

Intravenous and oral anticoagulants

Mechanisms of action

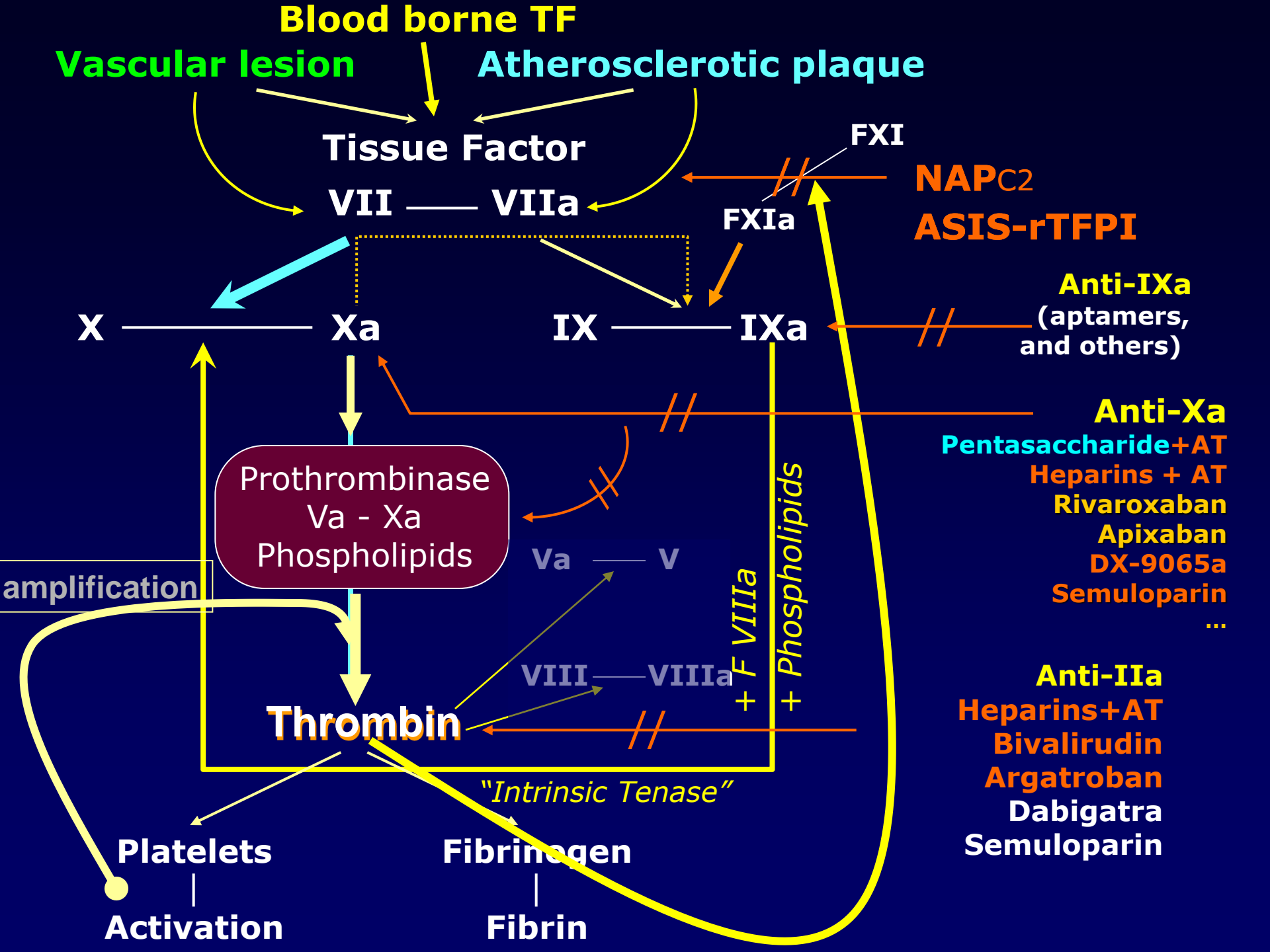
Grigoris T Gerotziafas



Groupe de Thrombose
Equipe de recherche ER2UPMC
Interactions cellulaires tumorales et leur environnement et réponses aux agents anticancéreux.



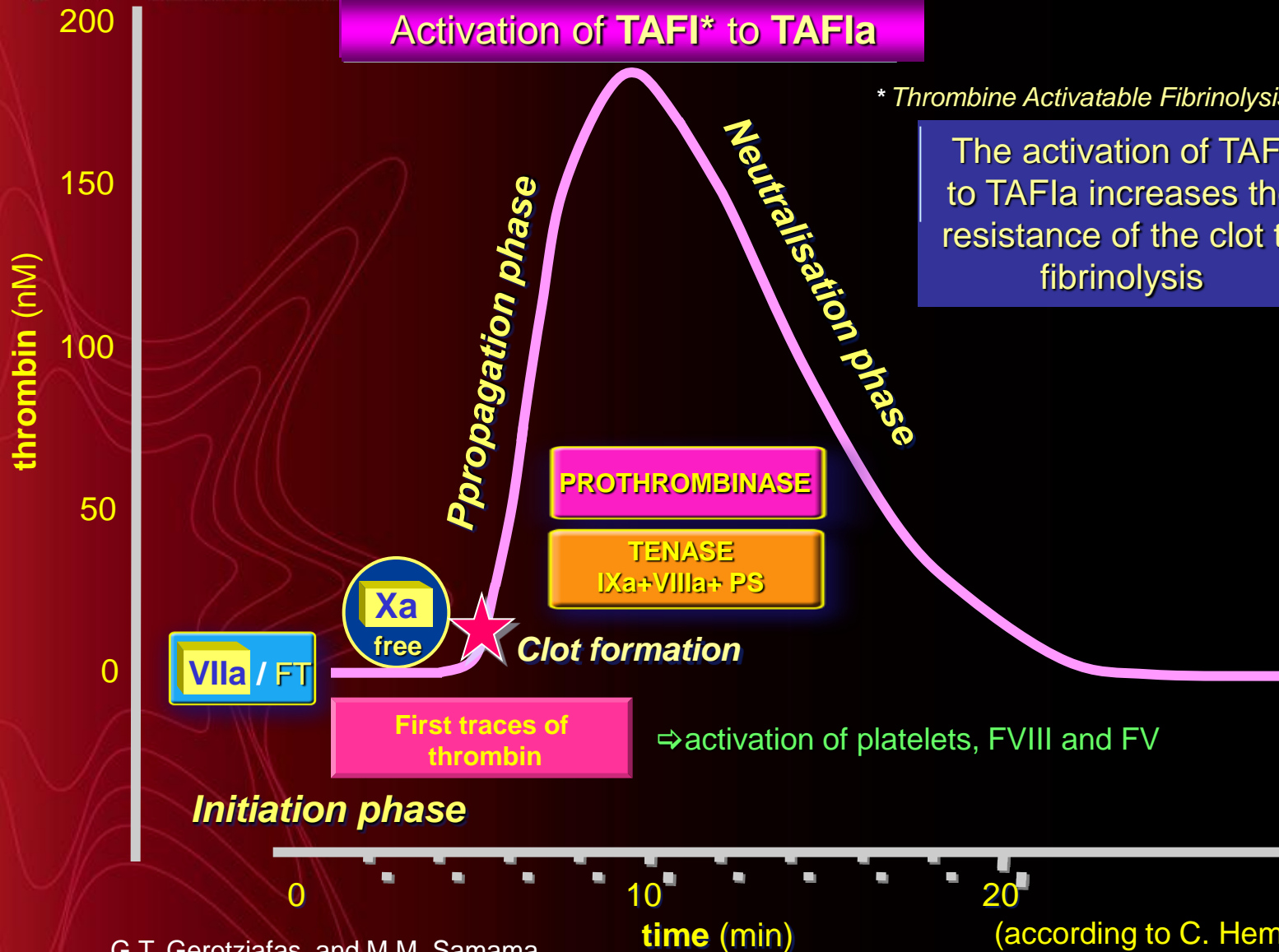
Service d'Hématologie
Biologique Hôpital Tenon,
APHP, Paris, France



