DPC

SRLF

Hémorragies

"Anticoagulants et nouveaux anticoagulants: mécanismes d'action"

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Paris
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université PARIS DIDEROT PARIS 7

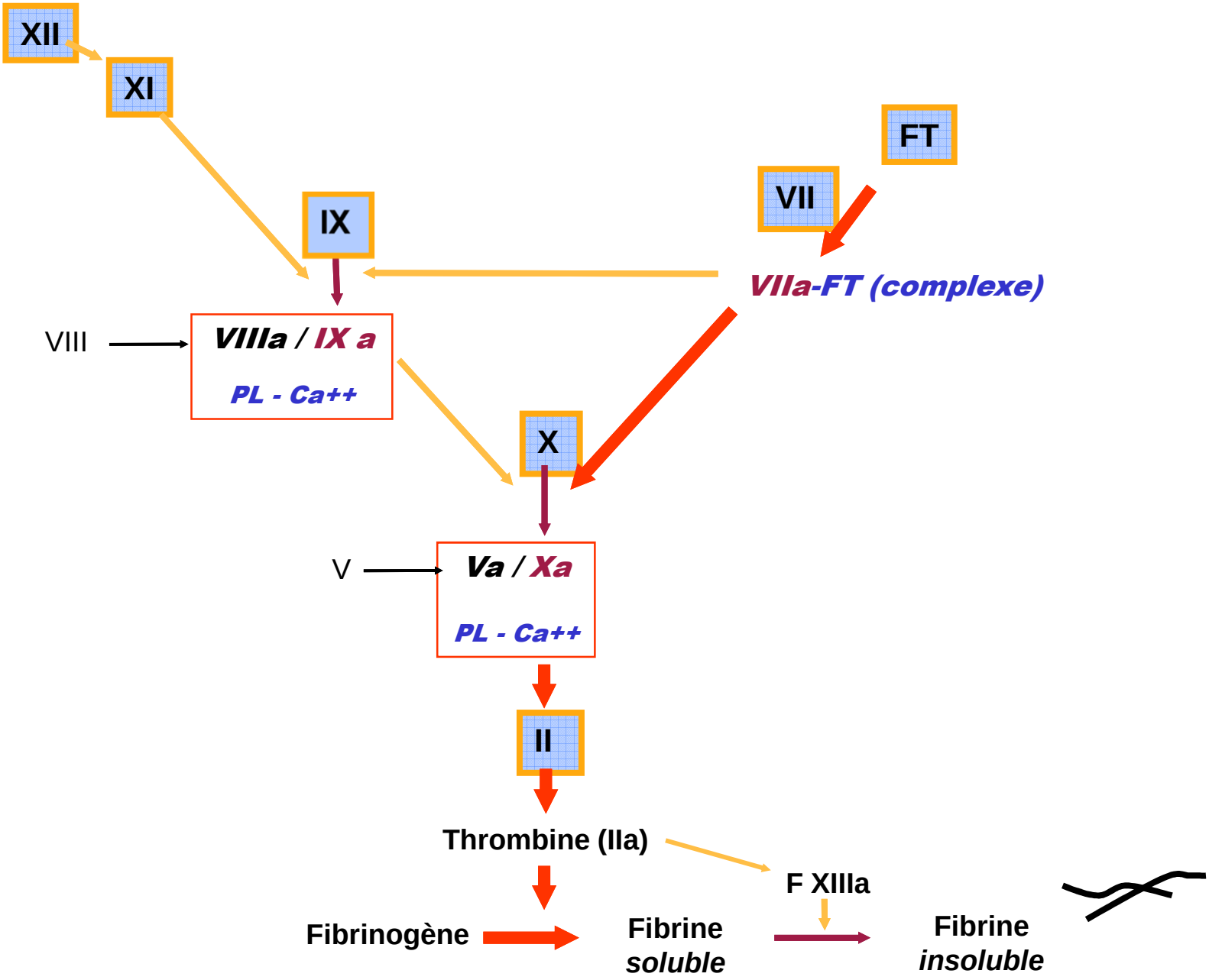
IVS

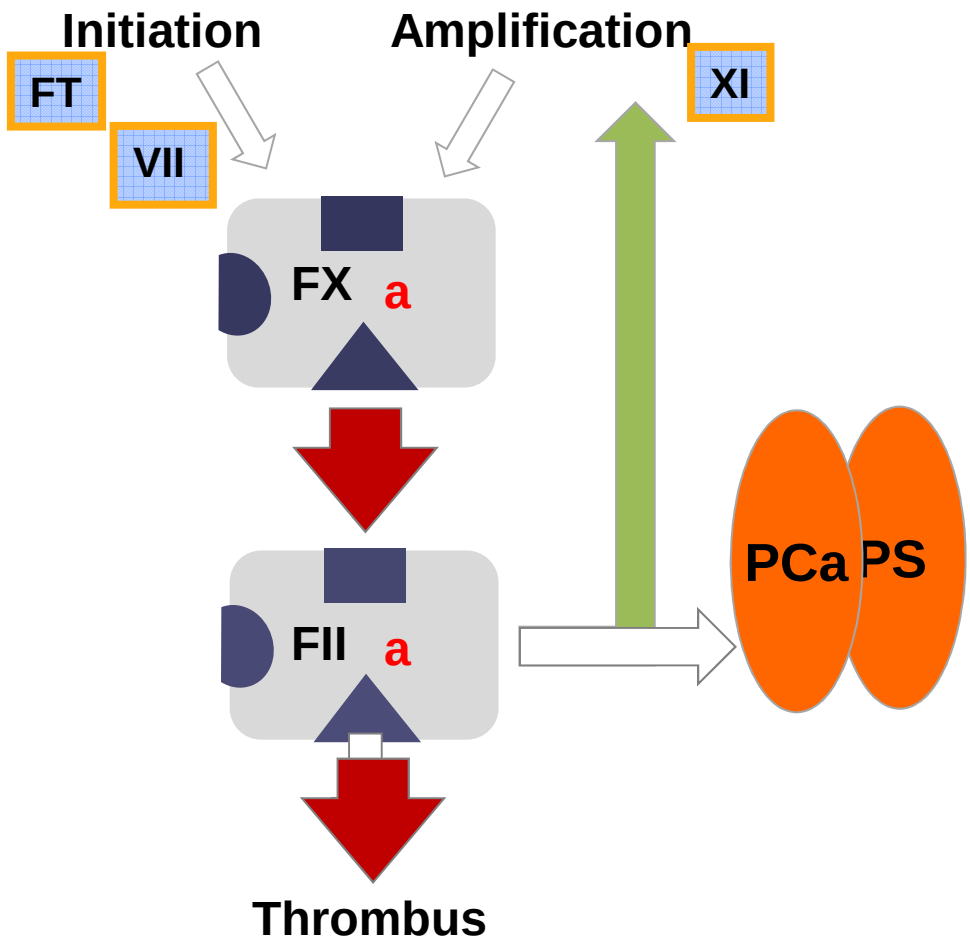
CREATIF Anticoagulation Clinic

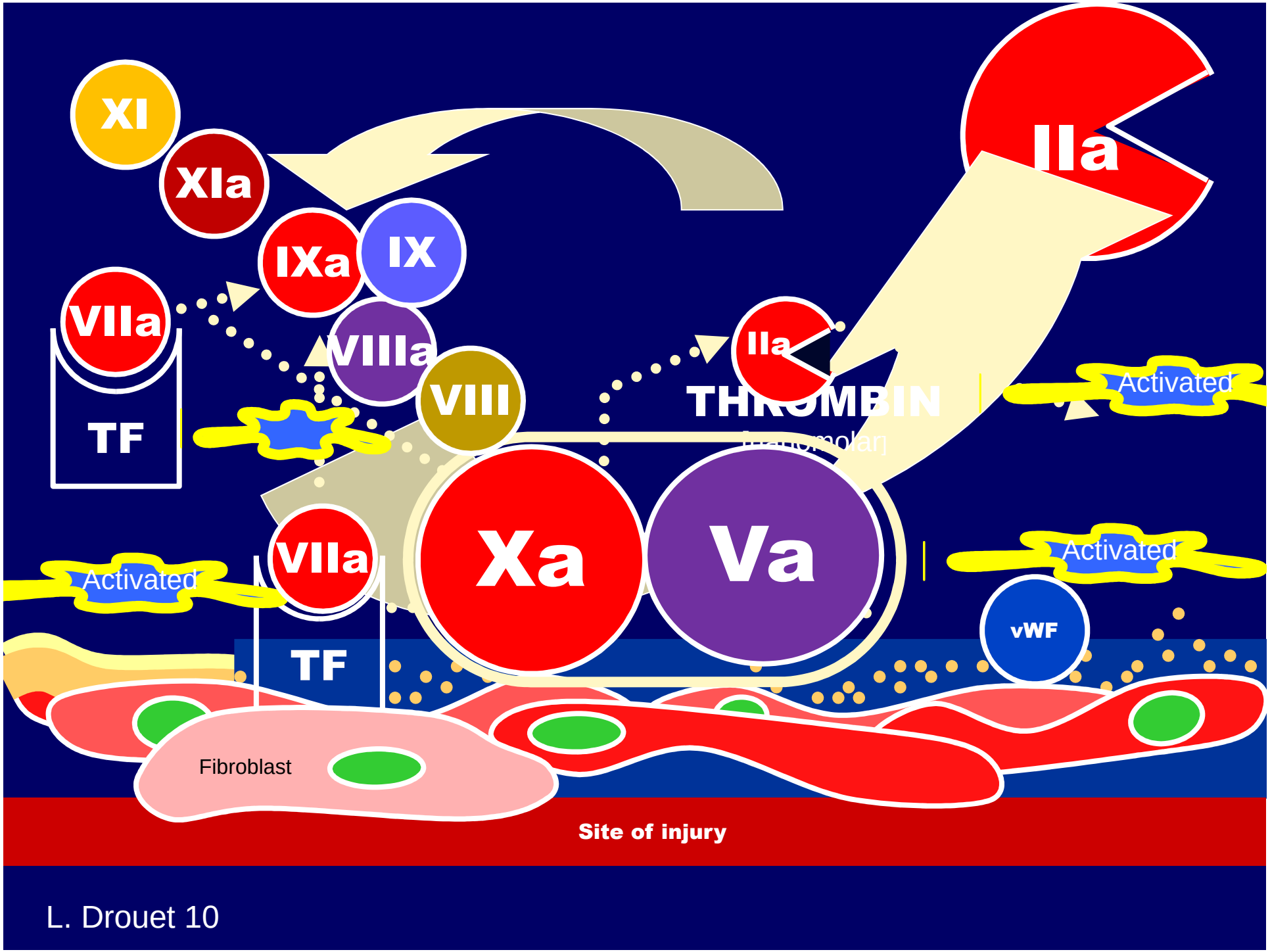
Déclaration de liens d'intérêt

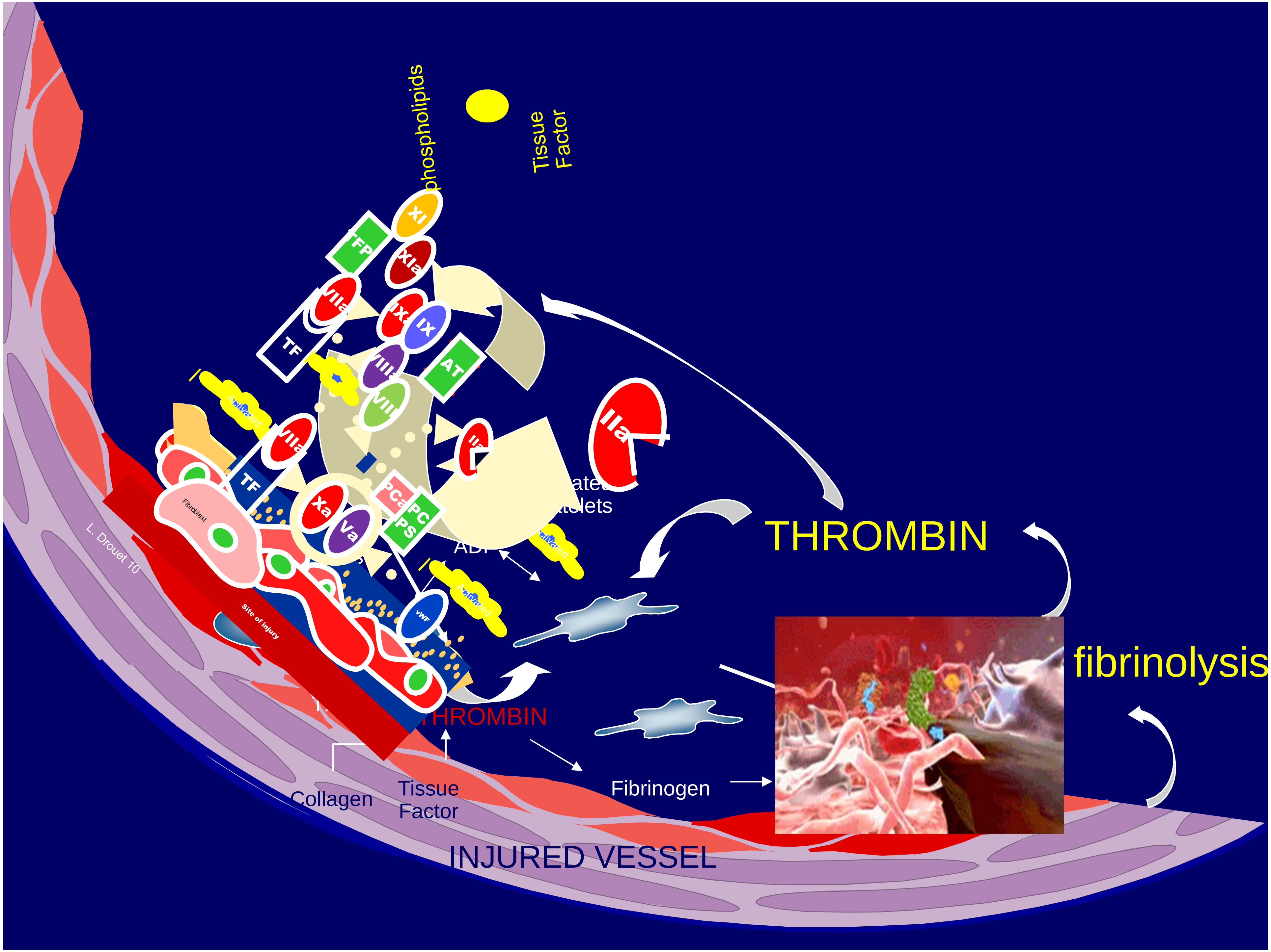
Research Support/P.I.	**No relevant conflicts of interest to declare**
Employee	**No relevant conflicts of interest to declare**
Consultant	**No relevant conflicts of interest to declare**
Major Stockholder	**No relevant conflicts of interest to declare**
Speakers Bureau	Sanofi, BMS-Pfizer, Lilly-Daiichi, AstraZeneca, Boehringer-Ingelheim, Bayer
Grant/support	Sanofi, Lilly-Daiichi
Scientific Advisory Board	Sanofi, BMS-Pfizer, Boehringer-Ingelheim, Lilly-Daiichi, AstraZeneca, Bayer

SRLF


XII
XI
IX
FT
VII
VIIa-FT (complexe)
VIII
VIIIa / IX a
PL - Ca++
X
V
Va / Xa
PL - Ca++
II
Thrombine (IIa)
F XIIIa
Fibrinogène
Fibrine
soluble
Fibrine
insoluble

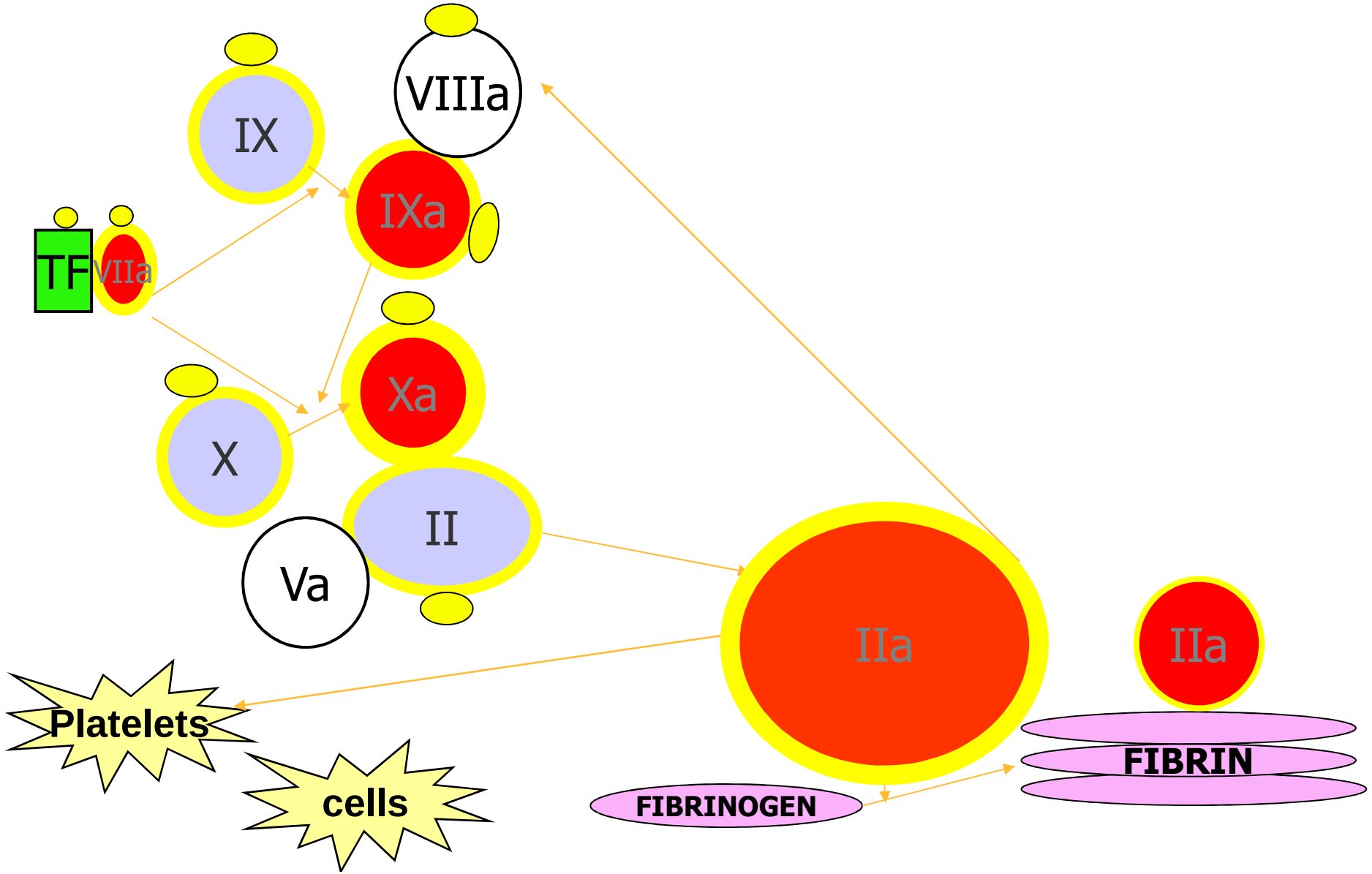

Initiation
Amplification
FT
VII
XI
FX a
FII a
PCa
PS
Thrombus


XI
XIa
IXa
IX
VIIa
TF
VIIIa
VIII
IIa
THROMBIN
Activated
Activated
VIIa
Xa
Va
Activated
vWF
TF
Fibroblast
Site of injury

