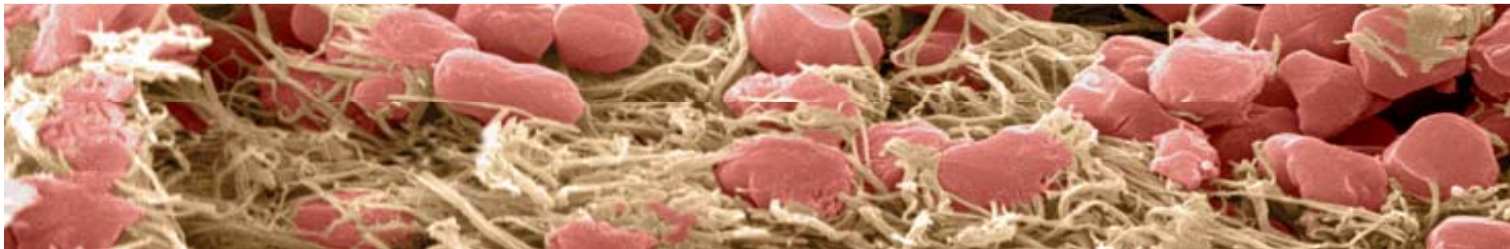


# EL PROCESO DE LA HEMOSTASIA. DIANAS TERAPEUTICAS



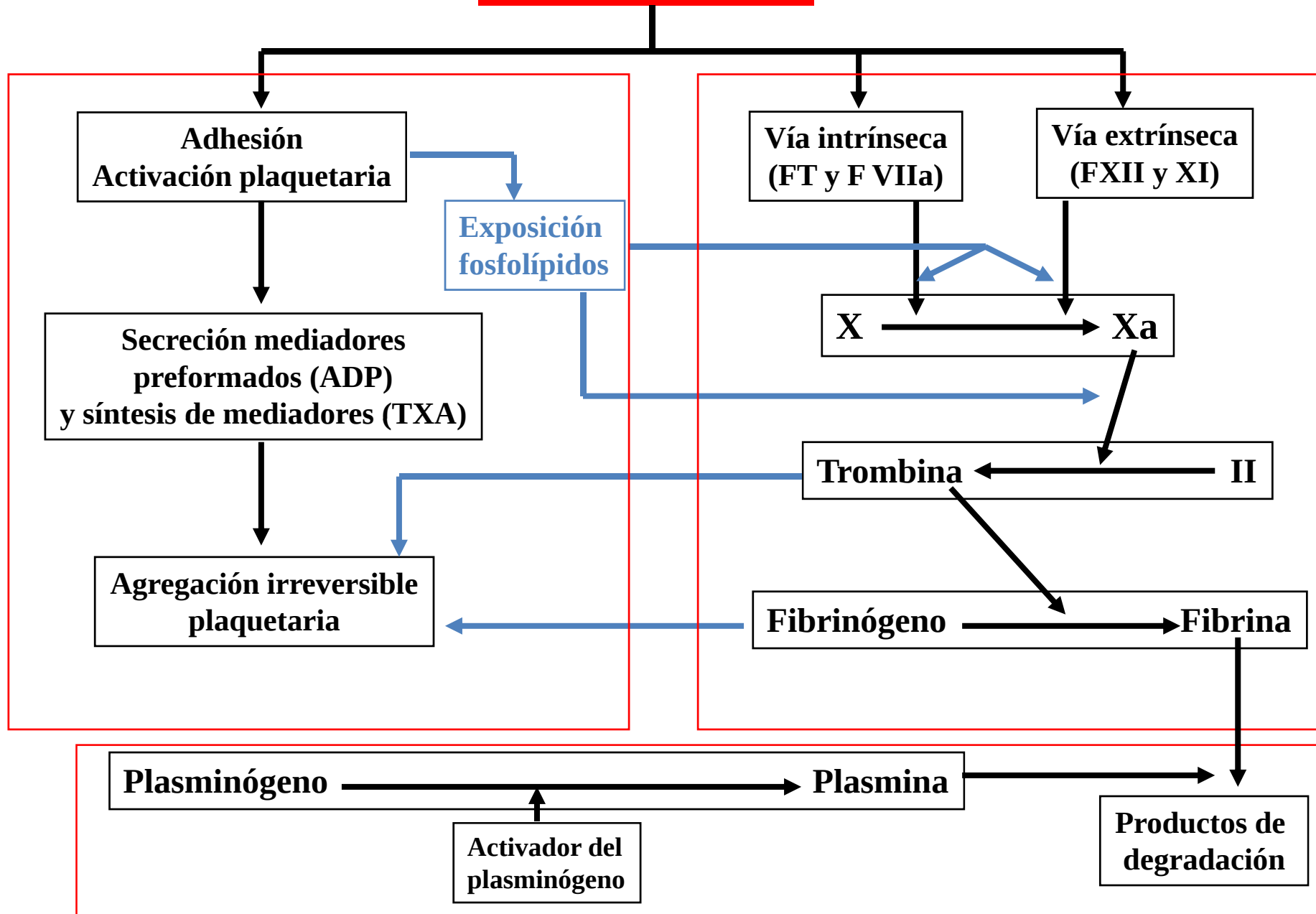
*Antonio Zarzuelo Zurita  
Departamento Farmacología  
Universidad de Granada*

# **FUNCIONES DE LA SANGRE**

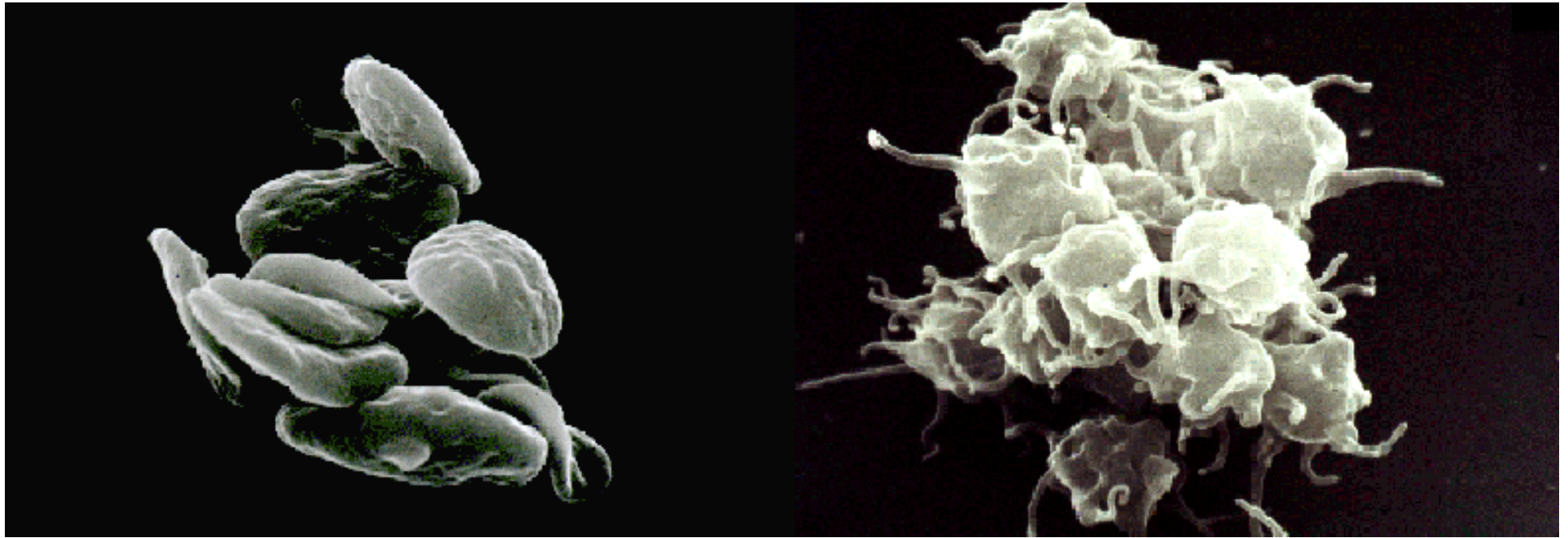
- Función de transporte de oxígeno y nutrientes a las células, o de productos de deshecho para ser eliminados.**
- Función defensiva y de reparación tisular.**
- Función reguladora para el mantenimiento del equilibrio de agua, de la temperatura corporal...**