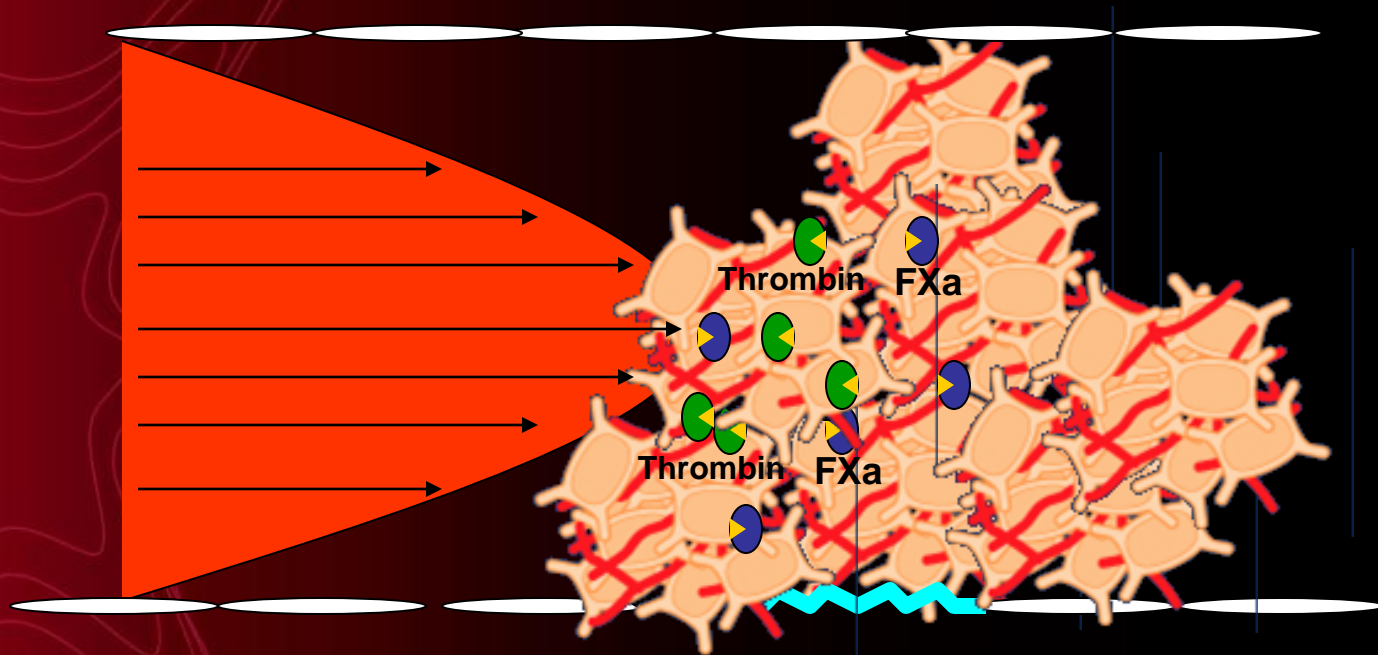
Thrombin generation after TF pathway activation in platelet rich plasma



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Thrombogenicity of thrombus



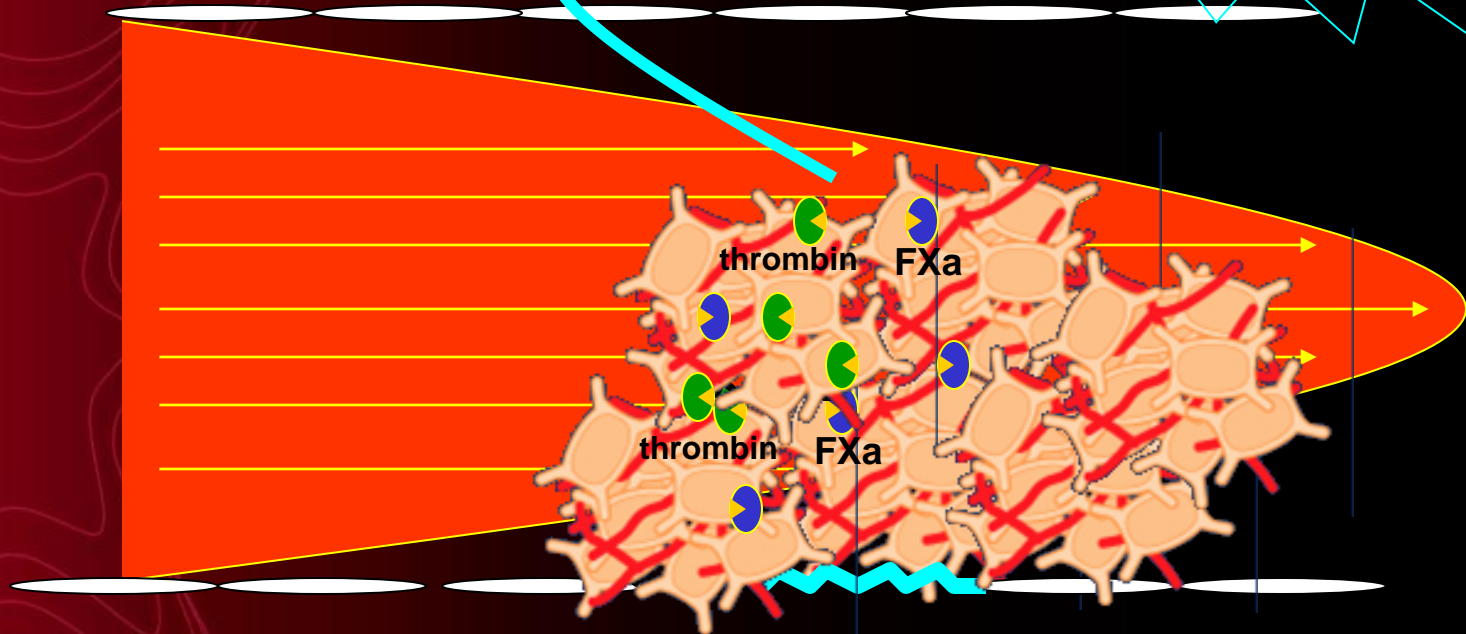
Thrombogenicity of thrombus



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& HAEMOSTASIS

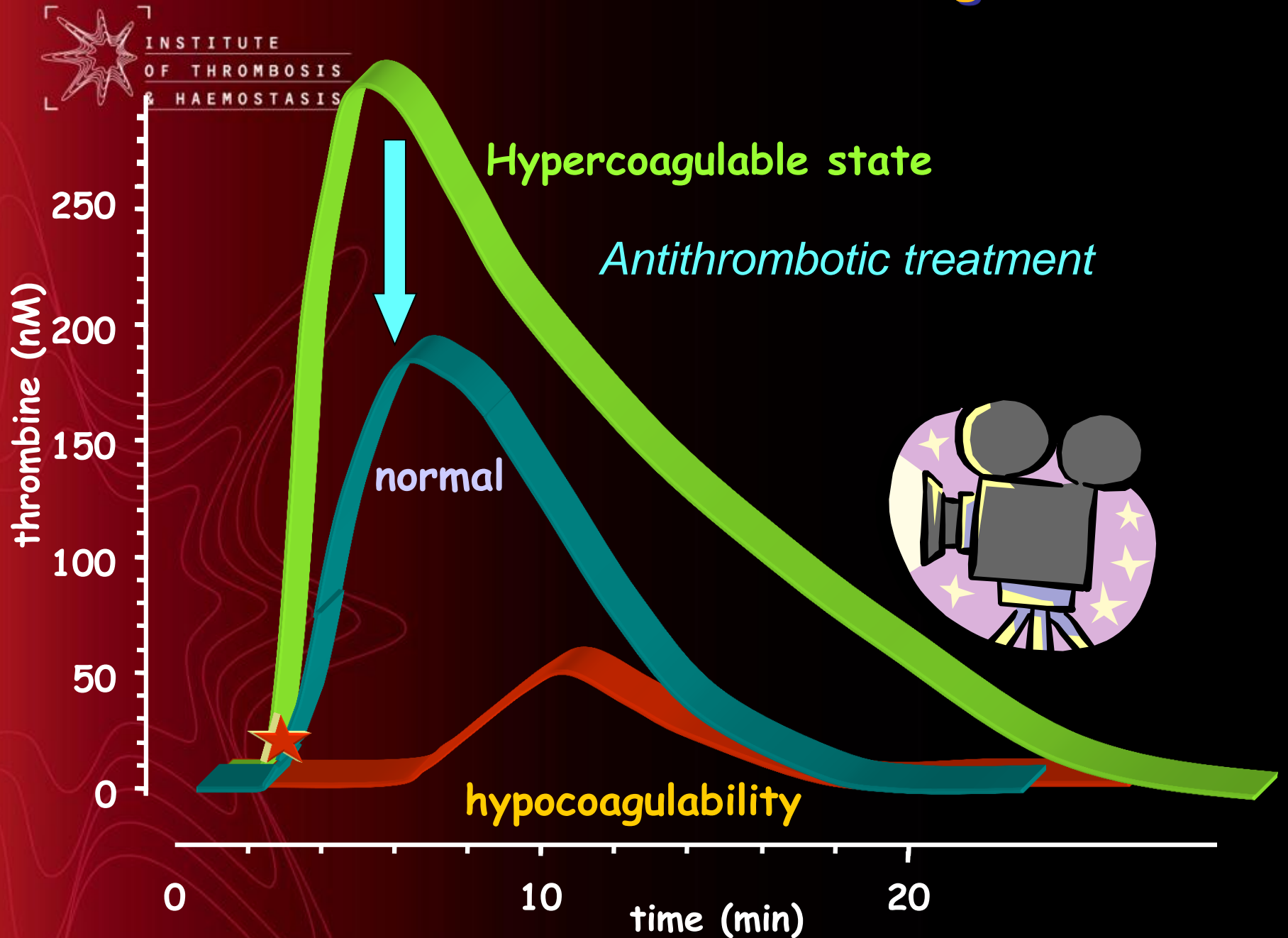
In accelerated lysis

Activation of platelets
Thrombin generation
Re-occlusion



Rivaroxaban, dabigatran, bivalirudin :
Inhibition of clot bound FXa or thrombin

Profile of thrombin generation



Simple classification of anticoagulants

Factor Xa

AT-dependent inhibitors:
Pentasaccharide, heparins

Direct inhibitors:
Rivaroxaban, apixaban,
edoxaban ...

