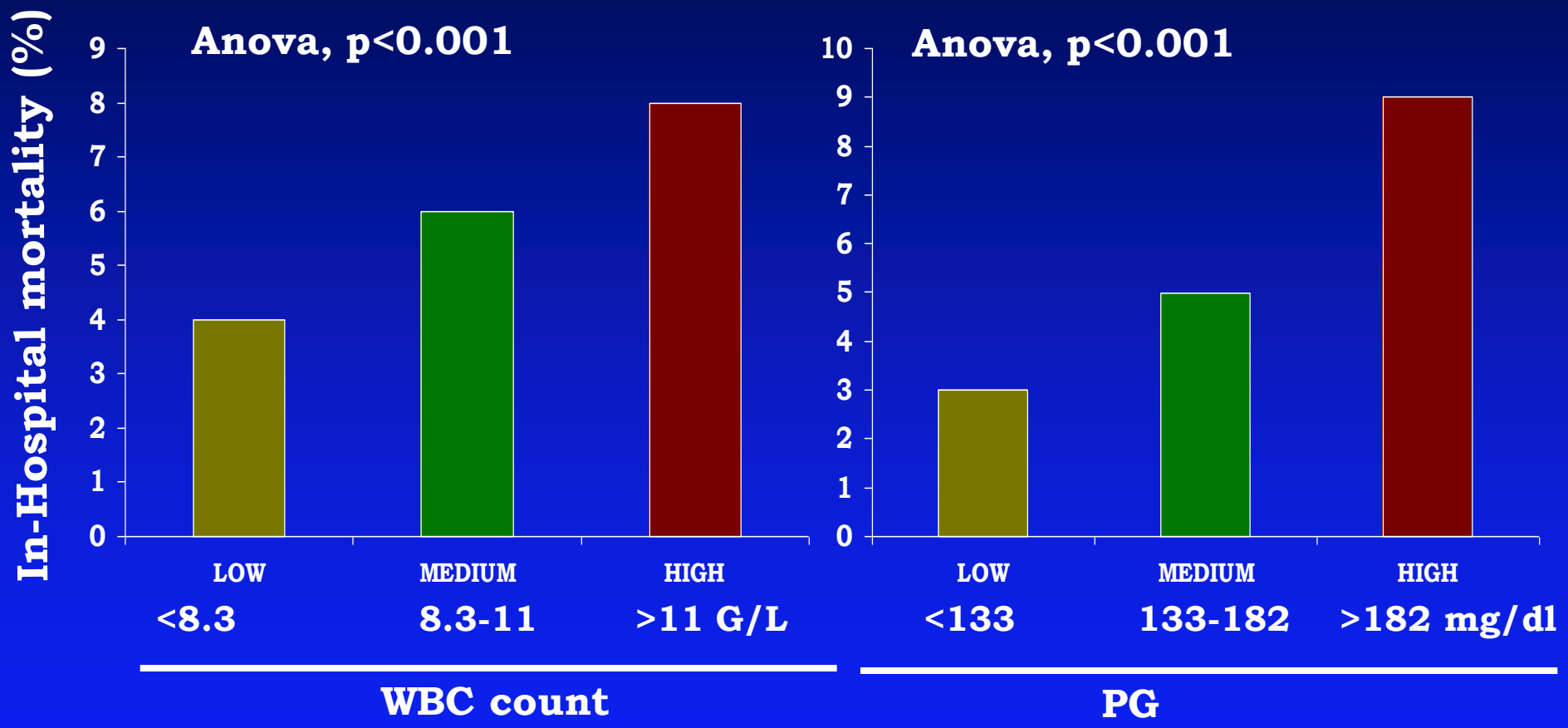

FT
Microparticles

développement
secondaire
d’un thrombus de
coagulation

Fuchs et al NET Impact on Deep Vein Thrombosis Arterioscler Thromb Vasc Biol **2012**

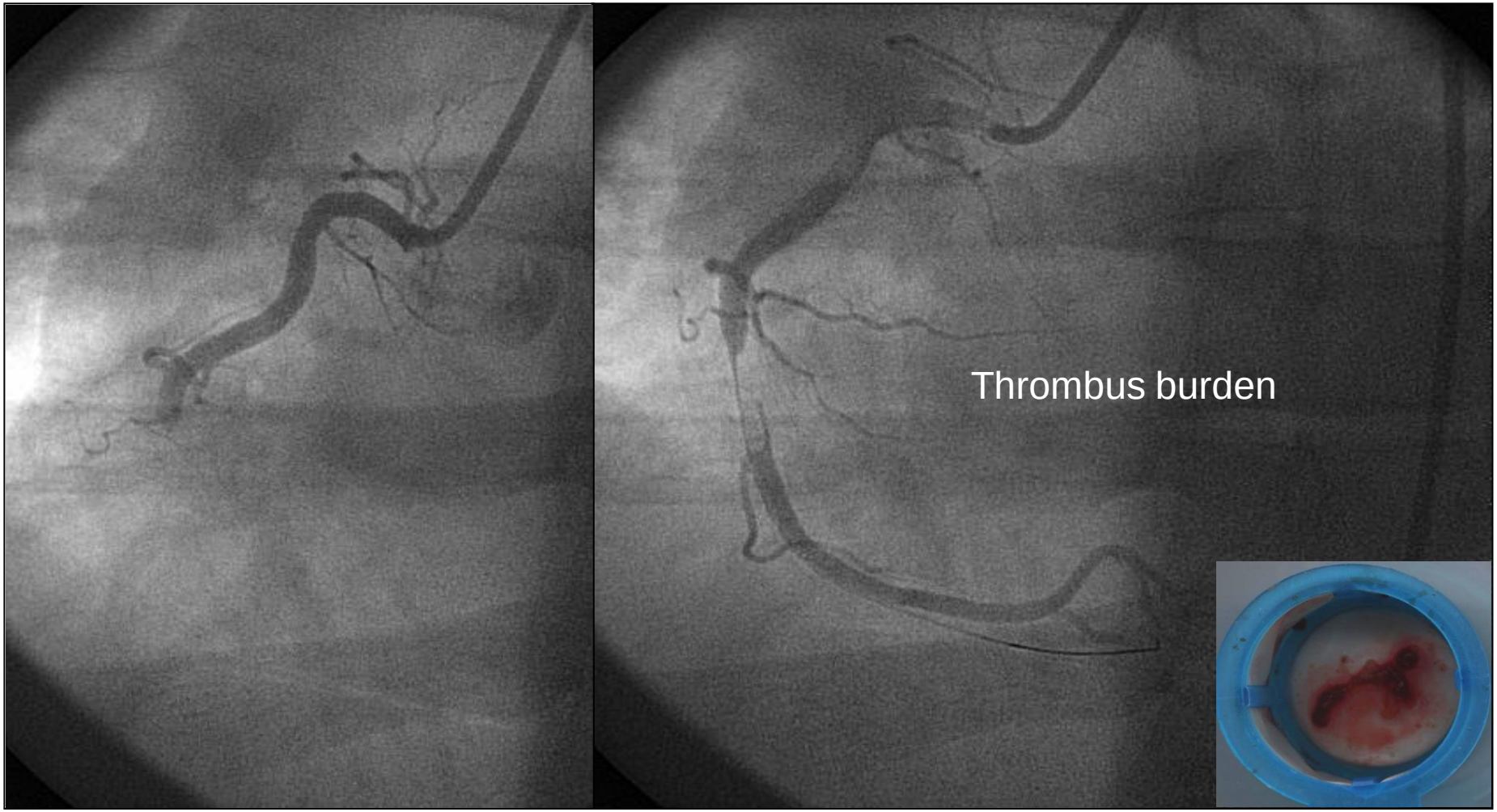


Usefulness of combined white blood cell count and plasma glucose for predicting in-hospital outcomes after acute myocardial infarction



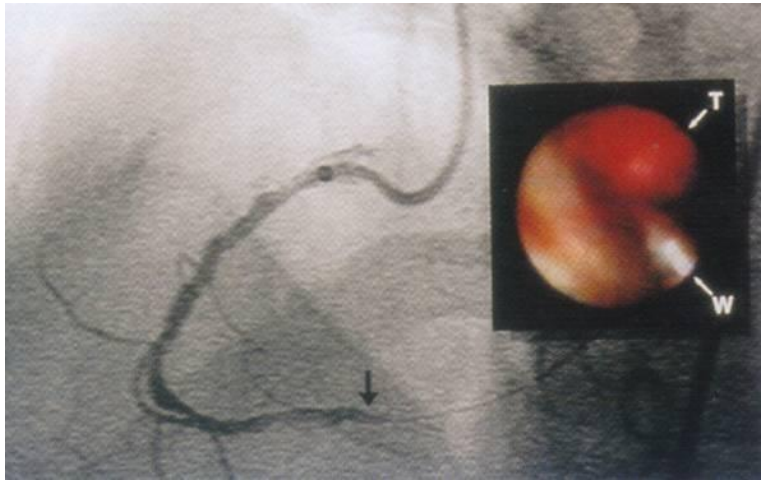
Ishihara M *et al.* Eur Heart J. 2006; 97:1558-1563.

L’angioplastie primaire est la méthode de reperfusion la plus efficace dans le traitement des IDM

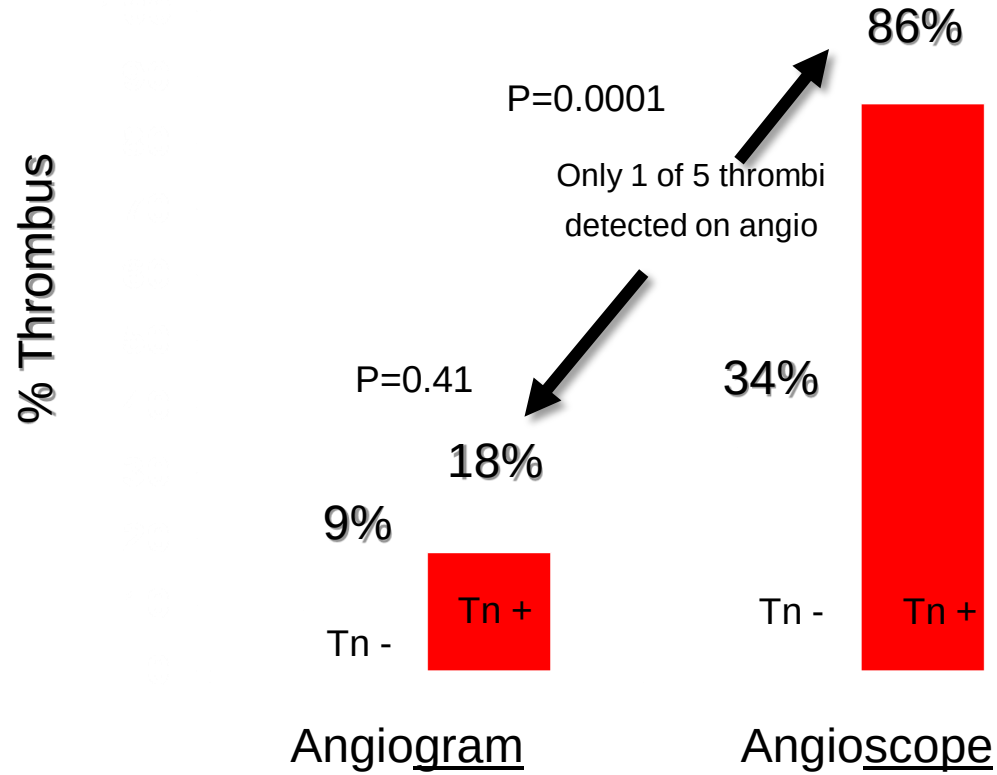


Importance du thrombus dans les SCA

- Many ACS patients already have significant clot burden

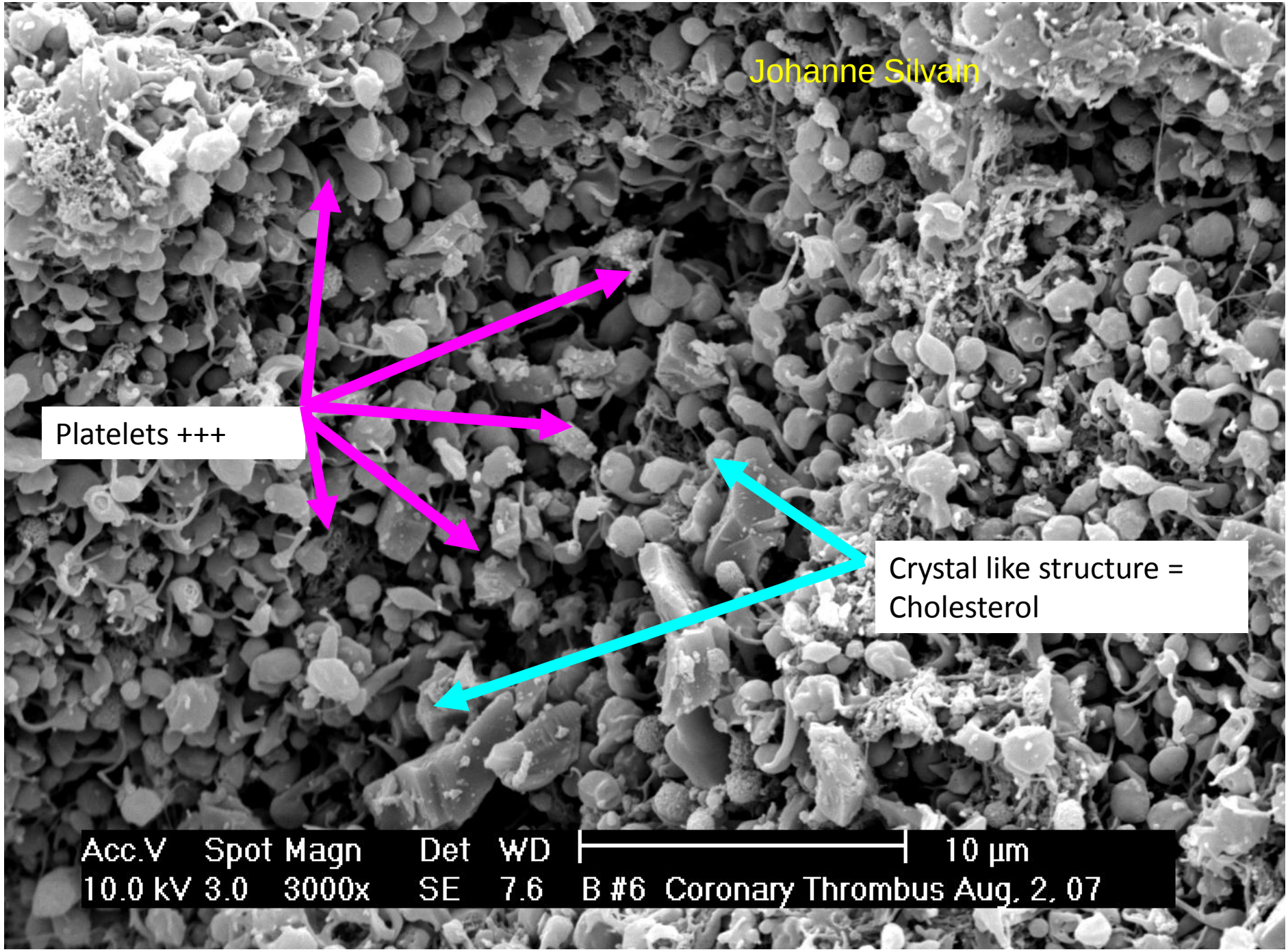


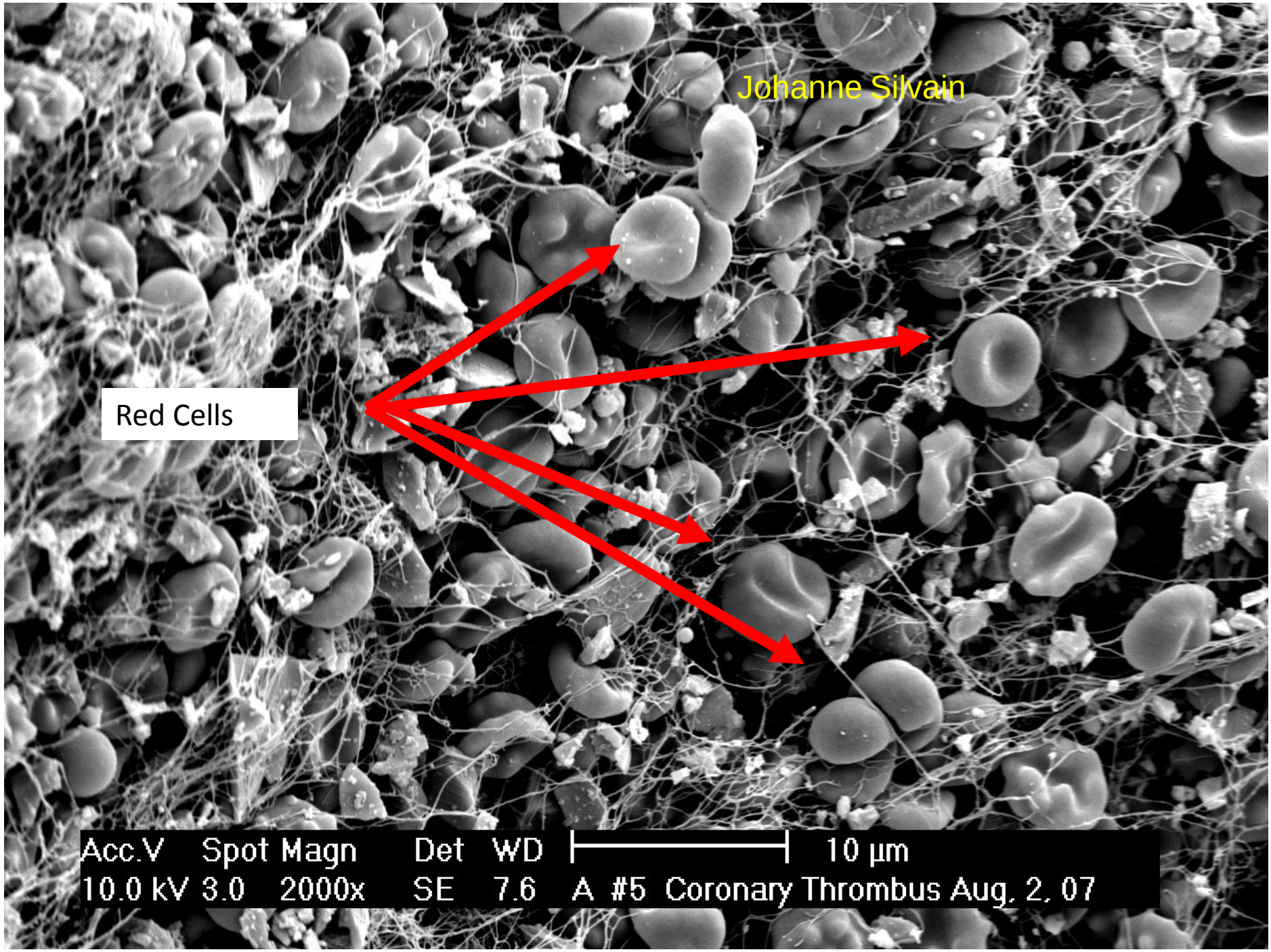
T=red, globular mass of thrombus (clot); UA=unstable angina; W=guidewire within the lumen.

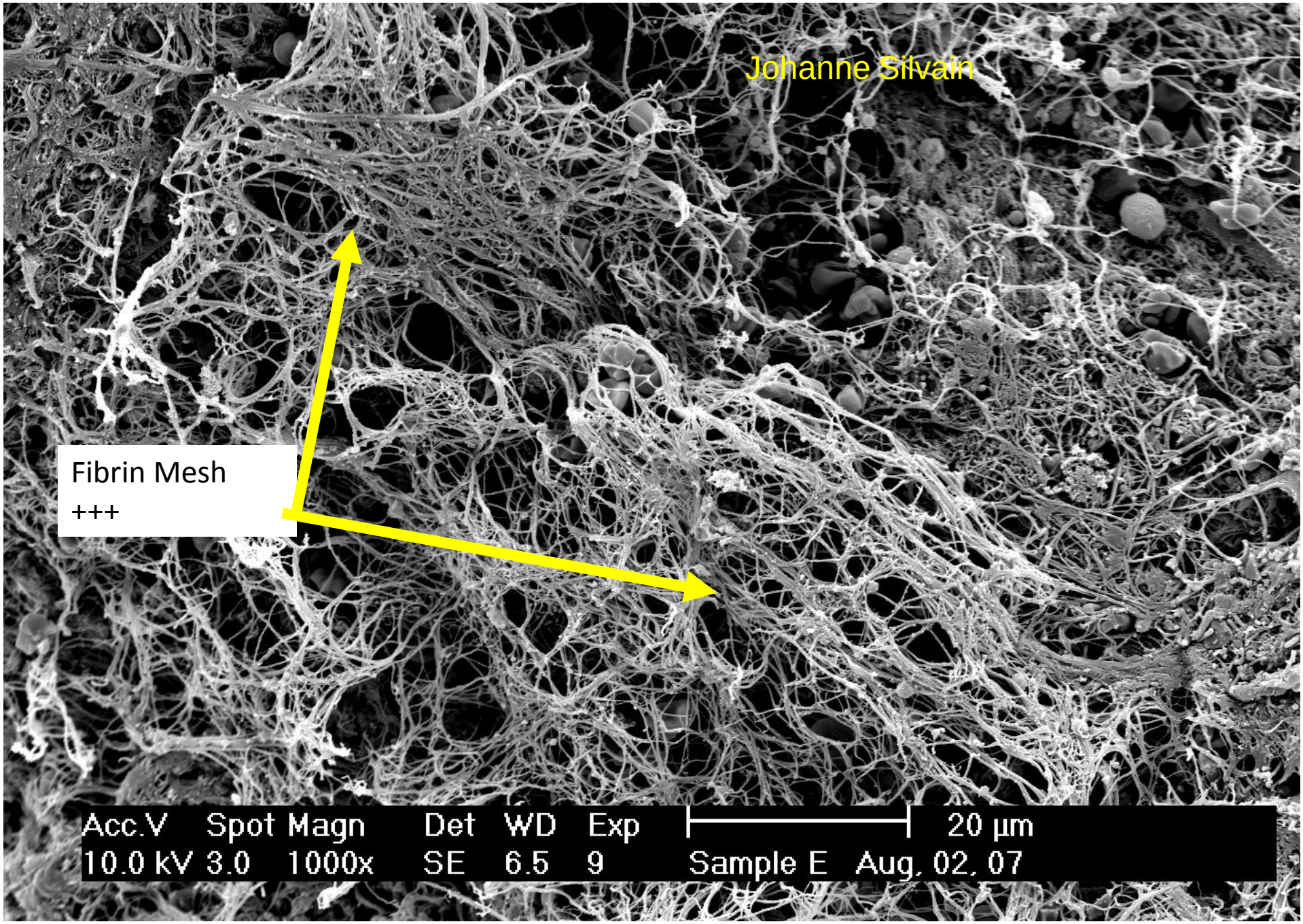


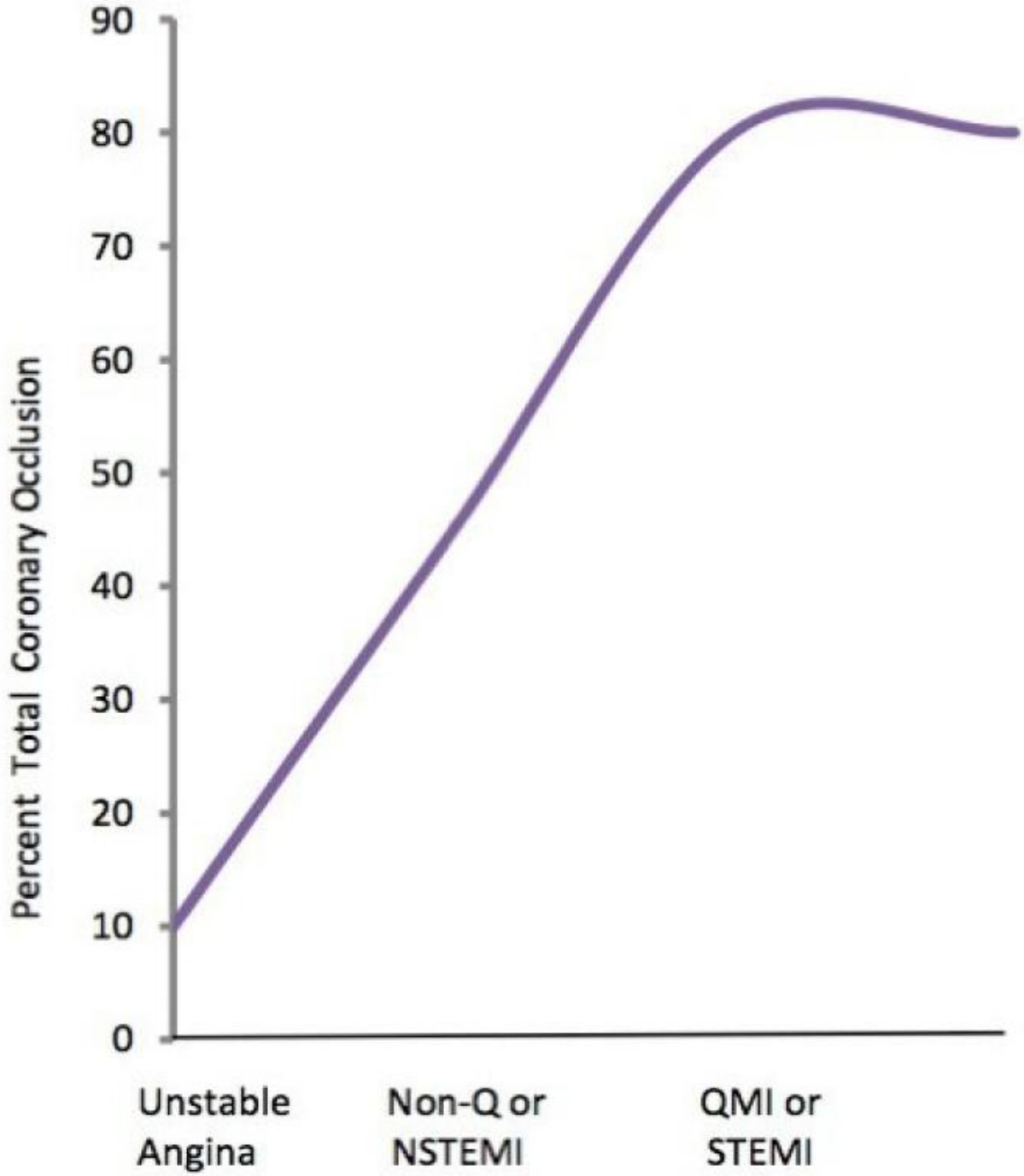
- Coronary arteriography is not sensitive in detecting thrombus seen with angioscopy—angiography misses 4 out of 5 thrombi in troponin positive patients

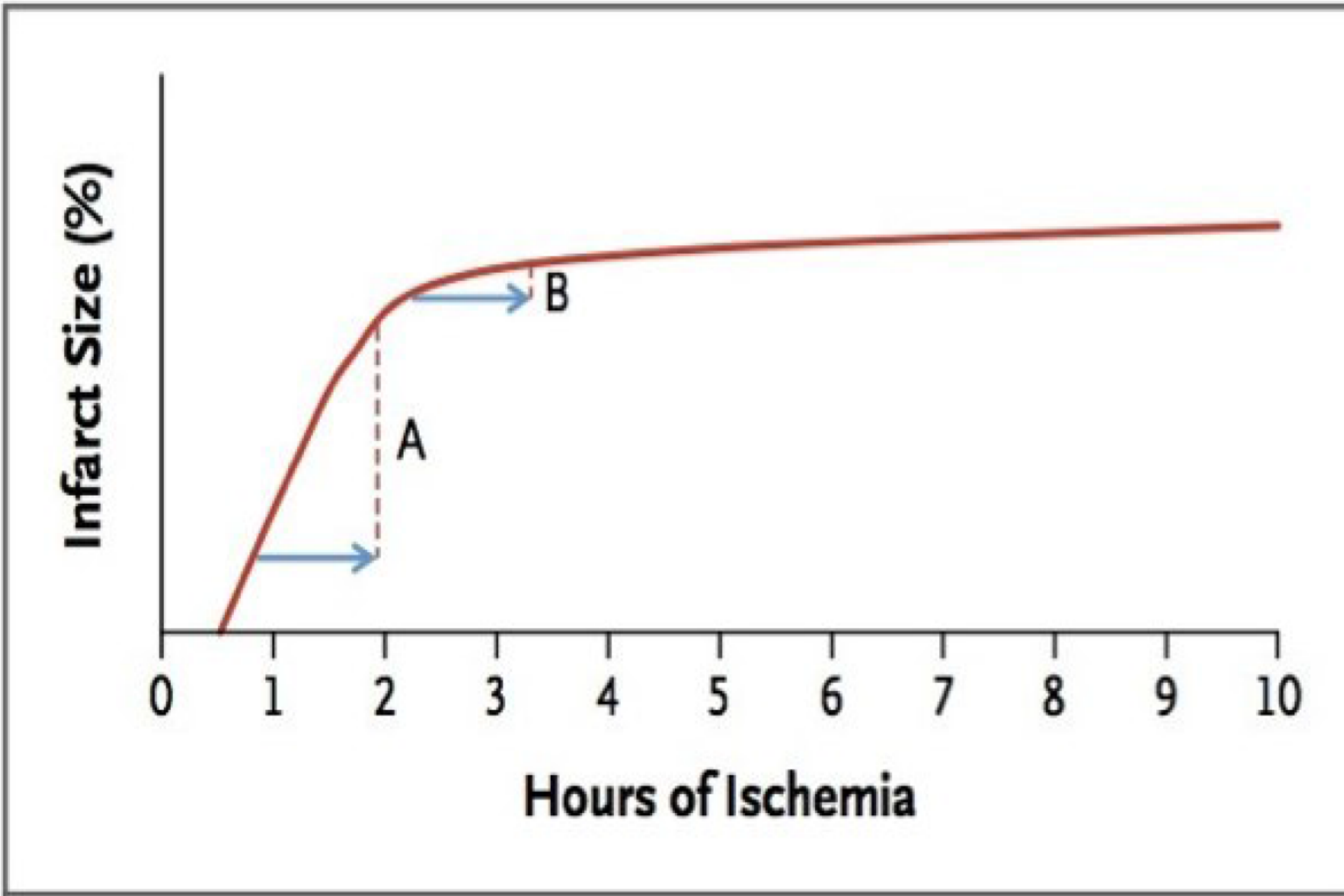
White CJ et al. In: Textbook of Interventional Cardiology. 2003:873-891.
Okamatsu et al, Circulation 2004; 109:465-470.


