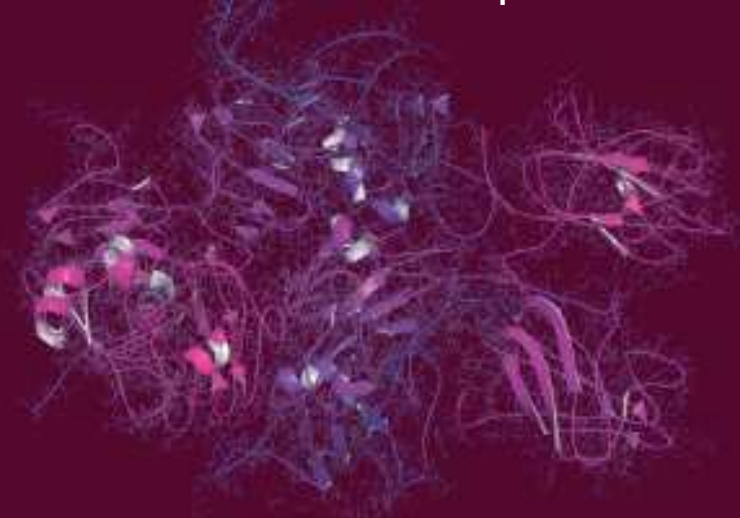


# **XII** jornadas farmacéuticas

## **SOBRE EL TRATAMIENTO DE LAS COAGULOPATÍAS CONGÉNITAS**

### **Nuevas Dianas y Opciones Terapéuticas en la Hemostasia**

Dr. R. Núñez Vázquez

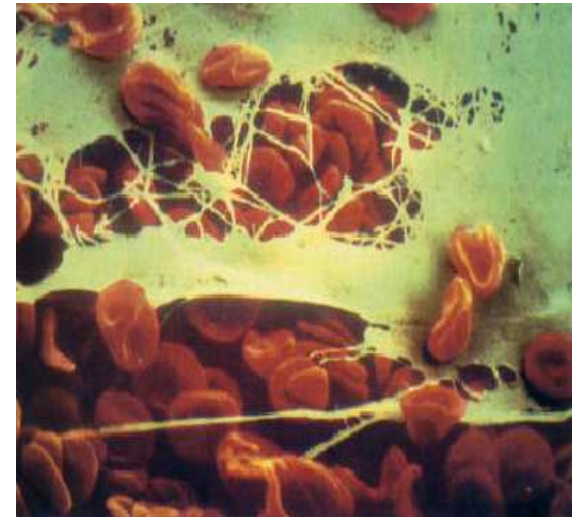


# Concepto de hemostasia

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Mecanismo de defensa constituido por un conjunto organizado de interacciones entre células y vasos sanguíneos, proteínas plasmáticas y sustancias de muy bajo peso molecular cuya función es:

- Prevenir la pérdida de sangre de los vasos intactos.
- Detener hemorragia de vasos lesionados.
- Mantener flujo sanguíneo.
- Interacción con otros sistemas biológicos: reparación de tejidos y vasos lesionados, defensa frente a microorganismos.



**Eficacia + Inocuidad: rápida, localizada y poco extensa.**

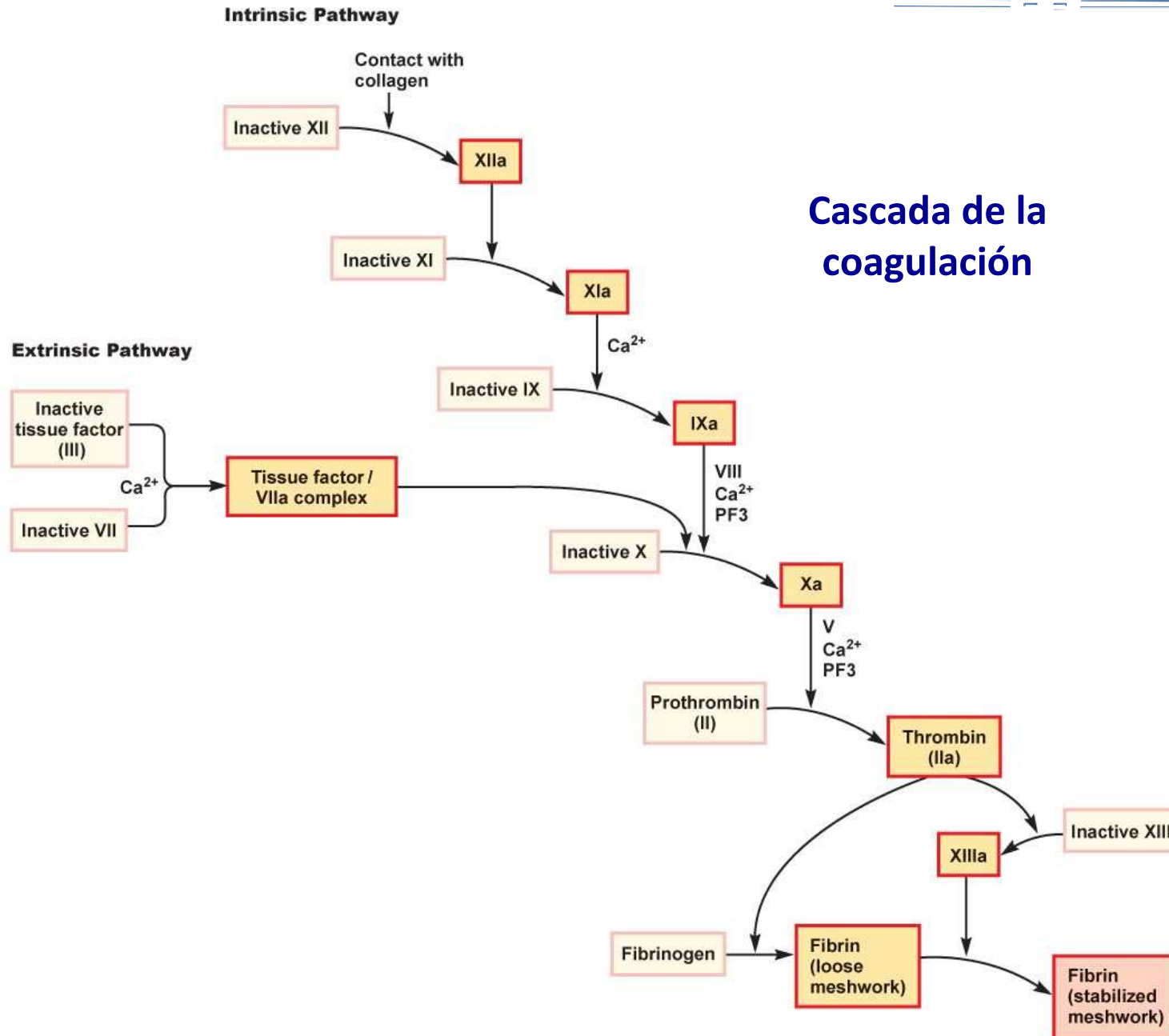
**Legend:**

- Contact Pathway (Orange)
- Tissue Factor Pathway (Yellow)
- Thrombin generation (Pink)
- Thrombin effects (Green)
- Control of Fibrinolysis (Light Blue)
- Transglutaminase (Dark Blue)
- Platelet Pathways (Grey)
- Tenase Complex (Brown)

