

2005

Les nouveaux antithrombotiques

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antithrombotiques*

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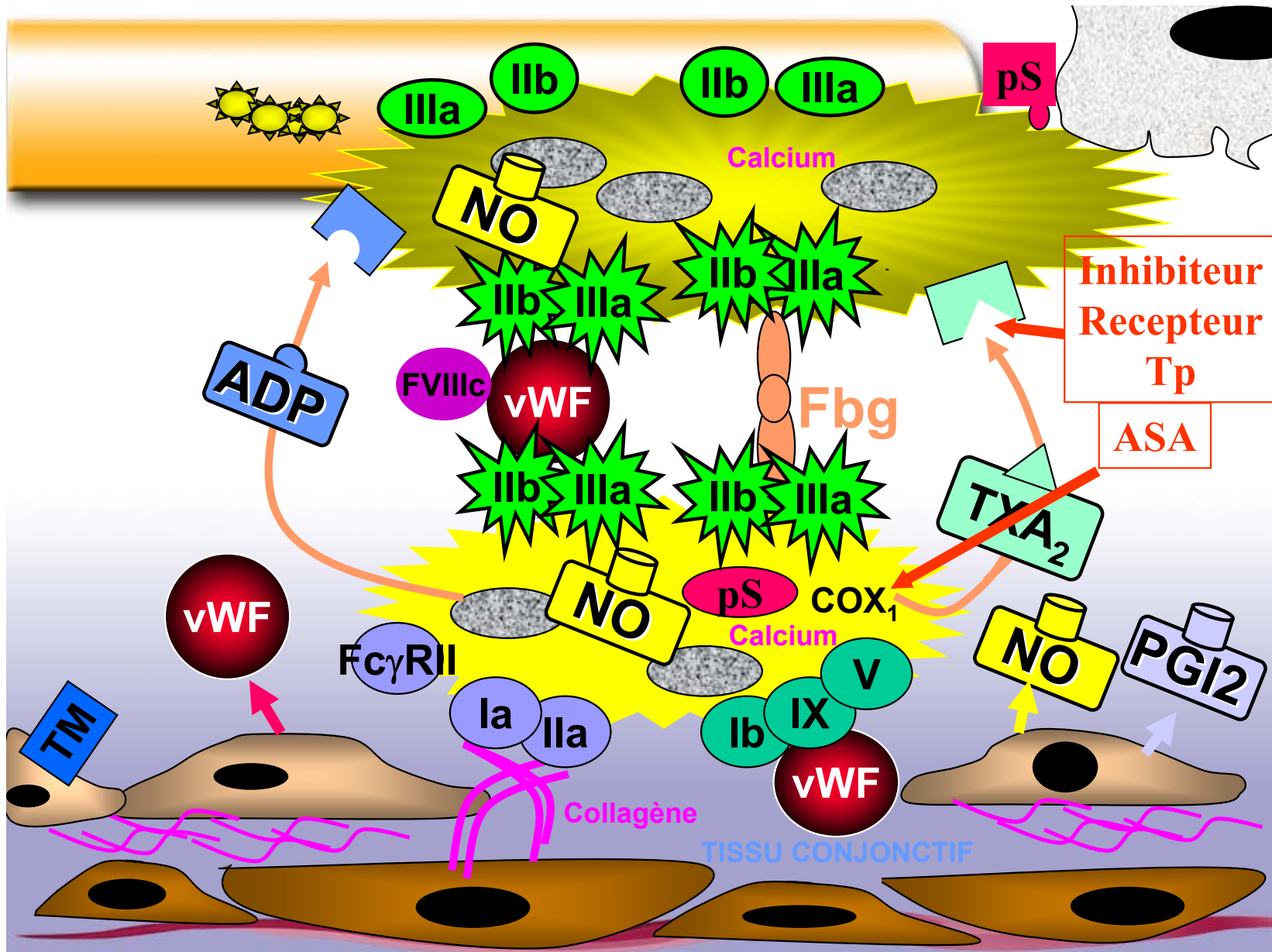
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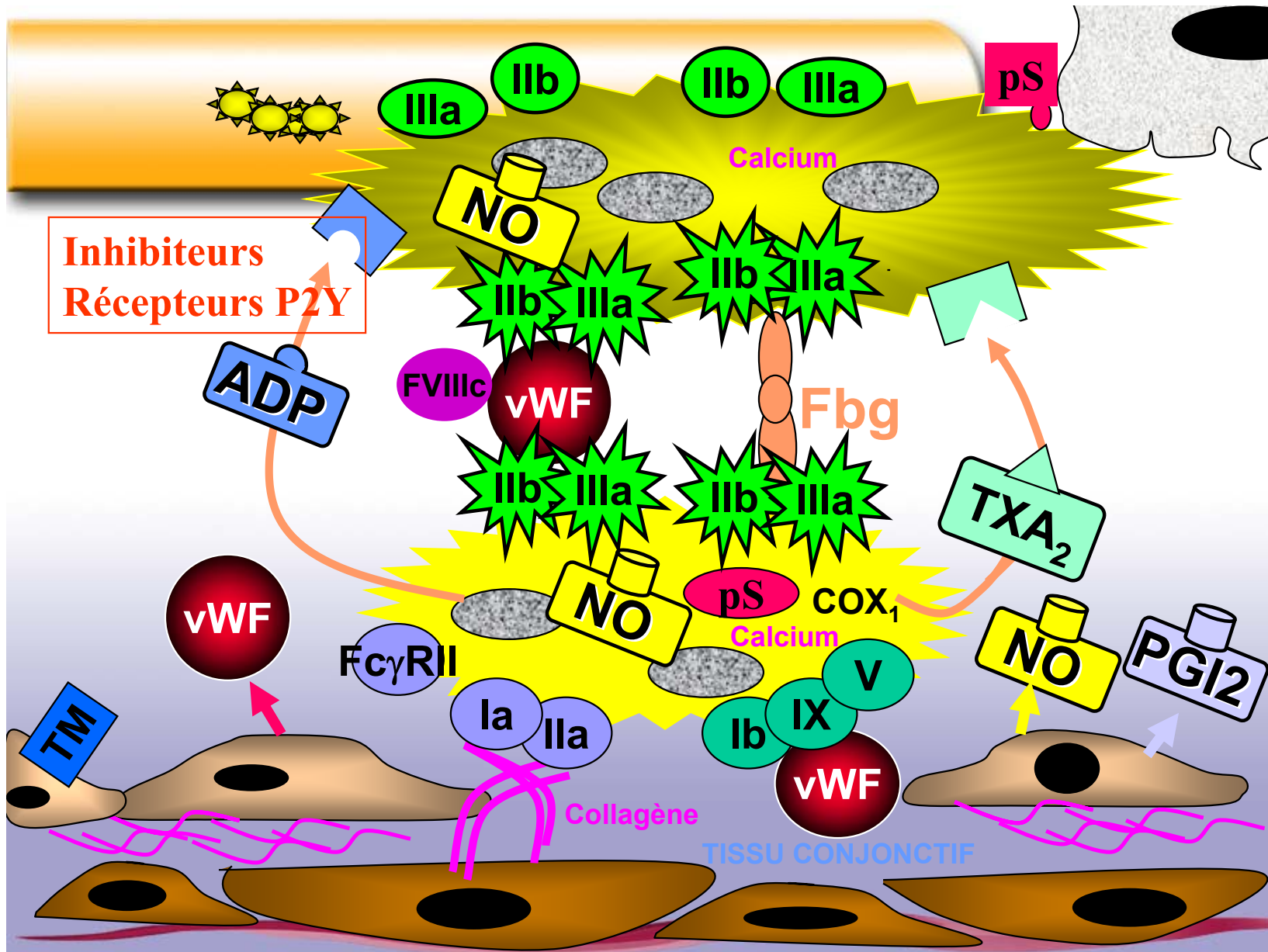


**LES NOUVEAUX
ANTITHROMBOTIQUES**

**Les
antiagregants
de demain ?**

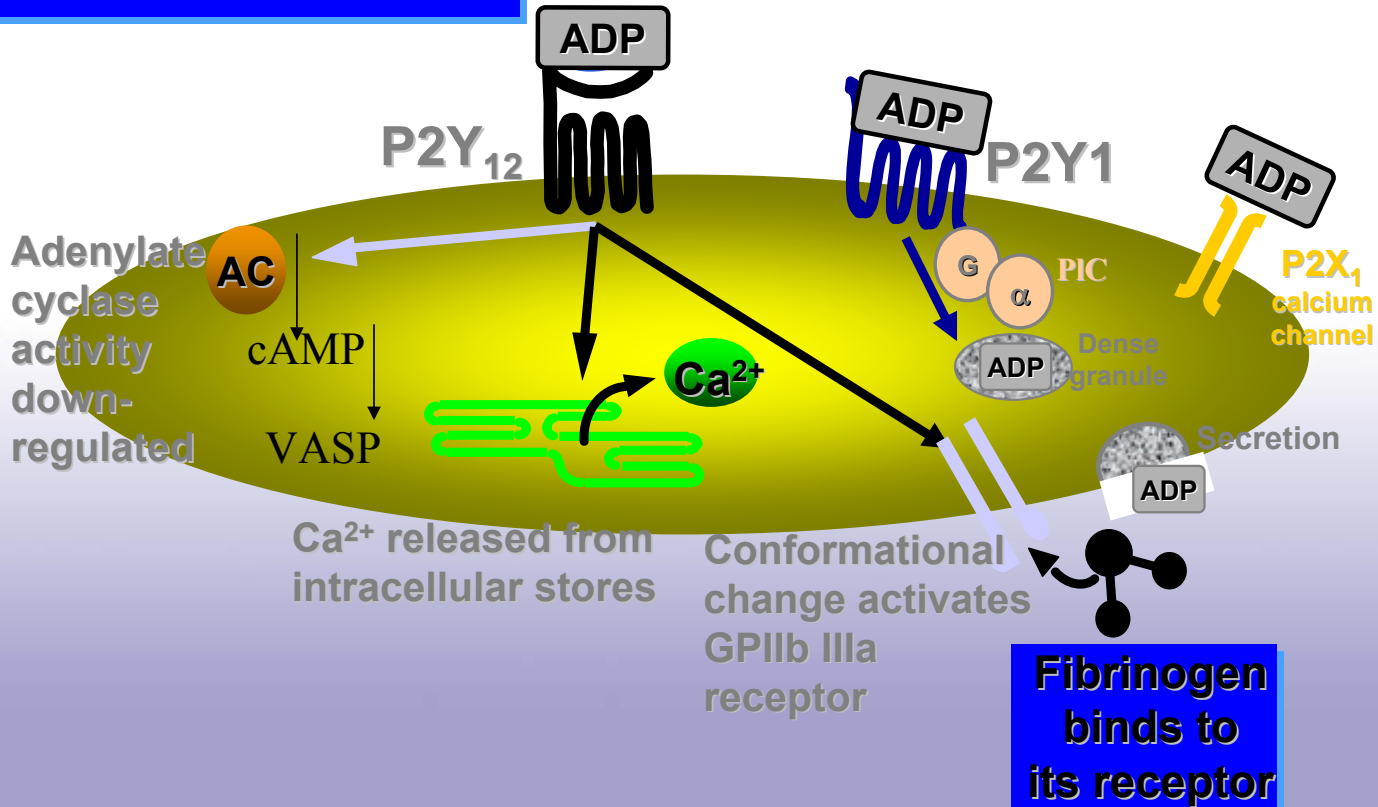
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(Angio-Hématologie, Hôpital Lariboisière-Paris)*





