Hemophilia

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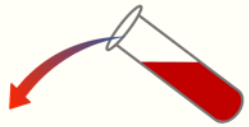
Disclosures

- Research support: (Last 24 Months)
  Biogen/Sanofi, Roche/Genentech, Spark, Pfizer, Takeda/Shire

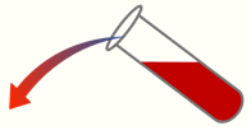
- Medical Advisory Board (Last 24 months)
  Genentech, CSL, Octapharma

- I will be discussing off-label use of medications



Objectives

- Accurately recognize the inheritance pattern, clinical presentation and laboratory evaluation for Hemophilia
- Understand the risks and benefits of clotting factor administration for the treatment
- Describe 3 approaches to improve the prevention of bleeding events in patients with Hemophilia

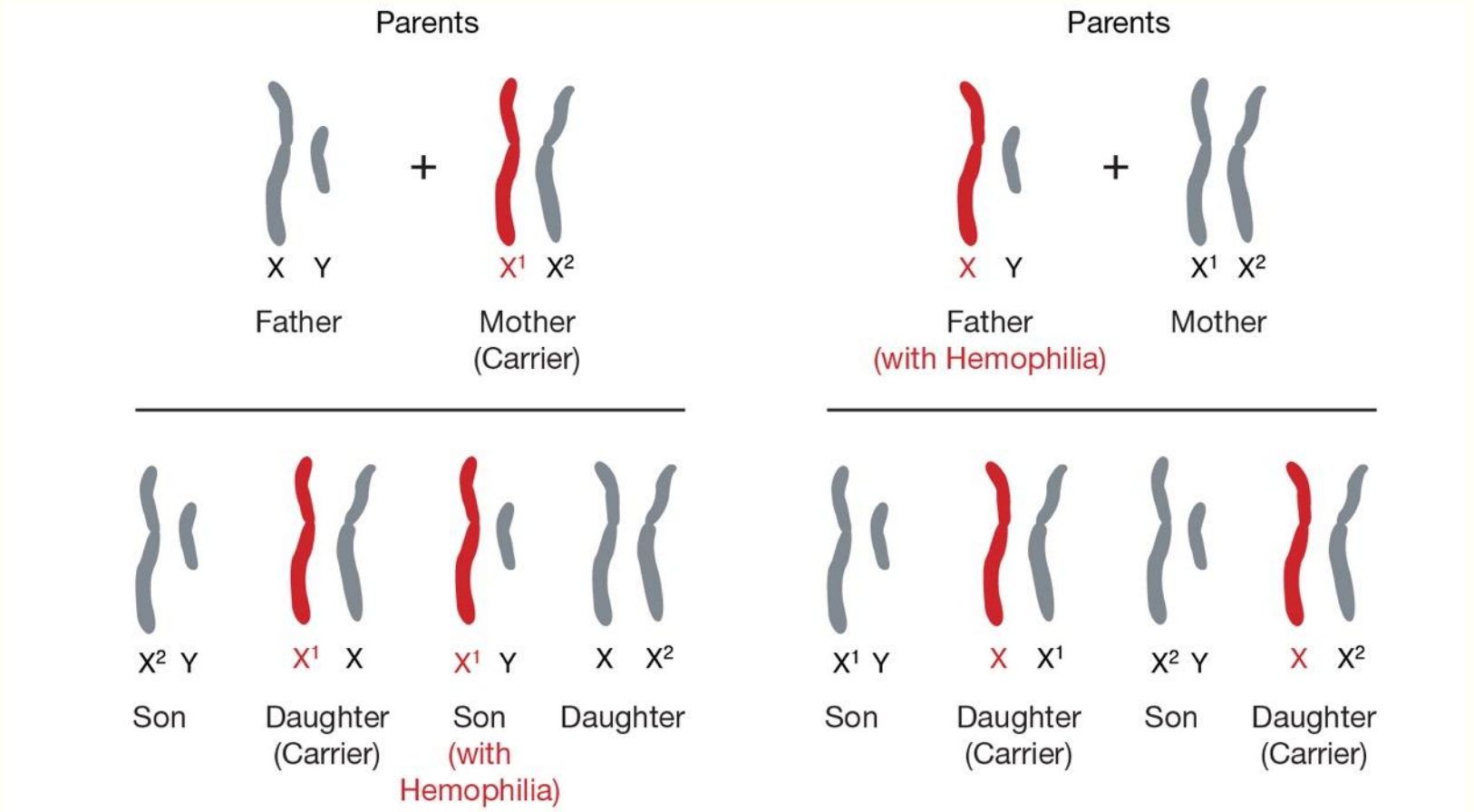


Hematology Consult Clinic

Maternal History

- Prenatal Genetic Screening :
  - Factor 9 (F9) Variant : c.277+4A>G
- Referred by OB/GYN to Hematology

Hemophilia A/B are X-linked disorders

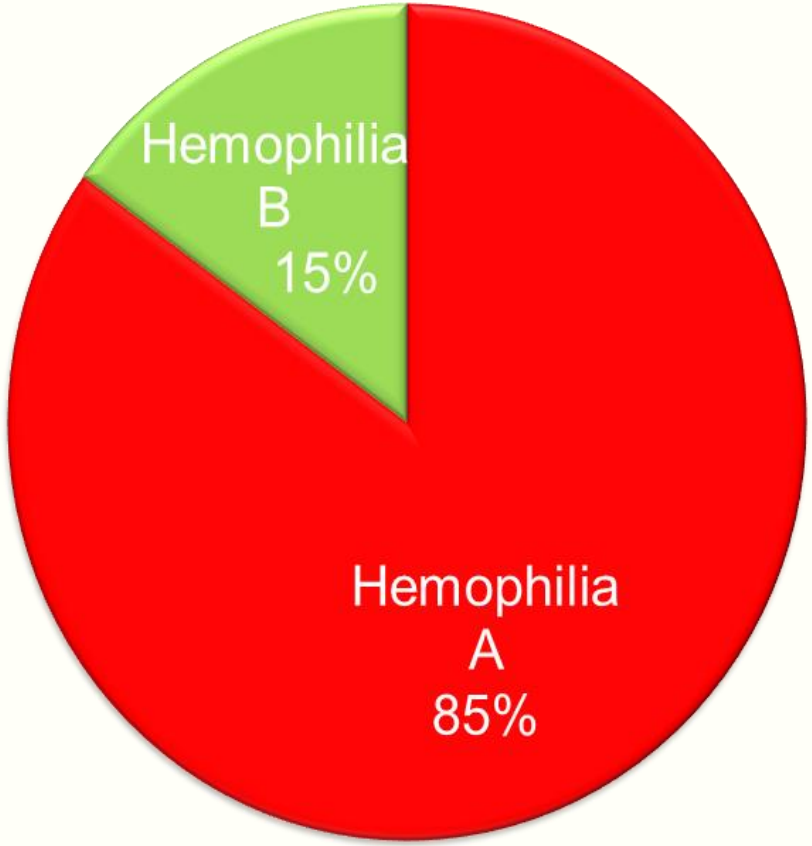


https://www.genome.gov/genetics-glossary/hemophilia

1/3 of patients with hemophilia with no family history

- 1 in 5,000 males (A)
- 1 in 30,000 males (B)

- 30% of cases have NO family history



- *** Advanced Paternal Age Hypothesis**

Rossiter et al. Hum. Mol. Gen. 1994, Carcao, M. Unpublished
Wolf and Lassila, 2019, Haemophilia

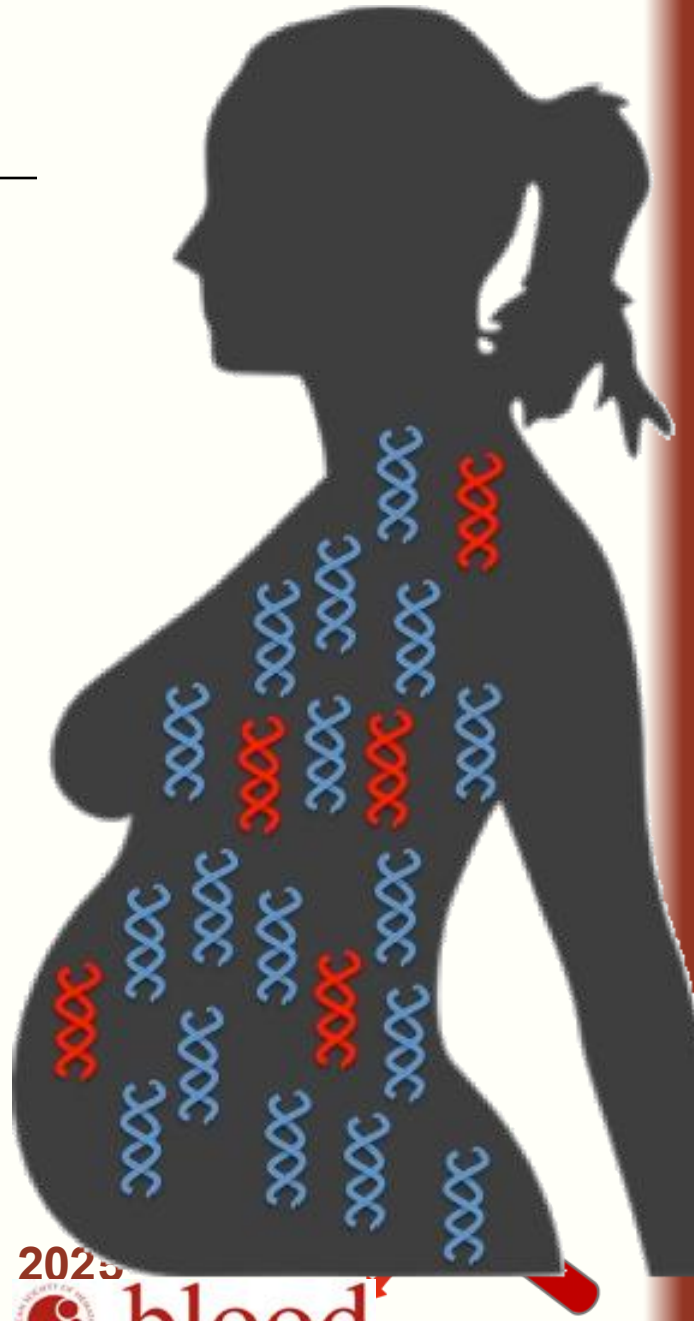
Women Can Have Hemophilia

- Lyonization of the normal X chromosome
- Turner syndrome (XO)
- Father with hemophilia / mom as a carrier
- vWD type 2N (Normandy) *

* Von Willebrand Disease

Prenatal and Genetic Counseling

- Ultrasound
- CVS / Amniocentesis
- Free Fetal DNA (Future State)
- Pre-Implantation Genetic Diagnosis
- Mode of Delivery



Tsui N B Y et al. Blood 2011;117:3684-3691

blood

Prenatal Diagnosis ….

Maternal History

PTT: Normal

FIX Level: 70 %

History: ISTH BAT=0

Fetal History:

CVS confirmation

- Factor 9 (F9) Variant : c.277+4A>G

c.277+4A>G N/A (N/A)

Mutation Type: Point **Domain:**- **Nucleotide number:**6706

Mutation Effect: Splice **Location:**Intron(3) **CpG:**N

No. of patients reported:4 **No. of bases:**1

Structural Information

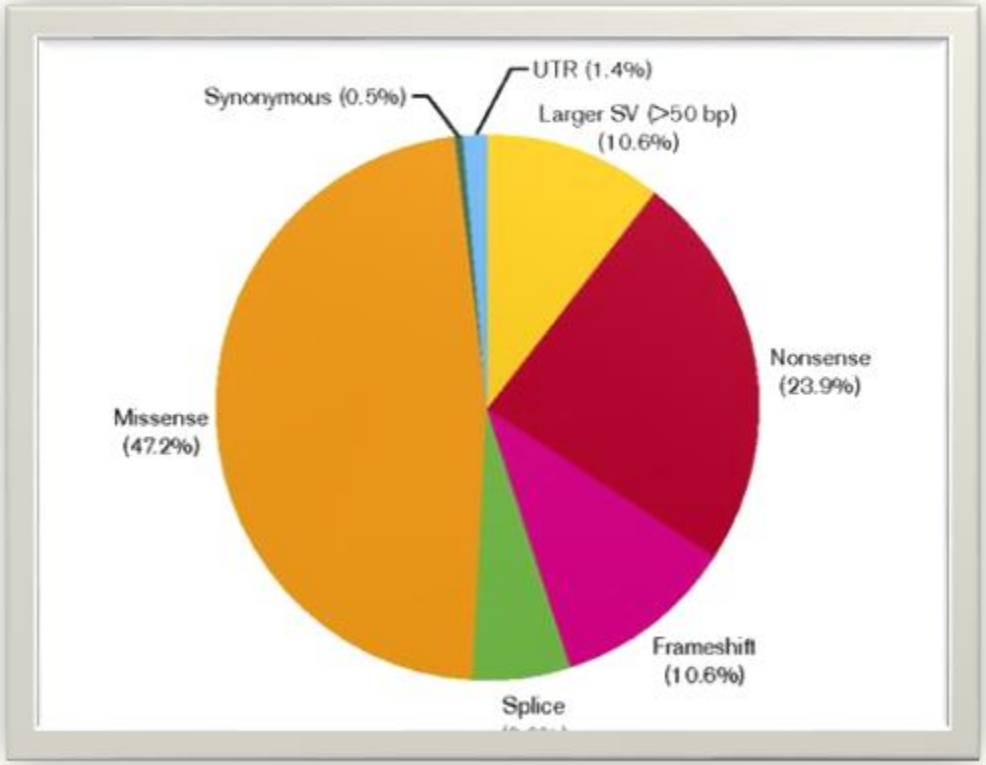
Structural Analysis is only available for **missense** mutations and cannot be performed for this type (Point | Splice) of mutation at Intron 3.

Patient Information : Hide

Patient	FIX:C(%)	FIX:Ag(%)	Inheritance	Severity	Type	Inhibitors	Country	Comments	Reference
1	-	<1			-		Spain	-	Montejo et al (1999)
2	<1	-		Severe	-		Germany	-	Wulff et al (1998)
3	-	-		Moderate	-		Germany	-	Wulff et al (1998)
4	-	-		Moderate	-	NO	Italy	-	Belvini et al (2005)

https://www.factorix.org/

F9 Gene Mutations

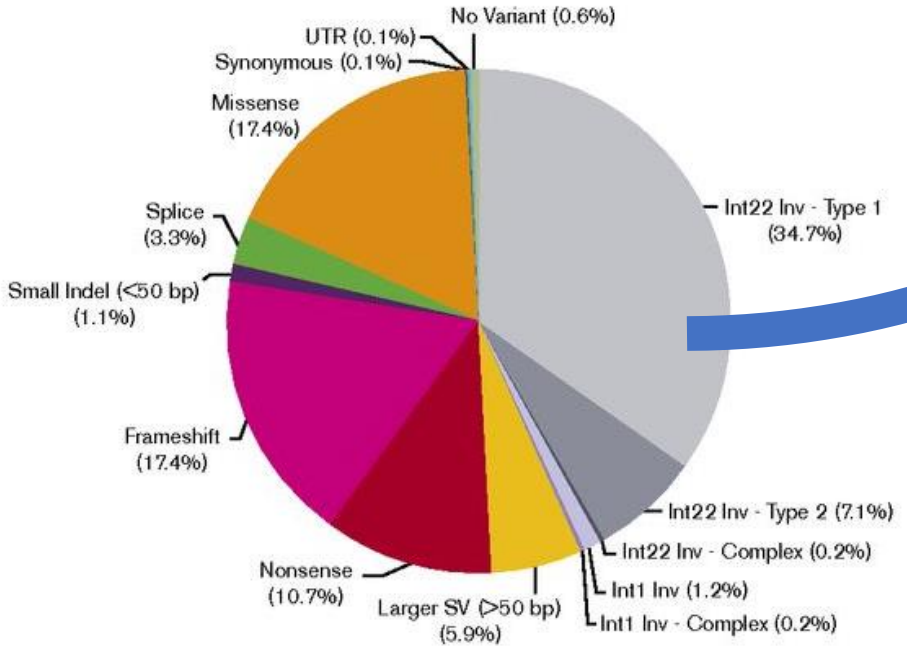


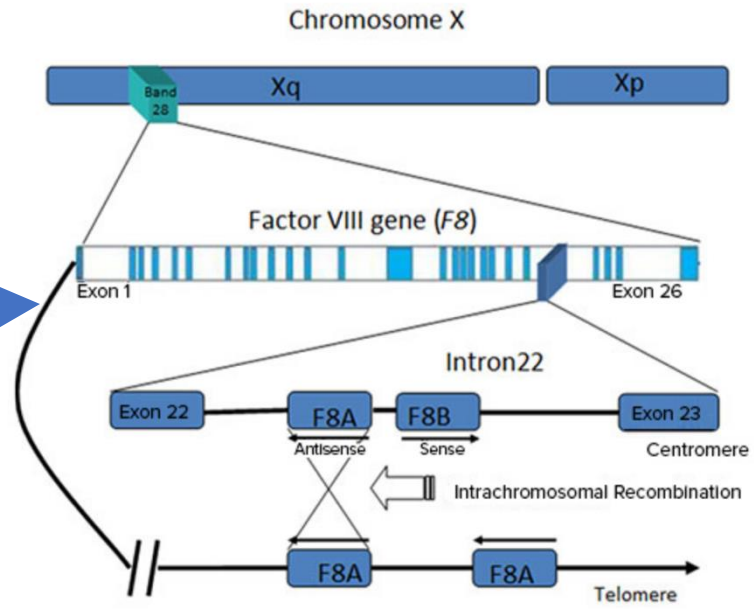
- Missense (47%)
- Nonsense (24%)
- Frameshift (10%)
- Splice Site (6%)

Johnsen, J et al. Blood Advances (2017)

Intron 22 inversion is the most common mutation

- Exact defect known: ~ 95%
- Mild-moderate hemophilia: Missense 85%
- Severe hemophilia:





Johnsen, J et al. Blood Advances (2017)
https://reference.medscape.com/features/slideshow/hemophilia-a#page=5

History of Hemophilia

2nd Century AD

Babylonian Talmud

11th -12 th Century

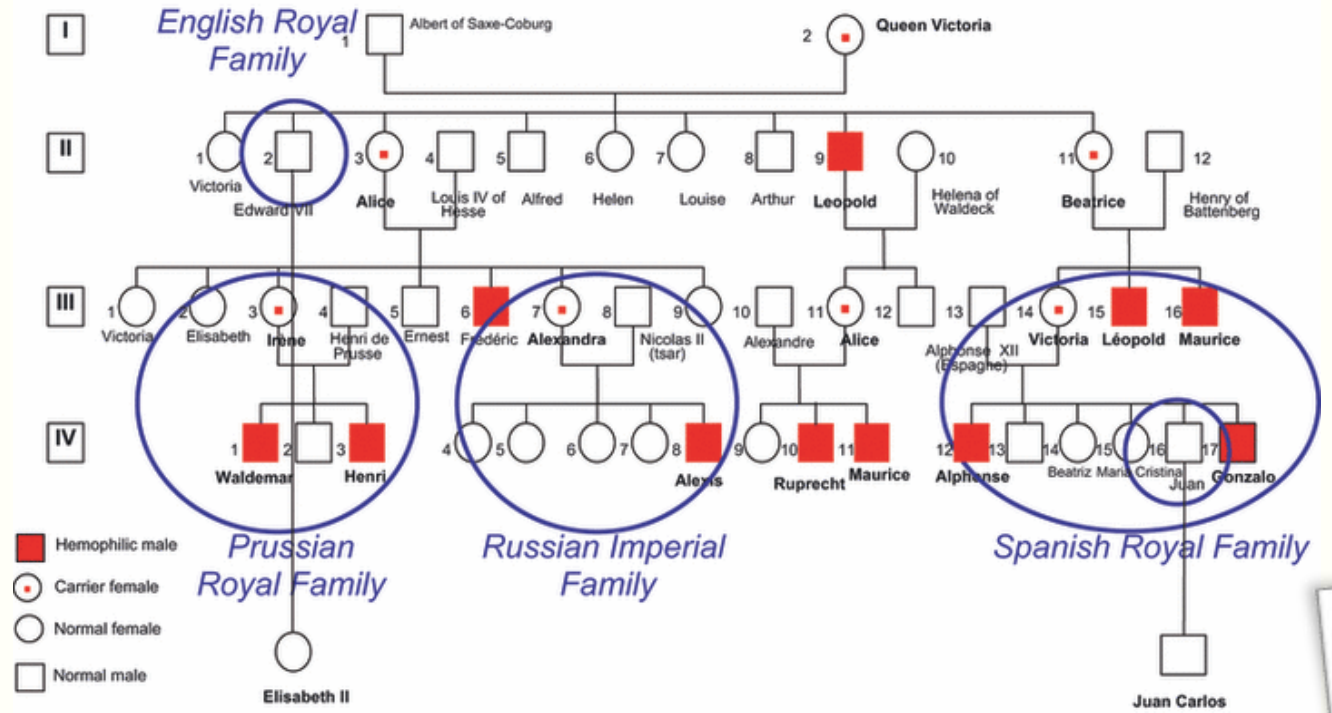
Albucasis

Maimonides

19th Century

- **Otto (1803)**
- **Hay (1813)**
- **Hopff (1828)**

The Royal Disease



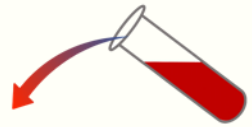
Rogaaev, et al. Hemophilia (2009)
www.sciencemag.org (State Archived of Russian Federation)
www.scientificanemrica.com

Mode of Delivery

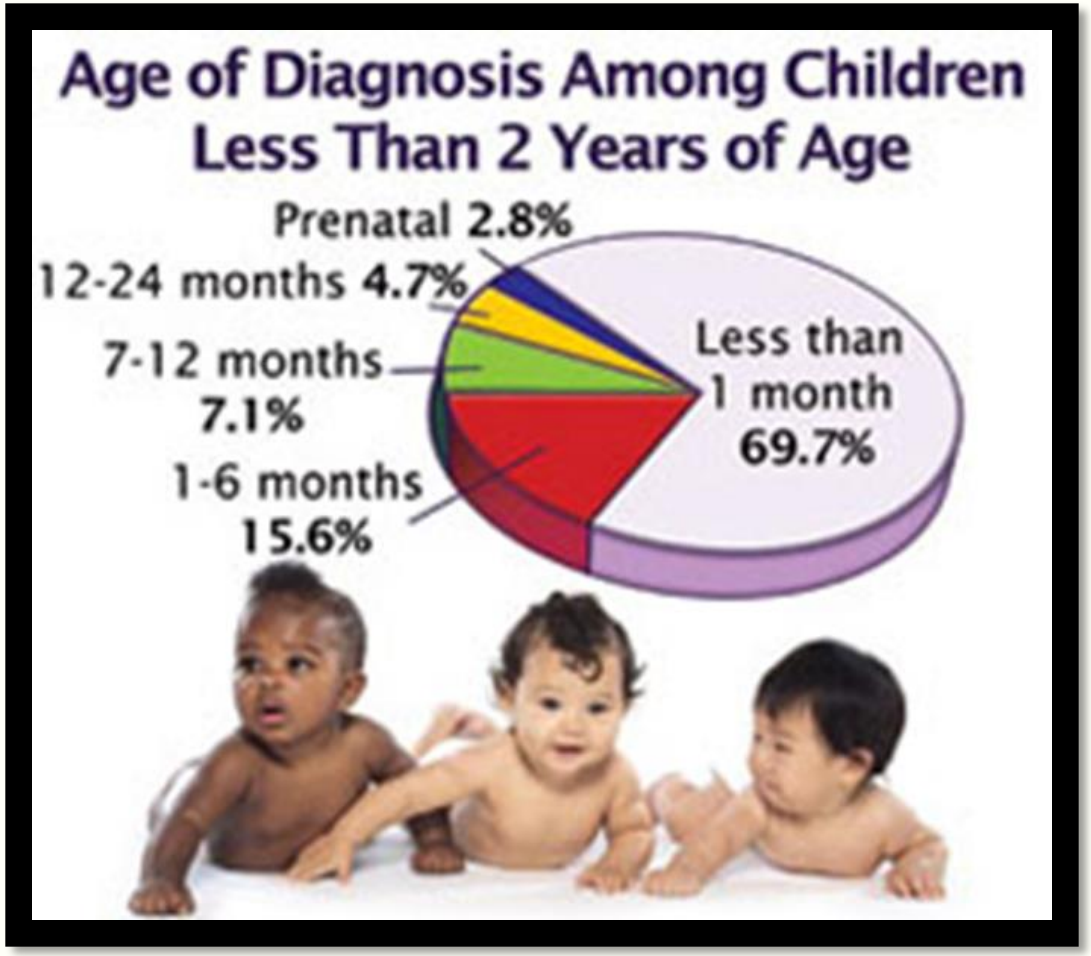
Planned Mode of Delivery	ICH	Risk
Vaginal	17/688	2.5%
- Spontaneous	8/541	1.5%
- Instrumented	7/68	10.2%
- C/S after labor	2/79	2.5%
Cesarean	2/125	1.6%