**Abbreviations:**

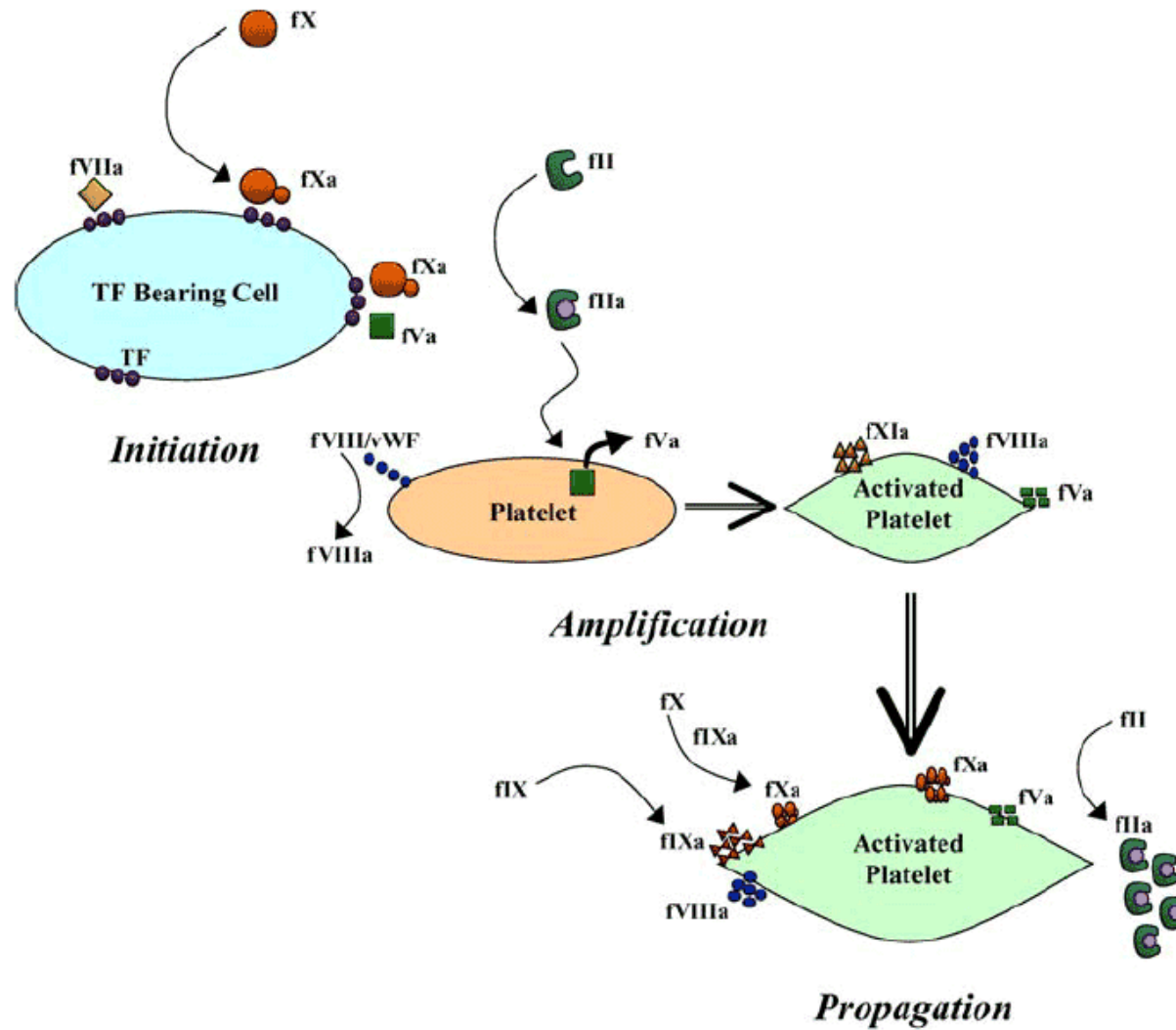
ADAM-TS: Disintegrin and Metalloproteinase with Thrombospondin Motifs  
APC: Activated Protein C  
AS: Ascorbic acid  
B2G2: Beta-2-Glycosaminoglycan  
GAG: Glycosaminoglycan  
HMW: High Molecular Weight  
HSP: Heat Shock Protein  
IIR: Interleukin-1 Receptor  
IIR-1: Interleukin-1 Receptor-1  
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## Cascada de la coagulación