Platelet ADP pathway

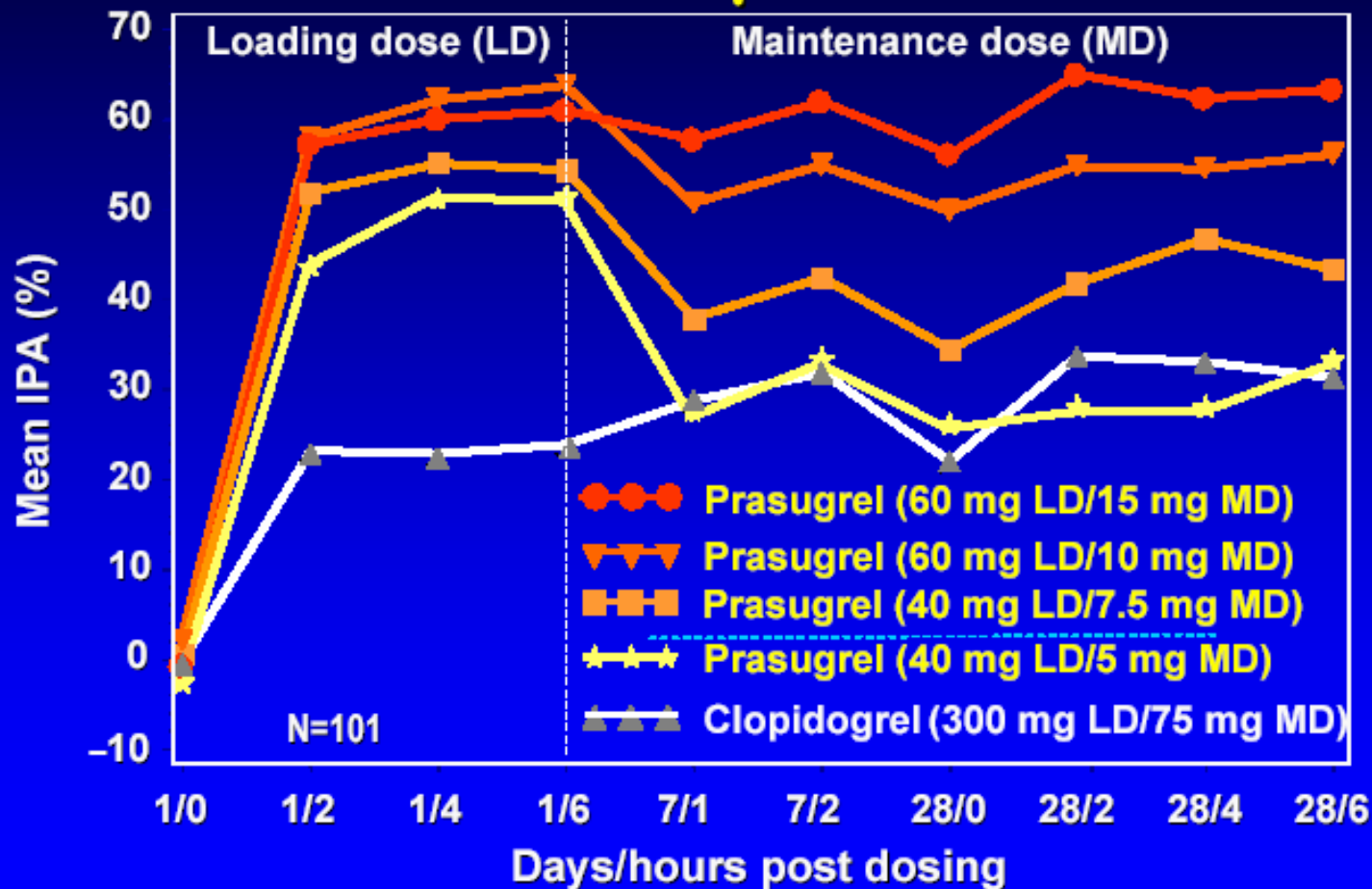
ADP binds to its receptors



ADP receptor antagonists as antithrombotic agents

| Antithrombotic agent | Current status | Route | Receptor |
|--------------------------|----------------|---------------|--|
| Clopidogrel | In use | Indirect | P2Y ₁₂ |
| Prasugrel | In development | Indirect | P2Y ₁₂ |
| AZD6140 | In development | Direct (oral) | P2Y ₁₂ |
| Cangrelor (AR-C69931) | In development | Direct | P2Y ₁₂ |
| A2P5P | Experimental | Direct | P2Y ₁ |
| A3P5P | Experimental | Direct | P2Y ₁ |
| MRS2179 | Experimental | Direct | P2Y ₁ |
| CoA derivatives | Experimental | Direct | P2Y ₁ and P2Y ₁₂ |

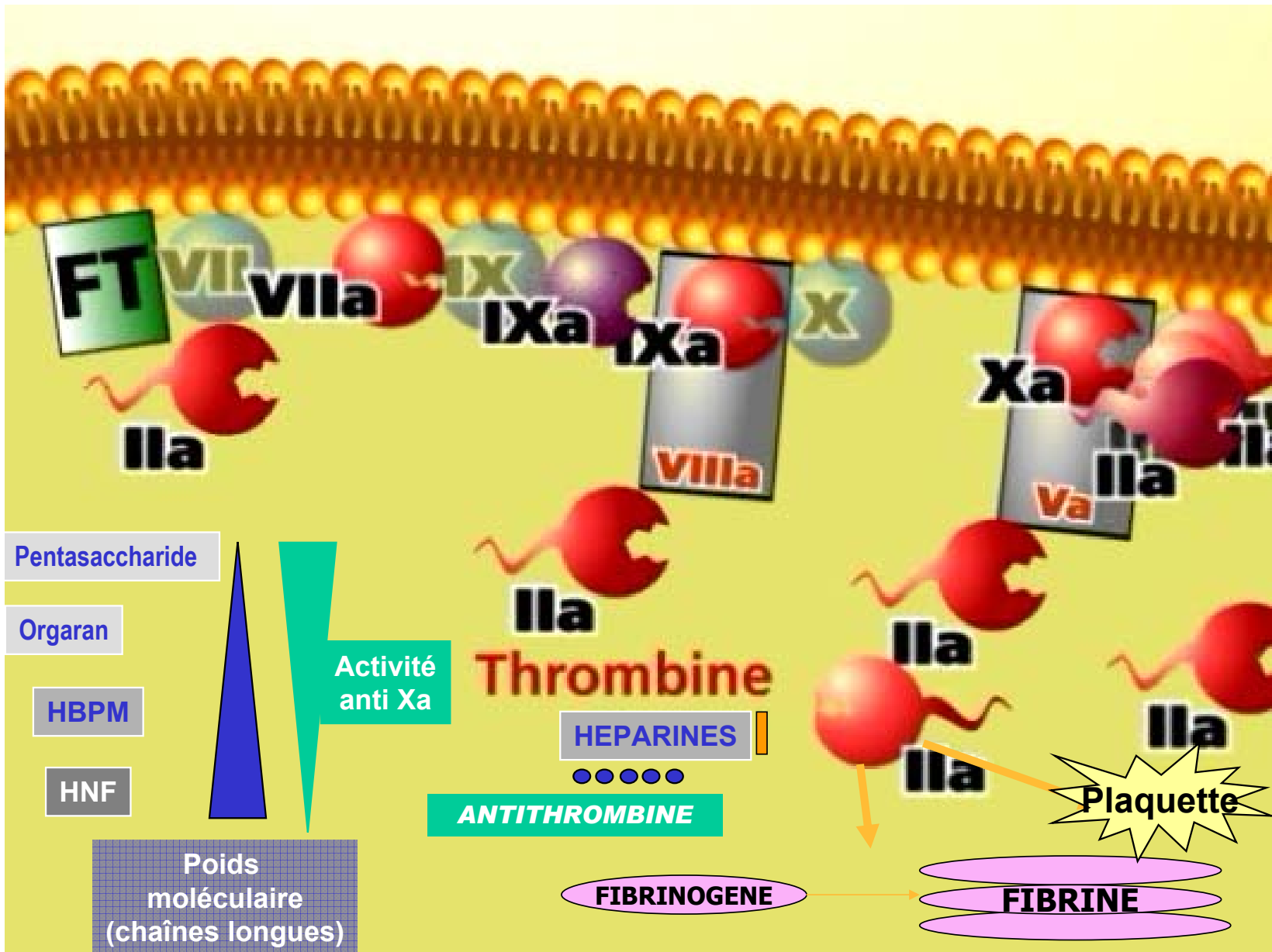
Stable atherosclerosis IPA to 20 μ M ADP



**LES NOUVEAUX
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**Les
anticoagulants
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Pentasaccharide

