Hospital Universitario La Paz

Parámetros diagnósticos y de tratamiento en la Hemofilia

Mª Teresa Álvarez Román

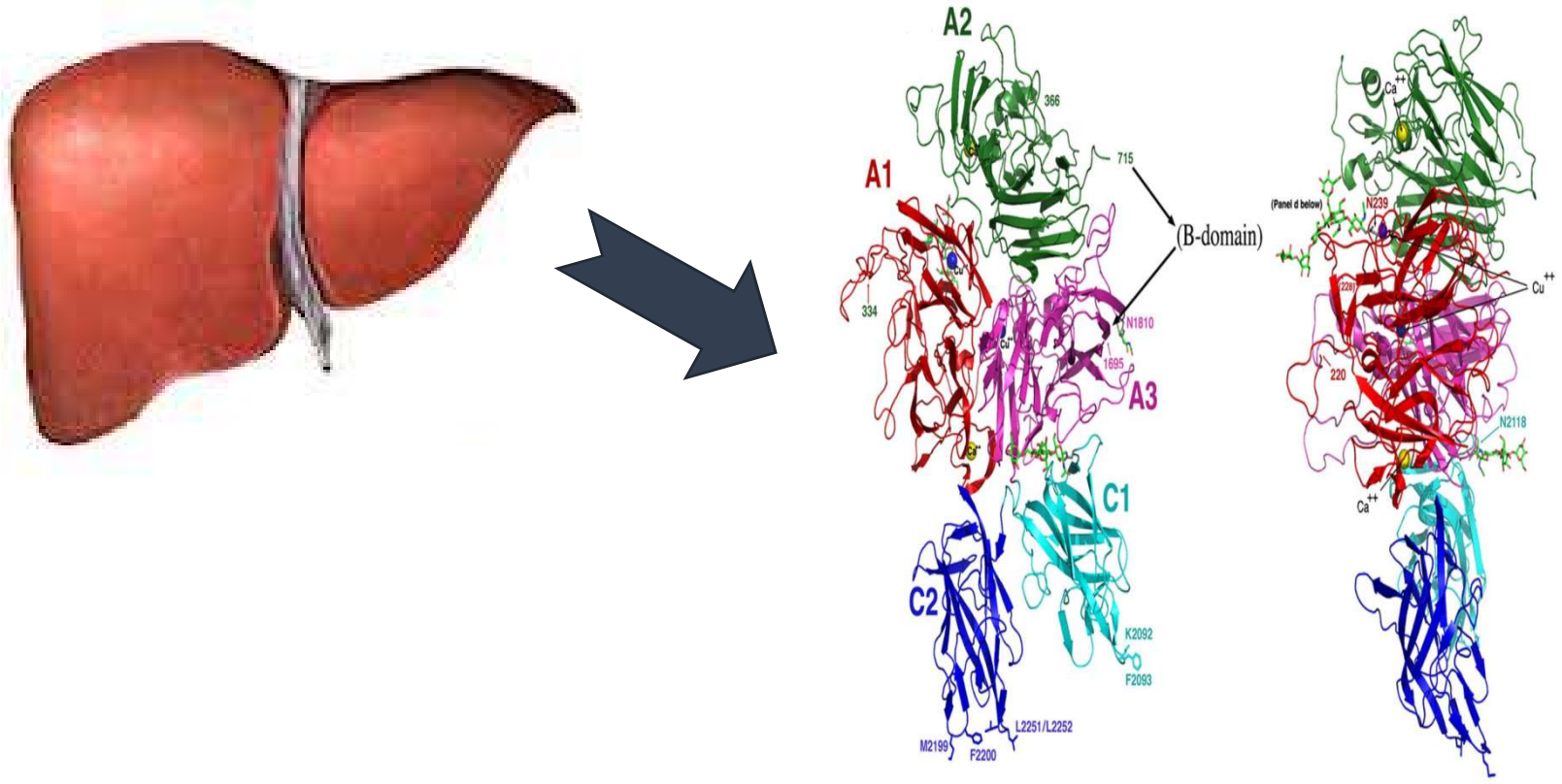
Jefe de Sección de Hemostasia

Temas a tratar

- **Parámetros diagnósticos en Hemofilia**

- **Tratamiento y monitorización**

Síntesis de FVIII



Journal of Thrombosis and Haemostasis, **12**: 36–42 DOI: 10.1111/jth.12412

IN FOCUS

Human liver sinusoidal endothelial cells but not hepatocytes contain factor VIII

T. SHAHANI,* K. COVENS,† R. LAVEND'HOMME,† N. JAZOULI,‡ E. SOKAL,‡ K. PEERLINCK† and M. JACQUEMIN†

**Department of Genetics and Molecular Medicine, Zanjan University of Medical Sciences, Zanjan, Iran; †Department of Cardiovascular Sciences, Center for Molecular and Vascular Biology, KU Leuven, Leuven; and ‡Laboratory of Pediatric Hepatology and Cell Therapy, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium*

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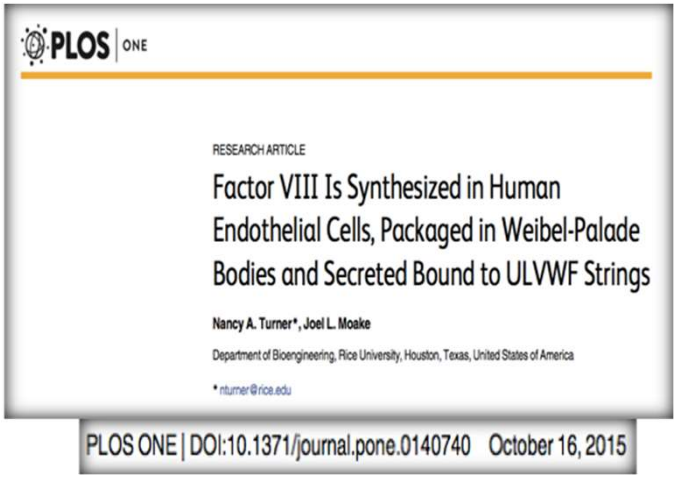
in LSECs than in hepatocytes. *Conclusions:* Our data demonstrate that LSECs, but not hepatocytes, contain measurable amounts of FVIII:C, and suggest that the former are the main cells producing FVIII in the human liver.



PLOS | ONE

RESEARCH ARTICLE

Factor VIII Is Synthesized in Human Endothelial Cells, Packaged in Weibel-Palade Bodies and Secreted Bound to ULVWF Strings

Nancy A. Turner*, Joel L. Moake

Department of Bioengineering, Rice University, Houston, Texas, United States of America

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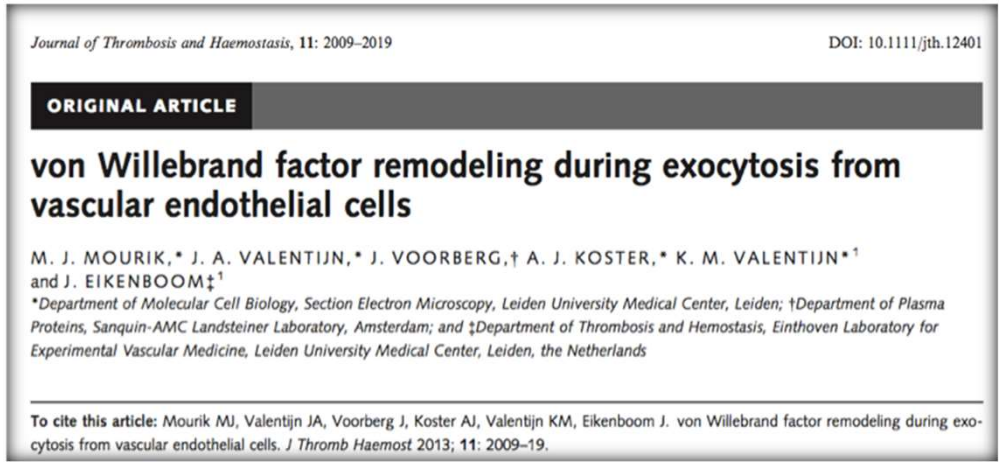
PLOS ONE | DOI:10.1371/journal.pone.0140740 October 16, 2015

El FVIII y el FVW se sintetizan en las células endoteliales, se almacenan en los cuerpos de Weibel-Palade y se liberan juntos al torrente circulatorio



Journal of Thrombosis and Haemostasis, **11**: 2009–2019 DOI: 10.1111/jth.12401

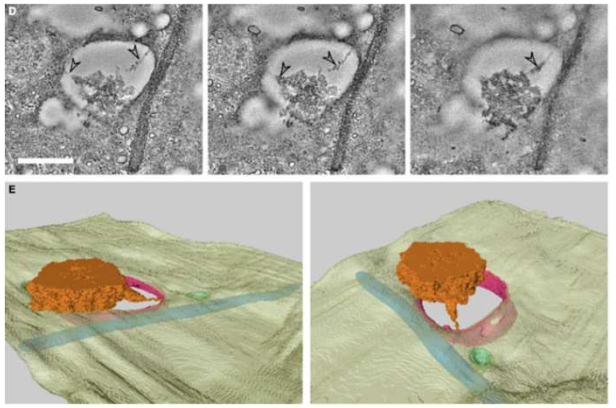
ORIGINAL ARTICLE

von Willebrand factor remodeling during exocytosis from vascular endothelial cells

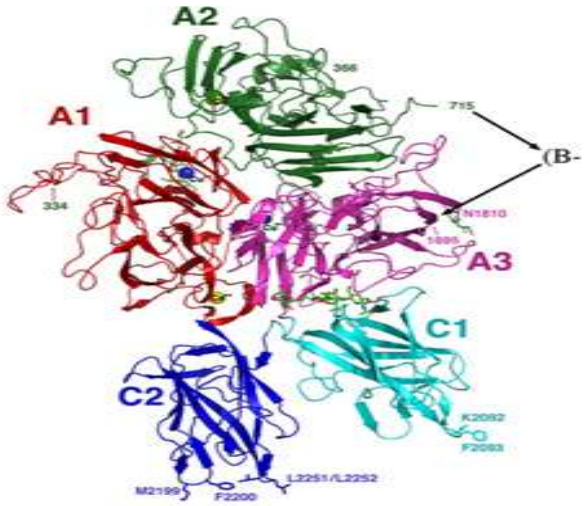
M. J. MOURIK,* J. A. VALENTIJN,* J. VOORBERG,† A. J. KOSTER,* K. M. VALENTIJN*[1] and J. EIKENBOOM‡[1]

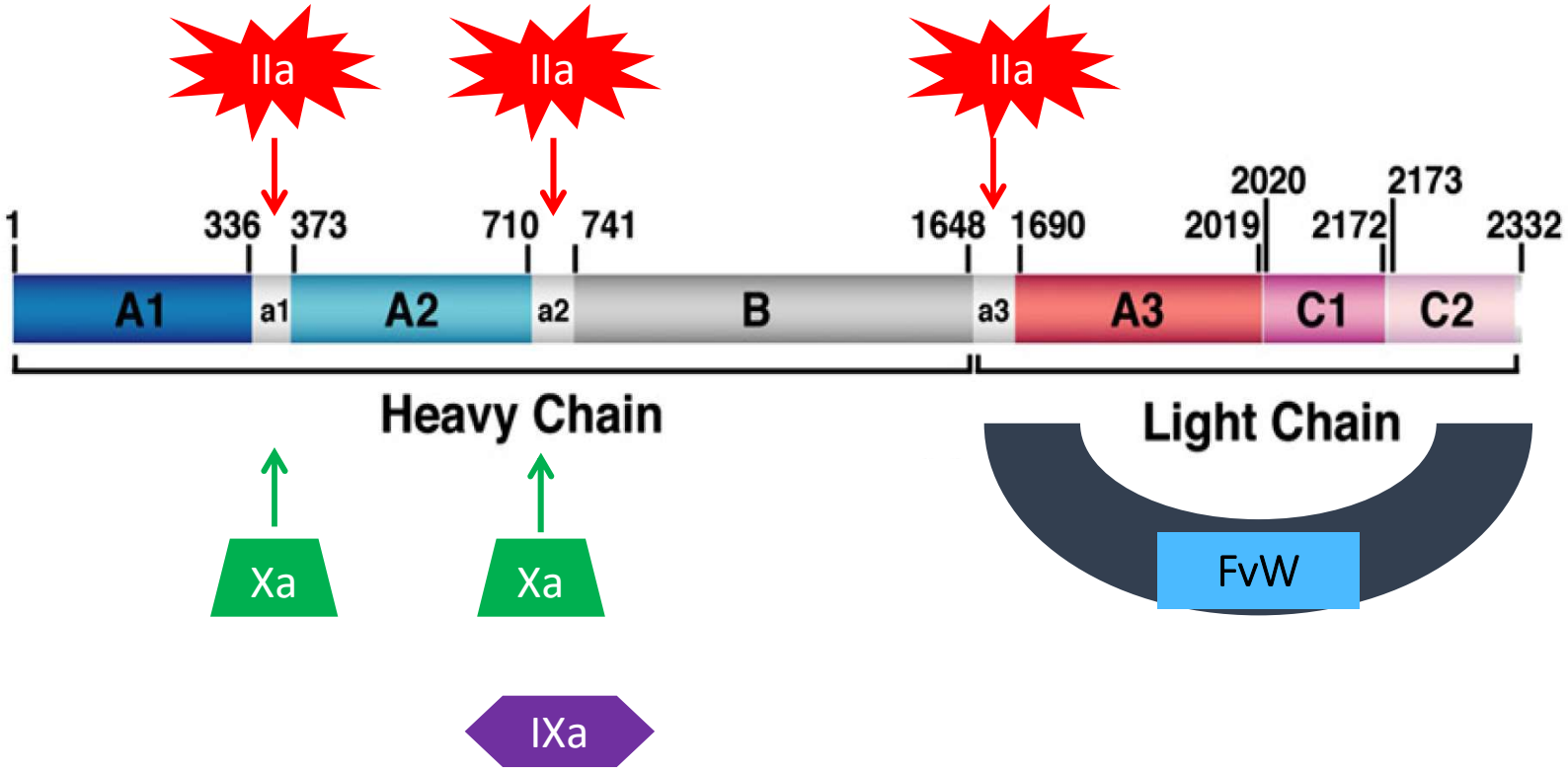
*Department of Molecular Cell Biology, Section Electron Microscopy, Leiden University Medical Center, Leiden; †Department of Plasma Proteins, Sanquin-AMC Landsteiner Laboratory, Amsterdam; and ‡Department of Thrombosis and Hemostasis, Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands

To cite this article: Mourik MJ, Valentijn JA, Voorberg J, Koster AJ, Valentijn KM, Eikenboom J. von Willebrand factor remodeling during exocytosis from vascular endothelial cells. *J Thromb Haemost* 2013; **11**: 2009–19.