- No fetal electrodes
- No FORCEPS
- No VACCUM
- Avoid HEELSTICK
- No IM Injection
- Cord Blood Sample

Anderson et al. Hematologica (2019)



Hemophilia Presentation

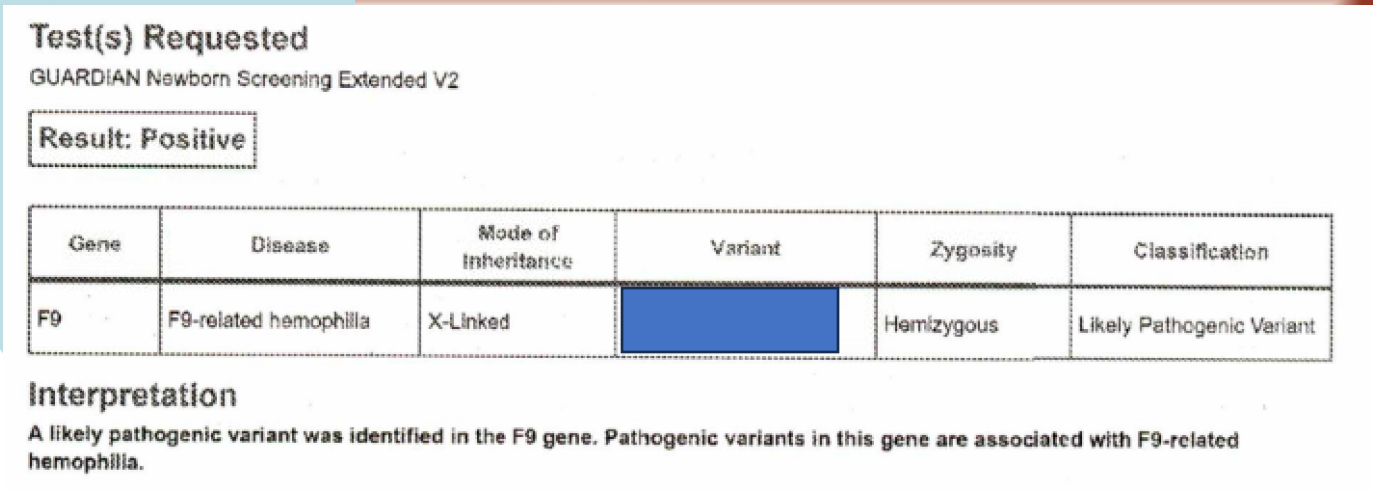


http://www.cdc.gov/ncbddd/hemophilia/data.html

GUARDIAN STUDY

NEW EXPANDED NEWBORN SCREENING STUDY

The GUARDIAN study is a new study that uses genome sequencing to screen for more conditions than those currently included in standard newborn screening.*



Test(s) Requested

GUARDIAN Newborn Screening Extended V2

Result: Positive

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Classification
F9	F9-related hemophilia	X-Linked	[redacted]	Hemizygous	Likely Pathogenic Variant

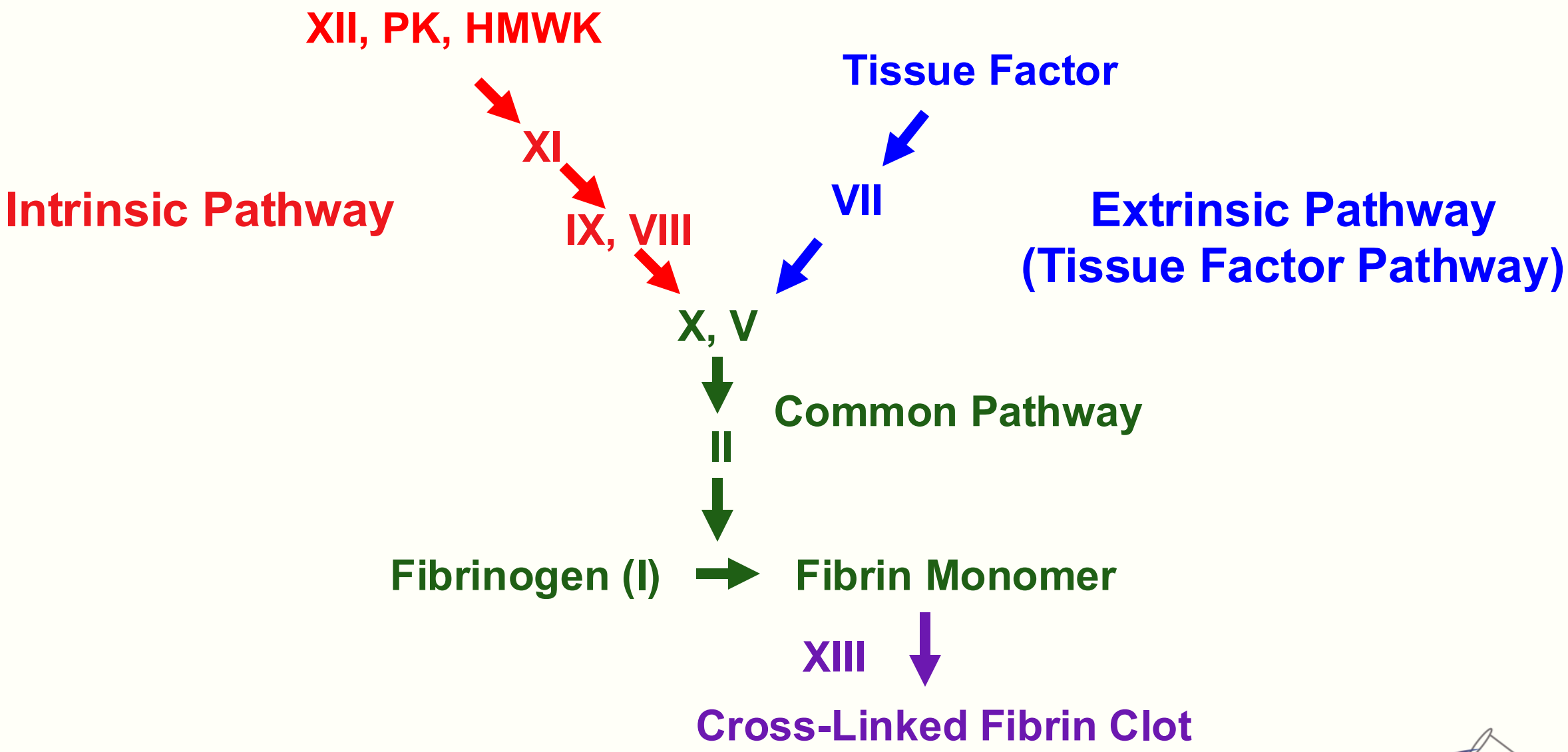
Interpretation

A likely pathogenic variant was identified in the F9 gene. Pathogenic variants in this gene are associated with F9-related hemophilia.

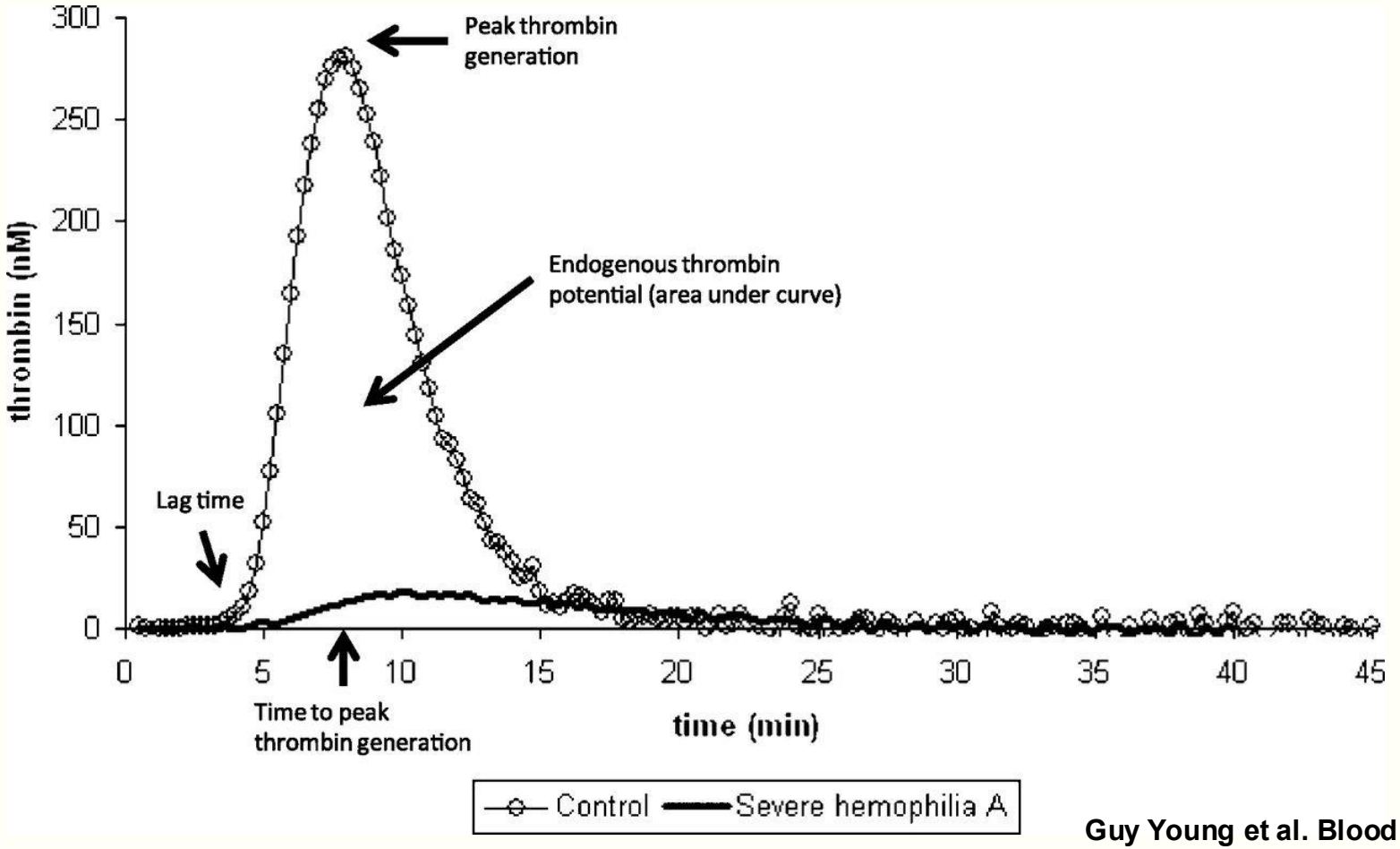
As we discussed by phone, your baby's additional genetic screening completed as part of the GUARDIAN study was positive for a likely pathogenic variant in F8, indicating likelihood your baby has F8-related hemophilia.

https://guardian-study.org/overview/

Coagulation Cascade

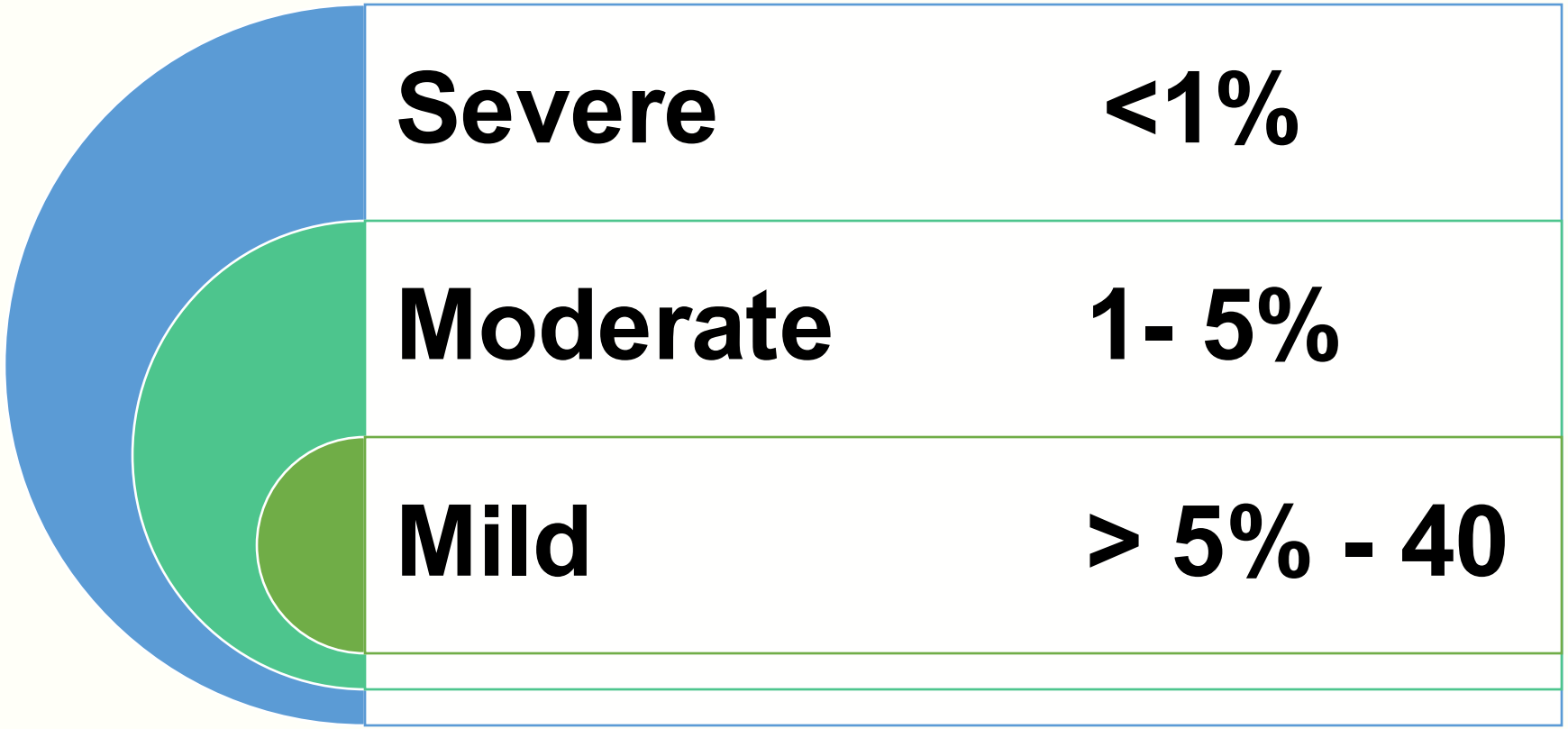


Hemophilia patients have poor thrombin generation



Guy Young et al. Blood (2013)

Laboratory classification of severity

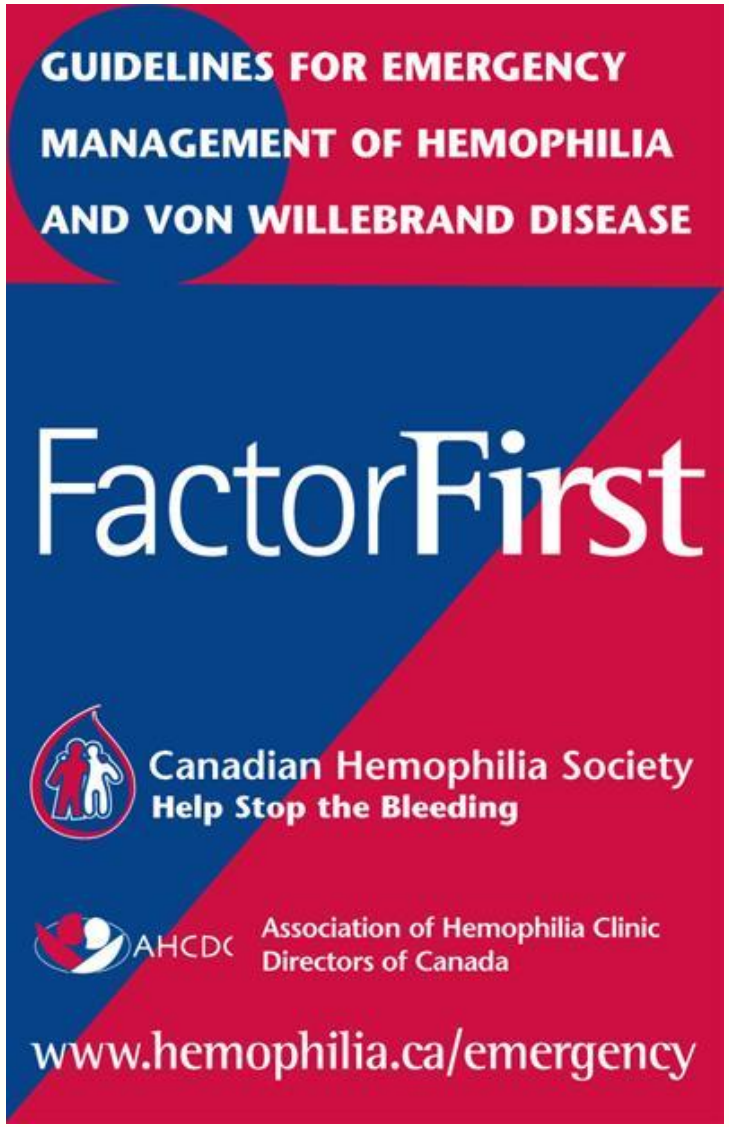


Joint disease progression in hemophilia

http://www.hemophilia.in/

Stop the bleeding!!

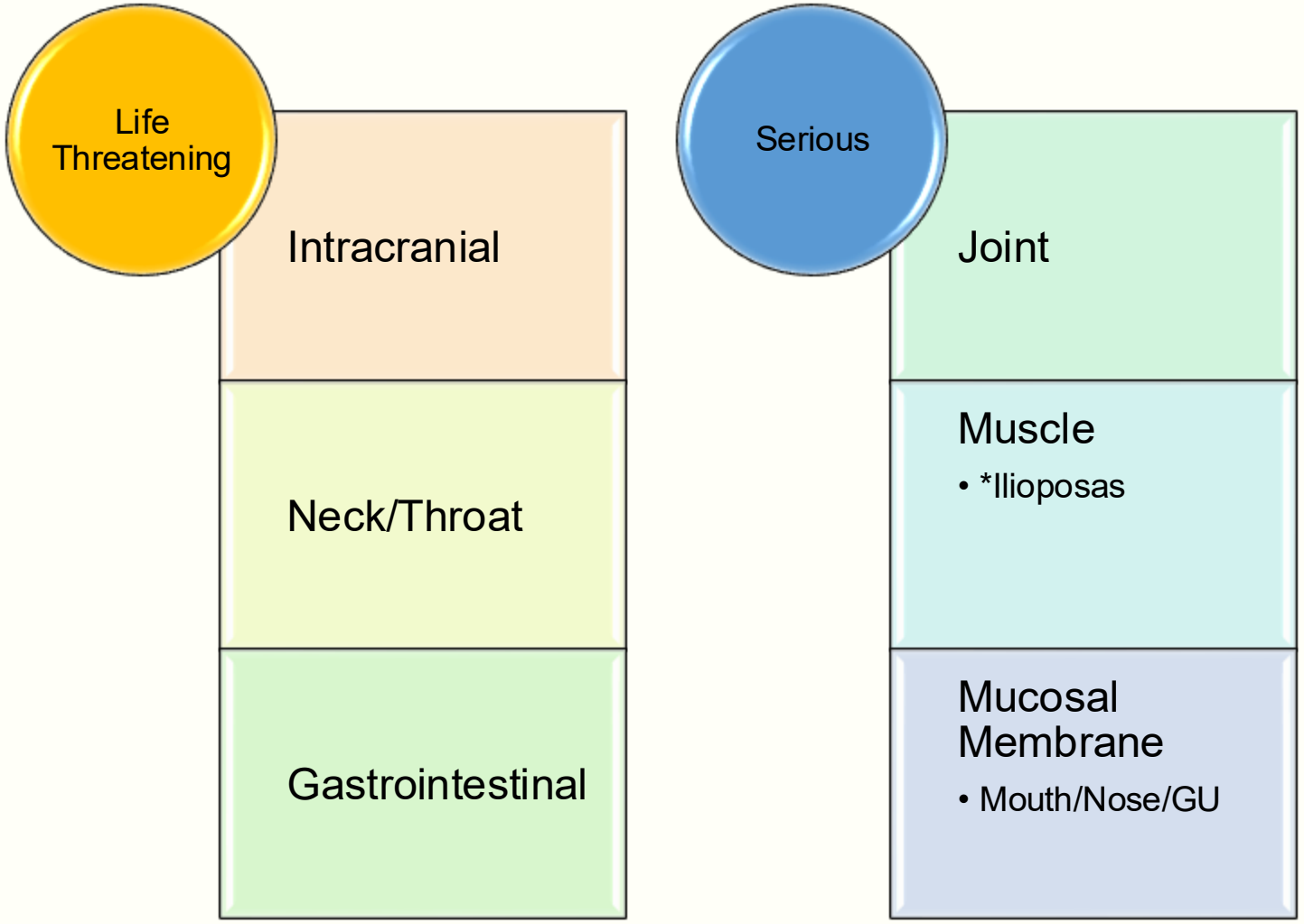
- High Priority @ Triage
- Treat first →
  Diagnostic testing later
- Treat based on history even in the absence of physical signs
- Patients often bring their clotting factor with them