Johanne Silvain
Platelets +++
Crystal like structure = Cholesterol
Acc.V Spot Magn Det WD 10 µm
10.0 kV 3.0 3000x SE 7.6 B #6 Coronary Thrombus Aug. 2, 07

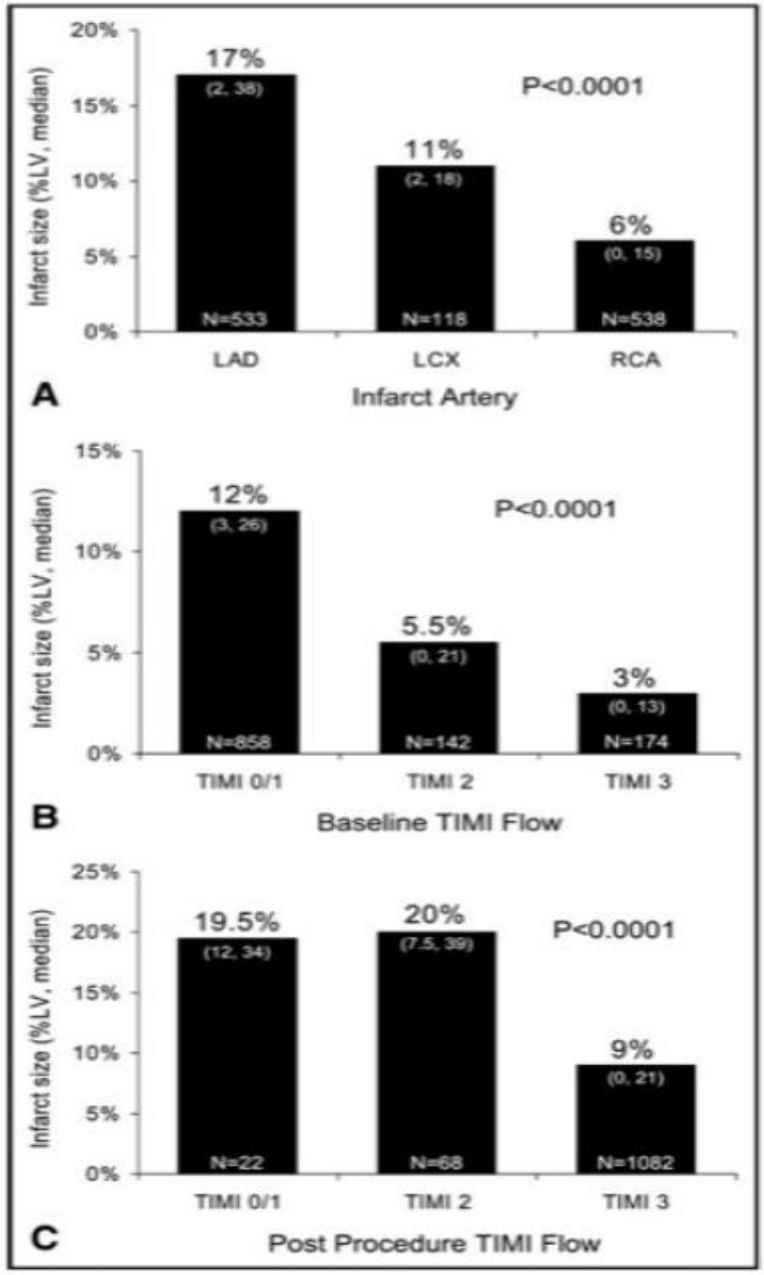

Johanne Silvain
Red Cells
Acc.V Spot Magn Det WD 10 µm
10.0 kV 3.0 2000x SE 7.6 A #5 Coronary Thrombus Aug. 2, 07


Johanne Silvain
Fibrin Mesh
+++
Acc.V Spot Magn Det WD Exp
10.0 kV 3.0 1000x SE 6.5 9
20 µm
Sample E Aug. 02, 07

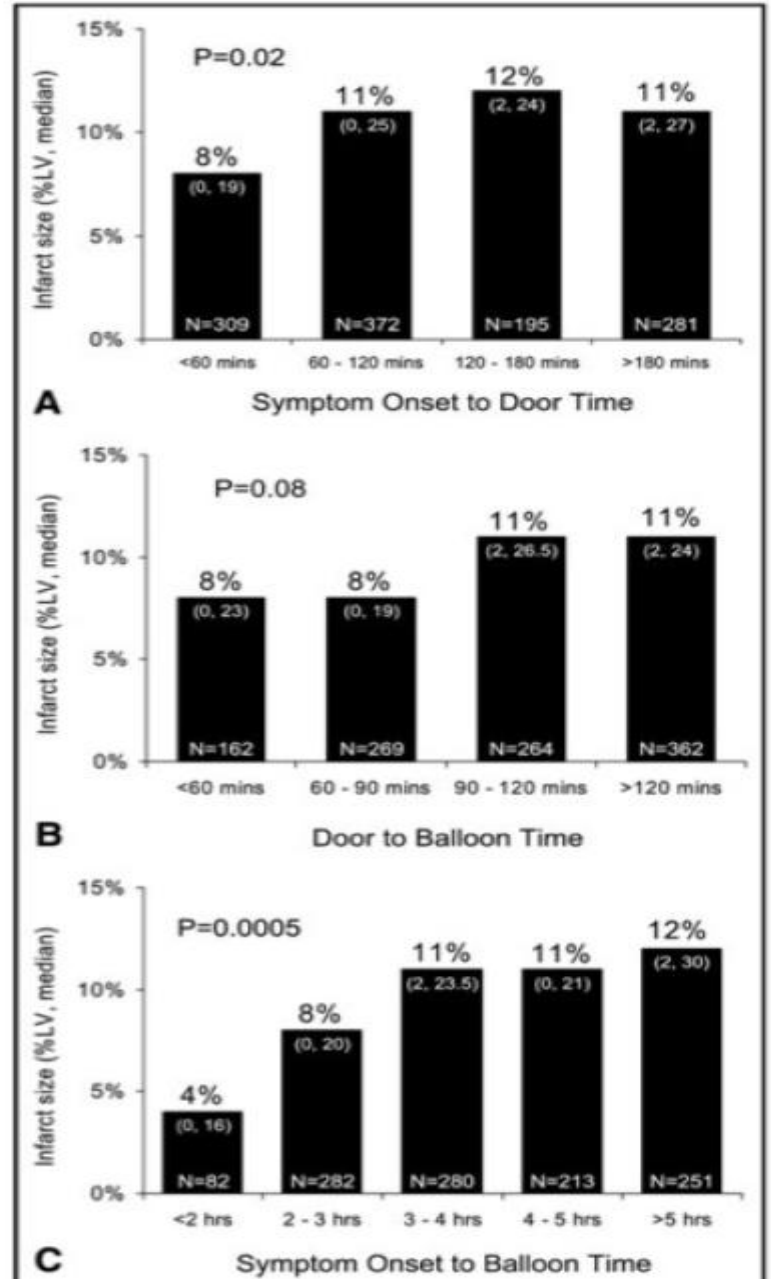

90
80
70
60
50
40
30
20
10
0
Percent Total Coronary Occlusion
Unstable Angina
Non-Q or NSTEMI
QMI or STEMI

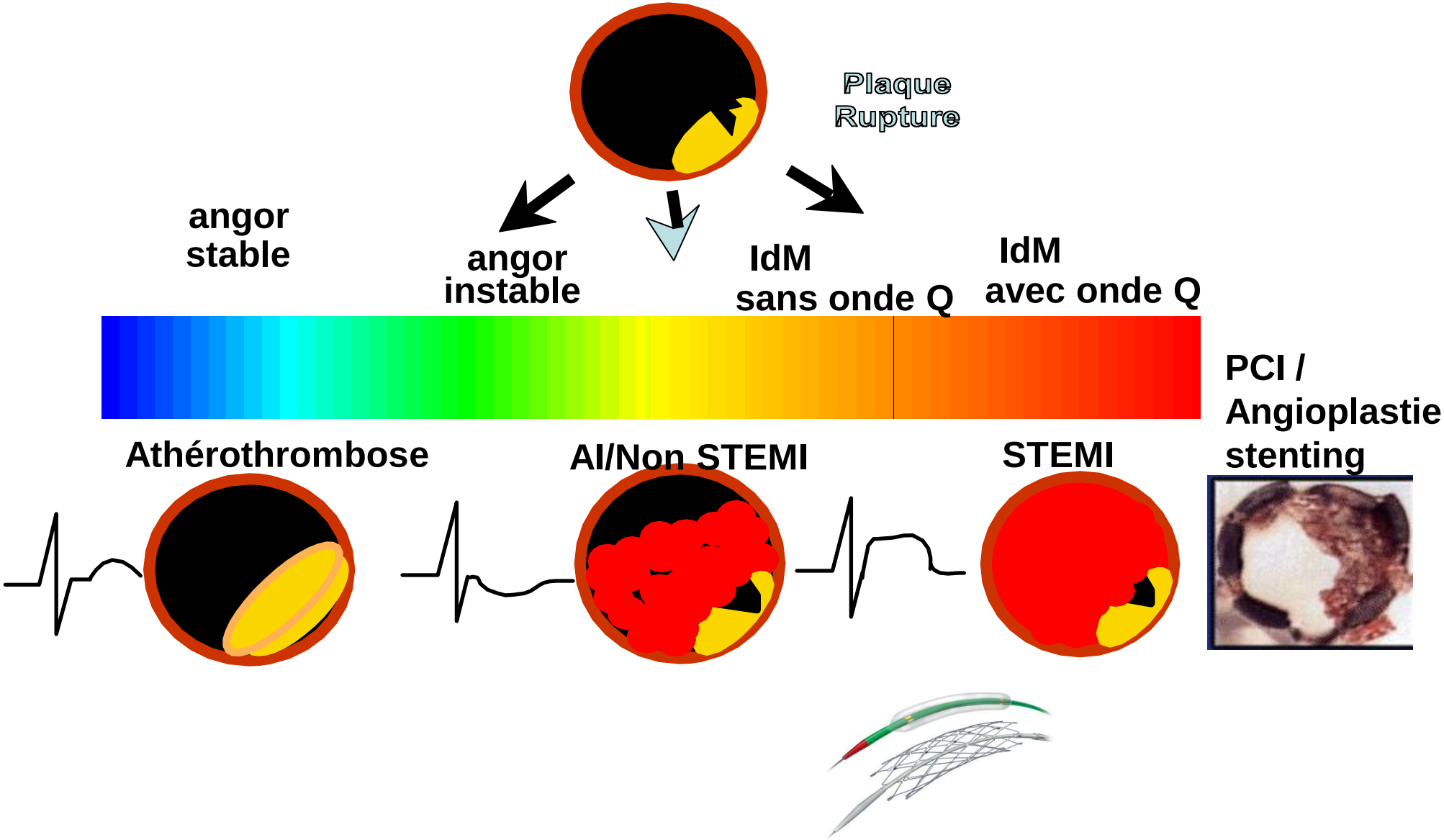

Infarct Size (%)
A
B
0
1
2
3
4
5
6
7
8
9
10
Hours of Ischemia

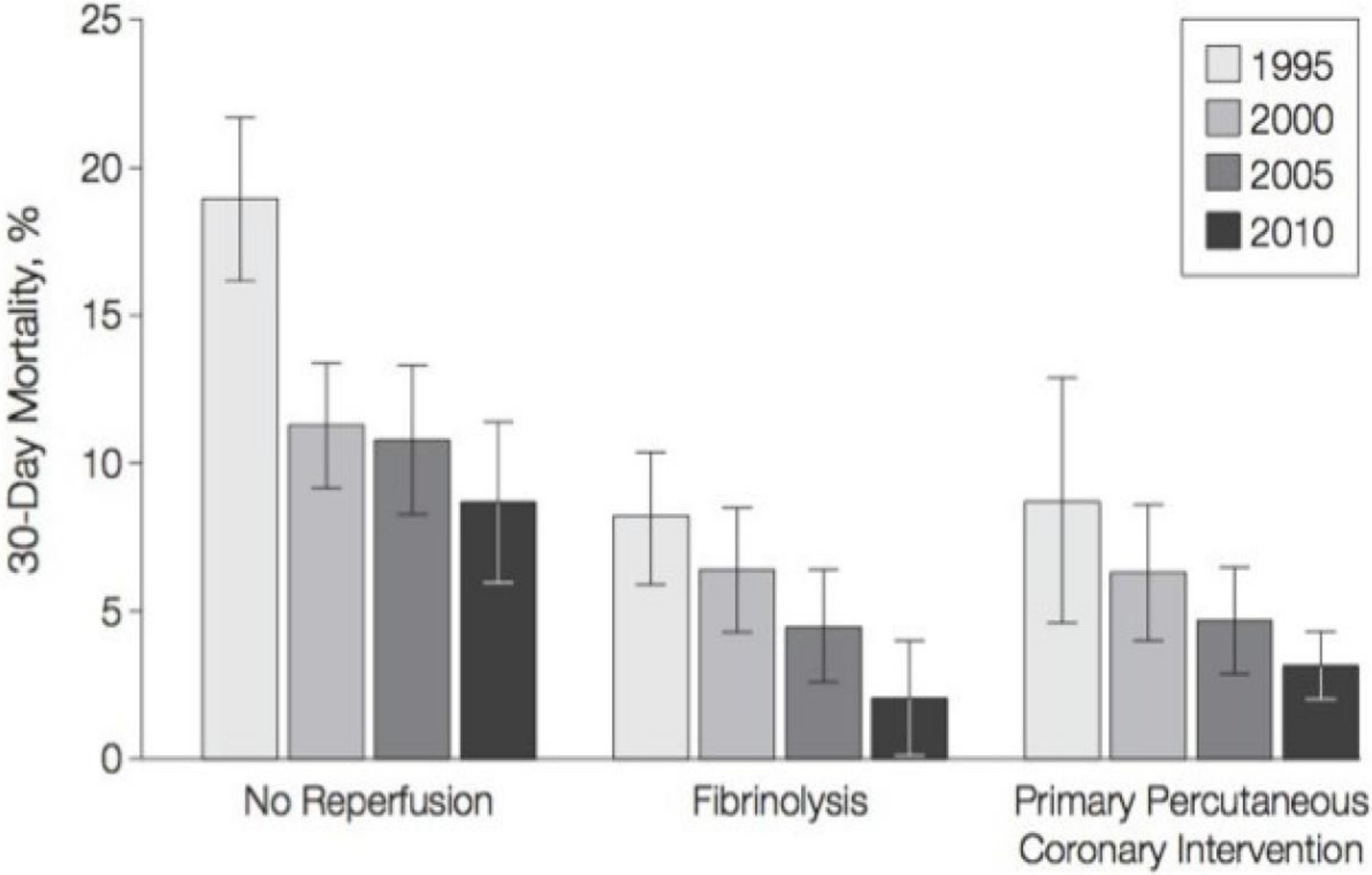
- Influence of infarct artery on infarct size



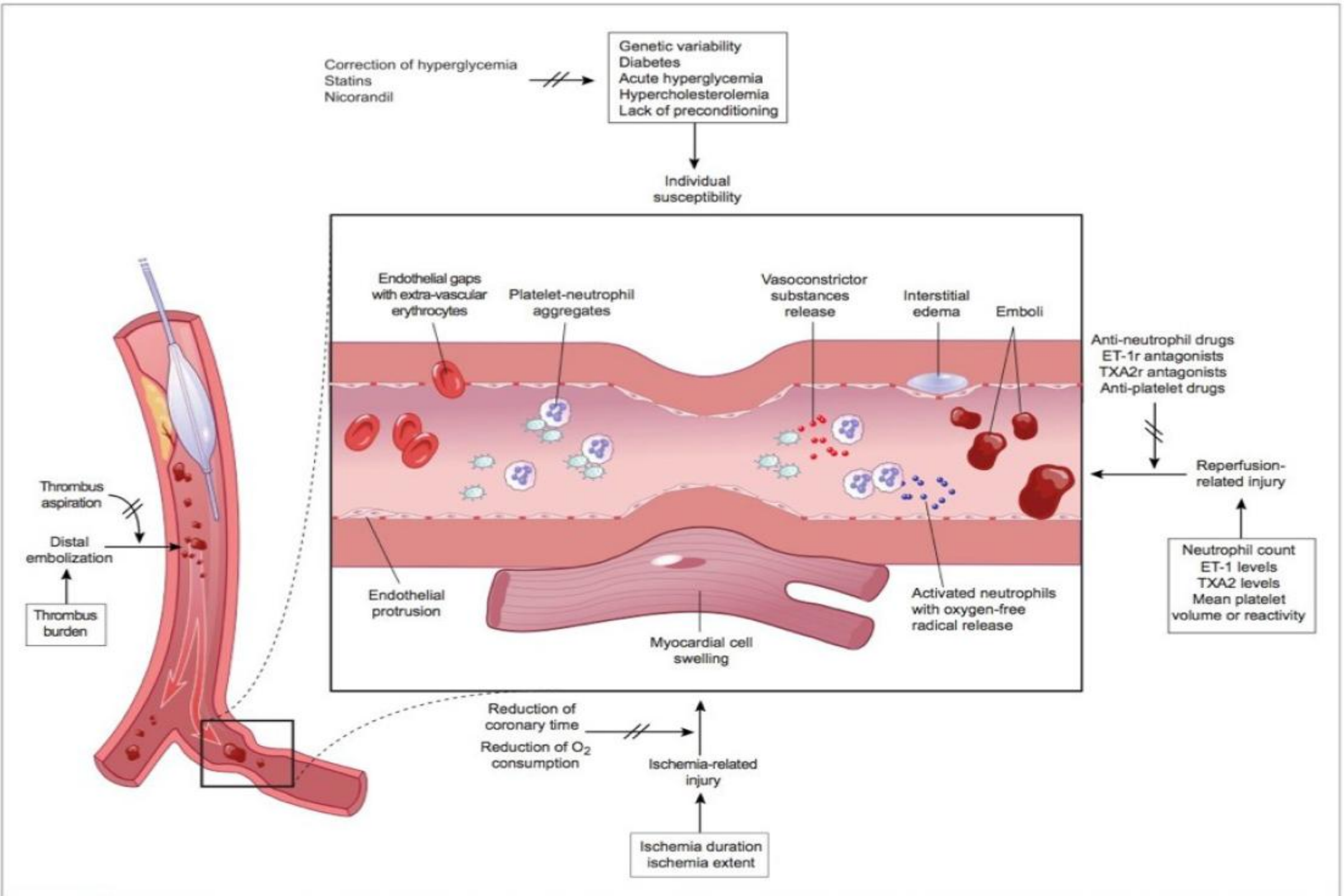
- Influence of treatment delays on infarct size

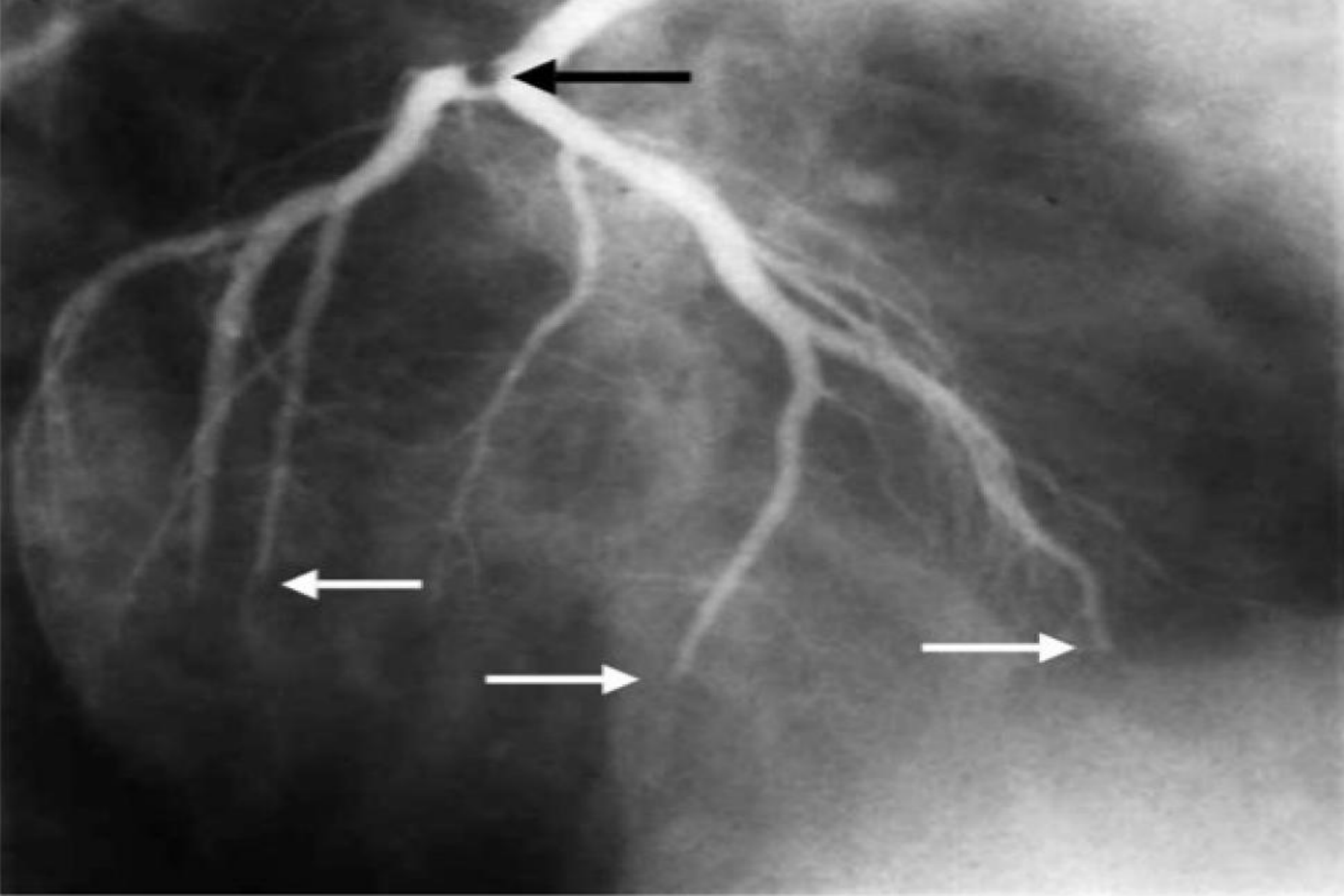


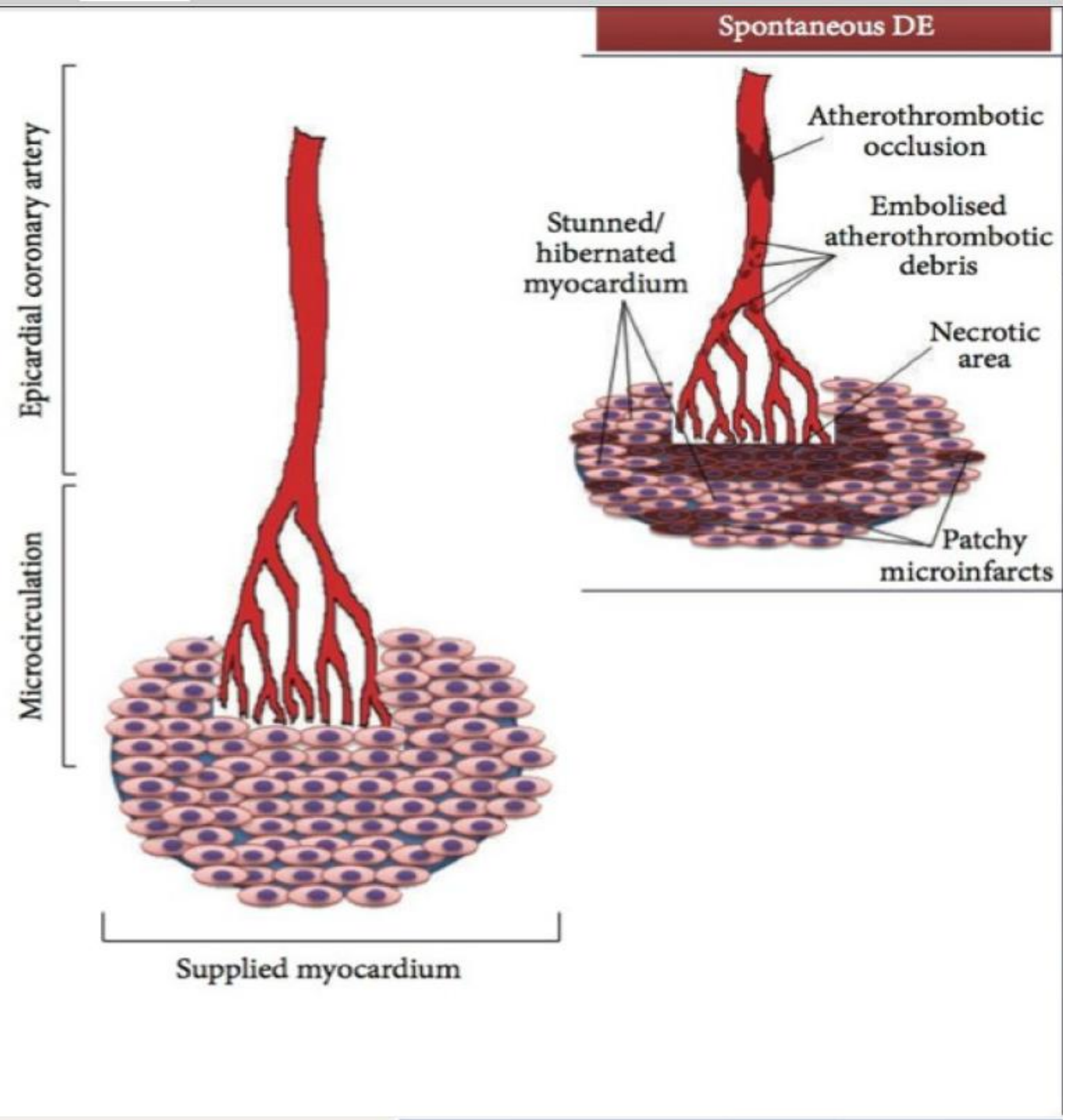

Plaque
Rupture
angor
stable
angor
instable
IdM
sans onde Q
IdM
avec onde Q
PCI /
Angioplastie
stenting
Athérothrombose
AI/Non STEMI
STEMI



No. of patients	777	870	591	435	576	545	465	238	183	429	555	1043


Correction of hyperglycemia
Statins
Nicorandil
Genetic variability
Diabetes
Acute hyperglycemia
Hypercholesterolemia
Lack of preconditioning
Individual susceptibility
Endothelial gaps with extra-vascular erythrocytes
Platelet-neutrophil aggregates
Vasoconstrictor substances release
Interstitial edema
Emboli
Anti-neutrophil drugs
ET-1r antagonists
TXA2r antagonists
Anti-platelet drugs
Reperfusion-related injury
Neutrophil count
ET-1 levels
TXA2 levels
Mean platelet volume or reactivity
Thrombus aspiration
Distal embolization
Thrombus burden
Endothelial protrusion
Myocardial cell swelling
Activated neutrophils with oxygen-free radical release
Reduction of coronary time
Reduction of O_2 consumption
Ischemia-related injury
Ischemia duration
ischemia extent




Spontaneous DE
Epicardial coronary artery
Microcirculation
Supplied myocardium
Atherothrombotic occlusion
Embolised atherothrombotic debris
Stunned/ hibernated myocardium
Necrotic area
Patchy microinfarcts

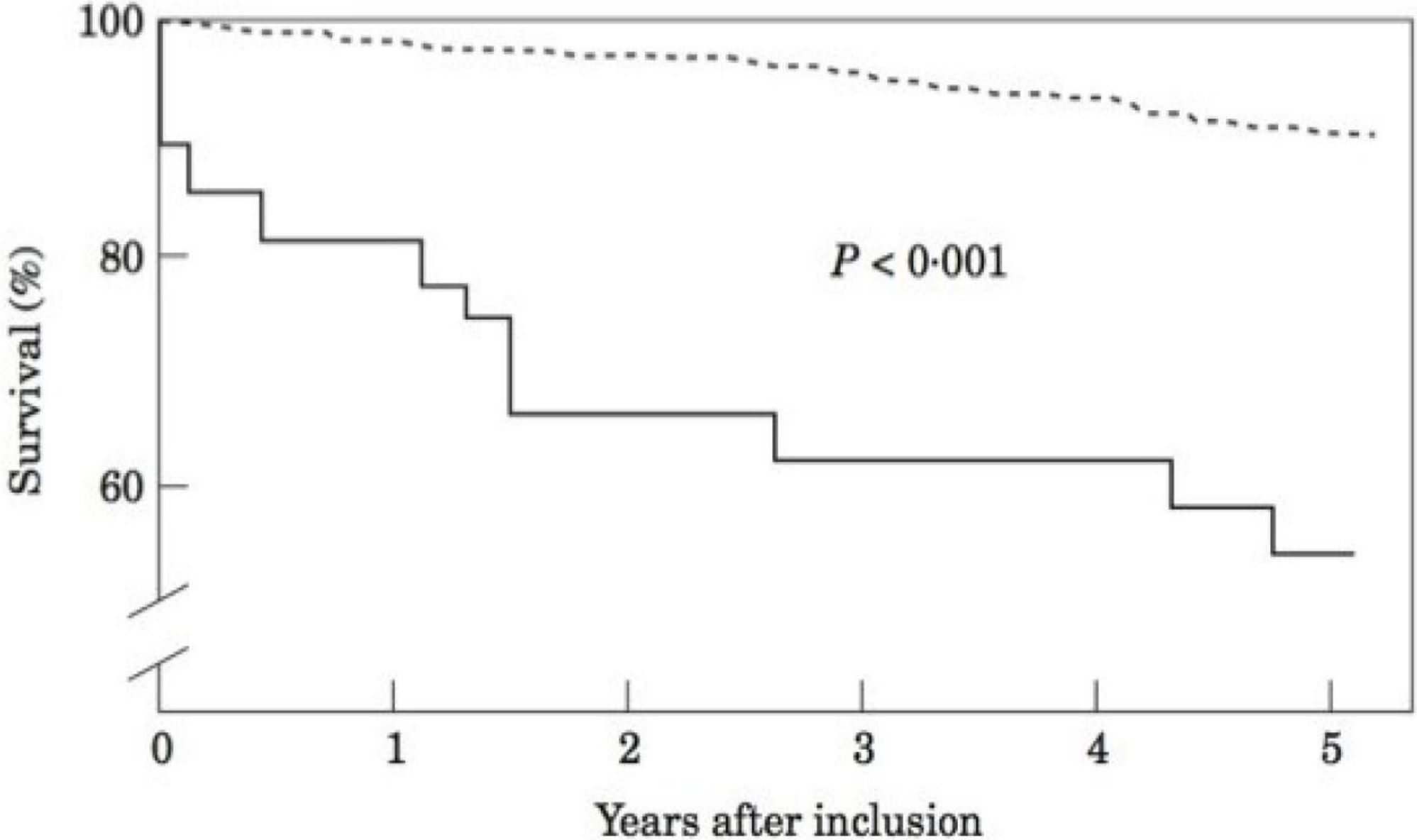
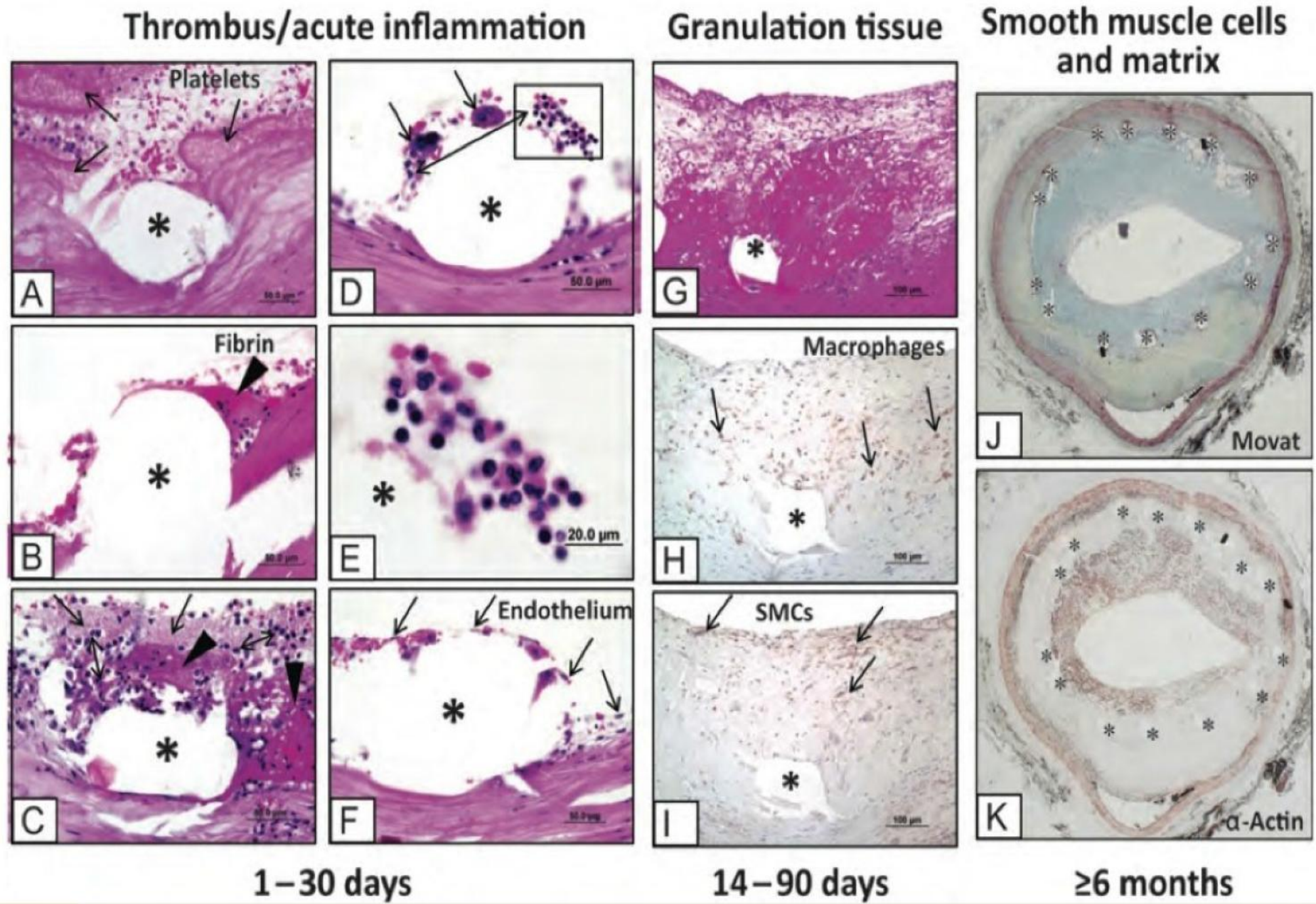


Figure 2 **Long-term survival in patients with (——) or without (– – –) distal embolization (*P*<0·001).**