# Modelo celular de la hemostasia



## Historia de sangrado

Test iniciales  
Hemograma, TP, TTPa, TT, TR, PFA-100

### Defectos de la hemostasia primaria

EVW

FVW: Ag  
FVW: Rco  
FVIII  
↓  
Multímeros  
RIPA

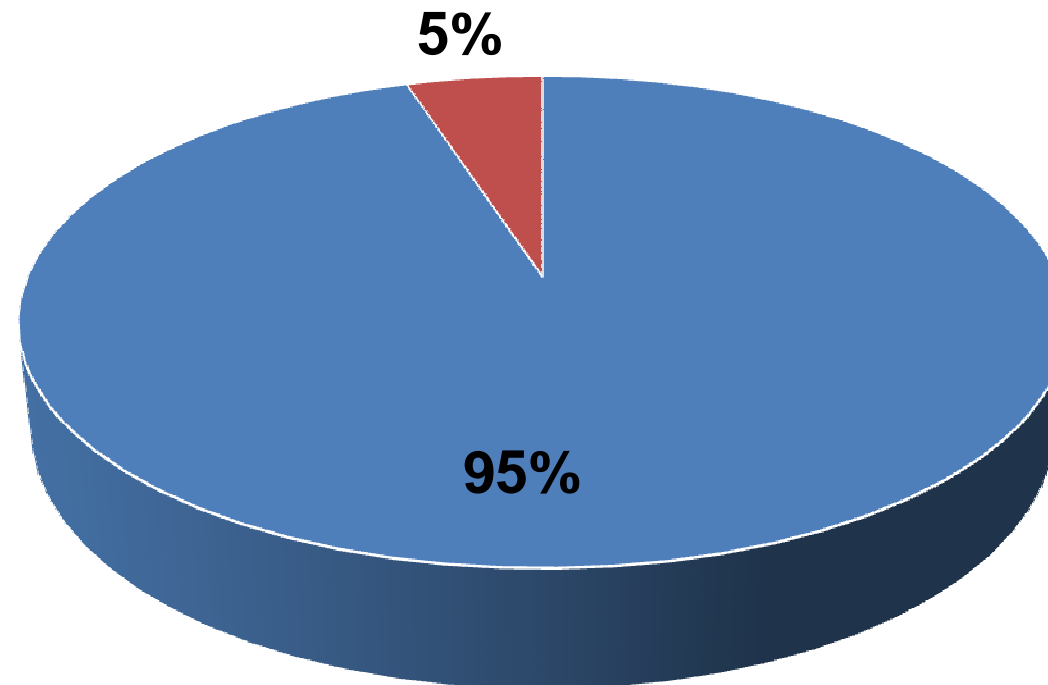
Alteraciones plaquetarias

Número de plaquetas  
Morfología de plaquetas  
Pruebas de función de plaquetas

### Defectos de los factores de coagulación

Dosificación específica de  
factor

## Enfermedades congénitas hemorrágicas de la coagulación

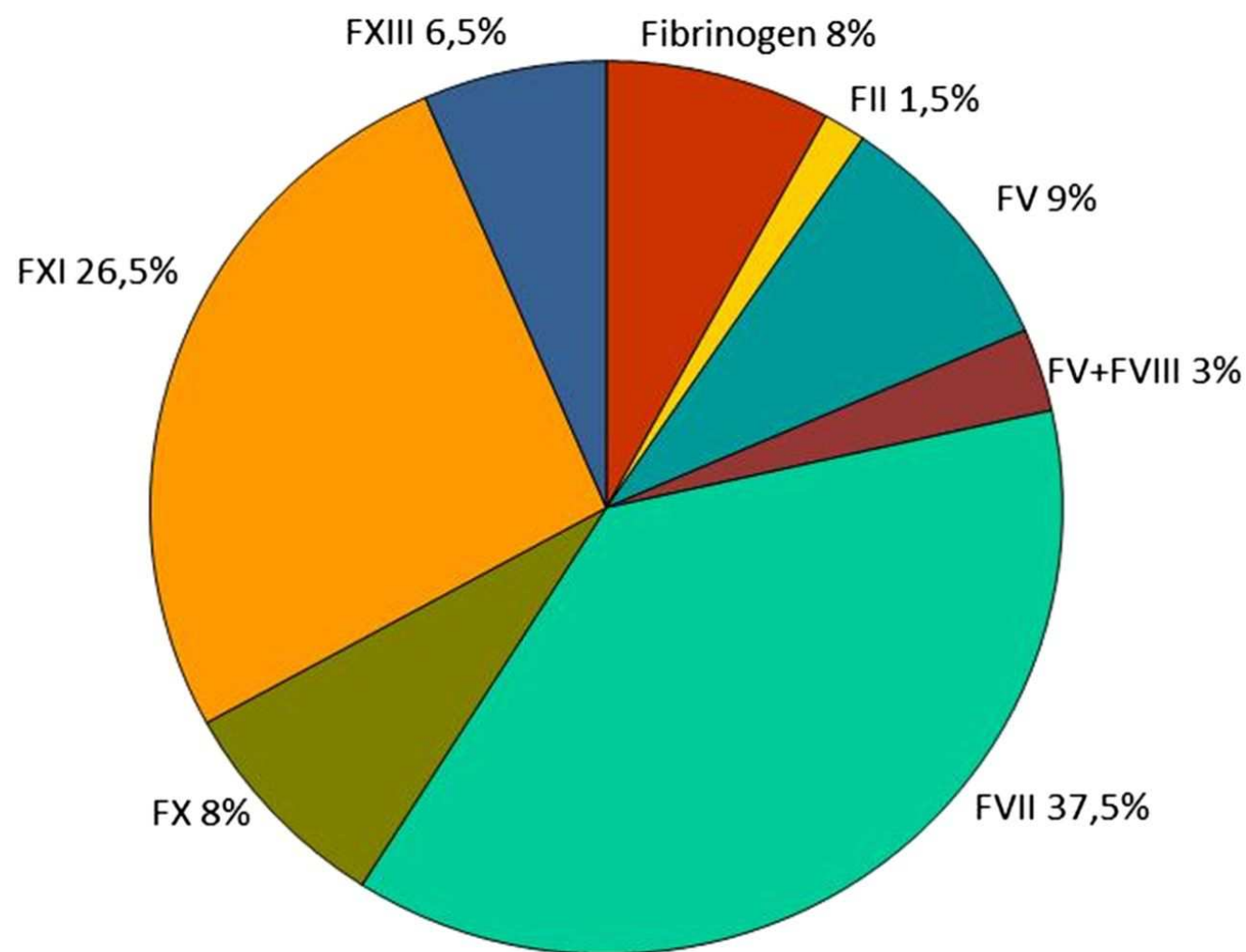


■ HA+HB+EvW

■ Otras deficiencias factoriales

- Coagulopatías hemorrágicas infrecuentes
- Rare Bleeding Disorders (RBD)

## Distribución de las RBDs. Registros WFH y EN-RBD





# Registros

---

- European Network of Rare Bleeding Disorders (EN-RBD; Peyvandi et al, 2012a),
- North American Rare Bleeding Disorders Registry (Acharya et al, 2004)
- Several disease-specific registries (Herrmann et al, 2006, 2009; Ivaskevicius et al, 2007; Bernardi et al, 2009).

# Prevalencia

Disorder	Worldwide prevalence	Gene(s) involved
Fibrinogen deficiency (F1D)	1:1 million (AR) Unknown (AD)	<i>FGA, FGB, FGB</i>
Prothrombin deficiency (F2D)	1:2 million	<i>F2</i>
Factor V deficiency (F5D)	1:1 million	<i>F5</i>
Factor VII deficiency (F7D)	1:0.5 million	<i>F7</i>
Factor X deficiency (F10D)	1:1 million	<i>F10</i>
Factor XI deficiency (F11D)	1:1 million (AR)	<i>F11</i>
Factor XIII deficiency (F13D)	1:2 million	<i>F13A, F13B</i>
Factor V + VIII deficiency (F5F8D)	1:1 million	<i>LMAN, MCDF2</i>
Vitamin K dependent coagulation factor deficiency (VKDCFD)	1:1 million	<i>GGCX, VKORC1</i>

AR, autosomal recessive; AD, autosomal dominant.

Hemofilia A (déficit FVIII)	1x 5.000 varones
Hemofilia B (deficit FIX)	1x 30.000 varones

# Manifestaciones clínicas

---

- Ampla variedad de síntomas, de leves a graves.
- Asociación variable entre el nivel de actividad del factor deficitario y el riesgo de sangrado.



- Epistaxis, menorragia, hemorragia postparto (FVIII)
- Sangrado postquirúrgico excesivo (FVIII)
- Hemorragia intracraneal: FVIII, FI, FX, FVII (FVIII, FII, FX, FVII)
- Cordón umbilical: FVIII, FI, FX (FVIII, FI, FX)
- Gastrointestinal: FX (FX)
- Hemartros: FI, FII, FX, FIX, FXIII (FI, FII, FX, FIX, FXIII)
- Muscular: FI, FII, FX. (FI, FII, FX)
- Trombosis: FI (FI)
- Abortos de repetición: FI, FXIII (FI, FXIII)
- Dificultad para cicatrización: FXIII (FXIII)

## OFFICIAL COMMUNICATION OF THE SSC

### Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity

F. PEYVANDI,\* D. DI MICHELE,† P. H. B. BOLTON-MAGGS,‡ C. A. LEE,§ A. TRIPODI¶ and A. SRIVASTAVA\*\* FOR THE PROJECT ON CONSENSUS DEFINITIONS IN RARE BLEEDING DISORDERS OF THE FACTOR VIII/FACTOR IX SCIENTIFIC AND STANDARDISATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

**Table 3** Proposal of the project on RBDs

Coagulant factor	Laboratory phenotype		
	Coagulant activity		
	Severe	Moderate	Mild
Fibrinogen	Undetectable clot	0.1–1 g L <sup>-1</sup>	> 1 g L <sup>-1</sup>
FII	Undetectable activity	≤ 10%	> 10%
FV	Undetectable activity	< 10%	≥ 10%
FV + FVIII	< 20%	20–40%	> 40%
FVII	< 10%	10–20%	> 20%
FX	< 10%	10–40%	> 40%
FXIII	Undetectable activity	< 30%	≥ 30%

- 1 Fibrinogen, FII, FX and FXIII deficiencies are RBDs with a *strong association* between clinical severity and coagulant activity level, with a few exceptions.
- 2 FV and FVII deficiencies are RBDs with a *poor association* between clinical severity and coagulant activity level.
- 3 FXI deficiency shows *no association* between clinical severity and coagulant activity level, both when undetectable or moderately reduced (< 20%).
- 4 Compound FV + FVIII deficiency is mainly associated with *mild or moderate clinical symptoms* and patients rarely experience severe bleeding.

