Treatment of hemophilia in the future – from standard to novel therapies

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Milwaukee, WI USA

versiti™

Ever Changing Hemophilia Landscape

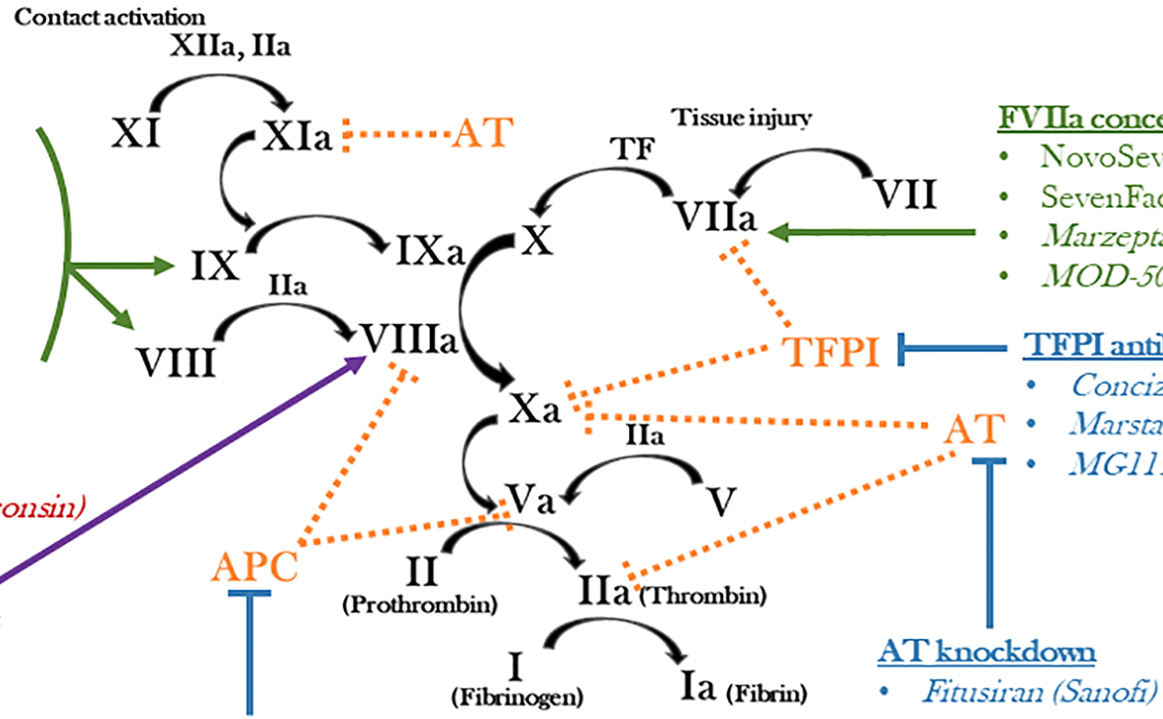
FVIII or FIX concentrates
- Standard half-life (SHL)
- Extended half-life (EHL)
- *BIVV001 (Sanofi)*
- *OCTA101 (Octapharma)*
- *BIVV002 (Sanofi)*
- *CB2679d (Catalyst Biosciences)*

Gene transfer
- *AAV FVIII*
- *AAV FIX*

Gene editing
- *SB-FIX (Sangamo Therapeutics)*

Cellular therapy
- *SIG-001 (Sigilon Therapeutics)*
- *Lenti-FVIII (Medical College Wisconsin)*

Bispecific antibody, FVIIIa mimetic
- Emicizumab (Genentech)
- *Mim8 (Novo Nordisk)*



APC inhibition
- *SerpinPC (ApcinteX Ltd)*

FVIIa concentrates
- NovoSeven (Novo Nordisk)
- SevenFact (LFB S.A, HEMA Biologics)
- *Marzeptacog Alfa (Catalyst Biosciences)*
- *MOD-5014 / (OPKO Health)*

TFPI antibodies, anti-Xa only
- *Concizumab (Novo Nordisk)*
- *Marstacimab (Pfizer)*
- *MG1113 (Green Cross)*

AT knockdown
- *Fitusiran (Sanofi)*

Options for Personalized Medicine

What is personalized medicine?

‘an approach to the practice of medicine that uses information about a patient’s unique genetic makeup and environment to customize the patient's medical care to fit his or her individual requirements.’

Current Management in Hemophilia

Prophylactic infusion of factor concentrate remains a standard of care

- for all adult and pediatric patients with severe hemophilia A & B
- and those with clinically severe phenotype

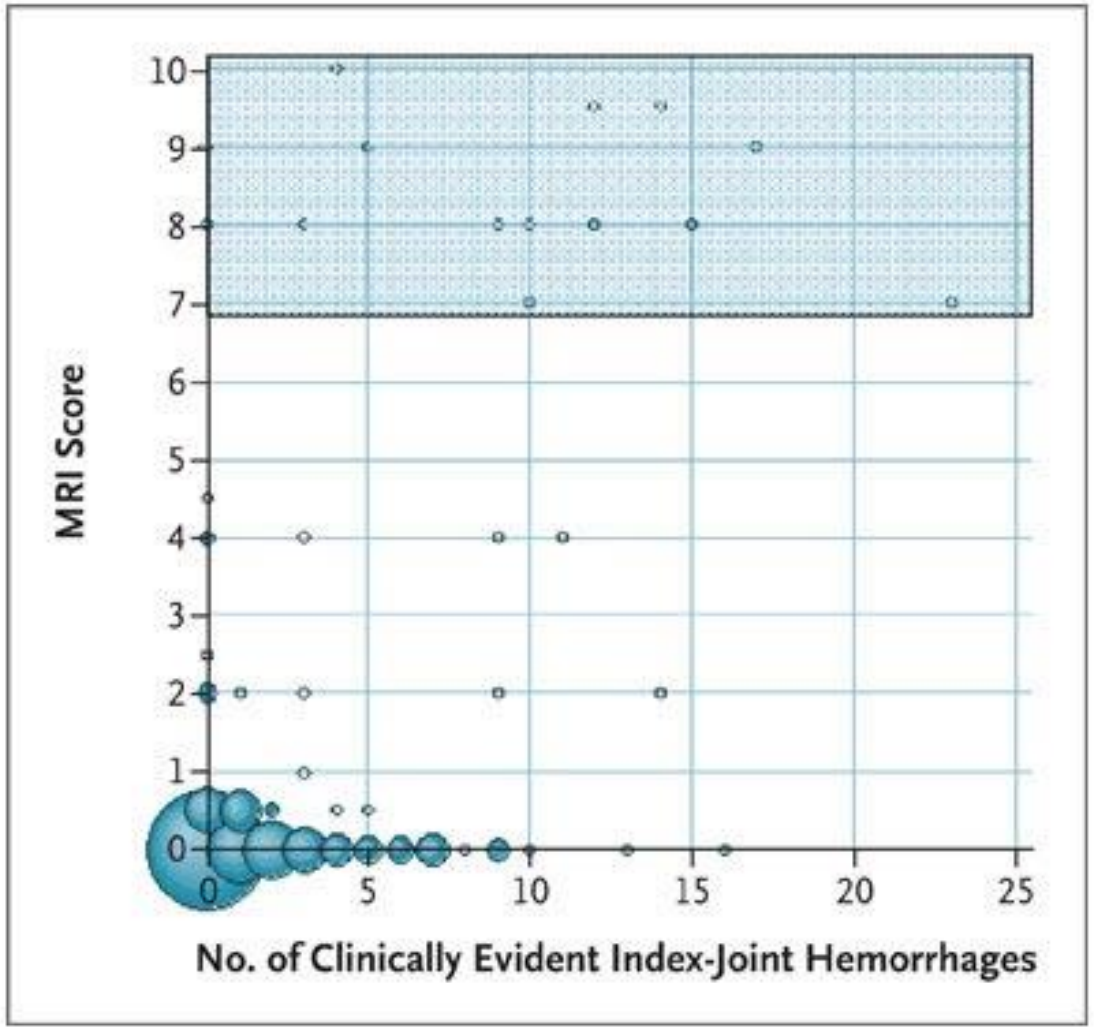
Joint Outcomes Study 2007

Table 2. Outcome Data.*

Variable	Prophylaxis (N=32)	Enhanced Episodic Therapy (N=33)	P Value
MRI findings			
No. of participants with primary outcome data	27	29	0.73
Joint damage — no. (%)	2 (7)	13 (45)	0.002
No joint damage — no. (%)	25 (93)	16 (55)	
Radiographic findings			
No. of participants with primary outcome data	28	27	0.73
Joint damage — no. (%)	1 (4)	5 (19)	0.10
No joint damage — no. (%)	27 (96)	22 (81)	
No. of days in study			
Mean	1,497	1,490	0.95
Total	47,895	49,179	
Reported no. of factor VIII infusions			
Mean	653±246	187±100	<0.001
Total	20,896	6,176	
Reported no. of factor VIII units infused			
Mean	352,793±150,454	113,237±65,494	<0.001
Total	11,289,372	3,736,807	
Joint hemorrhages (no./participant/yr)			
Mean	0.63±1.35	4.89±3.57	<0.001
Median	0.20	4.35	
Total hemorrhages (no./participant/yr)			
Mean	3.27±6.24	17.69±9.25	<0.001
Median	1.15	17.13	

* Plus–minus values are means ±SD. The data on MRI and radiographic findings include interim-analysis data for children who were removed from the study because of early joint failure.