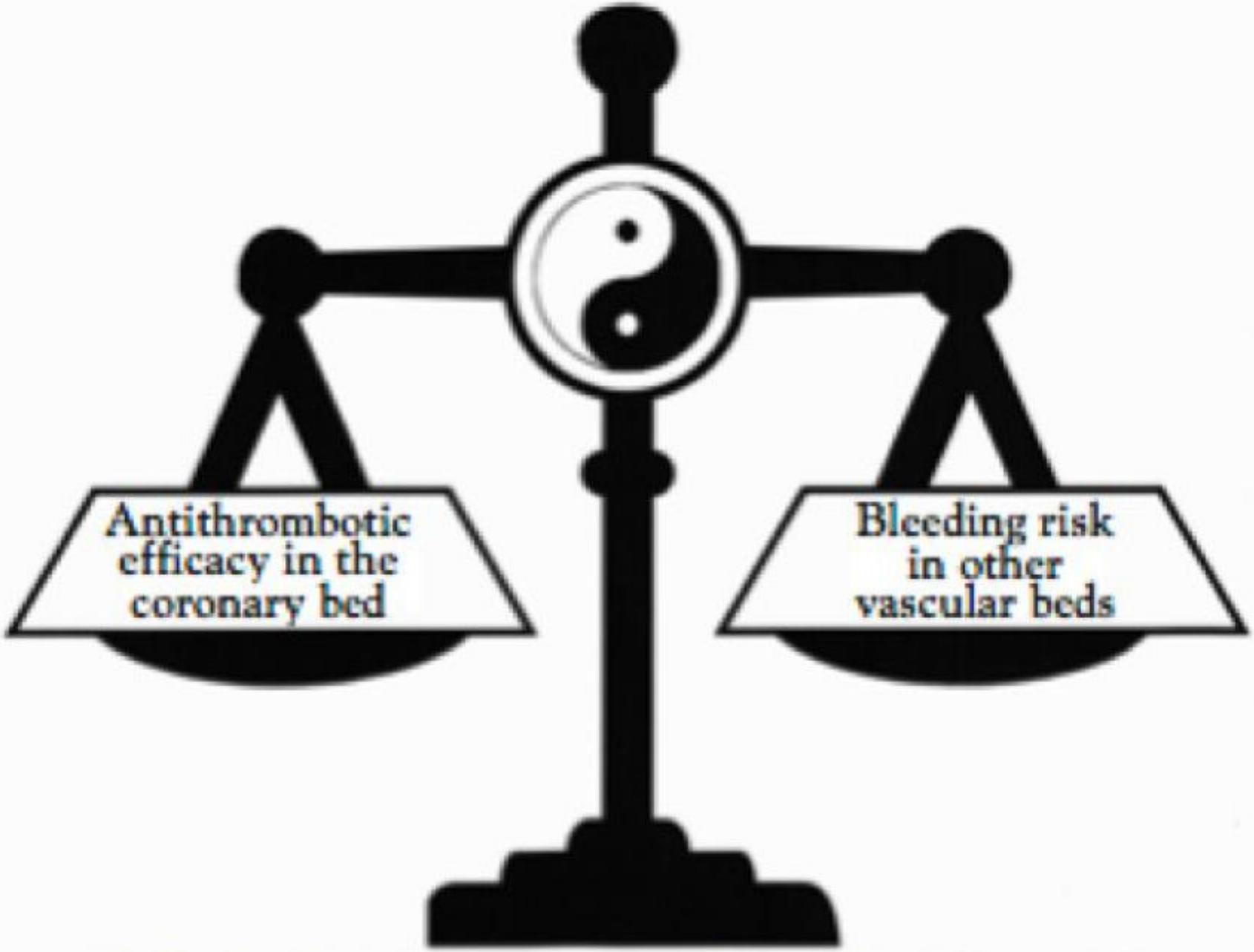
Angioplastie+stenting un modèle de thrombose artérielle / plaquettaire quasi expérimental

Thrombose de stent = thrombose plaquettaire


Thrombus/acute inflammation
Granulation tissue
Smooth muscle cells and matrix
Platelets
A
D
50.0 µm
G
J
Movat
Fibrin
B
E
20.0 µm
Macrophages
H
C
Endothelium
F
SMCs
I
K
α-Actin
1–30 days
14–90 days
≥6 months

Comprendre le pourquoi du traitement antithrombotique dans le SCA

- Le pourquoi du traitement antiplaquettaire
- Le pourquoi du traitement anticoagulant
  - Le pourquoi de l’héparine
  - Le pourquoi de l’inhibition de la thrombine


Antithrombotic efficacy in the coronary bed
Bleeding risk in other vascular beds

Comprendre le pourquoi du traitement antithrombotique dans le SCA

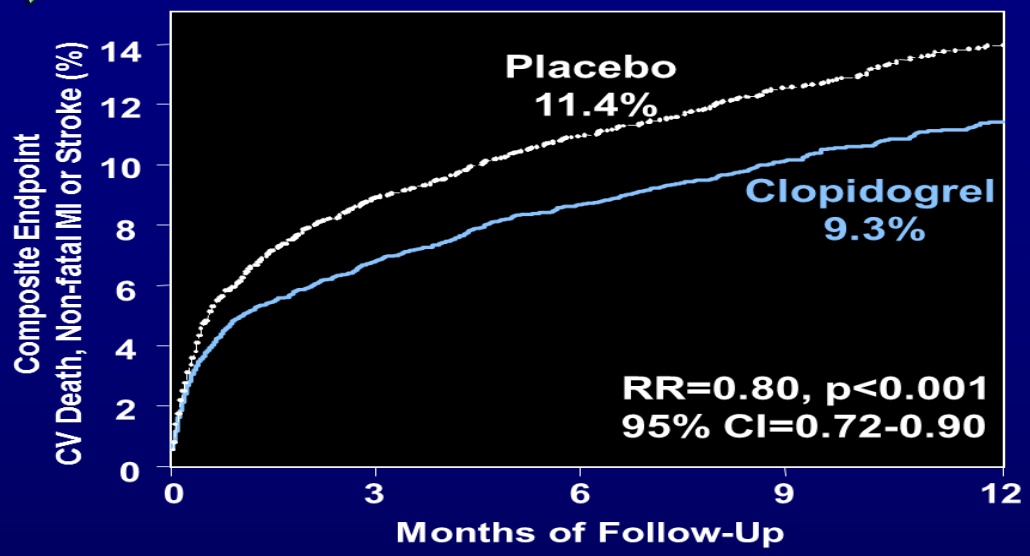
- Le pourquoi du traitement antiplaquettaire
  - Quel antiplaquettaire choisir
  - Quand débuter le traitement
- Le pourquoi du traitement anticoagulant
  - Arguments pour choisir une héparine
  - Arguments pour choisir l’inhibition directe de la thrombine

Comprendre le pourquoi du traitement antithrombotique dans le SCA

- Le pourquoi du traitement antiplaquettaire
  - Quel antiplaquettaire choisir
    - Le meilleur rapport efficacité antiplaquettaire /risque hémorragique
  - Quand débuter le traitement
    - Pour que l’on ait l’efficacité au moment où l’on en a besoin

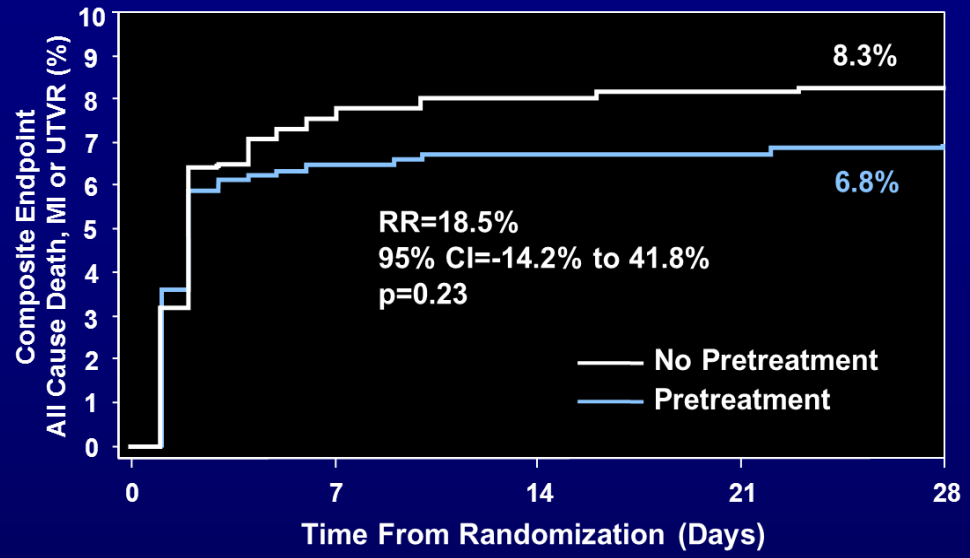
ACS

CURE Efficacy

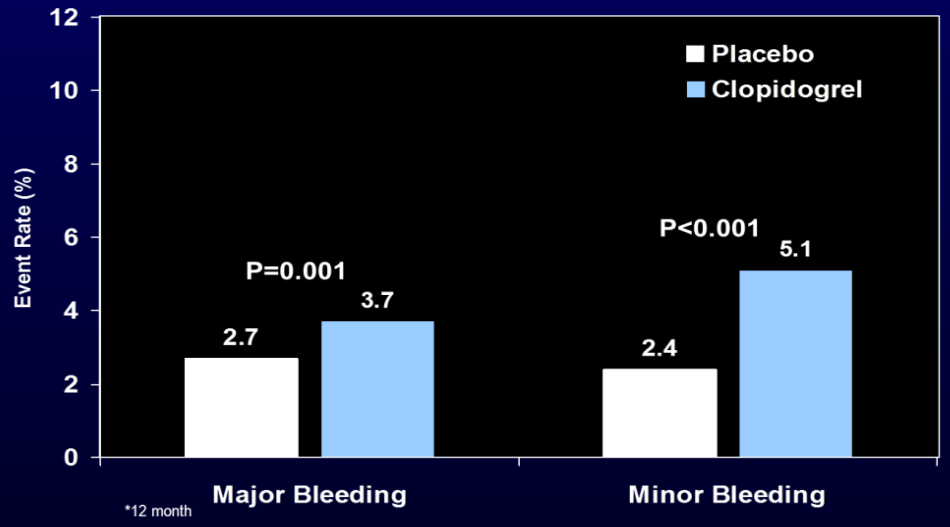


PCI

CREDO Efficacy

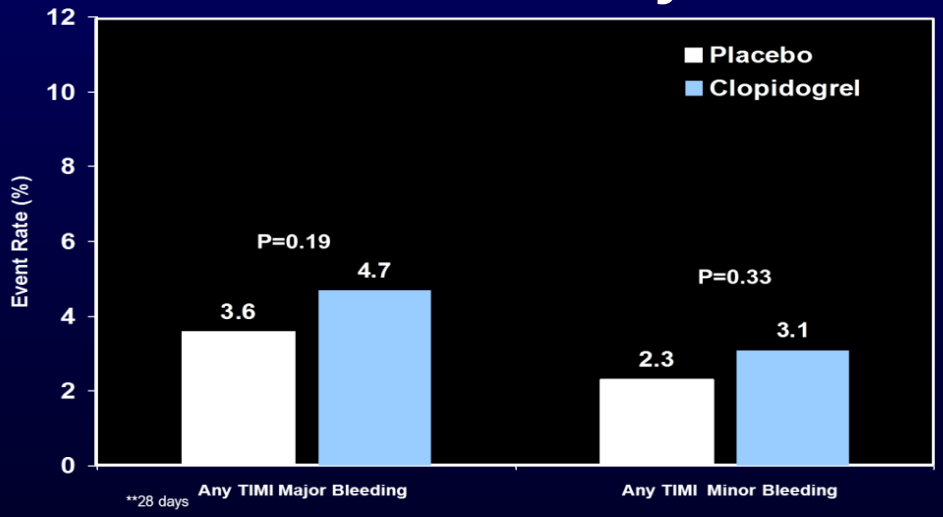


CURE Safety*



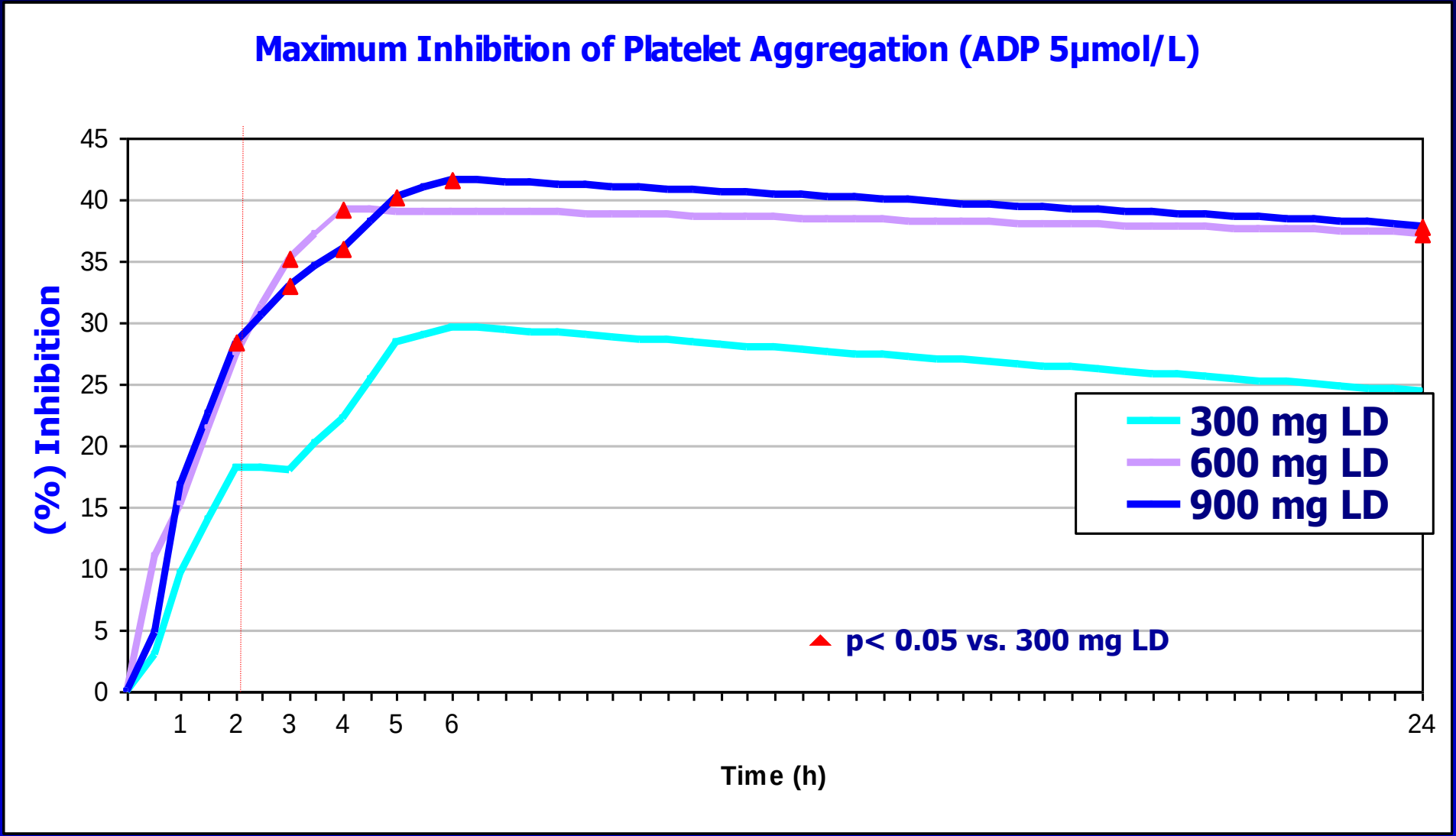
Yusuf S, et al. *N Engl J Med* 2001;345:494-502

CREDO Safety**

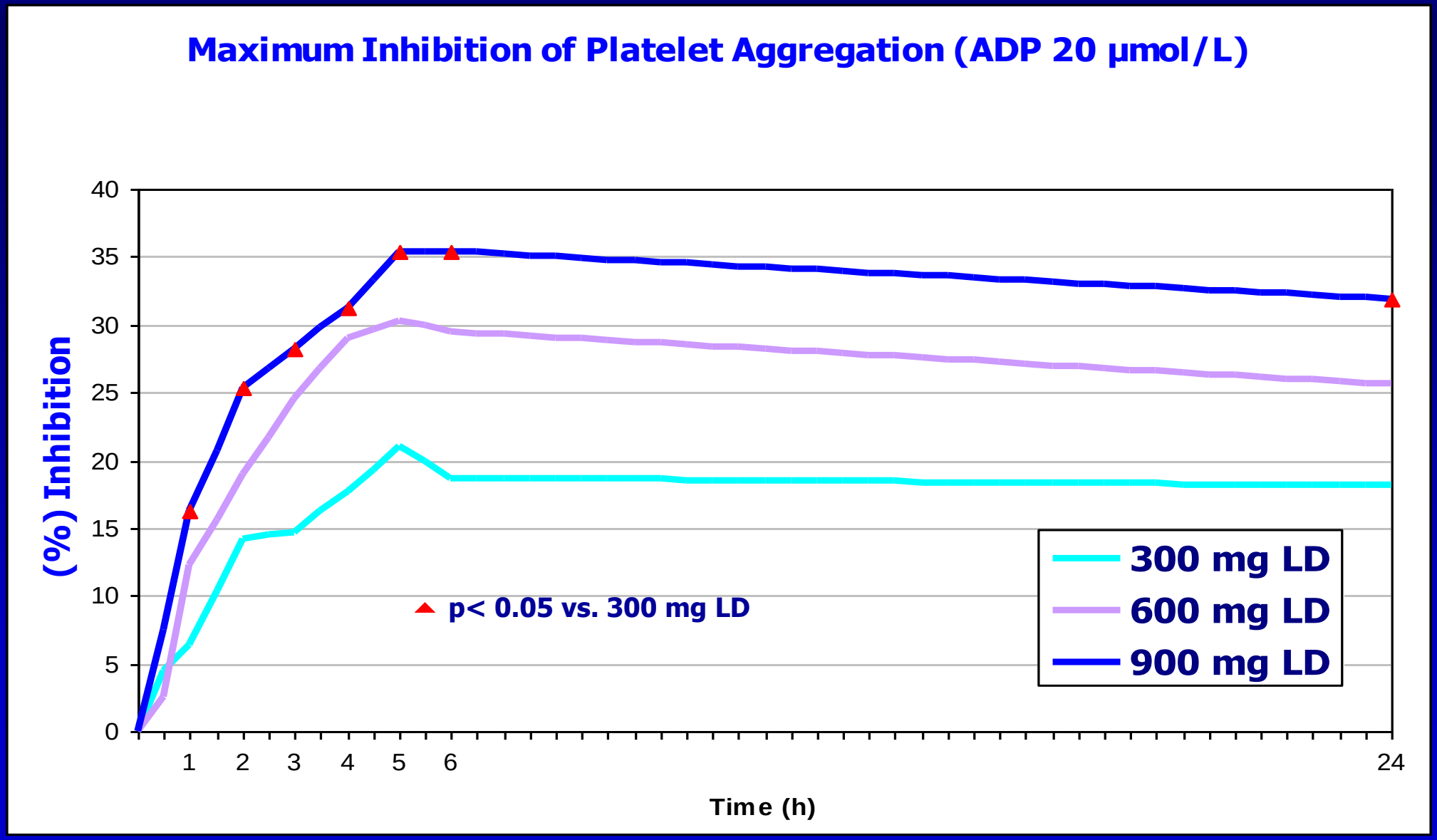


Steinhubl SR, et al. *JAMA* 2002;288:2411-2420

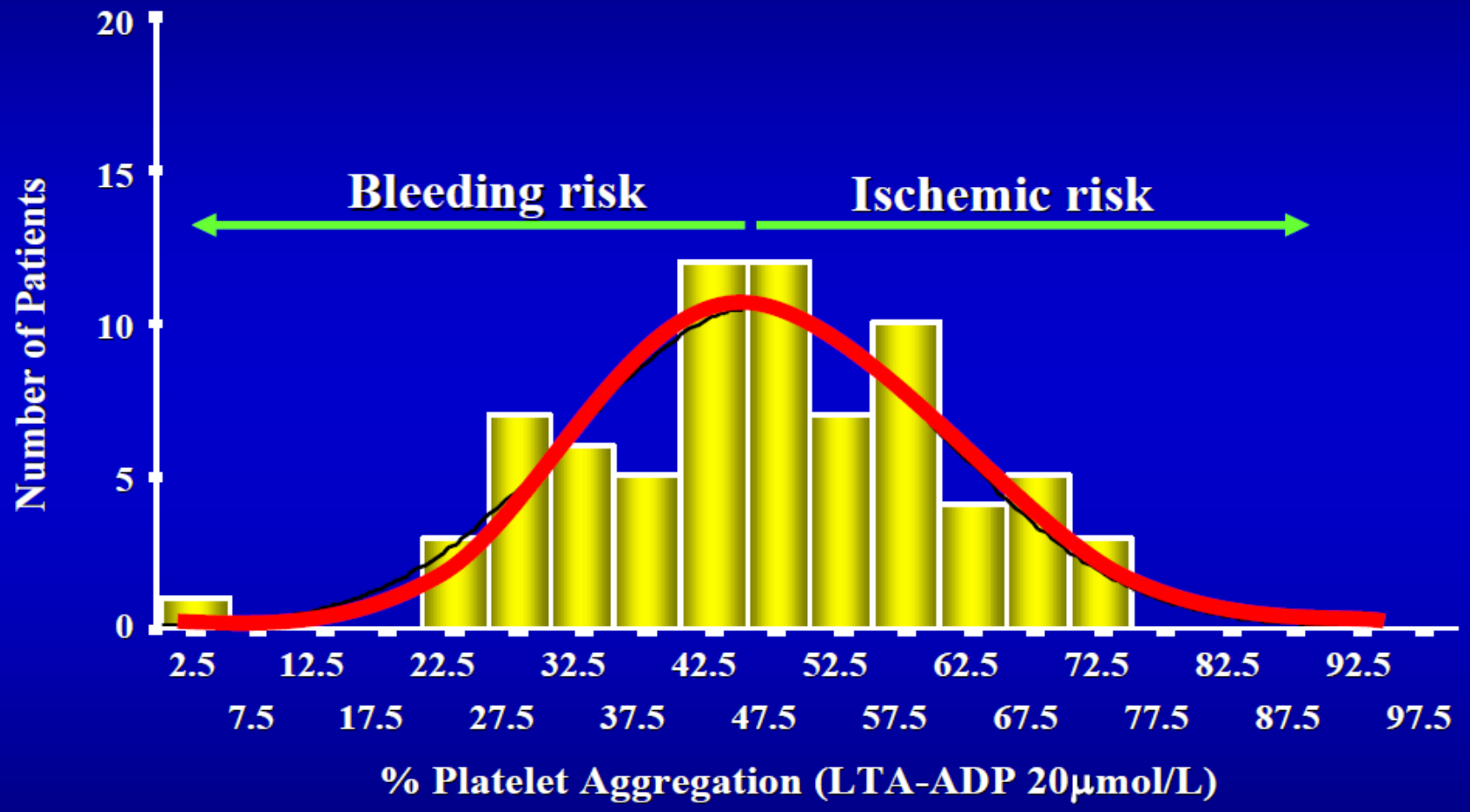
Primary Endpoint: Faster Onset of Action and Higher Level of Platelet Inhibition



Higher Levels of Inhibition of Platelet Aggregation Suggesting a Dose-Effect Relationship



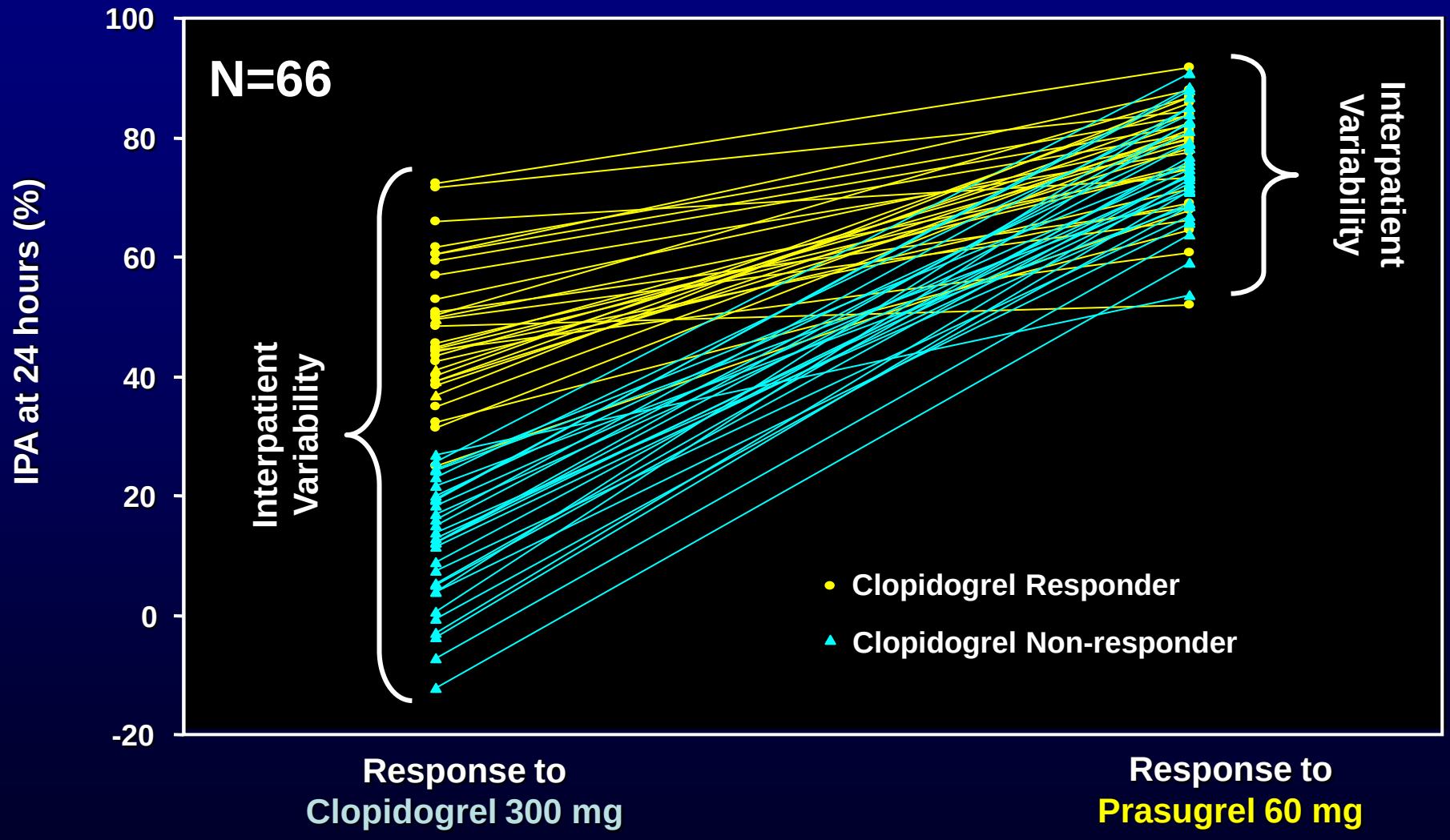
Individual Response Variability to Dual Antiplatelet Therapy in the *Steady State Phase* of Treatment



