ESTRATEGIAS EN EL TRATAMIENTO DE LOS PACIENTES CON INHIBIDOR

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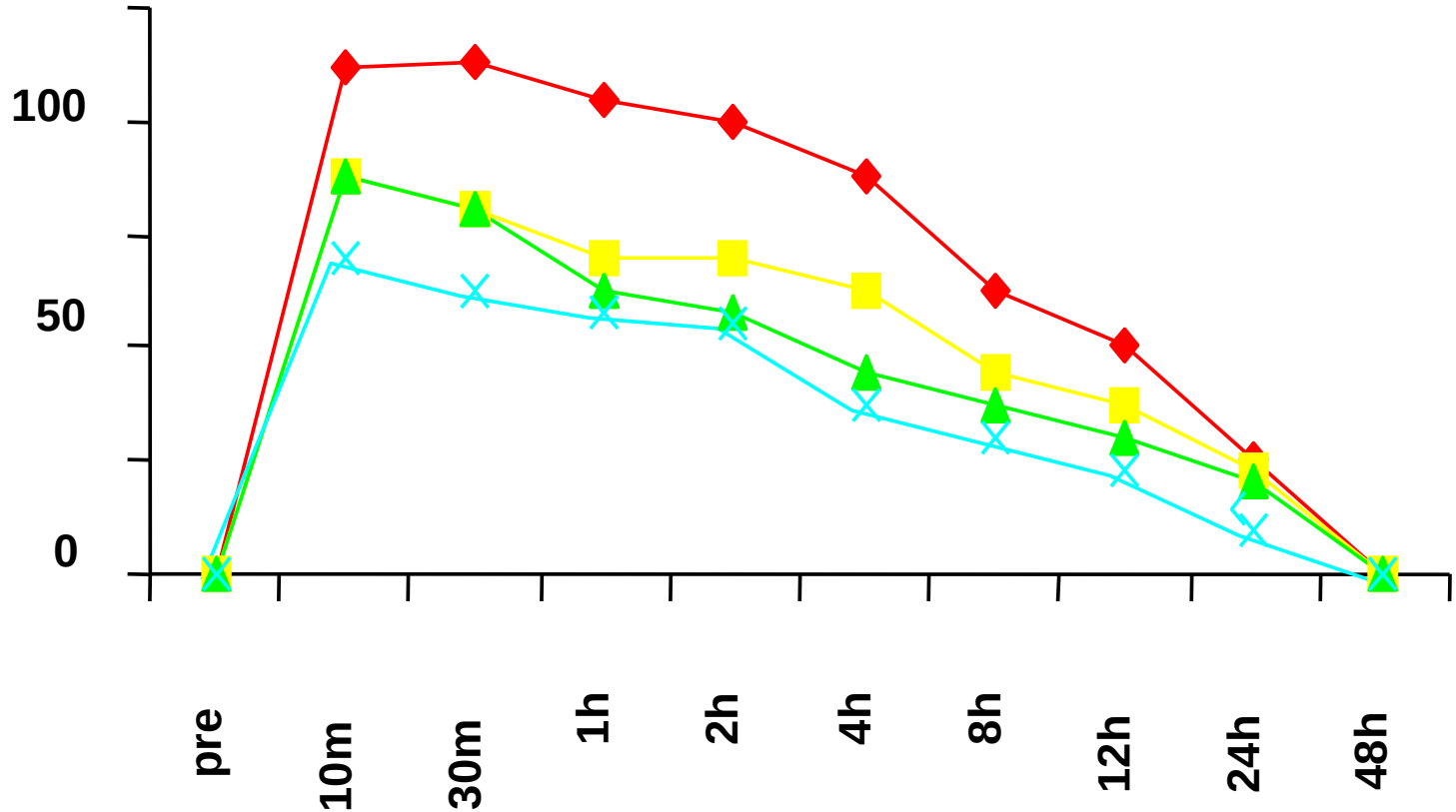
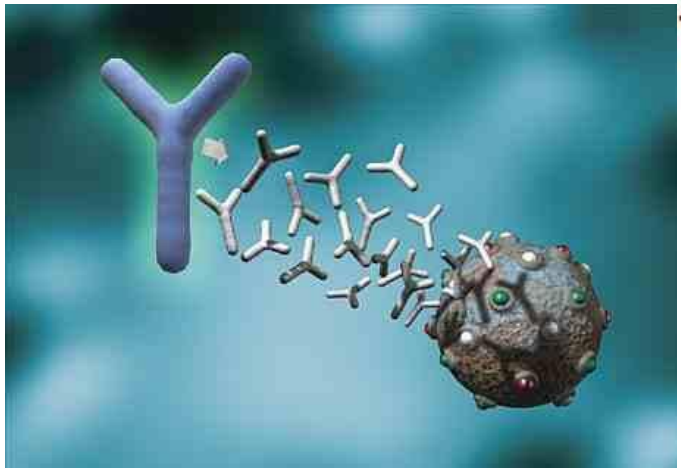
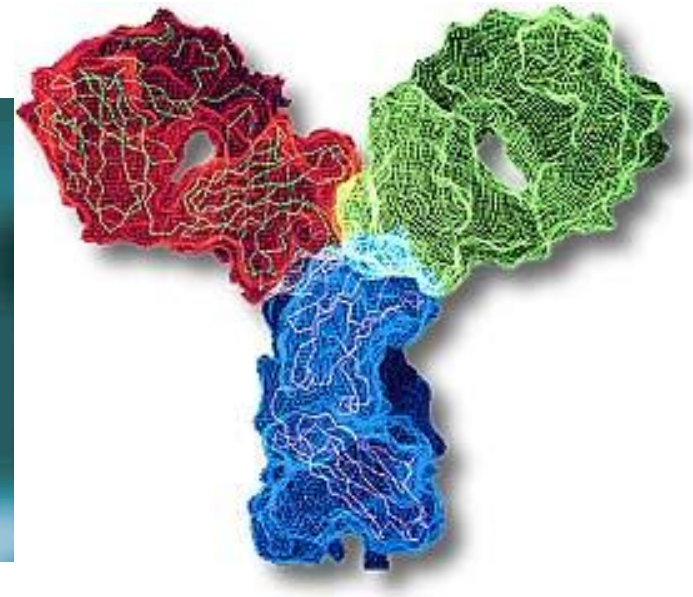
TRATAMIENTO: TERAPEUTICA SUSTITUTIVA

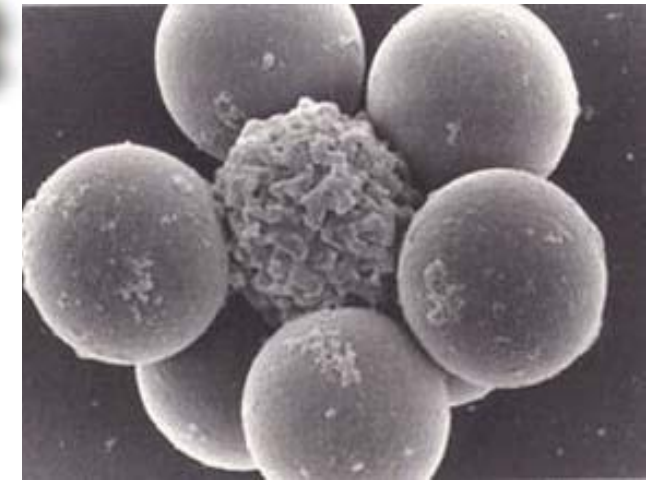


COMPLICACION DEL TRATAMIENTO

- INHIBIDOR: Anticuerpo IgG de alta afinidad de naturaleza policlonal frente al FVIII o FIX de la coagulación

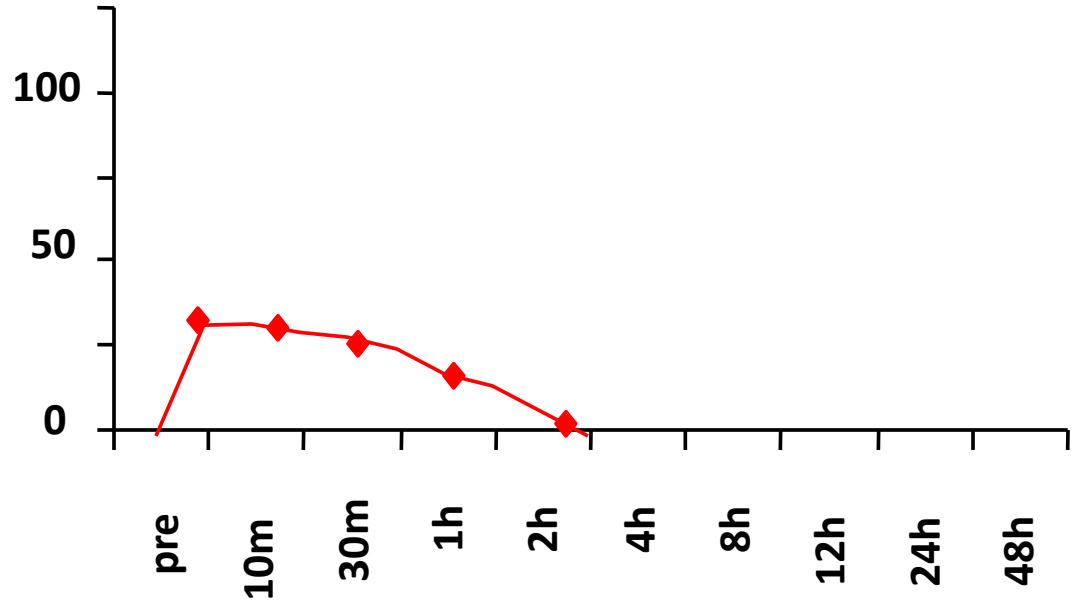






DESARROLLO DE INHIBIDORES

- Reduce vida media de los concentrados de factor
- Refractariedad a la terapia sustitutiva
- Reduce la calidad de vida de los pacientes



IMPORTANCIA DE LOS INHIBIDORES

- Incidencia:

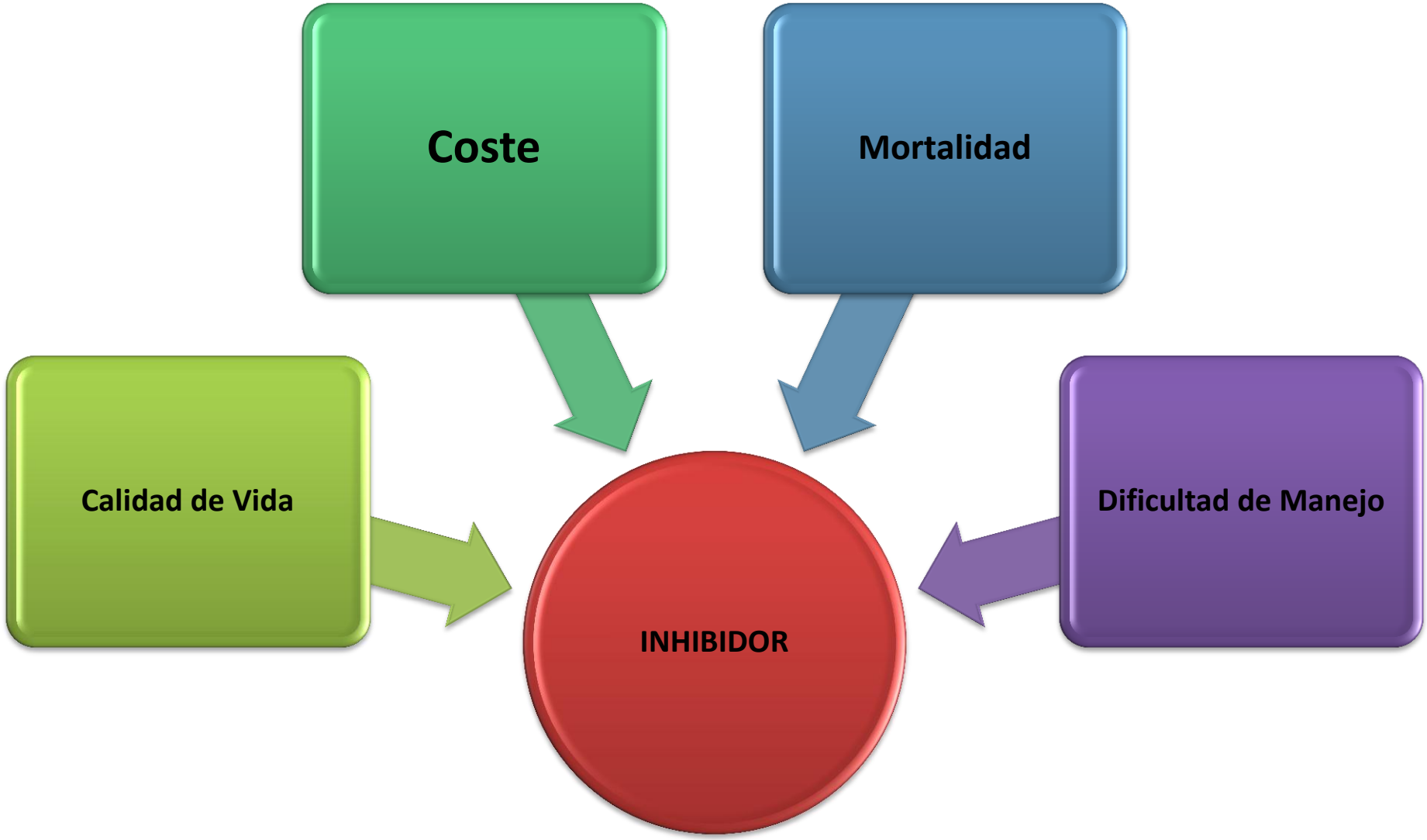
  Hemofilia A: 30 %

  Hemofilia B: 1-4 %

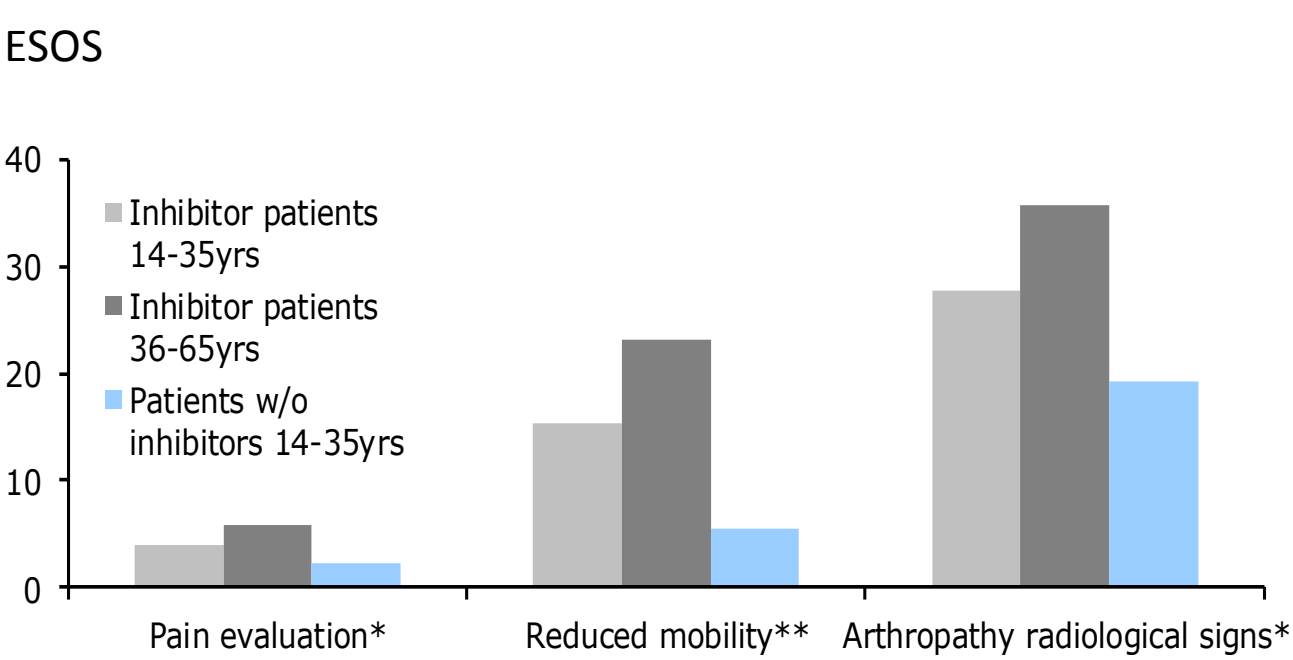
- Prevalencia:

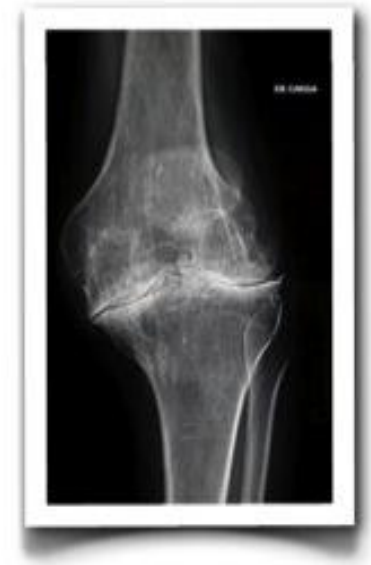
  Hemofilia A: 10-12 %

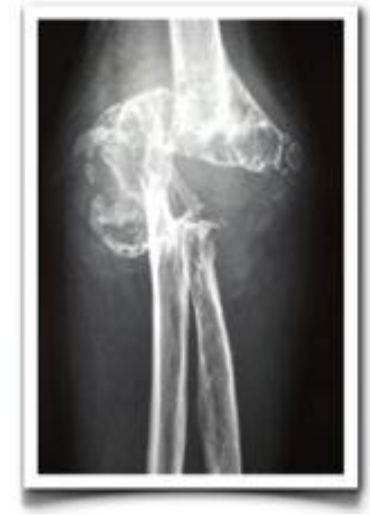
IMPORTANCIA DE LOS INHIBIDORES



IMPORTANCIA DE LOS INHIBIDORES







*Pettersson classification, scores per joint ranging from 0 to 13
**Gilbert classification, scores per joint ranging from 0 for no pain to 3 for maximum pain and for clinical examination, scores per joint ranging from 0 to 12 for knees and ankles, 0 to 10 for hips and 0 to 8 for elbows and shoulders

Source: Morfini et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 2007;13:606–12

¿Qué es lo sabemos en el desarrollo de inhibidores?