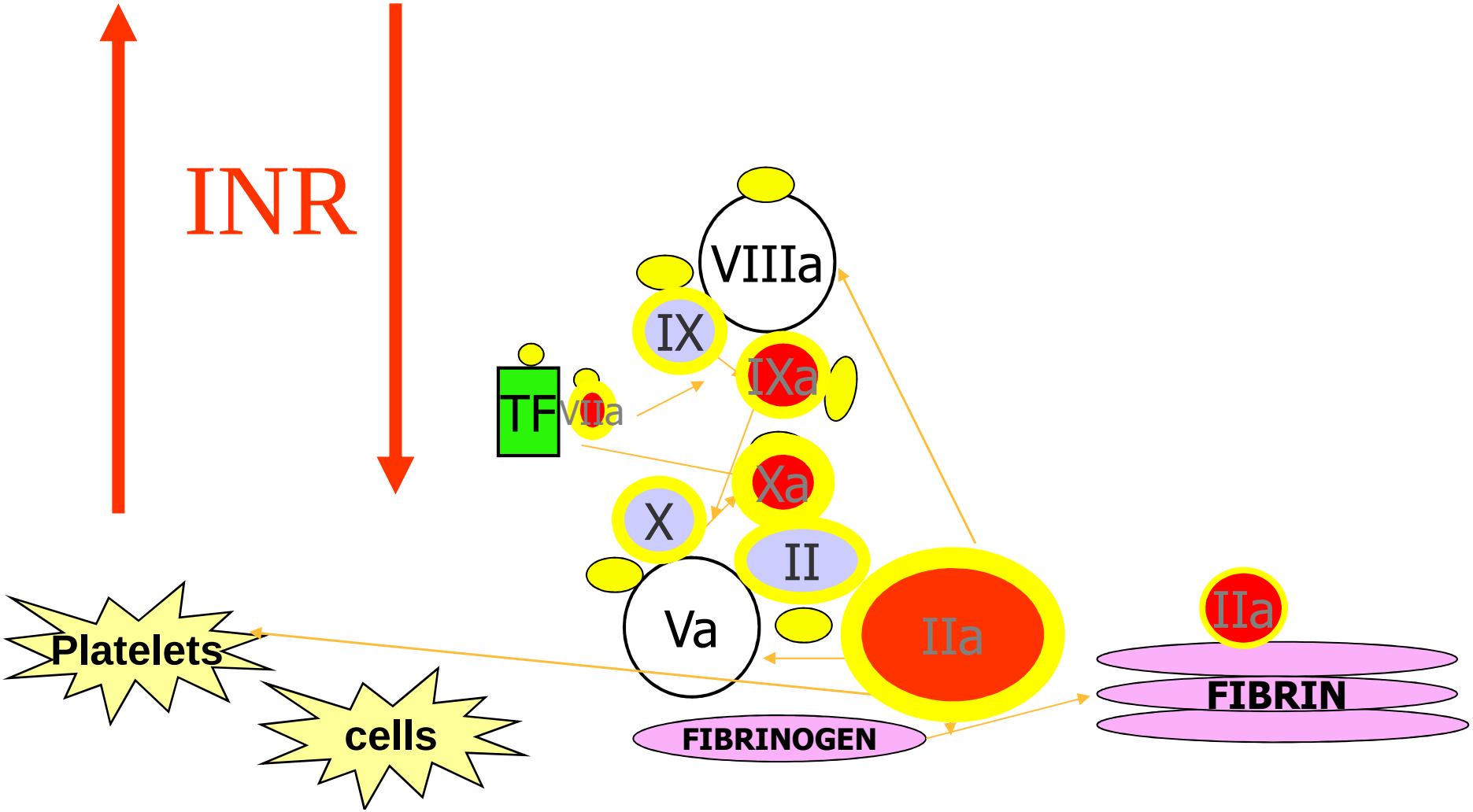

phospholipids
Tissue Factor
XI
TFPI
XIa
VIIa
IXa
IX
TF
AT
VIIIa
VIII
Activated
IIa
VIIa
TF
PCa
PC
PS
Xa
Va
Fibroblast
L. Drouet 10
Site of injury
vWF
ADP
THROMBIN
fibrinolysis
THROMBIN
Collagen
Tissue Factor
Fibrinogen
INJURED VESSEL

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

Antivitamine K

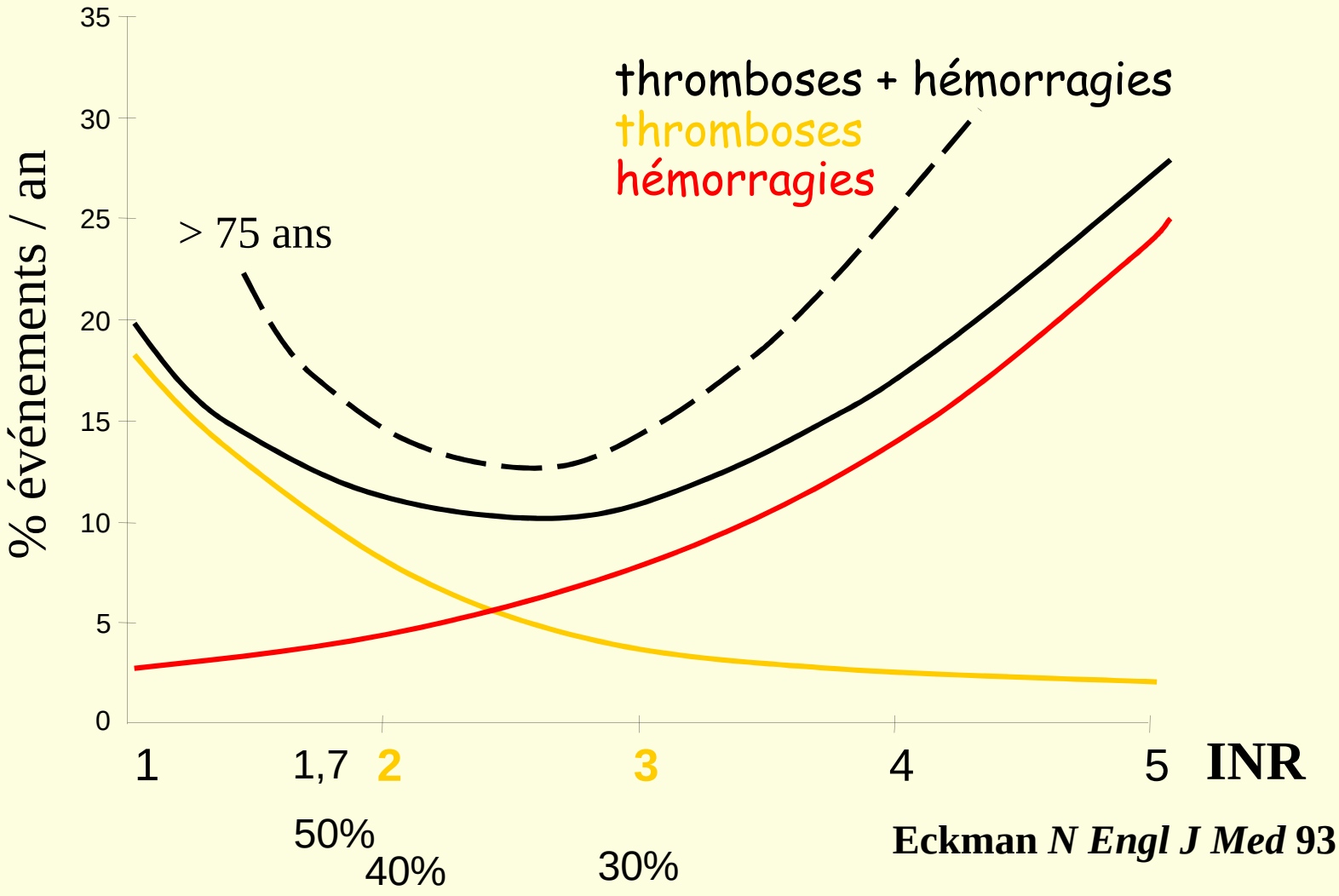


Antivitamine K

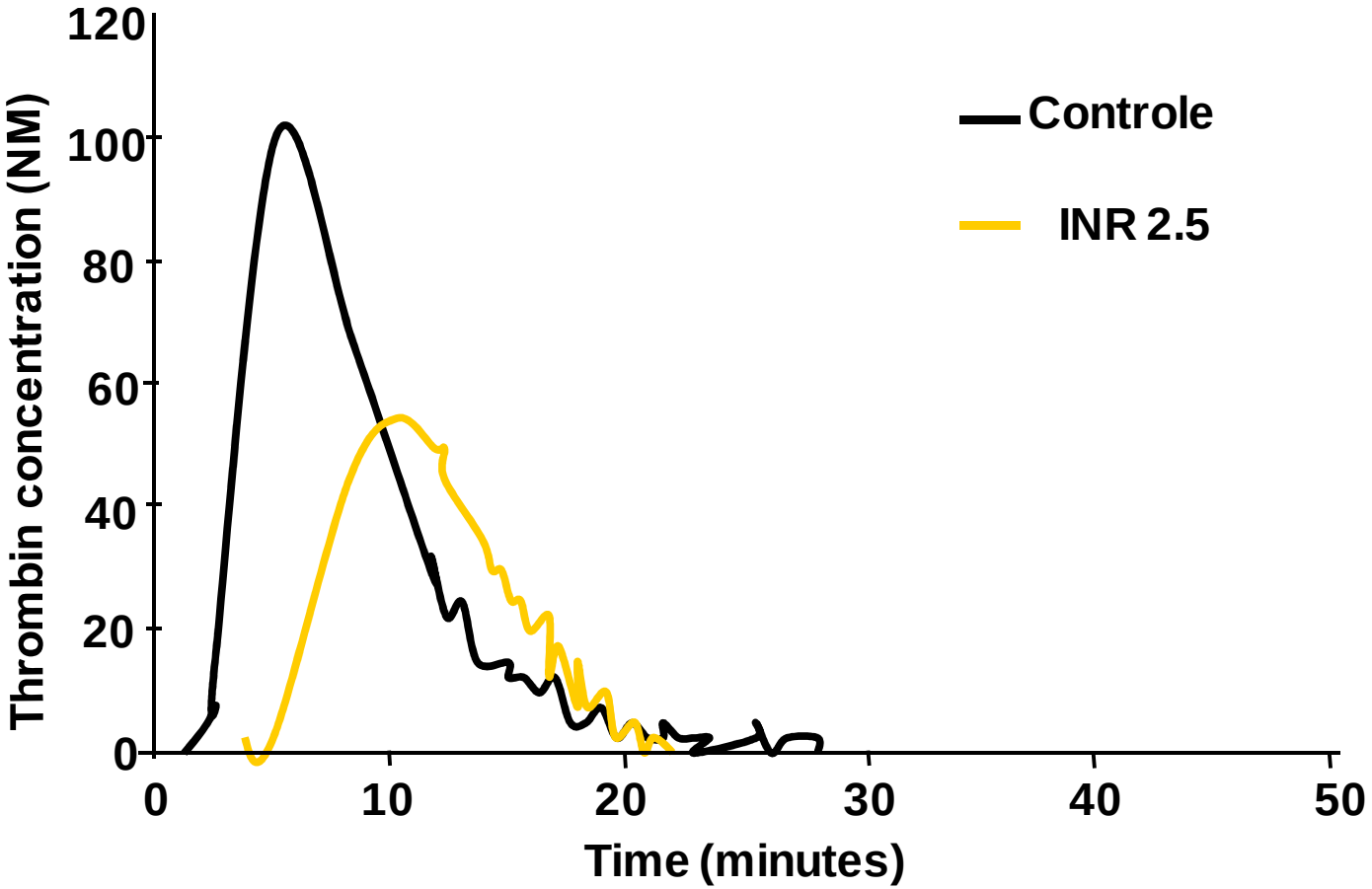


Limites des AVK

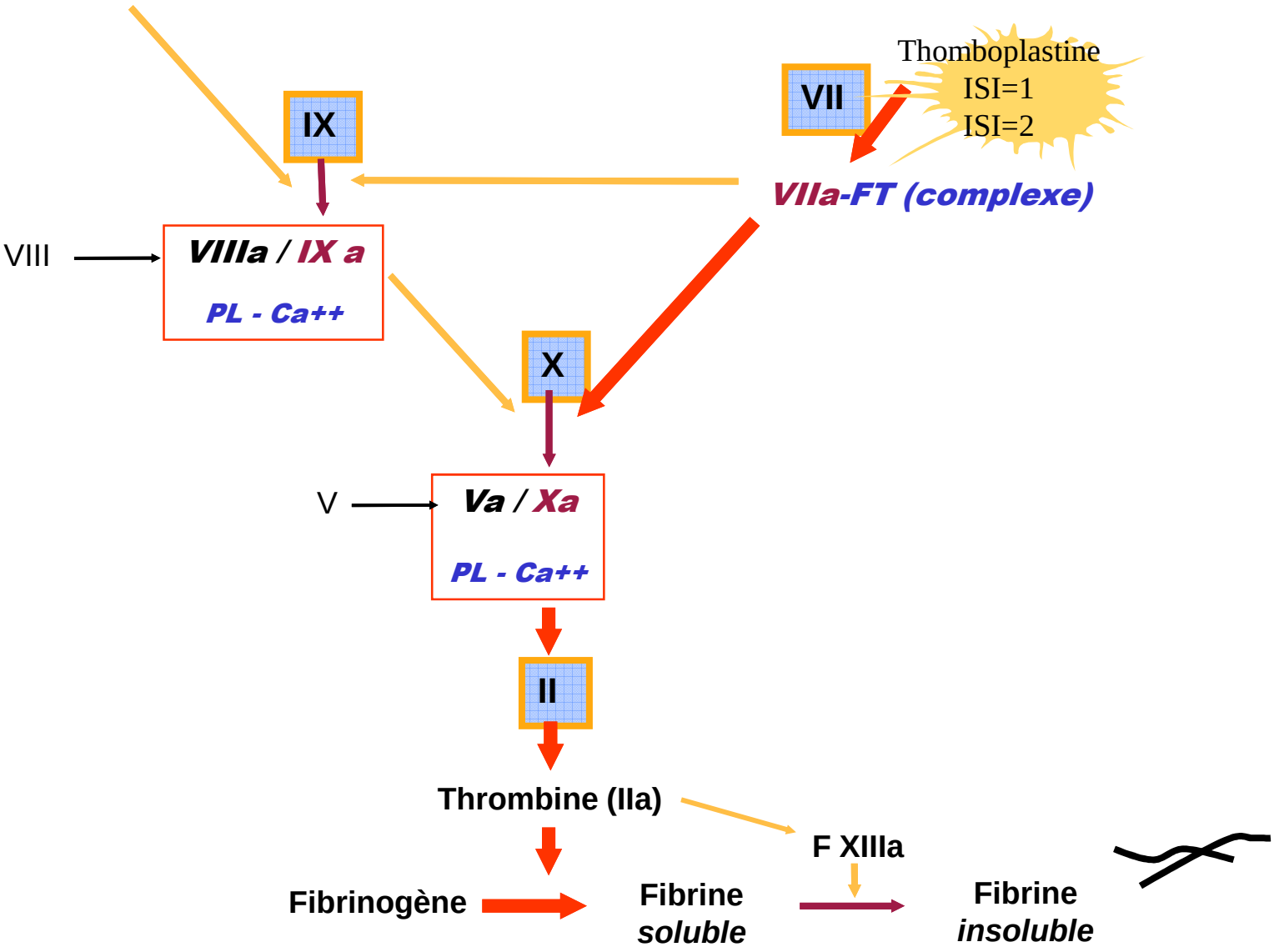
⇨ index thérapeutique étroit



Eckman *N Engl J Med* 93


120
100
80
60
40
20
0
Thrombin concentration (NM)
0
10
20
30
40
50
Time (minutes)
Controle
INR 2.5

Les AVK réduisent la fonctionnalité des facteurs de coagulation vitamine K dépendants
Le temps de Quick-TP-INR est un test de PK mais n'explore pas une étape physiologique de la coagulation



POCT destinés aux patients

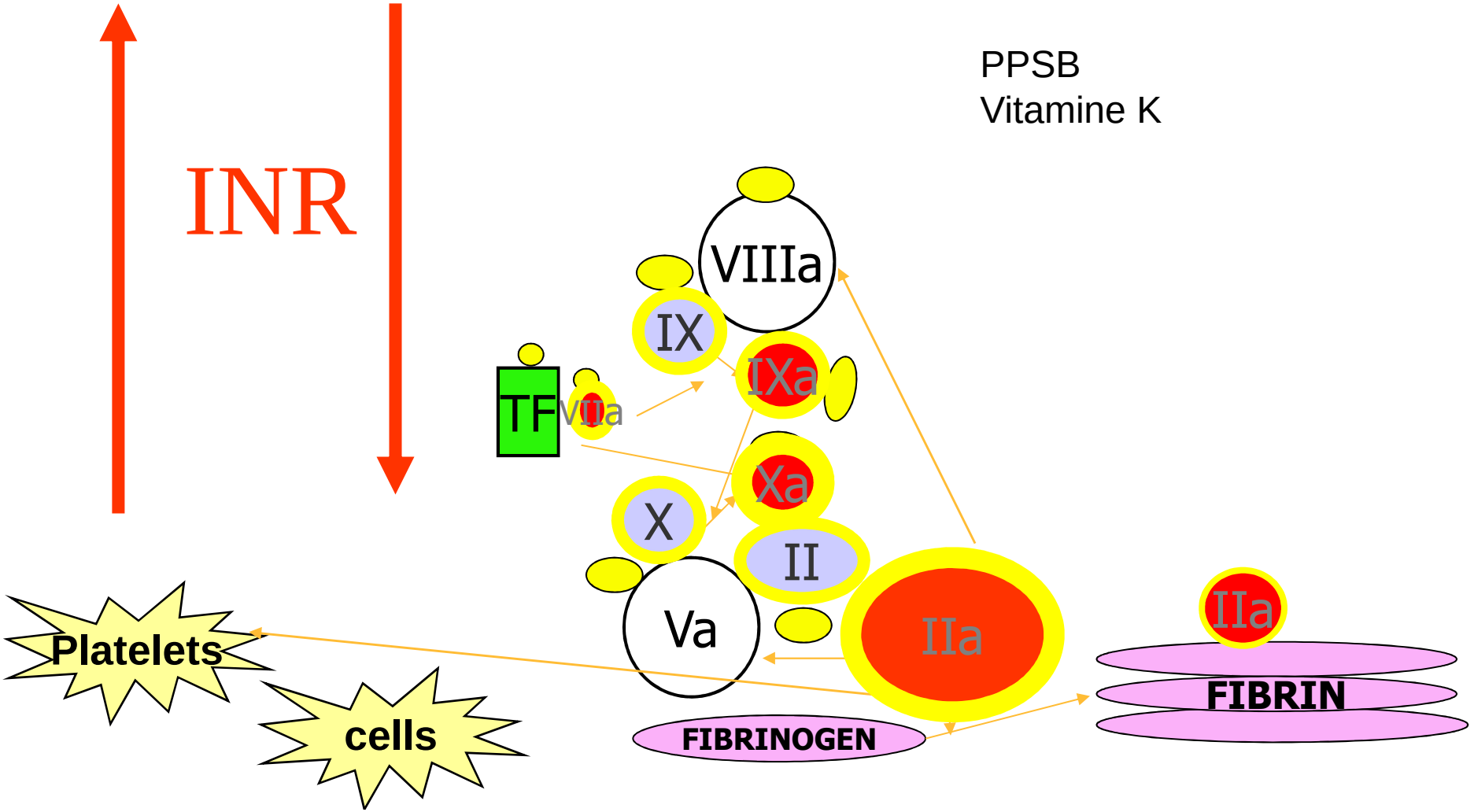
INRatio® (HemoSense)