 Parenteral

 Oral

Thrombin

AT-dependent inhibitors
Heparins, danaparoid

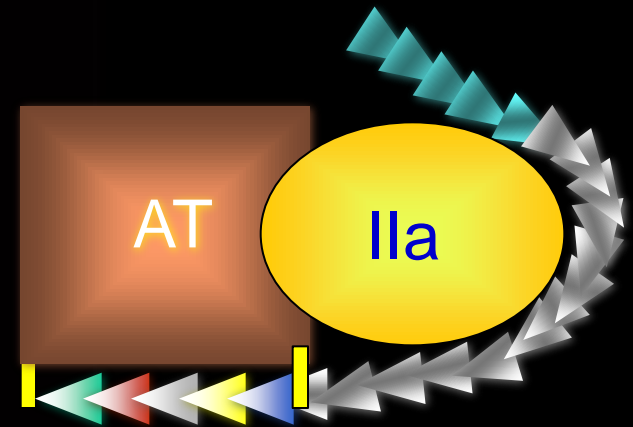
HCI-dependent inhibitors

Direct inhibitors:
Dabigatran, lepirudin,
bivalirudin...

Mechanism of action of UFH and LMWHs



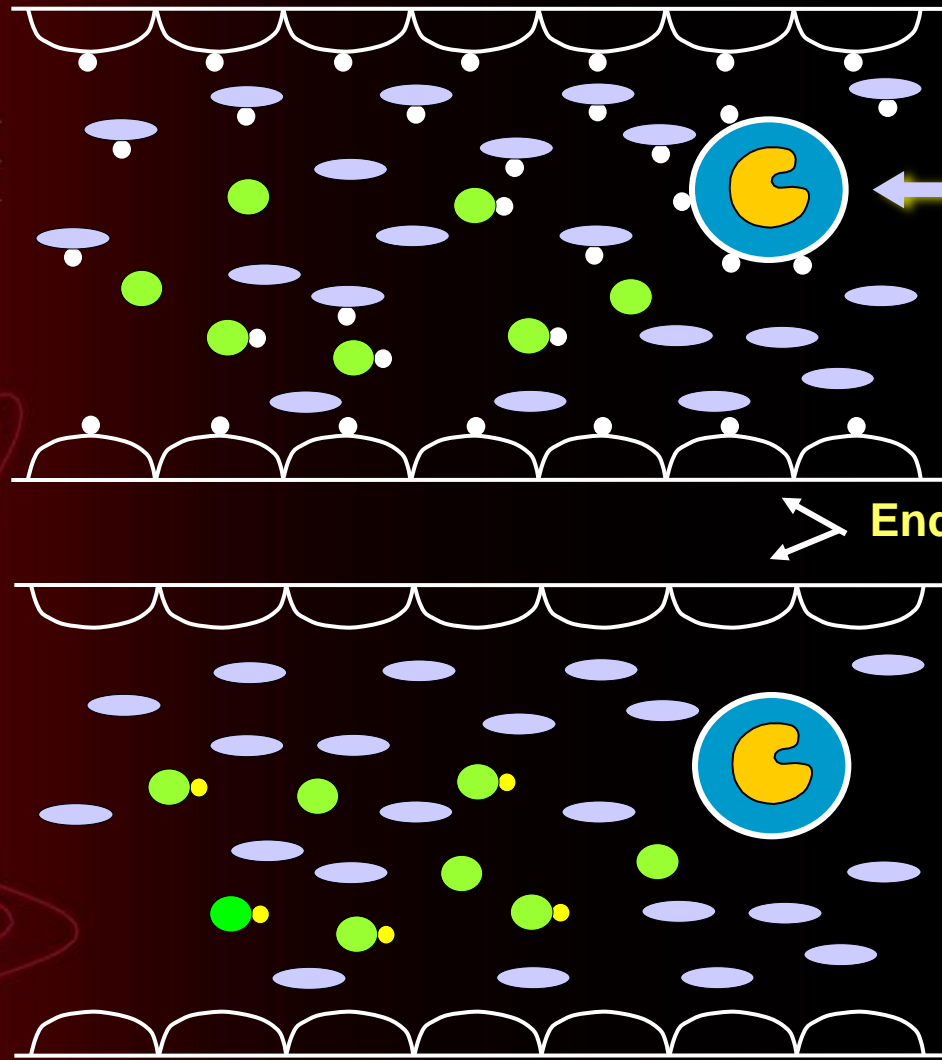
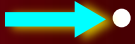
Below Critical Length Material
MW < 5400 Da
(< 18 monosaccharides)



Above Critical Length Material
> 5400 Da
(> 18 monosaccharides)

Similar mechanism for the inhibition of
FIXa

Heparin



Macrophage

Endothelial cells

Fondaparinux
Idraparinux



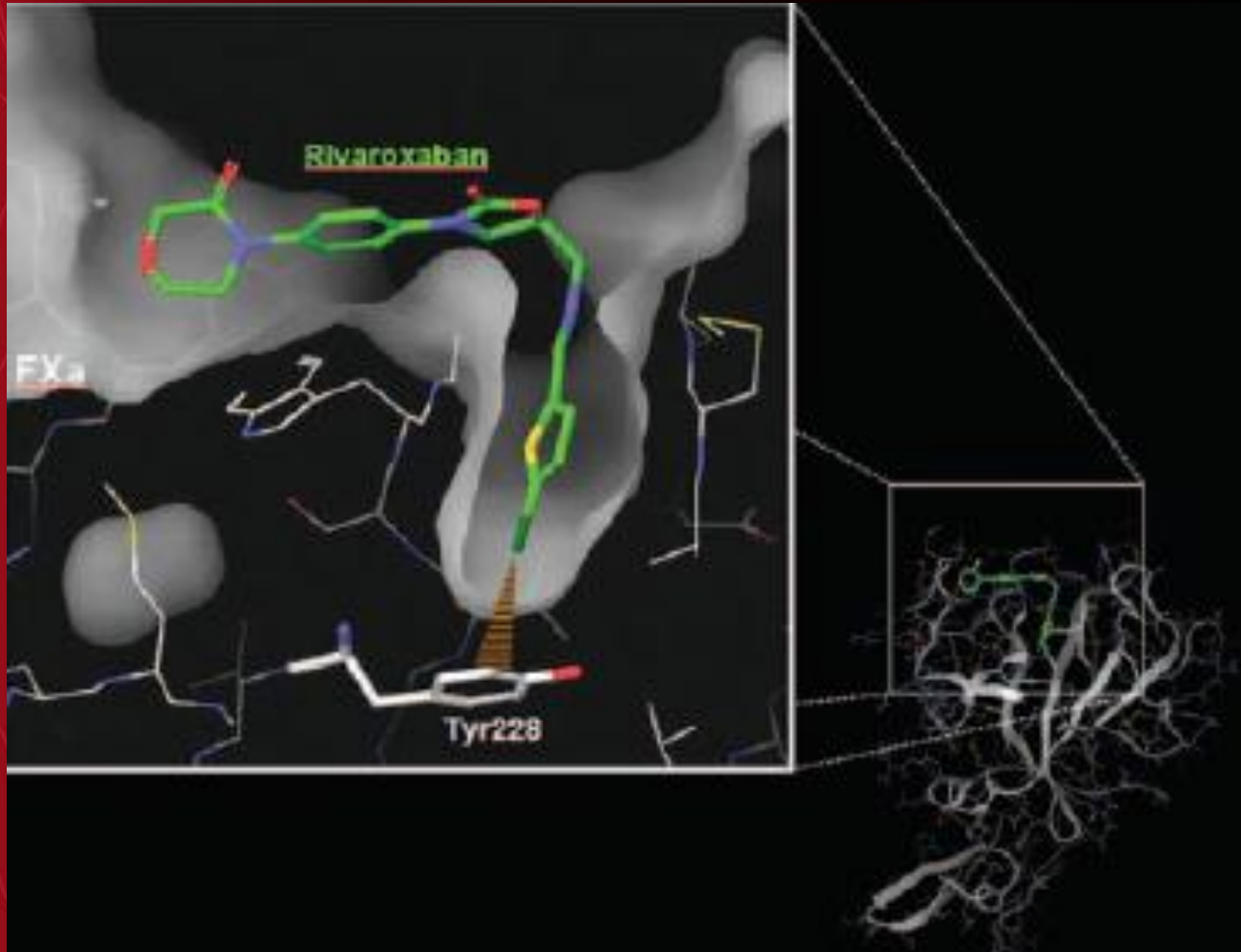
● antithrombin

● fondaparinux

● other plasma proteins

● Heparin

Selective binding of rivaroxaban on the active site of FXa



Effect of FXa inhibitors on free and prothrombinase bound FXa

Direct inhibitors of FXa
(rivaroxaban, DX9065a,...)