# Opciones terapéuticas

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- **Tratamiento sustitutivo**

- Plasma Fresco Congelado (PFC).
- Crioprecipitado (no utilizado en la UE).
- Concentrados de Complejo Protrombínico (CCP).
- Concentrados específicos:
  - Derivados del plasma: Fibrinógeno, FVII, FX, FXI y FXIII.
  - Recombinantes: FVIIa y FXIIIA2.

- **Terapias adyuvantes**

- Antifibrinolíticos.
- Desmopresina.
- Estrógenos/ progesterona.
- Trombina/fibrina tópicas.

# Opciones terapéuticas

---



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- **Terapias adyuvantes**

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- Desmopresina.
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## Deficiencia FVII

- Fase de inicio: Unión FT-FVIIa.
- **FVII vida media 3-5 h.**
- Nivel hemostático 10-20%

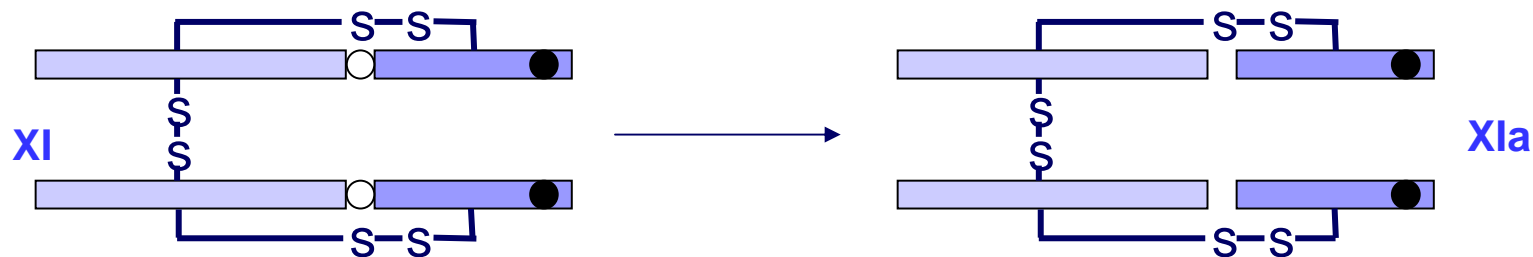
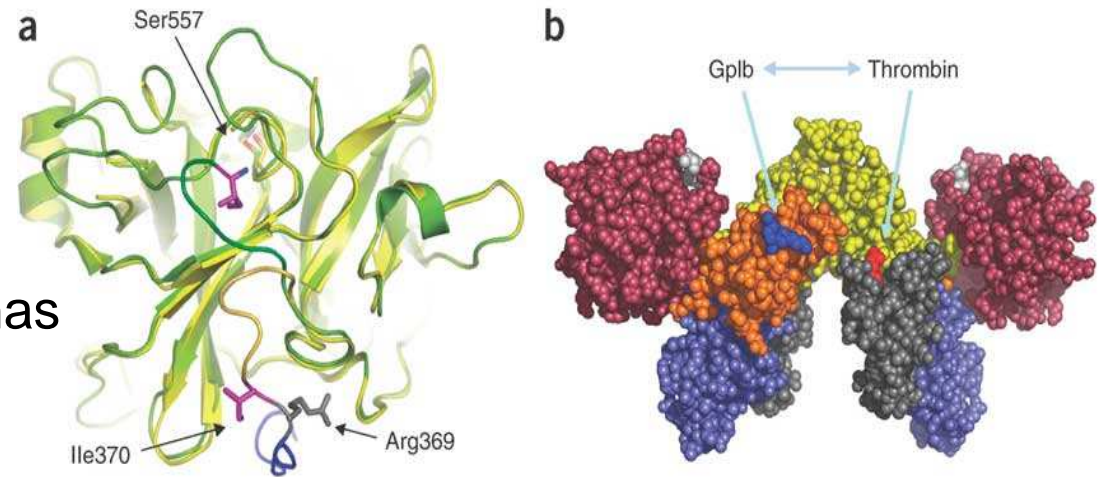
	Potencia (UI/mL)	Demanda	Profilaxis
PFC	1	15-20 ml/kg + 5 ml/12 h	--
PCCs	5-10	50 U Kg + 10-20 U/kg/8 h	--
pdFVII*	20-40	30-40 U/kg/6-24 h	--
rFVIIa	>25000	20-30 µg/Kg/4-6 h	20 µg/Kg/2-3xsem

\*No comercializado en España.

rFVIIa en hemofilia + inhibidor: 90-120 µg/Kg/2-3 h

# Deficiencia FXI

- Hemofilia C (1953).
- Síntesis hepática.
- Glicoproteína de dos cadenas idénticas (160 kD).
- **Vida media 48 h.**
- Función importante en amplificación de coagulación. Inhibición fibrinolisis.

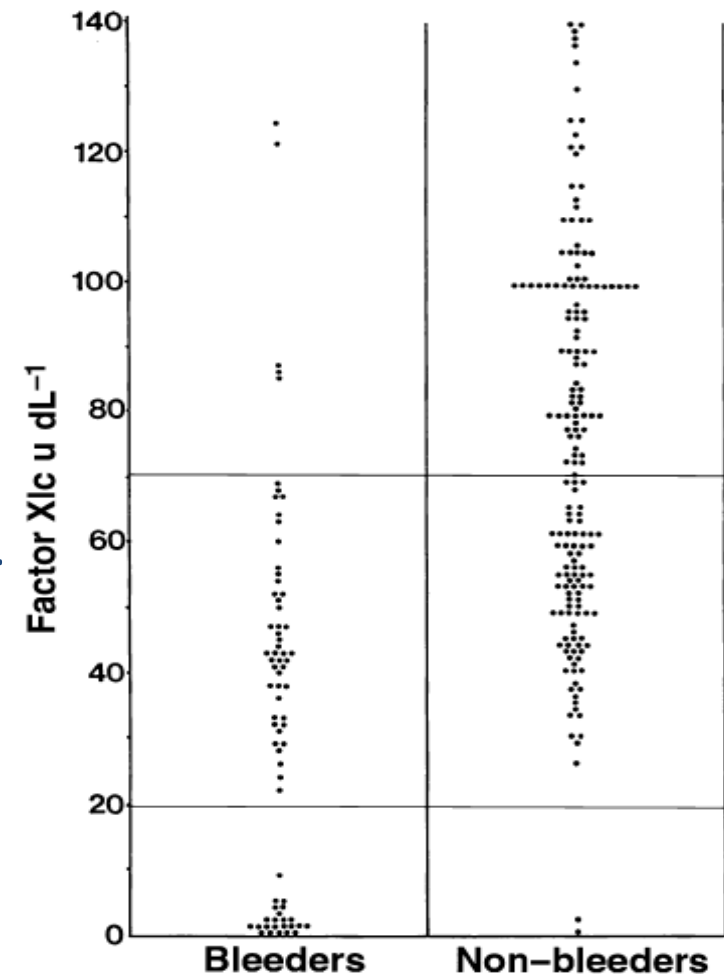


# Deficiencia FXI

- Clínica: HETEROGÉNEA.
- FXI > 20%: fenotipo muy variable.