- "Es un proceso complejo que implica diferentes factores":

Relacionado con el paciente (Genéticos y no modificables)	Relacionados con el tratmieto (No genéticos y modificables)
Raza	Número de días de exposición
Historia familiar	Edad de la primera exposición
FVIII mutación	Tipo de concentrado
MHC-clases	Infección intercurrente/estado inflamatorio
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)	Exposición intensiva al FVIII

- Kempton CL and White. Blood 2009; 113:11-17
- Coppola A. Haemophilia 2010; 16 (supp 1):13-19

Raza

Relacionado con el paciente (Genéticos y no modificables)
Raza
Historia familiar
FVIII mutación
MHC-clases
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)

- La prevacencia en raza negra es el doble
  - Aledort L. Haemophilia 1998;4:68
- Human *F8* contains four common nonsynonymous SNPs whose allelic combinations encode six distinct wild-type factor VIII proteins (H1-H6).
- Mismatched factor VIII replacement therapy may be a risk factor for the development of anti–factor VIII alloantibodies
  - Viel KR et al. N Engl J Med 2009; 1618-27

	H1	H2	H3	H4	H5	H6
FVIII products	✔	✔	✗	✗	✗	✗
Black population	++	++	++	+	+	-
White Population	+++	+	✗	✗	✗	✗

Kempton CL.. Blood 2009; 113:11-17

Coppola A. Haemophilia 2010; 16 (supp 1):13-19

- HIGS combined cohort :
  - …their findings not support a higher risk of inhibitors in the presence of a haplotype mismatch between the FVIII molecule infused and that of the individual
    - Schwarz J et al. Haemophilia 2012; Sep 7 Epub ahead of print

Historia familiar

Relacionado con el paciente (Genéticos y no modificables)
Raza
Historia familiar
FVIII mutación
MHC-clases
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)

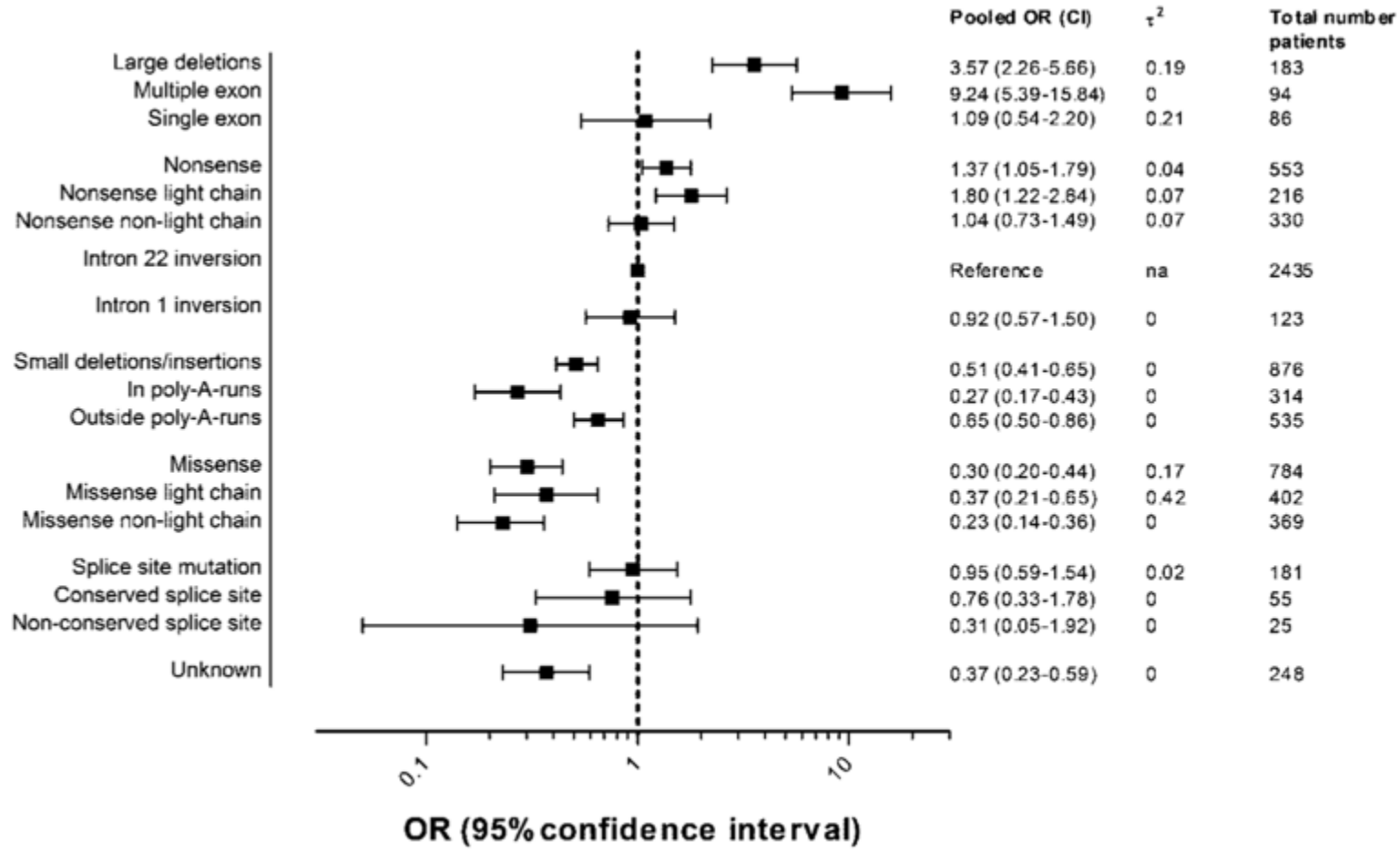
- Malmö International Brother Study (MIBS):
  - Mayor incidencia entre hermanos
  - El riesgo tres veces mayor: RR 3.2 (95% CI 2.1-4.9)
    - Astermark J et al. Haemophilia 2001; 7: 267-72

Kempton CL.. Blood 2009; 113:11-17

Coppola A. Haemophilia 2010; 16 (supp 1):13-19

Mutación FVIII

Relacionado con el paciente (Genéticos y no modificables)
Raza
Historia familiar
FVIII mutación
MHC-clases
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)



Kempton CL.. Blood 2009; 113:11-17

Coppola A. Haemophilia 2010; 16 (supp 1):13-19

- Gouw S et al. Blood 2012; 119:2922-34

MHC

Relacionado con el paciente (Genéticos y no modificables)
Raza
Historia familiar
FVIII mutación
MHC-clases
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)

Kempton CL.. Blood 2009; 113:11-17

Coppola A. Haemophilia 2010; 16 (supp 1):13-19

- Su papel es variable:
  - Mayor frecuencia DRB1*15 and DQB1*0602 alleles asi como el haplotipo DRB1*15/DQB1*0602 [odds ratio (OR) 1.9; $P < 0.05$].
    - Pavlova A et al. J Thromb Haemost 2009; 7: 2006-15
- MIBS cohort no encontró esta correlación
  - Astermark J et al. Blood 2006; 108: 3739-45

Polymorphisms of immune-response genes

Relacionado con el paciente (Genéticos y no modificables)
Raza
Historia familiar
FVIII mutación
MHC-clases
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)

- MIBS cohort :
  - Polymorphic microsatellite en la región promotora interleukin-10 (IL-10) gene:
    - allele 134: OR 5.4 (95% CI 2.1-9.5)
      - Astermark J et al. Blood 2006;107:3167-3172
  - Single nucleotide polymorphism (SNP) en la región promotora del tumour necrosis factor alfa gene en location –308:
    - 308 A/A genotype: OR 19.2 (95% CI 2.4-156.5)
      - Astermark J et al. Blood 2006;108:3739-3745
  - T alelo en the polymorphic site at –318 in the CTLA-4 gene efecto protector
    - Astermark J et al. J Thromb Haemost 2007;5:263-265

Kempton CL.. Blood 2009; 113:11-17

Coppola A. Haemophilia 2010; 16 (supp 1):13-19

Polymorphisms of immune-response genes

Relacionado con el paciente (Genéticos y no modificables)
Raza
Historia familiar
FVIII mutación
MHC-clases
Polimorfismos of de los genes que modifican las respuesta inmune (IL 10, TNF, CTLA4)

- HIGS combined cohort :
  - 14 626 SNPs: >100 asociados con inhibidor
    - Astermark J et al. Blood (ASH annual meeting abstracts) 2009;114:217.
  - *MAP*K9
  - *DOC*K2
  - CD36
  - F13A1
    - La mayoría implicado en la señalización de la respuesta inmune

- ..."There are several markers involved and the decisive genetic environment in which the immune response occurs is very complex"
  - Astermark J. Haemophilia 2012;18 (Suppl. 4),38-42

Kempton CL.. Blood 2009; 113:11-17

Coppola A. Haemophilia 2010; 16 (supp 1):13-19

Non-genetic factors

Relacionados con el tratamiento (No genéticos y modificables)		
Risk factor	**Relative risk**	**95% CI**
Age at first infusion < 6 months of age vs > 12 or 18 months	1.8 1.7	0.7-4.7 1.3-1.9
Surgery at first infusion vs treatment of a bleed at first infusion 5 days of treatment at first infusion vs 2 days	2.6 3.3	1.3-5.1 2.1-5.3
Prophylaxis vs no prophylaxis	0.4 0.2*	0.2-0.8 0.06-0.5
Plasma-derived product vs recombinant product	2.4 0.8	1.0-5.8 0.5-1.3

*Odds ratio

Kempton CL and White. Blood 2009; 113:11-17

TIPO DE CONCENTRADO PUPs (Meta-análisis)

ELSEVIER

Critical Reviews in Oncology/Hematology xxx (2011) xxx–xxx

CRITICAL REVIEWS IN
Oncology
Hematology
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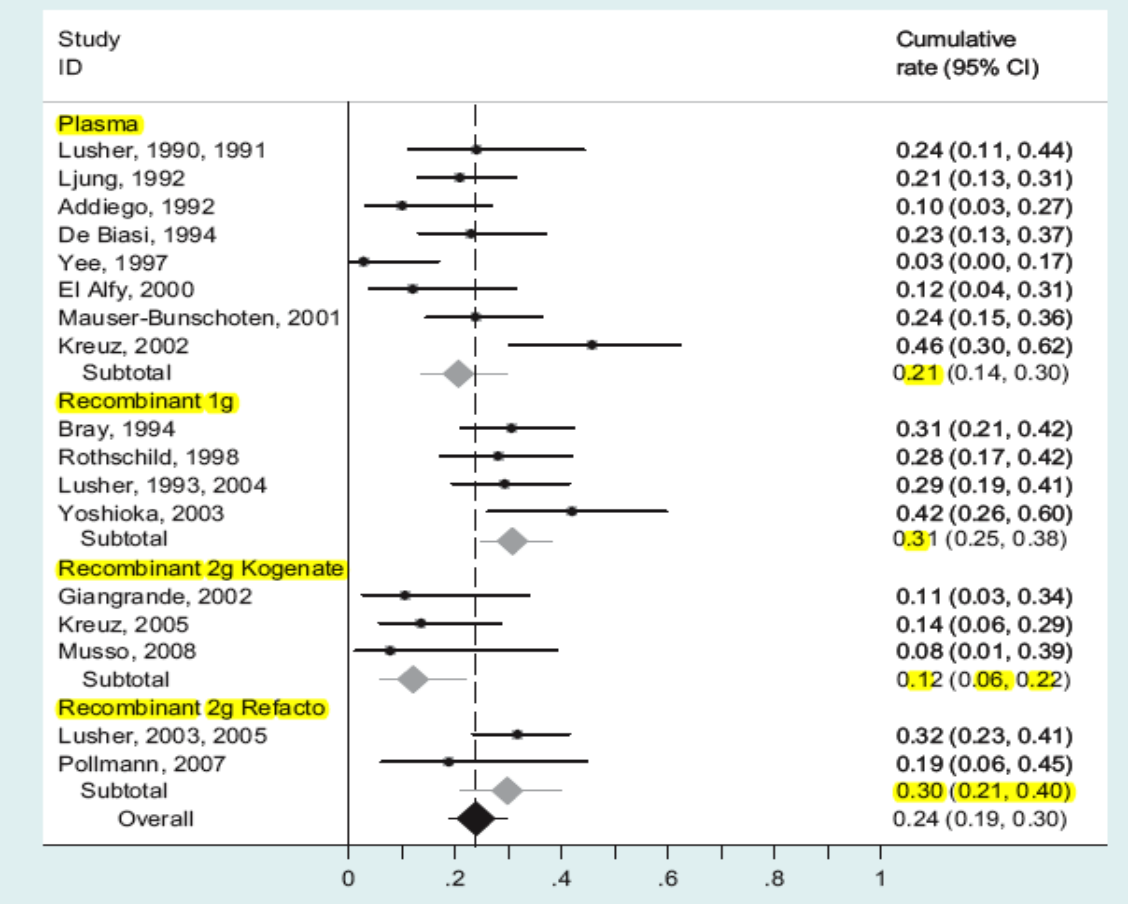
Cumulative inhibitor incidence in previously untreated patients with severe hemophilia A treated with plasma-derived versus recombinant factor VIII concentrates: A critical systematic review

Massimo Franchini [a,*], Annarita Tagliaferri [b], Carlo Mengoli [c], Mario Cruciani [d]

TIPO DE CONCENTRADO PUPs (Meta-análisis)



TIPO DE CONCENTRADO PUPs (Meta-análisis)

Journal of Thrombosis and Haemostasis, **8**: 1256–1265 DOI: 10.1111/j.1538-7836.2010.03823.x

ORIGINAL ARTICLE

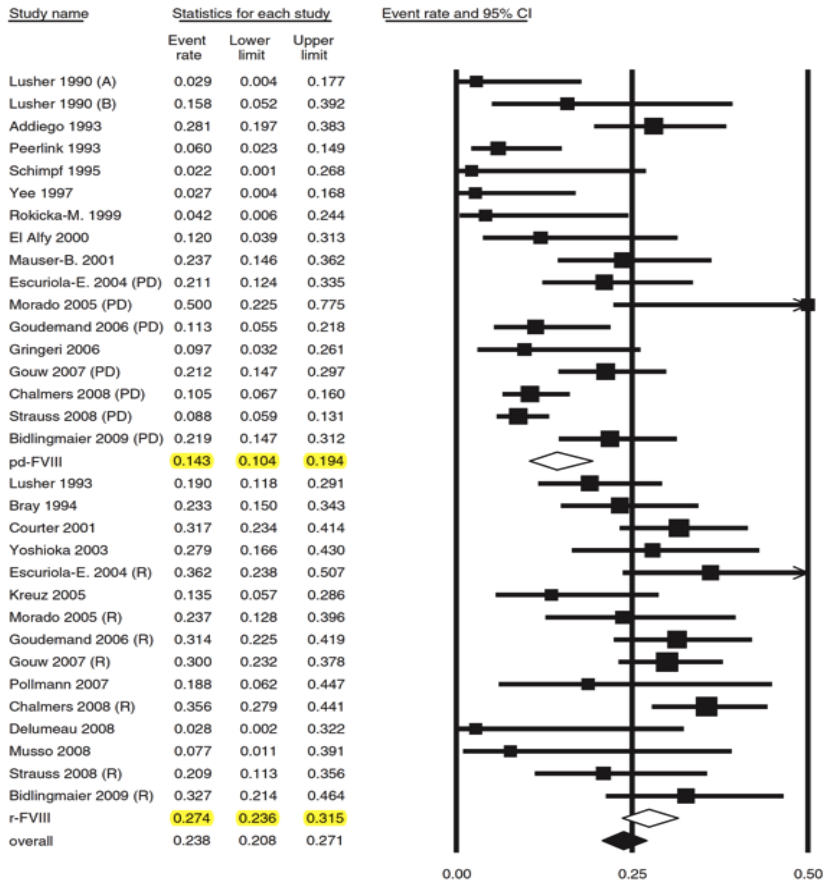
Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review

A. IORIO,* S. HALIMEH,† S. HOLZHAUER,‡ N. GOLDENBERG,§ E. MARCHESINI,* M. MARCUCCI,* G. YOUNG,¶ C. BIDLINGMAIER,‡‡ L. R. BRANDAO,§§ C. E. ETTINGSHAUSEN,¶¶ A. GRINGERI,** G. KENET,*** R. KNÖFLER,††† W. KREUZ,¶¶ K. KURNIK,‡‡ D. MANNER,†† E. SANTAGOSTINO,** P. M. MANNUCCI** and U. NOWAK-GÖTTL††

**Internal and Vascular Medicine &Hemophilia Centre, University of Perugia, Perugia, Italy; †Medical Thrombosis and Hemophilia Treatment/ Blood Transfusion Center Duisburg, Duisburg; ‡Department of Pediatric Hematology/Oncology, Charite, Berlin, Germany; §Department of Pediatrics, Hematology/Oncology/BMT, University of Colorado and The Children's Hospital, Denver, CO, USA; ¶Division of Hematology/ Oncology, Children's Hospital, Los Angeles, CA; **Department of Medicine and Medical Specialties, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy; ††Department of Pediatric Hematology/ Oncology, University Hospital Münster, Münster; ‡‡Department of Pediatrics, University Hospital Munich, Munich, Germany; §§Department of Pediatric Hematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada; ¶¶Department of Pediatric Hematology/Oncology, University Hospital Frankfurt, Frankfurt, Germany; ***The Israel National Hemophilia Centre, Sheba Medical Centre, Tel-Hashomer, Israel; and †††Department of Pediatric Hematology/Oncology, University Hospital Dresden, Dresden, Germany*

To cite this article: Iorio A, Halimeh S, Holzhauer S, Goldenberg N, Marchesini E, Marcucci M, Young G, Bidlingmaier C, Brandao LR, Ettingshausen CE, Gringeri A, Kenet G, Knöfler R, Kreuz W, Kurnik K, Manner D, Santagostino E, Mannucci PM, Nowak-Göttl U. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. *J Thromb Haemost* 2010; **8**: 1256–65.

TIPO DE CONCENTRADO PUPs (Meta-análisis)



	Main analysis		
	Plasma-derived FVIII	Recombinant FVIII	*P* value (pdFVIII vs. rFVIII)
	Event rate (95% CI)	Event rate (95% CI)	(Cohran Q)
All studies	14.3 (10.4–19.4)	27.4 (23.6–31.5)	< 0.001
	Sensitivity analyses		
	Event rate (95% CI) [number of studies]	Event rate (95% CI) [number of studies]	(Cohran Q)
Prospective studies			
All patients	9.1 (5.6–14.4) [9]	23.7 (18.5–29.7) [10]	< 0.001
Severe HA, HR only	6.0 (1.1–27.7) [2]	19.4 (9.0–36.9) [1]	0.195*
HR inhibitors			
All patients	9.3 (6.2–13.7) [13]	17.4 (14.2–21.2) [13]	0.004
Severe HA	9.0 (4.0–19.2) [5]	18.2 (13.9–23.5) [3]	0.009
Non-transient inhibitors			
All patients	11.8 (6.9–19.6) [8]	19.8 (15.3–25.3) [10]	0.076**
Severe HA	16.3 (0.8–30.1 [3]	25.8 (13.5–43.7) [1]	0.317***

TIPO DE CONCENTRADO PTPs

Haemophilia

Haemophilia (2010), **16**, 61–65 DOI: 10.1111/j.1365-2516.2010.02235.x

EPIDEMIOLOGY

Inhibitors in previously treated patients: a review of the literature

C. L. KEMPTON

Aflac Cancer Center and Blood Disorders Service and Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA

Table 1. Inhibitors in pivotal recombinant factor VIII (FVIII) clinical trials using previously treated patients (PTPs) as subjects.