## **FLUIDEZ**

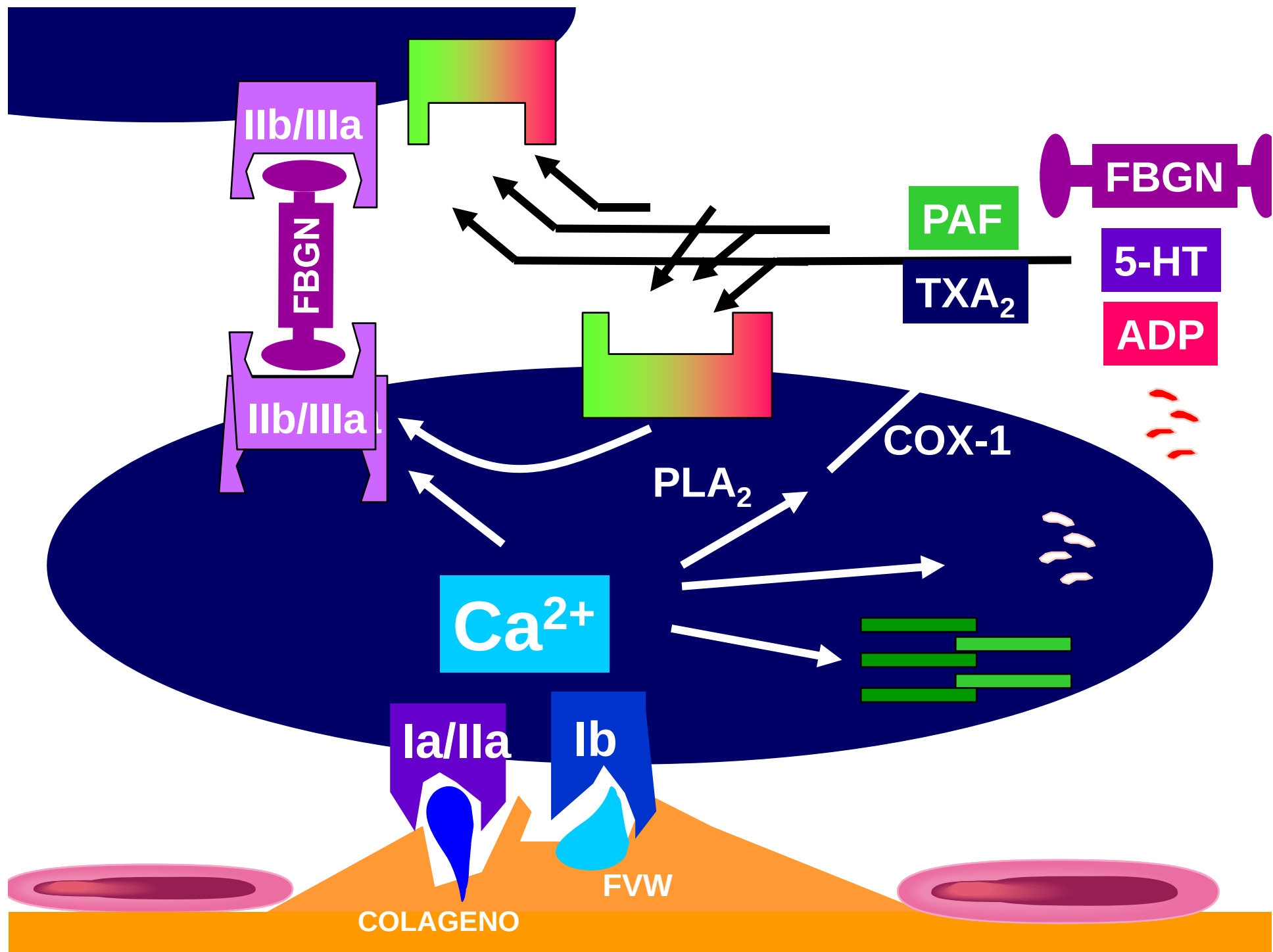
# Lesión vascular

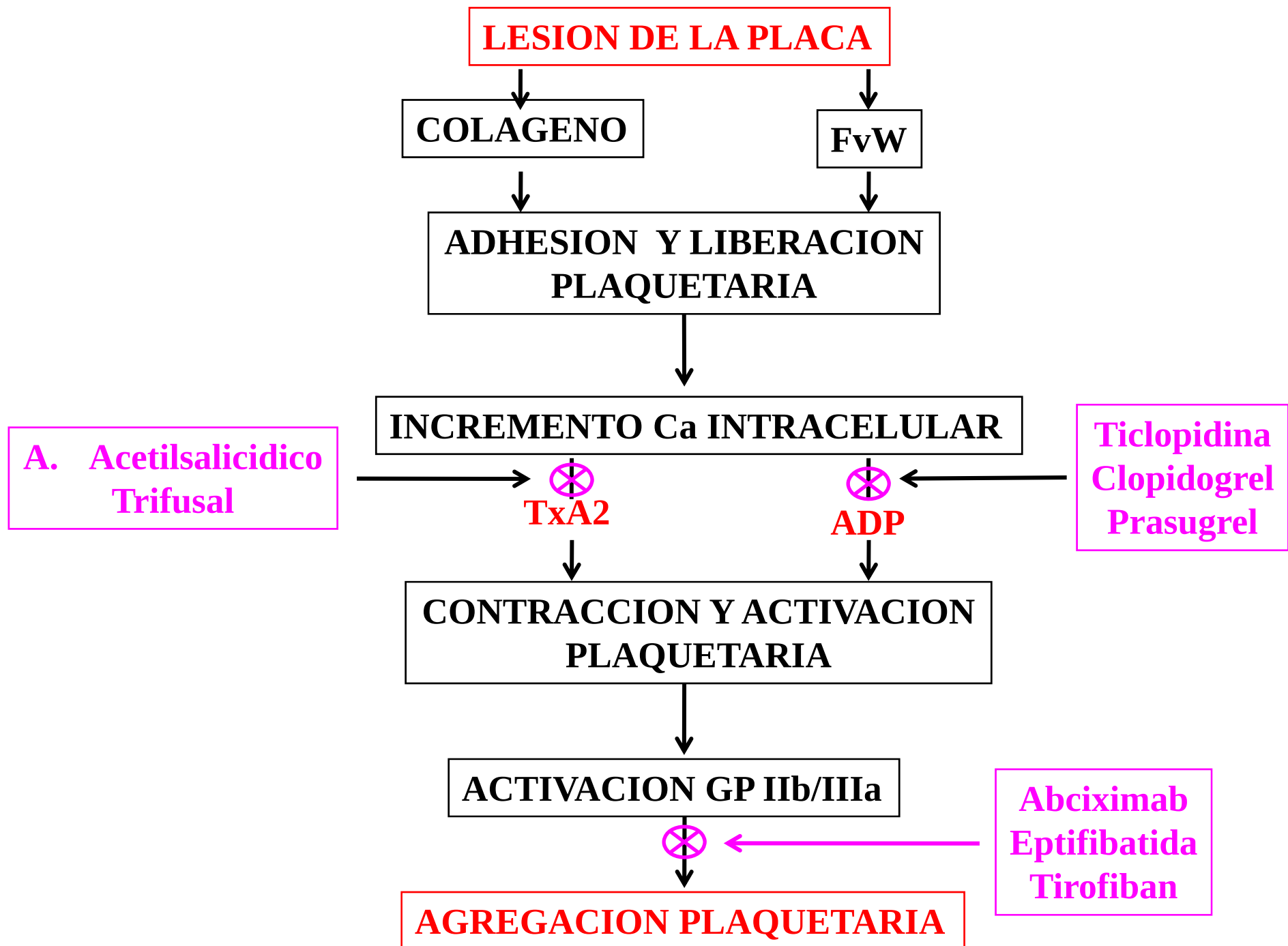


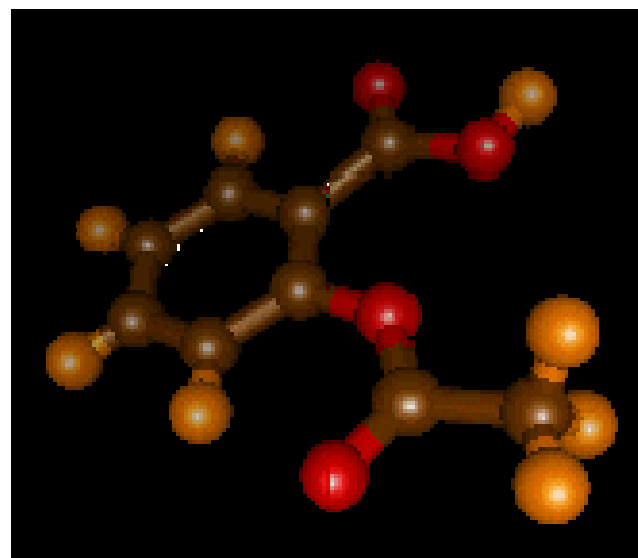
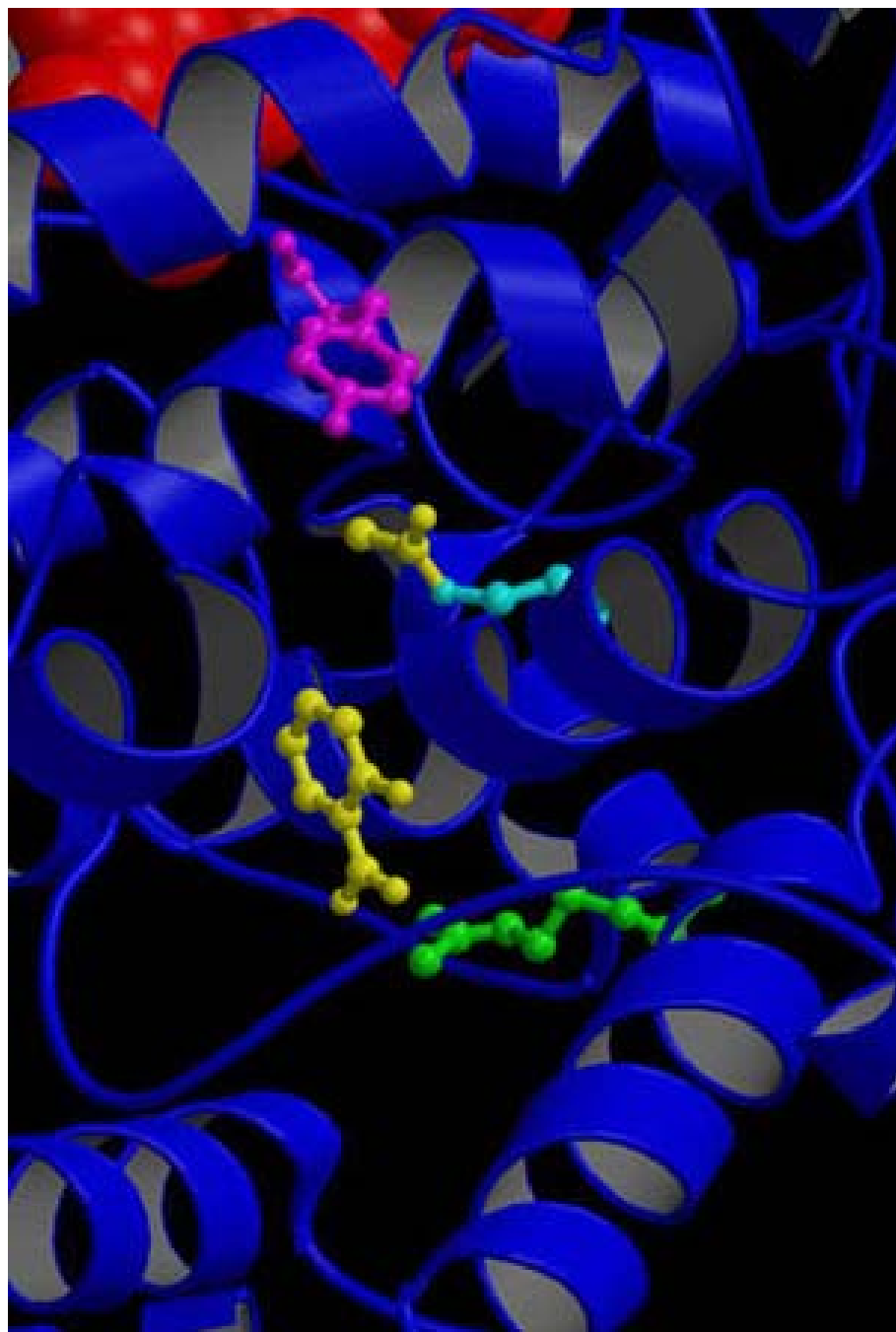
# AGREGACION PLAQUETARIA





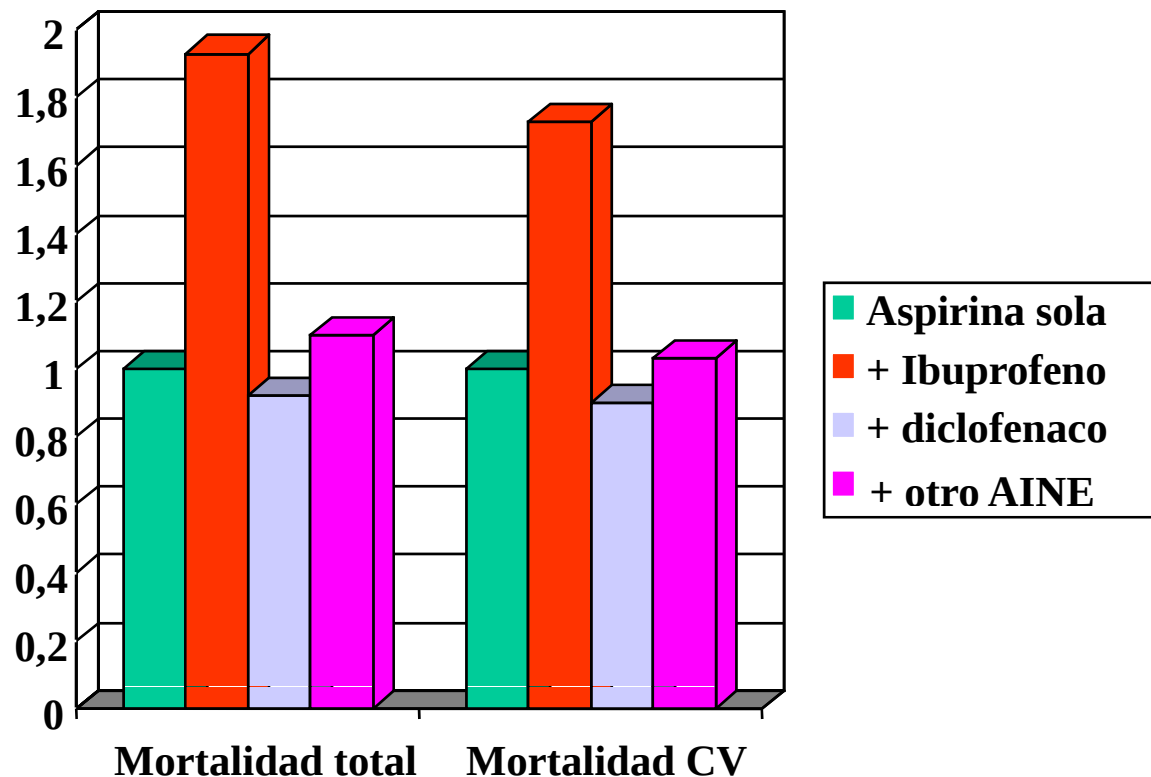