Organon

HBPM

HNF

Poids moléculaire (chaînes longues)

Activité anti Xa

Thrombine

HEPARINES

ANTITHROMBINE

FIBRINOGENE

FIBRINE

Plaquette

FT

VII

VIIa

IX

IXa

IXa

X

Xa

VIIIa

Va

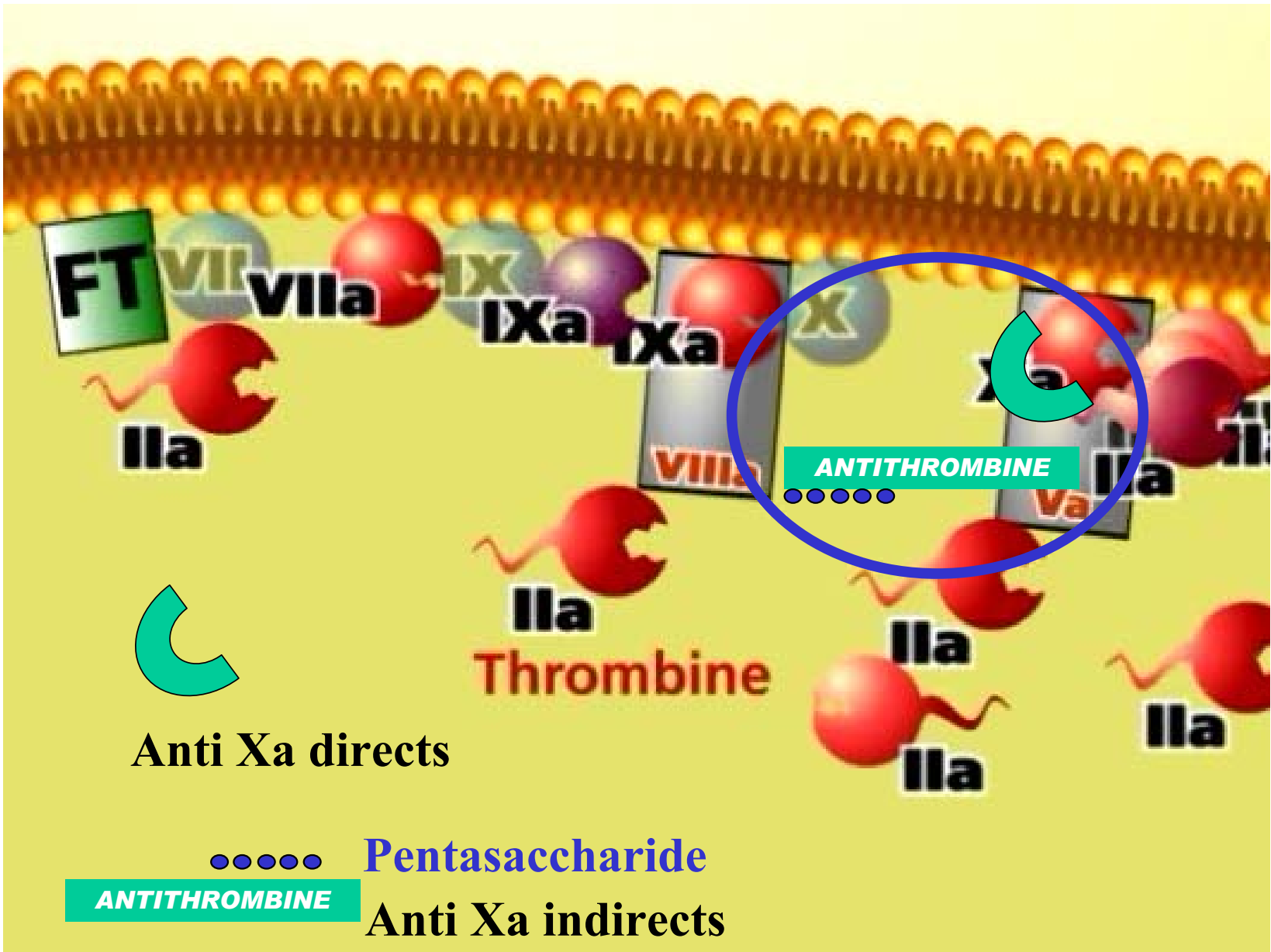
IIa

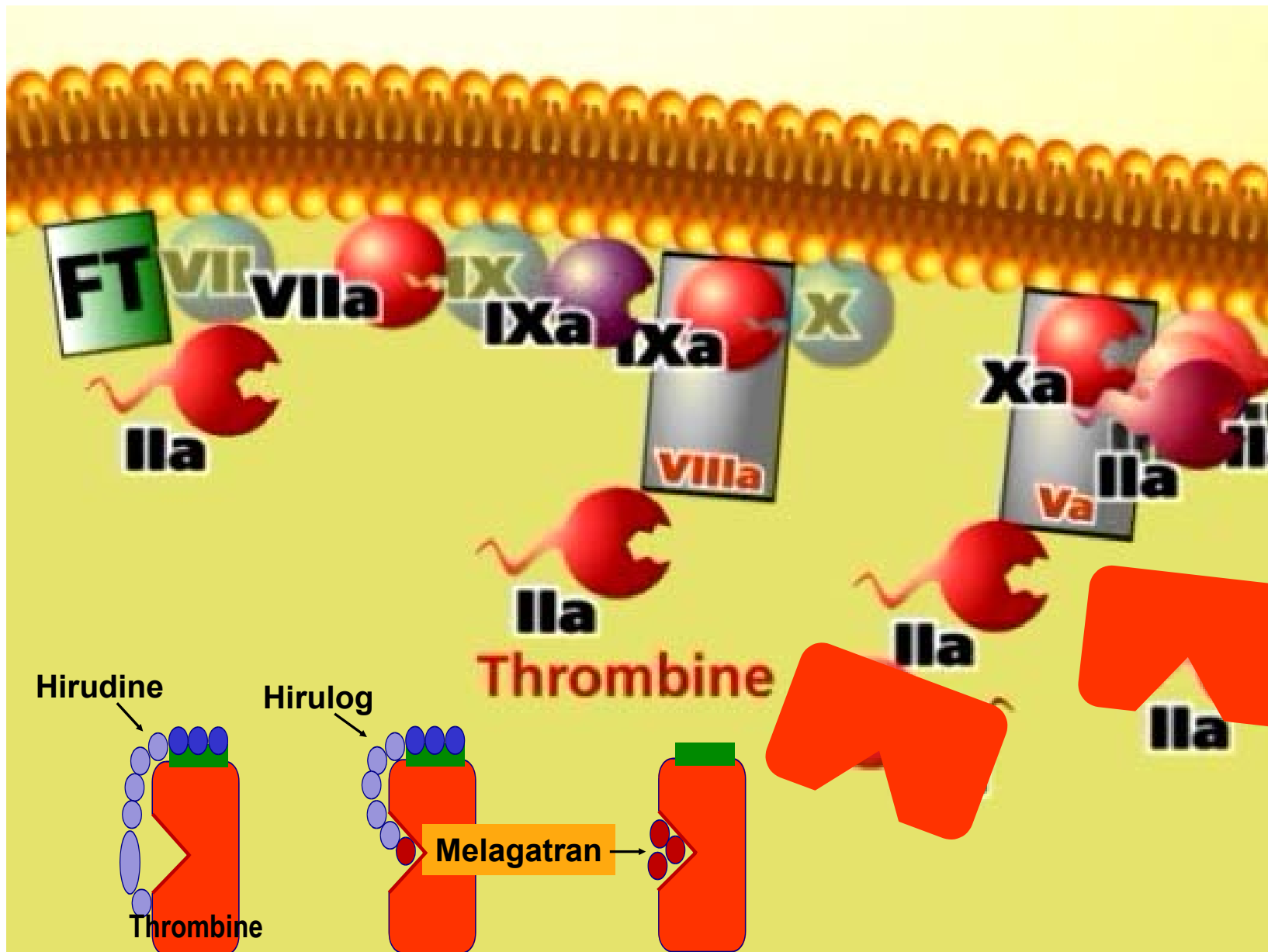
IIa

IIa

IIa

IIa

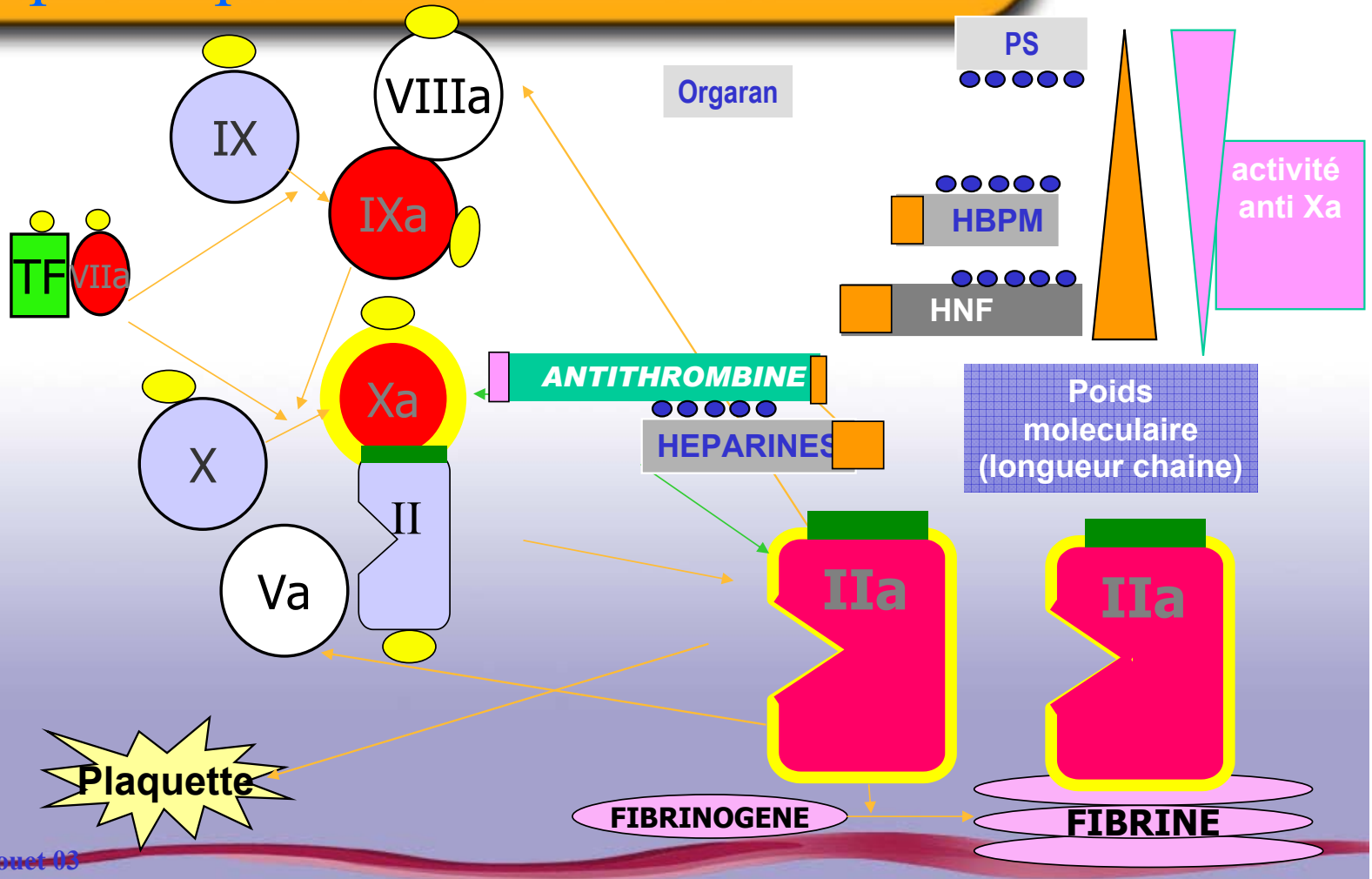


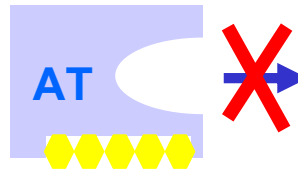
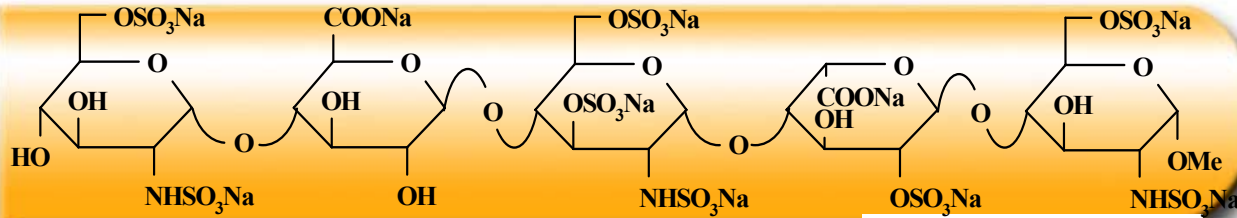




Inhibiteurs
du Facteur V en VIIa

Mode d'action des héparines et hépariniques





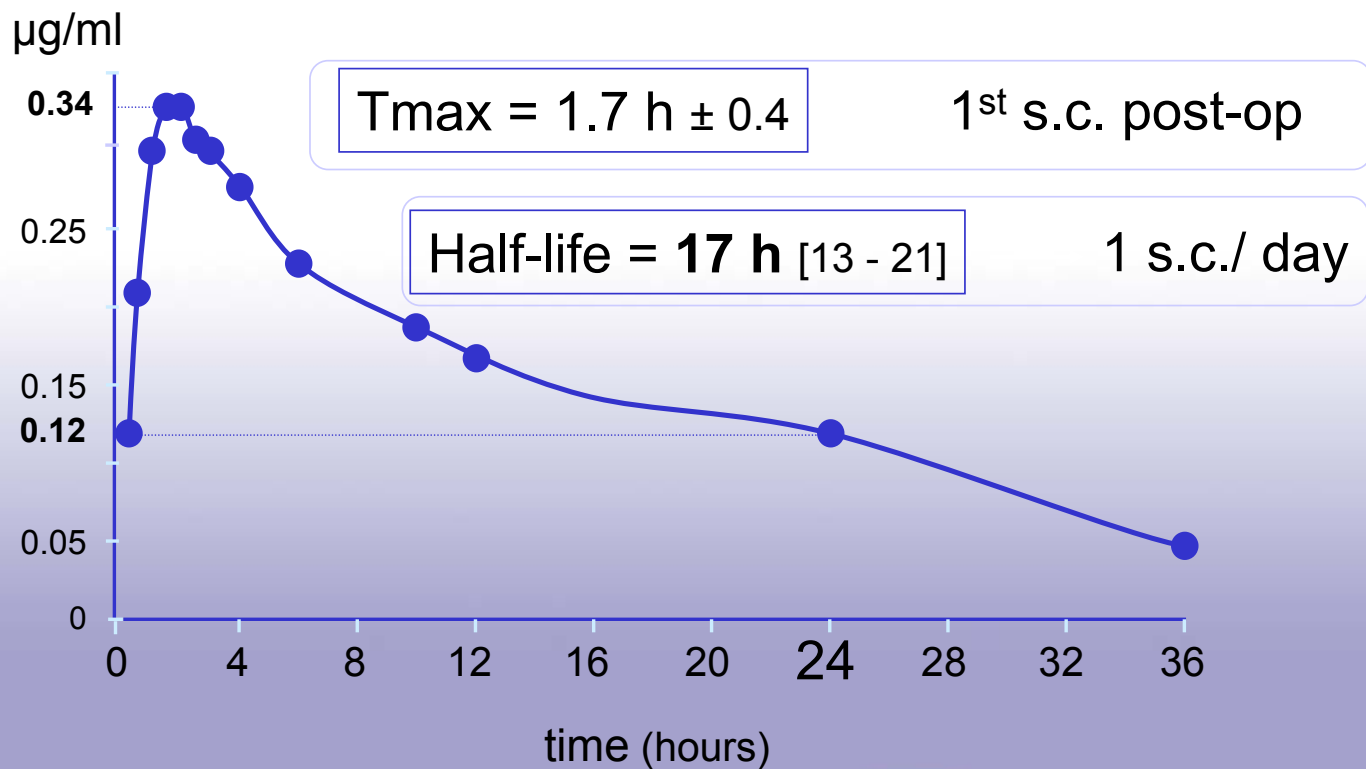
 Pentasaccharide (pentasaccharide)

specific and **selective** potentiation of the anti Xa activity of antithrombin

No potentiation of the **anti IIa** activity,
 → no effect on **aPTT** or on **PT / INR**
 for the doses tested

Pentasaccharide : pharmacokinetics

Young healthy volunteers: 2,5 mg injection s.c.



Renal elimination → potential factors of variability ?