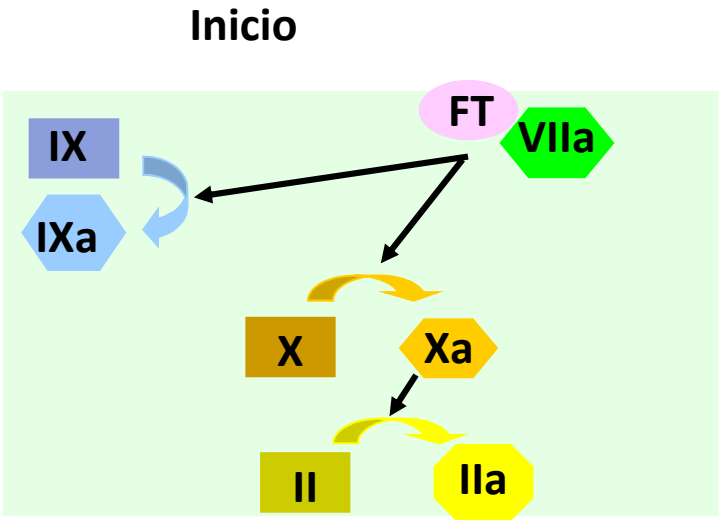


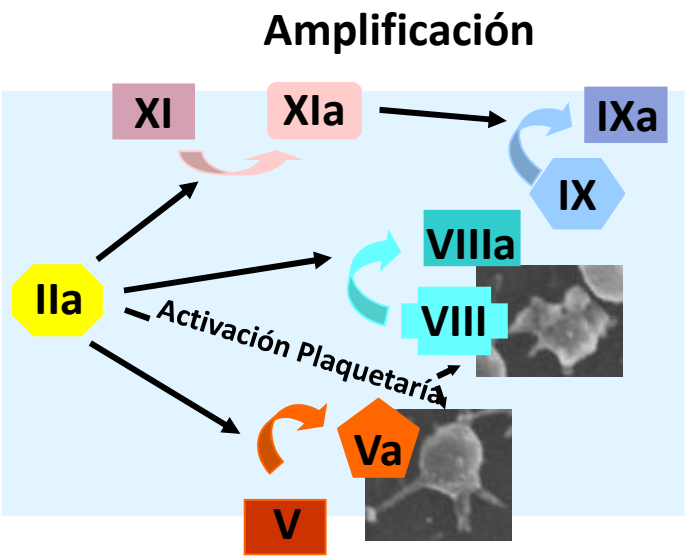
Estructura del FVIII

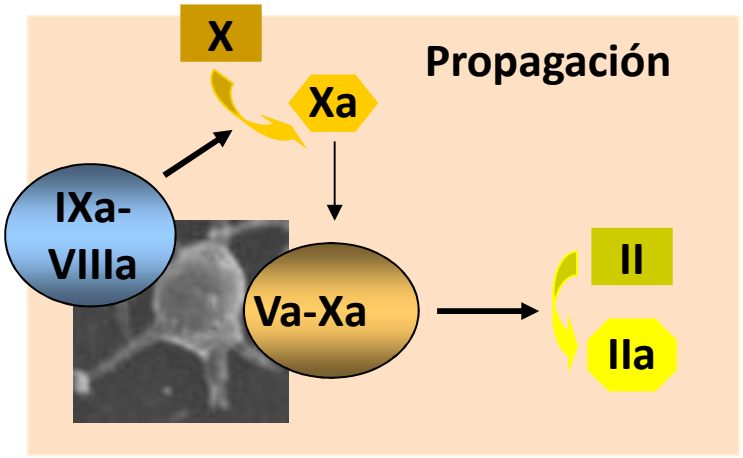




Papel del FVIII en la coagulación





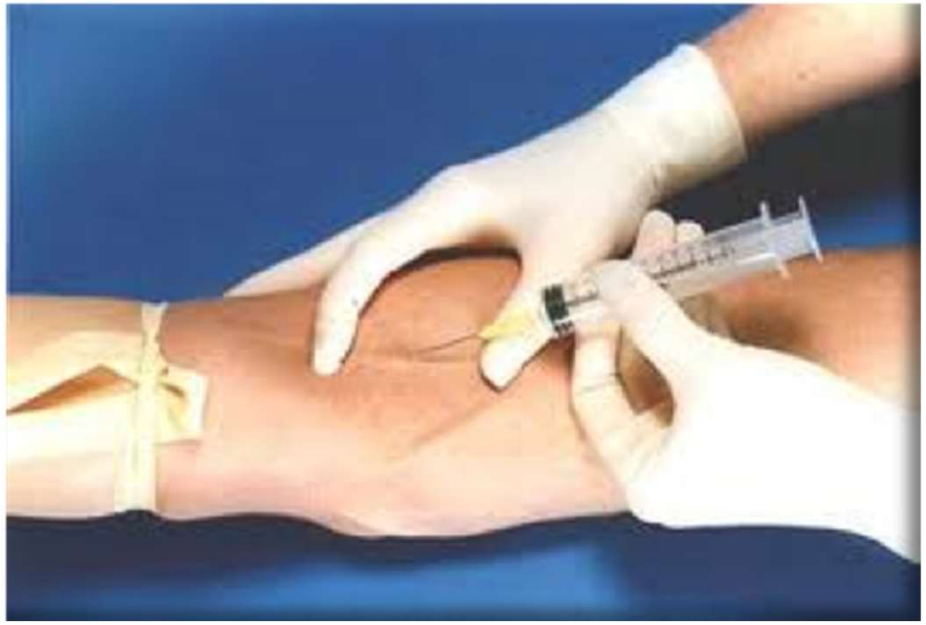


Papel fundamental en el paso

de FX ⟶ FXa.

Actúa como cofactor.

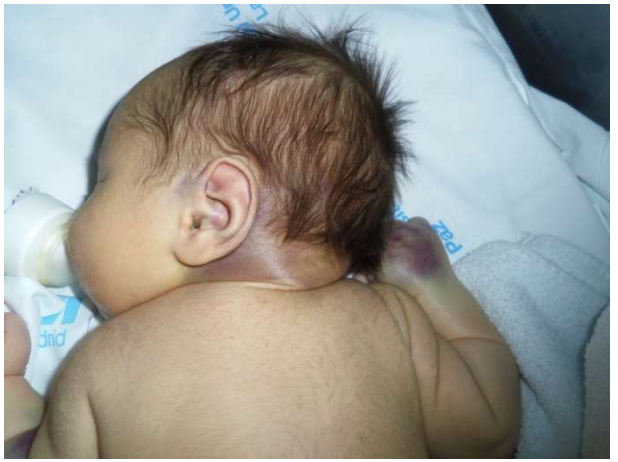
Diagnóstico. Fase preanalítica



Determinaciones necesarias

Table 41.1 Laboratory procedures commonly used in the diagnosis of hemophilia.

Platelet count	Platelet aggregation
TTPa	Agonists: collagen, ADP, ristocetin Activated partial thromboplastin time
PT	Prothrombin time
FVIII:C	Factor VIII procoagulant function (one-stage and/or chromogenic substrate method)
Factor VIII:Ag	Factor VIII antigenic determination
vWF: RCo	von Willebrand factor ristocetin cofactor
vWF:Ag	von Willebrand factor antigen
vWF:FVIIIB	von Willebrand factor/FVIII-binding capacity
Fibrinogen	Functional assay for fibrinogen
Factor XIII	Enzymatic factor XIII assay



Dosificación de FVIII

¿Por qué es importante una correcta dosificación?

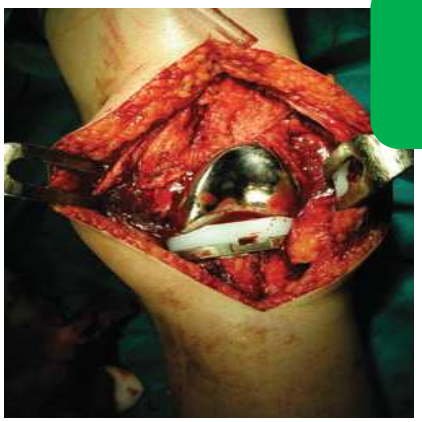
¿Qué problemas se nos presentan en la dosificación de FVIII?

¿Por qué es importante una correcta dosificación?

Diagnóstico correcto

Gravedad	FVIII:C	Clínica
Grave	<1%	Grave/Espontánea
Moderada	1-5%	Moderada
Leve	5-30%	Leve tras tr. o Q

Monitorización de tratamiento sustitutivo

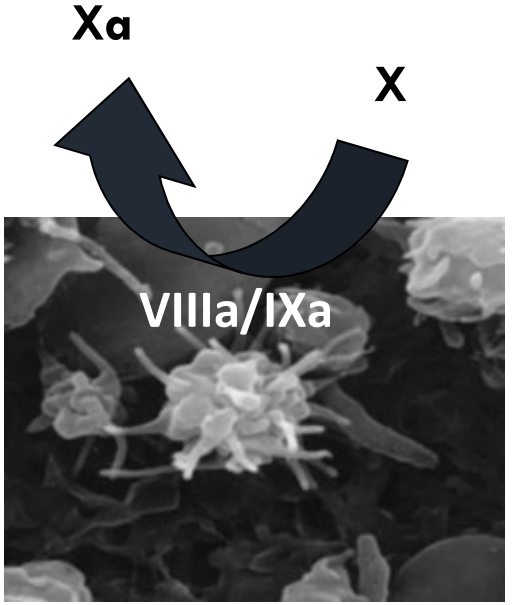


FVIII:C 100 %

¿Por qué es importante una correcta dosificación?

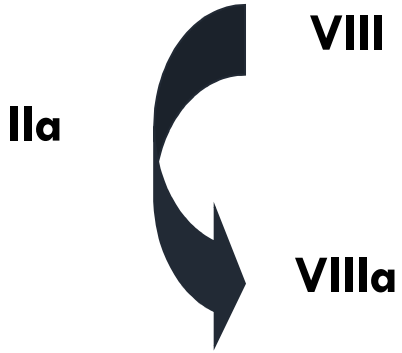
Potencia real de un concentrado

¿Qué problemas se nos presentan en la dosificación?



1) PAPEL DEL FVIII: COFACTOR

Actividad hay que medirla de forma indirecta.



2) NECESIDAD DE ACTIVACIÓN

Activación previa a ejercer como cofactor

La determinación resultaría mucho más sencilla si el FVIII no necesitara de una activación previa.

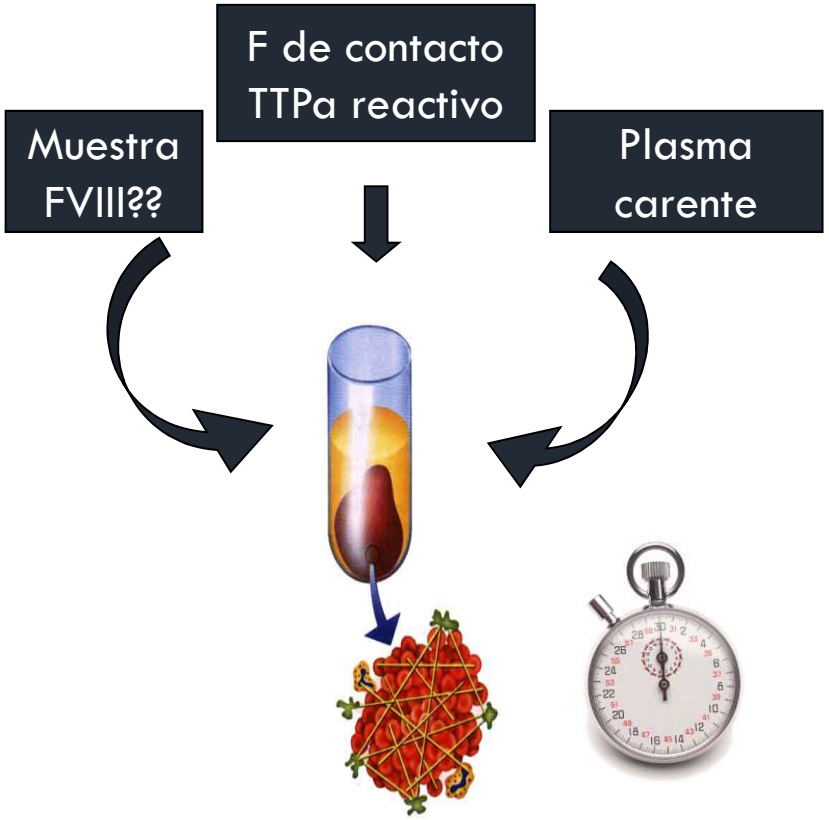
Métodos para la dosificación del FVIII

Miden el papel del FVIII como cofactor en la activación del FX

1. De forma indirecta: **MÉTODO COAGULATIVO**
2. De forma directa: **MÉTODO CROMOGÉNICO**

Método coagulativo en una etapa *(one-stage assay)*

Mide la capacidad del FVIII contenido en una muestra de **acortar el tiempo de formación de un coágulo** del plasma de un hemofílico A, tras una activación de la fase contacto y recalcificación.



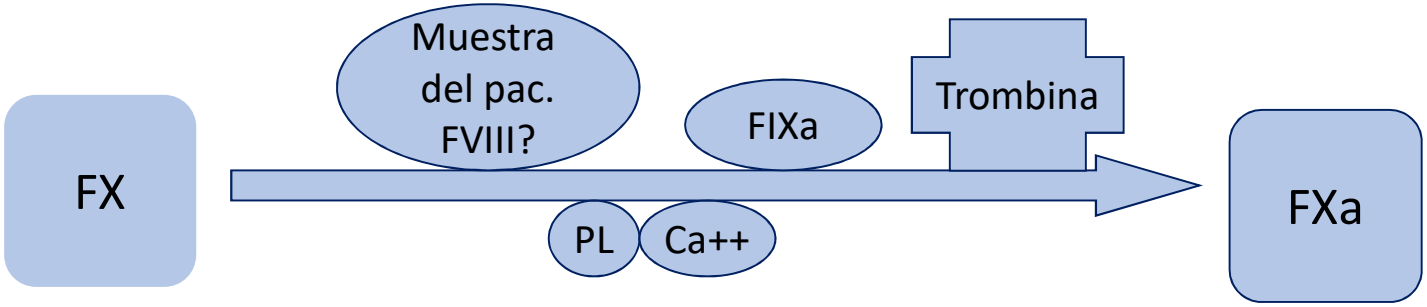
SITUACIÓN IDEAL

La **cantidad de FVIII existente en la muestra** es la que debe influir como **único factor** en el resultado final, cuando todos los demás factores se hallan en exceso.

