Fred Hutch Cancer Center

Bleeding Disorders

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Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

Disclosures

- Advisory Board/Consultant
  - Genentech/Roche
- Research Funding from
  - Genentech
  - Pfizer

1 von Willebrand Disease and von Willebrand Syndrome

2 Hemophilia A and B

3 Rare factor deficiencies

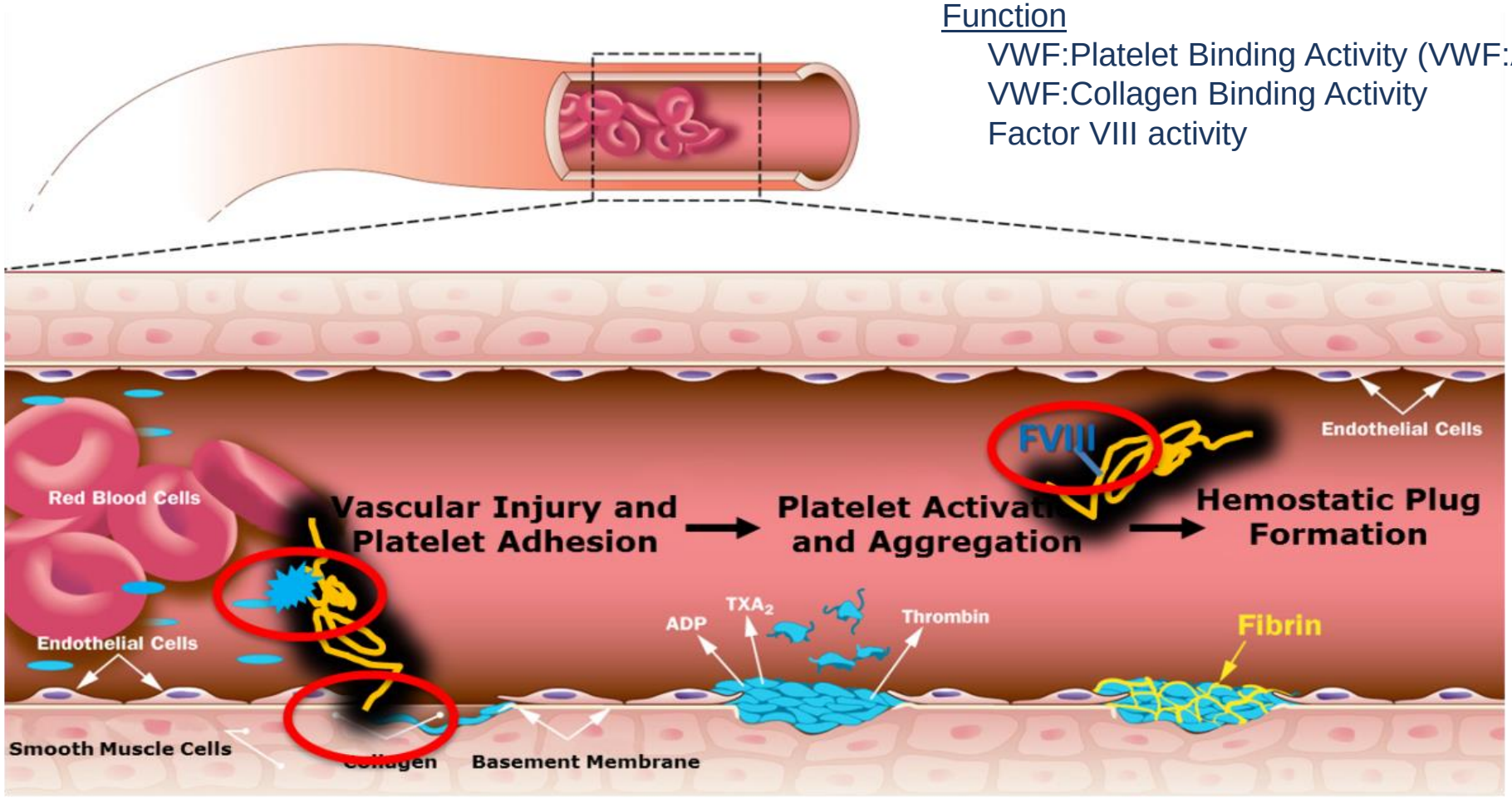
4 Inherited platelet disorders

von Willebrand Disease and Acquired von Willebrand Syndrome

von Willebrand Factor

Quantity
- VWF:Antigen (VWF:Ag)

Function
- VWF:Platelet Binding Activity (VWF:Act or VWF:RCo)
- VWF:Collagen Binding Activity
- Factor VIII activity



Collagen binding

Platelet binding

Factor VIII binding

Image adjusted from Victor S. Blanchette

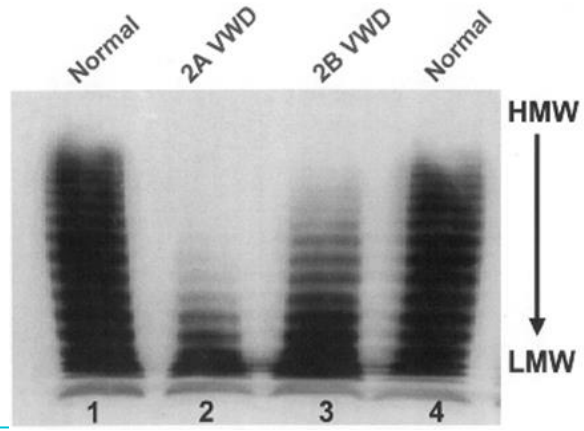
VWD: Clinical Manifestations

- Mucocutaneous Bleeding
  - Nosebleeds
  - Gum Bleeding
  - Bleeding after dental extractions
  - Bleeding after tonsillectomy
  - Excessive bruising
  - Heavy menstrual bleeding
  - Postpartum hemorrhage
  - GI bleeding (especially in Types 2 and 3)
- Hemorrhagic Ovarian Cysts
- Post-operative bleeding
- Hemarthrosis (especially Type 3)

Leebeek FWG and Eikenboom JCJ. N Engl J Med. 2016;375:2067

VWD: Testing

- aPTT
  - Will be prolonged if FVIII decreased enough
    - usually < 30-40%
  - May be normal in Types 1 and 2 VWD
- PFA-100
  - May be normal but always prolonged in more severe disease
- VWF antigen concentration
- VWF activity
  - Platelet binding (VWF:RCo, VWF:GPIbR, VWF:Ab, VWF:GPIbM)
  - Collagen binding
- FVIII activity
- VWF multimer analysis

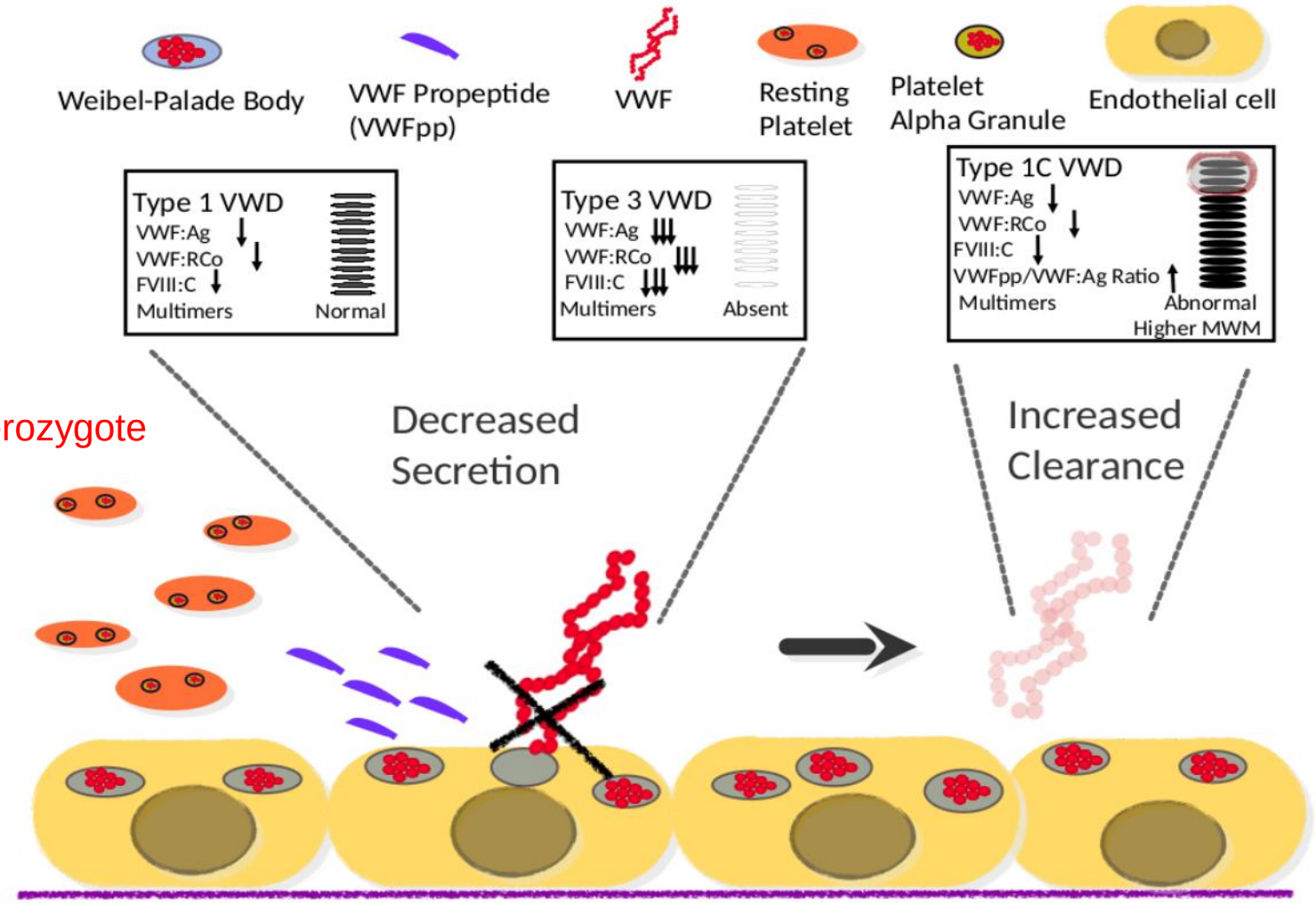


James PD et al. Blood Adv 2021;5:280.

Von Willebrand Disease – **Quantitative** Defects

Type 1
Mild, common

Type 3
Rare, severe
often compound heterozygote



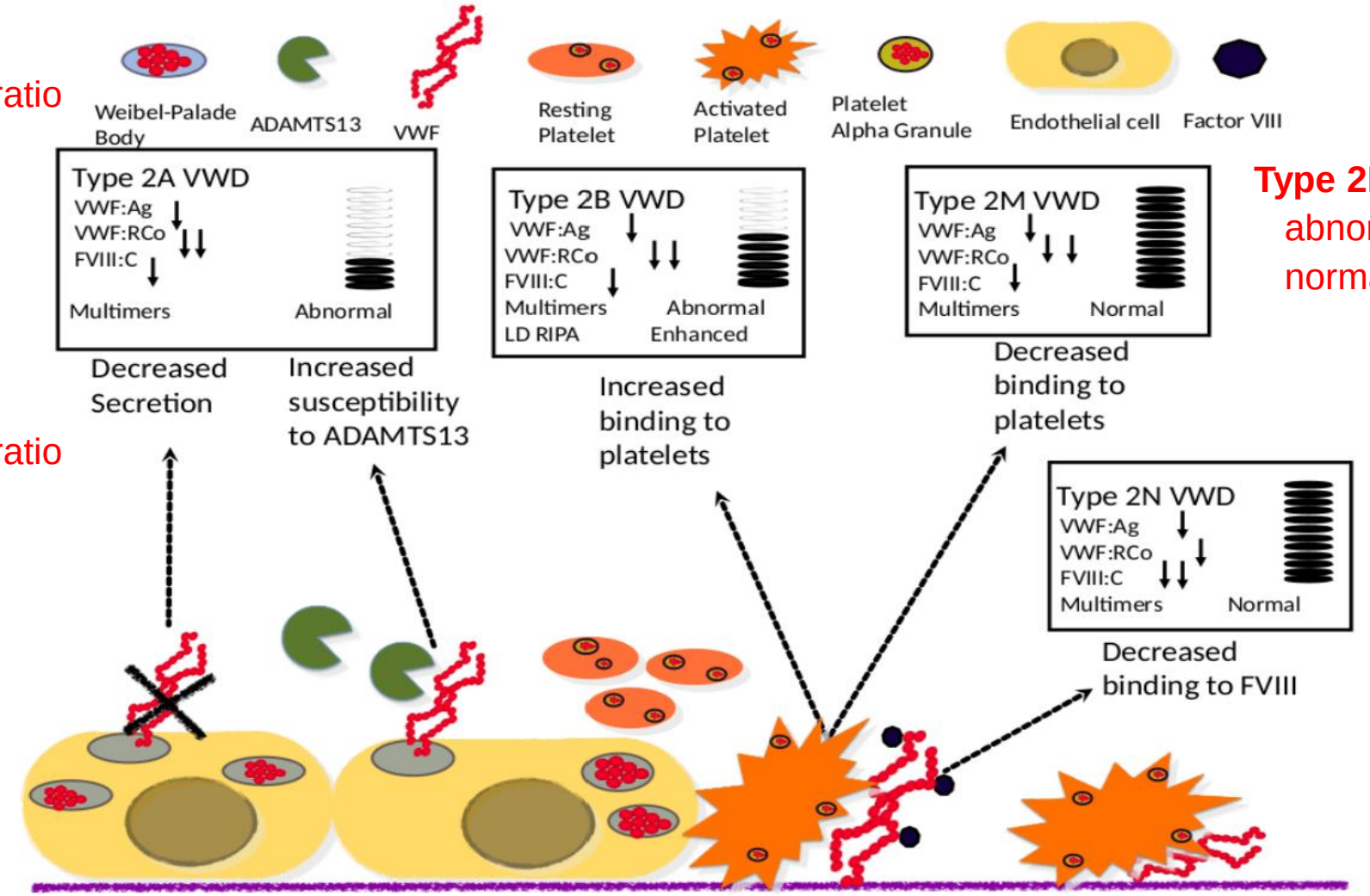
Type 1C
rapid clearance

http://what-when-how.com/acp-medicine/platelet-and-vascular-disorders-part-2/

Von Willebrand Disease – **Qualitative** Defects

Type 2A
- abnormal VWF:Act/Ag ratio
- abnormal multimers

Type 2B
- abnormal VWF:Act/Ag ratio
- abnormal multimers
- low platelets



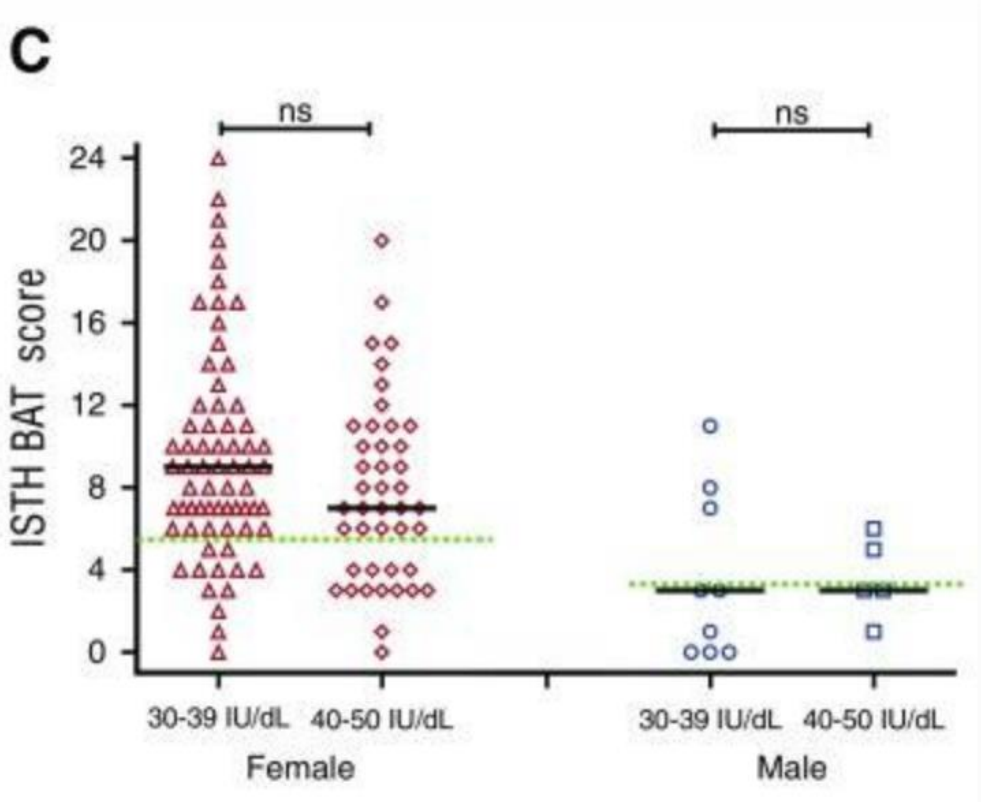
Type 2M
- abnormal VWF:Act/Ag ratio
- normal multimers

Type 2N
- very low FVIII
- normal multimers

http://what-when-how.com/acp-medicine/platelet-and-vascular-disorders-part-2/

Diagnosis of Type 1 VWD

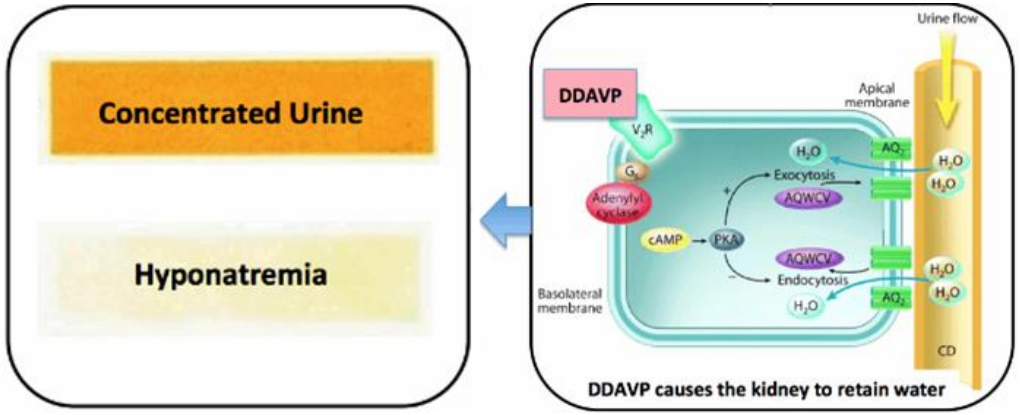
- VWF level <30% regardless of bleeding
- VWF < 50% with abnormal bleeding
  - 30% - 50%: Consider additional bleeding disorders
- No longer diagnosis of “low VWF”
  - Significant bleeding symptoms which need “VWD” treatment



James et al, Blood Adv 2021;5:280, Lavin et al, Blood 2017;130:2344.

Treatment of VWD

- Desmopressin (DDAVP – intranasal, SQ, IV)
  - Releases endogenous VWF and factor VIII from endothelium
  - Increases platelet adhesion to vessel wall
  - Increases tissue plasminogen activator
- Caution (Are there any stores? What is in the stores?)
  - Not effective in type 3
  - Less effective in type 1C
  - Less effective in type 2N
  - Caution in 2B (pseudothrombocytopenia)
  - DDAVP challenge (pre, at 90 min and 4 hours) to determine individual response
  - Tachyphylaxis and intravascular fluid retention



Connell NT Blood Adv. 2021;5:301, Kalot et al, Blood Adv 2022;6:3735.