AT/pentasaccharide

AT/Heparins

(UFH and LMWHs)

Fluide phase

FXa



FXa

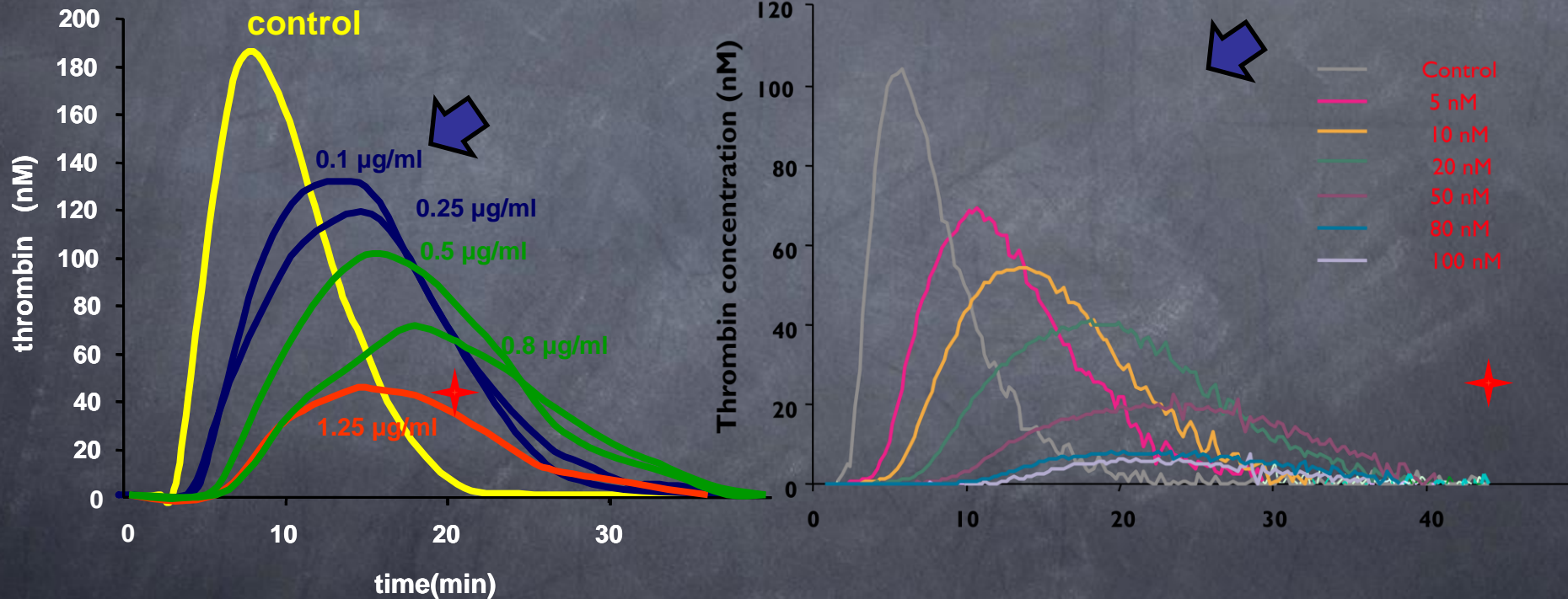
FVa **Ca²⁺**
Phospholipids

prothrombinase

Barrowcliffe et al Biochem J 1987; 243:31–37.
Pieters et al, J Biol Chem 1988; 263:15313–15318.
Hemker et al, Biochim Biophys Acta 1989; 992:409–411.
Herault et al J Pharmacol Exp Ther 1997; 283:16–22
Rezaie AR. Blood 2001; 97:2308–2313.
Herault et al J Thromb Haemost 2003;1:1959-65
Perzborn et al J Thromb Haemost 2005; 3: 514–21

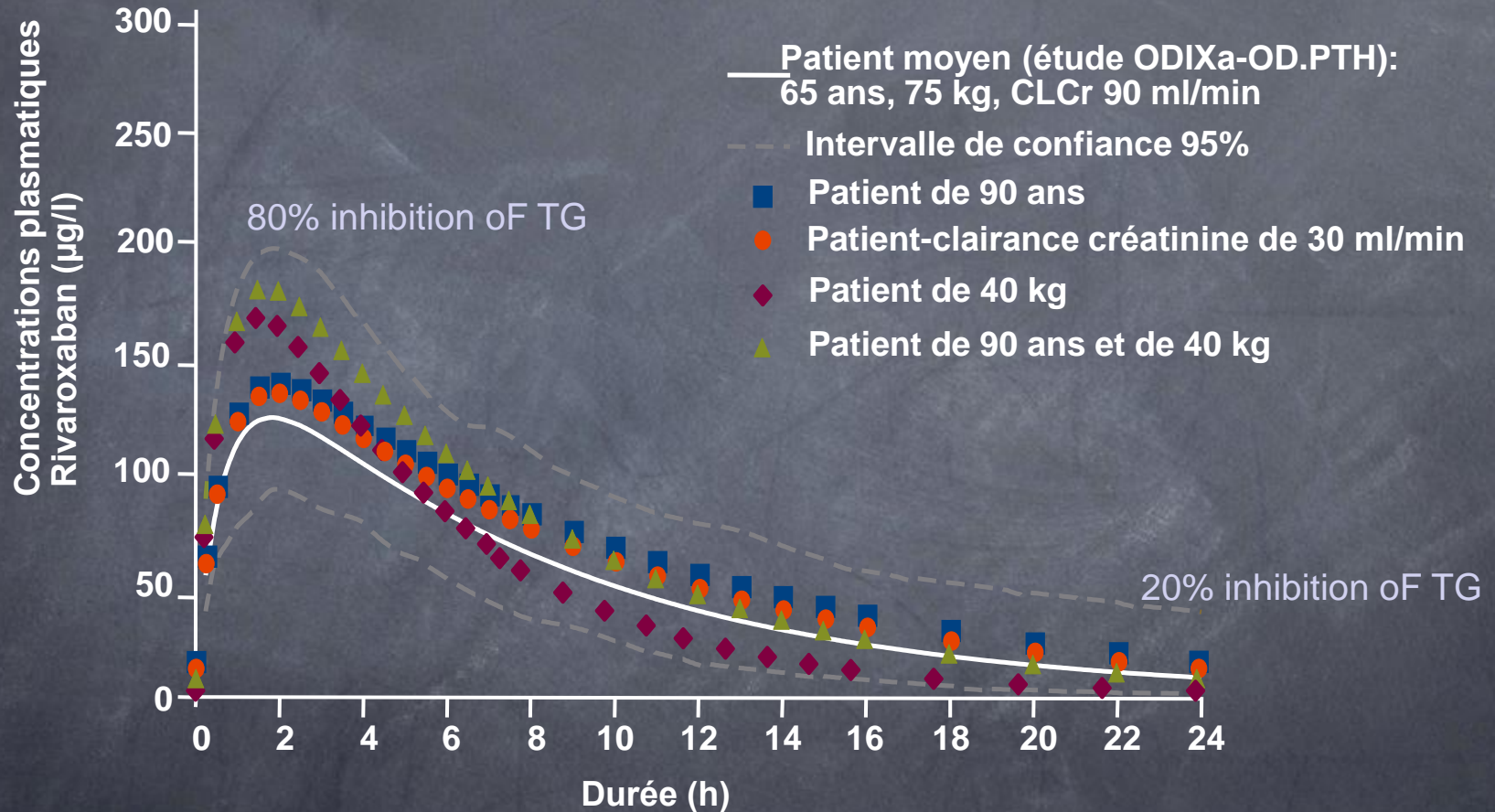
Comparison of the effect of enoxaparin and fondaparinux on thrombin generation

Influence of fondaparinux



PRP and Recombiplastin 1/1000 f.d.

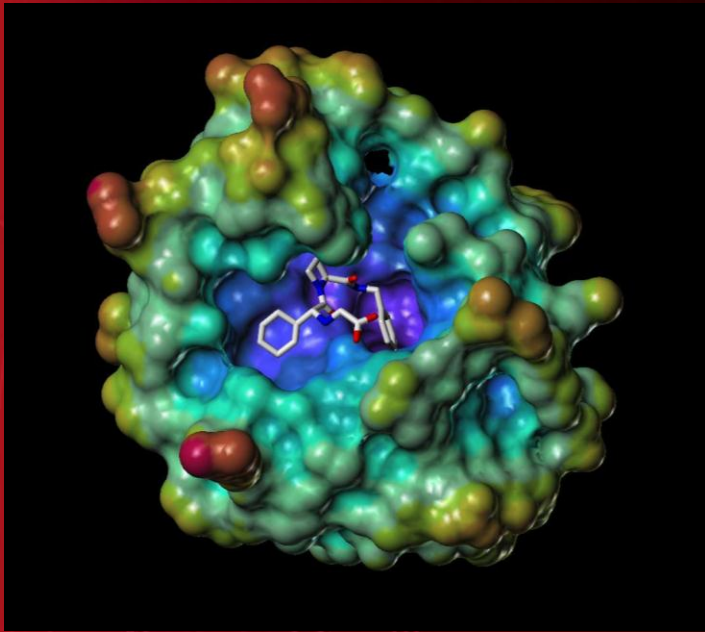
Xarelto[®] : pharmacocinétique



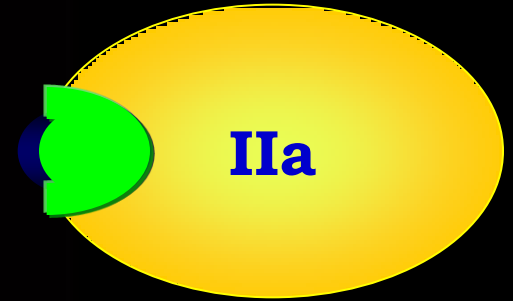
Heterogeneity of specific FXa inhibitors

	Idraparinux	Fondaparinux	Rivaroxaban	Otamixaban
Mode of action	AT-dependent Kd for AT= 1,4	AT-depentent Kd for AT= 58	Direct	Direct
Administration route	s.c.	s.c.	orall	i.v.
Half life	>80 h	17 h	4h	30 min
Cmax in plasma	0,3 – 1,5 µg/ml	0,3 – 1,5 µg/ml	500 nM	150 - 735 ng/ml
PT prolongation	no	no	+++	++
aPTT prolongation	no	no	+++	+++
Inhibition of prothrombinase bound FXa	Not assessed	no	yes	Not assessed
Inhibition of fibrin bound FXa	Not assessed	no	yes	Not assessed
Inhibition of FVIIa	Not assessed	yes	Not assessed	Not assessed