# IBUPROFENO EN EL EFECTO CARDIOPROTECTOR DE LA ASPIRINA

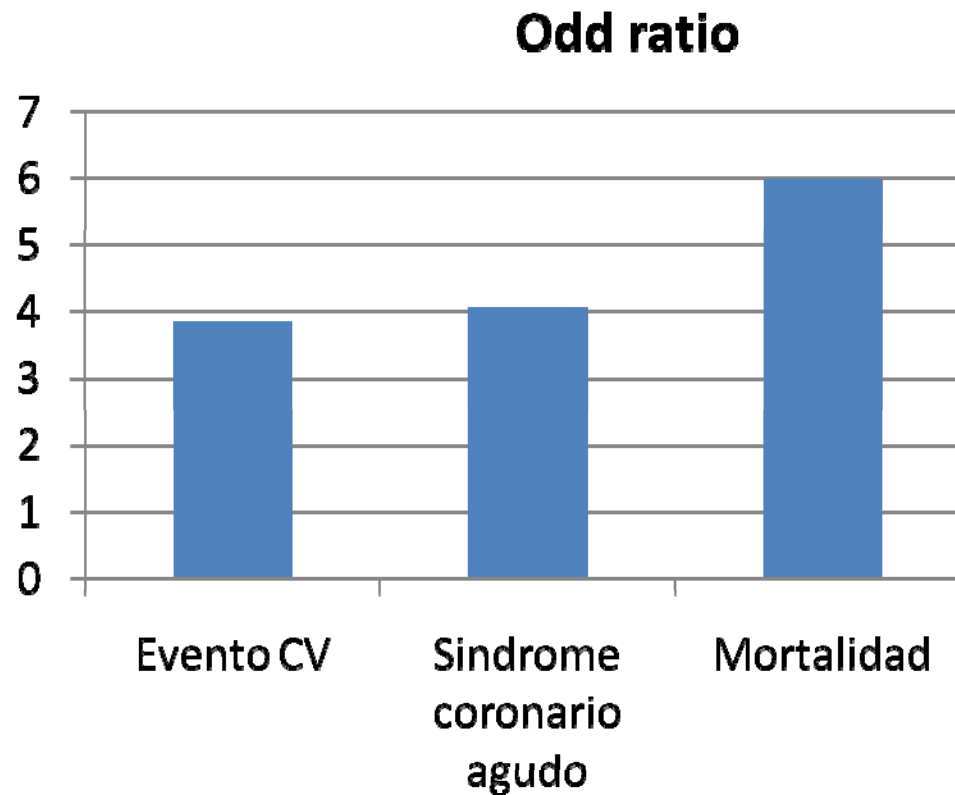
- 7107 pacientes con enfermedad CV previa y que sobrevivieron al menos 1 mes
- Todos dosis de aspirina < 325 mg/día, seguidos de 1989 a 1997