Coaguchek® XS Roche

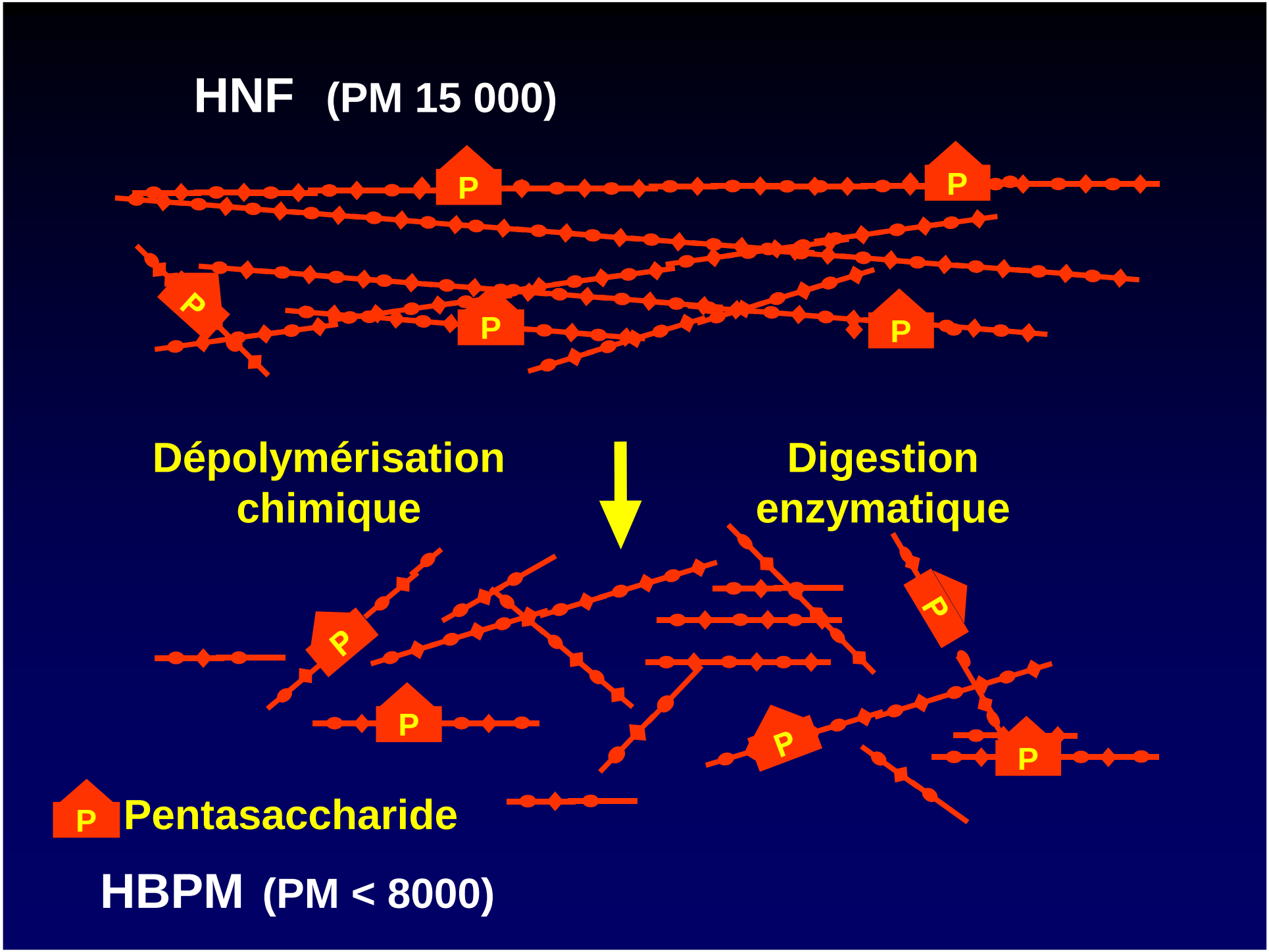
Antivitamine K

Réversion / antagonisation

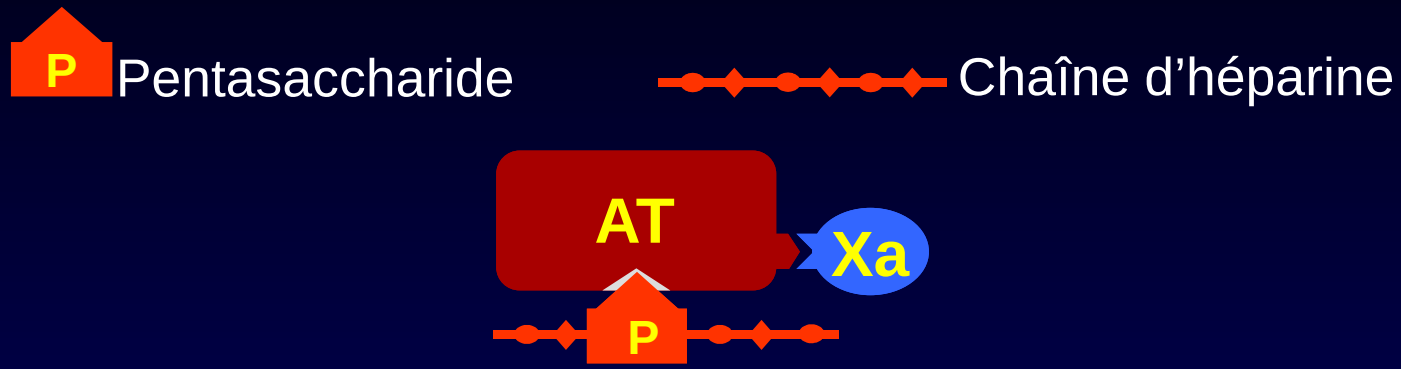
PPSB
Vitamine K



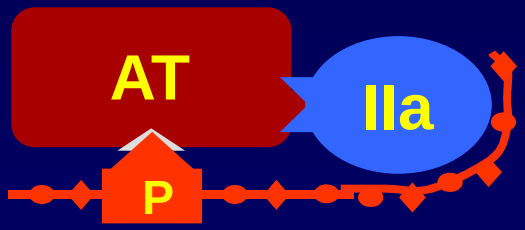

LOVENOX®
(enoxaparin sodium injection)
60mg/0.6mL
[100mg/mL]
Rx ONLY


HNF (PM 15 000)
P
P
P
P
P
Dépolymérisation chimique
Digestion enzymatique
P
P
P
P
P
P
Pentasaccharide
HBPM (PM < 8000)

LES HEPARINES : PHARMACOLOGIE



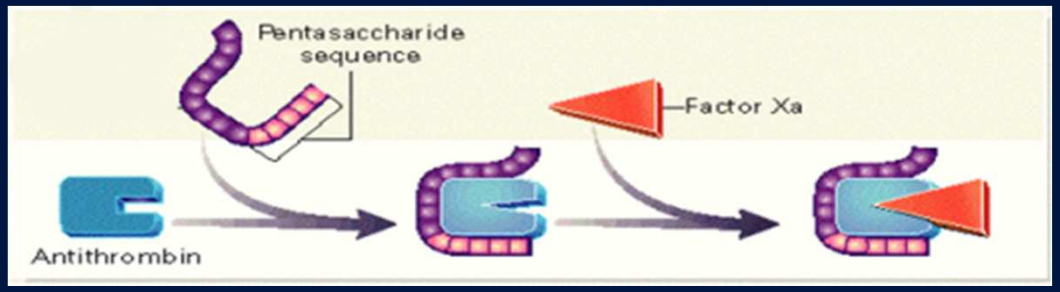
⟶ **Activité anti-Xa**

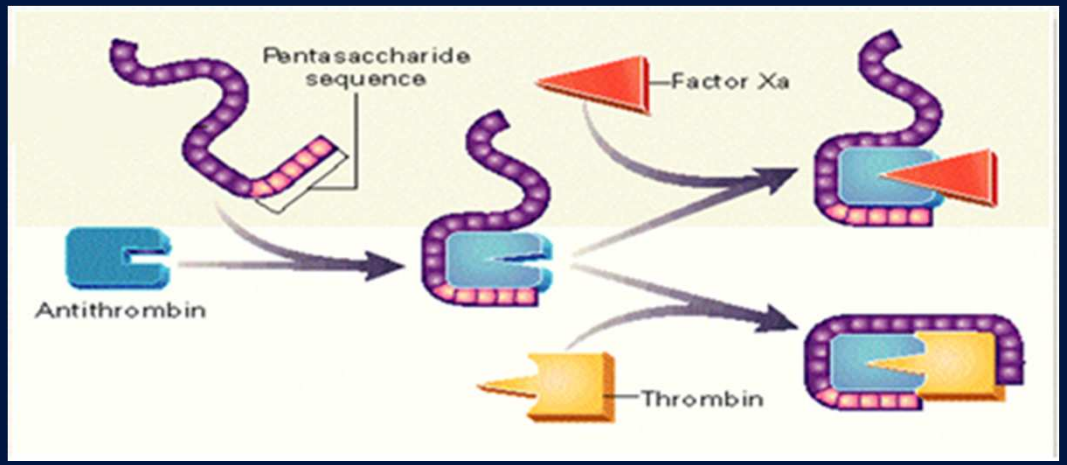


⟶ **Activité anti-IIa**

Heparins – Mechanism of action

Glycanic chains of heparins including the Pentasaccharidic Sequence (PS) exhibit indirect anticoagulant properties via their antithrombin cofactor activity

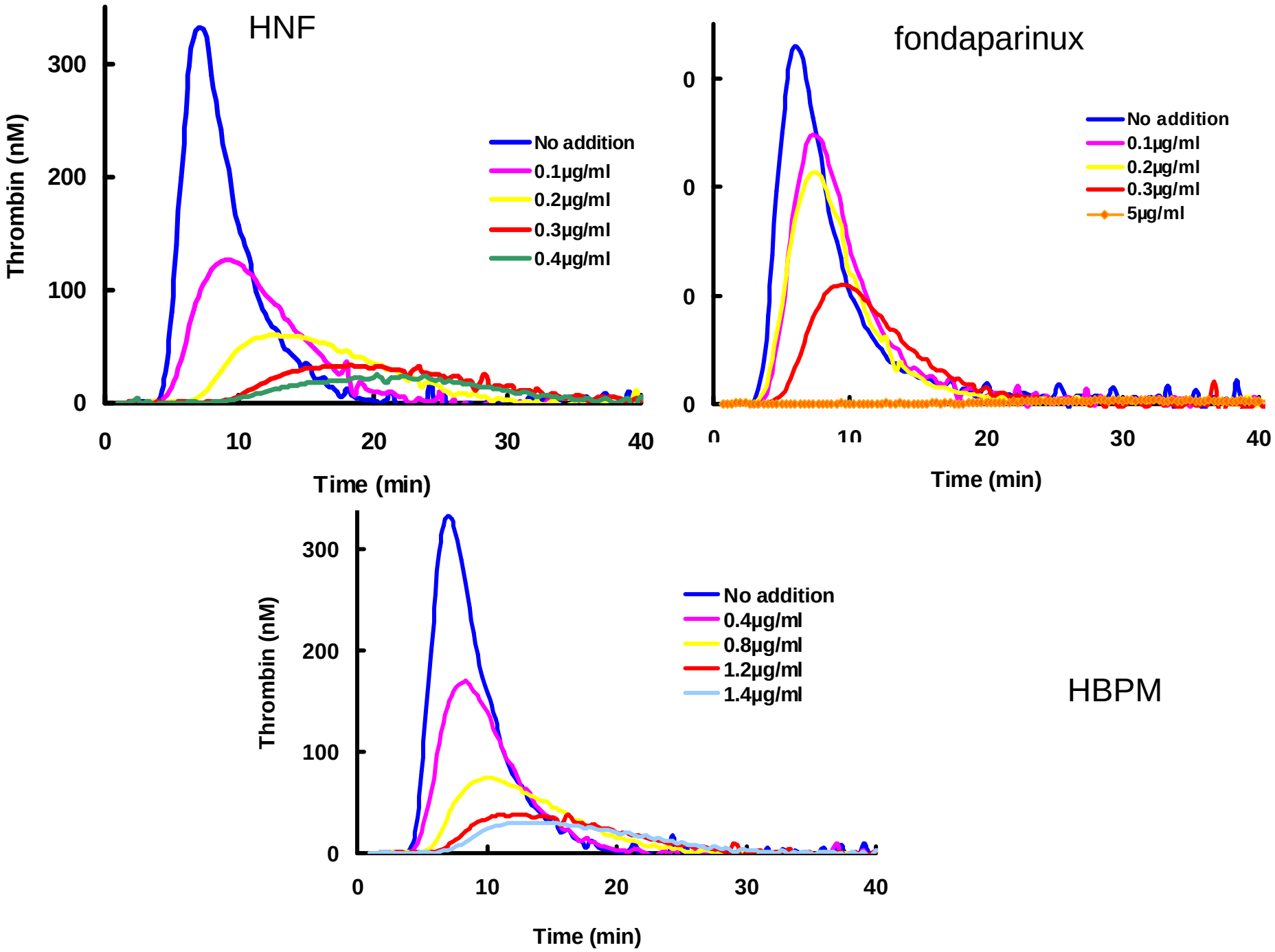




- Chains with PS bring at least an anti factor Xa activity
- **If these chains are long enough they can additionally bring an anti factor IIa activity**

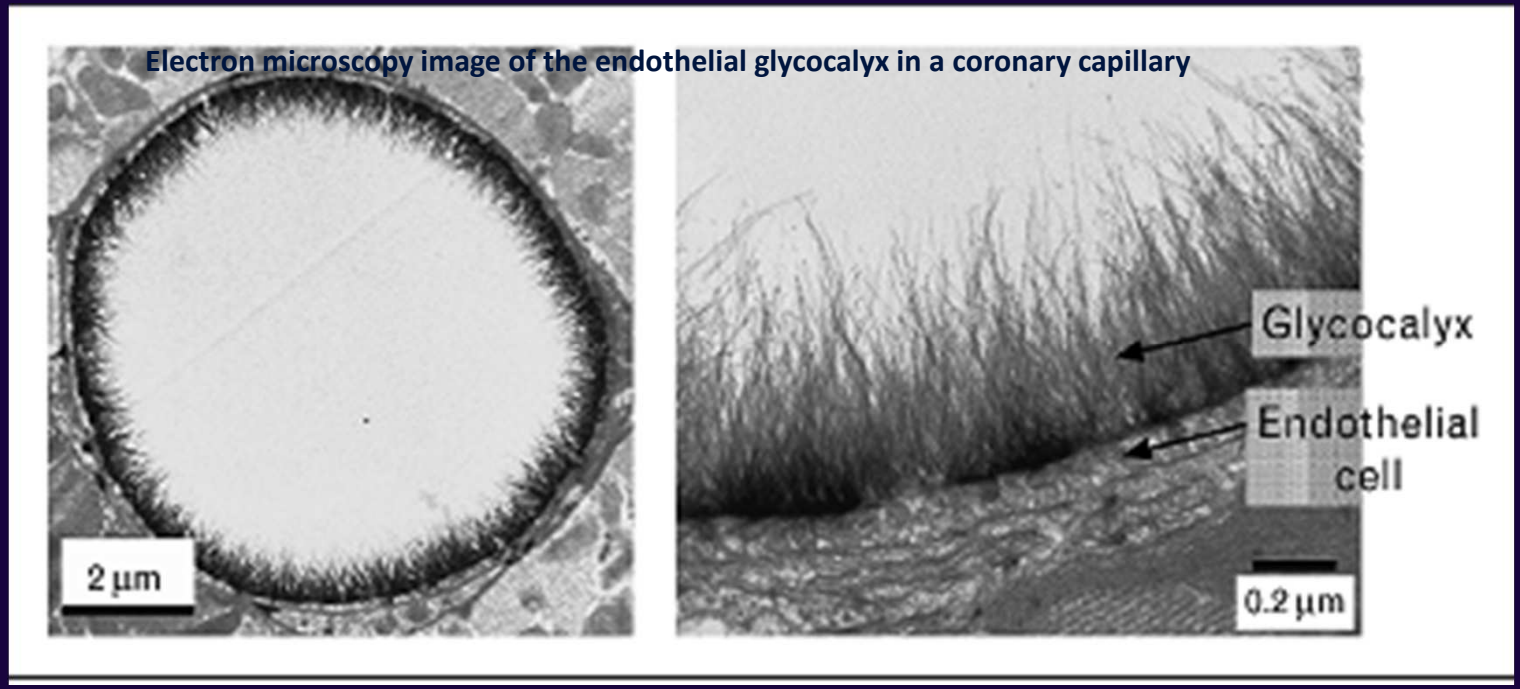
At least 18 saccharide units required to inactivate factor IIa

Adapted from Weitz J. N Engl J Med 1997;337:688–698.


HNF
Thrombin (nM)
300
200
100
0
0
10
20
30
40
Time (min)
No addition
0.1μg/ml
0.2μg/ml
0.3μg/ml
0.4μg/ml
fondaparinux
0
0
0
0
10
20
30
40
Time (min)
No addition
0.1μg/ml
0.2μg/ml
0.3μg/ml
5μg/ml
Thrombin (nM)
300
200
100
0
0
10
20
30
40
Time (min)
No addition
0.4μg/ml
0.8μg/ml
1.2μg/ml
1.4μg/ml
HBPM

The endothelial glycocalyx

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



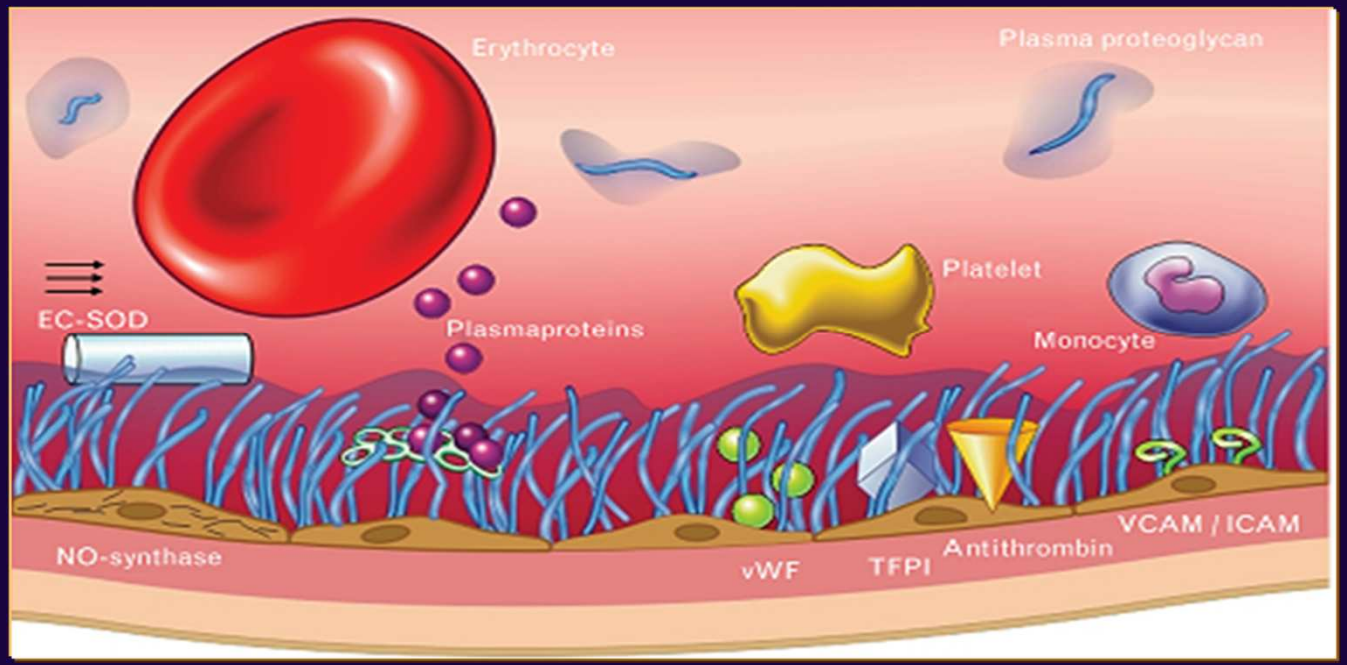
Nieuwdorp M et al. Curr Opin Lipidol 2005,16:507-511