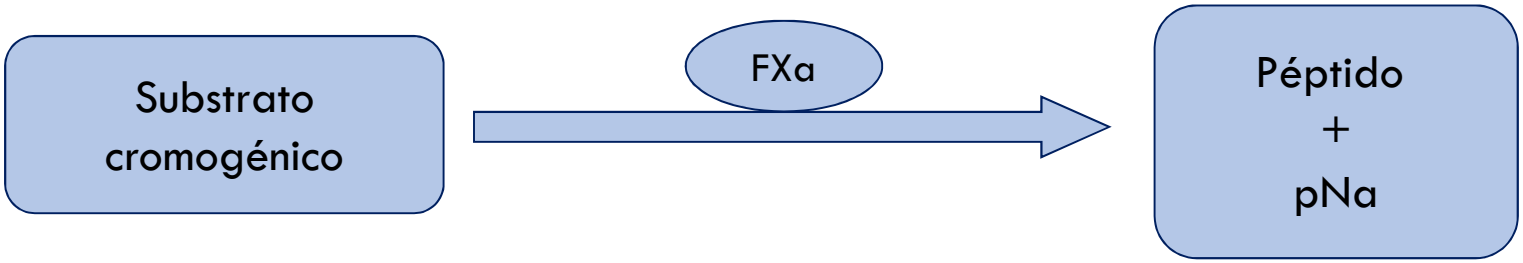
Método cromogénico

1ª reacción: activación del FX dependiente de FVIII

Muestra a estudio incubada con trombina, FIXa, FX, Ca++ y PL

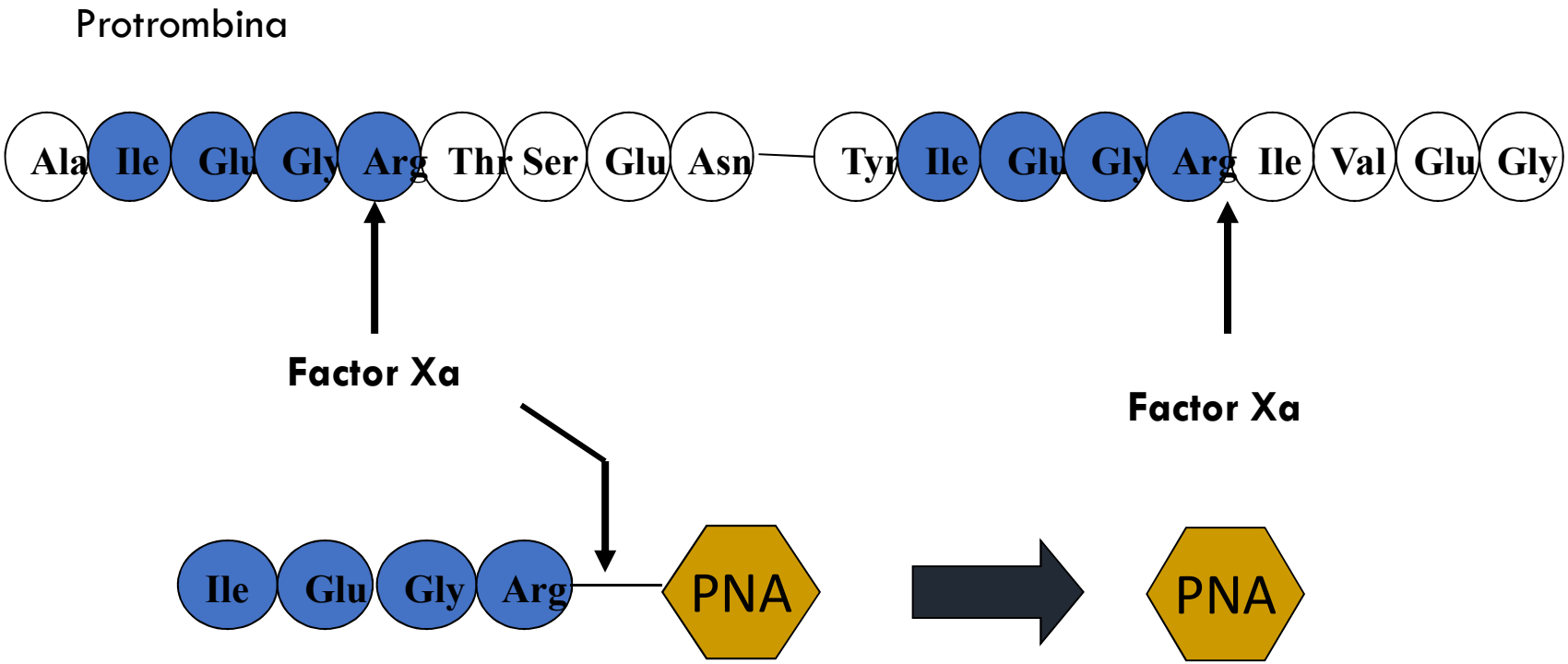


2ª reacción: mide la cantidad de FXa producido en la 1ª R



Hidrólisis de substrato cromogénico, liberación de color medido mediante espectrofotómetro a 405 nm

Método cromogénico

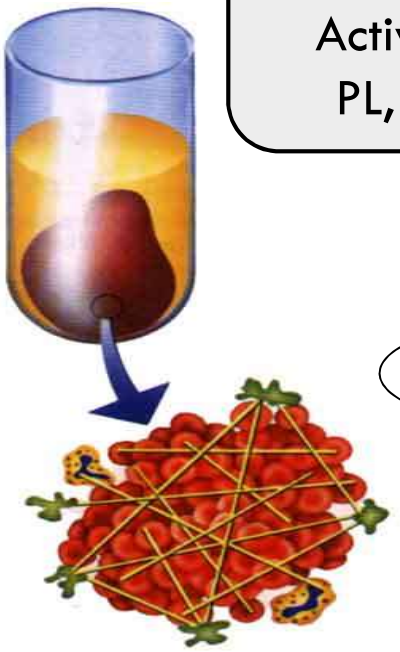


SUSTRATOS CROMOGÉNICOS

Péptidos sintéticos que reaccionan con enzimas proteolíticas conduciendo a la formación de color. Afinidad a la acción del enzima similar al substrato natural.

MÉTODO COAGULATIVO

Muestra FVIII?
Plasma carente
Activador
PL, Ca^{2+}

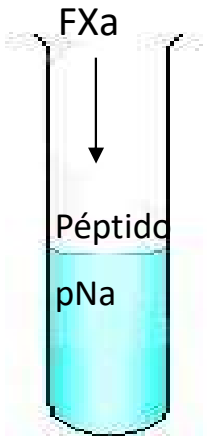


Fibrina

COAGULÓMETRO

MÉTODO CROMOGÉNICO

Muestra FVIII?
Trombina
FIXa, FX
PL, Ca^{2+}



Liberación de color

ESPECTROFOTÓMETRO

Diferencias entre métodos

Método coagulativo

- Langdell, 1953
- Derivado TTPa
- Barato, sencillo y automatizable
- Formación suprafisiológica FIXa
- Preactivación del FVIII
- Importante variabilidad interlaboratorios.

Método cromogénico

- Rosén, 1984
- Sustratos cromogénicos
- Reactivos comerciales
- Fácilmente automatizable
- **Caro para pocas muestras**
- Exigido para la titulación de concentrados
- **MENOR VARIABILIDAD INTERLABORATORIO**
- **UTILIDAD PARA LA MONITORIZACIÓN DE LOS EHL**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA U.S. FOOD & DRUG ADMINISTRATION

Método cromogénico

Método coagulativo

Temas a tratar

- Parámetros diagnósticos en Hemofilia

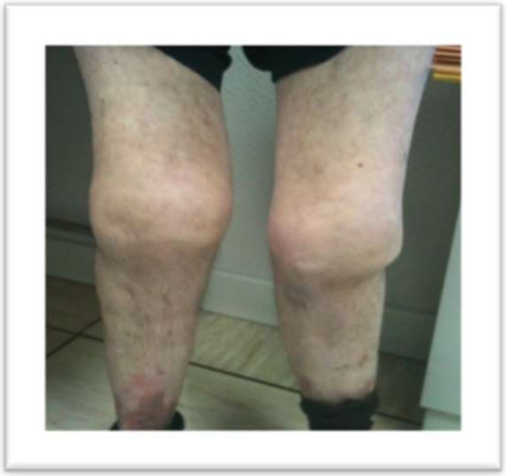
- **Tratamiento y monitorización**

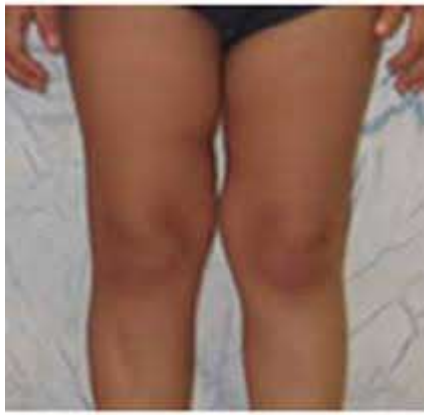
Tratamiento de la Hemofilia

Demanda

Profilaxis

Fundamento de la profilaxis





Gravedad	FVIII:C	Clínica
Grave	<1%	Grave Espontánea
Moderada	1-5%	Menos artropatía

Beneficios de la profilaxis

- >90% reducción de sangrado articular (AJBR<1)
- Mayor protección articular

Manco-Johnson MJ et al. N Engl J Med. 2007;357:535-544

- Menos discapacidad, menor necesidad de cirugía ortopédica.
- Menos dolor, menos absentismo escolar y laboral, mejor QoL

Soucie JM et al. Haemophilia. 2017;23:e287-e293

- Profilaxis protege de sangrados de riesgo vital como HIC, aumentando la esperanza de vida de los PWH

Andersson NG et al. Br J Haematol. 2017;179:298-307

Tratamientos disponibles para el tratamiento de la Hemofilia A

Concentrados plasmáticos						
Producto	**Principio activo**	**Presentaciones FVIII/FVW**	**Método fraccionamiento**	**Inactivación viral**	**Estabilización**	**Indicación aprobada**
Beriate P®	FVIII	250, 500, 1000	Cromatografía afinidad por intercambio iónico	Pasteurización	Sacarosa Glicina	Hemofilia A
Fanhdi®	Proteínas, FVIII, FVW	250/300, 500/600, 1.000/1.200, 1.500/1.800	Cromatografía afinidad a la heparina	S/D + 80 ºC, 72 h	Albúmina	Hemofilia A Enf. de von Willebrand
Octanate®	FVIII humano	250, 500, 1000	Cromatografía afinidad por intercambio iónico Precipitación con $Al(OH)_3$	S/D + 100 ºC, 30'	FVW	Hemofilia A
Haemate P®	FVIII, FVW	250/600, 500/1.200, 1.000/2.400	Precipitación múltiple	Pasteurización	Albúmina	Hemofilia A Enf. de von Willebrand
Wilate®	FVIII humano, FVW humano	450/400, 500/500, 900/800, 1.000/1.000	Precipitaciones, cromatografía de intercambio iónico y de exclusión por tamaño	TNPB/Triton ×100 calor seco terminal 100 ºC 120', humedad residual controlada	Sacarosa, glicina	Hemofilia A Enf. de von Willebrand

Adaptada de la Guía Terapéutica para el paciente con hemofilia publicada en el año 2012 por el Ministerio de Sanidad, Servicios Sociales e Igualdad[10].

Tratamientos disponibles para el tratamiento de la Hemofilia A

Producto	Principio activo	Presentaciones	Origen	Método de fraccionamiento	Inactivación viral	Estabilización	AE UI/mg FVIII
Helixate NexGen®	Octocog alfa	250, 500, 1.000, 2.000, 3.000	BHK	Recombinante: cromatografía de intercambio de iones y de inmunoafinidad	TNBP/polisorbato 80	Sacarosa	2.600-6.800
Kogenate®	Octocog alfa	250, 500, 1.000, 2.000, 3.000	BHK	Recombinante: cromatografía de intercambio de iones y de inmunoafinidad	TNBP/polisorbato 80	Sacarosa	2.600-6.800
Advate®	Octocog alfa	250, 500, 1.000, 1.500, 2.000, 3.000	CHO	Recombinante	TNBP/polisorbato 80 Triton × 100	Trehalosa y manitol	4.000-10.000
ReFacto AF®	Moroctocog alfa	500, 1.000, 2.000, 3.000	CHO	Recombinante	TNBP/polisorbato 80. Triton × 100	Sacarosa	13.000

Adaptada de la Guía para el paciente con hemofilia publicada en el año 2012 por el Ministerio de Sanidad.

Tratamientos disponibles para el tratamiento de la Hemofilia B

Concentrados Plasmáticos					
Producto	**Principio Activo**	**Presentaciones**	**Método fraccionamiento**	**Inactivación viral**	**AEs/ alb UI/mg FIX**
Factor IX Grifols	Factor IX proteínas	500, 1000, 1500	Precipitación y cromatografía múltiple	Solvente/ detergente; 15nm	150
Mononine	Factor IX	500, 1000	Cromatografía de inmunoafinidad	Tiocianato de sodio y ultrafiltración	190
Immunine	Factor IX	600, 1.200	Cromatografía de intercambio de iones y de interacción hidrofóbica	Polisorbato 80 y calor por vapor, 60ºC, 10h. 190 mbar, luego 80ºC, 1h, 375 mbar	Aprox. 100
Octanine	Factor IX	1000	Cromatografía de intercambio de iones y de afinidad	TNBP/ polisorbato 80 y nanofiltración	100

Adaptada de la Guía para el paciente con hemofilia publicada en el año 2012 por el Ministerio de Sanidad.

Tratamientos disponibles para el tratamiento de la Hemofilia B

Datos de PK	BENEFIX®	RIXUBIS®
IVR	0,73	0,87
$t_{1/2}$	22,4	26,70
AUC	940	1067,8

Datos recogidos de las FT de cada producto

Journal of Blood Medicine

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REVIEW

Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches?

This article was published in the following Dove Press journal:
Journal of Blood Medicine
15 June 2017
Number of times this article has been viewed

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REVIEW

Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches?

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15 June 2017
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Abstract: Hemophilia A (HA) is a common bleeding disorder caused by the deficiency of factor VIII (FVIII) with an incidence of ~1 in 5000 male births. Replacement of FVIII is necessary to prevent and treat bleeding episodes. However, with multiple new drugs in addition to old standards, choosing among the different FVIII treatment options is harder than ever. There are FVIII products that are plasma derived or recombinant, FVIII products designed to extend the half-life of FVIII, and the first single-chain FVIII product, recombinant factor VIII single chain (rFVIII-SC). As development of inhibitors to FVIII continues to be a major problem

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Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches?

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15 June 2017
Number of times this article has been viewed

Generation	Products	FVIII	Technology	Half-life*	Date of US FDA approval
Plasma derived	Antihemophilic factor (Hemofil M®, Koate-DVI®, Monarc-M®, Monoclate-P®)	Full length	Pooled human plasma	14.8–17.5 hours	1966 (Hemofil M), 1974 (Koate-DVI)
Plasma derived/VWF complex	Antihemophilic factor/VWF complex (Alphanate®, Humate-P®, Wilate®)	Full length with VWF	Pooled human plasma	12.2–17.9 hours	1978 (Alphanate), 1986 (Humate-P), August 2009 (Wilate)
Recombinant: first generation	Antihemophilic factor recombinant (Recombinate®)	Full length	BSA in culture and human albumin as stabilizer	14.6 ± 4.9 hours	December 1992
Recombinant: second generation	rFVIII-FS (Helixate®, Kogenate®)	Full length	Human plasma protein solution in culture	13.74 hours	June 2000
Recombinant: third generation	Antihemophilic factor recombinant (Advate®, Kovaltry®)	Full length	No human or animal protein added	12–14.2 hours	July 2003 (Advate), March 2016 (Kovaltry)
Recombinant: second generation	Moroctocog alfa (ReFacto®)	BDD	Human plasma protein solution in culture	14.5 ± 5.3 hours	March 2000
Recombinant: third generation	Moroctocog alfa (Xyntha®), Turoctocog alfa (Novoeight®)	BDD	No human or animal protein added	10.8–12 hours	February 2008 (Xyntha), October 2013 (Novoeight)
Recombinant: fourth generation	Simoctocog alfa (Nuwiq®)	BDD	HEK cells to allow human glycosylation	17.1 ± 11.2 hours	September 2015
Recombinant: third-generation EHL	Octocog alfa pegol (Adynovate®)	BDD-PEGylated	PEGylation to parent drug Advate	14.69 ± 3.79 hours	December 2016
Recombinant: fourth-generation EHL	rFVIII–Fc (Eloctate®)	BDD-rFVIII–Fc	HEK cells to allow human glycosylation	19.7 ± 2.3 hours	June 2014
Recombinant: third-generation EHL	rFVIII-SC (Afstyla®)	EHL single chain	No human or animal protein added	14.2 hours	May 2016

¿Por qué es necesario el desarrollo de nuevos tratamientos?

Problemas

ORIGINAL ARTICLE

Turning severe into moderate haemophilia by prophylaxis: are we reaching our goal?