Products	*n*	PTP definition	Baseline FVIII levels	No. of new inhibitors
Recombinate [21]	69	NR	≤5%	0
Kogenate® [16]	86	>1 dose	NR	1
Kogenate-FS® [22]	73	≥100 ED	<2%	0
Refacto® [17]	113	≥30 ED/year	<2%	1
Advate [18]	108	≥150 ED	<1%	1

ED, exposure day; NR, not reported.

New inhibitor formation in persons with haemophilia A and >150 lifetime exposures to FVIII concentrates is rare, occurring between 1.55 and 3.8 per 1000 person years. Higher rates can occur when exposed to neo-epitopes as occurred with changes in the pasteurization process in the 1990s.

Journal of Thrombosis and Haemostasis, **9**: 2180–2192 DOI: 10.1111/j.1538-7836.2011.04472.x

IN FOCUS

Can B-domain deletion alter the immunogenicity of recombinant factor VIII? A meta-analysis of prospective clinical studies

L. M. ALEDORT,* R. J. NAVICKIS† and M. M. WILKES†
**Mount Sinai School of Medicine, New York, NY; and †Hygeia Associates, Grass Valley, CA, USA*

To cite this article: Aledort LM, Navickis RJ, Wilkes MM. Can B-domain deletion alter the immunogenicity of recombinant factor VIII? A meta-analysis of prospective clinical studies. *J Thromb Haemost* 2011; **9**: 2180–92.

Journal of Thrombosis and Haemostasis, **9**: 2176–2179 DOI: 10.1111/j.1538-7836.2011.04480.x

COMMENTARY

Concentrate-related inhibitor risk: is a difference always real?

A. IORIO,* M. MARCUCCI† and M. MAKRIS‡
*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; †Department of Internal Medicine, University of Perugia, Perugia, Italy; and ‡Department of Cardiovascular Science, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK

To cite this article: Iorio A., Marcucci M., Makris M. Concentrate-related inhibitor risk: is a difference always real? *J Thromb Haemost* 2011; **9**: 2176–9.

Table 1 Guides for assessing causation

1.	*Plausibility*: Is there a credible biological or physical mechanism that can explain the association?
2.	*Biological gradient*: Are increasing exposures (i.e. dose duration) associated with increasing risks of the disease?
3.	*Experimental evidence*: Is there any evidence from true experiments in humans?
4.	*Strength of association*: How strongly associated is the putative risk with the outcome of interest?
5.	*Analogy*: Is there a known relation between a similar putative cause and effect?
6.	*Consistency*: Have the results been replicated by different studies, in different settings, by different investigators, and under different conditions?
7.	*Temporality*: Did the exposure precede the disease?
8.	*Coherence*: Is the association consistent with the natural history and epidemiology of the disease?
9.	*Specificity*: Is the exposure associated with a very specific disease rather than a wide range of diseases?

Modified from Hill, Austin Bradford. Principles of medical statistics. Oxford University Press, New York, 1971, with permission.
Items have been renumbered following their presentation in the text.

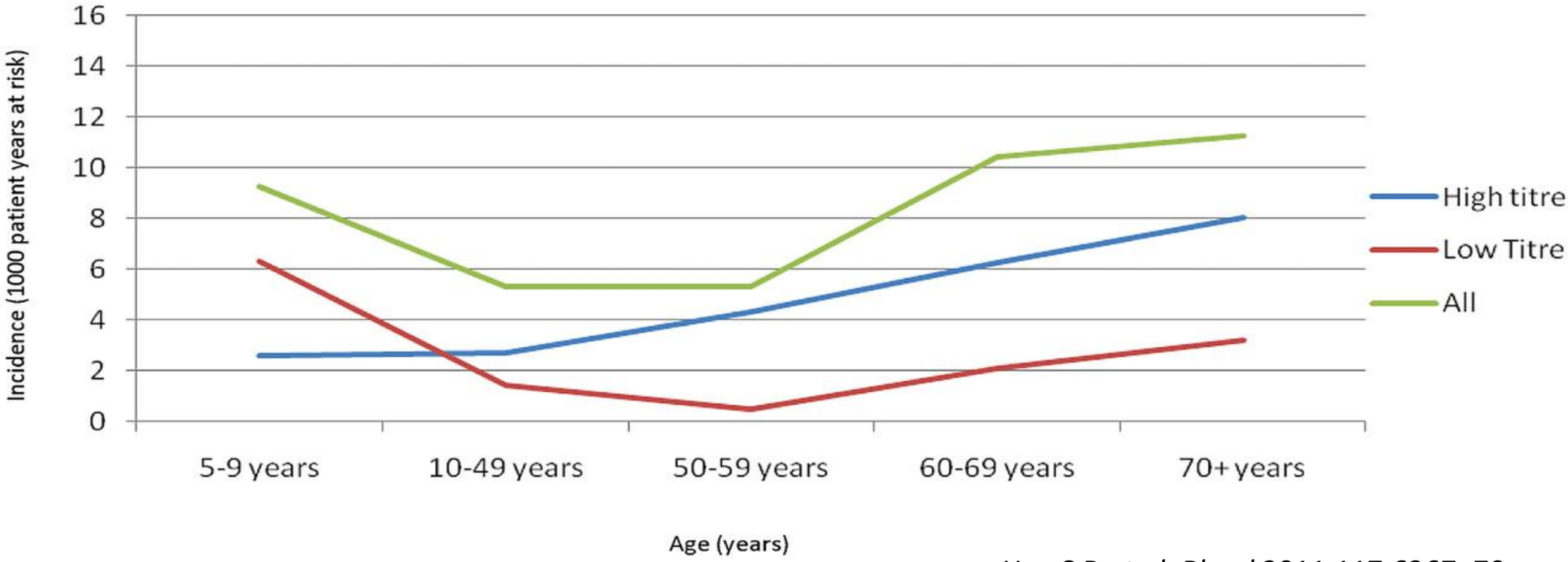
Factor VIII inhibitors in previously treated hemophilic patients

P. M. MANNUCCI
Scientific Direction, IRCCS Ca' Granda Maggiore Hospital Foundation, Milan, Italy

To cite this article: Mannucci PM. Factor VIII inhibitors in previously treated hemophilic patients. *J Thromb Haemost* 2011; **9**: 2328–9.

- El mensaje principal: "el desarrollo de inhibidores en PTPs es un **evento poco frecuente** (1.25%, IC 95%, 0.63-1.88%)
- Además, destaca que:
  - IC de los ratios de riesgo son muy amplios (2.12-24.9)
  - El análisis de la incidencia de los inhibidores se basa en un número bajo de eventos (n=35), no análisis multivariantes
  - Utilidad de meta-análisis en ausencia de estudios aleatorizados dudoso

Incidencia de inhibidor por edad en United Kingdom (1990–2009)



Hay C R *et al. Blood* 2011;117:6367–70.

Profilaxis a dosis bajas

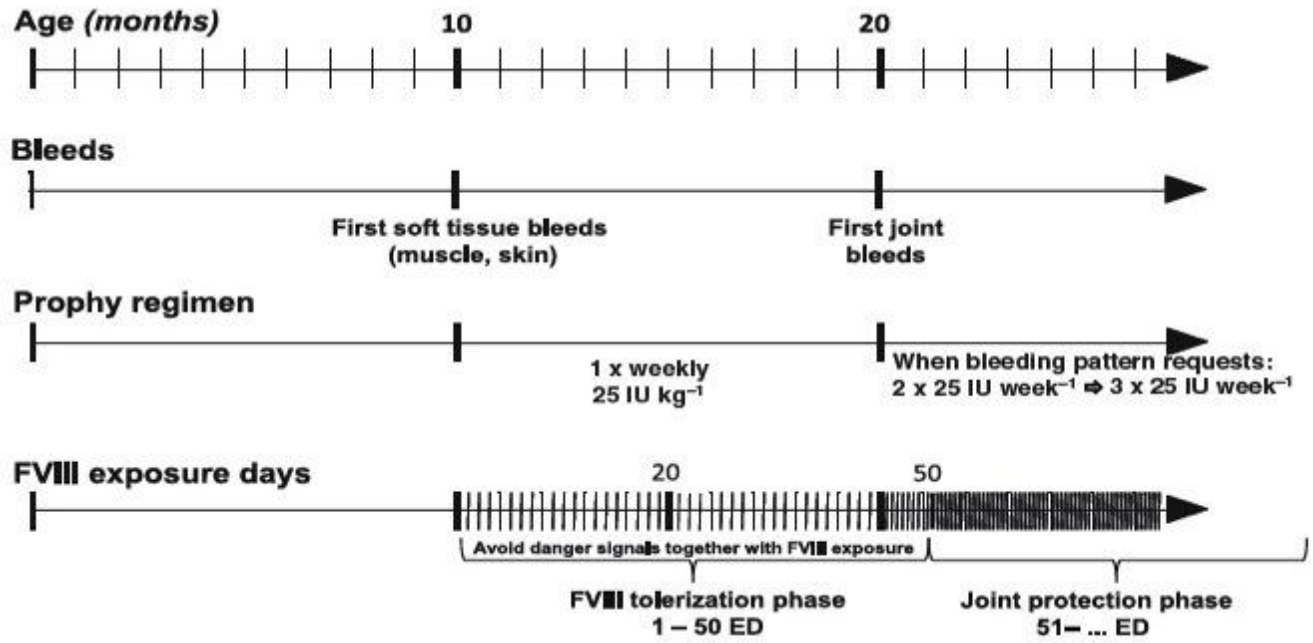
Haemophilia

Haemophilia (2010), **16**, 256–262 DOI: 10.1111/j.1365-2516.2009.02122.x

ORIGINAL ARTICLE *Clinical haemophilia*

New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development

K. KURNIK,* C. BIDLINGMAIER,* W. ENGL,† H. CHEHADEH,† B. REIPERT† and G. AUERSWALD‡
**Klinikum der Universität München, Dr. von Haunersches Childrens Hospital, Munich, Germany; †Baxter Innovations GmbH, Vienna, Austria; and ‡Prof. Hess Childrens Hospital, Klinikum Bremen-Mitte, Bremen, Germany*



Profilaxis a dosis bajas

Haemophilia

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ORIGINAL ARTICLE *Clinical haemophilia*

New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development

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**Klinikum der Universität München, Dr. von Haunersches Childrens Hospital, Munich, Germany; †Baxter Innovations GmbH, Vienna, Austria; and ‡Prof. Hess Childrens Hospital, Klinikum Bremen-Mitte, Bremen, Germany*

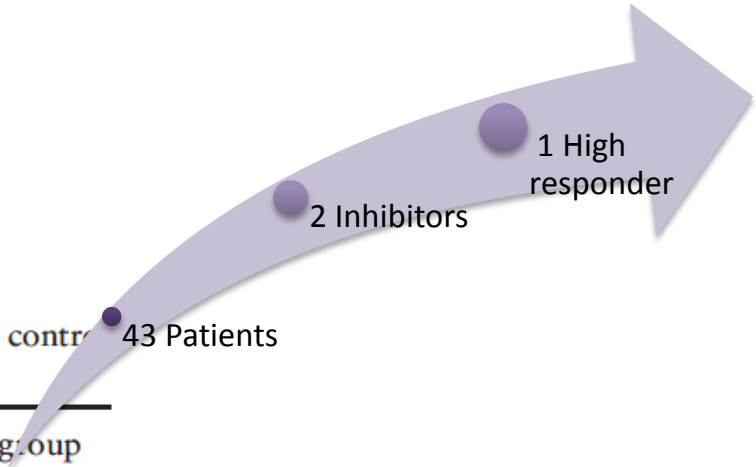


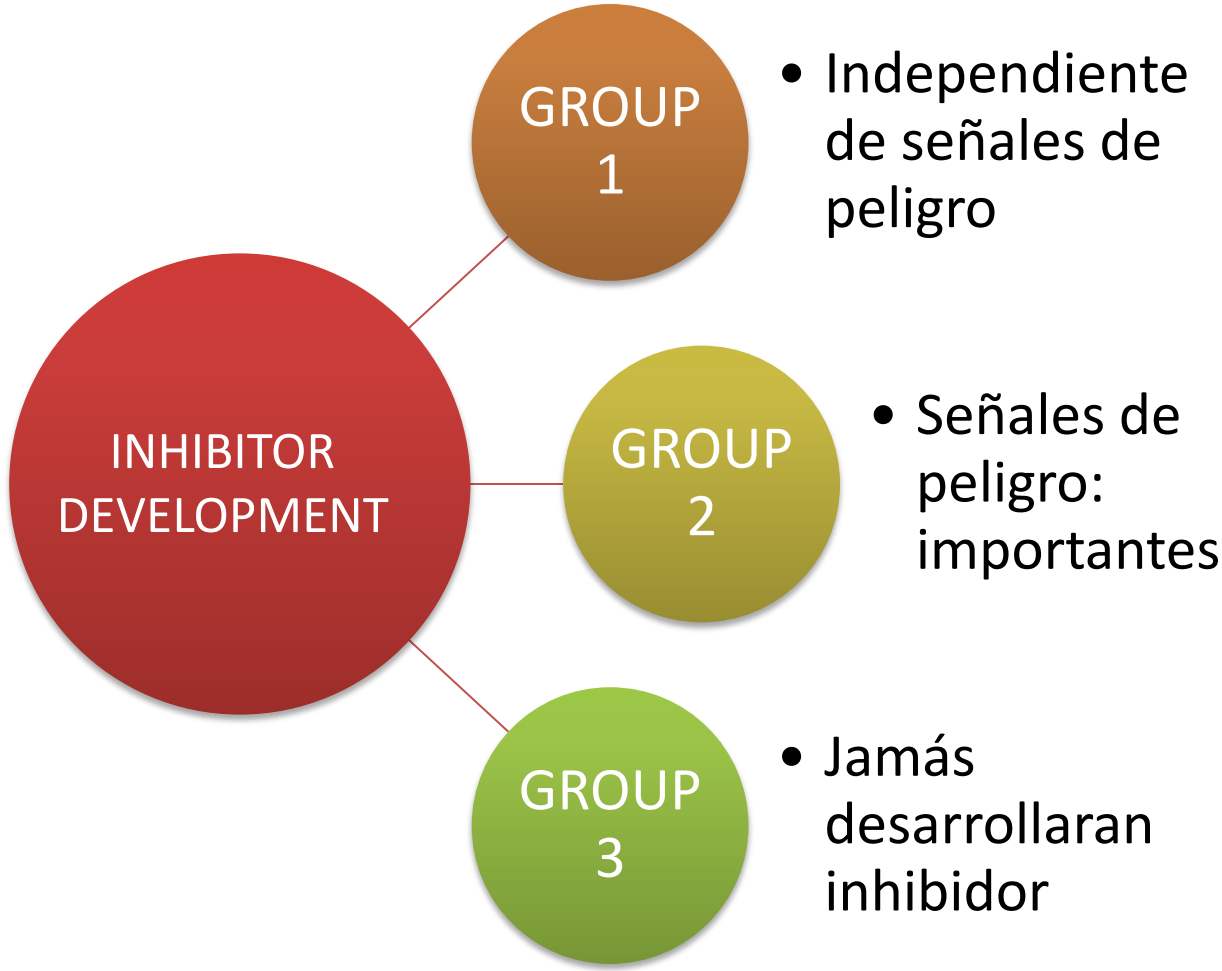
Table 1. Inhibitor incidence of the study group compared to the contr group.

	Historical control group (standard prophylaxis regimen) $n = 30$	Study group (new early tolerization regimen) $n = 40$
Inhibitors (%)	14 (47)	1 (2.5)
High responders (%)	8 (27)	0
Low responders (%)	6 (20)	1 (2.5)

Profilaxis a dosis bajas

- Swedish cohort: No confirman estos resultados
    - Lujng R (personal comunication)
    - Astermark J. Haemophilia 2012;18 (Suppl. 4),38-42
- The PedNet/Rodin Study group:
    - La profilaxis no afecta al desarrollo de inhibidores tempranos.
    - Si en desarrollo tardíos en pacientes con mutaciones de riesgo
        - Gouw S et al. Haemophilia 2012; 18: supp3: abstract 103
- EPIC study: ClinicalTrials.gov identifier: NCT01376700
    - No ha demostrado este efecto

Escenarios



- Astermark J. Haemophilia 2012;18 (Suppl. 4),38-42

Navaja de Ockham

- Ockham's razor:
  - "Other things being equal, a simpler explanation is better than a more complex one"

- Anti-razors:
  - "If three things are not enough to verify an affirmative proposition about things, a fourth must be added, and so on "
    - Walter of Chatton (1287-1347)

Ockham chooses a razor

¿COMO TRATAR LOS PACIENTES CON HEMOFILIA E INHIBIDOR?

CON MUCHA DIFICULTAD

EXPERIENCIA

CONOCIMIENTO

Tratamiento de los episodios hemorrágicos

- Bajo título de inhibidor o bajos respondedores (<5 U.B.)

  Concentrados factor VIII a altas dosis

- Alto título de inhibidor o altos respondedores (>5 U.B.)