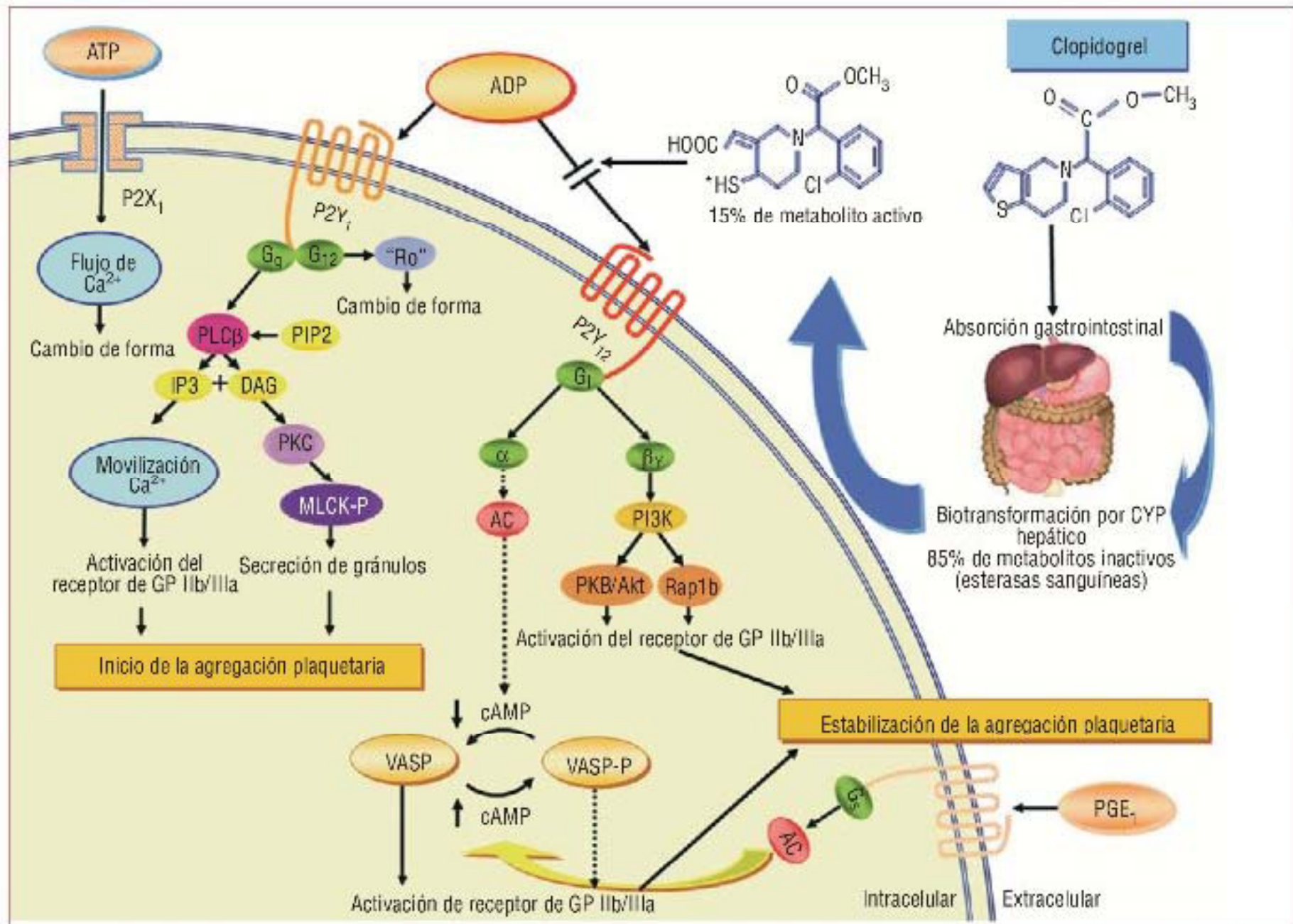
*MacDonald M (2003), Lancet 361: 573-574*

## Metaanálisis. Resistencia a la aspirina y riesgo de morbilidad cardiovascular

- 20 estudios, 2930 pacientes. 75 a 325 mg/día de ASS.
- 28% resistentes a la aspirina
- % eventos cardiovasculares: 39% para resistentes a AAS y 16% para no resistentes



*George Krasopoulos et al, BMJ 2008*



# INTERACCION CLOPIDOGREL E INHIBIDORES DE LA BOMBA DE PROTONES

**TABLE 1.** Adverse Outcomes Following Hospital Discharge for Acute Coronary Syndrome (ACS) in Patients With and Without Concomitant Proton Pump Inhibitor

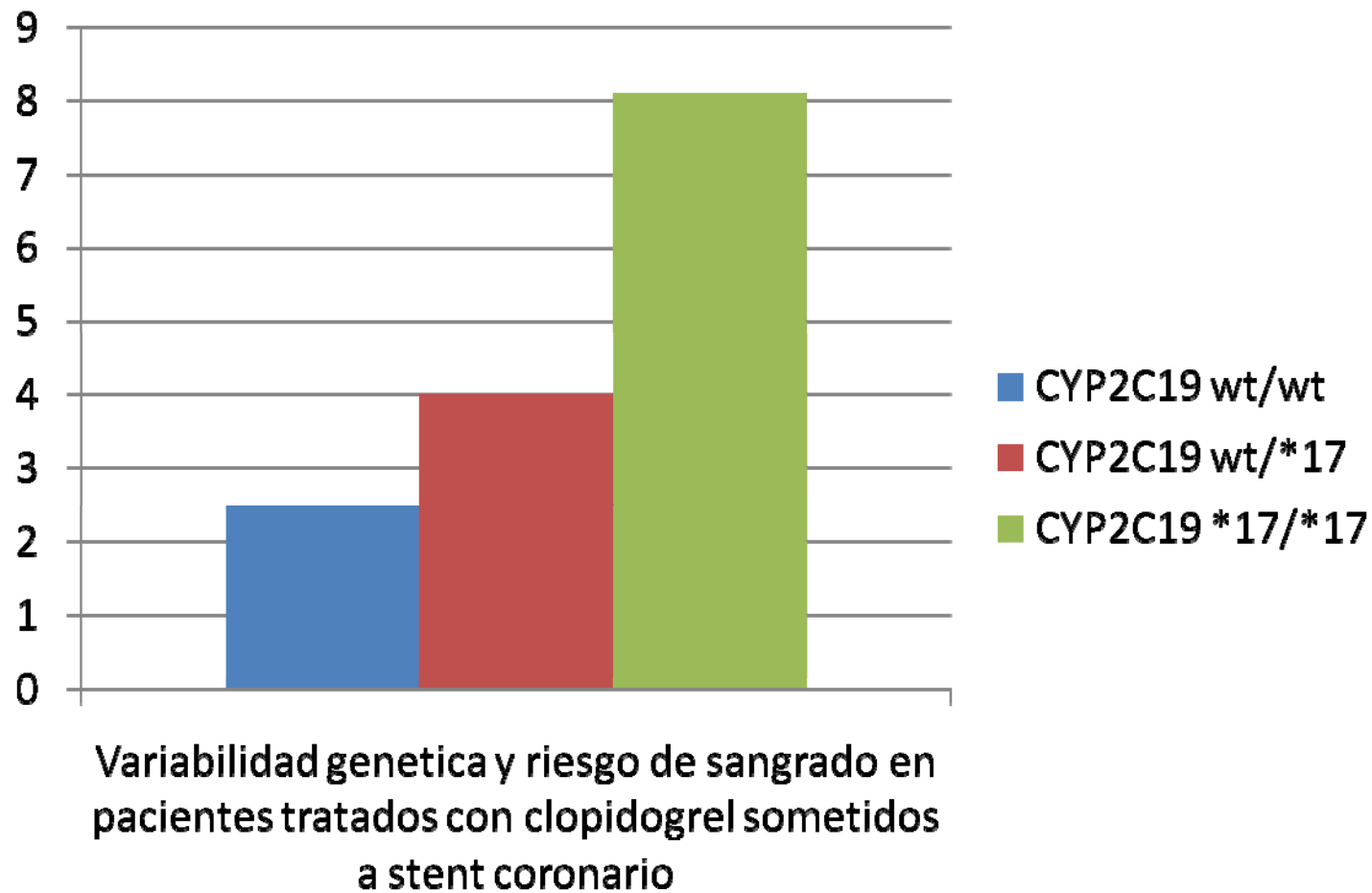
|                                    | No. (%) Events                        |                                    | Unadjusted OR<br>(95% CI) | Adjusted OR<br>(95% CI)* |
|------------------------------------|---------------------------------------|------------------------------------|---------------------------|--------------------------|
|                                    | Clopidogrel Without PPI<br>(n = 2961) | Clopidogrel With PPI<br>(n = 5244) |                           |                          |
| Primary outcome                    |                                       |                                    |                           |                          |
| Death or rehospitalization for ACS | 615 (20.8)                            | 1561 (29.8)                        | 1.62 (1.45–1.80)          | 1.25 (1.11–1.41)         |
| Secondary outcome                  |                                       |                                    |                           |                          |
| Rehospitalization for ACS          | 205 (6.9)                             | 764 (14.6)                         | 2.29 (1.95–2.69)          | 1.86 (1.57–2.20)         |
| Revascularization procedures       | 353 (11.9)                            | 815 (15.5)                         | 1.36 (1.19–1.55)          | 1.49 (1.30–1.71)         |
| Death (all-cause)                  | 493 (16.6)                            | 1042 (19.9)                        | 1.24 (1.10–1.40)          | 0.91 (0.80–1.05)         |

Reprinted with permission from *JAMA*. 2009;301:937–944.<sup>2</sup>

\*Adjusted for all variables in baseline characteristics except male sex.