Ingrid den Uijl[1,2], Douwe Biesma[3], Diederick Grobbee[2], Kathelijn Fischer[1,2]

[1]van Creveldkliniek, Department of Haematology; [2]Julius Centre for Health Sciences and Primary Care; [3]Department of Haematology, Medical University Centre Utrecht, Utrecht, The Netherlands

blood®
2015 125: 2038-2044
doi:10.1182/blood-2015-01-528414 originally published online February 23, 2015

Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens

Johannes Oldenburg

Problemas

Patient Related Outcome Measures
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REVIEW

A systematic review of patient-reported measures of burden of treatment in three chronic diseases

This article was published in the following Dove Press journal:
Patient Related Outcome Measures
4 June 2013
Number of times this article has been viewed

Haemophilia
The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society
Haemophilia (2015), 21, 612–621
DOI: 10.1111/hae.12660

ORIGINAL ARTICLE *Clinical haemophilia*

Unravelling adherence to prophylaxis in haemophilia: a patients' perspective

L. H. SCHRIJVERS,* M. C. KARS,† M. BEIJLEVELT-VAN DER ZANDE,‡ M. PETERS,‡ M. J. SCHUURMANS§¶ and K. FISCHER*†
*Van Creveldkliniek, University Medical Center Utrecht; †Julius Center for Health Sciences and Primary Care, University Medical Centre, Utrecht; ‡Haemophilia Treatment Centre, Academical Medical Center Amsterdam, ; §Faculty of Health Care, Nursing Science, University of Applied Science, Utrecht; and ¶Nursing Science, University Medical Center Utrecht, Utrecht, the Netherlands

Problemas

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

F. Peyvandi, P.M. Mannucci, I. Garagiola, A. El-Beshlawy, M. Elalfy, V. Ramanan, P. Eshghi, S. Hanagavadi, R. Varadarajan, M. Karimi, M.V. Manglani, C. Ross, G. Young, T. Seth, S. Apte, D.M. Nayak, E. Santagostino, M.E. Mancuso, A.C. Sandoval Gonzalez, J.N. Mahlangu, S. Bonanad Boix, M. Cerqueira, N.P. Ewing, C. Male, T. Owaidah, V. Soto Arellano, N.L. Kobrinsky, S. Majumdar, R. Perez Garrido, A. Sachdeva, M. Simpson, M. Thomas, E. Zanon, B. Antmen, K. Kavakli, M.J. Manco-Johnson, M. Martinez, E. Marzouka, M.G. Mazzucconi, D. Neme, A. Palomo Bravo, R. Paredes Aguilera, A. Prezotti, K. Schmitt, B.M. Wicklund, B. Zulfikar, and F.R. Rosendaal

Nuevos tratamientos

- Extended Half Life (FVIII, FIX)

- Tratamientos con otras dianas terapéuticas

Nuevos tratamientos

- Extended Half Life (FVIII, FIX)

- Tratamientos con otras dianas terapéuticas

Accepted: 20 January 2018
DOI: 10.1111/hae.13438

REVIEW ARTICLE

WILEY Haemophilia

Defining extended half-life rFVIII—A critical review of the evidence

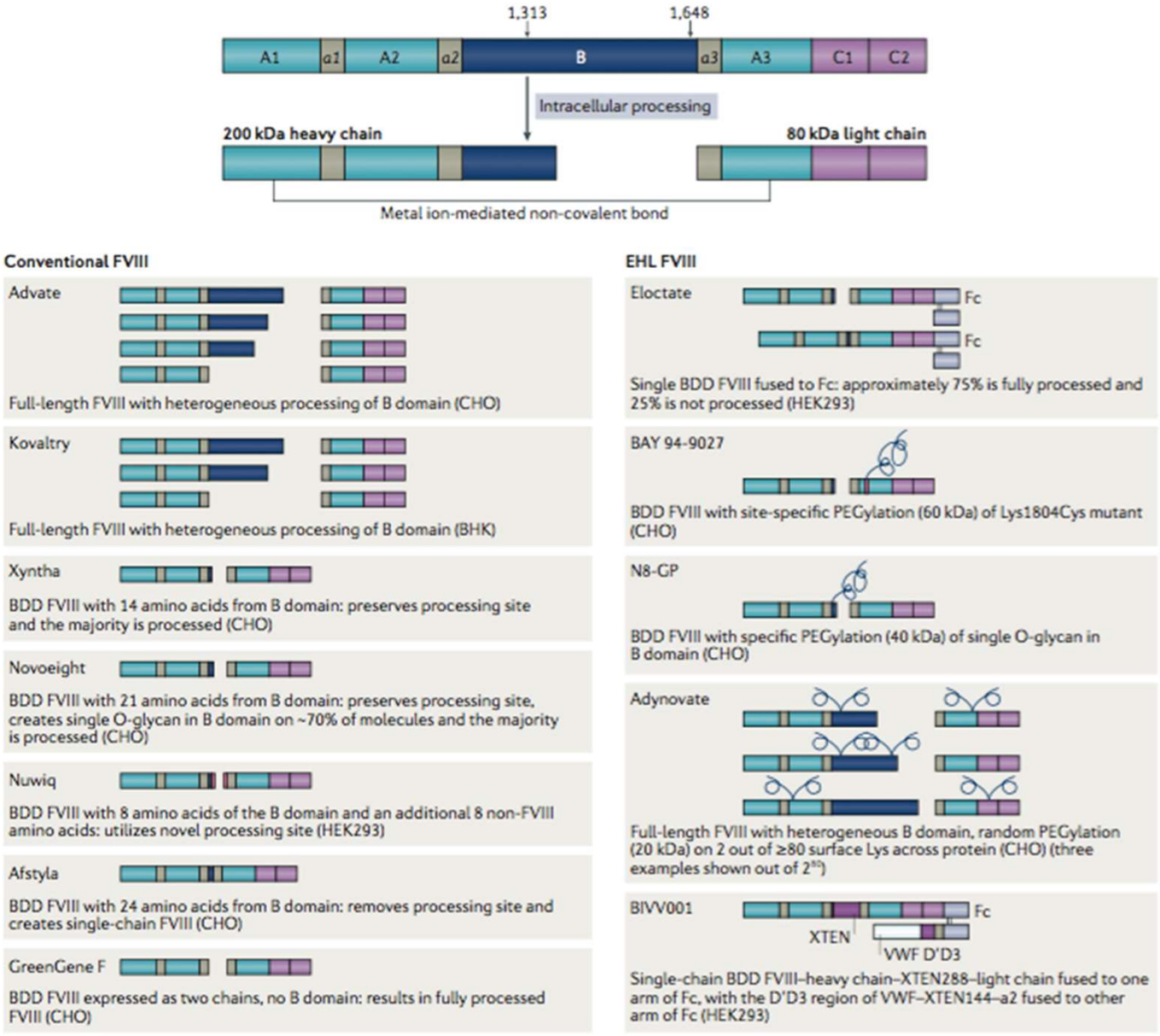
J. Mahlangu[1] | G. Young[2] | C. Hermans[3] | V. Blanchette[4] | E. Berntorp[5] | E. Santagostino[6]

- Utilizar una **tecnología destinada a aumentar la $t_{1/2}$.**
- En segundo lugar, que el **área bajo la curva esté por encima de** los rangos de equivalencia establecidos por la ISTH, es decir por encima de **1.25.**
- Finalmente, que el **ratio de $t_{1/2}$ esté por encima de 1.3**

Extended Half life, FVIII

		Advantages			Limitations			
Product	Mechanism	Dosing frequency	Route	Relative ease of compliance	Immunogenicity	Monitoring	Study population	Status
EHL-rFVIII								
Efmoroctocog alfa (BDD-rFVIII-Fc, Eloctate)[7]	IgG1-Fc fusion	Every 3-5 d	IV	Low	3% NNA	Standard	PTP	Approved
Rurioctacog alfa pegol (BAX 855, Adynovate)[8]	20-kDa pegylation	Twice weekly	IV	Low	4% NNA	Standard	PTP	Approved
Damoctocog alfa pegol (BAY 94-9027)[4]	60-kDa site-specific pegylation	Every 3-7 d	IV	Low	3% NNA0.6% anti-PEG	Chromogenic*	PTP	Phase 3
Turoctocog alfa pegol (N8-GP)[5]	40-kDa site-specific pegylation	Every 4 d	IV	Low	0.6% NNA 0.6% NAb†	TBD	PTP	Phase 3

Arruda V.R. et al. Blood. 2017;130(21):2251-2256



Peters R et al. Nature Reviews 2018; 493-508

Nuevos tratamientos

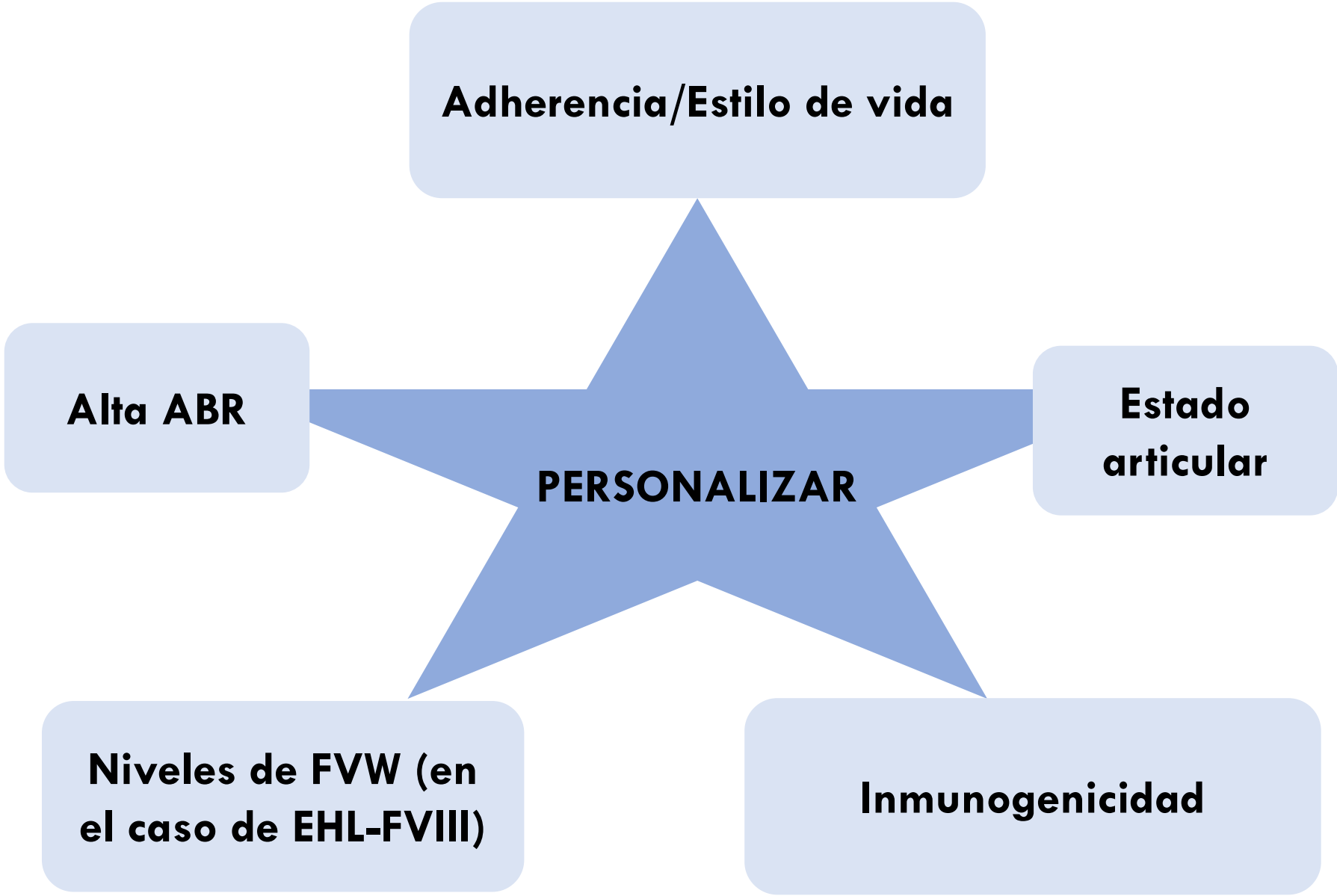
- Extended Half Life (FVIII, FIX)

- Tratamientos con otras dianas terapéuticas

Extended Half Life, FIX

	rFIXFc		rFIX-FP		N9-GP	
Dose	41IU/kg (16.7, 87.6)	100IU/kg	40IU/kg	75IU/kg	10IU/kg	40IU/kg
Frequency	7 days	14 days (7.7, 20.8)	7 days	14 days	7 days	7 days
Subjects	61	26	40	21	30	29
ABR	3.0 (1.0-4.4)	1.4 (0.0-3.4)	0.0 (0.0-1.9)	1.1 (0.0-2.7)	2.9 (0.9-6.0)	1.0 (0.0-4.0)
Efficacy (2 doses)	97.2%		96.7%		97.1%	
Trough	1-3u/dl	1-3u/dL	Mean 20u/dL	Mean 12u/dl	Mean 8.5u/dL	Mean 27u/dL
Change	Lab results		Clinical protocol		Fixed	

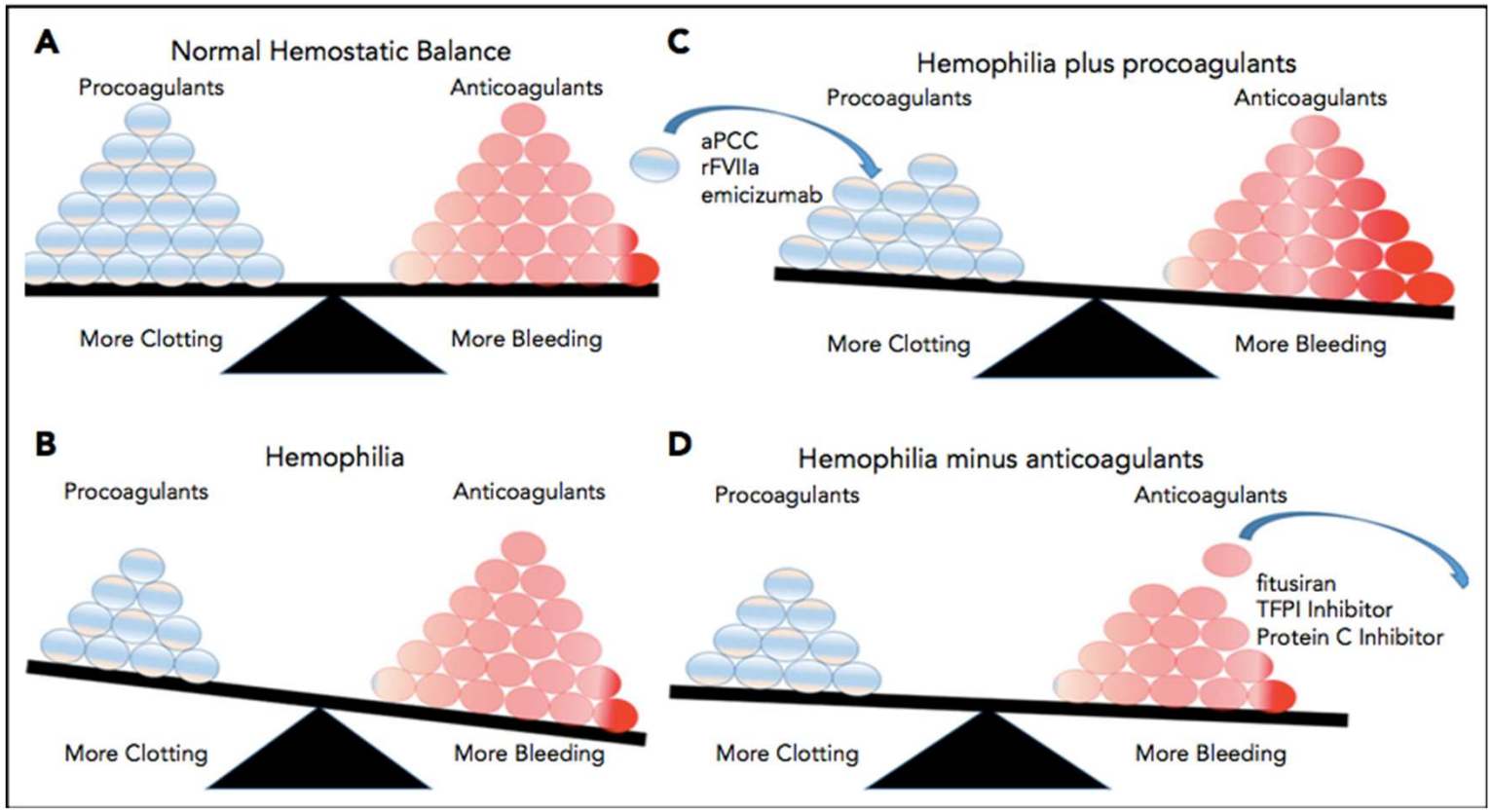
Collins et al, *Blood* 2014;124(26):3880-3886
Powell et al, *N Engl J Med* 2013;369(24):2313-2323
Santagostino et al, *Blood* 2016;127(14):1761-1769