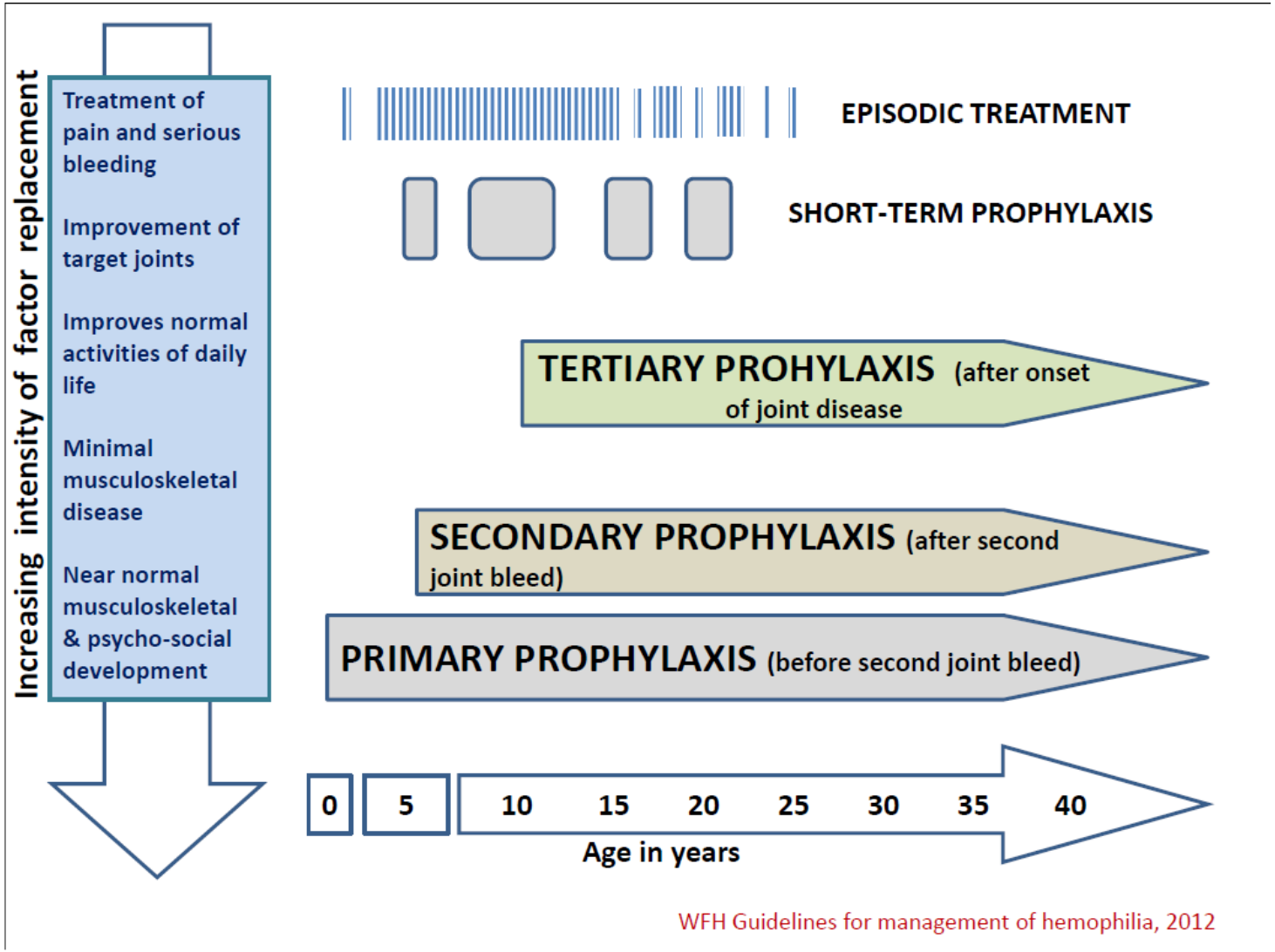
Joint Outcomes Study: Rethinking Old Data



Patients with subclinical bleeding events

Defining clinically severe disease

Defining Prophylaxis Through the Ages



WFH Guidelines for management of hemophilia, 2012

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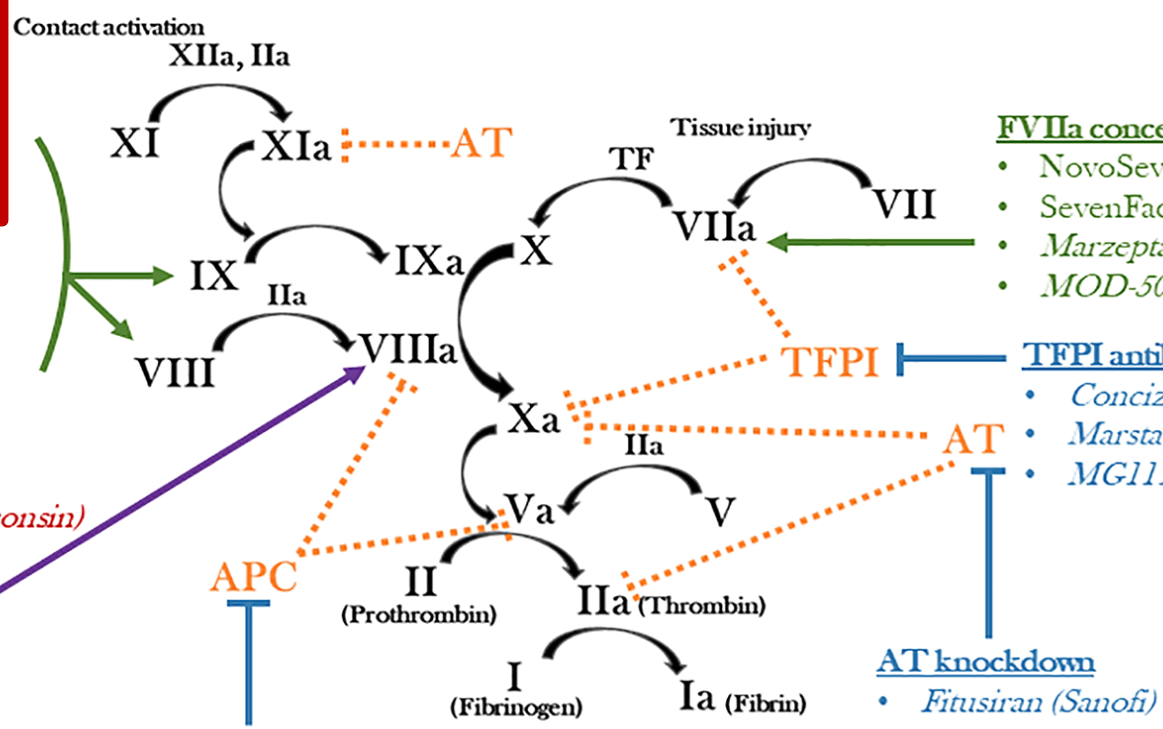

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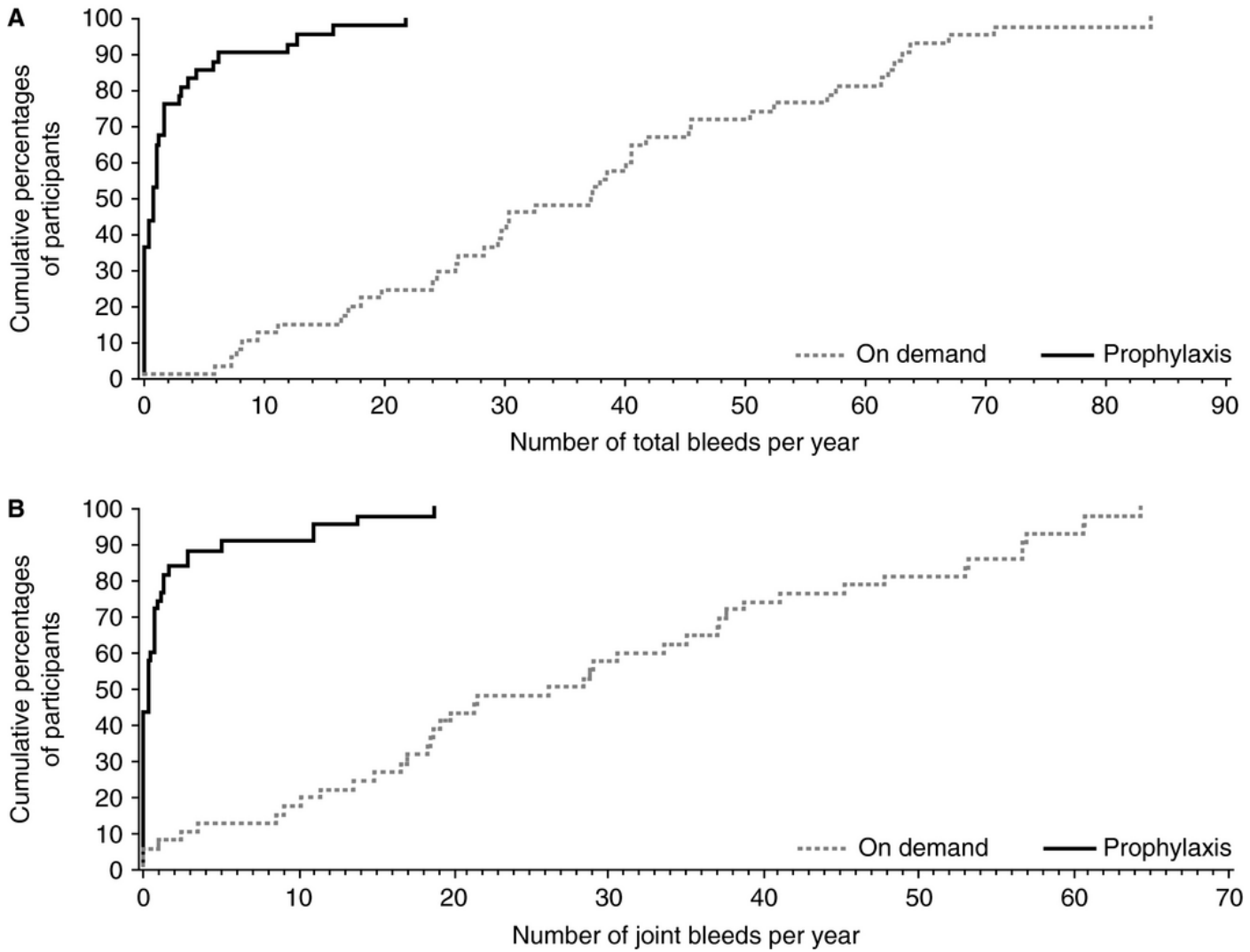
Exogenous Factor Replacement

Long-term data on safety and efficacy established for SHL products

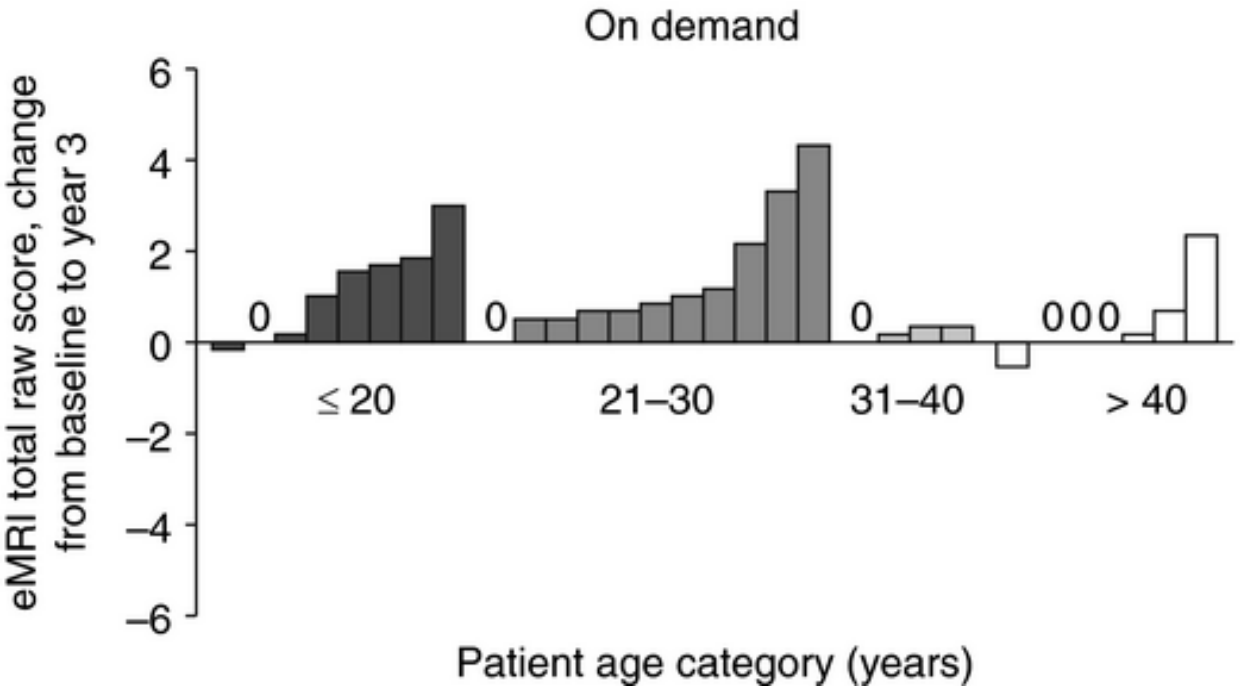
Data on safety and efficacy of EHL products now established with extensions studies, real world clinical data