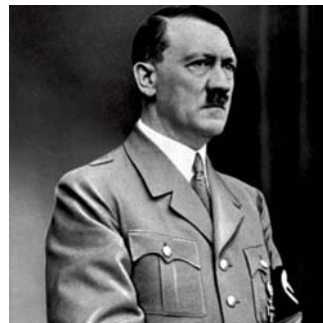
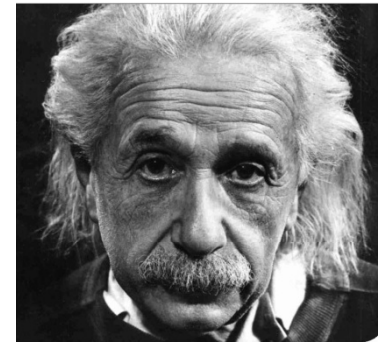
CI indicates confidence interval; OR, odds ratio; PPI, proton pump inhibitors.

**% Incidencia de sangrado después de 30 días**



*Dirk Sibbing, MD et al. Circulation. 2010;121:512-518*

# Las diferencias en el genoma de todos ellos es $<0.1\%$



# FARMACOGENETICA Y FARMACOGENOMICA

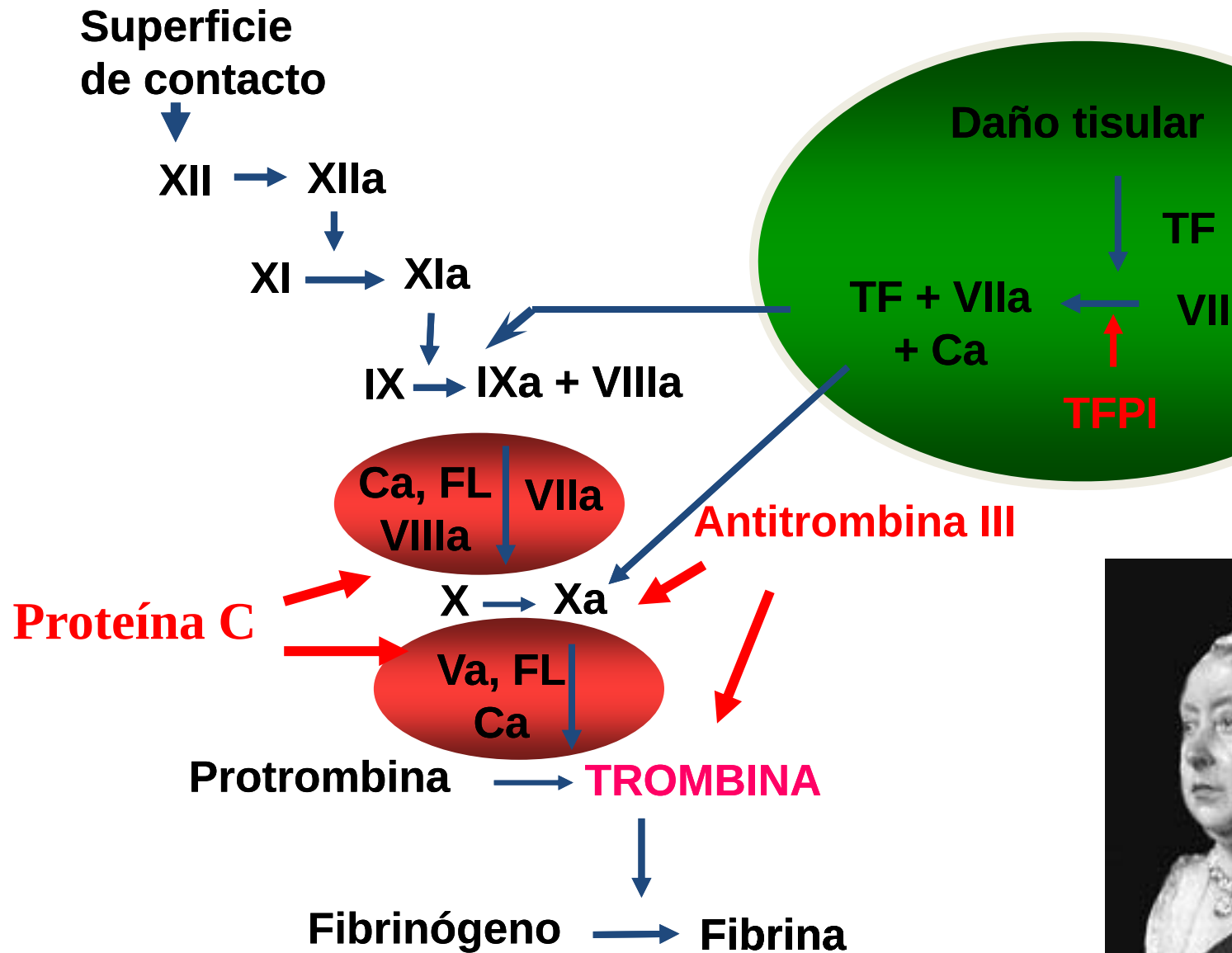


*“...si no fuera por la gran variabilidad entre los pacientes la medicina podría ser considerada como una ciencia y no un arte”*

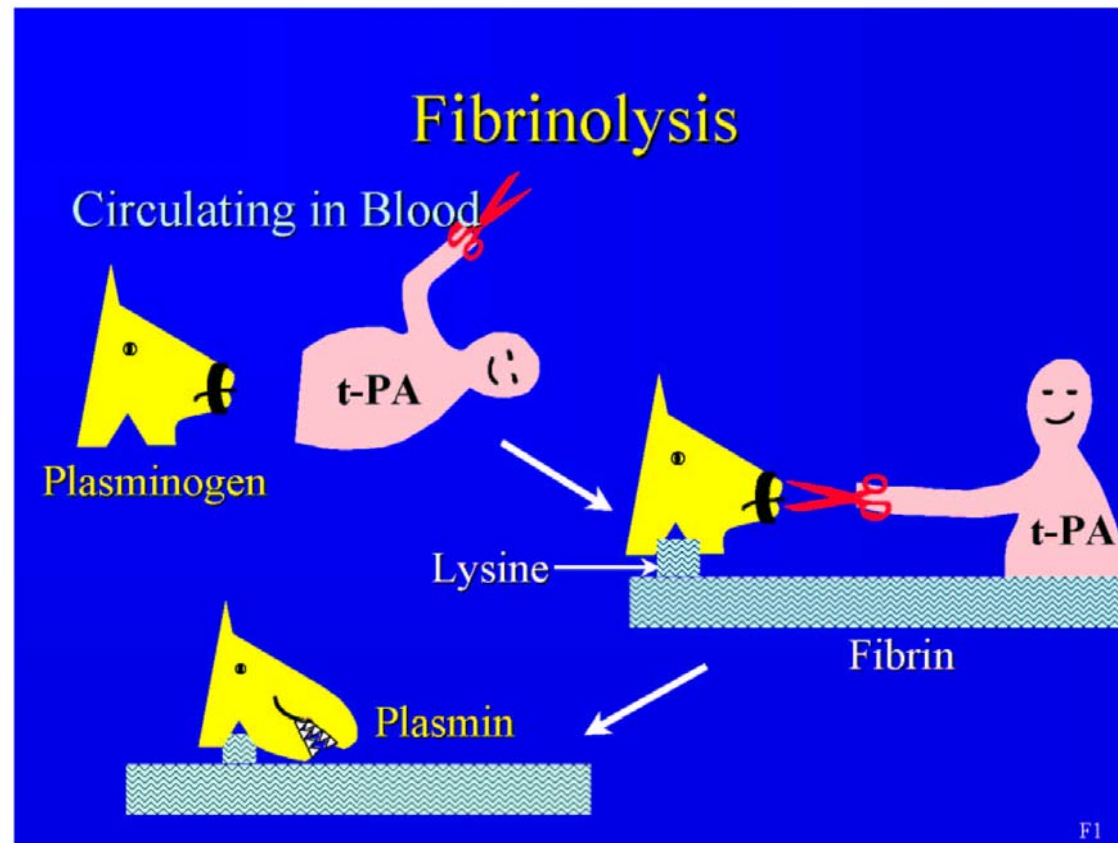
*“The Principles and Practice of Medicine” ,William Osler,  
1892*