Factor Replacement

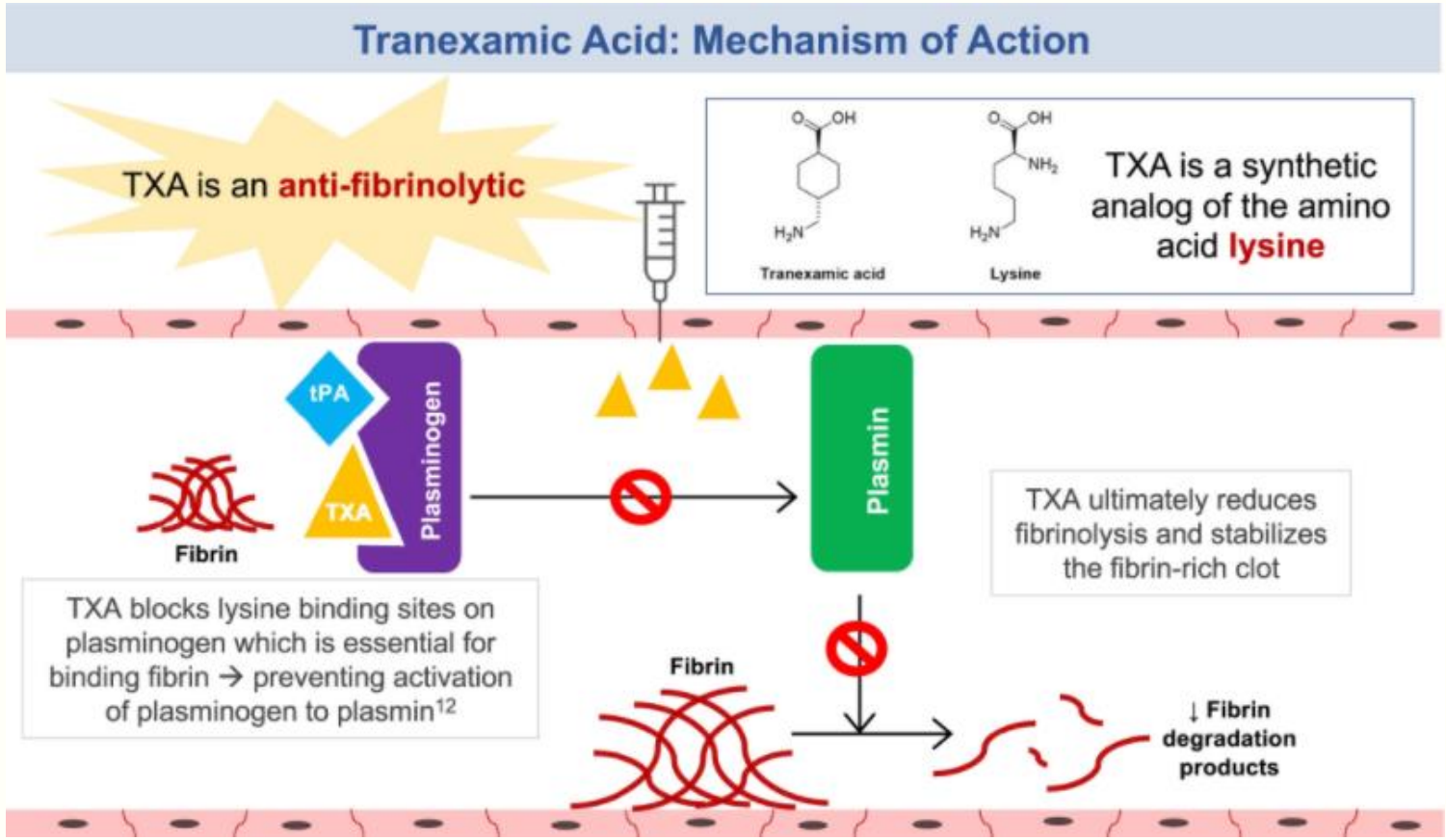
Factor VIII	1u/kg raises FVIII levels by 2%	1/2 life: 12 hrs
Factor IX	1u/kg raises FIX levels by 1%	1/2 life: 20-24 hrs • rFIX dosing = 1.3 x pFIX

High Risk Hemorrhage



Srivastava et al. WHF Guidelines for the Management of Hemophilia 3rd Ed. , 2020

Anti-Fibrinolytic Therapy

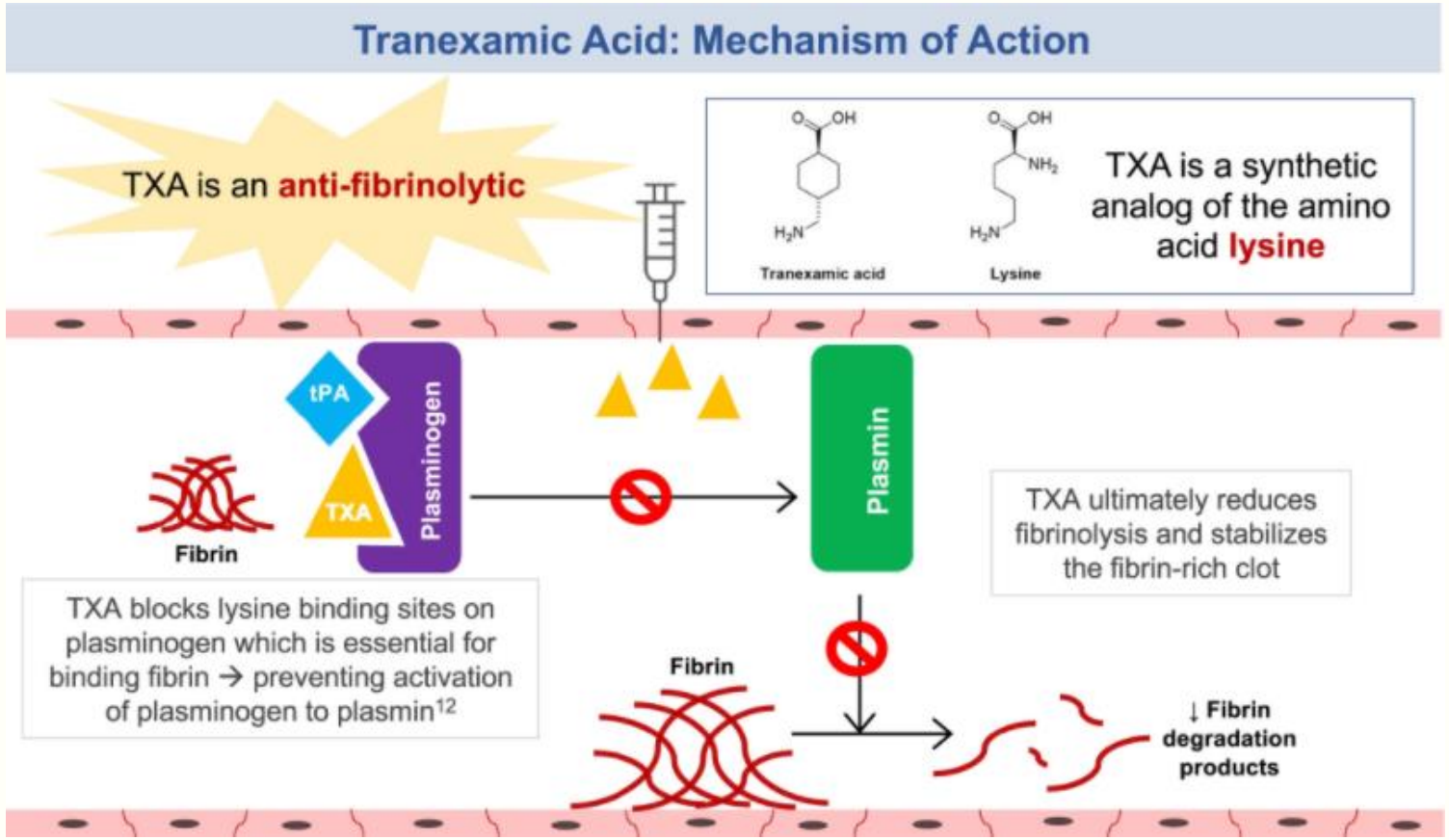


- Aminocaproic Acid
  50- 100mg/kg q6
- Tranexamic Acid
  10-20mg/kg q 8 IV
  1300mg po q8 PO

- Mucosal Bleeding
- Adjunctive Therapy

Relker, N. et al. RPTH (2021)

Anti-Fibrinolytic Therapy

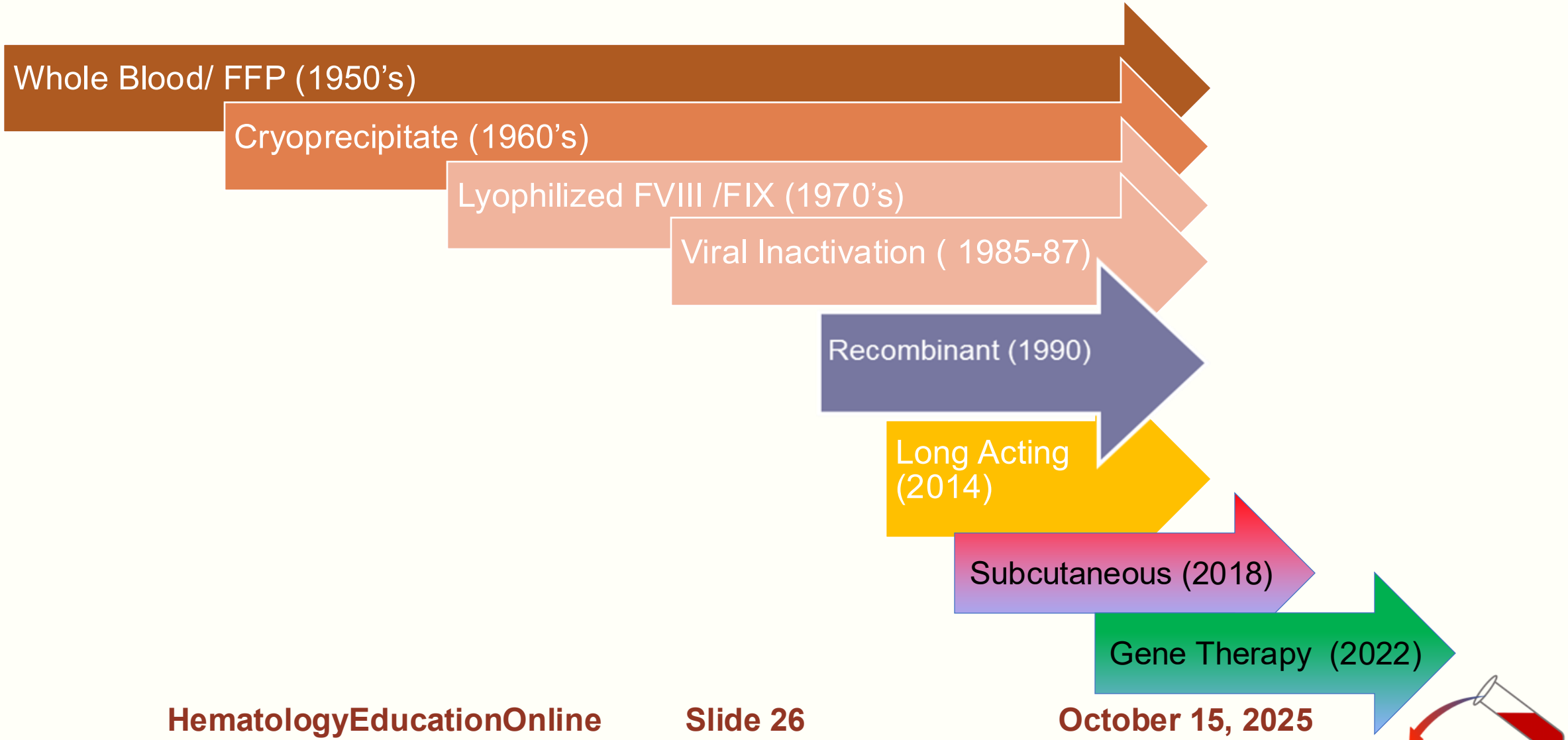


- Aminocaproic Acid
- Tranexamic Acid
- Mucosal Bleeding

Relker, N. et al. RPTH (2021)

Relker, N. et al. RPTH (2021)

Advances in safe, effective therapy

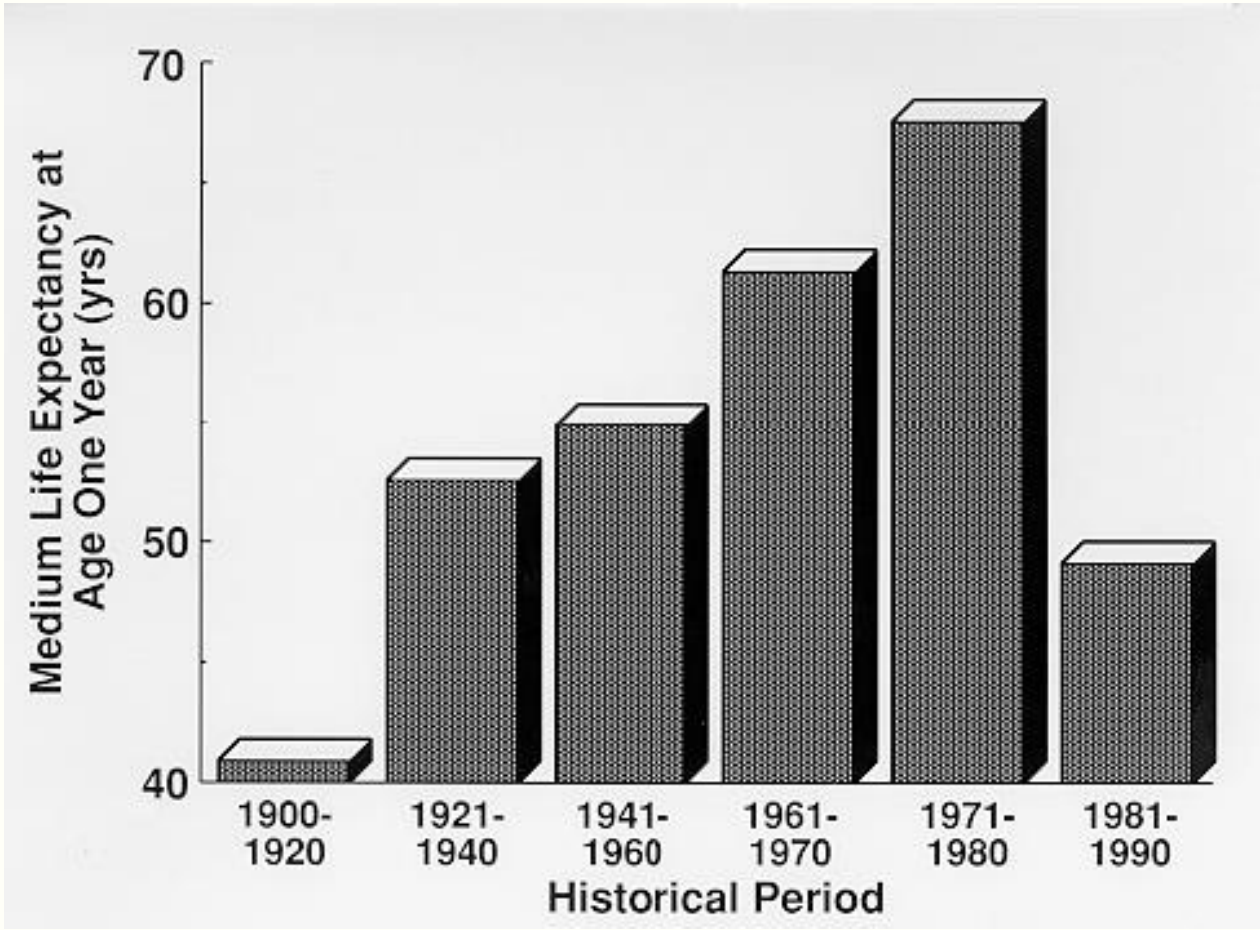


Infectious Complications

- Hepatitis A
- Hepatitis B
- Hepatitis C
- HIV

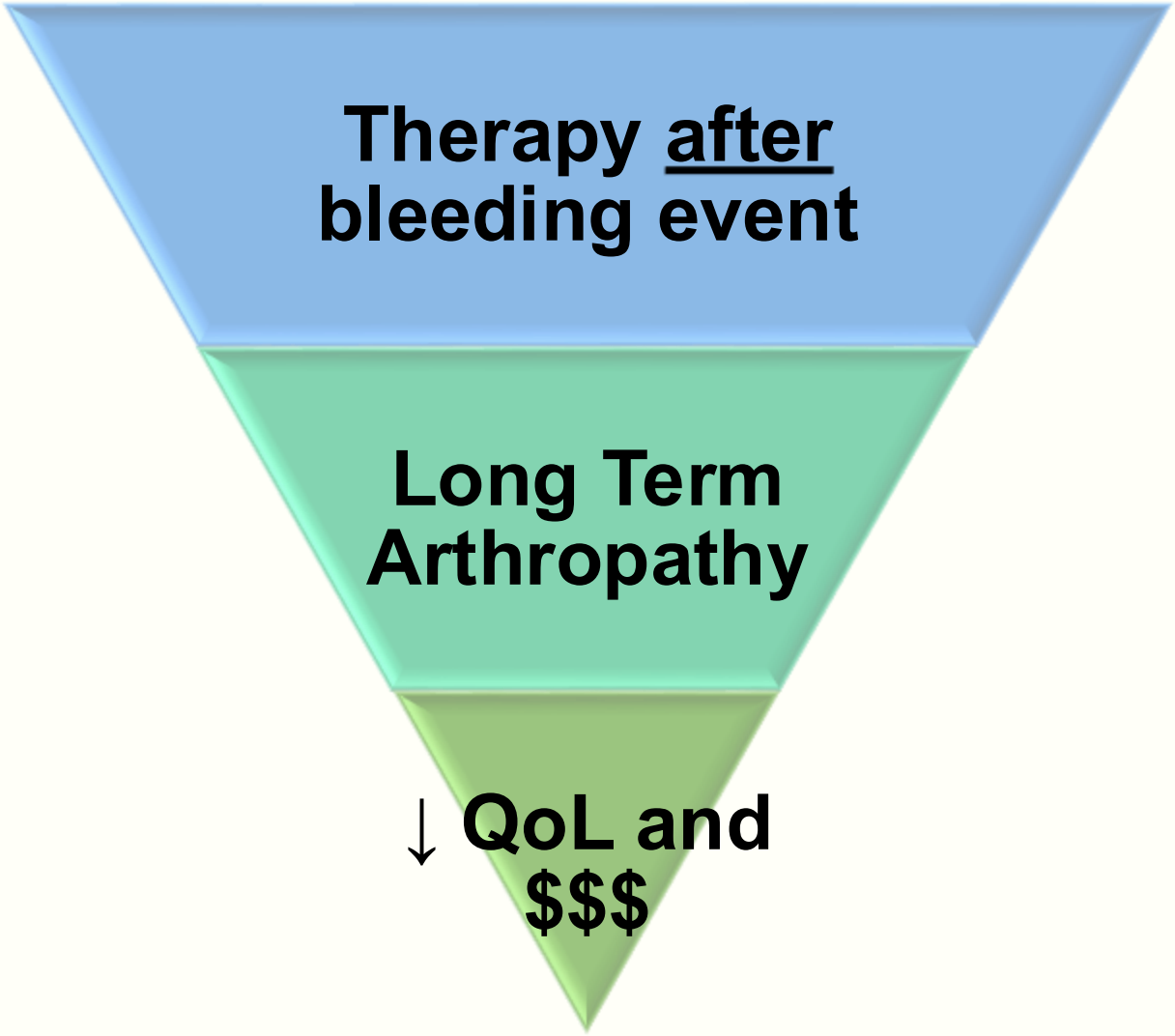
https://www.hemophiliafed.org/news-stories/2014/03/1980s-hemophilia-hivaids-hepatitis-c/

HIV Infection impact of hemophilia population



Jones and Ratnoff, 1991
http://www.niaid.nih.gov/topics/hivaids.

Treatment- On Demand



Joint Outcome Study: Prophylaxis Randomized Control Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., Michael L. Manco-Johnson, M.D., Sharon Funk, B.Sc., P.T., Linda Jacobson, B.S., Leonard A. Valentino, M.D., W. Keith Hoots, M.D., George R. Buchanan, M.D., Donna DiMichele, M.D., Michael Recht, M.D., Ph.D., Deborah Brown, M.D., Cindy Leissinger, M.D., Shirley Bleak, M.S.N., Alan Cohen, M.D., Prasad Mathew, M.D., Alison Matsunaga, M.D., Desiree Medeiros, M.D., Diane Nugent, M.D., Gregory A. Thomas, M.D., Alexis A. Thompson, M.D., Kevin McRedmond, M.D., J. Michael Soucie, Ph.D., Harlan Austin, Ph.D., and Bruce L. Evatt, M.D.

Manco-Johnson et al. NEJM (2007)

Prophylaxis prevents hemarthrosis

Table 2. Outcome Data.*

Variable	Prophylaxis (N = 32)	Enhanced Episodic Therapy (N = 33)	P Value
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.