Pobre correlación con la actividad basal del FXI  
Las decisiones terapéuticas deben **individualizarse**  
siempre en función del **fenotipo hemorrágico** del  
paciente

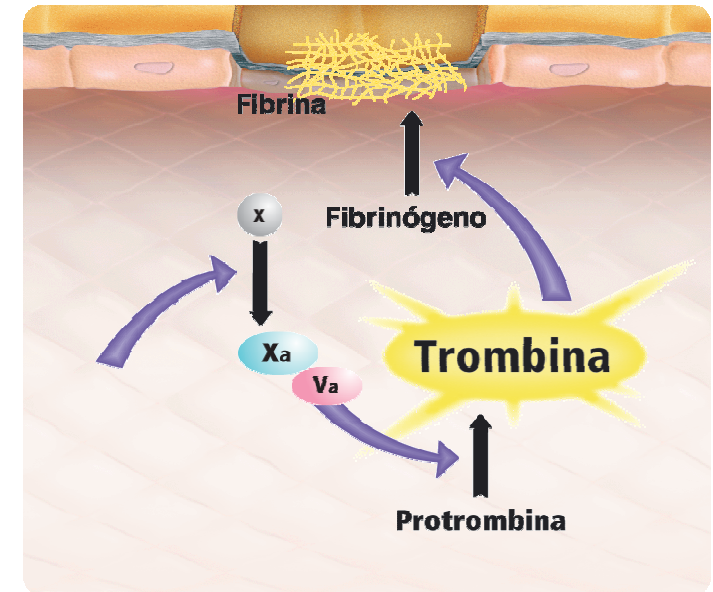
- Episodios leves: pueden no requerir tratamiento.
  - Antifibrinolíticos (no en hematurias).
- PFC:
  - Carga: 15-20 mL/kg.
  - Mantenimiento: 3-6 mL/kg cada 24 horas.
- Concentrados de FXI
  - Hemoleven. LFB, Francia
  - 10-15 UI/kg cada 24-48 h.



# Deficiencia FX.

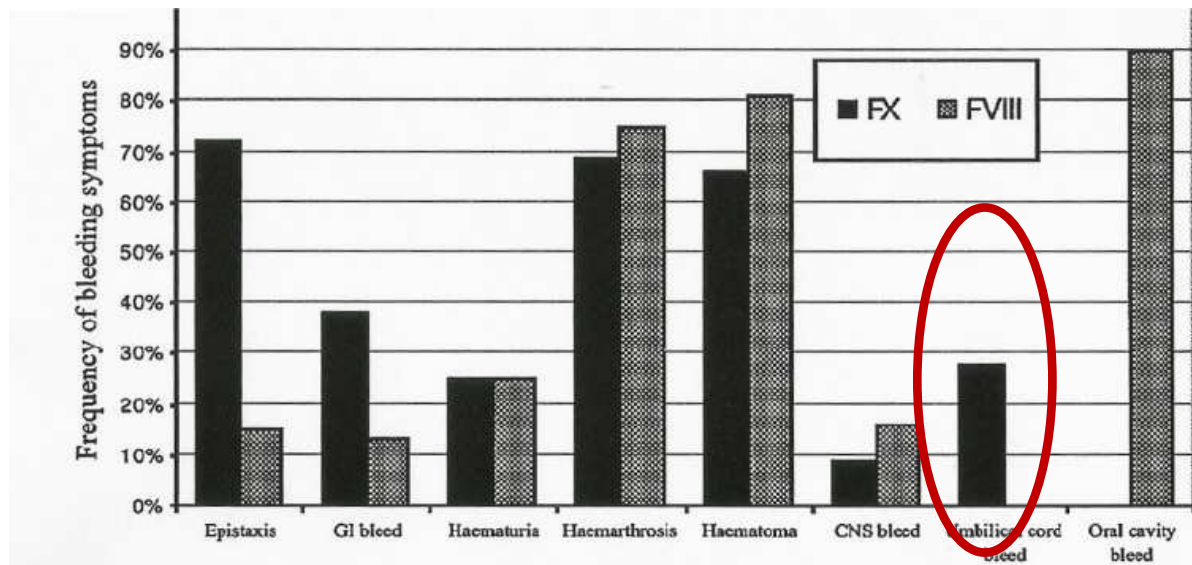
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- Descrita familias Stuart y Power 1956-57.
- Síntesis hepática (vit. K dependiente).
- Activador fisiológico de protrombina.
- Junto con el FV (complejo protrombinasa).
- **Vida media 40 h.**



## Deficiencia FX. Clínica

- Síntomas graves infrecuentes con niveles > 2%.
- Hemartros, tejidos blandos, gastrointestinal, hematuria, epistaxis, SNC.
- Sangrado de cordón umbilical (28%).



**Los pacientes con deficiencia grave: síntomas más severos de todas las coagulopatías infrecuentes**



## Deficiencia FX. Tratamiento

---

	Demanda	Profilaxis
PFC	15-20 ml/kg + 10 ml/24-48 h	-
CCP	30 U/Kg/48 h	-
FX-dp	10-20 U/kg/48 h	10-15 U/Kg/semana

FX vida media 40 h

Nivel hemostático 10-20%





## Deficiencia FX. Productos

---

- **Factor X P Behring (CSL, Marburg, Alemania).**
  - Inactivación viral: pasteurización a 60º, 10 h.
  - Contenido:
    - Factor X: 30-60 UI/mL.
    - Factor IX: 30 UI/mL.
  - Indicación:
    - Hemofilia B.
    - Otras deficiencias: FX.
  - Presentación: Factor IX P Behring 600 U.I.
- **pdFX; (Bio Products Laboratory, Elstree, UK). Marzo-2016.**
  - S/D, calor, filtración.

# Deficiencia FV

---

## Review article

### Factor V: a combination of Dr Jekyll and Mr Hyde

Kenneth G. Mann and Michael Kalafatis



Se requiere para un buen funcionamiento de la hemostasia

Fuente potencial de patologías hemorrágicas y trombóticas





# Deficiencia FV

---

- **No existe concentrado específico.**
- **PFC: opción terapéutica principal.**
  - Objetivo: FV 20%.
  - Vida media 36 h:
    - Dosis inicial 15-20 ml/kg.  
Mantenimiento 10 ml/kg cada 24 h (12 h episodios graves).  
Potenciales reacciones alérgicas, infecciones, sobrecarga de volumen.
  - Profilaxis: 15-20 ml/kg cada 48/72 h tras HIC.
- Plaquetas.
- rFVIIa.