  CCPA (Feiba®)

  rFVIIa (Novoseven®)

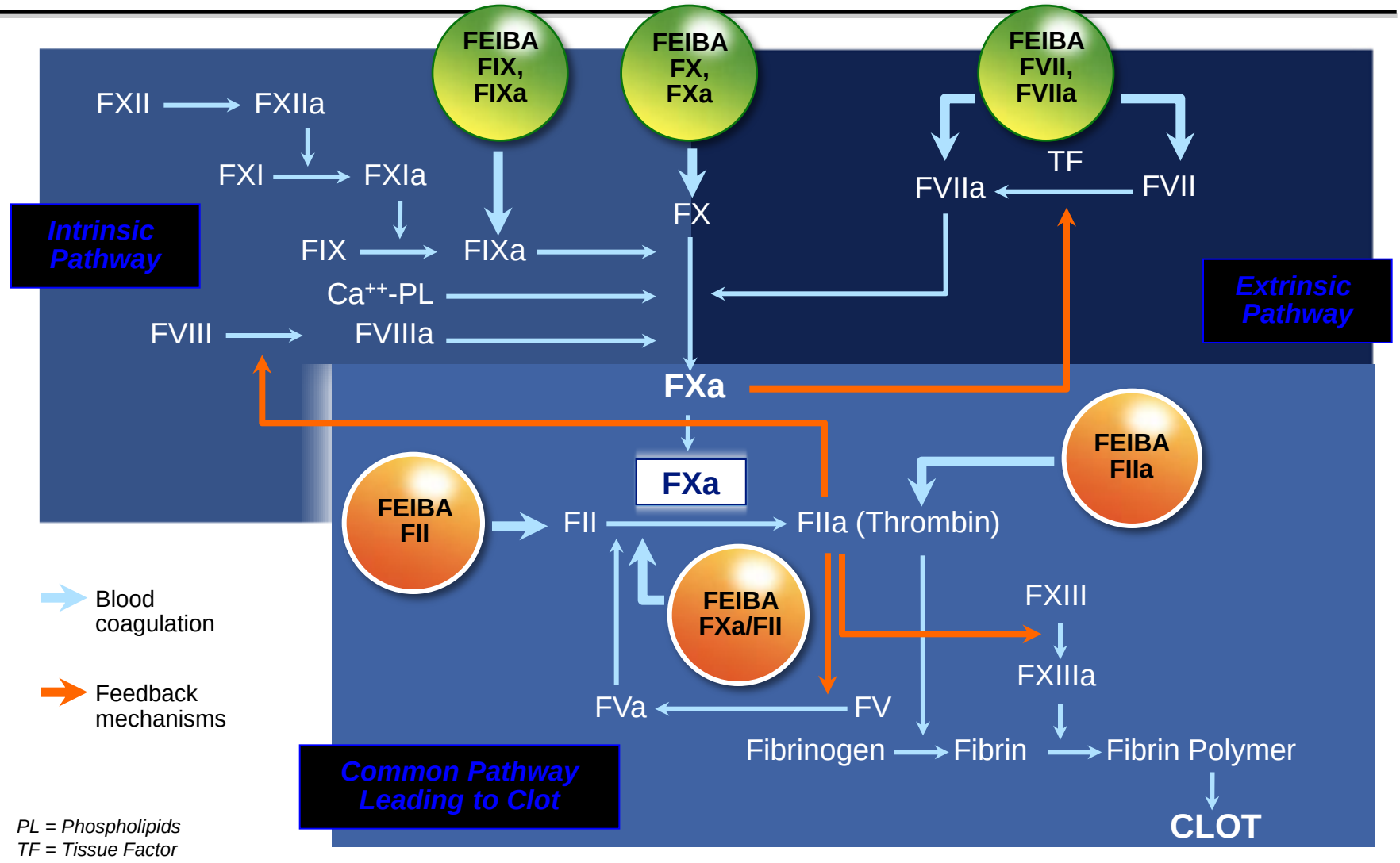
FEIBA: COMPOSICION

Factor VIII inhibitor bypassing activity

	FII	FVII	FIX	FX	Protein C	Thrombin	FVIIa	FIXa	FXa
U/U FEIBA	1.3	0.9	1.4	1.1	1.1	0.001	1.5	≥0.0004	0.006
SD	±0.3	±0.1	±0.1	±0.2	±0.2	±0.001	±0.2	±0.0001	±0.002

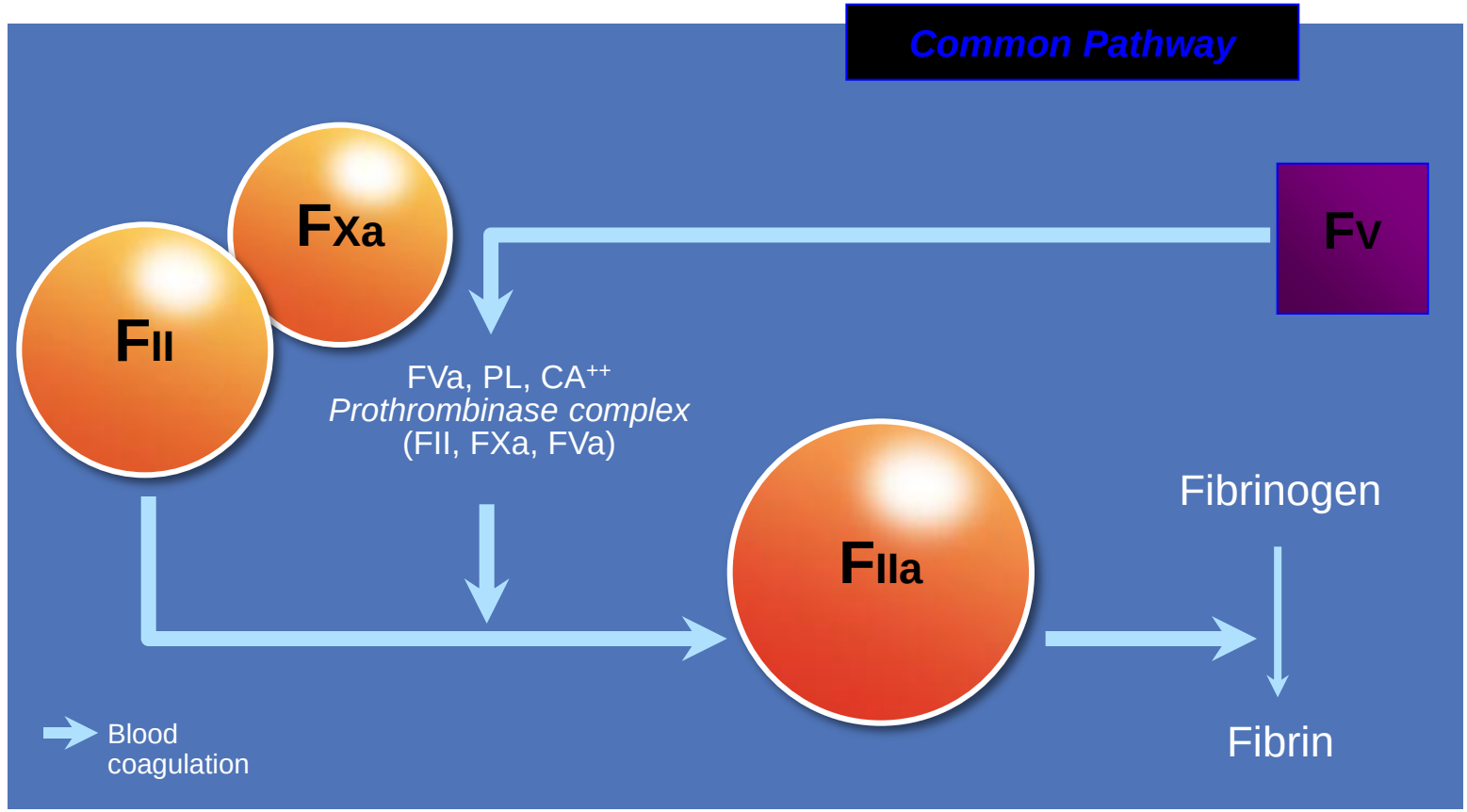
* Turecek PL et al. Presented at the XXIV International Congress of the World Federation of Hemophilia (WFH), July 16-21, 2000, Montreal.

FEIBA: Lugares de actuación



Turecek PL et al. Vox Sang 1999; 77 (suppl 1): 72-79.

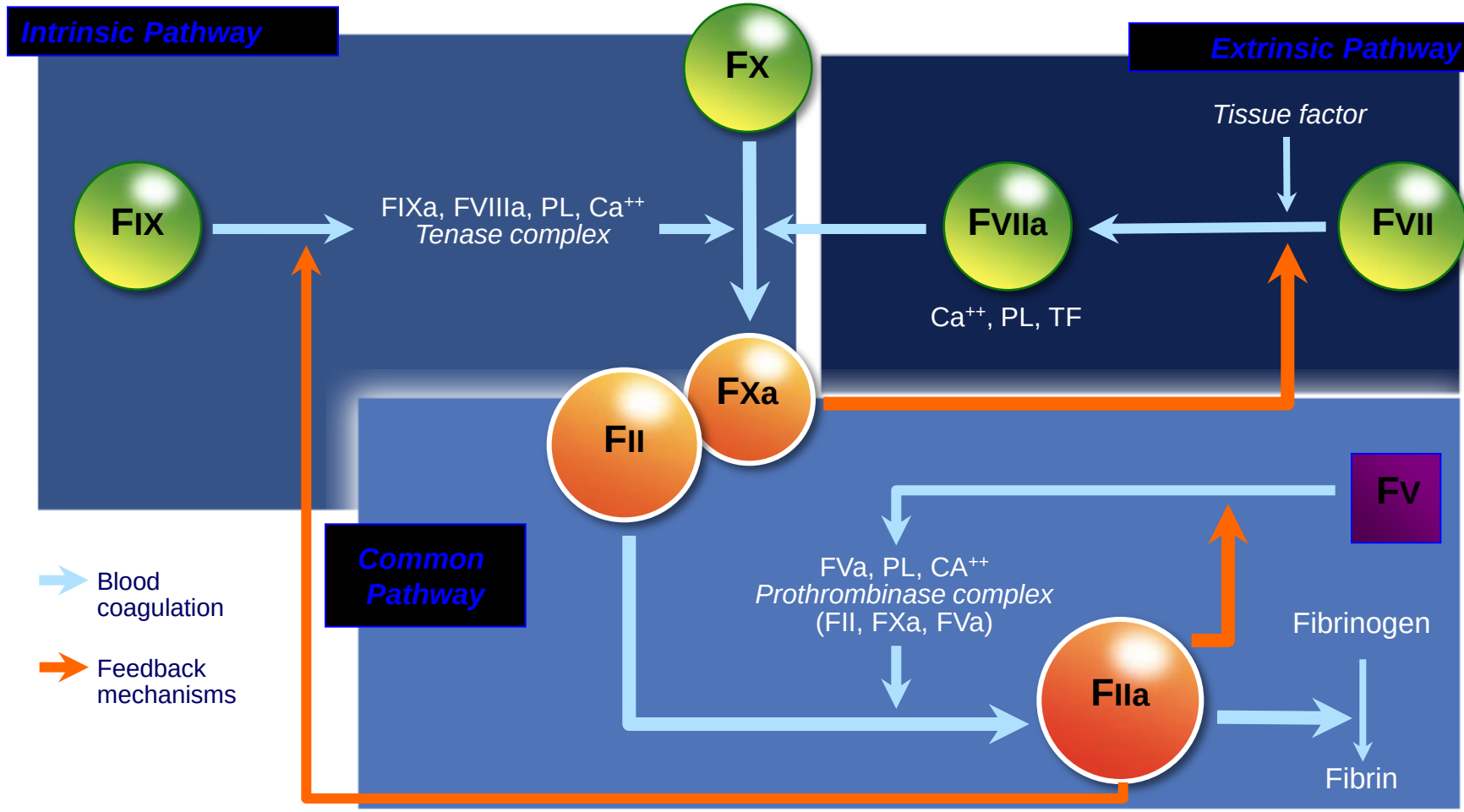
FEIBA: Mecanismo de Acción (I)



PL = Phospholipids

Turecek PL et al. Vox Sang 1999; 77 (suppl 1): 72 -79.

FEIBA: Mecanismo of Accion (II)



Turecek PL et al. Vox Sang 1999; 77 (suppl 1): 72 -79.

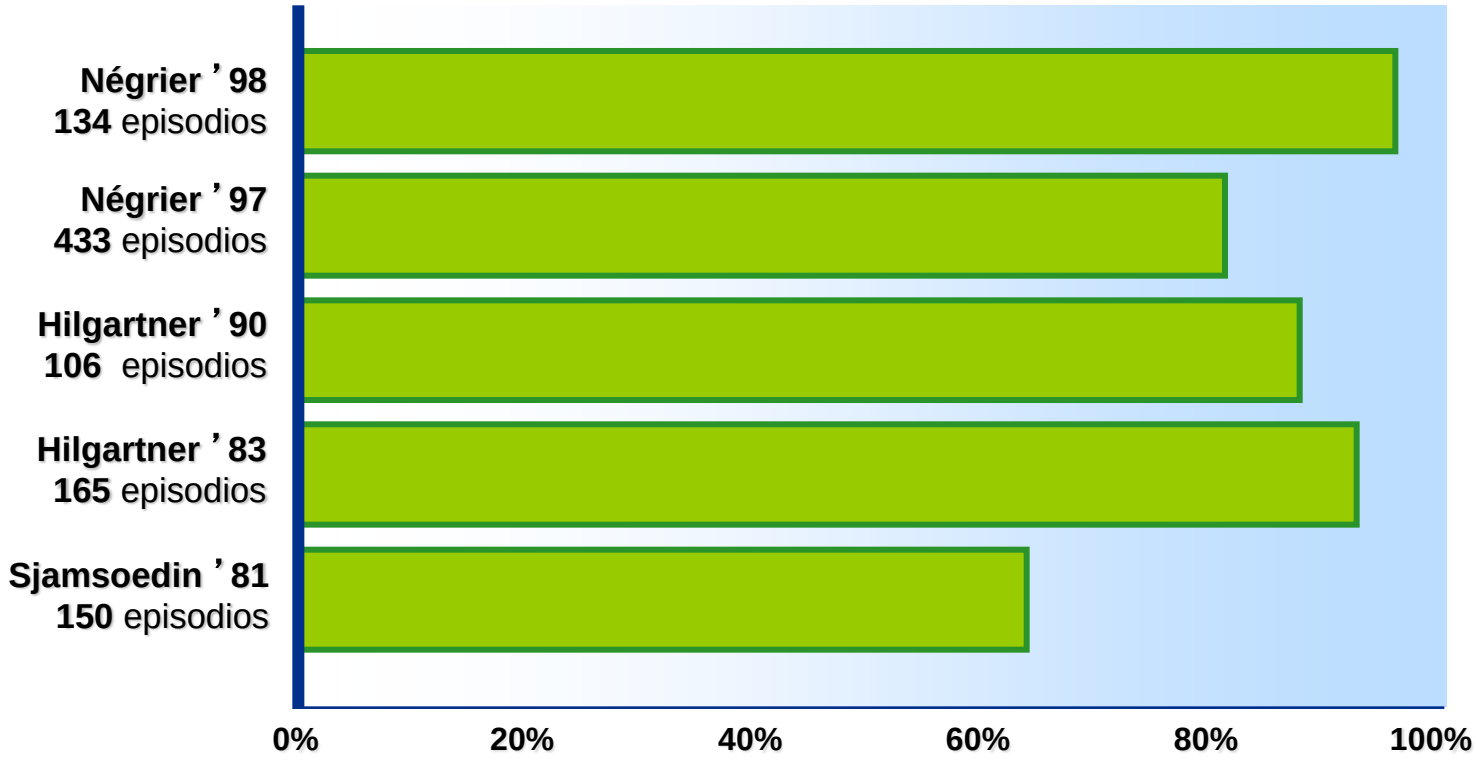
INDICACIONES

- Tratamiento y profilaxis de la hemorragia
  Hemofilia A y B con inhibidor
  Hemofilia Adquirida

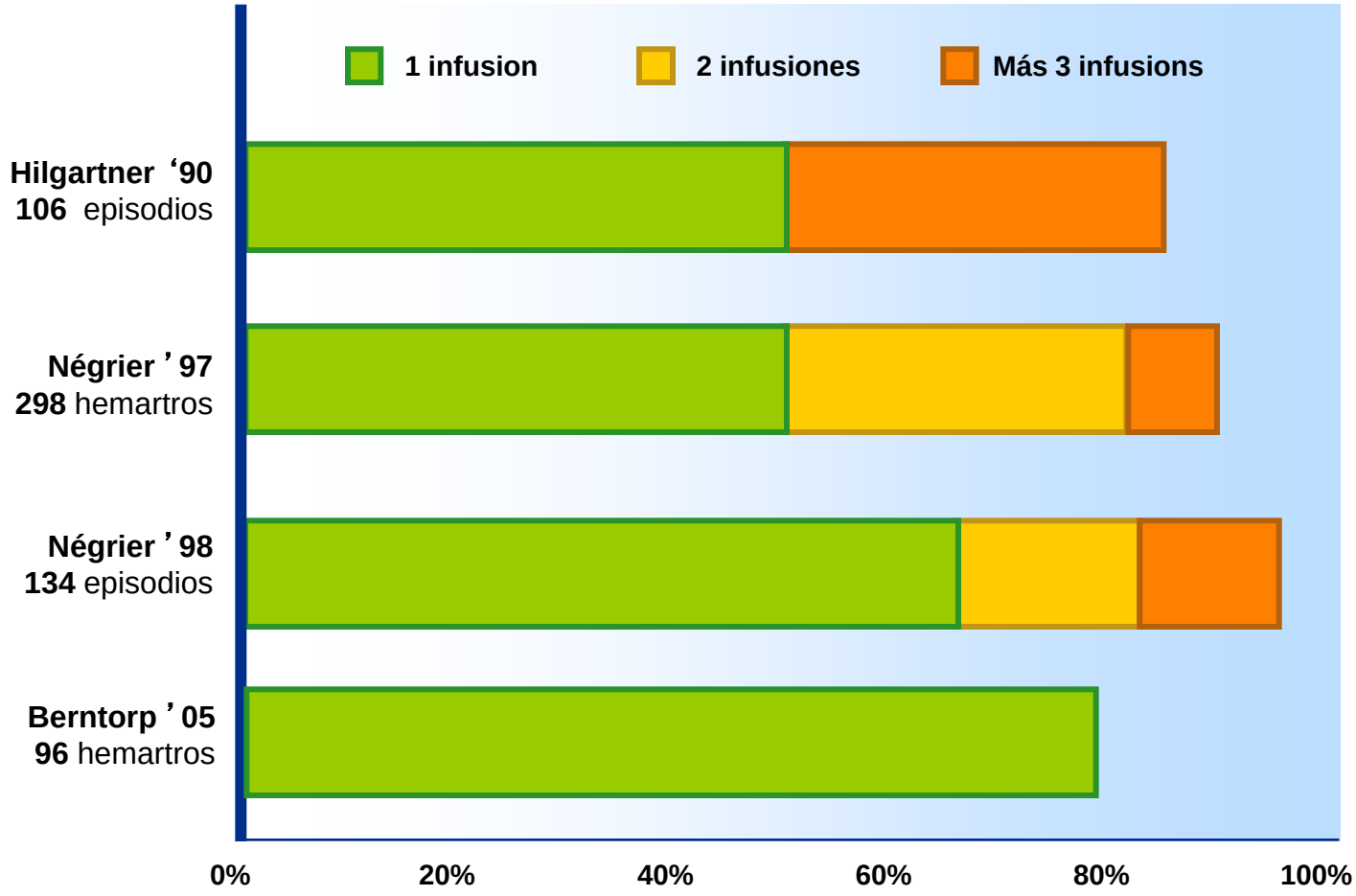
- Tratamiento concomitante con FVIII en IT

- Dosis Recomendada :
  - 50-100 u/Kg
  - No sobrepasar en dosis aislada 100 U/kg o de 200 U/kg como dosis diaria