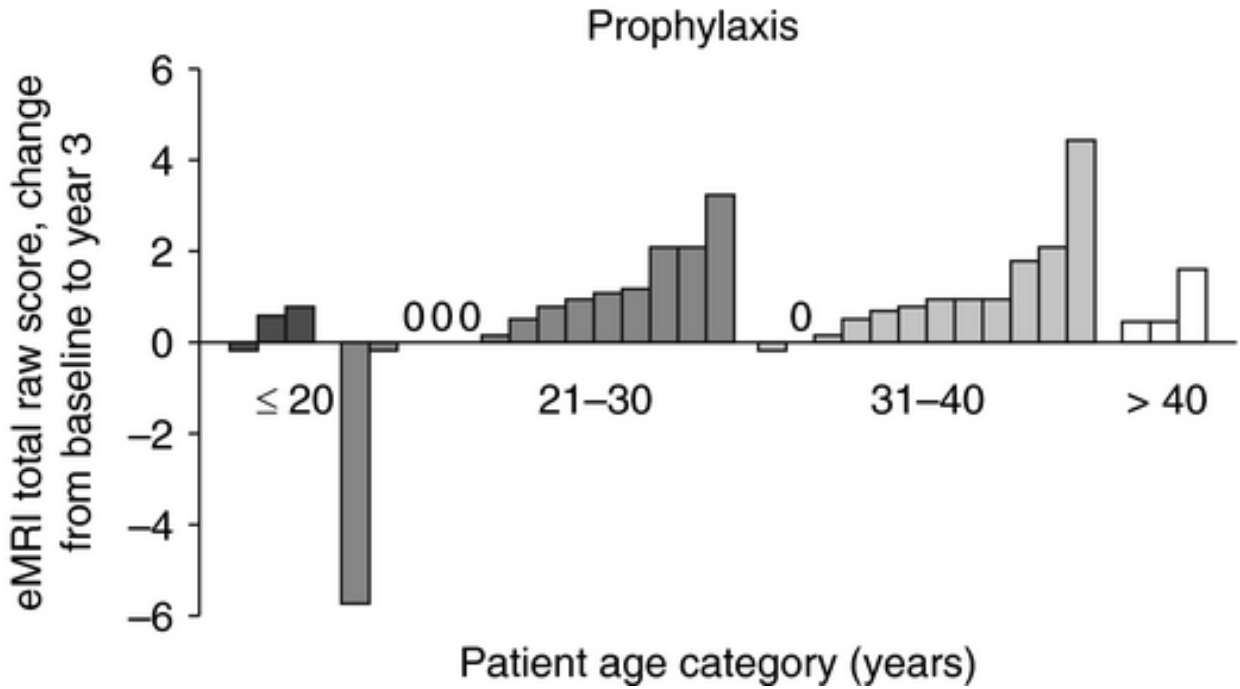
Adoption of EHLs in Heme A vs. Heme B

- Half-life extension limitations thus far in heme A → lesser numbers of patients on EHLs?



Journal of Thrombosis and Haemostasis
Volume 15, Issue 11, pages 2115-2124, 10 OCT 2017 DOI: 10.1111/jth.13811
http://onlinelibrary.wiley.com/doi/10.1111/jth.13811/full#jth13811-fig-0001





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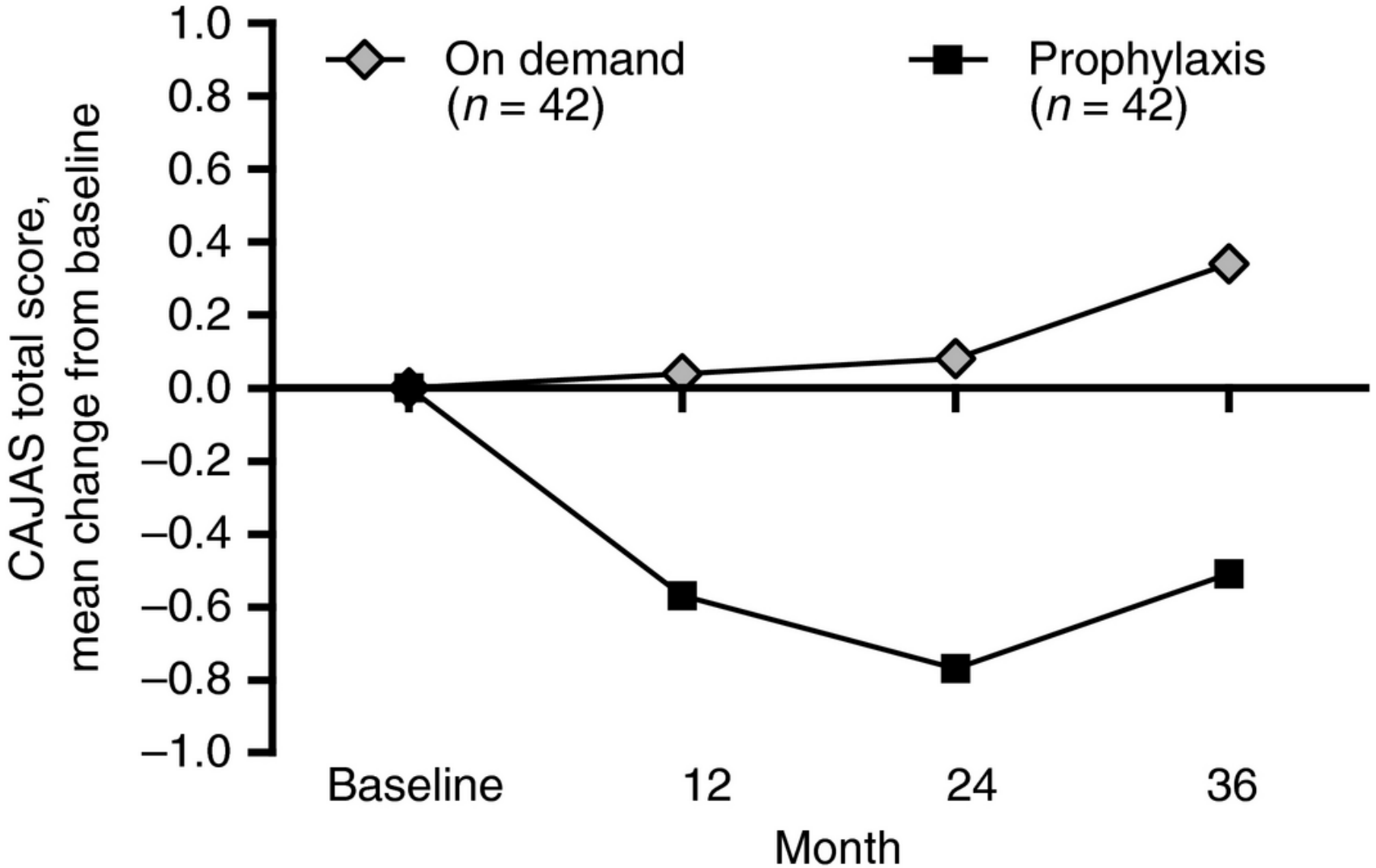

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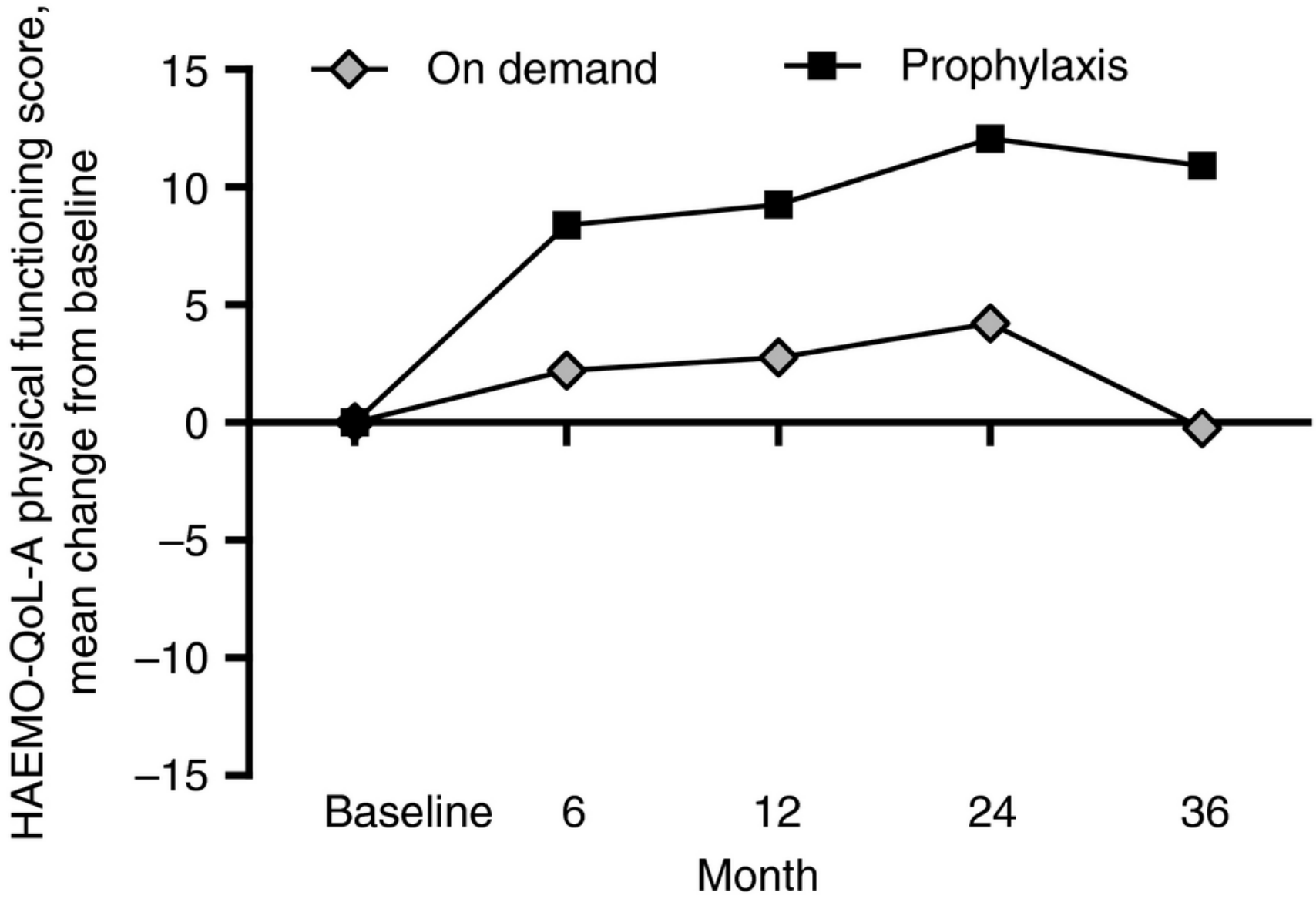