- Age
 - Renal function

Body weight ...

Factors of PK variability in healthy volunteers

Half-life : ~ **17h** if young → ~ **21h** if aged

Factors of PK variability in patients

THR ~ **70 ans**

Hip Fract. ~ **80 ans**

C_{max}* : THR ~ 0.39 µg/ml Hip Fract. ~ 0.50 µg/ml

C_{min}* : THR ~ 0.14 µg/ml Hip Fract. ~ 0.19 µg/ml

* C_{max} and C_{min} after 2,5 mg s.c. injection and at equilibrium

Pentacaccharide : pharmacokinetics

Factors of PK variability in patients

Age : > 75 years → half-life ~ 24h

➤ **Renal Function:** creatinin clearance (Cockcroft)

30 - 50 ml/mn → half-life ~ 29h

< 30 ml/mn → half-life ~ 72h

➤ **Body Weight** : ~ 9% variation clearance for 10 kg BW

Pentasaccharide : pharmacokinetics

limited variability

→ no need for dose adaptation:

to the anti-Xa activity *

➤ to the age

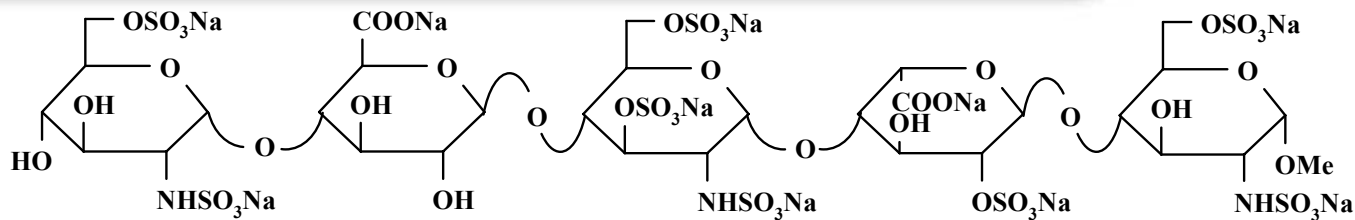
➤ to the renal function (if > 30 ml/mn) **

