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.

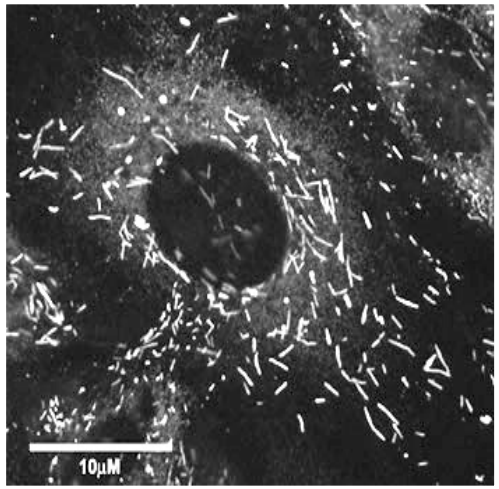
Disclosures [lifetime]

- Advisory Board/Consultant
  - Genentech/Roche, Hemab Therapeutics, Vega Therapeutics, Novo Nordisk, Takeda, Bayer, Genentech, Octapharma, Sanofi, CSL Behring, HEMA biologics, Pfizer, Spark therapeutics, Cerus
- Research Funding from
  - Octapharma

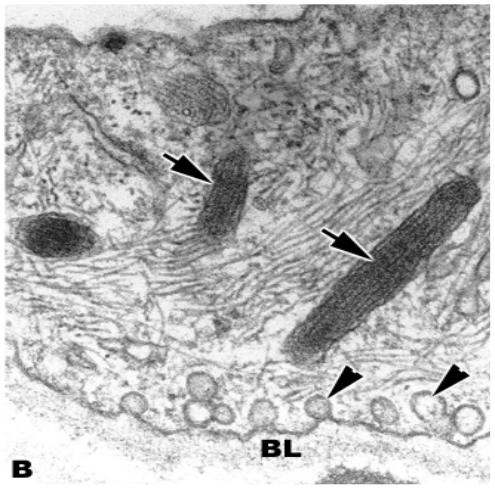
1. Von Willebrand Disease and Von Willebrand Syndrome
2. Hemophilia A and B
3. Rare factor deficiencies
4. Inherited platelet disorders

Von Willebrand Disease and Acquired Von Willebrand Syndrome

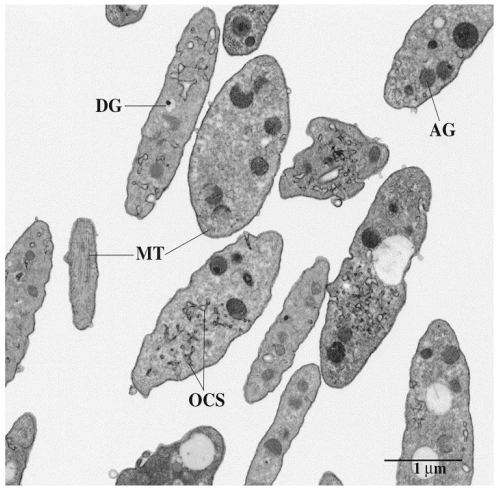
Von Willebrand Factor



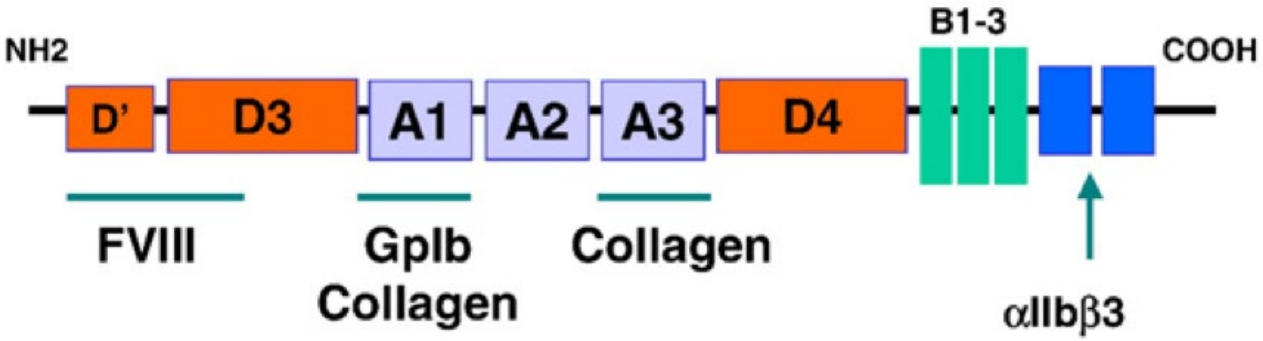
Vascular Endothelial Cell
von Willebrand factor



Vascular Endothelial Cell
Weibel-Palade Body

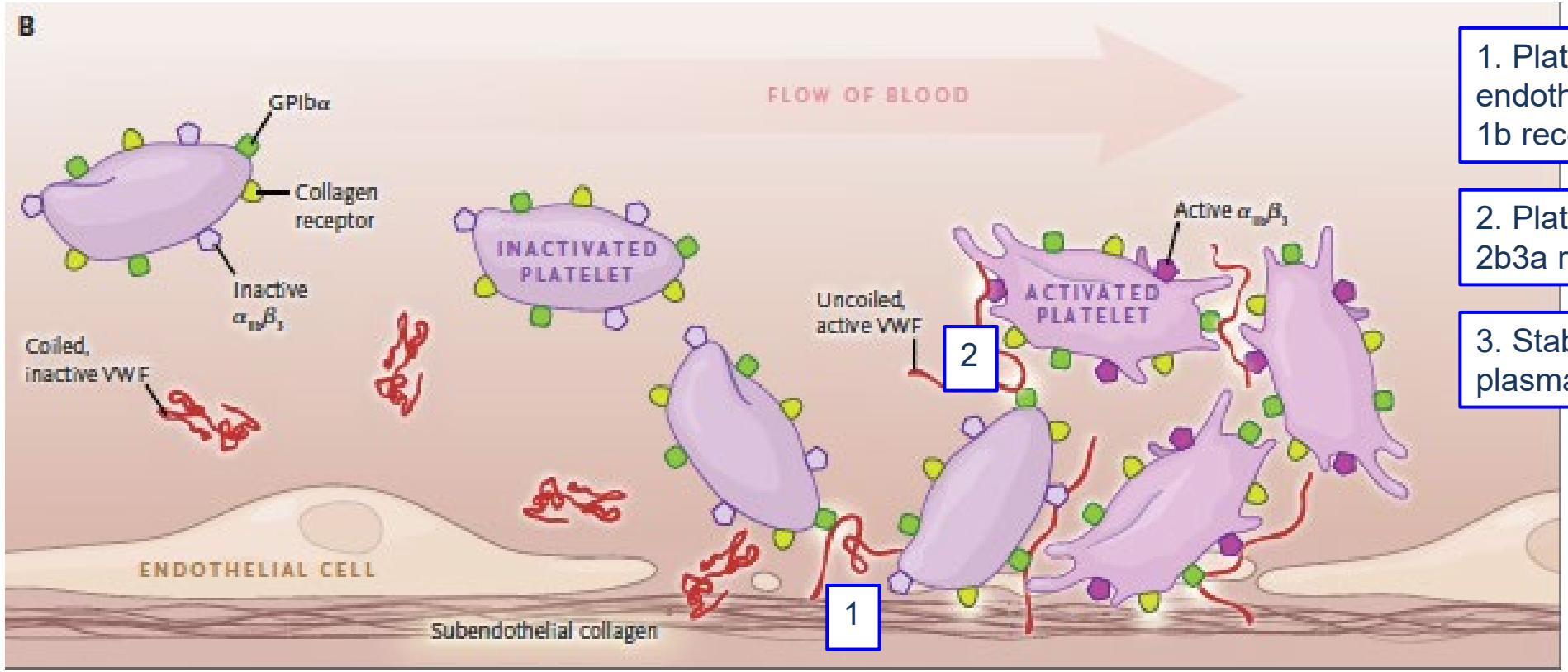


Platelets
α-granules



vWF
Multimer

Von Willebrand Factor Function



1. Platelet adhesion via sub-endothelial collagen and GP 1b receptor at the site of injury

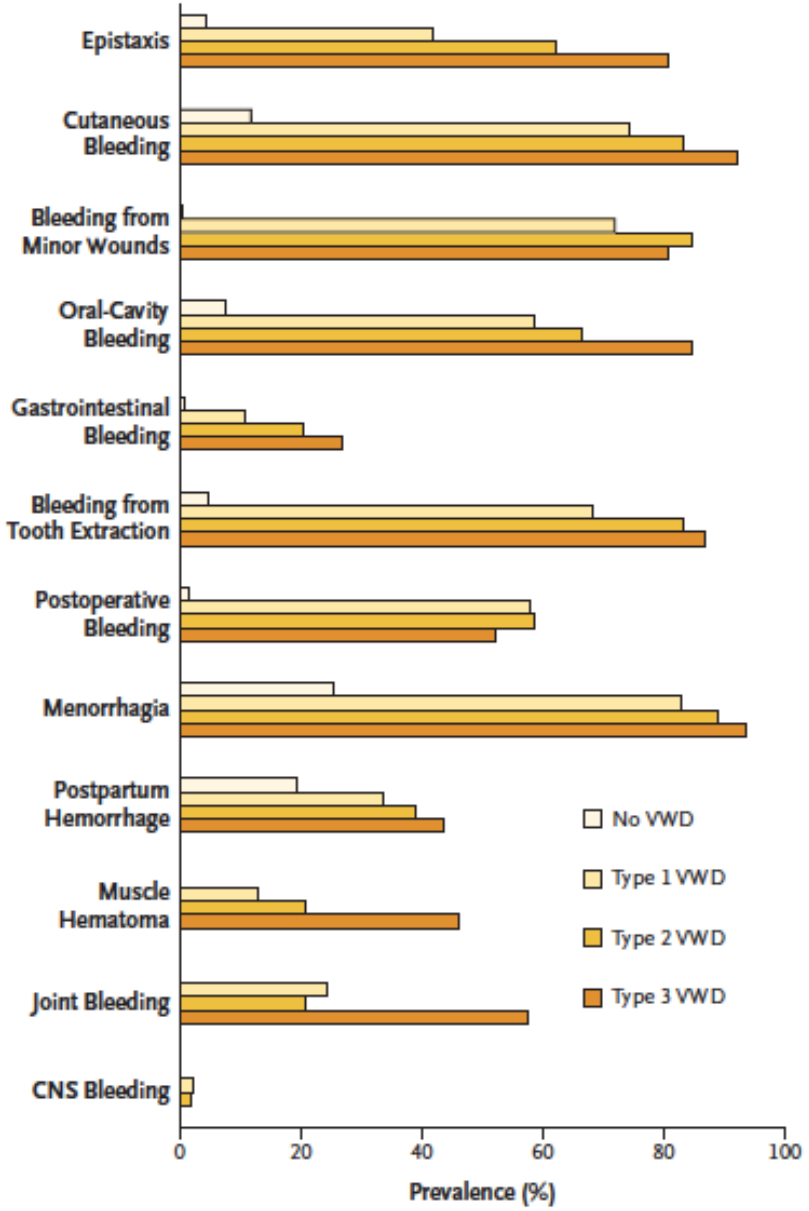
2. Platelet aggregation via GP 2b3a receptors

3. Stabilization of factor VIII in plasma

NEJM 2016;375:2067-80.

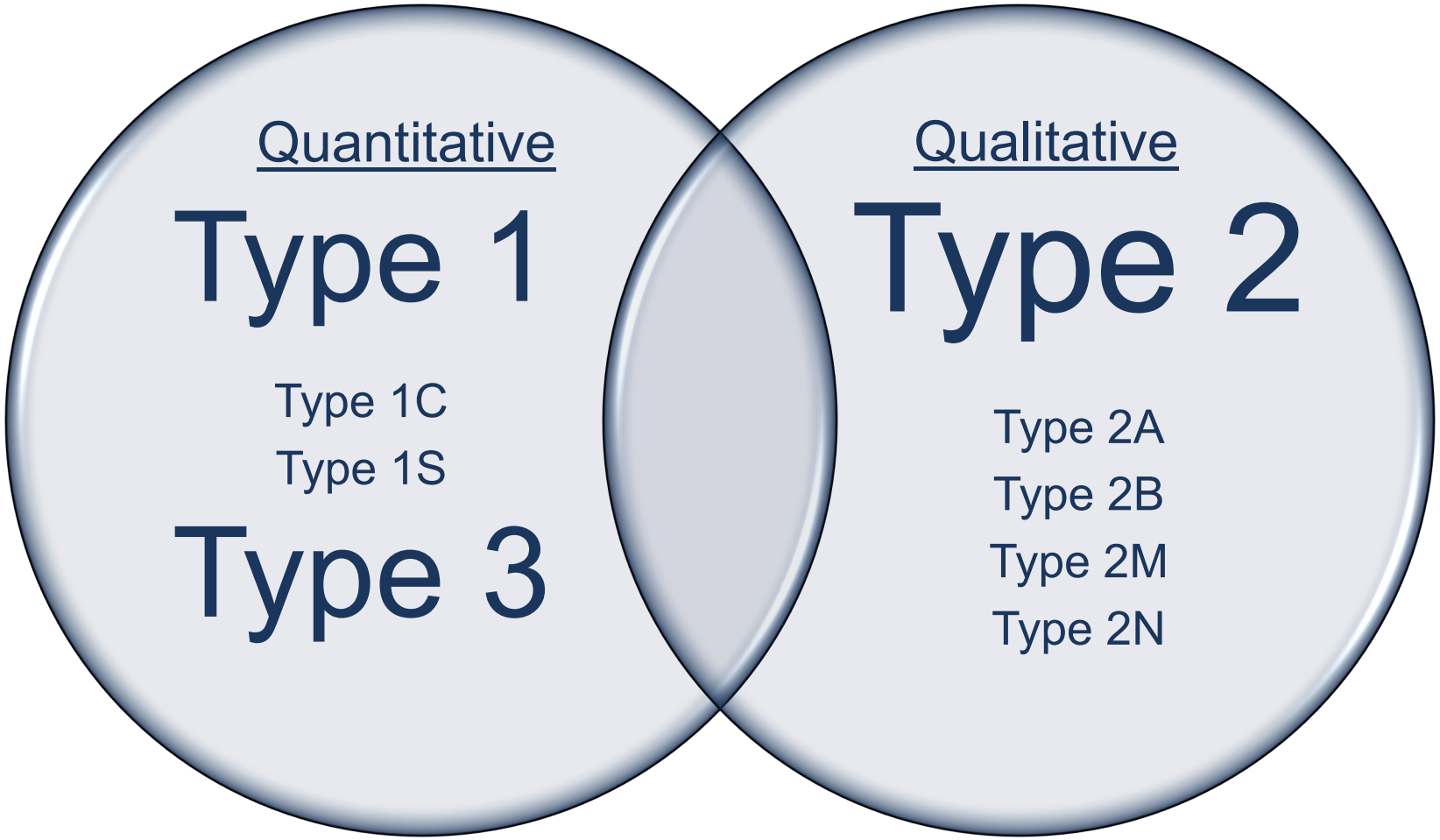
Von Willebrand Disease Clinical Manifestations

- Heterogeneous based on VWF level, disease subtype +/- age and sex
  - Children: bruising and epistaxis
  - Adults: hematomas, heavy menstrual bleeding, bleeding from minor wounds
- 60-80% will demonstrate post-operative bleeding, including s/p dental extractions



NEJM 2016;375:2067-80.

Von Willebrand Disease



How do we test for VWD?

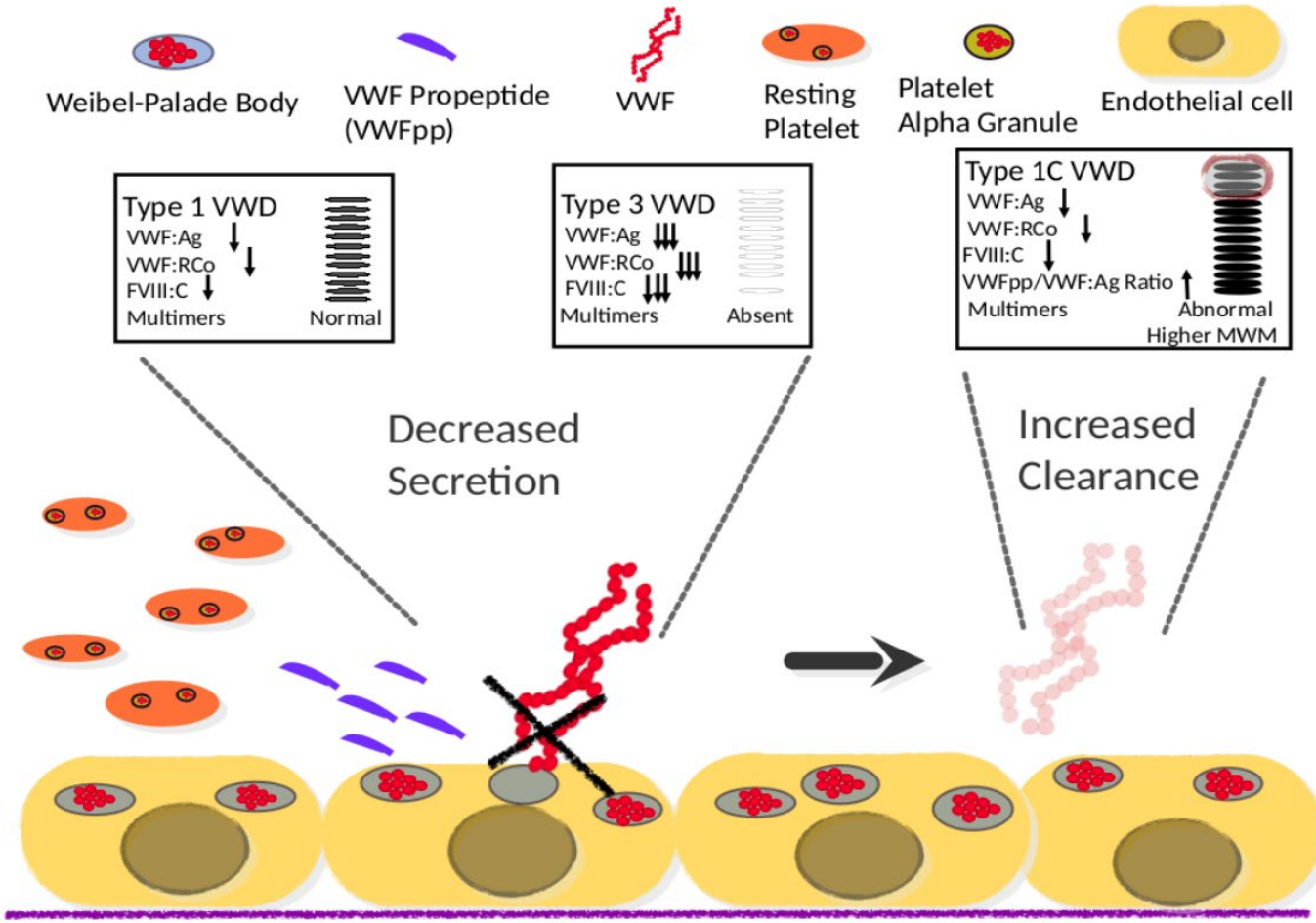
- Bleeding time
- Platelet Function Analyzer

Screening

- VWF:Antigen
- VWF: Platelet Binding Activity (RisCof, GP1bM)
- VWF: Collagen binding activity
- Factor VIII activity
- VWF:multimers