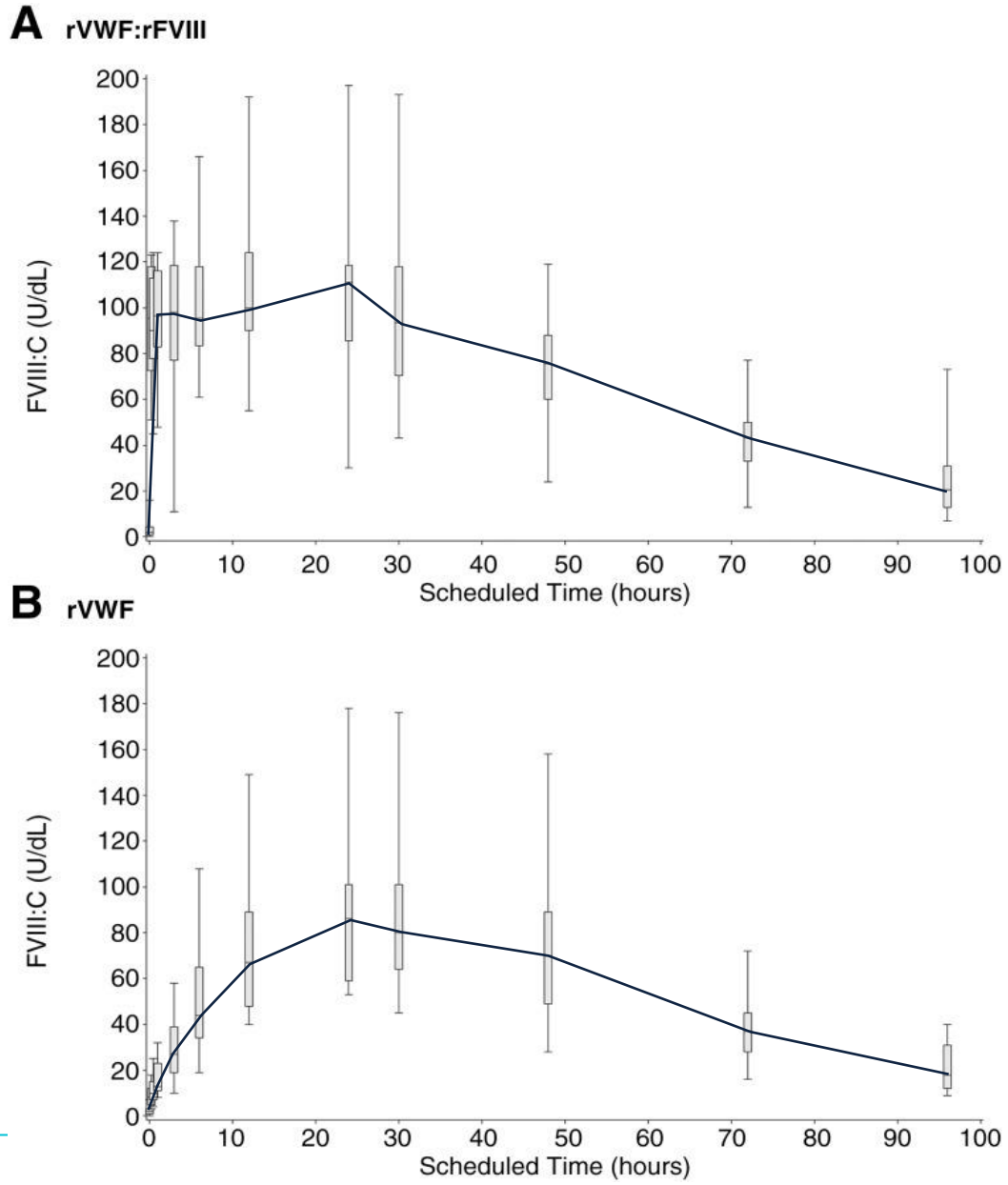
Treatment of VWD

- Antifibrinolytics
  - ε-aminocaproic acid (Amicar), tranexamic acid
  - Lysine analogs
  - Bind to plasminogen and prevent conversion to plasmin and thus fibrin degradation

Eghbali A, et al. Haemophilia 2016;22:e423.

Treatment of VWD

- VWF factor concentrates
  - Plasma derived - all contain factor VIII as well
    - Different VWF(RCo)/FVIII concentrations[1]
      - Humate-P 2.45/1
      - Alphanate 0.9/1
      - Wilate 0.9/1
  - Recombinant von Willebrand factor (rVWF)[2]
    - does not contain FVIII



[1]Castaman, Linari. Ther Clin Risk Manag. 2016; 12: 1029, [2]Gill et al. Blood. 2015 Oct 22;126:2038

Acquired von Willebrand syndrome (AVWS)

Rare

- underreported

Paucity of data

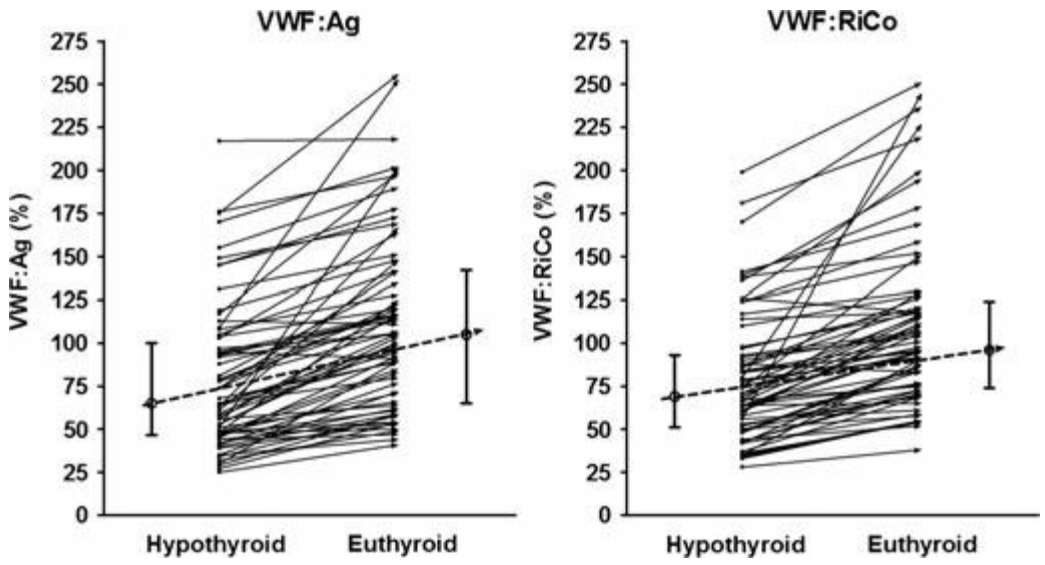
- largest data collection on the disorder today, the International Society of Thrombosis and Haemostasis International Registry on AVWS

Tiede A et al. Blood 2011;117:6777.

AVWS due to Decreased Production

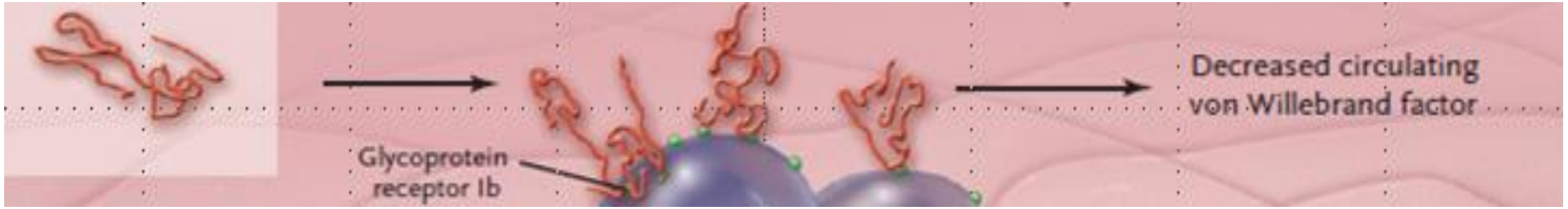
Decreased production of thyroid hormone → Decreased synthesis of von Willebrand factor

- Looks like a type 1 VWD (quantitative)
  - Low VWF:Ag and VWF:Activity
  - Normal multimers
  - Low VWF pro-peptide
- Study of 90 adults with primary overt hypothyroidism
  - **33%** had VWF:Ag and/or VWF:RCo levels of ≤50%
  - Most with levels 30-50%, none < 10%
  - Correlated with free thyroxine (FT4) levels



Stuijver et al. Haemophilia 2014

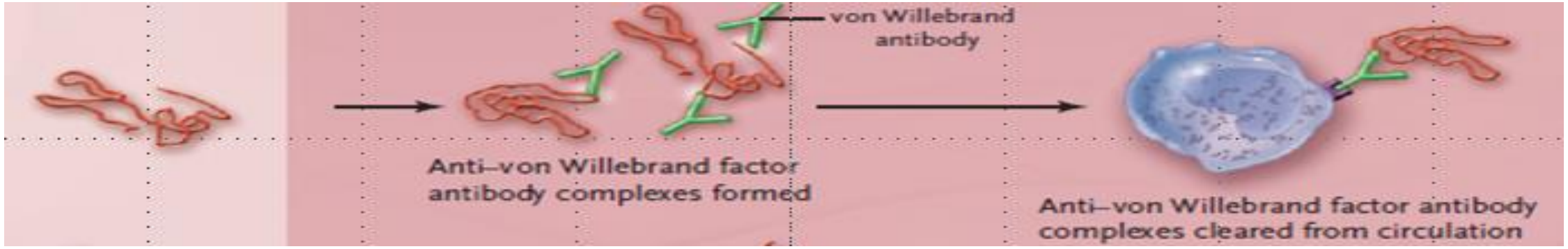
AVWS due to Adsorption



- Lymphoproliferative disorders (MM, WM, NHL, HCL), Myeloproliferative disorders (ET, PV), other thrombocytosis, malignancy
- Treat the underlying disease

Cuker et al, N Eng J Med 2009

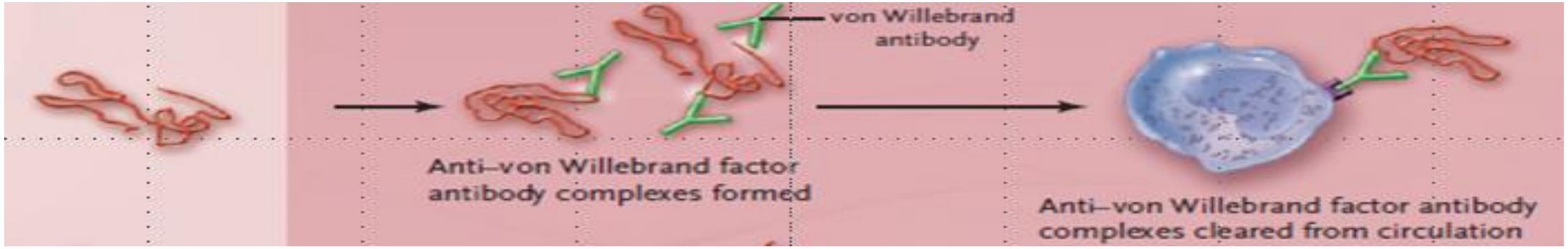
AVWS due to antibodies



- Associated conditions:
  - Monoclonal gammopathy of undetermined significance (MGUS)
  - Lymphoproliferative disorders
  - Systemic lupus erythematous
- Detection of actual antibodies remains challenging and not well standardized

Cuker et al, N Eng J Med 2009

AVWS due to antibodies



Intravenous immunoglobulin

- Usually corrects laboratory abnormalities within 24-48 hours
- Alleviates bleeding symptoms in IgG-MGUS but not IgM-MGUS.
- Response can be seen for about 21 days and periodic re-dosing can achieve long-term control

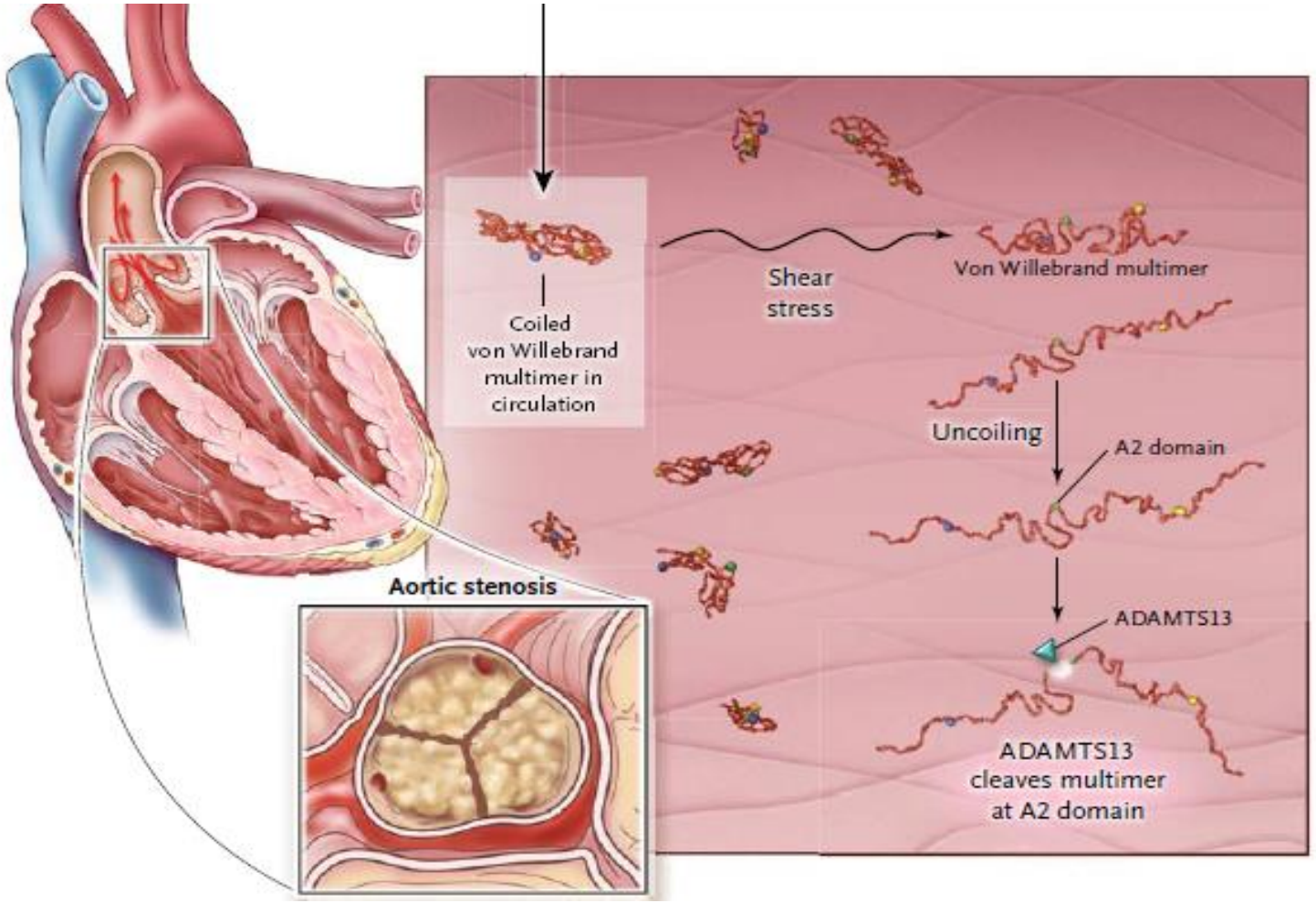
Prednisone, rituximab and other immunosuppressant

Not standardized and has varying results

Treat underlying disease

Cuker et al, N Eng J Med 2009

AVWS associated with cardiovascular abnormalities



Loscalzo. N Eng J Med 2012

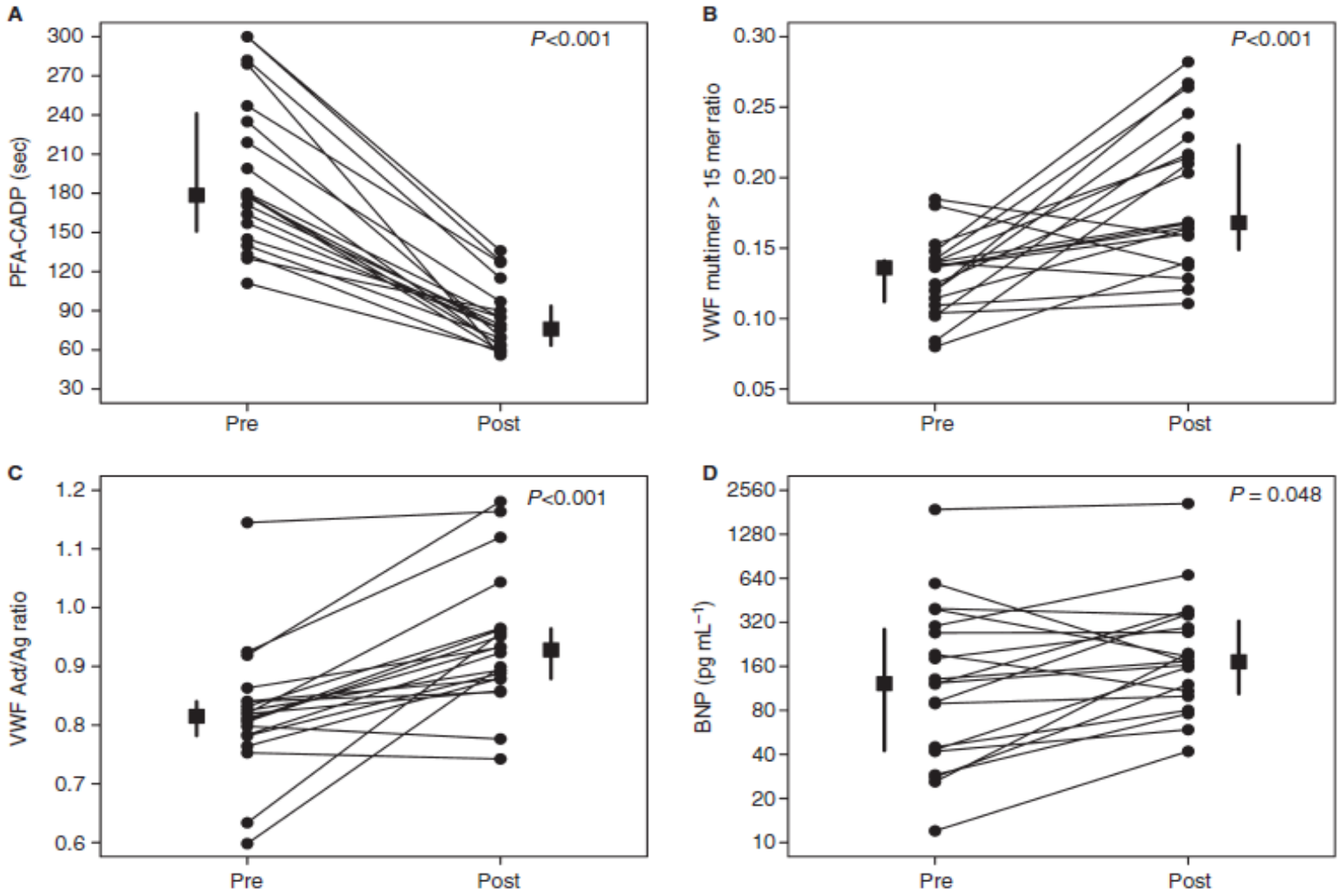
AVWS associated with cardiovascular abnormalities

- Etiology
  - acquired valve and other structural abnormalities
  - hypertrophic cardiomyopathy
  - intra-cardiac devices
- About 20% of adults with congenital heart disease have AVWS Laboratory
  - Often normal VWF:Ag, VWF:RCo, or VWF:CB levels
  - But reduced VWF:RCo/Ag and VWF:CB/Ag ratio
- Not all patients will have bleeding symptoms

Waldow et al. Int J Cardiol 2014;176:739.

AVWS associated with cardiovascular abnormalities

- Effect of mitral valve repair



Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

Hyde's Syndrome (Aortic Stenosis, AVMs, AVWS)

- Correspondence in NJEM 1958 by EC Heyde
  - Gastrointestinal Bleeding in Aortic Stenosis
- In Blacksmith study in hypertrophic cardiomyopathy
  - 8/20 (40%) had AVM's
- Etiology is poorly understood
  - normal vascular aging and an impairment of platelets to maintain vascular endothelium
- Bleeding symptoms resolve after valve replacement

Loscalzo. N Eng J Med 2012

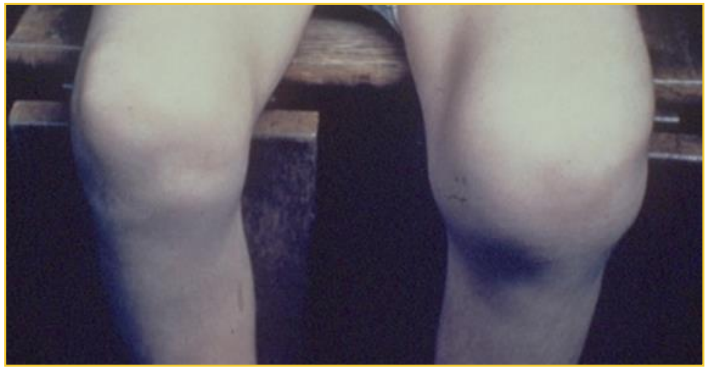
Fred Hutch Cancer Center

Congenital Hemophilia

Hemophilia A and B

Hemophilia: rare X-linked bleeding disorders

- Hemophilia A – deficiency of factor VIII (*F8* gene)
- Hemophilia B – deficiency of factor IX (*F9* gene)



Complication: bleeding

- joints and soft tissue
- trauma and surgeries

Hemophilia severity determined by factor activity level:

- Mild: >5%, Moderate: 1-5%, Severe: <1%

Standard of care: replacement of clotting factor (IV)

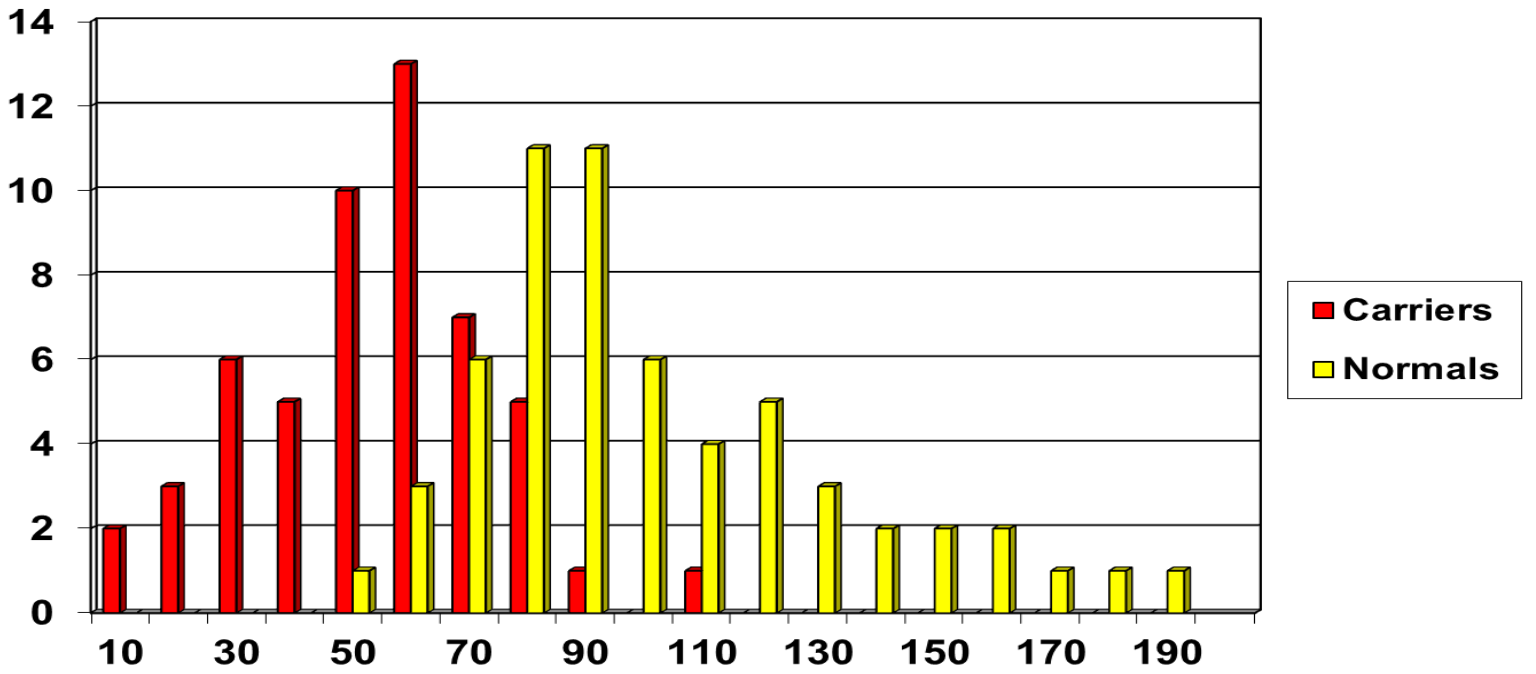
Complication of treatment: **inhibitors** (factor-neutralizing antibodies)

- ~30% in severe A (can also occur in mild hemophilia A), ~10% in severe B,

Berntorp E et al. Nat Rev Dis Primers 2021;7:45.