➤ to the body weight

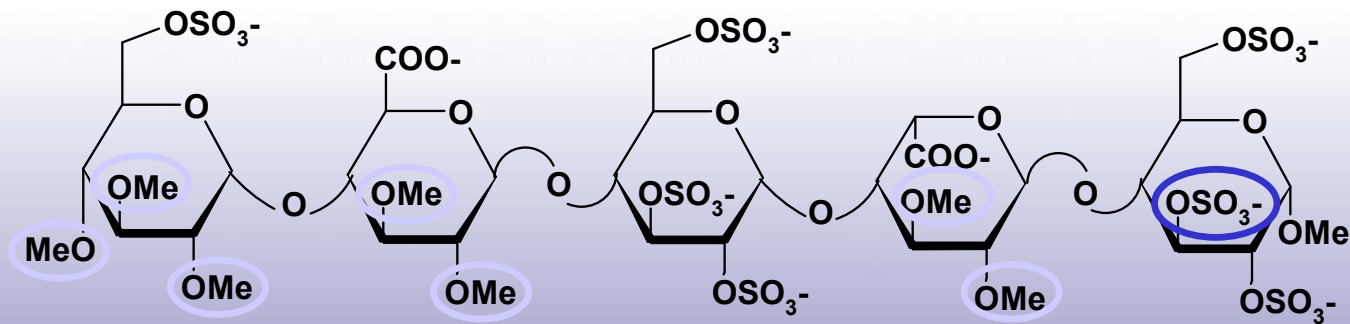
* No systematic biological monitoring

** Contraindicated if severe renal insuf. : < 30 ml/mn

Fondaparinux and Idraparinux



Fondaparinux

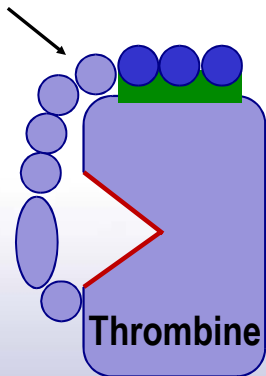


Idraparinux

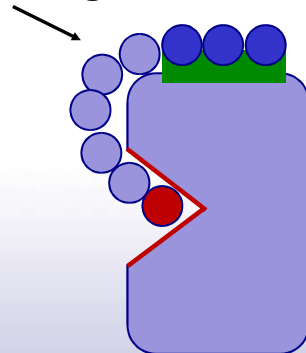
9 Na⁺

Les antithrombines directes

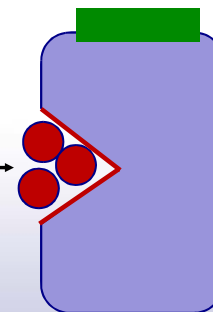
Hirudine



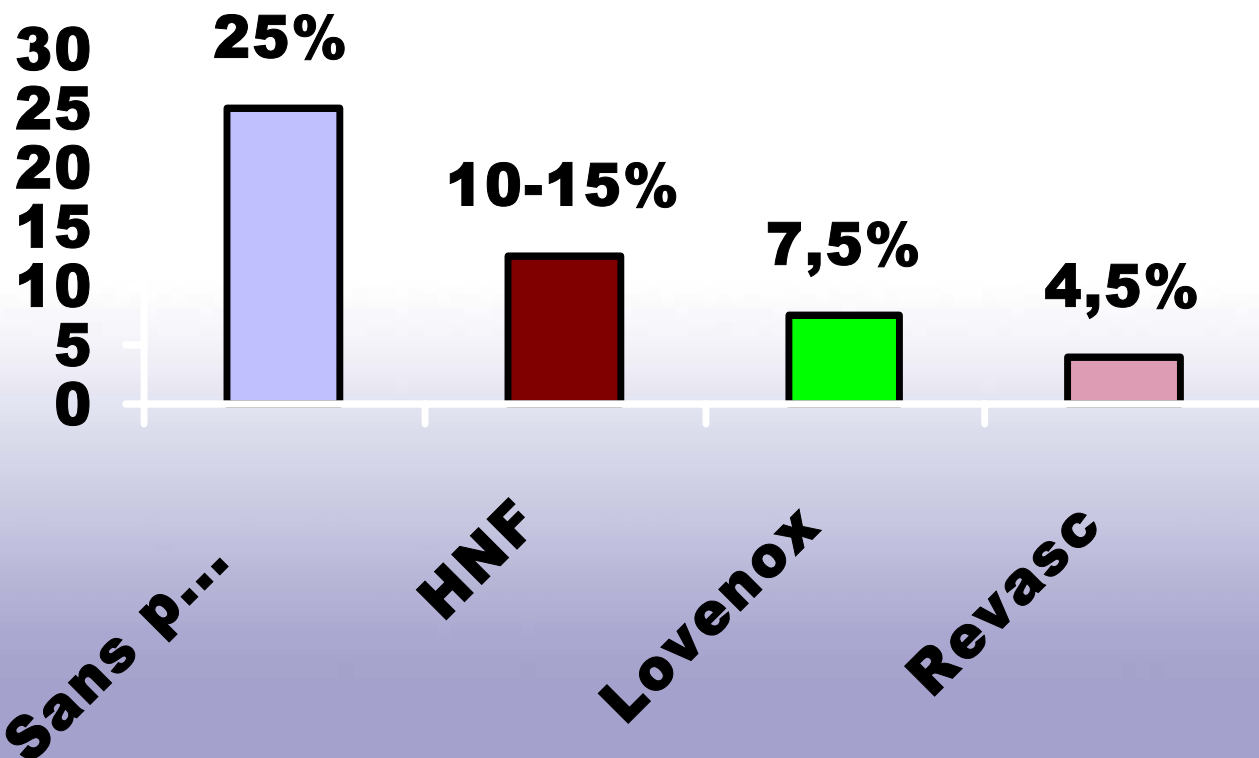
Hirulog



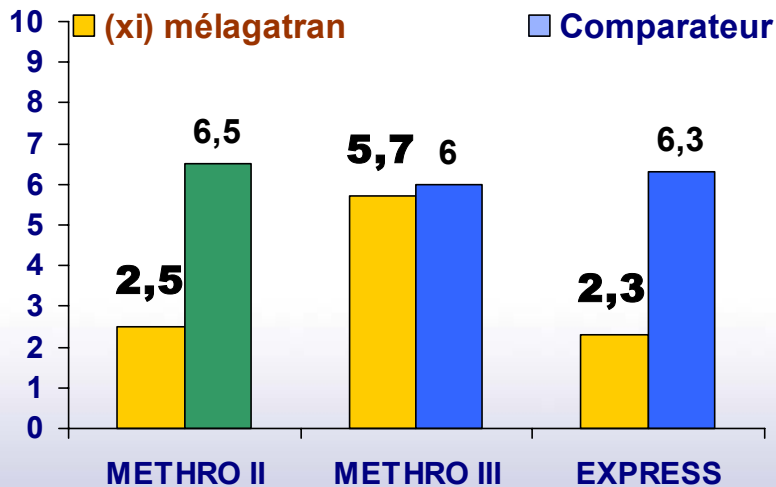
Melagatran



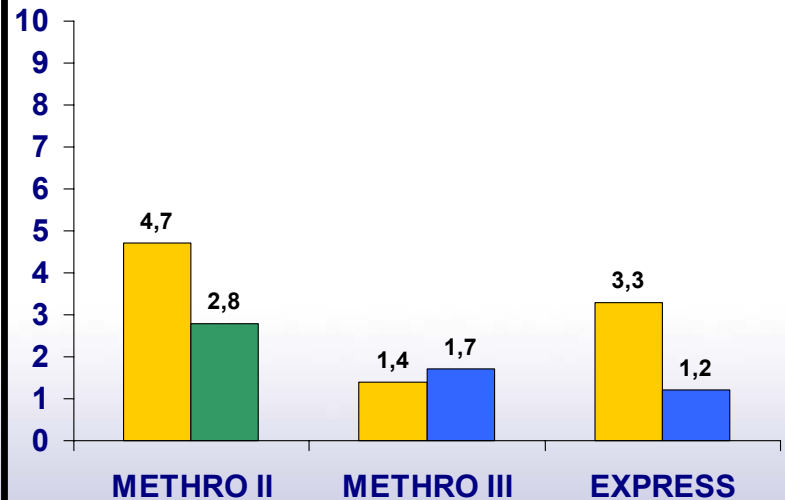
Prévention des TVP proximales phlébographiques en chirurgie orthopédique



EXANTA : synthèse des essais en orthopédie



TVP proximales
/EP



Hémorragies
sévères

SPORTIF III

***Stroke Prevention by ORal
Thrombin Inhibitor in Atrial
Fibrillation***

**Efficacy and Safety Study of the Oral Direct
Thrombin Inhibitor Exanta™ Compared with
Dose-Adjusted Warfarin in the Prevention of All
Strokes and Systemic Embolic Events (SEE) in
Patients with Nonvalvular Atrial Fibrillation**

**Stroke Prevention Using an
ORal Thrombin Inhibitor in Atrial Fibrillation
The SPORTIF III and V Trials**

**Patients With Nonvalvular AF
And Risk Factors for Stroke
n=7,329**

**Adjusted-dose
Warfarin
(INR 2-3)**

**Fixed-dose
Ximelagatran
(36 mg bid)**

SPORTIF III

23 nations

Open-label

(n=3,407)

SPORTIF V

US, Canada

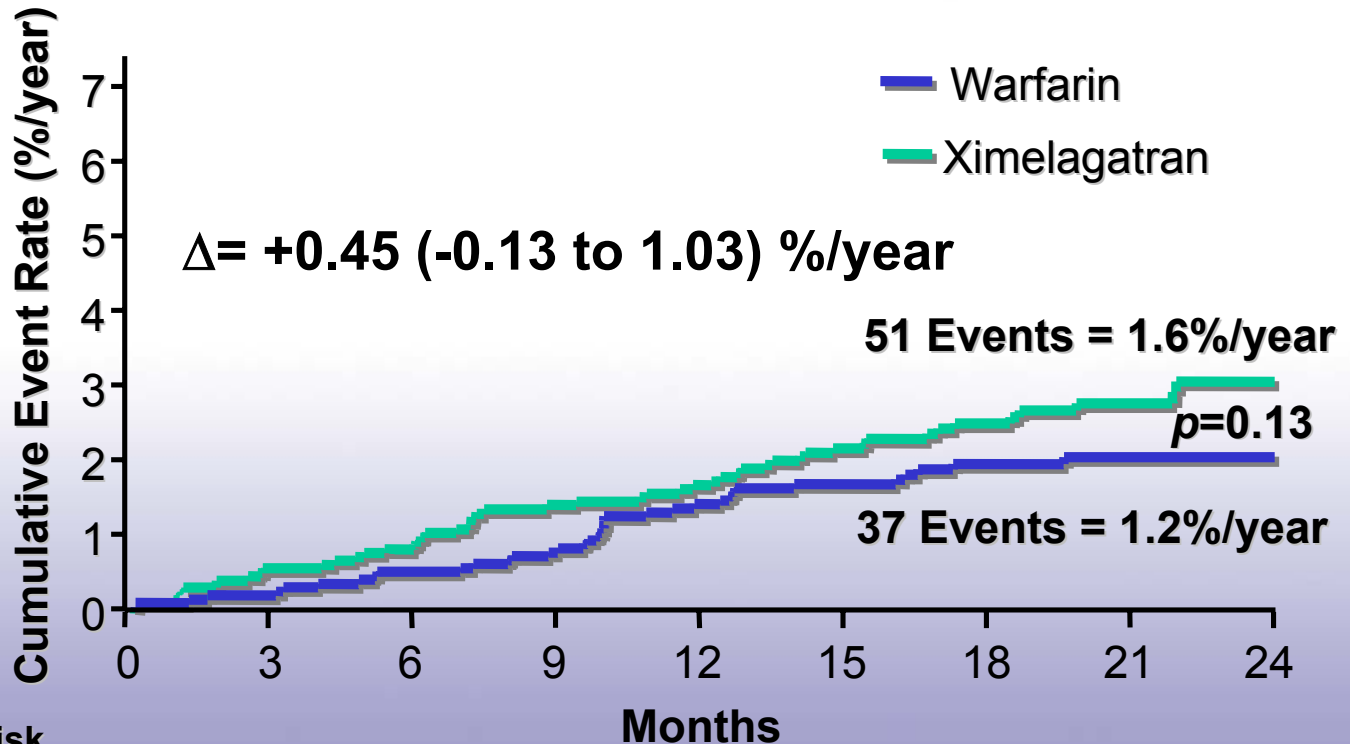
Double-blind

(n=3,922)