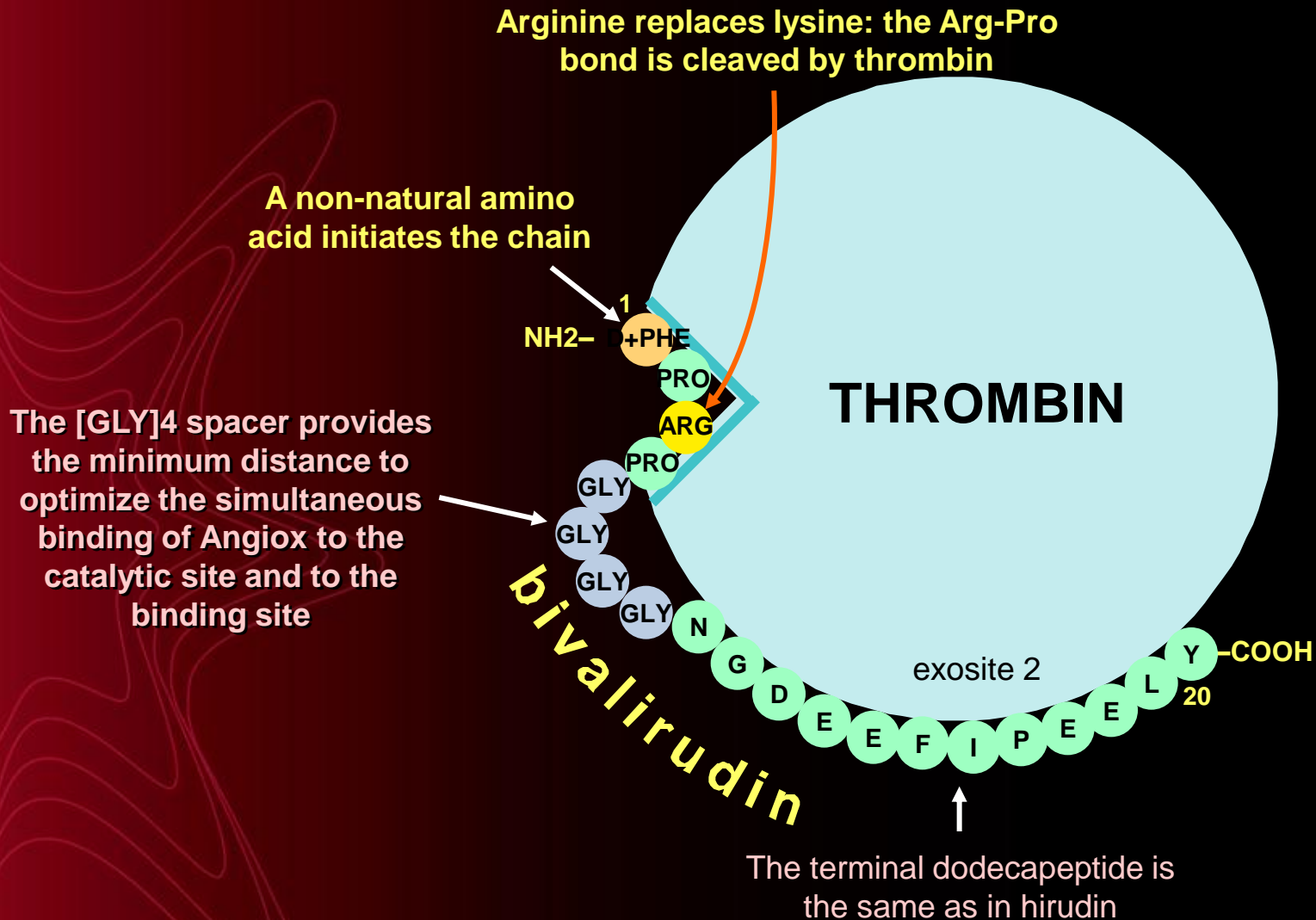
Direct inhibition of thrombin



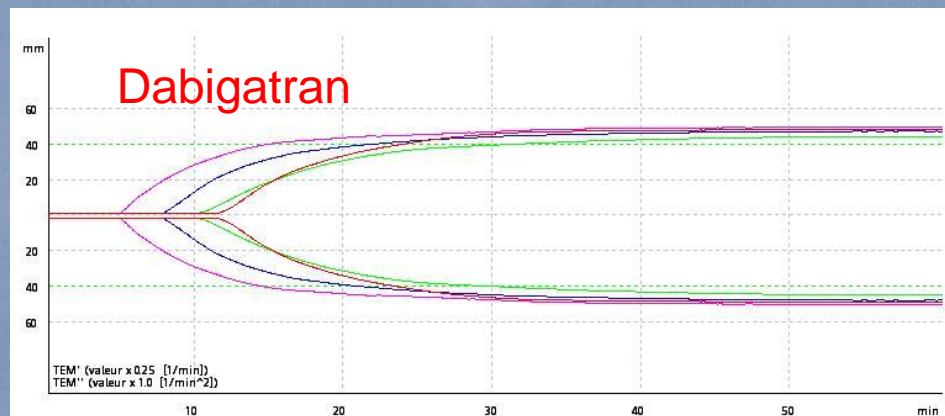
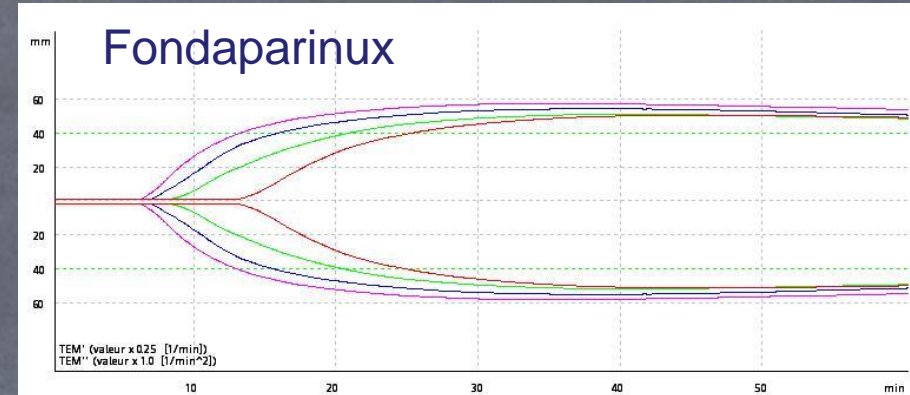
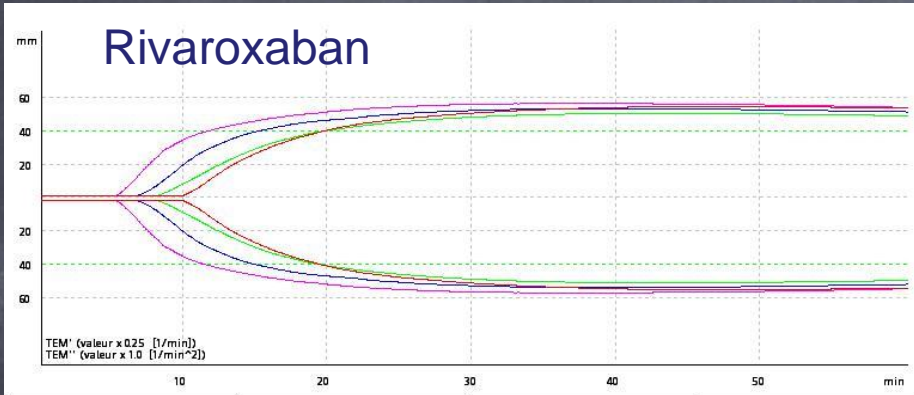
Dabigatran