Females with *F8* Genetic Variants

- ~ 30% have bleeding symptoms
- Newer terminology:
  - Females with hemophilia
  - Symptomatic carriers
  - Asymptomatic carriers



Van Galen, K et al. J Thromb Haemost. 2021;19:1883, Figure courtesy of C. Kasper

First Blood Transfusion for Hemophilia

1803

First Plasma Transfusion

1823

Cryoprecipitate discovered by Dr. Judith Pool

1840

First Factor Concentrates

1936

First Monoclonal Factor Concentrates

1964

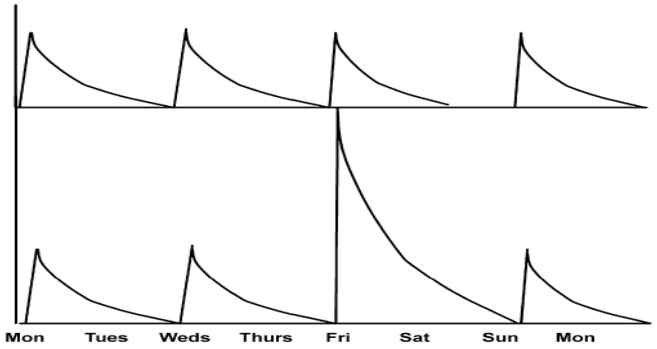
First Recombinant Factor Concent

1960/70's

Factor Prophylaxis In U.S.

1987

1993



2007

2014

2017

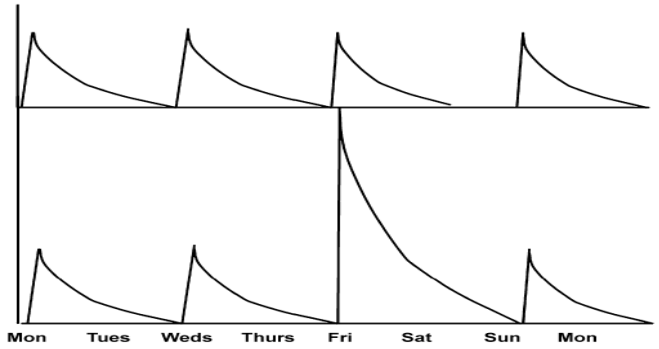
Mancuso ME et al. Lancet 2021;397:630.

Factor Prophylaxis In U.S.

Has to be given **IV**

Factor has a relatively **short half life**

- ~ 6-10 hours for factor VIII
- ~12-18 hours for factor IX
- Has to be given frequently
- Difficult to achieve troughs to maintain an active lifestyle



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1803 First Blood Transfusion for Hemophilia

1823 First Plasma Transfusion

1840 Cryoprecipitate discovered by Dr. Judith Pool

1936 First Factor Concentrates

1964 First Monoclonal Factor Concentrates

1960/70's First Recombinant Factor Concentrates

1987 Factor Prophylaxis In U.S.

1993 Extended half-life factors (EHL)

2007 Bi-specific Ab

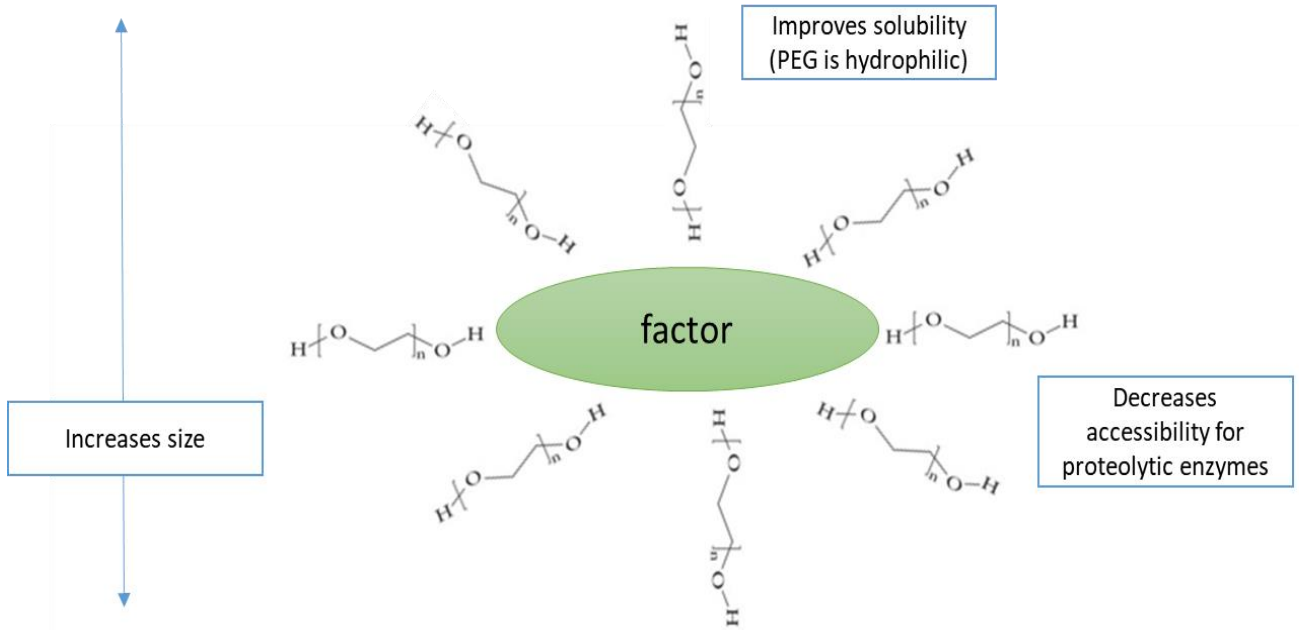
2014 Gene therapy

2017

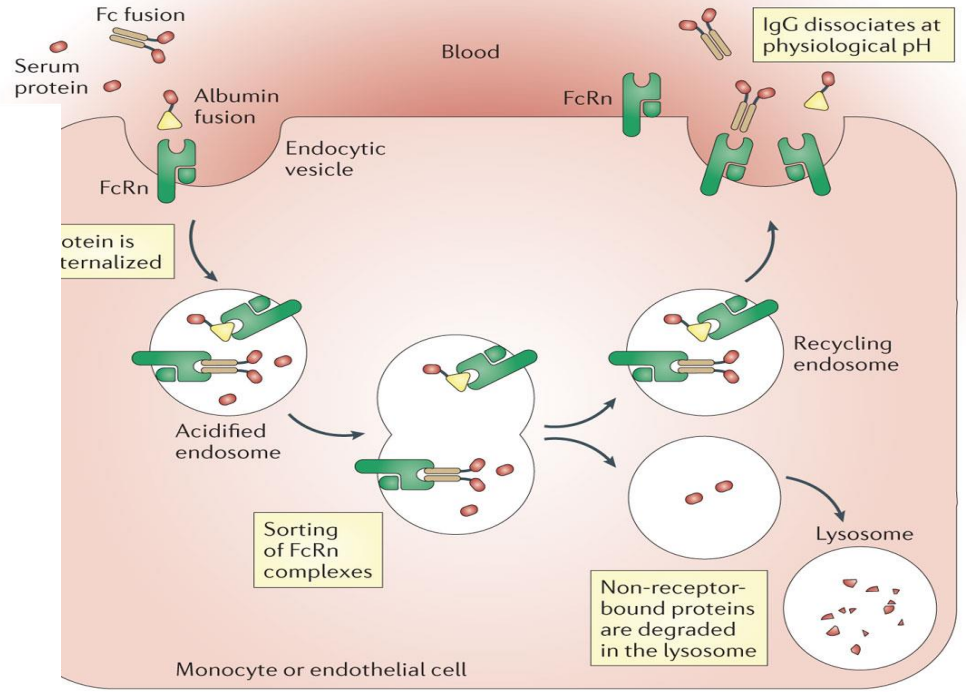
Mancuso ME et al. Lancet 2021;397:630.

Mechanism of Extended Half-life Colotting Factors

Pegylation



Fc or albumin fusion



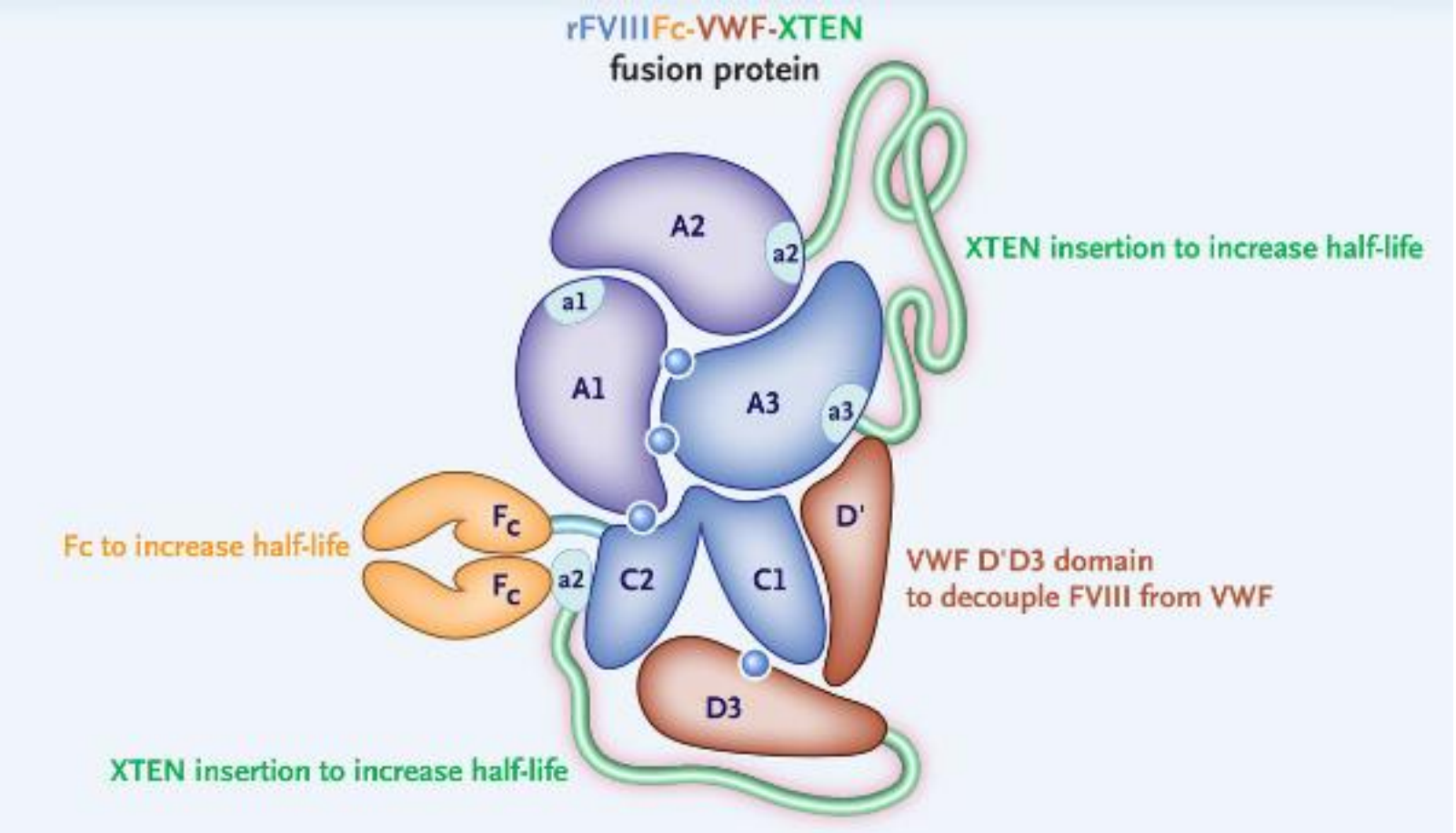
Nature Reviews | Drug Discovery

Recombinant Extended Half-life Products

Factor VIII			
Drug	**Mechanism**	**Fold Enhancement**	**FDA Approval**
rFVIIIFc (Eloctate®)	Fc fusion	1.5	6/2014
Adynovate®	Pegylation	1.5 to 2	11/2015
Esperoct®	Glycopegylation	2	2/2019
Jivi®	Pegylation	1.8	8/2018
BIVV001 (rFVIIIFc-VWF-XTEN, Altuviiio®)	Fc, XTEN, VWF D'D3	~ 4	6/2023
Factor IX			
rIXFc (Alprolix)	Fc fusion	2.4 fold	3/2014
rIX-FP (Idelvion)	Albumin fusion	> 5 fold	3/2016
N9-GP (Rebinyn)	Glycopegylation	> 5 fold	5/2017

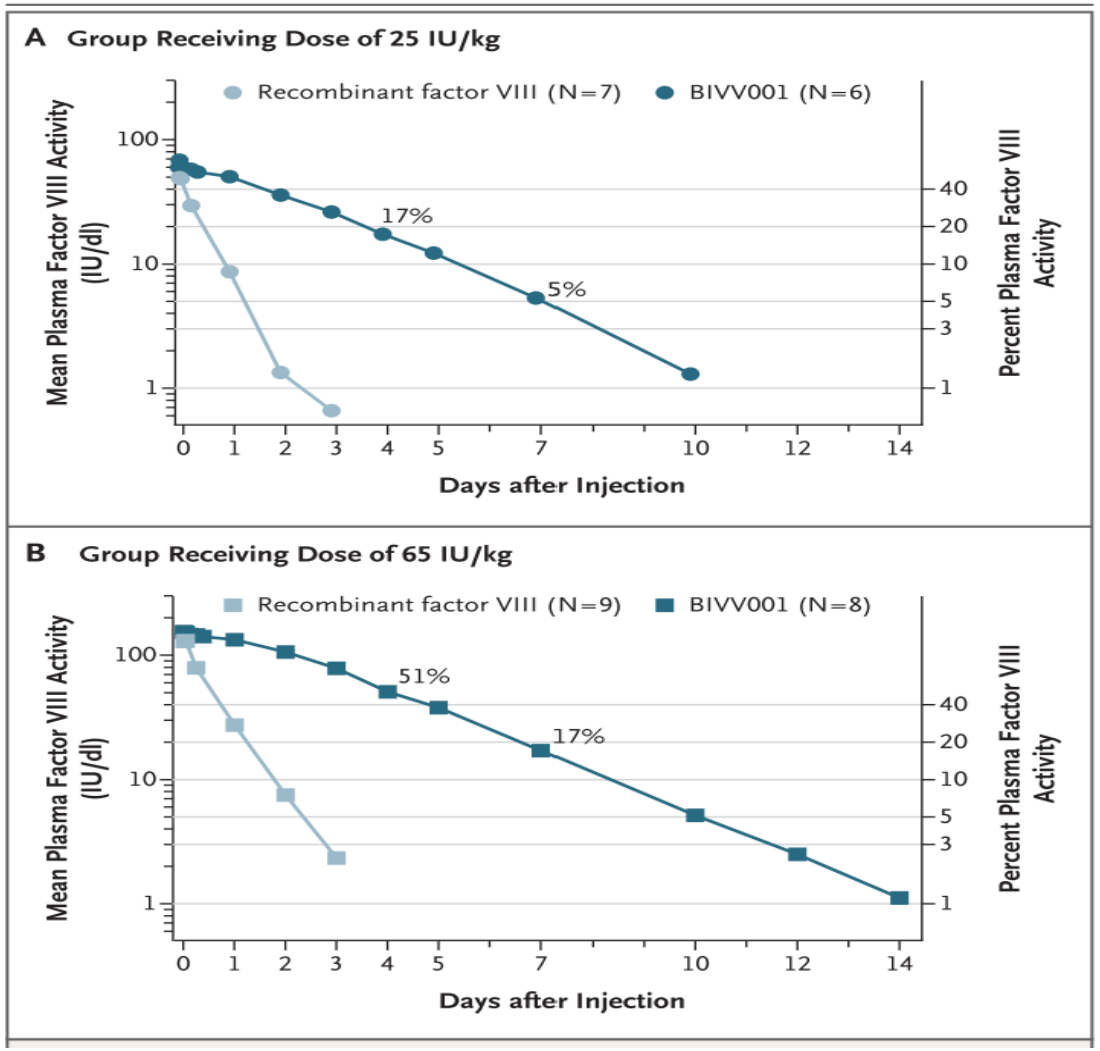
Santagostino et al. Blood 2016, Konkle et al NEJM 2020

BIVV001 (rFVIIIFc-VWF-XTEN, efanesoctocog alfa)



Konkle et al. N Engl J Med 2020;383:1018-1027

BIVV001 (rFVIIIFc-VWF-XTEN, efanesoctocog alfa)



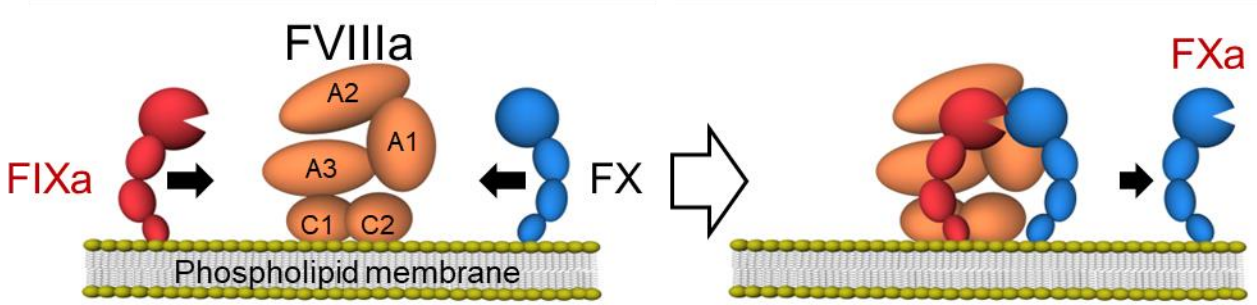
Konkle et al. N Engl J Med 2020;383:1018-1027

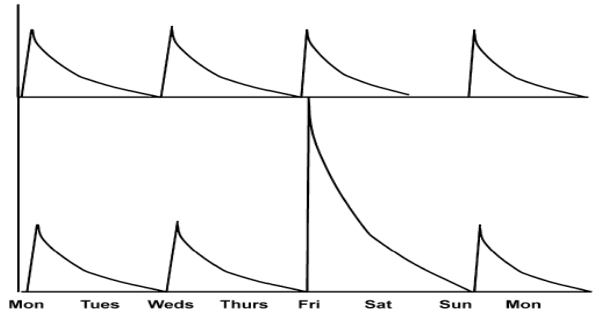
Major complication of FVIII treatment: Neutralizing antibody (inhibitor) formation

- **30%** of people with severe hemophilia A develop antibodies
- **Hemostatic approach**
  - High titer inhibitors do not respond to FVIII replacement
  - Need to treat bleeding with bypassing agents
    - recombinant factor VII activated (rFVIIa)
    - activated prothrombin complex concentrate (aPCC, contains factor II, VII, IX, X)
  - Bleeding prophylaxis with emicizumab
- **Inhibitor eradication**
  - Usually lengthy immune tolerance therapy (ITT) to eradicate inhibitor
  - Usually daily high dose factor VIII infusion for months

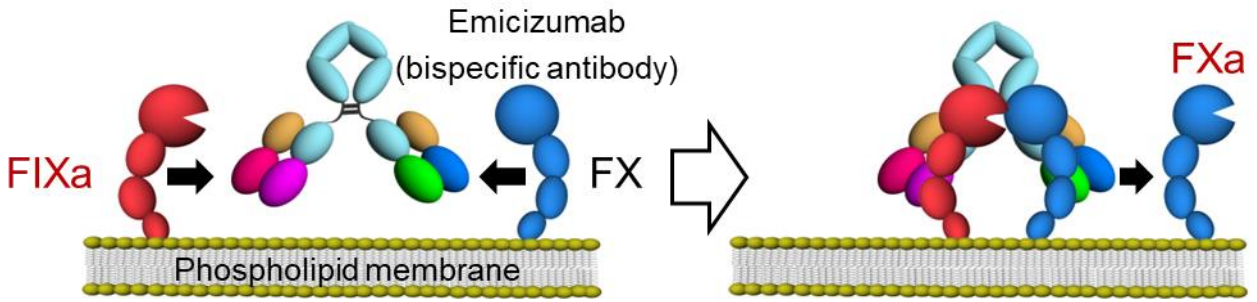
Berntorp E, et al. Nat Rev Dis Primers 2021;19:1883.