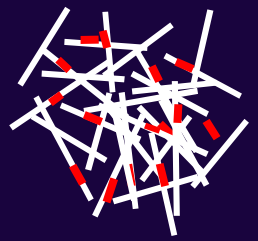
Endothelial glycocalyx

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

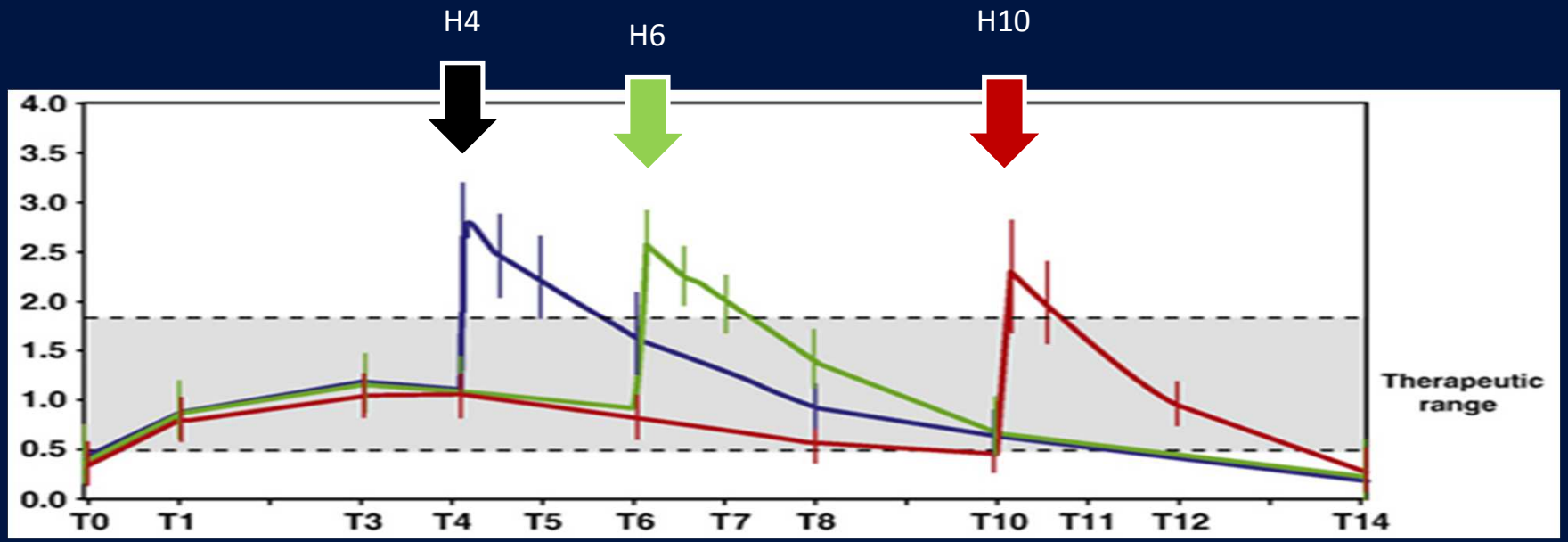
vasomotricity
Blood flow
regulation

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)

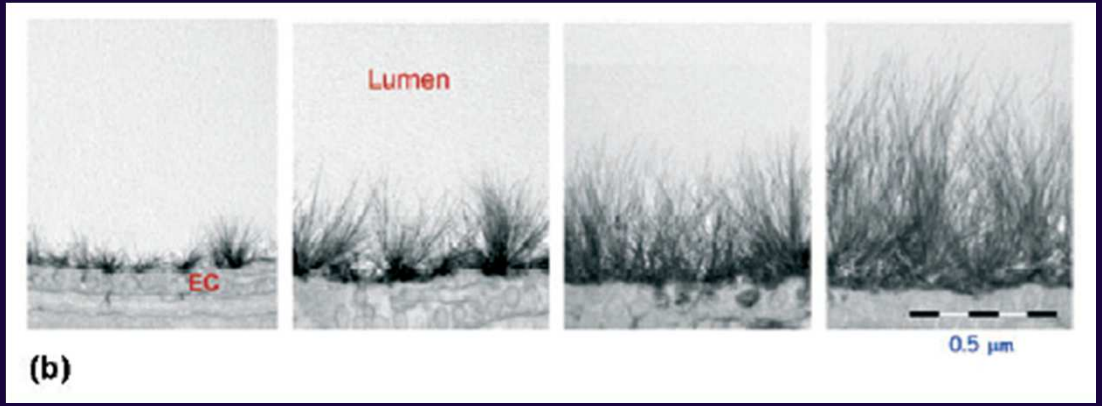


Time from last enoxaparin injection (hours)

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

Glycocalyx structure and role

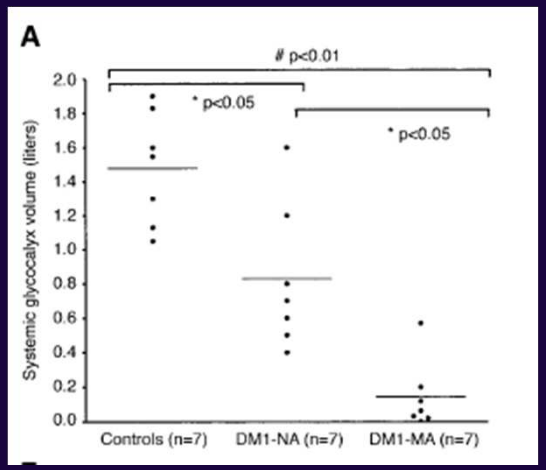
physiological heterogeneity of glycocalyx in the vascular system [1]

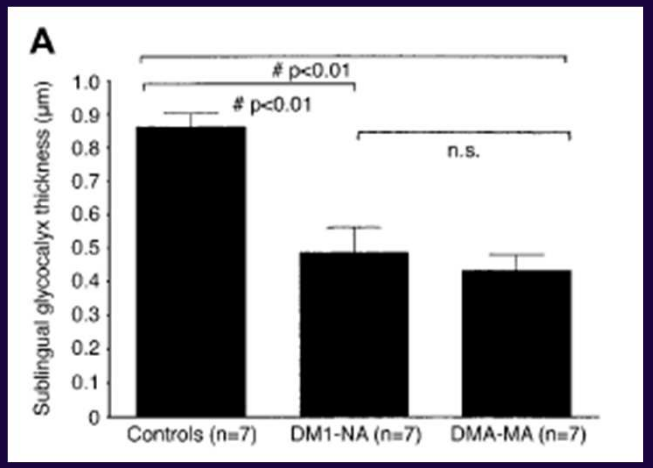


Examples of pathological condition with glycocalyx damage [2-6]

- Diabetes
- Inflammation
- Aging
- **Cancer/chemotherapy**

Decrease of glycocalix in diabetes melitus (DM)

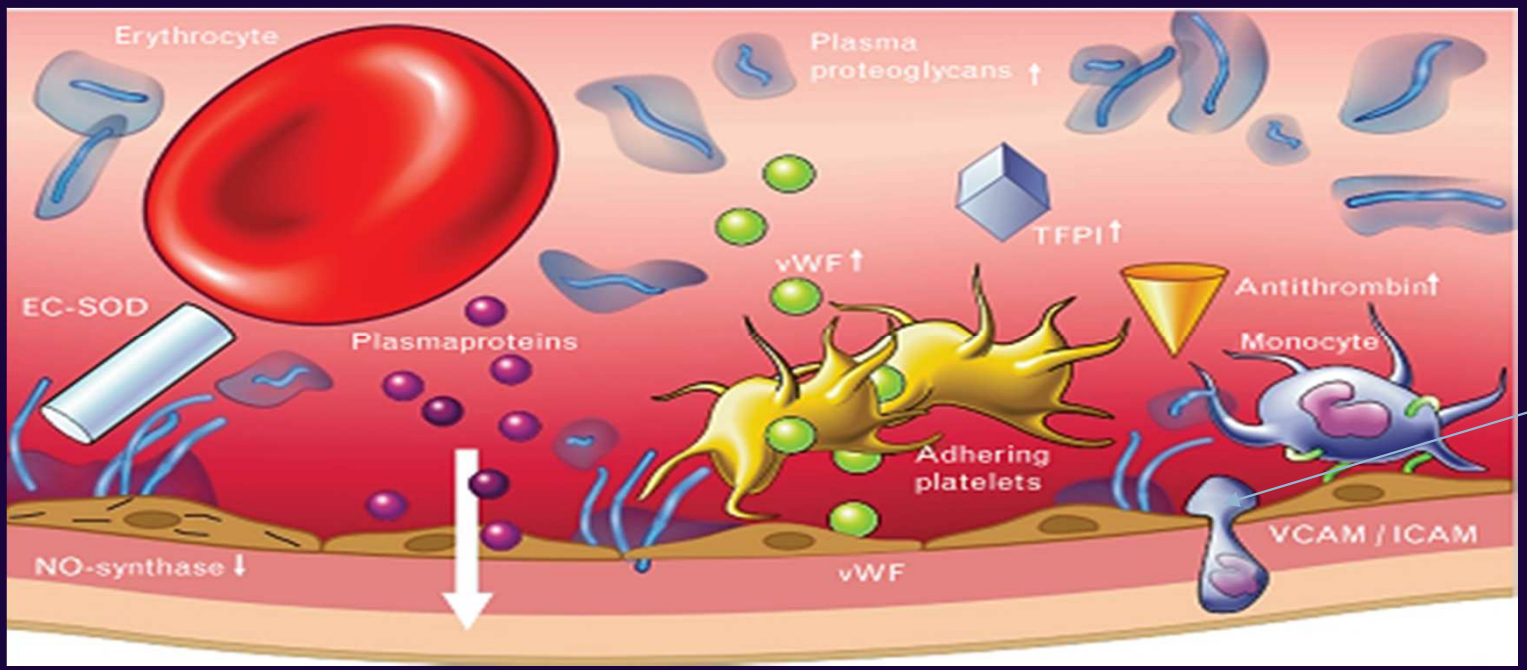


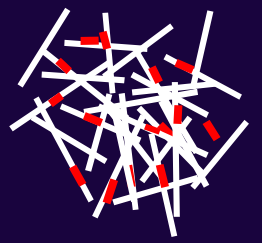


1. Gouverneur et al J. Intern. Med. 2009 259 (4) :393-400
2. Nieuwdorp M et al. Diabetes 55:1127–1132, 2006
3.Bihari-Varga M et al. Pathol Biol (Paris). 1981 Nov;29(9):555-61.
4. Sasisekharan R et al. Nat Rev Cancer 2002;2:521-528
5. Mousa SA et Petersen LJ. Thromb Haemost 2009;102:258-267
6. Yip GW et al. Mol Cancer Ther 2006;5:2139-2148

Endothelial glycocalyx
Damaging impact

Damaged Glycocalyx - Pathological Impact: endothelial dysfunction





Damaged glycocalyx

Endothelium

Subendothelial space

↘ NO availability
↗ Oxidative stress

↗ Leakage of macromolecules

↗ Platelet adhesion
↗ Thrombin generation

↗ Leukocyte adhesion
↗ Diapedesis

↘ FMD

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

Endothelial glycocalyx in pathological states
Impact on LMWH PK-PD

Anti Xa activity lower than expected/predicted in numerous pathological states

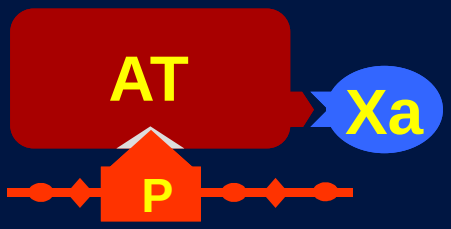
- Sepsis
- Polytrauma
- Extensive burn
- Obesity
- Pregnancy
- ACS
- Cancer / Chemotherapy

→ Clinical implications

LES HEPARINES : PHARMACOLOGIE

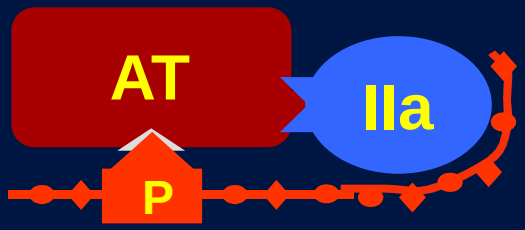
Pentasaccharide

Chaîne d'héparine



→ **Activité anti-Xa**

Monitoring
Activité anti Xa



→ **Activité anti-IIa**

LES HEPARINES : PHARMACOLOGIE

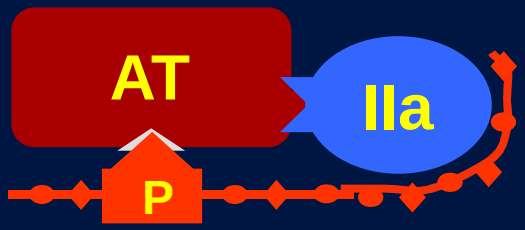
Pentasaccharide

Chaîne d'héparine

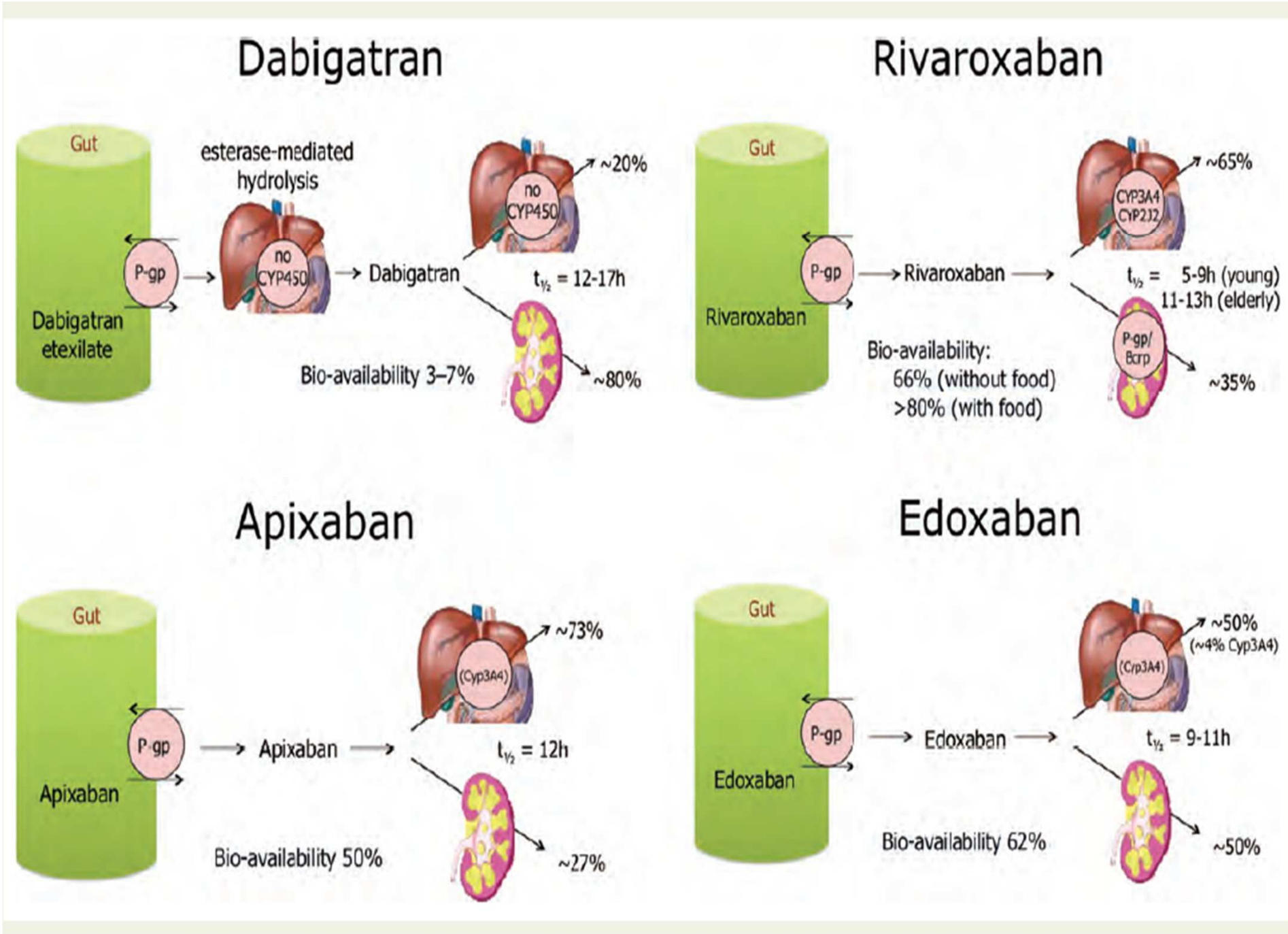
→ **Activité anti-Xa**

Reversion / antagonisation

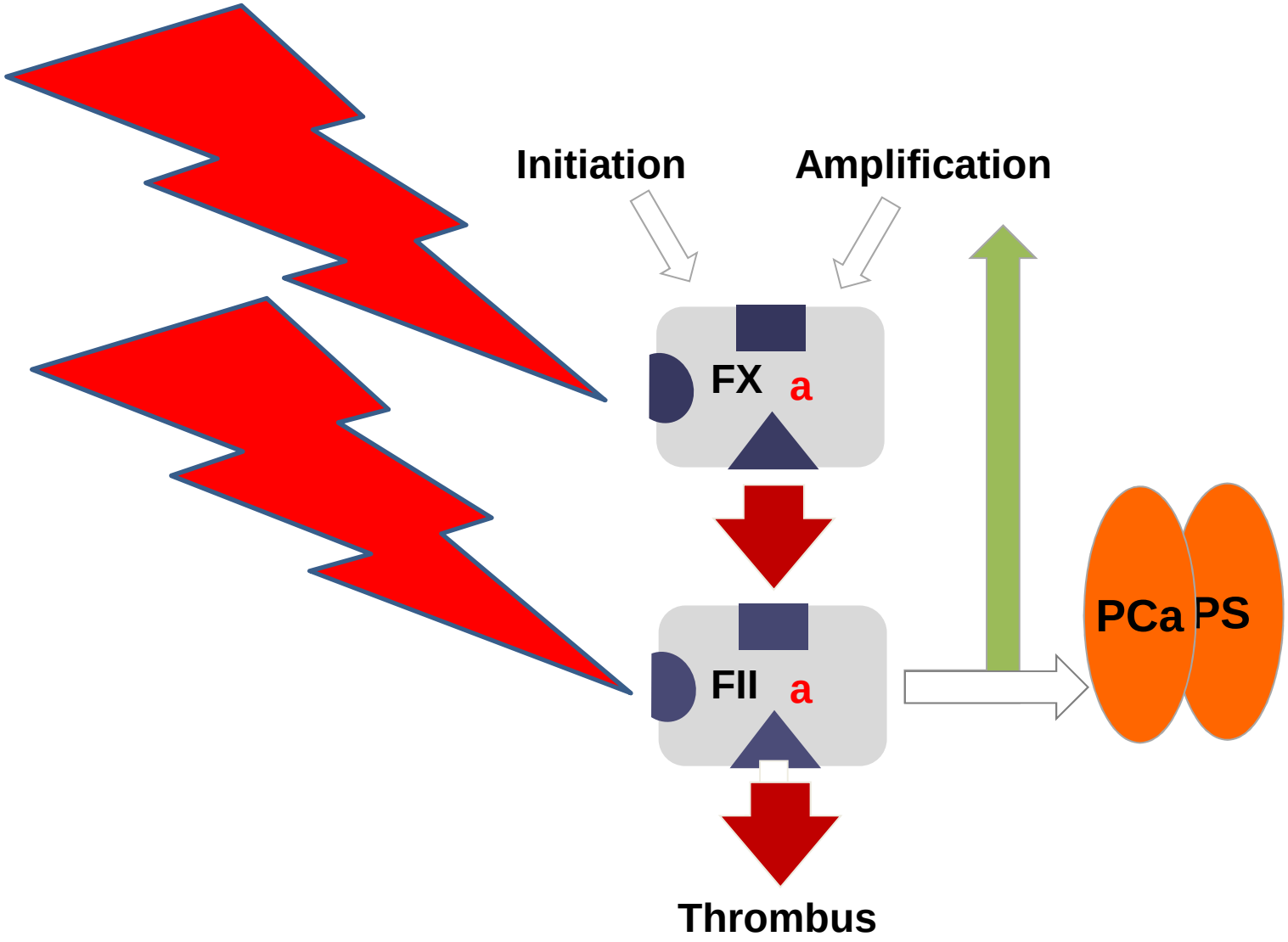
Protamine ????