Diagnosis & Function

Von Willebrand Disease – **Quantitative** Defects



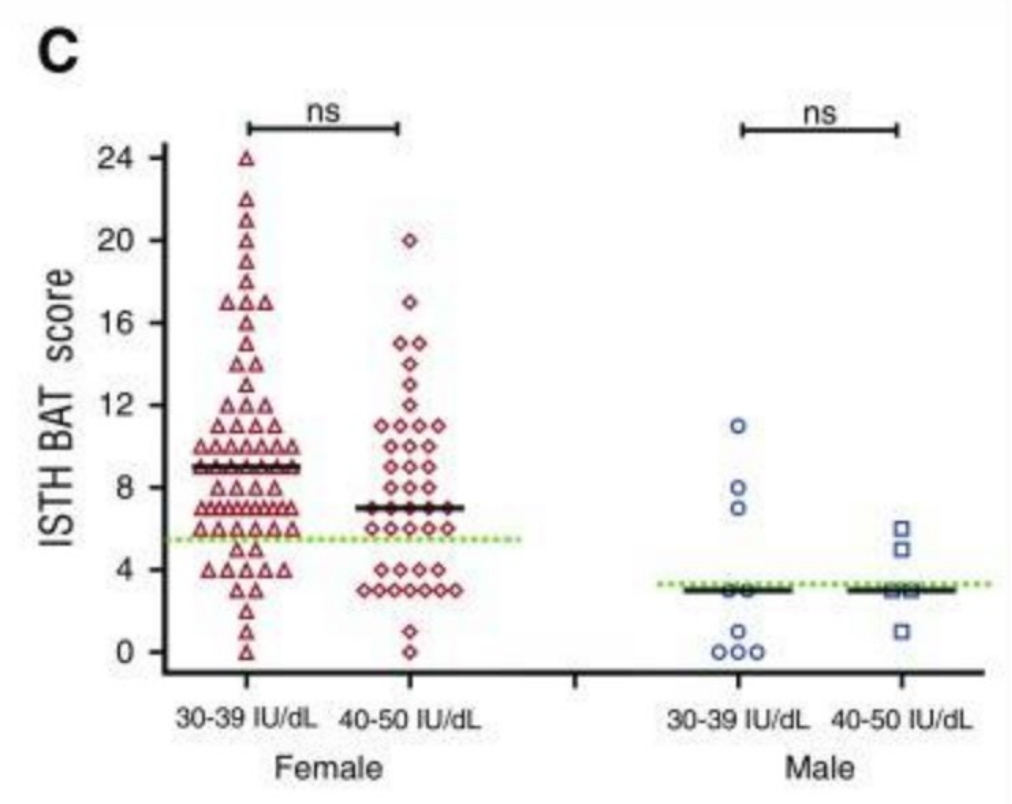
- Type 1 (reduced VWF)
  - Decreased production
  - Decreased secretion
  - Increased clearance (type 1C)
- Type 3 – marked decrease or absence of VWF
  - Autosomal recessive (homozygosity or compound heterozygosity)
  - Distinguish from type 1S with pro-peptide level

Di Paola Lab Image

Diagnosis of Type 1 VWD

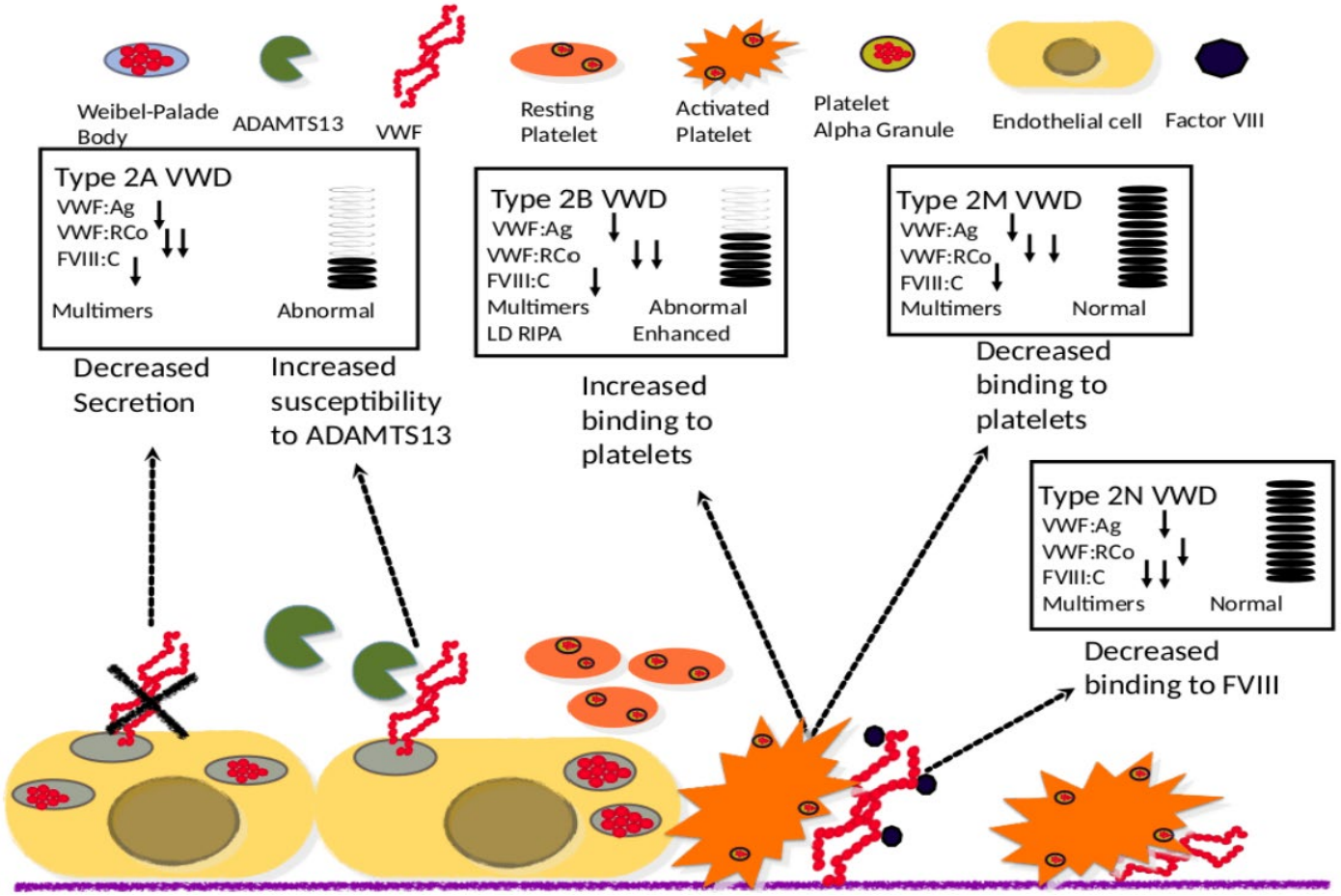
ASH ISTH NHF WFH 2021 Guidelines

- 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.

Von Willebrand Disease – **Qualitative** Defects



Decreased VWF activity/antigen (< 0.7)

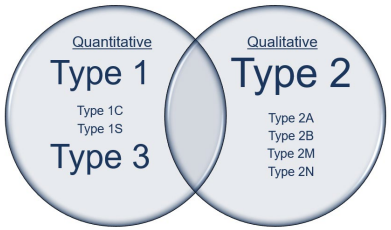
- Type 2A (reduced high molecular weight multimers)
  - Reduced dimerization or multimerization
- Type 2B (increased binding to platelets)
  - HMWM bind to platelets via GP1b and are sequestered from the circulation
- Type 2M (decreased binding to platelets)
  - Normal multimers

Decreased FVIII / VWF antigen (< 0.7)

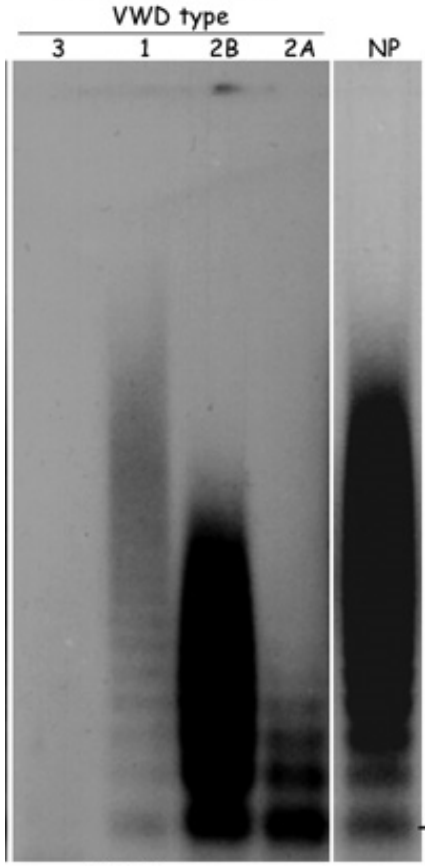
- Type 2N (decreased binding to factor VIII)
  - Recessive

Di Paola Lab Image

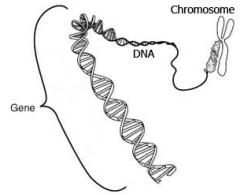
Von Willebrand Disease Diagnosis



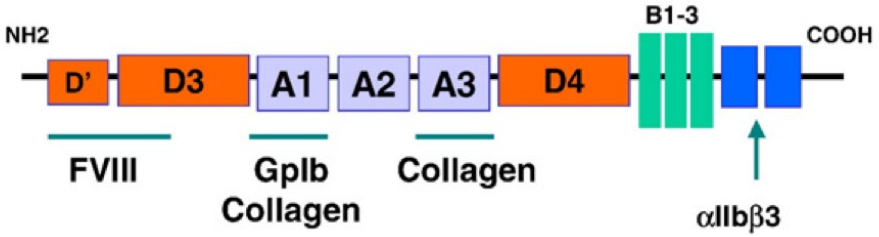
VW Subtype	Comment	%	VWF:Ag (IU/dL)	VWF:Act (IU/dL)	FVIII	Ratio	Multimers or Other
Type 1	Mild-to-moderate **quantitative** defect	75	<50	<50	> VWF	VWF:Act/Ag > 0.7	Normal multimer distribution
Type 2	**Qualitative** defects	20					
2A	Decrease in high molecular weight multimers		<30-200	<30	↓ or wnl	VWF:Act/Ag < 0.5-0.7	Decreased high molecular weight multimers
2B	Increased binding to platelet GP-1b		<30-200	<30	↓ or wnl		
2M	Decreased binding to platelets with normal multimers		<30-200	<30	↓ or wnl		Normal multimer distribution
2N	Decreased binding to FVIII		30-200	30-200	↓↓	VWF:VIII/Ag < 0.5-0.7	↓ FVIII-VWF binding assay
Type 3	Severe **quantitative** defect	<5		< 5	< 10	n/a	↓ VWF pro-peptide



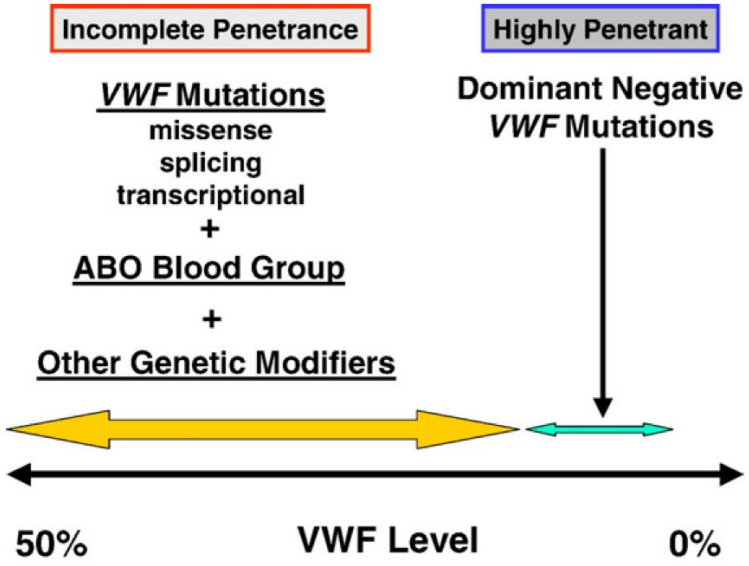
Genetic Testing for VWD



- 1985 – cloning of the gene for VWF
  - Short arm of chromosome 12
  - Partial VWF pseudogene on chromosome 22



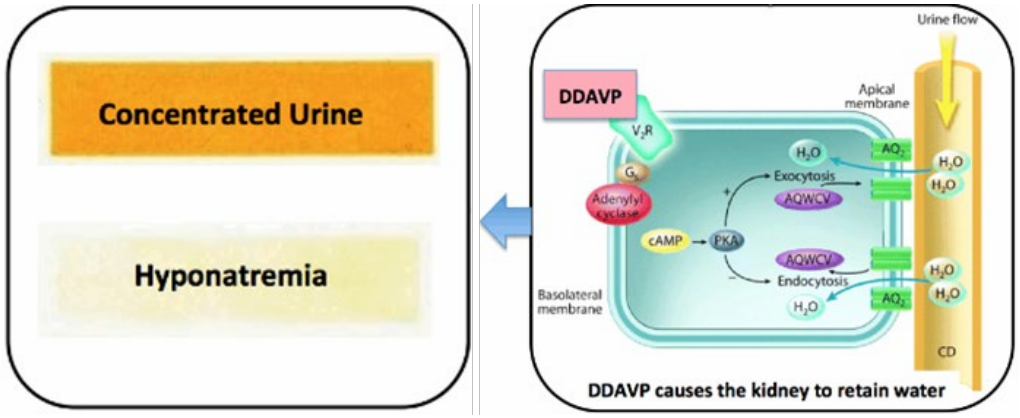
- Subtype mutation testing
  - Type 1 < 65% are mutation (+)
  - Type 2 50-90% are mutation (+)
    - Location specific
  - Type 3 > 90% are mutation (+)



James et al, Canadian Type 1 VWD Study, Blood, 2007

Treatment of VWD

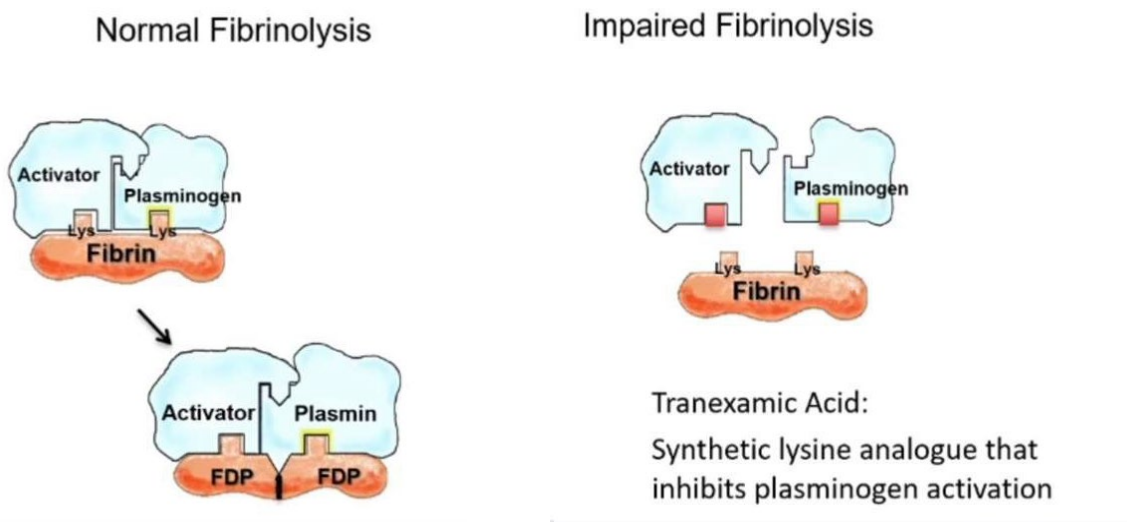
- Desmopressin (DDAVP – intranasal, SQ, IV)
  - Releases endogenous VWF and factor VIII from endothelium
  - Increases platelet adhesion to vessel wall
  - Increases tissue plasminogen activator
- Caution
  - Not effective in type 3
  - Less effective in type 1C
  - Less effective in type 2N
  - Caution in 2B (pseudothrombocytopenia)
  - DDAVP challenge (pre, 1- & 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

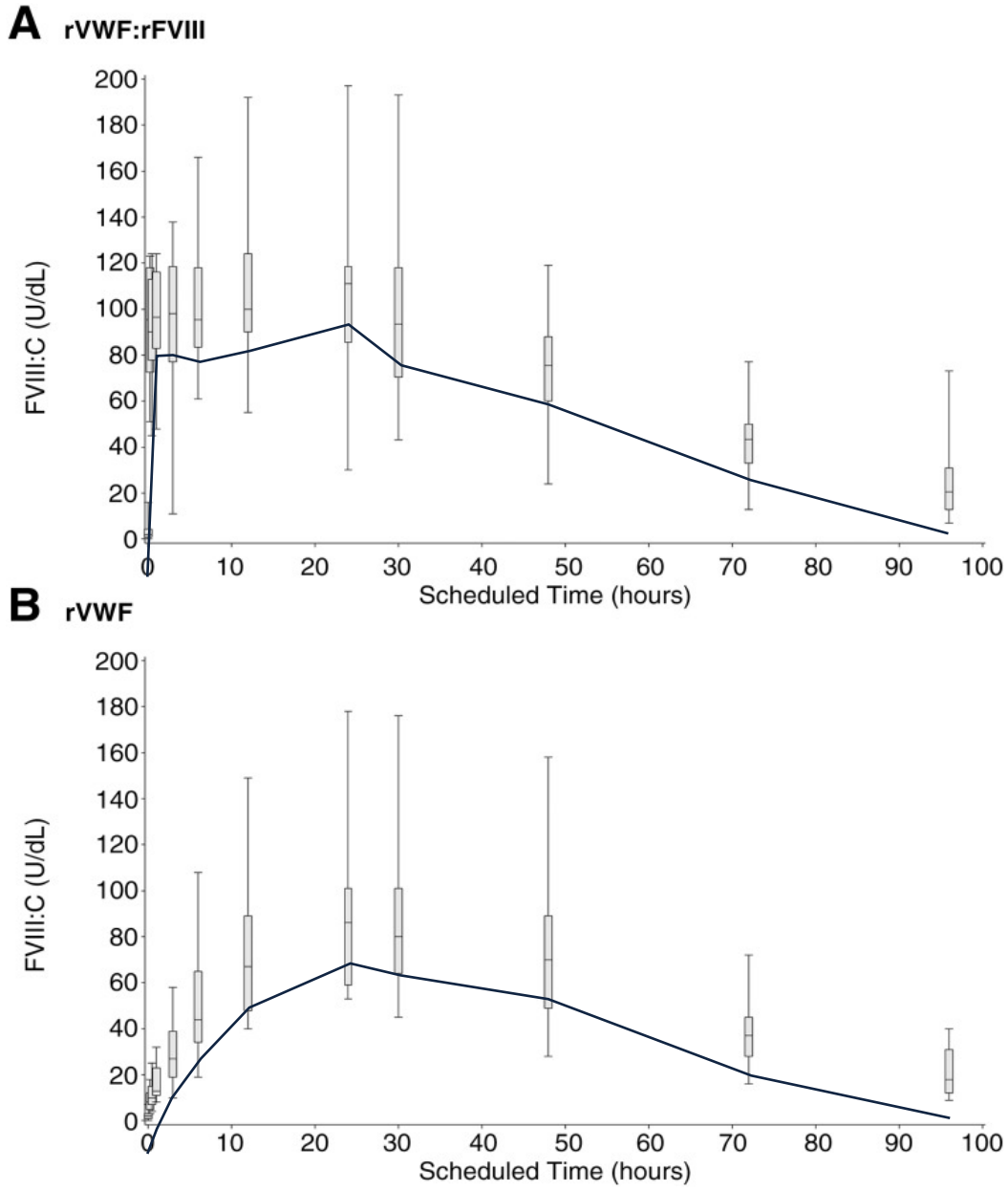
- Antifibrinolytics
  - ε-aminocaproic acid (Amicar), tranexamic acid
  - Lysine analogs
  - Bind to plasminogen and prevent conversion to plasmin and thus fibrin degradation



Eghbali A, et al. Haemophilia 2016;22:e423.
Adapted from Mannucci NEJM 1988.