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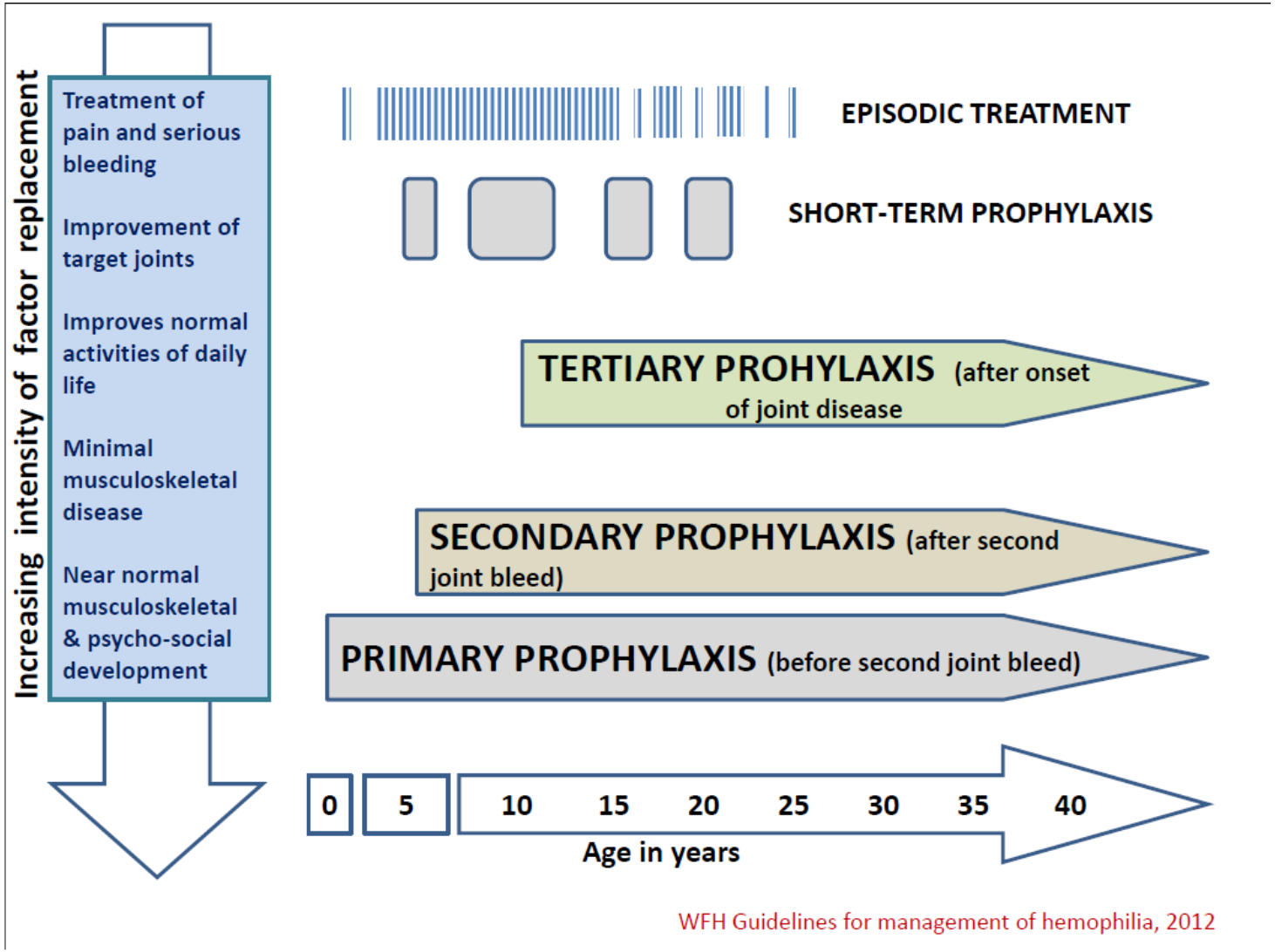
Never too late to optimize prophylaxis



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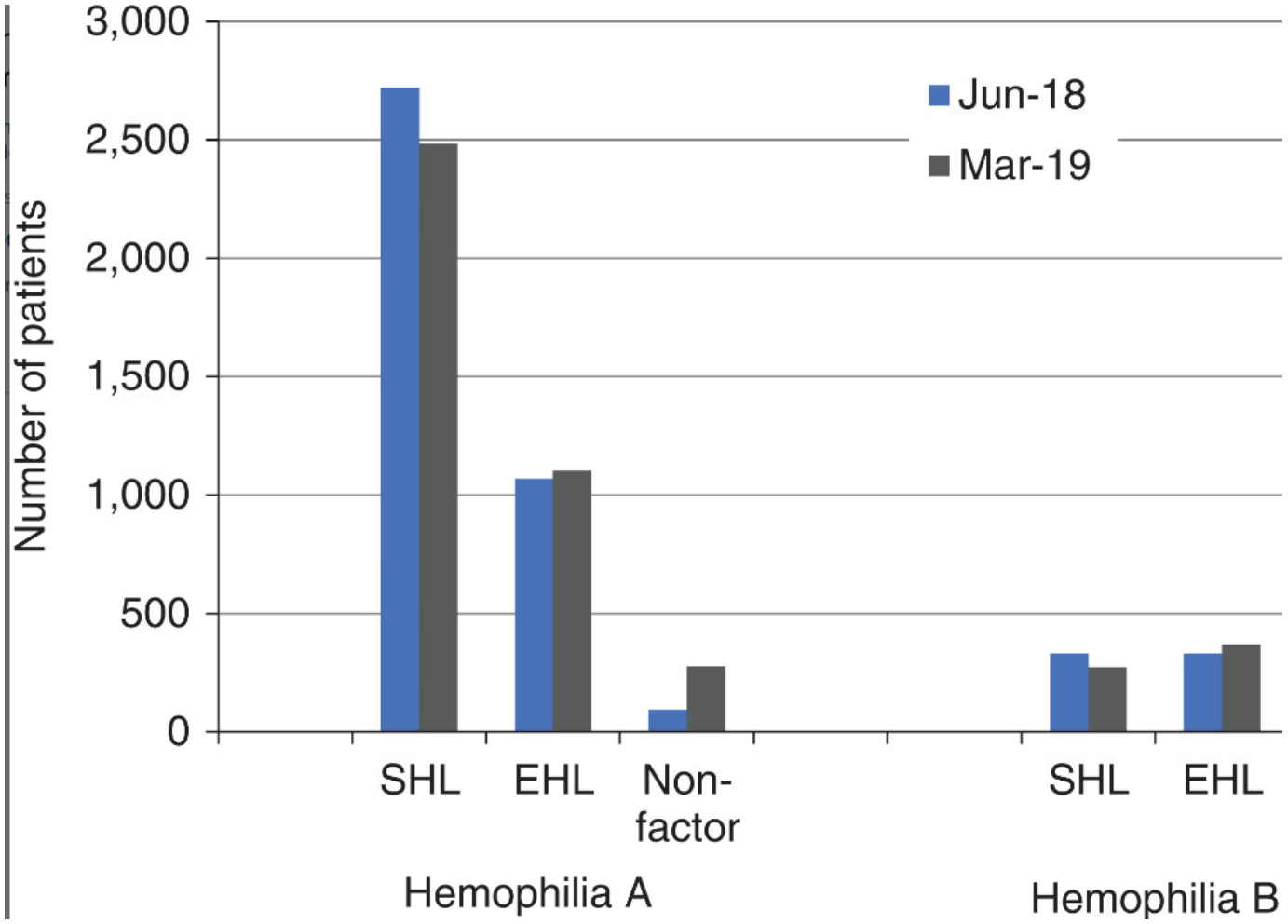
EHL Adoption in the US



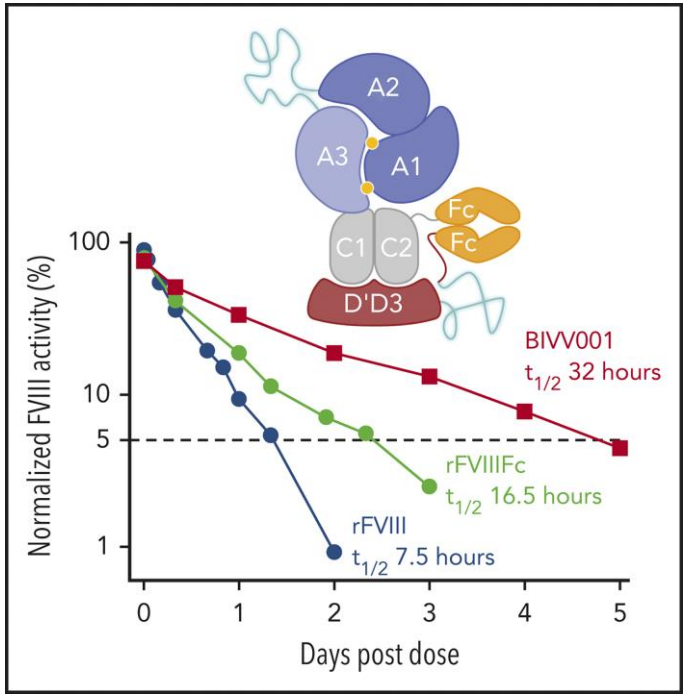
› Am J Hematol. 2020 Aug;95(8):960-965. doi: 10.1002/ajh.25844.

The impact of extended half–life factor concentrates on prophylaxis for severe hemophilia in the United States

Lynn M Malec [1 2], Dunlei Cheng [3], Char M Witmer [4], Julie Jaffray [5], Peter A Kouides [6], Kristina M Haley [7], Robert F Sidonio Jr [8], Kelsey Johnson [1], Michael Recht [3 7], Gilbert White [1 2], Stacy E Croteau [9], Margaret V Ragni [10 11]

Furthering Half-life Extension in Hemophilia A

BIVV001, a new class of factor VIII replacement for hemophilia A that is independent of von Willebrand factor in primates and mice



BIVV001: Dosing Schedule Similar to Heme B EHLs?