→ **Activité anti-IIa**


Dabigatran
Gut
Dabigatran etexilate
P-gp
esterase-mediated hydrolysis
no CYP450
Dabigatran
~20%
$t_{1/2}$ = 12-17h
~80%
Bio-availability 3–7%
Rivaroxaban
Gut
Rivaroxaban
P-gp
Rivaroxaban
CYP3A4 CYP2J2
~65%
$t_{1/2}$ = 5-9h (young) 11-13h (elderly)
P-gp/ Bcrp
~35%
Bio-availability:
66% (without food)
>80% (with food)
Apixaban
Gut
Apixaban
P-gp
Apixaban
(Cyp3A4)
~73%
$t_{1/2}$ = 12h
~27%
Bio-availability 50%
Edoxaban
Gut
Edoxaban
P-gp
Edoxaban
(Cyp3A4)
~50%
(~4% Cyp3A4)
$t_{1/2}$ = 9-11h
~50%
Bio-availability 62%

Pour montrer ce que l'on a intérêt à inhiber
On peut prendre un schéma simplifié de la coagulation

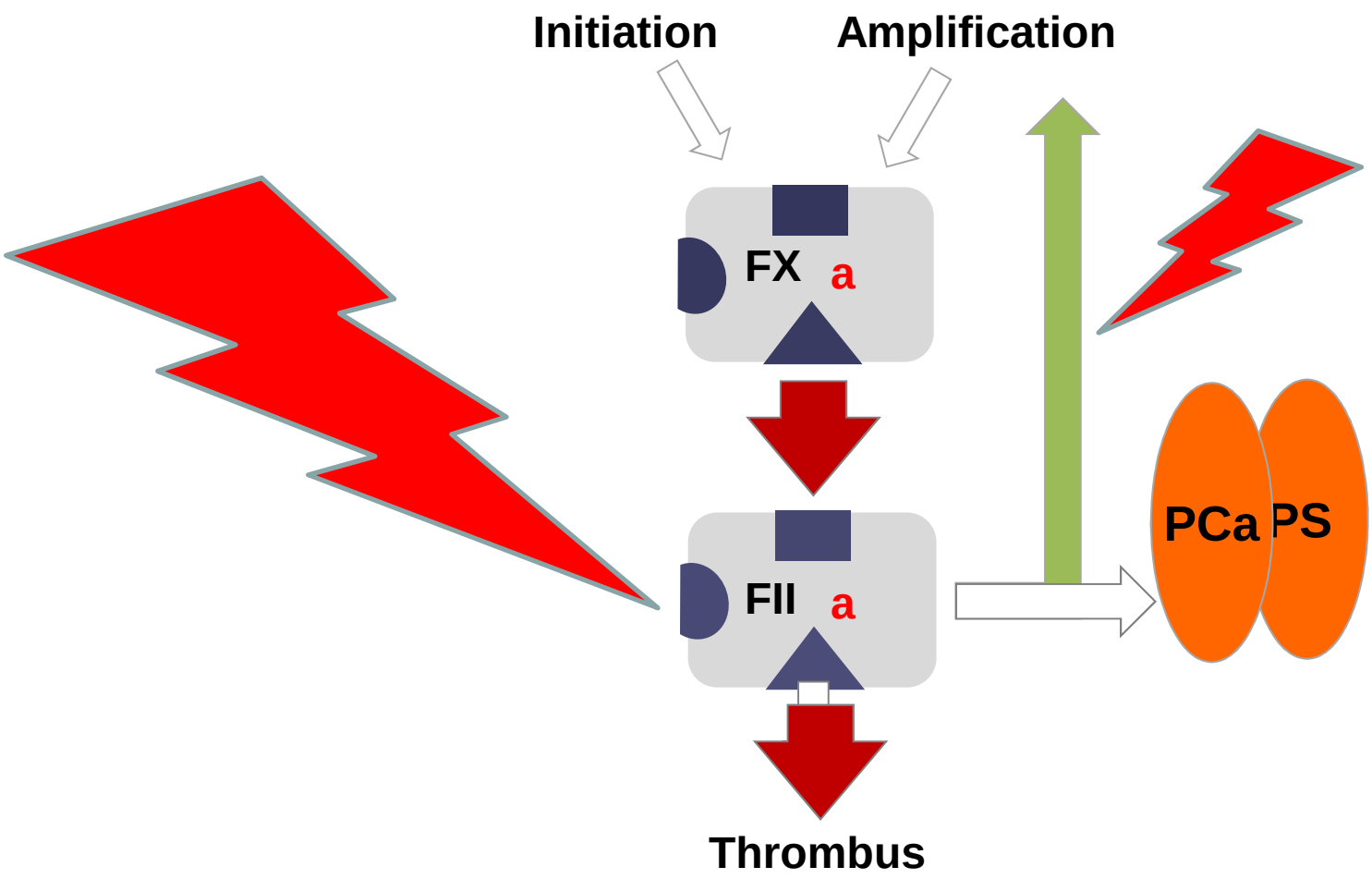


Votre traitement Anticoagulant oral

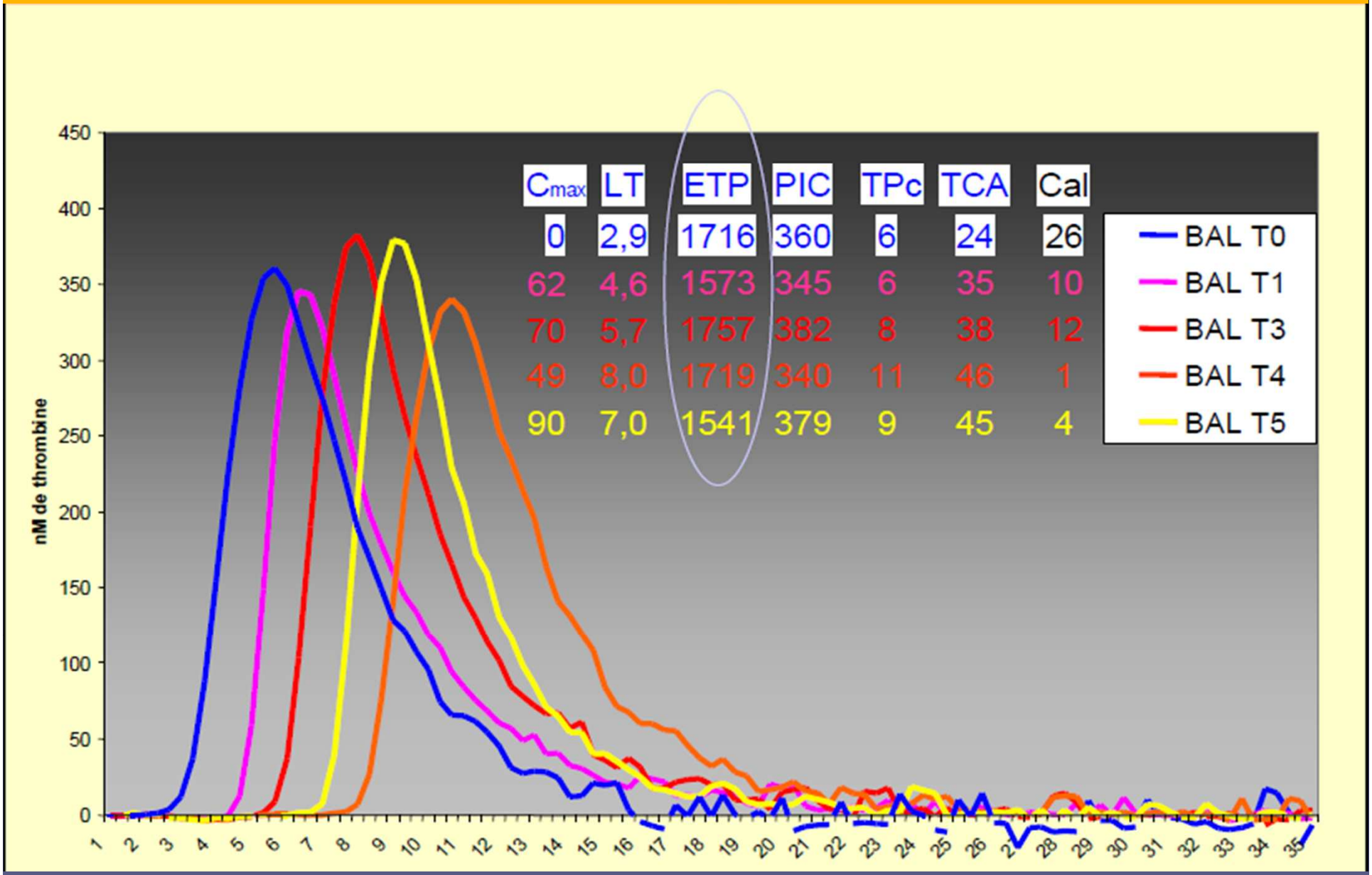
- **<u>PRADAXA</u>®**
  (Dabigatran)
- Gélules dosées à 150mg

- Gélules dosée à 110 mg

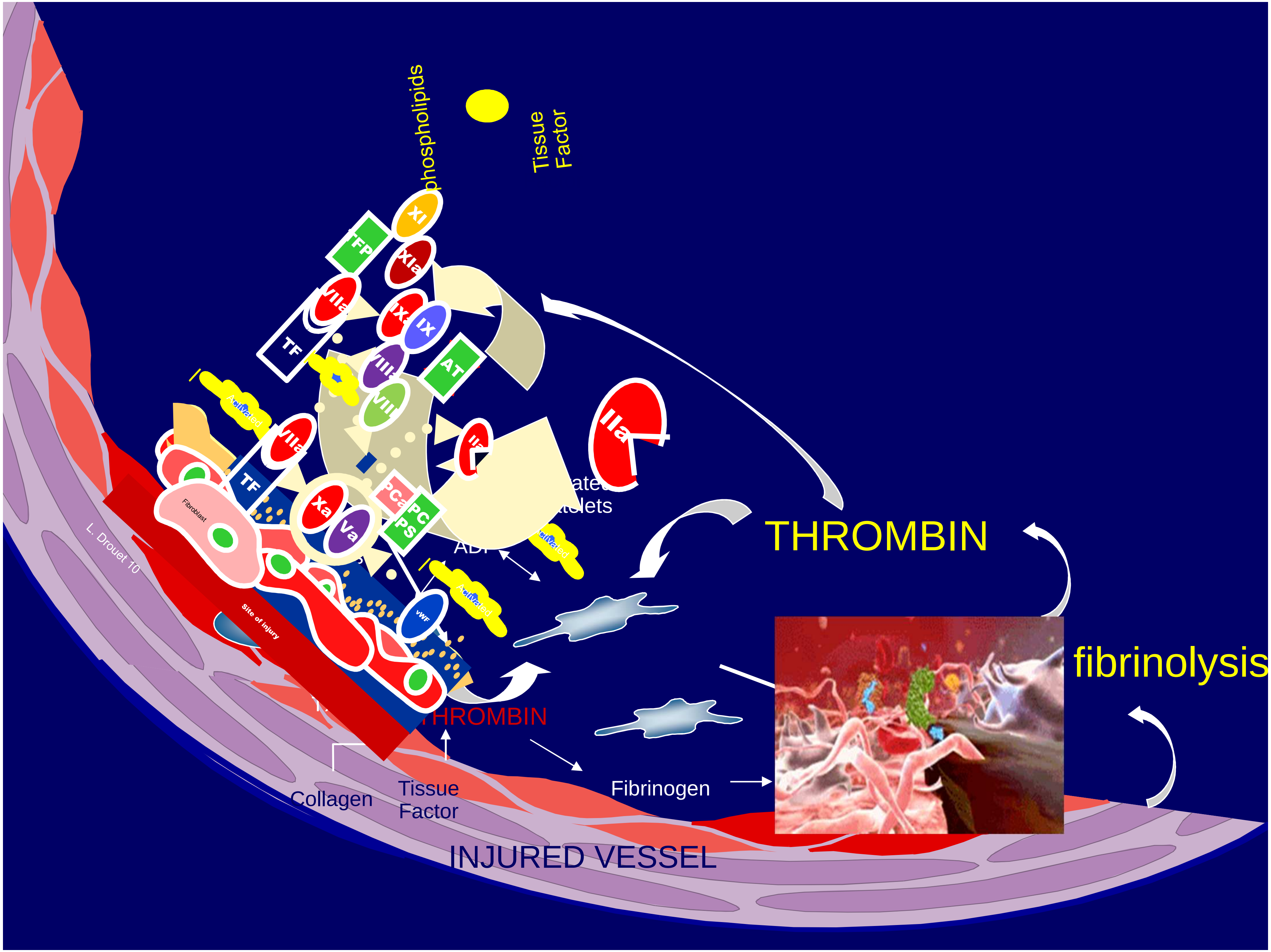
Mode d’action des antithrombine directes



Patient Bal. Effect of dabigatran on TGT

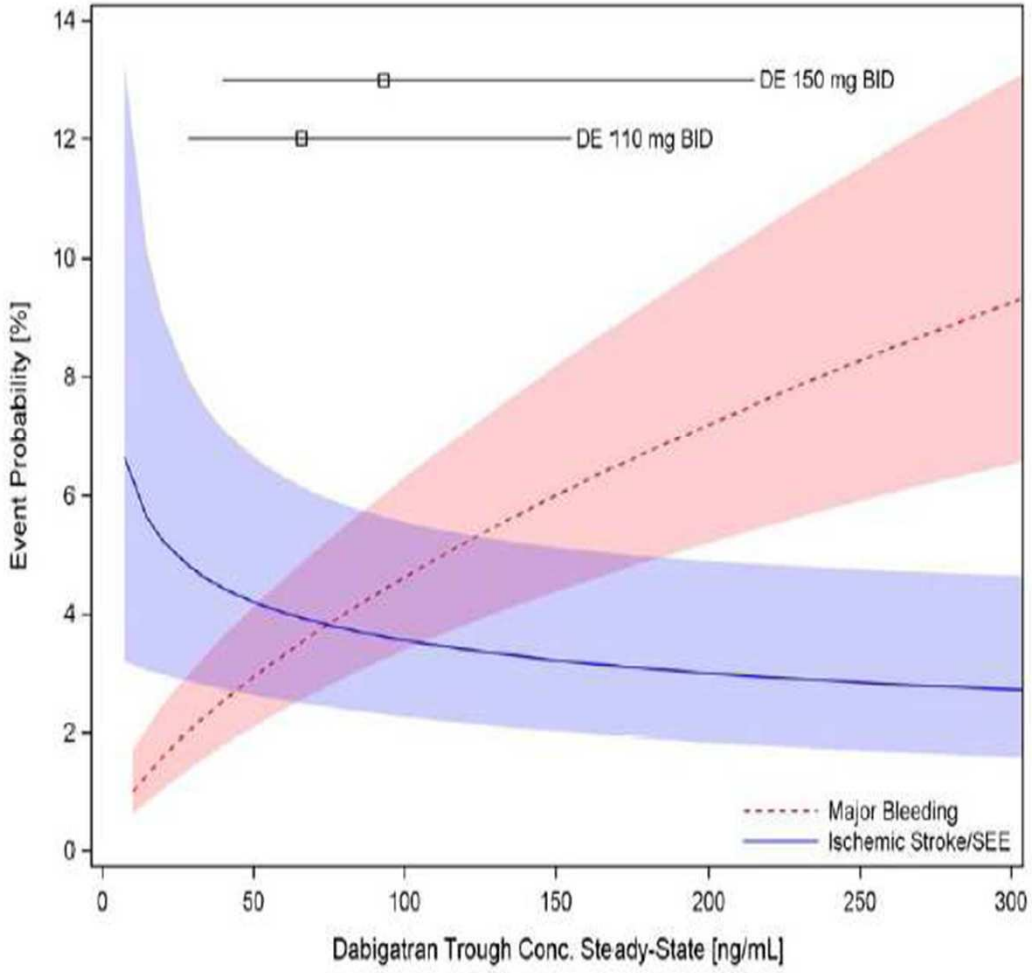


Freyburger G, et al, Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: Two observational studies in patients undergoing..., Thromb Res (2011),