## VIA INTRINSECA

## VIA EXTRINSECA



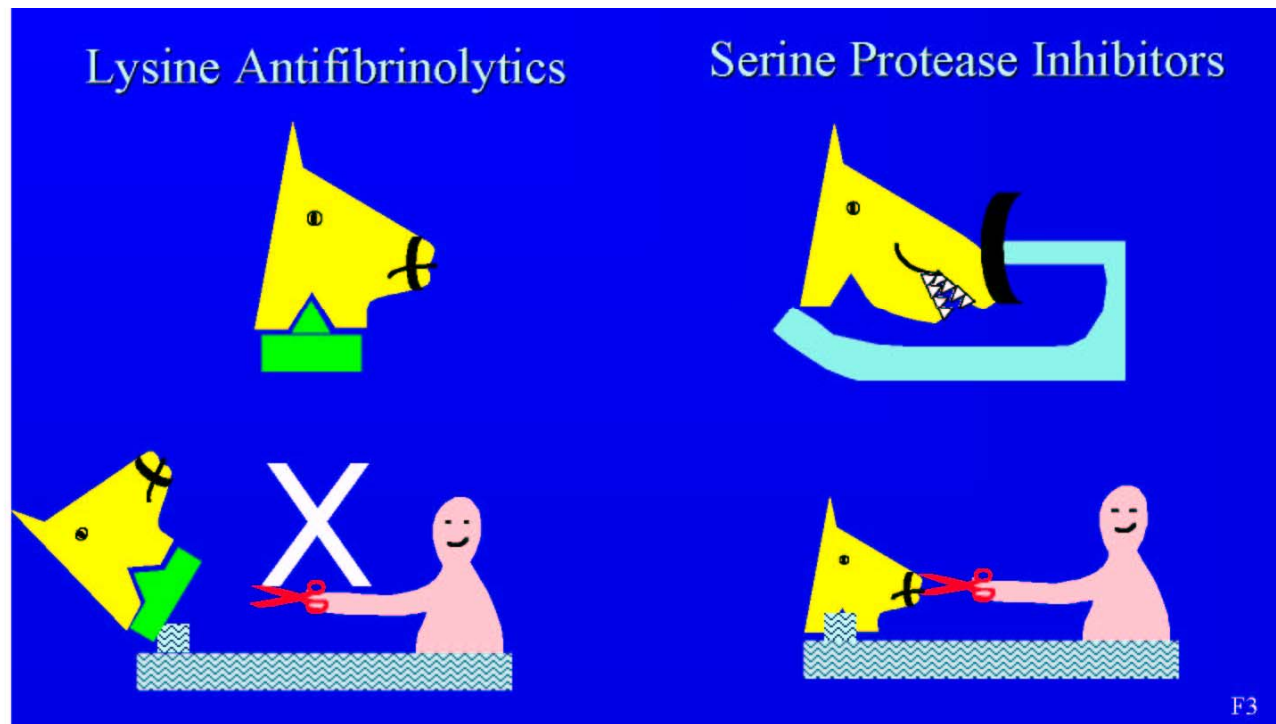
# Proceso de la Fibrinólisis



# Inhibición farmacológica de la fibrinólisis

**Acido tranexamico**

**Aprotinina**



## VIA INTRINSECA

Superficie  
de contacto

XII → XIIa

XI → XIa

IX → IXa + VIIIa

Ca, FL  
VIIIa

X → Xa

Va, FL  
Ca

Protrombina

**TROMBINA**

Fibrinógeno

**Fibrina**

## VIA EXTRINSECA

Daño tisular

FT

FT + VIIa  
+ Ca

VII

TFPI

PCA

PC

**IIa-TM**

TAFIa

TAFI

Productos de  
degradación

## VIA INTRINSECA

Superficie  
de contacto

XII → XIIa

XI → XIa

IX → IXa + VIIIa

Ca, FL  
VIIIa

X → Xa

Va, FL  
Ca

Protrombina → TROMBINA

Fibrinógeno → Fibrina

Vi. K

Warfarina  
Acenocumarol

## VIA EXTRINSECA

Daño tisular

TF

TF + VIIa  
+ Ca

VII

TFPI

Vit. K

ANTITROMBINA III

Heparina no fraccionada  
HBPM  
Fondaparinox

# INHIBIDORES DIRECTOS DE LA TROMBINA



## VIA INTRINSECA

Superficie  
de contacto

XII → XIIa

XI → XIa

IX → IXa + VIIIa

Ca, FL  
VIIIa

X → Xa

Va, FL  
Ca

Protrombina

TROMBINA

Fibrinógeno → Fibrina

Vi. K

Warfarina  
Acenocumarol

## VIA EXTRINSECA

Daño tisular

TF

TF + VIIa  
+ Ca

VII

TFPI

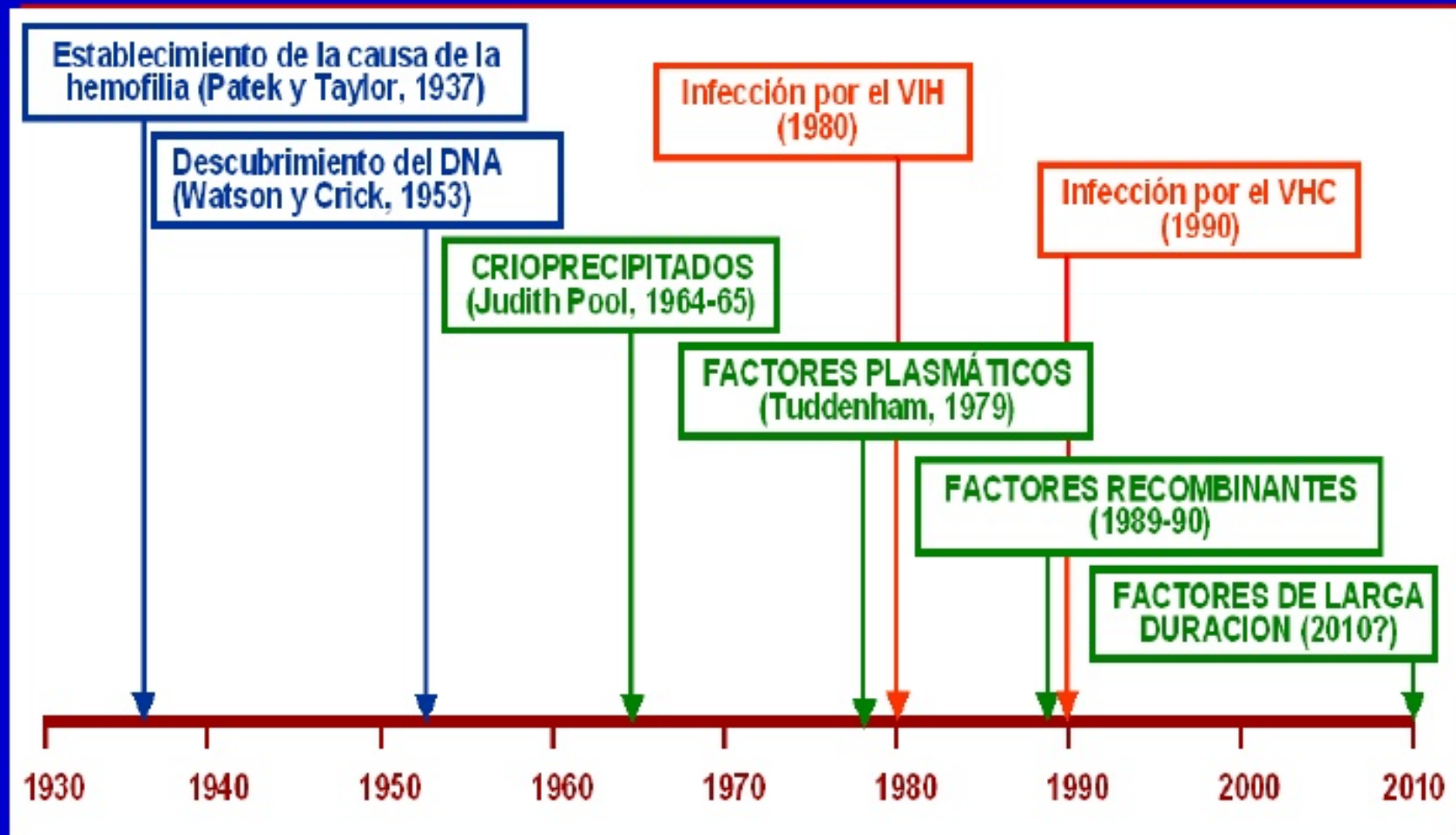
Vit. K

ANTITROMBINA III

Heparina no fraccionada  
HBPM  
Fondaparinox

Rivaroxaban

Etexilato de dabigatran



## LOBULINA ANTIHEMOFILICA HUMANA (1937)

### HEMOPHILIA. II. SOME PROPERTIES OF A SUBSTANCE OBTAINED FROM NORMAL HUMAN PLASMA EFFECTIVE IN ACCELERATING THE COAGULATION OF HEMOPHILIC BLOOD