SPORTIF V

Stroke and Systemic Embolism

Primary Analysis (Intention-to-treat)



Patients at risk

| | | | | | |
|--------------|------|------|------|-----|-----|
| Ximelagatran | 1960 | 1900 | 1596 | 848 | 243 |
| Warfarin | 1962 | 1910 | 1624 | 867 | 240 |

SPORTIF Program

Primary Analyses

Intention-to-treat Analysis

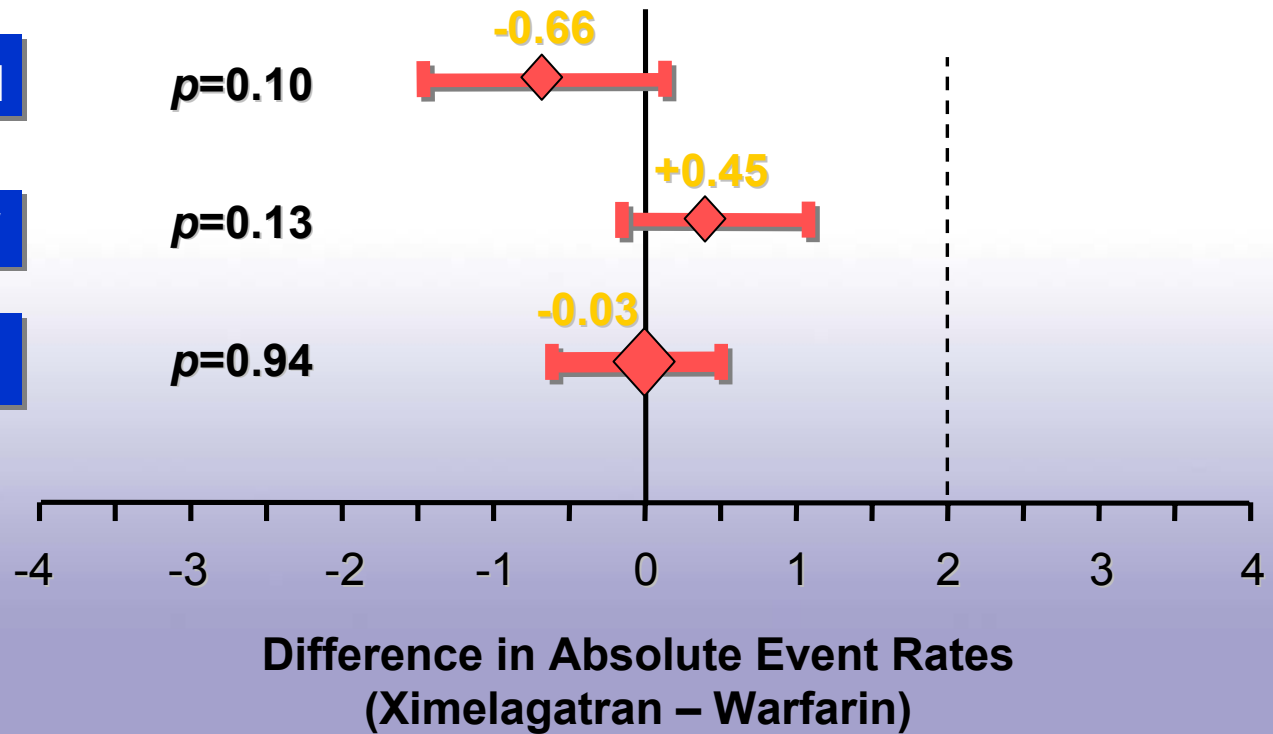
SPORTIF III

SPORTIF V

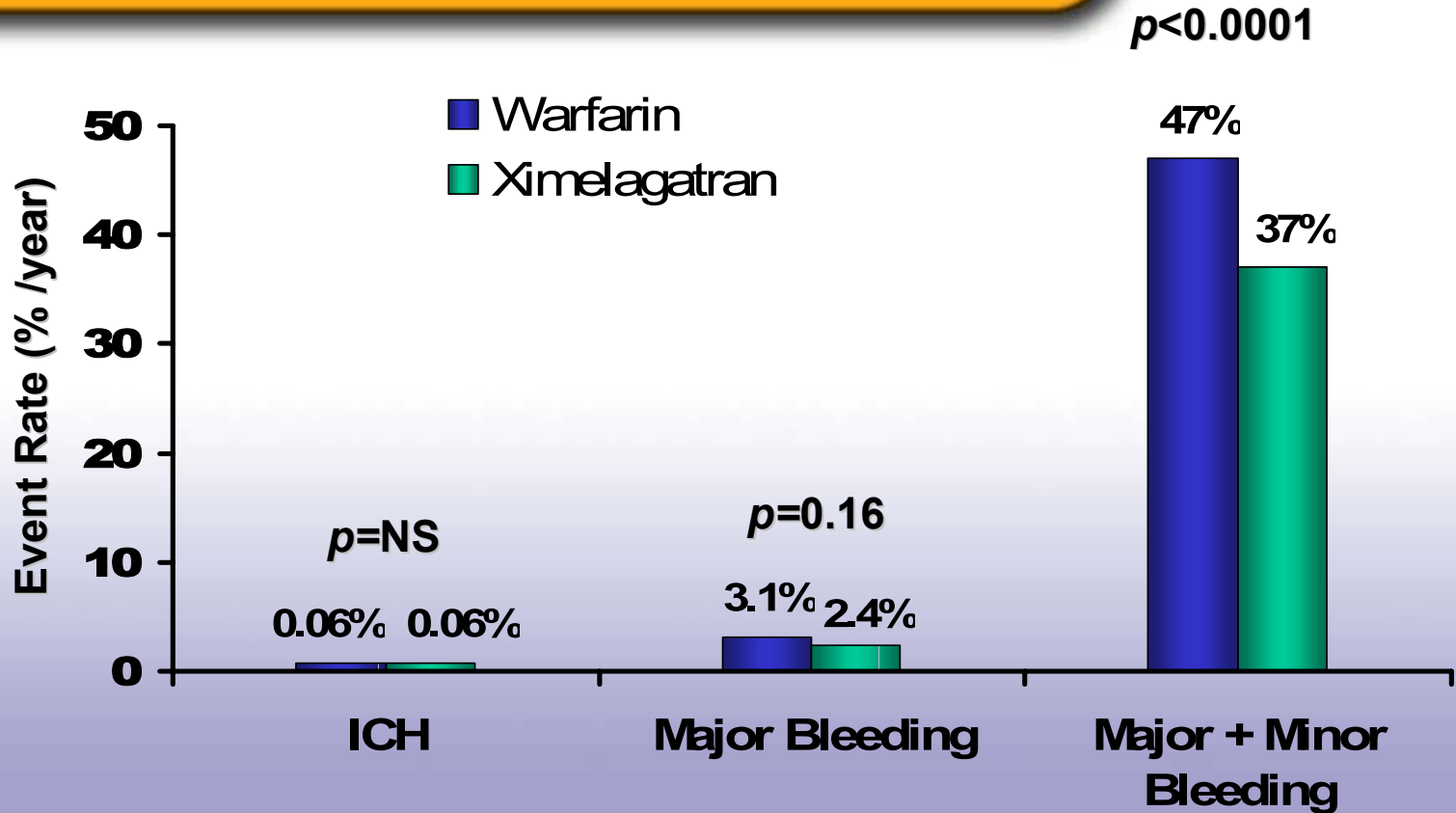
Pooled

Ximelagatran Better

Warfarin Better



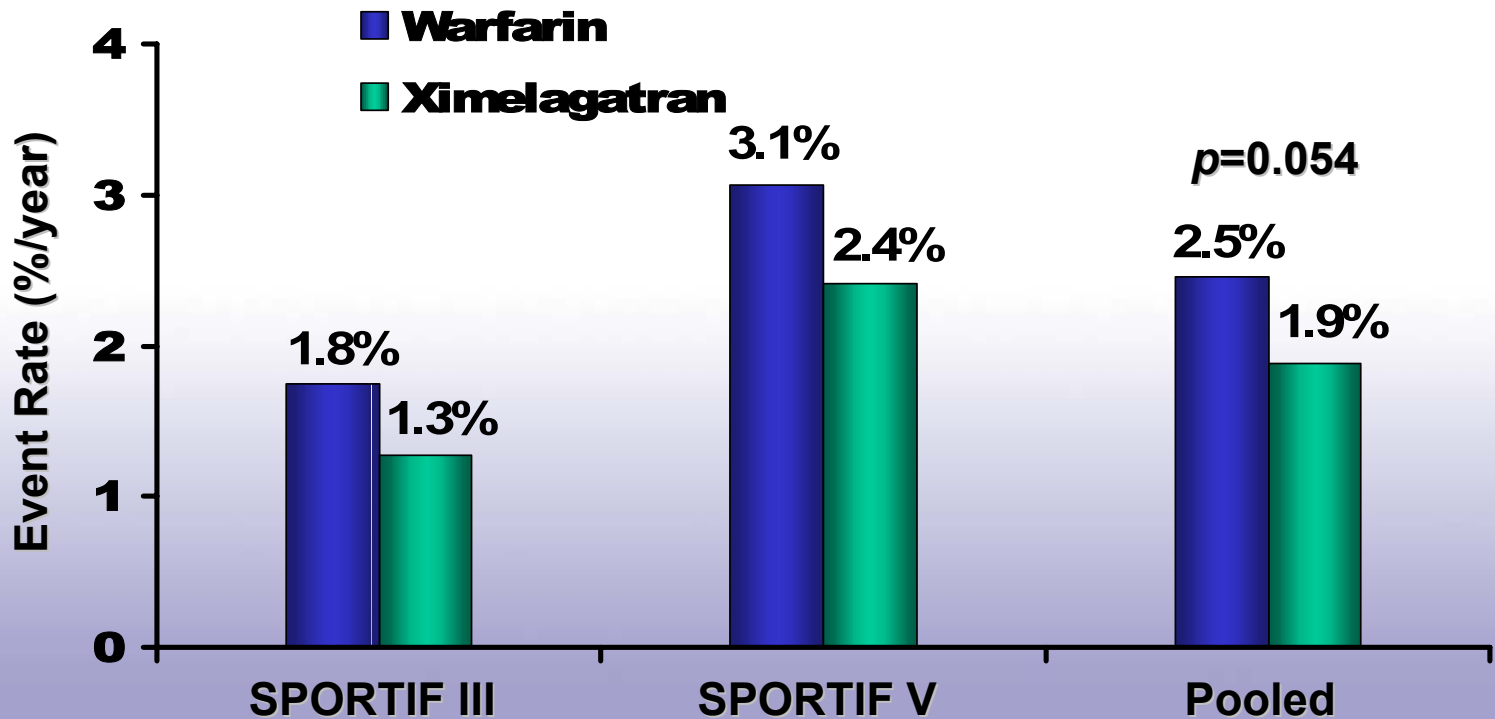