Treatment of VWD

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



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

Acquired Von Willebrand syndrome (AVWS)

Rare

- underreported

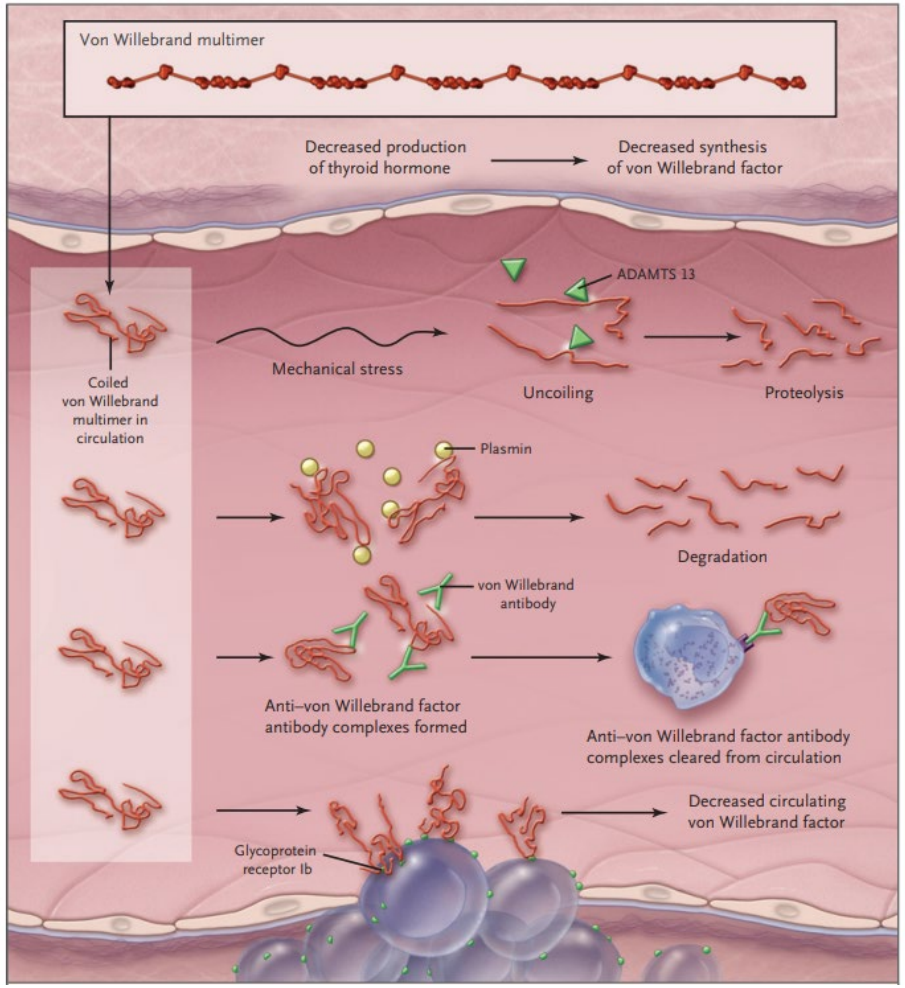
Paucity of data

- 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.

Pathophysiology of Acquired Von Willebrand Syndrome

Mechanism	Associated Disorder(s)
Decreased VWF synthesis	• Hypothyroidism
Shearing of high molecular weight multimers → mechanical stress or proteolysis by ADAMTS13	• Myeloproliferative disorders (MGUS, MM, NHL) • Cardiovascular diseases (aortic stenosis) • Uremia • Drugs
Degradation of VWF multimers by plasmin	• DIC
Autoantibodies → inhibition of VWF function and/or increased clearance	• Lymphoproliferative disorders (MGUS, MM, NHL) • Immunologic disorders (SLE, connective tissue disorders) • Nonhematologic neoplasms (gastric adenocarcinoma)
Adsorption → increased clearance of FVIII-VWF complex by malignant cells	• Lymphoproliferative disorders (MGUS, MM, NHL) • Myeloproliferative disorders (ET, PV, CML) • Nonhematologic neoplasms • Drugs



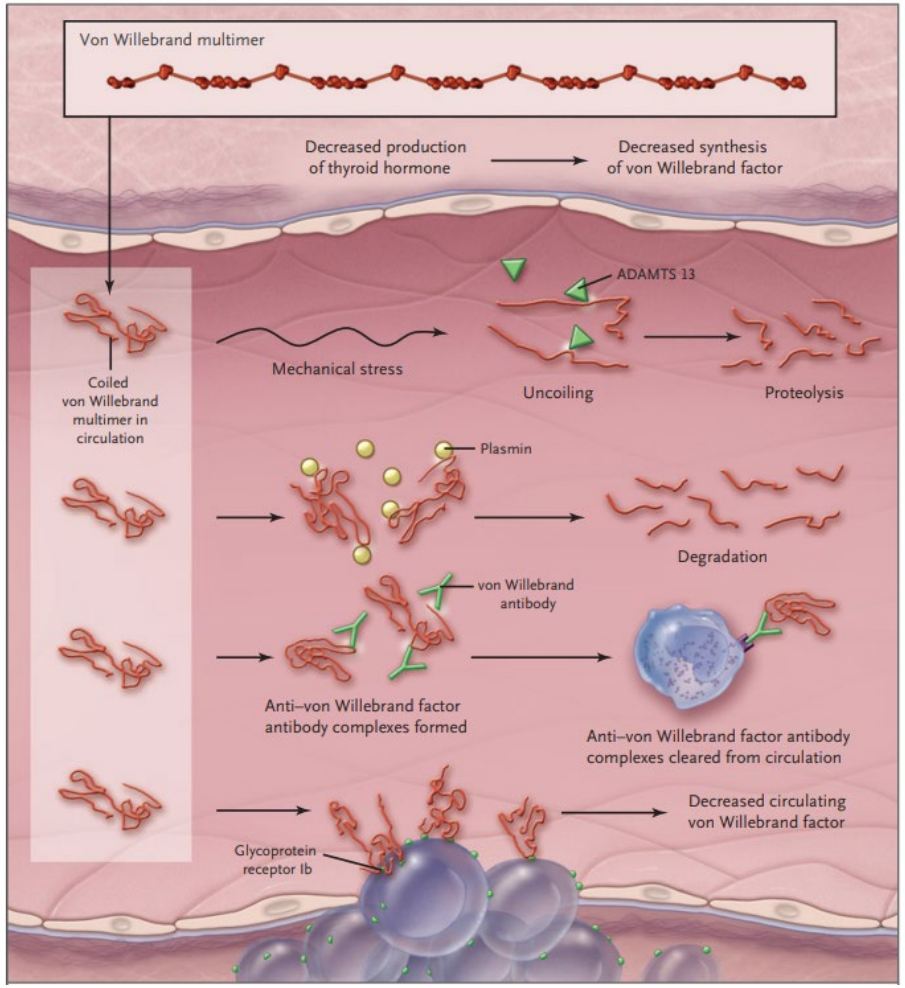
N Engl J Med 2009;361:1887-1894.

Treatment of Acquired Von Willebrand Syndrome

Mechanism	Treatment
Decreased VWF synthesis	• **Treatment of underlying disease** • VWF replacement
Shearing of high molecular weight multimers → mechanical stress or proteolysis by ADAMTS13	• **Treatment of underlying disease** • Surgical correction of cardiac abnormality
Degradation of VWF multimers by plasmin	• **Treatment of underlying disease**

Autoantibodies → inhibition of VWF function and/or increased clearance	• **Treatment of underlying disease**
	• Immune modulatory therapy
	  • IVIG
	  • Prednisone, rituximab, others

Adsorption → increased clearance of FVIII-VWF complex by malignant cells	• **Treatment of underlying disease**



N Engl J Med 2009;361:1887-1894.

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

- Correspondence in NEJM 1958 by EC Heyde
  - Gastrointestinal Bleeding in Aortic Stenosis

Congenital & acquired aortic stenosis

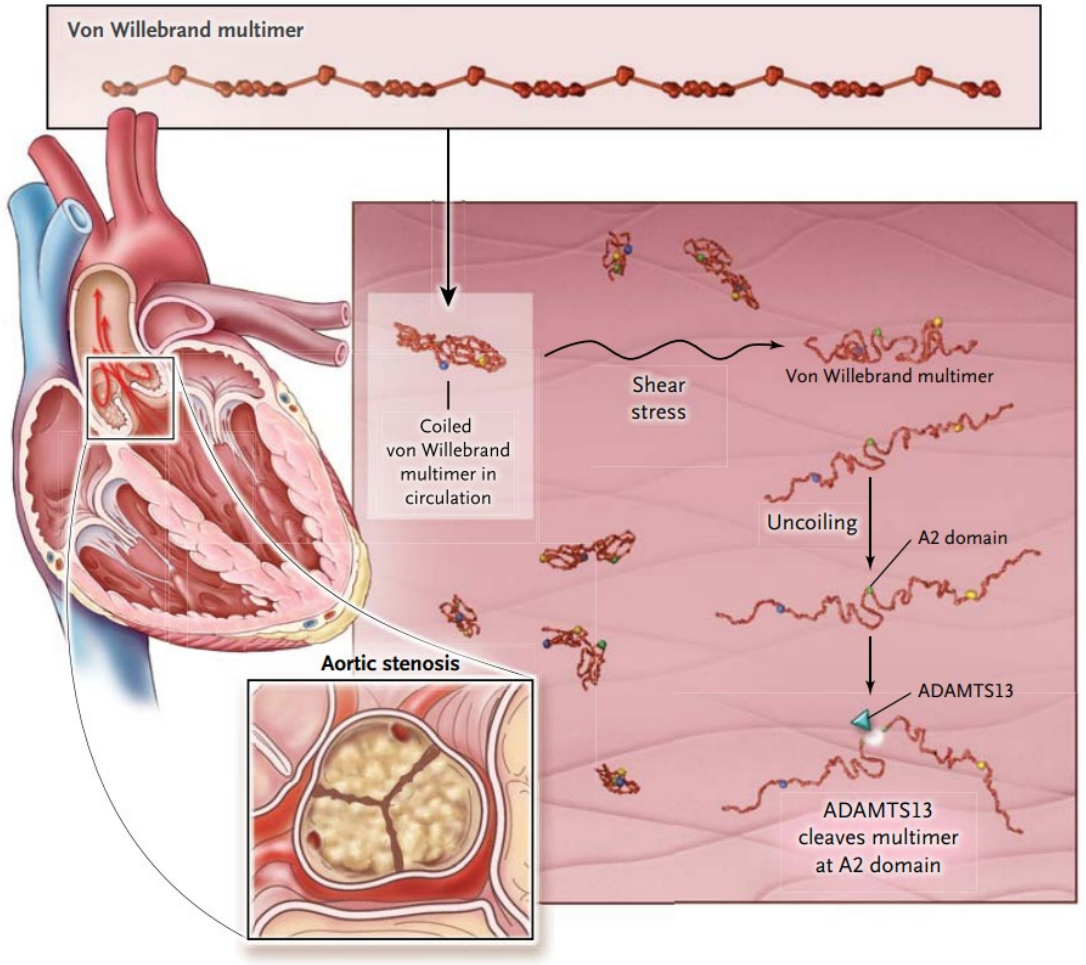
↓

Loss of high molecular weight multimers of VWF

&

Submucosal angiodysplasia

- Etiology: unclear.
  - Hypothesis: normal vascular aging and an impairment of platelets to maintain vascular endothelium
- Treatment: resolution of AVWS & bleeding with correction of cardiac abnormality



N Eng J Med 2012;367(20):1954-1956.

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Congenital Hemophilia

Hemophilia A and B

Diagnosis

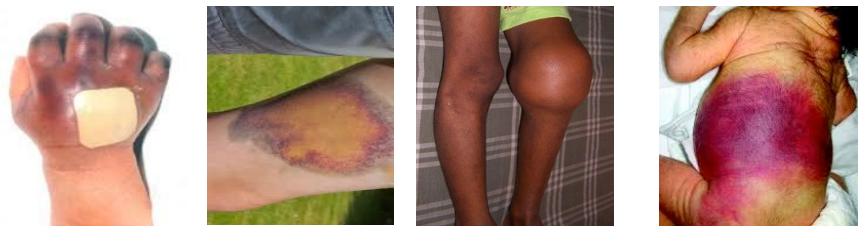
- Most common congenital disorder of thrombin generation
- Diagnosed with prolonged aPTT, then subsequent decreased factor activity

- Hemophilia A = Factor VIII deficiency
  - 1:5000-10,000 male births
- Hemophilia B = Factor IX deficiency
  - 1:30,000 male births

- Severity of disease
  - Mild 6-40%
  - Moderate 1-5%
  - Severe <1%

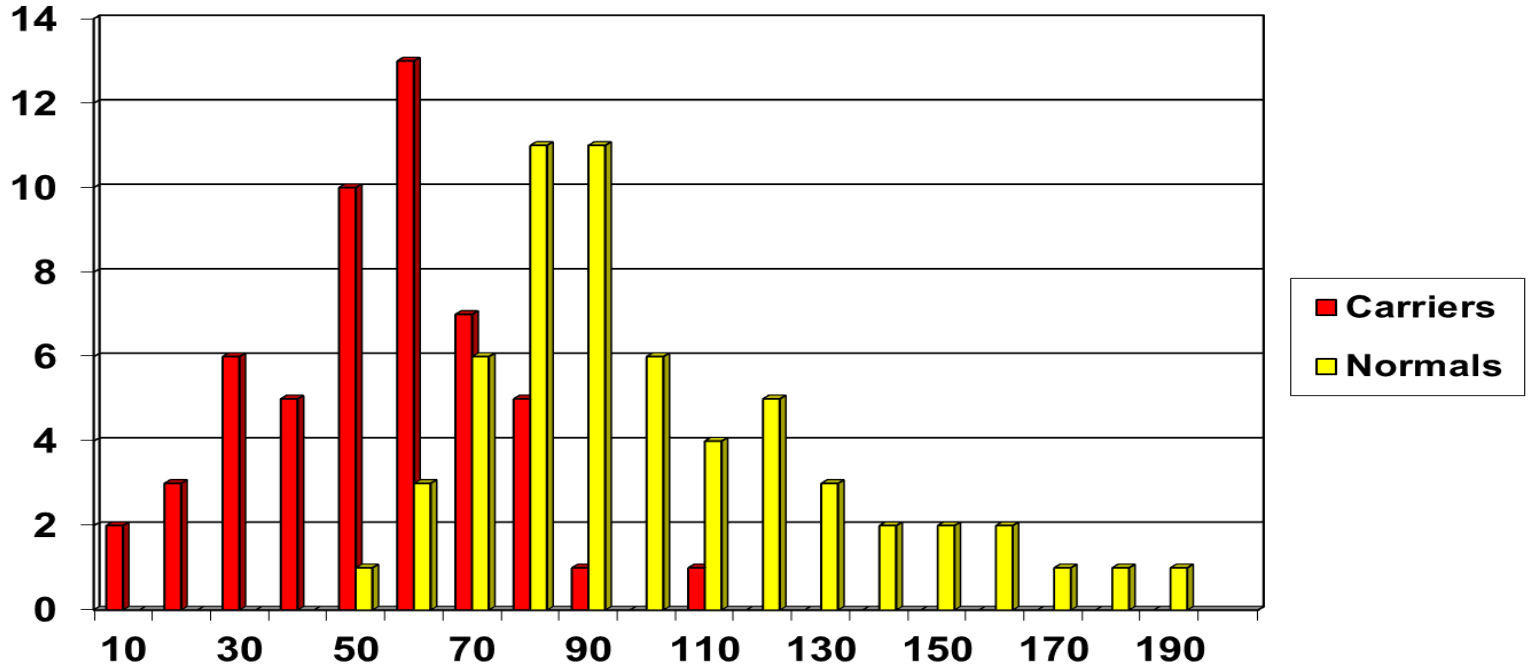
Bleeding Symptoms

- Joint bleeding
  - Begins after weight bearing
  - Leads to chronic inflammation and joint destruction (hemophilic arthropathy)
  - Knees > elbows > ankles >>> shoulders, hips, wrists
- Hematomas
  - Spontaneous or trauma related
- Life-threatening bleeds
  - Intracranial
  - Retroperitoneal
  - Soft tissue hemorrhage, trauma or post-surgical bleeding



Females with *F8* Genetic Variants

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



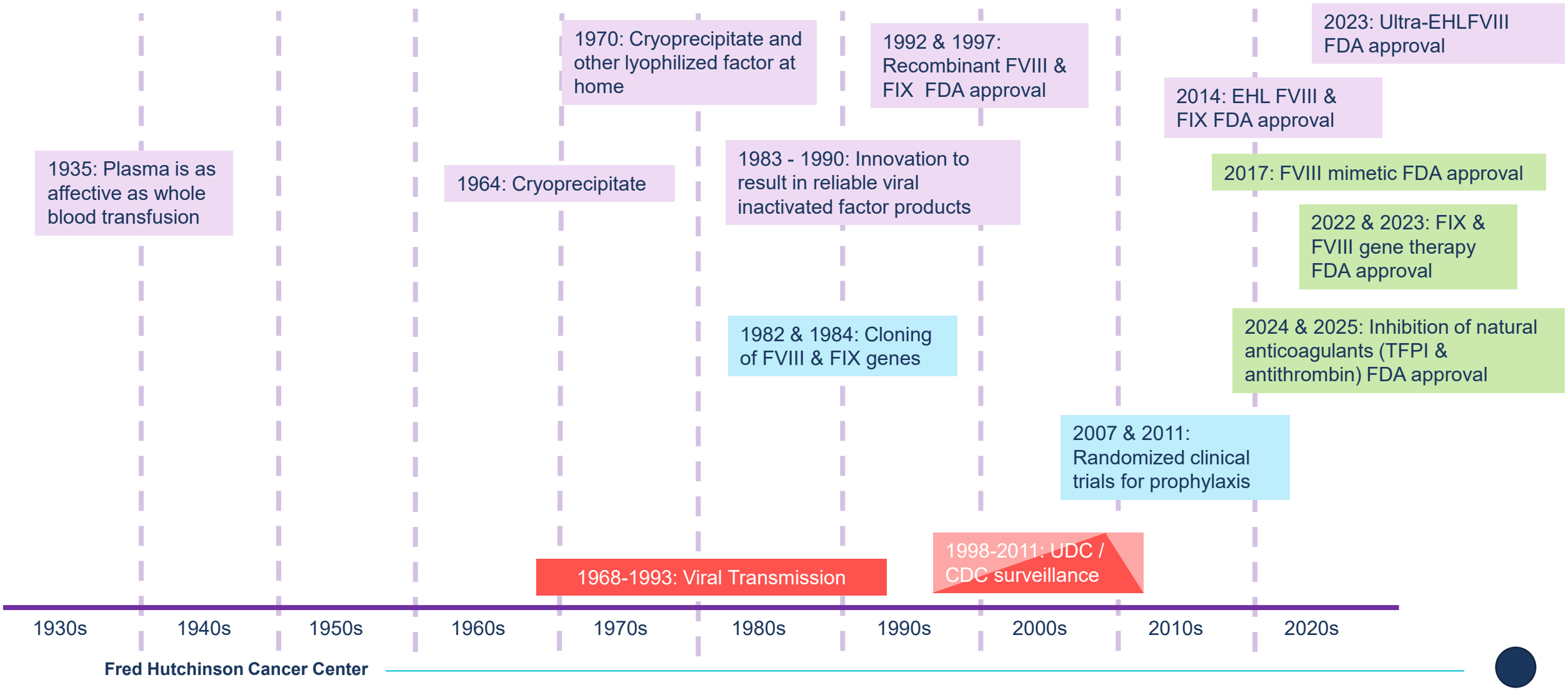
Van Galen, K et al. J Thromb Haemost. 2021;19:1883
Figure courtesy of C. Kasper

Hemophilia Treatment

- Prophylactic treatment
  - Primary prophylaxis: initiation of prophylaxis prior to joint bleeding (or after 1-2 joint bleeds, but no joint disease)
  - Secondary prophylaxis: initiation of prophylaxis after onset of joint disease (e.g., target joints)
  - Indications for prophylaxis:
    - Severe disease: all
    - Moderate / mild disease: > 2 joint bleeds (especially if spontaneous)

- On demand treatment: treatment only with bleeding symptoms
  - FVIII 25 – 50 U/kg (increases factor activity 50 – 100%)
  - FIX 70 – 140 U/kg (increases factor activity 50 – 100%)

Evolution of Hemophilia Treatment



Adapted from: Blood. 2016;127(24):3073-3081.