Adherencia/Estilo de vida
Alta ABR
PERSONALIZAR
Estado articular
Niveles de FVW (en el caso de EHL-FVIII)
Inmunogenicidad

Nuevos tratamientos

- Extended Half Life (FVIII, FIX)

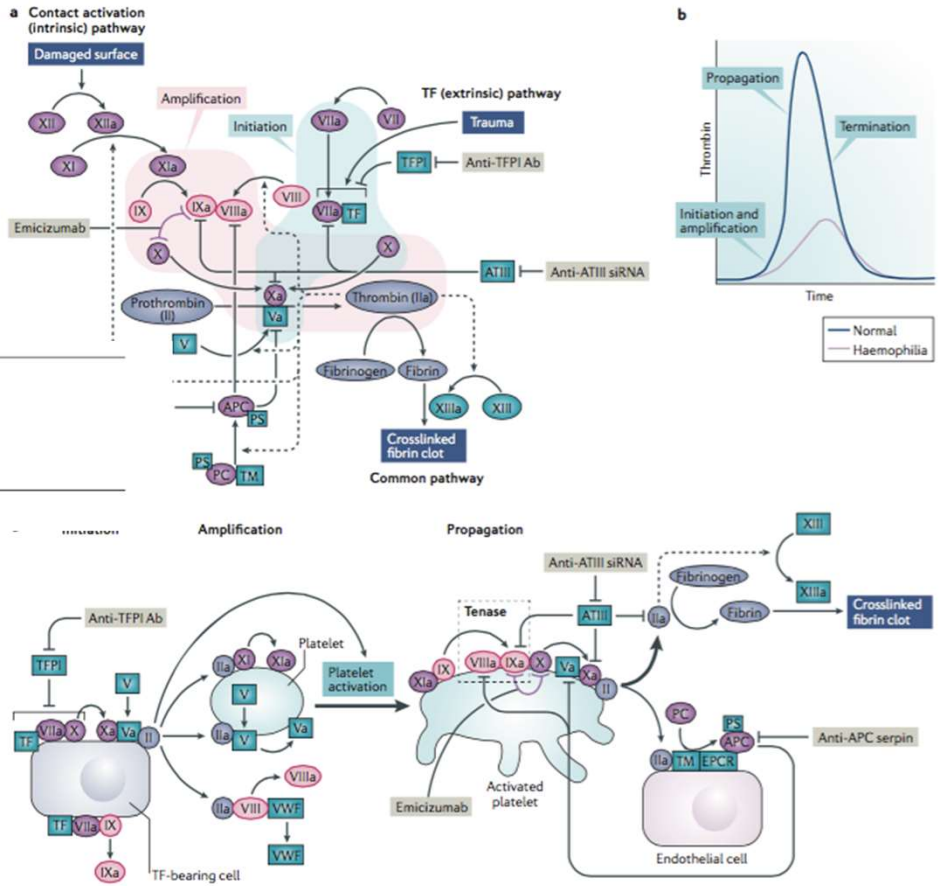
- Tratamientos con otras dianas terapéuticas

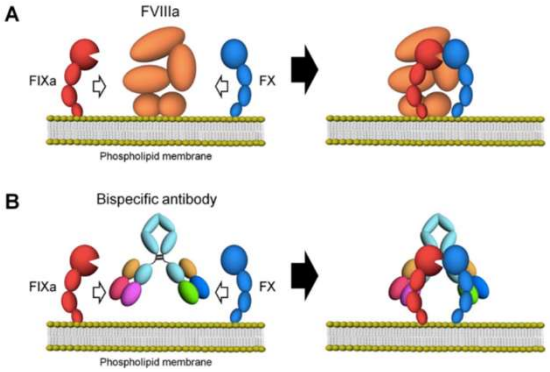


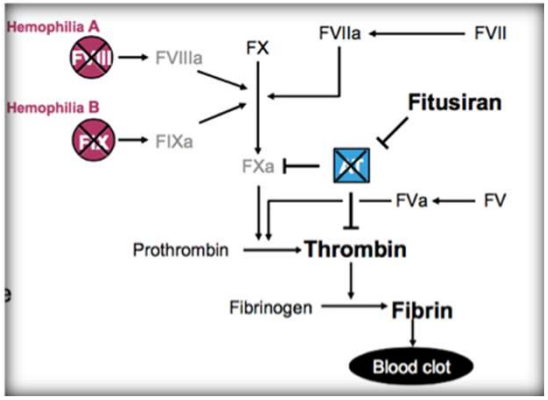
Callaghan MU et al. Blood 2018;132:23-30

Advances and innovations in haemophilia treatment

Rob Peters and Tim Harris*

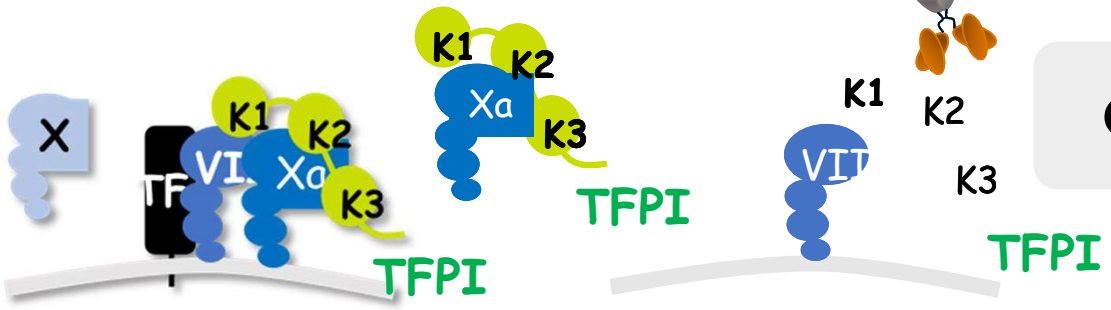






Emicizumab

Fitusiran

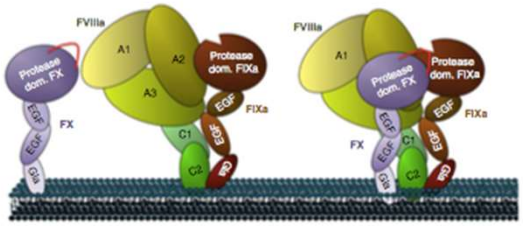
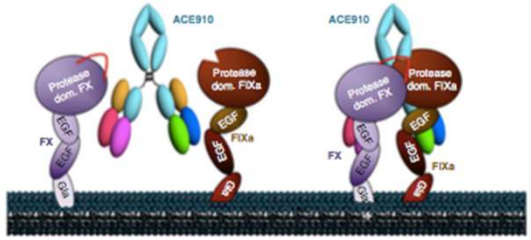


Concizumab

blood®
2017 130: 2463-2468
doi:10.1182/blood-2017-08-801662 originally published online October 17, 2017

Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII?

Peter J. Lenting, Cécile V. Denis and Olivier D. Christophe

FVIIIa	ACE910/Emicizumab
	
Multiple sites of interaction	Single sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*	Low affinity for enzyme & substrate *(micromolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*	No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*	Partial cofactor activity - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor	Antibody is in excess over enzyme and substrate
FVIIIa has on/off mechanism	Emicizumab has no on/off mechanism
High level of self-regulation	Low level of self-regulation

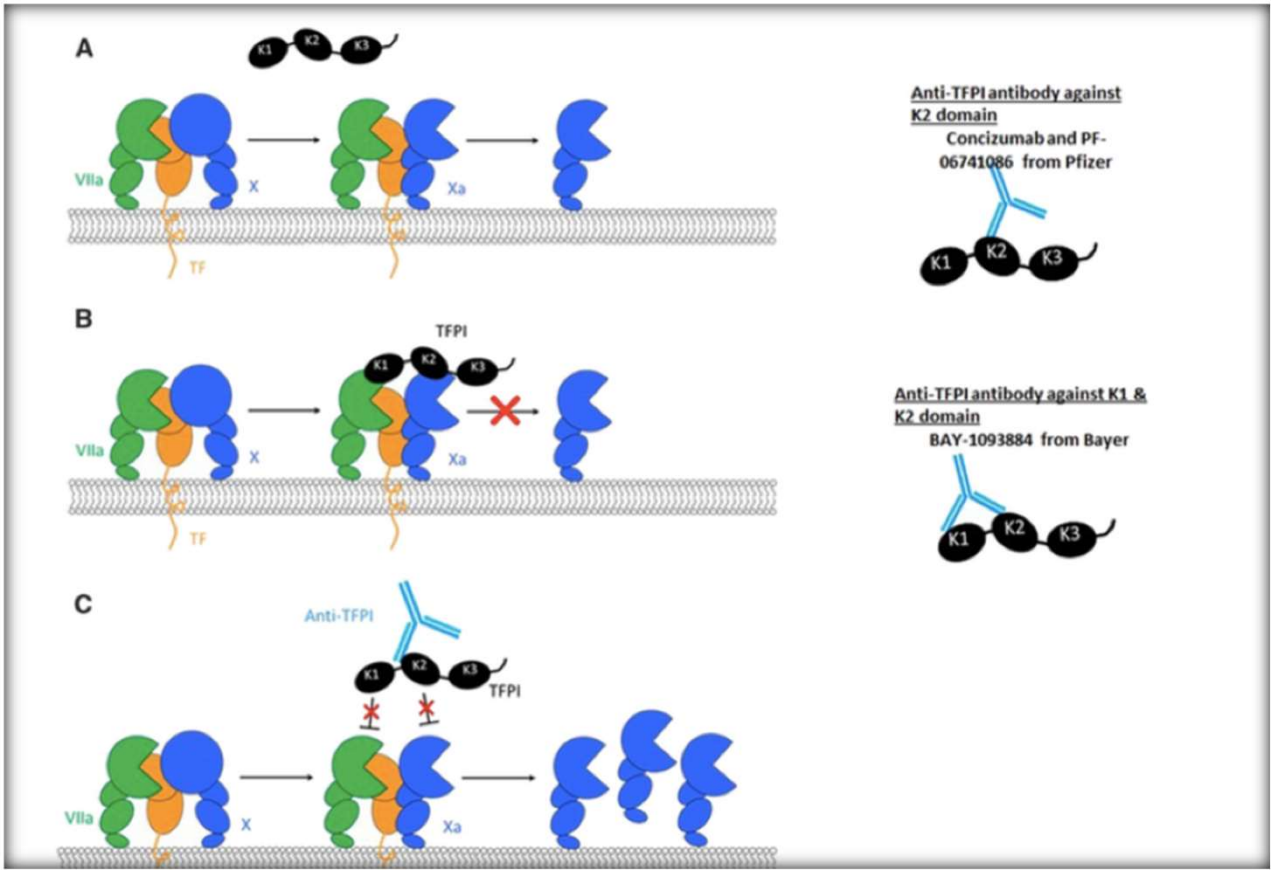
Drugs (2018) 78:881–890
https://doi.org/10.1007/s40265-018-0922-6

LEADING ARTICLE

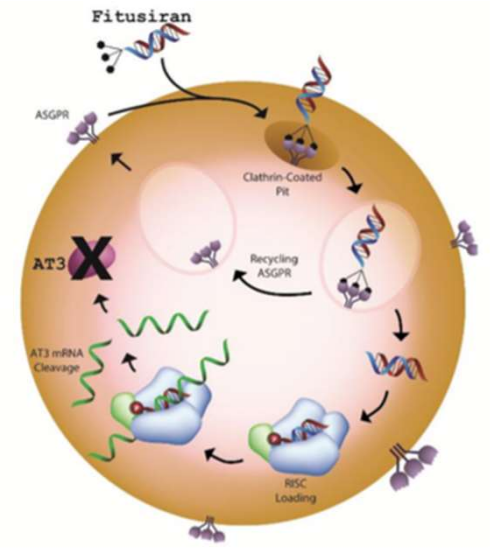
Inhibition of Tissue Factor Pathway Inhibitor (TFPI) as a Treatment for Haemophilia: Rationale with Focus on Concizumab

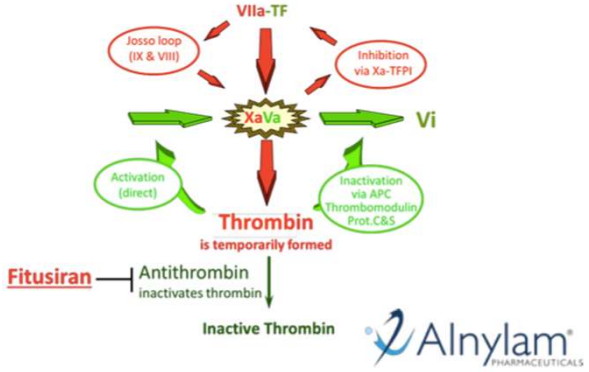
Pratima Chowdary[1]

Published online: 29 May 2018



ALN-AT3-FITUSIRAN

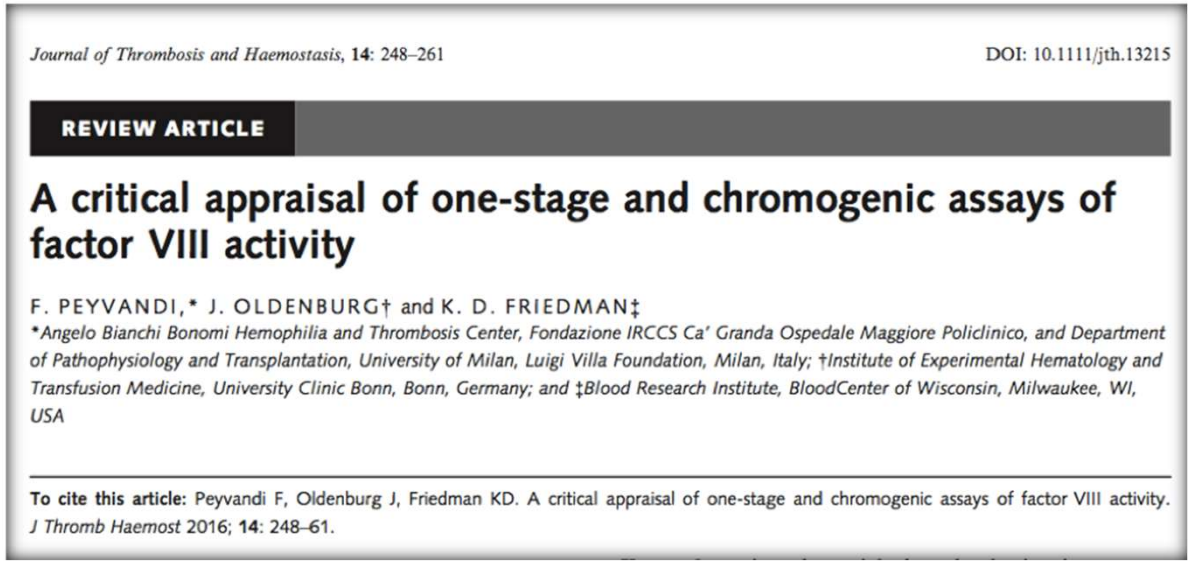




Monitorización de los nuevos tratamientos

- Extended Half life (FVIII, FIX)

- Tratamientos con otras dianas terapéuticas



Journal of Thrombosis and Haemostasis, **14**: 248–261 DOI: 10.1111/jth.13215

REVIEW ARTICLE

A critical appraisal of one-stage and chromogenic assays of factor VIII activity

F. PEYVANDI,* J. OLDENBURG† and K. D. FRIEDMAN‡

*Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and Department of Pathophysiology and Transplantation, University of Milan, Luigi Villa Foundation, Milan, Italy; †Institute of Experimental Hematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany; and ‡Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI, USA

To cite this article: Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. *J Thromb Haemost* 2016; **14**: 248–61.