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

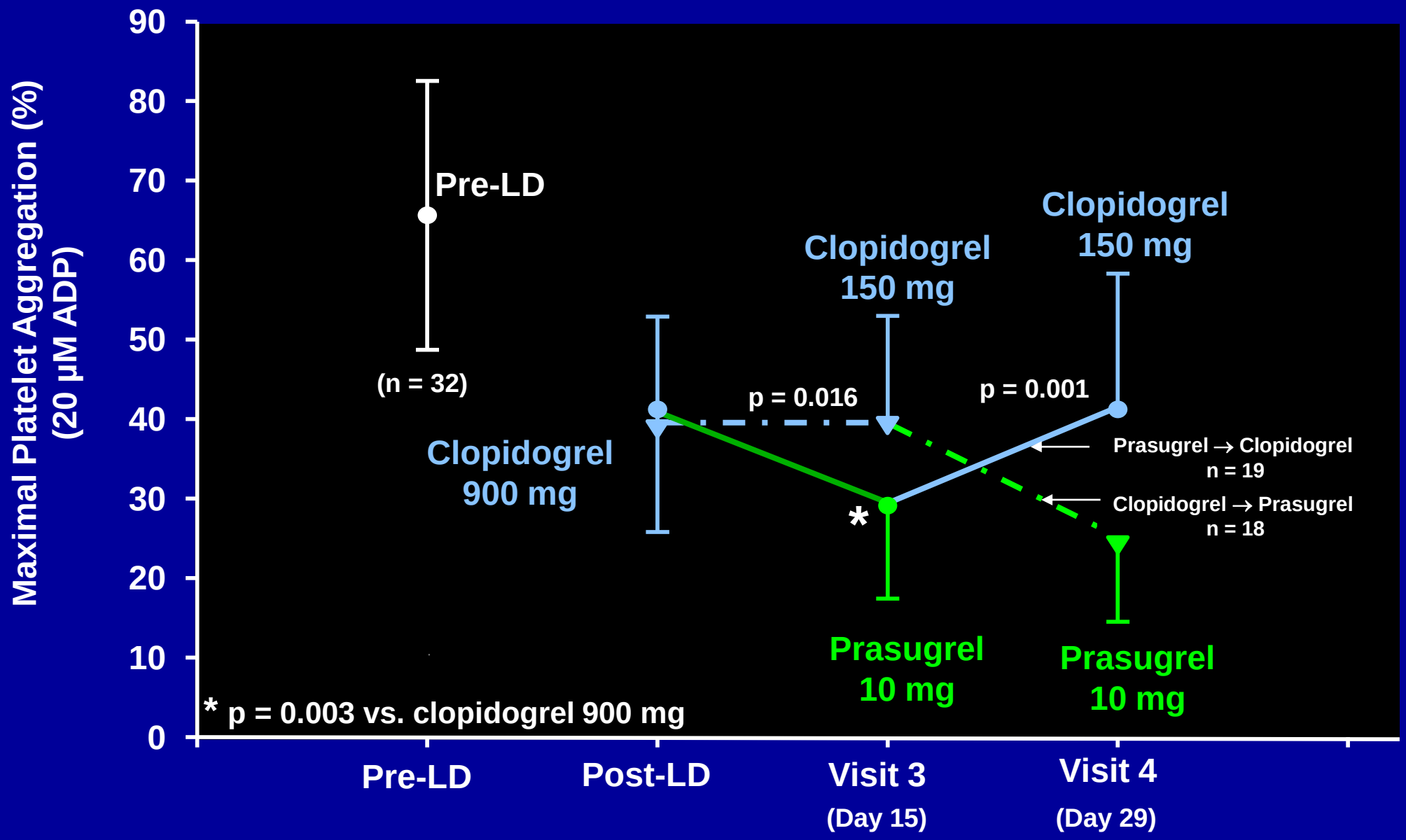
TRÎTON TIMI·38

Healthy Volunteer Crossover Study

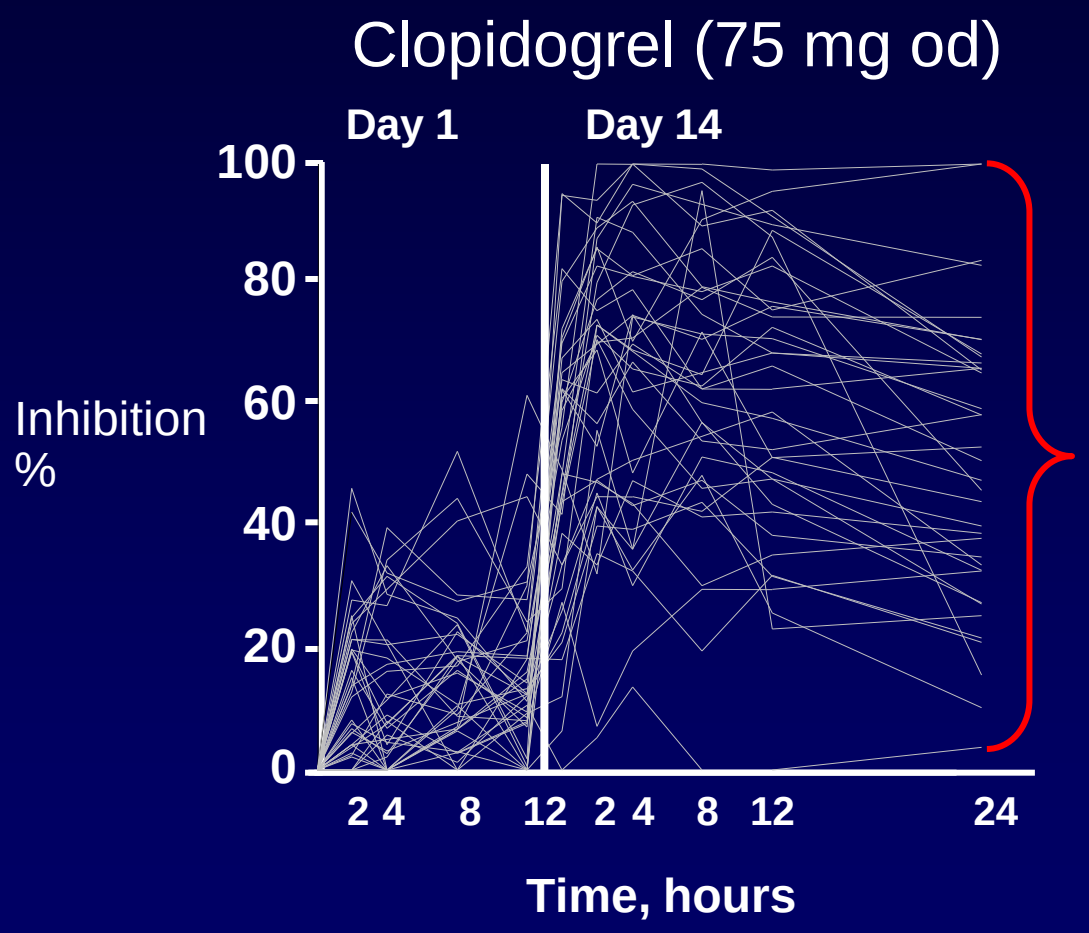


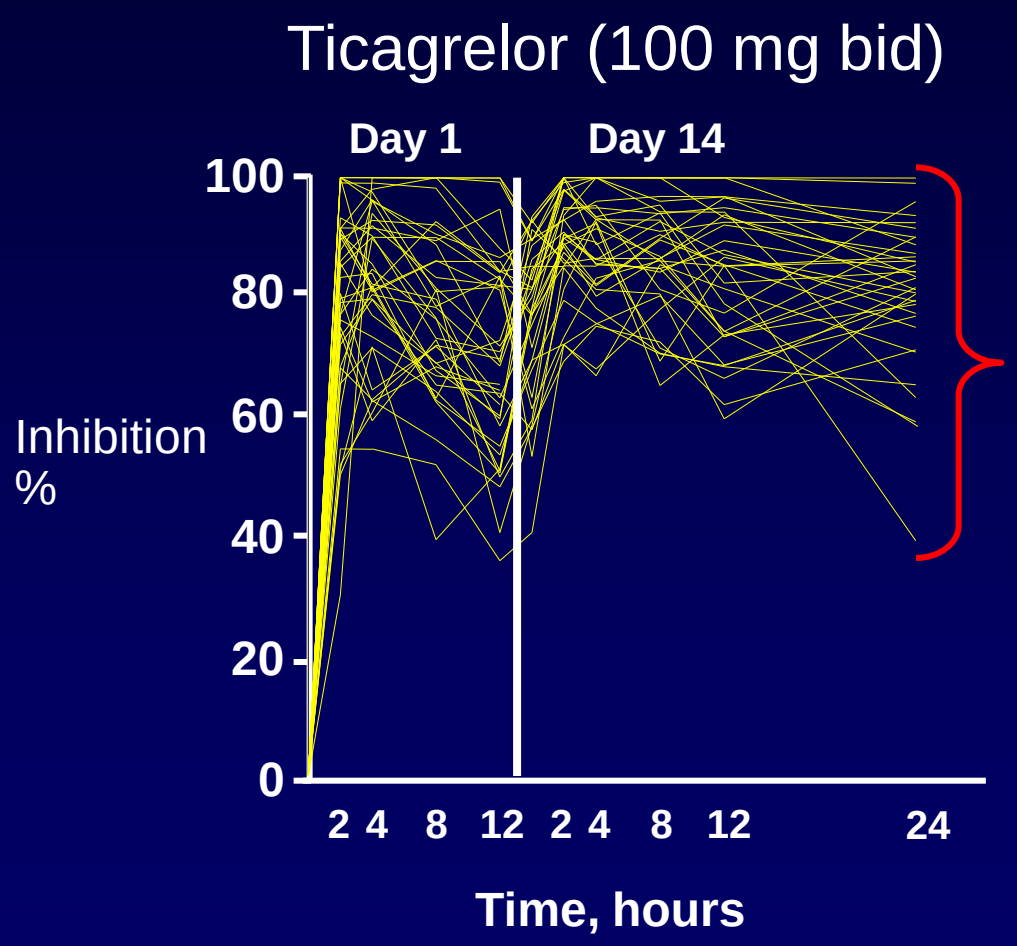
From Brandt JT AHJ 153: 66e9,2007

MPA by Treatment Sequence and Period



Inhibition of ADP-Induced Platelet Aggregation by Ticagrelor *vs.* Clopidogrel

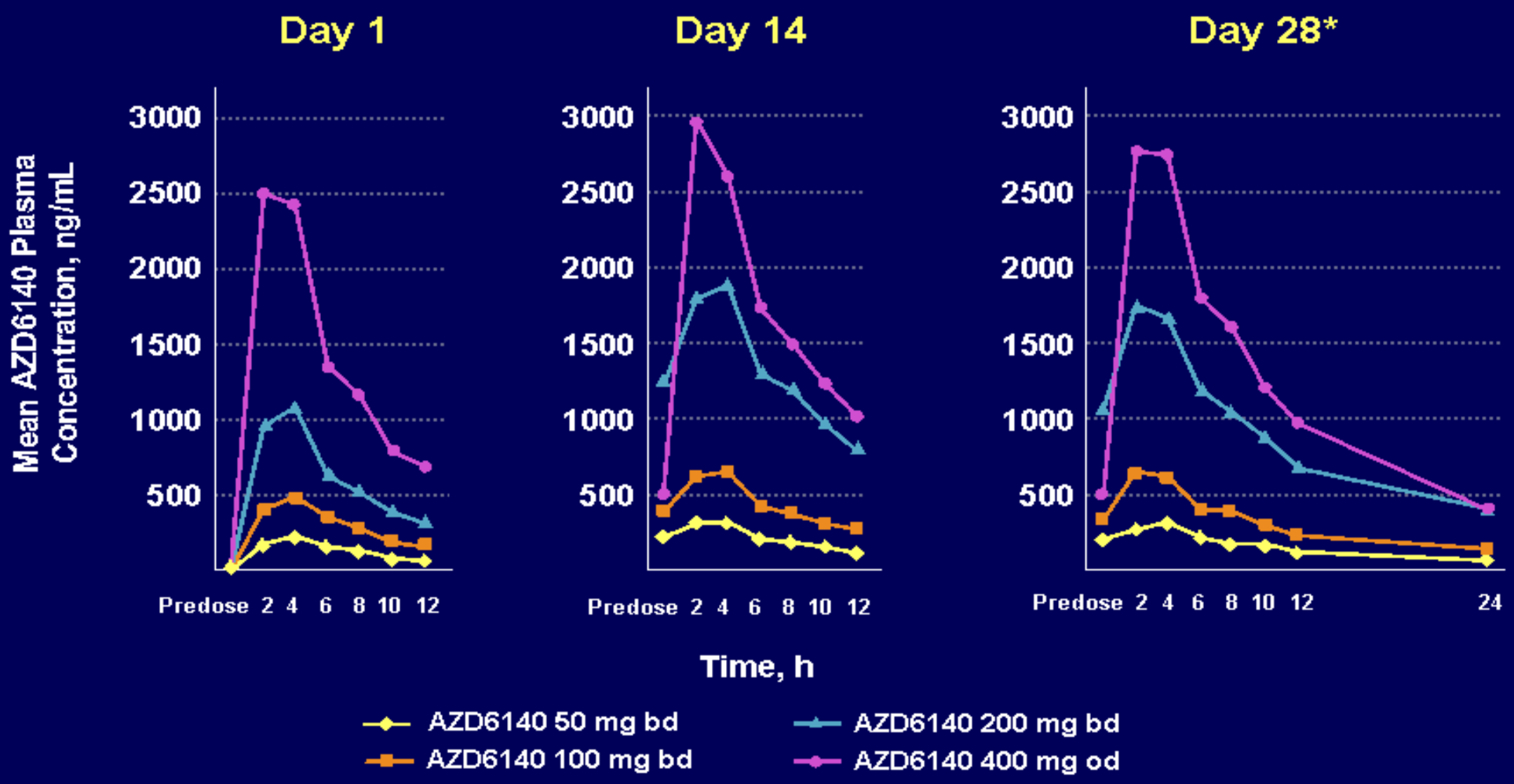




Husted SE, Eur Heart J, 2006;27:1038-47 DISPERSE STUDY . Stable CHD patients

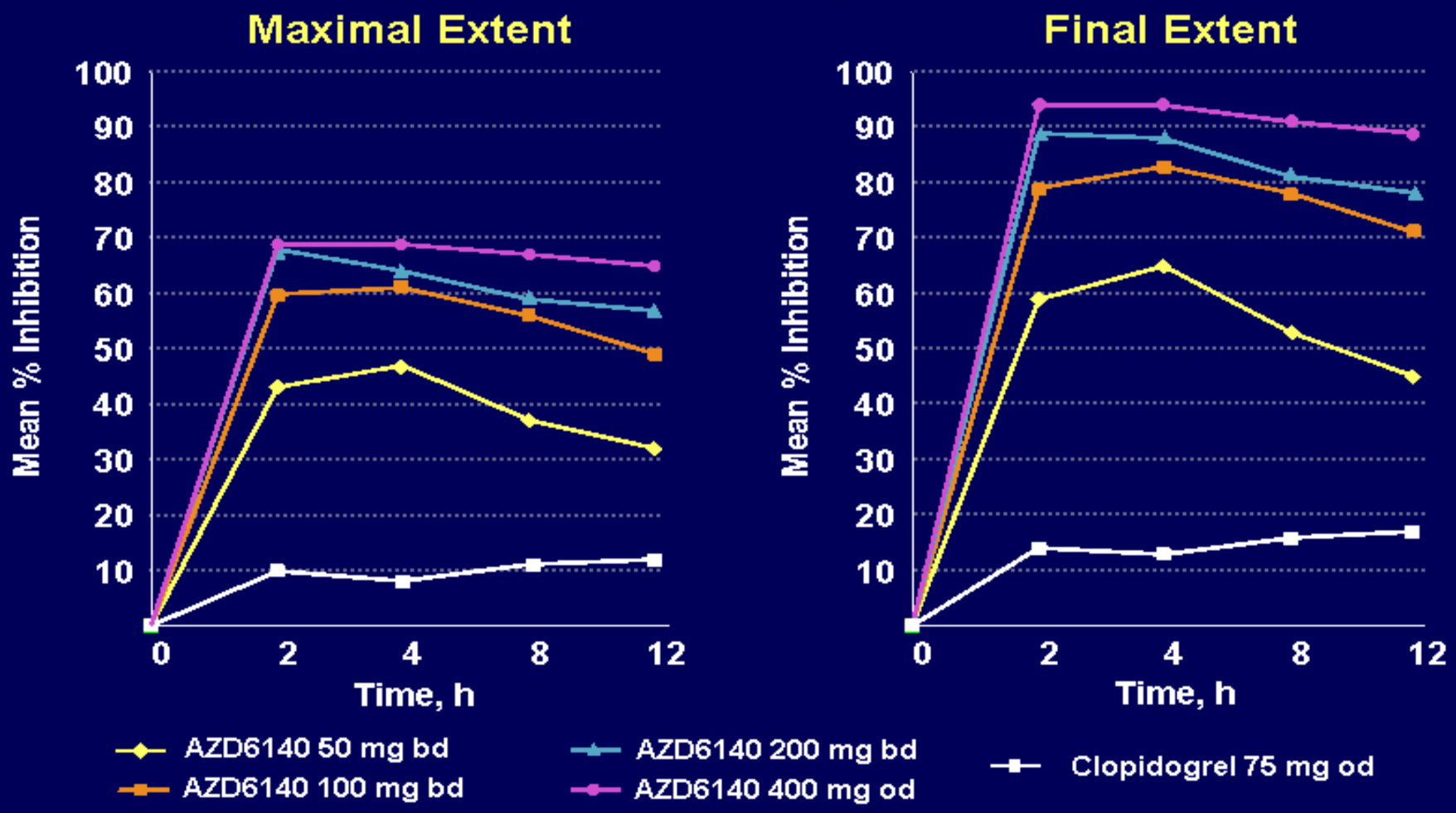
No loading dose

Pharmacokinetics of AZD6140



*No 12-hour dose on Day 28.
Husted SE, et al. *Eur Heart J.* 2006;27:1038-1047.

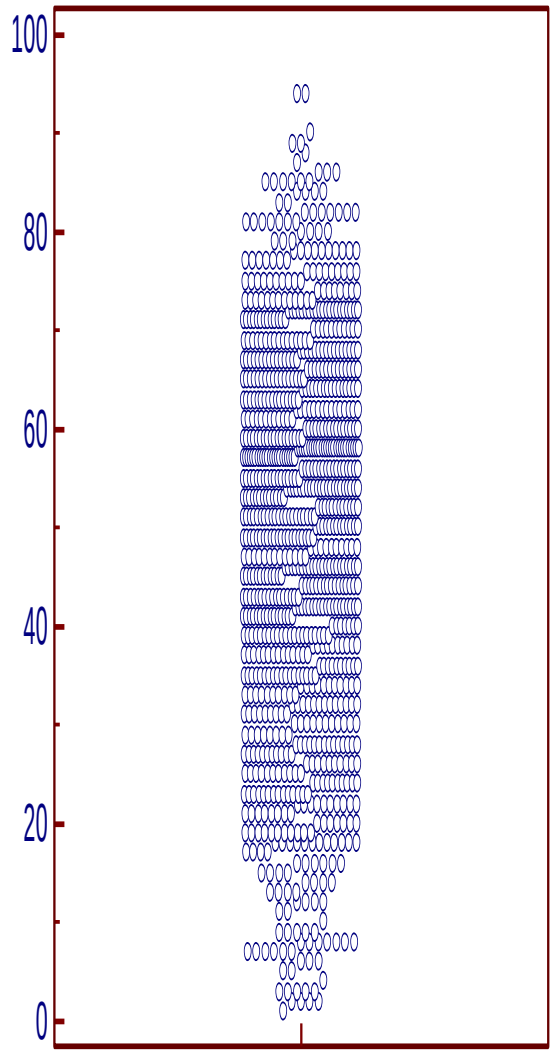
Rapid Onset of IPA with AZD6140 on Day 1



No loading dose in any treatment group

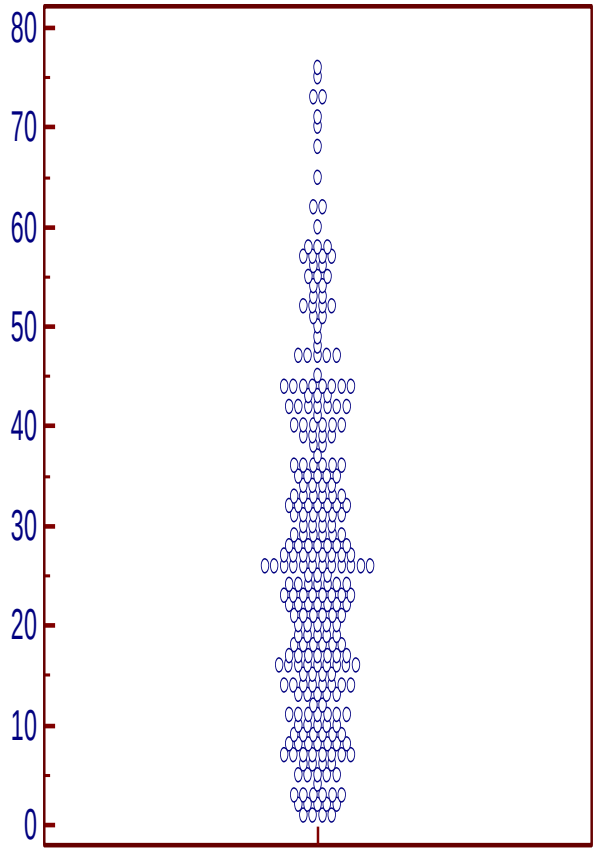
Husted SE, et al. *Eur Heart J.* 2006;27:1038-1047.

Clopidogrel



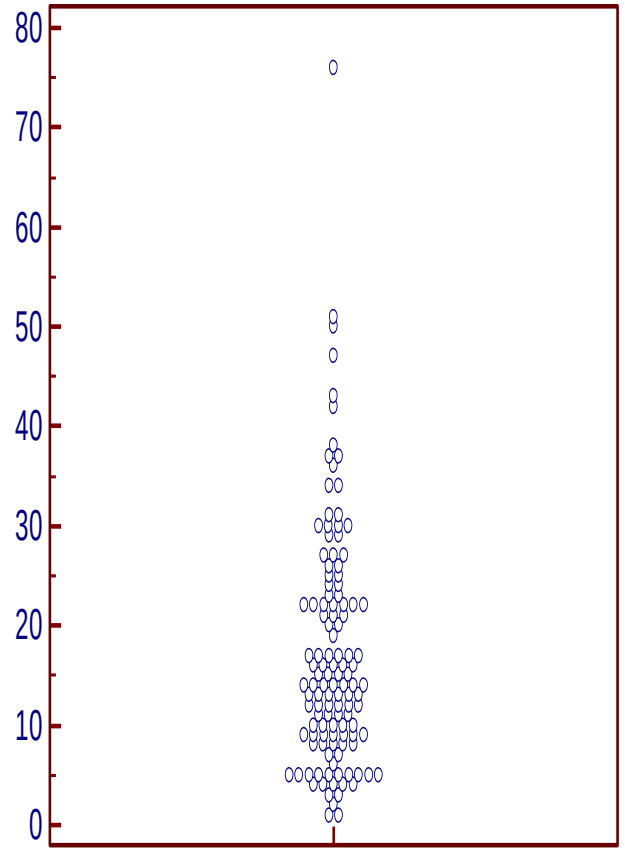
50 patients avec VASP<15 sur 947 patients soit 5.2%

Prasugrel



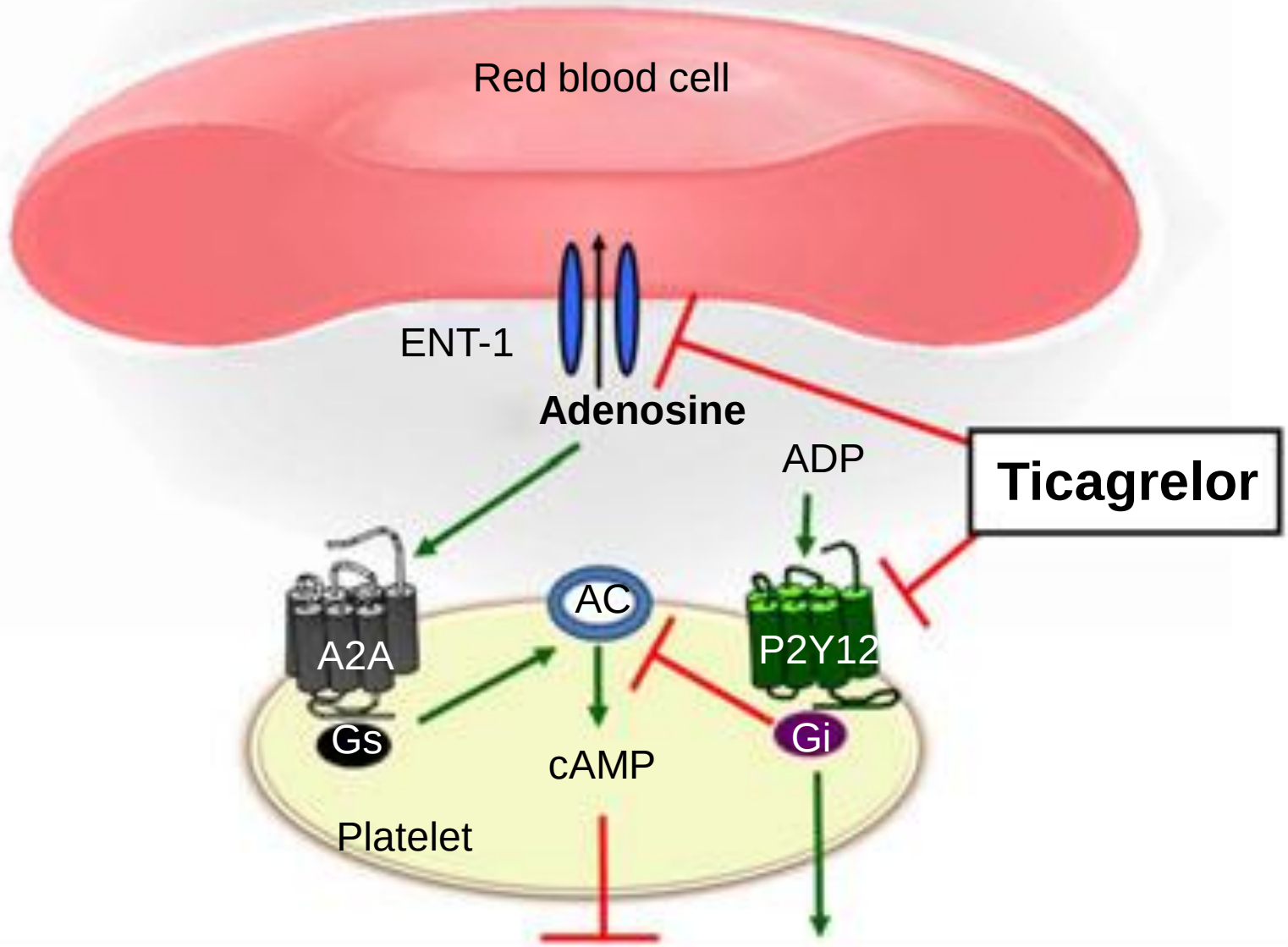
73 patients avec VASP<15 sur 285 patients soit 25.6%

Ticagrelor

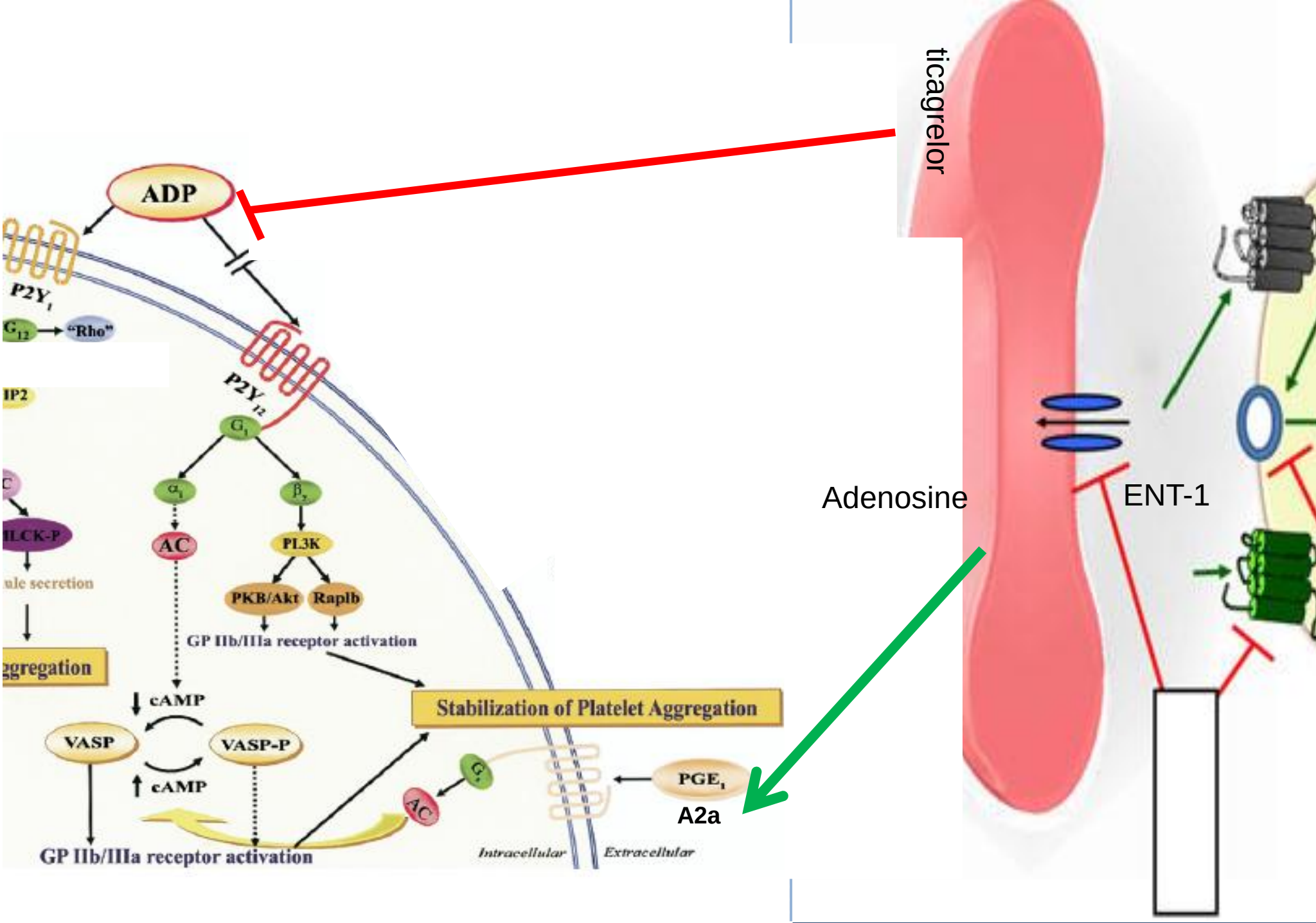


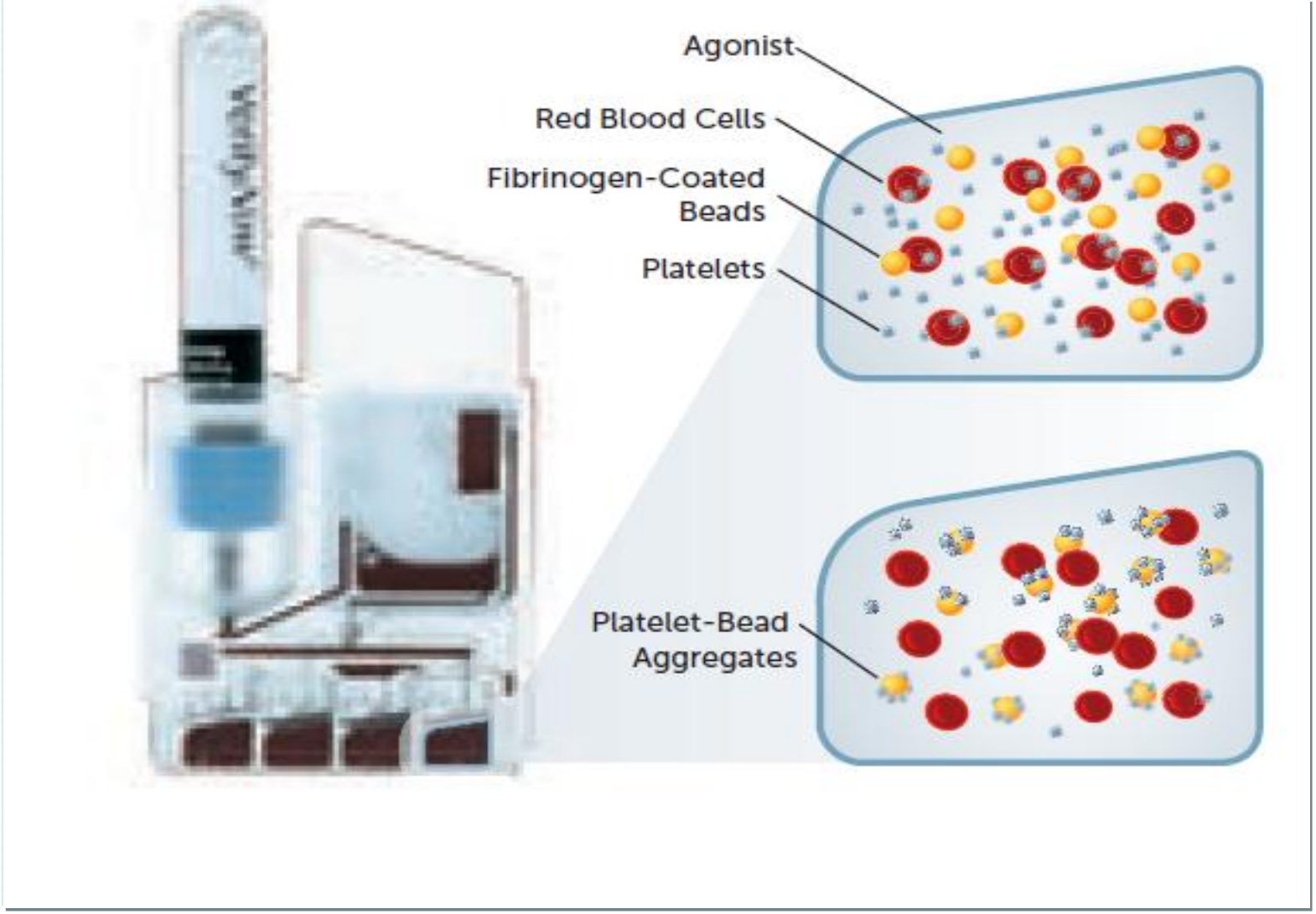
63 patients avec VASP<15 sur 122 patients soit 51.6 %

Nylander S et al JTH2013, 11: 1867-76



Platelet activation/aggregation


ADP
P2Y1
G12
"Rho"
P2Y12
Gi
αi
βγ
AC
PI3K
PKB/Akt
Rap1b
GP IIb/IIIa receptor activation
cAMP
VASP
VASP-P
cAMP
Stabilization of Platelet Aggregation
Gs
AC
PGE1
A2a
GP IIb/IIIa receptor activation
Intracellular
Extracellular
ticagrelor
Adenosine
ENT-1



The VerifyNow PRUTest also uses PGE1 to increase intraplatelet cAMP and reduce the contribution of the P2Y1 receptor on activation. This makes the test more specific for the effects of ADP on the P2Y12 receptor.

Mr R… 64 ans

Motif d'appel:

Douleur thoracique

Facteurs de risque:

Tabagisme actif (35 PA)
Dyslipidémie traitée par régime seul
HTA sous monotégrapie (IEC)

Antécédents médicaux:

SAS, adénome de prostate et cataracte bilatérale

HDLM:

Survenue le 18 Février vers 1h du matin, douleur thoracique rétrosternale irradiant dans les deux épaules.