BIVV001

*Mechanism of action**	• FVIII therapy with single-chain FVIII, the Fc domain of human immunoglobulin G1, 2 XTEN polypeptides, and the FVIII-binding D'D3 domain of VWF, designed to circulate in plasma independently of VWF, thereby breaking the VWF half-life ceiling[1]

	Possible Pros	Possible Cons
Indications	• Patients with haemophilia A (inferred from patients treated in studies carried out to date)[2]	• Results for this agent are not sufficiently mature to comment on limitations
Administration		• Intravenous
Monitoring	• Not established	
Efficacy	• Data from the completed Phase 1/2a EXTEN-A study of BIVV001 showed that a single 65 IU/kg dose of BIVV001 achieved average factor activity levels of 17% at 7 days post infusion and significantly extended the half-life of FVIII to 43 hours[2]	
Safety	• In EXTEN-A, BIVV001 was generally well tolerated with no development of inhibitors. No AEs of allergic reaction or anaphylaxis or treatment-related AEs were reported[2]	
Clinical trials	• EXTEN-A is an open-label, multicenter study that evaluated the safety, tolerability and pharmacokinetics of BIVV001 in both a 25 IU/kg dose and 65 IU/kg dose cohort of subjects aged 18-65 years with severe haemophilia A	

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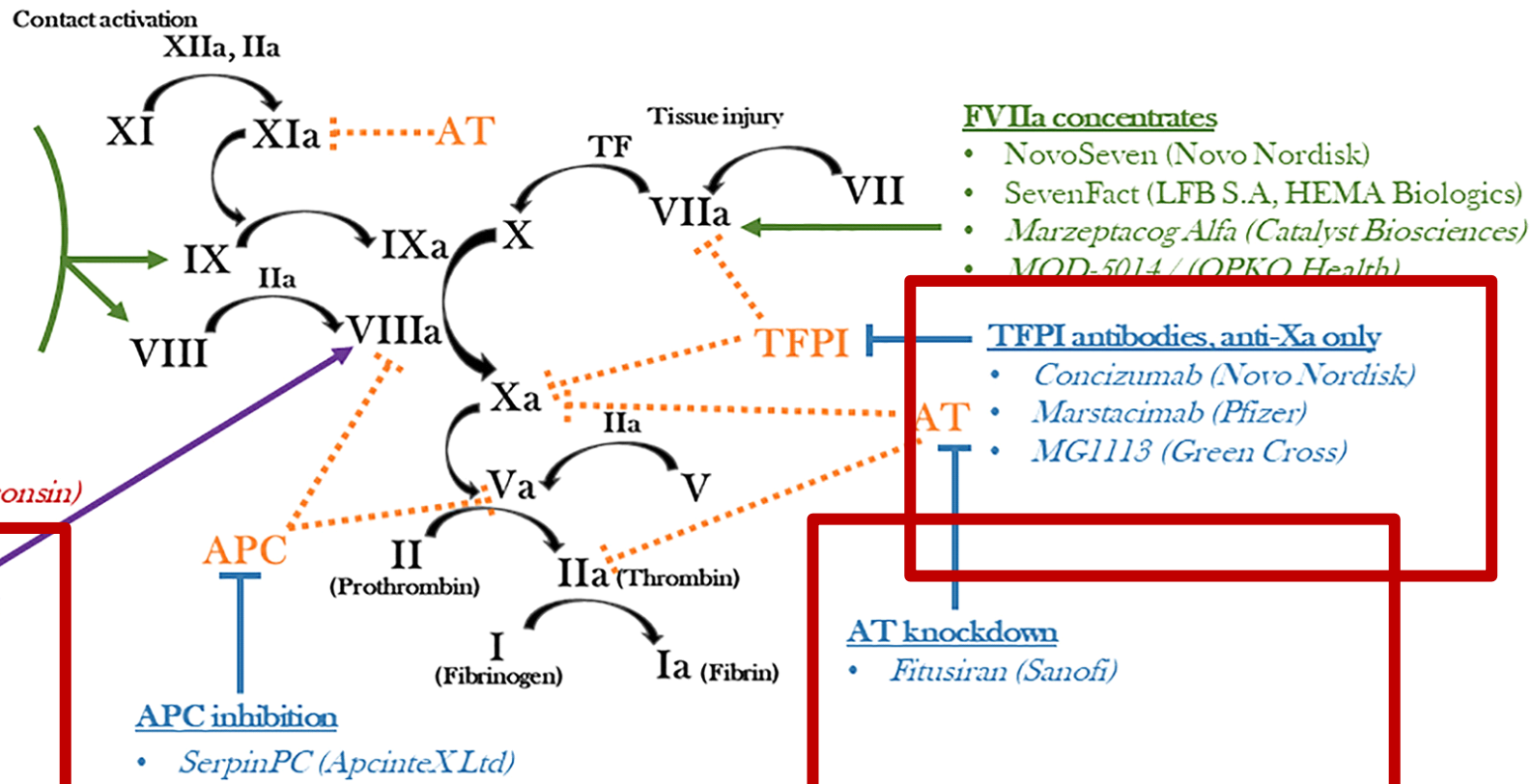

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Non-factor therapies

Approved products

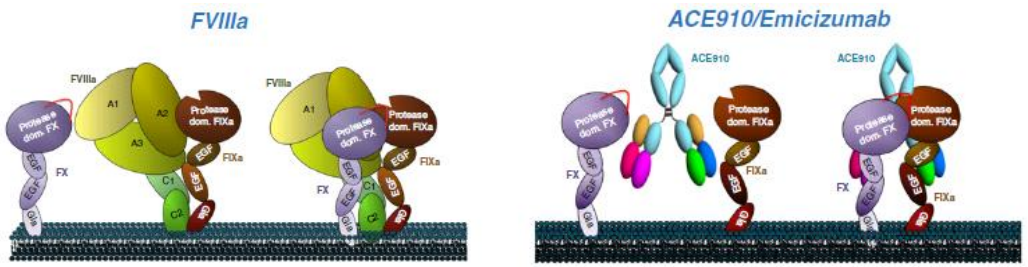
- Clinical trial data
- Real-world experience & post marketing Data

Emicizumab

- Approved 2017 for hemophilia A with inhibitors in US
- Approved 2018 for hemophilia A (without inhibitors) in US

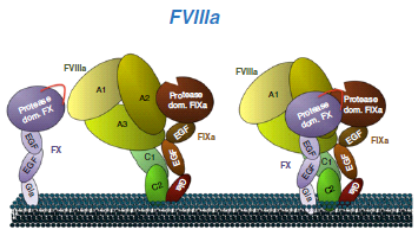
Emicizumab

Mechanism of Action

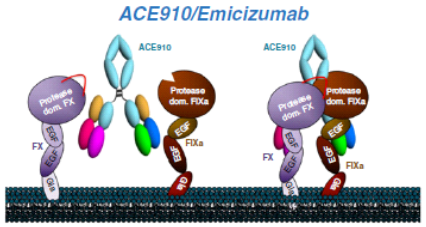


Lenting et al. Blood 2017;130(23):2463-2468.

Comparison with FVIIIa



Multiple sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor
FVIIIa has on/off mechanism
High level of self-regulation



Single sites of interaction
Low affinity for enzyme & substrate *(micromolar range)*
No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Partial cofactor activity - *bridges FIXa to FX*
Antibody is in excess over enzyme and substrate
Emicizumab has no on/off mechanism
Low level of self-regulation

Lenting et al. Blood 2017;130(23):2463-2468.

Bispecific Antibodies/Factor VIII Mimetics

Efficacy

- Bleed control
- Target joint Resolution

Safety

- Gaining data in real world regarding risks of TMA, thrombosis, other side effects
- Ongoing clinical trials

Additional Populations? PUPs, Acquired hemophilia, VWD

Antithrombin Knockdown

Antithrombin (Fitusiran)

*Mechanism of action**	• Non-biologic, chemically synthesized, with targeting ligand to specifically deliver to liver – site of AT synthesis[1,2] • Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels[2]
Clinical trials	• Phase 1 dose escalation study and Phase 2 open label extension study in healthy volunteers and patients with haemophilia[3] • Phase 3 study in patients with inhibitors currently ongoing[3]

	Possible Pros	Possible Cons
Indications	• Affects haemostasis more generally and may provide prophylaxis for multiple patient subgroups beyond (and including) haemophilia A[3]	• Available data was obtained from studies that did not include patients with inhibitors or complications[3]
Administration	• Small volume, once monthly SC dosing not based on body weight[4] • Potentially stable at room temperature and no reconstitution required[5]	• Data from ATLAS clinical trial program suggest Individualized bleed management plans may be required to reduce the risk of fatalities (eg, lower doses of factor or BPA, avoid combination with antifibrinolytics)[6]
Monitoring	• Effects can be monitored and reversed[6]	
Efficacy	• Specific and long-lasting attenuating effects on breakdown of clotting cascade via dose dependent decrease in AT and increase in thrombin[3,7] • Median ABR 1.08 in patients without inhibitors[8]	• Long median recovery of AT3 levels[6]
Safety		• Potential for severe AT3 deficiency that may lead to thrombosis[9] • Potentially unknown side effects due to largely unknown MoA[10] • Phase 2 open label extension study had to be temporarily closed after a fatal severe AE; study was reopened following the implementation of mitigation plan[3,7]

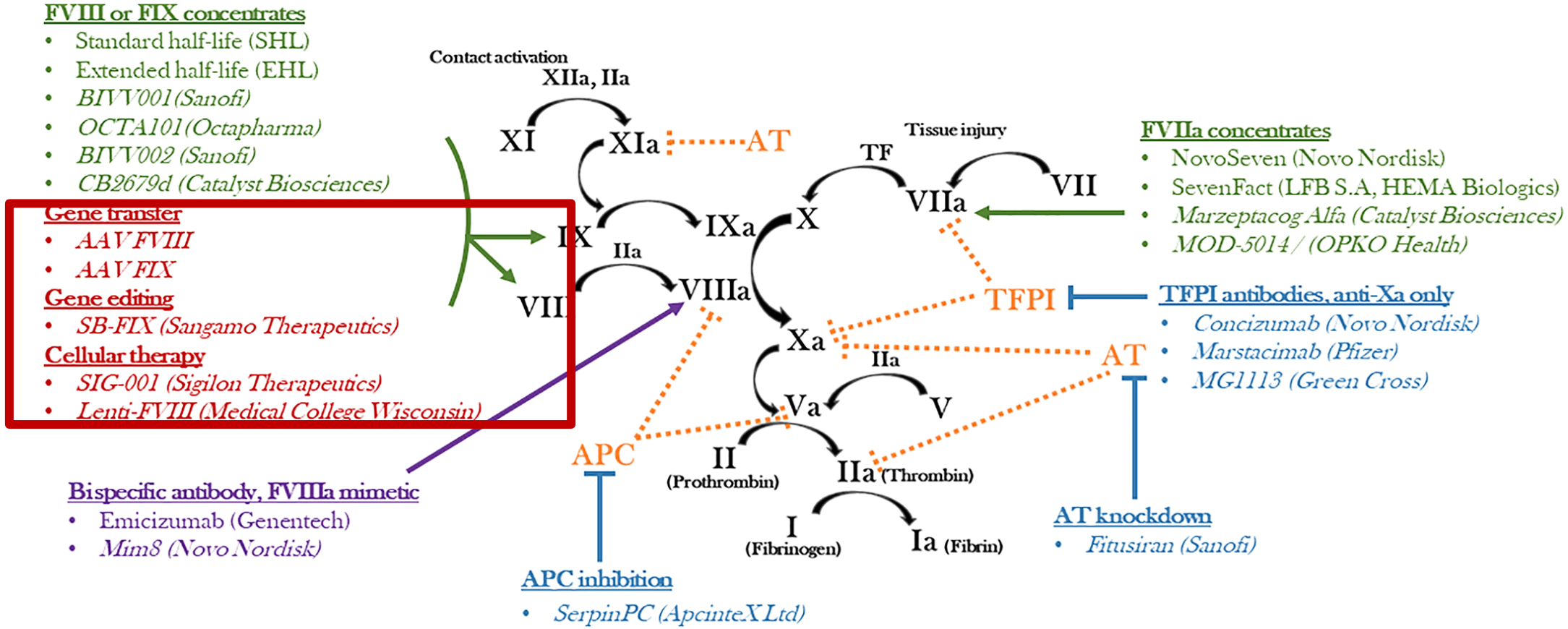
Anti-TFPI

Anti-TFPI (Concizumab)

*Mechanism of action**	• Monoclonal, humanized antibody specific for the second Kunitz domain of TFPI-α, which binds and inhibits FXa of the extrinsic clotting system inhibiting FVIIa, thereby abolishing the inhibitory effect of TFPI[1-3] • Blocks initiation of clotting cascade while leaving other regulatory mechanisms intact[1]
Clinical trials	• Explorer™ study program[3] • Phase 2 proof of concept multiple dose study in patients with haemophilia A and inhibitors is ongoing[1,3]