- Mayores discrepancias entre ambos métodos en:
  - Los niveles basales de pacientes con Hemofilia leve o moderada.
  - En el efecto de concentrados de FVIII con depleción del dominio B, o los **EHL que utilizan PEG para prolongación de su vida media.**
- **Aunque el coagulativo sigue siendo el test más utilizado para la monitorización del tratamiento tanto en Europa como en USA, puede que debido a estas discrepancias se cambie al método cromogénico.**

Journal of Thrombosis and Haemostasis, **14**: 248–261 DOI: 10.1111/jth.13215

REVIEW ARTICLE

A critical appraisal of one-stage and chromogenic assays of factor VIII activity

F. PEYVANDI,* J. OLDENBURG† and K. D. FRIEDMAN‡

**Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and Department of Pathophysiology and Transplantation, University of Milan, Luigi Villa Foundation, Milan, Italy; †Institute of Experimental Hematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany; and ‡Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI, USA*

To cite this article: Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. *J Thromb Haemost* 2016; **14**: 248–61.

Currently, the CSA is used less frequently than the OSA for clinical monitoring. However, its precision and suitability across all FVIII concentrations make it an attractive option. The evolution of CSA use may be accelerated if it is used to perform potency measurements and clinical monitoring during phase III studies of new modified rFVIII products, but considerable barriers remain. Less expensive CSA kits and reagents, and kits designed for lower sample throughput, will be needed if clinical laboratories are to consider their routine use. Overall, the ability of the CSA to accurately measure the FVIII activity levels of new modified rFVIII products will increase its role in potency assignment and probably also in clinical monitoring in the future.

Monitorización de los nuevos tratamientos

- Extended Half life (FVIII, FIX)

- Tratamientos con otras dianas terapéuticas:
  - Emicizumab
  - Concizumab

Monitorización

Sangrado

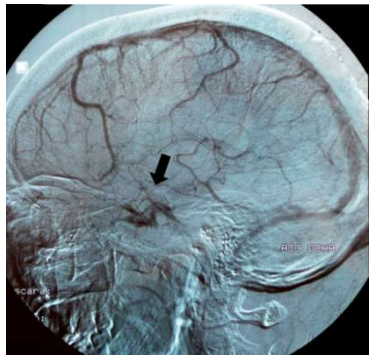
Cirugía

Monitorización del emicizumab

- Administración profiláctica del emicizumab

- Administración de emicizumab junto a otros tratamientos para control del sangrado

HEALTH NEWS | Wed Nov 2, 2016 | Adverse events in trial dent hopes for Roche hemophilia drug



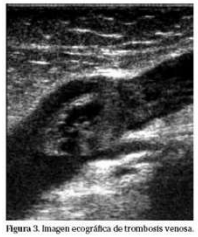
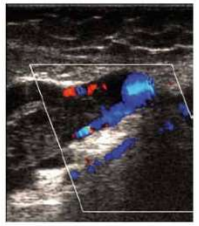
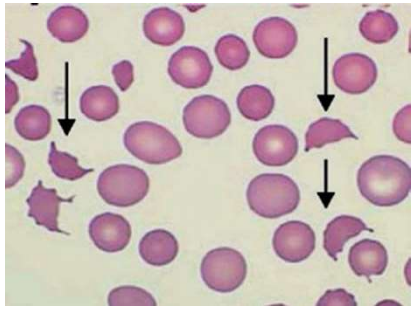


Figura 3. Imagen ecográfica de trombosis venosa.





¿Cómo podemos monitorizar el efecto del emicizumab cuando está siendo administrado como tratamiento profiláctico?

TEST UTILIZADOS

- **TTPa**
- **Niveles plasmáticos de emicizumab (target 45 mcg/mL)**
- **Determinación de FVIII por método cromogénico con reactivos humanos**
- Determinación de FVIII por método cromogénico con reactivos bovinos
- Test globales de la hemostasia (fundamentales cuando se asocia emicizumab a FVIII o BPA, por sangrado o cirugía):
    - Test de generación de trombina (TGA)
    - Técnicas viscoelastográficas (TEG).

TEST UTILIZADOS

- **TTPa**
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    - Técnicas viscoelastográficas (TEG).

Journal of Thrombosis and Haemostasis, **12**: 206–213 DOI: 10.1111/jth.12474

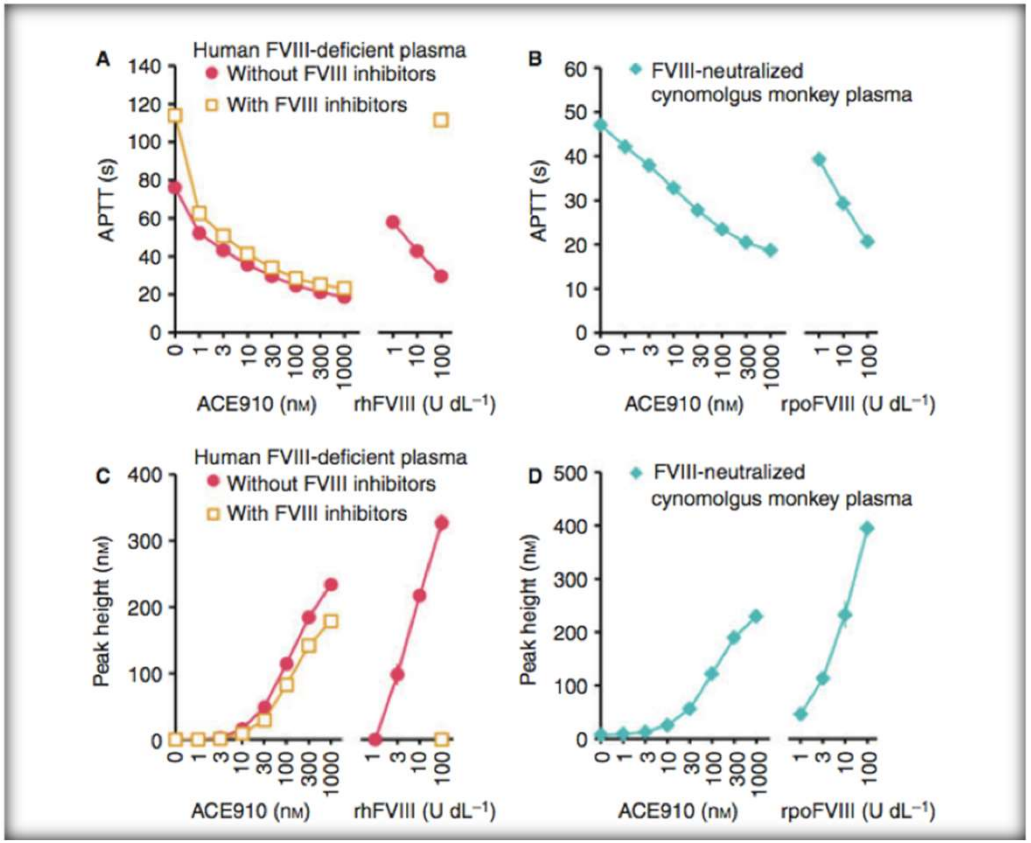
ORIGINAL ARTICLE

Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation

A. MUTO,* K. YOSHIHASHI,* M. TAKEDA,* T. KITAZAWA,* T. SOEDA,* T. IGAWA,* Y. SAKAMOTO,* K. HARAYA,* Y. KAWABE,* M. SHIMA,† A. YOSHIOKA‡ and K. HATTORI*

**Research Division, Chugai Pharmaceutical Co., Ltd, Gotemba, Shizuoka; †Department of Pediatrics, Nara Medical University; and ‡Nara Medical University, Kashihara, Nara, Japan*

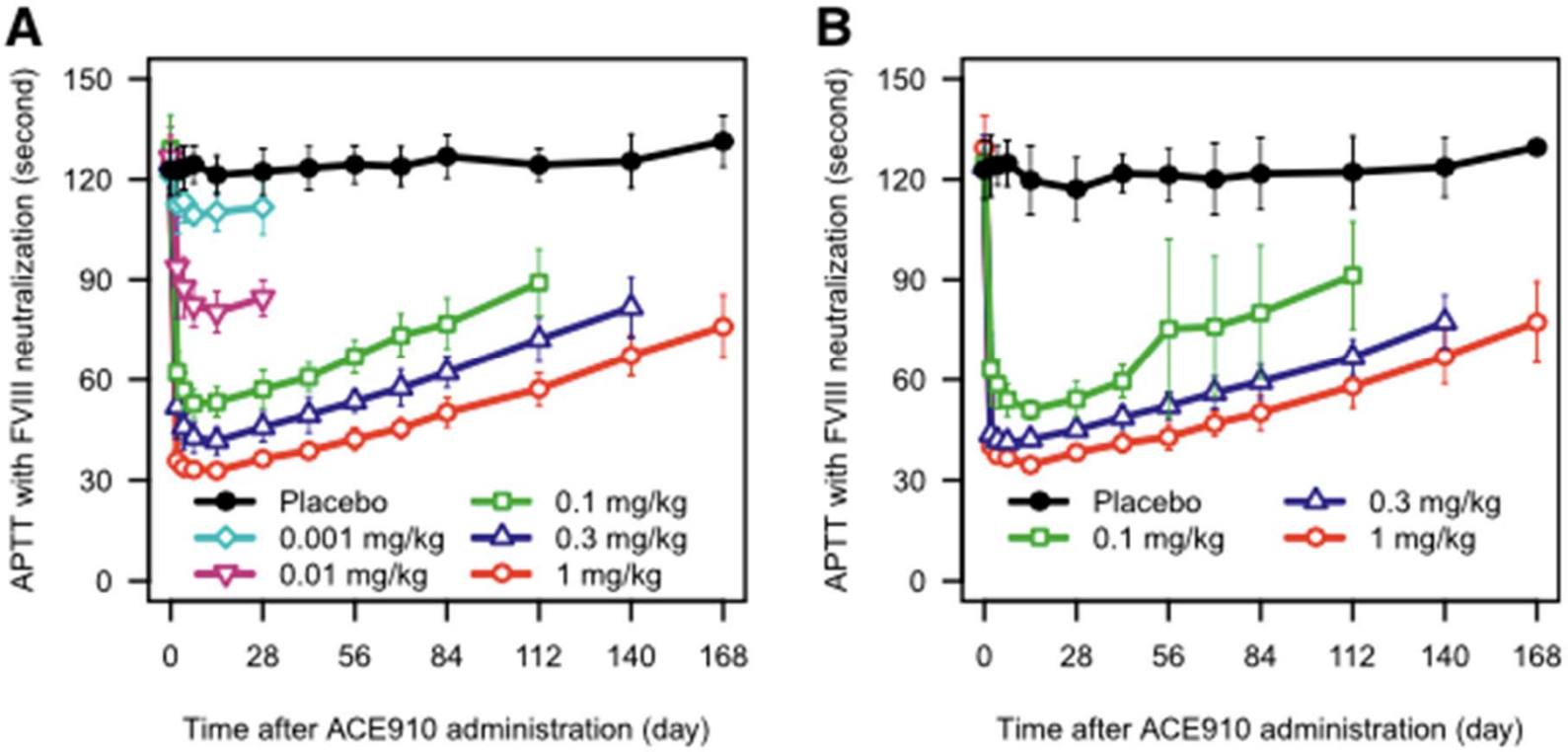
To cite this article: Muto A, Yoshihashi K, Takeda M, Kitazawa T, Soeda T, Igawa T, Sakamoto Y, Haraya K, Kawabe Y, Shima M, Yoshioka A, Hattori K. Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation. *J Thromb Haemost* 2014; **12**: 206–13.

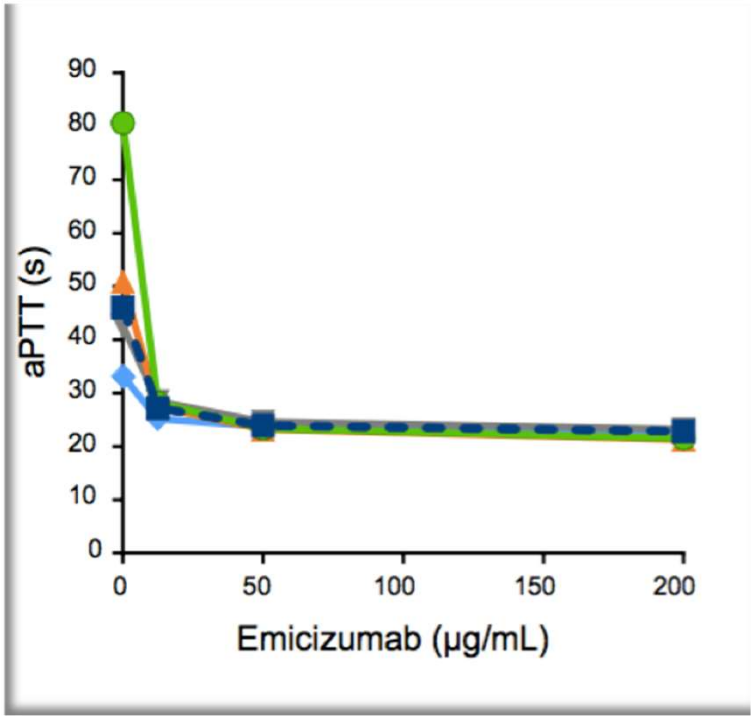


blood®
2016 127: 1633-1641
doi:10.1182/blood-2015-06-650226 originally published online December 1, 2015

A first-in-human phase 1 study of ACE910, a novel factor VIII–mimetic bispecific antibody, in healthy subjects

Naoki Uchida, Takehiko Sambe, Koichiro Yoneyama, Naoki Fukazawa, Takehiko Kawanishi, Shinichi Kobayashi and Midori Shima





Emicizumab y TTPa

Calatzis, A et al. 62nd Annual Meeting Society of Thrombosis and Haemostasis Research. 20 – 23 February 2018 | Vienna, Austria. OC 5.4

TEST UTILIZADOS

- TTPa
- **Niveles plasmáticos de emicizumab (target 45 mcg/mL)**
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    - Técnicas viscoelastográficas (TEG).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 31, 2017 VOL. 377 NO. 9

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

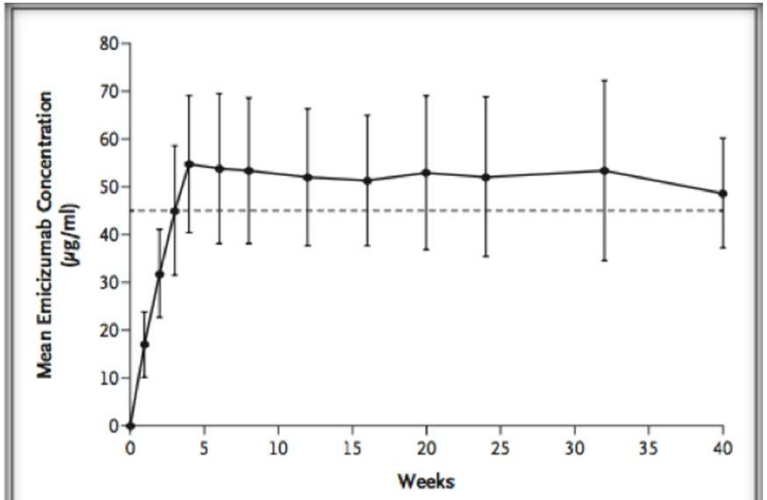


Figure 3. Observed Trough Plasma Concentrations of Emicizumab over Time with Once-Weekly Dosing (102 Patients).