Consulte son pharmacien vers 14h30 devant la persistance de la symptomatologie et appel du SAMU

Arrivée à 14h43, PA 102/63mmHg, FC=96min, Sat 94% AA

Traitement initial

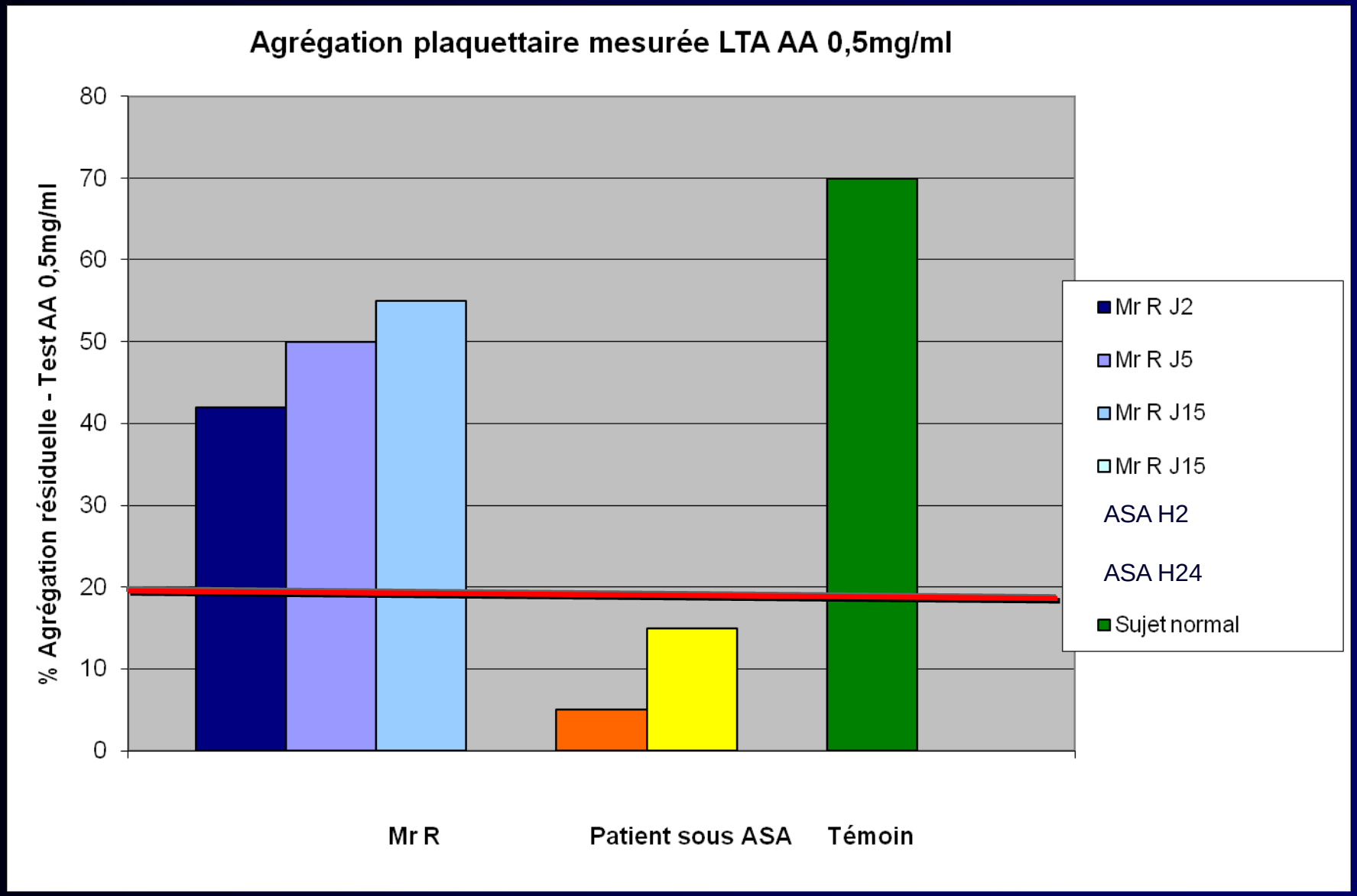
HNF 5000 UI

Prasugrel 60mg

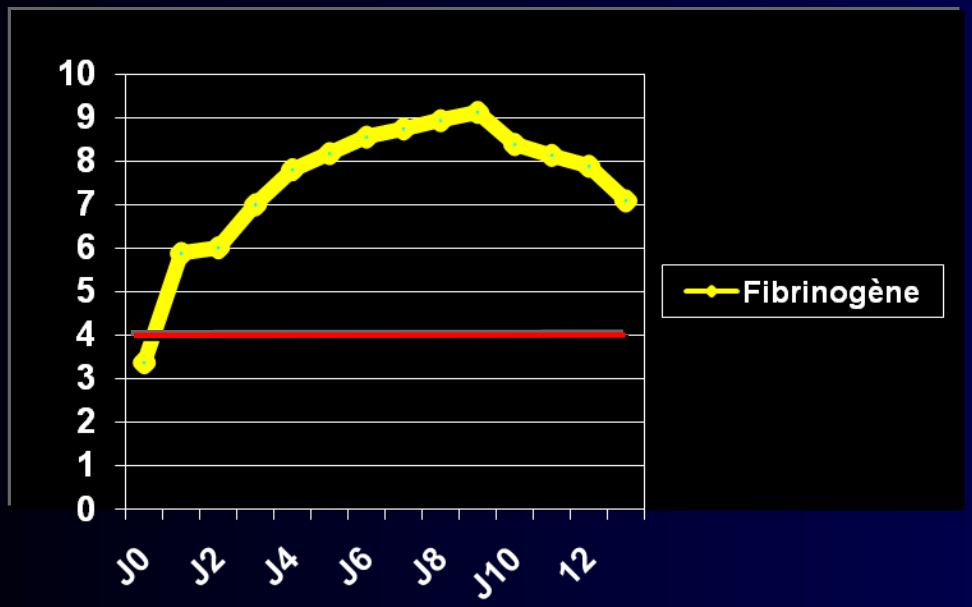
Aspégic 500mg IV

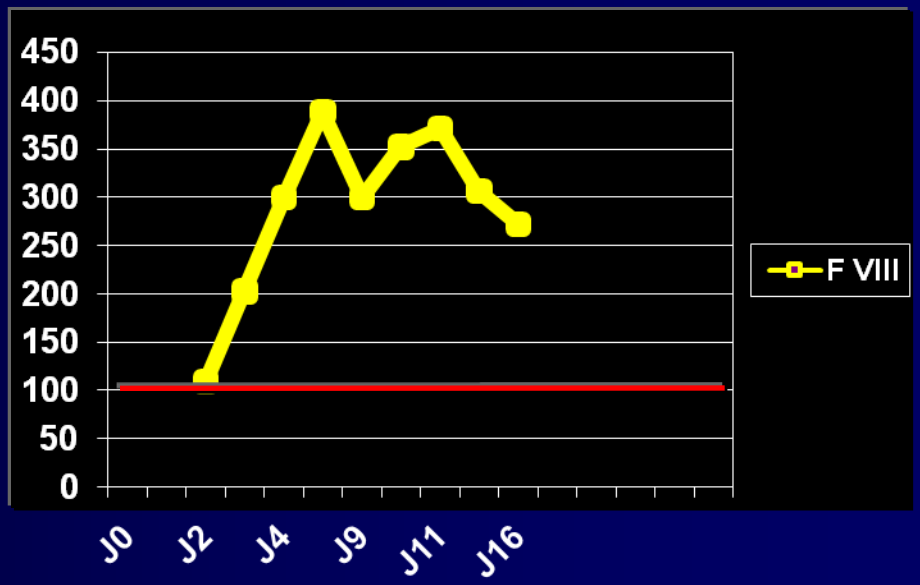
Bivalirudin en salle de KT

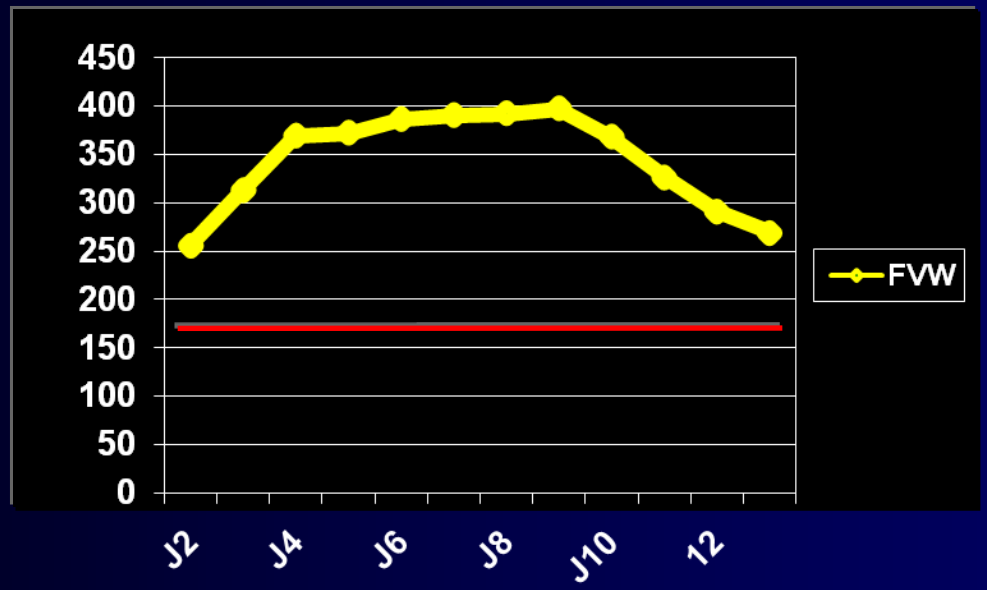
Exploration agrégation plaquettaire: Aspirine



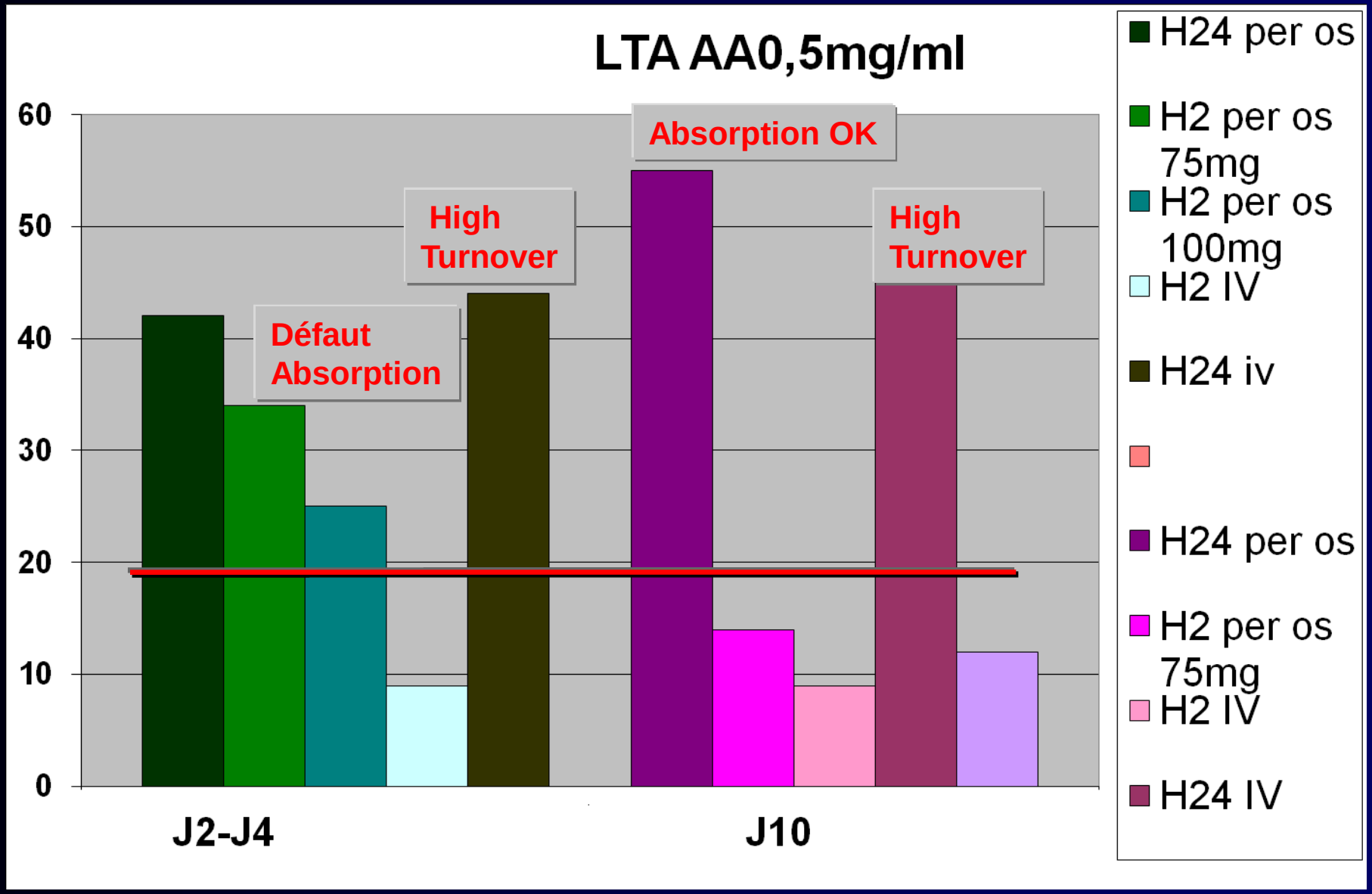
Coagulation – inflammation marqueurs



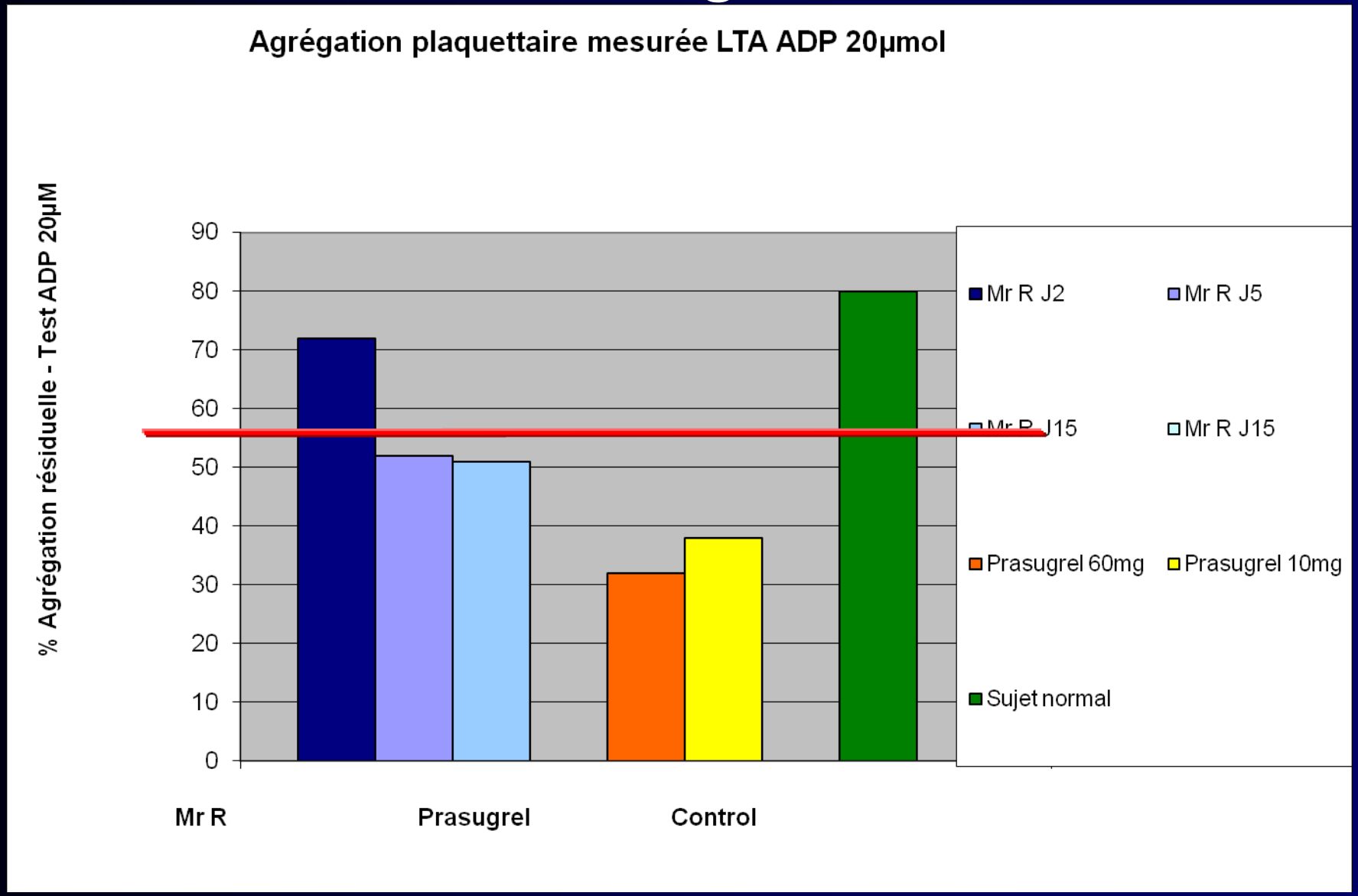




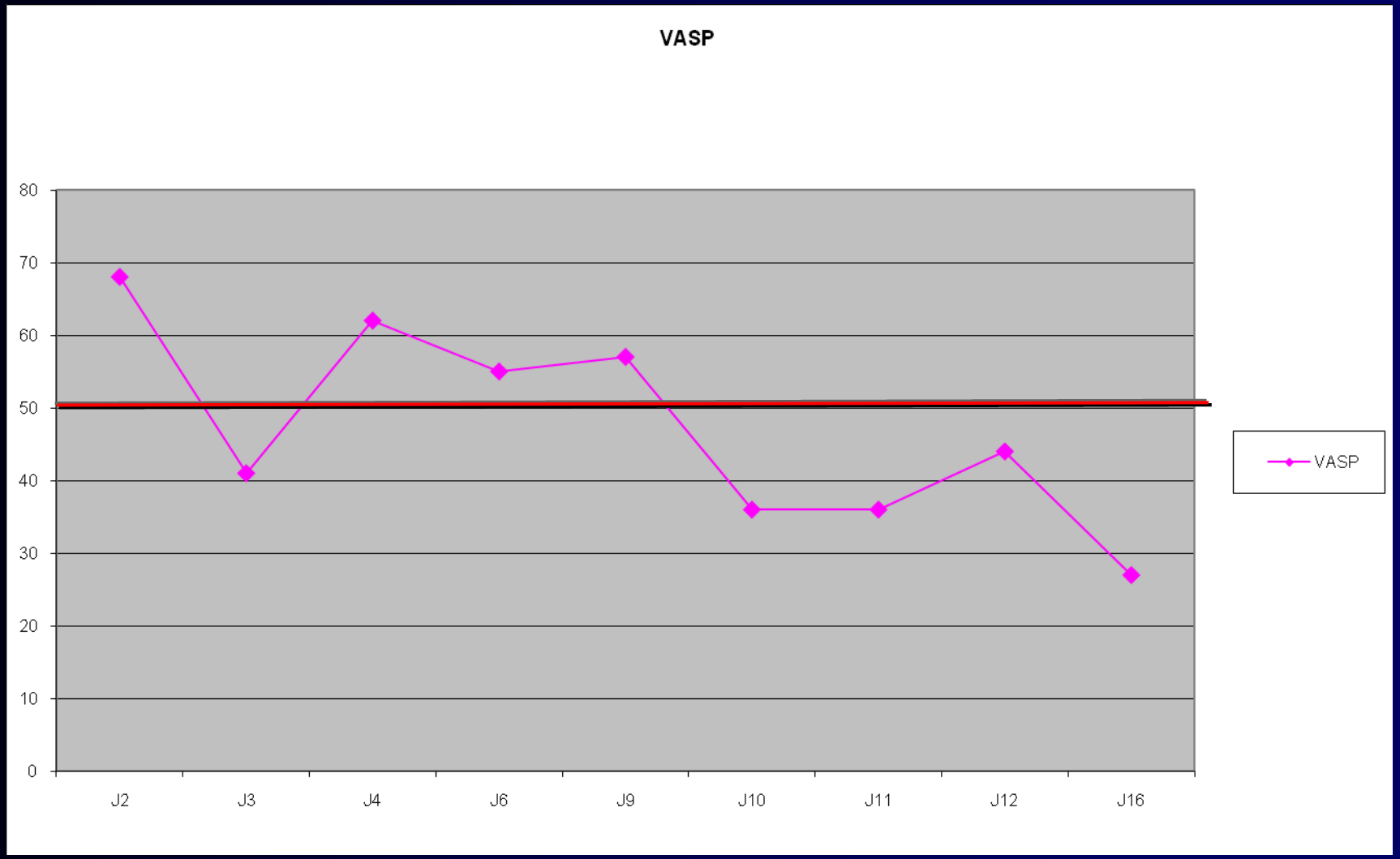
Exploration agrégation plaquettaire

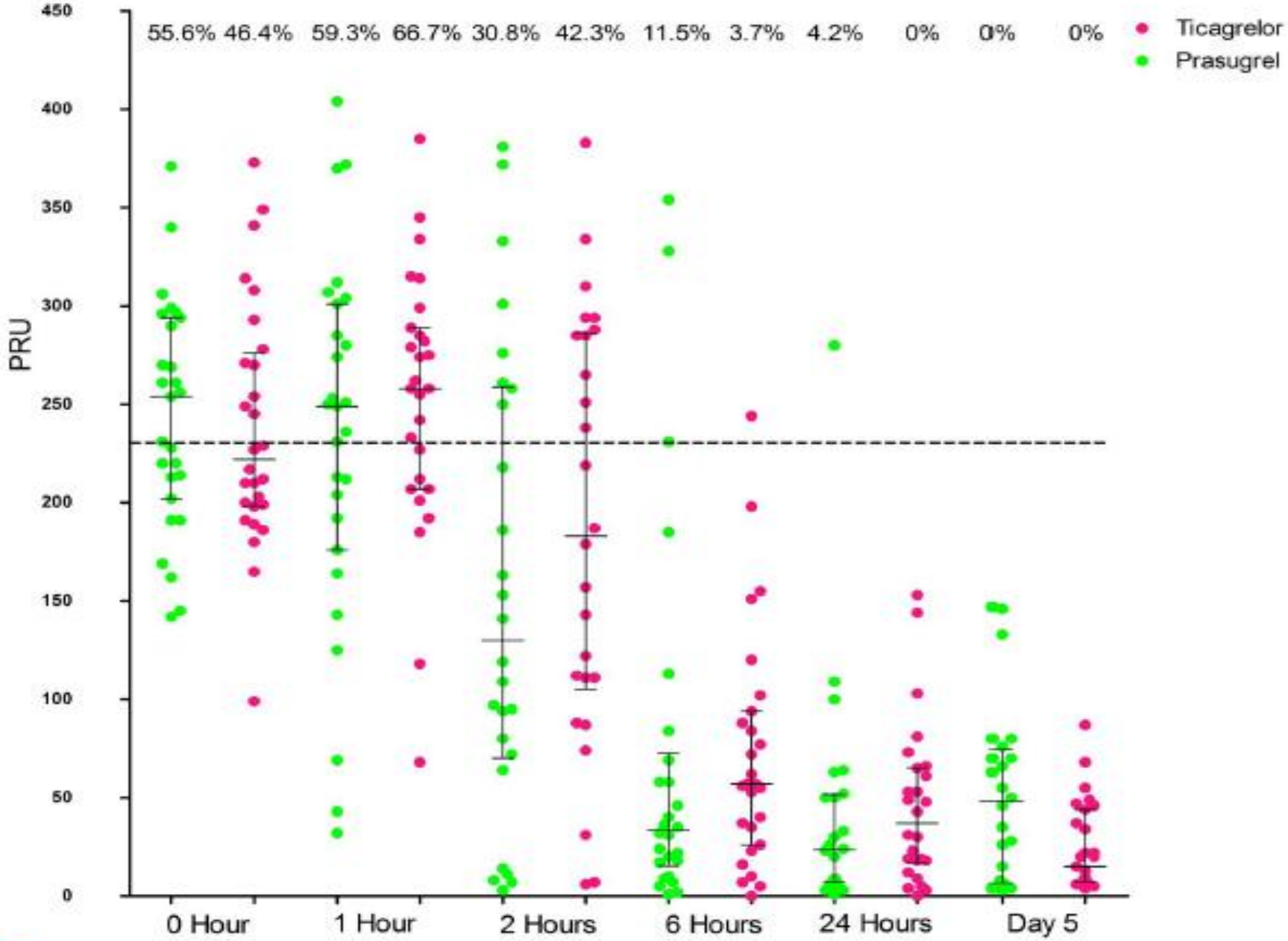


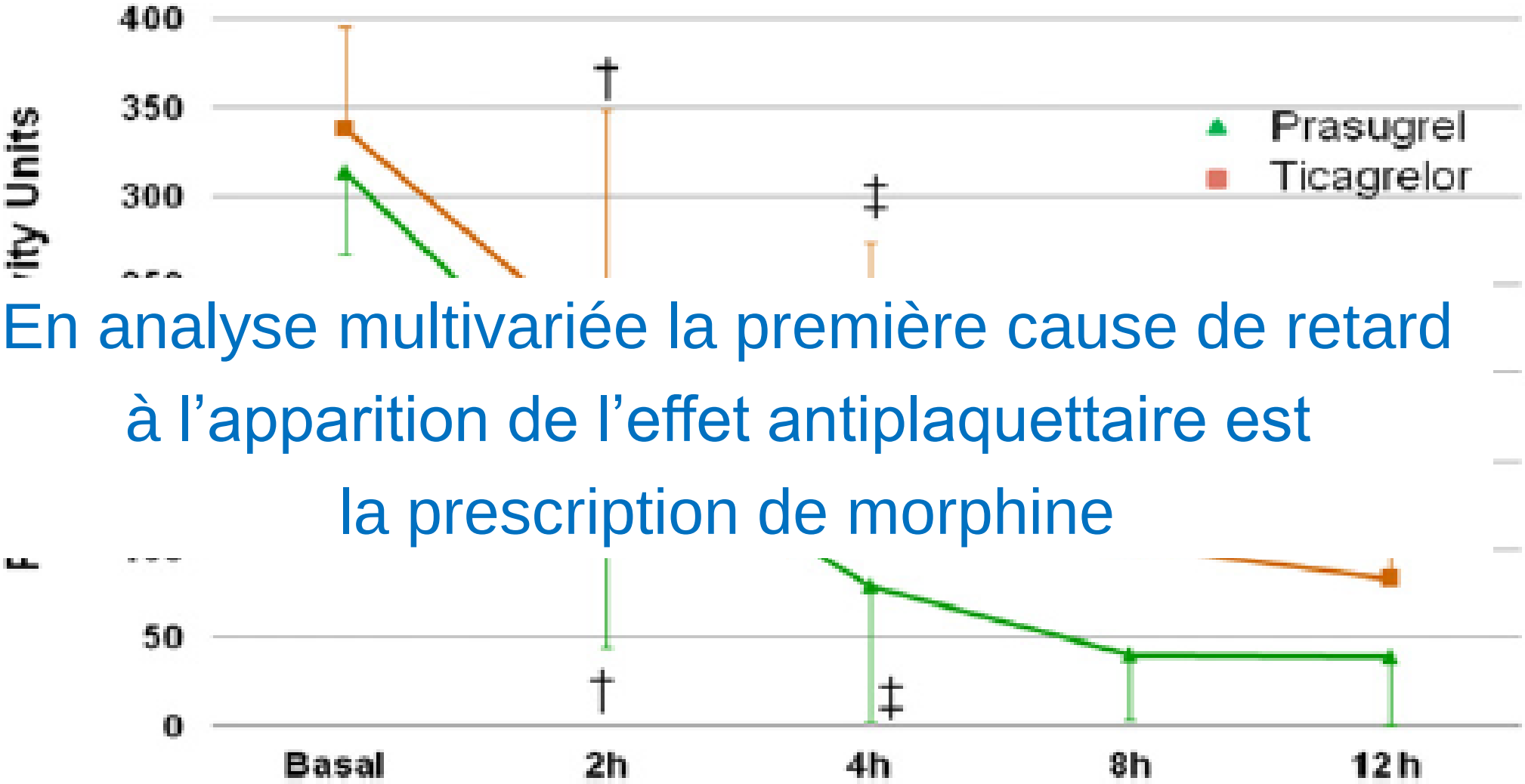
Exploration agrégation plaquettaire: Prasugrel



Prasugrel
Exploration plaquettaire: index VASP



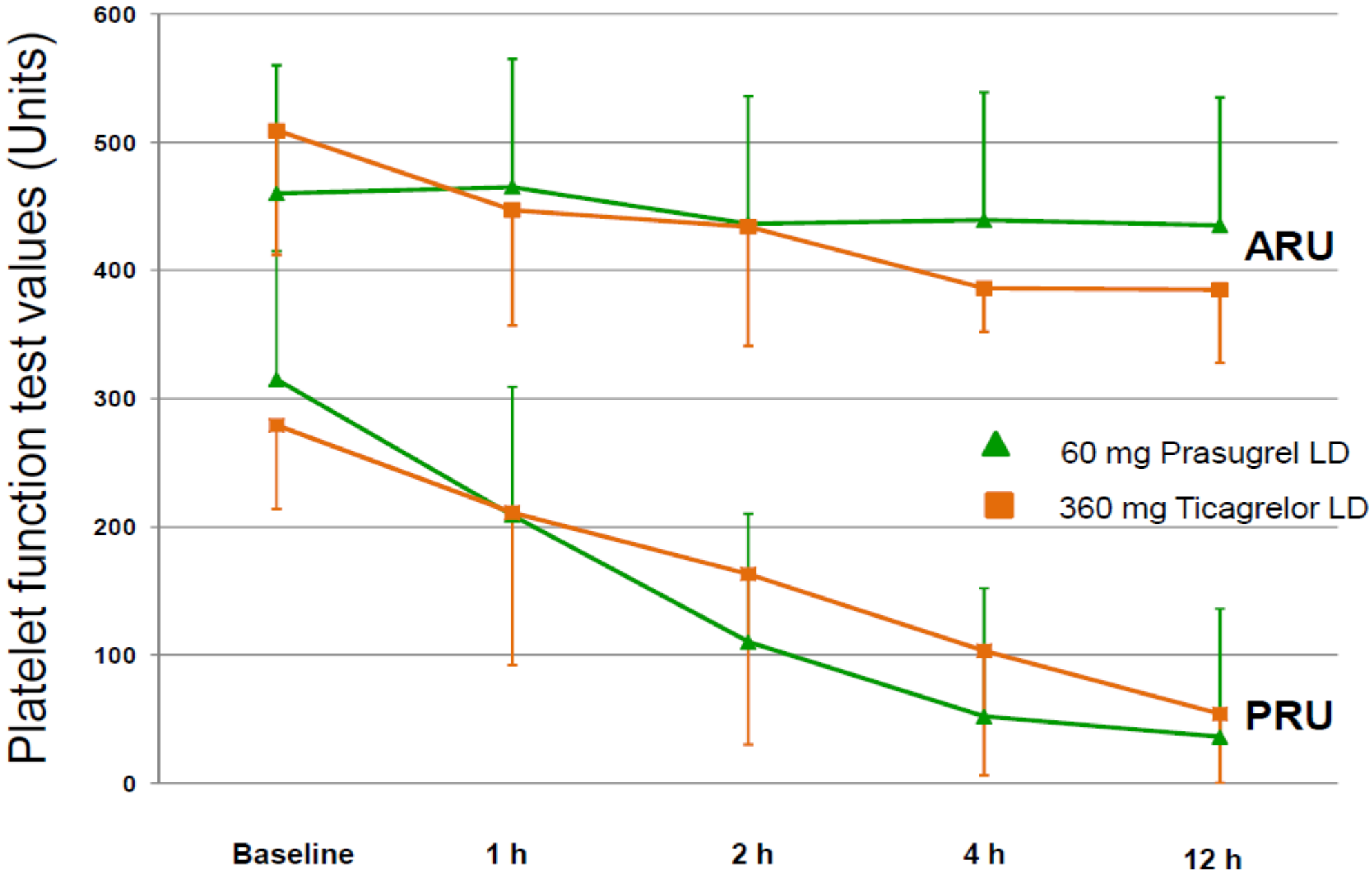

55.6% 46.4% 59.3% 66.7% 30.8% 42.3% 11.5% 3.7% 4.2% 0% 0% 0%
Ticagrelor
Prasugrel
PRU
450
400
350
300
250
200
150
100
50
0
0 Hour
1 Hour
2 Hours
6 Hours
24 Hours
Day 5



En analyse multivariée la première cause de retard à l'apparition de l'effet antiplaquettaire est la prescription de morphine

Figure 3 Kinetics of Platelet Inhibition Over Time

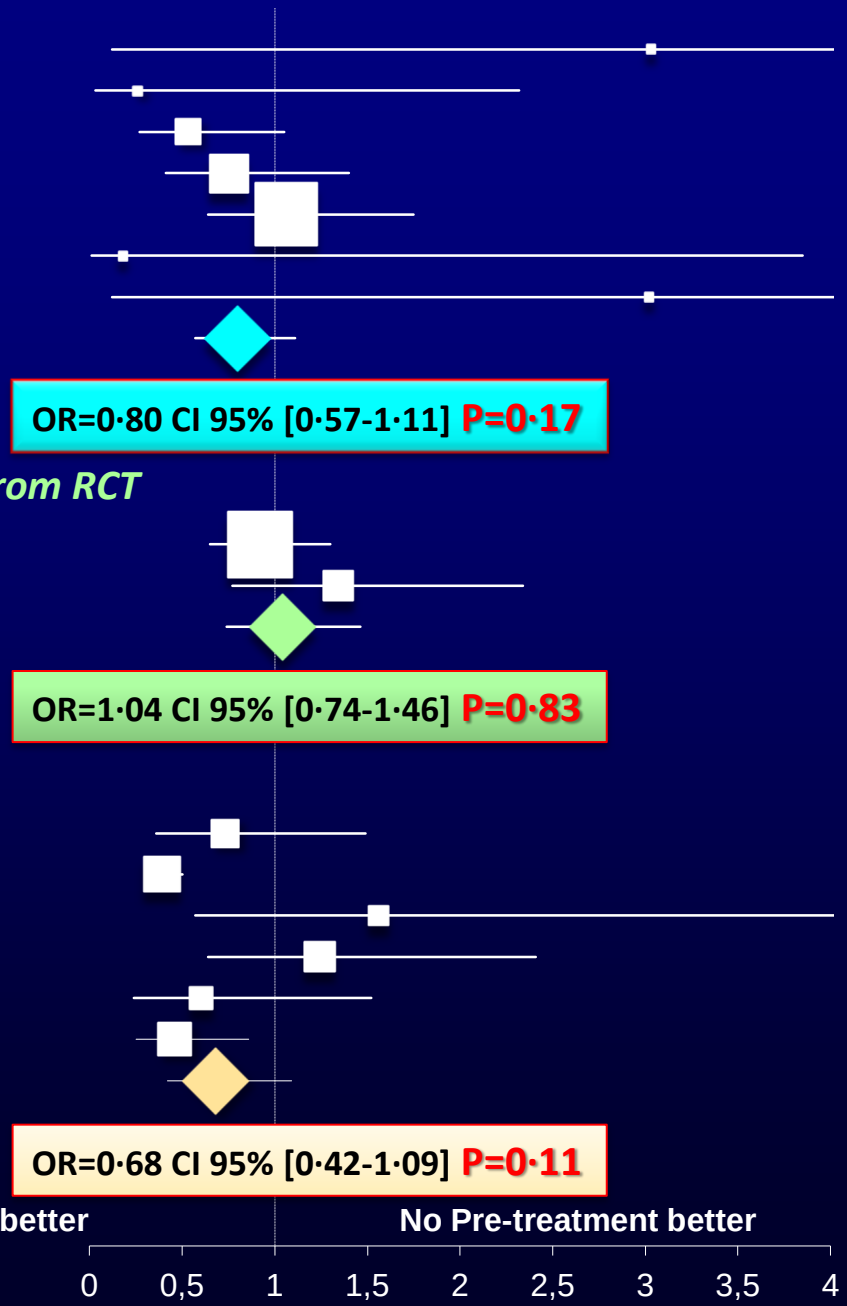
Parodi G et al Rapid study JACC 13


Platelet function test values (Units)
600
500
400
300
200
100
0
ARU
PRU
60 mg Prasugrel LD
360 mg Ticagrelor LD
Baseline
1 h
2 h
4 h
12 h