## Deficiencia FII. Tratamiento

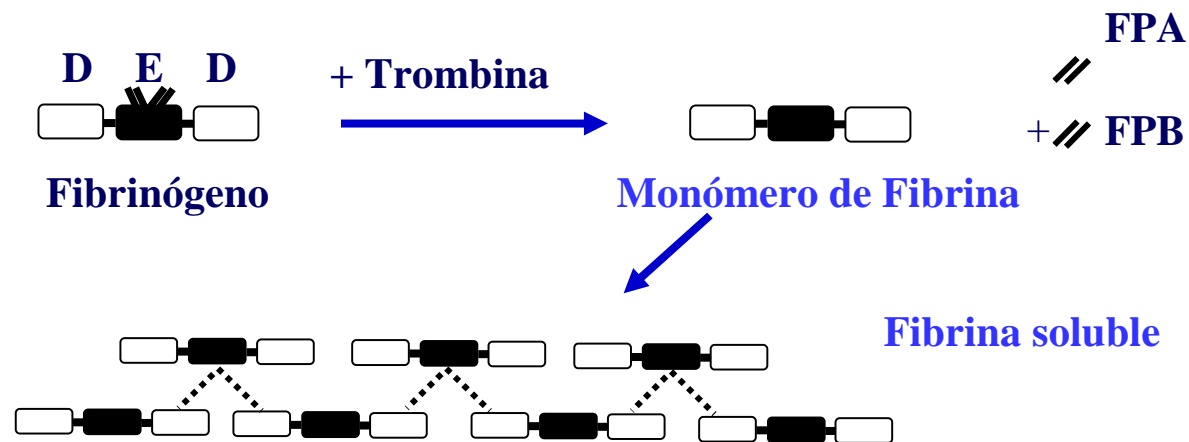
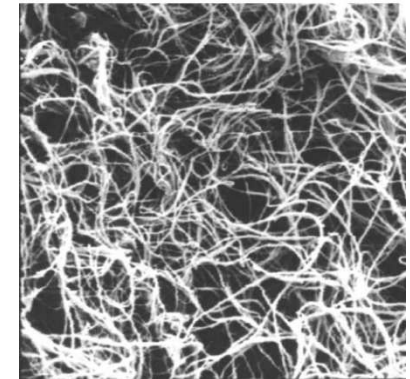
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- FII: Sustrato FXa+FV+Ca
- Vida media: 3-4 d.
- **Nivel hemostático: 20%**

	Demanda	Profilaxis
PFC	15-25 ml/kg/24-48 h	
CCPs	<b>30 U/kg/48 h</b>	<b>15-25 U/kg/semana</b>

# Deficiencia Fibrinógeno

- Autosómica recesiva. Disfibrinogenemia: AD
- Síntesis hepática.
- Paso final: formación de fibrina. Agregación plaquetaria.
- **Vida media: 4 días.**







## Deficiencia Fibrinógeno. Clínica

---

- Periodo neonatal: **cordón umbilical (75%)**.
- Infancia: **HIC** causa de muerte (10%).
- Hemartros 20%-54%.
- Hematomas, mucosas, gastrointestinal, genitourinario
- Rotura esplénica espontánea.
- Mujeres: abortos espontáneos precoces, metrorragias, h. postparto.
- Mala cicatrización de heridas, dehiscencia de suturas.
- **Trombosis arterial o venosa** (28% disfibrinogenemia).



## Deficiencia Fibrinógeno. Tratamiento

	<b>Demanda</b>	<b>Profilaxis</b>
<b>PFC</b>	15-20 ml/kg	--
<b>Crioprecipitado*</b>	1 bolsa/10 kg	--
<b>Fibrinógeno</b>	<b>30-50 U/kg/6-24 h</b>	<b>20-30 mg/kg/1-2 sem.</b>

**Niveles hemostáticos: 50-100 mg/dl**

Riesgo de complicaciones trombóticas.

\*150 mg de fibrinógeno por bolsa.

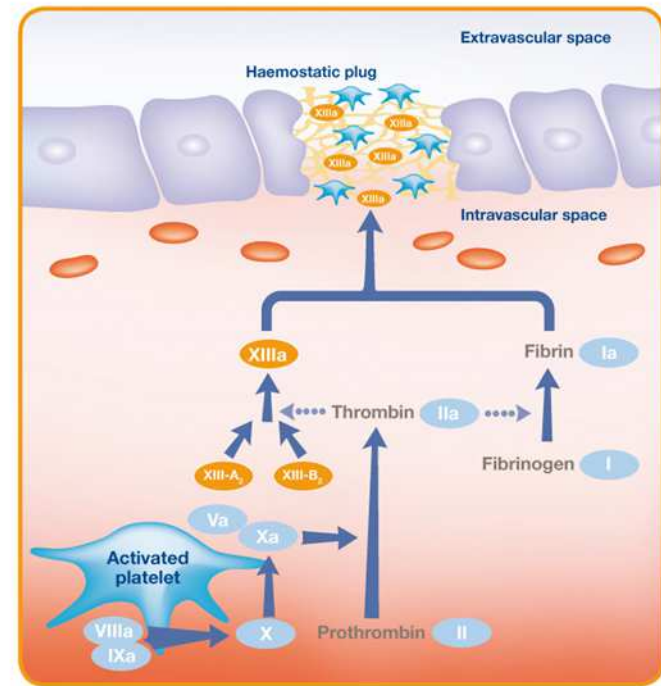
# **Deficiencia Fibrinógeno. Tratamiento**

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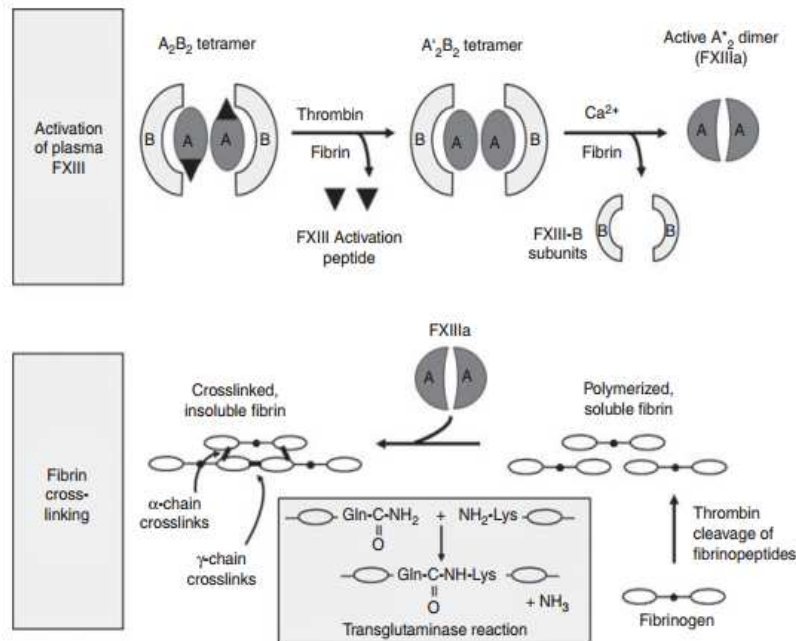
- **Riastap.** CSL Behring Marburg, Alemania.
- Inactivación: pasteurización, 60° C, 20 h.
- Adición de albúmina
- Indicaciones:
  - Tratamiento y profilaxis de diátesis hemorrágica afibrinogenemia congénita y adquirida (dis-hipofibrinogenemia).

# Deficiencia FXIII

- Heterotretámero
  - 2 cadenas  $\alpha$  (cromosoma 6).
  - 2 cadenas  $\beta$  (cromosoma 1).
- **Vida media: 7-10 días**
- Une y estabiliza los monómeros de fibrina.
- Deficiencia FXIII-A: tipo I (cuantitativa), tipo II
- Deficiencia FXIII-B (<5%).
- **FXIII > 3-10 UI/dL**: suficiente para evitar diátesis espontáneas.
- Manifestaciones precoces, con sangrado de **cordón umbilical (80%)**.  
**HIC: (30%)**, principal causa de muerte y discapacidad.