Manco-Johnson et al. NEJM (2007)

Weak correlation of clinical bleeding with MRI joint damage

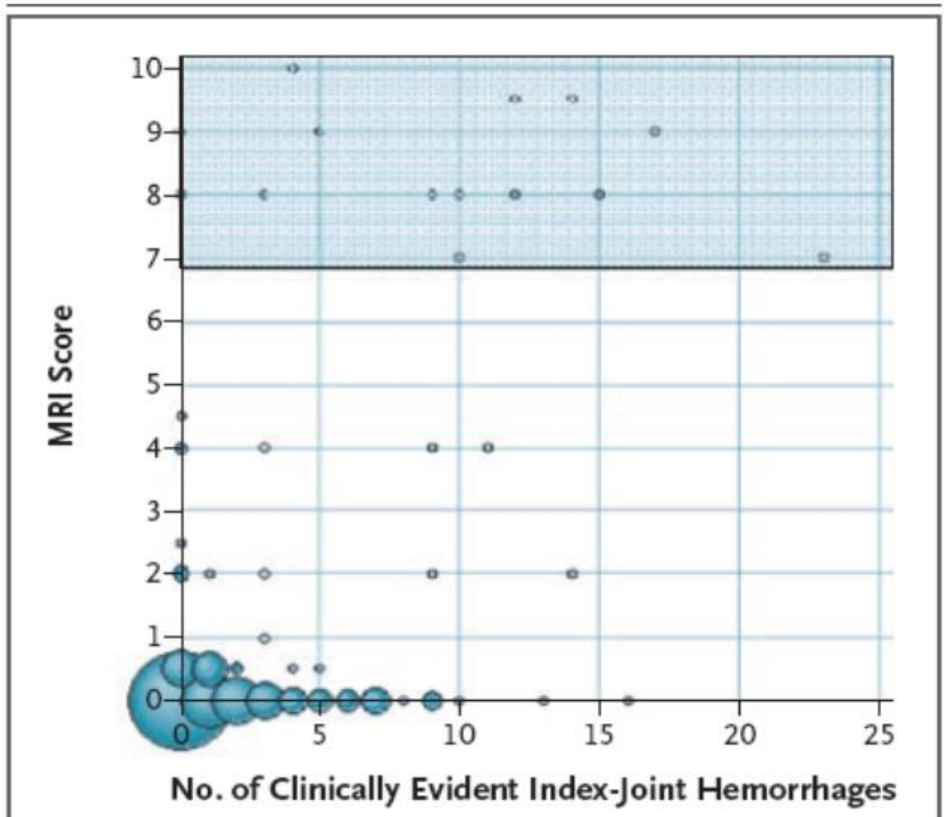
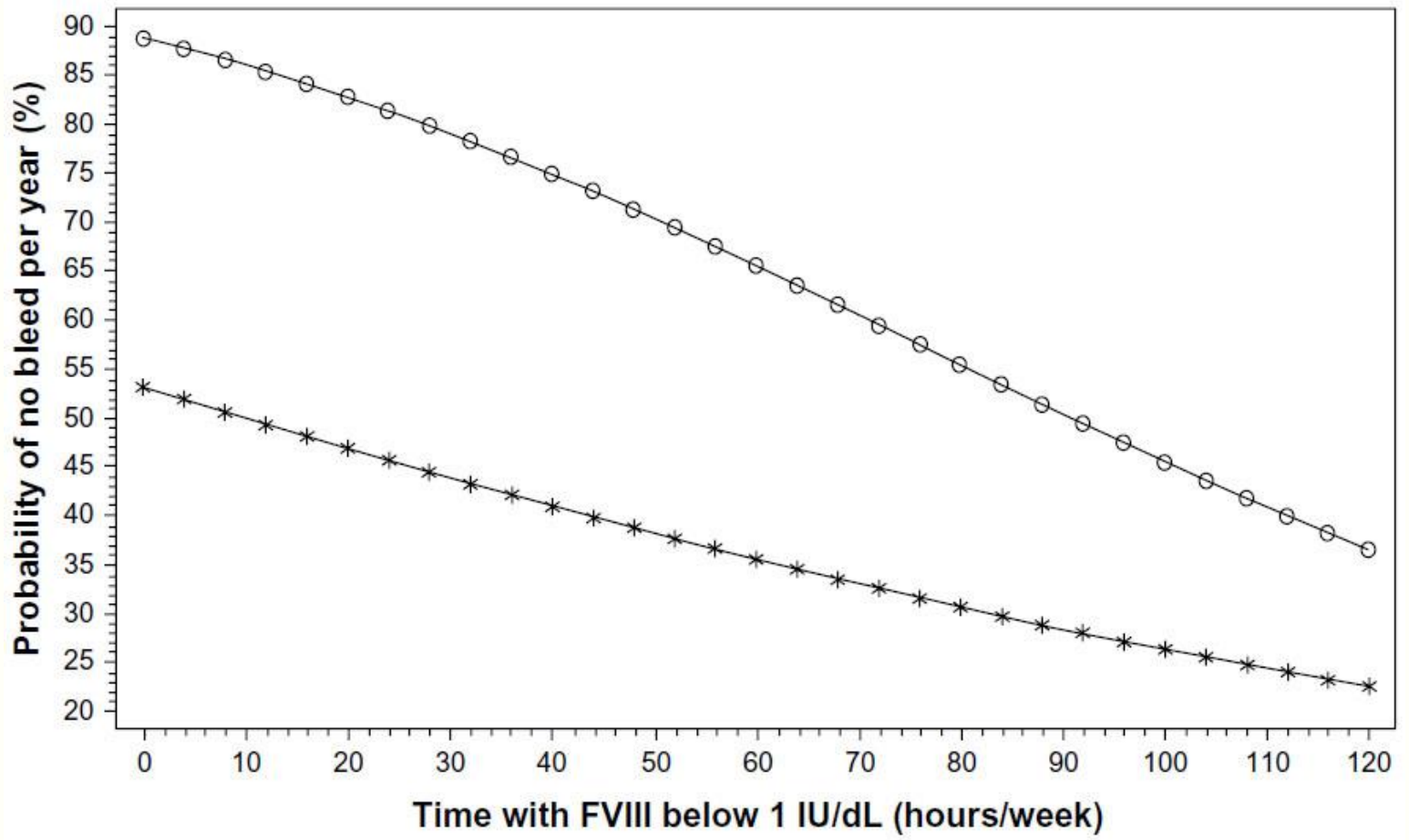


Figure 2. MRI Score for Index Joint According to the Number of Hemorrhages in That Joint for Both Treatment Groups.

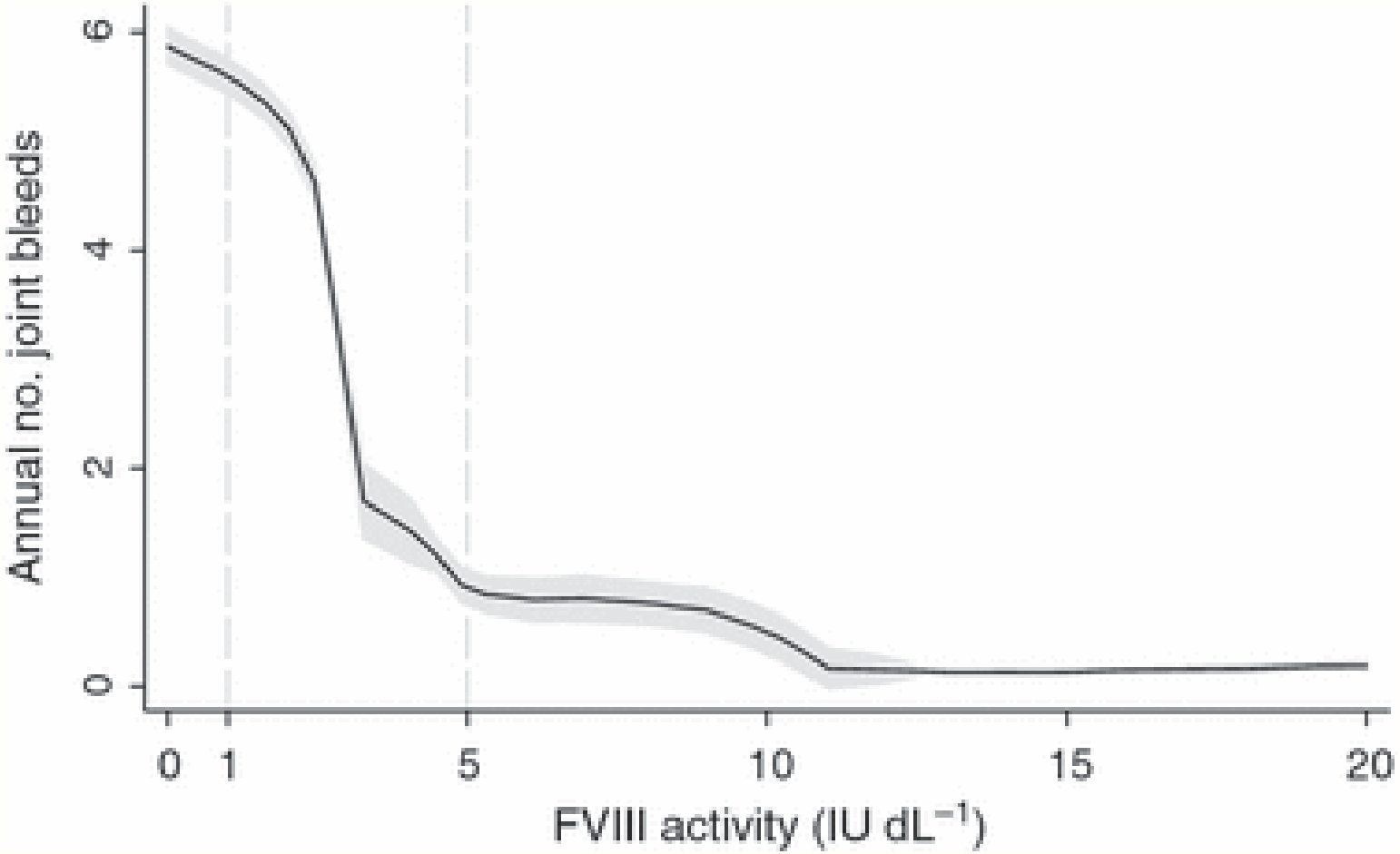
Manco-Johnson et al. NEJM (2007)

Time Below 1% → ↑ Risk of Bleeding



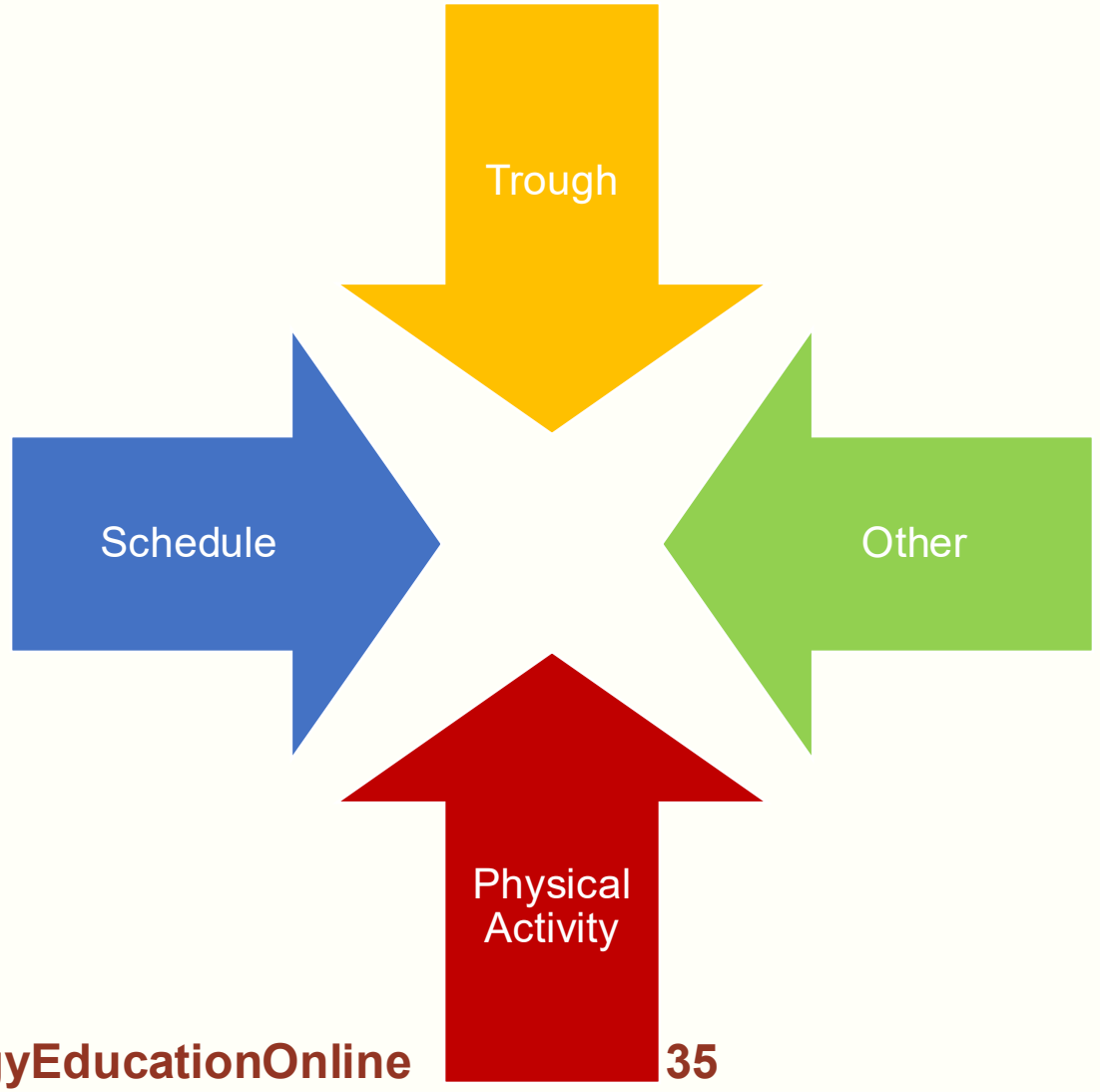
Collins PW, et al *J Thromb Haemost*. 2009;7(3):413–420.[33] Copyright © International Society on Thrombosis and Haemostasis

What is the ideal Target for Prophylaxis ?



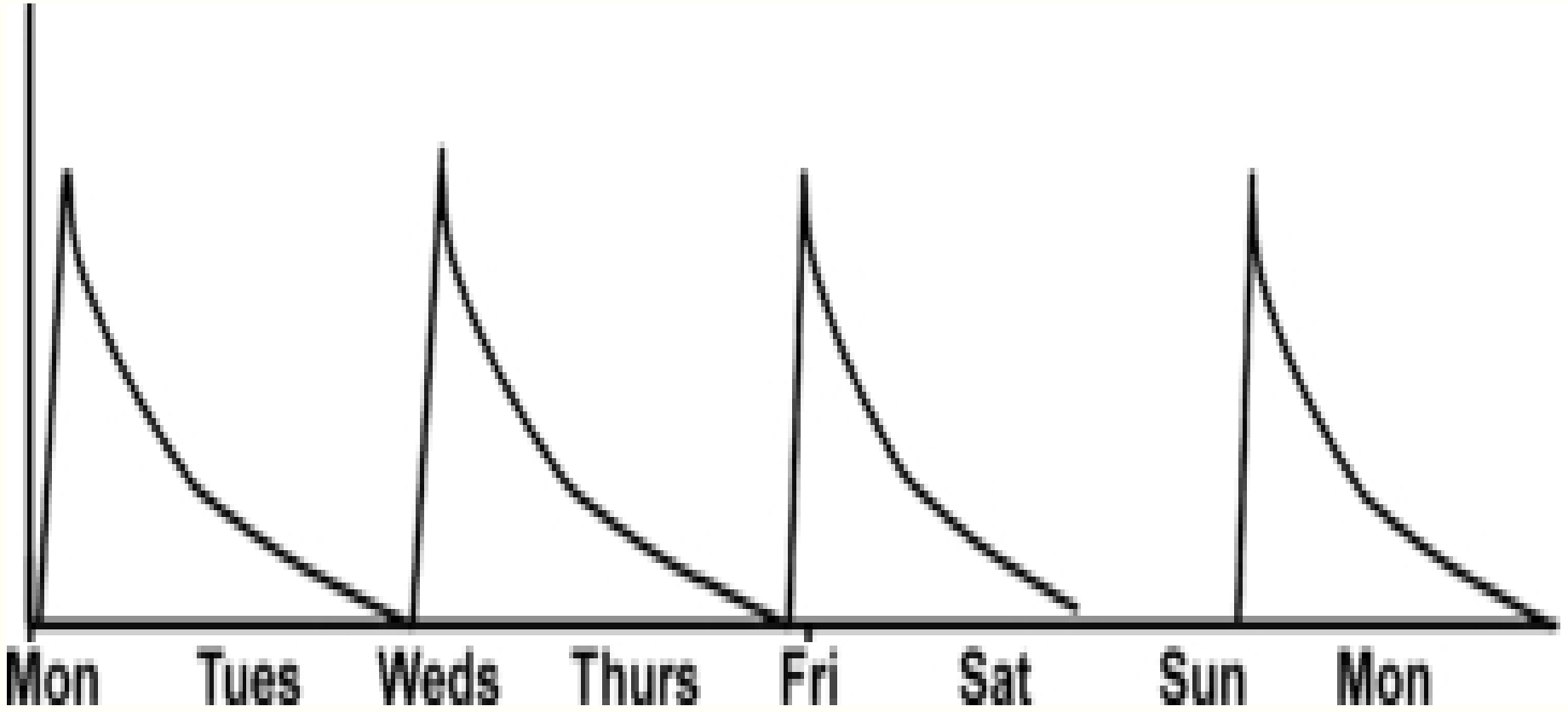
Haemophilia
Volume 17, Issue 6, pages 849–853, 5 MAY 2011 DOI: 10.1111/j.1365-2516.2011.02539.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2011.02539.x/full#f2

Decision Making



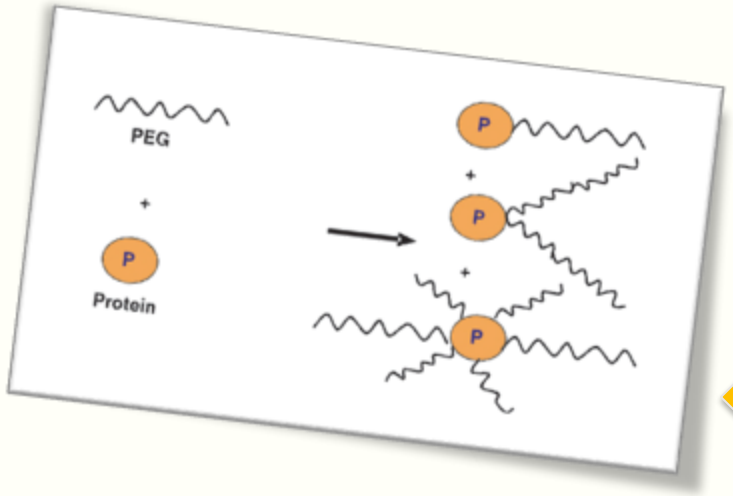
Cost
Delivery
Personal PK
Immunogenicity
Infectious Risk

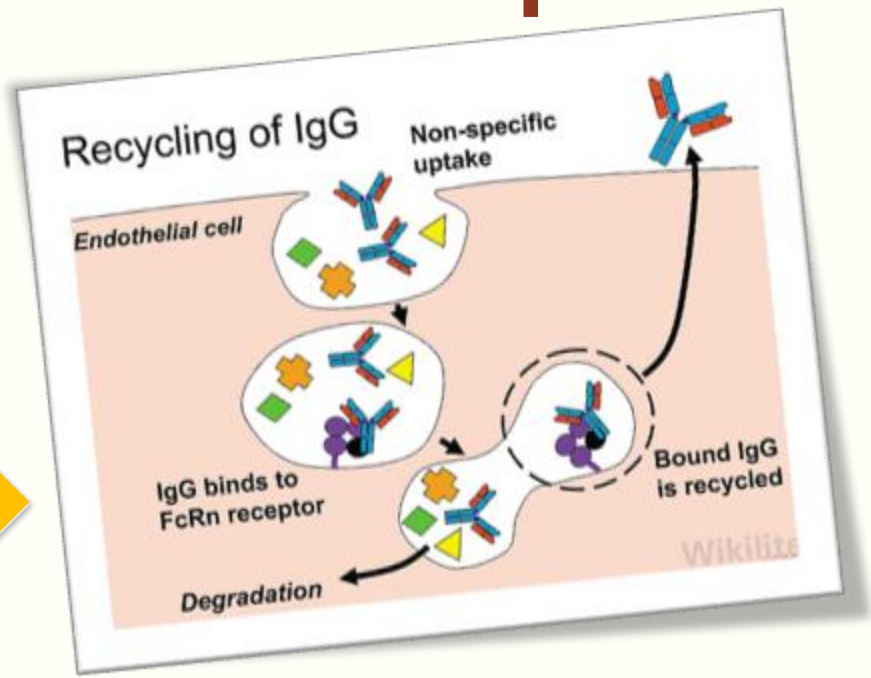
Personalized prophylaxis

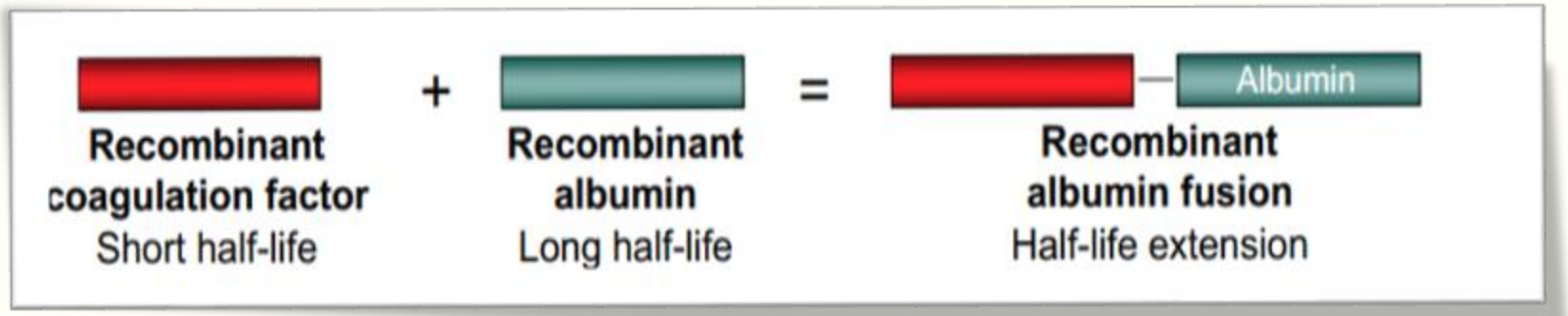


Haemophilia
pages 131-135, 25 JUN 2012 DOI: 10.1111/j.1365-2516.2012.02838.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2012.02838.x/full#f2

Long Acting Agents for Hemophilia







http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=317577&sk=&date=&pageID=3
Hobbs, J. http://www.wikilite.com/wiki/index.php/File:Recycling_of_IgG_by_FcRn.jpg / http://www.transfusion.com.au

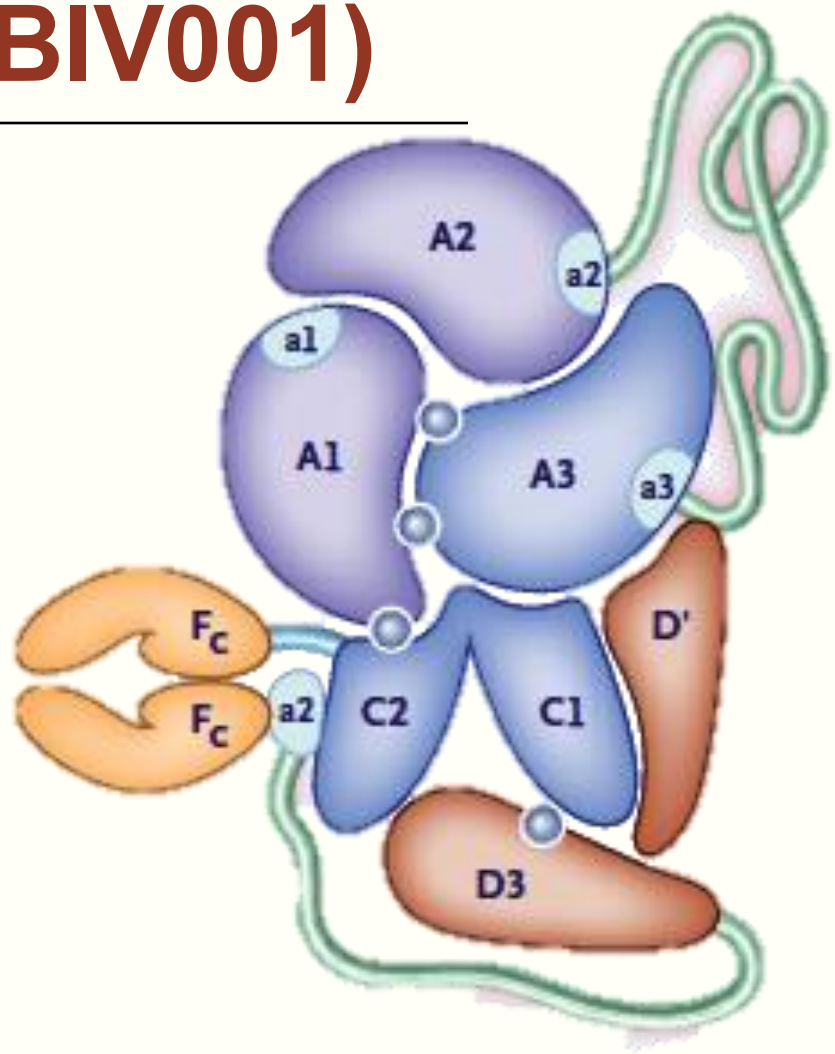
Efanesoctocog alfa
rFVIIIFc-VWF-XTEN (BIV001)

- Novel Fusion Protein
- Breakthrough the ceiling of VWF clearance

FVIII fused to VWF fragment with :