PCI meta-analysis

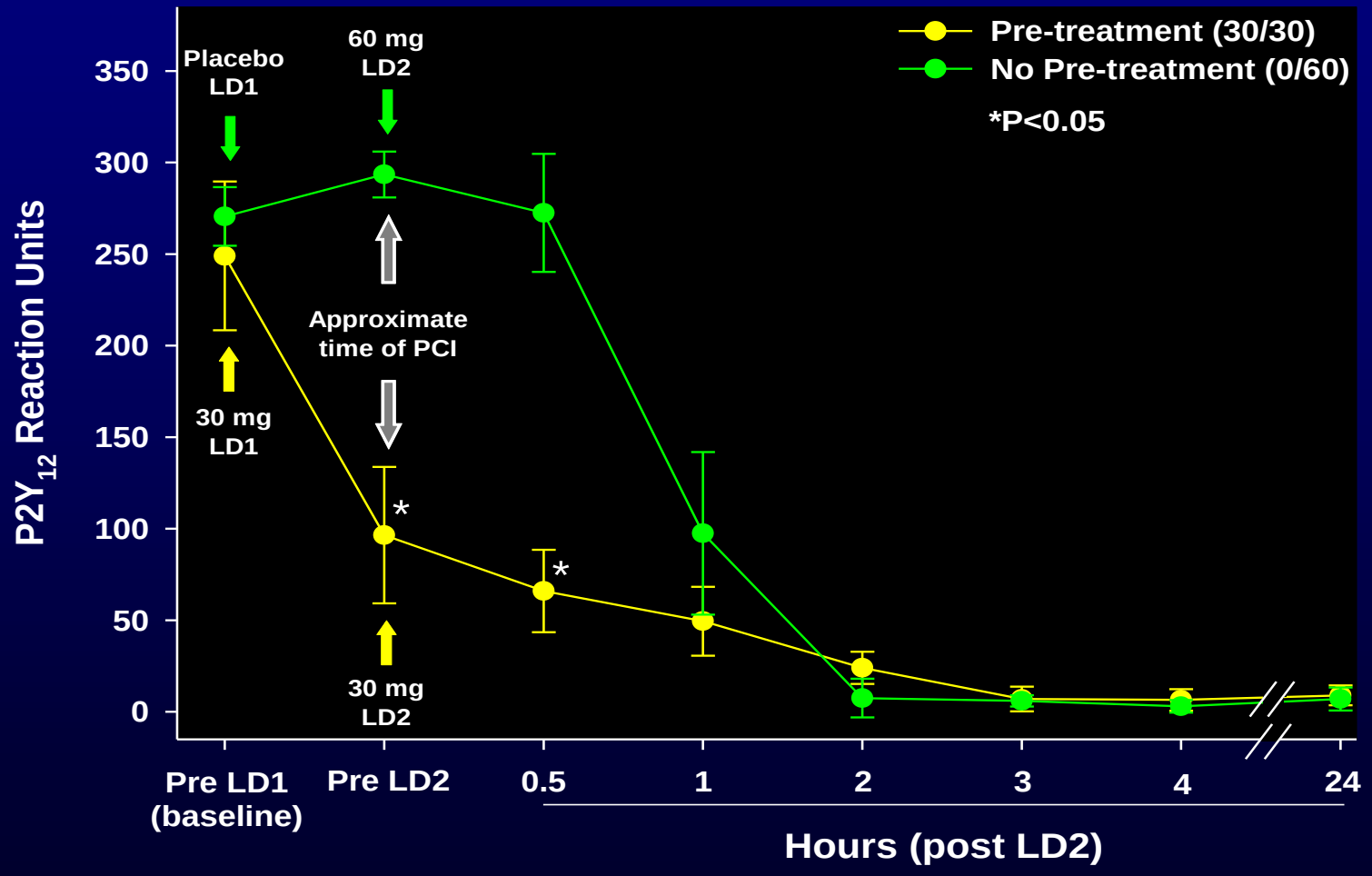
Death

	Events / Size, Clopidogrel Pretreatment	No Pretreat	OR [CI 95%]	Relative Weight [%]
Randomized CT				
ARMYDA5 Preload	1/204	0/205	3·03 [0·12-74·80]	1·0%
CIPAMI	1/164	4/171	0·26 [0·03-2·32]	2·2%
CLARITY PCI	13/933	24/930	0·53 [0·27-1·05]	23·2%
CREDO	18/1053	24/1063	0·75 [0·41-1·40]	28·3%
PCI CURE	32/1313	31/1345	1·06 [0·64-1·75]	43·1%
Davlouros et al.	0/103	2/96	0·18 [0·01-3·85]	1·2%
PRAGUE 8	1/513	0/515	3·02 [0·12-74·25]	1·0%
All *N=8,608*	66/4283	85/4325	0·80 [0·57-1·11]	100%
Observational from RCT				
ACUITY PCI	105/3511	49/1515	0·92 [0·65-1·30]	68·2%
REPLACE 2	114/5087	14/832	1·34 [0·77-2·34]	31·8%
All *N=10,945*	219/8598	63/2347	1·04 [0·74-1·46]	100%
Observational				
Amin et al.	13/923	19/990	0·73 [0·36-1·49]	16·2%
Dorler et al.	209/4879	110/1076	0·39 [0·31-0·50]	24·0%
Fefer et al.	12/217	6/166	1·56 [0·57-4·25]	11·9%
Feldman et al.	18/467	18/574	1·24 [0·64-2·41]	17·0%
Szuk et al.	6/1481	18/2679	0·60 [0·24-1·52]	12·9%
Chan et al.	76/4477	12/332	0·46 [0·25-0·86]	17·8%
All *N=18,261*	334/12444	183/5817	0·68 [0·42-1·09]	100%



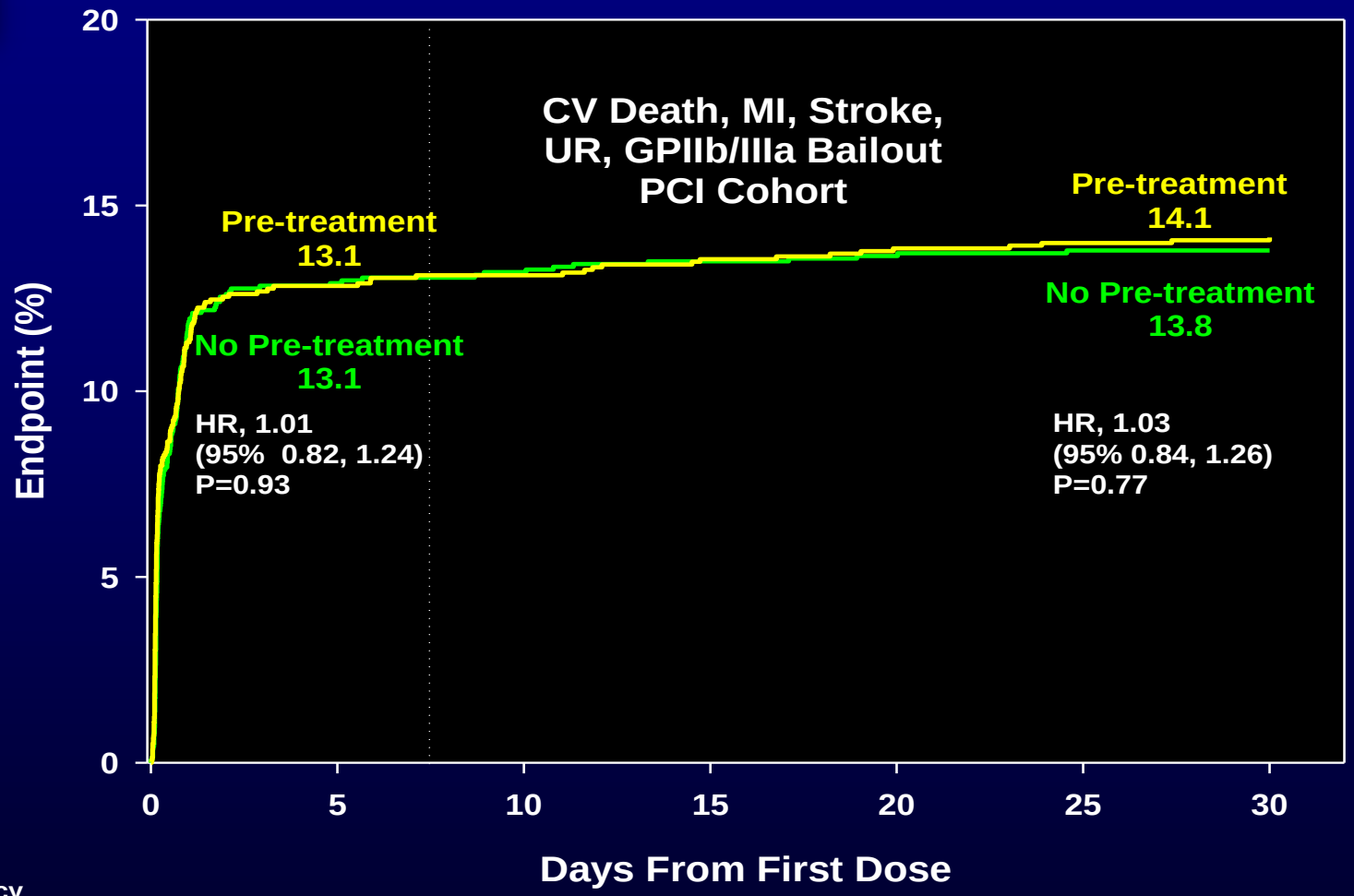
Bellemain-Appaix A et al. *JAMA* 2012;308:2507-2516

Pharmacodynamic Sub-Study



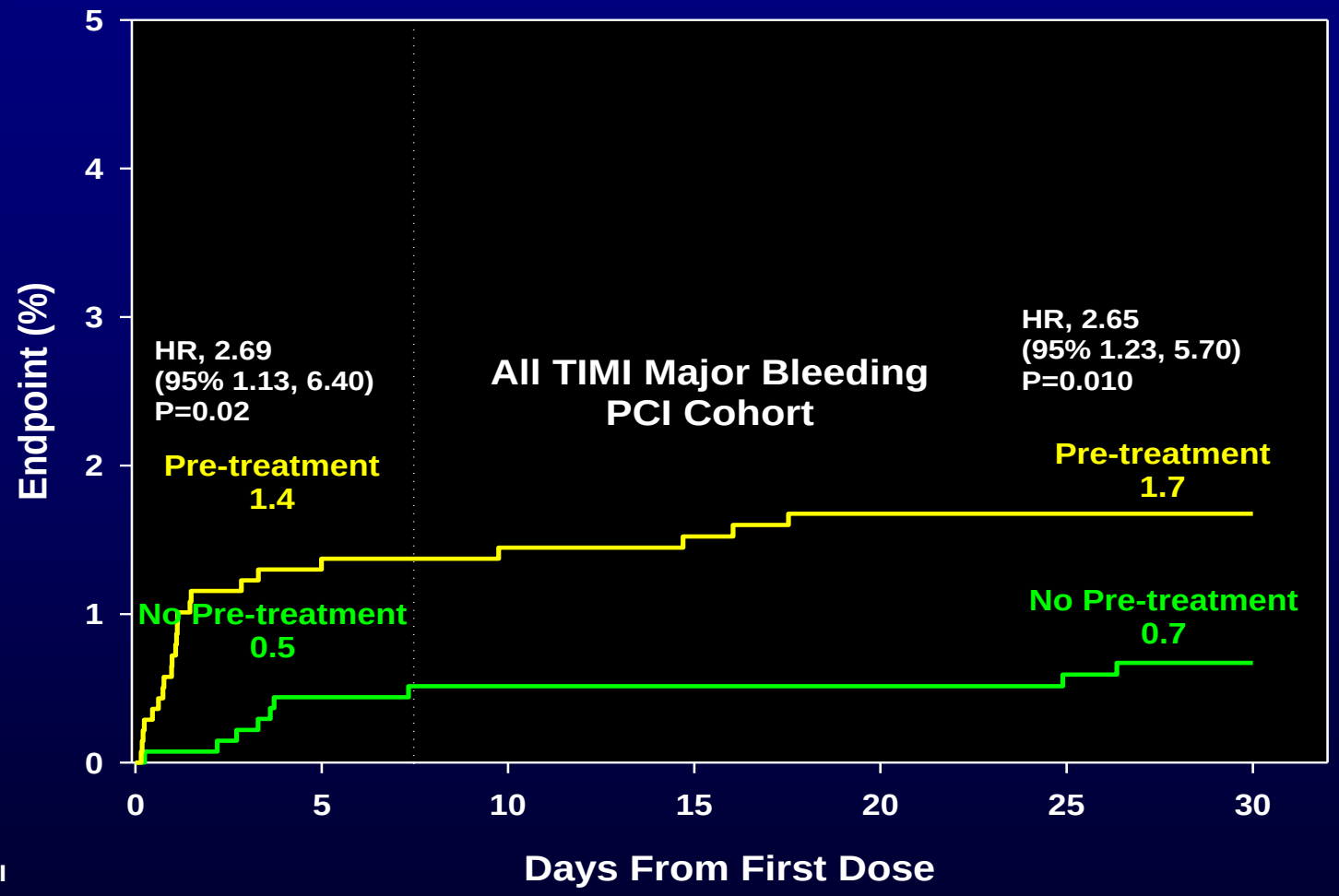
Data presented as median ± SEM. * p<0.05 relative to the No pre-treatment group. LD = loading dose.
Pretreatment=Prasugrel 30 mg/Prasugrel 30 mg; No Pre-treatment=Placebo/Prasugrel 60 mg

1° Efficacy Endpoint (PCI Patients)



No. at Risk, Efficacy End Point:							
No pre-treatment	1372	1191	1187	1183	1179	1177	1177
Pre-treatment	1389	1206	1202	1194	1189	1186	1172

All TIMI Major Bleeding (PCI Patients)



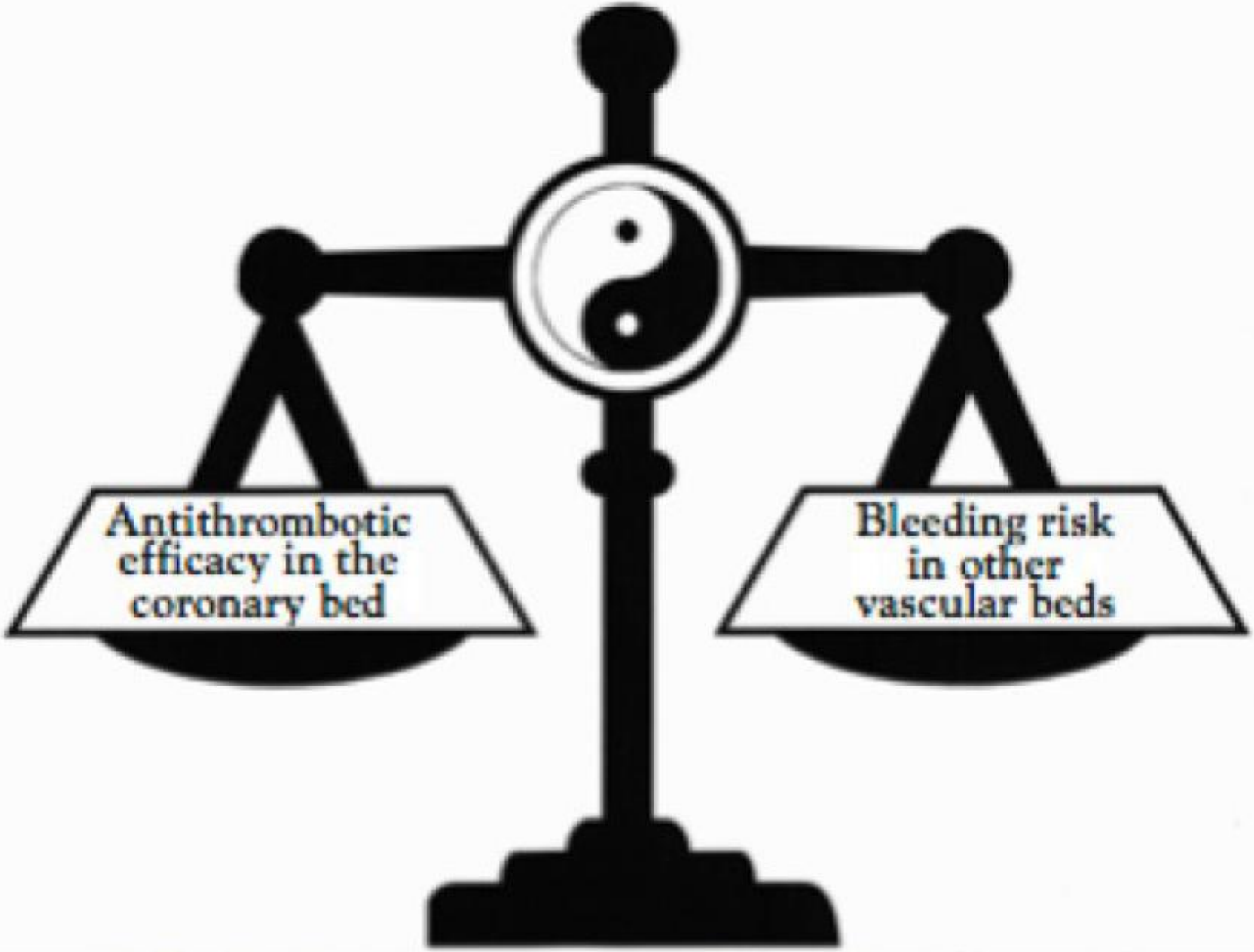
No. at Risk, All TIMI Major Bleeding:							
No pre-treatment	1372	1356	1302	1280	1272	1268	1249
Pre-treatment	1389	1364	1314	1293	1282	1280	1269

Comprendre le pourquoi du traitement antithrombotique dans le SCA

- Le pourquoi du traitement antiplaquettaire
- Le pourquoi du traitement anticoagulant
  - Le pourquoi de l’héparine
  - Le pourquoi de l’inhibition de la thrombine

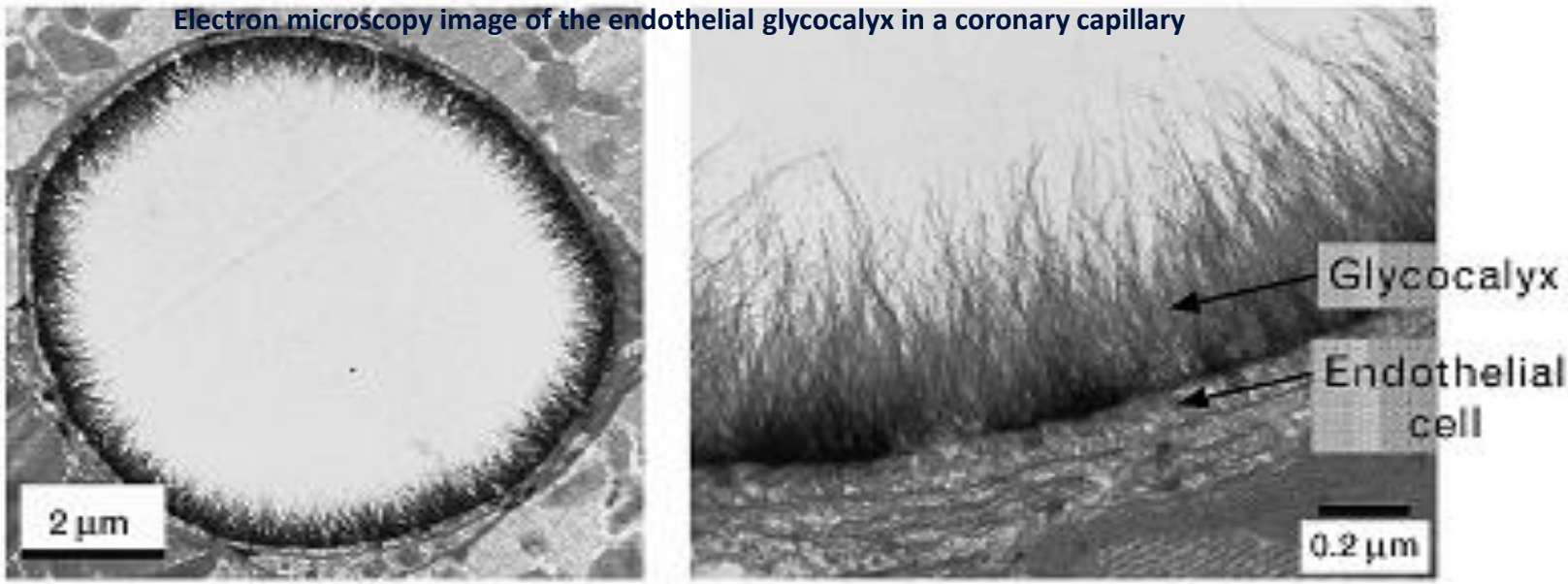
Comprendre le pourquoi du traitement antithrombotique dans le SCA

- Le pourquoi du traitement antiplaquettaire
- Le pourquoi du traitement anticoagulant
  - Le pourquoi de l’héparine
  - Le pourquoi de l’inhibition de la thrombine


Antithrombotic efficacy in the coronary bed
Bleeding risk in other vascular beds

The endothelial glycocalyx

- A negatively charged, organized mesh of membranous glycoproteins, proteoglycans, GAGs and plasma proteins
- Major components: Hyaluronic acid and heparan sulfate proteoglycans



Electron microscopy image of the endothelial glycocalyx in a coronary capillary

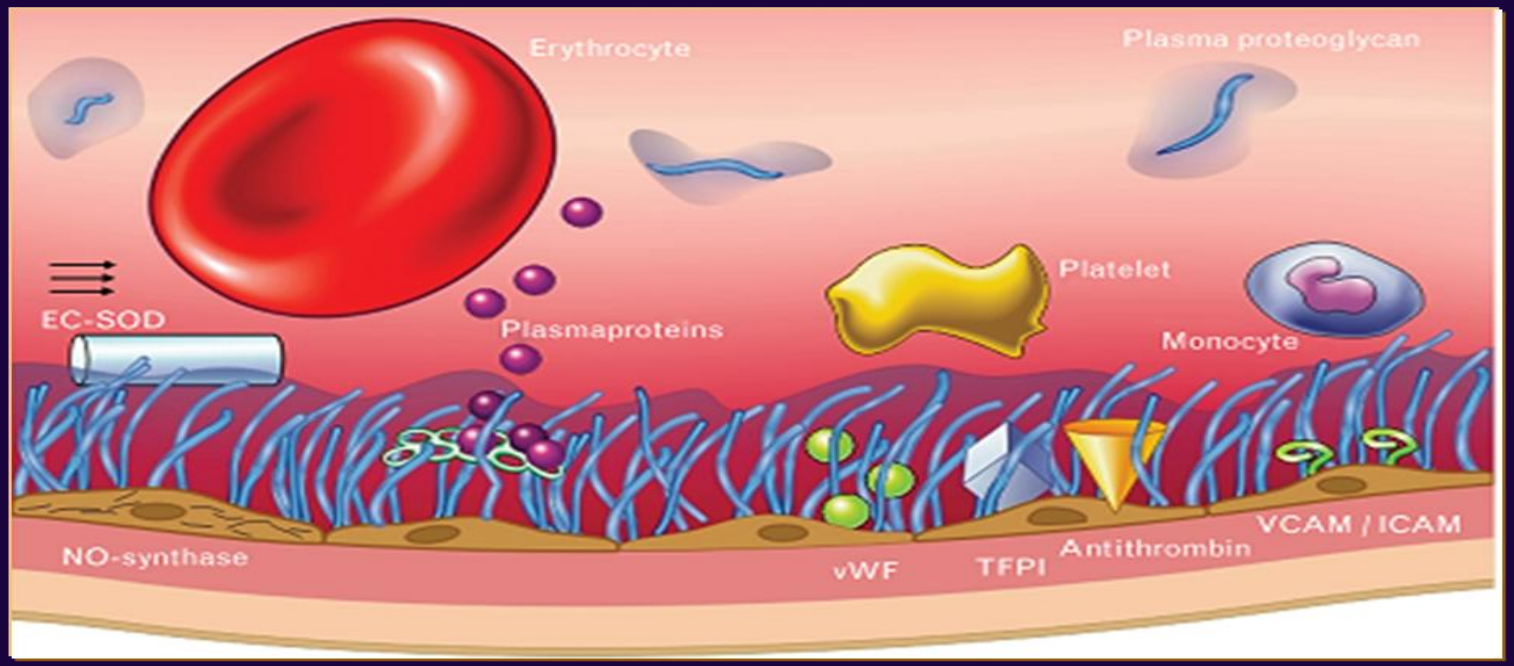
Nieuwdorp M et al. Curr Opin Lipidol 2005,16:507-511

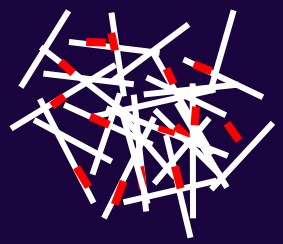
Endothelial glycocalyx

Physiological functions

Under physiological conditions

Roles: Barrier, storing compartment, coagulation/inflammation pathways, shear stress transducer





Glycocalyx

Endothelium

Subendothelial space

Endothelium
NO-synthesis,
superoxide dysmutation

Permeability
sieving barrier

Coagulation
Inhibition of platelet adhesion
Coagulation regulatory factors

Inflammation
Prevention of
Leukocyte
adhesion

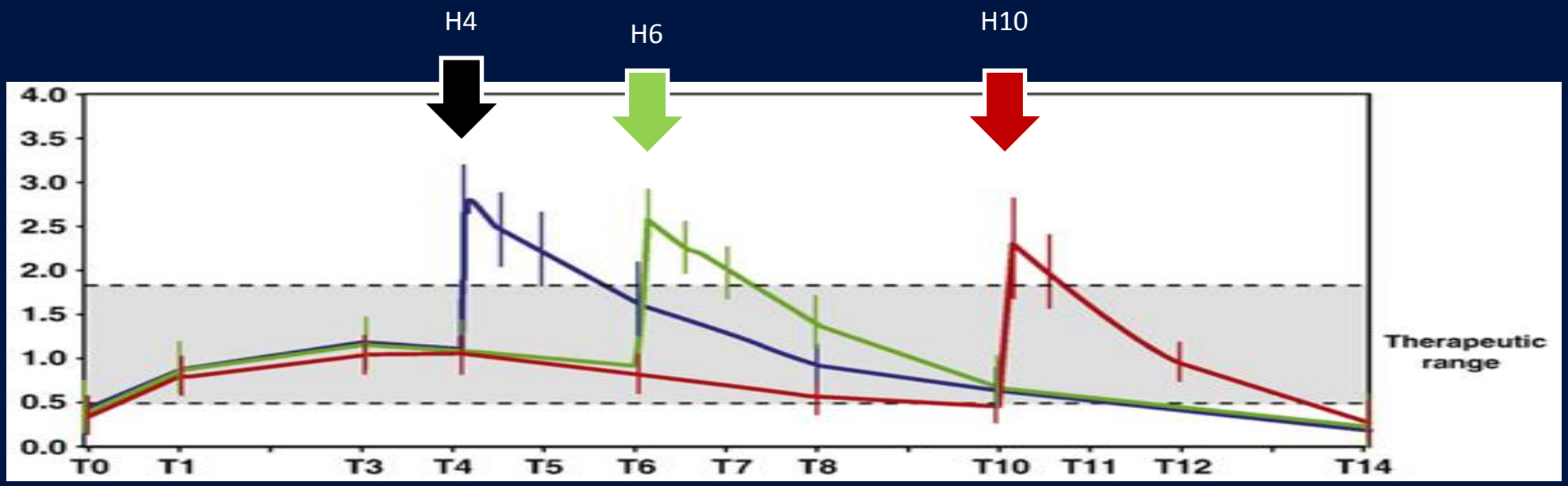
vasomotricity
Blood flow regulation

Nieuwdorp M et al. Curr Opin Lipidol 2005,16:507-511

STACKENOX - Results

Day 3 => Effect of 70/kg i.v. UFH bolus according to the timing of administration after SC enoxaparin in healthy subjects chronically treated with enoxaparin

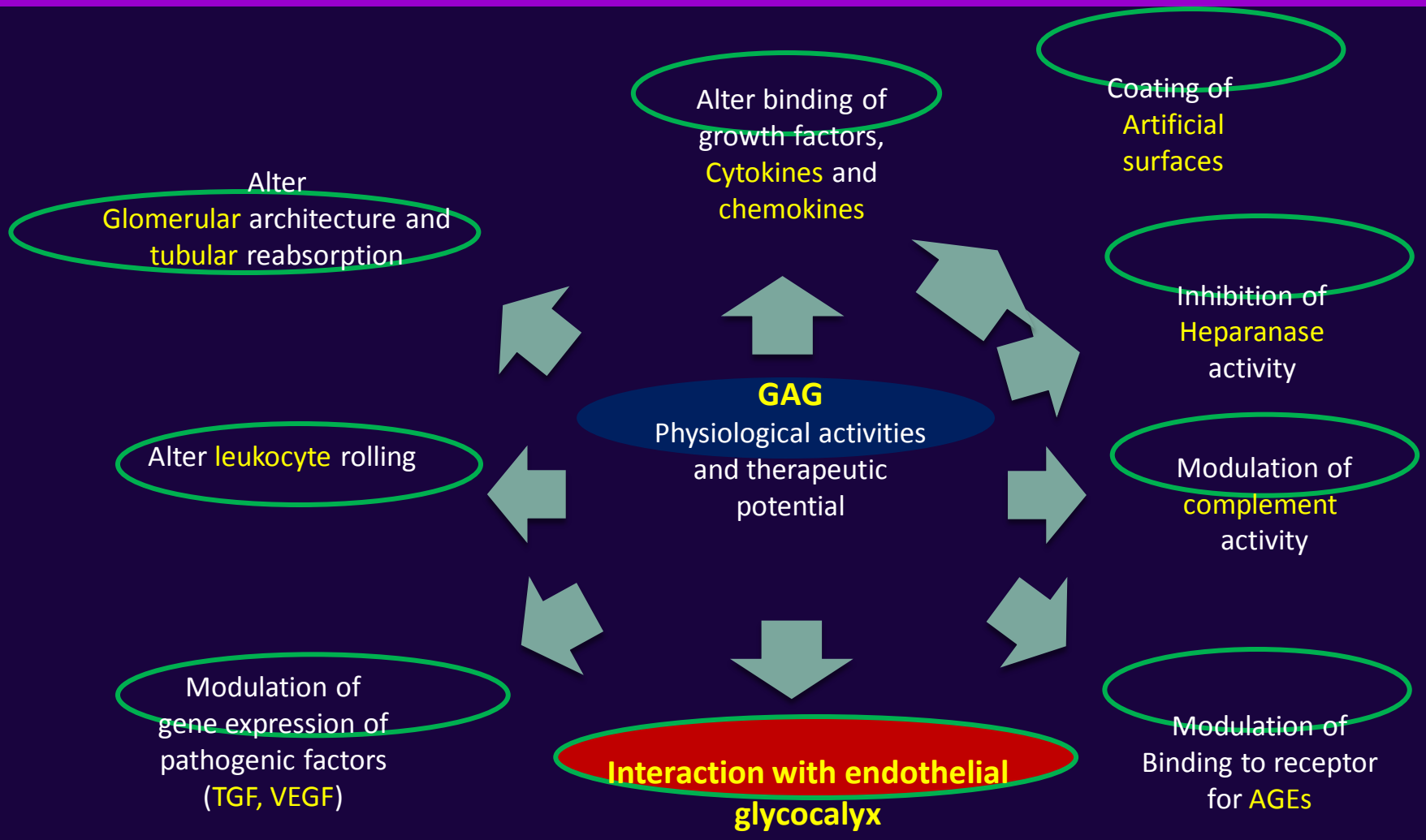
Effect on anti-Xa (median IU/mL)



Time from last enoxaparin injection (hours)

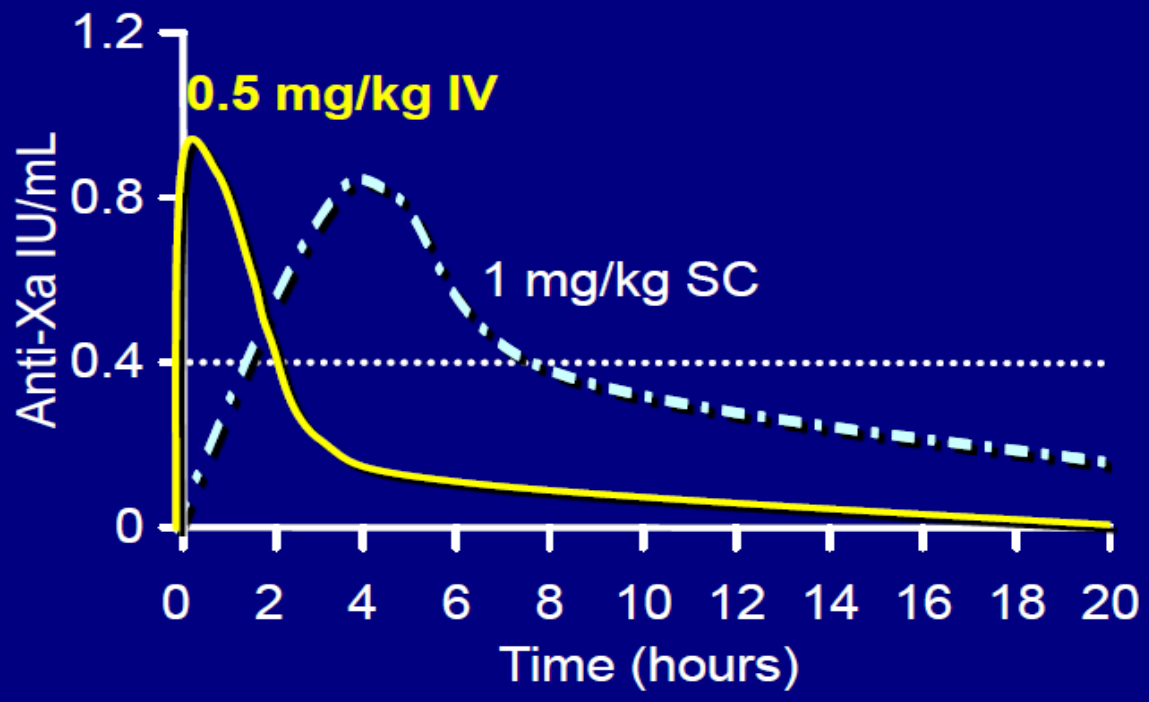
Drouet L et al Am Heart J. 2009 Aug;158(2):177-84.