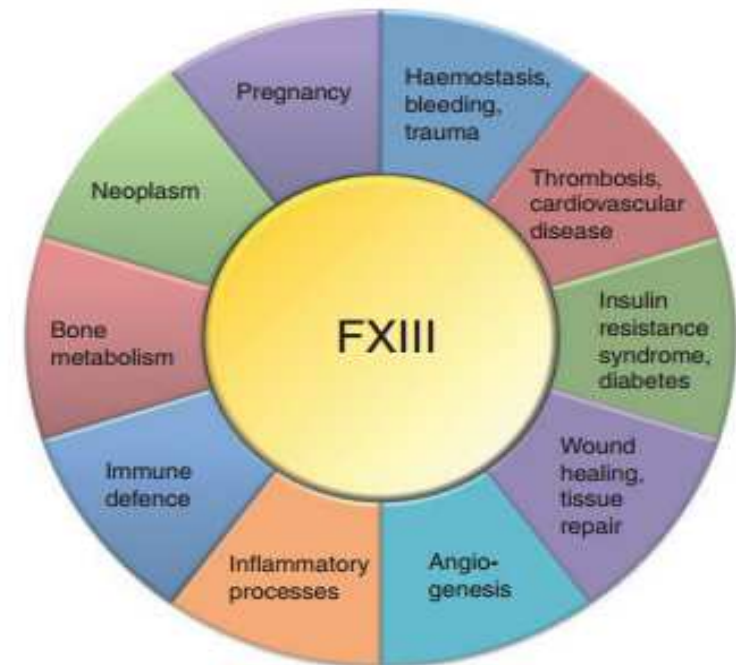


# Deficiencia FXIII



**Fig. 2.** Activation and action of plasma factor FXIII. Thrombin initiates FXIII activation by cleavage of the FXIII activation peptide. Then A- and B-subunits dissociate in the presence of  $Ca^{2+}$ . Both FXIII activation steps are enhanced by fibrinogen/fibrin. Thrombin also initiates conversion of fibrinogen into soluble fibrin by cleaving off fibrinopeptides A and B. Activated FXIII (FXIIIa) cross-links lysine (Lys) and glutamine (Gln) residues of fibrin  $\alpha$ - and  $\gamma$ -chains in a transglutaminase reaction leading to a three-dimensional, insoluble fibrin network.

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**Fig. 3.** Diversity of factor FXIII functions. As a result of its multiple functions, FXIII is involved in many different physiological and pathophysiological processes and hence FXIII is of interest in different areas of biology and medicine.

**Mala cicatrización de heridas. Abortos espontáneos recurrentes. Infertilidad.**

Schroeder V, Kohler HP. New developments in the area of factor XIII. J Thromb Haemost 2013; 11 (2): 234-44.



## Deficiencia FXIII. Tratamiento

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	Demanda	Profilaxis
PFC	10 ml/kg	--
pdFXIII*	20-40 U/kg	10 U/kg/4 sem
rFXIII-A**	-	35 U/Kg/4 sem

\***Fibrogammin P 250.** CSL Behring Marburg, Alemania

\*\***Novothirteen:** Novonordisk.



## Deficiencia FXIII

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Sangrado cordón umbilical/sangrado diferido + estudio básico de coagulación normal.



**FACTOR XIII**

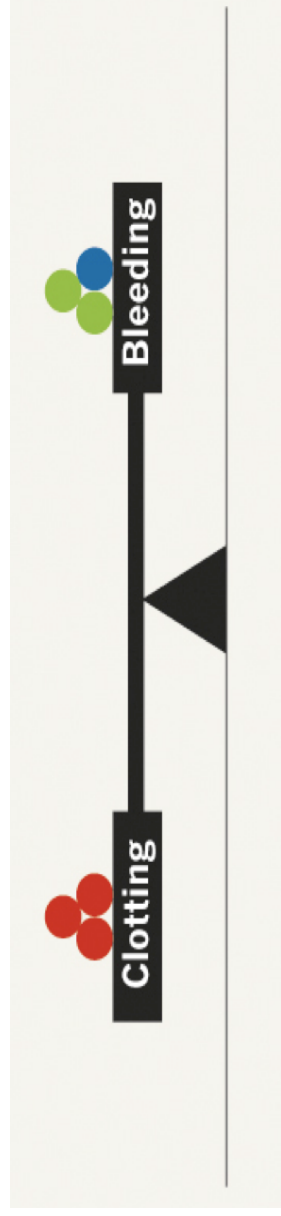
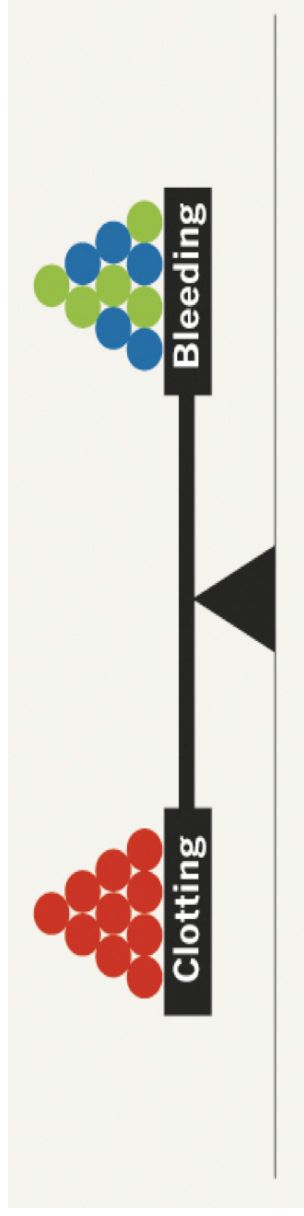
Riesgo de hemorragia intracraneal  
Profilaxis exigible