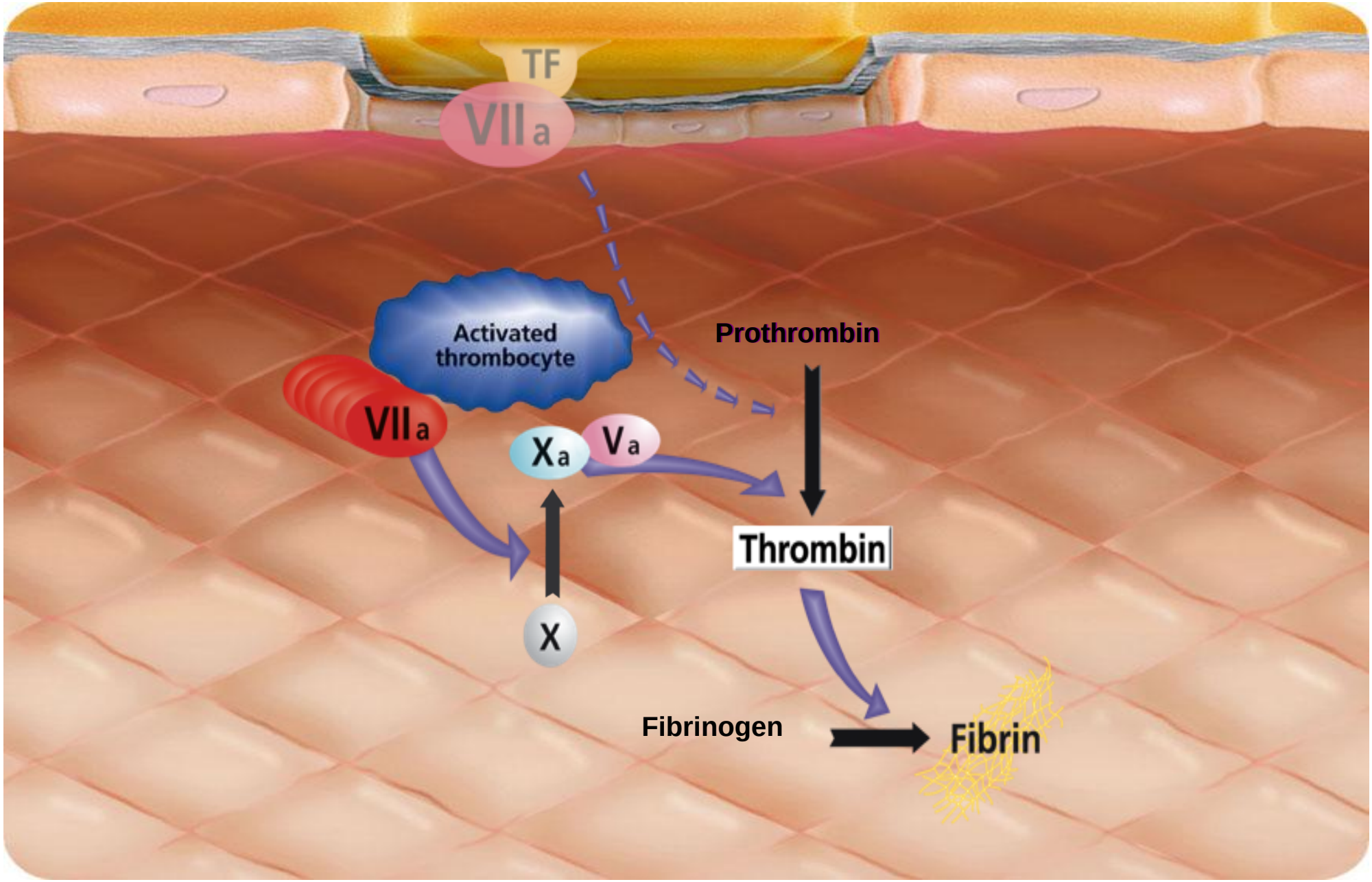
FEIBA: Experincia Internacional en diferentes episodios hemorrágicos.



FEIBA:Eficacia tras una sola administración

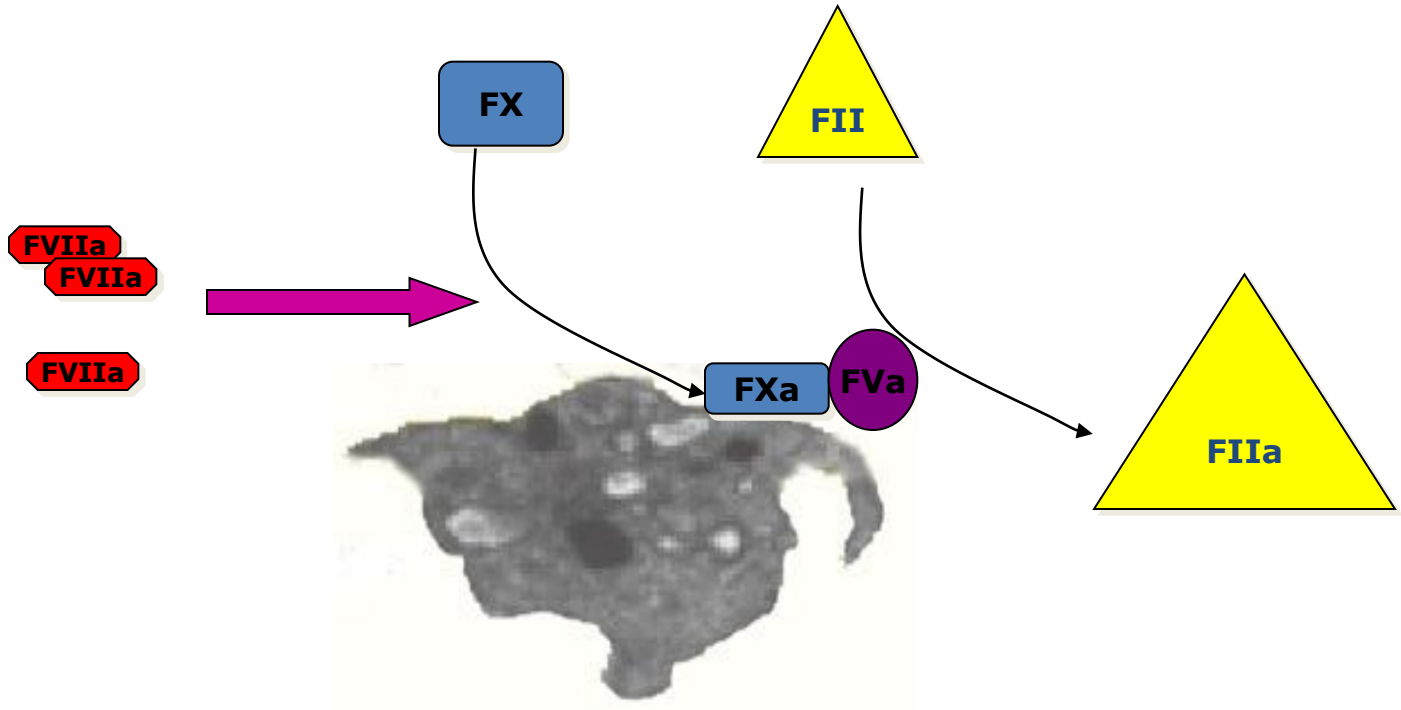


¿COMO ACTUA rFVIIa EN PACIENTES CON HEMOFILIA?



¿COMO ACTUA rFVIIa EN PACIENTES CON HEMOFILIA?

Hoffman M. *Semin Hematology 2001; 38: 6-9*



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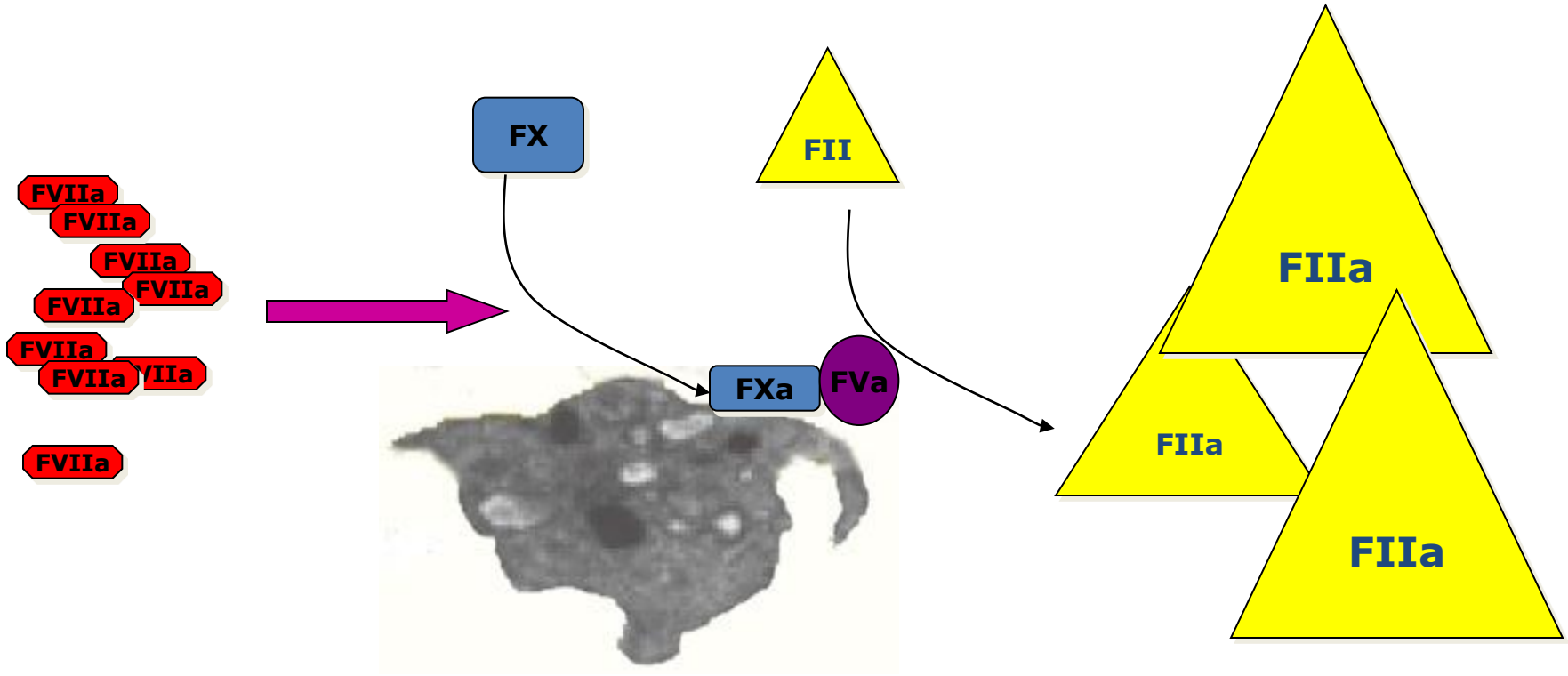
¿COMO ACTUA rFVIIa EN PACIENTES CON HEMOFILIA?

Hoffman M. *Semin Hematology 2001; 38: 6-9*



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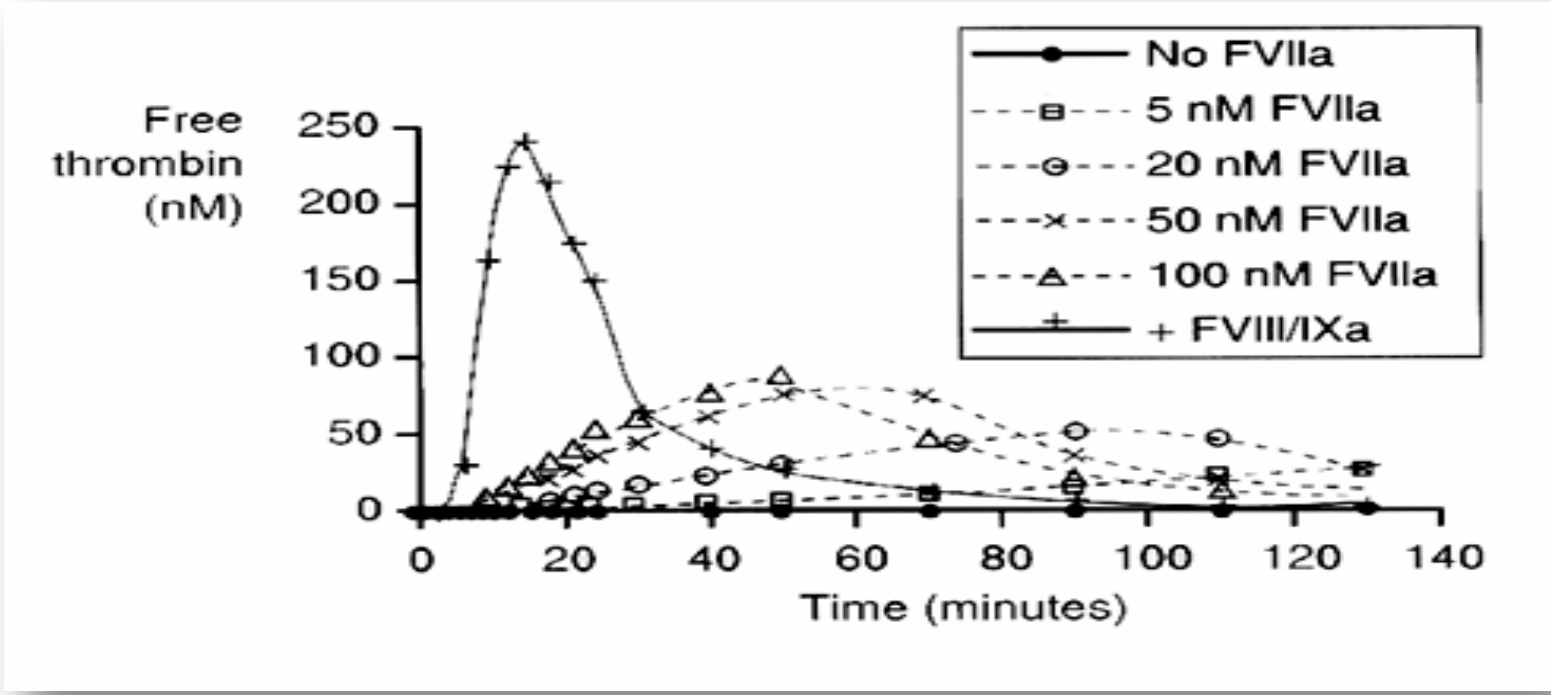
¿COMO ACTUA rFVIIa EN PACIENTES CON HEMOFILIA?

Allen GA. *Blood Coagul Fibrinol 2000;11:S3-S9.*



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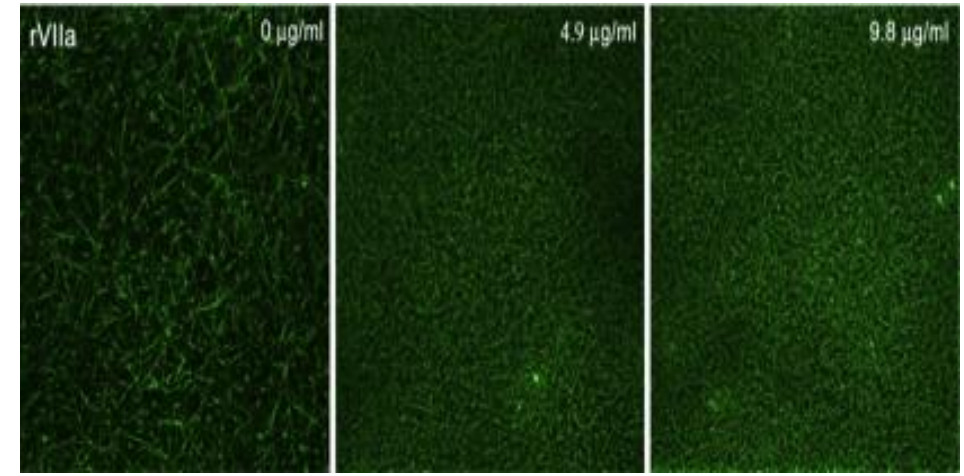
¿COMO ACTUA rFVIIa EN PACIENTES CON HEMOFILIA?