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

Dabigatran trough concentration and thrombotic and hemorrhagic risks



Reilly et al, JACC 2013

Votre traitement Anticoagulant oral

- **<u>XARELTO</u>®**
  (Rivaroxaban)
- Comprimés dosés à 15mg

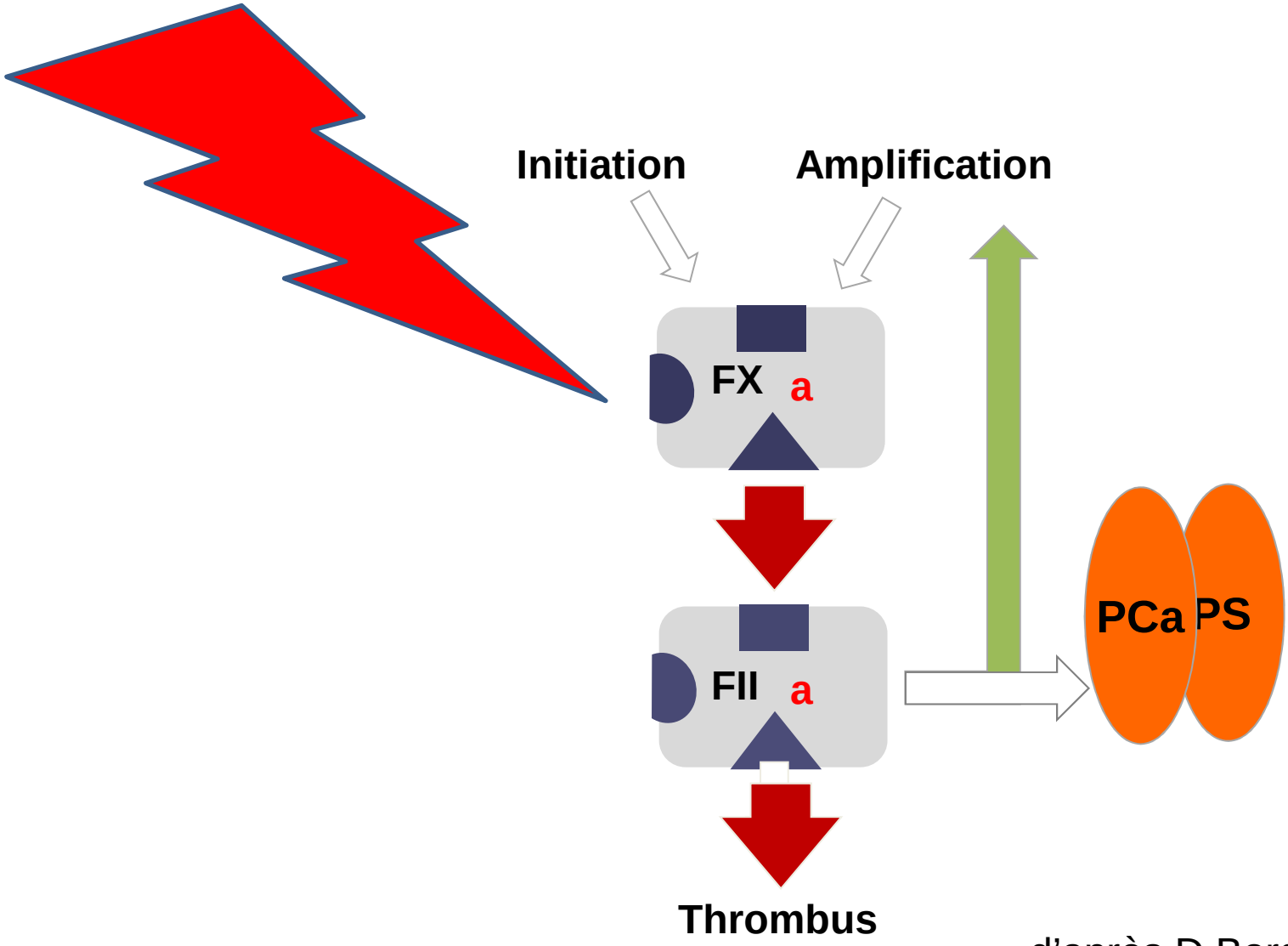
- Comprimés dosés à 20mg

Votre traitement Anticoagulant oral

- **<u>ELIQUIS</u>® (Apixaban)**
- Comprimés dosés à 2,5mg

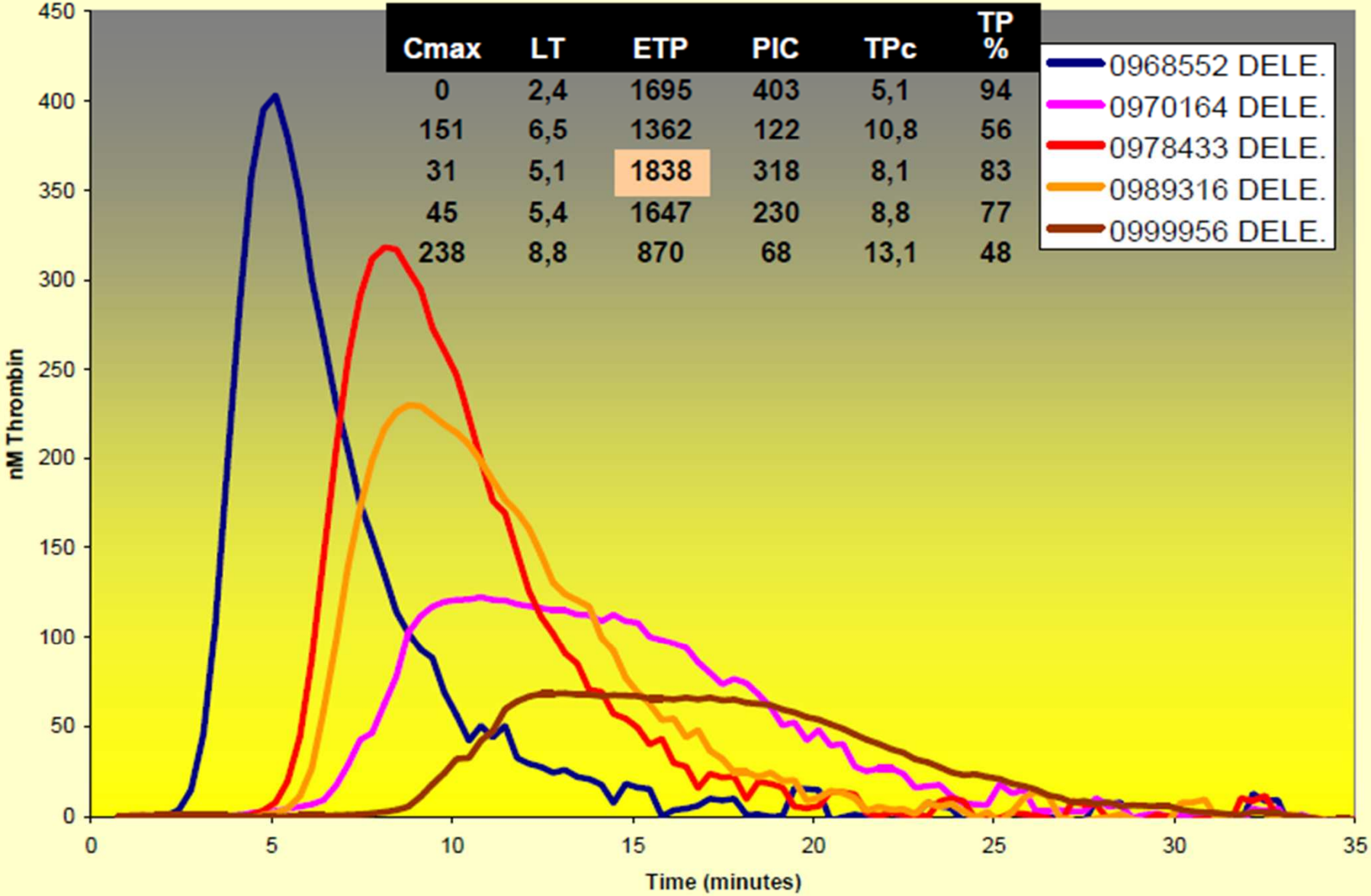
- 5mg

Mode d'action des anti Xa directes



d'après D Borgel

Patient DELE. Effect of rivaroxaban on TGT

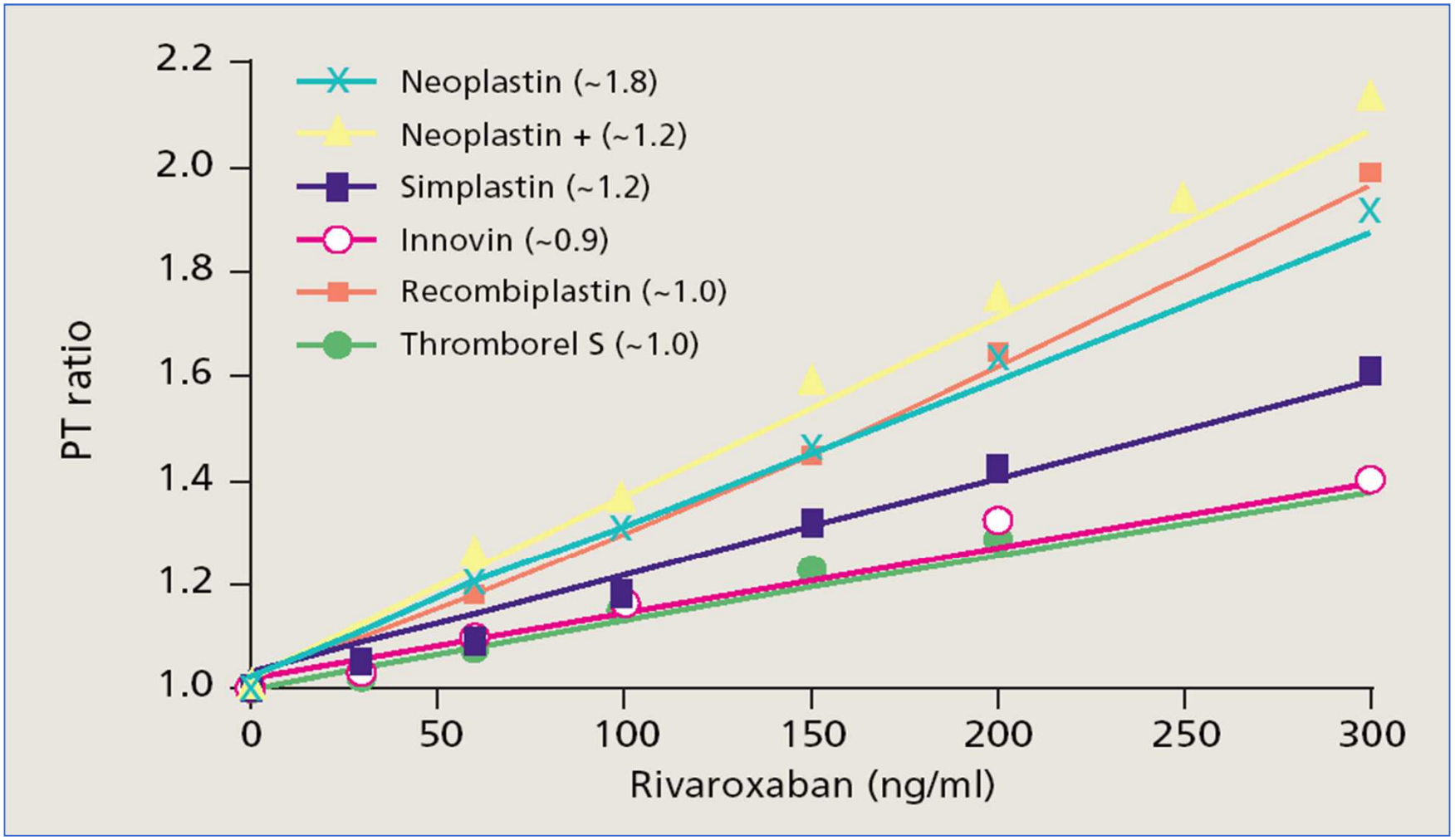


Freyburger G, et al, Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: Two observational studies in patients undergoing.... Thromb Res (2011),

Influence sur les tests de coagulation

	Dabigatran	Rivaroxaban	Apixaban
↗ TQ	+	++	+/-
↗ TCA	++	+	+/-
↗ TT ou Temps d'écarine	++	-	-
Anti-Xa	-	++	++
Anti-IIa	++	-	-

PT rivaroxaban with different thromboplastins

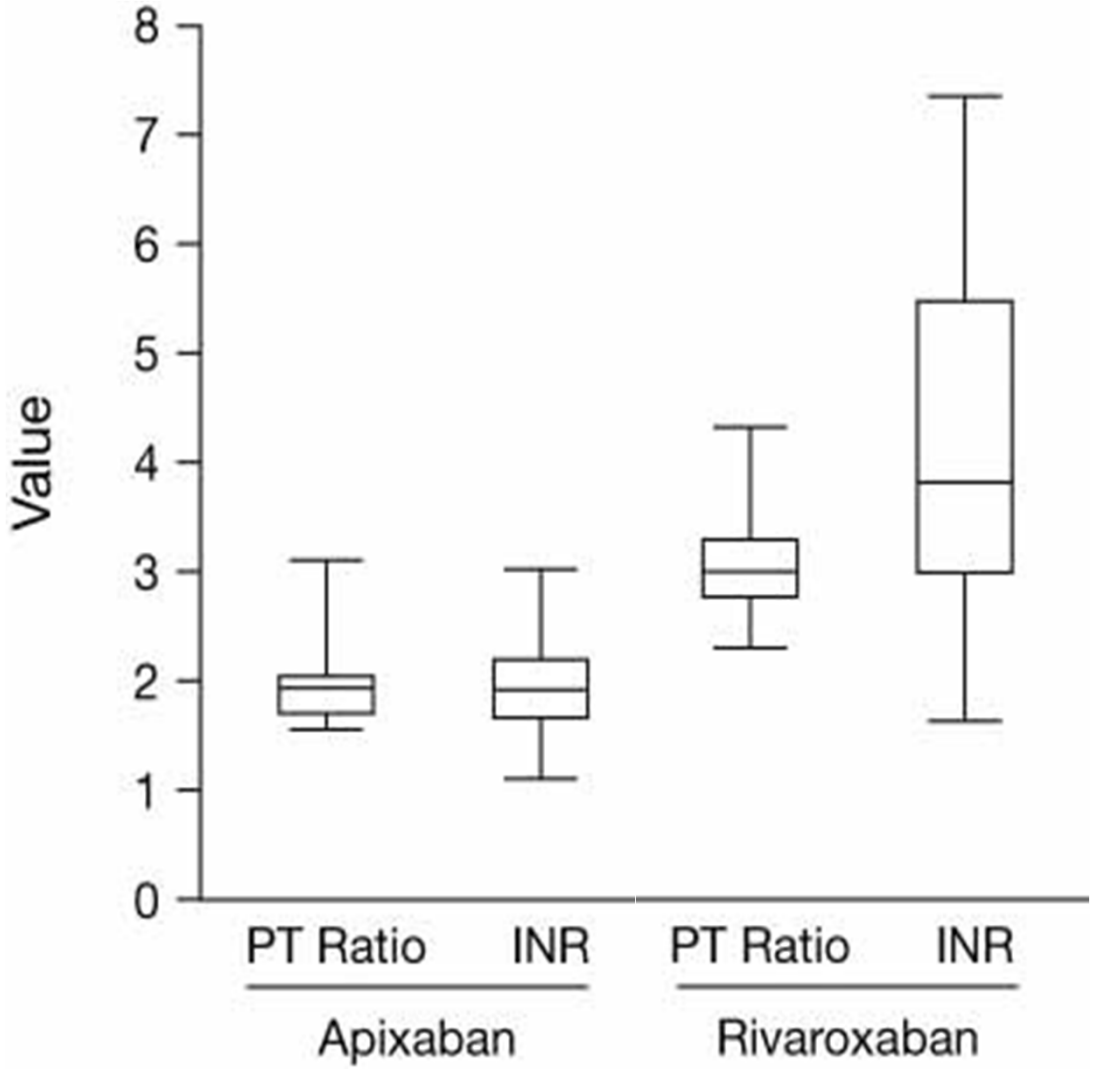


➢ Remark : *Fondaparinux doesn't prolong PT*

Correlation PT ratio (CoaguChek XS) and concentration of rivaroxaban R^2=0.997

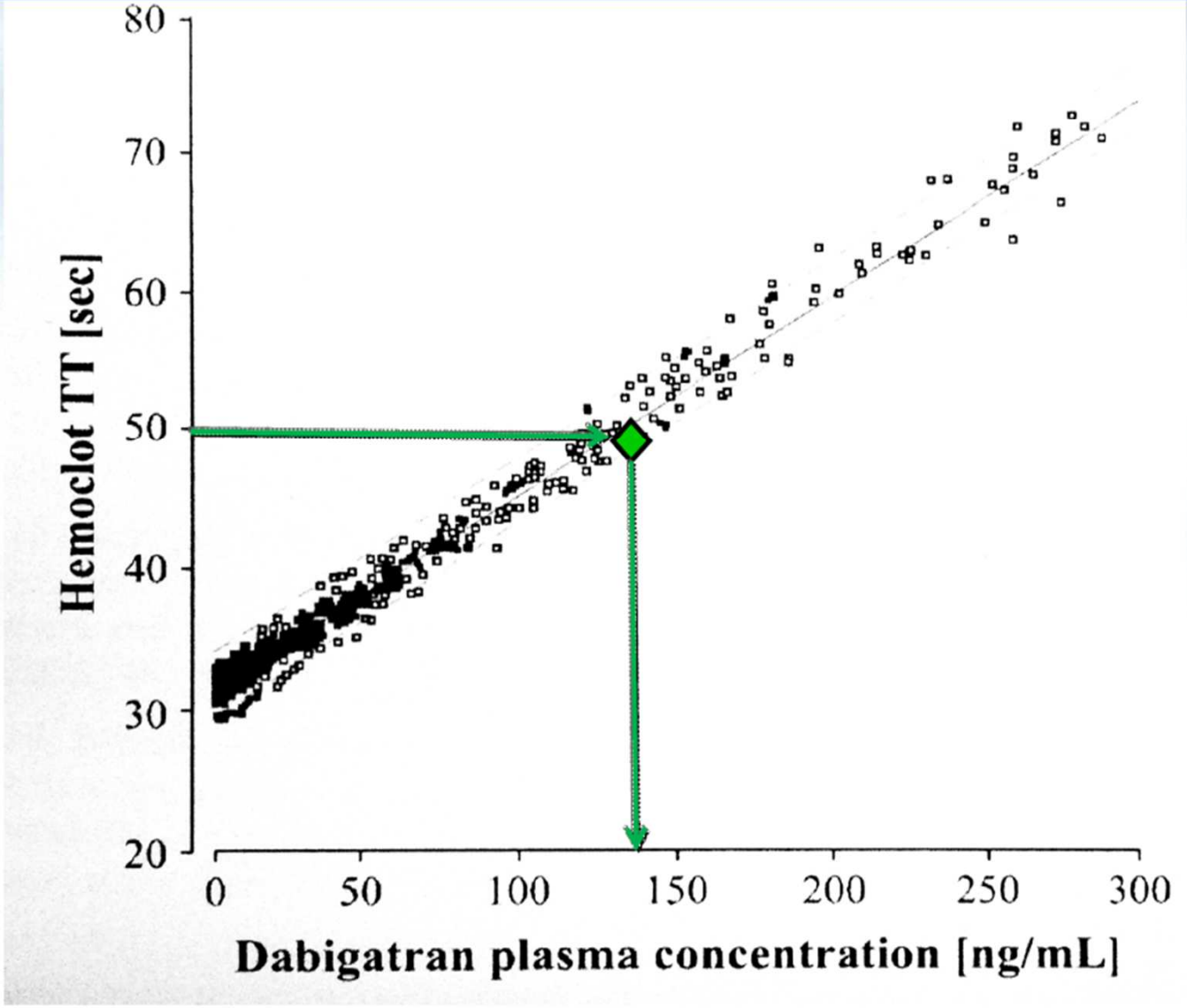
Samama et al. Thromb Haemost 2010

PT ratios and INR values of human PPP samples spiked with different factor Xa inhibitors at 1,000ng/ml concentration measured with 12 PT reagents



Barrett et al. Thromb & Haemost 2010

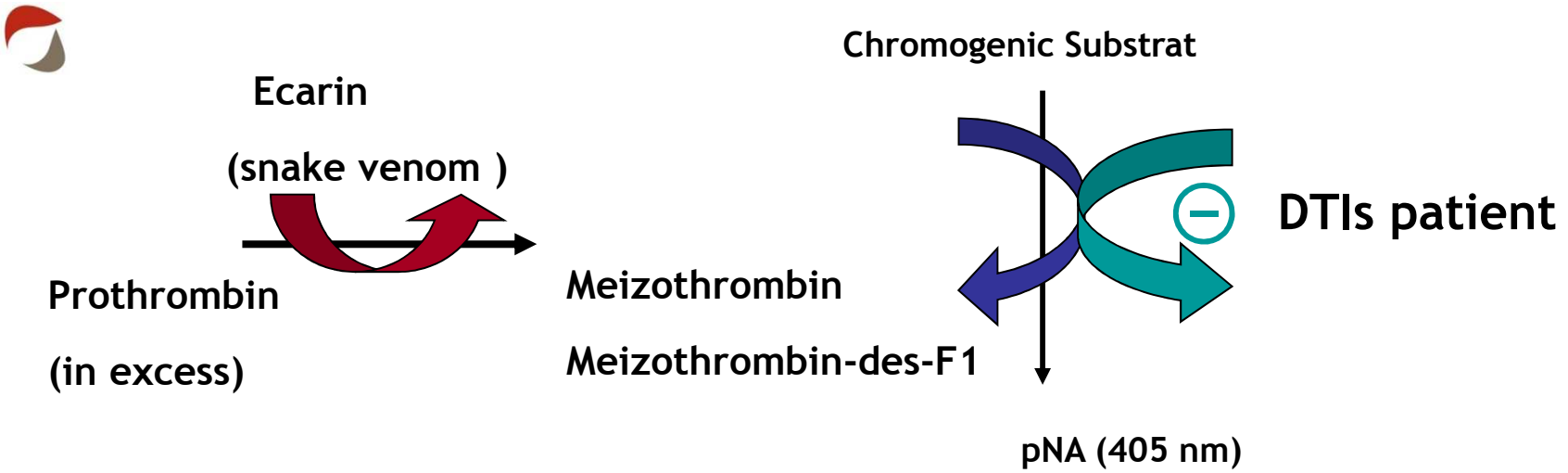
HÉMOCLOT TT® : CORRÉLATION AUX CONCENTRATIONS DE DABIGATRAN



van Ryn et al, Thromb Haemost 2010

Ecarin chromogenic Test

Principle

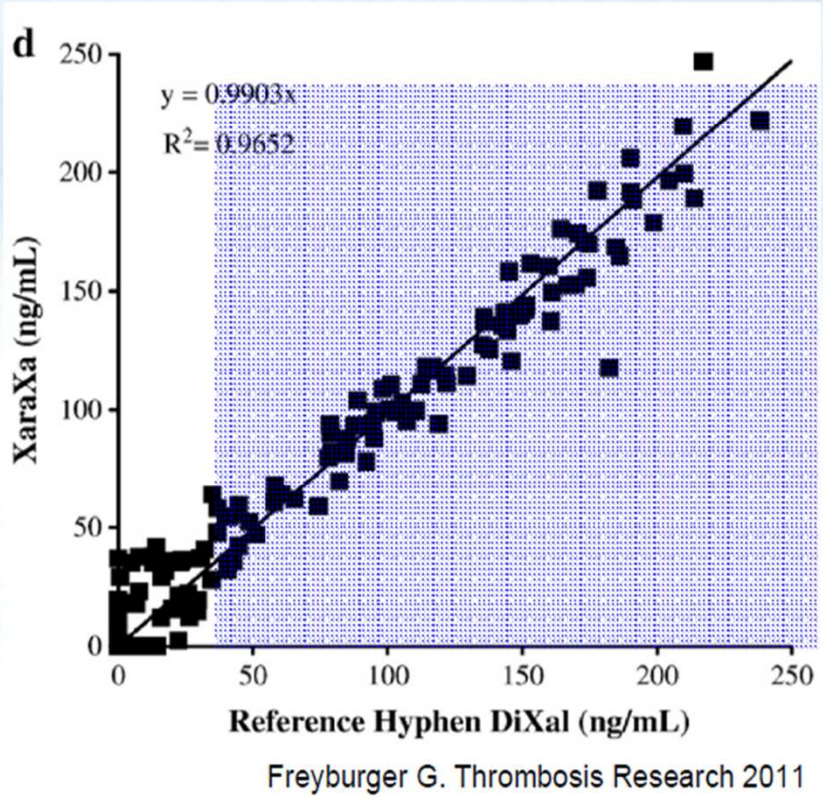


1- prothrombin provided in the kit is cleaved by ecarin, also provided

2- generated activation products (mainly meizothrombin) cleave the chromogenic substrate, which release p-Nitroaniline