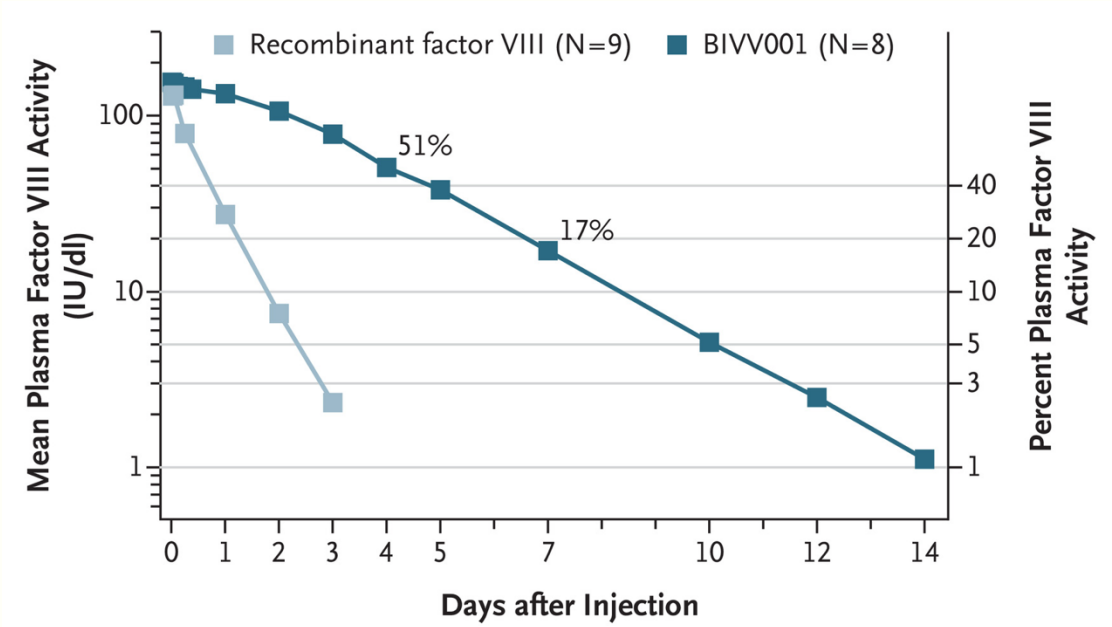
- D'D3 Domain *
- Dimeric Immunoglobulin G1 Fc
- XTEN Polypeptides

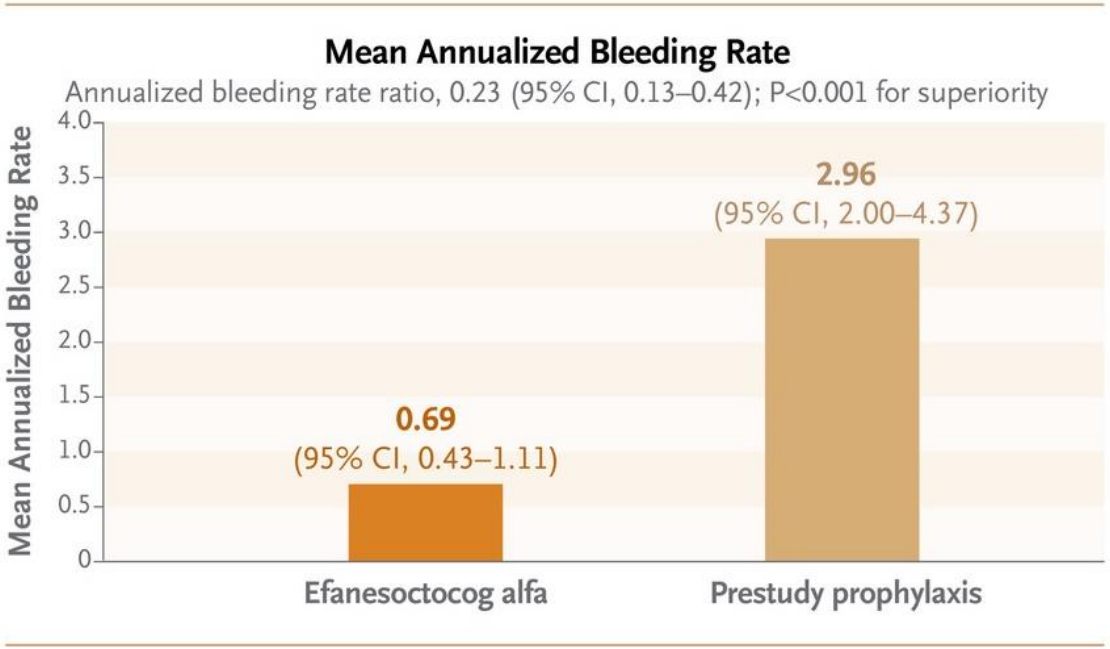
*Blocks the binding of FVIII with endogenous VWF



Konkle et al. NEJM 2020

Extended Half Life $T_{1/2}$ = 45.8 hours



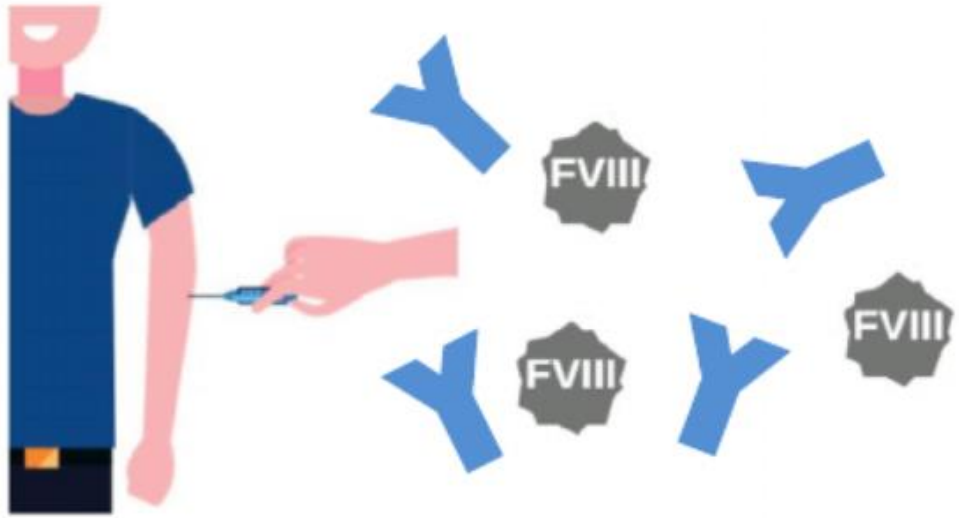


von Drygalski A et al. NJEM 2023

Konkle et al. NEJM 2020

Inhibitors – Alloantibody

- 25 - 30% in severe Hemophilia A
- 3%-10% in Hemophilia B FVIII
  - *~ 25% with allergic reaction phenotype
- Poor Control of Bleeding
- High Cost, Morbidity and Mortality



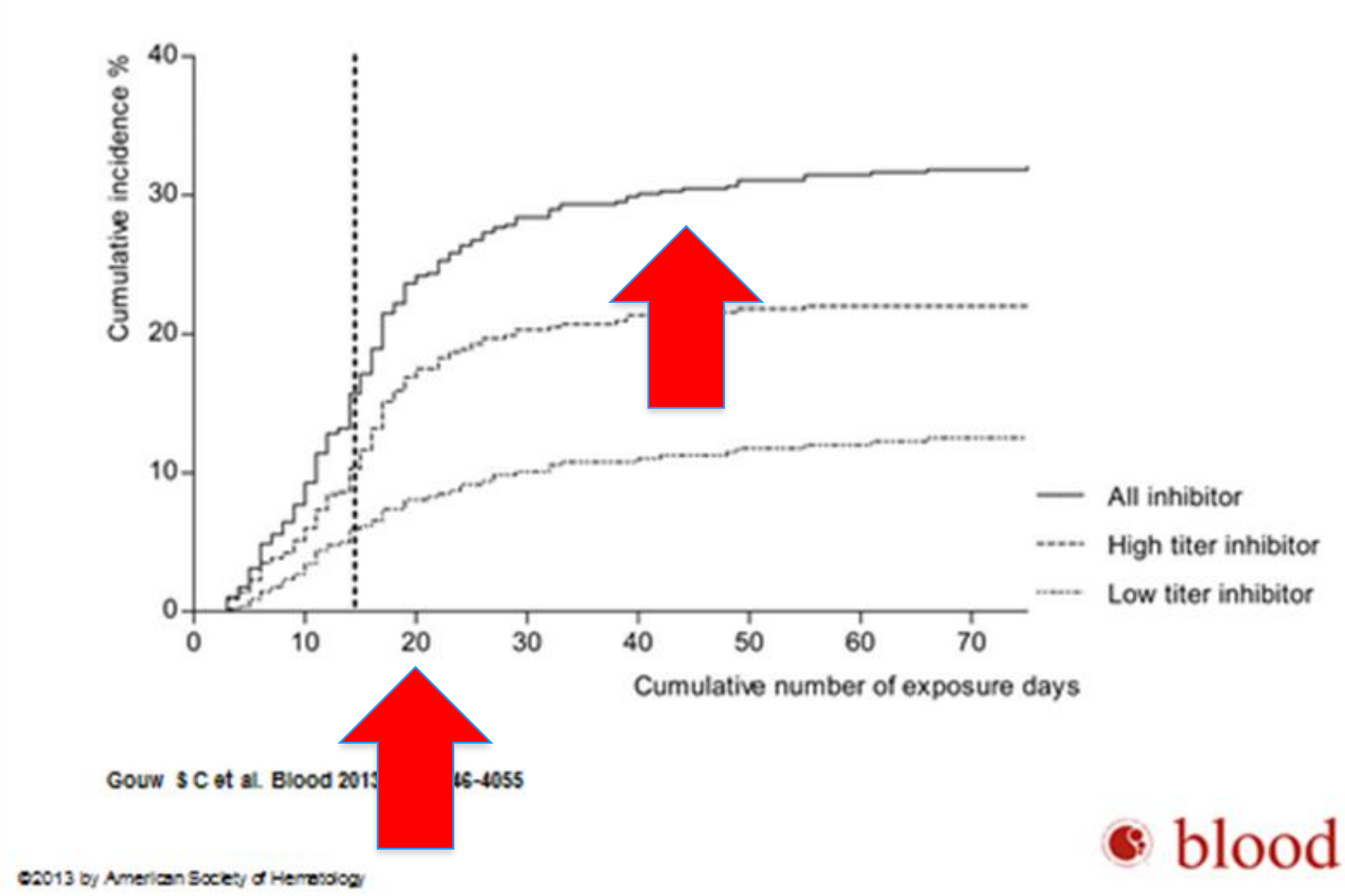
Jardim LL, et al, *Res Pract Thromb Haemost (2020)*
Katz et al. *Haemophilia* 1996;2:28–31.
Male et al Haematologica (2020)

Inhibitors

- High-titer inhibitor: >5 BU
- Low-titer inhibitor: <5 BU
- Transient inhibitor:
  - Persists for 6-8 months or less
  - Usually low titer

Jardim LL, et al, *Res Pract Thromb Haemost (2020)*

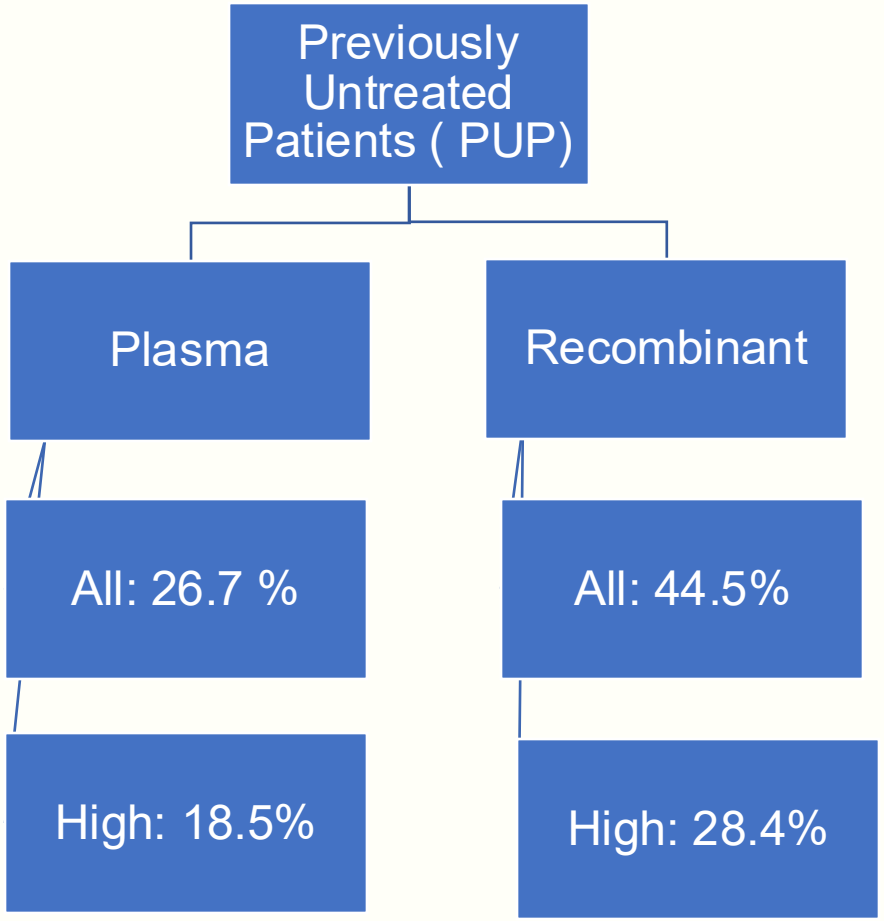
Inhibitors develop with median of 14.5 exposure days.

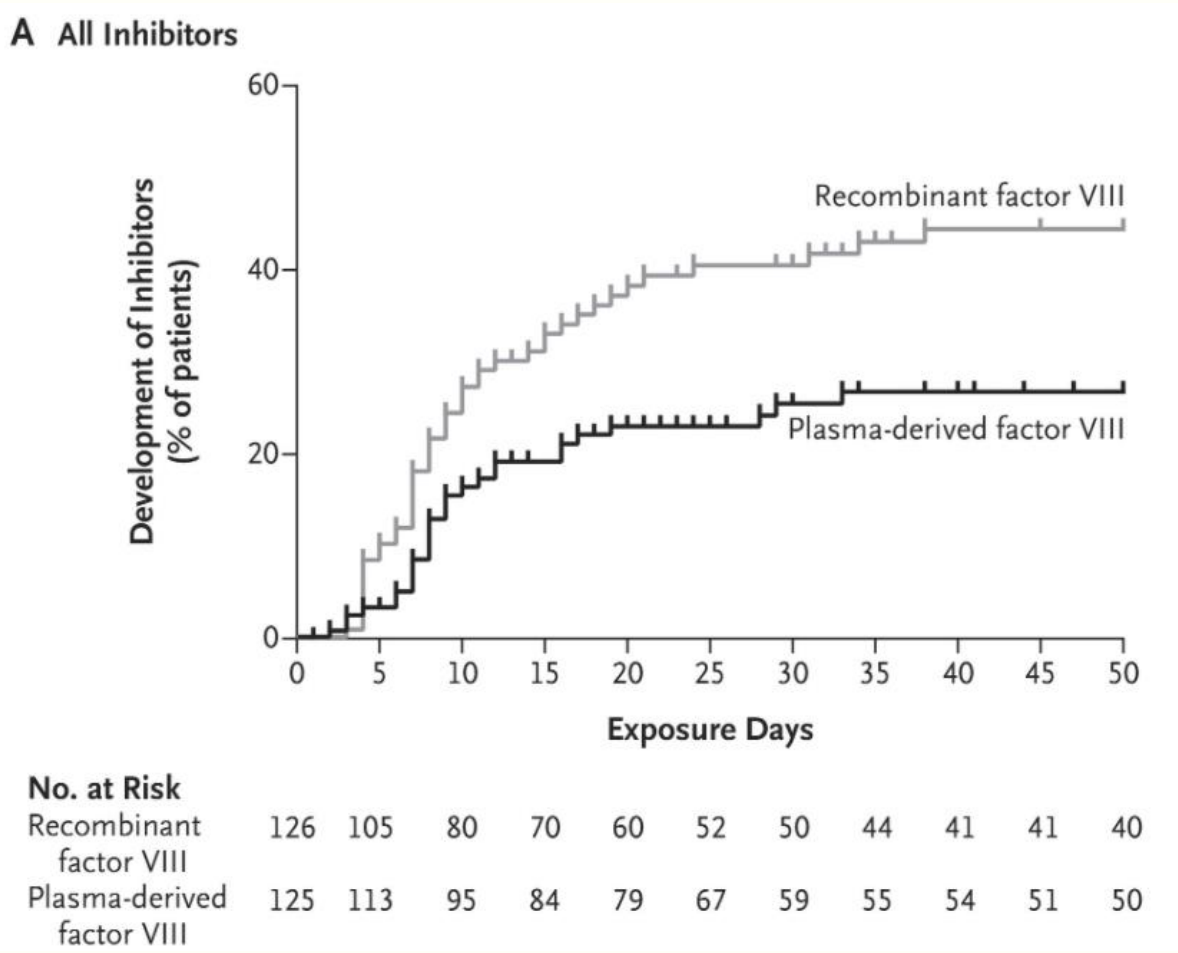


Gouw S C et al. Blood 2013 46-4055

blood

SIPPET STUDY
(Survey of Inhibitors in Plasma-Product Exposed Toddlers)





Peyvandi, F. et al NEJM (2016)

Immunogenicity of Inhibitors

Table 2. Characteristics of standard half-life (SHL) recombinant factor VIII products currently used for hemophilia A treatment.

Product (Brand)	Company	Year of First Licensing	rFVIII Generation	Cell Line	Stabilizer	FVIII	Half-Life (Hours)	Immunogenicity PTPs (%)	Immunogenicity PUPs (%)	Ref.
Octocog alfa (Recombinate)	Takeda	1992	First	CHO	Human albumin	full-length	15	0.12 All inhibitors 0.06 HT inhibitors	23.9 All inhibitors 11.3 HT Inhibitors	[44–46]
Octocog alfa (Kogenate FS)	Bayer	1993	Second	BHK	Sucrose	full-length	11	No inhibitors	15–50.1 All inhibitors 9.8–31.6 HT inhibitor	[9,23,47]
Octocog alfa (Advate)	Takeda	2003	Third	CHO	Trehalose	full-length	9–12	0.92 All inhibitors	29.1–38 All inhibitors 12.7–26 HT inhibitors	[48–50]
Moroctocog alfa (Xyntha/ ReFacto AF)	Pfizer	2008	Third	CHO	Sucrose	B-domain deleted	8–11	1.47 All inhibitors	33 All inhibitors 14.5 HT inhibitors	[51,52]
Turoctocog alfa (Novoeight)	Novo Nordisk	2013	Third	CHO	Sucrose	B-domain truncated	11	No inhibitors	43.1 All inhibitors 27.6 HT inhibitors	[53,54]
Simoctocog alfa (Nuwiq)	Octapharma	2015	Fourth	HEK	Sucrose/ arginine	full-length	12–17	No inhibitors	26.7 All inhibitors 16.2 HT inhibitors	[36,55]
Octogog alfa (Kovaltry)	Bayer	2016	Third	BHK	Sucrose	full-length	12.2–14.2	0.93 All inhibitors	54.8 All inhibitors 40.5 HT inhibitors *	[56,57]
Lonoctocog alfa (Afstyla)	CSL Behring	2016	Third	CHO	Sucrose/ L-histidine,	B-domain truncated single chain	14.5	No inhibitors	52 All inhibitors 26 HT inhibitors **	[58]

Product (Brand)	Company	Year of First Licensing	Technology	Cell Line	FVIII	Half-Life (Hours)	Immunogenicity PTPs (%)	Immunogenicity PUPs (%)	Ref.
Efmoroctocog alfa (Elocta, Eloctate)	Sanofi	2014	IgG1-Fc-fusion	HEK	B-domain deleted	19 (OSA) 20.9 (CSA)	No inhibitor No anaphylaxis	31.1 All inhibitors 15.6 HT inhibitors No anaphylaxis	[66,67,77,78]
Rurioctocog alfa pegol (Adynovi, Adynovate)	Takeda	2015	Random PEGylation	CHO	full-length	14.3–16 (OSA)	No inhibitor No anaphylaxis	19.2 All inhibitors	[63,73,79]
Damoctocog alfa pegol (JIVI)	Bayer	2018	Site-specific PEGylation	BHK	B-domain deleted	19 (OSA) (>12 yo) 15–16 (OSA) (<12 yo)	No inhibitor 1.5 hypersensibility 3.7 anti-PEG Ab	NA	[64,72]
Turoctocog alfa pegol (N8-GP, Esperoct)	Novo Nordisk	2019	Site-specific glycoPEGylation	CHO	B-domain truncated	15.8–19.9 (CSA) (>12 yo) 13.2–14.2 (CSA) (<12 yo)	0.6 All inhibitors 12.3 anti-PEG Ab (>12 yo) 29.4 anti-PEG Ab (<12 yo)	29.9 All inhibitors 14.9 HT inhibitors No anaphylaxis	[65,71,80]

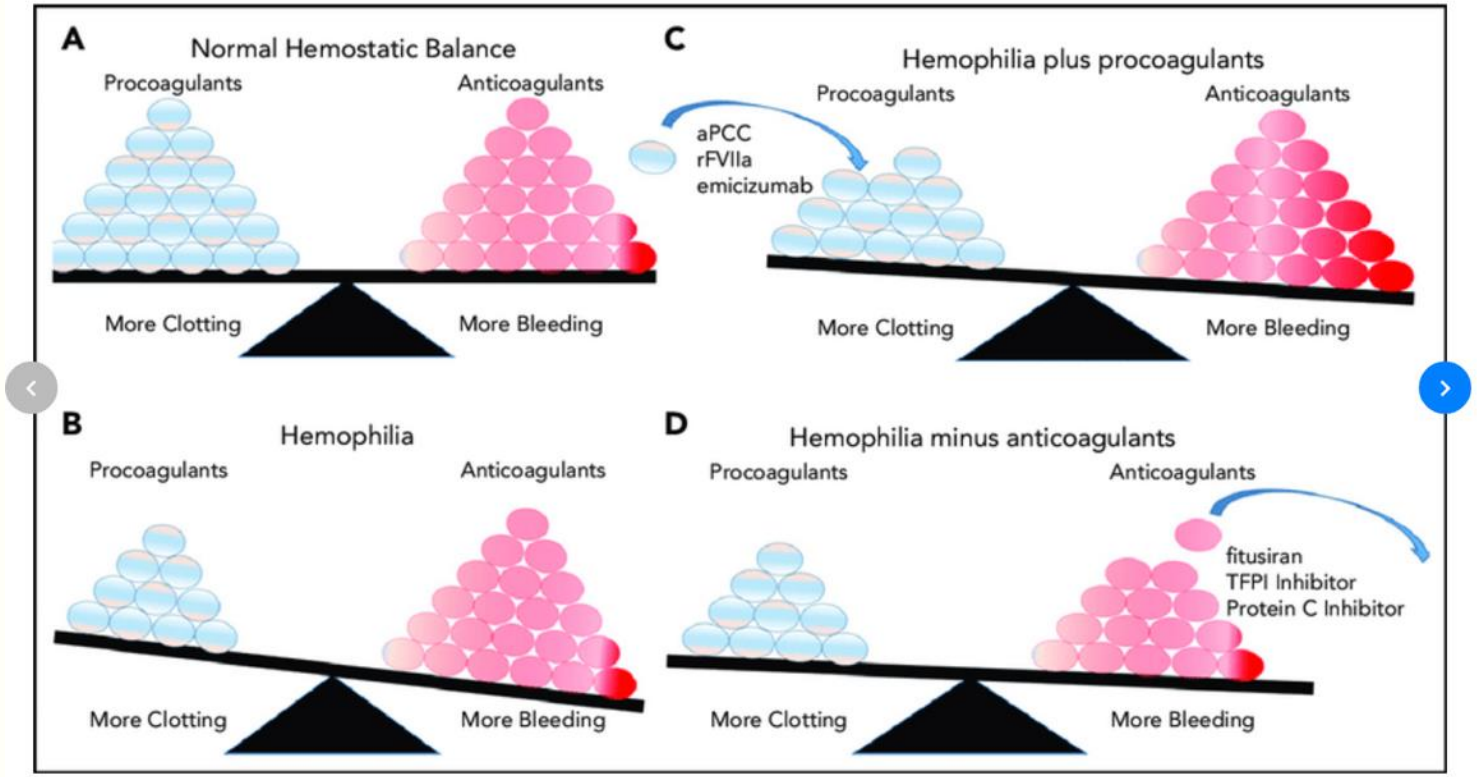
PTPs, previously treated patients; PUPs, previously untreated patients; FVIII, factor VIII; CHO, Chinese hamster ovary cell line, BHK, [illegible]; HEK, human embryonic kidney; OSA, one-stage clotting assay; CSA, chromogenic substrate assay; Ab, antibody; NA, not available; Ref., references.