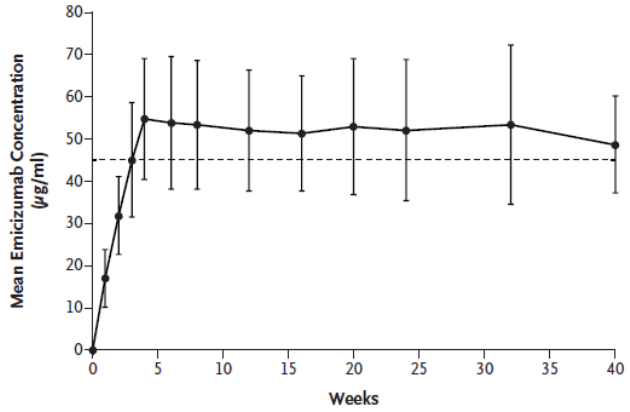
Bispecific Antibody: a Factor VIIIa - Mimetic





IV
$T_{1/2}$ ~ 8 hours





SQ
$T_{1/2}$ ~ 28 days

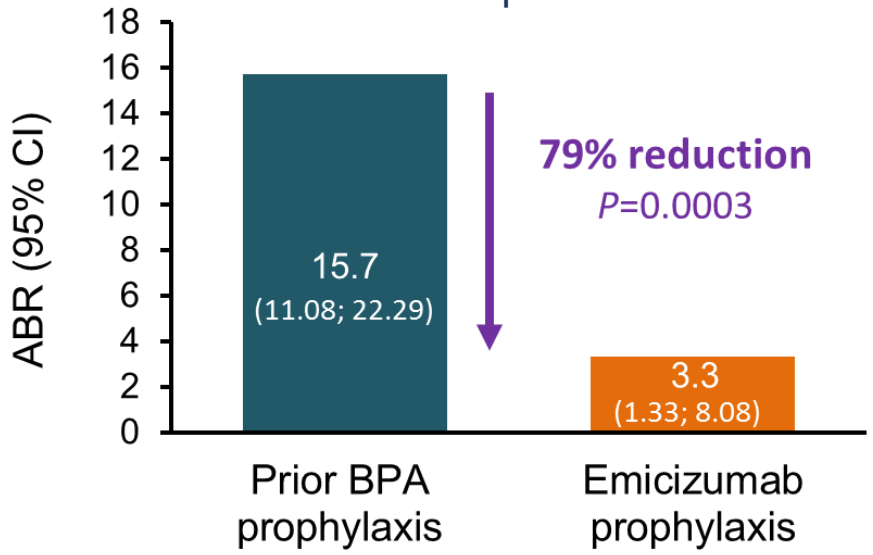
- SQ every 1-4 weeks
- Hemophilia A ONLY
- With and without inhibitors

FVIIIa=activated factor VIII; FIXa=activated factor IX; FX=factor X.

Kitazawa T et al. *Nat Med.* 2012;18:1570-1574; Sampei Z et al. *PLoS One.* 2013;8:e57479;
Muto A et al. *J Thromb Haemost.* 2014;12:206-213; Shima M et al. *N Engl J Med.* 2016;374:2044-2053.

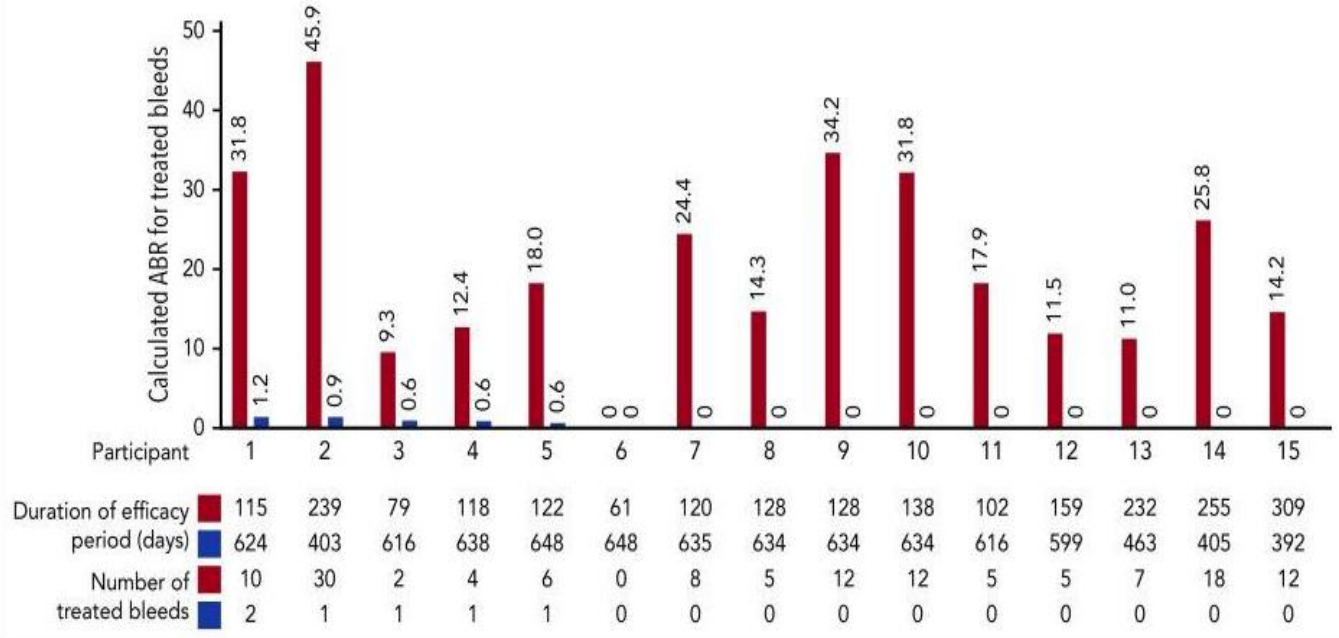
Efficacy of Emicizumab in Hemophilia A with inhibitors

Adult patients



(Oldenburg et al. N Engl J Med. 2017 Jul 10).

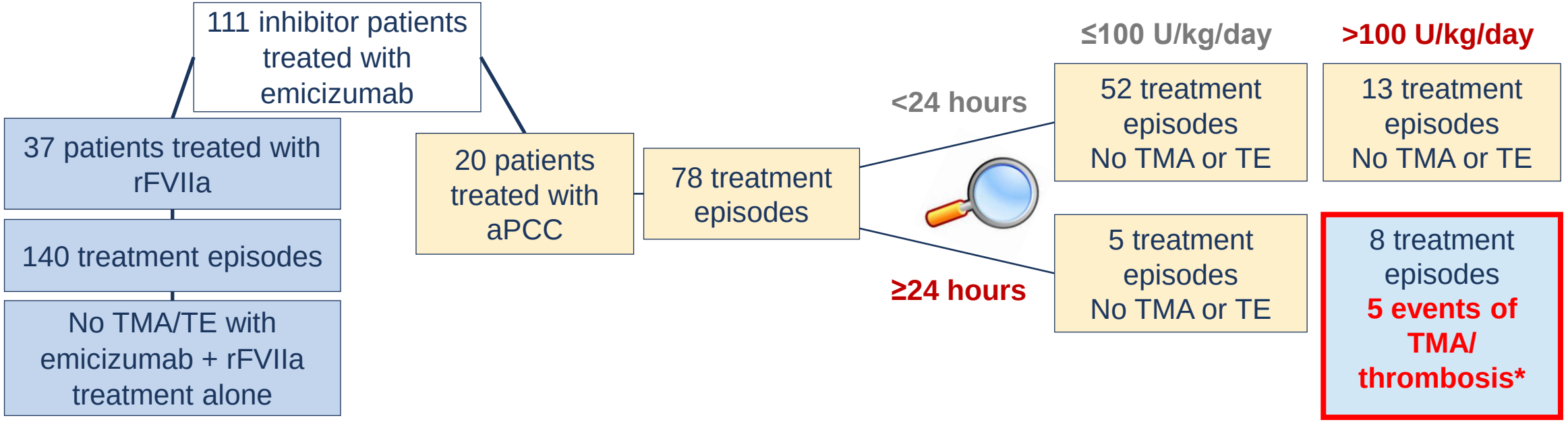
Pediatric patients



(Young G et al. Blood. 2019)

Breakthrough bleeding on Emicizumab

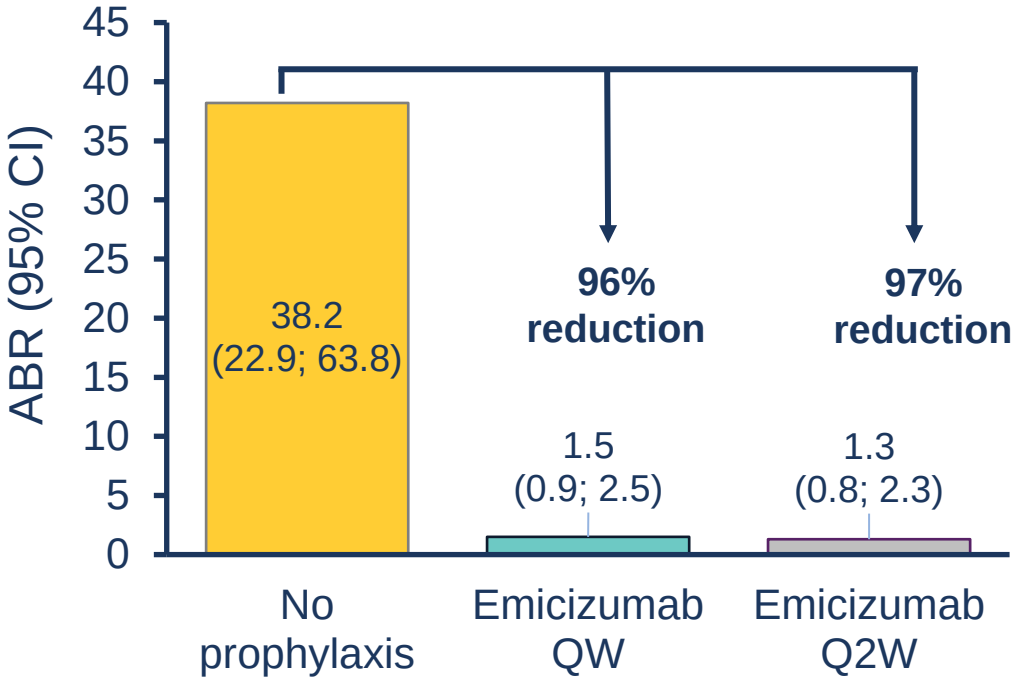
- Thrombotic events (TMA x 3, TE x 2) when given with aPCC



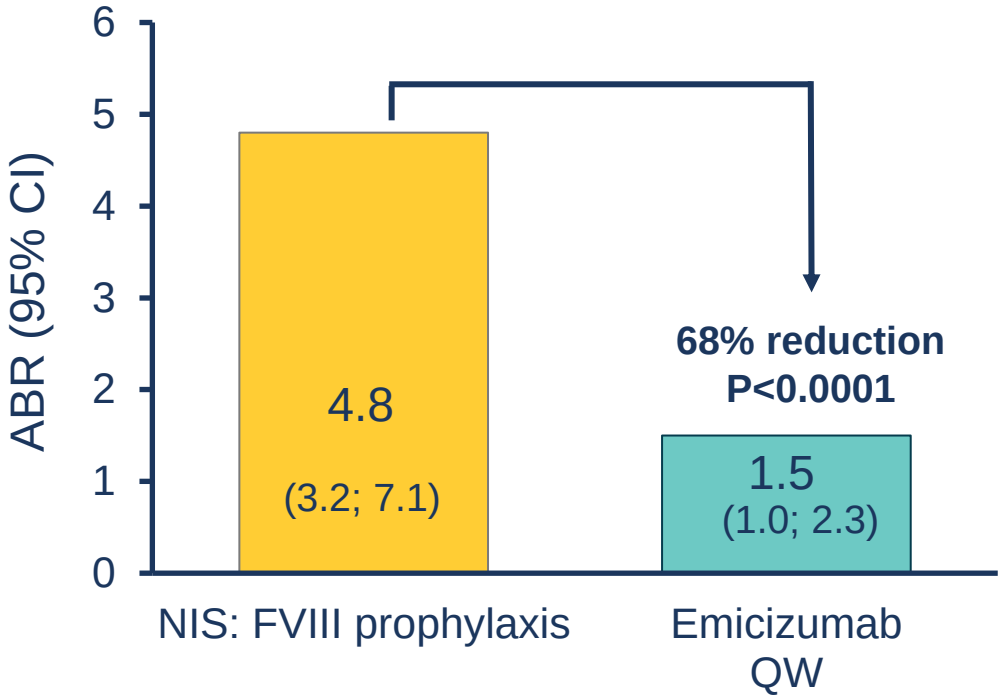
(Oldenburg et al. N Engl J Med. 2017 Jul 10).

Efficacy of emicizumab – Non-Inhibitor (HAVEN 3)

On demand FVIII

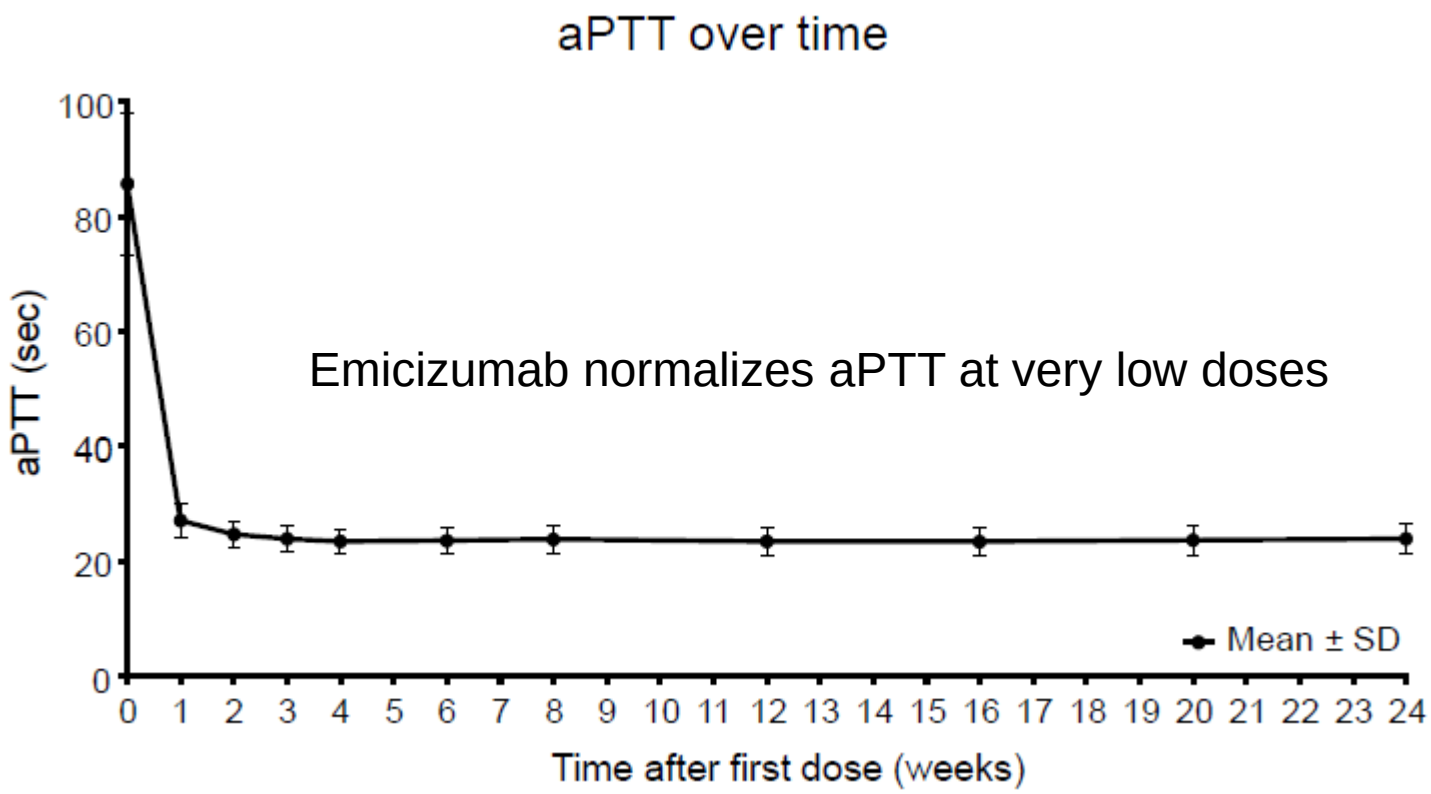


Prophylactic FVIII



Mahlangu et al. *NEJM*. 2018.

Emicizumab has a strong effect on aPTT

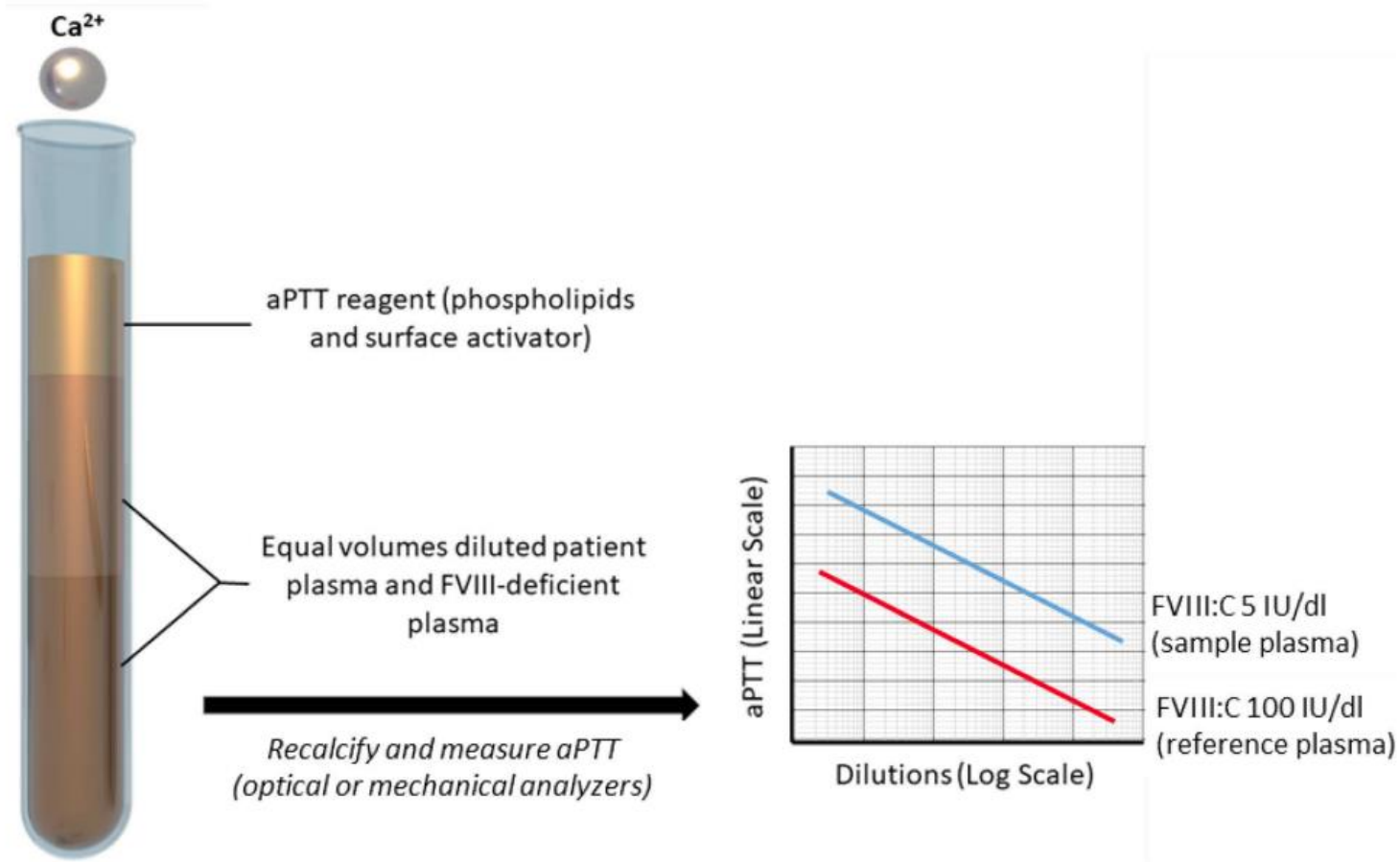


Emicizumab normalizes aPTT at very low doses

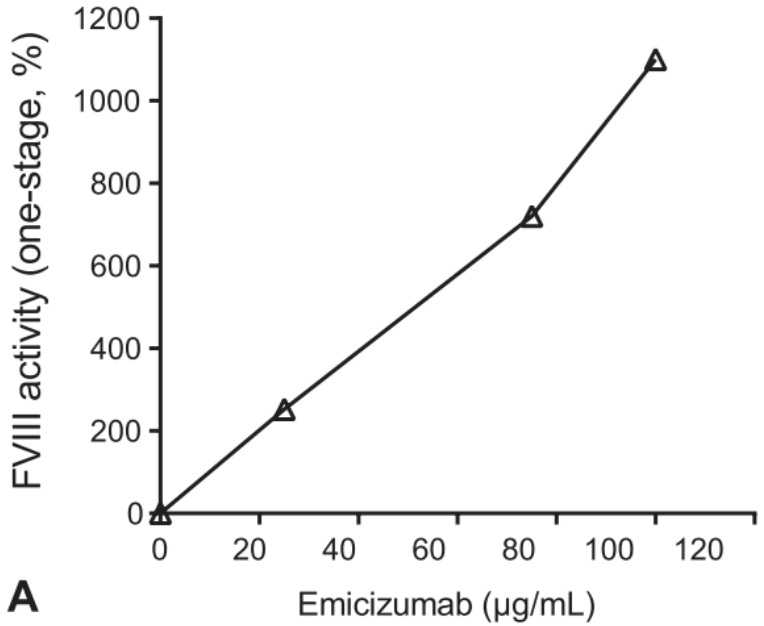
aPTT is not an accurate measure of hemostatic potential in the presence of emicizumab