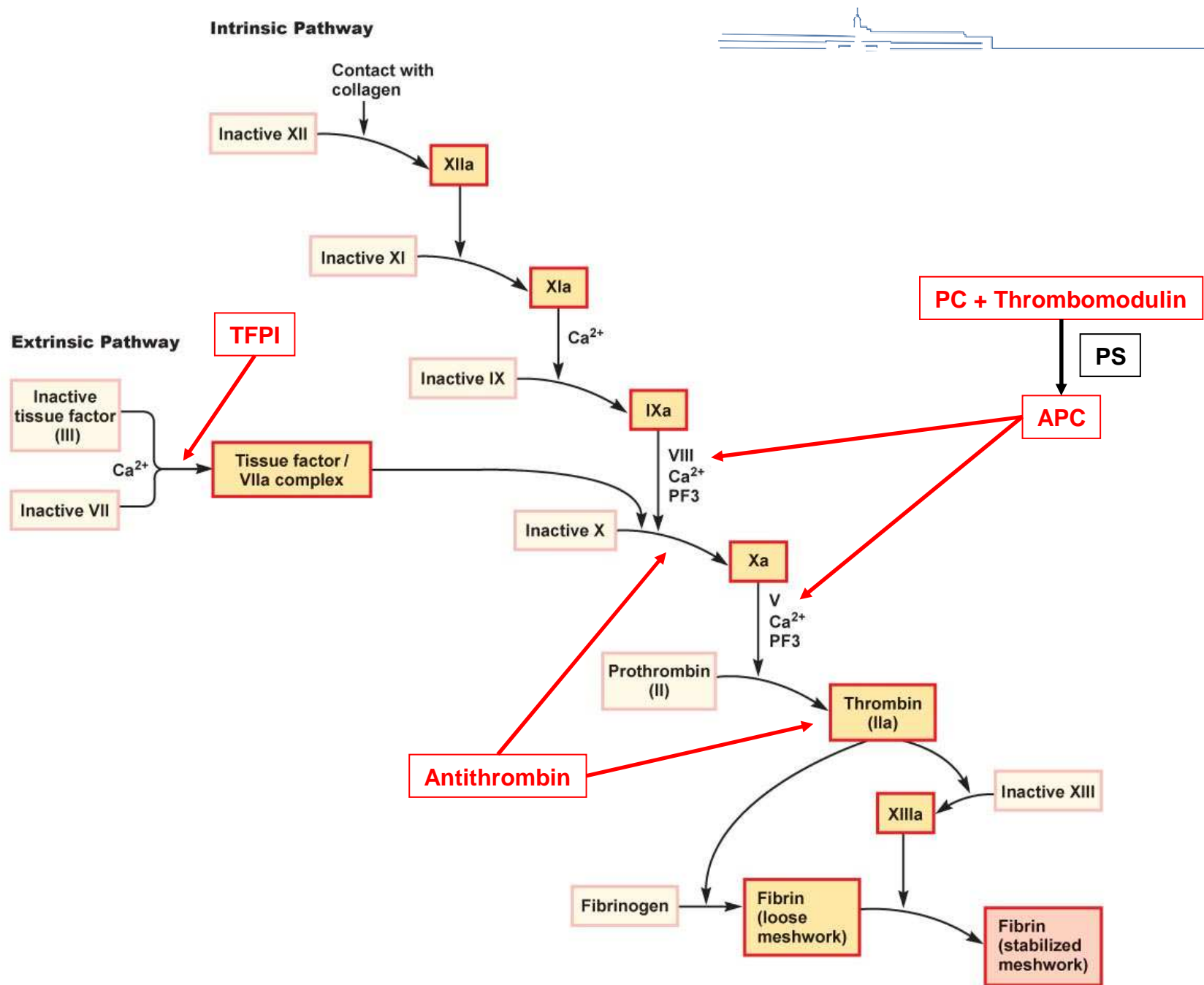


## Nuevas dianas

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# Nuevas dianas

Objective	Target	Product	Mechanism	Status
Improve thrombin generation by the suppression of anticoagulant pathways	APC	Peptide inhibitors (e.g. PNASN1)	Elimination of PC pathway effect on thrombin generation	<i>In vitro</i> experiments using haemophilic plasma
		RNA aptamer (APC99)	Inhibition of enzymatic activity of APC	<i>In vitro</i> experiments using haemophilic plasma
		ssDNA aptamer (HS02)	Inhibition of anticoagulant functions of APC and augmentation of its reactivity to protein C inhibitor	<i>In vitro</i> experiments using haemophilic plasma
	AT	ALN-AT3	siRNA-mediated suppression of liver production of AT specific mRNA	Phase 1 clinical trial Part A completed Part B ongoing
	TFPI	Fucoidan (AV513)	Specific blockade of extrinsic pathway downregulator	Experiments in haemophilic dogs, mice
		Mab2021	Inhibition of FXa amidolytic activity and inhibition of combined FXa activity and FX activation by TF/FVIIa	Preclinical and clinical trials
		DNA aptamers (BAX499 or ARC19499)	Inhibition of both TF/FVIIa and FXa	Premature termination of Phase 1 clinical trial
		Fusion peptide inhibitors (FP)	TFPI antagonists	<i>In vitro</i> studies

Objective	Target	Product	Mechanism	Status
Alternate by-passing agents	FX	FXa+ Phospholipids	Bypasses FVIII	Experiments in haemophilic mice
	<i>F10</i>	FXa variants (FXaI16L), FXa (V17A)	Inhibits the normal conformational change required for protease formation	Animal experiments
	MC710	Highly purified FVIIa and FX (protein weight ratio 1:10)	Increased half-life due to the increased half-life of substrate, i.e. FX	Phase 1 and Phase 2 clinical trials
	FV	FVa	Introduction of a disulphide bond between His609Cys-Glu1691Cys of FV between A2 and A3 domains to augment FVa cofactor activity	Experiments in haemophilic mice
	<i>F5</i>	<sup>super</sup> FVa	Introduction of mutations at Arg506/306/679Gln in addition to disulphide bonds between A2 and A3 domains to improve its biological stability	Experiments in haemophilic mice
	FIX	FIXa mab (224AE3)	Increased catalytic activity of the FVIIIa-FIXa-Ca <sup>2+</sup> -phospholipid complex	<i>In vitro</i> experiments using haemophilic plasma
	FIX/FX	Bispecific antibody to FIXa and FX (hBS23, ACE910)	Mimic FVIIIa	Experiments in non-primate and primate models
	FIX/FX	Bispecific antibody to FIXa and FX (ACE910)	Mimic FVIIIa	Phase 1 clinical trial
	<i>F9</i>	FVIII independent FX activation	Introduction of mutations at V181I/K265T/I383V	Experiments in haemophilic mice
	FXIII	FXIII or in combination with rFVIIa	Improved clot stability	<i>In vitro</i> experiments
	<i>Microparticles</i>	Chimera of p-selectin and immunoglobulin (P-Sel-Ig)	Interaction of P-Sel-Ig with PSGL-1 results in release of TF bearing MPs	Experiments in haemophilic mice





## Tratamientos disruptivos en hemofilia

Promotor	Clase	Nombre	Mecanismo de acción	Fase
NovoNordisk®	Anti-TFPI	NN-7415 (concizumab)	Anticuerpo anti-TFPI para disminuir el TFPI	Fase I/II
Alnylam®	iRNA-AT	ALN-AT3 (fitusiran)	RNAi terapéutico con diana en la antitrombina	Fase I/II
Roche®	Anticuerpo mimético del FVIII	ACE910 (emicizumab)	Anticuerpo bivalente unido a FIXa y FX para “sustituir” la actividad del cofactor de FVIII	Aprobado FDA Fases III: en marcha



- Baja prevalencia: 1 en 500.000 a 2.000.000 individuos.
- La mayoría se heredan de forma AR.
- Heterogeneidad genética y clínica. Sintomatología variable.
- Tratamientos individualizados en función de los antecedentes hemorrágicos familiares y personales
- Tratamiento específico.
- Utilidad de registros y colaboración internacional.
- Terapias disruptivas. Nuevas dianas terapéuticas.



# Deficiencia FV y VIII

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- Descenso concomitante de FV y VIII con niveles 5-20%.
- Asociado a la mutación del LMAN1 y MCFD2 (proteína transportadora intracelular de ambos factores)
- Prevalencia 1/2.000.000
- Clínica normalmente leve con predominio de sangrado mucocutáneo, postraumatismos o quirúrgico
- Niveles hemostáticos: 10-15%?



28 Febrero 2014  
Día de  
las Enfermedades  
Raras

*J. J. J.*



Muchas gracias