Extended Half-Life Factor Products

- Protein modification to extend half-life of exogenous FVIII and FIX has been examined to:
  - Achieve higher trough levels with standard infusion interval *or*
  - Extend infusion interval needed for successful prophylaxis

To date, 3 successful approaches have been established in hemophilia

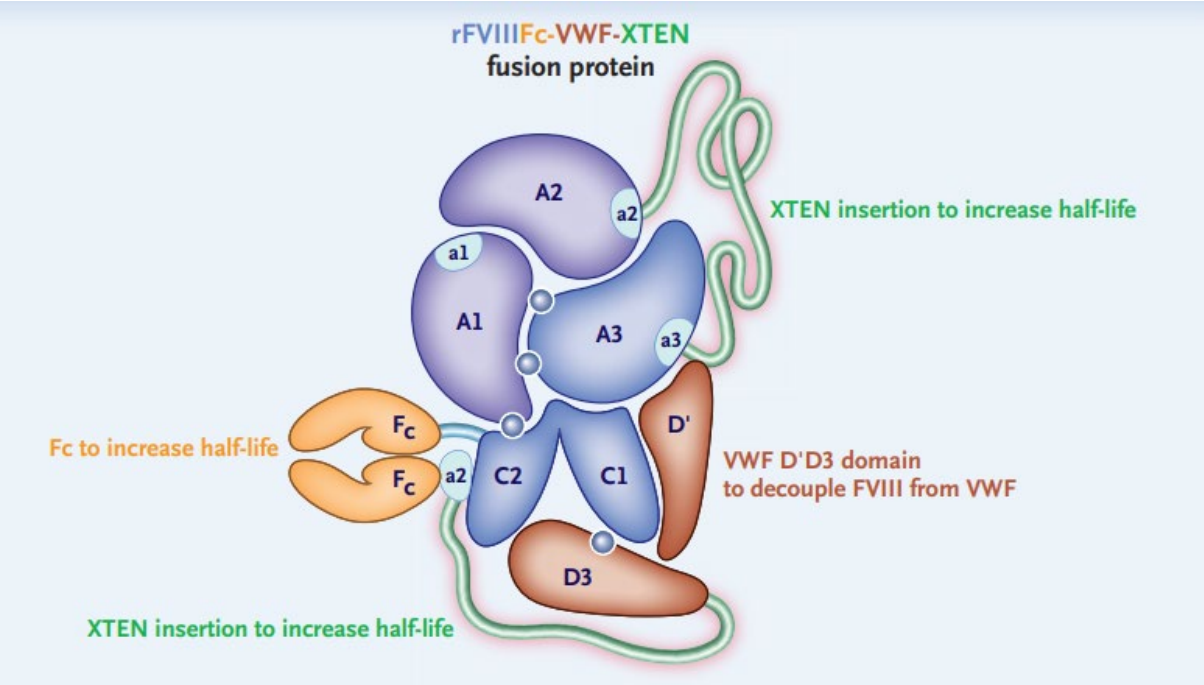
Fc fusion

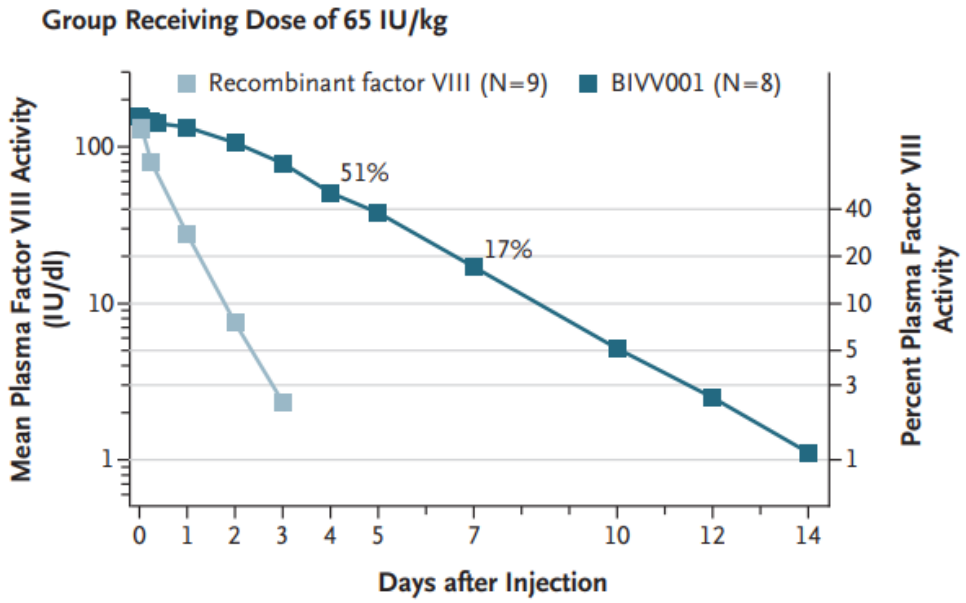
Albumin
(hemophilia B only)

PEGylation

Am J Hematol. 2016;91:1252.
Hematol Oncol Clin North Am. 2021;35:1143.

Efanesoctocog Alfa





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

Major Complication of Factor Treatment: Inhibitors

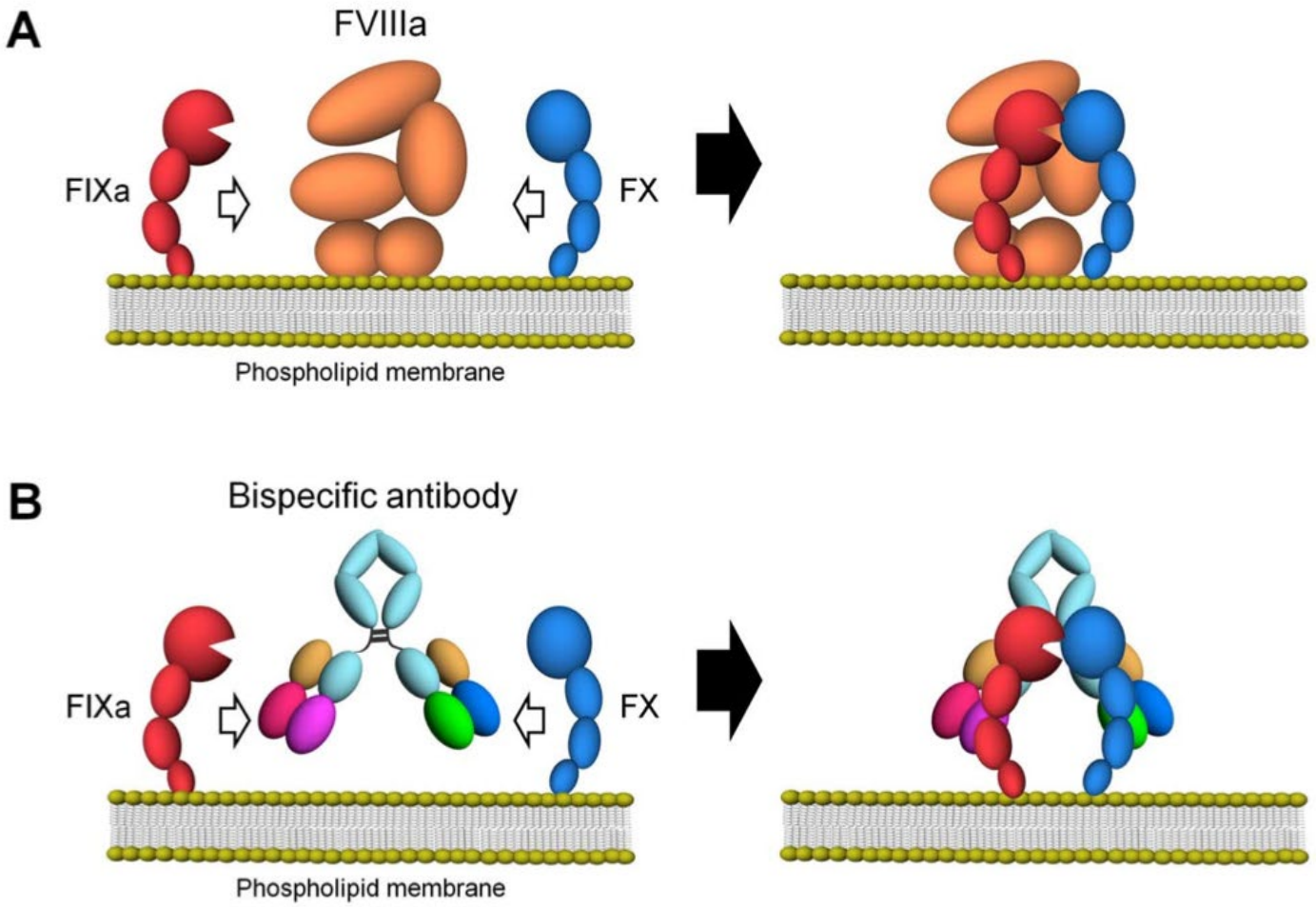
- **Inhibitors ➔ Factor-neutralizing antibodies**
  - ~30% in severe A (can also occur in mild hemophilia A)
  - ~10% in severe B,

- **Hemostatic approach**
  - Low titer inhibitors (< 5 BU) may respond to high dose factor
  - High titer inhibitors do not respond to factor replacement
  - Need to treat bleeding with bypassing agents
    - recombinant factor VII activated (rFVIIa)
    - activated prothrombin complex concentrate (aPCC, contains factor II, VII, IX, X)

- **Inhibitor eradication**
  - Usually lengthy immune tolerance induction therapy (ITI) to eradicate inhibitor
  - Usually daily high dose factor VIII infusion for months

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

Emicizumab (FVIII Mimetic)



- Administration: subcutaneous
- Dosing
  - Weekly loading (3 mg/kg) x 4
  - SQ every 1-4 weeks
- Hemophilia A ONLY
- With and without inhibitors

PLoS ONE 2013. 8(2): e57497.

Zero Treated Bleeds With Emicizumab Prophylaxis

HAVEN 1
Adults and adolescents with inhibitors

63%
(95% CI: 44.9%-78.5%)
1.5 mg/kg QW (n = 35)

HAVEN 2
Pediatric patients with inhibitors

77%
(95% CI: 64.8%-86.5%)
1.5 mg/kg QW (n = 65)

HAVEN 3
Adults and adolescents without inhibitors

56%
(95% CI: 38.1%-72.1%)
1.5 mg/kg QW (n = 36)

60%
(95% CI: 42.1%-76.1%)
3 mg/kg Q2W (n = 35)

HAVEN 4
Adults and adolescents with or without inhibitors

56%
(95% CI: 39.7%-71.5%)
6 mg/kg Q4W (n = 41)

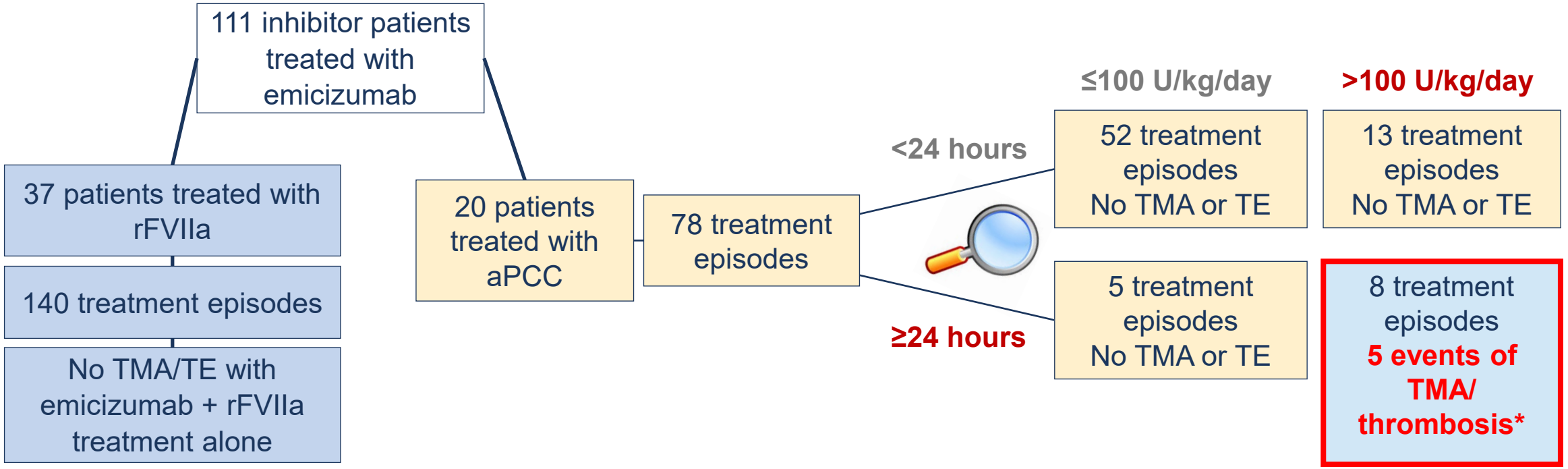
HAVEN 7
Infants without inhibitors

55%
3 mg/kg Q2W (n = 30)

Oldenburg. NEJM. 2017;377:809.
Young. Blood 2019; 34:2127.
Mahlangu. NEJM. 2018; 379:811.
Pipe. Lancet Haematol. 2019; 6:e295.
Pipe. Blood. 2024;143:1355.

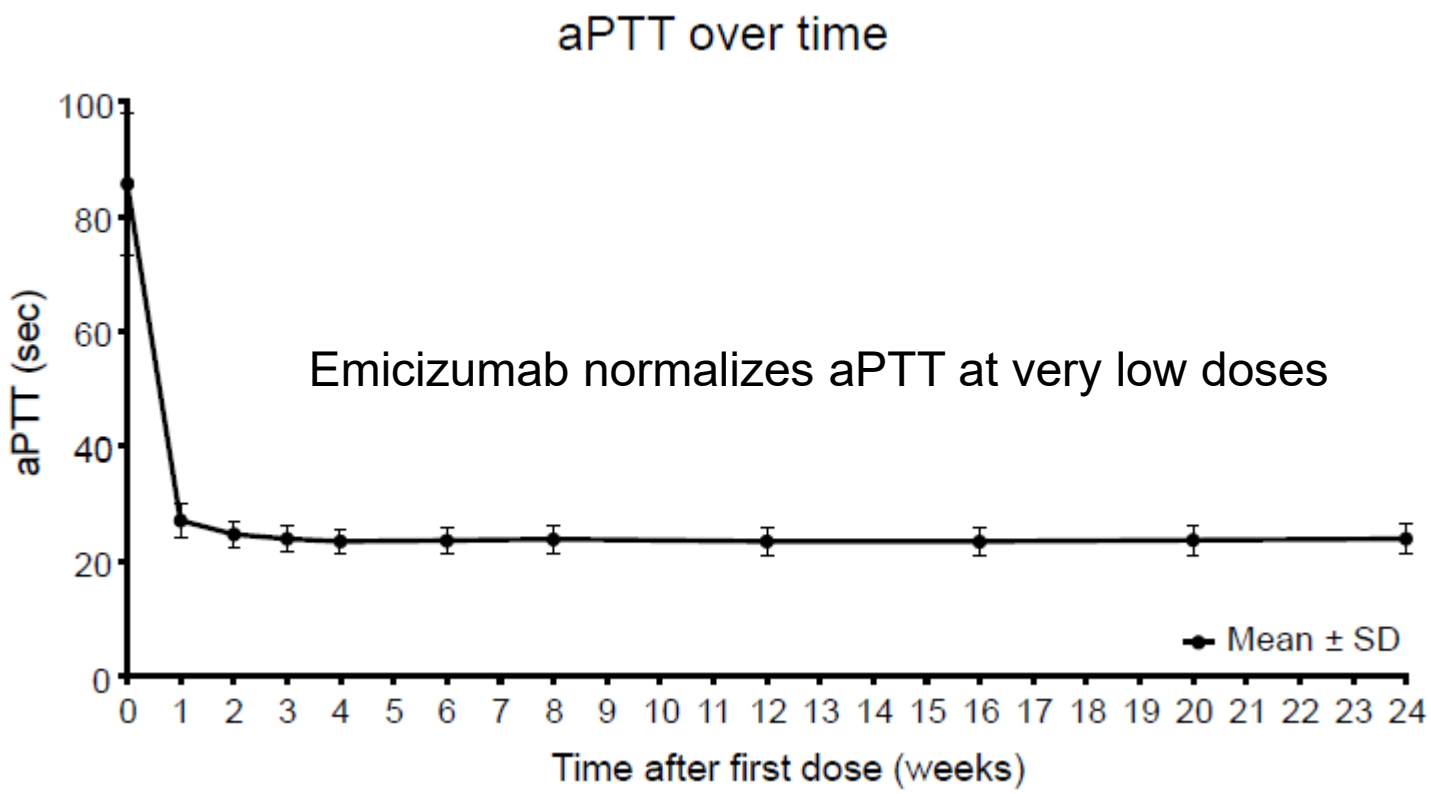
Safety of Emicizumab: Thrombotic Events

- Emicizumab + aPCC → Thrombotic Microangiopathy x 3, Thrombosis x 2)



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

Emicizumab has a strong effect on aPTT

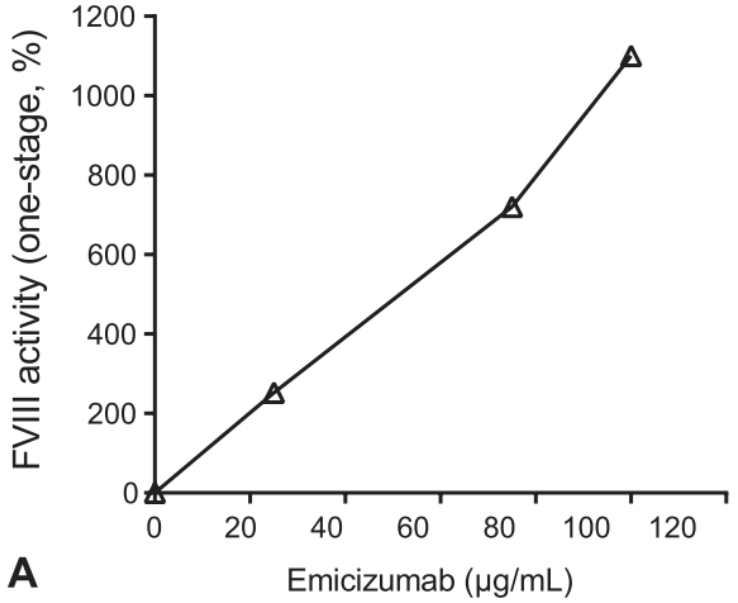


aPTT is not an accurate measure of hemostatic potential in the presence of emicizumab

Adamkewicz et al – data from HAVEN 1 study

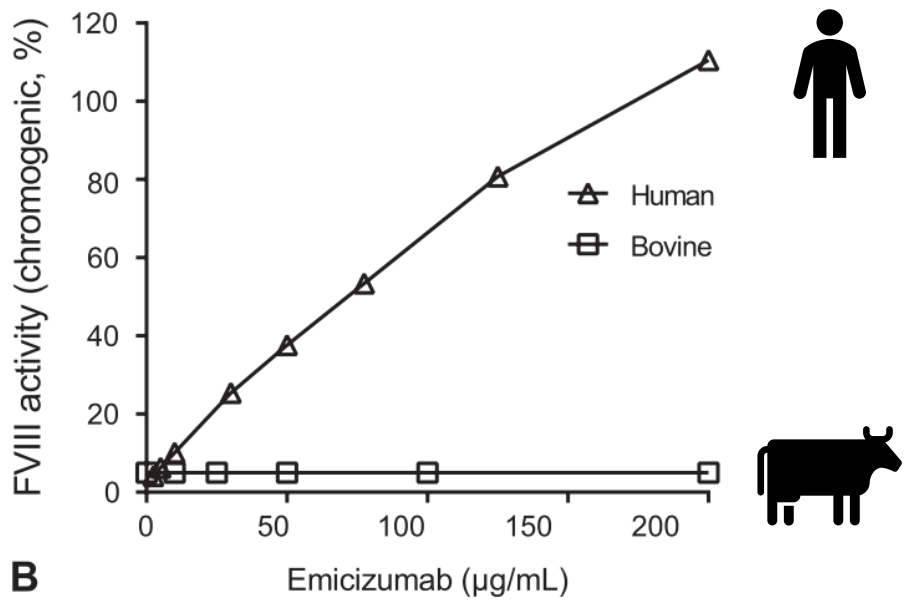
Factor & Inhibitor Assays

One-Stage FVIII Activity in an Emicizumab-Spiked FVIII-Deficient Plasma Sample



FVIII OSA grossly overestimates hemostatic potential

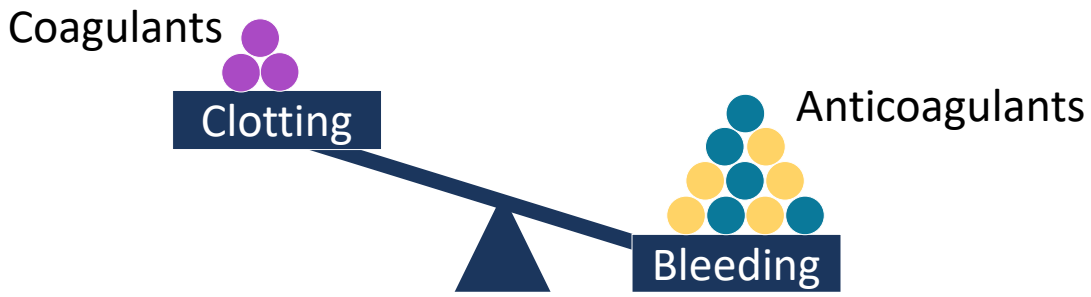
Chromogenic FVIII Activity in an Emicizumab-Spiked FVIII-Deficient Plasma Sample