	Possible Pros	Possible Cons
Indications	• Haemostatic rebalancing therapy that may provide prophylaxis for multiple patient subgroups beyond (and including) haemophilia A[1,2]	• Available data were obtained from studies not including patients with inhibitors or complications[3]
Administration	• Short acting agent allowing for more endogenous regulation[4] • Administration via once daily SC injection or IV[5,6]	• Unclear whether administration of FVIII or FVIIa is required for bleed management[3]
Monitoring		• Monitoring is challenging due to generally low plasma TFPI levels[7]
Efficacy	• Dose-dependent correlation with decreased plasma TFPI levels and reduced bleeding tendency[1-3] • ABR reduced across all subtypes of patients in EXPLORER 4 and 5[8]	• Efficacy and time frame of platelet TFPI inhibition unclear[5] • Exact therapeutic window for achievement of bleed prevention vs potential for thrombosis is not yet defined[3] • Effects of TFPI inhibition on FVIII activity unknown[5]
Safety		• Unknown potential side effects due to MoA; AE anticipation is less straightforward than fitusiran due to lack of data on TFPI[3-5]

Patient Case 1: PUP with Severe Hemophilia A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Contact activation
XIIa, IIa
XI
XIa
AT
IX
IXa
IIa
VIII
VIIIa
Tissue injury
TF
VIIa
VII
X
TFPI
Xa
IIa
AT
Va
V
APC
II
(Prothrombin)
IIa (Thrombin)
I
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Gene Transfer and Editing

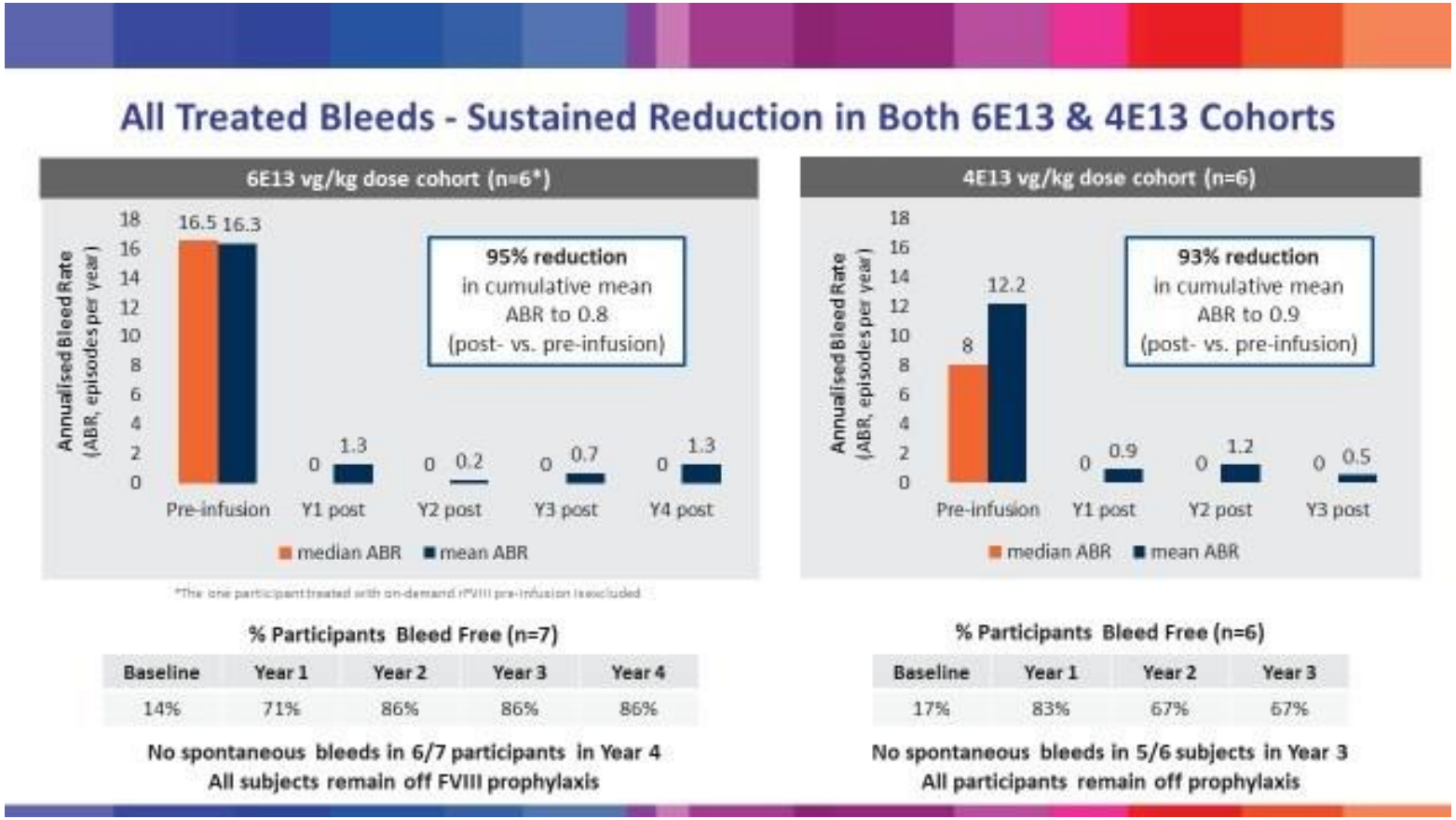
Several approaches to enable endogenous production of FVIII and FIX are now in clinical trials

- AAV vector strategy furthest in development

Considerations

- Study populations, limiting factors
- Short term challenges and toxicity
- Efficacy, durability and long-term outcomes

Looking at Efficacy of Gene Therapy



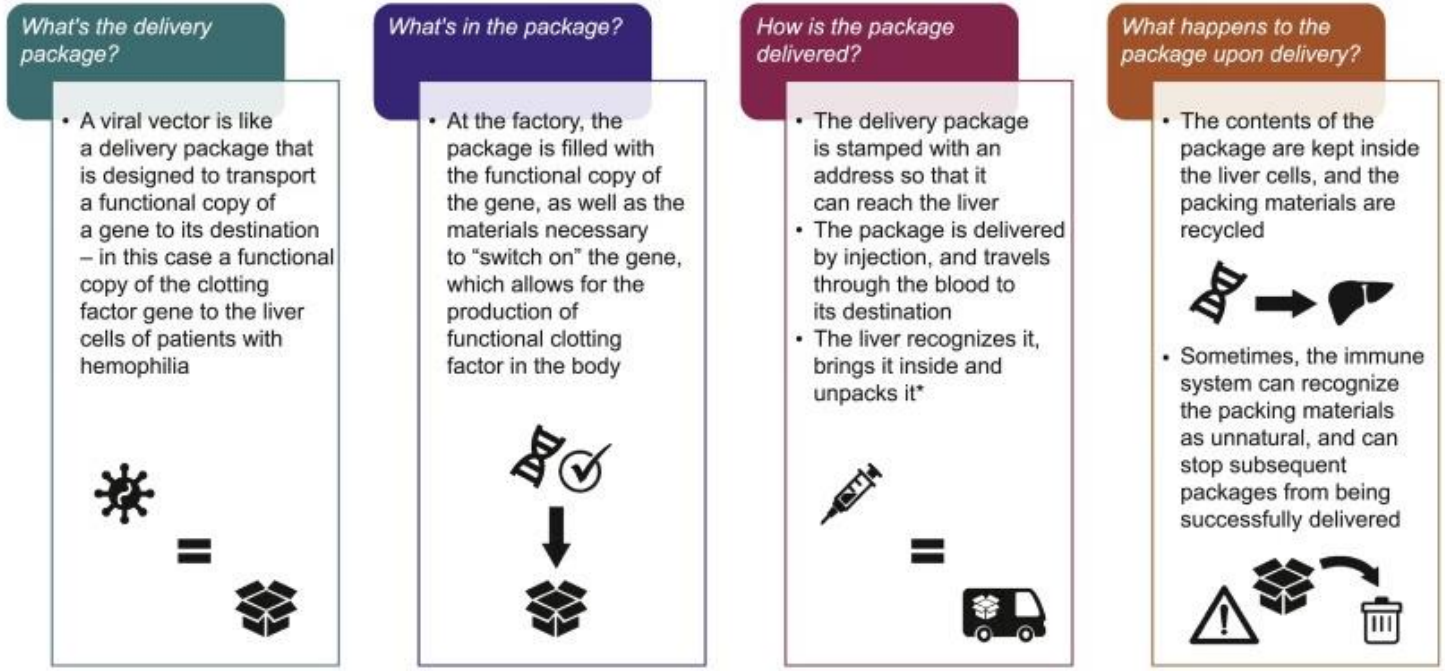
Annualized bleed rates →

Factor VIII/IX levels
(and sustainability over time)