- rFVIIa potencia la generación de trombina
- Activa más plaquetas y más factores, amplificando la respuesta
- Activa el FXIII, estabilizando la fibrina
- Activa el TAFI, impidiendo la lisis temprana del trombo formado

- rFVIIa disminuye la permeabilidad de los coágulos de fibrina en el plasma deficitario de FVIII y FIX
- rFVIIa induce una estructura de fibrina más sólida



rFVIIa en Hemofilia con Inhibidor: Eficacia

- 90-100% eficacia en cirugía mayor (90-100 µg/kg/2h 24 h)
  - Shapiro et al. Thromb Haemostais 1998; 80:773-8
  - Ingerslev. Haemostasis 1996;26(Suppl 1):118-23
- 83-95% eficacia en sangrados graves
  - Lusher et al. Blood Coagul Fibrinolysis 1998;9:119-28
  - Hedner & Ingerslev. Transf Sci 1998;9:163-76
- 92% eficacia en hemartros (tratamiento domiciliario)
  - Key et al. Thromb Haemostasis 1998; 80:912-8

rFVIIa en Hemofilia con Inhibidor: Administración

- DOSIS recomendada:

- 90-120 µgr/Kg
- 270 µgr/Kg dosis única

- Modo de administración:
- bolo generalmente
- Infusión continua: dosis elevadas (35-50µgr/kg/h)

- En algunos pacientes se pueden necesitar dosis más elevadas
- (200-300 µgr/Kg)

rFVIIa en Hemofilia con Inhibidor: Administración

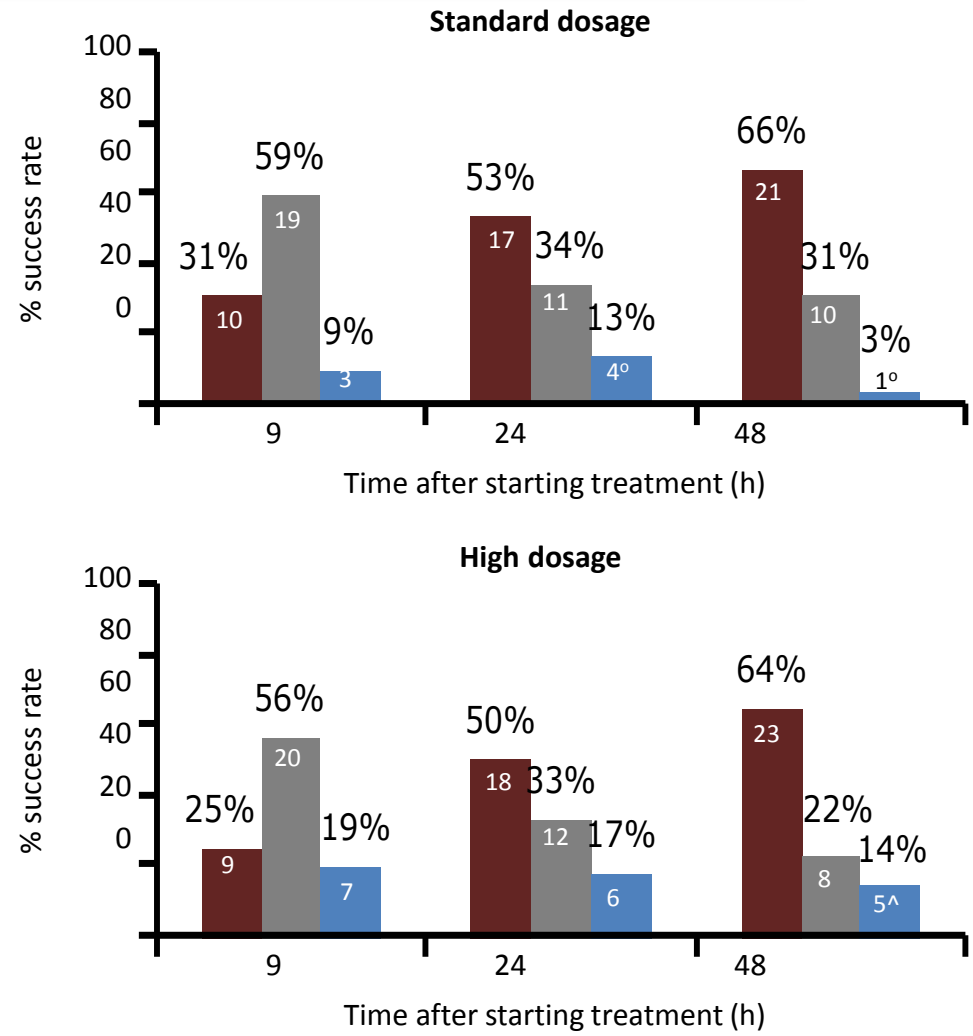
Intervalo de administración recomendada:

cada 2 horas inicialmente

cada 3-4 horas una vez conseguida la hemostasia

Altas dosis de rFVIIa en hemartros

- Resultados similares con ambas dosis
- Respuesta: 2/3 pacientes
- Todos presentaban articulaciones diana
- Target joints: respuesta peor y más dosis
- *Altas dosis: precisan menos dosis de rFVIIa*



Source: Santagostino *et al*. A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors. J Thromb Haemost 2006;4:367–71

ESTRATEGIAS TERAPEUTICAS

Haemophilia (2005), **11**, 611–619 DOI: 10.1111/j.1365-2516.2005.01161.x

GUIDELINES

Italian guidelines for the diagnosis and treatment of patients with haemophilia and inhibitors

A. GRINGERI and P. M. MANNUCCI, FOR THE ITALIAN ASSOCIATION OF HAEMOPHILIA CENTRES

Department of Internal Medicine and Dermatology, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Policlinico, Mangiagalli and Regina Elena Hospital Foundation and University of Milan, Milan, Italy

ESTRATEGIAS TERAPEUTICAS

ESTRATEGIAS TERAPEUTICAS

- In 2005, the Spanish Group for the Prevention and Treatment of Bleeding in Patients with Haemophilia and Inhibitors developed recommendations for surgical management using rFVIIa in adults:

	Preoperative dose	Days 1–5	Days 6–15
Minor surgery	90–120 µg/kg	Day 1: 90–120 µg/kg every 2 h for first 4 doses Days 1–2: every 3–4 h Days 3–5: every 3–6 h	
Major surgery	120 µg/kg*	Day 1: 90–120 µg/kg every 2 h* Day 2: every 2–3 h Day 3–5: every 4 h	90–120 µg/kg every 6 h
Continuous infusion	Bolus: 120 µg/kg	30–50 µg/kg/h	15–50 µg/kg/h

*Higher doses could be used

ESTRATEGIAS TERAPEUTICAS

- Recommendations for surgical management using rFVIIa in children:

	Preoperative dose	Days 1–5	Days 6–15
Minor surgery	120–150 µg/kg*	Day 1: 120–150 µg/kg* every 1.5–2 h for first 4 doses Days 1–2: every 2–4 h Days 3–5: every 3–6 h	
Major surgery	120–270 µg/kg*	Day 1: 120–270 µg/kg every 1.5–2 h for first 4 doses Day 1–2: 120–150 µg/kg every 2 h Day 3–5: 120–150 µg/kg every 3–4 h	120–150 µg/kg every 6 h
Continuous infusion	Bolus: 120–150 µg/kg	30–50 µg/kg/h	15–50 µg/kg/h

*Higher doses could be used

ESTRATEGIAS TERAPEUTICAS

- Recommendations for surgical management using FEIBA™:

	Preoperative dose	Days 1–5	Days 6–15
Minor surgery	50–75 U/kg	50–75 μ/kg every 12–24 h	
Major surgery	75–100 U/kg	75–100 μ/kg every 8–12 h	75–100 U/kg every 12 h

Maximum daily dose: 250 U/kg

ESTRATEGIAS TERAPEUTICAS

HEMATOMAS MUSCULARES

Las hemorragias intramusculares representan el 30% de los episodios hemorrágicos que se producen en el sistema músculo-esquelético en pacientes hemofílicos. Los hematomas del ílio-psoas representan el 1% de todos los episodios hemorrágicos y el 18% de las hemorragias intramusculares. La incidencia en pacientes hemofílicos con inhibidor se desconoce. En líneas generales las hemorragias intramusculares pueden dividirse en 3 grupos.

1. Hemorragias intramusculares periféricas agudas
2. Hemorragias intramusculares que comprometen la extremidad
3. Hematoma del ílio-psoas

» texto completo [doc 168 KB]

TRATAMIENTO HEMOSTÁTICO SECUENCIAL EN EL PACIENTE HEMOFÍLICO CON INHIBIDOR

Las pautas de tratamiento hemostático de pacientes hemofílicos con inhibidor son establecidas en general según la tasa de inhibidor. En caso de títulos de inhibidor inferiores a 5 Unidades Bethesda (UB) o pacientes bajos respondedores, la recomendación es iniciar tratamiento con altas dosis de factor deficiente (1). Si el título de inhibidor es superior a 5 UB o paciente alto respondedor, la terapia recomendada es el uso de agentes baipás. Definimos agente baipás en hemofilia, como aquel capaz de dar lugar a la producción de trombina salvando el complejo tenasa de la coagulación, deficiente en los pacientes con hemofilia A y B. Los agentes baipás disponibles en el mercado son: Concentrados de Complejo protrombínico (CCP), Concentrados de Complejo Protrombínico activado (CCPA) y Factor VII activado recombinante (rFVIIa) (Tabla 1.) En nuestro medio, FEIBA y Novoseven son los agentes utilizados de forma habitual (2-7). La elección de uno u otro producto se realiza en base al perfil de respuesta del paciente, seguridad, inmunogenicidad y disponibilidad del producto y experiencia del clínico.

» texto completo [doc 1,7 MB]

TRATAMIENTO DE LA HEMARTROSIS EN PACIENTES CON HEMOFILIA E INHIBIDOR

Las hemartrosis son las manifestaciones hemorrágicas mas frecuentes y de mayor morbilidad en los pacientes hemofílicos, siendo evidente la relación directa entre estos episodios y el desarrollo posterior de la artropatía hemofílica. Los estudios de autores como Jansen, Lafeber, y Roosendaal demuestran dicha relación. Por todo ello es fundamental en estos pacientes el tratar de evitar la aparición de dichos episodios, siendo eso posible gracias al tratamiento profiláctico en los pacientes hemofílicos sin inhibidor.

En pacientes hemofílicos con inhibidor la situación es diferente, puesto que la presencia del inhibidor dificulta el tratamiento de los episodios de hemartrosis, lo cual supone que este grupo de pacientes desarrollen más fácilmente dicha artropatía.

» texto completo [doc 79 KB]

SINOVIORTESIS RADIACTIVA

La presencia en una articulación de una membrana sinovial hipertrófica, muy vascularizada, favorecerá la aparición de hemartros de repetición, que a su vez perpetuará el proceso contribuyendo a la hipertrofia de la misma. El círculo vicioso hemartrosis-sinovitis-hemartrosis debe ser detenido lo antes posible con el fin de evitar el desarrollo de una artropatía hemofílica.

Una vez establecida la sinovitis, el tratamiento convencional incluye un programa de fisioterapia combinada con régimen intensivo de profilaxis. Cuando no se obtiene resultados o este programa no puede realizarse, como sucede en los hemofílicos con inhibidor, los pacientes pueden beneficiarse de una sinoviortesis radiactiva. El procedimiento consiste en la destrucción del tejido sinovial por la inyección intraarticular de un agente radiactivo, con disminución del infiltrado inflamatorio y eventual esclerosis de la sinovial.

» texto completo [doc 88 KB]

Haemophilia

Haemophilia (2011), **17**, e202–e210 DOI: 10.1111/j.1365-2516.2010.02377.x

ORIGINAL ARTICLE *Inhibitors*

Identifying non-responsive bleeding episodes in patients with haemophilia and inhibitors: a consensus definition

E. BERNTORP,* P. COLLINS,† R. D'OIRON,‡ N. EWING,§ A. GRINGERI,¶ C. NÉGRIER** and G. YOUNG††

ESTRATEGIAS TERAPEUTICAS

Table 2. Consensus definition: criteria to identify non-responsive joint and muscle bleeding episodes in patients with haemophilia and inhibitors.

Criteria	Subjective assessments*	Objective assessments*	Relative importance for joint bleeds	Relative importance for muscle bleeds
Pain	• Persistence or worsening of pain (with and without analgesics), reported by patient/parent via global self-assessment or VAS • Non-responsiveness to analgesics, reported by patient/parent	• Persistence or worsening of pain, evaluated by physician assessment • Need for analgesics • Non-responsiveness to analgesics, evaluated by physician assessment	Primary measure	Secondary measure
Swelling/tension	• Increase or persistence in swelling, reported by patient/parent	• Increase or persistence in swelling or tension relative to baseline, evaluated by size measurements or physician assessment	Secondary measure	Primary measure
Mobility	• Decrease in mobility, reported by patient/parent	• Decrease in mobility, evaluated by goniometric ROM measurements or physician assessment	Secondary measure	Of lesser importance
Patient perception	• Patient report of the sense of continuance of bleeding	–	Secondary measure	Of lesser importance
Laboratory evaluations	–	• Imaging studies (e.g. MRI, ultrasound, X-ray) • Arthrocentesis • TGA • Haemoglobin levels	TGAs can be used to confirm the haemostatic response to treatment	Haemoglobin levels and imaging are secondary measures

VAS, visual analogue scale; ROM, range of motion; MRI, magnetic resonance imaging; TGA, thrombin generation assay.
*Criteria should be assessed at 24 h from the initiation of treatment.

ESTRATEGIAS TERAPEUTICAS

Recombinant Factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with haemophilia and inhibitors (Review)

Iorio A, Matino D, D'Amico R, Makris M

AUTHORS' CONCLUSIONS

Implications for practice

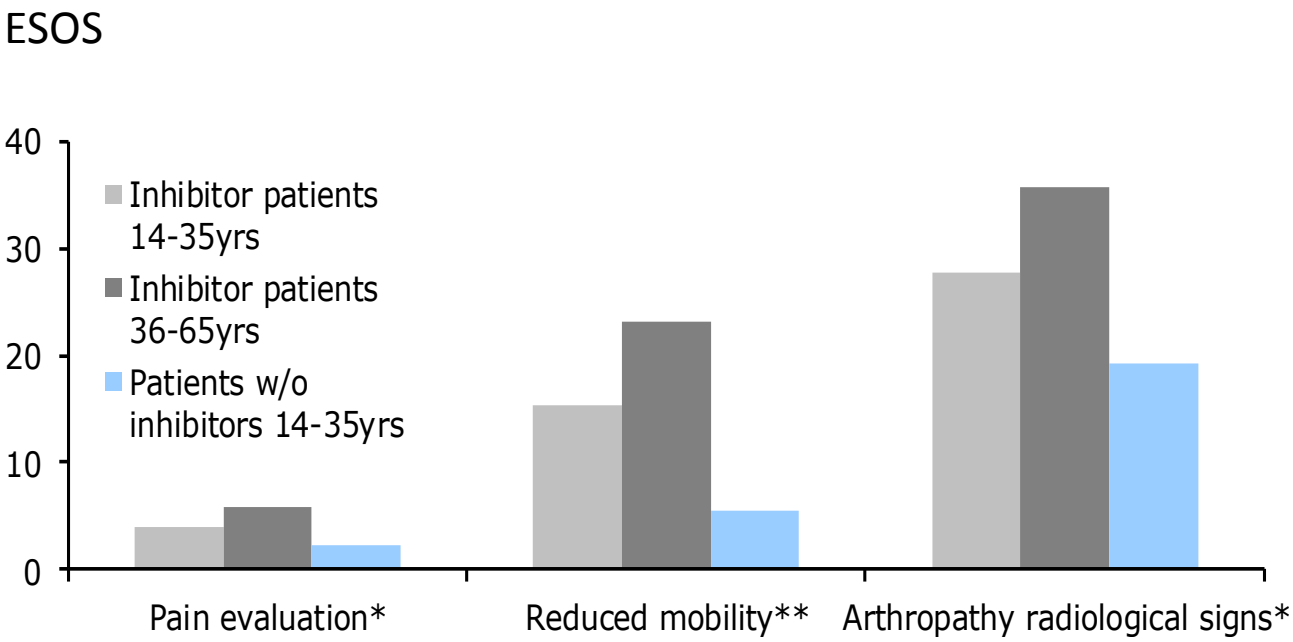
Based on the separate analysis of the two available randomised trials, rFVIIa and aPCC were found to be similar in efficacy and in causing a low risk of thromboembolic complications. Both drugs can be administered as single intravenous bolus (270 mcg/kg of rFVIIa, 75-100 IU/kg of aPCC). Other non-randomised evidence can be usefully taken into account in the choice of the more appropriate treatment in clinical practice. The choice between different regimens of rFVIIa is beyond the scope of this review, and should be mainly based on general considerations about the use of recombinant versus plasma-derived concentrates in specific categories of patients (i.e. children).

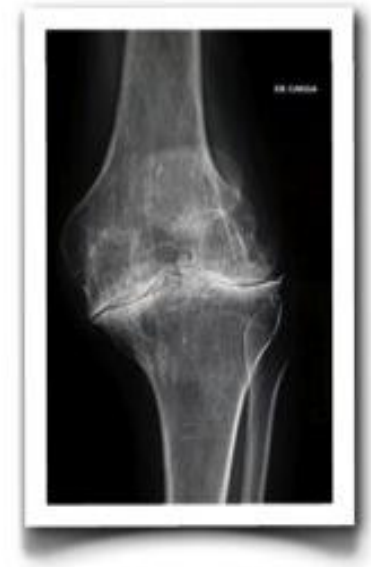
CONSIDERACIONES EN RELACION AL TRATAMIENTO

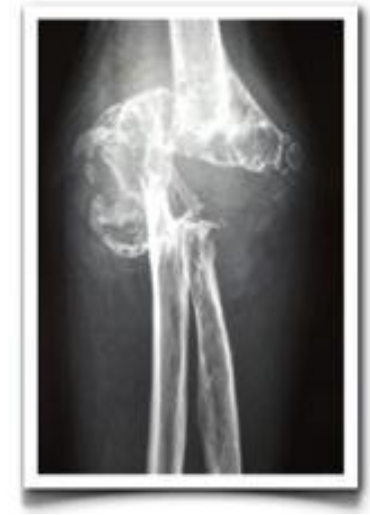
- Tratamiento muy complejo
- Importancia de la precocidad
- MANTENIMIENTO TIEMPO ADECUADO
- IDENTIFICAR LOS FRACASOS
- POSIBILIDAD DE CAMBIO

Profilaxis en pacientes con inhibidor

PROFILAXIS: ¿Una necesidad?







*Pettersson classification, scores per joint ranging from 0 to 13
**Gilbert classification, scores per joint ranging from 0 for no pain to 3 for maximum pain and for clinical examination, scores per joint ranging from 0 to 12 for knees and ankles, 0 to 10 for hips and 0 to 8 for elbows and shoulders

Source: Morfini et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 2007;13:606–12

PROFILAXIS: ¿Una necesidad?