GAGs - Beyond anticoagulation



Intravenous 0.5mg/kg Enoxaparin

PD experience



Sanchez-Pena P. Br J Clin Pharmacol. 2005;60:364-73.

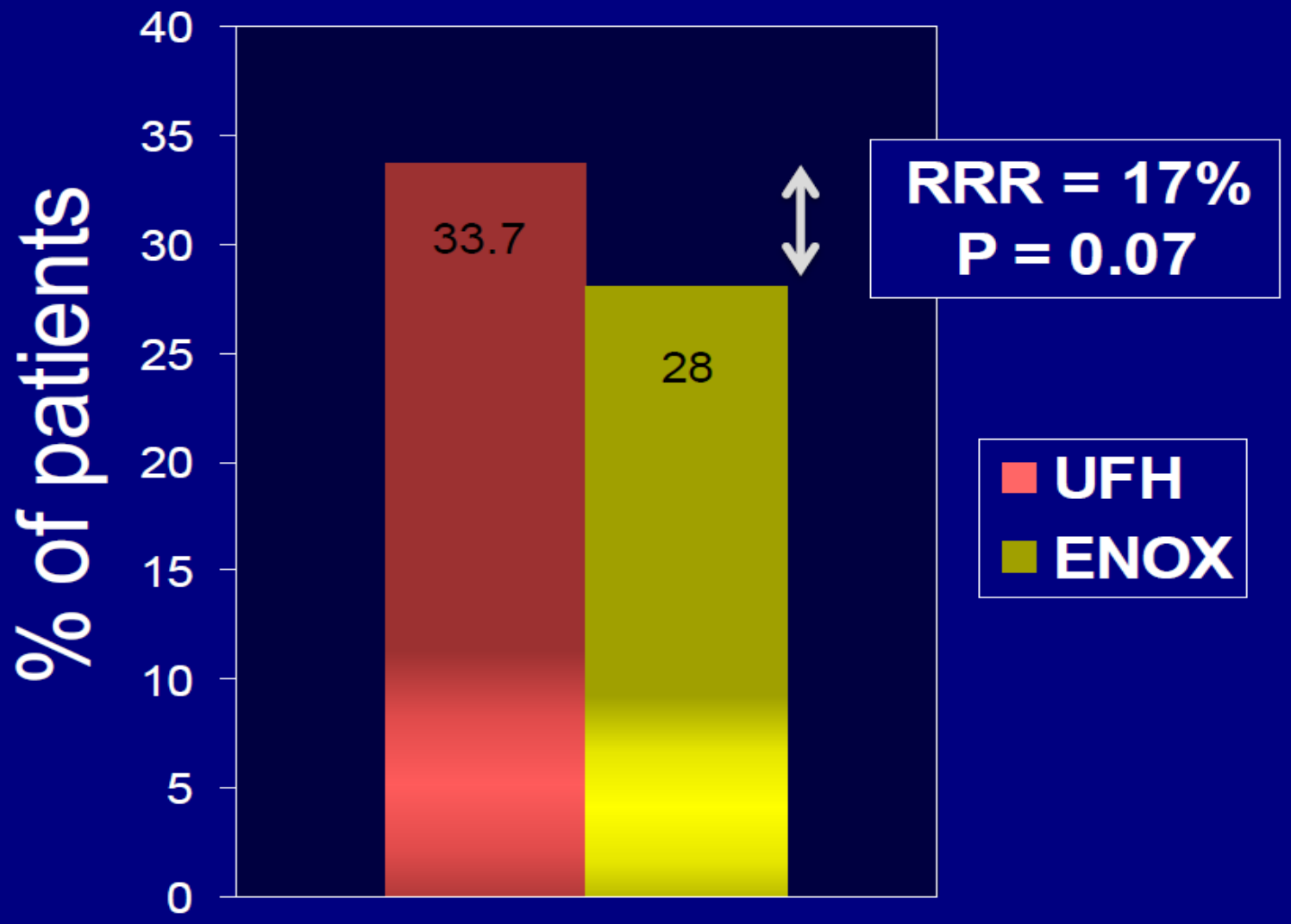
Clinical experience

- Choussat et al (elective PCI)
- Miller et al (ACS-PCI)
- Carnendran et al (elective PCI)
- STEEPLE (elective PCI)
- PROTECT –TIMI30 (ACS-PCI)
- Silvain et al (elective PCI)
- FINESSE (primary PCI)
- Brieger et al. (Primary PCI)

Choussat et al. JACC. 2002;40:1943-50.
Miller L. J Invasive Cardiol. 2002;14:247-50
Carnendran et al. J Invasive Cardiol. 2003;15:235-8.
Montalescot et al. N Engl J Med. 2006;355:1006-17.
Gibson et al. JACC. 2006;47:2364-2373
Silvain et al. JACC. 2010;55:617-25
Montalescot et al. JACC Cardiovasc Interv. 2010;3:203-12
Brieger et al. Catheter Cardiovasc Interv. 2010 [in press]

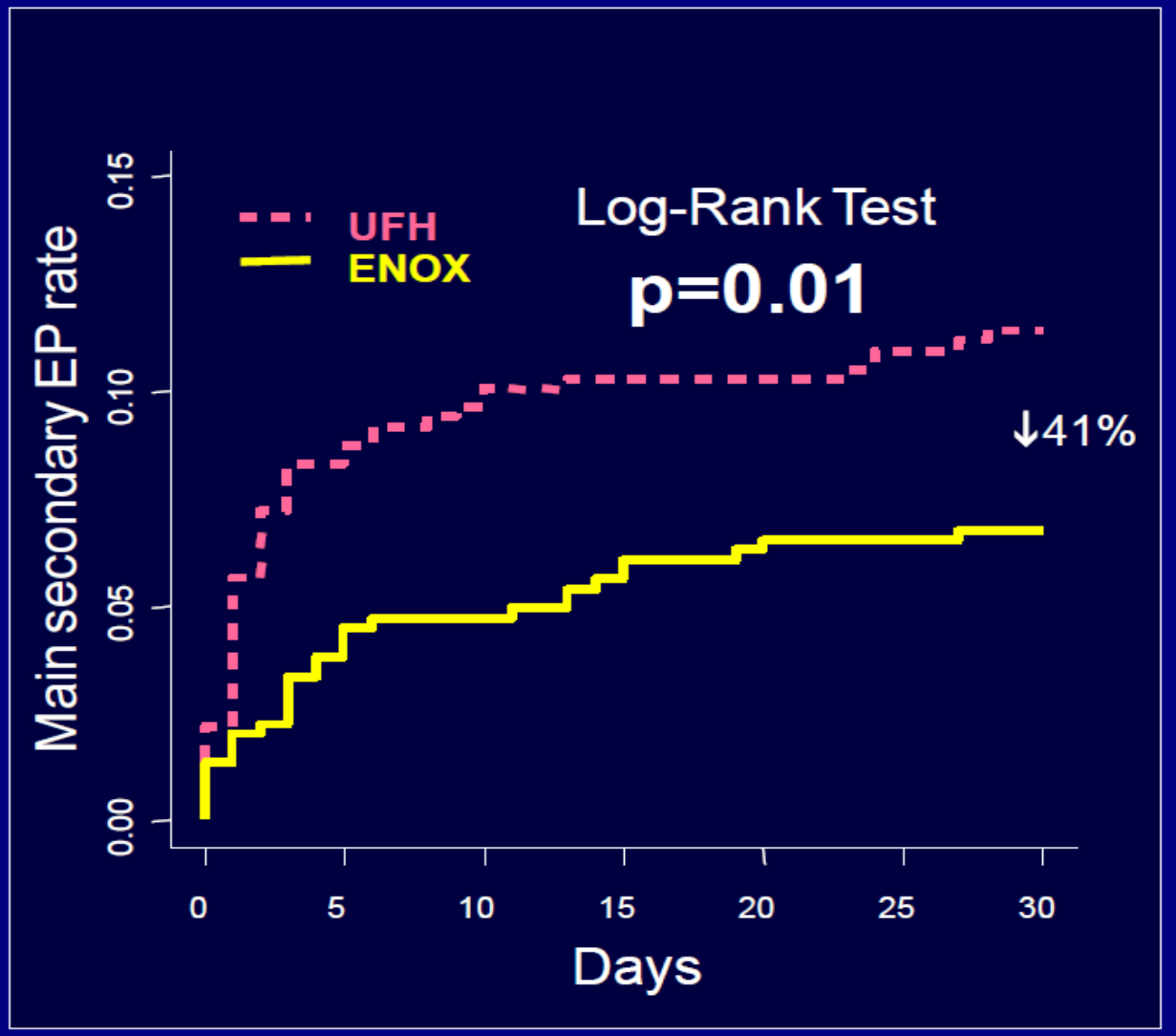
Primary Endpoint

Death, Complication of MI, Procedure Failure or Major Bleeding



Main Secondary Endpoint (ischemic)

Death, Recurrent MI/ACS or Urgent Revascularization

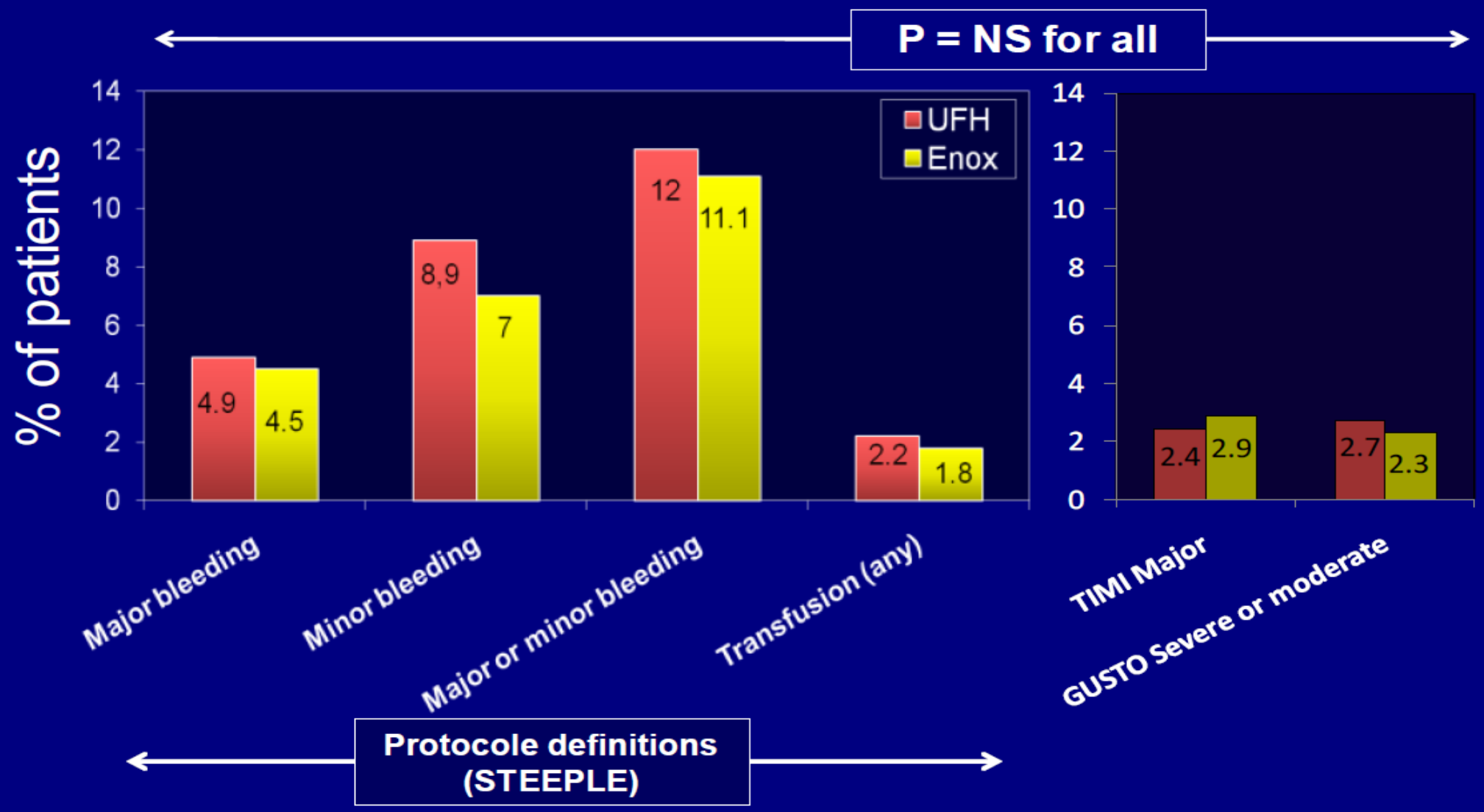


30d rate (%)

11.3%

6.7%

All Safety Endpoints



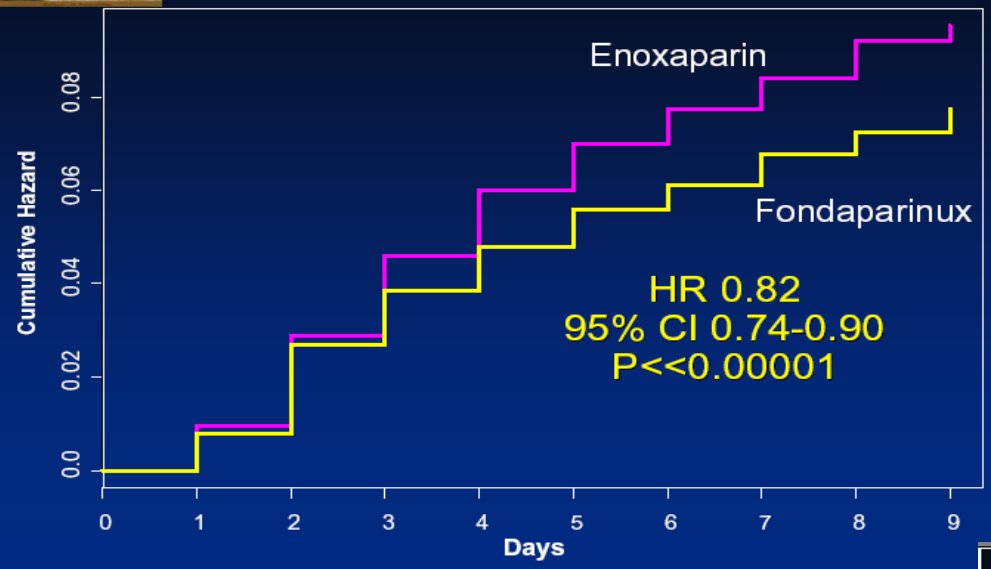
Quand l’angioplastie-stenting est réalisée sans héparine = augmentation des événements thrombotiques sur matériel et péri-procéduraux

les données cliniques :

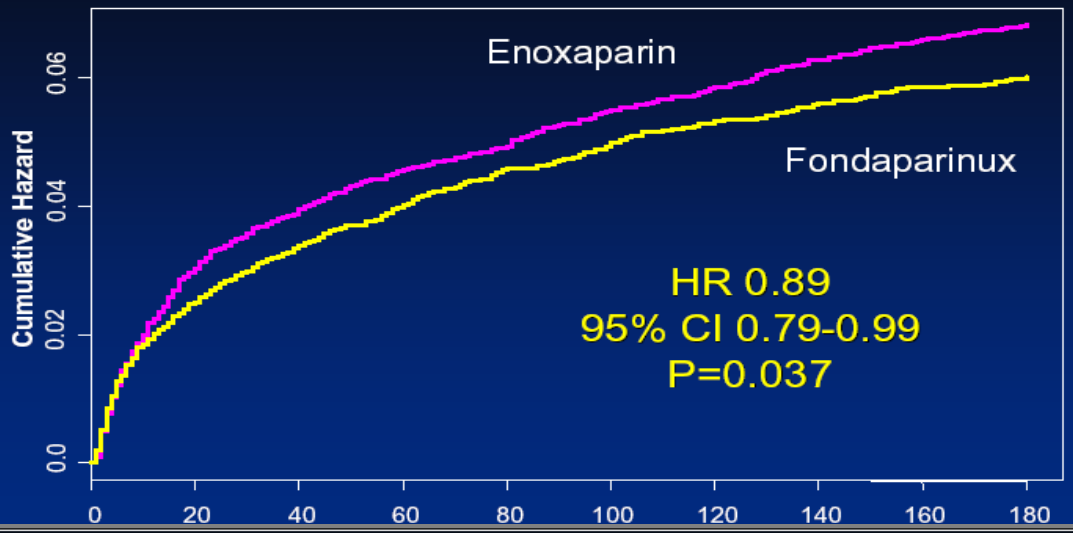
- Avec le fondaparinux (Oasis 5 et 6) amendement
- Avec la bivalirudine (Horizon et EuroMax)
- Avec l’otamixaban (TAO)

Mais pas avec l’enoxaparine (Essence, Atoll)

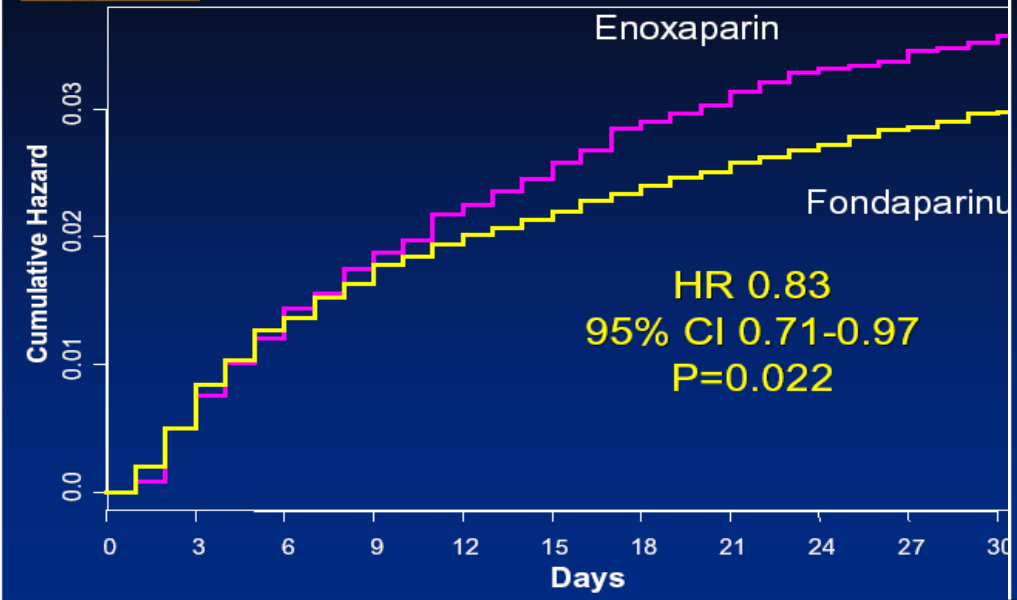
Efficacy-Safety Balance
Death/MI/RI/Maj Bleed: Day 9



Mortality at 6 Months



Mortality: Day 30



Efficacy at 6 Months

	Enox	Fonda	P value
Death/MI/RI	13.1%	12.1%	0.055
Death/MI	11.2%	10.3%	0.036
Death	6.3%	5.6%	0.037
MI	6.3%	6.0%	0.33
Strokes	1.6%	1.3%	0.029
Death/MI/Stroke	12.3%	11.1%	0.005

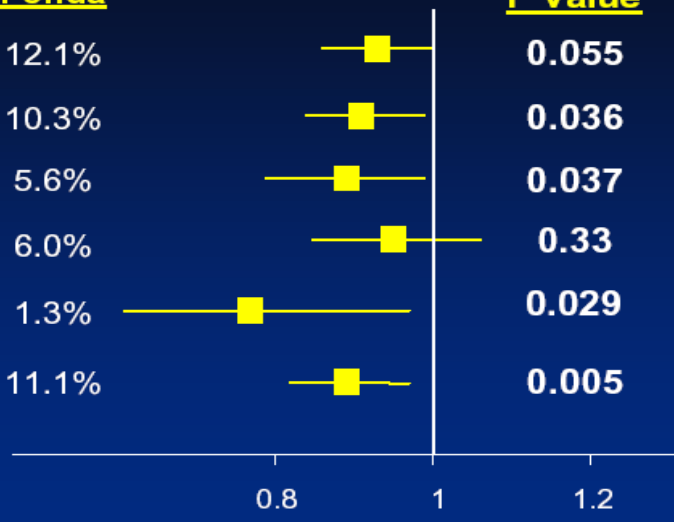


Table 3. Treatments, Complications, and Outcomes among Patients Undergoing Percutaneous Coronary Intervention (PCI) within the First Eight Days after Randomization.*

Variable	Enoxaparin (N=3104)	Fondaparinux (N=3135)	Relative Risk (95% CI)	P Value
	no. of events (% of patients)			
Concomitant antithrombotic drugs				
Unfractionated heparin	1724 (55.5)	651 (20.8)		
Glycoprotein IIb/IIIa inhibitor	1273 (41.0)	1308 (41.7)		
Thienopyridines	2317 (74.6)	2348 (74.9)		
Complications involving the vascular access site				
Any complication	251 (8.1)	103 (3.3)	0.41 (0.33–0.51)	<0.001
Pseudoaneurysm	49 (1.6)	31 (1.0)	0.63 (0.40–0.98)	
Large hematoma	138 (4.4)	50 (1.6)	0.36 (0.26–0.49)	
PCI-related coronary complication†				
Any complication	268 (8.6)	299 (9.5)	1.11 (0.94–1.29)	0.21
Abrupt closure, new thrombus with reduced flow, dissection, or no reflow	161 (5.2)	188 (6.0)	1.16 (0.94–1.42)	
Catheter-related thrombus not resulting in clinical complications‡	3 (0.1)	9 (0.3)	2.99 (0.81–11.04)	0.08
All catheter-related thrombi‡	8 (0.4)	29 (0.9)	3.59 (1.64–7.84)	0.001

OASIS 5 NEJM 2006

Besoin d'un minimum d'héparine au moment de la procédure

- In Atoll, the rate of guidewire or catheter thrombosis was extremely low and similar (1 and 1) in the arm receiving 0.5mg/KG iv bolus enoxaparin or UFH

- In TAO, the rate of guidewire or catheter thrombosis was lower with otamixaban. But the patients received an additional use of HNF for anticoagulation of the material at the time of PCI

Montalescot G et al Lancet 2011; 378 : 693–703, Steg G, et JAMA. 2013;310(11):1145-1155

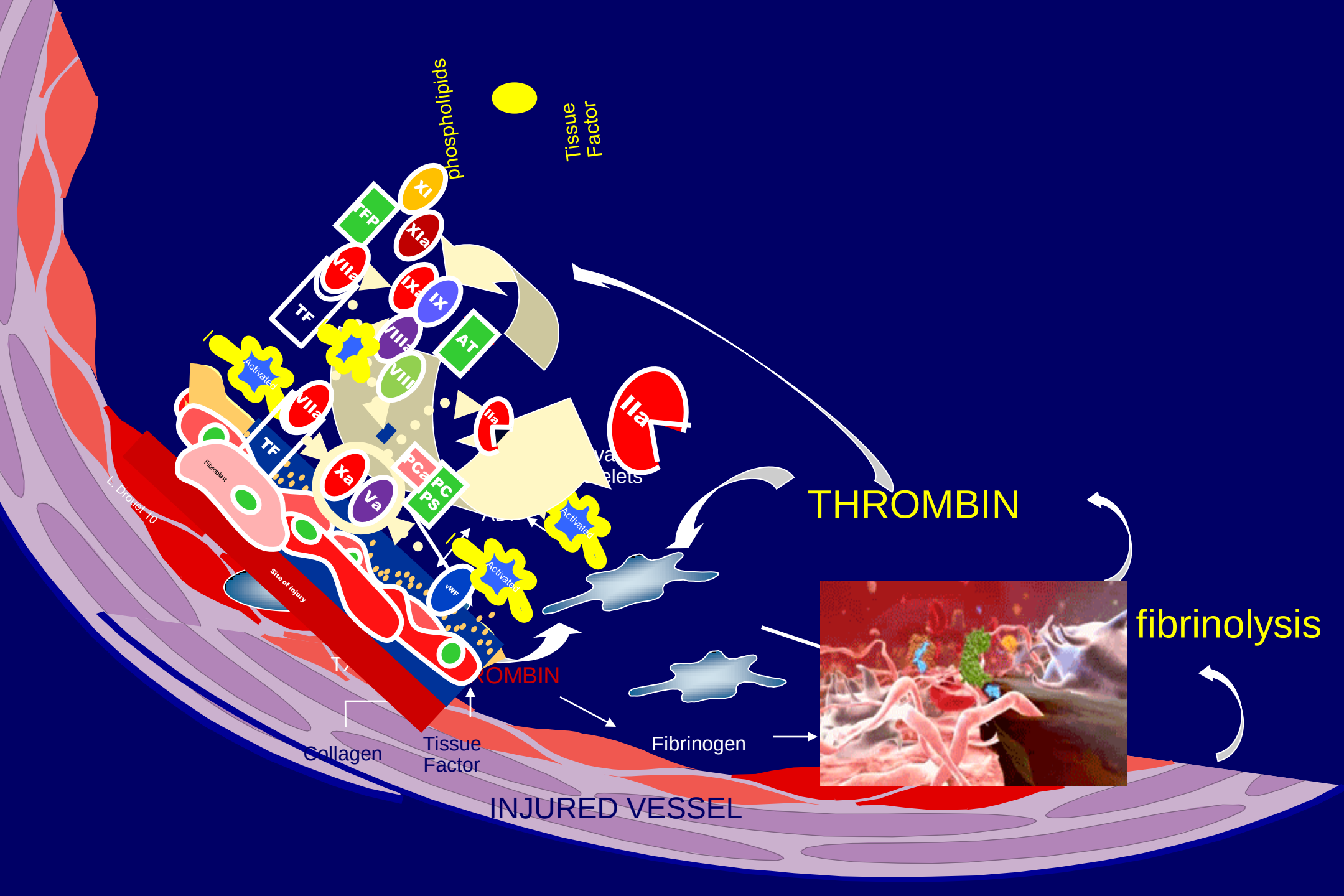
Quand l’angioplastie-stenting est réalisée sans héparine = augmentation des événements thrombotiques sur matériel et péri-procéduraux

les hypothèses physiopath :

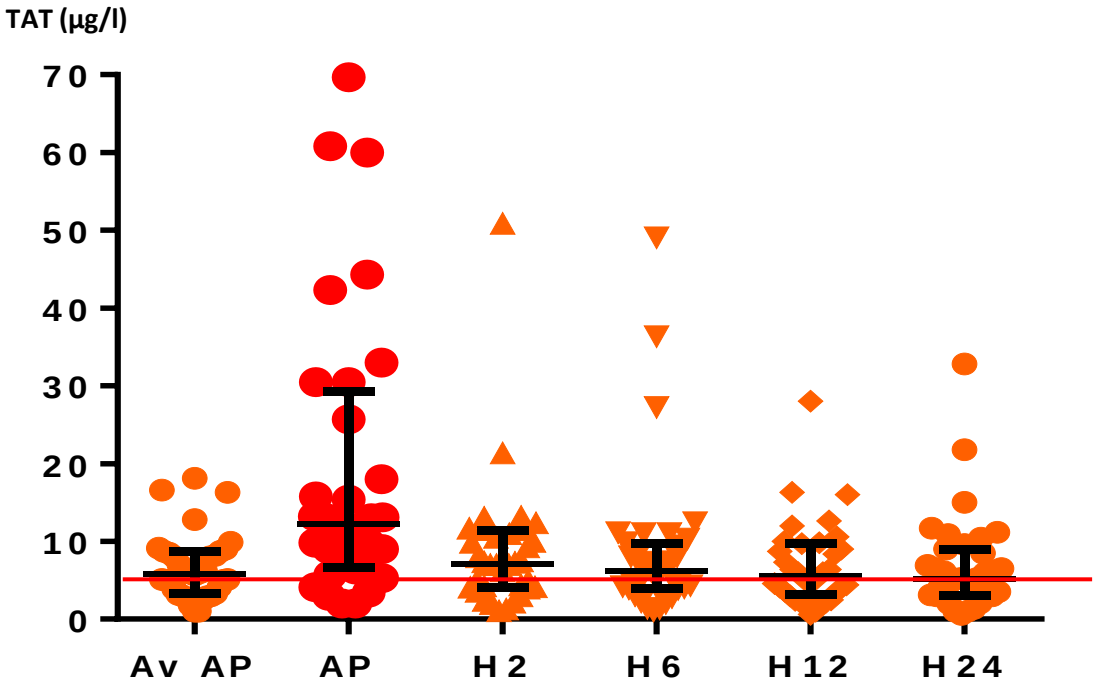
- Effet de surface des glycanes

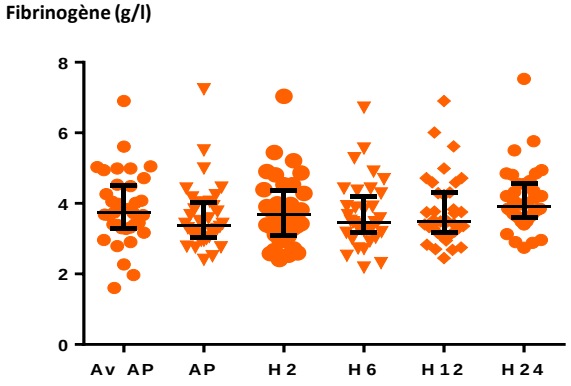
Comprendre le pourquoi du traitement antithrombotique dans le SCA

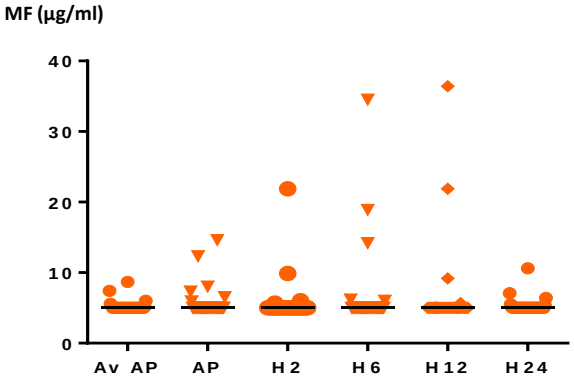
- Le pourquoi du traitement antiplaquettaire
- Le pourquoi du traitement anticoagulant
  - Le pourquoi de l’héparine
  - Le pourquoi de l’inhibition de la thrombine

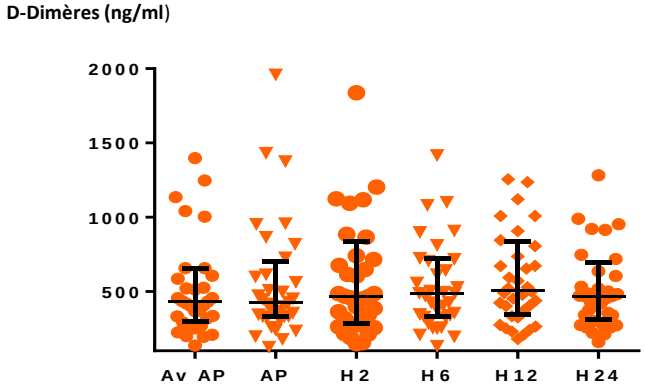

phospholipids
Tissue Factor
XI
XIa
TFP
VIIa
IXa
IX
TF
AT
VIII
VIIIa
Activated
VIIa
TF
IIa
IIa
Xa
Va
PCa
PC
PS
vWF
Activated
Activated
Fibroblast
L. Drouet 10
Site of injury
THROMBIN
Collagen
Tissue Factor
Fibrinogen
INJURED VESSEL
fibrinolysis