FVIII Chromogenic with Bovine Proteins Measures FVIII Accurately

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

Non-Factor Therapy



Hemophilia

Anticoagulant Inhibition Treatment

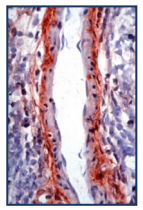
- Therapeutic approach aiming to restore balance by inhibiting natural anticoagulants
- Independent of FVIII and FIX activity

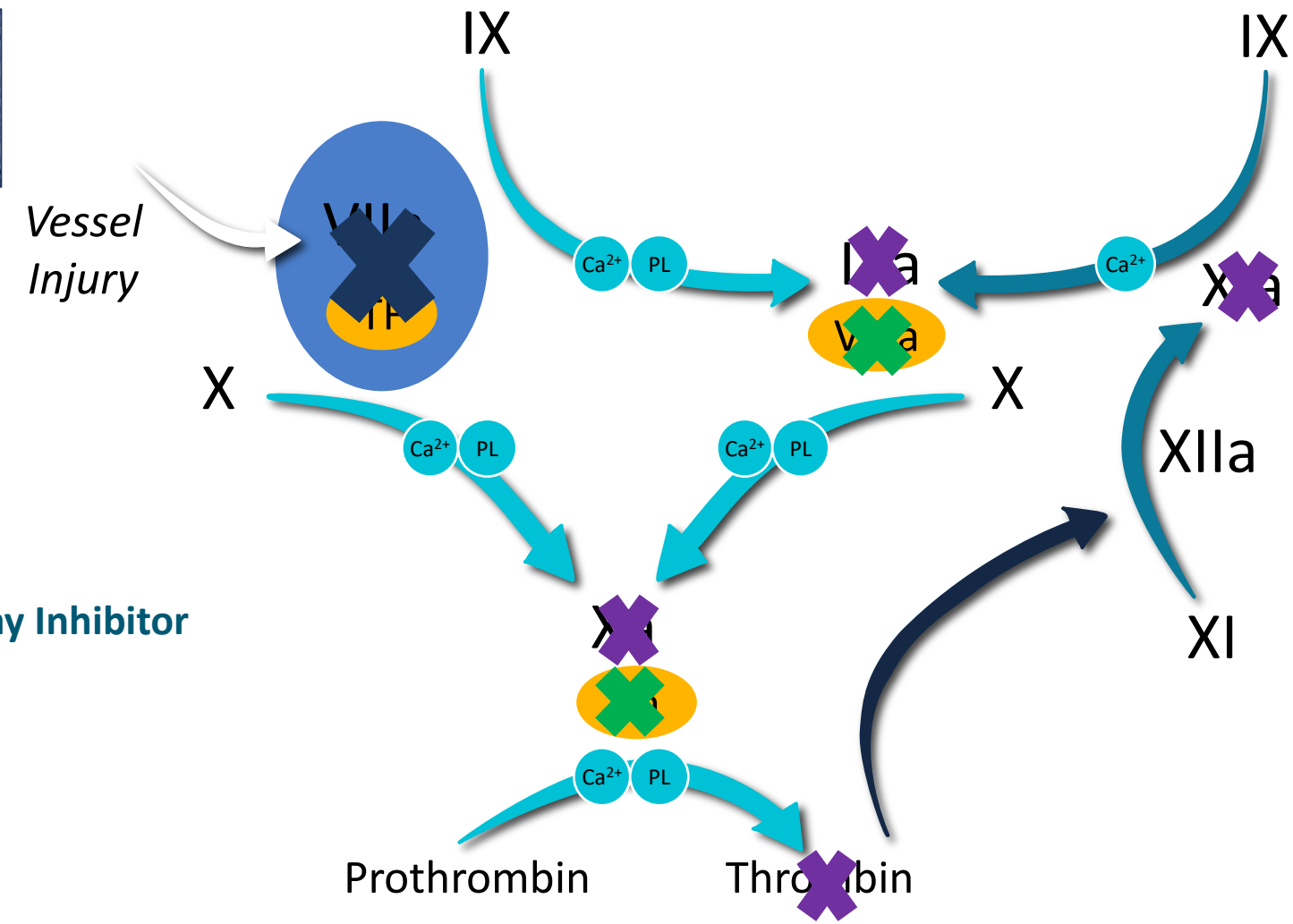
Factor Replacement

Anticoagulant Inhibition

Nature. 2014;515:S168.

Natural Anticoagulants





Tissue Factor Pathway Inhibitor

Antithrombin

Activated Protein C

Arterioscler Thromb Vasc Biol. 2016;36:1316.

Clinical Data for FDA Approved Drugs

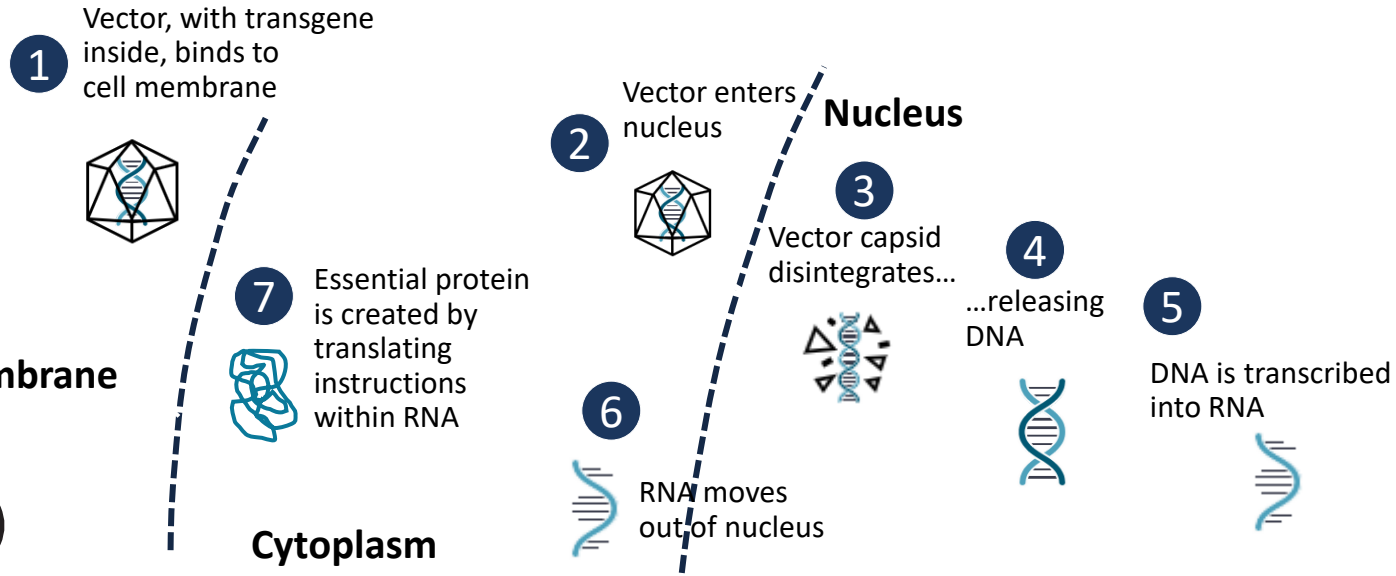
Drug	Mechanism	Efficacy (mean ABR)	Safety
Fitusiran	siRNA to antithrombin	ATLAS-INH: 1.7 ATLAS-A/B: 3.1 ATLAS-PPX: 2.3 (inh), 3.2 (non-inh)	Thrombosis x 5 → dose adjustment to maintain antithrombin 10-25%
Concizumab	IgG to K2 domain of TFPI	Explorer7: 2.1 (HA), 4.3 (HB) Explorer8: 3.9 (HA), 6.4 (HB)	Thrombosis x 3 → dose adjustment x 1 to confirm therapeutic range
Marstacimab	IgG to K2 domain of TFPI	Previously On-demand: 3.2 Previously Prophylaxis: 5.1	Thrombosis x 1

- Administration: subcutaneous
- Dosing varies – daily to monthly
- Hemophilia A & B
- With and without inhibitors

Gene Therapy

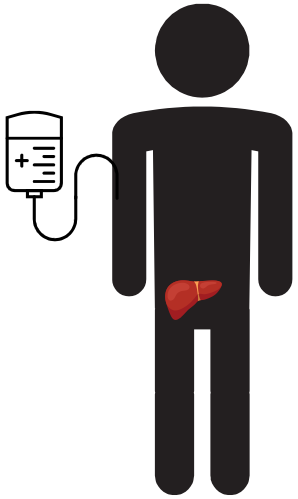
Gene Transfer

- Functional FVIII or FIX gene is inserted into vector
- Cell will use information to make functional factor VIII or FIX

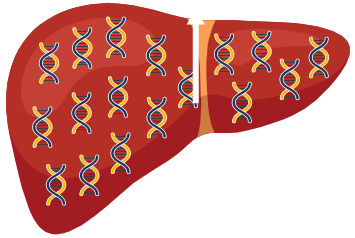


Functional gene

Vector carrying functional gene



Administration of vector as infusion



Protein production by liver

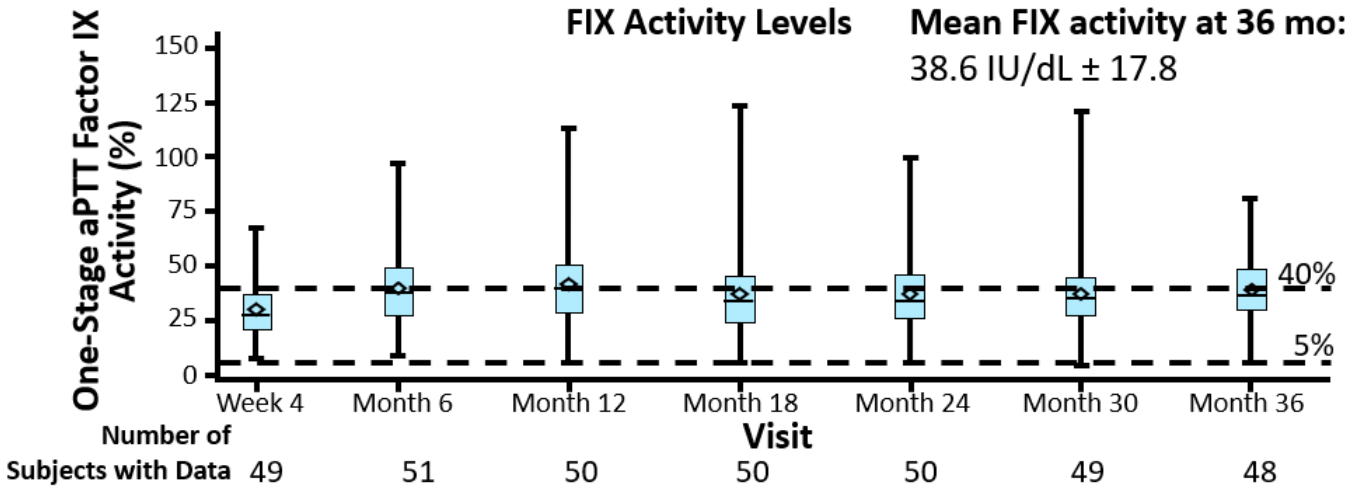
Hart. Orphanet J Rare Dis. 2021;16:189.
Sidonio. Blood Reviews. 2021;47:100759.

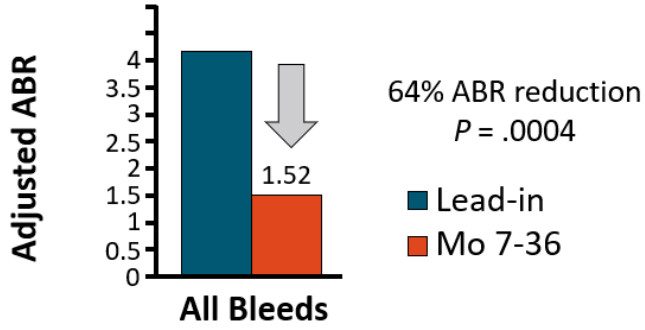
FDA-Approved Gene Therapies for Hemophilia

Gene Therapy	Indication	Approval Yr
Etranacogene dezaparvovec	Adults with hemophilia B who currently use FIX prophylaxis or have current or historical life-threatening hemorrhage or repeated, serious spontaneous bleeding episodes	2022
Valoctocogene roxaparvovec	Adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without preexisting antibodies to AAV-5 detected by an FDA-approved test	2023
Fidanacogene Elaparvovec	Adults with hemophilia B who currently use FIX prophylaxis or have current or historical life-threatening hemorrhage or repeated, serious spontaneous bleeding episodes, and do not have neutralizing antibodies to AAVRh74va capsid	2024

Etranacogene dezaparvovec PI.
Valoctocogene roxaparvovec PI.
Fidanacogene Elaparvovec PI.

Phase III Data for Etranacogene dezaparvovec (HB)

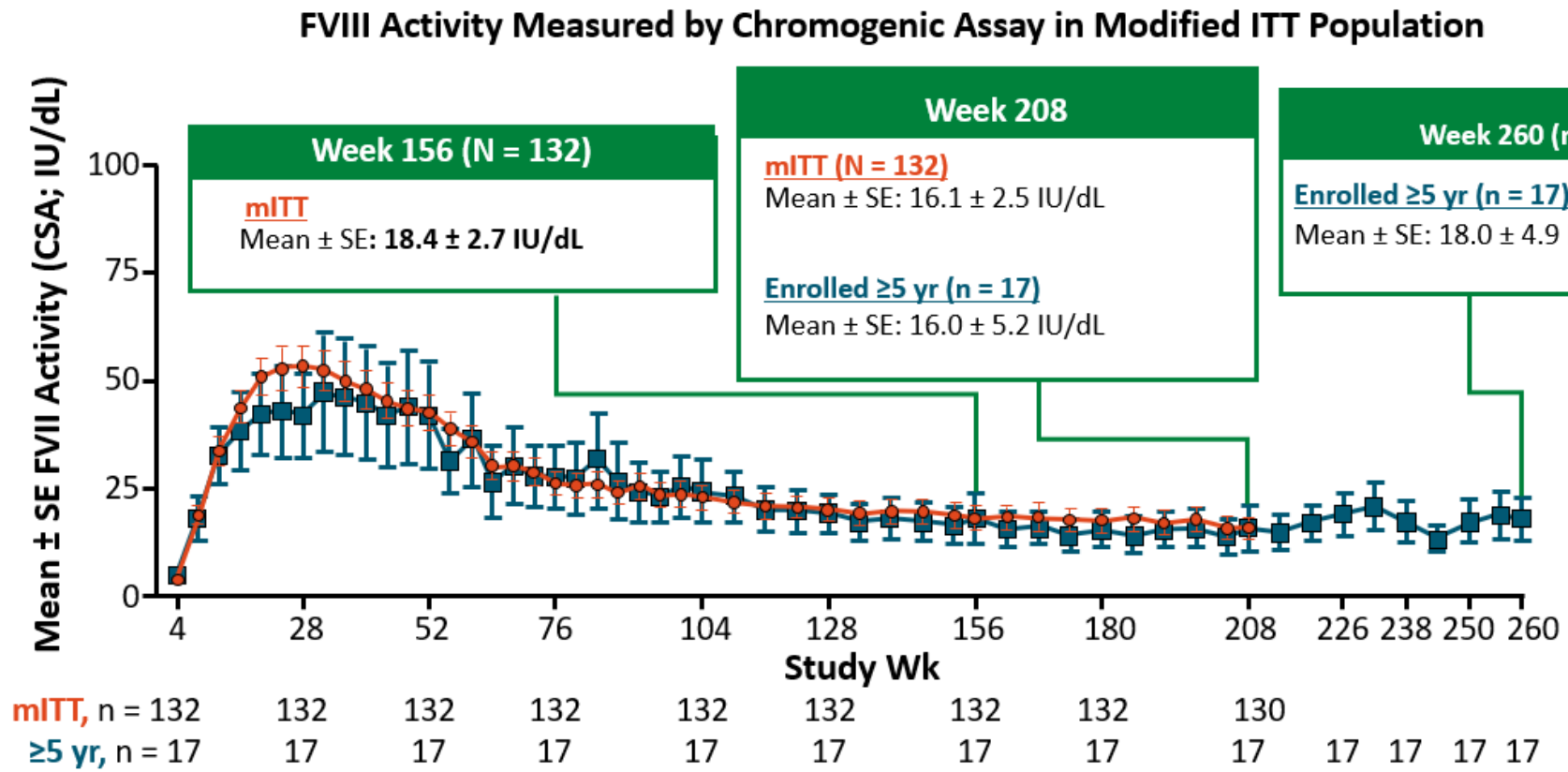




- Year 3: 94% (n = 51) participants remained FIX prophylaxis free
- 9 participants (16.7%) required steroid treatment; mean duration 81.4 days

N Engl J Med 2023;388:706-718

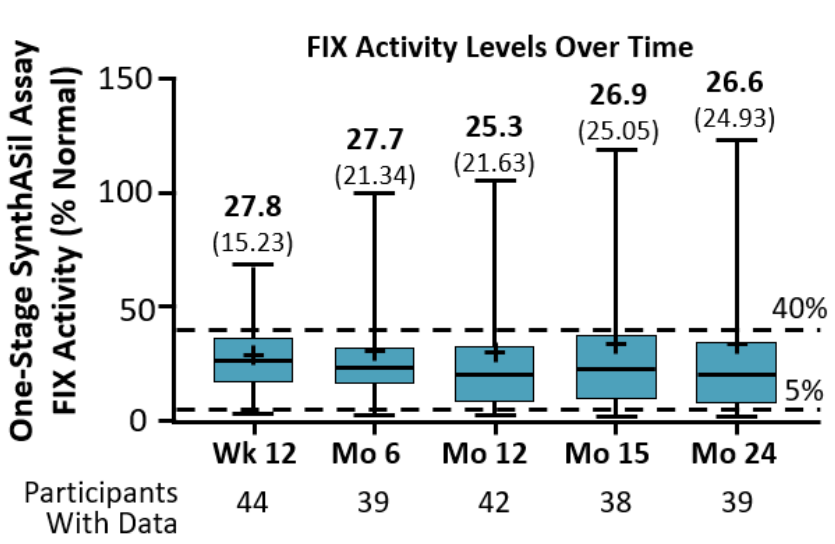
Phase III Data for Valoctocogene Roxaparvovec (HA)

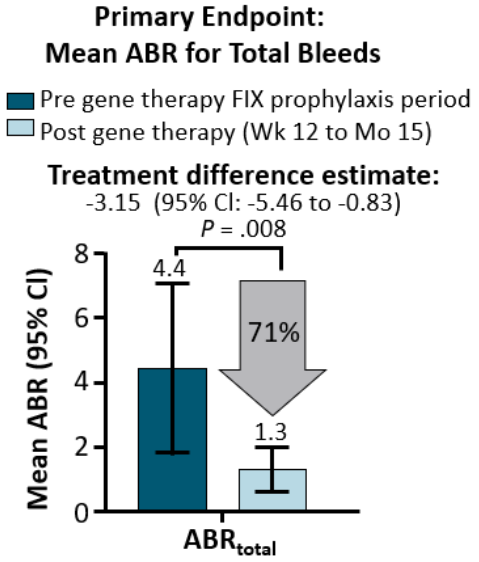


- Year 4: 24 of 134 participants resumed FVIII prophylaxis
- 106 participants (80%) required steroid treatment; mean duration 35 weeks

Leavitt. ISTH 2024. Abstr OC 30.2
Ozelo. NEJM. 2022;386:1013.

Phase III Data for Fidanacogene Elaparvovec (HB)





- Month 15: 13.3% (n = 6) resumed FIX prophylaxis
- 28 participants (62.2%) required at least 1 course of steroids; median duration 95 days

Fidanacogene Elaparvovec PI. Wang. ISTH2024. Abstract OC 30.5.