3- the DTI inhibits the cleavage, since it binds immediately to activation products. Released pNA is inversely correlated to the DTI concentration

CONCENTRATION EN RIVAROXABAN : ANTI-Xa DÉDIÉ



Freyburger G. Thrombosis Research 2011

Tests spécifiques :
Adaptation des tests de mesure de l'activité anti-Xa utilisés pour les héparines **calibration** avec plasmas titrés en rivaroxaban

Enzyme -cible	méthode	Nom du test	Fournisseur
facteur Xa	chromogénique	Biophen DiXal®	Hyphen BioMed
facteur Xa	chromogénique	STA Liquid anti-Xa®	Diagnostica Stago

Rivaroxaban
Taux au Pic et en Résiduel après des doses prophylactiques et thérapeutiques

Dose et Régime	C maximale (ng/ml)	C résiduelle (ng/ml)
10mg od **prophylaxie**	120 (90 - 190)	10 (3 – 25)
20mg od **traitement**	220 (170 – 320)	25 (7 – 65)

Mück *et al, Thromb Haemost* 2008; 100:453–461

Dabigatran
Taux au Pic et en Résiduel après des doses prophylactiques et thérapeutiques

Dose et Régime	C maximale (ng/ml)	C résiduelle (ng/ml)
220mg od **prophylaxie**	183 (62 - 447)	37 (10 – 96)[a]
150 mg bid **traitement**	184 (64 – 443)	90 (31 – 225)[b]

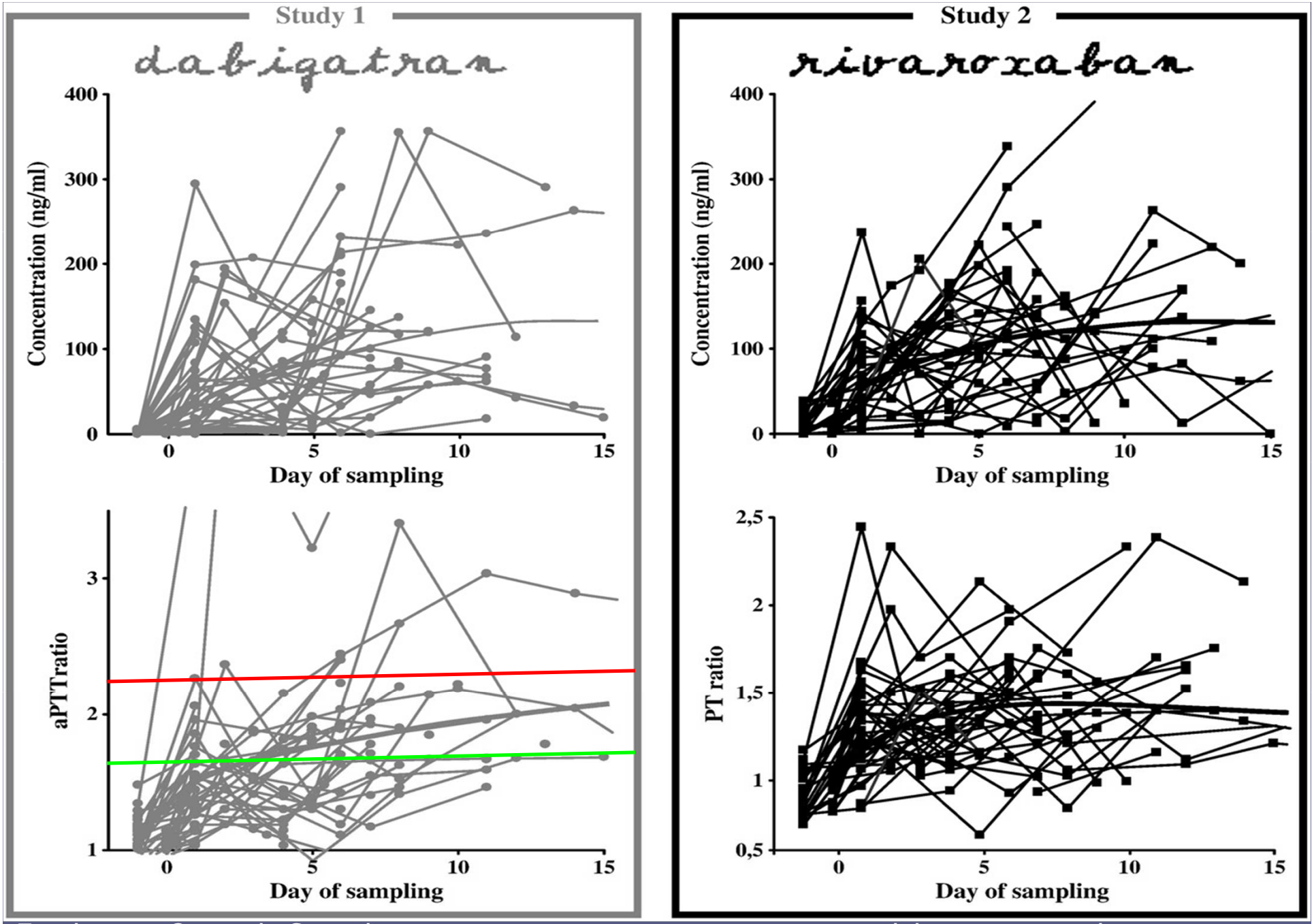
a : 24h après la prise
b : 12h après la prise

Van Ryn et al, Thromb Haemost 2010

Apixaban
Taux au Pic et en Résiduel après des doses prophylactiques et thérapeutiques Chez des volontaires sains (n=6)

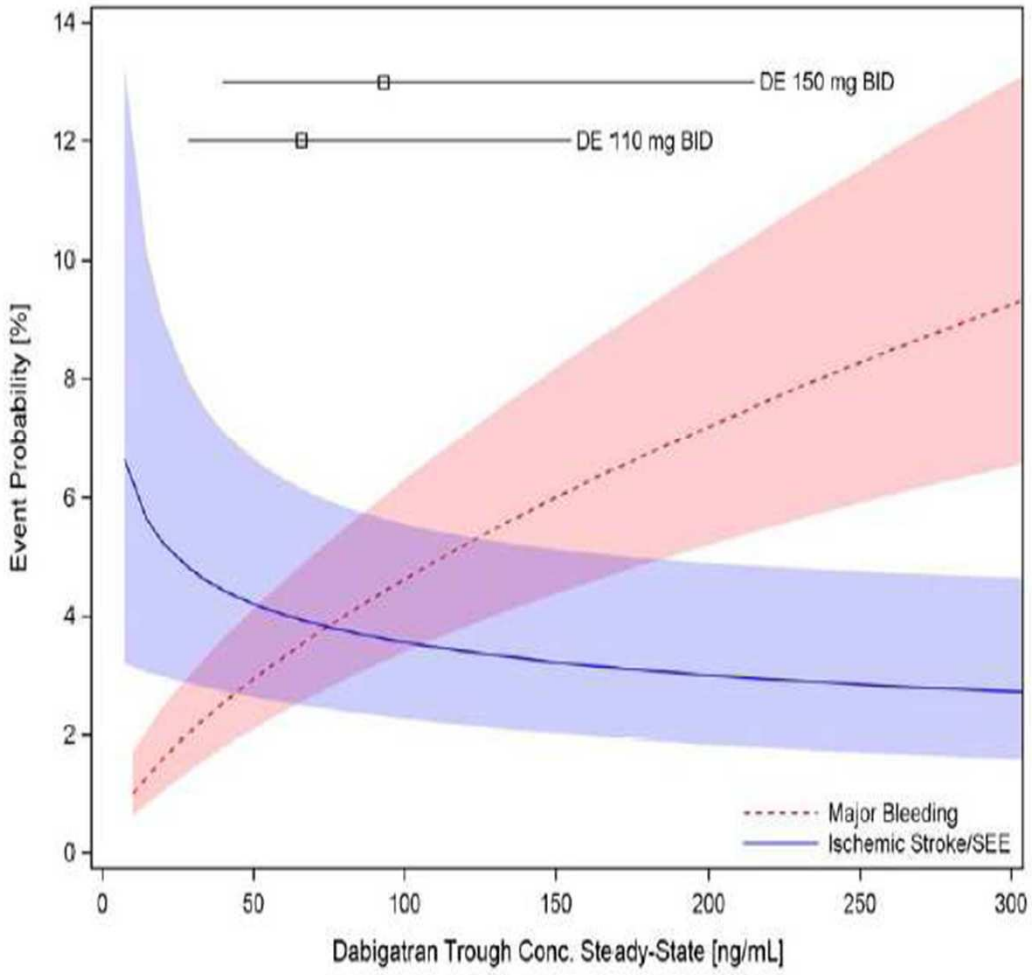
Dose et Régime	C maximale (ng/ml)	C résiduelle (ng/ml)
2,5 mg bid	62,3 ± 37	21±17
5 mg bid	128,5 ± 10	49,6 ± 20
10 mg bid	329,8 ± 45	103,8 ± 57

CV 185002



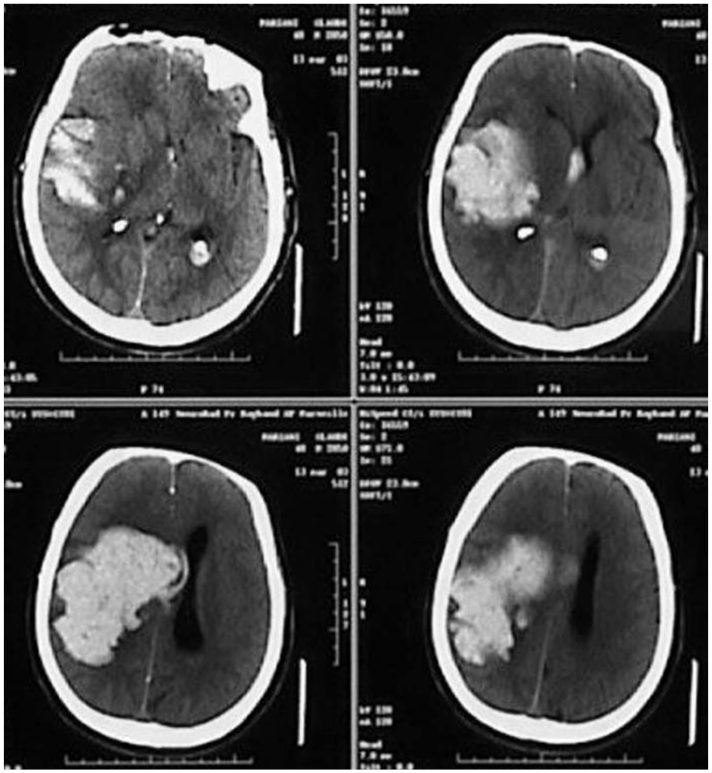
Freyburger G, et al, Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: Two observational studies in patients undergoing..., Thromb Res (2011),

Dabigatran
Cresiduelle- risk thrombotique et hémorragique



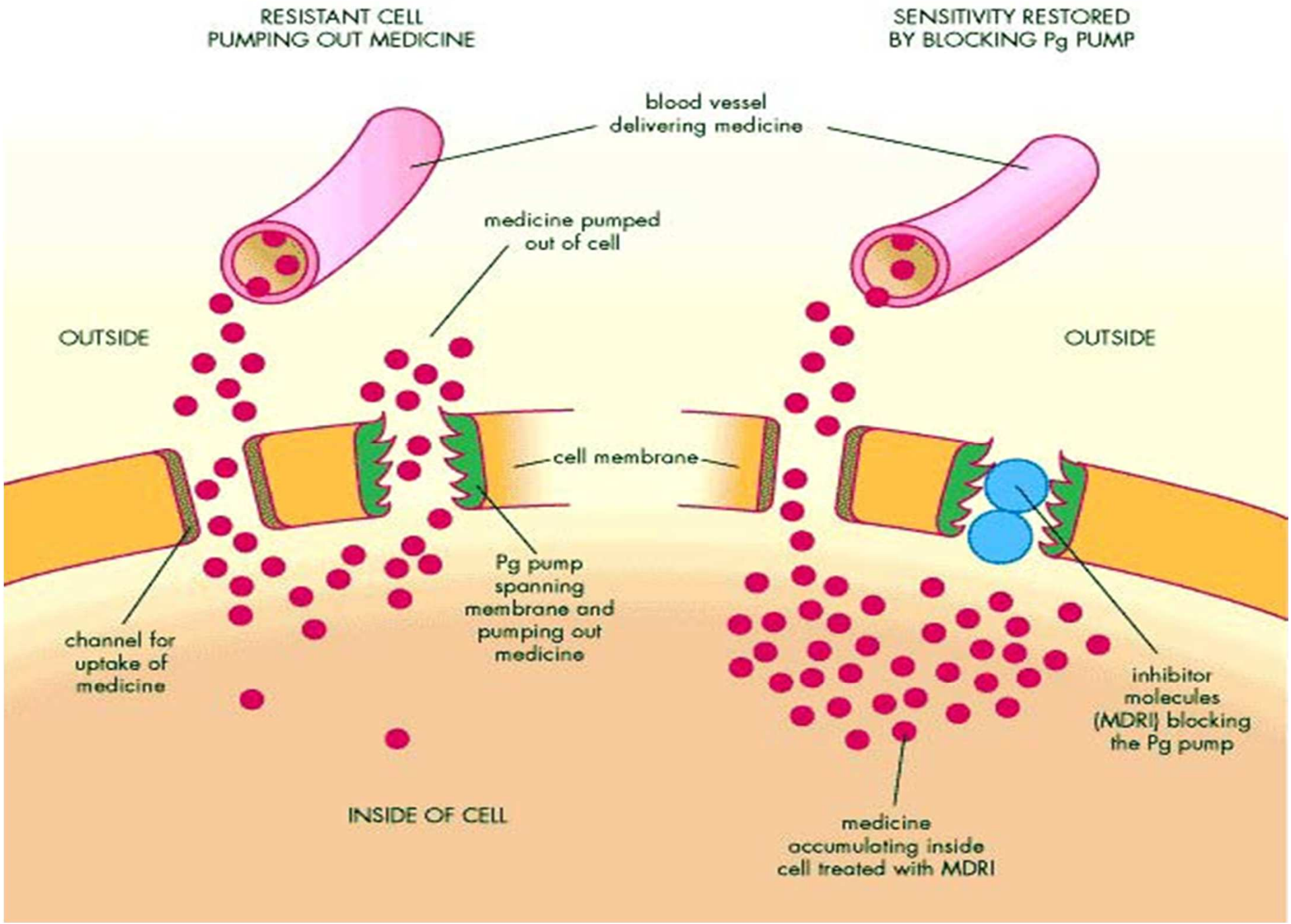
Reilly et al, JACC 2013

Understanding of the differential rate of intracerebral hemorrhages in patients treated by OACs vs VKA

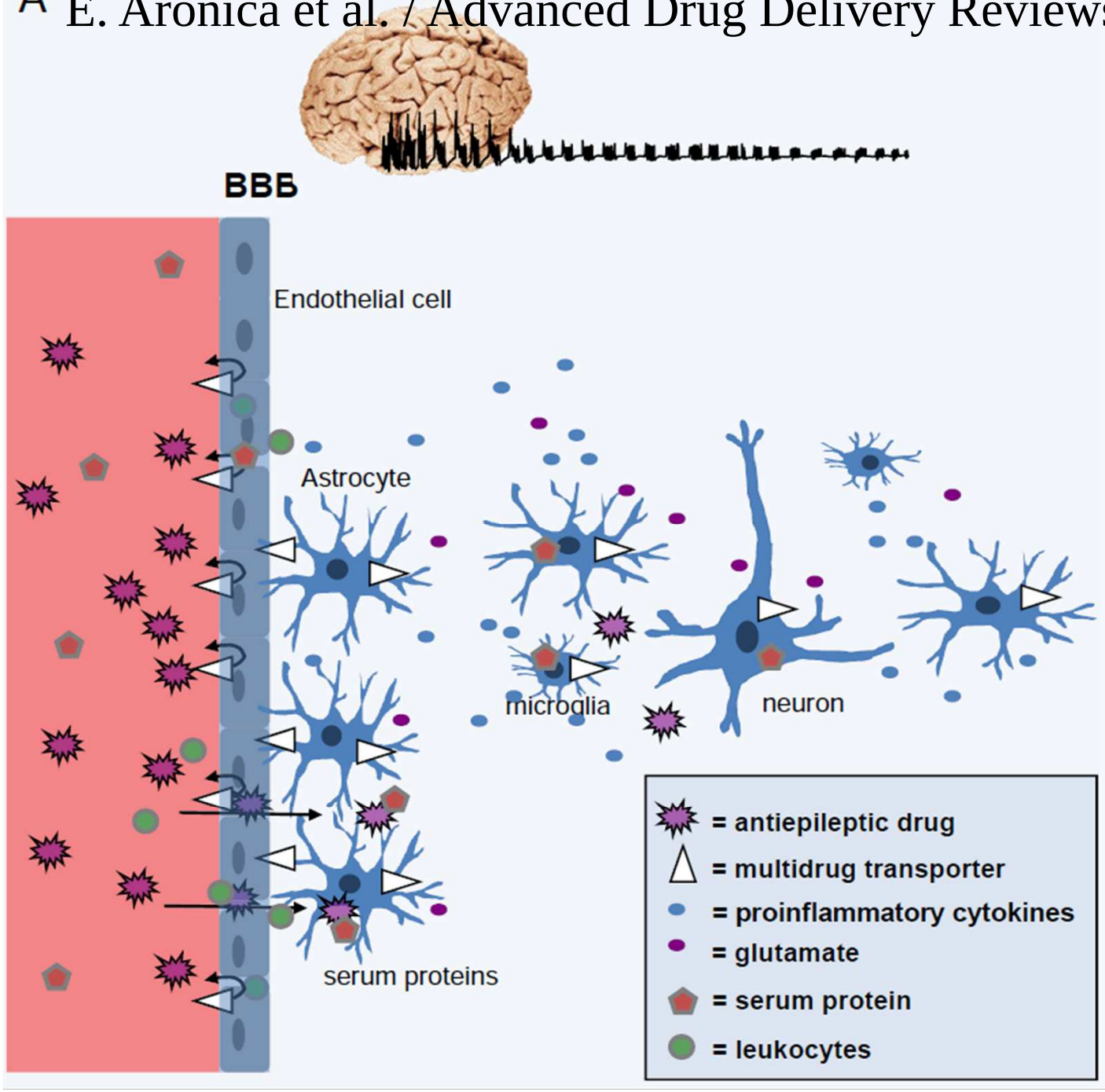


Understanding of the differential rate of intracerebral hemorrhages in patients treated by OACs vs VKA