Prezotti ANL, et al Pharmaceuticals (Basel). 2022
PMCID: PMC9331070.

Inhibitor Treatment Options

- High dose Factor therapy
- Bypassing Agents
- Non-Factor Therapy
- Immune tolerance: NOT BLEEDING treatment

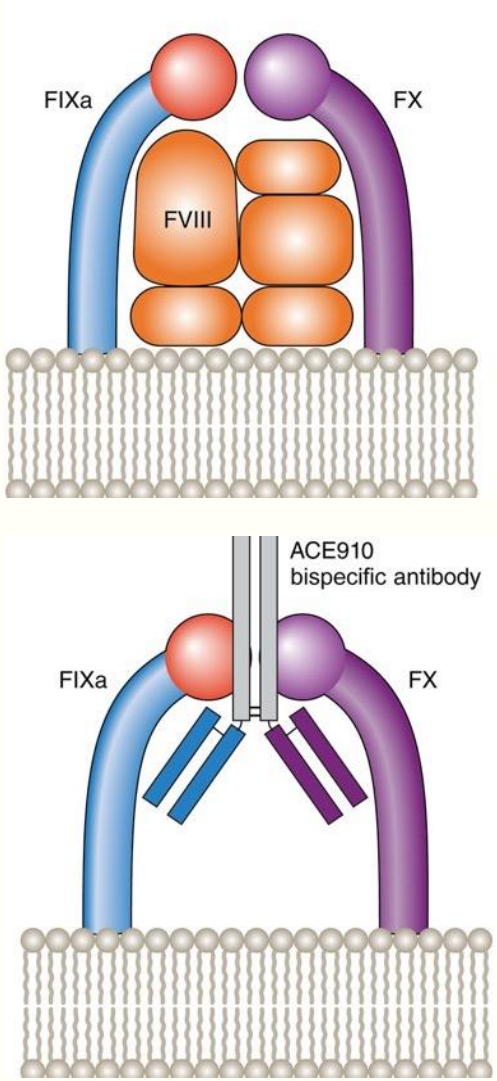
Rethink the approach



Mechanisms of novel hemophilia therapies. (A) Normal hemostatic balance tipped in favor of bleeding, for example, (B) in hemophilia A from lack of coagulation FVIII. (C) One approach to improve hemostatic balance in hemophilia is to add additional procoagulants; (D) another approach is to remove or inhibit anticoagulants. Adapted from Willyard. 64

Callaghan et al. Blood Advances (2018)

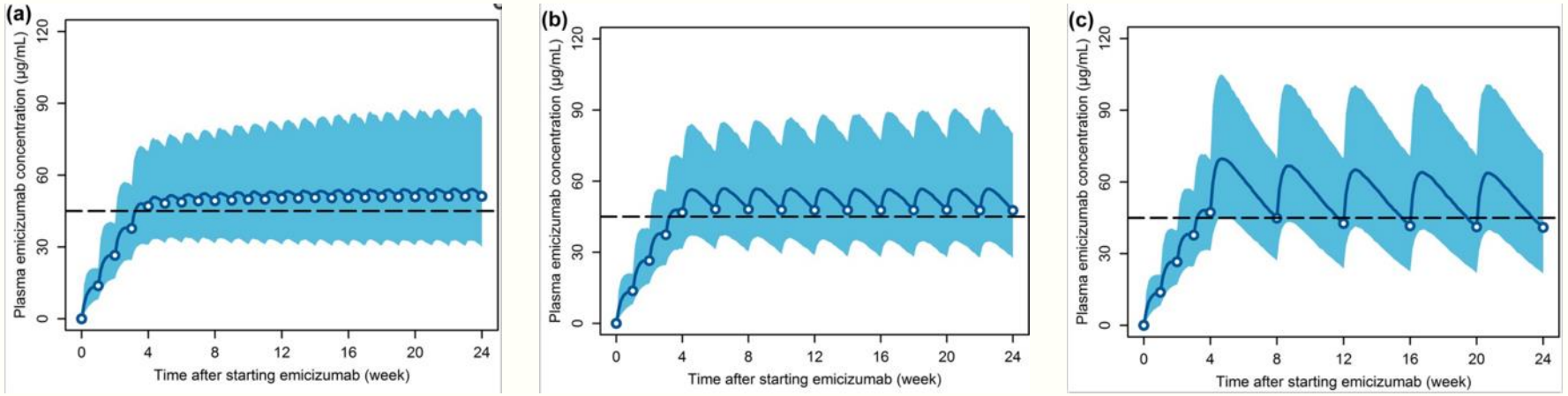
Non Factor Therapy



- Emicizumab (ACE-910)
- Humanized Bispecific Antibody
- Half Life ~ 3 weeks
- No structural homology to FVIII
- Hemophilia A with and without inhibitors
- Subcuatneous

Makris, Blood (2016)

Steady State Prevention of Bleeding



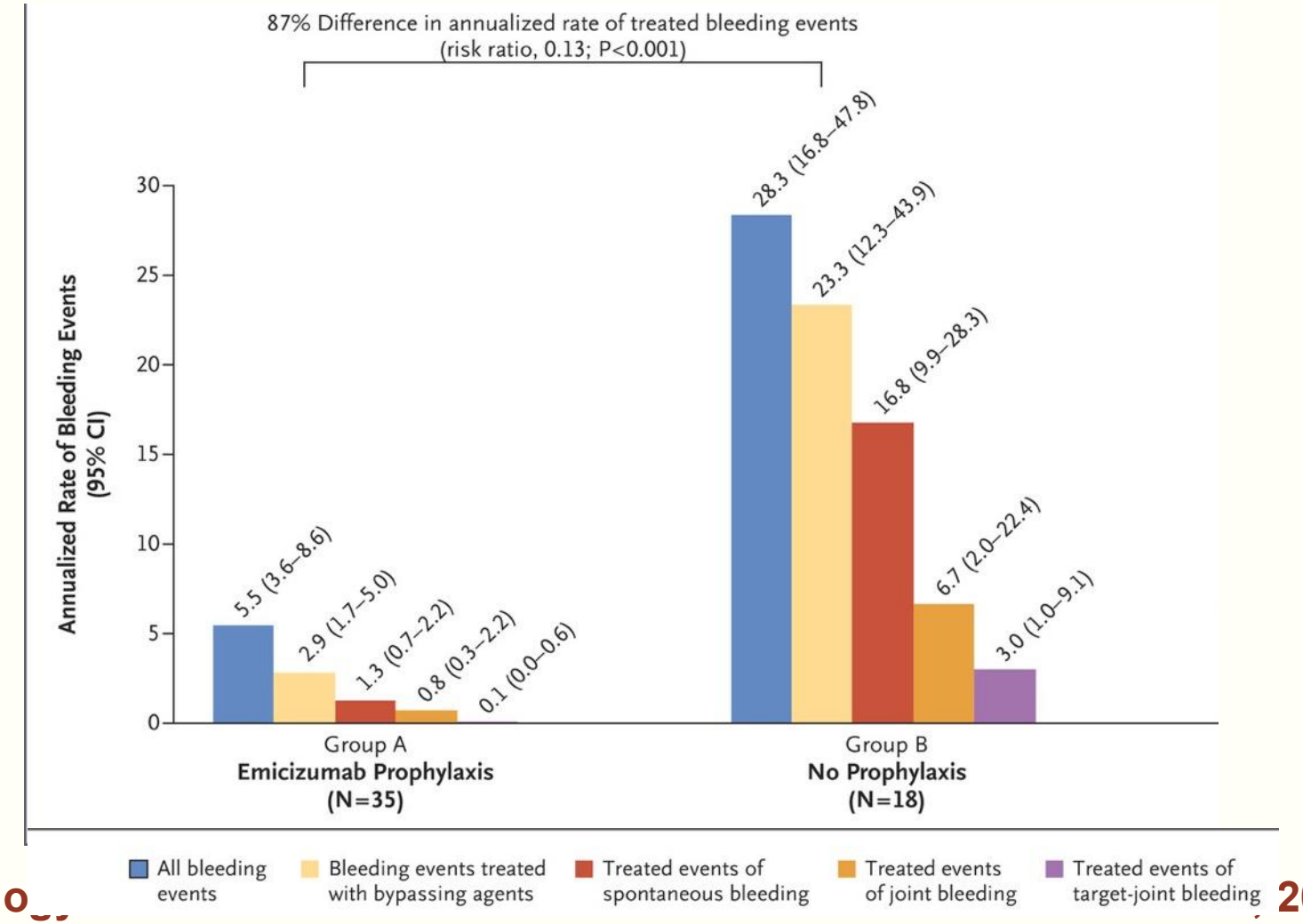
Weekly **q 2 weeks** **Monthly**

Yoneyama et al. Clinical Pharmacokinetics (2018)

HAVEN-1 :

BLEEDING. ↓

Hemophilia A Inhibitor Patients



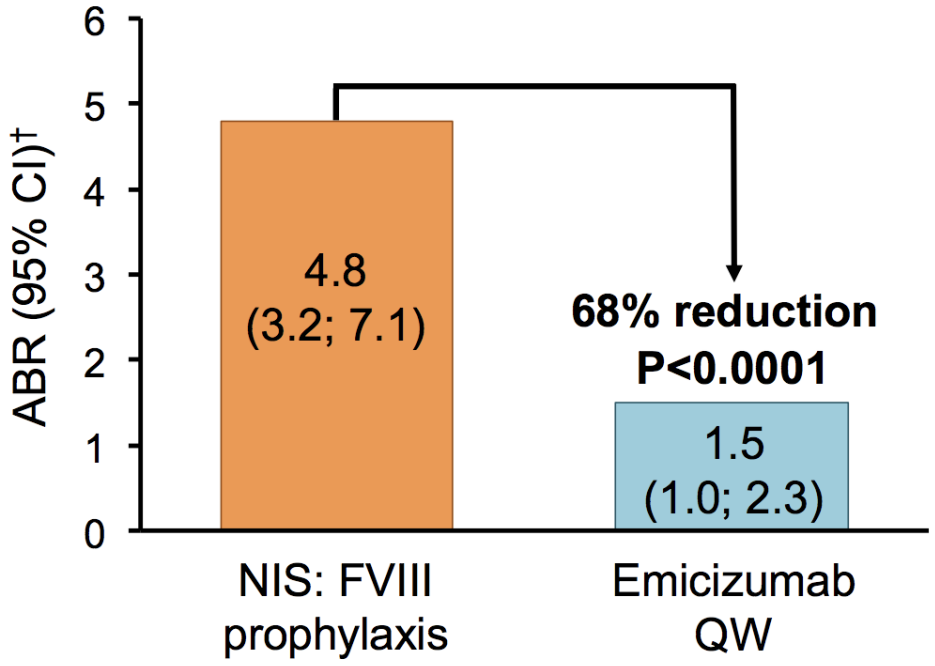
Hematolo… 2025

Oldenburg J et al. N Engl J Med 2017;377:809-818.

HAVEN -3 – Hemophilia A Non-Inhibitor

Table 2. Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group D), as Compared with Events in the Same Participants during Prophylactic Factor VIII Treatment Previously in the Noninterventional Study.*

Variable	Group D in Current Trial: Emicizumab Prophylaxis (N=48)	Noninterventional Study: Factor VIII Prophylaxis (N=48)
Median duration of efficacy period (range) — wk†	33.7 (20.1–48.6)	30.1 (5.0–45.1)
Annualized rate of bleeding events, model-based (95% CI)‡	1.5 (1.0–2.3)	4.8 (3.2–7.1)
Rate ratio vs. control (95% CI)	0.32 (0.20–0.51)	—
Percent difference vs. control	−68§	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Percent of participants with 0 bleeding events (95% CI)	54 (39–69)	40 (26–55)
Percent of participants with 0–3 bleeding events (95% CI)	92 (80–98)	73 (58–85)



Oldenberg et al. NEJM (2018))

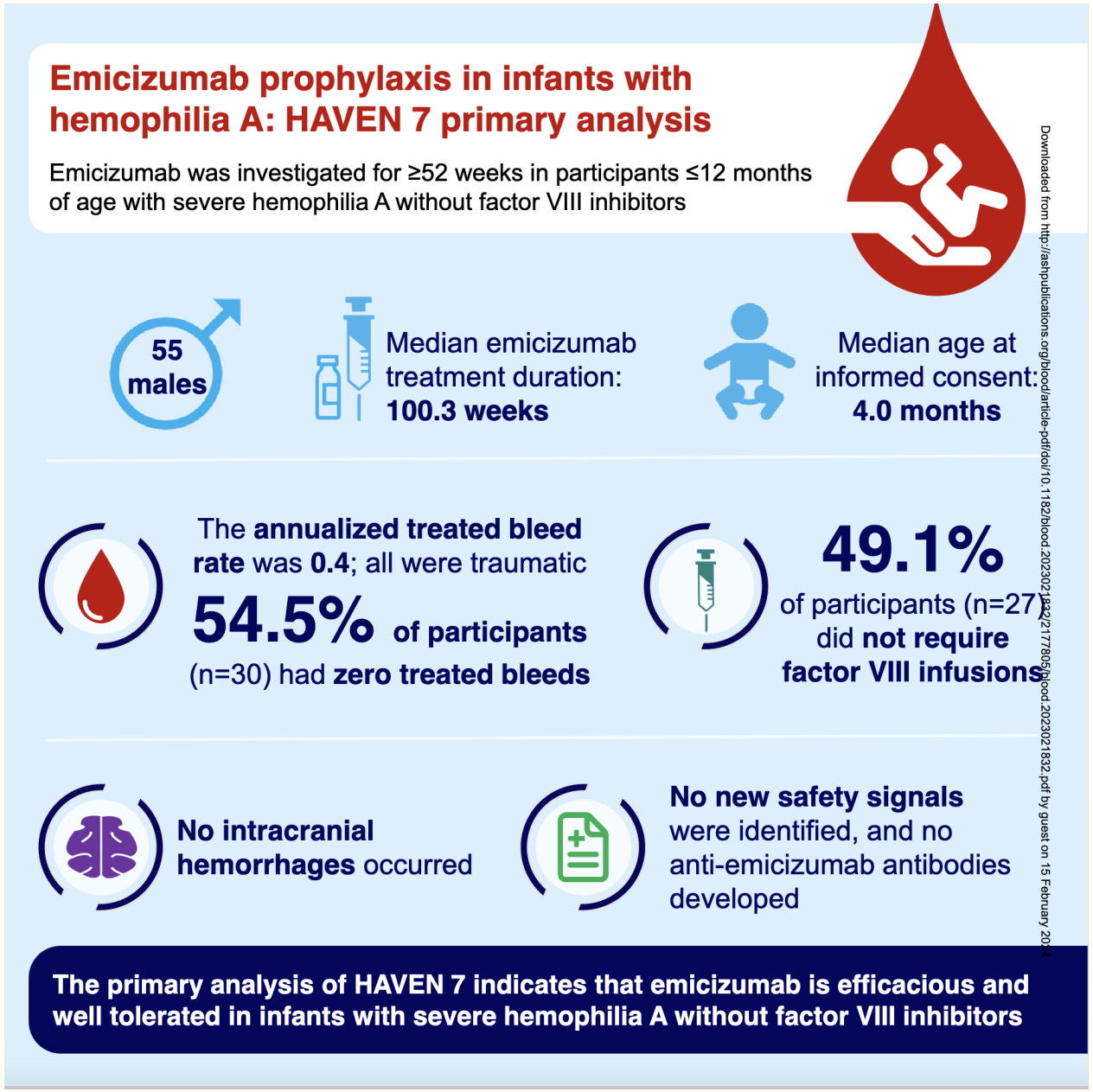
Emicizumab Clinical Data

Study, year[ref]	Study design	Study population	Dosing	Main results	
				Efficacy	*Safety*
HAVEN 1, 2017[26]	Phase III randomised open-label	109 (adolescent and adult haemophilia A with inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 1.5 mg/kg/week	Emicizumab prophylaxis *vs* no prophylaxis resulted in an 87% reduction of ABR	5 SAEs (3 thrombotic microangiopathies and 2 thromboses)
HAVEN 2, 2017[27]	Phase III non-randomised open-label	60 (paediatric haemophilia A with inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 1.5 mg/kg/week, or 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks	Emicizumab prophylaxis *vs* no prophylaxis resulted in a 99% reduction of ABR	No thrombotic events
HAVEN 3, 2018[28]	Phase III randomised open-label	152 (adolescent and adult haemophilia A without inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 1.5 mg/kg/week, or 3 mg/kg every 2 weeks	96% and 97% reduction in ABR in the two emicizumab arms, respectively, compared to episodic FVIII therapy	No major safety issues
HAVEN 4, 2017[29]	Phase III non-randomised open-label	48 (adolescent and adult haemophilia A with or without inhibitors)	Loading dose: 3 mg/kg/week for 4 weeks Maintenance dose: 6 mg/kg every 4 weeks	Efficacy results similar to HAVEN 1, 2, and 3	No major safety issues

ABR: annualised bleeding rate; SAEs: serious adverse events; FVIII: exogenous factor VIII.

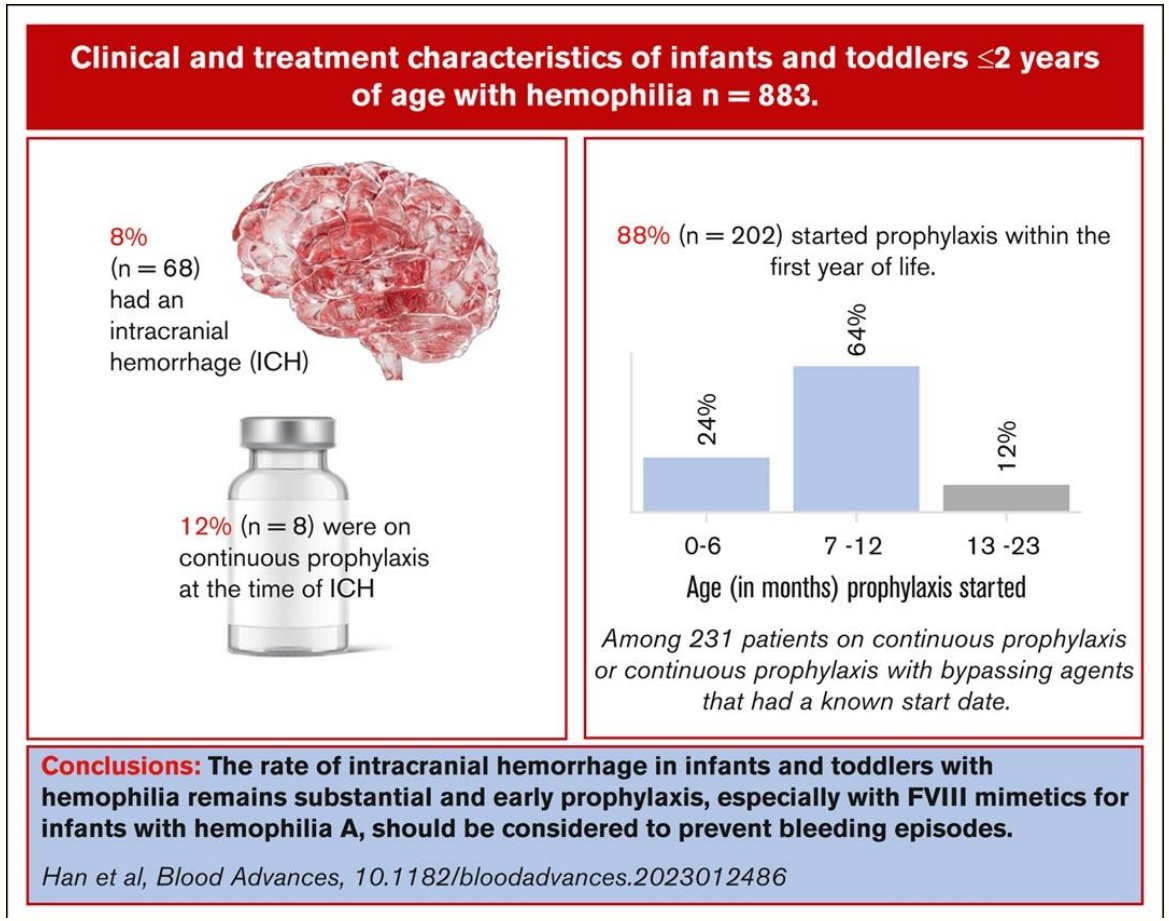
Franchini M, Marano G, Pati I, et al. *Blood Transfus*. 201

HAVEN -7



No participant in HAVEN 7 had tested positive for ADAs at CCOD. This reflects the low immunogenicity rate for emicizumab reported in a pooled analysis of the phase 3 clinical trials HAVEN 1–5, HOHOEMI, and STASEY, across which 5.1% of participants developed ADAs, including 0.6% for whom ADAs were associated with a decrease in emicizumab exposure.[35] In HAVEN 7, 24 participants were tested for FVIII inhibitors following at least three EDs or two consecutive doses of FVIII; two participants (3.6% of the trial population; 8.3% of those tested), both PUPs, tested positive for confirmed *de novo* FVIII inhibitors. As approximately half of the trial population (28/55) received FVIII treatment on study (with a median of one ED), and only 24/55 were tested for FVIII inhibitors, many participants are still in the ED risk period for inhibitor development. The long-term follow-up will provide further data on the impact of emicizumab on rate and timing of FVIII inhibitor development.