Dosing free intervals

Bleed free intervals

Discussing Gene Therapy with Patients

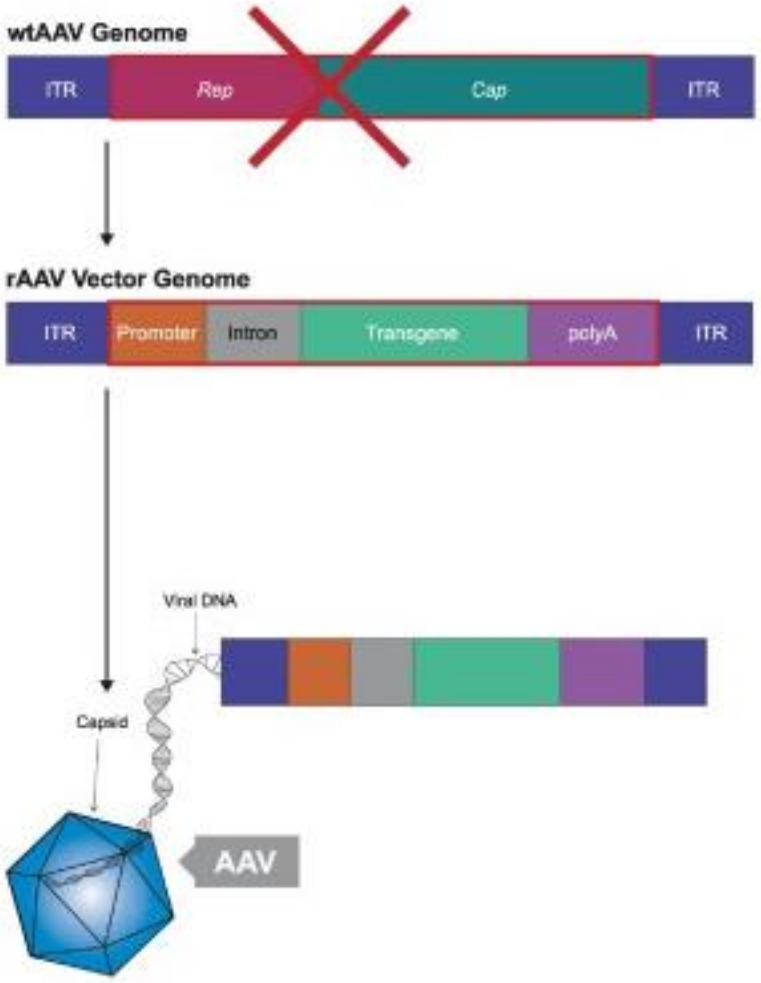


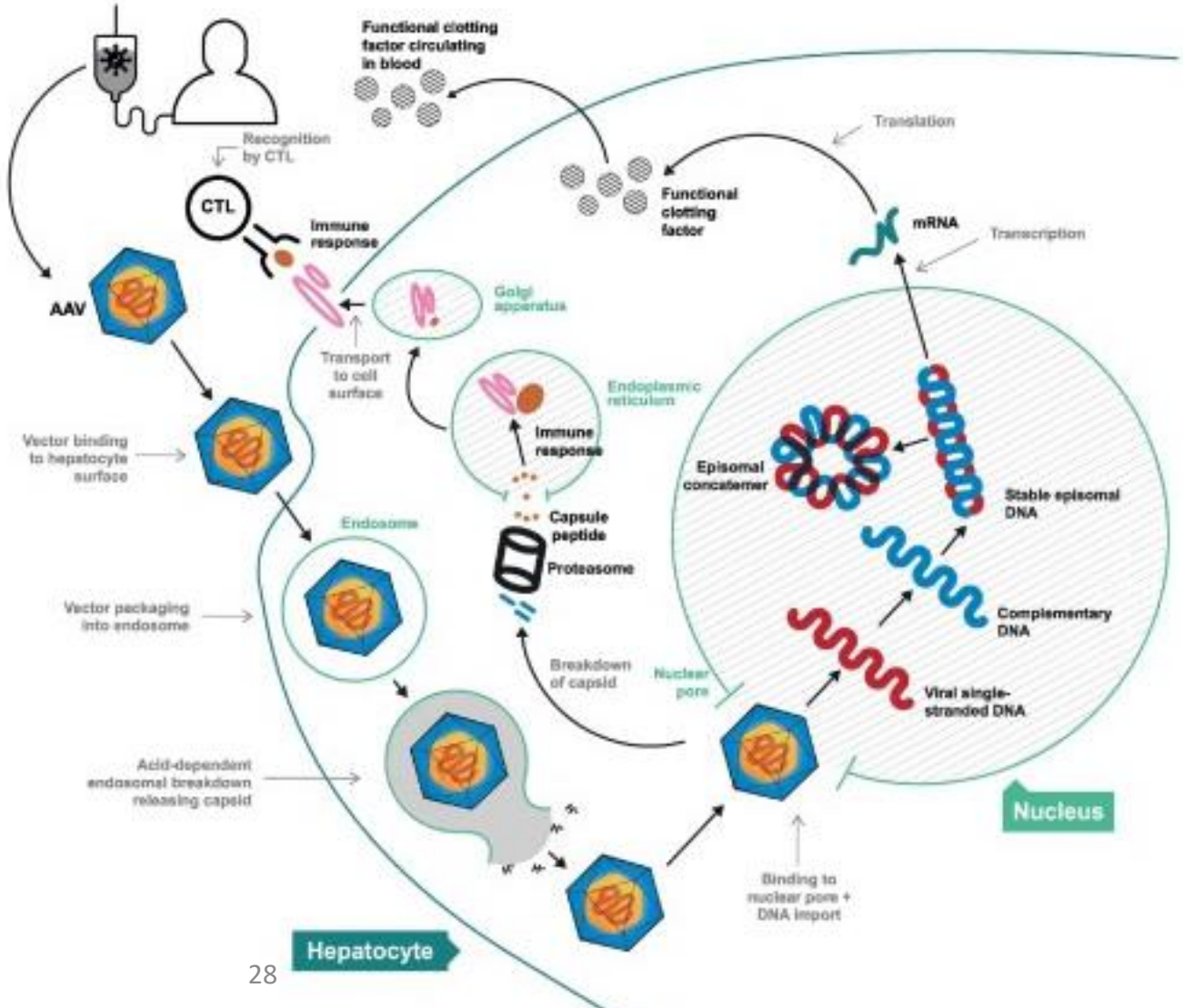
*While the package is delivered at a high rate to the liver, it will also arrive at, and be unpacked by, many other cell types in the body. However, the gene encoding the functional protein will only be expressed in the liver, because liver-specific promoters are used to drive gene expression.

Review › Blood Rev. 2021 May;47:100759. doi: 10.1016/j.blre.2020.100759. Epub 2020 Nov 10.

Discussing investigational AAV gene therapy with hemophilia patients: A guide

Robert F Sidonio Jr [1], Steven W Pipe [2], Michael U Callaghan [3], Leonard A Valentino [4], Paul E Monahan [5], Stacy E Croteau [6]


wtAAV Genome
ITR
Rep
Cap
ITR
rAAV Vector Genome
ITR
Promoter
Intron
Transgene
polyA
ITR
Viral DNA
Capsid
AAV


Functional clotting factor circulating in blood
Recognition by CTL
CTL
Immune response
AAV
Golgi apparatus
Transport to cell surface
Endoplasmic reticulum
Immune response
Vector binding to hepatocyte surface
Endosome
Capsule peptide
Proteasome
Vector packaging into endosome
Breakdown of capsid
Nuclear pore
Acid-dependent endosomal breakdown releasing capsid
Translation
Functional clotting factor
mRNA
Transcription
Episomal concatemer
Stable episomal DNA
Complementary DNA
Viral single-stranded DNA
Nucleus
Binding to nuclear pore + DNA import
Hepatocyte

Cellular Therapies

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 9654–9659, August 1999
Cell Biology

1999

Integrin αIIb promoter-targeted expression of gene products in megakaryocytes derived from retrovirus-transduced human hematopoietic cells

DAVID A. WILCOX*†, JOHN C. OLSEN*‡, LORI ISHIZAWA§, MICHAEL GRIFFITH§, AND GILBERT C. WHITE II*†¶‖

¶Center for Thrombosis and Hemostasis, Departments of *Medicine and †Pharmacology, and ‡Cystic Fibrosis/Pulmonary Research and Treatment Center, University of North Carolina, Chapel Hill, NC 27599; and §Nexell Therapeutics Inc., Irvine, CA 92618

Communicated by Inder M. Verma, The Salk Institute for Biological Studies, San Diego, CA, June 17, 1999 (received for review March 26, 1999)

Journal of Thrombosis and Haemostasis, **1**: 2477–2489

IN FOCUS

Induction of megakaryocytes to synthesize and store a releasable pool of human factor VIII

D. A. WILCOX,*†‡ Q. SHI,*† P. NURDEN,§ S. L. HABERICHTER,*‡ J. B. ROSENBERG,† B. D. JOHNSON,*‡ A. T. NURDEN,§ G. C. WHITE II¶ and R. R. MONTGOMERY*†‡

*Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin; †Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, Wisconsin; ‡Children's Hospital of Wisconsin, Milwaukee, Wisconsin, USA; §IFRN°4, Laboratoire d' Hematologie, Hôpital Cardiologique, Pessac, France; and ¶Center for Thrombosis and Hemostasis, Departments of Medicine and Pharmacology, University of North Carolina, Chapel Hill, North Carolina, USA

Research article Related Commentary, page 1840

2006

Factor VIII ectopically targeted to platelets is therapeutic in hemophilia A with high-titer inhibitory antibodies

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ORIGINAL ARTICLE

Lentivirus-mediated platelet-derived factor VIII gene therapy in murine haemophilia A

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ARTICLE

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Platelet-targeted gene therapy with human factor VIII establishes haemostasis in dogs with haemophilia A

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Comparison: Lentiviral Vectors/HSC/PLT FVIII and AAV/Liver/Plasma FVIII

Advantage of LV/HSC GT with Pleightlet™

Can include ≈40% of patients who make antibodies to AAV capsid[1]

Can include ≈30% of patients with inhibitory Abs to plasma FVIII[1]

May include patients with liver damage[1]

AAV loss of expression with only one treatment possible, while LV-HSC traditionally treat once because expression is stable *(multiple times if necessary)*[2]

Can treat patients <18 yrs. as BM proliferates & replicates for life[3,4]

Ex Vivo HSC manipulation should not transduce germ cells[5]

Can include diverse (age, gender) population with exception some medical conditions[3,4]

Has low potential for insertional mutagenesis, clonal expansion, cancer[6,7]

Protocol Overview

Objective: Determine feasibility of *ex vivo* lentiviral gene therapy vector Pleightlet™; and incidence of sustained platelet engraftment of FVIII-transduced human PBSC, seen 30 days after transplant

Key inclusion criteria *

Current: Adult males >18 years of age with severe hemophilia A and high titer FVIII inhibitors (>5 BU).

IRB Amendment Pending: Adult males >18 years of age with severe hemophilia A with a history of inhibitors to FVIII (≥ 0.6 BU)

Diagnosis of severe hemophilia A by undetectable plasma FVIII:C by one-stage PTT-based assay and Coatest chromogenic FVIII assay

Subject may use prophylactic therapy with FVIII bypassing agents or FVIII mimetics prior to referral for inclusion in the study

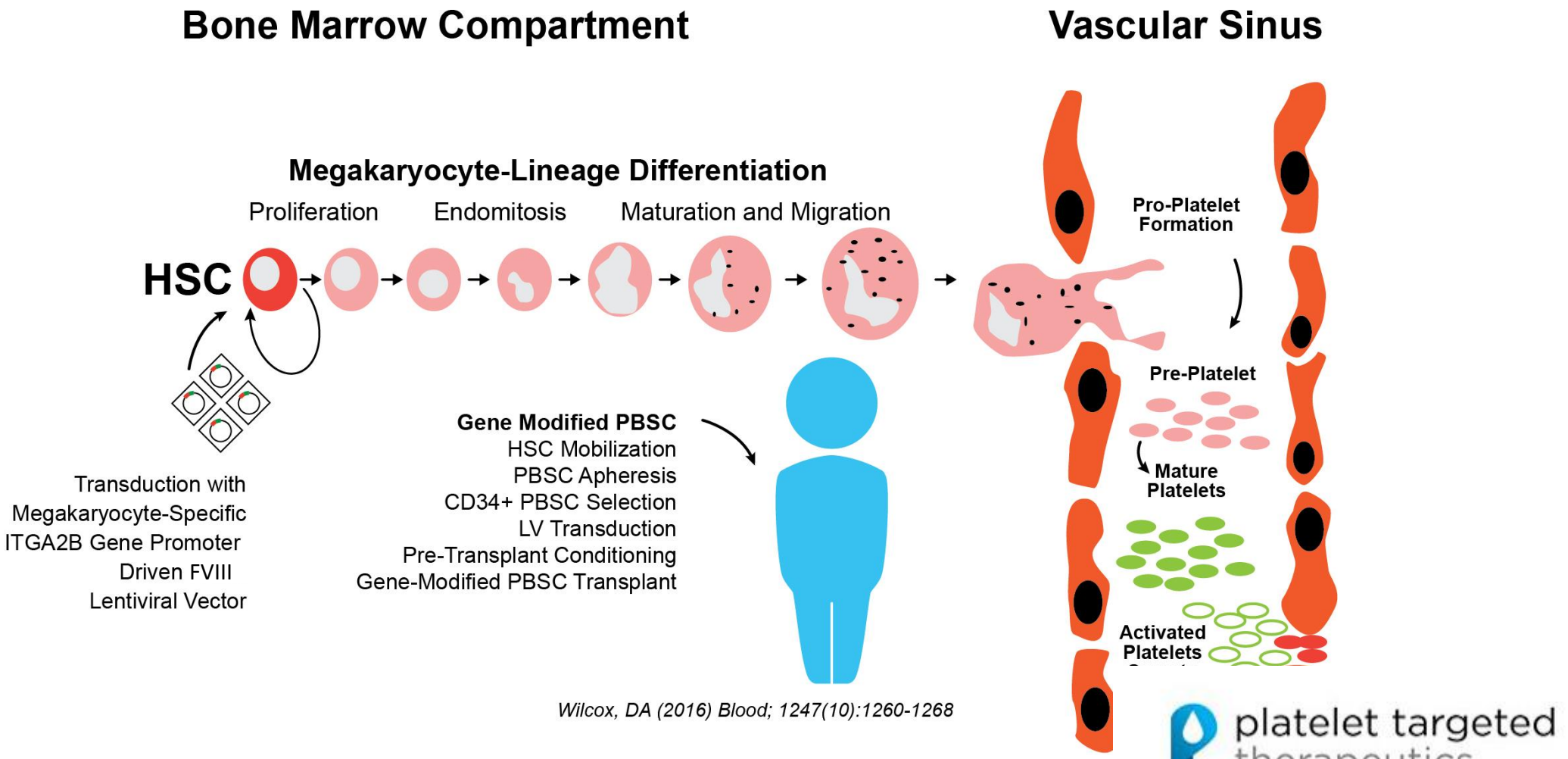
Key exclusion criteria *

Medical contraindication to PBSC cytokine mobilization, use of GCSF, PBSC apheresis procedure or conditioning regimen