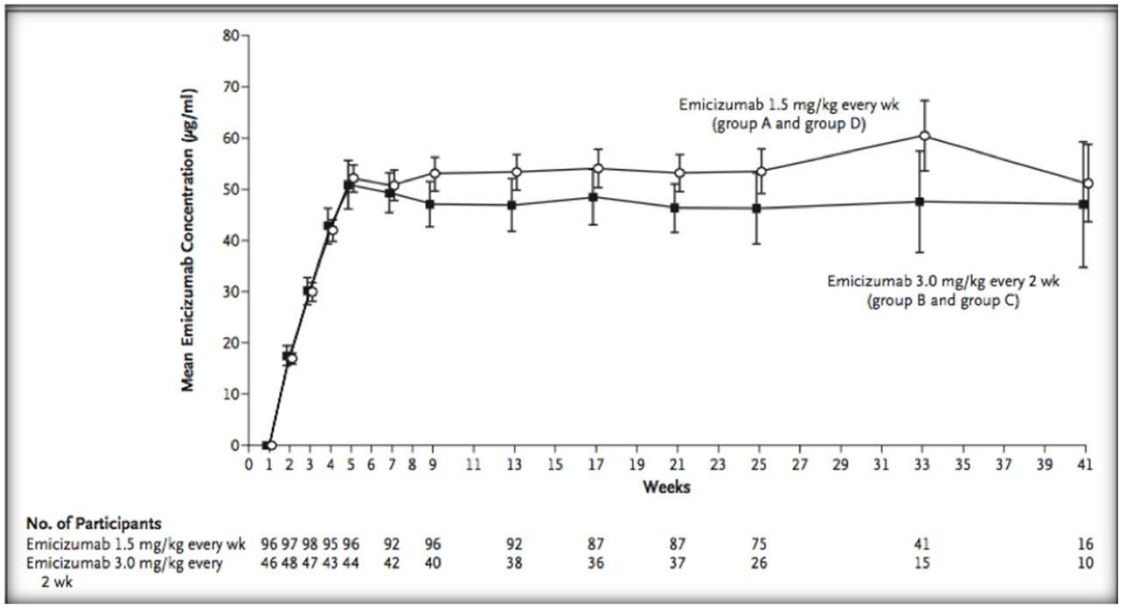
As determined by pharmacokinetic and pharmacodynamic modeling, emicizumab doses of 1.5 mg per kilogram of body weight per week were predicted to result in trough plasma concentrations of emicizumab of 45 μg per milliliter (dashed line). I bars indicate standard deviations.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2018 VOL. 379 NO. 9

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Negrier, M. Niggli, M.E. Mancuso, C. Schmitt, V. Jiménez-Yuste, C. Kempton, C. Dhalluin, M.U. Callaghan, W. Bujan, M. Shima, J.I. Adamkewicz, E. Asikanius, G.G. Levy, and R. Kruse-Jarres



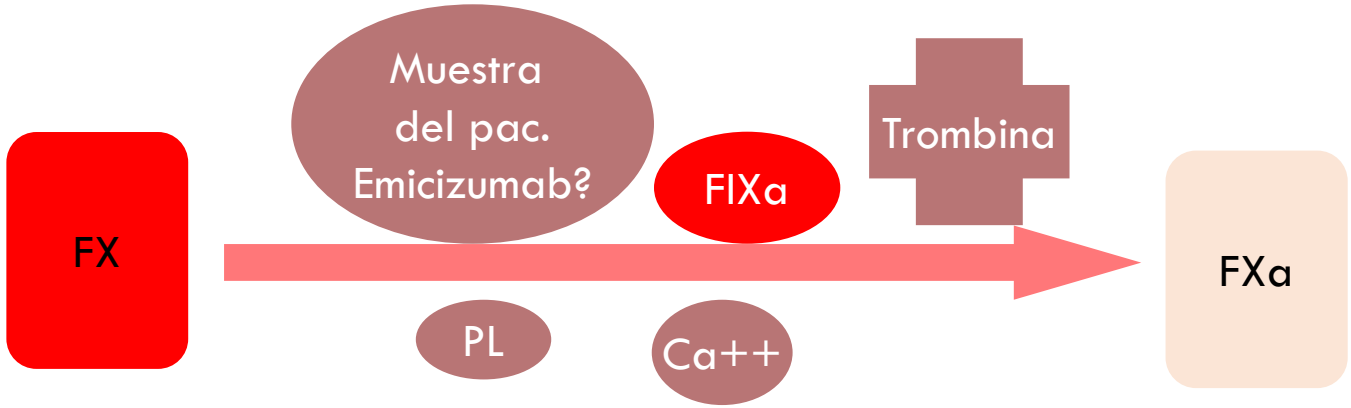
No. of Participants

Emicizumab 1.5 mg/kg every wk	96	97	98	95	96	92	96	92	87	87	75	41	16
Emicizumab 3.0 mg/kg every 2 wk	46	48	47	43	44	42	40	38	36	37	26	15	10

TEST UTILIZADOS

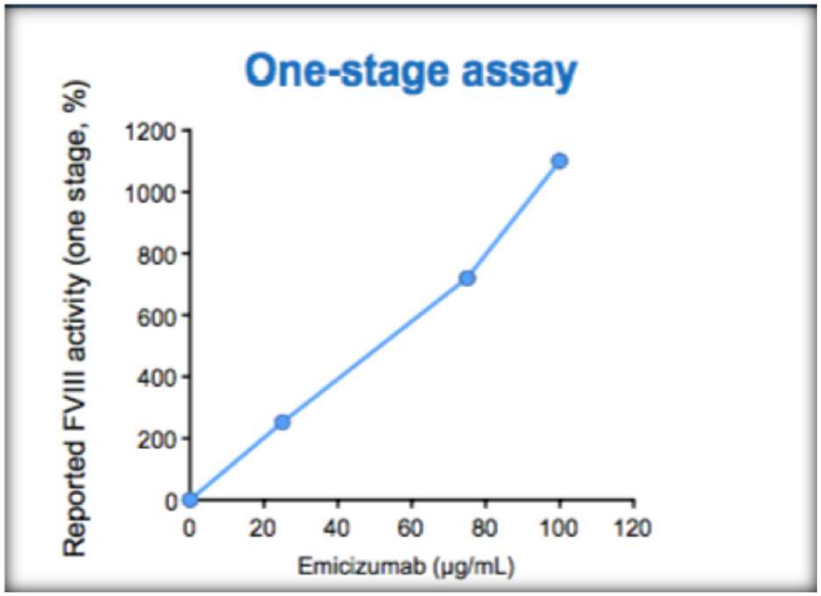
- TTPa
- Niveles plasmáticos de emicizumab (target 45 mcg/mL)
- **Determinación de FVIII por método cromogénico con reactivos humanos**
- Determinación de FVIII por método cromogénico con reactivos bovinos
- Test globales de la hemostasia (fundamentales cuando se asocia emicizumab a FVIII o BPA, por sangrado o cirugía):
    - Test de generación de trombina (TGA)
    - Técnicas viscoelastográficas (TEG).

Determinación de emicizumab por método cromogénico



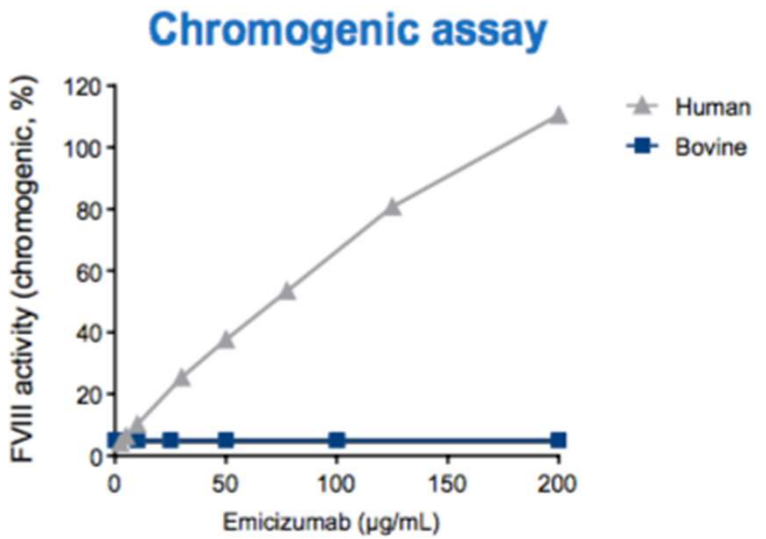
Los reactivos con factores de coagulación humanos responden al emicizumab, pero podrían sobreestimar su potencial hemostático clínico

Karen A. Moser and Dorothy M. (Adcock) Funk. American Journal of Hematology, Vol. 89, No. 7, July 2014



Emicizumab y dosificación FVIII:C método coagulativo

Calatzis, A et al. 62nd Annual Meeting Society of Thrombosis and Haemostasis Research. 20 – 23 February 2018 | Vienna, Austria. OC 5.4



Emicizumab y dosificación FVIII:C método cromogénico

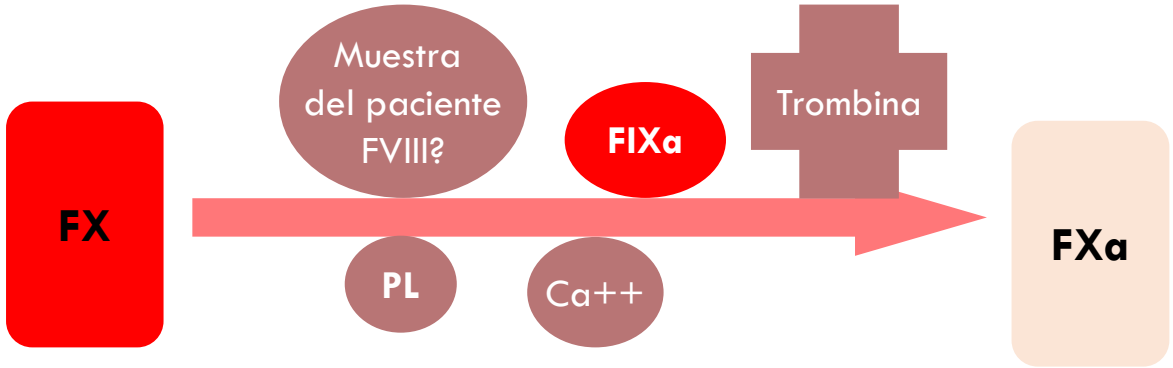
Calatzis, A et al. 62nd Annual Meeting Society of Thrombosis and Haemostasis Research. 20 – 23 February 2018 | Vienna, Austria. OC 5.4

¿Cómo podemos monitorizar el efecto del emicizumab cuando está siendo administrado concomitante con tratamiento sustitutivo con FVIII o BPA, para control del sangrado?

TEST UTILIZADOS

- TTPa
- Niveles plasmáticos de emicizumab (target 45 mcg/mL)
- Determinación de FVIII por método cromogénico con reactivos humanos
- **Determinación de FVIII por método cromogénico con reactivos bovinos**
- **Test globales de la hemostasia (fundamentales cuando se asocia emicizumab a FVIII o BPA, por sangrado o cirugía):**
    - **Test de generación de trombina (TGA)**
    - **Técnicas viscoelastográficas (TEG).**

Determinación de FVIII método cromogénico



- Los **reactivos de origen bovino** no son sensibles al emicizumab (se podrían utilizar para medir el FVIII endógeno o infundido) o para medir inhibidores anti-FVIII

- Para dosificación de inhibidores contra el FVIII, podría ser útil el método Bethesda cromogénico con FVIII bovino insensible al emicizumab.

TEST UTILIZADOS

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- Determinación de FVIII por método cromogénico con reactivos humanos
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    - **Técnicas viscoelastográficas (TEG).**

Use of thrombin generation assay to personalize treatment of breakthrough bleeds in a patient with hemophilia and inhibitors receiving prophylaxis with emicizumab

Yesim Dargaud,[1,2] Anne Lienhart,[1] Maissaa Janbain,[3] Sandra Le Quellec,[1,2] Nathalie Enjolras[2] and Claude Negrier[1,2]

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with a blood loss ranging between 170 and 600 mL. For several years, the patient was on APCC 75 U.kg^{-1} treatment on demand.

In 2016, the patient participated in the HAVEN-1 trial. On week six of the study, while receiving maintenance

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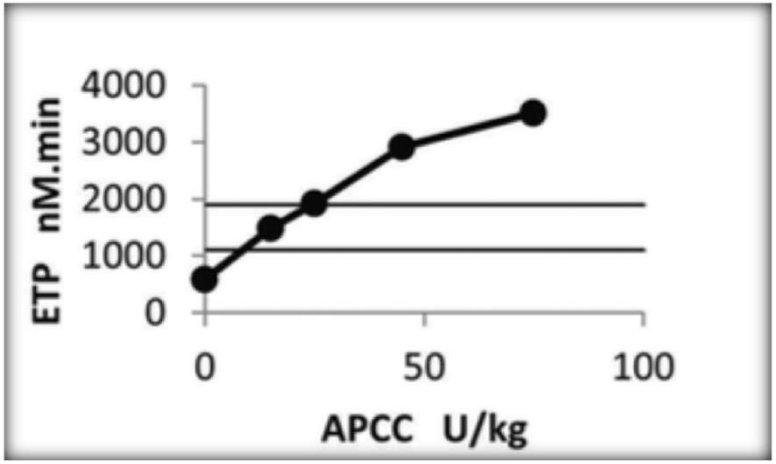

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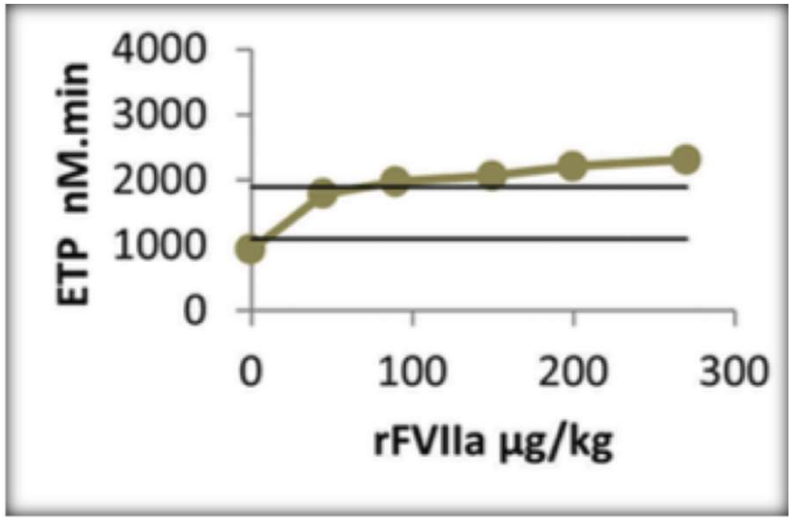

Journal of Thrombosis and Haemostasis, **16**: 1580–1591 DOI: 10.1111/jth.14203

ORIGINAL ARTICLE

In vitro studies show synergistic effects of a procoagulant bispecific antibody and bypassing agents

R. HARTMANN,* T. FEENSTRA,* L. VALENTINO,† M. DOCKAL* and F. SCHEIFLINGER*
**Shire, Vienna, Austria; and †Shire, Bannockburn, IL, USA*

To cite this article: Hartmann R, Feenstra T, Valentino L, Dockal M, Scheiflinger F. *In vitro* studies show synergistic effects of a procoagulant bispecific antibody and bypassing agents. *J Thromb Haemost* 2018; **16**: 1580–91.