- COCIS – en pacientes con inhibidor:
  - QoL se asocia con el status ortopédico
  - La percepción de salud global esta disminuída debido a problemas ortopédicos
  -
- ...Pero estrategias novedosas son efectivas y percividas como satisfactorias por los pacientes

    - Scalone L, *et al.* Haemophilia 2006;12:154–62

Profilaxis secundaria: Experiencia con rFVIIa

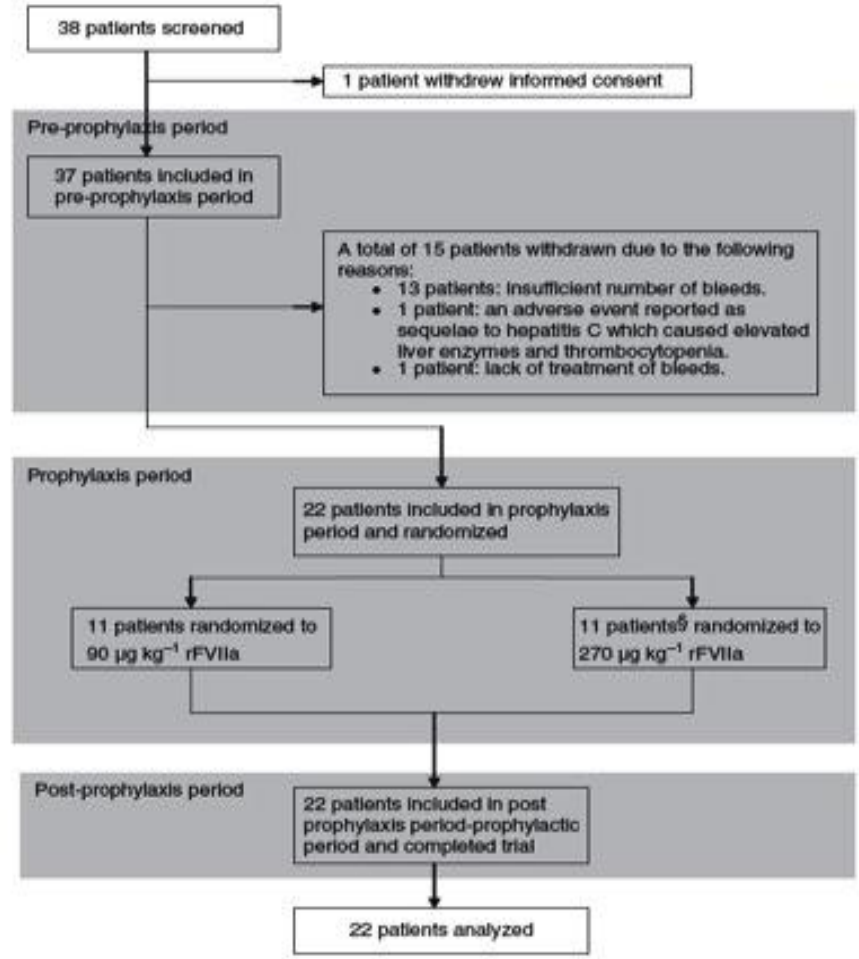
rnal of Thrombosis and Haemostasis, 5: 1904–1913

ORIGINAL ARTICLE

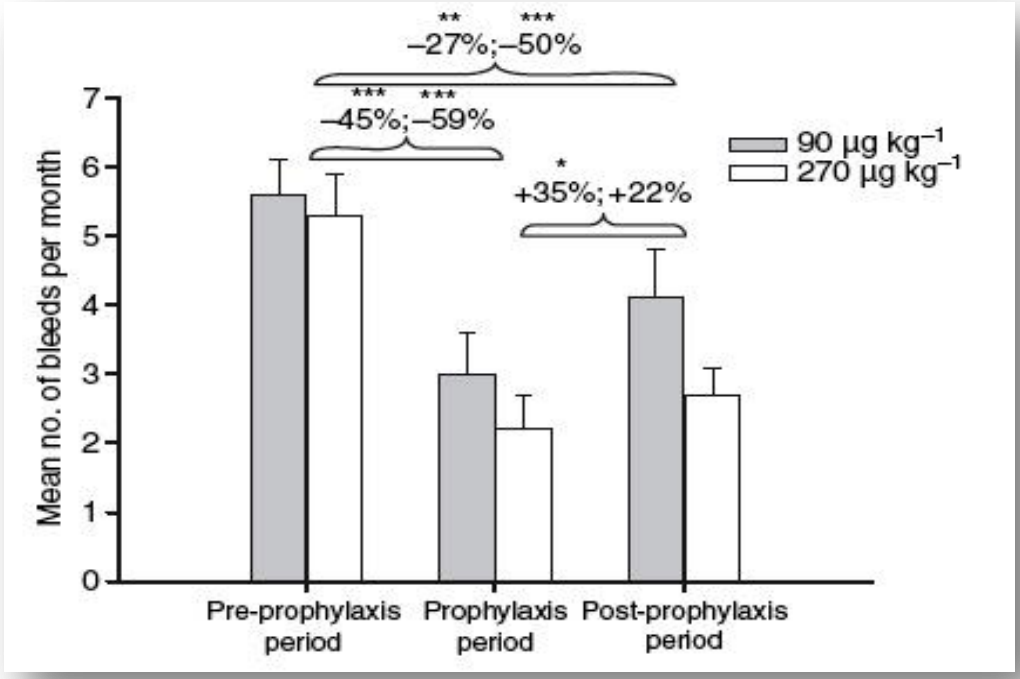
Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors

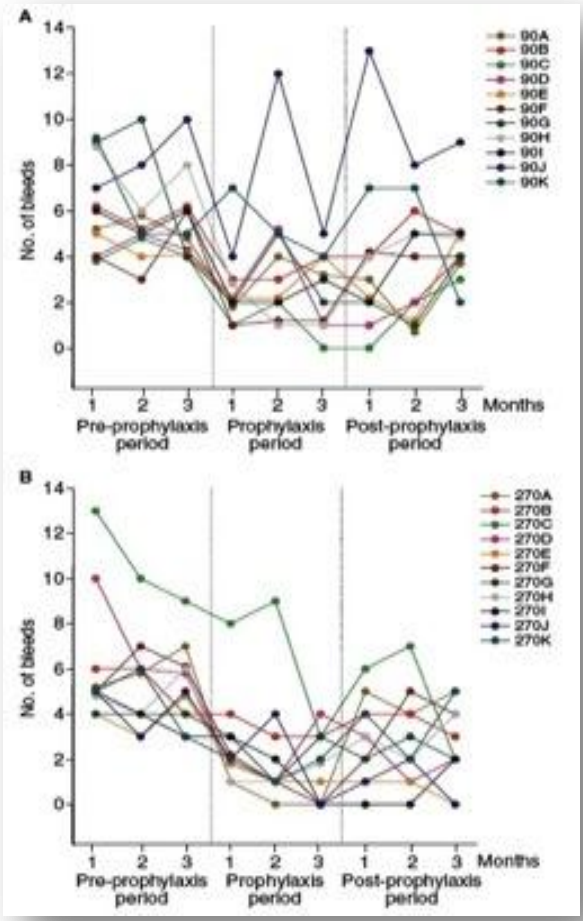
. A. KONKLE,* L. S. EBBESEN,† E. ERHARDTSEN,† R. P. BIANCO,‡ T. LISSITCHKOV,§ L. RUSEN¶ and
M. A. SERBAN**
*Penn Comprehensive Hemophilia Program, University of Pennsylvania, PA, USA; †Novo Nordisk A/S, Bagsvaerd, Denmark; ‡Instituto de Investigaciones Hematológicas, Academia Nacional de Medicina, Buenos Aires, Argentina; §National Centre of Hematology and Transfusiology, Sofia, Bulgaria; ¶National Institute of Hematology 'C.T. Nicolau', Bucharest, Romania; and **Clinical Pediatric Emergency Hospital 'Louis Turcanu', Timisoara, Romania

To cite this article: Konkle BA, Ebbesen LS, Erhardtsen E, Bianco RP, Lissitchkov T, Rusen L, Serban MA. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost* 2007; 5: 1904–13.

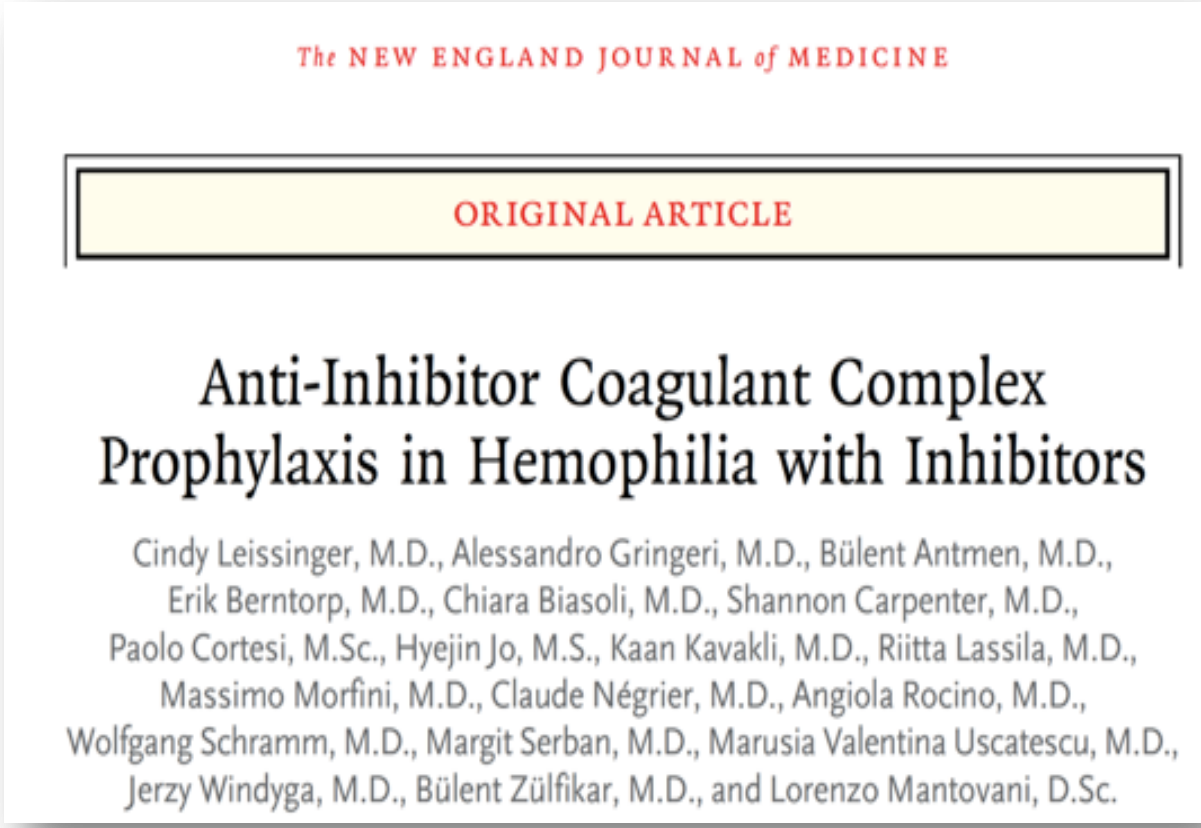


Profilaxis secundaria: Experiencia con rFVIIa





Pro-FEIBA



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

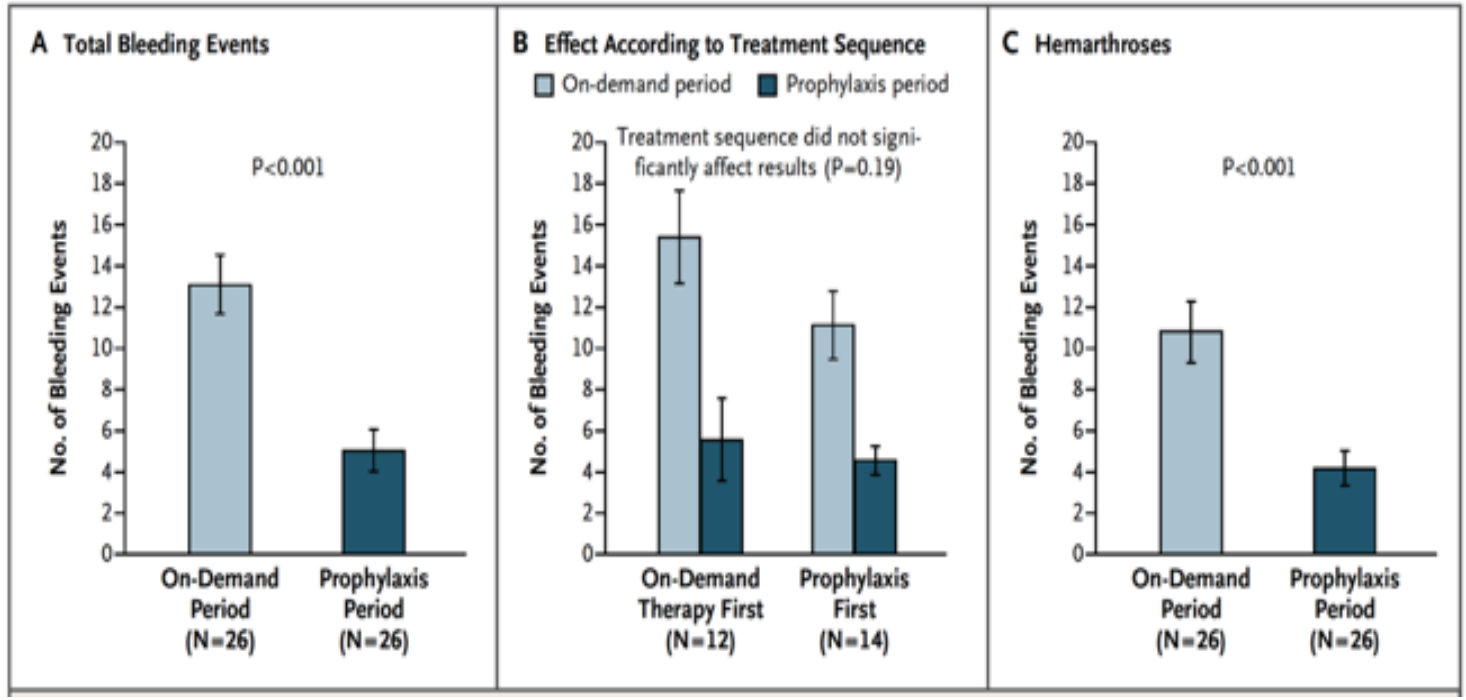
Anti-Inhibitor Coagulant Complex Prophylaxis in Hemophilia with Inhibitors

Cindy Leissinger, M.D., Alessandro Gringeri, M.D., Bülent Antmen, M.D., Erik Berntorp, M.D., Chiara Biasoli, M.D., Shannon Carpenter, M.D., Paolo Cortesi, M.Sc., Hyejin Jo, M.S., Kaan Kavakli, M.D., Riitta Lassila, M.D., Massimo Morfini, M.D., Claude Négrier, M.D., Angiola Rocino, M.D., Wolfgang Schramm, M.D., Margit Serban, M.D., Marusia Valentina Uscatescu, M.D., Jerzy Windyga, M.D., Bülent Zülfikar, M.D., and Lorenzo Mantovani, D.Sc.

Pro-FEIBA


34 Patients underwent randomization
17 Were assigned to prophylaxis (mo 1–6)
17 Were assigned to on-demand therapy (mo 1–6)
1 Withdrew before start of study
1 Withdrew at 2 mo
1 Was lost to follow-up at 3 mo
1 Withdrew at 4 mo
1 Withdrew at 6 mo
Washout (mo 7–9)
1 Died at 8 mo
14 Were assigned to on-demand therapy (mo 10–15)
14 Were assigned to prophylaxis (mo 10–15)
1 Withdrew because of allergic reaction at 10 mo
1 Died at 13 mo
14 Could be evaluated per protocol
12 Could be evaluated per protocol

Pro-FEIBA



RESULTS

Thirty-four patients underwent randomization; 26 patients completed both treatment periods and could be evaluated per protocol for the efficacy analysis. As compared with on-demand therapy, prophylaxis was associated with a 62% reduction in all bleeding episodes (P<0.001), a 61% reduction in hemarthroses (P<0.001), and a 72% reduction in target-joint bleeding (≥3 hemarthroses in a single joint during a 6-month treatment period) (P<0.001). Thirty-three randomly assigned patients re-

Pro-pact

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

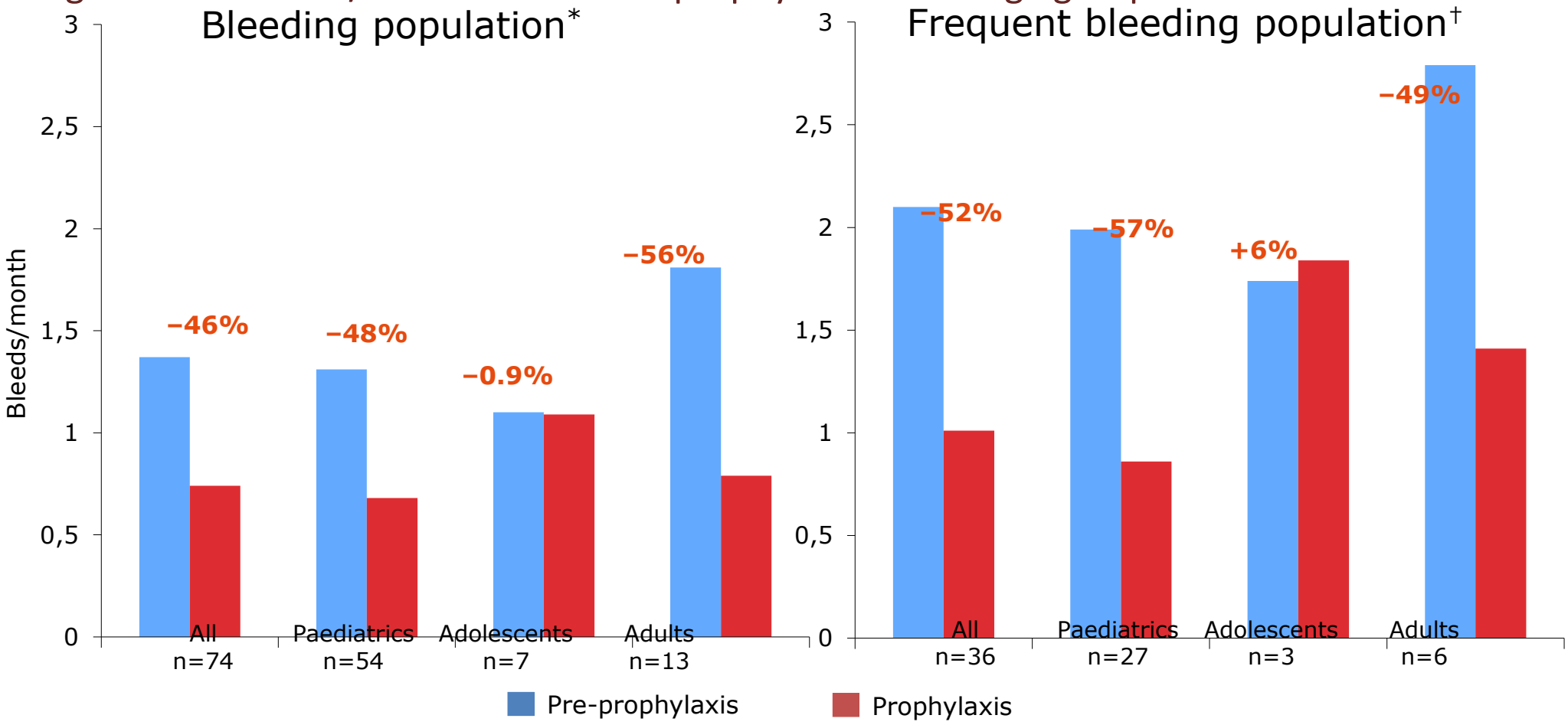
Regular Article

PRO-PACT: Retrospective observational study on the prophylactic use of recombinant factor VIIa in hemophilia patients with inhibitors

Guy Young [a,*], Guenter Auerswald [b], Victor Jimenez-Yuste [c], Thierry Lambert [d], Massimo Morfini [e], Elena Santagostino [f], Victor Blanchette [g]

Pro-PACT

Change in total bleeds/month with rFVIIa prophylaxis across age groups



Paediatrics: <12 years; Adolescents: 12–17 years; Adults: ≥18 years

*>0 and †≥1 bleeds/month pre-prophylaxis
Bleed frequencies are based on weighted means

Profilaxis Primaria: Experiencia con rFVIIa

"Primary prophylaxis" with rFVIIa in a patient with severe haemophilia a and inhibitor

Victor Jimenez-Yuste, Manuel Quintana, Maria Teresa Alvarez, Monica Martin-Salces and Fernando Hernandez-Navarro