SPORTIF V Hemorrhage



SPORTIF Program

Major Bleeding

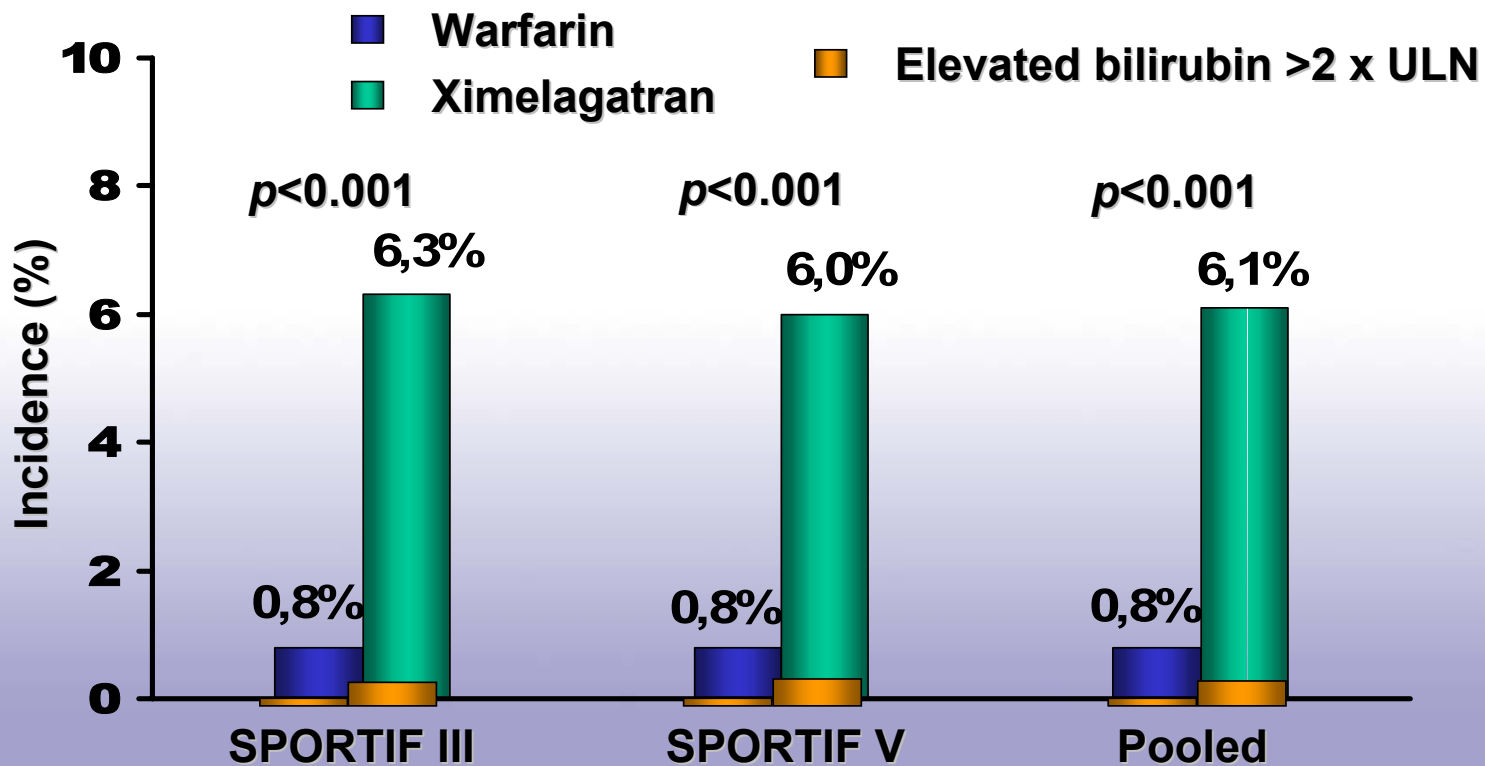
On-treatment Analysis



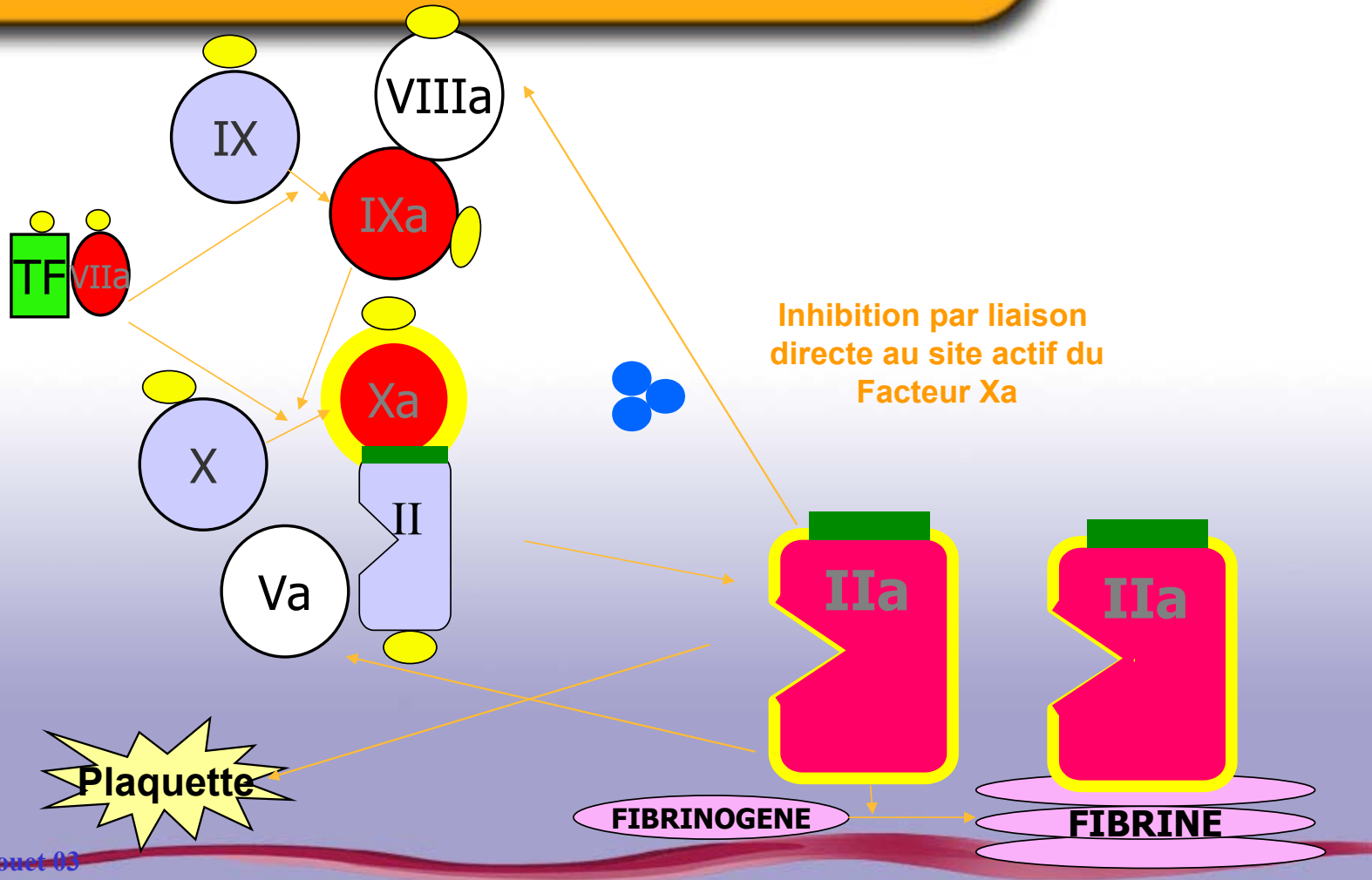
SPORTIF Program

Liver Enzyme Elevation

ALT >3 x ULN

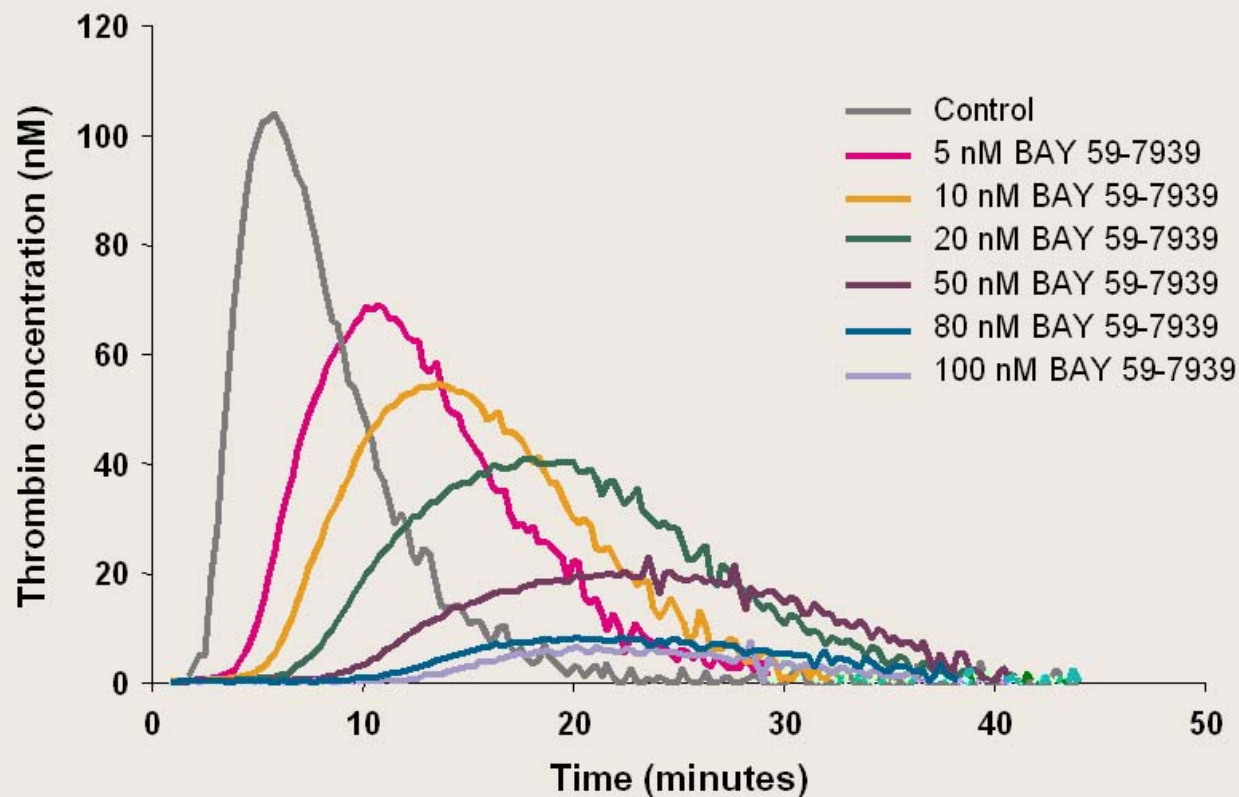


Mode d'action des anti Xa directes



BAY 59-7939 inhibits thrombin generation in a concentration-dependent manner

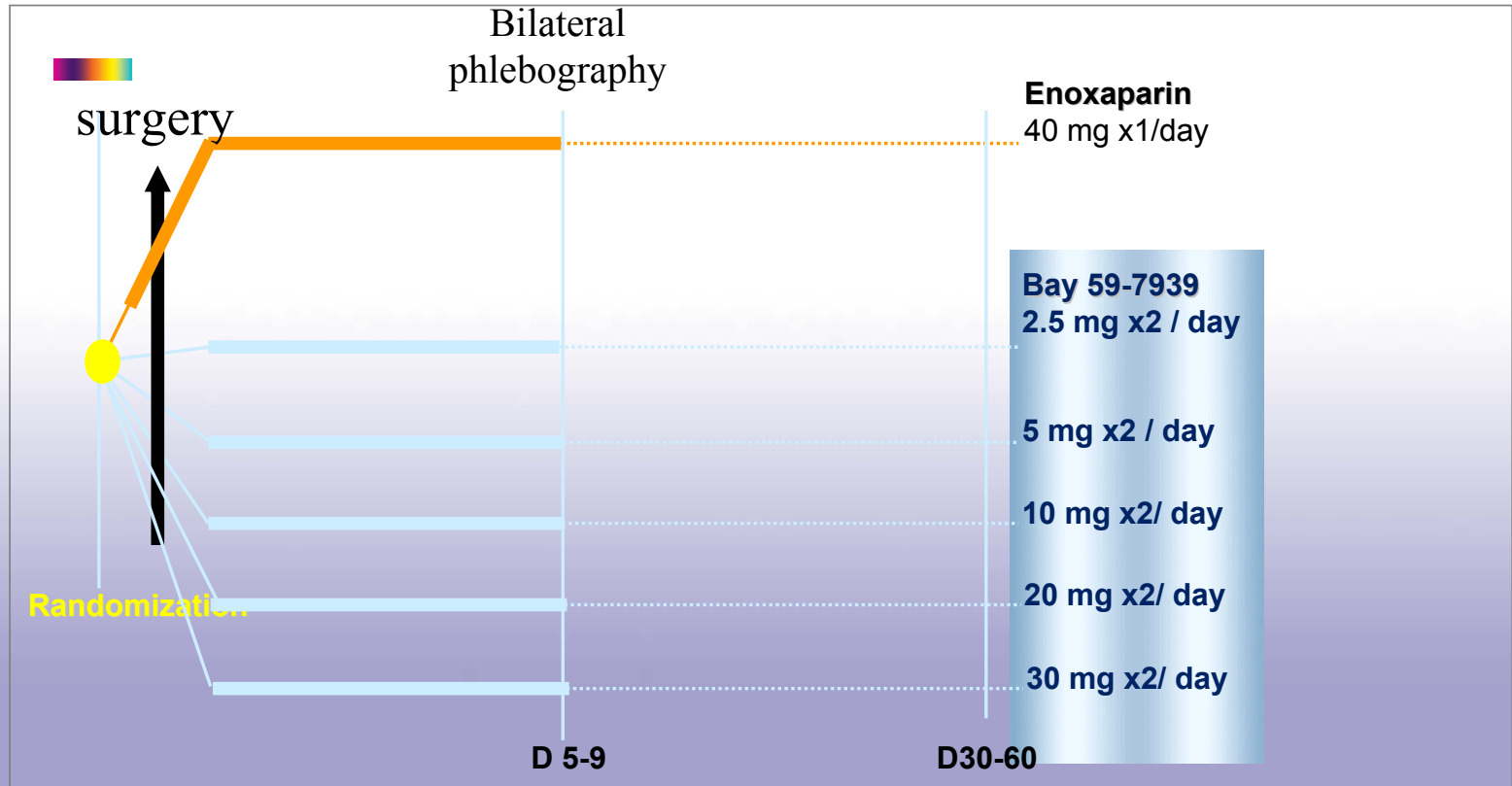
In vitro: platelet-rich human plasma activated by diluted tissue factor