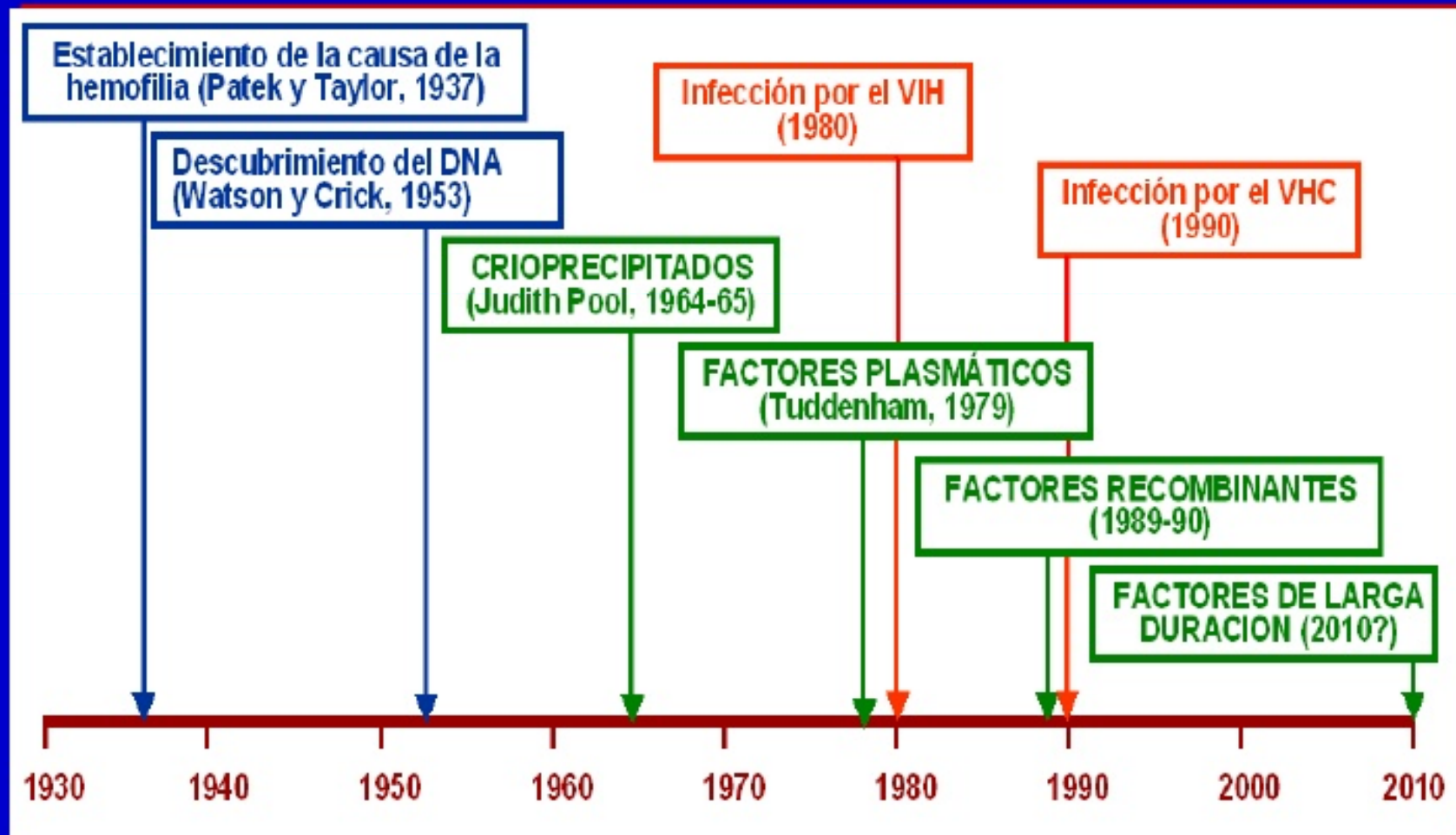
By ARTHUR J. PATEK, JR., AND T. H. L. TAYLOR

*(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston)*

*(Received for publication October 15, 1936)*

In previous studies (1) it was observed that citrated normal plasma rendered free of cellular elements by Berkefeld filtration, contained a substance which accelerated the clotting time of hemophilic blood. In the present study (2) a substance was isolated from such plasma by means of a special procedure. It was used in order to determine its properties. The substance was found to be a protein of molecular weight 16,000. It was found to be a protein of molecular weight 16,000. It was found to be a protein of molecular weight 16,000.

*J. Clin. Inv. 16: 113 (1937)*

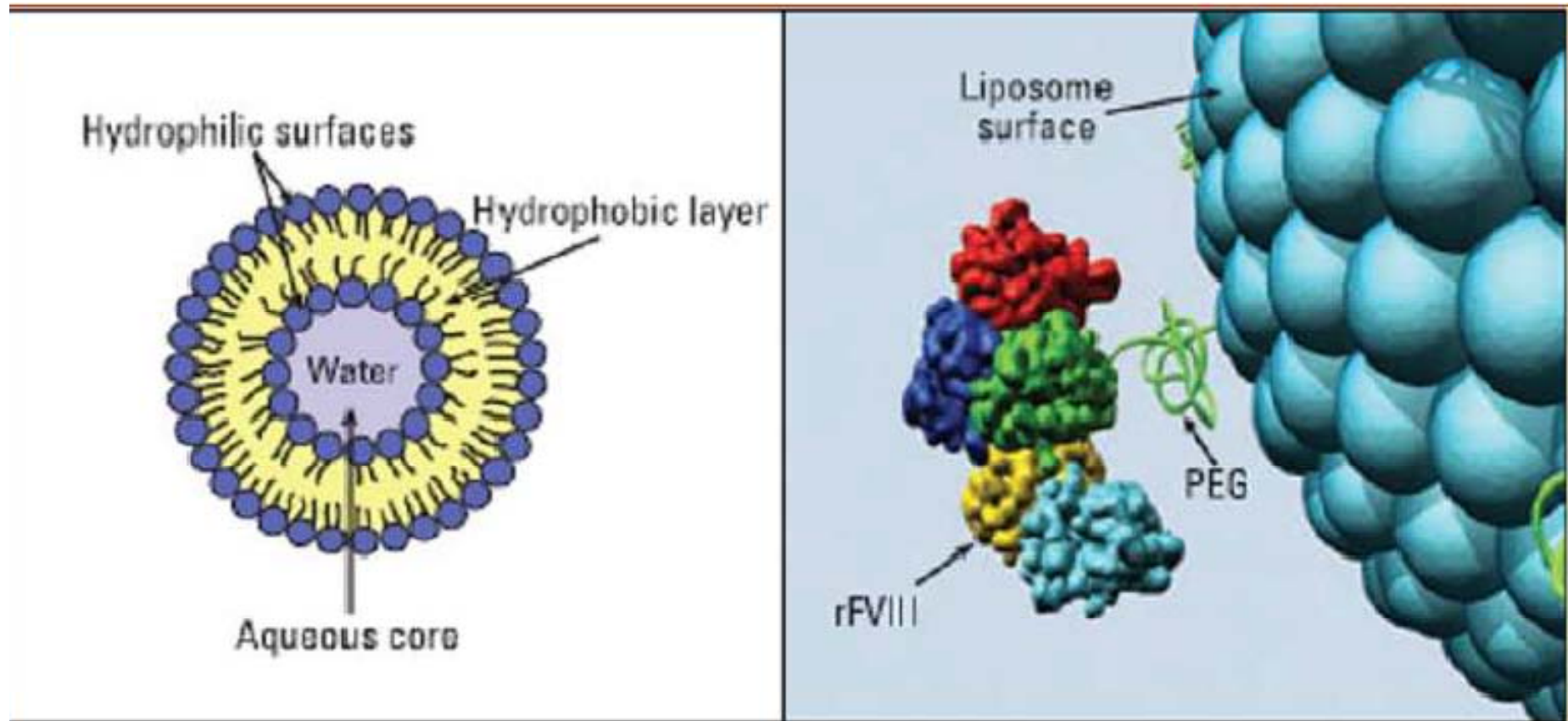


# **NUEVAS ESTRATEGIAS EN LA TERAPIA ANTIHEMOFÍLICA**

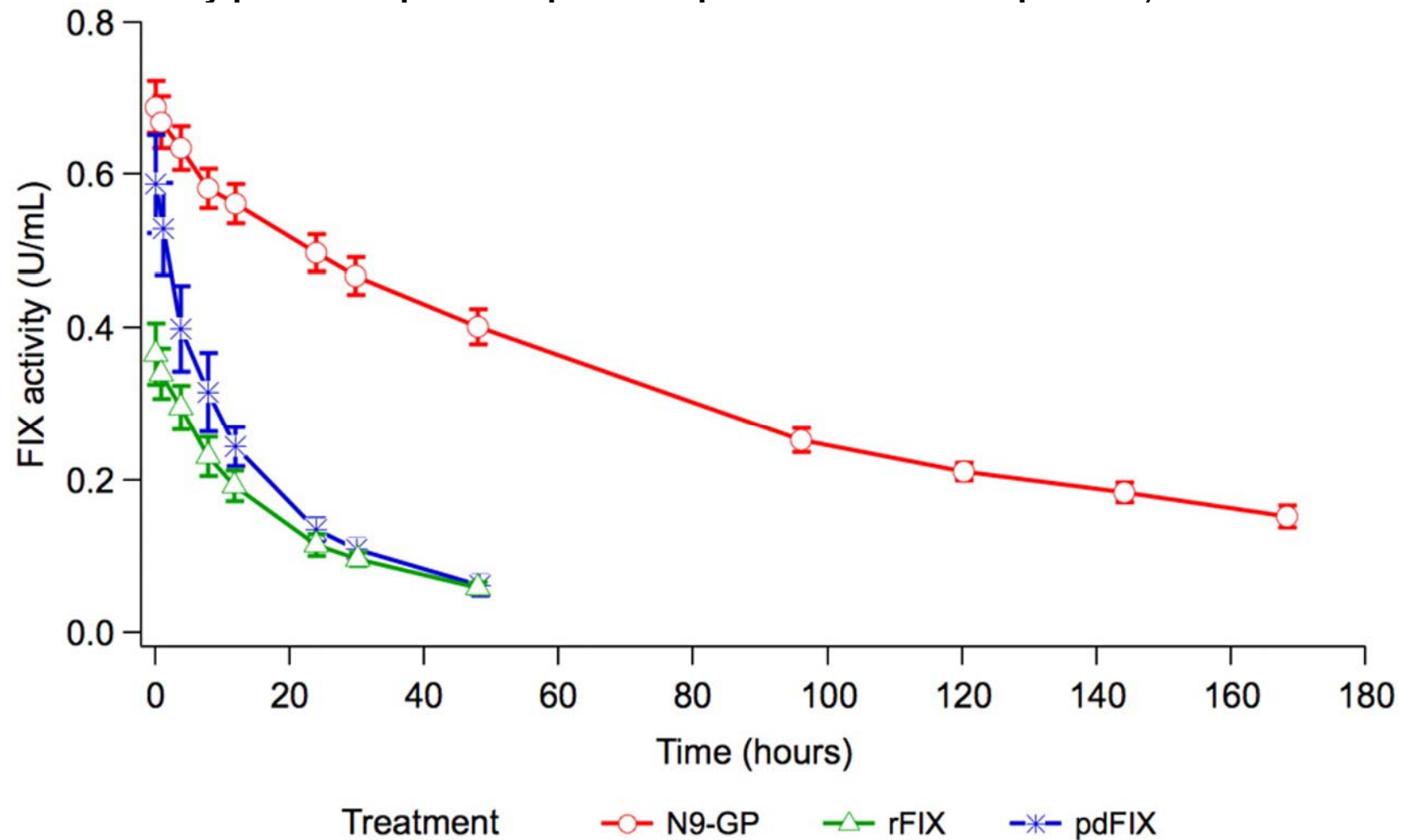
- Potenciar la actividad procoagulante**
- Mejorar el perfil farmacocinético**
- Reducir la inmunogenicidad**