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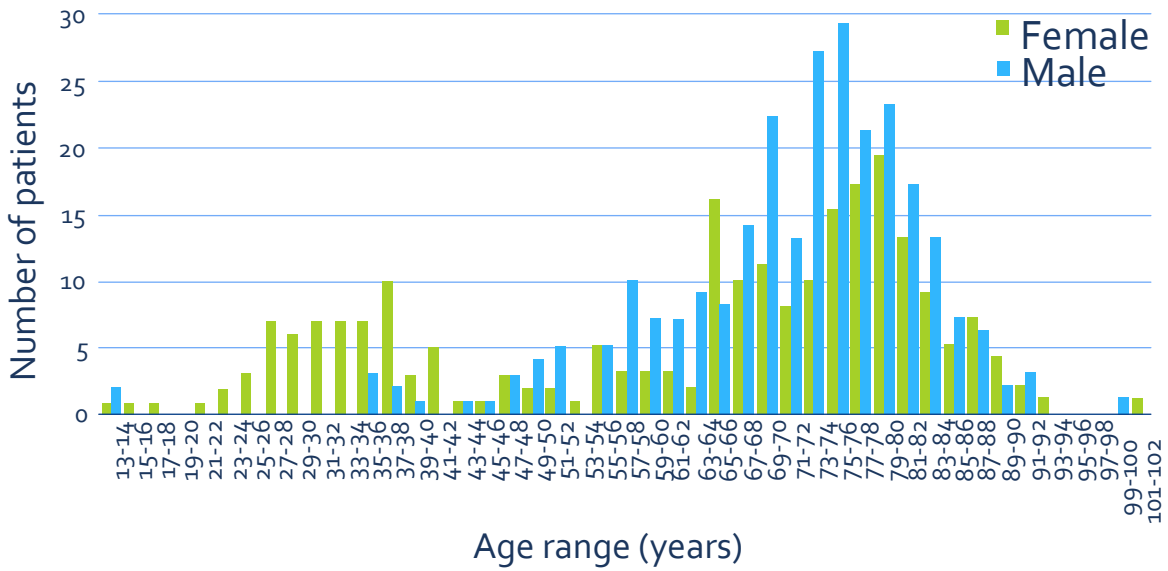
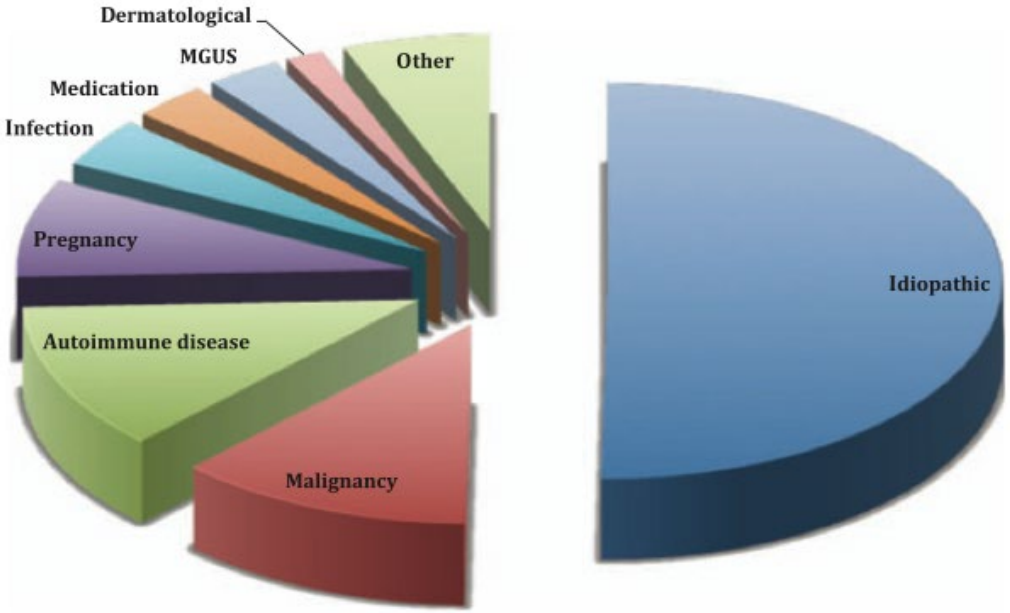
Acquired Hemophilia A

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

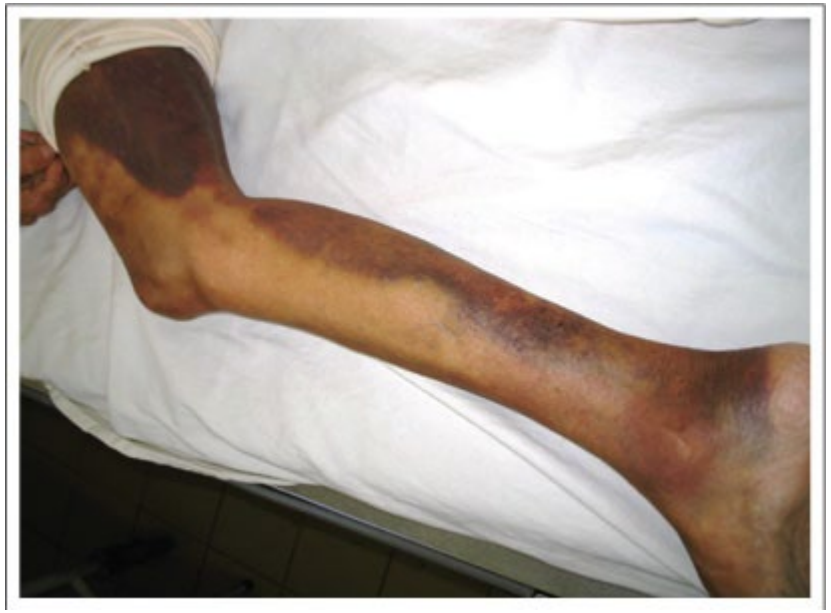


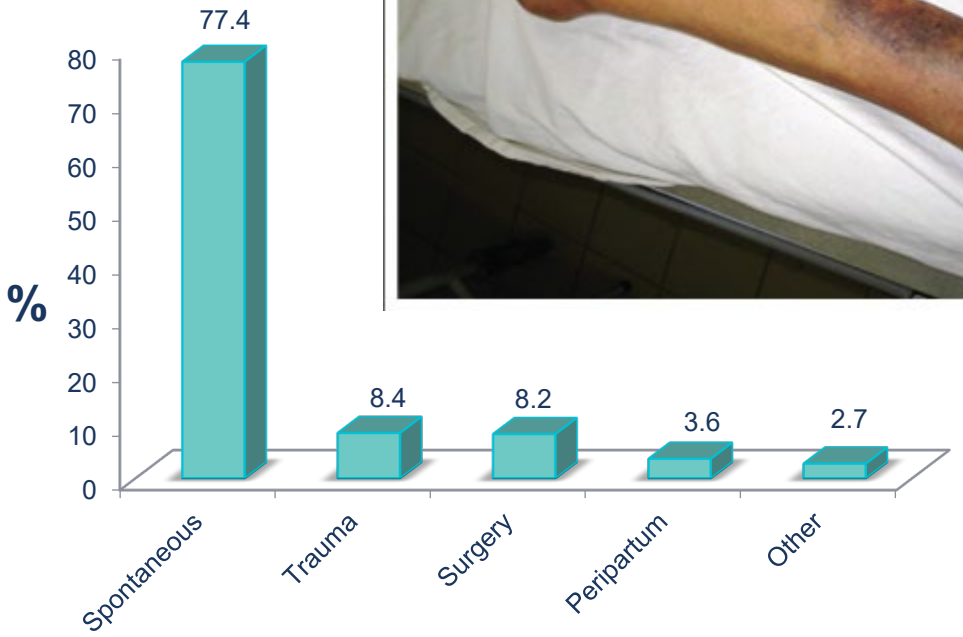


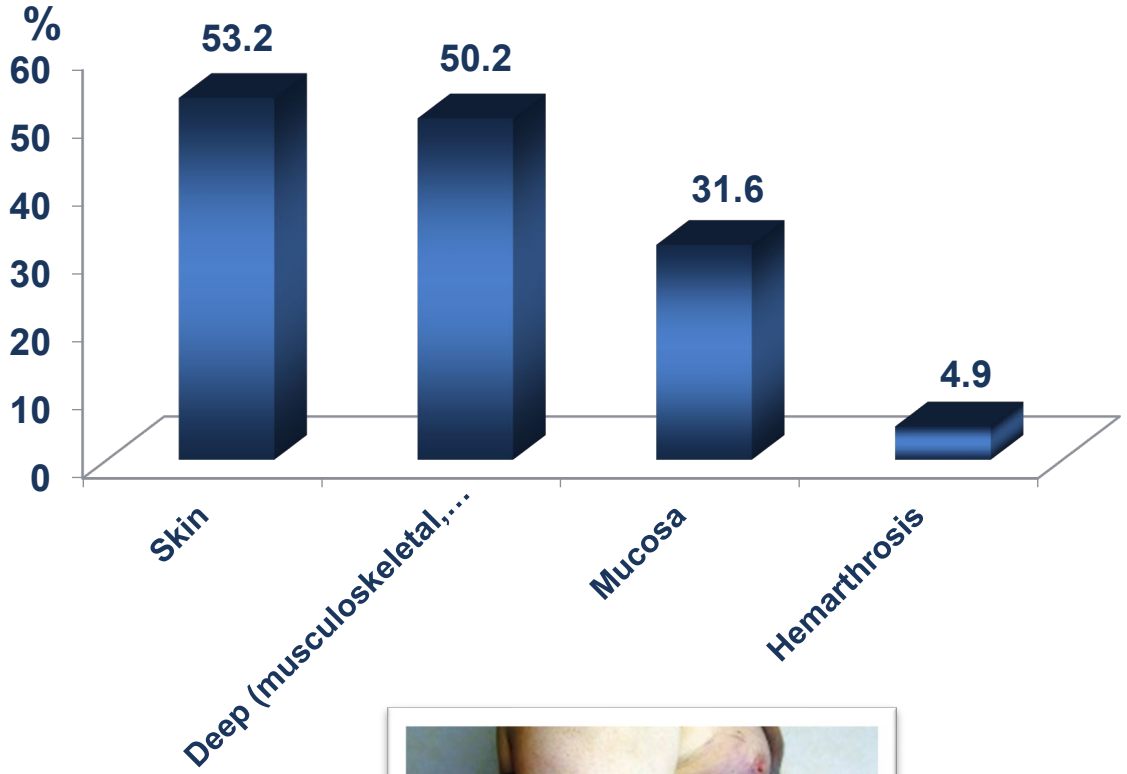
Collins et al Blood 2007

Knoebl, et al. J Thromb Haemost 2012

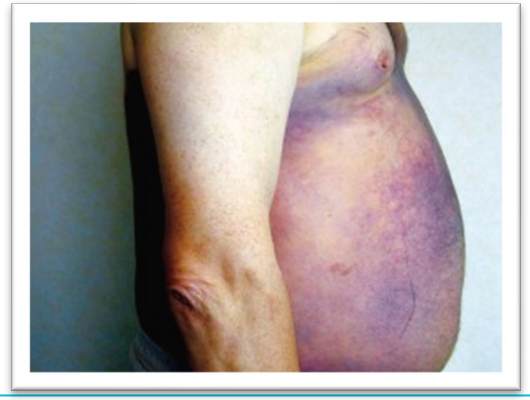
Bleeding Severity in AHA







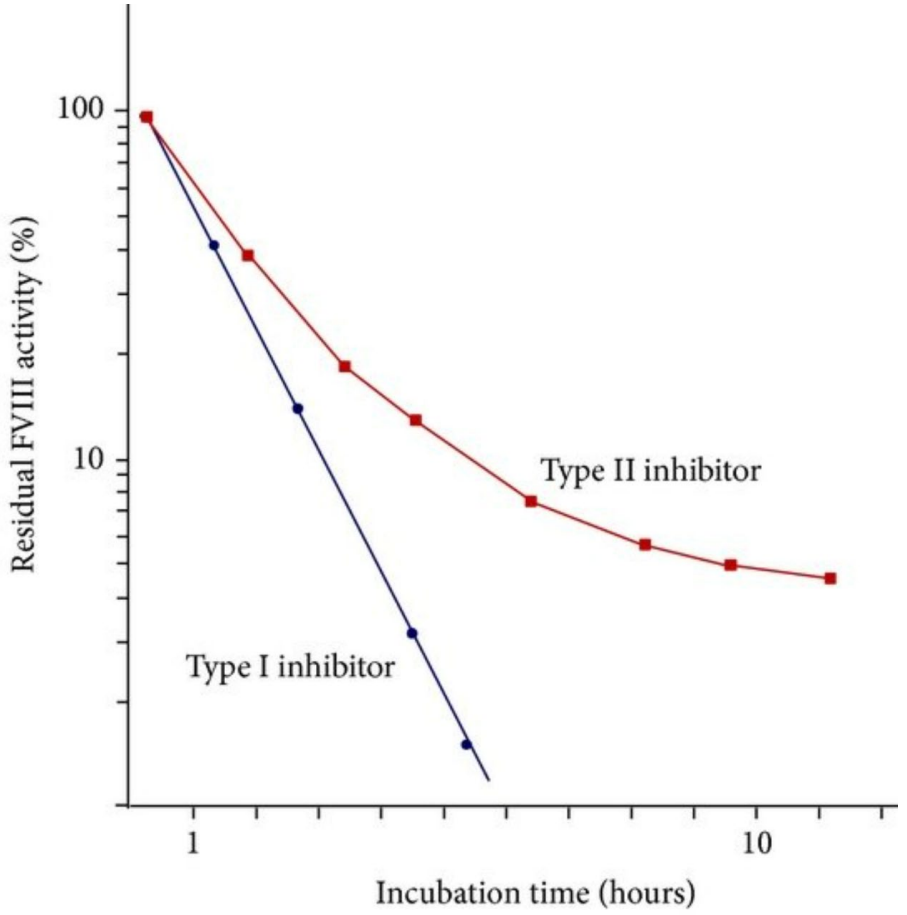
73% severe
Mortality – 8% to 22%



Zeitler H, et al. *Atheroscler Suppl*. 2013.
Collins P, et al. *BMC Res Notes*. 2010;3:161.

Diagnosis/Inhibitor Kinetics

- Consistent clinical presentation
- Prolonged aPTT, normal PT
  - Mixing Study: (classically) corrects immediately but prolongs with incubation at 37°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

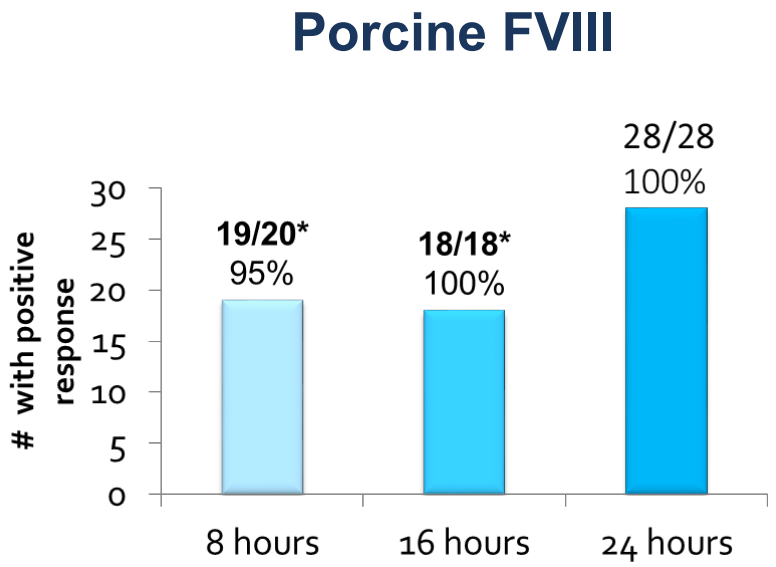
Treat Bleeding

Prevent Bleeding

Eradicate the Inhibitor

AHA – Hemostatic Treatment

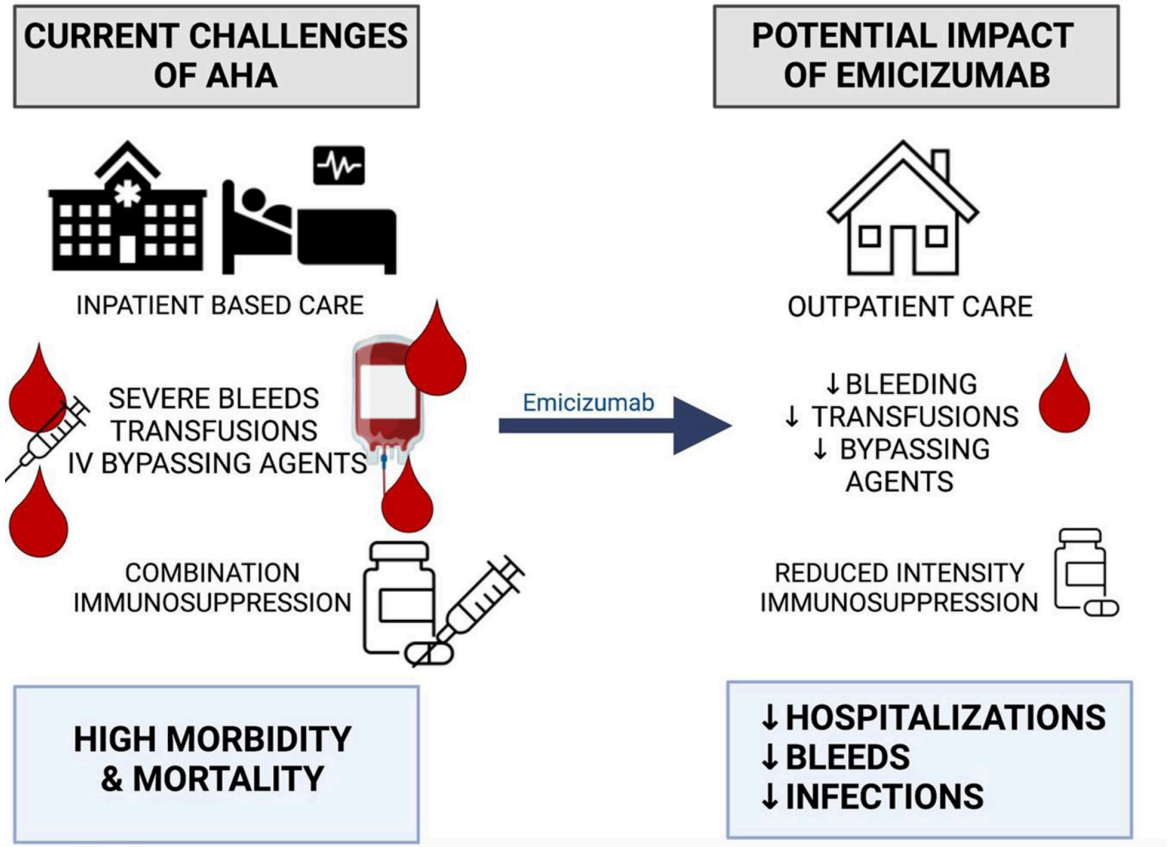
Rates of Control for First Bleeding Episodes by First-line Therapy	First-line Bleeding Control	
	n	%
Bypassing Agent	219	91.8
Recombinant factor VIIa	159	91.2
Activated prothrombin complex concentrate(aPCC)	60	93.3
Replacement Therapy	69	69.6
- FVIII	55	70.1
- DDAVP	14	64.3



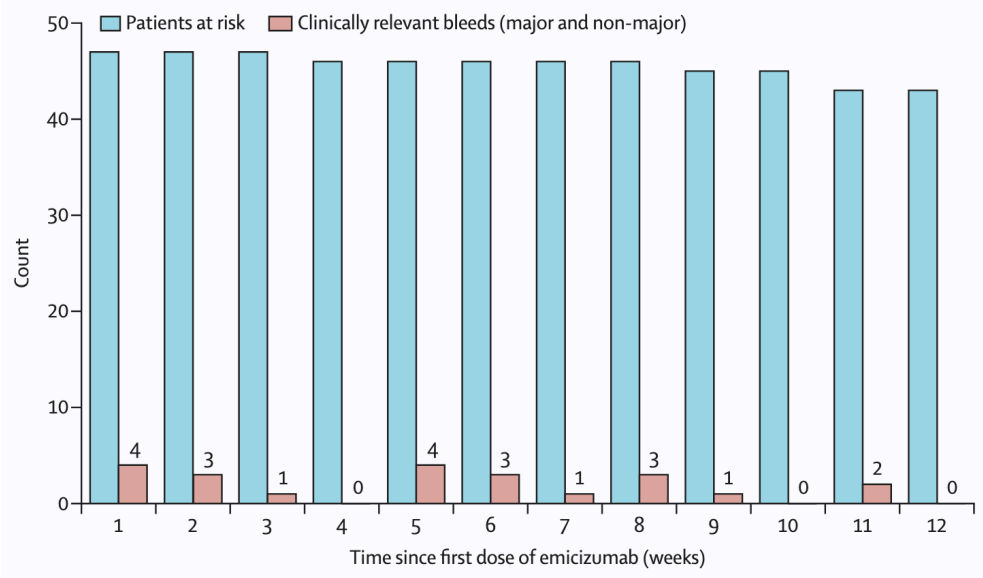
Note: Use of human or porcine FVIII replacement requires real time availability of FVIII measurements

Kruse-Jarres et al. Haemophilia 2015.
Table adapted from Baudo et al - Blood 2012.