Adamkewicz et al – data from HAVEN 1 study

One-stage clotting assay (OSA)



OSA FVIII Activity in an Emicizumab-Spiked FVIII-Deficient Plasma Sample



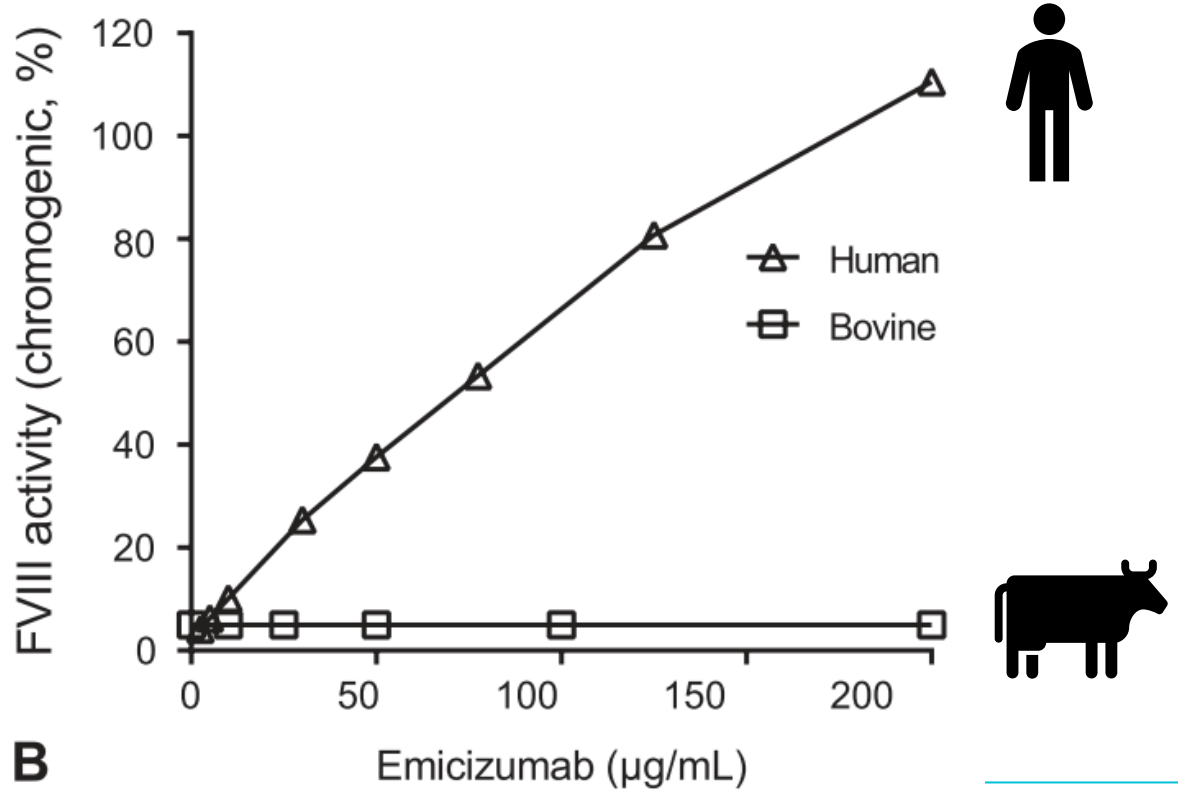
FVIII OSA grossly overestimates hemostatic potential

Al-Samkari H, Croteau SE. Am J Hematol. 2018 Jun 8

Adamkewicz JI et al. Thromb Haemost. 2019;119:1084-1093

Chromogenic substrate assay (CSA)

- Chromogenic assay is reliable



Detects emicizumab activity with **human** reagents

Detects FVIII activity with **bovine** reagents without measuring emicizumab

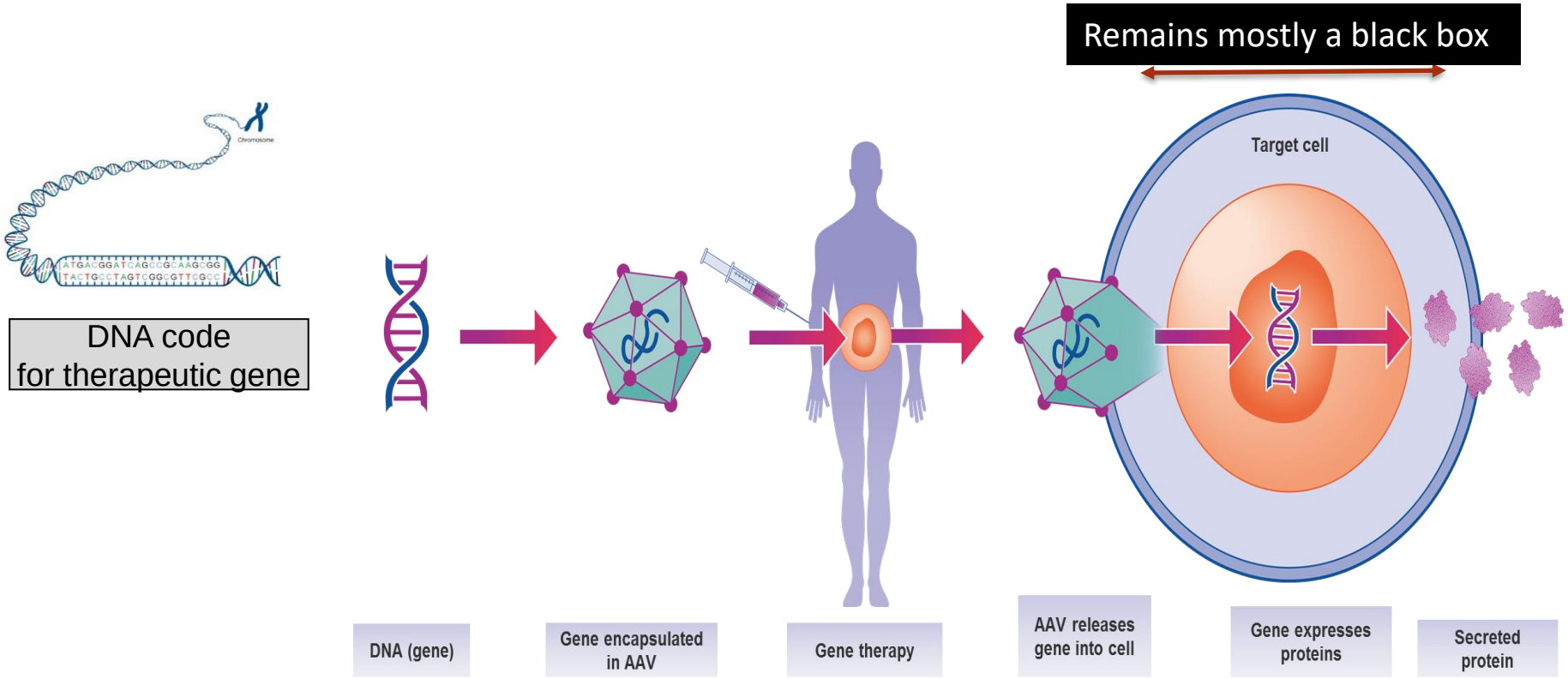
Fred Hutc

B

Adamkewicz JI et al. Thromb Haemost. 2019;119:1084-1093

Gene Therapy

Adeno-associated virus (AAV) mediated gene therapy



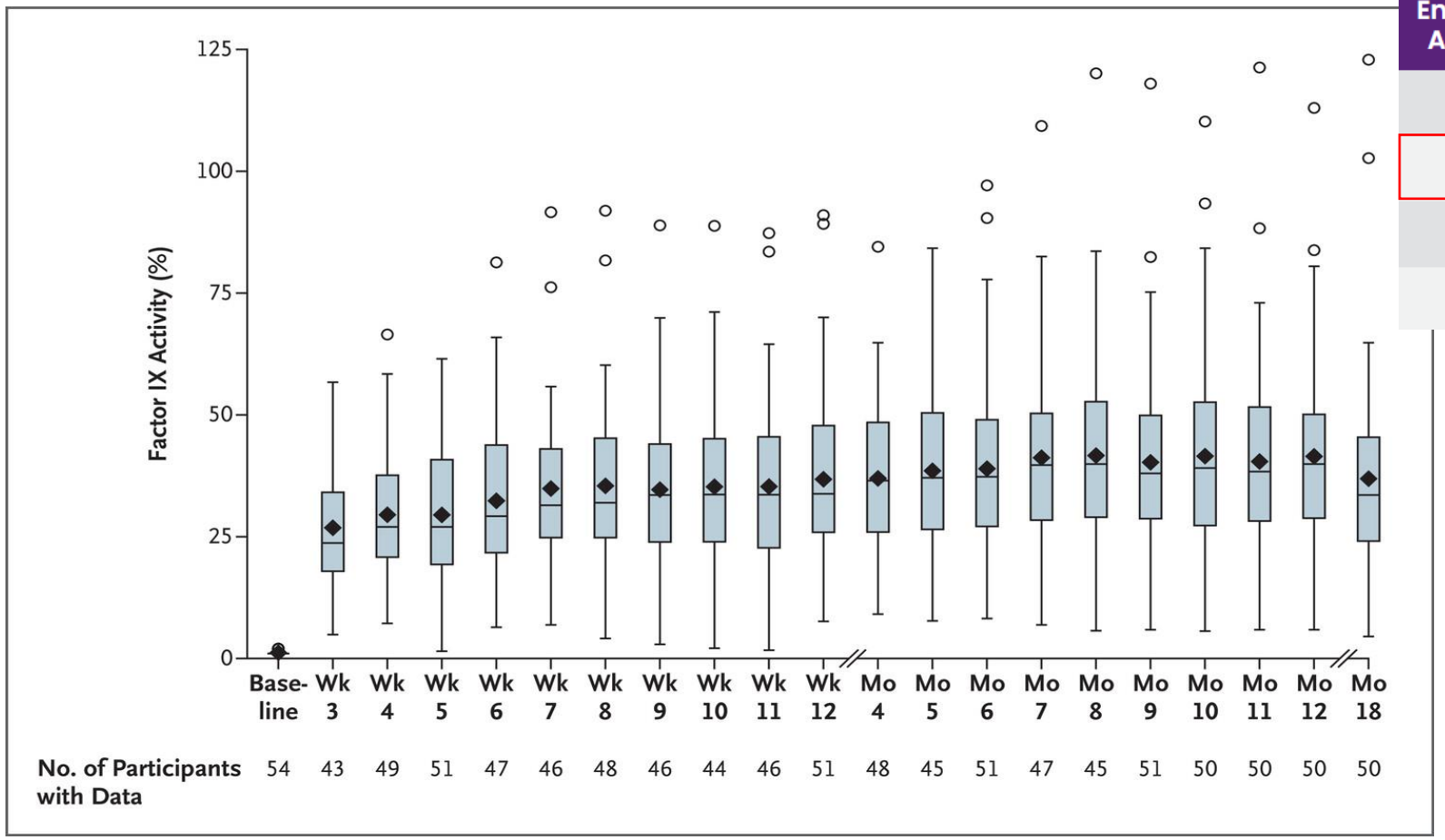
ssDNA virus, 2 genes-rep and cap, 20nm, non-pathogenic upon human or animal infection
>200 human trials using AAV – based gene therapy have been conducted in the past 30 years

Image: National Human Genome Research Institute's Talking glossary
(http://www.genome.gov/glossary/) http://www.abedia.com/wiley/vectors.php

Gene Therapy for Hemophilia - FDA Approvals

		FDA approval
Hemophilia B		
	ertanacogene dezaparvovec-drib (Hemegenix)	11/22/22
	fidanacogene elaparvovec-dzkt (Beqvez)	4/25/24
Hemophilia A		
	valoctocogene roxaparvovec-rvox (Roctavian)	6/29/23

Hemophilia B: Etranacogene Dezaparvovec (Hemgenix)

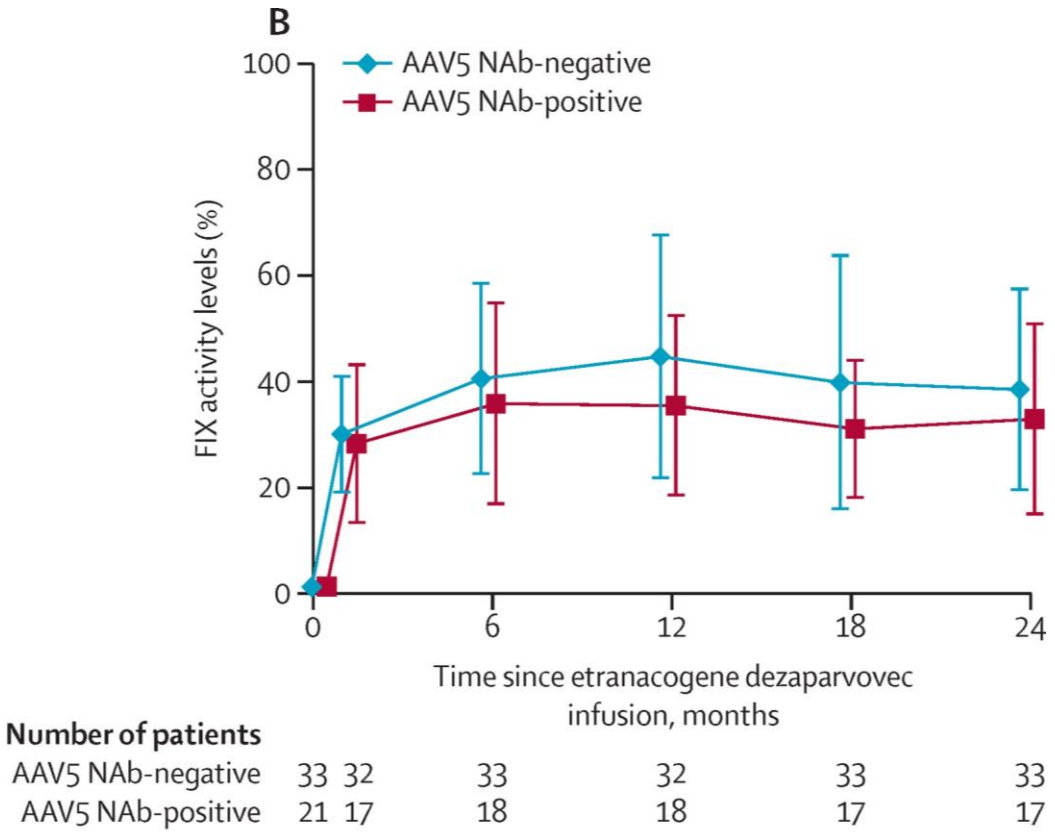


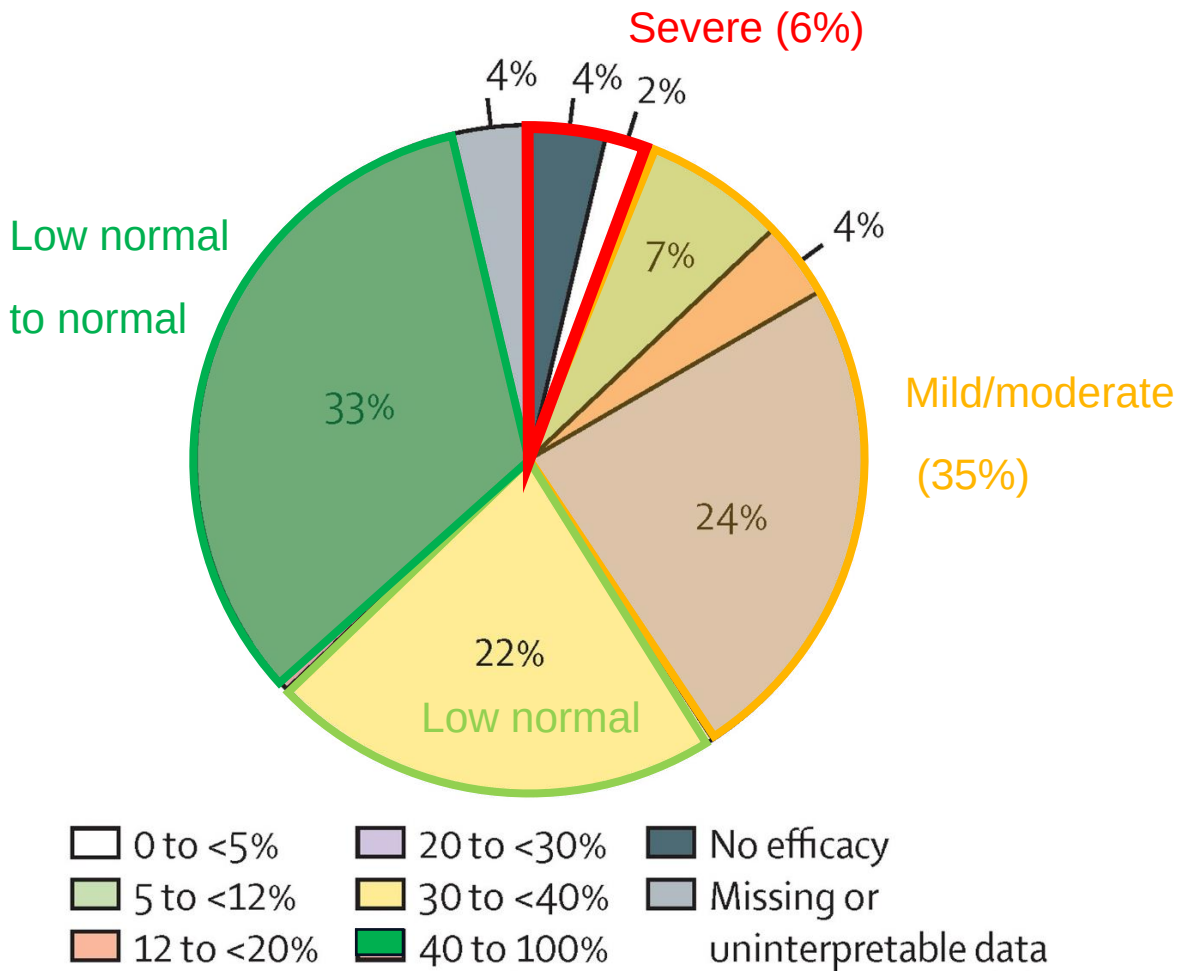
Pipe et al NEJM 2023

Endogenous FIX Activity Levels	At Year 2 (n=50)[3]	At Year 3 (n=48)[1]
Mean ± SD	36.7 ± 19.0%	38.6 ± 17.8%
Median	33.9%	36.0%
IQR	25.80–45.50%[4]	29.5–48.1%
Min - Max	4.7–99.2%	4.8–80.3%