Reversible inhibition of thrombin by bivalirudin



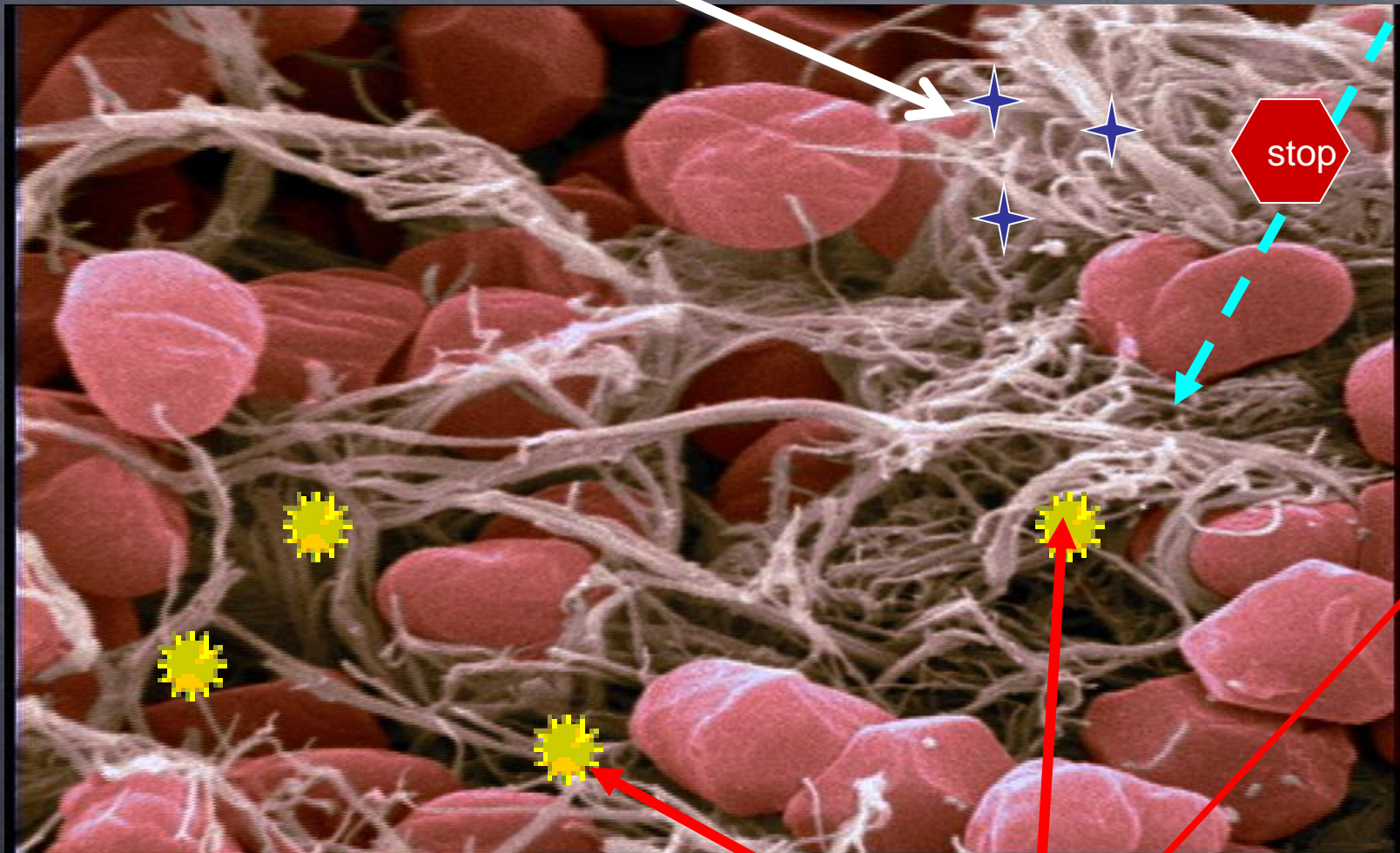
Influence of Rivaroxaban fondaparinux and dabigatran on TF-triggered whole blood thromboelastometry



EXTEM EXTEM EXTEM EXTEM

Direct FXa inhibitors

AT-heparin



★ = clot bound FXa

★ = free thrombin

★ = fibrin bound thrombin

rHirudin

dabigatran

RIVAROXABAN : ABSORPTION, DISTRIBUTION, MÉTABOLISATION, ELIMINATION

Absorption

Biodisponibilité : 80 - 100 %

C_{\max} : 2 - 4 h

Distribution

Liaison aux protéines plasmatiques de 92 - 95 %

Volume de distribution modéré

Métabolisation

~ 2/3 métabolisé, pas de métabolite actif circulant majeur

CYP 3A4, CYP 2J2, mécanismes indépendants des CYP

Elimination

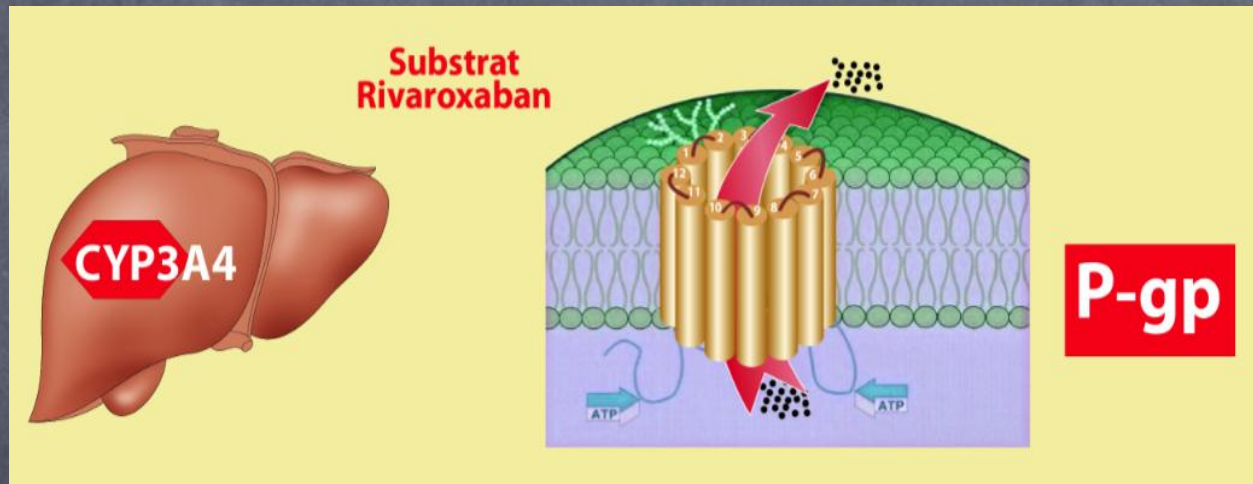
~ 1/3 non métabolisé : excrété sous forme active par voie rénale

2/3 métabolisé : 50 % éliminés par voie rénale,

Demi-vie d'élimination : 7 - 11 heures

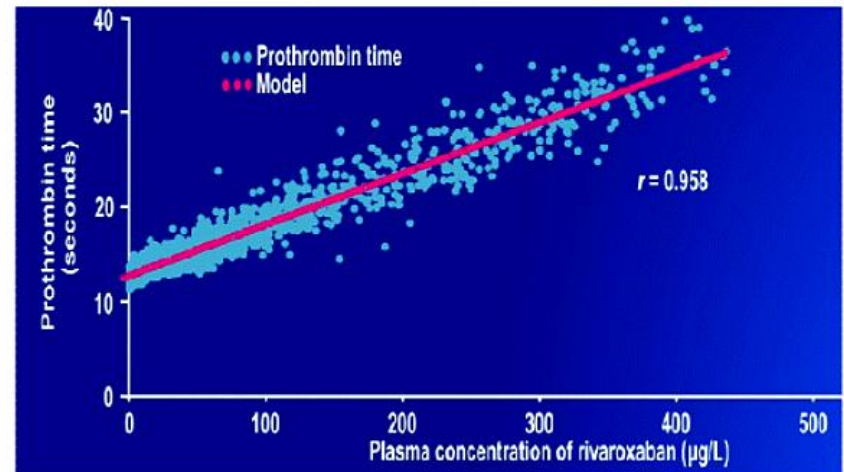
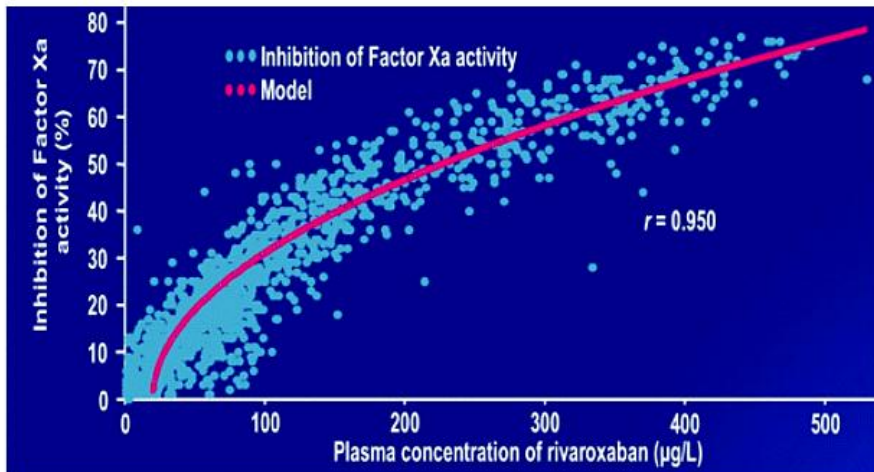
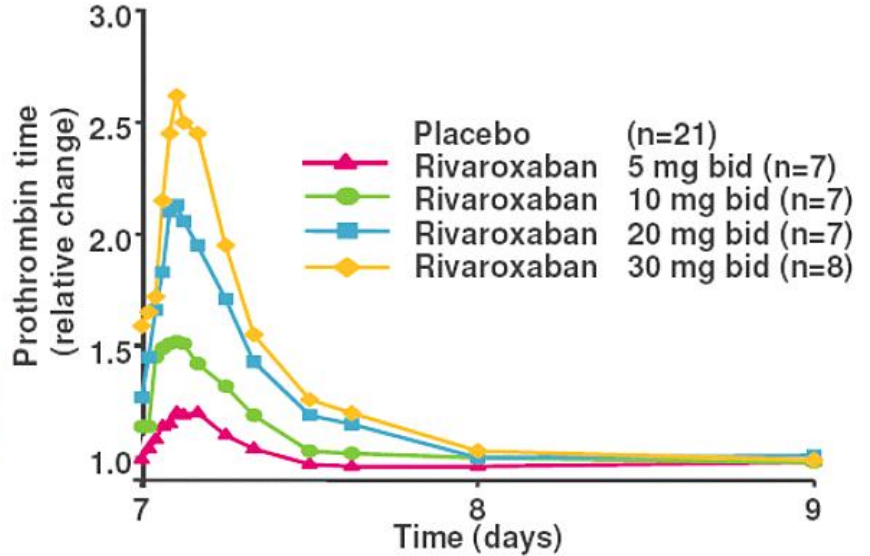
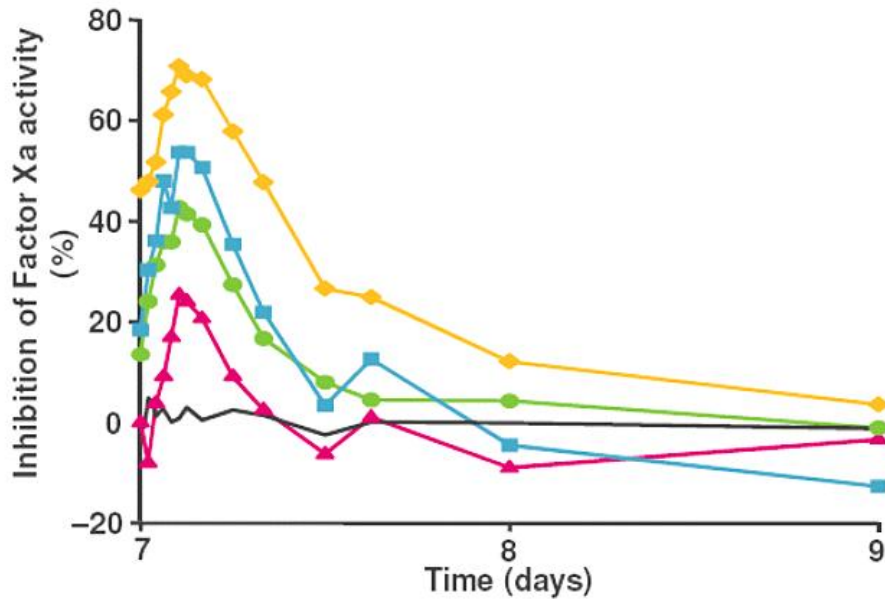
Xarelto® : pharmacodynamique