Essentials

- Patients with hemophilia A and inhibitors receiving emicizumab experience breakthrough bleeding.
- Safety concerns may exist when combining emicizumab with bypassing agents.
- Combined bypassing agent and bispecific antibody increased thrombin generation up to 17-fold.
- Thrombotic effects should be considered when combining emicizumab with plasma bypassing agent.

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Summary. *Background:* Investigational non-factor products such as emicizumab offer a treatment option for patients with hemophilia and inhibitors. However, their mechanism of action raises questions regarding safety when they are combined with treatments for breakthrough bleeding. *Objectives:* To evaluate *in vitro*

Monitorización de los nuevos tratamientos

- Extended Half life (FVIII, FIX)

- Tratamientos con otras dianas terapéuticas:
  - Emicizumab
  - Concizumab
  - Fitusiran

Journal of Thrombosis and Haemostasis, **13**: 743–754 DOI: 10.1111/jth.12864

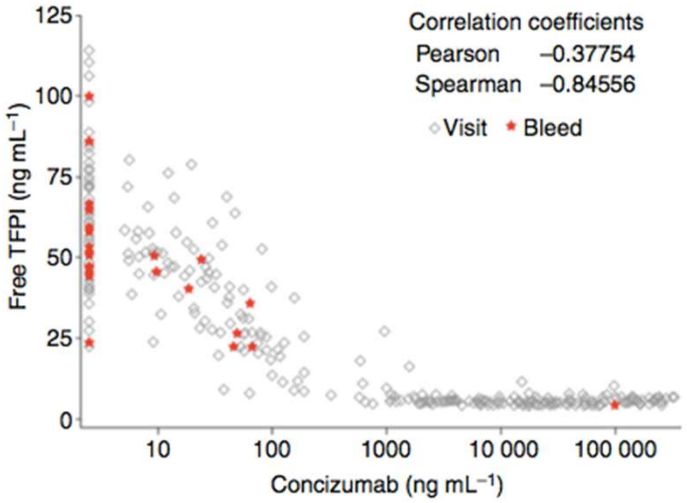
ORIGINAL ARTICLE

Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial

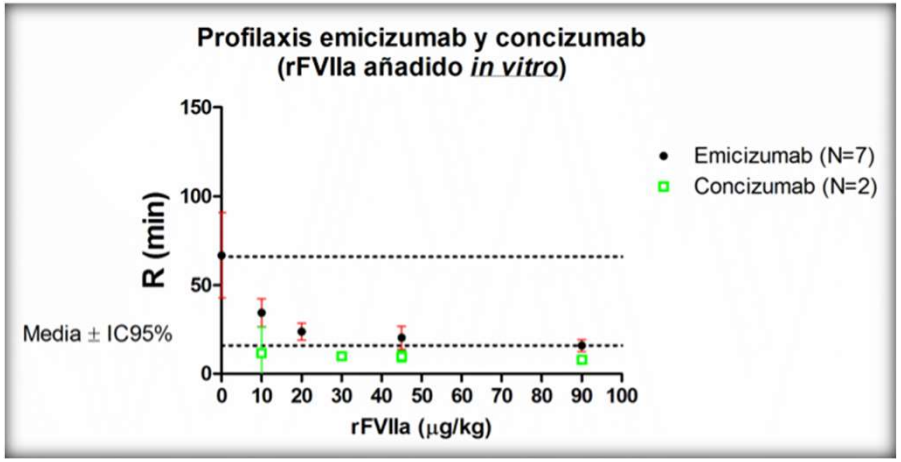
P. CHOWDARY,* S. LETHAGEN,†‡ U. FRIEDRICH,† B. BRAND,§ C. HAY,¶ F. ABDUL KARIM,** R. KLAMROTH,†† P. KNOEBL,‡‡ M. LAFFAN,§§ J. MAHLANGU,¶¶ W. MIESBACH,*** J. DALSGAARD NIELSEN,††† M. MARTÍN-SALCES‡‡‡ AND P. ANGCHAISUKSIRI§§§

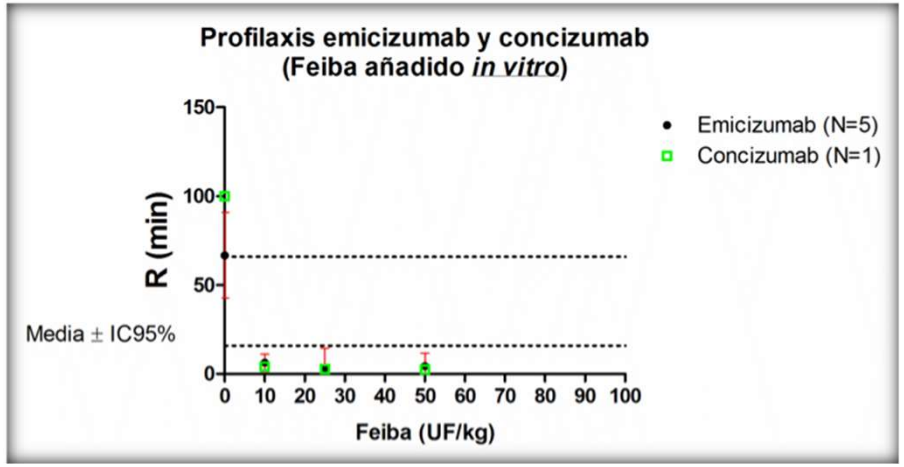
**Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free Hospital, London, UK; †Novo Nordisk A/S, Søborg, Denmark; ‡Copenhagen University, Copenhagen, Denmark; §Division of Hematology, University Hospital, Zurich, Switzerland; ¶University Department of Haematology, Manchester Royal Infirmary, Manchester, UK; **Haemophilia Centre, National Blood Centre, Kuala Lumpur, Malaysia; ††Department of Internal Medicine—Angiology, Haemostasis and Coagulation disorders, Vivantes Hospital im Friedrichshain, Berlin, Germany; ‡‡Division of Haematology and Haemostasis, Department of Medicine 1, Medical University of Vienna, Vienna, Austria; §§Imperial College London, Hammersmith Hospital, London, UK; ¶¶Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa; ***Zentrum für Innere Medizin, Med. Klinik III, Hämophilie-Zentrum, Frankfurt/M, Germany; †††Thrombosis and Haemostasis Unit, Department of Haematology, Rigshospitalet, Copenhagen, Denmark; ‡‡‡Haematology Department, Hospital Universitario La Paz, Madrid, Spain; and §§§Division of Hematology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand*

To cite this article: Chowdary P, Lethagen S, Friedrich U, Brand B, Hay C, Abdul Karim A, Klamroth R, Knoebl P, Laffan M, Mahlangu J, Miesbach W, Dalsgaard Nielsen J, Martín-Salces M, Angchaisuksiri P. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. *J Thromb Haemost* 2015; **13**: 743–54.




Hospital Universitario
La Paz


Profilaxis emicizumab y concizumab
(rFVIIa añadido *in vitro*)
R (min)
150
100
50
0
0 10 20 30 40 50 60 70 80 90 100
rFVIIa (µg/kg)
Media ± IC95%
Emicizumab (N=7)
Concizumab (N=2)


Profilaxis emicizumab y concizumab
(Feiba añadido *in vitro*)
R (min)
150
100
50
0
0 10 20 30 40 50 60 70 80 90 100
Feiba (UF/kg)
Media ± IC95%
Emicizumab (N=5)
Concizumab (N=1)

Monitorización de los nuevos tratamientos

- Extended Half life (FVIII, FIX)

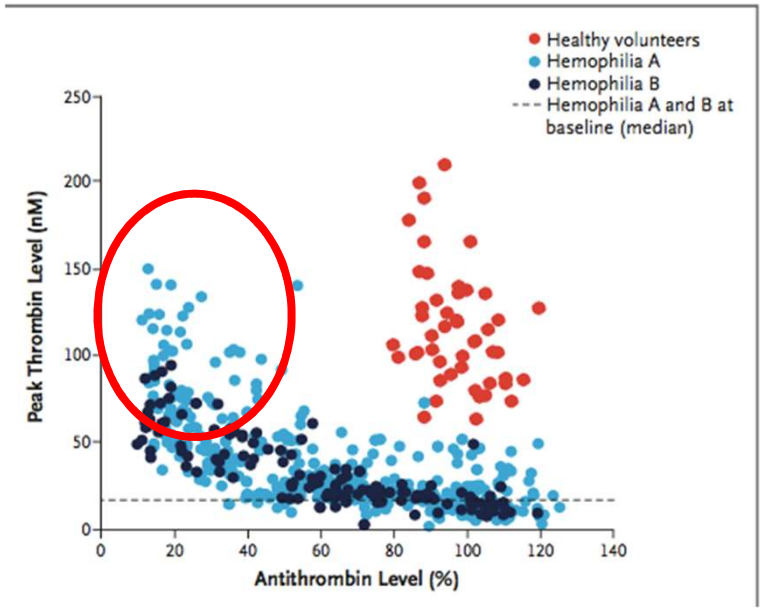
- Tratamientos con otras dianas terapéuticas:
  - Emicizumab
  - Concizumab
  - Fitusiran

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy

K.J. Pasi, S. Rangarajan, P. Georgiev, T. Mant, M.D. Creagh, T. Lissitchkov, D. Bevan, S. Austin, C.R. Hay, I. Hegemann, R. Kazmi, P. Chowdary, L. Gercheva-Kyuchukova, V. Mamonov, M. Timofeeva, C.-H. Soh, P. Garg, A. Vaishnaw, A. Akinc, B. Sørensen, and M.V. Ragni



Emerging therapeutic interventions in haemophilia **Special Collection**

Therapeutic Advances in Hematology *Review*

The role of patient and healthcare professionals in the era of new hemophilia treatments in developed and developing countries

Ther Adv Hematol

2018, Vol. 9(8) 239–249

DOI: 10.1177/2040620718784830

Fadi Nossair and Courtney D. Thornburg

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	No inhibitor			Inhibitor		
	On demand	**Prophylaxis**	**Curative**	**On demand**	**Prophylaxis**	**Immune tolerance induction**
Standard half-life (SHL) recombinant clotting factor	x	x				x
SHL, plasma derived (PD)	x	x				x
Extended half-life recombinant clotting factor	x	x				x
Recombinant bypassing clotting factor				x	x	
PD-bypassing clotting factor				x	x	
Nonfactor replacement		x*			x**	
Gene therapy			x*			

*Available only *via* clinical trial for patients with hemophilia A or B without inhibitor. **Commercially available or available *via* clinical trial for patients with hemophilia A and inhibitor; available only *via* clinical trial for patients with hemophilia A or B and inhibitor.

Emerging therapeutic interventions in haemophilia **Special Collection**

Therapeutic Advances in Hematology *Review*

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Fadi Nossair and Courtney D. Thornburg

Abstract: Medical decisions in hemophilia care are primarily related to the type of factor replacement and treatment regimen. With the growing number of treatment options for patients with hemophilia, decision making is more complex and requires careful consideration of benefits, risks, and patient goals. Shared decision making and decision-aid tools facilitate patient and healthcare provider communication. In this review, the overall role of shared decision making in medicine is outlined, with special emphasis on models for practical implementation. Examples of shared decision making in hemophilia are outlined, and application to new therapeutics is discussed through a case-based approach.

Journal of Blood Medicine

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REVIEW

Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches?

This article was published in the following Dove Press journal:
Journal of Blood Medicine
15 June 2017
Number of times this article has been viewed

cost of FVIII infusions will decrease enough to allow more children in developing countries to receive prophylactic therapy. Moreover, the recent success with gene therapy tri-

Accepted: 30 May 2018
DOI: 10.1111/hae.13558

COMMENTARY

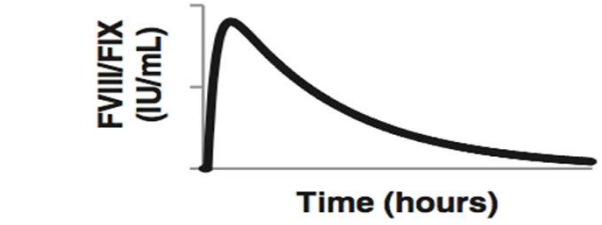
WILEY Haemophilia

Prophylaxis re-visited: The potential impact of novel factor and non-factor therapies on prophylaxis

M. Carcao[1] | T. Lambert[2] | C. Leissinger[3] | C. Escuriola-Ettingshausen[4] | E. Santagostino[5] | L. Aledort[6] | on behalf of the International Prophylaxis Study Group (IPSG)

The development and introduction of new haemostatic therapies in haemophilia are forcing us to revisit the concepts and definitions of prophylaxis. These new therapies (some already in clinical use and others still in development) include extended half-life (EHL) intravenously administered CFCs, subcutaneously administered CFCs,[16] FVIII mimetics (Emicizumab) and non-factor drugs that inhibit natural endogenous anticoagulants (antithrombin [AT], tissue factor pathway inhibitor [TFPI] and activated protein C [APC]).[17]

¿Cuál es el mejor tratamiento para cada paciente?



Pharmacokinetics of treatment

Clearance (Cl)
Volume of distribution (Vd)
Half-life (T1/2)
In vivo recovery (IVR)

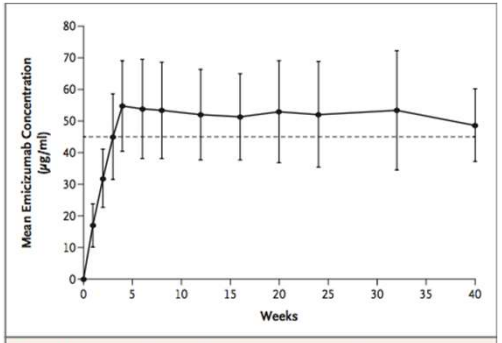


Figure 3. Observed Trough Plasma Concentrations of Emicizumab over Time with Once-Weekly Dosing (102 Patients).
As determined by pharmacokinetic and pharmacodynamic modeling, emicizumab doses of 1.5 mg per kilogram of body weight per week were predicted to result in trough plasma concentrations of emicizumab of 45 μg per milliliter (dashed line). I bars indicate standard deviations.

- Infusión intravenosa (CVC, inicio más tardío de la profilaxis, menos adherencia)
- Fácil monitorización

- Subcutáneo, en algunos pacientes una vez al mes
- Inicio de la profilaxis más precoz ¿rescates con FVIII?