Coppens et al Lancet 2024

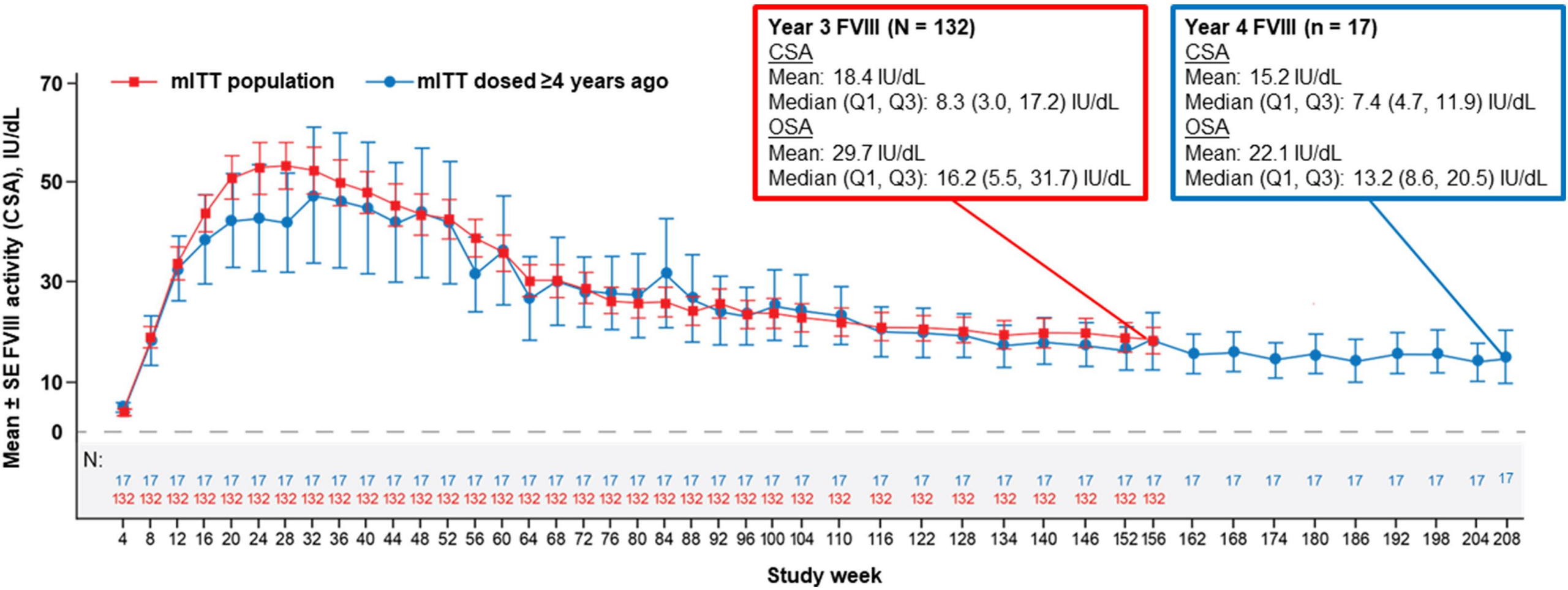
Hemophilia B: Etranacogene Dezaparvovec (Hemgenix)





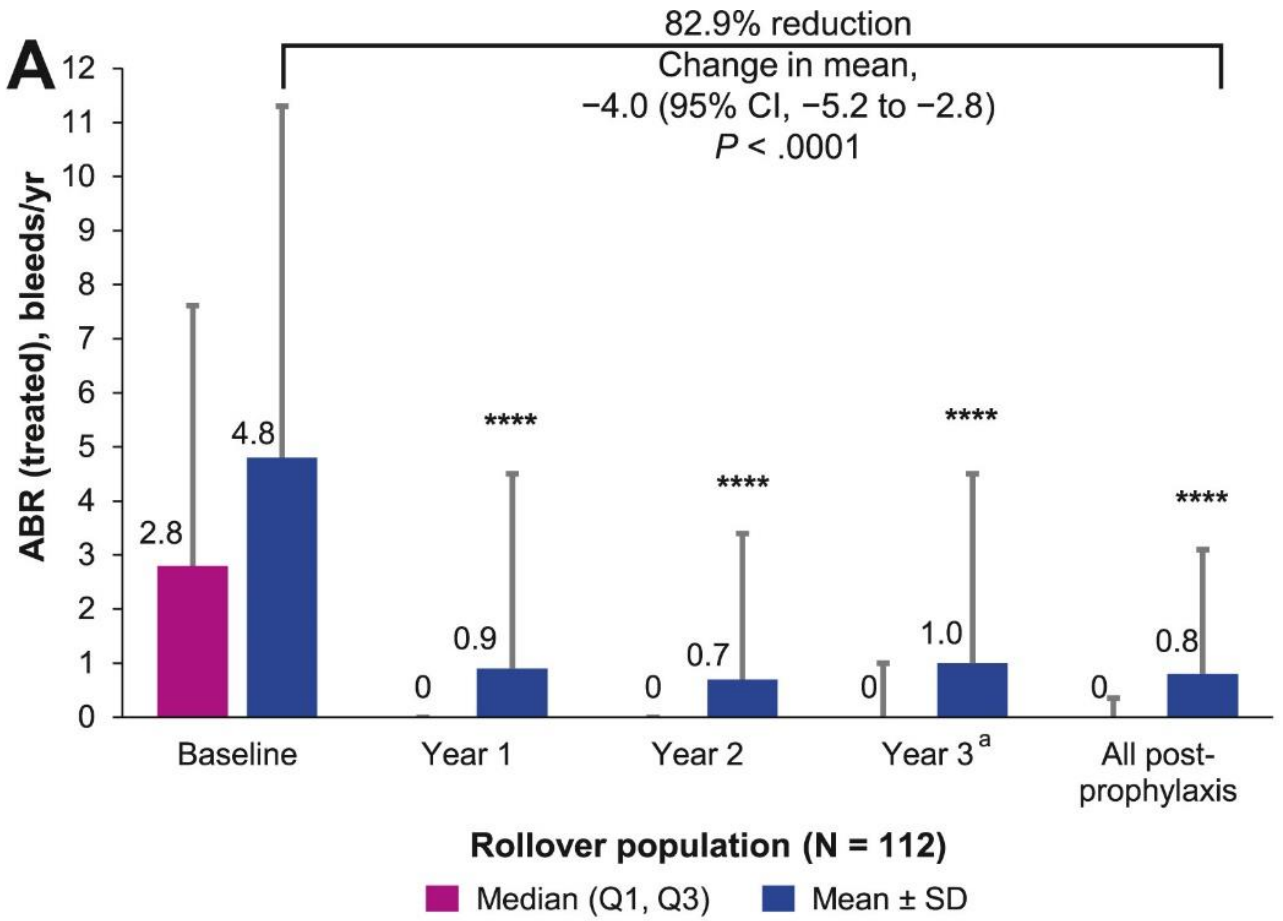
Pipe et al NEJM 2023 Coppens et al Lancet 2024

Hemophilia A: Valoctocogene Roxaparvovec (Roctavian)



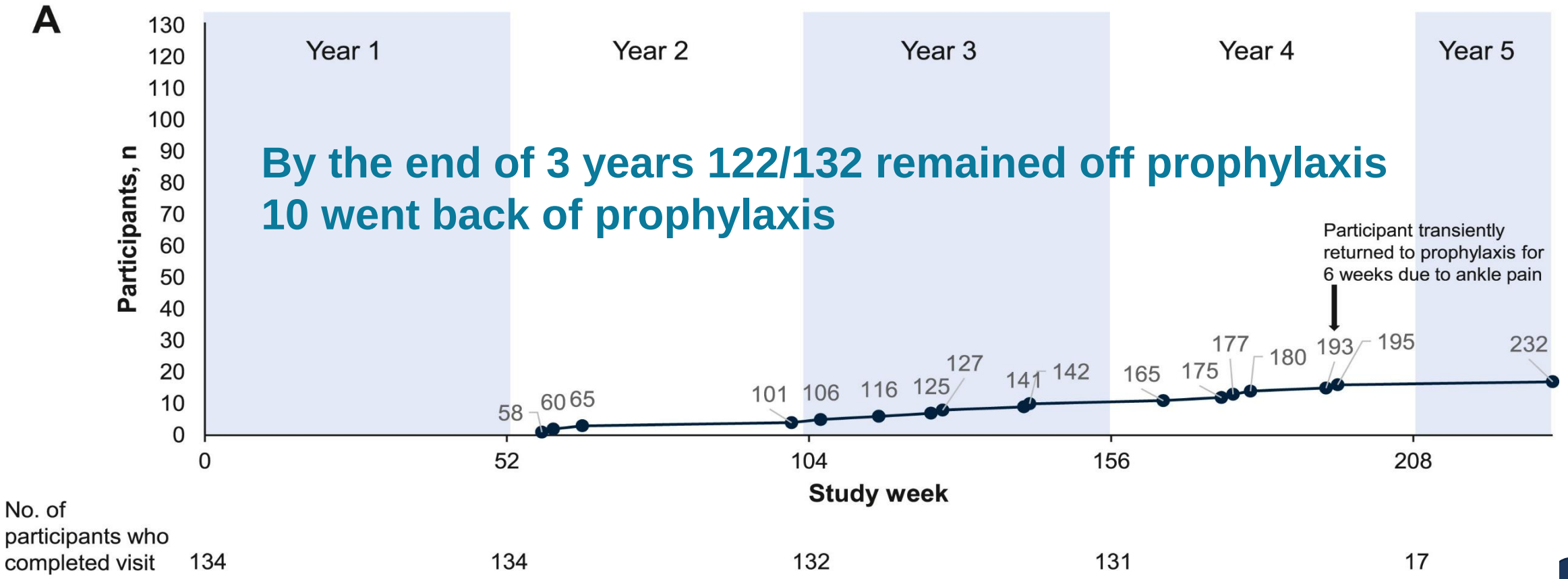
Madan et al. JTH 2024

Roctavian - efficacy



Madan et al. JTH 2024

Roctavian - efficacy



Madan et al. JTH 2024

Beqvez

- Bleeds were eliminated in 60% of patients compared to 29% in the prophylaxis arm
- Most common adverse reaction (incidence ≥5%) reported in Phase 3 and 1/2 clinical studies was an increase in transaminases (in 26/60 patients)
- At 15 months, mean factor level 27%
- At 26 months, at least 60% of patients had levels 15-40%

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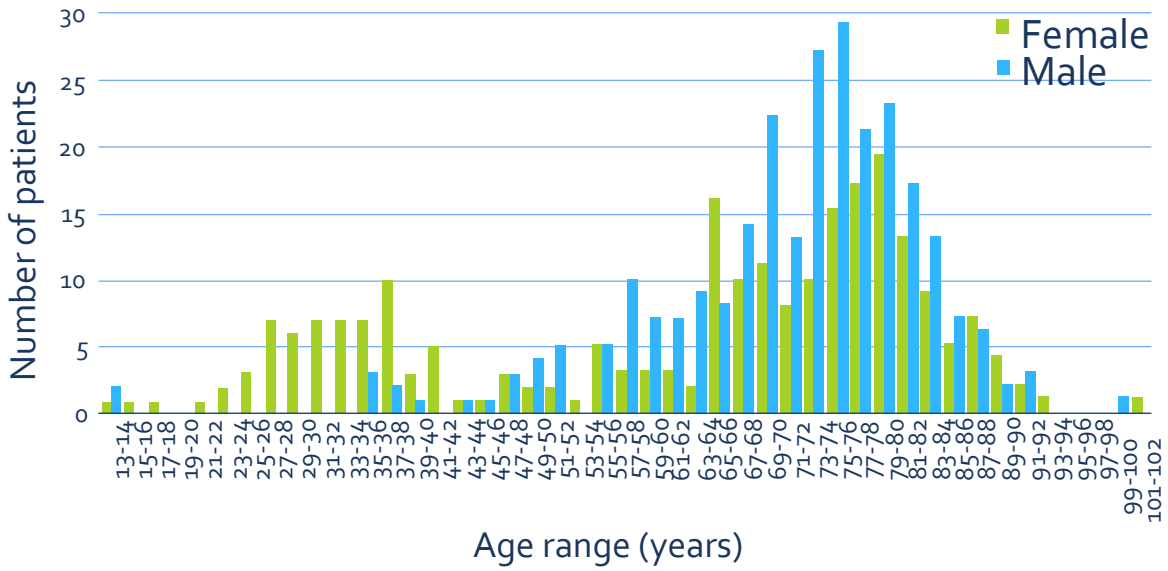
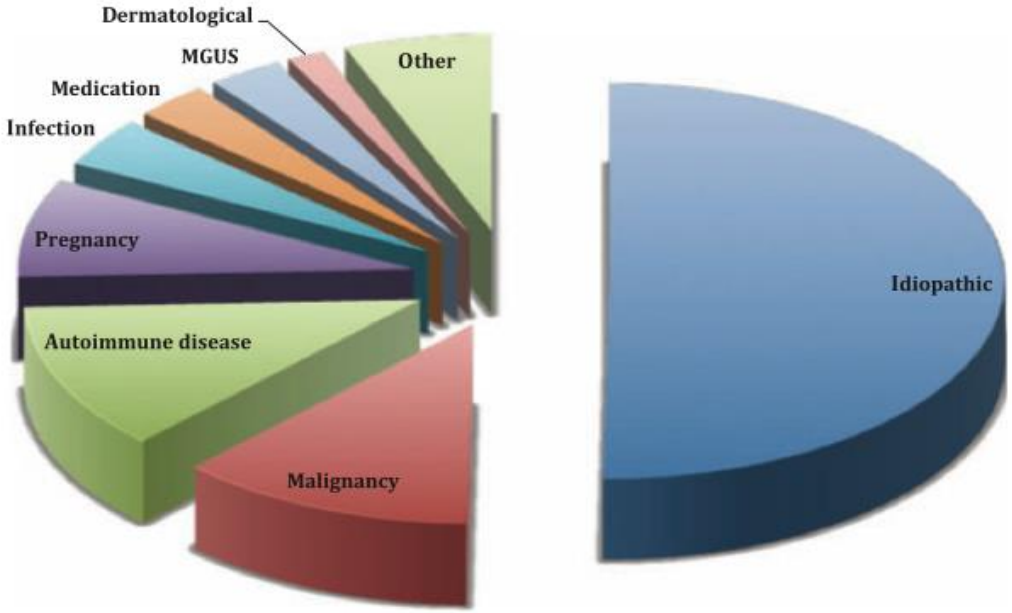
Acquired Hemophilia A

Epidemiology of Acquired Hemophilia (AHA)

- Rare bleeding condition caused by an autoantibody (inhibitor) to coagulation factor VIII (FVIII)
  - Incidence: 1.5 cases per million/year[1]

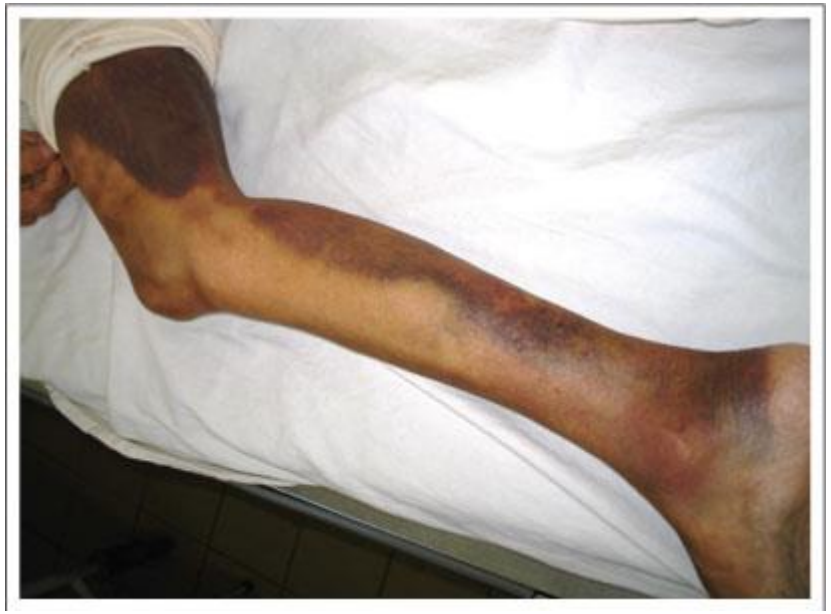
Incidence of AHA According to Age and Gender[2]

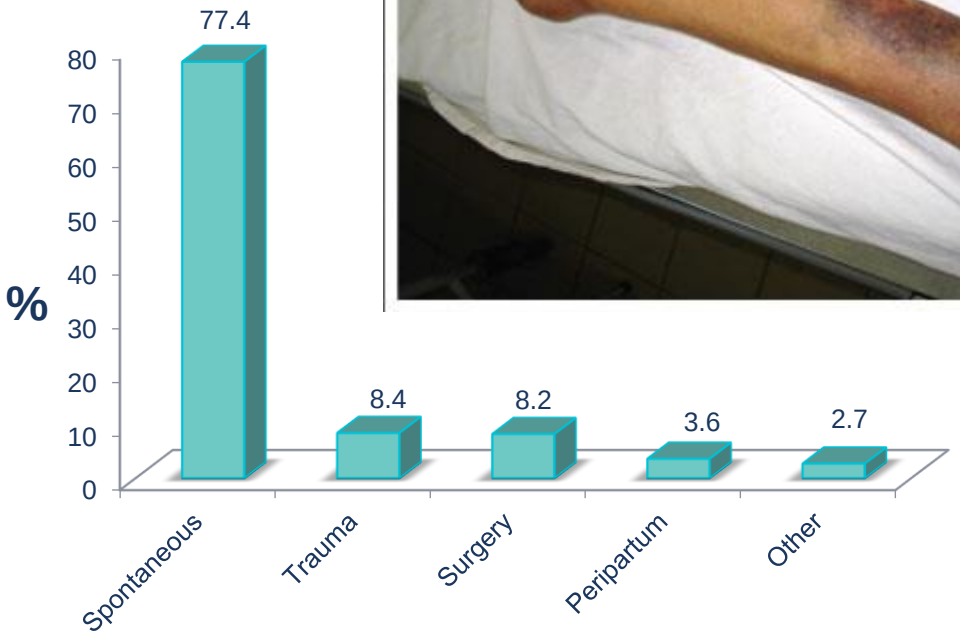


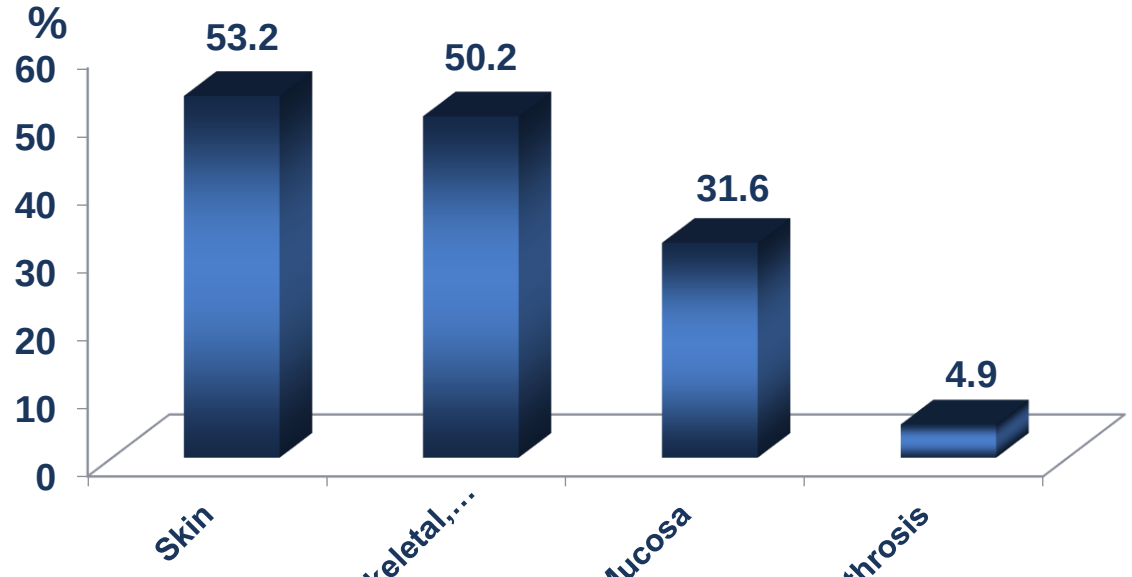


[1]Collins et al Blood 2007, [2]Knoebl, et al. J Thromb Haemost 2012

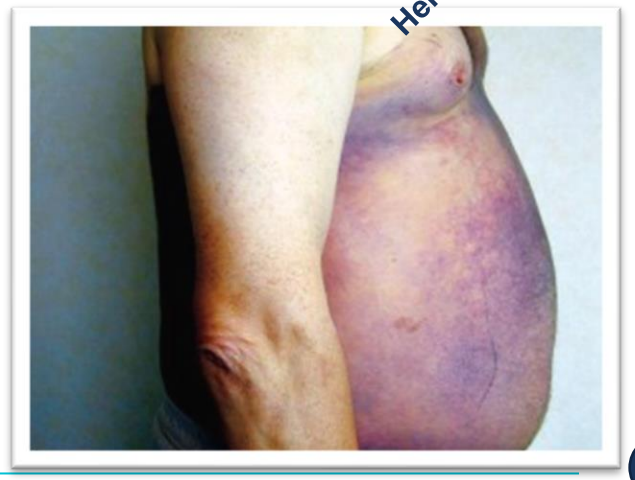
Bleeding Severity in AHA







73% severe
Mortality - 8% to 22%

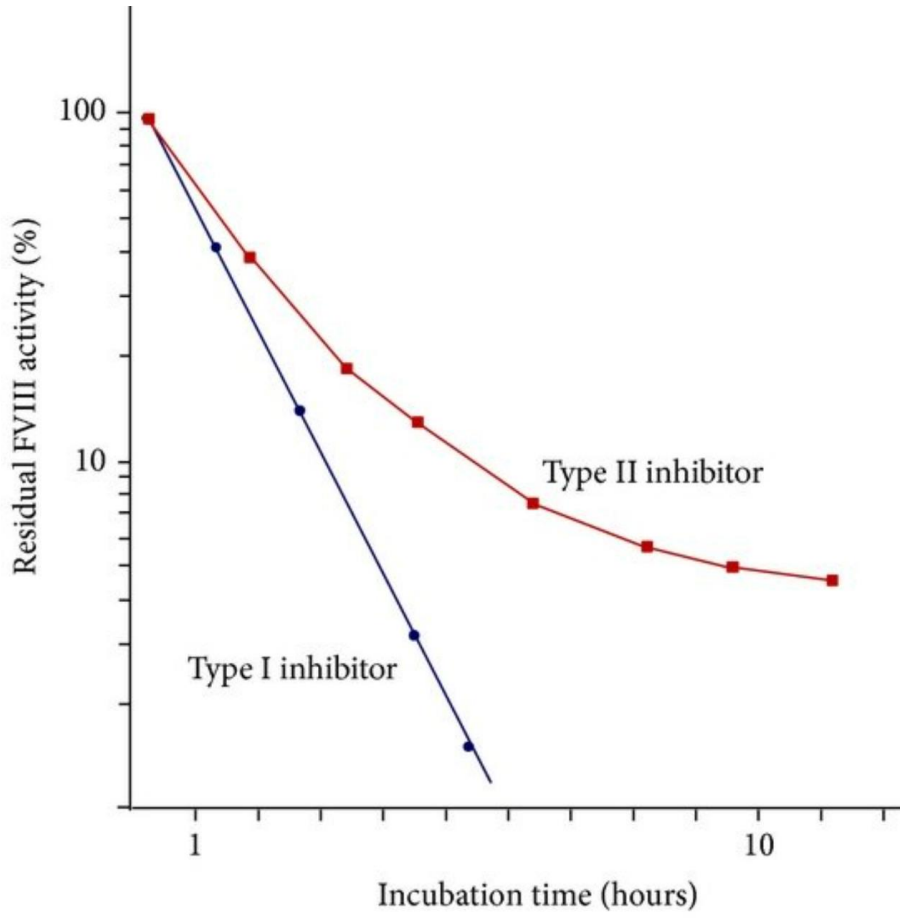


Collins P, et al. *BMC Res Notes*. 2010;3:161.