- Accumulation si : inhibiteur CYP3A4 (CI : ketoconazole, ritonavir...)
grand âge
insuffisance rénale sévère, atteinte hépatique

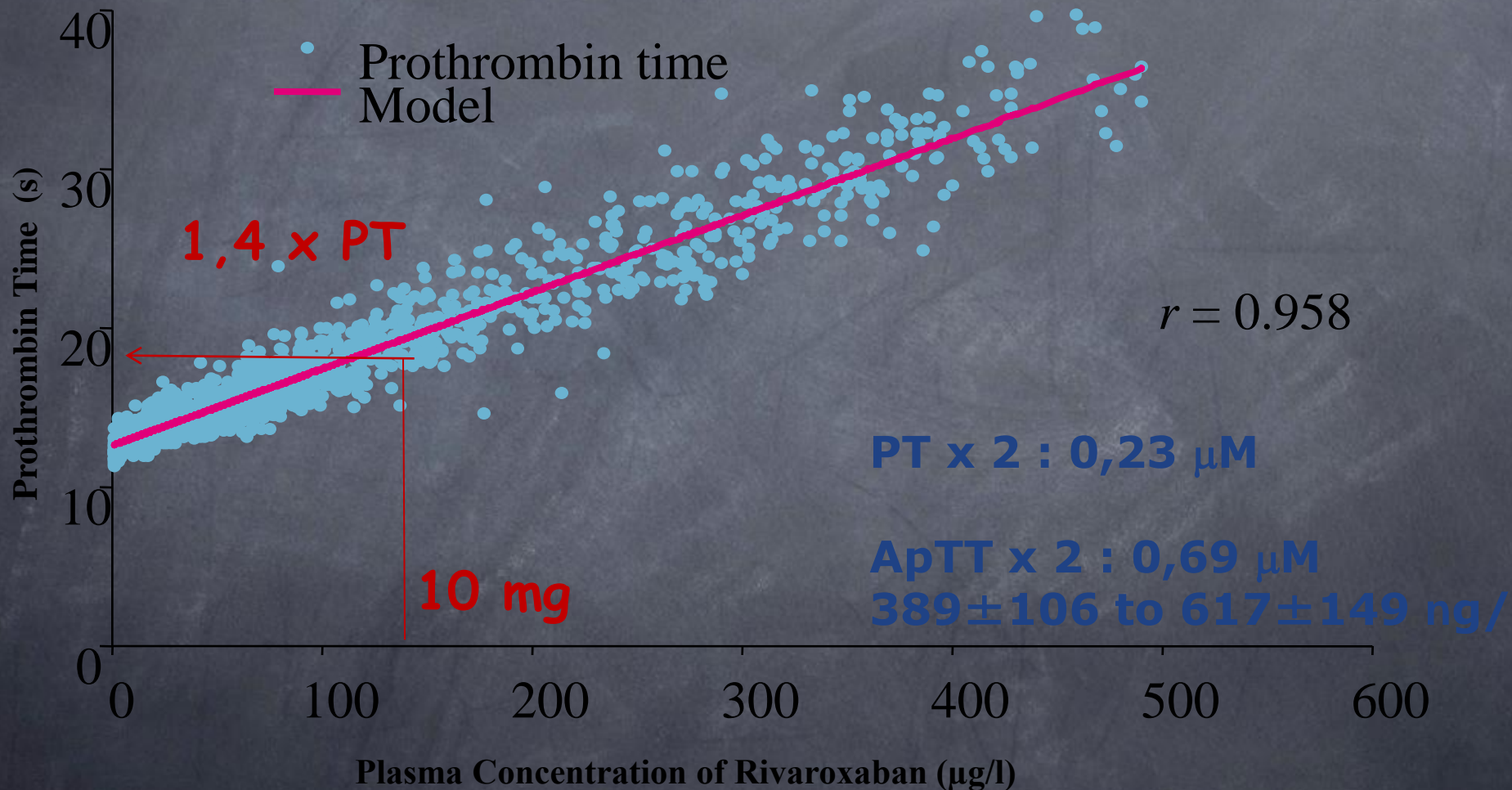


- Absorption accrue si prise alimentaire concomitante
- Pas d'interférence : inhibiteurs anti-acides
aspirine et AINS
digoxine
amiodarone