AHA – Hemostatic Prophylaxis



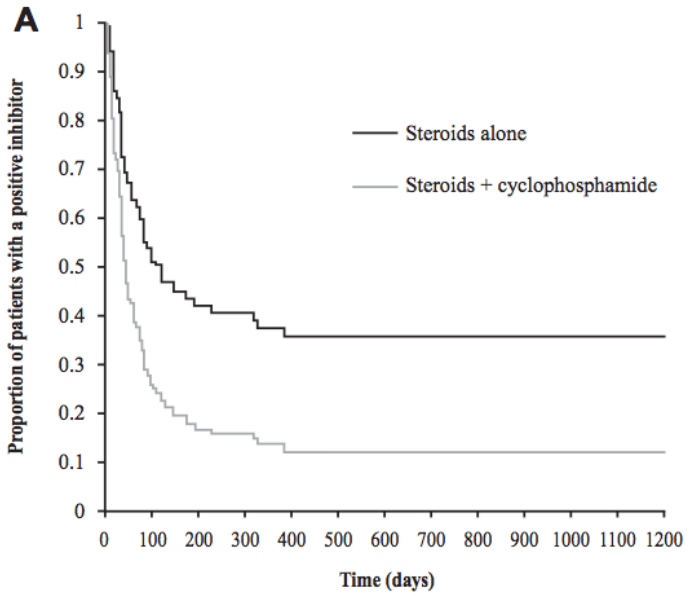
- Emicizumab prophylaxis in patients with acquired haemophilia A (GTH-AHA-EMI)
  - Prospective, open label, phase 2 study
  - Dosing
    - Rapid loading: 6 + 3 mg/kg on days 1 + 2
    - Maintenance: 1.5 mg/kg weekly until week 12

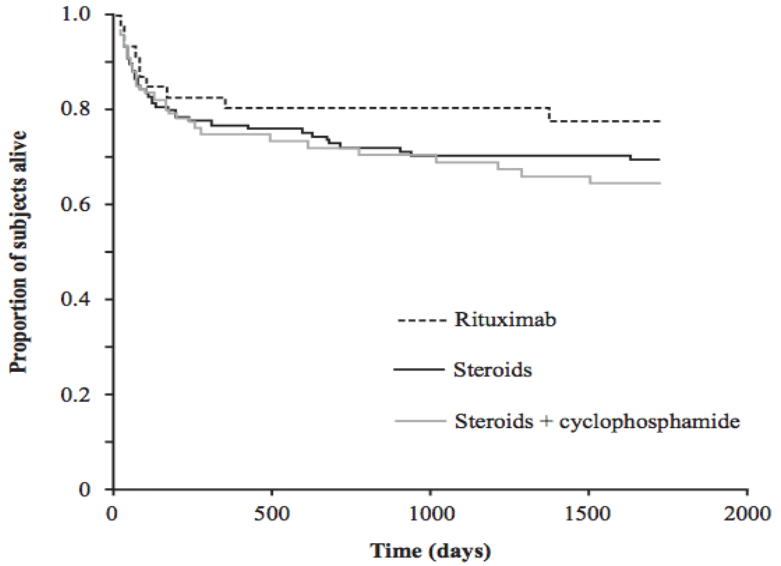


Hematology Am Soc Hematol Educ Program (2023) 2023 (1): 24–30.
Lancet Haematol 2023;10: e913–21.

AHA – Immunosuppressive Therapy

- 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%





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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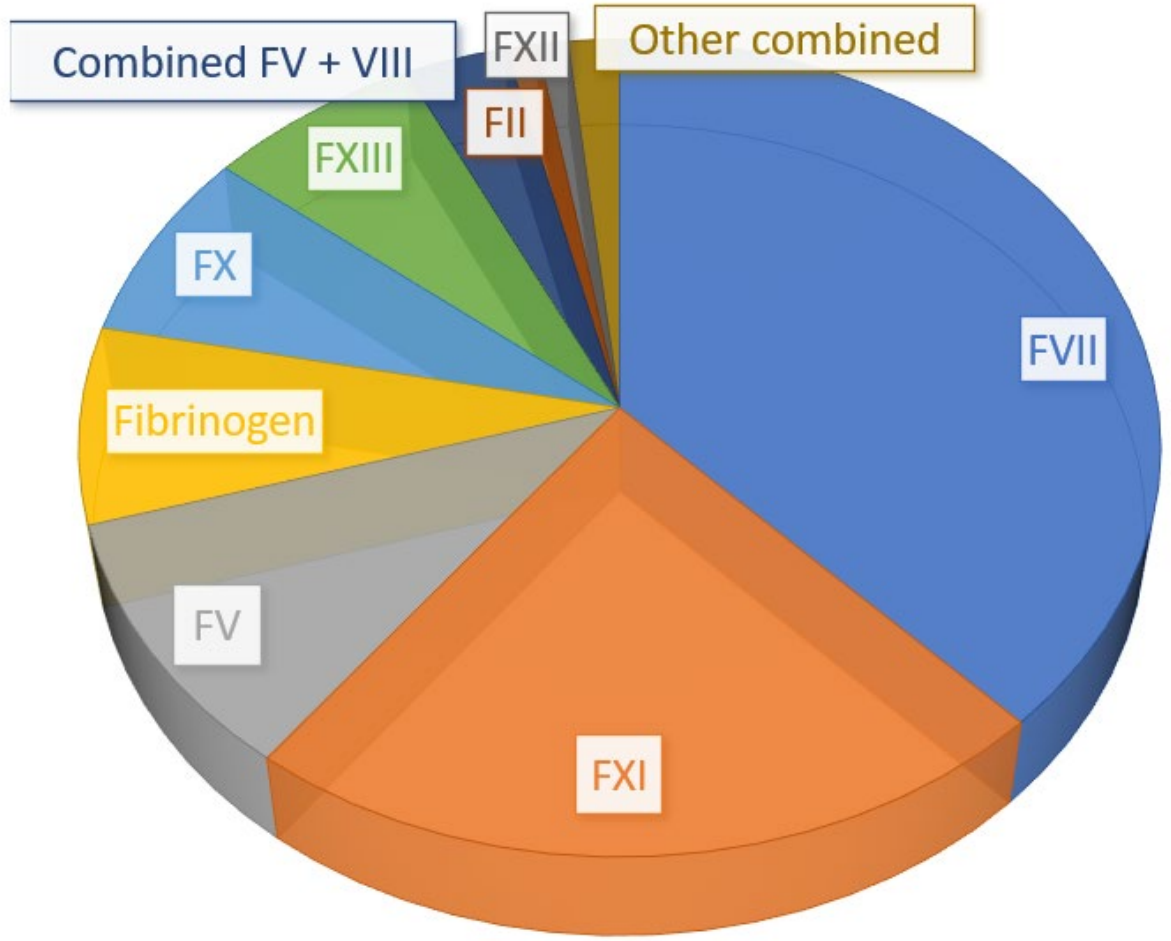
Other Clotting Factor Deficiencies

European Network of Rare Bleeding Disorders Database

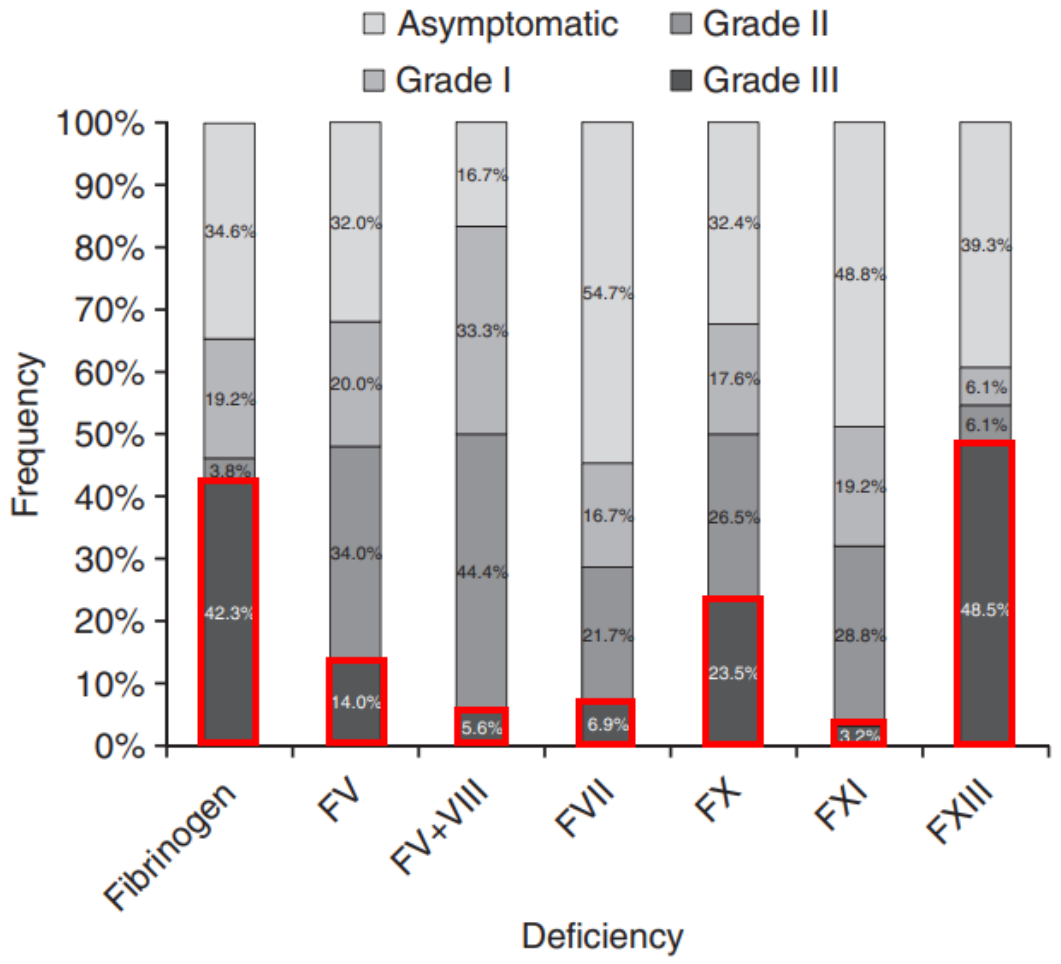
Type of deficiency	n (%)
FVII	224 (38)
FXI	133 (22)
FV	60 (10)
Fibrinogen	46 (8)
FX	45 (8)
FXIII	42 (7)
Combined FV + VIII	20 (3)
FII	6 (1)
FXII	6 (1)
Other combined	10 (2)



Peyvandi et al. JTH 2012

European Network of Rare Bleeding Disorders Database

- 592 patients
- Mean age 31 years (7 months to 95 years)
- 51% women



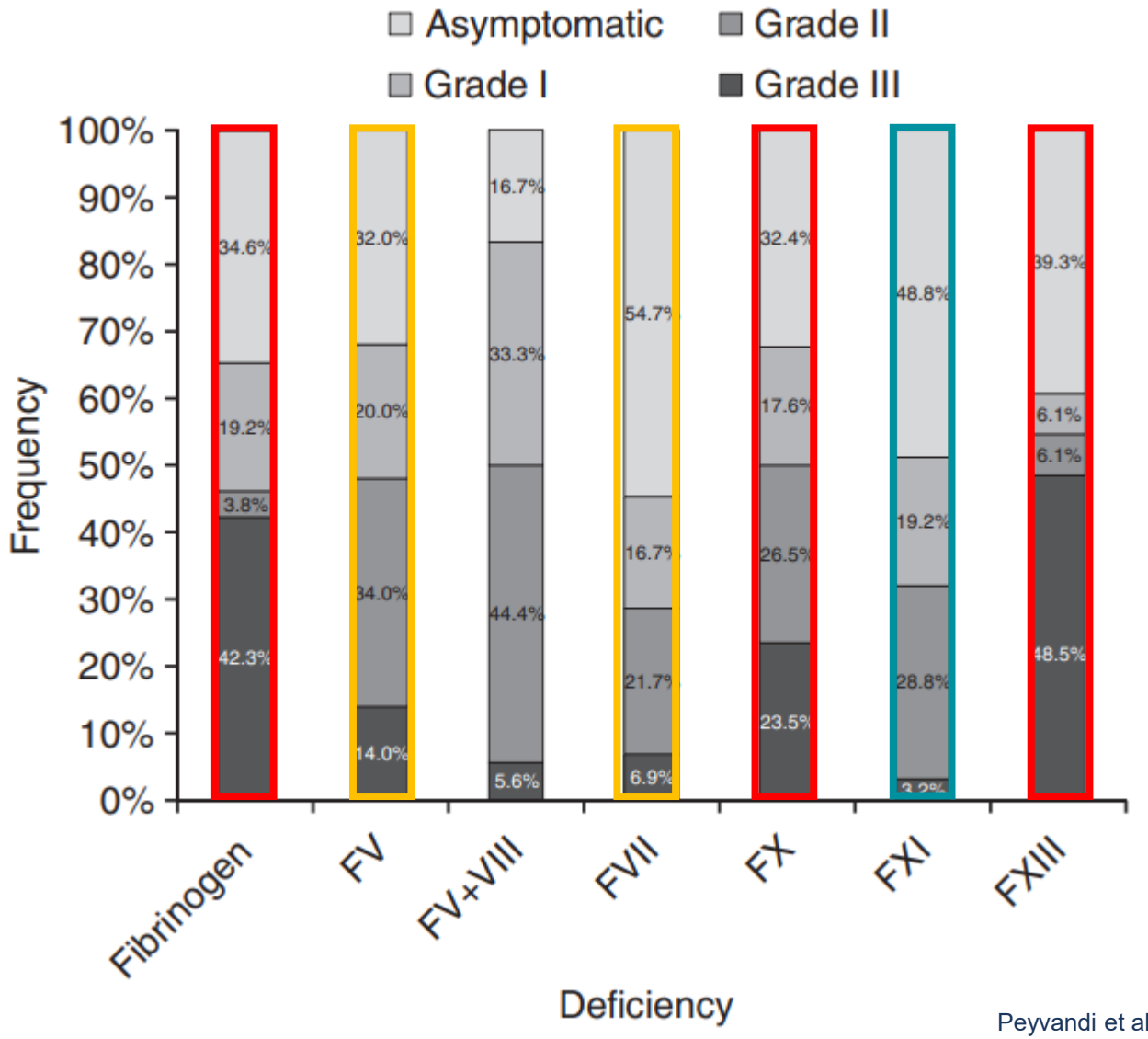
Peyvandi et al. JTH 2012

European Network of Rare Bleeding Disorders Database

- 592 patients
- Mean age 31 years (7 months to 95 years)
- 51% women

Does factor level matter?

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



Peyvandi et al. JTH 2012

Factor	Clinical	Incidence	Inheritance	Treatment
Fibrinogen (I) deficiency	• Post-trauma / surgery • Splenic rupture • Pregnancy loss	1:1 million	AR	• Fibrinogen (pd or recombinant) • Cryoprecipitate
Dysfibrinogenemia	• Bleeding or thrombosis • Abnormal ratio of fibrinogen antigen to activity	Variable	Variable	• Fibrinogen (pd or recombinant) • Cryoprecipitate
Prothrombin (II)	• Extremely rare • (Can be acquired in association with APS)	1:2 million	AR	• PCC
Factor V	• Extremely rare	1:1 million	AR	• Plasma • Platelets
Factor VII	• Mild, moderate, severe • Intracranial hemorrhage & mucocutaneous bleeding	1:300,000	AR	• rFVIIa
Factor VIII	• Mild (6-45%), moderate (1-5%), severe (< 1%) • Severe: spontaneous hemarthrosis (→ hemophilic arthropathy) & hematomas • Inhibitor development: FVIII 25%, FIX 5% • Note: “carriers” can have bleeding symptoms or ↓ factor activity	1:5-10,000 live male births	X-linked	• FVIII (pd or recombinant) • FVIII mimetics • Inhibitors of natural anticoagulants • Gene therapy
Factor IX		1:30,000 live male births	X-linked	• FIX (recombinant) • Inhibitors of natural anticoagulants • Gene therapy
Factor X	• Intracranial hemorrhage	1:1 million	AR	• PCC
Factor XI	• Post-trauma / surgery • ↑ frequency in Ashkenazi Jews (1:10 carriers, 1:200-400 affected)	1:1 million	AR	• Plasma • pd concentrate (Europe, Israel)
Factor XIII	• Umbilical stump bleeding			• FXIII (pd or recombinant)

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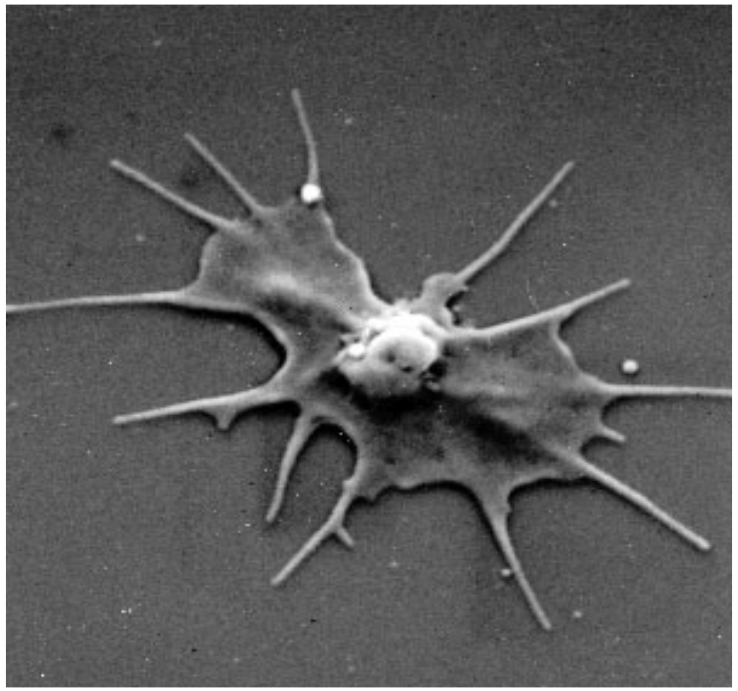
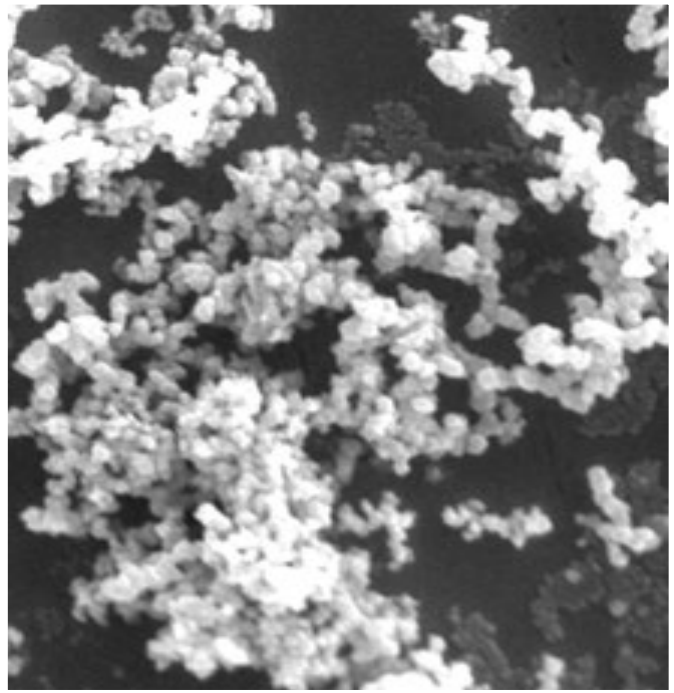
Inherited Platelet Disorders