Medically significant organ dysfunction that would prevent compliance with conditioning or would severely limit probability of survival based on clinical status

HSC Gene Therapy Strategy for Platelets

FVIII for Hemophilia A



platelet targeted therapeutics

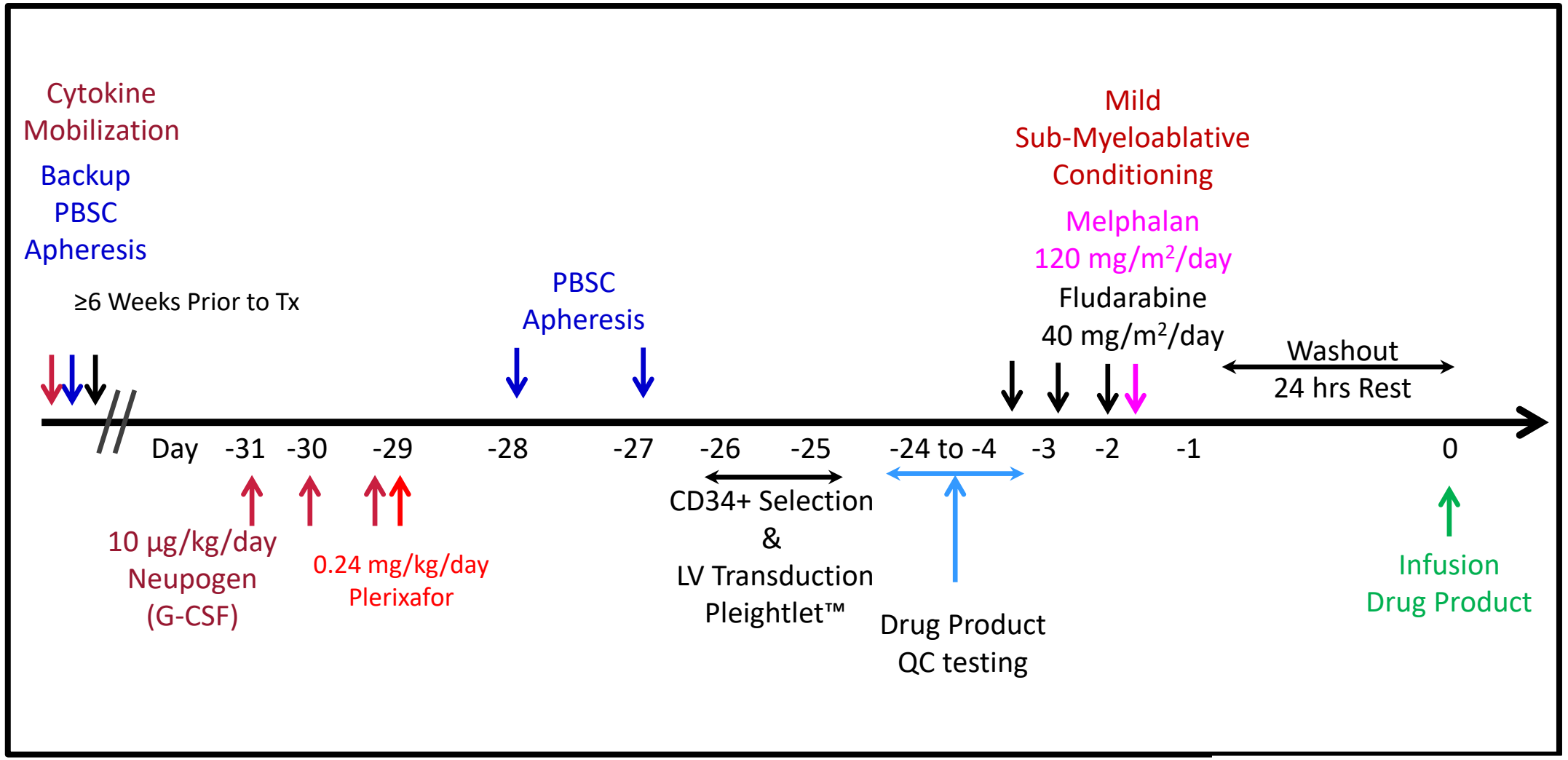
Adapted from Wilcox, DA (2016) Blood; 1247(10):1260-1268

Protocol Summary

Phase	I
Age	≥18 yr old Adult Male (X-Linked disorder)
N	5 Patients with Severe (≤1%FVIII) Hemophilia A with inhibitory antibodies to FVIII
Vector	-889ITGA2B BDDFVIII WPTS (MUT6) / Pleightlet™
Envelope	VSV-G
Source of CD34 (BM, mPB, UCB, more than one)	Neupogen/Plerixafor mobilized CD34+ PBSC Product of Apheresis & ClinicMacs Isolation
Fresh or frozen	Fresh Transduced/Frozen/Thawed Transplant
Target cell dose to infuse	≥ 3x10^6 to ≤20 x 10^6 CD34+PBSC/kg
Conditioning	Fludarabine 40 mg/m^2/day x 3 days Melphalan 120 mg/m^2/day x 1 day
Recruit over how many years	5 yrs, FDA request 6 months between pt 1 & 2
Follow-up duration	15 yrs
Funding for trial	NIH-NHLBI: U01 GGACT; R01 TAG/Philanthropic CRI MCW

versiti™

LV HSC Transduction/Transplant CMC Pleightlet™



platelet targeted therapeutics

Case 2: 26 y/o with SHA without prior inhibitor with target joint of both ankles

Key Considerations

Stability of his current joint assessment

- No progression → many options
- Progression → escalation and/or change of therapy

What is the role for gene therapy?

- Personal decision based on many different factors
  - Importance of being (nearly) ‘treatment free’
  - Patient specific factors gleaned from clinical trials?

Key Challenges

Capacity to balance patient and provider values and suggestions is difficult

Need to change from one model fits all to a more individualize approach

- How do we begin to do this?

In US, delivery of therapy (gene and cellular therapy) will be logistically challenging

Ever Changing → Ever Learning Clinicians and Patients

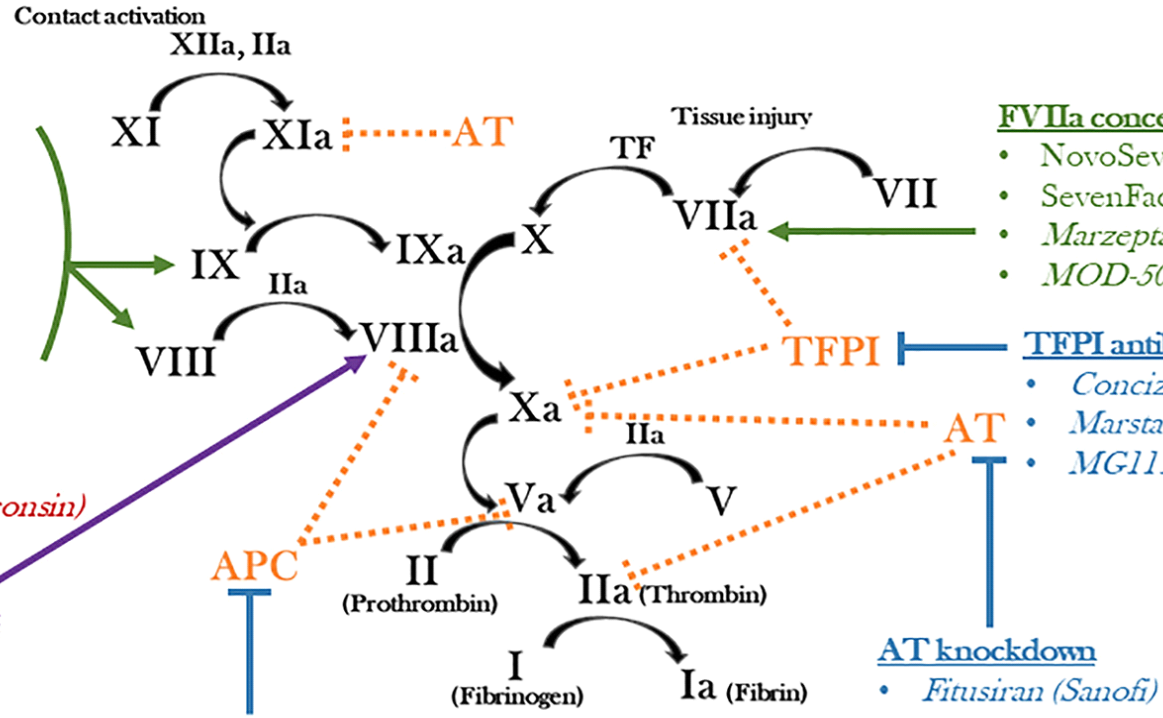
FVIII or FIX concentrates
- Standard half-life (SHL)
- Extended half-life (EHL)
- *BIVV001 (Sanofi)*
- *OCTA101 (Octapharma)*
- *BIVV002 (Sanofi)*
- *CB2679d (Catalyst Biosciences)*

Gene transfer
- *AAV FVIII*
- *AAV FIX*

Gene editing
- *SB-FIX (Sangamo Therapeutics)*

Cellular therapy
- *SIG-001 (Sigilon Therapeutics)*
- *Lenti-FVIII (Medical College Wisconsin)*

Bispecific antibody, FVIIIa mimetic
- Emicizumab (Genentech)
- *Mim8 (Novo Nordisk)*



APC inhibition
- *SerpinPC (ApcinteX Ltd)*

FVIIa concentrates
- NovoSeven (Novo Nordisk)
- SevenFact (LFB S.A, HEMA Biologics)
- *Marzeptacog Alfa (Catalyst Biosciences)*
- *MOD-5014 / (OPKO Health)*

TFPI antibodies, anti-Xa only
- *Concizumab (Novo Nordisk)*
- *Marstacimab (Pfizer)*
- *MG1113 (Green Cross)*

AT knockdown
- *Fitusiran (Sanofi)*