Zeitler H, et al. *Atheroscler Suppl*. 2013.

Diagnosis/Inhibitor Kinetics

- Consistent clinical presentation
- Prolonged aPTT, normal PT
  - Classically corrects immediately but prolongs with incubation at 37^{o}C
- Low FVIII with positive Bethesda titer
- FVIII level may not correlate with severity of bleeding
  - Type 2 kinetics



Kruse-Jarres et al, Am J Hematol 2017;92:695; Sakurai and Takeda, J Immunol Res 2014:320674

Principles of Treatment

Treat Bleeding

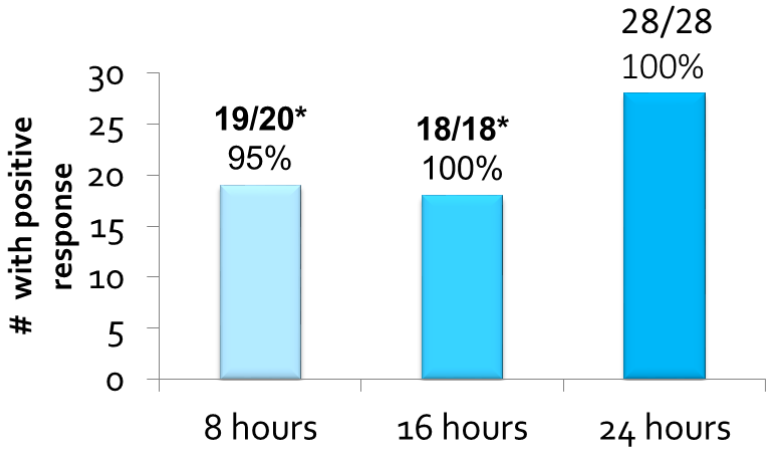
Eradicate the Inhibitor

Acquired Hemophilia – Hemostatic Treatment

Rates of Control for First Bleeding Episodes by First-line Therapy	First-line Bleeding Control	
	n	%
Bypassing Agent	219	91.8
- Recombinant factor VIIa	159	91.2
- Activated prothrombin complex concentrate (aPCC)	60	93.3
Replacement Therapy	69	69.6
- FVIII	55	70.1
- DDAVP	14	64.3

Table adapted from Baudo et al - Blood 2012.,

Porcine FVIII

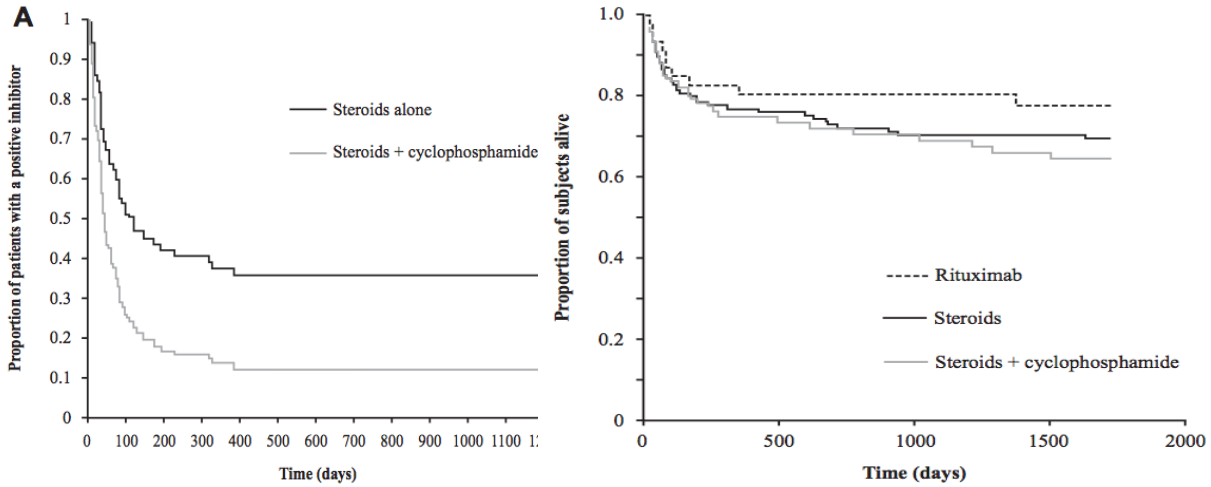


Note: Use of human or porcine FVIII replacement requires real time availability of FVIII measurements

Kruse-Jarres et al. Haemophilia 2015

Immunosuppressive therapy (IST)

- Autoantibodies rarely disappear spontaneously
- Higher risk of mortality if they persist
- Rate of complications from IST is about 30%
  - Mortality as high as 16-30%
- Emicizumab use may limit IST exposure
  - U.S. clinical trial ongoing



Regimen	n	Any	Infection	Neutropenia	Diabetes	Psychiatric disorder
Steroids alone	142	36 (25)	23 (16)	2 (1)	11 (8)	6 (4)
Steroids + cyclophosphamide	83	34* (41)	22 (27)	12 (14)	5 (6)	3 (4)
Rituximab-based regimens	51	19 (37)	6 (12)	9 (18)	11 (22)	1 (2)

Collins et al. Blood. 2012, Tiede A, ISTH 2023 .

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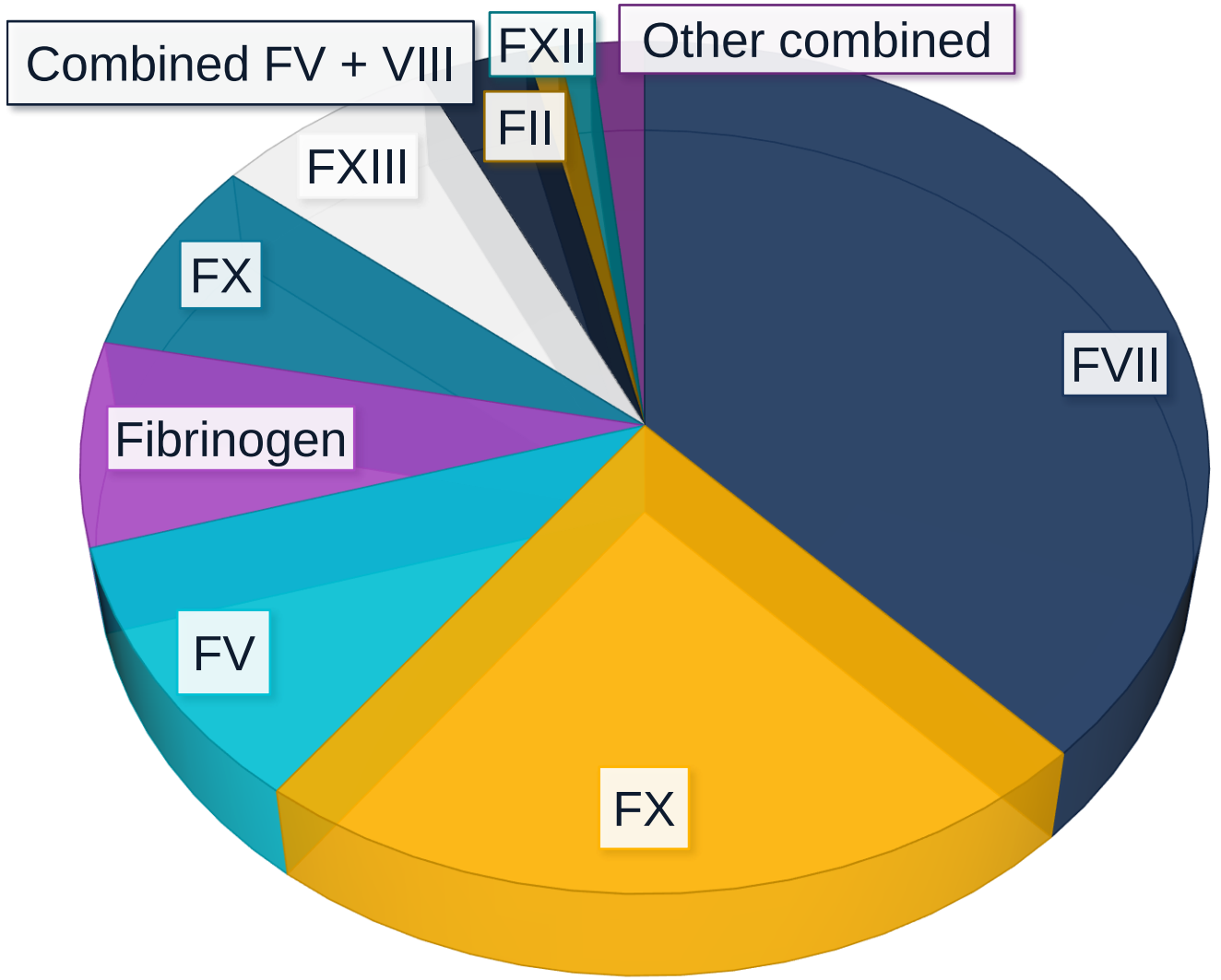
Other Clotting Factor Deficiencies

European Network of Rare Bleeding Disorders database

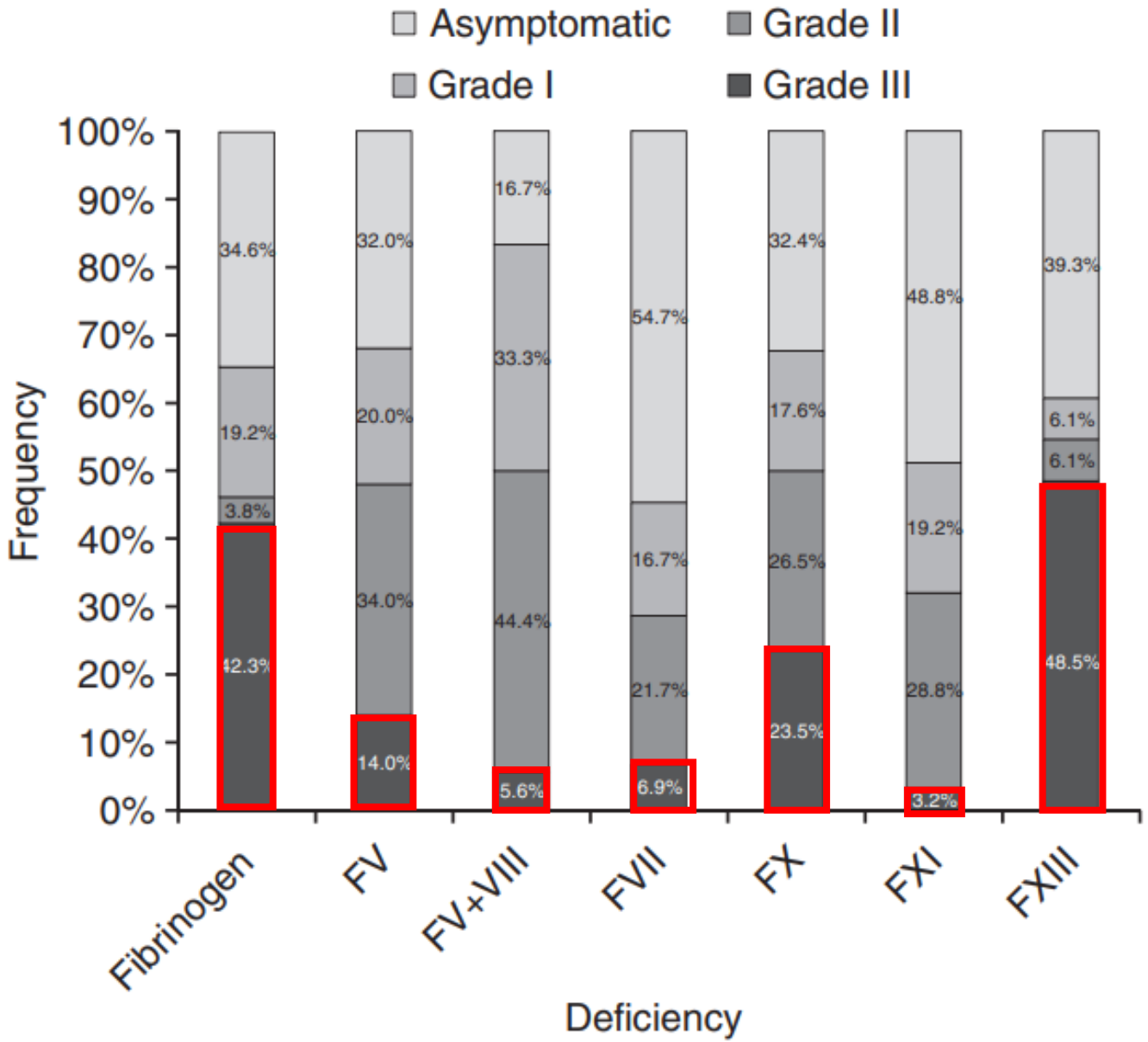
Type of deficiency	n (%)
FVII	224 (38)
FXI	133 (22)
FV	60 (10)
Fibrinogen	46 (8)
FX	45 (8)
FXIII	42 (7)
Combined FV + VIII	20 (3)
FII	6 (1)
FXII	6 (1)
Other combined	10 (2)



Peyvandi et al. JTH 2012

Bleeding Risk by Factor Level

- Database:
  - 592 patients
  - Mean age 31 years (7mo to 95 yrs
  - 51% women



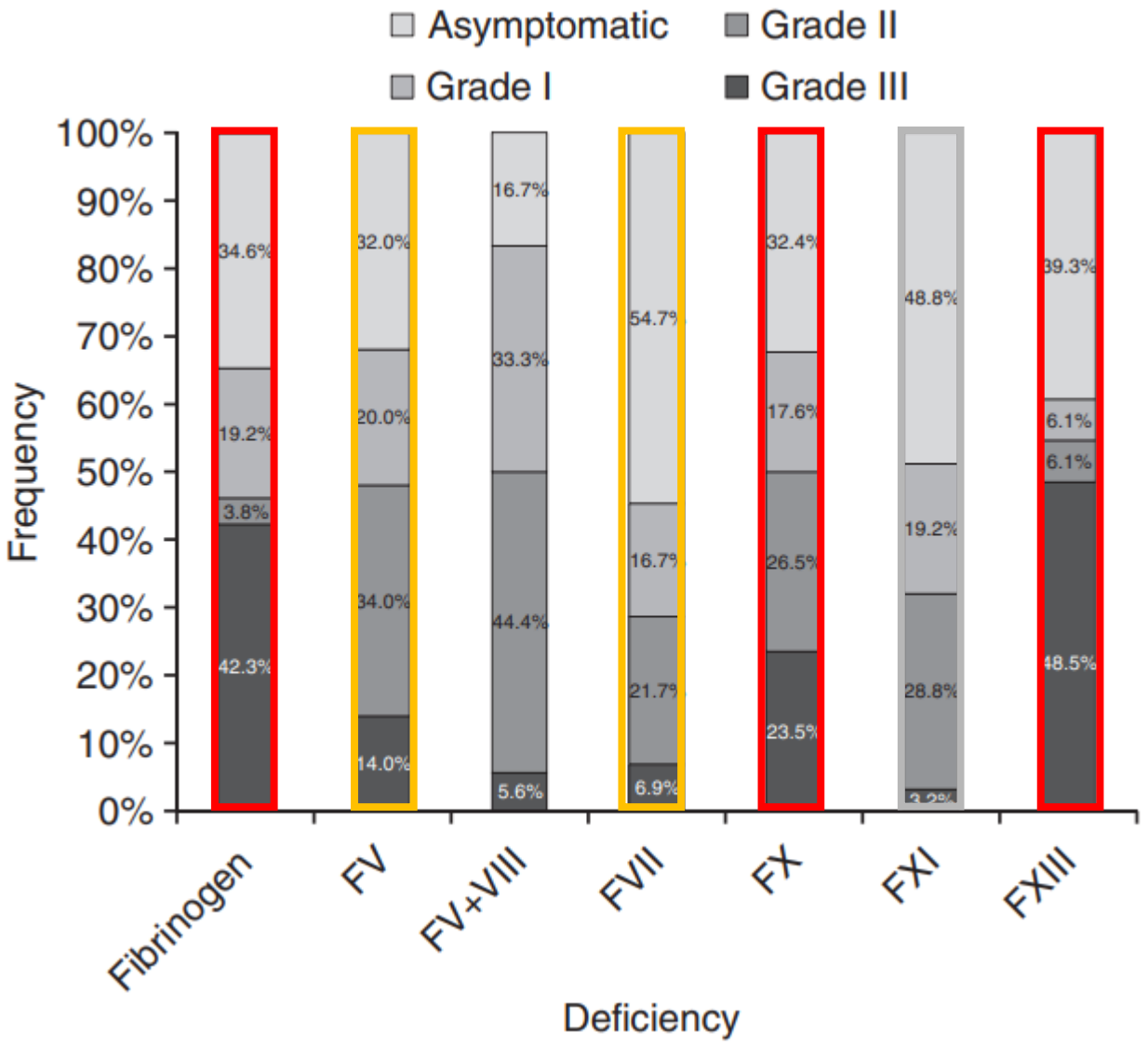
Peyvandi et al. JTH 2012

Bleeding risk: Association with factor level

- 592 patients
- Mean age 31 years (7 months tc
- 51% women

<u>Does factor level matter</u>?