Platelets

Inactive



Adhesion &
Activation



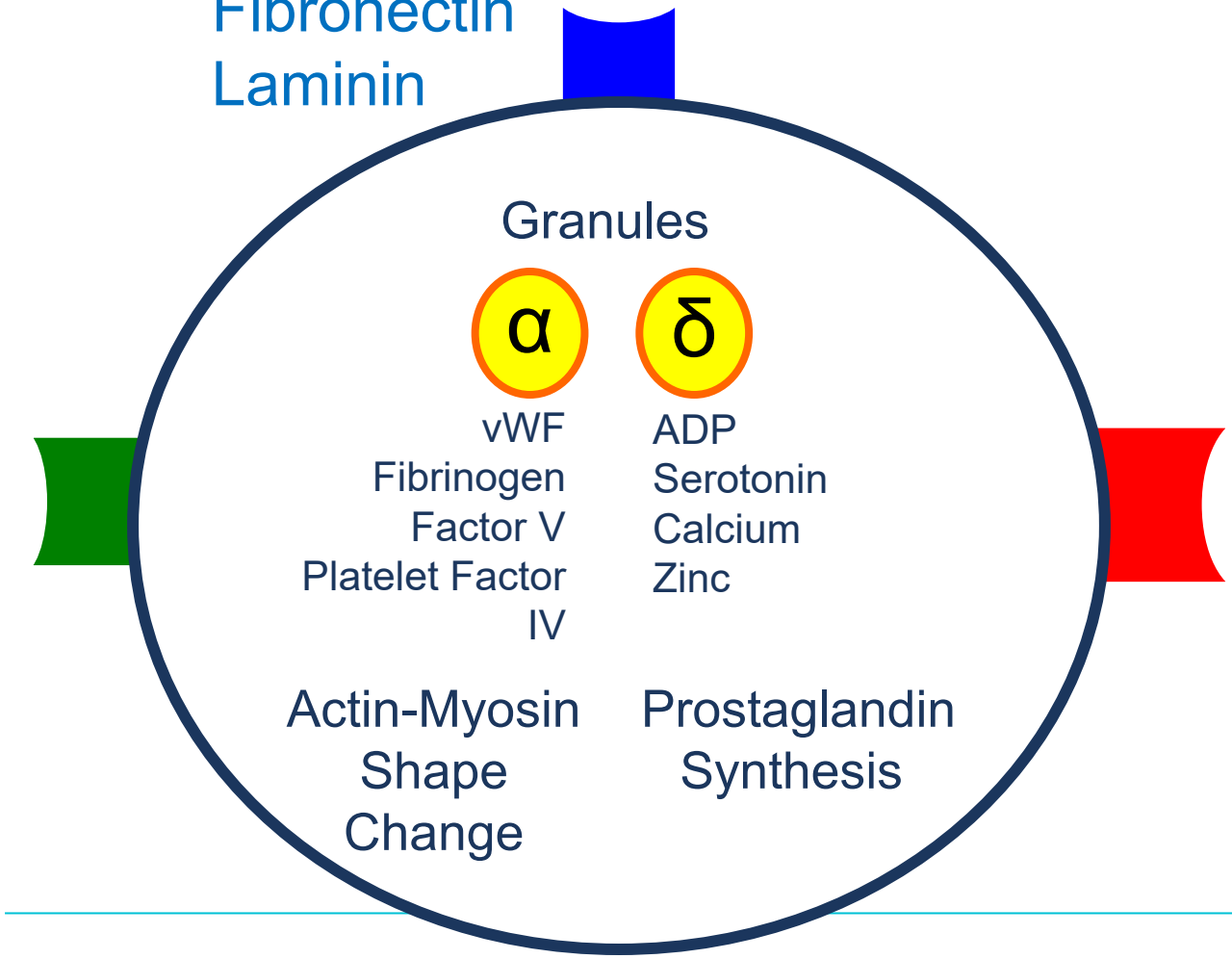
Aggregation

Adhesion (GP1b)

Collagen
Von Willebrand Factor
Fibronectin
Laminin

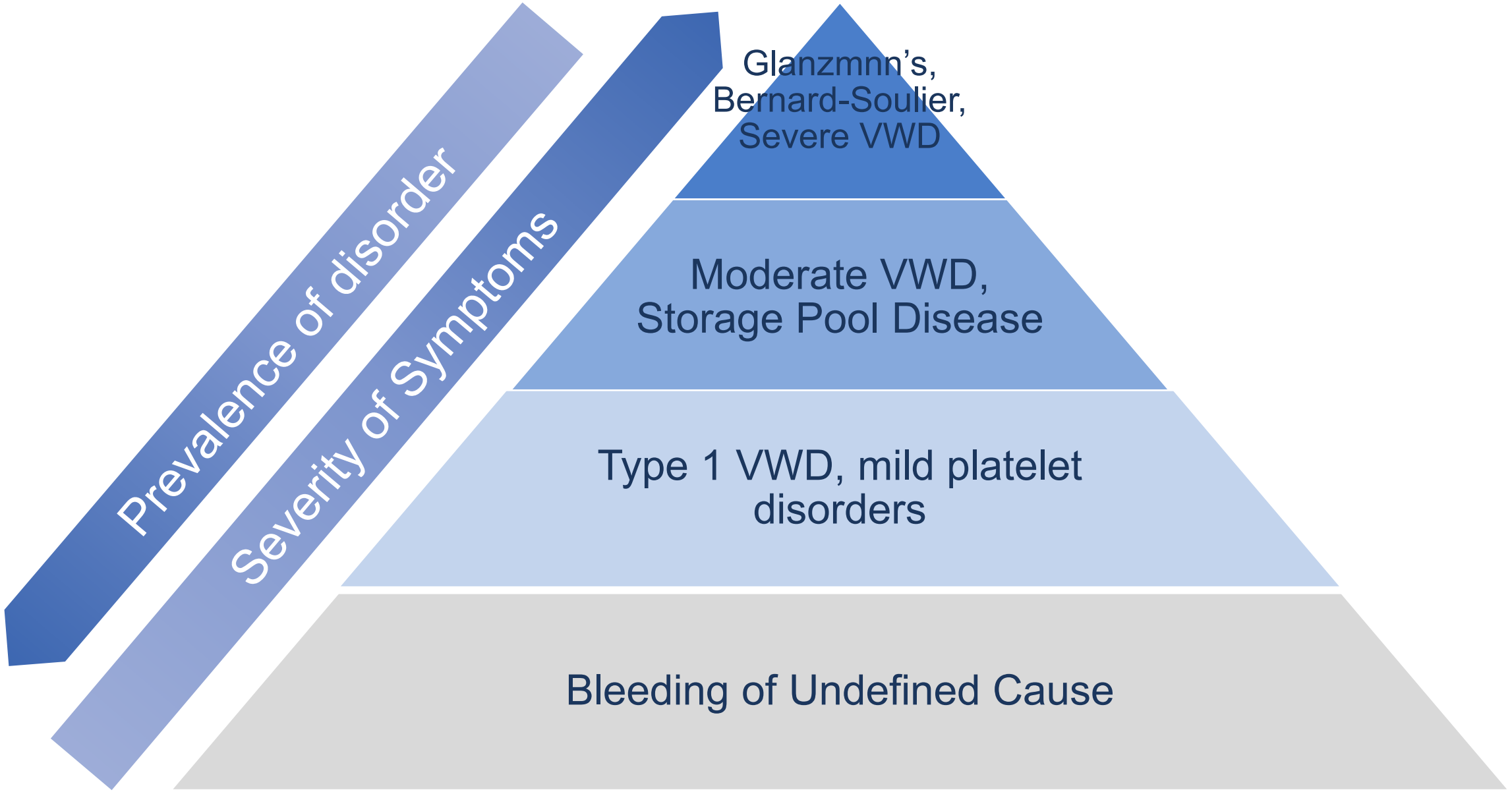
Soluble Platelet Activators

Epinephrine
ADP
Thrombin
Thromboxane

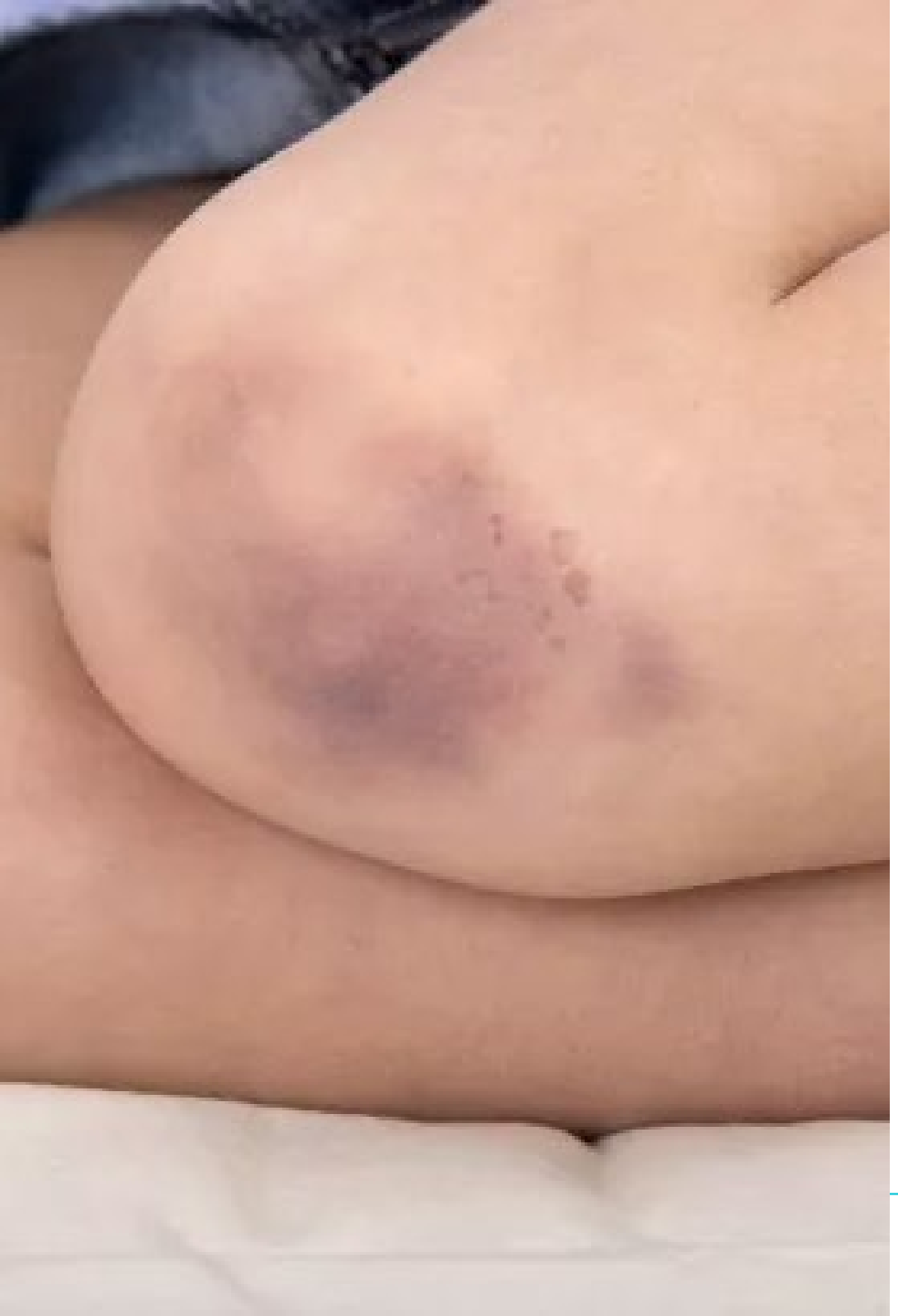


Aggregation (GP2b3a)

Von Willebrand Factor
Fibrinogen



Rodeghiiero et al, Hemasphere 2019;3:e286.



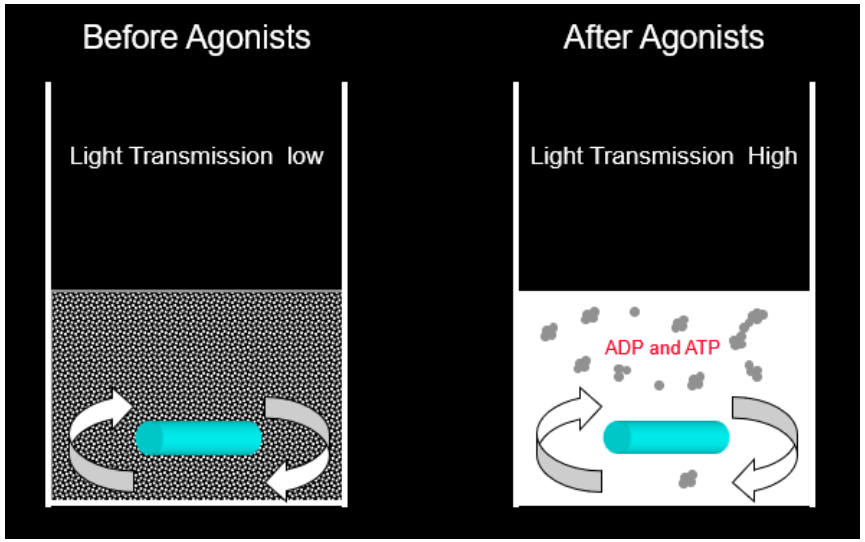
Symptoms of Platelet Function Disorders

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

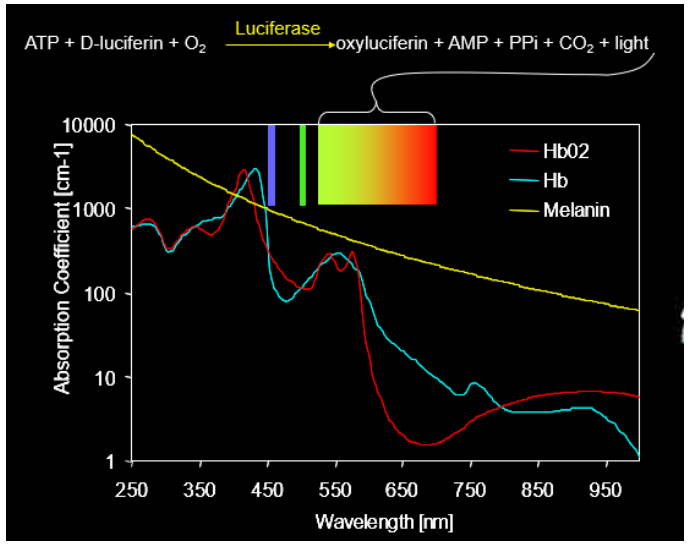
Testing is Tricky

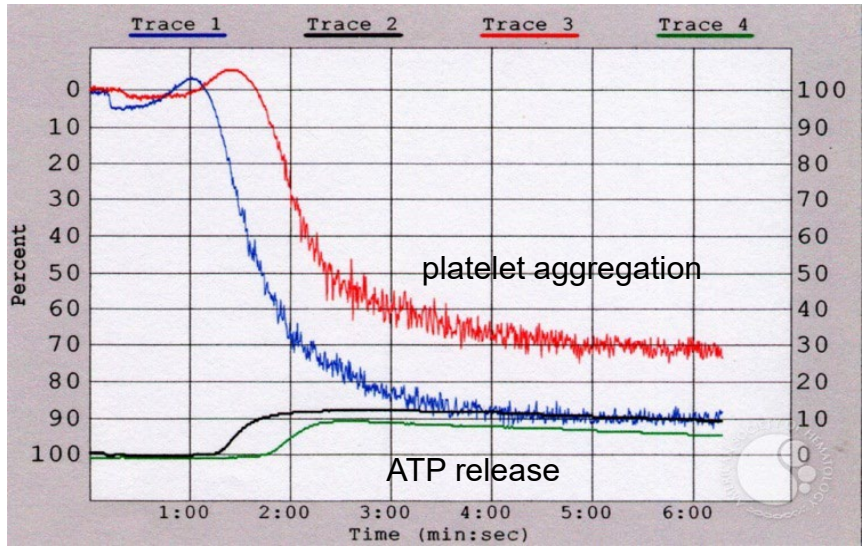
- Platelet number
- Platelet function analyser-100 (PFA-100), Bleeding time
  - PFA does not detect all platelet disorders
    - Particularly storage pool disorder
- Platelet aggregation studies
- Platelet electron microscopy
- Genetic testing

Platelet Aggregation



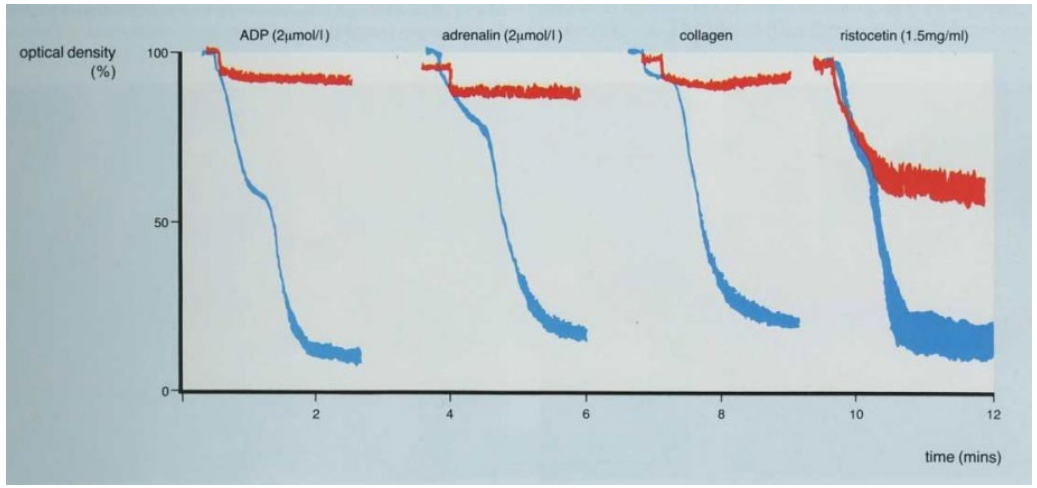
Luminometry





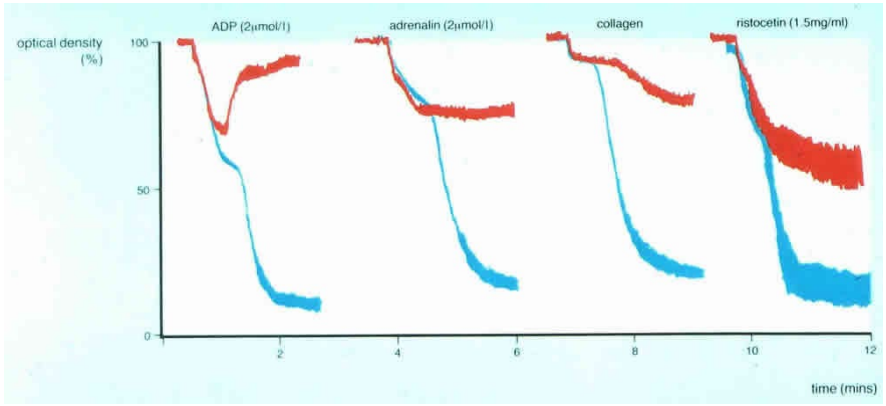
Hayward CPM. Transf Apher Sci. 2008;38:65, Warren JT & DiPaola J. Blood 2022;139:3264.

Platelet Aggregation Patterns



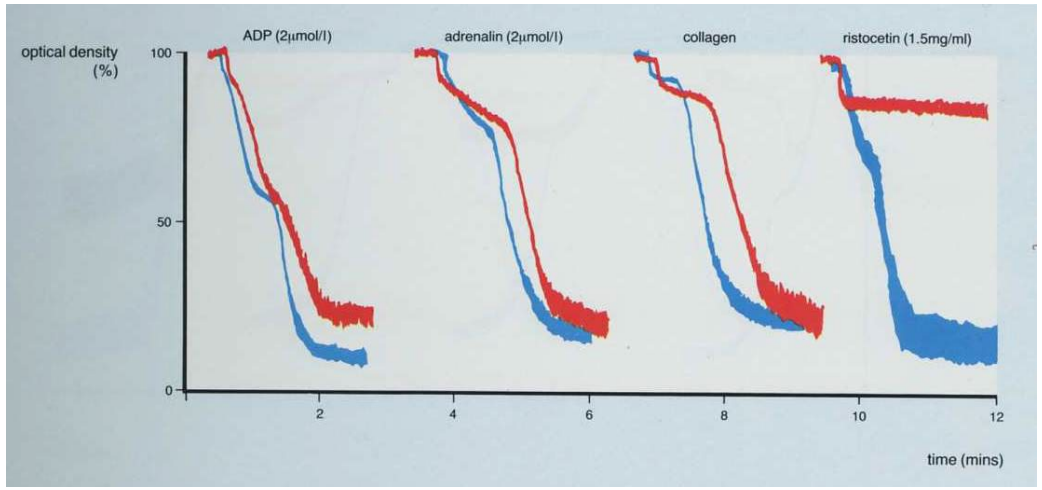
Glanzmann's Thrombasthenia

no activity with either CD41 or CD61
→ missing the GPIIb/IIIa complex



Storage Pool disease

Variable etiology and phenotype



Bernard-Soulier Syndrome

defective CD42 binding
→ consistent with absence of the GPIb-IX-V complex

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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