The development of antibodies that inhibit or neutralize replacement therapy with factor VIII or factor IX is today the most serious complication of haemophilia and its treatment. Inhibitor patients have more severe joint morbidity than patients without inhibitors, and older adults experience significant orthopaedic disabilities. Because of the serious and disabling consequences of persistent inhibitors, there is considerable clinical and research interest in establishing effective bypassing agent regimens to prevent bleeding in inhibitor patients in much the same way as prophylaxis procedure works in noninhibitor patients. In the majority of these patients, the bypass agent was used as a secondary prophylactic. In this report, the use of recombinant factor VIIa [illegible] patient with haemophilia A and high-titre inhibitor is described. *Blood Coagul Fibrinolysis* 19:719–720

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Keywords: haemophilia, inhibitor, prophylaxis, recombinant factor VIIa

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Profilaxis: Experiencia en nuestro Centro

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Haemophilia

ORIGINAL ARTICLE *Inhibitors*

Prophylaxis in 10 patients with severe haemophilia A and inhibitor: different approaches for different clinical situations

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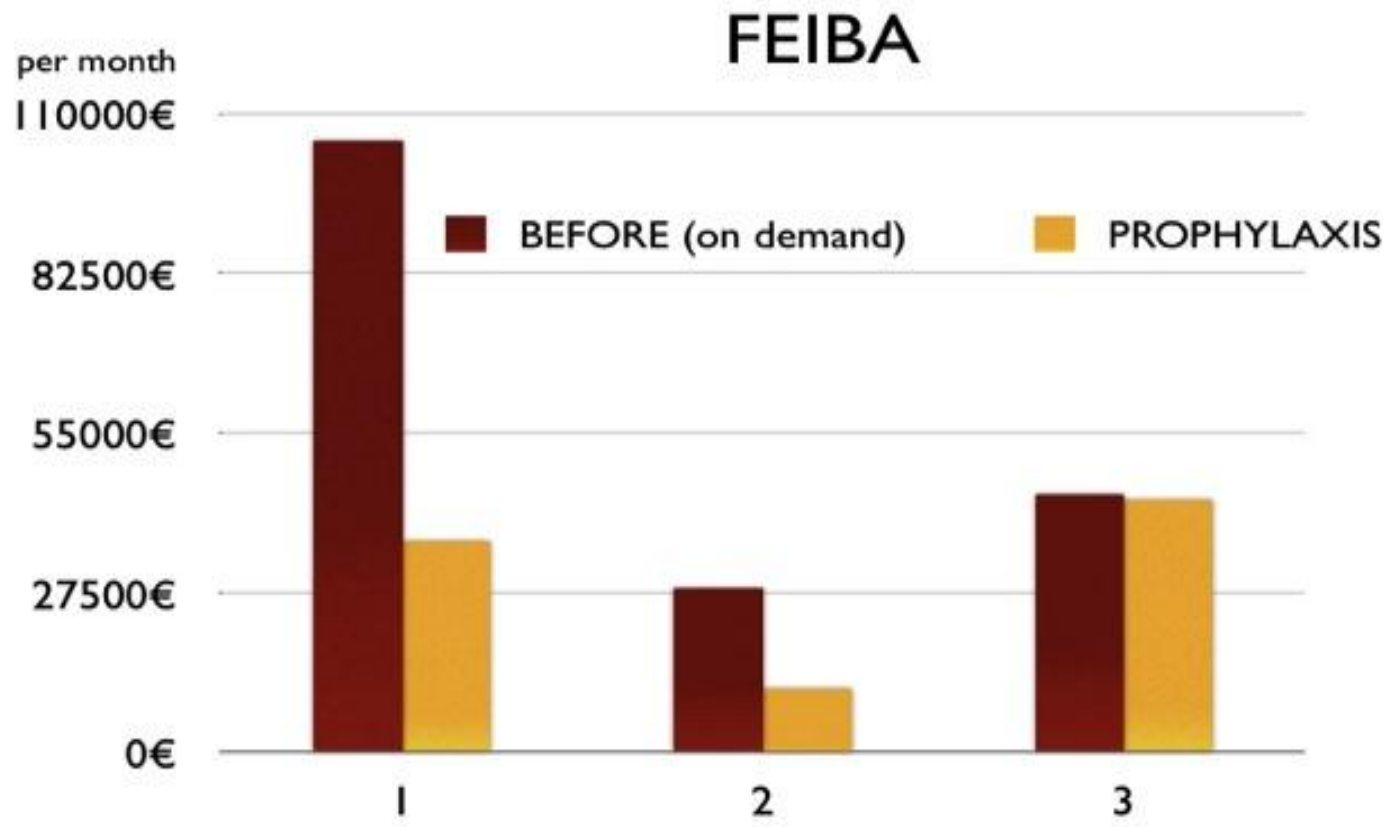
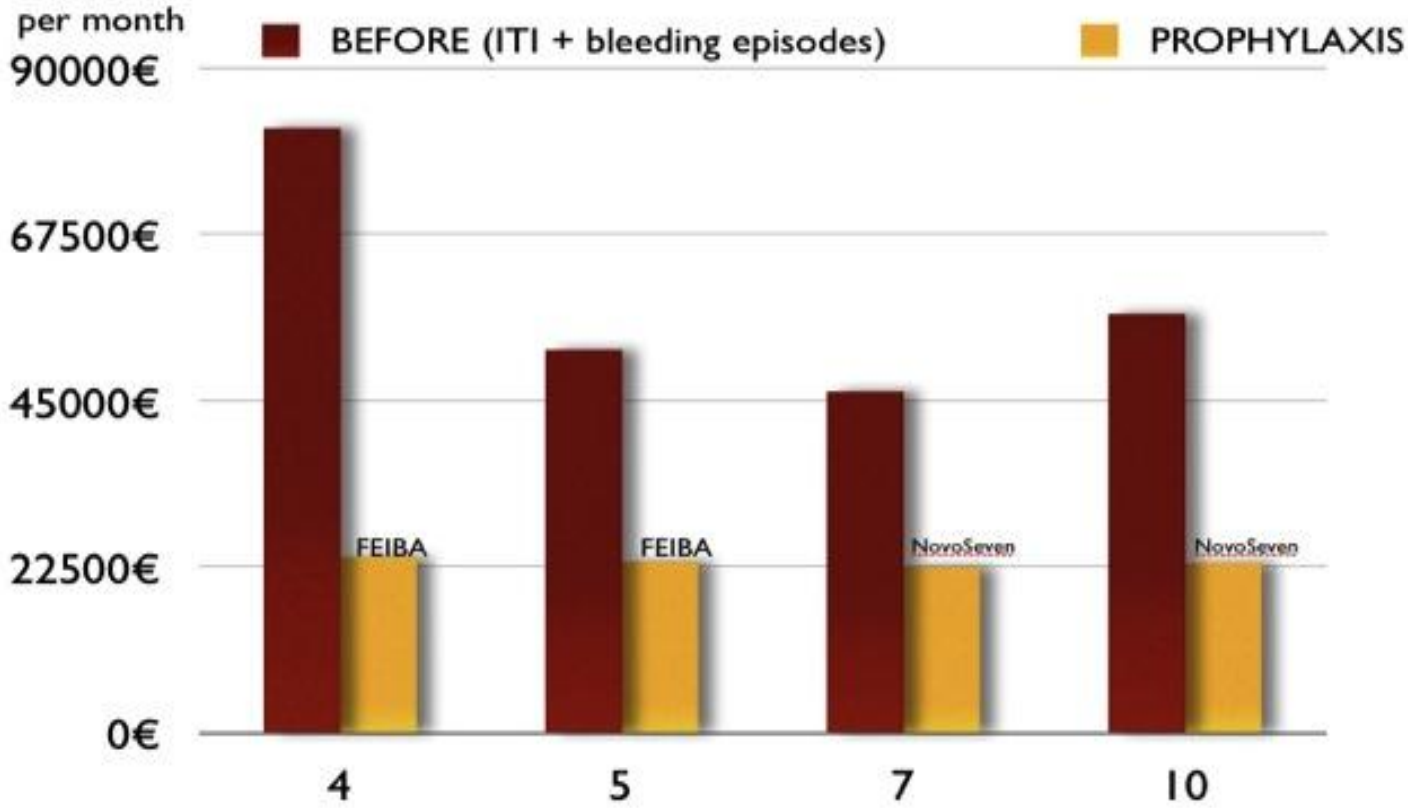
Patient	Age at prophylaxis (years)	Treatment Schedule before prophylaxis	Regimen	Duration (months)
1	15	On demand FEIBA	FEIBA 50 U/Kg/3 doses week	22
2	5	On demand FEIBA	FEIBA 50 U/Kg/3 doses week	24
3	31	On demand FEIBA	FEIBA 50 U/kg/48h	11
4	7	ITI + On demand bypass agents	FEIBA 60 U/kg/48h	13
5	11	ITI+ On demand bypass agents	FEIBA 70 U/kg/48h	11
6	2	On demand FVIII	rFVIIa 90 µg/kg/d	22
7	2	ITI+ On demand rFVIIa	rFVIIa 90 µg/kg/d	6
8	1,5	On demand FVIII	rFVIIa 100 µg/kg/d	9
9	1	Prophylaxis FVIII	rFVIIa 100 µg/kg/d	8
10	3	ITI + On demand rFVIIa	rFVIIa 90 µg/kg/d	19

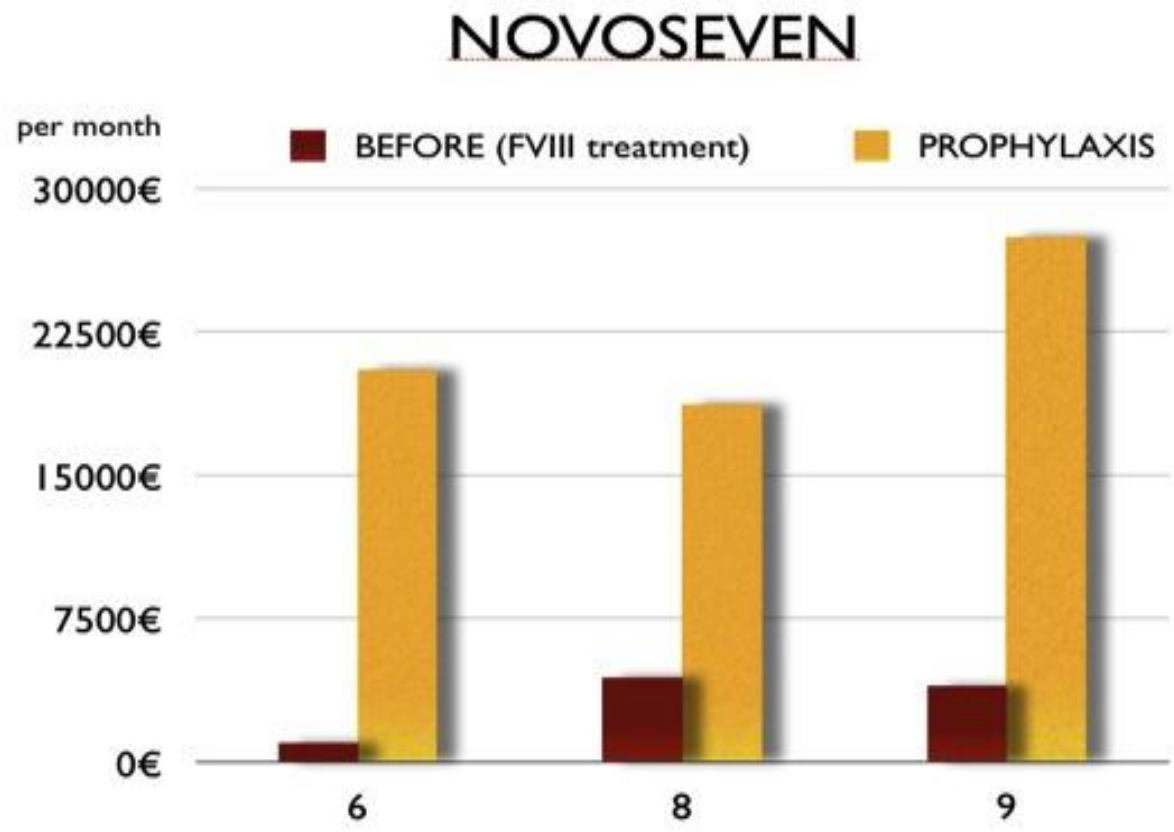
Profilaxis : Costes



Profilaxis secundaria: Experiencia con rFVIIa



Profilaxis secundaria: Experiencia con rFVIIa



Prophylaxis: Spanish Experiencie

JOURNAL OF COAGULATION DISORDERS REVIEW ARTICLE

Retrospective Evaluation of Secondary Episodic Prophylaxis with rFVIIa in Hemophilia Patients with Inhibitor

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Haemophilia

Haemophilia (2011), 1–9

REVIEW ARTICLE

When should prophylaxis therapy in inhibitor patients be considered?

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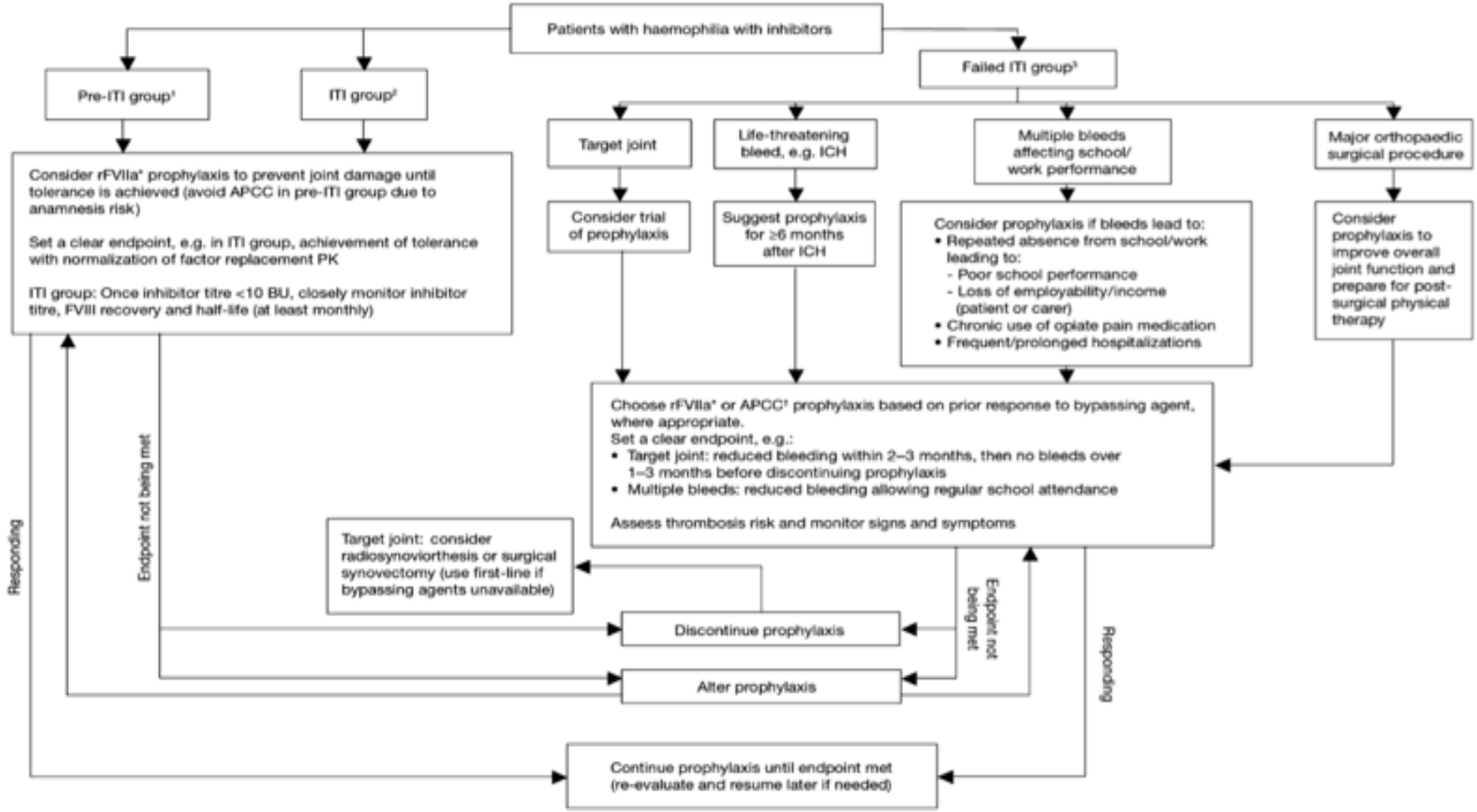
Patients with haemophilia with inhibitors
Pre-ITI group[1]
ITI group[2]
Failed ITI group[3]
Consider rFVIIa* prophylaxis to prevent joint damage until tolerance is achieved (avoid APCC in pre-ITI group due to anamnesis risk)
Set a clear endpoint, e.g. in ITI group, achievement of tolerance with normalization of factor replacement PK
ITI group: Once inhibitor titre <10 BU, closely monitor inhibitor titre, FVIII recovery and half-life (at least monthly)
Target joint
Life-threatening bleed, e.g. ICH
Multiple bleeds affecting school/ work performance
Major orthopaedic surgical procedure
Consider trial of prophylaxis
Suggest prophylaxis for ≥6 months after ICH
Consider prophylaxis if bleeds lead to:
• Repeated absence from school/work leading to:
- Poor school performance
- Loss of employability/income (patient or carer)
• Chronic use of opiate pain medication
• Frequent/prolonged hospitalizations
Consider prophylaxis to improve overall joint function and prepare for post-surgical physical therapy
Choose rFVIIa* or APCC† prophylaxis based on prior response to bypassing agent, where appropriate.
Set a clear endpoint, e.g.:
• Target joint: reduced bleeding within 2–3 months, then no bleeds over 1–3 months before discontinuing prophylaxis
• Multiple bleeds: reduced bleeding allowing regular school attendance
Assess thrombosis risk and monitor signs and symptoms
Responding
Endpoint not being met
Target joint: consider radiosynoviorthesis or surgical synovectomy (use first-line if bypassing agents unavailable)
Discontinue prophylaxis
Alter prophylaxis
Endpoint not being met
Responding
Continue prophylaxis until endpoint met (re-evaluate and resume later if needed)

Consideraciones: Profilaxis

1. ¿Se debe comenzar al desarrollo del inhibidor?
2. ¿Debe continuar durante la ITI?
3. ¿Cual es el mejor esquema para un profilaxis?
4. ¿Como debe ser el acceso venoso estos casos?
5. ¿Cual es coste y el coste-beneficio de la profilaxis?
6. ¿Cuales pueden ser las complicaciones de la profilaxis?

CONSIDERACIONES EN RELACION AL TRATAMIENTO

- Tratamiento muy complejo
- Importancia de la precocidad
- MANTENIMIENTO TIEMPO ADECUADO
- IDENTIFICAR LOS FRACASOS
- POSIBILIDAD DE CAMBIO
- PAPEL DE LA PROFILAXIS

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