- Pegilación, conjugación con ácidos polisiálicos**
- Proteínas de fusión**
- Terapia génica**

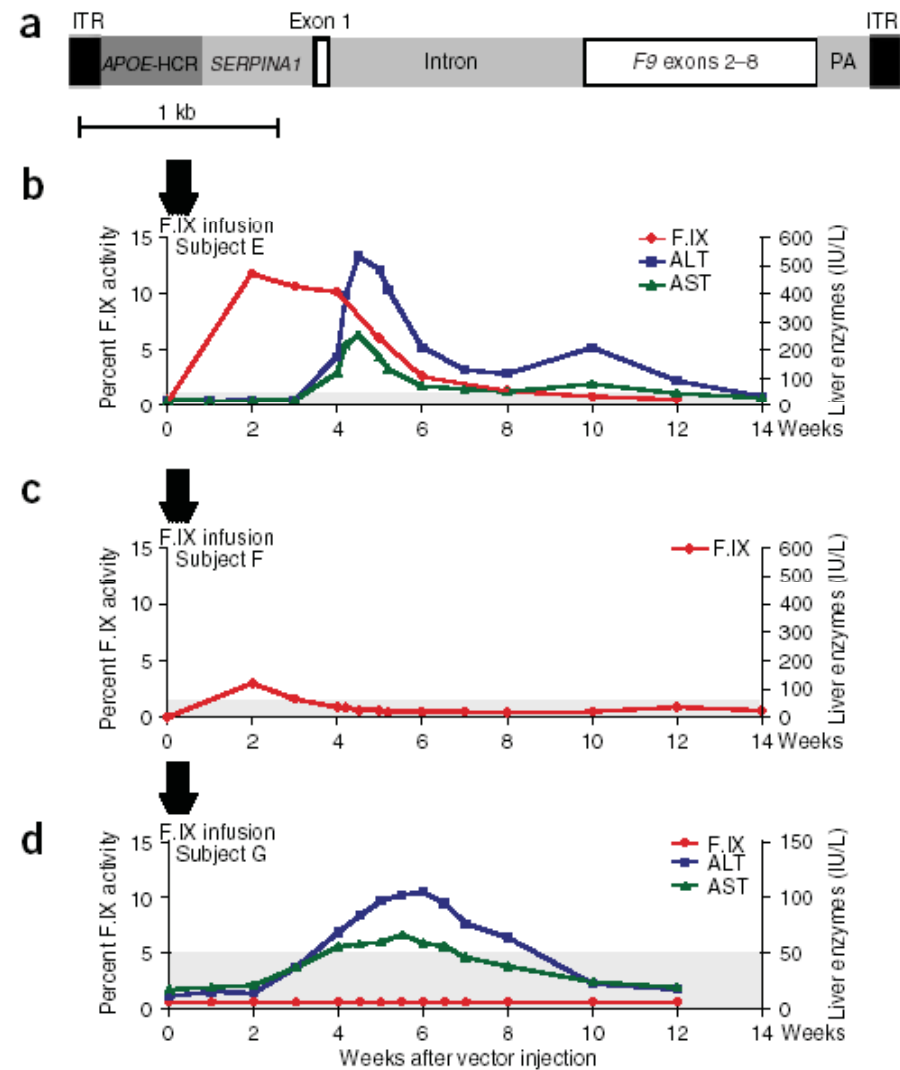
## Factor VIII con liposomas pegilados (FVIII-PEGLip)



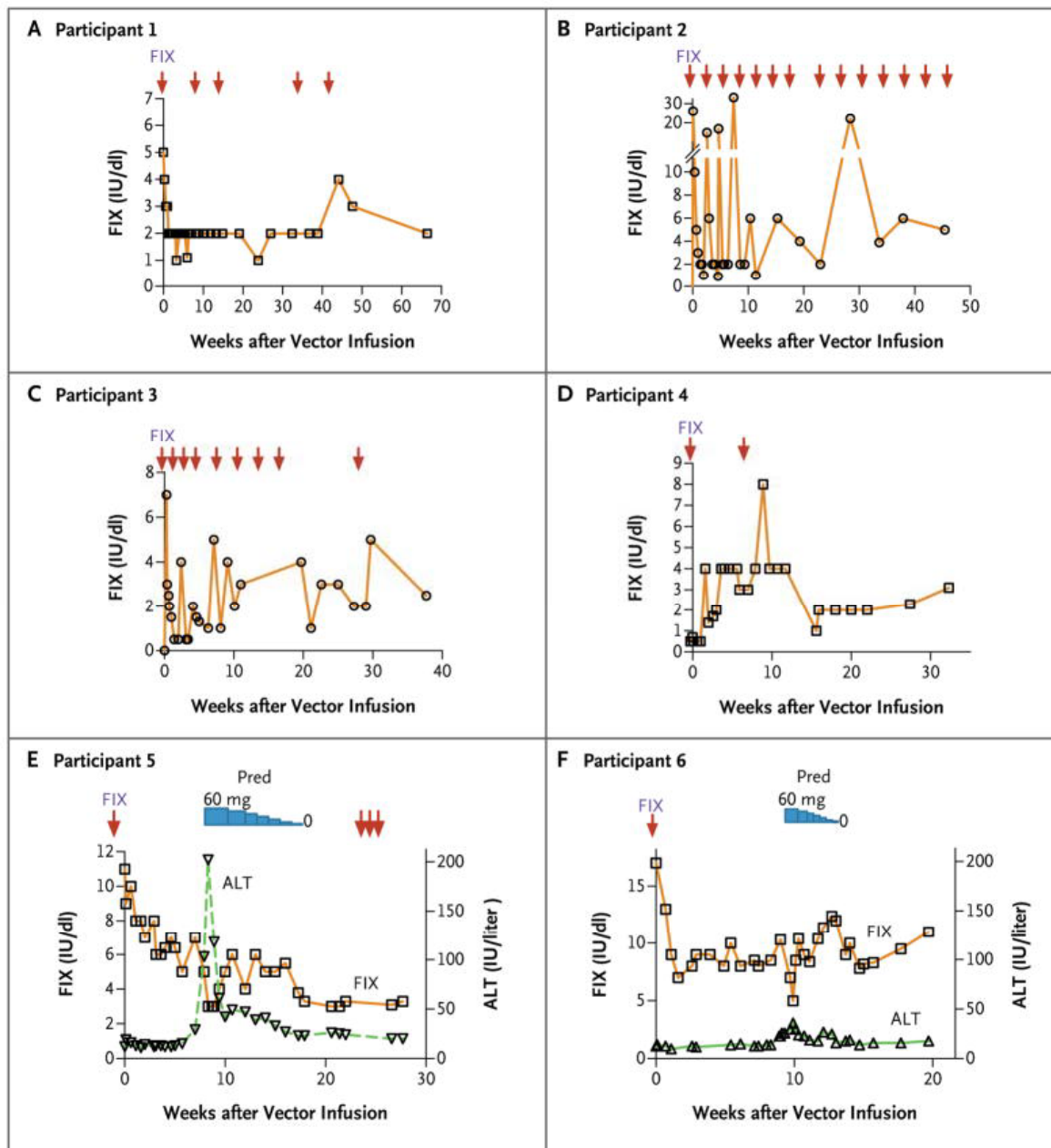
Estimated mean FIX activity profiles adjusted to a dose of 50 U/kg. rFIX indicates the FIX activity profile for patients' previous recombinant FIX product and pdFIX indicates the FIX activity profile for patients' previous plasma-derived FIX product, both m...



Negrier C et al. Blood 2011;118:2695-2701



*Kay et al (2006), Nature Medicine 2006 ; 12 (3): 342-347*



## Adenovirus-Associated Virus Vector-Mediated Gene Transfer in Hemophilia B

*Nathwani et al, (2011). N Engl J Med 365(25): 2357-2365*



La desesperanza está fundada en lo que sabemos,  
que es nada, y la esperanza sobre lo que  
ignoramos, que es todo.

[Maurice Maeterlinck](#) (1862-1949)