Bay 59-7939

dose finding studies (phase II)

6 Parallel groups, double blind, randomized

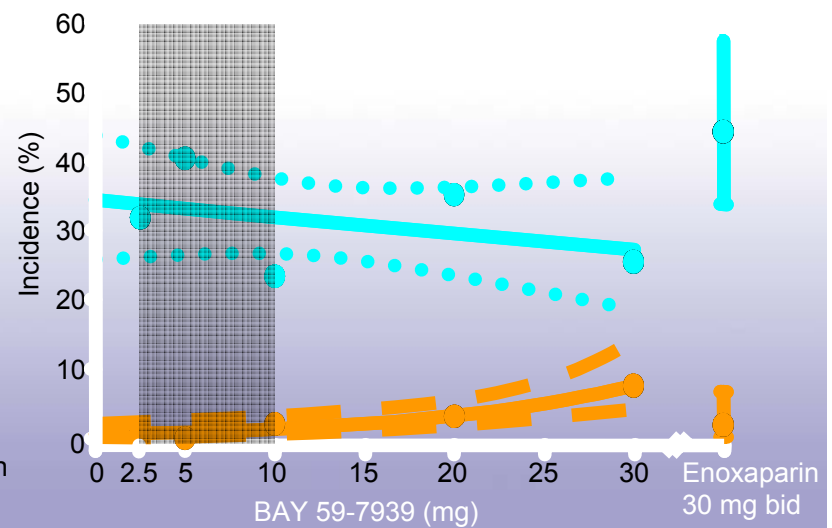
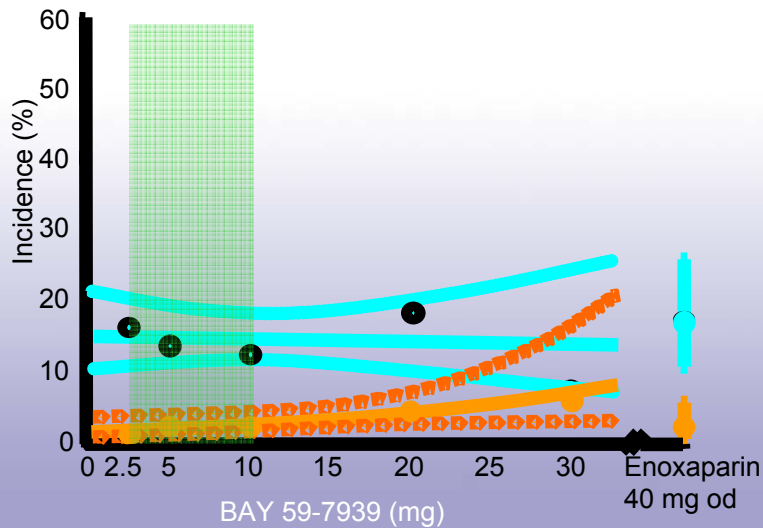


Dose-response relationships for BAY 59-7939

Hip surgery

Knee surgery

- Total venous thromboembolism and all-cause mortality
- Major, post-operative bleeding



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UTILISER LES ANCIENS COMME
LES NOUVEAUX**

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