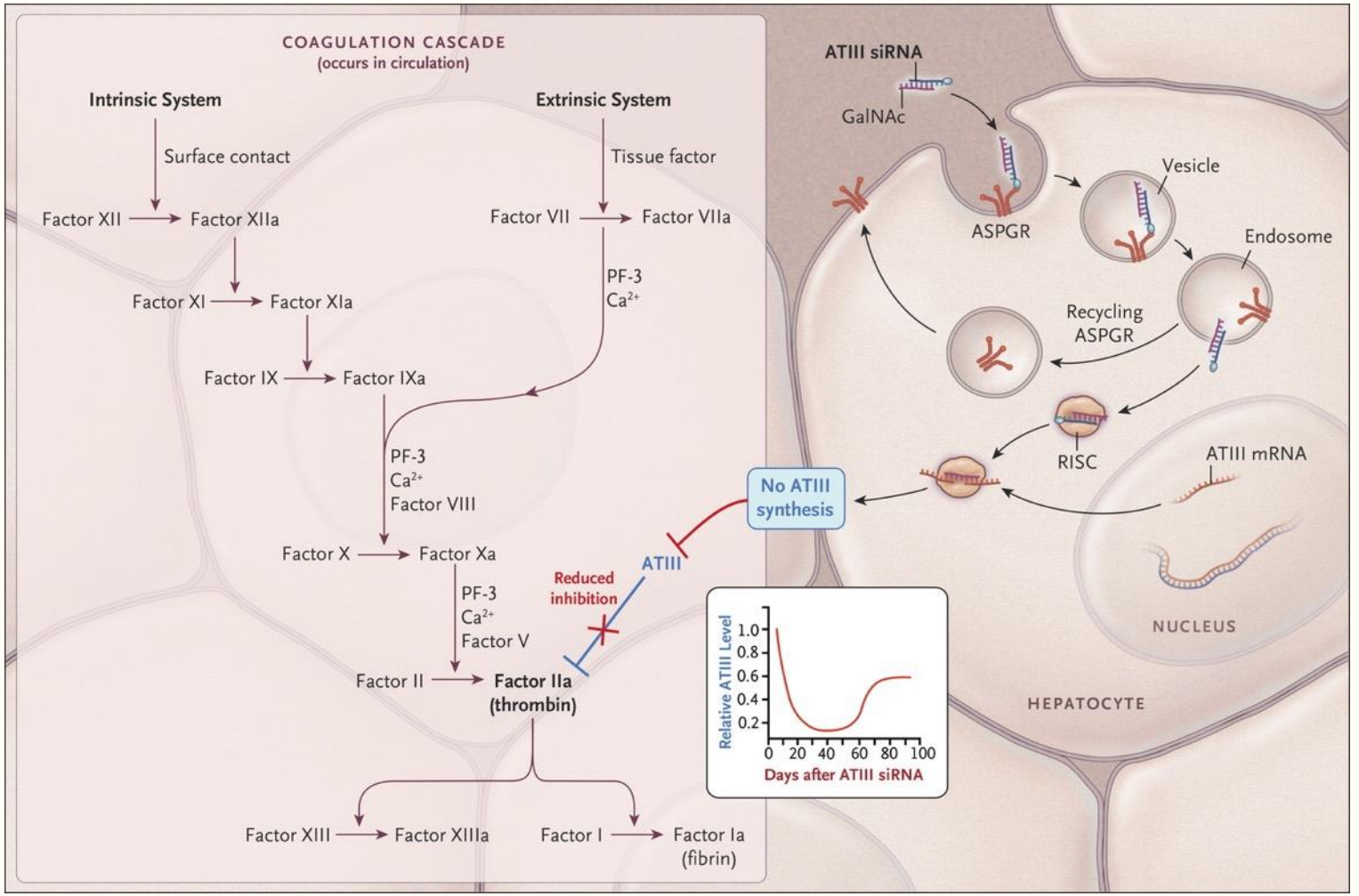
Era of Emicizumab …..



- Trauma/ Breakthrough Bleeding
- Interference with Lab Testing
- Inhibitors Development
- Immune Tolerance Therapy

Han et al. Blood Advances 2023

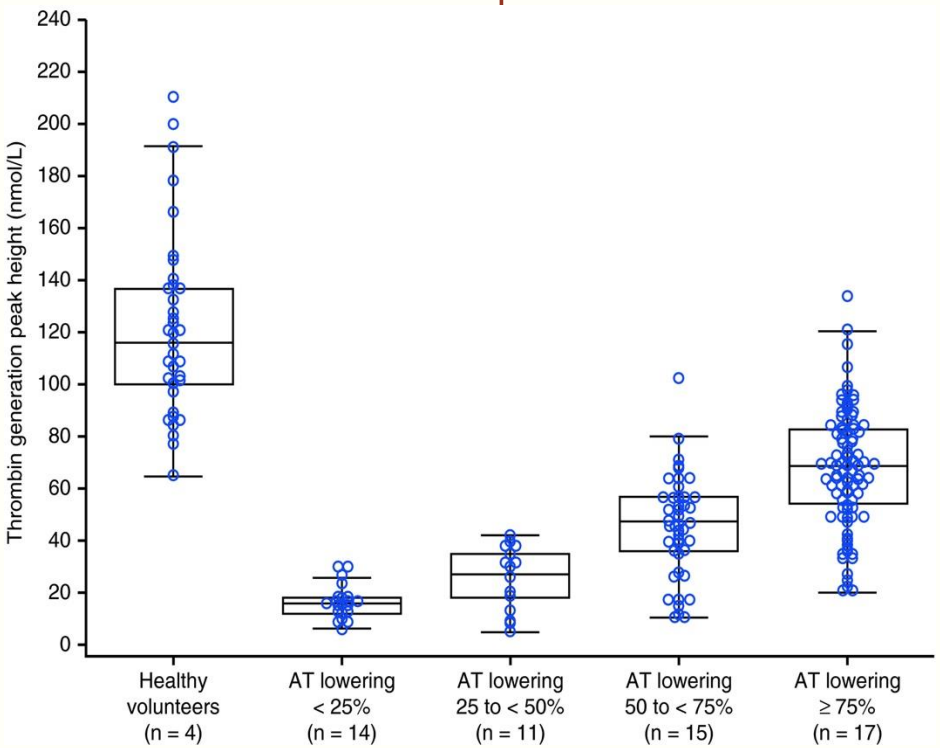
Antithrombin Modulation



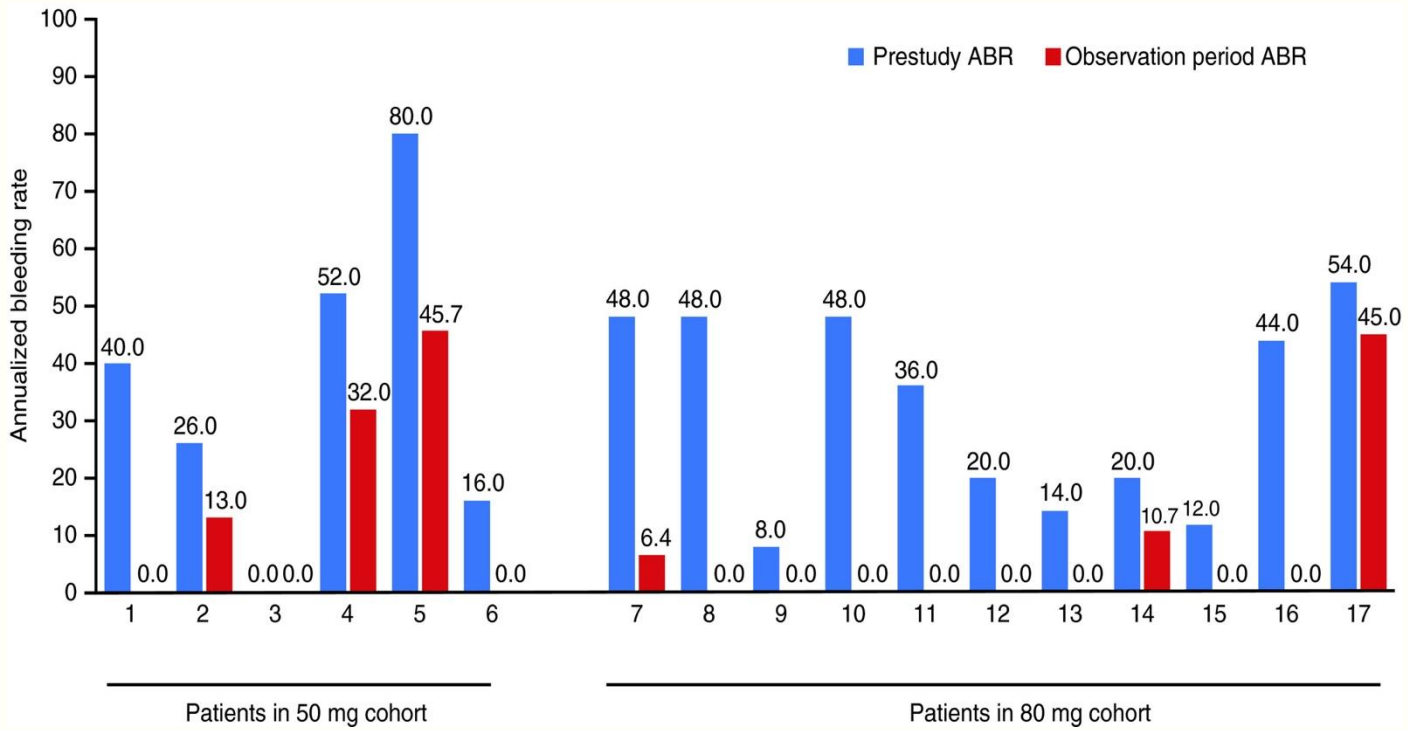
Ragni, NEJM (2015)

Antithrombin ATLAS Trials - Fitsuran

Thrombin Generation with AT

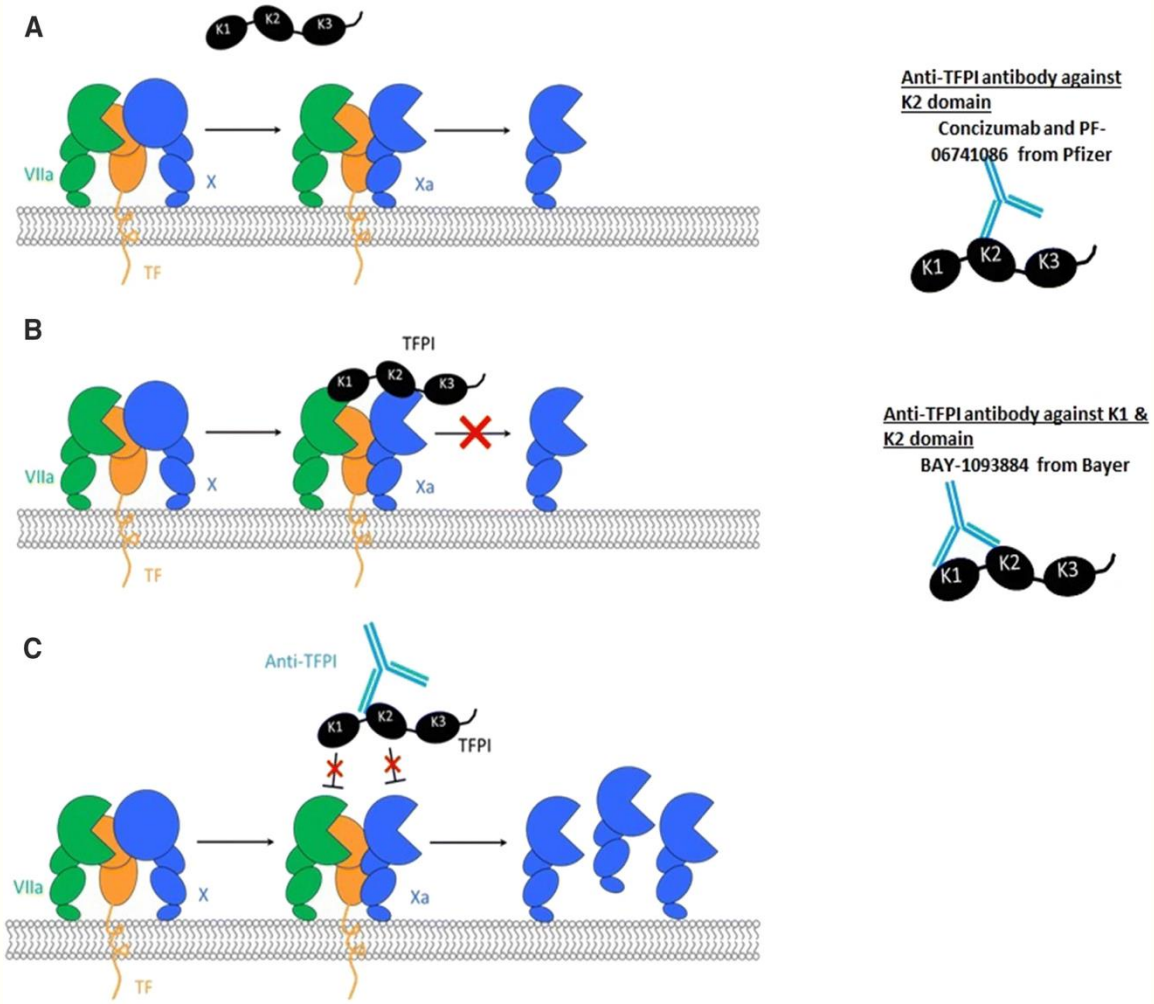


Annual Bleeding Rate



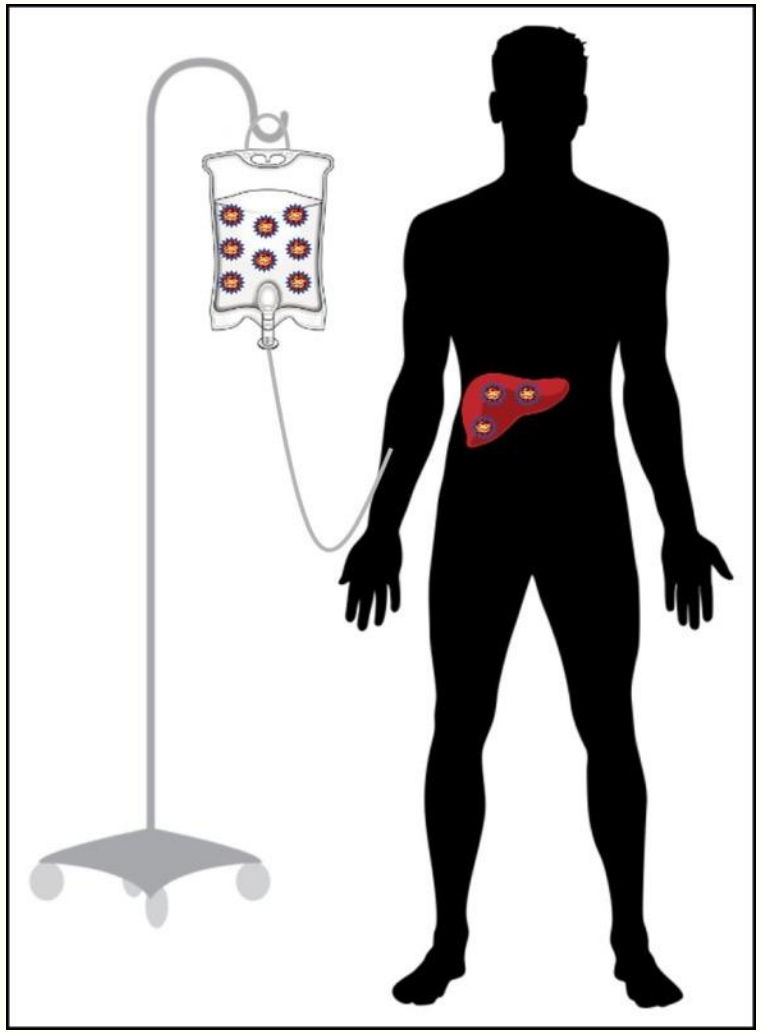
Pasi et al , JTH (2021)- Phase I Inhibitor Cohort (ATLAS)
Sponsor: Sanofi

Anti -Tissue Factor Pathway Inhibitor



Chowdary P. Drugs. 2018 Jun;78(9):881-890

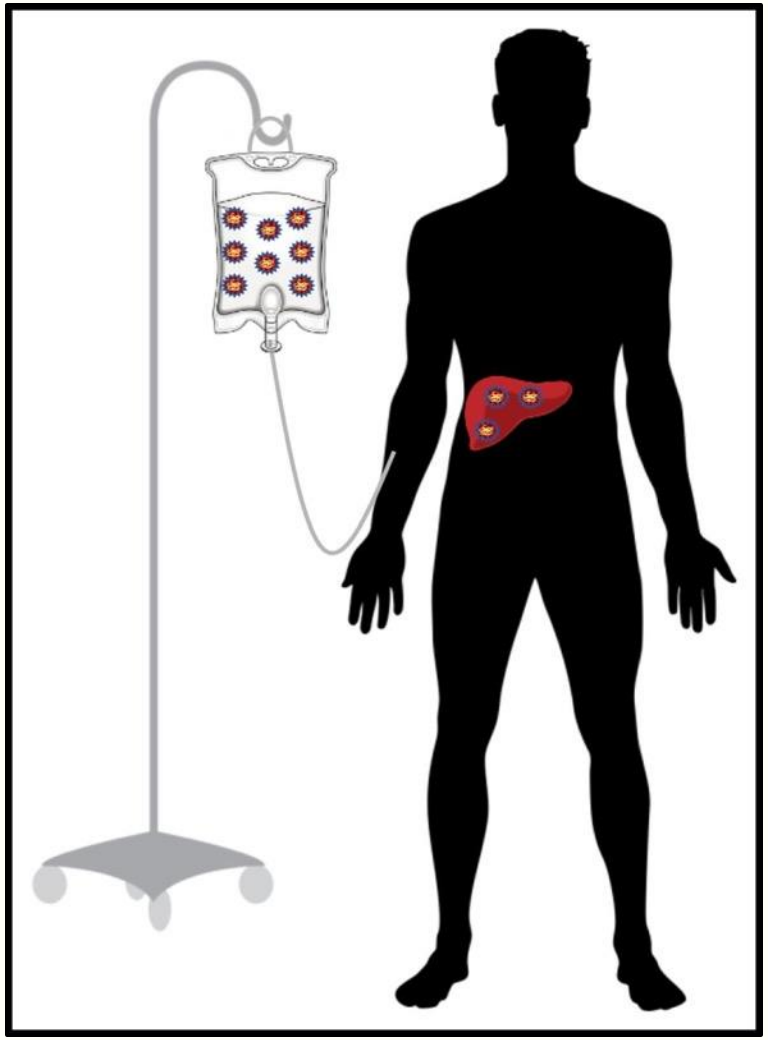
Gene Addition Therapy - Hemophilia

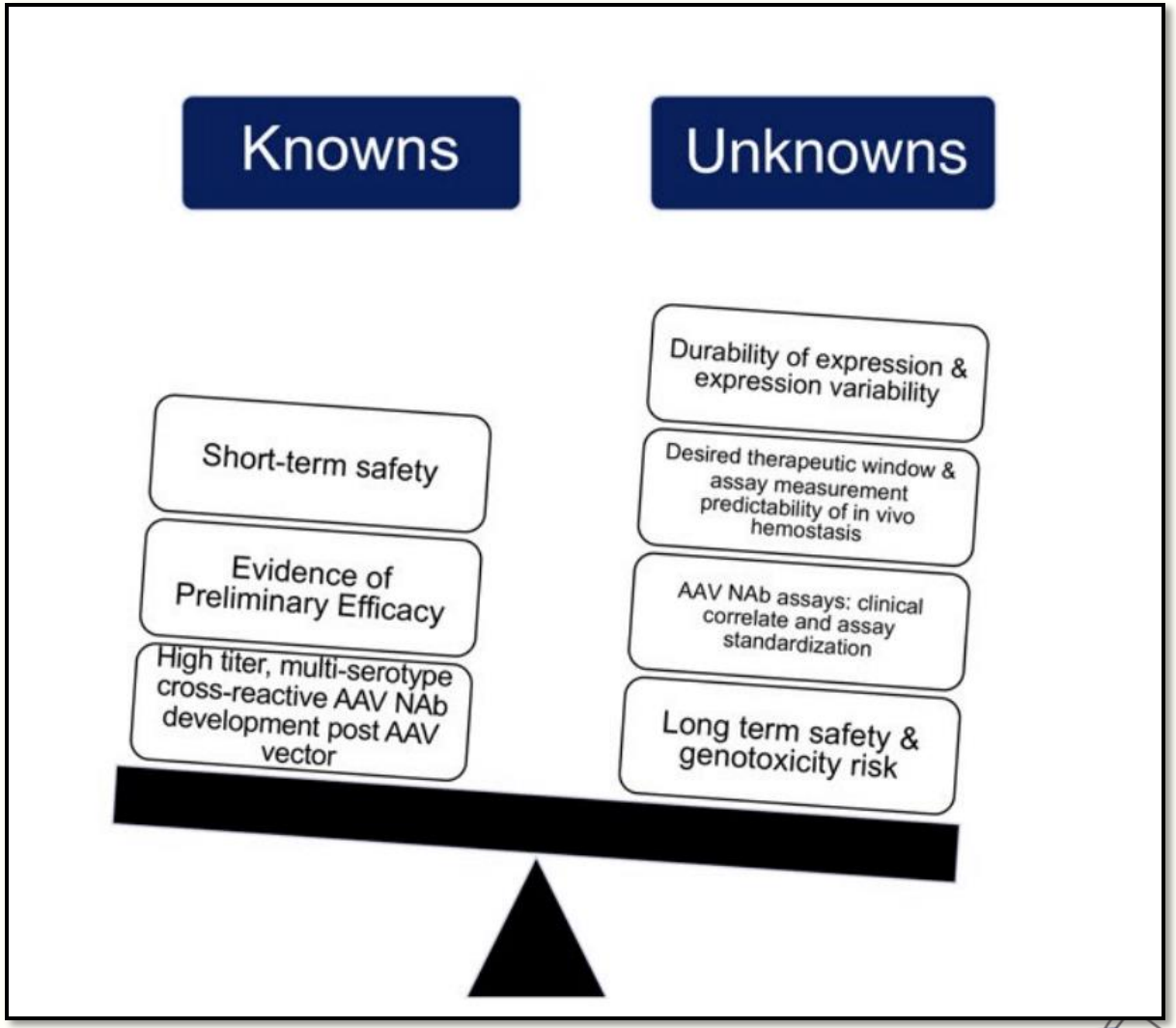


- Not Dominant Negative
- Molecular Characterization
- Animal Model
- Measurable biomarker
- Phenotype/Genotype Correlation
- Progressive Disease

Rogers and Herzog, Frontier in Bioscience, (2015), George, L. Blood advances (2017)