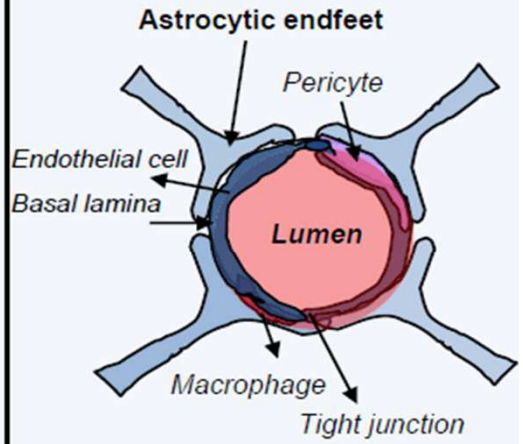
- Role of PgP in the passage across the blood-brain barrier


RESISTANT CELL
PUMPING OUT MEDICINE
SENSITIVITY RESTORED
BY BLOCKING Pg PUMP
blood vessel
delivering medicine
medicine pumped
out of cell
OUTSIDE
OUTSIDE
cell membrane
Pg pump
spanning
membrane and
pumping out
medicine
channel for
uptake of
medicine
inhibitor
molecules
(MDRI) blocking
the Pg pump
INSIDE OF CELL
medicine
accumulating inside
cell treated with MDRI

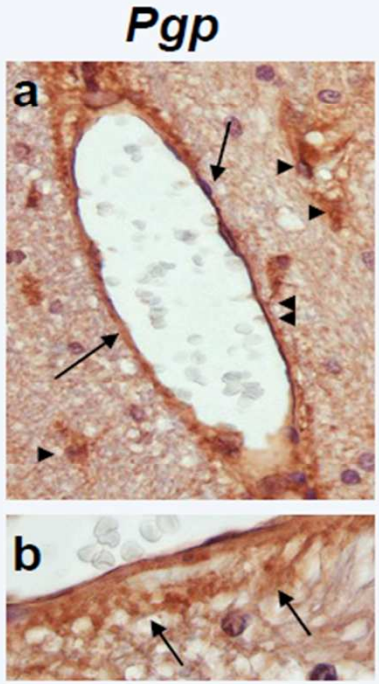
A E. Aronica et al. / Advanced Drug Delivery Reviews 2011



B



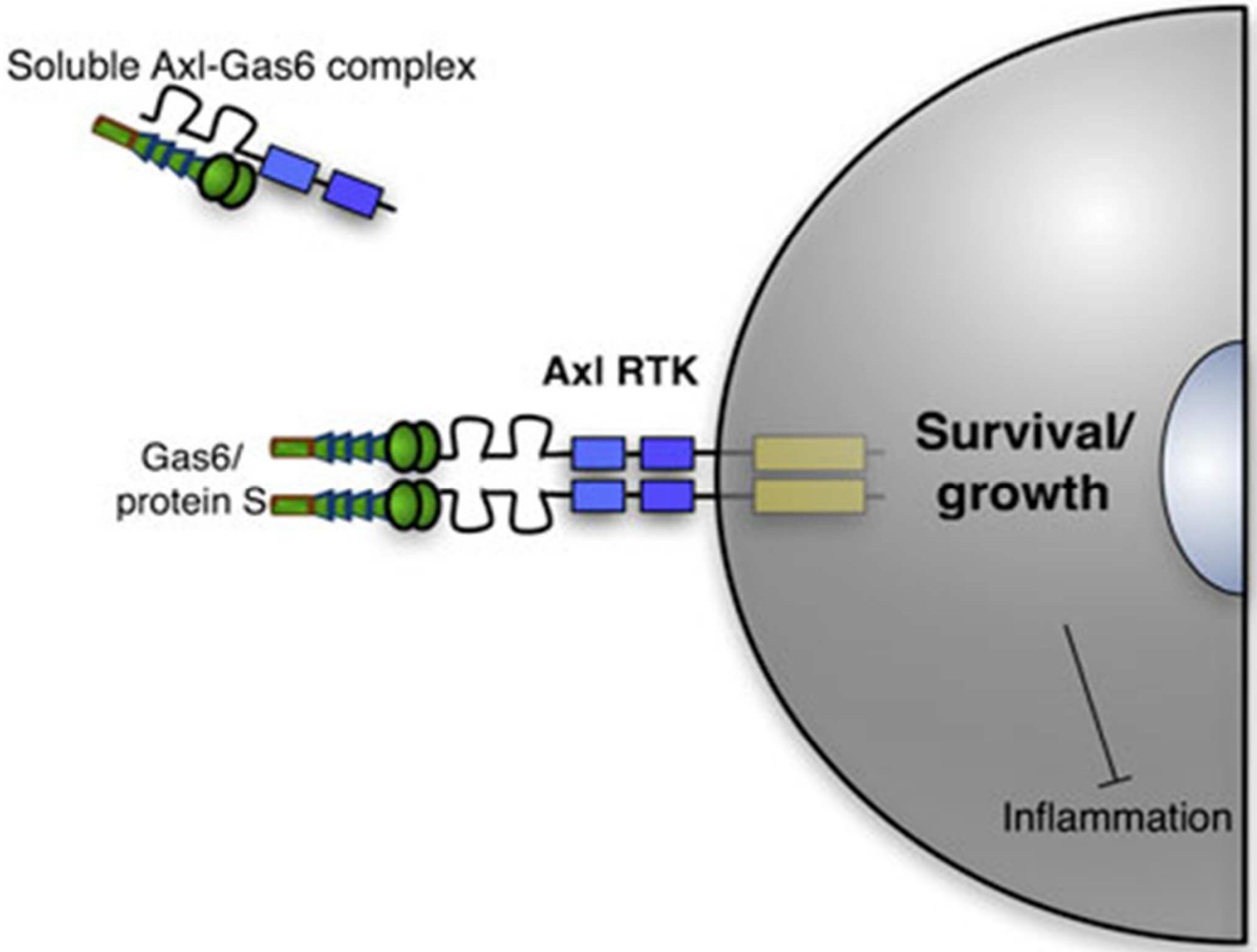
C



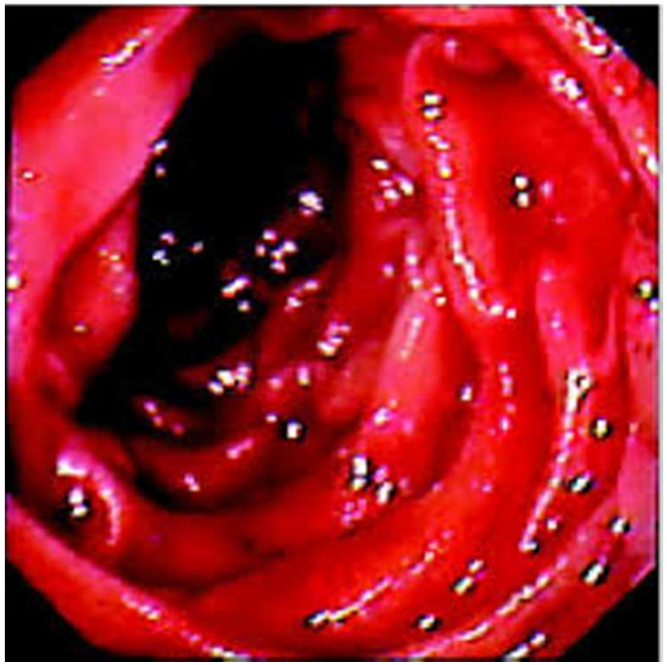
Understanding of the differential rate of intracerebral hemorrhages in patients treated by OACs vs VKA

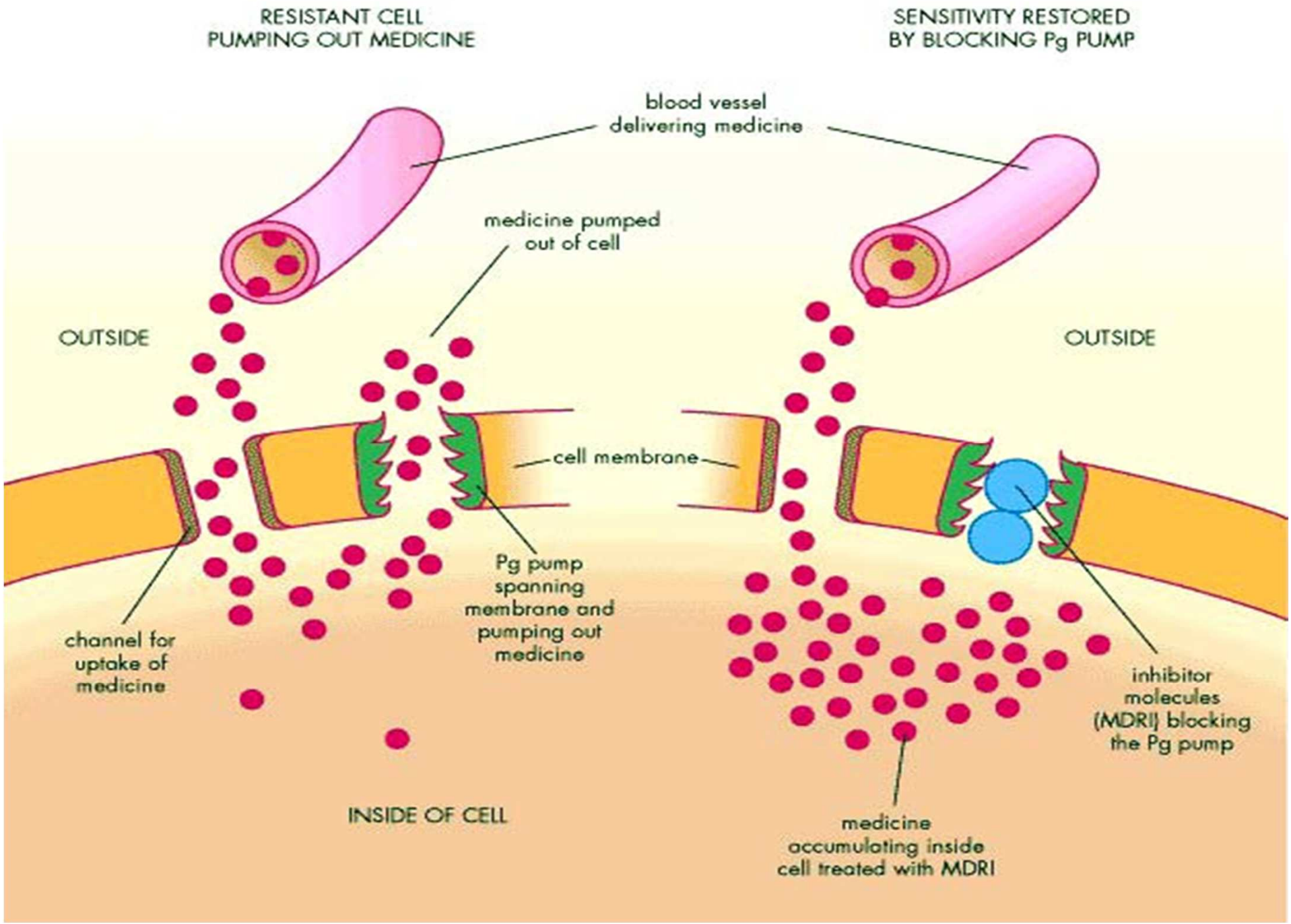
Role of PgP in the passage across the blood-brain barrier

A direct and specific pro-hemorrhagic effect of VKA at the blood brain barrier

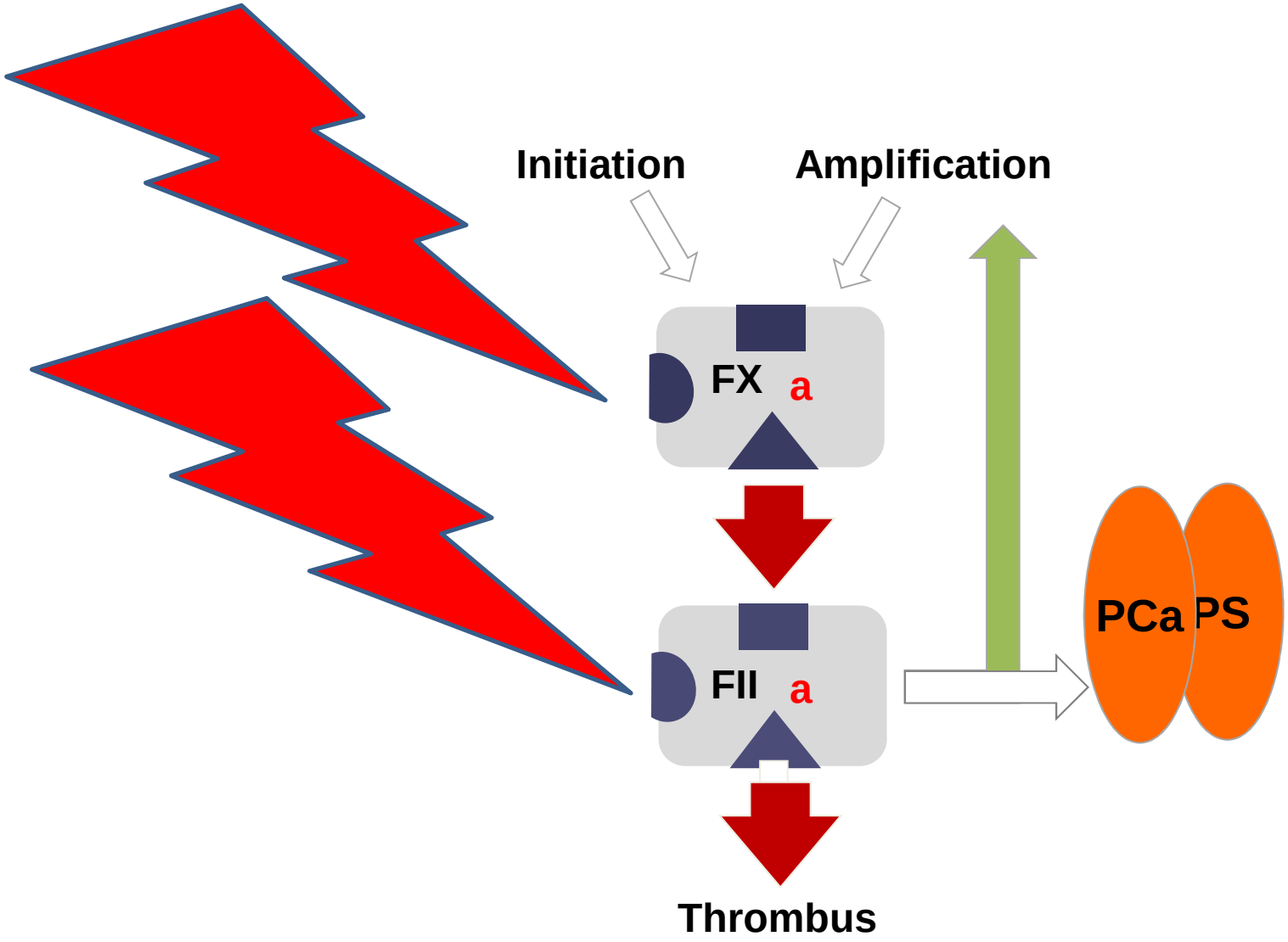

Soluble Axl-Gas6 complex
Axl RTK
Gas6/
protein S
Survival/
growth
Inflammation

Understanding of the differential rate of GI bleeding in patients treated by OACs vs VKA

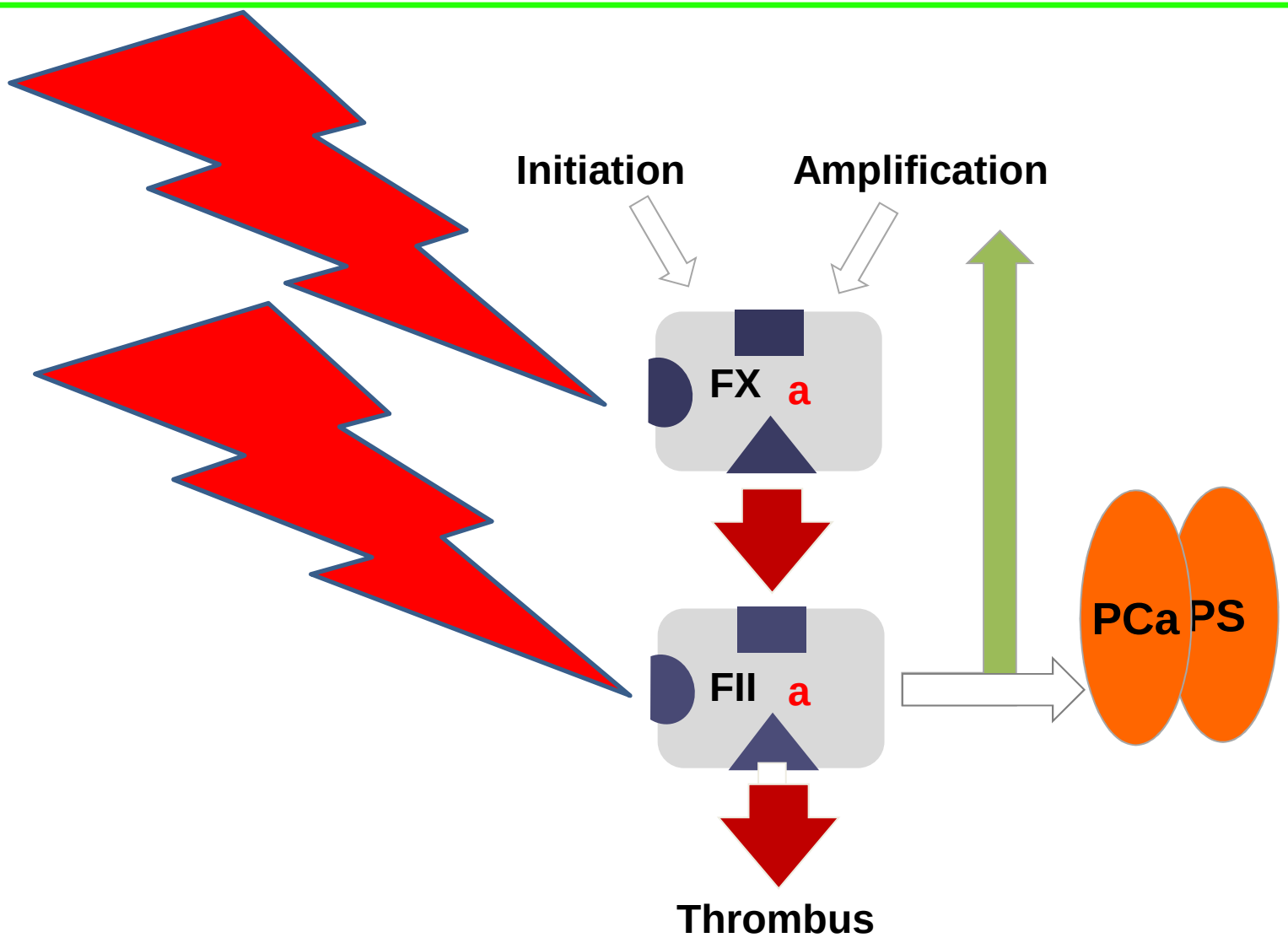



RESISTANT CELL
PUMPING OUT MEDICINE
SENSITIVITY RESTORED
BY BLOCKING Pg PUMP
blood vessel
delivering medicine
medicine pumped
out of cell
OUTSIDE
OUTSIDE
cell membrane
Pg pump
spanning
membrane and
pumping out
medicine
channel for
uptake of
medicine
inhibitor
molecules
(MDRI) blocking
the Pg pump
INSIDE OF CELL
medicine
accumulating inside
cell treated with MDRI

NOAC tests de monitoring : les tests spécifiques
Ou alors bien savoir interpréter les tests classiques



NOAC reversion antagonisation: les antidotes spécifiques
Ou alors le PPSB ou le FEIBA : efficacité, dose, risque thrombotique



DPC

SRLF

Hémorragies

"Anticoagulants et nouveaux anticoagulants: mécanismes d'action"

Ludovic Drouet
Hôpital Lariboisière,
Université Paris VII,
Paris France

Paris
Avenue claude vellefaux
Jeudi 11 septembre 2014

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IVS

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