- Strongest correlation in fibrinogen, FX, FXIII deficiency
- Poor correlation in FV and FVII deficiency
- No association in FXI deficiency



Peyvandi et al. JTH 2012

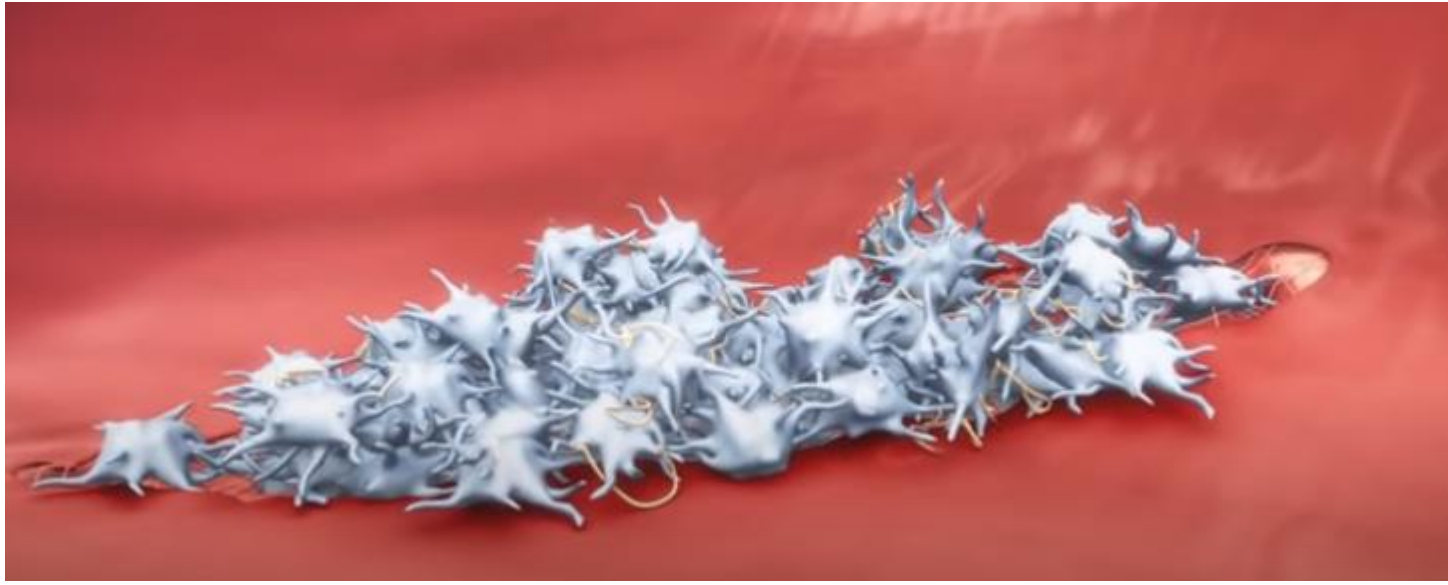
Rare factor deficiencies - Treatment

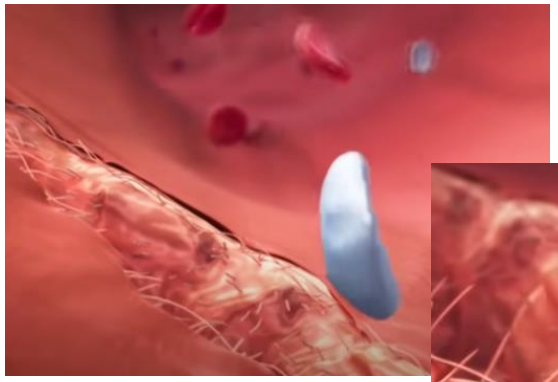
	Fibrinogen	FV	FVII	FX	FXI	FXIII
Factor concentrate	Human fibrinogen (RiaSTAP and Fibryga)	none	rFVIIa (NovoSeven) 15 to 30 mcg/kg every 4-6 hours	plasma-derived FX concentrate (pdFX; Coagadex®)	None in US	rXIII A subunit (Tretten) Plasma derived factor XIII (Corifact)
Alternate	cryoprecipitate	- FFP - Platelet transfusion*		-FFP -PCC (Factor II, VII, IX, X)	FFP 10 - 20 mL/kg, followed by 5 - 10 mL/kg every 24 to 48 hours	
Adjunct	-Antifibrinolytic agents	-Antifibrinolytic agents	-Antifibrinolytic agents	-Antifibrinolytic agents	-Antifibrinolytic agents -Fibrin sealant (fibrin glue) -Desmopressin (DDAVP) -Low dose rFVIIa	-Antifibrinolytic agents

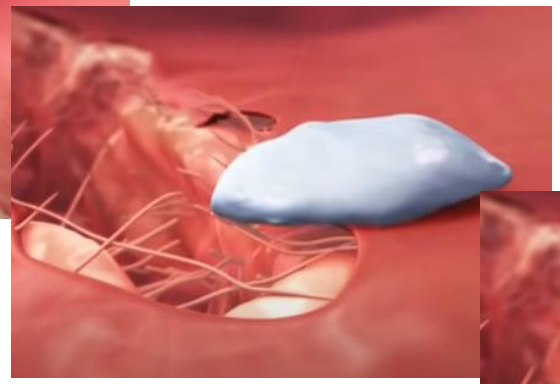
*25% of FV is stored within platelet alpha granules

FFP = fresh frozen plasma, PCC = prothrombin complex concentrate

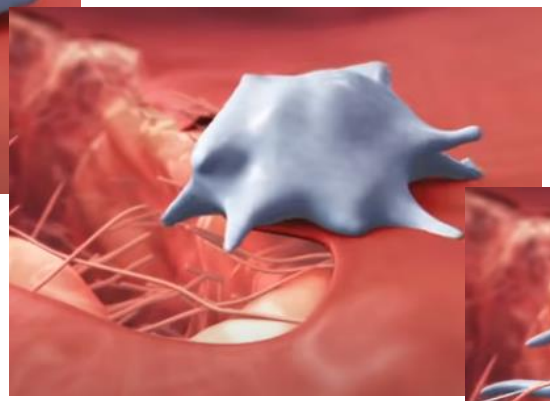
Platelet Function



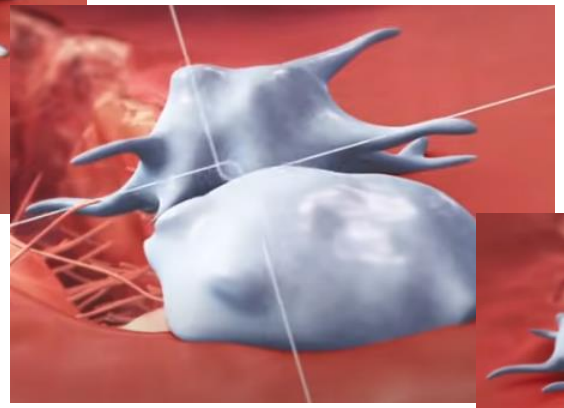




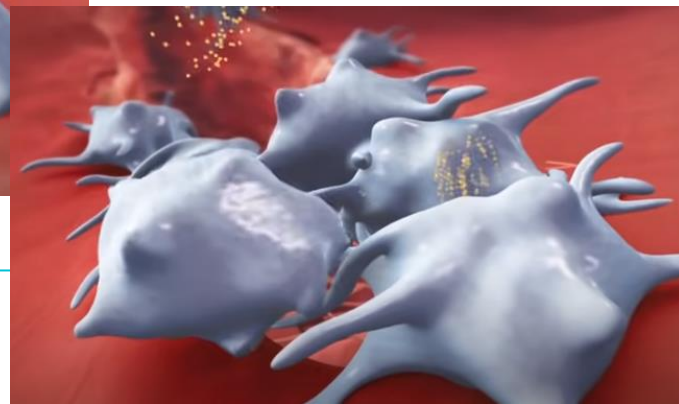
Adhesion

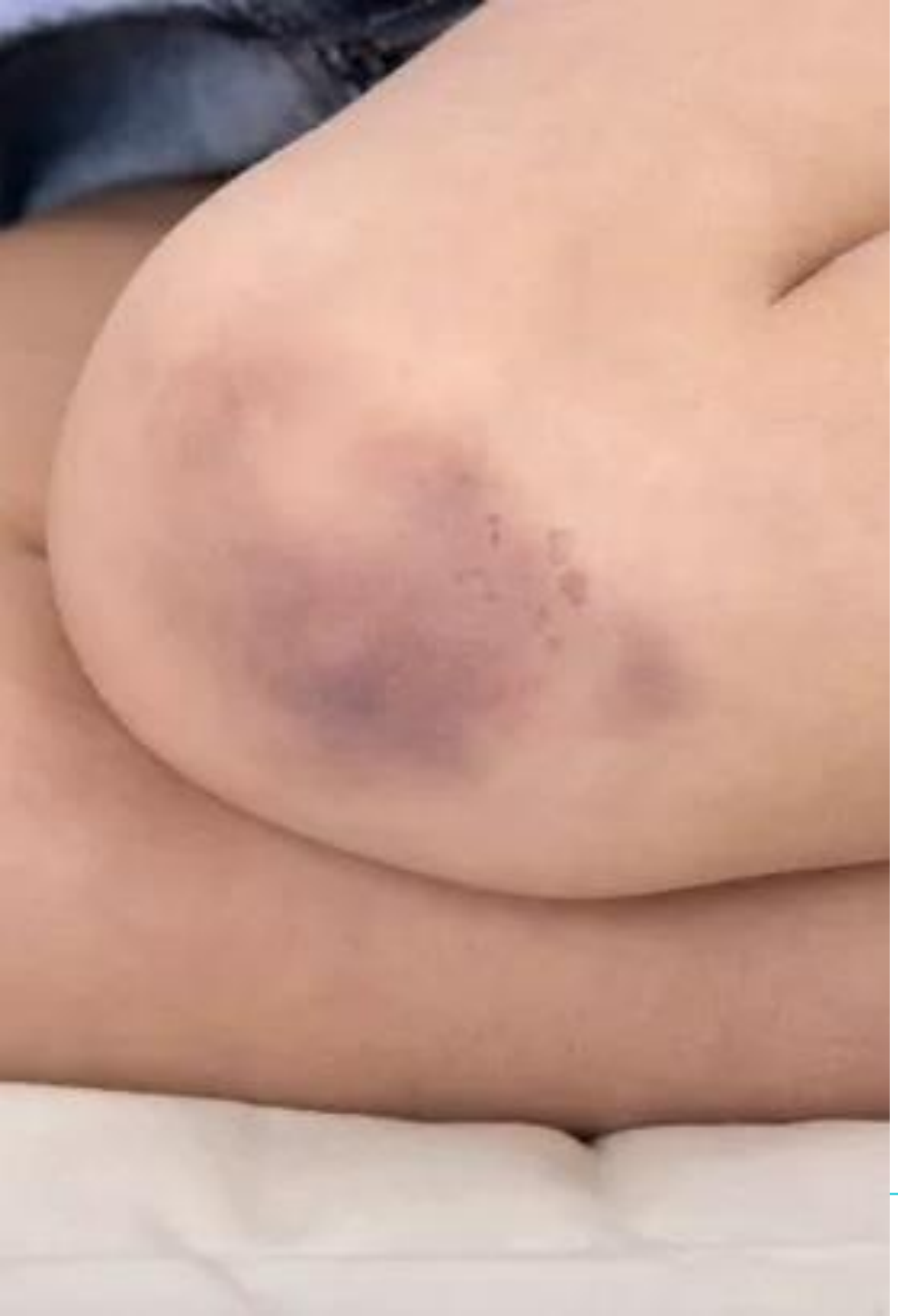


Activation



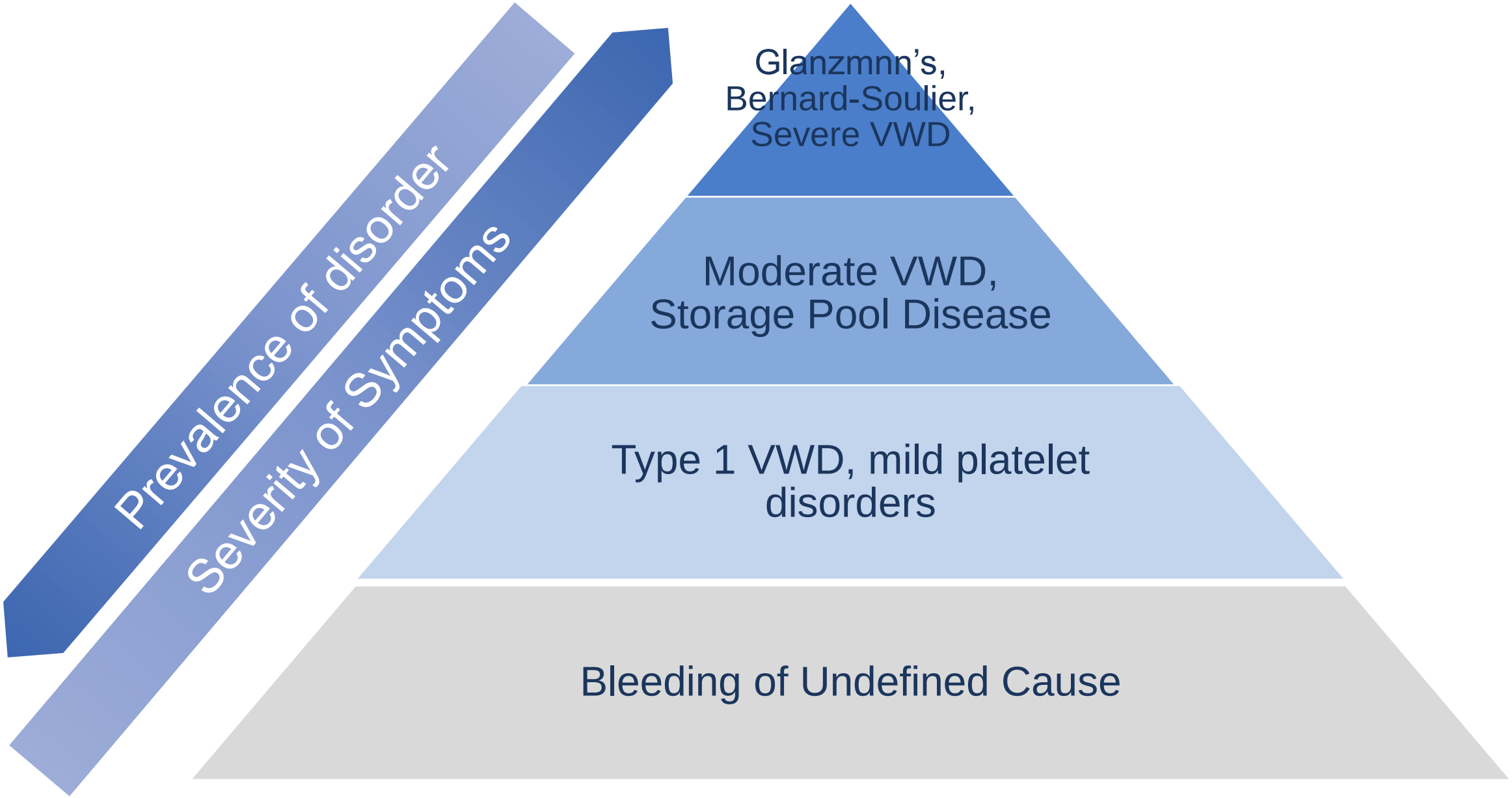
Aggregation





Symptoms of Platelet Function Disorders

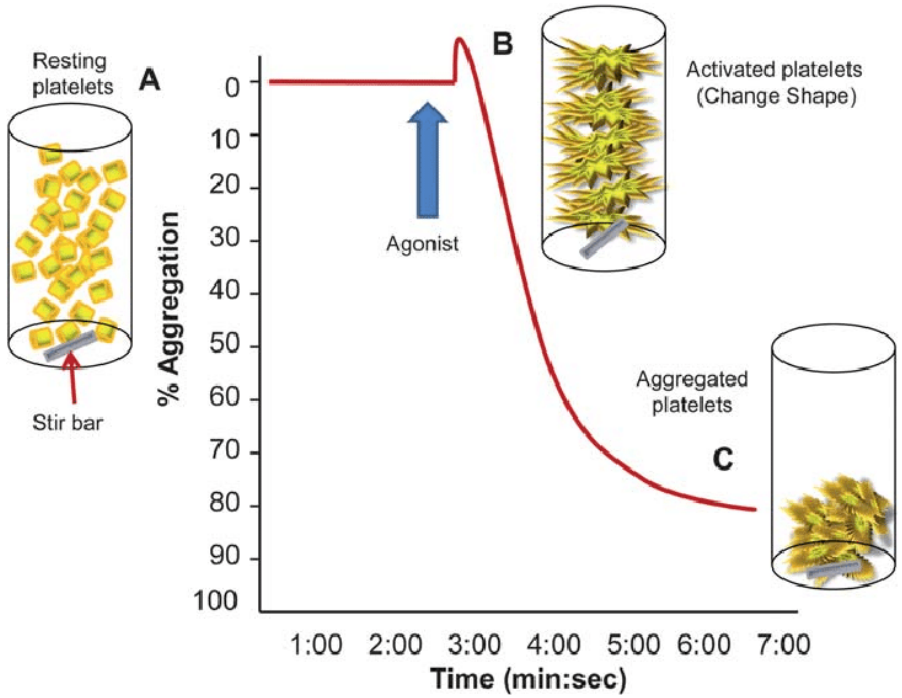
- Bruising
- Mucocutaneous bleeding
  - Nose bleeds
  - Gum bleeding
  - Oral bleeding
  - Excessive menstrual bleeding
  - GI bleeding
- Trauma and surgery-related bleeding

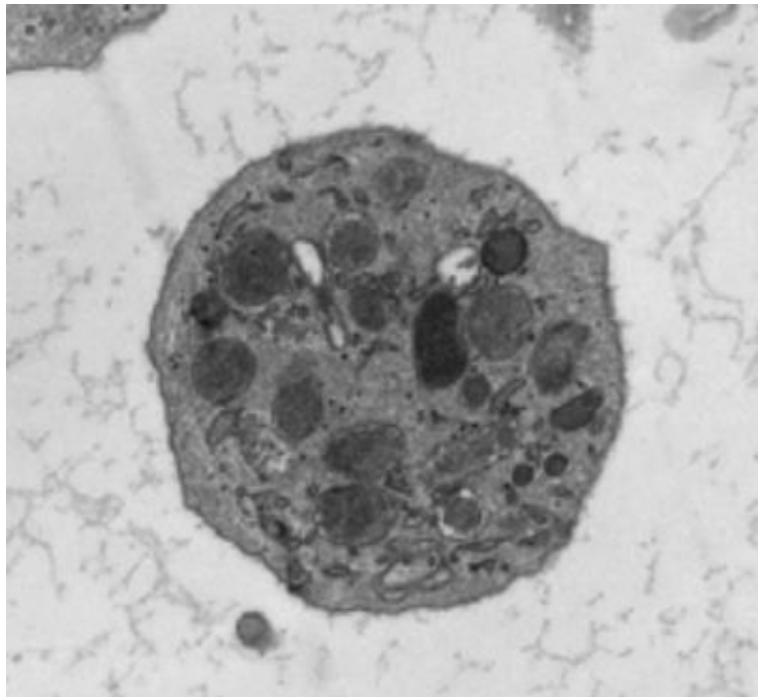


Rodeghiiero et al, Hemasphere 2019;3:e286.

Testing is tricky

- Platelet number
- Platelet function analyser-100 (PFA-100), Bleeding time
  - PFA does not detect all platelet disorders
    - Particularly storage pool disorder
- Platelet aggregation studies
- Platelet electron microscopy
- Genetic testing





Hayward CPM. Transf Apher Sci. 2008;38:65, Warren JT & DiPaola J. Blood 2022;139:3264.

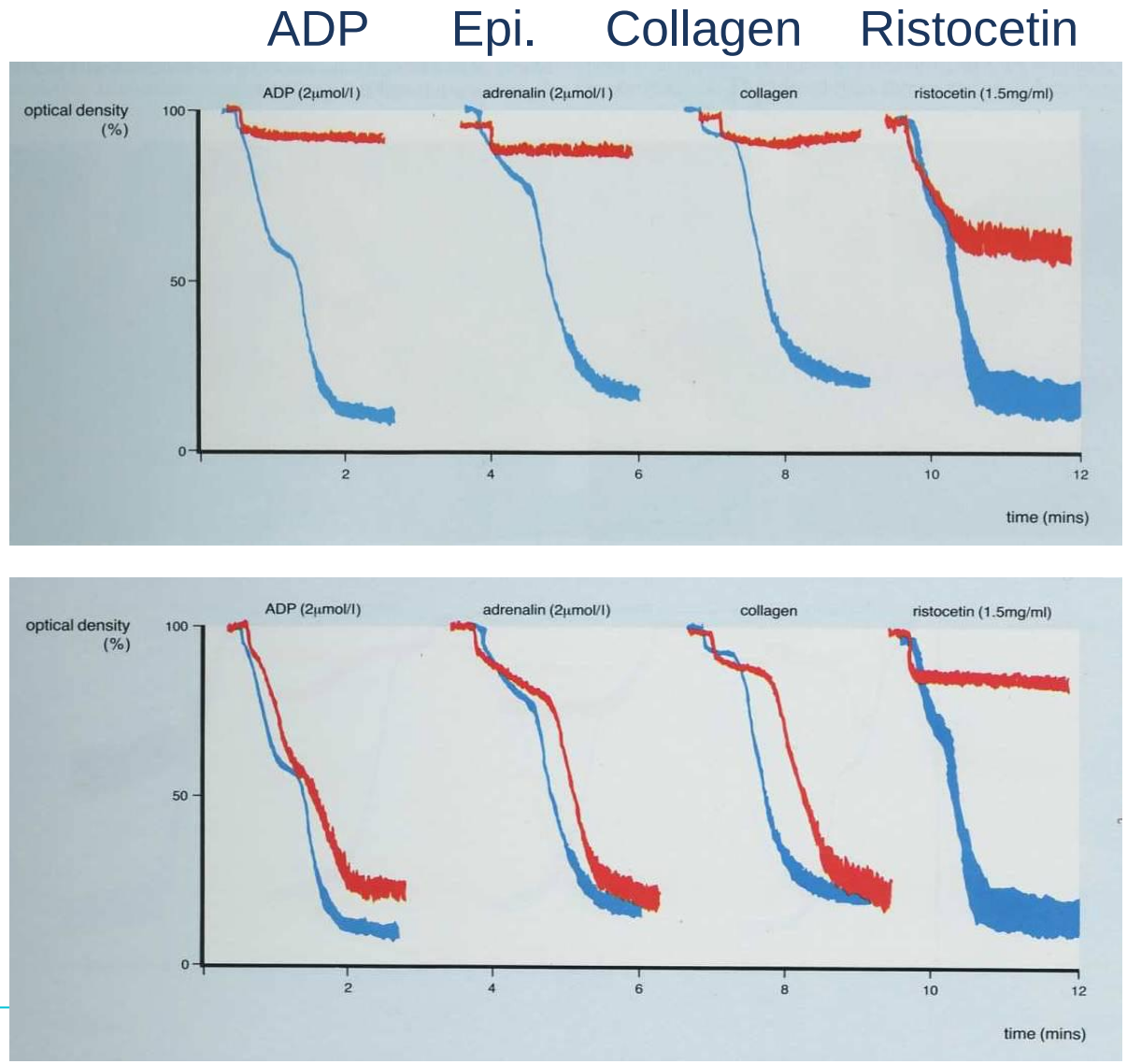
Platelet aggregation patterns

Glanzmann's Thrombasthenia

- deficiency of the αIIbβ3 (GPIIb/IIIa) receptor
- No CD41 or CD61 on flow

Bernard Soulier Syndrome

- (GP)Ib-IX-V complex on platelets
- mutations in the GP1BA, GP1BB, or GP9 genes
- Flow c/w defective CD42 binding



https://practical-haemostasis.com/Platelets/platelet_function_testing_lta.html

Summary

- Reviewed von Willebrand disease
  - Identify VWD subtypes and understand treatments
  - Various etiologies of Acquired von Willebrand Syndrome (AVWS) – treat underlying etiology
- New treatment options for congenital hemophilia
  - Mechanisms to extended half-life of clotting factor concentrates
  - Bispecific antibody – factor FVIII mimetic
  - 3 approved gene therapy options
- Recognition and treatment options for acquired hemophilia A
  - Bypassing agents (rFVIIa, aPCC, porcine FVIII)
- Some rarer factor deficiencies and their treatment approaches
- Recognition and treatment of platelet function disorders

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Thank you

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