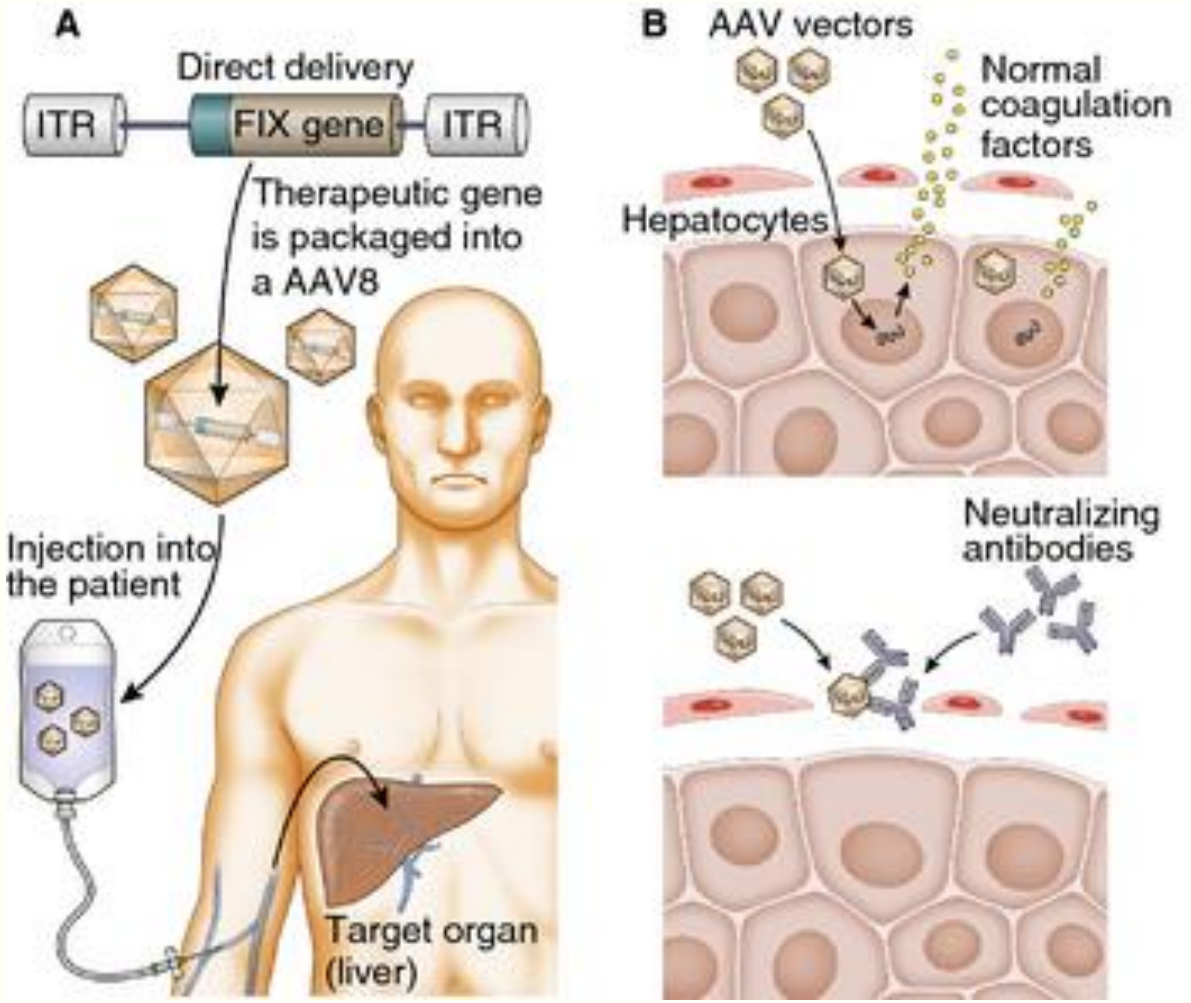
Challenges with Gene Therapy





Adapted : George LA. *Hematology Am Soc Hematol Educ Program* (2021) ;

AAV Based Gene Therapy - Hemophilia



Delivery to Target Tissue

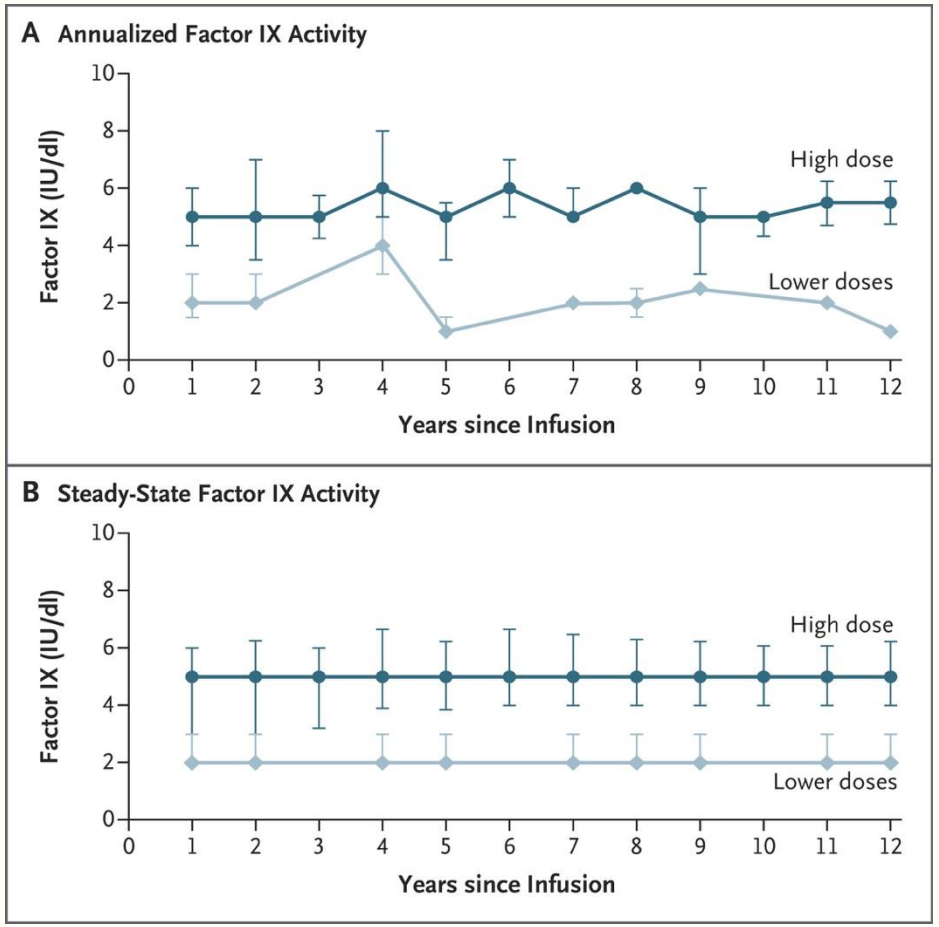
Transduction

Protein Synthesis

Ohmori et al JTH (2015)

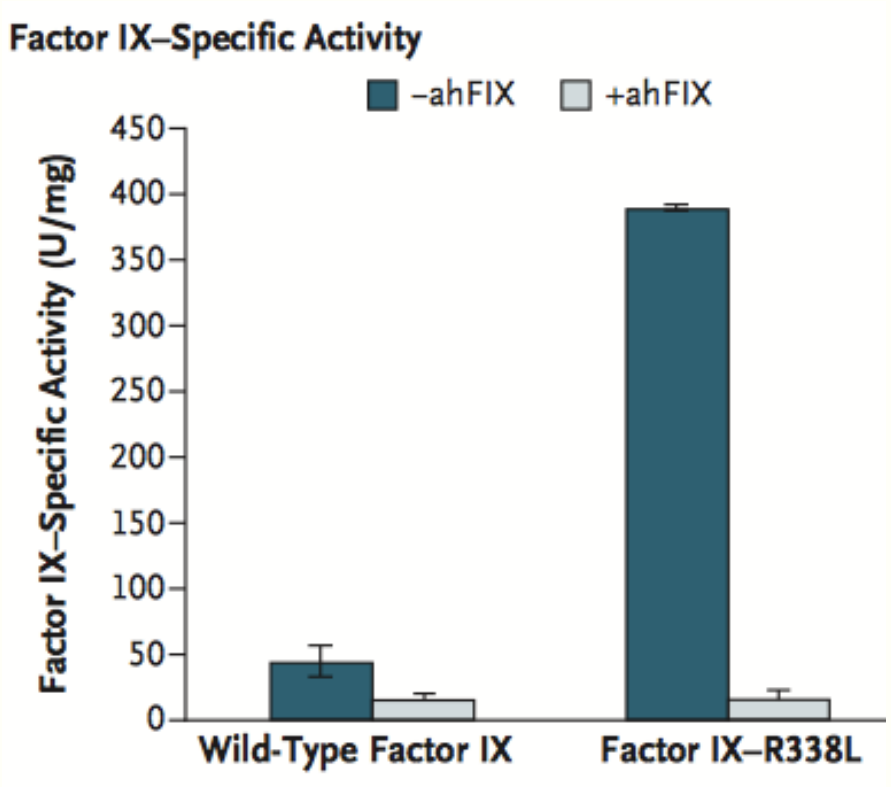
Hemophilia B Gene Therapy

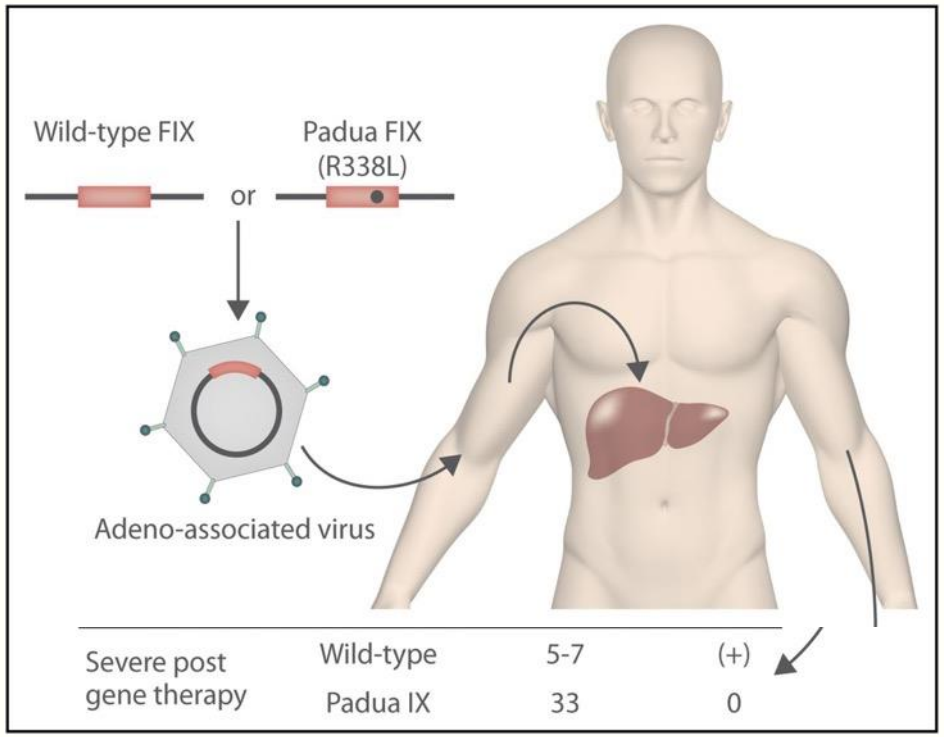
- 10 patients
- Single AAV Vector Infusion
- Peripheral Vein
- Factor IX 1-6% expression
- 13 + years of follow up
- No late toxic effects
- Stable Expression



Nathwani AC et al. NEJM (2014)
Riess et al. NEJM (2025)

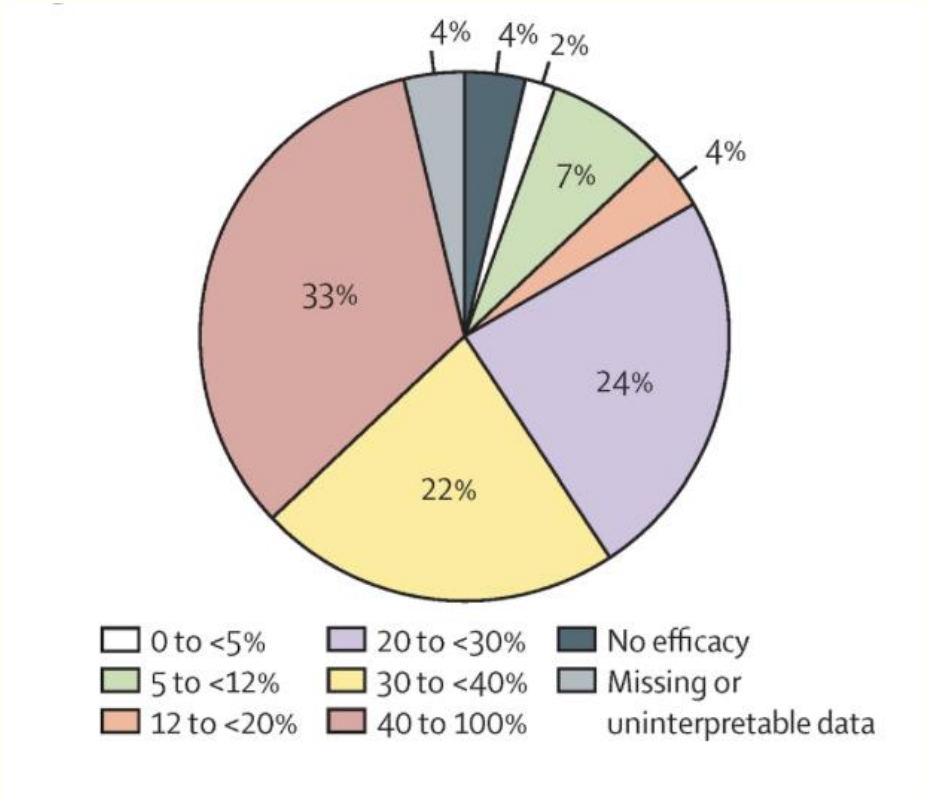
Padua FIX B Gene Therapy

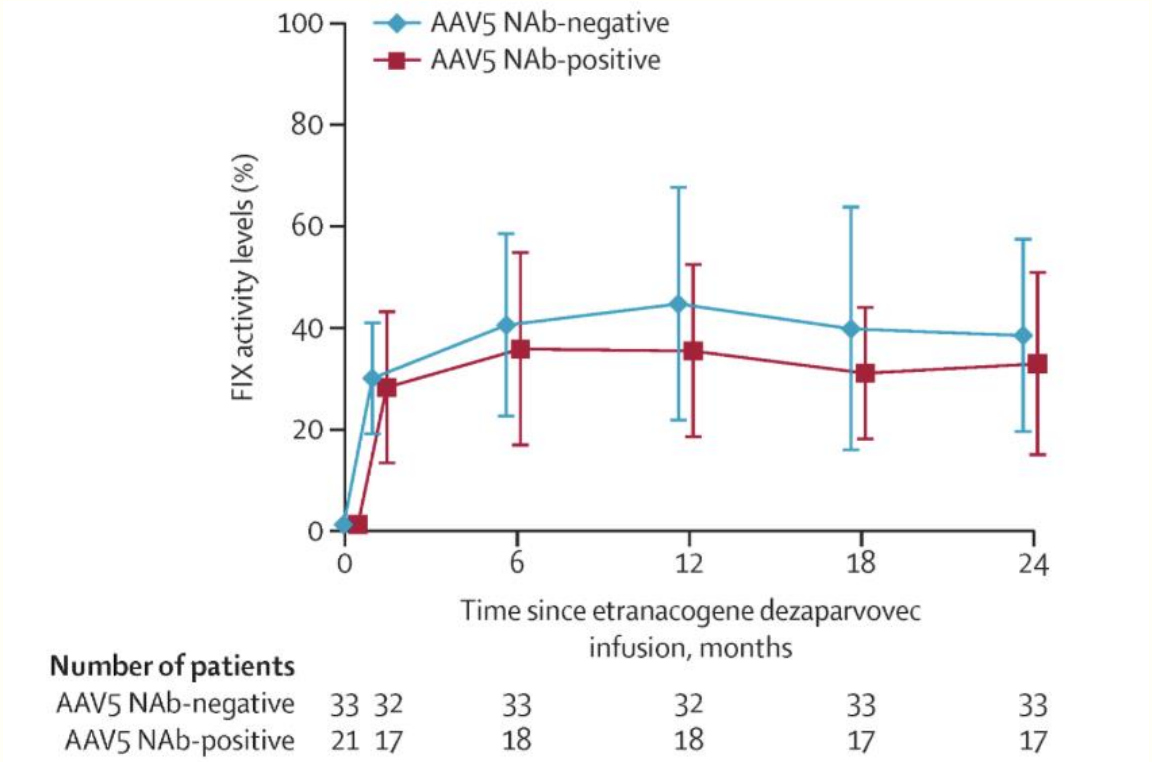




Makris M, Blood 2018;131:952-953
Simioni et al. NEJM, 2009

HOPE- B (Phase III – AMT-061)

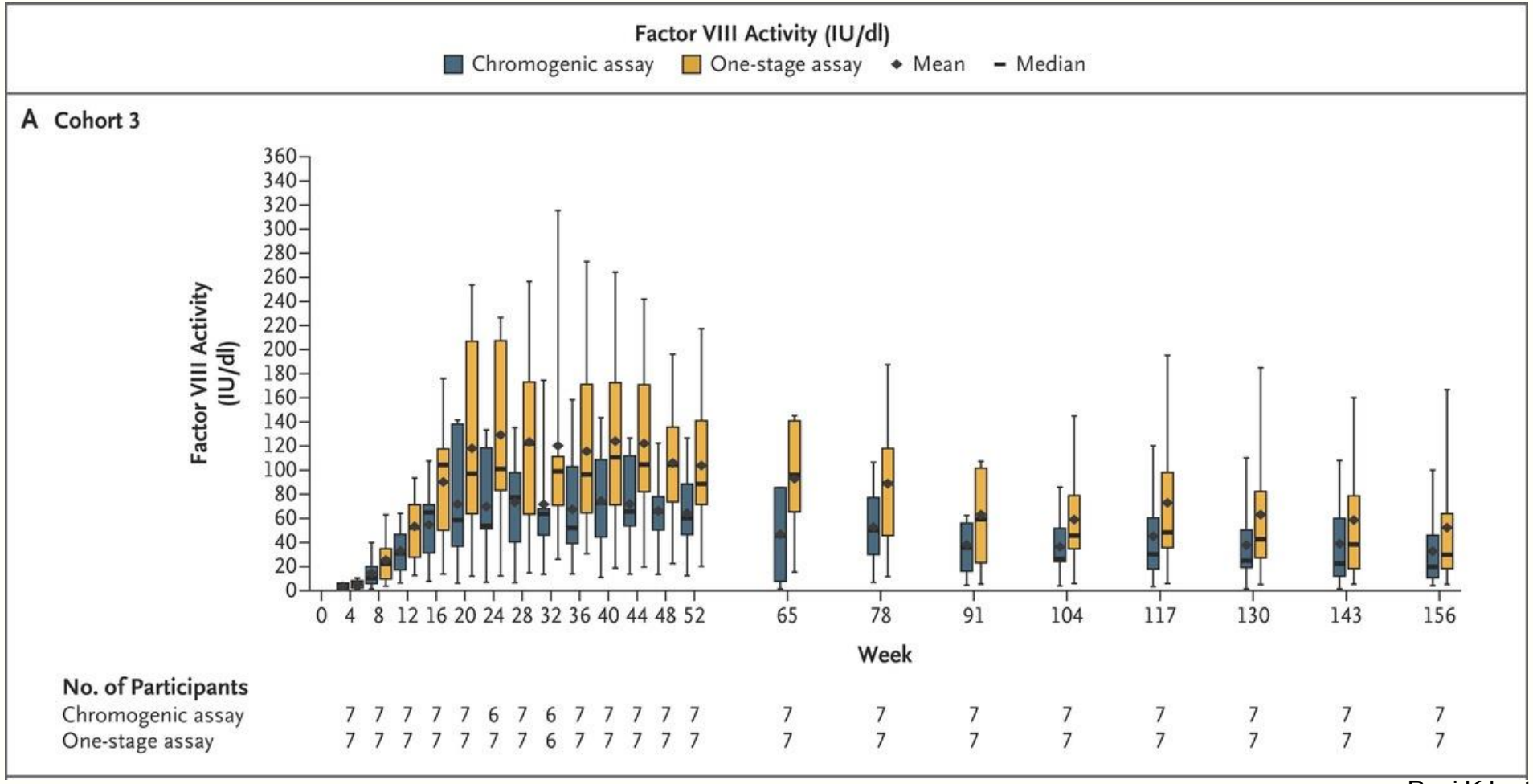




Coppens, Lancet 2024
Sponsor: Uniqure/CSL

Hemophilia A Gene Therapy – Durability

Factor VIII Activity Level BMN-270 6x 10e13

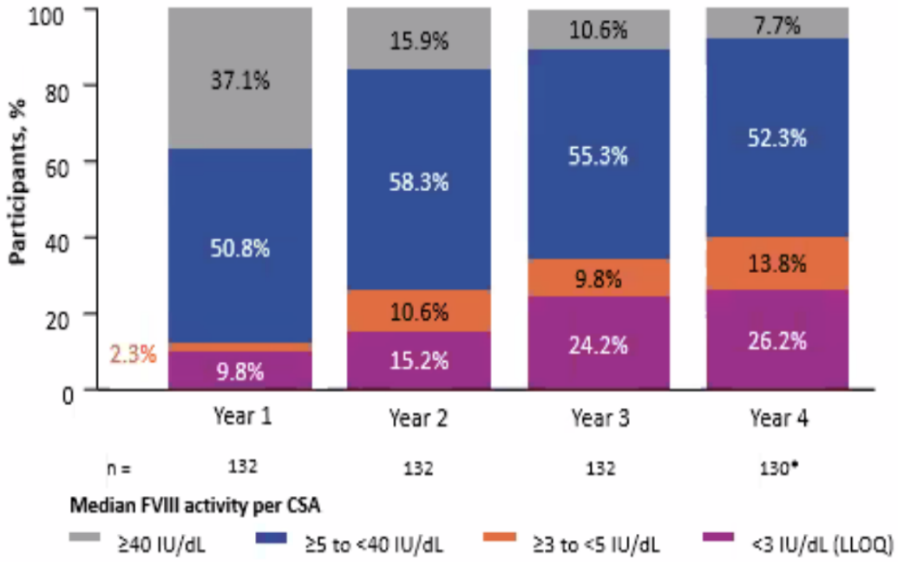


Pasi KJ, et al. NEJM 2020
Sponsor: Biomarin

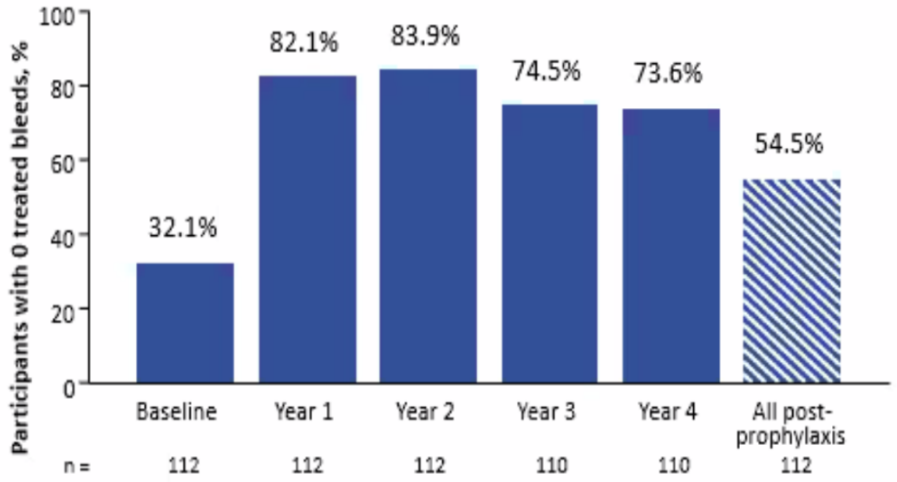
Hemophilia A Gene Therapy – Durability

- GENEr8-1: phase 3 GT for HA with 4 years follow-up
  - AAV5-hFVIII-SQ (valoctocogene roxaparvovec) $6x10^{13}$ vg/kg

Median FVIII activity over time



In year 4, >70% of participants had no treated bleeds



*2 participants did not reach year 4 follow-up, Week 208 data are based on 130 participants. For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.

CSA, chromogenic substrate assay; FVIII, factor VIII; GT, gene therapy; HA, haemophilia A; LLOQ, lower limit of quantification; mITT, modified intention-to-treat.

Leavitt AD (ISTH 2024)
Sponsor: Biomarin