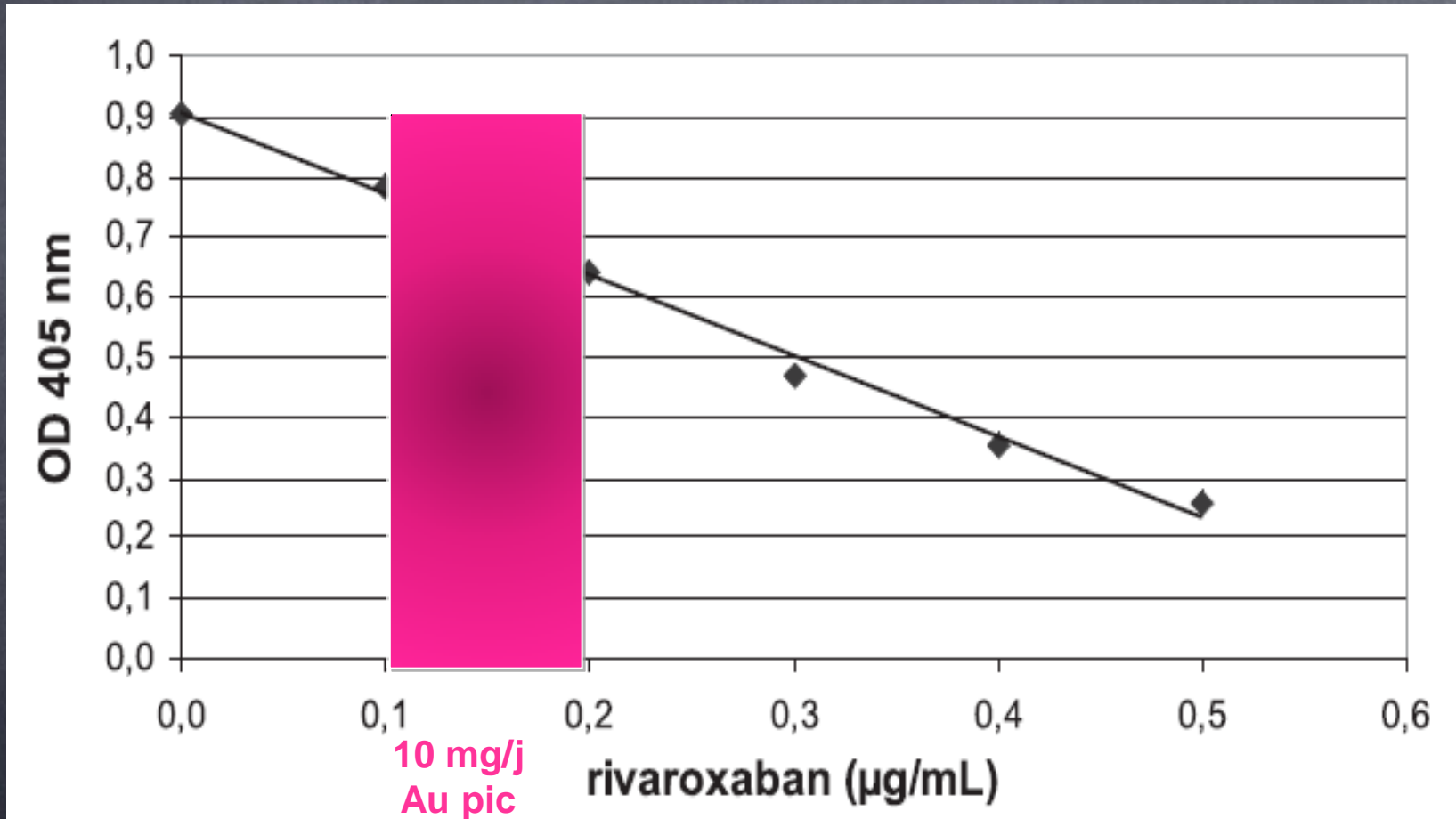
Xarelto® : Impact sur les tests



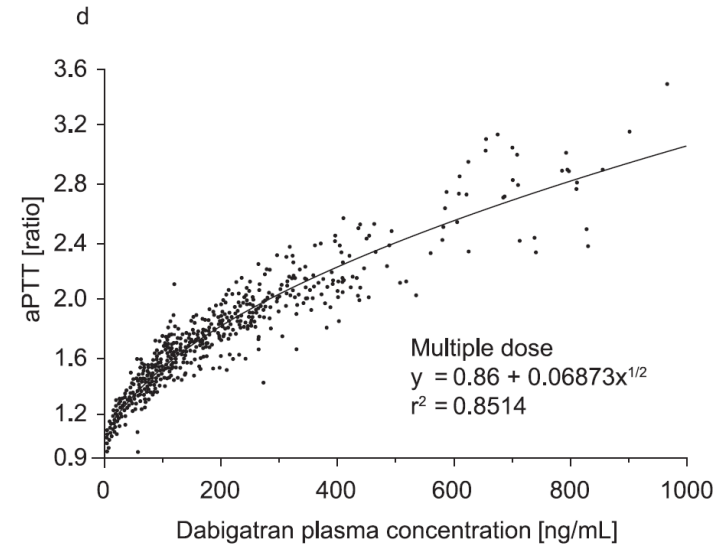
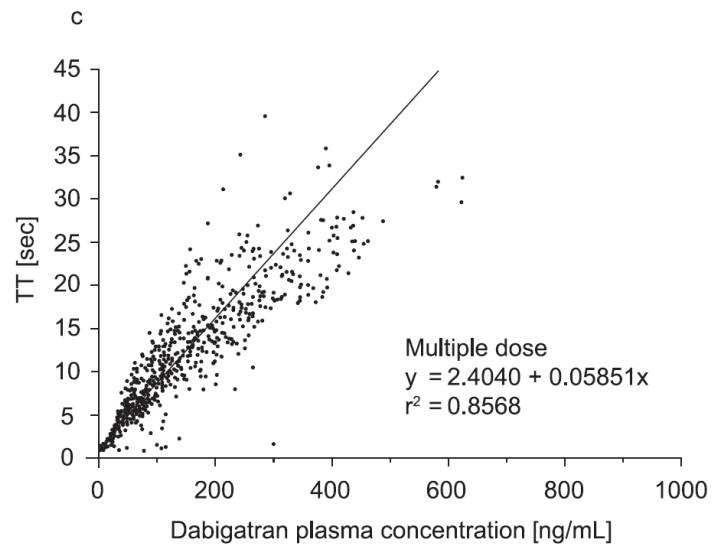
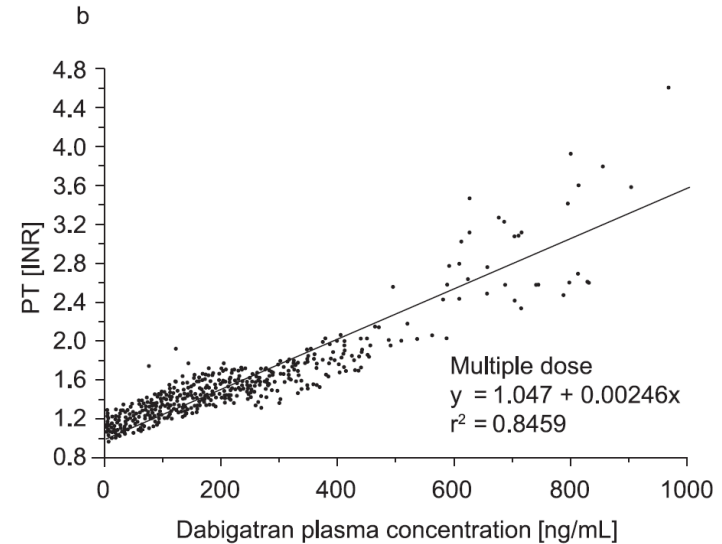
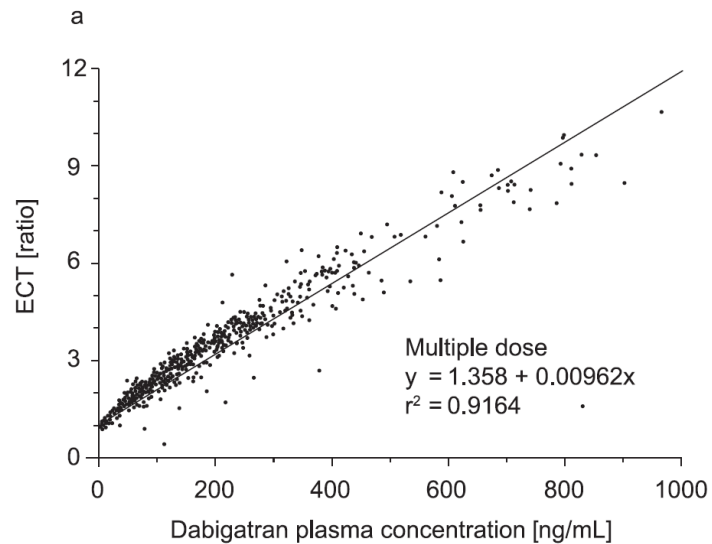
Correlation between PT and Rivaroxaban plasma concentration



Mesure de l'activité anti-Xa : méthode spécifique de l'anti-Xa direct

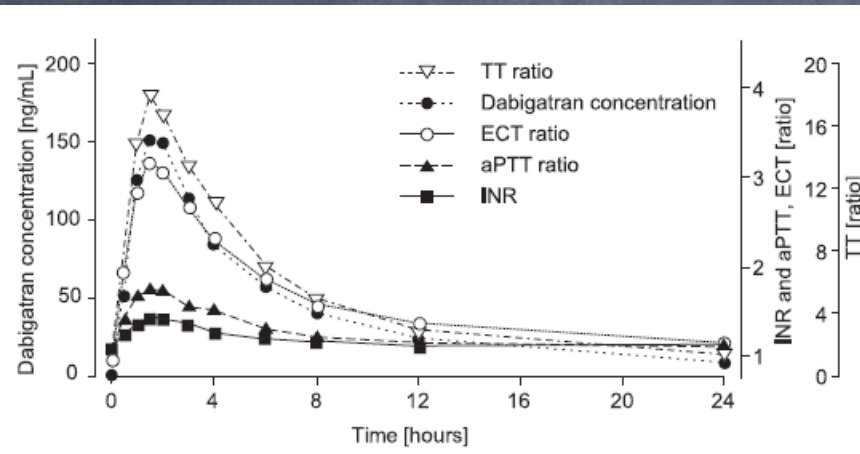


Effect of dabigatranon clotting tests in patients with AF

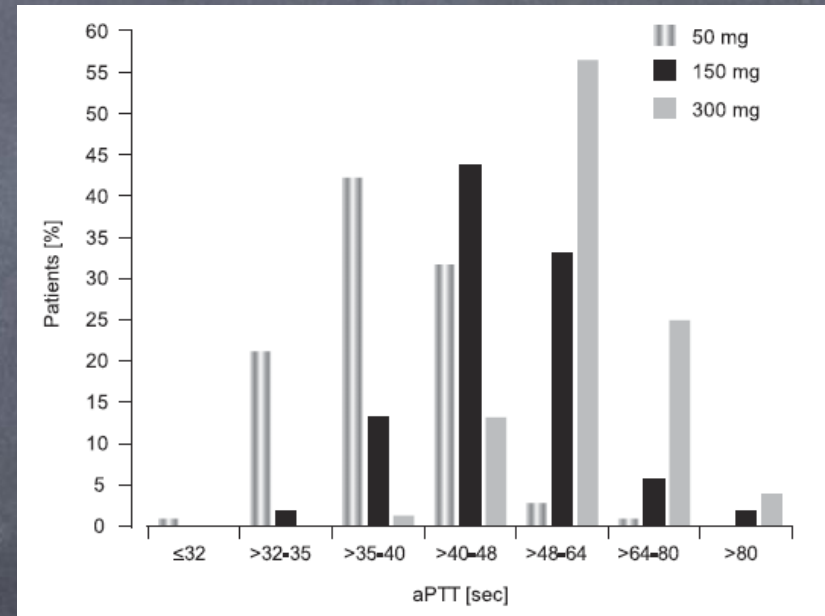


Effect of dabigatran on clotting assays in patients with AF

Pharmacodynamics of dabigatran following a single dose oral dose of 200 mg



Distribution of patients according to mean trough aPTT after oral administration of dabigatran etexilate twice daily



nouveaux

antithrombotiques

- Les inhibiteurs spécifiques du FXa ou du FIIa
 - sont efficaces
 - Dans la prophylaxie de la MTEV
 - Le traitement de la MTEV
 - Le traitement des SCA
 - ont une large fenêtre thérapeutique
 - Sont associés à un risque hémorragique négligeable mais présent
- Les inhibiteurs spécifiques du FXa ou du FIIa sont des molécules hétérogènes
- Dabigatran (inhibiteur spécifique de la thrombine) est efficace dans la prévention des AVC chez les patients avec ACFA et mieux toléré vs le traitement par AVK
- La multiplication des options thérapeutiques permettra l'optimisation de la stratégie antithrombotique à l'échelle individuelle