Cinétique des marqueurs plasmatiques

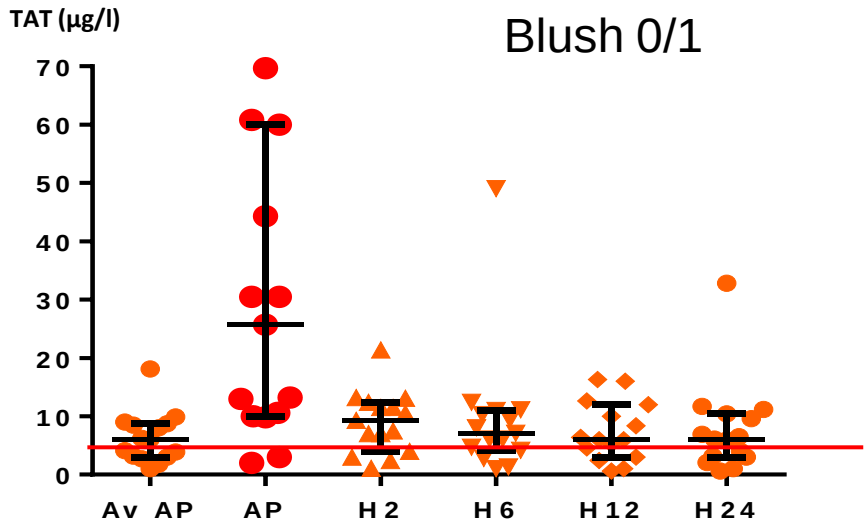


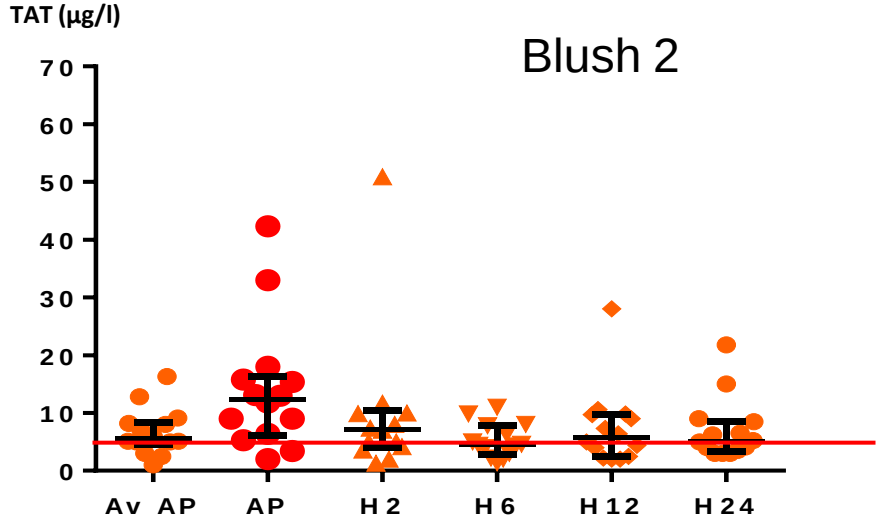


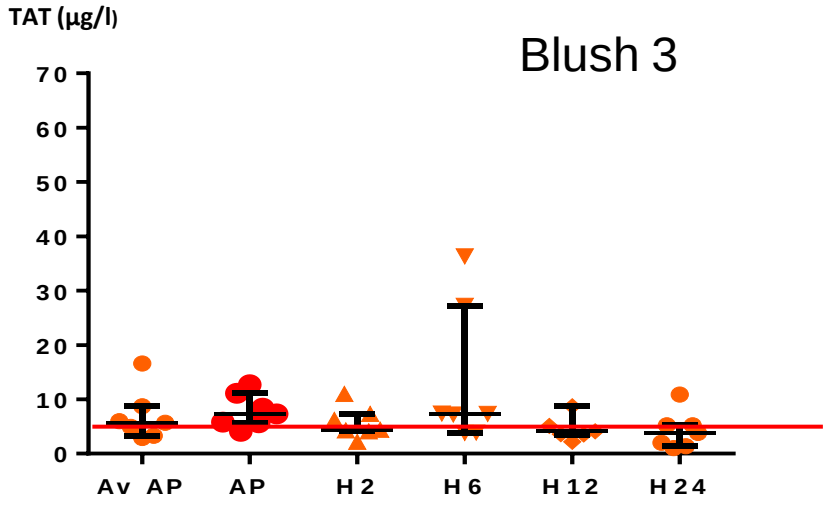


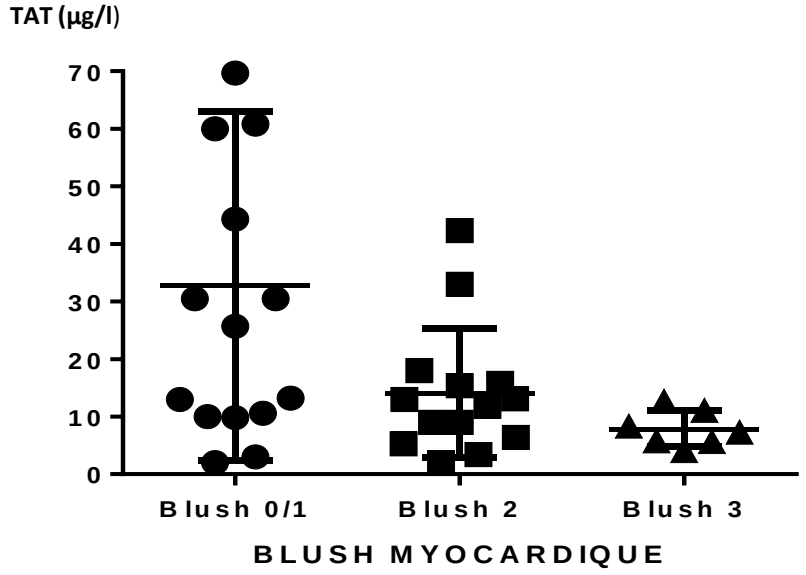


Cinétique des TAT selon le blush myocardique

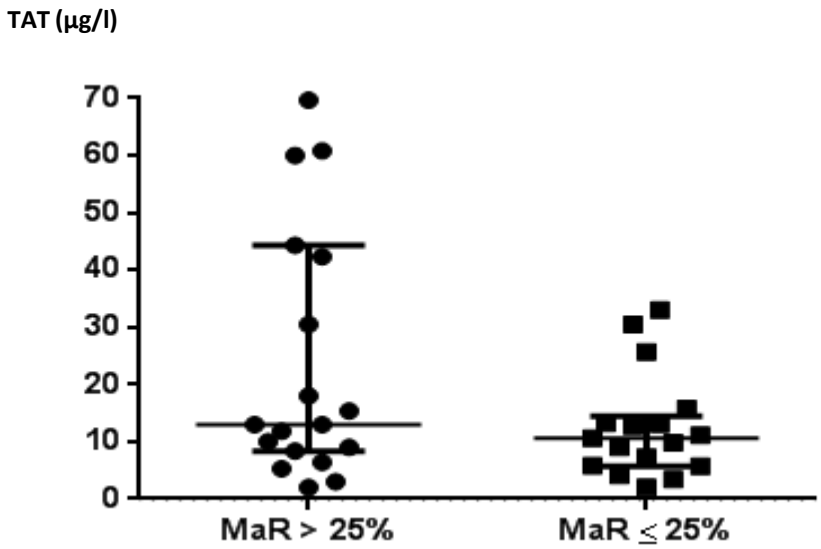


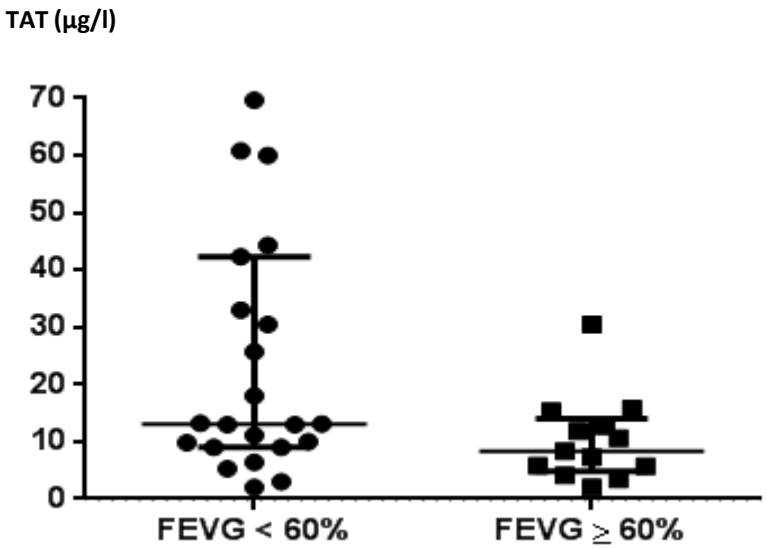




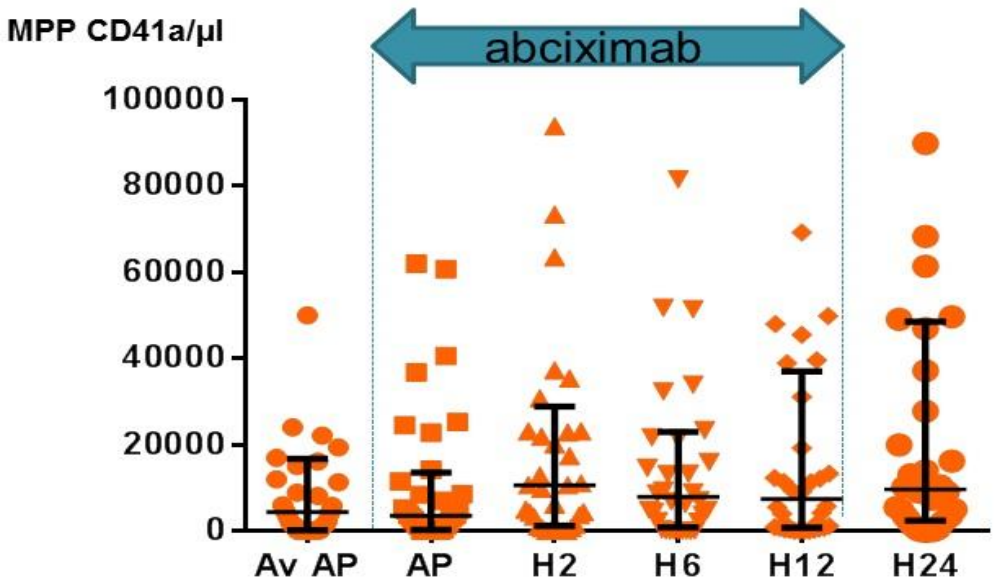


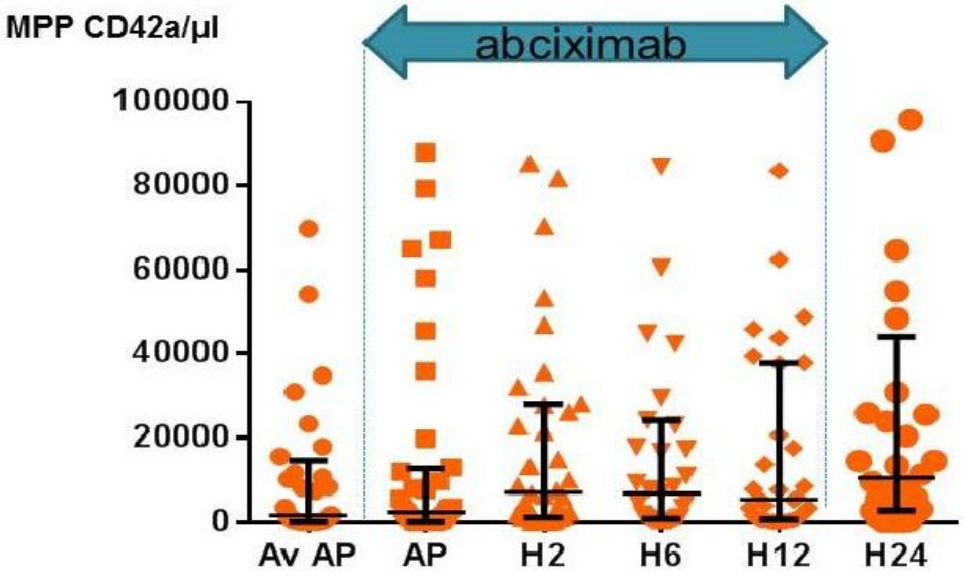
Burst de thrombine et paramètres de dommages myocardiques

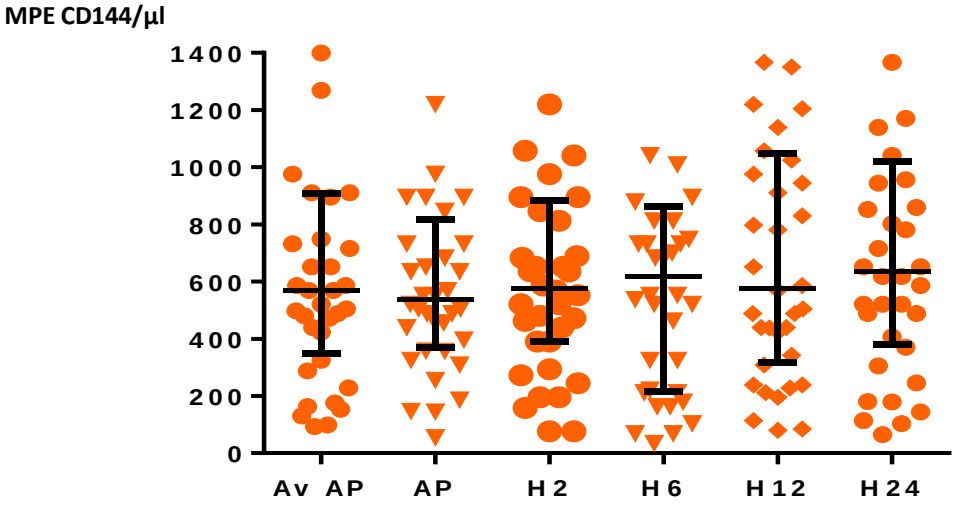




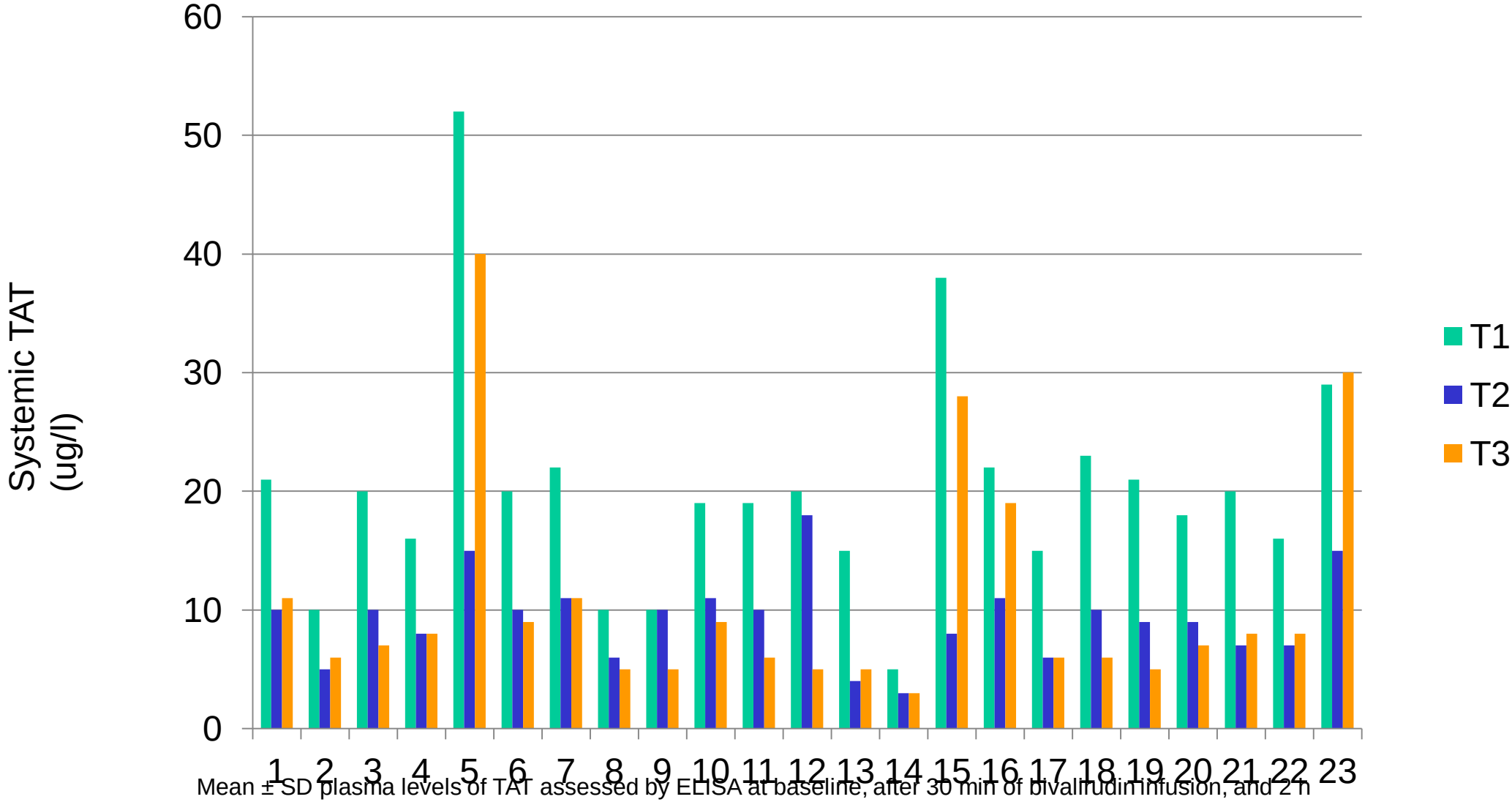
Cinétique des microparticules







Thrombin is inhibited by antithrombin. In vivo thrombin generation results is inactive proteinase/inhibitor complexes (TAT complex). The ex-vivo measrument of these complexes is an indicator of thrombin generation.

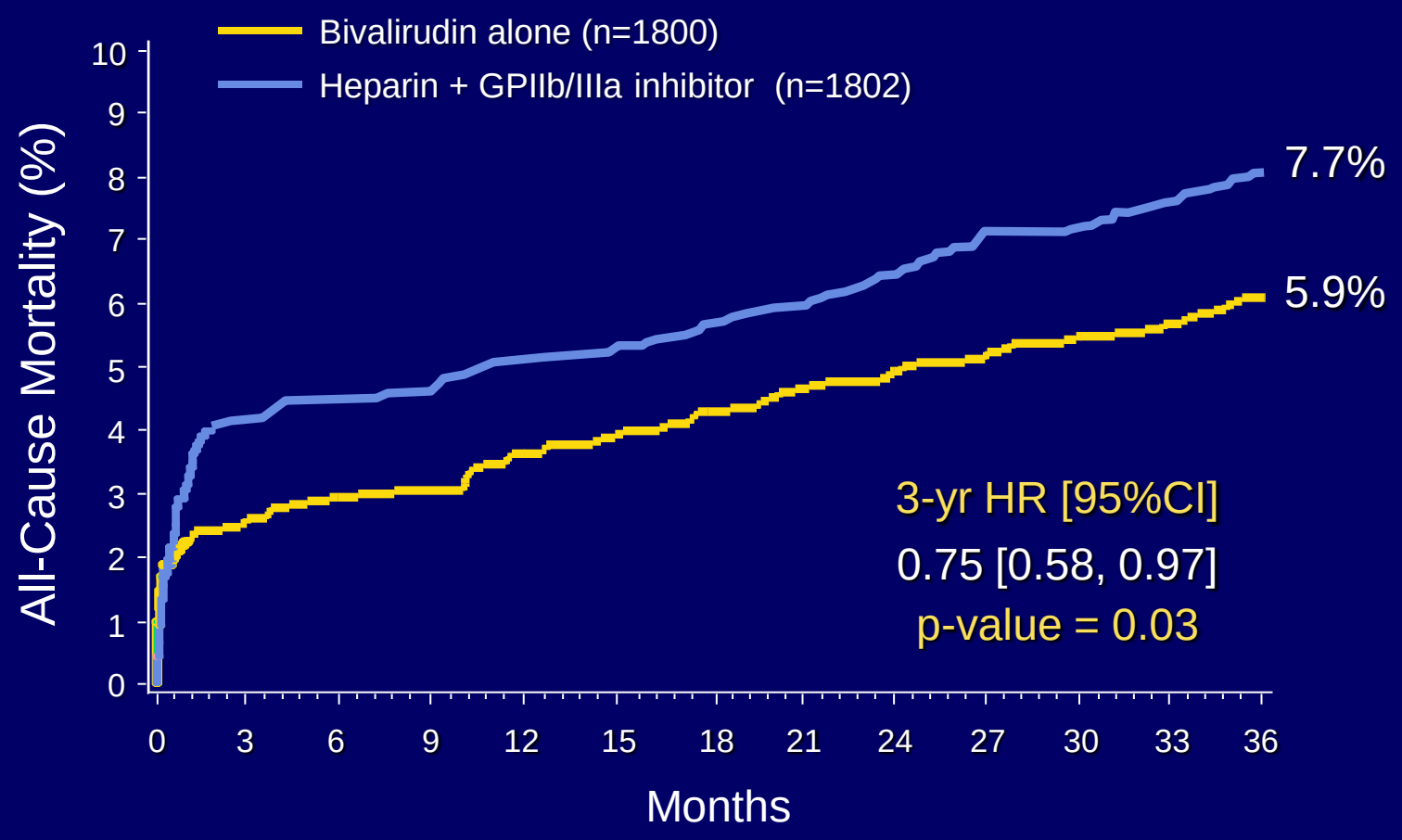


Mean ± SD plasma levels of TAT assessed by ELISA at baseline, after 30 min of bivalirudin infusion, and 2 h POST-termination of the infusion

Carey Kimmelstiel et al *Circ Cardiovasc Interv. 2011*

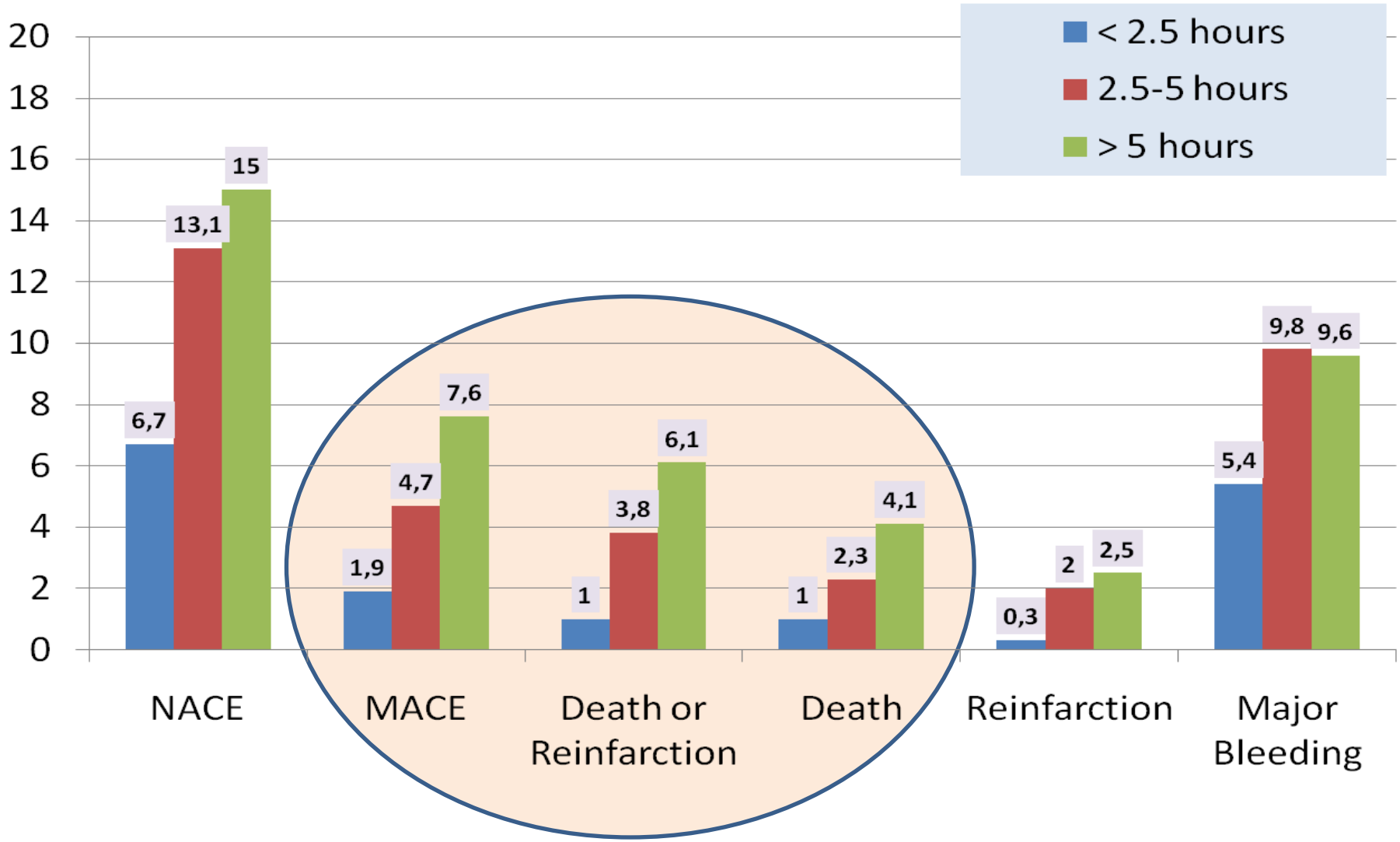
HORIZONS-AMI

- Three-year all cause mortality

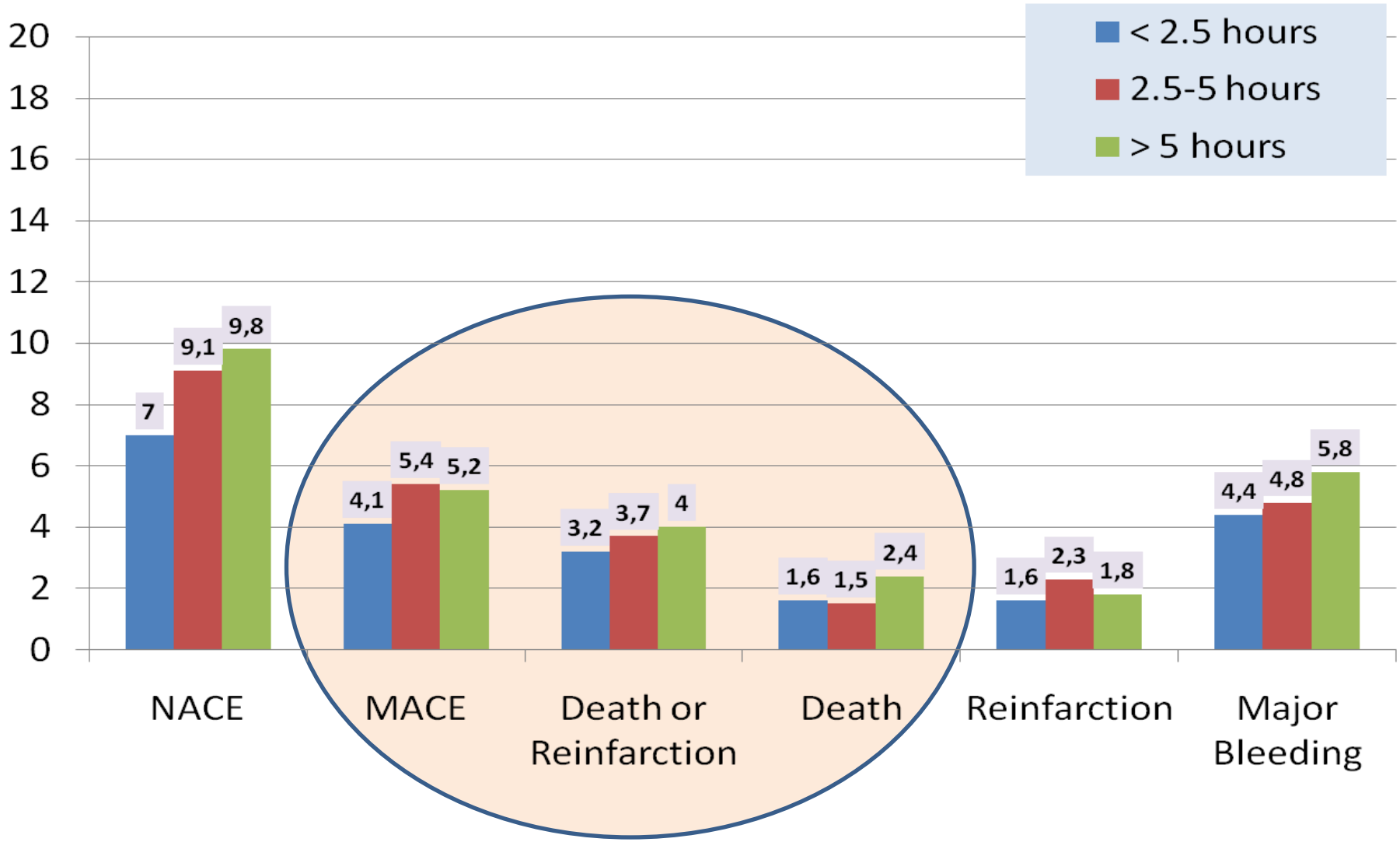


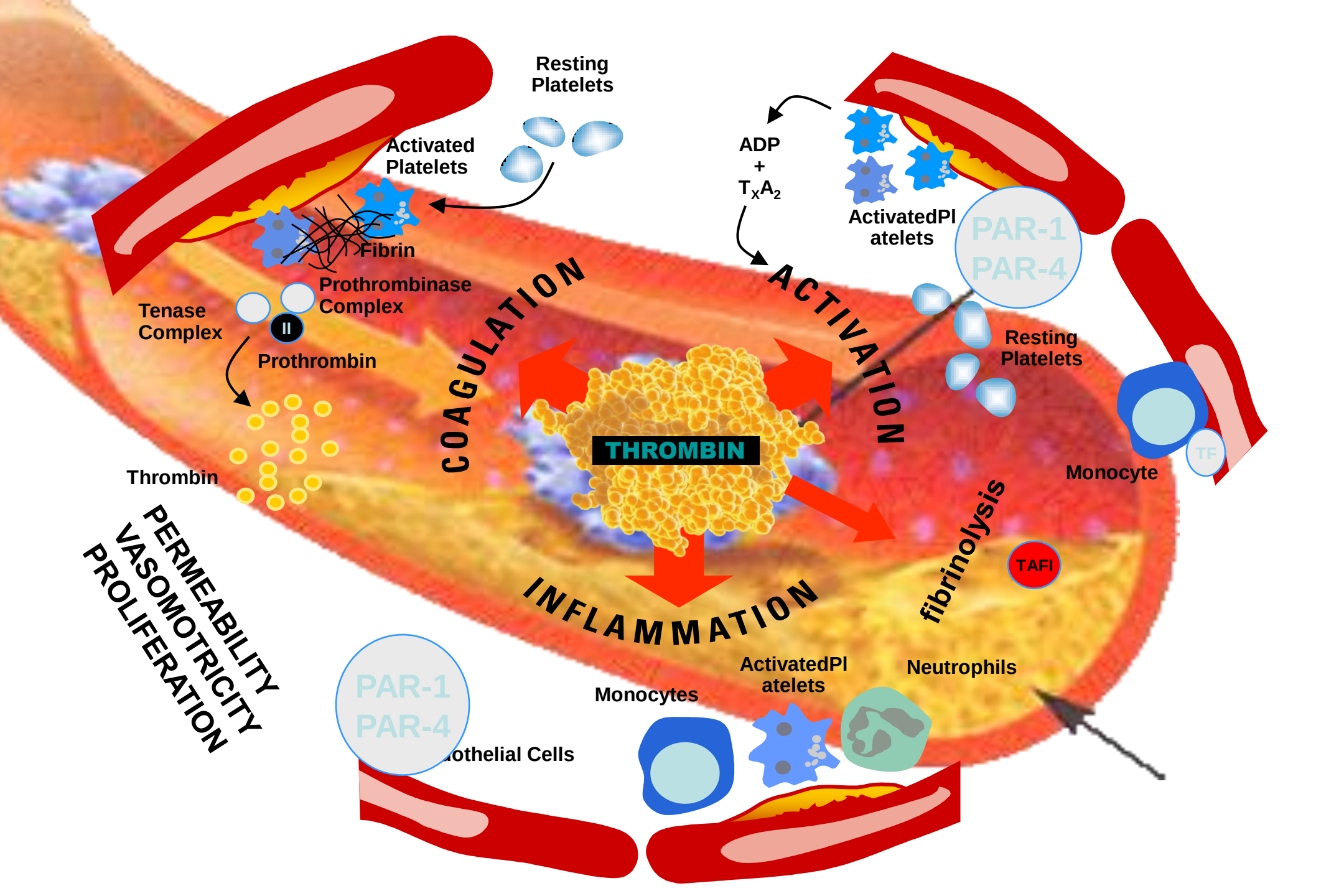
Stone GW et al. *Lancet* 2011;377:2193-204

UFH + GPI vs. Time: 30-Day Event Rate



Bivalirudin vs. Time: 30-Day Event Rate




Resting
Platelets
Activated
Platelets
Fibrin
Prothrombinase
Complex
Tenase
Complex
II
Prothrombin
Thrombin
ADP
+
T_XA_2
ActivatedPl
atelets
PAR-1
PAR-4
Resting
Platelets
COAGULATION
ACTIVATION
THROMBIN
Monocyte
TF
fibrinolysis
TAFI
INFLAMMATION
PERMEABILITY
VASOMOTRICITY
PROLIFERATION
PAR-1
PAR-4
ActivatedPl
atelets
Neutrophils
Monocytes
othelial Cells